US 20170247425A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2017/0247425 A1

UNGERECHTS et al. (43) Pub. Date: Aug. 31, 2017

(54) **RNA VIRUSES EXPRESSING IL-12 FOR IMMUNOVIROTHERAPY**

(71) Applicants: **DEUTSCHES KREBSFORSCHUNGSZENTRUM**, Heidelberg (DE); **RUPRECHT-KARLS UNIVERSITAET**, Heidelberg (DE)

(72) Inventors: **Guy UNGERECHTS**, Heidelberg (DE); **Christine ENGELAND**, Heidelberg (DE); **Ruta VEINALDE**, Heidelberg (DE)

(21) Appl. No.: **15/441,545**

(22) Filed: **Feb. 24, 2017**

Related U.S. Application Data

(60) Provisional application No. 62/299,788, filed on Feb. 25, 2016.

Publication Classification

(51) **Int. Cl.**

C07K 14/54	(2006.01)
C12N 7/00	(2006.01)
C07K 16/28	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 14/5434*** (2013.01); ***C07K 16/2827*** (2013.01); ***C12N 7/00*** (2013.01); *C12N 2760/18043* (2013.01); *A61K 2039/505* (2013.01)

(57) **ABSTRACT**

The present invention relates to a recombinant virus of the family Paramyxoviridae, comprising at least one expressible polynucleotide encoding an IL-12 polypeptide, wherein said IL-12 polypeptide is an IL-12 fusion polypeptide comprising a p35 subunit of an IL-12 and a p40 subunit of an IL-12; to a polynucleotide encoding the same, and to a kit comprising the same. Moreover, the present invention relates to a method for treating cancer in a subject afflicted with cancer, comprising contacting said subject with a recombinant virus of the family Paramyxoviridae of the invention, and thereby, treating cancer in a subject afflicted with cancer.

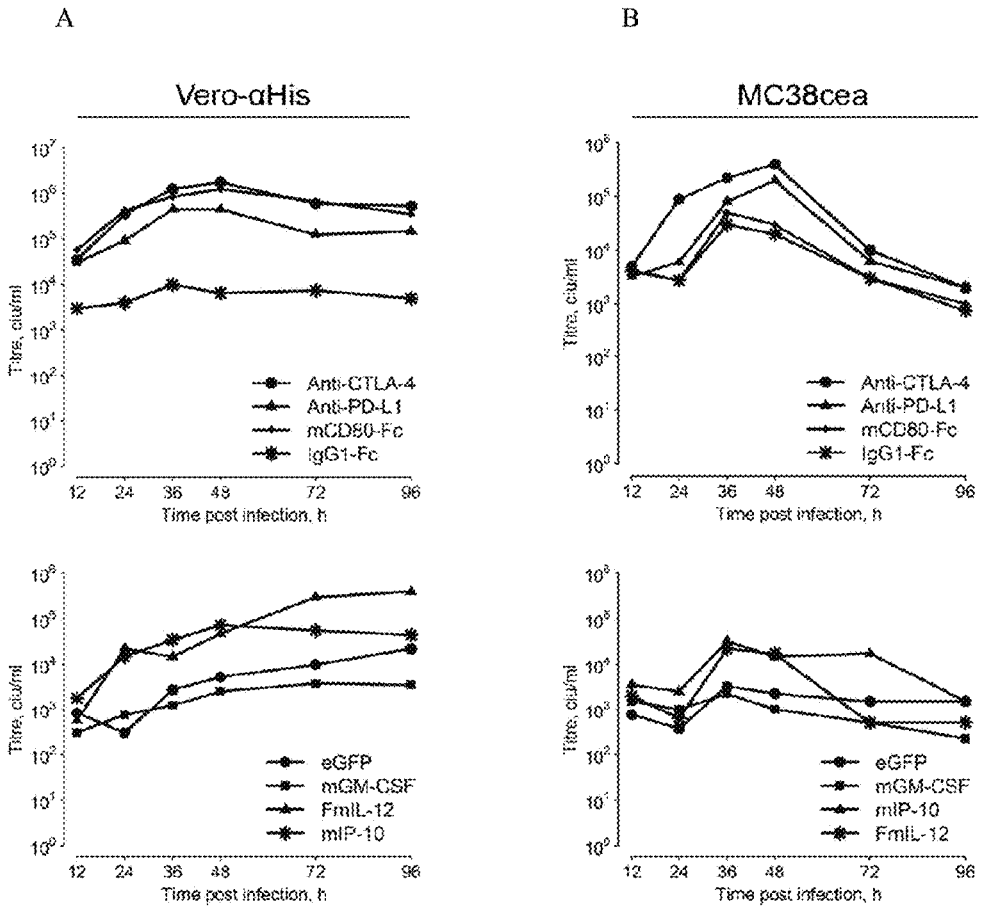
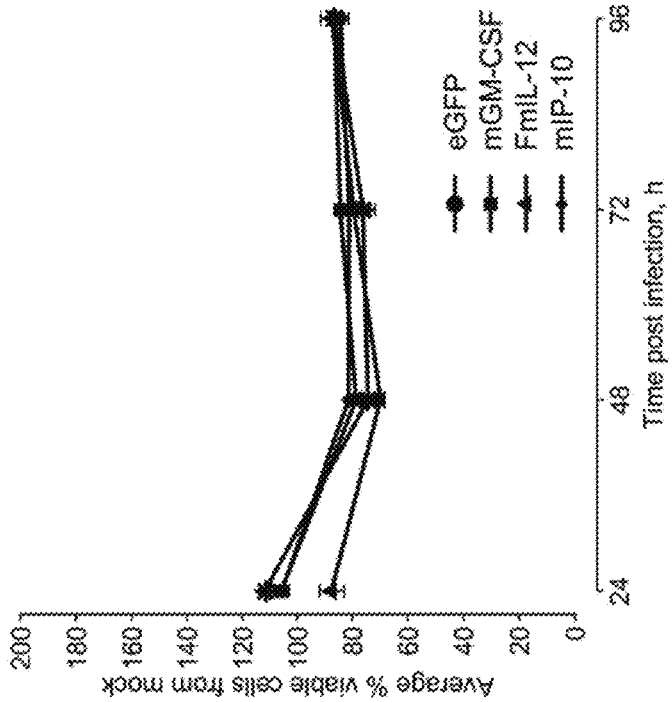

A
B
Vero-αHis
MC38cea
Titre, cfu/ml
Time post infection, h
12
24
36
48
72
96
Anti-CTLA-4
Anti-PD-L1
mCD80-Fc
IgG1-Fc
eGFP
mGM-CSF
FmIL-12
mIP-10

Fig. 1


Average % viable cells from mock
200
180
160
140
120
100
80
60
40
20
0
24
48
72
96
Time post infection, h
eGFP
mGM-CSF
FmiL-12
mIP-10

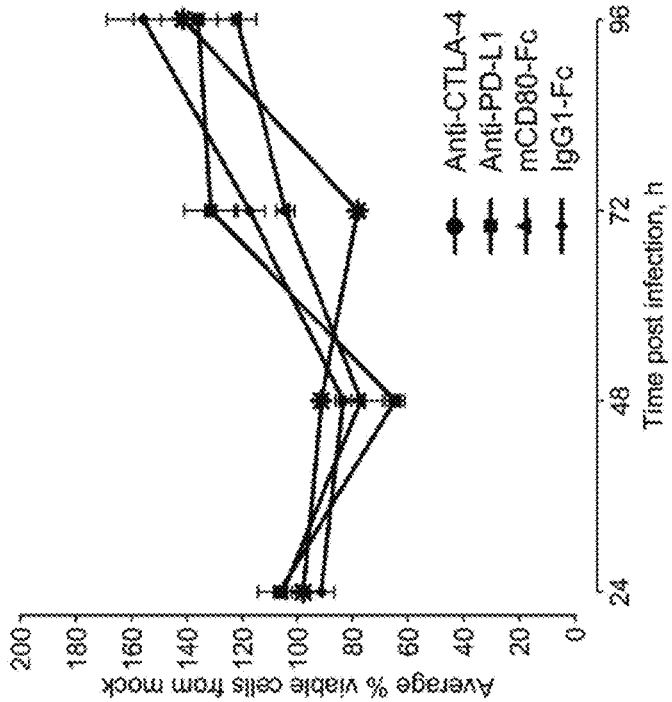

Average % viable cells from mock
200
180
160
140
120
100
80
60
40
20
0
24
48
72
96
Time post infection, h
Anti-CTLA-4
Anti-PD-L1
mCD80-Fc
IgG1-Fc

Fig. 2

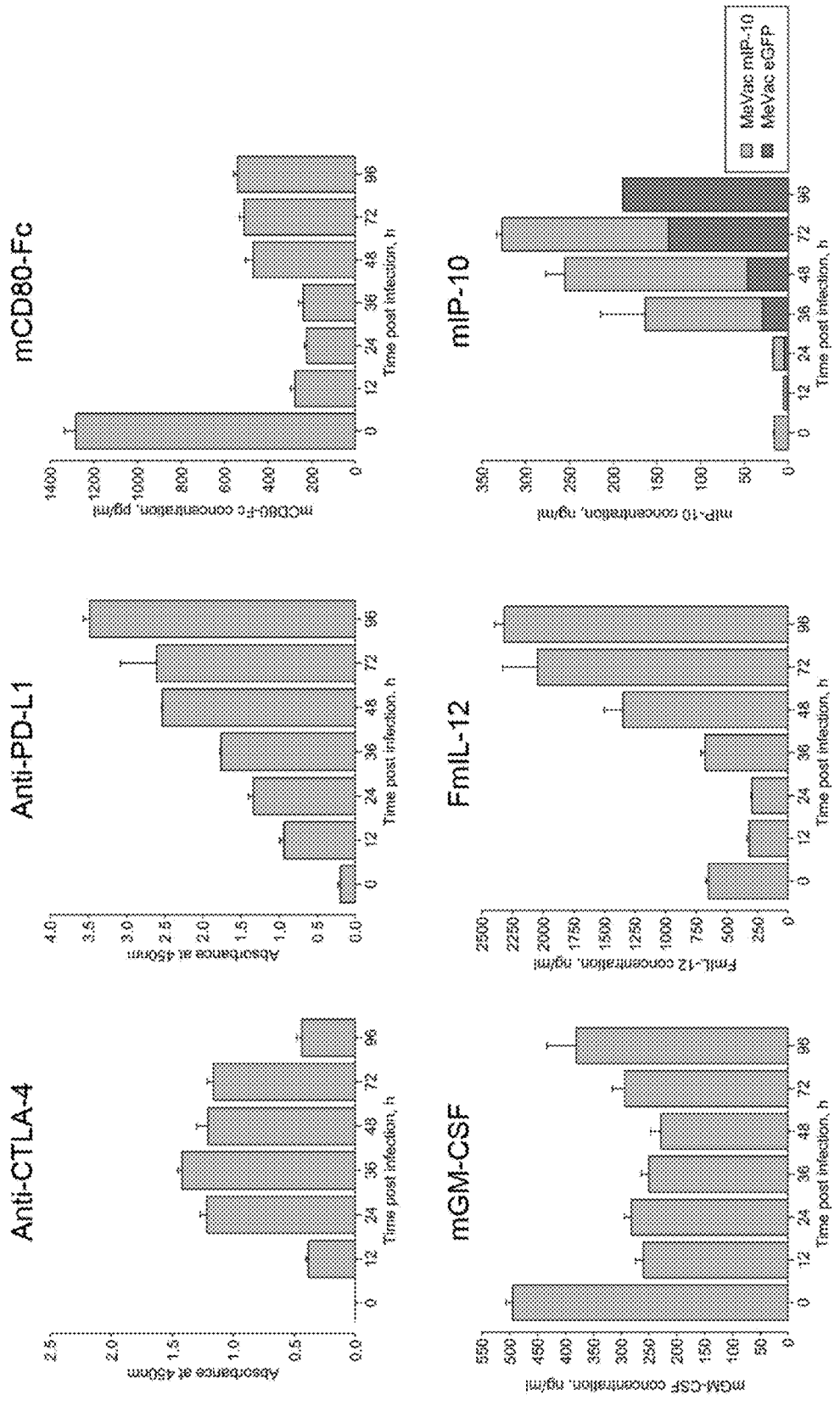
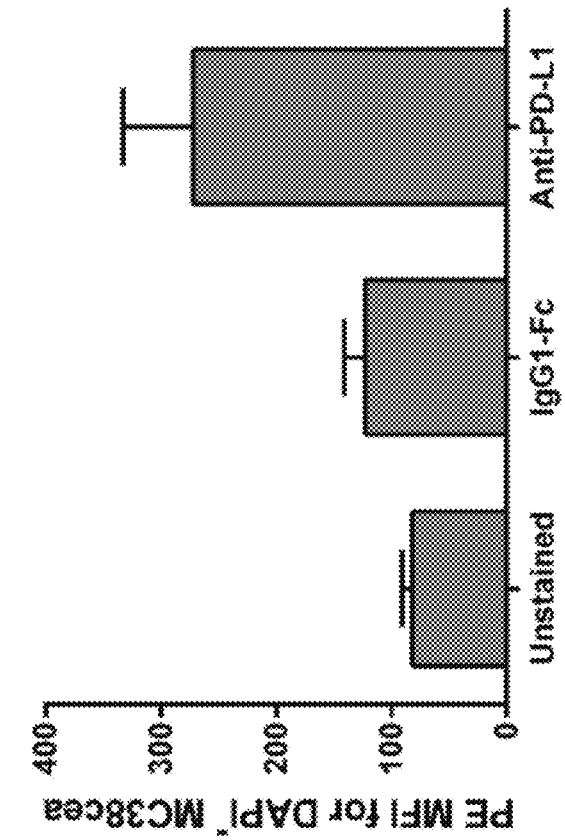

Anti-CTLA-4
Absorbance at 450nm
Time post infection, h
Anti-PD-L1
Absorbance at 450nm
Time post infection, h
mCD80-Fc
mCD80-Fc concentration, pg/ml
Time post infection, h
mGM-CSF
mGM-CSF concentration, ng/ml
Time post infection, h
FmIL-12
FmIL-12 concentration, ng/ml
Time post infection, h
mIP-10
mIP-10 concentration, ng/ml
Time post infection, h
MeVac mIP-10
MeVac eGFP

Fig. 3


PE MFI for DAPI⁻ MC38cea
400
300
200
100
0
Unstained
IgG1-Fc
Anti-PD-L1

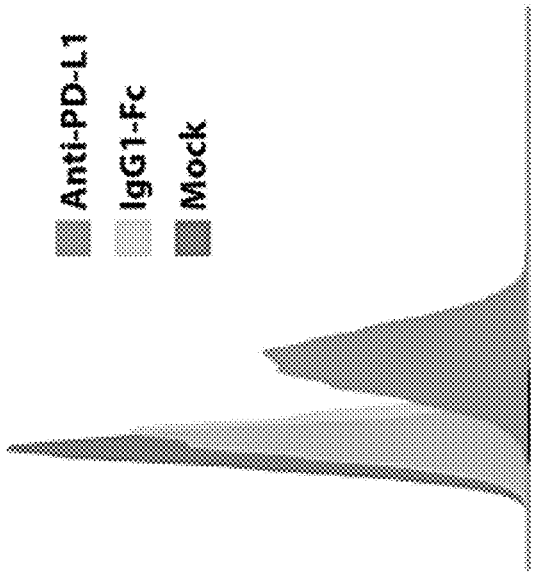
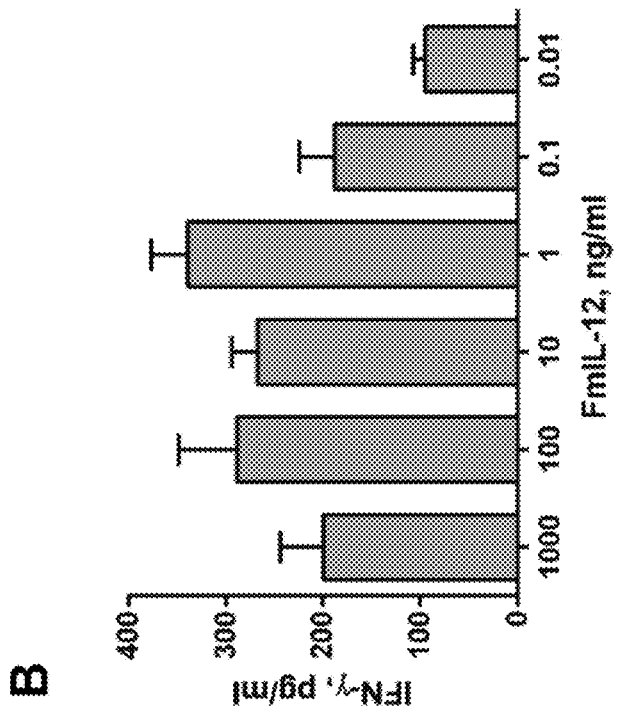

Anti-PD-L1
IgG1-Fc
Mock

Fig. 4


B
IFN-γ, pg/ml
400
300
200
100
0
1000
100
10
1
0.1
0.01
FmIL-12, ng/ml

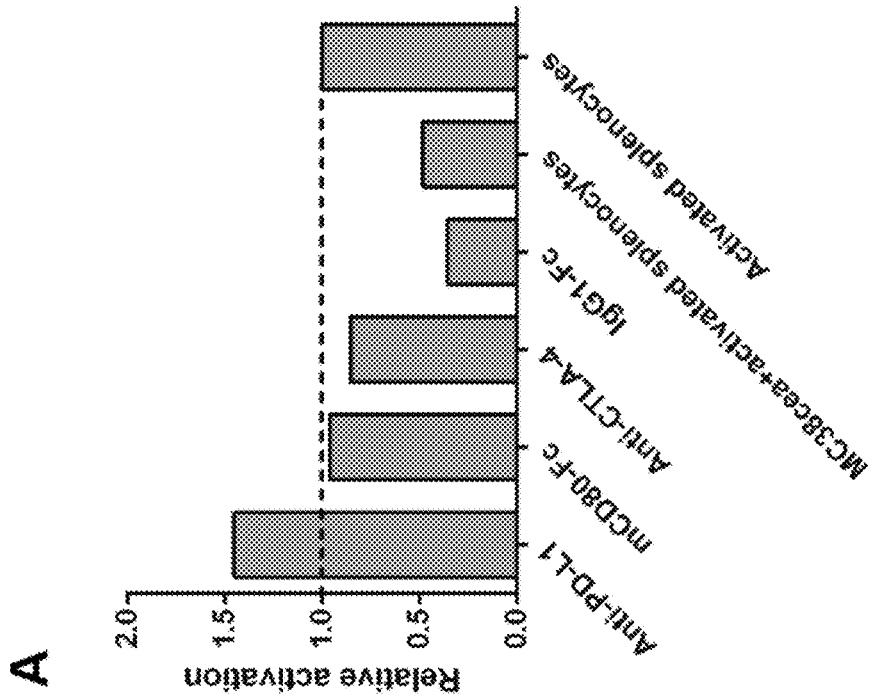

A
Relative activation
2.0
1.5
1.0
0.5
0.0
Anti-PD-L1
mCD80-Fc
Anti-CTLA-4
IgG1-Fc
MC38cea+activated splenocytes
Activated splenocytes

Fig. 5

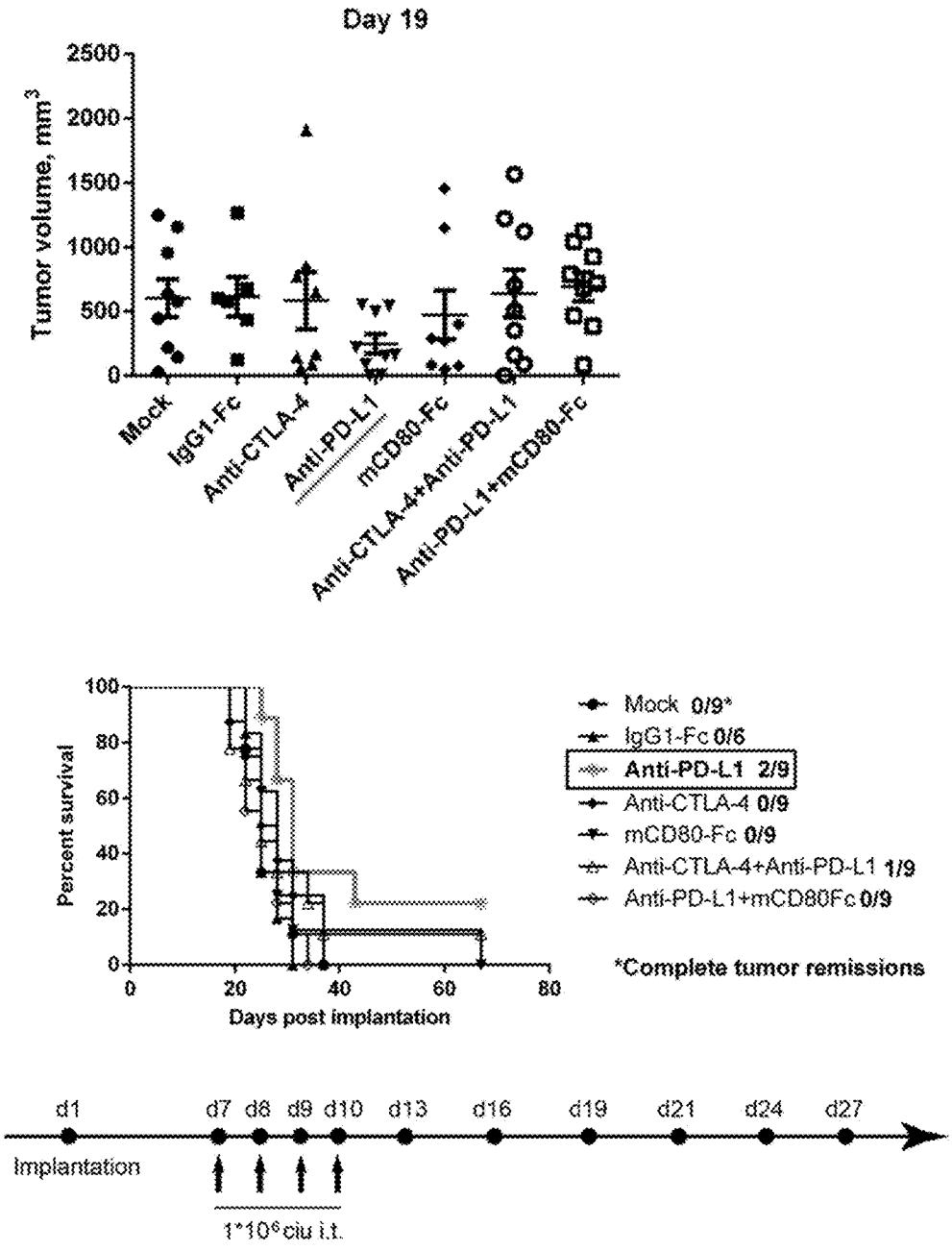

Day 19
Tumor volume, mm3
2500
2000
1500
1000
500
0
Mock
IgG1-Fc
Anti-CTLA-4
Anti-PD-L1
mCD80-Fc
Anti-CTLA-4+Anti-PD-L1
Anti-PD-L1+mCD80-Fc
Percent survival
100
80
60
40
20
0
0
20
40
60
80
Days post implantation
Mock 0/9*
IgG1-Fc 0/6
Anti-PD-L1 2/9
Anti-CTLA-4 0/9
mCD80-Fc 0/9
Anti-CTLA-4+Anti-PD-L1 1/9
Anti-PD-L1+mCD80Fc 0/9
*Complete tumor remissions
d1
d7 d8 d9 d10
d13
d16
d19
d21
d24
d27
Implantation
1*10^6 clu i.t.

Fig. 6

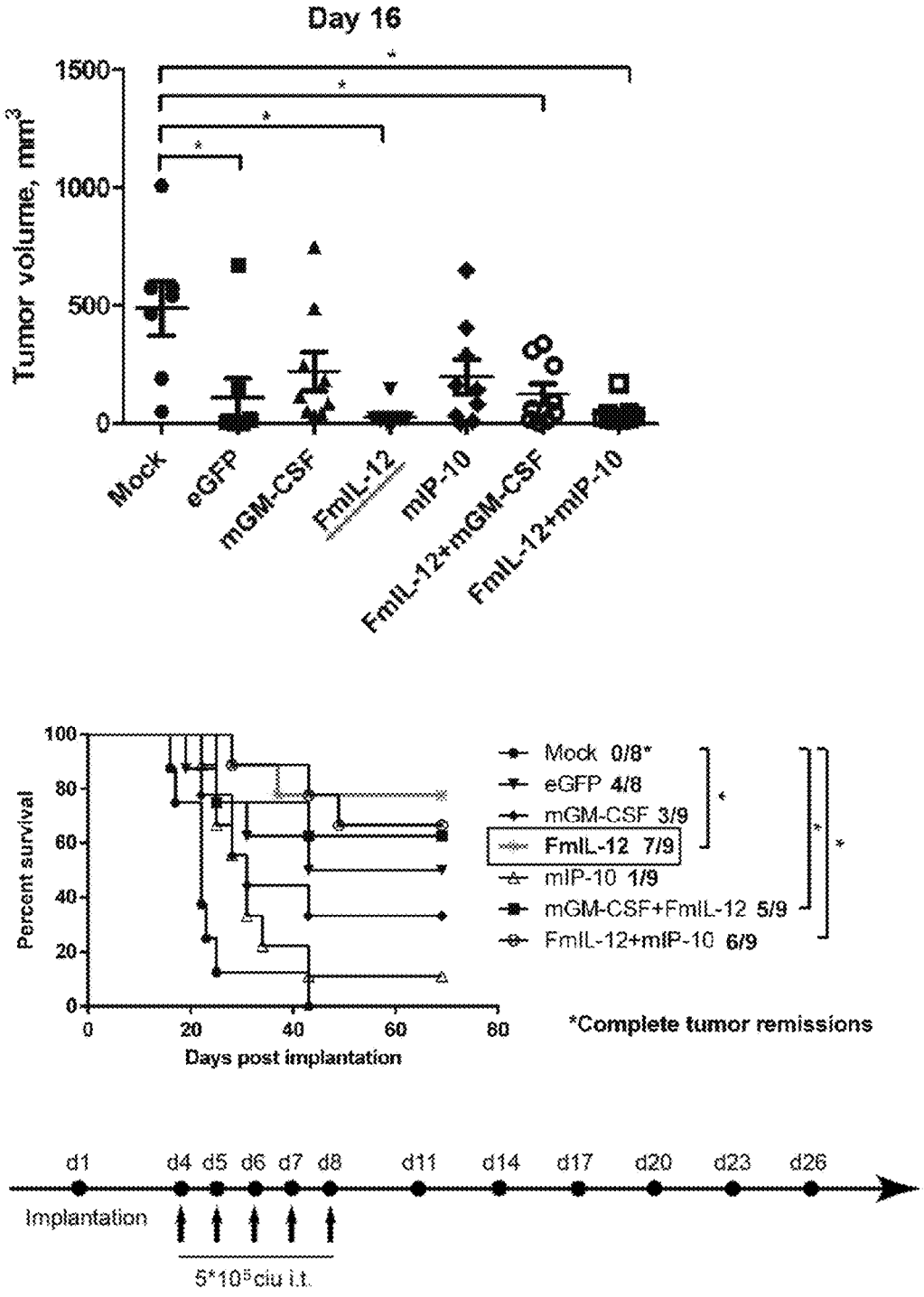

Day 16
Tumor volume, mm3
1500
1000
500
0
Mock
eGFP
mGM-CSF
FmIL-12
mIP-10
FmIL-12+mGM-CSF
FmIL-12+mIP-10
Percent survival
100
80
60
40
20
0
0
20
40
60
80
Days post implantation
Mock 0/8*
eGFP 4/8
mGM-CSF 3/9
FmIL-12 7/9
mIP-10 1/9
mGM-CSF+FmIL-12 5/9
FmIL-12+mIP-10 6/9
*Complete tumor remissions
d1
d4 d5 d6 d7 d8
d11
d14
d17
d20
d23
d26
Implantation
5*10^5 ciu i.t.

Fig.7

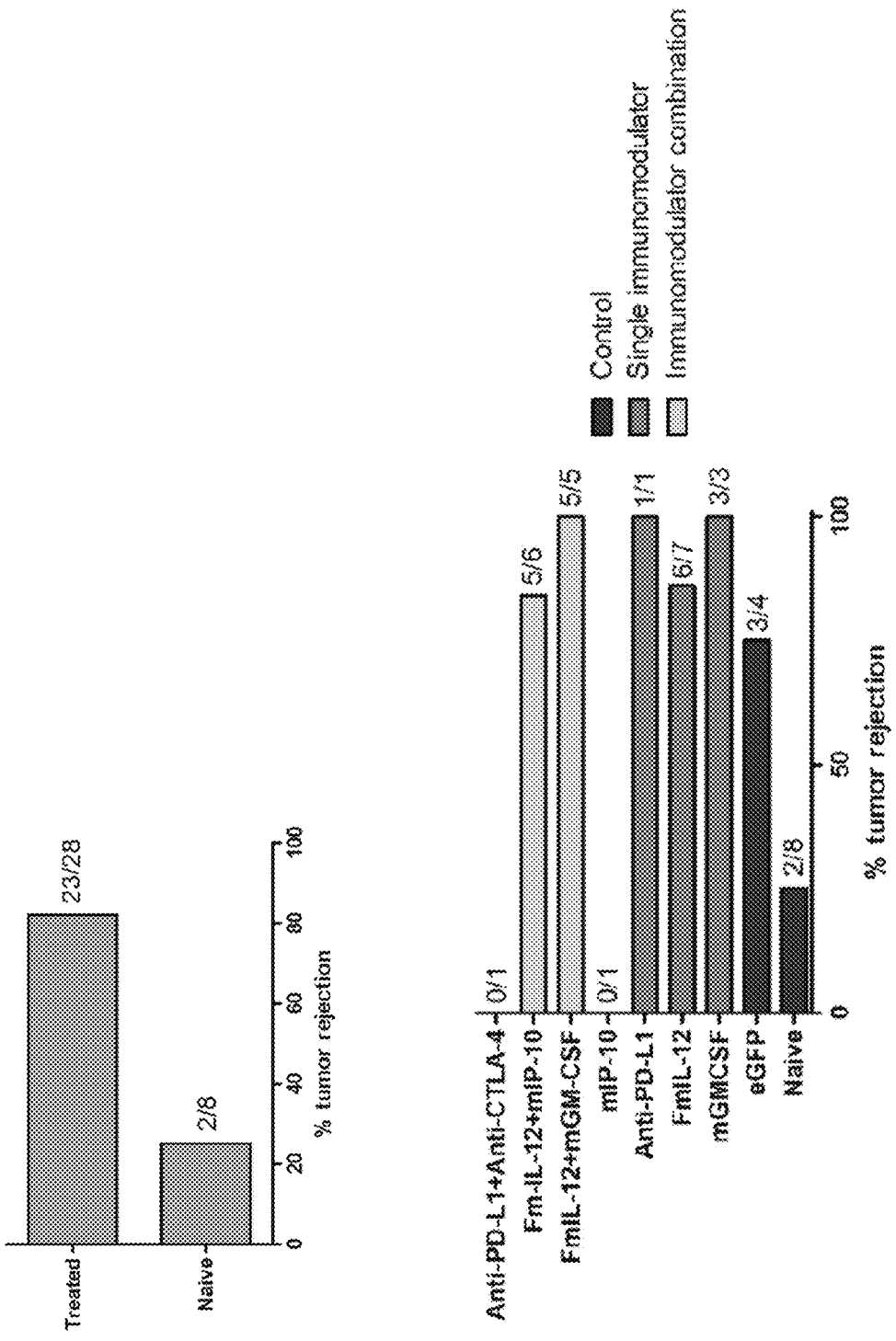

Treated
Naive
23/28
2/8
0
20
40
60
80
100
% tumor rejection
Anti-PD-L1+Anti-CTLA-4
Fm-IL-12+mIP-10
FmIL-12+mGM-CSF
mIP-10
Anti-PD-L1
FmIL-12
mGMCSF
eGFP
Naive
0/1
5/6
5/5
0/1
1/1
6/7
3/3
3/4
2/8
Control
Single immunomodulator
Immunomodulator combination
0
50
100
% tumor rejection

Fig. 8

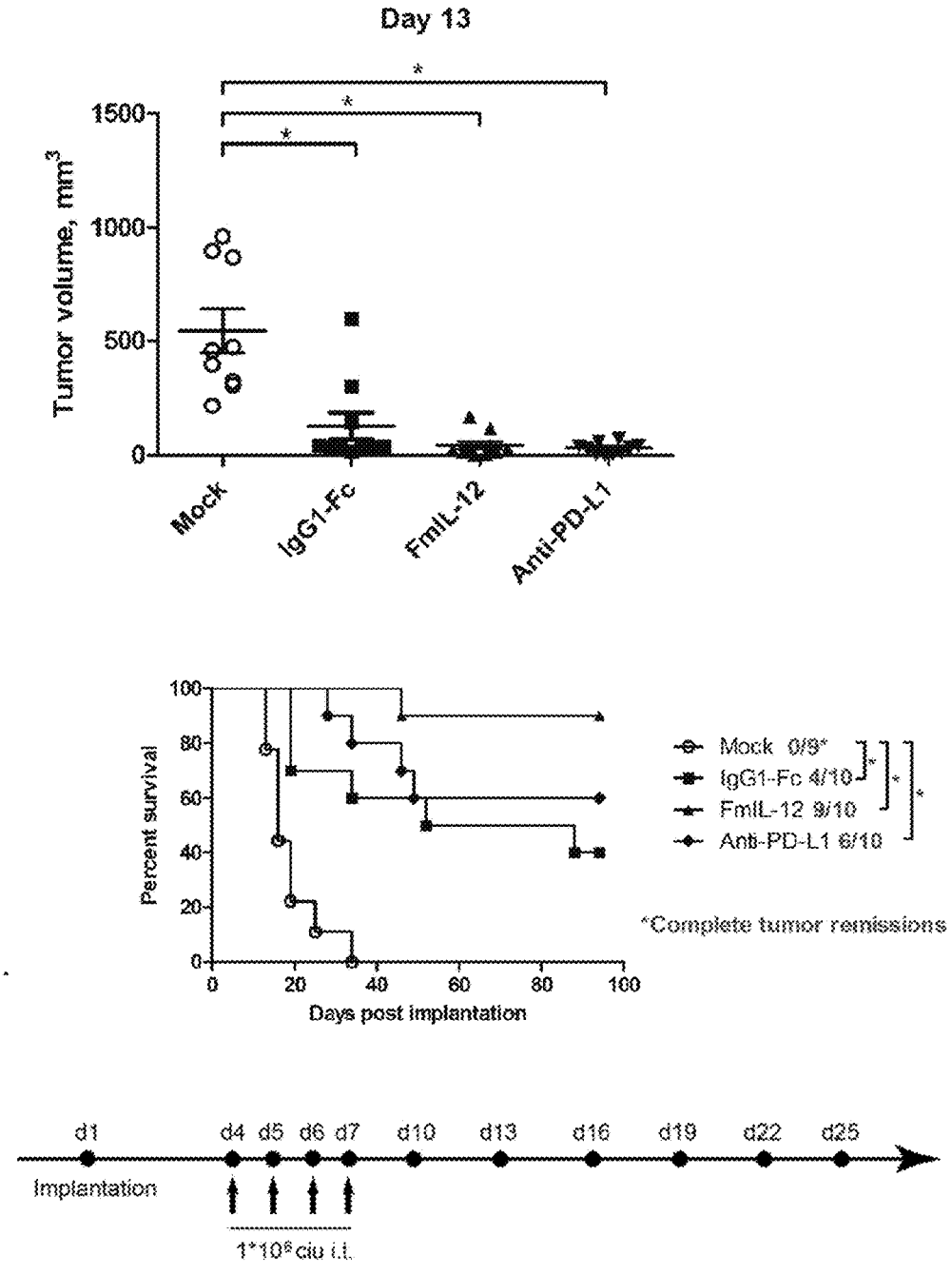
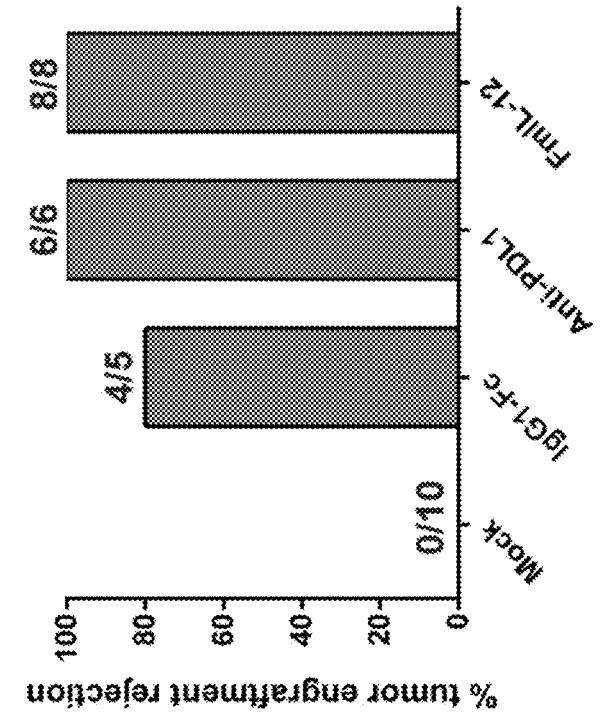

Day 13
Tumor volume, mm3
1500
1000
500
0
Mock
IgG1-Fc
FmIL-12
Anti-PD-L1
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
Days post implantation
Mock 0/9*
IgG1-Fc 4/10
FmIL-12 9/10
Anti-PD-L1 6/10
*Complete tumor remissions
d1
d4 d5 d6 d7
d10
d13
d16
d19
d22
d25
Implantation
1*10^6 ciu i.t.

Fig. 9


% tumor engraftment rejection
100
80
60
40
20
0
Mock
0/10
IgG1-Fc
4/5
Anti-PDL-1
6/6
FmIL-12
8/8

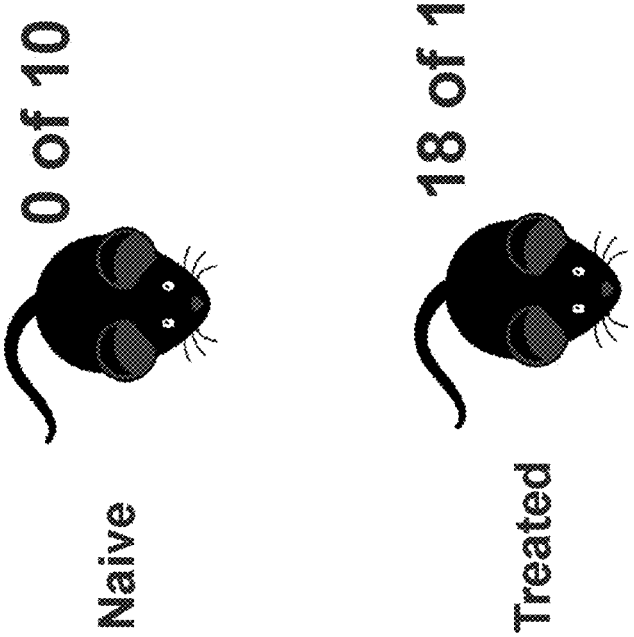

0 of 10
Naive
18 of 19
Treated

Fig. 10

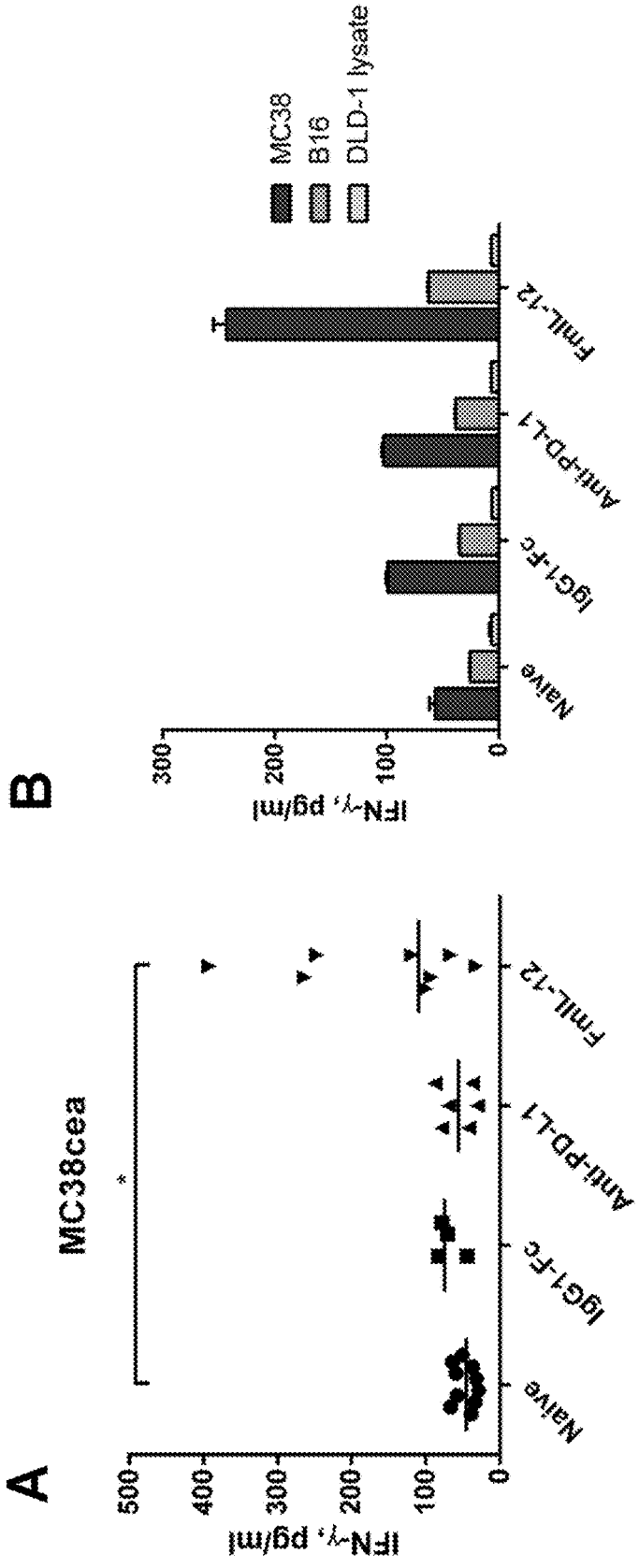

A
MC38cea
IFN-γ, pg/ml
500
400
300
200
100
0
*
Naive
IgG1-Fc
Anti-PD-L1
FmIL-12
B
MC38
B16
DLD-1 lysate
IFN-γ, pg/ml
300
200
100
0
Naive
IgG1-Fc
Anti-PD-L1
FmIL-12

Fig. 11

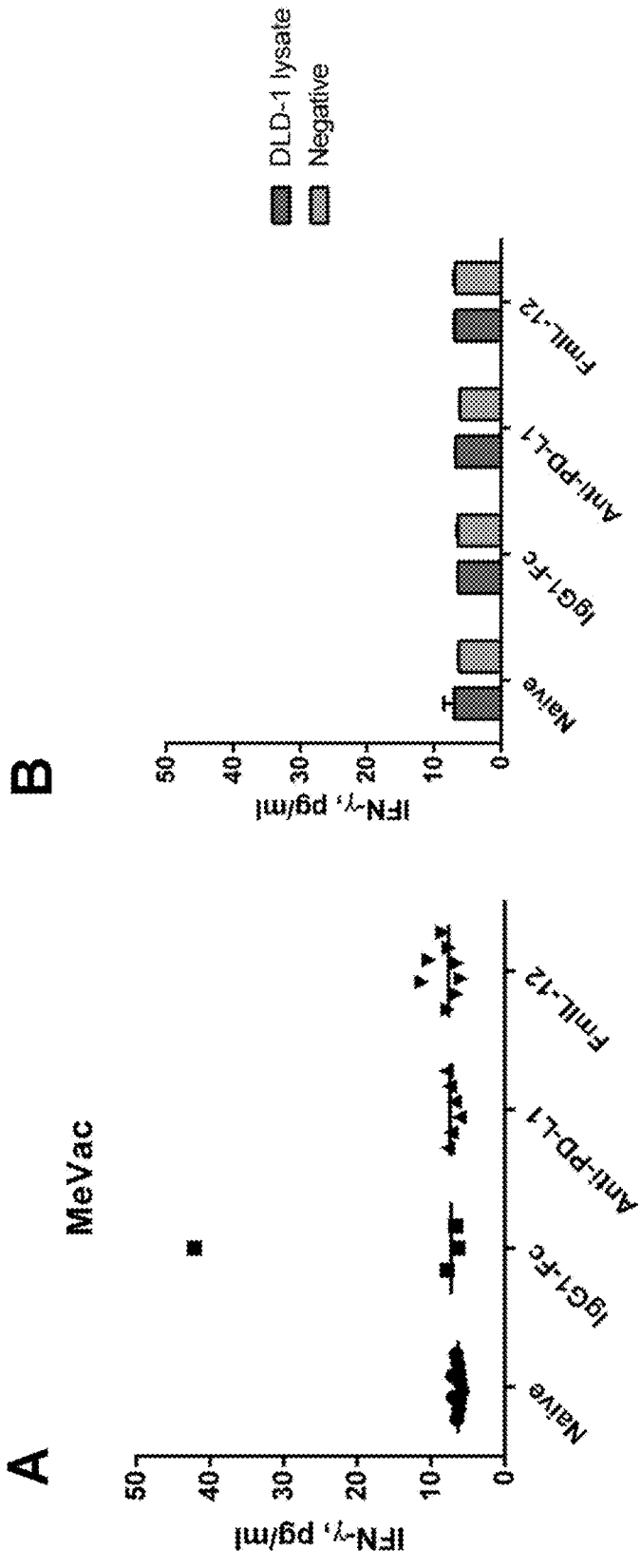

A
MeVac
IFN-γ, pg/ml
0
10
20
30
40
50
Naïve
IgG1-Fc
Anti-PD-L1
rmIL-12
B
DLD-1 lysate
Negative
IFN-γ, pg/ml
0
10
20
30
40
50
Naïve
IgG1-Fc
Anti-PD-L1
rmIL-12

Fig. 12

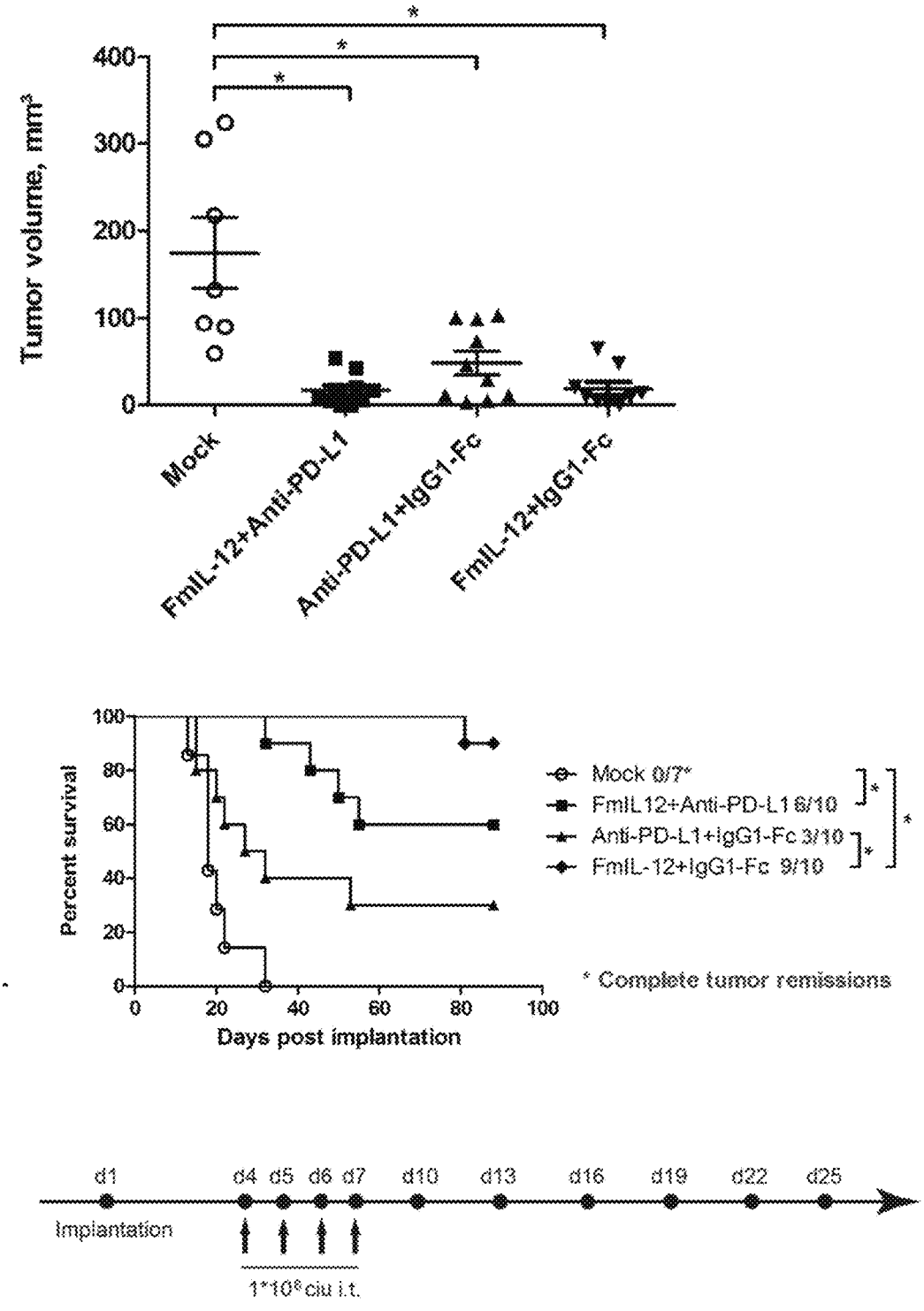
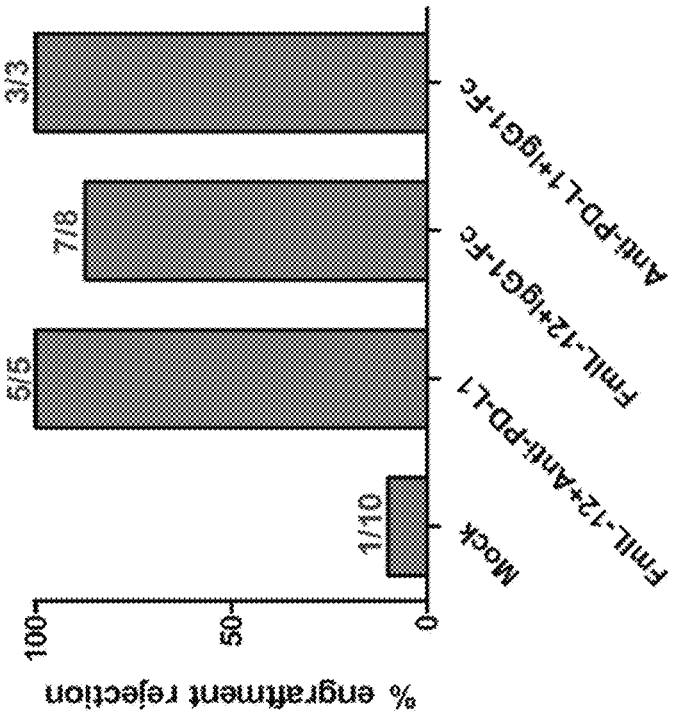

Tumor volume, mm³
400
300
200
100
0
*
*
*
Mock
FmIL-12+Anti-PD-L1
Anti-PD-L1+IgG1-Fc
FmIL-12+IgG1-Fc
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
Days post implantation
Mock 0/7*
FmIL12+Anti-PD-L1 6/10
Anti-PD-L1+IgG1-Fc 3/10
FmIL-12+IgG1-Fc 9/10
* Complete tumor remissions
d1
d4 d5 d6 d7
d10
d13
d16
d19
d22
d25
Implantation
1*10⁶ ciu i.t.

