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(71) Applicant(s)
Baylor College of Medicine

(72) Inventor(s)
Suzuki, Masataka;Rosewell Shaw, Amanda;Porter, Caroline Elaine;Watanabe, Norihiro;Brenner, Malcolm K.

(74) Agent / Attorney
FB Rice Pty Ltd, L 23 44 Market St, Sydney, NSW, 2000, AU

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(71) Applicant: BAYLOR COLLEGE OF MEDICINE

[US/US]; One Baylor Plaza, Houston, TX 77030 (US).

(72) Inventors: SUZUKI, Masataka; 7575 Kirby Drive, #2215, Houston, TX 77030 (US). ROSEWELL SHAW, Amanda; 12304 Winebrook Drive, Pearland, TX (US). PORTER, Caroline, Elaine; 7009 Almeda Road, #820, Houston, TX 77054 (US). WATANABE, Norihiro; 7550 Kirby Drive, #1542, Houston, TX 77030 (US). BRENNER, Malcolm, K.; 4802 Willow, Bellaire, TX 77401 (US).

(74) Agent: SISTRUNK, Melissa, L. et al.; Norton Rose Fulbright US LLP, 1301 McKinney, Suite 5100, Houston, TX 77010-3095 (US).

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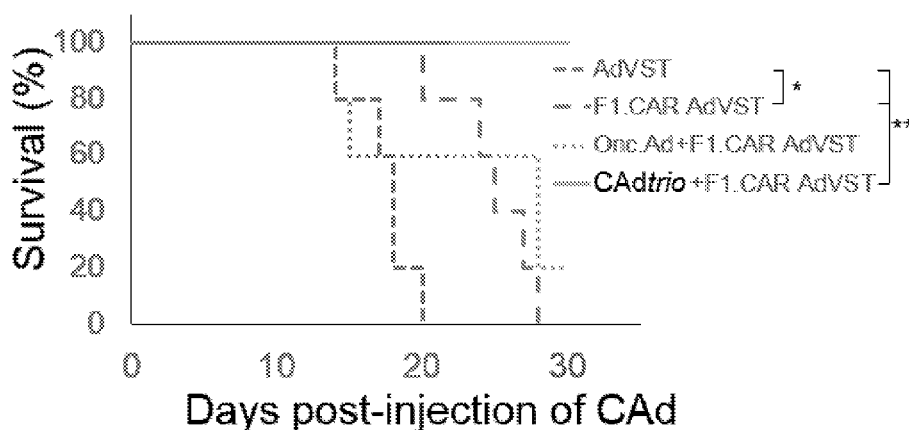


Figure 24D

(57) Abstract: The present disclosure concerns combination therapy for cancer that utilizes (i) an oncolytic virus; (ii) a virus comprising nucleic acid encoding an immunomodulatory factor; and (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen. In particular embodiments, the virus comprises nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding IL-12 and/or antagonist anti-PD-L1 antibody.





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Oncolytic Virotherapy and Immunotherapy

Technical Field

The present disclosure relates at least to the fields of cell biology, molecular biology, immunology, virology, and medicine, including cancer therapy. In particular embodiments the disclosure relates to combination treatments involving the use of oncolytic virotherapy and immunotherapy.

Background

Oncolytic virotherapy for squamous cell carcinoma of the head and neck (HNSCC)

HNSCC is the sixth leading cancer by incidence worldwide. Treatment of locally advanced, recurrent and metastatic HNSCC is often limited by an unfavorable efficacy to toxicity ratio and median survival for patients with metastatic disease remains less than one year (Zandberg and Strome, *Oral Oncology* (2014) 50: 627-632). Since HNSCC is a locoregional disease that presents at or close to the surface of the body, it is amenable to initial intratumoral injection of adenoviral vectors (Ads) to prompt a loco-regional and even a systemic anti-tumor immune response (Liu *et al.*, *Nature Clinical Practice Oncology* (2007) 4: 101-117). Several clinical trials of conditionally-replicating Ads (OncAds) or replication-deficient Ads encoding a therapeutic transgene have demonstrated the safety and feasibility of Ad gene therapy for HNSCC, but failed to show improved overall survival since intensive local treatment, even when combined with chemo/radiotherapy, did not prevent metastasis to distant sites (Liu *et al.*, *supra*). OncAds are generally administered intratumorally, and poorly re-target to metastasized tumors (Koksi *et al.*, *Molecular Therapy: The Journal of the American Society of Gene Therapy* (2015) 23:1641-1652).

OncAd with helper-dependent Ad (HDAd) expressing immunomodulatory molecules

Adenoviral-based vectors (Ads) can infect a range of malignant cells and express high levels of lytic antigens and immunogenic transgenes, making them attractive as agents for cancer gene therapy (Cerullo *et al.*, *Advances in Cancer Research* (2012) 115, 265-318). OncAds selectively replicate in cancer cells and are commonly used Ad-based vectors in clinical trials for cancer gene therapy. However, OncAds have a limited coding capacity for transgenes (~1.5 kb). Helper-dependent Ads (HDAds) are devoid of viral coding sequences, enabling a cargo capacity of up to 34 kb for insertion of multiple transgenes in a single vector (Suzuki *et al.*, *Human Gene Therapy* (2010) 21: 120-126). Since HDAd vector DNA encodes packaging signals, the OncAd replication machinery acts in *trans* to replicate and package both OncAd and HDAd within infected tumor cells, leading to multiple cycles of production and release of both the oncolytic virus and the transgenes encoded by the HDAd (combinatorial adenoviral vectors: CAd-VEC; Farzad *et al.*, *Molecular Therapy - Oncolytics* (2014) 1, 14008).

CAR T-cell therapy

The use of T-cells as agents for cancer therapy has recently been facilitated by the expression of cancer cell antigen-directed chimeric antigen receptors (CARs; reviewed in Kershaw *et al.*, Nature (2013) 13: 525-541). CAR-modified T-cells have shown promise for the treatment of hematological malignancies (Garfall *et al.*, The New England Journal of Medicine (2015) 373:1040-1047), but have been less effective in treating solid tumors, which may in part be a consequence of the highly immunosuppressive nature of the solid tumor microenvironment (Quail *et al.*, Nature Medicine (2013) 19:1423-1437). Due to immunosuppressive mechanisms at tumor site CAR T-cells fail to expand and persist long term despite the expression of one or two costimulatory endodomains.

The present disclosure provides a solution to a long-felt need for effective cancer therapies, including combinatorial cancer therapies.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

Brief Summary

In one aspect, the present invention provides a method of treating a cancer, comprising administering to a subject:

- (i) an oncolytic adenovirus (OncAd);
 - (ii) a helper-dependent adenovirus (HDA) comprising nucleic acid encoding IL-12 and an antagonist anti-PD-L1 antibody; and
 - (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen,
- wherein the cancer to be treated comprises cells expressing the cancer cell antigen for which the CAR is specific.

In another aspect, the present invention provides the use of (i) an oncolytic adenovirus (OncAd), (ii) a helper-dependent adenovirus (HDA) comprising nucleic acid encoding IL-12 and an antagonist anti-PD-L1 antibody, and (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, in the manufacture of a medicament for use in a method of treating a cancer,

wherein the cancer to be treated comprises cells expressing the cancer cell antigen for which the CAR is specific.

In another aspect, the present disclosure provides a method of treating a cancer, comprising administering to a subject:

- (i) an oncolytic virus;
- (ii) a virus comprising nucleic acid encoding an immunomodulatory factor; and
- (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen.

Also provided is a combination of (i) an oncolytic virus, (ii) a virus comprising nucleic acid encoding an immunomodulatory factor, and (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, for use in a method of treating a cancer.

Also provided is the use of (i) an oncolytic virus, (ii) a virus comprising nucleic acid encoding an immunomodulatory factor, and (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, in the manufacture of a medicament for use in a method of treating a cancer.

Also provided is a method of treating a cancer, comprising administering to a subject:

- (i) an oncolytic virus; and
- (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen.

Also provided is a combination of (i) an oncolytic virus, and (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, for use in a method of treating a cancer.

Also provided is the use of (i) an oncolytic virus, and (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, in the manufacture of a medicament for use in a method of treating a cancer.

5 In some embodiments the cell comprising a CAR is specific for the oncolytic virus.

Also provided is a method of treating a cancer, comprising administering to a subject:

(i) an oncolytic virus; and

(ii) at least one immune cell specific for the oncolytic virus.

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Also provided is a combination of (i) an oncolytic virus, and (ii) at least one immune cell specific for the oncolytic virus, for use in a method of treating a cancer.

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Also provided is the use of (i) an oncolytic virus, and (ii) at least one immune cell specific for the oncolytic virus, in the manufacture of a medicament for use in a method of treating a cancer.

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In some embodiments, the oncolytic virus is an oncolytic adenovirus (OncAd). In some embodiments, the oncolytic virus is derived from adenovirus 5 (Ad5). In some embodiments, the oncolytic virus encodes an E1A protein which displays reduced binding to Rb protein as compared to E1A protein encoded by Ad5. In some embodiments, the oncolytic virus encodes an E1A protein lacking the amino acid sequence LTCHEACF (SEQ ID NO:52). In some embodiments, the oncolytic virus encodes an E1A protein comprising, or consisting of or consisting essentially of, the amino acid sequence SEQ ID NO:34. In some embodiments, the oncolytic virus comprises nucleic acid having one or more binding sites for one or more transcription factors. In some embodiments, the oncolytic virus comprises nucleic acid having one or more binding sites for STAT1.

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In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor is a helper-dependent adenovirus (HDAd). In some embodiments, the immunomodulatory factor is selected from: an agonist of an effector immune response or antagonist of an immunoregulatory response. In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding IL-12 and/or antagonist anti-PD-L1 antibody. In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding an enzyme capable of catalysing conversion of a non-toxic factor to a cytotoxic form. In some embodiments, the enzyme is selected from: thymidine kinase, cytosine deaminase, nitroreductase, cytochrome P450, carboxypeptidase G2, purine nucleoside phosphorylase, horseradish peroxidase and carboxylesterase. In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding a thymidine kinase.

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In some embodiments, the at least one cell comprising a CAR specific for a cancer cell antigen is a T cell. In some embodiments, the CAR comprises an antigen binding domain capable of specific binding to HER2. In some embodiments, the CAR comprises an antigen binding domain comprising:

5 a VL domain comprising:
 LC-CRD1: SEQ ID NO:10;
 LC-CRD2: SEQ ID NO:11;
 LC-CRD3: SEQ ID NO:12;

 and a VH domain comprising:
 10 HC-CRD1: SEQ ID NO:13;
 HC-CRD2: SEQ ID NO:14;
 HC-CRD3: SEQ ID NO:15;

or

 a VL domain comprising:
 15 LC-CRD1: SEQ ID NO:18;
 LC-CRD2: SEQ ID NO:19;
 LC-CRD3: SEQ ID NO:20;

 and a VH domain comprising:
 20 HC-CRD1: SEQ ID NO:21;
 HC-CRD2: SEQ ID NO:22;
 HC-CRD3: SEQ ID NO:23;

or

 a VL domain comprising:
 25 LC-CRD1: SEQ ID NO:26;
 LC-CRD2: SEQ ID NO:27;
 LC-CRD3: SEQ ID NO:28;

 and a VH domain comprising:
 30 HC-CRD1: SEQ ID NO:29;
 HC-CRD2: SEQ ID NO:30;
 HC-CRD3: SEQ ID NO:31;

or

 a VL domain comprising:
 35 LC-CRD1: SEQ ID NO:57;
 LC-CRD2: SEQ ID NO:58;
 LC-CRD3: SEQ ID NO:59;

 and a VH domain comprising:
 HC-CRD1: SEQ ID NO:60;
 HC-CRD2: SEQ ID NO:61;
 HC-CRD3: SEQ ID NO:62.

In some embodiments, the CAR comprises an antigen binding domain comprising:

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:16 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:17;

or

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:24 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:25;

or

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:32 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:33;

or

a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:63 and a VH comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:64.

In some embodiments, the method additionally comprises:

(a) isolating at least one cell from a subject, and in specific embodiments the cell is an immune cell;

(b) modifying the at least one cell to express or comprise a CAR specific for a cancer cell antigen, or a nucleic acid encoding a CAR specific for a cancer cell antigen,

(c) optionally expanding the modified at least one cell, and;

(d) administering the modified at least one cell to a subject; in specific embodiments the modified cell upon administration is provided to the subject with one or more other agents for cancer therapy.

In some embodiments, the method of treating a cancer comprises:

(a) isolating at least one cell from a subject;

(b) modifying the at least one cell to express or comprise a CAR specific for a cancer cell antigen, or a nucleic acid encoding a CAR specific for a cancer cell antigen,

(c) optionally expanding the modified at least one cell, and;

(d) administering the modified at least one cell to a subject.

In some embodiments, the method of treating a cancer comprises:

- (a) isolating immune cells from a subject;
- (b) generating or expanding a population of immune cells specific for an oncolytic virus by a method comprising: stimulating the immune cells by culture in the presence of antigen presenting cells (APCs) presenting a peptide of the oncolytic virus, and;
- 5 (c) administering at least one immune cell specific for the oncolytic virus to a subject.

In some embodiments, the cancer is selected from head and neck cancer, nasopharyngeal carcinoma (NPC), cervical carcinoma (CC), oropharyngeal carcinoma (OPC), gastric carcinoma (GC), hepatocellular carcinoma (HCC) and lung cancer.

The present disclosure also provides an oncolytic adenovirus (OncAd) encoding an E1A protein comprising, or consisting of or consisting essentially of, the amino acid sequence SEQ ID NO:34.

The present disclosure also provides an oncolytic adenovirus (OncAd) comprising nucleic acid having one or more binding sites for STAT1. In some embodiments, the OncAd comprises a nucleic acid sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:51 or an equivalent sequence as a result of codon degeneracy.

Also provided is an OncAd comprising a nucleic acid sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:55 or an equivalent sequence as a result of codon degeneracy. In some embodiments the OncAd encodes an E1A protein comprising, or consisting of or consisting essentially of, the amino acid sequence SEQ ID NO:34.

The present disclosure also provides a helper-dependent adenovirus (HDA) comprising nucleic acid encoding IL-12 and/or antagonist anti-PD-L1 antibody. In some embodiments the HDA additionally comprises nucleic acid encoding an enzyme capable of catalysing conversion of a non-toxic factor to a cytotoxic form. In some embodiments the enzyme is selected from: thymidine kinase, cytosine deaminase, nitroreductase, cytochrome P450, carboxypeptidase G2, purine nucleoside phosphorylase, horseradish peroxidase and carboxylesterase.

In some embodiments, the HDA additionally comprises nucleic acid encoding a thymidine kinase. In cases wherein the HDA nucleic acid encodes IL-12 and anti-PD-L1 antibody, the respective expression sequences may or may not be regulated by the same regulatory sequence.

In such cases wherein the HDA nucleic acid encodes both IL-12 and anti-PD-L1 antibody, the positioning on the HDA nucleic acid may be of any suitable configuration, such as in a 5' to 3' direction the nucleic acid region encoding IL-12 being either upstream or downstream of the nucleic acid region encoding anti-PD-L1 antibody.

The present disclosure also provides a chimeric antigen receptor (CAR) comprising an antigen binding domain comprising:

a VL domain comprising:

LC-CRD1: SEQ ID NO:10;

LC-CRD2: SEQ ID NO:11;

LC-CRD3: SEQ ID NO:12;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:13;

HC-CRD2: SEQ ID NO:14;

HC-CRD3: SEQ ID NO:15;

or

a VL domain comprising:

LC-CRD1: SEQ ID NO:18;

LC-CRD2: SEQ ID NO:19;

LC-CRD3: SEQ ID NO:20;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:21;

HC-CRD2: SEQ ID NO:22;

HC-CRD3: SEQ ID NO:23;

or

a VL domain comprising:

LC-CRD1: SEQ ID NO:26;

LC-CRD2: SEQ ID NO:27;

LC-CRD3: SEQ ID NO:28;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:29;

HC-CRD2: SEQ ID NO:30;

HC-CRD3: SEQ ID NO:31;

or

a VL domain comprising:

LC-CRD1: SEQ ID NO:57;

LC-CRD2: SEQ ID NO:58;

LC-CRD3: SEQ ID NO:59;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:60;

HC-CRD2: SEQ ID NO:61;

HC-CRD3: SEQ ID NO:62.

In some embodiments, the CAR comprises an antigen binding domain comprising:

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:16 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:17;

5 or

a VL comprising, or consisting of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:24 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:25;

10 or

a VL comprising, or consisting of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:32 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO:33;

15 or

a VL comprising, or consisting of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% or greater sequence identity to SEQ ID NO:63 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO:64.

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The present disclosure also provides a nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), or the chimeric antigen receptor (CAR) according to the present disclosure.

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The present disclosure also provides a cell comprising the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), the chimeric antigen receptor (CAR), or the nucleic acid or plurality of nucleic acids according to the present disclosure.

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The present disclosure also provides a pharmaceutical composition comprising the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), the chimeric antigen receptor (CAR); the nucleic acid or plurality of nucleic acids or the cell according to the present disclosure may be associated with or comprised in a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

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The present disclosure also provides a method of treating cancer comprising administering to a subject the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), the chimeric antigen receptor (CAR), the nucleic acid or plurality of nucleic acids, the cell or the pharmaceutical composition according to the present disclosure.

The present disclosure also provides the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), the chimeric antigen receptor (CAR), the nucleic acid or plurality of nucleic acids, the cell or the pharmaceutical composition according to the present disclosure for use in a method of treating a cancer.

5

The present disclosure also provides the use of the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), the chimeric antigen receptor (CAR), the nucleic acid or plurality of nucleic acids, the cell or the pharmaceutical composition according to the present disclosure in the manufacture of a medicament for treating a cancer.

10

In some embodiments in accordance with various aspects of the present disclosure, the cancer is selected from head and neck cancer, nasopharyngeal carcinoma (NPC), cervical carcinoma (CC), oropharyngeal carcinoma (OPC), gastric carcinoma (GC), hepatocellular carcinoma (HCC) and lung cancer.

15

The present disclosure also provides a kit of parts comprising a predetermined quantity of the oncolytic adenovirus (OncAd), the helper-dependent adenovirus (HDAd), the chimeric antigen receptor (CAR), the nucleic acid or plurality of nucleic acids, the cell or the pharmaceutical composition according to the present disclosure.

20

Detailed Description

The present disclosure is concerned with the combined use of multiple therapeutic agents for the treatment of cancer. In particular, (i) oncolytic virus, (ii) virus providing immunomodulatory factor(s) and (iii) CAR-bearing immune cells (such as T cells) specific for a cancer cell antigen are used in combination as a cancer therapy. The therapeutic agents are combined to provide an improved treatment effect as compared to the effect seen when any one of the agents is used alone. In certain embodiments, at least two of the three therapeutic agents act in an additive manner to treat the cancer, whereas in other embodiments at least two of the three different therapeutic agents act synergistically to treat the cancer.

30

Without wishing to be bound by any particular theory, the improved treatment effect is thought to be achieved by combining the advantageous features of oncolytic virotherapy (e.g. effective treatment of solid tumours) and CAR-T cell therapy (e.g. effective treatment of diffuse/metastatic cancer), in conjunction with providing a favourable immune environment for CAR-T cell proliferation and activity.

35

Oncolytic virus

The present disclosure employs oncolytic virus. Oncolytic viruses and their use to treat cancer is reviewed, for example, in Chiocca and Rabkin Cancer Immunol Res (2014) 2(4): 295-300, which is hereby incorporated by reference in its entirety.

Oncolytic viruses replicate in, and cause lysis of, cancer cells. Often they are selective for cancer cells over non-cancerous cells; for example, oncolytic viruses commonly replicate in dividing cells in preference to non-dividing cells. Oncolytic viruses are therefore useful to selectively kill cancer cells and destroy tumours, without causing substantial damage to normal, non-cancerous cells/tissue.

Oncolytic virotherapy is associated with several advantages features. Oncolytic viruses often target several oncogenic pathways and use multiple mechanisms for cytotoxicity, minimising the chances of resistance arising. As noted above, because oncolytic viruses replicate selectively in tumours and are non-pathogenic they display minimal toxicity. Virus dose in the tumour also increases over time due to replication of the virus, and the oncolytic viruses can also be manipulated genetically to improve safety, e.g. by engineering sensitivity to a drug.

There are two main classes of oncolytic virus:

(i) viruses that naturally replicate preferentially in cancer cells, and which are non-pathogenic in humans often due to elevated sensitivity to innate antiviral signalling or dependence on oncogenic signalling pathways, including autonomous parvoviruses, myxoma virus (MYXV; poxvirus), Newcastle disease virus (NDV; paramyxovirus), reovirus, and Seneca valley virus (SVV; picornavirus); and

(ii) viruses that are genetically-manipulated, e.g. with mutations/deletions in genes required for replication in normal, but not cancer cells, including adenovirus (Ad), herpes simplex virus (HSV), vaccinia virus (VV), and vesicular stomatitis virus (VSV; rhabdovirus); or viruses that are genetically-manipulated for use as vaccine vectors including measles virus (MV; paramyxovirus), poliovirus (PV; picornavirus), and VV (poxvirus).

Genetic manipulation can include insertion/alteration of functional sequences to provide enhanced selectivity for cancer cells, safety, and/or to modify virus tropism.

For example, oncolytic virus may be genetically engineered to introduce tissue-specific internal ribosome entry sites (IRESs) only permitting viral translation in target cells, and/or to introduce miRNAs/miRNA response elements (MREs); differential miRNA expression between healthy cells or certain tissues vs. tumor cells allows viruses to be detargeted from healthy cells/tissues.

Oncolytic virus may also be engineered to place transcription of the viral genome under the control of a cell- or tissue-specific regulatory region, such as promoter/enhancers (e.g. tumour cell-specific promoter). In some embodiments, the oncolytic virus according to the present disclosure may comprise one or more modifications for such purpose.

Virus may also be modified for transductional targeting, e.g. through modification of virus receptors/coat proteins to target tumour cells and/or detarget healthy cells/tissues.

5 Oncolytic viruses may be administered in such a way as to minimise anti-oncolytic virus responses (e.g. neutralisation by anti-virus antibodies) in the subject and sequestration in the liver, and to maximise tumour delivery, as described in Chiocca and Rabkin, *supra*. For example, oncolytic virus may be administered in a cell carrier, e.g. in mesenchymal stromal cells, myeloid-derived suppresser cells (MDSCs), neural stem cells, T cells, cytokine-induced killer cells, or irradiated tumor cells, or can be coated in nanoparticles.

10 In some embodiments, the oncolytic virus of the present disclosure is, or is derived from, an adenovirus (Ad), herpes simplex virus (HSV), vaccinia virus (VV), vesicular stomatitis virus (VSV); autonomous parvovirus, myxoma virus (MYXV), Newcastle disease virus (NDV), reovirus, Seneca valley virus (SVV) morbillivirus virus, retrovirus, influenza virus, Sindbis virus (SINV) or poxvirus,
15 as examples. In some embodiments, the oncolytic virus is not vaccinia virus. In some embodiments, the oncolytic virus is not vaccinia virus JX-594.

20 As used herein, an oncolytic virus which is "derived from" a reference virus comprises a nucleic acid sequence or amino acid sequence which is possessed by the reference virus. In some embodiments an oncolytic virus which is "derived from" a reference virus comprises one or more genes possessed by the reference virus. In some embodiments an oncolytic virus which is "derived from" encodes one or more proteins encoded by the reference virus.

25 In some embodiments, an oncolytic virus which is derived from a reference virus may comprise nucleic acid sequence encoding one or more functional elements of the reference virus. A "functional element" may e.g. be a transcriptional regulator (e.g. a promoter/enhancer), a regulator of post-transcriptional processing, a translational regulator, a regulator of post-transcriptional processing, a response element, a repeat sequence, or a viral protein. In some embodiments, an oncolytic virus which is derived from a reference virus may comprise one or more genes of, or
30 proteins encoded by, the reference virus.

In some embodiments the oncolytic virus of the present disclosure is, or is derived from, an adenovirus (OncAd). OncAds are reviewed e.g. in Larson *et al.*, *Oncotarget*. (2015) 6(24): 19976–19989, which is hereby incorporated by reference in its entirety.

35 In some embodiments the OncAd is, or is derived from, a species A, B, C, D, E, F or G human adenovirus (i.e. HAdV-A, HAdV-B, HAdV-C, HAdV-D, HAdV-E, HAdV-F or HAdV-G). In some embodiments the OncAd is, or is derived from, a species C human adenovirus. In some embodiments the OncAd is, or is derived from, Ad5, Ad2, Ad1, Ad6 or Ad57.

In some embodiments the OncAd is a conditionally replicating adenovirus (or CRAd).

In some embodiments the OncAd has reduced ability to infect, replicate in and/or lyse non-cancerous cells (as compared to the ability to infect/replicate in and/or lyse equivalent cancerous cells), for example as a consequence of a genetic modification of the adenovirus from which the OncAd is derived.

In some embodiments the oncolytic virus comprises a modification to one or more protein encoding sequences. In some embodiments, the modification alters the production or activity of the encoded protein. In some embodiments, the modification is a truncation or deletion of the protein.

In some embodiments, the OncAd comprises modification to an adenovirus early protein. In some embodiments, the modification is to the region encoding E1A protein. In some embodiments, the OncAd encodes an E1A protein having reduced ability to bind to Rb protein as compared to wildtype E1A protein (e.g. E1A encoded by the adenovirus from which the OncAd is derived). In some embodiments the OncAd encodes an E1A protein lacking the amino acid sequence LTCHEACF (SEQ ID NO:52). An example of an OncAd comprising encodes an E1A protein lacking the amino acid sequence LTCHEACF (SEQ ID NO:52) is Onc5/3Ad2E1Δ24 shown in SEQ ID NO:55.

In some embodiments the oncolytic virus encodes an E1A protein comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:34.

In some embodiments, the oncolytic virus comprises a nucleic acid sequence providing one or more binding sites for one or more transcription factors. In some embodiments, the transcription factor is an activating transcription factor (i.e. a transcriptional activator). The one or more binding sites for one or more transcription factors are preferably provided upstream of (i.e. 5' to) to nucleic acid sequence encoding one or more functional elements (e.g. viral proteins).

In some embodiments, the transcription factor is a transcription factor having increased expression, or increased activity, in cancerous cells as compared to comparable non-cancerous cells (e.g. non-cancerous cells derived from the same tissue/cell type).

Herein, "expression" may refer to gene expression or protein expression. Gene expression can be measured by various means known to those skilled in the art, for example by measuring levels of mRNA by quantitative real-time PCR (qRT-PCR), or by reporter-based methods. Similarly, protein

expression can be measured by various methods well known in the art, e.g. by antibody-based methods, for example by western blot, immunohistochemistry, immunocytochemistry, flow cytometry, ELISA, ELISPOT, or reporter-based methods.

5 An example of an OncAd comprising one or more binding sites for one or more transcription factors is ICOVIR15 described in Rojas *et al.* 2010 Mol Ther 18 1960-1971, which is hereby incorporated by reference its entirety. ICOVIR15 comprises 8 binding sites for the transcription factor E2F.

10 In some embodiments the oncolytic virus comprises one or more binding sites for a transcription factor whose gene or protein expression, or activity in a cell, is upregulated in response to a factor produced or expressed by an immune cell. In some embodiments, a factor produced or expressed by an immune cell may at least one cytokine/chemokine produced by, or a protein expressed at the cell surface of, an effector immune cell, e.g. CD8+ cytotoxic T lymphocyte (CTL), CD4+ T
15 helper 1 (T_H1) cell, natural killer (NK) cell or natural killer T (NKT) cell.

In some embodiments, the oncolytic virus of the present disclosure comprises one or more binding sites for a STAT transcription factor. In some embodiments, the oncolytic virus comprises one or more binding sites for a STAT1. An ICOSTAT OncAd described herein possesses 8 binding sites
20 for STAT1, and STAT1 is known to be upregulated by IFN γ . In particular embodiments, ICOSTAT is a particularly effective treatment for a cancer because the host's immune response to the cancer cells will promote the replication of the oncolytic virus *in situ*.

In some embodiments, the oncolytic virus comprises more than one binding site for a STAT1, e.g.
25 at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 binding sites for STAT1. In some embodiments, a binding site for STAT1 may comprise or consist of or consist essentially of the sequence TTCCGGGAA (SEQ ID NO:53), or TTCTCGGAA (SEQ ID NO:54). In some embodiments, the oncolytic virus of the present disclosure comprises one or more copies of the sequence TTCCGGGAA (SEQ ID NO:53) or TTCTCGGAA (SEQ ID NO:54).

30 In some embodiments the oncolytic virus according to the present disclosure comprises, or consists of, or consists essentially of, a nucleic acid sequence having at least 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
35 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:51 or an equivalent sequence as a result of codon degeneracy.

In some embodiments the oncolytic virus according to the present disclosure comprises, or consists of, or consists essentially of, a nucleic acid sequence having at least 60%, 61%, 62%,

63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:55 or an equivalent sequence as a result of codon degeneracy.

5

In some embodiments the oncolytic virus according to the present disclosure encodes the same proteins as the proteins encoded by an oncolytic virus comprising, consisting of, or consisting essentially of, the nucleic acid shown in SEQ ID NO:55. In some embodiments the oncolytic virus according to the present disclosure encodes the same proteins as the proteins encoded by an oncolytic virus comprising, consisting of, or consisting essentially of, the nucleic acid shown in SEQ ID NO:51.

10

Virus comprising nucleic acid encoding an immunomodulatory factor

The present disclosure employs a virus comprising nucleic acid encoding an immunomodulatory factor. The virus acts as a vector for delivering the immunomodulatory factor. In certain embodiments, the virus comprises nucleic acid encoding more than one immunomodulatory factor(s).

15

Any virus capable of introducing the nucleic acid encoding an immunomodulatory factor into a cell (e.g. a primary human immune cell) may be used. Suitable viruses include gammaretrovirus (e.g. murine Leukemia virus (MLV)-derived vectors), lentivirus, adenovirus, adeno-associated virus, vaccinia virus and herpesvirus, e.g. as described in Maus *et al.*, Annu Rev Immunol (2014) 32:189-225 or Morgan and Boyerinas, Biomedicines 2016 4, 9, which are both hereby incorporated by reference in its entirety. In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor is, or is derived from, an adenovirus, lentivirus, retrovirus, or herpesvirus.

20

25

In some embodiments, the virus comprising nucleic acid encoding at least one immunomodulatory factor is an oncolytic virus comprising nucleic acid encoding at least one immunomodulatory factor.

30

An immunomodulatory factor(s) encoded by the virus comprising nucleic acid encoding the immunomodulatory factor(s) according to the present disclosure are preferably selected to facilitate the immune response to a cancer in a subject, in particular the cell-mediated immune response. In one embodiment, the immunomodulatory factor(s) provide favourable conditions for the activation, recruitment, proliferation, activity and/or survival of effector immune cells (e.g. CTLs, T_H1 cells, NK cells or NKT cells).

35

In some embodiments, the immunomodulatory factor may be an agonist of an effector immune response, e.g. a cytokine or chemokine promoting activation, recruitment, proliferation, activity

and/or survival of effector immune cells (e.g. IL-2, IL-7, IL-17, IL-12, IL-21, IL-15, MIP-1 α or RANTES), agonist antibody for a costimulatory receptor (e.g. 4-1BB, OX40, CD28, CD27, ICOS, CD30 or GITR), or ligand for a costimulatory receptor (e.g. 4-1BBL, OX40L, CD80, CD86, CD70, ICOSL, CD30L or GITRL). In some embodiments, the agonist of an effector immune response
5 may be an antagonist of an immune checkpoint inhibitor, or an antagonist of ligand for immune checkpoint inhibitor, e.g. antagonist antibody to PD-L1, PD-L2, PD-1, CTLA-4, LAG-3, TIM-3, Gal-9, TIGIT, VISTA or BTLA, or an antagonist of a cytokine/chemokine which is an antagonist of an effector immune response, e.g. TGF β (i.e. antagonist anti-TGF β antibody or soluble/decoy TGF β receptor). In some embodiments, an agonist of an effector immune response may be a molecule
10 for engaging and co-opting bystander effector immune cells such as T cells and NK cells.

In some embodiments, the immunomodulatory factor may be an antagonist of an immunoregulatory response, e.g. an antagonist of a cytokine/chemokine promoting activation, recruitment, proliferation, activity and/or survival of immunoregulatory cells such as regulatory T
15 cells (Tregs) and/or myeloid-derived suppressor cells (MDSCs), e.g. CCL9, CXCL10, CCL20, CCL22.

In some embodiments the virus comprising nucleic acid encoding an immunomodulatory factor may additionally comprise nucleic acid encoding further functional sequence(s). For example, the
20 virus may comprise nucleic acid encoding a protein(s) for reducing growth/proliferation/survival of infected cells, or protein(s) for rendering infected cells sensitive to treatment with a given agent, or protein(s) for disrupting tumour structure (e.g. enzymes for digesting tumour matrix) to facilitate immune cell infiltration.

In some embodiments the virus comprising nucleic acid encoding an immunomodulatory factor additionally comprises nucleic acid encoding an enzyme capable of catalysing conversion of a
25 non-toxic factor to a cytotoxic form. The enzyme may catalyse conversion of a non-toxic prodrug into its active, cytotoxic form.

Enzyme/prodrug systems are well known in the art and include those described in Malekshah et al. Curr Pharmacol Rep. (2016) 2(6): 299–308 which is hereby incorporated by reference in its
30 entirety. Examples of non-toxic prodrugs, their active cytotoxic forms and enzymes capable of catalysing conversion of the non-toxic prodrugs to their active cytotoxic forms are shown in Figure 2 of Malekshah et al.

In some embodiments the virus comprising nucleic acid encoding an immunomodulatory factor additionally comprises nucleic acid encoding a thymidine kinase, cytosine deaminase,
35 nitroreductase, cytochrome P450, carboxypeptidase G2, purine nucleoside phosphorylase, horseradish peroxidase and/or carboxylesterase.

For example, the virus may comprise nucleic acid encoding thymidine kinase for rendering cells expressing the virus sensitive to treatment with ganciclovir (GCV), aciclovir (ACV) and/or valaciclovir. The virus may comprise nucleic acid encoding cytosine deaminase for rendering cells
5 expressing the virus sensitive to treatment with 5-fluorocytosine (5-FC), which is converted by cytosine deaminase to 5-fluorouracil (5-FU). The virus may comprise nucleic acid encoding nitroreductase for rendering cells expressing the virus sensitive to treatment with CB1954, nitro-CBI-DEI and/or PR-104A. The virus may comprise nucleic acid encoding cytochrome P450 for rendering cells expressing the virus sensitive to treatment with oxazaphosphorine (e.g.
10 cyclophosphamide or ifosfamide). The virus may comprise nucleic acid encoding carboxypeptidase G2 for rendering cells expressing the virus sensitive to treatment with nitrogen mustard based drugs (e.g. CMDA or ZD2767P). The virus may comprise nucleic acid encoding purine nucleoside phosphorylase for rendering cells expressing the virus sensitive to treatment with 6-methylpurine 2-deoxyriboside and/or fludarabine (e.g. 6-methylpurine-2'-deoxyriboside
15 (MeP-dR), 2-F-2'-deoxyadenosine (F-dAdo) or arabinofuranosyl-2-F-adenine monophosphate (F-araAMP). The virus may comprise nucleic acid encoding horseradish peroxidase for rendering cells expressing the virus sensitive to treatment with indole-3-acetic acid (IAA). The virus may comprise nucleic acid encoding carboxylesterase for rendering cells expressing the virus sensitive to treatment with irinotecan.

20 In some embodiments the virus may comprise nucleic acid encoding antagonist of a growth factor.

In some embodiments, the virus may be a helper-dependent adenovirus (HDAd). HDAds are reviewed, for example, in Rosewell *et al.*, J Genet Syndr Gene Ther (2011) Suppl 5:001, which is
25 hereby incorporated by reference in its entirety.

HDAds are devoid of viral protein coding sequences, and therefore possess a large capacity (up to 37 Kb) for transduction of a coding sequence of interest. HDAds are non-integrating, and are able to efficiently transduce a wide variety of cell types independently of the cell cycle, and mediate
30 long-term transgene expression without chronic toxicity.

HDAds comprise only the *cis* acting viral elements required for genomic replication (inverted terminal repeats (ITRs)) and encapsidation (ψ), and are therefore dependent on helper virus for propagation. When a cell is infected with both the helper virus and the HDAd, the helper virus
35 replication machinery acts in *trans* to replicate and package HDAd.

In particular embodiments of the present disclosure, the oncolytic virus is an OncAd and the virus comprising nucleic acid encoding an immunomodulatory factor is a HDAd, and the OncAd and HDAd are able to co-infect and replicate in cells of a cancer.

Dependence of the HDAd on help from the OncAd provides highly localised expression of the immunomodulatory factor(s). That is, because the HDAd is only able to propagate in cells co-infected with the OncAd, and in turn because the OncAd is selective for replication in cancerous cells, expression of the factor(s) encoded by the HDAd is restricted to cancerous cells/tissue, minimising side effects.

Furthermore, because the OncAd and HDAd efficiently target and infect tumour cells, expression of the immunomodulatory factor(s) in those cells can change the normally immunosuppressive tumour microenvironment to provide conditions promoting the activation, recruitment (*i.e.* tumour penetration/infiltration), proliferation, activity and/or survival of effector immune cells.

In particular, in the context of the present disclosure wherein the methods of treatment employ the use of CAR-T cells, expression of the immunomodulatory factor(s) encoded by the HDAd provide for enhanced activation, recruitment, proliferation, activity and/or survival of the CAR-T cells.

