US011779604B2

(12) **United States Patent**
Bland-Ward et al.

(10) **Patent No.: US 11,779,604 B2**
(45) **Date of Patent: Oct. 10, 2023**

(54) **ANTIBODIES, COMBINATIONS COMPRISING ANTIBODIES, BIOMARKERS, USES AND METHODS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/346,675**

(22) PCT Filed: **Nov. 3, 2017**

(86) PCT No.: **PCT/EP2017/078202**
§ 371 (c)(1),
(2) Date: **May 1, 2019**

(87) PCT Pub. No.: **WO2018/083248**
PCT Pub. Date: **May 11, 2018**

(65) **Prior Publication Data**

US 2019/0275084 A1 Sep. 12, 2019

(30) **Foreign Application Priority Data**

Nov. 3, 2016	(GB)	1618529
Feb. 23, 2017	(GB)	1702965
Apr. 26, 2017	(GB)	1706639
Jul. 7, 2017	(GB)	1710953
Aug. 16, 2017	(GB)	1713147

(51) **Int. Cl.**

A61K 39/395	(2006.01)
A61K 39/00	(2006.01)
A61K 35/17	(2015.01)
A61P 37/06	(2006.01)
A61K 31/436	(2006.01)
C07K 16/28	(2006.01)
C12N 5/0783	(2010.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 35/17*** (2013.01); ***A61K 31/436*** (2013.01); ***A61K 39/3955*** (2013.01); ***A61P 37/06*** (2018.01); ***C07K 16/2875*** (2013.01); ***C12N 5/0637*** (2013.01); ***C12N 5/0638*** (2013.01); *A61K 45/06* (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/21* (2013.01); *C07K 2317/76* (2013.01); *C07K 2317/94* (2013.01); *C07K 2319/30* (2013.01); *C07K 2319/32* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to combinations comprising anti-human x OX40L antibodies, new biomarkers of autoimmune or alloimmune deseases, and their use in various therapeutic methods.

4 Claims, 70 Drawing Sheets

Specification includes a Sequence Listing.

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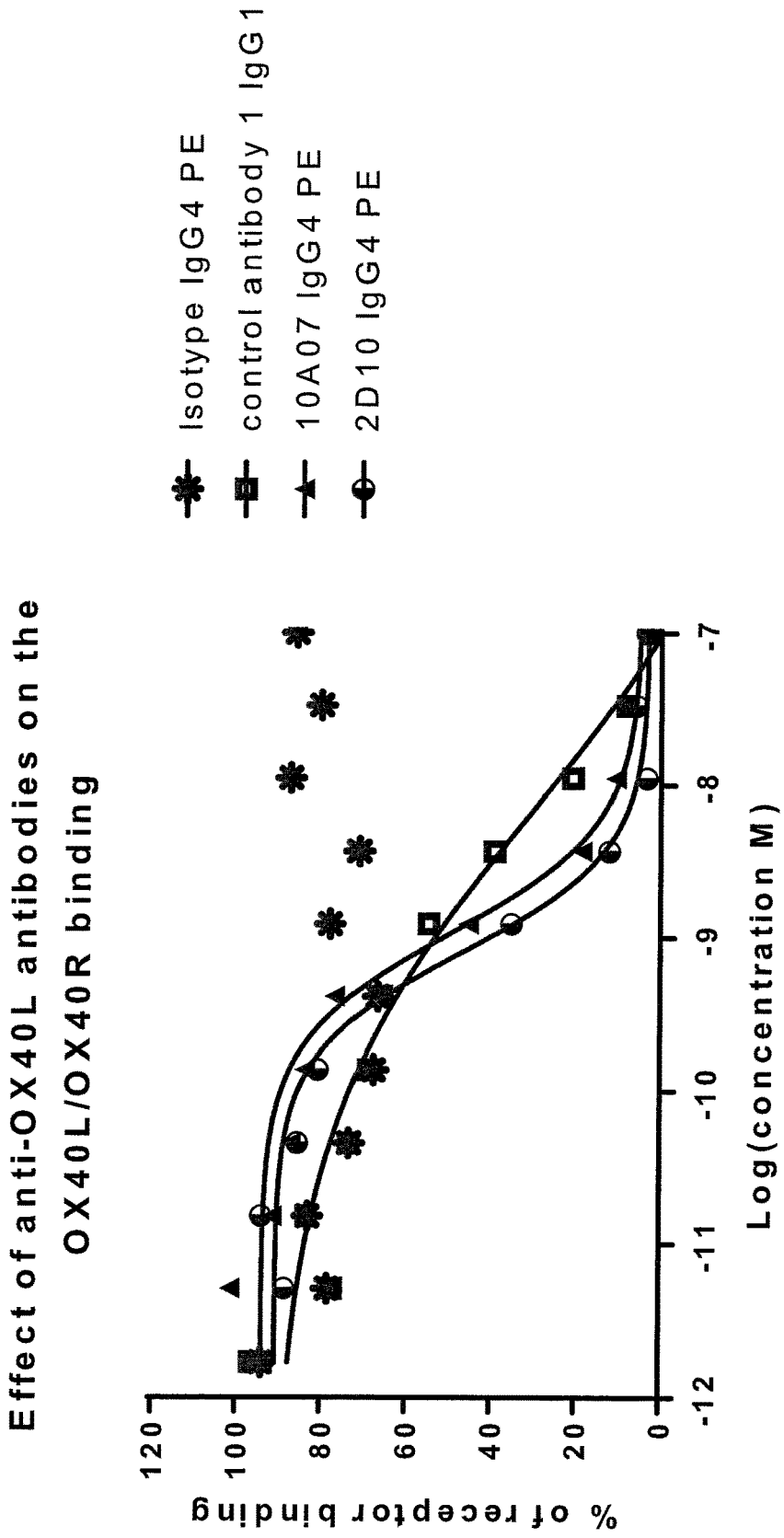
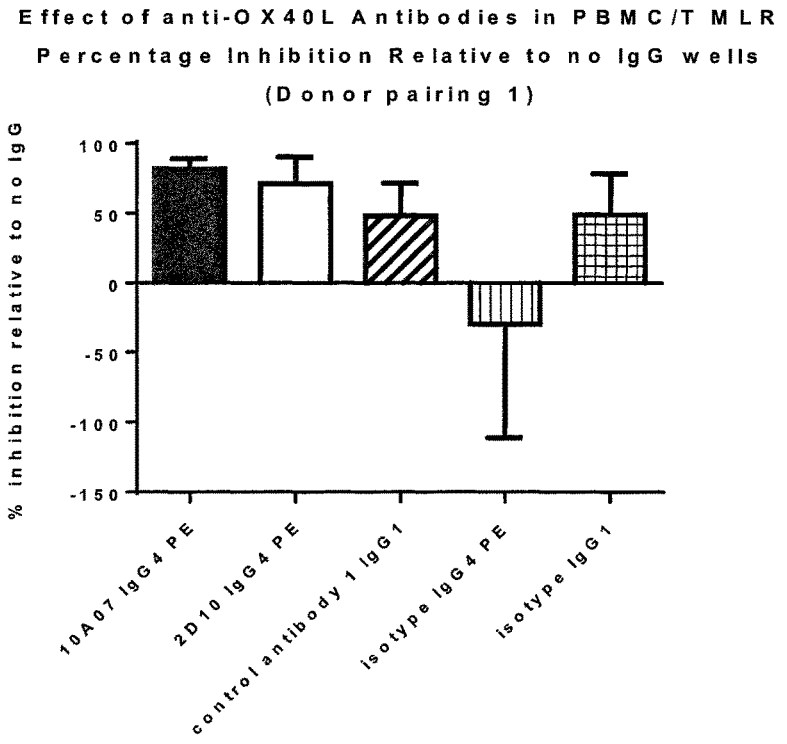

Effect of anti-OX40L antibodies on the OX40L/OX40R binding
Isotype IgG4 PE
control antibody 1 IgG1
10A07 IgG4 PE
2D10 IgG4 PE
% of receptor binding
120
100
80
60
40
20
0
-12
-11
-10
-9
-8
-7
Log(concentration M)

Figure 1

Figure 2


Effect of anti-OX40L Antibodies in PBMC/T MLR
Percentage Inhibition Relative to no IgG wells
(Donor pairing 1)
% inhibition relative to no IgG
100
50
0
-50
-100
-150
10A07 IgG4 PE
2D10 IgG4 PE
control antibody 1 IgG1
isotype IgG4 PE
isotype IgG1

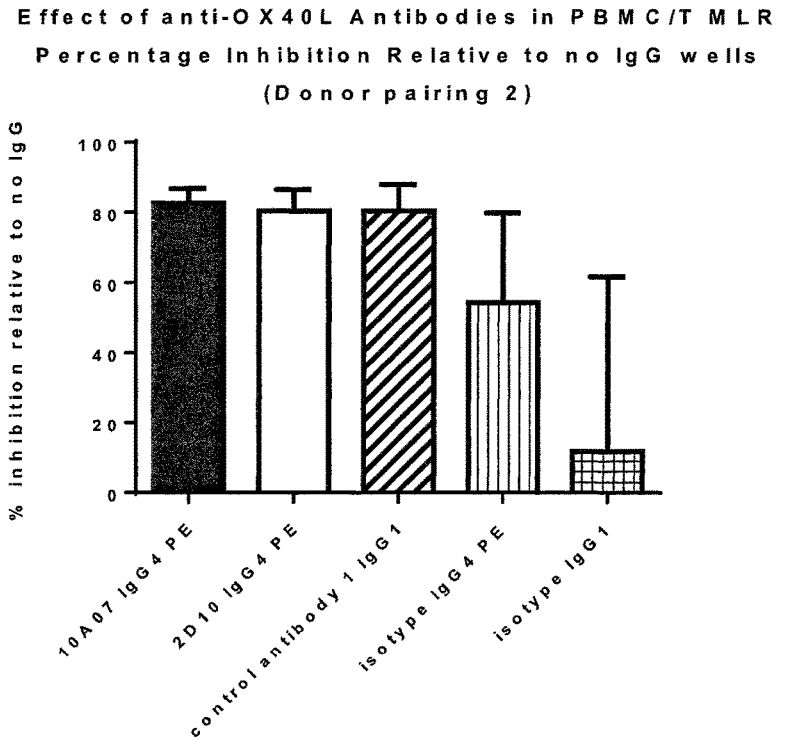
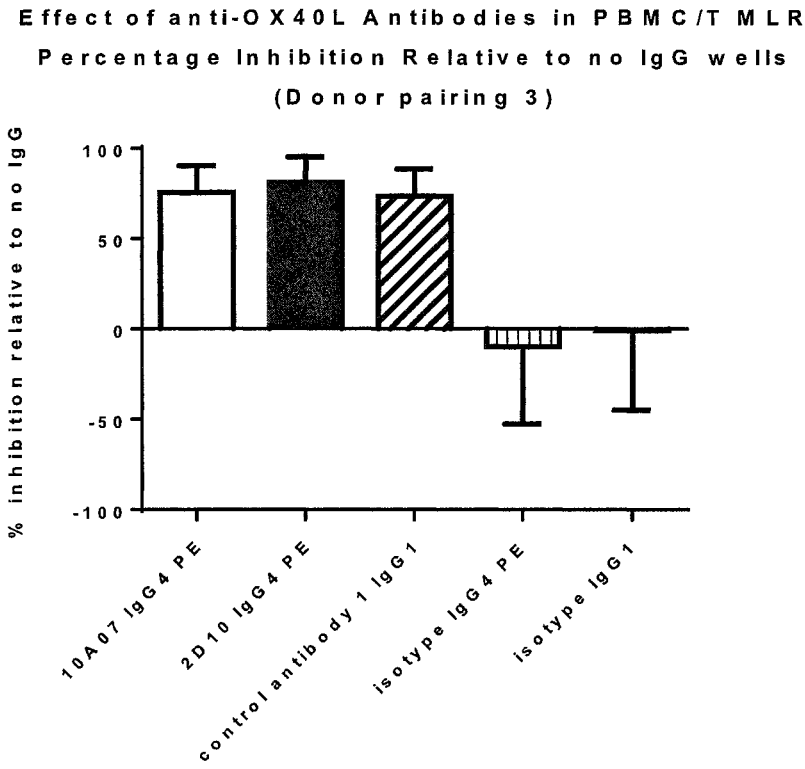

Effect of anti-OX40L Antibodies in PBMC/T MLR
Percentage Inhibition Relative to no IgG wells
(Donor pairing 2)
% inhibition relative to no IgG
100
80
60
40
20
0
10A07 IgG4 PE
2D10 IgG4 PE
control antibody 1 IgG1
isotype IgG4 PE
isotype IgG1

Figure 2 continued



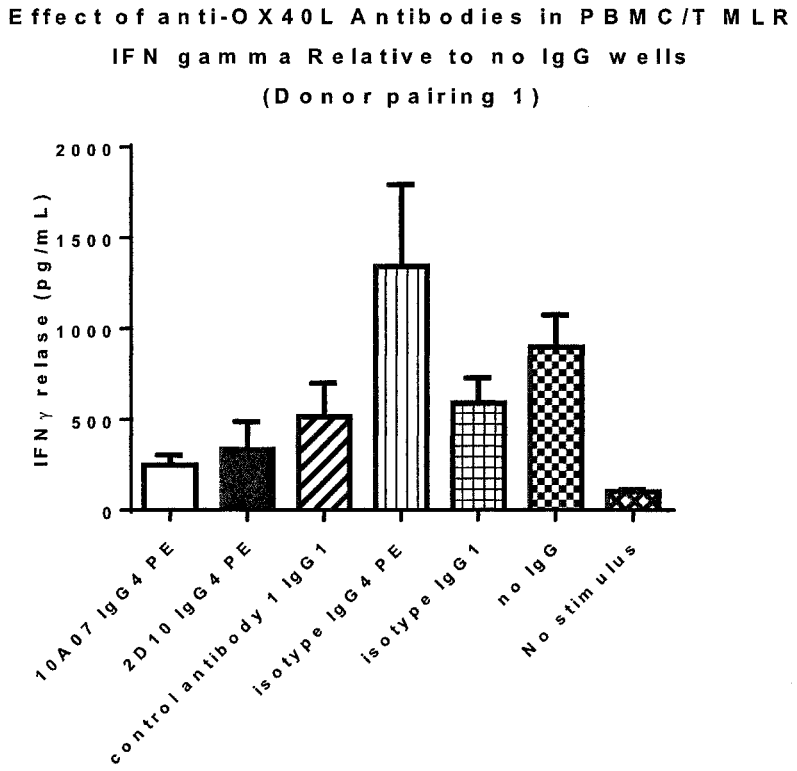
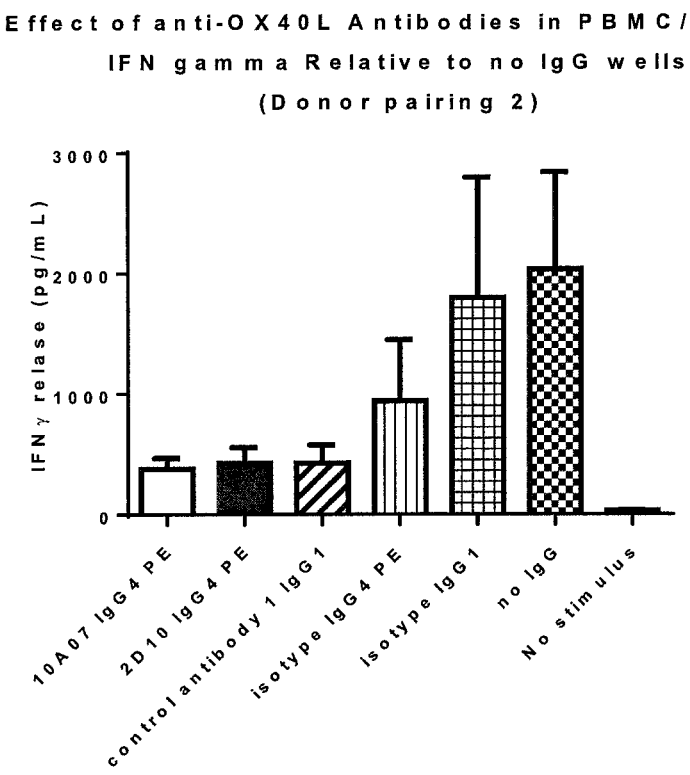
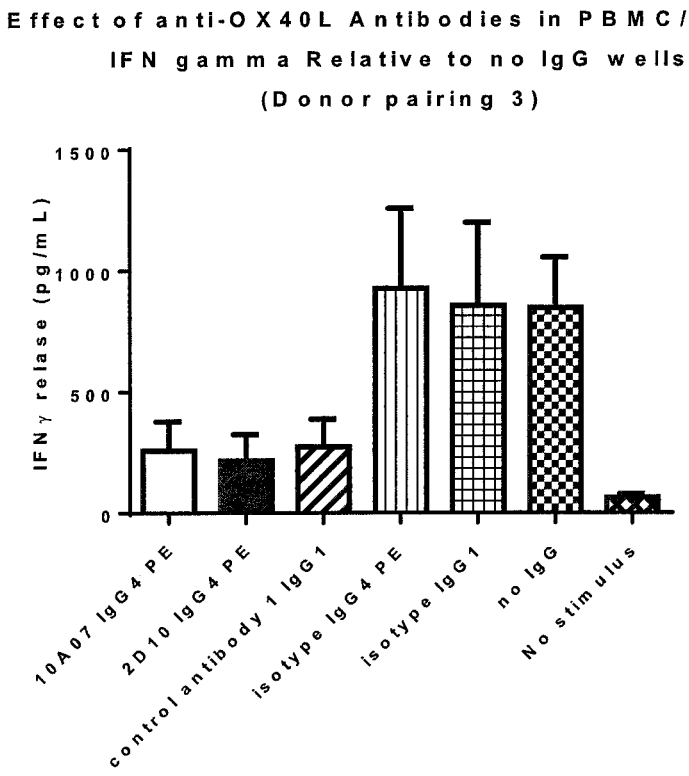


Figure 2 continued





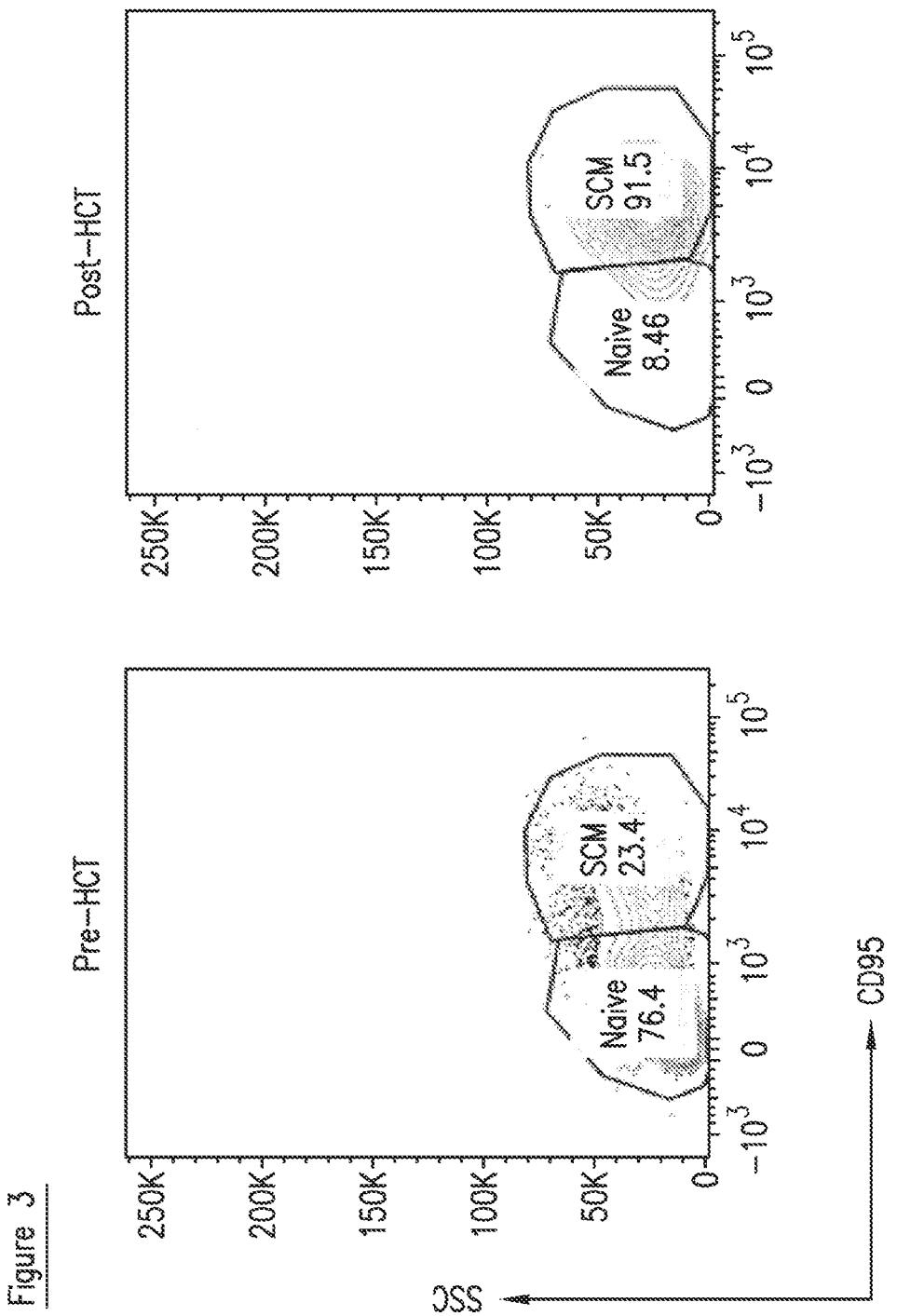
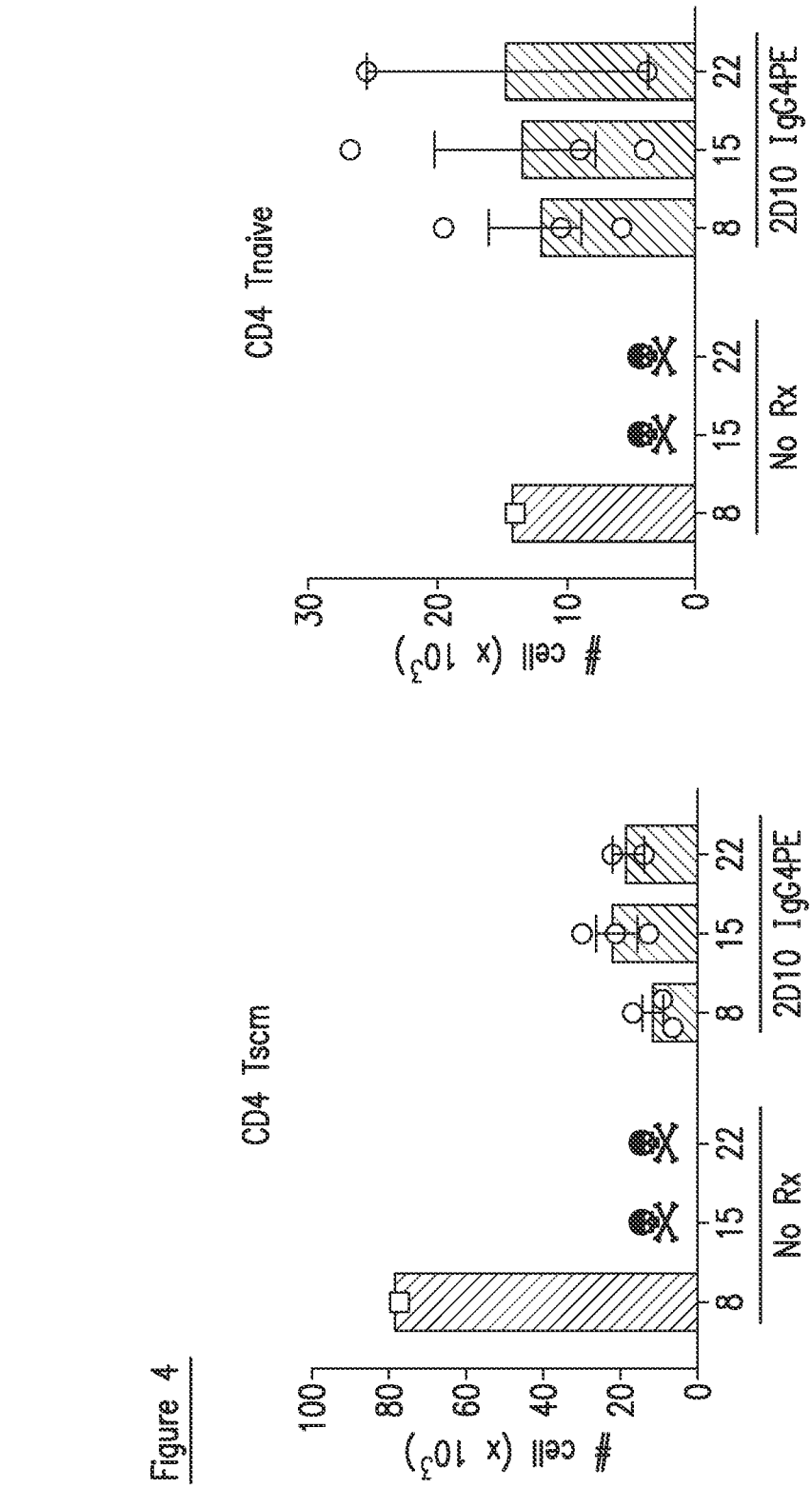

Pre-HCT
Post-HCT
SSC
CD95
250K
200K
150K
100K
50K
0
-10^3
0
10^3
10^4
10^5
Naive
76.4
SCM
23.4
Naive
8.46
SCM
91.5

Figure 3

Figure 4


CD4 Tscm
cell (x 10³)
100
80
60
40
20
0
8
15
22
No Rx
2D10 IgG4PE
CD4 Tnaive
cell (x 10³)
30
20
10
0
8
15
22
No Rx
2D10 IgG4PE

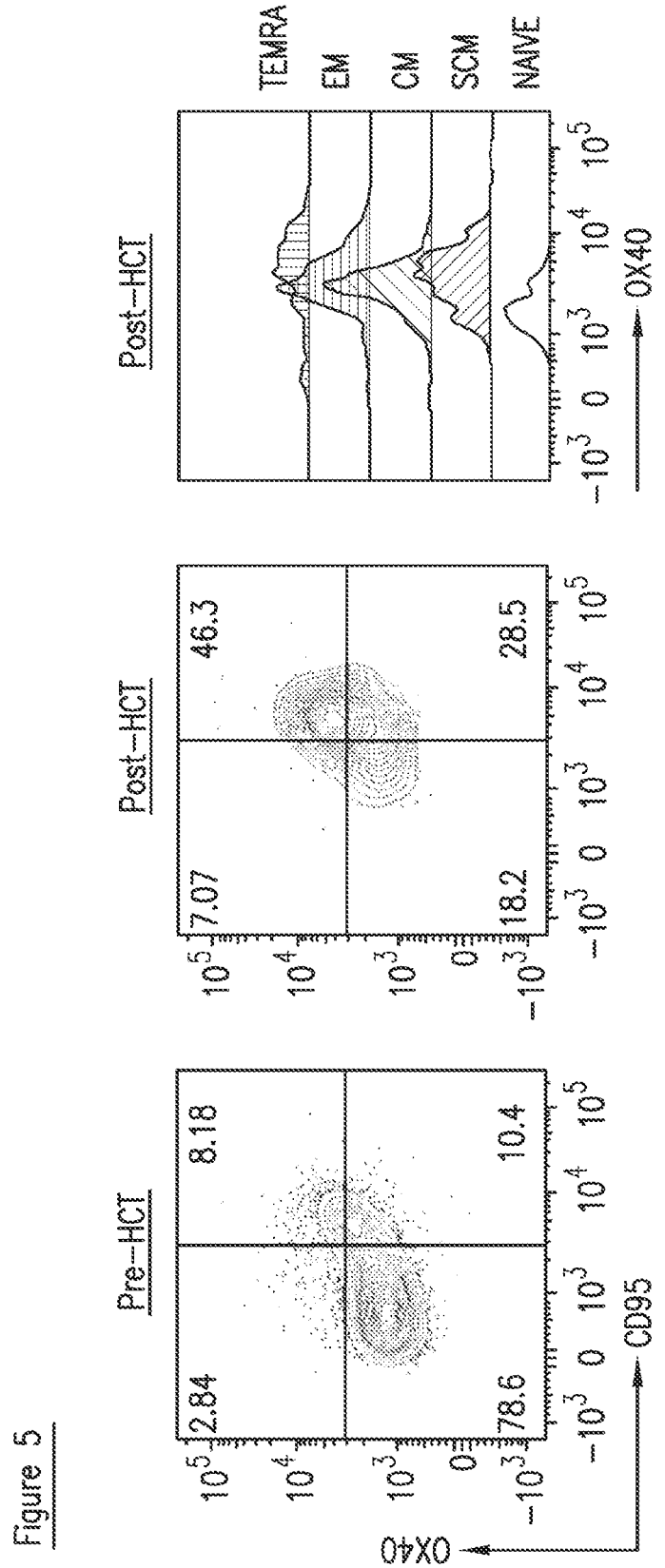

Pre–HCT
Post–HCT
Post–HCT
2.84
8.18
78.6
10.4
7.07
46.3
18.2
28.5
OX40
CD95
TEMRA
EM
CM
SCM
NAIVE
OX40

Figure 5

Figure 6A

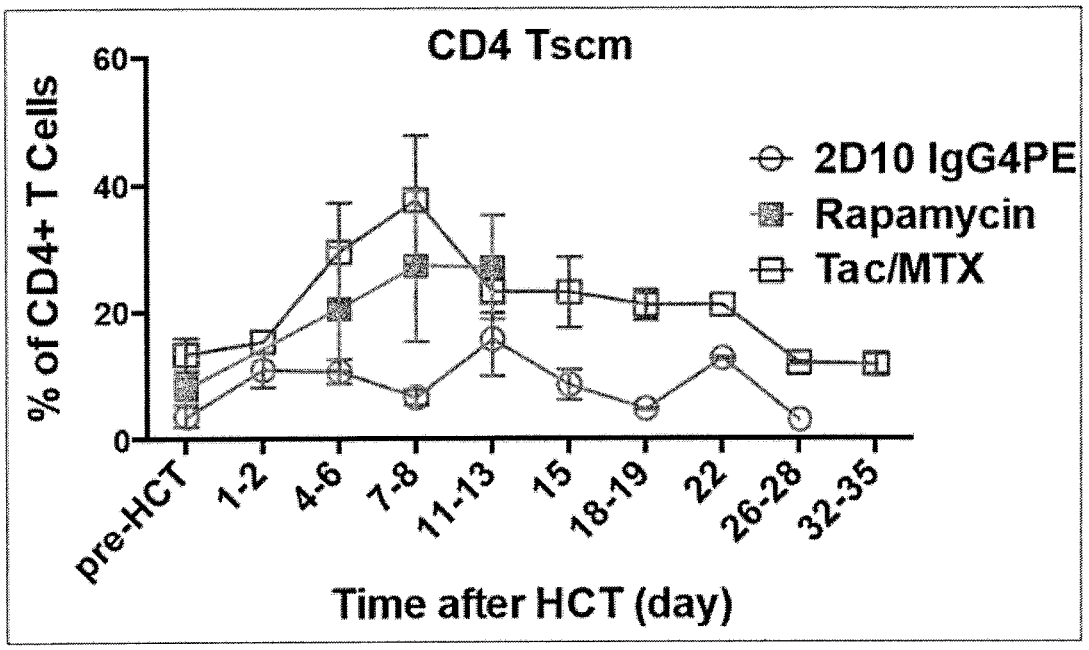


Figure 6B

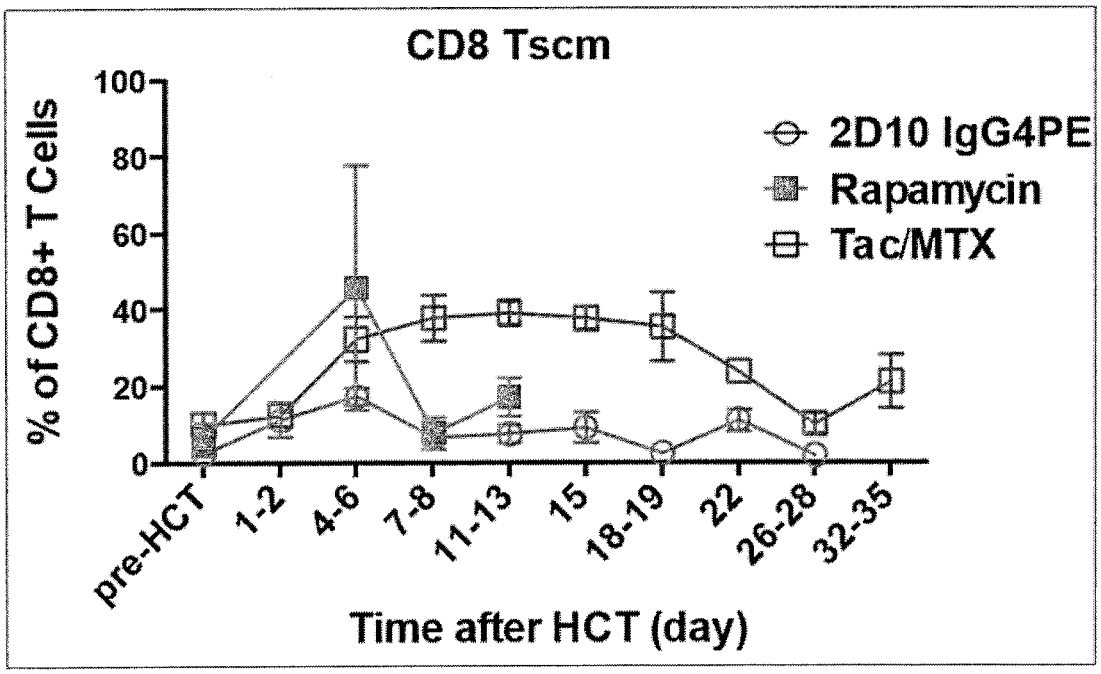


Figure 7A

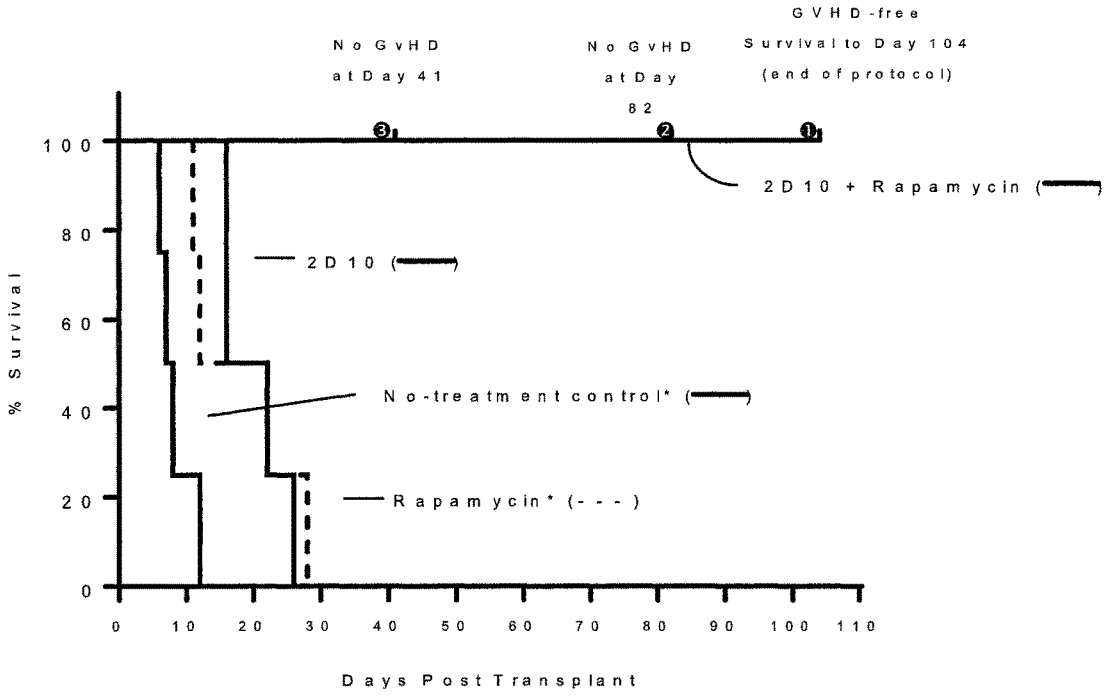


Figure 7B

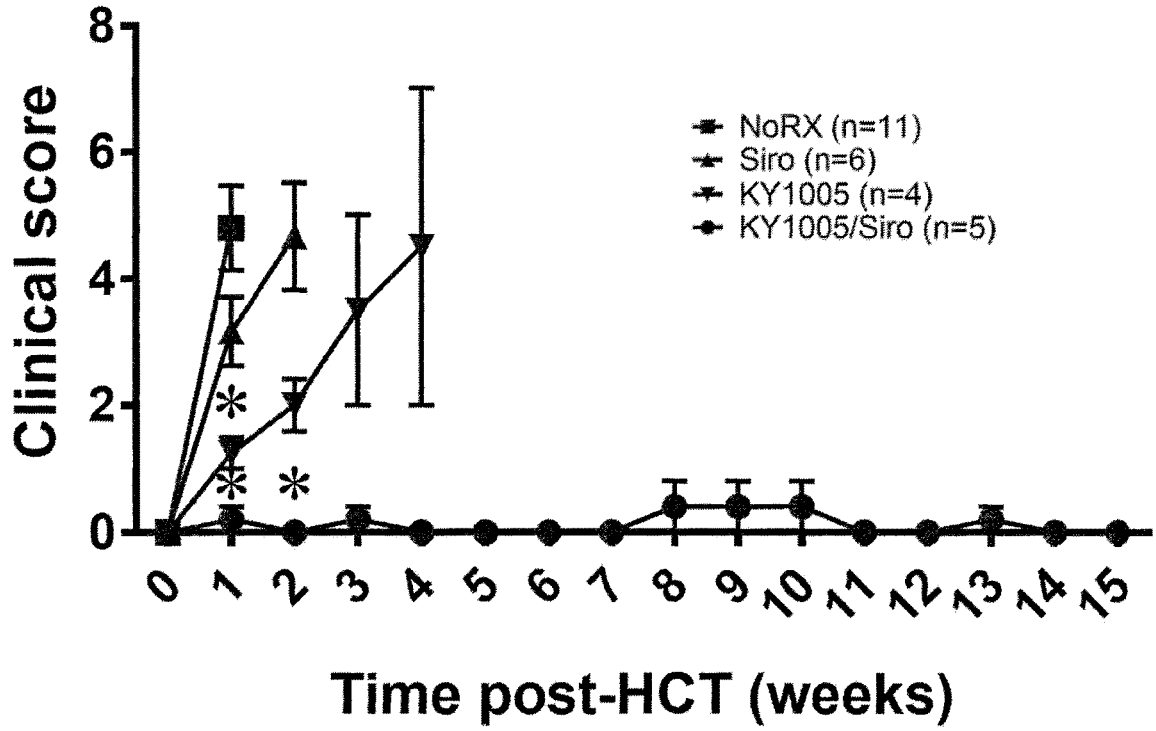


Figure 7C

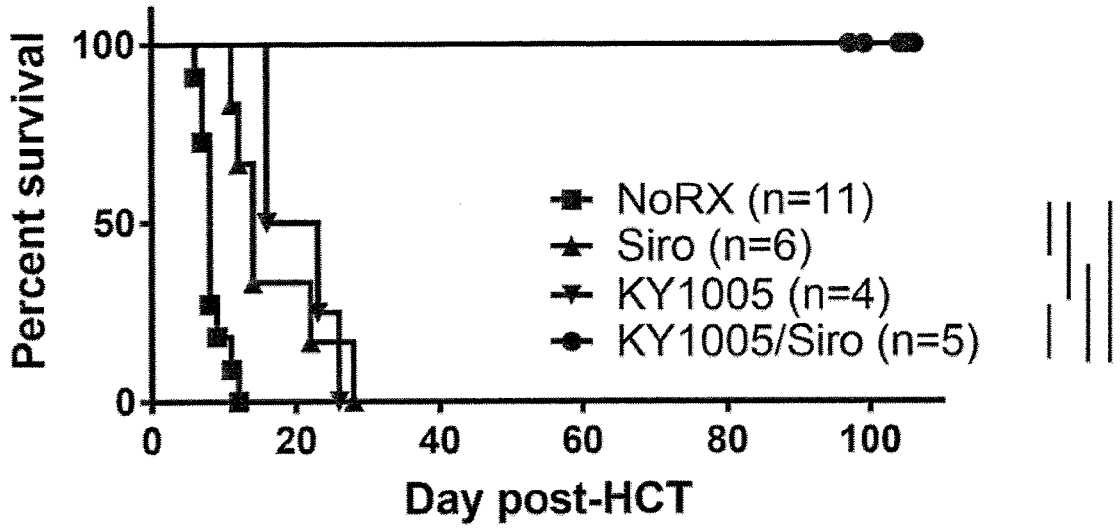
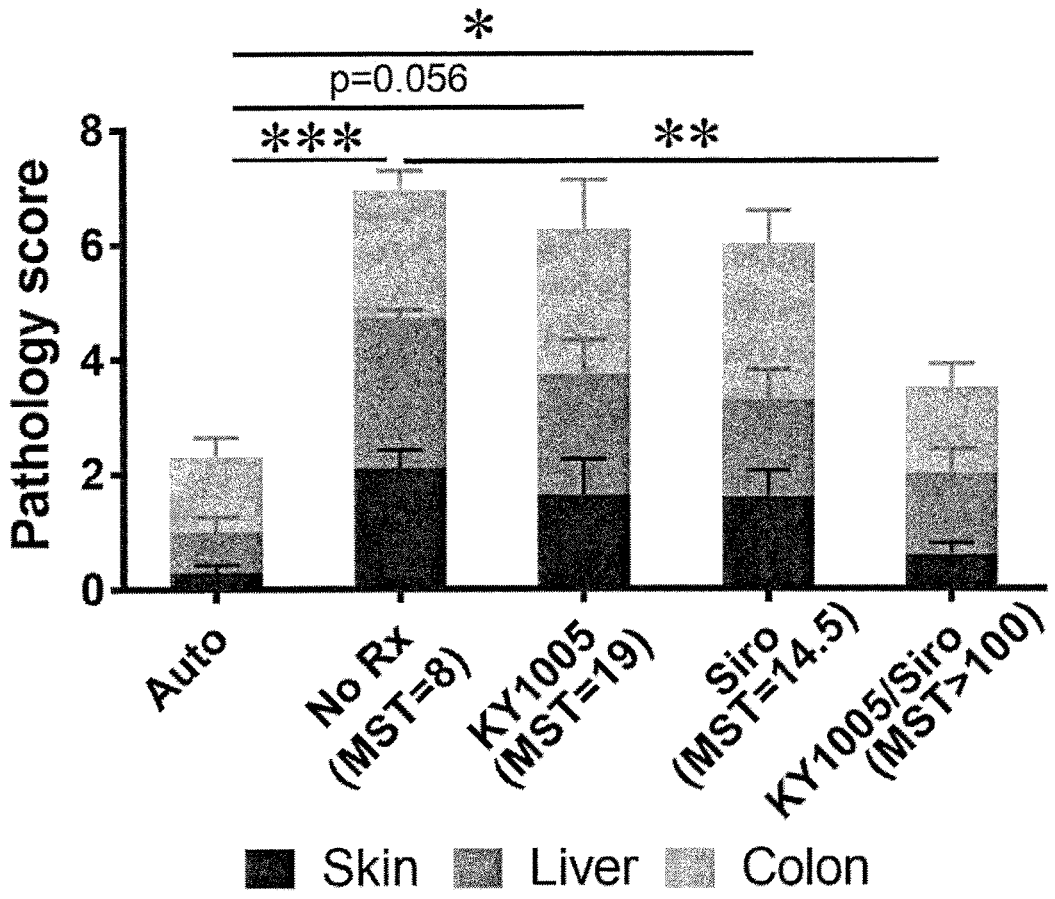


Figure 7D



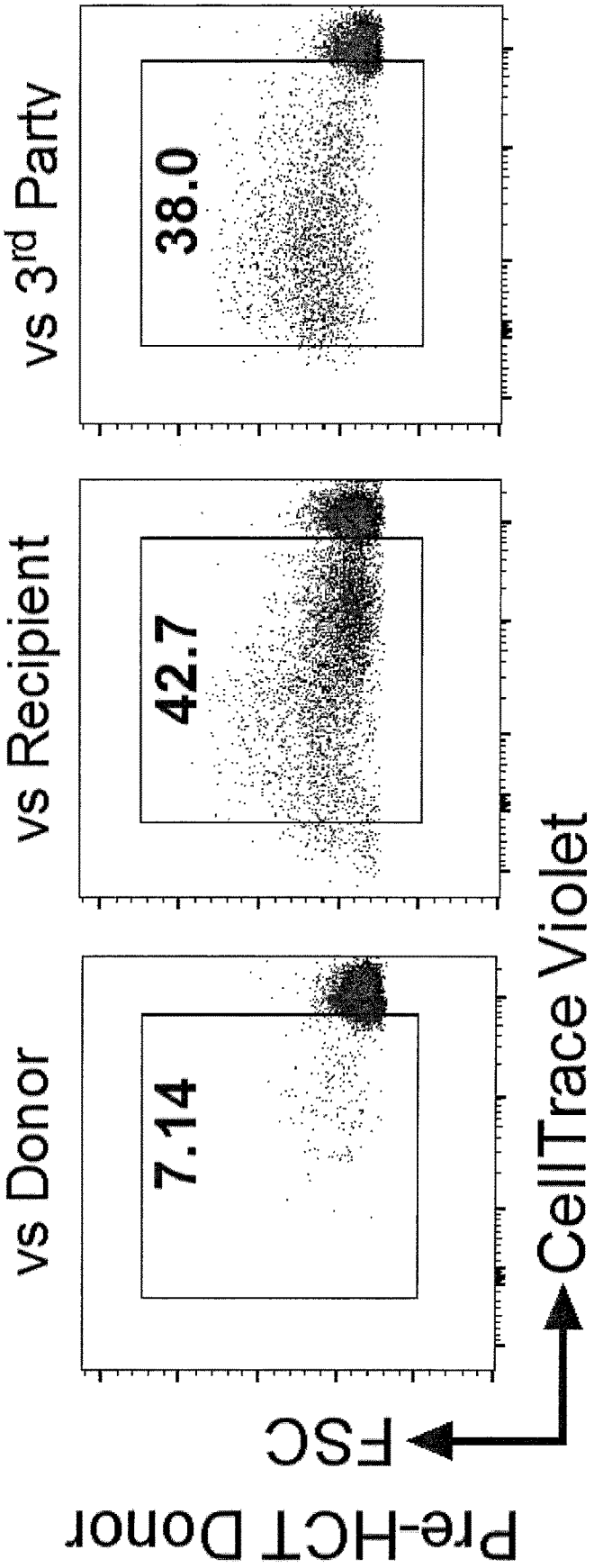

Pre-HCT Donor
FSC
CellTrace Violet
vs Donor
7.14
vs Recipient
42.7
vs 3rd Party
38.0

Figure 7E

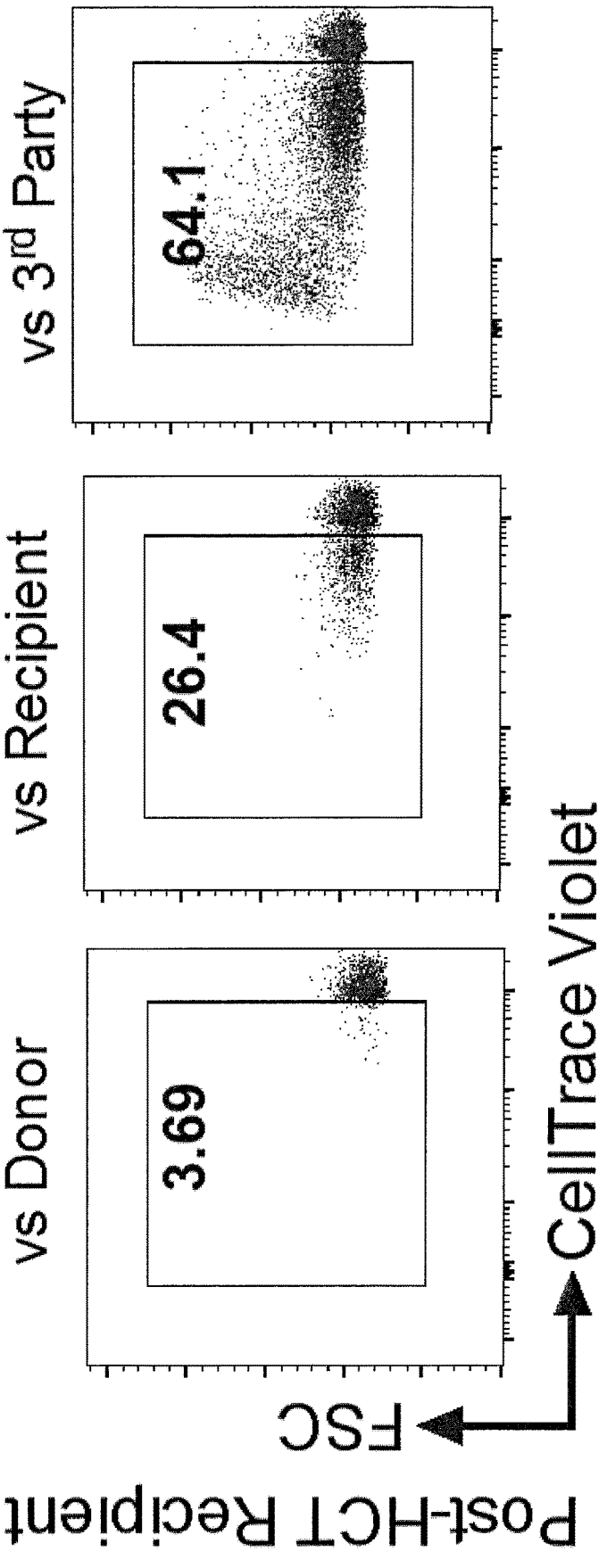
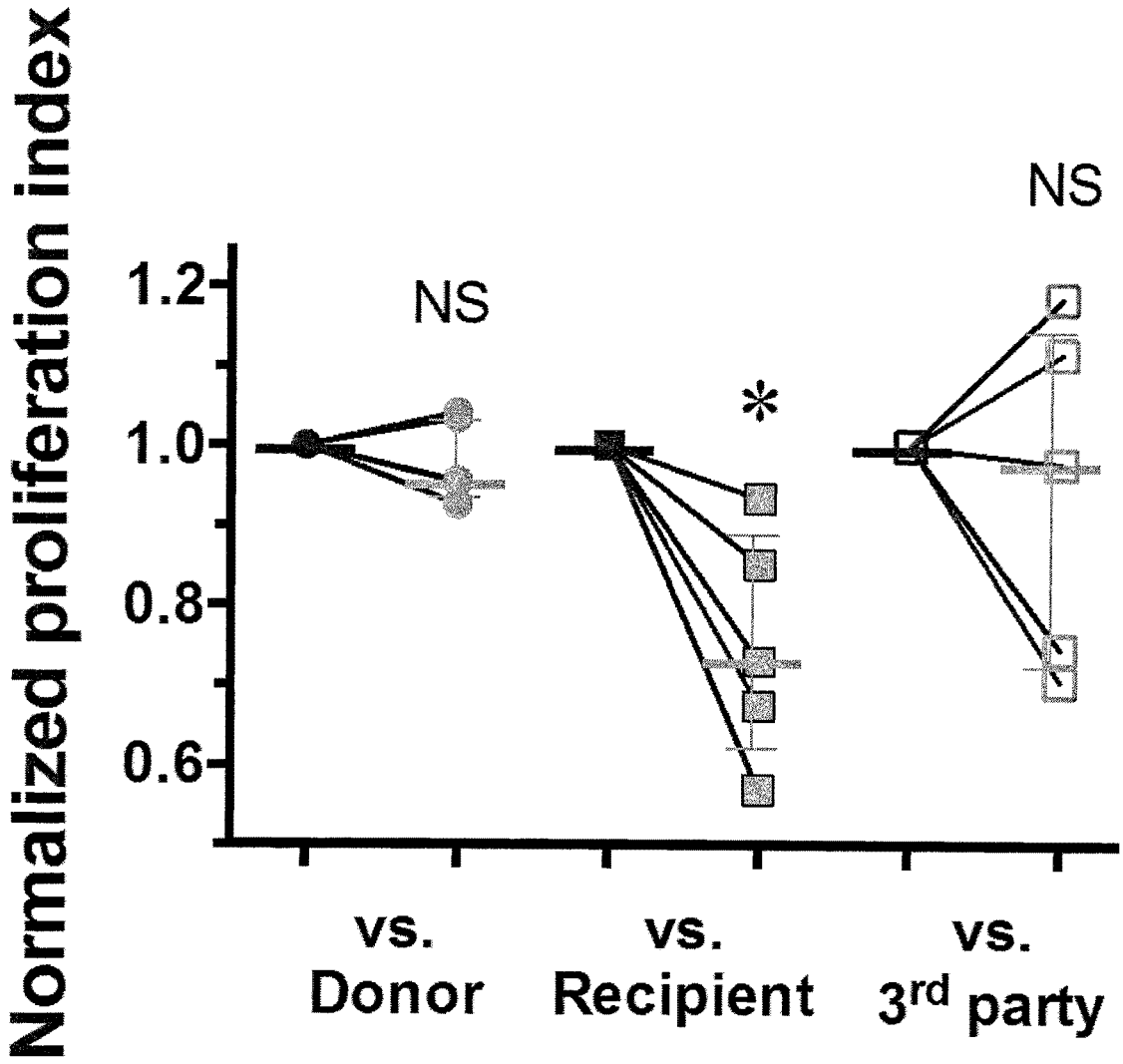

Post-HCT Recipient
FSC
CellTrace Violet
vs Donor
3.69
vs Recipient
26.4
vs 3rd Party
64.1

Figure 7F

Figure 7G


Normalized proliferation index
1.2
1.0
0.8
0.6
NS
*
NS
vs.
Donor
vs.
Recipient
vs.
3rd party

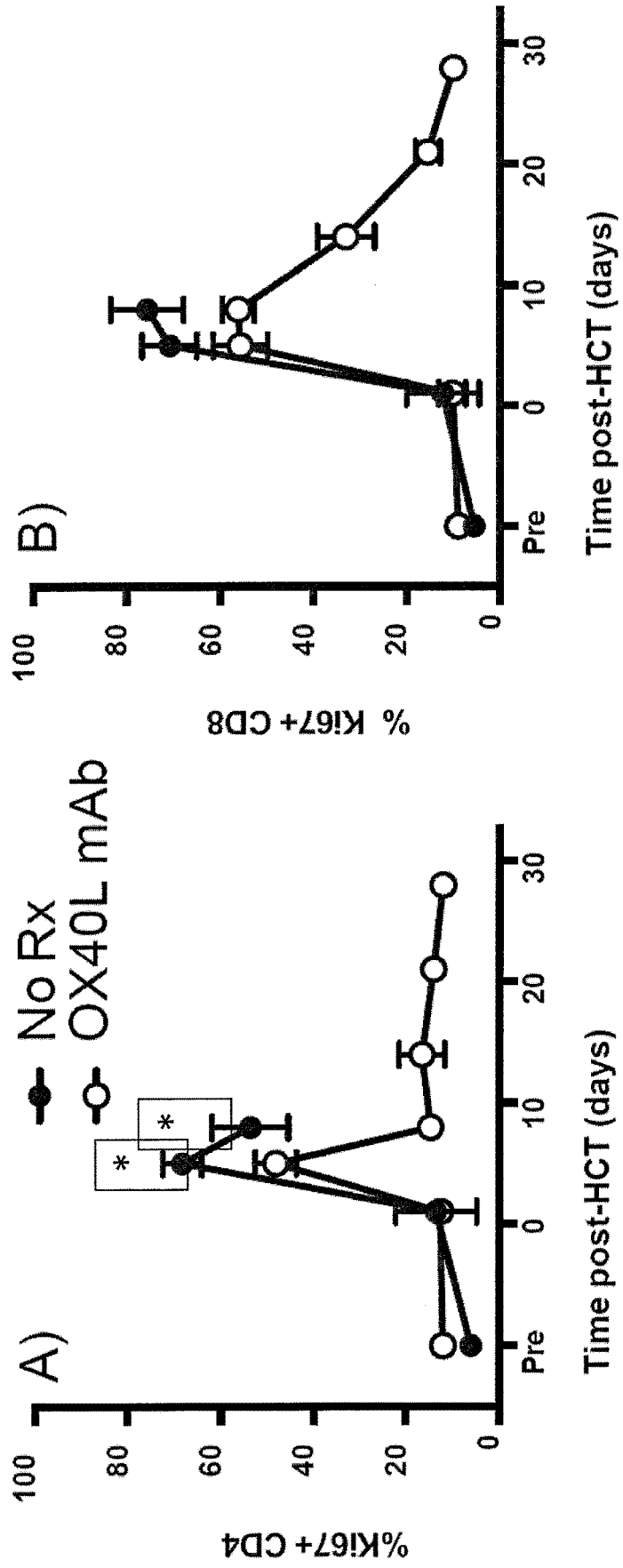
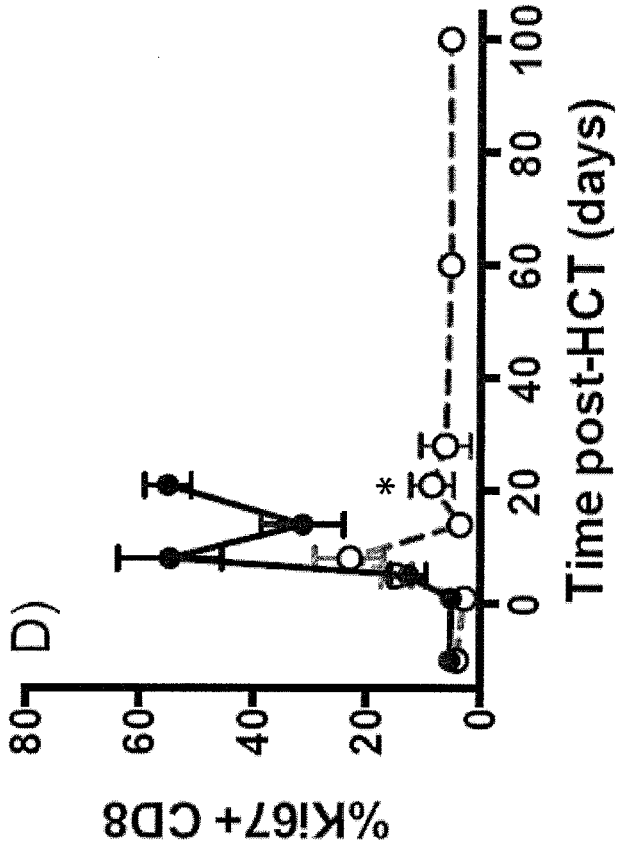

A)
B)
No Rx
OX40L mAb
%KI67+ CD4
% KI67+ CD8
Time post-HCT (days)
Pre
0
10
20
30
0
20
40
60
80
100
*
*

Figure 8



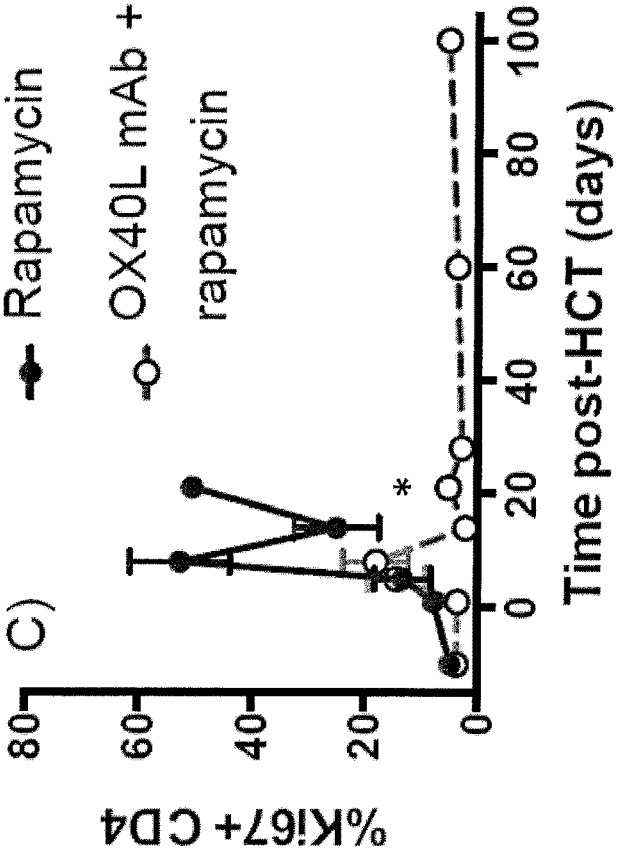


Figure 8 continued

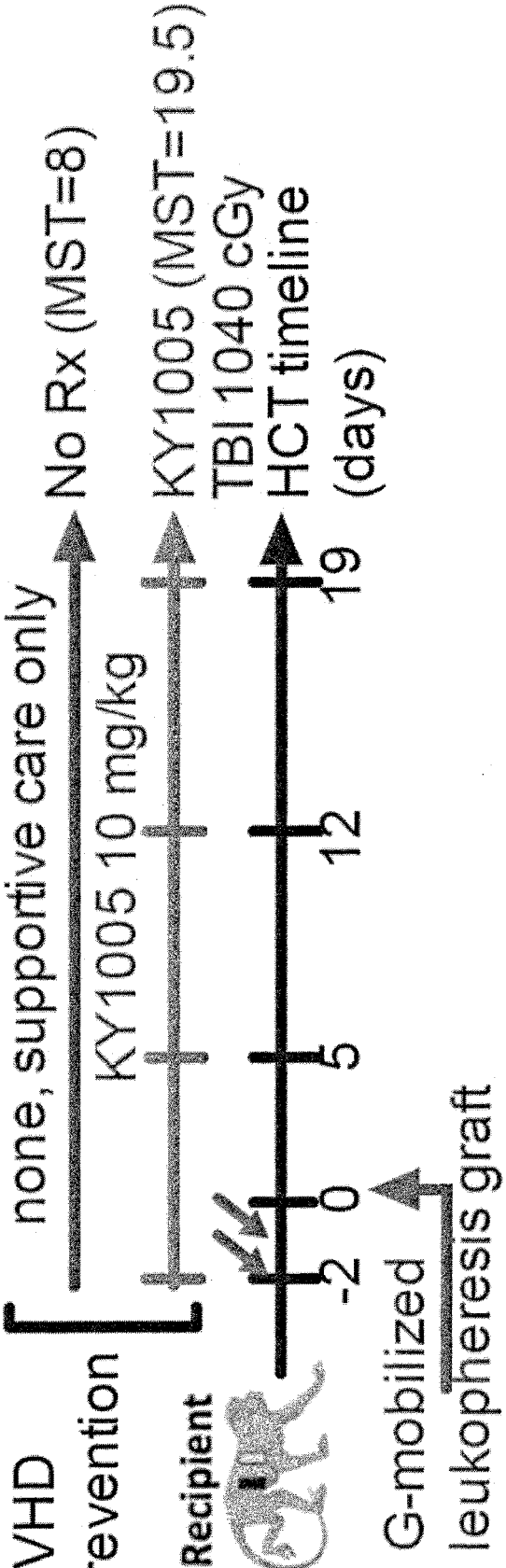

GVHD prevention
none, supportive care only
No Rx (MST=8)
KY1005 10 mg/kg
KY1005 (MST=19.5)
TBI 1040 cGy
HCT timeline
(days)
-2
0
5
12
19
Recipient
G-mobilized leukopheresis graft

Figure 8E

Figure 8F

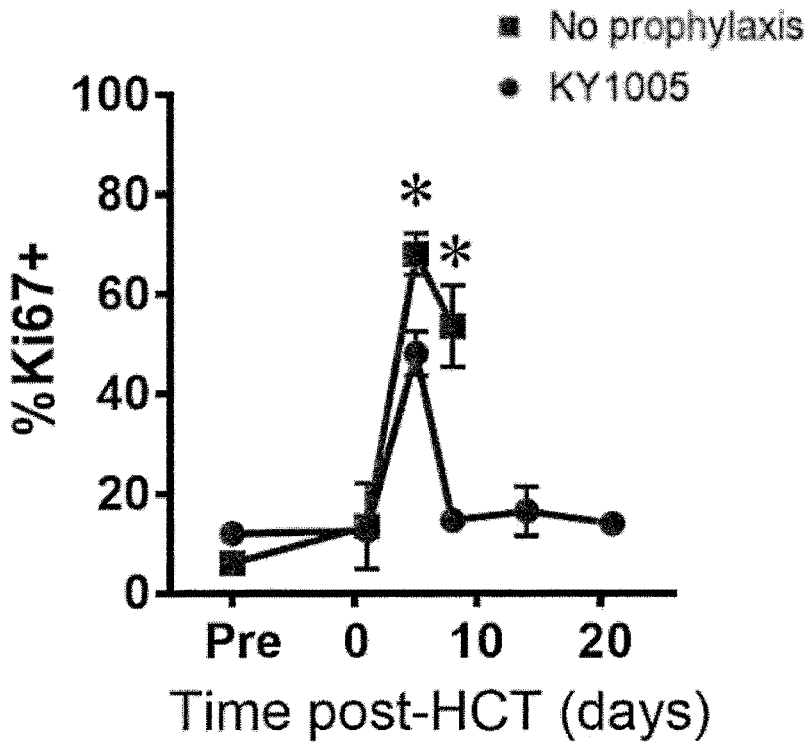


Figure 8G

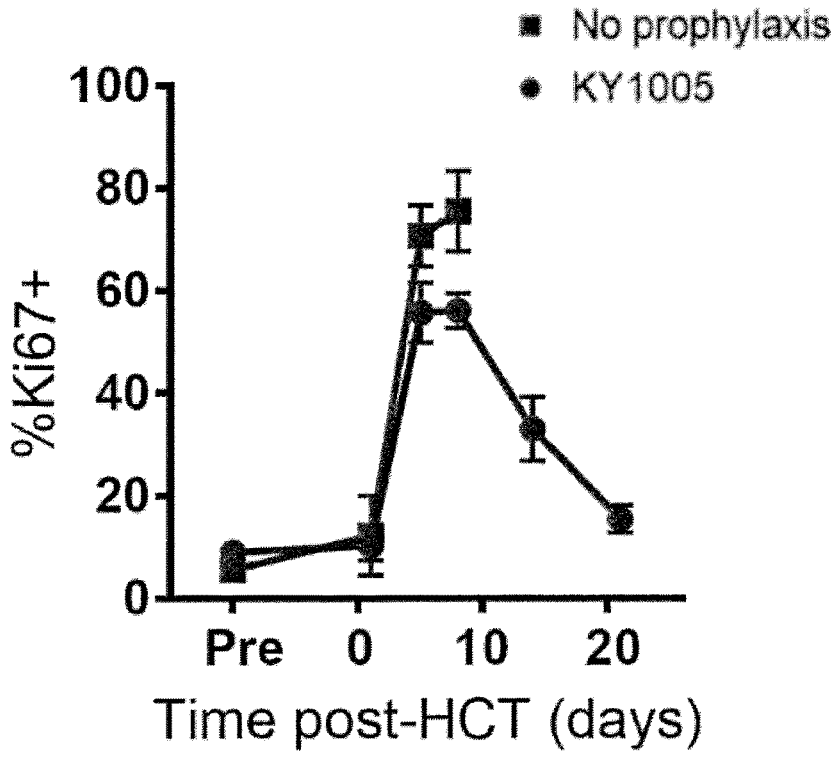


Figure 8H

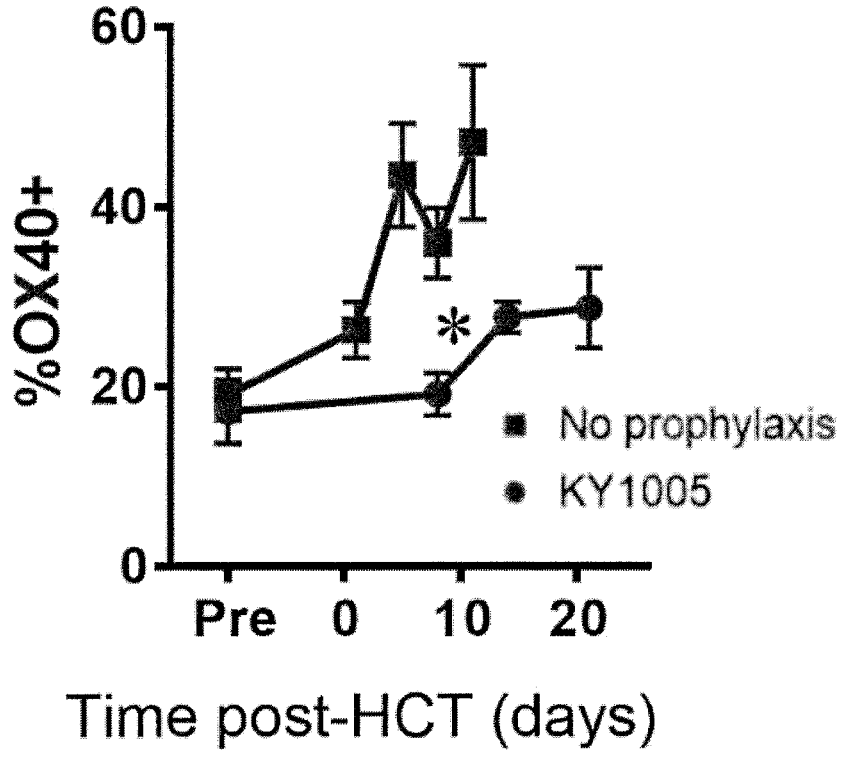


Figure 8I

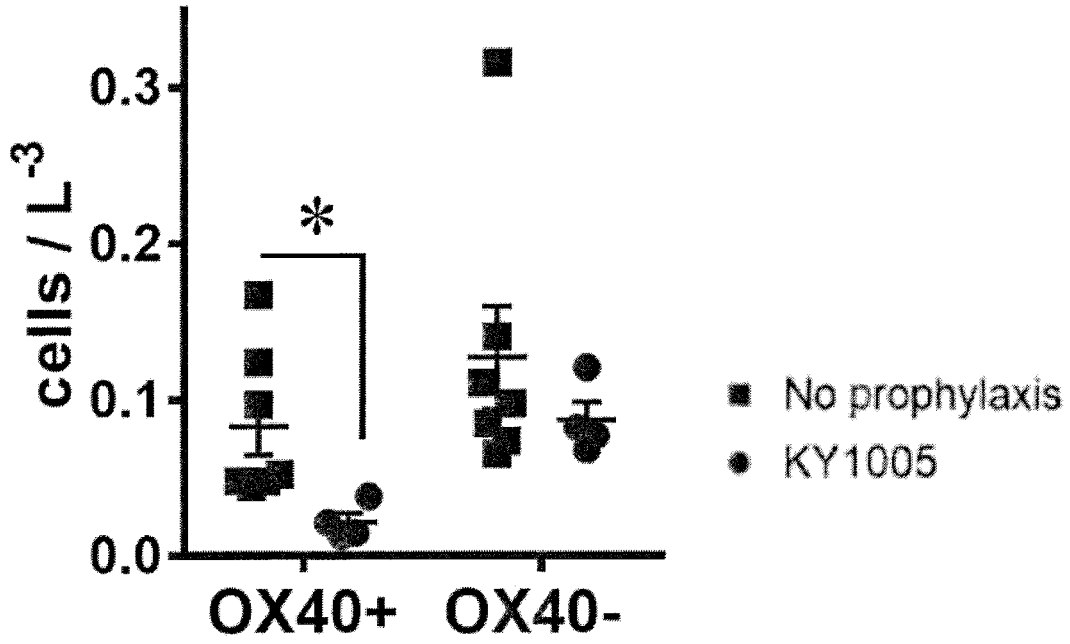


Figure 8J

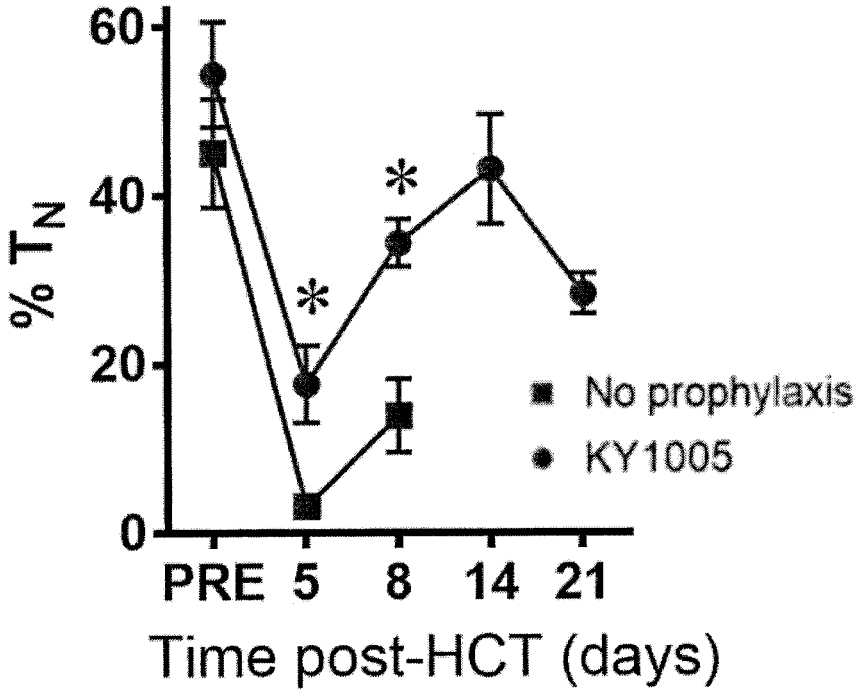


Figure 8K

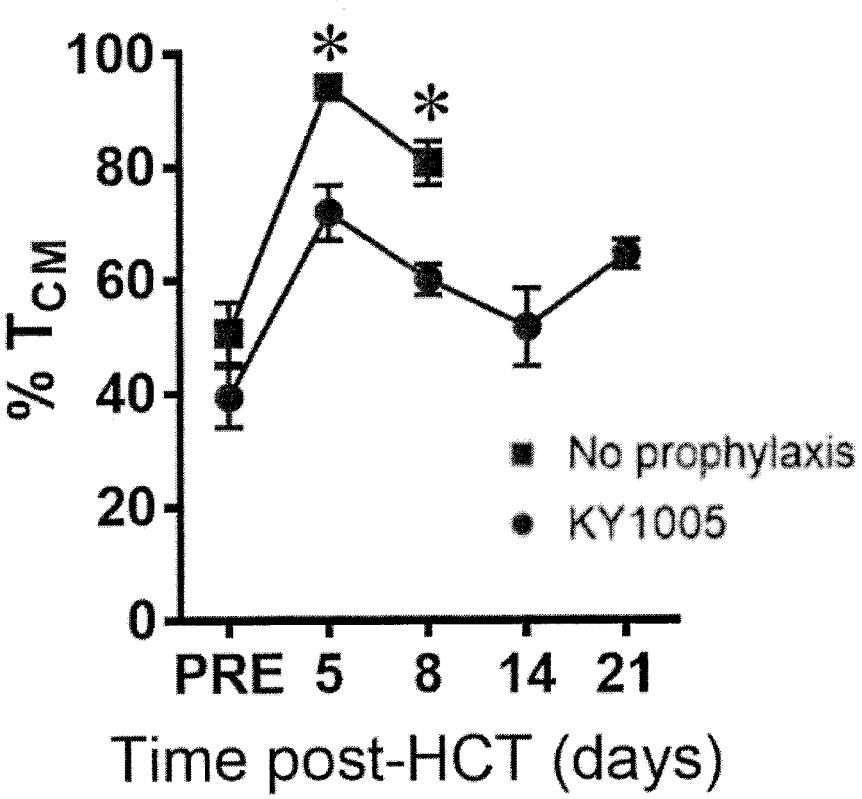


Figure 8L

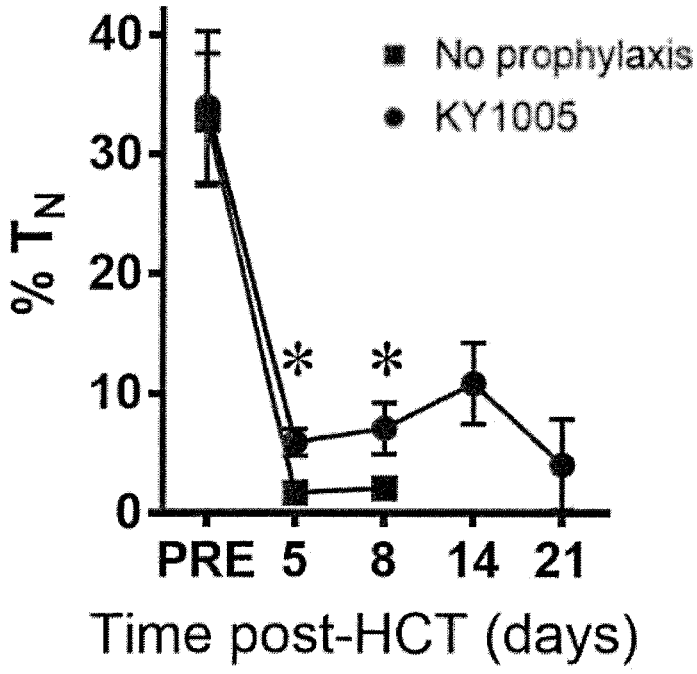


Figure 8M

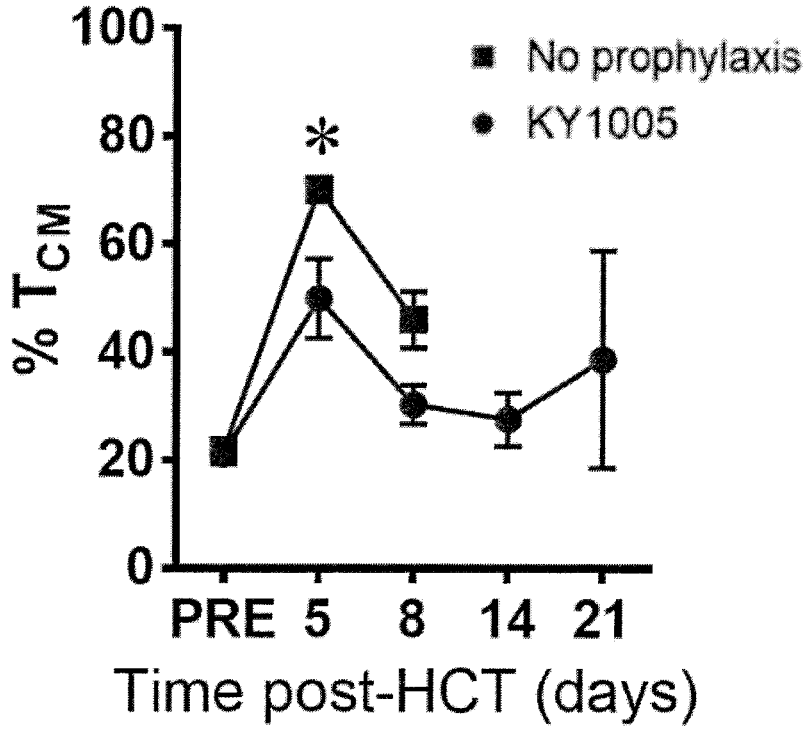


Figure 8N

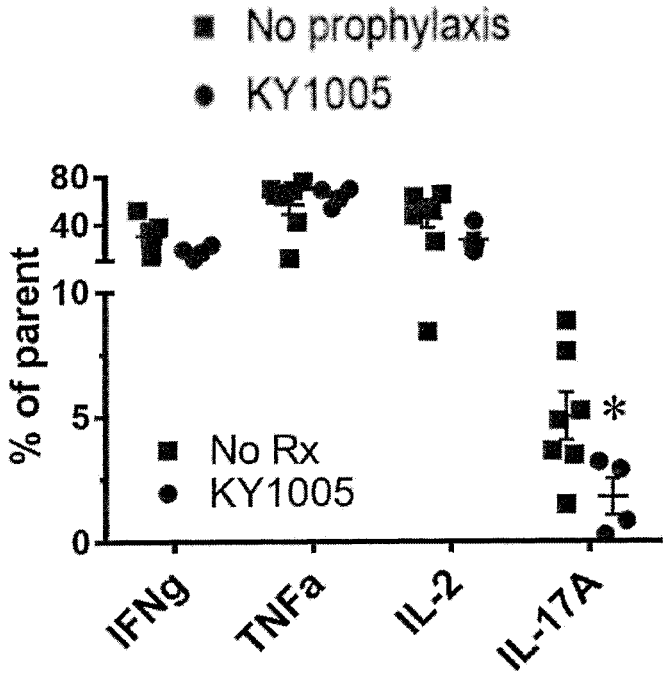


Figure 8O

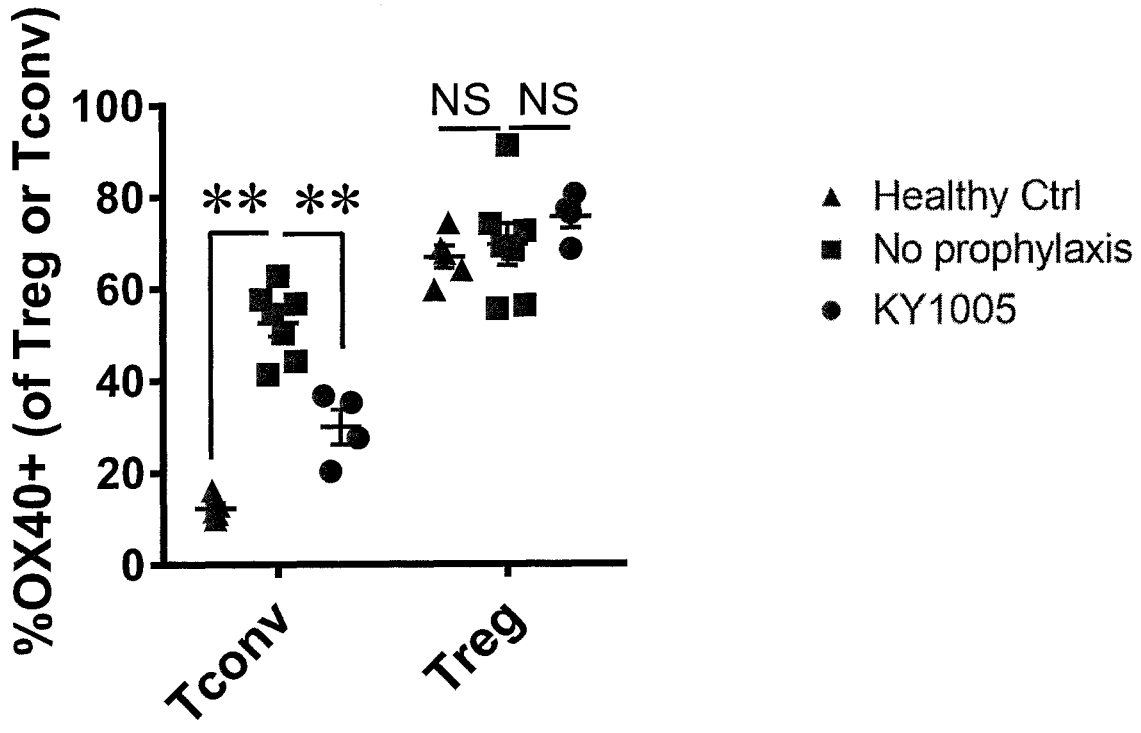


Figure 8O-1

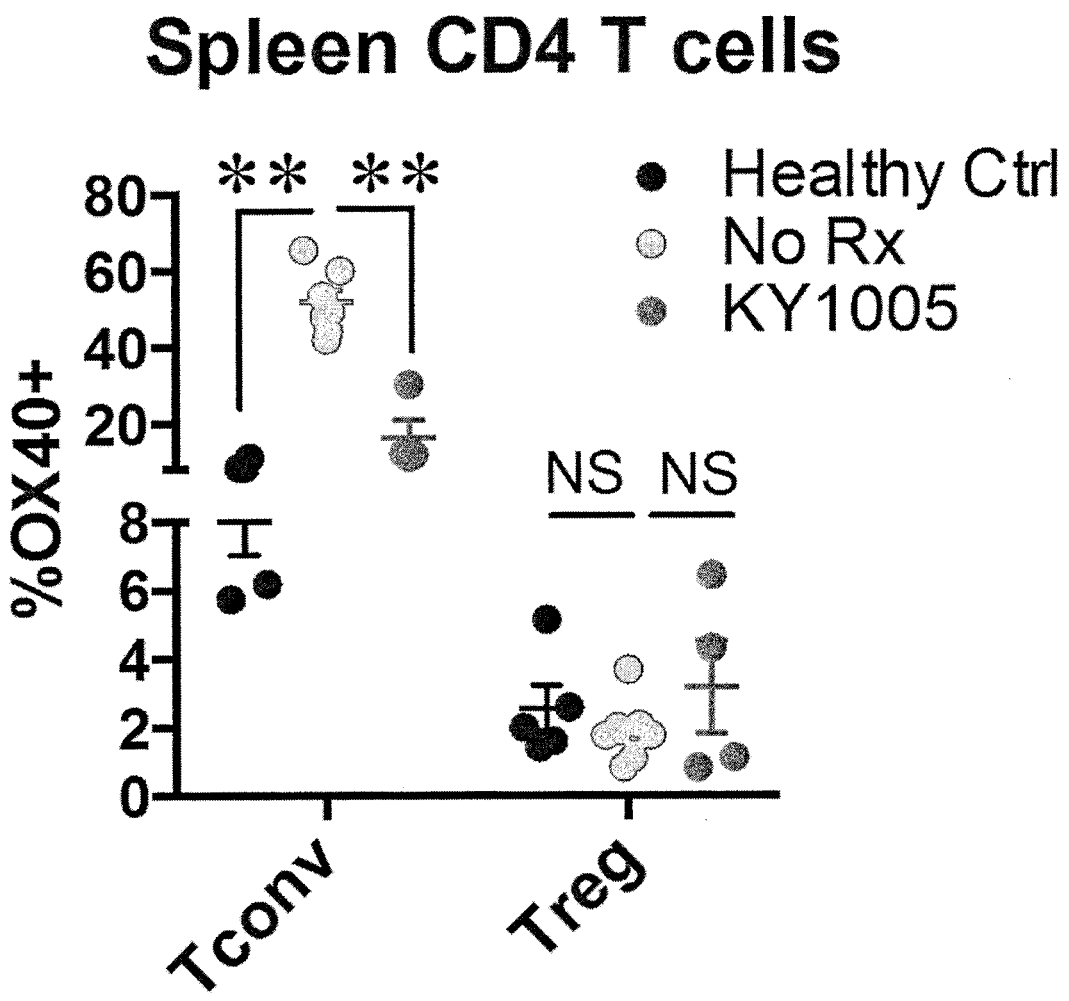
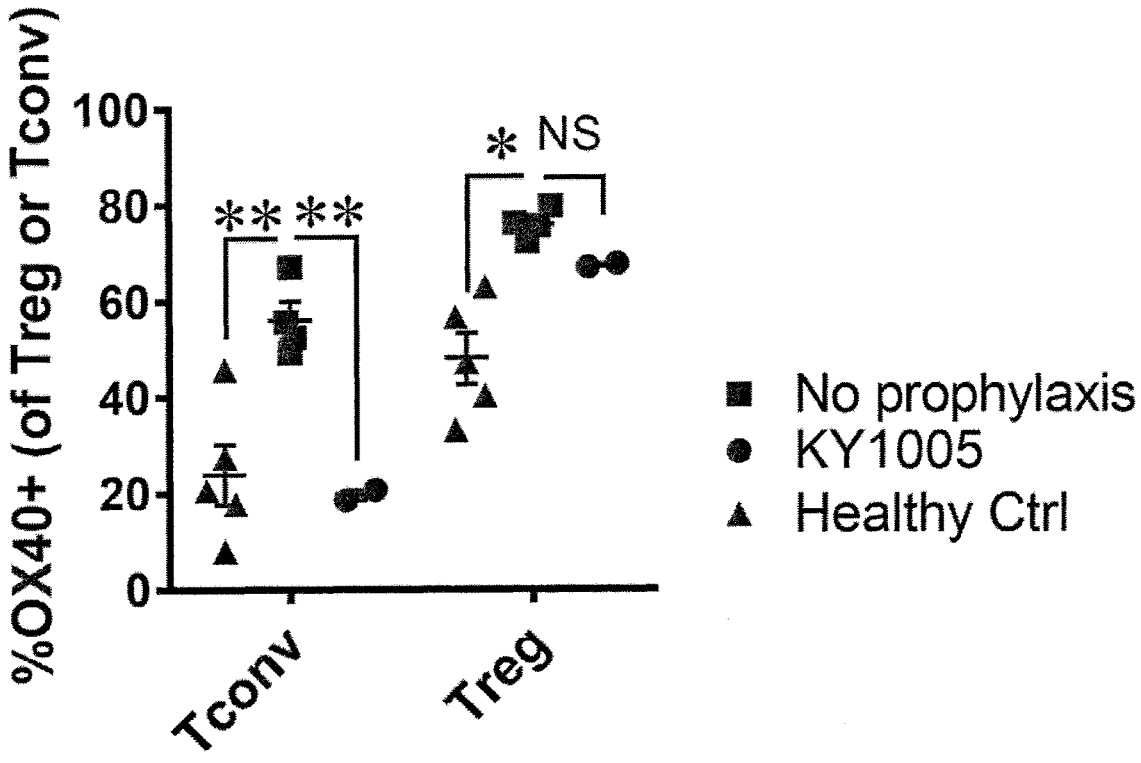

Spleen CD4 T cells
Healthy Ctrl
No Rx
KY1005
%OX40+
80
60
40
20
8
6
4
2
0
** **
NS NS
Tconv
Treg

Figure 8O-2


%OX40+ (of Treg or Tconv)
100
80
60
40
20
0
**
**
* NS
Tconv
Treg
No prophylaxis
KY1005
Healthy Ctrl

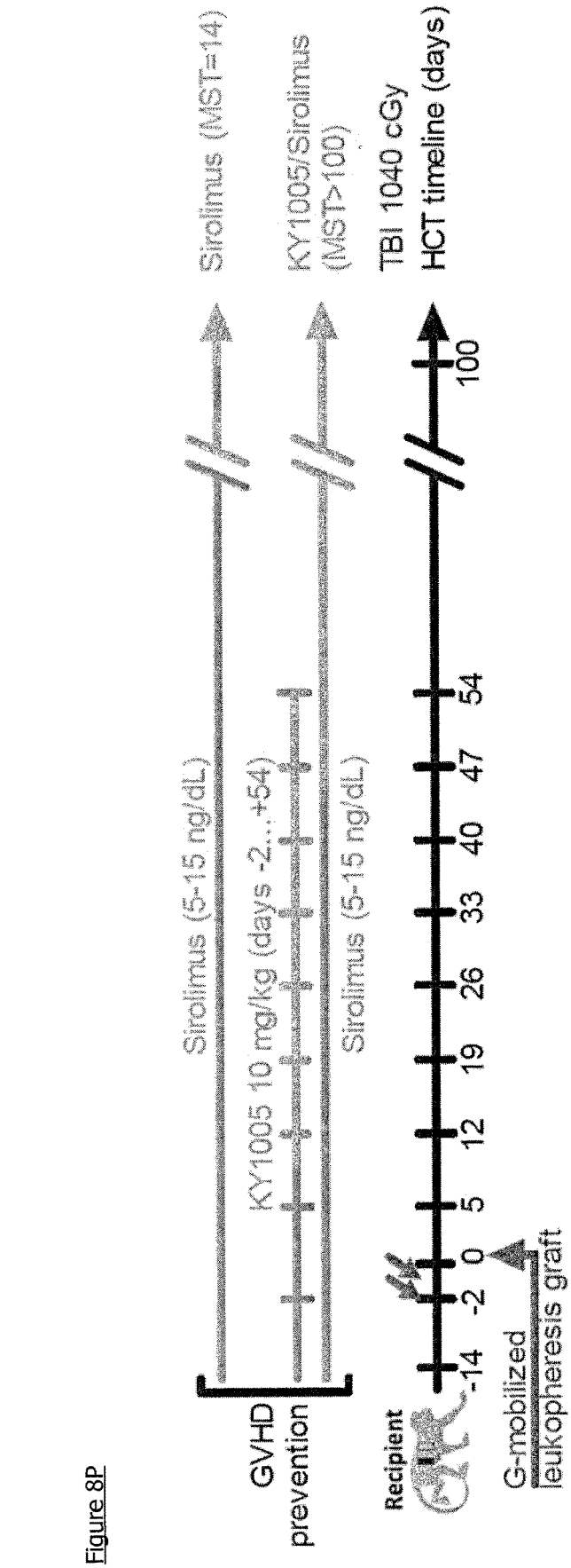

Sirolimus (MST=14)
KY1005/Sirolimus (MST>100)
TBI 1040 cGy
HCT timeline (days)
Sirolimus (5-15 ng/dL)
KY1005 10 mg/kg (days -2...+54)
Sirolimus (5-15 ng/dL)
GVHD prevention
Recipient
G-mobilized leukopheresis graft
-14
-2
0
5
12
19
26
33
40
47
54
100

Figure 8P

Figure 8Q

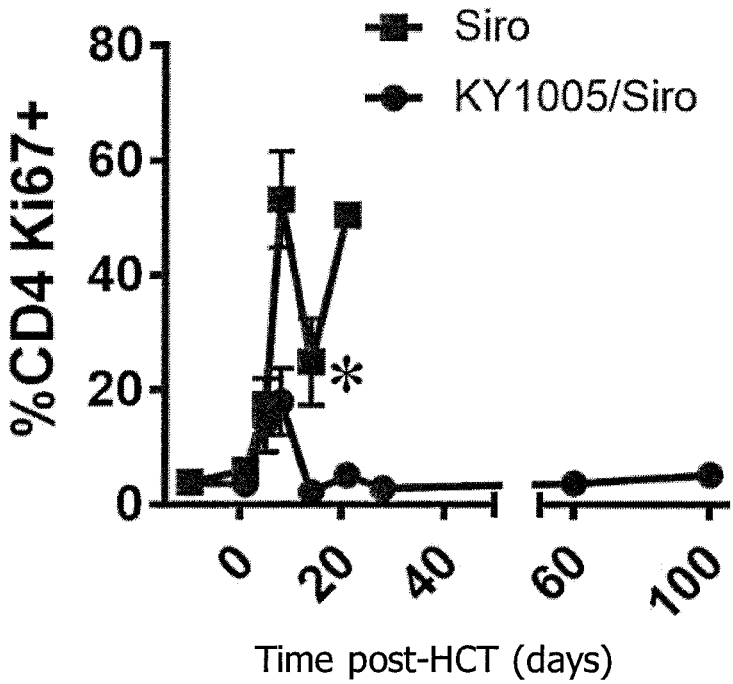


Figure 8R

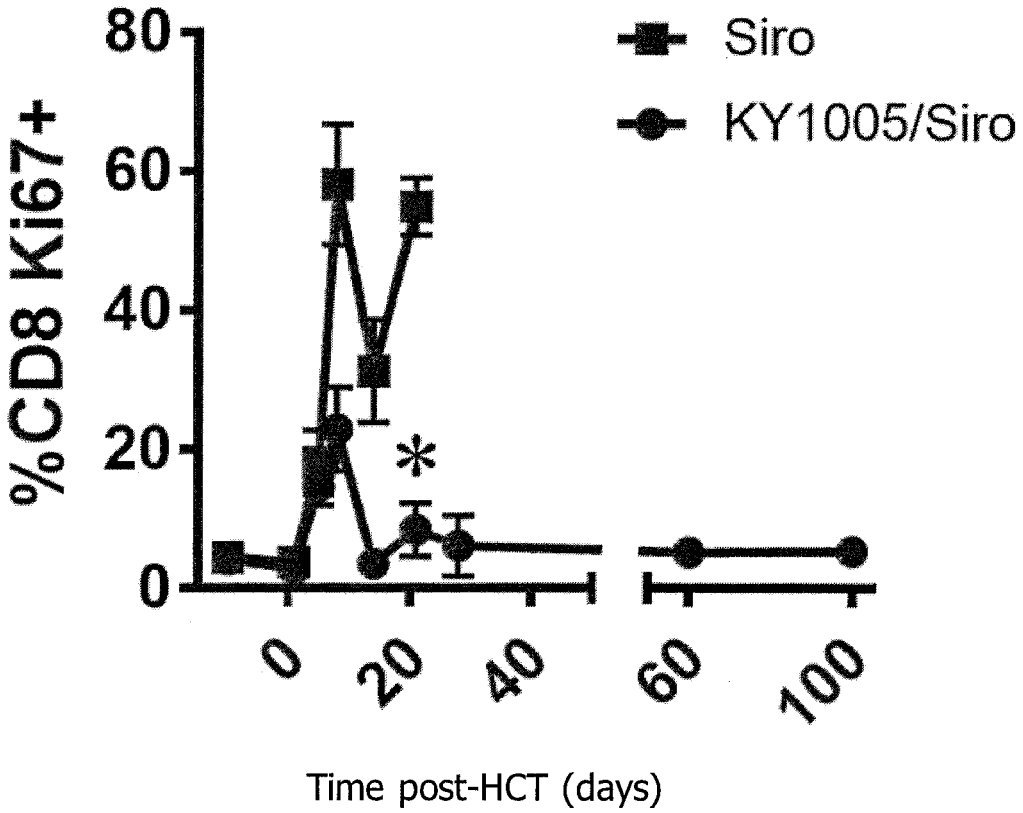


Figure 8S

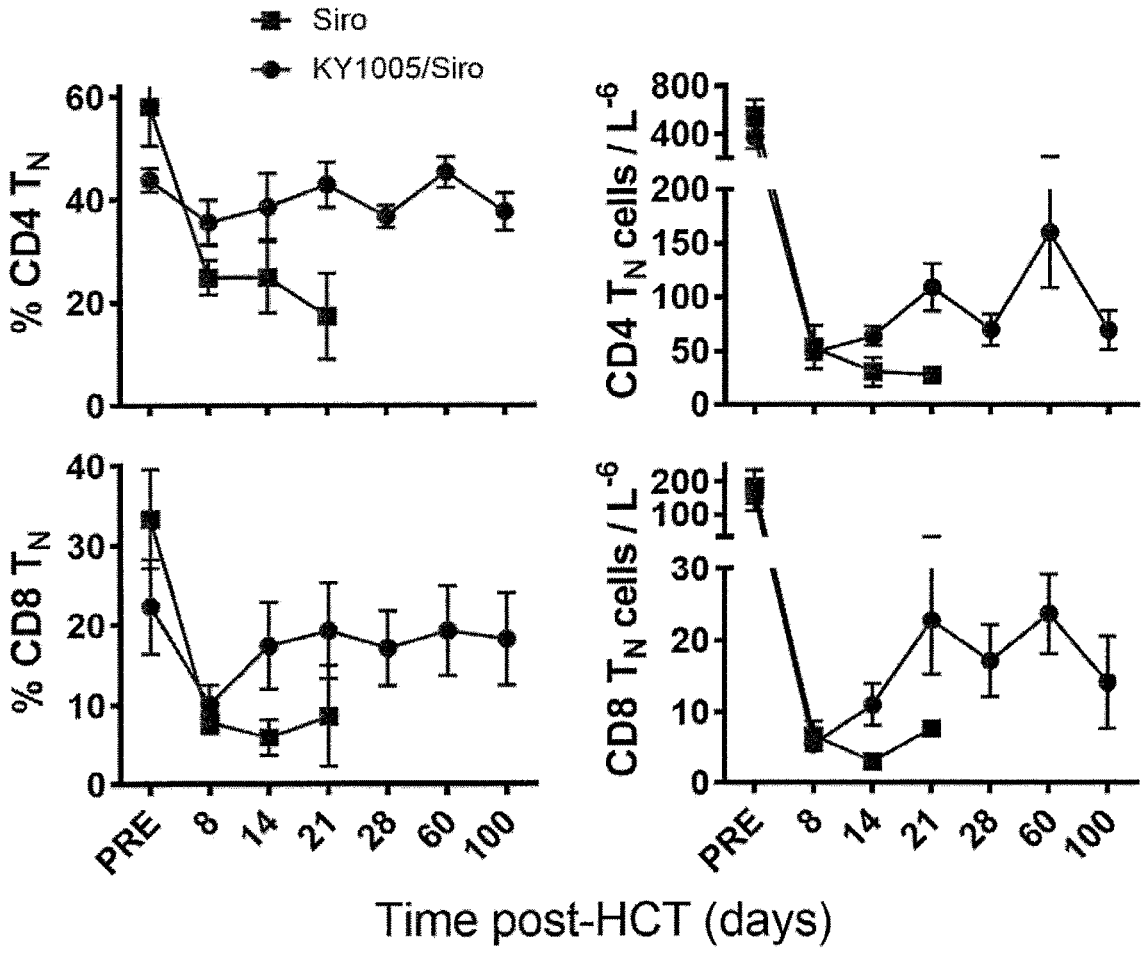

Siro
KY1005/Siro
% CD4 T_N
CD4 T_N cells / L^{-6}
% CD8 T_N
CD8 T_N cells / L^{-6}
PRE
8
14
21
28
60
100
Time post-HCT (days)

Figure 8T

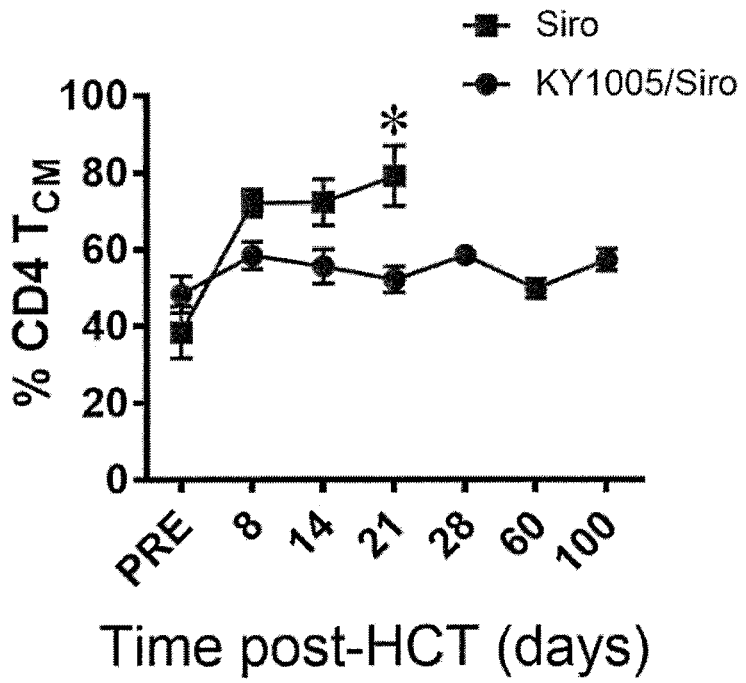


Figure 8U

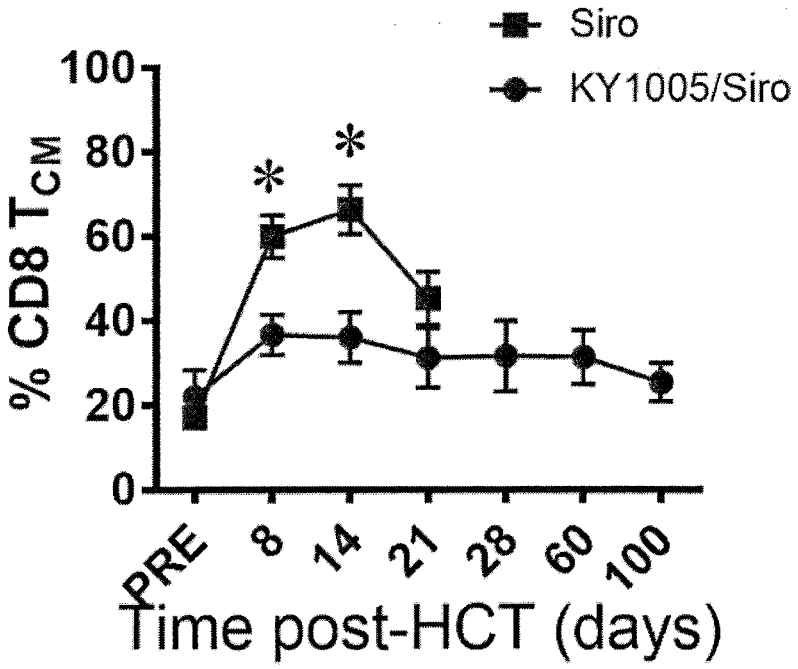


Figure 8V

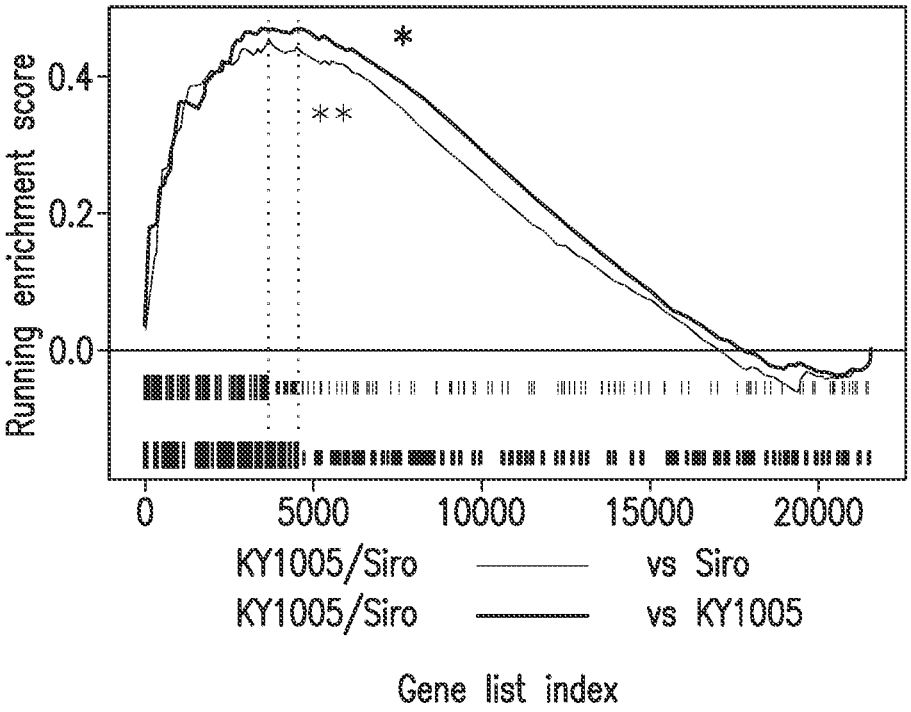
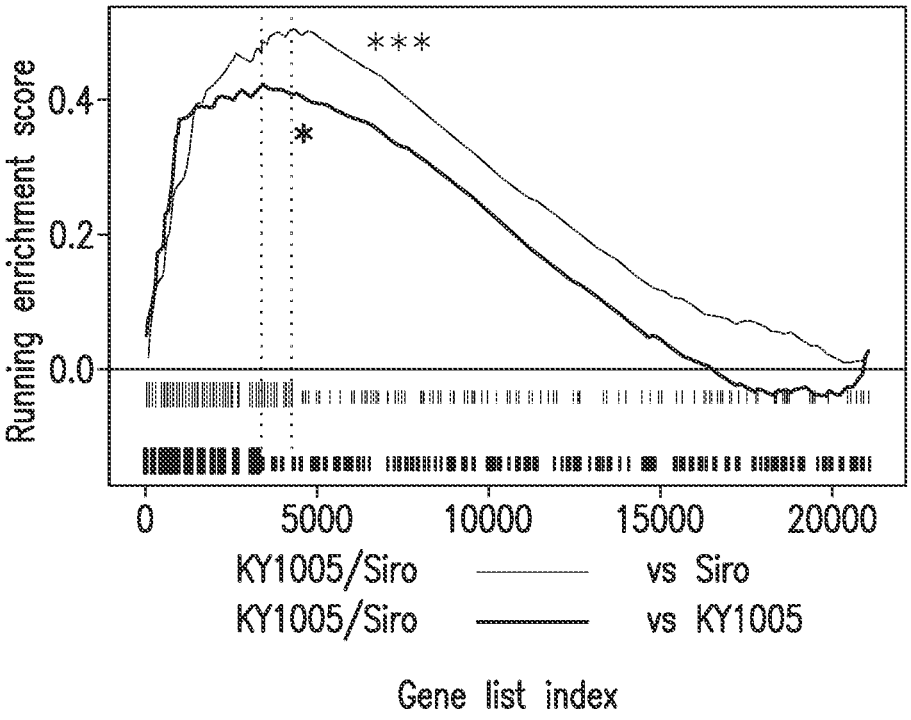


Figure 8W



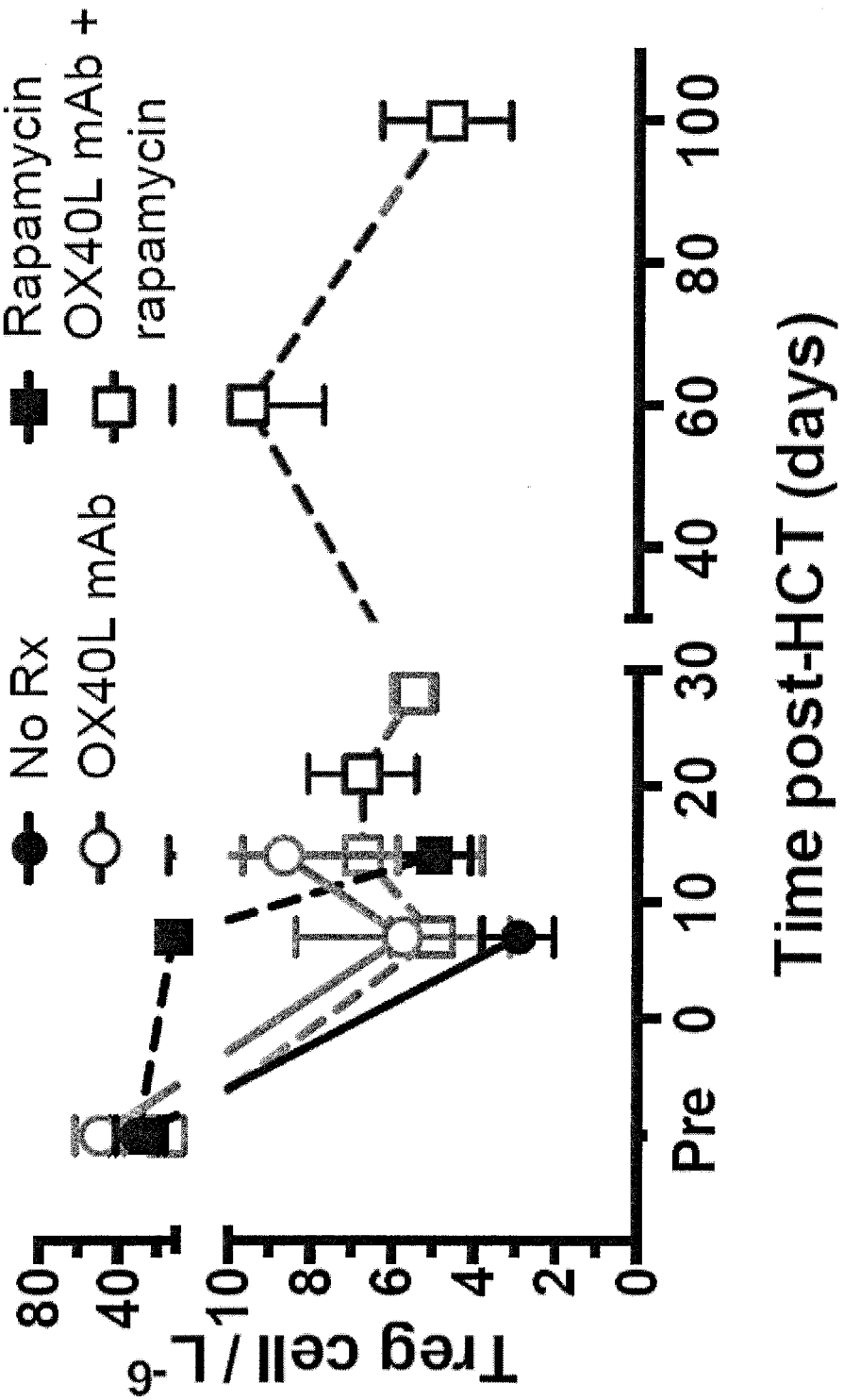
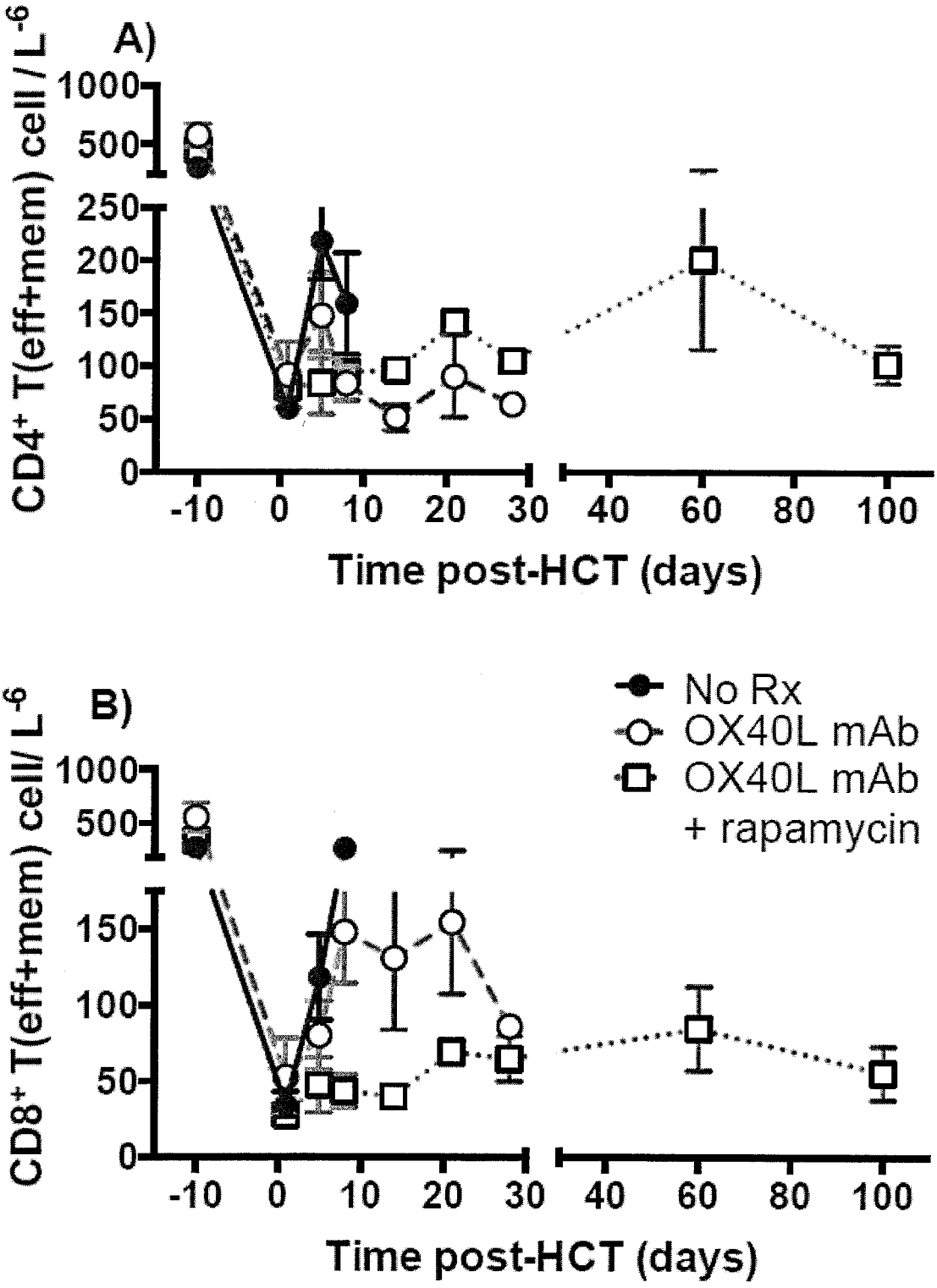

No Rx
OX40L mAb
Rapamycin
OX40L mAb + rapamycin
Treg cell / L-6
0
2
4
6
8
10
40
80
Pre
0
10
20
30
40
60
80
100
Time post-HCT (days)

Figure 9

Figure 10


A)
CD4+ T(eff+mem) cell / L-6
1000
500
250
200
150
100
50
0
-10
0
10
20
30
40
60
80
100
Time post-HCT (days)
B)
CD8+ T(eff+mem) cell/ L-6
1000
500
150
100
50
0
-10
0
10
20
30
40
60
80
100
Time post-HCT (days)
No Rx
OX40L mAb
OX40L mAb
+ rapamycin

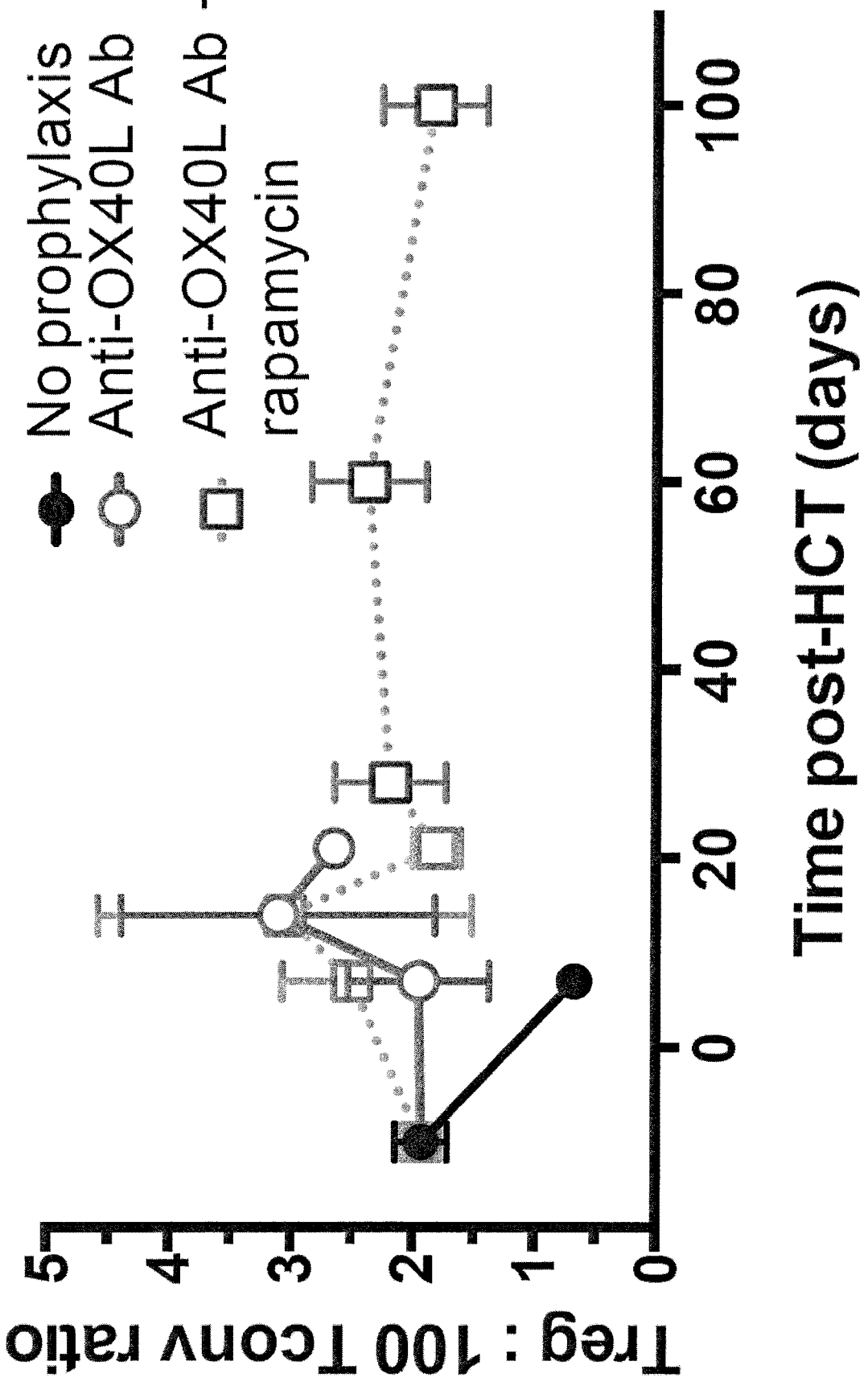

Treg : 100 Tconv ratio
0
1
2
3
4
5
0
20
40
60
80
100
Time post-HCT (days)
No prophylaxis
Anti-OX40L Ab
Anti-OX40L Ab +
rapamycin

Figure 11A

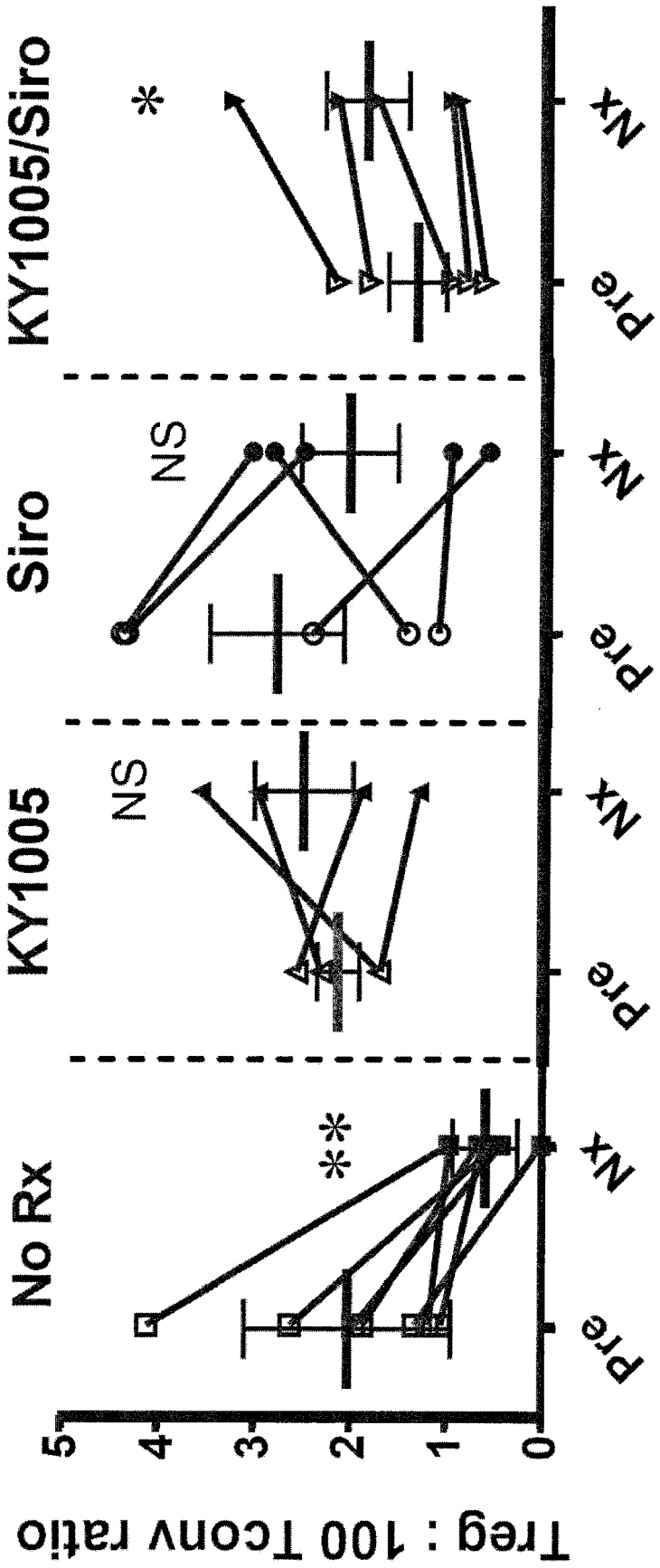

Treg : 100 Tconv ratio
5
4
3
2
1
0
No Rx
KY1005
Siro
KY1005/Siro
**
NS
NS
*
Pre
N+
Pre
N+
Pre
N+
Pre
N+

Figure 11B

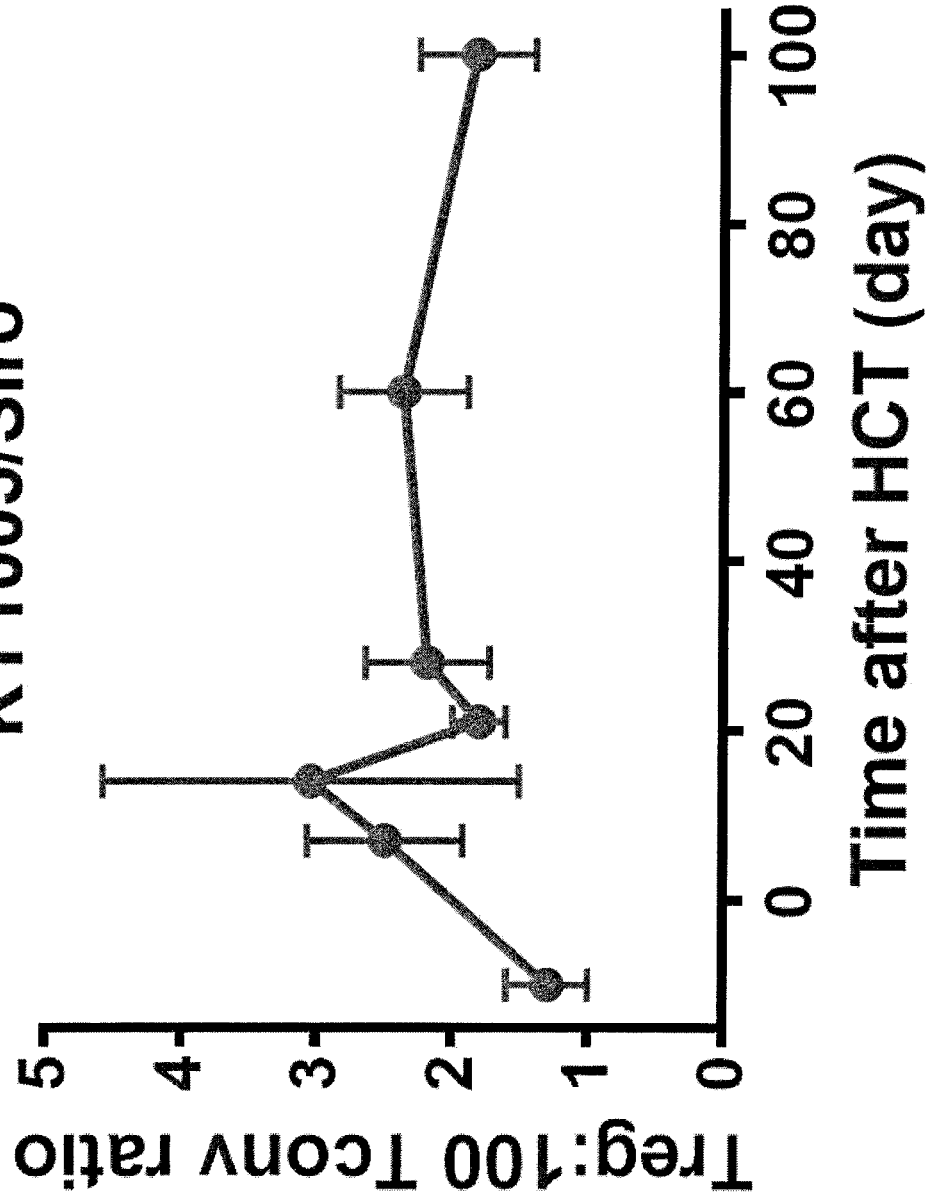

KY1005/Siro
Treg:100 Tconv ratio
0
1
2
3
4
5
0
20
40
60
80
100
Time after HCT (day)

Figure 11C

Figure 11D

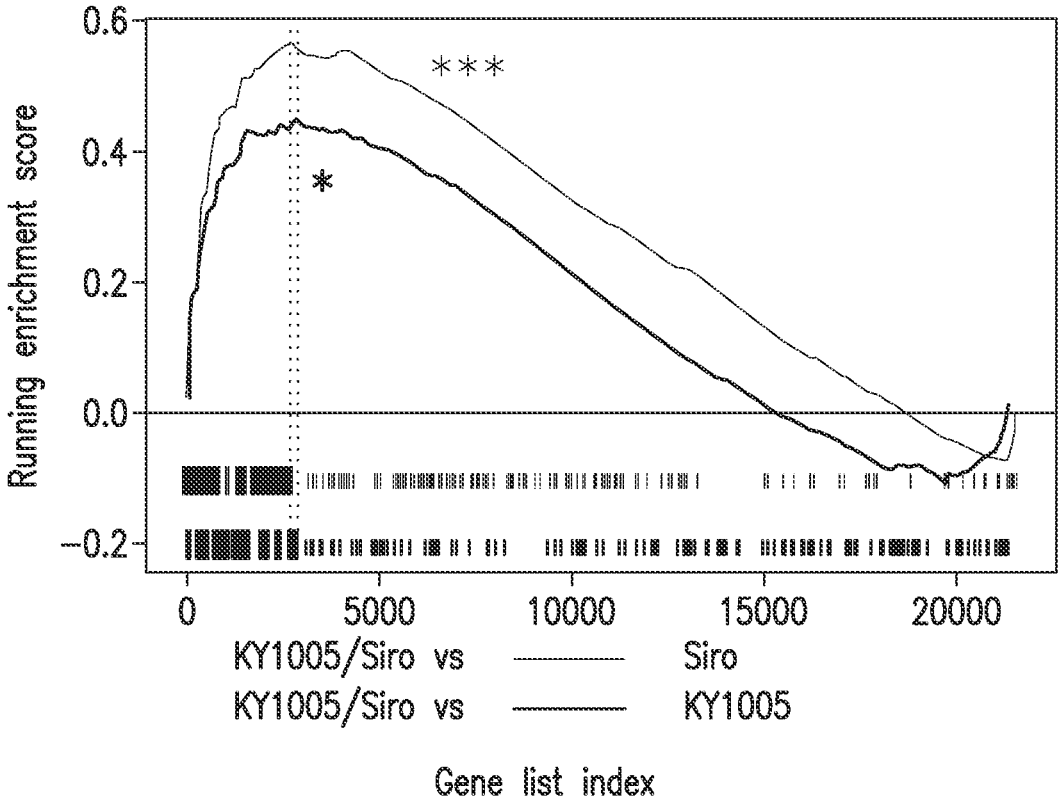

0.6
0.4
0.2
0.0
−0.2
Running enrichment score
***
*
0
5000
10000
15000
20000
KY1005/Siro vs Siro
KY1005/Siro vs KY1005
Gene list index