Fig. 13


% engraftment rejection
100
50
0
1/10
5/5
7/8
3/3
Mock
FmIL-12+Anti-PD-L1
FmIL-12+IgG1-Fc
Anti-PD-L1+IgG1-Fc

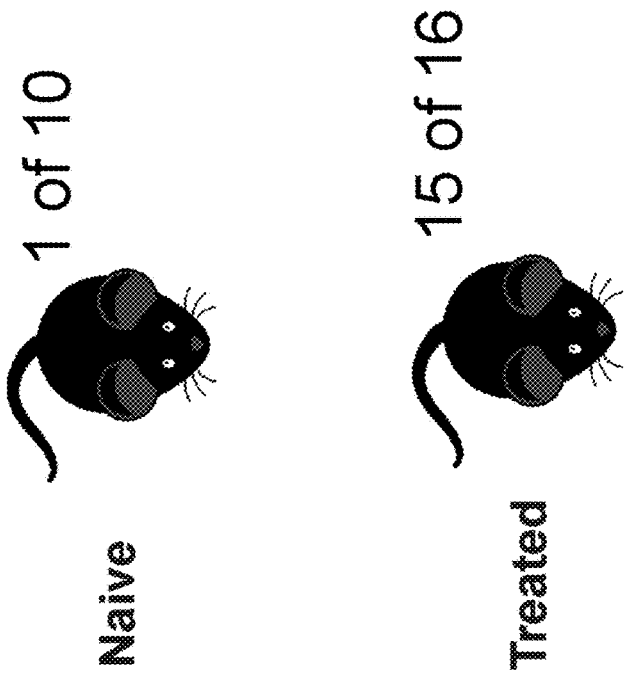

1 of 10
Naive
15 of 16
Treated

Fig. 14

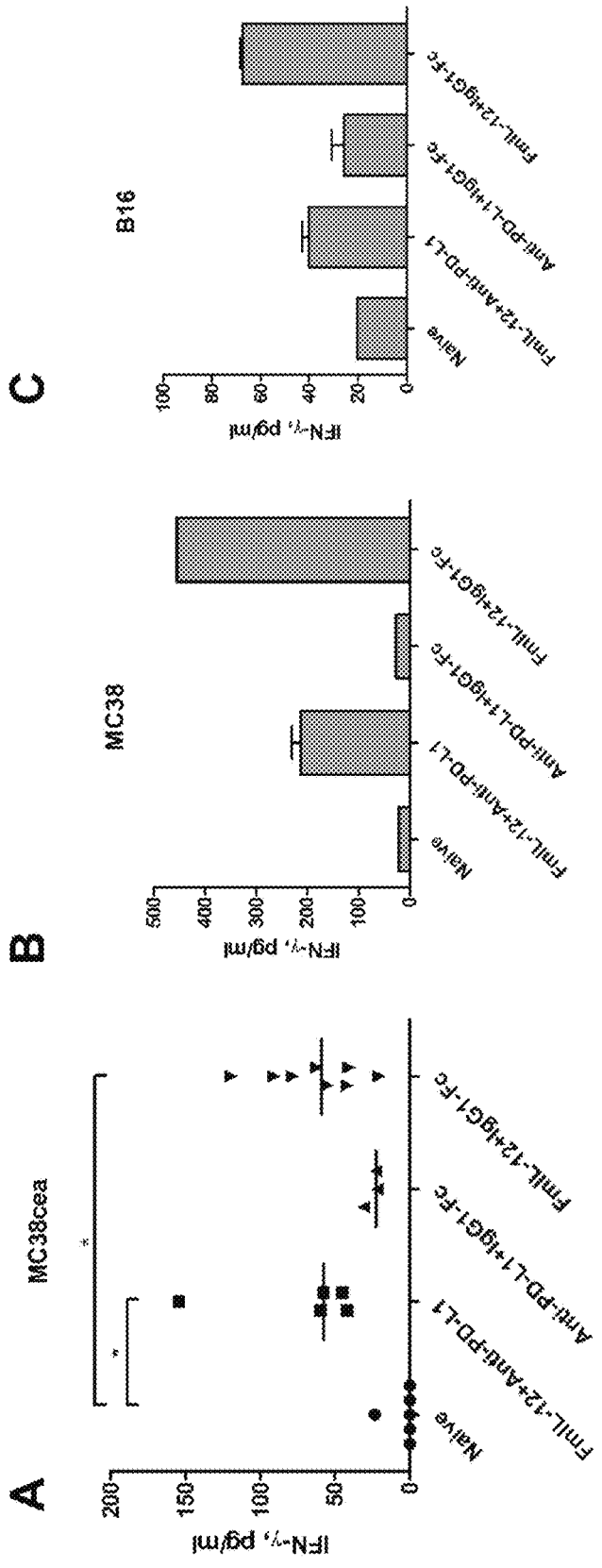
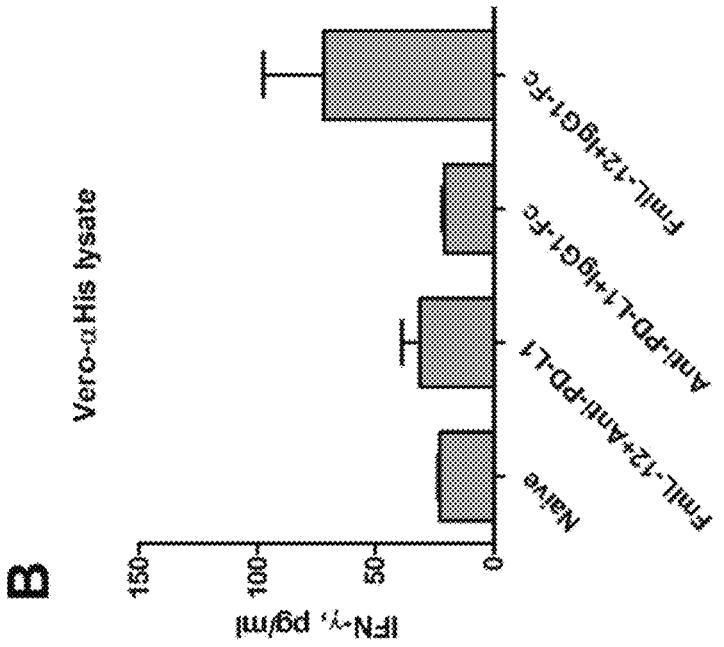

A
MC38cea
IFN-γ, pg/ml
200
150
100
50
0
Naïve
FmIL-12+Anti-PD-L1
Anti-PD-L1+IgG1-Fc
FmIL-12+IgG1-Fc
B
MC38
IFN-γ, pg/ml
500
400
300
200
100
0
Naïve
FmIL-12+Anti-PD-L1
Anti-PD-L1+IgG1-Fc
FmIL-12+IgG1-Fc
C
B16
IFN-γ, pg/ml
100
80
60
40
20
0
Naïve
FmIL-12+Anti-PD-L1
Anti-PD-L1+IgG1-Fc
FmIL-12+IgG1-Fc

Fig. 15


B
Vero-αHis lysate
IFN-γ, pg/ml
0
50
100
150
Naïve
Anti-PD-L1
Anti-PD-L1+hIgG1-Fc
rhIL-12+Anti-PD-L1
rhIL-12+hIgG1-Fc

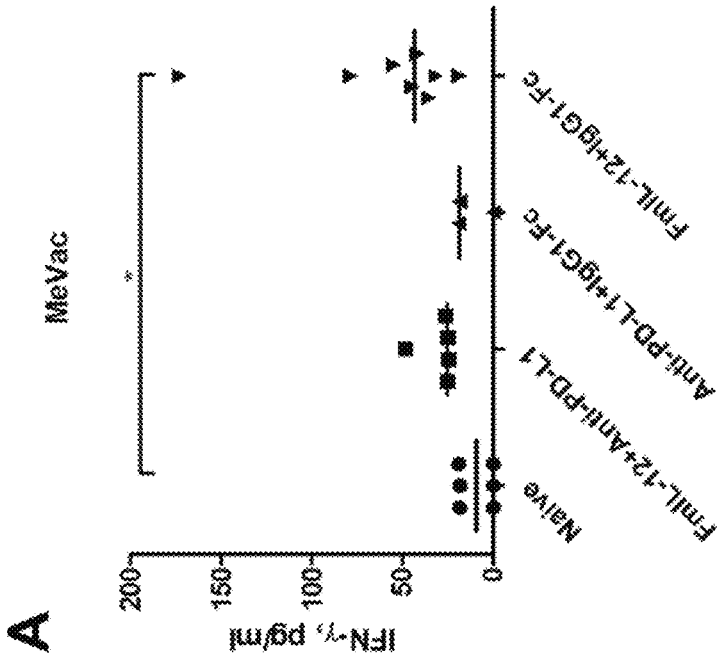

A
MeVac
IFN-γ, pg/ml
0
50
100
150
200
Naïve
Anti-PD-L1
Anti-PD-L1+hIgG1-Fc
rhIL-12+Anti-PD-L1
rhIL-12+hIgG1-Fc

Fig. 16

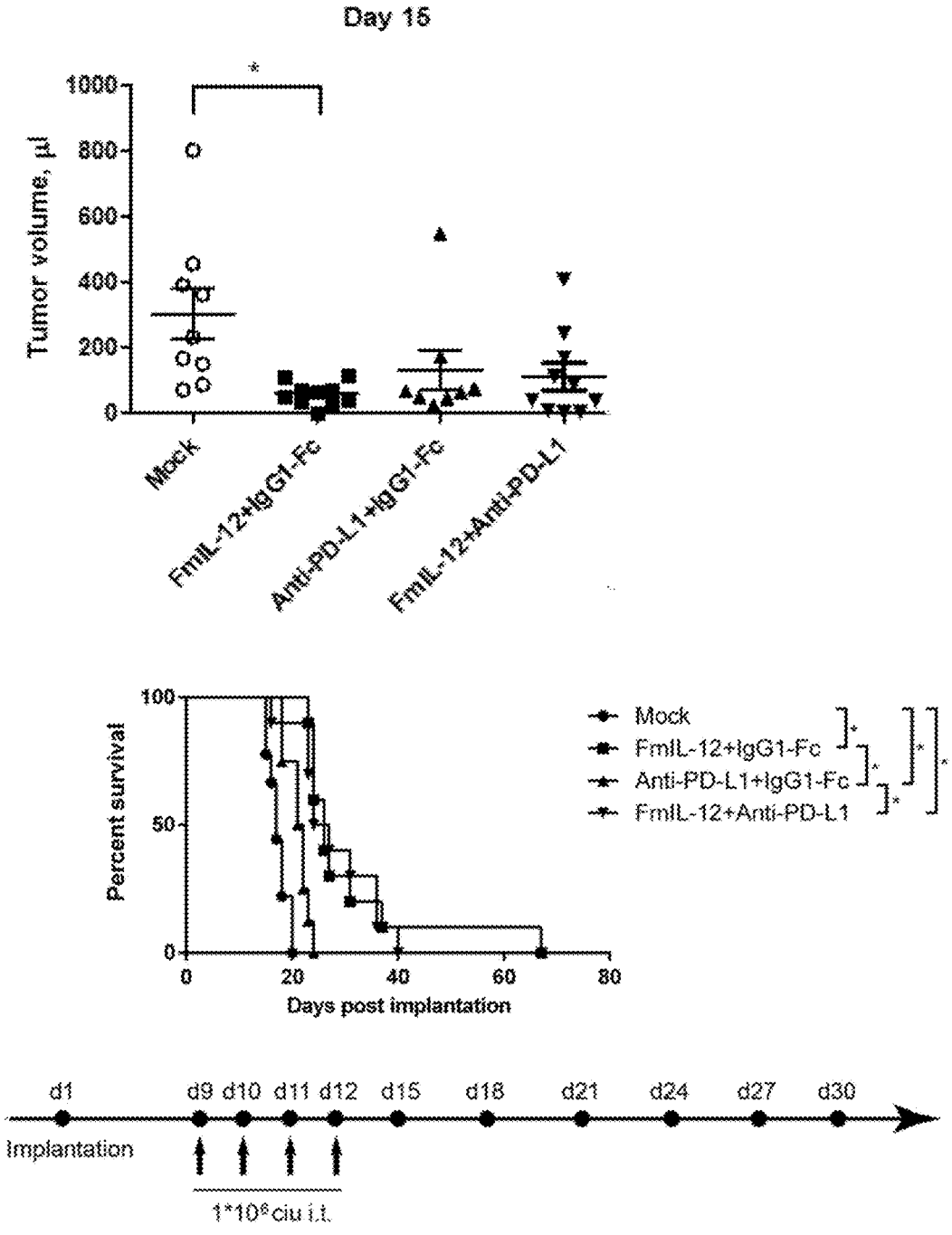

Day 15
Tumor volume, μl
1000
800
600
400
200
0
*
Mock
FmIL-12+IgG1-Fc
Anti-PD-L1+IgG1-Fc
FmIL-12+Anti-PD-L1
Percent survival
100
50
0
0
20
40
60
80
Days post implantation
Mock
FmIL-12+IgG1-Fc
Anti-PD-L1+IgG1-Fc
FmIL-12+Anti-PD-L1
d1
d9 d10 d11 d12
d15
d18
d21
d24
d27
d30
Implantation
1*10⁶ ciu i.t.

Fig. 17

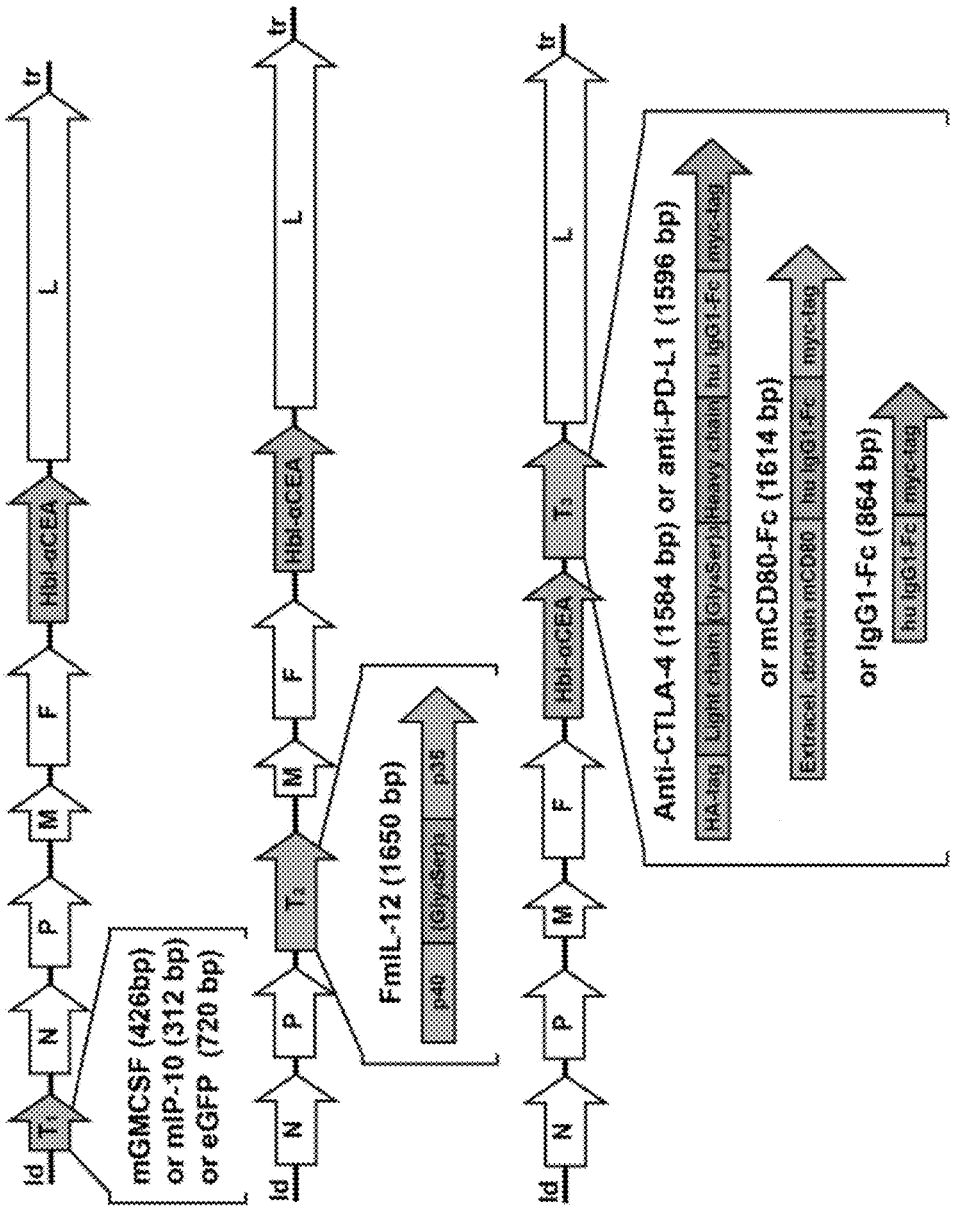

ld
T
N
P
M
F
HN-αCEA
L
tr
mGMCSF (426bp)
or mIP-10 (312 bp)
or eGFP (720 bp)
FmiL-12 (1650 bp)
p40
(G4S)3
p35
Anti-CTLA-4 (1584 bp) or anti-PD-L1 (1596 bp)
or mCD80-Fc (1614 bp)
or IgG1-Fc (864 bp)

Fig. 18

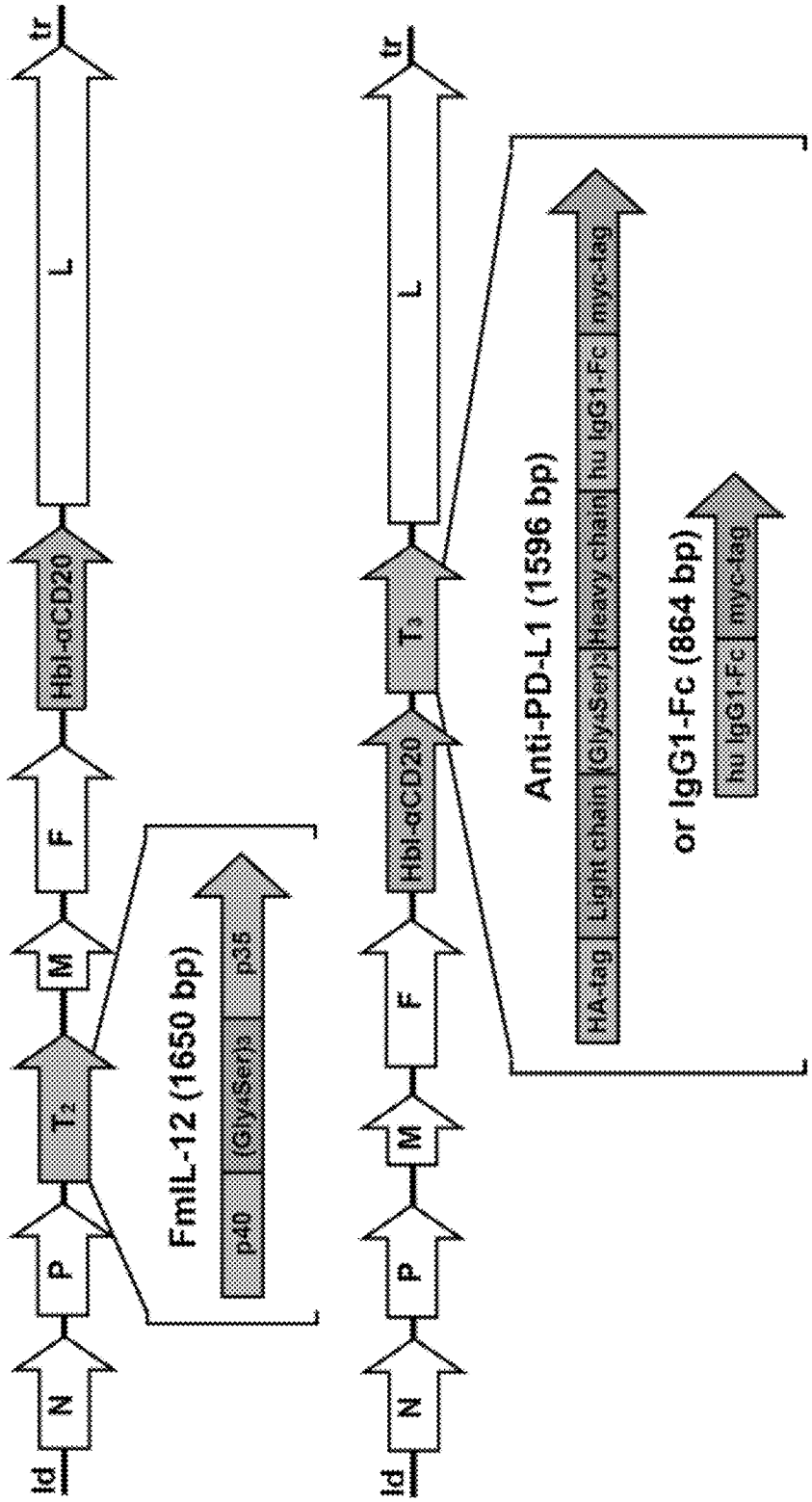

tr
L
Hbi-αCD20
F
M
T2
P
N
Id
FmIL-12 (1650 bp)
p40
(Gly4Ser)3
p35
tr
L
T2
Hbi-αCD20
F
M
P
N
Id
Anti-PD-L1 (1596 bp)
HA-tag
Light chain
(Gly4Ser)3
Heavy chain
hu IgG1-Fc
myc-tag
or IgG1-Fc (864 bp)
hu IgG1 Fc
myc-tag

Fig. 19

RNA VIRUSES EXPRESSING IL-12 FOR IMMUNOVIROTHERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/299,788, filed Feb. 25, 2016, which application is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates to biotechnology, including modified viruses, especially for the treatment or prevention of a human disease.

BACKGROUND

[0003] Interleukin 12 (IL-12) is a heterodimeric polypeptide interleukin consisting of two subunits, p35 and p40, encoded by two separate genes, IL-12A and IL-12B, respectively. IL-12 is produced in response to immune stimuli by dendritic cells, macrophages, neutrophils, and by human B-lymphoblastoid cells, and has been known as an important stimulator of immune cell activity, in particular of T cells and natural killer cells, which are, among other effects, stimulated to secrete IFN-γ by IL-12. IFN-γ, in turn, is known to stimulate expression of immune checkpoint blockade proteins on non-immune cells, e.g. of PD-L1, a mechanism used by cancer cells to evade the immune system (Abiko et al. (2015), British journal of cancer 112(9): 1501; Quetglas et al. (2015) Cancer Research 75(15 Supplement): 281). Due to the known immunostimulatory effects of IL-12, it was attempted to use a recombinant measles virus expressing both subunits of IL-12 as a vaccine to improve immune response against measles virus. However, it was found that the transgene had a detrimental effect on the neutralizing antibody response and that lymphoproliferative responses were not improved (Hoffman et al. (2003), J Infect Dis 188:1553).

[0004] Oncolytic viruses (OV) which replicate selectively in tumor cells are an emerging modality of cancer treatment. Aside from direct cytopathic effects and lysis of tumor cells, interactions of OV with the immune system can trigger systemic anti-tumor immunity. OV have been modified to express immunomodulatory transgenes to further enhance these effects (Melcher et al., Mol Ther. 2011, 19: 1008-1016). The vaccinia virus JX-594 and herpesvirus talimogene laherpavec (TVEC), both harboring GM-CSF, have shown promising results in clinical phase II and III trials (Heo et al., Nat Med. 2013, 19: 329-336 and Andtbacka et al. J Clin Oncol. 2013, 31, suppl; abstr LBA9008).

[0005] RNA viruses, in particular members of the family Paramyxoviridae like, e.g. measles virus (MV), have also shown potential use in oncolysis. Viruses of the family Paramyxoviridae are negative-sense single-stranded RNA viruses and include human pathogens like, e.g. human parainfluenza viruses, mumps virus, human respiratory syncytial virus, and measles virus. From wild type measles virus, several non-pathogenic strains, including a vaccine strain, have been derived, which have been shown to remain oncolytic. The measles virus vaccine strain has been developed as a vector platform to target multiple tumor entities and several clinical trials are ongoing (Russell et al., Nat Biotechnol. 2012, 30: 658-670). Recently, the capacity of oncolytic MV encoding GM-CSF to support the induction of a specific anti-tumor immune response in terms of a tumor vaccination effect was demonstrated (Grossardt et al. Hum Gene Ther. 2013, 24: 644-654.).

[0006] There is, however, still a need in the art for improved cancer therapies, in particular for improved oncolytic virus therapies. It is therefore an objective of the present invention to provide an improved oncolytic virus, which fully or partially avoids the short-comings of known oncolytic viruses.

SUMMARY OF THE INVENTION

[0007] The present invention relates to a recombinant virus of the family Paramyxoviridae, comprising at least one expressible polynucleotide encoding an IL-12 polypeptide, wherein said IL-12 polypeptide is an IL-12 fusion polypeptide comprising a p35 subunit of an IL-12 and a p40 subunit of an IL-12; to a polynucleotide encoding the same, and to a kit comprising the same. Moreover, the present invention relates to a method for treating cancer in a subject afflicted with cancer, comprising contacting said subject with a recombinant virus of the family Paramyxoviridae of the invention, and, thereby, treating cancer in a subject afflicted with cancer.

BRIEF DESCRIPTION OF THE FIGURES

[0008] FIG. **1**: One step growth curves in Vero-αHis (A) and MC38cea (B) cells: Cells were transduced with MeVac encoding the respective transgenes at MOI=3. Cell suspensions were collected by scraping in the culture medium and titre determined at the depicted time points.

[0009] FIG. **2**: Cytotoxic effect in the target MC8cea cells: Cells were transduced with MeVac encoding the respective transgenes at MOI=5 and cell viability was determined by XTT assay at the depicted time points. Mean results of triplicate infections per time point with standard errors of the mean (not visible for some data points) are shown.

[0010] FIG. **3**: Expression of MeVac encoded immunomodulators in MC38cea cells. MC38cea cells were transduced with MeVac encoding the respective immunomodulators and eGFP or IgG1-Fc as control vectors at MOI=3. Supernatant samples were collected at the depicted time points and transgene expression detected by ELISA. Unspecific binding was controlled by IgG1-Fc (upper panels) or eGFP (lower panels) supernatants and subtracted from the specific measurements. In case of mIP-10 an increase of the signal was observed in the eGFP controls which was not subtracted from the specific measurements and is depicted accordingly.

[0011] FIG. **4**: MeVac encoded anti-PD-L1 binding to MC38cea cells. MC38cea cells were incubated with supernatant from Vero-αHis infected with MeVac encoding anti-PD-L1 or IgG1-Fc. For detection of bound anti-PD-L1, cells were stained with primary Ab specific for HA tag and secondary Ab coupled to PE. DAPI staining was used to exclude dead cells and samples were analyzed by flow cytometry. (A) Overlay histogram for PE of DAPI-MC38cea populations from one of three independent experiments is shown on panel (B). (B) Average median fluorescence intensity (MFI) of PE for DAPI-populations with standard error of the means from the three independent experiments is shown on the left panel.

[0012] FIG. **5**: Functionality of MeVac encoded immunomodulators. (A) MC38cea cells were treated with superna-

tants from Vero-αHis cells infected with MeVac encoding the respective immunomodulators and cocultured in ratio 2:1 with murine splenocytes in the presence of PMA and ionomycin in 96-well plate. After 24 h the supernatants were collected and IFN-γ concentration measured by ELISA. Relative activation corresponds to ratio of the optical density (absorbance at 450 nm minus 570 nm) of the respective samples to activated splenocytes. Data for one of three independent experiments are shown; (B) splenocytes were stimulated with recombinant murine IL-2 and cultivated in the presence of medium from Vero-αHis infected with MeVac encoding FmIL-12 or eGFP. After 48 h the supernatants were collected and IFN-γ concentration measured by ELISA. Mean results with standard error of the mean of triplicate splenocyte cultures per FmIL-12 concentration are shown. IFN-γ concentration in the eGFP controls was close to background.

[0013] FIG. **6**: Therapeutic efficacy of immunomodulatory MeVac in vivo: Breaking immunosuppression: MC38cea cells were implanted subcutaneously (s.c.) into the right flank of C57BL/6J mice (6-9 animals per group). When tumors reached an average volume of 50 mm3 mice received intratumoral injections with 1×10^6 cell infectious units (ciu) with the respective viruses on four consecutive days in 100 μl. Tumor volume was determined every third day and mice were sacrificed when tumor volumes exceeded 1500 mm^3 or when ulceration occurred.

[0014] FIG. **7**: Therapeutic efficacy of immunomodulatory MeVac in vivo: Activating DCs and effector cells: Therapeutic. MC38cea cells were implanted subcutaneously (s.c.) into the right flank of C57BL/6J mice (6-9 animals per group). When tumors reached an average volume of 50 mm3 mice received intratumoral injections with 5×10^5 ciu with the respective viruses on five consecutive days in 100 μl. Tumor volume was determined every third day and mice were sacrificed when tumor volumes exceeded 1500 mm^3 or when ulceration occurred.

[0015] FIG. **8**: Rechallenge of long term survivors with MC38cea. Mice experiencing complete tumor remission in the experiments identifying the most effective MeVac vectors and were rechallenged with MC38cea cells 3 to 6 months after the initinal tumor cell implantation. Eight I mice served as a control group. 1×105 MC38cea cells were implanted subcutaneously (s.c.) in the left flank of the mice. Tumor engraftment rates were monitored.

[0016] FIG. **9**: Comparison of therapeutic efficacy of MeVac encoding FmIL-12 and anti-PD-L1. MC38cea cells were implanted subcutaneously (s.c.) into the right flank of C57BL/6J mice (10 animals per group). When tumors reached an average volume of 50 mm3 mice received intratumoral injections with 1×106 ciu with the respective viruses on four consecutive days in 100 μl. Tumor volume was determined every third day and mice were sacrificed when tumor volumes exceeded 1500 mm3 or when ulceration occurred.

[0017] FIG. **10**: Rechallenge of long term survivors from the experiment comparing efficacy of FmIL-12 and anti-PD-L1 encoding vectors with MC38cea. Mice were rechallenged with MC38cea cells ca. 6 months after the initinal tumor cell implantation. Ten I mice served as a control group. 1×105 MC38cea cells were implanted subcutaneously (s.c.) in the left flank of the mice. Tumor engraftment rates were monitored.

[0018] FIG. **11**: IFN-γ memory recall in murine splenocytes from mice experiencing complete tumor remissions in MeVac FmIL-12 versus MeVac anti-PD-L1 efficacy experiment. Anti-tumor: Freshly isolated splenocytes from mice treated with MeVac encoding the respective immunomodulators or naïve mice were stimulated with recombinant murine IL-2 and cocultivated with MC38cea (A) or MC38 (B) and B16 (B) tumor cells or irrelevant human cell lysate (DLD-1). After 48 h of cultivation cell culture medium was collected and IFN-γ concentration was measured by ELISA. IFN-γ concentrations in the individual cocultures with median in the group (A) or average concentration from two replicate measurements with standard error of the mean (SEM) are shown (B).

[0019] FIG. **12**: IFN-γ memory recall in murine splenocytes from mice experiencing complete tumor remissions in MeVac FmIL-12 versus MeVac anti-PD-L1 efficacy experiment: Anti-MeVac: Freshly isolated splenocytes from mice treated with MeVac encoding the respective immunomodulators or naïve mice were stimulated with recombinant murine IL-2 and cocultivated with MeVac (A) or as controls with an irrelevant human cell lysate (DLD-1) (B) or as a negative control splenocytes were cultivated alone. After 48 h of cultivation cell culture medium was collected and IFN-γ concentration was measured by ELISA. IFN-γ concentrations in the individual cocultures with median in the group (A) or average concentration from two replicate measurements with standard error of the mean (SEM) are shown (B).

[0020] FIG. **13**: Comparison of therapeutic efficacy of combination of MeVac encoding Fm-IL-12 and anti-PD-L1 with either vector in combination with a control vector encoding IgG1-Fc. MC38cea cells were implanted subcutaneously (s.c.) into the right flank of C57BL/6J mice (8-10 animals per group). When tumors reached an average volume of 50 mm3 mice received intratumoral injections with 1×106 ciu with the respective viruses on four consecutive days in 100 μl. Tumor volume was determined every third day and mice were sacrificed when tumor volumes exceeded 1500 mm3 or when ulceration occurred.

[0021] FIG. **14**: Rechallenge of long term survivors from the experiment comparing efficacy of combination of MeVac encoding Fm-IL-12 and anti-PD-L1 with either vector in combination with a control vector encoding IgG1-Fc. Mice were rechallenged with MC38cea cells ca. 5 months after the initinal tumor cell implantation. Ten I mice served as a control group. 1×105 MC38cea cells were implanted subcutaneously (s.c.) in the left flank of the mice. Tumor engraftment rates were monitored.

[0022] FIG. **15**: IFN-γ memory recall in murine splenocytes from mice experiencing complete tumor remissions in MeVac FmIL-12 and MeVac anti-PD-L1 combination experiment: Anti-tumor: Freshly isolated splenocytes from mice treated with MeVac encoding the respective immunomodulators or naïve mice were stimulated with recombinant murine IL-2 and cocultivated with MC38cea (A), MC38 (B) or B16 (C) tumor cells. After 48 h of cultivation cell culture medium was collected and IFN-γ concentration was measured by ELISA. IFN-γ concentrations in the individual cocultures with median in the group (A) or average concentration from two replicate measurements with standard error of the mean (SEM) are shown (B).

[0023] FIG. **16**: IFN-γ memory recall in murine splenocytes from mice experiencing complete tumor remissions in MeVac FmIL-12 and MeVac anti-PD-L1 combination

experiment: Anti-MeVac: Freshly isolated splenocytes from mice treated with MeVac encoding the respective immunomodulators or naïve mice were stimulated with recombinant murine IL-2 and cocultivated with MeVac (A) or Vero-αHis lysate (B). After 48 h of cultivation cell culture medium was collected and IFN-γ concentration was measured by ELISA. IFN-γ concentrations in the individual cocultures with median in the group (A) or average concentration from two replicate measurements with standard error of the mean (SEM) are shown (B).

[0024] FIG. **17**: Comparison of therapeutic efficacy of combination of MeVac encoding Fm-IL-12 and anti-PD-L1 with either vector in combination with a control vector encoding IgG1-Fc. B16-CD20 cells were implanted subcutaneously (s.c.) into the right flank of C57BL/6J mice (8-10 animals per group). When tumors reached an average volume of 50 mm3 mice received intratumoral injections with 1×106 ciu with the respective viruses on four consecutive days in 100 μl. Tumor volume was determined every third day and mice were sacrificed when tumor volumes exceeded 1500 mm3 or when ulceration occurred.

[0025] FIG. **18**: Schemes of the constructed recombinant MeVac genomes. Transgenes encoding different immunomodulators as well as eGFP and IgG1-Fc as controls were inserted in different positions of MeVac genome. Murine IL-12 was inserted as a fusion protein consisting of p40 and p35 protein subunits linked by a (Gly4Ser)3 linker (FmIL-12). Murine CD80 was inserted as a soluble form of the protein consisting of the extracellular part of the protein fused to a human IgG1-Fc (CD80-Fc). The MeVac H gene in the novel constructs was fully retargeted to human CEA (hCEA) antigen by ablating attachment to the natural receptors, fusing the H protein to a single chain antibody (7cab) against the hCEA and including a six-histidine tag at the C terminus to allow specific transduction of murine MC38cea cells via human CEA antigen and Vero-αHis cells via anti-His 7cab.

[0026] FIG. **19**: Scheme of MeVac genomes encoding FmIL-12 or anti-PD-L1 or IgG1-Fc retargeted to human CD20. MeVac H gene was fully retargeted to human CD20 antigen by ablating attachment to the natural receptors, fusing the H protein to a single chain antibody (7cab) against the CD20 and including a six-histidine tag at the C terminus to allow specific transduction of murine melanoma B16-CD20 cells via human CD20 antigen and Vero-αHis cells via anti-His 7cab.

DETAILED DESCRIPTION OF THE INVENTION

[0027] Accordingly, the present invention relates to a recombinant virus of the family Paramyxoviridae, comprising an expressible polynucleotide encoding an IL-12 polypeptide, wherein said IL-12 polypeptide is an IL-12 fusion polypeptide comprising a p35 subunit of an IL-12 and a p40 subunit of an IL-12.

[0028] As used in the following, the terms "have", "comprise" or "include" or any arbitrary grammatical variations thereof are used in a non-exclusive way. Thus, these terms may both refer to a situation in which, besides the feature introduced by these terms, no further features are present in the entity described in this context and to a situation in which one or more further features are present. As an example, the expressions "A has B", "A comprises B" and "A includes B" may both refer to a situation in which, besides B, no other element is present in A (i.e. a situation in which a solely and exclusively consists of B) and to a situation in which, besides B, one or more further elements are present in entity A, such as element C, elements C and D or even further elements.

[0029] Further, as used in the following, the terms "preferably", "more preferably", "most preferably", "particularly", "more particularly", "specifically", "more specifically" or similar terms are used in conjunction with optional features, without restricting alternative possibilities. Thus, features introduced by these terms are optional features and are not intended to restrict the scope of the claims in any way. The invention may, as the skilled person will recognize, be performed by using alternative features. Similarly, features introduced by "in an embodiment of the invention" or similar expressions are intended to be optional features, without any restriction regarding alternative embodiments of the invention, without any restrictions regarding the scope of the invention and without any restriction regarding the possibility of combining the features introduced in such way with other optional or non-optional features of the invention. Moreover, if not otherwise indicated, the term "about" relates to the indicated value with the commonly accepted technical precision in the relevant field, preferably relates to the indicated value ±20%.

[0030] The terms "virus" and "virus of the family Paramyxoviridae" are known to the skilled person. Preferably, the virus of the family Paramyxoviridae is a member of the genus Morbillivirus. More preferably, the virus of the family Paramyxoviridae is a measles virus (MV), still more preferably an MV of strain Edmonston A or B, preferably B. Most preferably, the virus of the family Paramyxoviridae is an MV of vaccine strain Schwarz/Moraten.