In particular embodiments herein the virus comprising nucleic acid encoding an immunomodulatory factor is a HDAd comprising nucleic acid encoding IL-12p70, HSV-1 thymidine kinase and an antagonist anti-PD-L1 minibody.

In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor according to the present disclosure encodes IL-12. In some embodiments the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:35.

In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor according to the present disclosure encodes an antagonist of PD-1/PD-L1 signalling. In some embodiments the antagonist of PD-1/PD-L1 signalling is an anti-PD-L1 antibody.

In some embodiments the anti-PD-L1 antibody comprises an antigen binding domain comprising a VL domain comprising:

LC-CRD1: SEQ ID NO:39;

LC-CRD2: SEQ ID NO:40;

LC-CRD3: SEQ ID NO:41;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:42;

HC-CRD2: SEQ ID NO:43;

HC-CRD3: SEQ ID NO:44.

In some embodiments the anti-PD-L1 antibody comprises a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:45 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:46.

In some embodiments the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:38.

In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor according to the present disclosure comprises an amino acid sequence encoding a thymidine kinase. In some embodiments the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:36.

In some embodiments, the virus comprising nucleic acid encoding an immunomodulatory factor according to the present disclosure comprises, or consists of or consist essentially of, a nucleic acid sequence having at least 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:50 or an equivalent sequence as a result of codon degeneracy.

Chimeric Antigen Receptors (CARs) and CAR-expressing cells

The present disclosure employs immune cells comprising a chimeric antigen receptor (CAR).

Chimeric Antigen Receptors (CARs) are recombinant receptors that provide both antigen-binding and immune cell activating functions. CAR structure and engineering is reviewed, for example, in Dotti *et al.*, Immunol Rev (2014) 257(1), hereby incorporated by reference in its entirety. CARs comprise an antigen-binding region linked to a cell membrane anchor region and a signaling region. An optional hinge region may provide separation between the antigen-binding region and cell membrane anchor region, and may act as a flexible linker.

The antigen-binding region of a CAR may be based on the antigen-binding region of an antibody which is specific for the antigen to which the CAR is targeted, or other agent capable of binding to the target. For example, the antigen-binding domain of a CAR may comprise amino acid sequences for the complementarity-determining regions (CDRs) or complete light chain and heavy chain variable region amino acid sequences of an antibody which binds specifically to the target protein. Antigen-binding domains of CARs may target antigen based on other protein:protein interaction, such as ligand:receptor binding; for example an IL-13R α 2-targeted CAR has been developed using an antigen-binding domain based on IL-13 (see *e.g.* Kahlon *et al.* 2004 Cancer Res 64(24): 9160-9166).

The CAR of the present disclosure comprises an antigen-binding region specific for a cancer cell antigen. The antigen binding region of the CAR may be provided with any suitable format, *e.g.* scFv, Fab, *etc.* In some embodiments, the antigen binding region of the CAR comprises or consists of a cancer cell antigen binding scFv.

A cancer cell antigen is an antigen which is expressed by a cancer cell. A cancer cell antigen may be any peptide/polypeptide, glycoprotein, lipoprotein, glycan, glycolipid, lipid, or fragment thereof. A cancer cell antigen's expression may be associated with a cancer. A cancer cell antigen may be abnormally expressed by a cancer cell (*e.g.* the cancer cell antigen may be expressed with abnormal localisation), or may be expressed with an abnormal structure by a cancer cell. A cancer cell antigen may be capable of eliciting an immune response.

In some embodiments, the antigen is expressed at the cell surface of the cancer cell (*i.e.* the cancer cell antigen is a cancer cell surface antigen). In some embodiments, the part of the antigen which is bound by the bispecific antigen binding polypeptide of the present disclosure is displayed on the external surface of the cancer cell (*i.e.* is extracellular). In some embodiments, the antigen is anchored to the cell membrane, *e.g.* via a transmembrane domain or other membrane anchor (*e.g.* a lipid anchor such as a GPI anchor). In some embodiments, the cancer cell antigen is expressed at the cell surface (*i.e.* is expressed in or at the cell membrane) of a cancerous cell, but may be expressed inside the cell (*i.e.* is expressed inside comparable non-cancerous cells).

The cancer cell antigen may be a cancer-associated antigen. In some embodiments the cancer cell antigen is an antigen whose expression is associated with the development, progression and/or severity of symptoms of a cancer. The cancer-associated antigen may be associated with the cause or pathology of the cancer, or may be expressed abnormally as a consequence of the cancer. In some embodiments, the antigen is an antigen whose expression is upregulated (*e.g.* at the RNA and/or protein level) by cells of a cancer, *e.g.* as compared to the level of expression of by comparable non-cancerous cells (*e.g.* non-cancerous cells derived from the same tissue/cell type).

In some embodiments, the cancer-associated antigen may be preferentially expressed by cancerous cells, and not expressed by comparable non-cancerous cells (e.g. non-cancerous cells derived from the same tissue/cell type). In some embodiments, the cancer-associated antigen may be the product of a mutated oncogene or mutated tumor suppressor gene. In some embodiments, the cancer-associated antigen may be the product of an overexpressed cellular protein, a cancer antigen produced by an oncogenic virus, an oncofetal antigen, or a cell surface glycolipid or glycoprotein.

Cancer cell antigens are reviewed by Zarour HM, DeLeo A, Finn OJ, *et al.* Categories of Tumor Antigens. In: Kufe DW, Pollock RE, Weichselbaum RR, *et al.*, editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Cancer cell antigens include oncofetal antigens: CEA, Immature laminin receptor, TAG-72; oncoviral antigens such as HPV E6 and E7; overexpressed proteins: BING-4, calcium-activated chloride channel 2, cyclin-B1, 9D7, Ep-CAM, EphA3, HER2/neu, telomerase, mesothelin, SAP-1, surviving; cancer-testis antigens: BAGE, CAGE, GAGE, MAGE, SAGE, XAGE, CT9, CT10, NY-ESO-1, PRAME, SSX-2; lineage restricted antigens: MART1, Gp100, tyrosinase, TRP-1/2, MC1R, prostate specific antigen; mutated antigens: β -catenin, BRCA1/2, CDK4, CML66, Fibronectin, MART-2, p53, Ras, TGF- β RII; post-translationally altered antigens: MUC1, idiotypic antigens: Ig, TCR. Other cancer cell antigens include heat-shock protein 70 (HSP70), heat-shock protein 90 (HSP90), glucose-regulated protein 78 (GRP78), vimentin, nucleolin, feto-acinar pancreatic protein (FAPP), alkaline phosphatase placental-like 2 (ALPPL-2), siglec-5, stress-induced phosphoprotein 1 (STIP1), protein tyrosine kinase 7 (PTK7), and cyclophilin B.

In some embodiments, the cancer cell antigen is HER2. In some embodiments, the CAR of the present disclosure comprises an antigen binding domain capable of specific binding to HER2. In some embodiments, the CAR comprises an antigen binding domain comprising the CDRs of an antibody capable of specific binding to HER2. In some embodiments, the CAR comprises an antigen binding domain comprising the VL and VH regions of an antibody capable of specific binding to HER2.

In particular embodiments, the cell expressing the CAR comprises two, separate CARs each that target different cancer cell antigens, and in particular aspects at least one of the CARs targets HER2. In some cases, the CAR is bispecific for two different cancer cell antigens, one of which may be HER2.

In some embodiments the CAR comprises an antigen binding domain comprising a VL domain comprising:

LC-CRD1: SEQ ID NO:10, SEQ ID NO:18, SEQ ID NO:26 or SEQ ID NO: 57;

LC-CRD2: SEQ ID NO:11, SEQ ID NO:19, SEQ ID NO:27 or SEQ ID NO: 58;

LC-CRD3: SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:28 or SEQ ID NO: 59;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:29 or SEQ ID NO: 60;

5 HC-CRD2: SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:30 or SEQ ID NO: 61;

HC-CRD3: SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:31 or SEQ ID NO: 62.

In some embodiments the CAR comprises an antigen binding domain comprising a VL domain comprising:

10 LC-CRD1: SEQ ID NO:10;

LC-CRD2: SEQ ID NO:11;

LC-CRD3: SEQ ID NO:12;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:13;

15 HC-CRD2: SEQ ID NO:14;

HC-CRD3: SEQ ID NO:15.

In some embodiments the CAR comprises an antigen binding domain comprising a VL domain comprising:

20 LC-CRD1: SEQ ID NO:18;

LC-CRD2: SEQ ID NO:19;

LC-CRD3: SEQ ID NO:20;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:21;

25 HC-CRD2: SEQ ID NO:22;

HC-CRD3: SEQ ID NO:23.

In some embodiments the CAR comprises an antigen binding domain comprising a VL domain comprising:

30 LC-CRD1: SEQ ID NO:26;

LC-CRD2: SEQ ID NO:27;

LC-CRD3: SEQ ID NO:28;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:29;

35 HC-CRD2: SEQ ID NO:30;

HC-CRD3: SEQ ID NO:31.

In some embodiments the CAR comprises an antigen binding domain comprising a VL domain comprising:

a VL domain comprising:

LC-CRD1: SEQ ID NO:57;

LC-CRD2: SEQ ID NO:58;

LC-CRD3: SEQ ID NO:59;

5 and a VH domain comprising:

HC-CRD1: SEQ ID NO:60;

HC-CRD2: SEQ ID NO:61;

HC-CRD3: SEQ ID NO:62.

10 In some embodiments the CAR comprises an antigen binding domain comprising a light chain variable region (VL) comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:16, 24, 32 or 63.

15 In some embodiments the CAR comprises an antigen binding domain comprising a heavy chain variable region (VH) comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:17, 25, 33 or 64.

20 In some embodiments the CAR comprises an antigen binding domain comprising a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:16 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:17.

25 In some embodiments the CAR comprises an antigen binding domain comprising a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:24 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:25.

30 In some embodiments the CAR comprises an antigen binding domain comprising a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:32 and a VH

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comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:33. In some embodiments the CAR comprises an antigen binding domain comprising a VL comprising, consisting of, or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:63 and a VH comprising, consisting of, or consisting essentially of, an amino acid sequence having at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:64.

In some embodiments, the CAR of the present disclosure comprises an antigen binding region which comprises or consists of or consists essentially of an antibody/antigen binding fragment according to the present disclosure.

The cell membrane anchor region is provided between the antigen-binding region and the signalling region of the CAR. The cell membrane anchor region provides for anchoring the CAR to the cell membrane of a cell expressing a CAR, with the antigen-binding region in the extracellular space, and signalling region inside the cell. Suitable transmembrane domains include transmembrane region derived from CD28, CD3- ζ , CD4 or CD8.

In some embodiments the cell membrane anchor region comprises, or consists of or consists essentially of, an amino acid sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:4.

The signalling region of a CAR allows for activation of the T cell. The CAR signalling regions may comprise the amino acid sequence of the intracellular domain of CD3- ζ , which provides immunoreceptor tyrosine-based activation motifs (ITAMs) for phosphorylation and activation of the CAR-expressing T cell. Signalling regions comprising sequences of other ITAM-containing proteins have also been employed in CARs, such as domains comprising the ITAM containing region of Fc γ RI (Haynes *et al.*, 2001 J Immunol 166(1):182-187). CARs comprising a signalling region derived from the intracellular domain of CD3- ζ are often referred to as first generation CARs.

In some embodiments the cell membrane anchor region comprises, or consists of or consists essentially of, an amino acid sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:6.

Signalling regions of CARs may also comprise co-stimulatory sequences derived from the signalling region of co-stimulatory molecules, to facilitate activation of CAR-expressing T cells upon binding to the target protein. Suitable co-stimulatory molecules include at least CD28, OX40, 4-1BB, ICOS and CD27. CARs having a signalling region including additional co-stimulatory sequences are often referred to as second generation CARs.

In some cases CARs are engineered to provide for co-stimulation of different intracellular signalling pathways. For example, signalling associated with CD28 costimulation preferentially activates the phosphatidylinositol 3-kinase (P13K) pathway, whereas the 4-1BB-mediated signalling is through TNF receptor associated factor (TRAF) adaptor proteins. Signalling regions of CARs therefore sometimes contain co-stimulatory sequences derived from signalling regions of more than one co-stimulatory molecule. CARs comprising a signalling region with multiple co-stimulatory sequences are often referred to as third generation CARs.

In some embodiments, the CAR of the present disclosure comprises one or more co-stimulatory sequences comprising or consisting of or consisting essentially of an amino acid sequence which comprises, consists of or consists essentially of, or is derived from, the amino acid sequence of the intracellular domain of one or more of CD28, OX40, 4-1BB, ICOS and CD27.

In some embodiments the cell membrane anchor region comprises, or consists of or consists essentially of, an amino acid sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:5.

An optional hinge region may provide separation between the antigen-binding domain and the transmembrane domain, and may act as a flexible linker. Hinge regions may be flexible domains allowing the binding moiety to orient in different directions. Hinge regions may be derived from IgG1 or the CH₂CH₃ region of immunoglobulin. In some embodiments, the CAR of the present disclosure comprises a hinge region comprising or consisting of or consisting essentially of an amino acid sequence which comprises, consists of or consists essentially of, or is derived from, the amino acid sequence of the hinge region of IgG1 or the CH₂CH₃ region of immunoglobulin.

In some embodiments the cell membrane anchor region comprises, or consists of or consists essentially of, an amino acid sequence having at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:9.

In some embodiments the CAR comprises, or consists of or consists essentially of, an amino acid sequence having at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or having 100% sequence identity to SEQ ID NO:1, 2, 3 or 56.

The present disclosure also provides a cell comprising or expressing a CAR according to the present disclosure. Also provided is a cell comprising or expressing a nucleic acid encoding a CAR according to the disclosure. Engineering of CARs into T cells may be performed during culture, *in vitro*, for transduction and expansion, such as happens during expansion of T cells for adoptive T cell therapy. Methods for engineering immune cells to express CARs are known to the skilled person and are described e.g. in Wang and Rivière *Mol Ther Oncolytics*. (2016) 3:16015, which is hereby incorporated by reference in its entirety. It will be appreciated that "at least one cell" encompasses plural cells, e.g. populations of such cells.

The cell comprising or expressing a CAR according to the present disclosure may be a eukaryotic cell, e.g. a mammalian cell. The mammal may be a human, or a non-human mammal (e.g. rabbit, guinea pig, rat, mouse or other rodent (including any animal in the order Rodentia), cat, dog, pig, sheep, goat, cattle (including cows, e.g. dairy cows, or any animal in the order Bos), horse (including any animal in the order Equidae), donkey, and non-human primate).

In some embodiments, the cell may be from, or may have been obtained from, a human subject. Where the CAR-expressing cell is to be used in the treatment of a subject, the cell may be from the subject to be treated with the CAR-expressing cell (*i.e.* the cell may be autologous), or the cell may be from a different subject (*i.e.* the cell may be allogeneic).

The cell may be an immune cell. The cell may be a cell of hematopoietic origin, e.g. a neutrophil, eosinophil, basophil, dendritic cell, lymphocyte, or monocyte. The lymphocyte may be e.g. a T cell, B cell, NK cell, NKT cell or innate lymphoid cell (ILC), or a precursor thereof. The cell may express e.g. CD3 polypeptides (e.g. CD3 γ CD3 ϵ CD3 ζ or CD3 δ), TCR polypeptides (TCR α or TCR β), CD27, CD28, CD4 or CD8.

In some embodiments, the cell is a T cell. In some embodiments, the T cell is a CD3 $^{+}$ T cell. In some embodiments, the T cell is a CD3 $^{+}$, CD8 $^{+}$ T cell. In some embodiments, the T cell is a cytotoxic T cell (e.g. a cytotoxic T lymphocyte (CTL)).

The use of CAR T-cells is associated with advantages that they can be systemically administered, and will home to both primary and metastasized tumors (Manzo *et al.*, *Human Molecular Genetics* (2015) R67-73).

In some embodiments, the cell is an antigen-specific T cell. In embodiments herein, an "antigen-specific" T cell is a cell which displays certain functional properties of a T cell in response to the antigen for which the T cell is specific, or a cell expressing said antigen. In some embodiments, the properties are functional properties associated with effector T cells, e.g. cytotoxic T cells.

In some embodiments, an antigen-specific T cell may display one or more of the following properties: cytotoxicity, e.g. to a cell comprising/expressing antigen for which the T cell is specific; proliferation, IFN γ expression, CD107a expression, IL-2 expression, TNF α expression, perforin expression, granzyme expression, granulysin expression, and/or FAS ligand (FASL) expression, e.g. in response to antigen for which the T cell is specific or a cell comprising/expressing antigen for which the T cell is specific. Antigen-specific T cells comprise a TCR capable of recognising a peptide of the antigen for which the T cell is specific when presented by the appropriate MHC molecule. Antigen-specific T cells may be CD4 $^{+}$ T cells and/or CD8 $^{+}$ T cells.

In some embodiments, the antigen for which the T cell is specific may be a peptide or polypeptide of a virus, e.g. Adenovirus, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), human papilloma virus (HPV), influenza virus, measles virus, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), lymphocytic choriomeningitis virus (LCMV), or herpes simplex virus (HSV).

A T cell which is specific for an antigen of a virus may be referred to herein as a virus-specific T cell (VST). VSTs may be CD4 $^{+}$ T cells (e.g. T $_H$ cells) and/or CD8 $^{+}$ T cells (e.g. CTLs). A T cell which is specific for an antigen of a particular virus may be described as being specific for the relevant virus; for example, a T cell which is specific for an antigen of an Adenovirus may be referred to as an Adenovirus-specific T cell, or "AdVST". The use of virus-specific T cells for the generation of CAR-T cells is associated with the advantage that whilst naïve T cells may have limited long-term persistence after infusion, virus-specific T-cells (VSTs) derived from the memory compartment, and genetically-modified VSTs have been shown to persist for over 10 years after infusion in stem cell transplant recipients (Cruz *et al.*, *Cytotherapy* (2010) 12:743-749). For example, VSTs expressing GD2.CARs have been shown to persist long-term after infusion and produce complete tumor responses in patients with low tumor burden (Sun *et al.*, *Journal for Immunotherapy of Cancer* (2015) 3:5 and Pule *et al.*, *Nature Medicine* (2008) 14: 1264-1270).

In some embodiments the cell comprising/expressing the CAR is a virus-specific T cell (VST, e.g. a virus-specific CD4 $^{+}$ T cell (e.g. T $_H$ cell) and/or a virus-specific CD8 $^{+}$ T cell (e.g. CTL). In some embodiments the CAR-expressing cell is an Adenovirus-specific T cell (AdVST), Cytomegalovirus-specific T cell (CMVST), Epstein-Barr virus-specific T cell (EBVST), influenza virus-specific T cell, measles virus-specific T cell, hepatitis B virus-specific T cell (HBVST), hepatitis C virus-specific T cell (HCVST), human immunodeficiency virus-specific T cell (HIVST), lymphocytic choriomeningitis virus-specific T cell (LCMVST), Herpes simplex virus-specific T cell (HSVST) or human papilloma virus (HPVST).

In some embodiments the cell comprising/expressing the CAR is an oncolytic virus-specific immune cell (e.g. an oncolytic virus-specific T cell), e.g. as described herein.

Any cells of the disclosure may be included in an isolated population of cells that may or may not be homogeneous. In specific embodiments, the cell population has a majority of cells that are immune cells specific for an oncolytic virus and/or that express a CAR. The cells in the cell population may comprise an oncolytic adenovirus (OncAd), a helper-dependent adenovirus (HDA), a chimeric antigen receptor (CAR) and/or nucleic acid or plurality of nucleic acids that encodes one or more of the OncAd, HDA, and/or CAR. In particular embodiments, the cell population has at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% of cells that comprise an oncolytic adenovirus (OncAd), a helper-dependent adenovirus (HDA), a chimeric antigen receptor (CAR) and/or nucleic acid or plurality of nucleic acids that encodes one or more of the OncAd, HDA, and/or CAR.

Oncolytic virus-specific immune cells

Aspects of the present disclosure provide oncolytic virus-specific immune cells (also referred to herein as immune cells specific for an oncolytic virus). Oncolytic virus-specific immune cells express/comprise a receptor capable of recognising a peptide of an antigen of an oncolytic virus (e.g. when presented by an MHC molecule). The immune cell may express/comprise such a receptor as a result of expression of endogenous nucleic acid encoding such antigen receptor, or as a result of having been engineered to express such a receptor.

In some embodiments an oncolytic virus-specific immune cell may be a cell of hematopoietic origin, e.g. a neutrophil, eosinophil, basophil, dendritic cell, lymphocyte, or monocyte. The lymphocyte may be e.g. a T cell, B cell, NK cell, NKT cell or innate lymphoid cell (ILC), or a precursor thereof. The cell may express e.g. CD3 polypeptides (e.g. CD3 γ CD3 ϵ CD3 ζ or CD3 δ), TCR polypeptides (TCR α or TCR β), CD27, CD28, CD4 or CD8. In some embodiments, the oncolytic virus-specific immune cell is a T cell, e.g. a CD3+ T cell. In some embodiments, the T cell is a CD3+, CD4+ T cell. In some embodiments, the T cell is a CD3+, CD8+ T cell. In some embodiments, the T cell is a T helper cell (T_H cell)). In some embodiments, the T cell is a cytotoxic T cell (e.g. a cytotoxic T lymphocyte (CTL)).

The oncolytic virus-specific immune cell (e.g. oncolytic virus-specific T cell) may be specific for an oncolytic virus as described herein. That is to say, the oncolytic virus-specific immune cell may be specific for one or more antigens of an oncolytic virus described herein.

Methods for generating/expanding populations of immune cells specific for antigen(s) of interest and/or a virus of interest are well known in the art, and are described e.g. in Wang and Rivière Cancer Gene Ther. (2015) 22(2):85–94, which is hereby incorporated by reference in its entirety.

Such methods may involve contacting heterogeneous populations of immune cells (e.g. peripheral blood mononuclear cells (PBMCs), peripheral blood lymphocytes (PBLs) tumor-infiltrating lymphocytes (TILs)) with one or more peptides of the antigen(s) of interest, or cells comprising/expressing the antigen(s)/peptides. Cells comprising/expressing the antigen(s)/peptides may do so as a consequence of infection with the virus comprising/encoding the antigen(s), uptake by the cell of the antigen(s)/peptides thereof or expression of the antigen(s)/peptides thereof. The presentation is typically in the context of an MHC molecule at the cell surface of the antigen-presenting cell.

Cells comprising/expressing the antigen(s)/peptides may have been contacted ("pulsed") with peptides of the antigen(s) according to methods well known to the skilled person. Antigenic peptides may be provided in a library of peptide mixtures (corresponding to one or more antigens), which may be referred to as pepmixes. Peptides of pepmixes may e.g. be overlapping peptides of 8-20 amino acids in length, and may cover all or part of the amino acid sequence of the relevant antigen.

Cells within the population of immune cells comprising receptors specific for the peptide(s) may be activated (and stimulated to proliferate), following recognition of peptide(s) of the antigen(s) presented by antigen-presenting cells (APCs) in the context of appropriate costimulatory signals. It will be appreciated that "an immune cell specific for an oncolytic virus" encompasses plural cells, e.g. populations of such cells. Such populations may be generated/expanded *in vitro* and/or *ex vivo*.

In some embodiments, an immune cell specific for an oncolytic virus is specific for an oncolytic adenovirus (OncAd), e.g. an OncAd as described herein. In some embodiments, an immune cell specific for an oncolytic virus is specific for an antigen of an OncAd. In some embodiments, the antigen is, or is derived from, an OncAd protein, e.g. a protein encoded by an early gene (e.g. E1 (e.g. E1A, E1B), E2 (e.g. E2A, E2B), E3 or E4), a protein encoded by a late gene (e.g. L1, L2, L3, L4 or L5), a protein encoded by IX, or a protein encoded by IVa2. In some embodiments, the antigen is, or is derived from, an OncAd hexon and/or penton.

In some embodiments in accordance with various aspects of the present disclosure an immune cell specific for a virus may be generated/expanded (or may have been generated/expanded) by a method comprising: stimulating a population of immune cells by culture in the presence of antigen presenting cells (APCs) presenting a peptide of the virus.

In some embodiments an immune cell specific for an oncolytic virus according to the present disclosure is prepared by a method employing a PepMix comprising a mixture of overlapping

peptides corresponding to Human Adenovirus 3 hexon and/or a PepMix comprising a mixture of overlapping peptides corresponding to Human Adenovirus 5 penton.

5 In some embodiments the oncolytic virus-specific immune cell expresses/comprises a CAR, e.g. a CAR as described herein. The oncolytic virus-specific immune cell may be engineered to express a CAR e.g. by transfection/transduction of the oncolytic virus-specific immune cell with nucleic acid encoding a CAR.

Combinations of the disclosure

10 Aspects of the present invention include compositions and methods comprising/employing (i) an oncolytic virus; (ii) a virus comprising nucleic acid encoding an immunomodulatory factor; and (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen.

15 Also provided are compositions and methods comprising/employing (i) an oncolytic virus; and (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen (i.e. without necessarily also employing a virus comprising nucleic acid encoding an immunomodulatory factor).

20 Also provided are compositions and methods comprising/employing (i) an oncolytic virus; and (ii) an immune cell specific for the oncolytic virus.

25 In some embodiments in accordance with various aspects described herein the cell comprising/expressing the CAR is specific for the oncolytic virus employed (e.g. comprises antigen receptor (e.g. TCR) specific for an antigen of the oncolytic virus). That is to say, in some embodiments the oncolytic virus and the specificity of the cell comprising/expressing the CAR are matched. By way of example, in some embodiments the oncolytic virus is an adenovirus, and the CAR-expressing cell comprising/expressing a CAR is an Adenovirus-specific T cell.

30 Similarly, in various aspects described herein an oncolytic virus is employed in combination with an immune cell specific for the oncolytic virus (i.e. the same oncolytic virus).

"Combinations" as referred to herein encompass products and compositions (e.g. pharmaceutical compositions) comprising the components of the combination. "Combinations" also encompass therapeutic regimens employing the the components of the combination.

35 In some embodiments the components of a combination are provided in separate compositions. In some embodiments more than one component of a combination is provided in a composition. In some embodiments the components of a combination are provided in one composition.

Similarly, in some embodiments the components of a combination are administered separately. In some embodiments a component of a combination is administered with another component of the combination. In some embodiments the components of a combination are administered together.

5 By way of illustration, in the example of a combination comprising an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor and at least one cell comprising a CAR specific for a cancer cell antigen, the oncolytic virus and the virus comprising nucleic acid encoding an immunomodulatory factor may be administered together, and the at least one cell comprising a CAR specific for a cancer cell antigen may be administered separately (e.g. subsequently).

Where components of a combination are administered together administration may be simultaneous administration as described hereinbelow. Where components of a combination are administered separately, administration may be simultaneous administration or sequential administration, as described hereinbelow. In cases wherein components of a combination are administered separately, the administration of the separate components may or may not be administered via the same administration routes

Functional properties

The agents of the present disclosure may be defined by reference to one or more functional properties. The agents may be evaluated for the functional properties, for example, by analysis as described in the experimental examples. Similarly, the combinations and methods of the present disclosure may be defined by reference to one or more functional properties and/or effects, and may be evaluated for such properties/effects e.g. by analysis as described in the experimental examples.

In some embodiments, an oncolytic virus according to the present disclosure may possess one or more of the following functional properties:

- ability to replicate in, and/or cause cell killing of, cancer cells;
- reduced ability to replicate in and/or cause cell killing of, non-cancerous cells as compared to the ability to replicate in, and/or cause cell killing of, cancer cells;
- comparable or improved ability to cause cell killing of cancer cells as compared to the ability of one or more oncolytic viruses known in the art;
- ability to help replication of helper-dependent adenovirus (HDAd);
- comparable or improved ability to replicate in cancer cells as compared to the ability of one or more oncolytic viruses known in the art.

In some embodiments, a cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen according to the present disclosure may possess one or more of the following functional properties:

- ability to bind to HER2;
- ability to bind to HER2-expressing cells;
- ability to cause cell killing of HER2-expressing cells;
- reduced ability to cause cell killing of cell not expressing HER2 as compared to the ability to cause cell killing of HER2-expressing cells.

In some embodiments the combination of an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory and at least one cell comprising a CAR specific for a cancer cell antigen may possess one or more of the following functional properties:

- improved ability to cause cell killing of cancer cells as compared to the ability to cause cell killing of cancer cells by any one of the components use alone, or by any two of the components used in combination.
- ability to cause cell killing of cancer cells which is synergistic (i.e. super-additive) as compared to the ability to cause cell killing of cancer cells by the components used alone.

In some embodiments the combination of an oncolytic virus and at least one cell comprising a CAR specific for a cancer cell antigen may possess one or more of the following functional properties:

- improved ability to cause cell killing of cancer cells as compared to the ability to cause cell killing of cancer cells by either component used alone.
- ability to cause cell killing of cancer cells which is synergistic (i.e. super-additive) as compared to the ability to cause cell killing of cancer cells by the components used alone.

In some embodiments the combination of an oncolytic virus and an immune cell specific for the oncolytic virus may possess one or more of the following functional properties:

- improved ability to cause cell killing of cancer cells as compared to the ability to cause cell killing of cancer cells by either component used alone.
- ability to cause cell killing of cancer cells which is synergistic (i.e. super-additive) as compared to the ability to cause cell killing of cancer cells the components used alone.

Analysis of the ability to cause cell killing of cancer cells may be assessed e.g. *in vitro*, by analysis of number/viability of cancer cells. Analysis of the ability to cause cell killing of cancer cells may also be analysed *in vivo* in an appropriate model, e.g. by analysis of number of cancer cells, tumor

size/volume and/or some other correlate of the number of cancer cells (e.g. disease progression, severity of symptoms of the cancer etc.).

Therapeutic applications

Aspects of the present disclosure are concerned in particular with the use of an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor and at least one T cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, in the treatment of a cancer in a subject.

Accordingly, the present disclosure provides a method of treating a cancer, comprising administering to a subject: an oncolytic virus; a virus comprising nucleic acid encoding an immunomodulatory factor; and at least one T cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen.

The present disclosure also provides an oncolytic virus; a virus comprising nucleic acid encoding an immunomodulatory factor; and at least one T cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen; for use in a method of treating a cancer. Also provided is the use of an oncolytic virus; a virus comprising nucleic acid encoding an immunomodulatory factor; and at least one T cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen; in the manufacture of a medicament for treating a cancer.

The present disclosure also provides a method of treating a cancer, comprising administering to a subject: (i) an oncolytic virus; and (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen. Also provided is (i) an oncolytic virus; and (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen for use in a method of treating a cancer. Also provided is the use of (i) an oncolytic virus; and (ii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen in the manufacture of a medicament for use in a method of treating a cancer.

The present disclosure also provides a method of treating a cancer, comprising administering to a subject: (i) an oncolytic virus; and (ii) an immune cell specific for the oncolytic virus. Also provided is (i) an oncolytic virus; and (ii) an immune cell specific for the oncolytic virus for use in a method of treating a cancer. Also provided is the use of (i) an oncolytic virus; and (ii) an immune cell specific for the oncolytic virus in the manufacture of a medicament for use in a method of treating a cancer.

Also provided are methods for treating cancer comprising administering the OncAds, HDAds, CARs, nucleic acids/plurality of nucleic acids, cells and pharmaceutical compositions of the present disclosure to a subject. Also provided are the OncAds, HDAds, CARs, nucleic acids/plurality of nucleic acids, cells and pharmaceutical compositions of the present disclosure for use in methods for treating cancer. Also provided are the use of the OncAds, HDAds, CARs,

nucleic acids/plurality of nucleic acids, cells and pharmaceutical compositions of the present disclosure in the manufacture of a medicament for treating cancer.

5 'Treatment' may, for example, be reduction in the development or progression of a cancer, alleviation of the symptoms of a cancer or reduction in the pathology of a cancer. Treatment or alleviation of a cancer may be effective to prevent progression of the cancer, e.g. to prevent worsening of the condition or to slow the rate of development of a more severe disease state. In some embodiments treatment or alleviation may lead to an improvement in the cancer, e.g. a reduction in the symptoms of the cancer or reduction in some other correlate of the severity/activity
10 of the cancer. Prevention of a cancer may refer to prevention of a worsening of the condition or prevention of the development of the cancer, e.g. preventing an early stage cancer developing to a later stage.

15 In some embodiments, the treatment may be aimed at reducing the number of cells of the cancer or the amount of tissue comprising cancerous cells in the subject. In some embodiments, the treatment may be aimed at reducing the size of and/or preventing the growth of at least one tumor in the subject.

20 In some embodiments, the treatment comprises administering an oncolytic virus according to the present disclosure to the subject. In some embodiments, the treatment may comprise administering to a subject a cell or population of cells comprising or encoding an oncolytic virus according to the present disclosure. In some embodiments, the treatment comprises administering an oncolytic virus and a virus encoding an immunomodulatory factor according to the present disclosure to the subject. In some embodiments, the treatment may comprise administering to a
25 subject a cell or population of cells comprising or encoding an oncolytic virus and/or virus encoding an immunomodulatory factor according to the present disclosure.

30 In some embodiments, the treatment may comprise modifying a cell or population of cells to comprise/express a CAR according to the present disclosure. In some embodiments, the treatment may comprise administering to a subject a cell or population of cells modified to comprise/express a CAR of the present disclosure. In some embodiments, the treatment is aimed at providing the subject with an immune cell or population of immune cells which having specificity for a cancer cell antigen, e.g. by administering a CAR-expressing cell according to the present disclosure, or generating a CAR-expressing cell according to the present disclosure.

35 In some embodiments, the treatment may comprise administering to a subject an immune cell/population of immune cells specific for an oncolytic virus according to the present disclosure. In some embodiments, the treatment is aimed at providing the subject with an immune cell/population of immune cells having specificity for an oncolytic virus. In some embodiments, the

treatment may comprise generating/expanding a population of immune cells specific for an oncolytic virus according to the present disclosure.

5 In some embodiments, the treatment may comprise administering to a subject an immune cell/population of immune cells specific for an oncolytic virus according to the present disclosure, modified to comprise/express a CAR according to the present disclosure. In some embodiments, the treatment is aimed at providing the subject with an immune cell/population of immune cells having specificity for an oncolytic virus also having specificity for a cancer cell antigen. In some
10 embodiments, the treatment may comprise generating/expanding a population of immune cells specific for an oncolytic virus according to the present disclosure, and modifying a cell or cells of the population to comprise/express a CAR according to the present disclosure.

15 The subject to be treated may be any animal or human. The subject is preferably mammalian, more preferably human. The subject may be a non-human mammal, but is more preferably human. The subject may be male or female or of any gender. The subject may be a patient. A subject may have been diagnosed with a cancer requiring treatment, may be suspected of having such a cancer, or may be at risk of developing such a cancer.

20 In some embodiments, the cancer to be treated comprises cells expressing a cancer cell antigen, *e.g.* a cancer cell antigen as described herein (*e.g.* HER2). In some embodiments, the cells express the cancer cell antigen (*e.g.* HER2) at the cell surface.

25 In some embodiments, the cancer to be treated comprises cells expressing a cancer cell antigen for which the CAR is specific. In some embodiments, the CAR comprises a cancer cell antigen binding domain, and the cancer to be treated comprises cells expressing the cancer cell antigen, *e.g.* cells expressing the cancer cell antigen at the cell surface.

30 In some embodiments, the cancer over-expresses the cancer cell antigen. Overexpression of a cancer cell antigen can be determined by detection of a level of expression of the cancer cell antigen which is greater than the level of expression by equivalent non-cancerous cells/non-tumor tissue.

35 In some embodiments the cancer is a cancer expressing HER2, *e.g.* a cancer expressing HER2 at the cell surface. In some embodiments, the cancer over-expresses HER2. Overexpression of HER2 can be determined by detection of a level of expression of HER2 which is greater than the level of expression of HER2 by equivalent non-cancerous cells/non-tumor tissue.

In some embodiments, the subject to be treated according to the present disclosure is selected for treatment on the basis detection of expression/overexpression of the cancer cell antigen by a cancer cell or tumour obtained from the subject.

5 Expression of a given cancer cell antigen may be determined by any suitable means. Expression may be gene expression or protein expression. Gene expression can be determined *e.g.* by detection of mRNA encoding the cancer cell antigen, for example by quantitative real-time PCR (qRT-PCR). Protein expression can be determined *e.g.* by detection of the cancer cell antigen, for example by antibody-based methods, for example by western blot, immunohistochemistry,
10 immunocytochemistry, flow cytometry, or ELISA.

The cancer to be treated/prevented in accordance with the present disclosure may be any unwanted cell proliferation (or any disease manifesting itself by unwanted cell proliferation), neoplasm or tumor. The cancer may be benign or malignant and may be primary or secondary
15 (metastatic). The cancer may be resistant (initially or following treatment) and/or the cancer may be recurring. A neoplasm or tumor may be any abnormal growth or proliferation of cells and may be located in any tissue. The cancer may be of tissues/cells derived from *e.g.* the adrenal gland, adrenal medulla, anus, appendix, bladder, blood, bone, bone marrow, brain, breast, cecum, central nervous system (including or excluding the brain) cerebellum, cervix, colon, duodenum,
20 endometrium, epithelial cells (*e.g.* renal epithelia), gallbladder, oesophagus, glial cells, heart, ileum, jejunum, kidney, lacrimal gland, larynx, liver, lung, lymph, lymph node, lymphoblast, maxilla, mediastinum, mesentery, myometrium, nasopharynx, omentum, oral cavity, ovary, pancreas, parotid gland, peripheral nervous system, peritoneum, pleura, prostate, salivary gland, sigmoid colon, skin, small intestine, soft tissues, spleen, stomach, testis, thymus, thyroid gland, tongue,
25 tonsil, trachea, uterus, vulva, white blood cells.