Figure 12A

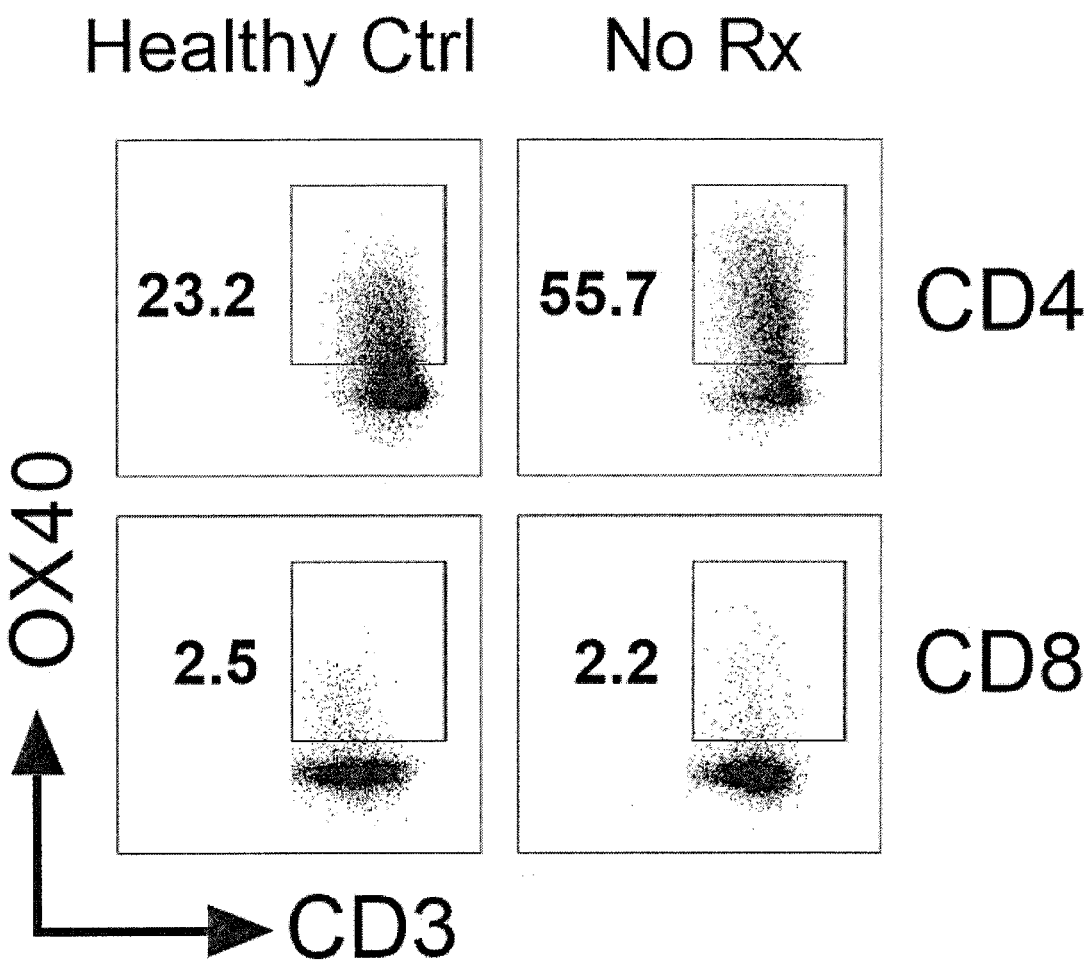


Figure 12B

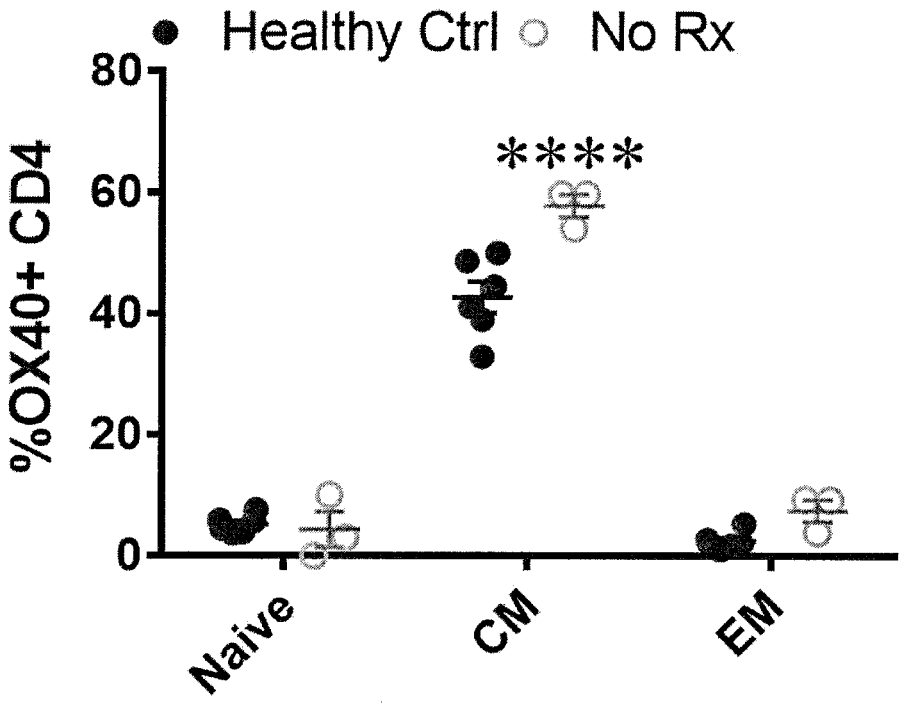


Figure 12C

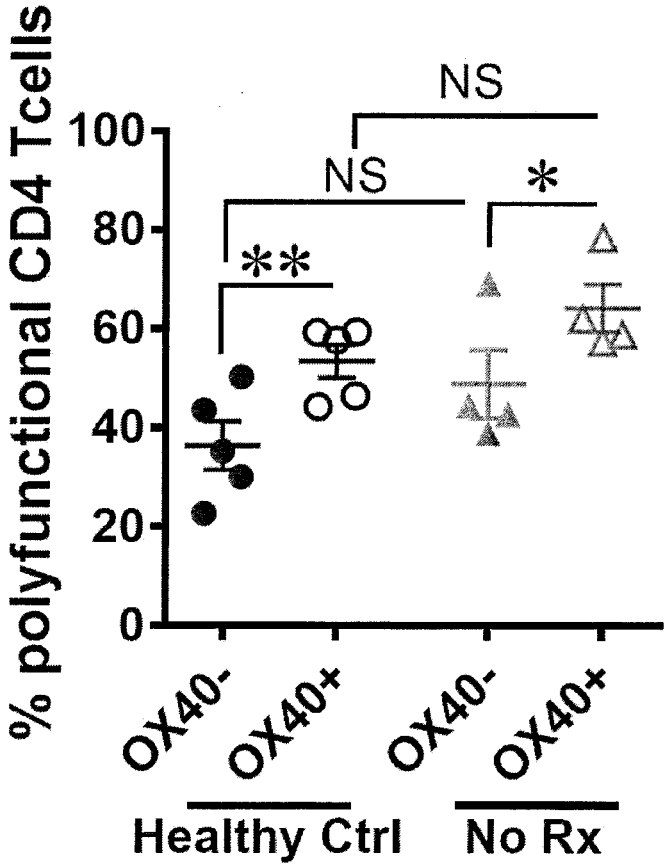


Figure 12D

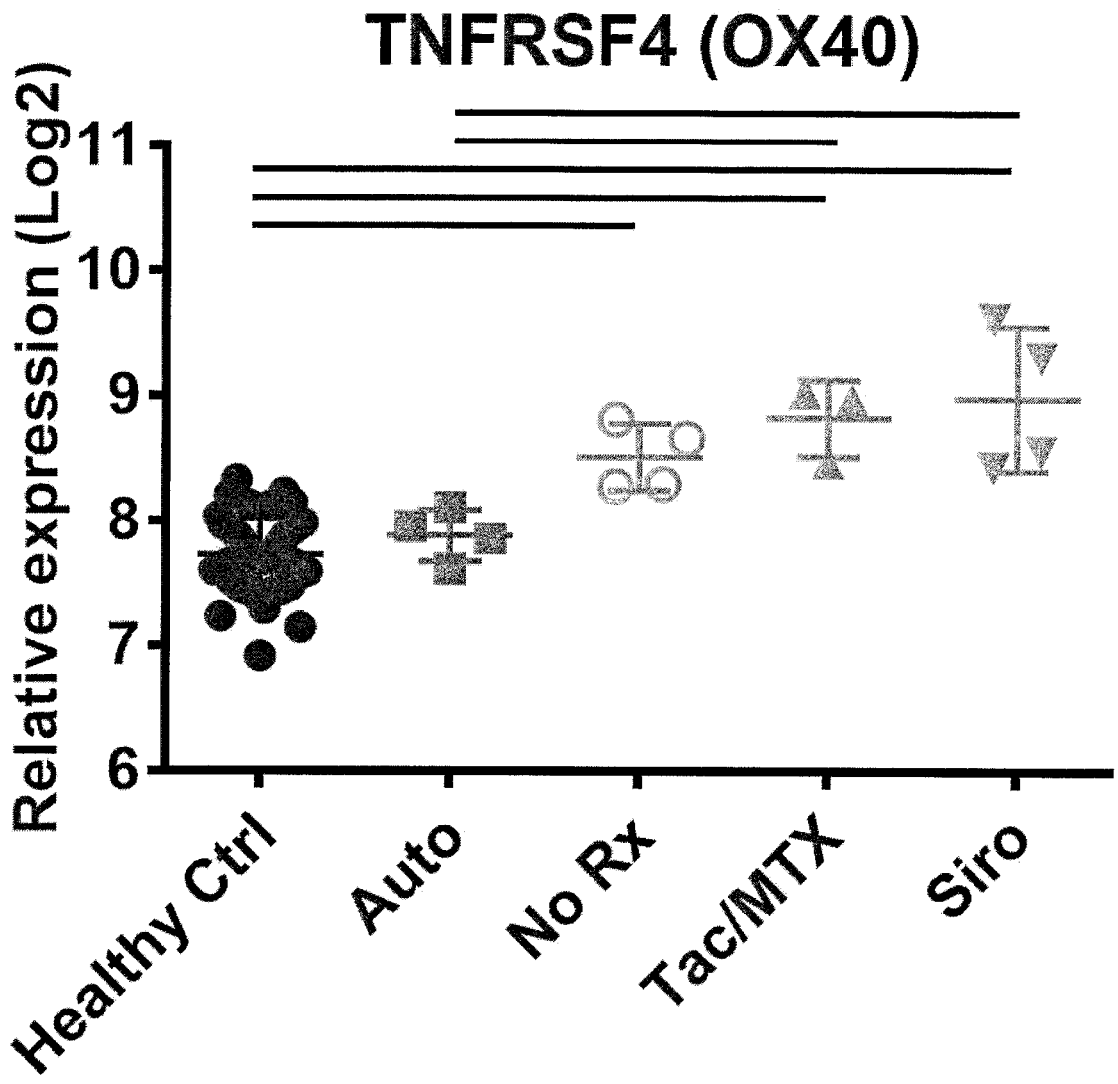

TNFRSF4 (OX40)
Relative expression (Log2)
11
10
9
8
7
6
Healthy Ctrl
Auto
No Rx
Tac/MTX
Siro

Figure 12E

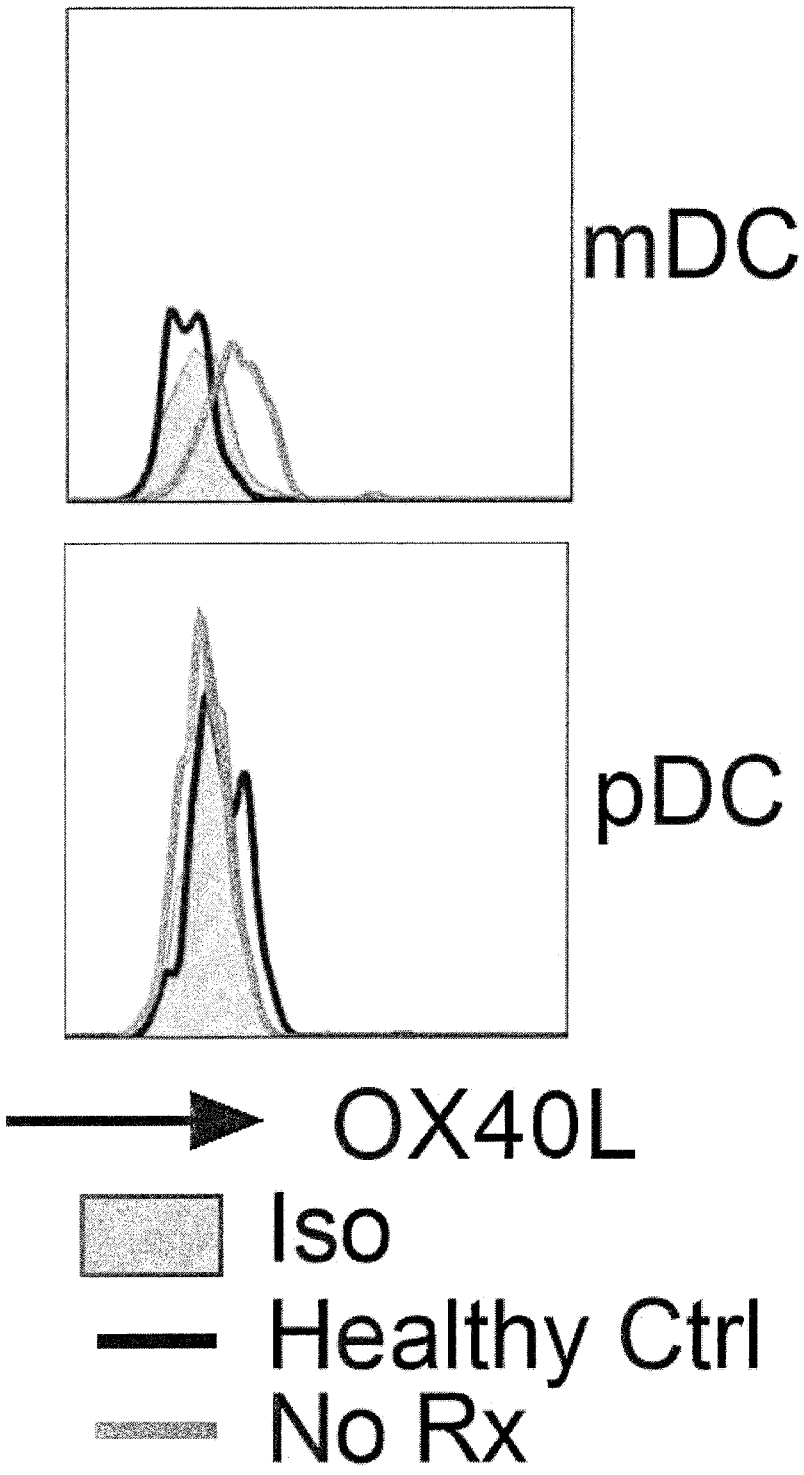


Figure 12F

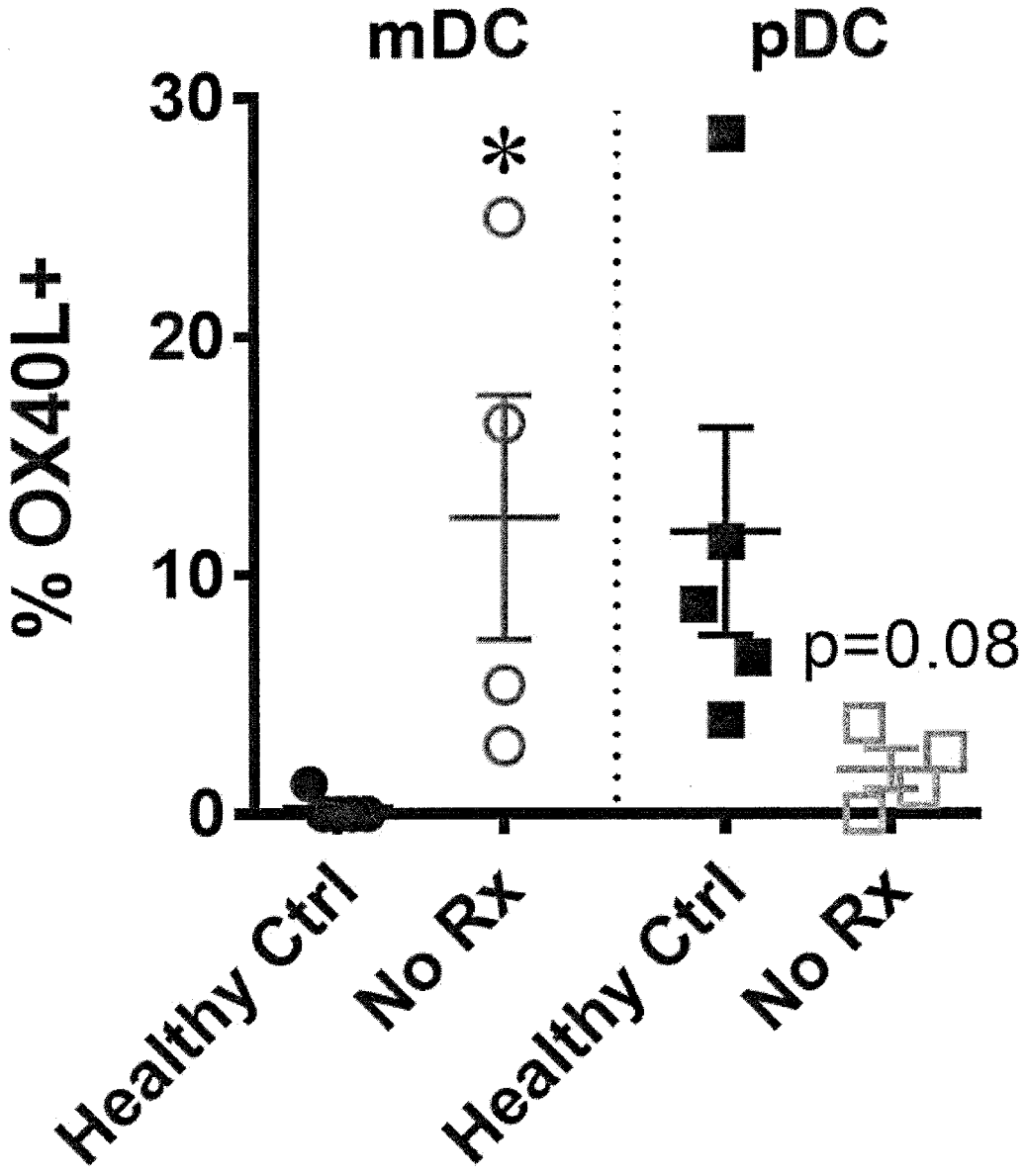

mDC
pDC
30
20
10
0
% OX40L+
*
p=0.08
Healthy Ctrl
No Rx
Healthy Ctrl
No Rx

Figure 12G

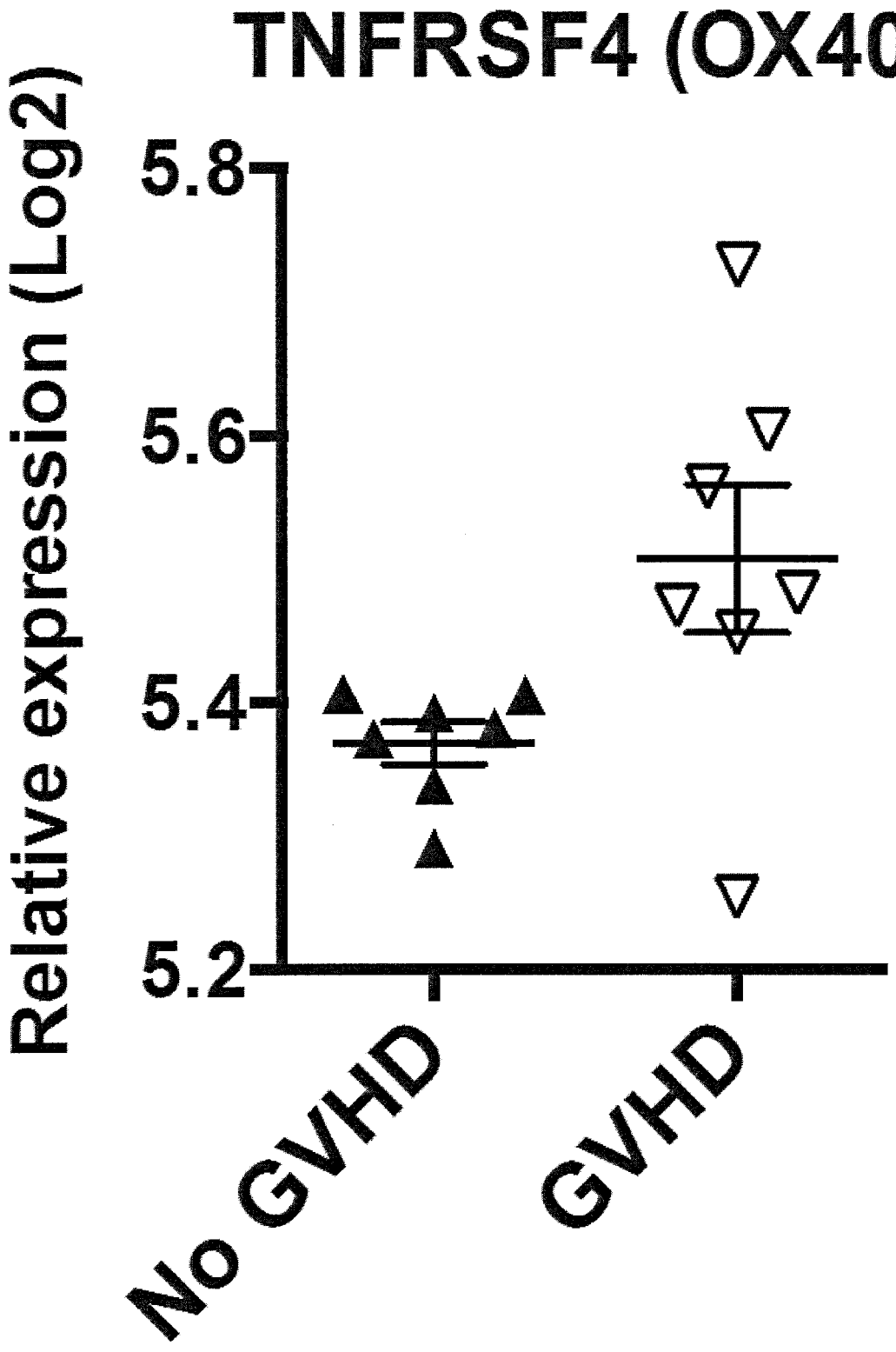

TNFRSF4 (OX40)
Relative expression (Log2)
5.8
5.6
5.4
5.2
No GVHD
GVHD

Figure 12H

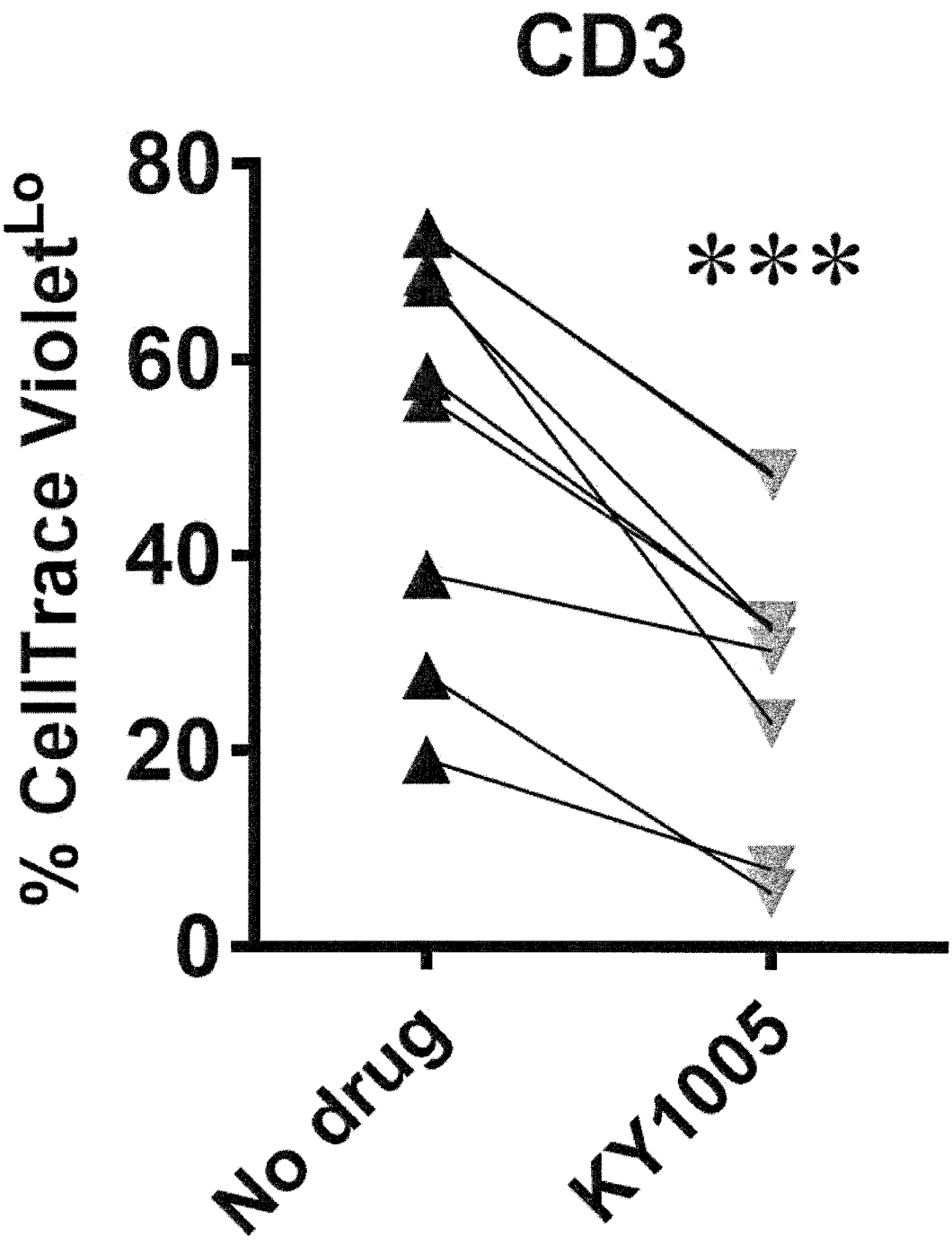


Figure 13A

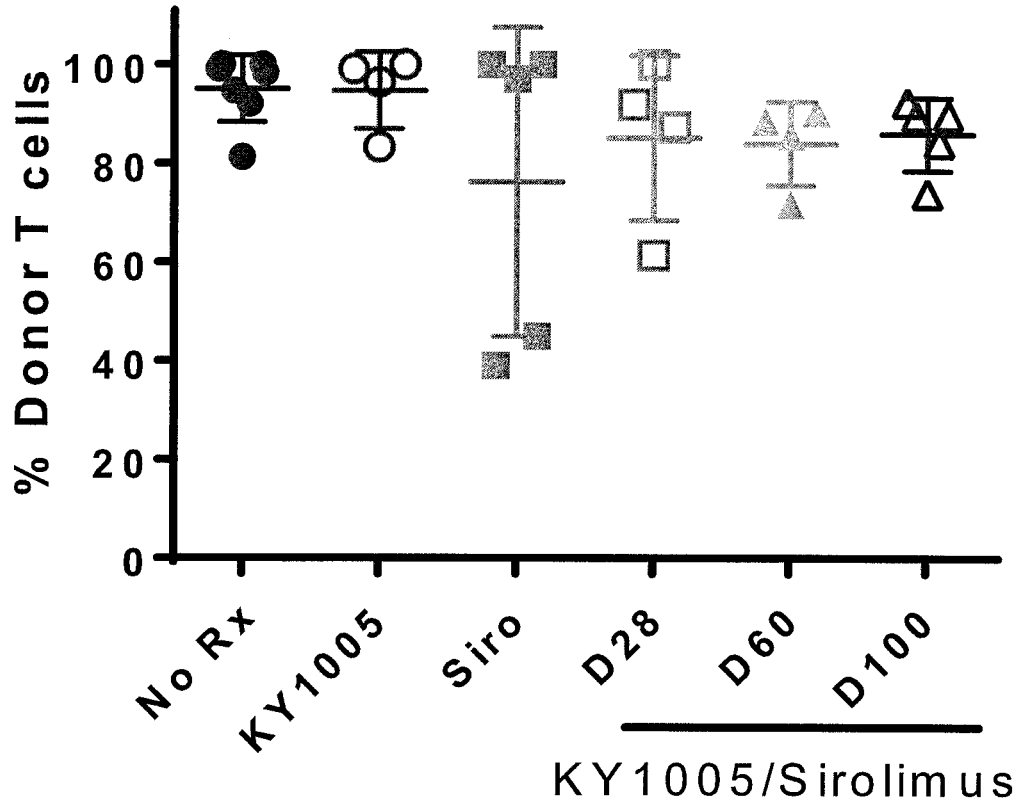


Figure 13B

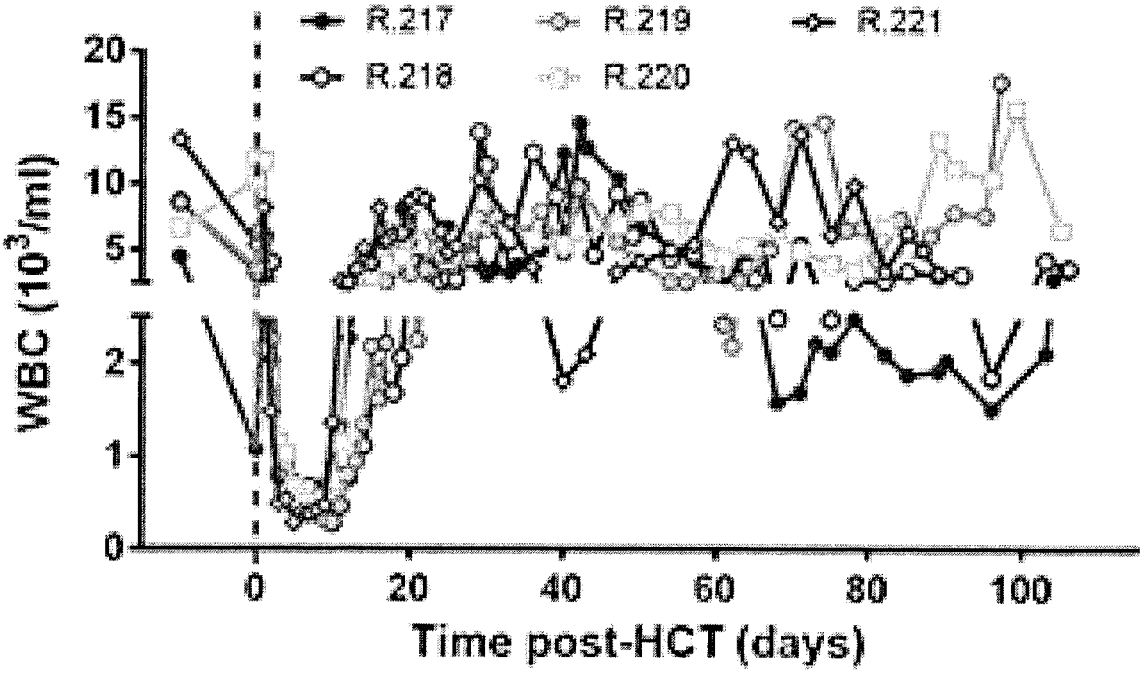


Figure 13C

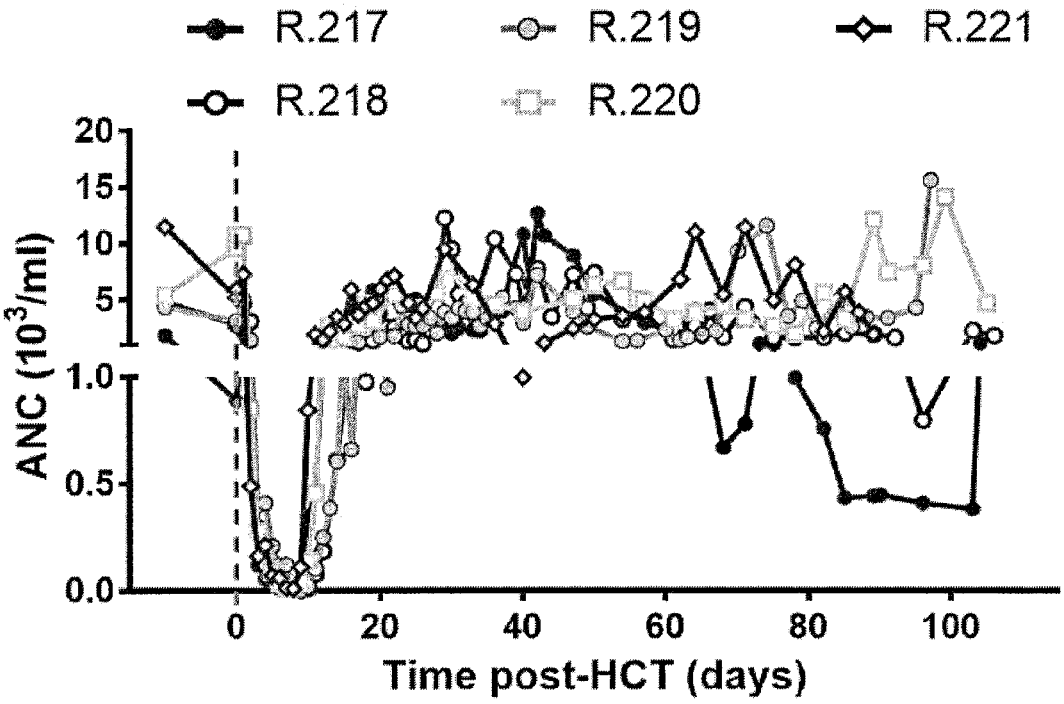


Figure 13C-1

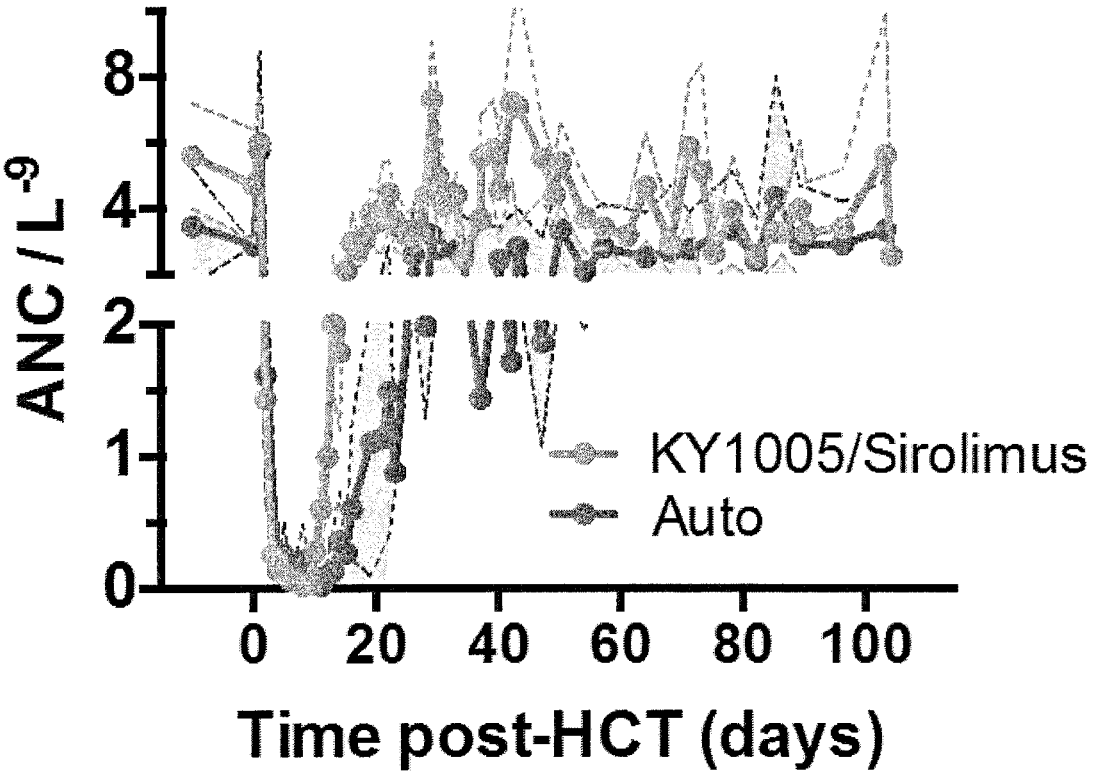


Figure 13D

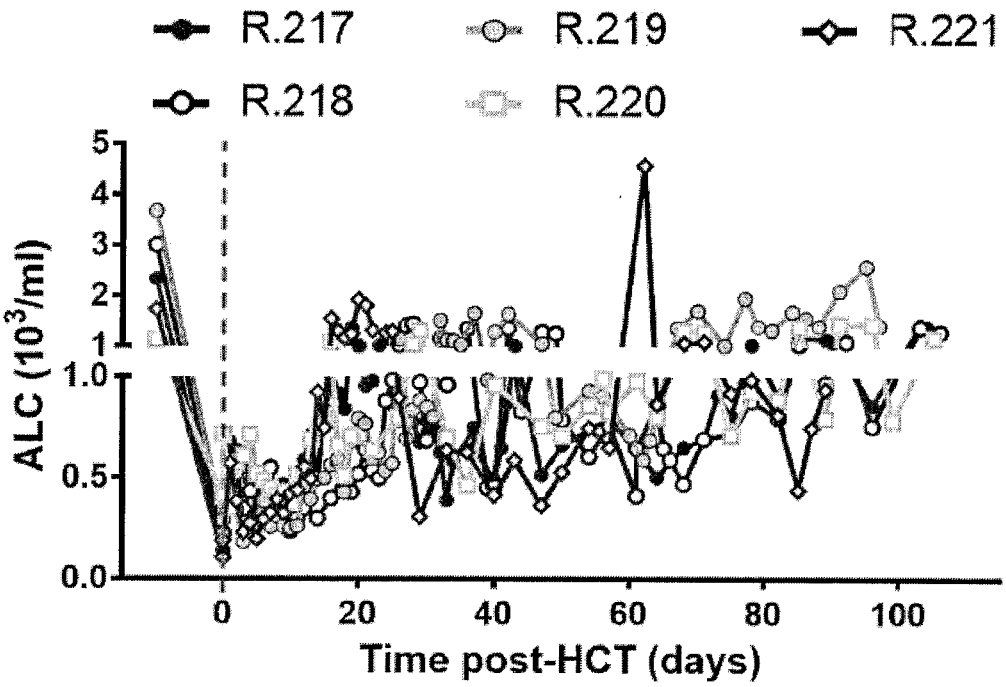


Figure 13D-1

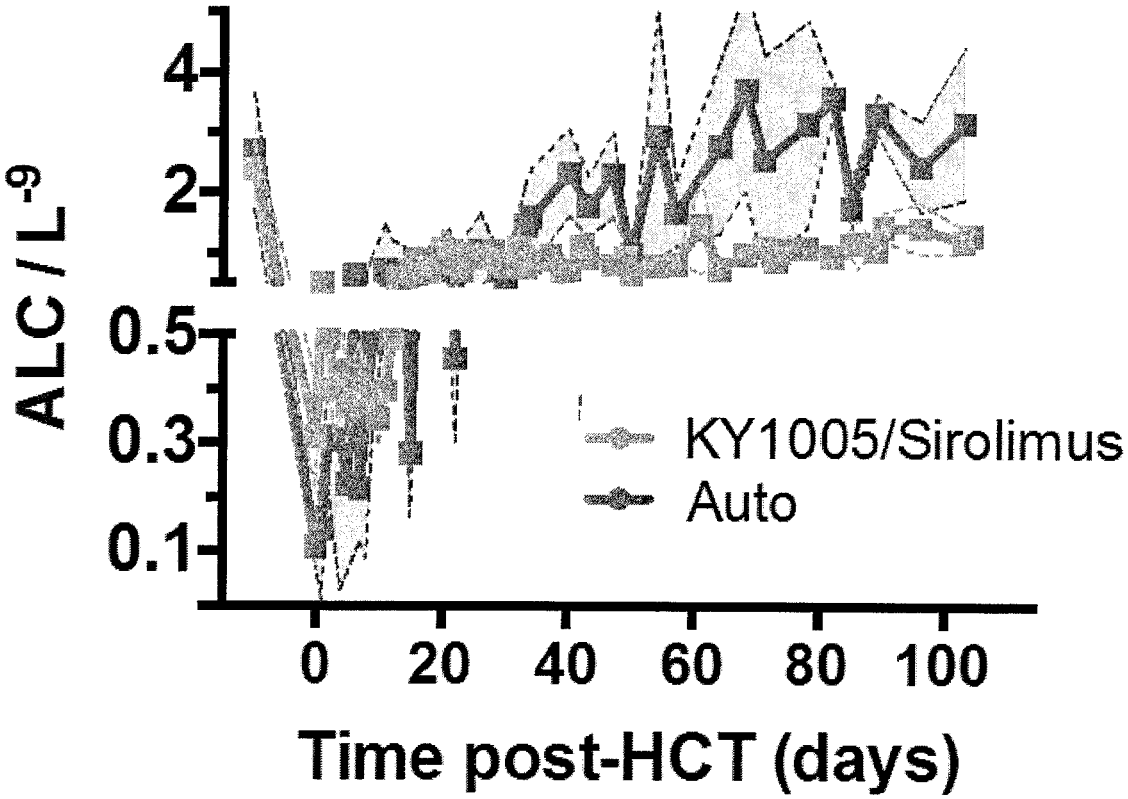


Figure 13E

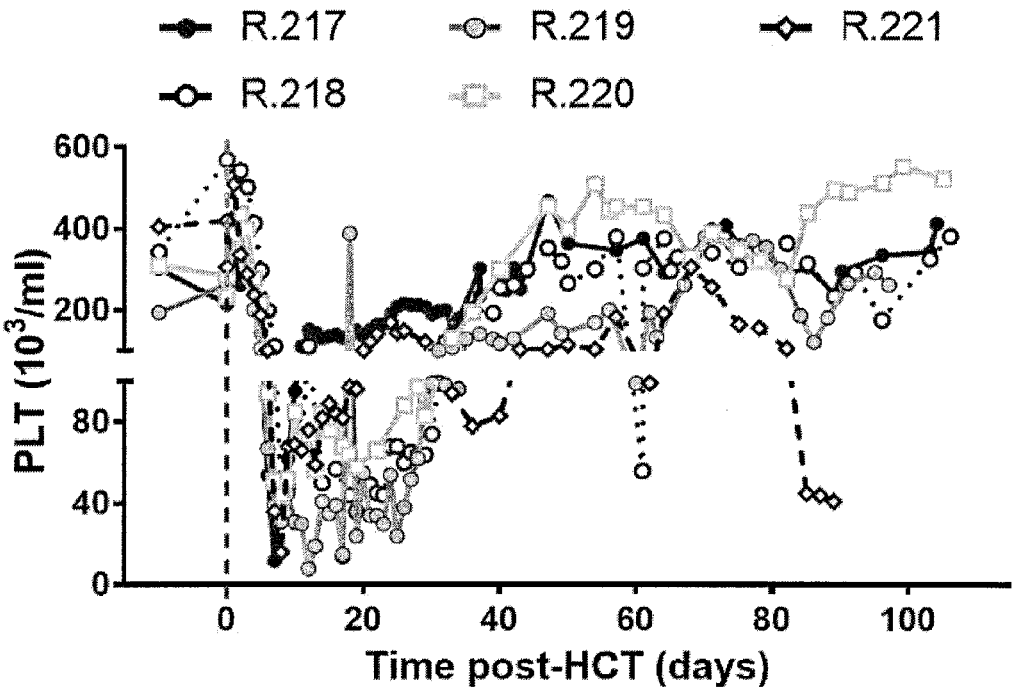


Figure 13E-1

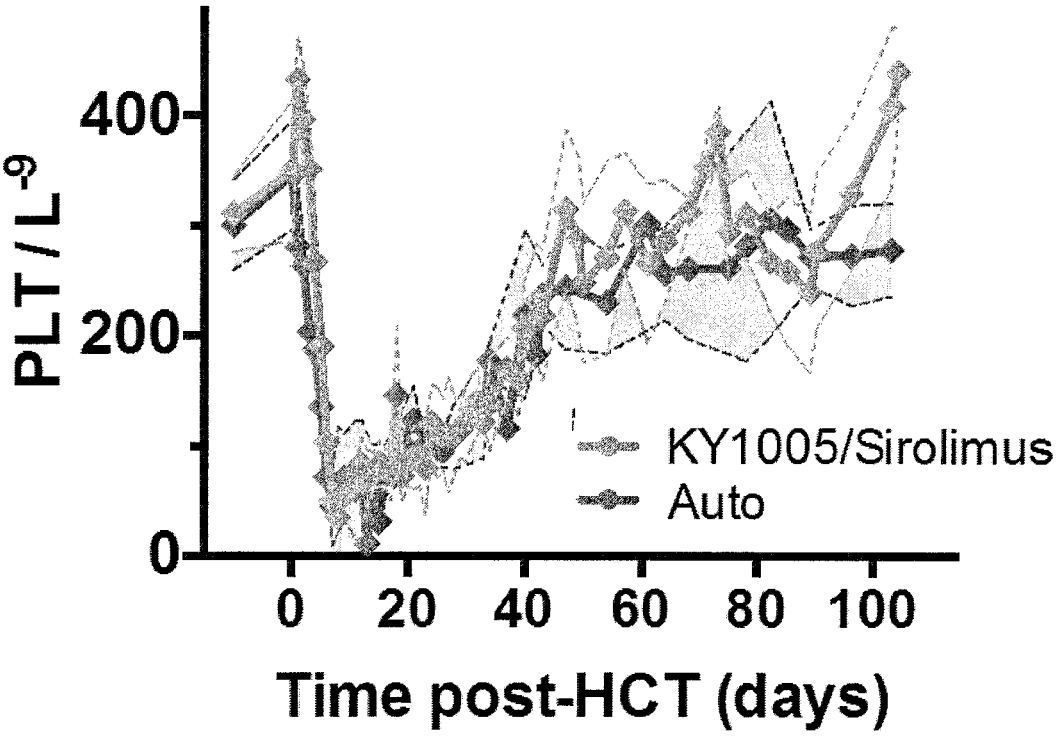


Figure 13F

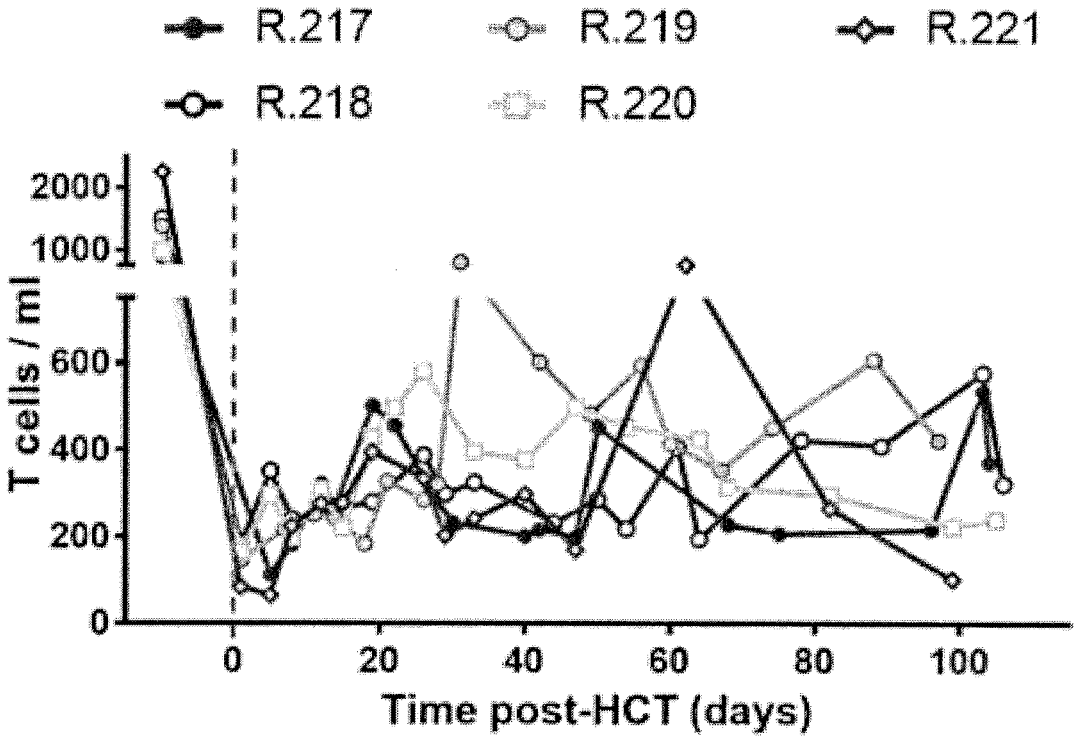


Figure 13F-1

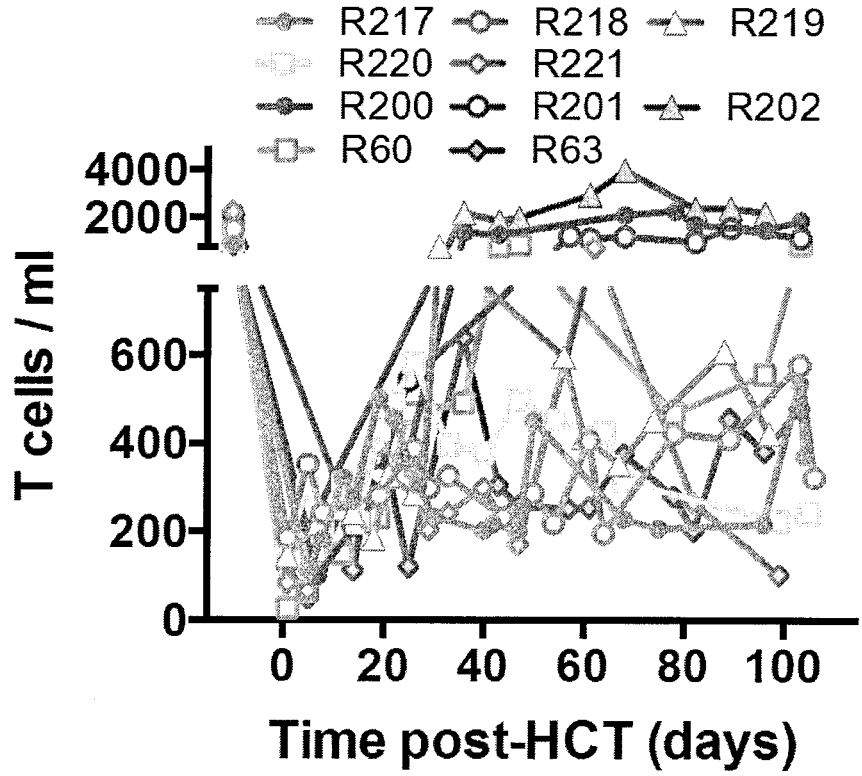


Figure 13G

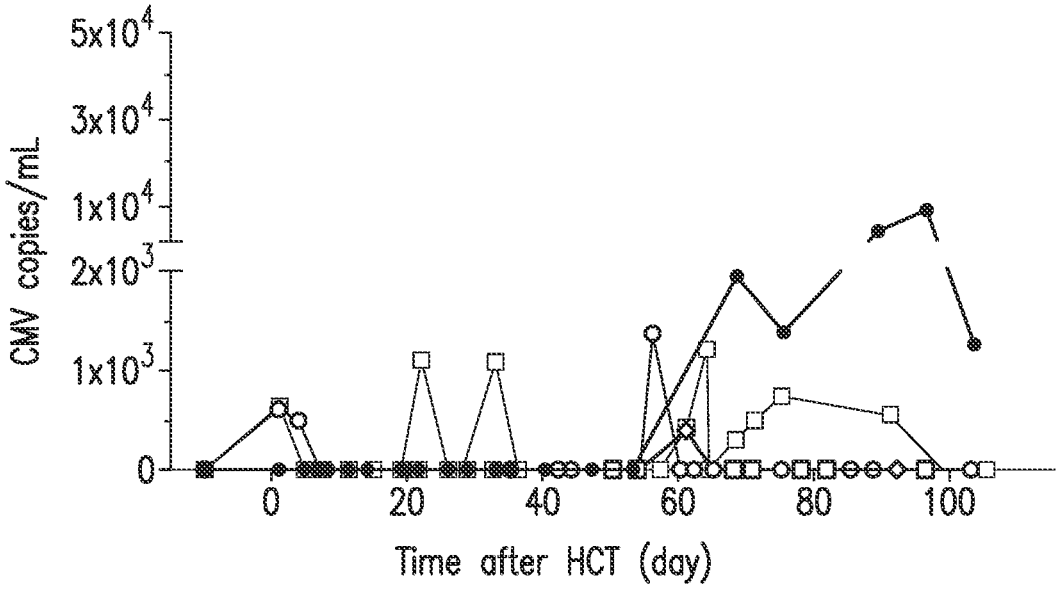


Figure 13G-1

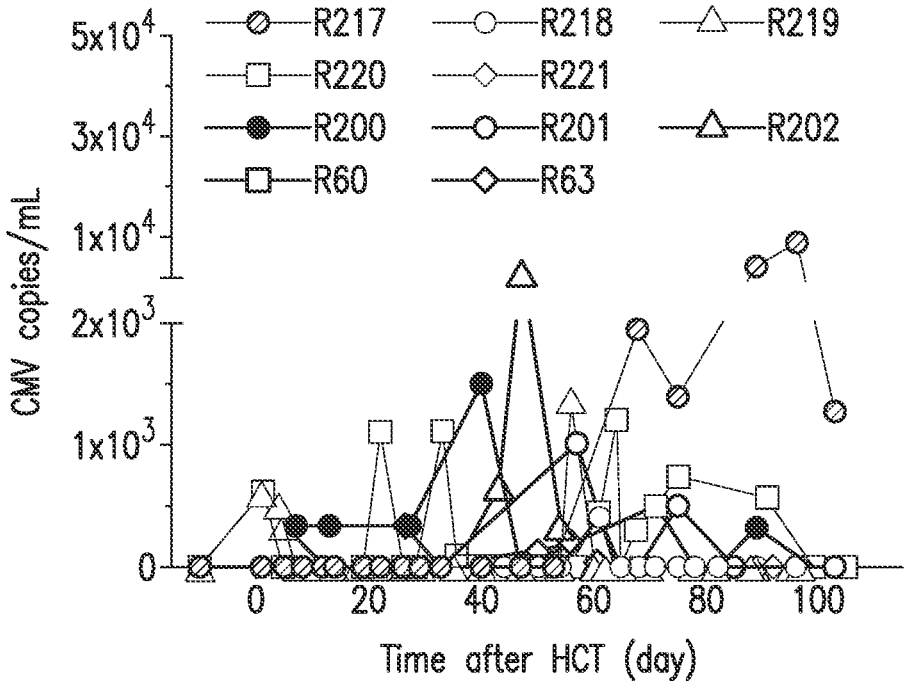


Figure 14A

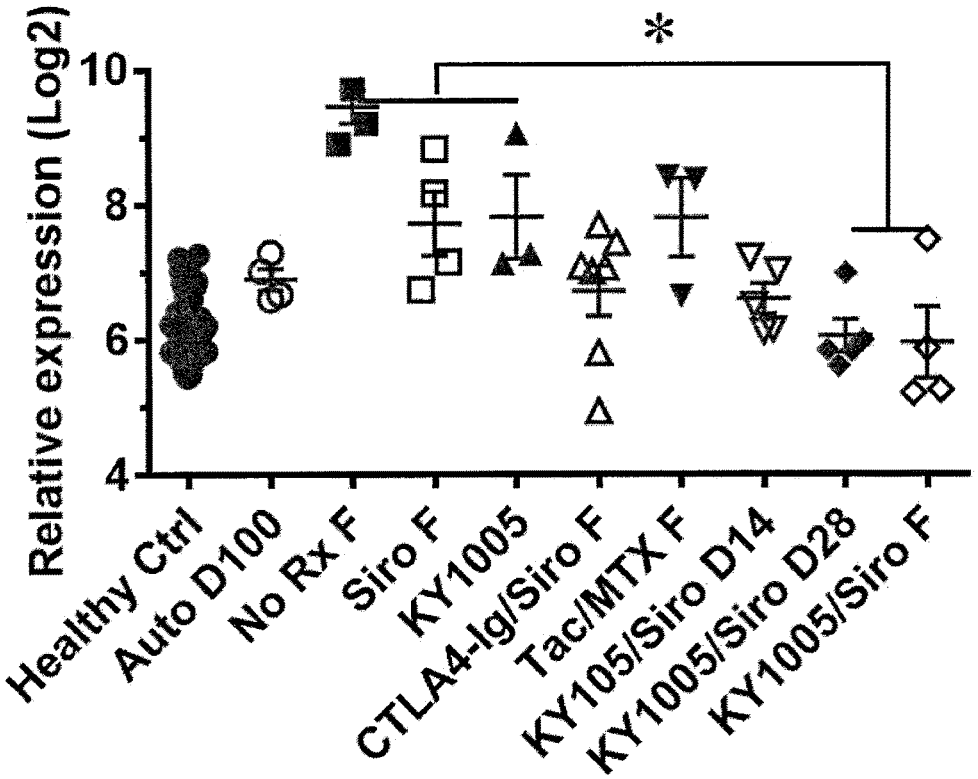


Figure 14B

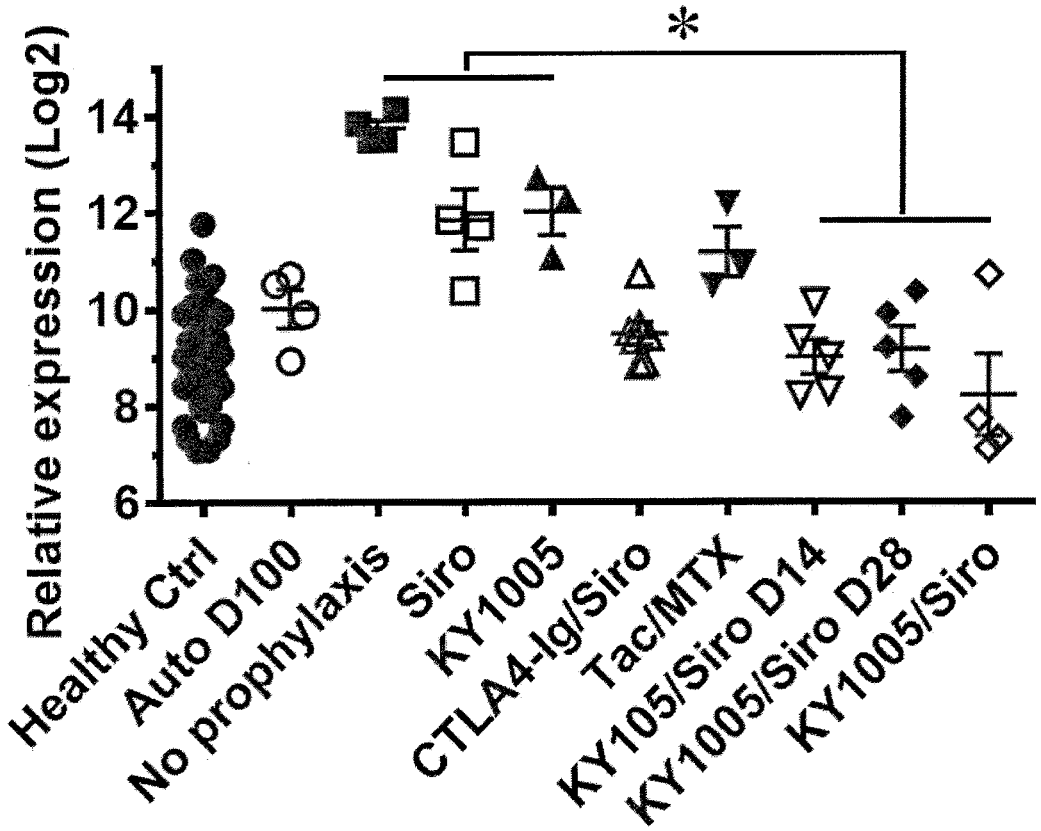


Figure 14C

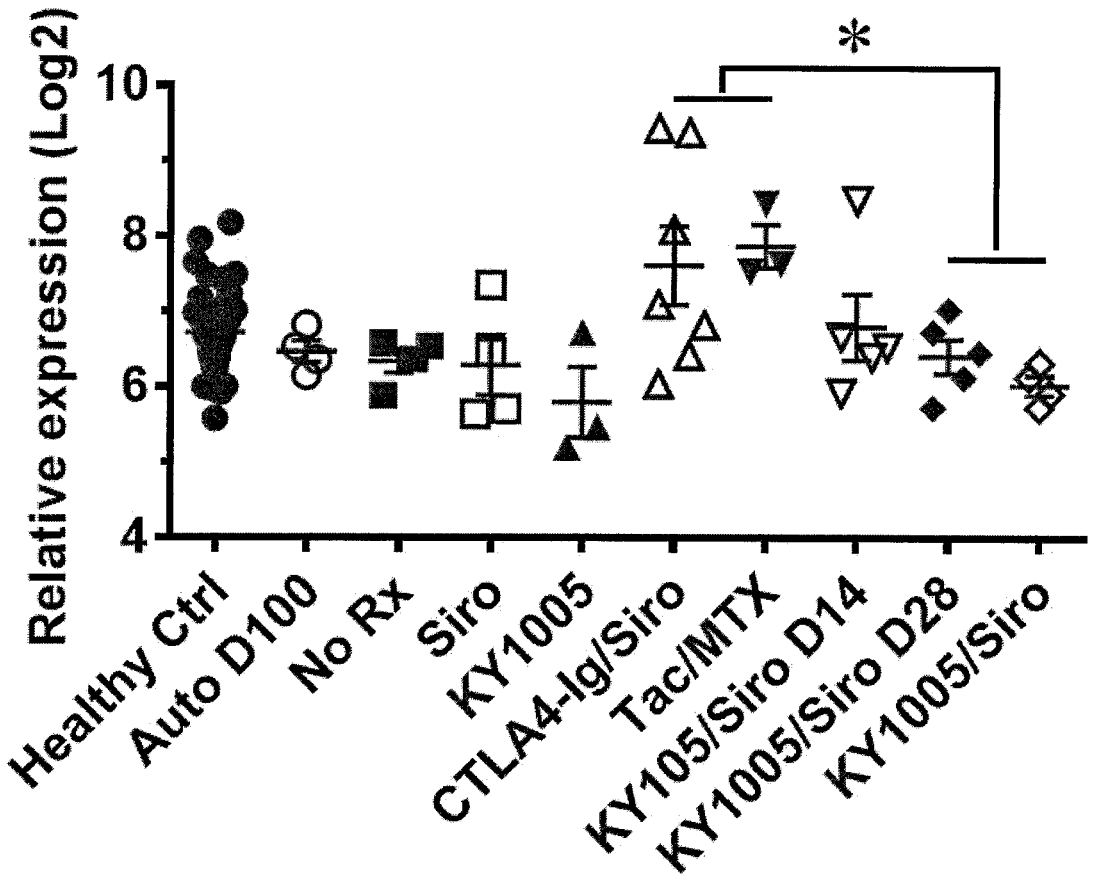

Relative expression (Log2)
10
8
6
4
*
Healthy Ctrl
Auto D100
No Rx
Siro
KY1005
CTLA4-Ig/Siro
Tac/MTX
KY105/Siro D14
KY1005/Siro D28
KY1005/Siro

Figure 14D

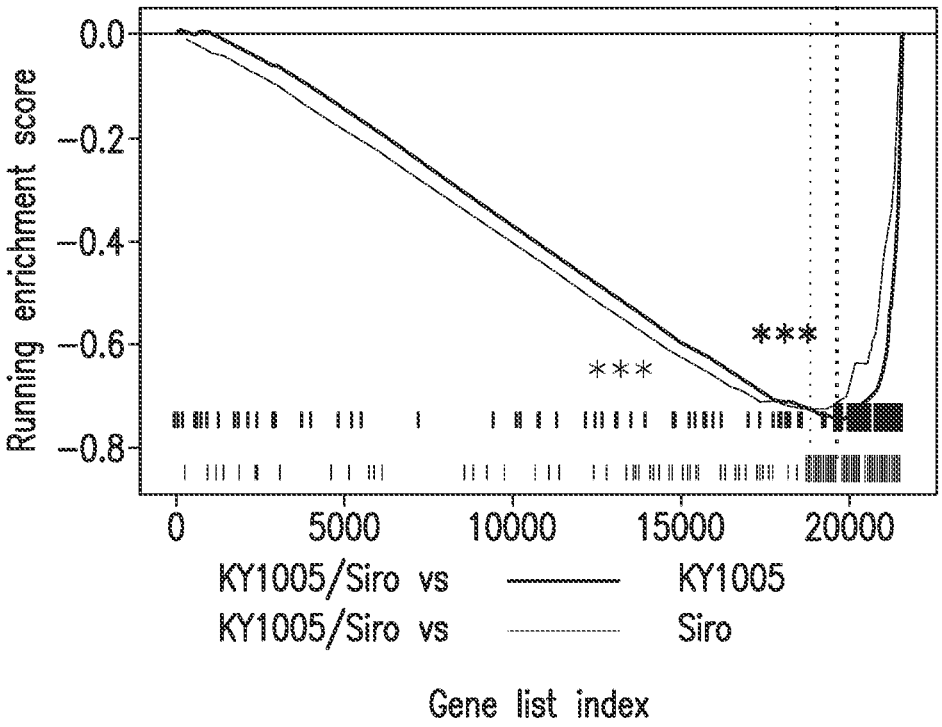


Figure 14E

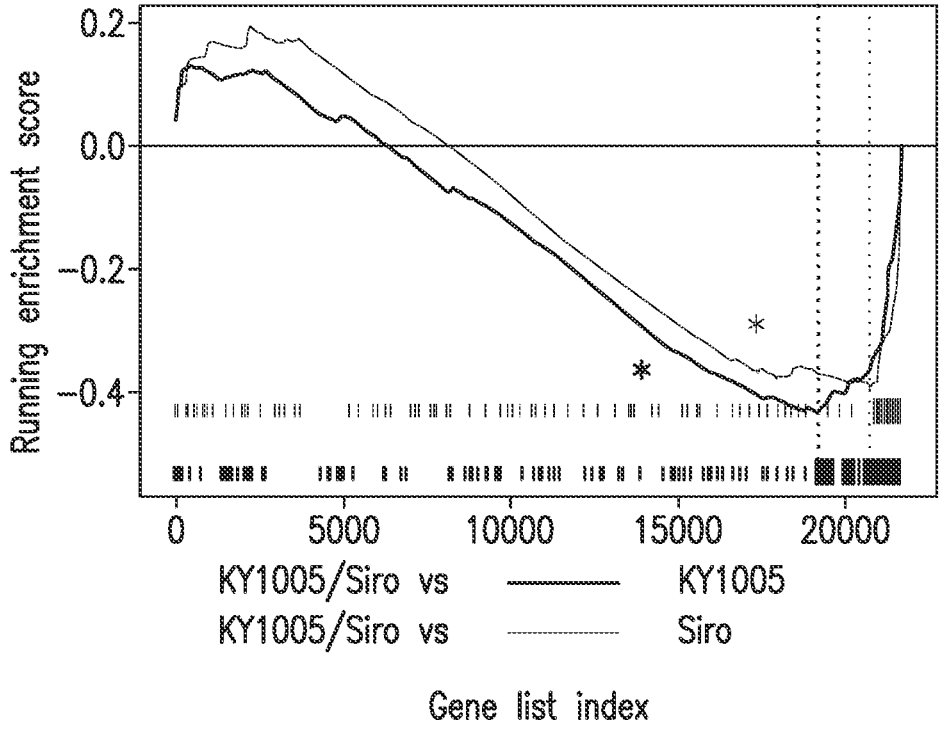


Figure 14F

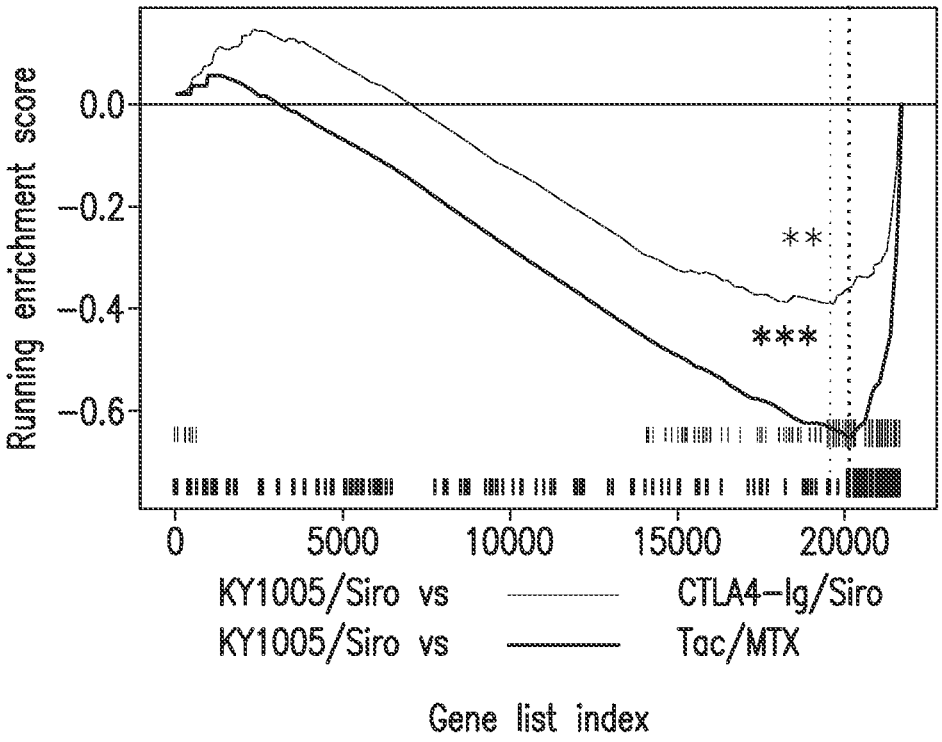
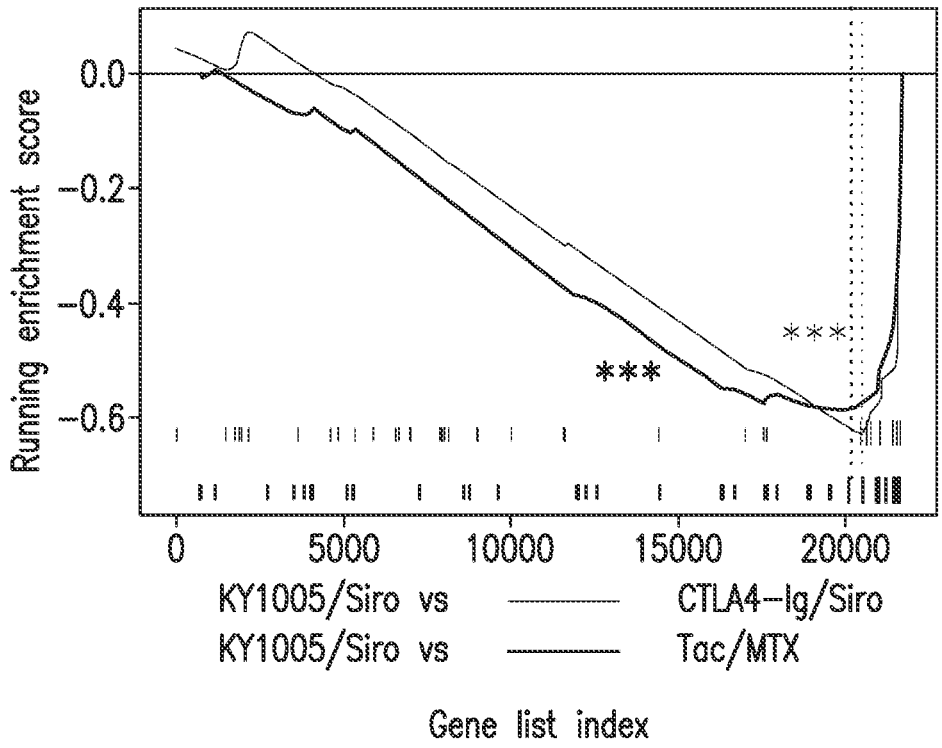


Figure 14G



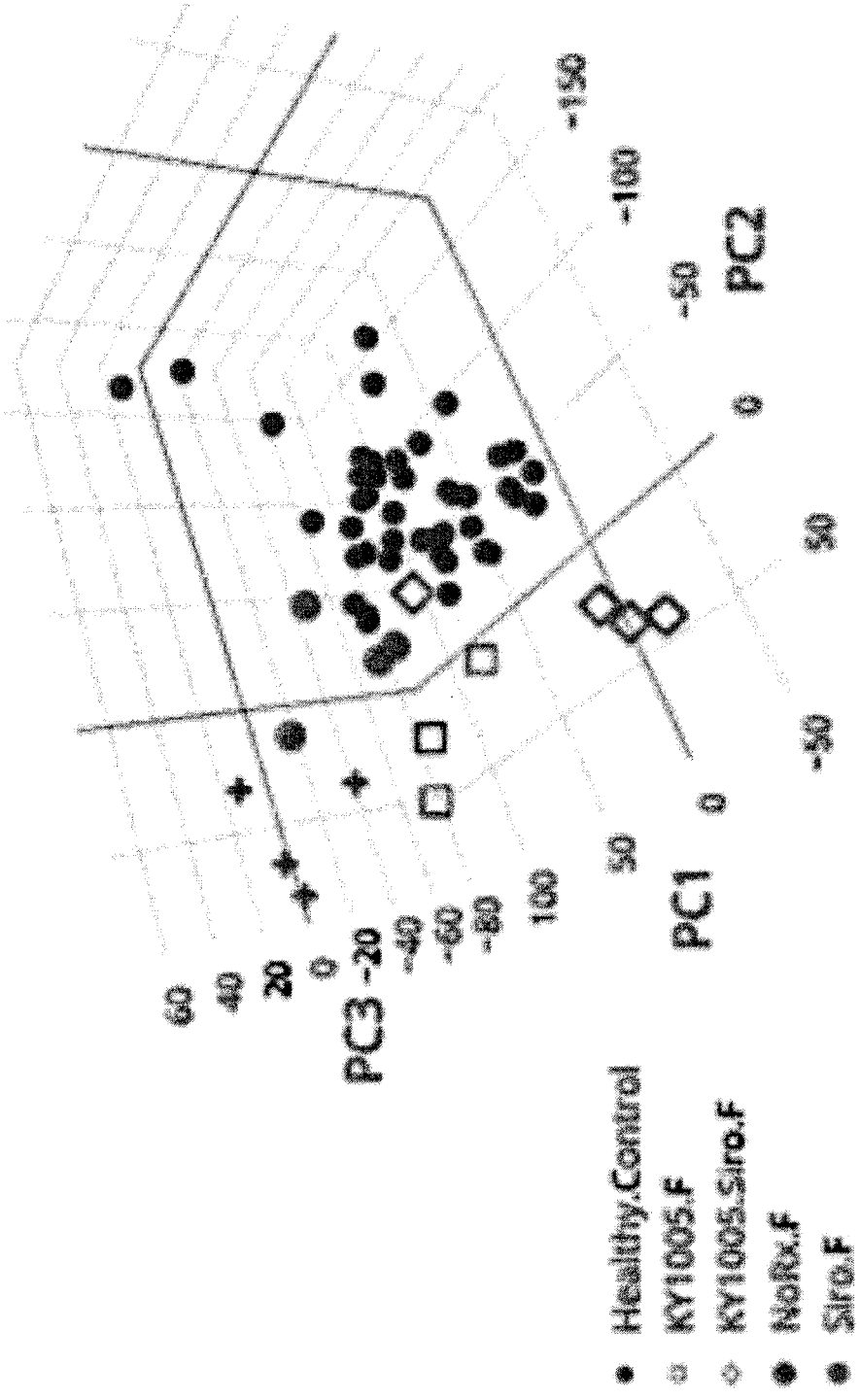

PC3
60
40
20
0
-20
-40
-60
-80
100
50
0
-50
PC1
-150
-100
-50
0
50
PC2
Healthy.Control
KY1005.F
KY1005.Siro.F
NoRx.F
Siro.F

Figure 15A

Figure 15A-1

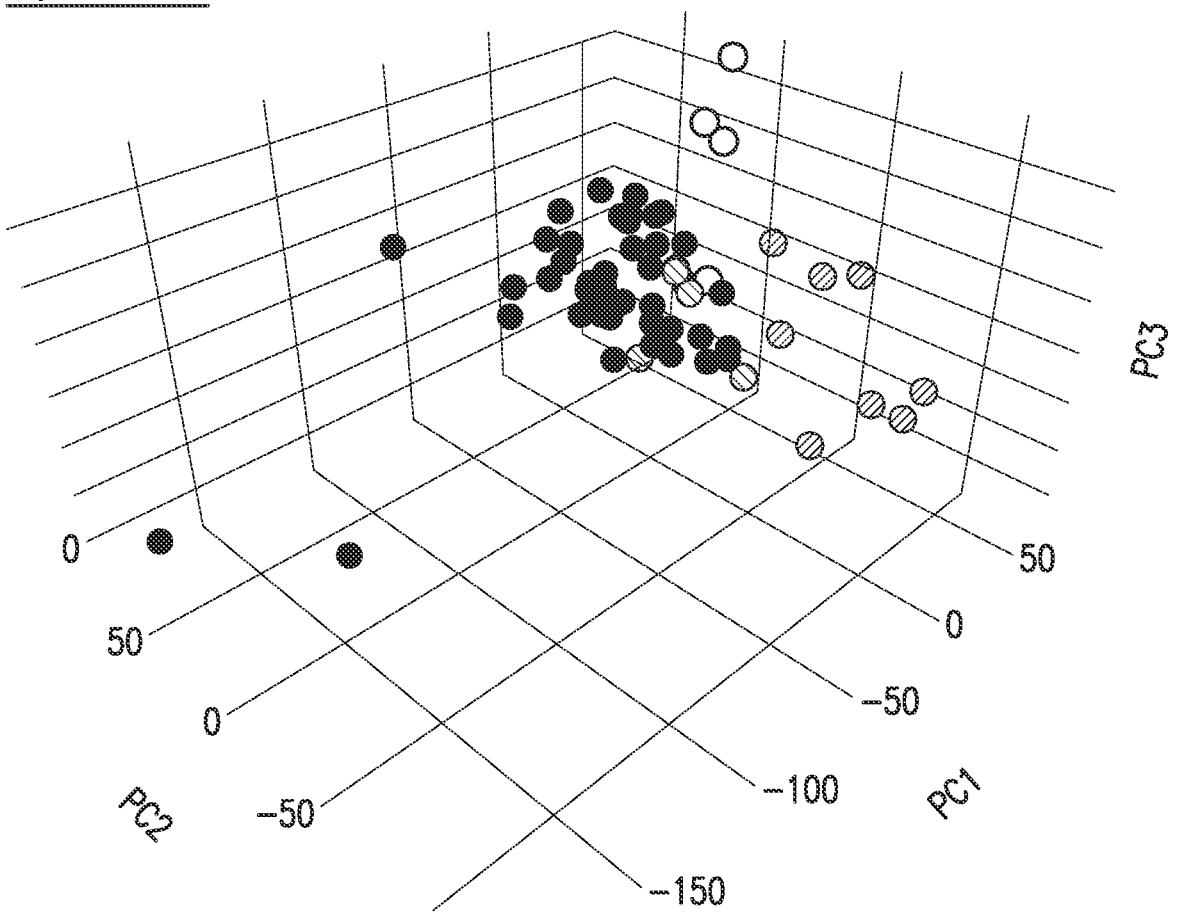
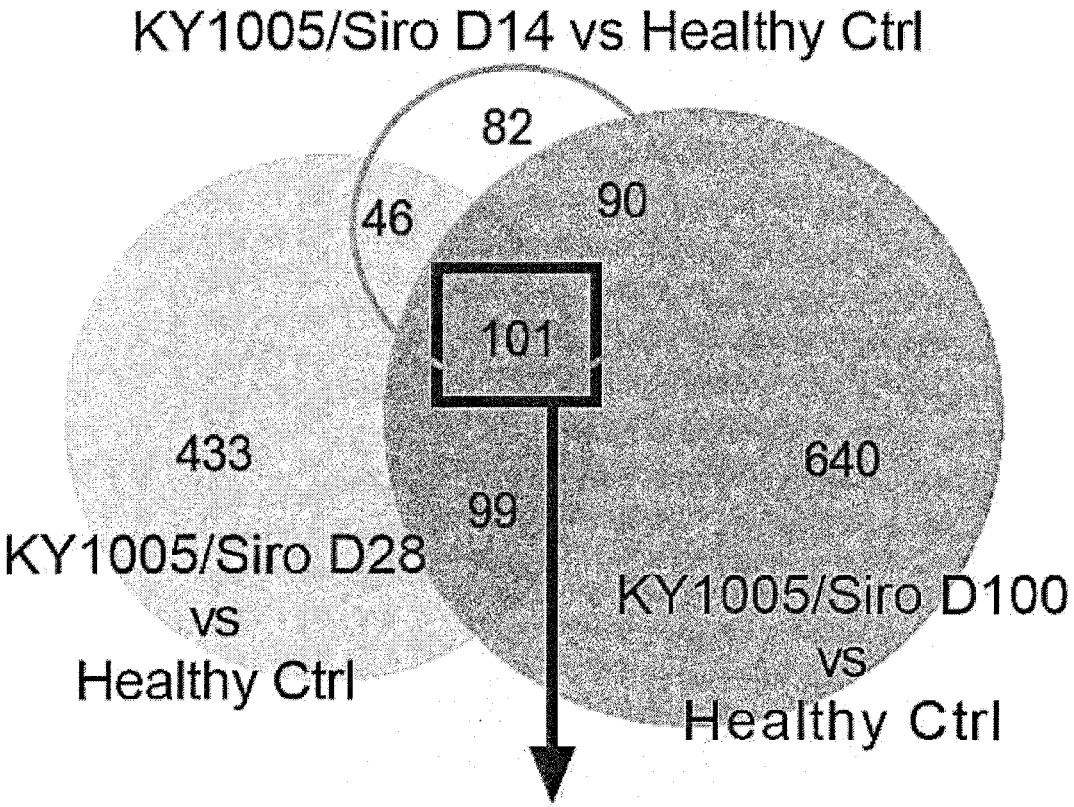


Figure 15B



Pathway'analysis	
Pathway	Benjamini p value
R-HSA-909733: IFN alpha/beta signaling	$7.0*10^{-3}$
HSA04630: JAK/STAT signaling	$3.6*10^{-2}$

Figure 15C

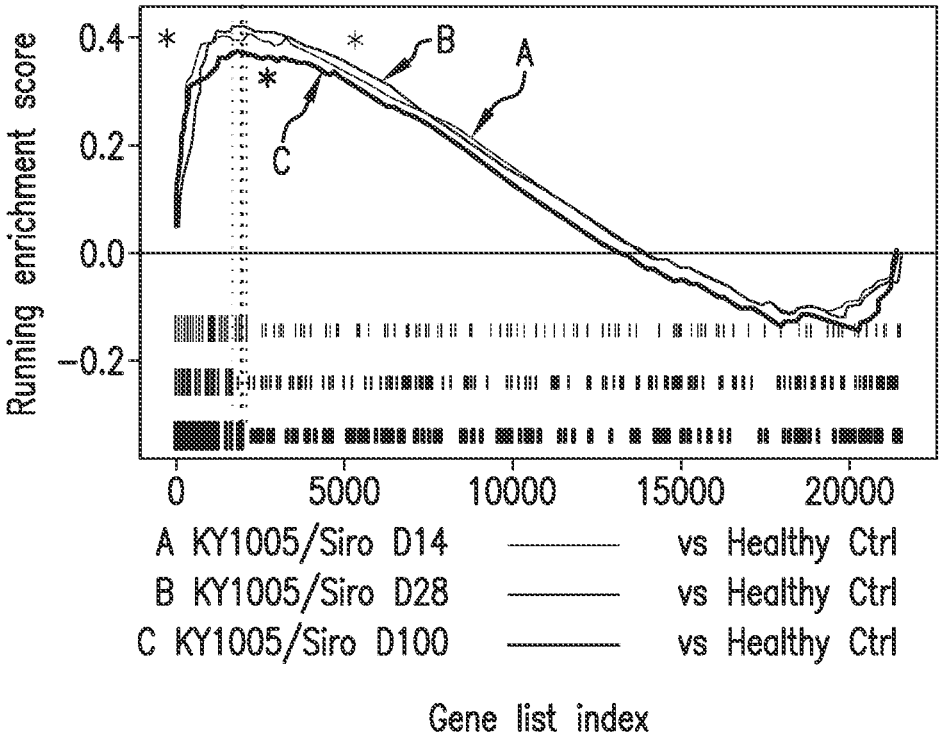


Figure 15D

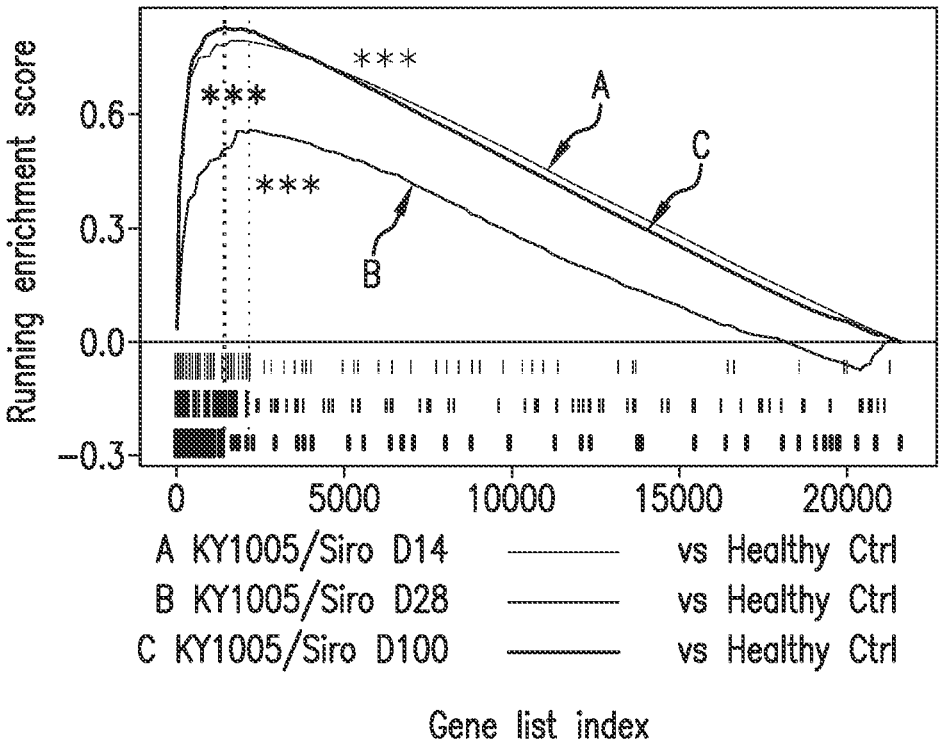


Figure 15E

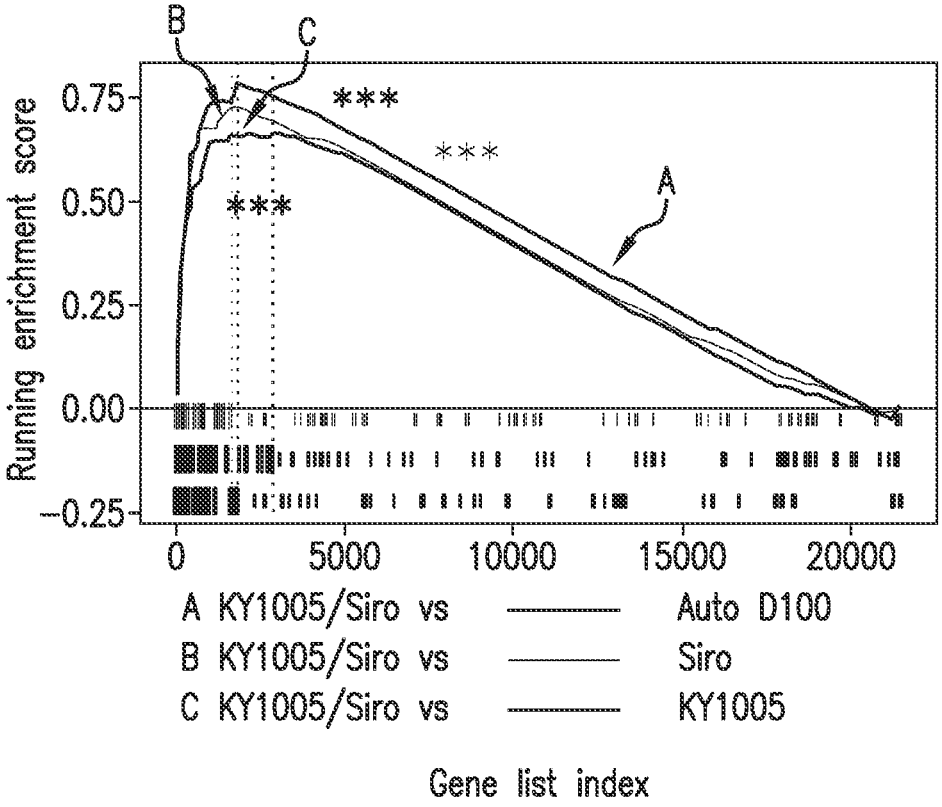

B
C
A
***
***
***
Running enrichment score
0.75
0.50
0.25
0.00
−0.25
0
5000
10000
15000
20000
A KY1005/Siro vs Auto D100
B KY1005/Siro vs Siro
C KY1005/Siro vs KY1005
Gene list index

Figure 16A

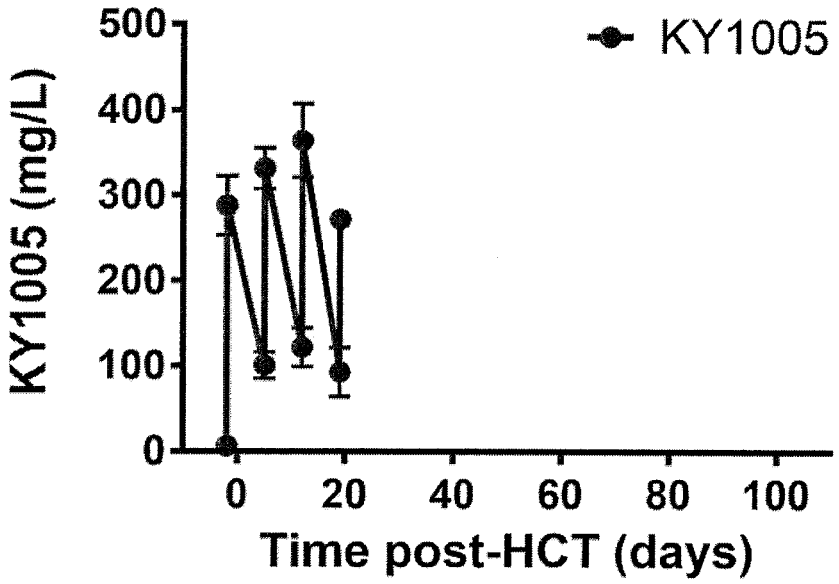
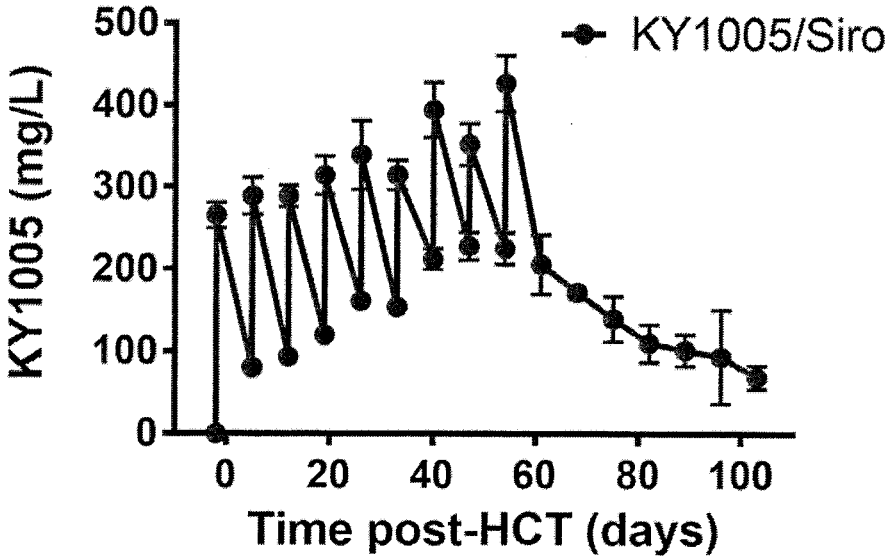


Figure 16B



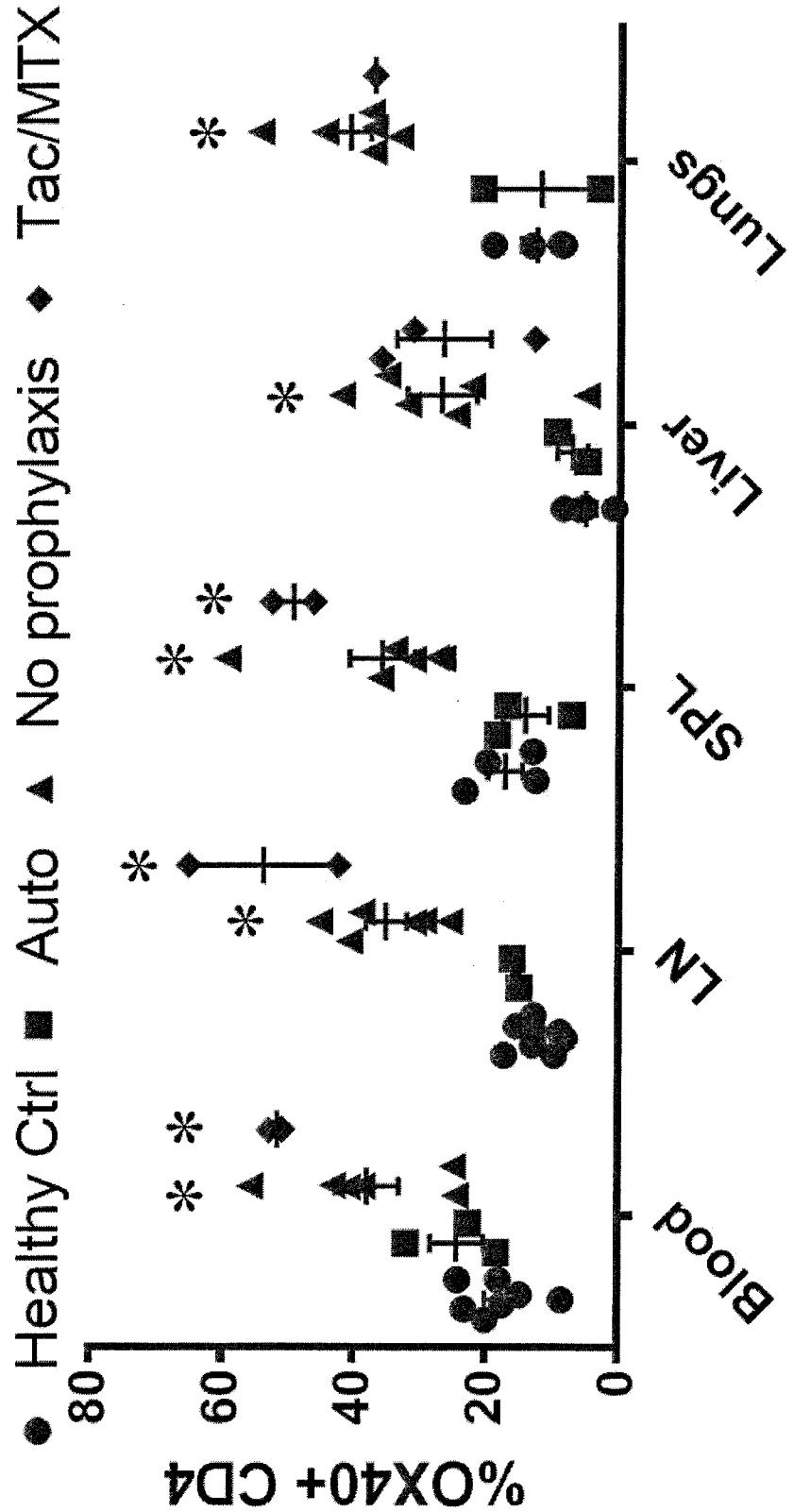

Healthy Ctrl
Auto
No prophylaxis
Tac/MTX
%OX40+ CD4
0
20
40
60
80
Blood
LN
SPL
Liver
Lungs

Figure 17A

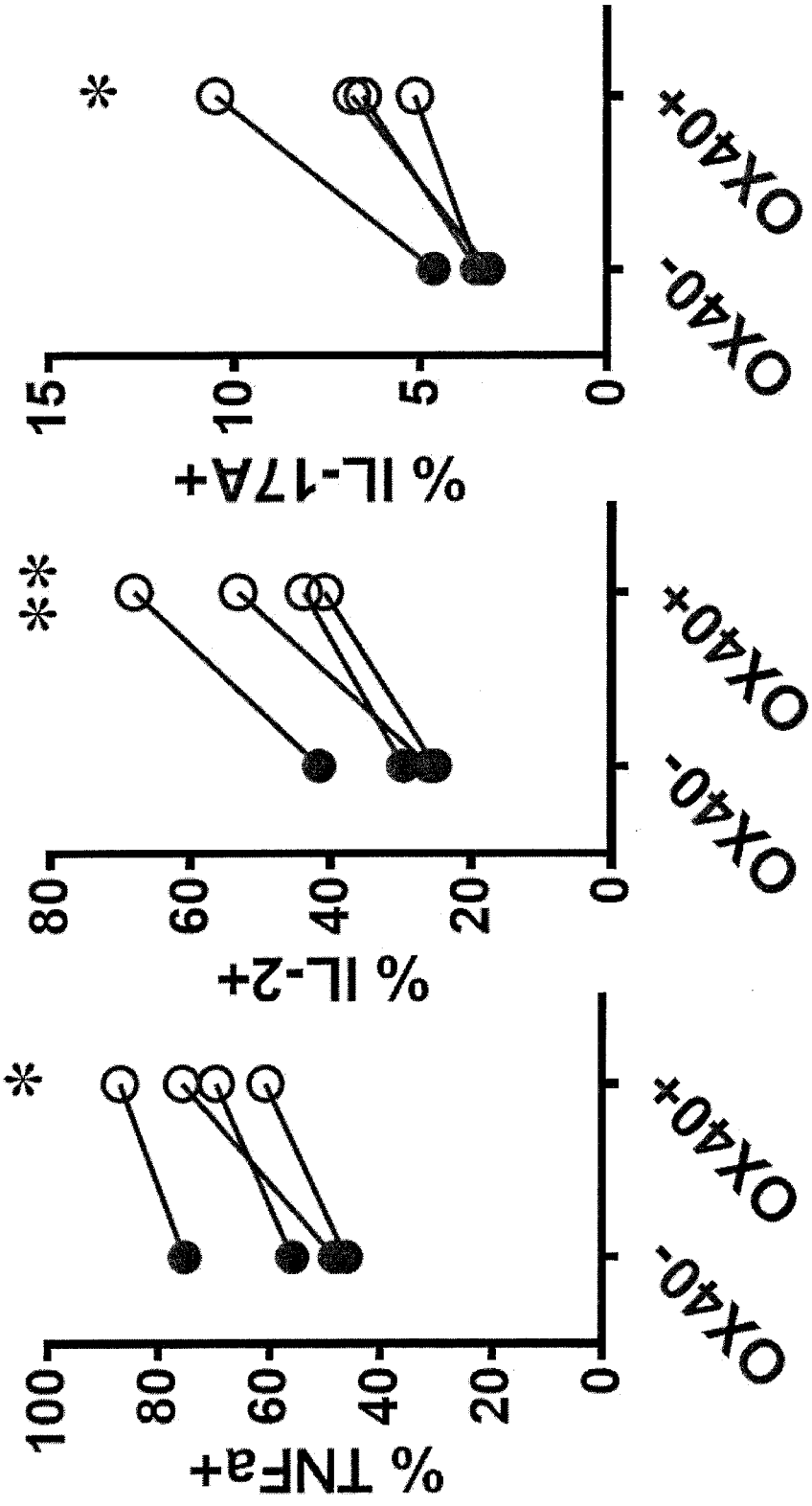

CD4
% TNFa+
100
80
60
40
20
0
*
OX40-
OX40+
% IL-2+
80
60
40
20
0
**
OX40-
OX40+
% IL-17A+
15
10
5
0
*
OX40-
OX40+

Figure 17B

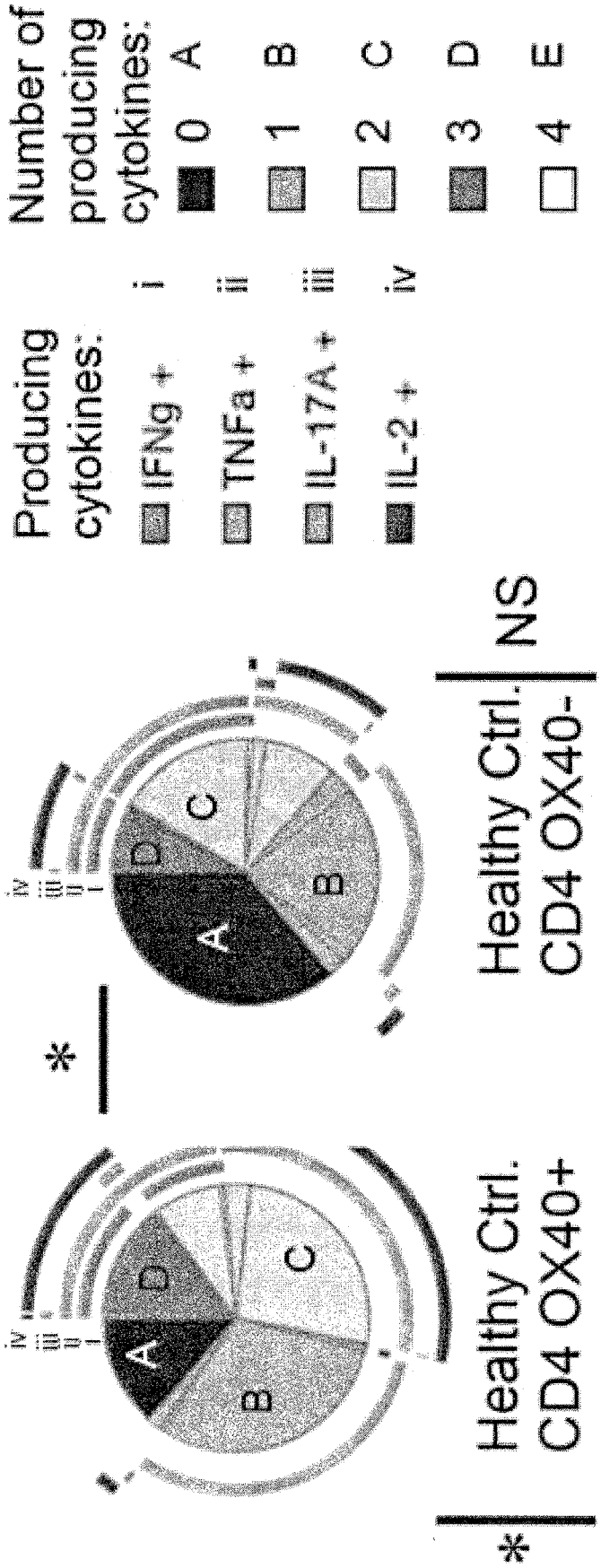

Number of producing cytokines:
0 A
1 B
2 C
3 D
4 E
Producing cytokines:
i IFNg +
ii TNFa +
iii IL-17A +
iv IL-2 +
Healthy Ctrl. CD4 OX40+
Healthy Ctrl. CD4 OX40-
NS
*
*

Figure 17C

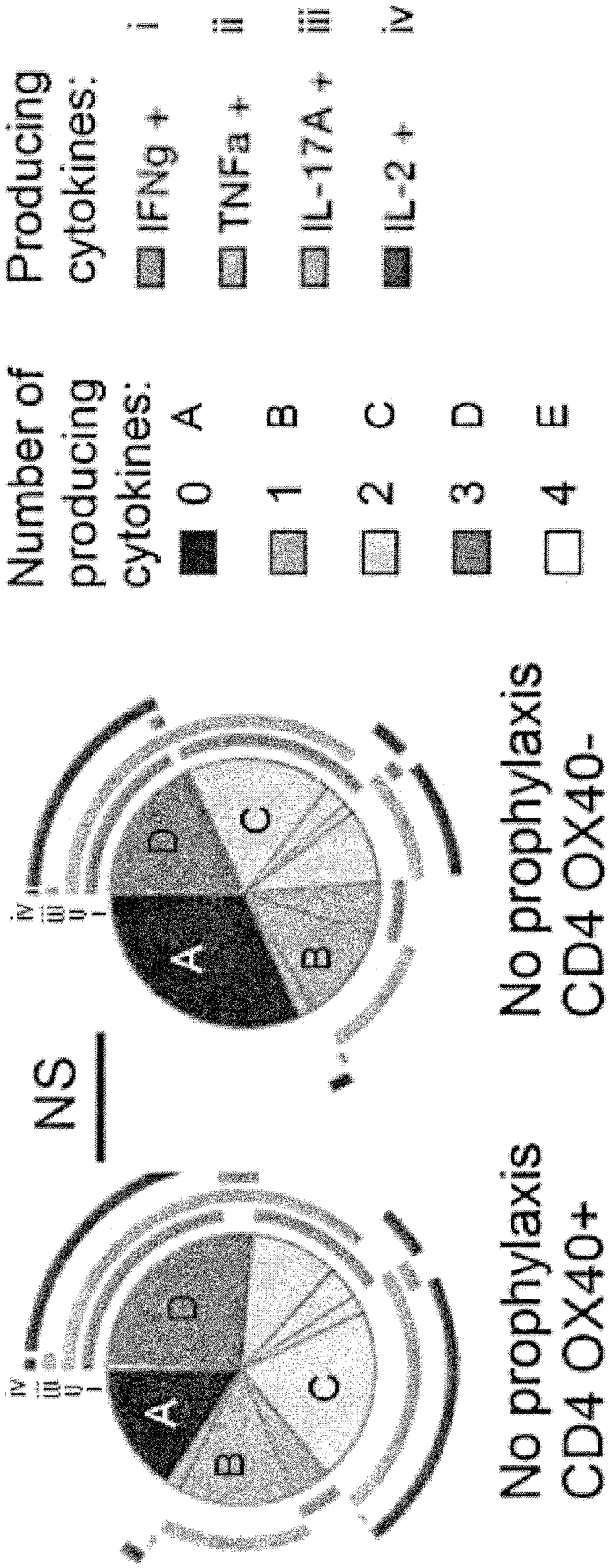


Figure 17C continued

Figure 18

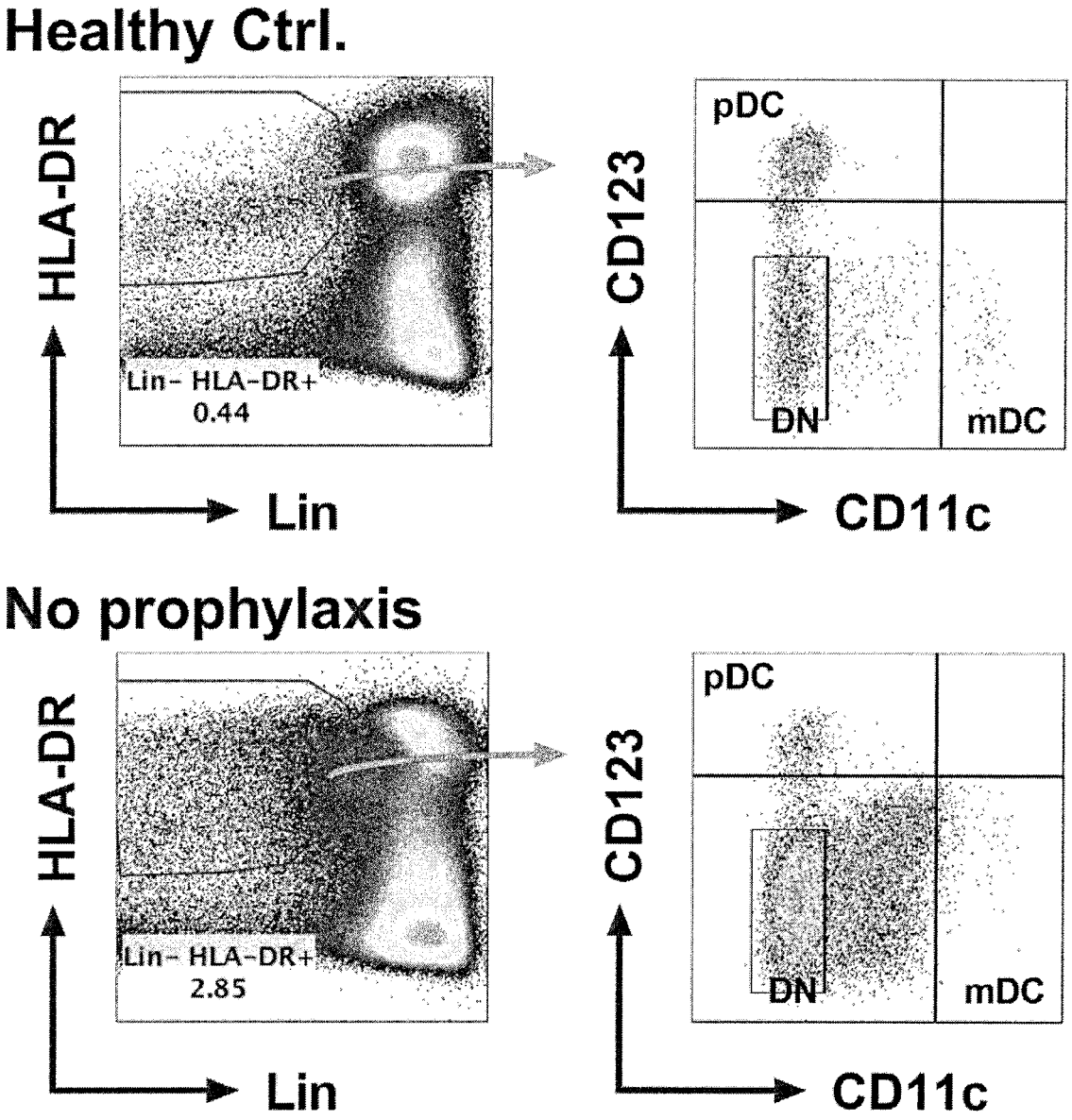

Healthy Ctrl.
HLA-DR
Lin- HLA-DR+
0.44
Lin
CD123
pDC
DN
mDC
CD11c
No prophylaxis
HLA-DR
Lin- HLA-DR+
2.85
Lin
CD123
pDC
DN
mDC
CD11c

Figure 19A

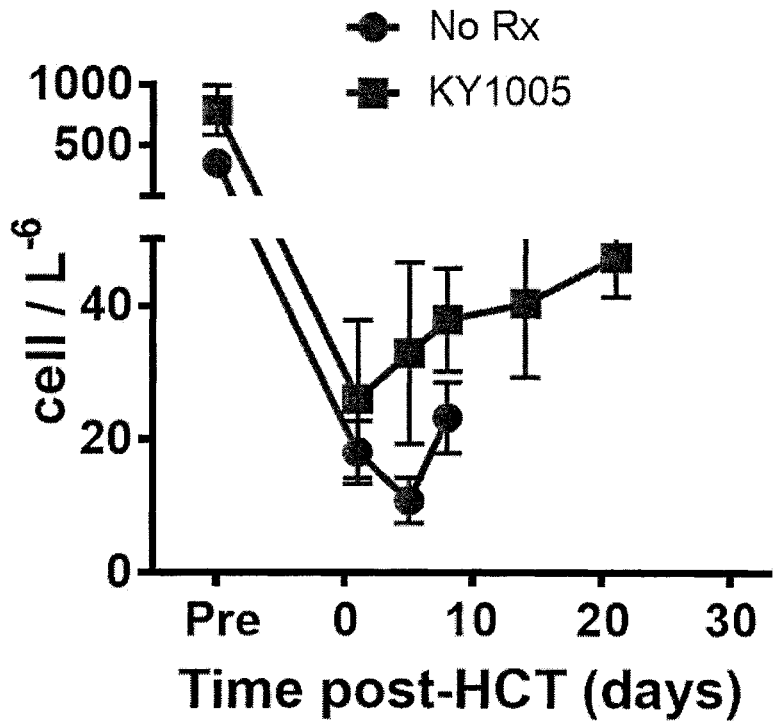


Figure 19B

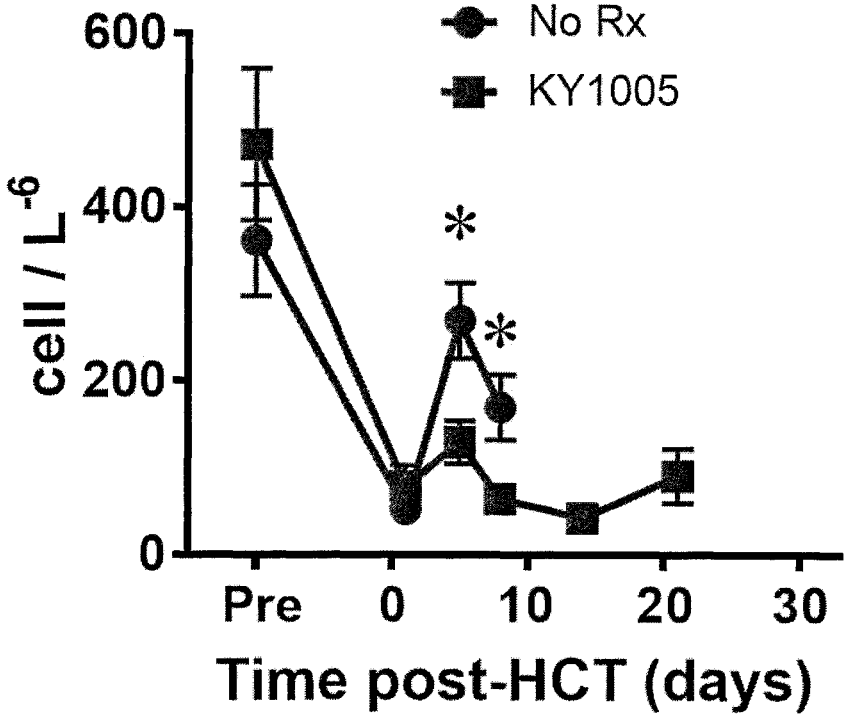


Figure 19C

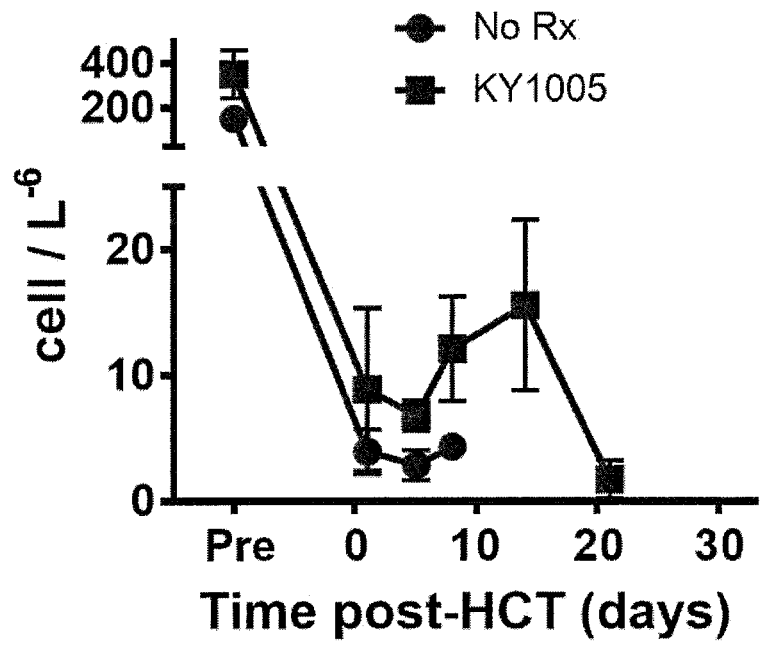


Figure 19D

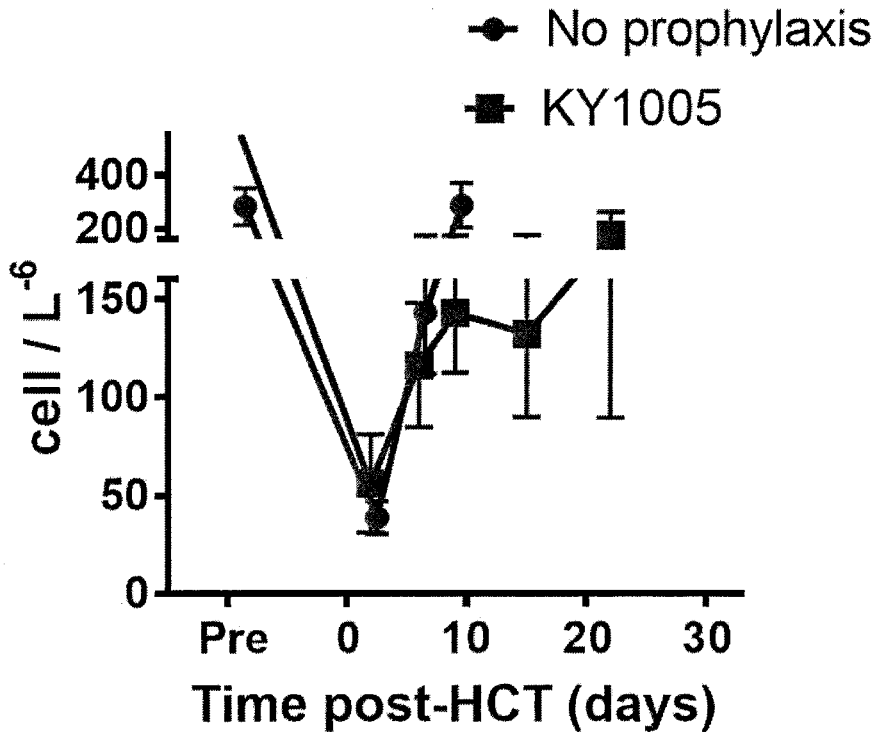


Figure 19D-1

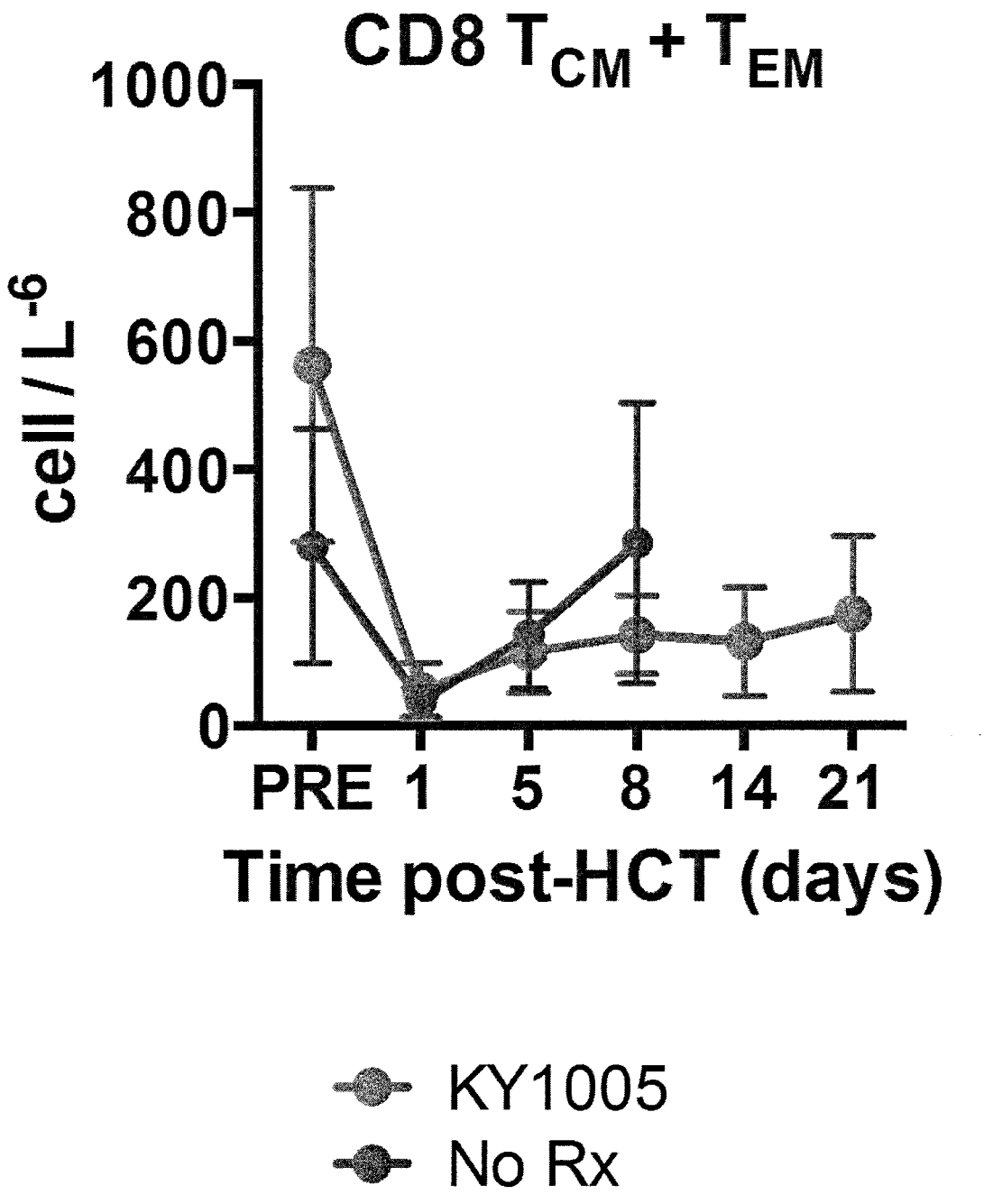

CD8 T_{CM} + T_{EM}
1000
800
600
400
200
0
cell / L-6
PRE
1
5
8
14
21
Time post-HCT (days)
KY1005
No Rx

Figure 19E

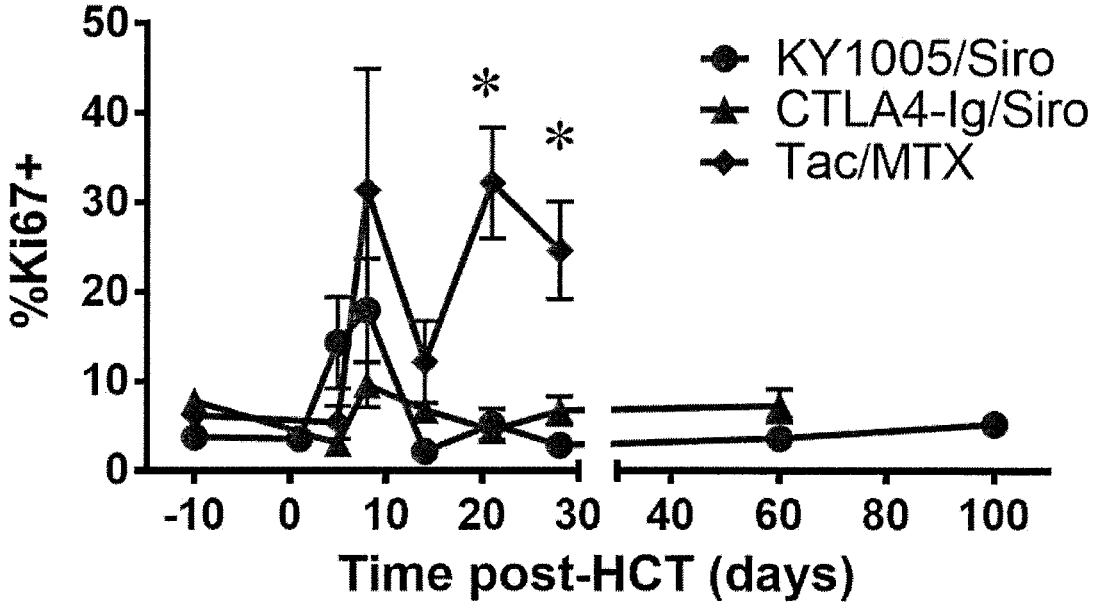
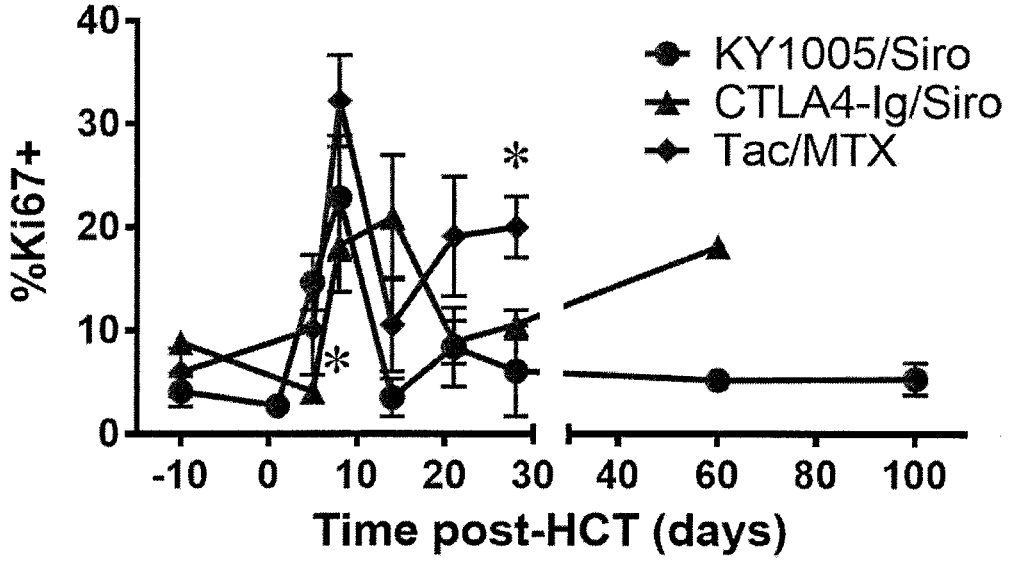


Figure 19F



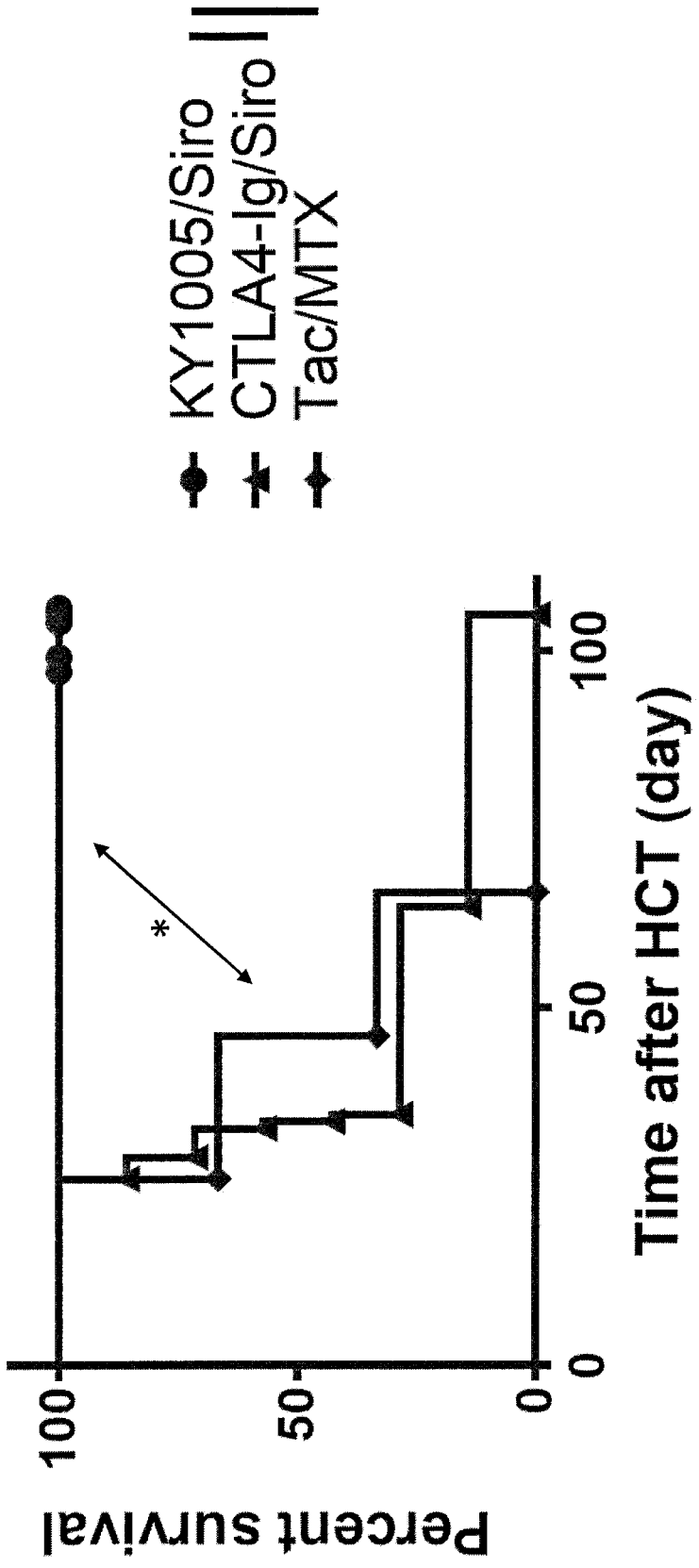
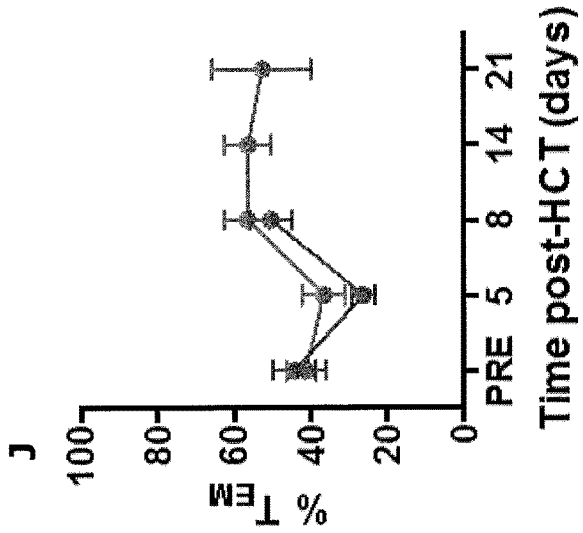
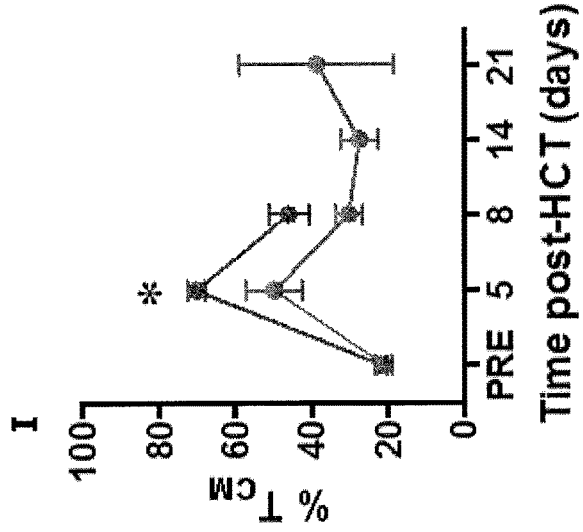

KY1005/Siro
CTLA4-Ig/Siro
Tac/MTX
Percent survival
100
50
0
0
50
100
Time after HCT (day)
*

Figure 19G





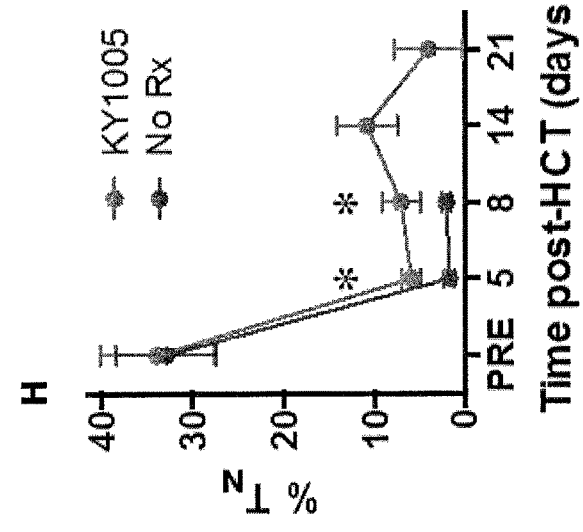
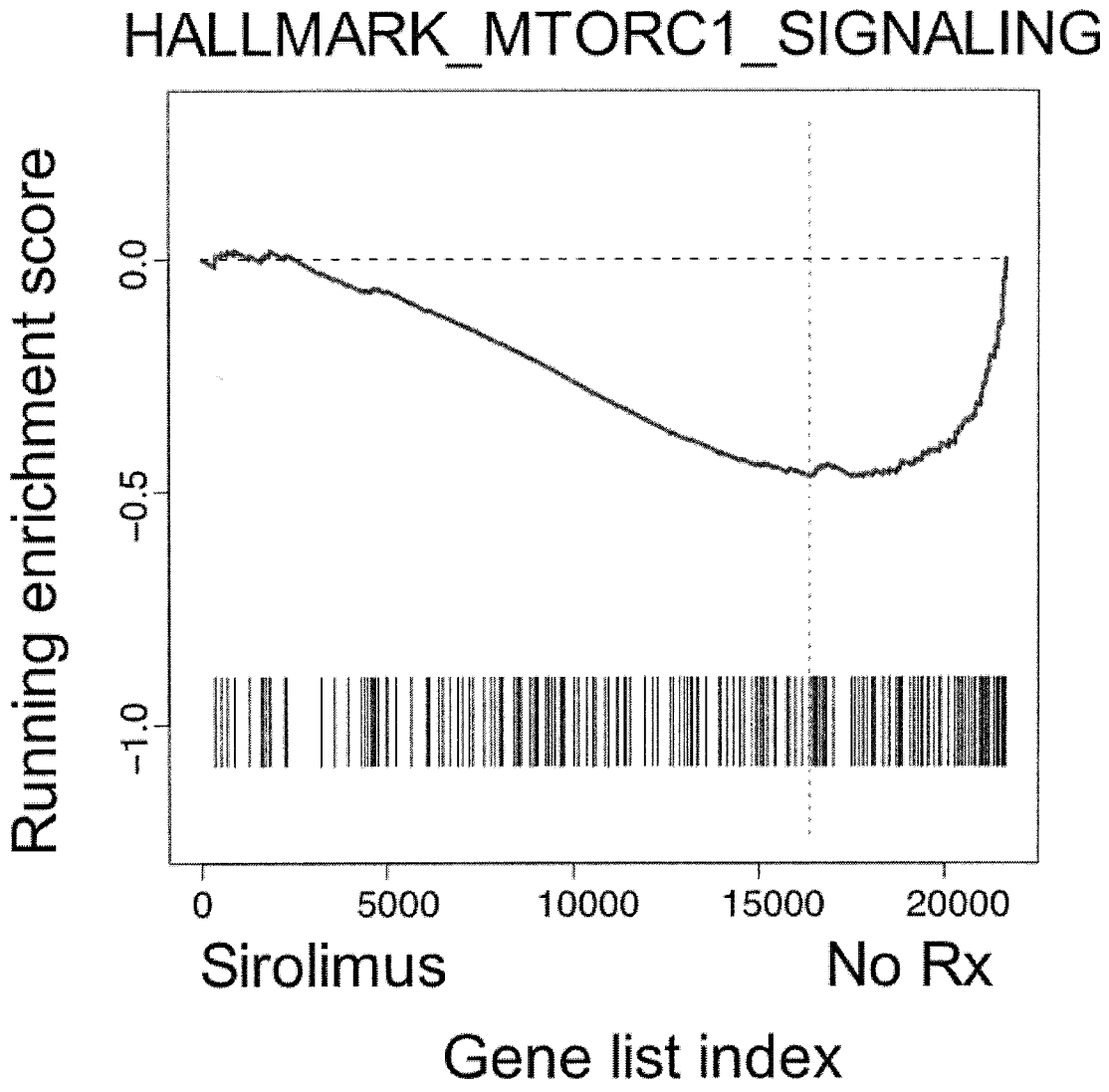


Figure 19 continued

Figure 20


HALLMARK_MTORC1_SIGNALING
Running enrichment score
0.0
−0.5
−1.0
0
5000
10000
15000
20000
Sirolimus
No Rx
Gene list index

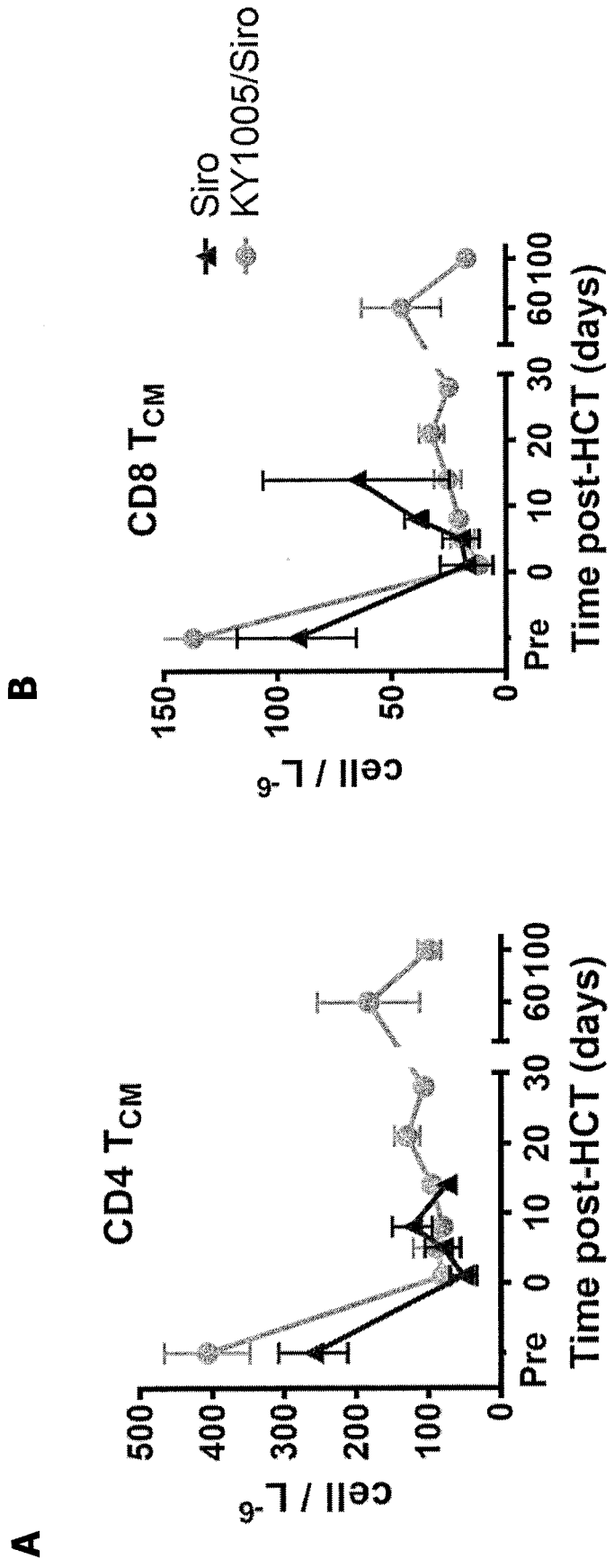

A
CD4 T_{CM}
cell / L^{-6}
500
400
300
200
100
0
Pre 0 10 20 30 60 100
Time post-HCT (days)
B
CD8 T_{CM}
Siro
KY1005/Siro
cell / L^{-6}
150
100
50
0
Pre 0 10 20 30 60 100
Time post-HCT (days)

Figure 21

ANTIBODIES, COMBINATIONS COMPRISING ANTIBODIES, BIOMARKERS, USES AND METHODS

This application is a national stage filing under 35 U.S.C. § 371 of International Application No. PCT/EP2017/078202, filed on Nov. 3, 2017, which claims priority of British Patent Application No. 1618529.0, filed Nov. 3, 2016, British Patent Application No. 1702965.3, filed Feb. 23, 2017, British Patent Application No. 1706639.0, filed Apr. 26, 2017, British Patent Application No. 1710953.9, filed Jul. 7, 2017, and British Patent Application No. 1713147.5, filed Aug. 16, 2017. The contents of these applications are each incorporated herein by reference.

