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### (12) United States Patent

#### Klein et al.

(54) COMBINATION THERAPY OF T CELL ACTIVATING BISPECIFIC ANTIGEN BINDING MOLECULES AND PD-1 AXIS BINDING ANTAGONISTS

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C07K 16/46	(2006.01)
A61K 39/00	(2006.01)

(52) U.S. Cl.

CPC ...... C07K 16/30 (2013.01); A61K 47/6829 (2017.08); A61K 47/6849 (2017.08); C07K 16/28 (2013.01); C07K 16/2803 (2013.01); C07K 16/2809 (2013.01); C07K 16/2818 (2013.01); C07K 16/3023 (2013.01); C07K 16/3046 (2013.01); C07K 16/3069 (2013.01); C07K 16/468 (2013.01); A61K 2039/505 (2013.01); A61K 2039/507 (2013.01); C07K 2317/21 (2013.01); C07K 2317/24 (2013.01); C07K 2317/31 (2013.01); C07K 2317/34 (2013.01); C07K 2317/35 (2013.01); C07K 2317/55 (2013.01); C07K 2317/56 (2013.01); C07K 2317/565 (2013.01); C07K 2317/73 (2013.01); C07K 2317/76 (2013.01); C07K 2317/77 (2013.01); C07K 2317/92 (2013.01); C07K 2319/55 (2013.01)

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(58) Field of Classification Search None

See application file for complete search history.

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#### (57) **ABSTRACT**

The present invention generally relates to T cell activating bispecific antigen binding molecules, PD-1 axis binding antagonists, and in particular to combination therapies employing such T cell activating bispecific antigen binding molecules and PD-1 axis binding antagonists, and their use of these combination therapies for the treatment of cancer.

#### 20 Claims, 76 Drawing Sheets (23 of 76 Drawing Sheet(s) Filed in Color)

#### Specification includes a Sequence Listing.

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Fig. 12N



Fig. 120



78



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Fig. 15C

Fig. 15B



Fig. 15A





Fig. 16F














Fig. 19G



Fig. 19H

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Fig. 21F







Fig. 21L

Fig. 21M



Fig. 21N















Fig. 23E

















Fig. 29A

Fig. 29B













Fig. 31






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PD-1

P0-1

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Fig. 35A

Fig. 35B











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Parieut-ID	Cancer type	Ristopathology	Material	Cender	Age [7]	in the second	cost [%	CD47[% ef CD37]	FolK1 <sup>-</sup> [%]	Falki
BS-160	ovatian canter	endometrioid sdenocarcinoms	piental ethaica	temale	%	369	13.2	318	10	14100
BS-164	fieng caucer	squattores celí cascinotta	pericacias effrasco	maie	11	35.2	33.2	623	33.8	1348
BS-189	hing cancer	adenocaminena	resected fumor	wsie	82	14.7	34.1	54.2		1861
BS-200	hung cancer	squaxous celi csuciaciai	resected tumor	fercale	£	49.2	31.5	57.6	9.6	
BS-202	hung cancer	uzdičerentiated carotroma	pleand effacion	aak	Ę	293	56.8	32	9.6	· · ·
BS-203	hug cancer	adenocuminena	plearal efficien	male	58	¥93	33.3	50.9	0.6	
BS-312	evanan cancer	ize.ous ademocarcinema	ascites	îemie	ŝ	382 1	2125	33.2	2.38	623
BS-314	sensi cancer	cless cell carcucons	resected tumor	ગ્રાથોલ	63	45.8	63.6	5.5	(2.9	4408
85-218	ovarian cancer	serous adenocarcinena	resected numor	female	2	36.3	777	893	513	3927
<b>B</b> S-132	hug cancer	squamous cell carcinomi	resected tumor	male	F	32.7	\$ <del>4</del> ,\$	38.1	80	335
85-245a	ovarian cancer	serons adenocarcinouus	resected fumore	temale	67	262	26.8	66.3	20.4	7886
85-240	renzi cancer	ciear cell carrinoma	pleural ethason	female	52 22	ۍ به م	28.5	50.1	6 ê	•
85-254	hing, caucar	súenoc arcinoms	resected framer	જાર્શક	63	£73	~ I†	6 St	96	8786
B5-264a	ovstian cancer	serous adence arcmoma	iesected francos	temale	ŧ,	543	43.7	₹.tt	2 B	Тас Ма
BS-268	hing caucar	s denocarcinomo	tesected framos	msiæ	63	30.3	51.6	43 3	63	10463
BS-269	inng cancer	sdenocarcinoms	resected framos	aisis	61	9 I.T	42 E	465	22	1136
85-274	hing cases	NOS	resected framor	maie	31	63	425	475	00	
85-275	hmg caucar	equaments cell exicinente	tesented humos	temale	z	564	-18 3	43 7	9.0	•
BS-279	heng caecer	large cell csscinoma	tesected frames	msie	ŝ	513	* 0†	50 S	03	33,8
BS-180	भाराह एडाएस	stienocarciusma.	pierrai effusioa	temale	09	785 785	308	703	ф.;	41.8
85-293	irmş cancar	squamous celà carcinentia	tesected hance	maie	67	81 S	606	28 S	03	813
<b>BS-299</b>	hug cancer	zdeuocaniacana	piearal efficion	aaik	\$\$	38.5	13.8	73	9.0	ł
BS-300	भव्वद्र रभ्वटल	adenocaminenas	resected namor	waie	74	575	25.7	69.5	0.4	5945
BS-301	evarian cancer	tetous silenovarciuenta	pierrai ettucion	temile	73	813	114	80.7	6 SZ	1045
BS-303	warian cancer	tercus adenocarrincena	piezzi efinion	female	ŝ	21	32.7	62.7	\$°\$	S053

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# COMBINATION THERAPY OF T CELL ACTIVATING BISPECIFIC ANTIGEN BINDING MOLECULES AND PD-1 AXIS BINDING ANTAGONISTS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/EP2015/076682, Publication No. WO2016/<sup>10</sup> 079050, filed Nov. 16, 2015, which claims priority to European Patent Application No. 14194136.9 filed Nov. 20, 2014, European Patent Application No. 15152141.6 filed Jan. 22, 2015, and European Patent Application No. 15167173.2 filed May 11, 2015, the disclosures of which are <sup>15</sup> incorporated herein by reference in their entirety.

## SEQUENCE LISTING

The instant application contains a Sequence Listing which <sup>20</sup> has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety.

Said ASCII copy, created on May 18, 2017, is named P32401US\_ST25.txt and is 527,186 bytes in size.

### FIELD OF THE INVENTION

The present invention relates to combination therapies employing T cell activating bispecific antigen binding molecule and a PD-1 axis binding antagonist, and, optionally, a <sup>30</sup> TIM3 antagonist, and the use of these combination therapies for the treatment of cancer.

#### BACKGROUND

Monoclonal antibodies are powerful therapeutic agents for the treatment of cancer that selectively target antigens which are differentially expressed on cancer cells.

Bispecific antibodies designed to bind with one antigen binding moiety to a surface antigen on target cells, and with 40 the second antigen binding moiety to an activating, invariant component of the T cell receptor (TCR) complex, have become of interest in recent years. The simultaneous binding of such an antibody to both of its targets will force a temporary interaction between target cell and T cell, causing 45 activation of any cytotoxic T cell and subsequent lysis of the target cell. Hence, the immune response is re-directed to the target cells and is independent of peptide antigen presentation by the target cell or the specificity of the T cell as would be relevant for normal MHC-restricted activation of CTLs. 50 In this context it is crucial that CTLs are only activated when a target cell is presenting the bispecific antibody to them, i.e., the immunological synapse is mimicked. Particularly desirable are bispecific antibodies that do not require lymphocyte preconditioning or co-stimulation in order to elicit 55 efficient lysis of target cells. It is not well understood how TCBs affect the T cell itself beyond activation of certain effector function.

Activation of resting T lymphocytes, or T cells, by antigen-presenting cells (APCs) appears to require two signal 60 inputs. Lafferty et al, Aust. J. Exp. Biol. Med. ScL 53: 27-42 (1975). The primary, or antigen specific, signal is transduced through the T-cell receptor (TCR) following recognition of foreign antigen peptide presented in the context of the major histocompatibility-complex (MHC). The second, or 65 co-stimulatory, signal is delivered to T-cells by co-stimulatory molecules expressed on antigen-presenting cells

(APCs), and promotes T-cell clonal expansion, cytokine secretion and effector function. Lenschow et al., Ann. Rev. Immunol. 14:233 (1996). In the absence of co-stimulation, T cells can become refractory to antigen stimulation, do not mount an effective immune response, and may result in exhaustion or tolerance to foreign antigens.

T cells can receive both positive and negative secondary co-stimulatory signals. The balance of positive and negative signals is important to elicit effective immune responses, while maintaining immune tolerance and preventing autoimmunity. Negative secondary signals appear necessary for induction of T-cell tolerance, while positive signals promote T cell activation.

 Recently, it has been discovered that T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1). One of its ligands, PD-L1 is overexpressed in many cancers and is often associated with poor
 prognosis (Okazaki T et al., Intern. Immun. 2007 19(7):813) (Thompson R H et al., Cancer Res 2006, 66(7):3381). Interestingly, the majority of tumor infiltrating T lymphocytes predominantly express PD-1, in contrast to T lymphocytes in normal tissues and peripheral blood T lymphocytes
 indicating that up-regulation of PD-1 on tumor-reactive T cells can contribute to impaired antitumor immune responses (Blood 2009 1 14(8): 1537).

T cell Immunoglobulin- and Mucin domain-containing molecule 3 (TIM3), is important in immune regulation. This cell surface protein is expressed, preferentially, by type 1 T helper cells and has been implicated in the regulation of macrophage activation, inflammatory conditions and cancer (Majeti R et al., PNAS, 106 (2009) 3396-3401 and WO2009/091547). Binding of TIM-3 to one of its ligands (e.g., galectin-9) can suppress the Th1 response by inducing programmed cell death, thereby supporting peripheral tolerance. Treatment with TIM-3 siRNA or with an anti-TIM-3 antagonist antibody increases secretion of interferon alpha from CD4 positive T-cells, supporting the inhibitory role of TIM-3 in human T cells. Examples of the anti-TIM-3 monoclonal antibodies include are disclosed in WO2013/ 06490 and US2012/189617 (Ngiow et al., Cancer Res 7:6567 (2011)).

FOLR1 is expressed on tumor cells of various origins, e.g., ovarian and lung cancer. Several approaches to target FOLR1 with therapeutic antibodies, such as farletuzumab, antibody drug conjugates, or adoptive T cell therapy for imaging of tumors have been described (Kandalaft et al., J Transl Med. 2012 Aug. 3; 10:157. doi: 10.1186/1479-5876-10-157; van Dam et al., Nat Med. 2011 Sep. 18; 17(10): 1315-9. doi: 10.1038/nm.2472; Clifton et al., Hum Vaccin. 2011 February; 7(2):183-90. Epub 2011 Feb. 1; Kelemen et al., Int J Cancer. 2006 Jul. 15; 119(2):243-50; Vaitilingam et al., J Nucl Med. 2012 July; 53(7); Teng et al., 2012 August; 9(8):901-8. doi: 10.1517/17425247.2012.694863. Epub 2012 Jun. 5. Some attempts have been made to target folate receptor-positive tumors with constructs that target the folate receptor and CD3 (Kranz et al., Proc Natl Acad Sci USA. Sep. 26, 1995; 92(20): 9057-9061; Roy et al., Adv Drug Deliv Rev. 2004 Apr. 29; 56(8):1219-31; Huiting Cui et al Biol Chem. Aug. 17, 2012; 287(34): 28206-28214; Lamers et al., Int. J. Cancer. 60(4):450 (1995); Thompson et al., MAbs. 2009 July-August; 1(4):348-56. Epub 2009 Jul. 19; Mezzanzanca et al., Int. J. Cancer, 41, 609-615 (1988).

There remains a need for such an optimal therapy for treating, stabilizing, preventing, and/or delaying development of various cancers.

## SUMMARY

Broadly, the present invention relates to bispecific antibodies combining a Folate Receptor 1 (FolR1) targeting antigen binding site with a second antigen binding site that 5 targets CD3 and their use in combination with a PD-1 axis binding antagonist, e.g., for the treatment of cancer. In one embodiment, the combination further comprises a TIM3 antagonist. The methods and combinations of the present invention enable enhanced immunotherapy. The advantage 10 over conventional treatment is the specificity of inducing T cell activation only at the site where FolR1 is expressed as well as the reduction and/or reversal of low T cell mediated activity also termed T cell exhaustion due to the combination with a PD-1 axis binding antagonist, and, optionally, a TIM3 15 antagonist.

Accordingly, in one aspect, the present invention provides a method for treating or delaying progression of a cancer in an individual comprising administering to the individual an effective amount of a T cell activating bispecific antigen 20 binding molecule and a PD-1 axis binding antagonist. In one embodiment, the T cell activating bispecific antigen binding molecule comprises a first antigen binding moiety capable of specific binding to CD3 and a second antigen binding moiety capable of specific binding to Folate Receptor 1 25 (FolR1). In one embodiment, the first antigen binding moiety comprises at least one heavy chain complementarity determining region (CDR) amino acid sequence selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR 30 selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34. In one embodiment, the first antigen binding moiety comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID 35 human tumor cell in vitro. NO: 31. In one embodiment, the T cell activating bispecific antigen binding molecule further comprises a third antigen binding moiety capable of specific binding to FolR1. In one embodiment, the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical 40 heavy chain complementarity determining region (CDR) and light chain CDR sequences. In one embodiment, the third antigen binding moiety is identical to the second antigen binding moiety. In one embodiment, at least one of the first, second and third antigen binding moiety is a Fab 45 molecule.

In one embodiment, the antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprises at least one heavy chain complementarity determining region (CDR) amino acid sequence selected from the group 50 consisting of SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34. In one embodiment, the antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprises a 55 variable heavy chain comprising an amino acid sequence of SEQ ID NO: 15 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31. In one embodiment, the antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprises at least one heavy 60 chain complementarity determining region (CDR) amino acid sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 56 and SEQ ID NO: 57 and at least one light chain CDR selected from the group of SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 65. In one embodiment, the 65 antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprises a variable heavy chain com-

prising an amino acid sequence of SEQ ID NO: 55 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 64. In one embodiment, the antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprises at least one heavy chain complementarity determining region (CDR) amino acid sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 50 and at least one light chain CDR selected from the group of SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54. In one embodiment, the antigen binding moiety capable of specific binding to FolR1 comprises:

a) a complementarity determining region heavy chain 1 (CDR-H1) amino acid sequences of SEQ ID NO: 8;

(b) a CDR-H2 amino acid sequence of SEQ ID NO: 9;

(c) a CDR-H3 amino acid sequence of SEQ ID NO: 50;

(d) a complementarity determining region light chain 1 (CDR-L1) amino acid sequence of SEQ ID NO: 52;

(e) a CDR-L2 amino acid sequence of SEQ ID NO: 53, and

(f) a CDR-L3 amino acid sequence of SEQ ID NO: 54. In one such embodiment, the antigen binding moiety capable of specific binding to FolR1 comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 49 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 51.

In one embodiment, the T cell activating bispecific antigen binding molecule binds to a human FolR1, a cynomolgus monkey FolR1 and a murine FolR1.

In one embodiment, the T cell activating bispecific antigen binding molecule induces proliferation of a human CD3 positive T cell in vitro.

In one embodiment, the T cell activating bispecific antigen binding molecule induces human peripheral blood mononuclear cell mediated killing of a FolR1-expressing human tumor cell in vitro.

In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of a FolR1-expressing human tumor cell in vitro. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of the FolR1-expressing human tumor cell in vitro with an EC50 of between about 36 pM and about 39573 pM after 24 hours. In one embodiment, the T cell activating bispecific antigen binding molecule induces upregulation of cell surface expression of at least one of CD25 and CD69 on the T cell as measured by flow cytometry. In one embodiment, the T cell activating bispecific antigen binding molecule binds human FolR1 with an apparent  $K_D$  of about 5.36 pM to about 4 nM. In one embodiment, the T cell activating bispecific antigen binding molecule binds human and cynomolgus FolR1 with an apparent K<sub>D</sub> of about 4 nM. In one embodiment, the T cell activating bispecific antigen binding molecule hinds murine FolR1 with an apparent  $K_D$  of about 1.5 nM. In one embodiment, the T cell activating bispecific antigen binding molecule binds human FolR1 with a monovalent binding  $K_D$ of at least about 1000 nM. In one embodiment, the T cell activating bispecific antigen binding molecule binds to FolR1 expressed on a human tumor cell. In one embodiment, the T cell activating bispecific antigen binding molecule binds to a conformational epitope on human FolR1. In one embodiment, the T cell activating bispecific antigen binding molecule does not bind to human Folate Receptor 2 (FolR2) or to human Folate Receptor 3 (FolR3). In one embodiment, the antigen binding moiety binds to a FolR1 polypeptide comprising the amino acids 25 to 234 of human FolR1 (SEQ ID NO:227). In one embodiment, the FolR1 antigen binding moiety binds to a FolR1 polypeptide comprising the amino acid sequence of SEQ ID NOs:227, 230 and 231, and wherein the FolR1 antigen binding moiety does not bind to a FolR polypeptide comprising the amino acid sequence of SEQ ID NOs:228 and 229. In one embodiment, the T cell activating bispecific antigen binding molecule 5 comprises a) a first antigen-binding site that competes for binding to human FolR1 with a reference antibody comprising a variable heavy chain domain (VH) of SEQ ID NO: 49 and a variable light chain domain of SEQ ID NO: 51; and b) a second antigen-binding site that competes for binding to human CD3 with a reference antibody comprising a variable heavy chain domain (VH) of SEQ ID NO: 36 and a variable light chain domain of SEQ ID NO: 31, wherein binding competition is measured using a surface plasmon resonance assay. 15

In one embodiment, the T cell activating bispecific antigen binding molecule comprises a first, a second, a third, a fourth and a fifth polypeptide chain that form a first, a second and a third antigen binding moiety, wherein the first antigen binding moiety is capable of binding CD3 and the second 20 and the third antigen binding moiety each are capable of binding Folate Receptor 1 (FolR1), wherein a) the first and the second polypeptide chain comprise, in amino (N)-terminal to carboxyl (C)-terminal direction, VLD1 and CLD1; b) the third polypeptide chain comprises, in N-terminal to 25 C-terminal direction, VLD2 and CH1D2; c) the fourth polypeptide chain comprises, in N-terminal direction, VHD1, CH2D1 and CH3D1; d) the fifth polypeptide chain comprises VHD1, CH1D1, VHD2, CLD2, CH2D2 and CH3D2; wherein 30

VLD1 is a first light chain variable domain

VLD2 is a second light chain variable domain

- CLD1 is a first light chain constant domain
- CLD2 is a second light chain constant domain
- VHD1 is a first heavy chain variable domain
- VHD2 is a second heavy chain variable domain
- CH1D1 is a first heavy chain constant domain 1
- CH1D2 is a second heavy chain constant domain 1
- CH2D1 is a first heavy chain constant domain 2
- CH2D2 is a second heavy chain constant domain 2
- CH3D1 is a first heavy chain constant domain 3
- CH3D2 is a second heavy chain constant domain 3. In one such embodiment,
- a. the third polypeptide chain and VHD2 and CLD2 of the fifth polypeptide chain form the first antigen binding 45 moiety capable of binding CD3;
- b. the first polypeptide chain and VHD1 and CH1D1 of the fourth polypeptide chain form the second binding moiety capable of binding to FolR1; and
- c. the second polypeptide chain and VHD1 and CH1D1 of 50 the fifth polypeptide chain form the third binding moiety capable of binding to FolR1.

In one such embodiment, the first and second polypeptide chain comprise the amino acid sequence of SEQ ID NO:399. In one such embodiment, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:86. In one such embodiment, the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:394. In one such embodiment, the fifth polypeptide chain comprises the amino acid sequence of SEQ ID NO:397. In one embodiment. PD-1 antibody is a monoclonal antibody. In some embodiments, the anti-PD-1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragments. In some embodiments, PD-1 binding antagonist is nivolumab, pembrolizumab, CT-011, or AMP-224. In some embodiments, the PD-1 axis binding antagonist is a PDL1 binding antagonist. In some embodiments, the PDL1 binding antagonist inhibits the binding of PDL1 to

- a. the first and second polypeptide chain comprise the amino acid sequence of SEQ ID NO:399;
- b. the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:86;

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c. the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:394; and

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 d. the fifth polypeptide chain comprise the amino acid sequence of SEQ ID NO:397.

In some embodiments, the bispecific antibody is bivalent both for FolR1 and CD3.

In some embodiments, the bispecific antibody comprises one or more Fab fragment(s) comprising an antigen binding site specific for CD3, wherein the variable regions or the constant regions of the heavy and light chain are exchanged.

In some embodiments, the bispecific antibody comprises 10 an Fc domain, at least one Fab fragment comprising the antigen binding site specific for FoIR1, and at least one Fab fragment comprising the antigen binding site specific for CD3 wherein either the variable regions or the constant regions of the heavy and light chain of at least one Fab 15 fragment are exchanged.

- In some embodiments, the bispecific antibody comprises: a) an Fc domain,
- b) a first and second Fab fragment each comprising an antigen binding site specific for FolR1,
- c) a third Fab fragment comprising an antigen binding site specific for CD3, wherein the third Fab fragment is connected at the C-terminus of the variable heavy chain (VH) to the second subunit of the Fc domain and wherein the third Fab fragment is connected at the N-terminus of the variable heavy chain to the C-terminus of the second Fab fragment.

In one embodiment at least one of said Fab fragments is connected to the Fc domain via a peptide linker.

In one embodiment said bispecific antibody comprises an 30 Fc domain, which comprises one or more amino acid substitution that reduces binding to Fc receptors and/or effector function. In one embodiment said one or more amino acid substitution is at one or more positions selected from the group of L234, L235, and P329. In one embodi-

35 ment each subunit of the Fc domain comprises three amino acid substitutions that abolish binding to an activating or inhibitory Fc receptor and/or effector function wherein said amino acid substitutions are L234A, L235A and P329G.

In some embodiments, the PD-1 axis binding antagonist 40 is selected from the group consisting of a PD-1 binding antagonist, a PDL1 binding antagonist and a PDL2 binding antagonist.

In some embodiments, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2. In some embodiments, PD-1 binding antagonist is an antibody. In some embodiments, the anti-PD-1 antibody is a monoclonal antibody. In some embodiments, the anti-PD-1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragments. In some embodiments, PD-1 binding antagonist is nivolumab, pembrolizumab, CT-011, or AMP-224.

In some embodiments, the PD-1 axis binding antagonist is a PDL1 binding antagonist. In some embodiments, the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1. In some embodiments, the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1. In some embodiments, the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1. In some embodiments, the PDL1 binding antagonist is an anti-PDL1 antibody. In some embodiments, the anti-PDL1 antibody is a monoclonal

antibody. In some embodiments, the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragments. In some embodiments, the anti-PDL1 antibody is a humanized antibody or a human antibody. In some embodiments, the PDL1 5 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

In some embodiments, the anti-PDL1 antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID 10 NO:289, HVR-H2 sequence of SEQ ID NO:290, and HVR-H3 sequence of SEQ ID NO:291; and a light chain comprising HVR-L1 sequence of SEQ ID NO:292, HVR-L2 sequence of SEQ ID NO:293, and HVR-L3 sequence of SEQ ID NO:294. In some embodiments, anti-PDL1 anti- 15 body comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:280 or SEQ ID NO:281 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:383. In some embodiments, the anti-PDL1 antibody comprises a heavy chain 20 comprising the amino acid sequence of SEQ ID NO:278 and/or a light chain comprising the amino acid sequence of SEQ ID NO:279.

In some embodiments, the PD-1 axis binding antagonist is a PDL2 binding antagonist. In some embodiments, PDL2 25 binding antagonist is an antibody. In some embodiments, the anti-PDL2 antibody is a monoclonal antibody. In some embodiments, the anti-PDL2 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragments. In some embodiments, PDL2 30 binding antagonist is an immunoadhesin.

In one embodiment, the method of any of the above embodiments further comprises administering to the individual a T cell immunoglobulin mucin 3 (TIM3) antagonist. In one embodiment, the TIM3 antagonist is an anti-TIM3 35 antibody. In one embodiment, the anti-TIM3 antibody induces internalization of TIM3 on a TIM3 expressing cell of at least 45% after 120 Minutes at 37° C. wherein internalization is measured by FACS analysis. In one embodiment, the anti-TIM3 antibody has one or more of the 40 following properties:

- a) competes for binding to TIM3 with an anti-Tim3 antibody comprising the VH of SEQ ID NO:7 and VL of of SEQ ID NO: 8
- b) binds to a human and cynomolgoues TIM3
- c) shows as immunoconjugate a cytotoxic activity on TIM3 expressing cells
- d) induces interferon-gamma release.

In one embodiment, the anti-TIM3 antibody has one or more of the following properties: 50

- a. competes for binding to TIM3 with an anti-Tim3 antibody comprising the VH of SEQ ID NO:7 and VL of of SEQ ID NO: 8
- b. binds to a human and cynomolgoues TIM3
- c. shows as immunoconjugate a cytotoxic activity on 55 TIM3 expressing cells
- d. induces interferon-gamma release.

In one embodiment, the anti-TIM3 antibody is a monoclonal antibody. In one embodiment, the anti-TIM3 antibody is a human, humanized, or chimeric antibody. In one 60 embodiment, the anti-TIM3 antibody is an antibody fragment that binds to TIM3. In one embodiment, the anti-TIM3 antibody is Fab fragment. In one embodiment, the anti-TIM3 antibody comprises:

 A) (a) a VH domain comprising (i) HVR-H1 comprising 65 the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:307; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309; or

- B) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:314; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309; or
- C) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ 1D NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:315; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309; or
- D) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:316, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:317, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:318; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:319; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:320 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:321; or
- E) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:324, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:325, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:326; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:327; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:328 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:329; or.
- F) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:332, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:333, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:334; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:335; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:336 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:337; or
- G) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:340, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:341, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:342; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:343; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:344 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:345; or

- H) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:348, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:349, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:350; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:351; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:352 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:353; or
- I) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:356, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:357, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:358; and (b) 15 a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:359; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:360 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:361; or 20
- J) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:364, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:365, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:366; and (b) 25 a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:367; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:368 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:369. 30

In one embodiment, the anti-TIM3 antibody is a full length  $IgG_1$  antibody with mutations S228P, L235E and P329G according to the EU index of Kabat numbering. In one embodiment, the anti-TIM3 antibody is any one of the antibodies described in WO 2011/155607, WO 2013/ 35 006490, WO 03/063792, WO 2009/097394, and WO 2011/ 159877. In one embodiment, the anti-TIM3 antibody is F38-2E2.

In one embodiment, the cancer contains a KRAS wildtype. In one embodiment, the cancer contains an activating 40 KRAS mutation.

In one embodiment, the treatment results in a sustained response in the individual after cessation of the treatment. In one embodiment, at least one of the T cell activating bispecific antigen binding molecule and the PD-1 axis 45 binding antagonist is administered continuously. In one embodiment, at least one of the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist is administered intermittently. In one embodiment, the PD-1 axis binding antagonist is administered before the 50 FolR1 TCB. In one embodiment, the PD-1 axis binding antagonist is administered simultaneous with the FolR1 TCB. In one embodiment, the PD-1 axis binding antagonist is administered after the FolR1 TCB. In one embodiment, the cancer is selected from the group consisting of ovarian 55 cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer. In one embodiment, at least one of the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist is administered intravenously, intramuscularly, subcutaneously, topically, orally, 60 transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

In one embodiment, T cells in the individual have enhanced activation, proliferation and/or effector function 65 relative to prior to the administration of the combination. In one embodiment, T cells in the individual have enhanced 10

activation, proliferation and/or effector function relative to administration of the T cell activating bispecific antigen binding molecule alone. In one embodiment, T cell effector function is secretion of at least one of IL-2, IFN- $\gamma$  and TNF- $\alpha$ . In one embodiment, the individual comprises less than about 15% PD-1<sup>hi</sup> expressing tumor-infiltrating T cells.

In one aspect, the invention provides for a method of enhancing immune function in an individual having a FolR1 positive cancer comprising administering to the individual an effective amount of a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a PD-1 axis binding antagonist. In one embodiment, T cells in the individual have enhanced activation, proliferation and/or effector function relative to prior to the administration of the combination. In one embodiment, T cells in the individual have enhanced activation, proliferation and/or effector function relative to administration of the T cell activating bispecific antigen binding molecule alone. In one embodiment, T cell o effector function is secretion of at least one of IL-2, IFN-γ and TNF-α.

In one embodiment, the individual comprises less than about 15%  $PD-1^{int}$  expressing tumor-infiltrating T cells.

In another aspect, the invention provides for a method for selecting a patient for treatment with a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a PD-1 axis binding antagonist comprising measuring the level of PD-1 expression, wherein a patient having less than about 15% PD-1<sup>*ht*</sup> expressing T cells is selected for treatment with the combination.

In another aspect, the invention provides for a kit comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a package insert comprising instructions for using the T cell activating bispecific antigen binding molecule with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual. In one embodiment, the kit further comprises instructions for using the T cell activating bispecific antigen binding molecule with a TIM3 antagonist.

In another aspect, the invention provides for a kit comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 and a PD-1 axis binding antagonist, and a package insert comprising instructions for using the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist to treat or delay progression of cancer in an individual. In one embodiment, the kit further comprises a TIM3 antagonist. In one embodiment, the PD-1 axis binding antagonist is an anti-PD-1 antibody or an anti-PDL-1 antibody. In one embodiment, the PD-1 axis binding antagonist is an anti-PD-1 immunoadhesin.

In another aspect, the invention provides for a pharmaceutical composition comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, a PD-1 axis binding antagonist and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition further comprises a TIM3 antagonist.

In another aspect, the invention provides for a use of a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 and a PD-1 axis binding antagonist in the manufacture of a medicament for the treatment of cancer. In one embodiment, the medicament is for treatment of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer.

In certain embodiments of all aspects of the present invention, advantageously said T cell activating bispecific antigen binding molecule and/or PD-1 axis binding antagonist is human or humanized.

In some embodiments, the bispecific antibody comprises 5 an Fc domain, at least one Fab fragment comprising the antigen binding site specific for FolR1, and at least one Fab fragment comprising the antigen binding site specific for CD3.

In one aspect, the invention provides for a method for 10 treating or delaying progression of a cancer in an individual comprising administering to the individual an effective amount of a T cell activating bispecific antigen binding molecule and a TIM3 antagonist. In some embodiments, the T cell activating bispecific antigen binding molecule com- 15 prises an Fc domain, two Fab fragments comprising each an antigen binding site specific for FolR1, and one Fab fragment comprising an antigen binding site specific for CD3.

In a further aspect, the present invention provides the use of a combination of a T cell activating bispecific antigen 20 binding molecule that binds to FoIR1 and CD3, and a PD-1 axis binding antagonist in the manufacture of a medicament for the treatment of cancer.

In a further aspect, the present invention provides the use of a combination of a T cell activating bispecific antigen 25 binding molecule that binds to FolR1 and CD3, a PD-1 axis binding antagonist and a TIM3 antagonist in the manufacture of a medicament for the treatment of cancer.

Embodiments of the present invention will now be described by way of example and not limitation with refer- 30 ence to the accompanying figures. However various further aspects and embodiments of the present invention will be apparent to those skilled in the art in view of the present disclosure.

disclosure of each of the two specified features or components with or without the other. For example "A and/or B" is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein.

Unless context dictates otherwise, the descriptions and 40 definitions of the features set out above are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments which are described.

### BRIEF DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIGS. 1A-I illustrate exemplary configurations of the T cell activating bispecific antigen binding molecules (TCBs) of the invention. All constructs except the kappa-lambda format in (FIG. 1I) have P329G LALA mutations and comprise knob-into-hole Fc fragments with knob-into-hole 55 IgGs to cells with different FolR1 expression levels. Binding modifications. (FIG. 1A) Illustration of the "FolR1 TCB 2+1 inverted (common light chain)". The FolR1 binder is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain comprising the knob modification. These constructs are not crossed and have 60 three times the same VLCL light chain. (FIG. 1B) Illustration of the "FolR1 TCB 1+1 head-to-tail (common light chain)". These constructs are not crossed and have two times the same VLCL light chain. (FIG. 1C) Illustration of the "FolR1 TCB 1+1 classical (common light chain)". These 65 constructs are not crossed and have two times the same VLCL light chain. (FIG. 1D) Illustration of the "FolR1TCB

2+1 classical (common light chain)". The CD3 binder is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain comprising the knob modification. These constructs are not crossed and have three times the same VLCL light chain. (FIG. 1E) Illustration of the "FolR1 TCB 2+1 crossfab classical". These constructs comprise a Ck-VH chain for the CD3 binder instead of the conventional CH1-VH chain. The CD3 binder is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain comprising the knob modification. (FIG. 1F) Illustration of the "FolR1 TCB 2+1 crossfab inverted". These constructs comprise a Ck-VH chain for the CD3 binder instead of the conventional CH1-VH chain. The FolR1 binder is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain comprising the knob modification. (FIG. 1G) Illustration of the "FolR1 TCB 1+1 crossfab head-to-tail". These constructs comprise a Ck-VH chain for the CD3 binder instead of the conventional CH1-VH chain. (FIG. 1H) Illustration of the "FolR1 TCB 1+1 crossfab classical". These constructs comprise a Ck-VH chain for the CD3 hinder instead of the conventional CH1-VH chain. FIG. 1I illustrates the CD3/FolR1 kappa-lambda antibody format. These constructs comprise a crossed common light chain VLCH1 and one crossed VHCL chain specific for CD3 and one crossed VHCL chain specific for FolR1.

FIGS. 2A-C depict graphs summarizing Binding of FoLR1 IgG binders to HeLa cells. Binding of newly generated FolR1 binders to FolR1 expressed on HeLa cells were determined by flow cytometry. Bound antibodies were detected with a fluorescently labeled anti-human secondary antibody.

FIGS. 3A-B depict graphs summarizing specificity of 'and/or" where used herein is to be taken as specific 35 FolR1 binders for FolR1. Binding of FolR1 IgGs to HEK cells transiently transfected with either FolR1 or FolR2 was analyzed by flow cytometry to identify clones which bind specifically to FolR1 and not to FolR2. The antibodies were detected with a fluorescently labeled anti-human secondary antibody.

> FIGS. 4A-B depict graphs summarizing cross-reactivity of FolR1 binders to cyFoLR1. Cross-reactivity of the FolR1 antibodies to cyno FolR1 was addressed on HEK cells transiently transfected with cyFolR1 by flow cytometry. The antibodies were detected with a fluorescently labeled antihuman secondary antibody.

FIG. 5 depicts a graph illustrating internalization of FolR1 TCBs after binding. Internalization of the four FolR1 TCBs after binding to FolR1 was tested on HeLa cells. Remaining 50 FolR1 TCBs on the surface were detected with a fluorescently labeled anti-human secondary antibody after indicated time points of incubation at 37° C. Percentage of internalization was calculated.

FIGS. 6A-E depict graphs summarizing binding of FolR1 of 9D11, 16D5 and Mov19 IgG to tumor cells with different FolR1 expression levels was analyzed by flow cytometry. DP47 IgG was included as isotype control and MKN-45 were included as FolR1 negative cell line. The antibodies were detected with a fluorescently labeled anti-human secondary antibody.

FIGS. 7A-L depict graphs summarizing T cell mediated killing of HT-29 and SKOV3 cells. FolR1 TCBs were used to test T cell mediated killing of HT-29 and SKOV3 tumor cells and upregulation of activation marker on T cells upon killing. (FIGS. 7A-D) T cell mediated killing of HT-29 and SKOV3 cells in the presence of 9D11 FolR1 TCB and 16D5

FolR1 TCB was measured by LDH release after 24 h and 48 h. DP47 TCB was included as negative control. After 48 h incubation upregulation of the activation marker CD25 and CD69 on CD8 T cells and CD4 T cells upon killing of SKOV3 (FIGS. 7E-H) or HT-29 (FIG. 7I-L) tumor cells was 5 assessed by flow cytometry.

FIG. **8** depicts a graph showing absence of anti-FolR1 binding to erythrocytes. Erythrocytes were gated as CD235a positive population and binding of 9D11 IgG, 16D5 IgG, Mov19 IgG and DP47 IgG to this population was deter- 10 mined by flow cytometry. The antibodies were detected with a fluorescently labeled anti-human secondary antibody.

FIGS. **9**A-D depict graphs summarizing activation marker upregulation in whole blood. CD25 and CD69 activation marker upregulation of CD4 T cells and CD8 T cells 24 h 15 after addition of 9D11 FolR1 TCB, 16D5 FolR1 TCB, Mov19 FolR1 TCB and DP47 TCB was analyzed by flow cytometry.

FIGS. **10**A-C depict T-cell killing induced by 36F2 TCB, 16D5 TCB, 16D5 TCB classical, 16D5 TCB 1+1 and 16D5 20 TCB HT of Hela (high FolR1) (FIG. **24**A), Skov-3 (medium FolR1) (FIG. **24**B) and HT-29 (low FolR1) (FIG. **24**C) human tumor cells (E:T=10:1, effectors human PBMCs, incubation time 24 h). DP47 TCB was included as non-binding control. 25

FIGS. **11**A-B show expression of inhibitory receptors on tumor-infiltrating T cells. CD8<sup>+</sup> and CD4<sup>+</sup> T cells in tumor samples were characterized by flow cytometry for their expression of inhibitory receptors.

FIGS. 12A-O show activation of CD8<sup>+</sup> T cells in tumor 30 digests and malignant effusions upon exposure to FolR1-TCB. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FolR1-TCB or the control TCB DP-47. The expression of activation markers or markers of T cell function on CD8+ T cells was determined 35 by flow cytometry (FIG. 12A-M). FIG. 12J-K show representative FACS plots showing FolR1-TCB-induced T cell activation in a high responding (BS-269) or a low responding patient (BS-212). FIG. 12L depicts FACS plots showing FolR1-TCB-induced activation marker expression in T cells 40 from a representative patient. The graphs in FIG. 12M depict the increase in marker expression after FolR1-TCB treatment with mean and standard deviations. As comparison, PBMC from healthy donors were co-cultured with the Skov3 tumor cell line and stimulated with FolR1-TCB. FIG. 45 12N depicts IFN-γ, IL-2, TNF and perforin in the cell culture supernatants as determined by Cytometric Bead Array or ELISA and normalized to the amount of  $1 \times 10^5$  CD3<sup>+</sup> T-cells (IFN-γ, TNF, IL-2) or CD3+CD8<sup>+</sup> T-cells (perforin) in the culture. FIG. 12O shows that FolR1-TCB-induced tumor 50 cell killing varies largely in tumor digests and malignant effusions. FolR1 positive and negative tumor digests, malignant effusions or PBMCs from healthy donors were cocultured with exogenously added fluorescently labeled FolR1<sup>+</sup> Skov3 cells at an E:T ratio of 1:1 for 24 h in the 55 presence or absence of FolR1-TCB. The FolR1-TCB-induced specific killing of the Skov3 cells was determined by flow cytometry by measuring activated caspase 3 and the live/dead marker LIVE/DEAD®-near-IR. FolR1-TCB-mediated killing was calculated as follows: % specific kill- 60 ing=100-[(% of Skov3 live cells in FolR1-TCB treated sample/% of Skov3 live cells in untreated sample)×100]. FACS plots show FolR1-TCB-induced killing in a representative patient. The p-values were calculated using the unpaired Mann-Whitney test.

FIGS. **13**A-C show that FolR1-TCB-induced T cell activation shows no correlation with E:T ratio (FIG. **13**A) or the

amount of FolR1<sup>+</sup> tumor cells (FIG. **13**B). Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FolR1-TCB. The FolR1-TCB induced expression of CD25 was correlated to E:T ratio or the amount of target cells. MFI: mean fluorescence intensity.

FIGS. **14**A-L show FolR1-TCB induced T cell activation inversely correlates with expression of PD-1 and Tim-3. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FolR1-TCB. The expression of activation markers or markers of T cell function on CD8<sup>+</sup> T cells was determined by flow cytometry. The FolR1-TCB induced expression of CD25 (FIG. **4**A-C), CD137 (FIG. **14**D-F), ICOS (FIGS. **14**G-I) and granzyme B (FIGS. **14**J-L) was correlated to baseline single- or co-expression of the inhibitory receptors PD-1 and Tim-3.

FIGS. **15**A-C show FolR1-TCB induced IL-2 secretion inversely correlates with co-expression of PD-1 and Tim-3. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FolR1 TCB. IL-2 in the cell culture supernatants was determined by ELISA and normalized to the amount of T cells. The FolR1 TCB induced IL-2 secretion was correlated to baseline single- or co-expression of the inhibitory receptors PD-1 and Tim-3.

FIGS. 16A-F show FolR1-TCB induced tumor cell killing
inversely correlates with co-expression of PD-1 and Tim-3. Tumor digests or malignant effusions were co-cultured with exogenously added fluorescence labelled Skov3 cells at a T cell to target cell ratio of 1:1 for 24 h in the presence or absence of FolR1 TCB. The FolR1-TCB specific killing of
the Skov3 cells was determined by flow cytometry by measuring activated caspase 3 and the live/dead marker Live/Dead-near-IR. The specific killing was correlated to baseline single or co-expression of the inhibitory receptors PD-1, Tim-3 and CTLA-4.

FIGS. **17**A-H show activation of tumor-infiltrating CD8<sup>+</sup> T cells upon exposure to catumaxomab. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of catumaxomab. (FIG. **17**A-D) The expression of activation markers or markers of T cell function on CD8<sup>+</sup> T cells was determined by flow cytometry. (FIG. **17**E-H) Graphs showing the baseline expression of inhibitory receptors.

FIGS. **18**A-R show Catumaxomab-induced T cell activation inversely correlates with co-expression of inhibitory receptors. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of catumaxomab. T cell activation and effector functions were correlated to the expression of PD-1 (FIG. **18**A-F), Tim-**3** (FIG. **18**G-L) or of the combination of PD-1 and Tim-**3** (FIG. **18**M-R).

FIGS. **19**A-H show expression of inhibitory receptors on tumor-infiltrating T cells in Non-small cell lung cancer patients. CD8+ and CD4<sup>+</sup> T cells in tumor samples were characterized by flow cytometry for their expression of inhibitory receptors (FIG. **19**A-F).

FIG. **19**G shows the gating strategy for one representative donor. FIG. **19**H shows results of analysis and heat mapping of indicated cell subsets based on the percentage of expression, with the use of an Excel conditional formatting program.

FIGS. **20**A-E show T cell activation and effector functions upon polyclonal stimulation by CD3/CD28 antibodies. Expression of CD25 and Granzyme B (FIG. **20**A-B) as well as IL-2, IFN- $\gamma$  and TNF- $\alpha$  (FIG. **20**C-E) as markers for T cell activation and effector function, respectively, was analyzed in T cells from digested tumor samples after stimulation of whole tumor digests with agonistic CD3 and CD28 antibodies.

FIGS. 21A-N show expression of inhibitory receptors and T cell dysfunction. Expression of CD25 and Granzyme B (FIG. **21**A-B) as well as IL-2, IFN- $\gamma$  and TNF- $\alpha$  (FIG. **21**C-E) upon polyclonal stimulation by an anti-CD3/anti-CD28 antibodies correlates with the cumulative expression 5 of inhibitory receptors indicated by the iR Score. FIG. 21F shows an exemplary calculation of iR scores. The percentage of expression of PD-1, Tim-3, CTLA-4, LAG-3 and BTLA was analyzed in all NSCLC samples and the median as well as interquartile ranges were determined. For the 10 calculation of the iR score each patient received points for the expression of each of the determined inhibitory receptors based on the quartile within which the expression coincided. A maximum of 15 points could be reached; the calculated score of each sample was normalized to this maximum 15 amount of points. FIG. 21G-K show expression of inhibitory receptors increases with tumor stage. Expression of inhibitory receptors on CD8+ tumor infiltrating T-cells was correlated to the TNM stage. FIG. 21L-N show increased cumulative expression of inhibitory receptors with tumor 20 progression. The cumulative expression of the inhibitory receptors PD-1, Tim-3, CTLA-4, LAG-3 and BTLA, as represented by the iR score, was correlated to the nodal status and the TNM stage.

FIGS. **22**A-I show expression of PD-1 and Tim-3 corre- 25 lates with T cell dysfunction. Expression of CD25 and Granzyme B (FIG. **22**A-C) as well as IL-2, IFN- $\gamma$  and TNF- $\alpha$  (FIG. **22**D-F) upon polyclonal stimulation by CD3/CD28 correlates with the expression of PD-1 (FIG. **22**A-C), Tim-3 (FIG. **22**D-F) or PD-1/Tim-3 (FIG. **22**G-I) on tumor- 30 infiltrating T cells.

FIGS. **23**A-E show that the effect of PD-1 or combined PD-1/Tim-3 blockade varies between patients. Digests were stimulated by agonistic anti-CD3/anti-CD28 antibodies with the addition of blocking antibodies to PD-1 alone or in 35 combination with Tim-3. Secretion of IFN-γ, TNF- $\alpha$  and IL-2 was determined by ELISA and normalized to 1×10<sup>6</sup> T cells. FIG. **23**A-C show T cells from a patient where T cell function can be rescued by addition of blocking Abs (BS-268) and T cells from a patient with no response to PD-1 or 40 PD-1/Tim-3 blockade. The difference in expression ([% expression Ab treated]-[% expression untreated]) is shown. FIG. **23**D shows respective flow cytometry plots with PD-1<sup>hi</sup> and PD-1<sup>int</sup> subsets. FIG. **23**E shows a summary of IL-2, TNF- $\alpha$  and IFN- $\gamma$  secretion by T cells from six patients, as 45 determined by ELISA and normalized to 1×10<sup>6</sup> CD<sub>3</sub>+T cells.

FIGS. **24**Å-F show that the effect of PD-1 or combined PD-1/Tim-3 blockade differs in PD-1<sup>*hi*</sup> and PD-1<sup>*int*</sup> subsets. Correlation of the increase in cytokine production by PD-1 or combined PD-1/Tim-3 blockade with PD-1<sup>*hi*</sup> and PD-1<sup>*int*</sup> 50 subsets are indicated by PD-1<sup>*hi*</sup>/PD-1<sup>*int*</sup> ratio.

FIGS. **25**A-I show activation of CD4<sup>+</sup> T cells in tumor digests and malignant effusions upon exposure to FolR1-TCB. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FolR1-TCB or the 55 control TCB DP-47. The expression of activation markers or markers of T cell function on CD8<sup>+</sup> T cells was determined by flow cytometry.

FIGS. **26**A-C show FolR1-TCB induced T cell activation is independent of CTLA-4, Lag-3 and BTLA expression. <sup>60</sup> Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FolR1-TCB. The expression of CD25 on CD8<sup>+</sup> T cells was determined by flow cytometry. The FolR1-TCB induced expression of CD25 was correlated to baseline expression of CTLA-4, Lag-3 and BTLA. <sup>65</sup>

FIGS. 27A-C show FolR1-TCB induces cytokine secretion only in patients with a low percentage of PD-1<sup>hi</sup> expressing CD8<sup>+</sup> T cells. Tumor digests or malignant effusions were cultured for 24 h in the presence or absence of FoIR1-TCB. IFN-γ, TNF and IL-2 in the cell culture supernatants was determined and normalized to the amount of  $1 \times 10^5$ T cells in the culture. The FoIR1-TCB induced cytokine secretion was correlated to baseline PD-1<sup>hi</sup> expression.

FIGS. **28**A-F show that treatment with a PD-1 blocking antibody fails to induce cytokine secretion in tumor digests or malignant effusions from patients with lung and ovarian cancer with a low percentage of PD-1<sup>*hi*</sup> expressing cells. Tumor digests or malignant effusions were cultured for 24 h with FolR1-TCB in the presence or absence of PD-1 blocking antibody (FIG. **28**A-C) or the combination of PD-1 and Tim-3 blocking antibodies (FIG. **28**D-F). IFN-γ, TNF and IL-2 in the cell culture supernatants was determined and normalized to the amount of  $1 \times 10^5$  T cells in the culture. The cytokine secretion induced by the blocking antibodies compared to FolR1-TCB treatment alone was correlated to baseline PD-1<sup>*hi*</sup> expression.

FIGS. **29**A-B show results from a FACS based internalization assay. The data show that the Fab fragment (<TIM-3> Fab) of anti-TIM3 antibody Tim3\_0022 (abbreviated as <TIM-3> Ab(022)) internalized into rec CHOK1 cells expressing huTIM-3 after incubation at 37° C. with similar kinetic as the antibody in the full IgG format.

FIGS. **30**A-B show binding of anti-TIM3 antibodies to RPMI-8226 cells (antibody designation clone 0016 refers to antibody Tim3\_0016, clone 0016 refers to antibody Tim3\_0018), clone 0022 refers to antibody Tim3\_00122, etc.). FIG. **30**B shows binding of anti-TIM3 antibodies to Pfeiffer cells (antibody designation clone 0016 refers to antibody Tim3\_0016, clone 0016 refers to antibody Tim3\_0016, clone 0016 refers to antibody Tim3\_0018), clone 0022 refers to antibody Tim3\_0012, etc.).

FIG. **31** shows expression level of TIM-3 on different patient AML cell samples by FACS using anti-TIM-3 mAbs.

FIG. **32** shows a heat map of expression of inhibitory receptors on NSCLC associated TILs. Co-expression of inhibitory receptors on tumor-infiltrating CD8<sup>+</sup> T-cells positive for the indicated immune checkpoint is shown as a heat map displaying the percentage of expression for the additional receptors.

FIG. **33** shows a radar plot of expression of inhibitory receptors on NSCLC associated TILs. Co-expression of inhibitory receptors on tumor-infiltrating CD8<sup>+</sup> T-cells positive for the indicated immune checkpoint is shown as a radar plot indicating the mean expression and standard deviation of the four other receptors.

FIGS. **34**A-D show the percentage of PD-1<sup>*hi*</sup> or PD-1<sup>*int*</sup> CD8<sup>+</sup> T cells expressing additional immune checkpoints. Each dot represents one patient samples. The p values were calculated using the Wilcoxon rank sum test.

FIGS. **35**A-F show intratumoral T cell inhibitory receptor expression and T cell function. FIG. **35**A shows the gating strategy for identification of PD-1<sup>*hi*</sup>, PD-1<sup>*int*</sup>, and PD-1<sup>*neg*</sup> CD8<sup>+</sup> subsets of T-cells from two representative patients. FIG. **35**B shows distribution of indicated T cell subsets in the tumor samples analyzed. FIG. **35**C shows that T-cell functions induced by anti-CD3/-CD28 stimulation depend on the PD-1 expression level of CD8<sup>+</sup> T-cells. Tumor digests and malignant effusions were cultured for 24 h in the presence or absence of agonistic anti-CD3/-CD28 antibodies. The increase in the expression of CD25 on CD8<sup>+</sup> T-cells (FIG. **35**C) and the increase in the effector cytokines IFN-γ, IL-2, and TNF (FIG. **35**D) were determined in PD-1<sup>*hi*</sup> scarce

60

65

and abundant tumors. p-values were calculated using the unpaired Mann-Whitney test. Tumor samples were divided according to the percentage of PD-1<sup>*hi*</sup> expressing CD8<sup>+</sup> cells in two groups with PD-1<sup>*hi*</sup> scarce and abundant expression, respectively (FIG. **35**E). The expression level of the inhibitory receptors PD-1, Tim-3, CTLA-4, Lag-3, and BTLA was determined by flow cytometry on CD8<sup>+</sup> T-cells from tumor digests or malignant effusions (Fir. 35F).

FIGS. **36**A-E show patterns of inhibitory receptor expression and percentage of scarce and abundant CD8<sup>+</sup> T-cells. FIG. **36**A-D show co-expression of Tim-3, CTLA-4, Lag-3, and BTLA on PD-1<sup>*hi*</sup>, PD-1<sup>*int*</sup>, and PD-1<sup>*neg*</sup> CD8<sup>+</sup> T-cells. The p-values were calculated using one-way ANOVA with Bonferroni post-hoc-test. FIG. **36**E: FolR1<sup>+</sup> tumor samples were divided according to the percentage of PD-1<sup>*hi*</sup> expressing CD8<sup>+</sup> cells in two groups with PD-1<sup>*hi*</sup> scarce and abundant expression, respectively.

FIGS. **37**Å-H show that FolR1-TCB-induced T-cell functions depend on the PD-1 expression level of CD8<sup>+</sup> T-cells. FolR1<sup>+</sup> tumor digests and malignant effusions were cultured for 24 h in the presence or absence of FolR1-TCB. The 20 increase in the expression of activation markers on CD8<sup>+</sup> T-cells (FIGS. **37**A-C) and the increase in the effector cytokines IFN- $\gamma$ , IL-2, TNF, and perforin (FIG. **37**D-G) was determined in PD-1<sup>*hi*</sup> scarce and abundant tumors. FIG. **37**H shows target cell killing. Both FolR1 positive and negative tumor samples were adjusted by addition of the FolR1<sup>+</sup> Skov3 cell line to an E:T ratio of 1:1 and killing was compared in PD-1<sup>*int*</sup> scarce and abundant tumors. p-values were calculated using the unpaired Mann-Whitney test.

FIGS. 38A-E show that PD-1 blockade increases cytokine production but not their cytolytic function in T-cells from PD-1<sup>hi</sup> scarce tumors only. FIG. **38**A-D: FolR1<sup>+</sup> tumor digests or malignant effusions were cultured for 24 h with FolR1-TCB in the presence or absence of a PD-1 blocking antibody. IFN-y, IL-2, TNF, and perform in the cell culture supernatants were determined by Cytometric Bead Array or 35 ELISA and normalized to the amount of 1×105CD3+ T-cells (IFN-y, IL-2, TNF, FIG. 38A-C) or CD3+CD8+ T-cells (perforin, FIG. 38D). The increase in cytokine secretion upon combined FoIR1-TCB and anti-PD-1 treatment compared with FolR1-TCB alone was determined in PD-1<sup>hi</sup> 40 scarce and abundant tumors. FIG. 38E: Tumor digests or malignant effusions were co-cultured with exogenously added fluorescently labeled Skov3 cells at an E:T ratio of 1:1 for 24 h in the presence or absence of a PD-1 blocking antibody and FolR1-TCB. The increase in specific killing by 45 the anti-PD-1 antibody was compared in PD-1<sup>hi</sup> scarce and abundant tumors. p-values were calculated using the unpaired Mann-Whitney test.

FIG. 39 shows detailed patient characteristics.

FIGS. **40**A-C show activation of CD8<sup>+</sup> T-cells upon exposure to increasing concentrations of FolR1-TCB. <sup>50</sup> PBMCs were co-cultured with Skov3 cells for 24 h in the presence or absence of FolR1-TCB or the unspecific control DP-47-TCB. FIG. **40**A shows the expression of FolR1 on Skov3. Shaded histogram: isotype control; open histogram: anti-FolR1-antibody. FIG. **40**B: The expression of the activation markers CD25, CD137, and ICOS on CD8<sup>+</sup> T-cells was determined by flow cytometry. FIG. **40**C: IFN- $\gamma$ , IL-2, and TNF in the cell culture supernatants were determined by ELISA and normalized to the amount of 1×10<sup>5</sup> CD3<sup>+</sup> T-cells.

## DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

### I. Definitions

An "acceptor human framework" for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

"Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

An "affinity matured" antibody refers to an antibody with one or more alterations in one or more hypervariable regions (HVRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

The term "A bispecific antibody that specifically binds Folate Receptor1 (FolR1) and CD3," "T cell activating bispecific antigen binding molecule specific for FolR1 and CD3" and "FolR1 TCB" are used interchangeably herein and refer to a bispecific antibody that is capable of binding FolR1 and CD3 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting CD3<sup>+</sup> T cells to FolR2<sup>+</sup> target cells.

The terms "anti-TIM3 antibody" and "TIM3 antibody" are used synonymously herein to refer to an antibody that specifically binds to TIM3<sup>-</sup>. An anti-TIM3 antibody described herein refers to an antibody that is capable of binding TIM3, especially a TIM3 polypeptide expressed on a cell surface, with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent. In one embodiment, the extent of binding of an antibody that specifically binds TIM3 to an unrelated non-TIM3 protein is less than about 10% of the binding of the antibody to TIM3 as measured, e.g., by a radioimmunoassay (RIA) or flow cytometry (FACS). In certain embodiments, an antibody that specifically binds TIM3 has a dissociation constant (Kd) of <1 µM, <100 nM, <10 nM, <1 nM, <0.1 nM, <0.01 nM, or <0.001 nM (e.g.,  $10^{-8}$  M or less, e.g. from  $10^{-8}$  M to  $10^{-13}$ M, e.g., from  $10^{-9}$ M to  $10^{-13}$  M). In certain embodiments, an antibody that specifically binds TIM3 binds to an epitope of TIM3 that is conserved among DR5 from different species. Preferably said antibody binds to human and cynomolgous monkey TIM3. The term "An antibody that specifically binds TIM3" also encompasses bispecific antibodies that are capable of binding TIM3 and a second antigen.

The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')2; diabodies, cross-Fab 5 fragments; linear antibodies; single-chain antibody molecules (e.g. scFv); and multispecific antibodies formed from antibody fragments. scFv antibodies are, e.g. described in Houston, J. S., Methods in Enzymol. 203 (1991) 46-96). In addition, antibody fragments comprise single chain poly- 10 peptides having the characteristics of a VH domain, namely being able to assemble together with a VL domain, or of a VL domain, namely being able to assemble together with a VH domain to a functional antigen binding site and thereby providing the antigen binding property of full length anti- 15 bodies.

As used herein, "Fab fragment" refers to an antibody fragment comprising a light chain fragment comprising a VL domain and a constant domain of a light chain (CL), and a VH domain and a first constant domain (CH1) of a heavy 20 chain. In one embodiment the bispecific antibodies of the invention comprise at least one Fab fragment, wherein either the variable regions or the constant regions of the heavy and light chain are exchanged. Due to the exchange of either the variable regions or the constant regions, said Fab fragment 25 is also referred to as "cross-Fab fragment" or "xFab fragment" or "crossover Fab fragment". Two different chain compositions of a crossover Fab molecule are possible and comprised in the bispecific antibodies of the invention: On the one hand, the variable regions of the Fab heavy and light 30 chain are exchanged, i.e. the crossover Fab molecule comprises a peptide chain composed of the light chain variable region (VL) and the heavy chain constant region (CH1), and a peptide chain composed of the heavy chain variable region (VH) and the light chain constant region (CL). This cross- 35 over Fab molecule is also referred to as CrossFab(VLVH). On the other hand, when the constant regions of the Fab heavy and light chain are exchanged, the crossover Fab molecule comprises a peptide chain composed of the heavy chain variable region (VH) and the light chain constant region 40 (CL), and a peptide chain composed of the light chain variable region (VL) and the heavy chain constant region (CH1). This crossover Fab molecule is also referred to as CrossFab<sub>(CLCH1)</sub>. Bispecific antibody formats comprising crossover Fab fragments have been described, for example, 45 in WO 2009/080252, WO 2009/080253, WO 2009/080251, WO 2009/080254, WO 2010/136172, WO 2010/145792 and WO 2013/026831.

A "single chain Fab fragment" or "scFab" is a polypeptide consisting of an antibody heavy chain variable domain 50 (VH), an antibody constant domain 1 (CH1), an antibody light chain variable domain (VL), an antibody light chain constant domain (CL) and a linker, wherein said antibody domains and said linker have one of the following orders in N-terminal to C-terminal direction: 55

a) VH—CH1-linker-VL-CL, b) VL-CL-linker-VH— CH1, c) VH-CL-linker-VL-CH1 or d) VL-CH1-linker-VH-CL; and wherein said linker is a polypeptide of at least 30 amino acids, preferably between 32 and 50 amino acids. Said single chain Fab fragments a) VH—CH1-linker-VL- 60 CL, b) VL-CL-linker-VH—CH1, c) VH-CL-linker-VL-CH1 and d) VL-CH1-linker-VH—CH1, c) VH-CL-linker-VL-CH1 disulfide bond between the CL domain and the CHI domain. In addition, these single chain Fab molecules might be further stabilized by generation of interchain disulfide bonds 65 via insertion of cysteine residues (e.g. position 44 in the variable heavy chain and position 100 in the variable light

chain according to Kabat numbering). The term "N-terminus denotes the last amino acid of the N-terminus. The term "C-terminus denotes the last amino acid of the C-terminus. By "fused" or "connected" is meant that the components (e.g. a Fab molecule and an Fc domain subunit) are linked by peptide bonds, either directly or via one or more peptide linkers.

The term "linker" as used herein refers to a peptide linker and is preferably a peptide with an amino acid sequence with a length of at least 5 amino acids, preferably with a length of 5 to 100, more preferably of 10 to 50 amino acids. In one embodiment said peptide linker is  $(G_xS)_n$  (SEQ ID NOS 384 and 385) or  $(G_xS)_nG_m$  (SEQ ID NOS 429 and 430) with G=glycine, S=serine, and (x=3, n=3, 4, 5 or 6, and m=0, 1,2 or 3) or (x=4, n=2, 3, 4 or 5 and m=0, 1, 2 or 3), preferably x=4 and n=2 or 3, more preferably with x=4, n=2. In one embodiment said peptide linker is (G<sub>4</sub>S)<sub>2</sub> (SEQ ID NO: 386). The term "immunoglobulin molecule" refers to a protein having the structure of a naturally occurring antibody. For example, immunoglobulins of the IgG class are heterotetrameric glycoproteins of about 150,000 daltons, composed of two light chains and two heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3), also called a heavy chain constant region. Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain, also called a light chain constant region. The heavy chain of an immunoglobulin may be assigned to one of five types, called a (IgA), 6 (IgD), c (IgE),  $\gamma$  (IgG), or  $\mu$  (IgM), some of which may be further divided into subtypes, e.g.  $\gamma_1$  (IgG\_1),  $\gamma_2$  (IgG\_2),  $\gamma_3$  $(IgG_3)$ ,  $\gamma_4$   $(IgG_4)$ ,  $\alpha_1$   $(IgA_1)$  and  $\alpha_2$   $(IgA_2)$ . The light chain of an immunoglobulin may be assigned to one of two types, called kappa ( $\kappa$ ) and lambda ( $\lambda$ ) based on the amino acid sequence of its constant domain. An immunoglobulin essentially consists of two Fab molecules and an Fc domain, linked via the immunoglobulin hinge region.

An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

The term "antigen binding domain" refers to the part of an antigen binding molecule that comprises the area which specifically binds to and is complementary to part or all of an antigen. Where an antigen is large, an antigen binding molecule may only bind to a particular part of the antigen, which part is termed an epitope. An antigen binding domain may be provided by, for example, one or more antibody variable domains (also called antibody variable regions). Preferably, an antigen binding domain comprises an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH).

The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species, usually prepared by recombinant DNA techniques. Chimeric antibodies comprising a rabbit variable region and a human constant region are preferred. Other preferred forms of "chimeric antibodies" encompassed by the present invention are those in which the constant region has been modified or changed from that of the original antibody to generate the properties according to the invention, especially in regard to Clq binding and/or Fc receptor (FcR) binding. Such chimeric antibodies are also referred to as "class-switched antibodies". Chimeric antibodies are the 5 product of expressed immunoglobulin genes comprising DNA segments encoding immunoglobulin variable regions and DNA segments encoding immunoglobulin constant regions. Methods for producing chimeric antibodies involve conventional recombinant DNA and gene transfection tech- 10 niques are well known in the art. See e.g. Morrison, S. L., et al., Proc. Natl. Acad. Sci. USA 81 (1984) 6851-6855; U.S. Pat. Nos. 5,202,238 and 5,204,244.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or 15 causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g.,  $At^{211}$ ,  $I^{131}$ ,  $I^{125}$ ,  $Y^{90}$ ,  $Re^{186}$ ,  $Re^{188}$ ,  $Sm^{153}$ ,  $Bi^{212}$ ,  $P^{32}$ ,  $Pb^{212}$  and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, adriamicin, vinca alkaloids (vincristine, 20 vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of 25 bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed below.

"Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with 30 the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); antibody-dependent cellular phagocytosis (ADCP), cytokine secretion, immune 35 complex-mediated antigen uptake by antigen presenting cells; down regulation of cell surface receptors (e.g. B cell receptor); and B cell activation.

As used herein, the terms "engineer, engineered, engineering", are considered to include any manipulation of the 40 peptide backbone or the post-translational modifications of a naturally occurring or recombinant polypeptide or fragment thereof. Engineering includes modifications of the amino acid sequence, of the glycosylation pattern, or of the side chain group of individual amino acids, as well as 45 combinations of these approaches.

The term "amino acid mutation" as used herein is meant to encompass amino acid substitutions, deletions, insertions, and modifications. Any combination of substitution, deletion, insertion, and modification can be made to arrive at the 50 final construct, provided that the final construct possesses the desired characteristics, e.g., reduced binding to an Fc receptor, or increased association with another peptide. Amino acid sequence deletions and insertions include amino- and/or carboxy-terminal deletions and insertions of 55 amino acids. Particular amino acid mutations are amino acid substitutions. For the purpose of altering e.g. the binding characteristics of an Fc region, non-conservative amino acid substitutions, i.e. replacing one amino acid with another amino acid having different structural and/or chemical prop- 60 erties, are particularly preferred. Amino acid substitutions include replacement by non-naturally occurring amino acids or by naturally occurring amino acid derivatives of the twenty standard amino acids (e.g. 4-hydroxyproline, 3-methylhistidine, ornithine, homoserine, 5-hydroxylysine). 65 other than hypervariable region (HVR) residues. The FR of Amino acid mutations can be generated using genetic or chemical methods well known in the art. Genetic methods

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may include site-directed mutagenesis, PCR, gene synthesis and the like. It is contemplated that methods of altering the side chain group of an amino acid by methods other than genetic engineering, such as chemical modification, may also be useful. Various designations may be used herein to indicate the same amino acid mutation. For example, a substitution from proline at position 329 of the Fc domain to glycine can be indicated as 329G, G329, G329, P329G, or Pro329Gly.

An "effective amount" of an agent, e.g., a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

The term "Fc domain" or "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an IgG heavy chain might vary slightly, the human IgG heavy chain Fc region is usually defined to extend from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. A "subunit" of an Fc domain as used herein refers to one of the two polypeptides forming the dimeric Fc domain, i.e. a polypeptide comprising C-terminal constant regions of an immunoglobulin heavy chain, capable of stable self-association. For example, a subunit of an IgG Fc domain comprises an IgG CH2 and an IgG CH3 constant domain.

A "modification promoting the association of the first and the second subunit of the Fc domain" is a manipulation of the peptide backbone or the post-translational modifications of an Fc domain subunit that reduces or prevents the association of a polypeptide comprising the Fc domain subunit with an identical polypeptide to form a homodimer. A modification promoting association as used herein particularly includes separate modifications made to each of the two Fc domain subunits desired to associate (i.e. the first and the second subunit of the Fc domain), wherein the modifications are complementary to each other so as to promote association of the two Fc domain subunits. For example, a modification promoting association may alter the structure or charge of one or both of the Fc domain subunits so as to make their association sterically or electrostatically favorable, respectively. Thus, (hetero)dimerization occurs between a polypeptide comprising the first Fc domain subunit and a polypeptide comprising the second Fc domain subunit, which might be non-identical in the sense that further components fused to each of the subunits (e.g. antigen binding moieties) are not the same. In some embodiments the modification promoting association comprises an amino acid mutation in the Fc domain, specifically an amino acid substitution. In a particular embodiment, the modification promoting association comprises a separate amino acid mutation, specifically an amino acid substitution, in each of the two subunits of the Fc domain.

"Framework" or "FR" refers to variable domain residues a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR and FR

sequences generally appear in the following sequence in VH (or VL): FR1-H1(L1)-FR2-H2(L2)-FR3-H3(L3)-FR4.

The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a 5 native antibody structure or having heavy chains that contain an Fc region as defined herein.

The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, includ-10 ing the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, 15 but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody 20 produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. 25 As also mentioned for chimeric and humanized antibodies according to the invention the term "human antibody" as used herein also comprises such antibodies which are modified in the constant region to generate the properties according to the invention, especially in regard to Clq binding 30 and/or FcR binding, e.g. by "class switching" i.e. change or mutation of Fc parts (e.g. from  $IgG_1$  to  $IgG_4$  and/or  $IgG_1/IgG_4$  mutation.)

The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, 35 expressed, created or isolated by recombinant means, such as antibodies isolated from a host cell such as a NSO or CHO cell or from an animal (e.g. a mouse) that is transgenic for human immunoglobulin genes or antibodies expressed using a recombinant expression vector transfected into a host cell. 40 Such recombinant human antibodies have variable and constant regions in a rearranged form. The recombinant human antibodies according to the invention have been subjected to in vivo somatic hypermutation. Thus, the amino acid sequences of the VH and VL regions of the recombinant 45 antibodies are sequences that, while derived from and related to human germ line VH and VL sequences, may not naturally exist within the human antibody germ line repertoire in vivo.

A "human consensus framework" is a framework which 50 represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of 55 sequences is a subgroup as in Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication 91-3242, Bethesda Md. (1991), vols. 1-3. In one embodiment, for the VL, the subgroup is subgroup kappa I as in Kabat et al., supra. In one embodiment, for the VH, the 60 subgroup is subgroup III as in Kabat et al., supra.

A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all 65 of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond

to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a nonhuman antibody, refers to an antibody that has undergone humanization. Other forms of "humanized antibodies" encompassed by the present invention are those in which the constant region has been additionally modified or changed from that of the original antibody to generate the properties according to the invention, especially in regard to C1q binding and/or Fc receptor (FcR) binding.

The term "hypervariable region" or "HVR," as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops ("hypervariable loops"). Generally, native four-chain antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). HVRs generally comprise amino acid residues from the hypervariable loops and/or from the "complementarity determining regions" (CDRs), the latter being of highest sequence variability and/or involved in antigen recognition. Exemplary hypervariable loops occur at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3). (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987).) Exemplary CDRs (CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-H3) occur at amino acid residues 24-34 of L1, 50-56 of L2, 89-97 of L3, 31-35B of H1, 50-65 of H2, and 95-102 of H3. (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991).) Hypervariable regions (HVRs) are also referred to as complementarity determining regions (CDRs), and these terms are used herein interchangeably in reference to portions of the variable region that form the antigen binding regions. This particular region has been described by Kabat et al., U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" (1983) and by Chothia et al., J. Mol. Biol. 196:901-917 (1987), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth below in Table A as a comparison. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

TABLE A

CDR Definitions <sup>1</sup>				
CDR	Kabat	Chothia	AbM <sup>2</sup>	
$V_H$ CDR1 $V_H$ CDR2 $V_H$ CDR3 $V_L$ CDR1 $V_L$ CDR2	31-35 50-65 95-102 24-34 50-56	26-32 52-58 95-102 26-32 50-52	26-35 50-58 95-102 24-34 50-56	

<sup>1</sup>Numbering of all CDR definitions in Table A is according to the numbering conventions set forth by Kabat et al. (see below).
<sup>2</sup> "AbM" with a lowercase "b" as used in Table A refers to the CDRs as defined by Oxford Molecular's "AbM" antibody modeling software.

Kabat et al. also defined a numbering system for variable region sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable region sequence, without reliance on any experimental data beyond 5 the sequence itself. As used herein, "Kabat numbering" refers to the numbering system set forth by Kabat et al., U.S. Dept. of Health and Human Services, "Sequence of Proteins of Immunological Interest" (1983). Unless otherwise specified, references to the numbering of specific amino acid 10 residue positions in an antibody variable region are according to the Kabat numbering system.

With the exception of CDR1 in VH, CDRs generally comprise the amino acid residues that form the hypervariable loops. CDRs also comprise "specificity determining 15 residues," or "SDRs," which are residues that contact antigen. SDRs are contained within regions of the CDRs called abbreviated-CDRs, or a-CDRs. Exemplary a-CDRs (a-CDR-L1, a-CDR-L2, a-CDR-L3, a-CDR-H1, a-CDR-H2, and a-CDR-H3) occur at amino acid residues 31-34 of L1, 20 50-55 of L2, 89-96 of L3, 31-35B of H1, 50-58 of H2, and 95-102 of H3. (See Almagro and Fransson, Front. Biosci. 13:1619-1633 (2008).) Unless otherwise indicated, HVR residues and other residues in the variable domain (e.g., FR residues) are numbered herein according to Kabat et al., 25 supra.

An "immunoconjugate" is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

An "individual" or "subject" is a mammal. Mammals 30 include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.

An "isolated" antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary elec- 40 trophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, e.g., Flatman et al., J. Chromatogr. B 848:79-87 (2007).

An "isolated" nucleic acid refers to a nucleic acid mol- 45 ecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location 50 that is different from its natural chromosomal location.

"Isolated nucleic acid encoding a bispecific antibody that specifically binds DR5 and FAP antibody" refers to one or more nucleic acid molecules encoding antibody heavy and light chains (or fragments thereof), including such nucleic 55 acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially 60 homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include

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different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phagedisplay methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

A "naked antibody" refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical formulation.

"Native antibodies" refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfidebonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa ( $\kappa$ ) and lambda ( $\lambda$ ), based on the amino acid sequence of its constant domain.

A "blocking" antibody or an "antagonist" antibody is one that inhibits or reduces a biological activity of the antigen it binds. In some embodiments, blocking antibodies or antagonist antibodies substantially or completely inhibit the biological activity of the antigen. For example, the anti-PD-L1 antibodies of the invention block the signaling through PD-1 so as to restore a functional response by T-cells (e.g., proliferation, cytokine production, target cell killing) from a dysfunctional state to antigen stimulation.

An "agonist" or activating antibody is one that enhances or initiates signaling by the antigen to which it binds. In some embodiments, agonist antibodies cause or activate signaling without the presence of the natural ligand.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

"No substantial cross-reactivity" means that a molecule (e.g., an antibody) does not recognize or specifically bind an antigen different from the actual target antigen of the molecule (e.g. an antigen closely related to the target antigen), particularly when compared to that target antigen. For example, an antibody may bind less than about 10% to less than about 5% to an antigen different from the actual target antigen, or may bind said antigen different from the actual target antigen at an amount consisting of less than about 10%, 9%, 8% 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.2%, or 0.1%, preferably less than about 2%, 1%, or 0.5%, and most preferably less than about 0.2% or 0.1% antigen different from the actual target antigen.

"Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and 5 introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are 10 within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve 15 maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was 20 authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South 25 San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a 35 certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

#### 100 times the fraction X/Y

where X is the number of amino acid residues scored as 40 identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence 45 B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 com- 50 puter program.

The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components 55 which are unacceptably toxic to a subject to which the formulation would be administered.

A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharma- 60 ceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

The term "PD-1 axis binding antagonist" is a molecule that inhibits the interaction of a PD-1 axis binding partner with either one or more of its binding partner, so as to 65 remove T-cell dysfunction resulting from signaling on the PD-1 signaling axis—with a result being to restore or

enhance T-cell function {e.g., proliferation, cytokine production, target cell killing). As used herein, a PD-1 axis binding antagonist includes a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist.

The term "PD-1 binding antagonists" is a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with one or more of its binding partners, such as PD-L1, PD-L2. In some embodiments, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to its binding partners. In a specific aspect, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1 and/or PD-L2. For example, PD-1 binding antagonists include anti-PD-1 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-1 with PD-L1 and/or PD-L2. In one embodiment, a PD-1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-1 so as render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some embodiments, the PD-1 binding antagonist is an anti-PD-1 antibody. In a specific aspect, a PD-1 binding antagonist is MDX-1106 described herein. In another specific aspect, a PD-1 binding antagonist is Merck 3745 described herein. In another specific aspect, a PD-1 binding antagonist is CT-01 1 described herein.

The term "PD-L1 binding antagonists" is a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L1 with either one or more of its binding partners, such as PD-1, B7-1. In some embodiments, a PD-L1 binding antagonist is a molecule that inhibits the binding of PD-L 1 to its binding partners. In a specific aspect, the PD-L1 binding antagonist inhibits binding of PD-L1 to PD-1 and/or B7-1. In some embodiments, the PD-L1 binding antagonists include anti-PD-L1 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L1 with one or more of its binding partners, such as PD-1, B7-1. In one embodiment, a PD-L1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L 1 so as to render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some embodiments, a PD-L1 binding antagonist is an anti-PD-L1 antibody. In a specific aspect, an anti-PD-L1 antibody is W/243.55.870 described herein. In another specific aspect, an anti-PD-L1 antibody is MDX-1 105 described herein. In still another specific aspect, an anti-PD-L1 antibody is MPDL3280A described herein.

The term "PD-L2 binding antagonists" is a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. In some embodiments, a PD-L2 binding antagonist is a molecule that inhibits the binding of PD-L2 to its binding partners. In a specific aspect, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1. In some embodiments, the PD-L2 antagonists include anti-PD-L2 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction

resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. In one embodiment, a PD-L2 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L2 so as render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some embodiments, a PD-L2 binding antagonist is an immunoadhesin.

A "PD-1 oligopeptide" "PD-L1 oligopeptide" or "PD-L2 oligopeptide" is an oligopeptide that binds, preferably specifically, to a PD-1, PD-L1 or PD-L2 negative costimulatory polypeptide, respectively, including a receptor, ligand or signaling component, respectively, as described herein. Such 15 oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. Such oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 20 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 25 98, 99, or 100 amino acids in length or more. Such oligopeptides may be identified using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in 30 the art (see, e.g., U.S. Pat. Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/ 03564; Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 81:3998-4002 (1984); Geysen et al, Proc. Natl. Acad. Sci. 35 U.S.A., 82: 178-182 (1985); Geysen et al, in Synthetic Peptides as Antigens, 130-149 (1986); Geysen et al., J. Immunol. Metk, 102:259-274 (1987); Schoofs et al., J. Immunol., 140:611-616 (1988), Cwirla, S. E. et al. Proc. Natl. Acad. Sci. USA, 87:6378 (1990); Lowman, H. B. et al. 40 Biochemistry, 30: 10832 (1991); Clackson, T. et al. Nature, 352: 624 (1991); Marks, J. D. et al., J. Mol. Biol., 222:581 (1991); Kang, A. S. et al. Proc. Natl. Acad. Sci. USA, 88:8363 (1991), and Smith, G. P., Current Opin. Biotechnol, 2:668 (1991). 45

The term "anergy" refers to the state of unresponsiveness to antigen stimulation resulting from incomplete or insufficient signals delivered through the T-cell receptor (e.g. increase in intracellular  $Ca^{+2}$  in the absence of ras-activation). T cell anergy can also result upon stimulation with 50 antigen in the absence of co-stimulation, resulting in the cell becoming refractory to subsequent activation by the antigen even in the context of costimulation. The unresponsive state can often be overriden by the presence of Interleukin-2. Anergic T-cells do not undergo clonal expansion and/or 55 acquire effector functions.

The term "exhaustion" refers to T cell exhaustion as a state of T cell dysfunction that arises from sustained TCR signaling that occurs during many chronic infections and cancer. It is distinguished from anergy in that it arises not 60 through incomplete or deficient signaling, but from sustained signaling. It is defined by poor effector function, sustained expression of inhibitory receptors and a transcriptional state distinct from that of functional effector or memory T cells. Exhaustion prevents optimal control of 65 infection and tumors. Exhaustion can result from both extrinsic negative regulatory pathways (e.g., immunoregu-

latory cytokines) as well as cell intrinsic negative regulatory (costimulatory) pathways (PD-1, B7-H3, B7-H4, etc.).

"Enhancing T-cell function" means to induce, cause or stimulate a T-cell to have a sustained or amplified biological function, or renew or reactivate exhausted or inactive T-cells. Examples of enhancing T-cell function include: increased secretion of  $\gamma$ -interferon from CD8<sup>+</sup> T-cells, increased proliferation, increased antigen responsiveness (e.g., viral, pathogen, or tumor clearance) relative to such levels before the intervention. In one embodiment, the level of enhancement is as least 50%, alternatively 60%, 70%, 80%, 90%, 100%, 120%, 150%, 200%. The manner of measuring this enhancement is known to one of ordinary skill in the art.

"Tumor immunity" refers to the process in which tumors evade immune recognition and clearance. Thus, as a therapeutic concept, tumor immunity is "treated" when such evasion is attenuated, and the tumors are recognized and attacked by the immune system. Examples of tumor recognition include tumor binding, tumor shrinkage and tumor clearance. [0046] "Immunogenecity" refers to the ability of a particular substance to provoke an immune response. Tumors are immunogenic and enhancing tumor immunogenicity aids in the clearance of the tumor cells by the immune response. Examples of enhancing tumor immunogenicity include treatment with anti-PDL antibodies and a ME inhibitor.

"Sustained response" refers to the sustained effect on reducing tumor growth after cessation of a treatment. For example, the tumor size may remain to be the same or smaller as compared to the size at the beginning of the administration phase. In some embodiments, the sustained response has a duration at least the same as the treatment duration, at least  $1.5\times$ , 2. OX,  $2.5\times$ , or 3. OX length of the treatment duration.

The term "Fibroblast activation protein (FAP)", as used herein, refers to any native FAP from any vertebrate source, including mammals such as primates (e.g. humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses "full-length," unprocessed FAP as well as any form of FAP that results from processing in the cell. The term also encompasses naturally occurring variants of FAP, e.g., splice variants or allelic variants. Preferably, an anti-FAP antibody of the invention binds to the extracellular domain of FAP. The amino acid sequence of exemplary FAP polypeptide sequences, including the sequence of human FAP, are disclosed in WO 2012/020006.

As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

The term cancer as used herein refers to proliferative diseases, such as the cancer is colorectal cancer, sarcoma, head and neck cancer, squamous cell carcinoma, breast cancer, pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer and mesothelioma, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. In one embodiment, the cancer is colorectal cancer and optionally the chemotherapeutic agent is Irinotecan. In embodiments in which the cancer is sarcoma, optionally the sarcoma is chondrosarcoma, leiomyosarcoma, gastrointestinal stromal 5 tumours, fibrosarcoma, osteosarcoma, liposarcoma or maligant fibrous histiocytoma.

The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable 10 domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al. Kuby Immunology, 6th ed., 15 W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary 20 VL or VH domains, respectively. See, e.g., Portolano et al., J. Immunol. 150:880-887 (1993); Clarkson et al., Nature 352:624-628 (1991).

As used herein, the term "antigen binding molecule" refers in its broadest sense to a molecule that specifically 25 binds an antigenic determinant. Examples of antigen binding molecules are immunoglobulins and derivatives, e.g. fragments, thereof.

The term "antigen-binding site of an antibody" when used herein refer to the amino acid residues of an antibody which 30 are responsible for antigen-binding. The antigen-binding portion of an antibody comprises amino acid residues from the "complementary determining regions" or "CDRs". "Framework" or "FR" regions are those variable domain regions other than the hypervariable region residues as 35 herein defined. Therefore, the light and heavy chain variable domains of an antibody comprise from N- to C-terminus the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Especially, CDR3 of the heavy chain is the region which contributes most to antigen binding and defines the anti- 40 body's properties. CDR and FR regions are determined according to the standard definition of Kabat et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, Md. (1991) and/or those residues from a "hyper- 45 variable loop".

Antibody specificity refers to selective recognition of the antibody for a particular epitope of an antigen. Natural antibodies, for example, are monospecific. "Bispecific antibodies" according to the invention are antibodies which 50 have two different antigen-binding specificities. Antibodies of the present invention are specific for two different antigens, i.e. DR5 as first antigen and FAP as second antigen.

The term "monospecific" antibody as used herein denotes an antibody that has one or more binding sites each of which 55 bind to the same epitope of the same antigen.

The term "bispecific" means that the antigen binding molecule is able to specifically bind to at least two distinct antigenic determinants. Typically, a bispecific antigen binding molecule comprises at least two antigen binding sites, 60 each of which is specific for a different antigenic determinant. In certain embodiments the bispecific antigen binding molecule is capable of simultaneously binding two antigenic determinants, particularly two antigenic determinants expressed on two distinct cells.

The antibody provided herein is a multispecific antibody, e.g. a bispecific antibody. Multispecific antibodies are

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monoclonal antibodies that have binding specificities for at least two different sites. Provided herein is a bispecific antibody, with binding specificities for FAP and DR5. In certain embodiments, bispecific antibodies may bind to two different epitopes of DR5. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express DR5. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.

Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, Nature 305: 537 (1983)), WO 93/08829, and Traunecker et al., EMBO J. 10: 3655 (1991)), and "knob-in-hole" engineering (see, e.g., U.S. Pat. No. 5,731,168). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/ 089004); cross-linking two or more antibodies or fragments (see, e.g., U.S. Pat. No. 4,676,980, and Brennan et al., Science, 229: 81 (1985)); using leucine zippers to produce bi-specific antibodies (see, e.g., Kostelny et al., J. Immunol., 148(5):1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (see, e.g., Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see, e.g. Gruber et al., J. Immunol., 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. J. Immunol. 147: 60 (1991).

Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (see, e.g. US 2006/0025576A1).

The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising at least one antigen binding site that binds to FAP or DR5 as well as another, different antigen (see, US 2008/0069820, for example).

The term "valent" as used within the current application denotes the presence of a specified number of binding sites in an antibody molecule. As such, the terms "bivalent", "tetravalent", and "hexavalent" denote the presence of two binding sites, four binding sites, and six binding sites, respectively, in an antibody molecule. The bispecific antibodies according to the invention are at least "bivalent" and may be "trivalent" or "multivalent" (e.g. "tetravalent" or "hexavalent").

Antibodies of the present invention have two or more binding sites and are bispecific. That is, the antibodies may be bispecific even in cases where there are more than two binding sites (i.e. that the antibody is trivalent or multivalent). Bispecific antibodies of the invention include, for example, multivalent single chain antibodies, diabodies and triabodies, as well as antibodies having the constant domain structure of full length antibodies to which further antigenbinding sites (e.g., single chain Fv, a VH domain and/or a VL domain, Fab, or (Fab)2) are linked via one or more peptide-linkers. The antibodies can be full length from a single species, or be chimerized or humanized.

The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

The term "amino acid" as used within this application denotes the group of naturally occurring carboxy a-amino

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acids comprising alanine (three letter code: ala, one letter code: A), arginine (arg, R), asparagine (asn, N), aspartic acid (asp, D), cysteine (cys, C), glutamine (gln, Q), glutamic acid (glu, E), glycine (gly, G), histidine (his, H), isoleucine (ile, I), leucine (leu, L), lysine (lys, K), methionine (met, M), phenylalanine (phe, F), proline (pro, P), serine (ser, S), threonine (thr, T), tryptophan (trp, W), tyrosine (tyr, Y), and valine (val, V).