The cancer to be treated/prevented may be any kind of cancer, including any one of an acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, AIDS-related cancer (*e.g.* Kaposi sarcoma, AIDS-related lymphoma, primary CNS lymphoma), anal
30 cancer, appendix cancer, astrocytoma, basal cell carcinoma of the skin, bile duct cancer (*e.g.* cholangiocarcinoma), bladder cancer, bone cancer (*e.g.* Ewing sarcoma, osteosarcoma, malignant fibrous histiocytoma), brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, carcinoma of unknown primary, cardiac tumor, central nervous system cancer (*e.g.* atypical teratoid/rhabdoid tumor, embryonal tumor, germ cell tumor, primary CNS lymphoma), cervical
35 cancer, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasm, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma (*e.g.* mycosis fungoides, Sézary syndrome), ductal carcinoma in situ (DCIS), endometrial cancer (uterine cancer), ependymoma, esophageal cancer, esthesioneuroblastoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer (*e.g.* intraocular

melanoma, retinoblastoma) fallopian tube cancer, malignant fibrous histiocytoma of bone, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), ovarian germ cell tumor, testicular cancer, gestational trophoblastic disease, hairy cell leukemia, head and neck cancer, heart tumor, hepatocellular (liver) cancer, histiocytosis, Langerhans cell, Hodgkin lymphoma, hypopharyngeal cancer, islet cell tumor (pancreatic neuroendocrine tumor), kidney (renal cell) cancer, laryngeal cancer, papillomatosis, leukemia, lip and oral cavity cancer, lung cancer (non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)) lymphoma, male breast cancer, melanoma, Merkel cell carcinoma, mesothelioma, metastatic cancer, metastatic squamous neck cancer with occult primary, midline tract carcinoma involving NUT gene, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasms, mycosis fungoides, myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasm, myelogenous leukemia, chronic myeloid leukemia, acute myeloid leukemia (AML), nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, oral cancer, lip and oral cavity cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus cancer, nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, pregnancy and breast cancer, primary peritoneal cancer, prostate cancer, rectal cancer, recurrent cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, vascular tumor, uterine sarcoma, skin cancer, small intestine cancer, squamous cell carcinoma of the skin, T-cell lymphoma, throat cancer, thymoma, thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, urethral cancer, vaginal cancer, vulvar cancer or Wilms tumor.

In some embodiments, the cancer to be treated is one or more of nasopharyngeal carcinoma (NPC; e.g. Epstein-Barr Virus (EBV)-positive NPC), cervical carcinoma (CC; e.g. human papillomavirus (HPV)-positive CC), oropharyngeal carcinoma (OPC; e.g. HPV-positive OPC), gastric carcinoma (GC; e.g. EBV-positive GC), hepatocellular carcinoma (HCC; e.g. Hepatitis B Virus (HBV)-positive HCC), lung cancer (e.g. non-small cell lung cancer (NSCLC)) and head and neck cancer (e.g. cancer originating from tissues of the lip, mouth, nose, sinuses, pharynx or larynx, e.g. head and neck squamous cell carcinoma (HNSCC)).

In some embodiments the cancer is associated with, or caused by, a virus. In some embodiments the cancer is an EBV-positive cancer. In some embodiments the cancer is an HPV-positive cancer.

In some embodiments, the cancer is one of a head and neck cancer, nasopharyngeal carcinoma (NPC), oropharyngeal cancer (OPC), cervical cancer (CC), gastric/stomach cancer, gastric carcinoma or lung cancer.

Methods of medical treatment may also involve *in vivo*, *ex vivo*, and adoptive immunotherapies, including those using autologous and/or heterologous cells or immortalized cell lines.

Administration

5 Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment, *e.g.* decisions on dosage *etc.*, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the condition to be treated, the condition of
10 the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins.

15 Viruses, CARs, nucleic acids, and cells according to the present disclosure may be formulated as pharmaceutical compositions or medicaments for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant. The composition may be formulated for topical, parenteral, systemic, intracavitary, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intraconjunctival, intratumoral, subcutaneous, intradermal, intrathecal, oral or transdermal routes of administration which may include injection or infusion. Suitable
20 formulations may comprise the viruses, CARs, nucleic acids, or cells in sterile or isotonic medium. Medicaments and pharmaceutical compositions may be formulated in fluid, including gel, form. Fluid formulations may be formulated for administration by injection or infusion (*e.g.* via catheter) to a selected region of the human or animal body.

25 The oncolytic virus and/or the virus comprising nucleic acid encoding an immunomodulatory factor may be formulated for intratumoral administration. In some embodiments, the methods may comprise intratumoral administration of the oncolytic virus and/or the virus comprising nucleic acid encoding an immunomodulatory factor.

30 The cell comprising a CAR and/or the immune cell specific for an oncolytic virus may be formulated for intravenous administration. In some embodiments, the methods may comprise intravenous administration of the cell comprising a CAR and/or the immune cell specific for an oncolytic virus.

35 Administration of the components of combinations of the present disclosure (*e.g.* oncolytic virus, virus comprising nucleic acid encoding an immunomodulatory factor; at least one T cell comprising a CAR specific for a cancer cell antigen; immune cell specific for an oncolytic virus in accordance with the present disclosure) may be simultaneous or sequential. The present disclosure also

contemplates simultaneous or sequential administration of the OncAds, HDAds, CARs, nucleic acids/plurality of nucleic acids, cells and pharmaceutical compositions of the present disclosure.

Simultaneous administration refers to administration of the agents together, for example as a pharmaceutical composition containing the agents (*i.e.* a combined preparation), or immediately after each other and optionally via the same route of administration, *e.g.* to the same artery, vein or other blood vessel. In particular embodiments, the oncolytic virus and virus comprising nucleic acid encoding an immunomodulatory factor may be administered simultaneously in a combined preparation. In certain embodiments upon simultaneous administration the two or more of the agents may be administered via different routes of administration. In some embodiments simultaneous administration refers to administration at the same time, or within *e.g.* 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 8 hrs, 12 hrs, 24 hrs, 36 hrs or 48 hrs.

Sequential administration refers to administration of one or more of the agents followed after a given time interval by separate administration of another of the agents. It is not required that the two agents are administered by the same route, although this is the case in some embodiments. The time interval may be any time interval, including hours, days, weeks, months, or years. In some embodiments sequential administration refers to administrations separated by a time interval of one of at least 10 min, 30 min, 1 hr, 6 hrs, 8 hrs, 12 hrs, 24 hrs, 36 hrs, 48 hrs, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 6 weeks, 2 months, 3 months, 4 months, 5 months or 6 months.

In some embodiments, the treatment may further comprise other therapeutic or prophylactic intervention, *e.g.* chemotherapy, immunotherapy, radiotherapy, surgery, vaccination and/or hormone therapy. Such other therapeutic or prophylactic intervention may occur before, during and/or after the therapies encompassed by the disclosure, and the deliveries of the other therapeutic or prophylactic interventions may occur via different administration routes as the therapies of the disclosure. Chemotherapy and radiotherapy respectively refer to treatment of a cancer with a drug or with ionising radiation (*e.g.* radiotherapy using X-rays or γ -rays). The drug may be a chemical entity, *e.g.* small molecule pharmaceutical, antibiotic, DNA intercalator, protein inhibitor (*e.g.* kinase inhibitor), or a biological agent, *e.g.* antibody, antibody fragment, nucleic acid or peptide aptamer, nucleic acid (*e.g.* DNA, RNA), peptide, polypeptide, or protein. The drug may be formulated as a pharmaceutical composition or medicament. The formulation may comprise

one or more drugs (e.g. one or more active agents) together with one or more pharmaceutically acceptable diluents, excipients or carriers.

The chemotherapy may be administered by one or more routes of administration, e.g. parenteral, intravenous injection, oral, subcutaneous, intradermal or intratumoral.

The chemotherapy may be administered according to a treatment regime. The treatment regime may be a pre-determined timetable, plan, scheme or schedule of chemotherapy administration which may be prepared by a physician or medical practitioner and may be tailored to suit the patient requiring treatment.

The treatment regime may indicate one or more of: the type of chemotherapy to administer to the patient; the dose of each drug or radiation; the time interval between administrations; the length of each treatment; the number and nature of any treatment holidays, if any *etc.* For a co-therapy a single treatment regime may be provided which indicates how each drug is to be administered.

Chemotherapeutic drugs and biologics may be selected from: alkylating agents such as cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide; purine or pyrimidine anti-metabolites such as azathiopurine or mercaptopurine; alkaloids and terpenoids, such as vinca alkaloids (e.g. vincristine, vinblastine, vinorelbine, vindesine), podophyllotoxin, etoposide, teniposide, taxanes such as paclitaxel (TaxolTM), docetaxel; topoisomerase inhibitors such as the type I topoisomerase inhibitors camptothecins irinotecan and topotecan, or the type II topoisomerase inhibitors amsacrine, etoposide, etoposide phosphate, teniposide; antitumor antibiotics (e.g. anthracycline antibiotics) such as dactinomycin, doxorubicin (AdriamycinTM), epirubicin, bleomycin, rapamycin; antibody based agents, such as anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-TIM-3 antibodies, anti-CTLA-4, anti-4-1BB, anti-GITR, anti-CD27, anti-BLTA, anti-OX43, anti-VEGF, anti-TNF α , anti-IL-2, antiGp11b/IIIa, anti-CD-52, anti-CD20, anti-RSV, anti-HER2/neu(erbB2), anti-TNF receptor, anti-EGFR antibodies, monoclonal antibodies or antibody fragments, examples include: cetuximab, panitumumab, infliximab, basiliximab, bevacizumab (Avastin[®]), abciximab, daclizumab, gemtuzumab, alemtuzumab, rituximab (Mabthera[®]), palivizumab, trastuzumab, etanercept, adalimumab, nimotuzumab; EGFR inhibitors such as erlotinib, cetuximab and gefitinib; anti-angiogenic agents such as bevacizumab (Avastin[®]); cancer vaccines such as Sipuleucel-T (Provenge[®]).

Further chemotherapeutic drugs may be selected from: 13-cis-Retinoic Acid, 2-Chlorodeoxyadenosine, 5-Azacitidine 5-Fluorouracil, 6-Mercaptopurine, 6-Thioguanine, Abraxane, Accutane[®], Actinomycin-D Adriamycin[®], Aducril[®], Afinitor[®], Agrylin[®], Ala-Cort[®], Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ[®], Alkeran[®], All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron[®],

Anastrozole, Arabinosylcytosine, Aranesp®, Aredia®, Arimidex®, Aromasin®, Arranon®, Arsenic Trioxide, Asparaginase, ATRA Avastin®, Azacitidine, BCG, BCNU, Bendamustine, Bevacizumab, Bexarotene, BEXXAR®, Bicalutamide, BiCNU, Bleomycin®, Bleomycin, Bortezomib, Busulfan, Busulfex®, Calcium Leucovorin, Campath®, Campsar®, Camptothecin-11, Capecitabine, 5 Carac™, Carboplatin, Carmustine, Casodex®, CC-5013, CCI-779, CCNU, CDDP, CeeNU, Cerubidine®, Cetuximab, Chlorambucil, Cisplatin, Citrovorum Factor, Cladribine, Cortisone, Cosmegen®, CPT-11, Cyclophosphamide, Cytadren®, Cytarabine Cytosar-U®, Cytoxan®, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome®, Decadron, Decitabine, Delta-Cortef®, 10 Deltasone®, Denileukin, Diftitox, DepoCyt™, Dexamethasone, Dexamethasone Acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodex, Docetaxel, Doxil®, Doxorubicin, Doxorubicin Liposomal, Droxia™, DTIC, DTIC-Dome®, Duralone®, Eligard™, Ellence™, Eloxatin™, Elspar®, Emcyt®, Epirubicin, Epoetin Alfa, Erbitux, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethiol Etopophos®, Etoposide, Etoposide Phosphate, 15 Eulexin®, Everolimus, Evista®, Exemestane, Faslodex®, Femara®, Filgrastim, Floxuridine, Fludara®, Fludarabine, Fluoroplex®, Fluorouracil, Fluoxymesterone, Flutamide, Folinic Acid, FUDR®, Fulvestrant, Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Gleevec™, Gliadel® Wafer, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Herceptin®, Hexadrol, Hexalen®, Hexamethylmelamine, HMM, Hycamtin®, 20 Hydrea®, Hydrocort Acetate®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab Tiuxetan, Idamycin®, Idarubicin, Ifex®, IFN-alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon alfa, Interferon Alfa-2b (PEG Conjugate), Interleukin - 2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa®, Irinotecan, Isotretinoin, Ixabepilone, 25 Ixempra™, Kidrolase, Lanacort®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine™, Leuprolide, Leurocristine, Leustatin™, Liposomal Ara-C, Liquid Pred®, Lomustine, L-PAM, L-Sarcosine, Lupron®, Lupron Depot®, Matulane®, Maxidex, Mechlorethamine, Mechlorethamine Hydrochloride, Medrolone®, Medrol®, Megace®, Megestrol, Megestrol Acetate, Melphalan, Mercaptopurine, Mesna, Mesnex™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticorten®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol®, 30 MTC, MTX, Mustargen®, Mustine, Mutamycin®, Myleran®, Mylocel™, Mylotarg®, Navelbine®, Nelarabine, Neosar®, Neulasta™, Neumega®, Neupogen®, Nexavar®, Nilandron®, Nilutamide, Nipent®, Nitrogen Mustard, Novaldex®, Novantrone®, Octreotide, Octreotide acetate, Oncospar®, Oncovin®, Ontak®, Onxal™, Oprevelkin, Orapred®, Orasone®, Oxaliplatin, Paclitaxel, Paclitaxel Protein-bound, Pamidronate, Panitumumab, Panretin®, Paraplatin®, PEDIAPRED®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON™, PEG-L-asparaginase, PEMETREXED, 35 Pentostatin, Phenylalanine Mustard, Platinol®, Platinol-AQ®, Prednisolone, Prednisone, Prelone®, Procarbazine, PROCRIT®, Proleukin®, Prolifeprospan 20 with Carmustine Implant Purinethol®, Raloxifene, Revlimid®, Rheumatrex®, Rituxan®, Rituximab, Roferon-A® (Interferon Alfa-2a),

Rubex®, Rubidomycin hydrochloride, Sandostatin® Sandostatin LAR®, Sargramostim, Solu-Cortef®, Solu-Medrol®, Sorafenib, SPRYCEL™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent®, Tamoxifen, Tarceva®, Targretin®, Taxol®, Taxotere®, Temodar®, Temozolomide, Temsirolimus, Teniposide, TESPAs, Thalidomide, Thalomid®, TheraCys®, Thioguanine, Thioguanine Tabloid®, Thiophosphoamide, Thioplex®, Thiotepa, TICE®, Toposar®, Topotecan, Toremifene, Torisel®, Tositumomab, Trastuzumab, Treanda®, Tretinoin, Trexall™, Trisenox®, TSPA, TYKERB®, VCR, Vectibix™, Velban®, Velcade®, VePesid®, Vesanoide®, Viadur™, Vidaza®, Vinblastine, Vinblastine Sulfate, Vincasar Pfs®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vorinostat, VP-16, Vumon®, Xeloda®, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolanza, Zometa®.

In embodiments of the present disclosure wherein a nucleic acid/virus encoding an enzyme capable of catalysing conversion of a non-toxic factor to a cytotoxic form is employed, the method may further comprise administration with a prodrug substrate for the enzyme. The prodrug may be administered simultaneously or sequentially to administration of the nucleic acid/virus encoding an enzyme capable of catalysing conversion of a non-toxic factor to a cytotoxic form.

In some embodiments the prodrug is selected from ganciclovir (GCV), aciclovir (ACV) and/or valaciclovir, e.g. where the nucleic acid/virus encodes a thymidine kinase. In some embodiments the prodrug is 5-fluorocytosine (5-FC), e.g. where the nucleic acid/virus encodes a cytosine deaminase. In some embodiments the prodrug is selected from CB1954, nitro-CBI-DEI and/or PR-104A, e.g. where the nucleic acid/virus encodes a nitroreductase. In some embodiments the prodrug is oxazaphosphorine (e.g. cyclophosphamide or ifosfamide), e.g. where the nucleic acid/virus encodes a cytochrome P450. In some embodiments the prodrug is a nitrogen mustard based drug (e.g. CMDA or ZD2767P), e.g. where the nucleic acid/virus encodes a carboxypeptidase G2. In some embodiments the prodrug is 6-methylpurine 2-deoxyriboside and/or fludarabine (e.g. 6-methylpurine-2'-deoxyriboside (MeP-dR), 2-F-2'-deoxyadenosine (F-dAdo) or arabinofuranosyl-2-F-adenine monophosphate (F-araAMP), e.g. where the nucleic acid/virus encodes a purine nucleoside phosphorylase. In some embodiments the prodrug is indole-3-acetic acid (IAA), e.g. where the nucleic acid/virus encodes a horseradish peroxidase. In some embodiments the prodrug is irinotecan, e.g. where the nucleic acid/virus encodes a carboxylesterase.

Multiple doses of the agents (e.g. viruses (OncAds, HdAds), CARs, nucleic acids/plurality of nucleic acids, vectors, cells, compositions, combinations, prodrugs) of the present disclosure may be provided. One or more, or each, of the doses may be accompanied by simultaneous or sequential administration of another therapeutic agent.

Multiple doses may be separated by a predetermined time interval, which may be selected to be one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or more hours

or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days, or 1, 2, 3, 4, 5, or 6 months. By way of example, doses may be given once every 7, 14, 21 or 28 days (plus or minus 3, 2, or 1 days).

Adoptive transfer

In embodiments of the present disclosure, the methods of treatment comprise adoptive transfer of immune cells. Adoptive cell transfer (ACT) generally refers to a process by which cells (*e.g.* immune cells) are obtained from a subject, typically by drawing a blood sample from which the cells are isolated. The cells are then typically treated or altered in some way, and then administered either to the same subject (adoptive transfer is of autologous cells) or to a different subject (adoptive transfer is of allogeneic cells). The treatment is typically aimed at providing population of cells with certain desired characteristics to a subject, or increasing the frequency of cells with such characteristics in that subject. In the present disclosure, adoptive transfer may be performed with the aim of introducing a cell or population of cells into a subject, and/or increasing the frequency of a cell or population of cells in a subject.

In some embodiments, the subject from which the cell is isolated is the subject administered with the modified cell (*i.e.*, adoptive transfer is of autologous cells). In some embodiments, the subject from which the cell is isolated is a different subject to the subject to which the modified cell is administered (*i.e.*, adoptive transfer is of allogeneic cells).

Adoptive transfer of T cells is described, for example, in Kalos and June 2013, *Immunity* 39(1): 49-60, which is hereby incorporated by reference in its entirety. Adoptive transfer of NK cells is described, for example, in Davis *et al.* 2015, *Cancer J.* 21(6): 486-491, which is hereby incorporated by reference in its entirety.

The cell may *e.g.* be a neutrophil, eosinophil, basophil, dendritic cell, lymphocyte, or monocyte. The lymphocyte may be *e.g.* a T cell, B cell, NK cell, NKT cell or innate lymphoid cell (ILC), or a precursor thereof. In some embodiments, the cell is a T cell. In some embodiments, the T cell is a CD3+ T cell. In some embodiments, the T cell is a CD3+, CD4+ T cell. In some embodiments, the T cell is a CD3+, CD8+ T cell. In some embodiments, the T cell is a T helper cell (T_H cell)). In some embodiments, the T cell is a cytotoxic T cell (*e.g.* a cytotoxic T lymphocyte (CTL)). In some embodiments, the T cell is a virus-specific T cell. In some embodiments, the T cell is specific for EBV, HPV, HBV, HCV or SHIV.

In some embodiments the cell is an immune cell specific for an oncolytic virus, as described herein. Accordingly, in some embodiments the methods comprise administration of at least one immune cell specific for an oncolytic virus to a subject. In some embodiments, the methods of the

disclosure comprise generating/expanding a population of immune cells specific for an oncolytic virus, and administering at least one immune cell specific for the oncolytic virus to a subject.

In some embodiments, the methods comprise:

- (a) isolating immune cells from a subject;
- (b) generating or expanding a population of immune cells specific for an oncolytic virus by a method comprising: stimulating the immune cells by culture in the presence of antigen presenting cells (APCs) presenting a peptide of the oncolytic virus, and;
- (c) administering at least one immune cell specific for the oncolytic virus to a subject.

In some embodiments the method steps for production of an immune cell specific for an oncolytic virus may comprise one or more of: taking a blood sample from a subject; isolating PBMCs from the blood sample; generating/expanding a population of immune cells specific for an oncolytic virus (e.g. by culturing PBMCs in the presence of cells (e.g. APCs) comprising/expressing antigen(s)/peptide(s) of the oncolytic virus); culturing immune cells specific for an oncolytic virus in *in vitro* or *ex vivo* cell culture; collecting immune cells specific for an oncolytic virus; mixing immune cells specific for an oncolytic virus with an adjuvant, diluent, or carrier; administering the modified cell to a subject.

The present disclosure also provides methods of treating a cancer in a subject comprising administering at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen. In connection with this feature of the disclosure, in some embodiments, the method additionally comprises steps for production of the at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen. The CAR may be a first generation, second generation or third or subsequent generation CAR. The CAR may comprise one, two, three, or more costimulatory domains, for example.

In some embodiments, the methods comprise modifying at least one cell obtained from a subject to express or comprise a CAR according to the disclosure, optionally expanding the modified at least one cell, and administering the modified at least one cell to a subject.

In some embodiments, the methods comprise:

- (a) isolating at least one cell from a subject;
- (b) modifying the at least one cell to express or comprise a CAR according to the present disclosure, or a nucleic acid encoding a CAR according to the present disclosure,
- (c) optionally expanding the modified at least one cell, and;
- (d) administering the modified at least one cell to a subject.

In some embodiments the cell comprising/expressing a CAR specific for a cancer cell antigen is an immune cell specific for an oncolytic virus, as described herein. In some embodiments, the

methods comprise modifying an immune cell specific for an oncolytic virus to express or comprise a CAR according to the disclosure, optionally expanding the modified immune cell specific for an oncolytic virus, and administering the modified immune cell specific for an oncolytic virus to a subject.

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In some embodiments, the methods comprise:

- (a) isolating immune cells from a subject;
- (b) generating or expanding a population of immune cells specific for an oncolytic virus by a method comprising: stimulating the immune cells by culture in the presence of antigen presenting cells (APCs) presenting a peptide of the oncolytic virus;
- (c) modifying at least one immune cell specific for an oncolytic virus to express or comprise a CAR according to the present disclosure, or a nucleic acid encoding a CAR according to the present disclosure,
- (d) optionally expanding the modified at least one immune cell specific for an oncolytic virus, and;
- (e) administering the modified at least one immune cell specific for an oncolytic virus to a subject.

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The at least one cell modified according to the present disclosure can be modified to comprise/express a CAR according to methods well known to the skilled person. The modification may comprise nucleic acid transfer for permanent or transient expression of the transferred nucleic acid. Any suitable genetic engineering platform may be used to modify a cell according to the present disclosure. Suitable methods for modifying a cell include the use of genetic engineering platforms such as gammaretroviral vectors, lentiviral vectors, adenovirus vectors, DNA transfection, transposon-based gene delivery and RNA transfection, for example as described in Maus *et al.*, Annu Rev Immunol (2014) 32:189-225, incorporated by reference hereinabove.

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In some embodiments the method steps for production of the at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen may comprise one or more of: taking a blood sample from a subject; isolating and/or expanding at least one cell from the blood sample; culturing the at least one cell in *in vitro* or *ex vivo* cell culture; introducing into the at least one cell a CAR as described herein, or a nucleic acid encoding a CAR as described herein, thereby modifying the at least one cell; expanding the at least one modified cell; collecting the at least one modified cell; mixing the modified cell with an adjuvant, diluent, or carrier; administering the modified cell to a subject.

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In some embodiments, the methods may additionally comprise treating the cell to induce/enhance expression of the CAR or nucleic acid encoding the CAR. For example, the nucleic acid may

comprise a control element for inducible upregulation of expression of the CAR from the nucleic acid in response to treatment with a particular agent. In some embodiments, treatment may be *in vivo* by administration of the agent to a subject having been administered with a modified cell according to the disclosure. In some embodiments, treatment may be *ex vivo* or *in vitro* by administration of the agent to cells in culture *ex vivo* or *in vitro*.

The skilled person is able to determine appropriate reagents and procedures for adoptive transfer of cells according to the present disclosure, for example by reference to Dai *et al.*, 2016 J Nat Cancer Inst 108(7): djv439, which is incorporated by reference in its entirety.

In a related aspect, the present disclosure provides a method of preparing a modified cell, the method comprising introducing into a cell a CAR according to the present disclosure or a nucleic acid encoding a CAR according to the present disclosure, thereby modifying the at least one cell. The method is preferably performed *in vitro* or *ex vivo*.

Compositions/products/kits

The present disclosure also provides an oncolytic virus as described herein, optionally isolated. Also provided is a nucleic acid encoding the oncolytic virus, optionally isolated. Also provided is a cell comprising the oncolytic virus, or comprising nucleic acid encoding the oncolytic virus, optionally isolated.

The present disclosure also provides a virus comprising nucleic acid encoding an immunomodulatory factor as described herein, optionally isolated. Also provided is a nucleic acid encoding the virus, optionally isolated. Also provided is a cell comprising the virus, or comprising nucleic acid encoding the virus, optionally isolated.

The present disclosure also provides a chimeric antigen receptor (CAR) as described herein, optionally isolated. Also provided is a nucleic acid encoding the CAR, optionally isolated. Also provided is a cell comprising the CAR, or comprising nucleic acid encoding the CAR, optionally isolated.

The present disclosure also provides compositions comprising an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor, a chimeric antigen receptor, a nucleic acid/plurality of nucleic acids, or a cell according to the disclosure.

The oncolytic virus, virus comprising nucleic acid encoding an immunomodulatory factor, chimeric antigen receptor, nucleic acid/plurality of nucleic acids or cell according to the present disclosure may be formulated as pharmaceutical compositions for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant. Combinations of the present

disclosure may be provided in a single composition, or may be provided as plural compositions comprising the components of the combination.

5 In accordance with the present disclosure methods are also provided for the production of pharmaceutically useful compositions, such methods of production may comprise one or more steps selected from: isolating an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor, a chimeric antigen receptor, a nucleic acid/plurality of nucleic acids, or a cell as described herein; and/or mixing an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor, a chimeric antigen receptor, a nucleic acid/plurality of nucleic acids,
10 or a cell as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

For example, a further aspect of the present disclosure relates to a method of formulating or producing a medicament or pharmaceutical composition for use in the treatment of a cancer, the
15 method comprising formulating a pharmaceutical composition or medicament by mixing an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor, a chimeric antigen receptor, a nucleic acid/plurality of nucleic acids, or a cell as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

20 The present disclosure also provides a kit of parts comprising one or more of an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor, a chimeric antigen receptor, a nucleic acid, a cell or a composition according to the present disclosure.

25 In some embodiments the kit may have at least one container having a predetermined quantity of an oncolytic virus, a virus comprising nucleic acid encoding an immunomodulatory factor, a chimeric antigen receptor, a nucleic acid/plurality of nucleic acids, or a cell according to the disclosure or a composition according to the present disclosure. The kit may have containers containing individual components of the combinations of the present disclosure, or may have containers containing combinations of the components of the combinations of the present
30 disclosure.

The kit may provide the oncolytic virus, virus comprising nucleic acid encoding immunomodulatory factor, CAR, nucleic acid, cell or composition with instructions for administration to a patient in order to treat a specified cancer. The oncolytic virus, virus comprising nucleic acid encoding
35 immunomodulatory factor, CAR, nucleic acid/plurality of nucleic acids, cell or composition may be formulated so as to be suitable for injection or infusion to a tumor or to the blood.

In some embodiments the kit may comprise materials for producing a cell according to the present disclosure. For example, the kit may comprise materials for modifying a cell to express or comprise

a virus or an antigen/peptide thereof, CAR or nucleic acid/plurality of nucleic acids according to the present disclosure, or materials for introducing into a cell the virus or an antigen/peptide thereof or nucleic acid/plurality of nucleic acids according to the present disclosure. The kit may comprise materials for producing an immune cell specific for an oncolytic virus; for example, the kit may

5 comprise pepmixes of one or more antigens of the oncolytic virus.

In some embodiments the kit may further comprise at least one container having a predetermined quantity of another therapeutic agent (e.g. anti-infective agent or chemotherapy agent). In such

10 embodiments, the kit may also comprise a second medicament or pharmaceutical composition such that the two medicaments or pharmaceutical compositions may be administered simultaneously or separately such that they provide a combined treatment for the cancer. The therapeutic agent may also be formulated so as to be suitable for injection or infusion to a tumor or to the blood.

Sequence Identity

Pairwise and multiple sequence alignment for the purposes of determining percent identity between two or more amino acid or nucleic acid sequences can be achieved in various ways known to a person of skill in the art, for instance, using publicly available computer software such as ClustalOmega (Söding, J. 2005, Bioinformatics 21, 951-960), T-coffee (Notredame *et al.* 2000, J. Mol. Biol. (2000) 302, 205-217), Kalign (Lassmann and Sonnhammer 2005, BMC

20 Bioinformatics, 6(298)) and MAFFT (Kato and Standley 2013, Molecular Biology and Evolution, 30(4) 772-780 software. When using such software, the default parameters, e.g. for gap penalty and extension penalty, are preferably used.

Sequences

SEQ ID NO:	DESCRIPTION	SEQUENCE
1	HER2(C5)-CD28TM,ICD-CD3Z CAR	MTRAMDWIWRILFLVGAATGAHSQVQLQESGPGLVKPSSETLSLTCTVSGGSIS SSSYWGWIRQPPGKGLEWIGSIYSGSTYYNPSLKSRTVISVDTSKNQFSLKL SSVTAADTAVYYCARYAPDSSGYLVAFDIWGGQTMVTVSSGGGGSGGGGSG GGGSQTVVTQEPSFSVSPGGTVTLTCGLSSGSVSTGYPSWYQQTPGQAPR TLIYSTNSRSGVPDRFSGSILGNKAALTITGAQADESDYYCVLYMGSGISVF GGGKLTVLGSEPKSCDKTHTCPTRFWLVVVGVLACYSLLVTVAFIIFWVRS KRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPAY QQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPQRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
2	HER2(E4)-CD28TM,ICD-CD3Z CAR	MTRAMDWIWRILFLVGAATGAHSQVQLQQWGAGLLKPSSETLSLTCAVYGGSF SGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKL SSVTTADTAVYYCARMGINSGGYLYGMDVWGQGTITVTVSSGGGGSGGGGS GGGSQTVVTQEPSFSVSPGGTVTLTCGLSSGSVSTSYPSWYQQIPGQAPR TLIYTNNIRSSGVDRFGSILGNKAALTITGAQAEDESYYCMLYMGSGIWWF GGGKLTVLGSEPKSCDKTHTCPTRFWLVVVGVLACYSLLVTVAFIIFWVRS KRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPAY QQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPQRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

3	HER2(F1)- CD28TM,ICD- CD3Z CAR	MTRAMDWIWRILFLVGAATGAHSQVQLVESGPGLVKPSGTLSTCAVSGGSIS SSNWWSWVRQPPGKGLEWIGEYHSGSTNYPNPSLKSRTISVDTSKNQFSLKL SSVTAADTAVYYCARMGANSGGYLYGMDVWGQGTITVTVSSGGGGSGGGGS GGGGSQTVVTQEPSFSVSPGGTVTLTCLSSGSVSTSYYPSSWYQQTPGQAP RTLIYSTNTRSSGVPDRFSGSILGNKAALTITGAQADESDYYCVLYMGSGIWW FGGGTKLTVLGSEPKSCDKTHTCPTRFWWLVVVGGVLACYSLLVTVAFIIFWVR SKRSRLLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPA YQQGQNQLYNELNLGRREEYDVLDRRRGRDPEMGGKPQRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR
4	CD28 TMD	FWWLTVVGGVLACYSLLVTVAFIIFWV
5	CD28 ICD	RSKRRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS
6	CD3Z ICD	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRRGRDPEMGGKPQR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKGGHDGLYQGLSTATKDTYD ALHMQALPPR
7	(G4S)3 linker	GGGGSGGGSGGGGS
8	hulG H leader	MDWIWRILFLVGAATGAHS
9	Hinge	EPKSCDKTHTCPTR
10	HER2(C5) LC- CDR1	GLSSGSVSTGYYPSS
11	HER2(C5) LC- CDR2	STNSRSS
12	HER2(C5) LC- CDR3	VLYMGSGISV
13	HER2(C5) HC- CDR1	SSSYWYG
14	HER2(C5) HC- CDR2	SIYSGSTYYNPSLKS
15	HER2(C5) HC- CDR3	YAPDSSGYLVAFDI
16	HER2(C5) VL	QTVVTQEPSFSVSPGGTVTLTCLSSGSVSTGYYPSSWYQQTPGQAPRTLIYST NSRSSGVPDRFSGSILGNKAALTITGAQADESDYYCVLYMGSGISVFGGGTK LTVLGS
17	HER2(C5) VH	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSSSYWGWIRQPPGKGLEWIGSI YYSGSTYYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARYAPDSSGY LVAFDIWGQGTMTVTVSS
18	HER2(E4) LC- CDR1	GLSSGSVSTSYYPSS
19	HER2(E4) LC- CDR2	TTNIRSS
20	HER2(E4) LC- CDR3	MLYMGSGIWW
21	HER2(E4) HC- CDR1	SGYYWS
22	HER2(E4) HC- CDR2	EINHSGSTNYPNPSLKS
23	HER2(E4) HC- CDR3	MGINSGGYLYGMDV
24	HER2(E4) VL	QTVVTQEPSFSVSPGGTVTLTCLSSGSVSTSYYPSSWYQQIPGQAPRTLIYTT NIRSSGVPDRFGGSILGNKAALTITGAQAEDESYYCMLYMGSGIWWFGGGTK LTVLGS
25	HER2(E4) VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEIN HSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTTADTAVYYCARMGINSGGYL YGMDVWGQGTITVTVSS
26	HER2(F1) LC- CDR1	GLSSGSVSTSYYPSS
27	HER2(F1) LC- CDR2	STNTRSS

28	HER2(F1) LC-CDR3	VLYMGSGIWW
29	HER2(F1) HC-CDR1	SSNWWWS
30	HER2(F1) HC-CDR2	EIYHSGSTNYPNPSLKS
31	HER2(F1) HC-CDR3	MGANSGGYLYGMDV
32	HER2(F1) VL	QTVVTQEFSFSVSPGGTVTLTCGLSSGSVSTSYYPSPWYQQTPGQAPRTLIIYST NTRSSGVDPDRFSGSILGNKAALTITGAQADDES DYCVLYMGSGIWWFGGGTK LTVLGS
33	HER2(F1) VH	QVQLVESGPGLVKPSGTLSTCAVSGGSISSSNWWWSWRQPPGKGLEWIGE YHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARMGANS GGYLYGMDVWGQGTITVTVSS
34	Ad2 E1AΔ24	MRHIIHGGGVITEEMASLLDQLIEEVLADNLPPPSHFEPPTLHELYDLDTAPE DPNEEAVSQIFPESVMLAVQEGIDLFTFPAPGSPEPPHLSRQPEQPEQRA LGPVSMPLNVPEVIDPPSDDDEEGEEFVLDYVEHPGHGCRSCHYHRRNTGDPD IMCSLCYMRTCGMFVYSPVSEPEPEPEPEPARPTRPKLPAILRRPTSPV SRECNSSTDSCDSGPSNTPPEIHPVVPLCPKPVAVRVGGRRQAVECIEDLLNE SGQPLDLSCKRPRP
35	hulL-12p70	MGHQQLVISWFSVLFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTC DTP EEDGITWTL DQSSEVLGSGKTLTIQVKEFGDAGQYTC HKGGEVL SHSLLLLHK KEDGIWSTDILKDQKEPKNTFLRCEAKNYSGRFTCW WLTITSTDLTF SVKSSR GSSDPQGVTCGAATLSAERVRGDNKEYEY SVEQCEDSACPAEESLPIEVMV DAVHKLKYENYTSSFFIRDI IKPDPKPNLQLKPLKNSRQVEVSWEYPDTWSTPH SYFSLTFCVQV QGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYSSSW SEWASVPCSVPGVGPVGARNLPVATPDGMPCLHHSQNLRAVSNMLQ KARQTFEYFCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETS FITNG SCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKR QIFLDQNMLA VIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILL HAFRIRAVTIDRVMSYLN AS
36	HSV1 TK	MASYPGHQHASAFDQAARSRGHSNRRTALRPRRQQEATEVRPEQKMP TLLR VYIDGPHGMGKTTTTQLLVALGSRDDIVYVPEPMTYWRVLG ASETIANIYTTQH RLDQGEISAGDAAVVMTSAQITMGMPYAVTDA VLAPHIGGEAGSSHAPPPALT LIFDRHPAIALLCYPAARYLMGSMTP QAVLAFVALIPPTLPGTNIVLGALPEDRHI DRLAKRQRPGERLDL AMLAAIRRVYGLLANTVRYLQGGGGSWREDWGQLSGT AVPPQGAEP QSNAGPRPHIGDTLFTLFRAPPELLAPNGDLYNVFAWALDVLAKR LRPMHVFILDYDQSPAGCRDALLQLTSGMIQTHVTPGSIPTICDLART FAREM GEAN
37	HA tag	YPYDVPDYA
38	PD-L1(H12_g1) minibody	MDWIIWRILFLVGAATGAHSEVQLVQSGAEVKKPGASVKVSCKASGG TFSSYAI SWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADK STSTAYMELSSLRS EDTAVYYCARSGHGYSYGAFDYWGQGT LTVSSGGGGSGGGGSGGGGSSQS VLTQPPSVSGAPGQRTISCTG SSSNIGAGYDVHWYQQLPGTAPKLLIYGNSN RPSGVPDRFSGSKSG TSASLAITGLQAEDEADYYCQSYDSSLSGSYVFGGG TKLTVLEAKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLN GKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFF LYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGKGGGG SYPDVDPDYAGYPYDVDPDYA
39	PD-L1(H12_g1) LC-CDR1	TGSSSNIGAGYDVH
40	PD-L1(H12_g1) LC-CDR2	GNSNRPS
41	PD-L1(H12_g1) LC-CDR3	QSYDSSLSGSYVV