[0031] The term "recombinant virus", as used herein, relates to a virus comprising a genome modified by biotechnological means as compared to known, naturally occurring, virus genomes. Preferably, the recombinant virus is a virus comprising a genome modified as compared to naturally occurring virus genomes. Preferred biotechnological means for modifying a viral genome are known to the skilled person and include any of the methods of molecular cloning, in particular recombinant DNA techniques including, without limitation, cleavage of DNA by restriction enzymes, ligation of DNA, polymerase chain reaction (PCR), cloning of viral genomes, and the like. It is understood by the skilled person that viruses of the family Paramyxoviridae have a single-stranded (−)-RNA as a genome. Accordingly, the genome of the recombinant virus of the present invention, preferably, is obtained by cloning an expression vector as described herein below comprising an expressible nucleotide sequence encoding said recombinant virus genome, followed by expressing said expressible nucleotide sequence encoding said recombinant virus in a permissive host cell. Alternatively, the recombinant virus genome may also be expressed in non-permissive host cells, e.g., preferably, from rodents or other higher eukaryotes. Preferably, the recombinant virus of the present invention is a recombinant virus of the family Paramyxoviridae, more preferably a recombinant Morbillivirus, most preferably, a recombinant measles virus (MV). As will be understood by the skilled person, the recombinant virus of he present invention may comprises further modifications as compared to a naturally occurring virus. Preferably, the recombinant virus comprises a polypeptide mediating a modified tropism and/or a polynucle-

otide encoding the same. More preferably, said polypeptide mediating a modified tropism is a fusion polypeptide of a viral membrane integral polypeptide or of a viral membrane associated polypeptide with a polypeptide mediating binding to a target, e.g. a cell, preferably a specific kind of cell, more preferably a cancer cell. Preferably, said fusion polypeptide comprises a viral hemagglutinin or a fragment thereof, preferably a membrane integral fragment thereof. Preferably, said fusion polypeptide comprises a single-chain antibody specifically binding to a target molecule, e.g. to Carcinoembryonic antigen (CEA) or CD20. Most preferably, said fusion polypeptide is a fusion polypeptide of a truncated viral hemagglutinin with an anti-CD20 single-chain antibody or with an anti-CEA single-chain antibody. Preferably, the recombinant virus comprises a polynucleotide comprising the nucleic acid sequence of any one of SEQ ID Nos: 4 to 7, 14, and 15. SEQ ID NO: 4 is an artificial MV genome encoding an IL-12 fusion polypeptide comprising the mouse p40 subunit of IL-12 and the mouse p35 subunit of IL-12 as specified elsewhere herein. SEQ ID NO: 5 is an artificial MV genome encoding an IL-12 fusion polypeptide comprising the human p40 subunit of IL-12 and the human p35 subunit of IL-12 as specified elsewhere herein. SEQ ID NO: 6 is an artificial MV genome encoding an IL-12 fusion polypeptide comprising the mouse p40 subunit of IL-12 and the mouse p35 subunit of IL-12 as specified elsewhere herein, and a fusion polypeptide comprising a viral hemagglutinin and an anti-human-CEA single-chain antibody. SEQ ID NO: 7 is an artificial MV genome encoding an IL-12 fusion polypeptide comprising the mouse p40 subunit of IL-12 and the mouse p35 subunit of IL-12 as specified elsewhere herein, and a fusion polypeptide comprising a viral hemagglutinin and an anti-human-CD20 single-chain antibody. SEQ ID NO: 14 is an artificial MV genome derived from strain Edmonston B encoding an IL-12 fusion polypeptide comprising the mouse p40 subunit of IL-12 and the mouse p35 subunit of IL-12 as specified elsewhere herein. SEQ ID NO: 15 is an artificial MV genome encoding an IL-12 fusion polypeptide comprising the human p40 subunit of IL-12 and the human p35 subunit of IL-12 as specified elsewhere herein.

[0032] As used herein, the term "IL-12" relates to an interleukin 12 which is, in principle, known to the skilled person. Preferably, IL-12 is the heterodimeric IL-12 having the activity of stimulating the immune response of a subject. Preferably, the IL-12 is an IL-12 of a vertebrate species, more preferably of a mammal, even more preferably of a rat, a mouse, or a human, most preferably of a human. Preferably, the IL-12 has the subunits of rat IL-12, i.e. p35 comprising the amino acid sequence of Genbank Acc. No: NP_445842.1 GI:16758120, and p40 comprising the amino acid sequence of Genbank Acc. No: NP_072133.1 GI:12018288. Preferably, the subunits of the rat IL-12 are encoded by a polynucleotide comprising the nucleic acid sequence of Genbank Acc. No: NM_053390.1 GI:16758119 (rat mRNA expressed from the rat IL-12A gene) and/or of Genbank Acc. No: NM_022611.1 GI:12018287 (rat mRNA expressed from the rat IL-12B gene). More preferably, the IL-12 has the subunits of mouse IL-12, i.e. p35 comprising the amino acid sequence of Genbank Acc. No: NP_001152896.1 GI:226874945, and p40 comprising the amino acid sequence of Genbank Acc. No: NP_001290173.1 GI:735997434. Preferably, the subunits of the mouse IL-12 are encoded by a polynucleotide comprising the nucleic acid sequence of Genbank Acc. No: NM_001159424.2 GI:746816821 (mouse mRNA expressed from the mouse IL-12A gene) and/or of Genbank Acc. No: NM_001303244.1 GI:735997433 (mouse mRNA expressed from the mouse IL-12B gene). Most preferably, the IL-12 has the subunits of human IL-12, i.e. p35 comprising the amino acid sequence of Genbank Acc. No: NP_000873.2 GI:24430219, and p40 comprising the amino acid sequence of Genbank Acc. No: NP_002178.2 GI:24497438. Preferably, the subunits of the human IL-12 are encoded by a polynucleotide comprising the nucleic acid sequence of Genbank Acc. No: NM_000882.3 GI:325974478 (human mRNA expressed from the human IL-12A gene) and/or of Genbank Acc. No: NM_002187.2 GI:24497437 (human mRNA expressed from the human IL-12B gene). In its natural form, IL-12 is a secreted interleukin, i.e. it is processed and transported from the interior of the producing cell to the exterior of the producing cell by said producing cell. Accordingly, IL-12 preferably is a secreted IL-12.

[0033] More preferably, the IL-12 according to the present invention is an IL-12 fusion polypeptide comprising a p40 subunit of an IL-12 and a p35 subunit of an IL-12, preferably comprising subunits as specified herein above. More preferably, the p40 subunit and the p35 subunit of said IL-12 fusion polypeptide are from the same species; i.e. preferably, the p40 subunit and the p35 subunit of said IL-12 fusion polypeptide are a rat p40 subunit and a rat p35 subunit, more preferably are a mouse p40 subunit and a mouse p35 subunit, most preferably are a human p40 subunit and a human p35 subunit. Preferably, said p40 subunit and said p35 subunit are comprised in the order N-terminus—p40 subunit—p35 subunit—C-terminus in said fusion polypeptide. Preferably, said p40 subunit and said p35 subunit are separated by a linker, i.e., the fusion polypeptide comprises the structure p40-linker-35.

[0034] The term "linker" is known to the skilled person and, preferably, relates to a short sequence of amino acids separating two domains of a polypeptide or two components of a fusion polypeptide. The skilled person knows how to select appropriate linker sequences in order to construct functional fusion polypeptides, e.g. from Xue et al. (2004), NAR 32 (Web server issue):W562. Preferably, said linker comprises of from 1 to 50, more preferably of from 2 to 25, most preferably of from 10 to 20 amino acids. Preferably, the amino acids of the linker are small amino acids and/or amino acids promoting turns in protein structure; accordingly, the amino acids comprised in the linker, preferably, are glycine, alanine, serine, and/or proline. Preferably, the linker has a repetitive structure; thus, preferably, the linker comprises of from 1 to 10, more preferably of from 2 to 5, most preferably 3 repetitions of an amino acid sequence comprising 3 or 4, preferably 5 amino acids. Preferably, the repetitive sequence of the linker comprises the sequence ($glycine_x$-serine), with x=3 to 6, preferably 4 to 6, more preferably 4 or 6. More preferably, the repetitive sequence of the linker comprises the sequence ($glycine_4$-serine), i.e. gly-gly-gly-gly-ser (SEQ ID NO:1), preferably repeated as specified above. Thus, preferably the linker comprises or consists of the amino acid sequence -($glycine_4$-serine)$_n$-, with n=1 to 10, preferably n=2 to 5, more preferably n=3. Most preferably, the linker has the amino acid sequence of SEQ ID NO:8. Also more preferably, the repetitive sequence of the linker comprises the sequence ($glycine_6$-serine), i.e. gly-gly-gly-gly-gly-gly-ser (SEQ ID NO 9).

[0035] As used herein, the term "fusion polypeptide" relates to a polypeptide wherein all components, e.g. p35 subunit, linker, and p40 subunit, are covalently linked and, preferably, are produced as a contiguous polypeptide chain. Thus, preferably, the fusion polypeptide of the present invention, preferably, is expressed from a single gene. Thus, the IL-12 of the present invention preferably is fused mouse IL-12 (FmIL-12), preferably comprising the amino acid sequence of SEQ ID NO:10, preferably encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO:11. More preferably, the IL-12 of the present invention preferably is fused human IL-12 (FhIL-12), preferably comprising the amino acid sequence of SEQ ID NO:12, preferably encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO:13.

[0036] The terms "polypeptide" and "fusion polypeptide", as used herein, preferably encompass variants of said polypeptides and fusion polypeptides as specified elsewhere herein.

[0037] Preferably, the recombinant virus of the family Paramyxoviridae of the present invention further comprises at least one expressible polynucleotide encoding a further activator of the immune response, preferably an immunoglobulin or part thereof, preferably a secreted immunoglobulin.

[0038] As used herein, the term "further activator of the immune response" relates to a compound which, when contacted with a mixture of immune cells and immune-response inducing cells, e.g. cancer cells, causes at least one type of immune cell to be more active as compared to an immune cell of the same type comprised in the same mixture but lacking said compound. As used herein, the term IL-12 as specified elsewhere herein relates to an activator of the immune response, but not to a further activator of the immune response. Preferably, the immune cell activated is a cell mediating a response increasing a subject's resistance to an antigen, i.e. preferably, said immune cell is not a tolerance-mediating immune cell. Preferably, the immune cell activated by the further activator of the immune response is a T-cell, more preferably a helper T-cell or a cytotoxic T-cell. Most preferably, the immune cell activated by the further activator of the immune response is a cytotoxic T-cell expressing PD-1. Measures of immune cell activity are known to the skilled person and include, preferably, expression of activation markers, production of antibodies, excretion of cytokines, and release of cytotoxins, e.g. perforin, granzymes, and/or granolysin.

[0039] Preferably, the further activator of the immune response is an antagonist of a signaling pathway causing at least one type of immune cell to become inhibited. Accordingly, preferably, the further activator of the immune response is a ligand for an immune checkpoint blockade protein. More preferably, the further activator of the immune response is a ligand for an immune checkpoint blockade protein. Still more preferably, the activator of the immune response is an inhibitor of PD-1 receptor signaling. It is understood by the skilled person that signaling through a receptor signaling pathway can be inhibited by either preventing the receptor from being activated, or by preventing the signal generated by the activated receptor from being further transmitted. Accordingly, preferably, the further activator of the immune response is a PD-L1 antagonist, the term "antagonist" relating to a compound binding to the molecule the effect of which is antagonized and through said binding preventing said molecule from interacting with its native binding partner in a productive, i.e. signaling-inducing, way. Preferred assays for said activity are described e.g. in WO 2015/128313 A1.

[0040] Preferably, the further activator of the immune response is an antagonist as described above selected from the list of molecule types consisting of a peptide aptamer, an anticalin, a Designed Ankyrin Repeat Protein (DARPin), an inhibitory peptide, and, preferably, an immunoglobulin, more preferably, an antibody.

[0041] In the context of this invention, a "peptide aptamer" is a peptide specifically binding its interaction partner and having the activity of activating the immune response as specified herein above, preferably, the activity of being an antagonist of PD-L1 as specified herein above. Peptide aptamers, preferably, are peptides comprising 8-80 amino acids, more preferably 10-50 amino acids, and most preferably 15-30 amino acids. They can e.g. be isolated from randomized peptide expression libraries in a suitable host system like baker's yeast (see, for example, Klevenz et al., Cell Mol Life Sci. 2002, 59: 1993-1998). A peptide aptamer, preferably, is a free peptide; it is, however, also contemplated by the present invention that a peptide aptamer is fused to a polypeptide serving as "scaffold", meaning that the covalent linking to said polypeptide serves to fix the three-dimensional structure of said peptide aptamer to one specific conformation. More preferably, the peptide aptamer is fused to a transport signal, in particular a peptide export signal.

[0042] As used herein, the term "anticalin" relates to an artificial polypeptide derived from a lipocalin specifically binding its interaction partner. Similarly, a "Designed Ankyrin Repeat Protein" or "DARPin", as used herein, is an artificial polypeptide comprising several 14cab14i14 repeat motifs and specifically binding its interaction partner. The anticalins and the DARPins of the present invention have the activity of activating the immune response as specified herein above, preferably, the activity of being an antagonist of PD-L1 as specified herein above.

[0043] As used herein, the term "inhibitory peptide" relates to any chemical molecule comprising at least one peptide having the activity of activating the immune response as specified herein above, preferably, the activity of being an antagonist PD-L1 as specified herein above. Preferably, the inhibitory peptide comprises a peptide having an amino acid sequence corresponding to an amino acid sequence of at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least 13, at least 14, or at least 15 consecutive amino acids comprised in a PD-L1 polypeptide. Preferably, the inhibitory peptide comprises a peptide having an amino acid sequence corresponding to an amino acid sequence of 5 to 200, more preferably 6 to 100, even more preferably 7 to 50, or, most preferably, 8 to 30 consecutive amino acids comprised in a PD-L1 polypeptide. Moreover, also encompassed are variants of the aforementioned inhibitory peptides. Such variants have at least the same essential biological activity as the specific inhibitory peptides.

[0044] As used herein, the term "immunoglobulin" relates to a polypeptide being a soluble immunoglobulin, preferably an antibody from any of the classes IgA, IgD, IgE, IgG, or IgM, preferably having the activity of binding, more preferably specifically binding, a molecule of interest. Immunoglobulins against antigens of interest can be prepared by

well known methods using, e.g., a purified molecule of interest or a suitable fragment derived therefrom as an antigen. A fragment which is suitable as an antigen may be identified by antigenicity determining algorithms well known in the art. Such fragments may be obtained either from one of the molecules of interest by proteolytic digestion, may be a synthetic peptide, or may be obtained by recombinant expression. Preferably, a peptide of a molecule of interest used as an antigen is located at the exterior of a cell expressing the molecule of interest; i.e. preferably, the epitope the binding domain interacts with, preferably, is an extracellular domain. Preferably, the immunoglobulin of the present invention is a monoclonal antibody, a human or humanized antibody or primatized, chimerized antibody or a fragment thereof, so long as they exhibit the desired binding activity as specified elsewhere herein. Also comprised as antibodies of the present invention are a bispecific antibody, a synthetic antibody, or a chemically modified derivative of any of these. Preferably, the antibody of the present invention shall specifically bind (i.e. does only to a negligible extent or, preferably, not cross react with other polypeptides or peptides) to a molecule of interest as specified above. Specific binding can be tested by various well known techniques. Antibodies or fragments thereof can be obtained by using methods which are described, e.g., in Harlow and Lane "Antibodies, A Laboratory Manual", CSH Press, Cold Spring Harbor, 1988. Monoclonal antibodies can be prepared by the techniques originally described in Köhler and Milstein, Nature. 1975. 256: 495; and Galfré, Meth. Enzymol. 1981, 73: 3, which comprise the fusion of mouse myeloma cells to spleen cells derived from immunized mammals. As will be understood by the skilled person, a molecule of interest, bound by an immunoglobulin of the present invention, may also be an Fc receptor or a complement protein binding an Fc part of an antibody; accordingly, the immunoglobulin preferably is an Fc domain of an antibody, more preferably a soluble Fc domain of an antibody, most preferably a secreted soluble Fc domain of an antibody. Preferably, said antibody the Fc domain is derived from is an IgG, more preferably an IgG1, most preferably a human IgG1. Preferably, the secreted soluble Fc domain comprises the amino acid sequence of SEQ ID NO: 16 or a variant thereof, preferably encoded by the nucleic acid sequence of SEQ ID NO: 17. More preferably, the immunoglobulin is an antagonistic anti-PD-L1 antibody, still more preferably comprising the amino acid sequence of SEQ ID NO:2 or a variant thereof, preferably encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO:3 or a variant thereof. More preferably, the immunoglobulin is an antagonistic anti-PD-L1 antibody, more preferably comprising the amino acid sequence of SEQ ID NO:2, preferably encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO:3.

[0045] "Immunoglobulin fragments" comprise a portion of an intact immunoglobulin, preferably of an antibody, in an embodiment, comprise the antigen-binding region thereof. Examples of antibody fragments and fusion proteins of variable regions include Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; single-domain-antibodies (VHH), also known as nanobodies, and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-combining sites and is still capable of cross-linking antigen. "Fv" is the minimum antibody fragment which contains a complete antigen-binding site. Preferably, a two-chain Fv species consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. In a single-chain Fv (scFv) species, one heavy- and one light-chain variable domain can be covalently linked by a flexible peptide linker such that the light and heavy chains can associate in a "dimeric" structure analogous to that in a two-chain Fv species. It is in this configuration that the three hypervariable regions (HVRs, also referred to as complementarity determining regions (CDRs)) of each variable domain interact to define an antigen-binding site. Collectively, the six HVRs of one scFv confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three HVRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site. The term "diabodies" refers to antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies may be bivalent or bispecific. Diabodies are described more fully in, for example, EP 0 404 097; WO 1993/01161; Hudson et al., Nat. Med. 9 (2003) 129-134; and Hollinger et al., PNAS USA 90 (1993) 6444-6448. Triabodies and tetrabodies are also described in Hudson et al., Nat. Med. 9 (2003) 129-134.

[0046] The term "secreted", as used herein, relates to a compound being transferred from the interior of a host cell to the exterior of said host cell by a mechanism intrinsic to said host cell. Preferably, secretion of a polypeptide or fusion polypeptide is mediated by a, preferably eukaryotic, signal peptide mediating import of said peptide or polypeptide into the lumen of the endoplasmic reticulum and, more preferably, by the absence of retention signals. Signal peptides causing secretion of peptides or polypeptides are known in the art. Preferably, the signal peptide is an IL-12 signal peptide. Also preferably, the signal peptide is or comprises an Ig leader sequence. More preferably, the signal peptide is or comprises a human Ig leader sequence. Still more preferably, the signal peptide is or comprises a matching leader sequence, i.e. a leader sequence selected from the same Ig kappa subgroup as the variable light chain of the antibody, preferably, of the single-chain antibody.

[0047] As used herein, the terms "polypeptide variant" relates to any chemical molecule comprising at least one polypeptide or fusion polypeptide as specified elsewhere herein, having the indicated activity, but differing in primary structure from said polypeptide or fusion polypeptide indicated above. Thus, the polypeptide variant, preferably, is a mutein having the indicated activity. Preferably, the polypeptide variant comprises a peptide having an amino acid sequence corresponding to an amino acid sequence of 5 to 200, more preferably 6 to 100, even more preferably 7 to 50, or, most preferably, 8 to 30 consecutive amino acids comprised in a polypeptide as specified above. Moreover, also encompassed are further polypeptide variants of the aforementioned polypeptides. Such polypeptide variants have at

least essentially the same biological activity as the specific polypeptides. Moreover, it is to be understood that a polypeptide variant as referred to in accordance with the present invention shall have an amino acid sequence which differs due to at least one amino acid substitution, deletion and/or addition, wherein the amino acid sequence of the variant is still, preferably, at least 50%, 60%, 70%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% identical with the amino acid sequence of the specific polypeptide. The degree of identity between two amino acid sequences can be determined by algorithms well known in the art. Preferably, the degree of identity is to be determined by comparing two optimally aligned sequences over a comparison window, where the fragment of amino acid sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the sequence it is compared to for optimal alignment. The percentage is calculated by determining, preferably over the whole length of the polypeptide, the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman (1981), by the homology alignment algorithm of Needleman and Wunsch (1970), by the search for similarity method of Pearson and Lipman (1988), by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, PASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, Wis.), or by visual inspection. Given that two sequences have been identified for comparison, GAP and BESTFIT are preferably employed to determine their optimal alignment and, thus, the degree of identity. Preferably, the default values of 5.00 for gap weight and 0.30 for gap weight length are used. Polypeptide variants referred to herein may be allelic variants or any other species specific homologs, paralogs, or orthologs. Moreover, the polypeptide variants referred to herein include fragments of the specific polypeptides or the aforementioned types of polypeptide variants as long as these fragments and/or variants have the biological activity as referred to above. Such fragments may be or be derived from, e.g., degradation products or splice variants of the polypeptides. Further included are variants which differ due to posttranslational modifications such as phosphorylation, glycosylation, ubiquitinylation, sumoylation, or myristylation, by including non-natural amino acids, and/or by being peptidomimetics.

[0048] The term "expressible polynucleotide", as used herein, relates to a polynucleotide operatively linked to at least one expression control sequence causing transcription of the nucleic acid sequence comprised in said polynucleotide to occur, preferably in eukaryotic cells or isolated fractions thereof, preferably into a translatable mRNA or into a viral genome. Regulatory elements ensuring expression in eukaryotic cells, preferably mammalian cells, are well known in the art. They, preferably, comprise regulatory sequences ensuring initiation of transcription and, optionally, poly-A signals ensuring termination of transcription and stabilization of the transcript. Additional regulatory elements may include transcriptional as well as translational enhancers. Preferably, the aforesaid at least one expression control sequence is an expression control sequence of a (−)strand RNA virus, more preferably of a Paramyxovirus as described herein above, most preferably of an MV. Thus, preferably, at least one expression control sequence comprises a (−)strand RNA viral regulatory sequence ensuring initiation of transcription (consensus "gene start signal", preferably consensus MV "gene start signal") and termination signals (consensus "gene stop signal", preferably, consensus MV "gene stop signal") ensuring termination of transcription and stabilization of the transcript. It is known in the art that production of viral particles in permissive host cells can be initiated by transfecting into said permissive host cells one or more expressible DNA constructs encoding (i) a recombinant viral anti-genome, (ii) the viral L gene, (iii) the viral P gene, and (iv) the viral N gene. It is also understood by the skilled person that, once a viral genome and the aforesaid viral genes were expressed in said host cell, replication and assembly of viral particles occurs in the cytoplasm of the host cell and is, therefore, solely dependent on viral regulatory signals. The term polynucleotide, as used herein, preferably encompasses polynucleotide variants as specified elsewhere herein. Preferably, the expressible polynucleotide encoding an IL-12 is comprised in the genome of the recombinant virus of the family Paramyxoviridae in a region corresponding to the region intervening the P and the M gene of measles virus.

[0049] The term "polynucleotide encoding a recombinant virus", as used herein, relates to a polynucleotide comprising a nucleic acid sequence or nucleic acid sequences required for generating a virus particle or a virus-like particle in a host cell. It is understood by the skilled person that a virus is constituted by a polynucleotide genome and at least one kind of capsid polypeptide. Accordingly, the polynucleotide encoding a recombinant virus of the present invention, preferably, comprises a recombinant virus genome. As will be understood by the skilled person, in case the polynucleotide encoding a recombinant virus is comprised in a virus according to the present invention, i.e. a virus of the family Paramyxoviridae, the polynucleotide is (−)strand RNA. It is also understood by the skilled person that in case the polynucleotide is DNA comprised in a host cell, at least an RNA-dependent RNA polymerase activity will additionally be required to produce viral particles from said DNA polynucleotide. Preferably, the polynucleotide encoding a recombinant virus comprises or consists of the nucleic acid sequence as specified elsewhere herein. As annotated herein, the sequence of the DNA copy of negative-strand (−)RNA viruses is annotated in the usual 5'→3'-orientation; this corresponds to the viral sequence in antigenomic (+)RNA orientation with respect to the natural 3'→5'-orientation of negative-strand (−)RNA viruses.

[0050] The term "polynucleotide variant", as used herein, relates to a variant of a polynucleotide related to herein comprising a nucleic acid sequence characterized in that the sequence can be derived from the aforementioned specific nucleic acid sequence by at least one nucleotide substitution, addition and/or deletion, wherein the polynucleotide variant shall have the activity as specified for the specific polynucleotide. Preferably, said polynucleotide variant is an ortholog, a paralog or another homolog of the specific polynucleotide. Also preferably, said polynucleotide variant is a naturally occurring allele of the specific polynucleotide. Polynucleotide variants also encompass polynucleotides comprising a nucleic acid sequence which is capable of

hybridizing to the aforementioned specific polynucleotides, preferably, under stringent hybridization conditions. These stringent conditions are known to the skilled worker and can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N. Y. (1989), 6.3.1-6.3.6. A preferred example for stringent hybridization conditions are hybridization conditions in 6× sodium chloride/sodium citrate (=SSC) at approximately 45° C., followed by one or more wash steps in 0.2×SSC, 0.1% SDS at 50 to 65° C. The skilled worker knows that these hybridization conditions differ depending on the type of nucleic acid and, for example when organic solvents are present, with regard to the temperature and concentration of the buffer. For example, under "standard hybridization conditions" the temperature differs depending on the type of nucleic acid between 42° C. and 58° C. in aqueous buffer with a concentration of 0.1× to 5×SSC (pH 7.2). If organic solvent is present in the abovementioned buffer, for example 50% formamide, the temperature under standard conditions is approximately 42° C. The hybridization conditions for DNA:DNA hybrids are preferably for example 0.1×SSC and 20° C. to 45° C., preferably between 30° C. and 45° C. The hybridization conditions for DNA:RNA hybrids are preferably, for example, 0.1×SSC and 30° C. to 55° C., preferably between 45° C. and 55° C. The abovementioned hybridization temperatures are determined for example for a nucleic acid with approximately 100 bp (=base pairs) in length and a G+C content of 50% in the absence of formamide. The skilled worker knows how to determine the hybridization conditions required by referring to textbooks such as the textbook mentioned above, or the following textbooks: Sambrook et al., "Molecular Cloning", Cold Spring Harbor Laboratory, 1989; Hames and Higgins (Ed.) 1985, "Nucleic Acids Hybridization: A Practical Approach", IRL Press at Oxford University Press, Oxford; Brown (Ed.) 1991, "Essential Molecular Biology: A Practical Approach", IRL Press at Oxford University Press, Oxford. Alternatively, polynucleotide variants are obtainable by PCR-based techniques such as mixed oligonucleotide primer-based amplification of DNA, i.e. using degenerated primers against conserved domains of a polypeptide of the present invention. Conserved domains of a polypeptide may be identified by a sequence comparison of the nucleic acid sequence of the polynucleotide or the amino acid sequence of the polypeptide of the present invention with sequences of other organisms. As a template, DNA or cDNA from bacteria, fungi, or plants preferably, from animals may be used. Further, variants include polynucleotides comprising nucleic acid sequences which are at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to the specifically indicated nucleic acid sequences. Moreover, also encompassed are polynucleotides which comprise nucleic acid sequences encoding amino acid sequences which are at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to the amino acid sequences specifically indicated. The percent identity values are, preferably, calculated over the entire amino acid or nucleic acid sequence region. A series of programs based on a variety of algorithms is available to the skilled worker for comparing different sequences. In this context, the algorithms of Needleman and Wunsch or Smith and Waterman give particularly reliable results. To carry out the sequence alignments, the program PileUp (J. Mol. Evolution., 25, 351-360, 1987, Higgins et al., CABIOS, 5 1989: 151-153) or the programs Gap and BestFit (Needleman and Wunsch (J. Mol. Biol. 48; 443-453 (1970)) and Smith and Waterman (Adv. Appl. Math. 2; 482-489 (1981))), which are part of the GCG software packet (Genetics Computer Group, 575 Science Drive, Madison, Wis., USA 53711 (1991)), are to be used. The sequence identity values recited above in percent (%) are to be determined, preferably, using the program GAP over the entire sequence region with the following settings: Gap Weight: 50, Length Weight: 3, Average Match: 10.000 and Average Mismatch: 0.000, which, unless otherwise specified, shall always be used as standard settings for sequence alignments.

[0051] A polynucleotide comprising a fragment of any of the specifically indicated nucleic acid sequences is also encompassed as a variant polynucleotide of the present invention. The fragment shall still encode a polypeptide or fusion polypeptide which still has the activity as specified. Accordingly, the polypeptide encoded may comprise or consist of the domains of the polypeptide of the present invention conferring the said biological activity. A fragment as meant herein, preferably, comprises at least 50, at least 100, at least 250 or at least 500 consecutive nucleotides of any one of the specific nucleic acid sequences or encodes an amino acid sequence comprising at least 20, at least 30, at least 50, at least 80, at least 100 or at least 150 consecutive amino acids of any one of the specific amino acid sequences.

[0052] The polynucleotides of the present invention either consist of, essentially consist of, or comprise the aforementioned nucleic acid sequences. Thus, they may contain further nucleic acid sequences as well. Specifically, the polynucleotides of the present invention may encode fusion proteins wherein one partner of the fusion protein is a polypeptide being encoded by a nucleic acid sequence recited above. Such fusion proteins may comprise as additional part polypeptides for monitoring expression (e.g., green, yellow, blue or red fluorescent proteins, alkaline phosphatase and the like) or so called "tags" which may serve as a detectable marker or as an auxiliary measure for purification purposes. Tags for the different purposes are well known in the art and are described elsewhere herein.

[0053] The polynucleotide of the present invention shall be provided, preferably, either as an isolated polynucleotide (i.e. isolated from its natural context) or in genetically modified form. The polynucleotide, preferably, is DNA, including cDNA, or RNA. The term encompasses single as well as double stranded polynucleotides. Moreover, preferably, comprised are also chemically modified polynucleotides including naturally occurring modified polynucleotides such as glycosylated or methylated polynucleotides or artificial modified one such as biotinylated polynucleotides.

[0054] As used herein, the term "host cell" relates to a vertebrate cell. Preferably, the cell is a mammalian cell, more preferably, a mouse, rat, cat, dog, hamster, guinea pig, sheep, goat, pig, cattle, or horse cell. Still more preferably, the host cell is a primate cell. Most preferably, the host cell is a human cell. Preferably, the host cell is a tumor cell, more preferably a cancer cell.

[0055] Advantageously, it was found in the work underlying the present invention that oncolytic measles virus can be engineered to express IL-12, in particular an IL-12 fusion polypeptide, while infecting cancer cells and that IL-12 expression strongly enhances the immune response induced by the measles virus against said cancer cells. Moreover, it

was found that by further expressing immunoglobulins, in particular an anti-PD-L1 antibody, measles virus can further augment the immunological response to cancer cells, thus further contributing to their elimination.

[0056] The definitions made above apply mutatis mutandis to the following. Additional definitions and explanations made further below also apply for all embodiments described in this specification mutatis mutandis.

[0057] The present invention further relates to a polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to the present invention.

[0058] The present invention further relates to a host cell comprising the recombinant virus of the family Paramyxoviridae of the present invention and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae of the present invention.

[0059] As used herein, the term "host cell" relates to a host cell as specified herein above. Moreover, the host cell comprising the polynucleotide encoding the recombinant virus of the family Paramyxoviridae of the present invention may also be a bacterial, yeast, or insect cell, preferably a bacterial cell of the genus *Escherichia*, more preferably an *Escherichia coli* cell.

[0060] The present invention also relates to a medicament comprising (a) (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist; (ii) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 fusion polypeptide of the present invention; (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii), (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to; or (v) any combination of (i) to (iv); and (b) at least one pharmacologically acceptable excipient.

[0061] The terms "medicament" and "pharmaceutical composition", as used herein, relate to the compounds of the present invention and optionally one or more pharmaceutically acceptable carrier, i.e. excipient. The compounds of the present invention can be formulated as pharmaceutically acceptable salts. Acceptable salts comprise acetate, methyl ester, HCl, sulfate, chloride and the like. The pharmaceutical compositions are, preferably, administered locally, topically or systemically. Suitable routes of administration conventionally used for drug administration are oral, intravenous, or parenteral administration as well as inhalation. A preferred route of administration is intra-tumoral administration. However, depending on the nature and mode of action of a compound, the pharmaceutical compositions may be administered by other routes as well. For example, polynucleotide compounds may be administered in a gene therapy approach by using viral vectors or viruses or liposomes.

[0062] Moreover, the compounds can be administered in combination with other drugs either in a common pharmaceutical composition or as separated pharmaceutical compositions wherein said separated pharmaceutical compositions may be provided in form of a kit of parts. The compounds are, preferably, administered in conventional dosage forms prepared by combining the drugs with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables.

[0063] The excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and being not deleterious to the recipient thereof. The excipient employed may be, for example, a solid, a gel or a liquid carrier. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are phosphate buffered saline solution, syrup, oil such as peanut oil and olive oil, water, emulsions, various types of wetting agents, sterile solutions and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax. Said suitable carriers comprise those mentioned above and others well known in the art, see, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. The diluent(s) is/are selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[0064] A therapeutically effective dose refers to an amount of the compounds to be used in a pharmaceutical composition of the present invention which prevents, ameliorates or treats the symptoms accompanying a disease or condition referred to in this specification. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50.

[0065] The dosage regimen will be determined by the attending physician and other clinical factors; preferably in accordance with any one of the above described methods. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Progress can be monitored by periodic assessment. A typical dose can be, for example, in the range of 1 to 1000 μg for a polypeptide or polynucleotide, or 10^4-10^8 viral particles for a virus or a virus-like particle; however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. Progress can be monitored by periodic assessment. The pharmaceutical compositions and formulations referred to herein are administered at least once in order to treat or ameliorate or prevent a disease or condition recited in this specification. However, the said pharmaceutical compositions may be administered more than one time, for example from one to four times daily up to a non-limited number of days. Specific pharmaceutical

compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound referred to herein above in admixture or otherwise associated with a pharmaceutically acceptable carrier or diluent. For making those specific pharmaceutical compositions, the active compound(s) will usually be mixed with a carrier or the diluent, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other suitable containers or vehicles. The resulting formulations are to be adapted to the mode of administration, i.e. in the forms of tablets, capsules, suppositories, solutions, suspensions or the like. Dosage recommendations shall be indicated in the prescribers or users instructions in order to anticipate dose adjustments depending on the considered recipient.

[0066] Accordingly, the present invention also relates to a method for treating cancer in a subject afflicted with cancer, comprising

a) contacting said subject with

[0067] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0068] (ii) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 fusion polypeptide of the present invention;

[0069] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0070] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae of (i) and/or (ii) and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to (iii); or

[0071] (v) any combination of (i) to (iv), and thereby,

b) treating cancer in a subject afflicted with cancer.

[0072] The methods of treatment of the present invention, preferably, may comprise steps in addition to those explicitly mentioned above. For example, further steps may relate, e.g., to localizing a tumor and/or diagnosing cancer for step a), or administration of additional medication for step b). Moreover, one or more of said steps may be performed by automated equipment. The method of the present invention, preferably, is an in vivo method of treatment.

[0073] The term "treatment" refers to an amelioration of the diseases or disorders referred to herein or the symptoms accompanied therewith to a significant extent. Said treating as used herein also includes an entire restoration of the health with respect to the diseases or disorders referred to herein. It is to be understood that treating as used in accordance with the present invention may not be effective in all subjects to be treated. However, the term shall require that, preferably, a statistically significant portion of subjects suffering from a disease or disorder referred to herein can be successfully treated. Whether a portion is statistically significant can be determined without further ado by the person skilled in the art using various well known statistic evaluation tools, e.g., determination of confidence intervals, p-value determination, Student's t-test, Mann-Whitney test etc. Preferred confidence intervals are at least 90%, at least 95%, at least 97%, at least 98% or at least 99%. The p-values are, preferably, 0.1, 0.05, 0.01, 0.005, or 0.0001. Preferably, the treatment shall be effective for at least 10%, at least 20% at least 50% at least 60%, at least 70%, at least 80%, or at least 90% of the subjects of a given cohort or population. Preferably, treating cancer is reducing tumor burden in a subject. As will be understood by the skilled person, effectiveness of treatment of e.g. cancer is dependent on a variety of factors including, e.g. cancer stage and cancer type.

[0074] As used herein, the term "subject" relates to a vertebrate. Preferably, the subject is a mammal, more preferably, a mouse, rat, cat, dog, hamster, guinea pig, sheep, goat, pig, cattle, or horse. Still more preferably, the subject is a primate. Most preferably, the subject is a human. Preferably, the subject is afflicted with a disease caused or aggravated by an insufficient response of the immune response of said subject, more preferably, the subject is afflicted with cancer.

[0075] The term "cancer", as used herein, relates to a disease of an animal, including man, characterized by uncontrolled growth by a group of body cells ("cancer cells"). This uncontrolled growth may be accompanied by intrusion into and destruction of surrounding tissue and possibly spread of cancer cells to other locations in the body. Preferably, also included by the term cancer is a relapse. Thus, preferably, the cancer is a solid cancer, a metastasis, or a relapse thereof.

[0076] Preferably, the cancer is selected from the list consisting of acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, aids-related lymphoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, brain stem glioma, breast cancer, burkitt lymphoma, carcinoid tumor, cerebellar astrocytoma, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal stromal tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, hepatocellular cancer, 27cab27i27 lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, intraocular melanoma, 27cab27i sarcoma, laryngeal cancer, medulloblastoma, medulloepithelioma, melanoma, merkel cell carcinoma, mesothelioma, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sézary syndrome, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, waldenström macroglobulinemia, and wilms tumor. More preferably, the cancer is a solid cancer, a metastasis, or a relapse thereof. Most preferably, the cancer is a tumor derived from malignant melanoma, head and neck cancer, hepatocellular car-

cinoma, pancreatic carcinoma, prostate cancer, renal cell carcinoma, gastric carcinoma, colorectal carcinoma, lymphomas or leukemias.

[0077] Preferably, the method of treatment of the present invention comprises contacting a subject with a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist. Thus, preferably, the method comprises contacting a subject with a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12, wherein said recombinant virus of the family Paramyxoviridae is not a virus disclosed in WO 2015/128313 A1. Preferably, said recombinant virus of the family Paramyxoviridae of (i) is a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 polypeptide and not comprising an expressible polynucleotide encoding a ligand for an immune checkpoint blockade protein. More preferably, the recombinant virus of the family Paramyxoviridae of (i) is a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 polypeptide as the only expressible polynucleotide encoding an activator of the immune response, i. e. preferably, the recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 does not comprise an expressible polynucleotide encoding a further activator of the immune response.

[0078] The present invention further relates to an in vitro method for activating immune cells with antitumor activity in a sample comprising cancer cells and immune cells, comprising

a) contacting said sample comprising cancer cells and immune cells with

[0079] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0080] (ii) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 fusion polypeptide of the present invention;

[0081] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0082] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae of (i) and/or (ii) and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to (iii); or

[0083] (v) any combination of (i) to (iv), and thereby,

b) activating immune cells with antitumor activity comprised in said sample.

[0084] The method for activating immune cells with antitumor activity may comprise steps in addition to those explicitly mentioned above. For example, further steps may relate, e.g., to providing the recombinant virus of the family Paramyxoviridae for step a), administering further activating compounds, e.g. cytokines, to the immune cells in step b), or separating immune cells from cancer cells after step b). Moreover, one or more of said steps may be performed by automated equipment.

[0085] Moreover, the present invention relates to a recombinant virus of the family Paramyxoviridae of the present invention for use in treatment of inappropriate cell proliferation.

[0086] The term "inappropriate cell proliferation" relates to any proliferation of cells of a subject which is not appropriate to the physiological state of said subject and/or to the tissue context of said cells. Preferably, inappropriate cell proliferation is caused or aggravated by an inhibition or insufficient activation of the immune system, more preferably inhibition or insufficient activation of T cells. Also preferably, inappropriate cell proliferation is cancer.

[0087] The present invention further relates to a kit comprising at least

[0088] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0089] (ii) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 fusion polypeptide of the present invention;

[0090] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0091] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae of (i) and/or (ii) and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to (iii); or

[0092] (v) any combination of (i) to (iv),

[0093] housed in a container.

[0094] The term "kit", as used herein, refers to a collection of the aforementioned components. Preferably, said components are combined with additional components, preferably within an outer container. The outer container, also preferably, comprises instructions for carrying out a method of the present invention. Examples for such the components of the kit as well as methods for their use have been given in this specification. The kit, preferably, contains the aforementioned components in a ready-to-use formulation. Preferably, the kit may additionally comprise instructions, e.g., a user's manual for applying the recombinant virus of the family Paramyxoviridae with respect to the applications provided by the methods of the present invention. Details are to be found elsewhere in this specification. Additionally, such user's manual may provide instructions about correctly using the components of the kit. A user's manual may be provided in paper or electronic form, e.g., stored on CD or CD ROM. The present invention also relates to the use of said kit in any of the methods according to the present invention.

[0095] Moreover, the present invention relates to a use of

[0096] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0097] (ii) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 fusion polypeptide of the present invention;

[0098] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0099] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae of (i) and/or (ii) and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to (iii); or

[0100] (v) any combination of (i) to (iv),

[0101] for the manufacture of a medicament for treating inappropriate cell proliferation, preferably for treating cancer.

[0102] Summarizing the findings of the present invention, the following embodiments are preferred:

[0103] 1. A recombinant virus of the family Paramyxoviridae, comprising an expressible polynucleotide encoding an IL-12 polypeptide, wherein said IL-12 polypeptide is an IL-12 fusion polypeptide comprising a p40 subunit of an IL-12 and a p35 subunit of an IL-12.

[0104] 2. The recombinant virus of the family Paramyxoviridae of embodiment 1, wherein said p40 subunit and said p35 subunit of said IL-12 fusion polypeptide are from the same species.

[0105] 3. The recombinant virus of the family Paramyxoviridae of embodiment 1 or 2, wherein said p40 subunit and said p35 subunit of said IL-12 fusion polypeptide are a mouse p40 subunit and a mouse p35 subunit or a variant thereof, preferably are a human p40 subunit and a human p35 subunit or a variant thereof.

[0106] 4. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 3, wherein said p40 subunit and said p35 subunit of said IL-12 fusion polypeptide are a Claim subunit and a mouse p35 subunit, preferably are a human p40 subunit and a human p35 subunit.

[0107] 5. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 4, wherein said IL-12 fusion polypeptide comprises the structure p40-linker-p35.

[0108] 6. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 5, wherein said linker is -(glycine$_4$-serine)$_n$-, with n=1 to 10, preferably n=2 to 5, more preferably n=3.

[0109] 7. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 5, wherein said linker is -(glycine$_6$-serine)-.

[0110] 8. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 7, wherein said expressible polynucleotide encoding an IL-12 is comprised in the genome of the recombinant virus of the family Paramyxoviridae in a region corresponding to the region intervening the P and the M gene of measles virus.

[0111] 9. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 8, further comprising at least one expressible polynucleotide encoding a further activator of the immune response.

[0112] 10. The recombinant virus of the family Paramyxoviridae of embodiment 9, wherein said further activator of the immune response is an immunoglobulin or fragment thereof.

[0113] 11. The recombinant virus of the family Paramyxoviridae of embodiments 9 or 10, wherein said further activator of the immune response is a secreted immunoglobulin.

[0114] 12. The recombinant virus of the family Paramyxoviridae of any one of embodiments 9 to 11, wherein said further activator of the immune response is an Fc domain of an antibody.

[0115] 13. The recombinant virus of the family Paramyxoviridae of any one of embodiments 9 to 12, wherein said further activator of the immune response is a secreted soluble Fc domain of a human IgG1 antibody.

[0116] 14. The recombinant virus of the family Paramyxoviridae of any one of embodiments 9 to 13, wherein said further activator of the immune response is a secreted soluble activator of the immune response.

[0117] 15. The recombinant virus of the family Paramyxoviridae of any one of embodiments 9 to 14, wherein said further activator of the immune response is a single-chain antibody or a nanobody.

[0118] 16. The recombinant virus of the family Paramyxoviridae of any one of embodiments 9 to 15, wherein said further activator of the immune response is a secreted soluble anti-PD-L1 antibody.

[0119] 17. The recombinant virus of the family Paramyxoviridae of embodiment 16, wherein said secreted soluble anti-PD-L1 antibody comprises an amino acid sequence according to SEQ ID NO: 2.

[0120] 18. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 17, wherein said recombinant virus is a recombinant Morbillivirus, preferably, a recombinant measles virus (MV).

[0121] 19. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 18, wherein said recombinant MV is derived from MV strain Edmonston A or B, preferably B, more preferably from MV vaccine strain Schwarz/Moraten.

[0122] 20. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 19, wherein the at least one expressible polynucleotide encoding an IL-12 polypeptide is comprised in a polynucleotide encoding the recombinant virus of the family Paramyxoviridae.

[0123] 21. The recombinant virus of the family Paramyxoviridae of any one of embodiments 1 to 20, wherein said polynucleotide encoding the recombinant virus of the family Paramyxoviridae comprises the nucleic acid sequence of any one of SEQ ID Nos: 4 to 7, 14, and 15.

[0124] 22. A polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to any one of embodiments 1 to 21.

[0125] 23. The polynucleotide according to embodiment 22, wherein said polynucleotide comprises the nucleic acid sequence any one of SEQ ID Nos: 4 to 7, 14, and 15.

[0126] 24. A host cell comprising the recombinant virus of the family Paramyxoviridae according to any one of embodiments 1 to 21 and/or the polynucleotide encoding the recombinant virus of the family Paramyxoviridae according to embodiment 21 or 22.

[0127] 25. A medicament comprising

[0128] (a) (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0129] (ii) a recombinant virus of the family Paramyxoviridae according of any one of embodiments 1 to 21,

[0130] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0131] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii) and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

[0132] (v) any combination of (i) to (iv); and

[0133] (b) at least one pharmacologically acceptable excipient.

[0134] 26. A method for treating cancer in a subject afflicted with cancer, comprising

[0135] a) contacting said subject with

[0136] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0137] (ii) a recombinant virus of the family Paramyxoviridae according of any one of embodiments 1 to 21,

[0138] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0139] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii) and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

[0140] (v) any combination of (i) to (iv); and, thereby,

[0141] b) treating cancer in a subject afflicted with cancer.

[0142] 27. The method of embodiment 26, wherein said recombinant virus of the family Paramyxoviridae of (i) is a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 polypeptide and not comprising an expressible polynucleotide encoding a ligand for an immune checkpoint blockade protein.

[0143] 28. The method of embodiment 26 or 27, wherein said recombinant virus of the family Paramyxoviridae of (i) is a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 polypeptide as the only expressible polynucleotide encoding an activator of the immune response.

[0144] 29. The method of any one of embodiments 26 to 28, wherein said cancer is a solid cancer, a metastasis, or a relapse thereof.

[0145] 30. The method of any one of embodiments 26 to 29, wherein treating cancer is reducing tumor burden.

[0146] 31. The method of any one of embodiments 26 to 30, wherein said cancer is malignant melanoma, head and neck cancer, hepatocellular carcinoma, pancreatic carcinoma, prostate cancer, renal cell carcinoma, gastric carcinoma, colorectal carcinoma, lymphomas or leukemias.