As used herein, the expressions "cell", "cell line", and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transfectants" and "transfected cells" include the primary subject cell and cultures derived there from without regard for the number of transfers. It is also understood that all progeny may not be 15 precisely identical in DNA content, due to deliberate or inadvertent mutations. Variant progeny that have the same function or biological activity as screened for in the originally transformed cell are included.

"Affinity" refers to the strength of the sum total of 20 noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., <sup>25</sup> antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

As used herein, the term "binding" or "specifically binding" refers to the binding of the antibody to an epitope of the antigen in an in-vitro assay, preferably in a surface plasmon 35 resonance assay (SPR, BIAcore, GE-Healthcare Uppsala, Sweden). The affinity of the binding is defined by the terms ka (rate constant for the association of the antibody from the antibody/antigen complex), kD (dissociation constant), and KD (kD/ka). Binding or specifically binding means a bind- 40 ing affinity (KD) of  $10^{-8}$  mol/l or less, preferably  $10^{-9}$  M to  $10^{-13}$  mol/l.

Binding of the antibody to the death receptor can be investigated by a BIAcore assay (GE-Healthcare Uppsala, Sweden). The affinity of the binding is defined by the terms 45 ka (rate constant for the association of the antibody from the antibody/antigen complex), kD (dissociation constant), and KD (kD/ka)

"Reduced binding", for example reduced binding to an Fc receptor, refers to a decrease in affinity for the respective 50 interaction, as measured for example by SPR. For clarity the term includes also reduction of the affinity to zero (or below the detection limit of the analytic method), i.e. complete abolishment of the interaction. Conversely, "increased binding" refers to an increase in binding affinity for the respec- 55 tive interaction.

"T cell activation" as used herein refers to one or more cellular response of a T lymphocyte, particularly a cytotoxic T lymphocyte, selected from: proliferation, differentiation, cytokine secretion, cytotoxic effector molecule release, 60 cytotoxic activity, and expression of activation markers. The T cell activating bispecific antigen binding molecules of the invention are capable of inducing T cell activation. Suitable assays to measure T cell activation are known in the art described herein.

A "target cell antigen" as used herein refers to an antigenic determinant presented on the surface of a target cell, for example a cell in a tumor such as a cancer cell or a cell of the tumor stroma. In particular "target cell antigen" refers to Folate Receptor 1.

As used herein, the terms "first" and "second" with respect to antigen binding moieties etc., are used for convenience of distinguishing when there is more than one of each type of moiety. Use of these terms is not intended to confer a specific order or orientation of the T cell activating bispecific antigen binding molecule unless explicitly so stated.

The term "epitope" includes any polypeptide determinant capable of specific binding to an antibody. In certain embodiments, epitope determinant include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl, or sulfonyl, and, in certain embodiments, may have specific three dimensional structural characteristics, and or specific charge characteristics. An epitope is a region of an antigen that is bound by an antibody

As used herein, the term "antigenic determinant" is synonymous with "antigen" and "epitope," and refers to a site (e.g. a contiguous stretch of amino acids or a conformational configuration made up of different regions of non-contiguous amino acids) on a polypeptide macromolecule to which an antigen binding moiety binds, forming an antigen binding moiety-antigen complex. Useful antigenic determinants can be found, for example, on the surfaces of tumor cells, on the surfaces of virus-infected cells, on the surfaces of other diseased cells, on the surface of immune cells, free in blood serum, and/or in the extracellular matrix (ECM). The proteins referred to as antigens herein, e.g., FolR1 and CD3, can be any native form the proteins from any vertebrate source, including mammals such as primates (e.g. humans) and rodents (e.g. mice and rats), unless otherwise indicated. In a particular embodiment the antigen is a human protein. Where reference is made to a specific protein herein, the term encompasses the "full-length", unprocessed protein as well as any form of the protein that results from processing in the cell. The term also encompasses naturally occurring variants of the protein, e.g. splice variants or allelic variants. Exemplary human proteins useful as antigens include, but are not limited to: FolR1 (Folate receptor alpha (FRA); Folate binding protein (FBP); human FolR1 UniProt no.: P15328; murine FolR1 UniProt no.: P35846; cynomolgus FolR1 UniProt no.: G7PR14) and CD3, particularly the epsilon subunit of CD3 (see UniProt no. P07766 (version 130), NCBI RefSeq no. NP\_000724.1, SEQ ID NO:150 for the human sequence; or UniProt no. Q95LI5 (version 49), NCBI GenBank no. BAB71849.1, for the cynomolgus [Macaca fascicularis] sequence). The T cell activating bispecific antigen binding molecule of the invention binds to an epitope of CD3 or a target cell antigen that is conserved among the CD3 or target antigen from different species. In certain embodiments the T cell activating bispecific antigen binding molecule of the invention binds to CD3 and FolR1, but does not bind to FolR2 (Folate receptor beta; FRB; human FolR2 UniProt no .: P14207) or FolR3 (Folate receptor gamma; human FolR3 UniProt no.: P41439).

As used herein, the terms "engineer, engineered, engineering," particularly with the prefix "glyco-," as well as the term "glycosylation engineering" are considered to include any manipulation of the glycosylation pattern of a naturally occurring or recombinant polypeptide or fragment thereof. Glycosylation engineering includes metabolic engineering of the glycosylation machinery of a cell, including genetic manipulations of the oligosaccharide synthesis pathways to achieve altered glycosylation of glycoproteins expressed in cells. Furthermore, glycosylation engineering includes the effects of mutations and cell environment on glycosylation. In one embodiment, the glycosylation engineering is an alteration in glycosyltransferase activity. In a particular embodiment, the engineering results in altered glucosami-<sup>5</sup> nyltransferase activity and/or fucosyltransferase activity.

### II. Compositions and Methods

In one aspect, the invention is based on the use of a <sup>10</sup> therapeutic combination of a T cell activating bispecific antigen binding molecule, e.g., a T cell activating bispecific antigen binding molecule comprising a first antigen binding site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, and a PD-1 axis <sup>15</sup> binding antagonist, e.g., for the treatment of cancer. In some embodiments the therapeutic combination further includes a TIM3 antagonist.

## A. Combination Therapies of a T Cell Activating Bispecific Antigen Binding Molecule and a PD-1 Axis Binding Antagonist

Broadly, the present invention relates to T cell activating bispecific antigen binding molecules and their use in com- 25 bination with a PD-1 axis binding antagonists. The advantage of the combination over monotherapy is that the T cell activating bispecific antigen binding molecules used in the present invention enable re-direction and activation of T cells to the targeted cell while the PD-1 axis binding 30 antagonist enhances T cell function by reducing T cell exhaustion.

In one aspect, provided herein is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a T 35 cell activating bispecific antigen binding molecules, e.g., a FolR1-TCB, and a PD-1 axis binding antagonist. In some embodiments, the treatment results in sustained response in the individual after cessation of the treatment. The methods of this invention may find use in treating conditions where 40 enhanced immunogenicity is desired such as increasing tumor immunogenicity for the treatment of cancer. A variety of cancers may be treated, or their progression may be delayed, including but are not limited to a cancer that may contain a BRAF V600E mutation, a cancer that may contain 45 a BRAF wildtype, a cancer that may contain a KRAS wildtype, or a cancer that may contain an activating KRAS mutation.

In some embodiments, the individual has endometrial cancer. The endometrial cancer may be at early stage or late 50 state. In some embodiments, the individual has melanoma. The melanoma may be at early stage or at late stage. In some embodiments, the individual has colorectal cancer. The colorectal cancer may be at early stage or at late stage. In some embodiments, the individual has lung cancer, e.g., 55 non-small cell lung cancer. The non-small cell lung cancer may be at early stage or at late stage. In some embodiments, the individual has pancreatic cancer. The pancreatice cancer may be at early stage or late state. In some embodiments, the individual has a hematological malignancy. The hematologi- 60 cal malignancy may be early stage or late stage. In some embodiments, the individual has ovarian cancer. The ovarian cancer may be at early stage or at late stage. In some embodiments, the individual has breast cancer. The breast cancer may be at early stage or at late stage. In some 65 embodiments, the individual has renal cell carcinoma. The renal cell carcinoma may be at early stage or at late stage.

In some embodiments, the individual is a mammal, such as domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In some embodiments, the individual treated is a human.

In another aspect, provided herein is a method of enhancing immune function in an individual having cancer comprising administering an effective amount of a T cell activating bispecific antigen binding molecules, specifically, a FolR1-TCB, and a PD-1 axis binding antagonist.

In some embodiments, the T cells in the individual have enhanced priming, activation, proliferation and/or effector function relative to prior to the administration of the T cell activating bispecific antigen binding molecules and the PD-1 pathway antagonist. In some embodiments, the T cell effector function is secretion of at least one of IL-2, IFN-y and TNF- $\alpha$ . In one embodiment, administering a FolR1-TCB and an anti-PDL-1 antibody results in increased T cell secretion of IL-2, IFN- $\gamma$  and TNF- $\alpha$ . In some embodiments, 20 the T cell is a CD8<sup>+</sup> T cell. In some embodiments, the T cell priming is characterized by elevated CD44 expression and/ or enhanced cytolytic activity in CD8 T cells. In some embodiments, the CD8 T cell activation is characterized by an elevated frequency of  $\gamma\text{-IFT}^{T}$  CD8 T cells. In some embodiments, the CD8 T cell is an antigen-specific T-cell. In some embodiments, the immune evasion by signaling through PD-L1 surface expression is inhibited. In some embodiments, the cancer has elevated levels of T-cell infiltration.

In some embodiments, the combination therapy of the invention comprises administration of a FolR1-TCB and a PD-1 axis binding antagonist. The FolR1-TCB and a PD-1 axis binding antagonist may be administered in any suitable manner known in the art. For example, FolR1-TCB and a PD-1 axis binding antagonist may be administered sequentially (at different times) or concurrently (at the same time). In some embodiments, the FolR1-TCB is administered continuously. In some embodiments, the FolR1-TCB is administered intermittently. In some embodiments, the FolR1-TCB is administered before administration of the PD-1 axis binding antagonist. In some embodiments, the FolR1-TCB is administered simultaneously with administration of the PD-1 axis binding antagonist. In some embodiments, the FolR1-TCB is administered after administration of the PD-1 axis binding antagonist.

In some embodiments, provided is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a T cell activating bispecific antigen binding molecules, e.g., a FolR1-TCB, and a PD-1 axis binding antagonist, further comprising administering an additional therapy. Specifically contemplated is an embodiment in which the additional therapy comprises a TIM-3 antagonist. Accordingly, in one aspect, provided herein is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a T cell activating bispecific antigen binding molecules, specifically, a FolR1-TCB, a PD-1 axis binding antagonist, and a TIM-3 antagonist. Any TIM3 antagonist, e.g., those described herein, can be used. The additional therapy may also be radiation therapy, surgery (e.g., lumpectomy and a mastectomy), chemotherapy, gene therapy, DNA therapy, viral therapy, R A therapy, immunotherapy, bone marrow transplantation, nanotherapy, monoclonal antibody therapy, or a combination of the foregoing. The additional therapy may be in the form of adjuvant or neoadjuvant therapy. In some embodiments, the additional therapy is the administration of

small molecule enzymatic inhibitor or anti-metastatic agent. In some embodiments, the additional therapy is the administration of side-effect limiting agents (e.g., agents intended to lessen the occurrence and/or severity of side effects of treatment, such as anti-nausea agents, etc.). In some embodi-5 ments, the additional therapy is radiation therapy. In some embodiments, the additional therapy is surgery. In some embodiments, the additional therapy is a combination of radiation therapy and surgery. In some embodiments, the additional therapy is gamma irradiation. In some embodi- 10 ments, the additional therapy is therapy targeting P13K/A T/mTOR pathway, HSP90 inhibitor, tubulin inhibitor, apoptosis inhibitor, and/or chemopreventative agent. The additional therapy may be one or more of the chemotherapeutic agents described hereabove. 15

T cell activating bispecific antigen binding molecules, e.g., a FolR1-TCB, and the PD-1 axis binding antagonist may be administered by the same route of administration or by different routes of administration. In some embodiments, T cell activating bispecific antigen binding molecules, e.g., 20 a FolR1-TCB is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraprbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the PD-1 axis binding antagonist is adminis- 25 tered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. An effective amount of the T cell activating bispecific antigen binding molecules and the PD-1 30 axis binding antagonist may be administered for prevention or treatment of disease. The appropriate dosage of the T cell activating bispecific antigen binding molecules and/or the PD-1 axis binding antagonist may be determined based on the type of disease to be treated, the type of the T cell 35 activating bispecific antigen binding molecules and the PD-1 axis binding antagonist, the severity and course of the disease, the clinical condition of the individual, the individual's clinical history and response to the treatment, and the discretion of the attending physician. 40

Any of the T cell activating bispecific antigen binding molecules, PD-1 axis binding antagonists and the TIM-3 antagonists known in the art or described below may be used in the methods.

In a further aspect, the present invention provides a 45 pharmaceutical composition comprising a T cell activating bispecific antigen binding molecules as described herein, a PD-1 axis binding antagonists as described herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition further comprises a TIM3 50 antagonist.

In a further aspect, the invention provides for a kit comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a package insert comprising instructions for using the T 55 cell activating bispecific antigen binding molecule with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual. In some embodiments, the kit further comprises instructions for using the T cell activating bispecific antigen binding molecule with a TIM3 antagonist. 60 In a further aspect, the invention provides for a kit comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 and a PD-1 axis binding antagonist, and a package insert comprising instructions for using the T cell activating bispecific antigen 65 binding molecule and the PD-1 axis binding antagonist to treat or delay progression of cancer in an individual. In one

embodiment, the kit further comprises a TIM3 antagonist. In one of the embodiments, the PD-1 axis binding antagonist is an anti-PD-1 antibody or an anti-PDL-1 antibody. In one embodiment, the PD-1 axis binding antagonist is an anti-PD-1 immunoadhesin.

In a further aspect, the invention provides a kit comprising:

- (i) a first container comprising a composition which comprises a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 as described herein; and
- (ii) a second container comprising a composition comprising a PD-1 axis binding antagonist.

In a further aspect, the invention provides a kit comprising:

- (i) a first container comprising a composition which comprises a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 as described herein;
- (ii) a second container comprising a composition comprising a PD-1 axis binding antagonist; and
- (iii) a third container comprising a composition comprising a TIM3 antagonist.
- B. Exemplary T Cell Activating Bispecific Antigen Binding Molecule for Use in the Invention

The T cell activating bispecific antigen binding molecule of the invention is bispecific, i.e. it comprises at least two antigen binding moieties capable of specific binding to two distinct antigenic determinants, i.e. to CD3 and to FolR1. According to the invention, the antigen binding moieties are Fab molecules (i.e. antigen binding domains composed of a heavy and a light chain, each comprising a variable and a constant region). In one embodiment said Fab molecules are human. In another embodiment said Fab molecules are humanized. In yet another embodiment said Fab molecules comprise human heavy and light chain constant regions.

The T cell activating bispecific antigen binding molecule of the invention is capable of simultaneous binding to the target cell antigen FolR1 and CD3. In one embodiment, the T cell activating bispecific antigen binding molecule is capable of crosslinking a T cell and a FolR1 expressing target cell by simultaneous binding to the target cell antigen FolR1 and CD3. In an even more particular embodiment, such simultaneous binding results in lysis of the FolR1 expressing target cell, particularly a FolR1 expressing tumor cell. In one embodiment, such simultaneous binding results in activation of the T cell. In other embodiments, such simultaneous binding results in a cellular response of a T lymphocyte, particularly a cytotoxic T lymphocyte, selected from the group of: proliferation, differentiation, cytokine secretion, cytotoxic effector molecule release, cytotoxic activity, and expression of activation markers. In one embodiment, binding of the T cell activating bispecific antigen binding molecule to CD3 without simultaneous binding to the target cell antigen FolR1 does not result in T cell activation.

In one embodiment, the T cell activating bispecific antigen binding molecule is capable of re-directing cytotoxic activity of a T cell to a FolR1 expressing target cell. In a particular embodiment, said re-direction is independent of MHC-mediated peptide antigen presentation by the target cell and and/or specificity of the T cell. Particularly, a T cell according to some of the embodiments of the invention is a cytotoxic T cell. In some embodiments the T cell is a  $CD4^+$  or a  $CD8^+$  T cell, particularly a  $CD8^+$  T cell.

The T cell activating bispecific antigen binding molecule 5 of the invention comprises at least one antigen binding moiety capable of binding to CD3 (also referred to herein as an "CD3 antigen binding moiety" or "first antigen binding moiety"). In a particular embodiment, the T cell activating bispecific antigen binding molecule comprises not more than 10 one antigen binding moiety capable of specific binding to CD3. In one embodiment the T cell activating bispecific antigen binding molecule provides monovalent binding to CD3. In a particular embodiment CD3 is human CD3 or cynomolgus CD3, most particularly human CD3. In a par- 15 ticular embodiment the CD3 antigen binding moiety is cross-reactive for (i.e. specifically binds to) human and cynomolgus CD3. In some embodiments, the first antigen binding moiety is capable of specific binding to the epsilon subunit of CD3 (see UniProt no. P07766 (version 130), 20 NCBI RefSeq no. NP\_000724.1, SEQ ID NO:150 for the human sequence; UniProt no. Q95L15 (version 49), NCBI GenBank no. BAB71849.1, for the cynomolgus [Macaca fascicularis] sequence).

In some embodiments, the CD3 antigen binding moiety 25 comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34. 30

In one embodiment the CD3 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the 35 light chain CDR3 of SEQ ID NO:34.

In one embodiment the CD3 antigen binding moiety comprises a variable heavy chain comprising an amino acid sequence of: SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of: SEQ ID NO: 31. 40

In one embodiment the CD3 antigen binding moiety comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 36 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% 45 identical to SEQ ID NO: 31.

The T cell activating bispecific antigen binding molecule of the invention comprises at least one antigen binding moiety capable of binding to the target cell antigen FolR1 (also referred to herein as an "FolR1 binding moiety" or 50 "second" or "third" antigen binding moiety). In one embodiment, the antigen binding moiety capable of binding to the target cell antigen FolR1 does not bind to FolR2 or FolR3. In a particular embodiment the FolR1 antigen binding moiety is cross-reactive for (i.e. specifically binds to) human 55 and cynomolgus FolR1. In certain embodiments, the T cell activating bispecific antigen binding molecule comprises two antigen binding moieties capable of binding to the target cell antigen FolR1. In a particular such embodiment, each of these antigen binding moieties specifically binds to the same 60 antigenic determinant. In an even more particular embodiment, all of these antigen binding moieties are identical. In one embodiment the T cell activating bispecific antigen binding molecule comprises not more than two antigen binding moieties capable of binding to FolR1. 65

The FolR1 binding moiety is generally a Fab molecule that specifically binds to FolR1 and is able to direct the T cell

activating bispecific antigen binding molecule to which it is connected to a target site, for example to a specific type of tumor cell that expresses FolR1.

In one aspect the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34; and
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1).

In one embodiment the first antigen binding moiety which is a Fab molecule capable of specific binding to CD3 comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.

In one embodiment the T cell activating bispecific antigen binding molecule additionally comprises

(iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to FolR1.

In one such embodiment the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences. In one such embodiment the third antigen binding moiety is identical to the second antigen binding moiety.

In one embodiment the T cell activating bispecific antigen binding molecule of any of the above embodiments additionally comprises an Fc domain composed of a first and a second subunit capable of stable association.

In one embodiment the first antigen binding moiety and the second antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or second subunit of the Fc domain.

In one embodiment the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety, optionally via a peptide linker.

In a further particular embodiment, not more than one antigen binding moiety capable of specific binding to CD3 is present in the T cell activating bispecific antigen binding molecule (i.e. the T cell activating bispecific antigen binding molecule provides monovalent binding to CD3).

### T Cell Activating Bispecific Antigen Binding Molecule with a Common Light Chain

The inventors of the present invention generated a bispecific antibody wherein the binding moieties share a common light chain that retains the specificity and efficacy of the parent monospecific antibody for CD3 and can bind a second antigen (e.g., FolR1) using the same light chain. The generation of a bispecific molecule with a common light chain that retains the binding properties of the parent antibody is not straight-forward as the common CDRs of the hybrid light chain have to effectuate the binding specificity for both targets. In one aspect the present invention provides a T cell activating bispecific antigen binding molecule comprising a first and a second antigen binding moiety, one of which is a Fab molecule capable of specific binding to CD3 and the other one of which is a Fab molecule capable of specific binding to FolR1, wherein the first and the second Fab molecule have identical VLCL light chains. In one embodiment said identical light chain (VLCL) comprises the light chain CDRs of SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34. In one embodiment said identical light chain (VLCL) comprises SEQ ID NO. 35.

In one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID 15 NO: 34;
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) and which comprises at least one heavy chain complementarity determining region (CDR) selected 20 from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.

In one such embodiment the CD3 antigen binding moiety 25 comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen 30 binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 16, the heavy chain CDR2 of SEQ ID NO: 17, the heavy chain CDR3 of SEQ ID NO:18, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 37, and the light chain CDR3 of SEQ ID NO:18, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34.

In one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding molecule comprising
   (i) a first antigen binding molecule which is a Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of 40 SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 15 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.

In a further embodiment, the antigen binding moiety that is specific for FolR1 comprises a heavy chain variable 50 region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:15 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 31 or variants thereof that retain functionality. 55

In one embodiment the T cell activating bispecific antigen binding molecule comprises a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 36, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ 60 ID NO:15, and a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 31.

In one embodiment the T cell activating bispecific antigen binding molecule additionally comprises

(iii) a third antigen binding moiety (which is a Fab molecule) capable of specific binding to FolR1.

In one such embodiment the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences. In one such embodiment the third antigen binding moiety is identical to the second antigen binding moiety.

Hence in one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34;
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.
- (iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.

In one such embodiment the CD3 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 16, the heavy chain CDR2 of SEQ ID NO: 17, the heavy chain CDR3 of SEQ ID NO:18, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34.

In one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 15 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 15 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.

In one embodiment the present invention provides a T cell 65 activating bispecific antigen binding molecule comprising

(i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID <sup>5</sup> NO: 34;

(ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) and which comprises at least one heavy chain 10 complementarity determining region (CDR) selected from the group consisting of SEQ ID NO:16, SEQ ID NO:402 and SEQ ID NO:400 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.

In one such embodiment the CD3 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34, and the FoIR1 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO:402, the heavy chain CDR3 of SEQ ID NO:400, the light chain CDR3 of SEQ ID NO:400, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO:402, the heavy chain CDR3 of SEQ ID NO:400, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO:34.

In one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding moiety which is a Fab molecule <sup>30</sup> capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab
   <sup>35</sup> molecule capable of specific binding to Folate Receptor
   1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO:401 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.

In a further embodiment, the antigen binding moiety that is specific for FolR1 comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:401 and a light chain 45 variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 31 or variants thereof that retain functionality.

In one embodiment the T cell activating bispecific antigen binding molecule comprises a polypeptide sequence that is <sup>50</sup> at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 36, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:401, and a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID <sup>55</sup> NO: 31.

In one embodiment the T cell activating bispecific antigen binding molecule additionally comprises

(iii) a third antigen binding moiety (which is a Fab  $_{60}$  molecule) capable of specific binding to FolR1.

In one such embodiment the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences. In one such 65 embodiment the third antigen binding moiety is identical to the second antigen binding moiety.

Hence in one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising

- (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34;
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO:16, SEQ ID NO:402 and SEQ ID NO:400 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.
- (iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) and which comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO:16, SEQ ID NO:402 and SEQ ID NO:400 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.

In one such embodiment the CD3 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain 30 CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO:16, the heavy chain CDR2 of SEQ ID NO:402, the 56 heavy chain CDR3 of SEQ ID NO:400, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34.

- In one embodiment the present invention provides a T cell activating bispecific antigen binding molecule comprising
  - (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
  - (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO:401 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
  - (iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO:401 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.

Thus, in one embodiment, the invention relates to bispecific molecules wherein at least two binding moieties have identical light chains and corresponding remodeled heavy chains that confer the specific binding to the T cell activating antigen CD3 and the target cell antigen FolR1, respectively. The use of this so-called 'common light chain' principle, i.e. combining two binders that share one light chain but still have separate specificities, prevents light chain mispairing. Thus, there are less side products during production, facilitating the homogenous preparation of T cell activating bispecific antigen binding molecules. The components of the T cell activating bispecific antigen binding molecule can be fused to each other in a variety of configurations. Exemplary configurations are depicted in FIGS. 1A-I and are further described below.

In some embodiments, said T cell activating bispecific <sup>5</sup> antigen binding molecule further comprises an Fc domain composed of a first and a second subunit capable of stable association. Below exemplary embodiments of T cell activating bispecific antigen binding molecule comprising an Fc domain are described. 10

## T Cell Activating Bispecific Antigen Binding Molecule with a Crossover Fab Fragment

The inventors of the present invention generated a second 15 bispecific antibody format wherein one of the binding moieties is a crossover Fab fragment. In one aspect of the invention a monovalent bispecific antibody is provided, wherein one of the Fab fragments of an IgG molecule is replaced by a crossover Fab fragment. Crossover Fab frag- 20 ments are Fab fragments wherein either the variable regions or the constant regions of the heavy and light chain are exchanged. Bispecific antibody formats comprising crossover Fab fragments have been described, for example, in WO2009080252, WO2009080253, WO2009080251, 25 WO2009080254, WO2010/136172, WO2010/145792 and WO2013/026831. In a particular embodiment, the first antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged. Such modi- 30 fication prevent mispairing of heavy and light chains from different Fab molecules, thereby improving the yield and purity of the T cell activating bispecific antigen binding molecule of the invention in recombinant production. In a particular crossover Fab molecule useful for the T cell 35 activating bispecific antigen binding molecule of the invention, the variable regions of the Fab light chain and the Fab heavy chain are exchanged. In another crossover Fab molecule useful for the T cell activating bispecific antigen binding molecule of the invention, the constant regions of 40 the Fab light chain and the Fab heavy chain are exchanged.

In one embodiment the T cell activating bispecific antigen binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID 50 NO: 34;
- (ii) a second antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of 55 SEQ ID NO: 8, SEQ ID NO: 56 and SEQ ID NO: 57 and at least one light chain CDR selected from the group of SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 65.

In one such embodiment the CD3 antigen binding moiety 60 comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen 65 binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 56, the heavy

chain CDR3 of SEQ ID NO:57, the light chain CDR1 of SEQ ID NO: 59, the light chain CDR2 of SEQ ID NO: 60, and the light chain CDR3 of SEQ ID NO:65.

In one embodiment, the second antigen binding moiety is a conventional Fab molecule.

In one embodiment the T cell activating bispecific antigen binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 55 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 64.

In one embodiment, the second antigen binding moiety is a conventional Fab molecule.

In a further embodiment, the antigen binding moiety that is specific for FolR1 comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:55 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 64 or variants thereof that retain functionality.

In one embodiment the T cell activating bispecific antigen binding molecule comprises a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 36, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 31, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:55, and a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:55, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 64.

In one embodiment the T cell activating bispecific antigen binding molecule additionally comprises

(iii) a third antigen binding moiety capable of specific binding to FoIR1.

a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity deter-

> In one such embodiment the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences. In one such embodiment the third antigen binding moiety is identical to the second antigen binding moiety.

> In one embodiment the T cell activating bispecific antigen binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34;
- (ii) a second antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 56 and SEQ ID NO: 57

and at least one light chain CDR selected from the group of SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 65.

(iii) a third antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprising at 5 least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 56 and SEQ ID NO: 57 and at least one light chain CDR selected from the group of SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID 10 NO: 65.

In one such embodiment the CD3 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID 15 NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 56, the heavy chain CDR3 of SEQ ID NO:57, the light chain CDR1 of 20 SEQ ID NO: 59, the light chain CDR2 of SEQ ID NO: 60, and the light chain CDR3 of SEQ ID NO:65.

In one embodiment, the second antigen binding moiety and the third antigen binding moiety are both a conventional Fab molecule.

In one embodiment the T cell activating bispecific antigen binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid 30 sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 55 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 64.
- (iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 40 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 55 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 64.

In one embodiment, the second antigen binding moiety 45 and the third antigen binding moiety are both a conventional Fab molecule.

In one embodiment the T cell activating bispecific antigen binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab 50 molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from 55 the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34;
- (ii) a second antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprising at least one heavy chain complementarity determining 60 region (CDR) selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 50 and at least one light chain CDR selected from the group of SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54.

In one such embodiment the CD3 antigen binding moiety 65 comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain

CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52, the light chain CDR2 of SEQ ID NO: 53, and the light chain CDR3 of SEQ ID NO:54.

In one embodiment, the second antigen binding moiety is a conventional Fab molecule. In one embodiment, the second antigen binding moiety is a crossover Fab molecule.

In one embodiment the T cell activating bispecific antigen binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 49 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 51.

In one embodiment, the second antigen binding moiety is a conventional Fab molecule. In one embodiment, the second antigen binding moiety is a crossover Fab molecule.

In a further embodiment, the antigen binding moiety that is specific for FolR1 comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:49 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 51 or variants thereof that retain functionality.

In one embodiment the T cell activating bispecific antigen binding molecule comprises a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 36, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 31, a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:49, and a polypeptide sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:51.

In one embodiment the T cell activating bispecific antigen binding molecule additionally comprises

(iii) a third antigen binding moiety capable of specific binding to FolR1.

nding molecule comprises (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3, compris-

> In one such embodiment the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences. In one such embodiment the third antigen binding moiety is identical to the second antigen binding moiety.

> In one embodiment the T cell activating bispecific antigen binding molecule comprises

(i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34;

- (ii) a second antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEO ID NO: 8, SEO ID NO: 9 and SEO ID NO: 49 and 5 at least one light chain CDR selected from the group of SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54.
- (iii) a third antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1) comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 50 and at least one light chain CDR selected from the group of SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54.

In one such embodiment the CD3 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the 20 light chain CDR3 of SEQ ID NO:34 and the FolR1 antigen binding moiety comprises the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52, the light chain CDR2 of SEQ ID NO: 53, 25 antigen binding molecule can be fused to each other in a and the light chain CDR3 of SEQ ID NO:54.

In one embodiment, the second antigen binding moiety and the third antigen binding moiety are both a conventional Fab molecule.

In one embodiment the T cell activating bispecific antigen 30 binding molecule comprises

- (i) a first antigen binding moiety which is a crossover Fab molecule capable of specific binding to CD3 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain 35 comprising an amino acid sequence of SEQ ID NO: 31.
- (ii) a second antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 49 and a 40 variable light chain comprising an amino acid sequence of SEQ ID NO: 51.
- (iii) a third antigen binding moiety which is a Fab molecule capable of specific binding to Folate Receptor 1 (FolR1) comprising a variable heavy chain compris- 45 ing an amino acid sequence of SEQ ID NO: 49 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 51.

In one embodiment, the second antigen binding moiety and the third antigen binding moiety are both a conventional 50 Fab molecule.

Thus, in one embodiment, the invention relates to bispecific molecules wherein two binding moieties confer specific binding to FolR1 and one binding moiety confers specificity to the T cell activating antigen CD3. One of the heavy chains 55 is modified to ensure proper pairing of the heavy and light chains, thus eliminating the need for a common light chain approach. The presence of two FolR1 binding sites enables appropriate engagement with the target antigen FolR1 and the activation of T cells. The components of the T cell 60 activating bispecific antigen binding molecule can be fused to each other in a variety of configurations. Exemplary configurations are depicted in FIGS. 1A-I and are further described below.

In some embodiments, said T cell activating bispecific 65 antigen binding molecule further comprises an Fc domain composed of a first and a second subunit capable of stable

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association. Below exemplary embodiments of T cell activating bispecific antigen binding molecule comprising an Fc domain are described.

### T Cell Activating Bispecific Antigen Binding Molecule Formats

As depicted above and in FIGS. 1A-I, in one embodiment the T cell activating bispecific antigen binding molecules comprise at least two Fab fragments having identical light chains (VLCL) and having different heavy chains (VHCL) which confer the specificities to two different antigens, i.e. one Fab fragment is capable of specific binding to a T cell activating antigen CD3 and the other Fab fragment is capable of specific binding to the target cell antigen FolR1.

In another embodiment the T cell activating bispecific antigen binding molecule comprises at least two antigen binding moieties (Fab molecules), one of which is a crossover Fab molecule and one of which is a conventional Fab molecule. In one such embodiment the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule and the second antigen binding moiety capable of specific binding to FolR is a conventional Fab molecule.

These components of the T cell activating bispecific variety of configurations. Exemplary configurations are depicted in FIGS. 1A-I.

In some embodiments, the first and second antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or the second subunit of the Fc domain. In a specific such embodiment, the T cell activating bispecific antigen binding molecule essentially consists of a first and a second antigen binding moiety, an Fc domain composed of a first and a second subunit, and optionally one or more peptide linkers, wherein the first and second antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or the second subunit of the Fc domain. In one such embodiment the first and second antigen binding moiety both are Fab fragments and have identical light chains (VLCL). In another such embodiment the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule and the second antigen binding moiety capable of specific binding to FolR is a conventional Fab molecule.

In one embodiment, the second antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or the second subunit of the Fc domain and the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding moiety. In a specific such embodiment, the T cell activating bispecific antigen binding molecule essentially consists of a first and a second antigen binding moiety, an Fc domain composed of a first and a second subunit, and optionally one or more peptide linkers, wherein the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding moiety, and the second antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or the second subunit of the Fc domain. In one such embodiment the first and second antigen binding moiety both are Fab fragments and have identical light chains (VLCL). In another such embodiment the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule and the second antigen binding moiety capable of specific binding to FolR is a

conventional Fab molecule. Optionally, the Fab light chain of the first antigen binding moiety and the Fab light chain of the second antigen binding moiety may additionally be fused to each other.

In other embodiments, the first antigen binding moiety is 5 fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or second subunit of the Fc domain. In a particular such embodiment, the second antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen 10 binding moiety. In a specific such embodiment, the T cell activating bispecific antigen binding molecule essentially consists of a first and a second antigen binding moiety, an Fc domain composed of a first and a second subunit, and optionally one or more peptide linkers, wherein the second 15 antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety, and the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or the second subunit of the Fc 20 domain. In one such embodiment the first and second antigen binding moiety both are Fab fragments and have identical light chains (VLCL). In another such embodiment the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule and the second antigen 25 binding moiety capable of specific binding to FolR is a conventional Fab molecule. Optionally, the Fab light chain of the first antigen binding moiety and the Fab light chain of the second antigen binding moiety may additionally be fused to each other.

The antigen binding moieties may be fused to the Fc domain or to each other directly or through a peptide linker, comprising one or more amino acids, typically about 2-20 amino acids. Peptide linkers are known in the art and are described herein. Suitable, non-immunogenic peptide link- 35 ers include, for example,  $(G_4S)_n$  (SEQ ID NO: 387),  $(SG_4)_n$ (SEQ ID NO: 388),  $(G_4S)_n$  (SEQ ID NO: 387) or  $G_4(SG_4)_n$ (SEQ ID NO: 389) peptide linkers. "n" is generally a number between 1 and 10, typically between 2 and 4. A particularly suitable peptide linker for fusing the Fab light 40 chains of the first and the second antigen binding moiety to each other is (G<sub>4</sub>S)<sub>2</sub> (SEQ ID NO: 386). An exemplary peptide linker suitable for connecting the Fab heavy chains of the first and the second antigen binding moiety is EPKSC (D)-(G<sub>4</sub>S)<sub>2</sub> (SEQ ID NOS 390 and 391). Additionally, link- 45 ers may comprise (a portion of) an immunoglobulin hinge region. Particularly where an antigen binding moiety is fused to the N-terminus of an Fc domain subunit, it may be fused via an immunoglobulin hinge region or a portion thereof, with or without an additional peptide linker. 50

It has been found by the inventors of the present invention that T cell activating bispecific antigen binding molecule comprising two binding moieties specific for the target cell antigen FolR have superior characteristics compared to T cell activating bispecific antigen binding molecule compris-55 ing only one binding moiety specific for the target cell antigen FolR.

Accordingly, in certain embodiments, the T cell activating bispecific antigen binding molecule of the invention further comprises a third antigen binding moiety which is a Fab 60 molecule capable of specific binding to FolR. In one such embodiment the second and third antigen binding moiety capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences, i.e., the heavy chain CDR 65 sequences of the second antigen binding moiety are the same as the heavy chain CDR sequences of the third antigen

binding moiety, and the light chain CDR sequences of the second antigen binding moiety are the same as the light chain CDR sequences of the third antigen binding moiety. In one such embodiment the third antigen binding moiety is identical to the second antigen binding moiety (i.e. they comprise the same amino acid sequences).

In one embodiment, the first and second antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or second subunit of the Fc domain and the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus to the N-terminus of the Fab heavy chain of the first antigen binding moiety. In a specific such embodiment, the T cell activating bispecific antigen binding molecule essentially consists of a first, a second and a third antigen binding moiety, an Fc domain composed of a first and a second subunit, and optionally one or more peptide linkers, wherein the first and second antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain and the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety. In one such embodiment the first, second and third antigen binding moiety are conventional Fab fragments and have identical light chains (VLCL). In another such embodiment the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule and the second and third antigen binding moiety capable of specific binding to FolR is a conventional Fab molecule. Optionally, the Fab light chain of the first antigen binding moiety and the Fab light chain of the third antigen binding moiety may additionally be fused to each other.

In another aspect, the invention provides for a bispecific antibody comprising a) a first antigen-binding site that competes for binding to human FolR1 with a reference antibody comprising a variable heavy chain domain (VH) of SEQ ID NO: 49 and a variable light chain domain of SEQ ID NO: 51; and b) a second antigen-binding site that competes for binding to human CD3 with a reference antibody comprising a variable heavy chain domain (VH) of SEQ ID NO: 36 and a variable light chain domain of SEQ ID NO: 31, wherein binding competition is measured using a surface plasmon resonance assay. In another aspect, the invention provides for a T cell activating bispecific antigen binding molecule comprising a first antigen binding moiety capable of specific binding to CD3, and a second antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1), wherein the T cell activating bispecific antigen binding molecule binds to the same epitope on human FolR1 as a first reference antibody comprising a variable heavy chain domain (VH) of SEQ ID NO: 49 and a variable light chain domain of SEQ ID NO: 51; and wherein the T cell activating bispecific antigen binding molecule binds to the same epitope on human CD3 as a second reference antibody comprising a variable heavy chain domain (VH) of SEQ ID NO: 36 and a variable light chain domain of SEQ ID NO: 31.

In another aspect, the invention provides for a T cell activating bispecific antigen binding molecule that comprises a first, second, third, fourth and fifth polypeptide chain that form a first, a second and a third antigen binding moiety wherein the first antigen binding moiety is capable of binding CD3 and the second and the third antigen binding moiety each are capable of binding Folate Receptor 1 (FolR1). The first and the second polypeptide chain comprise, in amino (N)-terminal to carboxyl (C)-terminal direction, a first light chain variable domain (VLD1) and a first light chain constant domain (CLD1).

The third polypeptide chain comprises, in N-terminal to C-terminal direction, second light chain variable domain (VLD2) and a second heavy chain constant domain 1 (CH1D2). The fourth polypeptide chain comprises, in N-terminal to C-terminal direction, a first heavy chain variable 5 domain (VHD1), a first heavy chain constant domain 1 (CH1D1), a first heavy chain constant domain 2 (CH2D1) and a first heavy chain constant domain 3 (CH3D1). The fifth polypeptide chain comprises VHD1, CH1D1, a second heavy chain variable domain (VHD2), a second light chain 10 constant domain (CLD2), a second heavy chain constant domain 2 (CH2D2) and a second heavy chain constant domain 3 (CH3D2). The third polypeptide chain and VHD2 and CLD2 of the fifth polypeptide chain form the first antigen binding moiety capable of binding CD3. The second 15 polypeptide chain and VHD1 and CH1D1 of the fifth polypeptide chain form the third binding moiety capable of binding to FolR1. The first polypeptide chain and VHD1 and CH1D1 of the fourth polypeptide chain form the second binding moiety capable of binding to FolR1.

In another embodiment, the second and the third antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first or second subunit of the Fc domain, and the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the 25 N-terminus of the Fab heavy chain of the second antigen binding moiety. In a specific such embodiment, the T cell activating bispecific antigen binding molecule essentially consists of a first, a second and a third antigen binding moiety, an Fc domain composed of a first and a second 30 subunit, and optionally one or more peptide linkers, wherein the second and third antigen binding moiety are each fused at the C-terminus of the Fab heavy chain to the N-terminus of the first subunit of the Fc domain and the first antigen binding moiety is fused at the C-terminus of the Fab heavy 35 chain to the N-terminus of the Fab heavy chain of the third antigen binding moiety. In one such embodiment the first, second and third antigen binding moiety are conventional Fab fragments and have identical light chains (VLCL). In another such embodiment the first antigen binding moiety 40 capable of specific binding to CD3 is a crossover Fab molecule and the second and third antigen binding moiety capable of specific binding to FolR is a conventional Fab molecule. Optionally, the Fab light chain of the first antigen binding moiety and the Fab light chain of the second antigen 45 binding moiety may additionally be fused to each other.

The antigen binding moieties may be fused to the Fc domain directly or through a peptide linker. In a particular embodiment the antigen binding moieties are each fused to the Fc domain through an immunoglobulin hinge region. In 50 a specific embodiment, the immunoglobulin hinge region is a human  $IgG_1$  hinge region.

In one embodiment the first and the second antigen binding moiety and the Fc domain are part of an immunoglobulin molecule. In a particular embodiment the immu-55 noglobulin molecule is an IgG class immunoglobulin. In an even more particular embodiment the immunoglobulin is an IgG<sub>1</sub> subclass immunoglobulin. In another embodiment the immunoglobulin is an IgG<sub>4</sub> subclass immunoglobulin. In a further particular embodiment the immunoglobulin is a 60 human immunoglobulin. In other embodiments the immunoglobulin is a chimeric immunoglobulin or a humanized immunoglobulin.

In a particular embodiment said T cell activating bispecific antigen binding molecule the first and the second 65 antigen binding molecule, and the Fc domain are part of an immunoglobulin molecule, and the third antigen binding

moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety, wherein the first, second and third antigen binding moiety are conventional Fab fragments and have identical light chains (VLCL), wherein the first antigen binding moiety capable of specific binding to CD3 comprises at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34; and the second and the third antigen binding moiety capable of specific binding to FolR1 comprise at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34.

In a particular embodiment said T cell activating bispecific antigen binding molecule the first and the second 20 antigen binding moiety and the Fc domain are part of an immunoglobulin molecule, and the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety, wherein the first, second and third antigen binding moiety are conventional Fab fragments and have identical light chains (VLCL), wherein the first antigen binding moiety capable of specific binding to CD3 comprises a variable heavy chain comprising a sequence of SEQ ID NO: 36, a variable light chain comprising a sequence of SEQ ID NO: 31; and the second and the third antigen binding moiety capable of specific binding to FolR1 comprise a variable heavy chain comprising a sequence of SEQ ID NO: 15, a variable light chain comprising a sequence of SEQ ID NO: 31.

In a particular embodiment said T cell activating bispecific antigen binding molecule the first and the second antigen binding moiety and the Fc domain are part of an immunoglobulin molecule, and the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety and the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule wherein either the variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 37, SEO ID NO: 38 and SEO ID NO: 39 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34; and the second and the third antigen binding moiety capable of specific binding to FolR1 comprise at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 56 and SEQ ID NO: 57 and at least one light chain CDR selected from the group of SEQ ID NO: 59, SEQ ID NO: 60 and SEQ ID NO: 65.

In a particular embodiment said T cell activating bispecific antigen binding molecule the first and the second antigen binding moiety and the Fc domain are part of an immunoglobulin molecule, and the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety and the first antigen binding moiety capable of specific binding to CD3 is a crossover Fab molecule wherein either the variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged, wherein the first antigen binding moiety capable of specific binding to CD3 comprises a variable heavy chain comprising a

sequence of SEQ ID NO: 36, a variable light chain comprising a sequence of SEQ ID NO: 31; and the second and the third antigen binding moiety capable of specific binding to FolR1 comprise a variable heavy chain comprising a sequence of SEQ ID NO: 55, a variable light chain comprising a sequence of SEQ ID NO: 65.

In one embodiment the T cell activating bispecific antigen binding molecule is monovalent for each antigen. In a particular embodiment the T cell activating bispecific antigen binding molecule can bind to human CD3 and human 10 folate receptor alpha (FolR1) and was made without employing a hetero-dimerization approach, such as, e.g., knob-into-hole technology. For example, the molecule can be produced by employing a common light chain library and CrossMab technology. In a particular embodiment, The 15 variable region of the CD3 binder is fused to the CH1 domain of a standard human IgG1 antibody to form the VLVH crossed molecule (fused to Fc) which is common for both specificities. To generate the crossed counterparts (VHCL), a CD3 specific variable heavy chain domain is 20 fused to a constant human  $\kappa$  light chain whereas a variable heavy chain domain specific for human FolR1 (e.g., isolated from a common light chain library) is fused to a constant human  $\kappa$  light chain. The resulting desired molecule with correctly paired chains comprises both kappa and lambda 25 light chains or fragments thereof. Consequently, this desired bispecific molecule species can be purified from mispaired or homodimeric species with sequential purification steps selecting for kappa and lambda light chain, in either sequence. In one particular embodiment, purification of the 30 desired bispecific antibody employs subsequent purification steps with KappaSelect and LambdaFabSelect columns (GE Healthcare) to remove undesired homodimeric antibodies.

#### Fc Domain

The Fc domain of the T cell activating bispecific antigen binding molecule consists of a pair of polypeptide chains comprising heavy chain domains of an immunoglobulin molecule. For example, the Fc domain of an immunoglobu-40 lin G (IgG) molecule is a dimer, each subunit of which comprises the CH2 and CH3 IgG heavy chain constant domains. The two subunits of the Fc domain are capable of stable association with each other. In one embodiment the T cell activating bispecific antigen binding molecule of the 45 invention comprises not more than one Fc domain.

In one embodiment according the invention the Fc domain of the T cell activating bispecific antigen binding molecule is an IgG Fc domain. In a particular embodiment the Fc domain is an IgG<sub>1</sub> Fc domain. In another embodiment 50 the Fc domain is an IgG<sub>4</sub> Fc domain. In a more specific embodiment, the Fc domain is an IgG<sub>4</sub> Fc domain comprising an amino acid substitution at position S228 (Kabat numbering), particularly the amino acid substitution S228P. This amino acid substitution reduces in vivo Fab arm 55 exchange of IgG<sub>4</sub> antibodies (see Stubenrauch et al., Drug Metabolism and Disposition 38, 84-91 (2010)). In a further particular embodiment the Fc domain is human. Fc Domain Modifications Promoting Heterodimerization

T cell activating bispecific antigen binding molecules 60 according to the invention comprise different antigen binding moieties, fused to one or the other of the two subunits of the Fc domain, thus the two subunits of the Fc domain are typically comprised in two non-identical polypeptide chains. Recombinant co-expression of these polypeptides and subsequent dimerization leads to several possible combinations of the two polypeptides. To improve the yield and purity of

T cell activating bispecific antigen binding molecules in recombinant production, it will thus be advantageous to introduce in the Fc domain of the T cell activating bispecific antigen binding molecule a modification promoting the association of the desired polypeptides.

Accordingly, in particular embodiments the Fc domain of the T cell activating bispecific antigen binding molecule according to the invention comprises a modification promoting the association of the first and the second subunit of the Fc domain. The site of most extensive protein-protein interaction between the two subunits of a human IgG Fc domain is in the CH3 domain of the Fc domain. Thus, in one embodiment said modification is in the CH3 domain of the Fc domain.

In a specific embodiment said modification is a so-called "knob-into-hole" modification, comprising a "knob" modification in one of the two subunits of the Fc domain and a "hole" modification in the other one of the two subunits of the Fc domain.

The knob-into-hole technology is described e.g. in U.S. Pat. Nos. 5,731,168; 7,695,936; Ridgway et al., Prot Eng 9, 617-621 (1996) and Carter, J Immunol Meth 248, 7-15 (2001). Generally, the method involves introducing a protuberance ("knob") at the interface of a first polypeptide and a corresponding cavity ("hole") in the interface of a second polypeptide, such that the protuberance can be positioned in the cavity so as to promote heterodimer formation and hinder homodimer formation. Protuberances are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains (e.g. tyrosine or tryptophan). Compensatory cavities of identical or similar size to the protuberances are created in the interface of the second polypeptide by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine).

Accordingly, in a particular embodiment, in the CH3 domain of the first subunit of the Fc domain of the T cell activating bispecific antigen binding molecule an amino acid residue is replaced with an amino acid residue having a larger side chain volume, thereby generating a protuberance within the CH3 domain of the first subunit which is positionable in a cavity within the CH3 domain of the second subunit, and in the CH3 domain of the second subunit of the Fc domain an amino acid residue is replaced with an amino acid residue having a smaller side chain volume, thereby generating a cavity within the CH3 domain of the second subunit of the second subunit within which the protuberance within the CH3 domain of the second subunit within which the protuberance within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit within which the protuberance within the CH3 domain of the Second subunit second subunit is positionable.

The protuberance and cavity can be made by altering the nucleic acid encoding the polypeptides, e.g. by site-specific mutagenesis, or by peptide synthesis.

In a specific embodiment, in the CH3 domain of the first subunit of the Fc domain the threonine residue at position 366 is replaced with a tryptophan residue (T366W), and in the CH3 domain of the second subunit of the Fc domain the tyrosine residue at position 407 is replaced with a valine residue (Y407V). In one embodiment, in the second subunit of the Fc domain additionally the threonine residue at position 366 is replaced with a serine residue (T366S) and the leucine residue at position 368 is replaced with an alanine residue (L368A).

In yet a further embodiment, in the first subunit of the Fc domain additionally the serine residue at position 354 is replaced with a cysteine residue (S354C), and in the second subunit of the Fc domain additionally the tyrosine residue at position 349 is replaced by a cysteine residue (Y349C). Introduction of these two cysteine residues results in formation of a disulfide bridge between the two subunits of the
Fc domain, thus further stabilizing the dimer (Carter, J Immunol Methods 248, 7-15 (2001)).

In a particular embodiment the antigen binding moiety capable of binding to CD3 is fused (optionally via the antigen binding moiety capable of binding to a target cell 5 antigen) to the first subunit of the Fc domain (comprising the "knob" modification). Without wishing to be bound by theory, fusion of the antigen binding moiety capable of binding to CD3 to the knob-containing subunit of the Fc domain will (further) minimize the generation of antigen 10 binding molecules comprising two antigen binding moieties capable of binding to CD3 (steric clash of two knobcontaining polypeptides).

In an alternative embodiment a modification promoting association of the first and the second subunit of the Fc 15 domain comprises a modification mediating electrostatic steering effects, e.g. as described in PCT publication WO 2009/089004. Generally, this method involves replacement of one or more amino acid residues at the interface of the two Fc domain subunits by charged amino acid residues so that 20 homodimer formation becomes electrostatically unfavorable but heterodimerization electrostatically favorable.

Fc Domain Modifications Abolishing Fc Receptor Binding and/or Effector Function

The Fc domain confers to the T cell activating bispecific 25 antigen binding molecule favorable pharmacokinetic properties, including a long serum half-life which contributes to good accumulation in the target tissue and a favorable tissue-blood distribution ratio. At the same time it may, however, lead to undesirable targeting of the T cell activat- 30 ing bispecific antigen binding molecule to cells expressing Fc receptors rather than to the preferred antigen-bearing cells. Moreover, the co-activation of Fc receptor signaling pathways may lead to cytokine release which, in combination with the T cell activating properties and the long 35 half-life of the antigen binding molecule, results in excessive activation of cytokine receptors and severe side effects upon systemic administration. Activation of (Fc receptorbearing) immune cells other than T cells may even reduce efficacy of the T cell activating bispecific antigen binding 40 molecule due to the potential destruction of T cells e.g. by NK cells.

Accordingly, in particular embodiments the Fc domain of the T cell activating bispecific antigen binding molecules according to the invention exhibits reduced binding affinity 45 to an Fc receptor and/or reduced effector function, as compared to a native  $IgG_1$  Fc domain. In one such embodiment the Fc domain (or the T cell activating bispecific antigen binding molecule comprising said Fc domain) exhibits less than 50%, preferably less than 20%, more preferably less 50 than 10% and most preferably less than 5% of the binding affinity to an Fc receptor, as compared to a native IgG<sub>1</sub> Fc domain (or a T cell activating bispecific antigen binding molecule comprising a native IgG<sub>1</sub> Fc domain), and/or less than 50%, preferably less than 20%, more preferably less 55 than 10% and most preferably less than 5% of the effector function, as compared to a native IgG<sub>1</sub> Fc domain domain (or a T cell activating bispecific antigen binding molecule comprising a native  $IgG_1$  Fc domain). In one embodiment, the Fc domain domain (or the T cell activating bispecific 60 antigen binding molecule comprising said Fc domain) does not substantially bind to an Fc receptor and/or induce effector function. In a particular embodiment the Fc receptor is an Fcy receptor. In one embodiment the Fc receptor is a human Fc receptor. In one embodiment the Fc receptor is an 65 activating Fc receptor. In a specific embodiment the Fc receptor is an activating human Fcy receptor, more specifi-

cally human FcyRIIa, FcyRI or FcyRIIa, most specifically human FcyRIIIa. In one embodiment the effector function is one or more selected from the group of CDC, ADCC, ADCP, and cytokine secretion. In a particular embodiment the effector function is ADCC. In one embodiment the Fc domain domain exhibits substantially similar binding affinity to neonatal Fc receptor (FcRn), as compared to a native IgG<sub>1</sub> Fc domain domain. Substantially similar binding to FcRn is achieved when the Fc domain (or the T cell activating bispecific antigen binding molecule comprising said Fc domain) exhibits greater than about 70%, particularly greater than about 80%, more particularly greater than about 90% of the binding affinity of a native IgG<sub>1</sub> Fc domain (or the T cell activating bispecific antigen binding molecule comprising a native  $IgG_1$  Fc domain) to FcRn.

In certain embodiments the Fc domain is engineered to have reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a non-engineered Fc domain. In particular embodiments, the Fc domain of the T cell activating bispecific antigen binding molecule comprises one or more amino acid mutation that reduces the binding affinity of the Fc domain to an Fc receptor and/or effector function. Typically, the same one or more amino acid mutation is present in each of the two subunits of the Fc domain. In one embodiment the amino acid mutation reduces the binding affinity of the Fc domain to an Fc receptor. In one embodiment the amino acid mutation reduces the binding affinity of the Fc domain to an Fc receptor by at least 2-fold, at least 5-fold, or at least 10-fold. In embodiments where there is more than one amino acid mutation that reduces the binding affinity of the Fc domain to the Fc receptor, the combination of these amino acid mutations may reduce the binding affinity of the Fc domain to an Fc receptor by at least 10-fold, at least 20-fold, or even at least 50-fold. In one embodiment the T cell activating bispecific antigen binding molecule comprising an engineered Fc domain exhibits less than 20%, particularly less than 10%, more particularly less than 5% of the binding affinity to an Fc receptor as compared to a T cell activating bispecific antigen binding molecule comprising a non-engineered Fc domain. In a particular embodiment the Fc receptor is an Fcy receptor. In some embodiments the Fc receptor is a human Fc receptor. In some embodiments the Fc receptor is an activating Fc receptor. In a specific embodiment the Fc receptor is an activating human Fcy receptor, more specifically human FcyRIIIa, FcyRI or FcyRIIa, most specifically human FcyRIIIa. Preferably, binding to each of these receptors is reduced. In some embodiments binding affinity to a complement component, specifically binding affinity to C1q, is also reduced. In one embodiment binding affinity to neonatal Fc receptor (FcRn) is not reduced. Substantially similar binding to FcRn, i.e. preservation of the binding affinity of the Fc domain to said receptor, is achieved when the Fc domain (or the T cell activating bispecific antigen binding molecule comprising said Fc domain) exhibits greater than about 70% of the binding affinity of a non-engineered form of the Fc domain (or the T cell activating bispecific antigen binding molecule comprising said non-engineered form of the Fc domain) to FcRn. The Fc domain, or T cell activating bispecific antigen binding molecules of the invention comprising said Fc domain, may exhibit greater than about 80% and even greater than about 90% of such affinity. In certain embodiments the Fc domain of the T cell activating bispecific antigen binding molecule is engineered to have reduced effector function, as compared to a non-engineered Fc domain. The reduced effector function can include, but is not

limited to, one or more of the following: reduced complement dependent cytotoxicity (CDC), reduced antibody-dependent cell-mediated cytotoxicity (ADCC), reduced antibody-dependent cellular phagocytosis (ADCP), reduced cytokine secretion, reduced immune complex-mediated 5 antigen uptake by antigen-presenting cells, reduced binding to NK cells, reduced binding to macrophages, reduced binding to monocytes, reduced binding to polymorphonuclear cells, reduced direct signaling inducing apoptosis, reduced crosslinking of target-bound antibodies, reduced 10 dendritic cell maturation, or reduced T cell priming. In one embodiment the reduced effector function is one or more selected from the group of reduced CDC, reduced ADCC, reduced ADCP, and reduced cytokine secretion. In a particular embodiment the reduced effector function is reduced 15 ADCC. In one embodiment the reduced ADCC is less than 20% of the ADCC induced by a non-engineered Fc domain (or a T cell activating bispecific antigen binding molecule comprising a non-engineered Fc domain).

In one embodiment the amino acid mutation that reduces 20 the binding affinity of the Pc domain to an Fc receptor and/or effector function is an amino acid substitution. In one embodiment the Fc domain comprises an amino acid substitution at a position selected from the group of E233, L234, L235, N297, P331 and P329. In a more specific embodiment 25 the Fc domain comprises an amino acid substitution at a position selected from the group of L234, L235 and P329. In some embodiments the Fc domain comprises the amino acid substitutions L234A and L235A. In one such embodiment, the Fc domain is an  $IgG_1$  Fc domain, particularly a human 30  $IgG_1$  Fc domain. In one embodiment the Fc domain comprises an amino acid substitution at position P329. In a more specific embodiment the amino acid substitution is P329A or P329G, particularly P329G. In one embodiment the Fc domain comprises an amino acid substitution at position 35 P329 and a further amino acid substitution at a position selected from E233, L234, L235, N297 and P331. In a more specific embodiment the further amino acid substitution is E233P, L234A, L235A, L235E, N297A, N297D or P331S. In particular embodiments the Fc domain comprises amino 40 ELISA, or by Surface Plasmon Resonance (SPR) using acid substitutions at positions P329, L234 and L235. In more particular embodiments the Fc domain comprises the amino acid mutations L234A, L235A and P329G ("P329G LALA"). In one such embodiment, the Fc domain is an  $IgG_1$ Fc domain, particularly a human IgG<sub>1</sub> Fc domain. The 45 "P329G LALA" combination of amino acid substitutions almost completely abolishes Fcy receptor binding of a human IgG<sub>1</sub> Fc domain, as described in PCT publication no. WO 2012/130831, incorporated herein by reference in its entirety. WO 2012/130831 also describes methods of pre- 50 paring such mutant Fc domains and methods for determining its properties such as Fc receptor binding or effector functions

IgG<sub>4</sub> antibodies exhibit reduced binding affinity to Fc receptors and reduced effector functions as compared to 55 IgG<sub>1</sub> antibodies. Hence, in some embodiments the Fc domain of the T cell activating bispecific antigen binding molecules of the invention is an IgG<sub>4</sub> Fc domain, particularly a human  $IgG_4$  Fc domain. In one embodiment the  $IgG_4$ Fc domain comprises amino acid substitutions at position 60 S228, specifically the amino acid substitution S228P. To further reduce its binding affinity to an Fc receptor and/or its effector function, in one embodiment the IgG<sub>4</sub> Fc domain comprises an amino acid substitution at position L235, specifically the amino acid substitution L235E. In another 65 embodiment, the IgG<sub>4</sub> Fc domain comprises an amino acid substitution at position P329, specifically the amino acid

substitution P329G. In a particular embodiment, the IgG<sub>4</sub> Fc domain comprises amino acid substitutions at positions S228, L235 and P329, specifically amino acid substitutions S228P, L235E and P329G. Such  $IgG_4$  Fc domain mutants and their Fcy receptor binding properties are described in PCT publication no. WO 2012/130831, incorporated herein by reference in its entirety.

In a particular embodiment the Fc domain exhibiting reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a native IgG<sub>1</sub> Fc domain, is a human IgG<sub>1</sub> Fc domain comprising the amino acid substitutions L234A, L235A and optionally P329G, or a human IgG<sub>4</sub> Fc domain comprising the amino acid substitutions S228P, L235E and optionally P329G.

In certain embodiments N-glycosylation of the Fc domain has been eliminated. In one such embodiment the Fc domain comprises an amino acid mutation at position N297, particularly an amino acid substitution replacing asparagine by alanine (N297A) or aspartic acid (N297D).

In addition to the Fc domains described hereinabove and in PCT publication no. WO 2012/130831, Fc domains with reduced Fc receptor binding and/or effector function also include those with substitution of one or more of Fc domain residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Pat. No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (U.S. Pat. No. 7,332,581).

Mutant Fc domains can be prepared by amino acid deletion, substitution, insertion or modification using genetic or chemical methods well known in the art. Genetic methods may include site-specific mutagenesis of the encoding DNA sequence, PCR, gene synthesis, and the like. The correct nucleotide changes can be verified for example by sequencing.

Binding to Fc receptors can be easily determined e.g. by standard instrumentation such as a BIAcore instrument (GE Healthcare), and Fc receptors such as may be obtained by recombinant expression. A suitable such binding assay is described herein. Alternatively, binding affinity of Fc domains or cell activating bispecific antigen binding molecules comprising an Fc domain for Fc receptors may be evaluated using cell lines known to express particular Fc receptors, such as human NK cells expressing FcyIIIa receptor.

Effector function of an Fc domain, or a T cell activating bispecific antigen binding molecule comprising an Fc domain, can be measured by methods known in the art. A suitable assay for measuring ADCC is described herein. Other examples of in vitro assays to assess ADCC activity of a molecule of interest are described in U.S. Pat. No. 5,500,362; Hellstrom et al. Proc Natl Acad Sci USA 83, 7059-7063 (1986) and Hellstrom et al., Proc Natl Acad Sci USA 82, 1499-1502 (1985); U.S. Pat. No. 5,821,337; Bruggemann et al., J Exp Med 166, 1351-1361 (1987). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, Calif.); and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, Wis.)). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g. in a animal model such as that disclosed in Clynes et al., Proc Natl Acad Sci USA 95, 652-656 (1998).

In some embodiments, binding of the Fc domain to a complement component, specifically to Clq, is reduced. 5 Accordingly, in some embodiments wherein the Fc domain is engineered to have reduced effector function, said reduced effector function includes reduced CDC. Clq binding assays may be carried out to determine whether the T cell activating bispecific antigen binding molecule is able to bind Clq and 10 hence has CDC activity. See e.g., Clq and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al., J Immunol Methods 202, 163 (1996); Cragg et al., Blood 101, 15 1045-1052 (2003); and Cragg and Glennie, Blood 103, 2738-2743 (2004)).

Fc Domain Modifications Promoting Heterodimerization The T cell activating bispecific antigen binding molecule of the invention comprise different antigen binding moieties, 20 some of which are fused to one or the other of the two subunits of the Fc domain, thus the two subunits of the Fc domain are typically comprised in two non-identical polypeptide chains. Recombinant co-expression of these polypeptides and subsequent dimerization leads to several possible combinations of the two polypeptides. To improve the yield and purity of the bispecific antibodies of the invention in recombinant production, it will thus be advantageous to introduce in the Fc domain of the bispecific antibodies of the invention a modification promoting the association of the 30 desired polypeptides.

Accordingly, in particular embodiments, the Fc domain of the bispecific antibodies of the invention comprises a modification promoting the association of the first and the second subunit of the Fc domain. The site of most extensive 35 protein-protein interaction between the two subunits of a human IgG Fc domain is in the CH3 domain of the Fc domain. Thus, in one embodiment said modification is in the CH3 domain of the Fc domain.

In a specific embodiment, said modification is a so-called 40 "knob-into-hole" modification, comprising a "knob" modification in one of the two subunits of the Fc domain and a "hole" modification in the other one of the two subunits of the Fc domain. The knob-into-hole technology is described e.g. in U.S. Pat. Nos. 5,731,168; 7,695,936; Ridgway et al., 45 Prot Eng 9, 617-621 (1996) and Carter, J Immunol Meth 248, 7-15 (2001).

Generally, the method involves introducing a protuberance ("knob") at the interface of a first polypeptide and a corresponding cavity ("hole") in the interface of a second 50 polypeptide, such that the protuberance can be positioned in the cavity so as to promote heterodimer formation and hinder homodimer formation. Protuberances are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains (e.g. tyrosine 55 or tryptophan). Compensatory cavities of identical or similar size to the protuberances are created in the interface of the second polypeptide by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine).

Accordingly, in a particular embodiment, in the CH3 60 domain of the first subunit of the Fc domain of the bispecific antibodies of the invention an amino acid residue is replaced with an amino acid residue having a larger side chain volume, thereby generating a protuberance within the CH3 domain of the first subunit which is positionable in a cavity 65 within the CH3 domain of the second subunit, and in the CH3 domain of the second subunit of the Fc domain an

amino acid residue is replaced with an amino acid residue having a smaller side chain volume, thereby generating a cavity within the CH3 domain of the second subunit within which the protuberance within the CH3 domain of the first subunit is positionable.

The protuberance and cavity can be made by altering the nucleic acid encoding the polypeptides, e.g. by site-specific mutagenesis, or by peptide synthesis.

In a specific embodiment, in the CH3 domain of the first subunit of the Fc domain the threonine residue at position 366 is replaced with a tryptophan residue (T366W), and in the CH3 domain of the second subunit of the Fc domain the tyrosine residue at position 407 is replaced with a valine residue (Y407V). In one embodiment, in the second subunit of the Fc domain additionally the threonine residue at position 366 is replaced with a serine residue (T366S) and the leucine residue at position 368 is replaced with an alanine residue (L368A).

In yet a further embodiment, in the first subunit of the Fc domain additionally the serine residue at position 354 is replaced with a cysteine residue (S354C), and in the second subunit of the Fc domain additionally the tyrosine residue at position 349 is replaced by a cysteine residue (Y349C). Introduction of these two cysteine residues results in formation of a disulfide bridge between the two subunits of the Fc domain, further stabilizing the dimer (Carter, J Immunol Methods 248, 7-15 (2001)).

In an alternative embodiment a modification promoting association of the first and the second subunit of the Fc domain comprises a modification mediating electrostatic steering effects, e.g. as described in WO 2009/089004. Generally, this method involves replacement of one or more amino acid residues at the interface of the two Fc domain subunits by charged amino acid residues so that homodimer formation becomes electrostatically unfavorable but heterodimerization electrostatically favorable.

In one embodiment, a T cell activating bispecific antigen binding molecule that binds to FolR1 and CD3 according to any of the above embodiments comprises an Immunoglobulin G (IgG) molecule with two binding sites specific for FolR1, wherein the Fc part of the first heavy chain comprises a first dimerization module and the Fc part of the second heavy chain comprises a second dimerization module allowing a heterodimerization of the two heavy chains of the IgG molecule.

In a further preferred embodiment, the first dimerization module comprises knobs and the second dimerization module comprises holes according to the knobs into holes strategy (see Carter P.; Ridgway J. B. B.; Presta L. G.: Immunotechnology, Volume 2, Number 1, February 1996, pp. 73-73(1)).

#### Biological Properties and Functional Characteristics of T Cell Activating Bispecific Antigen Binding Molecules

One of skill in the art can appreciate the advantageous efficiency of a molecule that selectively distinguishes between cancerous and non-cancerous, healthy cells. One way to accomplish this goal is by appropriate target selection. Markers expressed exclusively on tumor cells can be employed to selectively target effector molecules or cells to tumor cells while sparing normal cells that do not express such marker. However, in some instances, so called tumor cell markers are also expressed in normal tissue, albeit at lower levels. This expression in normal tissue raises the possibility of toxicity. Thus, there was a need in the art for molecules that can more selectively target tumor cells. The invention described herein provides for T cell activating bispecific antigen binding molecules that selectively target FolR1-positive tumor cells and not normal, non-cancerous cells that express FolR1 at low levels or not at all. In one 5 embodiment, the T cell activating bispecific antigen binding molecule comprises at least two, preferably two, FolR1 binding moieties of relatively low affinity that confer an avidity effect which allows for differentiation between high and low FolR1 expressing cells. Because tumor cells express 10 FolR1 at high or intermediate levels, this embodiment of the invention selectively binds to, and/or induces killing of, tumor cells and not normal, non-cancerous cells that express FolR1 at low levels or not at all. In one embodiment, the T cell activating bispecific antigen binding molecule is in the 15 2+1 inverted format. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of FolR1-positive tumor cells and not non-tumor cells and comprises a CD3 antigen binding moiety that comprises the heavy chain CDR1 of SEO ID 20 NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and two FolR1 antigen binding moieties that each comprise the 25 heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52, the light chain CDR2 of SEQ ID NO: 53, and the light chain CDR3 of SEQ ID NO:54.

In one specific embodiment, the T cell activating bispecific antigen binding molecule does not induce killing of a normal cells having less than about 1000 copies of FolR1 its surface.

embodiment of the invention does not require chemical cross linking or a hybrid approach to be produced. Accordingly, in one embodiment, the invention provides for T cell activating bispecific antigen binding molecule capable of production in CHO cells. In one embodiment, the T cell 40 nM and comprises a CD3 antigen binding moiety that activating bispecific antigen binding molecule comprises humanized and human polypeptides. In one embodiment, the T cell activating bispecific antigen binding molecule does not cause FcgR crosslinking. In one such embodiment, the T cell activating bispecific antigen binding molecule is 45 capable of production in CHO cells and comprises a CD3 antigen binding moiety that comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 50 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and two FolR1 antigen binding moieties that each comprise the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52,  $\ 55$ the light chain CDR2 of SEQ ID NO: 53, and the light chain CDR3 of SEQ ID NO:54.

As noted above, some embodiments contemplated herein include T cell activating bispecific antigen binding molecules having two binding moieties that confer specific 60 binding to FolR1 and one binding moiety that confers specificity to the T cell activating antigen CD3, wherein each individual FolR1 binding moiety engages the antigen with low affinity. Because the molecule comprises two antigen binding moieties that confer binding to FolR1, the overall 65 avidity of the molecule, nevertheless, provides effective binding to FolR1-expressing target cells and activation of T

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cells to induce T cell effector function. Considering that while FolR1 is expressed at various level on tumor cells, it is also expressed at very low levels (e.g., less than about 1000 copies on the cell surface) in certain normal cells, one of skill in the art can readily recognize the advantageous efficiency of such a molecule for use as a therapeutic agent. Such molecule selectively targets tumor cells over normal cells. Such molecule, thus, can be administered to an individual in need thereof with significantly less concern about toxicity resulting from FolR1 positive normal cells compared to molecules that bind to FolR1 with high affinity to induce effector function.

In one embodiment, the T cell activating bispecific antigen binding molecule binds human FolR1 with an apparent  $K_D$  of about 5.36 pM to about 4 nM. In one embodiment, the T cell activating bispecific antigen binding molecule binds human and cynomolgus FolR1 with an apparent  $K_D$  of about 4 nM. In one embodiment, the T cell activating bispecific antigen binding molecule binds murine FolR1 with an apparent  $K_D$  of about 1.5 nM. In one embodiment, the T cell activating bispecific antigen binding molecule binds human FolR1 with a monovalent binding  $K_D$  of at least about 1000 nM. In a specific embodiment, the T cell activating bispecific antigen binding molecule binds human and cynomolgus FolR1 with an apparent  $K_D$  of about 4 nM, binds murine FolR1 with an apparent  $K_D$  of about 1.5 nM, and comprises a CD3 antigen binding moiety that comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and two FolR1 antigen binding moieties that each comprise the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 In addition to the above advantageous characteristics, one 35 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52, the light chain CDR2 of SEQ ID NO: 53, and the light chain CDR3 of SEQ ID NO:54. In one embodiment, the T cell activating bispecific antigen binding molecule binds human FolR1 with a monovalent binding  $K_D$  of at least about 1000 comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and two FolR1 antigen binding moieties that each comprise the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52, the light chain CDR2 of SEQ ID NO: 53, and the light chain CDR3 of SEQ ID NO:54.

As described above, the T cell activating bispecific antigen binding molecules contemplated herein can induce T cell effector function, e.g., cell surface marker expression, cytokine production, T cell mediated killing. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of the FolR1-expressing target cell, such as a human tumor cell, in vitro. In one embodiment, the T cell is a CD8 positive T cell. Examples of FolR1-expressing human tumor cells include but are not limited to Hela, Skov-3, HT-29, and HRCEpiC cells. Other FolR1 positive human cancer cells that can be used for in vitro testing are readily available to the skilled artisan. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of the FolR1-expressing human tumor cell in vitro with an EC50 of between about 36 pM and about 39573 pM after 24 hours. Specifically contemplated are T cell activating bispecific antigen binding molecules that induce T cell mediated killing of the FolR1-expressing tumor cell in vitro with an EC50 of about 36 pM after 24 hours. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of the FolR1-expressing tumor cell in vitro with an EC50 of about 178.4 pM after 24 hours. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of the FolR1-expressing tumor cell in vitro with an EC50 of about 178.4 pM after 24 hours. In one embodiment, the T cell activating bispecific antigen binding molecule induces T cell mediated killing of the FolR1-expressing tumor cell in vitro with an EC50 of about 134.5 pM or greater after 48 hours. The EC50 can be measure by methods known in the art, for example by methods disclosed herein by the examples.

In one embodiment, the T cell activating bispecific antigen binding molecule of any of the above embodiments induces upregulation of cell surface expression of at least one of CD25 and CD69 on the T cell as measured by flow 15 cytometry. In one embodiment, the T cell is a CD4 positive T cell or a CD8 positive T cell.

In one embodiment, the T cell activating bispecific antigen binding molecule of any of the above embodiments binds to FoIR1 expressed on a human tumor cell. In one embodiment, the T cell activating bispecific antigen binding molecule of any of the above embodiments binds to a conformational epitope on human FolR1. In one embodiment, the T cell activating bispecific antigen binding molecule of any of the above embodiments does not bind to human Folate Receptor 2 (FolR2) or to human Folate Receptor 3 (FolR3). In one embodiment of the T cell activating bispecific antigen binding molecule of any of the above embodiments, the antigen binding moiety binds to a FolR1 polypeptide comprising the amino acids 25 to 234 of human FolR1 (SEQ ID NO:227). In one embodiment of the T cell activating bispecific antigen binding molecule of any 30 of the above embodiments, the FolR1 antigen binding moiety binds to a FolR1 polypeptide comprising the amino acid sequence of SEQ ID NOs:227, 230 and 231, and wherein the FolR1 antigen binding moiety does not bind to a FolR polypeptide comprising the amino acid sequence of SEQ ID NOs:228 and 229. In one specific embodiment, the T cell activating bispecific antigen binding molecule comprises a FolR1 antigen binding moiety that binds to a FolR1 polypeptide comprising the amino acid sequence of SEQ ID NOs:227, 230 and 231, and wherein the FolR1 antigen binding moiety does not bind to a FolR polypeptide com- 40 prising the amino acid sequence of SEQ ID NOs:228 and 229, and comprises a CD3 antigen binding moiety that comprises the heavy chain CDR1 of SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO:39, the light chain CDR1 of SEQ ID 45 NO: 32, the light chain CDR2 of SEO ID NO: 33, and the light chain CDR3 of SEQ ID NO:34 and two FolR1 antigen binding moieties that each comprise the heavy chain CDR1 of SEQ ID NO: 8, the heavy chain CDR2 of SEQ ID NO: 9, the heavy chain CDR3 of SEQ ID NO:50, the light chain CDR1 of SEQ ID NO: 52, the light chain CDR2 of SEQ ID 50 NO: 53, and the light chain CDR3 of SEQ ID NO:54.

With respect to the FolR1, the T cell activating bispecific antigen binding molecules contemplated herein can have agonist, antagonist or neutral effect. Examples of agonist effect include induction or enhancement of signaling through the FolR1 upon engagement by the FolR1 binding moiety with the FolR1 receptor on the target cell. Examples of antagonist activity include abrogation or reduction of signaling through the FolR1 upon engagement by the FolR1 binding moiety with the FolR1 receptor on the target cell. This can, for example, occur by blocking or reducting the interaction between folate with FolR1.

# Exemplary PD-1 Axis Binding Antagonists for Use in the Invention

Provided herein are methods for treating or delaying progression of cancer in an individual comprising adminis66

tering to the individual an effective amount of a T cell activating bispecific antigen binding molecule and a PD-1 axis binding antagonist. For example, a PD-1 axis binding antagonist includes a PD-1 binding antagonist, a PDL1 binding antagonist and a PDL2 binding antagonist. Alternative names for "PD-1" include CD279 and SLEB2. Alternative names for "PDL1" include B7-H1, B7-4, CD274, and B7-H. Alternative names for "PDL2" include B7-DC, Btdc, and CD273. In some embodiments, PD-1, PDL1, and PDL2 are human PD-1, PDL1 and PDL2.

In some embodiments, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to its ligand binding partners. In a specific aspect the PD-1 ligand binding partners are PDL1 and/or PDL2. In another embodiment, a PDL1 binding antagonist is a molecule that inhibits the binding of PDL1 to its binding partners. In a specific aspect, PDL1 binding partners are PD-1 and/or B7-1. In another embodiment, the PDL2 binding antagonist is a molecule that inhibits the binding of PDL2 to its binding partners. In a specific aspect, a PDL2 binding partner is PD-1. The antagonist may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. In some embodiments, the PD-1 binding antagonist is an anti-PD-1 antibody (e.g., a human antibody, a humanized antibody, or a chimeric antibody). In some embodiments, the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, and CT-011. In some embodiments, the PD-1 binding antagonist is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PDL1 or PDL2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 binding antagonist is AMP-224. Nivolumab, also known as MDX-1106-04, MDX-1106, ONO-4538, BMS-936558, and OPDIVO®, is an anti-PD-1 antibody described in WO2006/121168. Pembrolizumab, also known as MK-3475, Merck 3475, lambrolizumab, KEYTRUDA®, and SCH-900475, is an anti-PD-1 antibody described in WO2009/114335. CT-011, also known as hBAT or hBAT-1, is an anti-PD-1 antibody described in WO2009/ 101611. AMP-224, also known as B7-DCIg, is a PDL2-Fc fusion soluble receptor described in WO2010/027827 and WO2011/066342.

In some embodiments, the anti-PD-1 antibody is nivolumab (CAS Registry Number:946414-94-4). In a still further embodiment, provided is an isolated anti-PD-1 antibody comprising a heavy chain variable region comprising the heavy chain variable region amino acid sequence from SEQ ID NO:274 and/or a light chain variable region comprising the light chain variable region amino acid sequence from SEQ ID NO:275. In a still further embodiment, provided is an isolated anti-PD-1 antibody comprising a heavy chain and/or a light chain sequence, wherein:

(a) the heavy chain sequence has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to the heavy chain sequence:

(SEQ ID NO: 274)

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAV

 ${\tt IWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATND$ 

DYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV

65

TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDH

25

60

#### -continued

KPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK,

(b) the light chain sequences has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to the light chain sequence:

(SEO ID NO: 275) EIVLTOSPATLSLSPGERATLSCRASOSVSSYLAWYOOKPGOAPRLLIYD ASNRATGI PARFSGSGSGTDFTLTI SSLEPEDFAVYYCOOSSNWPRTFGO GTKVEIKRTVAAPSVFIFPPSDEOLKSGTASVVCLLNNFYPREAKVOWKV DNALOSGNSOESVTEODSKDSTYSLSSTLTLSKADYEKHKVYACEVTHOG LSSPVTKSFNRGEC

In some embodiments, the anti-PD-1 antibody is pembrolizumab (CAS Registry Number: 1374853-91-4). In a still further embodiment, provided is an isolated anti-PD-1 antibody comprising a heavy chain variable region compris- 30 ing the heavy chain variable region amino acid sequence from SEQ ID NO:276 and/or a light chain variable region comprising the light chain variable region amino acid sequence from SEQ ID NO:277. In a still further embodiment, provided is an isolated anti-PD-1 antibody comprising 35 a heavy chain and/or a light chain sequence, wherein:

(a) the heavy chain sequence has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to the  $\ ^{40}$ heavy chain sequence: QVQLVQSGVE

(SEO ID NO: 276) OVOLVOSGVE VKKPGASVKVSCKASGYTET NYYMYWVROA

PGOGLEWMGG INPSNGGTNF NEKFKNRVTLTTDSSTTTAY

MELKSLQFDD TAVYYCARRDYRFDMGFDYW

GQGTTVTVSSASTKGPSVFP LAPCSRSTSE

STAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLOSS

GLYSLSSVVT VPSSSLGTKTYTCNVDHKPS

NTKVDKRVESKYGPPCPPCP APEFLGGPSV

FLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVD

GVEVHNAKTK PREEQFNSTYRVVSVLTVLH

QDWLNGKEYKCKVSNKGLPS SIEKTISKAK

GQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVE

WESNGQPENN YKTTPPVLDSDGSFFLYSRL

TVDKSRWQEGNVFSCSVMHE ALHNHYTQKS LSLSLGK,

(b) the light chain sequences has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to the light chain sequence:

(SEO ID NO: 277) EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRL

 $\verb"LIYLASYLESGVPARFSGSSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPL"$ 

10 TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV

 ${\tt QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV}$ 

THQGLSSPVT KSFNRGEC.

In some embodiments, the PDL1 binding antagonist is anti-PDL1 antibody. In some embodiments, the anti-PDL1 binding antagonist is selected from the group consisting of YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736. MDX-1105, also known as BMS-936559, is an 20 anti-PDL1 antibody described in WO2007/005874. Antibody YW243.55.S70 (heavy and light chain variable region sequences shown in SEQ ID Nos. 20 and 21, respectively) is an anti-PDL1 described in WO 2010/077634 A1. MEDI4736 is an anti-PDL1 antibody described in WO2011/ 066389 and US2013/034559, each incorporated herein by

reference as if set forth in their entirety. Examples of anti-PDL1 antibodies useful for the methods of this invention, and methods for making thereof are

described in PCT patent application WO 2010/077634 A1 and U.S. Pat. No. 8,217,149, each incorporated herein by reference as if set forth in their entirety. In some embodiments, the PD-1 axis binding antagonist is an anti-PDL1 antibody. In some embodiments, the anti-PDL1 antibody is capable of inhibiting binding between PDL1 and PD-1 and/or between PDL1 and B7-1. In some embodiments, the anti-PDL1 antibody is a monoclonal antibody. In some embodiments, the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragments. In some embodiments, the anti-PDL1 antibody is a humanized antibody. In some embodiments, the anti-PDL1 antibody is a human antibody.

The anti-PDL1 antibodies useful in this invention, including compositions containing such antibodies, such as those described in WO 2010/077634 A1, may be used in combi-45 nation with a T cell activating antigen binding molecule, and, optionally an anti-TIM3 antagonist antibody, to treat cancer. In some embodiments, the anti-PDL1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:382 and a light chain variable 50 region comprising the amino acid sequence of SEQ ID NO:383.

In one embodiment, the anti-PDL1 antibody contains a heavy chain variable region polypeptide comprising an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein:

(a) the HVR-H1 sequence is GFTFSX1SWIH (SEQ ID 55 NO:283);

(b) the HVR-H2 sequence is AWIX2PYGGSX3-YYADSVKG (SEQ ID NO:284);

(c) the HVR-H3 sequence is RHWPGGFDY (SEQ ID NO:285);

further wherein: X1 is D or G; X2 is S or L; X3 is T or S. In one specific aspect, X1 is D; X2 is S and X3 is T. In another aspect, the polypeptide further comprises variable region heavy chain framework sequences juxtaposed

between the HVRs according to the formula: (HC-FR1)-65 (HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVRH3)-

(HC-FR4). In yet another aspect, the framework sequences

are derived from human consensus framework sequences. In a further aspect, the framework sequences are VH subgroup III consensus framework. In a still further aspect, at least one of the framework sequences is the following:

			(SEQ	ID	NO :	295)	
HC-FR1	is	EVQLVESGGGLVQPGGSLRLSC	AAS				
HC-FR2	is	WVRQAPGKGLEWV	(SEQ	ID	NO :	296)	10
			(SEQ	ID	NO :	297)	
HC-FR3	is	RFTISADTSKNTAYLQMNSLRA	EDTA	YYY	CAR		
HC-FR4	is	WGQGTLVTVSA.	(SEQ	ID	NO:	298)	15

In a still further aspect, the heavy chain polypeptide is further combined with a variable region light chain comprising an HVR-L1, HVR-L2 and HVR-L3, wherein:

- (a) the HVR-L1 sequence is RASQX4X5X6TX7X8A  $_{20}$  (SEQ ID NO:286);
- (b) the HVR-L2 sequence is SASX9LX10S, (SEQ ID NO:287);
- (c) the HVR-L3 sequence is QQX11X12X13X14PX15T (SEQ ID NO:288);

further wherein: X4 is D or V; X5 is V or I; X6 is S or N; X7 is A or F; X8 is V or L; X9 is F or T; X10 is Y or A; X11 is Y, G, F, or S; X12 is L, Y, F or W; X13 is Y, N, A, T, G, F or I; X14 is H, V, P, T or I; X15 is A, W, R, P or T.

In a still further aspect, X4 is D; X5 is V; X6 is S; X7 is A; X8 is V; X9 is F; X10 is Y; X11 is Y; X12 is L; X13 is Y; X14 is H; X15 is A. In a still further aspect, the light chain further comprises variable region light chain framework sequences juxtaposed between the HVRs according to the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LCFR4).