42	PD-L1(H12_g) HC-CDR1	SYAIS
43	PD-L1(H12_g) HC-CDR2	RIIPILGIANYAQKFQG
44	PD-L1(H12_g) HC-CDR3	SGHGYSYGAFDY
45	PD-L1(H12_g) VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGSYVVFG GGTKLTVL
46	PD-L1(H12_g) VH	EVQLVQSGAEVKKPGASVKVSKASGGTFSSYAISWVRQAPGQGLEWMGRII PILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARSGHGYSYG AFDYWGQGLTVTVSS
47	HER2(C5)- CD28TM,ICD- CD3Z CAR	AAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAAC AGGATATCTGTGGTAAGCAGTTCCTGCCCGGCTCAGGGCCAAGAACAGA TGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTG CCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTC AGCAGTTTCTAGAGAACCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGA AATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTCGCTTCTG TTCGCGCGCTTCTGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCAC TCGGCGCGCCAGTCCCTCCGATTGACTGAGTCGCCCGGGTACCCGTGTATC CAATAAACCCCTCTTGCACTTGCATCCGACTTGTGGTCTCGCTGTTCTTGG GAGGGTCTCCTCTGAGTGATTGACTACCCGTGAGCGGGGGTCTTTCATTTG GGGGCTCGTCCGGGATCGGGAGACCCCTGCCAGGGACCACCGACCCAC CACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTA GTGTCTATGACTGATTTTATGCGCCTGCGTCCGTACTAGTTAGCTAACTAGC TCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTCGGGAACACCCGGC CGCAACCCTGGGAGACGTCCTCCAGGGACTTCGGGGGCCGTTTTTGTGGCC GACCTGAGTCCTAAAATCCCGATCGTTTAGGACTCTTTGGTGCACCCCCCT TAGAGGAGGGATATGTGGTCTGGTAGGAGACGAGAACCCTAAAACAGTTCC CGCCTCCGTCTGAATTTTTGCTTTCCGTTTGGGACCGAAGCCGCGCCGCG CGTCTTGTCTGCTGCAGCATCGTTCTGTGTTGTCTCTGTCTGACTGTGTTTC TGTATTTGTCTGAAAATATGGGCCCGGGCTAGCCTGTTACCACTCCCTTAA GTTTGACCTTAGGTCACTGGAAAGATGTCGAGCGGATCGCTCACAACCAGT CGGTAGATGTCAAGAAGAGACGTTGGGTTACCTTCTGCTCTGCAGAATGGC CAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTC ATCACCCAGGTTAAGATCAAGGTCTTTTACCTGGCCCGCATGGACACCCA GACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTTTTGACCCCCCT CCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCTCCA TCCGCCCCGTCTCTCCCCCTTGAACCTCCTCGTTTCGACCCCGCCTCGATCC TCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCCATAT GAGATCTTATATGGGGCACCCCCCGCCCCCTTGTAACCTTCCCTGACCCTGAC ATGACAAGAGTTACTAACAGCCCCCTCTCTCCAAGCTCACTTACAGGCTCTCT ACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAA CAACTGGACCGACCGGTGGTACCTCACCTTACCGAGTCGGCGACACAGT GTGGGTCCGCGACACCAAGACTAAGAACCTAGAACCTCGCTGGAAAGGAC CTTACACAGTCCCTGCTGACCACCCCAACCGCCCTCAAAGTAGACGGCATC GCAGCTTGGATACACGCCGCCACGTGAAGGCTGCCGACCCCGGGGGTG GACCATGACTCGAGCCATGGATTGGATCTGGCGCATCCTGTTTCTCGTGGG AGCTGCCACAGGCGCCCATCTCAGGTTGAGCTGCAAGAGTCTGGCCCTG GCCTGGTCAAGCCTAGCGAAACACTGAGCCTGACCTGTACCGTGTCTGGC GGCAGCATCAGCAGCAGCTCTTACTACTGGGGCTGGATCAGACAGCCTCC TGGCAAAGGCCTGGAATGGATCGGCTCCATCTACTACAGCGGCAGCACCT ACTACAACCCAGCCTGAAGTCCAGAGTGACCATCAGCGTGGACACCAGC AAGAACCAGTTCTCCCTGAAGCTGAGCAGCGTGACAGCCGCCGATACAGC CGTGTACTACTGTGCCAGATACGCCCTGATAGCAGCGGCTACCTGGTGG CCTTTGATATCTGGGGCCAGGGCACAAATGGTCACCGTTTCTAGCGGAGGC GGAGGTTCTGGTGGCGGAGGAAGTGGCGGCGGAGGATCTCAGACAGTGG TCACACAAGAGCCAGCTTCTCCGTGTCTCCTGGCGGAACAGTGACCCTG ACATGTGGCCTTAGCTCTGGCTCTGTGTCCACCGGCTACTACCCAGCTGG

		TATCAGCAGACACCTGGACAGGCCCTCGGACACTGATCTACAGCACCAA CAGCAGATCCAGCGGCGTGCCCGATAGATTCAGCGGCTCTATCCTGGGCA ACAAGGCCGCACTGACAATCACAGGCGCTCAGGCCGATGACGAGAGCGAC TACTACTGCGTGCTGTACATGGGCAGCGGCATCTCCGTTTTTGGCGGAGG CACAAAGCTGACCGTGCTGGGATCCGAACCAAAGAGTTGCGACAAAACAC ACACCTGCCCTACGCGTTTTTGGGTGCTCGTGGTGGTGGTGGCGTGCTC GCTTGCTACTCACTTCTGGTGACCGTAGCGTTTATCATTTTTTGGGTCAGGA GCAAGCGATCCCGCCTATTGCACAGCGACTACATGAACATGACCCCCCGG CGCCCCGGGCCAACCCGGAAGCACTACCAGCCATATGCGCCTCCCCGCG ATTTGCGCAGCGTATCGGTCCCGGGTCAAATTTTACGGTCCGCTGACGCC CGGCCTATCAACAGGGGCCAGAATCAGCTGTATAATGAATTAACCTCGGTA GACGCGAGGAGTACGACGTCCTCGACAAGAGAAGGGGGGCGCGACCCAGA GATGGGAGGCAAACCGCAGCGCAGGAAGAATCCACAGGAGGGCCTGTAC AACGAATTACAGAAGGACAAGATGGCAGAGGCCTACAGCGAGATAGGAAT GAAGGGTGAAAGGCGTCGTGGAAAGGGCCACGATGGGCTTTACCAGGGC CTAAGTACTGCCACAAAAGATACGTATGACGCGCTGCATATGCAAGCCCTC CCCCCAGGTAAGCATGCAACCTCGATCCGGATTAGTCCAATTTGTTAAAG ACAGGATATCAGTGGTCCAGGCTCTAGTTTTGACTCAACAATATCACCAGCT GAAGCCTATAGAGTACGAGCCATAGATAAAATAAAAGATTTTATTTAGTCTC CAGAAAAAGGGGGGAATGAAAGACCCACCTGTAGGTTTGGCAAGCTAGC TTAAGTAACGCCATTTTGCAAGGCATGGAAAAATACATACTGAGAAATAGAG AAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAAC AGGATATCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGA TGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTG CCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTC AGCAGTTTCTAGAGAACCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGA AATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTCGCTTCTG TTCGCGCGCTTC
48	HER2(E4)- CD28TM,ICD- CD3Z CAR	AAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAAC AGGATATCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGA TGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTG CCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTC AGCAGTTTCTAGAGAACCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGA AATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTCGCTTCTG TTCGCGCGCTTCTGCTCCCCGAGCTCAATAAAAGAGGCCACAACCCCTCAC TCGGCGCGCCAGTCCTCCGATTGACTGAGTCGCCCGGGTACCCGTGTATC CAATAAACCCCTCTTGCACTTGCATCCGACTTGTGGTCTCGCTGTTCCCTTG GAGGGTCTCCTCTGAGTGATTGACTACCCGTCAGCGGGGGTCTTTCATTTG GGGGCTCGTCCGGGATCGGGAGACCCCTGCCAGGGACCACCGACCCAC CACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTA GTGTCTATGACTGATTTTATGCGCCTGCGTCGGTACTAGTTAGCTAACTAGC TCTGTATCTGGCGGACCCGTGGTGGAAGTACGAGTTCGGAACACCCGGC CGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGGCCGTTTTTGTGGCCC GACCTGAGTCCTAAAATCCCGATCGTTTAGGACTCTTGGTGACCCCCCT TAGAGGAGGGATATGTGGTCTGGTAGGAGACGAGAACCTAAAACAGTTCC CGCCTCCGTCTGAATTTTTGCTTTTGGTTTGGGACCGAAGCCGCGCCGCG CGTCTTGTCTGCTGCAGCATCGTTCTGTGTTGTCTGTCTGACTGTGTTTC TGTATTTGTCTGAAAATATGGGCCCGGGCTAGCCTGTTACCACTCCCTTAA GTTTGACCTTAGGTCACTGGAAAGATGTGAGCGGATCGCTCACAACCAAGT CGGTAGATGTCAAGAAGAGACGTTGGGTTACCTTCTGCTCTGCAGAATGGC CAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTC ATCACCCAGGTTAAGATCAAGGTCTTTTACCTGGCCCGCATGGACACCCA GACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTTTTGACCCCCCT CCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCTCCA TCCGCCCCGTCTCTCCCCCTTGAACCTCCTCGTTGACCCCGCCTCGATCC TCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCCATAT GAGATCTTATATGGGGCACCCCGCCCCCTTGTAACCTTCCCTGACCCTGAC ATGACAAGAGTTACTAACAGCCCTCTCTCCAAGCTCACTTACAGGCTCTCT ACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAA

		CAACTGGACCGACCGGTGGTACCTCACCCTTACCGAGTCGGCGACACAGT GTGGGTCCGCCGACACCAGACTAAGAACCTAGAACCTCGCTGGAAAGGAC CTTACACAGTCCTGCTGACCACCCCAACCGCCCTCAAAGTAGACGGCATC GCAGCTTGGATACACGCCGCCACGTGAAGGCTGCCGACCCCGGGGGTG GACCATGACTCGAGCCATGGATTGGATCTGGCGCATCCTGTTTCTCGTGGG AGCTGCCACAGGCGCCATTCTCAGGTTGAGCTGCAACAGTGGGGAGCCG GACTGCTGAAGCCTAGCGAAACACTGAGCCTGACCTGTGCCGTGTACGGC GGCAGCTTTAGCGGCTACTACTGGTCCTGGATCAGACAGCCTCCTGGCAA AGGCCTGGAATGGATCGGCGAGATCAATCACAGCGGCAGCACCAACTACA ACCCAGCCTGAAGTCCAGAGTGACCATCAGCGTGGACACCAGCAAGAAC CAGTTCTCCCTGAAGCTGAGCAGCGTGACCACAGCCGATACCGCCGTGTA CTACTGTGCCCGGATGGGCATCAATAGCGGCGGCTACCTGTACGGCATGG ATGTGTGGGGACAGGGCACCAACCGTGACAGTTTCTAGCGGAGGCGGAGGT TCTGGTGGCGGAGGAAGTGGCGGCGGAGGATCTCAGACAGTGGTCACAC AAGAGCCCAGCTTCTCCGTGTCTCCTGGCGGAACAGTGACCCTGACATGT GGCCTTAGCAGCGGCTCTGTGTCCACCAGCTACTACCCTAGCTGGTATCAG CAGATCCCCGGACAGGCCCTCGGACACTGATCTACACCACCAACATCAG ATCCAGCGGCGTGCCCGATAGATTGCGCGGATCTATCCTGGGCAACAAGG CCGCACTGACAATCACAGGTGCCAGGCCGAGGACGAGTCCGACTACTAC TGCATGCTGTACATGGGCAGCGGCATCTGGGTTTTCGGCGGAGGCACAAA GCTGACCGTTCTGGGATCCGAACCAAGAGTTGCGACAAAACACACACCTG CCCTACGCGTTTTTGGGTGCTCGTGGTGGTGGGTGGCGTGTCTCGTTGCT ACTCACTTCTGGTGACCGTAGCGTTTATCATTTTTTGGGTCAGGAGCAAGC GATCCCGCCTATTGCACAGCGACTACATGAACATGACCCCCCGCGCCCC GGGCCAACCCGGAAGCACTACCAGCCATATGCGCCTCCCCGCGATTTGCG AGCGTATCGGTCCCGGGTCAAATTTTACGGTCCGCTGACGCCCCGGCCT ATCAACAGGGCCAGAATCAGCTGTATAATGAATTAACCTCGGTAGACGCG AGGAGTACGACGTCCTCGACAAGAGAAGGGGGCGCGACCCAGAGATGGG AGGCAAACCGCAGCGCAGGAAGAATCCACAGGAGGGCCTGTACAACGAAT TACAGAAGGACAAGATGGCAGAGGCCTACAGCGAGATAGGAATGAAGGGT GAAAGGCGTCTGGAAAGGGCCACGATGGGCTTTACCAGGGCCTAAGTAC TGCCACAAAAGATACGTATGACGCGCTGCATATGCAAGCCCTCCCCCCCAG GTAAGCATGCAACCTCGATCCGGATTAGTCCAATTTGTTAAAGACAGGATAT CAGTGGTCCAGGCTCTAGTTTTGACTCAACAATATCACCAGCTGAAGCCTA TAGAGTACGAGCCATAGATAAAATAAAAGATTTTATTTAGTCTCCAGAAAAA GGGGGAATGAAAGACCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAA CGCCATTTTGCAAGGCATGGAAAAATACATAACTGAGAATAGAGAAGTTCA GATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATAT CTGTGGTAAGCAGTTCTGCCCCGGCTCAGGGCCAAGAACAGATGGAACA GCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCTGCCCCGG CTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGT TTCTAGAGAACCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGAC CCTGTGCCTTATTTGAACTAACCAATCAGTTCCGCTTCTCGCTTCTGTTCCG CGCTTC
49	HER2(F1)- CD28 TM ,ICD- CD3Z CAR	AAGTTCAGATCAAGGTGAGGAACAGATGGAACAGCTGAATATGGGCCAAAC AGGATATCTGTGGTAAGCAGTTCTGCCCCGGCTCAGGGCCAAGAACAGA TGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCTG CCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTC AGCAGTTTCTAGAGAACCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGA AATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTGCTTCTCGCTTCTG TTCGCGCGCTTCTGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCAC TCGGCGCGCCAGTCTCTCGATTGACTGAGTCGCCCCGGGTACCCGTGTATC CAATAAACCCCTCTTGCAAGTTGCATCCGACTTGTGGTCTCGCTGTTCTTGG GAGGGTCTCCTCTGAGTGATTGACTACCCGTGAGCGGGGGTCTTTTCAATTTG GGGGCTCGTCCGGGATCGGGAGACCCCTGCCAGGGACCACCGACCCAC CACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTA GTGTCTATGACTGATTTTATGCGCCTGCGTCGGTACTAGTTAGCTAACTAGC TCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTGGAACACCCGGC CGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGGCGTTTTTGTGGCCC

		GACCTGAGTCCTAAAATCCCGATCGTTTAGGACTCTTTGGTGCACCCCCCT TAGAGGAGGGATATGTGGTTCTGGTAGGAGACGAGAACCTAAAACAGTTCC CGCCTCCGTCTGAATTTTTGCTTTCGGTTTGGGACCGAAGCCGCGCCGCG CGTCTTGTCTGCTGCAGCATCGTTCTGTGTTGTCTCTGTCTGACTGTGTTTC TGTATTTGTCTGAAAATATGGGCCCCGGGCTAGCCTGTTACCACTCCCTTAA GTTTGACCTTAGGTCACTGGAAGATGTCGAGCGGATCGCTCACAACCAGT CGGTAGATGTCAAGAAGAGACGTTGGGTTACCTTCTGCTCTGCAGAATGGC CAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTC ATCACCCAGGTTAAGATCAAGGTCTTTTACCTGGCCCCGCATGGACACCCA GACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTTGGCTTTTGACCCCCCT CCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCCTCCA TCCGCCCCGTCTCTCCCCCTTGAACCTCCTCGTTGACCCCCGCTCGATCC TCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCCATAT GAGATCTTATATGGGGCACCCCCGCCCCCTTGTAACCTTCCCTGACCCTGAC ATGACAAGAGTTACTAACAGCCCCCTCTCTCCAAGCTCACTTACAGGCTCTCT ACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAA CAACTGGACCGACCGGTGGTACCTCACCTTACCGAGTCGGCGACACAGT GTGGGTCCGCGACACCAGACTAAGAACCTAGAACCTCGCTGGAAAGGAC CTTACACAGTCTCTGCTGACCACCCCCACCGCCCTCAAAGTAGACGGCATC GCAGCTTGGATACACGCCGCCACGTGAAGGCTGCCGACCCCGGGGTG GACCATGACTCGAGCCATGGATTGGATCTGGCGCATCTGTTTCTCGTGGG AGCTGCCACAGGCGCCATTCTCAGGTTTCAGCTGGTGGAATCTGGCCCTG GCCTGGTTAAGCCTAGCGGCACACTGTCTCTGACCTGTGCTGTGTCTGGC GGCAGCATCAGCAGCAGCAATTGGTGGTCTTGGGTCCGACAGCCTCCTGG CAAAGGCCTGGAATGGATCGGCGAGATCTACCACAGCGGCAGCACCAACT ACAACCCAGCCTGAAGTCCAGAGTGACCATCAGCGTGACACACCAGCAAG AACCAGTTCTCCCTGAAGCTGAGCAGCGTGACAGCCGCCGATACAGCCGT GTACTACTGTGCCAGAATGGGAGCCAATAGCGGCGGCTACCTGTACGGCA TGGATGTGTGGGGACAGGGCACCAACCGTGACAGTTTCTAGCGGAGGCGGA GGTTCTGGTGGCGGAGGAAGTGGCGGCGGAGGATCTCAGACAGTGGTCA CACAAGAGCCCAGCTTCTCCGTGTCTCCTGGCGGAACAGTGACCCTGACA TGTGGCCTTAGCAGCGGCTCTGTGTCTACCAGCTACTACCCCTCCTGGTAT CAGCAGACCCCTGGACAGGCTCCCCGGACACTGATCTACTCCACCAACAC CAGATCCAGCGGCGTGCCCGATAGATTCTCCGGCTCTATCCTGGGCAACA AGGCCGCACTGACAATCACAGGCGCTCAGGCCGATGACGAGAGCGACTAC TACTGCGTGCTGTACATGGGCAGCGGCATCTGGGTTTTTCGGCGGAGGCAC AAAGCTGACCGTTCTGGGATCCGAACCAAAGAGTTGCGACAAAACACACAC CTGCCCTACGCGTTTTTGGGTGCTCGTGGTGGTGGGTGGCGTGCTCGCTT GCTACTCACTTCTGGTGACCGTAGCGTTTATCATTTTTTGGGTGAGGAGCAA GCGATCCCGCCTATTGCACAGCGACTACATGAACATGACCCCCCGGCGCC CCGGGCCAACCCGGAAGCACTACCAGCCATATGCGCCTCCCGCGATTTT GCAGCGTATCGGTCCCGGGTCAAATTTTACGGTCCGCTGACGCCCCGGC CTATCAACAGGGCCAGAATCAGCTGTATAATGAATTAACCTCGGTAGACG CGAGGAGTACGACGTCCTCGACAAGAGAAGGGGGCGCGACCCAGAGATG GGAGGCCAAACCGCAGCGCAGGAAGATCCACAGGAGGGCCTGTACAACG AATTACAGAAGGACAAGATGGCAGAGGCCTACAGCGAGATAGGAATGAAG GGTGAAAGGCGTCGTGGAAAGGGCCACGATGGGCTTTACCAGGGCCTAAG TACTGCCACAAAAGATACGTATGACGCGCTGCATATGCAAGCCCTCCCCC CAGGTAAGCATGCAACCTCGATCCGGATTAGTCCAATTTGTTAAAGACAGG ATATCAGTGGTCCAGGCTCTAGTTTTGACTCAACAATATCACCAGCTGAAGC CTATAGAGTACGAGCCATAGATAAAATAAAAGATTTTTATTTAGTCTCCAGAA AAAGGGGGGAATGAAAGACCCACCTGTAGGTTTGGCAAGCTAGCTTAAGT AACGCCATTTTGCAAGGCATGGAAAAATACATAACTGAGAATAGAGAAGTTC AGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATA TCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAAGAACAGATGGAAC AGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTGCCCCGG CTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGT TTCTAGAGAACCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGAC
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		CCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTCGCTTCTGTTGCGCGCGCTTC
50	HDAdIL12p70_ TK_aPD-L1	AAACATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAG GGGGTGGAGTTTGTGACGTGGCGCGGGGCGTGGGAACGGGGCGGGTGA CGTAGTAGTGTGGCGGAAGTGTGATGTTGCAAGTGTGGCGGAACACATGT AAGCGACGGATGTGGCAAAAGTGACGTTTTTGGTGTGCGCCGGTGTACAC AGGAAGTGACAATTTTCGCGCGGTTTTAGGCGGATGTTGTAGTAAATTTGG GCGTAACCGAGTAAGATTTGGCCATTTTCGCGGGAAAACCTGAATAAGAGGA AGTGAATCTGAATAATTTTGTGTTACTCATAGCGCGTAATATTTGTCTAGG GCCGCGGGGACTTTGACCGTTTACGTGGAGACTCGCCCAGGTGTTTTTCTC AGGTGTTTTCCGCGTTCCGGGTCAAAGTTGGCGTTTTGATATCAAGCTTATC GATACCGTAACAAGTCTTTAATTCAAGCAAGACTTTAACAAGTTAAAAGGA GCTTATGGGTAGGAAGTAGTGTTATGATGTATGGGCATAAAGGGTTTTAAT GGGATAGTGAAAATGTCTATAATAACTTTAAATGGCTGCCCAATCACCTAC AGGATTGATGTAAACATGGAAAAGGTCAAAAACCTGGGTCACTAAAATAGAT GATTAATGGAGAGGATGAGGTTGATAGTTAAATGTAGATAAGTGGTCTTATT CTCAATAAAAATGTGAACATAAGGCGAGTTTCTACAAAGATGGACAGGACT CATTCAATGAAACAGCAAAAACCTGGACATTTGTTCTAATCTTTGAAGAGTATG AAAAATTCCTATTTTAAAGGTAAAACAGTAACTCACAGGAAATACCAACCCA ACATAAAATCAGAAACAATAGTCTAAAGTAATAAAAATCAAACGTTTGCACG ATCAAATTATGAATGAAATTCACACTAAAATTCACACTGATTTTGTTCATC CACAGTGTCAATGTTGTGATGCATTTCAATTGTGTGACACAGGCACACTGT GGATCAAAAGTGGTTTTCTGGTGCGACTTACTCTCTTGAGTATACCTGCAGT CCCCTTTCTTAAGTGTGTTAAAAAAAAGGGGGATTTCTTCAATTCGCCAAT ACTCTAGCTCTCCATGTGCTTTCTAGGAAACAAGTGTTAACCACCTTATTT GTCAAACCTAGCTCCAAAGGACTTTTGAATCCCCACAAACCGATGTAGCTC AAGAGAGGGTATCTGTCACCAGTATGTATAGTAAAAAAGTATCCCAAGTC CCAACAGCAATTCCTAAAGGAGTTTATTTAAAAAACACACACACCTGTAA AATAAGTATATATCCTCCAAGGTGACTAGTTTTAAAAAACAGTATTGGCTTT GATGTAAAGTACTAGTGAATATGTTAGAAAAATCTCACTGTAACCAAGTGAA ATGAAAGCAAGTATGGTTTGCAGAGATTCAAAGAAAATATAAGAAAACCTAC TGTTGCCACTAAAAAGAATCATATATTAATATACTCACACAATAGCTCTTCA GTCTGATAAAATCTACAGTCATAGGAATGGATCTATCACTATTTCTATTCACT GCTTTGATGTAATCCAGCAGGTCAGCAAGAATTTATAGCCCCCTTGAGC ACACAGAGGGCTACAATGTGATGGCCTCCCATCTCCTTCATCACATCTCGA GCAAGACGTTCACTCCTACAGAAATAAATCAGGAATTTAATAGAAAAGTTTC ATACATTAACTTTATAACAAACACCTCTTAGTCATTAACTTCCACACCAAC CTGGGCAATATAGTGAGACCCCATGCCTGCAAAAAAAAAAAAAATTAGCCAG GCATGGTAGCATGTACCTGTAGTCCCAGCTACTTGAGAGGTGAGGTGGGA AAATCACTTTAGTGCAGGATGTTGAGGCTGGAGTGAAGTGTGATTGTGCCA CTGCACTCCAGCCTGGACAATAGAGCAAGACCTTGTCTCAAAAAAATGCAT TAAAAATTTTTTTTAAATCTTCCACGTATCACATCCTTTGCCCTCATGTTTCAT AAGGTAAAAAATTTGATACCTTCAAAAAAACCAAGCATACCCTATCATAATT TTTTTTAAATGCAAATAAAAAACAAGTACCATTTTCACCTATCAGACTGGCAG GTTCTGATTAAATGAAATTTTCTGGATAATATACAATATTAAGAGAGACTGTGA GAAACTGGGCCAGTGGCTCATGCCTGTAATCCAGCACTTTGGGAGGGCTG GGTAACATGGCGAACCCTGTTTCTACAAAAATAAAATATTAGCTGGGAGTG GTGGCGCACACCTATAGTCCCAGCTACTCAGGAGGCTGAGGTGGAAGGAT CGCTTGAACCCAGGAGGTTGAGACTGCAGTGAAGTGTGATCATTCTGCTGC ACTGCACCCCAGCCTGGGCAACAGAGACCTTGTCTCAAAAAAAAAAAAAA AGAGACAAATTGTGAAGAGAAAGGTACTCTCATATAACATCAGGAGTATAAA ATGATTCAACTTCTTAGAGGAAAATTTGGCAATACCAAAATATTCAATAAACT CTTTCCCCTTGACCCAGAAATTCACCTTGAATAAAGCTGAACAAGTACCAAA CATGTAAAAGAATGTTTCTTCTAGTACAGTCGGTAAGAACAAAATAGTGTCT ATCAATAGTGGACTGGTTAAATCAGTTATGGTATCTCCATAAGACAGAATGC TATGCAACCTTTAAAAATATATTAGATAGCTCTAGACACACTAATATTAAGT GTCCAATAACATTTAAACTATACTCATACGTTAAATATAAATGTATATATG TACTTTTGCATATAGTATACATGCATAGGCCAGTGCTTGAGAAGAAATGTGT