[0147] 32. An in vitro method for activating immune cells with antitumor activity in a sample comprising cancer cells and immune cells, comprising

[0148] a) contacting said sample comprising cancer cells and immune cells with

[0149] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0150] (ii) a recombinant virus of the family Paramyxoviridae according of any one of embodiments 1 to 21,

[0151] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0152] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii) and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

[0153] (v) any combination of (i) to (iv); and thereby,

[0154] b) activating immune cells with antitumor activity comprised in said sample.

[0155] 33. Use of

[0156] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0157] (ii) a recombinant virus of the family Paramyxoviridae according of any one of embodiments 1 to 21,

[0158] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0159] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii) and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

[0160] (v) any combination of (i) to (iv);

[0161] for the manufacture of a medicament for treating cancer.

[0162] 34. A recombinant virus of the family Paramyxoviridae according to any one of embodiments 1 to 21 and/or a polynucleotide according to embodiment 22 or 23 for use in medical treatment.

[0163] 35. A recombinant virus of the family Paramyxoviridae

[0164] (i) comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist; and/or

[0165] (ii) according of any one of embodiments 1 to 21, for use in treatment of inappropriate cell proliferation.

[0166] 36. The recombinant virus of the family Paramyxoviridae for use of embodiment 35, wherein treatment of inappropriate cell proliferation is cancer treatment.

[0167] 37. A kit comprising

[0168] (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

[0169] (ii) a recombinant virus of the family Paramyxoviridae according of any one of embodiments 1 to 21,

[0170] (iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

[0171] (iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii)

and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

[0172] (v) any combination of (i) to (iv);

[0173] housed in a container.

[0174] All references cited in this specification are herewith incorporated by reference with respect to their entire disclosure content and the disclosure content specifically mentioned in this specification.

[0175] The following Examples shall merely illustrate the invention. They shall not be construed, whatsoever, to limit the scope of the invention.

EXAMPLES

Example 1: Cell Culture

[0176] Vero African green monkey kidney cells were obtained from the American Type Culture Collection (Manassas, Va.). Vero-αHis cell line stably expressing a single chain antibody (38cab) against His_6 tag (Nakamura et al. 2005) was a kind gift of S. J. Russel (Mayo Clinic, Rochester, Minn.). Murine colon adenocarcinoma cells MC38cea (transduced for stable expression of human CEA antigen) and the parental MC38 cell line were a gift of R. Cattaneo (Mayo Clinic, Rochester, Minn.). B16-CD20 have previously been generated by transducing the parental cell line with a lentiviral vector encoding human CD20 (Engeland et al. 2014). All cell lines were cultivated in either Dulbecco's modified Eagle's medium (DMEM; Life Technologies, Darmstadt, Germany) or Roswell Park Memorial Institute 1640 medium (RPMI 1640; Life Technologies) supplemented with 10% Fetal Calf Serum (FCS) at 37° C. in a humidified atmosphere with 5% CO_2 and routinely tested for mycoplasma contamination.

Example 2: Cloning of Recombinant MeVac Genomes

[0177] The cDNA plasmids encoding recombinant MeV genomes were constructed on the basis of the commercially used Schwarz/Moraten vaccine strain (MeVac) (Combredet et al. 2003). Transgenes were inserted in additional transcription units (ATUs) containing additional gene-end gene-start signals and a unique cloning site. Transgenes smaller than 1 kbp including murine GM-CSF (426 bp), murine IP-10 (312 bp) and eGFP (720 bp) were inserted into the leader position of pcMeVac as MluI-AscI fragments via the unique AscI restriction site. The mGM-CSF and eGFP fragments were amplified from the MeV Edmonston B (Nse) vaccine strain genomes encoding the respective transgenes (Grossardt et al. 2013). The mIP-10 (mCxcl10) gene was amplified with primers flanking the novel construct and adding a MluI site and a Kozak sequence (GCCACC) in the 5'-end and a two nucleotide TA spacer and AscI site in the 3'-end using cDNA obtained from murine splenocytes.

[0178] Cassette encoding a murine IL-12 fusion protein (FmIL-12) consisting of murine IL-12 p40 and p35 subunits linked by a $(Gly_4Ser)_3$ for insertion into MeV genome had previously been constructed by C. Grossardt (Grossardt 2013) based on results of Lieschke and colleagues (Lieschke et al. 1997). FmIL-12 construct (1650 bp) was excised from pCG expression vector (constructed by C. Grossardt) as Paul-MluI fragment and inserted into the MeVac genome downstream the P ORF via the unique MauBI cloning site.

[0179] Antibodies against negative murine T cell regulators CTLA-4 and PD-L1 as well as soluble form of murine CD80 T cell costimulatory molecule and human IgG1-Fc fragment for use as a control were inserted into the ATU downstream the H gene. Cassettes encoding antibodies against murine CTLA-4 and PD-L1 and human IgG1-Fc fragment previously designed by C. E. Engeland (Engeland et al. 2014) were used as templates. The respective constructs were excised from pCG expression vectors as MluI-Paul fragments and inserted into the pcMeVac H-ATU via the unique MauBI cloning site.

[0180] Murine CD80 molecule was inserted for expression from MeVac in a soluble form. CD80-Fc was constructed by fusing the extracellular part of the murine CD80 with the same human IgG1-Fc region as used in both anti-CTLA-4 and anti-PD-L1 constructs via fusion PCR. The first PCR fragment consisting of the MluI restriction site followed by Kozak sequence (GCCACC), murine CD80 signal peptide, extracellular part (up to the asparagine in position 246) of murine CD80 and first 26 nucleotides of the hinge of IgG1-Fc was synthesized using pCG vector encoding murine CD80 as a template. The second PCR fragment consisting of the human IgG1-Fc region followed by myc tag, stop codon and AscI restriction site was synthesized using pCG vector encoding human IgG1-Fc as a template. The obtained PCR products were fused with flanking primers in an overlap PCR obtaining the mCD80-Fc construct of 1614 bp. The mCD80-Fc was inserted into the pcMeVac H-ATU as a MluI-AscI fragment via the unique MauBI cloning site.

[0181] MeVac genomes encoding the previously described transgenes with a fully retargeted MeV H attachment gene were constructed to allow targeted transduction of murine MC38cea and B16-CD20 cells. MeVac H gene was exchanged for H gene with mutated attachment sites to the natural MeV receptors CD46 and CD150, fused to a single chain antibody (39cab) against human CEA or CD20 and containing a C-terminal His_6tag. The retargeting system allows a flexible change of the targeted antigen by exchanging the specific 39cab as a SfiI-NotI fragment.

Example 3: Virus Propagation and Titration

[0182] Recombinant MeVac particles were obtained from cDNA constructs according to Radecke et al. (Radecke et al. 1995) and propagated on Vero-αHis cells according to Nakamura et al. (Nakamura et al. 2005). For propagation Vero-αHis cells were infected at a multiplicity of infection (MOI) of 0.03 and cultivated at 37° C. 5% CO_2 until syncytia had spread across the whole cell layer (36-48 h post infection). Subsequently culture medium was completely removed, cells were scraped and collected and viral particles released by one freeze-thaw cycle. Cellular debris was removed by centrifugation at 6000×g for 5 min. The amount of viral particles was determined by 1:10 serial dilution titrations in octuplicates on 1.5×10^4Vero-αHis cells per well in 96-well cell culture plates. Individual syncytia were counted 72 h post infection and titers calculated as cell infectious units per ml (ciu/ml).

Example 4: Statistical Analyses

[0183] Statistical analyses were performed using GraphPad Prism software (version 5.04; GraphPad Software, La Jolla, Calif.). Tumor volumes and ELISA results in restimu-

lation experiments were analysed by one-way ANOVA with Tukey's multiple comparison test. Survival curves were analyzed by log-rank (Mantel-Cox) test with Bonferroni-Holm correction for multiple comparisons. Result was considered statistically significant if p value was lower than 0.05 after correcting for multiple comparisons.

Example 5: Characterization of Virus Replication

[0184] Vero-αHis and MC38cea cells were seeded in 12-well plates (1×10^5 cells per well). After 12 h the cell culture medium was removed and cells were infected with the respective viruses at MOI=3 in 300 μl OptiMEM in triplicates for each time point and cultivated at 37° C. 5% CO_2. After adsorption for ca. 2 h the inoculum was removed and substituted with 1 ml DMEM+10% FCS per well. Cells were scraped in the culture medium at the designated time points, collected and snap frozen in liquid nitrogen. The amount of viral particles was determined by 1:10 serial dilution titrations in quadruplicates on 1.5×10^4 Vero-αHis cells per well in 96-well cell culture plates. Individual syncytia were counted 72 h post infection and titers calculated as ciu/ml.

Example 6: Assessment of Virus Cytotoxic Potential In Vitro

[0185] MC38cea cells were seeded in 6-well plates (2×10^5 cells per well). After 12 h the cell culture medium was removed and cells were infected with the respective viruses at MOI=5 in 800 μl OptiMEM in triplicates for each time point and cultivated at 37° C. 5% CO_2. After adsorption for ca. 2 h the inoculum was removed and substituted with 2 ml DMEM+10% FCS per well. At the designated time points cell viability was determined using Colorimetric Cell Viability Kit III (XTT) (PromoKine, Heidelberg, Germany) according to instructions of the manufacturer.

Example 7: Characterization of Transgene Expression

[0186] MC38cea cells were seeded in 12-well plates (1×10^5 cells per well). After 12 h the cell culture medium was removed and cells were infected with the respective viruses at MOI=3 in 300 μl OptiMEM in triplicates for each time point and cultivated at 37° C. 5% CO_2. After adsorption for ca. 2 h 700 μl DMEM+10% FCS per well was added. Supernatants were collected at the designated time points. Time point 0 h was represented by inoculum in OptiMEM used for infection. Expression of the respective immunomodulators was detected by ELISA. Commercially available ELISA kits were used for detection of mGM-CSF, FmIL-12, mIP-10 (R&D Systems, Wiesbaden, Germany) and CD80-Fc (Boster Biological Technology, Offenbach, Germany) according to instructions of the manufacturer. Anti-CTLA-4 and anti-PD-L1 were detected by binding to their respective murine proteins. Ninety-six well plates (Nunc Maxisorp, Thermo Fisher Scientific, Schwerte, Germany) were coated with 100 ng recombinant His-tagged murine CTLA-4 or PD-L1 (Life Technologies). Wells were blocked and 100 μl of the respective samples were added and incubated for 2 h. After washing the antibodies were detected with anti-human IgG-Fc Biotin (clone HP-6071; Sigma-Aldrich, Taufkirchen, Germany), Peroxidase conjugated Streptavidin (Dianova, Hamburg, Germany) and 1-Step Ultra-TMB ELISA Substrate Solution (Thermo Scientific, Karlsruhe, Germany). Absorbance was measured using Infinite M200 Pro microplate reader and i-control software (Tecan, Mannedorf, Switzerland).

Example 8: Flow Cytometry for Detection of Anti-PD-L1 Binding to MC38cea Cells

[0187] Vero-αHis cells were seeded in 15 cm cell culture dishes and infected with MeVac encoding anti-PD-L1 or IgG1-Fc with M01=0.03. Supernatants were collected (15 ml per plate) when syncytia had spread over the whole cell layer (ca. 36 h post infection). 1×10^6 MC38cea cells were incubated with anti-PD-L1 or IgG1-Fc containing supernatant previously collected from one fully infected 15 cm dish for 1 h with rotation at room t°. After washing the bound anti-PD-L1 was detected by staining with anti-HA (clone HA-7; Sigma-Aldrich) and goat anti-mouse IgG PE (polyclonal; BD Biosciences, Heidelberg, Germany). The stained cells were resuspended in DPBS with 0.2 μg/ml DAPI (Sigma-Aldrich) and directly acquired on LSRII flow cytometer (BD Biosciences) collecting at least 10000 events per sample.

Example 9: Isolation of Murine Splenocytes

[0188] Spleens were aseptically isolated and maintained in RPMI 1640 (Life Technologies, Darmstadt, Germany) at 4° C. until further processing. Spleen was passed through a 100 μm nylon cell strainer (BD Biosciences, Heidelberg, Germany) into 10 ml RPMI 1640 and cells were pelleted at 300×g for 5 min. For red blood cell lysis pellet was resuspended in 1 ml ACK Lysing solution (Life Technologies), incubated 10 min at room t° and centrifuged at 300×g for 5 min. Cells were resuspended in DPBS (Life Technologies) and cell concentration determined using Neubauer hemocytometer and Trypan blue (Sigma-Aldrich) staining for dead cell exclusion.

Example 10: Functional Assay for MeVac Encoded Anti-PD-L1, CD80-Fc and Anti-CTLA-4

[0189] Vero-αHis cells were seeded in 15 cm cell culture dishes and infected with MeVac encoding anti-PD-L1, anti-CTLA-4, CD80-Fc or IgG1-Fc with M01=0.03. Supernatants were collected (15 ml per plate) when syncytia had spread over the whole cell layer (ca. 36 h post infection). 2×10^5 MC38cea cells were incubated with 2 ml medium collected from the Vero-αHis infected with the respective viruses for 5 min with rotation at room t° and pelleted by centrifugation 5 min at 300×g. The procedure was repeated six times. The treated cells were resuspended in 100 μl activation medium—RPMI 1640 supplemented with 5% FCS, 1% Penicillin-Streptomycin (Life Technologies), 500 μM ionomycin (Cayman Chemical Company, Hamburg, Germany) and 5 μM PMA (Cayman Chemical Company) and seeded in 96-well plate. 2×10^5 freshly isolated splenocytes from C57BL/6J mouse in 100 μl activation medium were added per each well with the treated MC38cea cells. Cells were cocultivated 24 h at 37° C. 5% CO_2 and supernatants collected subsequently. IFN-γ concentration was determined using mouse IFN gamma ELISA Ready-SET-Go!® (eBioscience, Frankfurt am Main, Germany) according to the instructions of the manufacturer.

Example 11: Functional Assay for MeVac Encoded FmIL-12

[0190] Vero-αHis cells were seeded in 15 cm cell culture dishes and infected with MeVac encoding FmIL-12 or eGFP.

Supernatants were collected (15 ml per plate) when syncytia had spread over the whole cell layer (ca. 36 h post infection). FmIL-12 concentration was assessed using Mouse IL-12 p70 Quantikine ELISA Kit (R&D Systems). 2×10^6 freshly isolated splenocytes from a C57BL/6J mouse were resuspended in RPMI 1640 supplemented with 10% FCS, 1% Penicillin-Streptomycin solution and 50 U/ml recombinant murine IL-2 (Miltenyi, Bergisch Gladbach, Germany) with varying concentrations of MeVac encoded FmIL-12 or respective parts of supernatant from cells infected with eGFP encoding MeVac. Splenocytes were seeded in 12-well plates and incubated 48 h at 37° C. 5% CO_2. Supernatants were collected and IFN-γ concentration assessed using mouse IFN gamma ELISA Ready-SET-Go!® (eBioscience) according to the instructions of the manufacturer.

Example 12: Assessment of Therapeutic Efficacy In Vivo

[0191] MC38cea cells were subcutaneously (s.c.) implanted into six to eight weeks old C57Bl/6J mice (Harlan Laboratories, Rossdorf Germany or DKFZ, Heidelberg, Germany). When average tumor volume reached 50-100 mm^3 (depending on experiment) treatment was initiated. Mice received intratumoral (i.t.) injections with the respective viruses on four or five consecutive days with 5×10^5 or 1×10^6 ciu in 100 μl. Mice in the mock group received treatment with 100 μl OptiMEM. Tumor volume was determined every third day measuring largest and smallest diameter with a caliper and calculating the volume using a formula: largest diameter×(smallest diameter)^2×0.5. Mice were sacrificed when tumor volume exceeded 1500 mm^3, ulceration occurred or signs of severe illness were observed.

Example 13: Antigen Specific IFN-γ Memory Recall with Murine Splenocytes

[0192] MC38cea, MC38 and B16 cells were treated with 20 μg/ml mitomycin-C(Sigma-Aldrich) for 2 h with shaking at 37° C. After subsequent washing three times with DPBS cells were resuspended in activation medium containing RPMI 1640 supplemented with 10% FCS, 1% Penicillin-Streptomycin and 50 U/ml recombinant murine IL-2. Freshly isolated murine splenocytes were resuspended in the same activation medium. Cocultures were prepared in 24-well plates seeding 1×10^5 mitomycin-c treated tumor cells or 1×10^6 ciu MeVac with 1×10^6 splenocytes per well in 0.5 ml total volume of activation medium. As controls 1×10^6 splenocytes were cocultivated also with Vero-αHis or DLD-1 cell lysates prepared by lysis of 1×10^6 cells per ml with one freeze-thaw cycle. Cells were cocultivated for 48 h, supernatants collected and IFN-γ concentration assessed using mouse IFN gamma ELISA Ready-SET-Go!® (eBioscience) according to the instructions of the manufacturer.

REFERENCES

[0193] Combredet, C. et al., 2003. A Molecularly Cloned Schwarz Strain of Measles Virus Vaccine Induces Strong Immune Responses in Macaques and Transgenic Mice A Molecularly Cloned Schwarz Strain of Measles Virus Vaccine Induces Strong Immune Responses in Macaques and Transgenic Mice.

[0194] Engeland, C. E. et al., 2014. CTLA-4 and PD-L1 Checkpoint Blockade Enhances Oncolytic Measles Virus Therapy. *Molecular Therapy,* 22(11), pp. 1949-1959.

[0195] Grossardt, C., 2013. *Engineering Targeted and Cytokine-armed Oncolytic Measles Viruses*. Ruperto-Carola University of Heidelberg.

[0196] Grossardt, C. et al., 2013. Granulocyte-Macrophage Colony-Stimulating Factor-Armed Oncolytic Measles Virus Is an Effective Therapeutic Cancer Vaccine. *Human Gene Therapy,* 24(7), pp. 644-654.

[0197] Lieschke, G. J. et al., 1997. Bioactive murine and human interleukin-12 fusion proteins which retain antitumor activity in vivo. *Nature biotechnology,* 15(1), pp. 35-40.

[0198] Nakamura, T. et al., 2005. Rescue and propagation of fully retargeted oncolytic measles viruses. *Nature biotechnology,* 23(2), pp. 209-14.

[0199] Radecke, F. et al., 1995. Rescue of measles viruses from cloned DNA. *The EMBO journal,* 14(23), pp. 5773-84. Available at:

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 17

<210> SEQ ID NO 1
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial linker sequence

<400> SEQUENCE: 1

Gly Gly Gly Gly Ser
1 5

<210> SEQ ID NO 2
<211> LENGTH: 502
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: anti-human PD-L1 single-chain antibody

<400> SEQUENCE: 2

-continued

```
Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser
            100                 105                 110

Asn Trp Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
    130                 135                 140

Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val
145                 150                 155                 160

Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Ser Thr Tyr Ala Ile
                165                 170                 175

Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Gly
            180                 185                 190

Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe Gln Gly
        195                 200                 205

Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu
    210                 215                 220

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
225                 230                 235                 240

Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val Trp Gly
                245                 250                 255

Gln Gly Thr Thr Val Thr Val Ser Ser Val Asp Glu Ala Lys Ser Cys
            260                 265                 270

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
        275                 280                 285

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
    290                 295                 300

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
305                 310                 315                 320

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
                325                 330                 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
            340                 345                 350

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
        355                 360                 365

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
    370                 375                 380

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
385                 390                 395                 400
```

-continued

```
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
                405                 410                 415

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
            420                 425                 430

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
        435                 440                 445

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
    450                 455                 460

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
465                 470                 475                 480

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
                485                 490                 495

Pro Gly Lys Val Asp Asn
            500
```

<210> SEQ ID NO 3
<211> LENGTH: 1509
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: anti-human PD-L1 single-chain antibody encoding sequence

<400> SEQUENCE: 3

```
atggaaaccc cagcacagct tctcttcctc ctgctgctct ggctcccaga taccactgga     60

gagattgtcc tgacacagag cccagctaca ctttccctgt ctccgggcga aagagcaacc    120

ctctcttgca gggctagcca gtctgtcagc tcttatctcg cctggtatca gcagaaacca    180

ggccaggctc ccagactgct gatctacgac gctagcaatc gcgccactgg cataccagca    240

cgcttttcag ggtccggcag tggtaccgac ttcaccctga ccatctcctc actggaacct    300

gaggactttg ccgtgtatta ctgtcaacag cggagtaact ggcccacctt tgggcagggc    360

actaaggtgg agatcaaacg cggtggtggt ggatcaggtg gaggcggaag tggaggtggc    420

ggatcccagg tgcaactggt acagagcggc gcagaagtga agaaacccgg gtcctcagtg    480

aaggtcagtt gcaagacatc cggggacacc ttctcaacgt atgccattag ctgggttaga    540

caggctcctg gtcaagggct tgagtggatg ggaggtatca ttcccatatt cgggaaagcg    600

cattatgccc agaagttcca aggcagggtc accatcactg ccgatgaatc cacaagtact    660

gcctacatgg agttgagctc cttgcgtagc gaggatactg cggtgtactt ttgtgcacgg    720

aagtttcact tcgtttcagg gagcccttc gggatggatg tttggggaca gggtacaacg    780

gtgacagtat ccagcgtcga cgaggccaaa tcttgtgaca aaactcacac atgcccaccg    840

tgcccagcac ccgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag    900

gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac    960

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag   1020

acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc   1080

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc   1140

ccagccccca tcgagaaaac catctccaaa gccaaggggc agccccgaga accacaggtg   1200

tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg   1260

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag   1320
```

-continued

aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1380

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1440

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaagtc 1500

gacaattaa 1509

<210> SEQ ID NO 4
<211> LENGTH: 17610
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: recombinant MV genome MeVac_P-FmIL-12