In a still further aspect, the framework sequences are derived from human consensus framework sequences. In a still further aspect, the framework sequences are VL kappa I consensus framework. In a still further aspect, at least one  $_{40}$  of the framework sequence is the following:

LC-FR1 i	is	DIQMTQSPSSLSASVGDRVTIT	(SEQ C	ID	NO :	300)	
LC-FR2 i	is	WYQQKPGKAPKLLIY	(SEQ	ID	NO :	301)	45
LC-FR3 i	is	GVPSRFSGSGSGTDFTLTISSL	(SEQ QPEDF	ID ATY	NO: YYC	302)	
LC-FR4 i	is	FGQGTKVEIKR.	(SEQ	ID	NO :	303)	50

In another embodiment, provided is an isolated anti-PDL1 antibody or antigen binding fragment comprising a heavy chain and a light chain variable region sequence, wherein: 55

- (a) the heavy chain comprises and HVR-H1, HVR-H2 and HVR-H3, wherein further:
- (i) the HVR-H1 sequence is GFTFSX1SWIH (SEQ ID NO:283)
- (ii) the HVR-H2 sequence is AWIX2PYGGSX3- 60 YYADSVKG (SEQ ID NO:284)
- (iii) the HVR-H3 sequence is RHWPGGFDY (SEQ ID NO:285)
- (b) the light chain comprises and HVR-L1, HVR-L2 and HVR-L3, wherein further:
- (i) the HVR-L1 sequence is RASQX4X5X6TX7X8A (SEQ ID NO:286)

- (ii) the HVR-L2 sequence is SASX9LX10S (SEQ ID NO:287)
- (iii) the HVR-L3 sequence is QQX11X12X13X14PX15T
  (SEQ ID NO:288) Further wherein: X1 is D or G; X2 is S or L; X3 is T or S; X4 is D or V; X5 is V or I; X6 is S or N; X7 is A or F; X8 is V or L; X9 is F or T; X10 is Y or A; X11 is Y, G, F, or S; X12 is L, Y, F or W; X13 is Y, N, A, T, G, F or I; X14 is H, V, P, T or I; X15 is A, W, R, P or T.

In a specific aspect, X1 is D; X2 is S and X3 is T. In another aspect, X4 is D; X5 is V; X6 is S; X7 is A; X8 is V; X9 is F; X10 is Y; X11 is Y; X12 is L; X13 is Y; X14 is H; X15 is A. In yet another aspect, X1 is D; X2 is S and X3 is T, X4 is D; X5 is V; X6 is S; X7 is A; X8 is V; X9 is F; X10

is Y; X11 is Y; X12 is L; X13 is Y; X14 is H and X15 is A. In a further aspect, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HCFR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVRL2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In a still further aspect, the framework sequences are derived from human consensus framework sequences. In a still further aspect, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further aspect, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further aspect, one or more of the heavy chain framework sequences is the following:

HC-FR1	( 90	тп	NO.	205)	
EVQLVESGGGLVQPGGSLRLSCAAS	(SEQ	тD	110:	295)	
HC-FR2	(000	ID	NO :	200	
WVRQAPGKGLEWV	(SEQ			290)	
HC-FR3	(CEO	-	110	207)	
RFTISADTSKNTAYLQMNSLRAEDTAV	YYCAF	202	щО:	297)	
HC-FR4	(CEO	-	110	2001	
WGQGTLVTVSA.	(SEQ	тр	110:	290)	

In a still further aspect, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further aspect, the light chain framework sequences are VL kappa I consensus framework. In a still further aspect, one or more of the light chain framework sequences is the following:

LC-FR1	(CEO	TD	NO	200)	
DIQMTQSPSSLSASVGDRVTITC	(SEQ	тD	110:	300)	
LC-FR2	(SEQ	ID	NO	201)	
WYQQKPGKAPKLLIY			110:	301)	
LC-FR3	(	-	NO	2021	
GVPSRFSGSGSGTDFTLTISSLQPEDF	(SEQ ATYYC	;	NO:	302)	
LC-FR4	(000	ID	NO	2021	
FGOGTKVEIKR.	(SEQ		110:	303)	

In a still further specific aspect, the antibody further comprises a human or murine constant region. In a still further aspect, the human constant region is selected from the group consisting of  $IgG_1$ ,  $IgG_2$ ,  $IgG_2$ ,  $IgG_3$ ,  $IgG_4$ . In a still further specific aspect, the human constant region is  $IgG_1$ . In a still further aspect, the murine constant region is selected from the group consisting of  $IgG_1$ ,  $IgG_2A$ ,  $IgG_2B$ ,  $IgG_3$ . In a still further aspect, the murine constant region if  $IgG_2A$ . In a still further specific aspect, the antibody has reduced or minimal effector function. In a still further specific aspect the minimal effector function results from an "effectorless Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region. 15

In yet another embodiment, provided is an anti-PDL1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:

- (a) the heavy chain further comprises and HVR-H1, HVR-H2 and an HVRH3 sequence having at least 85% 20 sequence identity to GFTFSDSWIH (SEQ ID NO:289), AWISPYGGSTYYADSVKG (SEQ ID NO:290), and RHWPGGFDY (SEQ ID NO:291), respectively, or
- (b) the light chain further comprises an HVR-L1, HVR- <sup>25</sup> L2 and an HVR-L3 sequence having at least 85% sequence identity to RASQDVSTAVA (SEQ ID NO:292), SASFLYS (SEQ ID NO:293) and QQYLYH-PAT (SEQ ID NO:294), respectively. In a specific aspect, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another aspect, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HCFR1)-35 (HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In yet another aspect, the framework sequences are derived from human consensus framework sequences. In a still further aspect, the heavy chain framework sequences are derived from a Kabat sub
  - group I, II, or III sequence. In a still further aspect, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further aspect, one or more of the heavy chain framework sequences is the following:

HC-FR1	(550	тп	NO :	295)
EVQLVESGGGLVQPGGSLRLSCAAS	(5EQ	10		2937
HC-FR2	(950	TD	NO:	2061
WVRQAPGKGLEWV	(SEQ	ID		296)
HC-FR3	(000	TD	No	007)
RFTISADTSKNTAYLQMNSLRAEDTAV	(SEQ /YYCAI	5 7 D	NO:	297)
HC-FR4	(000	TD	No	000)
WGOGTLVTVSA.	(SEQ	тD	NO:	Z98)

In a still further aspect, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV 65 subgroup sequence. In a still further aspect, the light chain framework sequences are VL kappa I consensus framework.

In a still further aspect, one or more of the light chain framework sequences is the following:

LC-FR1	(CEO	ID	NO :	2001
DIQMTQSPSSLSASVGDRVTITC	(SEQ			3007
LC-FR2	(SEQ	ID	NO:	201)
WYQQKPGKAPKLLIY				501)
LC-FR3	(970	тп	NO.	2021
GVPSRFSGSGSGTDFTLTISSLQPEDF	ATYYO	;	NO:	302)
LC-FR4	(980)	TD	NO :	303)
FGQGTKVEIKR.	(PEQ	тD		505)

In a still further specific aspect, the antibody further comprises a human or murine constant region. In a still further aspect, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific aspect, the human constant region is IgG1. In a still further aspect, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further aspect, the murine constant region if IgG2A. In a still further specific aspect, the antibody has reduced or minimal effector function. In a still further specific aspect the minimal effector function results from an "effectorless Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In a still further embodiment, provided is an isolated anti-PDL1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence:

(SEQ ID NO: 382) 40 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAW

ISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRH

WPGGFDYWGQGTLVTVSA,

(b) the light chain sequence has at least 85% sequence identity to the light chain sequence:

(SEQ ID NO: 383) DIOMTOSPSSLSASVGDRVTITCRASODVSTAVAWYOOKPGKAPKLLIYS

ASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQ

#### GTKVEIKR

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In a specific aspect, the sequence identity is 86%, 87%, 55 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another aspect, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HCFR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4),

and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(1-1VR-L3)-(LC-FR4). In yet another aspect, the framework sequences are derived from human consensus framework sequences. In a further aspect, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further aspect, the heavy chain framework

work sequence is a VH subgroup III consensus framework. In a still further aspect, one or more of the heavy chain framework sequences is the following:

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HC-FR1	(550	тп	NO ·	295)	
EVQLVESGGGLVQPGGSLRLSCAAS	(DEQ	10	NO .	255,	
HC-FR2	(SEO	тп	NO.	296)	
WVRQAPGKGLEWV	(DEQ	10	NO.	2907	10
HC-FR3	(000	TD	NO	207)	
RFTISADTSKNTAYLQMNSLRAEDTAV	YYYCAF	5 T D	NO:	297)	
HC-FR4	(0.00	TD	110	0.00)	15
WGQGTLVTVSA.	(SEQ	ID	NO:	298)	

In a still further aspect, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV <sup>20</sup> subgroup sequence. In a still further aspect, the light chain framework sequences are VL kappa I consensus framework. In a still further aspect, one or more of the light chain framework sequences is the following:

LC-FR1	(CEO ID NO. 200)		
DIQMTQSPSSLSASVGDRVTITC	(SEQ ID NO: 300)		
LC-FR2	(SEO TO NO. 201) 3	0	
WYQQKPGKAPKLLIY	(SEQ ID NO: 301)		
LC-FR3	(SEO ID NO. 202)		
GVPSRFSGSGSGTDFTLTISSLQPED	FATYYC 3	5	
LC-FR4	(SEO ID NO: 303)		
FGOGTKVEIKR.	(512 12 10. 505)		

In a still further specific aspect, the antibody further comprises a human or murine constant region. In a still  $^{\rm 40}$ further aspect, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific aspect, the human constant region is IgG1. In a still further aspect, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, 45 IgG3. In a still further aspect, the murine constant region if IgG2A. In a still further specific aspect, the antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from production in prokaryotic cells. In a still further specific 50 aspect the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In another further embodiment, provided is an isolated <sup>55</sup> anti-PDL1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence

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(SEQ ID NO: 280) EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAW

ISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRH

WPGGFDYWGQGTLVTVSS,

(b) the light chain sequence has at least 85% sequence identity to the light chain sequence:

(SEQ ID NO: 383) DIOMTOSPSSLSASVGDRVTITCRASODVSTAVAWYOOKPGKAPKLLIYS

ASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQ

#### 10 GTKVEIKR.

or

In a still further embodiment, provided is an isolated anti-PDL1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence:

(SEQ ID NO: 281) EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAW

ISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRH

WPGGFDYWGQGTLVTVSSASTK,

or (b) the light chain sequences has at least 85% sequence identity to the light chain sequence:

(SEQ ID NO: 282)

DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYS

 ${\tt ASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQ}$ 

#### GTKVEIKR.

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In a specific aspect, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another aspect, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HCFR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4),

and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-

(HVR-L3)-(LC-FR4). In yet another aspect, the framework sequences are derived from human consensus framework sequences. In a further aspect, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or HI sequence. In a still further aspect, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further aspect, one or more of the heavy chain framework sequences is the following:

HC-FR1	(SEQ	ID	NO:	295)
EVQLVESGGGLVQPGGSLRLSCAAS				293)
HC-FR2	( 950	тп	NO .	296)
WVRQAPGKGLEWV	(552	тD	110.	250,
HC-FR3	( 90	тп	NO.	297)
RFTISADTSKNTAYLQMNSLRAEDTAV	YYCAF	202	NO:	297)
HC-FR4	(CEO	TD	NO	200)
WGQGTLVTVSS.	(PEQ	чD	110:	2991

In a still further aspect, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV

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subgroup sequence. In a still further aspect, the light chain framework sequences are VL kappa I consensus framework. In a still further aspect, one or more of the light chain framework sequences is the following:

LC-FR1
(SEQ ID NO: 300)
DIQMTQSPSSLSASVGDRVTITC
LC-FR2
(SEQ ID NO: 301)
WYQQKPGKAPKLLIY
LC-FR3
(SEQ ID NO: 302)
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
LC-FR4
(SEQ ID NO: 303)
FGQGTKVEIKR.

In a still further specific aspect, the antibody further 20 comprises a human or murine constant region. In a still further aspect, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific aspect, the human constant region is IgG1. In a still further aspect, the murine constant region is 25 selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further aspect, the murine constant region if IgG2A. In a still further specific aspect, the antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from production in prokaryotic cells. In a still further specific 30 aspect the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In yet another embodiment, the anti-PDL1 antibody is 35 MPDL3280A (CAS Registry Number: 1422185-06-5). In a still further embodiment, provided is an isolated anti-PDL1 antibody comprising a heavy chain variable region comprising the heavy chain variable region amino acid sequence from SEQ ID NO:24 or SEQ ID NO:28 and/or a light chain variable region amino acid sequence from SEQ ID NO:21. In a still further embodiment, provided is an isolated anti-PDL1 antibody comprising a heavy chain and/or a light chain sequence, wherein:

(a) the heavy chain sequence has at least 85%, at least 45 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to the heavy chain sequence:

(SEQ ID NO: 278) EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAW	
ISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRH	55
WPGGFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY	55
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI	
CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD	
${\tt TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST$	60
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY	
TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD	
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG,	65

(b) the light chain sequences has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to the light chain sequence:

(SEQ ID NO: 279) DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYS

ASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQ

GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

 ${\tt DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG}$ 

15 LSSPVTKSFNRGEC.

In a still further embodiment, the invention provides for compositions comprising any of the above described anti-PDL1 antibodies in combination with at least one pharmaceutically acceptable carrier.

In a still further embodiment, provided is an isolated nucleic acid encoding a light chain or a heavy chain variable region sequence of an anti-PDL1 antibody, wherein: (a) the heavy chain further comprises and HVR-H1, HVR-H2 and an HVRH3 sequence having at least 85% sequence identity to GFTFSDSWIH (SEQ ID NO:289), AWISPYGGSTYY-ADSVKG (SEQ ID NO:290) and RHWPGGFDY (SEQ ID NO:291), respectively, and

(b) the light chain further comprises an HVR-L1, HVR-L2 and an HVR-L3 sequence having at least 85% sequence identity to RASQDVSTAVA (SEQ ID NO:292), SASFLYS (SEQ ID NO:293) and QQYLYH-PAT (SEQ ID NO:294), respectively.

In a specific aspect, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In aspect, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LCFR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-

(LC-FR4). In yet another aspect, the framework sequences are derived from human consensus framework sequences. In a further aspect, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further aspect, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further aspect, one or more of the heavy chain framework sequences is the following:

HC-FR1	(950	TD	NO:	205)
EVQLVESGGGLVQPGGSLRLSCAAS	(PEQ	ц		295)
HC-FR2	(SEQ	ID	NO:	296)
WVRQAPGKGLEWV				250,
HC-FR3	( 550	тп	NO ·	297)
RFTISADTSKNTAYLQMNSLRAEDTAV	YYCAF	2	10:	291)
HC-FR4	(SEQ	ID	NO :	298)
WGQGTLVTVSA.				290,

In a still further aspect, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV

subgroup sequence. In a still further aspect, the light chain framework sequences are VL kappa I consensus framework. In a still further aspect, one or more of the light chain framework sequences is the following:

LC-FR1	(970	тп	NO:	300)
DIQMTQSPSSLSASVGDRVTITC	(PEQ	10		3007
LC-FR2	(070	TD	NO :	201)
WYQQKPGKAPKLLIY	(SEQ	TD		301)
LC-FR3	(470			
GVPSRFSGSGSGTDFTLTISSLQPED	(SEQ FATYY)	с ТД	NO:	302)
LC-FR4	(			
FGQGTKVEIKR.	(SEQ	ΤD	NO :	303)

In a still further specific aspect, the antibody described 20 herein (such as an anti-PD-1 antibody, an anti-PDL1 antibody, or an anti-PDL2 antibody) further comprises a human or murine constant region. In a still further aspect, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific 25 aspect, the human constant region is IgG1. In a still further aspect, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further aspect, the murine constant region if IgG2A. In a still further specific aspect, the antibody has reduced or minimal effector 30 function. In a still further specific aspect, the minimal effector function results from production in prokaryotic cells. In a still further specific aspect the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further aspect, the effector-less Fc 35 mutation is an N297A or D265A/N297A substitution in the constant region.

In a still further aspect, provided herein are nucleic acids encoding any of the antibodies described herein. In some embodiments, the nucleic acid further comprises a vector 40 suitable for expression of the nucleic acid encoding any of the previously described anti-PDL1, anti-PD-1, or anti-PDL2 antibodies. In a still further specific aspect, the vector further comprises a host cell suitable for expression of the nucleic acid. In a still further specific aspect, the host cell is 45 a eukaryotic cell or a prokaryotic cell. In a still further specific aspect, the eukarvotic cell is a mammalian cell, such as Chinese Hamster Ovary (CHO).

The antibody or antigen binding fragment thereof, may be made using methods known in the art, for example, by a 50 process comprising culturing a host cell containing nucleic acid encoding any of the previously described anti-PDL1, anti-PD-1, or anti-PDL2 antibodies or antigen-binding fragment in a form suitable for expression, under conditions suitable to produce such antibody or fragment, and recov- 55 ering the antibody or fragment.

In some embodiments, the isolated anti-PDL1 antibody is aglycosylated.

Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohy- 60 drate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-Xthreonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the 65 presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked gly-

cosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. Removal of glycosylation sites form an antibody is conveniently accomplished by altering the amino acid sequence such that one of the above-described tripeptide sequences (for N-linked glycosylation sites) is removed. The alteration may be made by substitution of an asparagine, 10 serine or threonine residue within the glycosylation site another amino acid residue (e.g., glycine, alanine or a conservative substitution).

In any of the embodiments herein, the isolated anti-PDL1 antibody can bind to a human PDL1, for example a human 15 PDL1 as shown in UniProtKB/Swiss-Prot Accession No. O9NZO7.1, or a variant thereof.

In a still further embodiment, the invention provides for a composition comprising an anti-PDL1, an anti-PD-1, or an anti-PDL2 antibody or antigen binding fragment thereof as provided herein and at least one pharmaceutically acceptable carrier. In some embodiments, the anti-PDL1, anti-PD-1, or anti-PDL2 antibody or antigen binding fragment thereof administered to the individual is a composition comprising one or more pharmaceutically acceptable carrier.

Any of the pharmaceutically acceptable carriers described herein or known in the art may be used.

In some embodiments, the anti-PDL1 antibody described herein is in a formulation comprising the antibody at an amount of about 60 mg/mL, histidine acetate in a concentration of about 20 mM, sucrose in a concentration of about 120 mM, and polysorbate (e.g., polysorbate 20) in a concentration of 0.04% (w/v), and the formulation has a pH of about 5.8. In some embodiments, the anti-PDL1 antibody described herein is in a formulation comprising the antibody in an amount of about 125 mg/mL, histidine acetate in a concentration of about 20 mM, sucrose is in a concentration of about 240 mM, and polysorbate (e.g., polysorbate 20) in a concentration of 0.02% (w/v), and the formulation has a pH of about 5.5.

#### Exemplary TIM3 Antagonists for Use in the Invention

Provided herein are methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a T cell activating bispecific antigen binding molecule, a PD-1 axis binding antagonist, and a TIM-3 antagonist. In one embodiment, the TIM-3 antagonist is an anti-TIM-3 antibody. In some embodiments, the anti-TIM3 induces internalization of TIM3 expressed on a cell of at least 45% after 120 Minutes at 37° C. as determined by FACS analysis. The cell is, e.g., a RPMI8226 cells (ATCC CCL-155TM). In one embodiment, the antibody induces internalization of TIM3 on TIM3 expressing RPMI8226 cells (ATCC CCL-155™) of at least 55% after 120 Minutes at 37° C. as determined by FACS analysis. In one embodiment, the antibody induces internalization of TIM3 on TIM3 expressing RPMI8226 cells (ATCC® CCL-155™) of at least 60% after 240 Minutes at 37° C. as determined by FACS analysis. In one embodiment, the antibody induces internalization of TIM3 on TIM3 expressing RPMI8226 cells (ATCC® CCL-155TM) of at least 65% after 240 Minutes at 37° C. as determined by FACS analysis.

In some embodiments, the anti-TIM3 antibody competes for binding to TIM3 with an anti-Tim3 antibody comprising the VH and VL of Tim3\_0016. In some embodiments, the anti-TIM3 antibody binds to a human and cynomolgoues TIM3. In some embodiments, the anti-TIM3 antibody shows as a immunoconjugate a cytotoxic activity on TIM3 expressing cells. In one such embodiment, the immunoconjugate has a relative IC50 value of the cytotoxic activity as 5 Pseudomonas exotoxin A conjugate on RPMI-8226 cells of 0.1 or lower. In one embodiment, the anti-TIM3 antibody induces interferon-gamma release as determined by MLR assav.

In certain embodiments, the anti-TIM3 antibody binds to 10 a human and cynomolgoues TIM3 and induces interferongamma release as determined by a MLR assay.

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID 15 NO:304; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:306; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:307; or HVR-L1 comprising the amino acid sequence of SEO ID NO:314: 20 HVR-L1 comprising the amino acid sequence of SEQ ID NO:315; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

HVR-H1 comprising the amino acid sequence of SEQ ID NO:304; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:306; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:307; or HVR-L1 comprising the amino acid sequence of SEQ ID NO:314; or HVR-L1 comprising the amino acid sequence of SEQ ID NO:315; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308; and (I) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:304; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:306; (d) HVR-L1 comprising the 40 amino acid sequence of SEQ ID NO:307; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308; and (1) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

HVR-H1 comprising the amino acid sequence of SEQ ID NO:304; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:306; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:314; (e) HVR-L2 50 comprising the amino acid sequence of SEQ ID NO:308; and (f) HVR-L3 comprising the amino acid sequence of SEO ID NO:309.

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID 55 NO:304; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:306; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:315; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308; 60 and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 com- 65 prising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID

NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:307; or HVR-L1 comprising the amino acid sequence of SEO ID NO:314; or HVR-L1 comprising the amino acid sequence of SEO ID NO:315; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:307; or HVR-L1 comprising the amino acid sequence of SEQ ID NO:314; or HVR-L1 comprising the amino acid sequence of SEQ ID NO:315; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

In one embodiment, the anti-TIM3 antibody comprises (a) In one embodiment, the anti-TIM3 antibody comprises (a) 25 a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:307; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

> In one embodiment, the anti-TIM3 antibody comprises (a) 35 a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:314; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

In one embodiment, the anti-TIM3 antibody comprises (a) In one embodiment, the anti-TIM3 antibody comprises (a) 45 a VH domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:304, (ii) HVR-H2 comprising the amino acid sequence of SEO ID NO:305, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:306; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:315; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:308 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:309.

> In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:310 and a VL sequence of SEQ ID NO:311;

- ii) comprises a VH sequence of SEQ ID NO:312 and a VL sequence of SEQ ID NO:313;
- iii) or humanized variant of the VH and VL of the antibody under i) or ii).

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:316; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:317; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:318; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:319; (e) HVR-L2

comprising the amino acid sequence of SEQ ID NO:320; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:321.

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID 5 NO:316; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:317; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:318; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:319; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:320; 10 and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:321.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 com-15 prising the amino acid sequence of SEQ ID NO:316, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:317, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:318; and (b) a VL domain comprising at least one, at least two, or all three VL 20 HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:319; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:320 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:321. 25

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:316, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:317, and (iii) HVR-H3 comprising an amino acid sequence selected from 30 SEQ ID NO:318; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:319; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:320 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:321. 35

In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:322 and a VL

- sequence of SEQ ID NO:322 and sequence of SEQ ID NO:322 and
- ii) or humanized variant of the VH and VL of the antibody under i).

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:324; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:325; (c) HVR-H3 comprising the amino acid 45 sequence of SEQ ID NO:326; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:327; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:328; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:329. 50

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:324; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:325; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:326; (d) HVR-L1 comprising the 55 amino acid sequence of SEQ ID NO:326; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:328; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:329.

In one embodiment, the anti-TIM3 antibody comprises (a) 60 a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:324, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:325, and (iii) HVR-H3 comprising an amino acid 65 sequence selected from SEQ ID NO:326; and (b) a VL domain comprising at least one, at least two, or all three VL

HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:327; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:328 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:329.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:324, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:325, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:326; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:327; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:328 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:328 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:328 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:328 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:329.

- In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:330 and a VL sequence of SEQ ID NO:331;
- ii) or humanized variant of the VH and VL of the antibody under i).

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:332; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:333; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:334; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:335; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:336; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:337.

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:332; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:333; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:334; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:335; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:336; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:337.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:332, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:333, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:334; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:335; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:336 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:337.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:332, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:333, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:334; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:335; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:336 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:336 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:336 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:337.

- In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:338 and a VL sequence of SEQ ID NO:339;
- ii) or humanized variant of the VH and VL of the antibody under i).

In one aspect, the invention provides an anti-TIM3 antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:340; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:341; (c) HVR-H3 comprising the amino acid sequence of SEO ID NO:342; (d) HVR-L1 comprising the amino acid sequence of SEO ID NO:343; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:344; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:345.

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:340; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:341; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:342; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:343; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:344; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:345.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:340, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID 25 NO:341, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:342; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:343; (ii) HVR-L2 30 comprising the amino acid sequence of SEQ ID NO:344 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:345.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino 35 acid sequence of SEQ ID NO:340, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:341, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:342; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID 40 HVR-H1 comprising the amino acid sequence of SEQ ID NO:343; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:344 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:345.

In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:346 and a VL  $\,$  45

- sequence of SEQ ID NO:347; ii) or humanized variant of the VH and VL of the antibody
- under i).

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from 50 (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:348; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:349; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:350; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:351; (e) HVR-L2 55 comprising the amino acid sequence of SEQ ID NO:352; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:353.

In one aspect, the invention provides an anti-TIM3 antibody comprising (a) HVR-H1 comprising the amino acid 60 sequence of SEQ ID NO:348; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:349; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:350; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:351; (e) HVR-L2 comprising the amino acid sequence 65 of SEQ ID NO:352; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:353.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:348, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:349, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:350; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:351; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:352 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:353.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-HI comprising the amino acid sequence of SEQ ID NO:348, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:349, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:350; and (b) a VL domain comprising (i) 20 HVR-L1 comprising the amino acid sequence of SEO ID NO:351; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:352 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:353.

- In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:354 and a VL sequence of SEQ ID NO:355;
- ii) or humanized variant of the VH and VL of the antibody under i).

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:356; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:357; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:358; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:359; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:360; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:361.

In one embodiment, the anti-TIM3 antibody comprises (a) NO:356; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:357; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:358; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:359; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:360; and (f) HVR-L3 comprising the amino acid sequence of SEO ID NO:361.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:356, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 357, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 358; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 359; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:360 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:361.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 356, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 357, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 358; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID

NO: 359; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:360 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:361.

In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:362 and a VL 5 sequence of SEQ ID NO:363;

ii) or humanized variant of the VH and VL of the antibody under i).

In one embodiment, the anti-TIM3 antibody comprises at least one, two, three, four, five, or six HVRs selected from 10 (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:364; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:365; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:366; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:367; (e) HVR-L2 15 comprising the amino acid sequence of SEQ ID NO:368; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:369.

In one embodiment, the anti-TIM3 antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID 20 NO:364; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:365; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:366; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:367; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:368; 25 and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:369.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 com-30 prising the amino acid sequence of SEQ ID NO:364, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:365, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:366; and (b) a VL domain comprising at least one, at least two, or all three VL 35 HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:367; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:368 and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:369.

In one embodiment, the anti-TIM3 antibody comprises (a) a VH domain comprising (i) HVR-HI comprising the amino acid sequence of SEQ ID NO:364, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:365, and (iii) HVR-H3 comprising an amino acid sequence selected from 45 SEQ ID NO:366; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:367; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:368 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:369. 50

- In one embodiment such anti-TIM3 antibody comprises i) comprises a VH sequence of SEQ ID NO:370 and a VL sequence of SEQ ID NO:371;
- ii) or humanized variant of the VH and VL of the antibody under i).

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In any of the above embodiments, an anti-TIM3 antibody is humanized. In one embodiment, an anti-TIM3 antibody comprises HVRs as in any of the above embodiments, and further comprises an acceptor human framework, e.g. a human immunoglobulin framework or a human consensus <sup>60</sup> framework. In another embodiment, an anti-TIM3 antibody comprises HVRs as in any of the above embodiments, and further comprises a VH and VL comprising such HVRs. In a further aspect, the anti-TIM3 antibody hinds to the same epitope as an anti-TIM3 antibody provided herein. For <sup>65</sup> example, in certain embodiments, anti-TIM3 antibody binds to the same epitope as anti-TIM3 antibody comprising a VH 86

sequence of SEQ ID NO:310 and a VL sequence of SEQ ID NO:311, or anti-TIM3 antibody binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:312 and a VL sequence of SEQ ID NO:313, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:322 and a VL sequence of SEQ ID NO:323, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:330 and a VL sequence of SEQ ID NO:331, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:338 and a VL sequence of SEQ ID NO339, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:346 and a VL sequence of SEQ ID NO:347, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:354 and a VL sequence of SEQ ID NO:355, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:362 and a VL sequence of SEQ ID NO:363, or an antibody is provided that binds to the same epitope as anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:370 and a VL sequence of SEQ ID NO:371. In one preferred embodiment an antibody is provided that binds to the same epitope as an anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:310 and a VL sequence of SEQ ID NO:311.

In one embodiment, the anti-TIM3 competes for binding to human TIM3 with an anti-TIM3 antibody comprising a VH sequence of SEQ ID NO:310 and a VL sequence of SEQ ID NO:311 as determined in a competition assay using TIM3 expressing RPMI-8226 cells (ATCC CCL-155<sup>TM</sup>).

In one embodiment, the anti-TIM3 antibody according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human antibody. In one embodiment, an anti-TIM3 antibody is an antibody fragment, e.g., a Fv, Fab, Fab', scFv, diabody, or F(ab')2 frag-40 ment. In another embodiment, the antibody is a full length antibody, e.g., an intact IgG<sub>1</sub> or IgG<sub>4</sub> antibody or other antibody class or isotype as defined herein.

In a further aspect, an anti-TIM3 antibody according to any of the above embodiments may incorporate any of the features, singly or in combination, as described herein.

In one embodiment, the anti-TIM3 antibody is any of the antibodies described in WO 2011/155607. WO 2013/ 006490, WO 03/063792, WO 2009/097394, or WO 2011/ 159877. In one embodiment, the anti-TIM3 antibody is F38-2E2. In some embodiments, the anti-TIM-3 antibodies are antibodies from hybridomas 8B.2C12 and 25F.1D6 and prepared as disclosed in U.S. Patent application Nos: 2004/ 0005322 and 2005/0191721, Sabatos, C. A. et al., Nature Immunol. 4:1102-1110, 2003, and Sanchez-Fueyo, A. et al., Nature Immunol. 4:1093-101 2003, all of which are hereby incorporated by reference as if set forth in their entirety. Other antibodies to TIM-3 are specifically contemplated and can be produced, e.g., with the methods disclosed herein. The nucleotide and protein sequences of TIM3 human sequences can be found at Genbank accession number AF251707.1 and Uniprot accession number Q8TDQ0. An exemplary human TIM3 amino acid sequence is set forth at SEQ ID NO:380; an exemplary human TIM3 extracellular domain amino acid sequence is set forth at SEQ ID NO:381. Antibody Preparation

As described above, in some embodiments, the PD-1 binding antagonist is an antibody (e.g., an anti-PD-1 anti-

body, an anti-PDL1 antibody, or an anti-PDL2 antibody). In some embodiments, the TIM3 antagonist is an antibody (e.g., an anti-TIM3 antagonist antibody). The antibodies described herein may be prepared using techniques available in the art for generating antibodies, exemplary methods of 5 which are described in more detail in the following sections.

The antibody is directed against an antigen of interest. For example, the antibody may be directed against PD-1 (such as human PD-1), PDL1 (such as human PDL1), PDL2 (such as human PDL2), an TIM3 (such as human TIM3). Prefer-10 ably, the antigen is a biologically important polypeptide and administration of the antibody to a mammal suffering from a disorder can result in a therapeutic benefit in that mammal.

In certain embodiments, an antibody described herein has a dissociation constant (Kd) of 1µM, 150 nM, 100 nM, 50 15 nM, 10 nM, 1 nM, 0.1 nM, 0.01 nM, or 0.001 nM (e.g. 10-8 M or less, e.g. from 10-8 M to 10-13 M, e.g., from 10-9 M to 10-13 M). In one embodiment, Kd is measured by a radiolabeled antigen binding assay (RIA) performed with the Fab version of an antibody of interest and its antigen as 20 described by the following assay. Solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (125I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, 25 e.g., Chen et al., J. Mol. Biol. 293:865-881 (1999)). To establish conditions for the assay, MICROTITER® multiwell plates (Thermo Scientific) are coated overnight with 5 µg/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked 30 with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23° C.). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [125I]-antigen are mixed with serial dilutions of a Fab of interest. The Fab of interest is then incubated overnight; 35 however, the incubation may continue for a longer period (e.g., about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (e.g., for one hour). The solution is then removed and the plate washed eight times 40 with 0.1% polysorbate 20 (TWEEN-20) in PBS. When the plates have dried, 150 µl/well of scintillant (MICROSCINT-20 TM; Packard) is added, and the plates are counted on a TOPCOUNT<sup>™</sup> gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 45 20% of maximal binding are chosen for use in competitive binding assays.

According to another embodiment, Kd is measured using surface plasmon resonance assays using a BIACORE®-2000 or a BIACORE®-3000 (BIAcore, Inc., Piscataway, 50 N.J.) at 25° C. with immobilized antigen CM5 chips at ~10 response units (RU). Briefly, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) accord- 55 ing to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 µg/ml (~0.2 µM) before injection at a flow rate of 5 µl/minute to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to 60 block unreacted groups. For kinetics measurements, twofold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20<sup>™</sup>) surfactant (PBST) at 25° C. at a flow rate of approximately 25 µl/min. Association rates (kon) and dissociation rates (koff) 65 are calculated using a simple one-to-one Langmuir binding model (BIACORE® Evaluation Software version 3.2) by

simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (Kd) is calculated as the ratio koff/kon. See, e.g., Chen et al., *J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds 106 M–1 s–1 by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation=295 nm; emission=340 nm, 16 nm band-pass) at 25° C. of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophometer (Aviv Instruments) or a 8000-series SLM-AMINCO<sup>TM</sup> spectrophotometer (ThermoSpectronic) with a stirred cuvette.

In some embodiments, an anti-TIM3 antibody as described herein exhibits a binding affinity of at least 100 pM or less against human TIM3, a binding affinity of at least 300 pM or less against human TIM3, a binding affinity of at least 400 pM or less against human TIM3, a neutralizing ability of at least 40 nM or less against the human TIM3, a neutralizing ability of at least 120 nM or less against the human TIM3, and a neutralizing ability of at least 31 nM or less against the human TIM3. In these embodiments, binding affinity may be measured by surface plasmon resonance as described in U.S. Pat. No. 8,771,697,

Antibody Fragments

In certain embodiments, an antibody described herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, F(ab')2, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al. Nat. Med. 9:129-134 (2003). For a review of scFv fragments, see, e.g., Pluckthün, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Pat. Nos. 5,571,894 and 5,587,458. For discussion of Fab and F(ab')2 fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Pat. No. 5,869,046.

Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., Nat. Med. 9:129-134 (2003); and Hollinger et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., Nat. Med. 9:129-134 (2003). Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, Mass.; see, e.g., U.S. Pat. No. 6,248,516 B1). Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g. E. coli or phage), as described herein.

Chimeric and Humanized Antibodies

In certain embodiments, an antibody described herein is a chimeric antibody. Certain chimeric antibodies are described, e.g., in U.S. Pat. No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-

binding fragments thereof. In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a nonhuman antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized anti-5 body comprises one or more variable domains in which HVRs, e.g., CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the HVR residues are derived), e.g., to restore or improve antibody specificity or affinity. Human- 15 ized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, Front. Biosci. 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., Nature 332:323-329 (1988); Queen et al., Proc. Nat'l Acad. Sci. USA 86:10029-10033 (1989); U.S. Pat. Nos. 5.821,337, 20 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., Methods 36:25-34 (2005) (describing SDR (a-CDR) grafting); Padlan, Mol. Immunol. 28:489-498 (1991) (describing "resurfacing"); Dall'Acqua et al., Methods 36:43-60 (2005) (describing "FR shuffling"); and Osbourn et al., Methods 25 36:61-68 (2005) and Klimka et al., Br. J. Cancer, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).

Human framework regions that may be used for humanization include but are not limited to: framework regions 30 selected using the "best-fit" method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 35 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., 40 Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)). Human Antibodies

In certain embodiments, an antibody described herein is a human antibody. Human antibodies can be produced using 45 various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5: 368-74 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).

Human antibodies may be prepared by administering an 50 immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immu- 55 noglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see 60 Lonberg, Nat. Biotech. 23:1117-1125 (2005). See also, e.g., U.S. Pat. Nos. 6,075,181 and 6,150,584 describing XENO-MOUSE™ technology; U.S. Pat. No. 5,770,429 describing HUMAB® technology; U.S. Pat. No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application 65 Publication No. US 2007/0061900, describing VELOCI-MOUSE® technology). Human variable regions from intact

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antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region. Human antibodies can also be made by hybridomabased methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor J. Immunol., 133: 3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., J. Immunol., 147: 86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., Proc. Natl. Acad. Sci. USA, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Pat. No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, Xiandai Mianyixue, 26(4):265-268 (2006) (describing humanhuman hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, Histology and Histopathology, 20(3):927-937 (2005) and Vollmers and Brandlein. Methods and Findings in Experimental and Clinical Pharmacology, 27(3):185-91 (2005). Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below. Library-Derived Antibodies

Antibodies may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. For example, a variety of methods are known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, e.g., in Hoogenboom et al. in Methods in Molecular Biology 178:1-37 (O'Brien et al., ed., Human Press, Totowa, N.J., 2001) and further described, e.g., in the McCafferty et al., Nature 348:552-554; Clackson et al., Nature 352: 624-628 (1991); Marks et al., J. Mol. Biol. 222: 581-597 (1992); Marks and Bradbury, in Methods in Molecular Biology 248:161-175 (Lo, ed., Human Press, Totowa, N.J., 2003); Sidhu et al., J. Mol. Biol. 338(2): 299-310 (2004); Lee et al., J. Mol. Biol. 340(5): 1073-1093 (2004); Fellouse, Proc. Natl. Acad. Sci. USA 101(34): 12467-12472 (2004); and Lee et al., J. Immunol. Methods 284(1-2): 119-132(2004).

In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al., Ann. Rev. Immunol., 12: 433-455 (1994). Phage typically display antibody fragments, either as single chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al., EMBO J, 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement in vitro, as described by Hoogenboom and Winter, J. Mol. Biol., 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: U.S. Pat. No. 5,750,373, and US Patent Publication Nos. 2005/0079574,

2005/0119455, 2005/0266000, 2007/0117126, 2007/ 0160598, 2007/0237764, 2007/0292936, and 2009/ 0002360. Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein. Multispecific Antibodies

In certain embodiments, an antibody described herein is a multispecific antibody, e.g. a bispecific antibody. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. Examples of T 10 cell activating bispecific antigen binding molecules specific for FolR1 and CD3 are described herein. In some embodiments, the PD1 axis component antagonist is multispecific. In one of the binding specificities is for a PD-1 axis component (e.g., PD-1, PDL1, or PDL2) and the other is for 15 any other antigen. In some embodiments, one of the binding specificities is for IL-17 or IL-17R and the other is for any other antigen. In certain embodiments, bispecific antibodies may bind to two different epitopes of a PD-1 axis component (e.g., PD-1, PDL1, or PDL2), IL-17, or IL-17R. Bispecific 20 antibodies can be prepared as full length antibodies or antibody fragments.

In some embodiments, one of the binding specificities is for a PD-1 axis component (e.g., PD-1, PDL1, or PDL2) and the other is for IL-17 or IL-17R. Provided herein are 25 methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a multispecific antibody, wherein the multispecific antibody comprises a first binding specificity for a PD-1 axis component (e.g., PD-1, PDL1, or PDL2) and 30 a second binding specificity for IL-17 or IL-17R. In some embodiments, a multispecific antibody may be made by any of the techniques described herein and below.

Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two 35 immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, Nature 305: 537 (1983)), WO 93/08829, and Traunecker et al., EMBO J. 10: 3655 (1991)), and "knob-in-hole" engineering (see, e.g., U.S. Pat. No. 5,731,168). Multi-specific antibodies may also 40 be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/ 089004A1); crosslinking two or more antibodies or fragments (see, e.g., U.S. Pat. No. 4,676,980, and Brennan et al., Science, 229: 81 (1985)); using leucine zippers to produce 45 bi-specific antibodies (see, e.g., Kostelny et al., J. Immunol., 148(5):1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (see, e.g., Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see, e.g. Gruber et al., 50 J. Immunol., 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. J. Immunol. 147: 60 (1991). Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (see, e.g. US 2006/0025576A1). 55 The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising an antigen binding site that binds to a PD-1 axis component (e.g., PD-1, PDL1, or PDL2), IL-17, or IL-17R as well as another, different antigen (see, US 2008/0069820, for example).

C. Nucleic Acid Sequences, Vectors and Methods of Production

Polynucleotides encoding a T cell activating bispecific antigen binding molecule, e.g., a T cell activating bispecific antigen binding molecule comprising a first antigen binding 65 site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, and antibodies may be

used for production of the T cell activating bispecific antigen binding molecule and antibodies described herein. The T cell activating bispecific antigen binding molecule and antibodies of the invention may be expressed as a single polynucleotide that encodes the entire bispecific antigen binding molecule or as multiple (e.g., two or more) polynucleotides that are co-expressed. Polypeptides encoded by polynucleotides that are co-expressed may associate through, e.g., disulfide bonds or other means to form a functional T cell activating bispecific antigen binding molecule and antibody. For example, the light chain portion of a Fab fragment may be encoded by a separate polynucleotide from the portion of the bispecific antibody or the antibody binding to FolR1 comprising the heavy chain portion of the Fab fragment, an Fc domain subunit and optionally (part of) another Fab fragment. When co-expressed, the heavy chain polypeptides will associate with the light chain polypeptides to form the Fab fragment. In another example, the portion of the T cell activating bispecific antigen binding molecule or the FolR1 antigen binding portion provided therein comprising one of the two Fc domain subunits and optionally (part of) one or more Fab fragments could be encoded by a separate polynucleotide from the portion of the bispecific antibody or the antibody binding to FolR1 provided therein comprising the other of the two Fc domain subunits and optionally (part of) a Fab fragment. When co-expressed, the Fc domain subunits will associate to form the Fc domain.

In certain embodiments the polynucleotide or nucleic acid is DNA. In other embodiments, a polynucleotide of the present invention is RNA, for example, in the form of messenger RNA (mRNA). RNA of the present invention may be single stranded or double stranded.

D. Antibody Variants

In certain embodiments, amino acid sequence variants of the T cell activating bispecific antigen binding molecule specific for FolR1 and CD3 provided herein and antibodies are contemplated, in addition to those described above. For example, it may be desirable to improve the binding affinity and/or other biological properties of the T cell activating bispecific antigen binding molecule. Amino acid sequence variants of a T cell activating bispecific antigen binding molecule and antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the T cell activating bispecific antigen binding molecule or antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, e.g., antigen-binding.

1. Substitution, Insertion, and Deletion Variants

In certain embodiments, variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Conservative substitutions are shown in Table B under the 60 heading of "conservative substitutions." More substantial changes are provided in Table B under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest 65 and the products screened for a desired activity, e.g., retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

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Original Residue	Exemplary Substitutions	Preferred Substitutions	-
Ala (A)	Val; Leu; Ile	Val	5
Arg (R)	Lys; Gln; Asn	Lys	
Asn (N)	Gln; His; Asp, Lys; Arg	Gln	
Asp (D)	Glu; Asn	Glu	
Cys (C)	Ser; Ala	Ser	
Gln (Q)	Asn; Glu	Asn	
Glu (E)	Asp; Gln	Asp	10
Gly (G)	Ala	Ala	
His (H)	Asn; Gln; Lys; Arg	Arg	
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu	
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile	
Lys (K)	Arg; Gln; Asn	Arg	
Met (M)	Leu; Phe; Ile	Leu	15
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr	15
Pro (P)	Ala	Ala	
Ser (S)	Thr	Thr	
Thr (T)	Val; Ser	Ser	
Trp (W)	Tyr; Phe	Tyr	
Tyr (Y)	Trp; Phe; Thr; Ser	Phe	20
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu	20

Amino acids may be grouped according to common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

(2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g. a humanized or human antibody). Generally, 35 the resulting variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. 40 An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more HVR residues are mutated and the variant antibodies displayed on phage 45 and screened for a particular biological activity (e.g. binding affinity).

Alterations (e.g., substitutions) may be made in HVRs, e.g., to improve antibody affinity. Such alterations may be made in HVR "hotspots," i.e., residues encoded by codons 50 that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, Methods Mol. Biol. 207:179-196 (2008)), and/or SDRs (a-CDRs), with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from 55 secondary libraries has been described, e.g., in Hoogenboom et al. in Methods in Molecular Biology 178:1-37 (O'Brien et al., ed., Human Press, Totowa, N.J., (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a 60 variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-di- 65 rected approaches, in which several HVR residues (e.g., 4-6 residues at a time) are randomized. HVR residues involved

in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

In certain embodiments, substitutions, insertions, or dele-5 tions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made 10 in HVRs. Such alterations may be outside of HVR "hotspots" or SDRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) Science, 244:1081-1085. In this method, a residue or group of target residues (e.g., charged 20 residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating 25 functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigenantibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g. for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

2. Glycosylation Variants

In certain embodiments, a T cell activating bispecific antigen binding molecule or an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

Where the T cell activating bispecific antigen binding molecule or the antibody used with the invention comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al. TIBTECH 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in a bispecific antibody or an antibody binding to DR5 of the invention may be made in order to create antibody variants with certain improved properties.

In one embodiment, bispecific antibody variants or variants of antibodies are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose 5 within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e.g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at 10 about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ±3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation vari- 15 ants may have improved ADCC function. See, e.g., US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 20 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/ 0164328; US 2004/0093621; US 2004/0132140; US 2004/ 0110704; US 2004/0110282; US 2004/0109865; WO 2003/ 085119; WO 2003/084570; WO 2005/035586; WO 2005/ 035778; WO2005/053742; WO2002/031140; Okazaki et al. 25 J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. Arch. Biochem. Biophys. 249:533-545 (1986); US Pat 30 Appl No US 2003/0157108 A1, Presta, L; and WO 2004/ 056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004); Kanda, Y. et al., 35 Biotechnol. Bioeng., 94(4):680-688 (2006); and WO2003/ 085107).

T cell activating bispecific antigen binding molecule variants and antibody variants are further provided with bisected oligosaccharides, e.g., in which a biantennary oli- 40 gosaccharide attached to the Fc region of the T cell activating bispecific antigen binding molecule binding to FolR1 is bisected by GlcNAc. Such T cell activating bispecific antigen binding molecule variants may have reduced fucosylation and/or improved ADCC function. Examples of such 45 antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); U.S. Pat. No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody 50 variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.). 3. Cysteine Engineered Antibody Variants

In certain embodiments, it may be desirable to create 55 cysteine engineered T cell activating bispecific antigen binding molecule and antibodies, e.g., THIOMABS, in which one or more residues of the T cell activating bispecific antigen binding molecule are substituted with cysteine residues. In particular embodiments, the substituted residues 60 occur at accessible sites of the T cell activating bispecific antigen binding molecule. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or 65 linker-drug moieties, any one or more of the following

residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and 5400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, e.g., in U.S. Pat. No. 7,521,541.

E. Recombinant Methods and Compositions

T cell activating bispecific antigen binding molecule and antibodies of the invention may be obtained, for example, by solid-state peptide synthesis (e.g. Merrifield solid phase synthesis) or recombinant production. For recombinant production one or more polynucleotide encoding the T cell activating bispecific antigen binding molecule or antibodies (or fragments), e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such polynucleotide may be readily isolated and sequenced using conventional procedures. In one embodiment a vector, preferably an expression vector, comprising one or more of the polynucleotides of the invention is provided. Methods which are well known to those skilled in the art can be used to construct expression vectors containing the coding sequence of a T cell activating bispecific antigen binding molecule or an antibody along with appropriate transcriptional/translational control signals. These methods include in vitro recombinant DNA techniques, synthetic techniques and in vivo recombination/ genetic recombination. See, for example, the techniques described in Maniatis et al., MOLECULAR CLONING: A LABORA-TORY MANUAL, Cold Spring Harbor Laboratory, N.Y. (1989); and Ausubel et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Greene Publishing Associates and Wiley Interscience, N.Y (1989). The expression vector can be part of a plasmid, virus, or may be a nucleic acid fragment. The expression vector includes an expression cassette into which the polynucleotide encoding T cell activating bispecific antigen binding molecule (fragment) or an antibody (fragment) (i.e. the coding region) is cloned in operable association with a promoter and/or other transcription or translation control elements. As used herein, a "coding region" is a portion of nucleic acid which consists of codons translated into amino acids. Although a "stop codon" (TAG, TGA, or TAA) is not translated into an amino acid, it may be considered to be part of a coding region, if present, but any flanking sequences, for example promoters, ribosome binding sites, transcriptional terminators, introns, 5' and 3' untranslated regions, and the like, are not part of a coding region. Two or more coding regions can be present in a single polynucleotide construct, e.g. on a single vector, or in separate polynucleotide constructs, e.g. on separate (different) vectors. Furthermore, any vector may contain a single coding region, or may comprise two or more coding regions, e.g. a vector of the present invention may encode one or more polypeptides, which are post- or co-translationally separated into the final proteins via proteolytic cleavage. In addition, a vector, polynucleotide, or nucleic acid of the invention may encode heterologous coding regions, either fused or unfused to a polynucleotide encoding the T cell activating bispecific antigen binding molecule (fragment) or an antibody, or variant or derivative thereof. Heterologous coding regions include without limitation specialized elements or motifs, such as a secretory signal peptide or a heterologous functional domain. An operable association is when a coding region for a gene product, e.g. a polypeptide, is associated with one or more regulatory sequences in such a way as to place expression of the gene product under the influence or control of the regulatory sequence(s). Two DNA fragments (such as a polypeptide coding region and a promoter associated therewith) are "operably associated" if induction of

promoter function results in the transcription of mRNA encoding the desired gene product and if the nature of the linkage between the two DNA fragments does not interfere with the ability of the expression regulatory sequences to direct the expression of the gene product or interfere with the 5 ability of the DNA template to be transcribed. Thus, a promoter region would be operably associated with a nucleic acid encoding a polypeptide if the promoter was capable of effecting transcription of that nucleic acid. The promoter may be a cell-specific promoter that directs substantial 10 transcription of the DNA only in predetermined cells.

Other transcription control elements, besides a promoter, for example enhancers, operators, repressors, and transcription termination signals, can be operably associated with the polynucleotide to direct cell-specific transcription. Suitable 15 promoters and other transcription control regions are disclosed herein. A variety of transcription control regions are known to those skilled in the art. These include, without limitation, transcription control regions, which function in vertebrate cells, such as, but not limited to, promoter and 20 enhancer segments from cytomegaloviruses (e.g. the immediate early promoter, in conjunction with intron-A), simian virus 40 (e.g. the early promoter), and retroviruses (such as, e.g. Rous sarcoma virus). Other transcription control regions include those derived from vertebrate genes such as actin, 25 heat shock protein, bovine growth hormone and rabbit â-globin, as well as other sequences capable of controlling gene expression in eukaryotic cells. Additional suitable transcription control regions include tissue-specific promoters and enhancers as well as inducible promoters (e.g. 30 promoters inducible tetracyclins). Similarly, a variety of translation control elements are known to those of ordinary skill in the art. These include, but are not limited to ribosome binding sites, translation initiation and termination codons, and elements derived from viral systems (particularly an 35 internal ribosome entry site, or IRES, also referred to as a CITE sequence). The expression cassette may also include other features such as an origin of replication, and/or chromosome integration elements such as retroviral long terminal repeats (LTRs), or adeno-associated viral (AAV) 40 inverted terminal repeats (ITRs).

Polynucleotide and nucleic acid coding regions of the present invention may be associated with additional coding regions which encode secretory or signal peptides, which direct the secretion of a polypeptide encoded by a poly- 45 nucleotide of the present invention. For example, if secretion of the T cell activating bispecific antigen binding molecule or the antibody is desired, DNA encoding a signal sequence may be placed upstream of the nucleic acid encoding a bispecific antibody of the invention or the antibody binding 50 to DR5 of the invention or a fragment thereof. According to the signal hypothesis, proteins secreted by mammalian cells have a signal peptide or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has 55 been initiated. Those of ordinary skill in the art are aware that polypeptides secreted by vertebrate cells generally have a signal peptide fused to the N-terminus of the polypeptide, which is cleaved from the translated polypeptide to produce a secreted or "mature" form of the polypeptide. In certain 60 embodiments, the native signal peptide, e.g. an immunoglobulin heavy chain or light chain signal peptide is used, or a functional derivative of that sequence that retains the ability to direct the secretion of the polypeptide that is operably associated with it. Alternatively, a heterologous 65 mammalian signal peptide, or a functional derivative thereof, may be used. For example, the wild-type leader

sequence may be substituted with the leader sequence of human tissue plasminogen activator (TPA) or mouse  $\beta$ -glucuronidase.

DNA encoding a short protein sequence that could be used to facilitate later purification (e.g. a histidine tag) or assist in labeling the T cell activating bispecific antigen binding molecule may be included within or at the ends of the T cell activating bispecific antigen binding molecule (fragment) or the antibody (fragment) encoding polynucleotide.

In a further embodiment, a host cell comprising one or more polynucleotides of the invention is provided. In certain embodiments a host cell comprising one or more vectors of the invention is provided. The polynucleotides and vectors may incorporate any of the features, singly or in combination, described herein in relation to polynucleotides and vectors, respectively. In one such embodiment a host cell comprises (e.g. has been transformed or transfected with) a vector comprising a polynucleotide that encodes a T cell activating bispecific antigen binding molecule or an antibody of the invention or a part thereof. As used herein, the term "host cell" refers to any kind of cellular system which can be engineered to generate the T cell activating bispecific antigen binding molecule, e.g., the FolR1 T cell activating bispecific antigen binding molecules disclosed herein, or antibody, e.g., anti-PD-1 antibodies, anti-PD-L1 antibodies, and anti-TIM3 antibodies of the invention or fragments thereof. Host cells suitable for replicating and for supporting expression of T cell activating bispecific antigen binding molecule and antibodies of the invention are well known in the art. Such cells may be transfected or transduced as appropriate with the particular expression vector and large quantities of vector containing cells can be grown for seeding large scale fermenters to obtain sufficient quantities of the T cell activating bispecific antigen binding molecule and antibodies for clinical applications. Suitable host cells include prokaryotic microorganisms, such as E. coli, or various eukaryotic cells, such as Chinese hamster ovary cells (CHO), insect cells, or the like. For example, polypeptides may be produced in bacteria in particular when glycosylation is not needed. After expression, the polypeptide may be isolated from the bacterial cell paste in a soluble fraction and can be further purified. In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for polypeptideencoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized", resulting in the production of a polypeptide with a partially or fully human glycosylation pattern. See Gerngross, Nat Biotech 22, 1409-1414 (2004), and Li et al., Nat Biotech 24, 210-215 (2006). Suitable host cells for the expression of (glycosylated) polypeptides are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of Spodoptera frugiperda cells. Plant cell cultures can also be utilized as hosts. See e.g. U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES<sup>TM</sup> technology for producing antibodies in transgenic plants). Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293T cells as described, e.g., in Graham et al., J Gen Virol 36, 59 (1977)), baby hamster kidney cells (BHK), mouse sertoli cells (TM4 cells as described, e.g., in Mather, Biol Reprod 23, 243-251 (1980)), monkey kidney cells (CV1), African green monkey kidney cells (VERO-76), human cervical carcinoma cells (HELA), canine kidney cells (MDCK), buffalo rat liver cells (BRL 3A), human lung 5 cells (W138), human liver cells (Hep G2), mouse mammary tumor cells (MMT 060562), TRI cells (as described, e.g., in Mather et al., Annals N.Y. Acad Sci 383, 44-68 (1982)), MRC 5 cells, and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, 10 including dhfr- CHO cells (Urlaub et al., Proc Natl Acad Sci USA 77, 4216 (1980)); and myeloma cell lines such as YO, NSO, P3X63 and Sp2/0. For a review of certain mammalian host cell lines suitable for protein production, see, e.g., Yazaki and Wu, Methods in Molecular Biology, Vol. 248 (B. 15 K. C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003). Host cells include cultured cells, e.g., mammalian cultured cells, yeast cells, insect cells, bacterial cells and plant cells, to name only a few, but also cells comprised within a transgenic animal, transgenic plant or cultured plant 20 or animal tissue. In one embodiment, the host cell is a eukaryotic cell, preferably a mammalian cell, such as a Chinese Hamster Ovary (CHO) cell, a human embryonic kidney (HEK) cell or a lymphoid cell (e.g., YO, NSO, Sp20 cell). 25

Standard technologies are known in the art to express foreign genes in these systems. Cells expressing a polypeptide comprising either the heavy or the light chain of an antigen binding domain such as an antibody, may be engineered so as to also express the other of the antibody chains 30 such that the expressed product is an antibody that has both a heavy and a light chain.

Any animal species of antibody, antibody fragment, antigen binding domain or variable region can be used in the T cell activating bispecific antigen binding molecules of the 35 invention. Non-limiting antibodies, antibody fragments, antigen binding domains or variable regions useful in the present invention can be of murine, primate, or human origin. If the T cell activating bispecific antigen binding molecule is intended for human use, a chimeric form of 40 antibody may be used wherein the constant regions of the antibody are from a human. A humanized or fully human form of the antibody can also be prepared in accordance with methods well known in the art (see e.g. U.S. Pat. No. 5,565,332 to Winter). Humanization may be achieved by 45 various methods including, but not limited to (a) grafting the non-human (e.g., donor antibody) CDRs onto human (e.g. recipient antibody) framework and constant regions with or without retention of critical framework residues (e.g. those that are important for retaining good antigen binding affinity 50 or antibody functions), (b) grafting only the non-human specificity-determining regions (SDRs or a-CDRs; the residues critical for the antibody-antigen interaction) onto human framework and constant regions, or (c) transplanting the entire non-human variable domains, but "cloaking" them 55 with a human-like section by replacement of surface residues. Humanized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, Front Biosci 13, 1619-1633 (2008), and are further described, e.g., in Riechmann et al., Nature 332, 323-329 (1988); Queen et al., 60 Proc Natl Acad Sci USA 86, 10029-10033 (1989); U.S. Pat. Nos. 5,821,337, 7,527,791, 6,982,321, and 7,087,409; Jones et al., Nature 321, 522-525 (1986); Morrison et al., Proc Natl Acad Sci 81, 6851-6855 (1984); Morrison and Oi, Adv Immunol 44, 65-92 (1988); Verhoeyen et al., Science 239, 65 1534-1536 (1988); Padlan, Molec Immun 31(3), 169-217 (1994); Kashmiri et al., Methods 36, 25-34 (2005) (describ-

ing SDR (a-CDR) grafting); Padlan, Mol Immunol 28, 489-498 (1991) (describing "resurfacing"); Dall'Acqua et al., Methods 36, 43-60 (2005) (describing "FR shuffling"); and Osbourn et al., Methods 36, 61-68 (2005) and Klimka et al., Br J Cancer 83, 252-260 (2000) (describing the "guided selection" approach to FR shuffling). Human antibodies and human variable regions can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, Curr Opin Pharmacol 5, 368-74 (2001) and Lonberg, Curr Opin Immunol 20, 450-459 (2008). Human variable regions can form part of and be derived from human monoclonal antibodies made by the hybridoma method (see e.g. Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)). Human antibodies and human variable regions may also be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge (see e.g. Lonberg, Nat Biotech 23, 1117-1125 (2005). Human antibodies and human variable regions may also be generated by isolating Fv clone variable region sequences selected from human-derived phage display libraries (see e.g., Hoogenboom et al. in Methods in Molecular Biology 178, 1-37 (O'Brien et al., ed., Human Press, Totowa, N.J., 2001); and McCafferty et al., Nature 348, 552-554; Clackson et al., Nature 352, 624-628 (1991)). Phage typically display antibody fragments, either as singlechain Fv (scFv) fragments or as Fab fragments.

In certain embodiments, the antigen binding moieties useful in the present invention are engineered to have enhanced binding affinity according to, for example, the methods disclosed in U.S. Pat. Appl. Publ. No. 2004/ 0132066, the entire contents of which are hereby incorporated by reference. The ability of the T cell activating bispecific antigen binding molecule of the invention to bind to a specific antigenic determinant can be measured either through an enzyme-linked immunosorbent assay (ELISA) or other techniques familiar to one of skill in the art, e.g. surface plasmon resonance technique (analyzed on a BIA-CORE T100 system) (Liljeblad, et al., Glyco J 17, 323-329 (2000)), and traditional binding assays (Heeley, Endocr Res 28, 217-229 (2002)). Competition assays may be used to identify an antibody, antibody fragment, antigen binding domain or variable domain that competes with a reference antibody for binding to a particular antigen, e.g. an antibody that competes with the V9 antibody for binding to CD3. In certain embodiments, such a competing antibody binds to the same epitope (e.g. a linear or a conformational epitope) that is bound by the reference antibody. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in Methods in Molecular Biology vol. 66 (Humana Press, Totowa, N.J.). In an exemplary competition assay, immobilized antigen (e.g. CD3) is incubated in a solution comprising a first labeled antibody that binds to the antigen (e.g. V9 antibody, described in U.S. Pat. No. 6,054,297) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to the antigen. The second antibody may be present in a hybridoma supernatant. As a control, immobilized antigen is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to the antigen, excess unbound antibody is removed, and the amount of label associated with immobilized antigen is measured. If the amount of label associated with immobilized antigen is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to the antigen. See Harlow and Lane (1988) Antibodies: A Laboratory Manual ch.14 (Cold Spring Harbor 5 Laboratory, Cold Spring Harbor, N.Y.).

In certain embodiments, the antigen binding moieties useful in the present invention are engineered to have enhanced binding affinity according to, for example, the methods disclosed in U.S. Pat. Appl. Publ. No. 2004/ 10 0132066, the entire contents of which are hereby incorporated by reference. The ability of the T cell activating bispecific antigen binding molecule or the antibody of the invention to bind to a specific antigenic determinant can be measured either through an enzyme-linked immunosorbent 15 assay (ELISA) or other techniques familiar to one of skill in the art, e.g. surface plasmon resonance technique (analyzed on a BIACORE T100 system) (Liljeblad, et al., Glyco J 17, 323-329 (2000)), and traditional binding assays (Heeley, Endocr Res 28, 217-229 (2002)). Competition assays may 20 be used to identify an antibody, antibody fragment, antigen binding domain or variable domain that competes with a reference antibody for binding to a particular antigen. In certain embodiments, such a competing antibody binds to the same epitope (e.g. a linear or a conformational epitope) 25 that is bound by the reference antibody. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in Methods in Molecular Biology vol. 66 (Humana Press, Totowa, N.J.). In an exemplary competition assay, immobi- 30 lized antigen is incubated in a solution comprising a first labeled antibody that binds to the antigen and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to the antigen. The second antibody may be present in a hybridoma super- 35 natant. As a control, immobilized antigen is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody.

After incubation under conditions permissive for binding of the first antibody to the antigen, excess unbound antibody 40 is removed, and the amount of label associated with immobilized antigen is measured. If the amount of label associated with immobilized antigen is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for 45 binding to the antigen. See Harlow and Lane (1988) Antibodies: A Laboratory Manual ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.).

T cell activating bispecific antigen binding molecules and antibodies prepared as described herein may be purified by 50 art-known techniques such as high performance liquid chromatography, ion exchange chromatography, gel electrophoresis, affinity chromatography, size exclusion chromatography, and the like. The actual conditions used to purify a particular protein will depend, in part, on factors such as net 55 constructs are captured by an anti human Fab specific charge, hydrophobicity, hydrophilicity etc., and will be apparent to those having skill in the art. For affinity chromatography purification an antibody, ligand, receptor or antigen can be used to which the bispecific antibody or the antibody binding to DR5 binds. For example, for affinity 60 chromatography purification of bispecific antibodies of the invention, a matrix with protein A or protein G may be used. Sequential Protein A or G affinity chromatography and size exclusion chromatography can be used to isolate a bispecific antibody essentially as described in the Examples. The 65 purity of the bispecific antibody or the antibody binding to DR5 can be determined by any of a variety of well-known

analytical methods including gel electrophoresis, high pressure liquid chromatography, and the like.

F. Assays

T cell activating bispecific antigen binding molecules, e.g., a T cell activating bispecific antigen binding molecules comprising a first antigen binding site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, and antibodies, e.g., anti-PD-1 axis binding antagonist antibodies and anti-TIM3 antagonist antibodies provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

1. Affinity Assays

The affinity of the T cell activating bispecific antigen binding molecules, e.g., a T cell activating bispecific antigen binding molecules comprising a first antigen binding site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, and antibodies, e.g., anti-PD-1 axis binding antagonist antibodies and anti-TIM3 antagonist antibodies provided herein for their respective antigen, e.g., FolR1, PD-1, PD-L1, TIM3, can be determined in accordance with the methods set forth in the Examples by surface plasmon resonance (SPR), using standard instrumentation such as a BIAcore instrument (GE Healthcare), and receptors or target proteins such as may be obtained by recombinant expression. Alternatively, binding of T cell activating bispecific antigen binding molecules and antibodies provided therein to their respective antigen may be evaluated using cell lines expressing the particular receptor or target antigen, for example by flow cytometry (FACS).

 $K_D$  may be measured by surface plasmon resonance using a BIACORE® T100 machine (GE Healthcare) at 25° C. To analyze the interaction between the Fc-portion and Fc receptors, His-tagged recombinant Fc-receptor is captured by an anti-Penta His antibody (Qiagen) ("Penta His" disclosed as SEQ ID NO: 392) immobilized on CM5 chips and the bispecific constructs are used as analytes. Briefly, carboxymethylated dextran biosensor chips (CM5, GE Healthcare) are activated with N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) according to the supplier's instructions. Anti Penta-His antibody ("Penta His" disclosed as SEQ ID NO: 392) is diluted with 10 mM sodium acetate, pH 5.0, to 40 µg/ml before injection at a flow rate of 5 µl/min to achieve approximately 6500 response units (RU) of coupled protein. Following the injection of the ligand, 1 M ethanolamine is injected to block unreacted groups. Subsequently the Fcreceptor is captured for 60 s at 4 or 10 nM. For kinetic measurements, four-fold serial dilutions of the bispecific construct (range between 500 nM and 4000 nM) are injected in HBS-EP (GE Healthcare, 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% Surfactant P20, pH 7.4) at 25° C. at a flow rate of 30 µl/min for 120 s.

To determine the affinity to the target antigen, bispecific antibody (GE Healthcare) that is immobilized on an activated CM5-sensor chip surface as described for the anti Penta-His antibody ("Penta His" disclosed as SEQ ID NO: 392). The final amount of coupled protein is is approximately 12000 R U. The bispecific constructs are captured for 90 s at 300 nM. The target antigens are passed through the flow cells for 180 s at a concentration range from 250 to 1000 nM with a flowrate of 30  $\mu$ l/min. The dissociation is monitored for 180 s.

Bulk refractive index differences are corrected for by subtracting the response obtained on reference flow cell. The steady state response was used to derive the dissociation

constant  $K_D$  by non-linear curve fitting of the Langmuir binding isotherm. Association rates  $(k_{on})$  and dissociation rates  $(k_{off})$  are calculated using a simple one-to-one Langmuir binding model (BIACORE® T100 Evaluation Software version 1.1.1) by simultaneously fitting the association 5 and dissociation sensorgrams. The equilibrium dissociation constant  $(K_D)$  is calculated as the ratio  $k_{off}/k_{on}$ . See, e.g., Chen et al., J Mol Biol 293, 865-881 (1999).

2. Binding Assays and Other Assays

In one aspect, a T cell activating bispecific antigen binding molecules, e.g., a T cell activating bispecific antigen binding molecules comprising a first antigen binding site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, and antibodies, e.g., anti-PD-1 axis binding antagonist antibodies and anti-TIM3 antagonist 15 antibodies of the invention is tested for its antigen binding activity, e.g., by known methods such as ELISA, Western blot, etc.

In another aspect, competition assays may be used to identify an antibody or fragment that competes with a 20 specific reference antibody for binding to the respective antigens. In certain embodiments, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope) that is bound by a specific reference antibody. Detailed exemplary methods for mapping an 25 epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, N.J.). Further methods are described in the example section.

3. Activity Assays

In one aspect, assays are provided for identifying T cell activating bispecific antigen binding molecules, e.g., a T cell activating bispecific antigen binding molecules comprising a first antigen binding site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, 35 and antibodies, e.g., anti-PD-1 axis binding antagonist antibodies and anti-TIM3 antagonist antibodies provided herein having biological activity. Biological activity may include, e.g., inducing DNA fragmentation, induction of apoptosis and lysis of targeted cells. Antibodies having such biological 40 activity in vivo and/or in vitro are also provided.

In certain embodiments, T cell activating antigen binding molecule and antibody of the invention is tested for such biological activity. Assays for detecting cell lysis (e.g. by measurement of LDH release) or apoptosis (e.g. using the 45 TUNEL assay) are well known in the art. Assays for measuring ADCC or CDC are also described in WO 2004/ 065540 (see Example 1 therein), the entire content of which is incorporated herein by reference.

G. Pharmaceutical Formulations

Pharmaceutical formulations of a T cell activating bispecific antigen binding molecules, e.g., a T cell activating bispecific antigen binding molecule comprising a first antigen binding site specific for Folate Receptor 1 (FolR1) and a second antigen binding site specific for CD3, and anti- 55 bodies, e.g., anti-PD-1 axis binding antagonist antibodies and anti-TIM3 antagonist antibodies as described herein are prepared by mixing such T cell activating bispecific antigen binding molecules or antibody having the desired degree of purity with one or more optional pharmaceutically accept- 60 able carriers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are 65 not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and

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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 polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include insterstitial drug dispersion agents such as soluble neutralactive hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hvaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

Exemplary lyophilized antibody formulations are described in U.S. Pat. No. 6,267,958. Aqueous antibody formulations include those described in U.S. Pat. No. 6,171, 586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, 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 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semiper-<sup>50</sup> meable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. films, or microcapsules.

The formulations to be used for in vivo administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

H. Therapeutic Methods and Compositions

The therapeutic combinations comprising one or more of the T cell activating bispecific antigen binding molecules and the anti-PD-1 axis binding antagonist antibody and, optionally, the TIM3 antagonist provided herein may be used in therapeutic methods.

In one aspect, a T cell activating bispecific antigen binding molecules that binds to Folate Receptor 1 (FolR1) and CD3 for use as a medicament is provided for use in combination with an anti-PD-1 axis binding antagonist antibody. In certain embodiments, a T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3

for use in combination with an anti-PD-1 axis binding antagonist antibody is provided for use in a method of treatment. In certain embodiments, the combination further comprises a TIM3 antagonist, e.g., an anti-TIM3 antagonist antibody. In certain embodiments, the invention provides a 5 T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 and an anti-PD-1 axis binding antagonist antibody for use in a method of treating an individual having cancer comprising administering to the individual an effective amount of the T cell activating 10 bispecific antigen binding molecules that binds to FolR1 and CD3 and the anti-PD-1 axis binding antagonist antibody. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one TIM3 antagonist, e.g., as described below. An "individual" 15 according to any of the above embodiments is preferably a human. In one preferred embodiment, said cancer is pancreatic cancer, sarcoma or colorectal carcinoma. In other embodiments, the cancer is colorectal cancer, sarcoma, head and neck cancers, squamous cell carcinomas, breast cancer, 20 pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer or mesothelioma. In embodiments in which the cancer is breast cancer, the breast cancer may be triple negative breast cancer.

In a further aspect, the invention provides the use of a 25 therapeutic combination comprising a T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 and an anti-PD-1 axis binding antagonist antibody in the manufacture or preparation of a medicament. In one embodiment, the combination further comprises a TIM3 30 antagonist. In one embodiment, the medicament is for treatment of cancer. In a further embodiment, the medicament is for use in a method of treating cancer comprising administering to an individual having cancer an effective amount of the medicament. In one such embodiment, the 35 method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below. An "individual" according to any of the above embodiments may be a human.

In a further aspect, the invention provides a method for 40 treating cancer. In one embodiment, the method comprises administering to an individual having cancer an effective amount of a therapeutic combination comprising a T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 and an anti-PD-1 axis binding antagonist 45 antibody. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. In one such embodiment, the at least one additional therapeutic agent is an anti-TIM3 antagonist 50 antibody. An "individual" according to any of the above embodiments may be a human. In one preferred embodiment said cancer is pancreatic cancer, sarcoma or colorectal carcinoma. In other embodiments, the cancer is colorectal cancer, sarcoma, head and neck cancers, squamous cell 55 carcinomas, breast cancer, pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer or mesothelioma.

In a further aspect, the invention provides pharmaceutical formulations comprising any of the T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 provided herein, e.g., for use in any of the above therapeutic methods, and an anti-PD-1 axis binding antagonist antibody. In one embodiment, a pharmaceutical formulation comprises any of the T cell activating bispecific antigen binding 65 molecules that binds to FolR1 provided herein and a pharmaceutically acceptable carrier. In another embodiment, a

pharmaceutical formulation comprises any of T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 and an anti-PD-1 axis binding antagonist antibody provided herein and at least one additional therapeutic agent, e.g., as described below.

A bispecific antibody can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g. by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various timepoints, bolus administration, and pulse infusion are contemplated herein.

Bispecific antibodies may be be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The bispecific antibody need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/ clinically determined to be appropriate.

For the prevention or treatment of disease, the appropriate dosage of a bispecific antibody will depend on the type of disease to be treated, the type of antibody, the severity and course of the disease, whether the bispecific antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the bispecific antibody and the discretion of the attending physician. The bispecific antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1  $\mu$ g/kg to 15 mg/kg (e.g. 0.1 mg/kg-10 mg/kg) of the bispecific antibody or the novel antibody binding to DR5 can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the bispecific would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg may be administered to the patient. Such doses may be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about two to about twenty, or e.g. about six doses of the bispecific antibody). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

It is understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to the T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 and the anti-PD-1 axis binding <sup>5</sup> antagonist antibody, and, optionally, the anti-TIM3 antagonist antibody.

I. Articles of Manufacture

In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention 10 and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be 15 formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an 20 intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a bispecific antibody and an additional active agent is the further chemotherapeutic agent as described herein. The label or package insert indicates 25 that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises a bispecific antibody; and (b) a second container with a composition contained 30 therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or 35 additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other 40 materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

It is understood that any of the above articles of manufacture may include an immunoconjugate of the invention in <sup>45</sup> place of or in addition to the T cell activating bispecific antigen binding molecules that binds to FolR1 and CD3 and the anti-PD-1 axis binding antagonist antibody and, optionally, the anti-TIM3 antagonist antibody.

Although the foregoing invention has been described in <sup>50</sup> some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by <sup>55</sup> reference.

#### III. Examples

The following are examples of methods and compositions 60 of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.

General Methods

Recombinant DNA Techniques

Standard methods were used to manipulate DNA as described in Sambrook et al., Molecular cloning: A labora-

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tory manual; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. The molecular biological reagents were used according to the manufacturers' instructions. General information regarding the nucleotide sequences of human immunoglobulins light and heavy chains is given in: Kabat, E. A. et al., (1991) Sequences of Proteins of Immunological Interest, 5<sup>th</sup> ed., NIH Publication No. 91-3242.

DNA Sequencing

DNA sequences were determined by double strand sequencing.

Gene Synthesis

Desired gene segments where required were either generated by PCR using appropriate templates or were synthesized by Geneart AG (Regensburg, Germany) from synthetic oligonucleotides and PCR products by automated gene synthesis. In cases where no exact gene sequence was available, oligonucleotide primers were designed based on sequences from closest homologues and the genes were isolated by RT-PCR from RNA originating from the appropriate tissue. The gene segments flanked by singular restriction endonuclease cleavage sites were cloned into standard cloning/sequencing vectors. The plasmid DNA was purified from transformed bacteria and concentration determined by UV spectroscopy. The DNA sequence of the subcloned gene fragments was confirmed by DNA sequencing. Gene segments were designed with suitable restriction sites to allow sub-cloning into the respective expression vectors. All constructs were designed with a 5'-end DNA sequence coding for a leader peptide which targets proteins for secretion in eukaryotic cells.

Isolation of Primary Human Pan T Cells from PBMCs

Peripheral blood mononuclear cells (PBMCs) were prepared by Histopaque density centrifugation from enriched lymphocyte preparations (buffy coats) obtained from local blood banks or from fresh blood from healthy human donors. Briefly, blood was diluted with sterile PBS and carefully layered over a Histopaque gradient (Sigma, H8889). After centrifugation for 30 minutes at 450×g at room temperature (brake switched off), part of the plasma above the PBMC containing interphase was discarded. The PBMCs were transferred into new 50 ml Falcon tubes and tubes were filled up with PBS to a total volume of 50 ml. The mixture was centrifuged at room temperature for 10 minutes at 400×g (brake switched on). The supernatant was discarded and the PBMC pellet washed twice with sterile PBS (centrifugation steps at 4° C. for 10 minutes at 350×g). The resulting PBMC population was counted automatically (Vi-Cell) and stored in RPMI1640 medium, containing 10% FCS and 1% L-alanyl-L-glutamine (Biochrom, K0302) at 37° C., 5% CO<sub>2</sub> in the incubator until assay start.

T cell enrichment from PBMCs was performed using the Pan T Cell Isolation Kit II (Miltenyi Biotec #130-091-156), according to the manufacturer's instructions. Briefly, the cell pellets were diluted in 40 µl cold buffer per 10 million cells (PBS with 0.5% BSA, 2 mM EDTA, sterile filtered) and incubated with 10 µl Biotin-Antibody Cocktail per 10 million cells for 10 min at 4° C. 30 µl cold buffer and 20 µl Anti-Biotin magnetic beads per 10 million cells were added, and the mixture incubated for another 15 min at 4° C. Cells were washed by adding 10-20× the current volume and a subsequent centrifugation step at 300×g for 10 min. Up to 100 million cells were resuspended in 500 µl buffer. Magnetic separation of unlabeled human pan T cells was performed using LS columns (Miltenyi Biotec #130-042-401) according to the manufacturer's instructions. The resulting T cell population was counted automatically (ViCell) and

stored in AIM-V medium at  $37^{\circ}$  C., 5% CO, in the incubator until assay start (not longer than 24 h).

Isolation of Primary Human Naive T Cells from PBMCs

Peripheral blood mononuclar cells (PBMCs) were prepared by Histopaque density centrifugation from enriched 5 lymphocyte preparations (buffy coats) obtained from local blood banks or from fresh blood from healthy human donors. T-cell enrichment from PBMCs was performed using the Naive CD8<sup>+</sup> T cell isolation Kit from Miltenyi Biotec (#130-093-244), according to the manufacturer's 10 instructions, but skipping the last isolation step of CD8<sup>+</sup> T cells (also see description for the isolation of primary human pan T cells).

Isolation of Murine Pan T Cells from Splenocytes

Spleens were isolated from C57BU6 mice, transferred 15 into a GentleMACS C-tube (Miltenyi Biotech #130-093-237) containing MACS buffer (PBS+0.5% BSA+2 mM EDTA) and dissociated with the GentleMACS Dissociator to obtain single-cell suspensions according to the manufacturer's instructions. The cell suspension was passed through 20 a pre-separation filter to remove remaining undissociated tissue particles. After centrifugation at 400×g for 4 min at 4° C., ACK Lysis Buffer was added to lyse red blood cells (incubation for 5 min at room temperature). The remaining cells were washed with MACS buffer twice, counted and 25 used for the isolation of murine pan T cells. The negative (magnetic) selection was performed using the Pan T Cell Isolation Kit from Miltenyi Biotec (#130-090-861), following the manufacturer's instructions. The resulting T cell population was automatically counted (ViCell) and imme- 30 diately used for further assays.

Isolation of Primary Cynomolgus PBMCs from Heparinized Blood

Peripheral blood mononuclar cells (PBMCs) were prepared by density centrifugation from fresh blood from 35 healthy cynomolgus donors, as follows: Heparinized blood was diluted 1:3 with sterile PBS, and Lymphoprep medium (Axon Lab #1114545) was diluted to 90% with sterile PBS. Two volumes of the diluted blood were layered over one volume of the diluted density gradient and the PBMC 40 fraction was separated by centrifugation for 30 min at 520×g, without brake, at room temperature. The PBMC band was transferred into a fresh 50 ml Falcon tube and washed with sterile PBS by centrifugation for 10 min at 400×g at 4° C. One low-speed centrifugation was performed 45 to remove the platelets (15 min at 150×g, 4° C.), and the resulting PBMC population was automatically counted (Vi-Cell) and immediately used for further assays.

#### Example 1

#### Purification of Biotinylated Folate Receptor-Fc Fusions

To generate new antibodies against human FolR1 the 55 following antigens and screening tools were generated as monovalent Fc fusion proteins (the extracellular domain of the antigen linked to the hinge region of Fc-knob which is co-expressed with an Fc-hole molecule). The antigen genes were synthesized (Geneart, Regensburg, Germany) based on 60 sequences obtained from GenBank or SwissProt and inserted into expression vectors to generate fusion proteins with Fc-knob with a C-terminal Avi-tag for in vivo or in vitro biotinylation. In vivo biotinylation was achieved by co-expression of the bacterial birA gene encoding a bacterial 65 biotin ligase during production. Expression of all genes was under control of a chimeric MPSV promoter on a plasmid

containing an oriP element for stable maintenance of the plasmids in EBNA containing cell lines.

For preparation of the biotinylated monomeric antigen/Fc fusion molecules, exponentially growing suspension HEK293 EBNA cells were co-transfected with three vectors encoding the two components of fusion protein (knob and hole chains) as well as BirA, an enzyme necessary for the biotinylation reaction. The corresponding vectors were used at a 9.5:9.5:1 ratio ("antigen ECD-Fc knob-avi tag": "Fc hole": "BirA"). For protein production in 500 ml shake flasks, 400 million HEK293 EBNA cells were seeded 24 hours before transfection. For transfection cells were centrifuged for 5 minutes at 210 g, and supernatant was replaced by pre-warmed CD CHO medium. Expression vectors were resuspended in 20 mL of CD CHO medium containing 200 µg of vector DNA. After addition of 540 µL of polyethylenimine (PEI), the solution was mixed for 15 seconds and incubated for 10 minutes at room temperature. Afterwards, cells were mixed with the DNA/PEI solution, transferred to a 500 mL shake flask and incubated for 3 hours at 37° C. in an incubator with a 5% CO2 atmosphere. After the incubation, 160 mL of F17 medium was added and cells were cultured for 24 hours. One day after transfection, 1 mM valproic acid and 7% Feed 1 (Lonza) were added to the culture. The production medium was also supplemented with 100 µM biotin. After 7 days of culturing, the cell supernatant was collected by spinning down cells for 15 min at 210 g. The solution was sterile filtered (0.22 µm filter), supplemented with sodium azide to a final concentration of 0.01% (w/v), and kept at 4° C.

Secreted proteins were purified from cell culture supernatants by affinity chromatography using Protein A, followed by size exclusion chromatography. For affinity chromatography, the supernatant was loaded on a HiTrap ProteinA HP column (CV=5 mL, GE Healthcare) equilibrated with 40 mL 20 mM sodium phosphate, 20 mM sodium citrate pH 7.5. Unbound protein was removed by washing with at least 10 column volumes of 20 mM sodium phosphate, 20 mM sodium citrate pH 7.5. The bound protein was eluted using a linear pH-gradient created over 20 column volumes of 20 mM sodium citrate, 100 mM sodium chloride, 100 mM glycine, pH 3.0. The column was then washed with 10 column volumes of 20 mM sodium citrate, 100 mM sodium chloride, 100 mM glycine, pH 3.0. pH of collected fractions was adjusted by adding  $\frac{1}{10}$  (v/v) of 0.5 M sodium phosphate, pH 8.0. The protein was concentrated and filtered prior to loading on a HiLoad Superdex 200 50 column (GE Healthcare) equilibrated with 20 mM histidine, 140 mM sodium chloride, pH 6.0.

The protein concentration was determined by measuring the optical density (OD) at 280 nm, using the molar extinction coefficient calculated on the basis of the amino acid sequence. Purity and molecular weight of the FolR1-Fcfusion was analyzed by SDS capillary electrophoresis in the presence and absence of a reducing agent following the manufacturer instructions (instrument Caliper LabChipGX, Perkin Elmer). The aggregate content of samples was analyzed using a TSKgel G3000 SW XL analytical size-exclusion column (Tosoh) equilibrated in 25 mM K2HPO4, 125 mM NaCl, 200 mM L-arginine monohydrochloride, 0.02% (w/v) NaN3, pH 6.7 running buffer at 25° C.

Purified antigen-Fc-fusion proteins were analyzed by surface plasmon resonance assays using commercially available antibodies to confirm correct and natural conformation of the antigens (data not shown).

# TABLE 1

	Antigens	produced selection	for isolation, selection and counter n of human FolR1 antibodies	
Antigen	ECD (aa)	Accession number	Sequence	Seq ID No
human FolR1	25-234	IP15328	RIAWARTELLNVCMNAKHHKEKPGPEDKLHEQCRPWR KNACCSTNTSQEAHKDVSYLYRFNWNHCGEMAPACKR HFIQDTCLYECSPNLGPWIQQVDQSWRKERVLNVPLC KEDCEQWWEDCRTSYTCKSNWHKGWNWTSGFNKCAVG AACQPFHFYFPTPTVLCNEIWTHSYKVSNYSRGSGRC IQMWFDPAQGNPNEEVARFYAAAM	227
human FolR2	17-230	)P14207	TMCSAQDRTDLLNVCMDAKHHKTKPGPEDKLHDQCSP WKKNACCTASTSQELHKDTSRLYNFNWDHCGKMEPAC KRHFIQDTCLYECSPNLGPWIQQVNQSWRKERFLDVP LCKEDCQRWWEDCHTSHTCKSNWHRGWDWTSGVNKCP AGALCRTFESYFFTPAALCEGLWSHSYKVSNYSRGSG RCIQMWFDSAQGNPNEEVARFYAAAMHVN	228
human FolR3	24-243	3 P41439	SARARTDLLNVCMNAKHHKTQPSPEDELYGQCSPWKK NACCTASTSQELHKDTSRLYNFNWDHCGKMEPTCKRH FIQDSCLYECSPNLGPWIRQVNQSWRKERILNVPLCK EDCERWWEDCRTSYTCKSNWHKGWNWTSGINECPAGA LCSTFESYFPTPAALCEGLWSHSFKVSNYSRGSGRCI QMWFDSAQGNPNEEVAKFYAAAMNAGAPSRGIIDS	229
murine FolR1	25-232	2935846	TRARTELLNVCMDAKHHKEKPGPEDNLHDQCSPWKTN SCCSTNTSQEAHKDISYLYRFNWNHCGTMTSECKRHF IQDTCLYECSPNLGPWIQQVDQSWRKERILDVPLCKE DCQQWWEDCQSSFTCKSNWHKGWNWSSGHNECPVGAS CHPFTFYFPTSAALCEEIWSHSYKLSNYSRGSGRCIQ MWFDPAQGNPNEEVARFYAEAMS	230
cynomolgu: FolR1	s 25-234	G7PR14	EAQTRTARARTELLNVCMNAKHHKEKPGPEDKLHEQC RPWKKNACCSTNTSQEAHKDVSYLYRFNWNHCGEMAP ACKRHFIQDTCLYECSPNLGPWIQQVDQSWRKERVLN VPLCKEDCERWWEDCRTSYCKSNWHKGWNWTSGFNKC PVGAACQPFHFYFPTPTVLCNEIWTYSYKVSNYSRGS GRCIQMWFDPAQGNPNEEVARFYAAAMS	231

#### TABLE 2

Summary of the yield and final monomer content of the FolR- Fc- fusions.				
Antigen	Monomer [%] (SEC)	Yield		
huFolR1 cyFolR1 muFolR1 huFolR2 huFolR3	100 100 100 100 95	30 mg/L 32 mg/L 31 mg/L 16 mg/L 38 mg/L	45	

## Example 2

### Generation of Common Light Chain with CDR Specificity

The T cell activating bispecific molecules described herein comprise at least one CD3 binding moiety. This moiety can be generated by immunizing laboratory animals, screening phage library or using known anti-CD3 antibodies. The common light chain with CD36 specificity was 60 generated by humanizing the light chain of a murine parental anti-CD36 antibody (CH2527). For humanization of an antibody of non-human origin, the CDR residues from the non-human antibody (donor) have to be transplanted onto the framework of a human (acceptor) antibody. Generally, 65 acceptor framework sequences are selected by aligning the sequence of the donor to a collection of potential acceptor

sequences and choosing one that has either reasonable homology to the donor, or shows similar amino acids at some positions critical for structure and activity. In the present case, the search for the antibody acceptor framework was performed by aligning the mouse VL-domain sequence of the parental antibody to a collection of human germline sequences and choosing the human sequence that showed high sequence identity. Surprisingly, a good match in terms of framework sequence homology was found in a rather infrequent human light chain belonging to the V-domain family 7 of the lambda type, more precisely, hVL\_7\_46 (IMGT nomenclature, GenBank Acc No. Z73674). This infrequent human light chain was subsequently chosen as acceptor framework for humanization of the light chain of CH2527. The three complementarity determining regions (CDRs) of the mouse light chain variable domain were grafted onto this acceptor framework. Since the framework 55 4 region is not part of the variable region of the germline V-gene, the alignment for this region (J-element) was done individually. Hence the IGU3-02 sequence was chosen for humanization of this light chain.