	ACAGAAGGCTGAAAGGAGAGAACTTTAGTCTTCTTGTGTTTATGGCCTCCATA GTTAGAATATTTTATAACACAAATATTTTGATATTATAATTTTAAAAATAAAAAAC ACAGAATAGCCAGACATACAATGCAAGCATTCAATACCAGGTAAGGTTTTTC ACTGTAATTGACTTAACAGAAAAATTTTCAAGCTAGATGTGCATAATAATAAAA ATCTGACCTTGCCTTCATGTGATTCAGCCCCAGTCCATTACCCTGTTTAGGA CTGAGAAATGCAAGACTCTGGCTAGAGTTCCTTCTTCCATCTCCCTTCAATG TTTACTTTGTTCTGGTCCCTACAGAGTCCCCTACTATACCACAACCTGATACTAA GTAATTAGTAAGGCCCTCCTCTTTTATTTTAAATAAAGAAGATTTTAGAAAGC ATCAGTTATTTAATAAGTTGGCCTAGTTTATGTTCAAATAGCAAGTACTCAGA ACAGCTGCTGATGTTTGAAATTAACACAAGAAAAAGTAAAAAACCTCATTTT AAGATCTTACTTACCTGTCCATAATTAGTCCATGAGGAATAAACACCCCTTTC CAAATCCTCAGCATAATGATTAGGTATGCAAAAATAAATCAAGGTCATAACCT GGTTCATCATCACTAATCTGAAAAAGAAATATAGCTGTTTCAATGAGAGCAT TACAGGATACAAACATTTGATTGGATTAAGATGTTAAAAATAACCTTAGTCT ATCAGAGAAATTTAGGTGTAAGATGATATTAGTAACTGTAACTTTGTAGGT ATGATAATGAATTATGTAAGAAAAACAACAGGCCGGGCGGGTGGTTCACAC GTGTAATCCCAGCACTTTGGGAGGCTGAGGCAGGCAGACTGCCTGAGCTC AGGAGTTCGAGACCAGCCTGGGCAACACGGTGAAATCCCGTCTCTACTAAA AATACAAAAAATTAGCCGGGTGTGGTGACACATGCCTGTAGTCCCAGCTA CTTGGGAGGCTGAGGCAGGAGAATCACTTGAACCTGGGAGGTGAAGGTTG CAGTGAGCCAAGATGGCACCACCTTCACTCCAGCCTGGGAAACAGACGCAAG ACTCTGTCTCTGAGCTGAGATGGCACCACCTTCACTCCAGCCTGGGAAACAG AGCAAGACTCTGTCTCAAAAAAACAAAAACACACAAACAAAAAACAGGCTG GGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCG GGTGGATCACCTGAGGTCAGGAGTTCCAGACCAGCCTTGTCAACATGGTG AAACCTCCCCCGCCGTCTCTACTAAAAATACAAAAATTAGCCAGGCGTGG TGGCAGGAGCCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATC GCTTGTACCCAGAAGGCAGAGGTTGCACTGAGCTGAGATGGCACCATTGC ACTCCAGCCTGGGGGACAAGAGCGAGATTTCTGCTTTAAAAAACAAAAACA AAACAAAAAACCATGTAACATATGTCTTAGTCACTCTTAGTCAAGAATGTAGA AGTAAAGTGATAAGATATGGAATTTCTTTAGGTCACAAAGAGAAAAAGAAA AATTTTAAAGAGCTAAGACAAACGCAGCAAAATCTTTATATTTAATAATATTC TAAACATGGGTGATGAACATACGGGTATTCATTATACTATTCTCTCCACTTTT GAGTATGTTTGAAAATTTAGTAAACAAGTTTTAACACACTGTAGTCTAACAA GATAAAATATCACACTGAACAGGAAAAACTGGCATGGTGTGGTGGCTCACA CTTGTAATCCCAGTGCTTTGGGAGGCTGAGACAGGAGAGTTGCTTGAGGC CAGGAGTTCAAGACCGACATGGGGAATGTAGCAAGACCCCGTCCCTACAA AAAATTTGTAAAAATTTGCCAGGTATGGTGGTGCATACCTGTAGTCCCAGC TACTCGGGAGGCGGAGGCAGAAGGAATCACTTGAGCCCAGGAGTTTGAGG CTGCAGTGAGCTACGATCATACCACAGCACTCCAGCGTGGACAACAGAGTA AGACCTATCTCAAAAACAAAACAAAACAAAACAAAACAAAAAACACAAAG AAAACTGCTGGCTGATGCAGCGGCTCATGCCTGTAATCCCAGTATTTTGG GAGGCCAGGTGGGCGTATCACCTGAGGTCAGGAGTTAGAGACCAGCCTG GCCAACATGGTGAAACCCCATCTCTACTAAAAATACAAAATTAGCCAGGCAT GTGGCACGCGCCTGTAGTCCCAGTTACTGGGAGGCTGAAGCAGGAGGATC ACCTGAGCCCGGGAGGTGGAGGTTGCAGTGAGCCGAGATCACACCACTGC ACTCCAGCCTGGGTGACACAGCAATACCCTACCTCAAAATAAAAAAGAAAA AGAAAAAGAAAAGTTGCTGTCCCCGCTACCCCAATCCCAAATCCAAACAGCC TCTCTCATCTCACAGTAAGGGGGAAAAATCACCCAAAAAAGCTAAGTGATCT TTTGA AACCCAAACTCTTAGAAGTCTAAGATTATTATAGTCAACTCATGAAG TGTCATCATAAAAGATACTCTAATATTATTTAAGTAGAACACATATTGGTTG TCTTGGTATGTCTAGCCCCTGGCATACAAAATATTTAATAACACTGATATGG TACCTGTGATGTGAAAATGTACTATGAGTACAGCTTTATAAATACTATATATG TACCTATATACAGAAAAAATAACAACAAATCATAAAAGCACTTATCTTTGAA AGAGGAGTTACAGCAATTTTATTTAGTTCTTTATTGCTTTGCTATATATTCTA AATTTTTTTCAATGAATATATATCACTTTTAAAAAATTCATGGTCTTTCTTA TAAATTATCTTTGGCAGCATGCGTTTTTATATATACATATAAAATGTATGGGA AATTTTTTAAAGGATACATTAAATTAAGCAAAATATACAAACAAAAAATCAGA ATACAAAAAGATAAAAAGATTGGGAAGGGAGGGAGGGAGTAAGGAGGAAG
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		GGTGGGTGGGTATAGAGAAATATACCAAATAATGGTAAGAAGTGGGGTCTT GACACTTTCTACACTTTTTTTAAATAAAAAAATTTTTTCTCTCTTTTTTTT TTTTAGAGACGAAGTCTCGCTATGTTGCCAGGCTGGTCTTGAACCTCTGG GATCAAGAGATCCTCCTGCCTCAGCCTCCCAAGGTGCTTGGATTACAGGTG TGAGCCACCACGCCTGGTCACTTTCTACACTTTAATATATATATTTTTTCATT TTCAATGTCATTTTTATTAGTTAATTTATAATACCCATTCACCATTATATTCAA AGTCTATTTGAAGAAATAAACCAGAAAGAATGAAATACTCTAGCTCACATGC TATTCAATACTAAATTACCTTTCAAATCACATTCAAGAAGCTGATGATTTAAG CTTTGGCGGTTTCCAATAAAATATTGGTCAAACCATAATTAATCTCAATATAT CAGTTAGTACCTATTGAGCATCTCCTTTTACAACCTAAGCATTGTATTAGGT GCTTAAATACAAGCAGCTTGACTTTTAATACATTTAAAAATACATATTTAAGA CTTAAATCTTATTTATGGAATTCAGTTATATTTTGGAGGTTTCCAGTGCTGAG AAATTTGAGGTTTGTGCTGTCTTTCAGTCCCCAAAGCTCAGTTCTGAGTTCT CAGACTTTGGTGGAACCTTCATGTATTGTCAGGTTGGCCCGTAATACCTGTG GGACAACCTCAGCCCCGTGTGCACATGGCCAGGAGGCTGGTTGCAAACATTT TCAGGTAGGTGGACCAGGACATGCCCTGGTCATGGCCAGGTGGAGGCAT AGTGCTATACAGCAGGCAGAAAGTCAATATTGATTTGTTTTAAAGAAACATG TACTACTTTCATAAGCAGAAAAAATTTCTATTCTTGGGGGAAAAGATTATGC CAGATCCTCTAGGATTAAATGCTGATGCATCTGCTAAACCTTCACATATCAG AACATATTTACTATAGAAAGAATGAAAATGGGACATTTGTGTGTCACCTATG TGAACATTTCCAAAAATTTTTACAACAACATAAGTATTTTATAAATTTTATGAAC TGAAATTTAGTTCAAGTTCTAGGAAAATACAAACCTTGCTAGATATTATAAAA ATGATACAATATATATTCATTTTCAGGCTCATCAGAATATATCTGTTATCACTT GACAAGAATGAAAATGCACCATTTTGTAGTGCTTTAAAATCAGGAAGATCCA GAGTACTAAAAATGACTTCTTCTTGAAGCTTACTCACCAACTTCCTCCCAG TTACTCACTGCTTCTGCCACAAGCATAAACTAGGACCCAGCCAGAACTCCC TTGAAATATACACTTGCAACGATTACTGCATCTATCAAAATGGTTCAGTGCC TGGCTACAGGTTCTGCAGATCGACTAAGAATTTGAAAAGTCTTGTGTTATTTT AAAGGAAGCCCATGTGAATTCTGCCCAGAGTTCATCCCAGATATGCAGTCT AAGAATACAGACAGATCAGCAGAGATGTATTCTAAAACAGGAATTCTGGCA ATATAACAAATTGATTTCCAATCAAAACAGATTTACATACCATACTTATGTCA AGAAGTTGTTTTGTTTTATTGCATCCTAGATTTTATTTTTTTGATTTATGGTTT ACTTTAAGCATAAAAAATTTGTCAATACAACCTCTTCCCAAAGGCATAAACAA AAATTCATAAACTTGCATCACTTGAGATACTTCAGGTATGAATTCACAACTT TGTTACAACCTTACTATATATATGCACACATATATATATTTGGGTATATTGG GGGGGTTCTAATTTAAGAAATGCATAATTGGCTATAGACAGACAGTTGTCTG GAATGAAAATCAATACTTTTGCTATAATCGATTACTGAAATAATTTTACTTTC CAGTAAACTGGCATTATAATTTTTTTTAAATTTTAAAACCTTCATAATTTTTTG CCAGACTGACCCATGTAAACATACAAATTACTAATAATTATGCACGTCACAT CTGTAATAATGGCCTTCATGTAAACATTTTTGTGGTTTACACATAAAATCTCT AATTACAAAGCTATATTATCTAAATTACAGTAAGCAAGAAAATTAATCCAAG CTAAGACAATACTTGCAACATCAATTCATCATCTGTGACAAGGACTGCTTAA GTCTCTTTGTGGTTAAAAAGGAAAAAAAAAAAAAAAAAGACATGTTGGCCAGATG CGGTGGCTCACACCTGTAATCCCAGCACCTTTGGGAGGCTGAGGTGGGCGG ATCACCCCTGGCCTGCCAACATGGTGAAACCCCGTCTCTACTAAAAACAC AAAAATTAGCTGGGCGTGGTGGCGGGCGCCTGTAATTCAGCTACTCGGG AGGCTGAGGCAGGAGAATTGCTAGAACCCAGGAGGCAGAGATTGCAGTGA GCTGAGATTGCACCATTGCACTACAGTCTGGGCAACAAAAGTGAAACTCCA TCTTAAAAAAAAAAGACAATGTTCTGGTCCAAACAAGACTTAATGGAAG TGAGTCTAAAAATGAGCTATGTGGGCCAGGCGTAGTGGCTCCCACCTGTAA TCCCAGCACTTTGGGAGGCCGAAGCAGGCAGATCATGAGGTCAGGAGATG GAGACCATCCTGGCCAACACGGTGAAATCCTGTCTCTACAAAAATTAGCTG GGCGTGGTGGTGCCTGCCTGTAATCCCAGCTACTCAGAAGGCTCAGGCAG GAGAATCGCTTGAACCAGGGAGTCGGTGGCTAGAGTGAGCCGAGATTTGC ATCACTGCACTCCTGCCTGGTGACAGAGCAAGACTCCATCTCAAAAAAAC AAACAAAAATAAAAGATAAAAAATGAGCTATGTGAATTAAGAGGTATAACA ATAGATAAACCATATTTTATTTAATTCCTAGTAATGAGTAATATTTCCAACTT CTGGAATGGGCAGAAATTGCTAGTTGGCATATTTTACCTTTTATATTTCAGA TACATTAATCTCAAAAAAACACCTCAAAGCAGATGATCCGCCATCTC
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	CTTGGATAATTTGTGTTAACTCAGGATAACAGAAAACCAAAATTATGAGTTA CTGATGCAATATTCCTAAATGTAATAAATTAAGCTAATAGTAGATTCATC TTCCAATTTTCATATCAGTCTTACAAATAAACTACATATATAACTTGCTTGCCT TCCCTTCTGAGGGATAAAGCTGTTAGAAGAATTAATCAGCATTCTTGACT ATTCAACCAAGGGAGGGATAAATTATTACTCATTCTAGGGACATGGGCTCAT AACTACTACATGTGTAAGGACATGAATTTACCCAATATTACAATTTTTCCTTT TATTAGTGTGTACAGTGGAAGAATAGACATGTTCACTCTGGACAAAAA ATTATACTTATCAGTTATCAGAAGCACAATGCTGAAGACAGTAGTTCCATAA CAATTTGAAGTATGTGATCGAACTAGTAGATTATCTTAGTAGTAGTGAATTAT TGTAATGTTAGTAATTTGGCAGCCACTGGGCAGAAAAATAAGAATTGAGG CTCAATATTGATATTAATGGTGGTGATTGACACATAAATTTTATCAAGTCTAC ACAATATAAAATTACAGAAAGGTAGAAGAGTATACCAGTACAACCTTCAACAT ATCTTCACTACAAGGGAGTAAATGACATGGCCTAGTTACTATCTAATGAAC TGCAGAAAACATAAAGAAAACCTCAAGGCAACTCTTCTCTGCTGATCTGGTT GGTCCTTTTCTACCTTTTGAATACCCAGATACAAACAATGGATAGAAAAC AAAGTAGACTTGTAGTATGCAGGTCACAGTGCTAAATTCACAGAAAGAAAC CCCTGAACTGAACTGCTCTATTTCTGGTGGTCACAAAGAGTAATTCTGGTT TACACCTACAGATTGATGTCAATCTACACCCTGTTGATAACAGTGTGGCCAA GGACAAAAAAGGTGCTCCGTTTTACCAATTCTGTAAAAATTATTGGCAG GGTAAGCTCGGCTAGGGCAGGATTACATTTCTAGGACTACCATCCCCGAAA TTTAGAAGATATTATATCCACATAAAGCATATCTTTCACATTAATTTGCAAAA ATCTAAAAGCTTTTTCTTAGCTCAAGTGTGTCCAAGTTTACCCTGGCAGTTT AAAACGATAGTTACAAGCAGCATGGGTTGTATCAGACACATTTGAGGGCCA ATTTTCATGTAAGTGATATTGGGCAAGTTACTTCAACTATCTGTGCCTCCAAG GTCATACTAGTGTTTATTTACCTAAAGGGTACCTGTTATGTAACCTTAGGGT GTTTACATTAGATAATGCCTGCAAAATATTTACTTCAACGCCTAAAACATAGT TAAGTATTCAATAAATACCTACTATTGTCACTACTAACTTAAAGTTTAGAGA TTAAGAGCAGAATCTGGGGTGAGACAACTTAGGTTCAAATCCTAGTATTGT TGGGTAATCTTGGGCAAGTTACTTAACCTCTCTGATTTGTGTAATTTAAAAA TTAGTTAATATACATAACAGGGCTTAGAAGAGTATCTAGCACATAGCACCAT TTAAGCATTGTTATTGCTAACATGCAACAATTTAAGGGAAAGAAATTTTTT AAAAAGGAAGAGGGATTTGCAAACTAAAAACAATGAGTATCTTATGTTCAA GAAACTAACAAACAGCCAGCTCTAGCAATAATTAAATTCATATATACTGG GGCAGGCATCACACCCCAAGCTAAAAGCGTCTACCTAGGCCAGGCACGG TGGCTCATGCCTGTAATCCCAGCACTTTGGGAAGCAGAGGCGGGCAGATC GCTTGAGCTCAGGAGTTCAAGACCAGCCTGGACAACATGGCAAAACACCAT CTCTACAAAAATACAAATATTAGGCCGGGCGCAGTGGCTCACGCCTGTAA TCCCAGCACTTTGGGAGGCCAAGGCGGGTGGATCACCTGAGATCAGGAGT TCGAGAGTAGCCTGGCCAACATGGTGAACCTCGTCTCTATTAATAATACA AAAAATTAGCCAGGCATGGTGGCAGGCGCCTGTAATCCCAGCTACTCAGG GGGATGAGGTAGGAGAATCGCTTGAACCCGGGAGGCAGAGGTTGCACTGA GCCGAGATCATGCCACTGTACTCCAGCCCCGGGCAACAAGAGCGAACTCC ATCTCAAAAAATAAATAAATAAATAAATAAATAAAGTACAAATATTAGCCAG GGATGGTGGTGCGCACCTGTAGTCCCAGCTACTTGGGAGGCTGAAGTGGG AGAATCCCCTGAGCCTGGGGAGAGTACCCGAGGCGGGAAGTCGAGGCT GCAGTGAGCAGTGATTGTGCCACTGCACTCCATCCTAGGTGACAGAGTGA GACCCTGTCTCAAAAAAAGAAATTGGCAGAATTAAGTAAGTTGATGTTTAG AGATGAAAAATCAACATTTTTTCTCAGCAACTGAATAAAAAACAACAGCCAC TACCATTTTTTTGAGTACCTATTTGTAGCCTATTTTTTAACTGGTATTACTCG AGAGAGAGAGAGCTAGGTTTCGAGACAGAGCTCCTTCTCTTAATAACTGTAT GACCTAGGGTATGTCTGTTAGCCTCTCTGAGGCTTCAAAGGTTCTCATCT GTAAATGGTAATAATCATACCATTTGCTACAGGGCTGTTTTGAAGACTAATT AGGACTATGTAAGTAAACATGATGATGGCTATTATTACTGTTCCCCGCCAGG GGCCATGCAAGGGTTGCTGATTCACATAGACTGTCTTATAATCCTCTCAATA ACTCCAAGAGGTAGCCAGCACCTCAGATATACATAAAATGACTTAAGCCCA GAGAGGTGAAGTAAGTTGCCACAGCCACACAAGTAAATAGCCCAAAC AAGCTGGATTCCCAGTTAGACTCCGTTAATAGCACTGCTCTTACCTTAAGT CATTACAATGCCTAATATGAAATAGAATCGCTTCTTTCTTAGGGTTCAAGTG GTAAATTATTTAATGTATTCATTCAACAAACCATCATCGAGGACCTCTTACAA
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		GCCAAGTACTGTGCTAAGTGCTAGAGTTACGGCGGTGATTCCCTGCCCTTAA AAAGTTTTAGTGGGAGAAACAACAGGTAACCAGGTCATTGCCAAAACAACA AAAATAATCATAATAAAGCAGGCTAAAGCATATTTAACTGGCCGGGGTTTTG ACTATTTTAGCAAGCATGATCAGAACGGTTGAGGAGGGAGGCCAGCAGCTT GGCCGGTTCAACAAACAAGAAAAAACAGTGAGGGTGGAGCTAAGATACC AGAGGCTGATTACGGTTAAGAATGTTCTTGAAGGTAAGGACCAGATTCTCA TTTTCTATATCCTGGGGCATCGGTCAGCATGGAATCTGGATTCTAGCACAT GTGAATTTCCGGCTTGAAATGACCTAATGCCTTTCCCTAGTTCCTTCGTGTG TCAAATACGCATGGTTACCGCTACCAGAGCTGTAGTGGGGCTTCAATGAGG CCATGAGCATCTCCATAAAGATGAACTACAGTGTGTGCAAACTAAAGGCA AAACCTGGTCCCCACACGCCCTCCCAGGTGGTTCGCTTCCCGTGGCGAGGC CCCTCCAGAGGTGCCCCGAGAACCTCACCATCGCACCCCCAACTTCCAGG GAAGGGCTCTCCCGAGAAAGCCCCACGCCCCACCCCGCGCCATCATT CCCGAATCTGCCCTCGGCCCTCCCCGCAGCACGCTCGCAGGCGGCACAT GTCAACCAAAACGCCATTTCCACCTTCTCTTCCACACGCAGTCTCTTTTC CCAGGGCTCCCCCGAGGAGGGACCCACCCCAAACCCCGCCATTCCGTCT CCCTGCCGCCCTCGCGTGACGTAAAGCCGAACCCGGGAAACTGGCCGCC CCCGCCTGCGGGGTTCCCTGGGCCCGGCCGCTCTAGAACTAGTGGATCCC AATTGAAGGCCTGGTCTAAATGACTCCAAAATCACCCTTAATTCAAGAGAG TGATTTCCCTGAGTCAGGCCCCCTAAAGCAGCTATTTCAATGGGACAGGGA AACAACCCTAGGATCTGGATTAGAATCACTTGGGGCTGCCACACCCCCAG GGCTCTGATCCTGCCCTTCTCCACACGCACATTACATACTGCTGCAGTG ACCTTCCATTTCTAATGGGTTCTGGGCCATCTGTGAGGTATAGGGAATGG AAAAGGGGTTGGGGAGGCTCTGCTTCAGAAAGTTTGTGTGAGGGGCTCCC AGAGCCTCCACAGATAGATAGCAGGGGTCCCCACCCTACCATGGCAGCTA TAAATGTGATCAACATTTATTGGCCTAGGATACAGCAGTTAGCAAAATGCCT GATGTAGTTCCCACTCCGTGGAGGTTGCAGGCTAGCTCTTTCCTAATGAGC TTTACAGCAGAAGCTGTTTTATCGTTAAGTGCCCCACAGAGACACTTTACCA GGAGGCTGGGAGAGTTCTCCAGATTTGGGAGAGGCGCAGAGACAGTGTGT GAGCCGAGCCCTGTCTCAGCAATCCACCTGGAGGAGCTAGAGTATCCTCC TCCCTTTACCATTGAGACCGAGAGAAAAAGCCCAGCTTGTGTGCACCCTCG TGGGGTTAAGGCGAGCTGTTCTGGTTTAAAGCCTTTCAGTATTTGTTTTGA TGTAAGGCTCTGTGGTTTGGGGGGGAACATCTGTAAACATTATTAGTTGATT TGGGGTTTGTCTTTGATGTTTTCTATCTGCAATTATCGTCATGTATTTAAG TGTCTGTTATAGAAAACCCACACCCACTGTCCTGTAACTTTTCTCAGTGTC CAGACTTTCTGTAATCACATTTTAATTGCCACCTCGTATTTACCTCTACATT TGAAATCTGGCGTCTGTTTCAAGCCAGTGTGTTTTTCTTCGTTCTGTAATAA ACAGCCAGGAGAAAAAGTGCCCTCTATGTTTTTATTTTTCAAGGGAGTATTCAG TACCTACAAACCCAAGTCAGGAAGCCTGCTAGTGGCTTTGGTTCTTTCAGA GGCTGCTCGATGCCTTGTGTGTGCAAAAGAAAGATTGAGCAGTTTTGCATC ATGGCAAAGAAGCCTGTTATTTGGGGCTCAGCCCTCATTTTATAGAGGA TGAAACAGAGGGGGATGGGAGGTACAAAGACAACCTGCCCGGGAGCAG GTGTGGGGGAGACTTGCCCTGAGGGTCTAGACGCTCTGCACCACCGTCCCT GTCTCCCTTGCTGAAGACCACACATGCCCTTCTTTGACCAGACCCTGCCAC CTGATAGGCCAGGACCTGGTAGGCGGGTACCCAGGTTTCATGGATGGAAC CACATCTCCCCAAAAGTGGGGAGGTAGCTACTGGGATGCACGCCTCCCGC CATGTGCTATAGGAGAGCAGCTGAAGCAACAGTTGGGATCAGATGTAGTCA CAATTGAATGCATCATCACATTTATCCCTCTAAGTGGCTGGGAGAGTTGATA TCCTCATCCCTAAGGTACAAAATGTTCCAATTTGATCAGTGGCTTTCAGGAG CTGAGAAAGGCATGTGCTCTGAGGCAGAGCTGTTATGTCCCGCAGAGCCT AAAAATGCTCTAAGAACATGCTCCCTGCCAAAATTCTCAATGGCTGTGACAA GGGACAACGATCGACCAATGGGGGTGGAAGCAGACCTCCGCAGTCCAGG GGCCAGAGCTAGGACAGAGGGGTGCGAGAAAGAGTCATTTTCCCAACACT CCAGCTCTTGGCCAGTCTCACACAGTCCCCTCCTGCTTCTGCTGAGAGA GATATCCTCATAGGTCTGGGTAAAGTCCTTCAGTCAGCTTTCATTCCCTGTC ACCAACTTTGTCTCTGTTCTCCCTGCCCGTCTCAGGCAGCACTCCTCAGGA AACCTCTCCAAGAGCCAGCCTCACTGCAGCGCCCACTATTGTCCCTCTGCC TCAAGTGTCCCATCCATGCCAGGCCCCAGGCAGGCTGCAGCTTTCCTCA GGGCCACACCAAAGCACTTGGGCTCAGCTGTGCTGTCCCCCTCCATCACT
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		GAGCTCAGGGGCAGCAGGGGTGGGGTGCCAGGAGGCCATTACCCCTTC TCTGGCTCTGTGTTGGACCCACCTGCCAGCCACTGCTGCTTAGAACCTAC CCGCTGGGAAAATGAAGCCCTCCCGGAGGGGGCCACCTCAACCTGAGAGCC TCACGGATCACAGTTGTCCCCACTCAGCTCTGCCAGCCCTCAGAGACCCAT AGATAAAAGCTGAGCTTGGCTCGCAGAGCTGGTTCCATCTTCCATTCCCAG AGGGTTCAACTTCCTACCCCAACCACACAGGGAACCTCAAGGCTGAGCCA GTGTGGGCTGCAGTGCAGACCAGCTTCTTGACACGTCTGCCACCTGAC CCCAGGCTGGCCTCACTGCCCCTGGCACTCCTGACCCTATCCTCATTCTC CTGGCAGTGCCTGTTCTGCCATTCCGCTTTCCCTTAGCTGTCTCTCACTG TACTGTCAGCTTCTCCTTTTCCAGGTGCCCCCAGGGGCTTTCACATGAC CCTGTCACCCACAGCCCATCCAGCACCAATTCCAGCTCTCTGCCACCCTT CAAAGGAGTGACAGTGCCCTGCTTACCTCCCCTCAACCCAGCA GCAATCTGGCTCCAGTCTTGCTCCTTCCCCCTAAGTACTCTAGTCACAGTT CCAAATCTCCTCTGGTCATAAAGCCAAATGAAGCTTCTGGTCTCAGCGG ACTTGCCACTTCAGCAGTACTGGACTCTCTCTCCAGAAACCTGTTTCCC CTTGGCTCCTGGAGCCCACACTCTGCTGGAATCCTTCTGCCTCTCTGGCCT GTAGCCTGGCCCTCTCTCCCAACCTGAGGTCCATTCTCTCTGCTCCTCCA CAAGATGTTGCTCCTTCCATTACTTCTCTCCCTCTCAACCAAGCTCCTTCAT TAGCTCTTTATCTTCTGTTTTCTTCCCCTGGGCAGACGAATGGATTCAAGAG CCTGTGGCCCAGCAGCCCAGCACTCCAGGATCTCAGCACTTCAGCATCCC AGTACCCTAGCATCTCAATACCCAGCAGCCCAAGCAGCATAGTATCCAGC ACCCATTGTCCAAGCATCTCAGCACTCCAGCATCCAGCAGCCCAACACT CCAGCAGCCCAGAATCTCAGCACCTAGCACTGCAGCATCTCAGGAACCC AGCACTTCAGCATCCAGCACACTAGTACTCCAGCATCTCGGCACCCAGC ACCTAGGCATCCCAACACCCAGCACCCAGCACTTAAGCATCCCAACCTA CAGTATCTCAACACTCCAGCACCCAGCACCATAGTGTTCAGCACCCAG CATCCCAACACCCAGCACTTAAGCATCCCAACACCTCGGCATCCCAACAC CCCAGCACTGCAGCATCTCAGCACCTTAGCATCCAGTGCCCTAGCATCTC AATGCTCCAGCACACCAGTACTACAGTATTCCAGCACCCAGCACTCCAGC ATCTCAGCACTGCAGCACTGCAGCACTCCAGCATCCCAAAATCCAGCATC CCAACACCCAGCAGACCAGCAGACCAGCATCTCAGCACCCGAGCATCCA AGGACTATCCAGCATCCAGCAACCCAGCACCTCAGCATCCCAACACCC CAGCATTTAGCATGGCAACACCCAGTACCCAGCACTTCAGCACCCAG TATCCAGCATCTCAGCGACCCAGTATCACAAAACCTCAGCATCCTAGCAC CCCAGCACCCAGCACCTTAGCACCTTAGCATCCAGCATCTCAGCGCCTC AGCATCTTGATATTCTGGCTGAGGTGAGCGTGGTGTATCTAGTCAGGGTCC TAACCTTCACTTCGCAGGGAAATGCTGCTGGACTGGGTCTCATGTTGGGCT GAAGCTCTCTAGACCCCTTGAAGACAGCATAAAGAGCTTGGAGACGCTGG GTGTCCCCCATGGAAGAGTTCACTCTCATCCTGCTTTGACAACAGCCTTCT CTGGGGTCCCTCACGGGCCCCCTCTTTCTTACTGCAAGTTTGTCTCTGAGAA GACTGTGATGCAGAAGTCACTCAGCTGCCTGTGGCTCCTGAAGAGCTGAA GGTGGAGGCCTGTAGGCCTCCCTATGAGAGGCGCAGAAAAAACCATGATT GCTAGTGGGGAGGTGCTCCCTCTACAACCCACTCCATAATCTGCCCCGC CCAGCTCTGAGGCCAGCCCCAGGGGAAATGCCAGATCCCCAGGGAGGT GTGTGAGACCTCAGGGGCTCCCTCCTCCCTTACAGCAGGCTCAGGCCCCT GGGGGCTCAGGGCCAAGGTCTGTGGTAAGCTACTATCTCTCACTTGTCT CTCTAGCCACAAAAGCCAGGGAGATCTGGCAATGGACATGAGGTTCTGAA GAAGCACATATGACTGGCTTCTAATGCGTGGTTGTTCAGTGATTCAATAAA CACGCATGGGCCAGGCATGGGGAAATAGACAAACATGATCCCCAACCTCT CCCAGAGTGAACTGGGAGGGAGGAGTGTTTCATCCCTCAGGATTACACCAG AGAAACAAACCAGCAGGAGATATATATGGTTTTGGGGGGTCAAGAAAGAGG AAAAACCTGGCAAGGCAAGTCCAAAATCATAGGACAGGCTGTCAGGAAGG GCAGCCTGGAACCTCTCAAGCAGGAGCTGATGCTGCAGTCCACAGGCAGA ATTTCTTCTTCTCGGGGAAATCTCAGCTTTGTTCTTAAGGCCTTTCAACTG ATTGGCTGAGGTCTGCCCCTTCCCCACATTCTCCAGGATAATCTTCTTAC TTAAAGTCAACTATTAATCACAGCTACAAAATCCCTTTCAGCTACACATAG ATCAGTGTGATTGACGAACAGCCCCTACAGCCTAGCCAAGTTGACACAT AAAATAACCATCACAGGGGGACAAATGATGTAAACACATCAACAAATAAAA CAGTAACAAGTTAAGGTCTATGGAAAAACACAGAAGGGGCAGAGAGAAAG
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		GGAATTTGAGCCCCTCGCCTGGCGGGTTTGGCTGGTGGTCTTCTACTTCG GCTGCTTGTCTTGACCGTCTGGCTGCTCGAGGGGAGTTACGGTGGATCG GACCACCACGCCGCGCGAGCCAAAGTCCAGATGTCCGCGCGCGGGCGGT CGGAGCTTGATGACAACATCGCGCAGATGGGAGCTGTCCATGGTCTGGAG CTCCCGCGGCGTCAGGTCAGGCGGGAGCTCCTGCAGGTTTACCTCGCATA GACGGGTCAGGGCGCGGGCTAGATCCAGGTGATACCTAATTTCCAGGGGC TGGTTGGTGGCGGCGTCGATGGCTTGCAAGAGGCCGCATCCCCGCGGCG CGACTACGGTACCGCGCGGGCGGGCGGTGGGCCGCGGGGGTGTCTTGGG TGATGCATCTAAAAGCGGTGACGCGGGCGAGCCCCGGAGGTAGGGGGG GCTCCGGACCCGCCGGGAGAGGGGGCAGGGGCACGTCGGCGCCGCGCG CGGGCAGGAGCTGGTGTGCTGCGCGCGTAGGTTGCTGGCGAACGCGACGAC GCGGCGGTTGATCTCCTGAATCTGGCGCCTCTGCGTGAAGACGACGGGCC CGGTGAGCTTGAGCCTGAAAGAGAGTTTCGACAGAATCAATTTCCGGTGTCTG TGACGGCGGCGCTGGCGCAAATCTCCTGCACGTCTCCTGAGTTGTCTTGAT AGGCGATCTCGGCCATGAAGTCTCGATCTCTTCTCCTGGAGATCTCCGC GTCCGGCTCGCTCCACGGTGGCGGCGAGGTGCTTGGAAATGCGGGCCAT GAGCTGCGAGAAGGCGTTGAGGCCTCCCTCGTTCCAGACGCGGCTGTAGA CCACGCCCCCTTCGGCATCGCGGGCGCGCATGACCACCTGCGCGAGATT GAGCTCCACGTGCCGGGCGAAGACGGCGTAGTTTCGAGGCGCTGAAAG AGGTAGTTGAGGGTGGTGGCGGTGTGTTCTGCCACGAAGAAGTACATAAC CCAGCGTCGCAACGTGGATTGTTGATATCCCCCAAGGCCTCAAGGCGCT CCATGGCCTCGTAGAAGTCCACGGCGAAGTTGAAAAAAGTGGGAGTTGCGC GCCGACACGGTTAACTCCTCCTCCAGAAAGACGGATGAGCTCGGCGACAGT GTCGCGCACCTCGCGCTCAAAGGCTACAGGGGCCTCTTCTTCTTCTTCAAT CTCCTCTTCCATAAGGGCCTCCCTTCTTCTTCTTCTGGCGGCGGTGGGGG AGGGGGGACACGGCGGCGACGACGGCGCACCGGGAGGCGGTGACAAA GCGCTCGATCATCTCCCGCGGCGACGGCGCATGGTCTCGGTGACGGCG CGGCCGTTCTCGCGGGGGCGCAGTTGGAAGACGCCGCCCGTCATGTCCC GGTTATGGGTTGGCGGGGGGCTGCCATGCGGCAGGGATACGGCGCTAAC GATGCATCTCAACAATTGTTGTGTAGGTACTCCGCCGCCGAGGGACCTGAG CGAGTCCGCATCGACCGGATCGGAAAACCTCTCGAGAAAGGCGTCTAACC AGTCACAGTCGCAAGGTAGGCTGAGCACCGTGGCGGGCGGCAGCGGGCG GCGGTGCGGGTTGTTTCTGGCGGAGGTGCTGCTGATGATGTAATTAAAGTA GGCGGTCTTGAGACGGCGGATGGTCGACAGAAGCACCATGTCCTTGGGTC CGGCCTGCTGAATGCGCAGGCGGTGCGGCCATGCCCCAGGCTTCGTTTTGA CATCGGCGCAGGTCTTTGTAGTAGTCTTGATGAGCCTTTCTACCGGCACT TCTTCTTCTCCTTCTTGTCTGCTGATCTCTTGATCTATCGCTGCGGCGG CGGCGGAGTTTGGCCGTAGGTGGCGCCCTCTTCTCCCATGCGTGTGACC CCGAAGCCCCCTCATCGGCTGAAGCAGGGCTAGGTGCGCGACAACGCGCT CGGCTAATATGGCCTGCTGCACCTGCGTGAGGGTAGACTGGAAGTCATCC ATGTCCACAAAGCGGTGGTATGCGCCCGTGTGATGGTGAAGTGCAGTTG GCCATAACGGACCAAGTTAACGGTCTGGTGACCCGGCTGCGAGAGCTCGGT GTACCTGAGACGCGAGTAAGCCCTCGAGTCAAATACGTAGTCGTTGCAAGT CCGCACCAGGTACTGGTATCCCACCAAAAAGTGCGGCGGCGGCTGGCGGT AGAGGGGCCAGCGTAGGGTGGCCGGGCTCCGGGGCGAGATCTTCCAA CATAAGGCGATGATATCCGTAGATGTACCTGGACATCCAGGTGATGCCGGC GGCGGTGGTGGAGGCGCGCGGAAAGTCCGCGACGCGGTTCCAGATGTTG CGCAGCGGCAAAAAGTGCTCCATGGTCGGGACGCTCTGGCCGGTCAGGC GCGCGCAATCGTTGACGCTCTACCGTGCAAAAGGAGAGCCTGTAAGCGGG CACTCTTCCGTGGTCTGGTGGATAAATTCGCAAGGGTATCATGGCGGACGA CCGGGGTTCGAGCCCCGTATCCGGCCGTCCGCCGTGATCCATGCGGTTAC CGCCCGCGTGTGAACCCAGGTGTGCGACGTCAGACAACGGGGGAGTGC TCCTTTTGGCTTCTTCCAGGCGCGGCGGCTGCTGCGCTAGCTTTTTTGGC CACTGGCCGCGCGCAGCGTAAGCGGTTAGGCTGGAAAGCGAAAGCATTAA GTGGCTCGCTCCCTGTAGCCGGAGGGTTATTTTCCAAGGGTTGAGTCGCG GGACCCCCGTTTCGAGTCTCGGACCGGCCGACTGCGGCGAACGGGGGT TTGCCTCCCCGTATGCAAGACCCCGCTTGCAATTCTCCGGAAACAGGG ACGAGCCCCCTTTTTGCTTTTCCAGATGCATCCGGTGTGCGGCAGATGC GCCCCCTCCTCAGCAGCGGCAAGAGCAAGAGCAGCGGCAGACATGCAG
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		GGAGAATGTTTTAAAAAAGCATGATGCAAAATAAAAACTCACCAA GGCCATGGCACCAGCGTTGGTTTTCTTGTATTCCCCTTAGTATGCGGCGC GCGGCGATGTATGAGGAAGGTCTCTCCTCCTACGAGAGTGTGGTGAG CGCGGCGCCAGTGGCGGCGGCGCTGGGTTCTCCCTTCGATGCTCCCCTG GACCCGCCGTTTGTGCCTCCGCGGTACCTGCGGCCTACCGGGGGGAGAA ACAGCATCCGTTACTCTGAGTTGGCACCCCTATTGACACCACCCGTGTGT ACCTGGTGGACAACAAGTCAACGGATGTGGCATCCCTGAACTACCAGAAC GACCACAGCAACTTTCTGACCACGGTCATTCAAACAATGACTACAGCCCG GGGGAGGCAAGCACACAGACCATCAATCTTGACGACCGGTGCGACTGGGG CGGCGACCTGAAAACCATCCTGCATACCAACATGCCAAATGTGAACGAGTT CATGTTTACCAATAAGTTTAAGGCGCGGGTGATGGTGTGCGCGTTGCCTAC TAAGGACAATCAGGTGGAGCTGAAATACGAGTGGGTGGAGTTCACGCTGC CCGAGGGCAACTACTCCGAGACCATGACCATAGACCTTATGAACAACGCGA TCGTGGAGCACTACTTGAAAGTGGGCAGACAGAACGGGGTTCTGGAAAGC GACATCGGGGTAAAGTTTGACACCCGCAACTTCAGACTGGGGTTTGACCCC GTCATGGTCTTGTGCATGCCTGGGGTATATACAAACGAAGCCTTCCATCCA GACATCATTTTGTGCTGCCAGGATGCGGGGTGGACTTCACCCACAGCCGCT GAGCAACTTGTGGGCATCCGCAAGCGGCAACCCTTCCAGGAGGGCTTTA GGATCACCTACGATGATCTGGAGGGTGGTAACATTCCCGCACTGTTGGATG TGGACGCCTACCAGGCGAGCTTGAAAGATGACACCGAACAGGGCGGGGG TGGCGCAGGCGGCAGCAACAGCAGTGGCAGCGCGCGGAAGAGAACTCC AACGCGGCAGCCGCGGCAATGCAGCCGGTGGAGGACATGAACGATCATG CCATTGCGGCGACACCTTTGCCACACGGGCTGAGGAGAAGCGCGCTGAG GCCGAAGCAGCGGCCGAAGCTGCCGCCCCGCTGCGCAACCCGAGGTGCG AGAAGCCTCAGAAGAAACCGGTGATCAAACCCCTGACAGAGGACAGCAAG AAACGCAGTTACAACCTAATAAGCAATGACAGCACCTTCACCCAGTACCGC AGCTGGTACCTTGCATACAACTACGGCGACCCTCAGACCGGAATCCGCTCA TGGACCCTGCTTTGCACTCCTGACGTAACCTGCGGCTCGGAGCAGGTCTA CTGGTCGTTGCCAGACATGATGCAAGACCCCGTGACCTTCCGCTCCACGC GCCAGATCAGCAACTTTCCGGTGGTGGGCGCCGAGCTGTTGCCCGTGCAC TCCAAGAGCTTCTACAACGACCAGGCCGTCTACTCCCAACTCATCCGCCAG TTTACCTCTCTGACCCACGTGTTCAATCGCTTTCCCGAGAACCAGATTTTGG CGCGCCCGCCAGCCCCACCATCACCACCGTCAGTGAACACGTTTCTGCT CTCACAGATCACGGGACGCTACCGCTGCGCAACAGCATCGGAGGAGTCCA GCGAGTGACCATTAAGTACGCCAGACGCCGACCTGCCCTACGTTTACA AGGCCCTGGGCATAGTCTCGCCGCGCGTCTATCGAGCCGCACTTTTTGA GCAAGCATGTCCATCCTTATATCGCCAGCAATAACACAGGCTGGGGCCTG CGCTTCCCAAGCAAGATGTTTGGCGGGGCCAAGAAGCGCTCCGACCAACA CCAGTGCGCGTGCGCGGGCACTACCGCGCGCCCTGGGGCGCGCACAAA CGCGGCCGCACTGGGCGCACACCGTCGATGACGCCATCGACGCGGTGG TGGAGGAGGCGCGCAACTACACGCCACGCCGCCACCAAGTGTCCACAGT GGACGCGGCCATTGACACCGTGGTGCAGCGAGCCCGGCGCTATGCTAAA ATGAAGAGACGGCGGAGGCGCGTAGCACGTGCCACCGCCGCGGACCCG GCACTGCCGCCCAACGCGCGCGCGGCCCTGCTTAACCGCGCCAGCTCG CACCGGCCGACGGGCGGCCATGCGGGCGCTCGAAGGCTGGCCGCGGG TATTGTCACTGTGCCCCCAGGTCCAGGCGACGAGCGCGCGCGCAGCA GCCGCGGCCATTAGTGCTATGACTCAGGGTCGACAGGGGCAACGTGTATTG GGTGCGGACTCGGTTAGCGGCCTGCGCGTGCCCGTGCGCACCCGCCCC CCGCGCAACTAGATTGCAAGAAAAACTACTTAGACTCGTACTGTTGTATGT ATCCAGCGGCGGCGGCGCGCAACGAAGCTATGTCCAAGCGCAAAATCAA GAAGAGATGCTCCAGGTATCGCGCCGGAGATCTATGGCCCCCGAAGAA GGAAGAGCAGGATTACAAGCCCCGAAAGCTAAAGCGGGTCAAAAAGAAAA AGAAAGATGATGATGATGAACCTTGACGACGAGGTGGAAGTCTGCACGCTA CCGCGCCCAGGCGACGGGTACAGTGGAAGGTGACGCGTAAACGTGTT TTGCGACCCGGCACCAACCGTAGTCTTTACGCCCGGTGAGCGCTCCACCCG CACCTACAAGCGCGTGTATGATGAGGTGTACGGCGACGAGGACCTGCTTG AGCAGGCCAACGAGCGCCTCGGGGAGTTTGCCTACGGAAAGCGGCATAAG GACATGCTGGCGTTGCCGCTGGACGAGGGCAACCCAACACCTAGCCTAAA GCCCGTAACACTGCAGCAGGTGCTGCCCGCGCTTGACCGTCCGAAGAAA
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	AGCGCGGCCTAAAGCGCGAGTCTGGTGA CT TGGCACCCACCGTGCAGCTG ATGGTACCCAAGCGCCAGCGACTGGAAGATGTCTTGAAAAAATGACCGT GGAACCTGGGCTGGAGCCCGAGGTCCGCGTGCGGCCAATCAAGCAGGTG GCGCCGGGACTGGGCGTGCAGACCGTGGACGTTT CAGATACCCACTACCAG TAGCACCAGTATTGCCACCGCCACAGAGGGCATGGAGACACAAACGTCCC CGGTTGCCTCAGCGGTGGCGGATGCCGCGGTGCAGGCGGTGCTGCGGC CGCGTCCAAGACCTCTACGGAGGTGCAAACGGACCCGTGGATGTTTCGCG TTTCAGCCCCCGGCGCCCGCGCGGTTTCGAGGAAGTACGGCGCCGCCAG CGCGCTACTGCCCGAATATGCCCTACATCCTTCCATTGCGCCTACCCCCGG CTATCGTGGCTACACCTACCGCCCCAGAAAGACGAGCAACTACCCGACGCC GAACCACCACTGGAACCCGCGCGCCGCGCTCGCCGTGCCAGCCCCGTGCT GGCCCCGATTTCCGTGCGCAGGGTGGCTCGCGAAGGAGGCAGGACCCTG GTGCTGCCAACAGCGCGCTACCACCCCAGCATCGTTTTAAAGCCGGTCTTT GTGGTTCTTGCAGATATGGCCCTCACCTGCCGCTCCGTTTCCCGGTGCC GGGATTCCGAGGAAGAATGCACCGTAGGAGGGGCATGGCCGGCCACGGC CTGACGGGCGGCATGCGTCGTGCGCACCAACCGGCGGCGCGCGCTCG CACCGTCGCATGCGCGGCGGTATCCTGCCCTCCTTATTCCTACTGATCGC CGCGGCGATTGGCGCCGTGCCCGGAATTGCATCCGTGGCCTTGCAGGCG CAGAGACACTGATTA AAAACAAGTTGCATGTGAAAAATCAAATAAAAAGT CTGGA CTCTCACGCTCGCTTGGTCCTGTA ACTATTTTGTAAGATGGAAGAC ATCAACTTTGCGTCTCTGGCCCCGCGACACGGCTCGCGCCGTTTCATGGG AAACTGGCAAGATATCGGCACCAGCAATATGAGCGGTGGCGCCTTCAGCT GGGGCTCGCTGTGGAGCGGCATTAAAAATTTTCGTTCCACCGTTAAGAACT ATGGCAGCAAGGCCTGGAACAGCAGCACAGGCCAGATGCTGAGGGATAAG TTGAAAGAGCAAAATTTCCAACAAAAGGTGGTAGATGGCCTGGCCTCTGGC ATTAGCGGGGTGGTGGACCTGGCCAACCAGGCAGTGCAAAATAAGATTAA CAGTAAGCTTGATCCCCGCCCTCCCGTAGAGGAGCCTCCACCGGCCGTGG AGACAGTGTCTCCAGAGGGGCGTGCGCAAAAGCGTCCGCGCCCCGACAG GGAAGAACTCTGGTGACGCAAATAGACGAGCCTCCCTCGTACGAGGAGG CACTAAAGCAAGGCCTGCCACCACCGTCCCATCGCGCCCATGGCTACC GGAGTGCTGGGCCAGCACACACCCGTAACGCTGGACCTGCCTCCCCCG CCGACACCCAGCAGAAACCTGTGCTGCCAGGCCCGACCGCGCTTGTGTA ACCCGTCTAGCCGCGCGTCCCTGCGCCGCGCCGCCAGCGGTCCGCGAT CGTTGCGGCCCGTAGCCAGTG GCAACTGGCAAGCACACTGAACAGCATC GTGGGTCTGGGGGTGCAATCCCTGAAGCGCCGACGATGCTTCTGAATAGC TAACGTGTCTGTATGTGTGTATGTATGCGTCCATGTGCGCCGCCAGAGGAGC TGCTGAGCCGCGCGCGCCCCGCTTTCCAAGATGGCTACCCCTTCGATGAT GCCGCAGTGGTCTTACATGCACATCTCGGGCCAGGACGCCTCGGAGTACC TGAGCCCCGGGCTGGTGCAGTTTGCCCGCGCCACCGAGACGTA CTTCAGC CTGAATAACAAGTTTAGAAACCCACGGTGGCGCCTACGCACGACGTGAC CACAGACCGGTCCAGCGTTTGACGCTGCGGTTTATCCCTGTGGACCGTG AGGATACTGCGTACTCGTACAAGGCGCGGTTACCCCTAGCTGTGGGTGAT AACCGTGTGCTGGACATGGCTTCCACGTACTTTGACATCCGCGGCGTGCT GGACAGGGGCCCTACTTTTAAGCCCTACTCTGGCACTGCCTACAACGCCCT GGCTCCCAAGGGTGCCCCAAATCCTTGCGAATGGGATGAAGCTGCTACTG CTCTTGAAATAAACCTAGAAGAAGAGGACGATGACAACGAAGACGAAGTAG ACGAGCAAGCTGAGCAGCAAAAACTCACGTATTTGGGCAGGCGCCTTATT CTGGTATAAATATTACAAAGGAGGGTATTCAAATAGGTGTGCAAGGTCAAAC ACCTAAATATGCCGATAAAACATTTCAACCTGAACCTCAAATAGGAGAACT CAGTGGTACGAACTGAAATTAATCATGCAGCTGGGAGAGTCTTAAAAAG ACTACCCCAATGAAACCATGTTACGGTTCATATGCAAAACCCACAAATGAAA ATGGAGGGCAAGGCATTCTTGTAAGCAACAAAATGGAAAGCTAGAAAGTC AAGTGGAATGCAATTTTCTCACTACTGAGGCGACCGCAGGCAATGGTG ATACTTGACTCCTAAAGTGGTATTGTACAGTGAAGATGTAGATATAGAAC CCCAGACACTCATATTTCTTACATGCCCACTATTAAGGAAGGTA ACTCACGA GA ACTAATGGGCCAACAACTATGCCCAACAGGCCTAATTACATTGCTTTTA GGGACAATTTTATTGGTCTAATGTATTACAACAGCACGGGTAATATGGGTGT TCTGGCGGGCCAAGCATCGCAGTTGAATGCTGTTGTAGATTTGCAAGACAG AAACACAGAGCTTTCATACCAGCTTTTGCTTGATTCCATTGGTGATAGAACC
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	AGGTACTTTTCTATGTGGAATCAGGCTGTTGACAGCTATGATCCAGATGTTA GAATTATTGAAAATCATGGAACCTGAAGATGAACCTCCAAATTACTGCTTTCC ACTGGGAGGTGTGATTAATACAGAGACTCTTACCAAGGTAAAACCTAAAAAC AGGTCAGGAAAATGGATGGGAAAAAGATGCTACAGAATTTTCAGATAAAAAAT GAAATAAGAGTTGGAAATAATTTTGCATGGAAATCAATCTAAATGCCAACCC TGTGGAGAAATTTCTGTACTCCAACATAGCGCTGTATTTGCCCGACAAGC TAAAGTACAGTCCTTCCAACGTAAAAATTTCTGATAACCCAAACACCTACGA CTACATGAACAAGCGAGTGGTGGCTCCCGGGTTAGTGGACTGCTACATTAA CCTTGGAGCACGCTGGTCCCTTGACTATATGGACAACGTCAACCCATTAA CCACCACCGCAATGCTGGCCTGCGCTACCGCTCAATGTTGCTGGGCAATG GTCGCTATGTGCCCTTCCACATCCAGGTGCCTCAGAAGTTCTTTGCCATTA AAAACCTCCTTCTCCTGCCGGGCTCATACACCTACGAGTGGAACTTCAGGA AGGATGTTAACATGGTTCTGCAGAGCTCCCTAGGAAATGACCTAAGGGTTG ACGGAGCCAGCATTAAAGTTTGATAGCATTTGCCTTTACGCCACCTTCTTCCC CATGGCCCAACAACACCGCCTCCACGCTTGAGGGCATGCTTAGAAACGACA CCAACGACCAGTCCTTTAACGACTATCTCTCCGCCGCCAACATGCTCTACC CTATACCCGCCAACGCTACCAACGTGCCCATATCCATCCCTCCCGCAACT GGGCGGCTTTCCGCGGCTGGGCTTCACGCGCTTAAGACTAAGGAAACC CCATCACTGGGCTCGGGCTACGACCCTTATTACACCTACTCTGGCTCTATA CCCTACCTAGATGGAACCTTTTACCTCAACCACACCTTTAAGAAGGTGGCC ATTACCTTTGACTCTTCTGTGAGCTGGCCTGGCAATGACCGCTGCTTACC CCCAACGAGTTTGAAATTAAGCGCTCAGTTGACGGGGAGGGTTACAACGTT GCCAGTGTAACATGACCAAGACTGGTTCTGTTACAAATGCTAGCTAAC TACAACATTGGCTACCAGGGCTTCTATATCCCAGAGAGCTACAAGGACCGC ATGTACTCCTTCTTTAGAACTTCCAGCCCATGAGCCGTCAGGTGGTGGAT GATACTAAATACAAGGACTACCAACAGGTGGGCATCCTACACCAACACAAC AACTCTGGATTTGTTGGCTACCTTGCCCCCACCATGCGCGAAGGACAGGC CTACCCTGCTAACTTCCCCTATCCGCTTATAGGCAAGACCGCAGTTGACAG CATTACCCAGAAAAAGTTTCTTTGCGATCGCACCTTTGGCGCATCCCATTG TCCAGTAACTTTATGTCCATGGGCGCACTCACAGACCTGGGCCAAAACCTT CTCTACGCCAACTCCGCCACGCGCTAGACATGACTTTTGAGGTGGATCCC ATGGACGAGCCACCTTCTTTATGTTTTGTTTGAAGTCTTTGACGTGGTCC GTGTGCACCGGCCGCAACCGCGCGCTCATCGAAACCGTGACCTGCGCAC GCCCTTCTCGGCCGGAACGCCACAACATAAAGAAGCAAGCAACATCAACA ACAGCTGCCGCCATGGGCTCCAGTGAGCAGGAACCTGAAAGCCATTGTCAA AGATCTTGGTTGTGGGCCATATTTTTTGGGCACCTATGACAAGCGCTTTCCA GGCTTTGTTTCTCCACACAAGCTCGCCTGCGCCATAGTCAATACGGCCGGT CGCGAGACTGGGGGCGTACACTGGATGGCCTTTGCCTGGAACCCGCACTC AAAAACATGCTACCTCTTTGAGCCCTTTGGCTTTTCTGACCAGCGACTCAAG CAGGTTTACCAGTTTGAGTACGAGTCACTCCTGCGCCGTAGCGCCATTGCT TCTTCCCCCGACCGCTGTATAACGCTGGAAAAGTCCACCCAAAGCGTACAG GGGCCCAACTCGGCCGCTGTGGACTATTCTGCTGCATGTTTCTCCACGC CTTTGCCAACTGGCCCCAACTCCATGGATCACAACCCCAACCATGAACCT TATTACCGGGGTACCCAACTCCATGCTCAACAGTCCCCAGGTACAGCCAC CCTGCGTCGCAACCAGGAACAGCTCTACAGCTTCTGGAGCGCCACCTCGC CCTACTTCCGCGAGCCACAGTGCGCAGATTAGGAGCGCCACTTCTTTTTGTC ACTTGAAAAACATGTAAAAATAATGTACTAGAGACACTTTCAATAAAGGCAA ATGCTTTTATTTGTACACTCTCGGGTGATTATTTACCCCCACCTTGCCGTC TGCGCCGTTTAAAAATCAAAGGGGTTCTGCCGCGCATCGCTATGCGCCACT GGCAGGGACACGTTGCGATACTGGTGTAGTGCTCCACTTAACTCAGGC ACAACCATCCGCGGCAGCTCGGTGAAGTTTTCACTCCACAGGCTGCGCAC CATCACCACGCGTTTAGCAGGTGCGGCGCCGATATCTTGAAGTCGCAGTT GGGGCCTCCGCCCTGCGCGCGCAGTTGCGATACACAGGGTTGCAGCAC TGGAACACTATCAGCGCCGGGTGGTGCACGCTGGCCAGCACGCTCTTGTC GGAGATCAGATCCGCGTCCAGGTCTCCGCGTTGCTCAGGGCGAACGGAG TCAACTTTGGTAGCTGCCTTCCAAAAAGGGCGCGTGCCCAAGGCTTTGAGT TGCACCTCGCACCGTAGTGGCATCAAAAGGTGACCGTGCCCGGTCTGGGCG TTAGGATACAGCGCCTGCATAAAAGCCTTGATCTGCTTAAAGCCACCTGA GCCTTTGCGCCTTCAGAGAAGAACATGCCGCAAGACTTGCCGGAAAACTGA
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	TTGGCCGGACAGGCCGCGTCGTGCACGCAGCACCTTGCGTCGGTGTTGGA GATCTGCACCACATTTTCGGCCCCACCGGTTCTTCACGATCTTGGCCTTGCT AGACTGCTCCTTCAGCGCGCGCTGCCCGTTTTTCGCTCGTCACATCCATTTTC AATCACGTGCTCCTTATTTATCATAATGCTTCCGTGTAGACACTTAAGCTCG CCTTCGATCTCAGCGCAGCGGTGCAGCCACAACGCGCAGCCCCGTGGGCTC GTGATGCTTGTAGGTACCTCTGCAAACGACTGCAGGTACGCCTGCAGGA ATCGCCCCATCATCGTCACAAAGGTCTTGTGCTGGTGAAGGTGAGCTGCA ACCCGCGGTGCTCCTCGTTCAGCCAGGTCTTGCATACGGCCGCCAGAGCT TCCACTTGGTCAGGCAGTAGTTTGAAGTTCGCCTTTAGATCGTTATCCACGT GGTACTTGTCCATCAGCGCGCGCGCAGCCTCCATGCCCTTCTCCCACGCA GACACGATCGGCACACTCAGCGGGTTCATCACCGTAATTTCACTTTCCGCT TCGCTGGGCTCTTCCTCTTCTCTTGCCTCCGCATACCACGCGCCACTGGG TCGTCTTCATTACGCCGCCGCACTGTGCGCTTACCTCCTTTGCCATGCTTG ATTAGCACCGGTGGGTTGCTGAAACCCACCATTTGTAGCGCCACATCTTCT CTTTCTTCCTCGCTGTCCACGATTACCTCTGGTGATGGCGGGCGCTCGGGC TTGGGAGAAGGGCGCTTCTTTTTCTTCTTGGGCGCAATGGCCAAATCCGCC GCCGAGGTGATGGCCGCGGGCTGGGTGTGCGCGGCACCAGCGCGTCTT GTGATGAGTCTTCCTCGTCCTCGGACTCGATACGCCGCTCATCCGCTTTT TTGGGGGCGCCCCGGGAGGCGGCGGCGACGGGGACGGGGACGACACGT CCTCCATGGTTGGGGGACGTGCGCGCCGACCGCGTCCGCGCTCGGGGGT GGTTTCGCGCTGCTCCTCTTCCCGACTGGCCATTTCCTTCTCTATAGGCA GAAAAAGATCATGGAGTCAGTCGAGAAGAAGGACAGCCTAACCGCCCCCT CTGAGTTCGCCACCACCGCCTCCACCGATGCCGCCAACGCGCCTACCACC TTCCCCGTGAGGCAACCCCGCTTGAAGGAGGAGGAAGTGATTATCGAGCA GGACCCAGGTTTTGTAAAGCGAAGACGACGAGGACCGCTCAGTACCAACAG AGGATAAAAAGCAAGACCAGGACAACGCGAGAGGCAAACGAGGAACAAGTC GGGCGGGGGGACGAAAGGCATGGCGACTACCTAGATGTGGGAGACGACG TGCTGTTGAAGCATCTGCAGCGCCAGTGCGCCATTATCTGCGACGCGTTG CAAGAGCGCAGCGATGTGCCCTCGCCATAGCGGATGTCAGCCTTGCCTA CGAACGCCACCTATTCTACCGCGCGTACCCCCCAAACGCCAAGAAAACG GCACATGCGAGCCCAACCCGCGCCTCAACTTCTACCCCGTATTTGCCGTG CCAGAGGTGCTTGCCACCTATCACATCTTTTTCCAAAACGCAAGATACCCC TATCCTGCCGTGCCAACCGCAGCCGAGCGGACAAGCAGCTGGCCTTGCGG CAGGGCGCTGTCATACCTGATATCGCCTCGCTCAACGAAGTGCCAAAATC TTTGAGGGTCTTGACGCGACGAGAAGCGCGCGGCAAACGCTCTGCAACA GGAAAACAGCGAAAAATGAAAGTCACTCTGGAGTGTTGGTGGAACTCGAGG GTGACAACGCGCGCCTAGCCGTAATAAACGCGAGCATCGAGGTCACCCAC TTTGCCTACCCGGCACTTAACCTACCCCCCAAGGTCATGAGCACAGTCATG AGTGAGCTGATCGTGCGCCGTGCGCAGCCCCCTGGAGAGGGATGCAAATTT GCAAGAACAACAGAGGAGGGCCTACCCGCGAGTTGGCGACGAGCAGCTAG CGCGCTGGCTTCAAACGCGCGAGCCTGCCGACTTGGAGGAGCGACGCAA ACTAATGATGGCCGCAGTGCTCGTTACCGTGGAGCTTGAGTGCATGCAGC GGTTCTTTGCTGACCCGGAGATGCAGCGCAAGCTAGAGGAAACATTGCACT ACACCTTTCGACAGGGCTACGTACGCCAGGCCTGCAAGATCTCCAACGTG GAGCTCTGCAACCTGGTCTCCTACCTTGAATTTTGCACGAAAACCGCCTT GGGCAAAACGTGCTTCATTCCACGCTCAAGGGCGAGGCGCGCGCGACTA CGTCCGCGACTGCGTTTACTTATTTCTATGCTACACCTGGCAGACGGCCAT GGGCGTTTGGCAGCAGTGCTTGGAGGAGTGCAACCTCAAGGAGCTGCAGA AACTGCTAAAGCAAACTTGAAGGACCTATGGACGGCCTTCAACGAGCGCT CCGTGGCCGCGCACCTGGCGGACATCATTTTCCCCGAACGCCTGCTTAAA ACCCTGCAACAGGGTCTGCCAGACTTCACCAGTCAAAGCATGTTGCAGAAC TTTAGGAACTTTATCCTAGAGCGCTCAGGAATCTTGCCCCGCCACCTGCTGT GCACTTCTAGCGACTTTGTGCCATTAAAGTACCGCGAATGCCCTCCGCGG CTTTGGGGCCACTGCTACCTTCTGCAGCTAGCCAACTACCTTGCTTACCAC TCTGACATAATGGAAGACGTGAGCGGTGACGGTCTACTGGAGTGTCACTGT CGCTGCAACCTATGCACCCCGCACCGCTCCCTGGTTTGAATTCGAGCT GCTTAACGAAAGTCAAATTATCGGTACCTTTGAGCTGCAGGGTCCCTCGCC TGACGAAAAGTCCGCGGCTCCGGGGTTGAAACTCACTCCGGGGGCTGTGGA CGTCGGCTTACCTTCGCAAATTTGTACCTGAGGACTACCACGCCACGAGA
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	TTAGGTTCTACGAAGACCAATCCCGCCCGCCAAATGCGGAGCTTACCGCCT GCGTCATTACCCAGGGCCACATTCTTGCCCAATTGCAAGCCATCAACAAAG CCCGCCAAGAGTTTCTGCTACGAAAGGGACGGGGGGTTTACTTGGACCCC CAGTCCGGCGAGGAGCTCAACCCAATCCCCCGCCGCGCAGCCCTATCA GCAGCAGCCGCGGGGCCCTTGCTTCCCAGGATGGCACCCAAAAAGAAGCTG CAGCTGCCCGCCGCCACCCACGGACGAGGAGGAATACTGGGACAGTCAGG CAGAGGAGGTTTTGGACGAGGAGGAGGAGGACATGATGGAAGACTGGGA GAGCCTAGACGAGGAAGCTTCCGAGGTGCAAGAGGTGTCAGACGAAACAC CGTCACCCTCGGTGCGATTCCCCTCGCCGGCGCCCCAGAAATCGGCAACC GGTTCCAGCATGGCTACAACCTCCGCTCCTCAGGCGCCGCGCGGCACTGCC CGTTCGCGGACCCAACCGTAGATGGGACACCACTGGAACCAGGGCCGGTA AGTCCAAGCAGCCGCGCGCGGTTAGCCCAAGAGCAACAACAGCGCCAAGGC TACCGCTCATGGCGCGGGCACAAGAACGCCATAGTTGCTTGCTTGCAAGA CTGTGGGGGCAACATCTCCTTCGCCCCGCGCTTCTTCTCTACCATCACGG CGTGGCCTTCCCCGTAACATCCTGCATTACTACCGTCATCTCTACAGCCC ATACTGCACCGGCGGGCAGCGGCAGCGGCAGCAACAGCAGCGGCCACACA GAAGCAAAGGCGACCCGGATAGCAAGACTCTGACAAAGCCCCAAGAAATCCA CAGCGGCGGCAGCAGCAGGAGGAGGAGCGCTGCGTCTGGCGCCCCAACGA ACCCGTATCGACCCGCGAGCTTAGAAACAGGATTTTTCCCACTCTGTATGC TATATTTCAACAGAGCAGGGGGCCAAGAACAAGAGCTGAAAAATAAAAAACAG GTCTCTGCGATCCCTCACCCGACGCTGCCTGTATCACAAGGCGGAAGATCA GCTTCGGCGCACGCTGGAAGACGCGGAGGCTCTCTTCAGTAAATACTGCG CGCTGACTCTTAAGGACTAGTTTCGCGCCCTTTCTCAAATTTAAGCGCGAAA ACTACGTCATCTCCAGCGGCCACACCCGGCGCCAGCACCTGTCGTCAGCG CCATTATGAGCAAGGAAATTTCCACGCCCTACATGTGGAGTTACCAGCCAC AAATGGGACTTGCGGCTGGAGCTGCCCAAGACTACTCAACCCGAATAAACT ACATGAGCGCGGGACCCACATGATATCCCGGGTCAACGGAATCCGCGCC CACCGAAACCGAATTCTCTTGGAACAGGCGGCTATTACCACCACACCTCGT AATAACCTTAATCCCCGTAGTTGGCCCGCTGCCCTGGTGTACCAGGAAAGT CCCGCTCCCACTGTGGTACTTCCCAGAGACGCCAGGCCGAAGTTCA GATGACTAACTCAGGGGCGCAGCTTGGGGCGGCTTTTCGTACAGGGTGC GGTCGCCCCGGGCAGGGTATAACTCACCTGACAATCAGAGGGCGAGGTATT CAGCTCAACGACGAGTCGGTGAGCTCCTCGCTTGGTCTCCGTCCGGACGG GACATTTAGATCGGCGGCGCCGGCCGCTCTTCATTACGCTCGTCAGG CAATCCTAACTCTGCAGACCTCGTCCTCTGAGCCGCGCTCTGGAGGCATTG GAACTCTGCAATTTATTGAGGAGTTTGTGCCATCGGTCTACTTTAACCCCTT CTCGGGACCTCCCGGCCACTATCCGGATCAATTTATTCTAACTTTGACGC GGTAAAGGACTCGGCGGATGGCTACGACTGAATGTTAAGTGAGAGGGCAG AGCAACTGCGCCTGAAACACCTGGTCCACTGTCGCGGCCACAAGTGCTTT GCCCCGCACTCCGGTGAGTTTTGCTACTTTGAATTGCCCGAGGATCATATC GAGGGCCCCGGCGCACGGCGTCCGGCTTACCGCCCAGGGAGAGCTTGCCC GTAGCCTGATTCGGGAGTTTACCCAGCGCCCCCTGCTAGTTGAGCGGGAC AGGGGACCCTGTGTTCTCACTGTGATTTGCAACTGTCTAACCCTGGATTA CATCAAGATCTTTGTTGCCATCTCTGTGCTGAGTATAATAAATACAGAAATTA AAATATACTGGGGCTCCTATCGCCATCCTGTAAACGCCACCTCTTACCCC GCCCCAAGCAAACCAAGGCGAACCTTACCTGGTACTTTTAACATCTCTCCCT CTGTGATTTACAACAGTTTCAACCCAGACGGAGTGAGTCTACGAGAGAACC TCTCCGAGCTCAGCTACTCCATCAGAAAAAACACCACCCTCCTTACCTGCC GGGAACGTACGACCTAGGGATAACAGGGTAATAAGCAATTGACTCTATGTG GGATATGCTCCAGCGCTACAACCTTGAAGTCAGGCTTCTGGATGTCAGCA TCTGACTTTGGCCAGCACCTGTCCCGCGGATTTGTTCCAGTCCAACCTACAG CGACCCACCCTAACAGAGATGACCAACACAACCAACGCGGCCGCGCTAC CGGACTTACATCTACCACAAATACACCCCAAGTTTCTGCCTTTGTCAATAAC TGGGATAACTTGGGCATGTGGTGGTTCTCCATAGCGCTTATGTTTGTATGC CTTATTATTATGTGGCTCATCTGCTGCCTAAAGCGCAAACGCGCCCGACCA CCCATCTATAGTCCCATCATTGTGCTACACCCAAACAATGATGGAATCCATA GATTGGACGGACTGAAACACATGTTCTTTTCTTTACAGTATGATTAAATGA GACATGATTCTCGAGTTTTTATATTACTGACCCTTGTTGCGCTTTTTTGTGC GTGCTCCACATTGGCTGCGGTTTCTCACATCGAAGTAGACTGCATTCCAGC
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	CTTCACAGTCTATTTGCTTTACGGATTTGTCACCCCTCACGCTCATCTGCAGC CTCATCACTGTGGTCATCGCCTTTATCCAGTGCATTGACTGGGTCTGTGTG CGCTTTGCATATCTCAGACACCATCCCCAGTACAGGGACAGGACTATAGCT GAGCTTCTTAGAATTCTTTAATTATGAAATTTACTGTGACTTTTCTGCTGATT ATTTGCACCCTATCTGCGTTTTGTTCCCCGACCTCCAAGCCTCAAAGACATA TATCATGCAGATTCACCTCGTATATGGAATATTCCAAGTTGCTACAATGAAAA AAGCGATCTTTCCGAAGCCTGGTTATATGCAATCATCTCTGTTATGGTGTTC TGCAGTACCATCTTAGCCCTAGCTATATATCCCTACCTTGACATTGGCTGGA AACGAATAGATGCCATGAACCACCCAACCTTTCCCCGCGCCCGCTATGCTTC CACTGCAACAAGTTGTTGCCGGCGGCTTTGTCCCAGCCAATCAGCCTCGC CCCACTTCTCCACCCCCCACTGAAATCAGCTACTTTAATCTAACAGGAGGA GATGACTGACACCCTAGATCTAGAAATGGACGGAATTATTACAGAGCAGCG CCTGCTAGAAAAGACGCAGGGCAGCGGCCGAGCAACAGCGCATGAATCAAG AGCTCCAAGACATGGTTAACTTGCACCAGTGCAAAAGGGGTATCTTTTGTG TGGTAAAGCAGGCCAAAGTCACCTACGACAGTAATACCACCGGACACCGC CTTAGCTACAAGTTGCCAACCAAGCGTCAGAAATTGGTGGTCATGGTGGGA GAAAAGCCCATACCATAACTCAGCACTCGGTAGAAACCGAAGGCTGCATT CACTCACCTTGTCAAGGACCTGAGGATCTCTGCACCCTTATTAAGACCCTG TGCGGTCTCAAAGATCTTATTCCTTTAACTAATAAAAAAATAATAAAGCA TCACTTACTTAAATCAGTTAGCAAATTTCTGTCCAGTTTATTCAGCAGCACC TCTTGCCCTCCTCCCAGCTCTGGTATTGCAGCTTCTCCTGGCTGCAAAAC TTTCTCCACAATCTAAATGGAATGTCAGTTTCTCCTGTTCCTGTCCATCCG CACCCACTATCTTCATGTTGTTGCAGATGAAGCGCGCAAGACCGTCTGAAG ATACCTTCAACCCCGTGTATCCATATGACACGGAAACCGGTCTCCAACCTG TGCCCTTTTCTTACTCCTCCCTTTGTATCCCCCAATGGGTTTCAAGAGAGTCC CCCTGGGGTACTCTCTTTGCGCCTATCCGAACCTCTAGTTACCTCCAATGG CATGCTTGCGCTCAAATGGGCAACGGCCTCTCTCTGGACGAGGCCGGCA ACCTTACCTCCCAAATGTAACCACTGTGAGCCCACCTCTCAAAAAAACCA GTCAAACATAAACCTGGAAATATCTGCACCCCTCACAGTTACCTCAGAAGC CCTAACTGTGGCTGCCGCCGCACCTCTAATGGTCGCGGGCAACACACTCA CCATGCAATCACAGGCCCGCTAACCGTGCACGACTCCAACTTAGCATTG CCACCCAAGGACCCCTCACAGTGTGAGAAGGAAAGCTAGCCCTGCAAACA TCAGGCCCCCTCACACCACCGATAGCAGTACCCTTACTATCACTGCCTCA CCCCCTCTAACTACTGCCACTGGTAGCTTGGGCATTGACTTGAAAGAGCCC ATTTATACACAAAATGGAAAACCTAGGACTAAAGTACGGGGCTCCTTTGCATG TAACAGACGACCTAAACACTTTGACCGTAGCAACTGGTCCAGGTGTGACTA TTAATAATACTTCCTTGCAAACCTAAAGTTACTGGAGCCTTGGGTTTTGATTCA CAAGGCAATATGCAACTTAATGTAGCAGGAGGACTAAGGATTGATTCTCAA AACAGACGCCCTTATACTTGATGTTAGTTATCCGTTTGATGCTCAAAACCAAC TAAATCTAAGACTAGGACAGGGCCCTCTTTTTATAAACTCAGCCCACAACCTT GGATATTAACACAAAGGCCTTTACTTGTTCACAGCTTCAAACAATTCC AAAAAGCTTGAGGTTAACCTAAGCACTGCCAAGGGGTTGATGTTTGACGCT ACAGCCATAGCCATTAAATGCAGGAGATGGGCTTGAATTTGGTTACCTAAT GCACCAAAACACAAATCCCTCAAAAACAAAATGGCCATGGCCTAGAAATTT GATTCAAACAAGGCTATGGTTCTTAAACTAGGAACCTGGCCTTAGTTTTGACA GCACAGGTGCCATTACAGTAGGAAACAAAATAATGATAAGCTAACCCTAT GGACAGGTCCAAAACAGAAAGCCAACCTGCATAATTGAATACGGGAAACAAA ACCCAGATAGCAAACCTAATTTAATCCTTGTAAAAAATGGAGGAATTGTAA TGGATATGTAACGCTAATGGGAGCCTCAGACTACGTAAACACCTTATTTAAA AACAAAAATGTCTCCATTAAATGTAGAACTATACTTTGATGCCACTGGTCATAT ATTACCAGACTCATCTTCTCTTAAACAGATCTAGAACTAAAATACAAGCAAA CCGCTGACTTTAGTGCAAGAGGTTTTATGCCAAGTACTACAGCGTATCCATT TGTCTTCTAATGCGGGAACACATAATGAAAATTATTTTTGGTCAATGC TACTACAAAGCAAGCGATGGTGCCCTTTTTCCGTTGGAAGTTACTGTTATGC TTAATAAACGCCTGCCAGATAGTCGCACATCCTATGTTATGACTTTTTTATG GTCCTTGAATGCTGGTCTAGCTCCAGAACTACTCAGGCAACCCTCATAAC CTCCCCATTTACCTTTTCTATATTAGAGAAGATGACTAATAAACTCTAAAGA ATCGTTTGTGTTATGTTTCAACGTGTTTATTTTCAATTGCAGAAAATTTCAA GTCATTTTTTCATTACAGTAGTATAGCCCCACCACCACATAGCTTATACAGATC
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	ACCGTACCTTAATCAAACCTCACAGAACCCTAGTATTCAACCTGCCACCTCCC TCCCAACACACAGAGTACACAGTCCTTTCTCCCCGGCTGGCCTTAAAAAGC ATCATATCATGGGTAACAGACATATTCTTAGGTGTTATATTCCACACGGTTT CCTGTCGAGCCAAACGCTCATCAAGTGATATTAATAAACTCCCCGGGCAGC TCACTTAAGTTCATGTCGCTGTCCAGCTGCTGAGCCACAGGCTGCTGTCCA ACTTGCGGTTGCTTAACGGGCGGCGAAGGAGAAGTCCACGCCTACATGGG GGGAGAGTCATAATCGTGCATCAGGATAGGGCGGTGGTGTCTGCAGCAGCG CGCGAATAAACTGCTGCCGCCGCCGCTCCGTCCTGCAGGAATACAACATG GCAGTGGTCTCCTCAGCGATGATTGCGACCGCCCCGCAGCATAAGGCGCTT GTCTTCCGGGCACAGCAGCGCACCCCTGATCTCACTTAAATCAGCACAGTAA CTGCAGCACAGCACCACAATATTGTTCAAAATCCCACAGTGCAAGGCGCTG TATCCAAAGCTCATGGCGGGGACCACAGAACCACAGTGGCCATCATACCA CAAGCGCAGGTAGATTAAGTGGCGACCCCTCATAAACACGCTGGACATAAA CATTACCTCTTTTGGCATGTTGTAATTCACCACCTCCCGGTACCATATAAAC CTCTGATTAAACATGGCGCCATCCACCACCATCCTAAACCAGCTGGCCAAA ACCTGCCCCGCGGGGNTATACACTGCAGGGAACCGGGACTTGGACAATGA CAAGTGGGAGAGCCCAGGACTCGTAACCATGGATCATCATGCTCGTCATGA TATCAATGTTGGCACAACACAGGCACACGTGCATACACTTCCTCAGGATTA CAAGCTCCTCCCGCGTTAGAACCATATCCCAGGGAACAACCCATTCTGAA TCAGCGTAAATCCCACACTGCAGGGAAGACCTCGCACGTAACCTCACGTTGT GCATTGTCAAAGTGTTACATTTCGGGCAGCAGCGGATGATCCTCCAGTATGG TAGCGCGGGTTTCTGTCTCAAAGGAGGTAGACGATCCCTACTGTACGGAG TGCGCCGAGACAACCGAGATCGTGTTGGTCGTAGTGTATGCCAAATGGA ACGCCGACGTAGTCATATTTCTGAAGCAAAACCAGGTGCGGGCGTGAC AAACAGATCTGCGTCTCCGGTCTCGCCGCTTAGATCGCTCTGTGTAGTAGT TGTAGTATATCCACTCTCTCAAAGCATCCAGGCGCCCCCTGGCTTCGGGTT CTATGTAACTCCTTCATGCGCCGCTGCCCTGATAACATCCACCACCGCAG AATAAGCCACACCCAGCCAACCTACACATTCTGTTCTGCGAGTCACACACGG GAGGAGCGGGAAGAGCTGGAAGAACCATGTTTTTTTTTTTATTCCAAAAGAT TATCCAAAACCTCAAATGAAGATCTATTAAGTGAACGCGCTCCCCTCCGGT GGCGTGGTCAAACCTCTACAGCCAAAGAACAGATAATGGCATTGTGAAGATG TTGCACAATGGCTTCCAAAAGGCAAACGGCCCTCACGTCCAAGTGGACGTA AAGGCTAAACCCTTCAGGGTGAATCTCCTCTATAAACATTCCAGCACCTTCA ACCATGCCCAAATAATTCTCATCTCGCCACCTTCTCAATATATCTCTAAGCA AATCCCGAATATTTAAGTCCGGGCCATTGTAAAAAATTTGGCTCCAGAGCG CCCTCCACCTTCAGCCTCAAGCAGCGAATCATGATTGCAAAAATTCAGGTT CCTCACAGACCTGTATAAGATTCAAAAGCGGAACATTAACAAAAATACCGC GATCCCGTAGGTCCCTTCGCAGGGCCAGCTGAACATAATCGTGCAGGTCT GCACGGACCAAGCGCGGCCACTTCCCCGCCAGGAACCATGACAAAAGAACC CACACTGATTATGACACGCATACTCGGAGCTATGCTAACCAAGCGTAGCCCC GATGTAAGCTTGTGTCATGGGCGGCGATATAAAATGCAAGGTGCTGCTCAA AAAATCAGGCAAAGCCTCGCGCAAAAAGAAAGCACATCGTAGTCATGCTC ATGCAGATAAAGGCAGGTAAAGCTCCGGAACCACCACAGAAAAAGACACCAT TTTTCTCTCAAACATGTCTGCGGGTTTCTGCATAAACACAAAAATAAATAACA AAAAAACATTTAAACATTAGAAGCCTGTCTTACAACAGGAAAAACAACCCTT ATAAGCATAAGACGGACTACGGCCATGCCGGCGTGACCGTAAAAAAACTG GTCACCGTGATTAAAAAGCACCAACCGACAGCTCCTCGGTGAGTCCGGAGT CATAATGTAAGACTCGGTAAACACATCAGGTTGATTACATCGGTGAGTGT AAAAAGCGACCGAAATAGCCNNGGGGAATACAATACCCGCAGGCGTAGAG ACAACATTACAGCCCCCATAGGAGGTATAACAAAATTAATAGGAGAGAAAAA CACATAAACACCTGAAAAACCCTCCTGCCTAGGCAAAATAGCACCCCTCCCG CTCCAGAACAAACATACAGCGCTTCCACAGCGGCAGCCATAACAGTCAGCCT TACCAGTAAAAAAGAAAACCTATTAAAAAAACACCACTCGACACGGCACCA GCTCAATCAGTCACAGTGTAAGGAGGCAAGTGCAGAGCGAGTATATAT AGGACTAAAAAATGACGGTAACGGTTAAAGTCCACAAAAAACACCCAGAAA ACCGCACGCGAACCTACGCCAGAAACGAAAGCCAAAAAACCCACAACCTTC CTCAAATCGTCACTTCCGTTTTCCACGTTACGTCACTTCCATTTTAAGAA AACTACAATTCCCAACACATACAAGTTACTCCGCCCTAAACCTACGTCAAC CGCCCCGTTCCACAGCCCCGCGCCACGTCACAAACCTCACCCCCCTCATTA
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	TCATATTGGCTTCAATCCAAAATAAGGTATATTATTGATGATGTTAATTAACA TGCATGGATCCTCGTCTCGACGATGCCCTTGAGAGCCTTCAACCCAGTCAG CTCCTTCCGGTGGGCGCGGGGCATGACTATCGTCGCCGCACTTATGACTG TCTTCTTTATCATGCAACTCGTAGGACAGGTGCCGGCAGCGCTCTGGGTCA TTTTCGGCGAGGACCGCTTTCGCTGGAGCGCGACGATGATCGGCCTGTCTG CTTGCGGTATTCGGAATCTTGACGCGCCTCGCTCAAGCCTTCGTCACTGGT CCCGCCACCAAACGTTTCGGCGAGAAGCAGGCCATTATCGCCGGCATGGC GGCCGACGCGCTGGGCTACGTCTTGCTGGCGTTTCGCGACGCGAGGCTGG ATGGCCTTCCCCATTATGATTCTTCTCGCTTCCGGCGGCATCGGGATGCCC GCGTTGCAGGCCATGCTGTCCAGGCAGGTAGATGACGACCATCAGGGACA GCTTCAAGGATCGCTCGCGGCTCTTACCAGCCTAAGCTTCGATCACTGGACC GCTGATCGTCACGGCGATTTATGCCGCCTCGGCGAGCACATGGAACGGGT TGGCATGGATTGTAGGCGCCGCCCTATACCTTGTCTGCCTCCCCGCGTTG CGTCGCGGTGCATGGAGCCGGGCCACCTCGACCTGAATGGAAGCCGGCG GCACCTCGCTAACGGATTCAACACTCCAAGAATTGGAGCCAATCAATTCTT GCGGAGAACTGTGAATGCGCAAACCAACCCTTGGCAGAACATATCCATCGC GTCCGCCATCTCCAGCAGCCGCACGCGGCGCATCTCGGGCAGCGTTGGG TCCTGGCCACGGGTGCGCATGATCGTGCTCCTGTCTGTTGAGGACCCGGCT AGGCTGGCGGGGTTGCCTTACTGGTTAGCAGAATGAATCACCGATACGCG AGCGAACGTGAAGCGACTGCTGCTGCAAAACGTCTGCGACCTGAGCAACA ACATGAATGGTCTTCCGTTTCCGTGTTTCGTAAAGTCTGGAACCGCGAAG TCAGCGCCCTGCACCATTATGTTCCGGATCTGCATCGAGGATGCTGTGG CTACCCTGTGGAACACCTACATCTGTATTAACGAAGCGCTGGCATTGACCC TGAGTGATTTTTCTCTGGTCCCGCCGCATCCATACCGCCAGTTGTTTACCCT CACAACGTTCCAGTAACCGGGCATGTTTCATCATCAGTAACCCGTATCGTGA GCATCCTCTCTCGTTTCATCGGTATCATTACCCCATGAACAGAAATTCCCC CTTACACGGAGGCATCAAGTGACCAAACAGGAAAAAACGCCCTTAACATG GCCCGCTTTATCAGAAGCCAGACATTAACGCTTCTGGAGAACTCAACGAG CTGGACGCGGATGAACAGGCAGACATCTGTGAATCGCTTACGACCCACGC TGATGAGCTTTACCGCAGCTGCCTCGCGCGTTTCGGTGATGACGGTGAAAA CCTCTGACACATGCAGCTCCCGGAGACGGTCACAGCTTGTCTGTAAGCGG ATGCCGGGAGCAGACAAGCCCGTCAGGGCGCGTCAGCGGGTGTTGGCGG GTGTCCGGGGCGCAGCCATGACCCAGTCACGTAGCGATAGCGGAGTGTATA CTGGCTTAACATATCGCGCATCAGAGCAGATTGTAAGTGCACCATAT GCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAAATACCGCATCAGGC GCTCTTCCGCTTCTCGCTCACTGACTCGCTGCGCTCGGTCTGTTCCGGCTGC GGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAAT CAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCC AGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCC CCCTGACGAGCATCACAAAATCGACGCTCAAGTCAGAGGTGGCGAAACC CGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGC GCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCTTTCTCC CTTCGGGAAGCGTGCGCTTCTCAATGCTCACGCTGTAGGTATCTCAGTT CGGTGTAGTCTGTTCCGCTCCAAGCTGGGCTGTGTGCACGAACCCCGTT CAGCCCCGACCGCTGCCCTTATCCGGTAACATATCGTCTTGAAGTCCACCCG GTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGC AGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAA CTACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTCTGCTGAAGCC AGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAAACAAACCAC CGCTGGTAGCGGTGGTTTTTTTGTGTTGCAAGCAGCAGATTACGCGCAGAAA AAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCA GTGGAACGAAAACCTACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAG GATCTTCACCTAGATCCTTTTAAATTAATAAATGAAGTTTTAAATCAATCTAAA GTATATATGAGTAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGC ACCTATCTCAGCGATCTGTCTATTTTCGTTTCATCCATAGTTGCCTGACTCCCC GTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCT GCAATGATACCGCGAGACCCACGCTCACC GGCTCCAGATTTATCAGCAATA AACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATC CGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTC
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		GCCAGTTAATAGTTTGGCGCAACGTTGGTTGNNNNNNAAAAAGGATCTTCAC CTAGATCCTTTTCACGTAGAAAGCCAGTCCGCAGAAACGGTGCTGACCCCG GATGAATGTCAGCTACTGGGCTATCTGGACAAGGGAAAAACGCAAGCGCAA AGAGAAAGCAGGTAGCTTGCAGTGGGCTTACATGGCGATAGCTAGACTGG GCGGTTTTATGGACAGCAAGCGAACCAGGAATTGCCAGCTGGGGCGCCCTC TGGTAAGGTTGGGAAGCCCTGCAAAGTAACTGGATGGCTTTCTCGCCGC CAAGGATCTGATGGCGCAGGGGATCAAGCTCTGATCAAGAGACAGGATGA GGATCGTTTCGCATGATTGAACAAGATGGATTGCACGCAGGTTCTCCGGCC GCTTGGGTGGAGAGGCTATTCCGGCTATGACTGGGCACAACAGACAATCGG CTGCTCTGATGCCGCCGTGTTCCGGCTGTCAGCGCAGGGGCGCCCGGTTCT TTTTGTCAAGACCGACCTGTCCGGTGCCCTGAATGAACTGCAAGACGAGG CAGCGCGGCTATCGTGGCTGGCCACGACGGGCGTTTCTTGCGCAGCTGT GCTCGACGTTGTCACTGAAGCGGGAAGGGACTGGCTGCTATTGGGCGAAG TGCCGGGGCAGGATCTCCTGTCATCTCACCTTGCTCCTGCCGAGAAAGTAT CCATCATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACC TGCCCATTCGACCACCAAGCGAAACATCGCATCGAGCGAGCACGTACTCG GATGGAAGCCGGTCTTGTGATCAGGATGATCTGGACGAAGAGCATCAGG GGCTCGCGCCAGCCGAAGTGTTCGCCAGGCTCAAGGCGAGCATGCCCGA CGGCGAGGATCTCGTCGTGACCCATGGCGATGCCTGCTTGCCGAATATCA TGGTGGAATGGCCGCTTTTCTGGATTTCATCGACTGTGGCCGGCTGGGT GTGGCGGACCGCTATCAGGACATAGCGTTGGCTACCCGTGATATTGCTGA AGAGCTTGGCGGCGAATGGGCTGACCGCTTCCTCGTGCTTTACGGTATCG CCGCTCCCGATTTCGCAGCGCATCGCCTTCTATCGCCTTCTTGACGAGTTCT TCTGAATTTTGTAAAAATTTTGTAAATCAGCTCATTTTTTAACCAATAGGC CGAAATCGGCAACATCCCTTATAAATCAAAGAATAGACCGCGATAGGGTT GAGTGTGTTCCAGTTTGAACAAGAGTCCACTATTAAGAAGCTGGACTC CAACGTCAAAGGGCGAAAAACCGTCTATCAGGGCGATGGCCCACTACGTG AACCATCACCCAAATCAAGTTTTTTCGCGTGCAGGTGCCGTAAAGCTCTAA ATCGGAACCCCTAAAGGGAGCCCCCGATTTAGAGCTTGACGGGGAAAGCCG GCGAACGTGGCGAGAAAGGAAGGGAAGAAAGCGAAAGGAGCGGGCGCTA GGGCGCTGGCAAGTGTAGCGGTCACGCTGCGCGTAACCACCACACCCGC GCGCTTAATGCGCCGCTACAGGGCGCGTCCATTGCCATTGAGGATCGAA TTAATTCTTAAT
52	Amino acids 121-128 of Ad E1A protein	LTCHEACF
53	STAT1 binding site (1)	TTCCGGGAA
54	STAT1 binding site (2)	TTCTCGGAA
55	Ad5/3Ad2E1Δ 24	TAACATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAG GGGGTGGAGTTTGTGACGTGGCGCGGGGCGTGGAACGGGGCGGGTGA CGTAGTAGTGTGGCGGAAGTGTGATGTTGCAAGTGTGGCGGAACACATGT AAGCGACGGATGTGGCAAAAGTGACGTTTTTGGTGTGCGCCGGTGTACAC AGGAAGTGACAATTTTCGCGCGGTTTTAGGCGGATGTTGTAGTAAATTTGG GCGTAACCGAGTAAGATTTGGCCATTTTCGCGGGAAAAGTGAATAAGAGGA AGTGAAATCTGAATAATTTTGTGTTACTCATAGCGCGTAATATTTGTCTAGG GCCGCGGGGACTTTGACCGTTTACGTGGAGACTCGCCAGGTGTTTTCTC AGGTGTTTTTCGCGTTCCGGGTCAAAGTTGGCGTTTTATTATTATAGTCAGC TGACGTGTAGTGATTTTATACCCGGTGAGTTCTCAAGAGGCCACTCTTGA GTGCCAGCGAGTAGAGTTTTCTCCTCCGAGCCGCTCCGACACCGGGACTG AAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATGGCC GCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCA CCTCCTAGCCATTTTGAACCACCTACCCTTCACGAAGTGTATGATTTAGACG TGACGGCCCCCGAAGATCCCAACGAGGAGGCGGTTTTCGCAGATTTTCCC GAGTCTGTAATGTTGGCGGTGCAGGAAGGGATTGACTTATCACTTTTCCG CCGGCGCCCGGTTCTCCGGAGCCGCTCACCTTTCCCGGCAGCCCGAGC AGCCGGAGCAGAGAGCCTTGGGTCCGGTTTTCTATGCCAAACCTTGTGCCG GAGGTGATCGATCCACCCAGTGACGACGAGGATGAAGAGGGTGAGGAGTT