The present invention relates to combinations comprising anti-human OX40 or anti-human OX40L antibodies, new medical uses and methods.

BACKGROUND

OX40 ligand (OX40L) is a TNF family member; a 34 kDa type II transmembrane protein. The crystallized complex of human OX40 and OX40L is a trimeric configuration of one OX40L (trimer) and three OX40 monomers. The human extracellular domain is 42% homologous to mouse OX40L.

OX40L is not constitutively expressed but can be induced on professional APCs such as B-cells, dendritic cells (DCs) and macrophages. Other cell types such as Langerhans cells, endothelial cells, smooth muscle cells, mast cells and natural killer (NK) cells can be induced to express OX40L T-cells can also express OX40L. The OX40L receptor, OX40, is expressed on activated T-cells ($CD4^+$ and $CD8^+$ T-cells, Th2, Th1 and Th17 cells) and $CD4^+Foxp3^+$ cells, even in the absence of activation.

The interaction between OX40 and OX40L occurs during the T-cell-DC interaction 2 or 3 days after antigen recognition. After leaving DCs, the OX40-expressing T-cell may interact with an OX40L-expressing cell other than a DC and receive an OX40 signal from this cell, which may provide essential signals for the generation of memory T-cells, the enhancement of Th2 response and the prolongation of the inflammatory responses. OX40 signals into responder T-cells render them resistant to Treg mediated suppression.

Graft versus host disease is a major cause of mortality following allogeneic bone marrow treatment. In the acute version of the disease, mature T-cells present in the bone marrow graft recognise the donor tissue as foreign in an environment of damaged tissue, which, via host APC's cause the activation and proliferation of the donor T-cells, with subsequent T-cell migration into the liver, spleen, gut, skin and lungs, causing tissue damage by the CTL effector response and inflammatory cytokine/chemokne release. Onset for acute disease is usually within the first 100 days post transplantation (Hill-Ferrara, Blood May 1, 2000 vol. 95 no. 9 2754-275, Reddy-Ferrara Blood, Volume 17, Issue 4, December 2003).

Chronic GvHD usually appears 100 days post transplantation and several factors are thought to be involved, including thymic damage caused by prior acute GvHD which results in a reduced clearance of pathogenic T-cells (Zhang et a, Sep. 1, 2007 vol. 179 no. 5 3305-3314), up-regulation of TGF-β, which causes fibrosis (McCormick et al J Immuno, Nov. 15, 1999 vol. 163 no. 10 5693-5699), and a B-cell component driven by elevated B-Cell activating factor (BAFF) (Sarantopoulos eta, Cin Cancer Res Oct. 15, 2007 13; 6107) as well as auto-antibodies against platelet derived growth factor receptor (Svegllati et al, Blood Jul. 1, 2007 vol. 110 no. 1 237-241).

Clinical studies have shown that OX40 is up-regulated in both acute (Morante et al, Clinical and Experimental Immunology, 145:36-43) and chronic (Kotani et al, Blood Nov. 15, 2001 vol. 98 no. 10 3162-3164) GvHD. Administration of an antagonistic anti-OX40L enhanced survival in a lethal acute mouse model of GvHD, with a 70% survival in the treated group compared to the untreated who all died by day 43 (Tsukada et al, Blood, 1 Apr. 2000, Volume 95, Number 7) whereas treatment with an agonistic anti-OX40 Ab accelerated the disease and mortality (Blazar et al Blood May 1, 2003 vol. 101 no. 9 3741-3748). Blockade of the OX40-OX40L interaction has been shown to be efficacious in several other inflammatory diseases, with anti-OX40L Ab being used to treat a mouse model of colitis (Totsuka et al., AP-GI Apr. 1, 2003 vol. 284 no. 4 G595-G603), and that an anti-OX40L Ab could block the development of diabetes in NOD mice (Pakala et al European Journal of Immunology Volume 34, Issue 11, pages 3039-3046, November 2004).

REFERENCES

Lamb, L. S., Abhyankar, S. A., Hazlett, L., O'Neal, W., Folk, R. S., Vogt, S., Parrish, R. S., Bridges, K., Henslee-Downey, P. J. and Gee, A. P. (1999), Expression of CD134 (OX-40) on T-cells during the first 100 days following allogeneic bone marrow transplantation as a marker for lymphocyte activation and therapy-resistant graft-versus-host disease. Cytonetry, 38: 238-243.

Xupeng Ge, Julia Brown, Megan Sykes, Vassiliki A. Boussiotis, CD134-Alodepletion Allows Selective Elimination of Alloreactive Human T-cells without Loss of Virus-Specific and Leukemia-Specific Effectors, Biology of Blood and Marrow Transplantation, Volume 14, Issue 5, May 2008, Pages 518-530.

Naoto Ishii, Takeshi Takahashi, Pejman Soroosh, Kazuo Sugamura, Chapter 3—OX40-OX40 Ligand Interaction in T-Cell-Mediated Immunity and Immunopathology, In: Frederick W. Alt, Editor(s), Advances in Immunology, Academic Press, 2010, Volume 105, Pages 63-98.

Croft, M., So, T., Duan, W. and Soroosh, P. (2009), The significance of OX40 and OX40L to T-cell biology and immune disease. Immunological Reviews, 229: 173-191.

SUMMARY OF THE INVENTION

The invention provides anti-human OX40L (hOX40L) antibodies and fragments and novel medical applications for treating or preventing hOX40L-mediated diseases or conditions in humans. To this end, the invention provides:—

In a First Configuration

An antibody or a fragment thereof that specifically binds to hOX40L for treating or preventing a hOX40L-mediated disease or condition in a human in a method wherein the antibody or fragment is administered to said human, wherein the antibody or fragment is for treating or preventing said hOX40L-mediated disease or condition by decreasing one, more or all of

a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
b. the proliferation of leukocytes of the human; and
c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

In a Second Configuration

An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with an antibody selected from the group consisting of 02D10, 10A07, 09H04 and 19H01.

In a Third Configuration

Use of an antibody or a fragment thereof, that specifically binds to hOX40L in the manufacture of a medicament for administration to a human, for treating or preventing a hOX40L-mediated disease or condition in the human by decreasing one, more or all of

a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
b. the proliferation of leukocytes of the human; and
c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

In a Fourth Configuration

A method of treating or preventing a hOX40L-mediated disease or condition in a human by decreasing one, more or all of

a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
b. the proliferation of leukocytes of the human; and
c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L;
wherein the method comprises administering to said human a therapeutically effective amount of an antibody or fragment that specifically binds to hOX40L.

In a Fifth Configuration

An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY, wherein X is any amino acid.

In a Sixth Configuration

An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises the HCDR3 sequence of SEQ ID NO:40 or 46 or the HCDR3 sequence of SEQ ID NO:40 or 46 comprising less than 5 amino acid substitutions.

In a Seventh Configuration

A human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6, which specifically binds to hOX40L for treating or preventing an autoimmune disease selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection.

In an Eighth Configuration

Use of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6, which specifically binds to hOX40L in the manufacture of a medicament for administration to a human for treating or preventing a hOX40L mediated disease or condition in the human selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection.

In a Ninth Configuration

A method of treating or preventing a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection, comprising administering to said human a therapeutically effective amount of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6, which specifically binds to hOX40L, wherein the hOX40L mediated disease or condition is thereby treated or prevented.

The invention also provides pharmaceutical compositions, kits, nucleic acids, vectors and hosts.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**: Profiling of fully human recombinant anti-OX40L antibodies in HTRF Ligand/Receptor Neutralisation assay. Data shown is representative of three repeat experiments.

FIG. **2**: Determining effect of anti-OX40L antibodies in allogeneic PBMC/T Mixed Lymphocyte Reaction. Data shown is from three independent donor pairings where it is assumed each donor is a different individual.

FIG. **3**: Expansion of Tscm cells following allogeneic HCT. Plots are gated on $CD4^+CD45RA^+CCR7^+$ T-cells.

FIG. **4**: OX40L blockade controls expansion of $CD4^+$ Tscm cells while preserving $CD4^+$ T naïve cells following allogeneic HCT. Absolute numbers of peripheral blood $CD4^+$ Tscm (left) and T naïve (right) following allogeneic HCT in control animal and 2D10 IgG4-PE treated animals.

FIG. **5**: OX40 expression on naïve $CD4^+$ T and memory stem T-cells in a representative animal following allogeneic HCT. Left and middle FACS plots were gated on $CD3^+$ $CD4^+CD45RA^+CCR7^+$. The histogram on the right shows OX40 expression in different T-cell subsets of CD4+ T-cells: Naïve ($CD45RA^+CCR7^+CD95^-$), memory stem (SCM: $CD45RA^+CCR7^+CD95$), central memory (CM: $CD45RA^-CCR7^+$), effector memory (EM: $CD45RA^-CCR7^-$) and terminally differentiated effector-memory cells re-expressing CD45RA (TEMRA: $CD45RA^+CCR7^-$).

FIG. **6**A: Effects of OX40L blockade on SCM $CD4^+$ T-cells. Datapoints for 02D10 Ig4PE are shown by circles (●), rapamycin by filled squares (■) and tacrolimus plus methotrexate (Tac/MTX) by open squares (□).

FIG. **6**B: Effects of OX40L blockade on SCM $CD8^+$ T-cells. Datapoints for 02D10 Ig4PE are shown by circles (●), rapamycin by filled squares (■) and Tac/MTX by unfilled squares (□).

FIG. **7**A: Kaplan-Meier survival curve for rhesus monkey recipients of hematopoietic stem cell transplants derived from the peripheral blood of haploidentical half-sibling donors. Results are shown for animals that did not receive post-transplant prophylactic therapy (No-treatment control; median survival time, MST=8 days; n=4), and those receiving rapamycin monotherapy (MST=17 days; n=4), 2D10 monotherapy (MST=19 days; n=4), or rapamycin plus 2D10 (MST>82 days; n=3). Note that animals 2 and 3 indicated on the figure were on-study at the time of drafting; neither showed signs of GVHD at Day 82 or Day 41 post-transplant, respectively. Asterix * for the no treatment control and rapamycin monotherapy groups is data taken from Furlan et al., 2015, Science Translational Medicine, vol 7 (315), 315ra191.

FIGS. **7**B & **7**C: The combined clinical score (FIG. **7**B), as detailed in Example 11, and survival (FIG. **7**C) of recipients after allo-HCT in the unprophylaxed cohort

(n=11, No Rx; ■) and in cohorts prophylaxed with KY1005 (n=4, ▼), Sirolimus (n=6, Siro; ▲) and KY1005/Sirolimus (n=5, KY1005/Siro; ●). Differences between clinical scores were analysed using the Holm-Sidak multiple comparisons t-test, *p<0.05 (FIG. 7B). Bars indicate significantly different groups with p<0.05 using the long-rank method, **p>0.01 (FIG. 7C).

FIG. 7D: The combined GVHD pathology score (summarising liver, colon and skin) of untreated recipients following autologous (Auto; n=5) or unprophylaxed allogeneic HCT (No Rx; n=8), or animals prophylaxed with KY1005 (n=4), Sirolimus (Siro; n=5) or KY105/Sirolimus (KY1005/Siro; n=5). Histopathologic scorings were performed at the time of terminal analysis in a blinded manner. Statistical analysis was performed using one-way ANOVA with Fisher's LSD post-test for comparison between individual groups.

FIGS. 7E & 7F: Representative flow cytometry plots showing CellTrace Dilution profiles of $CD3^+$ (either $CD4^+$ or $CD8^+$) $CD14/CD20^-$ T-cells from donors (Figure E) and recipients at terminal analysis (Figure F) stimulated by donor PBMC (left), recipient PBMC (center) or third-party healthy control PBMC (right) after ex-vivo culture for 7 days. Inset numbers in FIGS. 7E & 7F indicate the percentage of cells undergoing ≥1 divisions.

FIG. 7G: The calculated Proliferation Indexes from recipient MLR cultures (Grey symbols) were normalised to the values of the Proliferation Indexes of the corresponding donor samples (Black symbols), and then plotted in pairwise fashion. The paired t-test was used for statistical analysis. *p<0.05, NS—not significant.

FIGS. 8A-8D: Peripheral blood mononuclear cells were isolated at different time points by Ficoll-Paque gradient and then were stained for cell surface markers (CD3, CD4, CD8) followed by fixation/permeabilisation (using BD Cytofix/Cytoperm kit) and intracellular staining for Ki-67. Plots show Ki-67 expression in NHP peripheral blood $CD4^+$ (FIG. 8A) and $CD8^+$ (FIG. 8B) T-cells before (pre-HCT) and following allo-HCT in recipients being untreated (No Rx) or treated with OX40L antibody. Plots show Ki-67 expression in NHP peripheral blood bulk $CD4^+$ (FIG. 8C) and $CD8^+$ (FIG. 8D) T-cells before (pre-HCT) and following allo-HCT in recipients treated with rapamycin and with a combination of rapamycin and anti-OX40L antibody. Statistical analysis was performed using Holm-Sidak multiple-comparison post-test. *p<0.05.

FIG. 8E: Impact of KY1005 on T-cell expansion and cytokine secretion after HCT. Experimental schema detailing the HCT protocol and KY1005-based GVHD immunoprophylaxis regimen used in this study.

FIGS. 8F & 8G: Ki67 expression in peripheral blood $CD4^+$ (FIG. 8F) and $CD8^+$ (FIG. 8G) T-cells before and after allogeneic HCT in recipients without GVHD immunoprophylaxis (n=7, No Rx; ■) or prophylaxed with KY1005 (n=4, ●). Statistical analysis was performed using Holm-Sidak multiple-comparison t-test, *p<0.05.

FIGS. 8H & 8I: OX40 expression on peripheral blood $CD4^+$ T-cells was quantified before and following allogeneic HCT in experiments shown in (FIGS. 8F and 8G), and the percentages of $OX40^+CD4^+$ T-cells (FIG. 8H) and the absolute numbers of $OX40^+$ and $OX40\text{-}CD4^+$ T-cells (FIG. 8I) were quantified on day 7 after allo-HCT in untreated (n=7, No Rx; ■) and prophylaxed with KY1005 (n=4, KY1005; ●) cohorts. Statistical analysis was performed using Holm-Sidak multiple-comparison t-test (on FIG. 8H) or Student's t-test (on FIG. 8I), *p<0.05.

FIGS. 8J-8M: The relative numbers of $CD28^+CD95^-$ Naïve (T_N), $CD28^+CD95^+$ central memory (T_{CM}) $CD4^+$ (FIGS. 8J and 8K) and $CD8^+$ (FIGS. 8L and 8M) T-cells in peripheral blood before and at different time points following allo-HCT in recipients without immunoprophylaxis (n=7, No Rx; ■) or prophylaxed with KY1005 (n=4, ●). Statistical analysis was performed using Holm-Sidak multiple-comparison t-test, *p<0.05, NS—not significant.

FIG. 8N: Peripheral blood mononuclear cells isolated from allo-HCT recipients without immunoprophylaxis (n=7, No Rx; ■) or prophylaxed with KY1005 (n=4, ●) were activated with PMA/Ionomycin and cultured 4 hours as detailed in Example 11, then were stained for CD3, CD4, CD8, CD14, CD20, OX40, IFNγ, TNFα, IL-2 and IL-17A (FIG. 8N). Numbers of T-cells producing the indicated cytokines were quantified in $OX40^+CD4^+$ T-cells subset. Statistical analysis was performed using Student's t-test, *p<0.05.

FIG. 8O: Spleen cells were isolated from healthy, immunologically-naïve Rhesus macaques (n=5, Healthy Ctrl, ▲) or from allo-HCT recipients either without immunoprophylaxis (n=7, No Rx; ■) or prophylaxed with KY1005 (n=4, ●) at the time of terminal analysis (FIG. 8O). The percentage of $OX40^+$ cells was quantified in Treg ($CD25^+CD127^-FoxP3^+$) and Tconv ($CD25^-CD12^+$) $CD4^+$ T-cell subsets and shown as the percentage of corresponding parent population (either Treg or Tconv, respectively). Statistical analysis was performed using Student's t-test. *p<0.05; **p<0.01, NS—not significant.

FIG. 8O-1: Spleen cells were isolated from healthy, immunologically-naïve Rhesus macaques (n=5, Healthy Ctrl, ●) or from allo-HCT recipients either without immunoprophylaxis (n=7, No Rx; ◍) or prophylaxed with KY1005 (n=4, ◍) at the time of terminal analysis. The percentage of $OX40^+$ cells was quantified in Treg ($CD25^+$ CD127-$FoxP3^+$) and Tconv ($CD25^-CD127^+$) $CD4^+$ T-cell subsets each as a % of total $CD4^+$ T-cells. Percentage of total $CD4^+$ T-cells statistical analysis was performed using Student's t-test. **p<0.01.

FIG. 8O-2: PBMC were isolated from healthy, immunologically-naïve Rhesus macaques (Healthy Ctrl, ▲) or from allo-HCT recipients either without immunoprophylaxis (No Rx; ■) or prophylaxed with KY1005 (●) at the time of terminal analysis. The percentage of $OX40^+$ cells was quantified in Treg ($CD25^+CD127^-FoxP3^+$) and Tconv ($CD25^-$ $CD127^+$) CD4 T-cell subsets and shown as the percentage of corresponding parent population (either Treg or Tconv, respectively). Statistical analysis was performed using Student's t-test. *p<0.05; **p<0.01, NS—not significant.

FIG. 8P: Experimental schema detailing the HCT protocol, sirolimus and KY1005/Sirolimus-based GVHD immunoprophylaxis regimens used in this study (FIG. 8P).

FIGS. 8Q & 8R: Ki67 expression in NHP peripheral blood $CD4^+$ (FIG. 8Q) and $CD8^+$ (FIG. 8R) T-cells after allo-HCT in recipients prophylaxed with Sirolimus (n=10, Siro; ■) and KY1005/Sirolimus (n=5, KY1005/Siro; ●). Statistical analysis was performed using the Holm-Sidak multiple-comparison t-test, *p<0.05.

FIG. 8S: The relative (FIG. 8S left panels) and absolute (FIG. 8S right panels) numbers of $CD28^+CD95^-$ Naïve (T_N) $CD4^+$ (top) and $CD8^+$ (bottom) T-cells in the peripheral blood measured longitudinally after allo-HCT in recipients prophylaxed with Sirolimus (n=10, Siro; ■) or KY1005/Sirolimus (n=5, KY1005/Siro; ●). Statistical analysis was performed using the Holm-Sidak multiple-comparison t-test, *p<0.05.

FIGS. **8**T & **8**U: The relative numbers of $CD28^+CD95^+$ central memory (T_{CM}) $CD4^+$ (FIG. **8**T) and $CD8^+$ (FIG. **8**U) T-cells in the peripheral blood of allo-HCT recipients prophylaxed with Sirolimus (Siro; ■) or KY1005/Sirolimus (KY1005/Siro; ●).

FIGS. **8**V & **8**W: Representative GSEA plots (FIGS. **8**V and **8**W) performed as previously described (Subramanian A, et al., Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles, Proc Natl Acad Sci USA, 102, 15545-15550 (2005)) showing naïve T-cell-related gene sets over-represented in KY1005/Sirolimus (n=4) versus sirolimus (n=4) and KY1005/Sirolimus versus KY1005 (n=3, *FDR q<0.05, **FDR q<0.01, ***FDR q<0.001.GSE11057 naïve vs memory $CD4^+$ T-cell UP (FIG. **8**V) and GSE9650 Naïve vs EFF $CD8^+$ T-cell UP (FIG. **8**W). All depicted gene sets are enriched in KY1005/Sirolimus cohort with FDR<0.05.

FIG. **9**: Peripheral blood mononuclear cells were isolated prior (pre-HCT) and during terminal analysis following allogeneic HCT without immunoprophylaxis (No Rx), or treatment with rapamycin, or treatment with anti-OX40L antibody, or treatment with a combination of anti-OX40L antibody and rapamycin by Ficoll-Paque gradient and then were stained for cell surface markers (CD3, CD4, CD25 and CD127) followed by fixation/permeabilisation (using BioLegend FoxP3 kit) and intracellular staining for FoxP3. The plot shows absolute numbers of $CD25^+CD127^-FoxP^+$ Treg cells in the peripheral blood tracked longitudinally by flow cytometry in No Rx (n=7), Ky1005 (n=4), Sirolimus (n=9) and Ky1005/sirolimus (n=5) cohorts. Data were normalised to the pre-HCT level for each experiment, in the peripheral blood before and at different time points after HCT. Animals were kept on the indicated immunoprophylaxis regimens. Time-points with n<3 were censored. Multiple t-test with Holm-Sidak correction was performed between the groups.

FIG. **10**: Whole blood cells were stained for CD3, CD4, CD8, CD14, CD20, CD45RA and CCR7 and then analysed by FACS. T-cells were defined as $CD3^+CD14^-CD20^-$ lymphocytes and divided into $CD4^+$ and $CD8^+$ T-cell subsets. Memory T-cells (Tmem) were defined as $CD45RA^-$ and effector Tcells (Teff) as $CD45RA^+CCR7^-$ Tcells in both CD4 and CD8 gates. Combined populations of memory+ effector $CD4^+$ (FIG. **10**A) and $CD8^+$ (FIG. **10**B) T-cells were longitudinally tracked before and at different time point following allo-HCT in recipients kept without immunoprophylaxis (No Rx) or treated with anti-OX40L antibody, treated with rapamycin, or with a combination of rapamycin and anti-OX40L antibody.

FIG. **11**A: Peripheral blood mononuclear cells were isolated prior (pre-HCT) and at different time points following allogeneic HCT from recipients without immunoprophylaxis (No Rx), and from anti-OX40L mAb-treated and anti-OX40L mAb in combination with rapamycin-treated cohorts by Ficoll-Paque gradient and then were stained for cell surface markers (CD3, CD4, CD8, CD25, CD127) followed by fixation/permeabilisation (using BioLegend FoxP3 kit) and intracellular staining for FoxP3. Treg cells were defined as $CD3^+CD4^+CD25^+CD127^-FoxP3^+$ cells and conventional T-cells (Tconv) were defined as total $CD4^+$ and $CD8^+$ T-cells excluding Treg cell population. Plot shows the Treg: 100 Tconv cells ratio in the peripheral blood before and at different time points after HCT. Animals are grouped by the immunoprophylaxis regimens. Time-points with n<2 were censored. Multiple t-test with Holm-Sidak correction was performed between the groups.

FIG. **11**B: The ratio of $CD25^+CD127^-FoxP3^+$ Tregs to 100 Tconv cells in the peripheral blood is shown before HCT (Pre) and at terminal analysis (Nx) (FIG. **11**B). Each line represents a single transplant recipient. Individual graphs indicate the different GVHD prophylaxis regimens: No immunoprophylaxis (n=7, No Rx; □ & ■), KY1005 (n=4, Δ & ▲), Sirolimus (n=4, Siro; ○& ●) and KY1005/Sirolimus (n=5, KY1005/Siro; ∇& ▼). Paired t-test was used for statistical analysis. *p<0.05, **p<0.01, NS—not significant.

FIG. **11**C: The ratio of $CD25^+CD127^-FoxP3^+$ Treg to 100 Tconv cells in the peripheral blood tracked longitudinally in the KY1005/Sirolimus cohort.

FIG. **11**D: Representative GSEA plots performed as previously described (Subramanian et al., 2005 infra) showing Treg-related gene sets over-represented with FDR q<0.05 in KY1005/Sirolimus (n=4) versus sirolimus (n=4) or versus KY1005 (n=3) cohorts. *FDR q<0.05, ***FDR q<0.001.

FIG. **12**A: OX40 and OX40L are upregulated during GVHD in NHP. Representative flow cytometry plots showing OX40 expression on peripheral blood $CD4^+$ and $CD8^+$ T-cells obtained from healthy, immunologically naïve Rhesus macaques (Healthy Ctrl) or from allo-HCT recipients transplanted without immunoprophylaxis, performed at terminal analysis (No Rx) and stained for OX40, CD3, CD4 and CD8.

FIG. **12**B: The percentages of $OX40^+$ T-cells in CD28 $CD95^-$ (Naïve), $CD28^+CD95^+$ (CM) and CD28-$CD95^+$ (EM) $CD4^+$ T-cells were quantified in healthy immunologically naïve animals (Healthy Ctrl, n=6; ●) and at terminal analysis in recipients transplanted without GVHD immunoprophylaxis (No Rx, n=3; ○) from a single experiment from a single experiment shown in FIG. **12**A. Data represent one of 2 similar experiments. Statistical analysis was performed using the Student's t-test ****p<0.001.

FIG. **12**C: Peripheral blood from the healthy immunologically naïve animals (n=5, Healthy Ctrl; * & ○) and after allo-HCT recipients transplanted without GVHD immunoprophylaxis, performed at terminal analysis (n=4, No Rx; ▼& ∇) were activated with PMA/Ionomycin and cultured 4 hours as detailed in Example 11, then were stained for CD3, CD4, CD8, CD14, CD20, OX40, IFNγ, TNFα, IL-2 and IL-17A. Numbers of T-cells co-producing ≥2 cytokines simultaneously were quantified in $OX40^-$ and $OX40^+CD4^+$ T-cells subsets. Statistical analysis was performed using a paired t-test (between OX40- and $OX40^+CD4^+$ T-cells belonging to the same animal) or an unpaired Student's t-test (between different experimental groups). *p<0.05, **p<0.01, NS—not significant.

FIG. **12**D: Relative expression (Log_2 normalised fluorescent intensity signal) of the TNFRSF4 gene transcript (encoding OX40) in $CD3^+CD20^-$ T-cells, flow cytometrically sorted from the peripheral blood of healthy immunologically naïve animals (Healthy Ctrl; ●), following autologous HCT at day 100 post-transplant (n=4, Auto; ■), following allogeneic HCT at the time of terminal analysis in experimental groups without GVHD immunoprophylaxis (n=4, No Rx; ○), prophylaxed with Tacrolimus/Methotrexate (n=3, Tac/MTX; ▲), or with Sirolimus (n=4, Siro; ▼). The transcripts levels were measured using the GeneChip *Rhesus Macaque* Genome Array (Affimetrix) as detailed in Example 11. Horizontal significance bars denote comparisons with a moderated t-statistic <0.05 corrected for multiple hypotheses testing using the Benjamini-Hochberg procedure.

FIGS. **12**E & **12**F: Representative flow cytometry plots showing anti-OX40L staining on $CD11c^+$ myeloid dendritic cell (mDC) and $CD123^+$ plasmacytoid dendritic cells (pDC),

both gated on HLA$^-$DR$^+$CD3-CD56-CD20$^-$ cells (FIG. **12**E) and the relative number of OX40L$^+$ mDC and pDC (FIG. **12**F). Flow cytometry was performed on lymph node cells from HC (n=5) and from No Rx animals (n=4), using both an OX40L antibody and an isotype control (Table 9). Staining is shown for mDC (top panel of FIG. **12**E) and pDC (bottom panel of FIG. **12**E) and is representative of 2 independent experiments. Statistical analysis was performed using Student's t-test, *p<0.05.

FIG. **12**G: Relative expression (Log_2 normalised fluorescent intensity signal) of the TNFRSF4 gene transcript (encoding OX40) in human T-cells (defined as CD4$^+$ or CD8$^+$ and CD11c/CD14/CD16/CD20/CD56$^-$ lymphocytes), flow cytometrically sorted from the peripheral blood of HCT recipients with (n=7, ∇) or without (n=7, ▲) GVHD on day 28 post-transplant. Gene expression was measured using the Human Transcriptome 2.0 Array (Affymetrix) as detailed in Example 11. Statistical analysis was performed using Student's t-test, *p<0.05.

FIG. **12**H: The percentage of human CD3$^+$ T-cells, isolated from healthy controls and labeled with CellTrace Violet dye, which underwent proliferation in an allogeneic mixed lymphocyte reaction in the absence (n=9, No drug; ▲) or the presence (n=9, ▼) of 150 μg/mL KY1005. ***p<0.001 using a paired t-test.

FIG. **13**A: Donor chimerism, determined using microsatellite analysis, in flow-cytometrically-sorted CD3$^+$CD20$^-$ T-cells following allo-HCT. Chimerism for the No Rx (n=7), KY1005 (n=4) and sirolimus (n=5) cohorts are shown at terminal analysis. Chimerism for the KY1005/Sirolimus cohort is shown at Day 28, 60 and 100 after transplant.

FIG. **13**B: Absolute blood cell counts: total white blood cell counts (WBC; FIG. **13**B) each line represents an individual recipient.

FIGS. **13**C-**13**F-**1**: Absolute blood cell counts: absolute neutrophil counts (ANC; FIG. **13**C & FIG. **13**C-**1**), absolute lymphocyte counts (ALC; FIGS. **13**D & **13**D-**1**), absolute platelet counts (PLT; FIGS. **13**E & **13**E-**1**), absolute CD3$^+$ CD14$^-$CD20$^-$ T-cell counts (T-cells; FIG. **13**F & FIG. **13**F-**1**). FIGS. **13**C, **13**D, **13**E and **13**F show allo-HCT recipients from the KY1005/Sirolimus cohort; each line represents an individual recipient. FIGS. **13**C-**1**, **13**D-**1** and **13**E-**1** data show allo-HCT recipients from the KY1005/Sirolimus cohort (n=5, light grey) and autologous HCT cohort (n=6, dark grey); data are shown as mean (line with symbols) with SEM (shaded area around the line). FIG. **13**F-**1** shows absolute CD3$^+$CD14$^-$CD20$^-$ T-cell counts in allo-HCT recipients from the KY1005/Sirolimus cohort (R217, R218, R219, R220 and R221) and autologous HCT cohort (R200, R201, R202, R60 and R63), each line represents an individual recipient.

FIGS. **13**G & **13**G-**1**: CMV viral load in the peripheral blood of KY1005/Sirolimus-prophylaxed recipients, each line represents an individual recipient. (FIG. **13**G). FIG. **13**G-**1** shows CMV viral load in the peripheral blood of auto-HCT recipients (R200, R201, R202, R60 and R63) and KY1005/Sirolimus-prophylaxed allo-HCT recipients (R217, R218, R219, R220 and R221). Each line represents an individual recipient.

FIGS. **14**A-**14**C: Relative expression (Log_2 normalised fluorescent intensity signal) of MKI67 (FIG. **14**A), GZMA (FIG. **14**B) and RORC (FIG. **14**C) gene transcripts (encoding Ki67, Granzyme A and RORγt, respectively) in CD3$^+$ CD20$^-$ T-cells, flow-cytometrically sorted from the peripheral blood of animals from the indicated experimental cohorts. The transcripts levels were measured using GeneChip *Rhesus Macaque* Genome Array (Affimetrix) as detailed in Example 11. * denotes comparisons with a moderated t-statistic *p<0.05 corrected for multiple hypotheses testing using the Benjamini-Hochberg procedure between the indicated experimental groups.

FIGS. **14**D & **14**E: Representative GSEA plots (FIGS. **14**D and **14**E) performed as previously described (Subramanian et al., 2005 infra) showing Th/Tc1-related gene sets under-represented in KY1005/Sirolimus on day 14 (n=5) versus Sirolimus (n=4, Siro) or versus KY1005 (n=3) cohorts at the time of necropsy, *FDR q<0.05; ***FDR q<0.001.

FIGS. **14**F & **14**G: Representative GSEA plots (FIGS. **14**F and **14**G) performed as previously described (Subramanian et al., 2005 infra) showing Th/Tc17-related gene sets under-represented in KY1005/Sirolimus on day 100 (n=4) versus CTLA4-Ig/Sirolimus (n=7, CTLA4-Ig/Siro) or versus Tacrolimus/Methotrexate (n=3, Tac/MTX) cohorts at the time of necropsy. **FDR q<0.01; ***FDR q<0.001.

FIG. **15**A & FIG. **15**A-**1**: First, second and third principal component (PC) projections reveal clustering of transplanted animals by immunoprophylactic regimens. Healthy controls (n=46; ●), No immunoprophylaxis (No Rx, n=4; ❁), Sirolimus (n=4; ❁), KY1005 (n=3; ❁) and KY1005/Sirolimus (n=4; ○). Each dot represents an individual array sample.

FIG. **15**B: Weighted Venn diagram showing the number of transcripts over-represented in the KY1005/Sirolimus cohort at different time points after transplant compared to HC (FIG. **15**B top diagram). Overlapping areas indicate over-represented transcripts shared between multiple comparisons. 101 transcripts, over-represented in the KY1005/Sirolimus cohort at all time-points, were then used for pathway analysis using DAVID (Huang da W, Sherman B T & Lempicki R A., Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources., Nat Protoc 4, 44-57 (2009)), which documented enrichment for type I Interferon signalling-related genes as well as for genes related to signalling through the JAK/STAT pathway.

FIGS. **15**C & **15**D: Representative GSEA plots performed as previously described (Subramanian et al., 2005 infra) showing JAK/STAT pathway-related gene sets and type I Interferon signalling-related gene set over-represented in gene arrays from the KY1005/Sirolimus cohort at Day 14 (n=5), 28 (n=5) and 100 (n=4) post-transplants versus HC. *FDR q<0.05; ***FDR q<0.001.

FIG. **15**E: Representative GSEA plot performed as previously described (Subramanian et al., 2005 infra) showing type I Interferon signalling-related gene sets over-represented in KY1005/Sirolimus versus T-cells purified from autologous HCT recipients at day 100 (n=4), from the sirolimus cohort (n=4) and from the KY1005 cohort (n=3). ***FDR q<0.001.

FIGS. **16**A & **16**B: KY1005 pharmacokinetics in animals who received KY1005 as a monotherapy (n=4, FIG. **16**A) or in combination with Sirolimus (FIG. **16**B). Serum samples were collected 30 minutes before and 30 minutes after each KY1005 dose (with each dose being 10 mg/kg body weight, given once weekly from days −2 until day +54). After KY1005 dosing was discontinued, serum samples were collected once weekly until the end of the study. Pharmacokinetic analysis was performed using an antigen (OX40L) capture electrochemiluminescence (ECL) assay on the MSD platform as detailed in Example 11. Data presented as mean±SEM.

FIG. **17**A: The relative numbers of OX40$^+$CD4$^+$ T-cells isolated from the blood and indicated organs at the time of terminal analysis from healthy control animals (n=8,

Healthy Ctrl; •) or recipients from the following cohorts: autologous HCT (n=3, Auto; ■); allogeneic HCT without GVHD immunoprophylaxis (n=6, No Rx; ▲); treated with Tacrolimus and Methotrexate (n=3, Tac/MTX; ♦) (FIG. **17**A). Statistical analysis was performed using the Holm-Sidak multiple comparison t-test, *p<0.05.

FIGS. **17**B & **17**C: T-cells from the peripheral blood from unprophylaxed allo-HCT recipients (n=4) at the time of terminal analysis (MST=8 days) were activated with PMA/Ionomycin and cultured for 4 hours as detailed in Example 11, then were stained for IFNγ, TNFα, IL-2 and IL-17A. The relative numbers of T-cells producing the indicated cytokines (FIG. **17**B) and co-producing 0-4 cytokines (FIG. **17**C) were quantified in the $OX40^-$ and $OX40^+CD4^+$ T-cells subsets. The pie-plot was made using the SPICE 5.35 program (NIAID) (Roederer M, et al SPICE: exploration and analysis of post-cytometric complex multivariate datasets. Cytometry A 79, 167-174 (2011)). Statistical analysis was performed using paired t-test (FIG. **17**B) or using two-way ANOVA (FIG. **17**C), *p<0.05, **p<0.01.

FIG. **18**: Gating strategy to identify mDC and pDC in NHP lymph nodes based on CD11c and CD123 expression in HLA^-DR^+Lin $(CD3/CD20/CD56)^-$ cells.

FIGS. **19**A & **19**B: The absolute number of $CD28^+CD95^-$ Naïve (T_N; FIG. **19**A), $CD28^+CD95^+$ central memory (T_{CM}; FIG. **19**B) $CD4^+$ T-cells longitudinally tracked by FACS in the peripheral blood before and at different timepoints following allo-HCT in recipients without GVHD immunoprophylaxis (n=7, ●), prophylaxed with KY1005 (n=4, ■). Statistical analysis was performed using the Holm-Sidak multiple-comparison t-test. *p<0.05 between the indicated time points and day 1 post-HCT in No Rx cohort.

FIGS. **19**C & **19**D: The absolute numbers of $CD28^+$ $CD95^-$ Naïve (T_N; FIG. **19**C), and the of combination of $CD28^+CD95^+$ central memory and $CD28^-CD95^+$ effector memory (T_{CM+EM}; FIG. **19**D) $CD8^+$ T-cells longitudinally tracked by FACS in the peripheral blood before and at different time points following allo-HCT in recipients without GVHD immunoprophylaxis (n=7, No prophylaxis ●) or in recipients prophylaxed with KY1005 (n=4, ■).

FIG. **19**D-**1**: The of combination of $CD28^+CD95^+$ central memory and $CD28^-CD95^+$ effector memory (T_{CM+EM}; FIG. **19**D) $CD8^+$ T-cells longitudinally tracked by FACS in the peripheral blood before and at different time points following allo-HCT in recipients without GVHD immunoprophylaxis (No prophylaxis: black. Data points end at Day 8) or in recipients prophylaxed with KY1005 (Grey. Data points end at Day 21).

FIGS. **19**E & **19**F: Ki67 expression in NHP peripheral blood $CD4^+$ (FIG. **19**E) and $CD8^+$ (FIG. **19**F) T-cells before (pre-HCT) and following allo-HCT in recipients treated with KY1005/Sirolimis (n=5, KY1005/Siro; ●), CTLA4-Ig/Sirolimus (n=7, CTLA4-Ig/Siro; ▲) and Tacrolimus/Methotrexate (n=3, Tac/MTX; ♦). Differences between experimental groups were analysed using the Holm-Sidak multiple-comparison t-test.

FIG. **19**G: Survival of recipients after allo-HCT with KY1005/Sirolimus-prophylaxed (n=5, KY1005/Siro; ●) compared with previously published results [Furlan et al., Blood, 2016; Furlan et al., Sci Transl Med, 2015; Miller et al., Blood, 2010; all infra] of recipients prophylaxed with CTLA4-Ig/Sirolimus (n=7, CTLA4-Ig/Siro; ▲) and Tacrolimus/Metothrexate-treated (n=3, Tac/MTX; ♦) cohorts. Bars indicate significantly different groups with p<0.05 using long-rank statistics.

FIG. **19**H-J: The relative numbers of $CD28^+CD95^-$ Naïve (T_N) (FIG. **19**H), $CD28^+CD95^+$ central memory (T_{CM}) (FIG. **19**I) and $CD28^-CD95^+$ effector memory (TEM) (FIG. **19**J) $CD8^+$ T-cells in peripheral blood before and at different time points following allo-HCT in recipients without immunoprophylaxis (n=7, No Rx; black. Data points end at day 8) or prophylaxed with KY1005 (n=4, Grey. Data points end at day 21). Statistical analysis was performed using Holm-Sidak multiple-comparison t-test, *p<0.05.

FIG. **20**: mTOR-dependent genes are under-represented in Sirolimus cohort in comparison to No Rx GVHD cohort. Representative GSEA plot showing mTOR-related gene sets under-represented (FDR q<0.001) in the Sirolimus cohort (n=4) versus the No Rx cohorts (n=4) at the time of terminal analysis.

FIG. **21**: The absolute numbers of $CD28^+CD95^+$ central memory (T_{CM}) $CD4^+$ (A) and $CD8^+$ (B) T-cells in the peripheral blood of allo-HCT recipients prophylaxed with sirolimus (n=9, A) or KY1005/sirolimus (n=5, ✺).

DETAILED DESCRIPTION OF THE INVENTION

The invention provides the following aspects 1 to 113.

The invention is useful, for example, for treating or preventing transplant rejection, e.g., graft versus host disease (GvHD) or allogeneic transplant rejection. The invention is also useful, for example, for treating or preventing an inflammatory bowel disease, e.g., UC or CD, or for treating or preventing an airway inflammatory disease or condition. In an example, this aspect is useful for treating or preventing asthma. The invention is also useful, for example, for treating or preventing fibrosis. The invention is also useful, for example, for treating or preventing diabetes. The invention is also useful, for example, for treating or preventing uveitis. The invention is also useful, for example, for treating or preventing pyoderma gangrenosum. The invention is also useful, for example, for treating or preventing giant cell arteritis. The invention is also useful, for example, for treating or preventing Schnitzler syndrome. The invention is also useful, for example, for treating or preventing non-infectious scleritis.

1. An antibody or a fragment thereof that specifically binds to hOX40L for treating or preventing a hOX40L-mediated disease or condition in a human in a method wherein the antibody or fragment is administered to said human, wherein the antibody or fragment is for treating or preventing said hOX40L-mediated disease or condition by decreasing one, more or all of
   a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
   b. the proliferation of leukocytes of the human; and
   c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

The inventors, thus identified for the first time decreases of (a), (b) and (c) as ways of treating and/or preventing OX40L-mediated disease and conditions in humans and they provide antibodies and antibody fragments for this purpose.

In an example, the secretion is leukocyte secretion. In an example, (a) is indicated by a significantly elevated level of the cytokine(s) in human blood, plasma or serum.

In an example, the cytokine is selected from (i) TNF alpha, (ii) IL-2 and (iii) interferon gamma. In example, the cytokine TNF alpha. In example, the cytokine is IL-2. In an example, the cytokine is interferon gamma. In an example, the cytokines are (i) and (ii); or (i) and (iii); or (ii) and (iii); or (i)-(iii).

In an example, the decrease of (a), (b) or (c) or any other decrease disclosed herein is a decrease of at least 10 or 20% compared to the level in a human at risk of or suffering from the hOX40L-mediated disease or condition. In an example, the latter is the human recited in aspect 1 prior to administration of the antibody or fragment; in another example, the latter human is a different human. In an example, said decrease is at least 10, 20, 30, 40, 50 or 60%.

(i) In an example, the antibody or fragment is capable of effecting a decrease of secretion of the relevant cytokine from leukocytes (eg, human T-cells) in an in vitro assay (as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of (a).

(ii) In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of leukocytes (eg, human PBMCs and/or human T-cells) in an in vitro assay (as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of (b).

(iii) In an example, the antibody or fragment is capable of effecting a decrease of the binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L in an in vitro assay (as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of (c).

In an example, (i) and (ii); or (i) and (iii); or (ii) and (iii); or (i)-(iii) apply.

In another embodiment, there is provided an antibody or a fragment thereof that specifically binds to hOX40L which:

i) Antagonises binding of OX40 to OX40L; and

ii) Comprises an IgG4 constant region (e.g. and IgG4-PE constant region, such as that described by SEQ ID No: 128); and

iii) decreases IL-2 secretion by at least 50% (e.g. 55%, 60%, 65% or 70%) as compared to IL-2 secretion in the absence of the anti-OX40L antibody or fragment, optionally wherein IL-2 secretion is measured in an allogenic mixed lymphocyte reaction (MLR) assay; and/or

iv) decreases IL-13 secretion by at least 50% (e.g. 55%, 60%, 65% or 70%) as compared to IL-2 secretion in the absence of the anti-OX40L antibody or fragment, optionally wherein IL-13 secretion is measured in an allogenic mixed lymphocyte reaction (MLR) assay; and/or

v) specifically binds to hOX40L with a Kd of from 1 nM to 0.01 nM, optionally wherein the specific binding is measured by surface plasmon resonance (SPR).

Additionally or alternatively, assessment of said decreases can be performed using samples from the treated human. For example, reference is made to J. Clin. Immunol., 2004 Jan. 24(1):74-85; *"Increased expression of CCL20 in human inflammatory bowel disease"*, Kaser A et al. This publication provides an example of a generally-applicable technique of using tissue biopsies and reading out decreased cytokine levels indicative of decreased cytokine secretion after treatment with an antibody in vivo. Similar methods can be used to determine decrease of the secretion of one or more cytokines in a human having received an antibody of the invention. The skilled person will be familiar with techniques for assessing cytokine levels in patients and patient samples, for example, by use of one or more of tissue biopsy, immunohistochemistry, immunofluorescence, tissue staining, cytokine mRNA quantification (e.g., using PCR, such as Taqman™ PCR), cytokine protein detection and quantification (e.g., using cytokine-specific tool antibody and quantification, such as by ELISA or another standard protein quantification technique). For example, where the disease or condition is one of the GI tract (e.g., IBD), one can perform biopsy of relevant gut tissue from a patient that has received an antibody of the invention, followed by quantification of cytokine mRNA and/or cytokine protein (e.g., using quantitative PCR). The result can be compared with a cytokine quantification in biopsied relevant tissue from the same patient prior to antibody administration or compared to another human patient suffering from the same disease or condition but receiving no anti-OX40L treatment or no treatment for the disease or condition. In this way, the skilled person can determine that the antibody of the invention decreases secretion of the cytokine in the human recipient. Instead of assessing gut tissue levels, one can instead use a different tissue or sample from the human patient dependent upon the nature and location of the disease or condition. For example, where the disease or condition is one of the airways (e.g., lung), it is possible to take a lung or other airway tissue sample for cytokine assessment. Alternatively, one can use a Bronchoalveolar lavage (BAL) sample, as will be apparent to the skilled person. In another example, for some disease or conditions one can assess the decrease in cytokine in a blood, serum or plasma sample taken from a human that has received an antibody of the invention, and then comparing to the level before receiving the antibody or comparing to the level in an untreated human, as discussed above.

As is known in the art, the term "leukocytes" includes, for example, one or more of lymphocytes, polymorphonuclear leukocyte and monocytes. As is also readily apparent to the skilled person the term "monocytes" includes, for example, peripheral blood mononuclear cells (PBMCs) or monocyte derived cells, e.g., dendritic cells (DCs). See, for example, Immunobiology, 2013 November, 218(11):1392-401. doi: 10.1016/j.imbio. 2013.07.005. Epub 2013 Jul. 25; "Leukoreduction system chambers are an efficient, valid, and economic source of functional monocyte-derived dendritic cells and lymphocytes", Pfeiffer I A et al.

The proliferation of leukocytes, e.g., lamina propria lymphocytes (LPLs), can be assessed using tissue biopsy, staining and histology, as will be apparent to the skilled person. Hematoxylin and eosin stain (H&E stain or HE stain) is, for example, commonly used in histology to look for infiltrating lymphocytes a whole range of human tissue and is one of the principal stains in histology. It is the most widely used stain in medical diagnosis and is often the gold standard, and as such can be used to assess proliferation of leukocytes as per the invention. For example, GI tract tissue (e.g., gut tissue) from a human that is suffering from or at risk of a hOX40L-mediated disease or condition can be obtained, stained and assessed for the extent of infiltration of LPLs. Comparison can be made between such tissue from a human that has received an antibody of the invention compared to the extent of infiltration in tissue obtained from the same human prior to administration of antibody or from another human that has not received treatment and is at risk of or suffering from the disease or condition. For example, the comparison is between human gut tissues taken from the same (or different) humans suffering from IBD.

One can, for example, determine if the antibody or fragment is capable of decreasing binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L using standard binding assays are familiar to the skilled person, e.g., using ELISA or SPR.

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder affecting the gastrointestinal tract with an

apparently ever-increasing incidence and tendency to more severe clinical phenotypes. The disease is characterised by an exaggerated immune response to the luminal flora, suggesting that deficiencies in barrier function of intestinal flora may be involved, and studies support this notion (Cucchiara et al., 2012; Jostins et al., 2012; Manichanh et al., 2012; Salzman et al., 2007, all cited in Deuring et al., "*The cell biology of the intestinal epithelium and its relation to inflammatory bowel disease*", The International Journal of Biochemistry & Cell Biology 45 (2013) 798-806). IBD includes two main groups: Crohn's disease (CD) and ulcerative colitis (UC). CD patients can have inflammatory lesions in their entire gastrointestinal tract, whereas the inflammation in UC patients is restricted to the colon. Reference is also made to Hisamatsu et al. ("*Immune aspects of the pathogenesis of inflammatory bowel disease*", Pharmacology & Therapeutics 137 (2013) 283-297) and the documents cited therein.

Granuloma formation is the one of the most important pathological characteristics of human Crohn's disease. Mizoguchi et a/demonstrated that F4/80-positive immature CD11c+dendritic cells (DCs) produce IL-23 and contribute to granuloma formation in a murine colitis model (Mizoguchi et al., 2007). A Th1 immune response is predominant in Crohn's disease. Indeed, $CD4^+$ T-cells in the LP of Crohn's disease expressed T-bet and produced large amounts of interferon (IFN)-γ (Matsuoka et al., 2004). Sakuraba eta/ demonstrated that DCs in the mesentric lymph nodes of patients with Crohn's disease strongly promoted a Th1 and Th17 immune response (Sakuraba et al., 2009). Mesentric lymph node DCs contribute to IBD pathogenesis, particularly that of Crohn's disease.

Role of Cytokines in Disease and Conditions

Reference is made to Muzes et al, *World J Gastroenterol* 2012 Nov. 7; 18(41): 5848-5861 ISSN 1007-9327 (print) ISSN 2219-2840 (online), "*Changes of the cytokine profile in inflammatory bowel Diseases*".

Cytokines are indispensable signals of the mucosa-associated immune system for maintaining normal gut homeostasis. An imbalance of their profile in favour of inflammation initiation may lead to disease states, such as that is observed in inflammatory bowel diseases (IBD), e.g., Crohn's disease (CD) and ulcerative colitis (UC). The role of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-2, -6, -8, -12, -17, -23, IFN-gamma, or TNF alpha in IBD is associated with the initiation and progression of UC and CD. CD is often described as a prototype of T-helper (Th) 1-mediated diseases because the primary inflammatory mediators are the Th1 cytokines such as interleukin (IL)-12, interferon (IFN)-γ, and tumour necrosis factor (TNF)-α.

Binding of TNF-like ligands to their receptors triggers intracellular pathways that are directly involved in cell proliferation, differentiation, and survival. Most members of the TNF/TNF-receptor protein superfamilies are expressed on immune cells and play a critical role in multiple components of the immune response. TNF-α is a master cytokine in the pathogenesis of IBD. It exerts its pleiotropic effects through the expression of adhesion molecules, fibroblast proliferation, procoagulant factors, as well as the initiation of cytotoxic, apoptotic and acute-phase responses. The source of TNF-α in IBD is partly the innate immune cells, such as macrophages or monocytes, and also differentiated Th1 cells. The serum levels of TNF-α correlate with the clinical activity of UC and CD[31]. It plays an orchestrating role in colonic inflammation in IBD. The role of TNF-α in CD has been widely investigated. Binding TNF-α to serum soluble TNF receptor 1 and 2 (sTNFR1 and 2) initiates pro-inflammatory signalling. The levels of sTNFR1 and 2 are elevated in CD.

Tumour necrosis factor-like factor (TL1A), another member of the TNF family, stimulates IFN-γ secretion by binding to death receptor 3 (DR3). DR3 is expressed by a high percentage of cells from mucosal biopsies of UC and CD, and an increase of IFN-γ level has been observed with disease activity in IBD patients. The TL1A/DR3 system is involved in the pathogenesis of CD. The macrophages of the lamina propria are a major producer of TL1A, which expression is markedly enhanced in CD. It has been found that TL1A and IL-23 synergistically promotes the production of IFN-γ by mucosal T-cells. FN-Y: is produced by TH1 T-cells. Once inflammation is initiated, IFN-γ is produced and subsequently acts through various molecules and pathways of the immune system to intensify the inflammatory process. There is an overwhelming body of literature extensively documenting the proinflammatory nature of IFN-γ which has led to the mainstream opinion that IFN-γ is a prime proinflammatory cytokine in inflammation and autoimmune disease. Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice (Ito et a, *Clinical and Experimental Immunology* (2006), 146:330-338). The study clearly demonstrated that IFN-$\gamma^{-/-}$ mice manifested attenuated colitis after stimulation with DSS, in terms of the degree of body weight loss, DAI, histological score and MPO activity. IFN-γ was increasingly produced in the colon of DSS-treated WT mice that showed severe IBD-like symptoms.

Interleukin-2 (IL-2) is produced by T-cells and is mostly important for T-cells to differentiate into effector T-cells. IL-2 is also important for T-cell proliferation. This is important for IBD because effector T-cells are thought to be a major cell type to cause damage in IBD.

IL-8 (interleukin-8; aka CXCL8) primarily mediates the activation and migration of neutrophils into tissue from peripheral blood and to sites of inflammation. The tissue level of IL-8 has been found to be higher in active UC compared to normal colonic tissue, and its serum concentration has been related to endoscopic and histological severity of UC. IL-8 is important for inflammatory settings and cancer (see, e.g., "*The Chemokine CXCL8 in Carcinogenesis and Drug Response*", ISRN Oncol. 2013 Oct. 9; 2013:859154; Gales D et al, and Future Oncol., 2010 January; 6(1):111-6. doi: 10.2217/fon.09.128; *"CXCL8 and its cognate receptors in melanoma progression and metastasis*", Singh S et al). In cancer particularly, IL-8 is thought to contribute also by supporting angiogenesis.

In any configuration, aspect, concept or example herein the antibody or fragment antagonises the binding of hOX40L to an OX40 receptor.

In any configuration, aspect, concept or example herein, the antibody or fragment antagonises the binding of hOX40L to OX40.

In any configuration, aspect, concept or example herein, the OX40L receptor can be human OX40.

In any configuration, aspect, concept or example herein the human is suffering from or at risk of asthma and the antibody or fragment decreases IgE in a human.

In any configuration, aspect, concept or example herein the human is suffering from or at risk of asthma and the antibody or fragment is for decreasing IgE in a human. 2. The antibody or fragment of aspect 1, wherein the antibody or fragment decreases the binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L and decreases the proliferation of human T-cells;

wherein the antibody or fragment is for treating or preventing said hOX40L-mediated disease or condition by decreasing the secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma.

In an example, the cytokine is selected from (i) TNF alpha, (ii) IL-2 and (iii) interferon gamma. In an example, the cytokine is TNF alpha. In an example, the cytokine is IL-2. In an example, the cytokine is interferon gamma. In an example, the cytokines are (i) and (ii); or (i) and (iii); or (ii) and (iii); or (i)-(iii).

3. The antibody or fragment of aspect 1, wherein the leukocytes are selected from the group consisting of polymorphonuclear leukocytes, monocytes, peripheral blood mononuclear cells (PBMCs), lymphocytes, T-cells, antigen presenting cells (APCs), dendritic cells (DC cells) and natural killer cells (NK cells).

In one embodiment, the leukocytes are peripheral blood mononuclear cells (PBMCs) and T-cells (e.g. PBMCs).

4. The antibody or fragment of aspect 3, wherein the leukocytes comprise lamina propria lymphocytes (LPLs) and the disease or condition is a disease or condition of the gastrointestinal tract (GI tract).

5. The antibody or fragment of any preceding aspect, wherein the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and airway (e.g., lung) epithelial cells.

In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

6. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by decreasing the proliferation of T-cells in said human.

In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of T-cells in an in vitro assay (e.g., in a human DC cell/T-cell in vitro assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the proliferation of T-cells in said human.

7. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by antagonising the interaction between hOX40L and leukocytes of the human, wherein the proliferation of leukocytes is decreased.

In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of leukocytes (e.g., monocuclear cells) in an in vitro assay (e.g., in a MLR in vitro assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the proliferation of leukocytes in said human.

8. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by decreasing the proliferation of leukocytes of the human by antagonising the OX40L/OX40L receptor interaction mediated by T-cells in said human.

In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of leukocytes (e.g., monocuclear cells) in an in vitro assay wherein the antibody or fragment antagonises OX40L/OX40L receptor interaction mediated by T-cells in said assay, and thus administration of such antibody or fragment to the human leads to decrease of the proliferation of leukocytes in said human.

9. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by decreasing the secretion of a cytokine selected from TNF alpha, IL-2 and interferon gamma in the human.

In an example, the antibody or fragment is for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the secretion of (i) IL-2 and interferon gamma, (ii) IL-2 and TNF alpha or (iii) interferon gamma and TNF alpha in the human.

In an example, the antibody or fragment is capable of effecting a decrease of the secretion of a cytokine selected from IL-2, TNF alpha and interferon gamma in an in vitro assay (e.g., in a MLR in vitro assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the secretion of said selected cytokine(s) in said human.

In an example, the antibody or fragment is capable of effecting a decrease of the secretion of IL-8 in an in vitro assay (e.g., in a MLR in vitro assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the secretion of IL-8 in said human.

10. The antibody or fragment of aspect 9, for treating or preventing said disease or condition by decreasing the secretion of said cytokine mediated by the interaction of dendritic cells (DC cells) with T-cells in the human.

In an example, the antibody or fragment is capable of effecting a decrease of said cytokine(s) secretion in a DC cell/T-cell in vitro assay (for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the secretion of said cytokine(s) in said human.

11. The antibody or fragment of any preceding aspect, wherein gastrointestinal cell, colon cell, intestinal cell or airway (e.g., lung) cell damage is a symptom or cause of said disease or condition in humans.

In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

12. The antibody or fragment of any preceding aspect, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, diabetes or airway inflammation in the human.

12a. The antibody or fragment of any preceding aspect, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation in the human.

In an example of any preceding aspect the human is suffering from or at risk of an inflammatory or autoimmune disease or condition or has been diagnosed as such.

In an example, the autoimmune disease or condition is selected from the following:—

Acute disseminated encephalomyelitis (ADEM)
Addison's disease
Allergic granulomatosis and angiitis or Churg-Strauss syndrome (CSS)
Alopecia or Alopecia Areata (AA)
Anklosing spondylitis
Autoimmune chronic active hepatitis (CAH)
Autoimmune hemolytic anemia
Autoimmune pancreatitis (AIP)
Autoimmune retinopathy (AR) see Retinopathy
Autoimmune thrombocytopenic purpura
Autoimmune neutropenia
Autoimmune Inner Ear Disease (AIED)
Antiphospholipid Syndrome (APS)
Autoimmune Lymphoproliferative Syndrome (ALPS)
Behcet's syndrome
Bullus pemphigoid
Celiac disease
Churg-Strauss Syndrome (CSS) or Allergic Granulomatosis Angiitis
Chronic bullous disease of childhood
Chronic inflammatory demyelinating Polyradiculoneuropathy (CIDP)
Cictricial pemphigoid (CP)
Central Nervous System Vasculitis
Crohn's Disease
Cryoglobulinemia
Dermatitis
Dermatitis herpetiformis (DH)
Discoid lupus erythematosus (DLE)
Encephalomyelitis
Epidermolysis bullosa acquisita (EBA)
Giant Cell Arteritis see Temporal arteritis
Graft-versus-host disease
Graves' Disease
Gullain-Barre syndrome
Hanot Syndrome see Primary biliary Cirrhosis
Hashimoto's thyroiditis also called autoimmune thyroiditis and chronic lymphocytic thyroiditis
Hypersensitivity Vasculitis (HV) or small vessel vasculitis
Immune-mediated infertility
Inflammatory bowel disease
Insulin-dependent diabetes mellitus
Isolated vasculitis of the Central nervous system or CNS Vasculitis
Isaacs' Syndrome: Neuromyotonia
Kawasaki disease (KD)
Lambert-Eaton myasthenic syndrome (LEMS)
Linear IgA disease
Lupus—see Systemic lupus erythematosus
Meniere's Disease
Microscopic Polyangiitis (MPA)
Mixed connective tissue disease or MCTD
Monoclonal Gammopathy
Myasthenia Gravis
Multiple Sclerosis
Multifocal motor neuropathy
Neuromyotonia or Isaac's syndrome
Neutropenia see Autoimmune Neutropenia
Oophoritis
Opsoclonus-myoclonus syndrome
orchitis
Paraneoplastic neurologic disorders
Pemphigus vulgaris
Pemphigus follaceus PF)
Pemphigoid gestationis (PG)
Pernicious anemia
Paraneoplastic pemphigus (PNP)
Polyangiitis—see Microscopic polyangiitis
Polyarteritis *nodosa* (PAN)
Polymyositis/Dermatomyositis
Polymyalgia Rheumatica
Primary biliary Cirrhosis (PBC) also called Hanot Syndrome
Primary sclerosing cholangitis (PSC)
Raynaud's phenomenon
Recoverin-associated retinopathy (RAR) see Retinopathy
Reactive Arthritis formerly known as Reiter's syndrome, Retinopathy
Rheumatoid arthritis (RA)
Sarcoidosis
Sclerosing cholangitis see Primary Sclerosing Cholangitis
Sjogren's syndrome
Systemic necrotizing vascolitides
Stiff man syndrome or Moersch-Woltmann syndrome
Systemic lupus erythematosus
Systemic sclerosis (scleroderma)
Temporal arteritis or giant cell arteritis (GCV)
Takayasu's arteritis
Thromboangiitis obliterans or Buerger's disease
Thyroiditis with hypothyroidism
Thyroiditis with hyperthyroidism
Type I autoimmune polyglandular syndrome (PAS)
Type II autoimmune polyglandular syndrome
Vasculitis
Vitiligo
Wegener's granulomatosis

In an example of any aspect, configuration, concept or embodiment, the human is suffering from uveitis. For example, the uveitis is non-infectious and/or autoimmune in nature, i.e. is non-infectious uveitis or is autoimmune uveitis. For example, the non-infectious/autoimmune uveitis is caused by and/or is associated with Behçet disease, Fuchs heterochromic iridocyclitis, granulomatosis with polyangiitis, HLA-B27 related uveitis, juvenile idiopathic arthritis, sarcoidosis, spondyloarthritis, sympathetic ophthalmia, tubulointerstitial nephritis or uveitis syndrome. In an example, the uveitis is systemic in nature, i.e. is systemic uveitis. For example, the systemic uveitis is caused by and/or is associated with ankylosing spondylitis, Behçet's disease, chronic granulomatous disease, enthesitis, inflammatory bowel disease, juvenile rheumatoid arthritis, Kawasaki's disease, multiple sclerosis, polyarteritis nodosa, psoriatic arthritis, reactive arthritis, sarcoidosis, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome or Whipple's disease.

In an example of any aspect, configuration, concept or embodiment, the human is suffering from pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome or non-infectious scleritis. In an example, the human is suffering from pyoderma gangrenosum. In an example, the human is suffering from giant cell arteritis. In an example, the human is suffering from Schnitzler syndrome. In an example, the human is suffering from non-infectious scleritis.

In an example of any aspect, configuration, concept or embodiment, the human is suffering from a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or

condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD. In another embodiment, the human is suffering from or is at risk from multiviscreal organ transplant rejection.

13. An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with an antibody selected from the group consisting of 02D10, 10A07, 09H04 and 19H01.

In an example of any aspect, configuration, concept or embodiment, competition is determined by surface plasmon resonance (SPR), such techniques being readily apparent to the skilled person. SPR can be carried out using Biacore™, Proteon™ or another standard SPR technique. Such competition may be due, for example, to the antibodies/fragments binding to identical or overlapping epitopes of hOX40L. In an example of any aspect, configuration, concept or embodiment, competition is determined by ELISA, such techniques being readily apparent to the skilled person. In an example of any aspect, configuration, concept or embodiment, competition is determined by homogenous time resolved fluorescence (HTRF), such techniques being readily apparent to the skilled person. In an example of any aspect, configuration, concept or embodiment, competition is determined by fluorescence activated cell sorting (FACS), such techniques being readily apparent to the skilled person. In one aspect, the HTRF, ELISA and/or FACS methods are carried out as described in the Examples hereinbelow.

14. The antibody or fragment of aspect 13, wherein the antibody or fragment is according to any one of aspects 1 to 12.

15. The antibody or fragment of any preceding aspect, comprising lambda light chain variable domains (optionally which are human).

In an example of any aspect, configuration, concept or embodiment of the present invention, the variable domains of the antibody or fragment are human or humanised. Additionally, optionally the antibody or fragment further comprises human or humanised constant regions (e.g., human Fc and/or human CL). In an example of any aspect of the present invention, the variable domains of the antibody or fragment are produced by a transgenic animal (e.g., a rodent, mouse, rat, rabbit, chicken, sheep, Camelid or shark). In an example of any aspect of the present invention, the variable domains of the antibody or fragment are produced or identified by phage display, ribosome display or yeast display.

In an example of any aspect, configuration, concept or embodiment of the present invention, the antibody or fragment is recombinant.

In an example of any aspect, configuration, concept or embodiment of the present invention, the antibody or fragment is produced by a recombinant mammalian, bacterial, insect, plant or yeast cell. In an example, the mammalian cell is a CHO or HEK293 cell and the antibody or fragment comprises CHO or HEK293 cell glycosylation.

In an example of any aspect, configuration, concept or embodiment of the present invention, the antibody or fragment is isolated.

16. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises a HCDR1 sequence selected from the group consisting of the HCDR1 of:
    a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
    d. 19H01, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.

17. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises a HCDR2 sequence selected from the group consisting of the HCDR2 of:
    a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
    d. 19H01, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.

18. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises a HCDR3 sequence selected from the group consisting of the HCDR3 of:
    a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
    d. 19H01, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.

19. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises (i) the CDR1 and 2, (ii) CDR1 and 3, (iii) CDR2 and 3 or (iv) CDR1, 2 and 3 sequences:
    a. recited in (a) of aspects 16-18, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. recited in (b) of aspects 16-18, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. recited in (c) of aspects 16-18, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; or
    d. recited in (d) of aspects 16-18, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.

20. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises an amino acid sequence selected from the group consisting of the VH amino acid sequences in the

SEQUENCE LISTING

In an aspect, the invention provides an anti-hOX40L antibody or fragment (optionally according to any other aspect recited herein) comprising a VH domain which comprises an amino acid sequence selected from the group consisting of the VH amino acid sequences in the sequence listing.

In an aspect, the VH domain comprises an amino acid sequence selected from Seq ID No:2, Seq ID No:34, Seq ID No:66, Seq ID No:94, Seq ID No:122, Seq ID No:124, Seq ID NO:126, Seq ID No:128, Seq ID No:132 or Seq ID No:134.

In another example of the invention, the antibody or fragment comprises a VH domain amino acid sequence set out in the sequence listing below. Additionally or alternatively, the antibody or fragment comprises a HCDR1 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42). Additionally or alternatively, the antibody or fragment comprises a HCDR2 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44). Additionally or alternatively, the antibody or fragment comprises a HCDR3 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46).

In an example of the invention, the antibody or fragment comprises a VL domain amino acid sequence set out in the sequence listing below. Additionally or alternatively, the antibody or fragment comprises a LCDR1 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56). Additionally or alternatively, the antibody or fragment comprises a LCDR2 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58). Additionally or alternatively, the antibody or fragment comprises a LCDR3 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60).

In an example of any aspect herein, the antibody or fragment comprises a heavy chain comprising a constant region selected from the group consisting of the heavy chain constant region SEQ ID NOs in the sequence listing (i.e. any of Seq ID Nos: 126, 128, 132, or 134, in particular the constant region of Seq ID No:128); and optionally a VH domain as recited in aspect 19 or 20. In an example, the antibody or fragment comprises two copies of such a heavy chain. In another example, the heavy chain comprise a rodent, rat, mouse, human, rabbit, chicken, Camelid, sheep, bovine, non-human primate or shark constant region (e.g., Fc), in particular a mouse constant region.

In an example of any aspect herein, the antibody or fragment comprises a heavy chain comprising a gamma (e.g., human gamma) constant region, e.g., a human gamma1 constant region. In another example of any aspect herein, the antibody of fragment comprises a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation (i.e. where the wild type leucine residue is mutated to a glutamic acid residue). In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4 comprising both the Leu235Glu mutation and the Ser228Pro mutation. This heavy chain constant region is referred to as "IgG4-PE" herein.

In an example of any aspect herein, the antibody or fragment is chimaeric, e.g., it comprises human variable domains and non-human (e.g., rodent, mouse or rat, such as mouse) constant regions.

21. The antibody or fragment of any one of aspects 16 to 20, comprising first and second copies of said VH domain.
22. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises a LCDR1 sequence selected from the group consisting of the LCDR1 of:
    a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
    d. 19H01, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.
23. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises a LCDR2 sequence selected from the group consisting of the LCDR2 of:
    a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
    d. 19H01, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.
24. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises a LCDR3 sequence selected from the group consisting of the LCDR3 of:
    a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
    d. 19H01, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.
25. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises (i) the CDR1 and 2, (ii) CDR1 and 3, (iii) CDR2 and 3 or (iv) CDR1, 2 and 3 sequences:
    a. recited in (a) of aspects 22-24, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
    b. recited in (b) of aspects 22-24, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
    c. recited in (c) of aspects 22-24, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; or
    d. recited in (d) of aspects 22-24, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.
26. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises an amino acid sequence selected from the group consisting of the VL amino acid sequences in the

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In an aspect of the invention, there is provided an anti-hOX40L antibody or fragment (optionally according to any

other aspect herein), comprising a VL domain which comprises an amino acid sequence selected from the group consisting of the VL amino acid sequences in the sequence listing (i.e. Seq ID No:16, Seq ID No:48, Seq ID No:80 or Seq ID No:108, in particular Seq ID No:48).

In an example of any aspect herein, the antibody or fragment comprises a light chain (e.g., lambda light chain) comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. Seq ID No: 136, Seq ID No: 138, Seq ID No: 140, Seq ID No: 142, Seq ID No:144, Seq ID No:146, Seq ID No: 148, Seq ID No:152, Seq ID No: 154, Seq ID No:156, Seq ID No:158, Seq ID No:160, Seq ID No:162, Seq ID No:164 or Seq ID No:166); and optionally a VL domain (e.g., lambda VL) as recited in aspect 25 or 26. In an example, the antibody or fragment comprises two copies of such a light chain (optionally also two copies of the heavy chain described above). In another example, the light chain comprises a rodent, rat, mouse, human, rabbit, chicken, Camelid, sheep, bovine, non-human primate or shark constant region.

In an example of any aspect herein, the antibody or fragment comprises a light chain (e.g., kappa light chain) comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. Seq ID No: 136, Seq ID No:138, Seq ID No:140, Seq ID No:142, Seq ID No:144, Seq ID No:146, Seq ID No: 148, Seq ID No:152, Seq ID No: 154, Seq ID No:156, Seq ID No:158, Seq ID No:160, Seq ID No:162, Seq ID No:164 or Seq ID No:166); and optionally a VL domain (e.g., kappa VL) as recited in aspect 25 or 26. In an example, the antibody or fragment comprises two copies of such a light chain (optionally also two copies of the heavy chain described above). In another example, the light chain comprises a rodent, rat, mouse, human, rabbit, chicken, Camelid, sheep, bovine, non-human primate or shark constant region.

In an example, the antibody or fragment comprises a lambda light chain comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. Seq ID No:146, Seq ID No:148, Seq ID No:152, Seq ID No:154, Seq ID No:156, Seq ID No: 158, Seq ID No: 160, Seq ID No: 162, Seq ID No: 164 or Seq ID No: 166); and optionally a lambda VL domain.

In an example, the antibody or fragment comprises a kappa light chain comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. i.e. Seq ID No:136, Seq ID No:138, Seq ID No:140, Seq ID No:142 or Seq ID No:144); and optionally a kappa VL domain.

In an example, the VL domains of the antibody or fragment are lambda Light chain variable domains. In an example, the VL domains of the antibody or fragment are kappa Light chain variable domains.

27. The antibody or fragment of any one of aspects 22 to 26, comprising first and second copies of said VL domain.

28. The antibody or fragment of any preceding aspect, wherein the hOX40L is human cell surface-expressed hOX40L, e.g., on endothelial cells (e.g., an airway or GI tract endothelial cell).

In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

29. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases the proliferation of human PBMCs or T-cells in the presence of hOX40L in an in vitro mixed lymphocyte reaction (MLR) assay by at least 20, 30, 40, 50 or 60% compared to the proliferation of human PBMCs or T-cells in the presence of hOX40L in an in vitro control MLR assay in the absence of an antibody that is specific for hOX40L. An illustration of a suitable assay is provided in the examples below. 30. The antibody or fragment of aspect 29, wherein the hOX40L in the assay is surface-expressed on human dendritic cells (DC cells).

An illustration of a suitable assay is provided in the examples below.

31. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases NF-κB activity in human HT-1080 cells expressing hOX40 receptor in vitro in the presence of hOX40L.

In an example, the antibody or fragment the decrease in NF-κB activity is determined by detecting a decrease in IL-8 secretion by HT-1080 cells (ATCC® CCL-121) (optionally transfected with hOX40 Receptor, in the presence of hOX40) in vitro.

32. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases IL-8 secretion from human HT-1080 cells expressing hOX40 receptor in vitro in the presence of hOX40L.

33. The antibody or fragment of aspect 32, wherein the antibody or fragment decreases IL-8 secretion by at least 20, 30, 40, 50 or 60% compared to the IL-8 production by HT-1080 cells expressing hOX40 receptor in vitro in the presence of hOX40L in the absence of an antibody that is specific for hOX40L.

34. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases hOX40L-stimulated human T-cell proliferation in vitro.

35. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases hOX40L-stimulated IL-2 secretion from human T-cells in vitro.

36. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases cytokine secretion mediated by the interaction of human dendritic cells (DC cells) with human T-cells, wherein the cytokine is selected from one, two, more or all of TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma.

This can be assessed, for example, using a MLR in vitro assay (e.g., a DC/T-cell MLR in vitro assay). An illustration of a suitable assay is provided in the examples below.

In an example, the DC cells are mismatched to the T-cells, e.g., MHC mis-matched, as is possible for example when the DC cells are from a human that is different from the T-cell human source. In an example, the DC cells are produced by in vitro induction of human monocytes with GMCSF and IL-4.

37. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases interferon gamma secretion by at least 20, 30, 40, 50 or 60% compared to the production of interferon gamma mediated by the interaction of human dendritic cells (DC cells) with human T-cells in the absence of an antibody that is specific for hOX40L.

38. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases TNF alpha

secretion by at least 20, 30, 40, 50 or 60% compared to the production of TNF alpha mediated by the interaction of human dendritic cells (DC cells) with human T-cells in the absence of an antibody that is specific for hOX40L.

39. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases IL-2 secretion by at least 10, 20, 30, 40, 50 or 60% compared to the production of IL-2 mediated by the interaction of human dendritic cells (DC cells) with human T-cells in the absence of an antibody that is specific for hOX40L.

40. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases cytokine secretion (e.g., leukocyte cytokine secretion) in a human peripheral blood mononuclear cell (PBMC) mixed lymphocyte (MLR) assay, wherein the cytokine is selected from one, two, more or all of TNF alpha, IL-2, IL-4, IL-3, IL-6, IL-8, IL-10, IL-17, RANTES and interferon gamma.

41. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases interferon gamma secretion by at least 20, 30, 40, 50 or 60% compared to the production of interferon gamma in a human PBMC MLR assay in the absence of an antibody that is specific for hOX40L.

In one embodiment, the comparison is to the production of interferon gamma in a human PBMC MLR assay in the absence of antibody.

42. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases TNF alpha secretion by at least 20, 30, 40, 50 or 60% compared to the production of TNF alpha in a human PBMC MLR assay in the absence of an antibody that is specific for hOX40L.

43. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases IL-2 secretion by at least 10, 20, 30, 40, 50 or 60% compared to the production of IL-2 in a human PBMC MLR assay in the absence of an antibody that is specific for hOX40L.

44. The antibody or fragment of any one of aspects 36 to 43, wherein the cells are primary cells.

A "primary cell" refers to a cell in a human or such a cell that has been taken from the patient for binding to the antibody or fragment of the invention in vitro (as may be useful, for example, in a method of diagnosis of OX40L status or disease/condition status in the human). Primary cells as used herein are not cells of human cell lines, which typically have undergone many cultures in vitro. The ability of the antibody or fragment of the invention to specifically inhibit hOX40L binding to receptor in this embodiment is advantageous since it provides a direct indication of the utility for addressing cells in human patients suffering or at risk of a hOX40L-mediated disease or condition.

45. The antibody or fragment of any preceding aspect, wherein the antibody or fragment inhibits binding of hOX40L to a hOX40L receptor (e.g., hOX40) with an IC_{50} of 1×10^{-8} or less in a HTRF (homogenous time resolved fluorescence) assay.

In an example, the IC_{50} is in the range from 1×10^{-8} to 1×10^{-11} or in the range from 1×10^{-9} to 1×10^{-10}.

46. A pharmaceutical composition for treating and/or preventing a OX40L-mediated condition or disease, the composition comprising an antibody or fragment of any preceding aspect and a diluent, excipient or carrier; and optionally further comprising an anti-inflammatory drug.

In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone), anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab) or anti-TNFa antibodies/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab, certolizumab pegol). In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone) and anti-LFA1 antibodies.

47. A pharmaceutical composition or kit for treating and/or preventing a OX40L-mediated condition or disease, the composition or kit comprising an antibody or fragment of the invention (and optionally an anti-inflammatory drug) optionally in combination with a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

48. A nucleic acid that encodes the HCDR3 of an antibody recited in any one of aspects 1 to 45.

In one embodiment, the HCDRs herein are according to Kabat nomenclature. In another embodiment, the HCDRs herein are according to the IMGT nomenclature.

49. The nucleic acid of aspect 48 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR3 sequence in the sequence listing.

In an aspect, the invention provides a nucleic acid comprising a nucleotide sequence that encodes a VH domain of an anti-hOX40L antibody, wherein the nucleotide sequence comprises a HCDR3 sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR3 sequence in the sequence listing. Optionally, the antibody is according to any other aspect herein.

In another embodiment, there is provided the nucleic acid of aspect 48 comprising a nucleotide sequence that is 100% identical to a HCDR3 sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

Amino acid substitutions include alterations in which an amino acid is replaced with a different naturally-occurring amino acid residue. Such substitutions may be classified as "conservative", in which case an amino acid residue contained in a polypeptide is replaced with another naturally occurring amino acid of similar character either in relation to polarity, side chain functionality or size. Such conservative substitutions are well known in the art. Substitutions encompassed by the present invention may also be "non-conservative", in which an amino acid residue which is present in a peptide is substituted with an amino acid having different properties, such as naturally-occurring amino acid from a different group (e.g., substituting a charged or hydrophobic amino; acid with alanine), or alternatively, in which a naturally-occurring amino acid is substituted with a non-conventional amino acid.

Additionally or alternatively, there is provided the nucleic acid of aspect 49 comprising a nucleotide sequence that is 100% identical to a HCDR3 sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

50. A nucleic acid that encodes the HCDR2 of an antibody recited in any one of aspects 1 to 45; optionally wherein the nucleic acid is according to aspect 48 or 49.

51. The nucleic acid of aspect 50 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR2 sequence in the sequence listing.

In an aspect, the invention provides a nucleic acid comprising a nucleotide sequence that encodes a VH domain of an anti-hOX40L antibody, wherein the nucleotide sequence comprises a HCDR2 sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR2 sequence in the sequence listing. Optionally, the antibody is according to any other aspect herein.

In another embodiment, there is provided the nucleic acid of aspect 51 comprising a nucleotide sequence that is 100% identical to a HCDR2 sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

Additionally or alternatively, there is provided the nucleic acid of aspect 50 comprising a nucleotide sequence that is 100% identical to a HCDR2 sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

52. A nucleic acid that encodes the HCDR1 of an antibody recited in any one of aspects 1 to 45; optionally wherein the nucleic acid is according to any one of aspects 48 to 51.

53. The nucleic acid of aspect 52 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical to or is 100% identical to a HCDR1 sequence in the sequence listing.

In an aspect, the invention provides a nucleic acid comprising a nucleotide sequence that encodes a VH domain of an anti-hOX40L antibody, wherein the nucleotide sequence comprises a HCDR1 sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR1 sequence in the sequence listing. Optionally, the antibody is according to any other aspect herein.

In another embodiment, there is provided the nucleic acid of aspect 52 comprising a nucleotide sequence that is 100% identical to a HCDR1 sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

Additionally or alternatively, there is provided the nucleic acid of aspect 52 comprising a nucleotide sequence that is 100% identical to a HCDR1 sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

54. A nucleic acid that encodes a VH domain and/or a VL domain of an antibody recited in any one of aspects 1 to 45.

55. The nucleic acid of aspect 54 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical to or is 100% identical to a VH domain nucleotide sequence in the

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In another embodiment, there is provided the nucleic acid of aspect 54 comprising a nucleotide sequence that is 100% identical to a VH domain nucleotide sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

Additionally or alternatively, there is provided the nucleic acid of aspect 54 comprising a nucleotide sequence that is 100% identical to a VH domain nucleotide sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

56. The nucleic acid of aspect 54 or 55 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical to or is 100% identical to a VL domain nucleotide sequence in the sequence listing.

In another embodiment, there is provided the nucleic acid of aspect 54 or 55 comprising a nucleotide sequence that is 100% identical to a VL domain nucleotide sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

Additionally or alternatively, there is provided the nucleic acid of aspect 54 or 55 comprising a nucleotide sequence that is 100% identical to a VL domain nucleotide sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

57. A nucleic acid that encodes a heavy chain or a light chain of an antibody recited in any one of aspects 1 to 45.

58. The nucleic acid of aspect 57, comprising a nucleotide sequence as recited in any one of aspects 48 to 56.

59. A vector (e.g., a mammalian expression vector) comprising the nucleic acid of any one of aspects 48 to 58; optionally wherein the vector is a CHO or HEK293 vector. In an example, the vector is a yeast vector, e.g., a *Saccharomyces* or *Pichia* vector.

60. A host comprising the nucleic acid of any one of aspects 48 to 58 or the vector of aspect 59. In an example, the host is a mammalian (e.g., human, e.g., CHO or HEK293) cell line or a yeast or bacterial cell line.

61. Use of an antibody or a fragment thereof, that specifically binds to hOX40L in the manufacture of a medicament for administration to a human, for treating or preventing a hOX40L-mediated disease or condition in the human by decreasing one, more or all of

a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;

b. the proliferation of leukocytes of the human; and

c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

The features of any of the previous aspects, configurations, concepts, examples or embodiments optionally apply mutatis mutandis to this use.

In an example, the human is suffering from or at risk of asthma and the antibody or fragment is for decreasing IgE in the human, thereby treating, preventing or reducing asthma in the human.

62. A method of treating or preventing a hOX40L-mediated disease or condition in a human by decreasing one, more or all of
    a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
    b. the proliferation of leukocytes of the human; and
    c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L;
    wherein the method comprises administering to said human a therapeutically effective amount of an antibody or fragment that specifically binds to hOX40L.

The features of any of the previous aspects, examples or embodiments optionally apply mutatis mutandis to this method.

The method of the invention treats or prevents said disease or condition in the human. A "therapeutically effective amount" of the antibody or fragment is that amount (administered in one or several doses, which may be spaced in time, e.g., substantially monthly administration) that is effective to bring about said treatment or prevention. This will be readily apparent to the skilled person and may vary according to the particular human patient and disease or condition being addressed.

In an example, the human is suffering from or at risk of asthma and the antibody or fragment decreases IgE in the human, thereby treating, preventing or reducing asthma in the human.

63. The method or use of aspect 61 or 62, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the proliferation of T-cells in said human.

64. The method or use of any one of aspects 61 to 63, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by antagonising the interaction between hOX40L and leukocytes of the human, wherein the proliferation of leukocytes is decreased.

65. The method or use of any one of aspects 61 to 64, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the proliferation of leukocytes of the human by antagonising the OX40L/OX40L receptor interaction mediated by T-cells in said human.

66. The method or use of any one of aspects 61 to 65, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the secretion of IL-8 cytokine in the human.

67. The method of aspect 66, for treating or preventing said disease, condition or epithelial cell damage by decreasing the secretion of said IL-8 mediated by the interaction of dendritic cells (DC cells) with T-cells in the human.

68. The method or use of any one of aspects 61 to 67, wherein gastrointestinal cell, colon cell, intestinal cell or airway (e.g., lung) cell damage is a symptom or cause of said disease or condition in humans.

In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

69. The method or use of any one of aspects 61 to 68, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, diabetes or airway inflammation in the human.

69a. The method or use of any one of aspects 61 to 68, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation in the human.

In any aspect, configuration, concept or embodiment, the human is suffering from or at risk of a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD. In any aspect, configuration, concept or embodiment, the human is suffering from or at risk of a hOX40L-mediated disease or condition which is a cancer and/or malignant tumour.

70. The method or use of any one of aspects 61 to 69a, wherein the antibody or fragment is according to any one of aspects 1 to 45 or any example, configuration, concept, aspect or embodiment described herein.

71. The antibody, fragment, composition, kit, method or use of any preceding aspect, for treating or preventing an inflammatory or automimmune disease or condition in a human or for reducing or preventing angiogenesis in a human.

72. The antibody, fragment, composition, kit, method or use of any preceding aspect, wherein the disease or condition is selected from the group consisting of an inflammatory bowel disease (IBD), Chrohn's disease, rheumatoid arthritis, psoriasis, bronchiolitis, gingivitis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), asthma, adult respiratory distress syndrome (ARDS), septic shock, ulcerative colitis, Sjorgen's syndrome, airway inflammation, systemic lupus erythematosus (SLE), diabetes, contact hypersensitivity, multiple sclerosis and atherosclerosis.

72a. The antibody, fragment, composition, kit, method or use of any preceding aspect, wherein the disease or condition is selected from the group consisting of an inflammatory bowel disease (IBD), Chrohn's disease, rheumatoid arthritis, psoriasis, bronchiolitis, gingivitis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), asthma, adult respiratory distress syndrome (ARDS), septic shock, ulcerative colitis, Sjorgen's syndrome, airway inflammation, systemic lupus erythematosus (SLE), uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infec-

tious scleritis, diabetes, contact hypersensitivity, multiple sclerosis and atherosclerosis.

In any aspect, configuration, concept or embodiment, the human is suffering from or at risk of a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

In an example, the disease or condition is an OX40L-mediated disease or condition disclosed in U.S. Pat. No. 7,812,133 or EP1791869.

In an example, the disease or condition is an inflammatory or autoimmune disease or condition. In an example, the disease or condition is transplant rejection.

As used herein, inflammatory disease or condition refers to pathological states resulting in inflammation, for example caused by neutrophil chemotaxis. Examples of such disorders include inflammatory skin diseases including psoriasis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); ischemic reperfusion; adult respiratory distress syndrome; dermatitis; meningitis; encephalitis; uveitis; autoimmune diseases such as rheumatoid arthritis, Sjorgen's syndrome, vasculitis; diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome secondary to septicaemia or trauma; alcoholic hepatitis, bacterial pneumonia, antigen-antibody complex mediated diseases; inflammations of the lung, including pleurisy, alveolitis, vasculitis, pneumonia, chronic bronchitis, bronchiectasis, and cystic fibrosis; etc. The preferred indications are bacterial pneumonia and inflammatory bowel disease such as ulcerative colitis. The invention is thus in an example provided for treating or preventing any one or more of such conditions.

In an example, the disease or condition is cancer.

In an example, the disease is uveitis, such as systemic uveitis or autoimmune/non-infectious uveitis.

73. An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY, wherein X is any amino acid.

The features of the antibodies of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply mutatis mutandis to these antibodies, e.g the antibody may be a human antibody or chimeric antibody having functional features as described herein. Competition may be determined as described in any aspect, embodiment, example, concept or configuration described herein, e.g. as determined by SPR, ELISA, HTRF or FACS.

In one embodiment, the antibody or fragment competes with the variable regions of 02D10 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 34 and the light chain variable region of SEQ ID No:48). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:62 and a light chain amino acid sequence of SEQ ID No:64.

In another embodiment, the antibody or fragment additionally or alternatively competes with 10A7. In one embodiment, the antibody or fragment competes with the variable regions of 10A7 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 2 and the light chain variable region of SEQ ID No:16). In another embodiment, the antibody or fragment competes with 10A7 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:30 and a light chain amino acid sequence of SEQ ID No:32.

In one embodiment, the amino acid is any naturally-occurring amino acid.

74. The antibody or fragment according to aspect 73, where X is a neutral amino acid, optionally P or G.

In an embodiment, X is P or G. In an embodiment, X is selected from P, N, A or G. In another embodiment, X is selected from P, G or N. In another embodiment, X is selected from P, G or A.

75. An antibody or a fragment thereof, optionally according to aspect 73 or 74, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises the HCDR3 sequence of SEQ ID NO:40 or 46 or the HCDR3 sequence of SEQ ID NO:40 or 46 comprising less than 5 amino acid substitutions.

The features of the antibodies of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply mutatis mutandis to these antibodies, e.g the antibody may be a human antibody or chimeric antibody having functional features as described herein. Competition may be determined as described in any aspect, embodiment, concept, example or configuration described herein, e.g. as determined by SPR, ELISA, HTRF or FACS.

In an embodiment, the HCDR3 sequence of SEQ ID NO:40 or 46 comprises less than 4 amino acid substitutions (i.e. 3 or fewer). In an embodiment, the HCDR3 sequence of SEQ ID NO:40 or 46 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the HCDR3 sequence of SEQ ID NO:40 or 46 comprises less than 2 amino acid substitutions (i.e. one substitution).

In one embodiment, the antibody or fragment competes with the variable regions of 02D10 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 34 and the light chain variable region of SEQ ID No:48). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:62 and a light chain amino acid sequence of SEQ ID No:64.

In another embodiment, the antibody or fragment additionally or alternatively competes with 10A7. In one embodiment, the antibody or fragment competes with the variable regions of 10A7 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 2 and the light chain variable region of SEQ ID No:16). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:30 and a light chain amino acid sequence of SEQ ID No:32.

76. An antibody or fragment according to any one of aspects 73 to 75, the VH domain comprising a HCDR3 of from 16 to 27 amino acids and which is derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

In an embodiment, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02, IGHJ6*03 and IGHJ6*04. In another embodiment, the human JH gene segment is

selected from IGHJ6*01, IGHJ6*02 and IGHJ6*04. In another embodiment, the JH gene segment is IGHJ6*02.

In a further embodiment, the human VH gene segment is IGHV3-23, for example selected from IGHV3-23*01, IGHV3-23*02, IGHV3-23*03, IGHV3-23*04 or IGHV3-23*05. In another embodiment, the human VH gene segment is IGHV3-23*01 or IGHV3-23*04, in particular IGHV3-23*04.

In a further embodiment, the human DH gene segment is IGHD3-10, for example selected from IGHD3-10*01 or IGHD3-10*02. In one embodiment, the human DH gene segment is IGHD3-10*01. In one embodiment, the human DH gene segment is IGHD3-10*02.

77. The antibody or fragment according to any one of aspects 73 to 76, the VH domain comprising the HCDR1 sequence of SEQ ID NO:36 or 42 or the HCDR1 sequence of SEQ ID NO:36 or 42 comprising less than 4 amino acid substitutions.

In an embodiment, the HCDR1 sequence of SEQ ID NO:36 or 42 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the HCDR1 sequence of SEQ ID NO:36 or 42 comprises less than 2 amino acid substitutions (i.e. one substitution).

78. The antibody or fragment according to any one of aspects 73 to 77, the VH domain comprising the HCDR2 sequence of SEQ ID NO:38 or 44, or the HCDR2 sequence of SEQ ID NO:38 or 44 comprising less than 5 amino acid substitutions.

In an embodiment, the HCDR2 sequence of SEQ ID NO:38 or 44 comprises less than 4 amino acid substitutions (i.e. 3 or fewer). In an embodiment, the HCDR2 sequence of SEQ ID NO:38 or 44 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the HCDR2 sequence of SEQ ID NO:38 or 44 comprises less than 2 amino acid substitutions (i.e. one substitution).

79. The antibody or fragment according to any one of aspects 73 to 78, the VH domain comprising an amino acid sequence of SEQ ID NO: 34, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%) identical to SEQ ID NO:34.

In an embodiment, the heavy chain variable domain amino acid sequence is at least 85%, at least 90%, at least 95%, least 96% at least 97% at least 98% or at least 99% identical to SEQ ID NO:34.

80. The antibody or fragment according to any one of aspects 73 to 79 comprising first and second copies of said VH domain.

81. The antibody or fragment according to any one of aspects 73 to 80, comprising a VL domain which comprises the LCDR1 sequence of SEQ ID NO:54 or 60, or the LCRD3 sequence of SEQ ID NO:54 or 60 comprising less than 5 amino acid substitutions.

In an embodiment, the LCRD3 sequence of SEQ ID NO:54 or 60 comprises less than 4 amino acid substitutions (i.e. 3 or fewer). In an embodiment, the LCRD3 sequence of SEQ ID NO:54 or 60 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the LCRD3 sequence of SEQ ID NO:54 or 60 comprises less than 2 amino acid substitutions (i.e. one substitution).

82. The antibody or fragment according to any one of aspects 73 to 81, comprising a or said VL domain, which VL domain comprises the LCDR2 sequence of SEQ ID NO:52 or 58, or the LCRD2 sequence of SEQ ID NO:52 or 58 comprising less than 2 amino acid substitutions.

83. The antibody or fragment according to any one of aspects 73 to 82, comprising a or said VL domain, which VL domain comprises the LCDR1 sequence of SEQ ID NO:54 or 60, or the LCRD1 sequence of SEQ ID NO:54 or 60 comprising less than 4 amino acid substitutions.

In an embodiment, the LCDR1 sequence of SEQ ID NO:54 or 60 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the LCDR1 sequence of SEQ ID NO:54 or 60 comprises less than 2 amino acid substitutions (i.e. one substitution).

84. The antibody or fragment according to any one of aspects 73 to 83, comprising a or said VL domain, which VL domain comprises an amino acid sequence of SEQ ID NOs: 48, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%) identical to SEQ ID NO:48.

In an embodiment, the light chain variable domain amino acid sequence is at least 85%, at least 90%, at least 95%, least 96% at least 97% at least 98% or at least 99% identical to SEQ ID NO:48.

85. The antibody or fragment according to any one of aspects 81 to 84, comprising first and second copies of said VL domain.

86. The antibody or fragment according to any one of aspects 81 to 85, wherein the antibody or fragment comprises a kappa light chain.

In another embodiment, the VL domain is a kappa VL domain. In an embodiment, the kappa VL domain is derived from the recombination of a human VL gene segment, and a human JL gene segment, wherein the human VL gene segment is IGKV1D-39. In another embodiment, the VL gene segment is IGKV1D-39*01.

In a further embodiment, the human JL gene segment is IGKJ1 or IGKJ3. In another embodiment, the JL gene segment is IGKJ1*01. In another embodiment, the JL gene segment is IGKJ3*01.

87. The antibody or fragment according to any one of aspects 75 to 86 wherein the amino acid substitutions are conservative amino acid substitutions, optionally wherein the conservative substitutions are from one of six groups (each group containing amino acids that are conservative substitutions for one another) selected from:

1) Alanine (A), Serine (S), Threonine (T);
2) Aspartic acid (D), Glutamic acid (E);
3) Asparagine (N), Glutamine (Q);
4) Arginine (R), Lysine (K);
5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W)

In an embodiment, the conservative amino acid substitutions are as described herein. For example, the substitution may be of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P. In another embodiment, the conservative amino acid substitutions may be wherein Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V.

88. The antibody or fragment according to any one of aspects 73 to 87, wherein the antibody or fragment comprises a constant region, e.g. an IgG4 constant region, optionally wherein the constant region is IgG4-PE (Seq ID No:128).

In another example of any aspect herein, the antibody of fragment comprises a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation (i.e. where the wild type leucine residue is mutated

to a glutamic acid residue). In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability.

An alternative effector null human constant region is a disabled IgG1 being an IgG1*01 allele comprising the L235A and/or G237A mutations. In one embodiment, the antibodies or antibody fragments disclosed herein comprise an IgG1 heavy chain constant region, wherein the sequence contains alanine at position 235 and/or 237 (EU index numbering).

89. The antibody according to any one of aspects 73 to 88, wherein the antibody comprises a heavy chain and a light chain, the heavy chain amino acid sequence consisting of the sequence of SEQ ID No:62 and the light chain amino acid sequence consisting of the sequence of SEQ ID No:64.

90. An antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102 for use in treating or preventing a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD.

The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments as described herein optionally apply mutatis mutandis to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply mnutatis mutandis to this use.

91. Use of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102 in the manufacture of a medicament for administration to a human for treating or preventing a hOX40L mediated disease or condition in the human selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant/host rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD.

The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments as described herein optionally apply mutatis mutandis to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply mutatis mutandis to this use.

92. A method of treating or preventing a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD in a human, comprising administering to said human a therapeutically effective amount of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102, wherein the hOX40L mediated disease or condition is thereby treated or prevented.

The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments as described herein optionally apply mutatis mutandis to this method. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply mutatis mutandis to this method.

93. The antibody or fragment according to aspect 90, the use according to aspect 91, or the method according to aspect 92, wherein the hOX40L-mediated disease or condition is GvHD.

In another embodiment, the antibody or fragment is capable of treating or preventing GvHD.

94. The antibody or fragment, the use or the method according to any one of aspects 90 to 93, wherein the antibody is administered prophylactically.

In an embodiment, the prophylaxis prevents the onset of the disease or condition or of the symptoms of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening, or onset, of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening of the disease or condition.

In another embodiment, said antibody is administered intravenously. In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered at a dose selected from about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg, in particular about 1 mg/kg, or about 3 mg/kg.

In another embodiment, said antibody is administered 1-4 days before transplant, e.g. 1-3 days before transplant or 1-2 days before transplant. In another embodiment, said antibody is administered twice a week, weekly, bi-weekly or monthly following transplant, e.g. bi-weekly. In a further embodiment, said antibody is administered intravenously prophylactically 1-3 days before transplant at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg) and then intravenously, bi-weekly at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg).

In another embodiment, the patient is monitored periodically post-transplant, for the presence of a biomarker predictive for the development of GvHD (e.g. acute GvHD), and the anti-OX40L antibody of the invention is administered once the biomarker levels are such that the patient is determined to be at risk of developing GvHD (e.g. acute GvHD). This strategy would avoid unnecessary dosing of drug and unnecessary suppression of the immune system. Examples of biomarkers which may be useful as predictive biomarkers of actue GvHD may be those identified in Levine et al., "*A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study*", Lancet Haematol 2015; 2:e21-29. These biomarkers include, but are not limited to TNFR1, ST-2, elafin and IL2Rα and Reg3α.

95. A human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02), which specifically binds to hOX40L for treating or preventing a hOX40L-mediated disease or condition selected

from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD (e.g. wherein the antibody is for the prevention of GvHD).

The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments optionally apply mutatis mutandis to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply mutatis mutandis to this use.

96. Use of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02), which specifically binds to hOX40L in the manufacture of a medicament for administration to a human for treating or preventing a hOX40L mediated disease or condition in the human selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD.

The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments optionally apply mutatis mutandis to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply mutatis mutandis to this use.

97. A method of treating or preventing a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD in a human, comprising administering to said human a therapeutically effective amount of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02), which specifically binds to hOX40L, wherein the hOX40L mediated disease or condition is thereby treated or prevented.

The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments optionally apply mutatis mutandis to this method. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply mutatis mutandis to this method.

In an embodiment of any one of aspects 95 to 97, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02, IGHJ6*03 and IGHJ6*04. In another embodiment of any one of aspects 95 to 97, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02 and IGHJ6*04. In another embodiment of any one of aspects 95 to 97, the JH gene segment is IGHJ6*02.

In a further embodiment of any one of aspects 95 to 97, the human VH gene segment is IGHV3-23, for example selected from IGHV3-23*01, IGHV3-23*02, IGHV3-23*03, IGHV3-23*04 or IGHV3-23*05. In another embodiment of any one of aspects 95 to 97 the human VH gene segment is IGHV3-23*01 or IGHV3-23*04, in particular IGHV3-23*04.

In a further embodiment of any one of aspects 95 to 97, the human DH gene segment is IGHD3-10, for example selected from IGHD3-10*01 or IGHD3-10*02. In one embodiment of any one of aspects 95 to 97, the human DH gene segment is IGHD3-10*01. In one embodiment of any one of aspects 95 to 97, the human DH gene segment is IGHD3-10*02.

In an embodiment of any one of aspects 90 to 97, the antibody is capable of treating or preventing GvHD. In another embodiment of any one of aspects 90 to 97, the antibody or fragment is used for the treatment or prevention of a disease other than GvD, but the antibody or fragment is capable of treating or preventing GvHD.

98. The antibody or fragment according to aspect 86, or the antibody or fragment according to aspect 95, the use according to aspect 96, or the method according to aspect 97, wherein the antibody or fragment comprises a kappa light chain, e.g. wherein the VL domain of the light chain is derived from the recombination of a human VL gene segment, and a human JL gene segment, wherein the human VL gene segment is IGKV1D-39 (e.g. IGKV1D-39*01), and optionally the human JL gene segment is IGKJ1 (e.g. IGKJ1*01) or IGKJ3 (e.g. IGKJ3*01).

In another embodiment, the VL domain is a kappa VL domain. In an embodiment, the kappa VL domain is derived from the recombination of a human VL gene segment, and a human JL gene segment, wherein the human VL gene segment is IGKV1D-39. In another embodiment, the VL gene segment is IGKV1D-39*01.

In a further embodiment, the human JL gene segment is IGKJ1. In another embodiment, the JL gene segment is IGKJ1*01. In a further embodiment, the human JL gene segment is IGKJ3. In another embodiment, the JL gene segment is IGKJ3*01

99. The antibody or fragment according to any one of aspects 73 to 89, 98, 101 or 102, or the antibody or fragment use or method according to any one of aspects 90 to 98, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation, optionally wherein the antibody is for the prevention of GvHD.

In another aspect, there is provided an antibody or fragment, use or method according to any one of aspects 95 to 98, wherein the antibody or fragment is for treating or preventing transplant rejection (e.g. GvHD) in a human by enabling greater than 80% stem cell donor chimerism by day 12 in said human following donor human hematopoietic stem cell transplantation.

In another embodiment, there is provided an antibody or fragment according to any one of aspects 73 to 89, 98, 101 or 102, wherein the antibody or fragment enables greater

than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

In one embodiment, the chimerism is T-cell ($CD3^+/CD20^-$) chimerism. In another embodiment, the chimerism is peripheral blood chimerism. In another embodiment, the chimerism is peripheral blood or T-cell ($CD3^+/CD20^-$) chimerism.

In one embodiment, the stem cell donor chimerism (e.g. the peripheral blood or T-cell ($CD3^+/CD20^-$) chimerism) is determined using divergent donor- and recipient-specific MHC-linked microsatellite markers, by comparing peak heights of the donor- and recipient-specific amplicons. In another embodiment, stem cell donor chimerism is determined as described in Kean, L S, et al., "*Induction of chimerism in rhesus macaques through stem cell transplant and costimulation blockade-based immunosuppression*", Am J Transplant. 2007 February; 7(2):320-35. In another embodiment, stem cell donor chimerism is determined as described in Example 7.

In one embodiment, the *Rhesus macaque* model of haploidentical haematopoietic stem cell is performed by the transplant (HSCT) recipient animals undergoing a conditioning procedure together with anti-OX40L antibody administration, followed by infusion of a peripheral blood product isolated from a half-sibling donor animal, following which animals continue to receive weekly doses of the anti-OX40L antibody of the invention, and blood samples are taken and analysed for chimerism.

In another embodiment, in the HSCT model, recipient animals receive a conditioning radiation dose of 1020 cGy in 4 dose fractions over 2 days (experimental Day −2 and Day −1) to ablate the host haematopoietic system before intravenous administration of an anti-OX40L antibody of the invention (Day −2, with subsequent intravenous doses on Days 5, 12, 19, 26, 33, 40, 47) and transplant of white blood cell- and stem cell-enriched peripheral blood from an MHC half-matched (half-sibling) donor animal to reconstitute the recipient's immune system, together with provision of continuous supportive care, blood sampling and monitoring for signs of GVHD.

In one embodiment, the antibody or fragment, use or method is for the prevention of GvHD.

In an embodiment, the anti-hOX40L antibody of the invention is administered prophylactically. In one embodiment, the prophylactic treatment prevents the worsening or onset of the disease or condition.

In another embodiment, said antibody is administered intravenously. In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered intravenously. In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered at a dose selected from about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg, in particular about 1 mg/kg, or about 3 mg/kg.

In another embodiment, said antibody is administered 1-4 days before transplant, e.g. 1-3 days before transplant or 1-2 days before transplant. In another embodiment, said antibody is administered twice-weekly, weekly, bi-weekly or monthly following transplant, e.g. bi-weekly. In a further embodiment, said antibody is administered intravenously prophylactically 1-3 days before transplant at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg) and then intravenously, bi-weekly at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg).

In another embodiment, the patient is monitored periodically post-transplant, for the presence of a biomarker predictive for the development of GvHD (e.g. acute GvHD), and the anti-OX40L antibody of the invention is administered once the biomarker levels are such that the patient is determined to be at risk of developing GvHD (e.g. acute GvHD). This strategy would avoid unnecessary dosing of drug and unnecessary suppression of the immune system. Examples of biomarkers which may be useful as predictive biomarkers of actue GvHD may be those identified in Levine et al., "A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study", Lancet Haematol 2015; 2:e21-29. These biomarkers include, but are not limited to TNFR1, ST-2, elafin and IL2Rα and Reg3α.

In a further embodiment, the HSCT model is conducted as described in Miller, Weston P., et al. "*GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaq ue model identifies CD28⁻CD8⁺T-cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression*." Blood, 116, 24(2010):5403-5418. In a further embodiment, the HSCT model is carried out as described in Example 7.

100. The antibody or fragment, use or method according to any one of aspects 95 to 99, wherein the antibody is as defined in any one of aspects 73 to 89, 98, 99, 101 or 102.

101. The antibody or fragment according to any one of aspects 73 to 89, 98, 99 or 102, or the antibody or fragment, use or method according to any one of aspects 90 to 100, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

In one embodiment, the expression level is greater than 1.0 g/L, greater than 1.1 g/L, greater than 1.2 g/L, greater than 1.3 g/L or greater than 1.4 g/L.

102. An antibody or fragment according to any one of aspects 73 to 89, 98, 99 or 101, or the antibody or fragment, use or method according to any one of aspects 90 to 101, wherein the antibody or fragment maintains a naïve population of $CD4^+$ T-cells of >20% of total $CD4^+$ T-cell population at day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

In another aspect, there is provided an antibody or fragment according to any one of aspects 73 to 89, 98, 99 or 101, or an antibody or fragment, use or method according to any one of aspects 90 to 101, wherein the antibody or fragment is for treating or preventing transplant rejection in a human by maintaining a naïve population of donor $CD4^+$ T-cells of >20% of total $CD4^+$ T-cell population at day 12 in said human following donor human hematopoietic stem cell transplantation

In one embodiment, the HSCT model is as described in any embodiment contemplated hereinabove, e.g. as described in connection with aspect 99.

In another embodiment, the naïve population is measured by evaluating the relative proportion of specific T-cell phenotypes using flow cytometry where cell subsets are identified by labelling with fluorescent antibody probes and whereby naïve $CD4^+$ or $CD8^+$ T-cells are labelled $CD4^+/CD28^+/CD95^-$ or $CD8^+/CD28^+/CD95^-$, respectively, central memory $CD4^+$ or $CD8^+$ T-cells are labelled $CD4^+/CD28^+/CD95^+$ or $CD8^+/CD28^+/CD95^+$, respectively, and

effector memory $CD4^+$ or $CD8^+$ T-cells are labelled $CD4^+/CD28^-/CD95^+$ or $CD8^+/CD28^-/CD95^+$, respectively.

103. The antibody or fragment, use or the method according to any one of aspects 90 to 102, further comprising administering to the human a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, in particular rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

In one embodiment, the further therapeutic agent is an anti-inflammatory drug. In aother embodiment, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone), anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab) or anti-TNFa antibodies/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab, certolizumab pegol). In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone) and anti-LFA1 antibodies.

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a derivative of rapamycin.

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basilixumab, daclizumab). In another embodiment, the immunosuppressant that modulates IL-2 signalling is an anti-IL-2 antibody or and anti-IL-2R antibody.

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and rapamycin (sirolimus). In another embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cyclophosphamide. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and mycophenolate mofetil.

104. The antibody or fragment, use or the method according to aspect 103, wherein the further therapeutic agent is administered sequentially or simultaneously with the anti-hOX40L antibody or fragment.

105. A pharmaceutical composition comprising an antibody of fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102 and a pharmaceutically acceptable excipient, diluent or carrier and optionally further comprising a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, in particular rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins. In another embodiment, the agent is an anti-IL-2 antibody.

The pharmaceutically acceptable excipients, diluents or carriers as described herein apply mutatis mutandis to these compositions.

106. In one embodiment, the further therapeutic agent is an anti-inflammatory drug. In aother embodiment, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone), anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab) or anti-TNFa antibodies/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab, certolizumab pegol). In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone) and anti-LFA1 antibodies. In another embodiment, the agent is an anti-IL-2 antibody.

In one embodiment, the further therapeutic agent is independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors

(e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

In one embodiment, the further therapeutic agent is independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basilixumab, daclizumab).

In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In another embodiment, the further therapeutic agent is tacrolimus. In another embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In another embodiment, the further therapeutic agent is ciclosporin. In another embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In another embodiment, the further therapeutic agent is cyclophosphamide. In another embodiment, the further therapeutic agent is mycophenolate mofetil

107. A pharmaceutical composition according to aspect 105, or a kit comprising a pharmaceutical composition as defined in aspect 105, wherein the composition is for treating and/or preventing a hOX40L-mediated condition or disease selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

The hOX40L-mediated diseases of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply mutatis mutandis to this combination.

108. A pharmaceutical composition according to aspect 105 or aspect 106 in combination with, or kit according to aspect 106 comprising a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

The labels, instructions, hOX40L-mediated diseases and condiutions of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply mutatis mutandis to this combination.

109. A nucleic acid that encodes the HCDR3 of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102.

110. A nucleic acid that encodes a VH domain and/or a VL domain of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102.

111. A nucleic acid according to aspect 109 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO: 33 and/or SEQ ID NO: 47.

In an example, the nuecleotide sequence is at least 85% identical, at least 90% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical or at least 99% identical to the sequence of SEQ ID NO: 33 and/or SEQ ID NO: 47.

112. A nucleic acid that encodes a heavy chain or a light chain of an antibody recited in any one of aspects 73 to 89, 98, 99, 101 or 102.

113. A vector comprising the nucleic acid of any one of aspects 108 to 111; optionally wherein the vector is a CHO or HEK293 vector.

114. A host comprising the nucleic acid of any one of aspects 108 to 111 or the vector of aspect 112.

The present invention furthermore relates to the following concepts:

Concept 1. A method of reducing the proportion of (e.g. of depleting or decreasing the level of) $CD45RA^+CCR7^+CD95^+OX40^+$ memory stem T-cells (Tscm) comprising combining said cells with an agent (such as an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), and whereby the proportion of said Tscm cells is reduced (e.g. whereby the level of said Tscm cells is decreased or depleted).

$CD45RA^+CCR7^+CD95^+OX40^+$ memory stem T-cells (Tscm) are thought to be a newly-defined subset of stem cell memory T-cells which are long-lived and have the capacity for self-renewal. Therefore, these cells may be detrimental in various diseases, such as GvHD and autoimmune disorders, because they are the source of a persistent and multipotent population of potentially self-reactive effector T-cells. It is known that T-cells develop through a pathway beginning with naïve T-cells (Tn), through stem cell memory T-cells (Tscm), through central memory T-cells (Tcm) and effector memory T-cells (Tem), before developing into short-lived effector T-cells (Teff), as described in Gattinoni and Restifo (2013), Inside Blood, 121(4), 567-568. At these various stages, different markers are expressed on the surface of the T-cells, which reflect the activation status of the T-cells, their tissue localisation and their responsiveness to various stimuli such as inflammatory cytokines.

Tscm cells as defined herein are characterised as $CD45RA^+CCR7^+CD95$ $OX40^+$. For alternative prior art classifications of different T-cell types, see the figure in Gattinoni and Restifo (2013). Further markers may be present or absent, but Tscm cells must at a minimum be $CD45RA^+CCR7^+CD95^+OX40^+$. The various cell-surface markers are, in one embodiment, identified using flow cytometry using methods which are well-known to those of skill in the art. In one embodiment, the Tscm cells may additionally be $CD8^+$. In another embodiment, the Tscm cells may additionally be CD62L+. Flow cytometry techniques are well-known to those skilled in the art. Agents which may be used in flow cytometry techniques are defined in Example 7 below. In one embodiment, the flow cytometry is carried out as described in Example 7 below. In another embodiment, the flow cytometry is carried out as described in Baumgarth & Roederer (2000), Journal of Immunological Methods, 243, 77-97. (see concept 25 hereinbelow).

In a particular embodiment, the Tscm cells are characterised as being $CD4^+CD45RA^+CCR7^+CD95^+OX40^+$.

Without being bound by theory, it is thought that reducing this Tscm population will have a number of benefits in various diseases, as set out herein. In one embodiment, the Tscm cells are active Tscm cells.

Throughout concepts 1 to 83 herein, the proportion or levels of Tscm cells may be reduced in a sample, or indeed in (a sample of) the blood of a subject. The proportion or levels of Tscm cells may be determined relative to the entire T-cell population in the sample. In one embodiment, the proportion or level of Tscm cells is determined relative to other T-cells in the sample. T-cells generally may be identified as being $CD3^+$, and include Tn cells, Tscm cells, Tcm cells, Tsm cells and Teff cells. In a particular embodiment, the proportion or level of Tscm cells is determined relative to Tn cells (as defined hereinbelow) in the sample. The proportion or level of Tscm cells may be altered by depletion or by a decrease. In one embodiment, a ratio of T-cell types

may be the same as a proportion of Tscm cells (e.g. as for concept 2 hereinbelow). In another embodiment, a level of T-cell types may be the same as a proportion of Tscm cells. In one embodiment, the ratio or proportion of Tscm:Tn is greater than 50:50. Particular ratios and proportions are as described in concepts 23 and 24.

As used in concepts 1 to 83 herein "depleting" and "depletes" describes an active effect following combination with an agent (such as an antibody) on the desired target to kill or remove the target cells (e.g. Tscm cells). When the agent is an antibody, this is usually achieved through effector functions, such as ADC, ADCC or CDC. Alternatively, the target may be killed or removed by a toxin, which may be conjugated to a drug or targeting moiety (such as an anti-OX40 or an anti-OX40L antibody). Such toxins will selectively kill or remove the cell to which they are targeted. Suitable immunoconjugates are described on page 176, and on pages 200 to 204, and 220 (in particular pages 200 to 204) herein.

"Decreasing" or "decreases" as used in concepts 1 to 83 herein refers to a mechanism other than depletion, which reduces the absolute number of cells in a given population. This may be achieved indirectly, for example through a blocking or neutralising agent (such as an antibody) against a target which indirectly results in the killing of a target cell (such as a Tscm), or prevents the expansion or growth of the target cells, resulting in an apparent decrease in proportions relative to another type of cell (such as Tn cells).

As used in concepts 1 to 83 herein, a "level" of a T-cell population may refer to the absolute number, or to the relative proportion of a type of T-cell.

Throughout the various concepts 1 to 83 described herein, an agent which reduces the proportion of Tscm cells may be, for example, an antibody or fragment thereof, a short interfering RNA (SiRNA), a zinc finger, a DARPin, an aptamer, a Spiegelmer, an ant-calin, a receptor-Fc fusion, a ligand-Fc fusion or a small molecule. In one embodiment, the agent targets OX40 (e.g. human OX40), or ligands of OX40. In another embodiment, the agent targets OX40L (e.g. human OX40L), or receptors of OX40L. In one example, the agent may be an OX40-Fc fusion protein (e.g. hOX40-Fc fusion), or may be an OX40L-Fc fusion protein (e.g. hOX40L-Fc fusion), both including functional fragments of OX40 and OX40L. These types of constructs are known to those skilled in the art. In another embodiment, the agent targets OX40 (e.g. human OX40). In another embodiment, the agent targets OX40L (e.g. human OX40L).

In a particular embodiment, the agent is an antibody or fragment thereof. Formats and structures of antibodies and fragments are described elsewhere herein and may be applied to any of the concepts disclosed herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein). In a particular embodiment, the agent is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab.

Concept 2. A method of altering the ratio of cell types in a T-cell population in a sample, the method comprising:

a. providing said population, wherein the population comprises a mixture of different T-cell types, wherein the population comprises $CD45RA^+CCR7^+CD95^+$ $OX40^+$ Tscm cells,
b. providing an agent which reduces the proportion of Tscm cells (or providing an anti-OX40 or an anti-OX40L antibody or fragment thereof); and
c. combining said cell population with an amount of said agent (e.g. antibody or fragment thereof) effective to alter the ratio (e.g. to reduce the proportion) of Tscm cells in said population.

Throughout concepts 1 to 83 herein, the ratio of T-cell types may be altered in a sample, for example by increasing the proportion of naïve T-cells (Tn, as defined hereinbelow). In another embodiment, the ratio of T-cell types may be altered by decreasing the proportion of Tscm cells. The ratio of Tscm cells may be determined relative to the entire sample. In one embodiment, the ratio of T-cells is determined by comparing the proportion of naïve T-cells or Tscm cells relative to other T-cells in the sample. T-cells generally may be identified as being $CD3^+$, and include Tn cells, Tscm cells, Tcm cells, Tem cells and Teff cells. In a particular embodiment, the ratio of T-cells is determined as the ratio of Tscm cells relative to naïve T-cells in the sample. The ratio of T-cells may be altered by depletion or by a decrease of Tscm cells. The ratio of T-cells may be altered by an increase or expansion of naïve T-cells.

Concept 3. A method according to concept 2, wherein in step a), the population further comprises $CD45RA^+CCR7^+$ $CD95^-$ naïve T-cells (Tn).

Naïve T-cells (Tn) as defined in concepts 1 to 83 herein are characterised as $CD45RA^+CCR7^+CD95^-$. Further markers may be present or absent, but Tn cells must at a minimum be $CD45RA^+CCR7^+CD95^-$. In one embodiment, Tn cells may additionally be $CD8^+$ or $CD4^+$, in particular $CD4^+$. It is thought that Tn are beneficial because these represent the entire pool of T-cells from which adaptive T-cell immune responses can develop to protect an indiviudal when exposed to potentially harmful pathogens and malignant cells.

Concept 4. A method according to concept 3 wherein the ratio of Tscm:Tn in the population of step a) is greater than 50:50.

Concept 5. A method according to any one of concepts 1 to 4, wherein the method is carried out ex vivo in a sample of blood extracted from a human donor subject.

Concept 6. A method according to concept 5, wherein blood produced by said method is reintroduced to a recipient human subject.

In one embodiment, the recipient human subject is the same donor human subject from whom the sample was removed. In another embodiment, the recipient human subject is different to the donor human subject. When the recipient is different to the donor, it is preferable that the donor is of the same gender as the recipient subject. In another embodiment, the donor may be of a similar age and ethnicity as the recipient subject. In another embodiment, the donor may have the same or similar allotype markers as the recipient subject.

In another embodiment, the recipient human donor may receive more than one transfusion of donor blood, according to the severity of the disease to be treated.

Concept 7. A method according to any one of concepts 1 to 4, wherein the method is carried out in vivo in a human subject.

Concept 8. A method according to concept 7, wherein the subject has or is at risk of a Tscm-mediated disease or condition.

As used herein, a subject may be identified as being "at risk of a Tscm-mediated disease or condition" when the cellular changes in their T-cell population have begun to take

place, but the subject has not yet presented symptoms or would not be diagnosed as having such a disease by any conventional method. Thus, the methods and uses disclosed herein may aid in the early identification of patients who will develop such diseases. In one embodiment, the disease is prevented (i.e. the treatment is prophylactic).

In a particular embodiment, the subject is at risk of GvHD or transplant rejection when they are pre-operative for a transplant. Potential transplant therapies are envisaged in concept 78 hereinbelow.

In any of concepts 1 to 83 described herein, a Tscm-mediated disease may be as defined in any of concepts 71 to 80 hereinbelow.

Concept 9. A method of treating or reducing the risk of a Tscm-mediated disease or condition in a subject, the method comprising combining a population of T-cells with an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), and whereby the proportion of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells is reduced in the population (e.g. whereby the level of said Tscm cells is decreased or depleted in said population).

As used in concepts 1 to 83 herein, the "treatment" of a Tscm-mediated disease includes the reduction of one or more symptom(s) of said Tscm-mediated disease. The "prevention" of a Tscm-mediated disease includes the prevention of one or more symptom(s) of said Tscm-mediated disease.

Concept 10. A method according to any one of concepts 7 to 9, wherein the agent (e.g. antibody or fragment thereof) is combined by administering said agent (e.g. antibody or fragment) in a therapeutically effective amount to said subject, whereby said Tscm-mediated disease or condition is treated or the risk of said Tscm-mediated disease or condition is reduced in said subject.

In one embodiment, the administration is prophylactic to reduce the risk of a Tscm-mediated disease.

In any of the concepts described herein, a therapeutically effective or prophylactically effective amount of the antibody or fragment is as described elsewhere (see page 29, 73, 189 to 191 for therapy, and pages 72, and 272 to 273 for prophylaxis). In any of the concepts described herein, modes and compositions for administration may be as described elsewhere (see pages 290 to 314 herein). In one embodiment, the antibody or fragment is administered by bolus injection (e.g. intravenously).

Concept 11. A method of treating or reducing the risk of a Tscm-mediated disease or condition in a subject comprising administering to said subject a therapeutically effective amount of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), and whereby the proportion of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells is reduced (e.g. whereby the level of said Tscm cells is decreased or depleted), wherein the Tscm-mediated disease or condition is thereby treated or the risk of said Tscm-mediated disease or condition is reduced.

Concept 12a. An agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for use in treating or reducing the risk of a Tscm-mediated disease or condition in a subject; or concept 12b. An anti-OX40 or an anti-OX40L antibody or fragment thereof for use in treating or reducing the risk of a Tscm-mediated disease or condition in a subject.