Thirteen humanized variants were generated (CH2527-VL7\_46-1 to VL7\_46-10, VL7\_46-12 to VL7\_46-14). These differ in framework residues (and combinations thereof) that were back-mutated to the murine V-domain sequence or in CDR-residues (Kabat definition) that could be kept identical to the human germline sequence. The following framework residues outside the CDRs were backmutated to the murine residues in the final humanized VL-domain variant VL7\_46-13 (murine residues listed):

V36, E38, F44, G46, G49, and G57, respectively. The human J-element IGLJ3-02 was 100% identical to the J-element of the murine parental antibody.

#### Example 3

# SPR Assessment of Humanized Variants with CD3E Specificity

Humanized VL variants were assessed as chimera in a 2+1 TCB format, i.e. humanized light chain V-domains were paired with murine heavy chain V-domains. SPR assessment was carried out on a ProteOn XPR36 instrument (Bio-Rad). More precisely, the variants were captured directly from the culture supernatant on an anti-Fab derivatized GLM sensorchip (Goat Anti-Human IgG, F(ab')2 Fragment Specific, Jackson ImmunoResearch) in vertical orientation. The following analytes were subsequently injected horizontally as single concentrations to assess binding to human and cynomolgus CD3 $\epsilon$ : 3 µM hu CD3 $\epsilon$ (-1-26)-Fc(knob)-avi (ID807)<sup>20</sup> and 2.5 µM cy CD3ε-(-1-26)-Fc(knob)-Avi-Fc(hole) (ID873), respectively. Binding responses were qualitatively compared to binding of the murine control construct and graded +(comparable binding observed), +/-(reduced bind-25 ing observed) and -(no binding observed). The capture antibody was regenerated after each cycle of ligand capture and analyte binding and the murine construct was re-injected at the end of the study to confirm the activity of the capture surface. The results are summarized in Table 3. 30

TABLE 3

sed on SPR for the humanized		
h the murine heavy chain of		
in variant that was finally chosen,		
ed in bold letters, exhibited		
comparable binding to human and cynomolgus CD3E.		
binding to CD3ε		
+		
-		

CH2527-VL7_40-2	-
CH2527-VL7_46-3	-
CH2527-VL7_46-4	-
CH2527-YL7_46-5	-
CH2527-VL7_46-6	-
CH2527-YL7_46-7	-
CH2527-VL7_46-8	-
CH2527-VL7_46-9	-
CH2527-VL7_46-10	-
CH2527-VL7_46-12	+/-
CH2527-VL7_46-13	+
CH2527-VL7_46-14	-

#### Example 4

#### Properties of Humanized Common Light Chain with CD3E Specificity

The light chain V-domain variant that was chosen for the humanized lead molecule is VL7\_46-13. The degree of humanness, i.e. the sequence homology of the humanized 60 V-domain to the human germline V-domain sequence was determined. For VL7\_46-13, the overall sequence identity with the closest human germline homolog is 65% before humanization and 80% afterwards. Omitting the CDR regions, the sequence identity is 92% to the closest human 65 germline homolog. As can be seen from Table 3, VL7\_46-13 is the only humanized VL variant out of a panel of 13

variants that showed comparable binding to the parental murine antibody and also retained its cross-reactivity to cynomolgus CD3E. This result indicates that it was not trivial to humanize the murine VL-domain without losing binding affinity to CD3E which required several backmutations to murine framework residues (in particular G46) while retaining G24 in CDR1. In addition, this result shows that the VL-domain plays a crucial role in target recognition. Importantly, the humanized VL-domain VL7\_46-13 based on an infrequent human germline belonging to the V-domain family 7 of the lambda type and retaining affinity and specificity for CD3E, is also suitable to be used as a common light chain in phage-displayed antibody libraries of the Fab-format and enables successful selection for novel specificities which greatly facilitates the generation and production of bispecific molecules binding to CD3E and e.g. a tumor target and sharing the same 'common' light chain.

# Example 5

# Generation of a Phage Displayed Antibody Library Using a Human Germ-Line Common Light Chain Derived from HVK1-39

Several approaches to generate bispecific antibodies that resemble full length human IgG utilize modifications in the Fc region that induce heterodimerization of two distinct heavy chains. Such examples include knobs-into-holes (Merchant et al., Nat Biotechnol. 1998 July; 16(7):677-81)
SEED (Davis et al., Protein Eng Des Sel. 2010 April; 23(4):195-202) and electrostatic steering technologies (Gunasekaran et al., J Biol Chem. 2010 Jun. 18; 285(25):19637-46). Although these approaches enable effective heterodimerization of two distinct heavy chains, appropriate pairing of cognate light and heavy chains remains a problem. Usage of a common light chain (LC) can solve this issue (Merchant, et al. Nat Biotech 16, 677-681 (1998)).

Here, we describe the generation of an antibody library for the display on a M13 phage. Essentially, we designed a 40 multi framework library for the heavy chain with one constant (or "common") light chain. This library is designed for generating multispecific antibodies without the need to use sophisticated technologies to avoid light chain mispairing.

45 By using a common light chain the production of these molecules can be facilitated as no mispairing occurs any longer and the isolation of a highly pure bispecific antibody is facilitated. As compared to other formats the use of Fab fragments as building blocks as opposed to e.g. the use of 50 scFv fragments results in higher thermal stability and the lack of scFv aggregation and intermolecular scFv formation. Library Generation

In the following the generation of an antibody library for the display on M13 phage is described. Essentially, we 55 designed a multi framework library for the heavy chain with one constant (or "common") light chain.

We used these heavy chains in the library (GenBank Accession Numbers in brackets):

IGHV1-46\*01 (X92343) (SEQ ID NO:104), IGHV1-69\*06 (L22583), (SEQ ID NO:105) IGHV3-15\*01 (X92216), (SEQ ID NO:106) IGHV3-23\*01 (M99660), (SEQ ID NO:107) IGHV4-59\*01 (AB019438), (SEQ ID NO:108) IGHV5-51\*01 (M99686), (SEQ ID NO:109)

All heavy chains use the IGHJ2 as J-element, except the IGHV1-69\*06 which uses IGHJ6 sequence. The design of the randomization included the CDR-H1, CDR-H2, and

CDR-H3. For CDR-H1 and CDR-H2 a "soft" randomization strategy was chosen, and the randomization oligonucleotides were such that the codon for the amino acid of the germ-line sequence was present at 50%. All other amino acids, except cysteine, were summing up for the remaining 50%. In 5 CDR-H3, where no germ-line amino acid is present due to the presence of the genetic D-element, oligonucleotides were designed that allow for the usage of randomized inserts between the V-element and the J-element of 4 to 9 amino acids in length. Those oligonucleotides contained in their randomized part e.g. The three amino acids G/Y/S are present to 15% each, those amino acids

A/D/T/R/P/UV/N/W/F/I/E are present to 4.6% each.

Exemplary methods for generation of antibody libraries 15 are described in Hoogenboom et al., Nucleic Acids Res. 1991, 19, 4133-413; Lee et. al J. Mol. Biol. (2004) 340, 1073-1093.

The light chain is derived from the human sequence hVK1-39, and is used in an unmodified and non-randomized 20 fashion. This will ensure that the same light chain can be used for other projects without additional modifications. Exemplary Library Selection:

Selections with all affinity maturation libraries are carried out in solution according to the following procedure using a 25 monomeric and biotinylated extracellular domain of a target antigen X.

1. 10<sup>12</sup> phagemid particles of each library are bound to 100 nM biotinylated soluble antigen for 0.5 h in a total volume of 1 ml. 2. Biotinylated antigen is captured and 30 specifically bound phage particles are isolated by addition of  $-5 \times 10^{7}$  streptavidin-coated magnetic beads for 10 min. 3. Beads are washed using 5-10×1 ml PBS/Tween20 and 5-10×1 ml PBS. 4. Elution of phage particles is done by addition of 1 ml 100 mM TEA (triethylamine) for 10 min 35 and neutralization by addition of 500 ul 1M Tris/HCl pH 7.4 and 5. Re-infection of exponentially growing E. coli TG1 bacteria, infection with helper phage VCSM13 and subsequent PEG/NaCl precipitation of phagemid particles is applied in subsequent selection rounds. Selections are car- 40 ried out over 3-5 rounds using either constant or decreasing (from 10<sup>-7</sup>M to 2×10<sup>-9</sup>M) antigen concentrations. In round 2, capture of antigen/phage complexes is performed using neutravidin plates instead of streptavidin beads. All binding reactions are supplemented either with 100 nM 45 of 4 to 9 amino acids in length. bovine serum albumin, or with non-fat milk powder in order to compete for unwanted clones arising from mere sticky binding of the antibodies to the plastic support.

Selections are being carried out over three or four rounds using decreasing antigen concentrations of the antigen start- 50 ing from 100 nM and going down to 5 nM in the final selection round. Specific binders are defined as signals ca.  $5 \times$  higher than background and are identified by ELISA. Specific binders are identified by ELISA as follows: 100 µl of 10 nM biotinylated antigen per well are coated on 55 neutravidin plates. Fab-containing bacterial supernatants are added and binding Fabs are detected via their Flag-tags by using an anti-Flag/HRP secondary antibody. ELISA-positive clones are bacterially expressed as soluble Fab fragments in 96-well format and supernatants are subjected to a kinetic 60 screening experiment by SPR-analysis using ProteOn XPR36 (BioRad). Clones expressing Fabs with the highest affinity constants are identified and the corresponding phagemids are sequenced. For further characterization, the Fab sequences are amplified via PCR from the phagemid 65 and cloned via appropriate restriction sites into human IgG<sub>1</sub> expression vectors for mammalian production.

Generation of a Phage Displayed Antibody Library Using a Humanized CD3E Specific Common Light Chain

Here, the generation of an antibody library for the display on M13 phage is described. Essentially, we designed a multi framework library for the heavy chain with one constant (or "common") light chain. This library was designed for the generation of Fc-containing, but FcgR binding inactive T cell bispecific antibodies of IgG1 P329G LALA or IgG4 SPLE PG isotype in which one or two Fab recognize a tumor surface antigen expressed on a tumor cell whereas the remaining Fab arm of the antibody recognizes CD3e on a T cell.

Library Generation

In the following the generation of an antibody library for the display on M13 phage is described. Essentially, we designed a multi framework library for the heavy chain with one constant (or "common") light chain. This library is designed solely for the generation of Fc-containing, but FcgR binding inactive T cell bispecific antibodies of IgG<sub>1</sub> P329G LALA or IgG<sub>4</sub> SPLE PG isotype.

Diversity was introduced via randomization oligonucleotides only in the CDR3 of the different heavy chains. Methods for generation of antibody libraries are well known in the art and are described in (Hoogenboom et al., Nucleic Acids Res. 1991, 19, 4133-413; or in: Lee et. al J. Mol. Biol. (2004) 340, 1073-1093).

We used these heavy chains in the library: IGHV1-46\*01 (X92343), (SEQ ID NO:104) IGHV1-69\*06 (L22583), (SEQ ID NO:105) IGHV3-15\*01 (X92216), (SEQ ID NO:106) IGHV3-23\*01 (M99660), (SEQ ID NO:107) IGHV4-59\*01 (AB019438), (SEQ ID NO:108) IGHV5-51\*01 (M99686), (SEQ ID NO:109)

We used the light chain derived from the humanized human and Cynomolgus CD3 specific antibody CH2527 in the library: (VL7\_46-13; SEQ ID NO:112). This light chain was not randomized and used without any further modifications in order to ensure compatibility with different bispecific binders.

All heavy chains use the IGHJ2 as J-element, except the IGHV1-69\*06 which uses IGHJ6 sequence. The design of the randomization focused on the CDR-H3 only, and PCR oligonucleotides were designed that allow for the usage of randomized inserts between the V-element and the J-element

#### Example 6

# Selection of Antibody Fragments from Common Light Chain Libraries (Comprising Light Chain with CD3E Specificity) to FolR1

The antibodies 16A3, 15A1, 18D3, 19E5, 19A4, 15H7, 15B6, 16D5, 15E12, 21D1, 16F12, 21A5, 21G8, 19H3, 20G6, and 20H7 comprising the common light chain VL7\_46-13 with CD3c specificity were obtained by phage display selections against different species (human, cynomolgus and murine) of FolR1. Clones 16A3, 15A1, 18D3, 19E5, 19A4, 15H7, 15B6, 21D1, 16F12, 19H3, 20G6, and 20H7 were selected from a sub-library in which the common light chain was paired with a heavy chain repertoire based on the human germline VH1\_46. In this sub-library, CDR3 of VH1\_46 has been randomized based on 6 different CDR3 lengths. Clones 16D5, 15E12, 21A5, and 21G8 were selected from a sub-library in which the common light chain was paired with a heavy chain repertoire based on the human germline VH3\_15. In this sub-library, CDR3 of VH3\_15 has

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been randomized based on 6 different CDR3 lengths. In order to obtain species cross-reactive (or murine FolR1reactive) antibodies, the different species of FolR1 were alternated (or kept constant) in different ways over 3 rounds of biopanning: 16A3 and 15A1 (human-cynomolgus-human 5 FolR1); 18D3 (cynomolgus-human-murine FolR1); 19E5 and 19A4 (3 rounds against murine FolR1); 15H7, 15B6, 16D5, 15E12, 21D1, 16F12, 21A5, 21G8 (human-cynomolgus-human FolR1); 19H3, 20G6, and 20H7 (3 rounds against murine FolR1).

Human, murine and cynomolgus FolR1 as antigens for the phage display selections as well as ELISA- and SPRbased screenings were transiently expressed as N-terminal monomeric Fc-fusion in HEK EBNA cells and in vivo site-specifically biotinylated via co-expression of BirA bio-15 tin ligase at the avi-tag recognition sequence located at the C-terminus of the Fc portion carrying the receptor chain (Fc knob chain). In order to assess the specificity to FolR1, two related receptors, human FolR2 and FolR3 were generated in the same way.

Selection rounds (biopanning) were performed in solution according to the following pattern:

- 1. Pre-clearing of  $\sim 10^{12}$  phagemid particles on maxisorp plates coated with 10 ug/ml of an unrelated human IgG to deplete the libraries of antibodies recognizing the Fc- 25 portion of the antigen.
- 2. Incubating the non-Fc-binding phagemid particles with 100 nM biotinylated human, cynomolgus, or murine FolR1 for 0.5h in the presence of 100 nM unrelated non-biotinylated Fc knob-into-hole construct for further 30 depletion of Fc-hinders in a total volume of 1 ml.
- 3. Capturing the biotinylated FolR1 and attached specifically binding phage by transfer to 4 wells of a neutravidin pre-coated microtiter plate for 10 min (in rounds 1 & 3).
- 4. Washing the respective wells using 5×PBS/Tween20 and 35 5×PBS.
- 5. Eluting the phage particles by addition of 250 ul 100 mM TEA (triethylamine) per well for 10 min and neutralization by addition of 500 ul 1 M Tris/HCl pH 7.4 to the pooled eluates from 4 wells.
- 6. Post-clearing of neutralized eluates by incubation on neutravidin pre-coated microtiter plate with 100 nM biotin-captured FoIR2 or FoIR3 for final removal of Fc- and unspecific binders.
- 7. Re-infection of log-phase E. coli TG1 cells with the 45 supernatant of eluted phage particles, infection with helperphage VCSM13, incubation on a shaker at 30° C. over night and subsequent PEG/NaCl precipitation of phagemid particles to be used in the next selection round. Selections were carried out over 3 rounds using constant 50

antigen concentrations of 100 nM. In round 2, in order to avoid enrichment of binders to neutravidin, capture of antigen: phage complexes was performed by addition of 5.4×107 streptavidin-coated magnetic beads. Specific binders were identified by ELISA as follows: 100 ul of 25 nM 55 were obtained by phage display selections based on generic biotinylated human, cynomolgus, or murine FolR1 and 10 ug/ml of human IgG were coated on neutravidin plates and maxisorp plates, respectively. Fab-containing bacterial supernatants were added and binding Fabs were detected via their Flag-tags using an anti-Flag/HRP secondary antibody. 60 Clones exhibiting signals on human FolR1 and being negative on human IgG were short-listed for further analyses and were also tested in a similar fashion against the remaining two species of FolR1. They were bacterially expressed in a 0.5 liter culture volume, affinity purified and further char-65 acterized by SPR-analysis using BioRad's ProteOn XPR36 biosensor.

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Affinities (K<sub>D</sub>) of selected clones were measured by surface plasmon resonance (SPR) using a ProteOn XPR36 instrument (Biorad) at 25° C. with biotinylated human, cynomolgus, and murine FolR1 as well as human FolR2 and FolR3 (negative controls) immobilized on NLC chips by neutravidin capture. Immobilization of antigens (ligand): Recombinant antigens were diluted with PBST (10 mM phosphate, 150 mM sodium chloride pH 7.4, 0.005% Tween 20) to 10 then injected at 30 µl/minute in vertical orientation. Injection of analytes: For 'one-shot kinetics' measurements, injection direction was changed to horizontal orientation, two-fold dilution series of purified Fab (varying concentration ranges) were injected simultaneously along separate channels 1-5, with association times of 200 s, and dissociation times of 600 s. Buffer (PBST) was injected along the sixth channel to provide an "in-line" blank for referencing. Association rate constants (kon) and dissociation rate constants (koff) were calculated using a simple one-to-one Langmuir binding model in ProteOn Manager v3.1 software by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant  $(K_D)$ was calculated as the ratio koff/kon. Table 4 lists the equilibrium dissociation constants  $(K_D)$  of the selected clones specific for FolR1.

TABLE 4

Equilibrium dissociation constants (KD) for anti-FolR1
antibodies (Fab-format) selected by phage display from common
light chain sub-libraries comprising VL7_46-13, a humanized
light chain specific for CD3E. KD in nM.

Clone	huFolR1 [nm]	cyFolR1 [nM]	muFolR1 [nM]	huFolR2 [nM]	huFolR3 [nM]
16A3 15A1 18D3 19E5 19A4 15H7 15B6 16D5 15E12 21D1 16F12 21A5 21G8 19H3 20G6	21.7 30.9 93.6 522 2050 13.4 19.1 39.5 55.7 62.6 68 68.8 130 no binding no binding	18 17.3 40.2 276 4250 72.5 13.9 114 137 32.1 90.9 131 261 no binding pa binding	very weak very weak 19.4 43.1 no binding no binding no binding no binding no binding no binding no binding 89.7 78 5	no binding no binding	no binding no binding
	0	0		0	0

#### Example 7

## Selection of Antibody Fragments from Generic Multi-Framework Libraries to FolR1

The antibodies 11F8, 36F2, 9D11, 5D9, 6B6, and 14E4 multi-framework sub-libraries against different species (human, cynomolgus and murine) of FolR1. In these multiframework sub-libraries, different VL-domains with randomized CDR3 (3 different lengths) are paired with different VH-domains with randomized CDR3 (6 different lengths). The selected clones are of the following VL/VH pairings: 11F8 (Vk\_1\_5/VH\_1\_69), 36F2 (Vk\_3\_20/VH\_1\_46), 9D11 (Vk2D\_28/VH1\_46), 5D9 (Vk3\_20/VH1\_46), 6B6 (Vk3\_20/VH1\_46), and 14E4 (Vk3\_20/VH3\_23). In order to obtain species cross-reactive (or murine FolR1-reactive) antibodies, the different species of FolR1 were alternated (or kept constant) in different ways over 3 or 4 rounds of

biopanning: 11F8 (cynomolgus-murine-human FolR1); 36F2 (human-murine-cynomolgus-murine FolR1); 9D11 (cynomolgus-human-cynomolgus FolR1); 5D9 (human-cynomolgus-human FolR1); 6B6 (human-cynomolgus-human FolR1) and 14E4 (3 rounds against murine FolR1).

Human, murine and cynomolgus FolR1 as antigens for the phage display selections as well as ELISA- and SPRbased screenings were transiently expressed as N-terminal monomeric Fc-fusion in HEK EBNA cells and in vivo site-specifically biotinylated via co-expression of BirA bio-10 tin ligase at the avi-tag recognition sequence located at the C-terminus of the Fc portion carrying the receptor chain (Fc knob chain). In order to assess the specificity to FolR1, two related receptors, human FolR2 and FolR3 were generated in the same way. 15

Selection rounds (biopanning) were performed in solution according to the following pattern:

- 1. Pre-clearing of  $\sim 10^{12}$  phagemid particles on maxisorp plates coated with 10 ug/ml of an unrelated human IgG to deplete the libraries of antibodies recognizing the Fc- 20 portion of the antigen.
- 2. Incubating the non-Fc-binding phagemid particles with 100 nM biotinylated human, cynomolgus, or murine FolR1 for 0.5h in the presence of 100 nM unrelated non-biotinylated Fc knob-into-hole construct for further 25 depletion of Fc-binders in a total volume of 1 ml.
- 3. Capturing the biotinylated FolR1 and attached specifically binding phage by transfer to 4 wells of a neutravidin pre-coated microtiter plate for 10 min (in rounds 1 & 3).
- 4. Washing the respective wells using 5×PBS/Tween20 and 30 5×PBS.
- 5. Eluting the phage particles by addition of 250 ul 100 mM TEA (triethylamine) per well for 10 min and neutralization by addition of 500 ul 1 M Tris/HCl pH 7.4 to the pooled eluates from 4 wells.
- Post-clearing of neutralized eluates by incubation on neutravidin pre-coated microtiter plate with 100 nM biotin-captured FolR2 or FolR3 for final removal of Fc- and unspecific binders.
- Re-infection of log-phase *E. coli* TG1 cells with the 40 supernatant of eluted phage particles, infection with helperphage VCSM13, incubation on a shaker at 30° C. over night and subsequent PEG/NaCl precipitation of phagemid particles to be used in the next selection round.

Selections were carried out over 3 rounds using constant 45 antigen concentrations of 100 nM. In round 2 and 4, in order to avoid enrichment of binders to neutravidin, capture of antigen: phage complexes was performed by addition of  $5.4 \times 10^7$  streptavidin-coated magnetic beads. Specific binders were identified by ELISA as follows: 100 ul of 25 nM 50 biotinylated human, cynomolgus, or murine FolR1 and 10 ug/ml of human IgG were coated on neutravidin plates and maxisorp plates, respectively. Fab-containing bacterial supernatants were added and binding Fabs were detected via their Flag-tags using an anti-Flag/HRP secondary antibody. 55 Clones exhibiting signals on human FolR1 and being negative on human IgG were short-listed for further analyses and were also tested in a similar fashion against the remaining two species of FolR1. They were bacterially expressed in a 0.5 liter culture volume, affinity purified and further char-60 acterized by SPR-analysis using BioRad's ProteOn XPR36 biosensor.

Affinities  $(K_D)$  of selected clones were measured by surface plasmon resonance (SPR) using a ProteOn XPR36 instrument (Biorad) at 25° C. with biotinylated human, 65 cynomolgus, and murine FolR1 as well as human FolR2 and FolR3 (negative controls) immobilized on NLC chips by

neutravidin capture. Immobilization of antigens (ligand): Recombinant antigens were diluted with PBST (10 mM phosphate, 150 mM sodium chloride pH 7.4, 0.005% Tween 20) to 10  $\mu$ g/ml, then injected at 30  $\mu$ l/minute in vertical orientation. Injection of analytes: For 'one-shot kinetics' measurements, injection direction was changed to horizontal orientation, two-fold dilution series of purified Fab (varying concentration ranges) were injected simultaneously along separate channels 1-5, with association times of 150 or 200 s, and dissociation times of 200 or 600 s, respectively. Buffer (PBST) was injected along the sixth channel to provide an "in-line" blank for referencing. Association rate constants  $(k_{on})$  and dissociation rate constants  $(k_{off})$  were calculated using a simple one-to-one Langmuir binding model in ProteOn Manager v3.1 software by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (KD) was calculated as the ratio k<sub>off</sub>/k<sub>on</sub>. Table 5 lists the equilibrium dissociation constants  $(\vec{K_D})$  of the selected clones specific for FolR1.

TABLE 5

Equilibrium dissociation constants $(K_D)$ for ant antibodies (Fab-format) selected by phage display fr multi-framework sub-libraries. $K_D$ in nM					R1 generic
			K <sub>D</sub> (nM)		
Clone	huFolR1	cyFolR1	muFolR1	huFolR2	huFolR3
1170	(22)	704	1200	1.1.12	1.1.11

11F8	632	794	1200	no binding	no binding
36F2	1810	1640	737	no binding	no binding
9D11	8.64	5.29	no binding	no binding	no binding
5D9	8.6	5.9	no binding	no binding	no binding
6B6	14.5	9.4	no binding	no binding	no binding
14E4	no binding	no binding	6.09	no binding	no binding

#### Example 8

# Production and Purification of Novel FolR1 Binders in IgG and T-Cell Bispecific Formats

To identify FolR1 binders which are able to induce T-cell dependent killing of selected target cells the antibodies isolated from a common light chain- or Fab-library were converted into the corresponding human IgG<sub>1</sub> format. In brief, the variable heavy and variable light chains of unique FolR1 binders from phage display were amplified by standard PCR reactions using the Fab clones as the template. The PCR products were purified and inserted (either by restriction endonuclease and ligase based cloning, or by 'recombineering' using the InFusion kit from Invitrogen) into suitable expression vectors in which they are fused to the appropriate human constant heavy or human constant light chain. The expression cassettes in these vectors consist of a chimeric MPSV promoter and a synthetic polyadenylation site. In addition, the plasmids contain the oriP region from the Epstein Barr virus for the stable maintenance of the plasmids in HEK293 cells harboring the EBV nuclear antigen (EBNA). After PEI mediated transfection the antibodies were transiently produced in HEK293 EBNA cells and purified by standard ProteinA affinity chromatography followed by size exclusion chromatography as described: Transient Transfection and Production

All (bispecific) antibodies (if not obtained from a commercial source) used herein were transiently produced in HEK293 EBNA cells using a PEI mediated transfection procedure for the required vectors as described below.

HEK293 EBNA cells are cultivated in suspension serum free in CD CHO culture medium. For the production in 500 ml shake flask 400 million HEK293 EBNA cells are seeded 24 hours before transfection (for alternative scales all amounts were adjusted accordingly). For transfection cells are centrifuged for 5 min by 210×g, supernatant is replaced by pre-warmed 20 nil CD CHO medium. Expression vectors are mixed in 20 ml CD CHO medium to a final amount of 200  $\mu$ g DNA. After addition of 540  $\mu$ l PEI solution is 10 (CH1C<sub> $\kappa$ </sub> (crossing) while for the clones from the common vortexed for 15 s and subsequently incubated for 10 min at room temperature. Afterwards cells are mixed with the DNA/PEI solution, transferred to a 500 ml shake flask and incubated for 3 hours by 37° C. in an incubator with a 5% 15 CO2 atmosphere. After incubation time 160 ml F17 medium is added and cell are cultivated for 24 hours. One day after transfection 1 mM valporic acid and 7% Feed 1 is added. After 7 days cultivation supernatant is collected for purification by centrifugation for 15 min at 210×g, the solution is sterile filtered (0.22 µm filter) and sodium azide in a final concentration of 0.01% w/v is added, and kept at 4° C. After production the supernatants were harvested and the antibody containing supernatants were filtered through 0.22 µm sterile <sup>25</sup> filters and stored at 4° C. until purification. Antibody Purification

All molecules were purified in two steps using standard procedures, such as protein A affinity purification (Akta 30 Explorer) and size exclusion chromatography. The supernatant obtained from transient production was adjusted to pH 8.0 (using 2 M TRIS pH 8.0) and applied to HiTrap PA FF (GE Healthcare, column volume (cv)=5 ml) equilibrated with 8 column volumes (cv) buffer A (20 mM sodium 35 phosphate, 20 mM sodium citrate, pH 7.5). After washing with 10 cv of buffer A, the protein was eluted using a pH gradient to buffer B (20 mM sodium citrate pH 3, 100 mM NaCl, 100 mM glycine) over 12 cv. Fractions containing the 4∩ protein of interest were pooled and the pH of the solution was gently adjusted to pH 6.0 (using 0.5 M Na<sub>2</sub>HPO4 pH 8.0). Samples were concentrated to 2 ml using ultra-concentrators (Vivaspin 15R 30.000 MWCO HY, Sartorius) and subsequently applied to a HiLoad<sup>™</sup> 16/60 Superdex<sup>™</sup> 200 45 preparative grade (GE Healthcare) equilibrated with 20 mM Histidine, pH 6.0, 140 mM NaCl, 0.01% Tween-20. The aggregate content of eluted fractions was analyzed by analytical size exclusion chromatography. Therefore, 30 µl of each fraction was applied to a TSKgel G3000 SW XL analytical size-exclusion column (Tosoh) equilibrated in 25 mM K2HPO4, 125 mM NaCl, 200 mM L-arginine monohydrochloride, 0.02% (w/v) NaN<sub>3</sub>, pH 6.7 running buffer at 25° C. Fractions containing less than 2% oligomers were 55 pooled and concentrated to final concentration of 1-1.5 mg/ml using ultra concentrators (Vivaspin 15R 30.000 MWCO HY, Sartorius). The protein concentration was determined by measuring the optical density (OD) at 280 60 nm, using the molar extinction coefficient calculated on the basis of the amino acid sequence. Purity and molecular weight of the constructs were analyzed by SDS capillary electrophoresis in the presence and absence of a reducing agent following the manufacturer instructions (instrument 65 Caliper LabChipGX, Perkin Elmer). Purified proteins were frozen in liquid N2 and stored at -80° C.

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Based on in vitro characterization results selected binders were converted into a T-cell bispecific format. In these molecules the FolR1:CD3 binding moieties are arranged in a 2:1 order with the FolR1 Fabs being located at the N-terminus. For clones isolated from the standard Fab library the CD3 binding part was generated as a CrossFab light chain library no crossing was necessary. These bispecific molecules were produced and purified analogously to the IgGs.

TABLE	6
** *** ***	~

Yield and monomer content of novel FolR1 binders							
IgG TCB							
#	Clone	Library	Yield [mg/L]	Monomer [%]	Yield [mg/L}	Monomer [%]	
1	11F8	Fab	8.03	96.26	_	_	
2	14E4	Fab	8.90	98.12	_	_	
3	15B6	CLC	7.72	100.00	_	—	
4	15E12	CLC	6.19	100.00	_	—	
5	15H7	CLC	8.94	100.00	_	—	
6	16A3	CLC	0.60	n.d.	_	—	
7	16D5	CLC	36.50	96.96	4.36	97.19	
8	16F12	CLC	5.73	97.17	_	_	
9	18D3	CLC	0.90	n.d.	_	_	
10	19A4	CLC	38.32	100.00	37.50	100.00	
11	19E5	CLC	46.09	100.00	_	_	
12	19H3	CLC	7.64	100.00	_	_	
13	20G6	CLC	24.00	100.00	_	—	
14	20H7	CLC	45.39	100.00	_	_	
15	21A5	CLC	1.38	98.56	47.31	95.08	
16	21D1	CLC	5.47	100.00	_	_	
17	21G8	CLC	6.14	97.28	9.27	100.00	
18	36F2	Fab	11.22	100.00	18.00	100.00	
19	5D9	Fab	20.50	100.00	0.93	97.32	
20	6B6	Fab	3.83	100.00	4.17	91.53	
21	9D11	Fab	14.61	100.00	2.63	100.00	

CLC: Common light chain

#### Example 9

# 2+1 and 1+1 T-Cell Bispecific Formats

Four different T-cell bispecific formats were prepared for one common light chain binder (16D5) and three formats for one binder from the Fab library (9D11) to compare their killing properties in vitro.

The standard format is the 2+1 inverted format as already described (FolR1:CD3 binding moieties arranged in a 2:1 order with the FolR1 Fabs located at the N-terminus). In the 2+1 classical format the FolR1:CD3 binding moieties are arranged in a 2:1 order with the CD3 Fab being located at the 5 N-terminus. Two monovalent formats were also prepared. The 1+1 head-to-tail has the FolR1:CD3 binding moieties arranged in a 1:1 order on the same arm of the molecule with the FolR1 Fab located at the N-terminus. In the 1+1 classical format the FolR1:CD3 binding moieties are present once, 10 each on one arm of the molecule. For the 9D11 clone isolated from the standard Fab library the CD3 binding part was generated as a CrossFab (CI-110c crossing) while for the 16D5 from the common light chain library no crossing was necessary. These bispecific molecules were produced 15 and purified analogously to the standard inverted T-cell bispecific format.

TABLE 7

Summary of the yield and final monomer bispecific forma	content of the c	lifferent T-cell	_
Construct	Monomer [%] (SEC)	Yield	
16D5 FolR1 TCB 2 + 1 (inverted)	96%	5.4 mg/L	-
16D5 FolR1 TCB 2 + 1 (classical)	90%	4.6 mg/L	
16D5 FolR1 TCB 1 + 1 (head-to-	100%	5.4 mg/L	
tail)			
16D5 FolR1 TCB 1 + 1 (classical)	100%	0.7 mg/L	
9D11 FolR1 TCB 2 + 1 (inverted)	100%	2.6 mg/L	-
9D11 FolR1 TCB 1 + 1 (head-to-	100%	6.1 mg/L	
tail)		U	
9D11 FolR1 TCB 1 + 1 (classical)	96%	1.3 mg/L	
Mov19 FolR1 TCB 2 + 1 (inverted)	98%	3 mg/L	
Mov19 FolR1 TCB 1 + 1 (head-to-	100%	5.2 mg/L	
tail)		U	3
,			_

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# Example 10

# Biochemical Characterization of FolR1 Binders by Surface Plasmon Resonance

Binding of FolR1 binders as IgG or in the T-cell bispecific format to different recombinant folate receptors (human FolR1, 2 and 3, murine FolR1 and cynomolgus FolR1; all as Fc fusions) was assessed by surface plasmon resonance (SPR). All SPR experiments were performed on a Biacore T200 at 25° C. with HBS-EP as running buffer (0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% Surfactant P20, Biacore, Freiburg/Germany).

# Single Injections

First the anti-FolR1 IgGs were analyzed by single injections (Table 1) to characterize their crossreactivity (to human, murine and cyno FolR1) and specificity (to human FolR1, human FolR2, human FolR3). Recombinant biotinylated monomeric Fc fusions of human, cynomolgus and
murine Folate Receptor 1 (FolR1-Fc) or human Folate Receptor 2 and 3 (FolR2-Fc, FolR3-Fc) were directly coupled on a SA chip using the standard coupling instruction (Biacore, Freiburg/Germany). The immobilization level was
about 300-400 RU. The IgGs were injected for 60 seconds at a concentration of 500 nM. IgGs binding to huFolR2 and huFolR3 were rejected for lack of specificity. Most of the binders are only crossreactive between human and cyno FolR1, additional crossreactivity to murine FolR1 went most of the time hand in hand with loss of specificity.

TABLE 8

Crossreactivity and specificity of 25 new folate receptor 1 binders (as IgGs) as well as of two control IgGs (Mov19 and Farletuzumab).						
Clone name	Binding to huFolR1	Binding to cyFolR1	Binding to muFolR1	Binding to huFolR2	Binding to huFolR3	
Mov19	+	+	-	_	_	
Farletuzumab	+	+	-	-	-	
16A3	+	+	+/-	-	-	
18D3	+	+	-	-	-	
19E5	+	+	+	+	+	
19A4	-	-	+	+	+	
15H7	+	+	+	-	-	
15B6	+	+	-	-	-	
16D5	+	+	-	-	-	
15E12	+	+	+/-	+	+	
21D1	+	+	+/-	-	-	
16F12	+	+	-	-	-	
21A5	+	+	-	-	+/-	
21G8	+	+	-	+	+	
19H3	-	-	+	-	-	
20G6	-	-	+	-	-	
20H7	-	-	+	-	-	
9D11	+	+	-	-	-	
5D9	+	+	-	+	+	
6B6	+	+	-	+	+	
11F8	+	+	+	+	+	
36F2	+	+	+	-	-	
14E4	-	-	+	-	-	

+ means binding,

means no binding,

+/- means weak binding.

Avidity to Folate Receptor 1

The avidity of the interaction between the anti-FolR1 IgGs or T cell bispecifics and the recombinant folate receptors was determined as described below (Table 9). Recombinant biotinylated monomeric Fc fusions of human, cynomolgus and murine Folate Receptor 1 (FolR1-Fc) were directly coupled on a SA chip using the standard coupling instruction (Biacore, Freiburg/Germany). The immobilization level was about 300-400 RU. The anti-FolR1 IgGs or T cell bispecifics were passed at a concentration range from 2.1 to 500 nM with a flow of 30  $\mu$ L/minutes through the flow cells over 180 seconds. The dissociation was monitored for 600 seconds. Bulk refractive index differences were corrected for by subtracting the response obtained on reference flow cell immobilized with recombinant biotinylated IL2 receptor Fc fusion. For the analysis of the interaction of 19H3 IgG and murine folate receptor 1, folate (Sigma F7876) was added in the HBS-EP running buffer at a concentration of 2.3  $\mu$ M. The binding curves resulting from  $_{20}$ the bivalent binding of the IgGs or T cell bispecifics were approximated to a 1:1 Langmuir binding and fitted with that model (which is not correct, but gives an idea of the avidity). The apparent avidity constants for the interactions were derived from the rate constants of the fitting using the Bia 25 Evaluation software (GE Healthcare).

 TABLE 9

 Bivalent binding (avidity with apparent KD) of selected FolR1 binders

Analyte	Ligand	ka (1/Ms)	kd (1/s)	Apparent KD (M)
16D5 TCB	huFolR1	8.31E+04	3.53E-04	4.24E-09
	cyFolR1	1.07E+05	3.70E-04	3.45E-09
9D11 TCB	huFolR1	1.83E+05	9.83E-05	5.36E-10
	cyFolR1	2.90E+05	6.80E-05	2.35E-10
21A5 TCB	huFolR1	2.43E+05	2.64E-04	1.09E-09
	cyFolR1	2.96E+05	2.76E-04	9.32E-10
36F2 IgG	huFolR1	2.62E+06	1.51E-02	5.74E-9
	cyFolR1	3.02E+06	1.60E-02	5.31E-9
	muFolR1	3.7E+05	6.03E-04	1.63E-9
Mov19 IgG	huFolR1	8.61E+05	1.21E-04	1.4E-10
	cyFolR1	1.29E+06	1.39E-04	1.08E-10
Farletuzumab	huFolR1	1.23E+06	9E-04	7.3E-10
	cyFolR1	1.33E+06	8.68E-04	6.5E-10
19H3 IgG	muFolR1	7.1E+05	1.1E-03	1.55E-09

I. Affinity to Folate Receptor 1

The affinity of the interaction between the anti-FolR1 IgGs or the T cell bispecifics and the recombinant folate receptors was determined as described below (Table 10).

For affinity measurement, direct coupling of around 6000-7000 resonance units (RU) of the anti-human Fab specific antibody (Fab capture kit, GE Healthcare) was performed on a CM5 chip at pH 5.0 using the standard amine coupling kit (GE Healthcare). Anti-FolR1 IgGs or T cell bispecifics were 55 captured at 20 nM with a flow rate of 10 µl/min for 20 or 40 sec, the reference flow cell was left without capture. Dilution series (6.17 to 500 nM or 12.35 to 3000 nM) of human or cyno Folate Receptor 1 Fc fusion were passed on all flow cells at 30  $\mu$ l/min for 120 or 240 sec to record the association 60 phase. The dissociation phase was monitored for 240 s and triggered by switching from the sample solution to HBS-EP. The chip surface was regenerated after every cycle using a double injection of 60 sec 10 mM Glycine-HCl pH 2.1 or pH 1.5. Bulk refractive index differences were corrected for by 65 subtracting the response obtained on the reference flow cell 1. The affinity constants for the interactions were derived

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from the rate constants by fitting to a 1:1 Langmuir binding using the Bia Evaluation software (GE Healthcare).

TABLE 10
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	Monovalent binding (affinity) of selected FolR1 binders as IgGs or as T-cell bispecifics (TCB) on human and cyno FolR1.							
	Ligand	Analyte	ka (1/Ms)	kd (1/s)	KD (M)			
)	16D5 TCB	huFolR1	1.53E+04	6.88E-04	4.49E-08			
		cyFolR1	1.32E+04	1.59E-03	1.21E-07			
	9D11 TCB	huFolR1	3.69E+04	3.00E-04	8.13E-09			
		cyFolR1	3.54E+04	2.06E-04	5.82E-09			
	21A5 TCB	huFolR1	1.79E+04	1.1E-03	6.16E-08			
		cyFolR1	1.48E+04	2.06E-03	1.4E-07			
_	Mov19 IgG	huFolR1	2.89E+05	1.59E-04	5.5E-10			
5		cyFolR1	2.97E+05	1.93E-04	6.5E-10			
	Farletuzumab	huFolR1	4.17E+05	2.30E-02	5.53E-08			
		cyFolR1	5.53E+05	3.73E-02	6.73E-08			

2. Affinity to CD3

The affinity of the interaction between the anti-FolR1 T cell bispecifics and the recombinant human CD3 $\epsilon$ \delta-Fc was determined as described below (Table 11).

For affinity measurement, direct coupling of around 9000 resonance units (RU) of the anti-human Fab specific antibody (Fab capture kit, GE Healthcare) was performed on a CM5 chip at pH 5.0 using the standard amine coupling kit (GE Healthcare). Anti-FolR1 T cell bispecifics were captured at 20 nM with a flow rate of 10  $\mu$ l/min for 40 sec, the reference flow cell was left without capture. Dilution series (6.17 to 500 nM) of human CD3E8-Fc fusion were passed on all flow cells at 30 µl/min for 240 sec to record the association phase. The dissociation phase was monitored for 240 s and triggered by switching from the sample solution to HBS-EP. The chip surface was regenerated after every cycle using a double injection of 60 sec 10 mM Glycine-HCl pH 2.1. Bulk refractive index differences were corrected for by subtracting the response obtained on the reference flow cell 1. The affinity constants for the interactions were derived from the rate constants by fitting to a 1:1 Langmuir binding using the Bia Evaluation software (GE Healthcare).

TABLE 11

45	I FolR1	Monovalent b T-cell bispe	oinding (affinity cifics (TCB) o	y) of selected n human CD3-	·Fc.
	Ligand	Analyte	ka (1/Ms)	kd (1/s)	KD (M)
	16D5 TCB 21A5 TCB	huCD3 huCD3	4.25E+04 3.72E+04	3.46E-03 3.29E-03	8.14E-08 8.8E-08
50					

The CD3 binding part is identical for all constructs and the affinity is similar for the measured T cell bispecifics (KD range between 60 and 90 nM).

# Example 11

#### Simultaneous Binding T Cell Bispecifics on Folate Receptor 1 and CD3

Simultaneous binding of the anti-FolR1 T cell bispecifics on recombinant Folate Receptor 1 and recombinant human CD3E8-Fc was determined as described below.

Recombinant biotinylated monomeric Fc fusions of human, cynomolgus and murine Folate Receptor 1 (FolR1-Fc) were directly coupled on a SA chip using the standard coupling instruction (Biacore, Freiburg/Germany). The immobilization level was about 300-400 RU. The anti-

15

20

25

45

FolR1 T cell bispecifics were injected for 60 s at 500 nM with a flow of 30 µL/minutes through the flow cells, followed by an injection of hu CDEô-Fc for 60 s at 500 nM. Bulk refractive index differences were corrected for by subtracting the response obtained on reference flow cell 5 immobilized with recombinant biotinylated IL2 receptor Fc fusion. The four T cell bispecifics tested (16D5 TCB, 21A5 TCB, 51C7 TCB and 45D2 TCB) were able to bind simultaneously to Folate Receptor 1 and human CD3 as expected.

#### Example 12

#### Epitope Binning

For epitope binning, the anti-FolR1 IgGs or T cell bispecifics were directly immobilized on a CM5 chip at pH 5.0 using the standard amine coupling kit (GE Healthcare), with a final response around 700 RU. 500 nM huFolR1-Fc was then captured for 60 s, followed by 500 nM of the different binders for 30 s. The surface was regenerated with two injections of 10 mM glycine pH 2 for 30 s each. It is assessed if the different binders can bind to huFolR1 captured on immobilized binders (Table 12).

TABLE 12

Epitope characterization of selected FolR1 binders as IgGs or as T-cell bispecifics (TCB) on human FolR1.					ers as folR1.			
		Analytes in solution						30
	On huFolR1	16D5 TCB	21A5 TCB	9D11 TCB	36F2 IgG	Mov19 IgG	Farletuzumab	
Im- mobi-	16D5 TCB	-	-	-	+	+	+	35
lized	21A5 TCB 9D11 TCB	- No	– o additi	– onal bii caj	+ nding of otured o	+ n FolR1 p on 9D11	+ ossible once	
	36F2 IgG Mov19 IgG	Measu +	ire not j +	possible +/-	e, huFol -	R1 dissoc –	iates too rapidly -	40

+ means binding.

means no binding,

+/- means weak binding

Based on these results and additional data with simultaneous binding on immobilized huFolR1, the binders were separated in three groups. It is not clear if 9D11 has a separate epitope because it displaces all the other binders. 16D5 and 21A5 seem to be in the same group and Mov19, 50 Farletuzumab (Coney et al., Cancer Res. 1991 Nov. 15; 51(22):6125-32; Kalli et al., Curr Opin Investig Drugs. 2007 December; 8(12):1067-73) and 36F2 in another (Table 13). However, 36F2 binds to a different epitope than Mov19 and Farletuzumab as it binds to human, cynomous and murine 55 FolR1.

TABLE 13

Epitope grouping of selected FolR1 binders as IgGs or as T-cell bispecifics (TCB) on human FolR1				
Epitope 1	Epitope 2	Epitope 3		
16D5 21A5	9D11	Mov19 Farletuzumab 36F2		

# 128

# Example 13

#### Selection of Binders

FolR1 binders in the IgG formats were screened by surface plasmon resonance (SPR) and by in vitro assay on cells to select the best candidates.

The anti-FolR1 IgGs were analyzed by SPR to characterize their crossreactivity (to human, murine and cynomolgus FolR1) and specificity (to human FolR1, human FolR2, human FolR3). Unspecific binding to human FolR2 and 3 was considered an exclusion factor. Binding and specificity to human FolR1 was confirmed on cells. Some binders did not bind on cells expressing FolR1 even though they recognized the recombinant human FoIR1 in SPR. Aggregation temperature was determined but was not an exclusion factor because the selected binders were all stable. Selected binders were tested in a polyreactivity ELISA to check for unspecific binding, which led to the exclusion of four binders. This process resulted in an initial selection of three binders: 36F2 (Fab library), 9D11 (Fab library) and 16D5 (common light chain). 36F2 dissociated rapidly from huFolR1 and was, therefore, initially not favored.

#### Example 14

Specific Binding of Newly Generated FolR1 Binders to Human FolR1 Positive Tumor Cells

New FolR1 hinders were generated via Phage Display using either a Fab library or a common light chain library using the CD3 light chain. The identified binders were converted into a human IgG1 format and binding to FolR1 5 high expressing HeLa cells was addressed. As reference molecule the human FolR1 binder Mov19 was included. Most of the binders tested in this assay showed intermediate to good binding to FolR1 with some clones binding equally well as Mov19 (see FIG. 2). The clones 16A3, 18D3, 15H7, 15B6, 21D1, 14E4 and 16F12 were excluded because binding to FolR1 on cells could not be confirmed by flow cytometry. In a next step the selected clones were tested for specificity to human FolR1 by excluding binding to the closely related human FolR2. HEK cells were transiently transfected with either human FolR1 or human FolR2 to address specificity. The clones 36F2 and 9D11 derived from the Fab library and the clones 16D5 and 21A5 derived from the CLC library hind specifically to human FolR1 and not to human FolR2 (see FIGS. 3A-B). All the other tested clones showed at least some binding to human FolR2 (see FIGS. 3A-B). Therefore these clones were excluded from further characterization. In parallel cross-reactivity of the FolR1 clones to cyno FolR1 was addressed by performing binding studies to HEK cells transiently transfected with cyno FolR1. All tested clones were able to bind cyno FolR1 and the four selected human FoLR1 specific clones 36F2, 9D11, 16D5 and 21A5 bind comparably well human and cyno FoLR1 (FIG. 4). Subsequently three human FolR1 specific cyno cross-reactive binders were converted into TCB format and tested for induction of T cell killing and T cell activation. These clones were 9D11 from the Fab library and 16D5 and 21A5 from the CLC library. As reference molecule Mov19 FolR1 TCB was included in all studies. These FoLR1 TCBs were then used to compare induction of 5 internalization after binding to FolR1 on HeLa cells. All three tested clones are internalized upon binding to FolR1 comparable to internalization upon binding of Mov19
FoLR1 TCB (FIG. 5). 21A5 FolR1 TCB was discontinued due to signs of polyreactivity.

#### Example 15

### T Cell-Mediated Killing of FolR1-Expressing Tumor Target Cells Induced by FolR1 TCB Antibodies

The FolR1 TCBs were used to determine T cell mediated <sup>10</sup> killing of tumor cells expressing FoLR1. A panel of potential target cell lines was used to determine FoLR1 binding sites by Qifikit analysis.

The used panel of tumor cells contains FolR1 high, <sup>15</sup> negative cell line.

TABLE 14

FolR1 binding sites on tumor cells				
Cell line	Origin	FolR1 binding sites		
Hela	Cervix adenocarcinoma	2'240'716		
Skov3	Ovarian adenocarcinoma	91'510		
OVCAR5	Ovarian adenocarcinoma	22'077		
HT29	Colorectal adenocarcinoma	10'135		
MKN45	Gastric adenocarcinoma	54		

Binding of the three different FoLR1 TCBs (containing 9D11, 16D5 and Mov19 binders) to this panel of tumor cell 30 lines was determined showing that the FoLR1 TCBs bind specifically to FolR1 expressing tumor cells and not to a FoLR1 negative tumor cell line. The amount of bound construct is proportional to the FolR1 expression level and there is still good binding of the constructs to the FolR1 low cell line HT-29 detectable. In addition there is no binding of the negative control DP47 TCB to any of the used cell lines (FIGS. **6**A-E). DP47 TCB is an untargeted TCB and was prepared as described in WO2014/131712.

The intermediate expressing cell line SKOV3 and the low expressing cell line HT-29 were further on used to test T cell 40 mediated killing and T cell activation using 16D5 TCB and 9D11 TCB; DP47 TCB was included as negative control. Both cell lines were killed in the presence of already very low levels of 16D5 TCB and 9D11 TCB and there was no difference in activity between both TCBs even though 9D11 45 TCB binds stronger to FolR1 than 16D5 TCB. Overall killing of SKOV3 cells was higher compared to HT-29 which reflects the higher expression levels of FolR1 on SKOV3 cells (FIGS. 7A-D). In line with this, a strong upregulation of the activation marker CD25 and CD69 on 50 CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells was detected. Activation of T cells was very similar in the presence of SKOV3 cells and HT-29 cells. The negative control DP47 TCB does not induce any killing at the used concentrations and there was no significant upregulation of CD25 and CD69 on T cells. 55

TABLE 15

	EC50 values of tumor cell killing and T cell activation with SKOV3 cells								
Construct	Killing 24 h (pM)	Killing 48 h (pM)	CD4+ CD69+ (%)	CD4+ CD25+ (%)	CD8+ CD69+ (%)	CD8+ CD25+ (%)			
9D11 FolR1 TCB	1.1	0.03	0.51	0.46	0.019	0.03	6		

130 TABLE 15-continued

			i o comm	lucu		
	EC50 T ce	values of t Il activation	umor cell 1 with SK	killing an OV3 cells	d	
Construct	Killing 24 h (pM)	Killing 48 h (pM)	CD4+ CD69+ (%)	CD4+ CD25+ (%)	CD8+ CD69+ (%)	CD8+ CD25+ (%)
16D5 FolR1 TCB	0.7	0.04	0.34	0.33	0.025	0.031

TABLE 16

	EC50 T ce	values of ti Il activatio	umor cell i n with HT	killing and -29 cells	1	
Construct	Killing 24 h (pM)	Killing 48 h (pM)	CD4+ CD69+ (%)	CD4+ CD25+ (%)	CD8+ CD69+ (%)	CD8+ CD25+ (%)
9D11 FolB1	2.3	0.1	1.22	1.11	0.071	0.084
TCB 16D5 FolR1 TCB	2.8	0.1	0.69	0.62	0.021	0.028

### Example 16

#### Binding of FolR1 TCB Antibodies to Erythrocytes and T Cell Activation in Whole Blood

To prove that there is no spontaneous activation in the absence of FoLR1 expressing tumor cells we tested if there is binding of the FolR1 clones to erythrocytes which might potentially express FolR1. We could not observe any specific binding of 9D11 IgG, 16D5 IgG and Mov19 IgG to erythrocytes, as negative control DP47 IgG was included (FIG. 8).

To exclude any further unspecific binding to blood cells or unspecific activation via FoLR1 TCB, 9D11 TCB, 16D5 TCB and Mov19 TCB were added into whole blood and upregulation of CD25 and CD69 on CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells was analyzed by flow cytometry. DP47 TCB was included as negative control. No activation of T cells with any of the tested constructs could be observed by analyzing upregulation of CD25 and CD69 on CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells (FIG. **9**).

### Example 17

#### T-Cell Killing Induced by 36F2 TCB and 16D5 TCB in Different Monovalent and Bivalent T-Cell Bispecific Formats

T-cell killing mediated by 36F2 TCB, 16D5 TCB, 16D5 TCB classical, 16D5 TCB 1+1 and 16D5 TCB HT antibodies of Hela, Skov-3 (medium FolR1, about 70000-90000 copies) and HT-29 (low FolR1, about 10000) human tumor cells was assessed. DP47 TCB antibody was included as negative control. Human PBMCs were used as effectors and the killing was detected at 24 h of incubation with the bispecific antibody. Briefly, target cells were harvested with Trypsin/EDTA, washed, and plated at density of 25 000 cells/well using flat-bottom 96-well plates. Cells were left to adhere overnight. Peripheral blood mononuclear cells (PB-MCs) were prepared by Histopaque density centrifugation of enriched lymphocyte preparations (buffy coats) obtained

from healthy human donors. Fresh blood was diluted with sterile PBS and layered over Histopaque gradient (Sigma, # H8889). After centrifugation (450×g, 30 minutes, room temperature), the plasma above the PBMC-containing interphase was discarded and PBMCs transferred in a new falcon 5 tube subsequently filled with 50 ml of PBS. The mixture was centrifuged (400×g, 10 minutes, room temperature), the supernatant discarded and the PBMC pellet washed twice with sterile PBS (centrifugation steps 350×g, 10 minutes). The resulting PBMC population was counted automatically 10 (ViCell) and stored in RPMI1640 medium containing 10% FCS and 1% L-alanyl-L-glutamine (Biochrom, K0302) at 37° C., 5% CO2 in cell incubator until further use (no longer than 24 h). For the killing assay, the antibody was added at the indicated concentrations (range of 0.01 pM-100 nM in 15 triplicates). PBMCs were added to target cells at final E:T ratio of 10:1. Target cell killing was assessed after 24 h of incubation at 37° C., 5% CO<sub>2</sub> by quantification of LDH released into cell supernatants by apoptotic/necrotic cells (LDH detection kit, Roche Applied Science, #11 644 793 20 001). Maximal lysis of the target cells (=100%) was achieved by incubation of target cells with 1% Triton X-100. Minimal lysis (=0%) refers to target cells co-incubated with effector cells without bispecific construct. The results show target-specific killing of all three FolR1<sup>+</sup> target cell lines 25 induced by 36F2 TCB and 16D5 TCB (FIG. 10).

#### Example 18

### Generation of Anti-TIM3 Antibodies

Immunization of mice NMRI mice were immunized genetically, using a plasmid expression vector coding for full-length human Tim-3 by intradermal application of 100 ug vector DNA (plasmid 15304\_hTIM3-fl), followed by 35 Electroporation (2 square pulses of 1000 V/cm, duration 0.1 ms, interval 0.125 s; followed by 4 square pulses of 287.5 V/cm, duration 10 ms, interval 0.125 s. Mice received either 6 consecutive immunizations at days 0, 14, 28, 42, 56, 70, and 84. Blood was taken at days 36, 78 and 92 and serum prepared, which was used for titer determination by ELISA (see below). Animals with highest titers were selected for boosting at day 96, by intravenous injection of 50 ug of recombinant human Tim-3 human Fc chimera, and monoclonal antibodies were isolated by hybridoma technology, by fusion of splenocytes to myeloma cell line 3 days after 45 boost.

Determination of serum titers (ELISA) Human recombinant Tim-3 human Fc chimera was immobilized on a 96-well NUNC Maxisorp plate at 0.3 ug/ml, 100 ul/well, in PBS, followed by: blocking of the plate with 2% Crotein C in PBS, 200 ul/well; application of serial dilutions of antisera, in duplicates, in 0.5% Crotein C in PBS, 100 ul/well; detection with HRP-conjugated goat anti-mouse antibody (Jackson Immunoresearch/Dianova 115-036-071; 1/16 000). For all steps, plates were incubated for 1 h at 37° C. Between

all steps, plates were washed 3 times with 0.05% Tween 20 in PBS. Signal was developed by addition of BM Blue POD Substrate soluble (Roche), 100 ul/well; and stopped by addition of 1 M HCl, 100 ul/well. Absorbance was read out at 450 nm, against 690 nm as reference. Titer was defined as dilution of antisera resulting in half-maximal signal.

#### Example 19

#### Characterization Anti-Tim3 Antibodies

ELISA for Tim3 Nunc-Maxi Sorp Streptavidine plates (MicroCoat #11974998/MC1099) were coated by 25 µl/well with Tim3-ECD-His-Biotin (biotinylated with BirA Ligase) and incubated at RT for 1 h while shaking at 400 rpm rotation. After washing (3×90 µl/well with PBST-buffer) 25 µl aTim3 samples or diluted (1:2 steps) reference antibody aTim3 F38-2E2 (Biolegend) was added and incubated 1h at RT. After washing (3×90 µl/well with PBST-buffer) 25 µl/well sheep-anti-mouse-POD (GE NA9310V) was added in 1:9000 dilution and incubated at RT for 1 h while shaking at 400 rpm rotation. After washing (4×90 µl/well with PBST-buffer) 25 µl/well TMB substrate (Calbiochem, # CL07) was added and incubated until OD 1.5-2.5. Then the reaction was stopped by addition of 25 µl/well 1N HCLsolution. Measurement took place at 370/492 nm. ELISA results are listed as EC50-values [ng/ml] in summary Table 17 below.

Cell ELISA for Tim3 Adherent CHO-K1 cell line stably transfected with plasmid 15312\_hTIM3-fl\_pUC\_Neo coding for full-length human Tim3 and selection with G418 (Neomycin restistance marker on plasmid) were seeded at a concentration of 1.2×10E6 cells/ml into 384-well flat bottom plates and grown over night.

At the next day 25 Tim3 sample or aTim3 reference antibody F38-2E2 Azide free (Biolegend, 354004) was added and incubated for 2h at 4° C. (to avoid internalization). After washing (3×90 µl/well PBST (BIOTEK Washer: Prog. 29, 1×90) cells were fixed by flicking out residual buffer and addition of 50 µl/well 0.05% Glutaraldehyde: Dilution 1:500 of 25% Glutaraldehyde (Sigma Cat. No: G5882) in 1×PBS-buffer and incubated for 1h at RT. After washing (3×90 µl/well PBST (BIOTEK Washer: Prog. 21, 3×90 GreinLysin) 25 µl/well secondary antibody was added for detection (Sheep-anti-mouse-POD; Horseradish POD linked F(ab')<sub>2</sub> Fragment; GE NA9310) followed by 2h incubation at RT while shaking at 400 rpm. After washing (3×90 µl/well PBST (BIOTEK Washer: Prog. 21, 3×90 GreinLysin) 25 µl/well TMB substrate solution (Roche 11835033001) was added and incubated until OD 1.5-2.5. Then the reaction was stopped by addition of 25 µl/well 1N HCL-solution. Measurement took place at 370/492 nm. Cell ELISA results are listed as "EC50 CHO-Tim3"-values [ng/ ml] in summary table Table 17 below.

TABLE 17

Binding Affinites of exemplary antibodies (ELISA and BIACORE)									
Assay	Tim3_0018	Tim3_0021	Tim3_0028	Tim3_0026	Tim3_0033	Tim3_0038			
Affinity KD [nM] mono/bivalent Tim3	3.4/1.1	204/4.1	173/2.8	6.2/1.5	n.f./3.1	7.6/0.6			
EC50 ELISA [nM]	0.56		0.22			0.501			
EC50 ELISA [ng/ml]	94	47	37	47	1321	83			
EC50 CHO-Tim3 [nM]	0.52		0.32			0.17			
EC50 CHO-Tim3 [ng/ml	] 87	73	53	69	3710	29			

Biacore characterization of the Tim3 ABs A surface plasmon resonance (SPR) based assay has been used to determine the kinetic parameters of the binding between several murine Tim3 binders as well as commercial human Tim3 binding references. Therefore, an anti-mouse IgG was 5 immobilized by amine coupling to the surface of a (Biacore) CM5 sensor chip. The samples were then captured and hu/cy Tim3-ECD was bound to them. The sensor chip surface was regenerated after each analysis cycle. The equilibrium constant  $K_D$  was finally gained by fitting the data to a 1:1 langmuir interaction model. About 12000 response units (RU) of 30 mg/ml anti-mouse IgG (GE Healthcare # BR-1008-38) were coupled onto the spots 1, 2, 4 and 5 of the flow cells 1-4 (spots 1, 5 are active and spots 2, 4 are reference spots) of a CM5 sensor chip in a Biacore B4000 15 at pH 5.0 by using an amine coupling kit supplied by GE Healthcare.

The sample and running buffer was HBS-EP+(0.01 M HEPES, 0.15 M NaCl, 3 mM EDTA, 0.05% v/v Surfactant P20, pH 7.4). Flow cell temperature was set to 25° C. and 20 sample compartment temperature to 12° C. The system was primed with running buffer. The samples were injected for 30 seconds with a concentration of 200 µg/ml and bound to the spots 1 and 5 of each flow cell, allowing the measurement of eight samples in parallel. Then a complete set of 25 different (monomeric cyno, monomeric human and huFc fused dimeric human Tim3-ECD) concentrations (s. Table X) was injected over each sample for 240 s followed by a dissociation time of 30/1800 s (s. Table 1). Each analysis cycle (sample capture, spot 1 and 5-Tim3 ECD injection) 30 was then regenerated with a 30 seconds long injection of Glycine-HCl pH 1.7. The flow rate was set to 30 µl/min for the whole run. Finally, the double referenced data was fitted to a 1:1 langmuir interaction model with the Biacore B4000 Evaluation Software. Resulting  $K_D$  values are shown in  $_{35}$ Table 17 and 18.

TABLE 18

Binding affinities determined by Biacore-KD values gained by a kinetic SPR measurement.							
Sample	huTim3 K <sub>D</sub> (25° C.) [M]	huTim3Fc K <sub>D</sub> (25° C.) [M]	cyTim3 K <sub>D</sub> (25° C.) [M]				
TIM3-0016	3.29E-09	1.09E-09	2.16E-08	45			
TIM3-0016 variant (0018)	3.40E-09	1.11E-09	4.19E-08				
TIM3-0021	2.04E-07	4.07E-09	n.f.				
TIM3-0022	1.26E-07	1.52E-09	2.84E-08				
TIM3-0026	6.23E-09	1.52E-09	n.f.				
TIM3-0028	1.73E-07	2.77E-09	n.f.	50			
TIM3-0030	3.11E-09	1.28E-09	n.f.				
TIM3-0033	n.f.	3.05E-09	n.f.	20			
TIM3-0038	7.56E–09	5.69E-10	n.f.				

134 TABLE 18-continued

Binding affinities d	etermined by Biac kinetic SPR measu	ore-KD values g irement.	ained by
Sample	huTim3 K <sub>D</sub> (25° C.) [M]	huTim3Fc K <sub>D</sub> (25° C.) [M]	cyTim3 K <sub>D</sub> (25° C.) [M]
Reference antibody Biolegend F38-2E2	1.36E-08	7.50E-09	1.68E-07
Reference antibody USB 11E365	1.34E-08	7.73E-09	1.41E-07

-n.f. means no fit possible, most likely due to no or weak binding.

#### Example 20

#### Generation of Anti-Tim3 Antibody Derivatives

Chimeric antibodies derivatives Chimeric Tim3 antibodies were generated by amplifying the variable heavy and light chain regions of the anti-TIM3 mouse antibodies Tim3-0016, Tim3-0016 variant (0018), Tim3-0021, Tim3-0022, Tim3-0026, Tim3-0028, Tim3-0030, and Tim3-0033, Tim3-0038 from via PCR and cloning them into heavy chain expression vectors as fusion proteins with human IgG<sub>1</sub> backbones/human CH1-Hinge-CH2-CH3 with LALA and PG mutations (Leucine 234 to Alanine, Leucine 235 to Alanine, Proline 329 to Glycine) abrogating effector functions and light chain expression vectors as fusion proteins to human C-kappa. LC and HC Plasmids were then cotransfected into HEK293 and purified after 7 days from supernatants by standard methods for antibody purification.

Removal of glycosylation site NYT: Modifying 1 HVR-L1 position in Tim3-0016, Tim3 0016 variant (named 0018 or Tim3\_0018) by substitution of N by Q or S Mutations within the variable light vchain region of Tim3\_0016 and Tim3\_0016 variant (0018) were generated by in vitro mutagenesis using Agilent "Quick Change Lightning Site-directed Mutagenesis Kit" according manufacturer's instructions. By this method theasparagine (N) of the glycoslyation site motif NYT in the light chain HVR-L1 (SEQ ID NO: 4) was replaced by glutamine (Q) (resulting in SEQ ID NO: 11=Tim3\_0016\_HVR-L1 variant 1\_NQ) or, alternatively, 40 the asparagine (N) was replaced by serine (5) (resulting in SEQ ID NO: 12=Tim3\_0016\_HVR-L1 variant 2\_NS). In both glycoslyation site motif NYT was successfully modified. LC and HC Plasmids coding for the variants were then cotransfected into HEK293 and purified after 7 days from supernatants by standard methods for antibody purification. The generated mutants were tested by ELISA on human Tim3, ELISA on cynomolgus Tim3 and cellular ELISA on adherent CHO-K1 cells expressing full-length human Tim3. All mutants generated were found to show even more functional binding to human TIM3 (human), cyno TIM3 (cyno) or human TIMR on CHO cells than the parental antibodies Tim3 0016 or the Tim3 0016 antibody variant Tim3\_0018 respectively.

TABLE	19
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	Biochem H	luman	Biochem (	Cyno	cellular bindg. CHO-Tim3		
Mutants tested	EC50 [ng/ml] values in relation to the sample's max value	Inflexion point [ng/ml]	EC50 [ng/ml] values in relation to the sample's max value	Inflexion point [ng/ml]	EC50 [ng/ml] values in relation to the sample's max value	Inflexion point [ng/ml]	
aTim3 F38 2E2	73.2	86.3	423.0	209871.5	150.2	224.3	
aTim3 0018	15.1	15.3	14.6	14.6	26.4	29.4	
aTim3 0018MutNQ	12.0	10.8	13.2	10.8	13.4	12.8	
aTim3 00118MutNS	10.3	6.5	11.9	6.5	11.2	11.1	
aTim3 0016 MutNQ	7.6	5.7	8.3	5.7	6.3	5.4	
aTim3 0016MutNS	8.5	6.5	9.7	5.5	0.1	8.5	

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### Example 21

### Fluorescent Labeling of Purified Monoclonal Antibody

The fluorescent labeling of the hybridoma derived monoclonal antibody was carried out by using Alexa Fluor 488 Monoclonal Antibody Labeling Kit (manufactured by Invitrogen) according to the manufacturer's instructions. After the labeling, each antibody was confirmed to be positively labeled with Alexa Fluor 488 (hereinafter referred to as "Alexa-488") by FACSCalibur (manufactured by BD Biosciences) analysis for TIM-3 expressing RPMI-8226 and Pfeiffer cells.

#### Example 22

### Classification of Binding Epitope Groups Using FACS Based Competition Assay

The relation of epitopes between generated anti-TIM3 antibodies and six anti-TIM3 reference antibodies was analyzed by a FACS based binding competition assay. The TIM3 reference antibodies were the following: antibodies 4177 and 8213 as described in US2012/189617, antibodies <sup>25</sup> 1.7E10 and 27.12E12 as described in WO2013/06490; antibody 344823 (Clone 344823, manufactured by R&D Systems) and antibody F38-2E2 (Clone F38-2E2, manufactured by BioLegend and R&D Systems). In brief, the test antibody 30 was allowed to interact and bind with the TIM-3 expressing RPMI-8226 cells (ATCC<sup>®</sup> CCL155<sup>™</sup>) and then it was evaluated by flow cytometry method whether another anti-TIM-3 antibody could also bind to TIM-3 expressing cells.

In short human TIM3 expressing RPMI-8226 cells were incubated with BD human Fc Block for 10 min at RT and stained in two different experimental setups to exclude the impact of the difference in the affinity of the tested antibodies on the binding: 1) with disclosed purified anti-TIM3 (10 µg/ml in BD staining buffer for 0.5h at 4° C.), which were conjugated with Alexa\*488 according to the manufacturer's  $^{40}$ instructions (Molecular Probes A-20181) with an average of 2.7 fluorophores per antibody. Then a) unlabeled (1-4) reference recombinant anti-TIM3 antibodies or Isotype control were added (10 µg/ml) for 0.5h at 4° C. in BD SB and after washing with BD SB stained with PE-labeled anti- 45 huFcy Abs (JIR, 109-116-098, 1:200, 0.5h at 4° C. in BD SB) or b) PE labeled (5-6) available reference anti-TIM3 antibodies or appropriate Isotype controls were added (10 µg/ml) for 0.5h at 4° C. in BD SB. After washing and centrifugation MFI signals of stained RPMI-8226 cells were 50 analyzed by BD Biosciences FACSCanto flow cytometer.

TABLE 20

	Summary of epitope characterization.							
	Ep.	itope grou a	1b	Ep.	itope grou	p 3	-	
	TIM3- 0016	TIM3- 0018	T1M3- 0026	T1M3- 0022	T1M3- 0028	T1M3- 0038	- 6	
clone 4177 clone 8213 clone 1-7E10 clone 27-12E12	$     \begin{array}{r}       1 \\       -2 \\       -5 \\       -1     \end{array} $	-9 9 15 4	29 9 24 22	79 9 0 40	-3 38 20 82	0 29 7 94	6	

TABLE 20-continued								
Summary of epitope characterization.								
		Max	% inhibit	ion of Bir	ıding			
	Epi	tope grou	itope group 3					
	1	a	1b	3a	3	ь		
	TIM3- 0016	TIM3- 0018	T1M3- 0026	T1M3- 0022	T1M3- 0028	T1M3- 0038		
clone 344823 clone F38-2E2 100 100 100 100	0 -7 >90 >50 >30 >20	0 -6	3 2	102 77	107 75	99 94		

Results from the FACS based epitope groups mapping show that Tim3\_0016 and Tim3\_0016 variant Tim3\_0018 show no binding competition with any tested anti-TIM-3 20 reference antibodies and it was suggested that these Abs recognized the new epitope different from the epitopes to which all previous described TIM3 reference antibodies recognized whereas Tim3\_0022, Tim3\_0026, Tim3\_0028 and Tim3\_0038 compete to different extend for binding to surface expressed TIM3 on JRPMI-8226 cells with various competitors.

#### Example 23

#### Effect of Human Anti-TIM-3 Antibodies on Cytokine Production in a Mixed Lymphocyte Reaction (MLR)

A mixed lymphocyte reaction was used to demonstrate the effect of blocking ther TIM-3 pathway to lymphocyte effector cells. T cells in the assay were tested for activation and theier IFN-gamma secretion in the presence or absence of an anti-TIM-3 mAbs. Human Lymphocytes were isolated from peripheral blood of healthy donor by density gradient centrifugation using Leukosep (Greiner Bio One, 227 288). Briefly, heparinized blood were diluted with the three fold volume of PBS and 25 ml aliquots of the diluted blood were layered in 50 ml Leukosep tubes. After centrifugation at 800×g for 15 min at room temperature (w/o break) the lymphocyte containing fractions were harvested, washed in PBS and used directly in functional assay or resuspended in freezing medium (10% DMSO, 90% FCS) at 1.0E+07 cells/ml and stored in liquid nitrogen. 1:1 target/responder cell ratio was used in MLR assay (i.e. each MLR culture contained -2.0E+05 PBMCs from each donor in a total volume of 200 µl. Anti-TIM3 monoclonal antibodies Tim3\_0016, Tim3\_0016 variant (Tim3\_0018), Tim3\_0021, Tim3\_0022, Tim3\_0026, Tim3\_0028, Tim3 0030. 5 Tim3\_0033, Tim3\_0038 and F38-2E2 (BioLegend), were added to each culture at different antibody concentrations. Either no antibody or an isotype control antibody was used as a negative control and rec hu IL-2 (20 EU/ml) was used as positive control. The cells were cultured for 6 days at 37° <sup>50</sup> C. After day 6 100 μl of medium was taken from each culture for cytokine measurement. The levels of IFN-gamma were measured using OptEIA ELISA kit (BD Biosciences)

The results are shown in Table 21 (IFN-g secretion/ release). The anti-TIM-3 monoclonal antibodies promoted T 5 cell activation and IFN-gamma secretion in concentration dependent manner. The anti-TIM3 antibodies Tim3\_0021, Tim3\_0022, Tim3\_0028, and Tim3\_0038 reduce release of the inflammatory cytokine IFN-gamma) more than the F38-2E2 antibody. Tim3\_0016, Tim3\_0016 variant (Tim3\_0018), Tim3\_0033 and Tim3\_0038 showed a similar release when compared the F38-2E2 antibody. In contrast, cultures containing the isotype control antibody did not show an 5 increase in IFN-gamma secretion.

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internalization depending on mono-vs. bivalency was estimated by FACS for selected candidates.

In short, human TIM3 stable expressing CHO-K1 cells were seeded  $(4 \times 10^5 \text{ cells/well/50 } \mu \text{l})$  into 98 well-v bottom MTP using fresh culture medium and incubated with Redimune<sup>®</sup> NF Liquid for 10 min at RT to block unspecific

TABLE 21

Percentage anti-Tim3 antibody induced IFNgamma release in comparison to rec hu IL-2 (20 EU/ml) (=100%) as positive control and no antibody as negative control (Donors													
Compound concentration	MLR + IL-2	Isotype	F38-	Tim3	Isotype								
	20 U/ml	IgG2a	2E2	0016	0018	0021	0022	0026	0028	0030	0033	0038	hIgG1
40 μg/ml	100	2	36	33	36	112	58	25	40	14	35	51	0
10 μg/ml		0	26	22	30	108	38	16	38	4	30	38	5
1 μg/ml		0	7	7	12	101	18	18	12	3	0	1	0

#### Example 24

#### Internalization of Anti-TIM-3 Antibodies into TIM-3 Expressing Cells

TIM-3-specific antibodies described herein can be internalized into TIM-3-expressing cells, including TIM-3 25 expressing lymphoma, multiple myeloma and AML cells. For example, the disclosed TIM-3 specific antibodies and fragments thereof are shown to be internalized into rec TIM3 CHO cells stabile expressing human TIM-3 as evaluated by cell based ELISA, flow cytometry (FACS) and confocal 30 microscopy.

Stable Tim3-transfected CHO-K1 cells (clone 8) (4×104 cells/well/100 µl) were seeded into 98 well-MTP using fresh culture medium. After overnight cell attachment, cell culture medium was removed and the test antibodies were added to 35 the cells (10 µg/ml in cell culture medium) and incubated for 0.5 hour at 4° C. As reference, a commercial mouse-antihuman antibody (TIM3 MAB 11E365 (US Biological, T5469-92P) was used. After washing (2× with cell culture medium) and centrifugation cells were incubated for 3 h at 40 a) 4° C. or b) 37° C. in 200 µl cell culture medium. Internalization typically occurs at 37° C., but not at 4° C., which provides another control for the reaction. Then cells were fixated with 100 µl/well 0.05% glutharaldehyde (Sigma Cat. No: G5882) in 1×PBS for 10 min at room 45 temperature (RT). This was followed by three washing steps with 200 µl PBS-T and secondary antibody sheep-antimouse-POD (Horseradish POD linked F(ab')<sub>2</sub> Fragment; GE NA9310)) were added for 1 hour at RT. After the final washing steps (3×PBS-T), TMB substrate was added (Roche 50 order no. 11835033001) for 15 min and color development was stopped using 1N HCl. Final ODs were determined by measurement at 450/620 nm in an ELISA reader. This cellular ELISA procedure was used for medium throughput evaluation of the internalizing capacity of the testing anti- 55 bodies which were purified from hybridoma supernatants.

The percentage of internalization was calculated as follow:

Internalization [%]=(1-ODsample\_37° C/OD sample\_4° C.)\*100

60

65

The results are shown in FIGS. **29**A and B for (Internalization). Almost all tested anti-TIM-3 monoclonal antibodies were similar well internalized into stable Tim3-transfected CHO-K1 cells after 3h incubation at 37° C. (not all data shown).

The determination of EC50 internalizing values (time dependency) as well as comparison of the kinetics of the

binding. Then 50 μl/well of selected purified anti-TIM3 (10 μg/ml in cell culture medium) were added and incubated for 1 h at 4° C. After washing (with cell culture medium) and centrifugation cells were incubated for 0.25, 0.5, 1, 2, 3, 4, 6 and 24 h at a) 4° C. or b) 37° C. in 200 μl cell culture medium. Than cells were washed with PBS/1% BSA and <sup>25</sup> secondary antibody Alexa Fluor 488 Goat-anti-mouseIgG, F(ab)2 were added for 1 hour at 4° C. After washing and centrifugation 125 μl of CellFix (BD Bioscience, 1:1000) were added and MFI signals of stained cells were analyzed by BD Biosciences FACSCanto flow cytometer.

The percentage of internalization was calculated as follow: Internalization [%]=(1-MFIsample\_37° C./MFIsample\_4° C.)\*100 Example for the evaluation of time dependent internalization of anti-TIM3 antibodies Tim3\_0016, Tim3\_0016 variant (Tim3\_0018), Tim3\_0021, Tim3\_0028, Tim3\_0030, Tim3\_0033, Tim3\_0038 on RPMI-8226 cells (ATCC CCL-155TM): The presently disclosed anti-TIM3 antibodies are internalized rapidly into TIM3 expressing RPMI-8226 cells (ATCC<sup>®</sup> CCL155<sup>™</sup>) at a high level. The experiments were conducted as described above with TIM3 expressing RPMI-8226 cells (ATCC® CCL-155™) instead of rec CHOK1 cells expressing huTIM-3. Results are shown in the Table 22. The following antibodies were used as TIM3 reference antibodies: antibody 8213 as described in US2012/ 189617, antibody 27.12E12 as described in WO2013/06490. Tim3\_0016, Tim3\_0016 variant (Tim3\_0018), Tim3\_0038 were used as human IgG<sub>1</sub> chimeric versions.

TABLE 22

	Percentage internalization at the indicated time point (0 min set as 0 percent).								
	Percentage internalization of anti-TIM3 antibodies								
Aı	ntibody	30 Min	60 Min	120 Min	240 Min	26 h			
82	13	22	22	43	52	72			
27	.12E12	19	22	25	46	59			
Ti	m3_0016	33	52	55	66	87			
Ti	m3_0018	39	41	80	70	88			
Ti	m3-0021	70	75	74	78	77			
Ti	m3-0028	50	59	67	68	83			
Ti	m3-0033	75	81	82	82	80			
Ti	m3_0038	22	20	45	46	63			

The results show that the tested antibodies are rapidly internalized at high percentage compared to reference antibodies on RPMI-8226 cells (ATCC<sup>®</sup> CCL-155<sup>TM</sup>).

### Example 25

### Binding of Anti-TIM-3 Antibodies to Isolated Human Monocytes Expressing TIM-3

CD14+ Monocytes were isolated from anticoagulated peripheral blood of healphy donors by density gradient centrifugation using Ficoll-Paque (GE Healthcare) (see General Protocols in the User Manuals or visit www.miltenyibiotec.com/protocols) and subsequent positiv selection via CD14 MicroBeads. First the CD14+ cells are magnetically labeled with CD14 MicroBeads. Then the cell suspension is loaded onto a MACS® Column which is placed in the magnetic field of a MACS Separator. The magnetically 15 labeled CD14+ cells are retained in the column. The unlabeled cells run through, this cell fraction is depleted of CD14+ cells. After removal of the column from the magnetic field, the magnetically retained CD14+ cells can be eluted as the positively selected cell fraction. After centrifu- 20 gation at 200×g for 10 min at room temperature the monocytes were harvested and and used directly in binding assay or resuspended in freezing medium (10% DMSO, 90% FCS) at 1.0E+07 cells/ml and stored in liquid nitrogen.

As shown in the literature Monocytes express constitu- 25 tively TIM3 on their surface. 1×105 CD14+ isolated human monocytes (50 µl/well) were put into 98 well-v bottom MTP in fresh culture medium and incubated with Redimune® NF Liquid for 15 min at RT to block unspecific binding. Than 50 µl/well of disclosed anti-TIM3 mAbs or reference anti-30 TIM-3 mAbs 344823 (R&D) and F38-2E2 (BioLegend) (10 µg/ml in cell culture medium) were added and incubated for 1 h at 4° C. Than cells were washed with PBS/1% BSA and secondary antibody PE-labeled Goat-anti-mouse F(ab')2 were (Jackson Lab 115-006-072) added for 1 hour at 4° C. 35 eter. After washing and centrifugation MFI signals of stained cells were analyzed by BD Biosciences FACSCanto flow cytometer.

The specific binding was calculated as follow:

Specific Binding [MFI]=Geom. Mean MFIsample- 40 Geom. Mean MFIisotype control The results are shown in Table 8: (Binding to human Monocytes). TIM3 clones Tim3\_0016, Tim3\_0018, Tim3\_0020, Tim3\_0028 and Tim3 0038 bind to human monocytes of different donors even better than the reference anti-TIM-3 Abs.

TABLE 23 Binding to human Monocytes.

donor1

(CD14+)

2122

2326

1917

1134

1468

1665

1411

1637

1351

480

144

516

1010

71

0

Tim3 0016

Tim3 0018

Tim3 0020

Tim3 0021

Tim3 0022

Tim3 0026

Tim3 0030

Tim3 0038

Tim3 0028

Tim3 0033

<TIM-3>PE Mab, M-IgG1 (Cl

F38-2E2; Biolegend) <TIM-3>PE Mab, Rat IgG2A

(Clone 344823, R&D) Rat-IgG2A-PE

M-IgG2b

M-IgG1

#### Example 26

Binding of Anti-TIM-3 Antibodies to Isolated Cyno Monocytes Expressing TIM-3

CD14+ Monocytes were isolated from cynomolgus monkey anticoagulated peripheral blood (Covance) by density gradient centrifugation using Ficoll-Paque (GE Healthcare) (see General Protocols in the User Manuals or visit www. miltenyibiotec.com/protocols) and subsequent positiv selection via NHP CD14 MicroBeads. First the CD14<sup>+</sup> cells are magnetically labeled with CD14 MicroBeads. Then the cell suspension is loaded onto a MACS® Column which is placed in the magnetic field of a MACS Separator. The magnetically labeled CD14<sup>+</sup> cells are retained in the column. The unlabeled cells run through, this cell fraction is depleted of CD14<sup>+</sup> cells. After removal of the column from the magnetic field, the magnetically retained CD14<sup>+</sup> cells can be eluted as the positively selected cell fraction. After centrifugation at 200×g for 10 min at room temperature the monocytes were harvested and and used directly in binding assay or resuspended in freezing medium (10% DMSO, 90% FCS) at 1.0E+07 cells/ml and stored in liquid nitrogen.

As shown in the literature Monocytes express constitutively TIM3 on their surface. 1×105 CD14+ isolated cyno monocytes (50 µl/well) were put into 98 well-v bottom MTP in fresh culture medium and incubated with Redimune® NF Liquid for 15 min at RT to block unspecific binding. Than 50 µl/well of Alexa488 labeled anti-TIM3 (10 µg/ml in cell culture medium) were added and incubated for 1 h at 4° C. After washing and centrifugation MR signals of stained cells were analyzed by BD Biosciences FACSCanto flow cytom-

The specific binding was calculated as follow:

Specific Binding [MFI]=Geom. Mean MFIsample-Geom. Mean MFIisotype control The results are shown in Table 9 (Binding to Cyno Monocytes). TIM3 clones Tim3\_0016, Tim3\_0018, Tim3\_0026, Tim3\_0028 and, Tim3\_0030 bind to cyno monocytes of different cyno donors.