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 TACACTGCAGGGAACCGGGACTGGAACAATGACAGTGGAGAGCCCAGGAC
 TCGTAACCATGGATCATCATGCTCGTCATGATATCAATGTTGGCACAACACA
 GGCACACGTGCATACACTTCTCAGGATTACAAGCTCCTCCCGCGTTAGAA
 CCATATCCCAGGGAACAACCCATTCTGAATCAGCGTAAATCCCACACTGC
 AGGGAAGACCTCGCACGTAACCTCACGTTGTGTCATTGTCAAAGTGTTCATT
 CGGGCAGCAGCGGATGATCCTCCAGTATGGTAGCGCGGGTTTCTGTCTCA
 AAAGGAGGTAGACGATCCCTACTGTACGGAGTGCGCCGAGACAACCGAGA
 TCGTGTTGGTCGTAGTGTGTCATGCCAAATGGAACGCCGGACGTAGTCATATT
 TCCTGAAGCAAAACCAGGTGCGGGCGTGACAAACAGATCTGCGTCTCCGG
 TCTCGCCGCTTAGATCGCTCTGTGTAGTAGTTGTAGTATATCCACTCTCTCA
 AAGCATCCAGGCGCCCCCTGGCTTCGGGTTCTATGTAACTCCTTCATGCG
 CCGCTGCCCTGATAACATCCACCACCGCAGAATAAGCCACACCCAGCCAA
 CCTACACATTGTTTCTGCGAGTCACACACGGGAGGAGCGGGAAGAGCTGG
 AAGAACCATGTTTTTTTTTTTATTCCAAAAGATTATCCAAAACCTCAAAATGA
 AGATCTATTAAGTGAACGCGCTCCCTCCGGTGGCGTGGTCAAACCTCTACA
 GCCAAAGAACAGATAATGGCATTGTGAAGATGTTGCACAATGGCTTCCAAAA
 GGCAAACGGCCCTCACGTCCAAGTGGACGTAAAGGCTAAACCCTTCAGGG
 TGAATCTCCTCTATAAACATTCCAGCACCTTCAACCATGCCCAAATAATTCT
 CATCTCGCCACCTTCTCAATATATCTCTAAGCAATCCCGAATATTAAGTCC