<400> SEQUENCE: 4

accaaacaaa gttgggtaag gatagttcaa tcaatgatca tcttctagtg cacttaggat 60

tcaagatcct attatcaggg acaagagcag gattagggat atccgagatg gccacacttt 120

taaggagctt agcattgttc aaaagaaaca aggacaaacc acccattaca tcaggatccg 180

gtggagccat cagaggaatc aaacacatta ttatagtacc aatccctgga gattcctcaa 240

ttaccactcg atccagactt ctggaccggt tggtgaggtt aattggaaac ccggatgtga 300

gcgggcccaa actaacaggg gcactaatag gtatattatc cttatttgtg gagtctccag 360

gtcaattgat tcagaggatc accgatgacc ctgacgttag cataaggctg ttagaggttg 420

tccagagtga ccagtcacaa tctggcctta ccttcgcatc aagaggtacc aacatggagg 480

atgaggcgga ccaatacttt tcacatgatg atccaattag tagtgatcaa tccaggttcg 540

gatggttcgg gaacaaggaa atctcagata ttgaagtgca agaccctgag ggattcaaca 600

tgattctggg taccatccta gcccaaattt gggtcttgct cgcaaaggcg gttacggccc 660

cagacacggc agctgattcg gagctaagaa ggtggataaa gtacacccaa caaagaaggg 720

tagttggtga atttagattg gagagaaaat ggttggatgt ggtgaggaac aggattgccg 780

aggacctctc cttacgccga ttcatggtcg ctctaatcct ggatatcaag agaacacccg 840

gaaacaaacc caggattgct gaaatgatat gtgacattga tacatatatc gtagaggcag 900

gattagccag ttttatcctg actattaagt ttgggataga aactatgtat cctgctcttg 960

gactgcatga atttgctggt gagttatcca cacttgagtc cttgatgaac ctttaccagc 1020

aaatgggggga aactgcaccc tacatggtaa tcctggagaa ctcaattcag aacaagttca 1080

gtgcaggatc ataccctctg ctctggagct atgccatggg agtaggagtg gaacttgaaa 1140

actccatggg aggtttgaac tttggccgat cttactttga tccagcatat tttagattag 1200

ggcaagagat ggtaaggagg tcagctggaa aggtcagttc cacattggca tctgaactcg 1260

gtatcactgc cgaggatgca aggcttgttt cagagattgc aatgcatact actgaggaca 1320

agatcagtag agcggttgga cccagacaag cccaagtatc atttctacac ggtgatcaaa 1380

gtgagaatga gctaccgaga ttgggggggca aggaagatag gagggtcaaa cagagtcgag 1440

gagaagccag ggagagctac agagaaaccg ggcccagcag agcaagtgat gcgagagctg 1500

cccatcttcc aaccggcaca cccctagaca ttgacactgc aacggagtcc agccaagatc 1560

cgcaggacag tcgaaggtca gctgacgccc tgcttaggct gcaagccatg gcaggaatct 1620

cggaagaaca aggctcagac acggacaccc ctatagtgta caatgacaga aatcttctag 1680

actaggtgcg agaggccgag ggccagaaca acatccgcct accatccatc attgttataa 1740

-continued

aaaacttagg aaccaggtcc acacagccgc cagcccatca accatccact cccacgattg 1800

gagccaatgg cagaagagca ggcacgccat gtcaaaaacg gactggaatg catccgggct 1860

ctcaaggccg agcccatcgg ctcactggcc atcgaggaag ctatggcagc atggtcagaa 1920

atatcagaca acccaggaca ggagcgagcc acctgcaggg aagagaaggc aggcagttcg 1980

ggtctcagca aaccatgcct ctcagcaatt ggatcaactg aaggcggtgc acctcgcatc 2040

cgcggtcagg gacctggaga gagcgatgac gacgctgaaa ctttgggaat ccccccaaga 2100

aatctccagg catcaagcac tgggttacag tgttattacg tttatgatca cagcggtgaa 2160

gcggttaagg gaatccaaga tgctgactct atcatggttc aatcaggcct tgatggtgat 2220

agcaccctct caggaggaga caatgaatct gaaaacagcg atgtggatat tggcgaacct 2280

gataccgagg gatatgctat cactgaccgg ggatctgctc ccatctctat ggggttcagg 2340

gcttctgatg ttgaaactgc agaaggaggg gagatccacg agctcctgag actccaatcc 2400

agaggcaaca actttccgaa gcttgggaaa actctcaatg ttcctccgcc cccggacccc 2460

ggtagggcca gcacttccgg gacacccatt aaaaagggca cagacgcgag attagcctca 2520

tttggaacgg agatcgcgtc tttattgaca ggtggtgcaa cccaatgtgc tcgaaagtca 2580

ccctcggaac catcagggcc aggtgcacct gcggggaatg tccccgagtg tgtgagcaat 2640

gccgcactga tacaggagtg gacacccgaa tctggtacca caatctcccc gagatcccag 2700

aataatgaag aaggggggaga ctattatgat gatgagctgt tctctgatgt ccaagatatt 2760

aaaacagcct tggccaaaat acacgaggat aatcagaaga taatctccaa gctagaatca 2820

ctgctgttat tgaagggaga agttgagtca attaagaagc agatcaacag gcaaaatatc 2880

agcatatcca ccctggaagg acacctctca agcatcatga tcgccattcc tggacttggg 2940

aaggatccca acgaccccac tgcagatgtc gaaatcaatc ccgacttgaa acccatcata 3000

ggcagagatt caggccgagc actggccgaa gttctcaaga aacccgttgc cagccgacaa 3060

ctccaaggaa tgacaaatgg acggaccagt tccagaggac agctgctgaa ggaatttcag 3120

ctaaagccga tcgggaaaaa gatgagctca gccgtcgggt ttgttcctga caccggccct 3180

gcatcacgca gtgtaatccg ctccattata aaatccagcc ggctagagga ggatcggaag 3240

cgttacctga tgactctcct tgatgatatc aaaggagcca atgatcttgc caagttccac 3300

cagatgctga tgaagataat aatgaagtag ctacagctca acttacctgc caaccccatg 3360

ccagtcgacc caactagcaa cctaaatcca ttataaaaaa cttaggaacc aggtccacac 3420

agctcgagtc gcgcgtggcc accatgtgtc ctcagaagct aaccatctcc tggtttgcca 3480

tcgttttgct ggtgtcccca ctcatggcca tgtgggagct ggagaaagac gtttatgttg 3540

tagaggtgga ctggactccc gatgcccctg gagaaacagt gaacctcacc tgtgacacgc 3600

ctgaagaaga tgacatcacc tggacctcag accagagaca tggagtcata ggctctggaa 3660

agaccctgac catcactgtc aaagagtttc tagatgctgg ccagtacacc tgccacaaag 3720

gaggcgagac tctgagccac tcacatctgc tgctccacaa gaaggaaaat ggaatttggt 3780

ccactgaaat tttaaaaaat ttcaaaaaca agactttcct gaagtgtgaa gcaccaaatt 3840

actccggacg gttcacgtgc tcatggctgg tgcaaagaaa catggacttg aagttcaaca 3900

tcaagagcag tagcagttcc cctgactctc gggcagtgac atgtggaatg gcgtctctgt 3960

ctgcagagaa ggtcacactg gaccaaaggg actatgagaa gtattcagtg tcctgccagg 4020

-continued

aggatgtcac ctgcccaact gccgaggaga ccctgcccat tgaactggcg ttggaagcac 4080

ggcagcagaa taaatatgag aactacagca ccagcttctt catcagggac atcatcaaac 4140

cagacccgcc caagaacttg cagatgaagc ctttgaagaa ctcacaggtg gaggtcagct 4200

gggagtaccc tgactcctgg agcactcccc attcctactt ctccctcaag ttctttgttc 4260

gaatccagcg caagaaagaa aagatgaagg agacagagga ggggtgtaac cagaaaggtg 4320

cgttcctcgt agagaagaca tctaccgaag tccaatgcaa aggcgggaat gtctgcgtgc 4380

aagctcagga tcgctattac aattcctcgt gcagcaagtg ggcatgtgtt ccctgcaggg 4440

tccgatccgg tggcggtggc tcgggcggtg gtgggtcggg tggcggcgga tctagggtca 4500

ttccagtctc tggacctgcc aggtgtctta gccagtcccg aaacctgctg aagaccacag 4560

atgacatggt gaagacggcc agagaaaaac tgaaacatta ttcctgcact gctgaagaca 4620

tcgatcatga agacatcaca cgggaccaaa ccagcacatt gaagacctgt ttaccactgg 4680

aactacacaa gaacgagagt tgcctggcta ctagagagac ttcttccaca acaagaggga 4740

gctgcctgcc cccacagaag acgtctttga tgatgaccct gtgccttggt agcatctatg 4800

aggacttgaa gatgtaccag acagagttcc aggccatcaa cgcagcactt cagaatcaca 4860

accatcagca gatcattcta gacaagggca tgctggtggc catcgatgag ctgatgcagt 4920

ctctgaatca taatggcgag actctgcgcc agaaacctcc tgtgggagaa gcagaccctt 4980

acagagtgaa aatgaagctc tgcatcctgc ttcacgcctt cagcacccgc gtcgtgacca 5040

tcaacagggt gatgggctat ctgagctccg cctgataatc gcgcgcgtgc tagtacaacc 5100

taaatccatt ataaaaaact taggagcaaa gtgattgcct cccaaggtcc acaatgacag 5160

agacctacga cttcgacaag tcggcatggg acatcaaagg gtcgatcgct ccgatacaac 5220

ccaccaccta cagtgatggc aggctggtgc cccaggtcag agtcatagat cctggtctag 5280

gcgacaggaa ggatgaatgc tttatgtaca tgtttctgct gggggttgtt gaggacagcg 5340

attccctagg gcctccaatc gggcgagcat ttgggttcct gcccttaggt gttggcagat 5400

ccacagcaaa gcccgaaaaa ctcctcaaag aggccactga gcttgacata gttgttagac 5460

gtacagcagg gctcaatgaa aaactggtgt tctacaacaa caccccacta actctcctca 5520

caccttggag aaaggtccta acaacaggga gtgtcttcaa cgcaaaccaa gtgtgcaatg 5580

cggttaatct gataccgctc gataccccgc agaggttccg tgttgtttat atgagcatca 5640

cccgtctttc ggataacggg tattacaccg ttcctagaag aatgctggaa ttcagatcgg 5700

tcaatgcagt ggccttcaac ctgctggtga cccttaggat tgacaaggcg ataggccctg 5760

ggaagatcat cgacaataca gagcaacttc ctgaggcaac atttatggtc cacatcggga 5820

acttcaggag aaagaagagt gaagtctact ctgccgatta ttgcaaaatg aaaatcgaaa 5880

agatgggcct ggtttttgca cttggtggga taggggggcac cagtcttcac attagaagca 5940

caggcaaaat gagcaagact ctccatgcac aactcgggtt caagaagacc ttatgttacc 6000

cgctgatgga tatcaatgaa gaccttaatc gattactctg gaggagcaga tgcaagatag 6060

taagaatcca ggcagttttg cagccatcag ttcctcaaga attccgcatt tacgacgacg 6120

tgatcataaa tgatgaccaa ggactattca aagttctgta gaccgtagtg cccagcaatg 6180

cccgaaaacg acccccctca caatgacagc cagaaggccc ggacaaaaaa gccccctccg 6240

aaagactcca cggaccaagc gagaggccag ccagcagccg acggcaagcg cgaacaccag 6300

-continued

gcggccccag cacagaacag ccctgacaca aggccaccac cagccacccc aatctgcatc 6360

ctcctcgtgg gacccccgag gaccaacccc caaggctgcc cccgatccaa accaccaacc 6420

gcatccccac caccccgggg aaagaaaccc ccagcaattg gaaggccccc ccccctcttc 6480

ctcaacacaa gaactccaca accgaaccgc acaagcgacc gaggtgaccc aaccgcaggc 6540

atccgactcc ctagacagat cctctctccc cggcaaacta aacaaaactt agggccaagg 6600

aacatacaca cccaacagaa cccagacccc ggcccacggc gccgcgcccc caacccccga 6660

caaccagagg gagcccccaa ccaatcccgc cggctccccc ggtgcccaca ggcagggaca 6720

ccaacccccg aacagaccca gcacccaacc atcgacaatc caagacgggg gggccccccc 6780

aaaaaaaggc ccccaggggc cgacagccag caccgcgagg aagcccaccc accccacaca 6840

cgaccacggc aaccaaacca gaacccagac caccctgggc caccagctcc cagactcggc 6900

catcaccccg cagaaaggaa aggccacaac ccgcgcaccc cagccccgat ccggcgggga 6960

gccacccaac ccgaaccagc acccaagagc gatccccgaa ggacccccga accgcaaagg 7020

acatcagtat cccacagcct ctccaagtcc cccggtctcc tcctcttctc gaagggacca 7080

aaagatcaat ccaccacacc cgacgacact caactcccca cccctaaagg agacaccggg 7140

aatcccagaa tcaagactca tccaatgtcc atcatgggtc tcaaggtgaa cgtctctgcc 7200

atattcatgg cagtactgtt aactctccaa acacccaccg gtcaaatcca ttggggcaat 7260

ctctctaaga taggggtggt aggaatagga agtgcaagct acaaagttat gactcgttcc 7320

agccatcaat cattagtcat aaaattaatg cccaatataa ctctcctcaa taactgcacg 7380

agggtagaga ttgcagaata caggagacta ctgagaacag ttttggaacc aattagagat 7440

gcacttaatg caatgaccca gaatataaga ccggttcaga gtgtagcttc aagtaggaga 7500

cacaagagat ttgcgggagt agtcctggca ggtgcggccc taggcgttgc cacagctgct 7560

cagataacag ccggcattgc acttcaccag tccatgctga actctcaagc catcgacaat 7620

ctgagagcga gcctggaaac tactaatcag gcaattgaga caatcagaca agcagggcag 7680

gagatgatat tggctgttca gggtgtccaa gactacatca ataatgagct gataccgtct 7740

atgaaccaac tatcttgtga tttaatcggc cagaagctcg ggctcaaatt gctcagatac 7800

tatacagaaa tcctgtcatt atttggcccc agtttacggg accccatatc tgcggagata 7860

tctatccagg ctttgagcta tgcgcttgga ggagacatca ataaggtgtt agaaaagctc 7920

ggatacagtg gaggtgattt actgggcatc ttagagagcg gaggaataaa ggcccggata 7980

actcacgtcg acacagagtc ctacttcatt gtcctcagta tagcctatcc gacgctgtcc 8040

gagattaagg gggtgattgt ccaccggcta gagggggtct cgtacaacat aggctctcaa 8100

gagtggtata ccactgtgcc caagtatgtt gcaacccaag ggtaccttat ctcgaatttt 8160

gatgagtcat cgtgtacttt catgccagag gggactgtgt gcagccaaaa tgccttgtac 8220

ccgatgagtc ctctgctcca agaatgcctc cgggggtaca ccaagtcctg tgctcgtaca 8280

ctcgtatccg ggtcttttgg gaaccggttc attttatcac aagggaacct aatagccaat 8340

tgtgcatcaa tcctttgcaa gtgttacaca acaggaacga tcattaatca agaccctgac 8400

aagatcctaa catacattgc tgccgatcac tgcccggtag tcgaggtgaa cggcgtgacc 8460

atccaagtcg ggagcaggag gtatccagac gctgtgtact tgcacagaat tgacctcggt 8520

cctcccatat cattggagag gttggacgta gggacaaatc tggggaatgc aattgctaag 8580

-continued

ttggaggatg ccaaggaatt gttggagtca tcggaccaga tattgaggag tatgaaaggt 8640

ttatcgagca ctagcatagt ctacatcctg attgcagtgt gtcttggagg gttgataggg 8700

atccccgctt taatatgttg ctgcaggggg cgttgtaaca aaaagggaga acaagttggt 8760

atgtcaagac caggcctaaa gcctgatctt acgggaacat caaaatccta tgtaaggtcg 8820

ctctgatcct ctacaactct tgaaacacaa atgtcccaca agtctcctct tcgtcatcaa 8880

gcaaccaccg cacccagcat caagcccacc tgaaattatc tccggcttcc ctctggccga 8940

acaatatcgg tagttaatca aaacttaggg tgcaagatca tccacaatgt caccacaacg 9000

agaccggata aatgccttct acaaagataa cccccatccc aagggaagta ggatagtcat 9060

taacagagaa catcttatga ttgatagacc ttatgttttg ctggctgttc tgtttgtcat 9120

gtttctgagc ttgatcgggt tgctagccat tgcaggcatt agacttcatc gggcagccat 9180

ctacaccgca gagatccata aaagcctcag caccaatcta gatgtaacta actcaatcga 9240

gcatcaggtc aaggacgtgc tgacaccact cttcaaaatc atcggtgatg aagtgggcct 9300

gaggacacct cagagattca ctgacctagt gaaattaatc tctgacaaga ttaaattcct 9360

taatccggat agggagtacg acttcagaga tctcacttgg tgtatcaacc cgccagagag 9420

aatcaaattg gattatgatc aatactgtgc agatgtggct gctgaagagc tcatgaatgc 9480

attggtgaac tcaactctac tggagaccag aacaaccaat cagttcctag ctgtctcaaa 9540

gggaaactgc tcagggccca ctacaatcag aggtcaattc tcaaacatgt cgctgtccct 9600

gttagacttg tatttaggtc gaggttacaa tgtgtcatct atagtcacta tgacatccca 9660

gggaatgtat gggggaactt acctagtgga aaagcctaat ctgagcagca aaaggtcaga 9720

gttgtcacaa ctgagcatgt accgagtgtt tgaagtaggt gttatcagaa atccgggttt 9780

gggggctccg gtgttccata tgacaaacta tcttgagcaa ccagtcagta atgatctcag 9840

caactgtatg gtggctttgg gggagctcaa actcgcagcc ctttgtcacg gggaagattc 9900

tatcacaatt ccctatcagg gatcagggaa aggtgtcagc ttccagctcg tcaagctagg 9960

tgtctggaaa tccccaaccg acatgcaatc ctgggtcccc ttatcaacgg atgatccagt 10020

gatagacagg ctttacctct catctcacag aggtgttatc gctgacaatc aagcaaaatg 10080

ggctgtcccg acaacacgaa cagatgacaa gttgcgaatg gagacatgct tccaacaggc 10140

gtgtaagggt aaaatccaag cactctgcga gaatcccgag tgggcaccat tgaaggataa 10200

caggattcct tcatacgggg tcttgtctgt tgatctgagt ctgacagttg agcttaaaat 10260

caaaattgct tcgggattcg ggccattgat cacacacggt tcagggatgg acctatacaa 10320

atccaaccac aacaatgtgt attggctgac tatcccgcca atgaagaacc tagccttagg 10380

tgtaatcaac acattggagt ggataccgag attcaaggtt agtccctacc tcttcactgt 10440

cccaattaag gaagcaggcg aagactgcca tgccccaaca tacctacctg cggaggtgga 10500

tggtgatgtc aaactcagtt ccaatctggt gattctacct ggtcaagatc tccaatatgt 10560

tttggcaacc tacgatactt ccagggttga acatgctgtg gtttattacg tttacagccc 10620

aagccgctca ttttcttact tttatccttt taggttgcct ataaaggggg tccccatcga 10680

attacaagtg gaatgcttca catgggacca aaaactctgg tgccgtcact tctgtgtgct 10740

tgcggactca gaatctggtg gacatatcac tcactctggg atggtgggca tgggagtcag 10800

ctgcacagtc acccgggaag atggaaccaa tcgcagatag ggctgctagt gaaccaatca 10860

-continued

catgatgtca cccagacatc aggcataccc actagtgtga aatagacatc agaattaaga 10920

aaaacgtagg gtccaagtgg ttccccgtta tggactcgct atctgtcaac cagatcttat 10980

accctgaagt tcacctagat agcccgatag ttaccaataa gatagtagcc atcctggagt 11040

atgctcgagt ccctcacgct tacagcctgg aggaccctac actgtgtcag aacatcaagc 11100

accgcctaaa aaacggattt tccaaccaaa tgattataaa caatgtggaa gttgggaatg 11160

tcatcaagtc caagcttagg agttatccgg cccactctca tattccatat ccaaattgta 11220

atcaggattt atttaacata gaagacaaag agtcaacgag gaagatccgt gaactcctca 11280

aaaaggggaa ttcgctgtac tccaaagtca gtgataaggt tttccaatgc ttaagggaca 11340

ctaactcacg gcttggccta ggctccgaat tgagggagga catcaaggag aaagttatta 11400

acttgggagt ttacatgcac agctcccagt ggtttgagcc ctttctgttt tggtttacag 11460

tcaagactga gatgaggtca gtgattaaat cacaaaccca tacttgccat aggaggagac 11520

acacacctgt attcttcact ggtagttcag ttgagttgct aatctctcgt gaccttgttg 11580

ctataatcag taaagagtct caacatgtat attacctgac atttgaactg gttttgatgt 11640

attgtgatgt catagagggg aggttaatga cagagaccgc tatgactatt gatgctaggt 11700

atacagagct tctaggaaga gtcagataca tgtggaaact gatagatggt ttcttccctg 11760

cactcgggaa tccaacttat caaattgtag ccatgctgga gcctctttca cttgcttacc 11820

tgcagctgag ggatataaca gtagaactca gaggtgcttt ccttaaccac tgctttactg 11880

aaatacatga tgttcttgac caaaacgggt tttctgatga aggtacttat catgagttaa 11940

ctgaagctct agattacatt ttcataactg atgacataca tctgacaggg gagattttct 12000

catttttcag aagtttcggc caccccagac ttgaagcagt aacggctgct gaaaatgtta 12060

ggaaatacat gaatcagcct aaagtcattg tgtatgagac tctgatgaaa ggtcatgcca 12120

tattttgtgg aatcataatc aacggctatc gtgacaggca cggaggcagt tggccaccgc 12180

tgaccctccc cctgcatgct gcagacacaa tccggaatgc tcaagcttca ggtgaagggt 12240

taacacatga gcagtgcgtt gataactgga aatcttttgc tggagtgaaa tttggctgct 12300

ttatgcctct tagcctggat agtgatctga caatgtacct aaaggacaag gcacttgctg 12360

ctctccaaag ggaatgggat tcagtttacc cgaaagagtt cctgcgttac gaccctccca 12420

agggaaccgg gtcacggagg cttgtagatg ttttccttaa tgattcgagc tttgacccat 12480

atgatgtgat aatgtatgtt gtaagtggag cttacctcca tgaccctgag ttcaacctgt 12540

cttacagcct gaaagaaaag gagatcaagg aaacaggtag acttttgct aaaatgactt 12600

acaaaatgag ggcatgccaa gtgattgctg aaaatctaat ctcaaacggg attggcaaat 12660

attttaagga caatgggatg gccaaggatg agcacgattt gactaaggca ctccacactc 12720

tagctgtctc aggagtcccc aaagatctca aagaaagtca caggggggg ccagtcttaa 12780

aaacctactc ccgaagccca gtccacacaa gtaccaggaa cgtgagagca gcaaaagggt 12840

ttatagggtt ccctcaagta attcggcagg accaagacac tgatcatccg gagaatatgg 12900

aagcttacga gacagtcagt gcatttatca cgactgatct caagaagtac tgccttaatt 12960

ggagatatga gaccatcagc ttgtttgcac agaggctaaa tgagatttac ggattgccct 13020

catttttcca gtggctgcat aagaggcttg agacctctgt cctgtatgta agtgaccctc 13080

attgcccccc cgaccttgac gcccatatcc cgttatataa agtccccaat gatcaaatct 13140

-continued

tcattaagta ccctatggga ggtatagaag ggtattgtca gaagctgtgg accatcagca 13200

ccattcccta tctatacctg gctgcttatg agagcggagt aaggattgct tcgttagtgc 13260

aaggggacaa tcagaccata gccgtaacaa aaagggtacc cagcacatgg ccctacaacc 13320

ttaagaaacg ggaagctgct agagtaacta gagattactt tgtaattctt aggcaaaggc 13380

tacatgatat tggccatcac ctcaaggcaa atgagacaat tgtttcatca catttttttg 13440

tctattcaaa aggaatatat tatgatgggc tacttgtgtc ccaatcactc aagagcatcg 13500

caagatgtgt attctggtca gagactatag ttgatgaaac aagggcagca tgcagtaata 13560

ttgctacaac aatggctaaa agcatcgaga gaggttatga ccgttacctt gcatattccc 13620

tgaacgtcct aaaagtgata cagcaaattc tgatctctct tggcttcaca atcaattcaa 13680

ccatgacccg ggatgtagtc ataccctcc tcacaaacaa cgacctctta ataaggatgg 13740

cactgttgcc cgctcctatt ggggggatga attatctgaa tatgagcagg ctgtttgtca 13800

gaaacatcgg tgatccagta acatcatcaa ttgctgatct caagagaatg attctcgcct 13860

cactaatgcc tgaagagacc ctccatcaag taatgacaca acaaccgggg gactcttcat 13920

tcctagactg ggctagcgac ccttactcag caaatcttgt atgtgtccag agcatcacta 13980

gactcctcaa gaacataact gcaaggtttg tcctgatcca tagtccaaac ccaatgttaa 14040

aaggattatt ccatgatgac agtaaagaag aggacgaggg actggcggca ttcctcatgg 14100

acaggcatat tatagtacct agggcagctc atgaaatcct ggatcatagt gtcacagggg 14160

caagagagtc tattgcaggc atgctggata ccacaaaagg cttgattcga gccagcatga 14220

ggaaggggg gttaacctct cgagtgataa ccagattgtc caattatgac tatgaacaat 14280

tcagagcagg gatggtgcta ttgacaggaa gaaagagaaa tgtcctcatt gacaaagagt 14340

catgttcagt gcagctggcg agagctctaa gaagccatat gtgggcgagg ctagctcgag 14400

gacggcctat ttacggcctt gaggtccctg atgtactaga atctatgcga ggccacctta 14460

ttcggcgtca tgagacatgt gtcatctgcg agtgtggatc agtcaactac ggatggtttt 14520

ttgtcccctc gggttgccaa ctggatgata ttgacaagga aacatcatcc ttgagagtcc 14580

catatattgg ttctaccact gatgagagaa cagacatgaa gcttgccttc gtaagagccc 14640

caagtcgatc cttgcgatct gctgttagaa tagcaacagt gtactcatgg gcttacggtg 14700

atgatgatag ctcttggaac gaagcctggt tgttggctag gcaaagggcc aatgtgagcc 14760

tggaggagct aagggtgatc actcccatct caacttcgac taatttagcg cataggttga 14820

gggatcgtag cactcaagtg aaatactcag gtacatccct tgtccgagtg gcgaggtata 14880

ccacaatctc caacgacaat ctctcatttg tcatatcaga taagaaggtt gatactaact 14940

ttatatacca acaaggaatg cttctagggt tgggtgtttt agaaacattg tttcgactcg 15000

agaaagatac cggatcatct aacacggtat tacatcttca cgtcgaaaca gattgttgcg 15060

tgatcccgat gatagatcat cccaggatac ccagctcccg caagctagag ctgagggcag 15120

agctatgtac caacccattg atatatgata atgcaccttt aattgacaga gatgcaacaa 15180

ggctatacac ccagagccat aggaggcacc ttgtggaatt tgttacatgg tccacacccc 15240

aactatatca cattttagct aagtccacag cactatctat gattgacctg gtaacaaaat 15300

ttgagaagga ccatatgaat gaaatttcag ctctcatagg ggatgacgat atcaatagtt 15360

tcataactga gtttctgctc atagagccaa gattattcac tatctacttg ggccagtgtg 15420

-continued

cggccatcaa ttgggcattt gatgtacatt atcatagacc atcagggaaa tatcagatgg 15480

gtgagctgtt gtcatcgttc ctttctagaa tgagcaaagg agtgtttaag gtgcttgtca 15540

atgctctaag ccacccaaag atctacaaga aattctggca ttgtggtatt atagagccta 15600

tccatggtcc ttcacttgat gctcaaaact tgcacacaac tgtgtgcaac atggtttaca 15660

catgctatat gacctacctc gacctgttgt tgaatgaaga gttagaagag ttcacatttc 15720

tcttgtgtga aagcgacgag gatgtagtac cggacagatt cgacaacatc caggcaaaac 15780

acttatgtgt tctggcagat ttgtactgtc aaccagggac ctgcccacca attcgaggtc 15840

taagaccggt agagaaatgt gcagttctaa ccgaccatat caaggcagag gctatgttat 15900

ctccagcagg atcttcgtgg aacataaatc caattattgt agaccattac tcatgctctc 15960

tgacttatct ccggcgagga tcgatcaaac agataagatt gagagttgat ccaggattca 16020

ttttcgacgc cctcgctgag gtaaatgtca gtcagccaaa gatcggcagc aacaacatct 16080

caaatatgag catcaaggct ttcagacccc cacacgatga tgttgcaaaa ttgctcaaag 16140

atatcaacac aagcaagcac aatcttccca tttcaggggg caatctcgcc aattatgaaa 16200

tccatgcttt ccgcagaatc gggttgaact catctgcttg ctacaaagct gttgagatat 16260

caacattaat taggagatgc cttgagccag gggaggacgg cttgttcttg ggtgagggat 16320

cgggttctat gttgatcact tataaagaga tacttaaact aaacaagtgc ttctataata 16380

gtggggtttc cgccaattct agatctggtc aaagggaatt agcaccctat ccctccgaag 16440

ttggccttgt cgaacacaga atgggagtag gtaatattgt caaagtgctc tttaacggga 16500

ggcccgaagt cacgtgggta ggcagtgtag attgcttcaa tttcatagtt agtaatatcc 16560

ctacctctag tgtggggttt atccattcag atatagagac cttgcctgac aaagatacta 16620

tagagaagct agaggaattg gcagccatct tatcgatggc tctgctcctg ggcaaaatag 16680

gatcaatact ggtgattaag cttatgcctt tcagcgggga ttttgttcag ggatttataa 16740

gttatgtagg gtctcattat agagaagtga accttgtata ccctagatac agcaacttca 16800

tctctactga atcttatttg gttatgacag atctcaaggc taaccggcta atgaatcctg 16860

aaaagattaa gcagcagata attgaatcat ctgtgaggac ttcacctgga cttataggtc 16920

acatcctatc cattaagcaa ctaagctgca tacaagcaat tgtgggagac gcagttagta 16980

gaggtgatat caatcctact ctgaaaaaac ttacacctat agagcaggtg ctgatcaatt 17040

gcgggttggc aattaacgga cctaagctgt gcaaagaatt gatccaccat gatgttgcct 17100

cagggcaaga tggattgctt aattctatac tcatcctcta cagggagttg gcaagattca 17160

aagacaacca aagaagtcaa caagggatgt tccacgctta ccccgtattg gtaagtagca 17220

ggcaacgaga acttatatct aggatcaccc gcaaatttctg ggggcacatt cttctttact 17280

ccgggaacaa aaagttgata aataagttta tccagaatct caagtccggc tatctgatac 17340

tagacttaca ccagaatatc ttcgttaaga atctatccaa gtcagagaaa cagattatta 17400

tgacgggggg tttgaaacgt gagtgggttt ttaaggtaac agtcaaggag accaaagaat 17460

ggtataagtt agtcggatac agtgccctga ttaaggacta attggttgaa ctccggaacc 17520

ctaatcctgc cctaggtggt taggcattat ttgcaatata ttaaagaaaa ctttgaaaat 17580

acgaagtttc tattcccagc tttgtctggt 17610

<210> SEQ ID NO 5

-continued

<211> LENGTH: 17570
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial MV genome MeVac_P-FhIL-12

<400> SEQUENCE: 5

accaaacaaa gttgggtaag gatagttcaa tcaatgatca tcttctagtg cacttaggat 60

tcaagatcct attatcaggg acaagagcag gattagggat atccgagatg gccacacttt 120

taaggagctt agcattgttc aaaagaaaca aggacaaacc acccattaca tcaggatccg 180

gtggagccat cagaggaatc aaacacatta ttatagtacc aatccctgga gattcctcaa 240

ttaccactcg atccagactt ctggaccggt tggtgaggtt aattggaaac ccggatgtga 300

gcgggcccaa actaacaggg gcactaatag gtatattatc cttatttgtg gagtctccag 360

gtcaattgat tcagaggatc accgatgacc ctgacgttag cataaggctg ttagaggttg 420

tccagagtga ccagtcacaa tctggcctta ccttcgcatc aagaggtacc aacatggagg 480

atgaggcgga ccaatacttt tcacatgatg atccaattag tagtgatcaa tccaggttcg 540

gatggttcgg gaacaaggaa atctcagata ttgaagtgca agaccctgag ggattcaaca 600

tgattctggg taccatccta gcccaaattt gggtcttgct cgcaaaggcg gttacggccc 660

cagacacggc agctgattcg gagctaagaa ggtggataaa gtacacccaa caaagaaggg 720

tagttggtga atttagattg gagagaaaat ggttggatgt ggtgaggaac aggattgccg 780

aggacctctc cttacgccga ttcatggtcg ctctaatcct ggatatcaag agaacacccg 840

gaaacaaacc caggattgct gaaatgatat gtgacattga tacatatatc gtagaggcag 900

gattagccag ttttatcctg actattaagt ttgggataga aactatgtat cctgctcttg 960

gactgcatga atttgctggt gagttatcca cacttgagtc cttgatgaac ctttaccagc 1020

aaatgggggа aactgcaccc tacatggtaa tcctggagaa ctcaattcag aacaagttca 1080

gtgcaggatc ataccctctg ctctggagct atgccatggg agtaggagtg gaacttgaaa 1140

actccatggg aggtttgaac tttggccgat cttactttga tccagcatat tttagattag 1200

ggcaagagat ggtaaggagg tcagctggaa aggtcagttc cacattggca tctgaactcg 1260

gtatcactgc cgaggatgca aggcttgttt cagagattgc aatgcatact actgaggaca 1320

agatcagtag agcggttgga cccagacaag cccaagtatc atttctacac ggtgatcaaa 1380

gtgagaatga gctaccgaga ttgggggggca aggaagatag gagggtcaaa cagagtcgag 1440

gagaagccag ggagagctac agagaaaccg ggcccagcag agcaagtgat gcgagagctg 1500

cccatcttcc aaccggcaca cccctagaca ttgacactgc aacggagtcc agccaagatc 1560

cgcaggacag tcgaaggtca gctgacgccc tgcttaggct gcaagccatg gcaggaatct 1620

cggaagaaca aggctcagac acggacaccc ctatagtgta caatgacaga aatcttctag 1680

actaggtgcg agaggccgag ggccagaaca acatccgcct accatccatc attgttataa 1740

aaaacttagg aaccaggtcc acacagccgc cagcccatca accatccact cccacgattg 1800

gagccaatgg cagaagagca ggcacgccat gtcaaaaacg gactggaatg catccgggct 1860

ctcaaggccg agcccatcgg ctcactggcc atcgaggaag ctatggcagc atggtcagaa 1920

atatcagaca acccaggaca ggagcgagcc acctgcaggg aagagaaggc aggcagttcg 1980

ggtctcagca aaccatgcct ctcagcaatt ggatcaactg aaggcggtgc acctcgcatc 2040

-continued

cgcggtcagg gacctggaga gagcgatgac gacgctgaaa ctttgggaat ccccccaaga 2100

aatctccagg catcaagcac tgggttacag tgttattacg tttatgatca cagcggtgaa 2160

gcggttaagg gaatccaaga tgctgactct atcatggttc aatcaggcct tgatggtgat 2220

agcaccctct caggaggaga caatgaatct gaaaacagcg atgtggatat tggcgaacct 2280

gataccgagg gatatgctat cactgaccgg ggatctgctc ccatctctat ggggttcagg 2340

gcttctgatg ttgaaactgc agaaggaggg gagatccacg agctcctgag actccaatcc 2400

agaggcaaca actttccgaa gcttgggaaa actctcaatg ttcctccgcc cccggacccc 2460

ggtagggcca gcacttccgg gacacccatt aaaaagggca cagacgcgag attagcctca 2520

tttggaacgg agatcgcgtc tttattgaca ggtggtgcaa cccaatgtgc tcgaaagtca 2580

ccctcggaac catcagggcc aggtgcacct gcggggaatg tccccgagtg tgtgagcaat 2640

gccgcactga tacaggagtg gacacccgaa tctggtacca caatctcccc gagatcccag 2700

aataatgaag aaggggggaga ctattatgat gatgagctgt tctctgatgt ccaagatatt 2760

aaaacagcct tggccaaaat acacgaggat aatcagaaga taatctccaa gctagaatca 2820

ctgctgttat tgaagggaga agttgagtca attaagaagc agatcaacag gcaaaatatc 2880

agcatatcca ccctggaagg acacctctca agcatcatga tcgccattcc tggacttggg 2940

aaggatccca acgaccccac tgcagatgtc gaaatcaatc ccgacttgaa acccatcata 3000

ggcagagatt caggccgagc actggccgaa gttctcaaga aacccgttgc cagccgacaa 3060

ctccaaggaa tgacaaatgg acggaccagt tccagaggac agctgctgaa ggaatttcag 3120

ctaaagccga tcgggaaaaa gatgagctca gccgtcgggt ttgttcctga caccggccct 3180

gcatcacgca gtgtaatccg ctccattata aaatccagcc ggctagagga ggatcggaag 3240

cgttacctga tgactctcct tgatgatatc aaaggagcca atgatcttgc caagttccac 3300

cagatgctga tgaagataat aatgaagtag ctacagctca acttacctgc caaccccatg 3360

ccagtcgacc caactagcaa cctaaatcca ttataaaaaa cttaggaacc aggtccacac 3420

agctcgagtc gcgcgtgcca ccatgtgtca ccagcagttg gtcatctctt ggttttccct 3480

ggtttttctg gcatctcccc tcgtggccat atgggaactg aagaaagatg tttatgtcgt 3540

agaattggat tggtatccgg atgcccctgg agaaatggtg gtcctcacct gtgacacccc 3600

tgaagaagat ggtatcacct ggaccttgga ccagagcagt gaggtcttag gctctggcaa 3660

aaccctgacc atccaagtca aagagtttgg agatgctggc cagtacacct gtcacaaagg 3720

aggcgaggtt ctaagccatt cgctcctgct gcttcacaaa aaggaagatg gaatttggtc 3780

cactgatatt ttaaaggacc agaaagaacc caaaaataag acctttctaa gatgcgaggc 3840

caagaattat tctggacgtt tcacctgctg gtggctgacg acaatcagta ctgatttgac 3900

attcagtgtc aaaagcagca gaggctcttc tgacccccaa ggggtgacgt gcggagctgc 3960

tacactctct gcagagagag tcagagggga caacaaggag tatgagtact cagtggagtg 4020

ccaggaggac agtgcctgcc cagctgctga ggagagtctg cccattgagg tcatggtgga 4080

tgccgttcac aagctcaagt atgaaaacta caccagcagc ttcttcatca gggacatcat 4140

caaacctgac ccacccaaga acttgcagct gaagccatta aagaattctc ggcaggtgga 4200

ggtcagctgg gagtaccctg acacctggag tactccacat tcctacttct ccctgacatt 4260

ctgcgttcag gtccagggca agagcaagag agaaaagaaa gatagagtct tcaccgacaa 4320

-continued

gacctcagcc acggtcatct gccgcaaaaa tgccagcatt agcgtgcggg cccaggaccg 4380

ctactatagc tcatcttgga gcgaatgggc atctgtgccc tgcagtggtg gcggtggcgg 4440

cggatctaga aacctccccg tggccactcc agacccagga atgttcccat gccttcacca 4500

ctcccaaaac ctgctgaggg ccgtcagcaa catgctccag aaggccagac aaactctaga 4560

attttaccct tgcacttctg aagagattga tcatgaagat atcacaaaag ataaaaccag 4620

cacagtggag gcctgtttac cattggaatt aaccaagaat gagagttgcc taaattccag 4680

agagacctct ttcataacta atgggagttg cctggcctcc agaaagacct cttttatgat 4740

ggccctgtgc cttagtagta tttatgaaga cttgaagatg taccaggtgg agttcaagac 4800

catgaatgca aagcttctga tggatcctaa gaggcagatc tttctagatc aaaacatgct 4860

ggcagttatt gatgagctga tgcaggccct gaatttcaac agtgagactg tgccacaaaa 4920

atcctccctt gaagaaccgg atttttataa aactaaaatc aagctctgca tacttcttca 4980

tgctttcaga attcgggcag tgactattga tagagtgatg agctatctga atgcttccta 5040

ggcgcgcgtg ctagtacaac ctaaatccat tataaaaaac ttaggagcaa agtgattgcc 5100

tcccaaggtc cacaatgaca gagacctacg acttcgacaa gtcggcatgg gacatcaaag 5160

ggtcgatcgc tccgatacaa cccaccacct acagtgatgg caggctggtg ccccaggtca 5220

gagtcataga tcctggtcta ggcgacagga aggatgaatg ctttatgtac atgtttctgc 5280

tgggggttgt tgaggacagc gattccctag ggcctccaat cgggcgagca tttgggttcc 5340

tgcccttagg tgttggcaga tccacagcaa agcccgaaaa actcctcaaa gaggccactg 5400

agcttgacat agttgttaga cgtacagcag ggctcaatga aaaactggtg ttctacaaca 5460

acaccccact aactctcctc acaccttgga gaaaggtcct aacaacaggg agtgtcttca 5520

acgcaaacca agtgtgcaat gcggttaatc tgataccgct cgataccccg cagaggttcc 5580

gtgttgttta tatgagcatc acccgtcttt cggataacgg gtattacacc gttcctagaa 5640

gaatgctgga attcagatcg gtcaatgcag tggccttcaa cctgctggtg acccttagga 5700

ttgacaaggc gataggccct gggaagatca tcgacaatac agagcaactt cctgaggcaa 5760

catttatggt ccacatcggg aacttcagga gaaagaagag tgaagtctac tctgccgatt 5820

attgcaaaat gaaaatcgaa aagatgggcc tggtttttgc acttggtggg atagggggca 5880

ccagtcttca cattagaagc acaggcaaaa tgagcaagac tctccatgca caactcgggt 5940

tcaagaagac cttatgttac ccgctgatgg atatcaatga agaccttaat cgattactct 6000

ggaggagcag atgcaagata gtaagaatcc aggcagtttt gcagccatca gttcctcaag 6060

aattccgcat ttacgacgac gtgatcataa atgatgacca aggactattc aaagttctgt 6120

agaccgtagt gcccagcaat gcccgaaaac gacccccctc acaatgacag ccagaaggcc 6180

cggacaaaaa agccccctcc gaaagactcc acggaccaag cgagaggcca gccagcagcc 6240

gacggcaagc gcgaacacca ggcggcccca gcacagaaca gccctgacac aaggccacca 6300

ccagccaccc caatctgcat cctcctcgtg ggacccccga ggaccaaccc ccaaggctgc 6360

ccccgatcca aaccaccaac cgcatcccca ccacccccgg gaaagaaacc cccagcaatt 6420

ggaaggcccc tccccctctt cctcaacaca agaactccac aaccgaaccg cacaagcgac 6480

cgaggtgacc caaccgcagg catccgactc cctagacaga tcctctctcc ccggcaaact 6540

aaacaaaact tagggccaag gaacatacac acccaacaga acccagaccc cggcccacgg 6600

-continued

cgccgcgccc ccaacccccg acaaccagag ggagccccca accaatcccg ccggctcccc 6660

cggtgcccac aggcagggac accaaccccc gaacagaccc agcacccaac catcgacaat 6720

ccaagacggg ggggcccccc caaaaaaagg cccccagggg ccgacagcca gcaccgcgag 6780

gaagcccacc caccccacac acgaccacgg caaccaaacc agaacccaga ccaccctggg 6840

ccaccagctc ccagactcgg ccatcacccc gcagaaagga aaggccacaa cccgcgcacc 6900

ccagccccga tccggcgggg agccacccaa cccgaaccag cacccaagag cgatccccga 6960

aggacccccg aaccgcaaag gacatcagta tcccacagcc tctccaagtc ccccggtctc 7020

ctcctcttct cgaagggacc aaaagatcaa tccaccacac ccgacgacac tcaactcccc 7080

acccctaaag gagacaccgg gaatcccaga atcaagactc atccaatgtc catcatgggt 7140

ctcaaggtga acgtctctgc catattcatg gcagtactgt taactctcca aacacccacc 7200

ggtcaaatcc attggggcaa tctctctaag ataggggtgg taggaatagg aagtgcaagc 7260

tacaaagtta tgactcgttc cagccatcaa tcattagtca taaaattaat gcccaatata 7320

actctcctca ataactgcac gagggtagag attgcagaat acaggagact actgagaaca 7380

gttttggaac caattagaga tgcacttaat gcaatgaccc agaatataag accggttcag 7440

agtgtagctt caagtaggag acacaagaga tttgcgggag tagtcctggc aggtgcggcc 7500

ctaggcgttg ccacagctgc tcagataaca gccggcattg cacttcacca gtccatgctg 7560

aactctcaag ccatcgacaa tctgagagcg agcctggaaa ctactaatca ggcaattgag 7620

acaatcagac aagcagggca ggagatgata ttggctgttc agggtgtcca agactacatc 7680

aataatgagc tgataccgtc tatgaaccaa ctatcttgtg atttaatcgg ccagaagctc 7740

gggctcaaat tgctcagata ctatacagaa atcctgtcat tatttggccc cagtttacgg 7800

gaccccatat ctgcggagat atctatccag gctttgagct atgcgcttgg aggagacatc 7860

aataaggtgt tagaaaagct cggatacagt ggaggtgatt tactgggcat cttagagagc 7920

ggaggaataa aggcccggat aactcacgtc gacacagagt cctacttcat tgtcctcagt 7980

atagcctatc cgacgctgtc cgagattaag ggggtgattg tccaccggct agaggggggtc 8040

tcgtacaaca taggctctca agagtggtat accactgtgc ccaagtatgt tgcaacccaa 8100

gggtacctta tctcgaattt tgatgagtca tcgtgtactt tcatgccaga ggggactgtg 8160

tgcagccaaa atgccttgta cccgatgagt cctctgctcc aagaatgcct ccgggggtac 8220

accaagtcct gtgctcgtac actcgtatcc gggtcttttg ggaaccggtt cattttatca 8280

caagggaacc taatagccaa ttgtgcatca atcctttgca agtgttacac aacaggaacg 8340

atcattaatc aagaccctga caagatccta acatacattg ctgccgatca ctgcccggta 8400

gtcgaggtga acggcgtgac catccaagtc gggagcagga ggtatccaga cgctgtgtac 8460

ttgcacagaa ttgacctcgg tcctcccata tcattggaga ggttggacgt agggacaaat 8520

ctggggaatg caattgctaa gttggaggat gccaaggaat tgttggagtc atcggaccag 8580

atattgagga gtatgaaagg tttatcgagc actagcatag tctacatcct gattgcagtg 8640

tgtcttggag ggttgatagg gatccccgct ttaatatgtt gctgcagggg gcgttgtaac 8700

aaaaagggag aacaagttgg tatgtcaaga ccaggcctaa agcctgatct tacgggaaca 8760

tcaaaatcct atgtaaggtc gctctgatcc tctacaactc ttgaaacaca aatgtcccac 8820

aagtctcctc ttcgtcatca agcaaccacc gcacccagca tcaagcccac ctgaaattat 8880

-continued

```
ctccggcttc cctctggccg aacaatatcg gtagttaatc aaaacttagg gtgcaagatc   8940
atccacaatg tcaccacaac gagaccggat aaatgccttc tacaaagata acccccatcc   9000
caagggaagt aggatagtca ttaacagaga acatcttatg attgatagac cttatgtttt   9060
gctggctgtt ctgtttgtca tgtttctgag cttgatcggg ttgctagcca ttgcaggcat   9120
tagacttcat cgggcagcca tctacaccgc agagatccat aaaagcctca gcaccaatct   9180
agatgtaact aactcaatcg agcatcaggt caaggacgtg ctgacaccac tcttcaaaat   9240
catcggtgat gaagtgggcc tgaggacacc tcagagattc actgacctag tgaaattaat   9300
ctctgacaag attaaattcc ttaatccgga tagggagtac gacttcagag atctcacttg   9360
gtgtatcaac ccgccagaga gaatcaaatt ggattatgat caatactgtg cagatgtggc   9420
tgctgaagag ctcatgaatg cattggtgaa ctcaactcta ctggagacca gaacaaccaa   9480
tcagttccta gctgtctcaa agggaaactg ctcagggccc actacaatca gaggtcaatt   9540
ctcaaacatg tcgctgtccc tgttagactt gtatttaggt cgaggttaca atgtgtcatc   9600
tatagtcact atgacatccc agggaatgta tgggggaact tacctagtgg aaaagcctaa   9660
tctgagcagc aaaaggtcag agttgtcaca actgagcatg taccgagtgt ttgaagtagg   9720
tgttatcaga aatccgggtt tgggggctcc ggtgttccat atgacaaact atcttgagca   9780
accagtcagt aatgatctca gcaactgtat ggtggctttg ggggagctca aactcgcagc   9840
cctttgtcac ggggaagatt ctatcacaat tccctatcag ggatcaggga aaggtgtcag   9900
cttccagctc gtcaagctag gtgtctggaa atccccaacc gacatgcaat cctgggtccc   9960
cttatcaacg gatgatccag tgatagacag gctttacctc tcatctcaca gaggtgttat  10020
cgctgacaat caagcaaaat gggctgtccc gacaacacga acagatgaca agttgcgaat  10080
ggagacatgc ttccaacagg cgtgtaaggg taaaatccaa gcactctgcg agaatcccga  10140
gtgggcacca ttgaaggata acaggattcc ttcatacggg gtcttgtctg ttgatctgag  10200
tctgacagtt gagcttaaaa tcaaaattgc ttcgggattc gggccattga tcacacacgg  10260
ttcagggatg gacctataca aatccaacca caacaatgtg tattggctga ctatcccgcc  10320
aatgaagaac ctagccttag gtgtaatcaa cacattggag tggataccga gattcaaggt  10380
tagtccctac ctcttcactg tcccaattaa ggaagcaggc gaagactgcc atgccccaac  10440
atacctacct gcggaggtgg atggtgatgt caaactcagt tccaatctgg tgattctacc  10500
tggtcaagat ctccaatatg ttttggcaac ctacgatact tccagggttg aacatgctgt  10560
ggtttattac gtttacagcc caagccgctc attttcttac ttttatcctt ttaggttgcc  10620
tataaagggg gtccccatcg aattacaagt ggaatgcttc acatgggacc aaaaactctg  10680
gtgccgtcac ttctgtgtgc ttgcggactc agaatctggt ggacatatca ctcactctgg  10740
gatggtgggc atgggagtca gctgcacagt cacccgggaa gatggaacca atcgcagata  10800
gggctgctag tgaaccaatc acatgatgtc acccagacat caggcatacc cactagtgtg  10860
aaatagacat cagaattaag aaaaacgtag ggtccaagtg gttccccgtt atggactcgc  10920
tatctgtcaa ccagatctta taccctgaag ttcacctaga tagcccgata gttaccaata  10980
agatagtagc catcctggag tatgctcgag tccctcacgc ttacagcctg gaggacccta  11040
cactgtgtca gaacatcaag caccgcctaa aaaacggatt ttccaaccaa atgattataa  11100
acaatgtgga agttgggaat gtcatcaagt ccaagcttag gagttatccg gcccactctc  11160
```

-continued

atattccata tccaaattgt aatcaggatt tatttaacat agaagacaaa gagtcaacga 11220

ggaagatccg tgaactcctc aaaaagggga attcgctgta ctccaaagtc agtgataagg 11280

ttttccaatg cttaagggac actaactcac ggcttggcct aggctccgaa ttgagggagg 11340

acatcaagga gaaagttatt aacttgggag tttacatgca cagctcccag tggtttgagc 11400

cctttctgtt ttggtttaca gtcaagactg agatgaggtc agtgattaaa tcacaaaccc 11460

atacttgcca taggaggaga cacacacctg tattcttcac tggtagttca gttgagttgc 11520

taatctctcg tgaccttgtt gctataatca gtaaagagtc tcaacatgta tattacctga 11580

catttgaact ggttttgatg tattgtgatg tcatagaggg gaggttaatg acagagaccg 11640

ctatgactat tgatgctagg tatacagagc ttctaggaag agtcagatac atgtggaaac 11700

tgatagatgg tttcttccct gcactcggga atccaactta tcaaattgta gccatgctgg 11760

agcctctttc acttgcttac ctgcagctga gggatataac agtagaactc agaggtgctt 11820

tccttaacca ctgctttact gaaatacatg atgttcttga ccaaaacggg ttttctgatg 11880

aaggtactta tcatgagtta actgaagctc tagattacat tttcataact gatgacatac 11940

atctgacagg ggagattttc tcatttttca gaagtttcgg ccaccccaga cttgaagcag 12000

taacggctgc tgaaaatgtt aggaaataca tgaatcagcc taaagtcatt gtgtatgaga 12060

ctctgatgaa aggtcatgcc atattttgtg gaatcataat caacggctat cgtgacaggc 12120

acggaggcag ttggccaccg ctgaccctcc ccctgcatgc tgcagacaca atccggaatg 12180

ctcaagcttc aggtgaaggg ttaacacatg agcagtgcgt tgataactgg aaatcttttg 12240

ctggagtgaa atttggctgc tttatgcctc ttagcctgga tagtgatctg acaatgtacc 12300

taaaggacaa ggcacttgct gctctccaaa gggaatggga ttcagtttac ccgaaagagt 12360

tcctgcgtta cgaccctccc aagggaaccg ggtcacggag gcttgtagat gttttcctta 12420

atgattcgag ctttgaccca tatgatgtga taatgtatgt tgtaagtgga gcttacctcc 12480

atgaccctga gttcaacctg tcttacagcc tgaaagaaaa ggagatcaag gaaacaggta 12540

gacttttgc taaaatgact tacaaaatga gggcatgcca agtgattgct gaaaatctaa 12600

tctcaaacgg gattggcaaa tattttaagg acaatgggat ggccaaggat gagcacgatt 12660

tgactaaggc actccacact ctagctgtct caggagtccc caaagatctc aaagaaagtc 12720

acagggggg gccagtctta aaaacctact cccgaagccc agtccacaca agtaccagga 12780

acgtgagagc agcaaaaggg tttatagggt tccctcaagt aattcggcag gaccaagaca 12840

ctgatcatcc ggagaatatg gaagcttacg agacagtcag tgcatttatc acgactgatc 12900

tcaagaagta ctgccttaat tggagatatg agaccatcag cttgtttgca cagaggctaa 12960

atgagattta cggattgccc tcatttttcc agtggctgca taagaggctt gagacctctg 13020

tcctgtatgt aagtgaccct cattgccccc ccgaccttga cgcccatatc ccgttatata 13080

aagtccccaa tgatcaaatc ttcattaagt accctatggg aggtatagaa gggtattgtc 13140

agaagctgtg gaccatcagc accattccct atctatacct ggctgcttat gagagcggag 13200

taaggattgc ttcgttagtg caaggggaca atcagaccat agccgtaaca aaaagggtac 13260

ccagcacatg gccctacaac cttaagaaac gggaagctgc tagagtaact agagattact 13320

ttgtaattct taggcaaagg ctacatgata ttggccatca cctcaaggca aatgagacaa 13380

ttgtttcatc acatttttttt gtctattcaa aaggaatata ttatgatggg ctacttgtgt 13440

-continued

```
cccaatcact caagagcatc gcaagatgtg tattctggtc agagactata gttgatgaaa  13500

caagggcagc atgcagtaat attgctacaa caatggctaa aagcatcgag agaggttatg  13560

accgttacct tgcatattcc ctgaacgtcc taaaagtgat acagcaaatt ctgatctctc  13620

ttggcttcac aatcaattca accatgaccc gggatgtagt catacccctc ctcacaaaca  13680

acgacctctt aataaggatg gcactgttgc ccgctcctat tgggggggatg aattatctga  13740

atatgagcag gctgtttgtc agaaacatcg gtgatccagt aacatcatca attgctgatc  13800

tcaagagaat gattctcgcc tcactaatgc ctgaagagac cctccatcaa gtaatgacac  13860

aacaaccggg ggactcttca ttcctagact gggctagcga cccttactca gcaaatcttg  13920

tatgtgtcca gagcatcact agactcctca agaacataac tgcaaggttt gtcctgatcc  13980

atagtccaaa cccaatgtta aaaggattat tccatgatga cagtaaagaa gaggacgagg  14040

gactggcggc attcctcatg gacaggcata ttatagtacc tagggcagct catgaaatcc  14100

tggatcatag tgtcacaggg gcaagagagt ctattgcagg catgctggat accacaaaag  14160

gcttgattcg agccagcatg aggaaggggg ggttaacctc tcgagtgata accagattgt  14220

ccaattatga ctatgaacaa ttcagagcag ggatggtgct attgacagga agaaagagaa  14280

atgtcctcat tgacaaagag tcatgttcag tgcagctggc gagagctcta agaagccata  14340

tgtgggcgag gctagctcga ggacggccta tttacggcct tgaggtccct gatgtactag  14400

aatctatgcg aggccacctt attcggcgtc atgagacatg tgtcatctgc gagtgtggat  14460

cagtcaacta cggatggttt tttgtcccct cgggttgcca actggatgat attgacaagg  14520

aaacatcatc cttgagagtc ccatatattg gttctaccac tgatgagaga acagacatga  14580

agcttgcctt cgtaagagcc ccaagtcgat ccttgcgatc tgctgttaga atagcaacag  14640

tgtactcatg ggcttacggt gatgatgata gctcttggaa cgaagcctgg ttgttggcta  14700

ggcaaagggc caatgtgagc ctggaggagc taagggtgat cactcccatc tcaacttcga  14760

ctaatttagc gcataggttg agggatcgta gcactcaagt gaaatactca ggtacatccc  14820

ttgtccgagt ggcgaggtat accacaatct ccaacgacaa tctctcattt gtcatatcag  14880

ataagaaggt tgatactaac tttatatacc aacaaggaat gcttctaggg ttgggtgttt  14940

tagaaacatt gtttcgactc gagaaagata ccggatcatc taacacggta ttacatcttc  15000

acgtcgaaac agattgttgc gtgatcccga tgatagatca tcccaggata cccagctccc  15060

gcaagctaga gctgagggca gagctatgta ccaacccatt gatatatgat aatgcacctt  15120

taattgacag agatgcaaca aggctataca cccagagcca taggaggcac cttgtggaat  15180

ttgttacatg gtccacaccc caactatatc acattttagc taagtccaca gcactatcta  15240

tgattgacct ggtaacaaaa tttgagaagg accatatgaa tgaaatttca gctctcatag  15300

gggatgacga tatcaatagt ttcataactg agtttctgct catagagcca agattattca  15360

ctatctactt gggccagtgt gcggccatca attgggcatt tgatgtacat tatcatagac  15420

catcagggaa atatcagatg ggtgagctgt tgtcatcgtt cctttctaga atgagcaaag  15480

gagtgtttaa ggtgcttgtc aatgctctaa gccacccaaa gatctacaag aaattctggc  15540

attgtggtat tatagagcct atccatggtc cttcacttga tgctcaaaac ttgcacacaa  15600

ctgtgtgcaa catggtttac acatgctata tgacctacct cgacctgttg ttgaatgaag  15660

agttagaaga gttcacattt ctcttgtgtg aaagcgacga ggatgtagta ccggacagat  15720
```

-continued

tcgacaacat ccaggcaaaa cacttatgtg ttctggcaga tttgtactgt caaccaggga 15780

cctgcccacc aattcgaggt ctaagaccgg tagagaaatg tgcagttcta accgaccata 15840

tcaaggcaga ggctatgtta tctccagcag gatcttcgtg gaacataaat ccaattattg 15900

tagaccatta ctcatgctct ctgacttatc tccggcgagg atcgatcaaa cagataagat 15960

tgagagttga tccaggattc attttcgacg ccctcgctga ggtaaatgtc agtcagccaa 16020

agatcggcag caacaacatc tcaaatatga gcatcaaggc tttcagaccc ccacacgatg 16080

atgttgcaaa attgctcaaa gatatcaaca caagcaagca caatcttccc atttcagggg 16140

gcaatctcgc caattatgaa atccatgctt tccgcagaat cgggttgaac tcatctgctt 16200

gctacaaagc tgttgagata tcaacattaa ttaggagatg ccttgagcca ggggaggacg 16260

gcttgttctt gggtgaggga tcgggttcta tgttgatcac ttataaagag atacttaaac 16320

taaacaagtg cttctataat agtggggttt ccgccaattc tagatctggt caaagggaat 16380

tagcacccta tccctccgaa gttggccttg tcgaacacag aatgggagta ggtaatattg 16440

tcaaagtgct ctttaacggg aggcccgaag tcacgtgggt aggcagtgta gattgcttca 16500

atttcatagt tagtaatatc cctacctcta gtgtggggtt tatccattca gatatagaga 16560

ccttgcctga caaagatact atagagaagc tagaggaatt ggcagccatc ttatcgatgg 16620

ctctgctcct gggcaaaata ggatcaatac tggtgattaa gcttatgcct ttcagcgggg 16680

attttgttca gggatttata agttatgtag ggtctcatta tagagaagtg aaccttgtat 16740

accctagata cagcaacttc atctctactg aatcttattt ggttatgaca gatctcaagg 16800

ctaaccggct aatgaatcct gaaaagatta agcagcagat aattgaatca tctgtgagga 16860

cttcacctgg acttataggt cacatcctat ccattaagca actaagctgc atacaagcaa 16920

ttgtgggaga cgcagttagt agaggtgata tcaatcctac tctgaaaaaa cttacaccta 16980

tagagcaggt gctgatcaat tgcgggttgg caattaacgg acctaagctg tgcaaagaat 17040

tgatccacca tgatgttgcc tcagggcaag atggattgct taattctata ctcatcctct 17100

acagggagtt ggcaagattc aaagacaacc aaagaagtca acaagggatg ttccacgctt 17160

accccgtatt ggtaagtagc aggcaacgag aacttatatc taggatcacc cgcaaattct 17220

gggggcacat tcttctttac tccgggaaca aaaagttgat aaataagttt atccagaatc 17280

tcaagtccgg ctatctgata ctagacttac accagaatat cttcgttaag aatctatcca 17340

agtcagagaa acagattatt atgacggggg gtttgaaacg tgagtgggtt tttaaggtaa 17400

cagtcaagga gaccaaagaa tggtataagt tagtcggata cagtgccctg attaaggact 17460

aattggttga actccggaac cctaatcctg ccctaggtgg ttaggcatta tttgcaatat 17520

attaaagaaa actttgaaaa tacgaagttt ctattcccag ctttgtctgg 17570

<210> SEQ ID NO 6
<211> LENGTH: 18400
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: recombinant measles virus expressing fused mouse IL-12 with MV H protein specifically targeting human CEA antigen (MeVac P-FmIL-12 Hbl-antiCEA)