TABLE 24

			Binding to	o Cyno Mono	cytes.	
rtes.		-		cyno1 (16719M) CD14+	cyno2 (17435M) CD14+	cyno3 (30085F) CD14+
(CD14+)	(CD14+)	50	AF + PI	75	83	84
. ,		•	HumTIM-3 Alexa488 R&D	158	121	143
1634	1690		(34482)			
1818	1943		Rat-IgG2A-Alexa488	84	86	91
1377	1462		hum TIM-3 A488 F38-2E2	135	136	124
951	1197	55	(NOVUS Biol)			
1111	1235		M-IgG1-Alexa 488	72	82	83
1016	900		Tim3_0016-A488	157	177	187
419	466		Tim3_0016 variant 0018-A488	301	480	417
1368	1401		Tim3 0022-A488	115	134	138
950	1607		Tim3 0026-A488	137	184	197
328	595	60	Tim3 0028-A488	3936	2996	4090
13	0	00	Tim3 0038-A488	97	107	120
55	213		Tim3_0020-A488	274	378	354
493	460		Tim3 0021 A488	348	473	399
			Tim3 0030 A488	119	163	144
917	814		Tim3 0033 A488	71	81	83
			TIM-3 (4177) A488	78	83	85
68	70	65	TIM-3 (8213) A488	75	83	87

30

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### Example 27

### Binding of Anti-TIM-3 Antibodies to NHL and MM Cell Lines Expressing TIM-3

The binding capacity of disclosed anti-TIM3 antibodies and two anti-TIM3 reference antibodies clones (1) 4177 and (2) 8213 (Kyowa) was analyzed by a FACS. In short human TIM3 expressing B cell lymphoma cells (exemplified as 10 Pfeiffer cells) and multiple myeloma cells (exemplified as RPMI-8226 cells) were incubated with BD human Fc Block for 10 min at RT to block unspecific binding. Then  $2 \times 10^5$ cells (50 µl/well) were put into 98 well-v bottom MTP and 15 50 µl/well of Alexa488 labeled anti-TIM3 (10 µg/ml in BD Staining buffer) were added and incubated for 1 h at 4° C. After washing and centrifugation MFI signals of stained cells were analyzed by BD Biosciences FACSCanto flow 20 cytometer.

The specific binding was calculated as follow:

Specific Binding [MFI]=Geom. Mean MFIsample-Geom. Mean MHisotype control

The results are shown in FIGS. 2A and 2B (Binding to RPMI-8226 and Pfeiffer cells).

#### Example 10: Cytotoxic Activity of Anti-TIM-3 Antibodies on TIM-3 Expressing NHL and MM Cells

TIM3-specific antibodies conjugated with pseudomonas exotoxin (PE 24) effectively kill TIM3-expressing cells. The cytotoxic activity of disclosed anti-TIM3 antibodies and one commercial available anti-TIM3 reference antibody clone 11E365 (available from US Biological) was analysed with Promega CellTiter-Glo Luminescent Cell Viability Assay. In short to 5×103 (50  $\mu l/well$  in 98 well MTP, in triplicate)  $^{40}$ recombinant CHO K1 stabile expressing human TIM-3 or 2×104 cells (50 µl/well in 98 well MTP, in triplicate) human TIM3 expressing B cell lymphoma cells (exemplified as Pfeiffer cells) or multiple myeloma cells (exemplified as 45 RPMI-8226 cells) were added 25 µl/well 1:5 serial dilution of disclosed anti-TIM-3 antibodies with the highest concentration of 10 µg/ml or appropriate media to untreated cells or Isotype control to untargeted treated cells. Treatment ranges 50 from 10 µg/ml to 1 ng/ml in triplicate. All antibodies were used as full length mouse Fcy versions. For conjugation of the conjugation of the Pseudomonas exotoxin 10 µg/ml of mouse Fcy fragment specific Fabs conjugated with PE 24 were added and incubated for 3 days at 37° C. Cycloheximide as a known protein synthesis inhibitor in eukaryotes was used as positive control. Viability of treated cells were measured with Promega CellTiter-Glo Luminescent Cell Viability Assay.

The cytotoxic activity was calculated as follow:

Rel. Inhibition [%]=(1-(Esampel-E negative control)/(E positive control-E negative

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The results are shown in Table 25.

#### TABLE 25

Cytotoxic activity of anti-TIM3 mAbs on TIM-3 expressing recombinant
NHL and MM cell lines in sandwich format.

#### Antibodies and references (all TIM3 antibodies

anti TIM3 antibodies conjugated	IC50 [nM]				
to a deimunized <i>Pseudomonas</i> exotoxin A)	recTIM-3 CHO cells	Pfeiffer cells	RPMI-8226		
Tim3_0016	0.04	0.09	0.55		
Tim3_0016 variant 1	0.05	0.10	0.66		
(Tim3_0018)					
Tim3_0020	0.07	0.11	>64		
Tim3_0021	0.04	0.10	5.9		
Tim3_0022	0.02	0.07	0.36		
Tim3_0023	0.03	0.08	>64		
Tim3_0026	0.03	0.08	>64		
Tim3_0030	0.03	0.10	>64		
Tim3_0033	0.11	0.20	0.79		
Tim3_0038	0.01	< 0.002	0.16		
US Biol. Clone 11E365	0.7	1.2	1.1		
Cells w/o Ab	_		_		
Cells + <mfc> Fab PE</mfc>			_		
IgG2A + <mfc> Fab PE</mfc>	_		_		
Cycloheximide	135	181	245		

All tested TIM3 clones are highly potent (IC50 range 0.01-0.2 nM) on recombinant CHO K1 stabile expressing human TIM-3 and Pfeiffer cells expressing high and moderate levels of TIM-3 and even more potent in their cytotoxic activity than the strong internalizing reference anti-TIM-3 Ab clone 11E365, US Biological. TIM3 clones 0016, 0018, 0021, 0022, 0033 and 0038 are also potent on RPMI-8226 cells expressing 5 fold lower TIM-3 level compare to recombinant CHO TIM-3 cells.

#### Example 28

Comparison of the cytotoxic activity of disclosed anti-TIM3 antibodies vs. two anti-TIM3 reference antibodies 1.7.E10 and 27-12E12 (as described in WO2013/06490).

The cytotoxic activity of disclosed anti-TIM3 antibodies and two anti-TIM3 reference antibodies the TIM3 reference antibodies 1.7E10 and 27.12E12 as described in WO2013/ 06490 was analysed with Promega CellTiter-Glo Luminescent Cell Viability Assay as described above. All antibodies were used as full length human  $IgG_1$  format including the human Fcgamma part. In this experiment conjugation of the Pseudomonas exotoxin was achieved via human Fcy fragment specific Fabs conjugated with PE 24 (10 µg/ml) which were added and incubated for 5 days at 37° C.

The results are shown in Table 26.

TABLE 26

Comparison	of cytotoxic	activity	of anti-TIM3	mAbs	on	TIM-3	expressing
		NHL an	id MM cell lii	nes.			

Antibodies and references (all anti TIM3 antibodies conjugated to a deimunized	Pfeiffd	er cells	RPMI-8	226 cells
Pseudomonas	Max.	Rel. IC50	Max.	Rel. IC50
exotoxin A)	killing	[nM]	killing	[nM]
Cycloheximide	100 [%]	271	100 [%]	111
1.7E10	60.3 [%]	0.68	65.7 [%]	2.544
27-12E12	75.7 [%]	0.02	86.6 [%]	0.111

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#### TABLE 26-continued

Comparison of cytotoxic a	activity of ar NHL and MN	nti-TIM3 mA M cell lines.	bs on TIM-	3 expressing	
Antibodies and references (all anti TIM3 antibodies conjugated to a deimunized	Pfeiff	er cells	RPMI-8226 cells		
Pseudomonas exotoxin A)	Max. killing	Rel. IC50 [nM]	Max. killing	Rel. IC50 [nM]	10
Tim3_0016 Tim3_0016 variant (Tim3_0018)	84.9 [%] 82.9 [%]	$\begin{array}{c} 0.05\\ 0.06\end{array}$	86.6 [%] 88.1 [%]	0.063 0.081	
Tim3_0026 Tim3_002 XIsotype Control hIgG1	78.3 [%] 82.6 [%] 3.2 [%]	<0.02 <0.02 N.A	83.1 [%] 83.8 [%] 0.4 [%]	0.067 0.047 N.A	15

All disclosed TIM3 clones are highly active (IC50 range 0.02-0.08 nM) on Pfeiffer and RPMI-8226 cells expressing <sup>20</sup> TIM-3 and even more potent in their cytotoxic activity than <sup>the</sup> strong internalizing reference anti-TIM-3 Ab clone 27-12E12. All antibodies were compared as *Pseudomonas* exotoxin (PE24) conjugates using the same *Pseudomonas* <sup>25</sup> exotoxin under the same conditions.

#### Example 28

## Cytotoxic Activity of Fab-PE24 Constructs of Disclosed Anti-TIM3 Antibodies on MM, NHL and AML Cell Lines (Expressing TIM3, but not PSMA)

The cytotoxic activity was analysed with Promega Cell-Titer-Glo Luminescent Cell Viability Assay as described above. 1:5 serial dilutions of Fab-fragments of disclosed <sup>40</sup> anti-TIM3 antibodies directly conjugated to PE24 with the highest concentration of 50 µg/ml or appropriate media to untreated cells or non-binding anti-PSMA Fab-PE24 control to untrageted treated cells were incubated with  $7.5 \times 10^3$  Pfeiffer cells or  $2 \times 10^3$  RPMI-8226 cells (50 µl/well in 98 well MTP) for 4 days at 37° C. Treatment ranges from 50 µg/ml to 8 ng/ml in triplicate. Cycloheximide was used as <sup>50</sup> positive control. 144

All tested Fab-PE24 constructs of disclosed anti-TIM3 antibodies are highly potent (IC50 range 1-10 nM) on MM (RPMI-8226) and NHL (Karpas-299) cells expressing moderate level of TIM-3 and demonstrate significant cytotoxic activity on AML cell lines (CMK, TF-1, MOLM-13) expressing very low levels of TIM-3.

#### Example 29

Cytotoxic Activity of Immuno Conjugates (*Pseudomonas* Exotoxin a Conjugates (Fab-PE24 Constructs) of Disclosed Anti-TIM3 on Primary Leukemic Stem/Progenitor AML Cells from Relapsed/Refractory Patients

<sup>20</sup> CD34<sup>+</sup> cells from peripheral blood of relapsed/refractory patients were obtained from AllCells, LLC, Alameda, Calif. After confirmation of purity and viability of all samples (purity range 84-94% and viability range 95-99%) the expression level of TIM-3 was evaluated by FACS as described in Example 7 using anti-TIM-3 mAbs 344823 (R&D). (see FIG. 31). All tested (4/4) primary leukemic stem/progenitor (CD34+) AML samples from relapsed/refractory patients demonstrate homogeneous expression of TIM-3 at different levels.

For the evaluation of cytotoxic activity of Fab-PE24 constructs of disclosed anti-TIM3 clones 0016 and 0022 on primary CD34+ AML cells  $1 \times 10^4$  cells (50 µl/well in 98 well MTP, in triplicate) were incubated with 1:5 serial dilutions of Fab-fragments with the highest concentration of 50 µg/ml or appropriate media to untreated cells or non-binding anti-PSMA Fab-PE24 control to untargeted treated cells for 3 days at 37° C. Cycloheximide was used as positive control. Cytotoxic activity was analysed with Promega CellTiter-Glo Luminescent Cell Viability Assay as described above in Example 28.

The results are shown in Table 27.

The results are shown in Table 28. (Cytotoxic activity of Fab-PE24 constructs of disclosed anti-TIM3 antibodies on primary CD34+ AML cells).

TABLE 27

Cytotoxic activity of I	Fab-PE24 co	onstructs	s of disclose	ed anti-T	'IM3 antibo	dies on	MM, NHL	and AM	L cell lines.	
Antibodies and references (all anti TIM3 antibodies	RPMI-8	226	Karpas-	299	CME	<u> </u>	TF-1		MOLM	-13
conjugated to a deimunized <i>Pseudomonas</i> exotoxin A)	Max.	IC50	Max.	IC50	Max.	IC50	Max.	IC50	Max.	IC50
	killing	[nM]	killing	[nM]	killing	[nM]	killing	[nM]	killing	[nM]
Cycloheximide	100 [%]	281	100 [%]	113	100 [%]	149.0	100 [%]	207	100 [%]	156
Anti_PSMA	10.5 [%]	N.A.	40.1 [%]	N.A.	8.98 [%]	N.A.	5.27 [%]	N.A.	18.9 [%]	N.A.
Tim3_0022	99.1 [%]	1.9	98.8 [%]	10	67.1 [%]	255	58.6 [%]	299	58.5 [%]	579
Tim3_0016	99.3 [%]	1.1	99.2 [%]	4	64.8 [%]	225	54.2 [%]	534	62.7 [%]	459

55

60

65

TABLE 28								
Cytotoxic activity o	f Fab-PE24 cc	onstructs of	f disclosed ant	i-TIM3 an	tibodies on pr	imary CD3	84+ AML cells	s).
Antibodies and references	D1; A	ML	D2; A	ML	D3; A	ML	D4; A	ML
(all anti TIM3 antibodies	CD34+ PB0	) <u>136 cell</u> s	CD34+ PB0	142 cells	CD34+ PB0	9 <u>135 cell</u> s	CD34+ PB0	)193 cells
conjugated to a deimunized <i>Pseudomonas</i> exotoxin A)	Max.	IC50	Max.	IC50	Max.	IC50	Max.	IC50
	killing	[nM]	killing	[nM]	killing	[nM]	killing	[nM]
Cycloheximide	100 [%]	212	100 [%]	262	100 [%]	121	100 [%]	208
anti-PSMA	2 [%]	N.A.	8 [%]	N.A.	18 [%]	N.A.	12 [%]	N.A.
TIM-3 0022-cFP	38 [%]	>691	75 [%]	107	31 [%]	>691	57 [%]	375
TIM-3 0016-cFP	48 [%]	>691	79 [%]	30	44 [%]	>691	69 [%]	116

and Tim3 0022 are highly potent on (2/4) primary AML samples (PB0142 and PB0135) (1050 range 30-116 nM) and demonstrate significant cytotoxic activity on all (4/4) primary leukemic stem/progenitor (CD34+) AML cells expressing different levels of TIM-3.

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#### Example 30

#### Comparison of Potency of Fab-PE24 Constructs of Selected Anti-TIM3 Antibodies on NHL and MM Cell Lines

The evaluation of cytotoxic activity of sortase coupled Fab-PE24 constructs of selected disclosed anti-TIM3 antibodies was analysed with Promega CellTiter-Glo Luminescent Cell Viability Assay as described above in Example 28.

The results are shown in Table 29.

#### TABLE 29

Cytotoxic activity of Fab-PE24 constructs of selected anti-TIM3 antibodies on NHL and MM cells.						
Antibodies and references (all anti TIM3 antibodies conjugated to a deimunized					40	
Pseudomonas	Pfeiffe	r cells	RPMI-82	226 cells	_	
exotoxin A)	Max. killing	IC50 [nM]	Max. killing	IC50 [nM]		
Cycloheximide anti-PSMA TIM-3 0022 TIM-3 0016 TIM-3 0021 TIM-3 0033 TIM-3 0038	100 [%] 25.2 [%] 99.9 [%] 99.6 [%] 98.4 [%] 99.8 [%] 99.6 [%]	271.1 N.A. 1.58 0.77 2.15 5.30 0.47	100 [%] 21.5 [%] 99.6 [%] 99.2 [%] 99.1 [%] 99.7 [%] 98.3 [%]	153 N.A. 2.14 0.61 3.61 5.73 0.32	45	
					<ul> <li>50</li> </ul>	

High cytotoxic potency was demonstrated with Fab-PE24 constructs of all selected disclosed anti-TIM3 antibodies (IC50 range 0.3-5 nM) on NHL (Pfeiffer) and MM (RPMI-8226) cells expressing moderate level of TIM-3.

The highest cytotoxic activity was observed with Fab-PE24 constructs of disclosed anti-TIM3 antibodies Tim3 0016 and Tim3 0038.

### Example 31

Comparison of Cytotoxic Activity of Fab-PE24 Construct vs. Total-IgG-Amatoxin Conjugate of the Same Clone of Disclosed Anti-TIM-3 Antibody on Pfeiffer Cells

The evaluation of cytotoxic activity of conjugated Fab-PE24 construct of disclosed anti-TIM3 clone 0016 vs. total

Fab-PE24 constructs of anti-TIM3 antibodies Tim3\_0016 15 IgG of the same clone conjugated with Amatoxin (according to th procedures described in WO2012/041504 (conjugated via the 6' C-atom of amatoxin amino acid 4, particularly via an oxygen atom bound to the 6' C-atom of amatoxin amino acid, and wherein the TIM3 antibody is connected by a 20 linker via a urea moiety) was analysed with Promega CellTiter-Glo Luminescent Cell Viability Assay as described above in Example 12. The results are shown in Table 30.

TABLE 30

Cytotoxic activity of Fab-PE24 construct vs. total IgG-Amatoxin conjugate of anti-TIM3 clone 0016 on NHL cells							
Pfeiffer cells	Max. killing	IC50 [nM]					
Cycloheximide Isotype hIgG1 Amatoxin TIM-3 0016-Amatoxin TIM-3 0016-PE24	100 [%] 28 [%] 93.3 [%] 99.8 [%]	163 N.A. 0.81 0.25					

Cytotoxic activity of Amanitin-conjugated anti-TIM-3 <sup>35</sup> clone 0016 (IC50 0.8 nM) is comparable with cytotoxic activity of Fab-PE24 construct of the same clone (IC50 0.3 nM) on NHL (Pfeiffer) cells expressing moderate level of TIM-3.

#### Example 32

#### Patients and Tumor Sample Processing

Freshly excised solid tumor lesions and malignant effusions were collected from 34 patients with non-small cell lung cancer, 7 patients with ovarian cancer and 1 patient with renal cell carcinoma (RCC) between. The solid tumor lesions were dissociated mechanically and digested using accutase (PAA), collagenase IV (Worthington), hyaluronidase (Sigma), and DNAse type IV (Sigma) directly after excision. Single-cell suspensions were prepared. The cellular fraction of malignant effusions was isolated by density gradient centrifugation using Histopaque-1119 (Sigma). All samples were stored in liquid nitrogen until further usage. The study was approved by the local Ethical Review Board (Ethikkommission Nordwestschweiz).

#### Example 33

### Tumor Sample Characterization

All tumor samples were comprehensively characterized by multicolor flow cytometry. The following antibodies were used for flow cytometric analysis:  $\alpha$ -CD4-PE,  $\alpha$ -CD8-PE-Cy7, α-CD11b-PerCP-eFluor710, α-CD45-PE-Cy7, a-CD45-PerCP-Cy5.5, a-CD137-FITC, a-BTLA-Biotin, α-CTLA-4-PE, α-ICOS-FITC, α-IFN-γ-FITC, α-Lag-3-

APC (all eBioscience),  $\alpha$ -CD3-PECF594,  $\alpha$ -CD25-BV605,  $\alpha$ -CD69-FITC,  $\alpha$ -Epcam-FITC,  $\alpha$ -granzyme B-PE,  $\alpha$ -active caspase 3-PE,  $\alpha$ -PD-1-BV605, Steptavidin-BV711 (all BD Bioscience),  $\alpha$ -CD45RA-BV421,  $\alpha$ -CCR7-AlexaFluor647,  $\alpha$ -FoxP3-AlexaFluor647,  $\alpha$ -Tim-3-BV421,  $\alpha$ -Tim-3-BV605 (all Biolegend). Dead cells were stained with LIVE/DEAD® Fixable Near-IR Dead Cell Stain Kit or LIVE/DEAD® Fixable Blue Dead Cell Stain Kit (Invitrogen). For intracellular stainings Fixation and Permeabilization Buffers from eBioscience were used. Samples were acquired for flow cytometric analysis on a BD LSR Fortessa. The human IL-2, IFN- $\gamma$  and TNF ELISA sets were all obtained from BD Bioscience.

CD8+ and CD4<sup>+</sup> T cells (CD45<sup>+</sup>CD3+) were characterized for the expression of the surface markers PD-1, Tim-3, CTLA-4, Lag-3, BTLA, CD25, CD69, CD137, ICOS, <sup>15</sup> CD45RA and CCR7. Tumor cells (CD45<sup>-</sup>Epcam<sup>+</sup>) were characterized for the expression of FolR1 comparing the binding of a FolR1 specific antibody with its matched isotype control. Only samples that were positive for FolR1 expression were used for treatment with FolR1-TCB, and <sup>20</sup> samples expressing EpCAM for treatment with catumaxomab, respectively.

#### Example 34

## Ex Vivo Treatment of Tumor Samples with FolR1-TCB

FolR1 positive tumor digests or malignant effusions were thawed, washed and plated in 96-well flat bottom cell culture 30 plates (BD Falcon) with a density of  $3{\times}10^5$  cells/200  $\mu l/well$ in complete medium (DMEM+Sodium Pyruvate (1 mM)+ MEM non essential AA (1x)+L-Glutamin (2 mM)+Penicillin/Streptomycin (100 ng/ml)+2-Mercaptoethanol (50 nM)+ Ciproxin (1 mg/ml)+10% human Serum). The samples were <sup>35</sup> cultured in the presence or absence of FolR1-TCB or DP47 TCB at a concentration of 2 nM for 24h. Activation of CD8+ and CD4+ T cells (CD45+CD3+) upon FolR1-TCB treatment was determined by multicolor flow cytometry by measuring the expression of the cell surface markers CD25, 40CD69, CD137, ICOS, PD-1 and Tim-3. Furthermore the expression of granzyme B and IFN-y was determined by intracellular staining. The concentration of IL-2 in the cell culture supernatants was measured by ELISA (human IL-2 ELISA set, BD OptEIA) following the instructions of the 45 manufacturer.

#### Example 35

# Ex Vivo Treatment of Tumor Samples with Catumaxomab

The trifunctional TCB catumaxomab (Removab®) was obtained from Fresenius. The experimental conditions were similar as indicated above for FolR1-TCB. Briefly, EpCAM 55 positive tumor digests or malignant effusions were cultured in the presence or absence of catumaxomab at a concentration of 10 ng/ml for 24h. Analysis of CD8+ and CD4<sup>+</sup> positive T cells (CD45<sup>+</sup>CD3+) was performed as described above. 60

#### Example 36

#### Killing Assay

To determine the FolR1-TCB induced tumor cell killing,  $3 \times 10^4$  CFSE-labelled Skov3 cells were cocultured with

tumor samples in the presence or absence of FolR1-TCB at a concentration of 2 nM for 24h in 96-well flat bottom cell culture plates. The E:T ratio (E: effector CD45<sup>+</sup>CD3<sup>+</sup> cells; T: target FolR1<sup>+</sup> cells from tumor and added Skov3 cells) was adjusted to 1:1 in each well and the cell number of the added tumor samples was calculated for each sample according to prior characterization by flow cytometry. Cell death of Skov3 cells was determined by flow cytometry by measuring activated caspase 3 and the live/dead marker Live/Dead-near-IR. The assay was performed in triplicates. The FolR1-TCB mediated killing was calculated according to the following equation: % of specific killing=100–[(% of Skov3 live cells in FolR1-TCB treated sample/% of Skov3 live cells in untreated sample)×100].

To compare the FolR1-TCB-induced killing capacity of T-cells between tumor samples, and to exclude additional factors suppressing T-cell functionality, such as expression of PD-L1 on the tumor cells, we exogenously added CFSElabeled FolR1<sup>+</sup> Skov3 cells to the tumor digests and adjusted the E:T ratio to 1:1, essentially as described above. We then measured the FolR1-TCB-induced killing of CFSE-labeled Skov3 cells, which allowed us to also include FolR1<sup>-</sup> tumor samples into the analysis. As some tumors from the initial cohort could not be used to characterize TCB-mediated tumor cell killing due to a very low amount of effector cells, a separate cohort of 12 tumor digests and 5 malignant effusions from 15 non-small cell lung cancer (NSCLC) and two epithelial ovarian carcinoma (EOC) patients was analyzed. All samples were characterized for their CD3+ effector and FolR1<sup>+</sup> target cell content (FIG. 39). Tumor cell killing of CD3+ T-cells from patients was compared with PBMC-derived T-cells from healthy donors. A substantial heterogeneity in tumor cell killing between individual patients was observed (26±11.8%) after 24 h (FIG. 12O). Of note, CD3<sup>+</sup> T-cells from healthy donors induced a significantly better killing than TILs (42.8±9.7%, p=0.013). Exposure to a control TCB with no binding to a tumor antigen (DP47-TCB) did not induce any tumor cell killing.

#### Example 37

#### Polyclonal Stimulation with Anti-CD3/CD28 Antibodies

A 96-well flat-bottom plate was precoated with 0.5 ug/ml anti-CD3c (clone OKT3, Biolegend) for 2 hrs at 37° C. Afterwards, the antibody solution was removed and the plate washed extensively. Frozen tumor suspensions were thawed, washed and cultured at 3×10<sup>5</sup> cells/200 µL/well in complete
medium with 2 µg/ml anti-CD28 antibody (clone 28.2, eBioscience) for 24 hrs. After 24 hrs of incubation cells were collected, washed and analyzed by flow cytometry for expression of activation markers e.g. CD25 and T cell effector functions e.g. granzyme B and IFN-γ on CD8<sup>+</sup> T
cells. Supernatants were collected for IL-2, IFN-γ and TNF-α ELISA which was performed according to the manufacturer's instructions.

#### Example 38

### Restoring of T Cell Function by PD-1 Blockade

Tumor digests were stimulated by agonistic anti-CD3 and anti-CD28 antibodies as described above in the presence or absence of 10 µg/ml anti-PD-1 antibody (MDX5C4) per well and incubated for 24 hrs. After 24 hrs cells were collected, washed and analyzed by flow cytometry. Super-

natants were collected for IL-2, IFN- $\gamma$  and TNF- $\alpha$  ELISA which was performed according to the manufacturer's instructions.

### Example 39

### Activation of T Cells in Tumor Digests and Malignant Effusions by FolR1 TCB

The T cell bispecific antibodies engaging CD3 and folate 10 receptor 1 (Mov19 based FolR1-TCB and the control antibody DP47-TCB were provided by Roche Glycart. The anti-PD-1 antibody 5C4 is described in U.S. Pat. No. 8,008, 449. The anti-Tim3 antibody F38-2EL was used. For flow cytometric characterization of FolR1 expression the anti-15 body anti-FolR1-APC (aa25-233) from LifeSpanBiosciences and its matched isotype control (Biolegend) were used. Tumor lesions from 15 patients with FolR1<sup>+</sup> tumors were characterized for T cell activation induced by FolR1 TCB. The samples consisted of 9 single cell suspensions and 20 6 malignant effusions derived from patients with NSCLC (n=7), ovarian cancer (n=7), and renal cell cancer (n=1). The amount of CD3+ T cells and of FolR1+ tumor cells was highly variable between patients (CD3+: mean 33.9%±standard deviation of 16.6%, FolR1+: 17.1%±16.8%). Charac- 25 terization of the expression of the inhibitory receptors PD-1, Tim-3, CTLA-4, Lag- and BTLA on T cells revealed a large heterogeneity among patients (FIG. 11A-B). While the tumor-infiltrating CD8<sup>+</sup> T cells showed high levels of PD-1, Tim-3 and CTLA-4 (31.6%±25%; 22.2%±20.8% and 30 18.7%±14.4%, respectively), Lag-3 and BTLA were only expressed on a minority of cells in all patients of this cohort (3.5%±4.9% and 2.3%±1.7%, respectively). Inhibitory receptors on CD4<sup>+</sup> T cells were distributed similarly, with a slightly more prominent expression of CTLA-4.

To determine FolR1-TCB induced T cell activation, tumor samples were cultured in the presence or absence of FolR1-TCB or the control TCB DP-47. Then, T cells were characterized by multicolor flow cytometry for expression of activation markers and T cell effector functions, as described 40 above. FIG. 12A-0 reveals a large heterogeneity in FolR1-TCB induced T cell activation between patients. In particular, while the vast majority of patients expressed CD69 already at baseline, upregulation of CD25, CD137, and ICOS, varying from 9-80%, 2.5-50% and 3.5-71%, respec- 45 tively was observed. Acquisition of effector functions such as IFN-y secretion, CD107 degranulation and expression of granzyme B was observed, ranging from 3.7-59%, a fold change of 1-7 or 1.3-64, respectively (FIG. 12A-I). The inhibitory receptors PD-1 and Tim-3 were further upregu- 50 lated as a marker of activation upon FolR1-TCB treatment, irrespective of their baseline expression. Exposure to TCB DP-47 did not induce any T cell activation. The upregulation of CD25 and ICOS induced by FolR1-TCB stimulation was significantly stronger in peripheral CD8+ T-cells from 55 healthy donors than for tumor-derived CM+ cells (p=0.002 and p<0.001, respectively; FIG. 12J, FIG. 12L, FIG. 12M). The secretion of T-cell effector cytokines IFN- $\gamma$ , IL-2, and TNF upon FolR1-TCB stimulation was largely diminished amongst TILs in the majority of tumors compared with 60 PBMCs from healthy donors (p=0.0047, p<0.001, and p=0.006, respectively; FIG. 12N). FolR1-TCB-induced perforin secretion was highly variable in TILs, and severely impaired in a subset of patients (FIG. 12N).

Similarly, despite a lower upregulation of granzyme B, 65 FolR1-TCB induced activation and acquisition of effector functions of CD4<sup>+</sup> T cells (FIG. **25**A-I). To assess whether

the abundance of intra-tumoral T cells or FolR1 expression impacts on T cell activation upon TCB exposure, the upregulation of activation markers was correlated to the E:T ratio (E: effector CD45<sup>+</sup>CD3<sup>+</sup> T cells; T: FolR1<sup>+</sup> cells) and to the percentage and to the level of tumor antigen expression of FolR1<sup>+</sup> cells (FIG. **13**A-C). The latter was determined by the mean fluorescence intensity of FolR1 on tumor cells (CD45<sup>-</sup> EpCAM<sup>+</sup>) using flow cytometry (FIG. **13**C). However, neither of these parameters did influence T cell activation, i.e., even low amounts of FolR1<sup>+</sup> cells, high E:T ratios, or poor T-cell infiltration have been sufficient for an efficient upregulation of activation and functional markers. In addition, the presence of potentially immune-suppressive cell populations such as regulatory T-cells or immature myeloid cells did not influence T-cell activation or T-cell function.

### Example 40

### FolR1-TCB Induced T Cell Activation Inversely Correlates with Expression of PD-1 and Tim-3

High expression of inhibitory receptors has been described as a hallmark of exhausted T cells. Therefore, a dysfunctional state of tumor-infiltrating T cells may impact efficacy of the FolR1 TCB and may be responsible, at least in part, for heterogeneous T cell activation upon TCB exposure. To this end, the co-expression of inhibitory receptors, as determined at baseline, was correlated to FolR1 TCB induced upregulation of activation markers and T cell effector functions. Both PD-1 and Tim-3 expression on CD8<sup>+</sup> T cells thereby negatively correlated with T cell activation determined by expression of CD25, CD137 and ICOS. CD8<sup>+</sup> T cells with a high expression of PD-1 or Tim-3 showed a marginal effect upon FolR1-TCB treatment, while T cells with a low expression of these inhibitory receptors could be strongly activated upon treatment with FolR1-TCB (FIG. 14A-I). Measurement of FolR1-TCB induced IL-2 secretion normalized to the content of T cells in the samples revealed the same dependencies on PD-1 and Tim-3 expression (FIG. 15A-C), while FolR1-TCB induced upregulation of granzyme B was less dependent on prior expression of these inhibitory receptors (FIG. 14J-L). Interestingly, the baseline expression of CTLA-4, Lag-3 and BTLA on CD8+ T cells did not correlate with FolR1-TCB induced T cell activation (FIG. 26A-C). Expression of inhibitory receptors on CD4<sup>+</sup> T cells was much less predictive for FolR1-TCB induced CD4<sup>+</sup> T cell activation compared to the expression of the same receptors on CD8<sup>+</sup> T cells.

### Example 41

#### FolR1-TCB Induced Tumor Cell Killing Inversely Correlates with Expression of PD-1 and Tim-3

To investigate FolR1-TCB induced killing of tumor cells at an adjusted E:T ratio of 1:1, CFSE-labelled Skov3 cells were exogenously added to the tumor digests which contain a previously determined amount of CD3<sup>+</sup> T cells using multicolor flow cytometry. FolR1-TCB induced killing of Skov3 cells was determined by measuring activated caspase 3 and a live/dead marker. In line with the FolR1-TCB induced T cell activation as measured by CD25 up-regulation, the specific killing upon FolR1-TCB exposure negatively correlated with single or co-expression of PD-1 and Tim-3 on CD8<sup>+</sup> T cells. Furthermore, FolR1-TCB induced killing was also influenced by the baseline expression of CTLA-4 and the co-expression of PD-1 and CTLA-4. How-

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ever, the impact of CTLA-4 expression on FolR1-TCB induced tumor cell killing was less pronounced compared to PD-1 and Tim-3 expression.

#### Example 42

### Treatment of Fresh Tumor Lesions with Catumaxomab-Activation of Tumor-Infiltrating T Cells Using Catumaxomab and Correlation with Expression of Inhibitory Receptors

To determine to which extent catumaxomab induces T cell activation and to confirm the findings described above using a second, independent T cell bispecific molecule, 4 tumor digests from patients with NSCLC were exposed to catumaxomab, a trifunctional bispecific antibody recognizing CD3 on T cells and EpCAM on tumor cells. Then, T cells were characterized by flow cytometry for expression of activation markers and T cell effector functions (FIG. 17A-D). Validating our data above for FolR1-TCB, we observed 20 a striking heterogeneity in catumaxomab induced T cell activation. Accordingly, the baseline expression of inhibitory receptors differed between the patients (FIG. 17E-H).

Analysis of T cell activation and effector function upon treatment with catumaxomab revealed two groups of 25 of PD-1 and Tim-3 to T cell dysfunction. patients according to PD-1 and/or Tim-3 expression on CD8<sup>+</sup> T cells confirming our findings with FolR1-TCB (FIG. **18**A-R). FD-1<sup>*low*</sup>, Tim-3<sup>*low*</sup>, and, even more pronounced, both PD-1<sup>*low*</sup>/Tim-3<sup>*low*</sup> expressing cells, failed to be activated by catumaxomab, whereas PD-1<sup>high</sup>, Tim-3<sup>high</sup>, <sup>30</sup> and PD-1<sup>high</sup>/Tim-3<sup>high</sup> T cells substantially upregulated CD25, CD69, CD137, ICOS, granzyme B and IFN-γ.

### Example 43

### Polyclonal Stimulation of Tumor-Infiltrating T Cells by CD3/CD28-Immune Phenotyping of Tumor-Infiltrating T Cell Subsets in Non-Small Cell Lung Cancer Samples

We investigated the expression of co-inhibitory T cell receptors and differentiation markers on tumor-infiltrating CD3+CD8+ and CD3+CD4+ T cell subsets from 34 patients NSCLC using multicolor flow cytometry. The majority of tumors showed a high expression of the inhibitory receptor 45 PD-1 (FIG. 19A-B), a major regulator of T cell exhaustion. Of note, expression of other checkpoint inhibitors such as Tim-3, CTLA-4, LAG-3 or BTLA showed substantial variation between T cells obtained from different tumors (FIG. 19A-B).

#### Example 44

#### Cumulative Expression of Inhibitory Receptors Defines T Cell Dysfunction

In this Example, polyclonal stimulation was used in a sub-optimal dose to assess the impact of inhibitory receptors on T cell function. The effect of stimulation with agonistic anti-CD3 and anti-CD28 antibodies on T cell activation, as 60 exemplified by CD25 expression, and on T cell effector function as analyzed by IFN- $\gamma$ , TNF- $\alpha$  and IL-2 production as well as granzyme B expression varied substantially between patients as determined by flow cytometry (FIGS. 20A-B) and ELISA (FIG. 20C-E). Of note, we observed 65 different levels of T cell function, varying from T cell populations that exhibit a largely preserved T cell function

(i.e., sustained CD25 and granzyme B expression, as well as IL-2, IFN- $\gamma$  and TNF- $\alpha$  production) to those with abrogated T cell function (loss of CD25 and granzyme B expression and of cytokine production).

To analyze the impact of multiple inhibitory receptors on T cell functionality we defined the inhibitory receptor (iR) score as a marker for the cumulative expression of inhibitory receptors on T cells. To this end, the percentage of expression of PD-1, Tim-3, CTLA-4, Lag-3 and BTLA was analysed in all NSCLC samples and a score based on the median and interquartile ranges of each expressed receptor was defined and calculated for each sample (e.g., FIG. 21F). Tumor-infiltrating CD8<sup>+</sup> T cells expressing a high iR score indicating expression of multiple inhibitory receptors showed a marginal effect upon polyclonal stimulation, correlating with their highly dysfunctional state, whereas T cells with a low iR score could be strongly activated upon polyclonal stimulation (FIG. 21A-E). Upregulation of T cell effector functions, indicated by IL-2, IFN- $\gamma$  and TNF- $\alpha$ production, not only correlated with the cumulative expression of inhibitory receptors but similarly with PD-1 and Tim-3 expression as well with the co-expression of both receptors (FIG. 22A-I), indicating a significant contribution

#### Example 45

#### Inhibitory Receptor Expression

Single and cumulative expression of inhibitory receptors increases with tumor progression. The expression of inhibitory receptors correlated with tumor stage and tumor progression. The number of PD-1, Tim-3 and LAG-3 positive 35 cells was clearly increased in advanced tumor stages (FIG. 21G-K). No clear correlation was observed for the expression of CTLA-4, which may indicate that this receptor acts via a different inhibitory mechanism. BTLA was generally expressed at a low level and only a small increase was found 40 in advanced tumor stages (FIG. 21K). A significant increase in the cumulative expression of inhibitory receptors, as reflected by the iR score, was observed in patients with nodal positive cancers and advanced tumor stages whereas primary tumor size did not significantly correlate with the iR score (FIG. 21L-M). These data suggest a gradual and continuous upregulation of inhibitory receptors, during tumor progression, which are most likely involved in T cell exhaustion in NSCLC.

Inhibitory receptors are gradually expressed on tumor-50 infiltrating T cells. To explore the role of simultaneous expression of distinct inhibitory receptors on single T cells, the concomitant expression of these receptors in CD8<sup>+</sup> T cells (FIGS. 32, 33) relative to the expression of any of the five analyzed receptors was analyzed. Expression is shown as heat map, displaying the percentage of expression for the individual patients (FIG. 32) or as a radar plot, which shows the expression as mean and standard deviation of the four respective receptors on CD8<sup>+</sup> T cells, pregated for the fifth, indicated immune checkpoint (FIG. 33). CD8+PD-1+T cells on average expressed the lowest percentages of other inhibitory receptors, whereas CD8+BTLA+ T cells expressed all of the four other inhibitory receptors at high levels, indicating that BTLA marks a particularly exhausted T cell subset (FIGS. 32, 33). An increase in the number of co-expressed inhibitory receptors was observed from CD8+Tim-3+T cells over CD8+CTLA-4+ T cells to CD8+LAG-3+ T cells (FIGS. 32, 33). These findings suggest a gradual acquisition of

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inhibitory receptors with PD-1 as a broadly expressed, early marker, while BTLA is upregulated rather late during T cell exhaustion.

### Example 46

#### Blockade of PD-1 can Partially Restore T Cell Function

Rescue of T cell function by PD-1 blocking antibodies 10 depends on the level of PD-1 expression. As we found a clear correlation between the expression of inhibitory receptors, particularly PD-1 and Tim-3, and T cell activation upon polyclonal stimulation, blockade of the PD-1 or PD-1/Tim-3 pathways might restore T cell function. However, addition 15 of a blocking antibody to PD-1 (5C4) or combined blockade of PD-1 and Tim-3 upon stimulation with agonistic anti-CD3 and anti-CD28 antibodies could restore T cell effector function such as production and secretion of IL-2, IFN-y and TNF- $\alpha$  only in some patients whereas in other patients only 20 a marginal effect was seen (FIG. 23A-D). As observed in a chronic murine LCMV infection model (Blackburn et al., PNAS 105(39):15016 (2008)), we identified PD-1<sup>hi</sup> and PD-1<sup>*int*</sup> subsets in tumor-infiltrating CD8<sup>+</sup> T cells from NSCLC patients. In brief, PD-PD-1<sup>*int*</sup>, and PD-1<sup>*neg*</sup> subsets 25 could be identified based on their measured fluorescence intensity. Cells from 33 patients were analysed for PD-1 expression to define uniform parameters for reproducible discernment of the three subsets. The analysis covered the whole spectrum of PD-1 expression levels and included 30 tumor samples with clearly distinguished PD-1<sup>neg</sup> or PD-1<sup>hi</sup> populations. This allowed to set the gates for this analysis, which was then applied to all samples.

Only PD-1<sup>*int*</sup> expressing T cell subsets appeared to be rescued in activation upon PD-1 or combined PD-1/Tim-3 35 blockade, while no effect in T cell activation was observed upon blockade in PD-1<sup>*int*</sup> cells (FIG. **24**). The latter may exhibit a more exhausted phenotype which appears to be resistant to PD-1 blockade alone.

This finding was confirmed in T cells activated by FolR1 40 TCB. T cells were stimulated with FolR1 as described above. Blockade of PD-1 further strengthened FolR1-TCB induced T cell activation of T cells from a subset of patients.

Measurement of FolR1-TCB induced IFN- $\gamma$ , TNF and IL-2 secretion normalized to the content of T cells in the 45 samples revealed that in patient cell populations with a substantial amount of PD-1<sup>*hi*</sup> expressing (approximately >15%) cells were not able to secret these cytokines. In contrast, cytokine secretion could be induced in most patient cell populations with a lower amount of PD-expressing 50 (approximately <15%) cells (FIG. **27**A-C). In the latter group, addition of a blocking antibody to PD-1 or combined blockade of PD-1 and Tim-3 upon stimulation by FolR1-TCB stimulation increased production of IL-2, IFN- $\gamma$  and TNF- $\alpha$  (FIG. **28**A-F). The PD-1<sup>*hi*</sup> expressing subset there-55 fore may exhibit a more exhausted phenotype which appears to be resistant to PD-1 blockade alone.

Thus, T cell effector functions such as production of IL-2, IFN- $\gamma$  and TNF- $\alpha$  could be restored in TILs from some NSCLC patients, whereas in other patients only a marginal 60 recovery of T cell functions could be achieved. The increase in cytokine production upon exposure to anti-CD3/CD28 stimulation in combination with the PD-1 blocking antibody was compared to the percentage of PD-1<sup>*hi*</sup> CD8<sup>+</sup> T cells from the PD-1 positive population per patient. The increase in 65 cytokine expression upon PD-1 blockade inversely correlated with the percentage of PD-1<sup>*hi*</sup> T cells, indicating that

patients expressing larger numbers of PD-1<sup>*int*</sup> T cells respond poorly to PD-1 blockade alone (FIG. **24**A-C). As T cell dysfunction correlates with the expression of multiple inhibitory receptors (i.e., patients with a high iR score) and response to a PD-1 directed therapy correlates with the expression levels of PD-1 on CD8<sup>+</sup> T cells, we further analyzed the expression of Tim-3, CTLA-4, LAG-3 and BTLA in PD-1<sup>*int*</sup> and PD-1<sup>*int*</sup> CD8<sup>+</sup> T cells. Remarkably, PD-1<sup>*hi*</sup> T cells expressed significantly higher levels of additional receptors compared to PD-1<sup>*int*</sup> subsets (FIG. **34**). Thus, PD-1<sup>*hi*</sup> and PD-1<sup>*int*</sup> may identify two distinct T cell populations where PD-1<sup>*hi*</sup> T cells may exhibit a more exhausted phenotype, which cannot be recovered by PD-1 blockade alone.

The data presented herein for the first time provides a comprehensive phenotypical and functional analysis of tumor-infiltrating CD8<sup>+</sup> T cells from patients with NSCLC. The data shows that these cells mainly possess an effector memory phenotype (CCR7-CD45RAlow) and show large heterogeneity in expression of inhibitory receptors such as PD-1, Tim-3, CTLA-4, LAG-3 and BTLA. Nevertheless, a clear increase in the number of receptors expressed on tumor-infiltrating lymphocytes (TILs) from late stage tumors was observed, which reflects the progress of T cell dysfunction during tumor development. The data presented herein shows that the effector functions of TILs were impaired in the vast majority of patients, and that impairment correlated with the expression of inhibitory receptors. To recover T cell function in a clinically relevant setting we combined polyclonal T cell stimulation with antibody-mediated inhibition of PD-1. The effect of PD-1 blockade on T cell functionality varied between TILs from different patients, but could be predicted by assessing the percentage of CD8<sup>+</sup> T cells expressing PD-1 at high levels.

Here, we could demonstrate that the functionality of TILs can be correlated with and is largely affected by the number and expression level of inhibitory receptors. Of note, even T cells expressing low levels of inhibitory receptors showed some degree of impaired functionality, as the secretion of IL-2 was impaired in the vast majority of patients. Overall the activation and effector function of CD8<sup>+</sup> T cells inversely correlated with the cumulative expression of inhibitory receptors, indicating a direct contribution of different inhibitory pathways to T cell dysfunction in NSCLC.

Our analysis of five inhibitory receptors on tumor infiltrating CD8<sup>+</sup> T cells showed a clear increase of the single and cumulative expression of these inhibitory receptors in tumor tissues from NSCLC patients presenting with tumorpositive lymph nodes and advanced tumor stages. Expression of CTLA-4 differed from the other four receptors with the highest percentage of positive cells at early stages, which may indicate a distinct role of CTLA-4 in regulating T cell immunity (Topalian et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N. Engl. J. Med. 366, 2443 (Jun. 28, 2012)). Co-expression analysis of additional inhibitory receptors on single cells, relative to the expression of one given receptor, showed a gradual expression, with early and late upregulation of PD-1 and BTLA, respectively. This may reflect the dynamic process of T cell exhaustion.

The findings presented herein underscore the clinical relevance of inhibitory receptor expression during NSCLC tumor progression, associated with progressive failure of immune control of tumor growth. We document here two populations of CD8<sup>+</sup> tumor-infiltrating T cells characterized by different levels of PD-1 expression (PD-1<sup>*hi*</sup> and PD-1<sup>*int*</sup> subsets). The occurrence of PD-1<sup>*hi*</sup> T cells did not correlate

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with the percentage of PD-1 expression. Interestingly, we observed that the effect of PD-1 blockade correlated with the levels of PD-1 expression, with minimal effects on responsiveness of TILs with high proportions of PD-1<sup>*hi*</sup> subpopulations. These findings are in line with experiments in a <sup>5</sup> murine, chronic LCMV infection model where the subset of PD-1<sup>*int*</sup> DbGP33-specific CD8<sup>+</sup> T cells could be restored upon PD-1 blockade. In contrast, the PD-1<sup>*hi*</sup> subset appeared more "exhausted," i.e., exhibited signs of functional exhaustion, and responded poorly to PD-1 blockade. Thus, the level <sup>10</sup> of PD-1 expression may represent a novel marker to define distinct T cell subsets in human cancers and, may serve as a predictor of responses to treatment with PD-1 blocking antibodies.

#### Example 47

#### Activation of T-Cells from Healthy Donors and Cancer Patients by FolR1-TCB

To assess the effect of FolR1-TCB on T-cell activation peripheral blood mononuclear cells (PBMCs) from healthy donors were co-cultured with the FolR1<sup>+</sup> ovarian cancer cell line Skov3 (FIG. **40**A). Upon exposure to increasing concentrations of FolR1-TCB ranging from 0.6 pM to 2 nM for <sup>25</sup> 24 h we observed a strong activation of CD8<sup>+</sup> T-cells with upregulation of CD25, CD137, and ICOS. In addition, T-cells secreted IL-2, IFN- $\gamma$ , and TNF. Exposure to DP47-TCB, a TCB directed against an irrelevant antigen, did not induce any T-cell activation (FIGS. **40B** and C). <sup>30</sup>

#### Example 48

#### Inhibitory Receptor Expression is Highly Diverse in Tumor-Infiltrating CD8<sup>+</sup> T-Cells

As tumor-resident T-cells frequently display a highly dysfunctional phenotype, the observed heterogeneity in T-cell activation among different patients after FolR1-TCB stimulation may be due to an impaired TIL functionality. A 40 hallmark of dysfunctional T-cells in both chronic viral infections and in tumors is the overexpression of inhibitory receptors. To this end, we determined the expression of the immune checkpoints PD-1, Tim-3, CTLA-4, Lag-3, and BTLA on tumor-infiltrating CD8<sup>+</sup> T-cells in all tumor 45 samples. We observed a high diversity in frequency and combined expression of these receptors amongst different tumors; PD-1 was found to be the most prominent inhibitory receptor with the highest percentage of expression (60.2±30%), followed by Tim-3 (29.5±24.4%), CTLA-4 50 (24.6±17.6%), Lag-3 (7.0±5.9%), and BTLA (3.9±2.6%) (FIG. 35F). As described previously in a murine chronic viral infection model (Blackburn et al., Proc Natl Acad Sci USA 2008; 105(39):15016-21) and, as shown herein, in human tumors, the PD-1<sup>+</sup> population could be divided into 55 a PD-1<sup>hi</sup> and a PD-1<sup>int</sup> expressing subpopulation (FIG. 35A). Analysis of additional inhibitory receptors expressed on these particular subsets showed a significantly higher expression of all other inhibitory receptors, including Tim-3, CTLA-4, Lag-3, and BTLA, in the PD-1<sup>hi</sup> subpopulation as 60 compared with the expression of these receptors in the PD-1<sup>int</sup> and PD-1<sup>neg</sup> subsets (FIG. 36A-D). Therefore, we used the percentage of PD-1<sup>hi</sup> T-cells in the CD8<sup>+</sup> subset as a surrogate marker for the cumulative expression of inhibitory receptors. The tumor samples were divided according to 65 the frequency of PD-1<sup>hi</sup> cells into two groups with high (PD-1<sup>hi</sup> abundant tumors) and low frequencies of PD-1<sup>int</sup>

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expressing T-cells (PD-1<sup>*hi*</sup> scarce tumors), respectively. A cut-off value of 30% PD-1<sup>*hi*</sup> expression was chosen to separate the two groups. The percentage of PD-1<sup>*hi*</sup> cells ranged from 39.1-60.5% in the PD-1<sup>*int*</sup> abundant (49.5±7.9%) and from 2.65-19.5% in the PD-1<sup>*hi*</sup> scarce group (8.4±5.7%; FIG. **36**E). The cut-off value was validated in a second cohort of 14 NSCLC and 2 ovarian cancer patients with a similar distribution in the frequency of PD-1<sup>*hi*</sup> cells, where we observed comparable results upon polyclonal stimulation by anti-CD3/anti-CD28 antibodies (FIG. **39**).

#### Example 49

#### FolR1-TCB-Induced T-Cell Activation Largely Depends on the Level of PD-1 Expression on CD8<sup>+</sup> T-Cells

We analyzed whether the expression of inhibitory receptors could be correlated with a diminished T-cell functionality upon FolR1-TCB treatment. Consistent with the results described in Example 41 above, FolR1-TCB-induced T-cell activation, as exemplified by CD25, CD137, and ICOS expression (p=0.028; p<0.001, and p=0.008, respectively), and T-cell effector functions, indicated by IFN-γ, IL-2, TNF, as well as perforin secretion, were significantly impaired in PD-1<sup>*hi*</sup> abundant tumors compared with PD-1<sup>*int*</sup> scarce tumors (p=0.019; p=0.007; p=0.028, and p=0.029, respectively; FIG. **37**A-G). Similarly, PD-1<sup>*hi*</sup> abundant tumors displayed a significantly reduced cytotoxicity upon FolR1-TCB stimulation whereas a strong tumor cell killing could be observed in the majority of PD-1<sup>*hi*</sup> scarce tumors (p=0.021; FIG. **37**H).

#### Example 50

# PD-1 Blockade Restores FolR1-TCB-Induced T-Cell Function Only in PD-1<sup>hi</sup> Scarce Tumors

As the level of PD-1 expression on TILs correlates with the efficacy of FolR1-TCB, we analyzed whether blockade of the PD-1/PD-L1 axis in combination with FolR1-TCB treatment might be able to restore T-cell function. We found that upon combined treatment with FolR1-TCB and the PD-1 blocking antibody nivolumab (MDX5C4) secretion of the effector cytokines IFN- $\gamma$ , TNF, and IL-2 as well as perforin could be increased only in some of the PD-1<sup>*hi*</sup> scarce tumors. In contrast, in PD-1<sup>*hi*</sup> abundant tumors PD-1 blockade failed to elicit any response (FIG. **38**A-D). Of note, cytotoxic tumor cell killing could neither be improved in T-cells from PD-1<sup>*int*</sup> scarce nor from PD-1<sup>*hi*</sup> abundant tumors by the additional PD-1 blockade (FIG. **38**E).

The examples set forth herein describe the immunomodulatory capacity of a CD3×FolR1-specific TCB in primary cancer lesions from patients with non-small cell lung cancer (NSCLC), epithelial ovarian carcinoma (EOC) and renal cell carcinoma (RCC). Compared with fully functional peripheral T-cells from healthy donors, we observed a substantial heterogeneity in FolR1-TCB-induced tumor cell killing and T-cell activation among different human tumor samples, resulting in partial or complete impairment of T-cell function in the majority of patients. Comprehensive analysis of inhibitory receptor expression on the cell surface of intratumoral T-cells revealed that the efficacy of T-cell activation by FolR1-TCB inversely correlated with the expression levels of PD-1. Patients with PD-1<sup>*hi*</sup> abundant tumors displayed impaired T-cell activation and effector function upon FolR1-TCB treatment. Additionally, these patients did not respond to PD-1 blockade in contrast to their PD-1<sup>*ht*</sup> scarce expressing counterparts. Thus, the bioactivity of bispecific antibodies is considerably hampered by T-cell dysfunction, which is orchestrated, at least in part, by the 5 sustained and highly diverse expression of inhibitory receptors.

We observed a strong upregulation of T-cell activation markers, effector cytokine secretion and tumor cell killing upon FolR1-TCB stimulation in PBMCs from healthy 10 donors (FIG. 40). In stark contrast, however, T-cell effector functions largely varied and were generally diminished in intratumoral T-cells. Particularly, killing capacity and effector cytokine production was significantly lower in TILs with complete loss of IL-2 production and severely impaired TNF 15 and IFN- $\gamma$  secretion in the majority of tumors. We documented the expression of the inhibitory receptors PD-1, Tim-3, CTLA-4, Lag-3, and BTLA on intratumoral CD8+ T-cells. PD-1 displayed the broadest expression of all analyzed inhibitory receptors. Observations from chronic 20 murine LCMV infections by Blackburn suggest the presence of functionally distinct PD-1 positive T-cell subsets, which can be separated on the basis of MFI levels, using flow cytometry (Blackburn et al., PNAS 105(39):15016 (2008)). Of note, PD-1<sup>hi</sup> T-cell subsets displayed a high co-expres- 25 sion of Tim-3 and CTLA-4 and to a lesser extent of Lag-3 and BTLA, while their PD-1<sup>int</sup> counterparts expressed only low levels of other inhibitory receptors, comparable to PD-1<sup>neg</sup> T-cells. The frequency of PD-1<sup>int</sup> CD8<sup>+</sup> T-cells differed largely between patients and allowed us to discrimi- 30 nate between PD-1<sup>hi</sup> abundant and scarce tumors. In contrast to patients with a PD-1<sup>hi</sup> scarce phenotype, FolR1-TCBmediated T-cell activation and tumor cell killing was sig-nificantly impaired in tumors displaying a PD-1<sup>*hi*</sup> abundant phenotype. These data extend and confirm previous obser- 35 vations that the activation and effector function of CD8+ T-cells correlates with the co-expression of multiple immune checkpoints (Sakuishi et al., J Exp Med 2010; 207(10):2187-94; Fourcade et al., J Exp Med 2010; 207(10):2175-86; Grosso et al., J Immunol 2009; 182(11):6659-69; Matsuzaki 40 et al., Proc Natl Acad Sci USA 2010; 107(17):7875-80; Fourcade et al., Cancer Res 2012; 72(4):887-96). The frequency of PD-1<sup>hi</sup> T-cells may therefore be useful as a surrogate marker for the functionality of TILs upon TCB activation as well as serve as a predictive marker for the 45 therapeutic responses to TCB treatment. This immune profile could guide the selection of patients who are likely to respond to immunotherapy such as TCBs. Its correlation with clinical benefits remains to be determined in prospective clinical interventions. 50

A promising avenue to improve the therapeutic efficacy of TCBs lies in the blockade of inhibitory signals on T-cells. As PD-1 was the most prominently expressed inhibitory receptor in all tumors analyzed we assessed whether PD-1 blockade could enhance T-cell effector functions upon TCB

activation. Of note, we observed increased secretion of effector cytokines upon combined FoIR1-TCB and anti-PD-1 treatment, though only in PD-1<sup>*hi*</sup> scarce tumors. Thus, novel therapeutic strategies, exploring the transformation of PD-1<sup>*hi*</sup> into PD-1<sup>*hi*</sup>T-cells to increase the susceptibility to PD-1/PD-L1 blockade, are clearly needed.

Remarkably, we observed no improvement on tumor cell killing upon concomitant PD-1 blockade in all of the tumor samples. Thus, blockade of a single immune checkpoint may not be sufficient to restore the cytolytic capacity of TILs. In a mouse tumor model, however, blockade of the PD-1/PD-L1 axis has been shown to increase T-cell infiltration into tumors (Curran et al., Proc Natl Acad Sci USA 2010; 107(9):4275-80), a characteristic of this treatment, which could not be addressed by our in vitro approach. Thus, the therapeutic effect of PD-1 blockade in vivo might not only result from improving T-cell cytotoxicity of residual intratumoral T-cells, but from the sustained functionality of newly infiltrating T-cells. TCB-induced T-cell activation has been shown to upregulate PD-1 expression, which may lead to secondary resistance in the presence of PD-L1 expressed on both tumor cells and infiltrating immune cells as recently demonstrated both with a Her2-specific TCB and with a carcinoembryonic antigen-(CEA) specific TCB (Junttila et al., Cancer Res 2014; 74(19):5561-71; Osada et al., Cancer Immunol Immunother 2015). Importantly, blockade of the PD-1/PD-L1 axis could completely restore TCB-induced T-cell function both in vitro and in a mouse tumor model. These observations indicate that co-administration of checkpoint inhibitors is capable of preventing secondary resistance, which may add to the dysfunctional state of TILs and limit the therapeutic efficacy of TCBs. Further work is clearly needed to determine optimal combination regimens of checkpoint inhibitors and TCBs. It will also be crucial to identify inhibitory and activating T-cell-receptors with nonredundant functions as potential therapeutic targets.

Our findings clearly indicate that bispecific antibodies such as FolR1-TCB are capable of causing T-cells to upregulate co-stimulatory molecules, produce inflammatory cytokines, and acquire cytolytic function. We have observed different states of T-cell dysfunction, which are orchestrated, at least in part, by the expression of inhibitory receptors and, in some instances, reduce the effectiveness of the TCB. As FolR1-TCB-induced effector functions could only be partially restored by PD-1 blockade, our results suggest a rather complex immune regulation, which utilizes multiple and eventually non-redundant pathways to maintain T-cell dysfunction within the tumor environment.

#### **SEQUENCES**

#### Amino Acid Sequences of Exemplary Embodiments

1) FolR Binders Useful in Common Light Chain Format, Variable Heavy Chain

Descript	Description Sequence	
16A3	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>NYYAGVTPFDY</u> WGQGTLVTVSS	1
18D3	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>NYYTGGSSAFDY</u> WGQGTLVTVS	2

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Description	n Sequence	Seq ID	No
15H7	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>NYYLFSTSFDY</u> WGQGTLVTVSS	3	
15B6	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>NYYIGIVPPDY</u> WGQGTLVTVSS	4	
21D1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCARNYYVGVSPFDYWGQGTLVTVSS	5	
16F12	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>NFTVLRVPFDY</u> WGQGTLVTVSS	6	
15A1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>NYYIGVVTFDY</u> WGQGTLVTVSS	7	
15A1_CDR1	SYYMH	8	
15A1_CDR2	IINPSGGSTSYAQKFQG	9	
15A1_CDR3	NYYIGVVTFDY	10	
19E5	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>GEWRRYTSFDY</u> WGQGTLVTVSS	11	
19E5_CDR1	SYYMH	8	
19E5_CDR2	IINPSGGSTSYAQKFQG	9	
19E5_CDR3	GEWRRYTSFDY	12	
19A4	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>GGWIRWEHFDY</u> WGQGTLVTVSS	13	
19A4_CDR1	SYYMH	8	
19A4_CDR2	IINPSGGSTSYAQKFQG	9	
19A4_CDR3	GGWIRWEHFDY	14	
16D5	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLE WVG <u>RIKSKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTED TAVYYCTT <u>PWEWSWYDY</u> WGQGTLVTVSS	15	
16D5_CDR1	NAWMS	16	
16D5_CDR2	RIKSKTDGGTTDYAAPVKG	17	
16D5_CDR3	PWEWSWYDY	18	
15E12	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLE WVG <u>RIKSKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTED TAVYYCTT <u>PWEWSYFDY</u> WGQGTLVTVSS	19	
15E12_CDR1	NAWMS	16	
15E12_CDR2	RIKSKTDGGTTDYAAPVKG	17	
15E12_CDR3	PWEWSYFDY	20	
21A5	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLE WVG <u>RIKSKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTED TAVYYCTT <u>EWEWAWFDY</u> WGQGTLVTVSS	21	
21A5_CDR1	NAWMS	16	
21A5_CDR2	RIKSKTDGGTTDYAAPVKG	17	
21A5 CDR3	PWEWAWPDY	22	

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Description Sequence		Seq ID No
21G8	EVQLVESGGGLVKPGGSLRLSCAASGFTF <u>SNAWMS</u> WVRQAPGKGLE WVG <u>RIKSKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTED TAVYYCTT <u>PWEWAYFDY</u> WGQGTLVTVSS	23
21G8_CDR1	NAWMS	16
21G8_CDR2	RIKSKTDGGTTDYAAPVKG	17
21G8_CDR3	PWEWAYFDY	24
19H3	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQ</u> GRVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>TGWSRWGYMDY</u> WGQGTLVTVSS	25
19H3_CDR1	SYYMH	8
19H3_CDR2	IINPSGGSTSYAQKFQG	9
19H3_CDR3	TGWSRWGYMDY	26
20G6	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQ</u> GRVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>GEWIRYYHFDY</u> WGQGTLVTVSS	27
20G6_CDR1	зүүмн	8
20G6_CDR2	IINPSGGSTSYAQKFQG	9
20G6_CDR3	GEWIRYYHFDY	28
20H7	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>VGWYRWGYMDY</u> WGQGTLVTVSS	29
20H7_CDR1	SYYMH	8
20H7_CDR2	IINPSGGSTSYAQKFQG	9
20H7_CDR3	VGWYRWGYMDY	30

## 2) CD3 Binder Common Light Chain (CLC)

Description	Sequence	Seq ID No
common CD3 light chain (VL)	QAVVTQEPSLTVSPGGTVTLTC <u>GSSTGAVTTSNYAN</u> WVQEKP GQAFRGLIG <u>GTNKRAP</u> GTPARFSGSLLGGKAALTLSGAQPED EAEYYC <u>ALWYSNLWV</u> FGGGTKLTVL	31
common CD3 light chain_CDR1	GSSTGAVTTSNYAN	32
common CD3 light chain_CDR2	GTNKRAP	33
common CD3 light chain_CDR3	ALWYSNLWV	34
common CD3 light chain (VLCL)	QAVVTQEPSLTVSPGGTVTLTC <u>GSSTGAVTTSNYAN</u> WVQEKP GQAFRGLIG <u>GTNKRAP</u> GTPARFSGSLLGGKAALTLSGAQPED EAEYYC <u>ALWYSNLWV</u> FGGGTKLTVLGQPKAAPSVTLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVA PTECS	35

3) CD3 Binder Heavy chain

Description	Sequence	Seq ID No
CD3 variable heavy chain (VH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS	36
CD3 heavy chain (VH)_CDR1	TYAMN	37
CD3 heavy chain (VH)_CDR2	RIRSKYNNYATYYADSVKG	38
CD3 heavy chain (VH)_CDR3	HGNFGNSYVSWFAY	39
CD3 full heavy chain (VHCH1)_	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>TYAMN</u> WVRQAPGKG LEWVS <u>RIRSKYNNYATYYADSVKG</u> RFTISRDDSKNTLYLQMNSL RAEDTAVYYCVR <u>HGNFGNSYVSWFAY</u> WGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSC	40
CD3 constant heavy chain CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSC	84

4) FolR Binders Useful for Crossfab Format

Description	Sequence	Seq ID No
11F8_VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFS <u>SYAIS</u> WVRQAPGQGLE WMG <u>GIIPIFGTANYAQKFQG</u> RVTITADKSTSTAYMELSSLRSEDTA VYYCAR <u>AVFYRAWYSFDY</u> WGQGTTVTVSS	41
11F8_VH_CDR1	SYAIS	42
11F8_VH_CDR2	GIIPIFGTANYAQKFQG	43
11F8_VH_CDR3	AVFYRAWYSFDY	44
11F8_VL	DIQMTQSPSTLSASVGDRVTITC <u>RASQSISSWLA</u> WYQQKPGKAPKL LIY <u>DASSLES</u> GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC <u>QQYT <u>SPPPT</u>FGQGTKVEIK</u>	45
11F8_VL_CDR1	RASQSISSWLA	46
11F8_VL_CDR2	DASSLES	47
11F8_VL_CDR3	QQYTSPPPT	48
36F2_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTHDTSTSTVYMELSSLRSEDTA VYYCAR <u>SFFTGFHLDY</u> WGQGTLVTVSS	49
36F2_VH_CDR1	SYYMH	8
36F2_VH_CDR2	IINPSGGSTSYAQKFQG	9
36F2_VH_CDR3	SFFTGFHLDY	50
36F2_VL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVSSSYLA</u> WYQQKPGQAPR LLIY <u>GASSRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQY</u> <u>TNEHYYT</u> FGQGTKVEIK	51
36F2_VL_CDR1	RASQSVSSSYLA	52
36F2_VL_CDR2	GASSRAT	53
36F2_VL_CDR3	QQYTNEHYYT	54

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Description	Sequence	Seq ID No
9D11_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGPTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>GDFAWLDY</u> WGQGTLVTVSS	55
9D11_VH_CDR1	SYYMH	8
9D11_VH_CDR2	IINPSGGPTSYAQKFQG	56
9D11_VH_CDR3	GDFAWLDY	57
9D11_VL	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPG QSPQLLIY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYY C <u>MQASIMNRT</u> FGQGTKVEIK	58
9D11_VL_CDR1	RSSQSLLHSNGYNYLD	59
9D11_VL_CDR2	LGSNRAS	60
9D11_VL_CDR3	MQASIMNRT	61
9D11_VL N95S	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPG QSPQLLIY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYY C <u>MQASIMSRT</u> FGQGTKVEIK	62
9D11_VL N95S_CDR3	MQASIMSRT	63
9D11_VL N95Q	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPG QSPQLLIY <u>LGSNRAS</u> GVPDRFSGSGSGSTDFTLKISRVEAEDVGVYY C <u>MQASIMQRT</u> FGQGTKVEIK	64
9D11_VL N95Q_CDR3	MQASIMQRT	65
9D11_VL T97A	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPG QSPQLLIY <u>LGSNRAS</u> GVPDRFSGSGSGSTDFTLKISRVEAEDVGVYY C <u>MQASIMNRA</u> FGQGTKVEIK	66
9D11_VL T97A	MQASIMNRA	67
9D11_VL T97N	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPG QSPQLLIY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYY C <u>MQASIMNRN</u> FGQGTKVEIK	68
9D11_VL T97N_CDR3	MQASIMNRN	69
5D9_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>SYIDMDY</u> WGQGTLVTVSS	70
5D9_VH_CDR1	SYYMH	8
5D9_VH_CDR2	IINPSGGSTSYAQKFQG	9
5D9_VH_CDR3	SYIDMDY	71
5D9_VL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVSSSYLA</u> WYQQKPGQAPR LLIY <u>GASSRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQD</u> <u>NWSPT</u> FGQGTKVEIK	72
5D9_VL_CDR1	RASQSVSSSYLA	52
5D9_VL_CDR2	GASSRAT	53
5D9_VL_CDR3	QQDNWSPT	73
6B6_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLE WMG <u>IINPSGGSTSYAQKFQG</u> RVTMTRDTSTSTVYMELSSLRSEDTA VYYCAR <u>SYVDMDY</u> WGQGTLVTVSS	74

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Description	Sequence	Seq ID No
6B6_VH_CDR1	SYYMH	8
6B6_VH_CDR2	IINPSGGSTSYAQKFQG	9
6B6_VH_CDR3	SYVDMDY	75
6B6_VL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVSSSYLA</u> WYQQKPGQAPR LLIY <u>GASSRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQD</u> <u>IWSPT</u> FGQGTKVEIK	76
6B6_VL_CDR1	RASQSVSSSYLA	52
6B6_VL_CDR2	GASSRAT	53
6B6_VL_CDR3	QQDIWSPT	77
14E4_VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYAMS</u> WVRQAPGKGLE WVS <u>AISGSGGSTYYADSVKG</u> RFTISRDNSKNTLYLQMNSLRAEDTA VYYCAK <u>DSSYVEWYAFDY</u> WGQGTLVTVSS	78
14E4_VH_CDR1	SYAMS	79
14E4_VH_CDR2	AISGSGGSTYYADSVKG	80
14E4_VH_CDR3	DSSYVEWYAFDY	81
14E4_VL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVSSSYLA</u> WYQQKPGQAPR LLIY <u>GASSRAT</u> GIPDRFSGSGSGTDSTLTISRLEPEDFAVYYC <u>QQP</u> <u>TSSPIT</u> FGQGTKVEIK	82
14E4_VL_CDR1	RASQSVSSSYLA	52
14E4_VL_CDR2	GASSRAT	53
14E4_VL_CDR3	QQPTSSPIT	83

### 5) CD3 Binder Useful in Crossfab Format

Description Sequence		Seq ID No
CD3 heavy chain (VH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPG KGLEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQ MNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS	36
CD3 heavy chain (VH)_CDR1	TYAMN	37
CD3 heavy chain (VH)_CDR2	RIRSKYNNYATYYADSVKG	38
CD3 heavy chain (VH)_CDR3	HGNFGNSYVSWFAY	39
CD3 light chain (VL)	QAVVTQEPSLTVSPGGTVTLTC <u>GSSTGAVTTSNYAN</u> WVQEKP GQAFRGLIG <u>GTNKRAP</u> GTPARFSGSLLGGKAALTLSGAQPED EAEYYC <u>ALWYSNLWV</u> FGGGTKLTVL	31
CD3 light chain_CDR1	GSSTGAVTTSNYAN	32
CD3 light chain_CDR2	GTNKRAP	33
CD3 light chain_CDR3	ALWYSNLWV	34
pETR12940: crossed common CD3 light	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKP GQAFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPED EAEYYCALWYSNLWVFGGGTKLTVLSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL	86

-continued

Description	n Sequence	Seq ID No
chain (VLCH1)	QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSC	
Crossed CD3 heavy chain (VHCK); e.g. in pCON1057	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMIWVRQAPG KGLEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQ MNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSA SVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	87
CD3-CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC	85
CD3- ckappa	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC	88

6) Exemplary Amino Acid Sequences of CD3-FolR <sup>20</sup> Bispecific Antibodies 2+1 Inverted Crossmab Format

Description	Sequence	Seq	ID No
VHCH1[9D11]_VHCL [CD3]_Fcknob_PGLALA pCON1057	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGPTSYAQKPQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGDFAWLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDGGGGSGGG SEVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWRQAPGKGL EWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAE DTAYYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GECKTHTCPPCPAPEAAGGPSVFLFPKEAVUNSKTRPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDMLNGKEYKCKVSNKALGAPIEKTISKAAGPREPQVYTLPPCR DELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		94
9D11_Fchole_PGLALA_HYRF	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGPTSYAQKPQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGDFAWLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALGAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCA VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		95
9D11_LC pCON1063	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQASIMNRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC		96
VLCH1[CD3] pETR12940	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAF RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEYYCAL WYSNLWVFGGGTKLTVLSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSC		86
CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYPPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCD	4	128
VHCH1[36F2]_VHCL [CD3]_Fcknob_PGLALA pCON1056	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTMTHDTSTSTVYMELSSLRSEDTA VYYCARSFFTGFHLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDGGGSGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGK GLEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLR AEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASVAAPSVFI	3	393

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Description	Sequence	Seq ID No
	FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREBQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPP CRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENVYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK	
36F2-Fc hole PGLALA pCON1050	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKPQGRVTMTHDTSTSTVYMELSSLRSEDTA VYYCARSFFTGFHLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDEEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALGAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLVSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	394
36F2 LC pCON1062	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQY TNEHYYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHXGLSSPVTKSFNRGEC	395
CD3 VLCH1 pETR12940	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAF RGLIGGTNKRAPGTPARPSGSLLGGKAALTLSGAQPEDEAEYYCAL WYSNLWVFGGGTKLTVLSSASTKGPSVPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSC	86

7) Exemplary Amino Acid Sequences of CD3-FolR Bispecific Antibodies with Common Light Chain

VHCH1[16D5]_VHCH1 [CD3]_Fcknob pCON999	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKG LEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSL KTEDTAVYYCTTPWEWSWYDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFS TYAMNWVRQAPGKGLEWVSRIRSKYNNYATYYADSVKGRFTISR DDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYMGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWVVDGVEVHN AKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALGA DIAVEWESNGQPENYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	89
VHCH1[16D5]_Fchole pCON983	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKG LEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSL KTEDTAVYYCTTPWEWSWYDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGOPREPQVC TLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNRFT QKSLSLSPGK	90
CD3_common light chain pETR13197	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQ AFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEY YCALWYSNLWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	35
VHCH1[CD3]_VHCH1 [16D5]_Fcknob_PGLALA pETR13932	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH	91

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	TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDGGGGSGGGGSEVQLVESGGGLVKPGGSLRLSCAAS GFTFSNAWMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVKGR FTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPWEWSWYDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSMNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGA PIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLWKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	
CD3_Fcknob_PGLALA pETR13917	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGGGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPR EPQVTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK	92
Fc_hole_PGLALA_HYRF pETR10755	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKPNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLP PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNRFTQKS LSLSPGK	93
VHCL[CD3]_Fcknob_PGLALA pETR13378	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGECDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAK GQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK	98
16D5 inverted 2 + 1 with N100A in CDR H3 pETR14096	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKG LEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSL KTEDTAVYYCTTPWEWSWYDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTPPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKVEP KSCDGGGGGGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFS TYAMWWRQAPGKGLEWVSRIRSKYNNYATYYADSVKGRFTISR DDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGASYVSWFAYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGA PIEKTISKAKGQPREPQVYTLPPCDELTKNQVSLWCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	99
16D5 inverted 2 + 1 with S100aA in CDR H3 pETR14097	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKG LEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSL KTEDTAVYYCTTPWEWSWYDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYPEPVTVSWNSGALTSGVHTPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFS TYAMMWVRQAPGKGLEWVSRIRSKYNNYATYYADSVKGRFTISR DDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNAYVSWFAYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYPPEPV TVSMNSGALTSGVHTPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGA PIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYP SDIAVEWSGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ OGNVFSCSVMHEALHNHYTOKSLSLSPGK	100

CD3 light	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQ	101
chain fused	AFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAOPEDEAEY	
to CH1:	VCALWYSNI, WYFCCCTKI, TVI, SCASTKCDSVEDI, ADSSKSTSCC	
FC_PGLALA;	TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL	
pETR13862	SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC	
	PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED	
	PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL	
	NGKEYKCKVSNKALGAPIEKTISKAKGOPREPOVYTLPPSRDEL	
	TKNOVSLTCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDG	
	SFFLYSKLTVDKSRWOOGNVFSCSVMHEALHNHYTOKSLSLSPG	
	K	
16D5 VH	EVOLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVROAPGKG	102
fused to	LEWVGRIKSKTDGGTTDYAAPVKGRETISEDDSKNTLYLOMNSL	
constant		
kanna		
-heda		
	IEQUSADSI ISUSSI LIUSAAD IEAAAN IACEV IAQGUSSPVIA	
PEIRI3859	SFIRGEC	
CD3 VH	FUOLLESCCCLUOPCCSLELSCAASCETESTVAMNWUROAPCKC	1.03
fugod to	LEWICDIDGEVINIVATVVADGUEGETIGDDGENITI VI OMNGI	103
rused to		
constant	RAEDTAVIICVRHGNFGNSIVSWFAIWGQGTLVTVSSASPRAAP	
Lambda	SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA	
chain;	GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST	
pETR13860	VEKTVAPTECS	
TOIDU		104
10001-	QVQLVQSGALVKAFGASVKVSCKASGYTFTSYYMH	104
46*UL	WVRQAPGQGLEWMGLINPSGGSTSYAQKFQGRVTM	
(X92343),	TRDTSTSTVYMELSSLRSEDTAVYYCARGGSGGSFD	
pius JH4	YWGQGTLVTVSS	
element		
IGHV1-	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW	105
69*06	VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITA	
(L22583),	DKSTSTAYMELSSLRSEDTAVYYCARGGSGGSMDA	
plus JH6	WGQGTTVTVSS	
element	-	
IGHV3-	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMS	106
15*01	WVROAPGKGLEWVGRIKSKTDGGTTDYAAPVKGRF	
(¥92216)	TT CODDCKNTT, VI. OMNCI, KTEDTA WYVCTTCCCCCCC	
nlug III	RDWGOGTI WTWGG	
alement	FDIWGQGILVIVSS	
erement		
TCHV3_	FUOLL FSCCCL. VODCCSLDLSCAASCFTFSSVAMSW	107
22*01		10,
23*01	VRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISR	
(M99660),	DNSKNTLYLQMNSLRAEDTAVYYCAKGGSGGSFDY	
plus JH4	WGQGTLVTVSS	
element		
1GHV4-	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWI	108
59*01	RQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTS	
(AB019438),	KNQFSLKLSSVTAADTAVYYCARGGSGGSFDYWGQ	
plus	GTLVTVSS	
JH4		
element		
IGHV5-	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGW	109
51*01	VRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISA	
(M99686),	DKSISTAYLOWSSLKASDTAMYYCARGGSGGSFDY	
plus JH4	WGOGTLVTVSS	
element		
CD3	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYAN	110
specific	WVOEK PGOA FRGI. TOOTNKPA POTPA PEGOTI. OOK	
antibody	A LTL COLOUPER EVICAL MUCHI MERCOMET	
and bour	TT TIDGAUFEDEREIICALMIDNUMVFGGGILTI	
pased on	ЧV	
humanized		
CH2527		
light chain		
hVK1-39	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQ	111
(JK4 J-	QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTI	
element)	SSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK	
VL7_46-	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYAN	112
13	WVQEKPGQAFRGLIGGTNKRAPGTPARFSGSLLGGK	

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(humanized	AALTLSGAQPEDEAEYYCALWYSNLWVFGGGTKLT
anti-CD3	VL
antibody	
light chain)	

<sup>8)</sup> Exemplary 16D5 Variants with Reduced Affinity a. Exemplary Light Chain Variants with Reduced Affinity

Name	Sequence	Seq ID N	0
K53A aa	$\label{eq:constraint} \begin{array}{l} \mathbb{Q}^{TVVT} \mathbb{Q} \text{EPSLTVSPGGTVTLTC} \underline{\mathbf{G}} \underline{\mathbf{S}} \mathbf{$	113	
K53A_VL_CDR1	GSSTGAVTTSNYAN	32	
K53A_VL_CDR2	GTNARAP	396	
K53A_VL_CDR3	ALWYSNLWV	34	
S93A aa	$\label{eq:constraint} \begin{array}{l} \mathbb{Q}^{TVVT} QEPSLTVSPGGTVTLTC \underline{GSSTGAVTTSNYAN} WVQQKPGQAPRGLIG\underline{G}\\ \underline{TNKRAP} \\ GTPARFSGSLLGGKAALTLSGVQPEDEAEYYC \underline{ALWYANLWV} \\ FGGGT\\ KLTVL \end{array}$	114	
S93A_VL_CDR1	GSSTGAVTTSNYAN	32	
S93A_VL_CDR2	GTNKRAP	33	
S93A_VL_CDR3	ALWYANLWV	397	

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b. Exemplary Heavy Chain Variants with Reduced Affin-

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Name	Sequence	Seq ID No
S35H aa	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMH</u> WVRQAPGKGLEWVG <u>RIK</u> SKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTT <u>PWEW</u> SWYDYWGQGTLVTVSSAS	115
S35H_VH_CDR1	NAWMH	398
S35H_VH_CDR2	RIKSKTDGGTTDYAAPVKG	17
S35H_VH_CDR3	PWEWSWYDY	18
G49S aa	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLEWVS <u>RIK</u> <u>SKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTT <u>PWEW</u> <u>SWYDY</u> WGQGTLVTVSSAS	116
G49S_VH_CDR1	NAWMS	16
G49S_VH_CDR2	RIKSKTDGGTTDYAAPVKG	17
G49S_VH_CDR3	PWEWSWYDY	18
R50S aa	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLEWVG <u>SIK</u> <u>SKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTT <u>PWEW</u> <u>SWYDY</u> WGQGTLVTVSSAS	117
R50S_VH_CDR1	NAWMS	16
R50S_VH_CDR2	SIKSKTDGGTTDYAAPVKG	399
R50S_VH_CDR3	PWEWSWYDY	18
W96Y aa	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <b>NAWMS</b> WVRQAPGKGLEWVG <u>RIK</u> <u>SKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTT <u>PYEW</u> <u>SWYDY</u> WGQGTLVTVSSAS	118
W96Y_VH_CDR1	NAWMS	16
W96Y_VH_CDR2	RIKSKTDGGTTDYAAPVKG	17

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Name	Sequence	Seq ID	No
W96Y_VH_CDR3	PYEWSWYDY	400	
W98Y aa	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLEWVG <u>RIK</u> <u>SKTDGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTT <u>PWEY</u> <u>SWYDY</u> WGQGTLVTVSSAS	119	
W98Y_VH_CDR1	NAWMS	16	
W98Y_VH_CDR2	RIKSKTDGGTTDYAAPVKG	17	
W98Y_VH_CDR3	PWEYSWYDY	232	

9) Additional Exemplary Embodiments Generated from a Phage Display Library (CDRS Underlined)

Name	Sequence	Seq ID No
90D7 aa	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLEWMG <u>IIN</u> PSGGSTSXAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARMYTIVV SPFDYWGQGTLVTVSSAS	120
90D7_VH_CDR1	зүүмн	8
90D7_VH_CDR2	IINPSGGSTSYAQKFQG	9
90D7_VH_CDR3	NYTIVVSPFDY	233
90C1 aa	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLEWMG <u>IIN</u> PSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR <u>MYFIGS</u> VAMDYWGQGTLVTVSSAS	121
90C1_VH_CDR1	SYYMH	8
90C1_VH_CDR2	IINPSGGSTSYAQKFQG	9
90C1_VH_CDR3	NYFIGSVAMDY	234
5E8 VH aa	$\underbrace{ \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \begin{array}{l} & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ \\ & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ \\ \\ & \end{array}{} \\ \\ \\ \end{array}{} \\ \\ \\ \end{array}{} \\ \\ \\ \end{array}{} \\ \\ \\ \end{array}{} \\ \end{array}{} \\ \\ \\ \end{array}{ } \\ \\ \end{array}{ } \\ \\ \end{array}{} \\ \\ \end{array}{} \\ \\ \end{array}{ } \\ \\ \\ \end{array}{ } \\ \end{array}{ } \\ \\ \\ \end{array}{ } \\ \end{array}{ } \\ \\ \\ \end{array}{ } \\ \end{array}{ } \\ \\ \end{array}{ } \\ \end{array}{ } \\ \\ \end{array}{ } \\ \end{array}{ } \\ \\ \end{array}{ } \\ \\ \end{array}{ } \\ \\ \\ \end{array}$ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\	122
5E8_VH_CDR1	SYYMH	8
5E8_VH_CDR2	IINPSGGSTSYAQKFQG	9
5E8_VH_CDR3	GLTYSMDY	235
5E8 VL aa	DIVMTQSPLSLPVTPGEPASISC <b>RSSQSLLHSNGYNYLD</b> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQALQIPNT</u> FG QGTKVEIKRT	123
5E8_VL_CDR1	RSSQSLLHSNGYNYLD	59
5E8_VL_CDR2	LGSNRAS	60
5E8_VL_CDR3	MQALQIPNT	236
12A4 VH aa	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYAMS</u> WVRQAPGKGLEWVS <u>AIS</u> GSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYAYALD YWGQGTLVTVSSAS	124
12A4_VH_CDR1	SYAMS	79
12A4_VH_CDR2	AISGSGGSTYYADSVKG	80
12A4_VH_CDR3	YAYALDY	237
12A4 VL aa	EIVLTQSPGTLSLSPGERATLSC <b>RASQSVSSSYLA</b> WYQQKPGQAPRLLIY <u>GA</u> <u>SSRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHGSSSTFGQGTKV EIKRT	125
12A4_VL_CDR1	RASQSVSSSYLA	52
12A4_VL_CDR2	GASSRAT	53