		GGCCATTGTAAAAATCTGCTCCAGAGCGCCCTCCACCTTCAGCCTCAAGCA GCGAATCATGATTGCAAAAATTCAGGTTCTCACAGACCTGTATAAGATTCA AAAGCGGAACATTAACAAAAATACCGCGATCCCGTAGGTCCCTTCGCAGGG CCAGCTGAACATAATCGTGCAGGTCTGCACGGACCAGCGCGGCCACTTCC CCGCCAGGAACCTTGACAAAAGAACCCACACTGATTATGACACGCATACTC GGAGCTATGCTAACCAGCGTAGCCCCGATGTAAGCTTTGTTGCATGGGCG GCGATATAAAATGCAAGGTGCTGCTCAAAAAATCAGGCAAAGCCTCGCGCA AAAAAGAAAGCACATCGTAGTCATGCTCATGCAGATAAAGGCAGGTAAGCT CCGGAACCACCACAGAAAAAGACACCATTTTTCTCTCAAACATGTCTGCGG GTTTCTGCATAAACACAAAATAAAATAACAAAAAACATTTAAACATTAGAAG CCTGTCTTACAACAGGAAAAACAACCCTTATAAGCATAAGACGGACTACGG CCATGCCGGCGTGACCGTAAAAAACTGGTCACCGTGATTAAAAAGCACCA CCGACAGCTCCTCGGTCTATGTCGGGAGTCATAATGTAAGACTCGGTAAACA CATCAGGTTGATTTCATCGGTCTAGTGCTAAAAAGCGACCGAAATAGCCCGGG GGAATACATACCCGCAGGCGTAGAGACAACATTACAGCCCCCATAGGAGG TATAACAAAATTAATAGGAGAGAAAAACACATAAACACCTGAAAAACCTCC TGCTTAGGCAAAATAGCACCTCCCGCTCCAGAACACATACAGCGCTTCA CAGCGGCAGCCTAACAGTCAGCCTTACCAGTAAAAAAGAAAACCTATTAAA AAAACACCACTCGACACGGCACCAGCTCAATCAGTCACAGTGTA AAAAAGG GCCAAGTGCAGAGCGAGTATATATAGGACTAAAAAATGACGTAACGGTTAA AGTCCACAAAAAACCCACAACTTCTCAAATCGTCACTTCCGTTTTCCACG GAAAGCCAAAAAACCCACAACTTCTCAAATCGTCACTTCCGTTTTCCACG TTACGTAACCTCCCATTTTAAGAAAACCTACAATTCCCAACACATACAAGTTAC TCCGCCCTAAACCTACGTACCCGCCCCGTTCCACGCCCGCCGCCACG TCACAACTCCACCCCTCATTATCATATTGGCTTCAATCCAAAATAAGGTA TATTATTGATGATGTTAAT
56	HER2(A3)- CD28TM,ICD- CD3Z CAR	MTRAMDWIWRILFLVGAATGAHSEVQLVQSGTEVKKPGASVRVSKSSGYTF TSYYIHWRQAPGQGLEWMAIINP GNGDTNYAQRFGQGRVTMTRDTSTSTVYM ELRSLRSDDTAVYFCAREIASYSGSYDYWGQGLTVTVSSGGGGSGGGGSG GGGSQAVVLQEPSLSVSPGGTVTLTCLSSGVSSTGHYASWYQQTPGQAPR TLFYNTNTRSSGVPDRFSGSIVGNKAALTITGAQADDESYYCVLYVGDGIWWF GGGKLTVLPEKSCDKTHTCPTRFWLVVVGGLVACYSLLVTVAFIIFWVRSKR SRLLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPAYQ QQQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPKRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
57	HER2(A3) LC- CDR1	GLSSGVSSTGHYAS
58	HER2(A3) LC- CDR2	NTNTRSS
59	HER2(A3) LC- CDR3	VLYVGDGIWW
60	HER2(A3) HC- CDR1	SYIIHWVRQA
61	HER2(A3) HC- CDR2	IINP GNGDTNYAQRFGQ
62	HER2(A3) HC- CDR3	EIASYSGSYDY
63	HER2(A3) VL	QAVVLQEPSLSVSPGGTVTLTCLSSGVSSTGHYASWYQQTPGQAPR TLFYNTNTRSSGVPDRFSGSIVGNKAALTITGAQADDESYYCVLYVGDGIWWF GGGT KLTVL
64	HER2(A3) VH	EVQLVQSGTEVKKPGASVRVSKSSGYTFTSYIIHWVRQAPGQGLEWMAIINP GNGDTNYAQRFGQGRVTMTRDTSTSTVYME LRSLRSDDTAVYFCAREIASYSGSYDYWGQGLTVTVSS

The disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

5 The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Aspects and embodiments of the present disclosure will now be illustrated, by way of example, with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

10 Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

15 It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

20 Where a nucleic acid sequence is disclosed the reverse complement thereof is also expressly contemplated.

25 **Brief Description of the Figures**

Embodiments and studies illustrating the principles of the disclosure will now be discussed with reference to the accompanying figures.

30 **Figures 1A and 1B.** Figure 1A shows schematic representations of examples of HER2-specific CAR constructs. Figure 1B shows a schematic of an example of a protocol for transducing T cells to produce HER2-specific CAR-T.

35 **Figure 2.** Graphs showing expression of the HER2-CARs, CCR7, CD45RO and PD-1 on T cells transduced with the indicated HER2-CAR constructs, as determined by flow cytometry.

Figure 3. Graphs showing expression of HER2-CAR, CCR7, CD45RO, PD-1, LAG-3 and TIM-3 on CD4 and CD8 T cells following transduction with anti-HER2 clone E4 CAR construct, as determined by flow cytometry.

Figures 4A and 4B. Figure 4A is a bar chart showing *in vitro* cell killing of MDA cells (which do not express HER2 at the cell surface; negative control), MDA-HER2 cells (which express HER2 at the cell surface; positive control), FaDu and SCC47 cells by anti-HER2 clone C5, E4 and F1 CAR-T cells (or non-transduced (NT) cells), as determined by ⁵¹Cr release assay. Figure 4B shows graphs indicating expression of HER2 on MDA-HER2 cells, FaDu and SCC47 cells but not on MDA cells, as determined by flow cytometry.

Figure 5. Bar chart showing *in vitro* cell killing of FaDu and SCC47 cells genetically modified to express firefly luciferase (ffLuc) by anti-HER2 clone C5, E4 and F1 CAR-T cells (or non-transduced (NT) cells), as determined by ffLuc activity assay. Data are presented as mean $\pm$ SD (n=4). **P* < 0.001.

Figure 6. Figure 6 shows a schematic representation of the sequences of an example of an ICOSTAT oncolytic adenovirus construct.

Figures 7A to 7F. Graphs showing the ability of ICOSTAT oncolytic adenovirus to kill A549 cells (Figures 7A and 7F), FaDu cells (Figure 7B), SCC47 cells (Figure 7C), WI-38 cells (Figure 7D) and ARPE-19 cells (Figure 7E) following infection with the indicated concentration of viral particles (Vp), as determined by MTS viability assay. Helper-dependent adenovirus (HDA) is included as a control condition.

Figures 8A and 8B. Bar charts showing ability of ICOSTAT oncolytic adenovirus to replicate and act as helper for replication of helper-dependent adenovirus (HDA), as determined by copy number analysis by quantitative real-time PCR. The virus designated "Onc5/3AdicoSTAT" is ICOSTAT. "+HD" indicates co-infection of ICOSTAT with HDA.

Figures 9A and 9B. Graphs showing the replication of ICOSTAT oncolytic adenovirus in FaDu cells (Figure 9A) and SCC47 cells (Figure 9B), in the presence or absence of 10 ng/ml IFN γ in the cell culture media.

Figures 10A to 10D. Figure 10A is a schematic representation of the HDA/IL-12 α _TK_PDL1 construct. Figure 10B is a bar chart showing production of IL-12p70 by cells transfected with the indicated helper-dependent adenovirus (HDA) constructs. Figure 10C is a photograph of a western blot showing production of anti-PD-L1 minibody by cells transfected with the HDA

constructs. Figure 10D is a photograph of a wells demonstrating HSV thymidine kinase production by cells transfected with the HDAd constructs.

Figure 11. Graph showing ELISA analysis of PD-L1 minibody avidity to recombinant human PD-L1, using serially diluted cell culture media of A549 cells which had been transfected with plasmid encoding GFP (pGFP; negative control), plasmid encoding the anti-PD-L1 minibody described in Tanoue *et al. supra*, (pPDL1 mini Tanoue) or plasmid encoding the anti-PD-L1 minibody encoded by HDAdIL-12_TK_PD-L1 (pPDL1 mini). Serially diluted anti-human PD-L1 antibody was used as a positive control (PDL1 IgG).

Figures 12A and 12B. Schematic representations of the sequences of (Figure 12A) an example of an Onc5/2E1Δ24 oncolytic adenovirus construct, and (Figure 12B) a plasmid encoding an Onc5/2E1Δ24 oncolytic adenovirus construct.

Figures 13A to 13D. Graphs showing the ability of Onc5/3Ad2E1A oncolytic adenovirus to kill FaDu cells (Figure 13A), SCC47 cells (Figure 13B), WI-38 cells (Figure 13C) and ARPE-19 cells (Figure 13D) following infection with the indicated concentration of viral particles (Vp), as determined by MTS viability assay. Helper-dependent adenovirus (HDAd) is included as a control condition.

Figure 14. Graph showing numbers of HER2-specific CAR T cells following the indicated number of days of *in vitro* cell culture after transduction with the indicated CAR constructs.

Figures 15A to 15C. Images and graph showing the results of *in vivo* analysis of the anticancer activity of adoptively-transferred luciferase-expressing T cells in an orthotopic FaDu cell-derived model of squamous cell head and neck carcinoma. Figures 15A and 15B show the number and location of luciferase-expressing non-transduced T cells (NT), and cells expressing luciferase-expressing T cells expressing C5, F1 or A3 HER2-specific CARs within mice at the indicated number of days after infusion of the cells. Figure 15C shows the percentage of surviving subjects in the different treatment groups at the indicated number of days after infusion of the cells. A negative control condition wherein mice were not administered with T cells is also shown (-).

Figures 16A to 16C. Images and graphs showing the results of *in vivo* analysis of adoptively-transferred T cells in NSG mice. Figure 16A shows the number and location of luciferase-expressing non-transduced T cells (NT), and cells expressing luciferase-expressing T cells expressing C5, F1 or A3 HER2-specific CARs within mice at the indicated number of days after infusion of the cells. Figure 16B shows measurements for total flux (in photons per second; p/s) of ventral surface for mice of the different groups at the indicated number of days after infusion of the cells. Figure 16C shows the weights of mice in the different treatment groups at the indicated number of days after infusion of the cells, expressed as a percentage of body weight at day 0.

Figures 17A to 17C. Scatterplots and histograms showing the results of characterisation by flow cytometry of F1 HER2-specific CAR T cells used in experiments for *in vivo* analysis of the anti-cancer activity of the combination of CAd Δ trio and adoptively-transferred T cells. Figure 17A shows the percentages of CD4 $^{+}$ T cells and CD8 $^{+}$ T cells within the F1.CAR-T population. Figure 17B shows the percentage cells expressing HER2 CAR at the cell surface. Figure 17C shows the percentages of cells within the F1.CAR-T population expressing CCR7 and/or CD45RO.

Figures 18A to 18D. Images and graphs showing the results of *in vivo* analysis of the anti-cancer activity of the combination of CAd Δ trio and adoptively-transferred T cells, in an orthotopic FaDu cell-derived model of squamous cell head and neck carcinoma. Figure 18A shows the number and location of luciferase-expressing non-transduced T cells (NT), and cells expressing luciferase-expressing T cells expressing F1 HER2-specific CAR within mice at the indicated number of days after infusion of the cells. Top right figure (Y-axis is labelled as Total Flux) is "Days post-injection of CAR T-cells". Bottom 2 figures are "Days post-injection of CAd Δ trio. Figure 18B shows measurements for total flux (in photons per second; p/s) of ventral surface for mice of the different groups at the indicated number of days after administration of CAd Δ trio. Figure 18C shows the weights of mice in the different treatment groups at the indicated number of days after administration of CAd Δ trio, expressed as a percentage of body weight at day 0. Figure 18D shows the percentage of surviving subjects in the different treatment groups at the indicated number of days after administration of CAd Δ trio. A negative control condition wherein mice were not administered with CAd Δ trio or T cells is also shown (-).

Figures 19A to 19C. Images and graphs showing the results of *in vivo* analysis of the anti-cancer activity of the combination of different ratios of Onc5/3Ad2E1 Δ 24:HDAdIL-12_TK_PD-L1 and adoptively-transferred HER2-specific CAR T cells, in an orthotopic FaDu cell-derived model of squamous cell head and neck carcinoma. Figure 19A shows the number and location of luciferase-expressing FaDu cells within mice at the indicated number of days after administration of CAd Δ trio. Figure 19B shows measurements for total flux (in photons per second; p/s) of ventral surface for mice of the different groups at the indicated number of days after administration of CAd Δ trio. Figure 19C shows the weights of mice in the different treatment groups at the indicated number of days after administration of CAd Δ trio, expressed as a percentage of body weight at day 0.

Figures 20A to 20D. Bar charts and graphs showing the results of *in vivo* analysis of the combination of Onc5/3Ad2E1 Δ 24 and HDAdIL-12_TK_PD-L1 and ganciclovir (GCV), in an ectopic FaDu cell-derived model of squamous cell head and neck carcinoma. Figures 20A and 20B show the GAPDH-normalised copy number of (Figure 20A) Onc5/3Ad2E1 Δ 24 and (Figure 20B) HDAdIL-12_TK_PD-L1 in tumors of mice administered with the combination of

Onc5/3Ad2E1Δ24 and HDAd/L-12_TK_PD-L1 (CAdtrio) at 22 days post infection, with or without GCV treatment. Figure 20C shows tumor volume in mm³ of mice administered with the combination of Onc5/3Ad2E1Δ24 and HDAd/L-12_TK_PD-L1 (CAdtrio) at the indicated number of days post-injection of CAdtrio, with or without GCV treatment. Figure 20D shows IL-12 levels detected by ELISA analysis of blood samples obtained at the indicated number of days post-injection of CAdtrio, with or without GCV treatment.

Figures 21A to 21C. Bar chart and images showing the results of analysis of transgene expression in cancer cell lines infected with different HDAd viruses, cultured in the presence or absence of ganciclovir (GCV). Figure 21A shows the level of IL-12 in cell culture supernatant as determined by ELISA. Figure 21B shows anti-PD-L1 minibody detected in cell culture supernatant by western blot. Figure 21C shows viable cells detected by Crystal Violet staining at the end of the experiment.

Figures 22A and 22B. Scatterplots showing the results of characterisation by flow cytometry of Adenovirus-specific T cells (AdvSTs) used in experiments of Example 9. Figure 22A shows the percentages of CD4⁺ T cells and CD8⁺ T cells within the AdvST population. Figure 22B shows the percentages of cells within the AdvST population expressing CCR7 and/or CD45RO.

Figures 23A to 23C. Scatterplots and histograms showing the results of characterisation by flow cytometry F1.CAR-transduced AdvSTs used in experiments of Example 9. Figure 23A shows the percentages of CD4⁺ T cells and CD8⁺ T cells within the transduced population. Figure 23B shows the percentage cells expressing HER2 CAR at the cell surface. Figure 23C shows the percentages of cells within the F1.CAR-AdvST population expressing CCR7 and/or CD45RO.

Figures 24A to 24D. Images and graphs showing the results of *in vivo* analysis of the anti-cancer activity of Adenovirus-specific T cells (AdvSTs), F1.CAR-transduced AdvSTs, the combination of F1.CAR-transduced AdvSTs with Onc5/3Ad2E1Δ24, and the combination of F1.CAR-transduced AdvSTs with Onc5/3Ad2E1Δ24 + HDAd/L-12_TK_PD-L1 ("CAdtrio"). Figure 24A shows the number and location of luciferase-expressing FaDu cells within mice at the indicated number of days after administration of CAdtrio. Figure 24B shows measurements for total flux (in photons per second; p/s) of ventral surface for mice of the different groups at the indicated number of days after administration of CAdtrio. Figure 24C shows the weights of mice in the different treatment groups at the indicated number of days after administration of CAdtrio, expressed as a percentage of body weight at day 0. Figure 24D shows the percentage of surviving subjects in the different treatment groups at the indicated number of days after administration of CAdtrio. *P < 0.04, **P < 0.07, ***P < 0.02 for Figure 24B. *P < 0.01, **P < 0.04, ***P < 0.02 for 24C. *P=0.03, **P=0.02 for Figure 24D.

Numbered statements of disclosure

Following numbered paragraphs (paras) describe particular aspects and embodiments of the present disclosure:

- 5 1. A method of treating a cancer, comprising administering to a subject:
- (i) an oncolytic virus;
 - (ii) a virus comprising nucleic acid encoding an immunomodulatory factor; and
 - (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell
- 10 antigen.
2. The method of para 1, wherein the oncolytic virus is an oncolytic adenovirus (OncAd).
3. The method of para 1 or para 2, wherein the oncolytic virus is derived from adenovirus 5 (Ad5).
- 15 4. The method of any one of paras 1 to 3, wherein the oncolytic virus encodes an E1A protein which displays reduced binding to Rb protein as compared to E1A protein encoded by Ad5.
5. The method of any one of paras 1 to 4, wherein the oncolytic virus encodes an E1A protein lacking the amino acid sequence LTCHEACF (SEQ ID NO:52).
- 20 6. The method of any one of paras 1 to 5, wherein the oncolytic virus encodes an E1A protein comprising, or consisting of, the amino acid sequence SEQ ID NO:34.
7. The method of any one of paras 1 to 6, wherein the oncolytic virus comprises nucleic acid
- 25 having one or more binding sites for one or more transcription factors.
8. The method of any one of paras 1 to 7, wherein the oncolytic virus comprises nucleic acid having one or more binding sites for STAT1.
- 30 9. The method of any one of paras 1 to 8, wherein the virus comprising nucleic acid encoding an immunomodulatory factor is a helper-dependent adenovirus (HDAd).
10. The method of any one of paras 1 to 9, wherein the immunomodulatory factor is selected from: an agonist of an effector immune response or antagonist of an immunoregulatory response.
- 35 11. The method of any one of paras 1 to 10, wherein the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding IL-12 and/or antagonist anti-PD-L1 antibody.

12. The method of any one of paras 1 to 11, wherein the virus comprising nucleic acid encoding an immunomodulatory factor comprises nucleic acid encoding a thymidine kinase.

13. The method of any one of paras 1 to 12, wherein the at least one cell comprising a CAR
5 specific for a cancer cell antigen is a T cell.

14. The method of any one of paras 1 to 13, wherein the CAR comprises an antigen binding domain capable of specific binding to HER2.

10 15. The method of any one of paras 1 to 14, wherein the CAR comprises an antigen binding domain comprising:

a VL domain comprising:

LC-CRD1: SEQ ID NO:10;

LC-CRD2: SEQ ID NO:11;

15 LC-CRD3: SEQ ID NO:12;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:13;

HC-CRD2: SEQ ID NO:14;

20 HC-CRD3: SEQ ID NO:15;

or

a VL domain comprising:

LC-CRD1: SEQ ID NO:18;

LC-CRD2: SEQ ID NO:19;

25 LC-CRD3: SEQ ID NO:20;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:21;

HC-CRD2: SEQ ID NO:22;

25 HC-CRD3: SEQ ID NO:23;

or

30 a VL domain comprising:

LC-CRD1: SEQ ID NO:26;

LC-CRD2: SEQ ID NO:27;

LC-CRD3: SEQ ID NO:28;

and a VH domain comprising:

35 HC-CRD1: SEQ ID NO:29;

HC-CRD2: SEQ ID NO:30;

HC-CRD3: SEQ ID NO:31.

16. The method of any one of paras 1 to 15, wherein the CAR comprises an antigen binding domain comprising:

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:16 and a VH comprising, or
 5 consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:17;

or

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:24 and a VH comprising, or
 10 consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:25;

or

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:32 and a VH comprising, or
 15 consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:33.

17. The method of any one of paras 1 to 16, wherein the method additionally comprises:

- (a) isolating at least one cell from a subject;
- 20 (b) modifying the at least one cell to express or comprise a CAR specific for a cancer cell antigen, or a nucleic acid encoding a CAR specific for a cancer cell antigen,
- (c) optionally expanding the modified at least one cell, and;
- (d) administering the modified at least one cell to a subject.

18. The method of any one of paras 1 to 17, wherein the cancer is selected from head and neck cancer, nasopharyngeal carcinoma (NPC), cervical carcinoma (CC), oropharyngeal carcinoma (OPC), gastric carcinoma (GC), hepatocellular carcinoma (HCC) and lung cancer.

19. An oncolytic adenovirus (OncAd) encoding an E1A protein comprising, or consisting of, the amino acid sequence SEQ ID NO:34.

20. An oncolytic adenovirus (OncAd) comprising nucleic acid having one or more binding sites for STAT1.

21. The OncAd according to para 20, wherein the OncAd comprises a nucleic acid sequence having at least 60% sequence identity to SEQ ID NO:51 or an equivalent sequence as a result of codon degeneracy.

22. A helper-dependent adenovirus (HDA_d) comprising nucleic acid encoding IL-12 and/or antagonist anti-PD-L1 antibody.

23. The HDA_d according to para 22, wherein the HDA_d additionally comprises nucleic acid encoding a thymidine kinase.

24. A chimeric antigen receptor (CAR) comprising an antigen binding domain comprising:

a VL domain comprising:

LC-CRD1: SEQ ID NO:10;

LC-CRD2: SEQ ID NO:11;

LC-CRD3: SEQ ID NO:12;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:13;

HC-CRD2: SEQ ID NO:14;

HC-CRD3: SEQ ID NO:15;

or

a VL domain comprising:

LC-CRD1: SEQ ID NO:18;

LC-CRD2: SEQ ID NO:19;

LC-CRD3: SEQ ID NO:20;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:21;

HC-CRD2: SEQ ID NO:22;

HC-CRD3: SEQ ID NO:23;

or

a VL domain comprising:

LC-CRD1: SEQ ID NO:26;

LC-CRD2: SEQ ID NO:27;

LC-CRD3: SEQ ID NO:28;

and a VH domain comprising:

HC-CRD1: SEQ ID NO:29;

HC-CRD2: SEQ ID NO:30;

HC-CRD3: SEQ ID NO:31.

25. The CAR according to para 24, wherein the CAR comprises an antigen binding domain comprising:

a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:16 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:17;

or

a VL comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:24 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:25;

or

a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:32 and a VH comprising, or consisting of or consisting essentially of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:33.

26. A nucleic acid, optionally isolated or man-made, encoding the oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, or the chimeric antigen receptor (CAR) according to para 24 or para 25.

27. A cell comprising the oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, the chimeric antigen receptor (CAR) according to para 24 or para 25, or the nucleic acid according to para 26, optionally wherein the cell is man-made and not found in nature.

28. A pharmaceutical composition comprising the oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, the chimeric antigen receptor (CAR) according to para 24 or para 25, the nucleic acid according to para 26 or the cell according to para 27 and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

29. A method of treating cancer comprising administering to a subject the oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, the chimeric antigen receptor (CAR) according to para 24 or para 25, the nucleic acid according to para 26, the cell according to para 27 or the pharmaceutical composition according to para 28.

30. The oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, the chimeric antigen receptor (CAR) according to para 24 or para 25, the nucleic acid according to para 26, the cell according to para 27 or the pharmaceutical composition according to para 28 for use in a method of treating a cancer.

31. Use of the oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, the chimeric antigen receptor

(CAR) according to para 24 or para 25, the nucleic acid according to para 26, the cell according to para 27 or the pharmaceutical composition according to para 28 in the manufacture of a medicament for treating a cancer.

32. The method, the use or the use according to any one of paras 29 to 31, wherein the cancer is selected from head and neck cancer, nasopharyngeal carcinoma (NPC), cervical carcinoma (CC), oropharyngeal carcinoma (OPC), gastric carcinoma (GC), hepatocellular carcinoma (HCC) and lung cancer.

33. A kit of parts comprising a predetermined quantity of the oncolytic adenovirus (OncAd) according to any one of paras 19 to 21, the helper-dependent adenovirus (HDAd) according to para 22 or para 23, the chimeric antigen receptor (CAR) according to para 24 or para 25, the nucleic acid according to para 26, the cell according to para 27 or the pharmaceutical composition according to para 28.

Examples

In the following Examples, the inventors describe the generation functional characterisation of novel HER-2 specific CARs and CAR-T cells, oncolytic adenoviruses and helper-dependent adenovirus.

Example 1: HER2-specific CAR-T cells

1.1 Generation of HER2-specific CAR constructs and CAR-T cells

HER2-binding CAR constructs were prepared. Briefly, DNA encoding scFv (*i.e.* VL domain and VH domain joined by a linker sequence) for the anti-HER2 antibody clone C5, E4, F1 or A3 was cloned into a CAR construct backbone comprising a 5' signal peptide (SP), and CD28 transmembrane (TM) and intracellular domain sequence, with a 3' CD3 ζ intracellular domain sequence. The three HER2-binding CAR constructs are represented schematically in Figure 1A.

HER2 specific CAR-T cells were generated as represented graphically in Figure 1B. Briefly, human PBMCs were isolated from blood samples by with Ficoll density gradient centrifugation.

Cells were treated by stimulation with anti-CD3(OKT3)/anti-CD28 in the presence of IL-2 to promote T cell activation and proliferation, and the cells were transduced with retrovirus encoding the HER2 CAR constructs. T-cells were expanded by culture in the presence of 100 IU/mL recombinant human IL-2, and were frozen at 6 days post-transduction. The HER2-specific CAR construct-transduced T cells were readily expanded by culture *in vitro* (see e.g. Figure 14).

T-cells were thawed and expanded in the presence of 100 IU/mL of recombinant human IL-2 for 5 days and used for *in vitro/in vivo* experiments and phenotypic analysis.

1.2 Characterisation of the HER2-specific CAR-T cells

1.2.1 Expression of surface markers and HER2 CARs

T cells transduced with HER2 CAR construct encoding scFv for anti-HER2 antibody clone E4 were characterised by flow cytometry for expression of different cell surface molecules. Expanded HER2 specific CAR T-cells were stained with fluorescently-labelled monoclonal antibodies for 30 minutes at 4 °C. Discrimination of live/dead cells was achieved by including 7AAD in stainings (BD Pharmingen). Stained cells were analyzed using a Gallios flow cytometer and Kaluza software (BD Bioscience), according to manufacturer's instructions.