Concept 13a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for the treatment or prevention of a Tscm-mediated disease or condition in a subject; or concept 13b. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof for the treatment or prevention of a Tscm-mediated disease or condition in a subject.

Concept 14a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) in the manufacture of a medicament for the treatment or prevention of a Tscm-mediated disease or condition in a subject; or concept 14b. The use of an anti-OX40 or an anti-OX40L antibody or fragment thereof in the manufacture of a medicament for the treatment or prevention of a Tscm-mediated disease or condition in a subject.

Concept 15a. A composition comprising an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for the treatment or prevention of a Tscm-mediated disease or condition in a subject; or concept 15b. A composition comprising an anti-OX40 or an anti-OX40L antibody or fragment thereof for the treatment or prevention of a Tscm-mediated disease or condition in a subject.

Concept 16. A method of treating a disease or condition in a subject in need thereof, comprising:

a. Performing an assay to measure the level of $CD45RA^+$ $CCR7^+CD95^-$ Tn cells and the level of $CD45RA^+$ $CCR7^+CD95^+OX40^+$ Tscm cells in a sample obtained from the subject; and
b. Administering an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), such as an anti-OX40 or an anti-OX40L antibody or fragment thereof, to the subject when the ratio of Tscm:Tn cells in the sample is determined in the assay to be greater than 50:50.

Concept 17a. An agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for use in therapy of a subject, wherein the agent is to be administered to a subject who has, or has been determined to have, a ratio of CD45RA*$CCR7^+$ $CD95^+OX40^+$ Tscm cells: $CD45RA^+CCR7^+CD95^-$ Tn cells of greater than 50:50; or concept 17b. An anti-OX40 or an anti-OX40L antibody or fragment thereof for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a ratio of $CD45RA^+CCR7^+CD95$ $OX40^+$ Tscm cells: $CD45RA^+CCR7^+CD95^-$ Tn cells of greater than 50:50.

Concept 18a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for therapy of a subject who has, or has been determined to have, a ratio of $CD45RA^+CCR7^+CD95$ $OX40^+$ Tscm cells: $CD45RA^+$ $CCR7^+CD95^-$ Tn cells of greater than 50:50; or concept 18b. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof for therapy of a subject who has, or has

been determined to have, a ratio of $CD45RA^+CCR7^+CD95^+$ $OX40^+$ Tscm cells: $CD45RA^+CCR7^+CD95^-$ Tn cells of greater than 50:50.

Concept 19a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) in the manufacture of a medicament for use in therapy of a subject, wherein the agent is to be administered to a subject who has, or has been determined to have, a ratio of $CD45RA^+CCR7^+CD95$ $OX40^+$ Tscm cells: $CD45RA^+CCR7^+CD95^-$ Tn cells of greater than 50:50; or concept 19b. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof in the manufacture of a medicament for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a ratio of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells: $CD45RA^+CCR7^+CD95^-$ Tn cells of greater than 50:50.

In any of concepts 17 to 19, the ratio is determined in a sample, for example, in a sample of blood obtained from said subject.

Concept 20. A method according to concept 16a or b, an agent or an antibody or fragment for the use according to concept 17a or b, or the use according to concept 18a or b or concept 19 a or b, wherein the therapy is the treatment or prevention of a Tscm-mediated disease or condition, preferably wherein the therapy is the treatment of a Tscm-mediated disease or condition.

In another embodiment, the subject has or is at risk of a Tscm-mediated disease or condition. The Tscm-mediated disease or condition may be as defined in any one of concepts 71 to 80 hereinbelow.

Concept 21. A method of classifying a subject as having or as being at risk of a Tscm-mediated disease or condition (e.g. which disease or condition is suitable for treatment with an anti-OX40 or an anti-OX40L antibody or fragment thereof), comprising:

a. performing an assay that detects (i) $CD45RA^+CCR7^+$ $CD95^+OX40^+$ Tscm cells, and (ii) $CD45RA^+CCR7^+$ $CD95^-$ Tn cells in a sample obtained from said subject; and
b. classifying the subject as having, or as being at risk of a Tscm-mediated disease or condition if the ratio of Tscm:Tn cells in the sample is greater than 50:50.

Concept 22. A method according to concept 21 further comprising the step of:

c. administering to said subject an anti-OX40 or an anti-OX40L antibody or fragment thereof which reduces the proportion of said Tscm cells in the blood of said subject, (e.g. which depletes or decreases the level of said Tscm cells) if said subject has been classified as having or as being at risk of a Tscm-mediated disease or condition in step b).

Tscm-mediated diseases or conditions which may be suitable for treatment with an anti-OX40 or an anti-OX40L antibody or fragment thereof are as described in any one of concepts 71 to 80 herein below.

Concept 23. A method according to any one of concepts 4, 16, or 20 to 22, an agent or an antibody or fragment for the use according to concept 17 or 20, or the use according to any one of concepts 18 to 20, wherein the ratio of Tscm:Tn cells is (or is determined or classified to be) greater than 60:40, or is greater than 70:30, or is greater than 75:25, such as greater than 70:30.

In another embodiment, the ratio is (or is determined or classified to be) greater than 55:45. In another embodiment, the ratio is (or is determined or classified to be) greater than 65:35.

Concept 24. A method, agent or an antibody or fragment for the use, or the use according to concept 23, wherein the ratio of Tscm:Tn cells is (or is determined or classified to be) greater than 80:20, or is greater than 85:15, for example greater than 90:10, e.g. greater than 95:5.

Concept 25. A method according to any one of concepts 4, 16, or 20 to 24, an agent or an antibody or fragment for the use according to any one of concepts 17, 20, 23 or 24, or the use according to any one of concepts 18 to 20, 23 or 24, wherein the ratio of Tscm:Tn cells is determined (or is determinable) by flow cytometry.

Flow cytometry techniques are well-known to those skilled in the art, as discussed above. Agents which may be used in flow cytometry techniques are defined in Example 7 below. In one embodiment, the flow cytometry is carried out as described in Example 7 below. In another embodiment, the flow cytometry is carried out as described in Baumgarth & Roederer (2000).

Concept 26. A method for treating or reducing the risk of a Tscm-mediated disease or condition with an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof, comprising the steps of:

a. determining whether the subject is a candidate for treatment by detecting the presence of OX40 on the surface of $CD45RA^+CCR7^+CD95^+$ Tscm cells obtained from a sample from the subject; and
b. administering said agent, such as said antibody or fragment, to the subject if the subject is identified as a candidate for treatment.

Concept 27. A method according to concept 26, wherein the presence of OX40 on the surface of the Tscm cells is determined using flow cytometry.

In one embodiment, the subject is a human and the OX40 is human OX40.

Concept 28. A method, comprising:

a. obtaining at least two T-cell samples derived from a subject who has or is at risk of a Tscm-mediated disease or condition, wherein said at least two samples comprise a first sample and a second sample,
b. determining levels of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells in said first and second samples;
c. treating said subject to reduce the proportion of $CD45RA^+CCR7^+CD95$ $OX40^+$ Tscm cells (e.g. to deplete or decrease the level of Tscm cells) by administering an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, if the levels of Tscm cells in said second sample are elevated as compared to said first sample, in order to treat or reduce the risk of said Tscm-mediated disease or condition.

The levels of Tscm in said first and second samples in step b. may be either the absolute number of Tscm cells, or may be the relative proportions of Tscm (e.g. the ratio of Tscm:Tn, or Tacm:total T-cell count). The levels of Tscm cells may be elevated in the second sample if they are statistically significantly higher than the levels in the first sample.

Concept 29. A method according to concept 28, wherein said first sample is collected:

i. before the onset of said disease or condition; or

ii. after the onset of said disease or condition; and optionally wherein said second sample is collected no longer than one month, e.g. no longer than one week after the first sample.

As used in the concepts herein, a subject may be determined to be "before the onset of a Tscm-mediated disease or condition" if the subject is presenting no symptoms which would conventionally be associated with said disease or condition or if the subject would not be diagnosed as having such a disease or condition by any conventional method. For example, the presence of signs and symptoms of acute GvHD may be staged and graded according to a standardised scale such as described in Przepiorka et al. (1995), 1994 Consensus Conference on Acute GvHD Grading Bone Marrow Transplant 1995; 15, 825-828. Similar disease grading scales are also in routine clinical use for other relevant diseases, such as rheumatoid arthritis and inflammatory bowel diseases.

Concept 30. A method according to concept 28 or concept 29, wherein the Tscm-mediated disease or condition is a transplant, and wherein in step c) the treatment is in order to reduce the risk of transplant rejection, optionally wherein the first sample is taken before the transplant, and the second sample is taken after the transplant.

The first sample may be taken pre-operatively, e.g. after the subject has been identified as a candidate for treatment. The second sample is taken after the transplant and may be used by physicians as a method of monitoring the acceptance of the transplant. Thus, it may be that the physician may take more than one sample after the transplant, e.g. a daily blood sample to monitor the subject for changes in the proportion of Tscm:Tn or the levels of Tscm in the sample. The samples may be taken every other day, weekly, monthly or longer (including yearly) according to the likelihood of transplant rejection. For example, if the transplant is autologous, then the likelihood of transplant rejection may be reduced as compared to an allogeneic transplant, and therefore the time period between sample collections post-transplant may be longer than with an allogeneic transplant, where the risk of rejection is higher.

Concept 31. A method according to concept 30, wherein in step a), the first sample is collected no longer than a week, e.g. no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days before said transplant.

Concept 32. A method according to any one of concepts 28 to 31, wherein the second sample is collected no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days after the first sample or after said transplant.

Concept 33. A method according to any one of concepts 28 to 32, wherein in step c), the levels of Tscm cells in said second sample are greater than double the levels as compared to said first sample, for example are greater than three times the level, or preferably are greater than 4 times the levels as compared to said first sample.

In one embodiment, in step c), the levels of Tscm cells in said second sample are greater than 4 times (e.g. greater than 4.5 times) the levels as compared to said first sample. In another embodiment, in step c), the levels of Tscm cells in said second sample are greater than 5 times the levels as compared to said first sample.

Concept 34. A method according to any one of concepts 30 to 33, wherein the subject is given a prophylactic dose of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or is given a prophylactic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, before said transplant, and the first sample is taken before administration of said agent, or antibody or fragment thereof, and wherein the second sample is taken after the transplant or after administration of the agent, or the antibody or fragment thereof (preferably, where in the second sample is taken after the transplant).

In one embodiment, the prophylactic dose is an effective prophylactic dose. By "effective", it is meant that the dose is effective to reduce the proportion or level of Tscm as described herein, or effective to prevent or reduce the risk of a Tscm-mediated disease or condition.

The methods as described herein may be used to correct an already-abberent level of Tscm cells, by administration of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or by administration of an anti-OX40 or an anti-OX40L antibody or fragment thereof, before a transplant, in order to reduce the risk of transplant rejection after the transplant. Therefore, multiple samples may be taken after administration of the agent (or of the anti-OX40 or an anti-OX40L antibody or fragment thereof), but before the transplant.

Comparison may be made between the collected samples and a sample obtained from a healthy donor.

Concept 35. A method according to any one of concepts 30 to 33, wherein the subject is given a therapeutic dose of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the transplant.

In one embodiment, the therapeutic dose is an effective therapeutic dose. By "effective", it is meant that the dose is effective to reduce the proportion or level of Tscm as described herein, or effective to treat a Tscm-mediated disease or condition.

In one embodiment, the second sample is taken after the administration of the agent, or antibody or fragment thereof. This would enable a physician to check that the levels or proportion of Tscm cells remain "normal", i.e. as compared to the first sample, or to a sample obtained from a healthy donor.

Concept 36. A method according to any one of concepts 30 to 33, wherein the subject is given a therapeutic dose of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the administration of said agent, or of said antibody or fragment thereof.

Concept 37. A method according to any one of concepts 34 to 36, further comprising the steps of:

d. obtaining a third sample derived from said subject;

e. determining the levels of $CD45RA^+CCR7^+CD95^+$ $OX40^+$ Tscm cells in said third sample;

f. treating said subject to reduce the proportion of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells (e.g. to deplete or decrease the level) of Tscm cells by administering an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, if the levels

of Tscm cells in said third sample are elevated as compared to said second or said first sample.

The levels are considered to be "elevated" as described hereinabove (e.g. as for concept 28 or 33).

Concept 38. A method according to concept 37, wherein steps d) to f) are repeated as necessary until the levels of Tscm cells remain at a therapeutically-effective, or at a prophylactically-effective level, e.g. at a substantially constant level in said subject.

As used in the concepts herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples.

Concept 39. A method according to any one of concepts 28 to 38, wherein the second sample is taken no longer than one month after the first sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the first sample, and optionally wherein the third sample is taken no longer than one month after the second sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the second sample.

Timepoints for taking any of the samples described in these concepts will depend on a number of factors, such as the likelihood of the subject having or being at risk of a Tscm-mediated disease (e.g. GvHD or transplant rejection), the level determined in the previous sample, the type of transplant, etc. A person skilled in the art will be able to determine appropriate time points as necessary or desired. The timepoints may be monthly, every other month, quarterly, half-yearly or yearly, if desired.

Concept 40. In vitro use of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells, as a diagnostic for a Tscm-mediated disease or condition in a subject (for example, which disease or condition can be treated or prevented with an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof in the subject).

In one embodiment, there is provided biomarker of an autoimmune disease, HIV-1, and a T-cell malignancy, wherein the biomarker is a $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cell. In another embodiment, the biomarker is of any of the diseases described in concepts 71 to 80 hereinbelow. In another embodiment, the Tscm cell is a $CD4^+CD45RA^+$ $CCR7^+CD95$ $OX40^+$ Tscm cell.

Concept 41. Use of a biomarker of a Tscm-mediated disease or condition, wherein the biomarker is $CD45RA^+$ $CCR7^+CD95^+OX40^+$ Tscm cells, in vitro as a diagnostic for a Tscm-mediated disease or condition (e.g. which disease or condition can be treated or prevented with an an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof in the subject).

In one embodiment, the Tscm-mediated diseases are any of those described in concepts 71 to 80 hereinbelow.

Concept 42. A method of maintaining $CD45RA^+CCR7^+$ $CD95^-$ Tn cells, whilst decreasing $CD45RA^+CCR7^+CD95$ $OX40^+$ Tscm cells in a population of T-cells in a sample, said method comprising contacting said sample with an effective amount of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof.

As used in concepts 1 to 83 herein, "maintains" or "maintaining" with respect to a level or a proportion may be described as substantially constant. A substantially constant level may be within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In one embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g greater than 97% or greater than 99%). "Statistically significant" may be as defined above in concept 28 herein.

Concept 43. A method according to concept 42, wherein the level of said Tn cells are at least maintained, whilst the levels of said Tscm cells are decreased in said sample, optionally wherein the sample is from a subject.

Concept 44. A method according to any one of concepts 2 to 8, 10, 16, 20, 21, 23 to 39, 42 or 43, an agent or an antibody or fragment thereof for the use according to any one of concepts 12, 17, 20, 21 or 23 to 25, the use according to any one of concepts 13, 14, 18 to 20 or 23 to 25, or the composition according to concept 15, wherein agent (e.g. the antibody or fragment thereof) reduces the proportion of $CD45RA^+CCR7^+CD95^+OX40^+$ Tscm cells (e.g. depletes or decreases the level of Tscm cells).

Concept 45. A method or fragment thereof according to any one of concepts 1 to 8, 10, 16, 20, 21, 23 to 39 or 42 to 44, an agent or an antibody or fragment thereof for the use according to any one of concepts 12, 17, 20, 21, 23 to 25, or 44, the use according to any one of concepts 13, 14, 18 to 20 or 23 to 25 or 44, or the composition according to concept 15 or concept 44, wherein the agent (e.g. the antibody or fragment thereof) maintains $CD45RA^+CCR7^+CD95^-$ Tn cells.

Concept 46. A method according to concept 42 or 45, an agent or an antibody or fragment thereof for the use according to concept 45, the use according to concept 45, or the composition according to concept 45, wherein the Tn cells are maintained at a level of not below 50% of the level of said Tn cells in a sample from a healthy donor or from said subject before the onset of disease.

The healthy donor is preferably of the same species at the subject, for example, wherein the subject is a human, the donor is most preferably also a human. The donor is also preferably of the same gender as the subject. The donor is preferably of a similar age and ethnicity as the subject.

Concept 47. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 46, wherein the Tn cells are maintained at a level of not below 55% (such as not below 60%, for example not below 65%, e.g. not below 70%).

Concept 48. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 47, wherein the Tn cells are maintained at a level of not below 75% (such as not below 80%, for example not below 85%, e.g. not below 90%)

Concept 49. A method according to any one of concepts 1 to 8, or 42 to 48, an agent or an antibody or fragment thereof for the use according to any one of concepts 44 to 48, the use according to any one of concepts 38 to 41, or the composition according to any one of concepts 44 to 48,

wherein the Tscm cells are depleted or decreased to a level of less than 50% of the level of said Tscm cells in a sample from a healthy donor or from said subject before the onset of disease.

Concept 50. A method, an antibody or fragment for the use, a use or a composition according to concept 49, wherein the Tscm cells are depleted or decreased to a level of less than 45% (such as less than 40%, for example less than 35%, e.g. less than 30% or less than 25%).

Concept 51. A method, an antibody or fragment for the use, a use or a composition according to concept 50, wherein the Tscm cells are depleted or decreased to a level of less than 20% (such as less than 15%, for example less than 10%.

Concept 52. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment is a depleting antibody or fragment that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.

The potency of Fc-mediated effects may be enhanced by engineering the Fc domain by various established techniques. Such methods increase the affinity for certain Fc-receptors, thus creating potential diverse profiles of activation enhancement. This can achieved by modification of one or several amino acid residues (e.g. as described in Lazar et al., 2006, Proc. Natl. Acad. Sci. U.S.A., March 14; 103(11): 4005-10, which modifications are incorporated herein by reference) or by altering the natural glycosylation profile of the Fc domain by, for example, generating under fucosylated or de-fucosylated variants (as described in Natsume et al., 2009, Drug Des Devel Ther., 3:7-16, which glycosylation profiles are incorporated herein by reference). For example, to increase ADCC, residues in the hinge region can be altered to increase binding to Fc-gamma RIII (see, for example, Shields et al, 2001, J Biol Chem., March 2; 276(9):6591-604, which modifications are incorporated herein by reference.).

Equally, the enhancement of CDC may be achieved by amino acid changes that increase affinity for C1q, the first component of the classic complement activation cascade (see Idusogie et al., J. Immunol., 2001; 166:2571-2575, which modifications are incorporated herein by reference). Another approach is to create a chimeric Fc domain created from human IgG1 and human IgG3 segments that exploit the higher affinity if IgG3 for Clq (Natsume et a., 2008, Cancer Res., which chimeras are incorporated herein by reference The antibody may be a targeting antibody (such as an anti-OX40 or an anti-OX40L antibody) which exhibits its effects through a toxin, to which the antibody may be conjugated. Such toxins will selectively kill or remove the cell to which they are targeted. Suitable immunoconjugates are described on page 176, and on pages 198 to 202, and 219 (in particular pages 198 to 200) herein.

Thus, in one embodiment, the antibody or fragment thereof is de-fucosylated. In another embodiment, the antibody or fragment thereof contains one or more mutations in the hinge or Fc region which enhances the ADCC and/or the CDC functionality.

Methods for determining depletion and/or ADCC and/or CDC functionality may be as described herein, or as well-known by those skilled in the art.

The OX40 antibodies may be as described in WO2014/148895 (Biocerox Products & Janssen Pharmaceuticals; see claims on pages 138 to 139 for specific sequences which are incorporated herein by reference), WO2013/068563 (Biocerox Products & Janssen Pharmaceuticals; see claims on pages 138 to 139 for specific sequences which are incorporated herein by reference), WO2013/130102 and WO2013/119202 (Providence Health & Services—Oregon, see mAb 9B12 as described in Weinberg, A. D., et al., J. Immunother., 29, 575-585 (2006), and fusions with IL-2 which are incorporated herein by reference), WO2013/038191 (Bioceros B. V.; see claims 4 to 11 for specific antibody sequences which are incorporated herein by reference), WO2013/028231 (Board of Regents, the University of Texas System; see claims 1 to 12 for specific antibody sequences which are incorporated herein by reference), WO2013/008171 (Glenmark Pharmaceuticals S.A.; see claims 1, 2, 5 to 12, 16 to 21 and 28 to 29 for specific antibody sequences which are incorporated herein by reference), WO2012/027328 (Board of Regents, the University of Texas System; see claims 1 to 11 for specific antibody sequences which are incorporated herein by reference), WO2010/096418 (UCB Pharma S.A.; see claims 1 to 9 and 11 to 14 for specific antibody sequences which are incorporated herein by reference), WO2009/079335 (Medarex, Inc & Pfizer, Inc; see claims 1 to 9 and 14 to 17 for specific antibody sequences which are incorporated herein by reference), WO2008/106116 (Genentech, Inc; see claims 1 to 12 for specific antibody sequences which are incorporated herein by reference), WO2007/062245 (Kirin Beer Kabushiki Kaisha & La Jolla Institute for Allergy and Immunology; see claim 12 for specific antibody deposit numbers, and claim 16 for specific antibody sequences, which are incorporated herein by reference) WO03/106498 (Crucell Holland B.V.; see claims 3 and 4 for specific antibody sequences which are incorporated herein by reference).

More generally anti-OX40 antibodies are described in WO99/42585, WO95/21251, WO95/21915 and WO95/12673, the disclosures of which with respect to antibody characterisation and sequences are incorporated herein by reference.

Concept 53. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is an antagonistic or blocking antibody.

Methods for determining antagonism or blocking functionality may be as described herein, or as well-known by those skilled in the art. For example, in vitro techniques include SPR and/or ELISA, which are described elsewhere herein.

Concept 54. A method, an antibody or fragment for the use, a use or a composition according to concept 53, wherein the antibody specifically binds to OX40L (in particular human OX40L).

The OX40L antibodies may be any antibody or fragment as described herein. In one embodiment, the OX40L antibody is the antagonist anti-human OX40L (gp34) antibody ik-1 described by Matsumura et al., J Immunol. (1999), 163:3007.

Concept 55. A method, an antibody or fragment for the use, a use or a composition according to concept 56, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

SPR and ELISA methods may be as described elsewhere herein.

Concept 56. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is a humanized, human or fully human antibody.

Other antibody constructs may be as described herein.

Concept 57. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is a fragment of an antibody

selected from the list of multispecific antibodies (eg. bispecific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

Concept 58. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

Concept 59. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

Concept 60. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

Concept 61. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises a HCDR3 selected from:

a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);

b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);

c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);

d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No: 106);

e. a CDR3 of any of the nanobodies disclosed in WO2011/073180 (Ablynx, Seq ID Nos: 161 to 167 therein, which are incorporated herein by reference);

f. an HCDR3 of any of the antibodies disclosed in WO2006/029879 (Roche/Genentech, Seq ID Nos: 33 to 38 therein, which are incorporated herein by reference); or

g. an HCDR3 of any of the antibodies disclosed in U.S. Pat. No. 7,812,133 (Genentech, Seq ID Nos: 11 or 12 therein, which are incorporated herein by reference).

Concept 62. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises:

a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);

b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);

c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);

d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No:104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);

e. the CDRs of any of the nanobodies disclosed in WO2011/073180 (Ablynx: Seq ID Nos: 161 to 167 therein for CDR3; Seq ID Nos: 147 to 153 therein for CDR2; and Seq ID Nos: 133 to 139 therein for CDR1, which sequences are incorporated herein by reference);

f. the CDRs of any of the antibodies disclosed in WO2006/029879 (Roche/Genentech: Seq ID Nos: 33 to 38 therein for CDRH3; Seq ID Nos: 21 to 25 therein for CDRH1 and Seq ID Nos: 26 to 32 therein for CDRH2; SEQ ID NOs: 39 to 44 therein for CDRL1; SEQ ID NOs: 45 to 50 therein for CDRL2; and SEQ ID NOs: 51 to 57 therein for CDRL3, which sequences are incorporated herein by reference); or

g. the CDRs of any of the antibodies disclosed in U.S. Pat. No. 7,812,133 (Genentech: Seq ID Nos: 11 or 12 therein for CDRH3; Seq ID Nos: 7 or 8 therein for CDRH1 and Seq ID Nos: 9 or 10 therein for CDRH2; SEQ ID NOs: 1 or 2 therein for CDRL1; SEQ ID NOs: 3 or 4 therein for CDRL2; and SEQ ID NOs: 5 or 6 therein for CDRL3, which sequences are incorporated herein by reference).

Concept 63. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);

b. the VH and/or VL domains of antibody 10A7 (Seq ID No: 2 for VH and/or Seq ID No: 16 for VL);

c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);

d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);

e. a VH domains of any of the nanobodies disclosed in WO2011/073180 (Ablynx, Seq ID Nos: 177 to 185, 199 to 226 therein, which sequences are incorporated herein by reference [reproduced herein as Seq ID Nos: 177 to 213]);

f. the VH and/or VL domains of any of the antibodies disclosed in WO2006/029879 (Roche/Genentech, Seq ID Nos: 2, 4, 6, 8, 10, 12, 17, 19 and 20 therein for VH domains; and Seq ID Nos: 1, 3, 5, 7, 9, 11, 16 and 18 therein for VL domains, which sequences are incorporated herein by reference [reproduced herein as Seq ID Nos: 214 to 230]); or

g. the VH and/or VL domains of any of the antibodies disclosed in U.S. Pat. No. 7,812,133 (Genentech, Seq ID Nos: 15 and 16 therein for VH domains; and Seq ID Nos: 13 and 14 therein for VL domains, which sequences are incorporated herein by reference [reproduced herein as Seq ID Nos: 231 to 234]).

Concept 64. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is oxelumab.

Concept 65. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, where in the Tscm cells and/or the Tn cells are $CD4^+$.

In another embodiment, the Tscm cells and/or the Tn cells are CD8+.

Concept 66. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 64, wherein the Tscm cells and/or the Tn cells are circulating T-cells.

Concept 67. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 65, wherein the Tscm cells and/or the Tn cells are in a sample of blood, e.g. peripheral blood.

Whereas T-cells present in blood are relatively straightforward to isolate and characterise, T-cells which are present in the tissues of a subject are generally more difficult to isolate. That said, it may be possible to isolate T-cells from various tissues (such as skin, tissues of the GI tract, e.g. bowel, and from inflamed joints, e.g. synovium)

Concept 68. A method according to any one of concepts 9 to 11, 16, 20 to 39 or 43 to 67, an agent or an antibody or fragment for the use according to any one of concepts 12, 17, 20, 21, 23 to 25 or 44 to 67, a use according to any one of concepts 13, 14, 18 to 20 or 23 to 25 or 44 to 67, or a composition according to any one of concepts 15 or 44 to 67, wherein the subject is a human patient.

Concept 69. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 68, wherein the subject is at risk of a Tscm-mediated disease or condition.

Concept 70. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 68, wherein the subject has a Tscm-mediated disease or condition.

Concept 71. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the Tscm-mediated disease or condition is mediated by $CD45RA^{+}CCR7$ $CD95^{+}OX40^{+}$ Tscm cells.

Concept 72. A method, an agent or an antibody or fragment for the use, a use or a composition according to any one of concept 68 to 70, wherein the Tscm-mediated disease or condition is characterised by having a ratio of $CD45RA^{+}$ $CCR7^{+}CD95*OX40^{+}$ Tscm cells: $CD45RA^{+}CCR7^{+}CD95^{-}$ Tn cells of greater than 50:50.

In another embodiment, the disease or condition is characterised by having a ratio of Tscm cells: Tn cells as set out in any of concepts 23 to 25.

Concept 73. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 72, wherein the Tscm-mediated disease or condition is characterised by having a ratio of Tscm:Tn of greater than 60:40, or greater than 70:30, or greater than 75:25, such as greater than 70:30.

Concept 74. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 73, wherein the Tscm-mediated disease or condition is characterised by having a ratio of Tscm:Tn of greater than 80:20, or greater than 85:15, for example greater than 90:10, e.g. greater than 95:5.

Concept 75. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the Tscm-mediated disease or condition is selected from an autoimmune disease, HIV-1, and a T-cell malignancy.

Concept 76. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 75, wherein the Tscm-mediated disease or condition is selected from GvHD, transplant rejection, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, juvenile dermatomyositis, T-cell lymphoma and T-cell leukemia.

Concept 77. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the Tscm-mediated disease or condition is GvHD or transplant rejection.

Concept 78. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the transplant is a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived. In one embodiment, the transplant is an HLA-matched allogeneic bone marrow or stem cell transplant. In another embodiment, the transplant is an HLA mis-matched allogeneic bone marrow or stem cell transplant.

In one embodiment, the transplant is a CAR T-cell transplant (chimeric antigen receptor).

Concept 79. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the Tscm-mediated disease or condition is a T-cell lymphoma selected from T-cell non-Hodgkin's lymphoma, peripheral T-cell lymphoma (PTCL), anaplastic large cell lymphoma (ALCL), angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma, blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma (T-LBL) and nasal NK/T-cell lymphoma.

Concept 80. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the Tscm-mediated disease or condition is a T-cell leukemia selected from large granular lymphocytic leukemia (LGLL), T-cell prolymphocytic leukemia (T-PLL), T-cell acute lymphoblastic leukemia (T-ALL) and Sezary syndrome.

115. Concept 81. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, further comprising administering to the human a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, in particular rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins. In another embodiment, the agent is an anti-IL-2 antibody.

In one embodiment, the further therapeutic agent is independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors

(e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

116. In one embodiment, the further therapeutic agent is independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basilixumab, daclizumab). In another embodiment, the agent is an anti-IL-2 antibody.

In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In another embodiment, the further therapeutic agent is tacrolimus. In another embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In another embodiment, the further therapeutic agent is ciclosporin. In another embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In another embodiment, the further therapeutic agent is cyclophosphamide. In another embodiment, the further therapeutic agent is mycophenolate mofetil.

Concept 82. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount of rapamycin.

Concept 83. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount of tacrolimus.

The inventors have surprisingly found that an anti-OX40L antibody may provide synergistic effects when administered as part of a combination therapy with a further therapeutic agent. To that end, further concepts are provided below:

Concept 101. An anti-OX40L antibody or fragment thereof for use in treating or reducing the risk of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

117. Concept 102. Use of an anti-OX40L antibody or fragment thereof for the treatment or prevention of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat. In another embodiment, the agent is an anti-IL-2 antibody.

Concept 103. Use of an anti-OX40L antibody or fragment thereof in the manufacture of a medicament for the treatment or prevention of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Concept 104. A composition comprising an an anti-OX40L antibody or fragment thereof for the treatment or prevention of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Concept 105. A method of treating or preventing an OX40L-mediated disease or condition in a subject comprising administering to said human a therapeutically effective amount of an anti-OX40L antibody or fragment thereof in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g.

daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the OX40L-mediated disease or condition is thereby treated or prevented.

In any of the concepts herein, the combination may be used in the prevention of an OX40L-mediated disease. In any of the concepts, the combination may be used to reduce the risk of an OX40L-mediated disease. In any of the concepts, the combination may be used in the treatment of an OX40L-mediated disease.

A "combination" as described here may be as defined elsewhere herein, for example on page 185, on pages 190 to 192, and on pages 203 to 204. In one embodiment, the disease is rheumatoid arthritis or psoriasis, and the further therapeutic agent is an anti-IL-17 antibody (such as brodalumab, secukinumab and ixekizumab). Combinations may be administered concomitantly or sequentially.

Administration may be via any of the methods disclosed herein, for example, as discussed in the section entitled "Methods of Administration and Dosing" beginning on page 214 herein.

As used in any of the concepts herein, the "treatment" of an OX40L-mediated disease includes the reduction of one or more symptom(s) of said OX40L-mediated disease. Treatment may be interpreted as described elsewhere herein, for example on page 107, and in the section entitled "Kits" (beginning on page 233, in particular page 236) Immunosuppressive drug intervention in the management of GvHD associated with hematopoietic stem cell transplant (HSCT) may be administered to treat patients with confirmed disease. GvHD grading may be determined as described below.

In one embodiment, the administration is prophylactic to reduce the risk of an OX40L-mediated disease. As used in the concepts herein, "prevention" (or "prevent" or "preventing" and the like) of an OX40L-mediated disease includes the prevention of one or more symptom(s) of said OX40L-mediated disease. Preventing may refer to the total or partial inhibition of the development, recurrence, onset or spread of an OX40L-mediated disease and/or symptom related thereto, resulting from the administration combination of therapies provided herein (e.g., a combination of prophylactic and/or therapeutic agents). Preventing may be interpreted as disclosed elsewhere herein.

Immunosuppressive drug intervention in the management of GvHD associated with hematopoietic stem cell transplant (HSCT) may be administered to prevent disease in patients known to be at risk.

Thus, in one embodiment, a prophylactically-effective dose is administered before the onset of an OX40L-mediated disease or condition. As used in the concepts herein, a subject may be determined to be "before the onset of an OX40L-mediated disease or condition" if the subject is presenting no symptoms which would conventionally be associated with said disease or condition or if the subject would not be diagnosed as having such a disease or condition by any conventional method. In another embodiment, administration which is before the onert of disease may be termed "pre-emptive treatment", which refers to the use of further therapeutic agents (such as immunosuppressant agents) and/or an anti-OX40L antibody of the invention in individuals at risk of developing disease and where there may be early signs that emergence of clinically-relevant GvHD is imminent. For example, an experimental or predictive serum or cellular biomarker may indicate the optimal time for initiation of pre-emptive GvHD treatment.

For example, the presence of signs and symtpoms of acute GvHD in a human may be staged and graded according to a standardised scale such as described in Przepiorka et al. In a primate, such as a *rhesus macaque* monkey, the presence of signs and symtpoms of acute GvHD may be staged and graded according to a standardised scale such as described herein in Example 7. Similar disease grading scales are also in routine clinical use for other relevant diseases, such as rheumatoid arthritis and inflammatory bowel diseases.

"Prevention" or "prophylaxis" may be as described in aspect 94 herein, with dosages and timings of administration of the anti-OX40L antibody as described. A prophylactic agent may be used in any of the methods described on page 187 to 188.

The OX40L-mediated diseases or conditions may be any of the diseases or conditions mentioned herein, including those which are defined elsewhere herein as Tscm-mediated diseases or conditions (see concepts 75 to 80 hereinabove). In one embodiment, the OX40L-mediated diseases or conditions are as described in any of aspects 12, 12a, 69, 69a, 71, 72, 72a, 90 to 93 as described herein. In one embodiment, the OX40L-mediated diseases or conditions are as described in any of aspects 12, 12a, 69, 69a, 71, 72, 72a, 90 to 93 as described herein. In one embodiment, the OX40L-mediated disease or condition is a hOX40L-mediated disease or condition as described herein, for example on pages 187 to 188, or on page 215. In another embodiment, the OX40L-mediated diseases or conditions are as described in the section entitled "Methods of Administration and Dosing" beginning on page 214 herein. In a preferred embodiment, the disease or condition is GvHD or transplant rejection, in particular, GvHD. In another embodiment, the OX40L-mediated disease of condition is Chron's disease. In another embodiment, the OX40L-mediated disease of condition is inflammatory bowel disease (IBD). In another embodiment, the OX40L-mediated disease of condition is ulcerative colitis. In another embodiment, the OX40L-mediated disease of condition is psoriasis.

In any of concepts described herein, the anti-OX40L antibody and/or the further therapeutic agent are administered to the subject. Administration may be by any method described herein, for example as described on page 177, or in the sections entitled "Pharmaceutical compositions" and "Methods of Administration" beginning on pages 202 and 214 respectively. In one embodiment, the anti-OX40L antibody of the invention is administered intravenously. In one embodiment, the anti-OX40L antibody of the invention is administered subcutaneously.

In one embodiment, the further therapeutic agent is rapamycin (sirolimus) and is administered orally. In one embodiment, the further therapeutic agent is tacrolimus and is administered orally. In one embodiment, the further therapeutic agent is methotrexate and is administered orally and/or intravenously. In one embodiment, the further therapeutic agent is ciclosporin and is administered intravenously and/or orally. In one embodiment, the further therapeutic agent is cyclophosphamide and is administered intravenously and/or orally. In one embodiment, the further therapeutic agent is methyl prednisolone and is administered orally and/or intravenously.

Concept 106. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 105, wherein the subject has a post-treatment or post-prophylaxis survival time of at least 14 days, or at least 21 days, or at least 28 days, or at least 40 days, or at least 50 days, or at least 60 days.

Concept 107. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 105, wherein post-prophylaxis, the

subject has at least 7 days, or at least 14 days, or at least 21 days, or at least 28 days, or at least 40 days, or at least 50 days, or at least 60 days disease-free.

Concept 108. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 105, wherein post-treatment, the subject has at least 7 days, or at least 14 days, or at least 21 days, or at least 28 days, or at least 40 days, or at least 50 days, or at least 60 days disease progression-free.

Concept 109. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 106 to 108, wherein the number of days of survival, the number of disease free days, or the number of disease-progression free days is at least 2 months, or at least 3 months, or at least 4 months, e.g. at least 5 months, such as at least 6 months.

Concept 110. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 109, wherein the number of days of survival, the number of disease free days, or the number of disease-progression free days is at least 9 months, or at least one year.

Concept 111. A method of preventing the onset of an OX40L-mediated disease or condition in a subject by administering a prophylactically-effective amount of an anti-OX40L antibody and administering a prophylactically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is prevented.

By "prophylactically-effective", it is meant that the dose is effective to prevent or reduce the risk of an OX40L-mediated disease or condition.

In one embodiment, the combination may be used to reduce the risk of an OX40L-mediated disease or condition. In concept 111, the anti-OX40L antibody of the invention and the further therapeutic agent may be administered to the patient prophylactically, which administration may be sequential or simultaneous. The dosing regimens and modes of administration may be those which are normal or traditionally administered by physicians for the further therapeutic agent. The dosing regimens and modes of administration may be those which are normal or traditionally administered by physicians for the anti-OX40L antibody of the invention. However, the concurrent use of both agents is expected to result in an improved prophylaxis as compared to either agent alone.

Concept 112. A method of treating an OX40L-mediated disease or condition in a subject by administering a prophylactically-effective amount of an anti-OX40L antibody and administering a therapeutically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is treated.

By "therapeutically effective", it is meant that the dose is effective to treat an OX40L-mediated disease or condition. Effective may be as defined on pages 180 to 181, or pn page 236 herein, and may provide serum concentrations as described in the section entitled "Parmacetical Compositions" starting on page 202 herein.

In concept 112, the anti-OX40L antibody of the invention may be administered to the patient, but despite prophylaxis, the onset of the OX40L-mediated disease or condition occurs (the onset may be delayed by a number of days or weeks, as compared with a patient who had not been receiving the antibody of the invention). In this case, a therapeutically-effective amount of a further therapeutic agent may be administered to treat the disease or condition.

Concept 113. A method of treating an OX40L-mediated disease or condition in a subject by administering a therapeutically-effective amount of an anti-OX40L antibody and administering a prophylactically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is treated.

In concept 113, the further therapeutic agent may be administered to the patient, but despite prophylaxis, the onset of the OX40L-mediated disease or condition occurs (the onset may be delayed by a number of days or weeks, as compared with a patient who had not been receiving the further therapeutic agent). In this case, a therapeutically-effective amount of an anti-OX40L antibody of the invention may be administered to treat the disease or condition.

Concept 114. A method of treating an OX40L-mediated disease or condition in a subject by administering a therapeutically-effective amount of an anti-OX40L antibody and administering a therapeutically-effective amount of a further

therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is treated.

In concept 114, both the anti-OX40L antibody of the invention and the further therapeutic agent are not administered until there are clinical signs of the OX40L-mediated disease or condition. The combination treatment of both agents may provide further benefits as compared to either agent alone.

Concept 115. A method according to concept 111 or concept 113, wherein the further therapeutic agent is independently selected from rapamycin (sirolimus), tacrolimus, a combination of tacrolimus and methotrexate, cyclophosphamide, ciclosporin, and a combination of ciclosporin and methotrexate.

In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is rapamycin (sirolimus). In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is tacrolimus. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is cyclophosphamide. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is ciclosporin. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is mycophenolate mofetil.

In one embodiment, the anti-OX40L antibody is administered to a patient who is already receiving rapamycin (sirolimus). In another embodiment, embodiment, the anti-OX40L antibody is administered to a patient who is already receiving tacrolimus. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving a combination of tacrolimus and methotrexate. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving a combination of ciclosporin and methotrexate. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving ciclosporin. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving cyclophophamide. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving mycophenolate mofetil.

These further therapeutic agents may be used prophylactically in the treatment of OX40L-mediated diseases or conditions. For example, in GvHD, preventive therapy (prophylaxis) is typically administered around the time of HSCT and is continued for a period of time following transplant to maintain immunosuppression during the period of greatest risk of developing acute GvHD. Specific drug regimens differ between transplant centres, but as an example prophylaxis with calcineurin inhibitors such as ciclosporin or tacrolimus, or with rapamycin (sirolimus) may be initiated within the 7 day period preceding transplant (such as Day −3, or Day −1 pre-HSCT), or immediately following the HSCT procedure (e.g. on Day 0, or Day +1 after transplant). Prophylaxis with mycophenolate mofetil is typically dosed following HSCT, for example starting between Day +1 to Day +5 post-transplant. Prophylaxis with these agents may be continued, for example, between 28 to 180 days or longer following transplant, with daily dosages calculated to maintain serum levels in the range to achieve effective immunosuppression without limiting side effects. In addition to calcineurin inhibitors, methotrexate is often used as an adjunct to prophylaxis, typically being administered on Days+1, +3, +6, and +11 post-transplant.

An anti-OX40L antibody of the invention may be used as prophylaxis in combination with tacrolimus, ciclosporin, a combination of tacrolimus and methotrexate, a combination of ciclosporin and methotrexate, cyclophosphamide, mycophenolate mofetil or rapamycin, where prophylaxis with any of these agents is started before or around the time of HSCT, or immediately following the transplant procedure, for example within the period 7 days before, to 7 days after transplant. Tacrolimus, or ciclosporin, or rapamycin may then be administered at therapeutically effective dose and frequency, for example daily, for up to 180 days following the transplant. An anti-OX40L antibody of the invention may be administered concurrently, starting before or around the time of HSCT, or immediately following the transplant procedure, for example within the period 7 days before, to 7 days after transplant. The anti-OX40L antibody may then be dosed at a therapeutically effective dose and frequency, for example biweekly or monthly, for up to 180 days following the transplant. Under these circumstances the combined activity of the anti-OX40L antibody and the additional prophylactic agent would be expected to display a synergistic effect in preventing the onset and/or severity of GvHD.

Concept 116. A method according to concept 112 or concept 114, wherein the further therapeutic agent is a corticosteroid (e.g. methylprednisolone).

In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is methylprednisolone.

In cases where breakthrough GvHD occurs (for example, even despite prophylaxis), treatment may be initiated immediately upon confirmation of Grade II or higher GvHD disease. Systemic corticosteroids such as methylprednisolone are the first-line treatment of choice, administered concurrently with ongoing prophylaxis with, for example, a calcineurin inhibitor such as ciclosporin or tacrolimus.

Where first-line treatment or prophylaxis fails to control GvHD, "salvage therapy" may be attempted in which case additional previously unused immunosuppressants such as rapamycin or mycophenolate mofetil may be administered. Thus, in one embodiment, a therapeutically effective amount of an anti-OX40L antibody of the invention is administered to a patient who is refractory to prophylaxis or treatment with any of: rapamycin, tacrolimus, tacrolimus in combination with methotrexate, cyclophosphamide, ciclosporin, ciclosporin in combination with methotrexate, or corticosteroids (e.g. methylprednisolone). In another embodiment, a therapeutically effective amount of an anti-OX40L antibody of the invention is administered to a patient who is refractory to prophylaxis or treatment with any of the further therapeutic agents mentioned herein. In another embodiment, an anti-OX40L antibody of the invention is administered as a salvage therapy.

Concept 117. A method of prolonging survival in a subject having or at risk of an OX40L-mediated disease or condition by administering a therapeutic or prophylactic combination of an anti-OX40L antibody and a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

In one embodiment, then OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. A number of factors affect the severity and disease progression in GvHD, such as the pre-transplant conditioning regimen (e.g. myeoablation by irradiation, preparative chemotherapy), degree of donor-recipient tissue matching (HLA matching, and/or relationship of donor-recipient), and therapeutic or prophylactic treatment regimens.

In general, however, in primates, such as *rhesus macaque* that have received haploidential stem cell transplants, the mean survival time (MST) post-transplant and in the absence of therapy is 8 days.

Concept 118. A method according to concept 117, wherein survival is increased by at least 7 days, or by at least 14 days, or by at least 20 days, or by at least 30 days or by at least 40 days, or by at least 50 days, or by at least 60 days, or by at least 70 days.

Concept 119. A method of increasing the number of disease-free, or disease-progression free, days in a a subject having or at risk of an OX40L-mediated disease or condition by administering a therapeutic or prophylactic combination of an anti-OX40L antibody and a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

In one embodiment, then OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In humans, the presence of signs and symptoms of acute GvHD may be staged and graded according to a standardised scale such as described in Przepiorka et al. In primates, such as rhesus macaques, the presence of signs and symptoms of acute GvHD may be staged and graded according to a standardised scale such as described herein in Example 7.

Thus, the number of disease free days may be measured by absence of clinical grading symptoms. The number of disease-progression free days may be measures as the number of days where the clinical grading score does not change.

Concept 120. A method according to concept 119, wherein the number of disease-free, or disease-progression free, days is at least 7 days, or at least 14 days, or at least 21 days, or at least 28 or at least 40 days, or at least 50 days, or by at least 60 days, or at least 70 days.

Concept 121. A method according to concept 120, wherein the number of disease free, or disease-progression free, days is at least 90 days, at least 180 days or at least 365 days.

Concept 122. A method of treating or reducing the risk of transplant rejection or GvHD in a subject by administering a therapeutic or prophylactic combination of an anti-OX40L antibody and a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the combination results in an increased survival in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation as compared to either the antibody or the further therapeutic agent as a monotherapy.

In one embodiment, the method is a method of preventing an OX40L-mediated disease or condition.

In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is a rapamycin (sirolimus). In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is tacroli-

mus. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is cyclophosphamide. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is ciclosporin. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is mycophenolate mofetil.

The *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation may be as described in aspect 99 herein.

Concept 123. A method according to any one of concepts 106, 109, 110, 117, 119, or 122, wherein the survival is increased by at least 7 days, or by at least 14 days, or by at least 21 days, or by at least 28 days, or by at least 40 days, or by at least 50 days, or by at least 60 days, or by at least 70 days as compared to either the antibody or the further therapeutic agent as a monotherapy.

Concept 124. A method according to any one of concepts 106, 109, 110, 117, 119, or 122, wherein survival is at least doubled, e.g tripled, as compared to either the antibody or the further therapeutic agent as a monotherapy.

Concept 125. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceeding concept, wherein the antibody specifically binds to human OX40L (hOX40L).

The hOX40L may be as described in aspect 28 or aspect 30 described herein.

In any of the concepts provided herein, the anti-OX40L antibody may be as described elsewhere herein. In one embodiment, the anti-OX40L antibody is as described in any of aspects 1 to 11, 13 to 27, 29, 31 to 43 or 45 described herein. In another embodiment, the anti-OX40L antibody is as described in aspects 73 to 89, or as in any of aspects 95 to 102 described herein. In another embodiment, the anti-OX40L antibody is as described in any of concepts 53 to 64 hereinabove. Other properties of anti-OX40L antibodies are described on pages 170 to 173, in the section entitled "bispecifics" beginning on page 176 herein, in the section entited "Antibodies" beginning on page 193 herein and in the section entitled "Methods of Administration and Dosing" beginning on page 130 herein.

Concept 126. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 125, which competes for binding to said hOX40L with an antibody selected from the group consisting of 02D10, 10A07, 09H04 and 19H01.

Competition between antibodies may be determined as described in aspect 13 or aspect 73, for example as determined by SPR, ELISA, HTRF or FACS. Methods related to the measurement methods are disclosed herein, including in the Examples.

Concept 127. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 126, which competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY, wherein X is any amino acid.

Concept 128. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceeding concept, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

Antagonism and inhibition may be carried out as defined on page 94 to 95.

Concept 129. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody is a humanized, human or fully human antibody.

Concept 130. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

Concept 131. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

Concept 132. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

Concept 133. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

Concept 134. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises a CDR selected from:

a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);

b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);

c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);

d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No: 106);

e. a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or

g. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234.

Concept 135. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises:

a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ

ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);

b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);

c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);

d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No:104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);

e. the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

g. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

Concept 136. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);

b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No:16 for VL);

c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);

d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);

e. a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

g. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

Concept 137. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody is oxelumab.

Concept 138. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the subject is a primate.

The term "subject" may be other subjects as described herein, for example as described on page 104. In one embodiment, the primate is a *rhesus macaque* monkey.

Concept 139. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the subject is a human.

In one embodiment, the subject is a human patient.

Concept 140. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the subject is at risk of an OX40L-mediated disease or condition.

In one embodiment, a subject may be identified as being "at risk of an OX40L-mediated disease or condition" if the subject has been previously identified as having an increased risk, e.g. by genotyping and/or phenotyping, but the subject has not yet presented symptoms or would not be diagnosed as having such a disease or condition by any conventional method. Thus, the methods and uses disclosed herein may aid in the early identification of patients who will develop such diseases or conditions. In one embodiment, the disease or condition is prevented (i.e. the treatment is prophylactic).

In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In a particular embodiment, the subject is at risk of GvHD or transplant rejection when they are pre-operative for a transplant. In particular, a subject is at risk of GvHD or tansplant rejection when they have commenced a pre-transplant conditioning regimen (e.g. myeoablation by irradiation, preparative chemotherapy), and when degree of donor-recipient tissue matching (HLA matching, and/or relationship of donor-recipient) is not 100%. Potential transplant therapies are envisaged in concept 78 hereinabove.

Concept 141. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 40, wherein the method, antibody or fragment for the use, the use or the composition is for the prevention of the OX40L-mediated disease or condition.

Concept 142. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 139, wherein the subject has an OX40L-mediated disease or condition.

A subject has an OX40L-mediated disease or condition if the subject is presenting symptoms which would conventionally be associated with said disease or condition or if the subject would be diagnosed as having such a disease or condition by any conventional method. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and a subject may be determined to have the disease by any of the methods mentioned in concepts 101 to 105 and 119 hereinabove.

Concept 143. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 142, wherein the method, antibody or fragment for the use, the composition for the use, or the use is for the treatment of the OX40L-mediated disease or condition.

In one embodiment, treatment is commenced when the OX40L-mediated disease or condition has been diagnosed as a confirmed disease or condition.

In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. GvHD grading may be determined as described herein (see concepts 101 to 105 and 119 hereinabove). In one embodiment, the subject is a human having Grade II clinical symptoms of GvHD.

Concept 144. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the OX40L-mediated disease or

condition is selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection.

Concept 145. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 144, wherein the OX40L-mediated disease or condition is selected from inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis.

Concept 146. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 145, wherein the OX40L-mediated disease or condition is GvHD or transplant rejection.

Concept 147. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 146, wherein the OX40L-mediated disease or condition is GvHD.

Concept 148. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 146, wherein the transplant is a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.

In one embodiment, the transplant is an HLA-matched allogeneic bone marrow or stem cell transplant. In another embodiment, the transplant is an HLA mis-matched allogeneic bone marrow or stem cell transplant.

Concept 149. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 146 to 148, wherein the anti-OX40L antibody or fragment thereof is administered before transplant.

Concept 150. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 146 to 148, wherein the anti-OX40L antibody or fragment thereof is administered after transplant.

Concept 151. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 149 or concept 150, wherein the further therapeutic agent is administered after transplant.

In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In one embodiment, the further therapeutic agent is tacrolimus. In one embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the further therapeutic agent is cyclophosphamide. In one embodiment, the further therapeutic agent is ciclosporin. In one embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the further therapeutic agent is mycophenolate mofetil. In one embodiment, the further therapeutic agent is methyl predinsolonel.

Concept 152. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 149 or concept 150, wherein the further therapeutic agent is administered before transplant.

In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In one embodiment, the further therapeutic agent is tacrolimus. In one embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the further therapeutic agent is cyclophosphamide. In one embodiment, the further therapeutic agent is ciclosporin. In one embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the further therapeutic agent is mycophenolate mofetil.

Concept 153. A pharmaceutical composition comprising an anti-OX40L antibody or fragment thereof and a pharmaceutically acceptable excipient, diluent or carrier and further comprising a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

In one embodiment, there is provided a composition or kit for treating and/or preventing a OX40L-mediated condition or disease, the composition or kit comprising an antibody or fragment of the invention in combination with a further therapeutic agent optionally in combination with a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

The composition may be as described in aspect 105, 106 or 107 herein. Excipients for use in pharmaceutical formulations are well-known to the skilled person and may be as defined on page 97 herein, or in the section entitled "Pharmaceutical Compositions" beginning on page 118 herein, or in the section entitled "Methods of Administration and Dosing" beginning on page 214 herein.

Concept 154. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, wherein the further therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

Other combinations may be with the anti-inflammatory drugs described in aspect 46 herein, or as described in aspect 103. Other combinations are as described in concepts 81 to 83 hereinabove, or in any of concepts 101 to 153 hereinabove.

Concept 155. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin, tacrolimus, ciclosporin, cyclophosphamide, corticosteroids (e.g. methylprednisolone), methotrexate or mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept) and anti-thymocyte globulins.

Concept 156. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin, tacrolimus, ciclosporin, cyclophosphamide, corticosteroids (e.g. methylprednisolone), methotrexate and mycophenolate mofetil.

Concept 157. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of an immunosuppressant that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus)), and anti-CD25 antibodies (e.g. basilixumab, daclizumab).

Concept 158. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

Concept 159. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of rapamycin.

Concept 160. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of tacrolimus.

Concept 161. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of tacrolimus and methotrexate.

Concept 162. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of ciclosporin.

Concept 163. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of ciclosporin and methotrexate.

Concept 164. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of cyclophosphamide.

Concept 165. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of mycophenolate mofetil.

Concept 166. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a corticosteroid (e.g. methyl prednisolone).

Concept 167. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, wherein the further therapeutic agent is administered sequentially or simultaneously with the anti-hOX40L antibody or fragment.

As explained in the examples, the inventors devised a set of criteria that is particularly useful for identifying antibodies and fragments of the invention, these criteria being:—

(a) The ability of the antibody or fragment to bind cell-surface hOX40L on CHO-S cells (optionally transfected with full length human OX40L) and/or bind recombinant hOX40L in a HTRF assay;

(b) The ability of the antibody or fragment to neutralise human OX40 (e.g. neutralise human OX40L binding to human OX40 Receptor) in a receptor neutralisation HTRF assay and/or a flow cytometry receptor neutralisation assay; and

(c) The ability of the antibody or fragment to specifically bind both human and rhesus monkey OX40L (useful so that the PK, PD, efficacy and other parameters of the antibody or fragment can be assessed in the rhesus model as a surrogate for humans).

Thus, in an example of the invention the antibody or fragment meets criteria (a), (b) and (c).

In an example, criterion (a) is set so that the antibody or fragment shows <70% receptor binding by FACS to hOX40L expressed by CHO-S cells.

In an example, criterion (a) is set so that the antibody or fragment shows <90% of receptor binding to OX40L in the HTRF assay.

In an example, criterion (a) is set so that the antibody or fragment shows at least a 20% effect in the HTRF assay.

In an example, OX40 is used in criterion (b).

In an embodiment, assaying or testing of an antibody or fragment of the invention is carried out at or substantially at pH7 (e.g., for in vitro tests and assays) and at or substantially at rtp.

Optionally, the antibody or fragment specifically binds hOX40L with an affinity (apparent affinity, Kd) of less than 1 microM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, e.g., in the range of 1 mM to 1 pM (e.g., 1 mM to 100 pM; 10 nM to 100 pM; 1 nM to 10 pM; or 100 pM to 1 pM) as determined by SPR, e.g., under SPR conditions disclosed herein). Additionally or alternatively, the antibody or fragment specifically binds rhesus monkey OX40L with an affinity (apparent affinity, Kd) of less than 1 microM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, e.g., in the range of 1 mM to 1 pM (e.g., 1 mM to 100 pM; 10 nM to 100 pM; 1 nM to 10 pM; or 100 pM to 1 pM) as determined by SPR, e.g., under SPR conditions disclosed herein). Such binding measurements can be made using a variety of binding assays known in the art, e.g., using surface plasmon resonance (SPR), such as by

Biacore™ or using the ProteOn XPR36™ (Bio-Rad®), using KinExA® (Sapidyne Instruments, Inc), or using ForteBio Octet (Pall ForteBio Corp.).

OX40L binding ability, specificity and affinity (Kd, K_{off} and/or K_{on}) can be determined by any routine method in the art, e.g., by surface plasmon resonance (SPR). The term "Kd", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

In one embodiment, the surface plasmon resonance (SPR) is carried out at 25° C. In another embodiment, the SPR is carried out at 37° C.

In one embodiment, the SPR is carried out at physiological pH, such as about pH7 or at pH7.6 (e.g., using Hepes buffered saline at pH7.6 (also referred to as HBS-EP)).

In one embodiment, the SPR is carried out at a physiological salt level, e.g., 150 mM NaCl.

In one embodiment, the SPR is carried out at a detergent level of no greater than 0.05% by volume, e.g., in the presence of P20 (polysorbate 20; e.g., Tween-20™) at 0.05% and EDTA at 3 mM.

In one example, the SPR is carried out at 25° C. or 37° C. in a buffer at pH7.6, 150 mM NaCl, 0.05% detergent (e.g., P20) and 3 mM EDTA. The buffer can contain 10 mM Hepes. In one example, the SPR is carried out at 25° C. or 37° C. in HBS-EP. HBS-EP is available from Teknova Inc (California; catalogue number H8022).

In an example, the affinity of the antibody or fragment is determined using SPR by

1. Coupling anti-mouse (or other relevant human, rat or non-human vertebrate antibody constant region species-matched) IgG (e.g., Biacore™ BR-1008-38) to a biosensor chip (e.g., GLM chip) such as by primary amine coupling;
2. Exposing the anti-mouse IgG (or other matched species antibody) to a test IgG antibody to capture test antibody on the chip;
3. Passing the test antigen over the chip's capture surface at 1024 nM, 256 nM, 64 nM, 16 nM, 4 nM with a 0 nM (i.e. buffer alone); and
4. And determining the affinity of binding of test antibody to test antigen using surface plasmon resonance, e.g., under an SPR condition discussed above (e.g., at 25° C. in physiological buffer). SPR can be carried out using any standard SPR apparatus, such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®).

Regeneration of the capture surface can be carried out with 10 mM glycine at pH1.7. This removes the captured antibody and allows the surface to be used for another interaction. The binding data can be fitted to 1:1 model inherent using standard techniques, e.g., using a model inherent to the ProteOn XPR36™ analysis software.

In an example, the antibody or fragment of the invention is contained in a medical container, e.g., a vial, syringe, IV container or an injection device (e.g., an intraocular or intravitreal injection device). In an example, the antibody or fragment is in vitro, e.g., in a sterile container. In an example, the invention provides a kit comprising the antibody or fragment of the invention, packaging and instructions for use in treating or preventing or diagnosing in a human a disease or condition mediated by the OX40L. In an example, the instructions indicate that the human should be genotyped for an OX40L variant sequence of the invention before administering the antibody or fragment to the human. In an example, the instructions indicate that the human should be phenotyped for an OX40L variant of the invention before administering the antibody or fragment to the human. In an example, the human is of Chinese (e.g., Han or CHS) ethnicity and the instructions are in Chinese (e.g., Mandarin).

In an example the binding site(s) of the antibody or fragment are selected from a plurality (e.g., library) of binding sites. For example, the plurality of binding sites comprises or consists of a plurality of 4-chain antibodies or fragments thereof, e.g., dAbs, Fabs or scFvs. Suitable methods for producing pluralities of binding sites for screening include phage display (producing a phage display library of antibody binding sites), ribosome display (producing a ribosome display library of antibody binding sites), yeast display (producing a yeast display library of antibody binding sites), or immunisation of a non-human vertebrate (e.g., a rodent, e.g., a mouse or rat, e.g., a Velocimouse™, Kymouse™, Xenomouse™, Aliva Mouse™, HuMab Mouse™, Omnimouse™, Omnirat™ or MeMo Mouse™) with hOX40L or a hOX40L epitope and isolation of a repertoire of antibody-producing cells (e.g., a B-cell, plasma cell or plasmablast repertoire) and/or a repertoire of isolated antibodies, fragments or binding sites.

The term "epitope" is a region of an antigen that is bound by an antibody or fragment. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

The term "isolated" with reference to any aspect of the invention, e.g., an antibody or fragment, means that a subject antibody or fragment etc. (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature. Typically, an "isolated" antibody, fragment, etc. constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50%, 60%, 70%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or >99% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode such an isolated antibody, fragment, etc. Preferably, the isolated antibody, fragment, etc. is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

For example, an "isolated" antibody is one that has been identified, separated and/or recovered from a component of its production environment (e.g., naturally or recombinantly). Preferably, the isolated polypeptide is free of association with all other components from its production environment, e.g., so that the antibody has been isolated to an FDA-approvable or approved standard. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In

preferred embodiments, the polypeptide will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, an isolated polypeptide or antibody will be prepared by at least one purification step.

The present inventors have identified a number of markers of disease which may be useful in the treatment and/or prevention of autoimmune or alloimmune diseases using various combinations. To that end, further arrangements are provided hereinbelow:

Arrangement 1. A method of preventing reduction in the proportion (e.g. number or level) of regulatory T-cells (Tregs) comprising combining said cells with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent, which combination prevents reduction of the proportion (e.g. number or level) of Treg cells, and whereby the proportion of said Treg cells is not substantially reduced.

T-cells include many different sub-populations, which have myriad functions, some of which are described elsewhere herein. T-cells include Tn cells, Tscm cells, Tmem cells, Tcm cells, Tsm cells, Treg and Teff cells. T-cells generally may be identified as being either $CD3^+CD4^+$ or $CD3^+CD8^+$. In one embodiment, T-cells may additionally be CD14-. In another embodiment, T-cells may additionally be $CD20^-$. In another embodiment, T-cells are identified as being $CD3^+CD14^-CD20^-$ and either $CD4^+$ or $CD8^+$.

Memory T-cells are a subset of antigen-specific T-cells, which remain in the immune system long-term after an infection has resolved. They quickly expand to large numbers of effector T-cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections. As used in the arrangements described herein, memory T-cells (Tmem) are defined herein as for T-cells above, but as additionally being $CD45RA^-$. Thus, in one embodiment, T(mem) cells are defined as $CD3^+CD14^-CD20^-CD45RA^-$ and either $CD4^+$ or $CD8^+$.

Effector T-cells are short-lived activated cells, which become activated when they are presented with antigens by the MHC class II molecules. As used in the arrangements described herein, effector Tcells (Teff) are defined as being $CD45RA^+$. Teff cells may additionally be $CCR7^-$. Thus, in one embodiment, Teff cells are identified as being $CD3^+$ $CD14^-CD20^-CD45RA^+CCR7^-$ and either $CD4^+$ or $CD8^+$.

Regulatory T-cells are a subpopulation of T-cells which function, inter alia, to inhibit the function of effector T-cells. As used in the arrangements described herein, regulatory T-cells (Tregs) are defined as being $FoxP3^+$. In another embodiment, the Treg cells may additionally be $CD25^+$. In another embodiment, the Treg cells may additionally be $CD127^-$. Thus, in one embodiment, Treg cells are identified as $CD25^+CD127^-FoxP3^+$. In another embodiment, Treg cells are identified as being $CD3^+CD4^+CD14^-CD20^-CD25^+$ $CD127^-FoxP3^+$. In another embodiment, Treg cells are identified as being $CD3^+CD4^+CD25^+CD127^-FoxP3+$.

Conventional T-cells (Tconv) is a term that is used to describe a pool or population of T-cells which may be responsive to antigen, and includes at least, Tn, Tmem and Teff. In one definition, Tconv is defined as all T-cells, but not including Treg cells. Thus, in one embodiment, in the arrangements herein, Tconv cells are defined as total $CD4^+$ and/or total $CD8^+$minus Tregs (which may be as defined above, but in one embodiment are defined as $CD3^+CD4^+$ $CD25^+CD127^-FoxP3^+$).

In another embodiment, as used in the arrangements herein, Tconv may be defined as a combination of Teffector and Tmemory cells.

For alternative classifications of different T-cell types, see the figure in Gattinoni and Restifo (2013). The various cell-surface markers are, in one embodiment, identified using flow cytometry using methods which are well-known to those of skill in the art. Flow cytometry techniques are well-known to those skilled in the art. Agents which may be used in flow cytometry techniques are defined in Example 7 below. In one embodiment, the flow cytometry is carried out as described in Example 7 below. In another embodiment, the flow cytometry is carried out as described in Baumgarth & Roederer (2000), Journal of Immunological Methods, 243, 77-97, see concept 25 herein.

Without being bound by theory, it is thought that preventing reduction of the proportion (e.g. number or level) of Treg cells will have a number of benefits in various diseases, as set out herein, and the inventors have surprisingly shown that this may be achieved using a combination as described herein more effectively than with either agent alone.

The proportion (e.g. number or level) of Treg cells may be determined relative to the entire T-cell population in the sample. In one embodiment, the proportion (e.g. number or level) of Treg cells is determined relative to other T-cells in the sample. In a particular embodiment, the proportion (e.g. number or level) of Treg cells is determined relative to a combination of Teff and Tmem cells (as defined hereinbelow) in the sample. The proportion (e.g. number or level) of Treg cells may be altered by allowing the expansion or increase in the absolute number of Treg cells, or by changing the number of other T-cell subtypes such that the relative proportion (e.g. number or level) of Treg cells appears to be maintained or increased.

Thus, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of Treg cells" or similar phrases may be replaced throughout by the phrase "slowing the reduction in proportion (e.g. number or level) of Treg cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of Treg cells" or similar phrases may be replaced with the phrase "maintaining the proportion (e.g. number or level) of Treg cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of Treg cells" or similar phrases may be replaced with the phrase "increasing the proportion (e.g. number or level) of Treg cells" or similar phrases. In any of the arrangements herein, the "proportion" may be the relative proportion (e.g. number or level) of Treg cells, or the absolute number of level of Treg cells. To illustrate this point, which may be applied in any of the arrangements herein, there is described arrangements 1a) to Id).

Thus, according to arrangement 1a), there is provided a method of slowing reduction in the proportion (e.g. number or level) of Tregs comprising combining said cells with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent, which combination slows reduction of the proportion (e.g. number or level) of Treg cells, and whereby reduction of the proportion (e.g. number or level) of Tregs cells is slowed.

Thus, according to arrangement 1b), there is provided a method of maintaining the proportion of (e.g. maintaining the number or level of) Tregs comprising combining said cells with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent, which combination maintains the proportion of (e.g. maintains the number or level of) Treg cells, and whereby the proportion of said Treg cells is maintained (e.g. whereby the number or level of said Treg cells is maintained).

Thus, according to arrangement Ic), there is provided a method of preventing depletion of the proportion of (e.g. the number or level of) Tregs comprising combining said cells with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent, which combination prevents depletion of the proportion of (e.g. i the number or level of) Treg cells, and whereby the proportion (e.g. the number or level) of said Treg cells is not substantially depleted.

Thus, according to arrangement Id), there is provided a method of increasing the proportion of (e.g. increasing the number or level of) Tregs comprising combining said cells with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent, which combination increases the proportion of (e.g. increases the number or level of) Treg cells, and whereby the proportion of said Treg cells is increased (e.g. whereby the number or level of said Treg cells is increased).

"Decreasing" or "decreases" as used in any of the arrangements herein, refers to a mechanism other than depletion, which reduces the absolute number or levels of cells in a given population. This may be achieved indirectly, for example through a blocking or neutralising agent (such as an antibody) against a target which indirectly results in the killing of a target cell (such as a Treg), or prevents the expansion or growth of the target cells, resulting in an apparent decrease in proportions relative to another type of cell (such as Teff or Tmem cells).

As used in any of the arrangements herein, a "level" of a T-cell population may refer to the absolute number, or to the relative proportion of a type of T-cell. Particular numbers of Treg cells are described elsewhere herein, for example in arrangement 2 below. Any of these levels or numbers may be applied to any arrangement which discusses Treg cells.

In a particular embodiment, the combination of any arrangement comprises an antibody or fragment thereof which in is a format or structure of any of the antibodies and fragments described elsewhere herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein, or any arrangement hereinbelow). In a particular embodiment, the antibody is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab. In another embodiment, the combination comprises an anti-OX40L antibody which is not oxelumab (having a VH region amino acid sequence of Seq ID No:215 and a VL region amino acid sequence of Seq ID No:214).

The second therapeutic agent contained within the combination is described in more detail in the arrangements hereinbelow, but is preferably an IL-2 modulating agent.

Arrangement 2. The method according to arrangement 1, wherein the proportion (e.g. the number or level) of Treg cells is at least 4×10^6 Treg/litre, for example at least 5×10^6 Treg/litre, or at least 6×10^6 Treg/litre, or at least 7×10^6 Treg/litre, or at least 8×10^6 Treg/litre after combining said cells with said combination.

The combinations of the present invention may provide a therapeutic effect by restoring Treg levels towards the levels seen in healthy patients (see for example, Alho et al., Blood, 4 Feb. 2016, Vol 127, No. 5, p 646-657, from which the numbers, levels and ratios ofT-cell populations are incorporated herein by reference). Thus, the combinations of the present invention may be able to counteract any disease or disorder which is mediated by a deficiency in Treg cells.

In another embodiment, the proportion is at least 10×10^6 Treg/litre, or at least 12×10^6 Treg/litre, or at least 14×10^6 Treg/litre, or at least 16×10^6 Treg/litre after combining said cells with said combination. In another embodiment, the proportion is at least 18×10^6 Treg/litre, or at least 20×10^6 Treg/litre, or at least 22×10^6 Treg/litre after combining said cells with said combination. In another embodiment, the proportion is at least 23×10^6 Treg/litre, or at least 24×10^6 Treg/litre, or at least 25×10^6 Treg/litre after combining said cells with said combination. In another embodiment, the proportion is at least 30×10^6 Treg/litre, or at least 35×10^6 Treg/litre, or at least 40×10^6 Treg/litre, or at least 45×10^6 Treg/litre, or at least 50×10^6 Treg/litre after combining said cells with said combination.

In another embodiment, the proportion is in a range of from 4 to 50×10^6 Treg/litre, or at from 4 to 25×10^6 Treg/litre, or from 4 to 15×10^6 Treg/litre, or from 4 to 10×10^6 Treg/litre after combining said cells with said combination. The upper limit may be any of the proportions provided before contact with the combination, and the lower limit may be any of the proportions provided for after contact with the combination.

In another embodiment, the proportion (e.g. number or level) of Treg cells remains at a (substantially) constant proportion after administration of said combination. As used in the arrangements herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g. greater than 97% or greater than 99%).

In another embodiment, the proportion (e.g. number or level) of Treg cells does not change substantially as compared to the first measurement taken.

These proportions (e.g. numbers or levels) of Treg cells may apply to any arrangement herein which relates to the proportion (e.g. number or level) of Treg cells after administration of the combination comprising (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent.

According to arrangement 2a, there is provided a method according to arrangement 1, wherein the proportion (e.g. the number or level) of Treg cells is less than 10×10^6 Treg/litre, or less than 8×10^6 Treg/litre, for example less than 7×10^6 Treg/litre, or less than 6×10^6 Treg/litre, or less than 5×10^6 Treg/litre, or less than 4×10^6 Treg/litre before combining said cells with said combination.

These proportions have been observed to be detrimental and indicative of the start of GvHD (see Example 10 herein), which is an example of a disease which is mediated by a deficiency in Treg cells. Hence, in another embodiment, the

proportion (e.g. number or level) is less than 3×10^6 Treg/litre, or less than 2×10^6 Treg/litre, or less than 1×10^6 Treg/litre before combining said cells with said combination.

In other diseases, the deficiency in Treg cells may not be as pronounced as in GvHD, but a reduction from normal, healthy levels is indicative of the onset of disease. Thus, in another embodiment, the proportion (e.g. number or level) of Treg cells is less than 25×10^6 Treg/litre, or less than 20×10^6 Treg/litre, or less than 15×10^6 Treg/litre, or less than 10×10^6 Treg/litre before combining said cells with said combination. In another embodiment, the proportion (e.g. number or level) of Treg cells is at least 35×10^6 Treg/litre, or at least 40×10^6 Treg/litre, or at least 45×10^6 Treg/litre before combining said cells with said combination.

These proportions (e.g. number of levels) of Treg cells may apply to any arrangement herein which relates to the proportion (e.g. number or level) of Treg cells before administration of the combination comprising (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) a second therapeutic agent.

Arrangement 3. A method of altering the ratio of cell types in a T-cell population in a sample, the method comprising:

(a) providing said population, wherein the population comprises a mixture of different T-cell types, wherein the population comprises Treg cells,

(b) providing a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent; and

(c) combining said cell population with an amount of said combination effective to alter the proportion (e.g. number or level) of Treg cells in said population.

The proportion may be altered by mechanisms such as preventing reduction in the proportion (e.g. number or level) of Treg cells in said population. Alternatively, the ratio may be altered by slowing the reduction in proportion (e.g. number or level) of Treg cells in said population. Alternatively, the ratio may be altered by increasing the proportion (e.g. the number or level) of Treg cells in said population. Alternatively, the ratio may be altered by preventing depletion of Treg cells in said population.

In one embodiment, the method further comprises a step (d) of obtaining or isolating a sample of T-cells in which the proportion (e.g. number or level) of Treg cells is altered. Such an obtained or isolated sample may be formulated into a product for cell transplant. The resulting product may be used in a method of treating any of the diseases associated with the arrangements herein (e.g. an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, or an OX40L-mediated disease or condition).

Arrangement 4. A method according to arrangement 3, wherein in step a), the population further comprises Tconv cells.

Arrangement 4a. A method according to arrangement 3, wherein in step a), the population further comprises Teffector cells and Tmemory cells [T(eff+mem)].

The proportions, numbers and/or levels of T(eff+mem) cells, Tconv cells or the ratio of Treg:Tconv may be any as described in the arrangements hereinbelow, either before or after contact with the combination or before or after administration of the combination.

Arrangement 5. A method according to arrangement 4, wherein the ratio of Treg:Tconv in the population of step a) is less than 1.5:100.

Example 10 hereinbelow shows a large decrease in the ratio of Treg:Tconv, as a result of disease. This reduction is expected to be seen in a number of other autoimmune or alloimmune diseases or disorders to a greater or lesser extent. Thus, in another embodiment, the ratio of Treg:Tconv is as set out in arrangements 22 and 23 below. In another embodiment, the ratio is less than 5:100, or less than 4:100, or less than 3:100, or less than 2:100. These ratios may be applied to any of the arrangements described herein which discuss a ratio of Treg:Tconv before a treatment with or administration of a combination as described herein.

Arrangement 6. A method according to arrangement 4 or arrangement 5, wherein the ratio of Treg:Tconv in the population of step c) is increased to greater than 2:100.

The combinations of the present invention may provide benefit by preventing further reductions in the ratio of Treg:Tconv, which will have occurred if the disease or disorder is already beginning to take effect, or has already taken hold. If used prophylactically, the combinations of the present invention may prevent any substantial change in the ratio of Treg:Tconv, because they are able to protect the patient from the detrimental cellular changes. Thus, in another embodiment, the ratio of Treg:Tconv remains at a substantially constant ratio after administration of the combination.

Substantially constant may be as described in arrangement 2.

Further beneficial effects may be seen by administration of the combinations of the present invention in that they may be able to correct a low ratio of Treg:Tconv by increasing the ratio or may further increase the ratio. Thus, in an alternative embodiment, the ratio is increased to greater than 3:100, or greater than 4:100, or greater than 5:100. In an alternative embodiment, the ratio is increased to greater than 1.6:100, to greater than 1.7:100, to greater than 1.8:100 or to greater than 1.9:100.

In an alternative embodiment, the ratio of Treg:Tconv remains at a range of from 1:100 to 3:100. The upper limit may be 2:100, 2.5:100 or 3:100. The upper limit may be any of the ratios disclosed in arrangement 6. The lower limit may be any of the ratios disclosed in arrangement 5. In one embodiment, the ratio remains at a range of from 1.5:100 to 2:100. These ratios may be applied to any of the arrangements described herein which discuss a ratio of Treg:Tconv after a treatment with or administration of a combination as described herein.

Arrangement 7. A method according to any one of arrangements 1 to 6, wherein the method is carried out ex vivo in a sample of blood extracted from a human donor subject.

Arrangement 8. A method according to arrangement 7, wherein blood produced by said method is introduced to a recipient human subject.

In one embodiment, the recipient human subject is the same donor human subject from whom the sample was removed. In another embodiment, the recipient human subject is different to the donor human subject. When the recipient is different to the donor, it is preferable that the donor is of the same gender as the recipient subject. In another embodiment, the donor may be of a similar age and ethnicity as the recipient subject. In another embodiment, the donor may have the same or similar allotype markers as the recipient subject.

In another embodiment, the recipient human donor may receive more than one transfusion of donor blood, according to the severity of the disease to be treated.

Arrangement 9. A method according to any one of arrangements 1 to 6, wherein the method is carried out in vivo in a human subject.

Arrangement 10. A method according to arrangement 9, wherein the subject has or is at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

Autoimmune and alloimmune disease are well-known to those skilled in the art, but may be as further defined in any of the arrangements disclosed herein. In another embodiment, the disease or disorder is additionally an OX40L-mediated disease or disorder. In any arrangement described herein, an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 may be as defined in any of arrangements 92 to 95 hereinbelow.

As used herein, a subject may be identified as being "at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100" when the cellular changes in their T-cell population (for example, a reduction in the proportion (e.g. number or level) of Treg cells in the population, or an increase in T(eff+mem) cells in the population, or a reduction in the ratio of Treg:Tconv) have begun to take place, but the subject has not yet presented symptoms or would not be diagnosed as having such a disease by any conventional method (for example, by reaching the stated level of less than 1.5:100). Thus, the methods and uses disclosed herein may aid in the early identification of patients who will develop such diseases. In one embodiment, the disease is prevented (i.e. the treatment is prophylactic).

In a particular embodiment, the subject is at risk of GvHD or transplant rejection when they are pre-operative for a transplant. Potential transplant therapies are envisaged in arrangement 95 hereinbelow.

Arrangement 11. A method of treating or reducing the risk of a disease or condition (e.g. an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100) in a subject, the method comprising combining a population of T-cells with combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, which combination prevents reduction in the proportion (e.g. number or level) of Treg cells, and whereby the proportion of said Treg cells is not reduced.

In one embodiment, the combination slows the reduction in proportion (e.g. number or level) of Treg cells in said population, and results in a slowing in reduction of the proportion (e.g. number or level) of Treg cells. In one embodiment, the combination maintains the proportion (e.g. number or level) of Treg cells, and results in maintenance of the proportion (e.g. number or level) of Treg cells. In one embodiment, the combination prevents depletion of the proportion (e.g. number or level) of Treg cells, and results in the proportion (e.g. number or level) of Treg cells not being depleted (or substantially depleted). In one embodiment, the combination increases the proportion (e.g. number or level) of Treg cells, and results in an increase in the proportion (e.g. number or level) of Treg cells.

Arrangement 12. A method according to any one of arrangements 9 to 11, wherein the combining of cells and the combination is by administering said combination in a therapeutically effective amount or prophylactically effective amount to said subject, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.

In one embodiment, the combination comprises a therapeutically effective amount of the anti OX40 or anti-OX40L antibody and a therapeutically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a therapeutically effective amount of the anti OX40 or anti-OX40L antibody and a prophylactically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a prophylactically effective amount of the anti OX40 or anti-OX40L antibody and a therapeutically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a prophylactically effective amount of the anti OX40 or anti-OX40L antibody and a prophylactically effective amount of the second therapeutic agent.

In another embodiment, the combination may be therapeutically or prophylactically effective, despite containing doses or amounts of either (i) the anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) the second therapeutic agent which, by themselves, would not necessarily be therapeutically or prophylactically effective. Hence, the risk of side effects may be reduced, as smaller amounts of therapeutic entities are being given to patients in need thereof.

Arrangement 13. A method of treating or reducing the risk of a disease or condition (e.g. an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100) in a subject comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent thereof, which combination prevents reduction in the proportion (e.g. number or level) of Treg cells, and whereby said proportion (e.g. number or level) of Treg cells is not reduced, wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.

In one embodiment, the combination slows the reduction in proportion (e.g. number or level) of Treg cells in said population, and results in a slowing in reduction of the proportion (e.g. number or level) of Treg cells. In one embodiment, the combination maintains the proportion (e.g. number or level) of Treg cells, and results in maintenance of the proportion (e.g. number or level) of Treg cells. In one embodiment, the combination prevents depletion of the proportion (e.g. number or level) of Treg cells, and results in the proportion (e.g. number or level) of Treg cells not being depleted (or substantially depleted). In one embodiment, the combination increases the proportion (e.g. number or level) of Treg cells, and results in an increase in the proportion (e.g. number or level) of Treg cells.

Arrangement 14. A combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for use in treating or reducing the risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject.

Arrangement 15. Use of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject.

Arrangement 16. Use of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject.

Arrangement 17. A composition comprising a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for the

treatment or prevention of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject.

In any of arrangements 14 to 17, in one embodiment, the administration of the combination results in the change in Treg cells, T(eff+mem) cells and/or the ratio of Treg:Tconv cells as described for arrangement 18, or results in a change of Ki-67$^+$ T-cells as described in arrangement 30a.

Arrangement 18. A method of treating or reducing the risk of a disease or condition in a subject in need thereof, comprising: a) performing an assay to measure the proportion (e.g. number or level) of Treg cells and the proportion (e.g. number or level) of Tconv cells in a sample obtained from the subject; and b) administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent to the subject when the ratio of Treg:Tconv cells in the sample is determined in the assay to be less than 1.5:100.

In one embodiment, the administration of the combination results in a prevention of reduction of the proportion (e.g. number or level) of Treg cells. In one embodiment, the administration of the combination results in a slowing in reduction of the proportion (e.g. number or level) of Treg cells. In one embodiment, the administration of the combination results in maintenance of the proportion (e.g. number or level) of Treg cells. In one embodiment, the administration of the combination results in the proportion (e.g. number or level) of Treg cells not being depleted (or substantially depleted). In one embodiment, the administration of the combination results in an increase in the proportion (e.g. number or level) of Treg cells. In another embodiment, the number of Treg cells after administration is as described in arrangement 2.

The combinations of the present invention prevent the unwanted rapid expansion of T(eff+mem) cells in a patient, as shown in Example 10. Thus, in one embodiment, the administration of the combination results in a prevention of increase (or of expansion) of the proportion (e.g. number or level) of T(eff+mem) cells. As used in the arrangements herein, the phrase "preventing the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases may be replaced throughout by the phrase "maintaining the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases may replaced with the phrase "decreasing (or reducing) the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases may be replaced with the phrase "not expanding (or increasing) the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases may be replaced with the phrase "increasing the proportion (e.g. number or level) of T(eff+mem) cells" or similar phrases. In any of the arrangements herein, the "proportion" may be the relative proportion (e.g. number or level) of T(eff+mem) cells, or the absolute number of level of T(eff+mem) cells.

In one embodiment, the administration of the combination results in a slowing of the increase (or of expansion) of the proportion (e.g. number or level) of T(eff+mem) cells. In one embodiment, the administration of the combination results in maintenance of the proportion (e.g. number or level) of T(eff+mem) cells. In one embodiment, the administration of the combination results in the proportion (e.g. number or level) of T(eff+mem) cells not being expanded or increased (or substantially expanded or increased). In one embodiment, the administration of the combination results in a decrease (or reduction) in the proportion (e.g. number or level) of T(eff+mem) cells. In any of these arrangements, in one embodiment, the T(eff+mem) cells are CD4$^+$. In another embodiment, the T(eff+mem) cells are CD8$^+$. These mechanisms of the combination on the proportion of T(eff+mem) cells may be applied to any of the arrangements herein.

The proportion (e.g. number or level) of T(eff+mem) cells may be determined relative to the entire T-cell population in the sample. In one embodiment, the proportion (e.g. number or level) of T(eff+mem) cells is determined relative to other T-cells in the sample. In a particular embodiment, the proportion (e.g. number or level) of T(eff+mem) cells is determined relative to Treg cells (as defined hereinbelow) in the sample. The proportion (e.g. number or level) of T(eff+mem) cells may be altered by allowing the expansion or increase in the absolute number of T(eff+mem) cells, or by changing the number of other T-cell subtypes such that the relative proportion (e.g. number or level) of T(eff+mem) cells appears to be maintained or decreased.

The combinations of the present invention may keep the proportion (e.g. number or level) of T(eff+mem) cells in a stable range, which is controlled such that these T-cells are not sufficiently expanded to cause further detrimental effects. Thus, in one embodiment, the proportion (e.g. number or level) of T(eff+mem) remains within a range of from 10 to 500×10^6 T(eff+mem)/litre, or from 20 to 300×10^6 T(eff+mem)/litre, or from 100 to 200×10^6 T(eff+mem)/litre, or from 30 to 100×10^6 T(eff+mem)/litre.

In one embodiment, the upper limit of the range of T(eff+mem) is 400×10^6T(eff+mem)/litre, or 300×10^6 T(eff+mem)/litre, or 250×10^6 T(eff+mem)/litre. In another embodiment, the upper limit of the range of T(eff+mem) is 200×10^6 T(eff+mem)/litre, or 150×10^6 T(eff+mem)/litre, or 100×10^6 T(eff+mem)/litre.

In one embodiment, the lower limit of the range of T(eff+mem) is 10×10^6 T(eff+mem)/litre, or 12×10^6 T(eff+mem)/litre, or 15×10^6 T(eff+mem)/litre or 17×10^6 T(eff+mem)/litre. In another embodiment, the lower limit of the range of T(eff+mem) is 20×10^6 T(eff+mem)/litre, or 25×10^6 T(eff+mem)/litre or 30×10^6 T(eff+mem)/litre or 35×10^6 T(eff+mem)/litre or 40×10^6 T(eff+mem)/litre. In one embodiment, the lower limit of the range of T(eff+mem) is 50×10^6 T(eff+mem)/litre, or 60×10^6 T(eff+mem)/litre, or 70×10^6 T(eff+mem)/litre, or 80×10^6 T(eff+mem)/litre. In another embodiment, the lower limit of the range of T(eff+mem) is 90×10^6 T(eff+mem)/litre, or 100×10^6 T(eff+mem)/litre.

The combinations of the present invention may keep the proportion (e.g. number or level) of T(eff+mem) cells below detrimental levels. Thus, in one embodiment, the proportion (e.g. number or level) of T(eff+mem) cells is less than 400×10^6 T(eff+mem)/litre, or less than 300×10^6 T(eff+mem)/litre, or less than 250×10^6 T(eff+mem)/litre. In another embodiment, the proportion (e.g. number or level) of T(eff+mem) cells is less than 200×10^6 T(eff+mem)/litre, or less than 150×10^6 T(eff+mem)/litre, or less than 100×10^6 T(eff+mem)/litre.

The rationale and ratios of Treg:Tconv in diseased patients may be as described in arrangements 5 and 6. In one embodiment, after administration of the combination, the ratio of Treg:Tconv remains at a substantially constant ratio.

In an alternative embodiment, the ratio is increased to greater than 3:100, or greater than 4:100, or greater than 5:100. In an alternative embodiment, the ratio is increased to greater than 1.6:100, to greater than 1.7:100, to greater than 1.8:100 or to greater than 1.9:100. In another embodiment, the ratio of Treg:Tconv after administration is as described in arrangement 6. Substantially constant may be as described in arrangement 2.

In an alternative embodiment, the ratio of Treg:Tconv remains at a range of from 1:100 to 3:100. The upper limit may be 2:100, 2.5:100 or 3:100. The upper limit may be any of the ratios disclosed in arrangement 6. The lower limit may be any of the ratios disclosed in arrangement 5. In one embodiment, the ratio remains at a range of from 1.5:100 to 2:100.

In another embodiment, the administration of the combination results in treatment of the disease or condition. Treatment, as used in any of the arrangements herein, may be reduction in one or more symptoms of the disease or disorder or, or reduction in the severity of one or more disease or disorder. In another embodiment, the administration of the combination reduces the risk of the disease or condition. Throughout the arrangements herein, a reduction in the risk of a disease or disorder may also be "prevention" of said disease or disorder, which includes the prevention of one or more symptom(s) of said disease or disorder.

Arrangement 19. A combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a ratio of Treg:Tconv cells of less than 1.5:100.

Arrangement 20. Use of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for therapy of a subject who has, or has been determined to have, a ratio of Treg:Tconv cells of less than 1.5:100.

Arrangement 21. Use of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent in the manufacture of a medicament for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a ratio of Treg:Tconv cells of less than 1.5:100.

In any of arrangement 18 to 21, the ratio is determined in a sample, for example, in a sample of blood obtained from said subject.

In any of arrangements 18 to 21, in one embodiment, the therapy is for treatment, for reducing the risk or for the prevention of an OX40L-mediated disease. In another embodiment, the therapy is for the treatment, for reducing the risk or for the prevention of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, which may be as described in any of the arrangements hereinbelow. In another embodiment, the therapy is for the treatment, for reducing the risk or for the prevention of a disease or condition (e.g. any of the diseases or conditions mentioned herein). In another embodiment, the therapy is for reducing the risk or preventing a disease or condition (e.g. any of the disease or conditions mentioned herein).

In any of arrangements 18 to 21, in one embodiment, the administration of the combination results in the change in Treg cells, T(eff+mem) cells and/or the ratio of Treg:Tconv cells as described for arrangement 18, or results in a change of Ki-67$^+$ T-cells as described in arrangement 30a.

Arrangement 22. A method according to any one of arrangements 5, 10, 14 to 18, or 42 to 53, a combination for the use according to arrangement 14 or 19, or the use according to any one of arrangements 15, 16, 20, 21, 54 or 55 wherein the ratio of Treg:Tconv cells is (or is determined to be) less than 1.25:100.

In one embodiment, the ratio is less than 5:100, or less than 4:100, or less than 3:100, or less than 2:100.

Arrangement 23. A method, a combination for the use, or the use according to arrangement 22, wherein the ratio of Treg:Tconv cells is (or is determined to be) less than 1:100, or less than 0.75:100, or less than 0.5:100.

In one embodiment, for any of arrangements 22 and 23, the lower limit of the ratio may be 1:10, or 1:9, or 1:8, or 1:7, or 1:6, or 1:5 Treg:Tconv.

In another embodiment, for any of arrangements 22 and 23, after administration of the combination, the ratio of Treg:Tconv remains at a substantially constant ratio. Substantially constant may be as described in arrangement 2. In an alternative embodiment, the ratio is increased to greater than 3:100, or greater than 4:100, or greater than 5:100. In an alternative embodiment, the ratio is increased to greater than 1.6:100, to greater than 1.7:100, to greater than 1.8:100 or to greater than 1.9:100.

In an alternative embodiment, the ratio of Treg:Tconv remains at a range of from 1:100 to 3:100. The upper limit may be 2:100, 2.5:100 or 3:100. The upper limit may be any of the ratios disclosed in arrangement 6. The lower limit may be any of the ratios disclosed in arrangement 5. In one embodiment, the ratio remains at a range of from 1.5:100 to 2:100.

Arrangements 5 and 6 disclose other ratios and rationales for the ratios which may be applied to any other arrangement herein which discusses the ratio of Treg:Tconv.

Arrangement 24. A method according to any one of arrangements 5, 10, 14 to 18, 23 or 24, a combination for the use according to arrangement 14, 19, 23 or 24 or the use according to any one of arrangements 15, 16, 20, 21, 23, or 24, wherein the ratio of Treg:Tconv cells is determined (or is determinable) by flow cytometry.

Flow cytometry techniques are well-known to those skilled in the art, as discussed above.

Agents which may be used in flow cytometry techniques are defined in Example 7 below. In one embodiment, the flow cytometry is carried out as described in Example 7 below. In another embodiment, the flow cytometry is carried out as described in Baumgarth & Roederer (2000).

In any of the arrangements herein, the proportion, ratio, number or level of particular T-cell subtypes may be determined by this method.

Arrangement 25. A method of treating a disease or condition in a subject in need thereof, comprising:

a) Performing an assay to measure the proportion (e.g. number or level) of Ki-67$^+$ T-cells in a sample obtained from the subject; and

b) Administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally (ii) a second therapeutic agent to the subject when the proportion (e.g. number or level) of Ki-67$^+$ T-cells is greater than 30% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Ki-67 is a known marker of T-cell proliferation. During interphase, the antigen can be exclusively detected within the nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. The fact that the Ki-67 protein is present during all active phases of the cell cycle (G(1), S, G(2), and mitosis), but is absent from resting cells (G(0)), makes it an excellent marker for deter-

mining the so-called growth fraction of a given cell population, (see Scholzen T., et al., J Cell Physiol. 2000 March; 182(3):311-22.). Without being bound by theory, Ki-67$^+$ T-cells may therefore be used as a biomarker, in order to indicate the start of a cellular process (e.g. T-cell proliferation) which will ultimately result in an autoimmune or alloimmune disease or disorder (for example any of the autoimmune or alloimmune disease or disorders disclosed in these arrangements). If the patient is treated in this preliminary phase, then it is expected that the patient will not progress to being symptomatic of the disease or disorder, and/or the patient will not progress to such a severe disease state. In another embodiment, the progress of the disease or disorder is slowed or prevented. The data presented in Example 10 shows that prophylactic treatment of GvHD with a combination as claimed is able to reduce the proportion of Ki-67$^+$ T-cells, and this data has led the inventors to consider the use of this biomarker in a treatment study protocol, as it may prove to be an early biomarker, which can be detected before disease has set in and/or before symptoms appear and/or before a diagnosis could be many using any traditional methods. In addition to being used as a marker for determining when to begin treatment, Ki-67$^+$ T-cells could also be used as a marker of efficacy in a prophylaxis regiment, where a reduction in the proportion (e.g. number or level) of Ki-67$^+$ T-cells can be used to show that a treatment is having the desired effect on the proliferation of T-cells.

The proportion (e.g. number or level) of Ki-67$^+$ T-cells may be determined relative to the entire T-cell population in the sample. In one embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells cells is determined relative to other T-cells in the sample, such as other CD4$^+$ T-cells, or other CD8$^+$ T-cells. The proportion (e.g. number or level) of Ki-67$^+$ T-cells may be altered by allowing the depletion or decrease in the absolute number of Ki-67$^+$ T-cells, or by changing the number of other T-cell subtypes such that the relative proportion (e.g. number or level) of Ki-67$^+$ T-cells appears to be depleted or decreased.

In another embodiment, and in any of the arrangements herein which discuss the proportion of Ki-67$^+$ T-cells before administration of the combination, the % of Ki-67$^+$ T-cells may be any of the % given in arrangements 33 and 34 hereinbelow. In another embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells is greater than 25% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

In another embodiment, the assay involves analysing the sample using flow cytometry, which is described in detail elsewhere herein.

Arrangement 26. A combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a proportion (e.g. number or level) of Ki-67$^+$ T-cells of greater than 30% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Arrangement 27. Use of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent for therapy of a subject who has, or has been determined to have, a proportion (e.g. number or level) of Ki-67$^+$ T-cells of greater than 30% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Arrangement 28. Use of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent in the manufacture of a medicament for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a proportion (e.g. number or level) of Ki-67$^+$ T-cells of greater than 30% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

In any of arrangements 25 to 28, in one embodiment, the administration of the combination results in the change in Treg cells, T(eff+mem) cells and/or the ratio of Treg:Tconv cells as described for arrangement 18. In another embodiment, the administration of the combination results in a change of Ki-67$^+$ T-cells, e.g. as described in arrangement 30a.

Arrangement 29. A method of determining a subject as having, or as being at risk of, an autoimmune or alloimmune disease or condition (for example, an autoimmune or alloimune disease or condition characterised by a ratio of Treg: Tconv of less than 1.5:100 and/or for example which disease or condition is suitable for treatment with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent), comprising:

a) performing an assay that detects the proportion of Ki-67$^+$ T-cells in a sample obtained from said subject; and

b) determining the subject as having said disease or condition if the proportion (e.g. number or level) of Ki-67$^+$ T-cells is greater than 30% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

A subject may be at risk of a disease or disorder if there are changes in the levels of Ki-67$^+$ T-cells, but the patient has not yet started displaying any symptoms by which he would conventionally be diagnosed, as explained in arrangement 25. The proportion of Ki-67$^+$ T-cells, and diseases or conditions are as described elsewhere herein, for example as in any of the arrangements herein.

Arrangement 30. A method according to arrangement 29 further comprising the step of:

c) administering to said subject a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, which combination prevents reduction in the proportion (e.g. number or level) of said Treg cells in the blood of said subject, if said subject has been determined as having a disease or condition in step b).

The change in Treg cells may be as described in arrangement 18.

Arrangement 30a. A method according to arrangement 29 further comprising the step of:

c) administering to said subject a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, which combination reduces the proportion (e.g. number or level) of Ki-67$^+$ T-cells cells in the blood of said subject, if said subject has been determined as having a disease or condition in step b).

In one embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells is reduced to below 20% of the total number of CD4$^+$ and/or CD8$^+$ T-cells. In one embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells is reduced to below 15%, or to below 10%, or to below 9%, or to below 8% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

In one embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells is maintained within a range of from 2 to 25%, or from 2 to 20%, or from 2 to 18%, or from 2 to 15% of the total number of CD4$^+$ and/or CD8$^+$ T-cells. In another embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells is maintained within a range of from 2 to 12%, or from 2 to 10%, or from 4 to 12%, or from 4 to 10% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Arrangement 30b. A method according to arrangement 29 further comprising the step of:

c) administering to said subject a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, which combination prevents the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells in the blood of said subject, if said subject has been determined as having a disease or condition in step b).

The changes in T(eff+mem) cells, and the levels and ranges may be as described in arrangement 18.

Arrangement 31. A method according to arrangement 29 further comprising the step of:

c) administering to said subject a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, which combination increases the ratio of Treg:Tconv cells in the blood of said subject, if said subject has been determined as having a disease or condition in step b).

The change in the ratio of Treg:Tconv cells may be as described in arrangement 18.

Arrangement 32. A method for treating an autoimmune or alloimmune disease or condition (for example, an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 and/or for example with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent), comprising the steps of:

a) determining whether the subject is a candidate for treatment by detecting the proportion (e.g. number or level) of Ki-67$^+$ T-cells obtained from a sample from the subject;

b) administering said combination to the subject if the subject has a proportion (e.g. number or level) of Ki-67$^+$ T-cells of greater than 30% of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Arrangement 33. A method according to any one of arrangements 25, or 29 to 32, a combination for the use according to arrangement 26, or the use according to arrangement 27 or arrangement 28, wherein the proportion (e.g. number or level) of Ki-67$^+$ T-cells is greater than 35% (for example greater than 40%, greater than 45%, e.g. greater than 50%) of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Arrangement 34. A method, combination for the use, or the use according to arrangement 33, wherein the proportion (e.g. number or level) of Ki-67$^+$ T-cells is greater than 55% (for example greater than 60%, greater than 65%, e.g. greater than 70%, or greater than 80%) of the total number of CD4$^+$ and/or CD8$^+$ T-cells.

Arrangement 35. A method according to any one of arrangements 25, or 29 to 34, a combination for the use according to any one of arrangements 26, 33 or 34 or the use according to any one of arrangements 27, 28, 33 or 34, wherein the proportion (e.g. number or level) of Ki-67$^+$ T-cells is determined (or is determinable) by flow cytometry.

Arrangement 36. A method according to arrangement 18, 22 to 25, or 29 to 35 a combination for the use according to arrangement 19, 22 to 24, 26, or 33 to 35 or the use according to any one of arrangements 20 to 24, 27, 28, or 33 to 35 wherein the therapy is the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, preferably wherein the therapy is the treatment of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

Arrangement 37. A method, comprising: a) obtaining at least two T-cell samples derived from a subject who has or is at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point, b) determining the proportion (e.g. number or level) of Treg cells in said first and second samples; c) treating said subject to prevent reduction of the proportion (e.g. number or level) of Treg cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Treg cells in said second sample are reduced as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

The change in Treg cells may be as described for arrangement 18. In any arrangement herein, the phrase "reduced", with respect to a certain T-cell sub-type means that the amount (e.g. ratio, proportion, level or number) of T-cells in the subsequent sample is statistically significantly lower than the amount (e.g. ratio, proportion, level or number) in the previous sample.

Arrangement 37a. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has or is at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Treg cells in said first and second samples;

c) treating said subject to increase the ratio of Treg:Tconv cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Treg cells in said second sample is reduced as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

The change in the ratio of Treg:Tconv cells may be as described for arrangement 18.

Arrangement 37b. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has or is at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Treg cells in said first and second samples;

c) treating said subject to reduce the proportion (e.g. number or level) of Ki-67$^+$ T-cells cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Treg cells in said second sample are reduced as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

The reduction in Ki-67$^+$ T-cells cells may be as described for arrangement 30a.

Arrangement 37c. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has or is at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein said at least two samples

comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Treg cells in said first and second samples;

c) treating said subject to prevent the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Treg cells in said second sample is reduced as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

The change in T(eff+mem) cells, and the levels and ranges may be as described for arrangement 18.

Arrangement 38. A method according to arrangement 37, wherein in step c), the proportion (e.g. number or level) of Treg cells in said second sample is less than 50% of the proportion (e.g. number or level) of Treg cells in said first sample, for example is less than 60% of the proportion, or preferably is less than 70% of the proportion (e.g. number or level) of Treg cells in said first sample.

In one embodiment, the proportion (e.g. number or level) of Treg cells in said second sample is less than 80%, or less than 90%, or less than 95% of the proportion (e.g. number or level) of Treg cells in said first sample. In another embodiment, the Treg cells are reduced by 100%, i.e. are completely ablated.

These reductions may apply to any arrangement where a comparison of the proportion (e.g. number or level) of Treg cells is being made.

Arrangement 39. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has, or is at risk of, an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said first and second samples;

c) treating said subject to prevent reduction of the proportion (e.g. number or level) of Treg cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said second sample is elevated as compared to said first sample, in order to treat or reduce the risk of said disease or condition.

If a patent is receiving prophylactic treatment of a drug, then this method could be used to monitor the therapy, in order to ensure that the prophylaxis is continuing to be effective. An increase in the proportion (e.g. number or level) of Ki-67$^+$ T-cells may be indicative that the prophylaxis is no longer being effective and it may be appropriate to change prophylactic regimens, for example, by administering a combination of the present invention. The change in Treg cells may be as described for arrangement 18.

In any arrangement herein, the phrase "elevated", with respect to a certain T-cell sub-type means that the amount (e.g. ratio, proportion, level or number) of T-cells in the subsequent sample is statistically significantly higher than the amount (e.g. ratio, proportion, level or number) in the previous sample.

Arrangement 39a. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has, or is at risk of, an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said first and second samples;

c) treating said subject to reduce the proportion (e.g. number or level) of Ki-67$^+$ T-cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion of Ki-67$^+$ T-cells in said second sample is elevated as compared to said first sample, in order to treat or reduce the risk of said disease or condition.

The reduction in Ki-67$^+$ T-cells cells may be as described for arrangement 30a.

Arrangement 39b. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said first and second samples;

c) treating said subject to prevent the increase (or the expansion) of the proportion (e.g. number or level) of T(eff+mem) cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Ki-67$^+$ T-cells cells in said second sample is elevated as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

The change in T(eff+mem) cells may be as described for arrangement 18.

Arrangement 40. A method according to any one of arrangements 37 to 39, further comprising the steps of:

d) obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;

e) determining the proportion (e.g. number or level) of Treg cells in said third sample;

f) treating said subject to prevent reduction of the proportion (e.g. number or level) of Treg cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Treg cells in said third sample is reduced as compared to said second or said first sample.

The change in Treg cells may be as described for arrangement 18.

Arrangement 40a. A method according to any one of arrangements 37 to 39, further comprising the steps of:

d) obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;

e) determining the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said third sample;

f) treating said subject to prevent reduction of the proportion (e.g. number or level) of Treg cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said third sample is elevated as compared to said second or said first sample.

The change in Treg cells may be as described for arrangement 18.

Arrangement 41. A method according to arrangement 40 or 40a, wherein steps d) to f) are repeated as necessary until the proportion (e.g. number or level) of Treg cells reaches a therapeutically-effective, or a prophylactically-effective levels, e.g. a substantially constant level in said subject.

Arrangement 41a. A method according to arrangement 40 or 40a, wherein steps d) to f) are repeated as necessary until the proportion (e.g. number or level) of Ki-67$^+$ T-cells reaches a therapeutically-effective, or a prophylactically-effective level, e.g. a substantially constant level in said subject.

Arrangement 41b. A method according to arrangement 40 or 40a, wherein steps d) to f) are repeated as necessary until the proportion (e.g. number or level) of T(eff+mem) cells reaches a therapeutically-effective, or a prophylactically-effective levels, e.g. a substantially constant level in said subject.

Arrangement 41c. A method according to arrangement 40 or 40a, wherein steps d) to f) are repeated as necessary until the ratio of Treg:Tconv cells reaches a therapeutically-effective, or a prophylactically-effective level, e.g. a substantially constant level in said subject.

In one embodiment, the levels are reached and maintained for a week, or two weeks, or three weeks or four weeks. In one embodiment, the levels are reached and maintained for a month, or two months, or three months or four months. In one embodiment, the levels are reached and maintained for a six months, or nine months or for a year.

The particular proportions, levels and numbers of Treg, T(eff+Mem) and Ki-67$^+$ T-cells, and the ratios of Treg:Tconv are as set out in arrangement 18s and 30a. Substantially constant may be as described in arrangement 2.

Arrangement 42. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has, or is at risk of, an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein said at least two samples comprise a first sample taken at a first time point and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said first and second samples;

c) treating said subject to increase the ratio of Treg:Tconv cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said second sample is elevated as compared to said first sample, in order to treat or prevent said disease or condition.

Arrangement 43. A method according to arrangement 42, further comprising the steps of:

d) obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;

e) determining the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said third sample;

f) treating said subject to increase the ratio of Treg:Tconv cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said third sample is elevated as compared to said second or said first sample.

The particular proportions, levels and numbers of Ki-67$^+$ T-cells may be as set out in arrangement 30a.

Arrangement 44. A method according to arrangement 43, wherein steps d) to f) are repeated as necessary until the ratio of Treg:Tconv cells reaches a therapeutically-effective, or prophylactically-effective ratio, e.g. a substantially constant ratio in said subject.

In one embodiment, the levels are reached and maintained for a week, or two weeks, or three weeks or four weeks. In one embodiment, the levels are reached and maintained for a month, or two months, or three months or four months. In one embodiment, the levels are reached and maintained for a six months, or nine months or for a year.

Substantially constant may be as described in arrangement 2.

Arrangement 42a. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the proportion (e.g. number or level) of T(eff+mem) cells in said first and second samples;

c) treating said subject to increase the ratio of Treg:Tconv cells, or to prevent reduction in the proportion (e.g. number or level) of Treg cells, or to prevent the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells, or to reduce the proportion (e.g. number or level) of Ki-67$^+$ T-cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of T(eff+mem) cells in said second sample is elevated as compared to said first sample, in order to treat or prevent said disease or condition.

Arrangement 43a. A method according to arrangement 42a, further comprising the steps of:

d) obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;

e) determining the proportion (e.g. number or level) of T(eff+mem) cells in said third sample;

f) treating said subject to increase the ratio of Treg:Tconv cells, or to prevent reduction in the proportion (e.g. number or level) of Treg cells, or to prevent the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells, or to reduce the proportion (e.g. number or level) of Ki-67$^+$ T-cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the proportion (e.g. number or level) of T(eff+Mem) cells in said third sample is elevated as compared to said second or said first sample.

In arrangement 42a or 43a the proportion (e.g. number or level) of T(eff+mem) cells are considered to be elevated in said second or third sample if the proportion (e.g. number or level) is less than half the proportion (e.g. number or level) of T(eff+mem) cells in said first or second sample, for example is two-fold less than the proportion in said first or second sample, or preferably is three-fold less than the proportion in said first or second sample.

In one embodiment, the proportion (e.g. number or level) is four-fold less, or 5-fold less, or 6-fold less than the proportion (e.g. number or level) of T(eff+mem) cells in said first or second sample. In one embodiment, the proportion (e.g. number or level) is 7-fold less, or 8-fold less, or 9-fold less, or 10-fold less than the proportion (e.g. number or level) of T(eff+mem) cells in said first or second sample.

These reductions may be applied to any arrangement where a comparison of the proportion (e.g. number or level) of T(eff+mem) cells is being made.

Arrangement 44a. A method according to arrangement 43a, wherein steps d) to f) are repeated as necessary until the ratio of Treg:Tconv cells, or the proportion (e.g. number or level) of Treg cells, T(eff+mem) cells or Ki-67$^+$ T-cells reaches a therapeutically-effective ratio, e.g. at a substantially constant ratio or proportion (e.g. number or level) in said subject.

In one embodiment, the levels are reached and maintained for a week, or two weeks, or three weeks or four weeks. In one embodiment, the levels are reached and maintained for a month, or two months, or three months or four months. In one embodiment, the levels are reached and maintained for a six months, or nine months or for a year.

For arrangements 42a, 43a and 44a, the particular proportions, levels and numbers of Treg, T(eff+mem) and Ki-67$^+$ T-cells, and the ratios of Treg:Tconv are as set out in arrangements 18 and 30a. Substantially constant may be as described in arrangement 2.

Arrangement 42b. A method, comprising:

a) obtaining at least two T-cell samples derived from a subject who has an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,

b) determining the ratio of Treg:Tconv cells in said first and second samples;

c) treating said subject to increase the ratio of Treg:Tconv cells, or to prevent reduction in the proportion (e.g. number or level) of Treg cells, or to prevent the increase (or expansion) of the proportion (e.g. number or level) of T(eff+mem) cells, or to reduce the proportion (e.g. number or level) of Ki-67$^+$ T-cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the ratio of Treg:Tconv is reduced in said second sample as compared to said first sample, in order to treat or prevent said disease or condition.

Arrangement 43b. A method according to arrangement 42b, further comprising the steps of:

d) obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;

e) determining the ratio of Treg:Tconv cells in said third sample;

f) treating said subject to increase the ratio of Treg:Tconv cells by administering a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent, if the ratio of Treg:Tconv cells is reduced in said third sample as compared to said second or said first sample.

In arrangement 42b or 43b the ratio of Treg:Tconv cells is considered to be reduced in said second or third sample if the ratio is less than 40% of the ratio of Treg:Tconv cells in said first or second sample, for example is less than 50% of the ratio, or preferably is less than 60% of the ratio of Treg:Tconv cells in said first or second sample.

In one embodiment, the ratio of Treg:Tconv cells in said second or third sample is less than 70%, or less than 80%, or less than 90%, or less than 95% of the ratio of Treg:Tconv cells in said first or second sample. In another embodiment, the ratio of Treg:Tconv cells is reduced by 100%, i.e. the Treg cells are completely ablated.

These reductions may apply to any arrangement where a comparison of the ratio of Treg:Tconv cells is being made.

Arrangement 44b. A method according to arrangement 43, wherein steps d) to f) are repeated as necessary until the ratio of Treg:Tconv cells reaches a therapeutically-effective ratio, e.g. at a substantially constant ratio in said subject.

In one embodiment, the levels are reached and maintained for a week, or two weeks, or three weeks or four weeks. In one embodiment, the levels are reached and maintained for a month, or two months, or three months or four months. In one embodiment, the levels are reached and maintained for a six months, or nine months or for a year.

For arrangements 42b, 43b and 44b, the particular proportions, levels and numbers of Treg, T(eff+mem) and Ki-67$^+$ T-cells, and the ratios of Treg:Tconv are as set out in arrangements 18 and 30a. Substantially constant may be as described in arrangement 2.

Arrangement 45. A method according to any one of arrangements 39 to 44, wherein in step c), or in step f) the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said second sample or third sample is greater than double the proportion (e.g. number or level) as compared to said first sample or second sample, for example is greater than three times, or preferably is greater than 4 times the proportion (e.g. number or level) as compared to said first sample.

In another embodiment, the proportion (e.g. number or level) of Ki-67$^+$ T-cells in said second sample or third sample is greater than 5 times the proportion (e.g. number or level) as compared to said first sample or second sample for example is greater than 10 times, or is greater than 15 times, or is greater than 20 times, or is greater than 25 times the number or levels as compared to said first sample.

Arrangement 45a. A method according to any one of arrangements 39 to 44, wherein in step c), or in step f) the proportion (e.g. number or level) of T(eff+mem) cells in said second sample or third sample is greater than double the proportion (e.g. number or level) as compared to said first sample or second sample, for example is greater than three times, or preferably is greater than 4 times the proportion (e.g. number or level) as compared to said first sample or said second sample.

In another embodiment, the proportion (e.g. number or level) of T(eff+mem) cells in said second sample or third sample is greater than 5 times the proportion (e.g. number or level) as compared to said first sample or second sample for example is greater than 10 times, or is greater than 15 times, or is greater than 20 times, or is greater than 25 times the proportion (e.g. number or level) as compared to said first sample.

Arrangement 45b. A method according to any one of arrangements 39 to 44, wherein in step c), or in step f) the ratio of Treg:Tconv cells in said second sample or third sample is less than double the ratio as compared to said first sample or second sample, for example is less than three times, or preferably is less than 4 times the ratio as compared to said first sample.

In another embodiment, the ratio of Treg:Tconv cells in said second sample or third sample is less than 5 times the ratio as compared to said first sample or second sample for example is less than 10 times, or is less than 15 times, or is less than 20 times, or is less than 25 times the ratio as compared to said first sample.

Arrangement 46. A method according to any one of arrangements 37 to 45, wherein said first sample is collected:

a) before the onset of said disease or condition; or

b) after the onset of said disease or condition; and

optionally wherein said second sample is collected no longer than one month, e.g. no longer than one week after the first sample.

As used in the arrangements herein, a subject may be determined to be "before the onset of a disease or condition"

if the subject is presenting no symptoms which would conventionally be associated with said disease or condition, or if the subject would not be diagnosed as having such a disease or condition by any conventional method. For example, the presence of signs and symtpoms of acute GvHD may be staged and graded according to a standardised scale such as described in Przepiorka et al. (1995), 1994 Consensus Conference on Acute GvHD Grading Bone Marrow Transplant 1995; 15, 825-828. Similar disease grading scales are also in routine clinical use for other relevant diseases, such as rheumatoid arthritis and inflammatory bowel diseases.

Arrangement 47. A method according to any one of arrangements 37 to 46, wherein the autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 is a transplant, and wherein in step c) the treatment is in order to reduce the risk of transplant rejection, optionally wherein the first sample is taken before the transplant, and the second sample is taken after the transplant.

The first sample may be taken pre-operatively, e.g. after the subject has been identified as a candidate for treatment. The second sample is taken after the transplant and may be used by physicians as a method of monitoring the acceptance of the transplant. Thus, it may be that the physician may take more than one sample after the transplant, e.g. a daily blood sample to monitor the subject for changes in the proportion (e.g. number or level) of Treg:Tconv cells, or the proportion (e.g. numbers or levels) of Treg cells or of T(eff+mem) cells in the sample. The samples may be taken every other day, weekly, monthly or longer (including yearly) according to the likelihood of transplant rejection. For example, if the transplant is autologous, then the likelihood of transplant rejection may be reduced as compared to an allogeneic transplant, and therefore the time period between sample collections post-transplant may be longer than with an allogeneic transplant, where the risk of rejection is higher.

Arrangement 48. A method according to arrangement 47, wherein in step a), the first sample is collected no longer than a week, e.g. no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days before said transplant.

Arrangement 49. A method according to arrangement 47 or arrangement 48, wherein the second sample is collected no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days after the first sample or after said transplant.

Arrangement 50. A method according to any one of arrangements 47 to 48, wherein the subject is given a prophylactic dose of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent before said transplant, and the first sample is taken before administration of said combination and wherein the second sample is taken after the transplant or after administration of the combination (preferably, where in the second sample is taken after the transplant).

In one embodiment, the prophylactic dose is an effective prophylactic dose. By "effective", it is meant that the dose is effective to increase the ratio of Treg:Tconv cells, or to increase the proportion (e.g. numbers or levels) of Treg cells, or to reduce the proportion (e.g. numbers or levels) of T(eff+mem) cells as described herein, or effective to prevent or reduce the risk of a disease or condition as described in any of the arrangements herein.

The methods as described herein may be used to correct an already-aberrant level of Treg and/or T(eff+mem) cells, or an already-aberrant ratio of Treg:Tconv by administration of the combinations disclosed herein, before a transplant, in order to reduce the risk of transplant rejection after the transplant. Therefore, multiple samples may be taken after administration of the combination, but before the transplant. Comparison may be made between the collected samples and a sample obtained from a healthy donor.

Arrangement 51. A method according to any one of arrangements 47 to 48, wherein the subject is given a therapeutic dose of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the transplant.

In one embodiment, the therapeutic dose is an effective therapeutic dose. By "effective", it is meant that the dose is effective to increase the ratio of Treg:Tconv cells, or to increase the proportion (e.g. numbers or levels) of Treg cells, or to reduce the proportion (e.g. numbers or levels) of T(eff+mem) cells as described herein, or effective to treat a disease or condition as described in any arrangement herein.

In one embodiment, the second sample is taken after the administration of the combination. This would enable a physician to check that the proportion (e.g. levels or numbers) of Treg or T(eff+mem) cells remain "normal", i.e. as compared to the first sample, or to a sample obtained from a healthy donor.

Arrangement 52. A method according to any one of arrangements 47 to 48, wherein the subject is given a therapeutic dose of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the administration of said combination.

Arrangement 53. A method according to any one of arrangements 37 to 52, wherein the second sample is taken no longer than one month after the first sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the first sample, and optionally wherein the third sample is taken no longer than one month after the second sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the second sample.

Timepoints for taking any of the samples described in these concepts will depend on a number of factors, such as the likelihood of the subject having or being at risk of a particular disease or condition (e.g. GvHD or transplant rejection), the level determined in the previous sample, the type of transplant, etc. A person skilled in the art will be able to determine appropriate time points as necessary or desired. The timepoints may be monthly, every other month, quarterly, half-yearly or yearly, if desired.

Arrangement 54. In vitro use of the ratio of Treg:Tconv cells, or the proportion (e.g. number or level) of Treg cells, as a diagnostic for an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject (for example, which disease or condition can be treated or prevented with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent).

Arrangement 54a. In vitro use of the proportion (e.g. number or level) of T(eff+mem) cells as a diagnostic for an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject (for example, which disease or condition can be treated or

prevented with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent in the subject).

Arrangement 54b. In vitro use of the proportion (e.g. number or level) of T_N cells or the proportion (e.g. number or level) of T_{CM} cells as a diagnostic for an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject (for example, which disease or condition can be treated or prevented with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the subject).

The autoimmune or alloimmune diseases may be any of the diseases or disorders as disclosed in the arrangements herein.

There is also provided a biomarker of an autoimmune or alloimmune diseases, wherein the biomarker is selected from the proportion (e.g. number or level) of Treg cells and T(eff+mem) cells. There is also provided a biomarker of an autoimmune or alloimmune diseases, wherein the biomarker is the ratio of Treg:Tconv cells. There is also provided a biomarker of an autoimmune or alloimmune diseases, wherein the biomarker is the proportion (e.g. number or level) of T_N cells or T_{CM} cells.

The autoimmune or alloimmune diseases may be any of the diseases or disorders as disclosed in the arrangements herein. In another embodiment, the use of the biomarker is ex vivo.

The various levels, proportions and ratios of Treg cells, T(eff+mem) cells and ratios of Tref:Tconv cells are as described in arrangement 18. The proportions of Ki-67$^+$ T-cells may be as described in arrangements 25, 33 and 34. The proportion (e.g. number or level) of T_N or T_{CM} cells are as described in arrangements 201 to 208, and 301 to 305 respectively, hereinbelow.

Arrangement 55. Use of a biomarker of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein the biomarker is the ratio of Treg:Tconv cells, or wherein the biomarker is the proportion (e.g. number or level) of Treg cells, in vitro as a diagnostic for an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 (for example, which disease or condition can be treated or prevented with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent).

Arrangement 55a. Use of a biomarker of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein the biomarker is the proportion (e.g. number or level) of T(eff+mem) cells, in vitro as a diagnostic for an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 (for example, which disease or condition can be treated or prevented with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent).

Arrangement 55a. Use of a biomarker of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, wherein the biomarker is the proportion (e.g. number or level) of T_N cells, or is the proportion (e.g. number or level) of T_{CM} cells in vitro as a diagnostic for an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 (for example, which disease or condition can be treated or prevented with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent).

The autoimmune or alloimmune diseases may be any of the diseases or disorders as disclosed in the arrangements herein. In another embodiment, the use of the biomarker is ex vivo.

The various levels, proportions and ratios of Treg cell, T(eff+mem) cells and ratios of Tref:Tconv cells are as described in arrangement 18. The proportion (e.g. number or level) of T_N or T_{CM} cells are as described in arrangements 201 to 208, and 301 to 305 respectively, hereinbelow.

Arrangement 56. A method of preventing the increase (or the expansion) of T(eff+mem) cells, (optionally whilst preventing reduction in the proportion (e.g. number or level) of Treg cells, optionally, as defined in any one of arrangements 1 to 10) in a population of T-cells in a sample, said method comprising contacting said sample with an effective amount of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent.

The various mechanisms of effect on the T(eff+mem) cells and/or Treg cells, along with proportions (e.g. numbers or levels) may be any of those described in arrangement 18.

Arrangement 57. A method according to arrangement 56, wherein the proportion (e.g. number or level) of said T(eff+mem) cells is at least maintained in said sample, optionally wherein the sample is from a subject.

As used in the arrangements herein, "at least maintained" with respect to the proportion of T(eff+mem) cells, means that there is substantially no increase in the proportion. A maximum limit may be applied, which may be any of the as set out in arrangement 18 for proportions of T(eff+mem) after administration of the combination. As used in the arrangements herein, "maintains" or "maintaining" with respect to a level or a proportion may be described as substantially constant.

Substantially constant may be as described in arrangement 2.

Arrangement 58. A method according to arrangement 56, wherein the proportion (e.g. number of level) of said T-cells is less than 400×10^6 T(eff+mem)/litre, or less than 300×10^6 T(eff+mem)/litre, or less than 250×10^6 T(eff+mem)/litre.

In another embodiment, the proportion (e.g. number or level) of T(eff+mem) cells is less than 200×10^6 T(eff+mem)/litre, or less than 150×10^6 T(eff+mem)/litre, or less than 100×10^6 T(eff+mem)/litre.

Arrangement 59. In vitro use of the proportion (e.g. number or level) of Ki-67$^+$ T-cells, as a diagnostic for an autoimmune or alloimmune disease or condition (for example, an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100) in a subject (for example, which disease or condition can be treated or prevented with a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent).

There is also provided a biomarker of an autoimmune or alloimmune diseases, wherein the biomarker is selected from the proportion (e.g. number or level) of Ki-67$^+$ T-cells.

Arrangement 60. Use of a biomarker of an autoimmune or alloimmune disease or condition (for example an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100), wherein the biomarker is the proportion (e.g. number or level) of Ki-67$^+$ T-cells, in vitro as a diagnostic (e.g. as a diagnostic for an autoimmune or alloimmune disease or condition, for example, an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100, and/or for example which disease or condition can be treated or prevented with a combination of (i) an anti-

OX40 or an anti-OX40L antibody or fragment thereof, and (ii) a second therapeutic agent).

The proportions of Ki-67$^+$ T-cells may be as described in arrangements 25, 33 and 34.

Arrangement 61. A method, a combination for the use, a use or a composition according to any one of arrangements 25 to 36, 39 to 53, 59, or 60, wherein the Ki-6^7 T-cells are CD4$^+$ and/or CD8$^+$.

In one embodiment, the Ki-6^7 T-cells may be defined as being Ki-67$^+$CD3$^+$. In one embodiment, the Ki-67$^+$ T-cells may be defined as being Ki-67$^+$FoxP3$^+$. In another embodiment, the Ki-67$^+$ T-cells cells may additionally be CD25$^+$. In another embodiment, the Ki-6^7 T-cells cells may additionally be CD127$^+$. Thus, in one embodiment, Ki-67$^+$ T-cells cells may be identified as Ki-67$^+$CD25$^+$CD127$^-$FoxP3$^+$. In another embodiment, Ki-67$^+$ T-cells are identified as being Ki-67$^+$CD3$^+$CD14$^-$CD20$^-$CD25$^+$FoxP3$^+$either with or without CD127$^+$.

Arrangement 62. A method, a combination for the use, a use or a composition according to arrangement 61, wherein the Ki-67$^+$ T-cells are circulating T-cells.

Arrangement 63. A method according to any one of arrangements 3 to 10, 12, 18, 22 to 25, 30 to 33 to 36, 42 to 53, 56 to 58, 61 or 62, a combination for the use according to any one of arrangements 14, 19, 21 to 24, or 33 to 36, or a use according to any one of arrangements 15, 16, 20 to 24, 27, 28, or 33 to 36, or the composition according to arrangement 17, wherein the combination prevents reduction of the proportion (e.g. number or level) of Treg cells.

Arrangement 63a. A method according to any one of arrangements 3 to 10, 12, 18, 22 to 25, 30 to 33 to 36, 42 to 53, 56 to 58, 61 or 62, a combination for the use according to any one of arrangements 14, 19, 21 to 24, or 33 to 36, or a use according to any one of arrangements 15, 16, 20 to 24, 27, 28, or 33 to 36, or the composition according to arrangement 17, wherein the combination prevents reduction of the proportion (e.g. number or level) of T_N cells or prevents reduction of the proportion (e.g. number or level) of T_{CM} cells.

The various mechanisms of effect on the Treg cells, along with proportions (e.g. numbers or levels) may be any of those described in arrangement 18. The various mechanisms of effect on the TN cells, along with proportions (e.g. numbers or levels) may be any of those described in arrangement 301 to 305.

Arrangement 64. A method, a combination for the use, a use, or a composition according to arrangement 63, wherein the Treg cells are increased to a number or level of 4×10^6 Treg/litre, for example at least 5×10^6 Treg/litre, or at least 6×10^6 Treg/litre, or at least 7×10^6 Treg/litre, or at least 8×10^6 Treg/litre.

Arrangement 65. A method, a combination for the use, a use or a composition according to arrangement 63, wherein the Treg cells are increased to at least 4×10^6 Treg/litre, for example at least 5×10^6 Treg/litre, or at least 6×10^6 Treg/litre, or at least 7×10^6 Treg/litre, or at least 8×10^6 Treg/litre after administration said combination.

Arrangement 66. A method, a combination for the use, a use or a composition according to arrangement 65, wherein the Treg cells are increased to at least 10×10^6 Treg/litre, or at least 12×10^6 Treg/litre, or at least 14×10^6 Treg/litre, or at least 16×10^6 Treg/litre after combining said cells with said combination.

Arrangement 67. A method according to any one of arrangements 4 to 13, 18, 22 to 25, 30 to 33 to 53, 56 to 58, or 61 to 66, a combination for the use according to any one of arrangements 14, 19, 21 to 24, 26, 33 to 36, or 66, or a use according to any one of arrangements 15, 16, 20 to 24, 27, 28, 33 to 36, or 66, or the composition according to any one of arrangements 17, or 63 to 66, wherein the combination prevents the increase (or the expansion) of T(eff+mem) cells.

The various mechanisms of effect on the T(eff+mem) cells, along with proportions (e.g. numbers or levels) may be any of those described in arrangement 18.

Arrangement 68. A method, a combination for the use, a use, or a composition according to arrangement 67, wherein the T(eff+mem) cells are maintained at a proportion (e.g. number or level) of less than 200×10^6 T(eff+mem)/litre, or less than 150×10^6 T(eff+mem)/litre, or less than 100×10^6 T(eff+mem)/litre.

The healthy donor is preferably of the same species at the subject, for example, wherein the subject is a human, the donor is most preferably also a human. The donor is also preferably of the same gender as the subject. The donor is preferably of a similar age and ethnicity as the subject.

Arrangement 69. A method, a combination for the use, a use or a composition according to arrangement 67, wherein the T(eff+mem) cells are maintained within a range of from 10 to 500×10^6 T(eff+mem)/litre, or from 20 to 300×10^6 T(eff+mem)/litre, or from 100 to 200×10^6 T(eff+mem)/litre, or from 30 to 100×10^6 T(eff+mem)/litre.

Arrangement 70. A method, a combination for the use, a use or a composition according to arrangement 69, wherein the T(eff+mem) cells are maintained at a proportion (e.g. number or level) of at least 10×10^6 T(eff+mem)/litre, or at least 12×10^6 T(eff+mem)/litre, or at least 15×10^6 T(eff+mem)/litre or at least 17×10^6 T(eff+mem)/litre.

Arrangement 71. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is a depleting antibody that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.

The various modifications may be any of those set out in concept 52 hereinabove.

Arrangement 72. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is an antagonistic or blocking antibody.

Methods for determining antagonism or blocking functionality may be as described herein, or as well-known by those skilled in the art. For example, in vitro techniques include SPR and/or ELISA, which are described elsewhere herein.

Arrangement 73. A method, a combination for the use, a use or a composition according to arrangement 72, wherein the antibody specifically binds to OX40L (in particular human OX40L).

The OX40L antibodies may be any antibody or fragment as described herein. In one embodiment, the OX40L antibody is the antagonist anti-human OX40L (gp34) antibody ik-1 described by Matsumura et a/., J Immunol. (1999), 163:3007, which antibody is incorporated herein by reference.

Arrangement 74. A method, a combination for the use, a use or a composition according to arrangement 73, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

SPR and ELISA methods may be as described elsewhere herein.

Arrangement 75. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is a humanized, human or fully human antibody.

Other antibody constructs may be as described herein.

Arrangement 76. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bispecific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

Arrangement 77. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

Arrangement 78. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

Arrangement 79. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

Arrangement 80. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises a CDR selected from:

a) the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);

b) the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);

c) the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);

d) the HCDR3 of antibody 19H01 (Seq ID No: 100 or Seq ID No:106);

e) a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213 (as disclosed in WO2011/073180 in the name of Ablynx, Seq ID Nos: 161 to 167 therein, which are incorporated herein by reference);

f) an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230 (as disclosed in WO2006/029879 in the name of Roche/Genentech, Seq ID Nos: 33 to 38 therein, which are incorporated herein by reference); or

g) an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234 (as disclosed in U.S. Pat. No. 7,812,133 in the name of Genentech, Seq ID Nos: 11 or 12 therein, which are incorporated herein by reference).