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Name	Sequence	Seq ID	No
12A4_VL_CDR3	QQHGSSST	238	
7A3 VH aa	$\label{eq:constraint} \begin{array}{l} \mathbb{Q} \mathbb{V} \mathbb{Q} \mathbb{L} \mathbb{V} \mathbb{Q} \mathbb{Q} \mathbb{Q} \mathbb{G} \mathbb{Q} \mathbb{Q} \mathbb{G} \mathbb{Q} \mathbb{G} \mathbb{Q} \mathbb{G} \mathbb{G} \mathbb{G} \mathbb{G} \mathbb{G} \mathbb{G} \mathbb{G} G$	126	
7A3_VH_CDR1	SYYMH	8	
7A3_VH_CDR2	IINPSGGSTSYAQKFQG	9	
7A3_VH_CDR3	GDFSAGRLMDY	239	
7A3 VL aa	DIVMTQSPLSLPVTPGEPASISC <b>RSSQSLLHSNGYNYLD</b> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQALQTPPIT</u> F GQGTKVEIKRT	127	
7A3_VL_CDR1	RSSQSLLHSNGYNYLD	59	
7A3_VL_CDR2	LGSNRAS	60	
7A3_VL_CDR3	MQALQTPPIT	240	
6E10 VH aa	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <b>SYYMH</b> WVRQAPGQGLEWMG <u>IIN</u> PSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGDYNAF DYWGHGTLVTVSSAS	128	
6E10_VH_CDR1	SYYMH	8	
6E10_VH_CDR2	IINPSGGSTSYAQKFQG	9	
6E10_VH_CDR3	GDYNAFDY	241	
6E10 VL aa	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQAWHSPT</u> FGQ GTKVEIKRT	129	
6E10_VL_CDR1	RSSQSLLHSNGYNYLD	59	
6E10_VL_CDR2	LGSNRAS	60	
6E10_VL_CDR3	MQAWHSPT	242	
12F9 VH aa	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <b>SYYMH</b> WVRQAPGQGLEWMG <u>IIN</u> PSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGATYTM DYWGQGTLVTVSSAS	130	
12F9_VH_CDR1	SYYMH	8	
12F9_VH_CDR2	IINPSGGSTSYAQKFQG	9	
12F9_VH_CDR3	GATYTMDY	243	
12F9 VL aa	DIVMTQSPLSLPVTPGEPASISC <b>RSSQSLLHSNGYNYLD</b> WYLQKPGQSPQLL IY <mark>LGSNRAS</mark> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQALQTPIT</u> FG QGTKVEIKRT	131	
12F9_VL_CDR1	RSSQSLLHSNGYNYLD	59	
12F9_VL_CDR2	LGSNRAS	60	
12F9_VL_CDR3	MQALQTPIT	244	

10) 9D11 Glycosite Variants: Variable Light Chain of Exemplary Embodiments (CDRs Underlined)

Variant	Sequence	Seq ID	No
N95S	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQASIM<b>S</b>RT</u> FG QGTKVEIK	132	

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Variant	Sequence	Seq ID No
12F9_VL_CDR2	LGSNRAS	60
12F9_VL_CDR3	MQASIMSRT	63
N95Q	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQASIMQRT</u> FG QGTKVEIK	133
N95Q_VL_CDR1	RSSQSLLHSNGYNYLD	59
N95Q_VL_CDR2	LGSNRAS	60
N95Q_VL_CDR3	MQASIMQRT	65
T97A	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQASIMNR<b>A</b></u> FG QGTKVEIK	134
T97A_VL_CDR1	RSSQSLLHSNGYNYLD	59
T97A_VL_CDR2	LGSNRAS	60
T97A_VL_CDR3	MQASIMNRA	67
T97N	DIVMTQSPLSLPVTPGEPASISC <u>RSSQSLLHSNGYNYLD</u> WYLQKPGQSPQLL IY <u>LGSNRAS</u> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <u>MQASIMNR<b>N</b></u> FG QGTKVEIK	135
T97N_VL_CDR1	RSSQSLLHSNGYNYLD	59
T97N_VL_CDR2	LGSNRAS	60
T97N_VL_CDR3	MQASIMNRN	69

### 11) Deamination Variants

Variant	Sequence	Seq ID No
16D5 VH_D52dE	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIK SKTEGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPWEW SWYDYWGQGTLVTVSS	248
16D5 VH_D52dQ	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIK SKTQGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPWEW SWYDYWGQGTLVTVSS	249
CD3_VH N100A	$\label{eq:scalar} \begin{split} & \texttt{EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIR} \\ & \texttt{SKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNF} \\ & \texttt{GASYVSWFAYWGQGTLVTVSS} \end{split}$	250
CD3_VH S100aA	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIR SKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNF GN <b>A</b> YVSWFAYWGQGTLVTVSS	251
16D5 [VHCH1]- CD3[VHCH1- N100A]- Fcknob_PGLALA	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIK SKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPWEW SWYDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYPPEP VTVSMNSGALTSGVHTPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASG FTFSTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYYADSVKGRFTISRDDSK NTLYLQMNSLRAEDTAVYYCVRHGNFGASYVSWFAYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVHKPSNTKVDKKVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGA PIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	252
16D5- Fchole- PGLALA	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIK SKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPWEW SWYDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNKK PSNTKVDKKVEFKSCDKTHTCPPCPAPEAAGGPSVFLFPFKKDTLMISRTP	253

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Variant	Sequence	Seq ID No
	EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVCTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVD KSRWQQGNVFSCSVMHEALHNRFTQKSLSLSPGK	
CD3-CLC	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAFRGLIGG TNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGT KLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKT VAPTECS	254
16D5 [VHCH1]- CD3[VHCH1- S100aA]- Fcknob_PGLALA	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIK SKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPWEW SWYDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDGGGGSGG GGSEVQLLESGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVS RIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRH GNFGNAYVSWFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPP CRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	255
9D11 [VHCH1]- CD3[VHCL- N100A]- Fcknob_PGLALA	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIIN PSGGPTSYAQKPQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGDFAWL DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFFF STYAMMWVRQAPGKGLEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTL YLQMNSLRAEDTAVYYCVRHGNFGASYVSWFAYWGQGTLVTVSSASVAAPSV FIFPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALG APIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	256
9D11- Fchole	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIIN PSGGPTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGDFAWL DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	257
9D11_LC [N95Q]	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLL IYLGSNRASGYPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQASIMQRTFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	258
CD3_VLCH1	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAFRGLIGG TNKRAPGTPARPSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGT KLTVLSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSC	259
9D11 [VHCH1]- CD3[VHCH1- S100aA]- Fcknob_PGLALA	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIIN PSGGPTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGDFAWL DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYPPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTF STYAMNWRQAPGKGLEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTL YLQMNSLRAEDTAVYYCVRHGNFGNAYVSWFAYWGQGTLVTVSSASVAAPSV FIFPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECDKTHT VVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALG	260

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Variant	Sequence	Seq ID No
	APIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	

## 12) Mov19 Based FolR1 TCBs of Exemplary Embodiments (CDRs Underlined)

Name	Sequence	Seq ID	No
pETR11646 Mov19 VH-CH1- Fchole PG/LALA	QVQLQQSGAELVKPGASVKISCKASGYSFTGYFMNWVKQSHGKSLEWIGRIH PYDGDTFYNQNFKDKATLTVDKSSNTAHMELLSLTSEDFAVYYCTRYDGSRA MDYWGQGTTVTVSSASTKGPSVPPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	136	
pETR11647 Mov19 VH-CH1- CD3 VH- CL- Fcknob PG/LALA	QVQLQQSGAELVKPGASVKISCKASGYSFTGYFMNWVKQSHGKSLEWIGRIH PYDGDTFYNQNFKDKATLTVDKSSNTAHMELLSITSEDFAVYYCTRYDGSRA MDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGYHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDGGGSGGGSGGGSVQVVSSGGLVQPKGSLKLSCAASGFT FNTYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDSQSI LYLQMNNLKTEDTAMYYCVRHGNFGNSVVSWFAYWGQGTLVTVSASVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECDKTH TCPPCPAPEAAGGPSVFLFPPKPKDIMISRTFEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIETISKARGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQGNVFSCSVMHEAL HNHYTQKSLSLSPGK	137	
pETR11644 Mov19 LC	$\label{eq:constraint} \begin{split} DIELTQSPASLAVSLGQRAIISC \\ & \textbf{KASQSVSFAGTSLMH} WYHQKPGQQPKLLI \\ Y \\ & \textbf{RASNLEA} GVPTRFSGSGSKTDFTLNIHPVEEEDAATYYCQQSREYPYTFGG \\ & GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN \\ & ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP \\ & VTKSFNRGEC \end{split}$	138	
Hu IgG1 Fc	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK	245	

13) Additional FolR1 TCBs with Intermediate Affinity <sup>45</sup> Binders (CDRs According to Kabat, Underlined)

Name	Sequence	Seq ID No
16D5 variant W96Y/D52E VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFS <u>NAWMS</u> WVRQAPGKGLEWV G <u>RIKSKTEGGTTDYAAPVKG</u> RFTISRDDSKNTLYLQMNSLKTEDTAVY YCTT <u>PYEWSWYDY</u> WGQGTLVTVSS	401
W96Y/D52E_VH CDR1	NAWMS	16
W96Y/D52E_VH CDR2	RIKSKTEGGTTDYAAPVKG	402
W96Y/D52E_VH CDR3	PYEWSWYDY	400
16D5 variant W96Y/D52E VL	QAVVTQEPSLTVSPGGTVTLTC <u>GSSTGAVTTSNYAN</u> WVQE KPGQAFRGLIG <u>GTNKRAP</u> GTPARFSGSLLGGKAALTLSGA QPEDEAEYYC <u>ALWYSNLWV</u> FGGGTKLTVL	31

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Name	Sequence	Seq ID	No
W96Y/D52E_CD3- VHCH1_Fc- knob_PGLALA pETR14945	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWV GRIKSKTEGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTPYEWSWVDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDGGGGSGGGGSEVQLLE SGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIRSK YNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHG NFGNSYVSWFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSNNSGALTSGVHTPPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKRNWYDGVEVHN AKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEK TISKAKQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK	403	
W96Y/D52E_Fc- hole_PGLALA_HYRF pETR14946	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWV GRIKSKTEGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTPYEWSWYDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH EALHNRFTQKSLSLSPGK	404	
14B1 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYAMS</u> WVRQAPGKGLEWV S <u>AISGSGGSTYYADSVKG</u> RFTISRDNSKNTLYLQMNSLRAEDTAVYYC AR <u>GDYRYRYFDY</u> WGQGTLVTVSS	405	
14B1 VL	SSELTQDPAVSVALGQTVRITC <u>QGDSLRSYYAS</u> WYQQKPGQAPVLVIY <u>GKNNRPB</u> GIPDRFSGSSSGNTASLTITGAQAEDEADYYC <u>NSRESPPTG</u> LVVFGGGTKLTVL	406	
14B1[EE]_CD3 [VLCH1]_Fc- knob_PGLALA pETR14976	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWV SAISGSGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARGDYRYRYPDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVEDYPPEPVTVSWNSGALTSGVHTPPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDEKVEPKSCDGGGGGGGGGGQAVVTQE PSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAFRGLIGGTNK RAPGTPARFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGG TKLTVLSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVY TLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK	407	
14B1[EE]_Fc- hole_PGLALA pETR14977	EVQLLESGGGLVQPGGSLRLSCAASGPTFSSYAMSWVRQAPGKGLEWV SAISGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARGDYRYRYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVEDYFPEPVTVSNNSGALTSGVHTPPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDEKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPFKPKDTLMISRTPEVTCVVVDVSHEDPEVKRNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEK TISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK	408	
14B1 LC [KK] Constant lambda pETR14979	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRESPPTG LVVFGGGTKLTVLGQPKAAPSVTLFPPSSKKLQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	409	
9C7 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFT <u>SYYMH</u> WVRQAPGQGLEWM GI <b>INPSGGSTSYAQKFQG</b> RVTMTRDTSTSTVYMELSSLRSEDTAVYYC AR <u>GDWSYYMDY</u> WGQGTLVTVSS	410	
9C7 VL	DIVMTQSPLSLPVTPGEPASISC <b>RSSQSLLHSNGYNYLD</b> WYLQKPGQS PQLLIY <b>LGSNRAS</b> GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC <b>MQA</b> R <b>QTPT</b> FGOGTKVEIK	411	

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Name	Sequence	Seq ID No
9C7[EE]_CD3 [VLCH1]_FC- knob_PGLALA pETR14974	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC ARGDWSYYMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVEDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDEKVEPKSCDGGGGSGGGGQAVVTQEP SLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAFRGLIGGTNKR APGTPARFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGT KLTVLSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYT LPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K	412
9C7[EE]_FC- hole_PGLALA pETR14975	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC ARGDWSYYMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVEDYPPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDEKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK	413
9C7 LC [RK] pETR14980	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQA RQTPTFGQGTKVEIKRTVAAPSVFIFPPSDRKLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC	414

## 14) Antigen Sequences

Antigen	Sequence	Seq ID No
hu FolR1	MAQRMTTQLLLLLVWVAVVGEAQTRIAWARTELLNVCMNAKHHKEKPGPEDKL HEQCRPWRKNACCSTNTSQEAHKDVSYLYRPNWNHCGEMAPACKRHFIQDTCL YECSPNLGPWIQQVDQSWRKERVLNVPLCKEDCEQWWEDCRTSYTCKSNWHKG WNWTSGFNKCAVGAACQPFHFYFPTPTVLCNEIWTHSYKVSNYSRGSGRCIQM WFDPAQGNPNEEVARFYAAAMSGAGPWAAWPFLLSLALMLLWLLS	139
huFolR1 ECD- AcTev- Fcknob- Avi tag	RIAWARTELLNVCMNAKHHKEKPGPEDKLHEQCRPWRKNACCSTNTSQEAHKD VSYLYRFNWNHCGEMAPACKRHFIQDTCLYECSPNLGPWIQQVDQSWRKERVL NVPLCKEDCEQWWEDCRTSYTCKSNWHKGWNWTSGFNKCAVGAACQPFHFYFP TPTVLCNEIWTHSYKVSNYSRGSGRCIQMWFDPAQCNPNEEVARFYAAAMVD <u>E</u> QLYFQGGSPKSADKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWVDGVEVHNAKTKPREQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGKSGGLNDIFEAQKIEWHE	140
Fchole	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAV EWESNGQPENNYKTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPGK	141
mu FolR1	MAHLMTVQLLLLVMWMAECAQSRATRARTELLNVCMDAKHHKEKPGPEDNLHD QCSPWKTNSCCSTNTSQEAHKDISYLYRFMWNHCGTMTSECKRHFIQDTCLYE CSPNLGPWIQQVDQSWRKERILDVPLCKEDCQQWWEDCQSSFTCKSNWHKGWN WSSGHNECPVGASCHPFTFYFPTSAALCEEIWSHSYKLSNYSRGSGRCIQMWF DPAQGNPNEEVARFYAEAMSGAGLHGTWPLLCSLSLVLLWVIS	142
mu FolR1 ECD- AcTev- Fcknob- Avitag	TRARTELLNVCMDAKHHKEKPGPEDNLHDQCSPWKTNSCCSTNTSQEAHKDIS YLYRFNWNHCGTMTSECKRHFIQDTCLYECSPNLGPWIQQVDQSWRKERILDV PLCKEDCQQWWEDCQSSFTCKSNWHKGWNWSSGHNECPVGASCHPFTFYFFTS AALCEEIWSHSYKLSNYSRGSGRCIQMWFDPAQGNPNEEVARFYAEAMVDEQL <u>YFQG</u> GSPKSADKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQGNV PSCSVMUPALWNYVSISIACBGCCONDIFPAOKIEWUF	143

Antigen	Sequence	Seq ID No
cy FolR1	MAQRMTTQLLLLLVWVAVVGEAQTRTARARTELLNVCMNAKHHKEKPGPEDKL HEQCRPWKKNACCSTNTSQEAHKDVSYLYRFNWNHCGEMAPACKRHFIQDTCL YECSPNLGPWIQQVDQSWRKERVLNVPLCKEDCERWWEDCRTSYTCKSNWHKG WNWTSGFNKCPVGAACQPFHFYFPTPTVLCNEIWTYSYKVSNYSRGSGRCIQM WFDPAQGNPNEEVARFYAAAMSGAGPWAAWPLLLSLALTLLWLLS	144
cy FolR1 ECD- AcTev- Fcknob- Avi tag	RTARARTELLNVCMNAKHHKEKPGPEDKLHEQCRPWKKNACCSTNTSQEAHKD VSYLYRFNWNHCGEMAPACKRHFIQDTCLYECSPNLGPWIQQVDQSWRKERVL NVPLCKEDCEQWWEDCRTSYTCKSNWHKGWNWTSGFNKCPVGAACQPFHFYFP TPTVLCNEIWTYSYKVSNYSRGSGRCIQMWFDPAQGNPNEEVARFYAAAMVD <u>E</u> <u>QLYFQG</u> GSPKSADKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQVNSTYRVVSVLTVLHQDWL MGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWC LVKGFYPSDIAVEWSNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGKSGGLNDIFEAQKIEWHE	145
hu FolR2	MVWKWMPLLLLLVCVATMCSAQDRTDLLNVCMDAKHHKTKPGPEDKLHDQCSP WKKNACCTASTSQELHKDTSRLYNFNWDHCGKMEPACKRHFIQDTCLYECSPN LGPWIQQVNQSWRKERFLDVPLCKEDCQRWWEDCHTSHTCKSNWHRGWDWTSG VNKCPAGALCRTFESYFPTPAALCEGLWSHSYKVSNYSRGSGRCIQMWFDSAQ GNPNEEVARFYAAAMHVNAGEMLHGTGGLLLSLALMLQLWLLG	146
hu FolR2 ECD- AcTev- Fcknob- Avi tag	TMCSAQDRTDLLNVCMDAKHHKTKPGPEDKLHDQCSPWKKNACCTASTSQELH KDTSRLYNFNWDHCGKMEPACKRHFIQDTCLYECSPNLGPWIQQVNQSWRKER FLDVPLCKEDCQRWWEDCHTSHTCKSNWHRGWDWTSGVNKCPAGALCRTFESY FPTPAALCEGLWSHSYKVSNYSRGSGRCIQMWFDSAQGNPNEEVARFYAAAMH VVD <u>EQLYFQG</u> GSPKSADKTHTCPPCPAPELLGBPSVFLFPPKPKDTLMISRTP EVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQV SLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSPFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGLNDIFEAQKIEWHE	147
hu FolR3	MAWQMMQLLLLALVTAAGSAQPRSARARTDLLNVCMNAKHHKTQPSPEDELYG QCSPWKKNACCTASTSQELHKDTSRLYNFNWDHCGKMEPTCKRHFIQDSCLYE CSPNLGPWIRQVNQSWRKERILNVPLCKEDCERWWEDCRTSYTCKSNWHKGWN WTSGINECPAGALCSTFESYFPTPAALCEGLWSHSFKVSNYSRGSGRCIQMWF DSAQGNPNEEVAKFYAAAMNAGAPSRGIIDS	148
hu FolR3 ECD- AcTev- Fcknob- Avi tag	SARARTDLLNVCMNAKHHKTQPSPEDELYGQCSPWKKNACCTASTSQELHKDT SRLYMPNWDHCGKMEPTCKRHFIQDSCLYECSPNLGPWIRQVNQSWRKERILN VPLCKEDCERWWEDCRTSYTCKSNWHKGWNWTSGINECPAGALCSTFESYPPT PAALCEGLWSHSFKVSNYSRGSGRCIQMWFDSAQGNPNEEVAKFYAAAMNAGA PSRGIIDSVDEQLYFQGGSPKSADKTHTCPPCPAPELLGGPSVFLFPPKPLDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVNNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRD ELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGLNDIFEAQKIEW HE	149
hu CD3€	MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVILTCPQYP GSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRGSKPE DANFYLYLRARVCENCMEMDVMSVATIVIVDICITGGLLLLVYYWSKNRKAKA KPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLYSGLNQRRI	150

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Description	Sequence	Seq ID No
6A3 CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTGTCTGAAGATACTGCA GTGTACTACTGTGCACGCAACTACCGCTGGTGTTACTCCGTTCG ACTATTGGGGTCAAGGCACCCCTGGTAACGGTTTCTTCT		151
15A1	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTGAAGATACTGCA	152

## 195

## 196

Description	Sequence	Seq ID No
	GTGTACTACTGTGCACGCAACTACTACATCGGTGTTGTTACTTTCG ACTATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCT	
18D3	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCGGGCCAGGGTCTGGAA TGGATGGCCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCGCTCACGATGACCCGGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCGTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCAACTACTACACTGGTGGTTCTTCTGCTT TCGACTATTGGGGTCAAGGCACCTCGTAACGGTTTCTTCT	153
19E5	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG NTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCGGGCCAGGGTCTGGAA TGGATGGCCATCATTAACCCAAGCGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCGCCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCGTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGGGTGAATGGCGTCGTTACACTTCTTCG ACTATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCT	154
19A4	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCGGGCCAGGGTCTGGAA TGGATGGCCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCGCCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCGTGGCTTCTGAAGATACTGCA GTGTACTACTGTGCACGGGTGGTTGGATCCGTTGGGAACATTTCG ACTATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCT	155
15H7	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCGCCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCGTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCAACTACTACCTGTTCTCTACTTCTTCG ACTATTGGGGTCAAGGCACCTCGTAACGGTTTCTTCT	156
1586	CAGGTGCAATTGGTTCAATCTGGTGCTGAGGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCGGGCCAGGGTCTGGAA TGGATGGCCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCAACTACTACATCGGTATCGTTCCGTTCG ACTATTGGGGTCAAGGCACCTCGTAACGGTTTCTTCT	157
16D5	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGAGCTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAG TGGGTTGGTCGTATCAAGTCTAAAACTGACGGTGGCACCACGAAT ACGCGGCTCCAGTTAAAGGTCGTTTTACCATTTCCCGCGACGATAG CAAAAACACTCTGTATCTGCAGATGAACTCTCTGAAAACTGAAGAC ACCGCAGTCTACTGTACTG	158
15E12	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCNGCGTCTGAGCTGCGCGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGAGCTGGGTTCGCCAGCCCCGGCCAAGGCCTCGAG TGGGTTGGTCGTATCAAGTCTAAAACTGACGGTGGCACCACGAGAT ACGCGGCTCCAGTTAAAGGTCGTTTTACCATTTCCCGCGACGAAG CAAAACACTCTGTATCTGCAGATGAACTCTCTGAAAACCGAAGAC ACCGCAGTCTACTGTACTG	159
21D1	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCAACTACTACGTTGGTGTTTCTCCCGTTCG ACTATTGGGGTCAAGGCACCTCGTAACGGTTTCTTCT	160
16F12	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAACCGGGCG NTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC	161

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Description	Sequence	Seq ID No
	CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCNTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCAACTTCACTGTTCTGCGTGTTCCGTTCG ACTATTGGGGTCAAGGCACCTCGTAACGGTTTCTTCT	
21A5	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGAGCTGGGTTCGCCAGCCCCGGCCAAGGCCTCGAG TGGGTTGGTCGTATCAAGTCTAAAACTGACGGTGGCACACGGATT ACGCGGCTCCAGTTAAAGTCGTTTTACCATTTCCCGGACGATAG CAAAACACTCTGTATCTGCAGATGAACTCTCTGAAAACTGAAGAC ACCGCAGTCTACTGTACTG	162
21G8	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGAGCTGGGTTCGCCAGGCCCCGGCAAAGGCCTCGAG TGGGTTGGTCGTATCAAGTCTAAAACTGACGGTGGCACCACGGAT ACGCGGCTCCAGTTAAAGTCGTTTTACCATTTCCCGCGACGATAG CAAAAACACTCTGTATCTGCAGATGAACTCTCTGAAAACCGAAGAC ACCGCAGTCTACTACTGTACTACCCTTGGGAATGGGCTTACTTCG ATTATTGGGGCCAGGGCACGCTGGTTACGGTGTCTTCC	163
19H3	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCGTGGCTTCTGAAGATACTGCA GTGTACTACTGTGCACGACTGGTTGGTCTCGTTGGGGTTACATGG ACTATTGGGGCCAAGGCACCCTCGTAACGGTTTCTTCT	164
20G6	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACCGC AGAAATTCCAGGGTCGCGCCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCGTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGGGTGAATGGATCCGTTACTACCATTTCG ACTATTGGGGTCAAGGCACCCTCGTAACGGTTTCTT	165
20H7	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGGC AGAAATTCCAGGGTCGCGTCCAGCCGTGGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGGGTTCTGAAGATACTGCA GTGTACTACTGGGCCCGGTGGTTGGTACCGTTGGGGTTACATGG ACTATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCT	166
11F8_VH	CAGGTGCAATTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGT CCTCGGTGAAGGTCTCCTGCAAGGCCTCCGGAGGCACATTCAGCAG CTACGCTATAAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTCGAG TGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTACGCAC AGAAGTTCCAGGGCAGGG	167
11F8_VL	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAG GAGACCGTGTCACCATCACTTGCCGTGCCAGTCAGAGTATTAGTAG CTGGTTGGCCTGGTATCAGCAGAAACCCAGGGAAAGCCCCTAAGCTC CTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCACGTT TCAGCGGCAGTGGATCCGGGACAGAATTCACTCTCACCATCAGCAG CTTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGTATACC AGCCCACCAACGTTTGGCCAGGGCACCAAAGTCGAGATCAAG	168
36F2_VH	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAQCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTGGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCATGACACTAGCACCTC TACCGTTTATATGAGGCTGTCCAGCCTGCGTTCCGAGAATACTGCA GTGTACTGTGGCACGCTCTTTCTTCACTGGTTTCCATCGGACT ATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCT	169

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## 200

Description	Sequence	Seq ID No
36F2_VL	GAAATCGTGTTAACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCACCCTGTCTTTGCAGGGCCAGGCAGGCTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGGAGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGATCCGGGACAGACTTCACTCTCACCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT ACCAACGAACATTATTATACGTTCGGCCAGGGGACCAAAGTGGAAA TCAAA	170
9D11_VH	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCGTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCCCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCGTGACTTCGCTTGGCTGGACTATTGGG GTCAAGGCACCCTCGTAACGGTTTCTTCT	171
9D11_VL	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAG GCGAACCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCA CTCCAACGGCTACAACTATCTCGATTGGTACCTGCAAAAACCGGGT CAGAGCCTCAGCTGCTGATCTACCTGGGCTCTAACCGGGCTTTCCG GTGTACCGGACCGTTTCAGCGGCCTCTGGATCCGGCACTGCACGATTTCAC GTTGAAAATCAGCCGTGTGAAGCAGAAGACGTGGGCGTTTATTAC TGTATGCAGGCAAGCATTATGAACCGGACTTTTGGTCAAGGCACCA AGGTCGAAATTAAA	172
9D11_VL N95S	GATATTGTTATGACTCAATCTCCACTGTCTCGCCGGTGACTCCAG GCGAACCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCA CTCCAACGGCTACAACTATCTCGATTGGTACCTGCAAAAACCGGGT CAGAGCCTCAGCTGCTGATCTACCTGGGCTCTAACCGGGCTTCCG GTGTACCGGACCGTTTCAGCGGCCTCTGGATCCGGCACTGCA GTTGAAAATCAGCCGTGTGAAGCAGAAGACGTGGGGCGTTTATTAC TGTATGCAGGCAAGCATTATGAGCCGGACTTTTGGTCAAGGCACCA AGGTCGAAATTAAA	173
9D11_VL N95Q	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAG GCGAACCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCA CTCCAACGGCTACAACTATCTCGATTGGTACCTGCAAAAACCGGGT CAGAGCCTCAGCTGCTGATCTACCTGGGCTCTAACCGGCATTCCG GTGTACCGGACCGTTTCAGCGGCCTCGGATCCGGCACCGATTTCAC GTTGAAAATCAGCCGTGTGAAGCAGAAGACGTGGGCGTTTATTAC TGTATGCAGGCAAGCATTATGCAGCGGACTTTTGGTCAAGGCACCA AGGTCGAAATTAAA	174
9D11_VL T97A	GATATTGTTATGACTCAATCTCCACTGTCTCGCCGGTGACTCCAG GCGAACCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCA CTCCAACGGCTACAACTATCTCGATTGGTACCTGCAAAAACCGGGT CAGAGCCCTCAGCTGCTGATCTACCTGGGCTCTAACCGCGCTTCCG GTGTACCGGACCGTTTCAGCGCCTCTGGATCCGGCACTGCATTTCAC GTTGAAAATCAGCCGTGTTGAAGCAGAAGACGTGGGCGTTTATTAC TGTATGCAGGCAAGCATTATGAACCGGGCTTTTGGTCAAGGCACCA AGGTCGAAATTAAA	175
9D11_VL T97N	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAG GCGAACCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCA CTCCAACGGCTACAACTATCTCGATTGGTACCTGCAAAAACCGGGT CAGAGCCCTCAGCTGCTGATCTACCTGGGCTCTAACCGCGCTTCCG GTGTACCGGACCGTTTCAGCGCCTCTGGATCCGGCACTGCAGTTTCAC GTTGAAAATCAGCCGTGTGAAGCAGAAGACGTGGGCGTTTATTAC TGTATGCAGGCAAGCATTATGAACCGGAATTTTGGTCAAGGCACCA AGGTCGAAATTAAA	176
5D9_VH	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCTCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTGAAGATACTGCA GTGTACTACTGTGCACGCTCTTACATCGACATGGACTATTGGGGTC AAGGCACCCTCGTAACGGTTTCTTCT	177
5D9_VL	GAAATCGTGTTAACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTTTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGGAGCATCCAGCAGGGCCACTGGCATCCCAGACA	178
201

# 202

Description	Sequence	Seq ID No
	GGTTCAGTGGCAGTGGATCCGGGACAGACTTCACTCTCACCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGGAT AACTGGAGCCCAACGTTCGGCCAGGGGACCAAAGTGGAAATCAAA	
6B6_VH	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGCATCATTAACCCAAGCGTGGCTCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGTGACACTAGCACCTC TACCGTTTATATGGAGCTGTCCAGCCTGGCTTCTGAAGATACTGCA GTGTACTACTGTGCACGCTTTCTGACATGGACTATTGGGGTC AAGGCACCCTCGTAACGGTTTCTTCT	179
6B6_VL	GAAATCGTGTTAACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTTTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACCTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGGAGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGATCCGGGACAGACTTCACTCTCACCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGGAT ATTTGGAGCCCAACGTTCGGCCAGGGGACCAAAGTGGAAATCAAA	180
14E4_VH	GAGGTGCAATTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCCGGATTCACCTTTAGCAG TTATGCCATGAGCTGCGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCAG ACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAA CACGCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGACTCTTCTTACGTTGAATGGTACGCTT TCGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCGAGT	181
14E4_VL	GAAATCGTGTTAACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTTTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGGAGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGATCCGGGACAGACTCCACTCTCACCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGCCA ACCAGCAGCCCAATTACGTTCGGCCAGGGGACCAAAGTGGAAATCA AA	182
CD3 heavy chain (VHCH1)	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCT GGCGGATCTCTGAGACTGAGCTGTGCCGCCAGCGGCTTCACC TTCAGCACCTACGCCATGAACTGGGTGCCCCGGCAGGCCCTGGC AAAGGCCTGGAATGGGTGTCCCGGATCAGAAGCAAGTACAAC AACTACGCCGCCCTACACGCCGGACAGCGTGAAGGGCCGGTTC ACCATCAGCCGGGCGGACGACAGCAGCAGAGAGCCGTGTACTATGT GTGCGGCACGGCA	183
Crossed CD3 heavy chain (VHCK)	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCG GATCTCTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAC CTACGCCATGAACTGGGTGCGCGCGGGCCCTGGCAAAGGCCTGGAA TGGGTGTCCCGGATCAGAAGCAAGTACAACTACGCCACCTACT ACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCGGGCCGAGGAC GAAGAACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGAC ACCGCCGTGTACTATTGTGTGCGGCACGGCA	184

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### 204

Description	Sequence	Seq ID No
Mutagenesis primer GAB7734 N95Q	GCAGGCAAGCATTATGCAGCGGACTTTTGGTCAAGG	185
Mutagenesis primer GAB7735 N95S	CAGGCAAGCATTATGAGCCGGACTTTTGGTCAAGG	186
Mutagenesis primer GAB7736 T97A	CATTATGAACCGGGCTTTTGGTCAAGGCACCAAGGTC	187
Mutagenesis primer GAB7737 T97N	CATTATGAACCGGAATTTTGGTCAAGGCACCAAGGTC	188
VHCH1[16D5]_VHCH1 [CD3]_Fcknob_PGLALA pCON999 (Inverted TCB with 16D5 2 + 1: pCON999 + pCON993 + pETR13197)	GA&GTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGCGCCCGGGCAAAGGCCTCGAG TGGGTTGGTCGTATCAAGTCTAAAACTGACGGTGGCACCACGGATT ACGCGGCTCCAGTTAAAGGTCGTTTACCCATTTCCCCGCGACGATAG CAAAAACTCTGTATCTGCAGATGAACTCTCTGAAACTGAAGC ACCGCAGTCTACTGTATCTGCAGATGAACTCTCTGAAACTGAAGC ACCGCAGTCTACTGTATCTGCAGTGTACCGTGGTATCGGCACCAGCA AAGGGCCCTAGCGTGTCCCTCTGGCACCCCAGCAGCAGAGACAC AAGGGCCGTAACGTGTCCCTCTGGCACCCCAGCAGCAAGAGCACA AGCGGCGGAACAGCCGCCGTGGTGCAGGAGCACCCTAACAAGCGG CGTGCACACTTTCCCTGCCGTGCTGCAGAGCAGCCCTGACAAGCGG CGTGCACACTTTCCCTGCCGTGCTGCAGAGCAGCCCTGACAAGCGG CGTGCACACTTTCCCTGCCGTGCTGCAGAGCAGCCCTGACAAGCGG CGTGCACACTTTCCCTGCCGTGCTGCAGAGCAGCCCTGGCCACCAAG CCTACATCTGCAACGTGACCACAAGCCCAGCAGCACCCCAGA CCTACATCTGCAACGTGACCACAAGCCGGCGAGCAGCCCCGGA GGCGGAGGATCCGAGGTGCAGCTGCTGGAACGACACCAAAGTGG TGCAGCCTGGAATGGGGTCCCGGAACGGCGGCGAGCCGGA GGCGGAGGATCCGAGGTCCCGGACCGGGCAGGCCCCTGG CAGGCCAGGC	189
VHCH1[16D5]_Fchole_PGLALA_HYRF pCON983	CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA GAGGTGCAATTGGTTGAATCTGGTGGTGGTGTGGT	190

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Description	Sequence	Seq ID No
	CGTGCACACCTTCCCCGCCGTGCTGCAGAGTTCTGGCCTGTATAGC CTGAGCAGCGTGGTCACCGTGCCTTCTAGCAGCCTGGGCACCCAGA CCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGA CAAGAAGGTGGAGCCCAAGAGCTGCGACAAAACTCACACATGCCCA	
	CCGTGCCCAGCACCTGAAGCTGCAGGGGGACCGTCAGTCTTCCTCT	
	GGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTC	
	CAAAGCCGCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	
	CGTCCTCACCGTCCTCGACCAGGACTGGCTGAATGGCAAGGACTAC AAGTGCAAGGTCTCCAACAAAGCCCTCGGCGCCCCCATCGAGAAA CCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTGCAC	
	CCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTC TCGTGCGCAGTCAAAGGCTTCTATCCCAGCGACCAGGCCGCGGGGT	
	GGGAGAGCAATGGGCAGCCGGGGAACAACTACAAGACCACGCCTCC CGTGGTGGACTCCGACGGCTCCTTCTTCTCCTCGTGAGCAAGCTCACC GTGGACAAGACCAGGTGGCAGCGGGAACGTCTTCTCATGCTCCG	
	TGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTC CCTGTCTCCGGGTAAA	
D3_common Light	CAGGCCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCG GCACCGTGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCAC CACCAACTACCCCAACTGTGCCGCACCACACACCCCCTGACCACCCCCTGACCACCCCCTGACCACCCCCTGACCACCCCCTGACCACCCCCTGACCACCACCCCCCCC	191
DETR13197	AGAGAACTACCTAACTGGGTGCAGGAAAAGCCCCGGCCAGGCCTTC AGAGGACTGATCGGCGGCACCAACAAGAGAGCCCCCTGGCACCCCTG CCAGATTCAGCGGGTCTCTGCTGGGGGAAGGCCCGCCCTGACACT	
	GTCTGGCGCCCAGCAGAGATGAGGCCGAGTACTACTGCGCCCTG TGGTACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAGCTGACAG TCCTAGGTCAACCCAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCC	
	CAGCAGCGAGGAACTGCAGGCCAACAAGGCCACCCTGGTCTGCCTG ATCAGCGACTTCTACCCAGGCGCCGTGACCGTGGCCTGGAAGGCCG ACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAA	
	GCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACC CCCGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCAGGTGACCC	
	ACGAGGGCAGCACCGTGGAGAAAACCGTGGCCCCCACCGAGTGCAG C	
HCH1[CD3]_VHCH1 16D5]_Fcknob_PGLALA PETR13932	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCG GATCTCTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAC CTACGCCATGAACTGGGTGCGCCAGGCCCCTGGCAAAGGCCTGGAA	192
Classical CB with 6D5; 2 + 1:	TGGGTGTCCCGGATCAGAAGCAAGTACAACTACGCCACCTACT ACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCGGGACGACAG CAAGAACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGAC	
ETR13932 + CON983 + .FTP13197)	ACCGCCGTGTACTATTGTGTGCGGCACGGCAACTTCGGCAACAGCT ATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACCCTCGTGACCGT GTCATCTGCTAGCACAAAGCGCCCTAGCGTGTCCCCTTGGCCCCC	
BIRIS 1977	AGCAGCAAGAGCACAAGCGGGGGAACAGCGCCCTGGGCTGCCTCG TGAAGGACTACTTCCCCGAGCCCGTGACAGTGTCTTGGAACAGCGG	
	AGCCCTGACAAGCGGCGTGCACACCTTCCCTGCCGTGCTGCAGAGC AGCGGCCTGTACTCCCTGAGCAGCGTGGTCACCGTGCCTAGCAGCA GCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAG	
	CAACACCAAAGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGATGGC GGAGGAGGGTCCGGAGGCGGAGGATCCGAGGTGCAATTGGTTGG	
	CGCGGCTTCCGGATCACCTTCTCCAACGCGGTGGGTGGCGTCGGGT CGCCGGCCTCCGGATCACCTTCTCCAACGCGTGGGTGGCGTGGGTGG	
	CTAAAACTGACGGTGGCACCACGGATTACGCGGCTCCAGTTAAAGG TCGTTTTACCATTTCCCGCGACGATAGCAAAAACACTCTGTATCTG CAGATGAACTCTCTGAAAACTGAAGACACCGCAGTCTACTACTGTA	
	CTACCCCGTGGGAATGGTCTTGGTACGATTATTGGGGCCAGGGCAC GCTGGTTACGGTGTCTAGCGCTAGTACCAAGGCCCCAGCGTGTTC CCCTGGCGCACGCCACGC	
	TGGGCTGTCTGGTGAAGACTACTTCCCCGAGCCCGTGACCGTGTC TTGGAACTCTGGCGCCCTGACCAGCGGCGTGCACACCGTGTC	
	GTGCTGCAGAGCAGCGGCCTGTACTCCCTGTCCTCCGTGGTCACCG TGCCCTCTAGCTCCCTGGGAACACAGACATATATCTGTAATGTCAA	
	TCACAAGCCTTCCAACACCAAAGTCGATAAGAAAGTCGAGCCCAAG	
	AGCTGCGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAG CTGCAGGGGGGACCGTCAGTCTTCCTCTTCCCCCCCAAAACCCCAAGGA	
	CACCCTCATGATCTCCCCGGACCCCTGAGGTCACATGCGTGGTGGTG	
	GACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCAGGGGGGGG	
	GTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC	
	CAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCCAACA	
	GCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATGCCGGGAT	
	GAGCTGACCAAGAACCAGGTCAGCCTGTGGTGCCTGGTCAAAGGCT	

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Description	Sequence	Seq ID No
	GGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCCGGGTAAA	
VHCH1[CD3]_Fcknob_PGLALA pETR13719 (16D5 IgG format 1 + 1: pETR13719 + pCON983 + pETR13197)	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCG GATCTCTGAGACTGGGTGGCCCAGGGCCTCGCCAAGGCCTGGAA TGGGTGTCCCGGATCAGAAGCAAGTACAACAACTACGCCACCTACT ACGCCGACAGCGTGAAGGGCCGGTCACACACACCACGCGACGA CAAGAACACCCTGTACCGCGCGGGCAGGCCAGCGACGAGG CAAGAACACCCTGTACCGCGCGGGCAGGCCAGCGGCGAGGAC ACCGCCGTGTACTATTGTGTGCGGCCAGGGCAACGCCTCGGGGCCGAGGAC ACCGCCGTGTACTATTGTGTGCGGCCAGGGCAACGCCCTCGGGCCGAGGAC CTCTCCCAAGAGCACCTCTGGGGCCAGGGCACCCCTGGGCCGG TCAAGGACTACTTCCCCGAACGGGCCAGGGGCCCGGGCTGCCTGG CGCCTGACCAGGGGCGTGCACGGTGTCGTGGAACTCAGG CGCCTGACCAGGGGCGTGCACCGGTGTCCTGCGGCCGG CGCCTGACCAGGGGCGTGCACACCTTCCCGGCTGCCTGCGCC TCCCCCAAGACCAGCGGGGGCACACGTGCCTGCGACCCG CGCCCGGACCCAGGCGTGCCACCTTGCCAGGCGTGCCTCCAGCA GCTGGGCACCCAGACCTACACTTGCGAACGTGAACCCAGCG CAACACCAAGGTGGAACCTACATCTGGAACGTGCAAGGCCCAG CAACACCAAGGTGGAACACAAGTTGACCCAAGGCCACG GAACACCAAGGTGGAACACGTGCAAGGCGCGGGGAGC CGTCAGTCTTCCTCTCCCCCCAAAACCCAAGGCCACCGCAGGGGGAC CGTCAGTCTTCTCTCCCCCCAAAACCCAAGGACACCCTCATGAT CTCCCGGACCCCTGAGGTCACATGCGTGGAGGGAGGGAGG	193
<pre>Fc_hole_PGLALA_HYRF pETR10755 (16D5 Head- to-tail, 1 + 1: pCON999 + pETR10755 + pETR13197)</pre>	GACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGG GGGGACCGTCAGTCTTCCTCTCTCCCCCCAAAACCCAAGGACACCCT CATGATCTCCCGGACCCTGAGGTCACATGCGTGGTGGTGGACGGGG TGGAGGTGCATAATGCCAAGGTCACATGCGTGGTGGTGGACGGG TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAA CAGCACTGACGTGTGGTCAGCGTCCTCCCACCAGGAC TGGCTGAATGGCAAGGAGACAACCATCTCCAAAGCCAACAGAGCC CCCAGCCCCCATCGAGAAAACCATCTCCCAAAGCCAAAGGGCAGCC CCGAGACCACAGGTGGTGCACCTGCCCCCATCCCGGGATGAGCTG ACCAAGAACCAGGTCGGCAGCCCTGCCCCGTCCCGGGATGAGCCG CCCAGGACCACGGCCGTGGGAGTGGGAGAGCAATGGGCAGCCC CCGAGCACCACGGCCGTGGGAGTGGGAGAGCAATGGGCAGCCGGAGAA CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCGCCCTTC TTCCTCGTGAGCAAGCCCCCCCGTGCTGGACTCCGACGGCGCGCGGGGGGGG	194
VHCH1[9D11]_VHCL [CD3]_Fcknob_PGLALA pCON1057 (9D11 inverted format, 2 + 1: pCON1057 + pCON1057 + pCON1051 + pCON1063 + pETR12940)	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAAA	195

GCGGATCTCTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAG CACCTACGCCATGAACTGGGTGCGCCAGGCCCCTGGCAAAGGCCTGGAATGGGTGTCCCGGATCAGAAGCAAGTACAACAACTACGCCACCT ACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCGGGACGA CAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAG GACACCGCCGTGTACTATTGTGTGCGGCACGGCAACTTCGGCAACA GCTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACCCTCGTGAC CGTGTCAAGCGCTAGTGTGGCCGCTCCCTCCGTGTTTATCTTTCCC CCATCCGATGAACAGCTGAAAAGCGGCACCGCCTCCGTCGTGTGTC

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Description	Sequence	Seq ID No
	TGCTGAACAATTTTTACCCTAGGGAAGCTAAAGTGCAGTGGAAAGT GGATAACGCACTGCAGTCCGGCAACTCCCAGGAATCTGTGACAGAA CAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACAAC TGTCTAAGGCTGATTATGAGAAACACAAAAGTCTACGCCTGCGAAGT CACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGG GGAGAGTGTGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTG AAGCTGCTGGCGGCCCTTCTGTGTTCCTGTCCCCCCAAAGCCCAA GGACACCCTGATGATCAGCCGGACCCCCGAAGTGACTCCACGTGGTG GTGGATGTGTCCCACGAGGACCCTGAAGTGAAG	
9D11_Fchole_PGLALA_HYRF pCON1051	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCG CTTCCGTTAAAGTGAGCTGCAAGCATCCGGATACACCTTCACTTC CTATTACATGCACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAA TGGATGGGCATCATTAACCCAAGCGGTGGCCCTACCTCCTACGCGC AGAAATTCCAGGGTCGCGTCACGATGACCCGGTGCACACTAGCACCTC TACCGTTTTATATGGAGCTGTCCAGCTGGGTTGGCAAGAGATACTGCA GTGTACTACTGTGCACGGTGACTCGCTTGGCTGGACTATTGGG GTCAAGGCACCCTCGTAACGGTTTCTTCTGCTAGCACCAAGGGCCC CTCCGTGTTCCCCCTGGCCCCAGCAGCAAGAGCACCAAGGGCGC ACAACGCGTGTCGGCGCGGTGCAAGGACTACTTCCCCGAGCCCG GTGCACGCGTGCTGGAACAGCGGAGCCCTGGACTACTCCCCGAGCGCGG GTGGCCACGGTGCCTGGCAGAGCTCTGGCCTGGACACCCGAGCCCG GTGGTCACCGTGCTTCTAGCAGCCTGGACCACCGGGCTGCACAC GTGGTCACCGTGCTTCTGGCAGAGCTCGGCCAGCCCAAGAGGT GGACCCCAAGAGCTCCAGAGCCCTGGCCACCCAGCCCCA GCACCGGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGT GGACCCCAAGAGCTGCACAAACCCAAGGTGGACAAGAAGGT GGACCCCAAGAGCTGCACAAACCCACGTCCTCTCTCCCCCCAA AACCCAAGGCGCGCGGAGGGCCACAAGCCCTGAGGTCACATG CGTGGTGGTGGACGGCGTGAAGGCGCCAGAGGCCCTGAGGTCACATG CGTGGTGGTGGACGGCGTGGAGGTGCATAATGCCAAGGTCACATG CGTGGTGGTGGACGGCGTGGAGGTGCATAATGCCAAGCACCATCCCC GGGAGGAGCAGTACAACACCACGTACCGTGGGTCAAGTCCAC GGTCCTGCACCAGGGCGGCGGCGGCGCCCCATGGAGAAACCATCTCCA AAGCCAAAGGCCTCCGGCGCCCCATGGAGACAAAGCCGCC GGGAGGAGCAGTACAACACCACGCCCCCATGGAGAAAACCATCTCCA AAGCCAAAGGCCTCCCGGGAGCCCCCATGGAGGACAAAGGCACCCC GTCCCGACAAAGGCCCCCGAGAACCACGGTCGCCCCCA ATCCCGGGAGGACGCGCGGAGCACAAGGTCACCGCCCCGGCAGAACACCACCTCCCA AAGCCAAAGGCTCTCTTCTCCTGGAGCACCGCGCGGGAGGAGACAA ATGGGCAGCGGCGGGAGAGCACCACGGCCCCGTGGAGGGAG	196
9D11_LC pCON1063	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAG GCGAACCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCA CTCCAACGGCTACAACTATCTCGATTGGTACCTGGCAACAAAACCGGGT CAGAGCCTTCAGCTGGTGAACCTGGGCTCTAACCGGCGTTCCG GTGTACCGGACCGTTTCAGCGGCTCTGGATCCGGCACCGATTTCAC GTTGAAAATCAGCCGTGTTGAAGCAGAAGACGTGGGCGGTTTATTAC TGTATGCAGGCAAGCATTATGAACCGGACTTTGGTCAAGGCACCA AGGTCGAAATTAAACGTACGGTGGCTGCACCACTCTGTCTTCATCTT CCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCCAGAGAGCCCAAAGTACAGTGGA AGGTCGAAATAACTTCTATCCCAGAGAGCCCAAGTACAGTGGA AGGTGGAAAACGCACCTCCAATCGGATACTCCCAGGAGAGTGTCAC AGGTGGACAGCAAGCACCTACGGCTACAGCCCAGGCACCCTG ACGCTGGACAGCAAGGACGCCAAAGACCTCCAGCAGCACCTG ACGCTGGACAAGCAAGCACCTACAGCCCCAAAGAGCTTCAA CAGGGGAGAGGTGT	197
VLCH1[CD3] pETR12940	CAGGCCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCG GCACCGTGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCAC CAGCAACTACGCCAACTGGGTGCAGGAAAAGCCCGGCCAGGCCTTC AGAGGACTGATCGGCGGCCACCAACAAGAGAGGCCCCTGGCACCCTG CCAGATTCAGCGGATCTCTGCTGGGAGGAGAAAGGCCGCCCTGACACT GTCTGGCGCCCAGCAGAAGATGAGGCCGAGAGAAGGCCGCCCTGACACT TGGTACAGCACCTGTGGGGTGTTCGGCGGAGGCACCAAGCTGACAG TGCTGAGCAGCGCTTCCACCAAAGGCCCTTCCGTGTTTCCTCTGGC TCCTAGCTCCAACTCCACCTCTGGAGGCACCGCTGCTCTCGGATGC	198

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Description	Sequence	Seq ID No
	CTCGTGAAGGATTATTTTCCTGAGCCTGTGACAGTGTCCTGGAATA GCGGAGCACTGACCTCTGGAGTGCATACTTTCCCCGCTGTGCTGCA GTCCTCTGGACTGTACAGCCTGAGCAGCGTGGTGACAGTGCCCAGC AGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGC CCAGCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCTTGT	
VHCL[CD3]_Fcknob_PGLALA pETR13378 (9D11 CrossMab format, 1 + 1: pETR13378 + pCON1051 + pCON1063 + pETR12940)	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCG GATCTCTGAGACTGGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAC CTACGCCATGAACTGGGTGGCCAGCCCCTGGCAAAGGCCTGGAA TGGGTGTCCCGGATCAGAAGCAAGTACAACAACTACGCCACCTACT ACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCGGGACGACAG CAAGAACACCCTGTAACGGCCGGTTCACCATCAGCCGGGCCGAGGAC ACCGCCGTGTACTATGTGTGCGGCACGGCA	199
16D5 inverted 2 + 1 with N100A in CDR H3 pETR14096 (pETR14096 + pCON983 + pETR13197)	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGACGTGTGTCGCAGGCCCGGGCAAAGGCCTCGAG TGGGTTGGTCGTATCAAGTCTAAAACTGACGGTGGCACCACGGACGATT ACGCGCTCCTGTTATCTGCAGATGAACTCTCTGAAAACTGAAGAC ACCGCAGTCTACTACTGTACTG	200

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Description	Sequence
	TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC GGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCCTGTCTCCGGGTAAA
16D5 inverted 2 + 1 with 5100ch im	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGGACTGGGTTCGCCAGGCCCCGGGCAAAGGCCCCGGG
DUGAA IN CDR H3 DETR14097 (DETR14097 +	ACGCGGCTCCAGTTAAAGTCTAAAACTGACGGTGCCACCAGATT ACGCGGCTCCAGTTAAAGGTCGTTTTACCATTTCCCCGCGACGATAG CAAAAACACTCTGTATCTGCAGATGAACTCTCGAAAACTGAAGAC ACGCAGTCTACTACTGCTACTACCCCCGTGGGAATGGTCTTGGTAACG
CON983 + DETR13197)	ATTATTGGGGCCAGGGCACGCTGGTTACGGTGTCTTCCGCTAGCAC AAAGGGCCCTAGCGTGTTCCCTCTGGCCCCCAGCAGCAGAGAGCACA AGCGGCGGAACAGCCGCCCTGGGCTGCCTCGTGAAGGACTACTTCC
	CCGAGCCCGTGACAGTGTCTTGGAACAGCGGAGCCCTGACAAGCGG CGTGCACACTTTCCCTGCCGTGCTGCAGAGCAGCGGCCTGTACTCC CTGAGCAGCGTGGTCACCGTGCCTAGCAGCAGCCTGGGCACCCAGA CCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAAGTGGA
	CAAGAAGGTGGAGCCCAAGAGCTGTGATGGCGGAGGAGGGTCCGGA GGCGGAGGATCCGAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGG TGCAGCCTGGCGGATCTCTGAGACTGAGCTGTGCCCCCCAGCGGCTT
	CACCTTCAGCACCTACGCCATGAACTGGGTGCGCCAGGCCCCTGGC AAAGGCCTGGAATGGGTGTCCCGGATCAGAAGCAAGTACAACAACT ACGCCACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAG
	CCGGGACGACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTG CGGGCCGAGGACACCGCCGTGTACTATTGTGTGCGGCACGGCAACT TCGGCAACGCCTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCAC
	CCTCGTGACCGTGTCAAGCGCTAGTACCAAGGGCCCCAGCGTGTTC CCCCTGGCACCCAGCAGCAAGAGCACATCTGGCGGAACAGGCCGCTC TGGGCTGTCTGGTGAAAGACTACTTCCCCGAGCCCGTGACCGTGTC
	TTGGAACTCTGGCGCCCTGACCACCGCCGGCACACCTTTCCAGCC GTGCTGCAGAGCAGCGGCCTGTACTCCCTGTCCTCCGGGACCG TGCCCTCTAGCTCCCTGGGAACACAGACATATCTGTAATGTCAA
	AGCTGCGACAAAACTCACACATGCCCACCGTGCCCAGCACGAG CTGCGGGGGACCGTCACGTCTCCCCCCCCACAACCCCGAGA CTGCAGGGGGCCGTCACGTCTTCCCCCCCAAAACCCCAAGGA
	CACCCTCATGATCTCCCCGGACCCCTGAGGTCACATGCGTGGTGGTG GACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGGAGGAGCA
	GTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGGTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA AAGCCCTCGGCGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGG
	GCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATGCCGGGAT GAGCTGACCAAGAACCAGGTCAGCCTGTGGTGCCTGGTGAAGGCT TCTATCCCAGCGACATCGCCGTGGGAGGGGAG
	TCCTTCTTCTCTCACAGCAGCTCACCGTGGACAAGAGCAGGTGGC AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCCTGTCTCCCGGGTAAA
CD3 light chain fused	CAGGCCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCG GCACCCTGACCATGTGGCAGTTCTACAGGCGCCGTGACCAC
to CHI; Fc_PGLALA; pETR13862	CAGCAACTACGCCAACTGGGTGCAGGAAAAGGCCCCGGCCAGGCCTTC AGAGGACTGATCGGCGGCACCAACAAGAGAGCCCCTGGCCCCTG CCAGATTCAGCGGAGTCTCTGCTGGGAGGAAAGGCCGCCTGACACT
(Rappa- lambda antibody with	TGGTACAGCCAGCCAGGGGGTGTCGGGGGGGCCCAGGCCCTGG TGGTACAGCAGCGGTGGGGGTGTCGGCGGAGGCACCAAGCGGCGGG TGCTGAGCAGCGCTAGCACCCAGGGCCCATCGGCCCTGGCC ACCCCCCCCCAACGGCCCTCGGGCCCACGGCCCTGGGCCCC
light chain fused to CH1 + Fc PGLALA.	CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGCGTGGGAACT CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGGCGTGCCTACA GTCCTCAGGACTCTACTCCCCCAGCAGCGTGGTGACCGTGCCCTCC
VHs fused to kappa or lambda	AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGC CCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGA CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCTGCAGGG
constant chain pETR13859 + pETR13860 +	GGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA TGATCTCCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAG CCACGAAGACCCTGAGGTCAACTTGCAACTGGTACGTGGACGGCGTG
pETR13862)	GAGGTGCATAATGCCAAGACAAAGCCGGGGGGGGGGGGG
	GGCGCCCCCATCGAGAAAACCATCTCCCAAAGCCAAAGGGCAGCCCC

GAGAACCA CAGGTGTACACCCTGCCCCATCCCGGGATGAGCTGACCAAGAACC AGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACAT 202

Seq ID No

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# 216

Description	Sequence	Seq ID No
	CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACA GCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAG AAGAGCCTCTCCCTGTCTCCGGGTAAA	
16D5 VH fused to constant kappa chain; pETR13859	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCG GTTCCCTGCGTCTGAGCTGCGCGGGCTTCCGGATTCACCTTCTCCAA CGCGTGGATGAGCTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAG TGGGTTGGTCTATACAGTCTAAAACTGACGGTGGCACCACGGACGAT ACGCGGCTCCAGTAAAGGTCGTTTACCATTTCCCGCCGACGATAG CAAAACACTCTGTATCTGCCAGTGAACTCTCTGAAAACTGAAGAC ACCGCAGTCTACTACTGTCACATCTCCCGACGACGACGAC ACCGCAGTCTACTACTGTCACTTCCCACCTTCCGACAGACGACG GGCCGCCCCCCGCGTGTCACTCTCCCACCTTCCGACGACGACGACG AAGTCCGGCCAGGGCACGCTGGTACGGCCTGCTGAACAACTCTACC CCGCGAGGCCAAGGTCCAGTGGAAGGTGGACAACGCCCTGCCAGGC CGGCAACGCCAGGGCCAGTGGAAGGTGGACAACGCCCTGCCAGGC ACCTACTCCTGTCCTCCACCTGCCAGGACACCTCCCAGGACACC CGCCAAGCCAA	203
CD3 VH fused to constant lambda chain; pETR13860	GAAGTGCAGCTGCTGGAATCCGGCGGAGGACTGGTGCAGCCTGGCG GATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCAC CTACGCCATGAACTGGGTGCGACAGGCTCCTGGCAAGGGCCTGGAA TGGGTGTCCCGGATCAGATCA	204
VHCH1[36F2]_VHCL [CD3]_Fcknob_PGLALA pCON1056	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCC GTTAAAGTGAGCTGCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	246

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# 218

Description	Sequence	Seq ID No
	TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGGCTCTG CACAACCACTACACGCAGAAGAGCCTCTCCCCTGTCTCCCGGGTAAA	
36F2-Fc hole PGLALA pCON1050	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCC GTTAAAGTGAGCTCCAAAGCATCCGGATACACCTTCACTTCCTATTACATG CACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	247
36F2 LC pCON1062	AAGAGCCTCTCCCTGTCTCCGGGTAAA GAAATCGTGTTAACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAA AGAGCCACCCTCTTTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTA GCCTGGTACCAGCAGGAAACCTGGCCAGGCTCCCAGGCTGCAGCAGTGGATCC GGGACCAGCAGGGCCACTGGCATCCCAGACAGGTCCAGGCAGTGGATCC GGGACCAGCTTCACTCTCACCATCACCAGCAGACTGGAGCCTGGAGAGTTCAGC GTGTATTACTGTCAGCAGTATACCAACGAACATTATTATACGTTCGGCCAG GGGACCAAAGTGGAAATCAAACGTACGAGCTGCACCACTGTCTTCATC TTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGGC CTGCTGAATAACTTCTATCCCAGGAGAGGCCAAAGTACAGTGGAAGGGGGAT AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGGCAGGACAGC AAGGACACCAACAGCCTCAGCAGCACCCTGACGCAGGACAGAC TACGAGAACACCAAAGTCTACGCCCGGAAGTGCCACCATCANGGCCTGAGC	97
CD3 VLCH1 pETR12940	CAGGCCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCGCACC GTGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCACCAGCAACTAC GCCAACTGGGTGCAGGAAAAGCCCGGCCAGGCCTTCAGAGGACTGATCGGC GGCACCAACAAGAAGACCCCTGGCACCCCTGCCAGATTCAGCGGATCTCTG CTGGGAGGAAAAGGCCGCCTGGCACCTGTCGGCGCCAGCAGAAGATGAG GCCGAGTACTACTGCGCCCTGGGACACCTGTGGGGTGTTCGGCGGA GGCACCAAGCTGACAGTGCTGAGCACCTGTGGGGTGTCGGCGGA GGCACCAAGCTGACAGTGCTCAAGTCCACCACCTGTGGGTGTTCGGCGGA GGCACCAAGCTGACAGTGCTCAAGTCCACCTGTGGAGCACCGCTGCTCCTG GAATGCCTCGTGAAGGATTATTTCCCTGAGCCTGTGACAGTGTCCTGGAAT AGCGGAGCACTGACCTCTGGAGCGCTGCTGCAGCTGCTGCAGTCC TCTCGGCTGTACAGCCTGGAGCGCTGGTGACAGTGCCCAGCAGCACCCG GGCACCAGACCTACATCTGCAACGTGGACAGTGCCCAGCAGCAGCCCG GGCACCAGACCTACATCTGCAACGTGGAACACGCCGCCGCCAGCAACACCAAG GTGGACAAGAAGGTGGAACCCACAGCGCCAGCCAGCCCAGCAACACCAAG	198

Name	Sequence	Seq ID No
к53А	CAGACCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCGGCACC	205
nt	GTGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCACCAGCAACTAC	
	GCCAACTGGGTGCAGCAGAAGCCAGGCCAGGCTCCCAGAGGACTGATCGGC	
	GGCACCAACGCCAGAGCCCCTGGCACCCCTGCCAGATTCAGCGGATCTCTG	
	CTGGGAGGAAAGGCCGCCCTGACACTGTCTGGCGTGCAGCCTGAAGATGAG	
	GCCGAGTACTACTGCGCCCTGTGGTACAGCAACCTGTGGGTGTTCGGCGGA	
	GGCACCAAGCTGACAGTCCTA	
S93A	CAGACCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCGGCACC	206
nt	GTGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCACCAGCAACTAC	

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Name	Sequence	Seq	ID	No
	GCCAACTGGGTGCAGCAGAAGCCAGGCCAGGCTCCCAGAGGACTGATCGGC GGCACCAACAAGAGAGCCCCTGGCACCCTGCCAGATTCAGCGGATCTCTG CTGGGAAGAAAGGCCGCCCTGACACTGTCTGGCGTGCAGCCTGAAGATGAG GCCGAGTACTACTGCGCCCTGTGGTACGCCAACCTGTGGGTGTTCGGCGGA GGCACCAAGCTGACAGTCCTA			

10

Name	Sequence	Seq ID	N
S35H nt	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCT CTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAAGGCCTGGATG CACTGGGTGCGCCAGGCCCTGGAAAAGGACTCGAGTGGGTGG	207	
G49S nt	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCT CTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACGCCTGGATG AGCTGGGTGCGCCAGGCCCTGGAAAAGGACTCGAGTGGGGTGCCCGGATC AAGAGCAAGACCGATGGCGGCACCACCGACTATGCCGCCCCTGTGAAGGGC CGGTTCACCATCAGCAGGAGGACGACGACGACGAAGAACACCCCTGTACCTGCAGAGG AACAGCCTGAAAACCGAGGACACCGCCGTGTACTACTGCACCACCCCCTGG GAGTGGTCTTGGTACGACTATTGGGGCCAGGGCACCCTCGTGACCGTGTC TCTGCTAGC	208	
R50S nt	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCT CTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACGCCTGGATG AGCTGGGTGCGCCAGGCCCCTGGAAAAGGACTCGAGTGGGTGG	209	
N96Y nt	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCT CTGAGACTGAGCTGTGCCGCCAGCGGGCTTCACCTTCAGCAACGCCTGGATG AGCTGGGTGCGCCAGGCCCCTGGAAAAGGACTCGAGTGGGTGG	210	
√98Y nt	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCT CTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACGCCTGGATG AGCTGGGTGCGCCAGGCCCCTGGAAAAGGACTCGACTGGGTGGG	211	

Name	Sequence	Seq ID No
90D7 nt	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCC GTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATG CACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	212

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Name	Sequence	Seq ID	No
90C1 nt	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCC GTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATG CACTGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	213	
5E8 VH nt	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCC GTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATG CACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	214	
5E8 VL nt	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAGGCGAA CCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTGCTGCACTCCAACGGC TACAACTATCTCGATTGGTACCTGCAAAAACCGGGTCAGAGCCCTCAGCG CTGATCTACCTGGGCTCTAAACGGCGCTCCGGTGCAGACCGTTCCAGC GGCTCTGGATCCGGCACCGATTTCACGTTGAAAATCAGCCGTGTGAAGCA GAAGACGTGGGCGTTTATTACTGTATGCAGGCACTGCAGATTCCAAACACT TTTGGTCAAGGCACCAAGGTCGAAATTAAACGTACG	215	
12A4 VH nt	GAGGTGCAATTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCCGGATTCACCTTTAGCAGTTATGCCATG AGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATT AGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTC ACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGC CTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAATACGCTTACGCT CTGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCGAGTGCTAGC	216	
12A4 VL nt	GAAATCGTGTTAACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAA AGAGCCACCCTCTCTTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTA GCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGA GCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGATCC GGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCA GTGTATTACTGTCAGCAGCATGGCAGCAGCAGCACGTTCGGCCAGGGGACC AAAGTGGAAATCAAACGTACG	217	
7A3 VH nt	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGGGGCTTCC GTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATG CACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	218	
7A3 VL nt	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAGGCGAA CCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCACTCCAACGGC TACAACTATCTCGATTGGTACCTGCAAAAACCGGGTCAGAGCCCTCAGCTG CTGATCTACCTGGGCTCTAACCGCGCTTCCGGTGTACCGGACCGTTTCAGC GGCTCTGGATCCGGCACCGATTTCACGTTGAAAATCAGCCGTGTTGAAGCA GAAGACGTGGGCGTTTATTACTGTATGCAGGCACTGCAGACCCCACCAATT ACCTTTGGTCAAGGCACCAAGGTCGAAATTAAACGTACG	219	
6E10 VH nt	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCC GTTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATG CACTGGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	220	
6E10 VL nt	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAGGCGAA CCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCACTCCAACGGC TACAACTATCTCGATTGGTACCTGCAAAAACCGGGTCAGAGCCCTCAGCTG CTGATCTACCTGGGCTCTAACCGCGCTTCCGGTGTAACGGACCGTTTCAGC GGCTCTGGATCCGGCACCGATTTCACGTTGAAAATCAGCCGTGTTGAAGCA GAAGACGTGGGCGTTTATTACTGTATGCAGGCATGGCAT	221	

Name	Sequence	Seq ID No
	AACCCAAGCGGTGGCTCTACCTCCTACGCGCAGAAATTCCAGGGTCGCGTC ACGATGACCCGTGACACTAGCACCTCTACCGTTTATATGGAGCTGTCCAGC CTGCGTTCTGAAGATACTGCAGTGTACTACTGTGCACGCGGTGCTACTTAC ACTATGGACTATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCTGCTAGC	
12F9 VL nt	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAGGCGAA CCGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCACTCCAACGGC TACAACTATCTCGATTGGTACCTGCAAAAACCGGGTCAGAGCCCTCAGCTG CTGATCTACCTGGCTCTAACCGCGCTTCCGGTGTACCGGACCGTTTCAGC GGCTCTGGACCGGCACCGATTTCACGTTGAAAATCAGCCGTGTTGAAGCA GAAGACGTGGGCGTTTATTACTGTATGCAGGCACTGCAGACCCCCAATTACT TTTGGTCAAGGCACCAAGGTCGAAATTAAACGTACG	223

Name	Sequence	Seq ID No
pETR11646 Mov19 VH- CH1-Fchole PG/LALA	CAGGTGCAGCTGCAGCAGTCTGGCGCCGAGCTCGTGAAACCTGGCGCCTCC GTGAAGATCAGCTGCAAGGCCAGGCGGCACAGCGTGCAAACCCTGGCGCACATTCAAG AACTGGGTCAAGCAGAGCCCGGCAAGAGCCTGGAATGGATCGCCAGAATC CACCCTACGACGGCGACACCTTCTACAACCAGAACTTCAAGGACAAGGCC ACCCTGACCGTGGACAAGACGCAGCAACACCGCCCACATGGAACTGCTGAGC CTGACCAGCGAGGACTTCGCCGTGTACTACTGCACCAGATACGACGGCGGC CGGCCCATGGATTATTGGGGCCAGGCACCACCGTGACAGTGTTCACGCGGC AGCACCAAGGGCCCCTCCGTGTTCCCCCTGGCCCCAGCAGCAGAGAGCACC AGCGCCGGCGCACGCGCTCTGGGCTGCCTGGTCAAGGACTACTTCCCCCGAG CCCGTGACCGTGCTCTGGAACAGCGGGACCCTGGCCTGG	224
pETR11647 Mov19 VH- CH1-CD3 VH-CL- Fcknob PG/LALA	CAGGTGCAGCTGCAGCAGTCTGGCGCCGAGCTCGTGAAAACCTGGCGCCTCC GTGAAGATCAGCTGCAAGGCCAGCGAAGAGCTGGGATGGAT	225

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Name	Sequence	Seq ID No
	GTGCACAACGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCGGCGCCCCCATCGAGAAA ACCATCTCCAAAGGCCAAAGGCCACCAAGAACCACAGGTGTACACCCTG CCCCCATGCCGGGATGAGGCGGCACAAGAACCAAGGTCGGCAGTGGCACTGG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGGCAATGGG CAGCCGGAGACAACTACAAGACCACGCCTCCCGTGGTGGAGTGGCAGCGG CAGCCGGAGACAACTACAAGACCACGCTCCCGTGGTGGAGCAGCAGC GGGAACGTCTTCTCATGCCCGTGGAGTCAGCCAGCAGCCACGC GGGAACGTCTTCTCATGCCCCGTGGAGGCCCTGGACAACCACTAC ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
pETR11644 Mov19 LC	GACATCGAGCTGACCCAGAGCCCTGCCTCTCTGGCCGTGTCTCTGGGACAG AGAGCCATCATCAGCTGCAAGGCCAGCCAGAGCGTGTCCTTTGCCGGCACC TCTCTGATGCACTGGTATCACCAGAAGCCGGGCGGCCAGCAGCCCAAGCTGGCG ATCTACAGAGCCAGCAACCTGGAAGCCGGCGTGCCCACAAGATTTTCCGGC AGCGGCAGCAAGACCACCACCACGACGACGACGCCCCGGCGG	226

Variant	Sequence	Seq ID	No
16D5 VH_D52dE	GAGGTGCAATTGGTTGAATCTGGTGGTGGTGGTCTGGTAAAACCGGGCGGTTCCC TGCGTCTGAGCTGCGCGCGCTTCCGGATTCACCTTCTCCAACGCGTGGATGAG CTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAGTGGGTTGGTCGTATCAAG TCTAAAACTGAGGGTGGCACCACGGATTACGCGGCTCCAGTTAAAGGTCGTT TTACCATTTCCCGCGACGATAGCAAAAACACTCTGTATCTGCAGAAGAACTC TCTGAAAACTGAAGACACCGCAGTCTACTACTGTACTACCCCGTGGGAATGG TCTTGGTACGATTATTGGGGCCAGGGCACGCTGGTTACGGTGTCTTCC	261	
16D5 VH_D52dQ	GAGGTGCAATTGGTTGAATCTGGTGGTGGTGGTCTGGTAAAACCGGGCGGTTCCC TGCGTCTGAGCTGCGCGCGCTTCCGGATTCACCTTCTCCAACGCGTGGATGAG CTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAGTGGGTTGGTCGTATCAAG TCTAAAACTCAGGGTGGCACCACGGATTACGCGGCTCCAGTTAAAGGTCGTT TTACCATTTCCCGCGACGATAGCAAAAACACTCTGTATCTGCAGATGAACTC TCTGAAAACTGAAGACACCGCAGTCTACTACTGTACTACCCCGTGGGAATGG TCTTGGTACGATTATTGGGGCCAGGGCACGCTGGTTACGGTGTCTTCC	262	
CD3_VH N100A	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTC TGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCACCTACGCCATGAA CTGGGTGCGCCAGGCCCCTGGCAAAGGCCTGGAATGGGTGTCCCGGATCAGA AGCAAGTACAACAACTACGCCACCTACTACGCCGCACGCGTGAAGGGCCGGGT TCACCATCAGCCGGGACGACGAAGAACACCCTGTACCTGCAGATGAACAG CCTGCGGGCCCAGGACACCGCGCGTGTACTATTGTGTGCGCCACGGCAACTTC GGCGCCAGCTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACCCTCGTGA CCTGTGTCAAGC	263	
CD3_VH S100aA	GAGGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTC TGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCACCTACGCCATGAA CTGGGTGCGCCAGGCCCCTGGCAAAGGCCTGGAATGGGTGTCCCGGATCAGA AGCAAGTACAACAACTACGCCACCTACTACGCCGCACGCGTGAAGGGCCGGT TCACCATCAGCCGGGACGACGACGAACAACCCTGTACCTGCAGATGAACAG CCTGCGGGCCCAGGACACCCCGCGTGTACTATTGTGCGCCACGGCAACTTC GGCAACGCCTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACCCTCGTGA CCGTGTCAAGC	264	
16D5 [VHCH1]- CD3[VHCH1- N100A]- Fcknob_PGLALA	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCGGTTCCC TGCGTCTGAGCTGCGCGCGCTTCCGGATTCACCTTCTCCAACGCGTGGATGAG CTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAGTGGGTTGGTCGTATCAAG TCTAAAACTGACGGTGGCACCACGGATTACGCGGGTCCAGTTAAAGGTCGTT TTACCATTTCCCGCGACGATAGCAAAAACACTCTGTATCTGCAGAGAAAGC TCTTGAAAACTGAAGACACCGCAGTCTACTGTACTG	265	

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Variant	Sequence	Seq	ID	No
	GAGGAGGGTCCGGAGGCGGAGGATCCGAGGTGCAGCTGCTGGAATCTGGCGG CGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGAGCTGTGCGCCACGGG TTCACCTTCAGCACCTAGGCATCAGAACTGGGTGCGCCAGGCCCTGGCAAAG GCCTGGAATGGGTGTCCCGGATCAGAAGCAGAGTACAACAACTACGCCACTA ACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACAACAGCAGCAA AACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACAACAGCCGGG CCCAGCGGTGTCCCCCTGCAACAGCCTGCGGGCCAGCAACTACGGCCGCGT ACTATTGTGTGCGGCCACGCAACTTCGGCGCCAGCTATGTGTCTTGGTTTGC CTACTGGGGCCAGGGCACCCTCCTGACCAGCGAGAGAGCACCTGCCGGGACCAG CCCAGCGTGTCCCCCTGGCACCCAGCAGAAGAGCACACTGGCGGGAACAG CCCCTGGGCTGTCTGGTGAAAGACTACTTCCCCGAGCCCGTGACCGTGT TTGGAACTCTGGCGCCCTGACCAGCGGCGGCGCACCCTTCCAGCCGTGT CCCGGGAACACAGACATATATCTCCCGGGGCACCCTTCCAGCCGTGT CCCCGGGAACACAGACATATATCTCAAGGCGCACAACTCCACACAC CAAAGTCGATAAGAAAGTCGAACCCAGAGGCGCCGCAACATCTCCCCTG CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCTGAGGTCACATG CGTGGTGGGGGAGGTGGCAACAGGCGCCCGGAGACAGC GTGGACGGCGTGGACGTGGACCACAAGGCCCCGGGGGGGG			
16D5- Fchole- PGLALA	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGGCGGTTCCC TGCGTTGAAGCTGCGCGGCTTCCGGATTCACCTTCTCCAACGCGTGGATGAG CTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAGTGGGTTGGTCGTATCAAG TCTAAAACTGACGGTGGCACCACGGATTACGCGGGTCCAGTTAAAGGTCGTT TTACCATTTCCCGCGACGATAGCAAAAACCCTCTGTATCTGCAGTGACACC TCTGAAAACTGAAGACACCGCAGTCTACTGTACTG	2	266	
CD3-CLC	CAGGCCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCGGCACCG TGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCACCAGCAACTACGC CAACTGGGTGCAGGAAAAGCCCGGCCAGGCCTTCAGAGGACTGATCGGCGGC ACCAACAAGAGAGCCCCTGGCACCCTGCCAGGATTCAGCGGATCTCTGCTGG GAGGAAAGGCCCCTGGGCACCCTGTCGCGCCAGCAGAAGATGAGGCCGA GTACTACTGCGCCCTGTGGTACAGCAACCTGTGGGTGTTCGGCGGAGGCACC AAGCTGACAGTCCTAGGTCAACCCAGGCGAGCCCCCAGCGAGGCCACCTGTTCC CCCCCAGCAGCAGGAACTGCAGCCACCAGGCCAGCAGCAGCAGCAGC CCCGTGAAGGCCGCGGGGGGGGCCGTGGACCACCGGGCGCAGCACACACA	2	267	
16D5 [VHCH1]- CD3[VHCH1- S100aA]- Fcknob_PGLALA	GAGGTGCAATTGGTTGAATCTGGTGGTGGTCTGGTAAAACCGGGCGGTTCCC TGCGTCTGAGCTGCGCGGCTCCGGATTCACCTTCTCCAACGCGTGGATGAG CTGGGTTCGCCAGGCCCCGGGCAAAGGCCTCGAGTGGGTGG	2	268	

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Variant	Sequence	Seq	ID	No
Variant	Sequence CGGCGGAACAGCCGCCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCC GTGACAGTGTCTGGAACAGCGGAGCCCTGACAAGCGGCGTGACACATTTCC CTGCCGTGCTGCAGAGCAGCGGCGCCTGAACACGGCGTGACACACTTCC CTGCCGTGCGACGCGGGCACCCAGACCTACATCTGCAACGTGAACCACAAG CCCAGCAACACCAAAGTGGACAAGAAGGTGGAGCCCAAGGCTGTGGTGGCG GAGGAGGGCCCGGAGGCCCAGGACCCAGAGCCCAAGGCCGTGGCAGCGC GGGACTGGTGCAGCCTGGCGGATCCTGAGACTGAGCTGTGCGGCAAGG CCCGGACAGCGTGCCGGGATCCTGAGACTGAGCCGGCCCAGGCCCCTGGCAAAG GCCTGGAAAGGGTGCCCGGATCCTGAGACTGAGCCGAGGACCACACAA CCCCGGACAGCGTGAAGGGCCGGTCACCACCACCAACAACTACGCCACCTA CTACGCCGACAGCGGAAGGACCGGTCCACCACCAACAACTACGCCACCTA CTACGCGGACAGCGGAACGCGGTCCACCACGAGGACCACCGCCGTGT CCACGGGCCAGGGCACCCCGGGACCACCACGCGGAGGACCACACGCCGTGT CTACTGGGGCCCGGGCACCCCGGGCCGAGGACCACCGCCGTGT CTGGGACCCGGGCCGGGCACCCCGTGGCCACGCCGTGGCCGAGGC CCCAGCGTGTTCCCCCTGGCACCAGCGCGTGCACACCTTCCAAGCGCGTGCT CCCGGGCCGGCCTGTACTCCCGTGGCCACGCCGTGGCCGAGGCC CCCAGCGGCCTGACCCCCGAGGCCCCAGGGCCCACGTCTCCAACCC CCCGGGCCCGGCCGGAGCCCCCCGTGGCCACCCTCCCAGCGCCTCACCT CCCGGGAACACAGACATATATCGTAAGCCACACCCTCCCAGGCCCCTCACCT CCCGGGCCCAGGCCCGGAGGCCCCCCAGGGCCGGGGAGACCACT CCCGGGCCCAGGCCGGAGGCCCCCCAGGGCCGGGGGACCCTCCGGGCCGGGAGACCACT CCCGGGCGCGGGGGGCCGTGACCCCCCAAGGCCCCGAGGCCCCCGAGGCCGGGAGAGCAGT ACAACCCAAGGACCCCCCAAGAGCCCCGAGGCCCCGGGGAGGA	Seq	ID	No
	CCGACGGCTCCTTCTTCTCACGCAAGCTCACCCGTGGACAAGAGCAGGTG GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC			
9D11 [VHCH1]- CD3[VHCL- N100A]- Fcknob_PGLALA	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGGCGCTTCCG TTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATGCA CTGGGTTCGTCAAGCCCCGGGCCAGGGTTGGAATGGATGG	2	269	

9D11-Fchole

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Variant	Sequence	Seq	ID	No
	CCAAGCGGTGGCCCTACCTCCTACGGCAGAAATTCCAGGGTCGCGTCACGA TGACCCGTGACACTAGCACTTCTACCGTTTATATGGAGCTGCCAGCGCGG GACTATTGGGGTCAAGGCACCTCGGTAACGGGTTCTTCTGCTGGCACCAGGG GCCCTCCGTGTCCCCCTGGCCCCAGCAGCAGAAGACCACGGCGGCAC AGCCGCTCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGTGACCGTG TCCTGGAACAGCGGAGCCCTGGCCCAGCGCGGCACACCTTCCCCCGCGTGG CCCGGCTCTGGCCTGGTCAAGGCCTGCACGCGGCACACCTTCCCCCGCGTG TGCAGAGTTCTGGCCTGATAGCCTGAGCGGCGCACACCTTCCCCCGCGTG CAGCCTGGGCACCCAGACCTGACTCCGCAGCGTGGCCACGCTGCTG CCCCCCAGGGCCCCAGACCTGACGCGCAGCGTGGCCAGGCCGCAGCCT CCCCCCAAGGTGGACGCCAGAGCCGCGAGCGTCAGCCTCTCT CCCCCCAAAACCCAGGACCCTCATGATCTCCCGGACCCCAGGGCCCCCGGGAGGACC AGCTGGGGCGCGGGGGGCCCAAGAGCCCTCAGGTCAAGCCCAGAGGCA GCGTGGGGGGGGGG			
9D11_LC [N95Q]	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAGGCGAAC CGGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCACTCCAACGGCTA CAACTATCTCGATTGGTACCTGCAAAAACCGGGTCAGAGCCCTCAGCTGCTG ATCTACCTGGGCCTTAACCGCGCTTCCGGTGTACCGGACCGTGTTCAGCGGCCT CTGGATCCGGCACCGATTTCACGTTGAAAATCAGCCGTGTGAAGCAGAAGA GGTGGGCGTTTATTACTGTATGCAGGCAGCACTATGCAGCGGACTTTTGGT CAAGGCACCAAGTCGAAATTAACGTACGTGGCTGCACCATCTGTCTTCA TCTTCCCGCCATCTGATGAGCAGTGAAATCTGGAACGGACTATTGTGTG CCTGCTGAATAACTTCTATCCCAGAGAGCCCAAAGTACAGTGGAAGGAGGAC AAGGCCTCCAATCGGGTAACTCCCAGGAGAGTCACCAGGAGCAGAACGACAGCA AGGACAACAAAGCCTCAGCGCCCCGGCGCAGCAGACAGCACGACAGCA CGAGAAACAAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCCAGCC	2	71	
CD3_VLCH1	CAGGCCGTCGTGACCCAGGAACCCAGCCTGACAGTGTCTCCTGGCGGCACCG TGACCCTGACATGTGGCAGTTCTACAGGCGCCGTGACCACCAGCAACTACGC CAACTGGGTGCAGGAAAAGCCCGGCCAGGCCTTCAGAGGACTGATCGGCGGC ACCAACAAGAGAGCCCCTGGCACCCCTGCCAGATTCAGCGGATCTCTGCTGG GAGGAAAGGCCGCCTGGGACACCTGTGGCGCGAGAGATGAGGCCGA GTACTACTGCGCCCTGTGGTACAGCAACCTGTGGGGGTGTCGGCGGAGGCACC AAGCTGACAGTGCTGAGCAGCGCTTCCACCAAAGGCCCTTCCGGATGTCCTC TGGCTCCTAGCTCCAAGTCCACCTCTGGAGGCACCGCTGCTCTCGGATGCCT CGTGAAGGATTATTTTCCTGAGCCTGTGGACAGTGCTCTGGAATAGCGGAGCA CTGACAGCTGAGGTGGCAACAGTGCCCAGCAGCAGCCTGGGCACCCAGAC CTGCACCTGGAGGCGGTGGCACAGTGCCCAGCAGCAGCCTGGGCACCCAGAC GTGCAACGTGAACGTGGACACGCCCAGCAGCACCCAAGGTGGACAAGAAG GTGGAACCCAAGTCTTGT	2	72	
9D11 [VHCH1]- CD3[VHCH1- S100aA]- Fcknob_PGLALA	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGGCGCTTCCG TTAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATGCA CTGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGG	2	73	

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Variant	Sequence	Seq	ID	No
	ATTATGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG			
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	TGTCCCCCTTGTCCTGCCCCTGAAGCTGCTGGCGGCCCTTCTGTGTTCCTGT			
	TCCCCCCAAAGCCCAAGGACACCCTGATGATCAGCCGGACCCCCGAAGTGAC			
	CTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGG			
	TACGTGGACGGCGTGGAAGTGCACAACGCCAAGACAAAGCCGCGGGAGGAGC			
	AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGA			
	CTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCGGC			
	GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC			
	AGGTGTACACCCTGCCCCATGCCGGGATGAGCTGACCAAGAACCAGGTCAG			
	CCTGTGGTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG			
	GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGG			
	ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAG			
	GTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC			
	AACCACTACACCACAACACCCCTCTCCCCTCTCCCCCCCTAAA			