<400> SEQUENCE: 6

accaaacaaa gttgggtaag gatagttcaa tcaatgatca tcttctagtg cacttaggat 60

-continued

tcaagatcct attatcaggg acaagagcag gattagggat atccgagatg gccacacttt 120

taaggagctt agcattgttc aaaagaaaca aggacaaacc acccattaca tcaggatccg 180

gtggagccat cagaggaatc aaacacatta ttatagtacc aatccctgga gattcctcaa 240

ttaccactcg atccagactt ctggaccggt tggtgaggtt aattggaaac ccggatgtga 300

gcgggcccaa actaacaggg gcactaatag gtatattatc cttatttgtg gagtctccag 360

gtcaattgat tcagaggatc accgatgacc ctgacgttag cataaggctg ttagaggttg 420

tccagagtga ccagtcacaa tctggcctta ccttcgcatc aagaggtacc aacatggagg 480

atgaggcgga ccaatacttt tcacatgatg atccaattag tagtgatcaa tccaggttcg 540

gatggttcgg gaacaaggaa atctcagata ttgaagtgca agaccctgag ggattcaaca 600

tgattctggg taccatccta gcccaaattt gggtcttgct cgcaaaggcg gttacggccc 660

cagacacggc agctgattcg gagctaagaa ggtggataaa gtacacccaa caaagaaggg 720

tagttggtga atttagattg gagagaaaat ggttggatgt ggtgaggaac aggattgccg 780

aggacctctc cttacgccga ttcatggtcg ctctaatcct ggatatcaag agaacacccg 840

gaaacaaacc caggattgct gaaatgatat gtgacattga tacatatatc gtagaggcag 900

gattagccag ttttatcctg actattaagt ttgggataga aactatgtat cctgctcttg 960

gactgcatga atttgctggt gagttatcca cacttgagtc cttgatgaac ctttaccagc 1020

aaatgggggа aactgcaccc tacatggtaa tcctggagaa ctcaattcag aacaagttca 1080

gtgcaggatc ataccctctg ctctggagct atgccatggg agtaggagtg gaacttgaaa 1140

actccatggg aggtttgaac tttggccgat cttactttga tccagcatat tttagattag 1200

ggcaagagat ggtaaggagg tcagctggaa aggtcagttc cacattggca tctgaactcg 1260

gtatcactgc cgaggatgca aggcttgttt cagagattgc aatgcatact actgaggaca 1320

agatcagtag agcggttgga cccagacaag cccaagtatc atttctacac ggtgatcaaa 1380

gtgagaatga gctaccgaga ttgggggggca aggaagatag gagggtcaaa cagagtcgag 1440

gagaagccag ggagagctac agagaaaccg ggcccagcag agcaagtgat gcgagagctg 1500

cccatcttcc aaccggcaca cccctagaca ttgacactgc aacggagtcc agccaagatc 1560

cgcaggacag tcgaaggtca gctgacgccc tgcttaggct gcaagccatg gcaggaatct 1620

cggaagaaca aggctcagac acggacaccc ctatagtgta caatgacaga aatcttctag 1680

actaggtgcg agaggccgag ggccagaaca acatccgcct accatccatc attgttataa 1740

aaaacttagg aaccaggtcc acacagccgc cagcccatca accatccact cccacgattg 1800

gagccaatgg cagaagagca ggcacgccat gtcaaaaacg gactggaatg catccgggct 1860

ctcaaggccg agcccatcgg ctcactggcc atcgaggaag ctatggcagc atggtcagaa 1920

atatcagaca acccaggaca ggagcgagcc acctgcaggg aagagaaggc aggcagttcg 1980

ggtctcagca aaccatgcct ctcagcaatt ggatcaactg aaggcggtgc acctcgcatc 2040

cgcggtcagg gacctggaga gagcgatgac gacgctgaaa ctttgggaat ccccccaaga 2100

aatctccagg catcaagcac tgggttacag tgttattacg tttatgatca cagcggtgaa 2160

gcggttaagg gaatccaaga tgctgactct atcatggttc aatcaggcct tgatggtgat 2220

agcaccctct caggaggaga caatgaatct gaaaacagcg atgtggatat tggcgaacct 2280

gataccgagg gatatgctat cactgaccgg ggatctgctc ccatctctat ggggttcagg 2340

-continued

gcttctgatg ttgaaactgc agaaggaggg gagatccacg agctcctgag actccaatcc 2400

agaggcaaca actttccgaa gcttgggaaa actctcaatg ttcctccgcc cccggacccc 2460

ggtagggcca gcacttccgg gacacccatt aaaaagggca cagacgcgag attagcctca 2520

tttggaacgg agatcgcgtc tttattgaca ggtggtgcaa cccaatgtgc tcgaaagtca 2580

ccctcggaac catcagggcc aggtgcacct gcggggaatg tccccgagtg tgtgagcaat 2640

gccgcactga tacaggagtg gacacccgaa tctggtacca caatctcccc gagatcccag 2700

aataatgaag aaggggggaga ctattatgat gatgagctgt tctctgatgt ccaagatatt 2760

aaaacagcct tggccaaaat acacgaggat aatcagaaga taatctccaa gctagaatca 2820

ctgctgttat tgaagggaga agttgagtca attaagaagc agatcaacag gcaaaatatc 2880

agcatatcca ccctggaagg acacctctca agcatcatga tcgccattcc tggacttggg 2940

aaggatccca acgaccccac tgcagatgtc gaaatcaatc ccgacttgaa acccatcata 3000

ggcagagatt caggccgagc actggccgaa gttctcaaga aacccgttgc cagccgacaa 3060

ctccaaggaa tgacaaatgg acggaccagt tccagaggac agctgctgaa ggaatttcag 3120

ctaaagccga tcgggaaaaa gatgagctca gccgtcgggt ttgttcctga caccggccct 3180

gcatcacgca gtgtaatccg ctccattata aaatccagcc ggctagagga ggatcggaag 3240

cgttacctga tgactctcct tgatgatatc aaaggagcca atgatcttgc caagttccac 3300

cagatgctga tgaagataat aatgaagtag ctacagctca acttacctgc caaccccatg 3360

ccagtcgacc caactagcaa cctaaatcca ttataaaaaa cttaggaacc aggtccacac 3420

agctcgagtc gcgcgtggcc accatgtgtc ctcagaagct aaccatctcc tggtttgcca 3480

tcgttttgct ggtgtcccca ctcatggcca tgtgggagct ggagaaagac gtttatgttg 3540

tagaggtgga ctggactccc gatgcccctg gagaaacagt gaacctcacc tgtgacacgc 3600

ctgaagaaga tgacatcacc tggacctcag accagagaca tggagtcata ggctctggaa 3660

agaccctgac catcactgtc aaagagtttc tagatgctgg ccagtacacc tgccacaaag 3720

gaggcgagac tctgagccac tcacatctgc tgctccacaa gaaggaaaat ggaatttggt 3780

ccactgaaat tttaaaaaat ttcaaaaaca agactttcct gaagtgtgaa gcaccaaatt 3840

actccggacg gttcacgtgc tcatggctgg tgcaaagaaa catggacttg aagttcaaca 3900

tcaagagcag tagcagttcc cctgactctc gggcagtgac atgtggaatg gcgtctctgt 3960

ctgcagagaa ggtcacactg gaccaaaggg actatgagaa gtattcagtg tcctgccagg 4020

aggatgtcac ctgcccaact gccgaggaga ccctgcccat tgaactggcg ttggaagcac 4080

ggcagcagaa taaatatgag aactacagca ccagcttctt catcagggac atcatcaaac 4140

cagacccgcc caagaacttg cagatgaagc ctttgaagaa ctcacaggtg gaggtcagct 4200

gggagtaccc tgactcctgg agcactcccc attcctactt ctccctcaag ttctttgttc 4260

gaatccagcg caagaaagaa aagatgaagg agacagagga ggggtgtaac cagaaaggtg 4320

cgttcctcgt agagaagaca tctaccgaag tccaatgcaa aggcgggaat gtctgcgtgc 4380

aagctcagga tcgctattac aattcctcgt gcagcaagtg ggcatgtgtt ccctgcaggg 4440

tccgatccgg tggcggtggc tcgggcggtg gtgggtcggg tggcggcgga tctagggtca 4500

ttccagtctc tggacctgcc aggtgtctta gccagtcccg aaacctgctg aagaccacag 4560

atgacatggt gaagacggcc agagaaaaac tgaaacatta ttcctgcact gctgaagaca 4620

-continued

tcgatcatga agacatcaca cgggaccaaa ccagcacatt gaagacctgt ttaccactgg 4680

aactacacaa gaacgagagt tgcctggcta ctagagagac ttcttccaca acaagaggga 4740

gctgcctgcc cccacagaag acgtctttga tgatgaccct gtgccttggt agcatctatg 4800

aggacttgaa gatgtaccag acagagttcc aggccatcaa cgcagcactt cagaatcaca 4860

accatcagca gatcattcta gacaagggca tgctggtggc catcgatgag ctgatgcagt 4920

ctctgaatca taatggcgag actctgcgcc agaaacctcc tgtgggagaa gcagacccct 4980

acagagtgaa aatgaagctc tgcatcctgc ttcacgcctt cagcacccgc gtcgtgacca 5040

tcaacagggt gatgggctat ctgagctccg cctgataatc gcgcgcgtgc tagtacaacc 5100

taaatccatt ataaaaaact taggagcaaa gtgattgcct cccaaggtcc acaatgacag 5160

agacctacga cttcgacaag tcggcatggg acatcaaagg gtcgatcgct ccgatacaac 5220

ccaccaccta cagtgatggc aggctggtgc cccaggtcag agtcatagat cctggtctag 5280

gcgacaggaa ggatgaatgc tttatgtaca tgtttctgct gggggttgtt gaggacagcg 5340

attccctagg gcctccaatc gggcgagcat ttgggttcct gcccttaggt gttggcagat 5400

ccacagcaaa gcccgaaaaa ctcctcaaag aggccactga gcttgacata gttgttagac 5460

gtacagcagg gctcaatgaa aaactggtgt tctacaacaa caccccacta actctcctca 5520

caccttggag aaaggtccta acaacaggga gtgtcttcaa cgcaaaccaa gtgtgcaatg 5580

cggttaatct gataccgctc gataccccgc agaggttccg tgttgtttat atgagcatca 5640

cccgtctttc ggataacggg tattacaccg ttcctagaag aatgctggaa ttcagatcgg 5700

tcaatgcagt ggccttcaac ctgctggtga cccttaggat tgacaaggcg ataggccctg 5760

ggaagatcat cgacaataca gagcaacttc ctgaggcaac atttatggtc cacatcggga 5820

acttcaggag aaagaagagt gaagtctact ctgccgatta ttgcaaaatg aaaatcgaaa 5880

agatgggcct ggtttttgca cttggtggga taggggcac cagtcttcac attagaagca 5940

caggcaaaat gagcaagact ctccatgcac aactcgggtt caagaagacc ttatgttacc 6000

cgctgatgga tatcaatgaa gaccttaatc gattactctg gaggagcaga tgcaagatag 6060

taagaatcca ggcagttttg cagccatcag ttcctcaaga attccgcatt tacgacgacg 6120

tgatcataaa tgatgaccaa ggactattca aagttctgta gaccgtagtg cccagcaatg 6180

cccgaaaacg acccccctca caatgacagc cagaaggccc ggacaaaaaa gccccctccg 6240

aaagactcca cggaccaagc gagaggccag ccagcagccg acggcaagcg cgaacaccag 6300

gcggccccag cacagaacag ccctgacaca aggccaccac cagccacccc aatctgcatc 6360

ctcctcgtgg gacccccgag gaccaacccc caaggctgcc cccgatccaa accaccaacc 6420

gcatccccac caccccgggg aaagaaaccc ccagcaattg gaaggccccc ccccctcttc 6480

ctcaacacaa gaactccaca accgaaccgc acaagcgacc gaggtgaccc aaccgcaggc 6540

atccgactcc ctagacagat cctctctccc cggcaaacta aacaaaactt agggccaagg 6600

aacatacaca cccaacagaa cccagacccc ggcccacggc gccgcgcccc caacccccga 6660

caaccagagg gagcccccaa ccaatcccgc cggctccccc ggtgcccaca ggcagggaca 6720

ccaacccccg aacagaccca gcacccaacc atcgacaatc caagacgggg gggccccccc 6780

aaaaaaaggc ccccaggggc cgacagccag caccgcgagg aagcccaccc accccacaca 6840

cgaccacggc aaccaaacca gaacccagac caccctgggc caccagctcc cagactcggc 6900

-continued

catcaccccg cagaaaggaa aggccacaac ccgcgcaccc cagccccgat ccggcgggga 6960

gccacccaac ccgaaccagc acccaagagc gatccccgaa ggacccccga accgcaaagg 7020

acatcagtat cccacagcct ctccaagtcc cccggtctcc tcctcttctc gaagggacca 7080

aaagatcaat ccaccacacc cgacgacact caactcccca cccctaaagg agacaccggg 7140

aatcccagaa tcaagactca tccaatgtcc atcatgggtc tcaaggtgaa cgtctctgcc 7200

atattcatgg cagtactgtt aactctccaa acacccaccg gtcaaatcca ttggggcaat 7260

ctctctaaga taggggtggt aggaatagga agtgcaagct acaaagttat gactcgttcc 7320

agccatcaat cattagtcat aaaattaatg cccaatataa ctctcctcaa taactgcacg 7380

agggtagaga ttgcagaata caggagacta ctgagaacag ttttggaacc aattagagat 7440

gcacttaatg caatgaccca gaatataaga ccggttcaga gtgtagcttc aagtaggaga 7500

cacaagagat ttgcgggagt agtcctggca ggtgcggccc taggcgttgc cacagctgct 7560

cagataacag ccggcattgc acttcaccag tccatgctga actctcaagc catcgacaat 7620

ctgagagcga gcctggaaac tactaatcag gcaattgaga caatcagaca agcagggcag 7680

gagatgatat tggctgttca gggtgtccaa gactacatca ataatgagct gataccgtct 7740

atgaaccaac tatcttgtga tttaatcggc cagaagctcg ggctcaaatt gctcagatac 7800

tatacagaaa tcctgtcatt atttggcccc agtttacggg accccatatc tgcggagata 7860

tctatccagg ctttgagcta tgcgcttgga ggagacatca ataaggtgtt agaaaagctc 7920

ggatacagtg gaggtgattt actgggcatc ttagagagcg gaggaataaa ggcccggata 7980

actcacgtcg acacagagtc ctacttcatt gtcctcagta tagcctatcc gacgctgtcc 8040

gagattaagg gggtgattgt ccaccggcta gagggggtct cgtacaacat aggctctcaa 8100

gagtggtata ccactgtgcc caagtatgtt gcaacccaag ggtaccttat ctcgaatttt 8160

gatgagtcat cgtgtacttt catgccagag gggactgtgt gcagccaaaa tgccttgtac 8220

ccgatgagtc ctctgctcca agaatgcctc cgggggtaca ccaagtcctg tgctcgtaca 8280

ctcgtatccg ggtcttttgg gaaccggttc attttatcac aagggaacct aatagccaat 8340

tgtgcatcaa tcctttgcaa gtgttacaca acaggaacga tcattaatca agaccctgac 8400

aagatcctaa catacattgc tgccgatcac tgcccggtag tcgaggtgaa cggcgtgacc 8460

atccaagtcg ggagcaggag gtatccagac gctgtgtact tgcacagaat tgacctcggt 8520

cctcccatat cattggagag gttggacgta gggacaaatc tggggaatgc aattgctaag 8580

ttggaggatg ccaaggaatt gttggagtca tcggaccaga tattgaggag tatgaaaggt 8640

ttatcgagca ctagcatagt ctacatcctg attgcagtgt gtcttggagg gttgataggg 8700

atccccgctt taatatgttg ctgcaggggg cgttgtaaca aaaagggaga acaagttggt 8760

atgtcaagac caggcctaaa gcctgatctt acgggaacat caaaatccta tgtaaggtcg 8820

ctctgatcct ctacaactct tgaaacacaa atgtcccaca agtctcctct tcgtcatcaa 8880

gcaaccaccg cacccagcat caagcccacc tgaaattatc tccggcttcc ctctggccga 8940

acaatatcgg tagttaatca aaacttaggg tgcaagatca tccacaatgt caccacaacg 9000

agaccggata aatgccttct acaaagataa cccccatccc aagggaagta ggatagtcat 9060

taacagagaa catcttatga ttgatagacc ttatgttttg ctggctgttc tgtttgtcat 9120

gtttctgagc ttgatcgggt tgctagccat tgcaggcatt agacttcatc gggcagccat 9180

-continued

ctacaccgca gagatccata aaagcctcag caccaatcta gatgtaacta actcaatcga 9240

gcatcaggtc aaggacgtgc tgacaccact cttcaaaatc atcggtgatg aagtgggcct 9300

gaggacacct cagagattca ctgacctagt gaaattaatc tctgacaaga ttaaattcct 9360

taatccggat agggagtacg acttcagaga tctcacttgg tgtatcaacc cgccagagag 9420

aatcaaattg gattatgatc aatactgtgc agatgtggct gctgaagagc tcatgaatgc 9480

attggtgaac tcaactctac tggagaccag aacaaccaat cagttcctag ctgtctcaaa 9540

gggaaactgc tcagggccca ctacaatcag aggtcaattc tcaaacatgt cgctgtccct 9600

gttagacttg tatttaggtc gaggttacaa tgtgtcatct atagtcacta tgacatccca 9660

gggaatgtat gggggaactt acctagtgga aaagcctaat ctgagcagca aaaggtcaga 9720

gttgtcacaa ctgagcatgt accgagtgtt tgaagtaggt gttatcagaa atccgggttt 9780

gggggctccg gtgttccata tgacaaacta tcttgagcaa ccagtcagta atgatctcag 9840

caactgtatg gtggctttgg gggagctcaa actcgcagcc ctttgtcacg gggaagattc 9900

tatcacaatt ccctatcagg gatcagggaa aggtgtcagc ttccagctcg tcaagctagg 9960

tgtctggaaa tccccaaccg acatgcaatc ctgggtcccc ttatcaacgg atgatccagt 10020

gatagacagg ctttacctct catctcacag aggtgttatc gctgacaatc aagcaaaatg 10080

ggctgtcccg acaacacgaa cagatgacaa gttgcgaatg gagacatgct tccaacaggc 10140

gtgtaagggt aaaatccaag cactctgcga gaatcccgag tgggcaccat tgaaggataa 10200

caggattcct tcatacgggg tcttgtctgt tgatctgagt ctgacagttg agcttaaaat 10260

caaaattgct tcgggattcg ggccattgat cacacacggt tcagggatgg acctatacaa 10320

atccaaccac aacaatgtgt attggctgac tatcccgcca atgaagaacc tagccttagg 10380

tgtaatcaac acattggagt ggataccgag attcaaggtt agtcccgcac tcttcactgt 10440

cccaattaag gaagcaggcg aagactgcca tgccccaaca tacctacctg cggaggtgga 10500

tggtgatgtc aaactcagtt ccaatctggt gattctacct ggtcaagatc tccaatatgt 10560

tttggcaacc tacgatactt ccgcggttga acatgctgtg gtttattacg tttacagccc 10620

aagccgccta tcgtcttact tttatccttt taggttgcct ataaaggggg tccccatcga 10680

attacaagtg gaatgcttca catgggacca aaaactctgg tgccgtcact tctgtgtgct 10740

tgcggactca gaatctggtg gacatatcac tcactctggg atggtgggca tgggagtcag 10800

ctgcacagtc acccgggaag atggaaccaa tgcggcccag ccggccatcg agggaaggat 10860

ggctcaggtg aaactgcagc agtctggggc agaacttgtg aggtcaggga cctcagtcaa 10920

gttgtcctgc acagcttctg gcttcaacat taaagactcc tatatgcact ggttgaggca 10980

ggggcctgaa cagtgcctcg agtggattgg atggattgat cctgagaatg gtgatactga 11040

atatgccccg aagttccagg gcaaggccac ttttactaca gacacatcct ccaacacagc 11100

ctacctgcag ctcagcagcc tgacatctga ggacactgcc gtctattatt gtaatgaggg 11160

gactccgact gggccgtact actttgacta ctggggccaa gggaccacgg tcaccgtctc 11220

ctcaggtgga ggcggttcag gcggaggtgg ctctggcggt ggcggatcag aaaatgtgct 11280

cacccagtct ccagcaatca tgtctgcatc tccaggggag aaggtcacca taacctgcag 11340

tgccagctca agtgtaagtt acatgcactg gttccagcag aagccaggca cttctcccaa 11400

actctggatt tatagcacat ccaacctggc ttctggagtc cctgctcgct tcagtggcag 11460

-continued

tggatctggg acctcttact ctctcacaat cagccgaatg gaggctgaag atgctgccac 11520

ttattactgc cagcaaagga gtagttaccc actcacgttc ggttgtggca ccaagctcga 11580

gctgaaacgg gcggccgcaa gaggttctca tcaccatcac catcactaat agggctgcta 11640

gtgaaccaat cacatgatgt cacccagaca tcaggcatac ccactagtgt gaaatagaca 11700

tcagaattaa gaaaaacgta gggtccaagt ggttccccgt tatggactcg ctatctgtca 11760

accagatctt ataccctgaa gttcacctag atagcccgat agttaccaat aagatagtag 11820

ccatcctgga gtatgctcga gtccctcacg cttacagcct ggaggaccct acactgtgtc 11880

agaacatcaa gcaccgccta aaaaacggat tttccaacca aatgattata aacaatgtgg 11940

aagttgggaa tgtcatcaag tccaagctta ggagttatcc ggcccactct catattccat 12000

atccaaattg taatcaggat ttatttaaca tagaagacaa agagtcaacg aggaagatcc 12060

gtgaactcct caaaaagggg aattcgctgt actccaaagt cagtgataag gttttccaat 12120

gcttaaggga cactaactca cggcttggcc taggctccga attgagggag gacatcaagg 12180

agaaagttat taacttggga gtttacatgc acagctccca gtggtttgag ccctttctgt 12240

tttggtttac agtcaagact gagatgaggt cagtgattaa atcacaaacc catacttgcc 12300

ataggaggag acacacacct gtattcttca ctggtagttc agttgagttg ctaatctctc 12360

gtgaccttgt tgctataatc agtaaagagt ctcaacatgt atattacctg acatttgaac 12420

tggttttgat gtattgtgat gtcatagagg ggaggttaat gacagagacc gctatgacta 12480

ttgatgctag gtatacagag cttctaggaa gagtcagata catgtggaaa ctgatagatg 12540

gtttcttccc tgcactcggg aatccaactt atcaaattgt agccatgctg gagcctcttt 12600

cacttgctta cctgcagctg agggatataa cagtagaact cagaggtgct ttccttaacc 12660

actgctttac tgaaatacat gatgttcttg accaaaacgg gttttctgat gaaggtactt 12720

atcatgagtt aactgaagct ctagattaca ttttcataac tgatgacata catctgacag 12780

gggagatttt ctcatttttc agaagtttcg gccaccccag acttgaagca gtaacggctg 12840

ctgaaaatgt taggaaatac atgaatcagc ctaaagtcat tgtgtatgag actctgatga 12900

aaggtcatgc catattttgt ggaatcataa tcaacggcta tcgtgacagg cacggaggca 12960

gttggccacc gctgaccctc cccctgcatg ctgcagacac aatccggaat gctcaagctt 13020

caggtgaagg gttaacacat gagcagtgcg ttgataactg gaaatctttt gctggagtga 13080

aatttggctg ctttatgcct cttagcctgg atagtgatct gacaatgtac ctaaaggaca 13140

aggcacttgc tgctctccaa agggaatggg attcagttta cccgaaagag ttcctgcgtt 13200

acgaccctcc caagggaacc gggtcacgga ggcttgtaga tgttttcctt aatgattcga 13260

gctttgaccc atatgatgtg ataatgtatg ttgtaagtgg agcttacctc catgaccctg 13320

agttcaacct gtcttacagc ctgaaagaaa aggagatcaa ggaaacaggt agacttttg 13380

ctaaaatgac ttacaaaatg agggcatgcc aagtgattgc tgaaaatcta atctcaaacg 13440

ggattggcaa atattttaag gacaatggga tggccaagga tgagcacgat ttgactaagg 13500

cactccacac tctagctgtc tcaggagtcc ccaaagatct caaagaaagt cacaggggg 13560

ggccagtctt aaaaacctac tcccgaagcc cagtccacac aagtaccagg aacgtgagag 13620

cagcaaaagg gtttataggg ttccctcaag taattcggca ggaccaagac actgatcatc 13680

cggagaatat ggaagcttac gagacagtca gtgcatttat cacgactgat ctcaagaagt 13740

-continued

actgccttaa ttggagatat gagaccatca gcttgtttgc acagaggcta aatgagattt 13800

acggattgcc ctcatttttc cagtggctgc ataagaggct tgagacctct gtcctgtatg 13860

taagtgaccc tcattgcccc cccgaccttg acgcccatat cccgttatat aaagtcccca 13920

atgatcaaat cttcattaag taccctatgg gaggtataga agggtattgt cagaagctgt 13980

ggaccatcag caccattccc tatctatacc tggctgctta tgagagcgga gtaaggattg 14040

cttcgttagt gcaaggggac aatcagacca tagccgtaac aaaaagggta cccagcacat 14100

ggccctacaa ccttaagaaa cgggaagctg ctagagtaac tagagattac tttgtaattc 14160

ttaggcaaag gctacatgat attggccatc acctcaaggc aaatgagaca attgtttcat 14220

cacatttttt tgtctattca aaaggaatat attatgatgg gctacttgtg tcccaatcac 14280

tcaagagcat cgcaagatgt gtattctggt cagagactat agttgatgaa acaagggcag 14340

catgcagtaa tattgctaca acaatggcta aaagcatcga gagaggttat gaccgttacc 14400

ttgcatattc cctgaacgtc ctaaaagtga tacagcaaat tctgatctct cttggcttca 14460

caatcaattc aaccatgacc cgggatgtag tcatacccct cctcacaaac aacgacctct 14520

taataaggat ggcactgttg cccgctccta ttgggggggat gaattatctg aatatgagca 14580

ggctgtttgt cagaaacatc ggtgatccag taacatcatc aattgctgat ctcaagagaa 14640

tgattctcgc ctcactaatg cctgaagaga ccctccatca agtaatgaca caacaaccgg 14700

gggactcttc attcctagac tgggctagcg acccttactc agcaaatctt gtatgtgtcc 14760

agagcatcac tagactcctc aagaacataa ctgcaaggtt tgtcctgatc catagtccaa 14820

acccaatgtt aaaaggatta ttccatgatg acagtaaaga agaggacgag ggactggcgg 14880

cattcctcat ggacaggcat attatagtac ctagggcagc tcatgaaatc ctggatcata 14940

gtgtcacagg ggcaagagag tctattgcag gcatgctgga taccacaaaa ggcttgattc 15000

gagccagcat gaggaagggg gggttaacct ctcgagtgat aaccagattg tccaattatg 15060

actatgaaca attcagagca gggatggtgc tattgacagg aagaaagaga aatgtcctca 15120

ttgacaaaga gtcatgttca gtgcagctgg cgagagctct aagaagccat atgtgggcga 15180

ggctagctcg aggacggcct atttacggcc ttgaggtccc tgatgtacta gaatctatgc 15240

gaggccacct tattcggcgt catgagacat gtgtcatctg cgagtgtgga tcagtcaact 15300

acggatggtt ttttgtcccc tcgggttgcc aactggatga tattgacaag gaaacatcat 15360

ccttgagagt cccatatatt ggttctacca ctgatgagag aacagacatg aagcttgcct 15420

tcgtaagagc cccaagtcga tccttgcgat ctgctgttag aatagcaaca gtgtactcat 15480

gggcttacgg tgatgatgat agctcttgga acgaagcctg gttgttggct aggcaaaggg 15540

ccaatgtgag cctggaggag ctaagggtga tcactcccat ctcaacttcg actaatttag 15600

cgcataggtt gagggatcgt agcactcaag tgaaatactc aggtacatcc cttgtccgag 15660

tggcgaggta taccacaatc tccaacgaca atctctcatt tgtcatatca gataagaagg 15720

ttgatactaa ctttatatac caacaaggaa tgcttctagg gttgggtgtt ttagaaacat 15780

tgtttcgact cgagaaagat accggatcat ctaacacggt attacatctt cacgtcgaaa 15840

cagattgttg cgtgatcccg atgatagatc atcccaggat acccagctcc cgcaagctag 15900

agctgagggc agagctatgt accaacccat tgatatatga taatgcacct ttaattgaca 15960

gagatgcaac aaggctatac acccagagcc ataggaggca ccttgtggaa tttgttacat 16020

-continued

ggtccacacc ccaactatat cacattttag ctaagtccac agcactatct atgattgacc 16080

tggtaacaaa atttgagaag gaccatatga atgaaatttc agctctcata ggggatgacg 16140

atatcaatag tttcataact gagtttctgc tcatagagcc aagattattc actatctact 16200

tgggccagtg tgcggccatc aattgggcat ttgatgtaca ttatcataga ccatcaggga 16260

aatatcagat gggtgagctg ttgtcatcgt tcctttctag aatgagcaaa ggagtgttta 16320

aggtgcttgt caatgctcta agccacccaa agatctacaa gaaattctgg cattgtggta 16380

ttatagagcc tatccatggt ccttcacttg atgctcaaaa cttgcacaca actgtgtgca 16440

acatggttta cacatgctat atgacctacc tcgacctgtt gttgaatgaa gagttagaag 16500

agttcacatt tctcttgtgt gaaagcgacg aggatgtagt accggacaga ttcgacaaca 16560

tccaggcaaa acacttatgt gttctggcag atttgtactg tcaaccaggg acctgcccac 16620

caattcgagg tctaagaccg gtagagaaat gtgcagttct aaccgaccat atcaaggcag 16680

aggctatgtt atctccagca ggatcttcgt ggaacataaa tccaattatt gtagaccatt 16740

actcatgctc tctgacttat ctccggcgag gatcgatcaa acagataaga ttgagagttg 16800

atccaggatt cattttcgac gccctcgctg aggtaaatgt cagtcagcca aagatcggca 16860

gcaacaacat ctcaaatatg agcatcaagg ctttcagacc cccacacgat gatgttgcaa 16920

aattgctcaa agatatcaac acaagcaagc acaatcttcc catttcaggg ggcaatctcg 16980

ccaattatga aatccatgct ttccgcagaa tcgggttgaa ctcatctgct tgctacaaag 17040

ctgttgagat atcaacatta attaggagat gccttgagcc aggggaggac ggcttgttct 17100

tgggtgaggg atcgggttct atgttgatca cttataaaga gatacttaaa ctaaacaagt 17160

gcttctataa tagtggggtt tccgccaatt ctagatctgg tcaaagggaa ttagcaccct 17220

atccctccga agttggcctt gtcgaacaca gaatgggagt aggtaatatt gtcaaagtgc 17280

tctttaacgg gaggcccgaa gtcacgtggg taggcagtgt agattgcttc aatttcatag 17340

ttagtaatat ccctacctct agtgtggggt ttatccattc agatatagag accttgcctg 17400

acaaagatac tatagagaag ctagaggaat tggcagccat cttatcgatg gctctgctcc 17460

tgggcaaaat aggatcaata ctggtgatta agcttatgcc tttcagcggg gattttgttc 17520

agggatttat aagttatgta gggtctcatt atagagaagt gaaccttgta taccctagat 17580

acagcaactt catctctact gaatcttatt tggttatgac agatctcaag gctaaccggc 17640

taatgaatcc tgaaaagatt aagcagcaga taattgaatc atctgtgagg acttcacctg 17700

gacttatagg tcacatccta tccattaagc aactaagctg catacaagca attgtgggag 17760

acgcagttag tagaggtgat atcaatccta ctctgaaaaa acttacacct atagagcagg 17820

tgctgatcaa ttgcgggttg gcaattaacg gacctaagct gtgcaaagaa ttgatccacc 17880

atgatgttgc ctcagggcaa gatggattgc ttaattctat actcatcctc tacagggagt 17940

tggcaagatt caaagacaac caaagaagtc aacaagggat gttccacgct taccccgtat 18000

tggtaagtag caggcaacga gaacttatat ctaggatcac ccgcaaattc tgggggcaca 18060

ttcttcttta ctccgggaac aaaaagttga taaataagtt tatccagaat ctcaagtccg 18120

gctatctgat actagactta caccagaata tcttcgttaa gaatctatcc aagtcagaga 18180

aacagattat tatgacgggg ggtttgaaac gtgagtgggt ttttaaggta acagtcaagg 18240

agaccaaaga atggtataag ttagtcggat acagtgccct gattaaggac taattggttg 18300

-continued

aactccggaa ccctaatcct gccctaggtg gttaggcatt atttgcaata tattaaagaa 18360

aactttgaaa atacgaagtt tctattccca gctttgtctg 18400

<210> SEQ ID NO 7
<211> LENGTH: 18420
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial MV genome
MeVac_P_FmIL-12_Hbl_anti_CD20