Arrangement 81. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises:

a) the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);

b) the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);

c) the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);

d) the CDRs of antibody 19H01 (Seq ID No: 100 or Seq ID No: 106 for CDRH3, SEQ ID No:98 or SEQ ID No: 104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);

e) the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213 (as disclosed in WO2011/073180 in the name of Ablynx: Seq ID Nos: 161 to 167 therein for CDR3; Seq ID Nos: 147 to 153 therein for CDR2; and Seq ID Nos: 133 to 139 therein for CDR1, which sequences are incorporated herein by reference);

f) the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228 (as disclosed in WO2006/029879 in the name of Roche/Genentech: Seq ID Nos: 33 to 38 therein for CDRH3; Seq ID Nos: 21 to 25 therein for CDRH1 and Seq ID Nos: 26 to 32 therein for CDRH2; SEQ ID NOs: 39 to 44 therein for CDRL1; SEQ ID NOs: 45 to 50 therein for CDRL2; and SEQ ID NOs: 51 to 57 therein for CDRL3, which sequences are incorporated herein by reference); or

g) the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233 (as disclosed in U.S. Pat. No. 7,812,133 in the name of Genentech: Seq ID Nos: 11 or 12 therein for CDRH3; Seq ID Nos: 7 or 8 therein for CDRH1 and Seq ID Nos: 9 or 10 therein for CDRH2; SEQ ID NOs: 1 or 2 therein for CDRL1; SEQ ID NOs: 3 or 4 therein for CDRL2; and SEQ ID NOs: 5 or 6 therein for CDRL3, which sequences are incorporated herein by reference).

Arrangement 82. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

a) the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);

b) the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No: 16 for VL);

c) the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);

d) the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);

e) a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to

213 (as disclosed in WO2011/073180 in the name of Ablynx, Seq ID Nos: 177 to 185, 199 to 226 therein, which sequences are incorporated herein by reference);

f) a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228 (disclosed in WO2006/029879 in the name of Roche/Genentech, Seq ID Nos: 2, 4, 6, 8, 10, 12, 17, 19 and 20 therein for VH domains; and Seq ID Nos: 1, 3, 5, 7, 9, 11, 16 and 18 therein for VL domains, which sequences are incorporated herein by reference); or

g) a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233 (as disclosed in U.S. Pat. No. 7,812,133 in the name of Genentech, Seq ID Nos: 15 and 16 therein for VH domains; and Seq ID Nos: 13 and 14 therein for VL domains, which sequences are incorporated herein by reference).

Arrangement 83. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is oxelumab.

In another embodiment, the antibody is not oxelumab. In another embodiment, the antibody is not oxelumab and the disease is not asthma.

Arrangement 84. A method, a combination for the use, a use or a composition according to any preceding arrangement, where in the Treg cells and/or the T(eff+mem) cells and/or the Tconv cells are $CD4^+$ and/or $CD8^+$.

The various markers for these cells may be as described in arrangement 1.

Arrangement 85. A method, a combination for the use, a use or a composition according to arrangement 84, wherein the Treg cells and/or the T(eff+mem) cells and/or the Tconv cells are circulating T-cells.

Arrangement 86. A method, a combination for the use, a use or a composition according to arrangement 84 or 85, wherein the Treg cells and/or the T(eff+mem) cells and/or the Tconv cells are in a sample of blood, e.g. peripheral blood.

Whereas T-cells present in blood are relatively straightforward to isolate and characterise, T-cells which are present in the tissues of a subject are generally more difficult to isolate. That said, it may be possible to isolate T-cells from various tissues (such as skin, tissues of the GI tract, e.g. bowel, and from inflamed joints, e.g. synovium).

Arrangement 87. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the subject is a human patient.

Arrangement 88. A method, a combination for the use, a use or a composition according to arrangement 87, wherein the subject is at risk of an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

Arrangement 89. A method, a combination for the use, a use or a composition according to arrangement 88, wherein the subject has an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100.

Arrangement 90. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 is mediated by a deficiency in Treg cells.

Arrangement 90a. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 is mediated by expansion of T(eff+mem) cells.

Arrangement 91. A method, a combination for the use, a use or a composition according to any one of arrangements 88 to 90, wherein the autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1:100, or less than 0.75:100, or less than 0.5:100.

In one embodiment, the ratio may be less than 1:10, or 1:9, or 1:8, or 1:7, or 1:6, or 1:5 Treg:Tconv Arrangement 92. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the autoimmune or alloimmune disease or condition is selected from graft versus host disease (GvHD), allogenic transplant rejection, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, atherosclerosis, uvetitis, ankylosing spondylitis and contact hypersensitivity.

Arrangement 93. A method, a combination for the use, a use or a composition according to arrangement 92, wherein the autoimmune or alloimmune disease or condition is selected from GvHD and allogenic transplant rejection.

Arrangement 94. A method, a combination for the use, a use or a composition according to arrangement 92, wherein the autoimmune or alloimmune disease or condition is selected from inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis.

Arrangement 95. A method, a combination for the use, a use or a composition according to arrangement 93, wherein the allogenic transplant rejection is rejection of a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or of a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.

In one embodiment, the transplant is a CAR T-cell transplant (chimeric antigen receptor). In one embodiment, the transplant is an HLA-matched allogeneic bone marrow or stem cell transplant.

In another embodiment, the transplant is an HLA mismatched allogeneic bone marrow or stem cell transplant.

Arrangement 96. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is an IL-2 modulating agent, such as a calcinueirn inhibitor or an mTOR inhibitor (for example the agent is selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), anti-IL2R antibodies (e.g. basilixumab), anti-IL-2 antibodies and anti-CD24-Fc fusion protein).

In another embodiment, the IL-2 modulating agent is recombinant IL-2. In another embodiment, the IL-2 modulating agent is an IL-2 inhibiting agent.

Arrangement 97. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is independently selected from the group consisting of methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globu-

lins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-CD25 antibodies (e.g. daclizumab), anti-TCONVFa/TCONVFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Arrangement 98. A method, a combination for the use, a use or a composition according to any one of arrangements 1 to 95, wherein the second therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

Arrangement 99. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is rapamycin.

Arrangement 100. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is tacrolimus.

In another embodiment, the second therapeutic agent is rapamycin or derivatives thereof.

Derivatives of rapamycin are well-known to those skilled in the art.

Following further experiment, the present inventors have found a number of further developments described in the following arrangements:

Arrangement 101. A method of normalising T-cell signalling in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of RORC, and whereby T-cell signalling is normalised.

Without being bound by theory, it is thought that reducing the level (e.g. expression or amount) of RORC will have a number of benefits in various diseases as set out herein, due its direct correlation with aberrant T-cell signalling, and the inventors have surprisingly shown that this may be achieved using an anti-OX40L antibody or a combination of that antibody and another therapeutic agent as described herein more effectively than with other therapies currently employed.

The level (e.g. expression or amount) of RORC may be determined by methods well-known to those skilled in the art, e.g. by flow cytometic analysis of T-cells in a sample, which may be obtained from a subject (see arrangements 1 to 100 hereinabove for further details, all of which apply mutatis mutandis to these further arrangements hereinbelow).

Thus, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of RORC" or similar phrases may be replaced throughout by the phrase "lowering the level (e.g. expression or amount) of RORC" or similar phrases. Further, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of RORC" or similar phrases may be replaced by the phrase "downregulating the level (e.g. expression or amount) of RORC" or similar phrases. In any of the arrangements herein, the "level" may be a relative level, or an absolute number.

"Reducing" or "reduces" as used in any of the arrangements herein, refers to a mechanism which reduces the apparent expression levels of RORC in a given sample. The sample may be a sample of blood, e.g. peripheral blood which may be processed by, for example, flow cytometry or by microarray analysis to extract RORC mRNA transcripts from the T-cells in the sample.

In a particular embodiment, the antibody or fragment thereof is in a format or structure of any of the antibodies and fragments described elsewhere herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein, or any arrangement hereinbelow). In a particular embodiment, the antibody is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab. In another embodiment, the combination comprises an anti-OX40L antibody which is not oxelumab (having a VH region amino acid sequence of Seq ID No:215 and a VL region amino acid sequence of Seq ID No:214).

The second therapeutic agent is described in more detail in the arrangements herein, but is preferably an IL-2 modulating agent.

The antibodies and combinations of the present invention may provide benefit by preventing increases in the level (e.g. expression or amount) of RORC, which will have occurred if the disease or disorder is already beginning to take effect, or has already taken hold. If used prophylactically, the antibodies and combinations of the present invention may prevent any substantial change in the level (e.g. expression or amount) of RORC, because they are able to protect the patient from the detrimental cellular changes. Thus, in another embodiment, the level (e.g. expression or amount) of RORC remains at a substantially constant level after administration of the combination. Substantially constant may be as described in arrangement 2 hereinabove.

Arrangement 102. A method of reducing the level (e.g. expression or amount) of RORC in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of RORC.

Arrangement 103. A method of reducing or inhibiting Th/Tc17 based activation of T-cells in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of RORC, and whereby Th/Tc17 activation of T-cells is reduced.

Arrangement 104. A method of reducing or inhibiting Th/Tc17 based activation of T-cells in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method downregulates or reduces the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 17 (FIG. **14**G) or Table 17 (FIG. **14**F), and whereby Th/Tc17 based activation of T-cells is reduced or inhibited.

Arrangement 105. A method according to arrangement 104, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**G); optionally selected from: IL12RB1, IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R, CXCL1, IL17F, CXCL9; for example, selected from: IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R; e.g. selected from: IL6, CCL2, IFNG; and alternatively selected from CCR5, IL12RB2 and IFNG.

As used throughout arrangements 101 to 187, "one or more" may mean from 1 to 15 genes (e.g. 1 to 14, or 1 to 13, or 1 to 12, or 1 to 11 genes) to make up a gene signature. In another embodiment, "one or more" means from 1 to 10

genes (e.g. 1 to 9, or 1 to 8, or 1 to 7, or 1 to 6 genes). In another embodiment, "one or more" means from 1 to 5 genes (e.g. 1 to 5, or 1 to 4, or 1 to 3, or 1 or 2 genes). In another embodiment, there may be 2, 3, 4 or 5 genes selected. In another embodiment, there may be 6, 7, 8, 9 or 10 genes selected. In another embodiment, there may be 11, 12, 13, 14 or 15 genes selected.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IFNG, IL6, TNF, IL18, IL23R, IL17A, CCL2, IL12RB1, CXCL1 and CXCL9. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IFNG, IL6, TNF, IL18, IL23R, IL17A and CCL2. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: IFNG, IL6, TNF, IL18 and IL23R. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: IFNG, IL6 and TNF.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R, CXCL1, IL17F and CXCL9. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IL6, CCL2, IFNG, IL17A, TNF, IL18 and IL23R. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: IL6, CCL2, IFNG, IL17A and TNF. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: IL6, CCL2 and IFNG.

In one embodiment, the genes are CCR5, IL12RB2 and IFNG. In another embodiment, the genes are CCR5 and IL12RB2. In another embodiment, the genes are CCR5 and IFNG. In another embodiment, the genes are IL12RB2 and IFNG. In another embodiment, the gene is CCR5. In another embodiment, the gene is IL12RB2. In another embodiment, the gene is IFNG.

Arrangement 106. A method according to arrangement 104, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**F); optionally selected from: selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, SAMD9L, IFIT1, IFIT3, KCNJ15, IFI44, EGR1, EGR2, SAMD9, RSAD2, FFAR2, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15, HIST1H2BB, GTSE1, AKAP12, CENPF, CASC5, MKI67, PRC1, PRR11, RACGAP1, SPAG5 and ARHGAP11A; for example, selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15 and HIST1H2BB; e.g. selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, ANLN, DUSP4, UBE2T, UHRF1 and KIF11.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, SAMD9L, IFIT1, IFIT3, KCNJ15 and IFI44. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1 and LILRA3. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5 and TYMP. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: MGAM, CYP4F3, MMP9, TNFAIP6 and CD163. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: MGAM, CYP4F3 and MMP9.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15, HIST1H2BB, GTSE1, AKAP12, CENPF, CASC5, MKI67, PRC1, PRR11, RACGAP1, SPAG5 and ARHGAP11A. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15, HIST1H2BB, GTSE1, AKAP12, CENPF, CASC5 and MKI67. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15 and HIST1H2BB. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK and RAD54B. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: ANLN, DUSP4, UBE2T, UHRF1 and KIF11. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: ANLN, DUSP4 and UBE2T.

Arrangement 107. A method of normalising cytotoxicity in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of Granzyme A, and whereby the cytotoxicity is normalised.

Without being bound by theory, it is thought that reducing the level (e.g. expression or amount) of Granzyme A will have a number of benefits in various diseases as set out herein, due its direct correlation with aberrant T-cell signalling and cytotoxicty, and the inventors have surprisingly shown that this may be achieved using an anti-OX40L antibody or a combination of that antibody and another therapeutic agent as described herein more effectively than with other therapies currently employed.

The level (e.g. expression or amount) of Granzyme A may be determined by methods well-known to those skilled in the art, e.g. by flow cytometric analysis of T-cells in a sample, which may be obtained from a subject (see arrangements 1 to 100 hereinabove for further details, all of which apply mutatis mutandis to these further arrangements hereinbelow).

Thus, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of Granzyme A" or similar phrases may be replaced throughout by the phrase "lowering the level (e.g. expression or amount) of Granzyme A" or similar phrases. Further, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of Granzyme A" or similar phrases may be replaced by the phrase "downregulating the level (e.g. expression or amount) of Granzyme A" or similar phrases. In any of the arrangements herein, the "level" may be a relative level, or an absolute number.

"Reducing" or "reduces" as used in any of the arrangements herein, refers to a mechanism which reduces the apparent expression levels of Granzyme A in a given sample. The sample may be a sample of blood, e.g. peripheral blood which may be processed by, for example, flow cytometry or by microarray analysis to extract Granzyme A mRNA transcripts from the T-cells in the sample.

In a particular embodiment, the antibody or fragment thereof is in a format or structure of any of the antibodies and fragments described elsewhere herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein, or any arrangement hereinbelow). In a particular embodiment, the antibody is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab. In another embodiment, the combination comprises an anti-OX40L antibody which is not oxelumab (having a

VH region amino acid sequence of Seq ID No:215 and a VL region amino acid sequence of Seq ID No:214).

The second therapeutic agent is described in more detail in the arrangements herein, but is preferably an IL-2 modulating agent.

The antibodies and combinations of the present invention may provide benefit by preventing increases in the level (e.g. expression or amount) of Granzyme A, which will have occurred if the disease or disorder is already beginning to take effect, or has already taken hold. If used prophylactically, the antibodies and combinations of the present invention may prevent any substantial change in the level (e.g. expression or amount) of Granzyme A, because they are able to protect the patient from the detrimental cellular changes. Thus, in another embodiment, the level (e.g. expression or amount) of Granzyme A remains at a substantially constant level after administration of the combination. Substantially constant may be as described in arrangement 2 hereinabove.

Arrangement 108. A method of reducing the level (e.g. expression or amount) of Granzyme A in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of Granzyme A.

Without being bound by theory, it is thought that reducing the level (e.g. expression or amount) of Granzyme A will have a number of benefits in various diseases as set out herein, due its direct correlation with aberrant T-cell signalling, and the inventors have surprisingly shown (see Example 11) that this may be achieved using an anti-OX40L antibody or a combination of that antibody and another therapeutic agent as described herein more effectively than with other therapies currently employed.

The level (e.g. expression or amount) of Granzyme A may be determined by methods well-known to those skilled in the art, e.g. by flow cytometric analysis of T-cells in a sample, which may be obtained from a subject (see arrangements 1 to 100 hereinabove for further details, all of which apply mutatis mutandis to these further arrangements hereinbelow).

Thus, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of Granzyme A" or similar phrases may be replaced throughout by the phrase "lowering the level (e.g. expression or amount) of Granzyme A" or similar phrases. Further, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of Granzyme A" or similar phrases may be replaced by the phrase "downregulating the level (e.g. expression or amount) of Granzyme A" or similar phrases. In any of the arrangements herein, the "level" may be a relative level, or an absolute number.

Arrangement 109. A method of reducing or inhibiting Th/Tc1 based activation of T-cells in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method downregulates or reduces the level (e.g. expression or amount) of Granzyme A, and whereby Th/Tc1 based activation of T-cells is reduced or inhibited.

Arrangement 110. A method according to any one of arrangements 107 to 110, wherein the levels (e.g. expression or amount) of Granzyme A before the combination step are at least 1.5-fold greater in the subject as compared to the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.

The levels of Granzyme A before the combination step may be any of those set out in arrangement 161 and 162 hereinbelow.

Arrangement 111. A method according to any one of arrangements 107 to 111, wherein the levels (e.g. expression or amount) of Granzyme A after the combination step are at least 1.5-fold lower in the subject as compared to the levels (e.g. expression or amount) of Granzyme A in said sample taken before the combination step.

Arrangement 111a. A method according to any one of arrangements 107 to 111, wherein the levels (e.g. expression or amount) of Granzyme A after the combination step are reduced by at least 1.5-fold in the subject as compared to the levels (e.g. expression or amount) of Granzyme A in said sample taken before the combination step.

The levels of Granzyme A before the combination step may be the opposite of any of those set out in arrangement 161 and 162 hereinbelow. For example, if arrangement 161 states that the levels are greater than 20-fold of the levels in a sample taken from a healthy donor, this embodiment would mean that the Granzyme A levels are reduced by at least 20-fold after the combination step, or are at least 20-fold lower after the combination step.

Arrangement 112. A method according to any one of arrangements 107 to 111, wherein the levels (e.g. expression or amount) of Granzyme A after the combination step are within 1.5-fold of the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.

In one embodiment, the levels (e.g. expression or amount) of Granzyme A after the combination step are substantially the same as the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.

Arrangement 113. A method of reducing or inhibiting Th/Tc1 based activation of T-cells in a subject comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method downregulates or reduces the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 16 (FIG. **14**E), and whereby Th/Tc1 based activation of T-cells is reduced or inhibited.

Arrangement 114. A method according to arrangement 113, wherein the one or more (e.g. 3, 4 or 5) genes is selected from: BCL2L14, SH2D1A, SAMD3, STAT4, SLA2, SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4, MKI67, GZMK, CD38, CTLA4, MYBL1, IRF4, SH2D1A, BCL2L14, PRF1, IL21 and HS3ST3B1X; for example, selected from: SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4 and MKI67; e.g. F2R, CCR5, IL12RB2, IFNG, TYMS and CASC5; and alternatively selected from CCR5, IL12RB2 and IFNG.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CCR5, IFNG, CASC5, TYMS, F2R, IL10, MKI67, PRF1, KLRD1, SLAMF1, GIMAP4, CTLA4, SLA2, STAT4 and HS3ST3B1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CCR5, IFNG, CASC5, TYMS, F2R, IL10, MKI67, PRF1, KLRD1 and SLAMF1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CCR5, IFNG, CASC5, TYMS, F2R, IL10 and MKI67. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: CCR5, IFNG, CASC5, TYMS and F2R. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: CCR5, IFNG and CASC5.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4, MKI67, GZMK, CD38,

CTLA4, MYBL1 and IRF4. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4 and MKI67. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10 and RRM2. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: CCR5, IL12RB2, IFNG, TYMS and CASC5. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: CCR5, IL12RB2 and IFNG. In another embodiment, the gene is CCR5.

In one embodiment, the genes are CCR5, IL12RB2 and IFNG. In another embodiment, the genes are CCR5 and IL12RB2. In another embodiment, the genes are CCR5 and IFNG. In another embodiment, the genes are IL12RB2 and IFNG. In another embodiment, the gene is CCR5. In another embodiment, the gene is IL12RB2. In another embodiment, the gene is IFNG.

Arrangement 115. A method of activating, upregulating or enhancing the Type 1 interferon (IFN) pathway or the Reactome HSA-909733 Interferon alpha/beta signalling pathway in a subject comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and a second therapeutic agent, which method activates, upregulates or enhances the Type 1 interferon (IFN) pathway or the Reactome HSA-909733 Interferon alpha/beta signalling pathway.

Arrangement 116. A method according to arrangement 115, wherein the activation, upregulation or enhancement is of the Type 1 IFN pathway.

Arrangement 117. A method according to arrangement 115, wherein the activation, upregulation or enhancement is of the Reactome HSA-909733 Interferon alpha/beta signalling pathway, wherein optionally activation, upregulation or enhancement is of one or more (e.g. 3, 4 or 5) of the genes is selected from IGS15, IFIT3, RSAD2, IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2; or is selected from from: IGS15, IFIT3 and RSAD2; or is alternatively selected from: IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: from IGS15, IFIT3, RSAD2, IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2. In another embodiment, the one, 2 or 3 genes are selected from: IGS15, IFIT3 and RSAD2. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2. In another embodiment, the one or more (e.g. 2, 3 or 4) genes are selected from: IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2. In another embodiment, the one or more (e.g. 2, 3 or 4) genes are selected from: IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2.

Arrangement 118. A method according to arrangement 117, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**D) or Table 15.

Arrangement 119. A method according to arrangement 118, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**D); optionally selected from: TYMP, ISG15, IFI44, IRF7, RSAD2, C1QA, CCL2, CXCL10, XAF1, IFIT5, PROS1, IFI6, PLSCR1, SERPING1, SAMD9L, C3AR1, GOS2, IL8, HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163, TNFAIP6, IFI27, MX1, ISG15, MX2, IFI44, IFIT2, OAS2, OASL, EPSTI1 and LILRA3; for example, selected from: ISG15, MX1, IFI44, IFI27, C3AR1, C1QA, CCL2, CXCL10, GOS2, IL8, HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163 and TNFAIP6; e.g. selected from: IFI27, MMP9, RSAD2, C3AR1, CD163, CXCL10, GOS2, IL8, HERC5, CMPK2, MMP9, IFIT1 and IFIT3; or may be selected from: CXCL10, CD163, IL8, CMPK2, IFI27, MMP9 and HERC5.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CXCL10, CD163, IL8, GOS2, C3AR1, TNFAIP6, IFI27, CCL2, CMPK2, C1QA, PLSCR1, ISG15, HERC5, RSAD2, MX1, OASL, IRF7, IFIT3, IFI44 and TYMP. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CXCL10, CD163, IL8, GOS2, C3AR1, TNFAIP6, IFI27, CCL2, CMPK2, C1QA, PLSCR1, ISG15, HERC5, RSAD2 and MX1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CXCL10, CD163, IL8, GOS2, C3AR1, TNFAIP6, IFI27, CCL2 and CMPK2. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CXCL10, CD163, IL8, GOS2, C3AR1, TNFAIP6 and IFI27. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: CXCL10, CD163, IL8, GOS2 and C3AR1. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: CXCL10, CD163 and IL8.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, IFI27, MMP9, HERC5, RSAD2, ISG15, IFI44, IL8, GOS2, MX1, CYP4F3, C3AR1, SAMD9L, SERPING1 and PLSCR1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, IFI27, MMP9, HERC5, RSAD2, ISG15, IFI44, IL8, GOS2 and MX1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, IFI27, MMP9, HERC5, RSAD2, ISG15 and IFI44.

In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: CMPK2, IFI27, MMP9, HERC5 and RSAD2. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: CMPK2, IFI27 and MMP9.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163, TNFAIP6, IFI27, MX1, ISG15, MX2, IFI44, IFIT2, OAS2, OASL, EPSTI1 and LILRA3. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163, TNFAIP6, IFI27, MX1, ISG15, MX2 and IFI44. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163 and TNFAIP6. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2 and CYP4F3. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: HERC5, CMPK2, MMP9, IFIT1 and IFIT3. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: HERC5, CMPK2 and MMP9.

Arrangement 120. A method according to arrangement 118, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 15; optionally selected from: HERC6, MMP25, GOS2, KCNJ15, IL8, OASL, DDX58, TYMP, MX2, OAS2, IFI44, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, EGR2, C3AR1, LILRA3, MX1, IFIT2, SAMD9L, IFIT1, MMP25 and ISG15; for example, selected from: MMP25, GOS2, KCNJ15, IL8, TYMP, OAS2, IFI44, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, EGR2, C3AR1, LILRA3, MX1,

IFIT2, SAMD9L and IFIT1; e.g. selected from: IL8, TYMP, IFI44, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, C3AR1, LILRA3, IFIT2 and IFIT1; or may be selected from: IL8, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, EGR1, IFIT3 and IFIT1.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, EGR2, C3AR1, LILRA3, MX1, IFIT2, SAMD9L, IFIT1, MMP25 and ISG15. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, EGR2, C3AR1, LILRA3 and MX1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6 and EGR1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM and CD163. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: CMPK2, HERC5, RSAD2, MMP9 and CYP4F3. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: CMPK2, HERC5 and RSAD2.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, IFIT1, IFIT3, CYP4F3, MGAM, RSAD2, IFIT2, IFI44, CMPK2, TNFAIP6, MX1, OAS2, MMP9, CD163, SAMD9L, MX2, LILRA3, TYMP, DDX58 and OASL. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, IFIT1, IFIT3, CYP4F3, MGAM, RSAD2, IFIT2, IFI44, CMPK2, TNFAIP6, MX1, OAS2, MMP9, CD163 and SAMD9L. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, IFIT1, IFIT3, CYP4F3, MGAM, RSAD2, IFIT2, IFI44, CMPK2 and TNFAIP6. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: HERC5, IFIT1, IFIT3, CYP4F3, MGAM, RSAD2 and IFIT2. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: HERC5, IFIT1, IFIT3, CYP4F3 and MGAM. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: HERC5, IFIT1 and IFIT3.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CYP4F3, IL8, HERC5, MGAM, EGR1, LILRA3, IFIT3, RSAD2, TYMP, C3AR1, CMPK2, KCNJ15, GOS2, MMP9, IFIT2, MP25, IFIT1, IFI44, HERC6 and TNFAIP6. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CYP4F3, IL8, HERC5, MGAM, EGR1, LILRA3, IFIT3, RSAD2, TYMP, C3AR1, CMPK2, KCNJ15, GOS2, MMP9 and IFIT2. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CYP4F3, IL8, HERC5, MGAM, EGR1, LILRA3, IFIT3, RSAD2, TYMP and C3AR1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: CYP4F3, IL8, HERC5, MGAM, EGR1, LILRA3 and IFIT3. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: CYP4F3, IL8, HERC5, MGAM and EGR1. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: CYP4F3, IL8 and HERC5.

Arrangement 121. A method of upregulating or enhancing the KEGG hsa04630:Jak-STAT signalling pathway in a subject comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method upregulates the KEGG hsa04630:Jak-STAT signalling pathway.

Arrangement 122. A method according to arrangement 121, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**C); optionally selected from: IFNA16, OSM, CBLB, IL6, PIK3R1, CCND2, JAK3, PIAS1, STAT4, IL22, IL4R, IL12RB2, IL26, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, CISH, IL6ST, SOCS1, IRF9, PIK3CB, PIM1, SOCS3, STAM2 and IFNGR2; for example, selected from: CCND2, IL6, STAT4, IL22, IL4R, IL12RB2, IL26, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, CISH, IL6ST, SOCS1, IRF9, PIM1 and SOCS3; e.g. selected from: CCND2, IL6, IL22, IL12RB2, IL26, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, IL6ST, SOCS1 and SOCS3; or may be selected from: IL6, IL22, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, STAT3, IL2RA, SOCS1 and SOCS3; and alternatively may be selected from: IL6, SOCS2, IL13RA1, CSF2RA, IL2RA and SOCS1.

Arrangement 122A. A method according to arrangement 121, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**C); optionally selected from: IL6R, IL6ST, IL26, OSM, IL2RA, IL10RB, CSF3R, IL32RA1, STAT1, STAT2, STAT3, SOCS1, SOCS2, PIM1, SOS1, SOS2, CISH, PIAS1 and SPRY1; optionally selected from: OSM, IL2RA, IL10RB, CSF3R and IL13RA1; or selected from STAT1, STAT2 and STAT3; or alternatively selected from SOCS1, SOCS2, PIM1, SOS1, SOS2, CISH, PIAS1 and SPRY1; or selected from transcripts encoding pro-inflammatory cytokines or cytokine receptors (optionally selected from: IL6, IL6R, IL6ST and IL26); or selected from transcripts encoding anti-inflamatory cytokines or cytokine receptors (optionally selected from OSM, IL2RA, IL10RB, CSF3R and IL32RA1).

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IL6, SOCS2, IL2RA, SOCS3, IL22, SOCS1, CSF2RA, IL26, SOS1, CCND2, JAK2, CISH, PIM1, CSF3R, CSF2RB, IFNGR2, CBLB, OSM, IL12RB2 and IFNA16. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IL6, SOCS2, IL2RA, SOCS3, IL22, SOCS1, CSF2RA, IL26, SOS1, CCND2, JAK2, CISH, PIM1, CSF3R and CSF2RB. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IL6, SOCS2, IL2RA, SOCS3, IL22, SOCS1, CSF2RA, IL26, SOS1 and CCND2. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: IL6, SOCS2, IL2RA, SOCS3, IL22, SOCS1 and CSF2RA. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: IL6, SOCS2, IL2RA, SOCS3 and IL22. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: IL6, SOCS2 and IL2RA.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL2RA, SOCS1, SOCS3, STAT3, SOS1, IL26, IL6ST, IL12RB2, JAK2, IL4R, IL22, IFNGR1, PIM1, STAT4, PIAS1, JAK3, CCND2, IFNGR2 and PIK3R1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL2RA, SOCS1, SOCS3, STAT3, SOS1, IL26, IL6ST, IL12RB2, JAK2, IL4R, IL22, IFNGR1, PIM1 and STAT4. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL2RA, SOCS1, SOCS3, STAT3, SOS1, IL26, IL6ST, IL12RB2, JAK2. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL2RA, SOCS1, SOCS3, STAT3, SOS1 and IL26. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes

are selected from: SOCS2, IL2RA, SOCS1, SOCS3 and STAT3. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: SOCS2, IL2RA and SOCS1.

In one embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, CISH, IL6ST, SOCS1, IRF9, PIK3CB, PIM1, SOCS3, STAM2 and IFNGR2. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, CISH, IL6ST, SOCS1 and IRF9. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3 and SOS1. In another embodiment, the one or more (e.g. 3, 4 or 5) genes are selected from: SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM and IFNGR1. In another embodiment, the one or more (e.g. 2, 3, 4 or 5) genes are selected from: SOCS2, IL13RA1, CSF2RA, CSF3R and CSF2RB. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: SOCS2, IL13RA1 and CSF2RA.

In one embodiment, the method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) genes selected from: IL6R, IL6ST, IL26, OSM, IL2RA, IL10RB, CSF3R, IL32RA1, STAT1, STAT2, STAT3, SOCS1, SOCS2, PIM1, SOS1, SOS2, CISH, PIAS1 and SPRY1. In another embodiment, the one or more (e.g. 2 or 3) genes are selected from: OSM, IL2RA, IL10RB, CSF3R and IL13RA1; or selected from STAT1, STAT2 and STAT3. In another embodiment, the one or more (e.g. 2, 3 or 4) genes are selected from SOCS1, SOCS2, PIM1, SOS1, SOS2, CISH, PIAS1 and SPRY1. In another embodiment, the method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 1 or 2) transcripts encoding pro-inflammatory cytokines or cytokine receptors (optionally selected from: IL6, IL6R, IL6ST and IL26). In another embodiment, the method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 1 or 2) transcripts encoding anti-inflamatory cytokines or cytokine receptors (optionally selected from OSM, IL2RA, IL10RB, CSF3R and IL32RA1).

Arrangement 123. A method according to any one of arrangements 101 to 122, wherein the subject has or is at risk of an OX40L-mediated disease.

Arrangement 124. A method according to any arrangement 123, wherein the subject has or is at risk of an autoimmune or alloimmune disease or condition, e.g. selected from graft versus host disease (GvHD), allogenic transplant rejection, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, atherosclerosis, uveitis, ankylosing spondylitis and contact hypersensitivity.

Arrangement 125. A method of treating or reducing the risk of a disease or condition (e.g. an autoimmune or alloimmune disease or condition) in a subject, the method comprising administering to said subject a therapeutically effective amount or prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method normalises T-cell signalling, or reduces or inhibits Th/Th17 based activation of T-cells, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.

In on embodiment, in any of the therapeutic methods of these arrangements, the methods include the use of a therapeutically effective amount or prophylactically effective amount of a combination of (i) an anti-OX40 or an anti-OX40L antibody or fragment thereof, and (i) a second therapeutic agent. These combinations are described further in the arrangements hereinabove. Thus, in one embodiment, the combination comprises a therapeutically effective amount of the anti OX40 or anti-OX40L antibody and a therapeutically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a therapeutically effective amount of the anti OX40 or anti-OX40L antibody and a prophylactically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a prophylactically effective amount of the anti OX40 or anti-OX40L antibody and a therapeutically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a prophylactically effective amount of the anti OX40 or anti-OX40L antibody and a prophylactically effective amount of the second therapeutic agent.

In another embodiment, the combination may be therapeutically or prophylactically effective, despite containing doses or amounts of either (i) the anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) the second therapeutic agent which, by themselves, would not necessarily be therapeutically or prophylactically effective. Hence, the risk of side effects may be reduced, as smaller amounts of therapeutic entities are being given to patients in need thereof.

Arrangement 126. A method according to arrangement 125, wherein the T-cell signalling is normalised, or wherein the Th/Th17 based activation of T-cells is reduced or inhibited by reducing the level (e.g. expression or amount) of RORC in a population of T-cells isolated from said subject.

Arrangement 127. A method according to arrangement 125, wherein the T-cell signalling is normalised, or wherein the Th/Th17 based activation of T-cells is reduced or inhibited by downregulation or reduction of the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 17 (FIG. **14**G) or Table 17 (FIG. **14**F).

In one embodiment, the genes are those described hereinabove for Arrangement 105 or 106.

Arrangement 128. A method according to arrangement 127, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**G); optionally selected from: IL12RB1, IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R, CXCL1, IL17F, CXCL9; for example, selected from: IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R; e.g. selected from: IL6, CCL2, IFNG.

Arrangement 129. A method according to arrangement 127, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**F); optionally selected from: selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, SAMD9L, IFIT1, IFIT3, KCNJ15, IFI44, EGR1, EGR2, SAMD9, RSAD2, FFAR2, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15, HIST1H2BB, GTSE1, AKAP12, CENPF, CASC5, MKI67, PRC1, PRR11, RACGAP1, SPAG5 and ARHGAP11A; for example, selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15 and HIST1H2BB; e.g. selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, ANLN, DUSP4, UBE2T, UHRF1 and KIF11.

Arrangement 130. A method of treating or reducing the risk of a disease or condition (e.g. an autoimmune or alloimmune disease or condition) in a subject, the method comprising administering to said subject a therapeutically

effective amount or prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method normalises cytotoxicity, or reduces or inhibits Th/Tc1 based activation of T-cells, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.

Arrangement 131. A method according to arrangement 130, wherein the cytotoxicity is normalised, or wherein the Th/Tc1 based activation of T-cells is reduced or inhibited by reducing the level (e.g. expression or amount) of Granzyme A in a T-cell population isolated from said subject.

Arrangement 132. A method according to arrangement 130, wherein the cytotoxicity is normalised, or wherein the Th/Tc1 based activation of T-cells is reduced or inhibited by downregulation or reduction of the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 16 (FIG. **14**E); optionally wherein the one or more (e.g. 3, 4 or 5) genes is selected from: BCL2L14, SH2D1A, SAMD3, STAT4, SLA2, SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4, MKI67, GZMK, CD38, CTLA4, MYBL1, IRF4, SH2D1A, BCL2L14, PRF1, IL21 and HS3ST3B1X; for example, selected from: SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4 and MKI67; e.g. F2R, CCR5, IL12RB2, IFNG, TYMS and CASC5.

In one embodiment, the genes are as those described in Arrangement 114 hereinabove.

Arrangement 133. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 134. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 135. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 136. A composition comprising an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 137. A method of treating or reducing the risk of a disease or condition in a subject in need thereof, comprising:

a. Performing an assay to measure the levels (e.g. expression or amount) of Granzyme A in a sample obtained from the subject; and

b. Administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent to the subject when the levels (e.g. expression or amount) of Granzyme A in the sample is determined in the assay to be at least 1.5-fold greater than in a sample taken from a healthy human donor.

Arrangement 138. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 139. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for therapy of a subject who has, or has been determined to have an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 140. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

In any of arrangement 138 to 140, the levels (e.g. expression or amount) are determined in a sample, for example, in a sample of blood obtained from said subject.

In any of arrangements 138 to 140, in one embodiment, the therapy is for treatment, for reducing the risk or for the prevention of an OX40L-mediated disease. In another embodiment, the therapy is for the treatment, for reducing the risk or for the prevention of an autoimmune or alloimmune disease or condition, e.g. which is characterised by a ratio of Treg:Tconv of less than 1.5:100, which may be as described in any of the arrangements hereinbelow. In another embodiment, the therapy is for the treatment, for reducing the risk or for the prevention of a disease or condition (e.g. any of the diseases or conditions mentioned herein). In another embodiment, the therapy is for reducing the risk or preventing a disease or condition (e.g. any of the disease or conditions mentioned herein).

Arrangement 141. A method of determining a subject as having, or as being at risk of, an autoimmune or alloimmune disease or condition, which disease or condition is suitable for treatment with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, comprising:

a. performing an assay that detects the levels (e.g. expression or amount) of Granzyme A in a sample obtained from said subject; and

b. determining the subject as having said disease or condition if there is an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 142. A method according to arrangement 141 further comprising the step of:

c. administering to said subject an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which antibody or fragment thereof:
   i. reduces or inhibit Th/Tc1 based activation of T-cells; and/or
   ii. normalises cytotoxicity; and/or
   iii. reduces the levels (e.g. expression or amount) of Granzyme A;

in a sample taken from said subject, if said subject has been determined as having a disease or condition in step b).

Arrangement 143. A method for treating an autoimmune or alloimmune disease or condition with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, comprising the steps of:

a. determining whether the subject is a candidate for treatment by detecting the levels (e.g. expression or amount) of Granzyme A in a sample from the subject;
b. administering said antibody or fragment thereof to the subject if the subject has an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 144. A method, comprising:

a. obtaining at least two samples derived from a subject who has or is at risk of an autoimmune or alloimmune disease or condition, wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,
b. determining the levels (e.g. expression or amount) of Granzyme A in said first and second samples;
c. treating said subject to:
   i. reduce or inhibit Th/Tc1 based activation of T-cells; and/or
   ii. normalise cytotoxicity; and/or
   iii. reduce the levels (e.g. expression or amount) of Granzyme A;

by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, if the levels (e.g. expression or amount) of Granzyme A in said second sample are elevated as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition.

Autoimmune and alloimmune disease are well-known to those skilled in the art, but may be as further defined in any of the arrangements disclosed herein. In another embodiment, the disease or disorder is additionally an OX40L-mediated disease or disorder. In any arrangement described herein, an autoimmune or alloimmune disease or condition my further be characterised by a ratio of Treg:Tconv of less than 1.5:100 may be as defined in any of arrangements 92 to 95 herein.

As used herein, a subject may be identified as being "at risk of an autoimmune or alloimmune disease or condition" when the cellular changes in their T-cell population (for example, reduction in the level (e.g. expression or amount) of Granzyme A or RORC, a reduction in the level, expression or amount of Treg cells in the population, or an increase in T(eff+mem) cells in the population, or a reduction in the ratio of Treg:Tconv) have begun to take place, but the subject has not yet presented symptoms or would not be diagnosed as having such a disease by any conventional method (for example, by reaching the stated level of less than 1.5:100). Thus, the methods and uses disclosed herein may aid in the early identification of patients who will develop such diseases. In one embodiment, the disease is prevented (i.e. the treatment is prophylactic).

In a particular embodiment, the subject is at risk of GvHD or transplant rejection when they are pre-operative for a transplant. Potential transplant therapies are envisaged in arrangement 95 herein.

Arrangement 145. A method according to arrangement 144, wherein in step c), the levels (e.g. expression or amount) of Granzyme A in said second sample is greater than 1.5-fold of the levels (e.g. expression or amount) of Granzyme A in said first sample, for example is greater than 2-fold or greater than 3-fold of the levels (e.g. expression or amount) of Granzyme A in said first sample.

Arrangement 146. A method according to any one of arrangements 142 to 145, further comprising the steps of

d. obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;
e. determining the levels (e.g. expression or amount) of Granzyme A in said third sample;
f. treating said subject to:
   i. reduce or inhibit Th/Tc1 based activation of T-cells; and/or
   ii. normalise cytotoxicity; and/or
   iii. reduce the levels (e.g. expression or amount) of Granzyme A;

by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, if the levels (e.g. expression or amount) of Granzyme A in said second sample are elevated as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition.

Arrangement 147. A method according to arrangement 146, wherein steps d) to f) are repeated as necessary until the levels (e.g. expression or amount) of Granzyme A reach a therapeutically-effective, or a prophylactically-effective levels, e.g. a substantially constant level in said subject.

In one embodiment, the levels are reached and maintained for a week, or two weeks, or three weeks or four weeks. In one embodiment, the levels are reached and maintained for a month, or two months, or three months or four months. In one embodiment, the levels are reached and maintained for a six months, or nine months or for a year.

In another embodiment, the levels (e.g. expression or amount) of Granzyme A remains at a (substantially) constant level after administration of said antibody or fragment (and optionally the second therapeutic agent). As used in the arrangements herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g. greater than 97% or greater than 99%).

Arrangement 148. A method according to any one of arrangements 142 to 147, wherein in step c), or in step f) the levels (e.g. expression or amount) of Granzyme A in said second sample or third sample is greater than double the levels (e.g. expression or amount) as compared to said first sample or second sample, for example is greater than three

times, or is greater than 4 times the levels (e.g. expression or amount) as compared to said first sample or second sample.

Arrangement 149. A method according to any one of arrangements 141 to 148, wherein said first sample is collected:

i. before the onset of said disease or condition; or

ii. after the onset of said disease or condition; and

optionally wherein said second sample is collected no longer than one month, e.g. no longer than one week after the first sample.

Arrangement 150. A method according to any one of arrangements 141 to 149, wherein the autoimmune or alloimmune disease or condition is a transplant, and wherein in step c) the treatment is in order to reduce the risk of transplant rejection, optionally wherein the first sample is taken before the transplant, and the second sample is taken after the transplant.

The first sample may be taken pre-operatively, e.g. after the subject has been identified as a candidate for treatment. The second sample is taken after the transplant and may be used by physicians as a method of monitoring the acceptance of the transplant. Thus, it may be that the physician may take more than one sample after the transplant, e.g. a daily blood sample to monitor the subject for changes in Granzyme A in the sample. The samples may be taken every other day, weekly, monthly or longer (including yearly) according to the likelihood of transplant rejection. For example, if the transplant is autologous, then the likelihood of transplant rejection may be reduced as compared to an allogeneic transplant, and therefore the time period between sample collections post-transplant may be longer than with an allogeneic transplant, where the risk of rejection is higher.

Arrangement 151. A method according to arrangement 150, wherein in step a), the first sample is collected no longer than a week, e.g. no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days before said transplant.

Arrangement 152. A method according to arrangement 150 or arrangement 151, wherein the second sample is collected no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days after the first sample or after said transplant.

Arrangement 153. A method according to any one of arrangements 150 to 152, wherein the subject is given a prophylactic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent before said transplant, and the first sample is taken before administration of said combination and wherein the second sample is taken after the transplant or after administration of the combination (preferably, where in the second sample is taken after the transplant).

Arrangement 154. A method according to any one of arrangements 150 to 152, wherein the subject is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the transplant.

Arrangement 155. A method according to any one of arrangements 150 to 152, wherein the subject is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the administration of said combination.

Arrangement 156. A method according to any one of arrangements 140 to 155, wherein the second sample is taken no longer than one month after the first sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the first sample, and optionally wherein the third sample is taken no longer than one month after the second sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the second sample.

Timepoints for taking any of the samples described in these arrangements will depend on a number of factors, such as the likelihood of the subject having or being at risk of a particular disease or condition (e.g. GvHD or transplant rejection), the level determined in the previous sample, the type of transplant, etc. A person skilled in the art will be able to determine appropriate time points as necessary or desired. The timepoints may be monthly, every other month, quarterly, half-yearly or yearly, if desired.

Arrangement 157. In vitro use of the levels (e.g. expression or amount) of RORC, or the levels (e.g. expression or amount) of Granzyme A, as a diagnostic for an autoimmune or alloimmune disease or condition in a subject, which disease or condition can be treated or prevented with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent.

Arrangement 158. Use of a biomarker of an autoimmune or alloimmune disease or condition, wherein the biomarker is the levels (e.g. expression or amount) of RORC, or wherein the biomarker is the levels (e.g. expression or amount) of Granzyme A, in vitro as a diagnostic for an autoimmune or alloimmune disease or condition, which disease or condition can be treated or prevented with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent.

There is also provided a biomarker of an autoimmune or alloimmune diseases, wherein the biomarker is the levels (e.g. expression or amount) of Granzyme A. The autoimmune or alloimmune diseases may be any of the diseases or disorders as disclosed in the arrangements herein. In another embodiment, the use of the biomarker is ex vivo.

Arrangement 159. A method, an antibody for the use, or a use according to any one of arrangements 110 to 112, 123, 124 or 130 to 158, wherein the levels (e.g. expression or amount) of Granzyme A are determined (or is determinable) by microarray analysis, e.g. target hybridization of RNA to GeneChip *Rhesus Macaque* Genome Array (Affymetrix), and for example further comprising processing and normalising the resultant fluorescent signals using the Robust Multichip Averaging (RMA) Method.

Arrangement 160. A method, an antibody for the use, or a use according to any one of arrangements 110 to 112, 123, 124 or 130 to 158, wherein the levels (e.g. expression or amount) of Granzyme A are determined (or is determinable) by flow cytometry.

Arrangement 161. A method, an antibody for the use, or a use according to any preceding arrangement, wherein the levels (e.g. expression or amount) of Granzyme A before administration of the antibody or fragment thereof are greater than 2-fold (or greater than 4-fold, or 6-fold, or 8-fold; for example 10-fold, or 15-fold, or 20-fold) the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.

Arrangement 162. A method, an antibody for the use, or a use according to any preceding arrangement, wherein the levels (e.g. expression or amount) of Granzyme A before

administration of the antibody or fragment thereof are greater than 30-fold (or greater than 40-fold, 50-fold or 60-fold; for example, greater than 70-fold, 80-fold or 90-fold; e.g. greater than 100-fold, greater than 125-fold or greater than 150-fold) the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.

Arrangement 163. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is a depleting antibody that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.

The various modifications may be any of those set out in concept 52 hereinabove.

Arrangement 164. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is an antagonistic or blocking antibody.

Methods for determining antagonism or blocking functionality may be as described herein, or as well-known by those skilled in the art. For example, in vitro techniques include SPR and/or ELISA, which are described elsewhere herein.

Arrangement 165. A method, a combination for the use, a use or a composition according to arrangement 164, wherein the antibody specifically binds to OX40L (in particular human OX40L).

The OX40L antibodies may be any antibody or fragment as described herein. In one embodiment, the OX40L antibody is the antagonist anti-human OX40L (gp34) antibody ik-1 described by Matsumura et a/., J Immunol. (1999), 163:3007, which antibody is incorporated herein by reference.

Arrangement 166. A method, a combination for the use, a use or a composition according to arrangement 165, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

SPR and ELISA methods may be as described elsewhere herein.

Arrangement 167. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is a humanized, human or fully human antibody.

Other antibody constructs may be as described herein.

Arrangement 168. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bispecific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

Arrangement 169. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

Arrangement 170. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

Arrangement 171. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

Arrangement 172. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises a CDR selected from:

a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);
b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);
c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);
d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No: 106);
e. a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
f. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or
g. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234.

Arrangement 173. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody or fragment thereof comprises:

a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);
b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);
c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);
d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No:104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);
e. the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
f. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or
g. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

Arrangement 174. A method, a combination for the use, a use or a composition according to any preceding arrange-

ment, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);
b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No: 16 for VL);
c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);
d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);
e. a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
f. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or
g. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

Arrangement 175. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the antibody is oxelumab.

In another embodiment, the antibody is not oxelumab. In another embodiment, the antibody is not oxelumab and the disease is not asthma.

Arrangement 176. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the Granzyme A is measured in a sample of blood, e.g. peripheral blood.

Whereas T-cells (and hence Granzyme A) present in blood are relatively straightforward to isolate and characterise, T-cells which are present in the tissues of a subject are generally more difficult to isolate. That said, it may be possible to isolate T-cells from various tissues (such as skin, tissues of the GI tract, e.g. bowel, and from inflamed joints, e.g. synovium).

Arrangement 177. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the subject is a human patient.

Arrangement 178. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the autoimmune or alloimmune disease or condition is mediated by a deficiency in Treg cells.

Arrangement 179. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the autoimmune or alloimmune disease or condition is selected from graft versus host disease (GvHD), allogenic transplant rejection, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, atherosclerosis, uveitis, ankylosing spondylitis and contact hypersensitivity.

Arrangement 180. A method, a combination for the use, a use or a composition according to arrangement 179, wherein the autoimmune or alloimmune disease or condition is selected from GvHD and allogenic transplant rejection.

Arrangement 181. A method, a combination for the use, a use or a composition according to arrangement 179, wherein the autoimmune or alloimmune disease or condition is selected from inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis.

Arrangement 182. A method, a combination for the use, a use or a composition according to arrangement 180, wherein the allogenic transplant rejection is rejection of a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or of a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.

In one embodiment, the transplant is an HLA-matched allogeneic bone marrow or stem cell transplant. In another embodiment, the transplant is an HLA mis-matched allogeneic bone marrow or stem cell transplant.

Arrangement 183. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is an IL-2 modulating agent, for example an IL-2 inhibiting agent, such as a calcinueirn inhibitor or an mTOR inhibitor (for example the agent is selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), anti-IL2R antibodies (e.g. basilixumab), anti-IL-2 antibodies and anti-CD24-Fc fusion protein).

In another embodiment, the IL-2 modulating agent is recombinant IL-2. In another embodiment, the IL-2 modulating agent is an IL-2 inhibiting agent.

Arrangement 184. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is independently selected from the group consisting of methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-CD25 antibodies (e.g. daclizumab), anti-TCONVFa/TCONVFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Arrangement 185. A method, a combination for the use, a use or a composition according to any one of arrangements 101 to 197, wherein the second therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

Arrangement 186. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is rapamycin.

In another embodiment, the second therapeutic agent is rapamycin or derivatives thereof. Derivatives of rapamycin are well-known to those skilled in the art.

Arrangement 187. A method, a combination for the use, a use or a composition according to any preceding arrangement, wherein the second therapeutic agent is tacrolimus.

The inventors have surprisingly found that following administration of an anti-OX40L antibody $CD4^+$ T-cells had a reduced ability to express IL-17A, whilst production of IFNγ, TNFα or IL-2 was unaffected. This unexpected result suggests that anti-OX40L antibodies may have further thera-

peutic uses in diseases where an IL-17A antagonist may be effective. Thus, there is provided:

Arrangement 201. A method of reducing the level (e.g. expression or amount) of IL-17A in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of IL-17 (e.g. IL-17A).

The level (e.g. expression or amount) of IL-17A may be determined by methods well-known to those skilled in the art, e.g. by flow cytometic analysis of T-cells in a sample, which may be obtained from a subject (see arrangements 1 to 100 hereinabove for further details, all of which apply mutatis mutandis to these further arrangements hereinbelow).

Thus, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of IL-17A" or similar phrases may be replaced throughout by the phrase "lowering the level (e.g. expression or amount) of IL-17A" or similar phrases. Further, as used in the arrangements herein, the phrase "reducing the level (e.g. expression or amount) of IL-17A" or similar phrases may be replaced by the phrase "downregulating the level (e.g. expression or amount) of IL-17A" or similar phrases. In any of the arrangements herein, the "level" may be a relative level, or an absolute number.

"Reducing" or "reduces" as used in any of the arrangements herein, refers to a mechanism which reduces the apparent expression levels of IL-17A in a given sample. The sample may be a sample of blood, e.g. peripheral blood which may be processed by, for example, flow cytometry or by microarray analysis to extract IL-17A mRNA transcripts from the T-cells in the sample.

The second therapeutic agent is described in more detail in the arrangements herein, but is preferably an IL-2 modulating agent.

The antibodies and combinations of the present invention may provide benefit by preventing increases in the level (e.g. expression or amount) of IL-17A, which will have occurred if the disease or disorder is already beginning to take effect, or has already taken hold. If used prophylactically, the antibodies and combinations of the present invention may prevent any substantial change in the level (e.g. expression or amount) of IL-17A, because they are able to protect the patient from the detrimental cellular changes. Thus, in another embodiment, the level (e.g. expression or amount) of IL-17A remains at a substantially constant level after administration of the combination. Substantially constant may be as described in arrangement 2 hereinabove.

Arrangement 202. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of IL-17 (e.g. IL-17A) as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 203. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of IL-17 (e.g. IL-17A) as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 204. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of IL-17 (e.g. IL-17A) as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

Arrangement 205. A method according to arrangement 201, wherein the subject has or is at risk of an IL-17A-mediated disease.

Arrangement 206. A method of treating or preventing an IL-17A-mediated disease in a subject comprising administering to said subject a therapeutically or prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of IL-17 (e.g. IL-17A), and whereby the IL-17A-mediated disease is thereby treated or prevented.

Arrangement 207. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an IL-17A-mediated disease, whereby the level (e.g. expression or amount) of IL-17 (e.g. IL-17A) is reduced, and whereby the IL-17A-mediated disease is thereby treated or prevented.

Arrangement 208. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an IL-17A-mediated disease, whereby the level (e.g. expression or amount) of IL-17 (e.g. IL-17A) is reduced, and whereby the IL-17A-mediated disease is thereby treated or prevented.

Arrangement 209. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an IL-17A-mediated disease.

Arrangement 210. A method, use or antibody for the use according to any one of arrangements 205 to 209, wherein the IL-17A-mediated disease is selected from an inflammatory disease or condition, an autoimmune disease or condition, an alloimmune disease or condition and an infectious disease or condition, optionally selected from colorectal cancer (CRC), colon cancer, pancreatic cancer, breast cancer, glioma, asthma, COPD, cystic fibrosis, transplant rejection (e.g. lung transplant rejection), multiple sclerosis, arthritis, rheumatoid arthritis (RA), reactive arthritis, psoriatic arthritis, atherosclerosis, spondyloarthropathies, juvenile-onset spondyloarthritis, inflammatory bowel disease, Chron's disease, systemic lupus erythematosus (SLE), psoriasis, ankylosing spondylitis, type 1 diabetes, stroke, depression, Behcet's disease, allograft rejection, nephritic syndrome, Hashimoto's thyroiditis, undifferentiated SpA, vitiligo, cardiovascular diseases, Hepatitis B virus (HBV) infection, Hepatitis C virus (HCV) infection and Human Immunodeficiency Virus (HIV) infection, in particular selected from colorectal cancer (CRC), colon cancer, asthma, COPD, cystic fibrosis, transplant rejection (e.g. lung transplant rejection), multiple sclerosis, arthritis, rheumatoid arthritis (RA), psoriatic arthritis, atherosclerosis, inflammatory bowel disease, Chron's disease, systemic lupus erythematosus (SLE), psoriasis, ankylosing spondylitis, type 1 diabetes and allograft rejection.

In one embodiment, the IL-17A-mediated disease is an inflammatory cancer. One such cancer is colorectal cancer (CRC), which is an inflammation-driven cancer that represents the third most prevalent malignancy and one of the major killers of cancer patients worldwide (Terzid J, et al., Inflammation and colon cancer, Gastroenterology, 138, 2101-2114 (2010)). In humans, CRC development is

strongly linked to the interleukin-23 (IL-23)-IL-17 pathway (Grivennikov S I, et al., Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth, Nature, 491, 254-258 (2012); Langowski J L, et al., IL-23 promotes tumour incidence and growth, Nature, 442, 461-465 (2006); Wang K, et al., Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis, Immunity, 41, 1052-1063 (2014)). IL-17 expression is associated with poor prognosis. Furthermore, microsatellite stable (MSS) CRC patients are poor responders to anti PD-1/PD-L1 therapies, except MSI-CRC patients (5% to 6% of the stage IV CRC) who respond well to checkpoint inhibitors. IL-17 promotes angiogenesis via stimulating VEGF production of cancer cells in CRC and IL-17RA signals directly within transformed colonic epithelial cells (enterocytes) to promote early tumour development (Wang et al., supra). IL-17RA signals are required for growth and progression of aberrant crypt foci, and IL-17RA activates ERK, p38 MAPK, and NF-κB in transformed enterocytes. Wu S, et a/., A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses, Nat. Med., 15, 1016-1022 (2009) showed that neutralization of IL-17A with a specific antibody prevented ETBF-induced acceleration of colonic tumorigenesis.

Other cancers have been shown to have an IL-17 component, for example breast cancer (Zhu X, et al., IL-17 expression by breast-cancer-associated macrophages: IL-17 promotes invasiveness of breast cancer cell lines, Breast Cancer Res, (2008), 10:R95), pancreatic cancer (Cully M., Cancer: Targeting IL-17 in pancreatic cancer, Nat. Rev. Drug Discov., (2014), 13:493) and glioma (Zambrano-Zaragoza J F, et al., Th17 cells in autoimmune and infectious diseases, Int. J. Inflam., (2014), 651503).

In another embodiment, the IL-17A-mediated disease is an autoimmune disease or condition, for example selected from rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel diseases, Chron's disease, SLE, Behcet's disease, allograft rejection and nephritic syndrome. See for example, Yamada H., Current perspectives on the role of IL-17 in autoimmune disease, J. Inflamm. Res., (2010), 3:33-44; Yang J, et al, Targeting Th17 cells in autoimmune diseases, Trends Pharmacol. Sci., (2014), 35:493-500; Chiricozzi A., Pathogenic role of IL-17 in psoriasis and psoriatic arthritis, Actas Dermosifiliogr., (2014), 1:9-20; and Komiyama Y et al., IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis, J. Immunol., (2006), 177:566-73.

In another embodiment, the IL-17A-mediated disease is an inflammatory disease or disorder, for example asthma, RA, MS, IBD, Chron's disease, COPD and cystic fibrosis (see Jin W & Dong C., IL-17 cytokines in immunity and inflammation, Emerg. Microbes Infect., (2013), 2(9):e60; Waisman A, et al., The role of IL-17 in CNS diseases, Acta Neuropathol., (2015), 129:625-637; Zambrano-Zaragoza J F, et al., supra, and Bullens D M, et al, IL-17A in human respiratory diseases: innate or adaptive immunity? Clinical implications, Clin. Dev. Immunol., (2013), 840315.

Arrangement 211. A method, use or antibody for the use according to any one of arrangements 205 to 209, wherein the IL-17A-mediated disease is a cancer in which IL-17A is overexpressed, for example a cancer selected from stomach adenocarcinoma, head & neck squamous cell carcinoma, oesophageal carcinoma, lung adenocarcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, uterine corpus endometrial carcinoma, lung squamous cell carcinoma, glioblastoma multiforme, prostrate adenocarcinoma, bladder urothelial carcinoma, sarcoma, pancreatic adenocarcinoma, uterine carcinosarcoma, brain lower grade glioma, rectum adenocarcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, breast invasive carcinoma, thyroid carcinoma, mesothelioma, skin cutaneous melanoma, kidney renal clear cell carcinoma, adrenocortical carcinoma, liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma and kidney chromophobe.

These cancers have been shown to have an IL-17A component to varying degrees, but all may be amenable to treatment with an anti-OX40 or anti-OX40L antibody of the present disclosure.

In any of arrangements 201 to 211, the anti-OX40 antibody may be as described in any of the aspects, concepts or arrangements described herein. In a particular embodiment, the antibody or fragment thereof is in a format or structure of any of the antibodies and fragments described elsewhere herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein, or any arrangement hereinbelow, and any concept, embodiment, aspect, arrangement or feature describing anti-OX40L antibodies or anti-OX40 antibodies herein applies mutatis mutandis to arrangements 201 to 208). In a particular embodiment, the antibody is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab. In another embodiment, the combination comprises an anti-OX40L antibody which is not oxelumab (having a VH region amino acid sequence of Seq ID No:215 and a VL region amino acid sequence of Seq ID No:214). In another embodiment, the antibody is not oxelumab. In another embodiment, the antibody is not oxelumab and the disease is not asthma.

The second therapeutic agent is any of those described elsewhere herein, in particular in arrangements 183 to 187 hereinabove.

Further provided herein are the following arrangements:

Arrangement 301. A method of preventing a reduction in the proportion (e.g. number or level) of naïve T-cells (T_N), and/or preventing an increase in the proportion (e.g. number or level) of central memory T-cells (T_{CM}) comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) prevents reduction of the proportion (e.g. number or level) of T_N cells, and whereby the proportion of said TN cells is not substantially reduced and/or which antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_N cells is not substantially increased.

Without being bound by theory, it is thought that preventing reduction of the proportion (e.g. number or level) of T_N cells and/or preventing an increase of the proportion (e.g. number or level) of T_{CM} cells will have a number of benefits in various diseases, as set out herein, and the inventors have surprisingly shown that this may be achieved using an anti-OX40L antibody by itself or in combination with a second agent which is sirolimus, see Example 10 hereinbelow. Naïve T-cells (T_N) as defined in the arrangements herein are characterised as $CD3^+CD14^-CD20^-CD28^+CD95^-$. Further markers may be present or absent, but T_N cells must at a minimum be $CD3^+CD14^-CD20^-CD28^+CD95^-$. In one embodiment, T_N cells may additionally be $CD8^+$ or $CD4^+$, in particular $CD4^+$. It is thought that TN are beneficial because

these represent the entire pool of T-cells from which adaptive T-cell immune responses can develop to protect an individual when exposed to potentially harmful pathogens and malignant cells. In one embodiment, the T_N cells are $CD4^+$. In another embodiment, the T_N cells are $CD8^+$.

Central memory T-cells (T_{CM}) as defined in the arrangements herein are characterised as $CD3^+CD14^-CD20^-CD28^+CD95^+$. Further markers may be present or absent, but T_{CM} cells must at a minimum be $CD3^+CD14^-CD20^-CD28^+CD95^+$. In one embodiment, T_{CM} cells may additionally be $CD8^+$ or $CD4^+$, in particular $CD4^+$. In one embodiment, the T_{CM} cells are $CD4^+$. In another embodiment, the T_{CM} cells are $CD8^+$.

The proportion (e.g. number or level) of T_N cells and/or T_{CM} cells may be determined relative to the entire T-cell population in the sample. In one embodiment, the proportion (e.g. number or level) of T_N cells and/or T_{CM} cells is determined relative to other T-cells in the sample. The proportion (e.g. number or level) of T_{CM} cells may be altered by allowing the expansion or increase in the absolute number of T_{CM} cells, or by changing the number of other T-cell subtypes such that the relative proportion (e.g. number or level) of T_{CM} cells appears to be maintained or increased. The proportion (e.g. number or level) of T_N cells may be altered by allowing the depletion or decrease in the absolute number of T_N cells, or by changing the number of other T-cell subtypes such that the relative proportion (e.g. number or level) of T_N cells appears to be maintained or decreased.

Thus, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of T_N cells and" or similar phrases may be replaced throughout by the phrase "slowing the reduction in proportion (e.g. number or level) of T_N cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of T_N cells" or similar phrases may be replaced with the phrase "maintaining the proportion (e.g. number or level) of T_N cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of T_N cells" or similar phrases may be replaced with the phrase "preventing depletion of the proportion (e.g. number or level) of T_N cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the reduction of the proportion (e.g. number or level) of T_N cells" or similar phrases may be replaced with the phrase "increasing the proportion (e.g. number or level) of T_N cells" or similar phrases. To illustrate this point, which may be applied in any of the arrangements herein, there is described arrangements 301a) to 301d).

Thus, as used in the arrangements herein, the phrase "preventing the increase of the proportion (e.g. number or level) of T_{CM} cells and" or similar phrases may be replaced throughout by the phrase "slowing the increase in proportion (e.g. number or level) of T_{CM} cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the increase of the proportion (e.g. number or level) of T_{CM} cells" or similar phrases may be replaced with the phrase "maintaining the proportion (e.g. number or level) of T_{CM} cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the increase of the proportion (e.g. number or level) of T_{CM} cells" or similar phrases may be replaced with the phrase "preventing expansion of the proportion (e.g. number or level) of T_{CM} cells" or similar phrases. Further, as used in the arrangements herein, the phrase "preventing the increase of the proportion (e.g. number or level) of T_{CM} cells" or similar phrases may be replaced with the phrase "decreasing the proportion (e.g. number or level) of T_{CM} cells" or similar phrases. To illustrate this point, which may be applied in any of the arrangements herein, there is described arrangements 301e) to 301h).

In any of the arrangements herein, the "proportion" may be the relative proportion (e.g. number or level) of T_N cells and/or T_{CM} cells, or the absolute number of level of T_N cells and/or T_{CM} cells.

Thus, according to arrangement 301a), there is provided a method of slowing the reduction in the proportion (e.g. number or level) of T_N cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) slows reduction of the proportion (e.g. number or level) of T_N cells and, and whereby reduction of the proportion (e.g. number or level) of T_N cells is slowed.

Thus, according to arrangement 301b), there is provided a method of maintaining the proportion of (e.g. maintaining the number or level of) T_N cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) maintains the proportion of (e.g. maintains the number or level of) TN cells, and whereby the proportion of said T_N cells is maintained (e.g. whereby the number or level of said T_N cells is maintained).

Thus, according to arrangement 301c), there is provided a method of preventing depletion of the proportion of (e.g. the number or level of) T_N cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) prevents depletion of the proportion of (e.g. the number or level of) TN cells, and whereby the proportion (e.g. the number or level) of said T_N cells is not substantially depleted.

Thus, according to arrangement 301d), there is provided a method of increasing the proportion of (e.g. increasing the number or level of) T_N cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) increases the proportion of (e.g. increases the number or level of) TN cells, and whereby the proportion of said T_N cells is increased (e.g. whereby the number or level of said T_N cells is increased).

Thus, according to arrangement 301e), there is provided a method of slowing the increase in the proportion (e.g. number or level) of T_{CM} cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) slows the increase in the proportion (e.g. number or level) of T_{CM} cells and, and whereby the increase in the proportion (e.g. number or level) of T_{CM} cells is slowed.

Thus, according to arrangement 301f), there is provided a method of maintaining the proportion of (e.g. maintaining the number or level of) T_{CM} cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) maintains the proportion of (e.g. maintains the number or level of) T_{CM} cells, and whereby the proportion of said T_{CM} cells is maintained (e.g. whereby the number or level of said T_{CM} cells is maintained).

Thus, according to arrangement 301g), there is provided a method of preventing expansion of the proportion of (e.g. the number or level of) T_{CM} cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or

fragment thereof and optionally a second therapeutic agent, which antibody (or combination) prevents expansion of the proportion of (e.g. the number or level of) T_{CM} cells, and whereby the proportion (e.g. the number or level) of said T_{CM} cells is not substantially expanded.

Thus, according to arrangement 301d), there is provided a method of decreasing the proportion of (e.g. decreasing the number or level of) T_{CM} cells comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) decreases the proportion of (e.g. decreases the number or level of) T_{CM} cells, and whereby the proportion of said T_{CM} cells is decreased (e.g. whereby the number or level of said T_{CM} cells is decreased).

"Decreasing" or "decreases" as used in any of the arrangements herein, refers to a mechanism which reduces the absolute number or levels of cells in a given population. This may be achieved indirectly, for example through a blocking or neutralising agent (such as an antibody) against a target which indirectly results in the killing of a target cell (such as a TN and/or T_{CM}), or prevents the expansion or growth of the target cells, resulting in an apparent decrease in proportions relative to another type of cell (such as Teff or Tmem cells).

"Increasing" or "increases" as used in any of the arrangements herein, refers to a mechanism which increases the absolute number or levels of cells in a given population. This may be achieved indirectly, for example through a blocking or neutralising agent (such as an antibody) against a target which indirectly results in the killing of a target cell other than TN and/or T_{CM}, or prevents the expansion or growth of the target cells other than TN and/or T_{CM}, resulting in an apparent increase in proportions of T_N and/or T_{CM} relative to the other cells.

As used in any of the arrangements herein, a "level" of a T-cell population may refer to the absolute number, or to the relative proportion of a type of T-cell. Particular numbers of T_N cells and T_{CM} cells are described elsewhere herein, for example in arrangements 302 and 303 below. Any of these levels or numbers may be applied to any arrangement which discusses T_N cells or T_{CM} cells.

In a particular embodiment, the combination of any arrangement comprises an antibody or fragment thereof which in is a format or structure of any of the antibodies and fragments described elsewhere herein, e.g. in any concept, embodiment, arrangement, aspect or feature. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein, or any arrangement hereinbelow). In a particular embodiment, the antibody is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab. In another embodiment, the combination comprises an anti-OX40L antibody which is not oxelumab (having a VH region amino acid sequence of Seq ID No:215 and a VL region amino acid sequence of Seq ID No:214).

In one embodiment, the antibody is an anti-OX40L antibody or fragment thereof. In another embodiment, the antibody is an anti-OX40L antibody or fragment thereof in combination with a second therapeutic agent. In another embodiment, the second therapeutic agent contained within the combination is described in more detail in the arrangements hereinbelow, but is preferably an IL-2 modulating agent.

Arrangement 302. The method according to arrangement 301, wherein the method prevents reduction in the proportion (e.g. the number or level) of T_N cells and wherein the proportion of T_N cells is at least 10 T_N cells/L^{-6}, for example at least 20 T_N cells/L^{-6}, or at least 30 T_N cells/L^{-6}, or at least 40 TN cells/L^{-6}, or at least 50 T_N cells/L^{-6} after combining said cells with said antibody (or combination).

In one embodiment, the proportion is at least 60 T_N cells/L^{-6}, or at least 70 T_N cells/L^{-6}, or at least 80 T_N cells/L^{-6}, or at least 90 T_N cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 100 T_N cells/L^{-6}, or at 110 T_N cells/L^{-6}, or at 120 T_N cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 130 T_N cells/L^{-6}, or at least 140 T_N cells/L^{-6}, or at least 150 TN cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 160 T_N cells/L^{-6}, or at least 170 T_N cells/L^{-6}, or at least 180 T_N cells/L^{-6}, or at least 190 T_N cells/L^{-6} or at least 200 T_N cells/L^{6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 250 T_N cells/L^{-6}, or at least 300 TN cells/L^{-6}, or at least 350 T_N cells/L^{-6}, or at least 400 T_N cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is no more than 800 T_N cells/L^{-6}, or no more than 700 T_N cells/L^{-6}, or no more than 600 T_N cells/L^{-6}, or no more than 500 T_N cells/L^{-6} after combining said cells with said antibody (or combination).

In one embodiment, the proportion is above 400 T_N cells/L^{-6}, or is above 500 T_N cells/L^{-6}, or is above 600 T_N cells/L^{-6} before combining said cells with said antibody (or combination). In another embodiment, the proportion is above 700 T_N cells/L^{-6}, or above 800 T_N cells/L^{-6}, or is above 900 TN cells/L^{-6}, before combining said cells with said antibody (or combination). In another embodiment, the proportion is about 1000 T_N cells/L^{-6}, or is at a maximum of 1500 (e.g. 1000) TN cells/L^{-6} before combining said cells with said antibody (or combination).

In another embodiment, the proportion is in a range of from 10 to 100 T_N cells/L^{-6}, or at from 10 to 75 T_N cells/L^{-6}, or from 10 to 50 T_N cells/L^{-6}, or from 10 to 30 T_N cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is in a range of from 50 to 200 T_N cells/L^{-6}, or at from 50 to 150 T_N cells/L^{-6}, or from 50 to 100 T_N cells/L^{-6} after combining said cells with said antibody (or combination). The upper limit may be any of the proportions provided before contact with the antibody (or combination), and the lower limit may be any of the proportions provided for after contact with the antibody (or combination).

In another embodiment, the proportion (e.g. number or level) of T_N cells remains at a (substantially) constant proportion after administration of said combination. As used in the arrangements herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g. greater than 97% or greater than 99%).

In another embodiment, the proportion (e.g. number or level) of T_N cells does not change substantially as compared to the first measurement taken.

These proportions (e.g. numbers or levels) of T_N cells may apply to any arrangement herein which relates to the proportion (e.g. number or level) of T_N cells after administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

These proportions (e.g. number of levels) of T_N cells may apply to any arrangement herein which relates to the proportion (e.g. number or level) of T_N cells before administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

Arrangement 303. The method according to arrangement 301, wherein the method prevents reduction in the proportion (e.g. the number or level) of T_N cells and wherein the proportion of T_N cells is above 5% of the total population of T-cells after combining said T_N cells with said antibody (or combination).

In one embodiment, the proportion of T_N cells is above 10, or above 15%, or above 20% of the total population of T-cells after combining said T_N cells with said antibody (or combination). In another embodiment, the proportion of T_N cells is above 25%, or above 30%, or above 35% of the total population of T-cells after combining said T_N cells with said antibody (or combination). In another embodiment, the proportion of T_N cells is above 40%, or above 45%, or above 50% of the total population of T-cells after combining said T_N cells with said antibody (or combination).

In one embodiment, the proportion of T_N cells is above 40%, or above 45%, or above 50% of the total population of T-cells before combining said T_N cells with said antibody (or combination). In one embodiment, the proportion of T_N cells is above 55%, or above 60%, or is about 65% of the total population of T-cells before combining said T_N cells with said antibody (or combination).

In another embodiment, the proportion is in a range of from 10 to 50%, or from 10 to 40%, or from 20 to 30% after combining said cells with said antibody (or combination). The upper limit may be any of the proportions provided before contact with the antibody (or combination), and the lower limit may be any of the proportions provided for after contact with the antibody (or combination).

In another embodiment, the proportion (e.g. number or level) of T_N cells remains at a (substantially) constant proportion after administration of said combination. As used in the arrangements herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g. greater than 97% or greater than 99%).

In another embodiment, the proportion (e.g. number or level) of T_N cells does not change substantially as compared to the first measurement taken.

These proportions of T_N cells may apply to any arrangement herein which relates to the proportion of T_N cells after administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

These proportions of T_N cells may apply to any arrangement herein which relates to the proportion of T_N cells before administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

Arrangement 304. The method according to arrangement 301, wherein the method prevents an increase in the proportion (e.g. the number or level) of T_{CM} cells and wherein the proportion of T_{CM} cells is at least 10 T_{CM} cells/L^6, for example at least 20 T_{CM} cells/L^{-6}, or at least 30 T_{CM} cells/L^6, or at least 40 T_{CM} cells/L^6, or at least 50 T_{CM} cells/L^6 after combining said cells with said antibody (or combination).

In one embodiment, the proportion is at least 60 T_{CM} cells/L^{-6}, or at least 70 T_{CM} cells/L^{-6}, or at least 80 T_{CM} cells/L^{-6}, or at least 90 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 100 T_{CM} cells/L^{-6}, or at least 110 T_{CM} cells/L^{-6}, or at least 120 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 130 T_{CM} cells/L^{-6}, or at least 140 T_{CM} cells/L^6, or at least 150 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is at least 160 T_{CM} cells/L^{-6}, or at least 170 T_{CM} cells/L^{-6}, or at least 180 T_{CM} cells/L^{-6}, or at least 190 T_{CM} cells/L^{-6} or at least 200 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination).

In one embodiment, the proportion is above 75 T_{CM} cells/L^{-6}, or is above 100 T_{CM} cells/L^{-6}, or is above 125 T_{CM} cells/L^6 before combining said cells with said antibody (or combination). In another embodiment, the proportion is above 250 T_{CM} cells/L^{-6}, or above 300 T_{CM} cells/L^{-6}, or is above 350 T_{CM} cells/L^{-6}, before combining said cells with said antibody (or combination). In another embodiment, the proportion is above 400 T_{CM} cells/L^{-6}, or above 4500 T_{CM} cells/L^{-6}, or is about 500 T_{CM} cells/L^{-6}, before combining said cells with said antibody (or combination). In another embodiment, the proportion is at a maximum of 600 (e.g. 700) T_{CM} cells/L^{-6} before combining said cells with said antibody (or combination).

In another embodiment, the proportion is in a range of from 10 to 250 T_{CM} cells/L^{-6}, or at from 10 to 75 T_{CM} cells/L^{-6}, or from 10 to 50 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination). In another embodiment, the proportion is in a range of from 50 to 200 T_{CM} cells/L^{-6}, or at from 50 to 150 T_{CM} cells/L^{-6}, or from 50 to 100 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination). The upper limit may be any of the proportions provided before contact with the antibody (or combination), and the lower limit may be any of the proportions provided for after contact with the antibody (or combination).

In another embodiment, the proportion (e.g. number or level) of T_{CM} cells remains at a (substantially) constant proportion after administration of said combination. As used in the arrangements herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one

embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g. greater than 97% or greater than 99%).

In another embodiment, the proportion (e.g. number or level) of T_{CM} cells does not change substantially as compared to the first measurement taken.

These proportions (e.g. numbers or levels) of T_{CM} cells may apply to any arrangement herein which relates to the proportion (e.g. number or level) of T_{CM} cells after administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

These proportions (e.g. number of levels) of T_{CM} cells may apply to any arrangement herein which relates to the proportion (e.g. number or level) of T_{CM} cells before administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

Arrangement 305. The method according to arrangement 301, wherein the method prevents an increase in the proportion (e.g. the number or level) of T_{CM} cells and wherein the proportion of T_{CM} cells is above 15% of the total population of T-cells after combining said T_{CM} cells with said antibody (or combination).

In one embodiment, the proportion of T_{CM} cells is above 20%, or above 25%, or above 30%, or above 35% of the total population of T-cells after combining said T_{CM} cells with said antibody (or combination). In another embodiment, the proportion of T_{CM} cells is above 40%, or above 45%, or above 50% of the total population of T-cells after combining said T_{CM} cells with said antibody (or combination). In another embodiment, the proportion of T_{CM} cells is above 55%, or above 60%, or above 65%, or above 70% of the total population of T-cells after combining said T_N cells with said antibody (or combination).

In one embodiment, the proportion of T_N cells is above 30%, or above 35%, or above 40% of the total population of T-cells before combining said T_{CM} cells with said antibody (or combination). In one embodiment, the proportion of T_{CM} cells is above 45%, or above 50%, or is about 55% of the total population of T-cells before combining said T_{CM} cells with said antibody (or combination).

In another embodiment, the proportion is in a range of from 20 to 70%, or from 20 to 50%, or from 20 to 40% after combining said cells with said antibody (or combination). In another embodiment, the proportion is in a range of from 50 to 70% after combining said cells with said antibody (or combination). The upper limit may be any of the proportions provided before contact with the antibody (or combination), and the lower limit may be any of the proportions provided for after contact with the antibody (or combination).

In another embodiment, the proportion (e.g. number or level) of T_{CM} cells remains at a (substantially) constant proportion after administration of said combination. As used in the arrangements herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g. greater than 97% or greater than 99%).

These proportions of T_{CM} cells may apply to any arrangement herein which relates to the proportion of T_{CM} cells after administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

These proportions of T_{CM} cells may apply to any arrangement herein which relates to the proportion of T_{CM} cells before administration of the anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent.

Arrangement 306. A method of altering the ratio of cell types in a T-cell population in a sample, the method comprising:

(a) providing said population, wherein the population comprises a mixture of different T-cell types, wherein the population comprises T_N cells and/or T_{CM},

(b) providing an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent; and

(c) combining said cell population with an amount of said antibody (or combination) effective to alter the proportion (e.g. number or level) of T_N cells and/or T_{CM} cells in said population.

The proportion may be altered by mechanisms such as preventing reduction in the proportion (e.g. number or level) of T_N cells in said population. Alternatively, the ratio may be altered by slowing the reduction in proportion (e.g. number or level) of T_N cells in said population. Alternatively, the ratio may be altered by increasing the proportion (e.g. the number or level) of T_N cells in said population. Alternatively, the ratio may be altered by preventing depletion of T_N cells in said population.

The proportion may be altered by mechanisms such as preventing an increase in the proportion (e.g. number or level) of T_{CM} cells in said population. Alternatively, the ratio may be altered by slowing the increase in proportion (e.g. number or level) of T_{CM} cells in said population. Alternatively, the ratio may be altered by decreasing the proportion (e.g. the number or level) of T_{CM} cells in said population. Alternatively, the ratio may be altered by preventing expansion of T_{CM} cells in said population.

In one embodiment, the method further comprises a step (d) of obtaining or isolating a sample of T-cells in which the proportion (e.g. number or level) of T_N cells and/or T_{CM} cells is altered. Such an obtained or isolated sample may be formulated into a product for cell transplant. The resulting product may be used in a method of treating any of the diseases associated with the arrangements herein (e.g. an OX40L-mediated disease, or an autoimmune or alloimmune disease or condition, e.g. an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100).

Arrangement 307. A method of treating or reducing the risk of an OX40L-mediated disease or condition (e.g. an autoimmune or alloimmune disease or condition) in a subject, the method comprising combining a population of T-cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby the proportion of said T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased.

In one embodiment, the antibody (or combination) slows the reduction in proportion (e.g. number or level) of T_N cells in said population, and results in a slowing in reduction of the proportion (e.g. number or level) of T_N cells. In one embodiment, the antibody (or combination) maintains the

proportion (e.g. number or level) of T_N cells, and results in maintenance of the proportion (e.g. number or level) of T_N cells. In one embodiment, the antibody (or combination) prevents depletion of the proportion (e.g. number or level) of T_N cells, and results in the proportion (e.g. number or level) of TN cells not being depleted (or substantially depleted). In one embodiment, the antibody (or combination) increases the proportion (e.g. number or level) of T_N cells, and results in an increase in the proportion (e.g. number or level) of T_N cells.

In one embodiment, the antibody (or combination) slows the increase in proportion (e.g. number or level) of T_{CM} cells in said population, and results in a slowing in the increase of the proportion (e.g. number or level) of T_{CM} cells. In one embodiment, the antibody (or combination) maintains the proportion (e.g. number or level) of T_{CM} cells, and results in maintenance of the proportion (e.g. number or level) of T_{CM} cells. In one embodiment, the antibody (or combination) prevents expansion of the proportion (e.g. number or level) of T_{CM} cells, and results in the proportion (e.g. number or level) of T_N cells not being expanded (or substantially expanded). In one embodiment, the antibody (or combination) decreases the proportion (e.g. number or level) of T_{CM} cells, and results in a decrease in the proportion (e.g. number or level) of T_{CM} cells.

Arrangement 308. A method according to arrangement 307, wherein the combining of cells and the antibody (or combination) is by administering said antibody (or combination) in a therapeutically effective amount or prophylactically effective amount to said subject, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.

In one embodiment, the administration is of a combination of an anti-OX40 or anti-OX40L antibody and a second therapeutic agent. In one embodiment, the combination comprises a therapeutically effective amount of the anti OX40 or anti-OX40L antibody and a therapeutically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a therapeutically effective amount of the anti OX40 or anti-OX40L antibody and a prophylactically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a prophylactically effective amount of the anti OX40 or anti-OX40L antibody and a therapeutically effective amount of the second therapeutic agent. In one embodiment, the combination comprises a prophylactically effective amount of the anti OX40 or anti-OX40L antibody and a prophylactically effective amount of the second therapeutic agent.

In another embodiment, the combination may be therapeutically or prophylactically effective, despite containing doses or amounts of either (i) the anti-OX40 or an anti-OX40L antibody or fragment thereof and (ii) the second therapeutic agent which, by themselves, would not necessarily be therapeutically or prophylactically effective. Hence, the risk of side effects may be reduced, as smaller amounts of therapeutic entities are being given to patients in need thereof.

Arrangement 309. A method of treating or reducing the risk of a disease or condition (e.g. an OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100) in a subject comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent thereof;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced, and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.

In one embodiment, the combination slows the reduction in proportion (e.g. number or level) of T_N cells in said population, and results in a slowing in reduction of the proportion (e.g. number or level) of T_N cells. In one embodiment, the combination maintains the proportion (e.g. number or level) of T_N cells, and results in maintenance of the proportion (e.g. number or level) of T_N cells. In one embodiment, the combination prevents depletion of the proportion (e.g. number or level) of T_N cells, and results in the proportion (e.g. number or level) of T_N cells not being depleted (or substantially depleted). In one embodiment, the combination increases the proportion (e.g. number or level) of T_N cells, and results in an increase in the proportion (e.g. number or level) of T_N cells.

In one embodiment, the antibody (or combination) slows the increase in proportion (e.g. number or level) of T_{CM} cells in said population, and results in a slowing in the increase of the proportion (e.g. number or level) of T_{CM} cells. In one embodiment, the antibody (or combination) maintains the proportion (e.g. number or level) of T_{CM} cells, and results in maintenance of the proportion (e.g. number or level) of T_{CM} cells. In one embodiment, the antibody (or combination) prevents expansion of the proportion (e.g. number or level) of T_{CM} cells, and results in the proportion (e.g. number or level) of T_N cells not being expanded (or substantially expanded). In one embodiment, the antibody (or combination) decreases the proportion (e.g. number or level) of T_{CM} cells, and results in a decrease in the proportion (e.g. number or level) of T_{CM} cells.

Arrangement 310. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an anti-OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of TN cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.

Arrangement 311. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an anti-OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject,

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number

or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.

Arrangement 312. A composition comprising an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an anti-OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of TN cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.

In any of arrangements 309 to 312, in one embodiment, the administration of the combination results in the change in T_N cells and/or T_{CM} cells is as described in arrangements 301 to 305. The In any of arrangements 201 to 211, the anti-OX40 antibody may be as described in any of the aspects, concepts or arrangements described herein. In a particular embodiment, the antibody or fragment thereof is in a format or structure of any of the antibodies and fragments described elsewhere herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein, or any arrangement hereinbelow, and any concept, embodiment, aspect, arrangement or feature describing anti-OX40L antibodies or anti-OX40 antibodies herein applies mutatis mutandis to arrangements 201 to 208). In a particular embodiment, the antibody is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab. In another embodiment, the combination comprises an anti-OX40L antibody which is not oxelumab (having a VH region amino acid sequence of Seq ID No:215 and a VL region amino acid sequence of Seq ID No:214).

The second therapeutic agent is any of those described elsewhere herein, in particular in arrangements 183 to 187 hereinabove.

The methods described in arrangements 301 to 312 are intended to be combinable with the methods of any other arrangement or concept herein, such that there may be a methods wherein different effects on the proportions (e.g. numbers or levels) of Treg, TN, T_{CM} and/or T(eff+mem) may be claimed. The biomarkers described elsewhere herein, e.g. Ki67, and granzyme A may also be combined with the levels of T_N and/or T_{CM} cells.

Immunoconjugates

The invention encompasses the antibody or fragment conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxin agents include any agent that is detrimental to cells. Examples of suitable cytotoxin agents and chemotherapeutic agents for forming immunoconjugates are known in the art, see for example, WO 05/103081, which is incorporated by reference herein in its entirety.

Bispecifics

The antibodies and fragments of the present invention may be monospecific, bispecific, or multispecific. Multispecific mAbs may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., (1991) J. Immunol. 147:60-69. The human anti-hOX40L antibodies or fragments can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment, to produce a bispecific or a multispecific antibody with a second binding specificity.

An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig CH3 domain binds Protein A and the second Ig CH3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second CH3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 include: D16E, L18M, N44S, K52N, V57M, and V821 (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N3845, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

In certain embodiments, the antibody or OX40L binding fragment thereof comprises less than six CDRs. In some embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3. In specific embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No: 102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No: 104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID

No:92, Seq ID No:114 or Seq ID No: 120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3).

In specific embodiments, an antibody of the invention is a fully human antibody, a monoclonal antibody, a recombinant antibody, an antagonist antibody, a hOX40L-neutralising antibody or any combination thereof or the invention provides a hOX40L binding fragment thereof. In an example, the antibody is a chimaeric antibody comprising human variable domains and non-human (e.g., mouse or rat or rabbit) constant domains. In particular embodiments, the antibody is a fully human antibody, such as a fully human monoclonal antibody, or antigen binding fragment thereof, that specifically binds to hOX40L. In preferred embodiments, the antibody is an antagonist antibody. In preferred embodiments, the antibody is a neutralising antibody.

In an example, the antibody or fragment is a lambda-type antibody or fragment (i.e., whose variable domains are lambda variable domains). Optionally, the antibody or fragment also comprises lambda constant domains.

In certain embodiments, the antibody competes (e.g., in a dose dependent manner) with OX40 or a fusion protein thereof (e.g., Fc:OX40), for binding to hOX40L, such as a cell surface-expressed hOX40L or soluble hOX40L. Exemplary competitive blocking tests are provided in the Examples herein.

In another aspect, provided herein are isolated nucleic acids encoding antibodies that specifically bind to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L), a hOX40L polypeptide fragment, or a hOX40L epitope. In certain embodiments, the nucleic acid encodes a VH chain, VL chain, VH domain, VL domain, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 as disclosed in the sequence listing (i.e. Seq ID No:30 or Seq ID No:62 for VH chains; Seq ID No:32 or Seq ID No:64 for VL chains; Seq ID No: Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34 for VH domains; Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48 for VL domains; Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No: 104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No: 114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3).

In another aspect, provided herein are vectors and host-cells comprising nucleic acids encoding antibodies or fragments of the invention.

In certain embodiments, the antibody specifically binds to one or more single nucleotide polymorphism (SNP) variants of hOX40L. In an example of any aspect of the invention, the hOX40L is a trimer of monomers.

In an aspect, provided herein is a method for decreasing (e.g., by at least 20, 30, 40 50 or 60%, or 70%, 80%, 90%, 95% or >90%) or completely inhibiting binding of hOX40L to OX40 in a subject (e.g., a human subject), comprising administering to the subject an effective amount of an antibody or fragment thereof of the invention that specifically binds to hOX40L (e.g., a cell surface-expressed or soluble hOX40L).

In an aspect, provided herein is a method of treating or preventing a hOX40L-mediated disease or condition in a subject (e.g., a human subject), the method comprising administering to the subject an effective amount of an antibody or fragment thereof of the invention that specifically binds to hOX40L (e.g., a cell surface-expressed or soluble hOX40L), wherein the disease or condition is treated or prevented by the antibody or fragment. In an example, the method comprises decreasing or inhibiting a hOX40L biological activity, such as secretion of one, more or all of IL-2, IL-8, TNF alpha and interferon gamma, in the subject. In an example, the biological activity is selected from the secretion of one, more or all of IL-2, TNF alpha and interferon gamma. In an example, the biological activity is selected from the secretion of one, more or all of IL-8, CCL20 and RANTES.

In an aspect, provided herein is a method of decreasing or inhibiting a hOX40L biological activity, such as secretion of one, more or all of IL-2, IL-8, TNF alpha and interferon gamma, in a subject (e.g., a human subject), the method comprising administering to the subject an effective amount of an antibody or fragment thereof of the invention that specifically binds to hOX40L (e.g., a cell surface-expressed or soluble hOX40L), wherein hOX40L biological activity is decreased by the antibody or fragment. In an example, the biological activity is selected from the secretion of one, more or all of IL-2, TNF alpha and interferon gamma. In an example, the biological activity is selected from the secretion of one, more or all of IL-8, CCL20 and RANTES.

The term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% (or 4%, or 3% or 2%, or, in an example, 1% or less) of a given value or range.

As used herein, "administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (e.g., an anti-hOX40L antibody provided herein) into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, or a symptom thereof, is being treated, administration of the substance typically occurs after the onset of the disease or symptoms thereof. When a disease, or symptoms thereof, are being prevented, administration of the substance typically occurs before the onset of the disease or symptoms thereof.

To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=number of identical overlapping positions/total number of positions×100%). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences (e.g., amino acid sequences or nucleic acid sequences) can also be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, e.g., for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the present invention. BLAST protein searches can be performed with the XBLAST program parameters set, e.g., to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule of the present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, Nucleic Acids Res. 25:3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (Id.). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (e.g., of XBLAST and NBLAST) can be used (see, e.g., National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

As used herein, an "antagonist" or "inhibitor" of hOX40L refers to a ligand (e.g., antibody or fragment) that is capable of inhibiting or otherwise decreasing one or more of the biological activities of hOX40L, such as in a cell expressing hOX40L or in a cell expressing a hOX40L ligand. For example, in certain embodiments, antibodies of the invention are antagonist antibodies that inhibit or otherwise decrease secretion of CCL20, IL-8 and/or RANTES from a cell having a cell surface-expressed OX40 when said antibody is contacted with said cell. In some embodiments, an antagonist of hOX40L (e.g., an antagonistic antibody of the invention) may, for example, act by inhibiting or otherwise decreasing the activation and/or cell signalling pathways of the cell expressing OX40L, thereby inhibiting a hOX40L-mediated biological activity of the cell the relative to the hOX40L-mediated biological activity in the absence of antagonist. In certain embodiments, the antibodies provided herein are fully human, antagonistic anti-hOX40L antibodies, preferably fully human, monoclonal, antagonistic anti-hOX40L antibodies.

The term "antibody" and "immunoglobulin" or "Ig" may be used interchangeably herein. An antibody or a fragment thereof that specifically binds to a hOX40L antigen may be cross-reactive with related antigens. Preferably, an antibody or a fragment thereof that specifically binds to a hOX40L antigen does not cross-react with other antigens (but may optionally cross-react with OX40L of a different species, e.g., rhesus, or murine). An antibody or a fragment thereof that specifically binds to a hOX40L antigen can be identified, for example, by immunoassays, BIAcore™, or other techniques known to those of skill in the art. An antibody or a fragment thereof binds specifically to a hOX40L antigen when it binds to a hOX40L antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). Typically a specific or selective reaction will be at least twice background signal or noise and more typically more than 10 times background. See, e.g., Paul, ed., 1989, Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 for a discussion regarding antibody specificity.

Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (e.g., including monospecific, bispecific, etc.), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. In particular, antibodies of the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., antigen binding domains or molecules that contain an antigen-binding site that specifically binds to a hOX40L antigen (e.g., one or more complementarity determining regions (CDRs) of an anti-hOX40L antibody). The antibodies of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2, in particular IgG4), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule. In preferred embodiments, the hOX40L antibodies are fully human, such as fully human monoclonal hOX40L antibodies. In certain embodiments, antibodies of the invention are IgG antibodies, or a class (e.g., human IgG1 or IgG4) or subclass thereof. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

The term "antigen binding domain," "antigen binding region," "antigen binding fragment," and similar terms refer to that portion of an antibody which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (e.g., the complementarity determining regions (CDRs)). The antigen binding region can be derived from any animal species, such as rodents (e.g., rabbit, rat or hamster) and humans. Preferably, the antigen binding region will be of human origin.

As used herein, the term "composition" is intended to encompass a product containing the specified ingredients (e.g., an antibody of the invention) in, optionally, the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in, optionally, the specified amounts.

In the context of a polypeptide, the term "derivative" as used herein refers to a polypeptide that comprises an amino acid sequence of a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or an antibody that specifically binds to a hOX40L polypeptide which has been altered by the

introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or an antibody that specifically binds to a hOX40L polypeptide which has been chemically modified, e.g., by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody may be chemically modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. The derivatives are modified in a manner that is different from naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide. A derivative of a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody may be chemically modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody described herein.

The term "effective amount" as used herein refers to the amount of a therapy (e.g., an antibody or pharmaceutical composition provided herein) which is sufficient to reduce and/or ameliorate the severity and/or duration of a given disease and/or a symptom related thereto. This term also encompasses an amount necessary for the reduction or amelioration of the advancement or progression of a given disease, reduction or amelioration of the recurrence, development or onset of a given disease, and/or to improve or enhance the prophylactic or therapeutic effect(s) of another therapy (e.g., a therapy other than anti-hOX40L antibody provided herein). In some embodiments, the effective amount of an antibody of the invention is from about 0.1 mg/kg (mg of antibody per kg weight of the subject) to about 100 mg/kg. In certain embodiments, an effective amount of an antibody provided therein is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg (or a range therein). In some embodiments, "effective amount" as used herein also refers to the amount of an antibody of the invention to achieve a specified result (e.g., inhibition of a hOX40L biological activity of a cell, such as inhibition of secretion of CCL20, IL-8 or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ from the cell).

The term "epitope" as used herein refers to a localized region on the surface of an antigen, such as hOX40L polypeptide or hOX40L polypeptide fragment, that is capable of being bound to one or more antigen binding regions of an antibody, and that has antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human, that is capable of eliciting an immune response. An epitope having immunogenic activity is a portion of a polypeptide that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of a polypeptide to which an antibody specifically binds as determined by any method well known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. A region of a polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide. The epitope may or may not be a three-dimensional surface feature of the antigen. In certain embodiments, a hOX40L epitope is a three-dimensional surface feature of a hOX40L polypeptide (e.g., in a trimeric form of a hOX40L polypeptide). In other embodiments, a hOX40L epitope is linear feature of a hOX40L polypeptide (e.g., in a trimeric form or monomeric form of the hOX40L polypeptide). Antibodies provided herein may specifically bind to an epitope of the monomeric (denatured) form of hOX40L, an epitope of the trimeric (native) form of hOX40L, or both the monomeric (denatured) form and the trimeric (native) form of hOX40L. In specific embodiments, the antibodies provided herein specifically bind to an epitope of the trimeric form of hOX40L but do not specifically bind the monomeric form of hOX40L.

The term "excipients" as used herein refers to inert substances which are commonly used as a diluent, vehicle, preservatives, binders, or stabilizing agent for drugs and includes, but not limited to, proteins (e.g., serum albumin, etc.), amino acids (e.g., aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, etc.), fatty acids and phospholipids (e.g., alkyl sulfonates, caprylate, etc.), surfactants (e.g., SDS, polysorbate, nonionic surfactant, etc.), saccharides (e.g., sucrose, maltose, trehalose, etc.) and polyols (e.g., mannitol, sorbitol, etc.). See, also, Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa., which is hereby incorporated by reference in its entirety.

In the context of a peptide or polypeptide, the term "fragment" as used herein refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may, for example, result from alternative RNA splicing or from in vivo protease activity. In certain embodiments, hOX40L fragments include polypeptides comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least contiguous 100 amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, or at least 250 contiguous amino acid residues of the amino acid sequence of a hOX40L polypeptide or an antibody that specifically binds to a hOX40L polypeptide. In a specific embodiment, a fragment of a hOX40L polypeptide or an antibody that specifically binds to a hOX40L antigen retains at least 1, at least 2, or at least 3 functions of the polypeptide or antibody.

The terms "fully human antibody" or "human antibody" are used interchangeably herein and refer to an antibody that comprises a human variable region and, most preferably a human constant region. In specific embodiments, the terms refer to an antibody that comprises a variable region and constant region of human origin. "Fully human" anti-hOX40L antibodies, in certain embodiments, can also encompass antibodies which bind hOX40L polypeptides and are encoded by nucleic acid sequences which are naturally occurring somatic variants of human germline immunoglobulin nucleic acid sequence. In a specific embodiment, the anti-hOX40L antibodies provided herein are fully human antibodies. The term "fully human antibody" includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Exemplary methods of producing fully human antibodies are provided, e.g., in the Examples herein, but any method known in the art may be used.

The phrase "recombinant human antibody" includes human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (e.g., a mouse or cow) that is transgenic and/or transchromosomal for human immunoglobulin genes (see e.g., Taylor, L. D. et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies can have variable and constant regions derived from human germline immunoglobulin sequences (See Kabat, E. A. et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivosomatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

The term "fusion protein" as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (i.e., a polypeptide or protein not normally a part of the antibody (e.g., a non-anti-hOX40L antigen antibody)). The term "fusion" when used in relation to hOX40L or to an anti-hOX40L antibody refers to the joining of a peptide or polypeptide, or fragment, variant and/or derivative thereof, with a heterologous peptide or polypeptide. Preferably, the fusion protein retains the biological activity of the hOX40L or anti-hOX40L antibody. In certain embodiments, the fusion protein comprises a hOX40L antibody VH domain, VL domain, VH CDR (one, two or three VH CDRs), and/or VL CDR (one, two or three VL CDRs), wherein the fusion protein specifically binds to a hOX40L epitope.

The term "heavy chain" when used in reference to an antibody refers to five distinct types, called alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant domain. These distinct types of heavy chains are well known and give rise to five classes of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG1, IgG3 and IgG4. Preferably the heavy chain is a human heavy chain. In one example, the heavy chain is a disabled IgG isotype, e.g. a disabled IgG4. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

The term "host" as used herein refers to an animal, preferably a mammal, and most preferably a human.

The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

The term "immunomodulatory agent" and variations thereof including, but not limited to, immunomodulatory agents, as used herein refer to an agent that modulates a host's immune system.

In certain embodiments, an immunomodulatory agent is an immunosuppressant agent. In certain other embodiments, an immunomodulatory agent is an immunostimulatory agent. In accordance with the invention, an immunomodulatory agent used in the combination therapies of the invention does not include an anti-hOX40L antibody or antigen-binding fragment. Immunomodulatory agents include, but are not limited to, small molecules, peptides, polypeptides, proteins, fusion proteins, antibodies, inorganic molecules, mimetic agents, and organic molecules.

As used herein, the term "in combination" in the context of the administration of other therapies refers to the use of more than one therapy. The use of the term "in combination" does not restrict the order in which therapies are administered to a subject with a disease. A first therapy can be administered before (e.g., 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks), concurrently, or after (e.g., 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks) the administration of a second therapy to a subject which had, has, or is susceptible to a hOX40L-mediated disease. Any additional therapy can be administered in any order with the other additional therapies. In certain embodiments, the antibodies of the invention can be administered in combination with one or more therapies (e.g., therapies that are not the antibodies of the invention that are currently administered to prevent, treat, manage, and/or ameliorate a hOX40L-mediated disease. Non-limiting examples of therapies that can be administered in combination with an antibody of the invention include analgesic agents, anesthetic agents, antibiotics, or immunomodulatory agents or any other agent listed in the U.S. Pharmacopoeia and/or Physician's Desk Reference.

An "isolated" or "purified" antibody is for example substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the

antibody is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the antibody is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a preferred embodiment, antibodies of the invention are isolated or purified.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a specific embodiment, a nucleic acid molecule(s) encoding an antibody of the invention is isolated or purified.

The term "human OX40L," "hOX40L" or "hOX40L polypeptide" and similar terms refers to the polypeptides ("polypeptides," "peptides" and "proteins" are used interchangeably herein) comprising the amino acid sequence in the sequence listing and related polypeptides, including SNP variants thereof. Related polypeptides include allelic variants (e.g., SNP variants); splice variants; fragments; derivatives; substitution, deletion, and insertion variants; fusion polypeptides; and interspecies homologs, preferably, which retain hOX40L activity and/or are sufficient to generate an anti-hOX40L immune response. Also encompassed are soluble forms of hOX40L which are sufficient to generate an anti-hOX40L immunological response. As those skilled in the art will appreciate, an anti-hOX40L antibody of the invention can bind to a hOX40L polypeptide, polypeptide fragment, antigen, and/or epitope, as an epitope is part of the larger antigen, which is part of the larger polypeptide fragment, which, in turn, is part of the larger polypeptide hOX40L can exist in a trimeric (native) or monomeric (denatured) form.

The terms "Kabat numbering," and like terms are recognized in the art and refer to a system of numbering amino acid residues which are more variable (i.e. hypervariable) than other amino acid residues in the heavy chain variable regions of an antibody, or an antigen binding portion thereof (Kabat et al. (1971) Ann. NY Acad. Sci. 190:382-391 and, Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region typically ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3.

The term "monoclonal antibody" refers to an antibody obtained from a population of homogenous or substantially homogeneous antibodies, and each monoclonal antibody will typically recognize a single epitope on the antigen. In preferred embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single hybridoma or other cell, wherein the antibody specifically binds to only a hOX40L epitope as determined, e.g., by ELISA or other antigen-binding or competitive binding assay known in the art or in the Examples provided herein. The term "monoclonal" is not limited to any particular method for making the antibody. For example, monoclonal antibodies of the invention may be made by the hybridoma method as described in Kohler et al.; Nature, 256:495 (1975) or may be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel et al., eds., John Wiley and Sons, New York). Other exemplary methods of producing other monoclonal antibodies are provided in the Examples herein.

The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated by a human being.

The term "pharmaceutically acceptable" as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

"Polyclonal antibodies" as used herein refers to an antibody population generated in an immunogenic response to a protein having many epitopes and thus includes a variety of different antibodies directed to the same and to different epitopes within the protein. Methods for producing polyclonal antibodies are known in the art (See, e.g., see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel et al., eds., John Wiley and Sons, New York).

As used herein, the term "polynucleotide," "nucleotide," nucleic acid" "nucleic acid molecule" and other similar terms are used interchangeable and include DNA, RNA, mRNA and the like.

As used herein, the terms "prevent," "preventing," and "prevention" refer to the total or partial inhibition of the development, recurrence, onset or spread of a hOX40L-mediated disease and/or symptom related thereto, resulting from the administration of a therapy or combination of therapies provided herein (e.g., a combination of prophylactic or therapeutic agents, such as an antibody of the invention).

As used herein, the term "prophylactic agent" refers to any agent that can totally or partially inhibit the development, recurrence, onset or spread of a hOX40L-mediated disease and/or symptom related thereto in a subject. In certain embodiments, the term "prophylactic agent" refers to an antibody of the invention. In certain other embodiments, the term "prophylactic agent" refers to an agent other than an antibody of the invention. Preferably, a prophylactic agent is an agent which is known to be useful to or has been or is currently being used to prevent a hOX40L-mediated disease and/or a symptom related thereto or impede the onset, development, progression and/or severity of a

hOX40L-mediated disease and/or a symptom related thereto. In specific embodiments, the prophylactic agent is a fully human anti-hOX40L antibody, such as a fully human anti-hOX40L monoclonal antibody.

In an embodiment, the prophylaxis prevents the onset of the disease or condition or of the symptoms of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening, or onset, of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening of the disease or condition.

In another embodiment, an anti-OX40L antibody of the invention is administered intravenously (e.g. before or concomitantly with a transplant, e.g. blood or organ transplant). In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered at a dose selected from about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg, in particular about 1 mg/kg, or about 3 mg/kg.

In another embodiment, said antibody is administered 1-4 days before transplant (e.g. of blood or organs), e.g. 1-3 days before transplant or 1-2 days before transplant. In another embodiment, said antibody is administered weekly, bi-weekly or monthly following transplant, e.g. bi-weekly. In a further embodiment, said antibody is administered intravenously prophylactically 1-3 days before transplant at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg) and then intravenously, bi-weekly at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg).

In another embodiment, the patient is monitored periodically post-transplant, for the presence of a biomarker predictive for the development of transplant rejection or of GvHD (e.g. acute GvHD), and the anti-OX40L antibody of the invention is administered once the biomarker levels are such that the patient is determined to be at risk of developing transplant rejection or of GvHD (e.g. acute GvHD). This strategy would avoid unnecessary dosing of drug and unnecessary suppression of the immune system. Examples of biomarkers which may be useful as predictive biomarkers of actue GvHD may be those identified in Levine et al., "A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study", Lancet Haematol 2015; 2:e21-29. These biomarkers include, but are not limited to TNFR1, ST-2, elafin and IL2Rα and Reg3α.

A region of a hOX40L contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide. The epitope may or may not be a three-dimensional surface feature of the antigen. A localized region on the surface of a hOX40L antigen that is capable of eliciting an immune response is a hOX40L epitope. The epitope may or may not be a three-dimensional surface feature of the antigen.

A "hOX40L-mediated disease" and "hOX40L-mediated condition" are used interchangeably and refer to any disease or condition that is completely or partially caused by or is the result of hOX40L. In certain embodiments, hOX40L is aberrantly (e.g., highly) expressed on the surface of a cell. In some embodiments, hOX40L may be aberrantly upregulated on a particular cell type. In other embodiments, normal, aberrant or excessive cell signalling is caused by binding of hOX40L to a hOX40L ligand. In certain embodiments, the hOX40L ligand is OX40, for example, that is expressed on the surface of a cell, such as a colonic epithelial cell. In certain embodiments, the hOX40L-mediated disease is an inflammatory bowel disease (IBD), such as Crohn's disease (CD) or ulcerative colitis (UC). In other embodiments, the hOX40L-mediated disease is graft-versus-host disease (GVHD). In other embodiments, the hOX40L-mediated disease is selected from pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis and uveitis (non-infectious/autoimmune and/or systemic). In other embodiments, a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

The terms "hOX40L receptor" or "hOX40L binding receptor" are used interchangeably herein and refer to a receptor polypeptide that binds to hOX40L. In specific embodiments, the hOX40L receptor is Hox40. In some embodiments, the hOX40L receptor is expressed on the surface of a cell, such as a colonic epithelial cell; or on graft or transplant tissue or on host tissue.

As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, a subject is preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats, etc.) or a primate (e.g., monkey and human), most preferably a human. In one embodiment, the subject is a mammal, preferably a human, having a hOX40L-mediated disease. In another embodiment, the subject is a mammal, preferably a human, at risk of developing a hOX40L-mediated disease.

As used herein "substantially all" refers to refers to at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100%.

The term "substantially free of surfactant" as used herein refers to a formulation of an antibody that specifically binds to a hOX40L antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants and/or less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants.

The term "substantially free of salt" as used herein refers to a formulation of an antibody that specifically binds to a hOX40L antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of inorganic salts.

The term "surfactant" as used herein refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and nonionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

As used herein, the term "tag" refers to any type of moiety that is attached to, e.g., a polypeptide and/or a polynucleotide that encodes a hOX40L or hOX40L antibody or antigen binding fragment thereof. For example, a polynucleotide that encodes a hOX40L, hOX40L antibody or antigen binding fragment thereof can contain one or more additional tag-encoding nucleotide sequences that encode a, e.g., a

detectable moiety or a moiety that aids in affinity purification. When translated, the tag and the antibody can be in the form of a fusion protein. The term "detectable" or "detection" with reference to a tag refers to any tag that is capable of being visualized or wherein the presence of the tag is otherwise able to be determined and/or measured (e.g., by quantitation). A non-limiting example of a detectable tag is a fluorescent tag.

As used herein, the term "therapeutic agent" refers to any agent that can be used in the treatment, management or amelioration of a hOX40L-mediated disease and/or a symptom related thereto. In certain embodiments, the term "therapeutic agent" refers to an antibody of the invention. In certain other embodiments, the term "therapeutic agent" refers to an agent other than an antibody of the invention. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management or amelioration of a hOX40L-mediated disease or one or more symptoms related thereto. In specific embodiments, the therapeutic agent is a fully human anti-hOX40L antibody, such as a fully human anti-hOX40L monoclonal antibody.

The combination of therapies (e.g., use of prophylactic or therapeutic agents) which is more effective than the additive effects of any two or more single therapies. For example, a synergistic effect of a combination of prophylactic and/or therapeutic agents permits the use of lower dosages of one or more of the agents and/or less frequent administration of said agents to a subject with a hOX40L-mediated disease. The ability to utilize lower dosages of prophylactic or therapeutic therapies and/or to administer said therapies less frequently reduces the toxicity associated with the administration of said therapies to a subject without reducing the efficacy of said therapies in the prevention, management, treatment or amelioration of a hOX40L-mediated disease. In addition, a synergistic effect can result in improved efficacy of therapies in the prevention, or in the management, treatment or amelioration of a hOX40L-mediated disease. Finally, synergistic effect of a combination of therapies (e.g., prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of any single therapy.

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat. In another embodiment the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

In some embodiments the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

In further embodiments the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basilixumab, daclizumab). In another embodiment, the immunosuppressant is an anti-IL-2 antibody or an anti-IL2R antibody.

Without being bound by theory, it is thought that the mechanism of action of an anti-OX40L antibody of the invention is complementary to further therapeutic agents which modulate immune function. In particular, agents that modulate IL-2 signalling or that inhibit IL-2/IL-2R-mediated T-cell proliferation may synergistically combine with an anti-OX40L antibody resulting in greater immune modulation than would be observed with either agent alone. As shown in Examples 7 and 9 hereinbelow, both tacrolimus and rapamycin display immune modulating activity. Tacrolimus and rapamycin are both agents which are known to modulate IL-2 signalling. In particular, rapamycin is known to act as an mTOR inhibitor, which reduces IL-2 and IL2R transcription, and inhibits cell cycle progression evoked by IL2R activation, but there may be other mechanisms on proliferation of T-cells by which mTOR inhibitors may function (Thomson et al, Nat. Rev. Immunol., 2009, 9(5), 324-337; Scheffert & Raza, J. Thorac. Dis., 2014, 6(8), 1039-1053). FIG. **6** herein shows that the mechanism of an anti-OX40L antibody is different with regards to Tscm population to both these agents, and FIG. **7** shows a synergistic effect on survival of an anti-OX40L antibody of the invention in combination with rapamycin. It is therefore thought that other agents having a similar mechanism of action to rapamycin and/or tacrolimus will also result in a synergistic effect when used in combination with the anti-OX40L antibodies of the invention.

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and rapamycin (sirolimus).

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus. In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a combination of tacrolimus and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cyclophosphamide. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and mycophenolate mofetil.

As used herein, the term "therapy" refers to any protocol, method and/or agent that can be used in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease (e.g., IBD or GVHD). In certain embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies

useful in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease known to one of skill in the art such as medical personnel.

As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of a hOX40L-mediated disease (e.g., IBD or GVHD) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents, such as an antibody of the invention). In specific embodiments, such terms refer to the reduction or inhibition of the binding of hOX40L to OX40, the reduction or inhibition of the production or secretion of CCL20 from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of IL-8 from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of RANTES from a cell expressing hOX40 or hOX40L, and/or the inhibition or reduction of one or more symptoms associated with a hOX40L-mediated disease, such as an IBD or GVHD. In specific embodiments, such terms refer to the reduction or inhibition of the binding of hOX40L to OX40, the reduction or inhibition of the production or secretion of INF-γ from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of TNF-α from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of IL-2 from a cell expressing hOX40 or hOX40L, and/or the inhibition or reduction of one or more symptoms associated with a hOX40L-mediated disease, such as an IBD or GVHD (in particular GvHD). In an example, the cell is a human cell. In specific embodiments, a prophylactic agent is a fully human anti-hOX40L antibody, such as a fully human anti-hOX40L monoclonal antibody.

The term "variable region" or "variable domain" refers to a portion of the OX40L and heavy chains, typically about the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complimentarily determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). The CDRs of the OX40L and heavy chains are primarily responsible for the interaction of the antibody with antigen. Numbering of amino acid positions used herein is according to the EU Index, as in Kabat et al. (1991) Sequences of proteins of immunological interest. (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed. ("Kabat et al."). In preferred embodiments, the variable region is a human variable region.

Antibodies

Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (e.g., including monospecific, bispecific, etc.), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds to a hOX40L antigen. The immunoglobulin molecules provided herein can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In a specific embodiment, an antibody provided herein is an IgG antibody, preferably an IgG1 or IgG4. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

Variants and derivatives of antibodies include antibody fragments that retain the ability to specifically bind to an epitope. Preferred fragments include Fab fragments; Fab' (an antibody fragment containing a single anti-binding domain comprising an Fab and an additional portion of the heavy chain through the hinge region); F(ab')2 (two Fab' molecules joined by interchain disulfide bonds in the hinge regions of the heavy chains; the Fab' molecules may be directed toward the same or different epitopes); a bispecific Fab (a Fab molecule having two antigen binding domains, each of which may be directed to a different epitope); a single chain Fab chain comprising a variable region, also known as, a sFv; a disulfide-linked Fv, or dsFv; a camelized VH (the variable, antigen-binding determinative region of a single heavy chain of an antibody in which some amino acids at the VH interface are those found in the heavy chain of naturally occurring camel antibodies); a bispecific sFv (a sFv or a dsFv molecule having two antigen-binding domains, each of which may be directed to a different epitope); a diabody (a dimerized sFv formed when the VH domain of a first sFv assembles with the VL domain of a second sFv and the VL domain of the first sFv assembles with the VH domain of the second sFv; the two antigen-binding regions of the diabody may be directed towards the same or different epitopes); and a triabody (a trimerized sFv, formed in a manner similar to a diabody, but in which three antigen-binding domains are created in a single complex; the three antigen binding domains may be directed towards the same or different epitopes). Derivatives of antibodies also include one or more CDR sequences of an antibody combining site. The CDR sequences may be linked together on a scaffold when two or more CDR sequences are present. In certain embodiments, the antibody to be used with the invention comprises a single-chain Fv ("scFv"). scFvs are antibody fragments comprising the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFvs see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

The antibodies of the invention may be from any animal origin including birds and mammals (e.g., human, murine, donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken). In certain embodiments, the antibodies of the invention are human or humanized monoclonal antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from mice that express antibodies from human genes.

In preferred embodiments, the antibodies of the invention are fully human antibodies, such as fully human antibodies

that specifically bind a hOX40L polypeptide, a hOX40L polypeptide fragment, or a hOX40L epitope. Such fully human antibodies would be advantageous over fully mouse (or other full or partial non-human species antibodies), humanized antibodies, or chimeric antibodies to minimize the development of unwanted or unneeded side effects, such as immune responses directed toward non-fully human antibodies (e.g., anti-hOX40L antibodies derived from other species) when administered to the subject.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a hOX40L polypeptide or may be specific for both a hOX40L polypeptide as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. In preferred embodiments, the antibodies provided herein are monospecific for a given epitope of a hOX40L polypeptide and do not specifically bind to other epitopes.

Also provided herein is a B-cell (e.g., an immortalised B-cell) or a hybridoma that produces an anti-hOX40L antibody or fragment described herein.

In certain embodiments, an isolated antibody is provided herein that specifically binds to a hOX40L epitope wherein the binding to the hOX40L epitope by the antibody is competitively blocked (e.g., in a dose-dependent manner) by an antibody or fragment of the invention. The antibody may or may not be a fully human antibody. In preferred embodiments, the antibody is a fully human monoclonal anti-hOX40L antibody, and even more preferably a fully human, monoclonal, antagonist anti-hOX40L antibody. Exemplary competitive blocking tests that can be used are provided in the Examples herein.

In some embodiments, the antibody or fragment of the invention competes (e.g., in a dose-dependent manner) with OX40 Receptor (or a fusion protein thereof) for binding to cell surface-expressed hOX40L. In other embodiments, the antibody or fragment of the invention competes (e.g., in a dose-dependent manner) with OX40 Receptor (or a fusion protein thereof) for binding to soluble hOX40L. Exemplary competitive binding assays that can be used are provided in the Examples herein. In one embodiment, the antibody or fragment partially or completely inhibits binding of hOX40 to cell surface-expressed OX40L, such as hOX40L. In another embodiment, the antibody partially or completely inhibits binding of hOX40 to soluble hOX40L. In some embodiments, the antibody or fragment partially or completely inhibits the secretion of CCL20, IL-8, and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ from a cell having cell surface-expressed OX40. In certain embodiments, the cell expressing the OX40 is a colonic epithelial cell.

Preferably, the antibodies of the invention are fully human, monoclonal antibodies, such as fully human, monoclonal antagonist antibodies, that specifically bind to hOX40L.

In some embodiments, the antibody or fragment provided herein binds to a hOX40L epitope that is a three-dimensional surface feature of a hOX40L polypeptide (e.g., in a trimeric form of a hOX40L polypeptide). A region of a hOX40L polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide A hOX40L epitope may be present in (a) the trimeric form ("a trimeric hOX40L epitope") of hOX40L, (b) the monomeric form ("a monomeric hOX40L epitope") of hOX40L, (c) both the trimeric and monomeric form of hOX40L, (d) the trimeric form, but not the monomeric form of hOX40L, or (e) the monomeric form, but not the trimeric form of hOX40L.

For example, in some embodiments, the epitope is only present or available for binding in the trimeric (native) form, but is not present or available for binding in the monomeric (denatured) form by an anti-hOX40L antibody. In other embodiments, the hOX40L epitope is linear feature of the hOX40L polypeptide (e.g., in a trimeric form or monomeric form of the hOX40L polypeptide). Antibodies provided herein may specifically bind to (a) an epitope of the monomeric form of hOX40L, (b) an epitope of the trimeric form of hOX40L, (c) an epitope of the monomeric but not the trimeric form of hOX40L, (d) an epitope of the trimeric but not the monomeric form of hOX40L, or (e) both the monomeric form and the trimeric form of hOX40L. In preferred embodiments, the antibodies provided herein specifically bind to an epitope of the trimeric form of hOX40L but do not specifically bind to an epitope the monomeric form of hOX40L.

The present invention also provides antibodies that specifically bind to a hOX40L epitope, the antibodies comprising derivatives of the VH domains, VH CDRs, VL domains, and VL CDRs described herein that specifically bind to a hOX40L antigen. The present invention also provides antibodies comprising derivatives of antibodies disclosed in the Examples, wherein said antibodies specifically bind to a hOX40L epitope. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In another embodiment, the derivatives have conservative amino acid substitutions. In a preferred embodiment, the derivatives have conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

In another embodiment, an antibody that specifically binds to a hOX40L epitope comprises a variable domain amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a variable domain amino acid sequence of the

SEQUENCE LISTING

In specific embodiments, the antibody is a fully human anti-human antibody, such as a fully human monoclonal antibody. Fully human antibodies may be produced by any method known in the art. Exemplary methods include immunization with a hOX40L antigen (any hOX40L polypeptide capable of eliciting an immune response, and optionally conjugated to a carrier) of transgenic animals (e.g., mice) that are capable of producing a repertoire of

human antibodies in the absence of endogenous immunoglobulin production; see, e.g., Jakobovits et a., (1993) Proc. Natl. Acad. Sci., 90:2551; Jakobovits et al., (1993) Nature, 362:255 258 (1993); Bruggermann et al., (1993) Year in Immunol., 7:33. Other methods of producing fully human anti-hOX40L antibodies can be found in the Examples provided herein.

Alternatively, fully human antibodies may be generated through the in vitro screening of phage display antibody libraries; see e.g., Hoogenboom et al, J. Mol. Biol., 227:381 (1991); Marks et al, J. Mol. Biol., 222:581 (1991), incorporated herein by reference. Various antibody-containing phage display libraries have been described and may be readily prepared by one skilled in the art. Libraries may contain a diversity of human antibody sequences, such as human Fab, Fv, and scFv fragments, that may be screened against an appropriate target.

The antibodies and fragments of the invention include antibodies and fragments that are chemically modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, but not by way of limitation, the antibody derivatives include antibodies that have been chemically modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Additionally, the antibody may contain one or more non-classical amino acids.

The present invention also provides antibodies that specifically bind to a hOX40L antigen which comprise a framework region known to those of skill in the art (e.g., a human or non-human fragment). The framework region may, for example, be naturally occurring or consensus framework regions. Most preferably, the framework region of an antibody of the invention is human (see, e.g., Chothia et al., 1998, J. Mol. Biol. 278:457-479 for a listing of human framework regions, which is incorporated by reference herein in its entirety). See also Kabat et al. (1991) Sequences of Proteins of Immunological Interest (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed.

In a specific embodiment, the present invention provides for antibodies that specifically bind to a hOX40L antigen, said antibodies comprising the amino acid sequence of one or more of the CDRs in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3) and human framework regions with one or more amino acid substitutions at one, two, three or more of the following residues: (a) rare framework residues that differ between the murine antibody framework (i.e., donor antibody framework) and the human antibody framework (i.e., acceptor antibody framework); (b) Vernier zone residues when differing between donor antibody framework and acceptor antibody framework; (c) interchain packing residues at the VH/VL interface that differ between the donor antibody framework and the acceptor antibody framework; (d) canonical residues which differ between the donor antibody framework and the acceptor antibody framework sequences, particularly the framework regions crucial for the definition of the canonical class of the murine antibody CDR loops; (e) residues that are adjacent to a CDR; (g) residues capable of interacting with the antigen; (h) residues capable of interacting with the CDR; and (i) contact residues between the VH domain and the VL domain. In certain embodiments, antibodies that specifically bind to a hOX40L antigen comprising the human framework regions with one or more amino acid substitutions at one, two, three or more of the above-identified residues are antagonistic hOX40L antibodies.

The present invention encompasses antibodies that specifically bind to a hOX40L antigen, said antibodies comprising the amino acid sequence of the VH domain and/or VL domain in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34 for VH domains; Seq ID No: 16, Seq ID No:48, Seq ID No:80, or Seq ID No: 108, in particular Seq ID No:48 for VL domains) but having mutations (e.g., one or more amino acid substitutions) in the framework regions. In certain embodiments, antibodies that specifically bind to a hOX40L antigen comprise the amino acid sequence of the VH domain and/or VL domain or an antigen-binding fragment thereof of an antibody disclosed in the Examples with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains.

In some embodiments, antibodies provided herein decrease or inhibit binding of hOX40L hOX40, and/or decrease or inhibit a hOX40L biological activity, such as secretion of CCL20, IL8 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ, in subject (e.g., a human subject). In certain embodiments, antibodies provided herein, such as a human monoclonal anti-hOX40L antibody, decreases or inhibits binding of a soluble or cell-surface expressed hOX40L to hOX40, and/or decreases or inhibits secretion of CCL20 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ after contact with a soluble or cell-surface expressed hOX40L, in a subject. Blocking activity of an antibody provided herein of hOX40L binding to hOX40 can be detected using an assay as described in the Examples. Inhibition of biological activity of cells expressing OX40 by a hOX40L antibody provided herein can be detected using an assay as described in the Examples.

The present invention also provides for fusion proteins comprising an antibody provided herein that specifically binds to a hOX40L antigen and a heterologous polypeptide. In some embodiments, the heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed hOX40L.

Antibody Conjugates and Fusion Proteins

The following discussion on conjugates and fusion proteins also applies to fragments so that disclosure mentioning antibodies can also apply mutatis mutandis to fragments of the invention.

In some embodiments, antibodies of the invention are conjugated or recombinantly fused to a diagnostic, detectable or therapeutic agent or any other molecule. The con-

jugated or recombinantly fused antibodies can be useful, e.g., for monitoring or prognosing the onset, development, progression and/or severity of a hOX40L-mediated disease as part of a clinical testing procedure, such as determining the efficacy of a particular therapy.

Such diagnosis and detection can be accomplished, for example, by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, and ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, and ^{111}In), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{53}Sm, ^{177}Lu, ^{59}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}p, ^{53}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Sn; and positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

The present invention further encompasses uses of the antibodies of the invention conjugated or recombinantly fused to a therapeutic moiety (or one or more therapeutic moieties). The antibody may be conjugated or recombinantly fused to a therapeutic moiety, such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Therapeutic moieties include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine); alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP), and cisplatin); anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin); antibiotics (e.g., d actinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)); Auristatin molecules (e.g., auristatin PHE, bryostatin 1, and solastatin 10; see Woyke et al., Antimicrob. Agents Chemother. 46:3802-8 (2002), Woyke et al., Antimicrob. Agents Chemother. 45:3580-4 (2001), Mohammad et al., Anticancer Drugs 12:735-40 (2001), Wall et al, Biochem. Biophys. Res. Commun 266: 76-80 (1999), Mohammad et al., Int. J. Oncol. 15:367-72 (1999), all of which are incorporated herein by reference); hormones (e.g., glucocorticoids, progestins, androgens, and estrogens), DNA-repair enzyme inhibitors (e.g., etoposide or topotecan), kinase inhibitors (e.g., compound ST1571, imatinib mesylate (Kantarjian et al., Clin Cancer Res. 8(7): 2167-76 (2002)); cytotoxic agents (e.g., paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogues or homologs thereof and those compounds disclosed in U.S. Pat. Nos. 6,245,759, 6,399,633, 6,383,790, 6,335,156, 6,271,242, 6,242,196, 6,218,410, 6,218,372, 6,057,300, 6,034,053, 5,985,877, 5,958,769, 5,925,376, 5,922,844, 5,911,995, 5,872,223, 5,863,904, 5,840,745, 5,728,868, 5,648,239, 5,587,459); farnesyl transferase inhibitors (e.g., R115777, BMS-214662, and those disclosed by, for example, U.S. Pat. Nos. 6,458,935, 6,451,812, 6,440,974, 6,436,960, 6,432,959, 6,420,387, 6,414,145, 6,410,541, 6,410,539, 6,403,581, 6,399,615, 6,387,905, 6,372,747, 6,369,034, 6,362,188, 6,342,765, 6,342,487, 6,300,501, 6,268,363, 6,265,422, 6,248,756, 6,239,140, 6,232,338, 6,228,865, 6,228,856, 6,225,322, 6,218,406, 6,211,193, 6,187,786, 6,169,096, 6,159,984, 6,143,766, 6,133,303, 6,127,366, 6,124,465, 6,124,295, 6,103,723, 6,093,737, 6,090,948, 6,080,870, 6,077,853, 6,071,935, 6,066,738, 6,063,930, 6,054,466, 6,051,582, 6,051,574, and 6,040, 305); topoisomerase inhibitors (e.g., camptothecin; irinotecan; SN-38; topotecan; 9-aminocamptothecin; GG-211 (GI 147211); DX-8951f; IST-622; rubitecan; pyrazoloacridine; XR-5000; saintopin; UCE6; UCE1022; TAN-1518A; TAN 1518B; KT6006; KT6528; ED-110; NB-506; ED-110; NB-506; and rebeccamycin); bulgarein; DNA minor groove binders such as Hoescht dye 33342 and Hoechst dye 33258; nitidine; fagaronine; epiberberine; coralyne; beta-lapachone; BC-4-1; bisphosphonates (e.g., alendronate, cimadronte, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate) HMG-CoA reductase inhibitors, (e.g., lovastatin, simvastatin, atorvastatin, pravastatin, fluvastatin, statin, cerivastatin, lescol, lupitor, rosuvastatin and atorvastatin); antisense oligonucleotides (e.g., those disclosed in the U.S. Pat. Nos. 6,277,832, 5,998,596, 5,885, 834, 5,734,033, and 5,618,709); adenosine deaminase inhibitors (e.g., Fludarabine phosphate and 2-Chlorodeoxyadenosine); ibritumomab tiuxetan (Zevalin®); tositumomab (Bexxar®)) and pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

Further, an antibody of the invention may be conjugated or recombinantly fused to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, γ-interferon, α-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-γ, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., 1994, J. Immunol., 6:1567-1574), and VEGF (see, International Publication No. WO 99/23105), an anti-angiogenic agent, e.g., angiostatin, endostatin or a component of the coagulation pathway (e.g., tissue factor); or, a biological response modifier such as, for example, a lymphokine (e.g., interferon gamma, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-5 ("IL-5"), interleukin-6 ("IL-6"', interleukin-7 ("IL-7"), interleukin 9 ("IL-9"), interleukin-10 ("IL-10"), interleukin-12 ("IL-12"), interleukin-15 ("IL-15"), interleukin-23 ("IL-23"), granulocyte macrophage colony stimulating factor ("GM-CSF", and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (e.g., growth hormone ("GH")), or a coagulation agent (e.g., calcium, vitamin K, tissue factors, such as but not limited to, Hageman factor (factor XII), high-molecular-weight kininogen (HMWK), prekal-

likrein (PK), coagulation proteins-factors II (prothrombin), factor V, XIIa, VIII, XIIIa, XI, XIa, IX, IXa, X, phospholipid, and fibrin monomer).

The present invention encompasses antibodies of the invention recombinantly fused or chemically conjugated (covalent or non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90 or about 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigen-binding fragment of an antibody of the invention (e.g., a Fab fragment, Fd fragment, Fv fragment, F(ab)2 fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. In one embodiment, the heterologous protein, polypeptide, or peptide that the antibody is fused to is useful for targeting the antibody to a particular cell type, such as a cell that expresses hOX40L or an hOX40L receptor. For example, an antibody that specifically binds to a cell surface receptor expressed by a particular cell type (e.g., an immune cell) may be fused or conjugated to a modified antibody of the invention.