Name	Sequence	Seq ID No
16D5 variant W96Y/D52E VH	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCTCT GAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACGCCTGGATGAGCT GGGTGCGCCAGGCCCCTGGAAAAGGACTCGAGTGGGTGGG	415
W96Y/D52ECD3- VHCH1_Fc- knob_PGLALA pETR14945	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGATCTCT GAGACTGAGCTGTGCCGCCCAGCGGCTTCACCTTCAGCAACGCCTGGATGAAGC GGTGCGCCAGGCCCCTGGAAAAGACCCCGAGTGGGTGGGACGGATCAAGAC CATCAGCAGGACACCACCACCACCACTATGCCGCCCCTACGAAGGACCACCGCC CATCAGCAGGACACCACCGCGTGTACTACTGCCACCCCCTACGAAGGACAACACCGCG TACGACTACTGGGCCCAGGCACCCCGTGTACTACTGCTAGCAGCAGCACAA GGGCCTAGCGTGTCCCCTGGCACCCCGGCAGCAAGAGCACAAGCGGGGAA CAGCCGCCTGGGCTCCTGGCACCGGGCGTGCACACCTTCCCTGGCGACGG GGCCTACATCTGCCACGGCGGGGTCACCCTTCCCCTGCGGGCAC CCAGACCACG GGCCTACATCTGCAACGGGAGCGTGGTCACCGGGCACACCCACAAGTGGAC CCAGACCACG GGCCTACATCTGCCACAGGCGGGCGTGCACACCTTCCCCGGGCAC CCAGACCTACATCTGCAACGTGAACCACAAGGCCAGGCACACCCAAGGGGAGGA TCCGAGGTGCAGCTGCGAACGCCGGGGCTCCACCAGCACCCAAGGCCTGGGGAC TCCGAGGTGCAGCTGCGGCACGGCGTCACCTTCAGCACCTACGGCGACG CCAGGTGCAGCTGCGGAACCCCTGGCGAGGGGGCCCGGAGGAGA ACGGGTGCAGCTGCGGCACGCCTGGCAAGGCCTGGCGACCCTGCGGAGCG CCAGGTGCAGCTGCTGGCAACGCCTGCCAGCGGCGTGCAGGCGTCCGGGGAGGA ACGGGTGCAGCTGCGGCACGCCGGCCTCACCTTCAGCCCTGGCGATCAGA ACGGGTGCAGCCCAGGCCCCTGGCAACGCCTGACGGCGACGGCACCGCGGTG AACAGCTATGACTGTGGCGCCGGACCCGGCAGGCACCCCCGGGCACGCC GGCGGCCGAGGACACCGCCGGTGTACCTTCTGGCGACCGCGGAGAGACACCCC TGCGGGCCAAGGCCCCAGCGGCTTGACCAGGCACGCCGGGACACACCC GGCGGCCGAGGCCCCAGCGGCCTGACCCGGCAGCACGCCCGGGACACACCC TGCGGGACAACGCCCCAGCGGCCTGGACCCCAGCAGCACCCCTGCGCCGG AACAGCTATGTGTTGGCTTGGGCACCCAGCGGCGCGCACCCCTGGCACCCCT GGCGGACCAACGCCCCAGCGCCTGACCCCAGCGGCCCGGACACACCC CCTAGCCCCCAGCGCCTGGACCCCGAGACCCCCAGCGGCCCGGACCCCT CCACACCCAAGGCCCCAGCGCCTGAACCCCCAGGGGCCCGGCACAAACCCCC CCTAGCCCCCAGGGCCTGTACCCCTGGCCCGGGACCGCCCGACACACCCC CCTAGCCCCCAGGGCCCTGAACGCCCCAGAGCCCCGGGACCGCCCCAAACCCCC ACATCCCCCCAAAGCCACGACCCCAGAGCCCCGAGGCCCCCGAGACCCCCGGGAGGCC CCCCCAGGCCGGAGGGCCCTGACCCCCGGGACCCGCGGGAGGCC CAAGGCGTGGAGGGCCCCAAAGACCCCGGGGGCCCCCCAAAGCCCCGGGAGGCC CCCCATGCCGGGAGGGCCTGACCCCGGAGGCCCCCGAGGACCCCCGGGAGGCCC CCCATGCCGGGAGGGCCTGACCCCGGGGGCCCCCCGAGAGCCCCGGGGAGCCC CCCATGCCGGGGAGGCCCCACGGCCCCCGGAGACCCCCGGGGAGCCGCC	416
W96Y/D52E_Fc- hole_PGLALA_HYRF pETR14946	GAGGTGCAATTGGTGGAAAGCGGAGGCGGCCTCGTGAAGCCTGGCGGATCTCT GAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACGCCTGGATGAGCT GGGTGCGCCAGGCCCCTGGAAAAGGACTCGAGTGGGTGGG	417

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Name	Sequence	Seq ID No
	AAACCGAGGACACCGCCGTGTACTACTGCACCACCCCCTACGAGTGGTCTTGG TACGACTACTGGGGCCAGGGCACCCTCGTGACCGTGTCATCTGCTAGCACCAA GGGCCCCTCCGTGTTCCCCCTGGCCCCAGCAGCAGCAGCAGCAGCGGCGGCA CAGCCGCTCTGGGCTGCCTGGTCAAGGACTACTTCCCCGGCGCGGCG TCCTGGAACAGCCGAGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGG GCAGAGTTCT GGCAGAGTTCT GGCCTGTATAGCCTGAGCAGCGTGGTCACCGTGCCACCACCACCACGAGCGCG CCAGACCTCACATCTGCAACGTGACCACACAGCCCAGCAACACCACAGGGGCAC CCAGACCTCACATCTGCAACGTGGACCACAAAGCCCAGCAACACCACAGGGGGCCC GGCAGACCTCATGATCTCCCGGGGCACAAAACTCACACATGCCCACCGTGGCCA GGACACCTCATGATCTCCCGGGCCCCTGAGGTCACATGCGTGGTGGTGGACG TGAGCCACGAAGACCCTGAGGTCAACTGCTAGCTGGACGGCGGGAGA GGACACCTCAAGACAAAGCCCCGGGGAGGAGCAGTACAACGGCAGGGGGAGCG TGGCATAATGCCAAGACAAAGCCCCGGGGAGGAGCAGTACAACGCACGTGAAG GGCATAATGCCAAGACAAAGCCCCGGGGAGGAGCAGTACAACGGCAGGAGAG TGCATAAGCCAAGGCACAGGCCCCGAGAACCACAGGTGGAAGGACC CCGGGATGAG CTGACCAAGAACCAGGTCAGCCTCTCGTGCGCAGTCAAAGGCTTCTATCCCAG CGACCACCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGA CCACGCCTCCGTGGCGGGAGAGCACGCCGGGAGAACAACTACAAGA CCACGCCTCCGTGGAGTGGCAGCCGCGGGGAACGCCTCTCTCT	
14B1 VH	GAGGTGCAATTGTTGGAGTCTGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCCGGATTCACCTTTAGCAGTTATGCCATGAGCT GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGGGGCCGGTTCACCATTAGTGGT AGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTC CAGAGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGAGAGCCG AGGACACGGCCGTATATTACTGTGGCGCGTGGTGACTACCGTTACCTTC GACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCGAGT	418
14B1 VL	TCTTCTGAACTGACTCAAGATCCAGCTGTTAGCGTGGCTCTGGGTCAGACTGT ACGTATCACCTGCCAAGGCGATTCTCTGCGCTCCTACTACGCAAGCTGGTACC AGCAGAAACCGGGTCAGGCCCCAGTTCTGGTGATTTACGGCAAAAACAACCACCGT CCGTCTGGGATCCCGGACCGTTTCTCCGGCAGCTCTTCCGGTAACACGGCGAG CCTCACCATCACTGGCGCTCAAGCAGAAGACGAGGCCGACTATTACTGTAACT CTCGGGAAAGCCCACCAACCGGCCTGGTTGTCTTCGGTGGCGGTACCAAGCTG ACCGTCCTA	419
14B1[EE]_CD3[VLCH1]_Fc- knob_PGLALA pETR14976	GAGGTGCAATTGTTGGAGCTTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCCGGATTCACCTTTAGCAGTATGCCATGAGCT GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGGTCTCAGCTATAGTGGGT AGTGGTGGTAGCACATACTACGCAGACTCCGTGAGAGGCCGGTCCACCATCTC CAGAGACACGGCCGTATATTACTGTGGGCGTGGTGACTACAGTTACCGTTACCGTTACTGTG GACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCGAGTGCTACCGTTACCGTTACCGTACCGTG GGCTCTGGGGCTCTGGCGCCTTCCAGCAAGTCCACCTTGGGGGAACTG CCGCTCTGGGGCTCGGTGGCACACCTTCCCAGCAGGTGCCGCGGGACCG GTGCACCGAGCCTGGCTCGCGCGTGGCGACACCTTCCAGCTGGCGCG GGGCACCCAGACCTACATCTGCAACGTGAACGACGCCGCGAGGCTCCCG GGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCCAACACCAAG GTGGACGAGAAGGTGGAACCCAAGTCCTGCGGACGGTGGCGGAGGTTCCCG GCGGCCCGTGACCTGGCGTGGCACGCGGCGGCGGAGGTTCCCGGAG GTGGACGAGAAGGTGGAACCCAAGTCCTGCGGACGTGGCGGAGGTTCTCCTG GCGGCCCCGGCCTGCCTGGCGGAGCCTTCCGGCGCCGGGCGCTCCGGAGG CGGGGCACCAACAAGAGCCCCGGCCAGGCCTCCAGCGCTCCG AACTACGCCAATTGGGTGCCCGGGACGCCTGGCGCGGGGGCGGAGG CCCCGAGTACTACTGCGCGGGGCCCTGGCACGCCTGCGGGAGG CCCCCAACTACGGCCCTGGCCCGGCCC	420

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### 238

Name	Sequence	Seq ID No
	GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTC CGGGTAAA	
14B1[EE]_FC- hole_PGLALA pETR14977	GAGGTGCAATTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCCGGATTCACCTTTAGCAGTTATGCCATGAGCT GGGTCCGCCAGGCTCCAGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGGT AGTGTGGTAGCACATACTACGCAGACTCCGTGAAGGCCCGTTCACCATCTC CAGAGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGAGAGCCG AGGACACGGCCGTATATTACTGTGCGCGTGGTGACTACCGTTACCGTTACCGTTACTTC GACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCGAGTGCTACCGTTCCCCTGGCCCCCTGGCCCCCCAGCAGCAAGAGACACCAGGGCGCCACAG CCCCTCCGGTGTTCCCCCTGGCCCCCAGCAGCACAGCCCGGCGCCACAG CCGCTCTGGGCCTGCTGGCCGAGGACTACTCCCCGGACCCAGCGCCGTGCCC TGGAACAGCGGAGCCCTGACCTCCGGGGTGCACACCTTCCCCGCCGTGTCC GGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCCCAGCACAAG GTGGACGAGGAGCCTGAAGCGCGGGACCAACACTCACCACAAGCC GTGGCCAGCACCTGAAGCCCAAGAGCGTCGACAAAACTCACACACA	421
14B1 LC [KK] Constant lambda pETR14979	TCTTCTGAACTGACTCAAGATCCAGCTGTTAGCGTGGCTCTGGGTCAGACTGT ACGTATCACCTGCCAAGGCGATTCTCTGCGCTCCTACTACGCAAGCTGGTACC AGCAGAAACCGGGTCAGGCCCCAGTTCTGGTGATTTACGGCAAAAACAACCGT CCGTCTGGGATCCCGGACCGTTTCTCCGGCAGCTCTTCCGGTAACACGGCGAG CCTCACCATCACTGGCGCTCAAGCAGAGAGACGCGACTATTACTGTAACT GTCGGGAAAGCCCACCAACCGGCCTGGTTGTCTTCGGTGGCGGTACCAAGCTG ACCGTCCTAGGTCAACCGAGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAG CAGCAAGAAACTGCAGGCCAACAAGGCCGCCCCTGGTCTGCCTGATCAGCGAC TCTACCCAGGCGCGTGACCCTGGACGCCGCCGTGACCCCTGGTAGCCGTGACC CCGCCTGAGCCACCACCGCCGCGCGAGCAAGCACCCCCGGGAGACGCCCCCGAGCAGC	422
9C7 VH	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCCGT TAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATGCACT GGGTTCGTCAAGCCCCGGGCCAGGGTCTGGAATGGATGGCATCATTAACCCA AGCGGTGGCTCTACCTCCTACGCGCAGAAATTCCAGGGTCGCGTCACGATGAC CCGTGACACTAGCACCTCTACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTG AAGATACTGCAGTGTACTACTGTGCACGCGTGACTGGTCTTACTACATGGAC TATTGGGGTCAAGGCACCCTCCGTAACGGTTTCTTCT	423
9C7 VL	GATATTGTTATGACTCAATCTCCACTGTCTCTGCCGGTGACTCCAGGCGAACC GGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCTGCACTCCAACGGCTACA ACTATCTCGATTGGTACCTGCAAAAACCGGGTCAGAGCCCTCAGCTGCTGATC TACCTGGGCTCTAACCGCGCTTCCGGTGTACCGGACCGTTTCAGCGGGCTCTGG ATCCGGCACCGATTTCACGTTGAAAATCAGCCGTGTTGAAGCAGAAGACGTGG GCGTTTATTACTGTATGCAGGCACGGCAGACCCCAACTTTTGGTCAAGGCACC AAGGTCGAAATTAAA	424
9C7[EE]_CD3[VLCH1]_Fc- knob_PGLALA pETR14974	CAGGTGCAATTGGTTCAATCTGGTGCTGAAGTAAAAAAACCGGGCGCTTCCGT TAAAGTGAGCTGCAAAGCATCCGGATACACCTTCACTTCCTATTACATGCACT GGGTTCGTCAAGCCCGGGCCAGGGTCTGGAATGGATGGGCATCATTAACCCA AGCGTGGCTCTACCTCCTACGCGCAGAAATTCCAGGGTCCGCGTCACGATGAC CCGTGACACTAGCACCTCTACCGTTTATATGGAGCTGTCCTGGCTGCGTCTG AAGATACTGCAGTGTACTACTGTGCACGCGGTGACTGGTCTTACTACATGGAC TATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCTGCTAGCACCAAGGGCC CTCCGTGTTTCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACTGCCG CTCTGGGCTGCTGGTGGAAGATTACTTCCCCGAGCCGTGACCGTGTCCTGG AATCCTGGCGCTCTGACCGCTGCCACACCTTTCCAGCTGGCCGCGCG GCCCGGGCTCTGACCTCCGTCGCGCGCACACCTTTCCAGCTGGCCGCTGC GCCCCGGCCTGTGCAACGTCCCCCGTGGCCGCCCCCCCCC	425

239

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	GTGAAGGACTACTTTCCTGAGCCTGTGACAGTGTCTTGGAACAGCGGAGCCCT	
	GACCAGCGGAGTGCACACATTCCCTGCAGTGCTGCAGAGCAGCGGCCTGTATA	
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	ATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGTGGTGTGCCCACGA	
	GGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACG	
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	AGGGCCAGCCCCGGGAACCCCAGGTGTACACCCTGCCCCCATGCCGGGATGAG	
	CTGACCAAGAACCAGGTCAGCCTGTGGTGCCTGGTCAAAGGCTTCTATCCCAG	
	CGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGA	
	CCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTC	
	GTAAA	
C7[FF] FC-	C2CCTCC22TTCC2TTC22TCTCCCTCC22CT22222222	426
OLE PGLALA	TAAAGTGAGCTGCAAAGCATCCGGATACACCCTTCACTTCCTATTACATGCACT	720
ETR14975	GGGTTCGTCAAGCCCCCGGCCCAGGGTCTGGAATGGATGG	
	AGCGGTGGCTCTACCTCCTACGCGCAGAAATTCCAGGGTCGCGTCACGATGAC	
	CCGTGACACTAGCACCTCTACCGTTTATATGGAGCTGTCCAGCCTGCGTTCTG	
	AAGATACTGCAGTGTACTACTGTGCACGCGGTGACTGGTCTTACTACATGGAC	
	TATTGGGGTCAAGGCACCCTCGTAACGGTTTCTTCTGCTAGCACCAAGGGCCC	
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	CTCTGGGCTGCCTGGTCGAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGG	
	AACAGCGGAGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAG	
	CCCAGCAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGA	
	CCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTG	
	GACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
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	ACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAG	
	GAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCGGCGCCCCCATCGAGAAAAC	
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	CATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTCTCGTGCGCAGTCAAA	
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	CTCCCTGTCTCCGGGTAAA	
C7 L.C	Ⴚຉຠຉຠໞຒຠຠຉຠຒຉ຺ຒຒຉຉຠຒຠຒຒຒຒຒຒຒຒຒຒຒຒຒຒຒຒຒຒຒຒ	407
EK]	GGCGAGCATTTCTTGCCGTTCCAGCCAGTCTCTGCCGGCGACTCCAGCGAGCTACA	72/
ETR14980	ACTATCTCGATTGGTACCTGCAAAAACCCGGGTCAGAGCCCTCAGCTGCTGATC	
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	GCGTTTATTACTGTATGCAGGCACGGCAGACCCCAACTTTTGGTCAAGGCACC	
	AAGGTCGAAATTAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCC	
	ATCTGATCGGAAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATA	
	ACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAA	
	TCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA	
	TCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGC	

Exemplary Anti-PD1 Antagonist Sequences

Description Sequence			D	No
anti-PDL1 antibody	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLE WVAVIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTA VYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAAL GCLVKDYPPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV PSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE	27	4	

Description	Sequence	Seq ID No
	VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKSLSLSLGK	
anti-PDL1 antibody	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSS NWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	275
anti-PDL1 antibody	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLE WMGGINPSNGGTNFNEKFKNRVTLTTDSSTTTAYMELKSLQPDDTA VYYCARRDYRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPFKPKDTLMISRTPEVTCVVDVSQEDPEVQPN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	276
anti-PDL1 antibody	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQ APRLLIYLASYLESGVPARFSGSGSGTDFTLTISSLEPEDFAVYYC QHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	277
heavy	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLE WVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCARRHWPGGFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKQQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	278
light	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYL YHPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	279
anti-PDL1 antibody VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLE WVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCARRHWPGGFDYWGQGTLVTVSS	280
anti-PDL1 antibody VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLE WVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCARRHWPGGFDYWGQGTLVTVSSASTK	281
anti-PDL1 antibody VL	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYL YHPATFGQGTKVEIKR	282
HVR-H1	GFTFSX1SWIH	283
HVR-H2	AWIX2PYGGSX3YYADSVKG	284
HVR-H3	RHWPGGFDY	285
HVR-L1	RASQX4X5X6TX7X8A	286
HVR-L2	SASX9LX10S	287
HVR-L3	QQX11X12X13X14PX15T	288
HVR-H1	GFTFSDSWIH	289
HVR-H2	AWISPYGGSTYYADSVKG	290
HVR-H3	RHWPGGFDY	291
HVR-L1	RASQDVSTAVA	292

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Description Sequence Seq ID N			No
HVR-L2	SASFLYS	293	
HVR-L3	QQYLYHPAT	294	
anti-PDL1 antibody HC-FR1	EVQLVESGGGLVQPGGSLRLSCAAS	295	
anti-PDL1 antibody HC-FR2	HC-FR2 is WVRQAPGKGLEWV	296	
anti-PDL1 antibody HC-FR3	RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR	297	
anti-PDL1 antibody HC-FR4	WGQGTLVTVSA	298	
anti-PDL1 antibody HC-FR4	WGQGTLVTVSS	299	
LC-FR1	DIQMTQSPSSLSASVGDRVTITC	300	
LC-FR2	WYQQKPGKAPKLLIY	301	
LC-FR3	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	302	
LC-FR4	FGQGTKVEIKR	303	
anti-PDL1 antibody VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLE WVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCARRHWPGGFDYWGQGTLVTVSA	382	
anti-PDL1 antibody VL	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYL YHPATFGQGTKVEIKR	383	

#### Exemplary Anti-TIM3 Antibody Sequences

Sequences of exemplary anti-TIM3 antibody amino acid <sup>40</sup> sequences and exemplary TIM3 sequences are set forth in the sequence listing below as follows:

SEQ ID NO: 304 heavy chain HVR-H1, Tim3\_0016 SEQ ID NO: 305 heavy chain HVR-H2, Tim3\_0016 SEQ ID NO: 306 heavy chain HVR-H3, Tim3\_0016 SEQ ID NO: 307 light chain HVR-L1, Tim3\_0016 SEQ ID NO: 308 light chain HVR-L2, Tim3\_0016 SEQ ID NO: 309 light chain HVR-L3, Tim3\_0016 SEQ ID NO: 310 heavy chain variable domain VH,  ${\tt Tim3\_0016}$ SEQ ID NO: 311 light chain variable domain VL,  ${\tt Tim3\_0016}$ SEQ ID NO: 312 heavy chain variable domain VH, Tim3\_0016 variant (0018) SEQ ID NO: 313 light chain variable domain VL, Tim3\_0016 variant (0018) SEQ ID NO: 314 light chain HVR-L1, Tim3\_0016 HVR-L1 variant 1\_NQ (removal of glycosylation sity by N to Q mutation) SEQ ID NO: 315 light chain HVR-L1, Tim3\_0016 HVR-L1 variant 2\_NS (removal of glycosylation sity by N to S mutation) SEQ ID NO: 316 heavy chain HVR-H1, Tim3\_0021 SEQ ID NO: 317 heavy chain HVR-H2, Tim3\_0021 SEQ ID NO: 318 heavy chain HVR-H3, Tim3\_0021 SEQ ID NO: 319 light chain HVR-L1, Tim3\_0021 SEQ ID NO: 320 light chain HVR-L2, Tim3\_0021 SEQ ID NO: 321 light chain HVR-L3, Tim3\_0021 SEQ ID NO: 322 heavy chain variable domain VH, Tim3\_0021 SEQ ID NO: 323 light chain variable domain VL, Tim3\_0021 SEQ ID NO: 324 heavy chain HVR-H1, Tim3\_0022 SEQ ID NO: 325 heavy chain HVR-H2, Tim3\_0022 SEQ ID NO: 326 heavy chain HVR-H3, Tim3\_0022 SEQ ID NO: 327 light chain HVR-L1, Tim3\_0022 SEQ ID NO: 328 light chain HVR-L2, Tim3\_0022 SEQ ID NO: 329 light chain HVR-L3, Tim3\_0022

-continued SEQ ID NO: 330 heavy chain variable domain VH, Tim3\_0022 SEQ ID NO: 331 light chain variable domain VL, Tim3\_0022 SEQ ID NO: 332 heavy chain HVR-H1, Tim3\_0026 SEQ ID NO: 333 heavy chain HVR-H2, Tim3\_0026 SEQ ID NO: 334 heavy chain HVR-H3, Tim3\_0026 SEQ ID NO: 335 light chain HVR-L1, Tim3\_0026 SEQ ID NO: 336 light chain HVR-L2, Tim3\_0026 SEQ ID NO: 337 light chain HVR-L3, Tim3\_0026 SEQ ID NO: 338 heavy chain variable domain VH, Tim3\_0026 SEQ ID NO: 339 light chain variable domain VL, Tim3\_0026 SEQ ID NO: 340 heavy chain HVR-H1, Tim3\_0028 SEQ ID NO: 341 heavy chain HVR-H2, Tim3\_0028 SEQ ID NO: 342 heavy chain HVR-H3, Tim3\_0028 SEQ ID NO: 343 light chain HVR-L1, Tim3\_0028 SEQ ID NO: 344 light chain HVR-L2, Tim3\_0028 SEQ ID NO: 345 light chain HVR-L3, Tim3\_0028 SEQ ID NO: 346 heavy chain variable domain VH, Tim3\_0028 SEQ ID NO: 347 light chain variable domain VL, Tim3\_0028 SEQ ID NO: 348 heavy chain HVR-H1, Tim3\_0030 SEQ ID NO: 349 heavy chain HVR-H2, Tim3\_0030 SEQ ID NO: 350 heavy chain HVR-H3, Tim3\_0030 SEQ ID NO: 351 light chain HVR-L1, Tim3\_0030 SEQ ID NO: 352 light chain HVR-L2, Tim3\_0030 SEQ ID NO: 353 light chain HVR-L3, Tim3\_0030 SEQ ID NO: 354 heavy chain variable domain VH, Tim3\_0030 SEQ ID NO: 355 light chain variable domain VL, Tim3\_0030 SEQ ID NO: 356 heavy chain HVR-H1,  ${\tt Tim3\_0033}$ SEQ ID NO: 357 heavy chain HVR-H2, Tim3\_0033 SEQ ID NO: 358 heavy chain HVR-H3, Tim3\_0033 SEQ ID NO: 359 light chain HVR-L1, Tim3\_0033 SEQ ID NO: 360 light chain HVR-L2, Tim3\_0033 SEQ ID NO: 361 light chain HVR-L3, Tim3\_0033 SEQ ID NO: 362 heavy chain variable domain VH, Tim3\_0033 SEQ ID NO: 363 light chain variable domain VL, Tim3\_0033 SEQ ID NO: 364 heavy chain HVR-H1, Tim3\_0038 SEQ ID NO: 365 heavy chain HVR-H2, Tim3\_0038 SEQ ID NO: 366 heavy chain HVR-H3, Tim3\_0038 SEQ ID NO: 367 light chain HVR-L1, Tim3\_0038 SEQ ID NO: 368 light chain HVR-L2, Tim3\_0038 SEQ ID NO: 369 light chain HVR-L3, Tim3\_0038 SEQ ID NO: 370 heavy chain variable domain VH, Tim3\_0038 SEQ ID NO: 371 light chain variable domain VL, Tim3\_0038 SEQ ID NO: 372 an exemplary Pseudomonas exotoxin A variant 1 (deimunized PE24 example) SEQ ID NO: 373 an exemplary Pseudomonas exotoxin A variant 2 (deimunized PE24 example) SEQ ID NO: 374 human kappa light chain constant region SEQ ID NO: 375 human lambda light chain constant region SEQ ID NO: 376 human heavy chain constant region derived from IgG1 SEQ ID NO: 377 human heavy chain constant region derived from IgG1 with mutations L234A and L235A SEQ ID NO: 378 human heavy chain constant region derived from IgG1 with mutations L234A, L235A and P329G SEQ ID NO: 379 human heavy chain constant region derived from IgG4 SEQ ID NO: 380 exemplary human Tim3 sequences SEQ ID NO: 381 human Tim3 Extracellular Domain (ECD) <210> 304 <211> 9 <212> PRT <213> Mus musculus <400> 304 Gly Phe Ser Leu Ser Thr Ser Gly Met 1 5 <210> 305 <211> 3 <212> PRT <213> Mus musculus <400> 305 Leu Asn Asp 1 <210> 306 <211> 8 <212> PRT <213> Mus musculus <400> 306 Asn Gly Tyr Leu Tyr Ala Leu Asp 1 5

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249
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 Ser Gly Ser Gly Arg Asp Tyr Ser Phe Asn Ile Asn Asn Leu Glu Pro

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 70
 75
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 Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Asn Leu Pro Phe

 85
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Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

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SEQUENCE LISTING

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Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45
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Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 65 70 75 80
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Gly
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Gln 1	Val	Gln	Leu	Val 5	Gln	Ser	Gly	Ala	Glu 10	Val	Lys	Lys	Pro	Gly 15	Ala
Ser	Val	Lys	Val 20	Ser	Сүз	Lys	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
Tyr	Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly	Ile 50	Ile	Asn	Pro	Ser	Gly 55	Gly	Ser	Thr	Ser	Tyr 60	Ala	Gln	Lys	Phe
Gln 65	Gly	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
Met	Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сүз
Ala	Arg	Gly	Glu 100	Trp	Arg	Arg	Tyr	Thr 105	Ser	Phe	Asp	Tyr	Trp 110	Gly	Gln
Gly	Thr	Leu 115	Val	Thr	Val	Ser	Ser 120								
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Gln 1	Val	Gln	Leu	Val 5	Gln	Ser	Gly	Ala	Glu 10	Val	Lys	Lys	Pro	Gly 15	Ala
Ser	Val	Lys	Val 20	Ser	Суз	Lys	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
Tyr	Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly	Ile 50	Ile	Asn	Pro	Ser	Gly 55	Gly	Ser	Thr	Ser	Tyr 60	Ala	Gln	Lys	Phe
Gln 65	Gly	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
Mat	<i>c</i> - 7	T	Cor	Sor	Lou	7~~~	Com	<i>c</i> 1	Agen	(m)		17-7	<b>Tr r r r r r r r r r</b>		<b>G</b> =

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<221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 17 Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala Ala Pro 1 5 10 15 Val Lys Gly <210> SEQ ID NO 18 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 18 Pro Trp Glu Trp Ser Trp Tyr Asp Tyr 5 1 <210> SEQ ID NO 19 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 19 Glu 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 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 Asp Gly Gly Thr Thr Asp Tyr Ala Ala 55 50 60 Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 75 70 65 80 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr 85 90 95 Tyr Cys Thr Thr Pro Trp Glu Trp Ser Tyr Phe Asp Tyr Trp Gly Gln 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 20 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 20 Pro Trp Glu Trp Ser Tyr Phe Asp Tyr 1 5

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Tyr Cys Thr Thr Pro Trp Glu Trp Ala Tyr Phe Asp Tyr Trp Gly Gln 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 24 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 24 Pro Trp Glu Trp Ala Tyr Phe Asp Tyr 5 1 <210> SEQ ID NO 25 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEOUENCE: 25 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1 5 10 15 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 20 25 30 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45 Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 55 60 50 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 65 70 75 80 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Thr Gly Tr<br/>p Ser Arg Tr<br/>p Gly Tyr Met Asp Tyr Tr<br/>p Gly Gln $% \left( {{\left( {{{\left( {{{\left( {{{\left( {{{}}} \right)}} \right.} \right.} \right)}_{{\left( {{1} \right)}}}} \right)}_{{\left( {{1} \right)}}} \right)}_{{\left( {{{\left( {{{\left( {{} \right)}} \right)}_{{\left( {{1} \right)}}} \right)}_{{\left( {{1} \right)}}} \right)}_{{\left( {{1} \right)}}} }}$ 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 26 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 26 Thr Gly Trp Ser Arg Trp Gly Tyr Met Asp Tyr 1 5 10 <210> SEQ ID NO 27 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source

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Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Gly Glu Trp Ile Arg Tyr Tyr His Phe Asp Tyr Trp Gly Gln 100 105 110
Gly Thr Leu Val Thr Val Ser Ser 115 120
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Val Gly Trp Tyr Arg Trp Gly Tyr Met Asp Tyr Trp Gly Gln 100 105 110
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Ala	Met	Asn 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Arg 50	Ile	Arg	Ser	Lys	Tyr 55	Asn	Asn	Tyr	Ala	Thr 60	Tyr	Tyr	Ala	Asp
Ser 65	Val	Lys	Gly	Arg	Phe 70	Thr	Ile	Ser	Arg	Asp 75	Asp	Ser	Гла	Asn	Thr 80
Leu	Tyr	Leu	Gln	Met 85	Asn	Ser	Leu	Arg	Ala 90	Glu	Asp	Thr	Ala	Val 95	Tyr
Tyr	Cys	Val	Arg 100	His	Gly	Asn	Phe	Gly 105	Asn	Ser	Tyr	Val	Ser 110	Trp	Phe
Ala	Tyr	Trp 115	Gly	Gln	Gly	Thr	Leu 120	Val	Thr	Val	Ser	Ser 125	Ala	Ser	Thr
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Gly 145	Gly	Thr	Ala	Ala	Leu 150	Gly	Сүв	Leu	Val	Lys 155	Asp	Tyr	Phe	Pro	Glu 160
Pro	Val	Thr	Val	Ser 165	Trp	Asn	Ser	Gly	Ala 170	Leu	Thr	Ser	Gly	Val 175	His
Thr	Phe	Pro	Ala 180	Val	Leu	Gln	Ser	Ser 185	Gly	Leu	Tyr	Ser	Leu 190	Ser	Ser
Val	Val	Thr 195	Val	Pro	Ser	Ser	Ser 200	Leu	Gly	Thr	Gln	Thr 205	Tyr	Ile	Сув
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Pro 225	Гλа	Ser	Сүз												
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Ser	Val	Lys	Val 20	Ser	Сүз	Lys	Ala	Ser 25	Gly	Gly	Thr	Phe	Ser 30	Ser	Tyr
Ala	Ile	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly	Gly 50	Ile	Ile	Pro	Ile	Phe 55	Gly	Thr	Ala	Asn	Tyr 60	Ala	Gln	Lys	Phe
Gln 65	Gly	Arg	Val	Thr	Ile 70	Thr	Ala	Asp	Lys	Ser 75	Thr	Ser	Thr	Ala	Tyr 80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Суз

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Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Thr Ser Pro Pro Pro 95 85 90 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 100 105 <210> SEQ ID NO 46 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 46 Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala 5 10 1 <210> SEQ ID NO 47 <211> LENGTH: 7 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 47 Asp Ala Ser Ser Leu Glu Ser 1 5 <210> SEQ ID NO 48 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 48 Gln Gln Tyr Thr Ser Pro Pro Pro Thr 5 1 <210> SEQ ID NO 49 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 49 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1 5 10 15 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 20 25 30 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45 Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 50 55 60 Gln Gly Arg Val Thr Met Thr His Asp Thr Ser Thr Ser Thr Val Tyr

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65 70 75 80 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Ser Phe Phe Thr Gly Phe His Leu Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 50 <211> LENGTH: 10 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 50 Ser Phe Phe Thr Gly Phe His Leu Asp Tyr 5 1 10 <210> SEQ ID NO 51 <211> LENGTH: 109 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 51 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 55 50 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 Thr Asn Glu His 85 90 Tyr Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 100 105 <210> SEQ ID NO 52 <211> LENGTH: 12 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 52 Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala 5 1 10 <210> SEQ ID NO 53 <211> LENGTH: 7 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence

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Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser 35 40 45 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro 55 50 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 Val Gly Val Tyr Tyr Cys Met Gln Ala 90 85 95 Ser Ile Met Gln Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 105 100 110 <210> SEQ ID NO 65 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 65 Met Gln Ala Ser Ile Met Gln Arg Thr 1 5 <210> SEQ ID NO 66 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 66 Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly 10 15 5 1 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser 20 25 30 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser 35 40 45 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro 50 55 60 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile 70 75 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala 85 90 Ser Ile Met Asn Arg Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 105 100 110 <210> SEQ ID NO 67 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 67 Met Gln Ala Ser Ile Met Asn Arg Ala 1 5

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Glu Pr	o Ala	Ser 20	Ile	Ser	Сүз	Arg	Ser 25	Ser	Gln	Ser	Leu	Leu 30	His	Ser
Asn Gl	y Tyr 35	Asn	Tyr	Leu	Asp	Trp 40	Tyr	Leu	Gln	Lys	Pro 45	Gly	Gln	Ser
Pro Gl 50	n Leu	Leu	Ile	Tyr	Leu 55	Gly	Ser	Asn	Arg	Ala 60	Ser	Gly	Val	Pro
Asp Ar 65	g Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
Ser Ar	g Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	Суз	Met	Gln 95	Ala
Ser Il	e Met	Asn 100	Arg	Asn	Phe	Gly	Gln 105	Gly	Thr	ГЛа	Val	Glu 110	Ile	Гла
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Met Gl 1	n Ala	Ser	Ile 5	Met	Asn	Arg	Asn							
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Gln Va 1	l Gln	Leu	Val 5	Gln	Ser	Gly	Ala	Glu 10	Val	Гла	Lys	Pro	Gly 15	Ala
Ser Va	l Lys	Val 20	Ser	Суз	Гла	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
Tyr Me	t His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly Il 50	e Ile	Asn	Pro	Ser	Gly 55	Gly	Ser	Thr	Ser	Tyr 60	Ala	Gln	Lys	Phe
Gln Gl 65	y Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
Met Gl	u Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суа
Ala Ar	g Ser	Tyr 100	Ile	Asp	Met	Asp	Tyr 105	Trp	Gly	Gln	Gly	Thr 110	Leu	Val

Thr Val Ser Ser 115

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Ser Val Lys Val 20	Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 25 30
Tyr Met His Trp <sup>.</sup> 35	Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 40 45
Gly Ile Ile Asn 5 50	Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 55 60
Gln Gly Arg Val	Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 70 75 80
Met Glu Leu Ser ,	Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Ser Tyr <sup>.</sup> 100	Val Asp Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
Thr Val Ser Ser	
115	
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Ser Tyr Val Asp 1 1	Met Asp Tyr 5
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Glu Ile Val Leu 1	Ihr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly 5 10 15
Glu Arg Ala Thr 20	Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser 25 30
Tyr Leu Ala Trp 35	Fyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu 40 45
Ile Tyr Gly Ala 50	Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser 55 60
Gly Ser Gly Ser 65	Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu 70 75 80
Pro Glu Asp Phe .	Ala Val Tyr Tyr Cys Gln Gln Asp Ile Trp Ser Pro 85 90 95
Thr Phe Gly Gln 100	Gly Thr Lys Val Glu Ile Lys 105
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Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys <210> SEQ ID NO 85 <211> LENGTH: 103 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 85 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys <210> SEQ ID NO 86 <211> LENGTH: 214 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 86 Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Phe Arg Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Ser Ser Ala 

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Ser	Thr	Lys 115	Gly	Pro	Ser	Val	Phe 120	Pro	Leu	Ala	Pro	Ser 125	Ser	Lys	Ser
Thr	Ser 130	Gly	Gly	Thr	Ala	Ala 135	Leu	Gly	Cys	Leu	Val 140	Lys	Asp	Tyr	Phe
Pro 145	Glu	Pro	Val	Thr	Val 150	Ser	Trp	Asn	Ser	Gly 155	Ala	Leu	Thr	Ser	Gly 160
Val	His	Thr	Phe	Pro 165	Ala	Val	Leu	Gln	Ser 170	Ser	Gly	Leu	Tyr	Ser 175	Leu
Ser	Ser	Val	Val 180	Thr	Val	Pro	Ser	Ser 185	Ser	Leu	Gly	Thr	Gln 190	Thr	Tyr
Ile	Суз	Asn 195	Val	Asn	His	Lys	Pro 200	Ser	Asn	Thr	ГЛа	Val 205	Asp	Lys	Lys
Val	Glu 210	Pro	Lys	Ser	Сүз										
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GIu 1	Val	GIn	Leu	Leu 5	Glu	Ser	GIY	GIY	GIY 10	Leu	Val	GIn	Pro	GIY 15	GIY
Ser	Leu	Arg	Leu 20	Ser	Сүз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30	Thr	Tyr
Ala	Met	Asn 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Arg 50	Ile	Arg	Ser	Lys	Tyr 55	Asn	Asn	Tyr	Ala	Thr 60	Tyr	Tyr	Ala	Asp
Ser 65	Val	Lys	Gly	Arg	Phe 70	Thr	Ile	Ser	Arg	Asp 75	Asp	Ser	Lys	Asn	Thr 80
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Val	Tyr 210	Ala	Суз	Glu	Val	Thr 215	His	Gln	Gly	Leu	Ser 220	Ser	Pro	Val	Thr
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Gly 225	Gly	Gly	Gly	Ser	Gly 230	Gly	Gly	Gly	Ser	Glu 235	Val	Gln	Leu	Leu	Glu 240
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Tyr	Asn 290	Asn	Tyr	Ala	Thr	Tyr 295	Tyr	Ala	Asp	Ser	Val 300	Lys	Gly	Arg	Phe
Thr 305	Ile	Ser	Arg	Asp	Asp 310	Ser	Гла	Asn	Thr	Leu 315	Tyr	Leu	Gln	Met	Asn 320
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Thr	Leu	Val 355	Thr	Val	Ser	Ser	Ala 360	Ser	Thr	Lys	Gly	Pro 365	Ser	Val	Phe
Pro	Leu 370	Ala	Pro	Ser	Ser	Lув 375	Ser	Thr	Ser	Gly	Gly 380	Thr	Ala	Ala	Leu
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Ala	Lys 530	Thr	Lys	Pro	Arg	Glu 535	Glu	Gln	Tyr	Asn	Ser 540	Thr	Tyr	Arg	Val
Val 545	Ser	Val	Leu	Thr	Val 550	Leu	His	Gln	Asp	Trp 555	Leu	Asn	Gly	Lys	Glu 560
Tyr	Lys	Суз	Lys	Val 565	Ser	Asn	Гла	Ala	Leu 570	Gly	Ala	Pro	Ile	Glu 575	Lys
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Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys As<br/>n Gln Val Ser Leu Trp595600 605

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Ser	Arg	Trp	Gln 660	Gln	Gly	Asn	Val	Phe 665	Ser	Сүз	Ser	Val	Met 670	His	Glu
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Trp	Asn	Ser	Gly	Ala 165	Leu	Thr	Ser	Gly	Val 170	His	Thr	Phe	Pro	Ala 175	Val
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Lys 225	Thr	His	Thr	Сув	Pro 230	Pro	Сүз	Pro	Ala	Pro 235	Glu	Ala	Ala	Gly	Gly 240
Pro	Ser	Val	Phe	Leu 245	Phe	Pro	Pro	Гла	Pro 250	Lys	Asp	Thr	Leu	Met 255	Ile
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu

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			260					265					270		
Asp	Pro	Glu 275	Val	Гла	Phe	Asn	Trp 280	Tyr	Val	Asp	Gly	Val 285	Glu	Val	His
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Glu	Tyr	Lys	Суз	Lys 325	Val	Ser	Asn	Lys	Ala 330	Leu	Gly	Ala	Pro	Ile 335	Glu
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Гла	Ser	Arg	Trp 420	Gln	Gln	Gly	Asn	Val 425	Phe	Ser	Суа	Ser	Val 430	Met	His
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Ala	Met	Asn 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	ГÀа	Gly	Leu 45	Glu	Trp	Val
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Tyr	Суз	Val	Arg 100	His	Gly	Asn	Phe	Gly 105	Asn	Ser	Tyr	Val	Ser 110	Trp	Phe
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ГЛа	Gly 130	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser
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Thr	Phe	Pro	Ala 180	Val	Leu	Gln	Ser	Ser 185	Gly	Leu	Tyr	Ser	Leu 190	Ser	Ser
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Asn	Val 210	Asn	His	rÀa	Pro	Ser 215	Asn	Thr	Lya	Val	Asp 220	rÀa	Lys	Val	Glu
Pro 225	ГÀа	Ser	Суз	Asp	Gly 230	Gly	Gly	Gly	Ser	Gly 235	Gly	Gly	Gly	Ser	Glu 240
Val	Gln	Leu	Val	Glu 245	Ser	Gly	Gly	Gly	Leu 250	Val	Lys	Pro	Gly	Gly 255	Ser
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Tyr	Lys	Cys	Lys	Val 565	Ser	Asn	Lys	Ala	Leu 570	Gly	Ala	Pro	Ile	Glu 575	Lys

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Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
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Asp	Ser	Asp	Gly	Ser 645	Phe	Phe	Leu	Tyr	Ser 650	ГЛЗ	Leu	Thr	Val	Asp 655	Lys
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Ser	Leu	Arg	Leu 20	Ser	Суз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30	Thr	Tyr
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65 Len	ጥንም	ניפיו	Gln	M⊖+	70 Aan	Ser	I.eu	Ara	۔ د ۲۵	75 Glu	Aan	Thr	حا∆	Val	80 Tyr
деu	түт	ыeu	1110	85	A911	Der	ыец	лчу	90	GIU	Чар	1111	лта	95	-y-
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Lys	Gly 130	Pro	Ser	Val	Phe	Pro 135	Leu	Ala	Pro	Ser	Ser 140	Lys	Ser	Thr	Ser
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Pro	210 Lvs	Ser	Cvs	Asp	Lvs	215 Thr	His	Thr	Cvs	Pro	220 Pro	Cvs	Pro	Ala	Pro
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Gyn       Thr Leu Pro Pro Ser Arg App Glu Leu Thr Lya An Glu Val Ser 135         Leu Ser Cys Ala Val Lyg Gly Phe Tyr Pro Ser Ang Ile Ala Val Glu 165         Trp Glu Ser Ang Gly Gln Pro Glu An Am Tyr Lyg Thr Thr Pro Pro 170         Val Leu Ang Ser Ang Trp Gln Gln Gly Ann Val Phe Ser Cyg Ser Val Met 180         Ang Lyg Ser Arg Trp Gln Gln Gly Ann Val Phe Ser Cyg Ser Val Met 210         Ang Lyg Ser Arg Trp Gln Gln Gly Ann Val Phe Ser Cyg Ser Val Met 210         Pro Gly Lyg         221         2210 SEQ ID NO 94         2211 LENGTH: S90         2212 S         2212 STPE: PRT 2213 ORAMISM: Artificial Sequence         2223 OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide"         2210 NEQUENCE: 94         Gln Val Gln Luy Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 30         Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gln Gly Lug Ulu Trp Met 45         Gly Ile Ile Ann Pro Ser Gly Gly Pro Thr Ser Tyr 30         Synthet His Trp Val Arg Gln Ala Pro Gly Gln Gly Lug Ulu Trp Met 55         Gln Gly Arg Val Thr Met Thr Arg Ang Thr Ser Thr Ser Thr Val Tyr 80         Net Glu Leu Ser Ser Leu Arg Ser Glu Ang Thr Ala Val Tyr Tyr Cyr 85         Ala Arg Gly Ang Phe Ala Trp Leu Ang Tyr Thr Gly Gln Gly Thr Leu 115         Yir Met His Trp Ala Ser Thr Ser Gly Gly Thr Ala Val Tyr Tyr Cyr 85         Ala Arg Gly Ang Phe Ala Trp Leu Ang Tyr Thr Gly Gln Gly Thr Leu 1160																
Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp 11e Ala Val Glu 165Tyr Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 175Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val 180Asp Lys Ser Arg Tyr Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 210110Call Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser 2102102210221022102211221122122212221222132214221522152215221022102210221022112211221222122212221222122212221222122212221222122212221222132214221422152215221522162216221722182218221822192219221122142214221522152215221622162217221822182218221922192219221922192210221022112211221122112211	Сув	Thr 130	Leu	Pro	Pro	Ser	Arg 135	Asp	Glu	Leu	Thr	Lys 140	Asn	Gln	Val	Ser
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Leu 145	Ser	Cys	Ala	Val	Lys 150	Gly	Phe	Tyr	Pro	Ser 155	Asp	Ile	Ala	Val	Glu 160
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Trp	Glu	Ser	Asn	Gly 165	Gln	Pro	Glu	Asn	Asn 170	Tyr	Гла	Thr	Thr	Pro 175	Pro
Asp Lys Ser Arg Trp Gin Gin Gin An Vil Phe Ser Cys Ser Val Met 200 $200$ $20$	Val	Leu	Asp	Ser 180	Asp	Gly	Ser	Phe	Phe 185	Leu	Val	Ser	Lys	Leu 190	Thr	Val
His       Glu Ala Leu His An       Arg Phe Thr Gln Ly Strate       Ser Leu Ser Leu Ser         Pro Gly Lys         2210       SEQ ID NO 94         C210> SEQ ID NO 94         C211> LENOTTH: 630         C212> TYEP PET         C212> TYEP PET         C212> TYENE         C400> SEQUENCE: 94         Gln Val Gln Leu Val       Gln Ser Gly Ala Glu Val       Lys Lys Pro Gly Ala         Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ty Thr Phe Thr Ser Tyr         Gln Yat Gln Leu Ser Ser Gly Gly Pro Thr Ser Tyr Ala Gln Lys Phe         Ser Val Lys Val Pro Ser Gly Gly Pro Thr Ser Tyr Ala Gln Lys Phe         Gly Leu Ser Ser Leu Arg Ser Glu Asp Thr Ser Thr Val Rom Thr Bo         Far Arg Gly Asp Phe Ala Trp Leu Asp Tyr Trp Gly Gly Gln Gly Thr Leu 100         Yat Thr Val Ser Ser Ala Ser Thr Ser Gly Gly Pro Ser Asp 110         Yat Thr Val Ser Fer Gly Clu Pro Val Thr Ala Val Val Qu Tyr 100         Yat Thr Val Ser Fer Gly Clu Pro Glu Pro Ala Thr Val Ser Trp Asp Ser	Asp	Lys	Ser 195	Arg	Trp	Gln	Gln	Gly 200	Asn	Val	Phe	Ser	Cys 205	Ser	Val	Met
Pro Gly Lys 225 (210) SEQ ID NO 94 (211) ELMGTH: 650 (212) TYPE: PRT (223) OTHER INFORMATION: /note="Description of Artificial Sequence: (223) OTHER INFORMATION: /note="Description of Artificial Sequence: (220) OTHER INFORMATION OTHER INFORMATIN	His	Glu 210	Ala	Leu	His	Asn	Arg 215	Phe	Thr	Gln	Lys	Ser 220	Leu	Ser	Leu	Ser
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Ghn Val Ghn Leu Val Ghn Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1 5 10 15 15 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 20 20 20 20 21 Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 25 25 20 20 21 71 70 71 21 71 71 71 71 71 71 71 71 71 71 71 71 71	<400	)> SH	EQUEI	ICE :	94											
Ser Val       Lys       Val       Ser       Cys       Lys       Ala       Ser       Gly       Tyr       Thr       Phe       Thr       Ser       Tyr         Tyr       Met       His       Trp       Val       Arg       Gln       Ala       Pro       Gly       Gln       Gly       Leu       Glu       Trp       Met         Gly       Ile       Has       Pro       Ser       Gly       Fry       Ala       Glu       Jry       Met         Gly       Ala       Ass       Pro       Ser       Gly       Ass       Thr       Ser       Thr       Ala       Tyr       Tyr       Tyr       Met       Met       Mat       Tyr       Tyr       Ala       Mat       Mat       Tyr       Tyr       Mat       Mat       Tyr       Tyr       Mat       Mat       Tyr       Mat       Mat       Tyr       Tyr       Tyr       Mat       Mat       Tyr       Tyr       Tyr       Mat       Mat       Mat       Tyr       Tyr       Mat	Gln 1	Val	Gln	Leu	Val 5	Gln	Ser	Gly	Ala	Glu 10	Val	ГЛЗ	Lys	Pro	Gly 15	Ala
Tyr       Met       His       Trp       Val       Arg       Gln       Ala       Pro       Gly       Gln       Glu       Fund       Ass       Glu       Arg       Gly       Pro       Trp       Ser       Trp       Ala       Gln       Lue       Gln       Ass       Pro       Ser       Gly       Pro       Th       Ser       Tyr       Ala       Gln       Lys       Pro         Gln       Gly       Arg       Val       Th       Met       Th       Arg       Asp       Th       Ser       Glu       Asp       Th       Ser       Thr       Asp       Tyr       Typ       Gyp       Asp       Tyr       Typ       Gyp       Typ       Gyp       Typ       Gyp       Typ       Gyp       Typ       Gyp       Typ       Gyp       Gyp       Gyp       Gyp       Gyp       Gyp       Typ       Gyp       Gyp       Gyp       Typ       Gyp       Gyp       Gyp </td <td>Ser</td> <td>Val</td> <td>Lys</td> <td>Val 20</td> <td>Ser</td> <td>Сүз</td> <td>Lys</td> <td>Ala</td> <td>Ser 25</td> <td>Gly</td> <td>Tyr</td> <td>Thr</td> <td>Phe</td> <td>Thr 30</td> <td>Ser</td> <td>Tyr</td>	Ser	Val	Lys	Val 20	Ser	Сүз	Lys	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
Gly       Ile       Ale       Are       Are       Ser       Gly       Gly       Fro       Th       Ser       Tyr       Ala       Gln       Lys       Phe         Gl       Gly       Arg       Val       Thr       Met       Thr       Arg       Asp       Thr       Ser       Thr       Leu       Asp       Trr       Gly       Gly       Gly       Gly       Gly       Gly       Gly       Gly       Gly       Thr       Ala       Leu       Thr       Leu       Ser       Thr       Ser       Gly       Gly       Fr       Ala       Leu       Gly       Ser       Val       Thr       Ser       Mai       Leu       Gly       Ser       Thr       Ser       Ser       Thr	Tyr	Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
G1n       G1y       Arg       Val       Thr       Met       Arg       Arg       Arg       Arg       Ser       Glu       Asp       Thr       Ala       Val       Tyr       Byr         Met       Glu       Leu       Ser       Ser       Leu       Arg       Ser       Glu       Asp       Thr       Ala       Val       Tyr       Byr       Cys         Ala       Arg       Gly       Asp       Pho       Ala       Trp       Leu       Asp       Tyr       Tyr       Gly       Gly       Thr       Leu         Val       Thr       Val       Ser       Ser       Ala       Ser       Thr       Leu       Asp       Tyr       Tyr       Gly       Gly       Thr       Leu         Val       Thr       Val       Ser       Ser       Ala       Ser       Thr       Ser       Gly       Rer       Thr       Ala       Ser       Yar       Thr       Ser       Yar       Ser       Itr       Ser       Ser       Itr       S	Gly	Ile 50	Ile	Asn	Pro	Ser	Gly 55	Gly	Pro	Thr	Ser	Tyr 60	Ala	Gln	Lys	Phe
Met       Glu       Leu       Ser       Leu       Arg       Ser       Leu       Arg       Ser       Leu       Arg       Leu       Arg       Ala       Arg       Ala       Arg       Ala       Arg       Ser       Ala       Th       Leu       Arg       Th       Ala       Th       Leu       Arg       Th       Val       Ser       Ser       Ala       Ser       Thr       Leu       Arg       Th       Leu       Th       Leu       Th       Arg       Arg       Th       Ser       Thr       Ser       Glu       Thr       Ala       Ala       Leu       Glu       Cyr       Th       Ala       Leu       Glu       Ser       Tr       Arg       Ser       Tr       Arg       Ser       Tr       Arg       Ser       Ser <td>Gln 65</td> <td>Gly</td> <td>Arg</td> <td>Val</td> <td>Thr</td> <td>Met 70</td> <td>Thr</td> <td>Arg</td> <td>Asp</td> <td>Thr</td> <td>Ser 75</td> <td>Thr</td> <td>Ser</td> <td>Thr</td> <td>Val</td> <td>Tyr 80</td>	Gln 65	Gly	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
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ValThrValSerSerAlaSerThrLysGlyProSerValPheProLeuAlaProSerSerLysSerThrSerGlyGlyThrAlaAlaLeuGlyCysLeuValLysAspTyrPheProGluProValThrAlaAlaLeuGlyCysLeuValLysAspTyrPheProGluProValThrValSerTrpAsnSerGlyAlaLeuThrSerGlyValHisThrPhoProAlaValLeuGlnSerGlyAlaLeuThrSerGlyValHisThrPhoProAlaValLeuGlnSerSerGlyLeuThrSerGlyValHisThrProProAlaValLeuGlnSerSerGlyLeuThrThrSerCysAsnValProSerSerSerSerLeuGlyThrThrThrNaNaNaNaSerSerSerSerSerLeuGlyThrThrNaNaNaNaSerSerSerSerSerSerSerSerLeuGlyThrThrSerSerSer<	Ala	Arg	Gly	Asp 100	Phe	Ala	Trp	Leu	Asp 105	Tyr	Trp	Gly	Gln	Gly 110	Thr	Leu
Ala 130Pro SerSer LysIn SerSer IndGly SerGly SerTh SerAla AlaAla LeuGly CysLeu 145Val LeuLys AspTyr SerPhe InfoPro GluPro SerVal SerThr SerVal SerSer Trp SerTrp Asn Ser InfoSer SerTrp Asn SerSer SerThr Ser SerVal SerFro SerVal SerV	Val	Thr	Val 115	Ser	Ser	Ala	Ser	Thr 120	Lys	Gly	Pro	Ser	Val 125	Phe	Pro	Leu
LeuValLysAspTyrPheProGluProValThrValSerTrpAsnSerGlyAlaLeuThrSerGlyValHisThrPhoProAlaValLeuGlnSerSerGlyLeuTyrSerLeuSerSerValThrProAlaValLeuGlnSerSerGlyLeuTyrSerLeuSerSerValThrValProSerSerSerLeuGlyThrGlnThrTyrTleCysAsnValAsnHisLysProSerAsnLeuGlyThrLysValAsnLysLysProSerAsnSerCysAsnLeuSerGlyClyLysValGluProLeuSerCysAsnGlyClyLeuValGlySerGlySerGluValGlnLeuSerClyClyClyLeuValGlyClyGlySerGluValGlnLeuSerClyClyClyLeuValGlnProGlySerCluValGlnLeuSerClyClyClyLeuValGlnProGlySerCluClyClyClyClyClyCly	Ala	Pro 130	Ser	Ser	Lys	Ser	Thr 135	Ser	Gly	Gly	Thr	Ala 140	Ala	Leu	Gly	Сүз
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser 175Ser Gly Leu Tyr Ser Leu Ser Ser Val 185Marchi Ser Gly Thr 180Leu Gly Thr Gln Thr Tyr IIMarchi Ser 195Thr Lys Val Asp Lys Lys Val Glu ProMarchi Ser Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Ser Cys Asp Gly Gly Gly 225Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser	Leu 145	Val	Lys	Asp	Tyr	Phe 150	Pro	Glu	Pro	Val	Thr 155	Val	Ser	Trp	Asn	Ser 160
SerGlyLeuTyrSerLeuSerSerValValThrValProSerSerSerLeuGlyThrGlnThrTyrTleCysAsnValAsnHisLysProSerAsnLeuGlyThrGlnThrTyrTleCysAsnValAsnHisLysProSerAsnThrLysValAspLysLysValGluProLysSerCysAspGlyGlyGlySerGlyGlyGlyGlySerGluValGlnLeuSerGlyGlyGlyGlyLeuValGlnProGlySerLeuAspLysAspSerGlyLeuValGlnProGlySerLeuAspLysAspGlyLeuValGlnProGlySerLeuSerCysAlaAlaSer	Gly	Ala	Leu	Thr	Ser 165	Gly	Val	His	Thr	Phe 170	Pro	Ala	Val	Leu	Gln 175	Ser
LeuGlyThrGlnThrTyrIleCysAsnValAsnHisLysProSerAsnThrLysValAspLysLysValGluProLysSerCysAspGlyGlyGly210SerGlyGlyGlyGlySerGluProLysSerCysAspGlyGlyGlyGlySerGlyGlyGlyGlySerGluValGlnLeuLeuGluSerGlyGlyGlyLeuValGlnProGlySerLeuAraLeuSerCysAlaAlaSer	Ser	Gly	Leu	Tyr 180	Ser	Leu	Ser	Ser	Val 185	Val	Thr	Val	Pro	Ser 190	Ser	Ser
ThrLysValAspLysLysValGluProLysSerCysAspGlyGlyGly210SerGlyGlyGlySerGluValGlnLeuLeuGluSerGlyGly225SerGlyGlySerGlySerLeuAspLeuSerGlyGlyGlyLeuValGlnProGlyGlySerLeuArgLeuSerCysAlaAlaGlyLeuValGlnProGlySerLeuArgLeuSerCysAlaAla	Leu	Gly	Thr 195	Gln	Thr	Tyr	Ile	Суз 200	Asn	Val	Asn	His	Lys 205	Pro	Ser	Asn
Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly 225 230 235 240 Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser	Thr	Lys 210	Val	Asp	Lys	Lys	Val 215	Glu	Pro	Lys	Ser	Сув 220	Asp	Gly	Gly	Gly
Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser	Gly 225	Ser	Gly	Gly	Gly	Gly 230	Ser	Glu	Val	Gln	Leu 235	Leu	Glu	Ser	Gly	Gly 240
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Tyr	Ala 290	Thr	Tyr	Tyr	Ala	Asp 295	Ser	Val	Lys	Gly	Arg 300	Phe	Thr	Ile	Ser
Arg 305	Asp	Asp	Ser	Lys	Asn 310	Thr	Leu	Tyr	Leu	Gln 315	Met	Asn	Ser	Leu	Arg 320
Ala	Glu	Aab	Thr	Ala 325	Val	Tyr	Tyr	Суа	Val 330	Arg	His	Gly	Asn	Phe 335	Gly
Asn	Ser	Tyr	Val 340	Ser	Trp	Phe	Ala	Tyr 345	Trp	Gly	Gln	Gly	Thr 350	Leu	Val
Thr	Val	Ser 355	Ser	Ala	Ser	Val	Ala 360	Ala	Pro	Ser	Val	Phe 365	Ile	Phe	Pro
Pro	Ser 370	Asp	Glu	Gln	Leu	Lys 375	Ser	Gly	Thr	Ala	Ser 380	Val	Val	Cys	Leu
Leu 385	Asn	Asn	Phe	Tyr	Pro 390	Arg	Glu	Ala	Lys	Val 395	Gln	Trp	Lys	Val	Asp 400
Asn	Ala	Leu	Gln	Ser 405	Gly	Asn	Ser	Gln	Glu 410	Ser	Val	Thr	Glu	Gln 415	Asp
Ser	Lys	Asp	Ser 420	Thr	Tyr	Ser	Leu	Ser 425	Ser	Thr	Leu	Thr	Leu 430	Ser	Lys
Ala	Asp	Tyr 435	Glu	Lys	His	Lys	Val 440	Tyr	Ala	Суз	Glu	Val 445	Thr	His	Gln
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Lys 465	Thr	His	Thr	Суз	Pro 470	Pro	Суз	Pro	Ala	Pro 475	Glu	Ala	Ala	Gly	Gly 480
Pro	Ser	Val	Phe	Leu 485	Phe	Pro	Pro	Lys	Pro 490	Lys	Asp	Thr	Leu	Met 495	Ile
Ser	Arg	Thr	Pro 500	Glu	Val	Thr	Суз	Val 505	Val	Val	Asp	Val	Ser 510	His	Glu
Asp	Pro	Glu 515	Val	Lys	Phe	Asn	Trp 520	Tyr	Val	Asp	Gly	Val 525	Glu	Val	His
Asn	Ala 530	Lys	Thr	Lys	Pro	Arg 535	Glu	Glu	Gln	Tyr	Asn 540	Ser	Thr	Tyr	Arg
Val 545	Val	Ser	Val	Leu	Thr 550	Val	Leu	His	Gln	Asp 555	Trp	Leu	Asn	Gly	Lys 560
Glu	Tyr	Lys	Cys	Lys 565	Val	Ser	Asn	Lys	Ala 570	Leu	Gly	Ala	Pro	Ile 575	Glu
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Trp	Cys 610	Leu	Val	ГЛа	Gly	Phe 615	Tyr	Pro	Ser	Asp	Ile 620	Ala	Val	Glu	Trp
Glu 625	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	F72	Thr	Thr	Pro	Pro	Val 640
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
Lys	Ser	Arg	Trp	645 Gln	Gln	Gly	Asn	Val	650 Phe	Ser	Суз	Ser	Val	655 Met	His
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Ser Lys Ala Ly 34	Gly Gln Pro	Arg Glu Pro G 345	n Val Cys Thr Leu 350	Pro
Pro Ser Arg As 355	) Glu Leu Thr	Lys Asn Gln Va 360	l Ser Leu Ser Cys 365	Ala
Val Lys Gly Ph 370	9 Tyr Pro Ser 375	Asp Ile Ala Va	l Glu Trp Glu Ser 380	Asn
Gly Gln Pro Gl 385	ı Asn Asn Tyr 390	Lys Thr Thr Pi 39	o Pro Val Leu Asp 5	Ser 400
Asp Gly Ser Ph	Phe Leu Val 405	Ser Lys Leu Th 410	r Val Asp Lys Ser 415	Arg
Trp Gln Gln Gl; 42	′Asn Val Phe	Ser Cys Ser Va 425	l Met His Glu Ala 430	Leu
His Asn His Ty 435	Thr Gln Lys	Ser Leu Ser Le 440	u Ser Pro Gly Lys 445	
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Asn Gly Tyr As: 35	ı Tyr Leu Asp	Trp Tyr Leu Gl 40	n Lys Pro Gly Gln 45	Ser
Pro Gln Leu Le 50	Ile Tyr Leu 55	Gly Ser Asn An	g Ala Ser Gly Val 60	Pro
Asp Arg Phe Se 65	Gly Ser Gly 70	Ser Gly Thr As 75	p Phe Thr Leu Lys	Ile 80
Ser Arg Val Gl	Ala Glu Asp 85	Val Gly Val Ty 90	r Tyr Cys Met Gln 95	Ala
Ser Ile Met As: 10	۱ Arg Thr Phe ۱	Gly Gln Gly Th 105	r Lys Val Glu Ile 110	Lys
Arg Thr Val Al 115	Ala Pro Ser	Val Phe Ile Ph 120	e Pro Pro Ser Asp 125	Glu
Gln Leu Lys Se 130	Gly Thr Ala 135	Ser Val Val Cy	s Leu Leu Asn Asn 140	Phe
Tyr Pro Arg Gl 145	Ala Lys Val 150	Gln Trp Lys Va 15	l Asp Asn Ala Leu 5	Gln 160
Ser Gly Asn Se	Gln Glu Ser 165	Val Thr Glu G 170	n Asp Ser Lys Asp 175	Ser
Thr Tyr Ser Le 18	Ser Ser Thr	Leu Thr Leu Se 185	r Lys Ala Asp Tyr 190	Glu
Lys His Lys Va 195	. Tyr Ala Cys	Glu Val Thr Hi 200	s Gln Gly Leu Ser 205	Ser
	a 51 3	Ara Cly Cly C	g	

60

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150

145

155

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Leu	Ser	Ser 195	Thr	Leu	Thr	Leu	Ser 200	Гла	Ala	Asp	Tyr	Glu 205	Lys	His	Lys
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Glu	Leu 370	Thr	Lys	Asn	Gln	Val 375	Ser	Leu	Trp	Сув	Leu 380	Val	Lys	Gly	Phe
Tyr 385	Pro	Ser	Asp	Ile	Ala 390	Val	Glu	Trp	Glu	Ser 395	Asn	Gly	Gln	Pro	Glu 400
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Phe	Leu	Tyr	Ser 420	ГЛа	Leu	Thr	Val	Asp 425	ГЛЗ	Ser	Arg	Trp	Gln 430	Gln	Gly
Asn	Val	Phe 435	Ser	Сүз	Ser	Val	Met 440	His	Glu	Ala	Leu	His 445	Asn	His	Tyr
Thr	Gln 450	ГÀа	Ser	Leu	Ser	Leu 455	Ser	Pro	Gly	Lys					
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< 400	)> SI	EQUEN	ICE :	99	_		_	_	_		_			_	_
Glu 1	val	GIN	Leu	Val 5	Glu	Ser	GIÀ	GIÀ	GIY 10	Leu	Val	гла	Pro	GLY 15	сту
Ser	Leu	Arg	Leu 20	Ser	Сүз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30	Asn	Ala
Trp	Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Gly	Arg	Ile	Lys	Ser	ГЛа	Thr	Asp	Gly	Gly	Thr	Thr	Asp	Tyr	Ala	Ala

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Tyr	Суз	Thr	Thr 100	Pro	Trp	Glu	Trp	Ser 105	Trp	Tyr	Asp	Tyr	Trp 110	Gly	Gln
Gly	Thr	Leu 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser	Thr	Lys	Gly 125	Pro	Ser	Val
Phe	Pro 130	Leu	Ala	Pro	Ser	Ser 135	Lys	Ser	Thr	Ser	Gly 140	Gly	Thr	Ala	Ala
Leu 145	Gly	Суз	Leu	Val	Lys 150	Asp	Tyr	Phe	Pro	Glu 155	Pro	Val	Thr	Val	Ser 160
Trp	Asn	Ser	Gly	Ala 165	Leu	Thr	Ser	Gly	Val 170	His	Thr	Phe	Pro	Ala 175	Val
Leu	Gln	Ser	Ser 180	Gly	Leu	Tyr	Ser	Leu 185	Ser	Ser	Val	Val	Thr 190	Val	Pro
Ser	Ser	Ser 195	Leu	Gly	Thr	Gln	Thr 200	Tyr	Ile	Суз	Asn	Val 205	Asn	His	Lys
Pro	Ser 210	Asn	Thr	ГÀа	Val	Asp 215	Lys	ГЛа	Val	Glu	Pro 220	ГÀа	Ser	Сув	Asp
Gly 225	Gly	Gly	Gly	Ser	Gly 230	Gly	Gly	Gly	Ser	Glu 235	Val	Gln	Leu	Leu	Glu 240
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Ala	Ala	Ser	Gly 260	Phe	Thr	Phe	Ser	Thr 265	Tyr	Ala	Met	Asn	Trp 270	Val	Arg
Gln	Ala	Pro 275	Gly	Lys	Gly	Leu	Glu 280	Trp	Val	Ser	Arg	Ile 285	Arg	Ser	Lys
Tyr	Asn 290	Asn	Tyr	Ala	Thr	Tyr 295	Tyr	Ala	Asp	Ser	Val 300	Lys	Gly	Arg	Phe
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Ser	Leu	Arg	Ala	Glu 325	Asp	Thr	Ala	Val	Tyr 330	Tyr	Сүз	Val	Arg	His 335	Gly
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Thr	Leu	Val 355	Thr	Val	Ser	Ser	Ala 360	Ser	Thr	Lys	Gly	Pro 365	Ser	Val	Phe
Pro	Leu 370	Ala	Pro	Ser	Ser	Lys 375	Ser	Thr	Ser	Gly	Gly 380	Thr	Ala	Ala	Leu
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Ser	Ser	Leu 435	Gly	Thr	Gln	Thr	Tyr 440	Ile	Суз	Asn	Val	Asn 445	His	Lys	Pro
Ser	Asn 450	Thr	Lys	Val	Asp	Lys 455	Lys	Val	Glu	Pro	Lys 460	Ser	Суз	Asp	Lys
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Pro	Glu	Val 515	Lys	Phe	Asn	Trp	Tyr 520	Val	Aab	Gly	Val	Glu 525	Val	His	Asn
Ala	Lys 530	Thr	Lys	Pro	Arg	Glu 535	Glu	Gln	Tyr	Asn	Ser 540	Thr	Tyr	Arg	Val
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Thr	Ile	Ser	Lys 580	Ala	LYa	Gly	Gln	Pro 585	Arg	Glu	Pro	Gln	Val 590	Tyr	Thr
Leu	Pro	Pro 595	Cys	Arg	Asb	Glu	Leu 600	Thr	Lys	Asn	Gln	Val 605	Ser	Leu	Trp
Суз	Leu 610	Val	Lys	Gly	Phe	Tyr 615	Pro	Ser	Asp	Ile	Ala 620	Val	Glu	Trp	Glu
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Ser	Arg	Trp	Gln 660	Gln	Gly	Asn	Val	Phe 665	Ser	Суз	Ser	Val	Met 670	His	Glu
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Ala	Lys 530	Thr	Lys	Pro	Arg	Glu 535	Glu	Gln	Tyr	Asn	Ser 540	Thr	Tyr	Arg	Val
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Суз	Leu 610	Val	Lys	Gly	Phe	Tyr 615	Pro	Ser	Asp	Ile	Ala 620	Val	Glu	Trp	Glu
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Asp	Ser	Aap	Gly	Ser 645	Phe	Phe	Leu	Tyr	Ser 650	ГÀа	Leu	Thr	Val	Asp 655	Lys
Ser	Arg	Trp	Gln 660	Gln	Gly	Asn	Val	Phe 665	Ser	Суз	Ser	Val	Met 670	His	Glu
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Leu	Ile 50	Gly	Gly	Thr	Asn	Lys 55	Arg	Ala	Pro	Gly	Thr 60	Pro	Ala	Arg	Phe
Ser 65	Gly	Ser	Leu	Leu	Gly 70	Gly	Lys	Ala	Ala	Leu 75	Thr	Leu	Ser	Gly	Ala 80
Gln	Pro	Glu	Asp	Glu 85	Ala	Glu	Tyr	Tyr	Суз 90	Ala	Leu	Trp	Tyr	Ser 95	Asn
Leu	Trp	Val	Phe 100	Gly	Gly	Gly	Thr	Lys 105	Leu	Thr	Val	Leu	Ser 110	Ser	Ala
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Pro 145	Glu	Pro	Val	Thr	Val 150	Ser	Trp	Asn	Ser	Gly 155	Ala	Leu	Thr	Ser	Gly 160
Val	His	Thr	Phe	Pro 165	Ala	Val	Leu	Gln	Ser 170	Ser	Gly	Leu	Tyr	Ser 175	Leu
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Pro	Lys	Asp	Thr	Leu 245	Met	Ile	Ser	Arg	Thr 250	Pro	Glu	Val	Thr	Cys 255	Val
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Val	Asp	Gly 275	Val	Glu	Val	His	Asn 280	Ala	Lys	Thr	Lys	Pro 285	Arg	Glu	Glu
Gln	Tyr 290	Asn	Ser	Thr	Tyr	Arg 295	Val	Val	Ser	Val	Leu 300	Thr	Val	Leu	His
Gln 305	Aab	Trp	Leu	Asn	Gly 310	Lys	Glu	Tyr	Lys	Cys 315	Lys	Val	Ser	Asn	Lys 320
Ala	Leu	Gly	Ala	Pro 325	Ile	Glu	Lys	Thr	Ile 330	Ser	Lys	Ala	Lys	Gly 335	Gln
Pro	Arg	Glu	Pro 340	Gln	Val	Tyr	Thr	Leu 345	Pro	Pro	Ser	Arg	Asp 350	Glu	Leu
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Ser	Asp 370	Ile	Ala	Val	Glu	Trp 375	Glu	Ser	Asn	Gly	Gln 380	Pro	Glu	Asn	Asn
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Tyr	Ser	Lys	Leu	Thr 405	Val	Asp	Lys	Ser	Arg 410	Trp	Gln	Gln	Gly	Asn 415	Val
Phe	Ser	Сув	Ser 420	Val	Met	His	Glu	Ala 425	Leu	His	Asn	His	Tyr 430	Thr	Gln
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Trp	Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Gly	Arg 50	Ile	Lys	Ser	Lys	Thr 55	Asp	Gly	Gly	Thr	Thr 60	Asp	Tyr	Ala	Ala
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Tyr	Суа	Thr	Thr 100	Pro	Trp	Glu	Trp	Ser 105	Trp	Tyr	Asp	Tyr	Trp 110	Gly	Gln
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Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <210> SEQ ID NO 103 <211> LENGTH: 231 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 103 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser 

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Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe 50 55 60 Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala 65 70 75 80 Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn 85 90 95 Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 100 105 <210> SEQ ID NO 111 <211> LENGTH: 107 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 111 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 5 10 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr 25 20 30 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 40 35 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 Ser Tyr Ser Thr Pro Leu 85 90 95 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys 100 105 <210> SEQ ID NO 112 <211> LENGTH: 109 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 112 Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly 5 10 1 Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Thr Ser 20 25 30 Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Phe Arg Gly 40 35 45 Leu Ile Gly Gly Thr Asn Lys  $\mbox{Arg}$  Ala Pro Gly Thr Pro Ala  $\mbox{Arg}$  Phe 50 55 60 Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala 65 75 70 80 Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn 90 85 95 Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 100 105

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Gly Ser Ile Lys Ser Lys Thr Asp 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 Pro Trp Glu Trp Ser Trp Tyr Asp Tyr Trp Gly Gln 105 100 110 Gly Thr Leu Val Thr Val Ser Ser Ala Ser 115 120 <210> SEQ ID NO 118 <211> LENGTH: 122 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 118 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly 1 5 10 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 Asp 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 Pro Tyr Glu Trp Ser Trp Tyr Asp Tyr Trp Gly Gln 100 105 110 Gly Thr Leu Val Thr Val Ser Ser Ala Ser 115 120 <210> SEQ ID NO 119 <211> LENGTH: 122 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 119 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly 1 5 10 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 Asp Gly Gly Thr Thr Asp Tyr Ala Ala 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

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Tyr Cys	Thr	Thr 100	Pro	Trp	Glu	Tyr	Ser 105	Trp	Tyr	Asp	Tyr	Trp 110	Gly	Gln
Gly Thr	Leu 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser						
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Tyr Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly Ile 50	Ile	Asn	Pro	Ser	Gly 55	Gly	Ser	Thr	Ser	Tyr 60	Ala	Gln	Lys	Phe
Gln Gly 65	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
Met Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala Arg	Asn	Tyr 100	Thr	Ile	Val	Val	Ser 105	Pro	Phe	Asp	Tyr	Trp 110	Gly	Gln
Gly Thr	Leu 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser						
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Ser Val	Lys	Val 20	Ser	Суз	ГЛа	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
Tyr Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly Ile 50	Ile	Asn	Pro	Ser	Gly 55	Gly	Ser	Thr	Ser	Tyr 60	Ala	Gln	Lys	Phe
Gln Gly 65	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
Met Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala Arg	Asn	Tyr 100	Phe	Ile	Gly	Ser	Val 105	Ala	Met	Asp	Tyr	Trp 110	Gly	Gln
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Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45 Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 55 50 60 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 65 70 75 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Gly Asp Phe Ser Ala Gly Arg Leu Met Asp Tyr Trp Gly Gln 100 105 Gly Thr Leu Val Thr Val Ser Ser Ala Ser 115 120 <210> SEQ ID NO 127 <211> LENGTH: 115 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEOUENCE: 127 Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly 15 1 5 10 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser 25 30 20 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser 35 40 45 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala 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 Val Gly Val Tyr Tyr Cys Met Gln Ala 85 90 95 Leu Gln Thr Pro Pro Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile 100 105 110 Lys Arg Thr 115 <210> SEQ ID NO 128 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 128 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 5 10 1 15 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 20 25 30 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45 Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe 55 50 60

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Gln Gly Arg Val	Thr Met Thr Arg	Asp Thr Ser Thr Ser Thr V	Val Tyr
65	70	75	80
Met Glu Leu Ser	Ser Leu Arg Ser	Glu Asp Thr Ala Val Tyr 7	Гуг Суз
	85	90	95
Ala Arg Gly Asp	Tyr Asn Ala Phe	Asp Tyr Trp Gly His Gly 1	Chr Leu
100 Wal Thr Wal Cor	Cor Mla Cor	105 110	
115 111 vai sei	SEL ALA SEL		
<pre>&lt;210&gt; SEQ ID NO &lt;211&gt; LENGTH: 1. &lt;212&gt; TYPE: PRT &lt;213&gt; ORGANISM: &lt;220&gt; FEATURE: &lt;221&gt; NAME/KEY: &lt;223&gt; OTHER INF Synthetic</pre>	129 13 Artificial Sequ source DRMATION: /note= polypeptide"	ence "Description of Artificial	. Sequence:
<400> SEQUENCE:	129		
Asp Ile Val Met	Thr Gln Ser Pro	Leu Ser Leu Pro Val Thr 1	Pro Gly
1	5	10	5
Glu Pro Ala Ser 20	Ile Ser Cys Arg	Ser Ser Gln Ser Leu Leu B 25 30	lis Ser
Asn Gly Tyr Asn	Tyr Leu Asp Trp	Tyr Leu Gln Lys Pro Gly (	Sln Ser
35	40	45	
Pro Gln Leu Leu	Ile Tyr Leu Gly	Ser Asn Arg Ala Ser Gly V	<i>l</i> al Pro
50	55	60	
Asp Arg Phe Ser	Gly Ser Gly Ser	Gly Thr Asp Phe Thr Leu 1	ys Ile
65	70	75	80
Ser Arg Val Glu	Ala Glu Asp Val	Gly Val Tyr Tyr Cys Met (	31n Ala
	85	90	95
Trp His Ser Pro 100	Thr Phe Gly Gln	Gly Thr Lys Val Glu Ile 1 105 110	lys Arg
Thr			
<pre>&lt;210&gt; SEQ ID NO &lt;211&gt; LENGTH: 1. &lt;212&gt; TYPE: PRT &lt;213&gt; ORGANISM: &lt;220&gt; FEATURE: &lt;221&gt; NAME/KEY: &lt;223&gt; OTHER INF% Synthetic</pre>	130 19 Artificial Sequ source DRMATION: /note= polypeptide"	ence "Description of Artificial	. Sequence:
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1	5	10	15
Ser Val Lys Val 20	Ser Cys Lys Ala	Ser Gly Tyr Thr Phe Thr S 25 30	Ger Tyr
Tyr Met His Trp	Val Arg Gln Ala	Pro Gly Gln Gly Leu Glu 7	Trp Met
35	40	45	
Gly Ile Ile Asn	Pro Ser Gly Gly	Ser Thr Ser Tyr Ala Gln 1	ys Phe
50	55	60	
Gln Gly Arg Val	Thr Met Thr Arg	Asp Thr Ser Thr Ser Thr V	Val Tyr
65	70	75	80
Met Glu Leu Ser	Ser Leu Arg Ser	Glu Asp Thr Ala Val Tyr 7	Гуг Сув
	85	90	95
Ala Arg Gly Ala	Thr Tyr Thr Met	Asp Tyr Trp Gly Gln Gly 1	Thr Leu

Val Thr Val Ser Ser Ala Ser 115

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Pro	Gln 50	Leu	Leu	Ile	Tyr	Leu 55	Gly	Ser	Asn	Arg	Ala 60	Ser	Gly	Val	Pro
Asp 65	Arg	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
Ser	Arg	Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	СЛа	Met	Gln 95	Ala
Ser	Ile	Met	Asn 100	Arg	Asn	Phe	Gly	Gln 105	Gly	Thr	Lys	Val	Glu 110	Ile	Lys
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<400	)> SI	EQUEI	ICE :	136											
Gln 1	Val	Gln	Leu	Gln 5	Gln	Ser	Gly	Ala	Glu 10	Leu	Val	ГЛа	Pro	Gly 15	Ala
Ser	Val	Lys	Ile 20	Ser	Сүз	Lys	Ala	Ser 25	Gly	Tyr	Ser	Phe	Thr 30	Gly	Tyr
Phe	Met	Asn 35	Trp	Val	Lys	Gln	Ser 40	His	Gly	Lys	Ser	Leu 45	Glu	Trp	Ile
Gly	Arg 50	Ile	His	Pro	Tyr	Asp 55	Gly	Asp	Thr	Phe	Tyr 60	Asn	Gln	Asn	Phe
Lys 65	Asp	Lys	Ala	Thr	Leu 70	Thr	Val	Asp	Lys	Ser 75	Ser	Asn	Thr	Ala	His 80
Met	Glu	Leu	Leu	Ser 85	Leu	Thr	Ser	Glu	Asp 90	Phe	Ala	Val	Tyr	Tyr 95	Суз
Thr	Arg	Tyr	Asp 100	Gly	Ser	Arg	Ala	Met 105	Asp	Tyr	Trp	Gly	Gln 110	Gly	Thr
Thr	Val	Thr 115	Val	Ser	Ser	Ala	Ser 120	Thr	Lys	Gly	Pro	Ser 125	Val	Phe	Pro
Leu	Ala 130	Pro	Ser	Ser	Lys	Ser 135	Thr	Ser	Gly	Gly	Thr 140	Ala	Ala	Leu	Gly
Cys 145	Leu	Val	Lys	Asp	Tyr 150	Phe	Pro	Glu	Pro	Val 155	Thr	Val	Ser	Trp	Asn 160
Ser	Gly	Ala	Leu	Thr 165	Ser	Gly	Val	His	Thr 170	Phe	Pro	Ala	Val	Leu 175	Gln
Ser	Ser	Gly	Leu 180	Tyr	Ser	Leu	Ser	Ser 185	Val	Val	Thr	Val	Pro 190	Ser	Ser
Ser	Leu	Gly 195	Thr	Gln	Thr	Tyr	Ile 200	Суз	Asn	Val	Asn	His 205	Lys	Pro	Ser
Asn	Thr 210	Lys	Val	Asp	Lys	Lys 215	Val	Glu	Pro	Lys	Ser 220	Суз	Asp	Lys	Thr
His 225	Thr	Суз	Pro	Pro	Cys 230	Pro	Ala	Pro	Glu	Ala 235	Ala	Gly	Gly	Pro	Ser 240
Val	Phe	Leu	Phe	Pro 245	Pro	Lys	Pro	Lys	Asp 250	Thr	Leu	Met	Ile	Ser 255	Arg
Thr	Pro	Glu	Val 260	Thr	Суа	Val	Val	Val 265	Asp	Val	Ser	His	Glu 270	Asp	Pro
Glu	Val	Lys 275	Phe	Asn	Trp	Tyr	Val 280	Asp	Gly	Val	Glu	Val 285	His	Asn	Ala

LYa	Thr 290	Lys	Pro	Arg	Glu	Glu 295	Gln	Tyr	Asn	Ser	Thr 300	Tyr	Arg	Val	Val	
Ser 305	Val	Leu	Thr	Val	Leu 310	His	Gln	Asp	Trp	Leu 315	Asn	Gly	Lys	Glu	Tyr 320	
Lys	Суз	Lys	Val	Ser 325	Asn	Lys	Ala	Leu	Gly 330	Ala	Pro	Ile	Glu	Lys 335	Thr	
Ile	Ser	Lys	Ala 340	Гла	Gly	Gln	Pro	Arg 345	Glu	Pro	Gln	Val	Cys 350	Thr	Leu	
Pro	Pro	Ser 355	Arg	Asp	Glu	Leu	Thr 360	Гла	Asn	Gln	Val	Ser 365	Leu	Ser	Суз	
Ala	Val 370	Lys	Gly	Phe	Tyr	Pro 375	Ser	Asp	Ile	Ala	Val 380	Glu	Trp	Glu	Ser	
Asn 385	Gly	Gln	Pro	Glu	Asn 390	Asn	Tyr	Lys	Thr	Thr 395	Pro	Pro	Val	Leu	Asp 400	
Ser	Asp	Gly	Ser	Phe 405	Phe	Leu	Val	Ser	Lys 410	Leu	Thr	Val	Aab	Lys 415	Ser	
Arg	Trp	Gln	Gln 420	Gly	Asn	Val	Phe	Ser 425	Суз	Ser	Val	Met	His 430	Glu	Ala	
Leu	His	Asn 435	His	Tyr	Thr	Gln	Lys 440	Ser	Leu	Ser	Leu	Ser 445	Pro	Gly	ГЛа	
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Gln 1	Val	Gln	Leu	Gln 5	Gln	Ser	Gly	Ala	Glu 10	Leu	Val	Lys	Pro	Gly 15	Ala	
Ser	Val	Lys	Ile 20	Ser	Сүз	Гла	Ala	Ser 25	Gly	Tyr	Ser	Phe	Thr 30	Gly	Tyr	
Phe	Met	Asn 35	Trp	Val	Lys	Gln	Ser 40	His	Gly	Lys	Ser	Leu 45	Glu	Trp	Ile	
Gly	Arg 50	Ile	His	Pro	Tyr	Asp 55	Gly	Asp	Thr	Phe	Tyr 60	Asn	Gln	Asn	Phe	
Lys 65	Aap	Lys	Ala	Thr	Leu 70	Thr	Val	Asp	Lys	Ser 75	Ser	Asn	Thr	Ala	His 80	
Met	Glu	Leu	Leu	Ser 85	Leu	Thr	Ser	Glu	Asp 90	Phe	Ala	Val	Tyr	Tyr 95	Сүз	
Thr	Arg	Tyr	Asp 100	Gly	Ser	Arg	Ala	Met 105	Asp	Tyr	Trp	Gly	Gln 110	Gly	Thr	
Thr	Val	Thr 115	Val	Ser	Ser	Ala	Ser 120	Thr	Lys	Gly	Pro	Ser 125	Val	Phe	Pro	
Leu	Ala 130	Pro	Ser	Ser	Lys	Ser 135	Thr	Ser	Gly	Gly	Thr 140	Ala	Ala	Leu	Gly	
Cys 145	Leu	Val	Lys	Asp	Tyr 150	Phe	Pro	Glu	Pro	Val 155	Thr	Val	Ser	Trp	Asn 160	
Ser	Gly	Ala	Leu	Thr 165	Ser	Gly	Val	His	Thr 170	Phe	Pro	Ala	Val	Leu 175	Gln	
Ser	Ser	Gly	Leu 180	Tyr	Ser	Leu	Ser	Ser 185	Val	Val	Thr	Val	Pro 190	Ser	Ser	
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	