<400> SEQUENCE: 7

accaaacaaa gttgggtaag gatagttcaa tcaatgatca tcttctagtg cacttaggat 60

tcaagatcct attatcaggg acaagagcag gattagggat atccgagatg gccacacttt 120

taaggagctt agcattgttc aaaagaaaca aggacaaacc acccattaca tcaggatccg 180

gtggagccat cagaggaatc aaacacatta ttatagtacc aatccctgga gattcctcaa 240

ttaccactcg atccagactt ctggaccggt tggtgaggtt aattggaaac ccggatgtga 300

gcgggcccaa actaacaggg gcactaatag gtatattatc cttatttgtg gagtctccag 360

gtcaattgat tcagaggatc accgatgacc ctgacgttag cataaggctg ttagaggttg 420

tccagagtga ccagtcacaa tctggcctta ccttcgcatc aagaggtacc aacatggagg 480

atgaggcgga ccaatacttt tcacatgatg atccaattag tagtgatcaa tccaggttcg 540

gatggttcgg gaacaaggaa atctcagata ttgaagtgca agaccctgag ggattcaaca 600

tgattctggg taccatccta gcccaaattt gggtcttgct cgcaaaggcg gttacggccc 660

cagacacggc agctgattcg gagctaagaa ggtggataaa gtacacccaa caaagaaggg 720

tagttggtga atttagattg gagagaaaat ggttggatgt ggtgaggaac aggattgccg 780

aggacctctc cttacgccga ttcatggtcg ctctaatcct ggatatcaag agaacacccg 840

gaaacaaacc caggattgct gaaatgatat gtgacattga tacatatatc gtagaggcag 900

gattagccag ttttatcctg actattaagt ttgggataga aactatgtat cctgctcttg 960

gactgcatga atttgctggt gagttatcca cacttgagtc cttgatgaac ctttaccagc 1020

aaatgggggа aactgcaccc tacatggtaa tcctggagaa ctcaattcag aacaagttca 1080

gtgcaggatc ataccctctg ctctggagct atgccatggg agtaggagtg gaacttgaaa 1140

actccatggg aggtttgaac tttggccgat cttactttga tccagcatat tttagattag 1200

ggcaagagat ggtaaggagg tcagctggaa aggtcagttc cacattggca tctgaactcg 1260

gtatcactgc cgaggatgca aggcttgttt cagagattgc aatgcatact actgaggaca 1320

agatcagtag agcggttgga cccagacaag cccaagtatc atttctacac ggtgatcaaa 1380

gtgagaatga gctaccgaga ttgggggggca aggaagatag gagggtcaaa cagagtcgag 1440

gagaagccag ggagagctac agagaaaccg ggcccagcag agcaagtgat gcgagagctg 1500

cccatcttcc aaccggcaca cccctagaca ttgacactgc aacggagtcc agccaagatc 1560

cgcaggacag tcgaaggtca gctgacgccc tgcttaggct gcaagccatg gcaggaatct 1620

cggaagaaca aggctcagac acggacaccc ctatagtgta caatgacaga aatcttctag 1680

actaggtgcg agaggccgag ggccagaaca acatccgcct accatccatc attgttataa 1740

aaaacttagg aaccaggtcc acacagccgc cagcccatca accatccact cccacgattg 1800

gagccaatgg cagaagagca ggcacgccat gtcaaaaacg gactggaatg catccgggct 1860

-continued

ctcaaggccg agcccatcgg ctcactggcc atcgaggaag ctatggcagc atggtcagaa 1920

atatcagaca acccaggaca ggagcgagcc acctgcaggg aagagaaggc aggcagttcg 1980

ggtctcagca aaccatgcct ctcagcaatt ggatcaactg aaggcggtgc acctcgcatc 2040

cgcggtcagg gacctggaga gagcgatgac gacgctgaaa ctttgggaat ccccccaaga 2100

aatctccagg catcaagcac tgggttacag tgttattacg tttatgatca cagcggtgaa 2160

gcggttaagg gaatccaaga tgctgactct atcatggttc aatcaggcct tgatggtgat 2220

agcaccctct caggaggaga caatgaatct gaaaacagcg atgtggatat tggcgaacct 2280

gataccgagg gatatgctat cactgaccgg ggatctgctc ccatctctat ggggttcagg 2340

gcttctgatg ttgaaactgc agaaggaggg gagatccacg agctcctgag actccaatcc 2400

agaggcaaca actttccgaa gcttgggaaa actctcaatg ttcctccgcc cccggacccc 2460

ggtagggcca gcacttccgg gacacccatt aaaaagggca cagacgcgag attagcctca 2520

tttggaacgg agatcgcgtc tttattgaca ggtggtgcaa cccaatgtgc tcgaaagtca 2580

ccctcggaac catcagggcc aggtgcacct gcggggaatg tccccgagtg tgtgagcaat 2640

gccgcactga tacaggagtg gacacccgaa tctggtacca caatctcccc gagatcccag 2700

aataatgaag aaggggggaga ctattatgat gatgagctgt tctctgatgt ccaagatatt 2760

aaaacagcct tggccaaaat acacgaggat aatcagaaga taatctccaa gctagaatca 2820

ctgctgttat tgaagggaga agttgagtca attaagaagc agatcaacag gcaaaatatc 2880

agcatatcca ccctggaagg acacctctca agcatcatga tcgccattcc tggacttggg 2940

aaggatccca acgaccccac tgcagatgtc gaaatcaatc ccgacttgaa acccatcata 3000

ggcagagatt caggccgagc actggccgaa gttctcaaga aacccgttgc cagccgacaa 3060

ctccaaggaa tgacaaatgg acggaccagt tccagaggac agctgctgaa ggaatttcag 3120

ctaaagccga tcgggaaaaa gatgagctca gccgtcgggt ttgttcctga caccggccct 3180

gcatcacgca gtgtaatccg ctccattata aaatccagcc ggctagagga ggatcggaag 3240

cgttacctga tgactctcct tgatgatatc aaaggagcca atgatcttgc caagttccac 3300

cagatgctga tgaagataat aatgaagtag ctacagctca acttacctgc caaccccatg 3360

ccagtcgacc caactagcaa cctaaatcca ttataaaaaa cttaggaacc aggtccacac 3420

agctcgagtc gcgcgtggcc accatgtgtc ctcagaagct aaccatctcc tggtttgcca 3480

tcgttttgct ggtgtcccca ctcatggcca tgtgggagct ggagaaagac gtttatgttg 3540

tagaggtgga ctggactccc gatgcccctg gagaaacagt gaacctcacc tgtgacacgc 3600

ctgaagaaga tgacatcacc tggacctcag accagagaca tggagtcata ggctctggaa 3660

agaccctgac catcactgtc aaagagtttc tagatgctgg ccagtacacc tgccacaaag 3720

gaggcgagac tctgagccac tcacatctgc tgctccacaa gaaggaaaat ggaatttggt 3780

ccactgaaat tttaaaaaat ttcaaaaaca agactttcct gaagtgtgaa gcaccaaatt 3840

actccggacg gttcacgtgc tcatggctgg tgcaaagaaa catggacttg aagttcaaca 3900

tcaagagcag tagcagttcc cctgactctc gggcagtgac atgtggaatg gcgtctctgt 3960

ctgcagagaa ggtcacactg gaccaaaggg actatgagaa gtattcagtg tcctgccagg 4020

aggatgtcac ctgcccaact gccgaggaga ccctgcccat tgaactggcg ttggaagcac 4080

ggcagcagaa taaatatgag aactacagca ccagcttctt catcagggac atcatcaaac 4140

-continued

cagacccgcc caagaacttg cagatgaagc ctttgaagaa ctcacaggtg gaggtcagct 4200

gggagtaccc tgactcctgg agcactcccc attcctactt ctccctcaag ttctttgttc 4260

gaatccagcg caagaaagaa aagatgaagg agacagagga ggggtgtaac cagaaaggtg 4320

cgttcctcgt agagaagaca tctaccgaag tccaatgcaa aggcgggaat gtctgcgtgc 4380

aagctcagga tcgctattac aattcctcgt gcagcaagtg ggcatgtgtt ccctgcaggg 4440

tccgatccgg tggcggtggc tcgggcggtg gtgggtcggg tggcggcgga tctagggtca 4500

ttccagtctc tggacctgcc aggtgtctta gccagtcccg aaacctgctg aagaccacag 4560

atgacatggt gaagacggcc agagaaaaac tgaaacatta ttcctgcact gctgaagaca 4620

tcgatcatga agacatcaca cgggaccaaa ccagcacatt gaagacctgt ttaccactgg 4680

aactacacaa gaacgagagt tgcctggcta ctagagagac ttcttccaca acaagaggga 4740

gctgcctgcc cccacagaag acgtctttga tgatgaccct gtgccttggt agcatctatg 4800

aggacttgaa gatgtaccag acagagttcc aggccatcaa cgcagcactt cagaatcaca 4860

accatcagca gatcattcta gacaagggca tgctggtggc catcgatgag ctgatgcagt 4920

ctctgaatca taatggcgag actctgcgcc agaaacctcc tgtgggagaa gcagaccctt 4980

acagagtgaa aatgaagctc tgcatcctgc ttcacgcctt cagcacccgc gtcgtgacca 5040

tcaacagggt gatgggctat ctgagctccg cctgataatc gcgcgcgtgc tagtacaacc 5100

taaatccatt ataaaaaact taggagcaaa gtgattgcct cccaaggtcc acaatgacag 5160

agacctacga cttcgacaag tcggcatggg acatcaaagg gtcgatcgct ccgatacaac 5220

ccaccaccta cagtgatggc aggctggtgc cccaggtcag agtcatagat cctggtctag 5280

gcgacaggaa ggatgaatgc tttatgtaca tgtttctgct gggggttgtt gaggacagcg 5340

attccctagg gcctccaatc gggcgagcat ttgggttcct gcccttaggt gttggcagat 5400

ccacagcaaa gcccgaaaaa ctcctcaaag aggccactga gcttgacata gttgttagac 5460

gtacagcagg gctcaatgaa aaactggtgt tctacaacaa caccccacta actctcctca 5520

caccttggag aaaggtccta acaacaggga gtgtcttcaa cgcaaaccaa gtgtgcaatg 5580

cggttaatct gataccgctc gataccccgc agaggttccg tgttgtttat atgagcatca 5640

cccgtctttc ggataacggg tattacaccg ttcctagaag aatgctggaa ttcagatcgg 5700

tcaatgcagt ggccttcaac ctgctggtga cccttaggat tgacaaggcg ataggccctg 5760

ggaagatcat cgacaataca gagcaacttc ctgaggcaac atttatggtc cacatcggga 5820

acttcaggag aaagaagagt gaagtctact ctgccgatta ttgcaaaatg aaaatcgaaa 5880

agatgggcct ggtttttgca cttggtggga taggggcac cagtcttcac attagaagca 5940

caggcaaaat gagcaagact ctccatgcac aactcgggtt caagaagacc ttatgttacc 6000

cgctgatgga tatcaatgaa gaccttaatc gattactctg gaggagcaga tgcaagatag 6060

taagaatcca ggcagttttg cagccatcag ttcctcaaga attccgcatt tacgacgacg 6120

tgatcataaa tgatgaccaa ggactattca aagttctgta gaccgtagtg cccagcaatg 6180

cccgaaaacg acccccctca caatgacagc cagaaggccc ggacaaaaaa gccccctccg 6240

aaagactcca cggaccaagc gagaggccag ccagcagccg acggcaagcg cgaacaccag 6300

gcggccccag cacagaacag ccctgacaca aggccaccac cagccacccc aatctgcatc 6360

ctcctcgtgg gacccccgag gaccaacccc caaggctgcc cccgatccaa accaccaacc 6420

-continued

gcatccccac caccccgggg aaagaaaccc ccagcaattg gaaggcccct ccccctcttc 6480

ctcaacacaa gaactccaca accgaaccgc acaagcgacc gaggtgaccc aaccgcaggc 6540

atccgactcc ctagacagat cctctctccc cggcaaacta aacaaaactt agggccaagg 6600

aacatacaca cccaacagaa cccagacccc ggcccacggc gccgcgcccc caacccccga 6660

caaccagagg gagcccccaa ccaatcccgc cggctccccc ggtgcccaca ggcagggaca 6720

ccaacccccg aacagaccca gcacccaacc atcgacaatc caagacgggg gggccccccc 6780

aaaaaaaggc ccccaggggc cgacagccag caccgcgagg aagcccaccc accccacaca 6840

cgaccacggc aaccaaacca gaacccagac caccctgggc caccagctcc cagactcggc 6900

catcaccccg cagaaaggaa aggccacaac ccgcgcaccc cagccccgat ccggcgggga 6960

gccacccaac ccgaaccagc acccaagagc gatccccgaa ggacccccga accgcaaagg 7020

acatcagtat cccacagcct ctccaagtcc cccggtctcc tcctcttctc gaagggacca 7080

aaagatcaat ccaccacacc cgacgacact caactcccca cccctaaagg agacaccggg 7140

aatcccagaa tcaagactca tccaatgtcc atcatgggtc tcaaggtgaa cgtctctgcc 7200

atattcatgg cagtactgtt aactctccaa acacccaccg gtcaaatcca ttggggcaat 7260

ctctctaaga taggggtggt aggaatagga agtgcaagct acaaagttat gactcgttcc 7320

agccatcaat cattagtcat aaaattaatg cccaatataa ctctcctcaa taactgcacg 7380

agggtagaga ttgcagaata caggagacta ctgagaacag ttttggaacc aattagagat 7440

gcacttaatg caatgaccca gaatataaga ccggttcaga gtgtagcttc aagtaggaga 7500

cacaagagat ttgcgggagt agtcctggca ggtgcggccc taggcgttgc cacagctgct 7560

cagataacag ccggcattgc acttcaccag tccatgctga actctcaagc catcgacaat 7620

ctgagagcga gcctggaaac tactaatcag gcaattgaga caatcagaca agcagggcag 7680

gagatgatat tggctgttca gggtgtccaa gactacatca ataatgagct gataccgtct 7740

atgaaccaac tatcttgtga tttaatcggc cagaagctcg ggctcaaatt gctcagatac 7800

tatacagaaa tcctgtcatt atttggcccc agtttacggg accccatatc tgcggagata 7860

tctatccagg ctttgagcta tgcgcttgga ggagacatca ataaggtgtt agaaaagctc 7920

ggatacagtg gaggtgattt actgggcatc ttagagagcg gaggaataaa ggcccggata 7980

actcacgtcg acacagagtc ctacttcatt gtcctcagta tagcctatcc gacgctgtcc 8040

gagattaagg gggtgattgt ccaccggcta gagggggtct cgtacaacat aggctctcaa 8100

gagtggtata ccactgtgcc caagtatgtt gcaacccaag ggtaccttat ctcgaatttt 8160

gatgagtcat cgtgtacttt catgccagag gggactgtgt gcagccaaaa tgccttgtac 8220

ccgatgagtc ctctgctcca agaatgcctc cgggggtaca ccaagtcctg tgctcgtaca 8280

ctcgtatccg ggtcttttgg gaaccggttc attttatcac aagggaacct aatagccaat 8340

tgtgcatcaa tcctttgcaa gtgttacaca acaggaacga tcattaatca agaccctgac 8400

aagatcctaa catacattgc tgccgatcac tgcccggtag tcgaggtgaa cggcgtgacc 8460

atccaagtcg ggagcaggag gtatccagac gctgtgtact tgcacagaat tgacctcggt 8520

cctcccatat cattggagag gttggacgta gggacaaatc tggggaatgc aattgctaag 8580

ttggaggatg ccaaggaatt gttggagtca tcggaccaga tattgaggag tatgaaaggt 8640

ttatcgagca ctagcatagt ctacatcctg attgcagtgt gtcttggagg gttgataggg 8700

-continued

atccccgctt taatatgttg ctgcaggggg cgttgtaaca aaaagggaga acaagttggt 8760

atgtcaagac caggcctaaa gcctgatctt acgggaacat caaaatccta tgtaaggtcg 8820

ctctgatcct ctacaactct tgaaacacaa atgtcccaca agtctcctct tcgtcatcaa 8880

gcaaccaccg cacccagcat caagcccacc tgaaattatc tccggcttcc ctctggccga 8940

acaatatcgg tagttaatca aaacttaggg tgcaagatca tccacaatgt caccacaacg 9000

agaccggata aatgccttct acaaagataa cccccatccc aagggaagta ggatagtcat 9060

taacagagaa catcttatga ttgatagacc ttatgttttg ctggctgttc tgtttgtcat 9120

gtttctgagc ttgatcgggt tgctagccat tgcaggcatt agacttcatc gggcagccat 9180

ctacaccgca gagatccata aaagcctcag caccaatcta gatgtaacta actcaatcga 9240

gcatcaggtc aaggacgtgc tgacaccact cttcaaaatc atcggtgatg aagtgggcct 9300

gaggacacct cagagattca ctgacctagt gaaattaatc tctgacaaga ttaaattcct 9360

taatccggat agggagtacg acttcagaga tctcacttgg tgtatcaacc cgccagagag 9420

aatcaaattg gattatgatc aatactgtgc agatgtggct gctgaagagc tcatgaatgc 9480

attggtgaac tcaactctac tggagaccag aacaaccaat cagttcctag ctgtctcaaa 9540

gggaaactgc tcagggccca ctacaatcag aggtcaattc tcaaacatgt cgctgtccct 9600

gttagacttg tatttaggtc gaggttacaa tgtgtcatct atagtcacta tgacatccca 9660

gggaatgtat gggggaactt acctagtgga aaagcctaat ctgagcagca aaaggtcaga 9720

gttgtcacaa ctgagcatgt accgagtgtt tgaagtaggt gttatcagaa atccgggttt 9780

gggggctccg gtgttccata tgacaaacta tcttgagcaa ccagtcagta atgatctcag 9840

caactgtatg gtggctttgg gggagctcaa actcgcagcc ctttgtcacg gggaagattc 9900

tatcacaatt ccctatcagg gatcagggaa aggtgtcagc ttccagctcg tcaagctagg 9960

tgtctggaaa tccccaaccg acatgcaatc ctgggtcccc ttatcaacgg atgatccagt 10020

gatagacagg ctttacctct catctcacag aggtgttatc gctgacaatc aagcaaaatg 10080

ggctgtcccg acaacacgaa cagatgacaa gttgcgaatg gagacatgct tccaacaggc 10140

gtgtaagggt aaaatccaag cactctgcga gaatcccgag tgggcaccat tgaaggataa 10200

caggattcct tcatacgggg tcttgtctgt tgatctgagt ctgacagttg agcttaaaat 10260

caaaattgct tcgggattcg ggccattgat cacacacggt tcagggatgg acctatacaa 10320

atccaaccac aacaatgtgt attggctgac tatcccgcca atgaagaacc tagccttagg 10380

tgtaatcaac acattggagt ggataccgag attcaaggtt agtcccgcac tcttcactgt 10440

cccaattaag gaagcaggcg aagactgcca tgccccaaca tacctacctg cggaggtgga 10500

tggtgatgtc aaactcagtt ccaatctggt gattctacct ggtcaagatc tccaatatgt 10560

tttggcaacc tacgatactt ccgcggttga acatgctgtg gtttattacg tttacagccc 10620

aagccgccta tcgtcttact tttatccttt taggttgcct ataaaggggg tccccatcga 10680

attacaagtg gaatgcttca catgggacca aaaactctgg tgccgtcact tctgtgtgct 10740

tgcggactca gaatctggtg gacatatcac tcactctggg atggtgggca tgggagtcag 10800

ctgcacagtc acccgggaag atggaaccaa tgcggcccag ccggccatcg agggaaggat 10860

ggctcaggtt cagctggtcc agtcaggggc tgagctggtg aagcctgggg cctcagtgaa 10920

gatgtcctgc aaggcttctg gctacacatt taccagttac aatatgcact gggtaaagca 10980

-continued

gacacctgga cagggcctgg aatggattgg agctatttat ccaggaaatg gtgatacttc 11040

ctacaatcag aagttcaaag gcaaggccac attgactgca gacaaatcct ccagcacagc 11100

ctacatgcag ctcagcagcc tgacatctga ggactctgcg gtctattact gtgcaagagc 11160

gcaattacga cctaactact ggtacttcga tgtctggggc gcagggacca cggtcaccgt 11220

gagcaagatc tctggtggcg gtggctcggg cggtggtggg tcgggtggcg gaggctcggg 11280

tggctcgagc gacatcgtgc tgtcgcagtc tccagcaatc ctgtctgcat ctccagggga 11340

gaaggtcaca atgacttgca gggccagctc aagtgtaagt tacatgcact ggtaccagca 11400

gaagccagga tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt 11460

ccctgctcgc ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt 11520

ggaggctgaa gatgctgcca cttattactg ccagcagtgg attagtaacc cacccacgtt 11580

cggtgctggg accaagctgg agctgaaggc ggccgcaaga ggttctcatc accatcacca 11640

tcactaatag ggctgctagt gaaccaatca catgatgtca cccagacatc aggcataccc 11700

actagtgtga aatagacatc agaattaaga aaaacgtagg gtccaagtgg ttccccgtta 11760

tggactcgct atctgtcaac cagatcttat accctgaagt tcacctagat agcccgatag 11820

ttaccaataa gatagtagcc atcctggagt atgctcgagt ccctcacgct tacagcctgg 11880

aggaccctac actgtgtcag aacatcaagc accgcctaaa aaacggattt tccaaccaaa 11940

tgattataaa caatgtggaa gttgggaatg tcatcaagtc caagcttagg agttatccgg 12000

cccactctca tattccatat ccaaattgta atcaggattt atttaacata gaagacaaag 12060

agtcaacgag gaagatccgt gaactcctca aaaaggggaa ttcgctgtac tccaaagtca 12120

gtgataaggt tttccaatgc ttaagggaca ctaactcacg gcttggccta ggctccgaat 12180

tgagggagga catcaaggag aaagttatta acttgggagt ttacatgcac agctcccagt 12240

ggtttgagcc ctttctgttt tggtttacag tcaagactga gatgaggtca gtgattaaat 12300

cacaaaccca tacttgccat aggaggagac acacacctgt attcttcact ggtagttcag 12360

ttgagttgct aatctctcgt gaccttgttg ctataatcag taaagagtct caacatgtat 12420

attacctgac atttgaactg gttttgatgt attgtgatgt catagagggg aggttaatga 12480

cagagaccgc tatgactatt gatgctaggt atacagagct tctaggaaga gtcagataca 12540

tgtggaaact gatagatggt ttcttccctg cactcgggaa tccaacttat caaattgtag 12600

ccatgctgga gcctctttca cttgcttacc tgcagctgag ggatataaca gtagaactca 12660

gaggtgcttt ccttaaccac tgctttactg aaatacatga tgttcttgac caaaacgggt 12720

tttctgatga aggtacttat catgagttaa ctgaagctct agattacatt ttcataactg 12780

atgacataca tctgacaggg gagatttttct catttttcag aagtttcggc caccccagac 12840

ttgaagcagt aacggctgct gaaaatgtta ggaaatacat gaatcagcct aaagtcattg 12900

tgtatgagac tctgatgaaa ggtcatgcca tattttgtgg aatcataatc aacggctatc 12960

gtgacaggca cggaggcagt tggccaccgc tgaccctccc cctgcatgct gcagacacaa 13020

tccggaatgc tcaagcttca ggtgaagggt taacacatga gcagtgcgtt gataactgga 13080

aatcttttgc tggagtgaaa tttggctgct ttatgcctct tagcctggat agtgatctga 13140

caatgtacct aaaggacaag gcacttgctg ctctccaaag ggaatgggat tcagtttacc 13200

cgaaagagtt cctgcgttac gaccctccca agggaaccgg gtcacggagg cttgtagatg 13260

-continued

ttttccttaa tgattcgagc tttgacccat atgatgtgat aatgtatgtt gtaagtggag 13320

cttacctcca tgaccctgag ttcaacctgt cttacagcct gaaagaaaag gagatcaagg 13380

aaacaggtag acttttgct aaaatgactt acaaaatgag ggcatgccaa gtgattgctg 13440

aaaatctaat ctcaaacggg attggcaaat attttaagga caatgggatg gccaaggatg 13500

agcacgattt gactaaggca ctccacactc tagctgtctc aggagtcccc aaagatctca 13560

aagaaagtca caggggggg ccagtcttaa aaacctactc ccgaagccca gtccacacaa 13620

gtaccaggaa cgtgagagca gcaaaagggt ttatagggtt ccctcaagta attcggcagg 13680

accaagacac tgatcatccg gagaatatgg aagcttacga gacagtcagt gcatttatca 13740

cgactgatct caagaagtac tgccttaatt ggagatatga gaccatcagc ttgtttgcac 13800

agaggctaaa tgagatttac ggattgccct catttttcca gtggctgcat aagaggcttg 13860

agacctctgt cctgtatgta agtgaccctc attgcccccc cgaccttgac gcccatatcc 13920

cgttatataa agtccccaat gatcaaatct tcattaagta ccctatggga ggtatagaag 13980

ggtattgtca gaagctgtgg accatcagca ccattcccta tctatacctg gctgcttatg 14040

agagcggagt aaggattgct tcgttagtgc aaggggacaa tcagaccata gccgtaacaa 14100

aaagggtacc cagcacatgg ccctacaacc ttaagaaacg ggaagctgct agagtaacta 14160

gagattactt tgtaattctt aggcaaaggc tacatgatat tggccatcac ctcaaggcaa 14220

atgagacaat tgtttcatca catttttttg tctattcaaa aggaatatat tatgatgggc 14280

tacttgtgtc ccaatcactc aagagcatcg caagatgtgt attctggtca gagactatag 14340

ttgatgaaac aagggcagca tgcagtaata ttgctacaac aatggctaaa agcatcgaga 14400

gaggttatga ccgttacctt gcatattccc tgaacgtcct aaaagtgata cagcaaattc 14460

tgatctctct tggcttcaca atcaattcaa ccatgacccg ggatgtagtc ataccctcc 14520

tcacaaacaa cgacctctta ataaggatgg cactgttgcc cgctcctatt ggggggatga 14580

attatctgaa tatgagcagg ctgtttgtca gaaacatcgg tgatccagta acatcatcaa 14640

ttgctgatct caagagaatg attctcgcct cactaatgcc tgaagagacc ctccatcaag 14700

taatgacaca acaaccgggg gactcttcat tcctagactg ggctagcgac ccttactcag 14760

caaatcttgt atgtgtccag agcatcacta gactcctcaa gaacataact gcaaggtttg 14820

tcctgatcca tagtccaaac ccaatgttaa aaggattatt ccatgatgac agtaaagaag 14880

aggacgaggg actggcggca ttcctcatgg acaggcatat tatagtacct agggcagctc 14940

atgaaatcct ggatcatagt gtcacagggg caagagagtc tattgcaggc atgctggata 15000

ccacaaaagg cttgattcga gccagcatga ggaaggggggg gttaacctct cgagtgataa 15060

ccagattgtc caattatgac tatgaacaat tcagagcagg gatggtgcta ttgacaggaa 15120

gaaagagaaa tgtcctcatt gacaaagagt catgttcagt gcagctggcg agagctctaa 15180

gaagccatat gtgggcgagg ctagctcgag gacggcctat ttacggcctt gaggtccctg 15240

atgtactaga atctatgcga ggccacctta ttcggcgtca tgagacatgt gtcatctgcg 15300

agtgtggatc agtcaactac ggatggtttt ttgtcccctc gggttgccaa ctggatgata 15360

ttgacaagga aacatcatcc ttgagagtcc catatattgg ttctaccact gatgagagaa 15420

cagacatgaa gcttgccttc gtaagagccc caagtcgatc cttgcgatct gctgttagaa 15480

tagcaacagt gtactcatgg gcttacggtg atgatgatag ctcttggaac gaagcctggt 15540

-continued

tgttggctag gcaaagggcc aatgtgagcc tggaggagct aagggtgatc actcccatct 15600

caacttcgac taatttagcg cataggttga gggatcgtag cactcaagtg aaatactcag 15660

gtacatccct tgtccgagtg gcgaggtata ccacaatctc caacgacaat ctctcatttg 15720

tcatatcaga taagaaggtt gatactaact ttatatacca acaaggaatg cttctagggt 15780

tgggtgtttt agaaacattg tttcgactcg agaaagatac cggatcatct aacacggtat 15840

tacatcttca cgtcgaaaca gattgttgcg tgatcccgat gatagatcat cccaggatac 15900

ccagctcccg caagctagag ctgagggcag agctatgtac caacccattg atatatgata 15960

atgcaccttt aattgacaga gatgcaacaa ggctatacac ccagagccat aggaggcacc 16020

ttgtggaatt tgttacatgg tccacacccc aactatatca cattttagct aagtccacag 16080

cactatctat gattgacctg gtaacaaaat ttgagaagga ccatatgaat gaaatttcag 16140

ctctcatagg ggatgacgat atcaatagtt tcataactga gtttctgctc atagagccaa 16200

gattattcac tatctacttg ggccagtgtg cggccatcaa ttgggcattt gatgtacatt 16260

atcatagacc atcagggaaa tatcagatgg gtgagctgtt gtcatcgttc ctttctagaa 16320

tgagcaaagg agtgtttaag gtgcttgtca atgctctaag ccacccaaag atctacaaga 16380

aattctggca ttgtggtatt atagagccta tccatggtcc ttcacttgat gctcaaaact 16440

tgcacacaac tgtgtgcaac atggtttaca catgctatat gacctacctc gacctgttgt 16500

tgaatgaaga gttagaagag ttcacatttc tcttgtgtga aagcgacgag gatgtagtac 16560

cggacagatt cgacaacatc caggcaaaac acttatgtgt tctggcagat ttgtactgtc 16620

aaccagggac ctgcccacca attcgaggtc taagaccggt agagaaatgt gcagttctaa 16680

ccgaccatat caaggcagag gctatgttat ctccagcagg atcttcgtgg aacataaatc 16740

caattattgt agaccattac tcatgctctc tgacttatct ccggcgagga tcgatcaaac 16800

agataagatt gagagttgat ccaggattca ttttcgacgc cctcgctgag gtaaatgtca 16860

gtcagccaaa gatcggcagc aacaacatct caaatatgag catcaaggct ttcagacccc 16920

cacacgatga tgttgcaaaa ttgctcaaag atatcaacac aagcaagcac aatcttccca 16980

tttcaggggg caatctcgcc aattatgaaa tccatgcttt ccgcagaatc gggttgaact 17040

catctgcttg ctacaaagct gttgagatat caacattaat taggagatgc cttgagccag 17100

gggaggacgg cttgttcttg ggtgagggat cgggttctat gttgatcact tataaagaga 17160

tacttaaact aaacaagtgc ttctataata gtggggtttc cgccaattct agatctggtc 17220

aaagggaatt agcaccctat ccctccgaag ttggccttgt cgaacacaga atgggagtag 17280

gtaatattgt caaagtgctc tttaacggga ggcccgaagt cacgtgggta ggcagtgtag 17340

attgcttcaa tttcatagtt agtaatatcc ctacctctag tgtggggttt atccattcag 17400

atatagagac cttgcctgac aaagatacta tagagaagct agaggaattg gcagccatct 17460

tatcgatggc tctgctcctg ggcaaaatag gatcaatact ggtgattaag cttatgcctt 17520

tcagcgggga ttttgttcag ggatttataa gttatgtagg gtctcattat agagaagtga 17580

accttgtata ccctagatac agcaacttca tctctactga atcttatttg gttatgacag 17640

atctcaaggc taaccggcta atgaatcctg aaaagattaa gcagcagata attgaatcat 17700

ctgtgaggac ttcacctgga cttataggtc acatcctatc cattaagcaa ctaagctgca 17760

tacaagcaat tgtgggagac gcagttagta gaggtgatat caatcctact ctgaaaaaac 17820

-continued

ttacacctat agagcaggtg ctgatcaatt gcgggttggc aattaacgga cctaagctgt 17880

gcaaagaatt gatccaccat gatgttgcct cagggcaaga tggattgctt aattctatac 17940

tcatcctcta cagggagttg gcaagattca aagacaacca aagaagtcaa caagggatgt 18000

tccacgctta ccccgtattg gtaagtagca ggcaacgaga acttatatct aggatcaccc 18060

gcaaattctg ggggcacatt cttctttact ccgggaacaa aaagttgata aataagttta 18120

tccagaatct caagtccggc tatctgatac tagacttaca ccagaatatc ttcgttaaga 18180

atctatccaa gtcagagaaa cagattatta tgacgggggg tttgaaacgt gagtgggttt 18240

ttaaggtaac agtcaaggag accaaagaat ggtataagtt agtcggatac agtgccctga 18300

ttaaggacta attggttgaa ctccggaacc ctaatcctgc cctaggtggt taggcattat 18360

ttgcaatata ttaaagaaaa ctttgaaaat acgaagtttc tattcccagc tttgtctggt 18420

<210> SEQ ID NO 8
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: linker sequence

<400> SEQUENCE: 8

ggggsggggs ggggs 15

<210> SEQ ID NO 9
<211> LENGTH: 7
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial linker sequence

<400> SEQUENCE: 9

ggggggs 7

<210> SEQ ID NO 10
<211> LENGTH: 543
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: FmIL-12 fusion polypeptide

<400> SEQUENCE: 10

Met Cys Pro Gln Lys Leu Thr Ile Ser Trp Phe Ala Ile Val Leu Leu
1 5 10 15

Val Ser Pro Leu Met Ala Met Trp Glu Leu Glu Lys Asp Val Tyr Val
20 25 30

Val Glu Val Asp Trp Thr Pro Asp Ala Pro Gly Glu Thr Val Asn Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Asp Ile Thr Trp Thr Ser Asp Gln
50 55 60

Arg His Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile Thr Val Lys
65 70 75 80

Glu Phe Leu Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Thr
85 90 95

Leu Ser His Ser His Leu Leu Leu His Lys Lys Glu Asn Gly Ile Trp
100 105 110

-continued

```
Ser Thr Glu Ile Leu Lys Asn Phe Lys Asn Lys Thr Phe Leu Lys Cys
        115                 120                 125

Glu Ala Pro Asn Tyr Ser Gly Arg Phe Thr Cys Ser Trp Leu Val Gln
    130                 135                 140

Arg Asn Met Asp Leu Lys Phe Asn Ile Lys Ser Ser Ser Ser Ser Pro
145                 150                 155                 160

Asp Ser Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser Ala Glu Lys
                165                 170                 175

Val Thr Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val Ser Cys Gln
            180                 185                 190

Glu Asp Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro Ile Glu Leu
        195                 200                 205

Ala Leu Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr Ser Thr Ser
    210                 215                 220

Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln
225                 230                 235                 240

Met Lys Pro Leu Lys Asn Ser Gln Val Glu Val Ser Trp Glu Tyr Pro
                245                 250                 255

Asp Ser Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Lys Phe Phe Val
            260                 265                 270

Arg Ile Gln Arg Lys Lys Glu Lys Met Lys Glu Thr Glu Glu Gly Cys
        275                 280                 285

Asn Gln Lys Gly Ala Phe Leu Val Glu Lys Thr Ser Thr Glu Val Gln
    290                 295                 300

Cys Lys Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg Tyr Tyr Asn
305                 310                 315                 320

Ser Ser Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val Arg Ser Gly
                325                 330                 335

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Val
            340                 345                 350

Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser Arg Asn Leu
        355                 360                 365

Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu Lys Leu Lys
    370                 375                 380

His Tyr Ser Cys Thr Ala Glu Asp Ile Asp His Glu Asp Ile Thr Arg
385                 390                 395                 400

Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu Leu His Lys
                405                 410                 415

Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr Thr Arg Gly
            420                 425                 430

Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr Leu Cys Leu
        435                 440                 445

Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu Phe Gln Ala
    450                 455                 460

Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile Ile Leu Asp
465                 470                 475                 480

Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser Leu Asn His
                485                 490                 495

Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu Ala Asp Pro
            500                 505                 510

Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala Phe Ser Thr
```

-continued

515 520 525

Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser Ser Ala
530 535 540

<210> SEQ ID NO 11
<211> LENGTH: 1632
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: FmIL-12 fusion polypeptide coding sequence

<400> SEQUENCE: 11

atgtgtcctc agaagctaac catctcctgg tttgccatcg ttttgctggt gtccccactc 60

atggccatgt gggagctgga gaaagacgtt tatgttgtag aggtggactg gactcccgat 120

gcccctggag aaacagtgaa cctcacctgt gacacgcctg aagaagatga catcacctgg 180

acctcagacc agagacatgg agtcataggc tctggaaaga ccctgaccat cactgtcaaa 240

gagtttctag atgctggcca gtacacctgc cacaaaggag gcgagactct gagccactca 300

catctgctgc tccacaagaa ggaaaatgga atttggtcca ctgaaatttt aaaaaatttc 360

aaaaacaaga ctttcctgaa gtgtgaagca ccaaattact ccggacggtt cacgtgctca 420

tggctggtgc aaagaaacat ggacttgaag ttcaacatca agagcagtag cagttcccct 480

gactctcggg cagtgacatg tggaatggcg tctctgtctg cagagaaggt cacactggac 540

caaagggact atgagaagta ttcagtgtcc tgccaggagg atgtcacctg cccaactgcc 600

gaggagaccc tgcccattga actggcgttg gaagcacggc agcagaataa atatgagaac 660

tacagcacca gcttcttcat cagggacatc atcaaaccag acccgcccaa gaacttgcag 720

atgaagcctt tgaagaactc acaggtggag gtcagctggg agtaccctga ctcctggagc 780

actccccatt cctacttctc cctcaagttc tttgttcgaa tccagcgcaa gaaagaaaag 840

atgaaggaga cagaggaggg gtgtaaccag aaaggtgcgt tcctcgtaga gaagacatct 900

accgaagtcc aatgcaaagg cgggaatgtc tgcgtgcaag ctcaggatcg ctattacaat 960

tcctcgtgca gcaagtgggc atgtgttccc tgcagggtcc gatccggtgg cggtggctcg 1020

ggcggtggtg ggtcgggtgg cggcggatcc agggtcattc cagtctctgg acctgccagg 1080

tgtcttagcc agtcccgaaa cctgctgaag accacagatg acatggtgaa gacggccaga 1140

gaaaaactga aacattattc ctgcactgct gaagacatcg atcatgaaga catcacacgg 1200

gaccaaacca gcacattgaa gacctgttta ccactggaac tacacaagaa cgagagttgc 1260

ctggctacta gagagacttc ttccacaaca agagggagct gcctgccccc acagaagacg 1320

tctttgatga tgaccctgtg ccttggtagc atctatgagg acttgaagat gtaccagaca 1380

gagttccagg ccatcaacgc agcacttcag aatcacaacc atcagcagat cattctagac 1440

aagggcatgc tggtggccat cgatgagctg atgcagtctc tgaatcataa tggcgagact 1500

ctgcgccaga aacctcctgt gggagaagca gacccttaca gagtgaaaat gaagctctgc 1560

atcctgcttc acgccttcag cacccgcgtc gtgaccatca acagggtgat gggctatctg 1620

agctccgcct ga 1632

<210> SEQ ID NO 12
<211> LENGTH: 532
<212> TYPE: PRT
<213> ORGANISM: Artificial

-continued

<220> FEATURE:
<223> OTHER INFORMATION: FhIL-12 fusion polypeptide

<400> SEQUENCE: 12

Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
165 170 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Asn Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Gly Gly Ser Arg
325 330 335

Asn Leu Pro Val Ala Thr Pro Asp Pro Gly Met Phe Pro Cys Leu His
340 345 350

His Ser Gln Asn Leu Leu Arg Ala Val Ser Asn Met Leu Gln Lys Ala
355 360 365

Arg Gln Thr Leu Glu Phe Tyr Pro Cys Thr Ser Glu Glu Ile Asp His
370 375 380

-continued

```
Glu Asp Ile Thr Lys Asp Lys Thr Ser Thr Val Glu Ala Cys Leu Pro
385                 390                 395                 400

Leu Glu Leu Thr Lys Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr Ser
                405                 410                 415

Phe Ile Thr Asn Gly Ser Cys Leu Ala Ser Arg Lys Thr Ser Phe Met
            420                 425                 430

Met Ala Leu Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln
        435                 440                 445

Val Glu Phe Lys Thr Met Asn Ala Lys Leu Leu Met Asp Pro Lys Arg
    450                 455                 460

Gln Ile Phe Leu Asp Gln Asn Met Leu Ala Val Ile Asp Glu Leu Met
465                 470                 475                 480

Gln Ala Leu Asn Phe Asn Ser Glu Thr Val Pro Gln Lys Ser Ser Leu
                485                 490                 495

Glu Glu Pro Asp Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile Leu Leu
            500                 505                 510

His Ala Phe Arg Ile Arg Ala Val Thr Ile Asp Arg Val Met Ser Tyr
        515                 520                 525

Leu Asn Ala Ser
    530


<210> SEQ ID NO 13
<211> LENGTH: 1599
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: FhIL-12 fusion polypeptide encoding sequence

<400> SEQUENCE: 13

atgtgtcacc agcagttggt catctcttgg ttttccctgg tttttctggc atctcccctc     60

gtggccatat gggaactgaa gaaagatgtt tatgtcgtag aattggattg gtatccggat    120

gcccctggag aaatggtggt cctcacctgt gacacccctg aagaagatgg tatcacctgg    180

accttggacc agagcagtga ggtcttaggc tctggcaaaa ccctgaccat ccaagtcaaa    240

gagtttggag atgctggcca gtacacctgt cacaaaggag gcgaggttct aagccattcg    300

ctcctgctgc ttcacaaaaa ggaagatgga atttggtcca ctgatatttt aaaggaccag    360

aaagaaccca aaaataagac ctttctaaga tgcgaggcca agaattattc tggacgtttc    420

acctgctggt ggctgacgac aatcagtact gatttgacat tcagtgtcaa aagcagcaga    480

ggctcttctg acccccaagg ggtgacgtgc ggagctgcta cactctctgc agagagagtc    540

agaggggaca acaaggagta tgagtactca gtggagtgcc aggaggacag tgcctgccca    600

gctgctgagg agagtctgcc cattgaggtc atggtggatg ccgttcacaa gctcaagtat    660

gaaaactaca ccagcagctt cttcatcagg gacatcatca aacctgaccc acccaacaac    720

ttgcagctga agccattaaa gaattctcgg caggtggagg tcagctggga gtaccctgac    780

acctggagta ctccacattc ctacttctcc ctgacattct gcgttcaggt ccagggcaag    840

agcaagagag aaaagaaaga tagagtcttc accgacaaga cctcagccac ggtcatctgc    900

cgcaaaaatg ccagcattag cgtgcgggcc caggaccgct actatagctc atcttggagc    960

gaatgggcat ctgtgccctg cagtggtggc ggtggcggcg gatctagaaa cctccccgtg   1020

gccactccag acccaggaat gttcccatgc cttcaccact cccaaaacct gctgagggcc   1080
```

-continued

gtcagcaaca tgctccagaa ggccagacaa actctagaat tttacccttg cacttctgaa 1140

gagattgatc atgaagatat cacaaaagat aaaaccagca cagtggaggc ctgtttacca 1200

ttggaattaa ccaagaatga gagttgccta aattccagag agacctcttt cataactaat 1260

gggagttgcc tggcctccag aaagacctct tttatgatgg ccctgtgcct tagtagtatt 1320

tatgaagact tgaagatgta ccaggtggag ttcaagacca tgaatgcaaa gcttctgatg 1380

gatcctaaga ggcagatctt tctagatcaa aacatgctgg cagttattga tgagctgatg 1440

caggccctga atttcaacag tgagactgtg ccacaaaaat cctcccttga agaaccggat 1500

ttttataaaa ctaaaatcaa gctctgcata cttcttcatg ctttcagaat tcgggcagtg 1560

actattgata gagtgatgag ctatctgaat gcttcctag 1599

<210> SEQ ID NO 14
<211> LENGTH: 17628
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial polynucleotide encoding Edmonston B MV encoding a murine IL12 fusion protein

<400> SEQUENCE: 14

accaaacaaa gttgggtaag gatagttcaa tcaatgatca tcttctagtg cacttaggat 60

tcaagatcct attatcaggg acaagagcag gattagggat atccgagatg gccacacttt 120

taaggagctt agcattgttc aaaagaaaca aggacaaacc acccattaca tcaggatccg 180

gtggagccat cagaggaatc aaacacatta ttatagtacc aatccctgga gattcctcaa 240

ttaccactcg atccagactt ctggaccggt tggtcaggtt aattggaaac ccggatgtga 300

gcgggcccaa actaacaggg gcactaatag gtatattatc cttatttgtg gagtctccag 360

gtcaattgat tcagaggatc accgatgacc ctgacgttag cataaggctg ttagaggttg 420

tccagagtga ccagtcacaa tctggcctta ccttcgcatc aagaggtacc aacatggagg 480

atgaggcgga ccaatacttt tcacatgatg atccaattag tagtgatcaa tccaggttcg 540

gatggttcga gaacaaggaa atctcagata ttgaagtgca agaccctgag ggattcaaca 600

tgattctggg taccatccta gcccaaattt gggtcttgct cgcaaaggcg gttacggccc 660

cagacacggc agctgattcg gagctaagaa ggtggataaa gtacacccaa caaagaaggg 720

tagttggtga atttagattg gagagaaaat ggttggatgt ggtgaggaac aggattgccg 780

aggacctctc cttacgccga ttcatggtcg ctctaatcct ggacatcaag agaacacccg 840

gaaacaaacc caggattgct gaaatgatat gtgacattga tacatatatc gtagaggcag 900

gattagccag ttttatcctg actattaagt ttgggataga aactatgtat cctgctcttg 960

gactgcatga atttgctggt gagttatcca cacttgagtc cttgatgaac ctttaccagc 1020

aaatggggga aactgcaccc tacatggtaa tcctggagaa ctcaattcag aacaagttca 1080

gtgcaggatc ataccctctg ctctggagct atgccatggg agtaggagtg gaacttgaaa 1140

actccatggg aggtttgaac tttggccgat cttactttga tccagcatat tttagattag 1200

ggcaagagat ggtaaggagg tcagctggaa aggtcagttc cacattggca tctgaactcg 1260

gtatcactgc cgaggatgca aggcttgttt cagagattgc aatgcatact actgaggaca 1320

agatcagtag agcggttgga cccagacaag cccaagtatc atttctacac ggtgatcaaa 1380

-continued

gtgagaatga gctaccgaga ttgggggggca aggaagatag gagggtcaaa cagagtcgag 1440

gagaagccag ggagagctac agagaaaccg ggcccagcag agcaagtgat gcgagagctg 1500

cccatcttcc aaccggcaca cccctagaca ttgacactgc atcggagtcc agccaagatc 1560

cgcaggacag tcgaaggtca gctgacgccc tgcttaggct gcaagccatg gcaggaatct 1620

cggaagaaca aggctcagac acggacaccc ctatagtgta caatgacaga aatcttctag 1680

actaggtgcg agaggccgag gaccagaaca acatccgcct accctccatc attgttataa 1740

aaaacttagg aaccaggtcc acacagccgc cagcccatca accatccact cccacgattg 1800

gagcagatgg cagaagagca ggcacgccat gtcaaaaacg gactggaatg catccgggct 1860

ctcaaggccg agcccatcgg ctcactggcc atcgaggaag ctatggcagc atggtcagaa 1920

atatcagaca acccaggaca ggagcgagcc acctgcaggg aagagaaggc aggcagttcg 1980

ggtctcagca aaccatgcct ctcagcaatt ggatcaactg aaggcggtgc acctcgcatc 2040

cgcggtcagg gacctggaga gagcgatgac gacgctgaaa ctttgggaat ccccccaaga 2100

aatctccagg catcaagcac tgggctacag tgtcattatg tttatgatca cagcggtgaa 2160

gcggttaagg gaatccaaga tgctgactct atcatggttc aatcaggcct tgatggtgat 2220

agcaccctct caggaggaga caatgaatct gaaaacagcg atgtggatat tggcgaacct 2280

gataccgagg gatatgctat cactgaccgg ggatctgctc ccatctctat ggggttcagg 2340

gcttctgatg ttgaaactgc agaaggaggg gagatccacg agctcctgag actccaatcc 2400

agaggcaaca actttccgaa gcttgggaaa actctcaatg ttcctccgcc cccggacccc 2460

ggtagggcca gcacttccgg gacacccatt aaaaagggca cagacgcgag attagcctca 2520

tttggaacgg agatcgcgtc ttcattgaca ggtggtgcaa cccaatgtgc tcgaaagtca 2580

ccctcggaac catcagggcc aggtgcacct gcggggaacg tccccgagtg tgtgagcaat 2640

gccgcactga tacaggagtg gacacccgaa tctggcacca caatctcccc gagatcccag 2700

aataatgaag aaggggggaga ccattatgat gatgagctgt tctctgatgt ccaagatatt 2760

aaaacagcct tggccaaaat acacgaggat aatcagaaga taatctccaa gctagaatca 2820

ctgctgttat tgaagggaga agttgagtca attaagaagc agatcaacag gcaaaatatc 2880

agcatatcca ccctggaagg acacctctca agcatcatga tcgccattcc tggacttggg 2940

aaggatccca acgaccccac tgcagatgtc gaaatcaatc ccgacttgaa acccatcata 3000

ggcagagatt caggccgagc actggccgaa gttctcaaga aacccgttgc cagccgacaa 3060

ctccaaggaa tgacaaatgg acggaccagt tccagaggac agctgctgaa ggaatttcag 3120

ctaaagccga tcgggaaaaa gatgagctca gccgtcgggt ttgttcctga caccggccct 3180

gcatcacgca gtgtaatccg ctccattata aaatccagcc ggctagagga ggatcggaag 3240

cgttacctga tgactctcct tgatgatatc aaaggagcca atgatcttgc caagttccac 3300

cagatgctgg tgaagataat aatgaagtag ctacagctca acttacctgc caaccccatg 3360

ccagtcgacc caactagcgt acacaaccta aatccattat aaaaaactta ggaaccaggt 3420

ccacacactc gagtcgcgcg tggccaccat gtgtcctcag aagctaacca tctcctggtt 3480

tgccatcgtt ttgctggtgt ccccactcat ggccatgtgg gagctggaga aagacgttta 3540

tgttgtagag gtggactgga ctcccgatgc ccctggagaa acagtgaacc tcacctgtga 3600

cacgcctgaa gaagatgaca tcacctggac ctcagaccag agacatggag tcataggctc 3660

-continued

tggaaagacc ctgaccatca ctgtcaaaga gtttctagat gctggccagt acacctgcca 3720

caaaggaggc gagactctga gccactcaca tctgctgctc cacaagaagg aaaatggaat 3780

ttggtccact gaaatttaa aaaatttcaa aaacaagact ttcctgaagt gtgaagcacc 3840

aaattactcc ggacggttca cgtgctcatg gctggtgcaa agaaacatgg acttgaagtt 3900

caacatcaag agcagtagca gttcccctga ctctcgggca gtgacatgtg gaatggcgtc 3960

tctgtctgca gagaaggtca cactggacca aagggactat gagaagtatt cagtgtcctg 4020

ccaggaggat gtcacctgcc caactgccga ggagaccctg cccattgaac tggcgttgga 4080

agcacggcag cagaataaat atgagaacta cagcaccagc ttcttcatca gggacatcat 4140

caaaccagac ccgcccaaga acttgcagat gaagcctttg aagaactcac aggtggaggt 4200

cagctgggag taccctgact cctggagcac tccccattcc tacttctccc tcaagttctt 4260

tgttcgaatc cagcgcaaga aagaaaagat gaaggagaca gaggaggggt gtaaccagaa 4320

aggtgcgttc ctcgtagaga agacatctac cgaagtccaa tgcaaaggcg ggaatgtctg 4380

cgtgcaagct caggatcgct attacaattc ctcgtgcagc aagtgggcat gtgttccctg 4440

cagggtccga tccggtggcg gtggctcggg cggtggtggg tcgggtggcg gcggatccag 4500

ggtcattcca gtctctggac ctgccaggtg tcttagccag tcccgaaacc tgctgaagac 4560

cacagatgac atggtgaaga cggccagaga aaaactgaaa cattattcct gcactgctga 4620

agacatcgat catgaagaca tcacacggga ccaaaccagc acattgaaga cctgtttacc 4680

actggaacta cacaagaacg agagttgcct ggctactaga gagacttctt ccacaacaag 4740

agggagctgc ctgcccccac agaagacgtc tttgatgatg accctgtgcc ttggtagcat 4800

ctatgaggac ttgaagatgt accagacaga gttccaggcc atcaacgcag cacttcagaa 4860

tcacaaccat cagcagatca ttctagacaa gggcatgctg gtggccatcg atgagctgat 4920

gcagtctctg aatcataatg gcgagactct gcgccagaaa cctcctgtgg gagaagcaga 4980

cccttacaga gtgaaaatga agctctgcat cctgcttcac gccttcagca cccgcgtcgt 5040

gaccatcaac agggtgatgg gctatctgag ctccgcctga taatagcgcg cgtcgtacga 5100

tgacgtccta gtacaaccta aatccattat aaaaaactta ggagcaaagt gattgcctcc 5160

caagttccac aatgacagag atctacgact tcgacaagtc ggcatgggac atcaaagggt 5220

cgatcgctcc gatacaaccc accacctaca gtgatggcag gctggtgccc caggtcagag 5280

tcatagatcc tggtctaggc gacaggaagg atgaatgctt tatgtacatg tttctgctgg 5340

gggttgttga ggacagcgat tccctagggc ctccaatcgg gcgagcattt gggtccctgc 5400

ccttaggtgt tggcagatcc acagcaaagc ccgaaaaact cctcaaagag gccactgagc 5460

ttgacatagt tgttagacgt acagcagggc tcaatgaaaa actggtgttc tacaacaaca 5520

ccccactaac tctcctcaca ccttggagaa aggtcctaac aacagggagt gtcttcaacg 5580

caaaccaagt gtgcaatgcg gttaatctga taccgctcga taccccgcag aggttccgtg 5640

ttgtttatat gagcatcacc cgtctttcgg ataacgggta ttacaccgtt cctggaagaa 5700

tgctggaatt cagatcggtc aatgcagtgg ccttcaacct gctggtgacc cttaggattg 5760

acaaggcgat aggccctggg aagatcatcg acaatacaga gcaacttcct gaggcaacat 5820

ttatggtcca catcgggaac ttcaggagaa agaagagtga agtctactct gccgattatt 5880

gcaaaatgaa aatcgaaaag atgggcctgg tttttgcact tggtgggata gggggcacca 5940

-continued

gtcttcacat tagaagcaca ggcaaaatga gcaagactct ccatgcacaa ctcgggttca 6000

agaagacctt atgttacccg ctgatggata tcaatgaaga ccttaatcga ttactctgga 6060

ggagcagatg caagatagta agaatccagg cagttttgca gccatcagtt cctcaagaat 6120

tccgcattta cgacgacgtg atcataaatg atgaccaagg actattcaaa gttctgtaga 6180

ccgtagtgcc cagcaatgcc cgaaaacgac ccccctcaca atgacagcca gaaggcccgg 6240

acaaaaaagc cccctccgaa agactccacg gaccaagcga gaggccagcc agcagccgac 6300

ggcaagcgcg aacaccaggc ggccccagca cagaacagcc ctgacacaag gccaccacca 6360

gccaccccaa tctgcatcct cctcgtggga cccccgagga ccaaccccca aggctgcccc 6420

cgatccaaac caccaaccgc atccccacca cccccgggaa agaaaccccc agcaattgga 6480

aggcccctcc ccctcttcct caacacaaga actccacaac cgaaccgcac aagcgaccga 6540

ggtgacccaa ccgcaggcat ccgactccct agacagatcc tctctccccg gcaaactaaa 6600

caaaacttag ggccaaggaa catacacacc caacagaacc cagaccccgg cccacggcgc 6660

cgcgccccca acccccgaca accagaggga gcccccaacc aatcccgccg gctcccccgg 6720

tgcccacagg cagggacacc aacccccgaa cagacccagc acccaaccat cgacaatcca 6780

agacgggggg gccccccaa aaaaaggccc ccaggggccg acagccagca ccgcgaggaa 6840

gcccacccac cccacacacg accacggcaa ccaaaccaga acccagacca ccctgggcca 6900

ccagctccca gactcggcca tcaccccgca gaaaggaaag gccacaaccc gcgcacccca 6960

gccccgatcc ggcggggagc cacccaaccc gaaccagcac ccaagagcga tccccgaagg 7020

acccccgaac cgcaaaggac atcagtatcc cacagcctct ccaagtcccc cggtctcctc 7080

ctcttctcga agggaccaaa agatcaatcc accacacccg acgacactca actccccacc 7140

cctaaaggag acaccgggaa tcccagaatc aagactcatc caatgtccat catgggtctc 7200

aaggtgaacg tctctgccat attcatggca gtactgttaa ctctccaaac acccaccggt 7260

caaatccatt ggggcaatct ctctaagata ggggtggtag gaataggaag tgcaagctac 7320

aaagttatga ctcgttccag ccatcaatca ttagtcataa aattaatgcc caatataact 7380

ctcctcaata actgcacgag ggtagagatt gcagaataca ggagactact gagaacagtt 7440

ttggaaccaa ttagagatgc acttaatgca gtgacccaga atataagacc ggttcagagt 7500

gtagcttcaa gtaggagaca caagagattt gcgggagtag tcctggcagg tgcggcccta 7560

ggcgttgcca cagctgctca gataacagcc ggcattgcac ttcaccagtc catgctgaac 7620

tctcaagcca tcgacaatct gagagcgagc ctggaaacta ctaatcaggc aattgaggca 7680

atcagacaag cagggcagga gatgatattg gctgttcagg gtgtccaaga ctacatcaat 7740

aatgagctga taccgtctat gaaccaacta tcttgtgatt taatcggcca gaagctcggg 7800

ctcaaattgc tcagatacta tacagaaatc ctgtcattat ttggccccag cttacgggac 7860

cccatatctg cggagatatc tatccaggct ttgagctatg cgcttggagg agacatcaat 7920

aaggtgttag aaaagctcgg atacagtgga ggtgatttac tgggcatctt agagagcaga 7980

ggaataaagg cccggataac tcacgtcgac acagagtcct acttcattgt cctcagtata 8040

gcctatccga cgctgtccga gattaagggg gtgattgtcc accggctaga gggggtctcg 8100

tacaacatag gctctcaaga gtggtatacc actgtgccca agtatgttgc aacccaaggg 8160

taccttatct cgaattttga tgagtcatcg tgtactttca tgccagaggg gactgtgtgc 8220

-continued

agccaaaatg ccttgtaccc gatgagtcct ctgctccaag aatgcctccg ggggtccacc 8280

aagtcctgtg ctcgtacact cgtatccggg tcttttggga accggttcat tttatcacaa 8340

gggaacctaa tagccaattg tgcatcaatc ctttgcaagt gttacacaac aggaacgatc 8400

attaatcaag accctgacaa gatcctaaca tacattgctg ccgatcactg cccggtagtc 8460

gaggtgaacg gcgtgaccat ccaagtcggg agcaggaggt atccagacgc tgtgtacttg 8520

cacagaattg acctcggtcc tcccatatca ttggagaggt tggacgtagg gacaaatctg 8580

gggaatgcaa ttgctaagtt ggaggatgcc aaggaattgt tggagtcatc ggaccagata 8640

ttgaggagta tgaaaggttt atcgagcact agcatagtct acatcctgat tgcagtgtgt 8700

cttggagggt tgatagggat ccccgcttta atatgttgct gcagggggcg ttgtaacaaa 8760

aagggagaac aagttggtat gtcaagacca ggcctaaagc ctgatcttac gggaacatca 8820

aaatcctatg taaggtcgct ctgatcctct acaactcttg aaacacaaat gtcccacaag 8880

tctcctcttc gtcatcaagc aaccaccgca cccagcatca agcccacctg aaattatctc 8940

cggtttccct ctggccgaac aatatcggta gttaattaaa acttagggtg caagatcatc 9000

cacaatgtca ccacaacgag accggataaa tgccttctac aaagataacc cccatcccaa 9060

gggaagtagg atagtcatta acagagaaca tcttatgatt gatagacctt atgttttgct 9120

ggctgttctg tttgtcatgt ttctgagctt gatcgggttg ctagccattg caggcattag 9180

acttcatcgg gcagccatct acaccgcaga gatccataaa agcctcagca ccaatctaga 9240

tgtaactaac tcaatcgagc atcaggtcaa ggacgtgctg acaccactct tcaaaatcat 9300

cggtgatgaa gtgggcctga ggacacctca gagattcact gacctagtga aattcatctc 9360

tgacaagatt aaattcctta atccggatag ggagtacgac ttcagagatc tcacttggtg 9420

tatcaacccg ccagagagaa tcaaattgga ttatgatcaa tactgtgcag atgtggctgc 9480

tgaagagctc atgaatgcat tggtgaactc aactctactg gagaccagaa caaccaatca 9540

gttcctagct gtctcaaagg gaaactgctc agggcccact acaatcagag gtcaattctc 9600

aaacatgtcg ctgtccctgt tagacttgta tttaggtcga ggttacaatg tgtcatctat 9660

agtcactatg acatcccagg gaatgtatgg gggaacttac ctagtggaaa agcctaatct 9720

gagcagcaaa aggtcagagt tgtcacaact gagcatgtac cgagtgtttg aagtaggtgt 9780

tatcagaaat ccgggtttgg gggctccggt gttccatatg acaaactatc ttgagcaacc 9840

agtcagtaat gatctcagca actgtatggt ggctttgggg gagctcaaac tcgcagccct 9900

ttgtcacggg gaagattcta tcacaattcc ctatcaggga tcagggaaag gtgtcagctt 9960

ccagctcgtc aagctaggtg tctggaaatc cccaaccgac atgcaatcct gggtcccctt 10020

atcaacggat gatccagtga tagacaggct ttacctctca tctcacagag gtgttatcgc 10080

tgacaaccaa gcaaaatggg ctgtcccgac aacacgaaca gatgacaagt tgcgaatgga 10140

gacatgcttc caacaggcgt gtaagggtaa aatccaagca ctctgcgaga atcccgagtg 10200

ggcaccattg aaggataaca ggattccttc atacggggtc ttgtctgttg atctgagtct 10260

gacagttgag cttaaaatca aaattgcttc gggattcggg ccattgatca cacacggttc 10320

agggatggac ctatacaaat ccaaccacaa caatgtgtat tggctgacta tcccgccaat 10380

gaagaaccta gccttaggtg taatcaacac attggagtgg ataccgagat tcaaggttag 10440

tccctacctc ttcactgtcc caattaagga agcaggcgga gactgccatg ccccaacata 10500

-continued

cctacctgcg gaggtggatg gtgatgtcaa actcagttcc aatctggtga ttctacctgg 10560

tcaagatctc caatatgttt tggcaaccta cgatacttcc agggttgaac atgctgtggt 10620

ttattacgtt tacagcccaa gccgctcatt ttcttacttt tatcctttta ggttgcctat 10680

aaaggggtc cccatcgaat tacaagtgga atgcttcaca tgggaccaaa aactctggtg 10740

ccgtcacttc tgtgtgcttg cggactcaga atctggtgga catatcactc actctgggat 10800

ggtgggcatg ggagtcagct gcacagtcac ccgggaagat ggaaccaatc gcagataggg 10860

ctgctagtga accaatcaca tgatgtcacc cagacatcag gcatacccac tagtgtgaaa 10920

tagacatcag aattaagaaa aacgtagggt ccaagtggtt ccccgttatg gactcgctat 10980

ctgtcaacca gatcttatac cctgaagttc acctagatag cccgatagtt accaataaga 11040

tagtagccat cctggagtat gctcgagtcc ctcacgctta cagcctggag gaccctacac 11100

tgtgtcagaa catcaagcac cgcctaaaaa acggattttc caaccaaatg attataaaca 11160

atgtggaagt tgggaatgtc atcaagtcca agcttaggag ttatccggcc cactctcata 11220

ttccatatcc aaattgtaat caggatttat ttaacataga agacaaagag tcaacgagga 11280

agatccgtga actcctcaaa aaggggaatt cgctgtactc caaagtcagt gataaggttt 11340

tccaatgctt aagggacact aactcacggc ttggcctagg ctccgaattg agggaggaca 11400

tcaaggagaa agttattaac ttgggagttt acatgcacag ctcccagtgg tttgagccct 11460

ttctgttttg gtttacagtc aagactgaga tgaggtcagt gattaaatca caaacccata 11520

cttgccatag gaggagacac acacctgtat tcttcactgg tagttcagtt gagttgctaa 11580

tctctcgtga ccttgttgct ataatcagta aagagtctca acatgtatat tacctgacat 11640

ttgaactggt tttgatgtat tgtgatgtca tagaggggag gttaatgaca gagaccgcta 11700

tgactattga tgctaggtat acagagcttc taggaagagt cagatacatg tggaaactga 11760

tagatggttt cttccctgca ctcgggaatc caacttatca aattgtagcc atgctggagc 11820

ctctttcact tgcttacctg cagctgaggg atataacagt agaactcaga ggtgctttcc 11880

ttaaccactg ctttactgaa atacatgatg ttcttgacca aaacgggttt tctgatgaag 11940

gtacttatca tgagttaatt gaagctctag attacatttt cataactgat gacatacatc 12000

tgacagggga gattttctca tttttcagaa gtttcggcca ccccagactt gaagcagtaa 12060

cggctgctga aaatgttagg aaatacatga atcagcctaa agtcattgtg tatgagactc 12120

tgatgaaagg tcatgccata ttttgtggaa tcataatcaa cggctatcgt gacaggcacg 12180

gaggcagttg gccaccgctg accctccccc tgcatgctgc agacacaatc cggaatgctc 12240

aagcttcagg tgatgggtta acacatgagc agtgcgttga taactggaaa tcttttgctg 12300

gagtgaaatt tggctgcttt atgcctctta gcctggatag tgatctgaca atgtacctaa 12360

aggacaaggc acttgctgct ctccaaaggg aatgggattc agtttacccg aaagagttcc 12420

tgcgttacga ccctcccaag ggaaccgggt cacggaggct tgtagatgtt ttccttaatg 12480

attcgagctt tgacccatat gatgtgataa tgtatgttgt aagtggagct tacctccatg 12540

accctgagtt caacctgtct tacagcctga aagaaaagga gatcaaggaa acaggtagac 12600

tttttgctaa aatgacttac aaaatgaggg catgccaagt gattgctgaa aatctaatct 12660

caaacgggat tggcaaatat tttaaggaca atgggatggc caaggatgag cacgatttga 12720

ctaaggcact ccacactcta gctgtctcag gagtccccaa agatctcaaa gaaagtcaca 12780

-continued

```
gggggggggcc agtcttaaaa acctactccc gaagcccagt ccacacaagt accaggaacg  12840

tgagagcagc aaaagggttt atagggttcc ctcaagtaat tcggcaggac caagacactg  12900

atcatccgga gaatatggaa gcttacgaga cagtcagtgc atttatcacg actgatctca  12960

agaagtactg ccttaattgg agatatgaga ccatcagctt gtttgcacag aggctaaatg  13020

agatttacgg attgccctca tttttccagt ggctgcataa gaggcttgag acctctgtcc  13080

tgtatgtaag tgaccctcat tgccccccg accttgacgc ccatatcccg ttatataaag  13140

tccccaatga tcaaatcttc attaagtacc ctatgggagg tatagaaggg tattgtcaga  13200

agctgtggac catcagcacc attccctatc tatacctggc tgcttatgag agcggagtaa  13260

ggattgcttc gttagtgcaa ggggacaatc agaccatagc cgtaacaaaa agggtaccca  13320

gcacatggcc ctacaacctt aagaaacggg aagctgctag agtaactaga gattactttg  13380

taattcttag gcaaaggcta catgatattg gccatcacct caaggcaaat gagacaattg  13440

tttcatcaca ttttttttgtc tattcaaaag gaatatatta tgatgggcta cttgtgtccc  13500

aatcactcaa gagcatcgca agatgtgtat tctggtcaga gactatagtt gatgaaacaa  13560

gggcagcatg cagtaatatt gctacaacaa tggctaaaag catcgagaga ggttatgacc  13620

gttaccttgc atattccctg aacgtcctaa aagtgataca gcaaattctg atctctcttg  13680

gcttcacaat caattcaacc atgacccggg atgtagtcat acccctcctc acaaacaacg  13740

acctcttaat aaggatggca ctgttgcccg ctcctattgg ggggatgaat tatctgaata  13800

tgagcaggct gtttgtcaga aacatcggtg atccagtaac atcatcaatt gctgatctca  13860

agagaatgat tctcgcctca ctaatgcctg aagagaccct ccatcaggta atgacacaac  13920

aaccgggggа ctcttcattc ctagactggg ctagcgaccc ttactcagca aatcttgtat  13980

gtgtccagag catcactaga ctcctcaaga acataactgc aaggtttgtc ctgatccata  14040

gtccaaaccc aatgttaaaa ggattattcc atgatgacag taaagaagag gacgagggac  14100

tggcggcatt cctcatggac aggcatatta tagtacctag ggcagctcat gaaatcctgg  14160

atcatagtgt cacaggggca agagagtcta ttgcaggcat gctggatacc acaaaaggct  14220

tgattcgagc cagcatgagg aaggggggtt taacctctcg agtgataacc agattgtcca  14280

attatgacta tgaacaattc agagcaggga tggtgctatt gacaggaaga aagagaaatg  14340

tcctcattga caaagagtca tgttcagtgc agctggcgag agctctaaga agccatatgt  14400

gggcgaggct agctcgagga cggcctattt acggccttga ggtccctgat gtactagaat  14460

ctatgcgagg ccaccttatt cggcgtcatg agacatgtgt catctgcgag tgtggatcag  14520

tcaactacgg atggtttttt gtcccctcgg gttgccaact ggatgatatt gacaaggaaa  14580

catcatcctt gagagtccca tatattggtt ctaccactga tgagagaaca gacatgaagc  14640

ttgccttcgt aagagcccca agtcgatcct tgcgatctgc tgttagaata gcaacagtgt  14700

actcatgggc ttacggtgat gatgatagct cttggaacga agcctggttg ttggctaggc  14760

aaagggccaa tgtgagcctg gaggagctaa gggtgatcac tcccatctca acttcgacta  14820

atttagcgca taggttgagg gatcgtagca ctcaagtgaa atactcaggt acatcccttg  14880

tccgagtggc gaggtatacc acaatctcca acgacaatct ctcatttgtc atatcagata  14940

agaaggttga tactaacttt atataccaac aaggaatgct tctagggttg ggtgttttag  15000

aaacattgtt tcgactcgag aaagataccg gatcatctaa cacggtatta catcttcacg  15060
```