A conjugated or fusion protein of the invention comprises any antibody of the invention described herein and a heterologous polypeptide. In one embodiment, a conjugated or fusion protein of the invention comprises the variable domains of an antibody disclosed in the Examples and a heterologous polypeptide.

In addition, an antibody of the invention can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alpha-emitters such as ^{213}Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{131}In, ^{131}Lu, ^{131}Y, ^{131}Ho, ^{31}Sm, to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7, 10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al, 1998, Clin Cancer Res. 4(10):2483-90; Peterson et al., 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman et al., 1999, Nucl. Med. Biol., 26(8):943-50, each incorporated by reference in their entireties.

Moreover, antibodies of the invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc.), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al, 1984, Cell 37:767), and the "FLAG" tag.

Methods for fusing or conjugating therapeutic moieties (including polypeptides) to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), Thorpe et al., 1982, Immunol. Rev. 62:119-58; U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, 5,723,125, 5,783,181, 5,908,626, 5,844,095, and 5,112,946; EP 307,434; EP 367,166; EP 394,827; PCT publications WO 91/06570, WO 96/04388, WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi et al., Proc. Natl. Acad. Sci. USA, 88: 10535-10539, 1991; Traunecker et al., Nature, 331:84-86, 1988; Zheng et al, J. Immunol., 154:5590-5600, 1995; Vil et al., Proc. Natl. Acad. Sci. USA, 89:11337-11341, 1992, which are incorporated herein by reference in their entireties.

Fusion proteins may be generated, for example, through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention (e.g., antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten et al., 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson et al, 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies, or the encoded antibodies, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

An antibody of the invention can also be conjugated to a second antibody to form an antibody heteroconjugate as described in U.S. Pat. No. 4,676,980, which is incorporated herein by reference in its entirety.

The therapeutic moiety or drug conjugated or recombinantly fused to an antibody of the invention that specifically binds to a hOX40L antigen should be chosen to achieve the desired prophylactic or therapeutic effect(s). In certain embodiments, the antibody is a modified antibody. A clinician or other medical personnel should consider the following when deciding on which therapeutic moiety or drug to conjugate or recombinantly fuse to an antibody of the invention: the nature of the disease, the severity of the disease, and the condition of the subject.

Antibodies of the invention may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Pharmaceutical Compositions

The following discussion on compositions also applies to fragments so that disclosure mentioning antibodies can also apply mutatis mutandis to fragments of the invention.

Therapeutic formulations containing one or more antibodies of the invention provided herein can be prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa.), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipi-

ents at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

The antibodies of the invention provided herein can also, for example, be formulated in liposomes. Liposomes containing the molecule of interest are prepared by methods known in the art, such as described in Epstein et al. (1985) Proc. Natl. Acad. Sci. USA 82:3688; Hwang et al. (1980) Proc. Natl. Acad. Sci. USA 77:4030; and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556.

Particularly useful immunoliposomes can be generated by the reverse phase evaporation method with a lipid composition containing phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of an antibody provided herein can be conjugated to the liposomes as described in Martin et al. (1982) J. Biol. Chem. 257:286-288 via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome; See Gabizon et al., (1989) J. National Cancer Inst. 81(19):1484.

Formulations, such as those described herein, can also contain more than one active compound as necessary for the particular indication being treated. In certain embodiments, formulations comprise an antibody of the invention and one or more active compounds with complementary activities that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. For example, an antibody of the invention can be combined with one or more other therapeutic agents. Such combined therapy can be administered to the patient serially or simultaneously or in sequence.

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat. In another embodiment the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

In some embodiments, the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

In further embodiments, the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basilixumab, daclizumab).

In one embodiment, the combination comprises an anti-OX40L antibody of the invention and rapamycin (sirolimus). In one embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus. In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a combination of tacrolimus and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cyclophosphamide. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and mycophenolate mofetil.

An antibody of the invention can also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa.

The formulations to be used for in vivo administration can be sterile. This is readily accomplished by filtration through, e.g., sterile filtration membranes.

Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antagonist, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(−)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of mol-

ecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C., resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S—S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the antibodies of the invention provided herein, and optionally one or more additional prophylactic of therapeutic agents, in a pharmaceutically acceptable carrier. Such pharmaceutical compositions are useful in the prevention, treatment, management or amelioration of a hOX40L-mediated disease, such as an inflammatory bowl disease, transplant rejection, GvHD or one or more of the symptoms thereof.

Pharmaceutical carriers suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the antibodies of the invention may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients (such as one or more other prophylactic or therapeutic agents).

The compositions can contain one or more antibodies of the invention. In one embodiment, the antibodies are formulated into suitable pharmaceutical preparations, such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. In one embodiment, the antibodies described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, e.g., Ansel (1985) Introduction to Pharmaceutical Dosage Forms, 4th Ed., p. 126).

In the compositions, effective concentrations of one or more antibodies or derivatives thereof is (are) mixed with a suitable pharmaceutical carrier. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates a hOX40L-mediated disease or symptom thereof.

In one embodiment, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected carrier at an effective concentration such that the treated condition is relieved, prevented, or one or more symptoms are ameliorated.

An antibody of the invention is included in the pharmaceutically acceptable carrier in an effective amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration can be determined empirically by testing the compounds in in vitro and in vivo systems using routine methods and then extrapolated therefrom for dosages for humans.

The concentration of antibody in the pharmaceutical composition will depend on, e.g., the physicochemical characteristics of the antibody, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

In one embodiment, a therapeutically effective dosage produces a serum concentration of antibody of from about 0.1 ng/ml to about 50-100 μg/ml. The pharmaceutical compositions, in another embodiment, provide a dosage of from about 0.001 mg to about 2000 mg of antibody per kilogram of body weight per day. Pharmaceutical dosage unit forms can be prepared to provide from about 0.01 mg, 0.1 mg or 1 mg to about 500 mg, 1000 mg or 2000 mg, and in one embodiment from about 10 mg to about 500 mg of the antibody and/or a combination of other optional essential ingredients per dosage unit form.

The antibody can be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and can be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values can also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens can be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Upon mixing or addition of the antibody, the resulting mixture can be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The antibody is, in one embodiment, formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the antibody sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms can be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

In preferred embodiments, one or more anti-hOX40L antibodies of the invention are in a liquid pharmaceutical formulation. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined

above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa.

Dosage forms or compositions containing antibody in the range of 0.005% to 100% with the balance made up from non-toxic carrier can be prepared. Methods for preparation of these compositions are known to those skilled in the art.

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms. In certain embodiments, the formulations are capsules or tablets. The tablets, pills, capsules, troches and the like can contain one or more of the following ingredients, or compounds of a similar nature: a binder; a lubricant; a diluent; a glidant; a disintegrating agent; a colouring agent; a sweetening agent; a flavouring agent; a wetting agent; an emetic coating; and a film coating. Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, molasses, polyinylpyrrolidine, povidone, crospovidones, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Colouring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavours. Flavouring agents include natural flavours extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

The antibodies of the invention can be provided in a composition that protects it/them from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition can also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colourings and flavours.

The antibody can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is an antibody or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

In all embodiments, tablets and capsules formulations can be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

In preferred embodiments, the formulations are liquid dosage forms. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives.

Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Colouring and flavouring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Colouring agents include any of the approved certified water soluble FD and C dyes, and mix-

tures thereof. Flavouring agents include natural flavours extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is, in one embodiment, encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, can be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations can be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Pat. Nos. RE28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

Parenteral administration, in one embodiment, is characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Pat. No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The antibody diffuses through the outer polymeric membrane in a release rate controlling step. The amount of antibody contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anaesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations can be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration can be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. In one embodiment, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, in certain embodiments more than 1% w/w of the active compound to the treated tissue(s).

The antibody can be suspended in micronized or other suitable form. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

In other embodiments, the pharmaceutical formulations are lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

The lyophilized powder is prepared by dissolving an antibody provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4° C. to room temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The antibodies of the invention can be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

The compounds can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts.

Other routes of administration, such as transdermal patches, including iontophoretic and electrophoretic devices, and rectal administration, are also contemplated herein.

Transdermal patches, including iotophoretic and electrophoretic devices, are well known to those of skill in the art. For example, such patches are disclosed in U.S. Pat. Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by moulding. The weight of a rectal suppository, in one embodiment, is about 2 to 3 gm.

Tablets and capsules for rectal administration can be manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

The antibodies and other compositions provided herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, e.g., U.S. Pat. Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874. In some embodiments, the anti-hOX40L antibodies of the invention are targeted (or otherwise administered) to the colon, such as in a patient having or at risk of having an IBD. In some embodiments, the anti-hOX40L antibodies of the invention

are targeted (or otherwise administered) to the eye, such as in a patient having or at risk of having uveitis.

In one embodiment, liposomal suspensions, including tissue-targeted liposomes, such as tumour-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art. For example, liposome formulations can be prepared as described in U.S. Pat. No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

Methods of Administration and Dosing

The present invention further provides for compositions comprising one or more antibodies or fragments of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease (or symptom thereof). Discussion in respect of antibodies also applies mutatis mutandis to fragments of the invention. In an alternative, the present invention further provides for compositions comprising one or more antibodies or fragments of the invention for use in the prevention, management, treatment and/or amelioration of an OX40L-mediated disease (or symptom thereof) in a subject, wherein the OX40L is non-human (e.g., canine, feline, equine, bovine, ovine or porcine) and the subject is respectively a dog, cat, horse, cow, sheep or pig.

In certain embodiments, provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease, such as IBD (e.g., ulcerative colitis or Crohn's disease), or a symptom thereof. IBD symptoms may range from mild to severe and generally depend upon the part of the intestinal tract involved. Exemplary symptoms of IBD include abdominal cramps and pain, bloody diarrhea, severe urgency to have a bowel movement, fever, loss of appetite, weight loss, anemia, fatigue, and/or sores on lower legs, ankles, calves, thighs, and arms. Exemplary intestinal complications of IBD include profuse bleeding from the ulcers, perforation or rupture of the bowel, strictures and obstruction, fistulae (abnormal passage) and perianal disease, toxic megacolon (e.g., acute nonobstructive dilation of the colon), and/or malignancy (e.g., cancer of the colon or small intestine). Exemplary extraintestinal complications of IBD include arthritis, skin conditions, inflammation of the eye, liver and kidney disorders, and/or bone loss. Any combination of these symptoms may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

In certain embodiments, provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of an hOX40L-mediated disease, such as GVHD, or a symptom thereof. GVHD generally occurs following allogeneic or matched unrelated bone marrow transplants (BMT).

In some embodiments, the GVHD is acute GVHD. The symptoms of acute GVHD can happen quickly and can be mild or severe. In certain instances, acute GVHD develops within about three months after transplant, such as when blood counts recover after transplant. It certain instances, the acute GVHD affects the skin, gastrointestinal (GI) tract and/or liver. For example, in some patients, acute skin GVHD begins with a rash, for example, on the palms of the patient's hands, soles of the feet, or shoulders. However, the rash can become widespread, and may be itchy and painful and/or might blister and peel. Acute liver GVHD may affect normal functions of the liver, such as liver enzymes, and may in turn, cause jaundice. Acute liver GVHD may also cause the patient's abdomen to become swollen and painful if the liver becomes enlarged. Finally, symptoms of acute gut GVHD (or GVHD of the digestive system) can include diarrhea, mucus or blood in the stool, cramping or abdominal pain, indigestion, nausea and/or loss of appetite. Other general symptoms of acute GVHD can include anemia, low grade fever, and/or being more prone to infections. Any combination of these symptoms of acute GVHD may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

In other embodiments, the GVHD is chronic GVHD. Chronic GVHD can occur from about three months to about a year or longer after transplant. Chronic GVHD can be mild or severe, and generally includes symptoms similar to those of acute GVHD. Chronic GVHD can affect the skin and digestive system, including the liver but can also involve other organs and the immune system (e.g., making the patient more prone to infections) and/or connective tissues. Symptoms of chronic skin GVHD include a rash, dry skin, tight skin, itchy skin, darkening of the colour of the skin, thickening of the skin, and/or may affect hair (e.g., hair loss, turning grey) or nails (e.g., hard or brittle nails). Chronic gut GVHD can affect the digestive system, mouth, oesophagus, lining of the stomach, and/or lining of the bowel, and symptoms can include diarrhea, dry or sore mouth, painful swallowing, low nutrient absorption by the stomach, bloating, stomach cramps. Chronic liver GVHD can cause damage and scarring of the liver (cirrhosis). Chronic GVHD of the eyes can affect the glands that make tears, causing eyes to become dry, burning and painful or difficult to tolerate bright light. Chronic lung GVHD can cause shortness of breath, wheezing, persistent cough, and/or being more prone to chest infections. Chronic GVHD affects tendons (e.g., inflammation) that connect muscle to bone causing difficulty straightening or bending your arms and legs. Any combination of these symptoms of chronic GVHD may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

In certain embodiments provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease, such as uveitis, or a symptom thereof.

In certain embodiments provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease, such as pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome or non-infectious scleritis.

In certain embodiments provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), dia-

betes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

In a specific embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises the OX40L binding sites of an antibody of the invention, e.g., an antibody disclosed in the Examples.

In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No: 102, in particular, Seq ID No:36 or Seq ID No:42). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s in the sequence listing (i.e. Seq ID No:6, Seq ID No: 12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44). In a preferred embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s in the sequence listing (i.e. Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46).

In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL domains having an amino acid sequence of any one of the VL domains in the sequence listing (i.e. Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No: 108, in particular Seq ID No:48) (optionally comprising also the cognate VH domain as set out in the sequence listing (i.e. Seq ID No:2/16, Seq ID No:34/48, Seq ID No:66/80 or Seq ID No:94/108, in particular Seq ID No:34/48). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s in the sequence listing (i.e. Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s in the sequence listing (i.e. Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58). In a preferred embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s in the sequence listing (i.e. Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60).

In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34), and one or more VL domains having an amino acid sequence of any one of the VL domains in the sequence listing (i.e. Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48).

In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42), and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s in the sequence listing (i.e. Seq ID No: 18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No: 10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42), and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s in the sequence listing (i.e. Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42), and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s having an amino acid sequence of any one of the VL CDR3s in the sequence listing (i.e. Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60).

As discussed in more detail elsewhere herein, a composition of the invention may be used either alone or in combination with other compounds or compositions. Moreover, the antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be

recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionucleotides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

In some embodiments, provided herein are methods for decreasing or inhibiting binding of hOX40L to an OX40L receptor or cognate ligand (e.g., OX40) in a subject (e.g., a human subject), comprising administering to the subject an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L). In some embodiments, a hOX40L biological activity, such as secretion of CCL20, IL8 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ or another cytokine disclosed herein, is also decreased in the subject, for example decreased by at least 10, 20, 30, 40, 50 or 60%, or 70%, or 80%, or 90% or 95% or >95%.

In certain embodiments, provided herein are methods for decreasing or inhibiting a hOX40L biological activity, such as secretion of interferon gamma, IL-2, CCL20, IL8 and/or RANTES or other cytokine, or INF-γ, TNF-α or IL-2, in particular INF-γ in a subject (e.g., a human subject), comprising administering to the subject an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed hOX40L), wherein hOX40L biological activity is decreased by the antibody.

In other embodiments, provided herein are methods for decreasing or inhibiting binding of hOX40L to an OX40L receptor or cognate ligand (e.g., OX40) in a cell having cell surface-expressed hOX40L, contacting the cell with an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L), such as a hOX40L polypeptide, a hOX40L polypeptide fragment, or a hOX40L epitope. In some embodiments, a hOX40L biological activity, such as secretion of interferon gamma, IL-2, CCL20, IL8 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ or other cytokine disclosed herein, is also decreased in the cell.

In certain embodiments, provided herein are methods for decreasing or inhibiting a hOX40L biological activity, such as secretion of interferon gamma, IL-2, CCL20, IL8 and/or RANTES or other cytokine disclosed herein, in a cell having a cell surface-expressed hOX40L receptor (such as OX40), contacting the cell with an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L) wherein hOX40L biological activity is decreased by the antibody.

Antibodies of the present invention may be used, for example, to purify, detect, and target hOX40L antigens, in both in vitro and in vivo diagnostic and therapeutic methods. For example, the modified antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of hOX40L in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

The invention also provides methods of preventing, managing, treating and/or ameliorating a hOX40L-mediated disease by administrating to a subject of an effective amount of an antibody, or pharmaceutical composition comprising an antibody of the invention. In one aspect, an antibody is substantially purified (i.e., substantially free from substances that limit its effect or produce undesired side-effects). In preferred embodiments, the antibody is a fully human monoclonal antibody, such as a fully human monoclonal antagonist antibody. The subject administered a therapy is preferably a mammal such as non-primate (e.g., cows, pigs, horses, cats, dogs, rodents, mice or rats) or a primate (e.g., a monkey, such as a rhesus or cynomolgous monkey, or a human). In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a human infant or a human infant born prematurely. In another embodiment, the subject is a human with a hOX40L-mediated disease.

Various delivery systems are known and can be used to administer a prophylactic or therapeutic agent (e.g., an antibody of the invention), including, but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of administering a prophylactic or therapeutic agent (e.g., an antibody of the invention), or pharmaceutical composition include, but are not limited to, parenteral administration (e.g., intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (e.g., intranasal and oral routes). In a specific embodiment, a prophylactic or therapeutic agent (e.g., an antibody of the present invention), or a pharmaceutical composition is administered intranasally, intramuscularly, intravenously, or subcutaneously. The prophylactic or therapeutic agents or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, intranasal mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, e.g., U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety.

In a specific embodiment, it may be desirable to administer a prophylactic or therapeutic agent, or a pharmaceutical composition of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion, by topical administration (e.g., by intranasal spray), by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering an antibody of the invention, care must be taken to use materials to which the antibody does not absorb.

In another embodiment, a prophylactic or therapeutic agent, or a composition of the invention can be delivered in a vesicle, in particular a liposome (see Langer, 1990, Science 249:1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

In another embodiment, a prophylactic or therapeutic agent, or a composition of the invention can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:20; Buchwald et al., 1980, Surgery 88:507; Saudek et al., 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of a

prophylactic or therapeutic agent (e.g., an antibodies of the invention) or a composition of the invention (see e.g., Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, J., Macromol. Sci. Rev. Macromol. Chem. 23:61; see also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 7 1:105); U.S. Pat. Nos. 5,679,377; 5,916,597; 5,912,015; 5,989,463; 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly (acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly (N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a controlled or sustained release system can be placed in proximity of the therapeutic target, i.e., the nasal passages or lungs, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)). Controlled release systems are discussed in the review by Langer (1990, Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the invention. See, e.g., U.S. Pat. No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning et al, 1996, "Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179-189, Song et al., 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek et al., 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam eta/., 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in their entirety.

In a specific embodiment, where the composition of the invention is a nucleic acid encoding a prophylactic or therapeutic agent (e.g., an antibody of the invention), the nucleic acid can be administered in vivo to promote expression of its encoded prophylactic or therapeutic agent, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see, e.g., Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

In a specific embodiment, a composition of the invention comprises one, two or more antibodies or fragments of the invention. In another embodiment, a composition of the invention comprises one, two or more antibodies or fragments of the invention and a prophylactic or therapeutic agent other than an antibody of the invention. Preferably, the agents are known to be useful for or have been or are currently used for the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease. In addition to prophylactic or therapeutic agents, the compositions of the invention may also comprise a carrier.

The compositions of the invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions (e.g., compositions that are suitable for administration to a subject or patient) that can be used in the preparation of unit dosage forms. In a preferred embodiment, a composition of the invention is a pharmaceutical composition. Such compositions comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (e.g., an antibody of the invention or other prophylactic or therapeutic agent), and a pharmaceutically acceptable carrier. Preferably, the pharmaceutical compositions are formulated to be suitable for the route of administration to a subject.

In a specific embodiment, the term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa. Such compositions will contain a prophylactically or therapeutically effective amount of the antibody, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anaesthetic such as lignocamne to ease pain at the site of the injection. Such compositions, however, may be administered by a route other than intravenous.

Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of

active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The invention also provides that an antibody of the invention is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of antibody. In one embodiment, the antibody is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, e.g., with water or saline to the appropriate concentration for administration to a subject. Preferably, the antibody is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 0.1 mg, at least 0.5 mg, at least 1 mg, at least 2 mg, or at least 3 mg, and more preferably at least 5 mg, at least 10 mg, at least 15 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 60 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, or at least 100 mg. The lyophilized antibody can be stored at between 2 and 8° C. in its original container and the antibody can be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, an antibody is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody. Preferably, the liquid form of the antibody is supplied in a hermetically sealed container at least 0.1 mg/ml, at least 0.5 mg/ml, or at least 1 mg/ml, and more preferably at least 5 mg/ml, at least 10 mg/ml, at least 15 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 40 mg/ml, at least 50 mg/ml, at least 60 mg/ml, at least 70 mg/ml, at least 80 mg/ml, at least 90 mg/ml, or at least 100 mg/ml.

The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of a prophylactic or therapeutic agent (e.g., an antibody of the invention), or a composition of the invention that will be effective in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease can be determined by standard clinical techniques.

Accordingly, a dosage of an antibody or a composition that results in a serum titer of from about 0.1 μg/ml to about 450 μg/ml, and in some embodiments at least 0.1 μg/ml, at least 0.2 μg/ml, at least 0.4 μg/ml, at least 0.5 μg/ml, at least 0.6 μg/ml, at least 0.8 μg/ml, at least 1 μg/ml, at least 1.5 μg/ml, and preferably at least 2 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 30 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 75 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 200 μg/ml, at least 250 μg/ml, at least 300 μg/ml, at least 350 μg/ml, at least 400 μg/ml, or at least 450 μg/ml can be administered to a human for the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of a hOX40L-mediated disease, and should be decided according to the judgment of the practitioner and each patient's circumstances.

Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For the antibodies of the invention, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. In some embodiments, the dosage administered to the patient is about 1 mg/kg to about 75 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 5 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of the antibodies of the invention may be reduced by enhancing uptake and tissue penetration of the antibodies by modifications such as, for example, lipidation.

In one embodiment, approximately 100 mg/kg or less, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less of an antibody or fragment the invention is administered 5 times, 4 times, 3 times, 2 times or, preferably, 1 time to manage a hOX40L-mediated disease. In some embodiments, an antibody of the invention is administered about 1-12 times, wherein the doses may be administered as necessary, e.g., weekly, biweekly, monthly, bimonthly, trimonthly, etc., as determined by a physician. In some embodiments, a lower dose (e.g., 1-15 mg/kg) can be administered more frequently (e.g., 3-6 times). In other embodiments, a higher dose (e.g., 25-100 mg/kg) can be administered less frequently (e.g., 1-3 times). However, as will be apparent to those in the art, other dosing amounts and schedules are easily determinable and within the scope of the invention.

In a specific embodiment, approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, approximately 0.1 mg/kg or less of an antibody or fragment the invention in a sustained release formulation is administered to a subject, preferably a human, to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease. In another specific embodiment, an approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less bolus of an antibody the invention not in a sustained release formulation is administered to a subject, preferably a human, to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease, and after a certain period of time, approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 5 mg/kg or less of an antibody of the invention in a sustained release is administered to said subject (e.g., intranasally or intramuscularly) two, three or four times (preferably one time). In accordance with this embodiment, a certain period of time can be 1 to 5 days, a week, two weeks, or a month.

In some embodiments, a single dose of an antibody or fragment of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, four, five, six, seven, eight, nine, ten, eleven, twelve times, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty five, or twenty six at bi-weekly (e.g., about 14 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each dose monthly dose may or may not be identical).

In another embodiment, a single dose of an antibody of the invention is administered to patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve times at about monthly (e.g., about 30 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each dose monthly dose may or may not be identical).

In one embodiment, a single dose of an antibody or fragment of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, four, five, or six times at about bi-monthly (e.g., about 60 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each bi-monthly dose may or may not be identical).

In some embodiments, a single dose of an antibody or fragment of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, or four times at about tri-monthly (e.g., about 120 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each tri-monthly dose may or may not be identical).

In certain embodiments, the route of administration for a dose of an antibody or fragment of the invention to a patient is intranasal, intramuscular, intravenous, or a combination thereof, but other routes described herein are also acceptable. In certain embodiments, the route of administration is intraocular. Each dose may or may not be administered by an identical route of administration. In some embodiments, an antibody or fragment of the invention may be administered via multiple routes of administration simultaneously or subsequently to other doses of the same or a different antibody or fragment of the invention.

In certain embodiments, antibodies or fragments of the invention are administered prophylactically or therapeutically to a subject. Antibodies or fragments of the invention can be prophylactically or therapeutically administered to a subject so as to prevent, lessen or ameliorate a hOX40L-mediated disease or symptom thereof.

Gene Therapy

In a specific embodiment, nucleic acids or nucleotide sequences of the invention are administered to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In an embodiment of the invention, the nucleic acids produce their encoded antibody, and the antibody mediates a prophylactic or therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention.

Diagnostic Use of Antibodies

Although antibodies are mentioned in respect of diagnostic uses, this disclosure is to be read as also applying mutatis mutandis to the fragments of the invention.

Labelled antibodies or of the invention and derivatives and analogues thereof, which specifically bind to a hOX40L antigen can be used for diagnostic purposes to detect, diagnose, or monitor a hOX40L-mediated disease. The invention provides methods for the detection of a hOX40L-mediated disease comprising: (a) assaying the expression of a hOX40L antigen in cells or a tissue sample of a subject using one or more antibodies of the invention that specifically bind to the hOX40L antigen; and (b) comparing the level of the hOX40L antigen with a control level, e.g., levels in normal tissue samples (e.g., from a patient not having a hOX40L-mediated disease, or from the same patient before disease onset), whereby an increase in the assayed level of hOX40L antigen compared to the control level of the hOX40L antigen is indicative of a hOX40L-mediated disease.

The invention provides a diagnostic assay for diagnosing a hOX40L-mediated disease comprising: (a) assaying for the level of a hOX40L antigen in cells or a tissue sample of an individual using one or more antibodies of the invention that specifically bind to a hOX40L antigen; and (b) comparing the level of the hOX40L antigen with a control level, e.g., levels in normal tissue samples, whereby an increase in the assayed hOX40L antigen level compared to the control level of the hOX40L antigen is indicative of a hOX40L-mediated disease. A more definitive diagnosis of a hOX40L-mediated disease may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the hOX40L-mediated disease.

Antibodies of the invention can be used to assay hOX40L antigen levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (e.g., see Jalkanen et al., 1985, J. Cell. Biol. 101:976-985; and Jalkanen et al., 1987, J. Cell. Biol. 105:3087-3096). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}1,

^{121}1) carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{121}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a hOX40L-mediated disease in a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labelled antibody that specifically binds to a hOX40L antigen; b) waiting for a time interval following the administering for permitting the labelled antibody to preferentially concentrate at sites in the subject where the hOX40L antigen is expressed (and for unbound labelled molecule to be cleared to background level); c) determining background level; and d) detecting the labelled antibody in the subject, such that detection of labelled antibody above the background level indicates that the subject has a hOX40L-mediated disease. Background level can be determined by various methods including, comparing the amount of labelled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99}Tc. The labelled antibody will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumour imaging is described in S. W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S. W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labelled antibody to preferentially concentrate at sites in the subject and for unbound labelled antibody to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In one embodiment, monitoring of a hOX40L-mediated disease is carried out by repeating the method for diagnosing the a hOX40L-mediated disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labelled molecule can be detected in the subject using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labelled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Pat. No. 5,441,050). In another embodiment, the molecule is labelled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labelled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labelled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Methods of Producing Antibodies

Antibodies and fragments of the invention that specifically bind to an antigen (OX40L) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. The practice of the invention employs, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described in the references cited herein and are fully explained in the literature. See, e.g., Maniatis et al. (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook et al. (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook et al. (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren et al. (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

Polyclonal antibodies that specifically bind to an antigen can be produced by various procedures well-known in the art. For example, a human antigen can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the human antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminium hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. Other exemplary methods of producing monoclonal antibodies are discussed elsewhere herein, such as e.g., use of the KM Mouse™. Additional exemplary methods of producing monoclonal antibodies are provided in the Examples herein.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. Briefly, mice can be immunized with a hOX40L antigen and once an immune response is detected, e.g., antibodies specific for hOX40L antigen are detected in

the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution.

Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilptrack et al., 1997 Hybridoma 16:381-9, incorporated by reference in its entirety). The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating antibodies by culturing a hybridoma cell secreting a modified antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with a hOX40L antigen with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind to a hOX40L antigen.

Antibody fragments which recognize specific hOX40L antigens may be generated by any technique known to those of skill in the art. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the Light chain constant region and the CH1 domain of the heavy chain. Further, the antibodies of the present invention can also be generated using various phage display methods known in the art.

For example, antibodies can also be generated using various phage display methods. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to a particular antigen can be selected or identified with antigen, e.g., using labelled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., 1995, J. Immunol. Methods 182:41-50; Ames et al., 1995, J. Immunol. Methods 184:177-186; Kettleborough et al., 1994, Eur. J. Immunol. 24:952-958; Persic et al, 1997, Gene 187:9-18; Burton et al, 1994, Advances in Immunology 57:191-280; PCT Application No. PCT/GB91/01134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Pat. Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax et al., 1992, BioTechniques 12(6):864-869; Sawai et al., 1995, AJRI 34:26-34; and Better et al., 1988, Science 240:1041-1043 (said references incorporated by reference in their entireties).

To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, e.g., the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, e.g., human kappa or lambda constant regions. The VH and VL domains may also cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, e.g., IgG, using techniques known to those of skill in the art.

For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also U.S. Pat. Nos. 4,444,887 and 4,716,111; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

In preferred embodiments, human antibodies are produced. Human antibodies and/or fully human antibodies can be produced using any method known in the art, including the Examples provided herein. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered nonfunctional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional

hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B-cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, Int. Rev. Immunol. 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Pat. Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, which are incorporated by reference herein in their entirety. Other methods are detailed in the Examples herein. In addition, companies such as Abgenix, Inc/Amgen. (Thousand Oaks, Calif.) OMT (Paolo Alto, Calif.), Argen-x (Breda, Netherlands), Ablexis (San Francisco, Calif.) or Harbour Antibodies (Cambridge, Mass.) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. Methods for producing chimeric antibodies are known in the art. See, e.g., Morrison, 1985, Science 229:1202; Oi et al., 1986, BioTechniques 4:214; Gillies et al, 1989, J. Immunol. Methods 125:191-202; and U.S. Pat. Nos. 5,807,715, 4,816,567, 4,816,397, and 6,331,415, which are incorporated herein by reference in their entirety.

A humanized antibody is an antibody or its variant or fragment thereof which is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and a CDR having substantially the amino acid sequence of a non-human immunoglobulin. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', F(ab')2, Fabc, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (i.e., donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG1, IgG2, IgG3 and IgG4. Usually the constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the class is typically IgG1. Where such cytotoxic activity is not desirable, the constant domain may be of the IgG2 class. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE. Examples of VL and VH constant domains that can be used in certain embodiments of the invention include, but are not limited to, C-kappa and C-gamma-1 (nG1m) described in Johnson et al (1997) J. Infect. Dis. 176, 1215-1224 and those described in U.S. Pat. No. 5,824,307. The humanized antibody may comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, e.g., the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the import antibody. Such mutations, however, will not be extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental FR and CDR sequences, more often 90%, and most preferably greater than 95%. Humanized antibodies can be produced using variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239,400; International publication No. WO 91/09967; and U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering 7(6):805-814; and Roguska et al, 1994, PNAS 91:969-973), chain shuffling (U.S. Pat. No. 5,565,332), and techniques disclosed in, e.g., U.S. Pat. Nos. 6,407,213, 5,766,886, WO 9317105, Tan et al., J. Immunol. 169:1119 25 (2002), Caldas et al, Protein Eng. 13(5):353-60 (2000), Morea et al., Methods 20(3):267 79 (2000), Baca et al., J. Biol. Chem. 272 (16):10678-84 (1997), Roguska et al, Protein Eng. 9(10):895 904 (1996), Couto et al., Cancer Res. 55 (23 Supp):5973s-5977s (1995), Couto et al., Cancer Res. 55(8):1717-22 (1995), Sandhu J S, Gene 150(2):409-10 (1994), and Pedersen et al., J. Mol. Biol. 235(3):959-73 (1994). See also U.S. Patent Pub. No. US 2005/0042664 A1 (Feb. 24, 2005), which is incorporated by reference herein in its entirety. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modelling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al, U.S. Pat. No. 5,585,089; and Reichmann et al., 1988, Nature 332:323, which are incorporated herein by reference in their entireties.)

Single domain antibodies, for example, antibodies lacking the light chains, can be produced by methods well-known in the art. See Riechmann et al, 1999, J. Immunol. 231:25-38; Nuttall et al., 2000, Curr. Pharm. Biotechnol. 1(3):253-263; Muylderman, 2001, J. Biotechnol. 74(4):277302; U.S. Pat. No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591, and WO 01/44301, each of which is incorporated herein by reference in its entirety.

Further, the antibodies that specifically bind to a hOX40L antigen can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" an antigen using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, 1989, FASEB J. 7(5):437-444; and Nissinoff, 1991, J. Immunol., 147(8):2429-2438).

Kits

The invention also provides a pharmaceutical or diagnostic pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention, such as one or more antibodies or fragments provided herein. Optionally associated with such

container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration, e.g., an authorisation number.

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated hOX40L antigen as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with the hOX40L antigen. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of a modified antibody to a hOX40L antigen (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized hOX40L antigen. The hOX40L antigen provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above described kit includes a solid support to which hOX40L antigen is attached. Such a kit may also include a non-attached reporter-labelled anti-human antibody. In this embodiment, binding of the antibody to the hOX40L antigen can be detected by binding of the said reporter-labelled antibody.

"Conservative amino acid substitutions" result from replacing one amino acid with another having similar structural and/or chemical properties, such as the replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine. Thus, a "conservative substitution" of a particular amino acid sequence refers to substitution of those amino acids that are not critical for polypeptide activity or substitution of amino acids with other amino acids having similar properties (e.g., acidic, basic, positively or negatively charged, polar or non-polar, etc.) such that the substitution of even critical amino acids does not reduce the activity of the peptide, (i.e. the ability of the peptide to penetrate the blood brain barrier (BBB)). Conservative substitution tables providing functionally similar amino acids are well known in the art. For example, the following six groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W). (See also Creighton, Proteins, W. H. Freeman and Company (1984), incorporated by reference in its entirety.) In some embodiments, individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids can also be considered "conservative substitutions" if the change does not reduce the activity of the peptide. Insertions or deletions are typically in the range of about 1 to 5 amino acids. The choice of conservative amino acids may be selected based on the location of the amino acid to be substituted in the peptide, for example if the amino acid is on the exterior of the peptide and expose to solvents, or on the interior and not exposed to solvents.

In alternative embodiments, one can select the amino acid which will substitute an existing amino acid based on the location of the existing amino acid, i.e. its exposure to solvents (i.e. if the amino acid is exposed to solvents or is present on the outer surface of the peptide or polypeptide as compared to internally localized amino acids not exposed to solvents). Selection of such conservative amino acid substitutions are well known in the art, for example as disclosed in Dordo et al, J. Mol Biol, 1999, 217, 721-739 and Taylor et al., J. Theor. Biol. 119(1986); 205-218 and S. French and B. Robson, J. Mol. Evol., 19(1983)171. Accordingly, one can select conservative amino acid substitutions suitable for amino acids on the exterior of a protein or peptide (i.e. amino acids exposed to a solvent), for example, but not limited to, the following substitutions can be used: substitution of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P.

In alternative embodiments, one can also select conservative amino acid substitutions encompassed suitable for amino acids on the interior of a protein or peptide, for example one can use suitable conservative substitutions for amino acids is on the interior of a protein or peptide (i.e. the amino acids are not exposed to a solvent), for example but not limited to, one can use the following conservative substitutions: where Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V. In some embodiments, non-conservative amino acid substitutions are also encompassed within the term of variants.

As used herein an "antibody" refers to IgG, IgM, IgA, IgD or IgE molecules or antigen-specific antibody fragments thereof (including, but not limited to, a Fab, F(ab')2, Fv, disulphide linked Fv, scFv, single domain antibody, closed conformation multispecific antibody, disulphide-linked scfv, diabody), whether derived from any species that naturally produces an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria. Antibodies can be humanized using routine technology.

As described herein, an "antigen" is a molecule that is bound by a binding site on an antibody agent. Typically, antigens are bound by antibody ligands and are capable of raising an antibody response in vivo. An antigen can be a polypeptide, protein, nucleic acid or other molecule or portion thereof. The term "antigenic determinant" refers to an epitope on the antigen recognized by an antigen-binding molecule, and more particularly, by the antigen-binding site of said molecule.

As used herein, the term "antibody fragment" refers to a polypeptide that includes at least one immunoglobulin variable domain or immunoglobulin variable domain sequence and which specifically binds a given antigen. An antibody fragment can comprise an antibody or a polypeptide comprising an antigen-binding domain of an antibody. In some embodiments, an antibody fragment can comprise a monoclonal antibody or a polypeptide comprising an antigen-binding domain of a monoclonal antibody. For example, an antibody can include a heavy (H) chain variable region (abbreviated herein as VH), and an OX40L (L) chain variable region (abbreviated herein as VL). In another example, an antibody includes two heavy (H) chain variable regions and two OX40L (L) chain variable regions. The term "antibody fragment" encompasses antigen-binding fragments of antibodies (e.g., single chain antibodies, Fab and sFab fragments, F(ab')2, Fd fragments, Fv fragments, scFv, and domain antibodies (dAb) fragments (see, e.g. de Wildt et al., Eur J. Immunol., 1996; 26(3):629-39; which is incorporated

by reference herein in its entirety)) as well as complete antibodies. An antibody can have the structural features of IgA, IgG, IgE, IgD, IgM (as well as subtypes and combinations thereof). Antibodies can be from any source, including mouse, rabbit, pig, rat, and primate (human and non-human primate) and primatized antibodies. Antibodies also include midibodies, humanized antibodies, chimeric antibodies, and the like.

As used herein, "antibody variable domain" refers to the portions of the OX40L and heavy chains of antibody molecules that include amino acid sequences of Complementarity Determining Regions (CDRs; i.e., CDR1, CDR2, and CDR3), and Framework Regions (FRs). VH refers to the variable domain of the heavy chain. VL refers to the variable domain of the Light chain. According to the methods used in this invention, the amino acid positions assigned to CDRs and FRs may be defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991)) or according to IMGT nomenclature.

As used herein, the term "antibody binding site" refers to a polypeptide or domain that comprises one or more CDRs of an antibody and is capable of binding an antigen. For example, the polypeptide comprises a CDR3 (e.g., HCDR3). For example the polypeptide comprises CDRs 1 and 2 (e.g., HCDR1 and 2) or CDRs 1-3 of a variable domain of an antibody (e.g., HCDRs1-3). In an example, the antibody binding site is provided by a single variable domain (e.g., a VH or VL domain). In another example, the binding site comprises a VH/VL pair or two or more of such pairs.

As used herein, "genotyping" refers to a process of determining the specific allelic composition of a cell and/or subject at one or more position within the genome, e.g. by determining the nucleic acid sequence at that position. Genotyping refers to a nucleic acid analysis and/or analysis at the nucleic acid level. As used herein, "phenotyping" refers a process of determining the identity and/or composition of an expression product of a cell and/or subject, e.g. by determining the polypeptide sequence of an expression product. Phenotyping refers to a protein analysis and/or analysis at the protein level.

As used herein, the terms "treat," "treatment," "treating," or "amelioration" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with a disease or disorder. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment). For treatment to be effective a complete cure is not contemplated. The method can in certain aspects include cure as well.

As used herein, the term "pharmaceutical composition" refers to the active agent in combination with a pharmaceutically acceptable carrier e.g. a carrier commonly used in the pharmaceutical industry. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "administering," refers to the placement of a compound as disclosed herein into a subject by a method or route which results in at least partial delivery of the agent at a desired site. Pharmaceutical compositions comprising the compounds disclosed herein can be administered by any appropriate route which results in an effective treatment in the subject.

Multiple compositions can be administered separately or simultaneously. Separate administration refers to the two compositions being administered at different times, e.g. at least 10, 20, 30, or 10-60 minutes apart, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 hours apart. One can also administer compositions at 24 hours apart, or even longer apart. Alternatively, two or more compositions can be administered simultaneously, e.g. less than 10 or less than 5 minutes apart. Compositions administered simultaneously can, in some aspects, be administered as a mixture, with or without similar or different time release mechanism for each of the components.

As used herein, "authorization number" or "marketing authorization number" refers to a number issued by a regulatory agency upon that agency determining that a particular medical product and/or composition may be marketed and/or offered for sale in the area under the agency's jurisdiction. As used herein "regulatory agency" refers to one of the agencies responsible for evaluating, e.g., the safety and efficacy of a medical product and/or composition and controlling the sales/marketing of such products and/or compositions in a given area. The Food and Drug Administration (FDA) in the US and the European Medicines Agency (EPA) in Europe are but two examples of such regulatory agencies. Other non-limiting examples can include SDA, MPA, MHPRA, IMA, ANMAT, Hong Kong Department of Health-Drug Office, CDSCO, Medsafe, and KFDA.

As used herein, "injection device" refers to a device that is designed for carrying out injections, an injection including the steps of temporarily fluidically coupling the injection device to a person's tissue, typically the subcutaneous tissue. An injection further includes administering an amount of liquid drug into the tissue and decoupling or removing the injection device from the tissue. In some embodiments, an injection device can be an intravenous device or IV device, which is a type of injection device used when the target tissue is the blood within the circulatory system, e.g., the blood in a vein. A common, but non-limiting example of an injection device is a needle and syringe.

As used herein, a "buffer" refers to a chemical agent that is able to absorb a certain quantity of acid or base without undergoing a strong variation in pH.

As used herein, "packaging" refers to how the components are organized and/or restrained into a unit fit for distribution and/or use. Packaging can include, e.g., boxes, bags, syringes, ampoules, vials, tubes, clamshell packaging, barriers and/or containers to maintain sterility, labeling, etc.

As used herein, "instructions" refers to a display of written, printed or graphic matter on the immediate container of an article, for example the written material displayed on a vial containing a pharmaceutically active agent, or details on the composition and use of a product of interest included in a kit containing a composition of interest. Instructions set forth the method of the treatment as contemplated to be administered or performed.

As used herein the term "comprising" or "comprises" is used in reference to antibodies, fragments, uses, compositions, methods, and respective component(s) thereof, that are essential to the method or composition, yet open to the inclusion of unspecified elements, whether essential or not.

The term "consisting of" refers to antibodies, fragments, uses, compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, "e.g." is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g." is synonymous with the term "for example."

Definitions of common terms in cell biology and molecular biology can be found in "The Merck Manual of Diagnosis and Therapy", 19th Edition, published by Merck Research Laboratories, 2006 (ISBN 0-911910-19-0); Robert S. Porter et al. (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); Benjamin Lewin, Genes X, published by Jones & Bartlett Publishing, 2009 (ISBN-10: 0763766321); Kendrew et al (eds.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8) and Current Protocols in Protein Sciences 2009, Wiley Intersciences, Coligan et al., eds.

Unless otherwise stated, the present invention was performed using standard procedures, as described, for example in Sambrook et al., Molecular Cloning: A Laboratory Manual (4 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (2012); Davis et al., Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1995); or Methods in Enzymology: Guide to Molecular Cloning Techniques Vol. 152, S. L. Berger and A. R. Kimmel Eds., Academic Press Inc., San Diego, USA (1987); Current Protocols in Protein Science (CPPS) (John E. Coligan, et al., ed., John Wiley and Sons, Inc.), Current Protocols in Cell Biology (CPCB) (Juan S. Bonifacino et a. ed., John Wiley and Sons, Inc.), and Culture of Animal Cells: A Manual of Basic Technique by R. Ian Freshney, Publisher: Wiley-Liss; 5th edition (2005), Animal Cell Culture Methods (Methods in Cell Biology, Vol. 57, Jennie P. Mather and David Barnes editors, Academic Press, 1st edition, 1998) which are all incorporated by reference herein in their entireties.

Other terms are defined herein within the description of the various aspects of the invention.

All patents and other publications; including literature references, issued patents, published patent applications, and co-pending patent applications; cited throughout this application are expressly incorporated herein by reference for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with the technology described herein. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

The description of embodiments of the disclosure is not intended to be exhaustive or to limit the disclosure to the precise form disclosed. While specific embodiments of, and examples for, the disclosure are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the disclosure, as those skilled in the relevant art will recognize. For example, while method steps or functions are presented in a given order, alternative embodiments may perform functions in a different order, or functions may be performed substantially concurrently. The teachings of the disclosure provided herein can be applied to other procedures or methods as appropriate. The various embodiments described herein can be combined to provide further embodiments. Aspects of the disclosure can be modified, if necessary, to employ the compositions, functions and concepts of the above references and application to provide yet further embodiments of the disclosure. Moreover, due to biological functional equivalency considerations, some changes can be made in protein structure without affecting the biological or chemical action in kind or amount. These and other changes can be made to the disclosure in OX40L of the detailed description. All such modifications are intended to be included within the scope of the appended claims.

Specific elements of any of the foregoing embodiments can be combined or substituted for elements in other embodiments. Furthermore, while advantages associated with certain embodiments of the disclosure have been described in the context of these embodiments, other embodiments may also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages to fall within the scope of the disclosure.

It will be understood that particular configurations, concepts, aspects, examples, clauses and embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine study, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims. All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the speci-

fication may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

Any part of this disclosure may be read in combination with any other part of the disclosure, unless otherwise apparent from the context.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in OX40L of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

EXAMPLES

Example 1

Antigen Preparation, Immunization Procedures, and Hybridoma Generation

The following example provides a detailed description of the generation and identification of a panel of anti-human OX40L monoclonal antibodies using the KyMouse™ system (see, e.g., WO2011/004192). To this end, genetically engineered mice containing a large number of human immunoglobulin genes were immunized with soluble recombinant human OX40L (commercial or in-house produced) or surface expressed human OX40L displayed on mouse embryonic fibroblast (MEF) cells. Various immunization regimes, including conventional intraperitoneal injections as well as a rapid immunisation at multiple sites regime were set up, boosting animals over several weeks. At the end of each regime, secondary lymphoid tissue such as the spleen, and in some cases, the lymph nodes were removed. Tissues were prepared into a single cell suspension and fused with SP2/0 cells to generate a stable hybridoma cell line.

Materials and Methods

Cloning Expression and Purification of Recombinant Rhesus and Human OX40L

cDNA encoding the extracellular domain of human OX40L was cloned into a pREP4 expression plasmid (Invitrogen) using standard molecular biology techniques. The constructs also contained a FLAG peptide motif to aid purification and an isoleucine zipper motif to aid trimerisation. Constructs were sequenced to ensure their correct sequence composition.

Rhesus (*Macaca mulatta*) OX40L was created using the human OX40L plasmid created above as a template and using site directed mutagenesis to introduce the amino acid changes.

Human OX40L well as Rhesus monkey OX40L were expressed transiently to produce recombinant protein using Invitrogen's FreeStyle™ CHO-S suspension adapted cell line. Plasmids were transfected into the cells using PEI (polyethylenimine MW 40000) and left to overgrow for a period of 13 days before harvesting the supernatant for purification. Cells were fed during the overgrow process with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process samples were taken regularly to monitor cell growth and viability.

FLAG-tagged OX40L proteins were purified in a two-step process; firstly the clarified tissue culture supernatants from the CHO-S expression were purified using M2 anti-FLAG affinity chromatography. The eluted fractions containing the OX40L protein were then subjected to size exclusion chromatography and assessed for purity by SDS-PAGE analysis and quantified by spectrophotometer reading at OD280 nm.

Cloning Expression and Purification of Recombinant Human OX40 Receptor

cDNA encoding the extracellular domain of human OX40 Receptor was cloned into a pREP4 expression plasmid (Invitrogen) using standard restriction enzyme digestion and ligation. The construct contained a human Fc portion to aid purification. Constructs were sequenced to ensure their correct sequence composition.

Human OX40 Receptor was expressed transiently to produce recombinant protein using Invitrogen's FreeStyle™ CHO-S suspension adapted cell line. Plasmids were transfected into the cells using PEI (polyethylenimine MW 40000) and left to overgrow for a period of 13 days before harvesting the supernatant for purification. Cells were fed during the overgrow process with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process, samples were taken regularly to monitor cell growth and viability.

The Fc tagged OX40 Receptor protein was purified in a two-step process; firstly the clarified tissue culture supernatants from the CHO-S expression were purified using Protein G affinity chromatography. The eluted fractions containing the OX40 Receptor protein were then subjected to size exclusion chromatography and assessed for purity by SDS-PAGE analysis and quantified by spectrophotometer reading at OD280 nm.

Generation of stably transfected MEF and CHO-S cells expressing human OX40L The full human OX40L sequences were codon optimized (Seq ID No:173) for mammalian expression and cloned into an expression vector under the CMV promoter flanked by 3' and 5' piggyBac specific terminal repeat sequences facilitating stable integration into the cell genome (see: "A hyperactive piggyBac transposase for mammalian applications"; Yusa K, Zhou L, Li M A, Bradley A, Craig N L. Proc Natl Acad Sci USA. 2011 Jan. 25). Furthermore, the expression vector contained either a puromycin or neomycin selection cassette to facilitate stable cell line generation. The hOX40L expression plasmid was co-transfected with a plasmid encoding piggyBac transposase into an in-house derived mouse embryonic fibroblast (MEF) cell line (embryos used to generate this line

were obtained from a 129S5 crossed to C57BL6 female mouse) and CHO-S cells using the FreeStyle Max transfection reagent (Invitrogen) according to manufacturer instructions. 24 hours after transfection, the media was supplemented with G418 or neomycin and grown for at least 2 weeks to select a stable cell line, with media being exchanged every 3-4 days. The expression of hOX40L was assessed by flow cytometry using an anti-human OX40L-PE conjugated antibody (eBioscience). Complete MEF media was made up of Dulbecco's Modified Eagle's Medium (Gibco) supplemented with 10% v/v fetal bovine serum (Gibco). Complete CHO-S media was made up of CD-CHO media supplemented with 8 mM glutamax (Gibco).

Generation of HT1080 Expressing OX40R and NF-Kappa Reporter Gene

The full human OX40 receptor sequence was codon optimised (Seq ID No: 175) for mammalian expression and cloned into an expression vector under the CMV promoter flanked by 3' and 5' piggyBac specific terminal repeat sequences facilitating stable integration into the cell genome (see: "A hyperactive piggyBac transposase for mammalian applications"; Yusa K, Zhou L, Li M A, Bradley A, Craig N L. Proc Natl Acad Sci USA. 2011 Jan. 25). Furthermore, the expression vector contained either a puromycin selection cassette to facilitate stable cell line generation. The hOX40 receptor expression plasmid was co-transfected with a plasmid encoding piggyBac transposase into HT1080 cells (ATCC® CCL-121) using the FreeStyle Max transfection reagent (Invitrogen) according to manufacturer instructions. 24 hours after transfection, the media was supplemented with puromycin and grown for at least 2 weeks to select a stable cell line with media being exchanged every 3-4 days. The expression of OX40 receptor was assessed by flow cytometry using an anti-human OX40 receptor-PE conjugated antibody (R&D, clone 443318). Following the generation of a stable cell line expressing the OX40 receptor, cells were transfected with the pNiFty-2-SEAP plasmid (invivogen) containing 5 repeated NFkB transcription factor binding sites followed by secreted alkaline phosphatase. Stable cells were selected with the addition to zeocin to the media with fresh media being added every 3-4 days. Complete HT1080 media was made up of MEM supplemented with 10% fetal calf serum.

Preparation of MEF Cells for Mouse Immunizations:

Cell culture medium was removed and cells washed once with 1×PBS. Cells were treated for 5 minutes with trypsin to loosen cells from tissue culture surface. Cells were collected and trypsin neutralized by the addition of complete media containing 10% v/v fetal bovine serum (FCS). Cells were then centrifuged at 300×g for 10 minutes and washed with 25 mL of 1×PBS. Cells were counted and resuspended at the appropriate concentration in 1×PBS.

Immunization Procedure:

Transgenic Kymice were immunized with hOX40L in either soluble recombinant form, expressed by CHO-S cells, or membrane bound form, expressed by stably transfected MEF cells.

When immunizing with cells, the adjuvant was mixed with cells at a 1:1 v/v ratio and gently mixed by pipetting before injecting intraperitoneally. When immunizing with protein, the adjuvant was mixed with protein at a 1:1 v/v ratio and vortexed repeatedly. All mice were bled before being primed and then boosted every three weeks. At least 3 serial bleeds spaced apart at least 2 weeks were collected and analysed for hOX40L specific IgG titre using an ELISA or flow cytometry based assay

Determination of Serum Titers by FACS Using CHO-S Expressed hOX40L

CHO-S cells expressing hOX40L or untransfected CHO-S cells, diluted in FACS buffer (PBS+1% w/v BSA+ 0.1% w/v NaN_3) were distributed to a 96 well V-bottom plate (Greiner) at a density of 1×10^5 cells per well. Cells were washed with 150 μL of PBS and centrifuged at 300×g for 3 min. Supernatant was aspirated and 150 μL of PBS added. This wash step was repeated. A titration of mouse serum was prepared, diluting samples in FACS buffer. 50 μL/well of this titration was then added to the cell plate. To determine the change in activity level due to immunization, serum from each animal prior to immunization was diluted to 1 in 100 in FACS buffer and 50 μL/well added to the cells. A suitable reference antibody (anti-OX40L antibody MAB10541, R&D systems) or mouse IgG1 control antibody (Sigma) were diluted in FACS buffer (between 1-9 μg/mL) and 50 μL added to cells. Cells were incubated at 4° C. for 30 minutes. Cells were washed twice with 150 μL of PBS, centrifuging after each wash step and aspirating supernatant (centrifuged at 300×g for 3 minutes). To detect antibody binding, APC goat-anti-mouse IgG (Jackson ImmunoResearch) was diluted 1 in 500 in FACS buffer and 50 μL was added to the cells. Cells were incubated 30 minutes at 4° C. in dark. Cells were washed twice with 150 μL of PBS centrifuging after each wash step and aspirating supernatant (centrifuged at 300×g for 3 minutes). To fix cells 100 μL 2% v/v paraformaldehyde was added and cells incubated for 30 minutes at 4° C., cells were pelleted by centrifugation at 300×g and the plates resuspended in 50 μL of FACS buffer. APC signal intensity (geomean) was measured by flow cytometry using a BD FACS Array instrument.

Determination of Serum Titers by DELFIA Immunoassay Using Recombinant hOX40L

Titers in mouse serum samples were determined using a reverse OX40L ELISA protocol. Anti-mouse IgG capture antibody (Southern Biotech) (4 μg/mL diluted in PBS, 50 μL/well) was adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4° C. Excess IgG was removed by washing with PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hr at RT, after which plates were washed as described previously. A titration of mouse serum was prepared, diluting samples in reagent diluent (0.1% w/v BSA/PBS). 50 μL/well of this titration was then added to ELISA plates. To determine the change in activity level due to immunization, serum from each animal prior to immunization was diluted to 1 in 100 in reagent diluent and 50 μL/well added to the ELISA plate. As a positive control for biotinylated OX40L binding an anti-OX40L antibody (MAB10541, R&D systems) diluted to 1 μg/mL was added to plates at 50 μL. Mouse IgG1 isotype control (Sigma) was included as a negative control and was diluted to 1 μg/mL in reagent diluent and 50 μL/well added to ELISA plate. In some instances serum sample from a mouse immunized with a non-relevant antigen was diluted 1 in 1000 and 50 μL/well was added to the ELISA plate. The plates were incubated at room temperature for at least 1 hour. Following incubation, plates were washed as before to remove unbound proteins. Biotinylated OX40L (100 ng/mL in reagent diluent; 50 μL/well) was then added to the plates and incubated at RT for 1 hour. Unbound biotinylated OX40L was removed by washing with PBS-Tween (0.1% v/v), while the remaining biotinylated OX40L was detected by streptavidin-Europium3$^+$conjugate (DELFIA® detection, PerkinElmer) diluted in DELFIA® assay buffer (Perkin Elmer) or streptavidin-HRP diluted in reagent diluent.

In the case of streptavidin-HRP, the plates were washed as described before and 50 μL of TMB (Sigma) was added to the plate. Then the reaction was stopped by adding 50 μL of 1M sulfuric acid (Fluka analytical). The OD at 450 nm was measured on an Envision plate reader (PerkinElmer).

In case of streptavidin-Europium3, the plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 200 μL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. The time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Fluorescence data was plotted as Europium counts.

Murine Tissue Isolation and Preparation:

Spleens were excised from immunised mice and washed in 1×PBS and kept on ice until further processing. Tissues were prepared in buffer containing 1×PBS (Invitrogen) and 3% heat-inactivated FBS (Invitrogen). Splenocytes were dispersed by mashing the tissue through a 45 μm strainer (BD Falcon) and rinsing with 30 mL 3% FBS/PBS buffer before centrifugation at 700 g for 10 minutes at 4° C. To remove red blood cells, the pelleted splenocytes were resuspended in 4 mL of Red Blood Cell Lysis Buffer (Sigma). After 4 minutes of incubation, the lysis reaction was stopped by addition of 3% FBS/1×PBS buffer. Cell clumps were filtered out with a 45 μm strainer. The remaining splenocytes were pelleted for further procedures

Hybridoma Fusion

For the KM055 experiment, pelleted splenocytes were progressed directly to fusion without any selection or overnight CpG stimulation. For the KM040 experiment, B-cells were subjected to a positive selection method using the MACS® Separation system. Cells were resuspended in 80 μL 3% FBS/PBS buffer per 1×10^7 cells, before adding the anti-mouse IgG1 plus anti-mouse IgG2a+b MicroBeads (Miltenyi Biotec) and incubated for 15 minutes at 4° C. The cells/MicroBeads mixture was then applied to a pre-wetted LS column placed in a magnetic MACS Separator and washed with 3% FBS/PBS buffer. IgG positive cells were collected in the labelled, column-bound fraction in 3% FBS/PBS buffer.

For the KM040 experiment, enriched B-cells were treated with CpG overnight (final concentration 25 μM) and the following day washed once in BSA fusion buffer (0.3M D-Sorbitol, 0.11 mM calcium acetate hydrate, 0.5 mM magnesium acetate tetrahydrate and 0.1% BSA (v/w), adjusted to pH7.2). For the KM055 experiment, pelleted splenocytes from red blood cell lysis were washed once in BSA fusion buffer on the same day as tissue preparation. Fusion proceeded in the same way for both experiments after this point. Washed cells were resuspended in 200 μL of BSA fusion buffer and cell count determined. SP2/0 cells were treated in the same way, but washed twice with BSA fusion buffer. B-cells were fused at a ratio of 3:1 with SP2/0 myeloma cells by electrofusion using a BTX ECM 2001 Electro Cell Manipulator (Harvard Apparatus). Each fusion was left overnight in recovery medium (Dulbecco's Modified Eagle's Medium-high glucose (no phenol red, no L-G) containing OPI (Sigma), L-Glutamax (Gibco), 20% FBS (Gibco, batch-tested for hybridoma) and 2-mercaptoethanol). On the final day, cells were pelleted and resuspended in 1 part recovery medium to 9 parts semi-solid medium (ClonaCell-HY Hybridoma Selection Medium D, Stemcell Technologies) and then seeded onto 10 cm petri dishes. Colonies were picked 12 days later into 96-well plates and cultured for another 2-3 days prior to screening.

Example 2

Hybridoma Supernatant Screening

After generation of hybridoma clones, the hybridoma supernatant was assessed in a sequential primary and secondary screen and appropriate hybridoma clones selected based on criteria of antibody binding to CHO expressed hOX40L and receptor neutralisation activity (see details in materials and methods) (Table 1).

For the primary screen, the inventors devised the following selection criteria: wells containing hybridoma clones were selected if antibodies present in the supernatant could bind to natively displayed hOX40L expressed on the cell surface. This assay was set up by plating CHO-S cells expressing hOX40L on the cell surface, followed by incubation with hybridoma supernatant, followed by a fluorescent detection antibody. The presence of an anti-OX40L antibody in the supernatant was read-out using a plate reader capable of reading the appropriate fluorescence. Furthermore, the inventors assessed hybridoma supernatant for binding to recombinantly expressed human OX40L using an HTRF (Homogeneous Time Resolved Fluorescence) assay. The inventors also determined whether the hybridoma supernatant had the ability to reduce the binding of human recombinant OX40L to human OX40R Fc. Clones meeting certain selection criteria (see further detailed description below), using data from the above mentioned three primary screen assays, were then cherry-picked and moved on to a secondary screen where the ability of each antibody to neutralise hOX40L binding to its receptors, OX40 Receptor (aka CD134), was determined. The inventors decided to assess this using a receptor neutralisation HTRF assay and a flow cytometry-based receptor neutralisation assay. Lastly, the inventors decided to analyse hybridoma supernatant by SPR to evaluate apparent affinity of the antibodies to recombinant trimeric human OX40L as well as cross-reactivity to Rhesus monkey OX40L.

Antibodies were defined as a secondary hit when antibodies in hybridoma supernatant bound to hOX40L, with high apparent affinity as well as cross-reacted with recombinant Rhesus monkey OX40L. Additionally, antibodies in the supernatant had to show the ability to neutralize OX40L binding to its receptor, i.e. OX40 Receptor (aka CD134) in either HTRF or flow cytometry based assay.

Materials and Methods

Primary Screen—Binding to Cell Expressed Human OX40L

Supernatants collected from hybridoma cells were tested to assess the ability of secreted antibodies to bind to hOX40L expressed on the surface of CHO-S cells. To determine CHO-S hOX40L binding, cells were plated in clear bottom tissue culture treated 384-well plates (Costar or BRAND) at 2×10^4 cells/well in F12 media (GIBCO) supplemented with 10% v/v FBS (GIBCO) and cultured overnight. Culture media was removed from 384-well assay plates. At least 40 μL of hybridoma supernatant or positive control anti-human OX40L reference antibody (at a final concentration of 1 μg/mL) or isotype IgG1 control antibody (referred to in some instances as Cm7, Sigma M9269, at a final concentration of 1 μg/mL) diluted in hybridoma maintaining media (HMM) were added to each well. Hybridoma maintaining media was made up of, Advanced DMEM (Gibco) supplemented with 1× Glutamax (Gibco), 20% v/v FBS (Gibco), 0.05 mM β-Mercaptoethanol, 1×HT supplement (Gibco), and 1×penicillin/streptomycin (Gibco). Plates were incubated for 1 hour at 4° C. Culture media was aspirated and 50 μL of goat anti-mouse Alexa Fluor 790 (Jackson ImmunoResearch, 115-655-071) at 1000 ng/mL supple-

mented with 0.2 μM DRAQ5 (Biostatus) diluted in FACS Buffer (PBS+1% w/v BSA+0.1% v/v NaN_3) were added. Plates were again incubated for 1 hour at 4° C. Supernatant was aspirated and 25 μL of 4% v/v paraformaldehyde added and plates were incubated 15 minutes at room temperature. Plates were washed twice with 100 μL PBS and then the wash buffer was completely removed. Fluorescence intensity was read by scanning plates using an Odyssey Infrared Imaging System (LI-COR®). Anti-mouse binding (800 nm channel) was normalised to cell number (700 nm channel) according to LI-COR® recommended algorithm. Percent effect was calculated as detailed below (Equation 1). Total binding was defined using reference antibody at a final assay concentration of 1 μg/ml. Non specific binding was defined using mouse IgG1 isotype control (Sigma) at a final assay concentration of 1 μg/mL. Wells were defined as hits where percent effect was greater than or equal to 5%.

Equation 1: Calculation of Percentage Effect from Primary Screen (LI-COR) and HTRF

(Using 800% Resp values (LI-COR) or 665/620 nm ratio (see Equation 2) (HTRF)

$$\text{Percent effect} = \frac{\text{sample well} - \text{non specific binding}}{\text{total binding} - \text{non specific binding}}$$

Non-specific binding=values from wells containing isotype control mouse IgG1 or HMM or buffer

Total Binding (Binding HTRF and LICOR)=values from wells containing reference antibody Total binding (OX40L/OX40RFc assay)=OX40L and OX40RFc

Primary Screen: Binding to Recombinant Human OX40L:

In parallel to screening for binding to CHO-S expressed OX40L, supernatants collected from hybridoma wells were also tested to assess the ability of secreted antibodies to bind to hOX40L expressed as a recombinant protein (produced in-house, see details in Example 1). Binding of secreted antibodies to recombinant hOX40L were identified by HTRF® (Homogeneous Time-Resolved Fluorescence, Cisbio) assay format using biotinylated hOX40L. 5 μL of hybridoma supernatant was transferred to a white 384 well low volume non binding surface polystyrene plate (Greiner). Then 5 μL of biotinylated hOX40L (working concentration 20 nM) diluted in HTRF buffer (PBS (Sigma)+0.53 M KF (Sigma)+0.1% w/v BSA (Sigma) was added. 5 μL of combined detection reagents Streptavidin D2 (Cisbio) diluted 1:100 in HTRF assay buffer for final dilution 1:400 and goat anti-mouse IgG (Southern Biotech) labelled with europium cryptate (Cisbio) diluted 1:100 in HTRF assay buffer for final dilution 1:400 were added. The concentration of goat anti-mouse IgG (Southern Biotech) labelled with europium cryptate was batch dependent and in some cases a dilution of 1:1000 was performed to achieve a final assay concentration of 1:4000. To adjust the total assay volume to 20 μL, 5 μL of HTRF assay buffer was added to all wells. To define non-specific binding, addition of positive control antibody or hybridoma media was replaced with HTRF assay buffer or HMM. The plate was left to incubate in dark for 3 hours prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). More details of the HTRF® assay technology can be found in Mathis (1995) Clinical Chemistry 41(9), 1391-1397. Data were analysed by calculating 665/620 ratio and percent effect for each sample according to Equation 2 and Equation 1 respectively.

Equation 2: Calculation of 665/620 Ratio

$$\text{665/620 ratio} = (\text{sample 665/620 nm value}) \times 10000$$

For clones derived from KM040-1 and KM055-1 a selection criteria of greater than or equal to 20 percent effect was applied by the inventors to define a well as a hit from recombinant hOX40L binding as described in Table 1.

Primary Screen: Human OX40L/Human OX40R Fc Binding Assay:

In order to determine whether supernatants collected from hybridoma wells inhibited the binding of OX40L to OX40RFc, secreted antibodies were tested in an OX40L/OX40RFc binding HTRF assay. 5 μL of hybridoma supernatant was transferred to a white 384 well low volume non-binding surface polystyrene plate (Greiner). Biotinylated OX40L was diluted in HTRF assay buffer to a working concentration of 2.4 nM and 5 μL added. OX40RFc was then diluted to working concentration of 4.8 nM and 5 μL added. Non-specific binding was defined by replacing OX40RFc with assay buffer or HMM. Streptavidin cryptate (CISBIO) and anti-human Fc D2 (CISBIO) were diluted in HTRF assay buffer to working concentration of 1:100 and 5 nM respectively. Plates were covered, protected from light and incubated at room temperature for 3 hrs prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). Data were analysed by calculating 665/620 ratio and percent effect for each sample according to Equation 2 and Equation 5 respectively.

For clones derived from KM040-1 and KM055-1, a selection criteria of less than or equal to 90 percent of the assay signal of OX40 receptor Fc binding to OX40L was applied by the inventors to define a well as a hit as described in Table 1.

Secondary Screen: Binding to Cell Expressed and Recombinant Human OX40L

To determine whether wells selected using the primary screen selection criteria had the required characteristics set by the inventors, a number of assays were performed. Hybridoma clones selected as hits from primary screening were cultured for 3 days and the supernatants collected from hybridoma cells were tested to assess whether the secreted antibodies that bind to CHO-S expressed hOX40L, in some case bind to untransfected CHO-S cells and whether they neutralise recombinant OX40R Fc binding to CHO-S hOX40L and ability to neutralise OX40R binding to recombinant biotinylated hOX40L.

Binding to CHO-S Expressed hOX40L and Receptor Neutralisation:

CHO-S cells expressing hOX40L or untransfected CHO-S cells, diluted in FACS buffer (PBS+1% w/v BSA+0.1% w/v NaN_3) were distributed to a 96 well V-bottom plate (Greiner) at a density of 1×10^5 cells per well. Cells were washed with 150 μL of PBS and centrifuged at 300×g for 3 min. Supernatant was aspirated and 150 IL of PBS added. This wash step was repeated.

25 μL of hybridoma supernatant or purified antibody from hybridoma supernatant diluted in FACS buffer was added to the washed cells and incubated for 10-15 minutes. Reference Antibody or mouse IgG1 control antibody (Sigma) were diluted in FACS buffer to 20 μg/mL and 25 μL added to cells. 25 μL of human OX40R Fc (in-house) diluted to 1000 ng/mL in FACS buffer were then added to wells. Cells were incubated at 4° C. for 30 minutes.

Cells were washed twice with 150 μL of PBS centrifuging after each wash step and aspirating supernatant (centrifuged at 300×g for 3 minutes).

To detect antibody and receptor binding, 50 μL of Goat anti-human IgG-PE (Jackson ImmunoResearch) and APC anti-mouse IgG (Jackson ImmunoResearch) diluted 1 in 500 in FACS buffer was added to the cells. Cells were incubated 30 minutes at 4° C. in the dark.

Cells were washed twice with 150 μL of PBS centrifuging after each wash step and aspirating supernatant (centrifuged at 300×g for 3 minutes).

To fix cells 100 μL 2% v/v paraformaldehyde was added and cells incubated for 30 minutes at 4° C., cells were pelleted by centrifugation 300×g and the plates and resuspended in 50 μL of FACS buffer. PE and APC signal intensity (geomean) was measured by flow cytometry using a BD FACS Array instrument.

% of control binding was calculated using geomean fluorescence as described in equation 1 where total binding was defined as reference antibody at 10 μg/mL and non-specific binding as mouse IgG1 antibody at 10 μg/mL. % receptor binding was calculated using Equation 3.

Equation 3: Percentage of Receptor Binding (FACS)
Based on geomean fluorescence

$$\%\ \text{of Receptor binding} = \frac{\text{sample value} - \text{non specific binding}}{\text{total binding} - \text{non specific binding}} \times 100$$

Non-specific binding=No antibody, no receptor

Total binding=receptor (OX40R) only binding (no inhibitor)+isotype control at 10 μg/mL

Secondary Screen—HTRF Ligand/Receptor Neutralisation

To determine whether antibodies identified from primary screen neutralise OX40L binding to OX40RFc an human OX40L/human OX40R Fc binding assay was performed as described for primary screen.

Plates were left to incubate in dark for 3 hours prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). More details of the HTRF® assay technology can be found in Mathis (1995) Clinical Chemistry 41(9), 1391-1397. Data were analysed by calculating delta F as described in Equation 4 and percentage of receptor for each sample according to Equation 5.

Equation 4: Calculation of % DeltaF

$$\%\ \text{delta } F = \frac{\text{(sample 665/620 nm ratio value)} - \text{(non-specific control 665/620 nm ratio value)}}{\text{(non-specific control 665/620 nm ratio)}} \times 100$$

Equation 5: Percentage of Receptor Binding (HTRF)
Based on calculation of % deltaF (Equation 4) or 665/620 ratio (Equation 2)

$$\%\ \text{of Receptor binding} = \frac{\text{sample value} - \text{non specific binding}}{\text{total binding} - \text{non specific binding}} \times 100$$

Non specific binding=HMM or buffer+OX40L (no receptor)

Total binding=receptor (OX40R) and OX40L (no inhibitor)

Hit Criteria Selection from Secondary Screening:

A panel of hits were selected based on binding and neutralisation assays. Hits in CHO-S OX40L binding assay were defined by the inventors as significant binding to CHO-S OX40L cells and no binding to CHO-S cells by FACS. Hits were further defined as having the ability to significantly reduce OX40RFc binding to recombinant OX40L (HTRF) and significantly reduce OX40RFc binding to hOX40L expressed on CHO cells. Data is summarised in Table 1. Apparent affinity measurements by SPR were also considered.

Example 3

Antibody Lead Characterisation

Based on the screening selected wells were expanded and murine/human chimeric antibodies purified using a standard Protein G based affinity chromatography purification (see method below). The antibodies were subjected to various assays to assess their ability to block hOX40L binding to it receptor OX40R, as well as the ability of each antibody to bind to human as well as Rhesus monkey OX40L with high apparent affinity. To decipher which antibodies were the best, selected clones were tested using OX40L/OX40RFc HTRF assay and OX40L induced IL2 release from primary human T-cells.

TABLE 1

mAb Lead Summary

Antibody	FACS Binding	HTRF Receptor Neutralisation IC_{50} nM (+/−SEM)	Primary T-cell Assay IC_{50} nM (+/−SEM)	Apparent Affinity hOX40L (nM)	Apparent Affinity RhsOX40L (nM)
10A07 (hybridoma)	YES	+++	+++	CNROR	CNROR
10A07 (human)	ND	+++	+++	CNROR	CNROR
		1.2 nM (+/−0.17)	0.83 nM (+/−1.2)		
2D10 (hybridoma)	YES	+++	ND	CNROR	CNROR
2D10 (human)	ND	+++	+++	CNROR	CNROR
		0.75 nM (+/−0.04)	0.81 nM (+/−0.06)		
9H04 (hybridoma)	YES	+	ND	5.3	ND
19H01 (hybridoma)	YES	++	ND	2.2	ND

CNROR = Cannot resolve off-rate

IC_{50} data represents arithmetic mean+/−standard error of mean (SEM) for three independent experiments or donors.

Materials and Methods:

Purification of Antibodies from Hybridoma Supernatant:

Antibodies were purified using Protein G affinity chromatography. Antibodies were eluted from the Protein G media using IgG Elute reagent (Pierce) and the eluted antibodies were buffer swapped into PBS prior to use. Antibody purity was assessed by SDS-PAGE analysis and quantified by spectrophotometer reading at OD280 nm.

Binding of antibodies purified from hybridoma supernatant was carried out as described herein.

HTRF Ligand/Receptor Neutralisation:

The following methods were carried out with a titration of inhibitor in order to establish the clone potency as measured by IC_{50} values in the assay. Antibody purified from hybridoma was titrated by diluting in HTRF assay buffer and 5 μL of this titration transferred to a white 384 well low volume non-binding surface polystyrene plate (Greiner). Biotinylated OX40L was diluted in HTRF assay buffer to a working concentration of 2.4 nM and 5 μL added. OX40RFc was then diluted to working concentration of 4.8 nM and 5 μL added. Non-specific binding was defined by replacing OX40RFc with assay buffer or HMM. Streptavidin cryptate (CISBIO) and anti-human Fc D2 (CISBIO) were diluted in HTRF assay buffer to working concentration of 1:100 and 5 nM respectively. Plates were covered, protected from light and incubated at room temperature for 3 hrs prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). Data were analysed by calculating delta F as described in Equation 4 and percentage of receptor for each sample according to Equation 5 or in some cases Equation 6. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 7).

Equation 6: Percentage of Receptor Binding (HTRF)

Based on calculation of % DeltaF (Equation 8)

$$\%\ \text{of Receptor binding} = \frac{\text{sample value}}{\text{total binding}} \times 100$$

Total binding=receptor (OX40R) and OX40L (no inhibitor)

Equation 7: Four Parameter Logistic Calculation

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom})/(1 + 10\hat{}((\text{Log IC50} - X) * \text{HillSlope}))$$

X=logarithm of concentration.

Y=specific binding (equation 6)

Top and Bottom=Plateus in same units as Y (specific binding)

Log IC_{50} in same units as X. Y starts at Bottom and goes to Top with a sigmoid shape. Specific binding decreases as X increases.

Profiling of Fully Human Recombinant Anti-OX40L Antibodies in HTRF Ligand/Receptor Neutralisation Assay

In order to determine whether recombinantly expressed fully human purified IgG inhibit human OX40L binding to OX40RFc the following method was carried out. Fully human purified IgG or other inhibitor were tested in order to establish the clone potency as measured by IC_{50} values in the assay. Antibodies recombinantly expressed and purified were titrated by diluting in HTRF assay buffer and 5 μL of this titration transferred to a white 384 well low volume non-binding surface polystyrene plate (Greiner). Biotinylated OX40L was diluted in HTRF assay buffer to a working concentration of 2.4 nM and 5 μL added. OX40RFc directly labelled with AF647 was then diluted to working concentration of 10 nM and 5 μL added. Non-specific binding was defined by replacing OX40RFc-AF647 with assay buffer or HMM. Streptavidin cryptate (CISBIO) was diluted in HTRF assay buffer to working concentration of 1:100 and 5 μL added to all wells of the plate. Plates were covered, protected from light and incubated at room temperature for 3 hrs prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). Data were analysed by calculating delta F as described in Equation 4 and percentage of receptor for each sample according to Equation 5 or in some cases Equation 6. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 7) (FIG. **1**).

Determining Effect of Anti-OX40L Antibodies on Recombinant OX40L Induced IL2 Release from Primary Isolated T-Cells

Recombinant human OX40L (in house) was diluted in culture media to a concentration of 400 ng/mL and 50 μL added to a tissue culture treated 96 well plate (Costar). Anti-OX40L antibodies or appropriate species isotype control (Sigma or in house) were titrated in culture media in a 96 well plate (greiner) and then 50 μL of titration transferred to the 96 well plate containing 50 μL OX40L. The antibody titration was incubated for 30 minutes at room temperature with the recombinant OX40L before CD3 positive T-cells were added.

PBMCs were isolated from leukoreduction system chambers (NHSBT) using Ficoll-Paque plus (GE Healthcare) by density gradient centrifugation. CD3 positive cells (T-cells) were isolated from human PBMC by negative selection using magnetic microbeads (Miltenyi Biotech) according to manufacturer's recommendations. The isolated cells were centrifuged at 300×g/5 min, resuspended in culture media (culture media was defined as either RPMI (Gibco)+10% v/v FBS or RPMI+5% v/v human AB serum) and 50 μL of the cell suspension added to the 96 well plate containing the recombinant OX40L and antibody titration to a achieve final concentration of 2×10^5 cells/well.

Then 50 μL of PHA at 8 μg/mL was added to all wells to achieve a final assay concentration of 2 μg/mL. The cells were incubated at 37° C. for 3 days before supernatant were harvested and analysed for IL-2 concentration. Maximal IL-2 release was defined by OX40L stimulation in the absence of inhibitor. Minimal IL-2 release was defined by culture media only (no OX40L).

IL-2 levels in supernatants were determined using human IL-2 Duoset ELISA kit (R & D) Systems) according to manufacturer's recommendations. IL-2 capture antibody (4 μg/mL diluted in PBS, 50 μL/well) was adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4° C. Excess IgG was removed by washing with PBS-Tween and the wells were blocked with 1% bovine serum albumin (BSA) in PBS for 1 hour at room temperature, after which plates were washed as described previously. 50 IL/well of conditioned culture media was then added IL-2 standards (from 2000 μg/mL, 1:2 dilution) were also added to ELISA plates as an ELISA control and the plates were incubated at room temperature for at least 1 hour.

Following incubation, plates were washed as before to remove unbound proteins. Biotinylated IL-2 detection Ab (200 ng/mL in reagent diluent (0.1% BSA/PBS); 50

μL/well) was then added to the plates and incubated at RT for 1 h. Unbound detection antibody was removed by washing with PBS-Tween (0.1% v/v), while the remaining biotinylated antibody was detected by streptavidin-Europium3+conjugate (DELFIA® detection, PerkinElmer). Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Fluorescence data was plotted as Europium counts or concentration of IL-2 release calculated from standard curve by linear regression according to manufacturer's recommendations. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 7).

Surface Plasmon Resonance Analysis:

SPR analysis was carried out using the ProteOn™ XPR36 Array System (BioRad). Anti-mouse IgG (GE Healthcare BR-1008-38) was immobilised on a GLM biosensor surface using amine coupling, the surface was then blocked using 1 M ethanolamine. Test antibodies were captured on this surface and recombinant hOX40L (human and rhesus) were used at a single concentration of 256 nM, binding sensorgrams were double referenced using a buffer injection (i.e. 0 nM) to remove baseline drift and injection artefacts. Apparent affinities for the OX40L-antibody interaction were determined using the 1:1 model inherent to the ProteOn XPR36 analysis software. The assay was run using HBS-EP (Teknova) as running buffer and carried out at 25° C.

Example 4

Sequence Recovery of Lead Antibody Candidates

After the selection and characterisation of lead candidates, their fully human variable domains were recovered using RT-PCR using a mixture of forward and reverse primers. Antibodies were reformatted into a human IgG4 backbone (IgG4-PE) and expressed using a transient expression system in CHO-S cells. A summary of all sequences is displayed in the Sequence Listing.

RNA Isolation from Hybridoma Cells:

Total RNA was extracted from hybridoma cells using TRIzol™ Reagent (Invitrogen). The quantity and quality of the isolated RNA was analysed spectrophotometrically.

Antibody Variable Domain Recovery by RT-PCR:

Selected clones were used for preparing total RNA, which was used in an RT-PCR reaction to recover the heavy chain V-regions. IgG specific reverse primers and Ig leader sequence specific forward primer sets or alternatively IgG specific reverse primers and Ig 5' untranslated region (UTR) sequence specific forward primer sets were used for the heavy chains. Kappa constant region specific reverse primers and kappa leader sequence specific forward primer sets or alternatively Kappa constant region specific reverse primers and kappa 5'UTR sequence specific forward primer sets were used for the kappa OX40L chains. The RT-PCR products were separated by agarose gel electrophoresis with the DNA of the predicted size being sequenced in the forward and reverse directions. Alternatively, the RT-PCR products were subcloned into a cloning vector and DNA of individual colonies submitted for sequencing.

Cloning of Recombinant Antibodies

DNA encoding the heavy chain variable region of mAb 10A7 was cloned into a pREP4 expression plasmid (Invitrogen) in frame with the Human IgG1 constant region and DNA encoding the light chain variable region of mAb 10A7 was cloned into a pREP4 expression plasmid in frame with the Human Kappa constant region using standard restriction enzyme digestion and ligation.

The heavy chain variable region coding sequences of mAbs 10A7 and 2D10 in frame with the Human IgG4-PE constant region were codon optimised for mammalian expression and cloned into a pXC-18.4 expression plasmid (Lonza) and the light chain coding sequences of mAbs 10A7 and 2D10 in frame with the Human Kappa constant region were codon optimised for mammalian expression and cloned into a pXC-17.4 expression plasmid (Lonza) using standard restriction enzyme digestion and ligation. For the simultaneous expression of the heavy and light chains the vectors a pXC-17.4 and a pXC-18.4 were fused into one single vector using standard restriction enzyme digestion and ligation.

All constructs were sequenced to ensure their correct sequence composition.

Transient Expression of OX40L Antibodies

Antibodies were expressed transiently to produce recombinant protein using Invitrogen's FreeStyle™ CHO-S suspension adapted cell line. Plasmids were transfected into the cells using PEI (polyethylenimine MW 40000) and left to overgrow for a period of 13 days before harvesting the supernatant for purification. Cells were fed during the overgrow process with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process samples were taken regularly to monitor cell growth and viability.

Generation of Stable Lonza Pools

In order to produce the gram amounts required for toxicology studies, 10A7 and 2D10 OX40L antibodies were transferred to the Lonza GS Xceed system for stable expression. The HC and LC for each antibody was first codon optimised for expression in CHO cells by Genewiz. The HC cassette (containing the optimised IgG4PE constant region) was then cloned into Lonza's pXC18.4 vector and LC cassette (containing the optimised kappa constant region) cloned into Lonza's pXC17.4 vector using standard restriction enzyme digestion and ligation. A double gene vector (DGV) encoding both the HC and LC sequences was then created by restriction enzyme digestion and ligation and sequence confirmed before expression.

Prior to stable pool creation; the single gene vectors encoding the HC and LC's separately as well as the DGV containing both, were expressed in the Lonza CHOK1SVKO cell line transiently using PEI (polyethylenimine MW 40000). Cells were left to overgrow for a period of 13 days before harvesting the supernatant for purification. During this period cells were fed with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process samples were taken regularly to monitor cell growth and viability. Once transient expression was confirmed and purified material analysed the antibodies were expressed as stable pools.

Stable pools were generated using Lonza's proprietary methods and media. 4 pools were created per antibody and left to recover over a period of 10-15 days. After the cells had recovered, pre-seed stocks (PSS) of cells were frozen down for later recovery and creation of MCB. Small scale (50 mL) shake flask fed batch overgrows were then set up using Lonza's proprietary media. Cells were left to overgrow for a period of 14 days. During this period cells were monitored for growth, viability and glucose levels. Cells were supplemented accordingly with Lonza's proprietary feed and 400 g/L glucose. Samples were also taken throughout the process for crude sample quantification. At the end of the overgrow process the supernatant was harvested for purification.

Stable pools were generated using Lonza's proprietary methods and media. 4 pools were created per antibody and left to recover over a period of 10-15 days. After the cells had recovered, pre-seed stocks (PSS) of cells were frozen down for later recovery and creation of MCB. Small scale (50 mL) shake flask fed batch overgrows were then set up using Lonza's proprietary media. Cells were left to overgrow for a period of 14 days. During this period cells were monitored for growth, viability and glucose levels. Cells were supplemented accordingly with Lonza's proprietary feed and 400 g/L glucose. Samples were also taken throughout the process for crude sample quantification. At the end of the overgrow process the supernatant was harvested for purification.

Whilst the 2D10 and 10A07 were similar in sequence, there expression profiles in the stable Lonza pools were different, 10A07 expressed to very low titres, whereas 2D10 expressed at much greater titres (see Table 2) under optimal conditions when using shake flasks in 4 separate generated stable pools.

TABLE 2

(Concentration in mg/L)

Stable pool	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
2D10-1	261	492	681	993	1157	1590	1530	1575
2D10-2	245	461	665	983	1127	1485	2025	1995
2D10-3	317	528	731	1163	1367	1785	1905	1860
2D10-4	372	677	785	1286	1350	1935	1965	1800
Control Antibody 1	92	129	167	229	297	357	416	N/A
Control Antibody 1	66	95	127	161	208	238	266	N/A
Control Antibody 1	68	102	132	192	266	324	314	N/A
Control Antibody 1	88	129	165	245	328	410	385	N/A

After expression, the antibody to be used in the *Rhesus Macaque* GvHD model was purified using a two-step purification process. The antibodies were first purified using MabSelect SuRe (GE Healthcare) affinity chromatography. Antibodies were eluted from the MabSelect SuRe media using IgG Elute reagent (Pierce) and the eluted antibodies were dialysed in sodium acetate (pH 5.5) buffer prior to the second purification step. Antibodies were then purified by cation exchange and eluted with sodium chloride in sodium acetate buffer. Eluted antibodies were dialysed in PBS. Antibodies were quantified by spectrophotometer reading at OD280 nm and adjusted to the desired concentration (10 mg/ml). Antibody purity was assessed by SDS-PAGE analysis and size exclusion chromatography. Endotoxin concentration was measured with Endosafe PTS and LAL Test Cartridges (Charles River Laboratories).

Example 5

Determining Effect of Anti-OX40L Antibodies in Allogeneic PBMC Mixed Lymphocyte Reaction

PBMCs are isolated from leukoreduction system chambers (NHSBT) using Ficoll-Paque plus (GE Healthcare) density gradient centrifugation. PBMC are pre-incubated with mitomycin C (Sigma) at 10 μg/mL in PBS for one hour at 37° C. Cells are then washed 3 times in PBS centrifuging at 300×g for 3 minutes, aspirating the supernatant after each wash. Allogeneic PBMC (not treated with mitomycin C) are added to a 96-well plate in RPMI supplemented with 10% v/v FBS at a concentration of 2×10^6/ml, 50 μL/well. Anti-OX40L antibodies are diluted in culture media and added to 96 well plate containing PBMC (not mitomycin C treated) at 50 μL/well. Mitomycin C treated PBMC are then added to allogeneic PBMC (not treated with mitomycin C) in 96-well plate at a final cell ratio in range of 1:1 to 4:1 mitomycin C treated to non mitomycin C based on number of cells/well. The cells are incubated for five days at 37° C./5% C02. After five days TNF-α, IFN-γ, and IL-2 are measured by duoset ELISA (R&D Systems) according to manufacturer's recommendations. Proliferation is measured by CFSE dilution according to manufacturer's recommendations.

PBMCs were isolated from leukoreduction system chambers (NHSBT) using Ficoll-Paque plus (GE Healthcare) density gradient centrifugation. PBMC were pre-incubated with mitomycin C (Sigma) at 10 μg/mL in PBS for one hour at 37° C. Cells were then washed 3 times in PBS centrifuging at 300 xg for 3 minutes, aspirating the supernatant after each wash. T-lymphocytes (T-cells) in some cases CD3 positive and in other cases CD4 and CD8 positive were isolated from allogeneic PBMC by negative selection using magnetic microbeads (Miltenyi Biotech) according to manufacturer's recommendations. In some cases, non-mytomycin C treated PBMC were used instead of T-cells. The isolated cells were centrifuged at 300×g/5 min, resuspended in culture media (culture media was defined as either RPMI (Gibco)+10% v/v FBS or RPMI+5% v/v human AB serum) and 50 μL of the cell suspension added to the 96 well plate containing the recombinant OX40L and antibody titration to a achieve final concentration of 2×10^5 cells/well. Anti-OX40L antibodies were diluted in culture media to a final assay concentration 100 nM or in some cases a titration of antibody was used. The antibodies were added to 96 well plate containing T-cells or non-mytomycin C treated PBMC at 50 μL/well. Mitomycin C treated PBMC were then added to Tcells or non mytomycin C treated PBMC in 96-well plate at a final cell ratio in range of 1:1 to 4:1 mitomycin C treated PBMC to T-cells (or PBMC) based on number of cells/well. The cells were incubated for five days at 37° C./5% CO_2. After five days, IFN-γ was measured by duoset ELISA (R&D Systems) according to manufacturer's recommendations.

Anti-OX40L antibodies were defined as inhibitors in allogeneic PBMC/T-cell MLR or PBMC/PBMCI MLR when >20% inhibition (see Equation 8) of factor release (IFN-γ,) or were observed relative to control wells in the absence of antibody. From four experiments performed, one experiment was a technical failure, defined as no MLR response (IFN-γ release) detected between allogeneic donors. Of the three remaining experiments, all three showed inhibition (>20% inhibition of factor release (IFN-γ,) observed relative to control wells in the absence of antibody) with 2D10, 10A07 and positive control 1, however in one of three experiments, significant inhibition was also observed with the isotype control antibody (FIG. **2**). For PBMC/PBMC MLR, three experiments were performed. Of three experiments, two were regarded as technical failure as there was no or low IFN-γ release. However, in another experiment 10A07 inhibited IFN-γ release when compared to the isotype control.

Equation 8: Percentage Inhibition (MLR)

Based on values from IFN-γ or IL2 release (pg/mL) determined as described

$$\%\ \text{inhibition} = 100 - \frac{\text{sample value} - \text{no stimulus}}{\text{No } IgG - \text{no stimulus}} \times 100$$

No Stimulus=wells where only T-cells or non-mytomycin C treated PBMC are added (no mitomycin C treated PBMC)

No IgG=wells where T-cells or in some cases non-mytomycin C treated PBMC along with mytomycin C treated PBMC are added but no IgG

Example 6

Determining Effect of Anti-OX40L Antibodies on CD3 Primed Primary Human T Lymphocytes

In order to determine whether anti-OX40L had the ability to induce T-cell responses in the absence of OX40L, the assay below was performed using method adapted from Wang et al., Hybridoma (Larchmt)., 2009 August; 28(4): 269-76, in which an agonist anti-OX40L antibody was described.

A mouse anti-human CD3 antibody (Becton Dickinson) was diluted to 0.5 μg/mL in sterile PBS and 50 μL/well added to a 96 well high binding sterile plate and incubated overnight at 4° C.

Following overnight incubation, the plate was washed three times with 100 μL of sterile PBS.

T-cells (CD3 positive) were isolated from PBMC derived from leukoreduction system chambers (NHSBT) as described in Example 3. Following isolation, the cells were added to wells in 100 μL to achieve a final concentration of 1×10^5 cells/well.

Test antibodies were diluted in RPMI+10% FBS and 50 μL or 100 μL/well added to cell plate to achieve a final assay concentration of 10 μg/mL. In some cases, a mouse anti-human CD28 antibody (Becton Dickinson) was also added to wells at a final concentration of 1 μg/ml

The assay was incubated for 5 days. After 5 days, harvest supernatants and IFN-γ levels in supernatant were determined as described in Example 5.

The assay was performed in four independent donors and no effect of adding 10A07 or 2D10 in IgG4PE format was observed (IFN-γ release) over that observed with human IgG4PE isotype control.

Example 7

Rhesus Macaque Graft Versus Host Disease (GvHD) Model

The effectiveness of antibody 2D10 IgG4PE as a monotherapy prophylactic for the prevention of GvHD was examined in a *Rhesus Macaque* model of haploidentical hematopoietic stem cell transplantation (HSCT). It had been previously described that monkeys undergoing HSCT in this model had a survival time of 6-8 days (Miller, Weston P., et al. "GVHD after haploidentical transplantation: a novel, MHC-defined *rhesus macaque* model identifies $CD28^-$ $CD8^+$ Tcells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression." Blood, 116, 24(2010):5403-5418.) All transplants were between half-sibling pairs that are mismatched at one MHC haplotype ("haploidentical-HCTs"). Recipient animals had irradiation based pre-myeloablative pre-transplant conditioning using a linear accelerator. Dose rate: 7cGy/min. Dose 1020 cGy given in 4 fractions. The leukapheresis donor animal underwent GCSF mobilisation and underwent leukapheresis using a Spectra Optia apheresis machine. The table below gives the dose per kg of total nucleated cells (TNC) dose of $CD3^+$ cells, and $CD34^+$ cells for the four successful experiments.

TABLE 3

Recipient ID#	Animal No.	Recipient Bodyweight (kg)	TNC (10^9/kg)	$CD3^+$ T-cells 10^6/kg	$CD34^+$ cells 10^6/kg
A14079	#2	9.75	1.13	149.76	0.51
A14081	#4	7.02	2.99	389.08	4.79
A14082	#5	7.6	2.24	312.95	2.69
A14087	#6	5.75	3.44	385.66	9.99

2D10 IgG4PE was dosed at 10 mg/kg i.v. according to a planned dosing schedule to take place on Day −2, Day +5, Day +12, Day +19, Day +26, Day +33, Day +40, Day +47 post-transplant. No serious adverse dosing side effects were seen with any of the animals as a result of administering 2D10 IgG4PE.

Samples were taken during the course of the study to monitor donor chimerism (Table 4) and white blood cell counts. The primary end point was based on survival, with a survival to 15 days deemed to be a sign of successful prophylactic therapy (and compared to the documented survival of 6-8 days with no prophylaxis; Miller et al 2010, supra). Though full pathology and histology with GvHD grading scores, markers of T-cell proliferation and activation (such as Ki-67 and granzyme B) and gene array analysis are planned, they were not available for inclusion at the time of drafting.

Methods for these studies are essentially as described in Miller W P et al., (2010) "*GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque* model identifies CD28− *CD8+T-cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression*", Blood 116:5403-5418.

Clinical staging of GvHD

Scoring of clinical symptoms was based on observational assessments and clinical chemistry, classified according to the criteria set out in Table 5.

Histopathology

Tissues, including lung, liver, skin and gastrointestinal tract were collected at necropsy and fixed in formalin and paraffin-embedded. Sections were cut, slide-mounted and stained with haematoxylin/eosin or with T-cell markers for visualisation of tissue infiltration by lymphocytes. Prepared slides are read by a histopathologist with specific expertise in GvHD using a semiquantitative scoring system.

Flow Cytometry

Longitudinal peripheral blood samples were collected before and after haematopoietic stem cell transplant and at necropsy for flow cytometric analysis of lymphocyte subsets. Lung, liver, colon spleen and lymph node (axillary and inguinal) tissues were collected at necropsy and dissociated or enzymatically digested as appropriate for subsequent analysis of lymphocyte infiltrates by flow cytometry. Samples were analysed by multicolour flow cytometry using a LSRFortessa cell analyser (BD Biosciences) using the following T lymphocyte marker probes: CD3 (APC-Cy7 label; clone SP34-2, BD Biosciences), CD4 (BV786 label; clone L200, BD Biosciences), CD8 (BUV395 label; clone RPA-T8, BD Bioscences), CD28 (PE-Cy7 label; clone

CD28.2, eBioscience), CD95 (BV605 label; clone DX2, Biolegend). Proliferating cell populations were identified using Ki-67 (FITC label, Dako). $CD4^+$ or $CD8^+$ T-cell subcompartments were labelled as follows: naïve T-cells ($CD28^+/CD95^-$), central memory T-cells ($CD28^+/CD95^+$), effector memory T-cells ($CD28^-/CD95^+$).

Blood was collected into tubes with Sodium EDTA, and then red blood cells were lysed with lysis buffer containing ammonium chloride. Remaining leukocytes were washed with FACS buffer (PBS with 2% FBS) and stained with antibody cocktail (Table 7) for 30 minutes at 4° C. After staining, cells were washed and fixed in 1×BD Stabilising Fixative. Acquisition of flow data was performed on BD LSR Fortessa cytometer. Data were analysed using FloJo. T-cells were defined as $CD3^+CD14/CD20^-$ lymphocytes.

Results:

1: Expansion of Memory Stem T-Cells after Transplantation

In a non-human primate model of acute Graft-versus-Host disease (GVHD), allogeneic hematopoietic cell transplantation (HCT) results in early expansion of both $CD4^+$ and $CD8^+$ memory stem T-cells (Tscm: $CD45RA^+CCR7^+CD95^+$) at the expense of reconstitution of bona fide naïve T-cells (Tn: $CD45RA^+CCR7^+CD95^-$) (FIG. **3**). These Tscm cells circulate in the blood, and also reside in both lymphoid (lymph nodes, spleen) and non-lymphoid organs (lung, liver and colon).

TABLE 7

List of used antibodies for T-cell immunophenotyping by flow cytometry

Antibody	Fluorochrome	Clone	Company
CD3	APC-Cy7	SP34-2	BD Biosciences
CD4	BV786	L200	BD Biosciences
CD8	BUV395	RPA-T8	BD Biosciences
CD14	PerCP-Cy5.5	M5E2	BD Biosciences
CD20	PerCP-Cy5.5	2H7	eBioscience
CD28	PE-Cy7	CD28.2	eBioscience
CD45RA	APC	2H4LDH11LDB9	Beckman Coulter
CD95	BV605	DX2	Biolegend
CCR7 (CD197)	BV421	G043H7	Biolegend
OX40 (CD134)	PE	L106	BD Biosciences

2: 2D10 IgG4PE Limits Expansion of Tscm

Treatment with the blocking anti-OX40L antibody, 2D10 IgG4PE, results in prolonged survival of animals after allogeneic HCT and reduces clinical symptoms of acute GVHD. This delay in GVHD progression was associated with limited $CD4^+$ Tscm expansion and preservation of $CD4^+$ Tn cells (FIG. **4**).

3: $CD4^+$ Tscm Cells Express OX40 on their Surface

As shown in FIG. **5**, $CD4^+$ Tscm express OX40 on their surface, but naïve T-cells do not. Moreover, the level of OX40 expression was comparable between $CD4^+$ Tscm and central memory cells (Tcm). Importantly, OX40 expression was detected on $CD4^+$ Tscm cells broadly. They are detected in naïve monkeys before transplantation (both in the blood and lymphoid organs), as well as in leukopheresis products. This expression is also seen in allogeneic HCT recipients longitudinally after transplantation.

4: Comparative Analysis of Tscm in 02D10 Iq4PE Treated Animals Compared to Standard GvHD Therapies

The proportion of post-HCT Tscm cells evident in the peripheral blood of rhesus monkeys that received 02D10 IgG4PE were compared with Tscm from separate groups of animals administered either sirolimus (rapamycin) or a combination of tacrolimus plus methotrexate (Tac/MTX). The results for $CD4^+$ Tscm cells are shown in FIG. **6***a*, and the results for $CD8^+$ Tscm cells are shown in FIG. **6***b*. Data indicate that treatment with anti-OX40L antibody 02D10 IgG4PE results in a sustained inhibition of the proportion of Tscm cells compared with the sirolimus and Tac/MTX treatment.

Conclusions:

An OX40-expressing subset of Tscm might be sensitive to 2D10 IgG4PE-mediated OX40L-blockade. This blockade may control Tscm expansion and therefore limit the progression of acute GVHD. The OX40 pathway is a potentially novel mechanism of Tscm regulation, which can be used in clinical practice to treat immune-mediated diseases or improve the outcome of adoptive immunotherapy.

Chimerism

Peripheral blood or T-cell ($CD3^+/CD20^-$) chimerism was determined using divergent donor- and recipient-specific MHC-linked microsatellite markers, by comparing peak heights of the donor- and recipient-specific amplicons (Penedo M C et al., (2005) "*Microsatelllite typing of the rhesus macaque MHC region*", Imunogenetics 57:198-209).

A total of six animals were selected to receive HSCT. Of these 6 animals, two of the experiments were deemed a technical failure, one animal experienced viral reactivation which may have hampered engraftment and it was seen that donor chimerism initially climbed but then dropped, indicating that second reconstitution was autologous repopulation. A single high cytomegalovirus (CMV) and *Rhesus macaque* Lymphocryptovirus (rhLCV) reading was seen at the same time as the drop in chimerism and autologous repopulation.

TABLE 5

Stage	Skin	Liver (Billirubin)	GI
0	No GVHD rash	<4-fold increase over baseline	No diarrhea
1	Rash <25% of body surface area	4- to 8-fold increase over baseline	"Mild" diarrhea
2	Rash 25-50% of body surface area	8- to 20-fold increase over baseline	"Moderate" diarrhea w/o any other cause
3	Rash >50% of body surface area	20- to 50-fold increase over baseline	"Severe" diarrhea w/o any other cause
4	Generalised erythroderma with bullous formation	>50-fold over baseline	"Very severe" diarrhea (with blood) w/o any other cause

The second technical failure was the result of failure of the apheresis machine to produce a suitable product for transplantation. Since the recipient animal had already been irradiated, it had to be sacrificed. The four other animals all survived to the primary endpoint of 15 days, exhibiting extended survival compared to both historical and contemporaneous no-prophylaxis controls. Table 6 below outlines the summary of each animal in this study.

Example 8

Pharmacokinetics

Rhesus macaques were dosed with 10 mg/kg of 2D10 or appropriate non-functional isotype control antibody on Day 0. Samples were taken, after +15 minutes, +1 hour, +8 hours, +24-36 hours, +72 hours, +96 hours, +Day 8, +Day 11, +Day 15, +Day 18, +Day 22, +Day 25. On Day 29, animals were dosed with 3 mg/kg of 2D10 or appropriate non-functional isotype control antibody. Samples were taken on Day 29 after +15 minutes, +1 hour, +8 hours and then 24-36 hours after Day 29. Samples continued to be taken on +Day 32, +Day 33, +Day 36, +Day 39, +Day 43, +Day 46, +Day 50, +Day 53, +Day 57, +Day 60, +Day 64, +Day 67 and +Day 71.

To determine the PK, anti-human IgG is diluted to 8 μg/mL in PBS and is adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4° C. Excess IgG is removed by washing with PBS-Tween and wells are blocked with 5% w/v non-fat dried milk (blocking buffer) for 1 hour at room temperature. Following incubation period, plates are washed. Plasma samples are diluted in blocking buffer (multiple dilutions). A standard curve is also generated using a titration of positive control anti-OX40L antibody diluted in blocking buffer from 10 μg/mL (1 in 3 dilution). Either titration or diluted plasma sample are added to plate and incubated for 1 hr at room temperature. Plates are then washed and biotinylated human OX40L is diluted to 500 ng/mL in blocking buffer added for 1 hour at room temperature. Plates are then washed and streptavidin-Europium3$^+$conjugate (DELFIA® detection, PerkinElmer) diluted in DELFIA® assay buffer (Perkin Elmer) is added. Plates are then washed 3 times in Tris Buffered Saline +0.1% tween. Then, DELFIA Enhancement solution (Perkin Elmer) is added to the plate and time-resolved fluorescence is measured at 615 nm on an Envision plate reader (PerkinElmer). The concentration of anti-OX40L antibody in the plasma is calculated by extrapolating fluorescence values from sample wells to those obtained from the standard curve generated from the titration of the positive control anti-OX40L antibody using a four parameter logistics curve fitting algorithm.

Example 9

Rhesus Macaque (GvHD) Model: Effect of Combined Prophylaxis with 2D10 IqG4PE Plus Rapamycin

A further *rhesus macaque* GvHD study was conducted to determine the effect of combined post-HSCT prophylaxis with 2D10 IgG4PE and rapamycin. The study was performed as described in Example 7, with dosing as follows: 2D10 IgG4PE was administered i.v. at 10 mg/kg on Day −2, Day +5, Day +12, Day +19, Day +26, Day +33, Day +40, Day +47 and Day +56 post-transplant. Rapamycin was administered at a loading dose of 0.1 mg/kg i.m. on Day −14, followed by daily i.m. maintenance doses of 0.025 mg/kg until the scheduled termination of the study at Day +100. Rapamycin dosing was adjusted to maintain serum trough levels within the range 5-15 ng/mL.

Results:

Post-HSCT administration of 2D10 IgG4PE together with rapamycin resulted in extended GvHD-free and absolute survival (median survival time, MST>82 days; n=3) compared to historical control animals that did not receive post-HSCT experimental treatment (MST=8 days; n=4; Furlan et al, Science Translational Medicine, Vol 7 (315); 315ra1910). The effect of combined 2D10 IgG4PE plus rapamycin dosing appeared also to be greater than the additive effect of each molecule when administered alone (FIG. **7**: MST for post-HSCT 2D10 IgG4PE and rapamycin were 19 and 17 days, respectively; both n−4). It is also noted that Furlan et al discloses a MST for combined prohylaxis with tacrolimus plus methotrexate of 49 days. It is expected that a combination of tacrolimus plus methotrexate and an anti-OX40L antibody (such as 2D10), or indeed a combination of tacrolimus and an anti-OX40L antibody (such as 2D10), would also provide the synergistic results as seen in this Example.

Without being bound by theory, any modulator of the IL-2 pathway may provide the synergistic effects seen with this example, for example and IL-2 inhibitor.

Example 10

Following the *rhesus macaque* combination study described in Example 9, histopathology and flow cytometry were carried out using procedures substantially identical to those described in Example 7.

Ki-67 Expression

Peripheral blood mononuclear cells were isolated at different time points by Ficoll-Paque gradient and then were stained for cell surface markers (CD3, CD4, CD8) followed by fixation/permeabilization (using BD Cytofix/Cytoperm kit) and intracellular staining for Ki-67. Ki-67 expression in NHP peripheral blood CD4$^+$ (FIG. **8**A) and CD8$^+$ (FIG. **8**B) was measured. T-cells before (pre-HCT) and following allogeneic HCT in recipients being untreated (No Rx) or treated with OX40L antibody. Plots show Ki-67 expression in NHP peripheral blood bulk CD4$^+$ (FIG. **8**C) and CD8$^+$ (FIG. **8**D) T-cells before (pre-HCT) and following allogeneic HCT in recipients treated with rapamycin and with a combination of rapamycin and anti-OX40L antibody. Statistical analysis was performed using Holm-Sidak multiple-comparison post-test. *$p<0.05$.

FIG. **8** shows that allogeneic HCT triggers expression of Ki-67 on T-cells, and that the anti-hOX40L antibody reverses that expression. Rapamycin has an initial effect, but does not effectively control the number of proliferating T-cells. The combination of rapamycin and the anti-hOX40L antibody shows the most effective suppression of T-cell proliferation, which may be synergistic.

Analysis of Treg Cells Over Time

Peripheral blood mononuclear cells were isolated prior (pre-HCT) and during terminal analysis following allogeneic HCT without immunoprophylaxis (No Rx), or treatment with rapamycin, or treatment with anti-OX40L antibody, or treatment with a combination of anti-OX40L antibody and rapamycin by Ficoll-Paque gradient and then were stained for cell surface markers (CD3, CD4, CD8, CD25, CD127 and OX40) followed by fixation/permeabilization (using BioLegend FoxP3 kit) and intracellular staining for FoxP3.

The plot shows absolute numbers of CD25$^+$CD127$^-$ FoxP3$^+$ Treg cells, normalised to the pre-HCT level for each

experiment, in the peripheral blood before and at different time points after HCT. Animals were kept on the indicated immunoprophylaxis regimens. Time-points with n<3 were censored. Multiple t-test with Holm-Sidak correction was performed between the groups.

FIG. **9** shows that peripheral blood Treg cells are substantially reduced following allogeneic HCT in monkeys. The combination of anti-OX40L mAb and rapamycin effectively prevents further decline in the numbers of peripheral blood Treg cells. Whilst initially rapamycin appears to maintain the level of Treg cells, the number of these cells rapidly declines, until the terminal endpoint is reached.

anti-OX40L antibody, treated with rapamycin, or with a combination of rapamycin and anti-OX40L antibody.

FIG. **10** shows that after allogeneic HCT, the donor T(eff+mem) cell population, left untreated, increases rapidly. The anti-OX40L mAb alone does not effectively suppress proliferation of $CD8^+$ T(eff+mem) cells, whereas the combination of rapamycin and the anti-OX40L mAb maintains prolonged suppression of this cell population.

Analysis of Treg:Tconv Cells Over Time

Peripheral blood mononuclear cells were isolated prior (pre-HCT) and at different time points following allogeneic HCT from recipients without immunoprophylaxis (No Rx),

TABLE 4

Animal No.	Animal ID	Survival Duration (days)	Whole Blood Chimerism (%) Day 0	Day 1	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 12	Day 14	Day 15	Day 16	Day 18	Day 20	Day 21	Day 23	Day 26
(#1)	(13189)	(24)	0		6.6			27.5		90.4		81.8			19.7		0		
#2	14079	16	0	5.7		31.7			66.3		82.3		88.2	79.8					
(#3)	(14075)	(0)																	
#4	14081	26		22.9		68.2			82.9		92.1		97.5			98.4		98.8	98.7
#5	14082	22				91.4			98.4		98.6		99.1			99.2		98.6	
#6	14087	16		16.6		66.3			97.4		99.5		99.4						

Data in brackets indicates experimental failure due to infection (animal 1) or technical failure (animal 3).

TABLE 6

2D10 IgG4PE Rhesus GvHD Study

Animal	Details
#1	Survival to day 24. Received 4 doses of 2D10 IgG4PE. Biphasic hematopoietic reconstitution; peripheral blood chimerism data indicated initial donor engraftment followed by autologous repopulation concurrent with evidence of CMV and rhLCV infection. Viral infection considered possible cause of graft failure. Recorded as Technical Failure.
#2	Survival to Day 16. Received 3 doses of 2D10 IgG4PE. Peak peripheral blood donor chimerism of 88% at Day 15. No evidence of CMV or rhLCV infection. Study terminated on veterinary advice due to wound at catheter site (not deemed to be treatment or GvHD related). GvHD staging at necropsy: skin 1 (rash < 25%); liver 0 (no bilirubin elevation); GI 0 (no diarrhoea).
#3	Recorded as Technical Failure. Apheresis equipment failure resulted in drastically suboptimal donor blood product.
#4	Survival to Day 26. Received 4 doses of 2D10 IgG4PE. Clear hematopoietic reconstitution with peak peripheral blood donor chimerism of 99% by Day 23. No evidence of CMV or rhLCV infection. Study terminated on veterinary advice due to scrotal oedema. GvHD staging at necropsy: skin 2 (rash 25-50%); liver 0 (no bilirubin elevation); GI 0 (no diarrhoea). Gross necropsy confirmed no overt visceral GvHD.
#5	Survival to Day 22. Received 4 doses of 2D10 IgG4PE. Clear hematopoietic reconstitution with peak peripheral blood donor chimerism of 99% by Day 12. No evidence of CMV or rhLCV infection. Study terminated due to persistent low platelet count with high bleeding risk and developing signs of acute systemic GVHD. GvHD staging at necropsy: skin 3 (rash >50%); liver 1 (4-8 x bilirubin elevation); GI 3 (severe diarrhoea).
#6	Survival to Day 16. Received 3 doses of 2D10 IgG4PE. Clear hematopoietic reconstitution with peak peripheral blood donor chimerism of 100% on Day 12. No evidence of CMV or rhLCV infection. GvHD staging at necropsy: skin 2 (rash 25-50%); liver 1 (4-8 x bilirubin elevation); GI 2 (moderate diarrhoea).

Analysis of T(Eff+Mem) Cells Over Time

Whole blood cells were stained for CD3, CD4, CD8, CD14, CD20, CD45RA and CCR7 and then analysed by FACS. T-cells were defined as $CD3^+CD14^-CD20^-$ lymphocytes and divided into $CD4^+$ and $CD8^+$ T-cell subsets. Memory T-cells (Tmem) were defined as $CD45RA^-$ and effector Tcells (Teff) as $CD45RA^+CCR7^-$ Tcells in both CD4 and CD8 gates. Combined populations of memory +effector $CD4^+$ (FIG. **10**A) and $CD8^+$ (FIG. **10**B) T-cells were longitudinally tracked before and at different time point following allogeneic HCT in recipients treated with and from anti-OX40L mAb-treated and anti-OX40L mAb in combination with rapamycin-treated cohorts by Ficoll-Paque gradient and then were stained for cell surface markers (CD3, CD4, CD8, CD25, CD127) followed by fixation/permeabilization (using BioLegend FoxP3 kit) and intracellular staining for FoxP3. Treg cells were defined as $CD3^+CD4^+CD25^+CD127^-FoxP3^+$ cells and conventional T-cells (Tconv) were defined as total $CD4^+$ and $CD8^+$ T-cells excluding Treg cell population. FIG. **11** shows the Treg: 100 Tconv cells ratio in the peripheral blood before and at different time points after allogeneic HCT. Animals are

grouped by the immunoprophylaxis regimens. Time-points with n<2 were censored. Multiple t-test with Holm-Sidak correction was performed between the groups.

FIG. **11** shows that without treatment following allogeneic HCT, there is a substantial reduction in the Treg:Tconv ratio preceding the terminal endpoint. The combination prophylaxis regimen results in maintenance of a fairly constant Treg:Tconv ratio at all time points measured.

Example 11

This Example describes the experiments carried out in Examples 7 to 10 in more detail with further analysis and clinical relevance.

Transplant Study Design

This was a cohort study in NHP designed to determine the clinical, immunologic and molecular outcomes of OX40L blockade during allogeneic HCT. Two cohorts of transplant recipients were studied: (1) Allogeneic transplants using the OX40L-blocking human IgG4-PE antibody 1D05 (described as 'KY1005' in this Example 11) as monotherapy for GVHD prophylaxis (abbreviated as 'KY1005'; n=4). KY1005 was given at a dose of 10 mg/kg starting on Days −2 and then once weekly until discontinuation on Days 54 (FIG. **8**E). The pharmacokinetics of this dosing regimen are shown in FIG. **16**A, which documents a peak of 320.1±18.3 mg/L and a trough of 107.9±11.7 mg/L during monoprophylaxis (cf. Example 7 hereinabove). (2) Allogeneic transplants using KY1005 in combination with Sirolimus (Rapamycin) (5-15 ng/dL) for GVHD prophylaxis (abbreviated as 'KY1005/Siro'; n=5). KY1005 was given at a dose of 10 mg/kg starting on Days −2 and then once weekly until discontinuation on Days 54 (FIG. **8**P). The pharmacokinetics of this dosing regimen are shown in FIG. **16**B, which documents a peak of 297.5±10.9 mg/L and a trough of 113.8±7.9 mg/L between days 0 and 30, a peak of 372.5±17.5 mg/L and a trough of 204.9±9.6 mg/L between days 31 and 60, with an estimated mean terminal half-life of 20±8 days (cf. Example 9 hereinabove). These two OX40L-blockade groups were compared to the following cohorts, aspects of which have been described previously (Furlan et al., 2015; Furlan et al., 2016; Miller et al., 2010) (1) Autologous transplants (abbreviated as 'Auto', n=6 for clinical and flow cytometric data and n=4 for transcriptomic analysis) (2); Allogeneic transplants with no GVHD prophylaxis (abbreviated as 'No Rx', n=11 for clinical and flow cytometric data and n=4 for transcriptomic analysis). (3) Allogeneic transplants using Sirolimus monotherapy for GVHD prophylaxis (LC laboratories, abbreviated as 'Siro', n=11 for flow cytometric analysis, n=4 for transcriptomic analysis). Sirolimus was given daily for the length of analysis as an intramuscular formulation with doses adjusted to achieve a serum trough of 5-15 ng/dL. This cohort contains a sub-group of animals prophylaxed with sirolimus alone (n=5) which were only evaluated until Day +9 post-transplant, and for which flow cytometry data were included in this study. (4) Allogeneic transplants using CTLA4-Ig plus sirolimus study (Furlan et al., 2016) (n=7). (5) Allogeneic transplants using tacrolimus plus methotrexate for GVHD prophylaxis (Furlan et al., 2015; Furlan et al., 2016) (abbreviated as 'Tac/MTX', n=3).

Transplant recipients and donors were chosen from breeding colonies based on their MHC-genotypes. For these studies, microsatellite and allele-specific MHC typing was utilised (Johnson et al., 2012; Wiseman eta., 2009; Lank et al., 2012) to choose donor: recipient pairs. The vast majority of our recipients and donors were half-siblings and were MHC haplo-identical, with a small number of pairs being unrelated and either haplo-identical or otherwise MHC mismatched (Table 7). Blinding was performed on all pathologic analysis and on the initial analysis of flow cytometry data, as well as on transcriptome sample handling and data processing.

Transplant Strategy

The previously-described strategy for allogeneic HCT in rhesus macaques was used (Miller et a/., 2010). Briefly, apheresis was performed after G-CSF mobilisation (Amgen, 50 mcg/kg for 5 days), and an unmanipulated G-CSF mobilised apheresis product was transplanted into transplant recipients. The transplanted total nucleated cell dose (TNC) and $CD3^+$cell doses are shown in Table 8. The pre-HCT preparative regimen consisted of total body irradiation (TBI) of 10.4 cGy given in two fractions per day for two days. Irradiation was delivered with a Varian Clinac 23EX (Varian), at a dose rate of 7 cGy/min. All KY1005 and KY1005/Sirolimus recipients had a central venous catheter placed for the length of the experiment, and were given antibacterial prophylaxis which included Vancomycin and Ceftazidime. To investigate increases in WBC or neutrophil count, even without other clinical signs of infectious disease, both bacterial and fungal blood cultures were drawn, and further antibacterial agents were added as needed. Antiviral prophylaxis (acyclovir, 10 mg/kg IV daily; cidofovir, 5 mg/kg IV weekly) and antifungal prophylaxis (fluconazole 5 mg/kg oral or IV, given daily) were also employed. Leukoreduced (using an LRF10 leukoreduction filter, Pall Medical) and irradiated (2200 rad) platelet-rich plasma or whole blood was given for a peripheral blood platelet count of $\leq 50\times10^3$ per μL or a hemoglobin <9 g/dL, respectively, or if clinically significant hemorrhage was noted. Blood product support adhered to ABO antigen matching principles.

The GVHD clinical score was assessed weekly for allotransplant recipients as previously described (Miller et al., 2010) and detailed in Table 5. Briefly, the acute GVHD (aGVHD) clinical score increases with cumulative GI-specific abnormalities (diarrhea), liver-specific abnormalities (hyperbilirubinemia) and skin-specific abnormalities (extent and character of rash). Statistical significance of the differences in clinical scores was determined using an unpaired t-test. It is important to note that the studies described focused on the natural history of aGVHD that developed during prophylaxis, such that animals were not given supplementary treatment when GVHD was diagnosed. Rather, when pre-defined clinical endpoints were met (based on National Primate Research Center veterinary standard operating procedures), animals were euthanized and a terminal analysis was performed. Thus, survival was directly related to the severity of clinical GVHD. Histopathologic scoring for GVHD was performed by an expert in GVHD histopathology (A.P.-M.) using a previously validated semi-quantitative scoring system (Grades 0.5-4) (Miller et al, 2010).

The pathologist was blinded to the treatment cohorts during the scoring process. The Kaplan-Meier product-limit method was used to calculate survival. Differences between groups were determined using log-rank statistics.

TABLE 7

			MHC typing characteristics				
Cohort	Recipient ID	Donor ID	Relationship and Matching	Recipient Haplotype 1	Recipient Haplotype 2	Donor Haplotype 1	Donor Haplotype 2
No prophylaxis	R.50	R.16	Half-sibs, haplo-identical	A004/B028/DR14a	A001/B047a/DR03a	A004/B028/DR14a	A002a/B012a/DR03f
No prophylaxis	R.51	R.36	Unrelated, MHC mismatched	A004/B001a/DR04a	A001/B047a/DR04a	A004/B012b/DR04a	A008/B024a/DR13a
No prophylaxis	R.52	R.58	Half-sibs, haplo-identical	A001/B017a/DR03a	A004/B012b/DR01a	A001/B017a/DR03a	A006/B069a/DR01a
No prophylaxis	R.53	R.59	Unrelated, haplo-identical	A008/B001b/DR04a	A016/B028/DR-Unkn	A008/B012b/DR03a	A004/B028/DR09a
No prophylaxis	R.229	R.222	Half-sibs, haplo-identical	A052/B003a/DR03f	A026/B056d/DR-unk2	A052/B003a/DR03f	A019/B039a/DR-unk1
No prophylaxis	R.230	R.223	Unrelated, haplo-identical	A001/B047a/DR04a	A002a/B012a/DR16	A004/B002/DR06	A002a/B012a/DR03f
No prophylaxis	R.231	R.224	Unrelated, haplo-identical	A001/B055/DR03g	A019/B015c/DR03a	A001/B055/DR03g	A002a/B015a/DR15a
No prophylaxis	R.232	R.225	Unrelated, haplo-identical	A004/B012b/DR04a	A001/B055/DR03g	A004/B012b/DR04a	A004/B002/DR06
No prophylaxis	R.233	R.226	Half-sibs, haplo-identical	A008/B069b/DR04a	A019/B015c/DR03a	A008/B069b/DR04a	A004/B015a/DR16
No prophylaxis	R.234	R.227	Half-sibs, haplo-identical	A026/B012a/DR04a	A007/B077a/DR02b	A026/B012a/DR04a	A008/B106/DR11a
No prophylaxis	R.235	R.228	Half-sibs, haplo-identical	A026/B012a/DR04a	A008/B015a/DR01a	A026/B012a/DR04a	A004/B069b/DR06
Sirolimus	R.243	R.36	Half-sibs, haplo-identical	A004/B012b/DR04a	A002a/B012a/DR16	A004/B012b/DR04a	A008/B024a/DR13a
Sirolimus	R.244	R.245	Half-sibs, haplo-identical*	Microsatellite data only	Microsatellite data only	A001/B001a/DR03a	A002a/B043b/DR09b
Sirolimus	R.13	R.32	Half-sibs, haplo-identical	A008/B069b/DR04a	A019b/B015c/DR03a	A008/B069b/DR04a	A004/B059b/DR03a
Sirolimus	R.16	R.37	Unrelated, MHC mismatched	A004/B028/DR14a	A002a/B012a/DR03f	A004/B012b/DR04a	A002a/B001c/DR15a/b
Sirolimus	R.17	R.248	Half-sibs, MHC mismatched	A110-A111/B043b/DR14b	A004/B015a/DR04a	A002a/B012a/DR03f	A004/B056b/DR15a/b
Sirolimus	R.18	R.33	Half-sibs, haplo-identical	A004/B012b/DR04a	A004/B069a/DR03a	A004/B012b/DR04a	A007/B012b/DR03a
Sirolimus	R.238	R.226	Half-sibs, haplo-identical	A008/B069b/DR04a	A002a/B015b/DR04a	A008/B069b/DR04a	A004/B015a/DR16
Sirolimus	R.239	R.237	Half-sibs, haplo-identical	A028/B055/DR03f	A008/B015b/DR11a	A028/B055/DR03f	A004/B012b/DR04a
Sirolimus	R.240	R.226	Half-sibs, haplo-identical	A008/B069b/DR04a	A023/B043a/DR06	A008/B069b/DR04a	A004/B015a/DR16
Sirolimus	R.236	R.215	Half-sibs, haplo-identical	A004/B012b/DR04a	A001/B047a/DR04a	A004/B012b/DR04a	A003/B012a/DR03f
Sirolimus	R.252	R.215	Half-sibs, haplo-identical	A004/B012b/DR04a	A016/B001a/DR13a	A004/B012b/DR04a	A003/B012a/DR03f
KY1005	R.206	R.209	Half-sibs, haplo-identical	A001/B055/DR11e	A004/B048/DR01a	A001/B055/DR11e	A002a/B043b/DR21a
KY1005	R.210	R.207	Half-sibs, haplo-identical	A001/B055/DR11e	A004/B056b/DR21a	A001/B055/DR11e	A023/B043b/DR17
KY1005	R.212	R.209	Half-sibs, haplo-identical	A001/B055/DR11e	A004/B017a/DR17	A001/B055/DR11e	A002a/B043b/DR21a
KY1005	R.211	R.208	Half-sibs, haplo-identical	A023/B012b/DR21c	A008/B043a/DR-Unkn	A023/B012b/DR21c	A004/B017a/DR17
KY1005/ Sirolimus	R.217	R.213	Half-sibs, haplo-identical	A019/B015c/DR03a	A012/B001a/DR-Unkn	A019/B015c/DR03a	A105/B048/DR-Unkn
KY1005/ Sirolimus	R.219	R.214	Half-sibs, haplo-identical	A004/B012b/DR04a	A049/B071/DR01a	A004/B012b/DR04a	A001/B047a/DR04a
KY1005/ Sirolimus	R.220	R.215	Half-sibs, haplo-identical	A004/B012b/DR04a	A028/B012a/DR03f	A004/B012b/DR04a	A003/B012a/DR03f
KY1005/ Sirolimus	R.218	R.214	Half-sibs, haplo-identical	A004/B012b/DR04a	A002a/B012a/DR03f	A004/B012b/DR04a	A001/B047a/DR04a
KY1005/ Sirolimus	R.221	R.216	Half-sibs, haplo-identical	A074/B001a/DR13a	A023/B055/DR01c	A074/B001a/DR13a	A004/B012b/DR04a

CMV Monitoring, Primary Prophylaxis and Treatment

Cytomegalovirus (CMV) monitoring was performed as previously described (Larsen et a., 2010) and is reported as CMV copies/mL of whole blood. Whole blood samples were collected and CMV viral load was measured twice weekly on days 0 to 30 post-HCT, then at least once weekly on days 31 to 60 post-HCT and then at least once every 2 weeks from day 61 until the experimental endpoint. CMV prophylaxis and treatment was performed according to our standard NHP strategy, as previously described (Zheng et al., 2017). Briefly, CMV prophylaxis was provided to all transplant recipients and included weekly Cidofovir, given at a dose of 5 mg/kg, along with renal protection with 3 doses of Probenecid (167 mg PO/dose) given within the first 24 hours after each cidofovir dose. Recipients who reactivated CMV continued cidofovir and were also treated with parenteral gancyclovir, which was given at 5 mg/kg/dose twice daily.

Gancyclovir treatment was continued until CMV levels were undetectable for two weeks and then discontinued.

Chimerism Determination

Flow cytometrically-sorted T-cells ($CD3^+/CD20^-$) were analysed for donor chimerism based on divergent microsatellite markers. Chimerism analysis was performed at the UC Davis veterinary genetics laboratory as previously described (Larsen et al., 2010; Kean et al., 2007).

NHP Ethics Statement

This study was conducted in strict accordance with USDA regulations and the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. They were approved by the Emory University and the University of Washington Institutional Animal Care and Use Committees.

KY1005 Pharmacokinetic (PK) Analysis

For PK analysis, serum samples were collected 30 minutes before and 30 minutes after each infusion of KY1005 and then once weekly after the last dose was given. The KY1005 concentration was measured using an antigen (OX40L) capture electrochemiluminescence (ECL) assay on the MSD platform. In this assay, an MSD streptavidin 96-well plate is first coated with biotinylated-OX40L, followed by the addition of test samples, followed by the detection of bound KY1005 by a ruthenylated anti-human IgG (pre-adsorbed against monkey serum for added specificity).