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		195					200					205			
Asn	Thr 210	Lys	Val	Asp	Lys	Lys 215	Val	Glu	Pro	Lys	Ser 220	Суз	Asp	Gly	Gly
Gly 225	Gly	Ser	Gly	Gly	Gly 230	Gly	Ser	Glu	Val	Gln 235	Leu	Val	Glu	Ser	Gly 240
Gly	Gly	Leu	Val	Gln 245	Pro	Lys	Gly	Ser	Leu 250	Lys	Leu	Ser	Суз	Ala 255	Ala
Ser	Gly	Phe	Thr 260	Phe	Asn	Thr	Tyr	Ala 265	Met	Asn	Trp	Val	Arg 270	Gln	Ala
Pro	Gly	Lys 275	Gly	Leu	Glu	Trp	Val 280	Ala	Arg	Ile	Arg	Ser 285	Lys	Tyr	Asn
Asn	Tyr 290	Ala	Thr	Tyr	Tyr	Ala 295	Asp	Ser	Val	Lys	Asp 300	Arg	Phe	Thr	Ile
Ser 305	Arg	Asp	Asp	Ser	Gln 310	Ser	Ile	Leu	Tyr	Leu 315	Gln	Met	Asn	Asn	Leu 320
ГЛа	Thr	Glu	Asp	Thr 325	Ala	Met	Tyr	Tyr	Суз 330	Val	Arg	His	Gly	Asn 335	Phe
Gly	Asn	Ser	Tyr 340	Val	Ser	Trp	Phe	Ala 345	Tyr	Trp	Gly	Gln	Gly 350	Thr	Leu
Val	Thr	Val 355	Ser	Ala	Ala	Ser	Val 360	Ala	Ala	Pro	Ser	Val 365	Phe	Ile	Phe
Pro	Pro 370	Ser	Asp	Glu	Gln	Leu 375	Lys	Ser	Gly	Thr	Ala 380	Ser	Val	Val	Суз
Leu 385	Leu	Asn	Asn	Phe	Tyr 390	Pro	Arg	Glu	Ala	Lys 395	Val	Gln	Trp	Lys	Val 400
Aap	Asn	Ala	Leu	Gln 405	Ser	Gly	Asn	Ser	Gln 410	Glu	Ser	Val	Thr	Glu 415	Gln
Asp	Ser	Lys	Asp 420	Ser	Thr	Tyr	Ser	Leu 425	Ser	Ser	Thr	Leu	Thr 430	Leu	Ser
ГÀа	Ala	Asp 435	Tyr	Glu	Lys	His	Lys 440	Val	Tyr	Ala	Суз	Glu 445	Val	Thr	His
Gln	Gly 450	Leu	Ser	Ser	Pro	Val 455	Thr	Гла	Ser	Phe	Asn 460	Arg	Gly	Glu	Суз
Asp 465	Lys	Thr	His	Thr	Cys 470	Pro	Pro	Сүз	Pro	Ala 475	Pro	Glu	Ala	Ala	Gly 480
Gly	Pro	Ser	Val	Phe 485	Leu	Phe	Pro	Pro	Lys 490	Pro	Lys	Asp	Thr	Leu 495	Met
Ile	Ser	Arg	Thr 500	Pro	Glu	Val	Thr	Cys 505	Val	Val	Val	Asp	Val 510	Ser	His
Glu	Asp	Pro 515	Glu	Val	Lys	Phe	Asn 520	Trp	Tyr	Val	Asp	Gly 525	Val	Glu	Val
His	Asn 530	Ala	ГЛа	Thr	Lys	Pro 535	Arg	Glu	Glu	Gln	Tyr 540	Asn	Ser	Thr	Tyr
Arg 545	Val	Val	Ser	Val	Leu 550	Thr	Val	Leu	His	Gln 555	Aap	Trp	Leu	Asn	Gly 560
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Gly	Ala	Pro	Ile
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	570 Gln	Pro	Arg	Glu	Pro	Gln	Val
Tyr	Thr	Leu	580 Pro	Pro	Суз	Arg	Asp	585 Glu	Leu	Thr	Lys	Asn	590 Gln	Val	Ser
Len	Trn	595 Cvs	Leu	Val	Lvs	Glv	600 Phe	Tvr	Pro	Ser	Asp	605 Ile	Ala	Val	Glu
Leu	610	~y 8	มะน	var	шүр	615	1116	- Y -		Det	620	116	11T CI	• a 1	JIU

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Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys <210> SEQ ID NO 138 <211> LENGTH: 218 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 138 Asp Ile Glu Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Ile Ile Ser Cys Lys Ala Ser Gln Ser Val Ser Phe Ala Gly Thr Ser Leu Met His Trp Tyr His Gln Lys Pro Gly Gln Gln Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ala Gly Val Pro Thr Arg Phe Ser Gly Ser Gly Ser Lys Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Arg Glu Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys 180 185 190 His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <210> SEQ ID NO 139 <211> LENGTH: 257 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 139

Met Ala Gln Arg Met Thr Thr Gln Leu Leu Leu Leu Val Trp Val

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1				5					10					15	
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Leu	Leu	Asn 35	Val	Сүз	Met	Asn	Ala 40	Lys	His	His	Lys	Glu 45	Lys	Pro	Gly
Pro	Glu 50	Asp	Lys	Leu	His	Glu 55	Gln	Суз	Arg	Pro	Trp 60	Arg	Lys	Asn	Ala
Суз 65	Суз	Ser	Thr	Asn	Thr 70	Ser	Gln	Glu	Ala	His 75	Lys	Aap	Val	Ser	Tyr 80
Leu	Tyr	Arg	Phe	Asn 85	Trp	Asn	His	Cys	Gly 90	Glu	Met	Ala	Pro	Ala 95	Cys
Lys	Arg	His	Phe 100	Ile	Gln	Asp	Thr	Cys 105	Leu	Tyr	Glu	Суз	Ser 110	Pro	Asn
Leu	Gly	Pro 115	Trp	Ile	Gln	Gln	Val 120	Asp	Gln	Ser	Trp	Arg 125	Lys	Glu	Arg
Val	Leu 130	Asn	Val	Pro	Leu	Cys 135	Lys	Glu	Asp	Сүз	Glu 140	Gln	Trp	Trp	Glu
Asp 145	Cys	Arg	Thr	Ser	Tyr 150	Thr	Сүз	Lys	Ser	Asn 155	Trp	His	Lys	Gly	Trp 160
Asn	Trp	Thr	Ser	Gly 165	Phe	Asn	Lys	Суз	Ala 170	Val	Gly	Ala	Ala	Cys 175	Gln
Pro	Phe	His	Phe 180	Tyr	Phe	Pro	Thr	Pro 185	Thr	Val	Leu	Суз	Asn 190	Glu	Ile
Trp	Thr	His 195	Ser	Tyr	Lys	Val	Ser 200	Asn	Tyr	Ser	Arg	Gly 205	Ser	Gly	Arg
Сүз	Ile 210	Gln	Met	Trp	Phe	Asp 215	Pro	Ala	Gln	Gly	Asn 220	Pro	Asn	Glu	Glu
Val 225	Ala	Arg	Phe	Tyr	Ala 230	Ala	Ala	Met	Ser	Gly 235	Ala	Gly	Pro	Trp	Ala 24(
Ala	Trp	Pro	Phe	Leu 245	Leu	Ser	Leu	Ala	Leu 250	Met	Leu	Leu	Trp	Leu 255	Le
Ser															
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<400	)> SI	EQUEN	ICE :	140											
Arg 1	Ile	Ala	Trp	Ala 5	Arg	Thr	Glu	Leu	Leu 10	Asn	Val	Суз	Met	Asn 15	Ala
Lys	His	His	Lys 20	Glu	Lys	Pro	Gly	Pro 25	Glu	Asp	Lys	Leu	His 30	Glu	Gln
СЛа	Arg	Pro 35	Trp	Arg	Lys	Asn	Ala 40	САа	Сүз	Ser	Thr	Asn 45	Thr	Ser	Glr
Glu	Ala 50	His	Lys	Aap	Val	Ser 55	Tyr	Leu	Tyr	Arg	Phe 60	Asn	Trp	Asn	Нi
Cys 65	Gly	Glu	Met	Ala	Pro 70	Ala	Сүз	ГЛа	Arg	His 75	Phe	Ile	Gln	Asp	Th 80
Суз	Leu	Tyr	Glu	Суз 85	Ser	Pro	Asn	Leu	Gly 90	Pro	Trp	Ile	Gln	Gln 95	Val

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Asp	Gln	Ser	Trp 100	Arg	Lys	Glu	Arg	Val 105	Leu	Asn	Val	Pro	Leu 110	Cys	Lya
Glu	Asp	Cys 115	Glu	Gln	Trp	Trp	Glu 120	Asp	Сув	Arg	Thr	Ser 125	Tyr	Thr	Сув
Lys	Ser 130	Asn	Trp	His	Lys	Gly 135	Trp	Asn	Trp	Thr	Ser 140	Gly	Phe	Asn	Lys
Cys 145	Ala	Val	Gly	Ala	Ala 150	Суз	Gln	Pro	Phe	His 155	Phe	Tyr	Phe	Pro	Thr 160
Pro	Thr	Val	Leu	Cys 165	Asn	Glu	Ile	Trp	Thr 170	His	Ser	Tyr	Lys	Val 175	Ser
Asn	Tyr	Ser	Arg 180	Gly	Ser	Gly	Arg	Cys 185	Ile	Gln	Met	Trp	Phe 190	Asp	Pro
Ala	Gln	Gly 195	Asn	Pro	Asn	Glu	Glu 200	Val	Ala	Arg	Phe	Tyr 205	Ala	Ala	Ala
Met	Val 210	Aab	Glu	Gln	Leu	Tyr 215	Phe	Gln	Gly	Gly	Ser 220	Pro	Lys	Ser	Ala
Asp 225	Lys	Thr	His	Thr	Cys 230	Pro	Pro	Суз	Pro	Ala 235	Pro	Glu	Leu	Leu	Gly 240
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Pro	Leu	Leu	Cys	Ser	Leu	Ser	Leu	Val	Leu	Leu	Trp	Val	Ile	Ser	240
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1 His Pro His Thu 65 Tyu Sen Cys	<ul> <li>Lys</li> <li>Trp</li> <li>Lys</li> <li>50</li> <li>Met</li> <li>Glu</li> <li>Trp</li> <li>Gln</li> </ul>	Glu Lys 35 Asp Thr Cys Arg Gln	Lys 20 Thr Ile Ser Ser Lys 100 Trp	5 Pro Asn Ser Glu Pro 85 Glu Trp	Gly Ser Tyr Cys 70 Asn Arg Glu	Pro Cys Leu Lys Leu Ile Asp	Glu Cys 40 Tyr Arg Gly Leu Cys 120	Asp 25 Ser Arg His Pro Asp 105 Gln	10 Asn Thr Phe Phe Trp 90 Val Ser	Leu Asn Asn Ile 75 Ile Pro Ser	His Thr Gln Leu Phe	Asp Ser 45 Asn Asp Gln Cys Thr 125	Gln 30 Gln His Thr Val Lys 110 Cys	15 Cys Glu Cys Cys Cys Glu Lys	Ser Ala Gly Leu 80 Gln Asp Ser
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1 His Pro- His This 55 Typ Ser Cys Ser Cys Val 145	<ul> <li>Lys</li> <li>Trp</li> <li>Lys</li> <li>50</li> <li>Met</li> <li>Glu</li> <li>Trp</li> <li>130</li> <li>Gly</li> <li>Lev</li> </ul>	Glu Lys 35 Asp Thr Cys Arg Gln 115 His Ala	Lys 20 Thr Ile Ser Ser Lys 100 Trp Lys Ser Glu	5 Pro Asn Ser Glu Pro 85 Glu Cys Gly	Gly Ser Tyr Cys 70 Asn Arg Glu Trp His 150	Pro Cys Leu Lys Leu Ile Asp 135 Pro	Glu Cys 40 Tyr Arg Gly Leu Cys 120 Trp Phe Ser	Asp 25 Ser Arg His Pro Asp 105 Gln Ser Thr	10 Asn Thr Phe Phe Trp 90 Val Ser Ser Phe	Leu Asn Asn Ile Pro Ser Gly Tyr 155	His Thr Trp 60 Gln Leu Phe His 140 Phe Lvs	Asp Ser 45 Asn Asp Gln Cys Thr 125 Asn Pro	Gln Gln His Thr Val Lys 110 Cys Glu Thr	15 Cys Glu Cys Cys Cys Glu Lys Cys Ser Asp	Ser Ala Gly Leu 80 Gln Asp Ser Pro Ala 160 Tvr
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gattacgcgg ctccagttaa aggtcgtttt accatttccc gcgacgatag caaaaacact	240
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teeggigtae eggaeegitt eageggetet ggateeggea eegattteae gttgaaa	att 240
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tacctgcaaa aaccgggtca gagcoctcag ctgctgatct acctgggctc taaccgc	gct 180

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teeggtgtae eggaeegttt eageggetet ggateeggea eegattteae gttgaaaat	c 240
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teeggtgtae eggacegttt eageggetet ggateeggea eegattteae gttgaaaat	c 240
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450

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JJJ J JJJJ JJJ JJJ JJJ JJ JJ JJ JJ JJ J

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467

## 468

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469

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471

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360

472

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ccgggccagg gtctggaatg gatgggcatc attaacccaa gcggtggctc tacctcctac	180
gcgcagaaat tccagggtcg cgtcacgatg acccgtgaca ctagcacctc taccgtttat	240
atggagetgt ceageetgeg ttetgaagat aetgeagtgt aetaetgtge aegeaaetae	300
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ccgggccagg gtctggaatg gatgggcatc attaacccaa gcggtggctc tacctcctac	180
gcgcagaaat tccagggtcg cgtcacgatg acccgtgaca ctagcacctc taccgtttat	240
atggagetgt ceageetgeg ttetgaagat aetgeagtgt aetaetgtge aegeggtetg	300
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tccggtgtac cggaccgttt cagcggctct ggatccggca ccgatttcac gttgaaaatc	240
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Synthetic polynucleotide"	
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ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac	180
gcagacteeg tgaagggeeg gtteaceate teeagagaea atteeaagaa eaegetgtat	240
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cctggccagg ctcccaggct cctcatctat ggagcatcca gcagggccac tggcatccca	180
gacaggttca gtggcagtgg atccgggaca gacttcactc tcaccatcag cagactggag	240
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ccgggccagg gtctggaatg gatgggcatc attaacccaa gcggtggctc tacctcctac	180
gcgcagaaat tccagggtcg cgtcacgatg acccgtgaca ctagcacctc taccgtttat	240
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tacctgcaaa aaccgggtca gagccctcag ctgctgatct acctgggctc taaccgcgct	180
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ccgggccagg gtctggaatg gatgggcatc attaacccaa gcggtggctc tacctcctac	180
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atggagetgt ecageetgeg ttetgaagat aetgeagtgt aetaetgtge aegeggtget	300
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## **48**7

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tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atgccgggat	1800
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gtgetggaet eegaeggete ettetteete taeageaage teaeegtgga eaagageagg	1980
tggcagcagg ggaacgtett eteatgetee gtgatgeatg aggetetgea caaceaetae	2040
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caccagaage eeggecagea geecaagetg etgatetaea gageeageaa eetggaagee	180
ggcgtgccca caagattttc cggcagcggc agcaagaccg acttcaccct gaacatccac	240
cccgtggaag aagaggacgc cgccacctac tactgccagc agagcagaga gtacccctac	300
acctteggeg gaggeaceaa getggaaate aagegtaegg tggetgeace atetgtette	360
atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg	420
aataacttot atoocagaga ggocaaagta cagtggaagg tggataacgo ootocaatog	480
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Lys His His Lys Glu Lys Pro Gly Pro Glu Asp Lys Leu His Glu Gln 20 25 30	
Cys Arg Pro Trp Arg Lys Asn Ala Cys Cys Ser Thr Asn Thr Ser Gln 35 40 45	
Glu Ala His Lys Asp Val Ser Tyr Leu Tyr Arg Phe Asn Trp Asn His 50 55 60	
Cys Gly Glu Met Ala Pro Ala Cys Lys Arg His Phe Ile Gln Asp Thr 65 70 75 80	
Cys Leu Tyr Glu Cys Ser Pro Asn Leu Gly Pro Trp Ile Gln Gln Val 85 90 95	
Asp Gln Ser Trp Arg Lys Glu Arg Val Leu Asn Val Pro Leu Cys Lys 100 105 110	
Glu Asp Cys Glu Gln Trp Trp Glu Asp Cys Arg Thr Ser Tyr Thr Cys 115 120 125	
Lys Ser Asn Trp His Lys Gly Trp Asn Trp Thr Ser Gly Phe Asn Lys 130 135 140	

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ProThrValLeuCysAsnGluIleTrpThrHisSerTyrLysValSerAsnTyrSerArgGlySerGlyArgCysIleGlnMetTrpPheAspProAlaGluGlySerGluGluValAlaArgPheTyrAlaAlaAlaAlaGluGluSerCuoValAlaArgPheTyrAlaAlaAla
Asn Tyr Ser Arg Gly Ser Gly Arg Cys Ile Gln Met Trp Phe Asp Pro 180 185 190 Ala Gln Gly Asn Pro Asn Glu Glu Val Ala Arg Phe Tyr Ala Ala Ala 195 200 205
Ala Gln Gly Asn Pro Asn Glu Glu Val Ala Arg Phe Tyr Ala Ala Ala 195 200 205
200 200
Met
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Asp Gln Cys Ser Pro Trp Lys Lys Asn Ala Cys Cys Thr Ala Ser Thr 35 40 45
Ser Gln Glu Leu His Lys Asp Thr Ser Arg Leu Tyr Asn Phe Asn Trp 50 55 60
Asp His Cys Gly Lys Met Glu Pro Ala Cys Lys Arg His Phe Ile Gln 65 70 75 80
Asp Thr Cys Leu Tyr Glu Cys Ser Pro Asn Leu Gly Pro Trp Ile Gln 85 90 95
Gln Val Asn Gln Ser Trp Arg Lys Glu Arg Phe Leu Asp Val Pro Leu 100 105 110
Cys Lys Glu Asp Cys Gln Arg Trp Trp Glu Asp Cys His Thr Ser His 115 120 125
Thr Cys Lys Ser Asn Trp His Arg Gly Trp Asp Trp Thr Ser Gly Val 130 135 140
Asn Lys Cys Pro Ala Gly Ala Leu Cys Arg Thr Phe Glu Ser Tyr Phe 145 150 155 160
Pro Thr Pro Ala Ala Leu Cys Glu Gly Leu Trp Ser His Ser Tyr Lys
Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg Cys Ile Gln Met Trp Phe
Asp Ser Ala Gln Gly Asn Pro Asn Glu Glu Val Ala Arg Phe Tyr Ala
Ala Ala Met His Val Asn
210
<210> SEQ ID NO 229 <211> LENGTH: 220 <212> TYPE: PRT <213> ORGANISM: Homo sapiens
<400> SEQUENCE: 229
Ser Ala Arg Ala Arg Thr Asp Leu Leu Asn Val Cys Met Asn Ala Lys 1 5 10 15
His His Lys Thr Gln Pro Ser Pro Glu Asp Glu Leu Tyr Gly Gln Cys 20 25 30

Ser Pro Trp Lys Lys Asn Ala Cys Cys Thr Ala Ser Thr Ser Gln Glu

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		35					40					45			
Leu	His 50	Lys	Asp	Thr	Ser	Arg 55	Leu	Tyr	Asn	Phe	Asn 60	Trp	Asp	His	Суз
Gly 65	Lys	Met	Glu	Pro	Thr 70	Суз	ГЛЗ	Arg	His	Phe 75	Ile	Gln	Asp	Ser	Суз 80
Leu	Tyr	Glu	Суз	Ser 85	Pro	Asn	Leu	Gly	Pro 90	Trp	Ile	Arg	Gln	Val 95	Asn
Gln	Ser	Trp	Arg 100	Lys	Glu	Arg	Ile	Leu 105	Asn	Val	Pro	Leu	Cys 110	Lys	Glu
Asp	Cys	Glu 115	Arg	Trp	Trp	Glu	Asp 120	Суз	Arg	Thr	Ser	Tyr 125	Thr	Cys	Lys
Ser	Asn 130	Trp	His	Гла	Gly	Trp 135	Asn	Trp	Thr	Ser	Gly 140	Ile	Asn	Glu	Суз
Pro 145	Ala	Gly	Ala	Leu	Cys 150	Ser	Thr	Phe	Glu	Ser 155	Tyr	Phe	Pro	Thr	Pro 160
Ala	Ala	Leu	Cys	Glu 165	Gly	Leu	Trp	Ser	His 170	Ser	Phe	Гла	Val	Ser 175	Asn
Tyr	Ser	Arg	Gly 180	Ser	Gly	Arg	Суа	Ile 185	Gln	Met	Trp	Phe	Asp 190	Ser	Ala
Gln	Gly	Asn 195	Pro	Asn	Glu	Glu	Val 200	Ala	Lys	Phe	Tyr	Ala 205	Ala	Ala	Met
Asn	Ala 210	Gly	Ala	Pro	Ser	Arg 215	Gly	Ile	Ile	Asp	Ser 220				
<400	)> SE	EQUE	NCE :	230	and Be	Lou	Lor	Acr	Wo I	(h)	Mot	⊼ crr	71-	Luc	ц! с
Thr 1	Arg	Ala	Arg	Thr 5	Glu	Leu	Leu	Asn	Val 10	Сүз	Met	Asp	Ala	Lys 15	His
His	Lys	Glu	Lys 20	Pro	Gly	Pro	Glu	Asp 25	Asn	Leu	His	Asp	Gln 30	Сүз	Ser
Pro	Trp	Lys 35	Thr	Asn	Ser	Сүз	Cys 40	Ser	Thr	Asn	Thr	Ser 45	Gln	Glu	Ala
His	Lys 50	Asp	Ile	Ser	Tyr	Leu 55	Tyr	Arg	Phe	Asn	Trp 60	Asn	His	Суз	Gly
Thr 65	Met	Thr	Ser	Glu	Cys 70	Lys	Arg	His	Phe	Ile 75	Gln	Asp	Thr	Суз	Leu 80
Tyr	Glu	Суз	Ser	Pro 85	Asn	Leu	Gly	Pro	Trp 90	Ile	Gln	Gln	Val	Asp 95	Gln
Ser	Trp	Arg	Lys 100	Glu	Arg	Ile	Leu	Asp 105	Val	Pro	Leu	Суз	Lys 110	Glu	Asp
Сүз	Gln	Gln 115	Trp	Trp	Glu	Aap	Cys 120	Gln	Ser	Ser	Phe	Thr 125	Сүз	Lys	Ser
Asn	Trp 130	His	Lys	Gly	Trp	Asn 135	Trp	Ser	Ser	Gly	His 140	Asn	Glu	Суа	Pro
Val 145	Gly	Ala	Ser	Суа	His 150	Pro	Phe	Thr	Phe	Tyr 155	Phe	Pro	Thr	Ser	Ala 160
Ala	Leu	Cys	Glu	Glu	Ile	Trp	Ser	His	Ser	Tyr	ГЛа	Leu	Ser	Asn	Tyr
				165					T / U					1/5	

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Gly Asn Pro Asn Glu Glu Val Ala Arg Phe Tyr Ala Glu Ala Met Ser 195 200 205 <210> SEQ ID NO 231 <211> LENGTH: 213 <212> TYPE: PRT <213> ORGANISM: Macaca fascicularis <400> SEQUENCE: 231 Glu Ala Gln Thr Arg Thr Ala Arg Ala Arg Thr Glu Leu Leu Asn Val 1 5 10 Cys Met Asn Ala Lys His His Lys Glu Lys Pro Gly Pro Glu Asp Lys 20 25 30 Leu His Glu Gln Cys Arg Pro Trp Lys Lys Asn Ala Cys Cys Ser Thr 40 35 Asn Thr Ser Gln Glu Ala His Lys Asp Val Ser Tyr Leu Tyr Arg Phe 60 55 50 Asn Trp Asn His Cys Gly Glu Met Ala Pro Ala Cys Lys Arg His Phe 65 70 75 80 Ile Gln Asp Thr Cys Leu Tyr Glu Cys Ser Pro Asn Leu Gly Pro Trp 85 90 95 Ile Gln Gln Val Asp Gln Ser Trp Arg Lys Glu Arg Val Leu Asn Val 100 105 110 Pro Leu Cys Lys Glu Asp Cys Glu Arg Trp Trp Glu Asp Cys Arg Thr 115 120 125 Ser Tyr Cys Lys Ser Asn Trp His Lys Gly Trp Asn Trp Thr Ser Gly 130 135 140 Phe Asn Lys Cys Pro Val Gly Ala Ala Cys Gln Pro Phe His Phe Tyr 145 150 155 160 Phe Pro Thr Pro Thr Val Leu Cys Asn Glu Ile Trp Thr Tyr Ser Tyr 165 170 175 Lys Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg Cys Ile Gln Met Trp 190 180 185 Phe Asp Pro Ala Gln Gly Asn Pro Asn Glu Glu Val Ala Arg Phe Tyr 195 200 205 Ala Ala Ala Met Ser 210 <210> SEQ ID NO 232 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 232 Pro Trp Glu Tyr Ser Trp Tyr Asp Tyr 1 5 <210> SEQ ID NO 233 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide"

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<210> SEQ ID NO 239 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 239 Gly Asp Phe Ser Ala Gly Arg Leu Met Asp Tyr 5 <210> SEQ ID NO 240 <211> LENGTH: 10 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 240 Met Gln Ala Leu Gln Thr Pro Pro Ile Thr 1 10 5 <210> SEQ ID NO 241 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 241 Gly Asp Tyr Asn Ala Phe Asp Tyr 1 5 <210> SEQ ID NO 242 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 242 Met Gln Ala Trp His Ser Pro Thr 1 5 <210> SEQ ID NO 243 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEOUENCE: 243 Gly Ala Thr Tyr Thr Met Asp Tyr 1 5 <210> SEQ ID NO 244 <211> LENGTH: 9 <212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 244 Met Gln Ala Leu Gln Thr Pro Ile Thr 1 5 <210> SEQ ID NO 245 <211> LENGTH: 227 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 245 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 5 10 15 1 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 20 25 30 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 35 40 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val 50 55 60 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr 65 70 75 80 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly 85 90 95 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile 100 105 110 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 115 120 125 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser 135 130 140 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu 150 145 155 160 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 165 170 175 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 180 185 190 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 195 200 205 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser 210 215 220 Pro Gly Lys 225 <210> SEQ ID NO 246 <211> LENGTH: 2076 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polynucleotide" <400> SEQUENCE: 246

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cccgtgctgg	actccgacgg	ctccttcttc	ctctacagca	agctcaccgt	ggacaagagc	1980
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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Synthetic polynucleotide"

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aacageggag eeetgaeete eggegtgeae acetteeeeg eegtgetgea gagttetgge	540
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag	780
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac	840
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acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag	960
tacaagtgca aggtetecaa caaageeete ggegeeeeea tegagaaaae catetecaaa	1020
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accaagaacc aggtcageet etegtgegea gteaaagget tetateeeag egacategee	1140
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg	1200
gacteegaeg geteettett eetegtgage aageteaeeg tggacaagag eaggtggeag	1260
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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 Thr65707580	
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr 85 90 95	

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Tyr Cys Thr Thr Pro Trp Glu Trp Ser Trp Tyr Asp Tyr Trp Gly Gln 105 100 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 249 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 249 Glu 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 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 Gln Gly Gly Thr Thr Asp Tyr Ala Ala 55 50 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 Pro Trp Glu Trp Ser Trp Tyr Asp Tyr Trp Gly Gln 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 250 <211> LENGTH: 125 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 250 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 Thr Tyr 20 25 30 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 50 55 60 Ser 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 Arg Ala Glu Asp Thr Ala Val Tyr 85 90 95 Tyr Cys Val Arg His Gly Asn Phe Gly Ala Ser Tyr Val Ser Trp Phe 100 105 110 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser 120 115 125

509

510

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Ala	Lys 530	Thr	Lys	Pro	Arg	Glu 535	Glu	Gln	Tyr	Asn	Ser 540	Thr	Tyr	Arg	Val
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Tyr	Гла	Суз	ГЛа	Val 565	Ser	Asn	Гла	Ala	Leu 570	Gly	Ala	Pro	Ile	Glu 575	ГЛа
Thr	Ile	Ser	Lys 580	Ala	ГЛа	Gly	Gln	Pro 585	Arg	Glu	Pro	Gln	Val 590	Tyr	Thr

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Leu	Pro	Pro 595	Сув	Arg	Asp	Glu	Leu 600	Thr	Гла	Asn	Gln	Val 605	Ser	Leu	Trp
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Ser 625	Asn	Gly	Gln	Pro	Glu 630	Asn	Asn	Tyr	Lys	Thr 635	Thr	Pro	Pro	Val	Leu 640
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Ser	Arg	Trp	Gln 660	Gln	Gly	Asn	Val	Phe 665	Ser	Суз	Ser	Val	Met 670	His	Glu
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Pro	Ser 210	Asn	Thr	Lys	Val	Asp 215	Lys	Lys	Val	Glu	Pro 220	ГÀа	Ser	Сув	Азр
Lys 225	Thr	His	Thr	Суа	Pro 230	Pro	Суз	Pro	Ala	Pro 235	Glu	Ala	Ala	Gly	Gly 240
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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

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Gln 65	Gly	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Thr	Ser	Thr	Val	Tyr 80
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Ala	Arg	Gly	Asp 100	Phe	Ala	Trp	Leu	Asp 105	Tyr	Trp	Gly	Gln	Gly 110	Thr	Leu
Val	Thr	Val 115	Ser	Ser	Ala	Ser	Thr 120	Lys	Gly	Pro	Ser	Val 125	Phe	Pro	Leu
Ala	Pro 130	Ser	Ser	ГЛа	Ser	Thr 135	Ser	Gly	Gly	Thr	Ala 140	Ala	Leu	Gly	Суз
Leu 145	Val	Lys	Aap	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln 175	Ser
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
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Ser	Ive	Ala	Ive	325 G1v	Gln	Pro	Ara	Glu	330 Pro	Gln	Val	Cve	Thr	335 Leu	Pro
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Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys <210> SEO ID NO 260 <211> LENGTH: 690 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" <400> SEQUENCE: 260 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Pro Thr Ser Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Asp Phe Ala Trp Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser 

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser

			180					185					190		
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Thr	Lys 210	Val	Asp	Lys	Lys	Val 215	Glu	Pro	Lys	Ser	Суз 220	Asp	Gly	Gly	Gly
Gly 225	Ser	Gly	Gly	Gly	Gly 230	Ser	Glu	Val	Gln	Leu 235	Leu	Glu	Ser	Gly	Gly 240
Gly	Leu	Val	Gln	Pro 245	Gly	Gly	Ser	Leu	Arg 250	Leu	Ser	Суз	Ala	Ala 255	Ser
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Gly	Lys	Gly 275	Leu	Glu	Trp	Val	Ser 280	Arg	Ile	Arg	Ser	Lys 285	Tyr	Asn	Asn
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Ala	Glu	Asp	Thr	Ala 325	Val	Tyr	Tyr	Суз	Val 330	Arg	His	Gly	Asn	Phe 335	Gly
Asn	Ala	Tyr	Val 340	Ser	Trp	Phe	Ala	Tyr 345	Trp	Gly	Gln	Gly	Thr 350	Leu	Val
Thr	Val	Ser 355	Ser	Ala	Ser	Val	Ala 360	Ala	Pro	Ser	Val	Phe 365	Ile	Phe	Pro
Pro	Ser 370	Asp	Glu	Gln	Leu	Lys 375	Ser	Gly	Thr	Ala	Ser 380	Val	Val	СЛа	Leu
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Ala	Asp	Tyr 435	Glu	Lys	His	Lys	Val 440	Tyr	Ala	Суз	Glu	Val 445	Thr	His	Gln
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Asp	Pro	Glu 515	Val	ГÀа	Phe	Asn	Trp 520	Tyr	Val	Asp	Gly	Val 525	Glu	Val	His
Asn	Ala 530	Lys	Thr	Γλa	Pro	Arg 535	Glu	Glu	Gln	Tyr	Asn 540	Ser	Thr	Tyr	Arg
Val 545	Val	Ser	Val	Leu	Thr 550	Val	Leu	His	Gln	Asp 555	Trp	Leu	Asn	Gly	Lys 560
Glu	Tyr	Lys	Сүз	Lys 565	Val	Ser	Asn	Lys	Ala 570	Leu	Gly	Ala	Pro	Ile 575	Glu
ГЛЗ	Thr	Ile	Ser 580	ГЛа	Ala	Lys	Gly	Gln 585	Pro	Arg	Glu	Pro	Gln 590	Val	Tyr
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Gly Lys 690

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

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Ser	Leu	Arg	Leu 20	Asp	Сүз	Lys	Ala	Ser 25	Gly	Ile	Thr	Phe	Ser 30	Asn	Ser	
Gly	Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val	
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Lys 65	Gly	Arg	Phe	Thr	Ile	Ser	Ara	7 an								
Leu					70		5	Азр	Asn	Ser 75	ГÀа	Asn	Thr	Leu	Phe 80	
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Lys	Asp	Thr	Leu	Met 245	Ile	Ser	Arg	Thr	Pro 250	Glu	Val	Thr	Cys	Val 255	Val	
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Ser 65	Gly	Ser	Gly	Thr	Asp 70	Phe	Thr	Leu	Thr	Ile 75	Ser	Ser	Leu	Glu	Pro 80	
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Val Gln Phe 275	Asn Trp	Tyr Val	Asp Gly 280	y Val	Glu	Val	His 285	Asn	Ala	Lys
Thr Lys Pro 290	Arg Glu	Glu Gln 295	Phe As:	n Ser	Thr	Tyr 300	Arg	Val	Val	Ser
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Cys Lys Val	Ser Asn 325	Lys Gly	Leu Pr	Ser 330	Ser	Ile	Glu	Lys	Thr 335	Ile
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Pro Ser Gln 355	Glu Glu	Met Thr	Lys As: 360	n Gln	Val	Ser	Leu 365	Thr	Cys	Leu
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Gly Gln Pro 385	Glu Asn	Asn Tyr 390	Lys Th	r Thr	Pro 395	Pro	Val	Leu	Asp	Ser 400
Asp Gly Ser	Phe Phe 405	Leu Tyr	Ser Ar	g Leu 410	Thr	Val	Asp	Lys	Ser 415	Arg
Trp Gln Glu	Gly Asn 420	Val Phe	Ser Cy 42	s Ser 5	Val	Met	His	Glu 430	Ala	Leu
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Ser Leu Glu	Pro Glu 85	Asp Phe	Ala Va	l Tyr 90	Tyr	Сүз	Gln	His	Ser 95	Arg
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Lys	Thr 290	Lys	Pro	Arg	Glu	Glu 295	Gln	Tyr	Ala	Ser	Thr 300	Tyr	Arg	Val	Val
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Lys	Сүз	Lys	Val	Ser 325	Asn	Lys	Ala	Leu	Pro 330	Ala	Pro	Ile	Glu	Lys 335	Thr
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Ser	Asp	Gly	Ser	Phe 405	Phe	Leu	Tyr	Ser	Lys 410	Leu	Thr	Val	Aap	Lys 415	Ser
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<pre>&lt;21: &lt;22: &lt;22: &lt;22: &lt;22: &lt;22: &lt;22: &lt;22:</pre>	<pre>&gt;&gt;&gt; FE &gt;&gt; NZ &gt;&gt; NZ &gt;&gt; OT &gt;&gt; SY &gt;&gt;&gt; SE Ile Arg Ala Ser Ser Asp Phe Ser Ala 130 Val</pre>	XATUF XATUF XME/F THER INTER Gln Val Trp 35 Ala Ser Gly Val 115 Ser Gln	SM: SE: EE: CEY: INFC ETIC ICE: Met Thr 20 Tyr Ser Gly Ala Gln 100 Phe Val Trp	Art. sound poly 279 Thr 5 Ile Gln Phe Thr Thr 85 Gly Ile Val Lys	Cree FION: Torpept Gln Thr Gln Leu Asp 70 Tyr Thr Phe Cys Val 150	<pre>// I Ser Cys Lys Tyr 55 Phe Tyr Lys Pro Leu 135 Asp</pre>	Pro Arg Pro 40 Ser Thr Cys Val Pro 120 Leu Asn	Ser Ala 25 Gly Leu Gln Glu 105 Ser Asn Ala	Ser 10 Ser Lys Val Thr Gln 90 Ile Asp Asn Leu	ion Leu Gln Ala Pro Ile 75 Tyr Lys Glu Phe Gln 155	of A Ser Asp Pro Ser Leu Arg Gln Tyr 140 Ser	Ala Val Lys 45 Arg Ser Tyr Thr Leu 125 Pro Gly	Ser Ser 30 Leu Phe Leu His Val 110 Lys Arg Asn	Val 15 Thr Leu Ser Gln Ser Ala Ser Glu Ser	equence: Gly Ala Ile Gly Pro 80 Ala Ala Gly Ala Gly Ala
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Ser 65	Gly	Ser	Gly	Arg	Asp 70	Tyr	Ser	Phe	Asn	Ile 75	Asn	Asn	Leu	Glu	Pro 80
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Asp	Gln	Ala	Ser 20	Ile	Ser	Суз	Arg	Ser 25	Ser	Arg	Thr	Ile	Leu 30	His	Ser
Ser	Gly	Asn 35	Thr	Tyr	Leu	Glu	Trp 40	Tyr	Leu	Gln	Lys	Pro 45	Gly	Gln	Ser
Pro	Lys 50	Leu	Leu	Ile	Tyr	Lys	Val	Ser	Asn	Arg	Phe	Ser	Gly	Val	Pro
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Asn	Ile
ser	Arg	Val	Glu	Ala	Glu	Asp	Leu	Gly	Val	75 Tyr	Tyr	Суа	Phe	Gln	Asp
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594

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Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys

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Asp Gln Ala Ser 20	Ile	Ser Cys A	Arg Ser 25	Ser	Arg	Ser	Ile	Val 30	His	Ser
Ser Gly Asn Thr 35	Tyr	Leu Glu T 4	frp Tyr 40	Leu	Gln	Lys	Pro 45	Gly	Gln	Ser
Pro Lys Leu Leu 50	Ile	Tyr Lys V 55	/al Ser	Asn	Arg	Phe 60	Ser	Gly	Val	Pro
Asp Arg Phe Ser 65	Gly	Ser Gly S 70	Ser Gly	Thr	Asp 75	Phe	Thr	Leu	Asn	Ile 80
Ser Arg Val Glu	Ala 85	Glu Asp I	Leu Gly	Val 90	Tyr	Tyr	Сүз	Phe	Gln 95	Asp
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597

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598

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Ser Gln Asp Leu Ala Ala Ile Trp Ala Gly Phe Tyr Ile Ala Gly Asp

# US 10,781,262 B2

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65					70					75					80
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Gly	Arg	Ile	Arg 100	Asn	Gly	Ala	Leu	Leu 105	Arg	Val	Tyr	Val	Pro 110	Ala	Ser
Ser	Leu	Pro 115	Gly	Phe	Tyr	Arg	Thr 120	Ser	Leu	Thr	Leu	Ala 125	Ala	Pro	Glu
Ala	Ala 130	Gly	Glu	Val	Glu	Arg 135	Leu	Ile	Gly	His	Pro 140	Leu	Pro	Leu	Ala
Leu 145	Asp	Ala	Ile	Thr	Gly 150	Pro	Glu	Glu	Glu	Gly 155	Gly	Arg	Leu	Glu	Thr 160
Ile	Leu	Gly	Trp	Pro 165	Leu	Ala	Glu	Arg	Thr 170	Val	Val	Ile	Pro	Ser 175	Ala
Ile	Pro	Thr	Asp	Pro	Arg	Asn	Val	Gly	Gly	Asp	Leu	Asp	Pro	Ser	Ser
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	210					215									
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Pro 1	Thr	~ Gly	Ala	Glu 5	Phe	Leu	Gly	Asp	Gly 10	Gly	Asp	Val	Ser	Phe 15	Ser
Thr	Arg	Gly	Thr 20	Gln	Asn	Trp	Thr	Val 25	Glu	Arg	Leu	Leu	Gln 30	Ala	His
Ala	Gln	Leu 35	Glu	Glu	Arq	Glv	Tvr	Val	Phe	Val	a1				
Ala	Leu				5	1	40				GIY	Tyr 45	His	Gly	Thr
		GIu	Ala	Ala	Gln	Ser	40 Ile	Val	Phe	Gly	Gly Gly	Tyr 45 Val	His Arg	Gly Ala	Thr Arg
Ser	Gln	GIu Asp	Ala Leu	Ala Arg	Gln Ala	Ser 55 Ile	40 Ile Trp	Val Arg	Phe Gly	Gly Phe	Gly 60 Tyr	Tyr 45 Val Ile	His Arg Ala	Gly Ala Gly	Thr Arg Asp
Ser 65 Pro	Gln Ala	Glu Asp His	Ala Leu Ala	Ala Arg Tyr	Gln Ala 70 Gly	Ser 55 Ile Tyr	40 Ile Trp Ala	Val Arg Gln	Phe Gly Asp	Gly Phe 75 Gln	Gly 60 Tyr Glu	Tyr 45 Val Ile Pro	His Arg Ala Asp	Gly Ala Gly Ala	Thr Arg Asp 80 Arg
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Tyr	Ile	Cys	Asn	Val 85	Asn	His	Lys	Pro	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Lys	Val	Glu	Pro 100	Lys	Ser	Суз	Asp	Lys 105	Thr	His	Thr	Суз	Pro 110	Pro	Cys
Pro	Ala	Pro 115	Glu	Leu	Leu	Gly	Gly 120	Pro	Ser	Val	Phe	Leu 125	Phe	Pro	Pro
Lys	Pro 130	Lys	Asp	Thr	Leu	Met 135	Ile	Ser	Arg	Thr	Pro 140	Glu	Val	Thr	Суз
Val 145	Val	Val	Asp	Val	Ser 150	His	Glu	Aab	Pro	Glu 155	Val	Lys	Phe	Asn	Trp 160
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Gln 225	Pro	Arg	Glu	Pro	Gln 230	Val	Tyr	Thr	Leu	Pro 235	Pro	Ser	Arg	Asp	Glu 240
Leu	Thr	Lys	Asn	Gln 245	Val	Ser	Leu	Thr	Cys 250	Leu	Val	Lys	Gly	Phe 255	Tyr
Pro	Ser	Asp	Ile 260	Ala	Val	Glu	Trp	Glu 265	Ser	Asn	Gly	Gln	Pro 270	Glu	Asn
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Val 305	Phe	Ser	Cys	Ser	Val 310	Met	His	Glu	Ala	Leu 315	His	Asn	His	Tyr	Thr 320
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Lys	Pro 130	Lys	Asp	Thr	Leu	Met 135	Ile	Ser	Arg	Thr	Pro 140	Glu	Val	Thr	Суз
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Pro	Ser	Asp	Ile 260	Ala	Val	Glu	Trp	Glu 265	Ser	Asn	Gly	Gln	Pro 270	Glu	Asn
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Ala Ser	Leu Lys	Ala 195 Glu	180 Leu Lys	Ile Ile	Phe Gln	Gly	Ala 200 Leu	185 Leu Ser	Ile Leu	Phe Ile	Lys Ser	Trp 205 Leu	190 Tyr Ala	Ser Asn	His Leu

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Ala	Arg	Ser	Phe 100	Phe	Thr	Gly	Phe	His 105	Leu	Asp	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Ala 120	Ser	Thr	Lys	Gly	Pro 125	Ser	Val	Phe
Pro	Leu 130	Ala	Pro	Ser	Ser	Lys 135	Ser	Thr	Ser	Gly	Gly 140	Thr	Ala	Ala	Leu

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-continued

145       150       135       160         Ann Ser Gly Als Lee Thr Ser Gly Val Kie Thr Phe Pro Als Val Leet 185       175         Oln Ser Ser Gly Lee Thr Ser Lee Ser Ser Val Val Thr Yal Pro Ser 185       186         Ser Ser Lee Gly Thr Gln Thr Tyr Ile Cyo Am Val Am Hie bye Pro 200       200         Ser Am Thr Lyo Val Am Lyo bye Val Glu Pro Lyo Am Val Am Hie bye Pro 210       200         Ser Val Phe Lee Phe Pro Pro Lyo Pro Cyo Am Val Am Hie Dye Pro 220       200         Ser Val Phe Lee Phe Pro Pro Lyo Pro Lyo Am Thr Lee Met 186       265         Arg Thr Pro Glu Val Thr Cyo Val Val Val Val Am D'Al Ser Hie Glu Amp 270       201         Ser Val Phe Lee Phe Pro Pro Lyo Val Am Cyr Val Gu Val Can 270       205         Pro Glu Val Thr Cyo Val Val Val Am Gr Thr Tyr Arg Val 200       205         Ser Val Lee Thr Val Eeu Hie Glu Am Try Tyr Val Am Gr Thr Tyr Arg Val 200       200         200       205       201 Val Lyr Pro Arg Glu Glu Glu Fro Arg Glu Val Glu Yal Glu Yal Glu 300         201 Val Lee Thr Val Lee Hie Glu Amp Try Lee Am Gly Hyr Glu 305       202         179 Lyr Cyr Lyr Val Ser Am Lyr Ala Lee Gly Ala Fro Glu Val Thr Glu 326       200         179 Lyr Cyr Lyr Val Larg Gly Glu Eeu Thr Lyr Am Glu Yal Cyr Thr 340       300         180 Cyr Cyr Lyr Val Ser Am Lyr Am Glu Yal Cyr Thr 340       300         191 Lyr Wal Am Lyr Glu Ma Am Try Lyr Thr Thr Pro Pro Val Leeu 345       300																	
Ann Ser Gly Ala Leu Thr fer Gly Val Hie Mr Phe Peo Ala Val Leu 150 160 Ser Ger Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Yal Pro Ser 160 Ser Ser Gen Gly Thr Gh Thr Tyr He Cye Ann Val Am Hie Lye Pro 200 201 Thr Hie Thr Cye Pro Pro Cye Pro Ala Pro Glu Ala Ala Gly Gly Pro 202 202 Thr Hie Thr Cye Pro Pro Cye Pro Ala Pro Glu Ala Ala Gly Gly Pro 203 204 Zer Val Pro Cue Pro Cye Pro Ala Pro Gly An Val Am Hie Lie Ser 205 205 Thr Hie Thr Cye Pro Pro Cye Pro Jyr An Thr Leu Net He Ser 205 207 Glu Val Thr Cye Val Val Val Val Val Am Val Ser His Glu Amp 207 208 Thr Hie Ver Pro Pro Cye Pro Jyr Val Amp Gly Val Glu Val Kin Amp 209 209 Thr Lye Pro Arg Glu Glu Glu Glu Glu Glu Glu Glu Gly Tyr Leu Net He Ser 200 200 Thr Lye Pro Arg Glu Glu Glu Glu Glu Glu Tyr Am Ser Thr Tyr Arg Val 200 200 Thr Lye Pro Arg Glu Glu Glu Glu Glu Gly Ala Pro Gly Val Glu Val Kin Amp 200 201 Val Leu Thr Val Leu Hie Gln Am Tyr Lye Arg Cly Tor 205 207 Lye Cye Lye Val Ser Am Lye Ala Leu Gly Ala Pro I Le Clu Lye 205 207 Lye Cye Lye Val Ser Am Lye Ala Leu Gly Ala Pro I Le Clu Lye 205 207 Lye Cye Lye Val Ser Am Lye Ala Leu Gly Ala Pro I Lye Jou Cye Thr 208 208 Am Gly Gln Pro Glu Am Am Tyr Lye Thr Thr Pro Pro Val Leu 209 209 Ser Am Gly Gln Pro Glu Am Am Tyr Lye Thr Thr Tyr Arg Lya 209 Ser Am Gly Gln Pro Glu Am Am Tyr Lye Thr Thr Thr Di Ala 200 Ser Am Gly Gln Pro Glu Am Am Tyr Lye Thr Thr Thr Di Ala 201 Leu Thr 205 202 Ser Am Gly Gln Pro Glu Am Am Tyr Lye Thr Thr Thr Di Ala 203 Ser Am Gly Gln Pro Glu Am Am Tyr Lye Thr Thr Thr Di Ala 204 Ser Arg Thr Gln Gln Glu Am Val Phe Ser Cye Ser Val He Hu Glu 205 207 Ser Thr 205 208 Thr 105 208 Ser Am Gly Ser Phe Phe Leu Val Ger Lye Ser Val Ku Hu Glu 209 Ser Am Gly Di Pro Thr Thr Gln Lye Ser Leu Ser Leu Ser 200 Ser Thr 205 200 Ser Thr 205 201 Leven MISSER: Attrificial Sequence 202 Ser Thr 205 202 Ser Thr 205 202 Ser Am Hie Thr 100 Am Val Phe Ser Cye Ser Val He Hu Glu Thr 205 203 Ser Am Gly Ser Thr 100 Am Val Phe Ser Cye Ser Val He Hu Gly Am Val Ser 204 Ser Am Gly Ser MISSER: A	145					150					155					160	
Gin Ser Ser Gily Leu Tyr Ser Leu Ser Ser Val Val Thr Yal Pro Ser 190       Ser Ser Leu Gily Thr Gin Thr Tyr 11e Cys Aen Val Aan Hie Lys Pro 201         Ser Ann Thr Hys Val Aap Lys Jys Val Giu Pro Lys Ser Cys Aep Lys 201       Ser Yal Pro Leu Pro Cys Pro Ala Pro Giu Ala Ala Gily Gily Pro 230         Ser Val Phe Leu Pye Pro Pro Cys Pro Lys Pro Lys Aep Thr Leu Het Te Ser 240       Ser Val Phe Leu Pye Pro Pro Cys Pro Lys Pro Lys Aep Thr Leu Het Te Ser 240         Arg Thr Pro Giu Val Thr Cys Val Cal Cu Gin Tyr Aen Sor Thr Tyr Arg Val 250       Ser Thr Yag Val Cal Cu Gin Thr Yan Sor Thr Tyr Arg Val 250         Yal Ser Val Leu Thr Val Leu His Gin Aep Trp Leu Aen Gily Lys Cin 310       Sar Thr Yag Val 250         Yal Ser Val Leu Thr Val Leu His Gin Aep Trp Leu Aen Gily Lys Cin 310       Sar Thr Yag Val 320         Yal Ser Val Leu Thr Val Leu His Gin Aep Trp Leu Aen Gily Cin 310       Sar Aen Lys Arg Gil U For Gin Val Ser Leu Ser 330         Yar Lys Cyc Lys Wal Ser Aen Lys Arg Gil U For Gin Val Ser Leu Ser 320       Sar Aen Gily Gily Phe Typ Tro Ser Aep Tie Ain Cin Val Ser Leu Ser 330         Yar Ser Ang Gily Gily Phe Typ Tro Ser Aep Tie Ain Val Gin Trp Gil 330       Sar Aen Gily Gily Phe Typ Tro Ser Aep Tie Ain Val Aep Lys 440         Ser Aen Gily Gil Phe Phe Leu Val Ser Lys Eeu Fro Cin 445       Sar Aep Gily Ser Phe Phe Leu Val Ser Lys Eeu Fro Cin 445         Ser Arg Tip Cin Cin Cin Ser Mer Hei Kei Ser Leu Ser Fro Cin 445       Sar Aep Gily Ser Phe Phe Leu Val Ser Leu Ser Leu Ser Pro Cin 445         Ser Lin Northwitter Stre 3220       Ser Lin No 395       Sar Aep Gily Ser Hei Phe Leu Val Ser	Asn	Ser	Gly	Ala	Leu 165	Thr	Ser	Gly	Val	His 170	Thr	Phe	Pro	Ala	Val 175	Leu	
See Ser Lea Gly Thr Gln Thr Tyr Ile Cyo Ann Val Am His Lyo Pro         See Ann Thr Lyo Val Am Lyo Ya Val Glu Pro Lyo See Cyo Am Lyo         Thr His Thr Cyo Pro Cyo Pro Ala Pro Glu Ala Ala Gly Gly Pro         216         Thr His Thr Cyo Pro Cyo Pro Ala Pro Glu Ala Ala Gly Gly Pro         248         Thr His Thr Cyo Pro Cyo Pro Lyo Any Thr Lea Met The Ser         246         Arg Thr Pro Glu Val Thr Cyo Val Val Val Any Cyl See His Glu Amp         246         250         Pro Glu Val Thr Cyo Val Glu Glu Glu Tyr Am See Thr Tyr Arg Val         200         Yal See Val Lea Thr Val Lea His Glu App         200         Yal See Tva Lyo Pro Arg Glu Glu Glu Tyr Am See Thr Tyr Arg Val         200         Yal See Val Lea Thr Val Lea His Glu App         200         Yal See Tva Lyo Pro Arg Glu Glu Glu Tyr Am See Thr Tyr Arg Val         200         Yal See Tal Lyo Gly Lyo Cys Lyo Cys Lyo Age Glu Glu Glu Pro Glu Yal For I Glu Lyo Glu         310       310         310       310         310       310         310       310         310       310         310       310         310       310         310       310         310       310	Gln	Ser	Ser	Gly 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pro	Ser	
Set Aun Thr Lya Val Aug Lya Lya Lya Val Glu Pro Lya Set Cya Aug Lya         212         213         214         215         215         215         216         217         218         219         210         211         212         213         214         215         215         216         217         218         218         219         219         210         211         211         212         213         214         215         215         216	Ser	Ser	Leu 195	Gly	Thr	Gln	Thr	Tyr 200	Ile	Суз	Asn	Val	Asn 205	His	Lys	Pro	
The His Thr Cys Pro 230       230       235       235       240       240         Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Apr Lys Apr Us Lew Het Is Ser 240       245       270         Arg Thr Pro Glu Val Thr Cys Val Val Val Val Ap Gly Val Glu Val His Apn 225       270       270         Pro Glu Val Lys Phe Asn Trp Tyr Val App Gly Val Glu Val His Apn 225       270       270         Val Ery Pho Arg Glu Glu Glu Glu Gn Tyr Ann Ser Thr Tyr Arg Val 200       200       231         Val Ery Val Leu Thr Val Leet His Gln App Trp Leu Aen Gly Lys Glu 315       200       200         Val Ery Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Ser Leu Ser 320       335       330         Tr Lie Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Ser Leu Ser 320       335       360         Lew Pro Pro Ser Arg Apg Glu Leu Thr Lys Ann Gln Val Ser Leu Ser 320       360       360         Cys Ala Val Lys Gly Phe Tyr Pro Ser App He Ala Val Glu Trp Glu 370       375       380         App Ser Apg Gly Ser Phe Phe Leu Val Sor Lys Leu Ser Lau Ser 400       425       425         Arg Tyr Gln Gln Gly Ann Val Phe Ser Cys Ser Val Net His Glu 420       425       425         Lys       Val Ser Phe Phe Leu Val Ser Leu Ser Leu Ser Pro Gly 425       425       425         Lys       Val Ser Tyr Che Ser Val Ser Val Ser Leu Ser Pro Gly 425       425       425         Lys       Val Se	Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Glu	Pro	Lys 220	Ser	Суз	Asp	Lys	
Set Val Phe Leu Phe Pro Pro Lys Pro Lys App The Leu Met Ile Set 255 Arg Thr Pro Glu Val Thr Cys Val Val Val Val App Val Set His Glu App 270 Pro Clu Val Lys Phe Am Trp Tyr Val App Gly Val Glu Val Glu Val Set His App 275 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Am See Thr Tyr Arg Val 290 Val Ser Val Leu Thr Val Leu His Gln App Trp Leu Am Gly Lys Glu 305 Tyr Lys Cys Lys Val Ser Am Lys Ala Leu Gly Ala Pro Ile Glu Lys 320 Tyr Lys Cys Lys Val Ser Am Lys Ala Leu Gly Ala Pro Gln Val Cys Thr 340 325 Thr Ile Ser Lyg Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr 340 As Pro Pro Ser Arg Apg Glu Leu Thr Lys Am Gln Val Ser Leu Ser 365 Cys Ala Val Lys Gly Phe Tyr Pro Ser App 1le Ala Val Glu Trp Glu 375 Ser Am Gly Gln Pro Glu Am Am Tyr Lys Thr Thr Pro Pro Val Leu 380 Arg Ser Am Gly Gln Pro Glu Am Am Tyr Lys Thr Thr Pro Pro Val Leu 400 Asp Ser Am Gly Gln Pro Gly Am Val Phe Ser Cys Ser Val Met His Glu 410 415 Ser Am Gly Gln Pro Glu App Val Dye Ser Leu Ser Pro Gly 415 Lys Val Ser Am His Tyr Thr Gln Lys Ser Leu Ser Pro Gly 445 Lys Culls LimGNEN: Artificial Sequence *220- NEXTORE: *221- NEMKYRTION: /notemito add *223- OTHER INFORMATION: /notemito add *224- SHARKYRT source *223- OTHER INFORMATION: /notemito add *224- SHARKYRT source *223- OTHER INFORMATION: /notemito add *224- SHARKYRT source *223- OTHER INFORMATION: /notemito add *224- CHARKYRT NOTER: *224- MARKYRT NOTER: *224- MARKYRT NOTER: Aga For Gly Thr Leu Ser Leu Ser Pro Gly 15 Glu The Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly 15 Glu The Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly 15 Glu The Val Leu Gry Arg Ala Ser Glu Ser Val Ser Pro Gly 15 Glu The Val Leu Ser Cys Arg Ala Ser Glu Ser Val Ser Ser Ser Ser 30 Ser Martone: 395 Glu The Val Leu Ser Cys Arg Ala Ser Glu Ser Val Ser Ser Ser 50 30	Thr 225	His	Thr	Cys	Pro	Pro 230	Сүз	Pro	Ala	Pro	Glu 235	Ala	Ala	Gly	Gly	Pro 240	
Arg The Pro Glu Val The Cyo Val Val Val Val App Val See His Glu App 260         Pro Glu Val Lyo Phe Am Trp Tyr Val App Gly Val Glu Val His Amn 280         Ala Lyo The Lyo Pro Arg Glu Glu Gln Tyr Am See The Tyr Arg Val 295         Yal See Val Lee Thr Val Leu His Gln App Trp Leu Am Gly Lye Glu 320         Tyr Lye Cys Lye Val Ser Am Lye Ala Leu Gly Ala Pro Ile Glu Lye 320         Tyr Lye Cys Lye Val Ser Am Lye Ala Leu Gly Ala Pro Ile Glu Lye 320         The Ile See Lys Ala Lye Gly Gln Pro Arg Glu Pro Gln Val Cye Thr 345         Leu Pro Pro Ser Arg App Glu Leu The Lye Am Gln Val Ser Leu Ser 365         Cys Ala Val Lye Gly Phe Tyr Pro Ser App 11e Ala Val Glu Trp Glu 356         Leu Pro Pro Ser Arg App Glu Leu The Lye Am Gln Val Ser Leu Ser 365         Cys Ala Val Lye Gly Phe Tyr Pro Ser App 11e Ala Val Glu Trp Glu 330         Ser Am Gly Gln Pro Glu Am Am Tyr Lye Thr The Pro Pro Val Leu 340         Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lye Leu Thr Val App Lye 400         Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lye Leu Thr Val App Lye 410         Ala Leu His Am His Tyr Thr Gln Lys Ser Leu Ser Pro Gly 410         Ata See MENTORS:         Callos EMENTRE:         Callos EMENTRE:         Callos EMENTRE:         Callos EMENTRE:         Callos Leu His Am His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly 410         Callos ComMINS:       Artificial Sequence         Callos ComMINS:       Artificial Sequence	Ser	Val	Phe	Leu	Phe 245	Pro	Pro	Lys	Pro	Lys 250	Asp	Thr	Leu	Met	Ile 255	Ser	
Pro Glu Val Lye Phe Am Try Tyr Val Amy Gly Val Clu Val Hie Am         275         Ala Lye Thr Lye Pro Arg Glu Glu Gln Tyr Am Ser Thr Tyr Arg Val         296         Val Ser Val Leu Thr Val Leu Hie Gln Amy Try Leu Am Gly Lye Glu         306         717         Lye Cye Lye Val Ser Am Lye Ala Leu Gly Ala Pro Ile Glu Lye         325         717         Lye Cye Lye Val Ser Am Lye Ala Lye Gly Clu Pro Gln Yal Cye Thr         340         718         109         719         119         721         721         721         725         723         725         724         725         725         725         726         727         728         729         720         721         725         727         728         729         729         720         720         720         720         720         720         720         720         720 </td <td>Arg</td> <td>Thr</td> <td>Pro</td> <td>Glu 260</td> <td>Val</td> <td>Thr</td> <td>Суз</td> <td>Val</td> <td>Val 265</td> <td>Val</td> <td>Asp</td> <td>Val</td> <td>Ser</td> <td>His 270</td> <td>Glu</td> <td>Asp</td> <td></td>	Arg	Thr	Pro	Glu 260	Val	Thr	Суз	Val	Val 265	Val	Asp	Val	Ser	His 270	Glu	Asp	
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Am Ser Thr Tyr Arg Val 290 Yal Ser Val Leu Thr Val Leu His Gln Aep Trp Leu Aen Gly Lys Glu 310 Tyr Lys Cys Lys Val Ser Aen Lys Ala Leu Gly Ala Pro Ile Glu Lys 325 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr 340 Ser Leu Pro Pro Ser Arg Aep Glu Leu Thr Lys Aen Gln Val Ser Leu Ser 355 Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 Ser Asn Gly Gln Pro Glu Aen Aen Tyr Lys Thr Thr Pro Pro Val Leu 385 Ser Asn Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val App Lys 400 Aep Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val App Lys 400 Ala Leu His Aon His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Fro Gly 415 Lys 2210 SEQ ID NO 395 2212 TYPE: FRT 2213 OKGANISM: Artificial Sequence 2213 OKGANISM: Artificial Sequence 2213 OKGANISM: Artificial Sequence 2213 OKGANISM: Artificial Sequence 2213 OKGANISM: Artificial Sequence 2214 NUME/KEY: Source 2215 SEQ ID NO 395 2215 UNDE 2216 OKGANISM: Artificial Sequence 2216 OKGANISM: Artificial Sequence 2217 TYPE: FRT 2213 OKGANISM: INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" 2214 NUME/KEY: Source 2215 OKGANISM: INFORMATION: /note="Description of Artificial Sequence: 2215 SEQ ID NO 395 2215 UNDE/KE: 2216 NUME/KEY: MOD RES 2216 OKGANISM: INFORMATION: /note= Description of Artificial Sequence: 2216 SEQUENCE: 395 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly 1 5 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser 20 20 21 21 21 21 21 21 21 21 21 21	Pro	Glu	Val 275	Lys	Phe	Asn	Trp	Tyr 280	Val	Asp	Gly	Val	Glu 285	Val	His	Asn	
All bear thatAll bear the Gln Aep Trp Leu Aon Gly Lys Glu 320305310311and Ap Trp Leu Aon Gly Lys Glu 320Tyr Lys Cys Lys Val Ser Aon Lys Ala Leu Gly Ala Pro Ile Glu Lys 325333Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr 340345200355360Cys Ala Val Lys Gly Pro Yr Pro Ser Asp Ile Ala Val Glu Trp Glu 370375Ser Ann Gly Gln Pro Glu Aan Aan Tyr Lys Thr Thr Pro Pro Val Leu 385400Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys 405410Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys 420413Ala Leu His Ann His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly 435420C210> SEQ ID NO 395 <211> LENVTH: 2162212< TYPE PreT 2230 ORGANISM: Artificial Sequence <220> EPATURE: <221> NAME/KEY: source <222> OTHER: INFORMATION: /note="Description of Artificial Sequence: synthetic polypeptide" <221> OTHER: INFORMATION: /note="Description of Artificial Sequence: <220> EPATURE: <221> OTHER: INFORMATION: /note="Description of Artificial Sequence: <221> OTHER: INFORMATION: /note="Description of Artificial Sequence: <222> OTHER: INFORMATION: /note="Description of Artificial Sequence: <222> OTHER: INFORMATION: /note="Description of Info400510101010101010101010101010 <td>Ala</td> <td>Lys 290</td> <td>Thr</td> <td>Lys</td> <td>Pro</td> <td>Arg</td> <td>Glu 295</td> <td>Glu</td> <td>Gln</td> <td>Tyr</td> <td>Asn</td> <td>Ser 300</td> <td>Thr</td> <td>Tyr</td> <td>Arg</td> <td>Val</td> <td></td>	Ala	Lys 290	Thr	Lys	Pro	Arg	Glu 295	Glu	Gln	Tyr	Asn	Ser 300	Thr	Tyr	Arg	Val	
TyrLitLitLitTyrLysCysLysLysSanTyrLysCysLysSanLysAlaSanSanSanSanSanThrIleSerLysAlaLysGluProArgSanSanSanSanSanSanSanLeuProProSerArgArgGluProGluSanSanSanSanSanSanSanCysAlaValLysGluPheTyrProSerArgSerArgGlySerPhePheLeuValSerLauSanSerArgGlySerPhePheLeuValSerLauSanSanSerArgGlySerPhePheLeuValSerLauSanSanSerArgGlySerPhePheLeuValSerSanLauSanSerArgGlySerPhePheLeuValSanSanSanSanSerArgGlySerPheLeuValSerLauLauSanSanSerArgGlySerLauValArgLauLauSanSanSanSanSanSanSanSanSanSanSanSanSanSan <td< td=""><td>Val 305</td><td>Ser</td><td>Val</td><td>Leu</td><td>Thr</td><td>Val 310</td><td>Leu</td><td>His</td><td>Gln</td><td>Asp</td><td>Trp 315</td><td>Leu</td><td>Asn</td><td>Gly</td><td>Lys</td><td>Glu 320</td><td></td></td<>	Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gln	Asp	Trp 315	Leu	Asn	Gly	Lys	Glu 320	
Thr Ile Ser Lys Ala Lys Gly Gln Pro Str 345       Str Gln Val Cys Thr 350         Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser 355       Str Gly Gln Pro Yr Pro Ser Asp Ile Ala Val Glu Trp Glu 370         370       375       380         Ser Aan Gly Gln Pro Glu Aan Asn Tyr Lys Thr Thr Pro Pro Val Leu 385       Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys 400         Asp Ser Asp Gly Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu 420       415         Ser Arg Trp Gln Gln Asn Tyr Thr Gln Lys Ser Leu Ser Pro Gly 430       445         Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Pro Gly 435       446         C210> SEQ ID NO 395	Tyr	Lys	Сув	Lys	Val 325	Ser	Asn	Lys	Ala	Leu 330	Gly	Ala	Pro	Ile	Glu 335	Lys	
Leu Pro Pro Ser Arg Arg Glu Leu Thr Lys Arg Glu Xal Ser Leu Ser 355 Cys Ala Val Lys Gly Phe Tyr Pro Ser Arg 11e Ala Val Glu Trp Glu 370 Ser Arg Gly Gin Pro Glu Asn Arg Tyr Lys Thr Thr Pro Pro Val Leu 385 Asp Ser Arg Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Aep Lys 405 405 Asp Ser Arg Trp Gln Gln Gly Arg Val Phe Ser Cys Ser Val Met His Glu 420 Ala Leu His Arg His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly 435 440 445 Lys <210> SEG ID NO 395 <211> LENGTH : 216 <2120> TFPE : PRT <213> ORGANISM: Artificial Sequence <220> FRATURE: <221> NAME/KEY: source <221> NAME/KEY: source <2220> FRATURE: <2220 FRATURE: <2220 FRATURE: <2220 CATION: (201)(201) <223> OHRE INFORMATION: Any amino acid <400> SEQUENCE: 395 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly 1 5 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser 20 20 20 21 21 21 20 21 21 21 21 21 21 22 20 21 21 21 22 20 22 22 22 22 22 22 22 22	Thr	Ile	Ser	Lys 340	Ala	Lys	Gly	Gln	Pro 345	Arg	Glu	Pro	Gln	Val 350	Cys	Thr	
Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 Ser Asp Gly Gln Pro Glu Aan Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys 405 Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Cys Ser Val Met His Glu 420 Ala Leu His Aan His Tyr Thr Gln Lys Ser Leu Ser Pro Gly 435 Lys 	Leu	Pro	Pro 355	Ser	Arg	Asp	Glu	Leu 360	Thr	Lys	Asn	Gln	Val 365	Ser	Leu	Ser	
See Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 390 390 400 400 400 400 400 400 400 400 400 4	Суз	Ala 370	Val	Гла	Gly	Phe	Tyr 375	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	
Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys 405 410 425 410 415 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu 420 425 430 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Pro Gly 435 440 445 445 445 445 445 445 44	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu 400	
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420425430Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Pro Gly 435440445Lys<210> SEQ ID NO 395 <211> LENGTH: 216 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <222> OTHER INFORMATION: /note="Description of Artificial Sequence: synthetic polypeptide" <222> OTHER INFORMATION: /note="Description of Artificial Sequence: synthetic polypeptide" <222> CATION: (201)(201) <223> OTHER INFORMATION: Any amino acid<400> SEQUENCE: 395Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly 1Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser 20202530	Ser	Arg	Trp	Gln	405 Gln	Gly	Asn	Val	Phe	410 Ser	Суз	Ser	Val	Met	415 His	Glu	
435 440 445 Lys <li>SEQ ID NO 395 &lt;211&gt; LENGTH: 216 &lt;212&gt; TYPE: PRT &lt;213&gt; ORGANISM: Artificial Sequence &lt;220&gt; FEATURE: &lt;221&gt; NAME/KEY: source &lt;222&gt; NAME/KEY: source &lt;223&gt; OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" &lt;220&gt; FEATURE: &lt;221&gt; NAME/KEY: MOD_RES &lt;222&gt; LOCATION: (201)(201) &lt;223&gt; OTHER INFORMATION: Any amino acid &lt;400&gt; SEQUENCE: 395 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</li>	Ala	Leu	His	420 Asn	His	Tyr	Thr	Gln	425 Lys	Ser	Leu	Ser	Leu	430 Ser	Pro	Gly	
<pre>&lt;210&gt; SEQ ID NO 395 &lt;211&gt; LENGTH: 216 &lt;212&gt; TYPE: PRT &lt;213&gt; ORGANISM: Artificial Sequence &lt;220&gt; FEATURE: &lt;221&gt; NAME/KEY: source &lt;223&gt; OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide" &lt;220&gt; FEATURE: &lt;221&gt; NAME/KEY: MOD_RES &lt;222&gt; LOCATION: (201)(201) &lt;223&gt; OTHER INFORMATION: Any amino acid &lt;400&gt; SEQUENCE: 395 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</pre>	ГЛа		435					440					445				
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	<210 <211 <212 <213 <220 <221 <223 <220 <221 <222 <223 <220 <221 <222 <223	$\begin{array}{llllllllllllllllllllllllllllllllllll$	EQ II ENGTI (PE: RGAN: EATUI AME/I CHER (nthe EATUI AME/I CCAT: CHER	O NO H: 2: PRT ISM: RE: KEY: INF( ≥tic RE: KEY: ION: INF( NCE:	395 16 Art: sou: DRMA poly MOD_ (20: DRMA 395	ific rce TION ypep _RES 1) TION	ial : : /n tide (201 : An	Seque ote=' '' y am:	ence "Deso ino a	crip	tion	of 2	Arti:	Eicia	al Se	equen	ice:
151015Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser 202530	<400 Glu	/> SH	vouel Val	Leu	395 Thr	Gln	Ser	Pro	Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly	
20 25 30	1 Glu	Ara	Ala	Thr	5 Leu	Ser	Cvs	Ara	- Ala	10 Ser	Gln	Ser	Val	Ser	15 Ser	Ser	
	GIU	чгд	лıd	20	ыец	ser	сув	лıд	25	ser	GTU	ser	var	30	Set	Set	

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu 40 35 45 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser 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 Thr Asn Glu His 85 90 95 Tyr Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val 100 105 Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys 115 120 Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg 130 135 140 Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn 155 145 150 160 Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser 165 170 175 Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys 180 185 190 Val Tyr Ala Cys Glu Val Thr His Xaa Gly Leu Ser Ser Pro Val Thr 195 200 205 Lys Ser Phe Asn Arg Gly Glu Cys 210 215 <210> SEQ ID NO 396 <211> LENGTH: 7 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 396 Gly Thr Asn Ala Arg Ala Pro 5 1 <210> SEQ ID NO 397 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide" <400> SEQUENCE: 397 Ala Leu Trp Tyr Ala Asn Leu Trp Val 1 5 <210> SEQ ID NO 398 <211> LENGTH: 5 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide"

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Asn	Phe	Gly	Asn 340	Ser	Tyr	Val	Ser	Trp 345	Phe	Ala	Tyr	Trp	Gly 350	Gln	Gly
Thr	Leu	Val 355	Thr	Val	Ser	Ser	Ala 360	Ser	Thr	Lys	Gly	Pro 365	Ser	Val	Phe
Pro	Leu 370	Ala	Pro	Ser	Ser	Lys 375	Ser	Thr	Ser	Gly	Gly 380	Thr	Ala	Ala	Leu
Gly 385	Cys	Leu	Val	Lys	Asp 390	Tyr	Phe	Pro	Glu	Pro 395	Val	Thr	Val	Ser	Trp 400
Asn	Ser	Gly	Ala	Leu 405	Thr	Ser	Gly	Val	His 410	Thr	Phe	Pro	Ala	Val 415	Leu
Gln	Ser	Ser	Gly 420	Leu	Tyr	Ser	Leu	Ser 425	Ser	Val	Val	Thr	Val 430	Pro	Ser
Ser	Ser	Leu 435	Gly	Thr	Gln	Thr	Tyr 440	Ile	Суз	Asn	Val	Asn 445	His	Lys	Pro
Ser	Asn 450	Thr	Lys	Val	Asp	Lys 455	Lys	Val	Glu	Pro	Lys 460	Ser	Cys	Asp	Lys
Thr 465	His	Thr	Сув	Pro	Pro 470	Суа	Pro	Ala	Pro	Glu 475	Ala	Ala	Gly	Gly	Pro 480
Ser	Val	Phe	Leu	Phe 485	Pro	Pro	Lys	Pro	Lys 490	Asp	Thr	Leu	Met	Ile 495	Ser
Arg	Thr	Pro	Glu 500	Val	Thr	Суз	Val	Val 505	Val	Asp	Val	Ser	His 510	Glu	Asp
Pro	Glu	Val 515	Lys	Phe	Asn	Trp	Tyr 520	Val	Asp	Gly	Val	Glu 525	Val	His	Asn
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	540 Leu	Asn	Gly	Lys	Glu
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Thr	Ile	Ser	Lys	565 Ala	Lys	Gly	Gln	Pro	570 Arg	Glu	Pro	Gln	Val	575 Tyr	Thr
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Cvs	Leu	595 Val	LVS	G]v	Phe	Tvr	600 Pro	Ser	Asp	Ile	Ala	605 Val	G] 11	Trp	Glu
Car	610	01	- <u>-</u> r5	Dma	<i>с</i> л	615	7		1P	The	620	Dre	Dere	P	Len
625	Asu	GTÀ	GTU	F10	630	ASU	Asu.	ıyr	цув	635		P10	P10	val	640
Aab	ser	Aab	σту	Ser 645	Pne	Pne	Leu	TYr	ser 650	гла	Leu	Thr	va⊥	Asp 655	гЛа
Ser	Arg	Trp	Gln 660	Gln	Gly	Asn	Val	Phe 665	Ser	Сүв	Ser	Val	Met 670	His	Glu
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Lys

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Tr	o Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Gl	y Arg 50	Ile	Lys	Ser	Lys	Thr 55	Glu	Gly	Gly	Thr	Thr 60	Asp	Tyr	Ala	Ala
Pr 65	o Val	Lys	Gly	Arg	Phe 70	Thr	Ile	Ser	Arg	Asp 75	Asp	Ser	Lys	Asn	Thr 80
Le	u Tyr	Leu	Gln	Met 85	Asn	Ser	Leu	ГЛа	Thr 90	Glu	Asp	Thr	Ala	Val 95	Tyr
ту	r Cys	Thr	Thr 100	Pro	Tyr	Glu	Trp	Ser 105	Trp	Tyr	Asp	Tyr	Trp 110	Gly	Gln
Gl	y Thr	Leu 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser	Thr	ГЛа	Gly 125	Pro	Ser	Val
Ph	e Pro 130	Leu	Ala	Pro	Ser	Ser 135	Lys	Ser	Thr	Ser	Gly 140	Gly	Thr	Ala	Ala
Le 14	u Gly 5	Суз	Leu	Val	Lys 150	Asp	Tyr	Phe	Pro	Glu 155	Pro	Val	Thr	Val	Ser 160
Tr	o Asn	Ser	Gly	Ala 165	Leu	Thr	Ser	Gly	Val 170	His	Thr	Phe	Pro	Ala 175	Val
Le	ı Gln	Ser	Ser 180	Gly	Leu	Tyr	Ser	Leu 185	Ser	Ser	Val	Val	Thr 190	Val	Pro
Se	r Ser	Ser 195	Leu	Gly	Thr	Gln	Thr 200	Tyr	Ile	Суз	Asn	Val 205	Asn	His	Lys
Pr	5 Ser 210	Asn	Thr	ГЛа	Val	Asp 215	Lys	ГÀа	Val	Glu	Pro 220	ГЛа	Ser	Суз	Asp
Ly 22	s Thr 5	His	Thr	СЛа	Pro 230	Pro	Сүз	Pro	Ala	Pro 235	Glu	Ala	Ala	Gly	Gly 240
Pr	o Ser	Val	Phe	Leu 245	Phe	Pro	Pro	Lys	Pro 250	Lys	Asp	Thr	Leu	Met 255	Ile
Se	r Arg	Thr	Pro 260	Glu	Val	Thr	Сүз	Val 265	Val	Val	Asp	Val	Ser 270	His	Glu
As	o Pro	Glu 275	Val	Lys	Phe	Asn	Trp 280	Tyr	Val	Asp	Gly	Val 285	Glu	Val	His
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Va 30	l Val 5	Ser	Val	Leu	Thr 310	Val	Leu	His	Gln	Asp 315	Trp	Leu	Asn	Gly	Lys 320
Gl	u Tyr	Lys	Сүз	Lys 325	Val	Ser	Asn	Гла	Ala 330	Leu	Gly	Ala	Pro	Ile 335	Glu
Ъγ	s Thr	Ile	Ser 340	Lys	Ala	Lys	Gly	Gln 345	Pro	Arg	Glu	Pro	Gln 350	Val	Суз
Th	r Leu	Pro 355	Pro	Ser	Arg	Asp	Glu 360	Leu	Thr	Гүз	Asn	Gln 365	Val	Ser	Leu
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Leu	Gly 370	Cys	Leu	Val	Lys	Asp 375	Tyr	Phe	Pro	Glu	Pro 380	Val	Thr	Val	Ser			
Trp 385	Asn	Ser	Gly	Ala	Leu 390	Thr	Ser	Gly	Val	His 395	Thr	Phe	Pro	Ala	Val 400			
Leu	Gln	Ser	Ser	Gly 405	Leu	Tyr	Ser	Leu	Ser 410	Ser	Val	Val	Thr	Val 415	Pro			
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Glu	Ala	Leu	His	645 Asn	His	Tvr	Thr	Gln	650 Lvs	Ser	Leu	Ser	Leu	655 Ser	Pro			
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Ala	Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
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Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сув
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Pro	Leu 130	Ala	Pro	Ser	Ser	Lys 135	Ser	Thr	Ser	Gly	Gly 140	Thr	Ala	Ala	Leu
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Asn	Ser	Gly	Ala	Leu 165	Thr	Ser	Gly	Val	His 170	Thr	Phe	Pro	Ala	Val 175	Leu
Gln	Ser	Ser	Gly 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pro	Ser
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Ser	Asn 210	Thr	Lys	Val	Asp	Glu 215	Lys	Val	Glu	Pro	Lys 220	Ser	Суз	Asp	Гла
Thr 225	His	Thr	Суз	Pro	Pro 230	Cys	Pro	Ala	Pro	Glu 235	Ala	Ala	Gly	Gly	Pro 240
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СЛа	Ala 370	Val	Lys	Gly	Phe	Tyr 375	Pro	Ser	Asp	Ile	Ala 380	Val	Glu	Trp	Glu
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Asp	Ser	Asp	Gly	Ser 405	Phe	Phe	Leu	Val	Ser 410	Lys	Leu	Thr	Val	Asp 415	Гла
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Ser	Trp	Tyr 35	Gln	Gln	Lys	Pro	Gly 40	Gln	Ala	Pro	Val	Leu 45	Val	Ile	Tyr
Gly	Lys 50	Asn	Asn	Arg	Pro	Ser 55	Gly	Ile	Pro	Asp	Arg 60	Phe	Ser	Gly	Ser
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Asp	Glu	Ala	Asp	Tyr 85	Tyr	Сув	Asn	Ser	Arg 90	Glu	Ser	Pro	Pro	Thr 95	Gly
Leu	Val	Val	Phe 100	Gly	Gly	Gly	Thr	Lys 105	Leu	Thr	Val	Leu	Gly 110	Gln	Pro
LYs	Ala	Ala 115	Pro	Ser	Val	Thr	Leu 120	Phe	Pro	Pro	Ser	Ser 125	Lys	Lys	Leu
Gln	Ala 130	Asn	Lys	Ala	Thr	Leu 135	Val	Суз	Leu	Ile	Ser 140	Asp	Phe	Tyr	Pro
Gly 145	Ala	Val	Thr	Val	Ala 150	Trp	Lys	Ala	Asp	Ser 155	Ser	Pro	Val	Lys	Ala 160
Gly	Val	Glu	Thr	Thr 165	Thr	Pro	Ser	Lys	Gln 170	Ser	Asn	Asn	Lys	Tyr 175	Ala
Ala	Ser	Ser	Tyr 180	Leu	Ser	Leu	Thr	Pro 185	Glu	Gln	Trp	Lys	Ser 190	His	Arg
Ser	Tyr	Ser 195	Cys	Gln	Val	Thr	His 200	Glu	Gly	Ser	Thr	Val 205	Glu	Lys	Thr
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<400	)> SI	EQUEI	ICE :	410											
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Ser	Val	Lys	Val 20	Ser	Cys	Lys	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
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70 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95

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Ser	Leu	Thr	Val	Ser 245	Pro	Gly	Gly	Thr	Val 250	Thr	Leu	Thr	Cys	Gly 255	Ser
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Tyr	Сүз	Ala	Leu	Trp 325	Tyr	Ser	Asn	Leu	Trp 330	Val	Phe	Gly	Gly	Gly 335	Thr
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Pro	Glu	Val	Lys	485 Phe	Asn	Trp	Tyr	Val	490 Asp	Gly	Val	Glu	Val	495 His	Asn
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Lys															
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Hi 22	s Thr 5	суз	Pro	Pro	Cys 230	Pro	Ala	Pro	Glu	Ala 235	Ala	Gly	Gly	Pro	Ser 240
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Al	a Val 370	. Lys	Gly	Phe	Tyr	Pro 375	Ser	Asp	Ile	Ala	Val 380	Glu	Trp	Glu	Ser
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As 65	p Arg	) Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
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Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys 180 185 190	
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cctggaaaag gactcgagtg ggtgggacgg atcaagagca agaccgaggg cggcaccacc	180
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667

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n	n	y,
v	v	

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	$\sim \sim$	110		aca	

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The invention claimed is:

**1**. A method for treating or delaying progression of a cancer in an individual comprising administering to the <sup>25</sup> individual an effective amount of a T cell activating bispecific antigen-binding molecule and a PD-1 axis binding antagonist antibody, and wherein the T cell activating bispecific antigen-binding molecule comprises a first antigen-binding molecy that binds to CD3 and a second antigen-<sup>30</sup> binding moiety that binds to Folate Receptor 1 (FolR1), wherein the second antigen-binding moiety comprises:

- (a) a complementarity determining region (CDR) heavy chain 1 (CDR-H1) comprising the amino acid sequence of SEQ ID NO: 16,
- (b) a CDR heavy chain 2 (CDR-H2) comprising the amino acid sequence of SEQ ID NO: 17,
- (c) a CDR heavy chain 3 (CDR-H3) comprising the amino acid sequence of SEQ ID NO: 18,
- (d) a CDR light chain 1 (CDR-L1) comprising the amino acid sequence of SEQ ID NO: 32,
- (e) a CDR light chain 2 (CDR-L2) comprising the amino acid sequence of SEQ ID NO: 33, and
- (f) a CDR light chain 3 (CDR-L3) comprising the amino 45 acid sequence of SEQ ID NO: 34.

2. The method of claim 1, wherein the first antigenbinding moiety comprises:

- (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 37,
- (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 38,
- (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 39,
- (d) a CDR-L1 comprising the amino acid sequence of 55 SEQ ID NO: 32,
- (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 33, and
- (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 34.

**3**. The method of claim **2**, wherein the first antigenbinding moiety comprises a variable heavy chain comprising the amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising the amino acid sequence of SEQ ID NO: 31.

4. The method of claim 1, wherein the T cell activating bispecific antigen-binding molecule further comprises a

third antigen-binding moiety, wherein the third antigenbinding moiety binds to FolR1.

- 5. The method of claim 4, wherein the third antigenbinding moiety comprises:
  - (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 16,
  - (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 17,
  - (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 18,
  - (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 32,
  - (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 33, and
  - (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 34.
- 6. The method of claim 5, wherein the third antigenbinding moiety is identical to the second antigen-binding moiety.

7. The method of claim 4, wherein at least one of the first, second, and third antigen-binding moiety is a Fab molecule.

**8**. The method of claim **1**, wherein the second antigenbinding moiety comprises a variable heavy chain comprising the amino acid sequence of SEQ ID NO: 15 and a variable light chain comprising the amino acid sequence of SEQ ID NO: 31.

**9**. The method of claim **1**, wherein the PD-1 axis binding antagonist antibody is selected from the group consisting of 50 a PD-1 binding antagonist antibody, a PD-L1 binding antagonist antibody, and a PD-L2 binding antagonist antibody.

**10**. The method of claim **9**, wherein the PD-1 axis binding antagonist antibody is a PD-1 binding antagonist antibody.

**11**. The method of claim **9**, wherein the PD-1 axis binding antagonist antibody is a PD-L1 binding antagonist antibody.

**12**. The method of claim **9**, wherein the PD-1 axis binding antagonist antibody is a PD-L2 binding antagonist antibody.

**13**. The method of claim **1**, further comprising adminis-60 tering to the individual a T cell immunoglobulin mucin **3** (TIM3) antagonist.

14. The method of claim 13, wherein the TIM3 antagonist is an anti-TIM3 antibody.

15. The method of claim 1, wherein the cancer is selected from the group consisting of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, and endometrial cancer.

16. The method of claim 1, wherein the individual comprises less than about 15% PD-1<sup>hi</sup> expressing tumor-infiltrating T cells.

**17**. The method of claim **1**, wherein the first antigenbinding moiety and the second antigen-binding moiety are 5 Fab molecules.

**18**. A method of enhancing immune function in an individual having a FolR1-positive cancer comprising administering to the individual an effective amount of a combination of: 10

(a) a T cell activating bispecific antigen-binding molecule specific for FolR1 and CD3, wherein the T cell activating bispecific antigen-binding molecule comprises a first antigen-binding moiety that binds to CD3 and a second antigen-binding moiety that binds to FolR1, 15 wherein the second antigen-binding moiety comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 16, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 17, a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-L1 20 comprising the amino acid sequence of SEQ ID NO: 32, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 32, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 34; and

(b) a PD-1 axis binding antagonist antibody. 25 **19**. The method of claim **18**, wherein T cells in the individual have enhanced activation, proliferation, and/or effector function relative to administration of the T cell activating bispecific antigen binding molecule alone.

**20**. The method of claim **18**, wherein the individual  $_{30}$  comprises less than about 15% PD-1<sup>*hi*</sup> expressing tumor-infiltrating T cells.

\* \* \* \* \*