-continued

tcgaaacaga ttgttgcgtg atcccgatga tagatcatcc caggataccc agctcccgca 15120

agctagagct gagggcagag ctatgtacca acccattgat atatgataat gcacctttaa 15180

ttgacagaga tgcaacaagg ctatacaccc agagccatag gaggcacctt gtggaatttg 15240

ttacatggtc cacaccccaa ctatatcaca ttttagctaa gtccacagca ctatctatga 15300

ttgacctggt aacaaaattt gagaaggacc atatgaatga aatttcagct ctcatagggg 15360

atgacgatat caatagtttc ataactgagt ttctgctcat agagccaaga ttattcacta 15420

tctacttggg ccagtgtgcg gccatcaatt gggcatttga tgtacattat catagaccat 15480

cagggaaata tcagatgggt gagctgttgt catcgttcct ttctagaatg agcaaaggag 15540

tgtttaaggt gcttgtcaat gctctaagcc acccaaagat ctacaagaaa ttctggcatt 15600

gtggtattat agagcctatc catggtcctt cacttgatgc tcaaaacttg cacacaactg 15660

tgtgcaacat ggtttacaca tgctatatga cctacctcga cctgttgttg aatgaagagt 15720

tagaagagtt cacatttctc ttgtgtgaaa gcgacgagga tgtagtaccg gacagattcg 15780

acaacatcca ggcaaaacac ttatgtgttc tggcagattt gtactgtcaa ccagggacct 15840

gcccaccaat tcaaggtcta agaccggtag agaaatgtgc agttctaacc gaccatatca 15900

aggcagaggc tatgttatct ccagcaggat cttcgtggaa cataaatcca attattgtag 15960

accattactc atgctccctg acttatctcc ggcgaggatc gatcaaacag ataagattga 16020

gagttgatcc aggattcatt ttcgacgccc tcgctgaggt aaatgtcagt cagccaaaga 16080

tcggcagcaa caacatctca aatatgagca tcaaggcttt cagaccccca cacgatgatg 16140

ttgcaaaatt gctcaaagat atcaacacaa gcaagcacaa tcttcccatt tcaggggca 16200

atctcgccaa ttatgaaatc catgctttcc gcagaatcgg gttgaactca tctgcttgct 16260

acaaagctgt tgagatatca acattaatta ggagatgcct tgagccaggg gaggacggct 16320

tgttcttggg tgagggatcg ggttctatgt tgatcactta taaggagata cttaaactaa 16380

gcaagtgctt ctataatagt ggggtttccg ccaattctag atctggtcaa agggaattag 16440

cacctatcc ctccgaagtt ggccttgtcg aacacagaat gggagtaggt aatattgtca 16500

aagtgctctt taacgggagg cccgaagtca cgtgggtagg cagtgtagat tgcttcaatt 16560

tcatagttag taatatccct acctctagtg tggggtttat ccattcagat atagagacct 16620

tgcctgacaa agatactata gagaagctag aggaattggc agccatctta tcgatggctc 16680

tgctcctggg caaaatagga tcaatactgg tgattaagct tatgcctttc agcggggatt 16740

ttgttcaggg atttataagt tatgtagggt ctcattatag agaagtgaac cttgtatacc 16800

ctagatacag caacttcatc tctactgaat cttatttggt tatgacagat ctcaaggcta 16860

accggctaat gaatcctgaa aagattaagc agcagataat tgaatcatct gtgaggactt 16920

cacctggact tataggtcac atcctatcca ttaagcaact aagctgcata caagcaattg 16980

tgggagacgc agttagtaga ggtgatatca atcctactct gaaaaaactt acacctatag 17040

agcaggtgct gatcaattgc gggttggcaa ttaacggacc taagctgtgc aaagaattga 17100

tccaccatga tgttgcctca gggcaagatg gattgcttaa ttctatactc atcctctaca 17160

gggagttggc aagattcaaa gacaaccaaa gaagtcaaca agggatgttc cacgcttacc 17220

ccgtattggt aagtagcagg caacgagaac ttatatctag gatcacccgc aaattctggg 17280

ggcacattct tctttactcc gggaacaaaa agttgataaa taagtttatc cagaatctca 17340

-continued

agtccggcta tctgatacta gacttacacc agaatatctt cgttaagaat ctatccaagt 17400

cagagaaaca gattattatg acgggggttt tgaaacgtga gtgggttttt aaggtaacag 17460

tcaaggagac caaagaatgg tataagttag tcggatacag tgccctgatt aaggactaat 17520

tggttgaact ccggaaccct aatcctgccc taggtggtta ggcattattt gcaatatatt 17580

aaagaaaact ttgaaaatac gaagtttcta ttcccagctt tgtctggt 17628

<210> SEQ ID NO 15
<211> LENGTH: 17571
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial polynucleotide encoding MV MeVac_H_FhIL-12

<400> SEQUENCE: 15

accaaacaaa gttgggtaag gatagttcaa tcaatgatca tcttctagtg cacttaggat 60

tcaagatcct attatcaggg acaagagcag gattagggat atccgagatg gccacacttt 120

taaggagctt agcattgttc aaaagaaaca aggacaaacc acccattaca tcaggatccg 180

gtggagccat cagaggaatc aaacacatta ttatagtacc aatccctgga gattcctcaa 240

ttaccactcg atccagactt ctggaccggt tggtgaggtt aattggaaac ccggatgtga 300

gcgggcccaa actaacaggg gcactaatag gtatattatc cttatttgtg gagtctccag 360

gtcaattgat tcagaggatc accgatgacc ctgacgttag cataaggctg ttagaggttg 420

tccagagtga ccagtcacaa tctggcctta ccttcgcatc aagaggtacc aacatggagg 480

atgaggcgga ccaatacttt tcacatgatg atccaattag tagtgatcaa tccaggttcg 540

gatggttcgg gaacaaggaa atctcagata ttgaagtgca agaccctgag ggattcaaca 600

tgattctggg taccatccta gcccaaattt gggtcttgct cgcaaaggcg gttacggccc 660

cagacacggc agctgattcg gagctaagaa ggtggataaa gtacacccaa caaagaaggg 720

tagttggtga atttagattg gagagaaaat ggttggatgt ggtgaggaac aggattgccg 780

aggacctctc cttacgccga ttcatggtcg ctctaatcct ggatatcaag agaacacccg 840

gaaacaaacc caggattgct gaaatgatat gtgacattga tacatatatc gtagaggcag 900

gattagccag ttttatcctg actattaagt ttgggataga aactatgtat cctgctcttg 960

gactgcatga atttgctggt gagttatcca cacttgagtc cttgatgaac ctttaccagc 1020

aaatggggga aactgcaccc tacatggtaa tcctggagaa ctcaattcag aacaagttca 1080

gtgcaggatc ataccctctg ctctggagct atgccatggg agtaggagtg gaacttgaaa 1140

actccatggg aggtttgaac tttggccgat cttactttga tccagcatat tttagattag 1200

ggcaagagat ggtaaggagg tcagctggaa aggtcagttc cacattggca tctgaactcg 1260

gtatcactgc cgaggatgca aggcttgttt cagagattgc aatgcatact actgaggaca 1320

agatcagtag agcggttgga cccagacaag cccaagtatc atttctacac ggtgatcaaa 1380

gtgagaatga gctaccgaga ttgggggggca aggaagatag gagggtcaaa cagagtcgag 1440

gagaagccag ggagagctac agagaaaccg ggcccagcag agcaagtgat gcgagagctg 1500

cccatcttcc aaccggcaca cccctagaca ttgacactgc aacggagtcc agccaagatc 1560

cgcaggacag tcgaaggtca gctgacgccc tgcttaggct gcaagccatg gcaggaatct 1620

cggaagaaca aggctcagac acggacaccc ctatagtgta caatgacaga aatcttctag 1680

-continued

actaggtgcg agaggccgag ggccagaaca acatccgcct accatccatc attgttataa 1740

aaaacttagg aaccaggtcc acacagccgc cagcccatca accatccact cccacgattg 1800

gagccaatgg cagaagagca ggcacgccat gtcaaaaacg gactggaatg catccgggct 1860

ctcaaggccg agcccatcgg ctcactggcc atcgaggaag ctatggcagc atggtcagaa 1920

atatcagaca acccaggaca ggagcgagcc acctgcaggg aagagaaggc aggcagttcg 1980

ggtctcagca aaccatgcct ctcagcaatt ggatcaactg aaggcggtgc acctcgcatc 2040

cgcggtcagg gacctggaga gagcgatgac gacgctgaaa ctttgggaat ccccccaaga 2100

aatctccagg catcaagcac tgggttacag tgttattacg tttatgatca cagcggtgaa 2160

gcggttaagg gaatccaaga tgctgactct atcatggttc aatcaggcct tgatggtgat 2220

agcaccctct caggaggaga caatgaatct gaaaacagcg atgtggatat tggcgaacct 2280

gataccgagg gatatgctat cactgaccgg ggatctgctc ccatctctat ggggttcagg 2340

gcttctgatg ttgaaactgc agaaggaggg gagatccacg agctcctgag actccaatcc 2400

agaggcaaca actttccgaa gcttgggaaa actctcaatg ttcctccgcc cccggacccc 2460

ggtagggcca gcacttccgg gacacccatt aaaaagggca cagacgcgag attagcctca 2520

tttggaacgg agatcgcgtc tttattgaca ggtggtgcaa cccaatgtgc tcgaaagtca 2580

ccctcggaac catcagggcc aggtgcacct gcggggaatg tccccgagtg tgtgagcaat 2640

gccgcactga tacaggagtg gacacccgaa tctggtacca caatctcccc gagatcccag 2700

aataatgaag aaggggggaga ctattatgat gatgagctgt tctctgatgt ccaagatatt 2760

aaaacagcct tggccaaaat acacgaggat aatcagaaga taatctccaa gctagaatca 2820

ctgctgttat tgaagggaga agttgagtca attaagaagc agatcaacag gcaaaatatc 2880

agcatatcca ccctggaagg acacctctca agcatcatga tcgccattcc tggacttggg 2940

aaggatccca acgaccccac tgcagatgtc gaaatcaatc ccgacttgaa acccatcata 3000

ggcagagatt caggccgagc actggccgaa gttctcaaga aacccgttgc cagccgacaa 3060

ctccaaggaa tgacaaatgg acggaccagt tccagaggac agctgctgaa ggaatttcag 3120

ctaaagccga tcgggaaaaa gatgagctca gccgtcgggt ttgttcctga caccggccct 3180

gcatcacgca gtgtaatccg ctccattata aaatccagcc ggctagagga ggatcggaag 3240

cgttacctga tgactctcct tgatgatatc aaaggagcca atgatcttgc caagttccac 3300

cagatgctga tgaagataat aatgaagtag ctacagctca acttacctgc caaccccatg 3360

ccagtcgacc caactagtac aacctaaatc cattataaaa aacttaggag caaagtgatt 3420

gcctcccaag gtccacaatg acagagacct acgacttcga caagtcggca tgggacatca 3480

aagggtcgat cgctccgata caacccacca cctacagtga tggcaggctg gtgccccagg 3540

tcagagtcat agatcctggt ctaggcgaca ggaaggatga atgctttatg tacatgtttc 3600

tgctgggggt tgttgaggac agcgattccc tagggcctcc aatcgggcga gcatttgggt 3660

tcctgccctt aggtgttggc agatccacag caaagcccga aaaactcctc aaagaggcca 3720

ctgagcttga catagttgtt agacgtacag cagggctcaa tgaaaaactg gtgttctaca 3780

acaacacccc actaactctc ctcacacctt ggagaaaggt cctaacaaca gggagtgtct 3840

tcaacgcaaa ccaagtgtgc aatgcggtta atctgatacc gctcgatacc ccgcagaggt 3900

tccgtgttgt ttatatgagc atcacccgtc tttcggataa cgggtattac accgttccta 3960

-continued

gaagaatgct ggaattcaga tcggtcaatg cagtggcctt caacctgctg gtgaccctta 4020

ggattgacaa ggcgataggc cctgggaaga tcatcgacaa tacagagcaa cttcctgagg 4080

caacatttat ggtccacatc gggaacttca ggagaaagaa gagtgaagtc tactctgccg 4140

attattgcaa aatgaaaatc gaaaagatgg gcctggtttt tgcacttggt gggatagggg 4200

gcaccagtct tcacattaga agcacaggca aaatgagcaa gactctccat gcacaactcg 4260

ggttcaagaa gaccttatgt tacccgctga tggatatcaa tgaagacctt aatcgattac 4320

tctggaggag cagatgcaag atagtaagaa tccaggcagt tttgcagcca tcagttcctc 4380

aagaattccg catttacgac gacgtgatca taaatgatga ccaaggacta ttcaaagttc 4440

tgtagaccgt agtgcccagc aatgcccgaa aacgaccccc ctcacaatga cagccagaag 4500

gcccggacaa aaaagccccc tccgaaagac tccacggacc aagcgagagg ccagccagca 4560

gccgacggca agcgcgaaca ccaggcggcc ccagcacaga acagccctga cacaaggcca 4620

ccaccagcca ccccaatctg catcctcctc gtgggacccc cgaggaccaa cccccaaggc 4680

tgcccccgat ccaaaccacc aaccgcatcc ccaccacccc cgggaaagaa acccccagca 4740

attggaaggc ccctcccccc cttcctcaac acaagaactc cacaaccgaa ccgcacaagc 4800

gaccgaggtg acccaaccgc aggcatccga ctccctagac agatcctctc tccccggcaa 4860

actaaacaaa acttagggcc aaggaacata cacacccaac agaacccaga ccccggccca 4920

cggcgccgcg cccccaaccc ccgacaacca gagggagccc ccaaccaatc ccgccggctc 4980

ccccggtgcc cacaggcagg gacaccaacc cccgaacaga cccagcaccc aaccatcgac 5040

aatccaagac ggggggggcc ccccaaaaaa aggcccccag gggccgacag ccagcaccgc 5100

gaggaagccc acccacccca cacacgacca cggcaaccaa accagaaccc agaccaccct 5160

gggccaccag ctcccagact cggccatcac cccgcagaaa ggaaaggcca caacccgcgc 5220

accccagccc cgatccggcg gggagccacc caacccgaac cagcacccaa gagcgatccc 5280

cgaaggaccc ccgaaccgca aaggacatca gtatcccaca gcctctccaa gtcccccggt 5340

ctcctcctct tctcgaaggg accaaaaagat caatccacca cacccgacga cactcaactc 5400

cccacccctа aaggagacac cgggaatccc agaatcaaga ctcatccaat gtccatcatg 5460

ggtctcaagg tgaacgtctc tgccatattc atggcagtac tgttaactct ccaaacaccc 5520

accggtcaaa tccattgggg caatctctct aagatagggg tggtaggaat aggaagtgca 5580

agctacaaag ttatgactcg ttccagccat caatcattag tcataaaatt aatgcccaat 5640

ataactctcc tcaataactg cacgagggta gagattgcag aatacaggag actactgaga 5700

acagttttgg aaccaattag agatgcactt aatgcaatga cccagaatat aagaccggtt 5760

cagagtgtag cttcaagtag gagacacaag agatttgcgg gagtagtcct ggcaggtgcg 5820

gccctaggcg ttgccacagc tgctcagata acagccggca ttgcacttca ccagtccatg 5880

ctgaactctc aagccatcga caatctgaga gcgagcctgg aaactactaa tcaggcaatt 5940

gagacaatca gacaagcagg gcaggagatg atattggctg ttcagggtgt ccaagactac 6000

atcaataatg agctgatacc gtctatgaac caactatctt gtgatttaat cggccagaag 6060

ctcgggctca aattgctcag atactataca gaaatcctgt cattatttgg ccccagttta 6120

cgggacccca tatctgcgga gatatctatc caggctttga gctatgcgct tggaggagac 6180

atcaataagg tgttagaaaa gctcggatac agtggaggtg atttactggg catcttagag 6240

-continued

agcggaggaa taaaggcccg gataactcac gtcgacacag agtcctactt cattgtcctc 6300

agtatagcct atccgacgct gtccgagatt aaggggtga ttgtccaccg gctagagggg 6360

gtctcgtaca acataggctc tcaagagtgg tataccactg tgcccaagta tgttgcaacc 6420

caagggtacc ttatctcgaa ttttgatgag tcatcgtgta ctttcatgcc agaggggact 6480

gtgtgcagcc aaaatgcctt gtacccgatg agtcctctgc tccaagaatg cctccggggg 6540

tacaccaagt cctgtgctcg tacactcgta tccgggtctt ttgggaaccg gttcatttta 6600

tcacaaggga acctaatagc caattgtgca tcaatccttt gcaagtgtta cacaacagga 6660

acgatcatta atcaagaccc tgacaagatc ctaacataca ttgctgccga tcactgcccg 6720

gtagtcgagg tgaacggcgt gaccatccaa gtcgggagca ggaggtatcc agacgctgtg 6780

tacttgcaca gaattgacct cggtcctccc atatcattgg agaggttgga cgtagggaca 6840

aatctgggga atgcaattgc taagttggag gatgccaagg aattgttgga gtcatcggac 6900

cagatattga ggagtatgaa aggtttatcg agcactagca tagtctacat cctgattgca 6960

gtgtgtcttg gagggttgat agggatcccc gctttaatat gttgctgcag ggggcgttgt 7020

aacaaaaagg gagaacaagt tggtatgtca agaccaggcc taaagcctga tcttacggga 7080

acatcaaaat cctatgtaag gtcgctctga tcctctacaa ctcttgaaac acaaatgtcc 7140

cacaagtctc ctcttcgtca tcaagcaacc accgcaccca gcatcaagcc cacctgaaat 7200

tatctccggc ttccctctgg ccgaacaata tcggtagtta atcaaaactt agggtgcaag 7260

atcatccaca atgtcaccac aacgagaccg gataaatgcc ttctacaaag ataacccccа 7320

tcccaaggga agtaggatag tcattaacag agaacatctt atgattgata gaccttatgt 7380

tttgctggct gttctgtttg tcatgtttct gagcttgatc gggttgctag ccattgcagg 7440

cattagactt catcgggcag ccatctacac cgcagagatc cataaaagcc tcagcaccaa 7500

tctagatgta actaactcaa tcgagcatca ggtcaaggac gtgctgacac cactcttcaa 7560

aatcatcggt gatgaagtgg gcctgaggac acctcagaga ttcactgacc tagtgaaatt 7620

aatctctgac aagattaaat tccttaatcc ggatagggag tacgacttca gagatctcac 7680

ttggtgtatc aacccgccag agagaatcaa attggattat gatcaatact gtgcagatgt 7740

ggctgctgaa gagctcatga atgcattggt gaactcaact ctactggaga ccagaacaac 7800

caatcagttc ctagctgtct caaagggaaa ctgctcaggg cccactacaa tcagaggtca 7860

attctcaaac atgtcgctgt ccctgttaga cttgtattta ggtcgaggtt acaatgtgtc 7920

atctatagtc actatgacat cccagggaat gtatggggga acttacctag tggaaaagcc 7980

taatctgagc agcaaaaggt cagagttgtc acaactgagc atgtaccgag tgtttgaagt 8040

aggtgttatc agaaatccgg gtttgggggc tccggtgttc catatgacaa actatcttga 8100

gcaaccagtc agtaatgatc tcagcaactg tatggtggct ttgggggagc tcaaactcgc 8160

agccctttgt cacggggaag attctatcac aattccctat cagggatcag ggaaaggtgt 8220

cagcttccag ctcgtcaagc taggtgtctg gaaatcccca accgacatgc aatcctgggt 8280

ccccttatca acggatgatc cagtgataga caggctttac ctctcatctc acagaggtgt 8340

tatcgctgac aatcaagcaa aatgggctgt cccgacaaca cgaacagatg acaagttgcg 8400

aatggagaca tgcttccaac aggcgtgtaa gggtaaaatc caagcactct gcgagaatcc 8460

cgagtgggca ccattgaagg ataacaggat tccttcatac ggggtcttgt ctgttgatct 8520

-continued

gagtctgaca gttgagctta aaatcaaaat tgcttcggga ttcgggccat tgatcacaca 8580

cggttcaggg atggacctat acaaatccaa ccacaacaat gtgtattggc tgactatccc 8640

gccaatgaag aacctagcct taggtgtaat caacacattg gagtggatac cgagattcaa 8700

ggttagtccc tacctcttca ctgtcccaat taaggaagca ggcgaagact gccatgcccc 8760

aacataccta cctgcggagg tggatggtga tgtcaaactc agttccaatc tggtgattct 8820

acctggtcaa gatctccaat atgttttggc aacctacgat acttccaggg ttgaacatgc 8880

tgtggtttat tacgtttaca gcccaagccg ctcatttttct tacttttatc cttttaggtt 8940

gcctataaag ggggtcccca tcgaattaca agtggaatgc ttcacatggg accaaaaact 9000

ctggtgccgt cacttctgtg tgcttgcgga ctcagaatct ggtggacata tcactcactc 9060

tgggatggtg ggcatgggag tcagctgcac agtcacccgg gaagatggaa ccaatcgcag 9120

atagggctgc tagtgaacca atcacatgat gtcacccaga catcaggcat acccactagt 9180

catccatcat tgttataaaa aacttaggaa ccaggtccac acagctcgag tcgcgcgtgc 9240

caccatgtgt caccagcagt tggtcatctc ttggttttcc ctggtttttc tggcatctcc 9300

cctcgtggcc atatgggaac tgaagaaaga tgtttatgtc gtagaattgg attggtatcc 9360

ggatgcccct ggagaaatgg tggtcctcac ctgtgacacc cctgaagaag atggtatcac 9420

ctggaccttg gaccagagca gtgaggtctt aggctctggc aaaaccctga ccatccaagt 9480

caaagagttt ggagatgctg gccagtacac ctgtcacaaa ggaggcgagg ttctaagcca 9540

ttcgctcctg ctgcttcaca aaaaggaaga tggaatttgg tccactgata ttttaaagga 9600

ccagaaagaa cccaaaaata agacctttct aagatgcgag gccaagaatt attctggacg 9660

tttcacctgc tggtggctga cgacaatcag tactgatttg acattcagtg tcaaaagcag 9720

cagaggctct tctgaccccc aaggggtgac gtgcggagct gctacactct ctgcagagag 9780

agtcagaggg gacaacaagg agtatgagta ctcagtggag tgccaggagg acagtgcctg 9840

cccagctgct gaggagagtc tgcccattga ggtcatggtg gatgccgttc acaagctcaa 9900

gtatgaaaac tacaccagca gcttcttcat cagggacatc atcaaacctg acccacccaa 9960

caacttgcag ctgaagccat taaagaattc tcggcaggtg gaggtcagct gggagtaccc 10020

tgacacctgg agtactccac attcctactt ctccctgaca ttctgcgttc aggtccaggg 10080

caagagcaag agagaaaaga aagatagagt cttcaccgac aagacctcag ccacggtcat 10140

ctgccgcaaa aatgccagca ttagcgtgcg ggcccaggac cgctactata gctcatcttg 10200

gagcgaatgg gcatctgtgc cctgcagtgg tggcggtggc ggcggatcta gaaacctccc 10260

cgtggccact ccagacccag gaatgttccc atgccttcac cactcccaaa acctgctgag 10320

ggccgtcagc aacatgctcc agaaggccag acaaactcta gaattttacc cttgcacttc 10380

tgaagagatt gatcatgaag atatcacaaa agataaaacc agcacagtgg aggcctgttt 10440

accattggaa ttaaccaaga atgagagttg cctaaattcc agagagacct ctttcataac 10500

taatgggagt tgcctggcct ccagaaagac ctcttttatg atggccctgt gccttagtag 10560

tatttatgaa gacttgaaga tgtaccaggt ggagttcaag accatgaatg caaagcttct 10620

gatggatcct aagaggcaga tctttctaga tcaaaacatg ctggcagtta ttgatgagct 10680

gatgcaggcc ctgaatttca acagtgagac tgtgccacaa aaatcctccc ttgaagaacc 10740

ggatttttat aaaactaaaa tcaagctctg catacttctt catgctttca gaattcgggc 10800

-continued

agtgactatt gatagagtga tgagctatct gaatgcttcc taggcgcgcg ttctagtgtg 10860

aaatagacat cagaattaag aaaaacgtag ggtccaagtg gttccccgtt atggactcgc 10920

tatctgtcaa ccagatctta taccctgaag ttcacctaga tagcccgata gttaccaata 10980

agatagtagc catcctggag tatgctcgag tccctcacgc ttacagcctg gaggacccta 11040

cactgtgtca gaacatcaag caccgcctaa aaaacggatt ttccaaccaa atgattataa 11100

acaatgtgga agttgggaat gtcatcaagt ccaagcttag gagttatccg gcccactctc 11160

atattccata tccaaattgt aatcaggatt tatttaacat agaagacaaa gagtcaacga 11220

ggaagatccg tgaactcctc aaaaagggga attcgctgta ctccaaagtc agtgataagg 11280

ttttccaatg cttaagggac actaactcac ggcttggcct aggctccgaa ttgagggagg 11340

acatcaagga gaaagttatt aacttgggag tttacatgca cagctcccag tggtttgagc 11400

cctttctgtt ttggtttaca gtcaagactg agatgaggtc agtgattaaa tcacaaaccc 11460

atacttgcca taggaggaga cacacacctg tattcttcac tggtagttca gttgagttgc 11520

taatctctcg tgaccttgtt gctataatca gtaaagagtc tcaacatgta tattacctga 11580

catttgaact ggttttgatg tattgtgatg tcatagaggg gaggttaatg acagagaccg 11640

ctatgactat tgatgctagg tatacagagc ttctaggaag agtcagatac atgtggaaac 11700

tgatagatgg tttcttccct gcactcggga atccaactta tcaaattgta gccatgctgg 11760

agcctctttc acttgcttac ctgcagctga gggatataac agtagaactc agaggtgctt 11820

tccttaacca ctgctttact gaaatacatg atgttcttga ccaaaacggg ttttctgatg 11880

aaggtactta tcatgagtta actgaagctc tagattacat tttcataact gatgacatac 11940

atctgacagg ggagattttc tcatttttca gaagtttcgg ccaccccaga cttgaagcag 12000

taacggctgc tgaaaatgtt aggaaataca tgaatcagcc taaagtcatt gtgtatgaga 12060

ctctgatgaa aggtcatgcc atattttgtg gaatcataat caacggctat cgtgacaggc 12120

acggaggcag ttggccaccg ctgaccctcc ccctgcatgc tgcagacaca atccggaatg 12180

ctcaagcttc aggtgaaggg ttaacacatg agcagtgcgt tgataactgg aaatcttttg 12240

ctggagtgaa atttggctgc tttatgcctc ttagcctgga tagtgatctg acaatgtacc 12300

taaaggacaa ggcacttgct gctctccaaa gggaatggga ttcagtttac ccgaaagagt 12360

tcctgcgtta cgaccctccc aagggaaccg ggtcacggag gcttgtagat gttttcctta 12420

atgattcgag ctttgaccca tatgatgtga taatgtatgt tgtaagtgga gcttacctcc 12480

atgaccctga gttcaacctg tcttacagcc tgaaagaaaa ggagatcaag gaaacaggta 12540

gacttttttgc taaaatgact tacaaaatga gggcatgcca agtgattgct gaaaatctaa 12600

tctcaaacgg gattggcaaa tattttaagg acaatgggat ggccaaggat gagcacgatt 12660

tgactaaggc actccacact ctagctgtct caggagtccc caaagatctc aaagaaagtc 12720

acagggggggg gccagtctta aaaacctact cccgaagccc agtccacaca agtaccagga 12780

acgtgagagc agcaaaaggg tttatagggt tccctcaagt aattcggcag gaccaagaca 12840

ctgatcatcc ggagaatatg gaagcttacg agacagtcag tgcatttatc acgactgatc 12900

tcaagaagta ctgccttaat tggagatatg agaccatcag cttgtttgca cagaggctaa 12960

atgagattta cggattgccc tcatttttcc agtggctgca taagaggctt gagacctctg 13020

tcctgtatgt aagtgaccct cattgccccc ccgaccttga cgcccatatc ccgttatata 13080

-continued

aagtccccaa tgatcaaatc ttcattaagt accctatggg aggtatagaa gggtattgtc 13140

agaagctgtg gaccatcagc accattccct atctatacct ggctgcttat gagagcggag 13200

taaggattgc ttcgttagtg caaggggaca atcagaccat agccgtaaca aaaagggtac 13260

ccagcacatg gccctacaac cttaagaaac gggaagctgc tagagtaact agagattact 13320

ttgtaattct taggcaaagg ctacatgata ttggccatca cctcaaggca aatgagacaa 13380

ttgtttcatc acatttttt gtctattcaa aaggaatata ttatgatggg ctacttgtgt 13440

cccaatcact caagagcatc gcaagatgtg tattctggtc agagactata gttgatgaaa 13500

caagggcagc atgcagtaat attgctacaa caatggctaa aagcatcgag agaggttatg 13560

accgttacct tgcatattcc ctgaacgtcc taaaagtgat acagcaaatt ctgatctctc 13620

ttggcttcac aatcaattca accatgaccc gggatgtagt catacccctc ctcacaaaca 13680

acgacctctt aataaggatg gcactgttgc ccgctcctat tgggggatg aattatctga 13740

atatgagcag gctgtttgtc agaaacatcg gtgatccagt aacatcatca attgctgatc 13800

tcaagagaat gattctcgcc tcactaatgc ctgaagagac cctccatcaa gtaatgacac 13860

aacaaccggg ggactcttca ttcctagact gggctagcga cccttactca gcaaatcttg 13920

tatgtgtcca gagcatcact agactcctca agaacataac tgcaaggttt gtcctgatcc 13980

atagtccaaa cccaatgtta aaaggattat tccatgatga cagtaaagaa gaggacgagg 14040

gactggcggc attcctcatg gacaggcata ttatagtacc tagggcagct catgaaatcc 14100

tggatcatag tgtcacaggg gcaagagagt ctattgcagg catgctggat accacaaaag 14160

gcttgattcg agccagcatg aggaaggggg ggttaacctc tcgagtgata accagattgt 14220

ccaattatga ctatgaacaa ttcagagcag ggatggtgct attgacagga agaaagagaa 14280

atgtcctcat tgacaaagag tcatgttcag tgcagctggc gagagctcta agaagccata 14340

tgtgggcgag gctagctcga ggacggccta tttacggcct tgaggtccct gatgtactag 14400

aatctatgcg aggccacctt attcggcgtc atgagacatg tgtcatctgc gagtgtggat 14460

cagtcaacta cggatggttt tttgtcccct cgggttgcca actggatgat attgacaagg 14520

aaacatcatc cttgagagtc ccatatattg gttctaccac tgatgagaga acagacatga 14580

agcttgcctt cgtaagagcc ccaagtcgat ccttgcgatc tgctgttaga atagcaacag 14640

tgtactcatg ggcttacggt gatgatgata gctcttggaa cgaagcctgg ttgttggcta 14700

ggcaaagggc caatgtgagc ctggaggagc taagggtgat cactcccatc tcaacttcga 14760

ctaatttagc gcataggttg agggatcgta gcactcaagt gaaatactca ggtacatccc 14820

ttgtccgagt ggcgaggtat accacaatct ccaacgacaa tctctcattt gtcatatcag 14880

ataagaaggt tgatactaac tttatatacc aacaaggaat gcttctaggg ttgggtgttt 14940

tagaaacatt gtttcgactc gagaaagata ccggatcatc taacacggta ttacatcttc 15000

acgtcgaaac agattgttgc gtgatcccga tgatagatca tcccaggata cccagctccc 15060

gcaagctaga gctgagggca gagctatgta ccaacccatt gatatatgat aatgcacctt 15120

taattgacag agatgcaaca aggctataca cccagagcca taggaggcac cttgtggaat 15180

ttgttacatg gtccacaccc caactatatc acattttagc taagtccaca gcactatcta 15240

tgattgacct ggtaacaaaa tttgagaagg accatatgaa tgaaatttca gctctcatag 15300

gggatgacga tatcaatagt ttcataactg agtttctgct catagagcca agattattca 15360

-continued

ctatctactt gggccagtgt gcggccatca attgggcatt tgatgtacat tatcatagac 15420

catcagggaa atatcagatg ggtgagctgt tgtcatcgtt cctttctaga atgagcaaag 15480

gagtgtttaa ggtgcttgtc aatgctctaa gccacccaaa gatctacaag aaattctggc 15540

attgtggtat tatagagcct atccatggtc cttcacttga tgctcaaaac ttgcacacaa 15600

ctgtgtgcaa catggtttac acatgctata tgacctacct cgacctgttg ttgaatgaag 15660

agttagaaga gttcacattt ctcttgtgtg aaagcgacga ggatgtagta ccggacagat 15720

tcgacaacat ccaggcaaaa cacttatgtg ttctggcaga tttgtactgt caaccaggga 15780

cctgcccacc aattcgaggt ctaagaccgg tagagaaatg tgcagttcta accgaccata 15840

tcaaggcaga ggctatgtta tctccagcag gatcttcgtg gaacataaat ccaattattg 15900

tagaccatta ctcatgctct ctgacttatc tccggcgagg atcgatcaaa cagataagat 15960

tgagagttga tccaggattc attttcgacg ccctcgctga ggtaaatgtc agtcagccaa 16020

agatcggcag caacaacatc tcaaatatga gcatcaaggc tttcagaccc ccacacgatg 16080

atgttgcaaa attgctcaaa gatatcaaca caagcaagca caatcttccc atttcagggg 16140

gcaatctcgc caattatgaa atccatgctt tccgcagaat cgggttgaac tcatctgctt 16200

gctacaaagc tgttgagata tcaacattaa ttaggagatg ccttgagcca ggggaggacg 16260

gcttgttctt gggtgaggga tcgggttcta tgttgatcac ttataaagag atacttaaac 16320

taaacaagtg cttctataat agtggggttt ccgccaattc tagatctggt caaagggaat 16380

tagcacccta tccctccgaa gttggccttg tcgaacacag aatgggagta ggtaatattg 16440

tcaaagtgct ctttaacggg aggcccgaag tcacgtgggt aggcagtgta gattgcttca 16500

atttcatagt tagtaatatc cctacctcta gtgtggggtt tatccattca gatatagaga 16560

ccttgcctga caaagatact atagagaagc tagaggaatt ggcagccatc ttatcgatgg 16620

ctctgctcct gggcaaaata ggatcaatac tggtgattaa gcttatgcct ttcagcgggg 16680

attttgttca gggatttata agttatgtag ggtctcatta tagagaagtg aaccttgtat 16740

accctagata cagcaacttc atctctactg aatcttattt ggttatgaca gatctcaagg 16800

ctaaccggct aatgaatcct gaaaagatta agcagcagat aattgaatca tctgtgagga 16860

cttcacctgg acttataggt cacatcctat ccattaagca actaagctgc atacaagcaa 16920

ttgtgggaga cgcagttagt agaggtgata tcaatcctac tctgaaaaaa cttacaccta 16980

tagagcaggt gctgatcaat tgcgggttgg caattaacgg acctaagctg tgcaaagaat 17040

tgatccacca tgatgttgcc tcagggcaag atggattgct taattctata ctcatcctct 17100

acagggagtt ggcaagattc aaagacaacc aaagaagtca acaagggatg ttccacgctt 17160

accccgtatt ggtaagtagc aggcaacgag aacttatatc taggatcacc cgcaaattct 17220

gggggcacat tcttctttac tccgggaaca aaaagttgat aaataagttt atccagaatc 17280

tcaagtccgg ctatctgata ctagacttac accagaatat cttcgttaag aatctatcca 17340

agtcagagaa acagattatt atgacggggg gtttgaaacg tgagtgggtt tttaaggtaa 17400

cagtcaagga gaccaaagaa tggtataagt tagtcggata cagtgccctg attaaggact 17460

aattggttga actccggaac cctaatcctg ccctaggtgg ttaggcatta tttgcaatat 17520

attaaagaaa actttgaaaa tacgaagttt ctattcccag ctttgtctgg t 17571

-continued

<210> SEQ ID NO 16
<211> LENGTH: 282
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial subsequence of IgG1 (Fc)

<400> SEQUENCE: 16

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Gly Ala
20 25 30

Gln Pro Ala Val Asp Glu Ala Lys Ser Cys Asp Lys Thr His Thr Cys
35 40 45

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
50 55 60

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
65 70 75 80

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
85 90 95

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
100 105 110

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
115 120 125

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
130 135 140

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
145 150 155 160

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
165 170 175

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
180 185 190

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
195 200 205

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
210 215 220

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
225 230 235 240

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
245 250 255

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Val Asp Glu
260 265 270

Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn
275 280

<210> SEQ ID NO 17
<211> LENGTH: 852
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: artificial sequence encoding IgG1-Fc

<400> SEQUENCE: 17

atggagacag acacactcct gctatgggta ctgctgctct gggttccagg ttccactggt 60

gactatccat atgatgttcc agattatgct ggggcccagc cggccgtcga cgaggccaaa 120

-continued

```
tcttgtgaca aaactcacac atgcccaccg tgcccagcac ccgaactcct gggggggaccg    180

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag    240

gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac    300

gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc    360

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag    420

tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa    480

gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggatgagctg    540

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc    600

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg    660

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag    720

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag    780

aagagcctct ccctgtctcc gggtaaagtc gacgaacaaa aactcatctc agaagaagat    840

ctgaattgat ag                                                        852
```

The claimed invention is:

1. A recombinant virus of the family Paramyxoviridae, comprising an expressible polynucleotide encoding an IL-12 polypeptide, wherein said IL-12 polypeptide is an IL-12 fusion polypeptide comprising a p35 subunit of an IL-12 and a p40 subunit of an IL-12.

2. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said p35 subunit and said p40 subunit of said IL-12 fusion polypeptide are from the same species.

3. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said IL-12 fusion polypeptide comprises the structure p35-linker-p40.

4. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said linker is -(glycine$_4$-serine)$_n$-, with n=1 to 10.

5. The recombinant virus of the family Paramyxoviridae of claim **1**, further comprising at least one expressible polynucleotide encoding a further activator of the immune response.

6. The recombinant virus of the family Paramyxoviridae of claim **5**, wherein said further activator of the immune response is a secreted immunoglobulin.

7. The recombinant virus of the family Paramyxoviridae of claim **5**, wherein said further activator of the immune response is an Fc domain of an antibody.

8. The recombinant virus of the family Paramyxoviridae of claim **5**, wherein said further activator of the immune response is a secreted soluble activator of the immune response.

9. The recombinant virus of the family Paramyxoviridae of claim **5**, wherein said further activator of the immune response is a secreted soluble anti-PD-L1 antibody.

10. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said recombinant virus is a recombinant Morbillivirus.

11. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said recombinant virus is derived from a measles virus strain Edmonston A or B.

12. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein the at least one expressible polynucleotide encoding an IL-12 polypeptide is comprised in a polynucleotide encoding the recombinant virus of the family Paramyxoviridae.

13. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said polynucleotide encoding the recombinant virus of the family Paramyxoviridae comprises the nucleic acid sequence of any one of SEQ ID NOs:4 to 7, 14, and 15.

14. A medicament comprising

(a) (i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

(ii) a recombinant virus of the family Paramyxoviridae according to claim **1**,

(iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

(iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii) and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

(v) any combination of (i) to (iv); and

(b) at least one pharmacologically acceptable excipient.

15. A method for treating cancer in a subject afflicted with cancer, comprising

a) contacting said subject with

(i) a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 and not comprising an expressible polynucleotide encoding a CTLA-4 antagonist, a PD-1 antagonist, a CD80 antagonist, a CD86 antagonist, or a PD-L1 antagonist;

(ii) a recombinant virus of the family Paramyxoviridae according of claim **1**,

(iii) a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (i) and/or (ii),

(iv) a host cell comprising the recombinant virus of the family Paramyxoviridae according to (i) or (ii) and/or a polynucleotide encoding the recombinant virus of the family Paramyxoviridae of (iii); or

(v) any combination of (i) to (iv); and, thereby,

b) treating cancer in a subject afflicted with cancer.

16. The method of claim **15**, wherein said recombinant virus of the family Paramyxoviridae of (i) is a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 polypeptide and not comprising an expressible polynucleotide encoding a ligand for an immune checkpoint blockade protein.

17. The method of claim **15**, wherein said recombinant virus of the family Paramyxoviridae of (i) is a recombinant virus of the family Paramyxoviridae comprising an expressible polynucleotide encoding an IL-12 polypeptide as the only expressible polynucleotide encoding an activator of the immune response.

18. The method of claim **15**, wherein said cancer is a solid cancer, a metastasis, or a relapse thereof.

19. The method of claim **15**, wherein treating cancer is reducing tumor burden.

20. The method of claim **15**, wherein said cancer is malignant melanoma, head and neck cancer, hepatocellular carcinoma, pancreatic carcinoma, prostate cancer, renal cell carcinoma, gastric carcinoma, colorectal carcinoma, lymphomas or leukemias.

21. The recombinant virus of the family Paramyxoviridae of claim **1**, wherein said p35 subunit and said p40 subunit of said IL-12 fusion polypeptide are a mouse p35 subunit and a mouse p40 subunit or a variant thereof, or a human p35 subunit and a human p40 subunit or a variant thereof.

* * * * *