Flow Cytometry: Longitudinal Flow Cytometric Analysis (Cf Examples 7 and 10 Hereinabove)

Multicolor flow cytometric analysis was performed using an LSRII or LSR Fortessa flow cytometers (BD Biosciences) on all transplant recipients, using the following gating strategy. First, cells were gated on FSC-A versus FSC-H and then on SSC-A versus SSC-H to discriminate doublets. Lymphocytes were then gated based on well-characterized FSC-A and SSC-A characteristics. The following phenotypic characteristics were then used to define immune cell populations:: $CD4^+$ T-cells: $CD4^+/CD3^+/CD8^-/CD14^-/CD20^-$ lymphocytes; $CD8^+$ T-cells: $CD8^+/CD3^+/CD4^-/CD14^-/CD20^-$ lymphocytes; Naïve $CD4^+$ or $CD8^+$ (T_N) T-cells were determined as $CD28^+/CD95^-$; Central memory T-cells (T_{CM}) were determined as $CD28^+CD95^+$; and Effector memory T-cells (TEM) were determined as CD28-$CD95^+$ T-cells. In addition, the levels of OX40 and Ki-67 were determined on both $CD4^+$ and $CD8^+$ T-cells. Relative percentages of each of these subpopulations were determined using FlowJo software (TreeStar) and absolute numbers of each of the subpopulations were determined by calculations from the complete blood count and absolute lymphocyte count analysis. To assess regulatory T-cells, PBMC were stained with extracellular antibodies (CD3, CD4, CD25, and CD127), followed by fixation/permeabilization with FoxP3 Fixation/Permeabilization kit (BioLegend) and staining with FoxP3 antibodies. Regulatory T-cells

TABLE 8

Transplant characteristics of the experiments reported in this study

Cohort	Animal ID	Site	TNC ($\times 10^9$/kg)	T-cells ($\times 10^6$/kg)	$CD34^+$ cells ($\times 10^6$/kg)	Survival (day)
Autologous	R.202[1,2]	Seattle	0.84	187	ND	N/A
Autologous	R.201[1,2]	Seattle	1.34	350	ND	N/A
Autologous	R.200[1,2]	Seattle	2.2	242	ND	N/A
Autologous	R.62[1,2]	Emory	0.71	30	ND	N/A
Autologous	R.63[1,2]	Emory	0.64	337	ND	N/A
Autologous	R.60[1,2]	Emory	0.55	185	ND	N/A
No prophylaxis	R.50[1,2]	Emory	0.31	40.00	ND	6
No prophylaxis	R.51[1,2]	Emory	1.88	238.00	ND	8
No prophylaxis	R.52[1,2]	Emory	0.75	260.00	ND	7
No prophylaxis	R.53[1,2]	Emory	0.56	92.00	ND	12
No prophylaxis	R.229	Seattle	2.75	313.03	9.34	8
No prophylaxis	R.230	Seattle	1.06	170.40	1.59	7
No prophylaxis	R.231	Seattle	2.55	99.35	1.66	11
No prophylaxis	R.232	Seattle	1.68	115.92	4.21	8
No prophylaxis	R.233	Seattle	2.99	337.47	1.91	8
No prophylaxis	R.234	Seattle	3.05	435.98	7.01	9
No prophylaxis	R.235	Seattle	2.04	312.79	7.16	8
Sirolimus	R.243[1,2]	Emory	0.85	ND	ND	14
Sirolimus	R.244[1,2]	Emory	0.45	120.00	ND	14
Sirolimus	R.13[1,2]	Emory	1.10	260.00	ND	12
Sirolimus	R.16[1,2]	Emory	0.20	24.00	ND	11
Sirolimus	R.17[1,2]	Emory	0.60	132.00	ND	28
Sirolimus	R.18[1,2]	Emory	0.64	74.00	ND	22
Sirolimus	R.238	Seattle	5.69	432.71	5.69	N/A
Sirolimus	R.239	Seattle	7.47	1330.08	6.80	N/A
Sirolimus	R.240	Seattle	4.62	442.76	9.23	N/A
Sirolimus	R.236	Seattle	6.79	523.58	8.15	N/A
Sirolimus	R.252	Seattle	5.06	667.68	2.83	N/A
KY1005	R.206	Seattle	1.13	149.76	0.51	16
KY1005	R.210	Seattle	2.99	389.08	4.79	26
KY1005	R.212	Seattle	2.24	312.95	2.69	23
KY1005	R.211	Seattle	3.44	385.66	9.99	16
KY1005/Sirolimus	R.217	Seattle	5.18	709.06	6.73	105
KY1005/Sirolimus	R.219	Seattle	4.77	514.78	5.72	97
KY1005/Sirolimus	R.220	Seattle	5.55	537.54	6.11	106
KY1005/Sirolimus	R.218	Seattle	3.03	348.55	2.42	104
KY1005/Sirolimus	R.221	Seattle	3.61	432.78	6.49	99

[1]Akimova et al., 2012

[2]Furukawa et al., 2016

were defined as $CD25^+CD127^-FoxP^+CD4^+$ T-cells. When staining was performed on thawed cells, LIVE/DEAD Aqua dye (Invitrogen) was used to discriminate livable cells from cell debris. For intracellular cytokines assays cryopreserved peripheral blood mononuclear cells or tissue-infiltrating mononuclear cells samples were thawed and cultured in X-VIVO 15 media (Lonza) supplemented with 10% FBS, 2 mM L-Glutamine, 100 U/ml Penicillin, 100 μg/ml Streptomycin (all from Invitrogen) and 50 μM beta-Mercaptoethanol (Sigma) for 4 hours in presence of either Cell Stimulation Cocktail with protein inhibitors or Protein Inhibitors Cocktail only (both from eBioscience). When samples were labeled with LIVE/DEAD Aqua dye according the manufacturer protocol (Invitrogen), stained for extracellular marker followed by fixation and permeabilisation steps and intracellular staining for IFNγ, TNFα, IL-2 and IL-17A. The sources and clones used for each of the antibodies used in this study are shown in Table 9.

Mixed Lymphocyte Reaction (MLR)

MLRs were performed on PBMC samples isolated by Ficoll fractionation from HCT donors, HCT recipients, (with samples purified both before transplant and at the time of terminal analysis) and from non-donor, non-recipient, 'third-party' healthy control animals. Responder PBMC samples either from HCT donors or from HCT recipients at the time of terminal analysis were labeled with 2.5 μM CellTrace Violet (Invitrogen) and were co-cultured with irradiated (3500 cGy) stimulator PBMC samples in three comparisons: (1) from donor PBMCs ('vs. Donor'); (2) from pre-transplant recipient PBMC samples ('vs. Recipient'); (3) from third-party healthy control monkey ('vs. 3rd Party'). MLR cultures were maintained for 7 days at 37° C. in XVivol5 (Lonza) supplemented with 10% FCS, 2 mM glutamine, penicillin-streptomycin and gentamycin and beta-Mercaptoethanol. On Day 7, cells were collected from the cultures, and were stained with antibodies against CD3, CD4, CD8, and then 7-AAD was added to exclude dead cells and debris. CellTrace Violet dilution was then measured in $CD3^+$ (either $CD4^+$ or $CD8^+$), $7\text{-}AAD^-$ cells by flow cytometry. Following acquisition of flow cytometry data, the number of cells that underwent 0 to 9 cell divisions was measured, followed by the calculation of the Proliferation index (PI: the average number of cell divisions that occurred in cells that had divided at least once) using FlowJo as described previously (Munson, 2010). The proliferation index of post-HCT recipient T-cells were then normalised to the Proliferation Index values of the individual donors pre-HCT (Normalised $PI=PI_{Recipient}/PI_{Donor}$).

Human Mixed Lymphocyte Reaction:

Human MLRs were performed on unrelated healthy controls. PBMC samples were freshly isolated by Ficoll fractionation, followed by magnetic pan T-cell isolation using the Miltenyi Biotec human pan-T-cell isolation kit. Isolated T-cells were labeled with 2.5 μM CellTrace Violet (Invitrogen) and were co-cultured with irradiated (3500 cGy) on-column T-cell-depleted cell fractions from unrelated allogeneic individuals. MLR cultures were maintained for 7 days at 37° C. in XVivo15 (Lonza) supplemented with 10% FCS, 2 mM glutamine, penicillin-streptomycin and gentamycin and beta-Mercaptoethanol. KY1005 was added to the cultures at day 0 at a dose of 150 μg/L. On Day 7, cells were collected from the cultures, and were stained with antibodies against CD3, CD4, CD8, and then Live/Dead Aqua (Molecular Probes/Invitrogen) was added to exclude dead cells and debris. CellTrace Violet dilution was then measured in $CD3^+$, Live/Dead Aqua-cells by flow cytometry.

Statistical Analysis of Histopathologic and Flow Data

Distributions of values within all groups were checked for Gaussian distribution using D'Agostino-Pearson normality test. Both paired and unpaired Student's t-test (for normally distributed values) or the Mann-Whitney test (for non-normal data) was then used where appropriate. ANOVA analysis with Holm-Sidak multiple comparison t-test was used for comparing multiple groups. Groups were considered as significantly different when $p<0.05$.

Flow Cytometric $CD3^+$ T-Cell Sorting and Microarray Cohort Designation

Using a FACSAria or FACSJazz Cell Sorter (BD), T-cells were sorted from 1) healthy controls, 2) autologous controls at day +14, day +36 and day +100, 3) allo-HCT recipients at day +14 post-transplant (as survival allowed), 4) allo-HCT recipients at day +28 post-transplant (as survival allowed) and 5) allo-HCT recipients at the time of terminal analysis. T-cells were identified as $CD3^+/CD20^-$ lymphocytes and were >90% pure based on post-sorting flow cytometric analysis as previously described (Furlan et al., 2015).

NHP Microarray and Data Analysis

Following T-cell purification, RNA was stabilised in T-cell lysates with RLT buffer (Qiagen) supplemented with 1% (vol/vol) beta-mercaptoethanol (Sigma) and RNA was purified using RNEasy Column Kit (Qiagen). RNA was quantified using a Nanodrop Spectrophotometer (Thermo Scientific) and purity was confirmed with an RNA 6000 Nano Kit (Agilent). The purified RNA was sent to the Vanderbilt Technologies for Advanced Genomics Core and to the Oregon Health Sciences University Gene Profiling Shared Resource where RNA quantity and quality were verified, followed by cDNA/cRNA synthesis, and target hybridisation to GeneChip *Rhesus Macaque* Genome Array (Affymetrix). The resultant fluorescent signals were processed and normalised using the Robust Multichip Averaging (RMA) Method (Irizarry et al., 2003). The microarrays were performed in 5 batches, with all batches containing samples from both healthy controls and transplanted animals. The "ComBat" algorithm was implemented to adjust for batch effects (Johnson et al., 2007) and probe-sets containing low signal-to-noise measurement were filtered out in order to enhance statistical testing power (Bourgon et al., 2010). Probe-sets were annotated using 1) annotation file from Dr. Robert B. Norgren Jr (Duan et al., 2010); 2) the annotation file provided by the chip manufacturer (release 33); and 3) data provided by Ingenuity Systems (Ingenuity Systems, www.inaenuity.com) for the small number of probe-sets that were not annotated by the chip manufacturer.

Principal Component Analysis (PCA) was applied to summarise gene array variance using the Bioconductor MADE4 package (Culhane et al., 2005). Analyses of gene differential expression (DE) was performed using an empirical Bayes moderated t-statistic, with a cutoff of 0.05, corrected for multiple hypothesis testing using Benjamini-Hochberg procedure and an absolute fold change cutoff >1.4 with the limma package (Gentleman, 2005). Further analysis of differentiating characteristics of T-cell transcriptional profiles involved Gene Set Enrichment Analysis (GSEA) using gene-sets from the Molecular Signatures Database v5.0 both on aggregate sample data from each cohort as a whole (Johnson et al., 2007; Subramanian et al., 2005; Mootha et al., 2003). In the current analysis, gene sets were ranked using a signal to noise ratio difference metric with 1000 permutations of gene set labels. Pathway analysis was performed using the DAVID 6.8 functional annotation tool (Huang et al., 2009a). Class neighbor analysis was performed as previously described by Golub et al., 1999.

TABLE 9

Flow Cytometry Reagents Used in this Study

Marker	Fluorochrome	Clone	Vendor	Cat#
CCR7	BV421	G043H7	Biolegend	353208
CD11c	PE	3.9	Biolegend	301605
CD123	BV785	7G3	BD Biosciences	564196
CD127	PE	eBioRDR5	eBioscience	15-1278-42
CD127	PE-Cy7	eBioRDR5	eBioscience	25-1278-42
CD14	PerCP-Cy5.5	M5E2	BD Biosciences	550787
CD20	PerCP-Cy5.5	2H7	eBioscience	45-0209-42
CD25	PE	4E3	Miltenyi Biotech	130-091-024
CD25	APC	4E3	Miltenyi Biotech	130-092-858
CD279	BV605	EH12.2H7	Biolegend	329923
CD28	PE-Cy7	CD28.2	eBioscience	25-0289-42
CD3	APC-Cy7	SP34-2	BD Biosciences	557757
CD3	PE-Cy7	SP34-2	BD Biosciences	557749
CD4	BV785	L200	BD Biosciences	563914
CD45RA	APC	2H4LDH11LDB9	Beckman Coulter	B14807
CD56	PE-Cy7	B159	BD Biosciences	560916
CD8	BUV396	RPA-T8	BD Biosciences	563795
CD95	BV605	DX2	Biolegend	305628
HLA-DR	PerCP-Cy5.5	L243	BD Biosciences	339194
IFN-gamma	APC	B27	BD Biosciences	554702
IFN-gamma	PE-Cy7	B27	BD Biosciences	557643
IL-17A	PE	eBio64CAP17	eBioscience	12-7178-42
IL-2	BV421	MQ1-17H12	Biolegend	500327
IL-2	BUV737	MQ1-17H12	BD Biosciences	564446
Ki-67	FITC	Ki-67	Dako	F0788
OX40	PE	L106	BD Biosciences	340420
OX40L	BV421	ik1	BD Biosciences	563766
TNF-alfa	FITC	Mab11	BD Biosciences	552889
FoxP3	AlexaFluor488	20D6	Biolegend	320112
FoxP3	V450	259D/C7	BD Biosciences	560459

Transcriptional Studies of Patient Samples

Human Studies Ethics Statement: The patients and healthy participants described in this manuscript were enrolled in clinical trials that were conducted according to the principles set forth in the Declaration of Helsinki, and which were approved by the institutional review boards (IRB). Written informed consent was received from all participants.

Human Study Design

This study was designed as a retrospective, case-control study. Available cryopreserved patient peripheral blood mononuclear cell (PBMC) samples were obtained from patients enrolled in HCT clinical trials performed at Emory University and the University of Minnesota. Patients from Emory University were enrolled on two contemporaneous IRB-approved clinical trials: (1) The Bone Marrow Immune Monitoring Protocol and (2) The Abatacept Feasibility Study as previously described (Koura et al., 2013; Suessmuth et al., 2015). The patients from the University of Minnesota were enrolled on an immune monitoring protocol approved by the University of Minnesota IRB. We used samples collected on day 28 from patients with confirmed GVHD diagnosis or from HCT recipients without GVHD who were matched for sample collection day, preparative regimen intensity, disease, stem cell source, and GVHD prophylaxis. Patients were on GVHD prophylaxis with Calceneurin inhibitors (Cyclosporin A or Tacrolimus) plus anti-proliferative agent (MMF or Methotrexate). Clinical details pertaining to each of the samples included in the clinical gene array analysis are shown in Table 9A.

Transcriptional Analysis

To prepare for gene array, PBMC were thawed and labeled with the following antibodies (all from BD Biosciences, except CD56): CD4 (Clone L200), CD8 (Clone RPA-T8), CD11c (Clone B-Ly6), CD14 (Clone M5E2), CD16 (Clone 3G8), CD20 (Clone 2H7), CD56 (Clone AF12-7H3 from Miltenyi). Cells positive for either CD4 or CD8 but negative for the remainder of markers were sorted and subsequently preserved in RLT buffer (Qiagen). T-cell lysates were then sent to Oregon Health Sciences University Gene Profiling Shared Resource where total RNA was obtained using the RNEasy kit (Qiagen) and quantified using a Nanodrop Spectrophotometer (Thermo Scientific). Purity was confirmed with an RNA 6000 Nano Kit (Agilent, Santa Clara, Calif.) and samples were then hybridised to Human Transcriptome 2.0 Array (Affymetrix). CEL files were downloaded and fluorescent signals were normalised using the Robust Multi-array Averaging (RMA) method using Expression Console Software (Affymetrix). CEL files were downloaded and fluorescent signals were normalized using the Robust Multi-array Averaging (RMA) method using Expression Console Software (Affymetrix). Probe-set data was then analysed in similar fashion to the NHP arrays, with the exception of annotation, which was performed using release 35 of the HTA-2.0 annotation file.

OX40 and OX40L are Up-Regulated on $CD4^+$ T-Cells and CD11c+mDC During aGVHD

To understand the biological role and potential therapeutic significance of OX40/OX40L signalling in aGVHD, expression of OX40 and OX40L was measured in healthy control NHP (HC) and compared this expression to that in NHP transplant recipients that developed aGVHD following T-cell-replete haploidentical HCT in the absence of immunosuppression (referred to as the "No Rx" cohort), using the previously published NHP aGVHD model (Furlan et al., 2015; Furlan et al., 2016; Miller et al., 2010; Kaliyaperumal et al., 2014). OX40 protein expression was up-regulated on the cell surface of peripheral blood $CD4^+$ T-cells during aGVHD, while $CD8^+$ T-cells expressed very low levels of OX40 both in HC and in the No Rx cohort (FIG. **12**A). The

upregulation of OX40 could be measured on CD4+ T-cells isolated from the peripheral blood (FIG. **12**A), as well as from lymphoid and non-lymphoid organs during unprophylaxed GVHD, and during aGVHD that occurred in the setting of standard Tac/MTX prophylaxis (FIG. **17**A), suggesting that up-regulation of OX40 might be a hallmark of alloreactive CD4+ T-cells regardless immunoprophylaxis regimen. The majority of OX40 expression was found in the CD4+ central memory (T_{CM}) compartment, while naïve and effector memory CD4+ T-cells remained largely OX40-negative prior to and after HCT (FIG. **12**B). Consistent with this, OX40+CD4+ T-cells bore hallmarks of a differentiated cell population, expressing more effector cytokines (including IL-2, TNFa, and IL17) and with a higher proportion of polyfunctional T-cells (simultaneously expressing >2 cytokines) than their OX40− counterparts (FIG. **12**C and FIGS. **17**B & **17**C). This observation was consistent among T-cells isolated from HC and those from recipients diagnosed with aGVHD following unprophylaxed allo-HCT. Transcriptional studies demonstrated that expression of the OX40-encoding transcript, TNFRSF4, were increased in peripheral blood CD3 CD20− T-cells isolated after from the No Rx cohort, as well as from NHP recipients prophylaxed with either Tac/Mtx or with sirolimus monotherapy. (FIG. **12**D). Importantly, this observation was also made in clinical samples (Furlan et al, 2016) from patients diagnosed with aGVHD within the first month of transplant compared to those that did not develop GVHD (FIG. **12**G). Moreover, OX40L blockade using the novel human anti-OX40L antibody KY1005, could inhibit allo-proliferation of human cells in vitro, (FIG. **12**H) suggesting that blockade of this pathway could be an important target for in vivo GVHD prevention.

OX40L is Upregulated on Myeloid Dendritic Cells During Primate aGVHD

OX40L has previously been shown to be expressed on activated antigen-presenting cells (APC), including myeloid dendritic cells (mDC; reviewed in Croft et al(2010)) and this expression has been shown to play an important role in APC:T-cell interactions (Blazar et al., 2003; Chen et al, 1999; Ito et al., 2004; Murata et al., 2000). Thus, we monitored the expression of OX40L on lymph-node-derived HLA-DR+CD3-CD20−CD56−DC from HV and from the No Rx cohort, which were subdivided into CD123+ plasmacytoid (pDC) and CD11c+myeloid (mDC) subsets (FIG. **18**). As shown in FIGS. **12**E & **12**F, the percentage of OX40L+ mDC was increased during aGVHD, while there was no parallel increase in OX40L+pDC. Indeed, as shown in the Figure, pDC demonstrated a trend towards reduced OX40L expression, a notable finding given the tolerogenic properties of pDC compared to their mDC counterparts (Banovic et al., 2009; Sela et al., 2011; Wakkach et al., 2003).

TABLE 9A

Patient Clinical Characteristics

Patient ID	Patient Age	Diagnosis	Transplant Type/HLA matching	Conditioning Regimen Intensity	Conditioning Regimen	GVHD Prophylaxis	GVHD/ No GVHD	AGVHD Grade	Sample Day Post-transplant
UM1	50	NHL, DIFFUSED LG CELL	MSD	Myeloablative	Cy/Bu	CSA/MTX	GVHD	4	28 d
UM2	58	MULTIPLE MYELOMA	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF	GVHD	2	28 d
UM5	58	AML	MSD	Myeloablative	Cy/TBI	Tacrolimus/Mtx	GVHD	3	28 d
UM7	58	AML	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF	GVHD	3	28 d
UM8	73	AML	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF	GVHD	3	28 d
UM10	68	MDS-RARS	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF/ATG	GVHD	4	28 d
UM12	50	MULTIPLE MYELOMA	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF	GVHD	2	28 d
UM11	52	NHL, FOLLICULAR	MSD	Myeloablative	Cy/TBI	CSA/MTX	No GVHD	None	28 d
UM15	53	AML	MSD	Full Preparation	Flu/Bu	Tacrolimus/MTX	No.GVHD	None	28 d
UM17	43	AML	MSD	Non-myeloblative	Flu/Bu	Tacrolimus/MTX	No.GVHD	None	28 d
UM18	67	AML	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF	No GVHD	None	28 d
UM20	62	MDS	MSD	Non-myeloblative	Cy/Flu/TBI	CSA/MMF/ATG	No GVHD	None	28 d
ABA-001-001	46	AML	MMUD	Myeloablative	Bu/Cy	CSA/MTX	No GVHD	None	28 d
ABA-001-002	61	AML	MMUD	Myeloablative	Flu/Mel	CSA/MTX	No GVHD	None	28 d

OX40 Blockade Controls the Expansion of Conventional CD4+ T-Cells after HCT while Preserving Tregs

To determine the impact of isolated OX40L blockade on T-cell reconstitution and GVHD, we performed monotherapy experiments, where transplant recipients were prophylaxed with the KY1005 antibody alone in the peri-transplant period (beginning on Day −2 and continuing weekly thereafter, using 10 mg/kg KY1005 per dose, FIG. **8**E). While prophylaxis with KY1005 did not affect the rapid initial burst of CD4+ T-cell proliferation that occurred after HCT in the absence of immunosuppression, it had a significant inhibitory impact on sustained CD4+ T-cell proliferation, as measured by Ki67 expression (FIGS. **8**F & **8**G). Thus, as shown in the figure, in the presence of KY1005, CD4+ T-cell proliferation persisted during the first week post-transplant, after which there was a decrease in the number of proliferating cells, which correlated with the decrease in accumulation of OX40+ T-cells in these animals (FIGS. **8**H & **8**I). KY1005 as a monotherapy had less effect on the proliferation of CD8+ T-cells, which is consistent with the low OX40 expression of this T-cell subset (FIGS. **8**F & **8**G).

To determine which CD4+ T-cell subpopulations were most prominently affected by OX40L blockade, we measured the relative impact of KY1005 on naïve (T_N), central memory (T_{CM}) and effector memory (T_{EM}) T-cells. We have previously shown that NHP aGVHD is associated with the expansion of CD4+ T_{CM} and CD8+ T_{CM}/T_{EM}, (Miller et al/., 2010) and in the current study we documented that CD4+ T_{CM} cells represent the major reservoir of OX40+ lymphocytes (FIG. **12**B). FIGS. **8**J-M and FIGS. **19**A-D-**1** & **19**H-J document that KY1005's predominant impact on conventional T-cells was within the CD4+ T_{CM} compartment, leading to significant reductions ($p<0.05$) in both the relative and absolute numbers of CD4+ T_{CM} cells, without similar impact on CD8+ T_{CM} cells after HCT. In contrast, the naïve T-cell compartment of both CD8+ and CD4+ T-cells was preserved after transplant with KY1005 prophylaxis. Notably, monoprophylaxis with OX40L blockade did not impair CD8+ T_{EM} cell expansion, with similar levels of expansion observed in both the No Rx and KY1005 cohorts. OX40L blockade also produced a targeted impact on the ability of CD4+ T-cells to produce cytokines after transplant, specifically reducing their ability to express IL17A, without affecting their production of IFNγ, TNFα or IL-2 (FIG. **8**N).

In addition to determining its impact on conventional T-cell populations, we also interrogated the impact of KY1005 on CD4+ Tregs, given the fact that these cells express significant amounts of OX40, evidenced both in HC and in the No Rx cohort (FIGS. **8**O, **8**O-**1** & **8**O-**2**). Of note, and pertinent to the control of GVHD, while KY1005 reduced the relative numbers of OX40+ T-cells after transplant, this effect was restricted to conventional T-cells with the relative numbers of OX40+ Tregs remaining stable after transplant, even during KY1005 prophylaxis (FIG. **8**O, FIGS. **8**O-**1** & **8**O-**2**). Both FIG. **8**O and FIG. **8**O-**1** present the same data, however the data are plotted differently. In FIG. **8**O, data was plotted as a percentage of OX40+ Tconv and Treg cells out of the corresponding parent populations of Tconv cells and Treg cells respectively. For example, this was calculated by calculating the percentage of OX40+ Tconv cells out of total Tconv cells and likewise, percentage OX40+ Treg cells out of total Treg cells. Whereas in FIG. **8**O-**1**, data was plotted as a percentage of total CD4+T-cells. FIG. **9**O-**1** therefore accounts for the frequency of Tconv and Treg cells in the sample. Both FIGS. **8**O and **8**O-**1** demonstrate that KY1005 does not affect the frequency of OX40+ Treg cells.

OX40L Blockade Extends GVHD-Free Survival

The ability KY1005 to restrain CD4+ T_{CM} proliferation and expansion was associated with clinical benefit: Thus, even as a monotherapy, KY1005 delayed clinical signs of GVHD and extended GVHD-free survival in NHP (FIGS. **7**B & **7**C). However, likely due to its predominant impact on CD4+ T-cells without significant effects on CD8+ T-cells, the clinical outcome differential of KY1005 monotherapy was relatively modest, leading to an improvement in GVHD-free survival from 8 days in the No Rx cohort to 19.5 days ($p<0.05$), and with histopathologic evidence for significant disease at terminal analysis (FIG. **7**D).

Combination Prophylaxis with KY1005 Plus Sirolimus Synergistically Controls T-Cell Activation while Preserving Robust Hematopoietic Reconstitution after Allo-HCT

We have previously demonstrated that mTOR inhibition with Sirolimus as a monotherapy also modestly prolonged survival following allo-HCT in NHP (MST=14 days vs 8 days without GVHD prophylaxis, $p<0.001$) (Furlan et al., 2015; Miller, W. P. et al. 2010;). However, despite maintaining therapeutic serum concentrations (5-15 ng/mL) and successfully blocking mTOR signaling pathways as measured by gene set enrichment analysis (FIG. **20** and Table 18), we have previously shown that sirolimus alone was insufficient to fully control T-cell proliferation (Furlan et al(2015) and FIGS. **8**Q & **8**R) and recipients ultimately developed severe disease with clinical and immunpathologic features similar to unprophylaxed aGVHD (FIGS. **7**B-**7**C and Furlan et al (2015) and Miller et al (2010)). However, when we combined sirolimus with KY1005 (transplant schema shown in FIG. **8**P), there was striking synergy, resulting in significant control of both CD4+ and CD8+ T-cell proliferation (FIGS. **8**Q & **8**R & **19**E & **19**F). Importantly, KY1005/Sirolimus sustained the reconstitution of naïve CD4+ and CD8+ T-cells following allo-HCT, while controlling the expansion of both CD4+ T_{CM} and CD8+ T_{CM}/T_{EM} cells (FIGS. **8**S-U & FIGS. **21**A & **21**B). This preservation of the naïve T-cell phenotype in both CD4+ and CD8+ T-cells was also in evidence transcriptomically: Gene set enrichment analysis (GSEA) (Subramanian et al., 2005) revealed over-representation of gene sets associated with naïve CD4+ and CD8+ T-lymphocytes in the KY1005/Sirolimus cohort in comparison to both the KY1005 and the Sirolimus monotherapy cohorts (FIGS. **8**V & **8**W and Table 10).

Importantly, all recipients prophylaxed with KY1005/Sirolimus demonstrated successful donor engraftment, with high levels of T-cell chimerism (FIG. **13**A) and with robust hematologic reconstitution post-transplant, with all recipients demonstrating prompt multilineage hematologic recovery (FIG. **13**B-F-**1**) and recipients being clinically healthy post-transplant without viral, fungal or symptomatic bacterial disease (Table 11). Notably, CMV reactivation and disease were monitored prospectively, with no recipients developing viral disease. As expected after myeloablative HCT, low-to-moderate levels CMV reactivation did occur in some (3 of 5) recipients similar to autologous controls (FIG. **13**G-**1**), with all episodes of viral reactivation controlled with cidofovir prophylaxis and standard gancyclovir therapy (Table 11, FIG. **13**G).

KY1005/Sirolimus Preserved Treg Reconstitution Following Allo-HCT.

To determine the impact of HCT on Tregs, we tracked these cells in the peripheral blood of transplant recipients. We found that the development of fulminant aGVHD in unprophylaxed transplant recipients resulted in a rapid decline of absolute Treg cell numbers in the peripheral blood (30.0±11.0 before HCT vs 2.9±0.9 at terminal analysis; $P<0.05$) as well as in a significant decrease in the Treg:100 Tconv ratio (2.0±0.4 before HCT vs 0.6±0.1, $p<0.001$, FIG. **11**B). As monoprophylactic regimens, both KY1005 and sirolimus protected against the significant drop in the Treg to Tconv ratio (FIG. **11**B). In contrast, KY1005/Sirolimus combined prophylaxis was able to not only preserve, but to significantly augment the Treg:Tcon ratio in all transplant recipients, an effect that was stable for the duration of analysis (FIGS. **11**B & **11**C) and was associated with preservation of the absolute number of Tregs in the peripheral blood for the duration of the experiment (FIG. **9**). Transriptomic analysis confirmed these flow cytometric findings, with enrichment for Treg-associated gene sets in the KY1005/Sirolimus cohort compared to KY1005 and Sirolimus monotherapy (FIG. **11**D and Table 12).

TABLE 18

List of genes from the leading edges of the corresponding GSEA performed (FIG. 20) HALLMARK_MTORC1_SIGNALING Sirolimus vs NoRx

#	Gene
1	BUB1
2	RRM2
3	MCM4
4	PSAT1
5	GLRX
6	ATP6V1D
7	PHGDH
8	MCM2
9	DHFR
10	IFI30
11	FADS1
12	CDC25A
13	ELOVL6
14	RAB1A
15	SDF2L1
16	WARS
17	ETF1
18	RIT1
19	HSPD1
20	ACSL3
21	GLA
22	NAMPT
23	INSIG1
24	HSP90B1
25	CYB5B
26	CD9
27	UCHL5
28	PDAP1
29	SHMT2
30	UNG
31	YKT6
32	ERO1L
33	SYTL2
34	ACTR3
35	CTH
36	EBP
37	ELOVL5
38	PLK1
39	PIK3R3
40	CYP51A1
41	GOT1
42	COPS5
43	ENO1
44	SEC11A

TABLE 18-continued

List of genes from the leading edges of the corresponding GSEA performed (FIG. 20) HALLMARK_MTORC1_SIGNALING Sirolimus vs NoRx

#	Gene
45	PSMC4
46	SLC2A1
47	PSMA4
48	ATP5G1
49	PSMB5
50	BCAT1
51	USO1
52	PSMC6
53	DDX39A
54	CCNF
55	HMBS
56	FDXR
57	ASNS
58	GMPS
59	EIF2S2
60	GAPDH
61	EPRS
62	SC5DL
63	PSME3
64	AURKA
65	CFP
66	LDHA
67	PSMD14
68	TPI1
69	SORD
70	NFIL3
71	SLC1A5
72	PSMD13
73	POLR3G
74	HMGCS1
75	IDH1
76	SQLE
77	HSPE1
78	TXNRD1
79	ADIPOR2
80	PPA1
81	ME1
82	G6PD
83	FKBP2
84	PGK1
85	TES
86	ITGB2

TABLE 10

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 8V & 8W Leading Edge Gene Lists)

GSE11057_NAIVE_VS_MEMORY_CD4_TCELL_UP (FIG. 8V)				GSE9650_NAIVE_VS_EFF_CD8_TCELL_UP (FIG. 8W)			
KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro		KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro	
#	GENE	#	GENE	#	GENE	#	GENE
1	SLC25A37	1	TMEM170B	1	KIT	1	IGF1R
2	HIPK2	2	SLC25A37	2	RAB3IP	2	ZBTB20
3	TIMP2	3	IGF1R	3	C3AR1	3	CLK4
4	ZNF516	4	KLHL24	4	HLA-DOB	4	IL6ST
5	HEMGN	5	GPR160	5	ABCG1	5	KCTD12
6	TMEM170B	6	NUDT12	6	DUSP6	6	LIPA
7	GPR160	7	PADI4	7	TCF4	7	RAB3IP
8	NBEA	8	ZNF516	8	SMAD1	8	PLEKHA1
9	AIF1	9	LMLN	9	SIPA1L2	9	PELI1
10	PADI4	10	EEA1	10	WFS1	10	RALGPS2
11	GP5	11	SCML1	11	DTX1	11	TLR6
12	MAML2	12	ITGA6	12	AMPD3	12	SCAMP1
13	BTBD3	13	MPP7	13	CCR9	13	GADD45A

TABLE 10-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 8V & 8W Leading Edge Gene Lists)

GSE11057_NAIVE_VS_MEMORY_CD4_TCELL_UP (FIG. 8V)				GSE9650_NAIVE_VS_EFF_CD8_TCELL_UP (FIG. 8W)			
KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro		KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro	
#	GENE	#	GENE	#	GENE	#	GENE
14	TTC28	14	TTC28	14	RALGPS2	14	TTC3
15	CHI3L2	15	SIAH1	15	MAP7	15	FAM101B
16	PLAG1	16	AIF1	16	LIPA	16	C3AR1
17	SCML1	17	ZMYND8	17	NIT2	17	CTSS
18	FLJ13197	18	NBEA	18	KCTD12	18	IL6R
19	FCGRT	19	TIMP2	19	SSBP2	19	CCR9
20	SIAH1	20	HEMGN	20	TLR6	20	GSN
21	LMLN	21	CAMK4	21	IL6R	21	SLC44A1
22	IGF1R	22	BNIP3L	22	PHTF2	22	NR4A3
23	ZC4H2	23	MYB	23	IGF1R	23	MBTD1
24	KLHL24	24	FCGRT	24	PCCB	24	ABLIM1
25	MANSC1	25	PECAM1	25	IL7R	25	TCF4
26	ME3	26	PIK3IP1	26	ZBTB20	26	KIT
27	CD248	27	MEF2A	27	SESN1	27	AMPD3
28	NUCB2	28	MLXIP	28	SLC44A1	28	PCCB
29	MPP1	29	ABLIM1	29	GSN	29	TTC27
30	ZNF238	30	SNRPN	30	MPP1	30	MPP1
31	ITGA6	31	TSPAN3	31	XPC	31	SESN1
32	SERPINE2	32	MPP1	32	FAM101B	32	EVL
33	MPP7	33	PDE3B	33	EPHX1	33	DTX1
34	CLCN5	34	RAPGEF6	34	GNB2L1	34	SIPA1L2
35	MALL	35	MAML2	35	CYB5R1	35	ZNF638
36	MYB	36	FAM134B	36	RPS4X	36	PCM1
37	CHMP7	37	RHPN2	37	PTOV1	37	HPCAL1
38	GAL3ST4	38	PDK1	38	APP	38	MYCBP2
39	SH3RF3	39	C6orf170	39	TBCEL	39	FAM134B
40	TARBP1	40	PLAG1	40	MAP4K3	40	CD2AP
41	SETD1B	41	ZNF182	41	ST6GAL1	41	PDK1
42	UBE2E2	42	GPRASP2	42	POU2F1	42	RNF38
43	LPHN1	43	GPRASP1	43	C15orf39	43	IL7R
44	GPRC5B	44	SLC11A2	44	IL6ST	44	MORF4L2
45	BNIP3L	45	BEND5	45	CD2AP	45	HSD17B11
46	CD55	46	GPRC5B	46	CASK	46	METTL9
47	ZMYND8	47	CHMP7	47	CTSS	47	SLC11A2
48	METAP1D	48	SATB1	48	FAM134B	48	SSBP2
49	NPAS2	49	CLCN5			49	P4HA1
50	STAP1	50	TGFBR2			50	ST6GAL1
51	GPRASP2	51	ZNF238			51	POU2F1
52	MEF2A	52	BACH2			52	USP34
53	GNAI1	53	ZNRD1-AS1			53	DUSP6
54	ANKRD36BP2	54	SERTAD2			54	NECAP1
55	BACH2	55	PDE7A			55	SATB1
56	EEA1	56	KLHDC1			56	SMAD1
57	PKIG	57	HSF2			57	HLA-DOB
58	FAM134B	58	SCAI			58	PTOV1
59	PTPRK	59	SNPH			59	ZNF281
60	TAF4B	60	CRLF3			60	MLL
61	MLXIP	61	LPHN1			61	XPC
62	ACER1	62	C10orf58			62	MAX
63	PIGL	63	DFNB59			63	MAP4K3
64	PIK3IP1					64	AKAP9
65	CAMK4					65	GNL3
66	NUDT12					66	CYB5R1
67	RHPN2					67	APP
68	RNF175					68	CRLF3
69	SNPH					69	MDN1
70	C6orf170					70	SELL
71	EDAR					71	NOP56
72	ZNF546					72	CTSL2
73	VPS52					73	MAP7
74	HSF2					74	WFS1
75	LOC282997					75	MTF2
						76	APEX1
						77	RNF141
						78	C15orf39
						79	RPL5
						80	CCR7
						81	CASK

TABLE 11

Viral, Bacterial and Fungal Infections after Transplant in the KY1005/Sirolimus Cohort

Recipient	CMV Reactivation/Disease*	Pathogenic Bacteremia and Other Bacterial Infections	Documented fungal infection
R.217	Asymptomatic CMV reactivation on days 68-105 (See FIG. 13G & 13G-1).	1. Bacteremia (both asymptomatic): *Staphylococcus* sp.and *Leuconostoc lactis* on Day 28; 2. *Moraxella* sp. (asymptomatic) Isolated from liver at necropsy	NO
R.218	NO	1. *Stenotrophomonas maltophilia* isolated from liver and spleen at necropsy; 2. *Leuconostoc* sp. Isolated from liver at necropsy	NO
R.219	Asymptomatic CMV reactivation on days 1-4, 56 (See FIG. 13G & 13G-1)	1. Bacteremia (asymptomatic): (*Staphylococcus* sp.) on Day 86; 2. *Enterococcus gallunarum* (asymptomic) Isolated from pericardial fluid at necropsy	NO
R.220	Asymptomatic CMV reactivation on days 1, 22, 33, 75, 91 (See FIG. 13G & 13G-1)	1. Bacteremia (asymptomatic): (*Leuconostoc* sp.) on day 78	NO
R.221	NO	1. *Leuconostoc* sp. Isolated from spleen at necropsy	NO

CMV results considered positive if 1) positive results are obtained from ≥2 out of 3 technical replicates and 2) viral loads were ≥500 copies/ml.

TABLE 12

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 11D Leading Edge Gene Lists) GSE42021_TREG_VS_TCONV_PLN_UP (FIG. 11D)

KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro	
#	GENE	#	GENE
1	HERC5	1	HERC5
2	IDO1	2	IFIT1
3	CEBPD	3	IFIT3
4	SP140L	4	RSAD2
5	LMO2	5	IFIT2
6	IFIT3	6	IFI44
7	RSAD2	7	MX1
8	TYMP	8	OAS2
9	DOCK4	9	LMO2
10	IFIT2	10	MX2
11	HLA-A	11	DOCK4
12	IFIT1	12	TYMP
13	IFI44	13	DDX58
14	DRAM1	14	OASL
15	CEACAM1	15	CEBPD
16	HERC6	16	DDX60
17	OASL	17	HERC6
18	NKX3-1	18	IFIT5
19	XAF1	19	IDO1
20	PLAUR	20	XAF1
21	ISG15	21	BMPR2
22	RTP4	22	B2M
23	SAMD9	23	ISG15
24	SEPX1	24	TRIM5
25	TMEM140	25	IFI27
26	OAS3	26	SAMD9

TABLE 12-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 11D Leading Edge Gene Lists) GSE42021_TREG_VS_TCONV_PLN_UP (FIG. 11D)

KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro	
#	GENE	#	GENE
27	MX1	27	PLAUR
28	USP15	28	SEPX1
29	USP18	29	APOL2
30	IFIT5	30	CEACAM1
31	TLR3	31	IRF7
32	BMPR2	32	CTSS
33	CALCOCO2	33	RRAGC
34	IFI30	34	GBP1
35	C5orf13	35	CREM
36	SECTM1	36	STAT3
37	IL15	37	DRAM1
38	IFITM3	38	RAB27A
39	BATF3	39	IRF1
40	IRF7	40	SECTM1
41	DDX60	41	IFI16
42	IRF1	42	PMAIP1
43	EIF2AK2	43	JAK2
44	SERPING1	44	USP15
45	DDX58	45	EIF2AK2
46	MYD88	46	USP18
47	ZRSR2	47	OAS3
48	TRIM14	48	FMR1
49	RASGRP3	49	IRF9
50	SPATS2L	50	TMEM140
51	MX2	51	FAM208B
52	ZNF277	52	SP110

TABLE 12-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 11D Leading Edge Gene Lists) GSE42021_TREG_VS_TCONV_PLN_UP (FIG. 11D)

KY1005/Siro D100 vs KY1005		KY1005/Siro D14 vs Siro	
#	GENE	#	GENE
53	C16orf7	53	SP140L
54	LGALS3BP	54	TLR3
55	STAT2	55	HLA-A
56	IFIH1	56	RNF114
57	PARP12	57	TRIM38
		58	IFI30
		59	UBE2D1
		60	STAT2
		61	MAFF
		62	TRIM22
		63	IL10RB
		64	NBN
		65	TOP1
		66	C5orf13
		67	ZRSR2
		68	RNF19B
		69	TRIM14
		70	IFIH1
		71	IL15

KY1005/Sirolimus Combination Prophylaxis Synergistically Protects Against Clinical and Pathologic aGVHD

The ability of KY1005/Sirolimus to control Teff activation while preserving Treg reconstitution resulted in the synergistic protection against aGVHD in this cohort. The combined therapy provided potent control of the clinical signs of aGVHD (FIG. **7**B), which resulted in prolonged (>100 day) disease-free (GVHD-free) survival following transplantation (FIG. **7**C) even after discontinuation of KY1005 at Day 54 post-transplant (FIG. **16**B). This survival was significantly different than all comparator cohorts ($p<0.01$). Thus, while both sirolimus and KY1005 as monotherapies extended survival compared to no prophylaxis (MST=14 and 19.5 days, respectively, $p<0.05$ for both), KY1005/Sirolimus effectively controlled clinical aGVHD for the length of the planned analysis (FIG. **7**B) resulting in an MST>100 days, $p<0.001$ compared to NoRx, Sirolimus and KY1005, (FIG. **7**C) and which was confirmed by histopathologic analysis (FIG. **7**D). KY1005/Sirolimus also displayed superior control of aGVHD and survival compared to previously published (Furlan et al., 2015; Furlan et al., 2016) Tac/MTX and CTLA4-Ig/Sirolimus cohorts (FIG. **19**G), underscoring the unique ability of this strategy to control alloreactivity.

Engrafting T-Cells Demonstrate Diminished Donor/Recipient Alloreactivity with Relative Maintainance of Third-Party Responses

The sprolonged GVHD-free survival with KY1005/Sirolimus led us to determine the specificity of control of alloreactivity in these recipients. To determine this, we performed ex vivo MLR studies to measure the ability of reconstituting donor T-cells to allo-proliferate against either recipient or third-party stimulator cells. The results of these studies are shown in FIG. **7**E-G. As shown in the Figure, and as expected, donor PBMC samples minimally responded to autologous stimulator PBMC, both before and after HCT (FIGS. **7**E & **7**F left column and FIG. **7**G). However, in the pre-HCT setting, these cells demonstrated significantly more proliferation when stimulated by either recipient or third-party cells (FIG. **7**E, middle and right columns and FIG. **7**G) than when stimulated by autologous donor cells. Importantly, when responder PBMC were harvested from recipients at the terminal post-transplant time-point, in the setting of high donor T-cell chimerism, significantly less allo-proliferation was measured against recipient cells, while proliferation against third-party stimulators was better preserved, with equal or greater proliferation against third-party cells observed in 3 of 5 recipients (FIG. **7**F, middle and right columns and FIG. **7**G).

Longitudinal transcriptional analysis identifies $CD3^+$ T-cell gene expression signatures associated with long-term control of aGVHD with KY1005/sirolimusGiven that KY1005/Sirolimus enabled aGVHD-free T-cell reconstitution following allo-HCT, we interrogated the transcriptome of these T-cells, in order to gain detailed insights into the mechanisms associated with its successful control of alloreactivity. We hypothesised that the transcriptional signature of the T-cells in the GVHD-free cohort would encapsulate both positive and negative signalling pathways, and that defining these pathways would establish a new transcriptional standard for aGVHD control. We first probed the positive signals inherent in long-term aGVHD control. As previously discussed and shown in FIGS. **8**V-**8**W and **11**D we found that naïve T-cell gene-sets (FIG. **8**V-**8**W) and Treg-associated gene-sets (FIG. **11**D) were enriched in T-cells in the KY1005/Sirolimus cohort when compared to sirolimus and KY1005 monotherapies, providing critical transcriptional support for our flow cytometric analyses.

We also identified several new pathways that were enriched in the KY1005/Sirolimus cohort, which provide important insights into the transcriptional programs associated with the Teff/Treg balance induced in this cohort. The comparison that first revealed these pathways was designed to interrogate the transcriptional differences between T-cells from the KY1005/Sirolimus cohort and those from non-transplanted healthy controls. This assessment was prompted by the fact that, while KY1005/Sirolimus-prophylaxed recipients were healthy, the transcriptome of T-cells that reconstituted in these recipients were, nonetheless, distinct from those in untransplanted HC. Thus, as documented with Principle Component Analysis (PCA, FIGS. **15**A & **15**A-**1**) the KY1005/Sirolimus transcriptomes were distinct from all others, including those from HC. To elucidate transcriptional signals that distinguished KY1005/sirolimus from HC, pathway analysis was performed. Analysis strategy wasdesigned to focus on the most stable enriched pathways in KY1005/Sirolimus recipients, defined as those that were enriched at all three post-transplant time-points analysed (Day +14, +28, +100). FIG. **15**B depicts our analysis strategy, showing the numbers of enriched transcripts when comparing T-cells from the longitudinal KY1005/Sirolimus samples to those from HC, revealing that 101 transcripts that were stably enriched (Table 13b). Analysis of the resulting dataset using DAVID (Huang et a., 2009a; Huang et al., 2009b) revealed statistically significant enrichment for two pathways: The KEGG hsa04630:Jak-STAT signalling pathway and the Reactome HSA-909733 Interferon alpha/beta signalling pathway. Enrichment in the Jak-STAT pathway was identified with both DAVID-based pathway analysis and GSEA (FIG. **15**C and Table 14) and revealed a complex enrichment pattern, that included transcripts encoding both pro- and anti-inflammatory cytokines/cytokine receptors (pro-inflammatory transcripts included IL6, IL6R and IL6ST (Chen et al., 2009); IL26 (Ohnuma et al., 2015); anti-inflammatory transcripts included OSM (Son et al., 2017), IL2RA and IL-10RB (Henden et al., 2015), CSF3R (Yang et al., 2016), and IL13RA1 (Newcomb et al., 2011). In addition, both positive and negative regulators of

Jak-STAT and TCR signaling cascades were enriched (positive regulators included STAT1, STAT2 and STAT3 (Villarino et al., 2017); negative regulators included SOCS1 (Ahmed eta/., 2015; Lu et al., 2009; Yao et al., 2012), SOCS2 (Knosp et al., 2011; Knosp et al., 2013; Yeste et al., 2016), PIM1 (Chen et al, 2002; Peltola et al, 2004), SOS1 and SOS2 (Guittard et al., 2015), CISH (Palmer et al., 2015), PIAS1 (Liu et al., 2007), SPRY1 (Lee et al., 2009).

TABLE 13a

Gene list of 261 genes up-regulated in KY1005/Siro cohort vs both Tac/MTX and CTLA4-Ig/Siro cohorts

Column 1	. . . cont	. . . cont	. . . cont	. . . cont	. . . cont	. . . cont
B3GNT5	CEACAM8	TP53INP2	IL13RA1	UNKL	CD302	GPR27
NFE2	LMLN	OSBP	TBXAS1	ARRDC4	PHF17	EIF5
MSL1	ORM1	CYP4F3	SLC36A4	GAB2	RARA	PADI4
PTEN	SCIN	EMR1	AGK	SLC11A1	CLEC4D	RBM14
AMICA1	SRSF11	NR2E1	CCDC90B	LAMA5	FCGRT	TMEM38A
CAPN3	CD36	IFIT2	NCF1	IFRD1	LOC715356	SNX18
CDK14	ABHD2	HP	IRAK3	LILRA5	BATF2	LOC722730
SLC25A37	DCAF12	BTK	LIPA	MMP1	FOXO3B	CYP4F2
AQP9	NCF2	CLTCL1	P2RY2	EFHC2	CCDC125	CALM1
RAB3IP	SLC12A6	TNFAIP6	DRAM1	RSBN1L	HHEX	PRIMA1
IRF1	SOS2	STEAP4	TSPAN33	NFAM1	CXCR1	SEPX1
MAP3K3	GUCY2C	SLC46A2	REPS2	PTAR1	NAMPT	GK3P
GK	NIPBL	SIRPB1	FCAR	LIMK2	LOC714792	SIRPA
SORL1	IDO2	PRO0628	SFRS2IP	DHRS9	CCNL1	VNN1
ALOX5	FGD4	NAIP	SULF2	ZNF862	PFKFB2	APTR
CSF3R	KCNE3	MEPCE	KDM6B	CREB5	SP110	DOK3
EPS8	LRRK2	LPCAT2	OLIG1	ZNF608	KIAA0513	SLC22A15
BASP1	C13orf18	TLR8	ZBTB47	FPR1	CA4	CREG1
ENTPD3	USP32	PGLYRP1	TEKT2	TMEM67	BAT2L2	WIPI1
HES1	IL6R	SAMD9L	ACPP	MGAM	ATP9A	BAZ2B
PROK2	PLD1	BEST1	SLC7A11	P2RY13	GPR97	GNAQ
ZC3H7A	C17orf60	CD177	SLC31A2	LOC344887	PYGL	CEP85L
DYSF	CD300A	SPP1	DOCK4	ZCCHC6	TLR10	KLF5
CLEC4E	GCA	BEND7	MME	FCGR2A	WDFY3	DGAT2

		. . . cont	. . . cont	. . . cont	. . . cont
		ACSL1	MAP1LC3A	IGF2R	CRISPLD2
		SCARB2	SPAG1	BMX	GAB1
		SLC30A1	CREBRF	MBOAT7	TRIM25
		CEP19	ST6GALNAC2	BCL11A	DGCR2
		LOC100170939	CTBP2	STAC3	LOC712466
		IL17RA	EMR3	SAMD9	PGD
		RAB32	RBMX	NLRP12	SESTD1
		TGFA	GLRB	LCN2	GOLGA4
		CNIH4	ATP6V0D2	PI16	DAPK1
		RNF24	LOC100506935	DAW1	ABTB1
		ST3GAL4	LOC100429845	ARHGAP24	HGF
		GPAM	LOC722757	AGBL2	STK17B
		JMJD1C	ADCY4	PFKFB4	TYMP
		GPR84	FPR2	CEACAM1	ACSL4
		ZFYVE16	MXD1	TREM1	C1orf162
		TWIST2	LILRA3	JDP2	CSF2RB
		TLR4	AZI2	ODF3B	IFIT3
		LOC709119	CSF2RA	TLR2	C19orf59
		HERC5	CUX1	RBM25	CKAP4
		SFRS18	FNDC3B	CEBPB	MMP9
		BRWD3	CLEC4A	HAS1	WLS
		PTAFR	RNF130	BPI	
		ZFAND5	IGSF6	VNN2	
		PPP6R3	PIP5K1B	KCNJ15	

TABLE 13b

Gene Lists for Comparisons of the KY1005/Sirolimus Cohort with HC

Column 1	. . . cont	. . . cont	. . . cont	. . . cont
S100A9	IL2RA	PPAPDC1B	PCDH8	LOC706236
S100A8	CD200	APOL6	HERC6	TXK
SERPINE2	IFI6	MAP3K5	MTHFD1L	NCOA7
AKAP12	SLC39A8	LOC709614	NIT2	MAP2K4
PGAP1	SOCS1	LINS	BAX	AZI2
SOCS2	GIPC2	USP18	LOC718240	
IFI27	CYP1B1	MDM2	RAG1AP1	
LPL	CDK6	BCL2	TSHZ2	
MYB	HERC5	ENTPD1	PROS1	
VEGFA	ARL4A	VPS54	ZC3H12D	
DHRS2	RSAD2	LOC707407	LOXL1	
SETBP1	UPP1	WARS	MDFIC	
ZDHHC14	ZMAT3	HRASLS2	PARP11	

TABLE 13b-continued

Gene Lists for Comparisons of the KY1005/Sirolimus Cohort with HC

Column 1	. . . cont	. . . cont	. . . cont	. . . cont
ANXA3	PIM1	RALGAPA2	LOC718036	
NFIL3	NOSTRIN	HEMK1	FAM119A	
ISG15	SOS1	SYNE2	FAM100B	
SESN3	NUMB	ETV6	SBNO2	
PTCHD1	B4GALT4	CHD7	LTA	
UGCG	STARD4	CRIM1	ATP2C1	
MMP1	JAK2	FBXO6	SERPING1	
TNFSF10	LDLR	ZAK	TET2	
CMPK2	PIM3	SYNPO	DKFZP586I1420	
TUSC3	LINS1	IRF4	GNG10	
PCGF5	DPP4	IFNGR2	ITM2A	

TABLE 14

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 15C and 15D Leading Edge Gene Lists)

HECKER_IFNB1_TARGETS (FIG. 15D)						KEGG_JAK_STAT_SIGNALLING_PATHWAY (FIG. 15C)					
KY1005/Sirolimus D 14 vs Healthy Ctrl		KY1005/Sirolimus D 28 vs Healthy Ctrl		KY1005/Sirolimus D 100 vs Healthy Ctrl		KY1005/Sirolimus D 14 vs Healthy Ctrl		KY1005/Sirolimus D 28 vs Healthy Ctrl		KY1005/Sirolimus D 100 vs Healthy Ctrl	
#	GENE	#	GENE	#	GENE	#	GENE	#	GENE	#	GENE
1	CXCL10	1	CMPK2	1	HERC5	1	IL6	1	SOCS2	1	SOCS2
2	CD163	2	IFI27	2	CMPK2	2	SOCS2	2	IL2RA	2	IL13RA1
3	IL8	3	MMP9	3	MMP9	3	IL2RA	3	SOCS1	3	CSF2RA
4	G0S2	4	HERC5	4	IFIT1	4	SOCS3	4	SOCS3	4	CSF3R
5	C3AR1	5	RSAD2	5	IFIT3	5	IL22	5	STAT3	5	CSF2RB
6	TNFAIP6	6	ISG15	6	RSAD2	6	SOCS1	6	SOS1	6	OSM
7	IFI27	7	IFI44	7	CYP4F3	7	CSF2RA	7	IL26	7	IFNGR1
8	CCL2	8	IL8	8	MGAM	8	IL26	8	IL6ST	8	JAK2
9	CMPK2	9	G0S2	9	CD163	9	SOS1	9	IL12RB2	9	STAT3
10	C1QA	10	MX1	10	TNFAIP6	10	CCND2	10	JAK2	10	SOS1
11	PLSCR1	11	CYP4F3	11	IFI27	11	JAK2	11	IL4R	11	IL2RA
12	ISG15	12	C3AR1	12	MX1	12	CISH	12	IL22	12	CISH
13	HERC5	13	SAMD9L	13	ISG15	13	PIM1	13	IFNGR1	13	IL6ST
14	RSAD2	14	SERPING1	14	MX2	14	CSF3R	14	PIM1	14	SOCS1
15	MX1	15	PLSCR1	15	IFI44	15	CSF2RB	15	STAT4	15	IRF9
16	OASL	16	IFI6	16	IFIT2	16	IFNGR2	16	PIAS1	16	PIK3CB
17	IRF7	17	IFIT3	17	OAS2	17	CBLB	17	JAK3	17	PIM1
18	IFIT3	18	PROS1	18	OASL	18	OSM	18	CCND2	18	SOCS3
19	IFI44	19	IFIT5	19	EPSTI1	19	IL12RB2	19	IFNGR2	19	STAM2
20	TYMP	20	XAF1	20	LILRA3	20	IFNA16	20	PIK3R1	20	IFNGR2
21	SAMD9L	21	IRF7	21	SAMD9L	21	IFNA2	21	PIK3CD	21	SOS2
22	IFIT1	22	DDX60	22	C3AR1	22	IL15RA	22	IRF9	22	IL6R
23	MX2	23	HERC6	23	XAF1	23	IL21	23	SOS2	23	SPRY1
24	MMP9	24	OASL	24	TYMP	24	STAT3	24	JAK1	24	IL10RB
25	IFI6	25	LAP3	25	EGR1	25	IL13RA1	25	STAM2	25	IFNAR2
26	EGR2	26	LGALS3BP	26	IRF7	26	IFNAR2			26	STAT2
27	EPSTI1	27	MX2	27	IL8	27	LIF			27	PIAS1
28	XAF1	28	OAS2	28	TMEM140	28	STAT2			28	STAT1
29	SERPING1	29	IFIT2	29	DDX58	29	IL12RB1			29	CCND2
30	DDX60	30	EPSTI1	30	KCNJ15	30	GH1				
31	PROS1	31	EIF2AK2	31	GBP1						
32	LGALS3BP			32	PLSCR1						
33	APOBEC3A			33	IFI6						
34	OAS2			34	DDX60						
35	HERC6			35	EGR2						
36	IFIT2			36	IFIT5						
37	EGR1			37	MMP25						
38	CMTM2			38	G0S2						
39	DHX58			39	CXCL10						
40	IFI35			40	HERC6						
41	CCL8			41	SAMD9						
42	EIF2AK2			42	PROS1						
43	SCO2			43	SCO2						
44	CLU			44	DHX58						
45	CABP5			45	MS4A4A						
46	DTX3L			46	OAS3						
47	C1QC			47	EIF2AK2						

TABLE 14-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 15C and 15D Leading Edge Gene Lists)

HECKER_IFNB1_TARGETS (FIG. 15D)						KEGG_JAK_STAT_SIGNALLING_PATHWAY (FIG. 15C)					
KY1005/Sirolimus D 14 vs Healthy Ctrl		KY1005/Sirolimus D 28 vs Healthy Ctrl		KY1005/Sirolimus D 100 vs Healthy Ctrl		KY1005/Sirolimus D 14 vs Healthy Ctrl		KY1005/Sirolimus D 28 vs Healthy Ctrl		KY1005/Sirolimus D 100 vs Healthy Ctrl	
#	GENE	#	GENE	#	GENE	#	GENE	#	GENE	#	GENE
48	ARG1			48	PARP9						
49	LILRA3			49	SERPING1						
50	CHI3L1			50	APOBEC3A						
51	OAS1			51	TREML1						
52	MMP25			52	RTP4						
				53	FFAR2						
				54	IFI35						

In addition to enrichment for Jak-STAT negative signalling, we also uncovered enrichment for Interferon alpha/beta signalling pathways in the KY1005/Sirolimus versus HC comparison (FIG. **15**D, Table 14). The identification of these pathways as a defining feature of the T-cell expression profile in the KY1005/Sirolimus cohort was consistant across three independent enrichment measures, including the pathway analysis described above, as well as by GSEA and Class Neighbor (CN) analysis. GSEA also demonstrated enrichment of these pathways in the KY1005/Sirolimus cohort as compared to both KY1005 and Sirolimus monotherapies, as well as compared to autologous transplant controls (FIG. **15**E, Table 15). Likewise, CN analysis followed by pathway analysis (Golub et al, 1999), which identifies transcripts whose expression level predominates the signature of one cohort relative to others, also uncovered the Reactome Interferon alpha/beta signalling pathway as significantly enriched in a comparison of KY1005/Sirolimus versus HC, as well as versus the autologous, No Rx, Sirolimus, KY1005, CTLA4-Ig/Sirolimus and Tac/MTX cohorts (Table 14A-14I). These analyses identify several notable transcripts as highly associated with the KY1005/Sirolimus cohort, each of which had been previously recognised to serve a critical function in IFNα/β sensing or signal transduction (including IGS15, IFIT3. RSAD2) (Liu et al., 2011; Fitzgerald, 2011; Skaug & Chen, 2010) or in the effector anti-viral response (IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2, RSAD2) (Fitzgerald, 2011; Diamon & Farzan, 2011; Schoggins & Rice, 2011). The identification of IFNα/β signalling pathways in the KY1005/Sirolimus cohort aligns well with several recent studies that have documented activation of Type I Interferon signalling in the control of alloreactivity, through both effector and Treg-mediated effects (Robb et al., 2012; Robb et al., 2011; Stewart et al, 2013). These results highlight the power of a systems approach to post-transplant/immune analysis in identifying otherwise unexpected pathways and signalling molecules that are associated with long-term GVHD-free survival after transplant and therefore may play critical roles in immune control and/or impact on the immune landscape.

As a final test of the mechanisms/pathways associated with the ability of KY1005/Sirolimus to control aGVHD, we interrogated whether their transcriptomes provided evidence for control of pathways that we have previously demonstrated to be activated during acute GVHD, in both NHP and human T-cells (Furlan et al., 2015; Furlan et al., 2016). Our previous studies have identified two categories of acute GVHD, encompassing Th/Tc1-driven Hyperacute as well as Th/Tc17-driven Breakthough Acute disease (Furlan et al., 2015; Furlan et al., 2016). With respect to Hyperacute GVHD, T-cells in the KY1005/sirolimus cohort we observed significantly downregulatedion of canonical Hyperacute GVHD transcripts and gene-sets including the proliferation and cytotoxicity transcripts, Ki67 and Granzyme A, (FIGS. **14**A & **14**B), as well as Th1-associated gene sets in the KY1005/Sirolimus cohort (including the canonical Th/Tc1 genes CCR5, IL12RB2, and IFNG; FIGS. **14**D & **14**E; Table 16). Of note, despite down-regulation of the above Th/Tc1-associated transcripts, the expression level of TBX21 (encoding Tbet) itself was not significantly changed during GVHD compared to healthy controls (not shown). With respect to Breakthrough GVHD, we found that KY1005/Sirolimus successfully normalised expression of the Th17-defining transcription factor, RORC (FIG. **14**C), and successfully inhibited Th/Tc17-associated gene sets (FIGS. **14**F & **14**G; Table 17) when compared to Tac/MTX and CTLA4-Ig/Sirolimus, both of which we have previously shown are associated with Breakthrough Acute disease (Furlan et al., 2016).

Given the wealth of data that document the centrality of both these pathways to aGVHD pathology, the ability of KY1005/Sirolimusto control them is striking. It suggests establishment of a new transcriptional standard for the control of alloreactivity which includes the positive signalling pathways described above along with potent control of both Th/Tc1- and Th/Tc17-mediated immune pathology.

TABLE 14A

List of Class Neighbor (CN) Genes (Autologous)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
Autologous	SCD5	ST8SIA1	C14orf45	VANGL1	SAMD3	GBE1
Autologous	PALLD	LOC645323	PGM5	ITGB2	S100A10	UHMK1
Autologous	RAB27A	GAS6	PRR5L	PPP2R2B	ZEB2	ENPP4
Autologous	IL17RD	S1PR5	C1orf21	HSPA4	CLCF1	FLOT2

TABLE 14A-continued

List of Class Neighbor (CN) Genes (Autologous)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
Autologous	TPD52	ISL2	ZFYVE28	SLC41A2	CCR5	APOL2
Autologous	AKR1C3	FSD1L	IDH1	HPGD	HECW2	PTPN22
Autologous	PTGDR	DSCR6	FRY	MCOLN2	DYNLT3	PAFAH1B1
Autologous	RARRES1	CHN2	REEP1	RAP2B	MAP3K8	SEMA3G
Autologous	GPR141	JAKMIP2	FOSL2	GNS	SYNE1	GPR56
Autologous	FLJ12120	ACSL5	SLCO4C1	USP31	TNS3	RUNX3
Autologous	HLA-DPA1	STAT4	USP28	PLCG2	KLRG1	ZNF532
Autologous	NUDT11	PLCB1	WEE1	FAR2	SNTB1	KIF21A
Autologous	RHOBTB3	SGCB	GLT8D2	ZBTB8A	ND4L	COPB2
Autologous	CDK1	TSHZ3	HIST3H2A	FAM49A	LRRC40	CX3CR1
Autologous	IL7	TPPP	AFAP1L2	CLIC5	LOC400794	ASAH1
Autologous	FAM150B	TSPAN2	RGAG4	IDI1	OSR2	
Autologous	COL11A1	PALM2-AKAP2	LIMA1	APBB2	STXBP4	

TABLE 14B

List and pathway analysis of Class Neighbor (CN) Genes (CTLA4-Ig/sirolimus)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
CTLA4-Ig/Sirolimus	PCDH8	LPL	QPCT	CHN1	LOC100423631	HS6ST2
CTLA4-Ig/Sirolimus	AKAP12	C11orf73	FCN1	CPM	IFI27	MTHFD2L
CTLA4-Ig/Sirolimus	CXCL13	ST6GALNAC5	PTPN14	RNF217	SAP30	PARD3
CTLA4-Ig/Sirolimus	TWIST1	RGS17	PYGL	C5AR1	KYNU	RBM47
CTLA4-Ig/Sirolimus	DHRS2	SOCS2	FAM95A	MYO5C	ENOX1	GNA15
CTLA4-Ig/Sirolimus	TUSC3	ADAMTS17	TRIM9	PTGFRN	PTGS2	PTX3
CTLA4-Ig/Sirolimus	SERPINE2	PDE7B	TCEA3	EMP1	VDR	NOSTRIN
CTLA4-Ig/Sirolimus	S100A9	VCAN	SESN3	FCGR2B	XIST	CD109
CTLA4-Ig/Sirolimus	PTCHD1	SYNJ2	ANXA4	PLS3	MYB	S100P
CTLA4-Ig/Sirolimus	ITPRIPL2	TSHZ2	IL26	NLRP3	PLSCR1	Dst
CTLA4-Ig/Sirolimus	TNFSF11	MITF	MATN2	ITGA2	SLC24A3	CCL20
CTLA4-Ig/Sirolimus	LOC100292165	ROBO2	WDFY3	ZAK	CSTA	FOS
CTLA4-Ig/Sirolimus	OLFM4	CDKN2B	IL22	NPDC1	AIM2	VEGFA
CTLA4-Ig/Sirolinnus	SGMS2	ARNTL2	KHDRBS3	MNDA	HECTD2	EGLN3
CTLA4-Ig/Sirolimus	S100A8	RGS16	RAPH1	ANXA3	AQP3	PLBD1
CTLA4-Ig/Sirolimus	ZDHHC14	ZNF503	PGAP1	SERPINB2	MAP7D2	
CTLA4-Ig/Sirolimus	LPPR4	CD200	CMPK2	TMEM170B	PTHLH	

TABLE 14C

List and pathway analysis of Class Neighbor (CN) Genes (Healty control)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
Healthy Control	RFX8	TANC2	COL11A1	SNRK	KLRG1	IGF1R
Healthy Control	DNTT	DNAJC6	PLK2	ZNF638	ABCG1	PREX2
Healthy Control	NOG	ADRB1	PTGDR	PLEKHG1	WDR86	KLF3
Healthy Control	MAMDC2	FSIP1	RIMKLB	XG	SMAD1	FCRL3
Healthy Control	SOX4	DCHS1	GLIPR1	ST8SIA1	PPP2R2B	ACVR2A
Healthy Control	FAM110C	DEPDC7	FBXL4	GCNT4	ABCB1	STXBP6
Healthy Control	KRT222	LOC722265	CD33	JAKMIP2	DSP	C1orf21
Healthy Control	SYN2	CD1A	PDE6H	NGFRAP1	RASGRF2	ZBTB20
Healthy Control	CPE	MAML3	SMAD7	MOXD1	GGT7	YME1L1
Healthy Control	CAMTA1	INADL	RHOBTB1	ARMCX4	AUTS2	CX3CR1
Healthy Control	SLC14A1	FHL1	GRAMD1C	SLC40A1	GPR56	FCHO2
Healthy Control	BMPR1B	NUDT11	TMEM63A	TSPAN6	HPCAL4	USP53
Healthy Control	LEFTY1	SLC22A23	ANKH	POU6F1	NTN4	C20orf194
Healthy Control	SLC16A10	TTC28	TPD52	PAIP2B	KLRF1	TCP11L2
Healthy Control	SEPPI	SLC5A3	NR3C2	EFCC1	LOC100291103	HEMGN
Healthy Control	ANKRD50	KLRB1	FZD10	PTCH1	AASS	
Healthy Control	MSRB3	40239	CACNA1D	LOC698572	C2orf67	

TABLE 14D

List and pathway analysis of Class Neighbor (CN) Genes (KY1005)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
KY1005	MMP8	EMP1	PRRX1	CAMP	TOP2A	ESM1
KY1005	ZBED2	LOC100292051	TNFRSF9	CENPA	ERAP2	BAG2
KY1005	LCN2	ADAMTS17	BCL2L11	GPR34	IFI27	PBK
KY1005	VEGFA	LTF	WDR63	LOC701920	ANLN	TPX2
KY1005	S100A9	KERA	CD86	VNN1	CTLA4	SPC25
KY1005	S100A8	TYMS	CXCR6	ENTPD1	NET1	FCN1
KY1005	ITPRIPL2	FAM111B	CYBB	EPSTI1	HDGFRP3	UGCG
KY1005	PLS3	CEP55	CCNB2	PSAP	ASPM	DUSP5
KY1005	PTH2R	GM2A	SOCS2	KDELC2	S100P	CDC25A
KY1005	VNN2	GCA	NFKBIZ	F5	PDK4	MX2
KY1005	ATP9A	CTSC	SKIL	OAS2	LXN	ACTR2
KY1005	TRIM9	PTP4A1	PLSCR1	PLIN2	IFNG	SGOL2
KY1005	MOCOS	GZMA	UHRF1	SERPINB1	RNA45S5	PRO0628
KY1005	KLRC1	LOC714891	PREX2	NTRK1	GPSM2	APOL6
KY1005	HAVCR2	LAG3	CD177	ATP6V1A	DEPDC1	BPI
KY1005	PTGER2	CCR5	TRIM59	MMP9	TRIM5	
KY1005	SERPINE2	TNFSF11	CASC5	SLC25A13	DDX3Y	

TABLE 14E

List and pathway analysis of Class Neighbor (CN) Genes (KY1005/Sirolimus)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
KY1005/Sirolimus	AKAP12	PLA2G7	NCF1	SESN3	PTCHD1	OASL
KY1005/Sirolimus	HERC5	OLFM4	RNASE3	LTF	SAT1	CAMP
KY1005/Sirolimus	VNN2	IFIT1B	PLBD1	CD300A	RNF24	S100A9
KY1005/Sirolimus	SLC25A37	LITAF	SESTD1	FCN1	ALOX5	JDP2
KY1005/Sirolimus	SOCS2	PCDH8	PIP5K1B	IRAK3	CSTA	MNDA
KY1005/Sirolimus	TMEM170B	ANXA3	SEMA6D	ZCCHC6	FCAR	DAPK1
KY1005/Sirolimus	IGF2BP3	CTBP2	OSBP	MS4A6A	TDRD6	MCTP1
KY1005/Sirolimus	IFIT3	ORM1	IFIT2	GNAQ	OAS2	LOC100423631
KY1005/Sirolimus	LPL	SPP1	PYGL	CA2	LOC722757	NFIL3
KY1005/Sirolimus	CMPK2	TRIM58	MX1	PARD3	FAM198B	LRRK2
KY1005/Sirolimus	EPS8	MMP9	F13A1	CYP4F2	SGK1	CFD
KY1005/Sirolimus	RSAD2	ZDHHC14	PRO0628	CYP4F3	CLEC4A	CYP1B1
KY1005/Sirolimus	SERPINE2	IGSF6	GCA	CRISPLD2	RTD1A	BACE2
KY1005/Sirolimus	NFE2	NCF2	HBB	IDO1	ISG15	GCNT1
KY1005/Sirolimus	MYO5C	IFI44	RBM47	MGAM	ST6GALNAC2	TREM1
KY1005/Sirolimus	THBS1	RGS18	NOSTRIN	ACSL6	IL13RA1	
KY1005/Sirolimus	IFIT1	HBA1	QPCT	SNX18	STEAP4	

TABLE 14F

List and pathway analysis of Class Neighbor (CN) Genes (No Rx)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
No Rx	ASPM	CDKN3	KIF14	CDCA5	CENPH	GINS2
No Rx	CEP55	MZB1	NEK2	IFI27	BCL2L14	FOXM1
No Rx	BUB1	CDC20	DTL	BIRC5	CDC25A	IRF8
No Rx	DLGAP5	SPAG5	NCAPG	DSCC1	ATP8B4	DIAPH3
No Rx	CCNB2	UHRF1	LAG3	SKA3	BCL2L11	POLE2
No Rx	TYMS	VDR	SPC25	MELK	RAD51	CDCA2
No Rx	RRM2	IL17F	NUSAP1	MCM4	CIT	IQGAP3
No Rx	KIF15	KIAA0101	MLF1IP	CHEK1	ZBED2	LOC714891
No Rx	GTSE1	TOP2A	ZBTB32	BAG2	CCNA2	CCNE2
No Rx	SHCBP1	CENPA	SERPINE2	KIF2C	UBE2C	MCM2
No Rx	KIF11	MOCOS	GEN1	S100A9	ENTPD1	KIF23
No Rx	E2F8	GZMA	DEPDC1	S100P	CLC	APOBEC3G
No Rx	SGOL2	CHAF1A	DEPDC1B	KIF4A	MCM3	HIST1H2AK
No Rx	PBK	SUCNR1	C6orf173	CCNB1	ADAM19	PSAT1
No Rx	IL12RB2	MYL6B	BUB1B	EPHX4	FAM72A	SLCO4A1
No Rx	OIP5	MKI67	HAVCR2	SKA1	S100A8	
No Rx	PRR11	NUF2	RAD51AP1	E2F2	SERPINB1	

TABLE 14G

List and pathway analysis of Class Neighbor (CN) Genes (Sirolimus)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
Sirolimus	SERPINE2	VDR	CEP55	BAG2	LOC100294459	PRC1
Sirolimus	VEGFA	DSCC1	IL12RB2	CHEK1	LOC714891	RDM1
Sirolimus	ITPRIPL2	ENTPD1	SKA3	PTGS1	STAP1	MEST
Sirolimus	E2F7	CCNB2	KIF11	TRIB1	KCNK13	ZNF670
Sirolimus	PTGFRN	ANLN	GZMA	KIF2C	NPDC1	IL1RL1
Sirolimus	PRR11	SYNJ2	CD200	AG2	SHCBP1	EXO1
Sirolimus	PDE7B	TRIM9	UBE2C	SPAG5	RAPH1	CDCA3
Sirolimus	ITGA2	LAG3	EPHX4	OIP5	AGAP1	SPC25
Sirolimus	RRM2	FAM95A	MELK	E2F8	DEPDC1	ARNTL2
Sirolimus	ESR1	TYMS	TIMD4	KIF4A	RPS27A	SETBP1
Sirolimus	NEK2	KIF15	DLGAP5	KIF23	PTCHD1	KIF14
Sirolimus	MOCOS	NUSAP1	ZBED2	PTPN14	TTK	CXCL5
Sirolimus	HUNK	IRF8	NUF2	P2RX5	IL2RA	GNPDA1
Sirolimus	BUB1	BUB1B	CLCN4	TNFSF11	KSR2	ASPM
Sirolimus	GTSE1	DIAPH3	ZBTB32	CEBPA	NTRK1	SGOL2
Sirolimus	PBK	AHNAK2	C1R	WDR63	HAVCR2	
Sirolimus	TOP2A	UHRF1	SLC16A1	PTGER2	HDGFRP3	

TABLE 14H

List and pathway analysis of Class Neighbor (CN) Genes (Tac/Mtx)

Experimental cohort	CN Genes	CN Genes continued . . .	CTN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .	CN Genes continued . . .
Tac/Mtx	MATN2	TP63	PALM2-AKAP2	DSCC1	ND2	NUF2
Tac/Mtx	KIF11	FAM111B	KIF18A	VEGFA	TYMS	STON1
Tac/Mtx	SNX5	CMPK2	UBA6	NEK2	SLC4A10	PHLDA1
Tac/Mtx	TWIST1	JUN	OIP5	SEMA6D	IL12RB2	BCL2L14
Tac/Mtx	FOS	DEPDC1B	HSD11B1	HBB	SPC25	HLF
Tac/Mtx	MOCOS	NMU	HIST1H3D	E2F8	HIST1H3F	CRISP3
Tac/Mtx	CD70	LOC100428522	CEP55	TNF	HRASLS2	TTC39B
Tac/Mtx	LOC701920	PGGT1B	BUB1	LOC100133583	MX2	GPSM2
Tac/Mtx	TRIM9	FAM72A	CD86	TPH1	CCR6	ZNF846
Tac/Mtx	PRRX1	IFNG	MACROD2	KIR3DH	CHN2	VRK2
Tac/Mtx	ANXA3	SETD9	CXCL3	EGLN3	CDK1	CCNB2
Tac/Mtx	ANLN	HLA-DQA1	RRM2	SCN2A	UHRF1	RDX
Tac/Mtx	CA1	C6orf105	PVRL3	GTSE1	PRR11	RYR2
Tac/Mtx	SIGLEC12	ANXA4	IL22	S100A8	LDLRAD3	SGOL2
Tac/Mtx	KIR3DL2	S100A9	CD160	IL8	KIF23	HIST1H3C
Tac/Mtx	CCL3	CDKN2A	LOC100293820	E2F7	PBK	
Tac/Mtx	HPGD	CGA	CHEK1	IFI27	IL26	

TABLE 14I

Neighbor Genes

Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
8	8.24742268	1.71E−07	IFIT3, IFIT2, IFIT1, OASL, ISG15, RSAD2, OAS2, MX1	58	67	9075	18.68244982	1.56E−05	1.56E−05	1.87E−04
4	4.12371134	0.00122455	NCF2, NCF1, CAMP, LTF	58	34	9075	18.40770791	0.10551095	0.05422569	1.32693339
4	4.12371134	0.00130995	GNAQ, IDO1, HBA1, HBB	47	33	6910	17.8207608	0.14105775	0.14105775	1.48435022
3	3.09278351	0.00135652	HBA1, CA2, HBB	58	9	9075	52.15517241	0.11620204	0.0403394	1.46897077
3	3.09278351	0.00289207	HBA1, CA2, HBB	58	13	9075	36.10742706	0.23168788	0.06376597	3.10814593
3	3.09278351	0.00753965	CYP4F3, ALOX5, CYP4F2	58	21	9075	22.35221675	0.49777525	0.12867611	7.919598
4	4.12371134	0.01071044	IFIT1, ISG15, HERC5, MX1	58	73	9075	8.573453	0.62465395	0.15067878	11.0765333
3	3.09278351	0.0301586	MMP9, THBS1, DAPK1	47	41	6910	10.75765439	0.97133951	0.83070592	29.4867393
3	3.09278351	0.04183085	HBA1, THBS1, HBB	47	49	6910	9.001302649	0.99296453	0.80838429	38.5846318
4	4.12371134	0.04801752	ORM1, F13A1, THBS1, CFD	58	130	9075	4.814323607	0.98864375	0.47255593	41.519022
2	2.06185567	0.04917563	NCF2, NCF1	58	8	9075	39.11637931	0.98983453	0.43650385	42.2899681
2	2.06185567	0.05515302	CYP1B1, CYP4F2	58	9	9075	34.77011494	0.99427343	0.43652172	46.1243066

TABLE 14I-continued

Neighbor Genes										
Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
3	3.09278351	0.06372668	CYP4F3, ALOX5, CYP4F2	47	62	6910	7.113932739	0.99951838	0.85185846	52.822194
2	2.06185567	0.07286455	CYP4F3, CYP4F2	58	12	9075	26.07758621	0.99897664	0.49765395	56.1673508
2	2.06185567	0.07286455	CYP4F3, CYP4F2	58	12	9075	26.07758621	0.99897664	0.49765395	56.1673508
2	2.06185567	0.07869559	NCF2, NCF1	58	13	9075	24.07161804	0.99942365	0.49240544	59.0809014
4	4.12371134	0.08103945	FCAR, NCF2, NCF1, THBS1	47	153	6910	3.843693506	0.99994474	0.85923739	61.8705748
2	2.06185567	0.09024979	CYP4F3, CYP4F2	58	15	9075	20.86206897	0.99981722	0.51191768	64.3407

TABLE 15

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 15E Leading Edge Gene Lists)
HECKER_IFNB1_TARGETS

KY1005/Sirolimus D100 vs Auto D100		KY1005/Sirolimus D100 vs Siro		KY1005/Sirolimus D100 vs KY1005	
#	GENE	#	GENE	#	GENE
1	CMPK2	1	HERC5	1	CYP4F3
2	HERC5	2	IFIT1	2	IL8
3	RSAD2	3	IFIT3	3	HERC5
4	MMP9	4	CYP4F3	4	MGAM
5	CYP4F3	5	MGAM	5	EGR1
6	MGAM	6	RSAD2	6	LILRA3
7	CD163	7	IFIT2	7	IFIT3
8	IL8	8	IFI44	8	RSAD2
9	TNFAIP6	9	CMPK2	9	TYMP
10	EGR1	10	TNFAIP6	10	C3AR1
11	IFIT3	11	MX1	11	CMPK2
12	EGR2	12	OAS2	12	KCNJ15
13	C3AR1	13	MMP9	13	G0S2
14	LILRA3	14	CD163	14	MMP9
15	MX1	15	SAMD9L	15	IFIT2
16	IFIT2	16	MX2	16	MMP25
17	SAMD9L	17	LILRA3	17	IFIT1
18	IFIT1	18	TYMP	18	IFI44
19	MMP25	19	DDX58	19	HERC6
20	ISG15	20	OASL	20	TNFAIP6
21	IFI44	21	DDX60	21	OASL
22	G0S2	22	HERC6	22	XAF1
23	IFI27	23	KCNJ15	23	FFAR2
24	OASL	24	IFIT5	24	ISG15
25	TYMP	25	XAF1	25	RTP4
26	KCNJ15	26	IFI6	26	SAMD9

TABLE 15-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIG. 15E Leading Edge Gene Lists)
HECKER_IFNB1_TARGETS

KY1005/Sirolimus D100 vs Auto D100		KY1005/Sirolimus D100 vs Siro		KY1005/Sirolimus D100 vs KY1005	
#	GENE	#	GENE	#	GENE
27	PLSCR1	27	ISG15	27	TMEM140
28	XAF1	28	G0S2	28	OAS3
29	IRF7	29	IFI27	29	CD163
30	FCER1A	30	SAMD9	30	SCO2
31	STAP1	31	IRF7	31	MX1
32	TMEM140	32	C3AR1	32	IFIT5
33	GBP1	33	IL8	33	TREML1
34	HERC6	34	GBP1	34	DHX58
35	MS4A4A	35	MS4A4A	35	IRF7
36	IFI6	36	MMP25	36	DDX60
37	PROS1	37	EPSTI1	37	IFI6
38	IFIT5	38	DHX58	38	EIF2AK2
39	DDX58	39	EIF2AK2	39	SERPING1
40	SAMD9	40	OAS3	40	DDX58
41	OAS2	41	PROS1	41	MX2
42	CLU	42	TMEM140	42	TCL1A
43	SCO2	43	TREML1	43	LGALS3BP
44	MX2	44	SCO2	44	STAP1
45	EIF2AK2			45	SAMD9L
46	DHX58			46	PARP12
47	FFAR2				
48	EPSTI1				
49	OAS3				
50	TREML1				

TABLE 16

Full list of genes from the leading edges of the corresponding GSEA performed (FIGS. 14D and 14E Leading Edge Gene Lists)

CHANG_CYCLING_GENES (FIG. 14D)				BOSCO_TH1_CYTOTOXIC_MODULE (FIG. 14E)			
KY1005/Siro D 14 vs KY1005		KY1005/Siro D 14 vs Siro		KY1005/Siro D 14 vs KY1005		KY1005/Siro D 14 vs Siro	
#	GENE	#	GENE	#	GENE	#	GENE
1	WSB1	1	PRR11	1	CCR5	1	CCR5
2	ANLN	2	BUB1	2	IFNG	2	IL12RB2
3	CCNB2	3	ANLN	3	CASC5	3	IFNG
4	DLGAP5	4	PBK	4	TYMS	4	TYMS
5	PBK	5	DLGAP5	5	F2R	5	CASC5
6	BUB1	6	BUB1B	6	IL10	6	IL10
7	DEPDC1B	7	CCNB2	7	MKI67	7	RRM2
8	WDR76	8	GTSE1	8	PRF1	8	P2RX5
9	DEPDC1	9	NUSAP1	9	KLRD1	9	GIMAP4
10	PRR11	10	MELK	10	SLAMF1	10	MKI67
11	BUB1B	11	HMMR	11	GIMAP4	11	GZMK

TABLE 16-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIGS. 14D and 14E Leading Edge Gene Lists)

CHANG_CYCLING_GENES (FIG. 14D)				BOSCO_TH1_CYTOTOXIC_MODULE (FIG. 14E)			
KY1005/Siro D 14 vs KY1005		KY1005/Siro D 14 vs Siro		KY1005/Siro D 14 vs KY1005		KY1005/Siro D 14 vs Siro	
#	GENE	#	GENE	#	GENE	#	GENE
12	FAM111B	12	SKA3	12	CTLA4	12	CD38
13	CCNA2	13	DIAPH3	13	SLA2	13	CTLA4
14	CDKN3	14	KIF23	14	STAT4	14	MYBL1
15	GTSE1	15	SPAG5	15	HS3ST3B1	15	IRF4
16	TPX2	16	DEPDC1	16	SAMD3	16	SH2D1A
17	CENPA	17	WDR76	17	GZMK	17	BCL2L14
18	RRM1	18	CDKN3	18	SH2D1A	18	PRF1
19	MELK	19	GAS2L3	19	IRF4	19	IL21
20	KIF23	20	RRM2	20	BCL2L14	20	HS3ST3B1
21	NUSAP1	21	CDC25C	21	CD38		
22	DIAPH3	22	FAM83D	22	RRM2		
23	CKS2	23	DEPDC1B	23	NKG7		
24	GMNN	24	CCNA2	24	P2RX5		
25	SKA3	25	EXO1	25	GIMAP8		
26	HIST1H2AC	26	CDCA8	26	IL21		
27	UBE2T	27	WSB1	27	MYBL1		
28	CENPF	28	TOP2A	28	RNASE2		
29	KIF22	29	UBE2C	29	GZMB		
30	HMMR	30	NUF2	30	CD5		
31	FAM83D	31	ESCO2	31	GNLY		
32	CDC6	32	CDCA7				
33	CDCA8	33	BARD1				
34	CDK1	34	CENPF				
35	PRPS2	35	CDK1				
36	GAS2L3	36	CENPA				
37	CDC25A	37	RAD51AP1				
38	SMC4	38	CDC6				
39	SPAG5	39	UBE2T				
40	TOP2A	40	MET				
41	KIFC1	41	CKS2				
42	PTTG1	42	CENPM				
43	ESCO2	43	NCAPH				
44	RAD51AP1	44	UHRF1				
45	CENPQ	45	ATAD2				
46	BARD1	46	KIAA0101				
47	PRIM2	47	BIRC5				
48	ATAD2	48	CKAP2				
49	NUF2	49	PTTG1				
50	UBE2C	50	FOXM1				
51	UHRF1	51	CKAP2L				
52	CDC25C	52	KIF22				
53	NCAPH	53	CENPQ				
54	KIAA0101	54	HELLS				
55	CKAP2	55	PHTF2				
56	IFIT1	56	CDC25A				
57	CASP3	57	AURKA				
58	FEN1	58	GMNN				
59	CDCA7	59	KIF20B				
60	MAD2L1	60	GINS3				
61	DHFR	61	MAD2L1				
62	CDCA5	62	FEN1				
63	HJURP	63	PRIM2				
64	HELLS	64	PRPS2				
65	EXO1	65	CDCA5				
66	AURKA	66	TPX2				
67	RRM2	67	HIST1H2AC				
68	BUB3	68	MCM4				
69	RANGAP1	69	GINS2				
70	G2E3	70	LMNB1				
71	ANP32E	71	DHFR				
72	KIF20B	72	H2AFX				
73	TIPIN	73	HN1				
74	FOXM1	74	SMC4				
75	CKAP2L	75	C7orf41				
76	CENPM	76	FAM64A				
77	FAM64A	77	RRM1				
78	BIRC5	78	KIFC1				
79	LMNB1	79	PSRC1				
80	CCNF	80	MCM6				

TABLE 16-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIGS. 14D and 14E Leading Edge Gene Lists)

CHANG_CYCLING_GENES (FIG. 14D)				BOSCO_TH1_CYTOTOXIC_MODULE (FIG. 14E)			
KY1005/Siro D 14 vs KY1005		KY1005/Siro D 14 vs Siro		KY1005/Siro D 14 vs KY1005		KY1005/Siro D 14 vs Siro	
#	GENE	#	GENE	#	GENE	#	GENE
81	USP1	81	TRIP13				
82	UBE2S	82	CCNF				
83	ITGB3	83	FAM111B				
84	TUBB	84	PLK1				
		85	MCM5				
		86	RECQL4				

TABLE 17

Full list of genes from the leading edges of the corresponding GSEA performed (FIGS. 14F and 14G Leading Edge Gene Lists)

PID_IL23_PATHWAY (FIG. 14G)				GSE27241_WT_VS_RORGT_KO_TH17_POLARIZED_CD4_T_CELLS_UP (FIG. 14F)			
KY1005/Sirolimus vs Tac/MTX		KY1005/Sirolimus vs CTLA4-Ig/Siro		KY1005/Sirolimus vs Tac/MTX		KY1005/Sirolimus vs CTLA4-Ig/Siro	
#	GENE	#	GENE	#	GENE	#	GENE
1	IFNG	1	IL6	1	MGAM	1	ANLN
2	IL6	2	CCL2	2	CYP4F3	2	DUSP4
3	TNF	3	IFNG	3	MMP9	3	UBE2T
4	IL18	4	IL17A	4	TNFAIP6	4	UHRF1
5	IL23R	5	TNF	5	CD163	5	KIF11
6	IL17A	6	IL18	6	HERC5	6	TTK
7	CCL2	7	IL23R	7	TYMP	7	RAD54B
8	IL12RB1	8	CXCL1	8	IFIT2	8	E2F8
9	CXCL1	9	IL17F	9	C3AR1	9	KIF15
10	CXCL9	10	CXCL9	10	LILRA3	10	HIST1H2BB
11	IL2	11	IL1B	11	SAMD9L	11	GTSE1
		12	CD4	12	IFIT1	12	AKAP12
		13	SOCS3	13	IFIT3	13	CENPF
		14	IL12RB1	14	KCNJ15	14	CASC5
				15	IFI44	15	MKI67
				16	EGR1	16	PRC1
				17	EGR2	17	PRR11
				18	SAMD9	18	RACGAP1
				19	RSAD2	19	SPAG5
				20	FFAR2	20	ARHGAP11A
				21	XAF1	21	CDCA2
				22	IFIT5	22	ECT2
				23	DDX58	23	KIF23
				24	MMP25	24	CCNA2
				25	CMPK2	25	BRIP1
				26	FCER1A	26	GMNN
				27	HERC6	27	HIST1H1B
				28	TMEM140	28	PTCHD3
				29	SCO2	29	POLE
				30	GBP1	30	CCNF
				31	MX1	31	BCOR
				32	G0S2	32	BARD1
				33	MS4A4A	33	CDC6
				34	DDX60	34	PLK1
				35	PLSCR1	35	TTF2
				36	IFI6	36	TOP2A
				37	ISG15	37	NEIL3
						38	STMN1
						39	KIF14
						40	SHC1
						41	NTN1
						42	GSG2
						43	SMC2

TABLE 17-continued

Full list of genes from the leading edges of the corresponding GSEA performed (FIGS. 14F and 14G Leading Edge Gene Lists)			
PID_IL23_PATHWAY (FIG. 14G)		GSE27241_WT_VS_RORGT_KO_TH17_POLARIZED_CD4_T_CELLS_UP (FIG. 14F)	
KY1005/Sirolimus vs Tac/MTX	KY1005/Sirolimus vs CTLA4-Ig/Siro	KY1005/Sirolimus vs Tac/MTX	KY1005/Sirolimus vs CTLA4-Ig/Siro
# GENE	# GENE	# GENE	# GENE
			44 POP1
			45 BMP7
			46 EZH2

Discussion

In order for immunomodulatory strategies to successfully control alloreactivity in transplant patients, they must reach a high bar: They must simultaneously control effector T-cell activation while still permitting regulatory T-cell reconstitution. Towards this end, there has been significantly more success in controlling the Teff response than in supporting Treg function, given that the majority of the clinically-available agents are not Treg-friendly. This includes CNIs (Akimova et al., 2012; Furukawa et al, 2016), the anti-proliferative agents, as well as other therapeutics including anti-IL2R agents (Bluestone et al., 2008; Locke et al., 2016; Vondran et al., 2010)), steroids, and anti-thymocyte globulins (Gurkan et al., 2010; Na et al., 2013), amongst others. Of the agents currently clinically available, the notable exception to this paradigm is the mTOR inhibitor sirolimus, which has been shown to support Treg homeostasis both in vitro and in vivo (Akimova et al., 2012; Gao et al., 2007; Zeiser et al., 2006; Singh et al., 2014; Sugiyama et al., 2014). However, sirolimus alone, or in combination with tacrolimus or MMF is not sufficient to control GVHD (Cutler et al., 2014; Bejanyan et al., 2016) likely due to its inability to control Teff activation as a monotherapy and to effectively support Treg homeostasis when combined with CNIs. Thus, the search for an effective partner for sirolimus, in order to best capitalise on its tolerogenic properties while successfully controlling Teff activation. In this study, we have identified OX40L blockade as a highly synergistic combinatorial strategy with sirolimus, as well as the immune pathways that associate with the potent control of aGVHD that occurs with this combination.

OX40:OX40L co-signalling represents one of the few pathways for which there are data to suggest a potentially dichotomous effect on conventional versus regulatory T-cells. Thus, it is well-documented that OX40 is upregulated on $CD4^+$>>$CD8^+$conventional T-cells during activation (Kinnear et al., 2013; Chen et al., 1999; Kopf et al., 1999; Kinnear et al., 2010) and that OX40:OX40L blockade in murine aGVHD models can augment survival of allo-HCT recipients, with the major effects observed on $CD4^+$ T-cell-mediated aGVHD (Blazar et al., 2003; Tsukada et al., 2000; Sanchez eta/., 2004; Miura et a/., 2005;). Of particularly note are the observations that, in contrast to the positive impact that OX40 ligation makes on conventional T-cells, OX40 ligation on Tregs can result in the opposite effect, i.e. inhibition of Treg survival (Kinnear et al., 2013) and an inhibition of their ability to suppress effector T-cell activation (Vu et al., 2007; Kinnear et al, 2013; Valzasina eta., 2005; Piconese et al., 2008). This suggests that blocking the OX40:OX40L pathway might, paradoxically, have salutary effects on Treg function. There has been controversy concerning this effect, however, and several studies have argued that OX40 signalling enhances Treg survival and expansion, particularly during lymphopenia and inflammation (Baeyens et al., 2015; Ruby et al, 2009; Takeda et al, 2004; Kroemer et al., 2007; Piconese et a/., 2010). However, these studies were all performed in mice, and until this study, it remained undetermined which of the effects of OX40:OX40L blockade would translate to primates or how the presence of combinatorial immunomodulation would alter these outcomes. This is especially important, given that combination therapies will certainly be necessary for successful clinical translation. For the first time, these results provide these answers in a primate model of aGVHD. They identify highly synergistic immune control afforded by OX40L blockade combined with sirolimus, which together were able to simultaneously control effector T-cells while supporting Treg homeostasis after transplant. These results have the potential to impact clinical practice, based on two key attributes: First, they combine OX40L blockade with sirolimus, an established immunomodulation platform. Second, the anti-OX40L antibody studied, KY1005, is a fully human antibody, developed for clinical use (Lee et a/., 2014). Trials of combinatorial prophylaxis with KY1005/Sirolimus will be critical to establish the clinical safety and efficacy of this strategy, including its impact on other clinical outcomes, most importantly including graft-versus leukemia (GVL) effects. While previous murine studies demonstrated that the elimination of $OX40^+$ T-cells from an allograft could simultaneously reduce aGVHD while preserving both GVL and anti-viral immunity (Ge eta/, 2008), there is no leukemia model in NHP, and thus this issue cannot be directly evaluated in primates prior to clinical evaluation. As with all new immunomodulatory strategies, early phase clinical trials with KY1005/sirolimus will thus need to employ strong stopping rules to mitigate any increased risk of relapse.

While interrogating synergies in the setting of combination therapies is critical, one of the strengths of NHP models is their ability to also specifically probe bio-activity and mechanism-of-action of novel agents through monotherapy experiments. Indeed, these results demonstrate that OX40L blockade with KY1005, even as a monotherapy, has several important attributes: It was able to significantly control conventional $CD4^+$ T-cell proliferation and effector maturation, and, importantly, could stabilise the Treg:Tconv ratio, that was otherwise seriously degraded after transplant. However, despite the clear biologic effect of KY1005 as a monotherapy, and likely due to its predominant impact on $CD4^+$>>$CD8^+$ T-cell proliferation and activation, it was, as expected, insufficient to fully protect from aGVHD. Like-

wise, sirolimus monotherapy, as we have previously reported, could also better maintain the Treg:Tconv ratio compared to recipients not receiving immune prophylaxis (Na et al., 2013) but also was insufficient to control effector T-cell activation, leading to severe aGVHD in these recipients (Furlan eta/., 2015; Furlan et al., 2016).

However, when OX40L blockade was combined with sirolimus producedimpressive results. Recipients prophylaxed with KY1005/Sirolimus demonstrated all of the clinical and immunologic characteristics desired post-transplant: The combined therapy was able to potently control T-cell activation, while still allowing successful hematologic reconstitution and donor engraftment post-transplant. Transplant recipients prophylaxed with this combination remained clinically healthy, and without signs of GVHD, even with weaning of KY1005 after Day 54 post-transplant. Importantly, they demonstrated recipient-specific blunting of ex-vivo alloreactivity, with better maintenance of anti-third-party proliferative responses. This is the first time that we have successfully controlled GVHD for >100 days post-transplant in NHP undergoing high-risk T-cell replete MHC haploidentical HCT (Furlan et al., 2015; Furlan et al., 2016; Miller eta., 2010), and as such represents a milestone for this model. Although technically challenging, the question of very long-term control of alloreactivity (with analysis extending to years post-transplant rather than months) can be accomplished in NHP (Larsen et al., 2010; Zheng et al., 2017). Such studies would allow us to evaluate the ability of KY1005/Sirolimus to reset the immune balance and prevent GVHD even after weaning sirolimus. They represent a critical area for future investigations.

Flow cytometric and transcriptomic analyses allowed us to probe the mechanisms driving the control of alloreactivity in KY1005/sirolimus-prophylaxed animals. One of the most notable findings was the ability of this combination strategy to enhance the Treg: Tconv ratio after transplant, an effect that was durable for the length of analysis, even after the weaning of KY1005 after day 54 post-transplant. While these experiments did not allow us to specifically test whether the expanding Tregs were donor-specific, this result nonetheless supports the hypothesis that in aGVHD, OX40L blockade does indeed have dichotomous effects on Treg compared to Teff, an effect that is strengthened by combination with sirolimus. Transcriptome analysis supported this observation, underscoring the enrichment of Treg signatures during combinatorial prophylaxis. As such, this represents a critical observation supporting clinical translation of this therapeutic strategy, given its unique ability to potently suppress effector T-cell activation while simultaneously supporting Treg reconstitution.

In addition to identifying the naïve T-cell and Treg signatures in the KY1005/Sirolimus-prophylaxed T-cells, transcriptome analysis revealed other enriched pathways that deserve special discussion. These include the Jak-STAT signaling pathway and the Type 1 interferon (IFN) pathways, which were robustly enriched in KY1005/Sirolimus T-cells compared to all other cohorts. The enrichment in Jak-STAT signaling is somewhat unexpected given the well-established role of cytokine signaling in promoting alloreactivity after HCT (Henden et al., 2015) as well as the promising results of clinical trials utilizing Jak-STAT inhibitors for GVHD prevention (Spoerl et al., 2014; Zeiser et al., 2015). However, the detailed analysis of this Jak-STAT signature revealed that enrichment in transcripts encoding pro-inflammatory cytokines/cytokine receptors was counterbalanced by the enrichment in genes encoding anti-inflammatory cytokines and their receptors, suggesting complex regulation of this pathway in the setting of combined mTOR/OX40L blockade.

While the Type 1 IFN pathways, canonically associated with anti-viral and other pathogen-driven responses, are classically attributed to innate cells, but also well-documented to be present in T-cells (Crouse et al., 2015; Kabelitz et al., 2007). Given that we observed CMV reactivation in recipients who were prophylaxed with KY1005/Sirolimus, these pathways may have been activated as part of an anti-viral response. However, wither incited by viral reactivation or induced directly during combined OX40L and mTOR blockade, the activation of these pathways may also have contributed to the potent control of aGVHD mediated by KY1005/Sirolimus. Thus, previous studies have documented significant activity of Type I IFN pathways against aGVHD (Robb et al., 2012; Robb et al., 2011), in addition to evidence supporting the ability of these signalling pathways to restrain Th17-driven inflammation in autoimmune models (Guo et al., 2008; Shinohara et al., 2008) and in patients with IBD (Moschen et al., 2008). Moreover, type I IFNs have also been shown to enhance Treg survival and anti-inflammatory function in both mice and humans (Stewart et al., 2013; Kole et al., 2013; Chen et al., 2012; Kanto et al., 2012; Lee et al, 2012; Metidji et al., 2015). However, the data surrounding IFNs are complex; some experiments indicatethat these pathways can also potentiate CD8-dependent alloimmunity and in so doing, can potentiate graft-versus leukemia responses and overcome tumor-driven T-cell tolerance, (Horkheimer et al., 2009) while also potentially augmenting, rather than controlling, GVHD (Robb et al., 2009; Robb et al., 2012) Our dataset underscores the influence of canonical innate signalling pathways on the adaptive immune response and indicates that these pathways may enhance rather than impede the control of GVHD. They point to a critical area for future investigation, aimed at dissecting the potentially important role that classic anti-viral immune activation may have in immune tolerance-induction.

One of the most important observations in the current study is the degree to which previously established transcriptomic signatures of both Hyerpacute and Breakthrough Acute GVHD (Furlan et al., 2016; Furlan et al., 2015) were normalised in T-cells emerging during KY1005/Sirolimus prophylaxis. This includes the Th/Tc1 signatures that characterise Hyperacute GVHD, as well as the Th/Tc17 pathways that are prototypical of Breakthrough Acute GVHD. These pathways have been identified during GVHD that occurs despite both Tac/Mtx- and sirolimus-based combinatorial immunoprophylaxis, and therefore define key, clinically-relevant immunologic barriers to aGVHD control. These results suggest that KY1005/Sirolimus sets a new transcriptomic standard for aGVHD prevention, and for pathways leading to intact T-cell homeostasis after transplant. The ability of KY1005/Sirolimus to control pathology in the complex, clinically-relevant NHP model of GVHD suggests that this regimen may be an exceptional candidate for clinical translation.

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SEQUENCE LISTING

SEQ ID NO:			
1	10A07	VH Nucleotide Sequence	GAGGTGCAACTGGTGGAGTCTGGGGGAGTCTTGGTACAGCCGGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGTTATATTATGACTTGG GTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTAGTGGTAG TGGTGGTGGTACATACTACGCAGACTCCATGAAGGGCCGGTTCACCATCTCCAG AGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGAGAGTCGAGGA CACGGCCGTATATTACTGTGCGAAAGATCGGTTAGGTCCGATTACTTTGGTTCG GGGGGGCTATTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCG TCTCCTCA
2		VH Amino Acid Sequence	EVQLVESGGVLVQPGGSLRLSCAASGFTFSSYIMTWVRQAPGKGLEWVSGISGSG GGTYYADSMKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDRLGPITLVRGGY YYGMDVWGQGTTVTVSS
3		HCDR1 Nucleotide Sequence (IMGT)	GGATTCACCTTTAGCAGTTATATT
4		HCDR1 Amino Acid Sequence (IMGT)	GFTFSSYI
5		HCDR2 Nucleotide Sequence (IMGT)	ATTAGTGGTAGTGGTGGTGGTACA
6		HCDR Amino Acid Sequence (IMGT)	ISGSGGGT
7		HCDR3 Nucleotide Sequence (IMGT)	GCGAAAGATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTACTACGGT ATGGACGTC
8		HCDR3 Amino Acid Sequence (IMGT)	AKDRLGPITLVRGGYYYGMDV
9		HCDR1 Nucleotide Sequence (KABAT)	AGTTATATTATGACT
10		HCDR1 Amino Acid Sequence (KABAT)	SYIMT
11		HCDR2 Nucleotide Sequence (KABAT)	GGTATTAGTGGTAGTGGTGGTGGTACATACTACGCAGACTCCATGAAGGGC
12		HCDR2 Amino Acid Sequence (KABAT)	GISGSGGGTYYADSMKG
13		HCDR3 Nucleotide Sequence (KABAT)	GATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTACTACGGTATGGAC GTC
14		HCDR3 Amino Acid Sequence (KABAT)	DRLGPITLVRGGYYYGMDV
15		VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCGACTATTTAAATTGGTATCA GCAGAAACCAGGGAAAGCCCCTAAGTTCCTGATCTATGCTGCATCCAGTTTGCAA AGTGGAGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC ACCGTCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT ACAGTACCCCTCGGACGTTCGGCCAAGGGACCAGGGTGGAAATCAAA

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SEQUENCE LISTING

SEQ ID NO:		
16	VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISDYLNWYQQKPGKAPKFLIYAASSLQS GVPSRFSGSGSGTDFTLIVSSLQPEDFATYYCQQSYSTPRTFGQGTRVEIK
17	LCDR1 Nucleotide Sequence (IMGT)	CAGAGCATTAGCGACTAT
18	LCDR1 Amino Acid Sequence (IMGT)	QSISDY
19	LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
20	LCDR2 Amino Acid Sequence (IMGT)	MS
21	LCDR3 Nucleotide Sequence (IMGT)	CAACAGAGTTACAGTACCCCTCGGACG
22	LCDR3 Amino Acid Sequence (IMGT)	QQSYSTPRT
23	LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGAGCATTAGCGACTATTTAAAT
24	LCDR1 Amino Acid Sequence (KABAT)	RASQSISDYLN
25	LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCAGTTTGCAAAGT
26	LCDR2 Amino Acid Sequence (KABAT)	AASSLQS
27	LCDR3 Nucleotide Sequence (KABAT)	CAACAGAGTTACAGTACCCCTCGGACG
28	LCDR3 Amino Acid Sequence (KABAT)	QQSYSTPRT
29	Heavy Chain Nucleotide Sequence	GAGGTCCAGCTCGTGGAAAGCGGAGGAGTGCTCGTGCAGCCTGGAGGCAGCCT CAGGCTGTCCTGTGCCGCCTCCGGCTTCACCTTCAGCAGCTACATCATGACCTG GGTGAGGCAGGCTCCCGGAAAAGGCCTGGAGTGGGTGTCCGGCATCTCCGGAT CCGGAGGAGGCACATACTACGCCGACAGCATGAAGGGCCGGTTCACCATCAGCC GGGACAATAGCAAGAATACCCTCTACCTGCAAATGAACAGCCTGCGGGTGGAGG ATACCGCCGTGTACTACTGCGCCAAAGATAGGCTGGGCCCCATTACCCTCGTGA GGGGAGGCTATTACTACGGCATGGATGTGTGGGGCCAGGGCACCACCGTGACA GTGTCCAGCGCCAGCACCAAGGGCCCTTCCGTGTTCCCCCTGGCCCCTTGCAGC AGGAGCACCTCCGAATCCACAGCTGCCCTGGGCTGTCTGGTGAAGGACTACTTT CCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCTCTGACATCCGGCGTCCAC ACCTTTCCTGCCGTCCTGCAGTCCTCCGGCCTCTACTCCCTGTCCTCCGTGGTGA CCGTGCCTAGCTCCTCCCTCGGCACCAAGACCTACACCTGTAACGTGGACCACAA ACCCTCCAACACCAAGGTGGACAAACGGGTCGAGAGCAAGTACGGCCCTCCCTG CCCTCCTTGTCCTGCCCCCGAGTTCGAAGGCGGACCCAGCGTGTTCCTGTTCCC TCCTAAGCCCAAGGACACCCTCATGATCAGCCGGACACCCGAGGTGACCTGCGT GGTGGTGGATGTGAGCCAGGAGGACCCTGAGGTCCAGTTCAACTGGTATGTGG ATGGCGTGGAGGTGCACAACGCCAAGACAAAGCCCCGGGAAGAGCAGTTCAACT CCACCTACAGGGTGGTCAGCGTGCTGACCGTGCTGCATCAGGACTGGCTGAACG GCAAGGAGTACAAGTGCAAGGTCAGCAATAAGGGACTGCCCAGCAGCATCGAGA AGACCATCTCCAAGGCTAAAGGCCAGCCCCGGGAACCTCAGGTGTACACCCTGC

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SEQUENCE LISTING

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			CTCCCAGCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGA AGGGATTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCG AGAACAATTATAAGACCACCCCTCCCGTCCTCGACAGCGACGGATCCTTCTTTCT GTACTCCAGGCTGACCGTGGATAAGTCCAGGTGGCAGGAAGGCAACGTGTTCAG CTGCTCCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGAG CCTGTCCCTGGGAAAG
30		Heavy Chain Amino Acid Sequence	EVQLVESGGVLVQPGGSLRLSCAASGFTFSSYIMTWVRQAPGKGLEWVSGISGSG GGTYYADSMKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDRLGPITLVRGGY YYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK
31		Light Chain Nucleotide Sequence	GACATCCAGATGACCCAGTCCCCTTCCTCCCTGTCCGCCTCCGTGGGAGACAGG GTGACCATCACCTGCCGGGCCAGCCAGTCCATCAGCGACTACCTGAACTGGTAT CAGCAGAAGCCCGGCAAGGCCCCTAAGTTCCTGATCTACGCCGCTTCCTCCCTG CAGTCCGGAGTGCCCAGCAGGTTTTCCGGCTCCGGATCCGGCACCGACTTCACC CTGACCGTGTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAG AGCTACAGCACCCCCAGGACATTTGGCCAGGGCACCCGGGTGGAGATCAAGAGG ACCGTCGCTGCCCCCTCCGTGTTTATCTTCCCCCCCAGCGACGAGCAGCTGAAAT CCGGCACCGCCTCCGTGGTCTGCCTGCTGAATAACTTCTACCCTCGGGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGAAACTCCCAGGAGAGC GTGACCGAGCAGGACTCCAAGGACTCCACATACTCCCTGTCCTCCACCCTGACAC TGTCCAAGGCCGATTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACC AGGGACTGTCCTCCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
32		Light Chain Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISDYLNWYQQKPGKAPKFLIYAASSLQS GVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQSYSTPRTFGQGTRVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
33	02D10	VH Nucleotide Sequence	GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCATTTTAGCAACTATGCCATGAACTGG GTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGCGGAAG TGGTGGTGCCACAAGGTATGCAGACTCCGTGAAGGGCCGATTCACCATATCCAG AGACAATTCCAGGAACACGGTGTATCTGCAAATGAACAGCCTGAGAGTCGAGGA CACGGCCGTTTTTTACTGTACGAAAGATCGGCTCATTATGGCTACGGTTCGGGG ACCCTATTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGICACCGICTC CTCA
34		VH Amino Acid Sequence	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKGLEWVSTISGSG GATRYADSVKGRFTISRDNSRNIVYLQMNSLRVEDTAVFYCTKDRLIMATVRGPYY YGMDVWGQGTTVTVSS

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SEQ ID NO:		
35	HCDR1 Nucleotide Sequence (IMGT)	GGATTCACTTTTAGCAACTATGCC
36	HCDR1 Amino Acid Sequence (IMGT)	GFTFSNYA
37	HCDR2 Nucleotide Sequence (IMGT)	ATTAGCGGAAGTGGTGGTGCCACA
38	HCDR2 Amino Acid Sequence (IMGT)	ISGSGGAT
39	HCDR3 Nucleotide Sequence (IMGT)	ACGAAAGATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACGGTATG GACGTC
40	HCDR3 Amino Acid Sequence (IMGT)	TKDRLIMATVRGPYYYGMDV
41	HCDR1 Nucleotide Sequence (KABAT)	AACTATGCCATGAAC
42	HCDR1 Amino Acid Sequence (KABAT)	NYAMN
43	HCDR2 Nucleotide Sequence (KABAT)	ACTATTAGCGGAAGIGGTGGTGCCACAAGGTATGCAGACTCCGTGAAGGGC
44	HCDR2 Amino Acid Sequence (KABAT)	TISGSGGATRYADSVKG
45	HCDR3 Nucleotide Sequence (KABAT)	GATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACGGTATGGACGTC
46	HCDR3 Amino Acid Sequence (KABAT)	DRLIMATVRGPYYYGMDV
47	VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA GCAGAAACCAGGGAAAGCCCCTAACCTCCTGATCTATGCTGCATCCAGTTTGCAA AGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGAGACAGATTTCACTCTC ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTC ACAGTGTCTCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA
48	VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAASSLQSG VPSRFSGSGSETDFTLTISSLQPEDFATYYCQQSHSVSFTFGPGTKVDIK
49	LCDR1 Nucleotide Sequence (IMGT)	CAGAGCATTAGCAGCTAT
50	LCDR1 Amino Acid Sequence (IMGT)	QSISSY
51	LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
52	LCDR2 Amino Acid Sequence (IMGT)	MS
53	LCDR3 Nucleotide Sequence (IMGT)	CAACAGAGICACAGIGTCTCATTCACT
54	LCDR3 Amino Acid Sequence (IMGT)	QQSHSVSFT

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SEQUENCE LISTING

SEQ ID NO:		
55	LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGAGCATTAGCAGCTATTTAAAT
56	LCDR1 Amino Acid Sequence (KABAT)	RASQSISSYLN
57	LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCAGTTTGCAAAGT
58	LCDR2 Amino Acid Sequence (KABAT)	AASSLQS
59	LCDR3 Nucleotide Sequence (KABAT)	CAACAGAGTCACAGTGTCTCATTCACT
60	LCDR3 Amino Acid Sequence (KABAT)	QQSHSVSFT
61	Heavy Chain Nucleotide Sequence	GAAGTGCAACTGGTGGAGTCCGGAGGAGGCCTGGTGCAGCCTGGAGGAAGCCT GAGGCTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACTACGCCATGAACTG GGTGAGGCAGGCCCCTGGCAAGGGACTGGAGTGGGTCTCCACCATCAGCGGCT CCGGAGGCGCTACACGGTACGCCGATAGCGTGAAGGGCCGGTTTACCATTTCCC GGGACAACTCCCGGAACACCGTGTACCTCCAGATGAACAGCCTGAGGGTGGAGG ATACCGCCGTGTTCTACTGCACCAAGGACAGGCTGATTATGGCCACCGTGAGGG GACCTTACTACTATGGCATGGATGTGTGGGGCCAGGGCACAACCGTCACCGTGT CCTCCGCCTCCACCAAGGGACCTAGCGTGTTCCCTCTCGCCCCCTGTTCCAGGTC CACAAGCGAGTCCACCGCTGCCCTCGGCTGTCTGGTGAAAGACTACTTTCCCGA GCCCGTGACCGTCTCCTGGAATAGCGGAGCCCTGACCTCCGGCGTGCACACATT TCCCGCCGTGCTGCAGAGCAGCGGACTGTATAGCCTGAGCAGCGTGGTGACCGT GCCCAGCTCCAGCCTCGGCACCAAAACCTACACCTGCAACGTGGACCACAAGCCC TCCAACACCAAGGTGGACAAGCGGGTGGAGAGCAAGTACGGCCCCCCTTGCCCT CCTTGTCCTGCCCCTGAGTTCGAGGGAGGACCCTCCGTGTTCCTGTTTCCCCCC AAACCCAAGGACACCCTGATGATCTCCCGGACACCCGAGGTGACCTGTGTGGTC GTGGACGTCAGCCAGGAGGACCCCGAGGTGCAGTTCAACTGGTATGTGGACGG CGTGGAGGTGCACAATGCCAAAACCAAGCCCAGGGAGGAGCAGTTCAATTCCAC CTACAGGGTGGTGAGCGTGCTGACCGTCCTGCATCAGGATTGGCTGAACGGCAA GGAGTACAAGTGCAAGGTGTCCAACAAGGGACTGCCCAGCTCCATCGAGAAGAC CATCAGCAAGGCTAAGGGCCAGCCGAGGGAGCCCCAGGTGTATACCCTGCCTCC TAGCCAGGAAGAGATGACCAAGAACCAAGTGTCCCTGACCTGCCTGGTGAAGGG ATTCTACCCCTCCGACATCGCCGTGGAGTGGGAGAGCAATGGCCAGCCCGAGAA CAACTACAAAACAACCCCTCCCGTGCTCGATAGCGACGGCAGCTTCTTTCTCTAC AGCCGGCTGACAGTGGACAAGAGCAGGTGGCAGGAGGGCAACGTGTTCTCCTG TTCCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTCTCCCTG TCCCTGGGCAAG
62	Heavy Chain Amino Acid Sequence	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKGLEWVSTISGSG GATRYADSVKGRFTISRDNSRNTVYLQMNSLRVEDTAVFYCTKDRLIMATVRGPYY YGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN

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63		Light Chain Nucleotide Sequence	GACATCCAGATGACCCAGTCCCCTTCCTCCCTGAGCGCTAGCGTGGGAGATAGG GTGACCATCACCTGCAGGGCCTCCCAAAGCATCTCCTCCTACCTGAACTGGTACC AGCAGAAACCCGGCAAGGCCCCCAACCTGCTGATCTACGCTGCCTCCTCCCTCCA GTCCGGCGTGCCTAGCAGGTTTAGCGGCTCCGGAAGCGAGACCGACTTCACCCT GACCATCTCCTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAATCC CACAGCGTGTCCTTCACCTTCGGCCCCGGCACCAAGGTGGACATCAAGAGGACC GTGGCCGCCCCCTCCGTGTTCATCTTTCCCCCCTCCGATGAACAGCTGAAGAGC GGCACCGCTAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGAGGCCAAG GTGCAGTGGAAGGTGGACAATGCCCTGCAGTCCGGCAACAGCCAGGAGAGCGT GACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGTCCTCCACCCTGACCCT GTCCAAGGCCGACTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCATCA GGGCCTGAGCTCCCCCGTGACCAAGTCCTTTAACAGGGGCGAGTGC
64		Light Chain Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAASSLQSG VPSRFSGSGSETDFTLTISSLQPEDFATYYCQQSHSVSFTFGPGTKVDIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
65	09H04	VH Nucleotide Sequence	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT GAGACTCTCCTGTGCAGCCTCTCGATTCACCCTCAGTGACTACTACATGACCTGG ATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTAGT GGTAATACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGG GACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCCGTGTATTACTGTGCGAGAGATCTGAGTGGGAGCTACTGGGACTACTAC TACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
66		VH Amino Acid Sequence	QVQLVESGGGLVKPGGSLRLSCAASRFTLSDYYMTWIRQAPGKGLEWVSYISSSGN TIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDLSGSYWDYYYGM DVWGQGTTVTVSS
67		HCDR1 Nucleotide Sequence (IMGT)	CGATTCACCCTCAGTGACTACTAC
68		HCDR1 Amino Acid Sequence (IMGT)	RFTLSDYY
69		HCDR2 Nucleotide Sequence (IMGT)	ATTAGTAGTAGTGGTAATACCATA
70		HCDR2 Amino Acid Sequence (IMGT)	ISSSGNTI
71		HCDR3 Nucleotide Sequence (IMGT)	GCGAGAGATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGACGTC
72		HCDR3 Amino Acid Sequence (IMGT)	ARDLSGSYWDYYYGMDV
73		HCDR1 Nucleotide Sequence (KABAT)	GACTACTACATGACC

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SEQUENCE LISTING

SEQ ID NO:			
74		HCDR1 Amino Acid Sequence (KABAT)	DYYMT
75		HCDR2 Nucleotide Sequence (KABAT)	TACATTAGTAGTAGTGGTAATACCATATACTACGCAGACTCTGTGAAGGGC
76		HCDR2 Amino Acid Sequence (KABAT)	YISSSGNTIYYADSVKG
77		HCDR3 N ucleotide Sequence (KABAT)	GATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGACGTC
78		HCDR3 Amino Acid Sequence (KABAT)	DLSGSYWDYYYGMDV
79		VL Nucleotide Sequence	GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTACATCTGTAGGAGACAGAG TCACCATCGCTTGCCGGGCAAGTCAGGGCATTAACAATGCTTTAGCCTGGTATC AGCAGAAACCAGGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGG AAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTC TCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCAACAGTT TAATAGTTACCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA
80		VL Amino Acid Sequence	AIQLTQSPSSLSTSVGDRVTIACRASQGINNALAWYQQKPGKAPKLLIYDASSLESG VPSRFSGSGSGTDFTLTISSLQPEDFAMCQQFNSYPRTFGQGTKVEIK
81		LCDR1 Nucleotide Sequence (IMGT)	CAGGGCATTAACAATGCT
82		LCDR1 Amino Acid Sequence (IMGT)	QGINNA
83		LCDR2 Nucleotide Sequence (IMGT)	GATGCCTCC
84		LCDR2 Amino Acid Sequence (IMGT)	DAS
85		LCDR3 Nucleotide Sequence (IMGT)	CAACAGTTTAATAGTTACCCTCGGACG
86		LCDR3 Amino Acid Sequence (IMGT)	QQFNSYPRT
87		LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGGGCATTAACAATGCTTTAGCC
88		LCDR1 Amino Acid Sequence (KABAT)	RASQGINNALA
89		LCDR2 Nucleotide Sequence (KABAT)	GATGCCTCCAGTTTGGAAAGT
90		LCDR2 Amino Acid Sequence (KABAT)	DASSLES
91		LCDR3 Nucleotide Sequence (KABAT)	CAACAGTTTAATAGTTACCCTCGGACG
92		LCDR3 Amino Acid Sequence (KABAT)	QQFNSYPRT
93	19H01	VH Nucleotide Sequence	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGGGGGTCCCT TAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAACGCCTGGATGAGCTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTGGCCGTATTAAAAGCA

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SEQUENCE LISTING

SEQ ID NO:		
		AAACTGAAGGTGGGACAACAGACTACGCTGCACCCGTGAAAGGCAGATTCACCA TCTCAAGAGATGATTCAAAAAACACGCTGTATCTGCAAATGAACAGCCTGAAAAC CGAGGACACAGCCGTGTATTACTGTACCACAGATTTTCTATGGTTCGGGGAGTT CCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
94	VH Amino Acid Sequence	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKSKT EGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTDFLWFGEFPFD YWGQGTLVTVSS
95	HCDR1 Nucleotide Sequence (IMGT)	GGATTCACTTTCAGTAACGCCTGG
96	HCDR1 Amino Acid Sequence (IMGT)	GFTFSNAW
97	HCDR2 Nucleotide Sequence (IMGT)	ATTAAAAGCAAAACTGAAGGTGGGACAACA
98	HCDR2 Amino Acid Sequence (IMGT)	IKSKTEGGTT
99	HCDR3 Nucleotide Sequence (IMGT)	ACCACAGATTTTCTATGGTTCGGGGAGTTCCCTTTTGACTAC
100	HCDR3 Amino Acid Sequence (IMGT)	TTDFLWFGEFPFDY
101	HCDR1 Nucleotide Sequence (KABAT)	AACGCCTGGATGAGC
102	HCDR1 Amino Acid Sequence (KABAT)	NAWMS
103	HCDR2 Nucleotide Sequence (KABAT)	CGTATTAAAAGCAAAACTGAAGGTGGGACAACAGACTACGCTGCACCCGTGAAA GGC
104	HCDR2 Amino Acid Sequence (KABAT)	RIKSKTEGGTTDYAAPVKG
105	HCDR3 Nucleotide Sequence (KABAT)	GATTTTCTATGGTTCGGGGAGTTCCTTTTGACTAC
106	HCDR3 Amino Acid Sequence (KABAT)	DFLWFGEFPFDY
107	VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG TCACCATCACTTGCCGGGCGAGTCAGGGCATTAGCAATTATTTAGCCTGGTATCA GCAGAAACCAGGGAAAATTCCTAAGCTCCTGATCTATGCTGCATCCACTTTGCAA TCAGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC ACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAAAGTATA ACAGTGCCCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA
108	VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKIPKLLIYAASTLQSG VPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPRTFGQGTKVEIK
109	LCDR1 Nucleotide Sequence (IMGT)	CAGGGCATTAGCAATTAT
110	LCDR1 Amino Acid Sequence (IMGT)	QGISNY

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SEQUENCE LISTING

SEQ ID NO:				
111			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
112			LCDR2 Amino Acid Sequence (IMGT)	MS
113			LCDR3 Nucleotide Sequence (IMGT)	CAAAAGTATAACAGTGCCCCTCGGACG
114			LCDR3 Amino Acid Sequence (IMGT)	QKYNSAPRT
115			LCDR1 Nucleotide Sequence (KABAT)	CGGGCGAGTCAGGGCATTAGCAATTATTTAGCC
116			LCDR1 Amino Acid Sequence (KABAT)	RASQGISNYLA
117			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCACTTTGCAATCA
118			LCDR2 Amino Acid Sequence (KABAT)	AASTLQS
119			LCDR3 Nucleotide Sequence (KABAT)	CAAAAGTATAACAGTGCCCCTCGGACG
120			LCDR3 Amino Acid Sequence (KABAT)	QKYNSAPRT
121	Human IgG4 heavy chain constant region #1	IGHG* 01	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtccccatgcccatcatgcccagcacctgagttcctgggggg accatcagtatcctgttcccccaaaacccaaggacactctcatgatctcccggacccctgaggtcacgtg cgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtggatggcgtggagg tgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctca ccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgt cctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgcccc catcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcg acatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg gactccgacggctccttcttcctctacagcaggctaaccgtggacaagagcaggtggcaggaggggaat gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctg ggtaaa
122			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVWSWNSGALTSGVHTFPAVL QSSGLYSLSSWTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEF LGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
123	Human IgG4 heavy chain constant region #2	IGHG* 02	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg

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124			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEF LGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
125	Human IgG4 heavy chain constant region #3	IGHG* 03	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtcccccatgcccatcatgcccagcacctgagttcctgggggg accatcagtcttcctgttcccccccaaaacccaaggacactctcatgatctcccggacccctgaggtcacgtg cgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtggatggcgtggagg tgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctca ccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgt cctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgcccc catcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcg acatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg gactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcaggaggggaac gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctctg ggtaaa
126			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVWSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
127	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence-Synthetic Version A	gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacggccg ccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtcccccatgcccaccatgcccagcgcctgaatttgaggggggg accatcagtatcctgttcccccaaaacccaaggacactctcatgatctcccggacccctgaggtcacgtg cgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtggatggcgtggagg

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128	IgG4 heavy chain constant region-IgG4-PE	Heavy Chain Constant Region Amino Acid Sequence-Encoded by Synthetic Version A, B & C	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEF EGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
129	IgG4 heavy chain constant region	Heavy Chain Constant Region Nucleotide Sequence-Synthetic Version B	Gcctccaccaagggacctagcgtgttccctctcgccccctgttccaggtccacaagcgagtccaccgctgc cctcggctgtctggtgaaagactactttcccgagcccgtgaccgtctcctggaatagcggagccctgacct ccggcgtgcacacatttcccgccgtgctgcagagcagcggactgtatagcctgagcagcgtggtgaccgt gcccagctccagcctcggcaccaaaacctacacctgcaacgtggaccacaagccctccaacaccaaggt ggacaagcgggtggagagcaagtacggccccccttgccctccttgtcctgcccctgagttcgagggagg accctccgtgttcctgtttcccccaaacccaaggacaccctgatgatctcccggacacccgaggtgacctg tgtggtcgtggacgtcagccaggaggaccccgaggtgcagttcaactggtatgtggacggcgtggaggt gcacaatgccaaaaccaagcccagggaggagcagttcaattccacctacagggtggtgagcgtgctga ccgtcctgcatcaggattggctgaacggcaaggagtacaagtgcaaggtgtccaacaagggactgccca gctccatcgagaagaccatcagcaaggctaagggccagccgagggagccccaggtgtataccctgcctc ctagccaggaagagatgaccaagaaccaagtgtccctgacctgcctggtgaagggattctacccctccga catcgccgtggagtgggagagcaatggccagcccgagaacaactacaaaacaacccctcccgtgctcg atagcgacggcagcttctttctctacagccggctgacagtggacaagagcaggtggcaggagggcaac gtpctcctgttccgtgatgcacgaggccctgcacaatcactacacccagaagagcctctccctgtccctg ggcaag
130	IgG4 heavy chain constant region	Heavy Chain Constant Region Nucleotide Sequence-Synthetic Version C	gccagcaccaagggcccttccgtgttcccccctggcccccttgcagcaggagcacctccgaatccacagctg ccctgggctgtctggtgaaggactactttcccgagcccgtgaccgtgagctggaacagcggcgctctgac atccggcgtccacacctttcctgccgtcctgcagtcctccggcctctactccctgtcctccgtggtgaccgtg cctagctcctccctcggcaccaagacctacacctgtaacgtggaccacaaaccctccaacaccaaggtgga caaacgggtcgagagcaagtacggccctccctgccctccttgtcctgccccgagttcgaaggcggaccc agcgtgttcctgttccctcctaagcccaaggacaccctcatgatcagccggacacccgaggtgacctgcgt ggtggtggatgtgagccaggaggaccctgaggtccagttcaactggtatgtggatggcgtggaggtgca caacgccaagacaaagccccgggaagagcagttcaactccacctacagggtggtcagcgtgctgaccgt gctgcatcaggactggctgaacggcaaggagtacaagtgcaaggtcagcaataagggactgcccagca gcatcgagaagaccatctccaaggctaaaggccagccccgggaacctcaggtgtacaccctgcctccca gccaggaggagatgaccaagaaccaggtgagcctgacctgcctggtgaagggattctacccttccgaca tcgccgtggagtgggagtccaacggccagcccgagaacaattataagaccacccctcccgtcctcgaca gcgacggatccttctttctgtactccaggctgaccgtggataagtccaggtggcaggaaggcaacgtgttc agctgctccgtgatgcacgaggccctgcacaatcactacacccagaagtccctgagcctgtccctgggaa ag

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131	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence-Synthetic Version D	gcctccaccaagggcccatccgtcttcccccctggcgccctgctccaggagcacctccgagagcacggccg ccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtcccccatgcccaccatgcccagcgcctccagttgcgggggg accatcagtcttcctgttcccccaaaacccaaggacactctcatgatctcccggaccctgaggtcacgtg cgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtggatggcgtggagg tgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctca ccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgt catcgatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgccc ccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagc gacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgct ggactccgacggatccttcttcctctacagcaggctaaccgtggacaagagcaggtggcaggaggggaa tgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctg ggtaaa
132			Heavy Chain Constant Region Amino Acid Sequence-encoded by Synthetic Version D (PVA mutation)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPPV AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
133	Human IgG1 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence	gcctccaccaagggcccatcggtaccccctggcaccctcctccaagagcacctctgggggcacagcgg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggt ggacaagaaagtggagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaact cgcgggggcaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccctg aggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtc agcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaa gccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgta caccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttc tatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgc ctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcag caggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctc cctgtctccgggtaaa
134			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCINSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
135	Human Cκ constant	IGKC* 01	Cκ Light Chain Constant Region Nucleotide Sequence	cgtacggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgcttct gtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtggacaacgccctg

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136			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAINQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
137	Human Cκ constant region	IGKC* 02	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagcacctacagcctcagcagcac cctgacgctgagcaaagcagactacgagaaacacaaagtctacgccggcgaagtcacccatcagggcc tgagctcgcccgtcacaaagagcttcaacaggggagagtgt
138			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCENNFYPREAWQWKVDNALQSGNSQESV TEQESKDSTYSLSSTLTLSKADYEKHKVYAGEVTHQGLSSPVTKSFNRGEC
139	Human Cκ constant region	IGKC* 03	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagcggaaggtggataacgccctcca atcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagcacctacagcctcagcagc accctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcaggg cctgagctcgcccgtcacaaagagcttcaacaggggagagtgt
140			Cκ Light Chain Constant Region Amino Acid Sequence	RIVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQRKVDNALQSGNSQESVT EQESKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
141	Human Cκ constant region	IGKC* 04	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcac cctgacgctgagcaaagcagactacgagaaacacaaactctacgcctgcgaagtcacccatcagggcct gagctcgcccgtcacaaagagcttcaacaggggagagtgt
142			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAINQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKLYACEVTHQGLSSPVTKSFNRGEC
143	Human Cκ constant region	IGKC* 05	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcaacac cctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcct gagctcgcccgtcacaaagagcttcaacaggggagagtgc
144			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCENNFYPREAWQWKVDNALQSGNSQESV TEQDSKDSTYSLSNTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
145	Human Cλ constant region	IGCλ 1*01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggccaaccccacggtcactctgttcccgccctcctctgaggagctccaagccaacaaggccacac tagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcttggaaggcagatggcagccccgtc aaggcgggagtggagacgaccaaaccctccaaacagagcaacaacaagtacgcggccagcagctacc tgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaagggagc accgtggagaagacagtggcccctacagaatgttca
146			Cλ Light Chain Constant Region Amino Acid Sequence	PKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
147	Human Cλ	IGCλ	Cλ Light Chain Constant Region	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctctgaggagctccaagccaacaagg

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	constant region	1*02	Nucleotide Sequence	ccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatggcag ccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaacaagtacgcggccagc agctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaa gggagcaccgtggagaagacagtggcccctacagaatgttca
148			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
149	Human Cλ constant region	IGCλ 2*01	Cλ Light Chain Constant Region Nucleotide Sequence-Version A	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctctgaggagctccaagccaacaagg ccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatggcag ccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaacaagtacgcggccagc agctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaa gggagcaccgtggagaagacagtggcccctacagaatgttca
150			Cλ Light Chain Constant Region Nucleotide Sequence-Version 6	ggccagcctaaggccgctccttctgtgaccctgttccccccatcctccgaggaactgcaggctaacaaggc caccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggctgatagctctc ctgtgaaggccggcgtggaaaccaccacccctccaagcagtccaacaacaaatacgccgcctcctccta cctgtccctgacccctgagcagtggaagtcccaccggtcctacagctgccaagtgacccacgagggctcc accgtggaaaagaccgtggctcctaccgagtgctcc
151			Cλ Light Chain Constant Region Nucleotide Sequence-Version C	ggccagcctaaagctgcccccagcgtcaccctgtttcctccctccagcgaggagctccaggccaacaagg ccaccctcgtgtgcctgatctccgacttctatcccggcgctgtgaccgtggcttggaaagccgactccagcc ctgtcaaagccggcgtggagaccaccacaccctccaagcagtccaacaacaagtacgccgcctccagct atctctccctgaccctgagcagtggaagtcccaccggtcctactcctgtcaggtgacccacgagggctcc accgtggaaaagaccgtcgccccccaccgagtgctcc
152			Cλ Light Chain Constant Region Amino Acid Sequence-Encoded by Version A, B & C	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
153	Human Cλ constant region	IGCλ 2*02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcagc cccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagca gctatctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaag ggagcaccgtggagaagacagtggcccctacagaatgttca
154			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
155	Human Cλ constant region	IGCλ 3*01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggccacact ggtgtgtctcataagtgacttctacccgggagccgtgacagttgcctggaaggcagatagcagccccgtc aaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagcagctacc tgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgcatgaagggagc accgtggagaagacagttgcccctacggaatgttca
156			Cλ Light Chain Constant Region Amino Acid Sequence	PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPS KQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
157	Human Cλ constant region	IGCλ 3*02	CA Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccggggccagtgacagttgcctggaaggcagatagcagc cccgtcaaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagca gctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgcatgaag ggagcaccgtggagaagacagtggcccctacggaatgttca

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SEQUENCE LISTING

SEQ ID NO:				
158			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGPVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
159	Human Cλ constant region	IGCA 3*03	Cλ Light Chain Constant Region Nudeotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcagc cccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagca gctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgcatgaag ggagcaccgtggagaagacagtggcccctacagaatgttca
160			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
161	Human Cλ constant region	IGCA 3*04	Cλ Light Chain Constant Region Nudeotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcagc cccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagca gctacctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaag ggagcaccgtggagaagacagtggcccctacagaatgttca
162			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
163	Human Cλ constant region	IGCλ 6*01	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggc cacactggtgtgcctgatcagtgacttctacccgggagctgtgaaagtggcctggaaggcagatggcag ccccgtcaacacgggagtggagaccaccacaccctccaaacagagcaacaacaagtacgcggccagc agctacctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaa gggagcaccgtggagaagacagtggcccctgcagaatgttca
164			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETT TPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS
165	Human Cλ constant region	IGCλ 7*02	Cλ Light Chain Constant Region Nudeotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcgtaagtgacttctacccgggagccgtgacagtggcctggaaggcagatggcagc cccgtcaaggtgggagtggagaccaccaaaccctccaaacaaagcaacaacaagtatgcggccagca gctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccgggtcacgcatgaa gggagcaccgtggagaagacagtggcccctgcagaatgctct
166			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFYPGAVTVAWKADGSPVKVGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
167	Recombinant Human OX40L (Leader sequence, Isoleutine Zipper and FLAG Sequence Included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCAC AGCGATTACAAGGATGACGACGATAAGCGTATGAAACAGATCGAAGATAAAATT GAAGAGATCTTGAGCAAAATCTATCATATCGAAAACGAAATTGCGCGTATCAAAA AGCTGATTGGCGAACGTGGCGGTGGCAGCGGTGGCGGTAGCGGCGGTGGCAGC CAGGTGTCCCACCGATACCCCAGGATCCAGTCCATCAAGGTCCAGTTCACCGAG TACAAAAAGGAGAAGGGATTCATCCTGACCTCCCAAAAGGAGGACGAGATCATG AAGGTGCAAAACAACTCCGTGATCATCAACTGCGACGGCTTCTACCTGATCTCCC TGAAGGGCTACTTCTCCCAGGAGGTGAACATCTCCCTGCACTACCAGAAGGACG AGGAGCCCCTGTTCCAGCTGAAGAAGGTGAGGICCGTGAATTCCCTGATGGTGG CCAGCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACCACCGACAACACCA GCCTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCTGATCCATCAGAACC

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SEQUENCE LISTING

SEQ ID NO:			
			CCGGCGAGTTTTGCGTCCTG
168		Amino Acid Sequence	MGWSCIILFLVATATGVHSDYKDDDDKRMKQIEDKIEEILSKIYHIENEIARIKKLIG ERGGGSGGGSGGGSQVSHRYPRIQSIKVQFTEYKKEKGFILTSQKEDEIMKVQNNS VIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVY LNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL
169	Recombinant Rhesus OX40L (Leader Sequence, FLAG and Isoleucine zipper included)	Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCAC AGCGATTACAAGGATGACGACGATAAGCGTATGAAACAGATCGAAGATAAAATT GAAGAGATCTTGAGCAAAATCTATCATATCGAAAACGAAATTGCGCGTATCAAAA AGCTGATTGGCGAACGTGGCGGTGGCAGCGGTGGCGGTAGCGGCGGTGGCAGC CAGGTGTCCCACCAATACCCCAGGATCCAGTCCATCAAGGTCCAGTTCACCGAGT ACAAAAAGGAGGAGGGATTCATCCTGACCTCCCAAAAGGAGGACGAGATCATGA AGGTGCAAAACAACTCCGTGATCATCAACTGCGACGGCTTCTACCTGATCTCCCT GAAGGGCTACTTCTCCCAGGAGGTGAACATCTCCCTGCACTACCAGAAGGACGA GGAGCCCCTGTTCCAGCTGAAGAAGGTGAGGTCCGTGAATTCCCTGATGGTGGC CAGCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACCACCGACAACACCAG CCTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCTGATCCATCAGAACCC CGGCGAGTTTTGCGTCCTG
170		Amino Acid Sequence	MGWSCIILFLVATATGVHSDYKDDDDKRMKQIEDKIEEILSKIYHIENEIARIKKLIG ERGGGSGGGSGGGSQVSHQYPRIQSIKVQFTEYKKEEGFILTSQKEDEIMIWQNNS VIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVY LNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL
171	Recombinant Human OX40R (Leader Sequence and Human Fc Sequence included)	Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCAC AGCCTGCATTGCGTGGGCGACACCTATCCCTCCAACGACAGGTGCTGCCACGAG TGCAGGCCTGGAAACGGCATGGTGAGCAGGTGCAGCCGGTCCCAGAATACCGTG TGTAGGCCCTGCGGCCCCGGCTTTTACAACGACGTGGTGTCCTCCAAGCCCTGC AAGCCCTGCACATGGTGCAACCTGCGGTCCGGCAGCGAGAGGAAGCAGCTCTGC ACAGCCACCCAGGACACCGTCTGTAGGTGTAGGGCTGGCACCCAGCCTCTGGAC TCCTACAAGCCCGGCGTGGATTGTGCTCCTTGCCCTCCCGGCCATTTCTCCCCTG GCGACAACCAGGCTTGCAAGCCCTGGACCAACTGTACCCTGGCCGGCAAGCATA CACTGCAGCCTGCTTCCAACTCCTCCGACGCTATCTGCGAGGATAGGGACCCCC CTGCCACACAACCCCAGGAGACACAGGGCCCTCCTGCTAGGCCCATCACAGTCC AACCCACCGAAGCCTGGCCCAGGACATCCCAAGGCCCTTCCACCAGGCCTGTGG AAGTGCCTGGAGGAAGGGCTGTGGCCATTGAAGGTCGTATGGATGAACCCAAGT CCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCG GACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCG GACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGT GAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCC TAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCT GCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGC CCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGA ACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGT GTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATG GGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGA CTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCCCGGTG GCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCA

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SEQUENCE LISTING

SEQ ID NO:			
			CTACACCCAGAAGTCCCTGTCCCTGAGCCCCTGA
172		Amino Acid Sequence	MGWSCIILFLVATATGVHSLHCVGDTYPSNDRCCHECRPGNGMVSRCSRSQNTVC RPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCRCRAGTQPLDSY KPGVDCAPCPPGHFSPGDNQACKPWTNCTLAGKHTLQPASNSSDAICEDRDPPAT QPQETQGPPARPITVQPTEAWPRTSQGPSTRPVEVPGGRAVAIEGRMDEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLIVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
173	Cell Expressed OX40L (CHO/MEF) (Leader sequence included)	Nucleotide Sequence	ATGGAGAGGGTGCAGCCCCTCGAGGAGAACGTGGGAAACGCCGCCAGGCCTAG GTTCGAGAGGAACAAGCTGCTGCTGGTGGCTTCCGTGATCCAAGGACTCGGCCT GCTGCTCTGCTTCACCTACATCTGCCTCCACTTCAGCGCCCTGCAGGTGTCCCAC CGATACCCCAGGATCCAGTCCATCAAGGTCCAGTTCACCGAGTACAAAAAGGAG AAGGGATTCATCCTGACCTCCCAAAAGGAGGACGAGATCATGAAGGTGCAAAAC AACTCCGTGATCATCAACTGCGACGGCTTCTACCTGATCTCCCTGAAGGGCTACT TCTCCCAGGAGGTGAACATCTCCCTGCACTACCAGAAGGACGAGGAGCCCCIGT TCCAGCTGAAGAAGGTGAGGTCCGTGAATTCCCTGATGGIGGCCAGCCTGACCT ACAAGGACAAGGTCTACCTGAACGTGACCACCGACAACACCAGCCTGGACGACT TCCATGTCAACGGCGGCGAGCTGATCCTGATCCATCAGAACCCCGGCGAGTTTT GCGTCCTGTAA
174		Amino Acid Sequence	MERVQPLEENVGNAARPRFERNKLLLVASVIQGLGLLLCFTYICLHFSALQVSHRYP RIQSIKVQFTEYKKEKGFILTSQKEDEIMKVQNNSVIINCDGFYLISLKGYFSQEVNI SLHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVYLNVTTDNTSLDDFHVNGGELI LIHQNPGEFC
175	Cell Expressed OX40 receptor (HT1080)	Nucleotide Sequence	ATGTGCGTGGGGGCTCGGCGGCTGGGCCGCGGGCCGTGTGCGGCTCTGCTCCT CCTGGGCCTGGGGCTGAGCACCGTGACGGGGCTCCACTGTGTCGGGGACACCT ACCCCAGCAACGACCGGTGCTGCCACGAGTGCAGGCCAGGCAACGGGATGGTGA GCCGCTGCAGCCGCTCCCAGAACACGGTGTGCCGTCCGTGCGGGCCGGGCTTCT ACAACGACGTGGTCAGCTCCAAGCCGTGCAAGCCCTGCACGTGGTGTAACCTCA GAAGTGGGAGTGAGCGGAAGCAGCTGTGCACGGCCACACAGGACACAGTCTGC CGCTGCCGGGCGGGCACCCAGCCCCTGGACAGCTACAAGCCTGGAGTTGACTGT GCCCCCTGCCCTCCAGGGCACTTCTCCCCAGGCGACAACCAGGCCTGCAAGCCC TGGACCAACTGCACCTTGGCTGGGAAGCACACCCTGCAGCCGGCCAGCAATAGC TCGGACGCAATCTGTGAGGACAGGGACCCCCCAGCCACGCAGCCCCAGGAGACC CAGGGCCCCCCGGCCAGGCCCATCACTGTCCAGCCCACTGAAGCCTGGCCCAGA ACCTCACAGGGACCCTCCACCCGGCCCGTGGAGGTCCCCGGGGGCCGTGCGGTT GCCGCCATCCTGGGCCTGGGCCTGGTGCTGGGGCTGCTGGGCCCCCTGGCCAT CCTGCTGGCCCTGTACCTGCTCCGGAGGGACCAGAGGCTGCCCCCCGATGCCCA CAAGCCCCCTGGGGGAGGCAGTTTCCGGACCCCCATCCAAGAGGAGCAGGCCGA CGCCCACTCCACCCTGGCCAAGATCTGA
176		Amino Acid Sequence	MCVGARRLGRGPCAALLLLGLGLSTVTGLHCVGDTYPSNDRCCHECRPGNGMVSR CSRSQNTVCRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCRCR AGTQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWINCTLAGKHTLQPASNSSDAI CEDRDPPATQPQETQGPPARPITVQPTEAWPRTSQGPSTRPVEVPGGRAVAAILGL

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SEQUENCE LISTING

SEQ ID NO:		
		GLVLGLLGPLAILLALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI
177	OX40L15B07	Amino Acid Sequence of OX40L15B07 (Seq ID No 179 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELVATITGGSS INYGDFVKGRFTISIDNAKNIVYLQMNNLKPEDTAVYYCNFNKYVTSRDTWGQGT QVTVSS
178	OX40L01B11	Amino Acid Sequence of OX40L01B11 (Seq ID No 180 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCVASGRSFSTYIMGWFRQAPGKEREFVATISRSGI TIRSADSVKGRFTISRDNAKNIVYLQMNSLKPEDTAVYYCAAGPYVEQTLGLYQTL GPWDYWGQGTQVTVSS
179	OX40L01E07	Amino Acid Sequence of OX40L01E07 (Seq ID No 181 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFVAAISRSG RSTSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAVGGATIVTASEW DYWGLGTQVTVSS
180	OX40L01E10	Amino Acid Sequence of OX40L01E10 (Seq ID No 182 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGDSLRLSCAASGLTFSSFAMGWFRQAPGKEREFVAAISRSGY GTSEADSVRDRFIISRDNAKNIVTLHLSRLKPEDTAVYYCAAEHTLGRPSRSQINYL YWGQGTQVTVSS
181	OX40L18E09	Amino Acid Sequence of OX40L18E09 (Seq ID No 183 in WO2011/073180, Table A-1)	EvQLVESGGGLVQAGGSLRLSCAASRNILSLNTMGVVYRHAPGKPRELVARISSNSK TDYADSVKGRFTISRDNAKNTVLLQMNSLKPEDTGVYYCNLNVWRTSSDYWGQG TQVTVSS
182	OX40L19A07	Amino Acid Sequence of OX40L19A07 (Seq ID No 184 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSRIKISNG RTIYAGSVKGRFTISSDNAKNTVYLQMNSLNAEDTAVYYCAADRSSLLFGSNWDR KARYDYWGQGTQVTVSS
183	OX40L19D08	Amino Acid Sequence of OX40L19D08 (Seq ID No 185 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGASLRLSCAASGRRFISNYAMGWFRQAPGQERAFVAAISRSG SITYYTDSVKGRFSISRDYAKSTVYLQMDNLKPEDTAVYYCAADGGAVRDLTTNLP DYWGRGTQVTVSS
184	OX40L075	Amino Acid Sequence of OX40L075 (Seq ID No 199 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASGRSFSTYIMGWFRQAPGKEREFVATISRSGI TTRSADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAGPYVEQTLG LYQTLGPWDYWGQGTLVTVSS
185	OX40L024	Amino Acid Sequence of OX40L024 (Seq ID No 200 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
186	OX40L025	Amino Acid Sequence of OX40L025 (Seq ID No 201 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFV AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
187	OX40L026	Amino Acid Sequence of OX40L026 (Seq ID No 202 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
188	OX40L027	Amino Acid Sequence of OX40L027 (Seq	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFV

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SEQUENCE LISTING

SEQ ID NO:		
	ID No 203 in WO2011/073180, Table A-2)	AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
189 OX40L028	Amino Acid Sequence of OX40L028 (Seq ID No 204 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
190 OX40L039	Amino Acid Sequence of OX40L039 (Seq ID No 205 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFV AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
191 OX40L030	Amino Acid Sequence of OX40L030 (Seq ID No 206 in WO2011/073180, Table A-2)	DVQLVESGGGLVQAGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG D FVKG RFTISID NAKNTVYLQM N N LKPEDTAVYYCN FN KYVTSRDTWGQGTQVTVSS
192 OX40L040	Amino Acid Sequence of OX40L040 (Seq ID No 207 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYGD FVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
193 OX40L041	Amino Acid Sequence of OX40L041 (Seq ID No 208 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHATGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
194 OX40L042	Amino Acid Sequence of OX40L042 (Seq ID No 209 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
195 OX40L043	Amino Acid Sequence of OX40L043 (Seq ID No 210 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGKPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
196 OX40L044	Amino Acid Sequence of OX40L044 (Seq ID No 211 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHAPGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
197 OX40L045	Amino Acid Sequence of OX40L045 (Seq ID No 212 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASRSIG RLD RMGWYRHATG KPRE LV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
198 OX40L046	Amino Acid Sequence of OX40L046 (Seq ID No 213 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYG D FVK GRFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
199 OX40L047	Amino Acid Sequence of OX40L047 (Seq ID No 214 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHAPGKPRELV ATITGGSSINYG D FVKG RFTISRDNSKNNYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS

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SEQUENCE LISTING

SEQ ID NO:		
200 OX40L048	Amino Acid Sequence of OX40L048 (Seq ID No 215 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYADFVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KYYTSRDTWGQGTLVTVSS
201 OX40L049	Amino Acid Sequence of OX40L049 (Seq ID No 216 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG DSVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
202 OX40L050	Amino Acid Sequence of OX40L050 (Seq ID No 217 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
203 OX40L053	Amino Acid Sequence of OX40L053 (Seq ID No 218 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYGDFVKGRFTISIDNSKNTVYLQM NSLRPEDTAVYYCN FNK YVTSRDTVVGQGTLVTVSS
204 OX40L054	Amino Acid Sequence of OX40L054 (Seq ID No 219 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG D FVKG RFTISRDNAKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
205 OX40L055	Amino Acid Sequence of OX40L055 (Seq ID No 220 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYGDFVKGRFTISRDNSKNTVYLQM NN LRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
206 OX40L056	Amino Acid Sequence of OX40L056 (Seq ID No 221 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISRD NSKNIVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
207 OX40L069	Amino Acid Sequence of OX40L069 (Seq ID No 222 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISID NSKNTVYLQM NSLRPE DTAVYYCN FN K YVTSRDTWGQGTLVTVSS
208 OX40L070	Amino Acid Sequence of OX40L070 (Seq ID No 223 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISRD NSKNTVYLQM N N LRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
209 OX40L071	Amino Acid Sequence of OX40L071 (Seq ID No 224 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISI DNSKNTVYLQM N N LRPEDTAVYYCN FN KYYTSRDTWGQGTLVWSS
210 OX40L082	Amino Acid Sequence of OX40L082 (Seq ID No 225 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGEPRELVA TITGGSSINYGDSVKGRFTISIDNSKNNYLQM NSLRPEDTAVYYCNFNKY VTS RDTWGQGTLVTVSS
211 OX40L083	Amino Acid Sequence of OX40L083 (Seq ID No 226 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYGDSVKGRFTISIDNSKNTVYLQMNSLRPEDTAVYYCN FNK YVTSRDTWGQGTLVTVSS

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SEQUENCE LISTING

SEQ ID NO:			
212	OX40L benchmark antibody heavy chain	Amino acid sequence of OX40L benchmark antibody heavy chain (Seq ID No: 177 in WO2011/073180, Table A-5)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEW VSIISGSGG FMADSVKG RFTISRDNSRTTLYLQM NSLRAEDTAVYYCA KDRLVAPGTFDYWGQGALVWSSASTKG PSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSL GTQTYICNVNH KPSNTKVDKWEPKSCDKTHTCPPCPAPELLGGPSVFLF P PKPKDTLM IS RTPEVTCVVVDVSH E D PEVKFNWYVDGVEVH NAKTKP REEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVNS NKALPAPI EKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPE N N YKTIPPVLDSDGSFFLYSKLTVD KSRWQQ GNVFSCSVM H EALH N HYTQ KSLSLSPGK
213	OX40L benchmark antibody light chain	Amino acid sequence of OX40L benchmark antibody light chain (Seq ID No: 178 in WO2011/073180, Table A-5)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNSYPYTFG QGTKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLL N N FYPREAKVQWK VDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTH QGLSSPVTKSFNRGEC
214	κ light chain variable region of LC.001	Amino acid sequence of kappa light chain variable region of LC.001 (Seq ID No: 1 in WO2006/029879)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQS GVPSRFSGSGSGTDFILTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK
215	γ heavy chain variable region of LC.001	Amino acid sequence of γ heavy chain variable region of LC.001 (Seq ID No: 2 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEVVVSIISGSG GFTYYADSVKGRFTISRDNSRTTLYLQMNSLRAEDTAVYYCAKDRLVAPGTFDYW GQGALVWSS
216	κ light chain variable region of LC.005	Amino acid sequence of kappa light chain variable region of LC.005 (Seq ID No: 3 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSFTFGPGTKVDIK
217	γ heavy chain variable region of LC.005	Amino acid sequence of γ heavy chain variable region of LC.005 (Seq ID No: 4 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAAIWYD GHDKYYSYYVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDSSSWYRYFDY WGQGTLVTVSS
218	κ light chain variable region of LC.010	Amino acid sequence of kappa light chain variable region of LC.010 (Seq ID No: 5 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSFTFGPGTKVDIK

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SEQUENCE LISTING

SEQ ID NO:			
219	γ heavy chain variable region of LC.010	Amino acid sequence of γ heavy chain variable region of LC.010 (Seq ID No: 6 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAAIWYD GHDKYYAYYVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDSSSWYRYFDY WGQGTLVTVSS
220	κ light chain variable region of LC.029	Amino acid sequence of kappa light chain variable region of LC.029 (Seq ID No: 7 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAAIWYD GHDKYYSYYVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDSSSWYRYFDY WGQGTLVTVSS
221	γ heavy chain variable region of LC.029	Amino acid sequence of γ heavy chain variable region of LC.029 (Seq ID No: 8 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVAVIWYD GSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARKNWSFDFWGQ GTLVTVSS
222	κ light chain variable region of LC.019	Amino acid sequence of kappa light chain variable region of LC.019 (Seq ID No: 9 in WO2006/029879)	EIVLTQSPATLSLSPGERATLSCRASQGVSRYLAWYQQKPGQAPRLLIYDASNRAT GIPARVSGSGPGTDFTLTISSLEPEDFAVDYCQQRSNWQYTFGQGTKLEI
223	γ heavy chain variable region of LC.019	Amino acid sequence of γ heavy chain variable region of LC.019 (Seq ID No: 10 in WO2006/029879)	QKQLVEFGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVIWND GSNKYYVDSVKGRFIISRDNSKNTLYLQMNSLRAEDTAVYYCARDRMGIYYYGMD VWGQGTTVTVSS
224	κ light chain variable region of LC.033	Amino acid sequence of kappa light chain variable region of LC.033 (Seq ID No: 11 in WO2006/029879)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATG IPARFSGSGSGTDFILTISSLEPEDFAVYYCQQRSNWTFGQGTINEI
225	γ heavy chain variable region of LC.033	Amino acid sequence of γ heavy chain variable region of LC.033 (Seq ID No: 12 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEWVSIISGSG GFTYYADSVKGRFTISRDNSRTTLYLQMNSLRAEDTAVYYCAKDRLVAPGTFDYW GQGALVTVSS
226	mutant κ light chain variable	Amino acid sequence of mutant kappa light chain variable region of LC.033 (Seq ID No: 16 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSFTFGPGTKVDIK

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SEQUENCE LISTING

SEQ ID NO:			
	region of LC.033		
227	γ heavy chain variable region of LC.059	Amino acid sequence of γ heavy chain variable region of LC.059 (Seq ID No: 17 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGSG GFTYYADSVKGRFTISRDNSKNTLYLQMNRLRAEDTAIYFCAKDDIPAAGTFDPWG QGTLVTVSS
228	κ light chain variable region of LC.060	Amino acid sequence of kappa light chain variable region of LC.060 (Seq ID No: 18 in WO2006/029879)	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDVSSLESG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYWTFGQGTKVEIK
229	γ heavy chain variable region of LC.060	Amino acid sequence of γ heavy chain variable region of LC.060 (Seq ID No: 19 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSLISGSG GLTKYADSVKGRFTISRDNSKRTLYLQMNSLRAEDTAVYYCAKDILVTGALDYWGQ GTLVTVSS
230	γ heavy chain variable region of LC.063	Amino acid sequence of γ heavy chain variable region of LC.063 (Seq ID No: 20 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEVVVSIISGSG GFTYYADSVKGRFTISRDNSKKTLYLQMSRLRAEDTAIYFCAKDDIPAAGTFDPWG QGTLVTVSS
231	8E12 light chain variable region	Amino acid sequence of 8E12 light chain variable region (Seq ID No: 13 in US7,812,133)	DILMTQTPLSLPVSLGDQASISCRSSQSIVHGNGNTYLEWHLQKPGQSPKLLIYRVS NRFSGVPDRFSGSGSGTDFTLKINRVEAEDLGVYYCFQGSHVPYTFGGGTKVEIKR
232	8E12 heavy chain variable region	Amino acid sequence of 8E12 heavy chain variable region (Seq ID No: 14 in US7,812,133)	DIVMTQTPLSLPVSLGDQASMYCRSSQSPVHSNGNTYLHWYLQKPGQSPKLLIYKV SNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHIPWTFGGGTKVEIKR
233	13G5 light chain variable region	Amino acid sequence of 13G5 light chain variable region (Seq ID No: 15 in US7,812,133)	QVQLQQPGAELVRPGASVkLSCKASGYTFTSYWLNWVKQRPGQGLEWIVMIDPSD SETHYNQVFKDKATLTVDKSSSTAYMQLSSLTSEDSAVYYCIRGRGNFYGGSHAME YWGQGTLLTVSS
234	13G5 heavy chain variable region	Amino acid sequence of 13G5 heavy chain variable region (Seq ID No: 16 in US7,812,133)	QVQLQQPGAELVKPGTSVKLSCKASGYSFTSYWMHGVRQRPGQGLEWIGEIDPSN GRTNYNEKFKSKATLTVDKSSSTAYIQLSSLTSEDSAVYYCTRERSPRYFDVWGAG TTLTVSS

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SEQ ID NO:	SEQUENCE LISTING

IMGT indicates that CDR is determined using IMGT nomenclature;
KABAT indicates that CDR is determined using Kabat nomenclature.
The numbering in the sequence correlation table takes precedence over any inconsistent numbering elsewhere in this text.

Statements of Invention (Biomarkers)

1. A method of normalising T-cell signalling in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of RORC, and whereby T-cell signalling is normalised.
2. A method of reducing the level (e.g. expression or amount) of RORC in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of RORC.
3. A method of reducing or inhibiting Th/Tc17 based activation of T-cells in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of RORC, and whereby Th/Tc17 activation of T-cells is reduced.
4. A method of reducing or inhibiting Th/Tc17 based activation of T-cells in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method downregulates or reduces the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 17 (FIG. **14**G) or Table 17 (FIG. **14**F), and whereby Th/Tc17 based activation of T-cells is reduced or inhibited.
5. A method according to statement 4, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**G); optionally selected from: IL12RB1, IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R, CXCL1, IL17F, CXCL9; for example, selected from: IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R; e.g. selected from: IL6, CCL2, IFNG; and alternatively selected from CCR5, IL12RB2 and IFNG.
6. A method according to statement 4, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**F); optionally selected from: selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, SAMD9L, IFIT1, IFIT3, KCNJ15, IFI44, EGR1, EGR2, SAMD9, RSAD2, FFAR2, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15, HIST1H2BB, GTSE1, AKAP12, CENPF, CASC5, MKI67, PRC1, PRR11, RACGAP1, SPAG5 and ARHGAP11A; for example, selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15 and HIST1H2BB; e.g. selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, ANLN, DUSP4, UBE2T, UHRF1 and KIF11.
7. A method of normalising cytotoxicity in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of Granzyme A, and whereby the cytotoxicity is normalised.
8. A method of reducing the level (e.g. expression or amount) of Granzyme A in a subject, comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of Granzyme A.
9. A method of reducing or inhibiting Th/Tc1 based activation of T-cells in a subject comprising combining T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method downregulates or reduces the level (e.g. expression or amount) of Granzyme A, and whereby Th/Tc1 based activation of T-cells is reduced or inhibited.
10. A method according to any one of statements 7 to 10, wherein the levels (e.g. expression or amount) of Granzyme A before the combination step are at least 1.5-fold greater in the subject as compared to the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.
11. A method according to any one of statements 7 to 11, wherein the levels (e.g. expression or amount) of Granzyme A after the combination step are at least 1.5-fold lower in the subject as compared to the levels (e.g. expression or amount) of Granzyme A in said sample taken before the combination step.
12. A method according to any one of statements 7 to 11, wherein the levels (e.g. expression or amount) of Granzyme A after the combination step are within 1.5-fold of the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.
13. A method of reducing or inhibiting Th/Tc1 based activation of T-cells in a subject comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method downregulates or reduces the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 16 (FIG. **14**E), and whereby Th/Tc1 based activation of T-cells is reduced or inhibited.
14. A method according to statement 13, wherein the one or more (e.g. 3, 4 or 5) genes is selected from: BCL2L14, SH2D1A, SAMD3, STAT4, SLA2, SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4, MKI67, GZMK, CD38, CTLA4, MYBL1, IRF4, SH2D1A, BCL2L14, PRF1, IL21 and HS3ST3B1X; for example, selected from: SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4 and MKI67; e.g. F2R, CCR5, IL12RB2, IFNG, TYMS and CASC5; and alternatively selected from CCR5, IL12RB2 and IFNG.
15. A method of activating, upregulating or enhancing the Type 1 interferon (IFN) pathway or the Reactome HSA-909733 Interferon alpha/beta signalling pathway in a subject comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and a second therapeutic agent, which method activates, upregulates or enhances the Type 1 interferon (IFN) pathway or the Reactome HSA-909733 Interferon alpha/beta signalling pathway.
16. A method according to statement 15, wherein the activation, upregulation or enhancement is of the Type 1 IFN pathway
17. A method according to statement 15, wherein the activation, upregulation or enhancement is of the Reactome HSA-909733 Interferon alpha/beta signalling pathway, wherein optionally activation, upregulation or enhancement is of one or more (e.g. 3, 4 or 5) of the genes is selected from IGS15, IFIT3, RSAD2, IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2; or is selected from from: IGS15, IFIT3 and RSAD2; or is alternatively selected from: IFIT1, IFIT2, IFIT3, MX1, OASL, OAS2 and RSAD2.
18. A method according to statement 17, which method upregulates or enhances the level (e.g. expression or

amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**D) or Table 15.

19. A method according to statement 18, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**D); optionally selected from: TYMP, ISG15, IFI44, IRF7, RSAD2, C1QA, CCL2, CXCL10, XAF1, IFIT5, PROS1, IFI6, PLSCR1, SERPING1, SAMD9L, C3AR1, GOS2, IL8, HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163, TNFAIP6, IFI27, MX1, ISG15, MX2, IFI44, IFIT2, OAS2, OASL, EPSTI1 and LILRA3; for example, selected from: ISG15, MX1, IFI44, IFI27, C3AR1, C1QA, CCL2, CXCL10, GOS2, IL8, HERC5, CMPK2, MMP9, IFIT1, IFIT3, RSAD2, CYP4F3, MGAM, CD163 and TNFAIP6; e.g. selected from: IFI27, MMP9, RSAD2, C3AR1, CD163, CXCL10, GOS2, IL8, HERC5, CMPK2, MMP9, IFIT1 and IFIT3; or may be selected from: CXCL10, CD163, IL8, CMPK2, IFI27, MMP9 and HERC5.

20. A method according to statement 18, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 15; optionally selected from: HERC6, MMP25, GOS2, KCNJ15, IL8, OASL, DDX58, TYMP, MX2, OAS2, IFI44, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, EGR2, C3AR1, LILRA3, MX1, IFIT2, SAMD9L, IFIT1, MMP25 and ISG15; for example, selected from: MMP25, GOS2, KCNJ15, IL8, TYMP, OAS2, IFI44, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, EGR2, C3AR1, LILRA3, MX1, IFIT2, SAMD9L and IFIT1; e.g. selected from: IL8, TYMP, IFI44, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, CD163, IL8, TNFAIP6, EGR1, IFIT3, C3AR1, LILRA3, IFIT2 and IFIT1; or may be selected from: IL8, CMPK2, HERC5, RSAD2, MMP9, CYP4F3, MGAM, EGR1, IFIT3 and IFIT1.

21. A method of upregulating or enhancing the KEGG hsa04630:Jak-STAT signalling pathway in a subject comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method upregulates the KEGG hsa04630:Jak-STAT signalling pathway.

22. A method according to statement 21, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**C); optionally selected from: IFNA16, OSM, CBLB, IL6, PIK3R1, CCND2, JAK3, PIAS1, STAT4, IL22, IL4R, IL12RB2, IL26, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, CISH, IL6ST, SOCS1, IRF9, PIK3CB, PIM1, SOCS3, STAM2 and IFNGR2; for example, selected from: CCND2, IL6, STAT4, IL22, IL4R, IL12RB2, IL26, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, CISH, IL6ST, SOCS1, IRF9, PIM1 and SOCS3; e.g. selected from: CCND2, IL6, IL22, IL12RB2, IL26, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, OSM, IFNGR1, JAK2, STAT3, SOS1, IL2RA, IL6ST, SOCS1 and SOCS3; or may be selected from: IL6, IL22, SOCS2, IL13RA1, CSF2RA, CSF3R, CSF2RB, STAT3, IL2RA, SOCS1 and SOCS3; and alternatively may be selected from: IL6, SOCS2, IL13RA1, CSF2RA, IL2RA and SOCS1.

23. A method according to statement 21, which method upregulates or enhances the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 14 (FIG. **15**C); optionally selected from: IL6R, IL6ST, IL26, OSM, IL2RA, IL10RB, CSF3R, IL32RA1, STAT1, STAT2, STAT3, SOCS1, SOCS2, PIM1, SOS1, SOS2, CISH, PIAS1 and SPRY1; optionally selected from: OSM, IL2RA, IL10RB, CSF3R and IL13RA1; or selected from STAT1, STAT2 and STAT3; or alternatively selected from SOCS1, SOCS2, PIM1, SOS1, SOS2, CISH, PIAS1 and SPRY1; or selected from transcripts encoding pro-inflammatory cytokines or cytokine receptors (optionally selected from: IL6, IL6R, IL6ST and IL26); or selected from transcripts encoding anti-inflamatory cytokines or cytokine receptors (optionally selected from OSM, IL2RA, IL10RB, CSF3R and IL32RA1).

24. A method according to any one of statements 1 to 23, wherein the subject has or is at risk of an OX40L-mediated disease.

25. A method according to any statement 24, wherein the subject has or is at risk of an autoimmune or alloimmune disease or condition, e.g. selected from graft versus host disease (GvHD), allogenic transplant rejection, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, atherosclerosis, uveitis, ankylosing spondylitis and contact hypersensitivity.

26. A method of treating or reducing the risk of a disease or condition (e.g. an autoimmune or alloimmune disease or condition) in a subject, the method comprising administering to said subject a therapeutically effective amount or prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method normalises T-cell signalling, or reduces or inhibits Th/Th17 based activation of T-cells, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.

27. A method according to statement 26, wherein the T-cell signalling is normalised, or wherein the Th/Th17 based activation of T-cells is reduced or inhibited by reducing the level (e.g. expression or amount) of RORC in a population of T-cells isolated from said subject.

28. A method according to statement 26, wherein the T-cell signalling is normalised, or wherein the Th/Th17 based activation of T-cells is reduced or inhibited by downregulation or reduction of the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 17 (FIG. **14**G) or Table 17 (FIG. **14**F).

29. A method according to statement 28, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**G); optionally selected from: IL12RB1, IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R, CXCL1, IL17F, CXCL9; for example, selected from: IL6, CCL2, IFNG, IL17A, TNF, IL18, IL23R; e.g. selected from: IL6, CCL2, IFNG.

30. A method according to statement 28, wherein the one or more (e.g. 3, 4 or 5) genes is listed in Table 17 (FIG. **14**F); optionally selected from: selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, SAMD9L, IFIT1, IFIT3, KCNJ15, IFI44, EGR1, EGR2, SAMD9, RSAD2, FFAR2, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15, HIST1H2BB, GTSE1, AKAP12, CENPF, CASC5, MKI67, PRC1, PRR11, RACGAP1, SPAG5 and ARHGAP11A; for example, selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, HERC5, TYMP, IFIT2, C3AR1, LILRA3, ANLN, DUSP4, UBE2T, UHRF1, KIF11, TTK, RAD54B, E2F8, KIF15

and HIST1H2BB; e.g. selected from: MGAM, CYP4F3, MMP9, TNFAIP6, CD163, ANLN, DUSP4, UBE2T, UHRF1 and KIF11.

31. A method of treating or reducing the risk of a disease or condition (e.g. an autoimmune or alloimmune disease or condition) in a subject, the method comprising administering to said subject a therapeutically effective amount or prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method normalises cytotoxicity, or reduces or inhibite Th/Tc1 based activation of T-cells, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.
32. A method according to statement 31, wherein the cytotoxicity is normalised, or wherein the Th/Tc1 based activation of T-cells is reduced or inhibited by reducing the level (e.g. expression or amount) of Granzyme A in a T-cell population isolated from said subject.
33. A method according to statement 31, wherein the cytotoxicity is normalised, or wherein the Th/Tc1 based activation of T-cells is reduced or inhibited by downregulation or reduction of the level (e.g. expression or amount) of one or more (e.g. 3, 4 or 5) of the genes listed in Table 16 (FIG. **14**E); optionally wherein the one or more (e.g. 3, 4 or 5) genes is selected from: BCL2L14, SH2D1A, SAMD3, STAT4, SLA2, SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4, MKI67, GZMK, CD38, CTLA4, MYBL1, IRF4, SH2D1A, BCL2L14, PRF1, IL21 and HS3ST3B1X; for example, selected from: SLAMF1, KLRD1, F2R, CCR5, IL12RB2, IFNG, TYMS, CASC5, IL10, RRM2, P2RX5, GIMAP4 and MKI67; e.g. F2R, CCR5, IL12RB2, IFNG, TYMS and CASC5.
34. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.
35. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.
36. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.
37. A composition comprising an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.
38. A method of treating or reducing the risk of a disease or condition in a subject in need thereof, comprising:
    a. Performing an assay to measure the levels (e.g. expression or amount) of Granzyme A in a sample obtained from the subject; and
    b. Administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent to the subject when the levels (e.g. expression or amount) of Granzyme A in the sample is determined in the assay to be at least 1.5-fold greater than in a sample taken from a healthy human donor.
39. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.
40. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for therapy of a subject who has, or has been determined to have an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.
41. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a heathy donor.
42. A method of determining a subject as having, or as being at risk of, an autoimmune or alloimmune disease or condition, which disease or condition is suitable for treatment with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, comprising:
    a. performing an assay that detects the levels (e.g. expression or amount) of Granzyme A in a sample obtained from said subject; and
    b. determining the subject as having said disease or condition if there is an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a heathy donor.
43. A method according to statement 42 further comprising the step of:
    c. administering to said subject an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which antibody or fragment thereof:
        i. reduces or inhibit Th/Tc1 based activation of T-cells; and/or
        ii. normalises cytotoxicity; and/or
        iii. reduces the levels (e.g. expression or amount) of Granzyme A;
    in a sample taken from said subject, if said subject has been determined as having a disease or condition in step b).
44. A method for treating an autoimmune or alloimmune disease or condition with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, comprising the steps of:

a. determining whether the subject is a candidate for treatment by detecting the levels (e.g. expression or amount) of Granzyme A in a sample from the subject;
b. administering said antibody or fragment thereof to the subject if the subject has an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of Granzyme A as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

45. A method, comprising:
a. obtaining at least two samples derived from a subject who has or is at risk of an autoimmune or alloimmune disease or condition, wherein said at least two samples comprise a first sample taken at a first time point, and a second sample taken at a subsequent time point,
b. determining the levels (e.g. expression or amount) of Granzyme A in said first and second samples;
c. treating said subject to:
i. reduce or inhibit Th/Tc1 based activation of T-cells; and/or
ii. normalise cytotoxicity; and/or
iii. reduce the levels (e.g. expression or amount) of Granzyme A;
by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, if the levels (e.g. expression or amount) of Granzyme A in said second sample are elevated as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition.

46. A method according to statement 45, wherein in step c), the levels (e.g. expression or amount) of Granzyme A in said second sample is greater than 1.5-fold of the levels (e.g. expression or amount) of Granzyme A in said first sample, for example is greater than 2-fold or greater than 3-fold of the levels (e.g. expression or amount) of Granzyme A in said first sample.

47. A method according to any one of statements 43 to 46, further comprising the steps of
d. obtaining a third sample derived from said subject taken at a time point subsequent to the second sample;
e. determining the levels (e.g. expression or amount) of Granzyme A in said third sample;
f. treating said subject to:
i. reduce or inhibit Th/Tc1 based activation of T-cells; and/or
ii. normalise cytotoxicity; and/or
iii. reduce the levels (e.g. expression or amount) of Granzyme A;
by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, if the levels (e.g. expression or amount) of Granzyme A in said second sample are elevated as compared to said first sample, in order to treat or reduce the risk of said autoimmune or alloimmune disease or condition.

48. A method according to statement 47, wherein steps d) to f) are repeated as necessary until the levels (e.g. expression or amount) of Granzyme A reaches a therapeutically-effective, or a prophylactically-effective levels, e.g. a substantially constant level in said subject.

49. A method according to any one of statements 43 to 48, wherein in step c), or in step f) the levels (e.g. expression or amount) of Granzyme A in said second sample or third sample is greater than double the levels (e.g. expression or amount) as compared to said first sample or second sample, for example is greater than three times, or is greater than 4 times the levels (e.g. expression or amount) as compared to said first sample or second sample.

50. A method according to any one of statements 42 to 49, wherein said first sample is collected:
i. before the onset of said disease or condition; or
ii. after the onset of said disease or condition; and
optionally wherein said second sample is collected no longer than one month, e.g. no longer than one week after the first sample.

51. A method according to any one of statements 42 to 50, wherein the autoimmune or alloimmune disease or condition is a transplant, and wherein in step c) the treatment is in order to reduce the risk of transplant rejection, optionally wherein the first sample is taken before the transplant, and the second sample is taken after the transplant.

52. A method according to statement 51, wherein in step a), the first sample is collected no longer than a week, e.g. no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days before said transplant.

53. A method according to statement 51 or statement 52, wherein the second sample is collected no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days after the first sample or after said transplant.

54. A method according to any one of statements 51 to 53, wherein the subject is given a prophylactic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent before said transplant, and the first sample is taken before administration of said combination and wherein the second sample is taken after the transplant or after administration of the combination (preferably, where in the second sample is taken after the transplant).

55. A method according to any one of statements 51 to 53, wherein the subject is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the transplant.

56. A method according to any one of statements 51 to 53, wherein the subject is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the administration of said combination.

57. A method according to any one of statements 41 to 56, wherein the second sample is taken no longer than one month after the first sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the first sample, and optionally wherein the third sample is taken no longer than one month after the second sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the second sample.

58. In vitro use of the levels (e.g. expression or amount) of RORC, or the levels (e.g. expression or amount) of Granzyme A, as a diagnostic for an autoimmune or alloimmune disease or condition in a subject, which disease or condition can be treated or prevented with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent.

59. Use of a biomarker of an autoimmune or alloimmune disease or condition, wherein the biomarker is the levels (e.g. expression or amount) of RORC, or wherein the biomarker is the levels (e.g. expression or amount) of Granzyme A, in vitro as a diagnostic for an autoimmune or alloimmune disease or condition, which disease or condition can be treated or prevented with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent.
60. A method, an antibody for the use, or a use according to any one of statements 10 to 12, 24, 25 or 31 to 59, wherein the levels (e.g. expression or amount) of Granzyme A are determined (or is determinable) by microarray analysis, e.g. target hybridization of RNA to GeneChip *Rhesus Macaque* Genome Array (Affymetrix), and for example further comprising processing and normalising the resultant fluorescent signals using the Robust Multichip Averaging (RMA) Method.
61. A method, an antibody for the use, or a use according to any one of statements 10 to 12, 24, 25 or 31 to 59, wherein the levels (e.g. expression or amount) of Granzyme A are determined (or is determinable) by flow cytometry.
62. A method, an antibody for the use, or a use according to any preceding statement, wherein the levels (e.g. expression or amount) of Granzyme A before administration of the antibody or fragment thereof are greater than 2-fold (or greater than 4-fold, or 6-fold, or 8-fold; for example 10-fold, or 15-fold, or 20-fold) the levels (e.g. expression or amount) of Granzyme A in a sample taken from a healthy donor.
63. A method, an antibody for the use, or a use according to any preceding statement, wherein the levels (e.g. expression or amount) of Granzyme A before administration of the antibody or fragment thereof are greater than 30-fold (or greater than 40-fold, 50-fold or 60-fold; for example, greater than 70-fold, 80-fold or 90-fold; e.g. greater than 100-fold, greater than 125-fold or greater than 150-fold) the levels (e.g. expression or amount) of Granzyme A in a sample taken from a heathy donor.
64. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a depleting antibody that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.
65. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is an antagonistic or blocking antibody.
66. A method, a combination for the use, a use or a composition according to statement 65, wherein the antibody specifically binds to OX40L (in particular human OX40L).
67. A method, a combination for the use, a use or a composition according to statement 66, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.
68. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a humanized, human or fully human antibody.
69. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.
70. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.
71. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.
72. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).
73. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises a CDR selected from:
    a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);
    b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);
    c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);
    d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No: 106);
    e. a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
    f. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or
    g. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234.
74. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises:
    a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);
    b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);
    c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);
    d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No: 104 for CDRH2, SEQ ID No:96 or SEQ ID No: 102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for

CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);

e. the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

g. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

75. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);

b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No:16 for VL);

c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);

d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);

e. a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

g. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

76. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is oxelumab.

77. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the Granzyme A is measured in a sample of blood, e.g. peripheral blood.

78. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the subject is a human patient.

79. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the autoimmune or alloimmune disease or condition is mediated by a deficiency in Treg cells.

80. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the autoimmune or alloimmune disease or condition is selected from graft versus host disease (GvHD), allogenic transplant rejection, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, atherosclerosis, uvetitis, ankylosing spondylitis and contact hypersensitivity.

81. A method, a combination for the use, a use or a composition according to statement 80, wherein the autoimmune or alloimmune disease or condition is selected from GvHD and allogenic transplant rejection.

82. A method, a combination for the use, a use or a composition according to statement 80, wherein the autoimmune or alloimmune disease or condition is selected from inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis.

83. A method, a combination for the use, a use or a composition according to statement 81, wherein the allogenic transplant rejection is rejection of a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or of a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.

84. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is an IL-2 modulating agent, for example an IL-2 inhibiting agent, such as a calcinueirn inhibitor or an mTOR inhibitor (for example the agent is selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), anti-IL2R antibodies (e.g. basilixumab), anti-IL-2 antibodies and anti-CD24-Fc fusion protein).

85. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is independently selected from the group consisting of methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-CD25 antibodies (e.g. daclizumab), anti-TCONVFa /TCONVFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

86. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

87. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is rapamycin.

88. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is tacrolimus.

Statements of Invention (IL17A)

1. A method of reducing the level (e.g. expression or amount) of IL-17A in a subject, comprising combining

T-cells from said subject with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of IL-17 (e.g. IL-17A).

2. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of IL-17 (e.g. IL-17A) as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

3. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of IL-17 (e.g. IL-17A) as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

4. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an autoimmune or alloimmune disease or condition characterised by an elevation or increase of at least 1.5-fold in the levels (e.g. expression or amount) of IL-17 (e.g. IL-17A) as compared to the levels (e.g. expression or amount) in a sample taken from a healthy donor.

5. A method according to any one of statements 1 to 4, wherein the subject has or is at risk of an IL-17A-mediated disease.

6. A method of treating or preventing an IL-17A-mediated disease in a subject comprising administering to said subject a therapeutically or prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, which method reduces the level (e.g. expression or amount) of IL-17 (e.g. IL-17A), and whereby the IL-17A-mediated disease is thereby treated or prevented.

7. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an IL-17A-mediated disease, whereby the level (e.g. expression or amount) of IL-17 (e.g. IL-17A) is reduced, and whereby the IL-17A-mediated disease is thereby treated or prevented.

8. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an IL-17A-mediated disease, whereby the level (e.g. expression or amount) of IL-17 (e.g. IL-17A) is reduced, and whereby the IL-17A-mediated disease is thereby treated or prevented.

9. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent in the manufacture of a medicament for the treatment or prevention of an IL-17A-mediated disease.

10. A method, use or antibody for the use according to any one of statements 5 to 9, wherein the IL-17A-mediated disease is selected from an inflammatory disease or condition, an autoimmune disease or condition, an alloimmune disease or condition and an infectious disease or condition, optionally selected from colorectal cancer (CRC), colon cancer, pancreatic cancer, breast cancer, glioma, asthma, COPD, cystic fibrosis, transplant rejection (e.g. lung transplant rejection), multiple sclerosis, arthritis, rheumatoid arthritis (RA), reactive arthritis, psoriatic arthritis, atherosclerosis, spondyloarthropathies, juvenile-onset spondyloarthritis, inflammatory bowel disease, Chron's disease, systemic lupus erythematosus (SLE), psoriasis, ankylosing spondylitis, type 1 diabetes, stroke, depression, Behcet's disease, allograft rejection, nephritic syndrome, Hashimoto's thyroiditis, undifferentiated SpA, vitiligo, cardiovascular diseases, Hepatitis B virus (HBV) infection, Hepatitis C virus (HCV) infection and Human Immunodeficiency Virus (HIV) infection, in particular selected from colorectal cancer (CRC), colon cancer, asthma, COPD, cystic fibrosis, transplant rejection (e.g. lung transplant rejection), multiple sclerosis, arthritis, rheumatoid arthritis (RA), psoriatic arthritis, atherosclerosis, inflammatory bowel disease, Chron's disease, systemic lupus erythematosus (SLE), psoriasis, ankylosing spondylitis, type 1 diabetes and allograft rejection

11. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a depleting antibody that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.

12. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is an antagonistic or blocking antibody.

13. A method, a combination for the use, a use or a composition according to statement 12, wherein the antibody specifically binds to OX40L (in particular human OX40L).

14. A method, a combination for the use, a use or a composition according to statement 13, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

15. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a humanized, human or fully human antibody.

16. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

17. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

18. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

19. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

20. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises a CDR selected from:

a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);

b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);

c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);

d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No: 106);

e. a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or

g. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234.

21. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises:

a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);

b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);

c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);

d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No:104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);

e. the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

g. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

22. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);

b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No:16 for VL);

c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);

d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);

e. a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;

f. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

g. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

23. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is oxelumab.

24. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the subject is a human patient.

25. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the autoimmune or alloimmune disease or condition is mediated by a deficiency in Treg cells.

26. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is an IL-2 modulating agent, for example an IL-2 inhibiting agent, such as a calcinueirn inhibitor or an mTOR inhibitor (for example the agent is selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), anti-IL2R antibodies (e.g. basilixumab), anti-IL-2 antibodies and anti-CD24-Fc fusion protein).

27. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is independently selected from the group consisting of methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-CD25 antibodies (e.g. daclizumab), anti-TCONVFa/TCONVFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

28. A method, a combination for the use, a use or a composition according to any one of statements 1 to 26, wherein the second therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

29. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is rapamycin or a derivative thereof.

30. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is tacrolimus.

Statements of Invention (T_N and T_{CM} Cells)

1. A method of preventing a reduction in the proportion (e.g. number or level) of naïve T-cells (T_N), and/or preventing an increase in the proportion (e.g. number or level) of central memory T-cells (T_{CM}) comprising combining said cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof and optionally a second therapeutic agent, which antibody (or combination) prevents reduction of the proportion (e.g. number or level) of T_N cells, and whereby the proportion of said T_N cells is not substantially reduced and/or which antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_N cells is not substantially increased.
2. The method according to statement 1, wherein the method prevents reduction in the proportion (e.g. the number or level) of T_N cells and wherein the proportion of T_N cells is at least 10 T_N cells/L^{-6}, for example at least 20 T_N cells/L^{-6}, or at least 30 T_N cells/L^{-6}, or at least 40 T_N cells/L^{-6}, or at least 50 T_N cells/L^{-6} after combining said cells with said antibody (or combination).
3. The method according to statement 1, wherein the method prevents reduction in the proportion (e.g. the number or level) of T_N cells and wherein the proportion of T_N cells is above 5% of the total population of T-cells after combining said T_N cells with said antibody (or combination).
4. The method according to statement 1, wherein the method prevents an increase in the proportion (e.g. the number or level) of T_{CM} cells and wherein the proportion of T_{CM} cells is at least 10 T_{CM} cells/L^{-6}, for example at least 20 T_{CM} cells/L^{-6}, or at least 30 T_{CM} cells/L^{-6}, or at least 40 T_{CM} cells/L^{-6}, or at least 50 T_{CM} cells/L^{-6} after combining said cells with said antibody (or combination).
5. The method according to statement 1, wherein the method prevents an increase in the proportion (e.g. the number or level) of T_{CM} cells and wherein the proportion of T_{CM} cells is above 15% of the total population of T-cells after combining said T_{CM} cells with said antibody (or combination).
6. A method of altering the ratio of cell types in a T-cell population in a sample, the method comprising:

(a) providing said population, wherein the population comprises a mixture of different T-cell types, wherein the population comprises T_N cells and/or T_{CM};

(b) providing an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent; and

(c) combining said cell population with an amount of said antibody (or combination) effective to alter the proportion (e.g. number or level) of T_N cells and/or T_{CM} cells in said population.
7. A method of treating or reducing the risk of an OX40L-mediated disease or condition (e.g. an autoimmune or alloimmune disease or condition) in a subject, the method comprising combining a population of T-cells with an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent, wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby the proportion of said T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased.
8. A method according to statement 7, wherein the combining of cells and the antibody (or combination) is by administering said antibody (or combination) in a therapeutically effective amount or prophylactically effective amount to said subject, and whereby said disease or condition is treated, or the risk of said disease or condition is reduced in said subject.
9. A method of treating or reducing the risk of a disease or condition (e.g. an OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100) in a subject comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent thereof;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced, and/or

wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.
10. An anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for use in treating or reducing the risk of an anti-OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.
11. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a second therapeutic agent for the treatment or prevention of an anti-OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.
12. A composition comprising an anti-OX40 or an anti-OX40L antibody or fragment thereof, and optionally a

second therapeutic agent for the treatment or prevention of an anti-OX40L-mediated disease or condition, or an autoimmune or alloimmune disease or condition, or an autoimmune or alloimmune disease or condition characterised by a ratio of Treg:Tconv of less than 1.5:100 in a subject;

wherein the antibody (or combination) prevents reduction in the proportion (e.g. number or level) of T_N cells, and whereby said proportion (e.g. number or level) of T_N cells is not reduced and/or wherein the antibody (or combination) prevents an increase in the proportion (e.g. number or level) of T_{CM} cells, and whereby the proportion of said T_{CM} cells is not increased; and

wherein the disease or condition is thereby treated, or the risk of said disease or condition is reduced.

13. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a depleting antibody that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.

14. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is an antagonistic or blocking antibody.

15. A method, a combination for the use, a use or a composition according to statement 14, wherein the antibody specifically binds to OX40L (in particular human OX40L).

16. A method, a combination for the use, a use or a composition according to statement 15, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

17. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a humanized, human or fully human antibody.

18. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

19. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

20. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-Xceed™ at level greater than 1.5 g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

21. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

22. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises a CDR selected from:

a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);
b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No: 14);
c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);
d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No: 106);
e. a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
f. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or
g. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234.

23. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises:

a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);
b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);
c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);
d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No: 104 for CDRH2, SEQ ID No:96 or SEQ ID No: 102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);
e. the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
f. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or
g. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light

chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

24. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:
    a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);
    b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No:16 for VL);
    c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);
    d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);
    e. a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
    f. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 216, 218, 220, 222, 224, 226 or 228; or
    g. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.
25. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the antibody is oxelumab.
26. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the subject is a human patient.
27. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the autoimmune or alloimmune disease or condition is mediated by a deficiency in Treg cells.
28. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the autoimmune or alloimmune disease or condition is selected from graft versus host disease (GvHD), allogenic transplant rejection, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, atherosclerosis, uvetitis, ankylosing spondylitis and contact hypersensitivity.
29. A method, a combination for the use, a use or a composition according to statement 28, wherein the autoimmune or alloimmune disease or condition is selected from GvHD and allogenic transplant rejection.
30. A method, a combination for the use, a use or a composition according to statement 28, wherein the autoimmune or alloimmune disease or condition is selected from inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis.
31. A method, a combination for the use, a use or a composition according to statement 29, wherein the allogenic transplant rejection is rejection of a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or of a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.
32. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is an IL-2 modulating agent, for example an IL-2 inhibiting agent, such as a calcinueirn inhibitor or an mTOR inhibitor (for example the agent is selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), anti-IL2R antibodies (e.g. basilixumab), anti-IL-2 antibodies and anti-CD24-Fc fusion protein).
33. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is independently selected from the group consisting of methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-CD25 antibodies (e.g. daclizumab), anti-TCONVFa/TCONVFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.
34. A method, a combination for the use, a use or a composition according to any one of statements 1 to 33, wherein the second therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.
35. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is rapamycin.
36. A method, a combination for the use, a use or a composition according to any preceding statement, wherein the second therapeutic agent is tacrolimus.

SEQUENCE LISTING

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<400> SEQUENCE: 1

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tcctgtgcag cctctggatt cacctttagc agttatatta tgacttgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaggt attagtggta gtggtggtgg tacatactac 180

gcagactcca tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcagatga acagcctgag agtcgaggac acggccgtat attactgtgc gaaagatcgg 300

ttaggtccga ttactttggt tcgggggggc tattactacg gtatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc ctca 384

<210> SEQ ID NO 2
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - VH Amino Acid Sequence

<400> SEQUENCE: 2

Glu Val Gln Leu Val Glu Ser Gly Gly Val Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ile Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Met
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Gly Pro Ile Thr Leu Val Arg Gly Gly Tyr Tyr
100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 3
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 3

ggattcacct ttagcagtta tatt 24

<210> SEQ ID NO 4
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 4

Gly Phe Thr Phe Ser Ser Tyr Ile
1 5

<210> SEQ ID NO 5

<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR2 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 5

attagtggta gtggtggtgg taca 24

<210> SEQ ID NO 6
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR2 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 6

Ile Ser Gly Ser Gly Gly Gly Thr
1 5

<210> SEQ ID NO 7
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 7

gcgaaagatc ggttaggtcc gattactttg gttcgggggg gctattacta cggtatggac 60

gtc 63

<210> SEQ ID NO 8
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 8

Ala Lys Asp Arg Leu Gly Pro Ile Thr Leu Val Arg Gly Gly Tyr Tyr
1 5 10 15

Tyr Gly Met Asp Val
20

<210> SEQ ID NO 9
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 9

agttatatta tgact 15

<210> SEQ ID NO 10
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 10

Ser Tyr Ile Met Thr
1 5

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<210> SEQ ID NO 11
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 11

ggtattagtg gtagtggtgg tggtacatac tacgcagact ccatgaaggg c 51

<210> SEQ ID NO 12
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 12

Gly Ile Ser Gly Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Met Lys
1 5 10 15

Gly

<210> SEQ ID NO 13
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 13

gatcggttag gtccgattac tttggttcgg gggggctatt actacggtat ggacgtc 57

<210> SEQ ID NO 14
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - HCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 14

Asp Arg Leu Gly Pro Ile Thr Leu Val Arg Gly Gly Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> SEQ ID NO 15
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - VL Nucleotide Sequence

<400> SEQUENCE: 15

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc gactatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagttcct gatctatgct gcatccagtt tgcaaagtgg agtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccgtcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctcggac gttcggccaa 300

gggaccaggg tggaaatcaa a 321

<210> SEQ ID NO 16
<211> LENGTH: 107
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - VL Amino Acid Sequence

<400> SEQUENCE: 16

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Arg Val Glu Ile Lys
100 105

<210> SEQ ID NO 17
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 17

cagagcatta gcgactat 18

<210> SEQ ID NO 18
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 18

Gln Ser Ile Ser Asp Tyr
1 5

<210> SEQ ID NO 19

<400> SEQUENCE: 19

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<210> SEQ ID NO 20

<400> SEQUENCE: 20

000

<210> SEQ ID NO 21
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 21

caacagagtt acagtacccc tcggacg 27

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<210> SEQ ID NO 22
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 22

Gln Gln Ser Tyr Ser Thr Pro Arg Thr
1 5

<210> SEQ ID NO 23
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 23

cgggcaagtc agagcattag cgactattta aat 33

<210> SEQ ID NO 24
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 24

Arg Ala Ser Gln Ser Ile Ser Asp Tyr Leu Asn
1 5 10

<210> SEQ ID NO 25
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 25

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 26
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 26

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 27
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 27

caacagagtt acagtacccc tcggacg 27

<210> SEQ ID NO 28
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - LCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 28

Gln Gln Ser Tyr Ser Thr Pro Arg Thr
1 5

<210> SEQ ID NO 29
<211> LENGTH: 1365
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - Heavy Chain Nucleotide Sequence

<400> SEQUENCE: 29

gaggtccagc tcgtggaaag cggaggagtg ctcgtgcagc ctggaggcag cctcaggctg 60

tcctgtgccg cctccggctt caccttcagc agctacatca tgacctgggt gaggcaggct 120

cccggaaaag gcctggagtg ggtgtccggc atctccggat ccggaggagg cacatactac 180

gccgacagca tgaagggccg gttcaccatc agccgggaca atagcaagaa tacccctctac 240

ctgcaaatga acagcctgcg ggtggaggat accgccgtgt actactgcgc caaagatagg 300

ctgggcccca ttaccctcgt gaggggaggc tattactacg gcatggatgt gtggggccag 360

ggcaccaccg tgacagtgtc cagcgccagc accaagggcc cttccgtgtt ccccctggcc 420

ccttgcagca ggagcacctc cgaatccaca gctgccctgg gctgtctggt gaaggactac 480

tttcccgagc ccgtgaccgt gagctggaac agcggcgctc tgacatccgg cgtccacacc 540

tttcctgccg tcctgcagtc ctccggcctc tactccctgt cctccgtggt gaccgtgcct 600

agctcctccc tcggcaccaa gacctacacc tgtaacgtgg accacaaacc ctccaacacc 660

aaggtggaca aacgggtcga gagcaagtac ggccctccct gccctccttg tcctgccccc 720

gagttcgaag gcggacccag cgtgttcctg ttccctccta agcccaagga caccctcatg 780

atcagccgga cacccgaggt gacctgcgtg gtggtggatg tgagccagga ggaccctgag 840

gtccagttca actggtatgt ggatggcgtg gaggtgcaca acgccaagac aaagccccgg 900

gaagagcagt tcaactccac ctacagggtg gtcagcgtgc tgaccgtgct gcatcaggac 960

tggctgaacg gcaaggagta caagtgcaag gtcagcaata agggactgcc cagcagcatc 1020

gagaagacca tctccaaggc taaaggccag ccccgggaac ctcaggtgta caccctgcct 1080

cccagccagg aggagatgac caagaaccag gtgagcctga cctgcctggt gaagggattc 1140

taccttccg acatcgccgt ggagtgggag tccaacggcc agcccgagaa caattataag 1200

accacccctc ccgtcctcga cagcgacgga tccttctttc tgtactccag gctgaccgtg 1260

gataagtcca ggtggcagga aggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320

cacaatcact acacccagaa gtccctgagc ctgtccctgg gaaag 1365

<210> SEQ ID NO 30
<211> LENGTH: 455
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - Heavy Chain Amino Acid Sequence

<400> SEQUENCE: 30

Glu Val Gln Leu Val Glu Ser Gly Gly Val Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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Ile Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Gly Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Met
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Arg Leu Gly Pro Ile Thr Leu Val Arg Gly Gly Tyr Tyr
            100                 105                 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
    130                 135                 140

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
145                 150                 155                 160

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
                165                 170                 175

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
            180                 185                 190

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
        195                 200                 205

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
    210                 215                 220

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
                325                 330                 335

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445
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Leu Ser Leu Ser Leu Gly Lys
450 455

<210> SEQ ID NO 31
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - Light Chain Nucleotide Sequence

<400> SEQUENCE: 31

gacatccaga tgacccagtc cccttcctcc ctgtccgcct ccgtgggaga cagggtgacc 60

atcacctgcc gggccagcca gtccatcagc gactacctga actggtatca gcagaagccc 120

ggcaaggccc ctaagttcct gatctacgcc gcttcctccc tgcagtccgg agtgcccagc 180

aggttttccg gctccggatc cggcaccgac ttcaccctga ccgtgtccag cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag agctacagca cccccaggac atttggccag 300

ggcacccggg tggagatcaa gaggaccgtc gctgcccccc ccgtgtttat cttccccccc 360

agcgacgagc agctgaaatc cggcaccgcc tccgtggtct gcctgctgaa taacttctac 420

cctcgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg aaactcccag 480

gagagcgtga ccgagcagga ctccaaggac tccacatact ccctgtcctc caccctgaca 540

ctgtccaagg ccgattacga gaagcacaag gtgtacgcct gcgaggtgac ccaccaggga 600

ctgtcctccc ccgtgaccaa gtccttcaac cggggcgagt gc 642

<210> SEQ ID NO 32
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 10A07 - Light Chain Amino Acid Sequence

<400> SEQUENCE: 32

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Arg Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 33
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - VH Nucleotide Sequence

<400> SEQUENCE: 33

gaggtgcagt tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacttttagc aactatgcca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaact attagcggaa gtggtggtgc cacaaggtat 180

gcagactccg tgaagggccg attcaccata tccagagaca attccaggaa cacggtgtat 240

ctgcaaatga acagcctgag agtcgaggac acggccgttt tttactgtac gaaagatcgg 300

ctcattatgg ctacggttcg gggaccctat tactacggta tggacgtctg gggccaaggg 360

accacggtca ccgtctcctc a 381

<210> SEQ ID NO 34
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - VH Amino Acid Sequence

<400> SEQUENCE: 34

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Gly Ala Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Phe Tyr Cys
85 90 95

Thr Lys Asp Arg Leu Ile Met Ala Thr Val Arg Gly Pro Tyr Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 35
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 35

ggattcactt ttagcaacta tgcc 24

<210> SEQ ID NO 36
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 36

Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> SEQ ID NO 37
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR2 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 37

attagcggaa gtggtggtgc caca 24

<210> SEQ ID NO 38
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR2 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 38

Ile Ser Gly Ser Gly Gly Ala Thr
1 5

<210> SEQ ID NO 39
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 39

acgaaagatc ggctcattat ggctacggtt cggggaccct attactacgg tatggacgtc 60

<210> SEQ ID NO 40
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 40

Thr Lys Asp Arg Leu Ile Met Ala Thr Val Arg Gly Pro Tyr Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> SEQ ID NO 41
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 41

aactatgcca tgaac 15

<210> SEQ ID NO 42
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 42

Asn Tyr Ala Met Asn
1 5

<210> SEQ ID NO 43
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 43

actattagcg gaagtggtgg tgccacaagg tatgcagact ccgtgaaggg c 51

<210> SEQ ID NO 44
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 44

Thr Ile Ser Gly Ser Gly Gly Ala Thr Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 45
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 45

gatcggctca ttatggctac ggttcgggga ccctattact acggtatgga cgtc 54

<210> SEQ ID NO 46
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - HCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 46

Asp Arg Leu Ile Met Ala Thr Val Arg Gly Pro Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> SEQ ID NO 47
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - VL Nucleotide Sequence

<400> SEQUENCE: 47

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaacctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgagacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agtcacagtg tctcattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 48
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - VL Amino Acid Sequence

<400> SEQUENCE: 48

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Val Ser Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 49
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 49

cagagcatta gcagctat 18

<210> SEQ ID NO 50
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 50

Gln Ser Ile Ser Ser Tyr
1 5

<210> SEQ ID NO 51

<400> SEQUENCE: 51

000

<210> SEQ ID NO 52

<400> SEQUENCE: 52

000

<210> SEQ ID NO 53
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 53

caacagagtc acagtgtctc attcact 27

<210> SEQ ID NO 54
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 54

Gln Gln Ser His Ser Val Ser Phe Thr
1 5

<210> SEQ ID NO 55
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 55

cgggcaagtc agagcattag cagctattta aat 33

<210> SEQ ID NO 56
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 56

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 57
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 57

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 58
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 58

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 59
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 59

caacagagtc acagtgtctc attcact 27

<210> SEQ ID NO 60
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - LCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 60

Gln Gln Ser His Ser Val Ser Phe Thr
1 5

<210> SEQ ID NO 61
<211> LENGTH: 1362
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - Heavy Chain Nucleotide Sequence

<400> SEQUENCE: 61

gaagtgcaac tggtggagtc cggaggaggc ctggtgcagc ctggaggaag cctgaggctg 60

agctgtgccg ccagcggctt caccttcagc aactacgcca tgaactgggt gaggcaggcc 120

cctggcaagg gactggagtg ggtctccacc atcagcggct ccggaggcgc tacacggtac 180

gccgatagcg tgaagggccg gtttaccatt tcccgggaca actcccggaa caccgtgtac 240

ctccagatga acagcctgag ggtggaggat accgccgtgt tctactgcac caaggacagg 300

ctgattatgg ccaccgtgag gggaccttac tactatggca tggatgtgtg gggccagggc 360

acaaccgtca ccgtgtcctc cgcctccacc aagggaccta gcgtgttccc tctcgccccc 420

tgttccaggt ccacaagcga gtccaccgct gccctcggct gtctggtgaa agactacttt 480

cccgagcccg tgaccgtctc ctggaatagc ggagccctga cctccggcgt gcacacattt 540

cccgccgtgc tgcagagcag cggactgtat agcctgagca gcgtggtgac cgtgcccagc 600

tccagcctcg gcaccaaaac ctacacctgc aacgtggacc acaagccctc caacaccaag 660

gtggacaagc gggtggagag caagtacggc ccccttgcc ctccttgtcc tgcccctgag 720

ttcgagggag gaccctccgt gttcctgttt cccccaaac ccaaggacac cctgatgatc 780

tcccggacac ccgaggtgac ctgtgtggtc gtggacgtca gccaggagga ccccgaggtg 840

cagttcaact ggtatgtgga cggcgtggag gtgcacaatg ccaaaaccaa gcccagggag 900

gagcagttca attccaccta cagggtggtg agcgtgctga ccgtcctgca tcaggattgg 960

ctgaacggca aggagtacaa gtgcaaggtg tccaacaagg gactgcccag ctccatcgag 1020

aagaccatca gcaaggctaa gggccagccg agggagcccc aggtgtatac cctgcctcct 1080

agccaggaag agatgaccaa gaaccaagtg tccctgacct gcctggtgaa gggattctac 1140

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ccctccgaca tcgccgtgga gtgggagagc aatggccagc ccgagaacaa ctacaaaaca 1200

acccctcccg tgctcgatag cgacggcagc ttctttctct acagccggct gacagtggac 1260

aagagcaggt ggcaggaggg caacgtgttc tcctgttccg tgatgcacga ggccctgcac 1320

aatcactaca cccagaagag cctctccctg tccctgggca ag 1362

<210> SEQ ID NO 62
<211> LENGTH: 454
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - Heavy Chain Amino Acid Sequence

<400> SEQUENCE: 62

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Gly Ala Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Phe Tyr Cys
85 90 95

Thr Lys Asp Arg Leu Ile Met Ala Thr Val Arg Gly Pro Tyr Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
115 120 125

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
130 135 140

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
145 150 155 160

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
165 170 175

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
180 185 190

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr
195 200 205

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
210 215 220

Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
225 230 235 240

Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
245 250 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
260 265 270

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
275 280 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
290 295 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305 310 315 320

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```
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
                325                 330                 335

Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
        355                 360                 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
                405                 410                 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
            420                 425                 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

Ser Leu Ser Leu Gly Lys
    450
```

<210> SEQ ID NO 63
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - Light Chain Nucleotide Sequence

<400> SEQUENCE: 63

```
gacatccaga tgacccagtc cccttcctcc ctgagcgcta gcgtgggaga tagggtgacc     60

atcacctgca gggcctccca aagcatctcc tcctacctga actggtacca gcagaaaccc    120

ggcaaggccc ccaacctgct gatctacgct gcctcctccc tccagtccgg cgtgcctagc    180

aggtttagcg gctccggaag cgagaccgac ttcaccctga ccatctcctc cctgcagccc    240

gaggacttcg ccacctacta ctgccagcaa tcccacagcg tgtccttcac cttcggcccc    300

ggcaccaagg tggacatcaa gaggaccgtg gccgcccccc ccgtgttcat ctttcccccc    360

tccgatgaac agctgaagag cggcaccgct agcgtggtgt gcctgctgaa caacttctac    420

cccagggagg ccaaggtgca gtggaaggtg gacaatgccc tgcagtccgg caacagccag    480

gagagcgtga ccgagcagga ctccaaggac agcacctaca gcctgtcctc caccctgacc    540

ctgtccaagg ccgactacga gaagcacaaa gtgtacgcct gcgaagtgac ccatcagggc    600

ctgagctccc ccgtgaccaa gtcctttaac aggggcgagt gc                       642
```

<210> SEQ ID NO 64
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 02D10 - Light Chain Amino Acid Sequence

<400> SEQUENCE: 64

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45
```

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```
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Val Ser Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 65
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - VH Nucleotide Sequence

<400> SEQUENCE: 65

```
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc     60

tcctgtgcag cctctcgatt caccctcagt gactactaca tgacctggat ccgccaggct    120

ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtaatac catatactac    180

gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat    240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagatctg    300

agtgggagct actgggacta ctactacggt atggacgtct ggggccaagg gaccacggtc    360

accgtctcct ca                                                        372
```

<210> SEQ ID NO 66
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - VH Amino Acid Sequence

<400> SEQUENCE: 66

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Leu Ser Asp Tyr
            20                  25                  30

Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Asn Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Ser Gly Ser Tyr Trp Asp Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 67
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 67

cgattcaccc tcagtgacta ctac 24

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 68

Arg Phe Thr Leu Ser Asp Tyr Tyr
1 5

<210> SEQ ID NO 69
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR2 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 69

attagtagta gtggtaatac cata 24

<210> SEQ ID NO 70
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR2 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 70

Ile Ser Ser Ser Gly Asn Thr Ile
1 5

<210> SEQ ID NO 71
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 71

gcgagagatc tgagtgggag ctactgggac tactactacg gtatggacgt c 51

<210> SEQ ID NO 72
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 72

Ala Arg Asp Leu Ser Gly Ser Tyr Trp Asp Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 73
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 73

gactactaca tgacc 15

<210> SEQ ID NO 74
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 74

Asp Tyr Tyr Met Thr
1 5

<210> SEQ ID NO 75
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 75

tacattagta gtagtggtaa taccatatac tacgcagact ctgtgaaggg c 51

<210> SEQ ID NO 76
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 76

Tyr Ile Ser Ser Ser Gly Asn Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 77
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 77

gatctgagtg ggagctactg ggactactac tacggtatgg acgtc 45

<210> SEQ ID NO 78
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - HCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 78

Asp Leu Ser Gly Ser Tyr Trp Asp Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 79
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - VL Nucleotide Sequence

<400> SEQUENCE: 79

gccatccagt tgacccagtc tccatcctcc ctgtctacat ctgtaggaga cagagtcacc 60

atcgcttgcc gggcaagtca gggcattaac aatgctttag cctggtatca gcagaaacca 120

gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tttaatagtt accctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 80
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - VL Amino Acid Sequence

<400> SEQUENCE: 80

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Ala Cys Arg Ala Ser Gln Gly Ile Asn Asn Ala
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 81
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 81

cagggcatta acaatgct 18

<210> SEQ ID NO 82
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: 09H04 - LCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 82

Gln Gly Ile Asn Asn Ala
1 5

<210> SEQ ID NO 83

<400> SEQUENCE: 83

000

<210> SEQ ID NO 84

<400> SEQUENCE: 84

000

<210> SEQ ID NO 85
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 85

caacagttta atagttaccc tcggacg 27

<210> SEQ ID NO 86
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 86

Gln Gln Phe Asn Ser Tyr Pro Arg Thr
1 5

<210> SEQ ID NO 87
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 87

cgggcaagtc agggcattaa caatgcttta gcc 33

<210> SEQ ID NO 88
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 88

Arg Ala Ser Gln Gly Ile Asn Asn Ala Leu Ala
1 5 10

<210> SEQ ID NO 89
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR2 Nucleotide Sequence (KABAT)

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<400> SEQUENCE: 89

gatgcctcca gtttggaaag t 21

<210> SEQ ID NO 90
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 90

Asp Ala Ser Ser Leu Glu Ser
1 5

<210> SEQ ID NO 91
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 91

caacagttta atagttaccc tcggacg 27

<210> SEQ ID NO 92
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 09H04 - LCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 92

Gln Gln Phe Asn Ser Tyr Pro Arg Thr
1 5

<210> SEQ ID NO 93
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - VH Nucleotide Sequence

<400> SEQUENCE: 93

gaggtgcagc tggtggagtc tgggggaggc ttggtaaagc ctggggggtc ccttagactc 60

tcctgtgcag cctctggatt cactttcagt aacgcctgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggttggccgt attaaaagca aaactgaagg tgggacaaca 180

gactacgctg cacccgtgaa aggcagattc accatctcaa gagatgattc aaaaaacacg 240

ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatta ctgtaccaca 300

gattttctat ggttcgggga gttccctttt gactactggg gccagggaac cctggtcacc 360

gtctcctca 369

<210> SEQ ID NO 94
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - VH Amino Acid Sequence

<400> SEQUENCE: 94

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Lys Ser Lys Thr Glu Gly Gly Thr Thr Asp Tyr Ala Ala
    50                  55                  60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Thr Asp Phe Leu Trp Phe Gly Glu Phe Pro Phe Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 95
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR1 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 95

ggattcactt tcagtaacgc ctgg                                          24


<210> SEQ ID NO 96
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 96

Gly Phe Thr Phe Ser Asn Ala Trp
1               5


<210> SEQ ID NO 97
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR2 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 97

attaaaagca aaactgaagg tgggacaaca                                    30


<210> SEQ ID NO 98
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR2 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 98

Ile Lys Ser Lys Thr Glu Gly Gly Thr Thr
1               5                   10


<210> SEQ ID NO 99
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR3 Nucleotide Sequence (IMGT)
```

-continued

<400> SEQUENCE: 99

accacagatt ttctatggtt cggggagttc ccttttgact ac 42

<210> SEQ ID NO 100
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 100

Thr Thr Asp Phe Leu Trp Phe Gly Glu Phe Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 101
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 101

aacgcctgga tgagc 15

<210> SEQ ID NO 102
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 102

Asn Ala Trp Met Ser
1 5

<210> SEQ ID NO 103
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 103

cgtattaaaa gcaaaactga aggtgggaca acagactacg ctgcacccgt gaaaggc 57

<210> SEQ ID NO 104
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 104

Arg Ile Lys Ser Lys Thr Glu Gly Gly Thr Thr Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> SEQ ID NO 105
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 105

gattttctat ggttcgggga gttccctttt gactac 36

<210> SEQ ID NO 106
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - HCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 106

Asp Phe Leu Trp Phe Gly Glu Phe Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 107
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - VL Nucleotide Sequence

<400> SEQUENCE: 107

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca gggcattagc aattatttag cctggtatca gcagaaacca 120

gggaaaattc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtcaaaag tataacagtg cccctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 108
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - VL Amino Acid Sequence

<400> SEQUENCE: 108

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ile Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 109
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR1 Nucleotide Sequence (IMGT)

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<400> SEQUENCE: 109

cagggcatta gcaattat 18

<210> SEQ ID NO 110
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR1 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 110

Gln Gly Ile Ser Asn Tyr
1 5

<210> SEQ ID NO 111

<400> SEQUENCE: 111

000

<210> SEQ ID NO 112

<400> SEQUENCE: 112

000

<210> SEQ ID NO 113
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR3 Nucleotide Sequence (IMGT)

<400> SEQUENCE: 113

caaaagtata acagtgcccc tcggacg 27

<210> SEQ ID NO 114
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR3 Amino Acid Sequence (IMGT)

<400> SEQUENCE: 114

Gln Lys Tyr Asn Ser Ala Pro Arg Thr
1 5

<210> SEQ ID NO 115
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR1 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 115

cgggcgagtc agggcattag caattattta gcc 33

<210> SEQ ID NO 116
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR1 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 116

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> SEQ ID NO 117
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR2 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 117

gctgcatcca ctttgcaatc a 21

<210> SEQ ID NO 118
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR2 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 118

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> SEQ ID NO 119
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR3 Nucleotide Sequence (KABAT)

<400> SEQUENCE: 119

caaaagtata acagtgcccc tcggacg 27

<210> SEQ ID NO 120
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19H01 - LCDR3 Amino Acid Sequence (KABAT)

<400> SEQUENCE: 120

Gln Lys Tyr Asn Ser Ala Pro Arg Thr
1 5

<210> SEQ ID NO 121
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGHG*01 - Heavy Chain Constant Region
Nucleotide Sequence

<400> SEQUENCE: 121

gcttccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag 60

agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc 240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc 300

aaatatggtc ccccatgccc atcatgccca gcacctgagt tcctgggggg accatcagtc 360

-continued

```
ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg    420

tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat    480

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac    540

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag    600

tgcaaggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa    660

gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag    720

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag    780

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc    840

gacggctcct tcttcctcta cagcaggcta accgtggaca agagcaggtg gcaggagggg    900

aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc    960

ctctccctgt ctctgggtaa a                                              981
```

<210> SEQ ID NO 122
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGHG*01 - Heavy Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 122

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
```

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```
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> SEQ ID NO 123
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGHG*02 - Heavy Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 123

```
gcttccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag     60

agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca    180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc    240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc    300

aaatatggtc ccccgtgccc atcatgccca gcacctgagt tcctgggggg accatcagtc    360

ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg    420

tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat    480

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac    540

cgtgtggtca gcgtcctcac cgtcgtgcac caggactggc tgaacggcaa ggagtacaag    600

tgcaaggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa    660

gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag    720

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag    780

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc    840

gacggctcct tcttcctcta cagcaggcta accgtggaca agagcaggtg gcaggagggg    900

aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc    960

ctctccctgt ctctgggtaa a                                              981
```

<210> SEQ ID NO 124
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGHG*02 - Heavy Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 124

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15
```

-continued

```
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> SEQ ID NO 125
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGHG*03 - Heavy Chain Constant Region
Nucleotide Sequence

<400> SEQUENCE: 125

```
gcttccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag     60

agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca    180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc    240
```

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```
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc    300

aaatatggtc ccccatgccc atcatgccca gcacctgagt tcctgggggg accatcagtc    360

ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg    420

tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat    480

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac    540

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag    600

tgcaaggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa    660

gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag    720

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag    780

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc    840

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcaggagggg    900

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc    960

ctctccctgt ctctgggtaa a                                              981
```

<210> SEQ ID NO 126
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGHG*03 - Heavy Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 126

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
```

-continued

```
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> SEQ ID NO 127
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IgG4 Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version A

<400> SEQUENCE: 127

```
gcctccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag     60

agcacggccg ccctgggctg cctggtcaag gactacttcc ccgaaccagt gacggtgtcg    120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca    180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc    240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc    300

aaatatggtc ccccatgccc accatgccca gcgcctgaat ttgaggggggg accatcagtc    360

ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg    420

tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat    480

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac    540

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag    600

tgcaaggtct ccaacaaagg cctcccgtca tcgatcgaga aaaccatctc caaagccaaa    660

gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag    720

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag    780

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc    840

gacggatcct tcttcctcta cagcaggcta accgtggaca agagcaggtg gcaggagggg    900

aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc    960

ctctccctgt ctctgggtaa a                                              981
```

<210> SEQ ID NO 128
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IgG4-PE - Heavy Chain Constant Region Amino Acid Sequence - Encoded by Synthetic Version A, B & C

-continued

<400> SEQUENCE: 128

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> SEQ ID NO 129
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version B

-continued

<400> SEQUENCE: 129

gcctccacca agggacctag cgtgttccct ctcgcccccc gttccaggtc cacaagcgag 60

tccaccgctg ccctcggctg tctggtgaaa gactactttc ccgagcccgt gaccgtctcc 120

tggaatagcg gagccctgac ctccggcgtg cacacatttc ccgccgtgct gcagagcagc 180

ggactgtata gcctgagcag cgtggtgacc gtgcccagct ccagcctcgg caccaaaacc 240

tacacctgca acgtggacca caagccctcc aacaccaagg tggacaagcg ggtggagagc 300

aagtacggcc ccccttgccc tccttgtcct gcccctgagt tcgagggagg accctccgtg 360

ttcctgtttc cccccaaacc caaggacacc ctgatgatct cccggacacc cgaggtgacc 420

tgtgtggtcg tggacgtcag ccaggaggac cccgaggtgc agttcaactg gtatgtggac 480

ggcgtggagg tgcacaatgc caaaaccaag cccagggagg agcagttcaa ttccacctac 540

agggtggtga gcgtgctgac cgtcctgcat caggattggc tgaacggcaa ggagtacaag 600

tgcaaggtgt ccaacaaggg actgcccagc tccatcgaga agaccatcag caaggctaag 660

ggccagccga gggagcccca ggtgtatacc ctgcctccta gccaggaaga gatgaccaag 720

aaccaagtgt ccctgacctg cctggtgaag ggattctacc cctccgacat cgccgtggag 780

tgggagagca atggccagcc cgagaacaac tacaaaacaa cccctcccgt gctcgatagc 840

gacggcagct tctttctcta cagccggctg acagtggaca agagcaggtg gcaggagggc 900

aacgtgttct cctgttccgt gatgcacgag gccctgcaca atcactacac ccagaagagc 960

ctctccctgt ccctgggcaa g 981

<210> SEQ ID NO 130
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain Constant Region Nucleotide
Sequence - Synthetic Version C

<400> SEQUENCE: 130

gccagcacca agggcccttc cgtgttcccc ctggcccctt gcagcaggag cacctccgaa 60

tccacagctg ccctgggctg tctggtgaag gactactttc ccgagcccgt gaccgtgagc 120

tggaacagcg gcgctctgac atccggcgtc cacacctttc ctgccgtcct gcagtcctcc 180

ggcctctact ccctgtcctc cgtggtgacc gtgcctagct cctccctcgg caccaagacc 240

tacacctgta acgtggacca caaaccctcc aacaccaagg tggacaaacg ggtcgagagc 300

aagtacggcc ctccctgccc tccttgtcct gcccccgagt tcgaaggcgg acccagcgtg 360

ttcctgttcc ctcctaagcc caaggacacc ctcatgatca gccggacacc cgaggtgacc 420

tgcgtggtgg tggatgtgag ccaggaggac cctgaggtcc agttcaactg gtatgtggat 480

ggcgtggagg tgcacaacgc caagacaaag ccccgggaag agcagttcaa ctccacctac 540

agggtggtca gcgtgctgac cgtgctgcat caggactggc tgaacggcaa ggagtacaag 600

tgcaaggtca gcaataaggg actgcccagc agcatcgaga agaccatctc caaggctaaa 660

ggccagcccc gggaacctca ggtgtacacc ctgcctccca gccaggagga gatgaccaag 720

aaccaggtga gcctgacctg cctggtgaag ggattctacc cttccgacat cgccgtggag 780

tgggagtcca acggccagcc cgagaacaat tataagacca cccctcccgt cctcgacagc 840

-continued

gacggatcct tctttctgta ctccaggctg accgtggata agtccaggtg gcaggaaggc 900

aacgtgttca gctgctccgt gatgcacgag gccctgcaca atcactacac ccagaagtcc 960

ctgagcctgt ccctgggaaa g 981

<210> SEQ ID NO 131
<211> LENGTH: 981
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version D

<400> SEQUENCE: 131

gcctccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag 60

agcacggccg ccctgggctg cctggtcaag gactacttcc ccgaaccagt gacggtgtcg 120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc 240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc 300

aaatatggtc ccccatgccc accatgccca gcgcctccag ttgcgggggg accatcagtc 360

ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg 420

tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat 480

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac 540

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag 600

tgcaaggtct ccaacaaagg cctcccgtca tcgatcgaga aaaccatctc caaagccaaa 660

gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag 720

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 780

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 840

gacggatcct tcttcctcta cagcaggcta accgtggaca agagcaggtg gcaggagggg 900

aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 960

ctctccctgt ctctgggtaa a 981

<210> SEQ ID NO 132
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain Constant Region Amino Acid Sequence - encoded by Synthetic Version D (PVA mutation)

<400> SEQUENCE: 132

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

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```
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> SEQ ID NO 133
<211> LENGTH: 990
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Heavy Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 133

```
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg     60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca    180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc    240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agtggagccc    300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cgcgggggca    360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct    420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg    480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac    540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag    600
```

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gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggatgag 720

ctgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 900

cagcaggggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 960

cagaagagcc tctccctgtc tccgggtaaa 990

<210> SEQ ID NO 134
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Heavy Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 134

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

-continued

```
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> SEQ ID NO 135
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*01 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 135

```
cgtacggtgg ccgctccctc cgtgttcatc ttcccacctt ccgacgagca gctgaagtcc     60

ggcaccgctt ctgtcgtgtg cctgctgaac aacttctacc cccgcgaggc caaggtgcag    120

tggaaggtgg acaacgccct gcagtccggc aactcccagg aatccgtgac cgagcaggac    180

tccaaggaca gcacctactc cctgtcctcc accctgaccc tgtccaaggc cgactacgag    240

aagcacaagg tgtacgcctg cgaagtgacc caccagggcc tgtctagccc cgtgaccaag    300

tctttcaacc ggggcgagtg t                                              321
```

<210> SEQ ID NO 136
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*01 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 136

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```

<210> SEQ ID NO 137
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*02 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 137

```
cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct     60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag    120
```

tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggag 180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag 240

aaacacaaag tctacgccgg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag 300

agcttcaaca ggggagagtg t 321

<210> SEQ ID NO 138
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*02 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 138

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Glu Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Gly Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 139
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*03 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 139

cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct 60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120

cggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggag 180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag 240

aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag 300

agcttcaaca ggggagagtg t 321

<210> SEQ ID NO 140
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*03 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 140

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

-continued

```
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Arg Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Glu Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 141
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*04 - C? Light Chain Constant Region
      Nucleotide Sequence

<400> SEQUENCE: 141

cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct     60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag    120

tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac    180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag    240

aaacacaaac tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag    300

agcttcaaca ggggagagtg t                                              321


<210> SEQ ID NO 142
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*04 - C? Light Chain Constant Region Amino
      Acid Sequence

<400> SEQUENCE: 142

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 143
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: IGKC*05 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 143

cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct 60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120

tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac 180

agcaaggaca gcacctacag cctcagcaac accctgacgc tgagcaaagc agactacgag 240

aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag 300

agcttcaaca ggggagagtg c 321

<210> SEQ ID NO 144
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGKC*05 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 144

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Asn Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 145
<211> LENGTH: 312
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?1*01 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 145

cccaaggcca accccacggt cactctgttc ccgccctcct ctgaggagct ccaagccaac 60

aaggccacac tagtgtgtct gatcagtgac ttctacccgg gagctgtgac agtggcttgg 120

aaggcagatg gcagccccgt caaggcggga gtggagacga ccaaaccctc caaacagagc 180

aacaacaagt acgcggccag cagctacctg agcctgacgc ccgagcagtg gaagtcccac 240

agaagctaca gctgccaggt cacgcatgaa gggagcaccg tggagaagac agtggccct 300

acagaatgtt ca 312

<210> SEQ ID NO 146
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:

<223> OTHER INFORMATION: IGC?1*01 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 146

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
1 5 10 15

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
20 25 30

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
35 40 45

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
50 55 60

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
65 70 75 80

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
85 90 95

Thr Val Ala Pro Thr Glu Cys Ser
100

<210> SEQ ID NO 147
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?1*02 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 147

ggtcagccca aggccaaccc cactgtcact ctgttcccgc cctcctctga ggagctccaa 60

gccaacaagg ccacactagt gtgtctgatc agtgacttct acccgggagc tgtgacagtg 120

gcctggaagg cagatggcag ccccgtcaag gcgggagtgg agaccaccaa accctccaaa 180

cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcccga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 148
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?1*02 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 148

Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 149
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?2*01 - C? Light Chain Constant Region
Nucleotide Sequence - Version A

<400> SEQUENCE: 149

ggtcagccca aggccaaccc cactgtcact ctgttcccgc cctcctctga ggagctccaa 60

gccaacaagg ccacactagt gtgtctgatc agtgacttct acccgggagc tgtgacagtg 120

gcctggaagg cagatggcag ccccgtcaag gcgggagtgg agaccaccaa accctccaaa 180

cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcccga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 150
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?2*01 - C? Light Chain Constant Region
Nucleotide Sequence - Version B

<400> SEQUENCE: 150

ggccagccta aggccgctcc ttctgtgacc ctgttccccc catcctccga ggaactgcag 60

gctaacaagg ccaccctcgt gtgcctgatc agcgacttct accctggcgc cgtgaccgtg 120

gcctggaagg ctgatagctc tcctgtgaag gccggcgtgg aaaccaccac cccttccaag 180

cagtccaaca acaaatacgc cgcctcctcc tacctgtccc tgaccccctga gcagtggaag 240

tcccaccggt cctacagctg ccaagtgacc cacgagggct ccaccgtgga aaagaccgtg 300

gctcctaccg agtgctcc 318

<210> SEQ ID NO 151
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?2*01 - C? Light Chain Constant Region
Nucleotide Sequence - Version C

<400> SEQUENCE: 151

ggccagccta aagctgcccc cagcgtcacc ctgtttcctc cctccagcga ggagctccag 60

gccaacaagg ccaccctcgt gtgcctgatc tccgacttct atcccggcgc tgtgaccgtg 120

gcttggaaag ccgactccag ccctgtcaaa gccggcgtgg agaccaccac accctccaag 180

cagtccaaca acaagtacgc cgcctccagc tatctctccc tgaccccctga gcagtggaag 240

tcccaccggt cctactcctg tcaggtgacc cacgagggct ccaccgtgga aaagaccgtc 300

gcccccaccg agtgctcc 318

<210> SEQ ID NO 152
<211> LENGTH: 106

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?2*01 - C? Light Chain Constant Region Amino Acid Sequence - Encoded by Version A, B & C

<400> SEQUENCE: 152

Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 153
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?2*02 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 153

ggtcagccca aggctgcccc ctcggtcact ctgttcccgc cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg 120

gcctggaagg cagatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa 180

caaagcaaca acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 154
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?2*02 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 154

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 155
<211> LENGTH: 312
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*01 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 155

cccaaggctg ccccctcggt cactctgttc ccaccctcct ctgaggagct tcaagccaac 60

aaggccacac tggtgtgtct cataagtgac ttctacccgg gagccgtgac agttgcctgg 120

aaggcagata gcagccccgt caaggcgggg gtggagacca ccacaccctc caaacaaagc 180

aacaacaagt acgcggccag cagctacctg agcctgacgc ctgagcagtg gaagtcccac 240

aaaagctaca gctgccaggt cacgcatgaa gggagcaccg tggagaagac agttgccct 300

acggaatgtt ca 312

<210> SEQ ID NO 156
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*01 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 156

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
1 5 10 15

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
20 25 30

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
35 40 45

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
50 55 60

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
65 70 75 80

Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
85 90 95

Thr Val Ala Pro Thr Glu Cys Ser
100

<210> SEQ ID NO 157
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*02 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 157

ggtcagccca aggctgcccc ctcggtcact ctgttcccac cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcata agtgacttct acccggggcc agtgacagtt 120

gcctggaagg cagatagcag ccccgtcaag gcgggggtgg agaccaccac accctccaaa 180

-continued

caaagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag 240

tcccacaaaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacgg aatgttca 318

<210> SEQ ID NO 158
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*02 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 158

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Pro Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 159
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*03 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 159

ggtcagccca aggctgcccc ctcggtcact ctgttcccac cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg 120

gcctggaagg cagatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa 180

caaagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag 240

tcccacaaaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 160
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*03 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 160

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 161
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*04 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 161

ggtcagccca aggctgcccc ctcggtcact ctgttcccgc cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg 120

gcctggaagg cagatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa 180

caaagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 162
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?3*04 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 162

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 163
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?6*01 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 163

ggtcagccca aggctgcccc atcggtcact ctgttcccgc cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgcctgatc agtgacttct acccgggagc tgtgaaagtg 120

gcctggaagg cagatggcag ccccgtcaac acgggagtgg agaccaccac accctccaaa 180

cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctgcag aatgttca 318

<210> SEQ ID NO 164
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?6*01 - C? Light Chain Constant Region Amino Acid Sequence

<400> SEQUENCE: 164

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Lys Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Asn Thr Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
100 105

<210> SEQ ID NO 165
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?7*02 - C? Light Chain Constant Region Nucleotide Sequence

<400> SEQUENCE: 165

ggtcagccca aggctgcccc atcggtcact ctgttcccac cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcgta agtgacttct acccgggagc cgtgacagtg 120

gcctggaagg cagatggcag ccccgtcaag gtgggagtgg agaccaccaa accctccaaa 180

caaagcaaca acaagtatgc ggccagcagc tacctgagcc tgacgcccga gcagtggaag 240

tcccacagaa gctacagctg ccgggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctgcag aatgctct 318

<210> SEQ ID NO 166
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IGC?7*02 - C? Light Chain Constant Region Amino Acid Sequence

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<400> SEQUENCE: 166

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Val Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Lys Val Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Arg Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
100 105

<210> SEQ ID NO 167
<211> LENGTH: 615
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant Human OX40L (Leader sequence, Isoleucine Zipper and FLAG Sequence Included) - Nucleotide Sequence

<400> SEQUENCE: 167

atgggctggt cctgcatcat cctgtttctg gtggccaccg ccaccggcgt gcacagcgat 60

tacaaggatg acgacgataa gcgtatgaaa cagatcgaag ataaaattga agagatcttg 120

agcaaaatct atcatatcga aaacgaaatt gcgcgtatca aaaagctgat tggcgaacgt 180

ggcggtggca gcggtggcgg tagcggcggt ggcagccagg tgtcccaccg ataccccagg 240

atccagtcca tcaaggtcca gttcaccgag tacaaaaagg agaagggatt catcctgacc 300

tcccaaaagg aggacgagat catgaaggtg caaaacaact ccgtgatcat caactgcgac 360

ggcttctacc tgatctccct gaagggctac ttctcccagg aggtgaacat ctccctgcac 420

taccagaagg acgaggagcc cctgttccag ctgaagaagg tgaggtccgt gaattccctg 480

atggtggcca gcctgaccta caaggacaag gtctacctga acgtgaccac cgacaacacc 540

agcctggacg acttccatgt caacggcggc gagctgatcc tgatccatca gaaccccggc 600

gagttttgcg tcctg 615

<210> SEQ ID NO 168
<211> LENGTH: 205
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant Human OX40L (Leader sequence, Isoleucine Zipper and FLAG Sequence Included) - Amino Acid Sequence

<400> SEQUENCE: 168

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Arg Met Lys Gln Ile
20 25 30

Glu Asp Lys Ile Glu Glu Ile Leu Ser Lys Ile Tyr His Ile Glu Asn
35 40 45

Glu Ile Ala Arg Ile Lys Lys Leu Ile Gly Glu Arg Gly Gly Gly Ser
50 55 60

Gly Gly Gly Ser Gly Gly Gly Ser Gln Val Ser His Arg Tyr Pro Arg
65 70 75 80

Ile Gln Ser Ile Lys Val Gln Phe Thr Glu Tyr Lys Lys Glu Lys Gly
85 90 95

Phe Ile Leu Thr Ser Gln Lys Glu Asp Glu Ile Met Lys Val Gln Asn
100 105 110

Asn Ser Val Ile Ile Asn Cys Asp Gly Phe Tyr Leu Ile Ser Leu Lys
115 120 125

Gly Tyr Phe Ser Gln Glu Val Asn Ile Ser Leu His Tyr Gln Lys Asp
130 135 140

Glu Glu Pro Leu Phe Gln Leu Lys Lys Val Arg Ser Val Asn Ser Leu
145 150 155 160

Met Val Ala Ser Leu Thr Tyr Lys Asp Lys Val Tyr Leu Asn Val Thr
165 170 175

Thr Asp Asn Thr Ser Leu Asp Asp Phe His Val Asn Gly Gly Glu Leu
180 185 190

Ile Leu Ile His Gln Asn Pro Gly Glu Phe Cys Val Leu
195 200 205

<210> SEQ ID NO 169
<211> LENGTH: 615
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant Rhesus OX40L (Leader Sequence, FLAG and Isoleucine zipper included) - Nucleotide Sequence

<400> SEQUENCE: 169

atgggctggt cctgcatcat cctgtttctg gtggccaccg ccaccggcgt gcacagcgat 60

tacaaggatg acgacgataa gcgtatgaaa cagatcgaag ataaaattga agagatcttg 120

agcaaaatct atcatatcga aaacgaaatt gcgcgtatca aaaagctgat tggcgaacgt 180

ggcggtggca gcggtggcgg tagcggcggt ggcagccagg tgtcccacca ataccccagg 240

atccagtcca tcaaggtcca gttcaccgag tacaaaaagg aggagggatt catcctgacc 300

tcccaaaagg aggacgagat catgaaggtg caaaacaact ccgtgatcat caactgcgac 360

ggcttctacc tgatctccct gaagggctac ttctcccagg aggtgaacat ctccctgcac 420

taccagaagg acgaggagcc cctgttccag ctgaagaagg tgaggtccgt gaattccctg 480

atggtggcca gcctgaccta caaggacaag gtctacctga acgtgaccac cgacaacacc 540

agcctggacg acttccatgt caacggcggc gagctgatcc tgatccatca gaaccccggc 600

gagttttgcg tcctg 615

<210> SEQ ID NO 170
<211> LENGTH: 205
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant Rhesus OX40L (Leader Sequence, FLAG and Isoleucine zipper included) - Amino Acid Sequence

<400> SEQUENCE: 170

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

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Val His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Arg Met Lys Gln Ile
            20                  25                  30

Glu Asp Lys Ile Glu Glu Ile Leu Ser Lys Ile Tyr His Ile Glu Asn
        35                  40                  45

Glu Ile Ala Arg Ile Lys Lys Leu Ile Gly Glu Arg Gly Gly Gly Ser
    50                  55                  60

Gly Gly Gly Ser Gly Gly Gly Ser Gln Val Ser His Gln Tyr Pro Arg
65                  70                  75                  80

Ile Gln Ser Ile Lys Val Gln Phe Thr Glu Tyr Lys Lys Glu Glu Gly
                85                  90                  95

Phe Ile Leu Thr Ser Gln Lys Glu Asp Glu Ile Met Lys Val Gln Asn
            100                 105                 110

Asn Ser Val Ile Ile Asn Cys Asp Gly Phe Tyr Leu Ile Ser Leu Lys
        115                 120                 125

Gly Tyr Phe Ser Gln Glu Val Asn Ile Ser Leu His Tyr Gln Lys Asp
    130                 135                 140

Glu Glu Pro Leu Phe Gln Leu Lys Lys Val Arg Ser Val Asn Ser Leu
145                 150                 155                 160

Met Val Ala Ser Leu Thr Tyr Lys Asp Lys Val Tyr Leu Asn Val Thr
                165                 170                 175

Thr Asp Asn Thr Ser Leu Asp Asp Phe His Val Asn Gly Gly Glu Leu
            180                 185                 190

Ile Leu Ile His Gln Asn Pro Gly Glu Phe Cys Val Leu
        195                 200                 205
```

<210> SEQ ID NO 171
<211> LENGTH: 1332
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant Human OX40R (Leader Sequence and Human Fc Sequence included) - Nucleotide Sequence

<400> SEQUENCE: 171

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atgggctggt cctgcatcat cctgtttctg gtggccaccg ccaccggcgt gcacagcctg     60

cattgcgtgg gcgacaccta tccctccaac gacaggtgct gccacgagtg caggcctgga    120

aacggcatgg tgagcaggtg cagccggtcc cagaataccg tgtgtaggcc ctgcggcccc    180

ggcttttaca acgacgtggt gtcctccaag ccctgcaagc cctgcacatg gtgcaacctg    240

cggtccggca gcgagaggaa gcagctctgc acagccaccc aggacaccgt ctgtaggtgt    300

agggctggca cccagcctct ggactcctac aagcccggcg tggattgtgc tccttgccct    360

cccggccatt tctcccctgg cgacaaccag gcttgcaagc cctggaccaa ctgtaccctg    420

gccggcaagc atacactgca gcctgcttcc aactcctccg acgctatctg cgaggatagg    480

gaccccccctg ccacacaacc ccaggagaca cagggccctc ctgctaggcc catcacagtc    540

caacccaccg aagcctggcc caggacatcc caaggccctt ccaccaggcc tgtggaagtg    600

cctggaggaa gggctgtggc cattgaaggt cgtatggatg aacccaagtc ctgcgacaag    660

acccacacct gtccccctttg tcctgccccct gaactgctgg gcggaccttc cgtgttcctg    720

ttcccccccaa agcccaagga caccctgatg atctcccgga cccccgaagt gacctgcgtg    780

gtggtggatg tgtcccacga ggaccctgaa gtgaagttca attggtacgt ggacggcgtg    840

gaagtgcaca acgccaagac caagcctaga gaggaacagt acaactccac ctaccgggtg    900

gtgtccgtgc tgaccgtgct gcaccaggat tggctgaacg gcaaagagta caagtgcaag    960
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gtgtccaaca aggccctgcc tgcccccatc gaaaagacca tctccaaggc caagggccag 1020

ccccgggaac cccaggtgta cacactgccc cctagcaggg acgagctgac caagaaccag 1080

gtgtccctga cctgtctcgt gaaaggcttc taccctccg atatcgccgt ggaatgggag 1140

tccaacggcc agcctgagaa caactacaag accacccccc ctgtgctgga ctccgacggc 1200

tcattcttcc tgtacagcaa gctgacagtg gacaagtccc ggtggcagca gggcaacgtg 1260

ttctcctgct ccgtgatgca cgaggccctg cacaaccact acacccagaa gtccctgtcc 1320

ctgagccccc ga 1332

<210> SEQ ID NO 172
<211> LENGTH: 443
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant Human OX40R (Leader Sequence and Human Fc Sequence included) - Amino Acid Sequence

<400> SEQUENCE: 172

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Leu His Cys Val Gly Asp Thr Tyr Pro Ser Asn Asp Arg
20 25 30

Cys Cys His Glu Cys Arg Pro Gly Asn Gly Met Val Ser Arg Cys Ser
35 40 45

Arg Ser Gln Asn Thr Val Cys Arg Pro Cys Gly Pro Gly Phe Tyr Asn
50 55 60

Asp Val Val Ser Ser Lys Pro Cys Lys Pro Cys Thr Trp Cys Asn Leu
65 70 75 80

Arg Ser Gly Ser Glu Arg Lys Gln Leu Cys Thr Ala Thr Gln Asp Thr
85 90 95

Val Cys Arg Cys Arg Ala Gly Thr Gln Pro Leu Asp Ser Tyr Lys Pro
100 105 110

Gly Val Asp Cys Ala Pro Cys Pro Pro Gly His Phe Ser Pro Gly Asp
115 120 125

Asn Gln Ala Cys Lys Pro Trp Thr Asn Cys Thr Leu Ala Gly Lys His
130 135 140

Thr Leu Gln Pro Ala Ser Asn Ser Ser Asp Ala Ile Cys Glu Asp Arg
145 150 155 160

Asp Pro Pro Ala Thr Gln Pro Gln Glu Thr Gln Gly Pro Pro Ala Arg
165 170 175

Pro Ile Thr Val Gln Pro Thr Glu Ala Trp Pro Arg Thr Ser Gln Gly
180 185 190

Pro Ser Thr Arg Pro Val Glu Val Pro Gly Gly Arg Ala Val Ala Ile
195 200 205

Glu Gly Arg Met Asp Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
210 215 220

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
225 230 235 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
245 250 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
260 265 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
275 280 285

```
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440


<210> SEQ ID NO 173
<211> LENGTH: 552
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Cell Expressed OX40L (CHO/MEF) (Leader sequence
      included) - Nucleotide Sequence

<400> SEQUENCE: 173

atggagaggg tgcagcccct cgaggagaac gtgggaaacg ccgccaggcc taggttcgag     60

aggaacaagc tgctgctggt ggcttccgtg atccaaggac tcggcctgct gctctgcttc    120

acctacatct gcctccactt cagcgccctg caggtgtccc accgataccc caggatccag    180

tccatcaagg tccagttcac cgagtacaaa aaggagaagg gattcatcct gacctcccaa    240

aaggaggacg agatcatgaa ggtgcaaaac aactccgtga tcatcaactg cgacggcttc    300

tacctgatct ccctgaaggg ctacttctcc caggaggtga acatctccct gcactaccag    360

aaggacgagg agcccctgtt ccagctgaag aaggtgaggt ccgtgaattc cctgatggtg    420

gccagcctga cctacaagga caaggtctac ctgaacgtga ccaccgacaa caccagcctg    480

gacgacttcc atgtcaacgg cggcgagctg atcctgatcc atcagaaccc cggcgagttt    540

tgcgtcctgt aa                                                        552


<210> SEQ ID NO 174
<211> LENGTH: 181
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Cell Expressed OX40L (CHO/MEF) (Leader sequence
      included) - Amino Acid Sequence

<400> SEQUENCE: 174

Met Glu Arg Val Gln Pro Leu Glu Glu Asn Val Gly Asn Ala Ala Arg
1               5                   10                  15

Pro Arg Phe Glu Arg Asn Lys Leu Leu Leu Val Ala Ser Val Ile Gln
            20                  25                  30
```

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```
Gly Leu Gly Leu Leu Leu Cys Phe Thr Tyr Ile Cys Leu His Phe Ser
        35                  40                  45

Ala Leu Gln Val Ser His Arg Tyr Pro Arg Ile Gln Ser Ile Lys Val
    50                  55                  60

Gln Phe Thr Glu Tyr Lys Lys Glu Lys Gly Phe Ile Leu Thr Ser Gln
65                  70                  75                  80

Lys Glu Asp Glu Ile Met Lys Val Gln Asn Asn Ser Val Ile Ile Asn
                85                  90                  95

Cys Asp Gly Phe Tyr Leu Ile Ser Leu Lys Gly Tyr Phe Ser Gln Glu
            100                 105                 110

Val Asn Ile Ser Leu His Tyr Gln Lys Asp Glu Glu Pro Leu Phe Gln
        115                 120                 125

Leu Lys Lys Val Arg Ser Val Asn Ser Leu Met Val Ala Ser Leu Thr
    130                 135                 140

Tyr Lys Asp Lys Val Tyr Leu Asn Val Thr Thr Asp Asn Thr Ser Leu
145                 150                 155                 160

Asp Asp Phe His Val Asn Gly Gly Glu Leu Ile Leu Ile His Gln Asn
                165                 170                 175

Pro Gly Glu Phe Cys
            180
```

<210> SEQ ID NO 175
<211> LENGTH: 834
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Cell Expressed OX40 receptor (HT1080) - Nucleotide Sequence

<400> SEQUENCE: 175

```
atgtgcgtgg gggctcggcg gctgggccgc gggccgtgtg cggctctgct cctcctgggc     60

ctggggctga gcaccgtgac ggggctccac tgtgtcgggg acacctaccc cagcaacgac    120

cggtgctgcc acgagtgcag gccaggcaac gggatggtga gccgctgcag ccgctcccag    180

aacacggtgt gccgtccgtg cgggccgggc ttctacaacg acgtggtcag ctccaagccg    240

tgcaagccct gcacgtggtg taacctcaga agtgggagtg agcggaagca gctgtgcacg    300

gccacacagg acacagtctg ccgctgccgg gcgggcaccc agcccctgga cagctacaag    360

cctggagttg actgtgcccc ctgccctcca gggcacttct ccccaggcga caaccaggcc    420

tgcaagccct ggaccaactg caccttggct gggaagcaca ccctgcagcc ggccagcaat    480

agctcggacg caatctgtga ggacagggac cccccagcca cgcagcccca ggagacccag    540

ggcccccggg ccaggcccat cactgtccag cccactgaag cctggcccag aacctcacag    600

ggaccctcca cccggcccgt ggaggtcccc gggggccgtg cggttgccgc catcctgggc    660

ctgggcctgg tgctggggct gctgggcccc ctggccatcc tgctggccct gtacctgctc    720

cggagggacc agaggctgcc ccccgatgcc cacaagcccc ctgggggagg cagtttccgg    780

acccccatcc aagaggagca ggccgacgcc cactccaccc tggccaagat ctga          834
```

<210> SEQ ID NO 176
<211> LENGTH: 277
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Cell Expressed OX40 receptor (HT1080) - Amino Acid Sequence

-continued

<400> SEQUENCE: 176

Met Cys Val Gly Ala Arg Arg Leu Gly Arg Gly Pro Cys Ala Ala Leu
1 5 10 15

Leu Leu Leu Gly Leu Gly Leu Ser Thr Val Thr Gly Leu His Cys Val
20 25 30

Gly Asp Thr Tyr Pro Ser Asn Asp Arg Cys Cys His Glu Cys Arg Pro
35 40 45

Gly Asn Gly Met Val Ser Arg Cys Ser Arg Ser Gln Asn Thr Val Cys
50 55 60

Arg Pro Cys Gly Pro Gly Phe Tyr Asn Asp Val Val Ser Ser Lys Pro
65 70 75 80

Cys Lys Pro Cys Thr Trp Cys Asn Leu Arg Ser Gly Ser Glu Arg Lys
85 90 95

Gln Leu Cys Thr Ala Thr Gln Asp Thr Val Cys Arg Cys Arg Ala Gly
100 105 110

Thr Gln Pro Leu Asp Ser Tyr Lys Pro Gly Val Asp Cys Ala Pro Cys
115 120 125

Pro Pro Gly His Phe Ser Pro Gly Asp Asn Gln Ala Cys Lys Pro Trp
130 135 140

Thr Asn Cys Thr Leu Ala Gly Lys His Thr Leu Gln Pro Ala Ser Asn
145 150 155 160

Ser Ser Asp Ala Ile Cys Glu Asp Arg Asp Pro Pro Ala Thr Gln Pro
165 170 175

Gln Glu Thr Gln Gly Pro Pro Ala Arg Pro Ile Thr Val Gln Pro Thr
180 185 190

Glu Ala Trp Pro Arg Thr Ser Gln Gly Pro Ser Thr Arg Pro Val Glu
195 200 205

Val Pro Gly Gly Arg Ala Val Ala Ala Ile Leu Gly Leu Gly Leu Val
210 215 220

Leu Gly Leu Leu Gly Pro Leu Ala Ile Leu Leu Ala Leu Tyr Leu Leu
225 230 235 240

Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly
245 250 255

Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser
260 265 270

Thr Leu Ala Lys Ile
275

<210> SEQ ID NO 177
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L15B07 (Seq ID No 179 in WO2011/073180, Table A-1)

<400> SEQUENCE: 177

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

-continued

```
Gly Arg Phe Thr Ile Ser Ile Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> SEQ ID NO 178
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L01B11 (Seq ID No 180 in WO2011/073180, Table A-1)

<400> SEQUENCE: 178

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Arg Ser Phe Ser Thr Tyr
            20                  25                  30

Ile Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

Ala Thr Ile Ser Arg Ser Gly Ile Thr Ile Arg Ser Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ala Gly Pro Tyr Val Glu Gln Thr Leu Gly Leu Tyr Gln Thr Leu
            100                 105                 110

Gly Pro Trp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125
```

<210> SEQ ID NO 179
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L01E07 (Seq ID No 181 in WO2011/073180, Table A-1)

<400> SEQUENCE: 179

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
            20                  25                  30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
        35                  40                  45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
    50                  55                  60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65                  70                  75                  80

Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
            100                 105                 110
```

-continued

Tyr Trp Gly Leu Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 180
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L01E10 (Seq ID No 182 in WO2011/073180, Table A-1)

<400> SEQUENCE: 180

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Leu Thr Phe Ser Ser Phe
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Ser Arg Ser Gly Tyr Gly Thr Ser Glu Ala Asp Ser Val
50 55 60

Arg Asp Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Thr
65 70 75 80

Leu His Leu Ser Arg Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Glu His Thr Leu Gly Arg Pro Ser Arg Ser Gln Ile Asn Tyr
100 105 110

Leu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 181
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L18E09 (Seq ID No 183 in WO2011/073180, Table A-1)

<400> SEQUENCE: 181

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Asn Ile Leu Ser Leu Asn
20 25 30

Thr Met Gly Trp Tyr Arg His Ala Pro Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Arg Ile Ser Ser Asn Ser Lys Thr Asp Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Leu Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr Tyr Cys Asn
85 90 95

Leu Asn Val Trp Arg Thr Ser Ser Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 182
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L19A07 (Seq ID No 184 in WO2011/073180, Table A-1)

<400> SEQUENCE: 182

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Asp Tyr
20 25 30

Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

Ser Arg Ile Lys Ile Ser Asn Gly Arg Thr Thr Tyr Ala Gly Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Asn Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Asp Arg Ser Ser Leu Leu Phe Gly Ser Asn Trp Asp Arg Lys
100 105 110

Ala Arg Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 183
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L19D08 (Seq ID No 185 in WO2011/073180, Table A-1)

<400> SEQUENCE: 183

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Ala
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Arg Phe Ile Ser Asn
20 25 30

Tyr Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Gln Glu Arg Ala Phe
35 40 45

Val Ala Ala Ile Ser Arg Ser Gly Ser Ile Thr Tyr Tyr Thr Asp Ser
50 55 60

Val Lys Gly Arg Phe Ser Ile Ser Arg Asp Tyr Ala Lys Ser Thr Val
65 70 75 80

Tyr Leu Gln Met Asp Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Ala Asp Gly Gly Ala Val Arg Asp Leu Thr Thr Asn Leu Pro
100 105 110

Asp Tyr Trp Gly Arg Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 184
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L075 (Seq ID No 199 in WO2011/073180, Table A-2)

<400> SEQUENCE: 184

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ser Phe Ser Thr Tyr
            20                  25                  30

Ile Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

Ala Thr Ile Ser Arg Ser Gly Ile Thr Thr Arg Ser Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ala Gly Pro Tyr Val Glu Gln Thr Leu Gly Leu Tyr Gln Thr Leu
            100                 105                 110

Gly Pro Trp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 185
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L024 (Seq ID No 200
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 185

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
            20                  25                  30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
        35                  40                  45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
    50                  55                  60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65                  70                  75                  80

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
            100                 105                 110

Tyr Trp Gly Leu Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 186
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L025 (Seq ID No 201
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 186

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
            20                  25                  30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
        35                  40                  45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
    50                  55                  60
```

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```
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val
65                  70                  75                  80

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
            100                 105                 110

Tyr Trp Gly Leu Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 187
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L026 (Seq ID No 202
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 187

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
            20                  25                  30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
        35                  40                  45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
    50                  55                  60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65                  70                  75                  80

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 188
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L027 (Seq ID No 203
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 188

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
            20                  25                  30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
        35                  40                  45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
    50                  55                  60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val
65                  70                  75                  80

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
            100                 105                 110
```

-continued

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 189
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L028 (Seq ID No 204 in WO2011/073180, Table A-2)

<400> SEQUENCE: 189

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
20 25 30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
35 40 45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
100 105 110

Tyr Trp Gly Leu Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 190
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L039 (Seq ID No 205 in WO2011/073180, Table A-2)

<400> SEQUENCE: 190

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
20 25 30

Tyr Ala Lys Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
35 40 45

Val Ala Ala Ile Ser Arg Ser Gly Arg Ser Thr Ser Tyr Ala Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Ala Val Gly Gly Ala Thr Thr Val Thr Ala Ser Glu Trp Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 191
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: Amino Acid Sequence of OX40L030 (Seq ID No 206
in WO2011/073180, Table A-2)

<400> SEQUENCE: 191

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Ile Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 192
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L040 (Seq ID No 207
in WO2011/073180, Table A-2)

<400> SEQUENCE: 192

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 193
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L041 (Seq ID No 208
in WO2011/073180, Table A-2)

<400> SEQUENCE: 193

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Ala Thr Gly Glu Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 194
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L042 (Seq ID No 209
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 194

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Glu Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 195
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L043 (Seq ID No 210
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 195

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Lys Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
    50                  55                  60
```

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 196
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L044 (Seq ID No 211 in WO2011/073180, Table A-2)

<400> SEQUENCE: 196

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Ala Pro Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 197
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L045 (Seq ID No 212 in WO2011/073180, Table A-2)

<400> SEQUENCE: 197

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Ala Thr Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 198
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L046 (Seq ID No 213 in WO2011/073180, Table A-2)

<400> SEQUENCE: 198

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 199
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L047 (Seq ID No 214 in WO2011/073180, Table A-2)

<400> SEQUENCE: 199

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Ala Pro Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 200
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L048 (Seq ID No 215 in WO2011/073180, Table A-2)

<400> SEQUENCE: 200

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Ala Asp Phe Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 201
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L049 (Seq ID No 216 in WO2011/073180, Table A-2)

<400> SEQUENCE: 201

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 202
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L050 (Seq ID No 217 in WO2011/073180, Table A-2)

<400> SEQUENCE: 202

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 203
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L053 (Seq ID No 218
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 203

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Ile Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 204
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L054 (Seq ID No 219
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 204

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
    50                  55                  60
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```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 205
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L055 (Seq ID No 220
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 205

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Thr Gly Glu Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Phe Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Asn Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 206
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L056 (Seq ID No 221
      in WO2011/073180, Table A-2)

<400> SEQUENCE: 206

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Lys Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110
```

Val Thr Val Ser Ser
115

<210> SEQ ID NO 207
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L069 (Seq ID No 222 in WO2011/073180, Table A-2)

<400> SEQUENCE: 207

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Ile Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 208
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L070 (Seq ID No 223 in WO2011/073180, Table A-2)

<400> SEQUENCE: 208

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Asn Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 209
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: Amino Acid Sequence of OX40L071 (Seq ID No 224
in WO2011/073180, Table A-2)

<400> SEQUENCE: 209

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Lys Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Ile Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Asn Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 210
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L082 (Seq ID No 225
in WO2011/073180, Table A-2)

<400> SEQUENCE: 210

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
20 25 30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Glu Pro Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Ile Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 211
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino Acid Sequence of OX40L083 (Seq ID No 226
in WO2011/073180, Table A-2)

<400> SEQUENCE: 211

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Gly Arg Leu Asp
            20                  25                  30

Arg Met Gly Trp Tyr Arg His Arg Pro Gly Lys Pro Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Gly Gly Ser Ser Ile Asn Tyr Gly Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Ile Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Phe Asn Lys Tyr Val Thr Ser Arg Asp Thr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 212
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of OX40L benchmark antibody
      heavy chain (Seq ID No:177 in WO2011/073180, Table A-5)

<400> SEQUENCE: 212

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Ser Gly Gly Phe Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Arg Leu Val Ala Pro Gly Thr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Ala Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240
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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 213
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of OX40L benchmark antibody
      light chain (Seq ID No:178 in WO2011/073180, Table A-5)

<400> SEQUENCE: 213

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125
```

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```
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 214
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain
      variable region of LC.001 (Seq ID No: 1 in WO2006/029879)

<400> SEQUENCE: 214

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 215
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable
      region of LC.001 (Seq ID No: 2 in WO2006/029879)

<400> SEQUENCE: 215

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ile Ile Ser Gly Ser Gly Gly Phe Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Lys Asp Arg Leu Val Ala Pro Gly Thr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Ala Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 216
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain
      variable region of LC.005 (Seq ID No: 3 in WO2006/029879)

<400> SEQUENCE: 216

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 217
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable
      region of LC.005 (Seq ID No: 4 in WO2006/029879)

<400> SEQUENCE: 217

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ala Ile Trp Tyr Asp Gly His Asp Lys Tyr Tyr Ser Tyr Tyr Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Ser Ser Ser Trp Tyr Arg Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 218
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain variable region of LC.010 (Seq ID No: 5 in WO2006/029879)

<400> SEQUENCE: 218

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 219
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable region of LC.010 (Seq ID No: 6 in WO2006/029879)

<400> SEQUENCE: 219

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ala Ile Trp Tyr Asp Gly His Asp Lys Tyr Tyr Ala Tyr Tyr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Ser Ser Trp Tyr Arg Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 220
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain variable region of LC.029 (Seq ID No: 7 in WO2006/029879)

<400> SEQUENCE: 220

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
20 25 30

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Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ala Ile Trp Tyr Asp Gly His Asp Lys Tyr Tyr Ser Tyr Tyr Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Ser Ser Ser Trp Tyr Arg Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 221
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable
      region of LC.029 (Seq ID No: 8 in WO2006/029879)

<400> SEQUENCE: 221

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Lys Asn Trp Ser Phe Asp Phe Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210> SEQ ID NO 222
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain
      variable region of LC.019 (Seq ID No: 9 in WO2006/029879)

<400> SEQUENCE: 222

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Val Ser Arg Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Val Ser Gly
    50                  55                  60

Ser Gly Pro Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
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Glu Asp Phe Ala Val Asp Tyr Cys Gln Gln Arg Ser Asn Trp Gln Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105

<210> SEQ ID NO 223
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable region of LC.019 (Seq ID No: 10 in WO2006/029879)

<400> SEQUENCE: 223

Gln Lys Gln Leu Val Glu Phe Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Asn Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Met Gly Ile Tyr Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 224
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain variable region of LC.033 (Seq ID No: 11 in WO2006/029879)

<400> SEQUENCE: 224

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Thr Phe
85 90 95

Gly Gln Gly Thr Lys Val Glu Ile
100

<210> SEQ ID NO 225
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable region of LC.033 (Seq ID No: 12 in WO2006/029879)

<400> SEQUENCE: 225

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ile Ile Ser Gly Ser Gly Gly Phe Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Val Ala Pro Gly Thr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Ala Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 226
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of mutant kappa light chain variable region of LC.033 (Seq ID No: 16 in WO2006/029879)

<400> SEQUENCE: 226

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 227
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable region of LC.059 (Seq ID No: 17 in WO2006/029879)

<400> SEQUENCE: 227

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ile Ile Ser Gly Ser Gly Gly Phe Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Arg Leu Arg Ala Glu Asp Thr Ala Ile Tyr Phe Cys
                85                  90                  95

Ala Lys Asp Asp Ile Pro Ala Ala Gly Thr Phe Asp Pro Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 228
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of kappa light chain
      variable region of LC.060 (Seq ID No: 18 in WO2006/029879)

<400> SEQUENCE: 228

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Val Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Trp Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 229
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable
      region of LC.060 (Seq ID No: 19 in WO2006/029879)

<400> SEQUENCE: 229

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Ser Gly Gly Leu Thr Lys Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Arg Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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Ala Lys Asp Ile Leu Val Thr Gly Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 230
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of ? heavy chain variable region of LC.063 (Seq ID No: 20 in WO2006/029879)

<400> SEQUENCE: 230

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ile Ile Ser Gly Ser Gly Gly Phe Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Arg Leu Arg Ala Glu Asp Thr Ala Ile Tyr Phe Cys
85 90 95

Ala Lys Asp Asp Ile Pro Ala Ala Gly Thr Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 231
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of 8E12 light chain variable region (Seq ID No: 13 in US7,812,133)

<400> SEQUENCE: 231

Asp Ile Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Gly
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp His Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Asn Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> SEQ ID NO 232
<211> LENGTH: 113

-continued

<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of 8E12 heavy chain variable region (Seq ID No: 14 in US7,812,133)

<400> SEQUENCE: 232

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Met Tyr Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Ile Pro Trp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> SEQ ID NO 233
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of 13G5 light chain variable region (Seq ID No: 15 in US7,812,133)

<400> SEQUENCE: 233

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Leu Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Val Met Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Val Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ile Arg Gly Arg Gly Asn Phe Tyr Gly Gly Ser His Ala Met Glu Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Leu Thr Val Ser Ser
115 120

<210> SEQ ID NO 234
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of 13G5 heavy chain variable region (Seq ID No: 16 in US7,812,133)

<400> SEQUENCE: 234

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Thr
1 5 10 15

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Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Trp Met His Gly Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asp Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Glu Arg Ser Pro Arg Tyr Phe Asp Val Trp Gly Ala Gly Thr
            100                 105                 110

Thr Leu Thr Val Ser Ser
        115
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The invention claimed is:

1. A method for increasing the ratio of T_{reg}:T_{conv} cells in a patient with an anti-OX40L antibody or antibody fragment that specifically binds to human OX40L (hOX40L), comprising:

a) selecting a patient with a ratio of T_{reg}:T_{conv} cells of 2:100 or less,

b) administering to the selected patient an anti-OX40L antibody or antibody fragment that specifically binds to human OX40L (hOX40L), wherein

the antibody or antibody fragment comprises:

(a) a HCDR1 amino acid sequence of SEQ ID NO: 36 or 42;

(b) a HCDR2 amino acid sequence of SEQ ID NO: 38 or 44;

(c) a HCDR3 amino acid sequence of SEQ ID NO: 40 or 46;

(d) a LCDR1 amino acid sequence of SEQ ID NO: 50 or 56;

(e) a LCDR2 amino acid sequence of AAS or SEQ ID NO: 58; and

(f) a LCDR3 amino acid sequence of SEQ ID NO: 54 or 60, wherein

T_{reg} cells are CD25+CD127−FoxP3+ and T_{conv} cells are CD25−CD127+, and wherein the patient has dermatitis.

2. The method of claim **1**, wherein the ratio of T_{reg}:T_{conv} cells in the patient is less than 1.5:100.

3. The method of claim **1**, wherein the antibody or antigen-binding fragment thereof comprises a VH amino acid sequence of SEQ ID NO: 34 and a VL amino acid sequence of SEQ ID NO: 48.

4. The method of claim **1**, wherein the antibody or antigen-binding fragment thereof further comprises a heavy chain constant region, and wherein the heavy chain constant region is IgG4-PE.

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