The results are shown in Figures 2 and 3. Strong surface expression of the HER2-CARs was detected on the transduced cells (Figure 2).

Figure 3 shows the results of characterisation of T cells transduced with HER2(E4)-CAR. CD3+ cells, CD4+ cells and CD8+ cells expressing HER2(E4)-CAR were shown to have increased expression of PD-1, LAG-3 and TIM-3, and to have reduced level of expression of CCR7 as compared to non-transduced cells (Figure 3).

1.2.2 Cell killing activity

The HER2-CAR-T cells were analysed for their ability to kill HER2 expressing cancer cells *in vitro* in cell killing assays.

In a first experiment, cells of the HER2 negative MDA cell line (negative control), MDA cells stably expressing HER2 (MDA-HER2; positive control), pharynx squamous cell carcinoma cell line FaDu or the head and neck squamous carcinoma cell line SCC47 cells were labelled with Chromium-51 (⁵¹Cr) and co-cultured with non-transduced T-cells (NT) or the HER2-CAR-T cells expressing the indicated CARs at an effector:target cell ratio of 20:1 for 4 hours. After centrifugation, ⁵¹Cr levels in the cell culture media were counted using a liquid scintillation counter. The results are shown in Figure 4A; the HER2-CAR-T cells were shown to kill HER2-expressing cancer cells. Similar results were obtained when the experiments were performed using an effector:target cell ratio of 10:1.

Expression of HER2 on MDA-HER2, FaDu and SCC47 was confirmed by flow cytometry. Briefly, the cells were stained with fluorescently-labelled monoclonal anti-HER2 antibody or isotype control antibody for 30 minutes at 4 °C. Discrimination of live/dead cells was achieved by including 7AAD in stainings (BD Pharmingen). Stained cells were analyzed using a Gallios flow cytometer and Kaluza software (BD Bioscience), according to manufacturer's instructions. The results are shown in Figure 4B; MDA cells were confirmed not to express HER2, whilst MDA-HER2, FaDu and SCC47 express HER2.

In a separate experiment, FaDu and SCC47 cells genetically modified to express firefly luciferase (ffLuc) were seeded in wells of 24-well plates, and co-cultured with HER2(C5)-CAR-T cells,

HER2(E4)-CAR-T cells, or HER2(F1)-CAR-T cells at an effector:target cell ratio of 1:5 for 3 days, and fLuc activity was measured using a plate reader (Life Technologies). The results are shown in Figure 5; the HER2-CAR-T cells were shown to kill HER2-expressing cancer cells, as evidenced by a reduction in fLuc activity (relative light units, RLU). Similar results were obtained when the experiment was performed using an effector:target cell ratio of 1:20.

Example 2: OncAd constructs

2.1 Generation of OncAd constructs

Novel constructs encoding oncolytic adenovirus are prepared using recombinant DNA techniques. In particular embodiments, an OncAd is produced upon modification of a known virus. For example, a region encoding E1A protein from adenovirus 5, such as one lacking the sequence LTCHEACF (SEQ ID NO:52) involved in binding the Rb protein, is replaced with sequence encoding E1A protein from adenovirus 2, similarly lacking the sequence LTCHEACF (SEQ ID NO:52).

ICOSTAT shown in Figure 6 was produced from ICOVIR15 disclosed e.g. in Rojas *et al.* 2010 Mol Ther 18 1960-1971. Briefly, the region of ICOVIR15 encoding eight copies of a binding site for the transcription factor E2F was replaced with a region encoding eight tandem copies of a binding site for the transcription factor STAT1. The sequence of ICOSTAT is shown in SEQ ID NO:51.

Onc5/3Ad2E1Δ24 (also referred to herein as "Onc5/2E1Δ24") shown in SEQ ID NO:55 and represented schematically in Figure 12 was also prepared by using recombinant DNA techniques. Onc5/3Ad2E1Δ24 has a similar structure as Onc5Δ24 disclosed e.g. in Fueyo *et al.* 2000 Oncogene 19:2-12 (hereby incorporated by reference in its entirety; Onc5Δ24 is also referred to in Fueyo *et al.* as "Δ24"), but differs in that Onc5/3Ad2E1Δ24 encodes E1A protein from adenovirus type 2 (Ad2) lacking the sequence LTCHEACF (SEQ ID NO:52), rather than E1A protein from adenovirus type 5 (Ad5) lacking the sequence LTCHEACF (SEQ ID NO:52).

2.2 Cell killing activity

The ability of an oncolytic adenovirus of choice or ICOSTAT as generated in Example 2.1 to kill cancer cells may be analysed for example by MTS assay. Briefly, cells of the human alveolar basal epithelial adenocarcinoma cell line A549 cells, FaDu cells, SCC47 cells, or non-cancerous WI-38 human lung fibroblasts or ARPE-19 human retinal pigmented epithelial cells were seeded in wells of 96-well plates and infected with different amounts of a helper-dependent, non-replicating adenovirus (HDA₂; as a negative control), an oncolytic adenovirus of choice (e.g.

Onc5/3Ad2E1Δ24 described in Example 2.1), or ICOSTAT described in Example 2.1 above.

Cells may be cultured for 4 days, for example, and then MTS reagents (Promega) may be added to each well, with cells being incubated at 37°C for 2 hours. Live cells may be analyzed by measuring the absorbance at 490nm with a plate reader. Readings may be normalized using the

readings for untreated cells of each type (*i.e.* untreated cells = 100% cell viability), and wells lacking cells would be considered 0%.

In particular embodiments, the oncolytic virus of choice is able to kill cancer cells in a dose-dependent manner. The oncolytic virus of choice also exhibits a lower level of cell killing of non-cancerous cells, such as WI-38 and ARPE-19 cells as compared to the level of killing by the virus of cancerous cells, in specific embodiments.

Figures 7A to 7F show that ICOSTAT is able to kill cancer cells (*i.e.* A549, FaDu and SCC47 cells) in a dose-dependent manner (Figures 7A to 7C and 7F), and exhibits a lower level of cell killing of non-cancerous cells WI-38 and ARPE-19 cells as compared to the level of killing of the cancerous cells (Figures 7D and 7E).

Figures 13A to 13D show that Onc5/3Ad2E1Δ24 is able to kill cancer cells (*i.e.* FaDu and SCC47 cells) in a dose-dependent manner (Figures 13A and 13B), and exhibits a lower level of cell killing of non-cancerous WI-38 and ARPE-19 cells as compared to the level of killing of the cancerous cells (Figures 13C and 13D).

2.3 Ability to help helper-dependent adenovirus (HDA)

The ability of an oncolytic adenovirus of choice or ICOSTAT as generated in Example 2.1 to assist replication of a helper-dependent adenovirus (HDA) may be analysed by co-infecting cancer cells with the OncoAd and HDA, and determining virus copy number. Briefly, FaDu or SCC47 cells are plated in 24-well plates and infected with 10 viral particles per cell of HDA alone, or OncoAd + HDA (at an OncoAd:HDA ratio of 1:10). Cells are harvested at 48 hours post-infection, DNA is extracted and both HDA and OncoAd vector copies are analyzed by quantitative real-time PCR (10 min at 95 °C and then 45 cycles of 10 s at 95°C, 15 s at 60°C, and 30 s at 72°C) using a Bio-Rad iQ5 real-time PCR detection system (Bio-Rad), and Applied Biosystems SYBR green PCR master mix (Life Technologies). Copy number is normalized using copy number detected for GAPDH.

In particular embodiments, the oncolytic virus of choice is able to replicate itself and the HDA sufficiently.

Figures 8A and 8B show that ICOSTAT (designated "Onc5/3AdicoSTAT" in the figures) was found to be able to replicate itself (Figure 8A) and the HDA (Figure 8B).

2.4 Effect of IFN γ on replication of ICOSTAT in cancer cells

The effect of IFN γ treatment on replication of ICOSTAT OncoAd was analysed. Briefly, FaDu and SCC47 cells are plated in 24-well plates, and the cells are infected with 10 vp/cell of the oncolytic

virus of choice or icoSTAT 3 hours post-infection cell culture medium is replaced with medium containing, or not containing, 10 ng/mL recombinant IFN γ at 3 hours post-infection, and cell culture media are replaced with fresh media with/without 10 ng/mL recombinant IFN γ again at 24 and 48 hours post-infection. Cells are harvested at 3, 24, 48 and 72 hours post-infection, DNA is extracted from the cells, viral copy numbers are analysed by quantitative real-time PCR and normalized using copy number detected for GAPDH.

Figures 9A and 9B show that ICOSTAT was able to replicate in FaDu cells and SCC47 cells, in the presence or absence of IFN γ .

Example 3: Helper-dependent Ad (HDA) constructs

3.1 HDA constructs and production

A novel construct encoding a helper-dependent adenovirus was prepared using recombinant DNA techniques. The coding sequence of the resulting construct designated HDA Δ IL-12_TK_PD-L1 is represented schematically in Figure 10A. HDA Δ IL-12_TK_PD-L1 contains sequence encoding expression cassettes for (i) human IL-12p70 (sequence encoding alpha and beta chains), (ii) HSV-1 thymidine kinase, and (iii) an anti-PD-L1 minibody (comprising the CDRs of anti-PD-L1 clone H12_g1 described e.g. in WO 2016111645 A1) including a HA tag. The three coding sequences each have their own polyA signal sequences.

The HDA HDA Δ 28E4EGFP construct containing an EGFP transgene driven by the CMV promoter (HDA Δ eGFP) was produced as described in Farzad *et al.* Oncolytics 2014 1: 14008.

The HDA "HDIL12_PDL1" contains sequence encoding human IL-12p70 protein and anti-PD-L1 minibody derived from YW243.55.S70 (atezolizumab). The anti-PD-L1 minibody of this construct consists of scFv for YW243.55.S70 fused with a hinge, CH2 and CH3 regions of human IgG1 and a C-terminal HA tag (as described e.g. in Tanoue *et al.* Cancer Res. (2017) 77(8):2040-2051).

3.2 Expression of encoded proteins

Cancer cells were transfected with plasmid HDA vectors, and medium samples were collected to analyze IL-12p70 and anti-PD-L1 minibody levels in the cell culture media of the transfected cells at 48 hours post-transfection.

IL-12p70 levels in media were measured using the BD cytokine multiplex bead array system (BD Biosciences), according to manufacturer's instructions. The results are shown in Figure 10B. Cells transfected with the HDA Δ IL-12_TK_PD-L1 construct were found to produce higher levels of IL-12p70 than cells transfected with the HDIL-12_PD-L1 construct.

Secretion of anti-PD-L1 minibodies into the cell culture medium was detected by western blot analysis, using an anti-HA antibody (to detect the HA-tagged minibodies). Figure 10C shows that

cells transfected with the HDAd/IL-12_TK_PD-L1 construct secreted the anti-PD-L1 minibody into the cell culture medium.

In another experiment, cells were transfected with the different constructs and at 8 hours post-transfection the cell culture media was replaced with medium containing 10 ng/ml Ganciclovir (GCV). Cell culture medium was then replaced with medium containing 10 ng/ml every 24 hours, and after 7 days, the wells were stained with Crystal Violet solution to reveal viable cells.

The results are shown in Figure 10D, and confirm that cells transfected with the HDAd/IL-12_TK_PD-L1 construct express thymidine kinase.

In further experiments A549, FaDu or SCC47 cells (n = 4 wells per condition) were infected *in vitro* with HDAd/IL-12_TK_PD-L1, HDAd_PD-L1 (see e.g. Tanoue *et al.*, *supra*), or a control HDAd encoding eGFP (see Farzad *et al.*, *supra*). The cells were either cultured for 48 hours in the absence of ganciclovir, or medium was changed at 8 hours post-infection and every 24 hours thereafter with medium containing 10 ng/ml ganciclovir.

Secretion of IL-12 into the cell culture supernatant was analysed by ELISA, and secretion of anti-PD-L1 minibody was analysed by western blot using an anti-HA antibody (the anti-PD-L1 minibody comprises a C-terminal HA-tag). At the end of the experiment wells were stained with Crystal Violet solution to reveal viable cells.

The results are shown in Figures 21A to 21C, and confirmed expression of the transgenes encoded by the HDAds in the different cancer cell lines analysed.

3.3 Confirmation of anti-PD-L1 minibody binding to PD-L1

The ability of the anti-PD-L1 minibody encoded by HDAd/IL-12_TK_PD-L1 to bind to PD-L1 was analysed by ELISA.

Briefly, Immulon 2 high binding 96-well plates (VWR) were coated with 500 ng/well of recombinant human PD-L1 (BioVision). After blocking plate with PBS-T containing 3% BSA, serially diluted cell culture media of A549 cells which had been transfected with plasmid encoding GFP (pGFP; negative control), plasmid encoding the anti-PD-L1 minibody described in Tanoue *et al. supra*, (pPDL1 mini Tanoue) or plasmid encoding the anti-PD-L1 minibody encoded by HDAd/IL-12_TK_PD-L1 (pPDL1 mini) were added and incubated at 4°C for 24 hours. Serially diluted anti-human PD-L1 antibody starting from 10 µg/well (BioLegend) was used as a positive control (PDL1 IgG). After washing plate with PBS-T, HRP-labeled anti-human IgG (for PD-L1 mini and PDL1 mini Tanoue) or HRP-labeled anti-mouse IgG (BioRad; for PD-L1 IgG and Iso IgG) were added for

detection, and incubated at room temperature for 1 hour. The plate was then developed, and absorbance at 450 nm was measured using Tecan reader (TECAN).

The results are shown in Figure 11. The anti-PD-L1 minibody comprising the CDRs of anti-PD-L1 antibody clone H12 was found to bind to human PD-L1 in a dose-dependent fashion, with comparable (or greater) avidity as compared to the avidity of binding by anti-PD-L1 minibody described in Tanoue *et al. supra*.

Example 4: Analysis of treatment of cancer *in vivo*

The anticancer effect of treatment with the combination of (1) an oncolytic virus of choice + HDAd/IL-12_TK_PD-L1 + HER2-CAR-T and (2) ICOSTAT + HDAd/IL-12_TK_PD-L1 + HER2-CAR-T is demonstrated *in vivo* in mouse xenograft tumour models.

In a first experiment, 1×10^6 FaDu cells are injected subcutaneously in PBS into NSG male mice. After 12 days, 1×10^8 viral particles (1) oncolytic virus and HDAd/IL-12_TK_PD-L1 or (2) ICOSTAT + HDAd/IL-12_TK_PD-L1 are injected intratumorally at an OncAd:HDAd ratio of 1:20.

In a second experiment, 0.5×10^6 FaDu cells are injected orthotopically into NSG male mice. After 6 days, 1×10^8 viral particles (1) oncolytic virus and HDAd/IL-12_TK_PD-L1 or (2) ICOSTAT + HDAd/IL-12_TK_PD-L1 are injected intratumorally at an OncAd:HDAd ratio of 1:20.

In both experiments, 3 days after administration of the viral particles, 1×10^6 HER2-CAR T cells are administered intravenously.

In both experiments, control conditions are included as follows:

Condition	OncAd	HDAd	CAR T
1 (test condition)	Of choice	HDAd/IL-12_TK_PD-L1	HER2 CAR-T
2 (test condition)	ICOSTAT	HDAd/IL-12_TK_PD-L1	HER2 CAR-T
3	-	HDAd/IL-12_TK_PD-L1	HER2 CAR-T
4	Of choice	-	HER2 CAR-T
5	ICOSTAT	-	HER2 CAR-T
6	Of choice	HDAd/IL-12_TK_PD-L1	-
7	ICOSTAT	HDAd/IL-12_TK_PD-L1	-
8	Of choice	-	-
9	ICOSTAT	-	-
10	-	HDAd/IL-12_TK_PD-L1	-
11	-	-	HER2 CAR-T

Tumor size is monitored and tumour volumes are calculated using the formula: $\text{Width}^2 \times \text{Length} \times 0.5$.

5 The use of the combination of oncolytic virus, HDAdIL-12_TK_PD-L1 and HER2 CAR-T (test condition 1) is found to have an improved antitumour effect as compared to the use of any of the agents alone (conditions 8, 10 or 11), or compared to the use of two of the three agents (conditions 3, 4 and 6).

10 Similarly, the use of the combination of ICOSTAT, HDAdIL-12_TK_PD-L1 and HER2 CAR-T (test condition 2) is found to have an improved antitumour effect as compared to the use of any of the agents alone (conditions 9, 10 or 11), or compared to the use of two of the three agents (conditions 3, 5 and 7).

15 Similar results are observed when xenograft tumours are established using SCC47 cells and A549 cells.

Example 5: Analysis of the anti-cancer activity of the HER2-specific CAR-T cells *in vivo*

The anti-cancer activity of the HER2-specific CAR-T cells (see Example 1 above) was investigated *in vivo* in a FaDu cell-derived xenograft model of squamous cell head and neck cancer.

20 Briefly, 0.5×10^6 FaDu cells were injected orthotopically into NSG male mice. After 9 days, mice were injected via the tail vein with 1×10^6 T cells genetically modified to express firefly luciferase, which had not been transduced with a HER2-CAR construct, or with 1×10^6 firefly luciferase-expressing T cells which had been transduced with the C5, F1 or A3 CAR constructs. A control condition was included in the experiment in which mice were not injected with T cells at day 9.

25 Luciferase activity (and thus number and distribution of the administered T cells), body weight, survival of the mice was monitored over time. Luciferase activity was monitored by intraperitoneal injection of D-Luciferin (1.5 mg per mouse), and imaging of the mice 10 min later using an IVIS imager (Xenogen).

30 Figures 15A and 15B show the images acquired on days 0, 4, 7, 14, 28, 42, 56 and 70 following injection of the luciferase-expressing T cells (i.e. the non-transduced T cells or HER2-specific CAR-T cells) (days refer to days after fLuc T cell injection). The systemically infused T cells were shown to migrate to the site of the orthotopic tumors. The T cells which had not been modified to express HER2-specific CARs were undetectable after 7 days. By contrast, the HER2-specific CAR-T cells persisted and remained detectable throughout the experiment.

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Figure 15C shows percentage survival of mice subjected to the different treatments over the course of the experiment. Administration of HER2-specific CAR-T cells was found to increase survival.

In a separate experiment NOD scid gamma (NSG) mice were injected via the tail vein with 1×10^6 firefly luciferase-expressing T cells which had not been transduced with a HER2-CAR construct, or with 1×10^6 firefly luciferase-expressing T cells which had been transduced with the C5, F1 or A3 CAR construct. Luciferase activity was monitored as described above, and body weight of the mice was also monitored over time.

The results of the experiment are shown in Figures 16A to 16C. The C5 CAR-T cells were found to expand non-specifically in NSG mice (Figure 16A). No significant weight loss was observed in NSG mice administered with the HER2-specific CAR-T cells (Figure 16C).

Example 6: Analysis of the anti-cancer activity of the combination of oncolytic virus, HDAd virus and HER2-specific CAR-T cells *in vivo*

The anti-cancer activity of a combination of oncolytic virus, HdAd and HER-specific CAR-T cell therapy was investigated *in vivo* in a FaDu cell-derived xenograft model of squamous cell head and neck cancer.

Briefly, 0.5×10^6 FaDu cells were injected orthotopically into NSG male mice. After 6 days, one group of mice was then injected intratumorally with a combination of Onc5/3Ad2E1Δ24 (described in Example 2.1) and HDAd/L-12_TK_PD-L1 described in Example 3.1 (this combination of OncAd and HdAd is referred to herein as "CAdtrio"). A total of 1×10^7 viral particles were administered, at a 1:10 ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1.

Three days later, mice were injected via the tail vein with 1×10^6 T cells engineered to express firefly luciferase, which had been transduced with the HER2-specific CAR construct corresponding to clone F1. A control group of mice which had not been administered with CAdtrio was injected via the tail vein with 1×10^6 firefly luciferase-expressing T cells which had not been transduced with a HER2-CAR construct, and a further control group of mice was not administered with CAdtrio nor injected with T cells. Luciferase activity, body weight and survival of the mice was monitored over time.

Prior to their use in the experiment the F1.CART cells were characterised flow cytometry, and the results are shown in Figures 17A to 17C. The cells were found to comprise 72.5% CD4+ cells and CD8+ cells. 87% of the cells were determined to express HER2 CAR at the cell surface. 39% of the cells were CCR7+CD45RO+, and 59.2% of the cells were CCR7-CD45RO+.

The results of the experiments analysing the therapeutic efficacy of the combination of oncolytic virus, HDAd virus and HER2-specific CAR-T cells to treat cancer *in vivo* are shown in Figures 18A to 18D. The combination of Onc5/3Ad2E1Δ24, HDAd/L-12_TK_PD-L1 and F1.CART was found to improve survival over treatment with F1.CART cells alone.

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In further experiments two different ratios of Onc5/3Ad2E1Δ24 to HDAd/L-12_TK_PD-L1 were investigated.

10

Briefly, 0.5×10^6 FaDu cells modified to express firefly luciferase were injected orthotopically into NSG male mice. After 6 days, mice were injected intratumorally with:

(i) 1×10^7 viral particles of CAd Δ trio, at a ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1 of 1:10;

(ii) 1×10^7 viral particles of CAd Δ trio, at a ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1 of 1:20;

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(iii) 1×10^8 viral particles of CAd Δ trio, at a ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1 of 1:10; or

(iv) 1×10^8 viral particles of CAd Δ trio, at a ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1 of 1:20.

20

Three days later, mice were injected via the tail vein with 1×10^6 T cells which had been transduced with the F1 CAR construct (not expressing firefly luciferase). The cancer was monitored over time by analysis of luciferase activity as described above, and the body weight of the mice was also monitored.

25

The results of the experiments are shown in Figures 19A to 19C. Mice administered with a 1:10 ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1 generally had fewer luciferase-expressing FaDu cells than those administered with a 1:20 ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1, and mice administered with 1×10^8 viral particles of CAd Δ trio generally had fewer luciferase-expressing FaDu cells than those administered with 1×10^7 viral particles of CAd Δ trio (Figure 19B).

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Example 7: Analysis of the anti-cancer activity of the combination of oncolytic virus, HDAd virus and ganciclovir (GCV) *in vivo*

The anti-cancer activity of a combination of oncolytic virus and HdAd (encoding thymidine kinase) (i.e., CAd Δ trio) in conjunction with ganciclovir (GCV) was investigated *in vivo* in a FaDu cell-derived xenograft model of squamous cell head and neck cancer.

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Ectopic FaDu tumors were established by subcutaneous injection of FaDu cells into the flanks of mice. The mice were subsequently injected intratumorally with 1×10^8 viral particles of CAd Δ trio, at a ratio of Onc5/3Ad2E1Δ24:HDAd/L-12_TK_PD-L1 of 1:10. One group of mice (n=5) was then

injected intraperitoneally on days 2, 3, 4, 5, 7, 10, 14, 17 and 21 days after CAd_{trio} injection with 10 mg/kg of ganciclovir.

Blood samples were collected from the mice on days 2, 7, 14 and 21 and analysed by ELISA for IL-12 expression. Tumor volumes were monitored throughout the experiment. At day 22 Onc.Ad and HDAd vector copy numbers were determined in DNA extracted from the tumors by quantitative real-time PCR analysis, and normalised using the copy number detected for GAPDH.

The results of the experiments are shown in Figures 20A to 20D. Ganciclovir (GCV) treatment did not significantly influence Onc.Ad vector copy number at day 22 (Figure 20A), but significantly decreased HDAd vector copy number (Figure 20B). GCV treatment was also found to improve tumor control (Figure 20C), but did not significantly influence the levels of IL-12 in the blood (Figure 20D).

Example 8: Generation of oncolytic virus-specific T cells and HER-specific CAR-expressing oncolytic virus-specific T cells

8.1 Generation and characterisation of oncolytic virus-specific T cells

Adenovirus-specific T cells (AdvSTs) and activated T cells (ATCs) were prepared as follows.

Anti-CD3 (clone OKT3) and anti-CD28 agonist antibodies were coated onto wells of tissue culture plates by addition of 0.5 ml of 1:1000 dilution of 1 mg/ml antibodies, and incubation for 2-4 hr at 37°C, or at 4°C overnight.

PBMCs were isolated from blood samples obtained from healthy donors according to the standard Ficoll-Paque method.

ATCs:

1 x 10⁶ PBMCs (in 2 ml of cell culture medium) were stimulated by culture on the anti-CD3/CD28 agonist antibody-coated plates in CTL cell culture medium (containing 50% Advanced RPMI, 50% Click's medium, 10% FBS, 1% GlutaMax, 1% Pen/Strep) supplemented with 10 ng/ml IL-7 and 5 ng/ml IL-15. The cells were maintained at 37°C in a 5% CO₂ atmosphere. The next day, 1 ml of the cell culture medium was replaced with fresh CTL medium containing 20 ng/ml IL-7 and 10 ng/ml IL-15.

ATCs were maintained in culture, and subsequently harvested and used in experiments or cryopreserved between days 5-7.

AdvSTs:

1 x 10⁶ PBMCs (in 2 ml of cell culture medium) were stimulated by culture on the anti-CD3/CD28 agonist antibody-coated plates in CTL cell culture medium supplemented with 10 ng/ml IL-7 and 100 ng/ml IL-15.

20 µl of a 200-fold dilution of Adenovirus-specific Hexon Pepmix (JPT Cat# PM-HAdV3) or Penton PepMix (JPT Cat# PM-HAdV5) was added to the wells. The cells were maintained at 37°C in a 5% CO₂ atmosphere. After 48 hours cells were fed with CTL medium, with added IL-7 and IL-15 to a final concentration of 10 ng/ml IL-7 and 100 ng/ml IL-15.

8.2 Generation of CAR-expressing, oncolytic virus-specific T cells

On day 3, AdvSTs were resuspended at a concentration of 0.125 x 10⁶ cells/ml in CTL cell culture medium containing 10 ng/ml IL-7 and 100 ng/ml IL-15.

Retronectin coated plates were prepared by incubation of RetroNectin (Clontech) diluted 1:100 in PBS for 2-4 hr at 37°C, or at 4°C overnight. The wells were washed with CTL medium, 1 ml of retroviral supernatant of HER2-specific CAR retrovirus was added to wells, and plates were centrifuged at 2000g for 1.5 hr. At the end of the centrifugation step retroviral supernatant was aspirated, and 2 ml of AdvST suspension (i.e. 0.25 x 10⁶ cells) was added to wells of the plate. Plates were centrifuged at 400g for 5 min, and incubated at 37°C in a 5% CO₂ atmosphere.

After 48 hrs (i.e. on day 6) the cell culture medium was aspirated and replaced with CTL cell culture medium containing 10 ng/ml IL-7 and 100 ng/ml IL-15.

On day 9 cells were harvested and used in experiments or cryopreserved, or subjected to a second stimulation to expand CAR-expressing AdvSTs (see Example 8.3).

8.3 Expansion of AdvSTs and CAR-AdvSTs

AdvSTs and CAR-expressing AdvSTs were expanded by further stimulations as desired, as follows.

Pepmix-pulsed autologous ATCs were used as APCs, and K562cs cells (see e.g. Ngo et al., J Immunother. (2014) 37(4):193-203) were used as costimulatory cells. The final ratio of AdvSTs or CAR-AdvSTs:ATCs:K562cs cells in the stimulation cultures was 1:1:3-5.

AdvSTs or CAR-AdvSTs were resuspended to a concentration of 0.2 x 10⁶ cells/ml in CTL medium.

1 x 10⁶ ATCs were incubated with 10 µl of 200-fold dilution of Adenovirus-specific Hexon Pepmix (JPT Cat# PM-HAdV3) or Penton PepMix (JPT Cat# PM-HAdV5) at 37°C for 30 min. The ATCs

were subsequently irradiated at 30Gy and harvested. $3-5 \times 10^6$ K562cs cells were irradiated at 100Gy.

The ATCs and K562cs cells were then mixed in a total volume of 5 ml CTL medium, and 20 ng/ml IL-7 and 200 ng/ml IL-15 was added, 1 ml of this mixture was added to wells of a 24 well plate, and 1 ml of AdvST suspension or CAR-AdvST suspension was added to the wells.

Cells were maintained at 37°C in a 5% CO₂ atmosphere. After 3-4 days cell culture medium was added as necessary, and after 6-7 days cells the expanded AdvSTs or CAR-AdvSTs were harvested for use in experiments.

Example 9: Analysis of the anti-cancer activity of combinations of oncolytic virus, HDAd, oncolytic virus-specific T cells and CAR-expressing oncolytic virus-specific T cells *in vivo*

The anti-cancer activity of different combinations of oncolytic virus, HDAd, oncolytic virus-specific T cells and CAR-expressing oncolytic virus-specific T cells was investigated *in vivo* in a FaDu cell-derived xenograft model of squamous cell head and neck cancer.

Briefly, 0.5×10^6 FaDu cells engineered to express firefly luciferase were injected orthotopically into NSG male mice. After 6 days groups of mice were injected intratumorally with:

(i) 1×10^7 viral particles of CAd Δ trio, at a ratio of Onc5/3Ad2E1Δ24:HDAd/IL-12_TK_PD-L1 of 1:10; or

(ii) 1×10^7 viral particles of Onc5/3Ad2E1Δ24.

Three days later, mice were injected via the tail vein with:

(a) 1×10^6 AdvSTs, or

(b) 1×10^6 AdvSTs transduced with anti-HER2 CAR clone F1 (prepared as described in Example 8).

Prior to their use in the experiment the AdvSTs and F1.CAR-AdvSTs were characterised by flow cytometry, and the results of the analysis are shown in Figures 22A and 22B, and Figures 23A to 23C.

The cancer was monitored over time by analysis of luciferase activity as described above, and the body weight of the mice was also monitored.

The results of the experiments are shown in Figures 24A to 24D. The greatest level of tumor control was observed in mice treated with a combination of CAd Δ trio + HER2-specific CAR-expressing AdvSTs (i.e. treatment group (i)(b)).

Claims:

1. A method of treating a cancer, comprising administering to a subject:
 - (i) an oncolytic adenovirus (OncAd);
 - (ii) a helper-dependent adenovirus (HDAd) comprising nucleic acid encoding IL-12 and an antagonist anti-PD-L1 antibody; and
 - (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen,wherein the cancer to be treated comprises cells expressing the cancer cell antigen for which the CAR is specific.
2. Use of (i) an oncolytic adenovirus (OncAd), (ii) a helper-dependent adenovirus (HDAd) comprising nucleic acid encoding IL-12 and an antagonist anti-PD-L1 antibody, and (iii) at least one cell comprising a chimeric antigen receptor (CAR) specific for a cancer cell antigen, in the manufacture of a medicament for use in a method of treating a cancer,wherein the cancer to be treated comprises cells expressing the cancer cell antigen for which the CAR is specific.
3. The method or use according to claim 1 or claim 2, wherein the oncolytic adenovirus is derived from adenovirus 5 (Ad5).
4. The method or use according to any one of claims 1 to 3, wherein the oncolytic adenovirus encodes an E1A protein which displays reduced binding to Rb protein as compared to E1A protein encoded by Ad5.
5. The method or use according to any one of claims 1 to 4, wherein the oncolytic adenovirus encodes an E1A protein lacking the amino acid sequence LTCHEACF (SEQ ID NO:52).
6. The method or use according to any one of claims 1 to 5, wherein the oncolytic adenovirus encodes an E1A protein comprising, or consisting of, the amino acid sequence SEQ ID NO:34.
7. The method or use according to any one of claims 1 to 6, wherein the at least one cell comprising a CAR specific for a cancer cell antigen is a T cell.
8. The method or use according to any one of claims 1 to 7, wherein the CAR comprises an antigen binding domain capable of specific binding to HER2.
9. The method or use according to any one of claims 1 to 8, wherein the CAR comprises an antigen-binding domain comprising:

- 5 a VL domain comprising:
 LC-CRD1: SEQ ID NO:10;
 LC-CRD2: SEQ ID NO:11;
 LC-CRD3: SEQ ID NO:12;
and a VH domain comprising:
 HC-CRD1: SEQ ID NO:13;
 HC-CRD2: SEQ ID NO:14;
 HC-CRD3: SEQ ID NO:15;
or
10 a VL domain comprising:
 LC-CRD1: SEQ ID NO:18;
 LC-CRD2: SEQ ID NO:19;
 LC-CRD3: SEQ ID NO:20;
and a VH domain comprising:
15 HC-CRD1: SEQ ID NO:21;
 HC-CRD2: SEQ ID NO:22;
 HC-CRD3: SEQ ID NO:23;
or
20 a VL domain comprising:
 LC-CRD1: SEQ ID NO:26;
 LC-CRD2: SEQ ID NO:27;
 LC-CRD3: SEQ ID NO:28;
and a VH domain comprising:
25 HC-CRD1: SEQ ID NO:29;
 HC-CRD2: SEQ ID NO:30;
 HC-CRD3: SEQ ID NO:31;
or
30 a VL domain comprising:
 LC-CRD1: SEQ ID NO:57;
 LC-CRD2: SEQ ID NO:58;
 LC-CRD3: SEQ ID NO:59;
and a VH domain comprising:
35 HC-CRD1: SEQ ID NO:60;
 HC-CRD2: SEQ ID NO:61;
 HC-CRD3: SEQ ID NO:62.

10. The method or use according to claim 9, wherein the CAR comprises an antigen binding domain comprising:

- 5 or
a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:16 and a VH comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:17;
- 10 or
a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:24 and a VH comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:25;
- 15 or
a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:32 and a VH comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:33;
- or
a VL comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:63 and a VH comprising, or consisting of, an amino acid sequence having at least 75% sequence identity to SEQ ID NO:64.

20 11. The method or use according to any one of claims 1 to 10, wherein the helper-dependent adenovirus comprising nucleic acid encoding IL-12 and and an antagonist anti-PD-L1 antibodyfurther comprises a nucleic acid encoding a thymidine kinase.

12. The method or use according to claim 11, wherein the thymidine kinase is HSV-1 thymidine kinase.

25 13. The method or use according to any one of claims 1 to 12, wherein the method of treating a cancer comprises:

- 30 (a) isolating at least one cell from a subject;
(b) modifying the at least one cell to express or comprise a CAR specific for a cancer cell antigen, or a nucleic acid encoding a CAR specific for a cancer cell antigen,
(c) optionally expanding the modified at least one cell, and;
(d) administering the modified at least one cell to a subject.

35 14. The method or use according to any one of claims 1 to 13, wherein the cancer is selected from head and neck cancer, nasopharyngeal carcinoma (NPC), cervical carcinoma (CC), oropharyngeal carcinoma (OPC), gastric carcinoma (GC), hepatocellular carcinoma (HCC) and lung cancer.

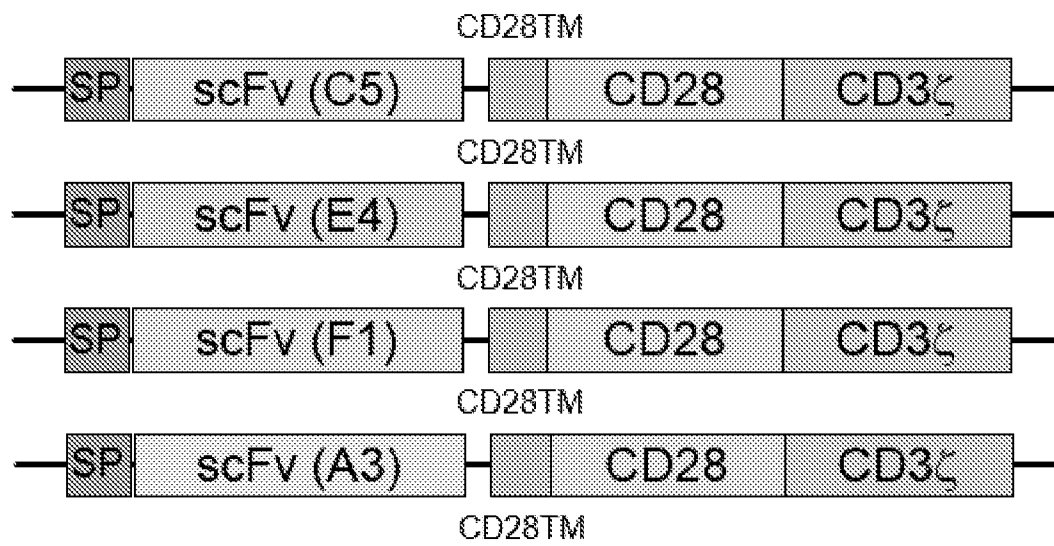


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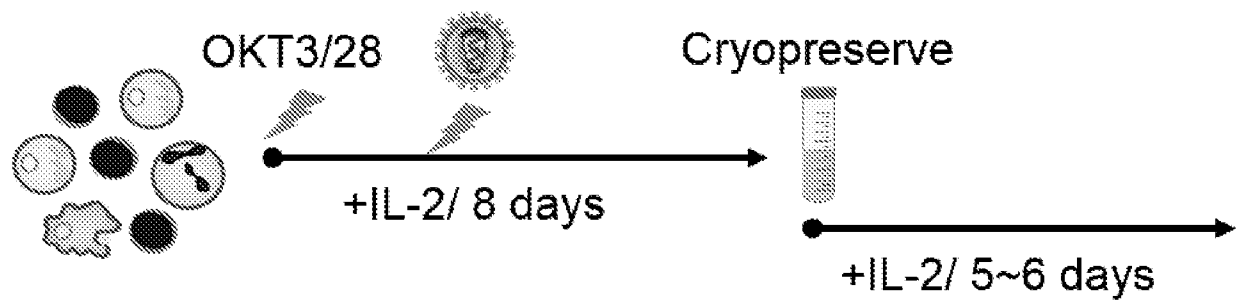


Figure 1B

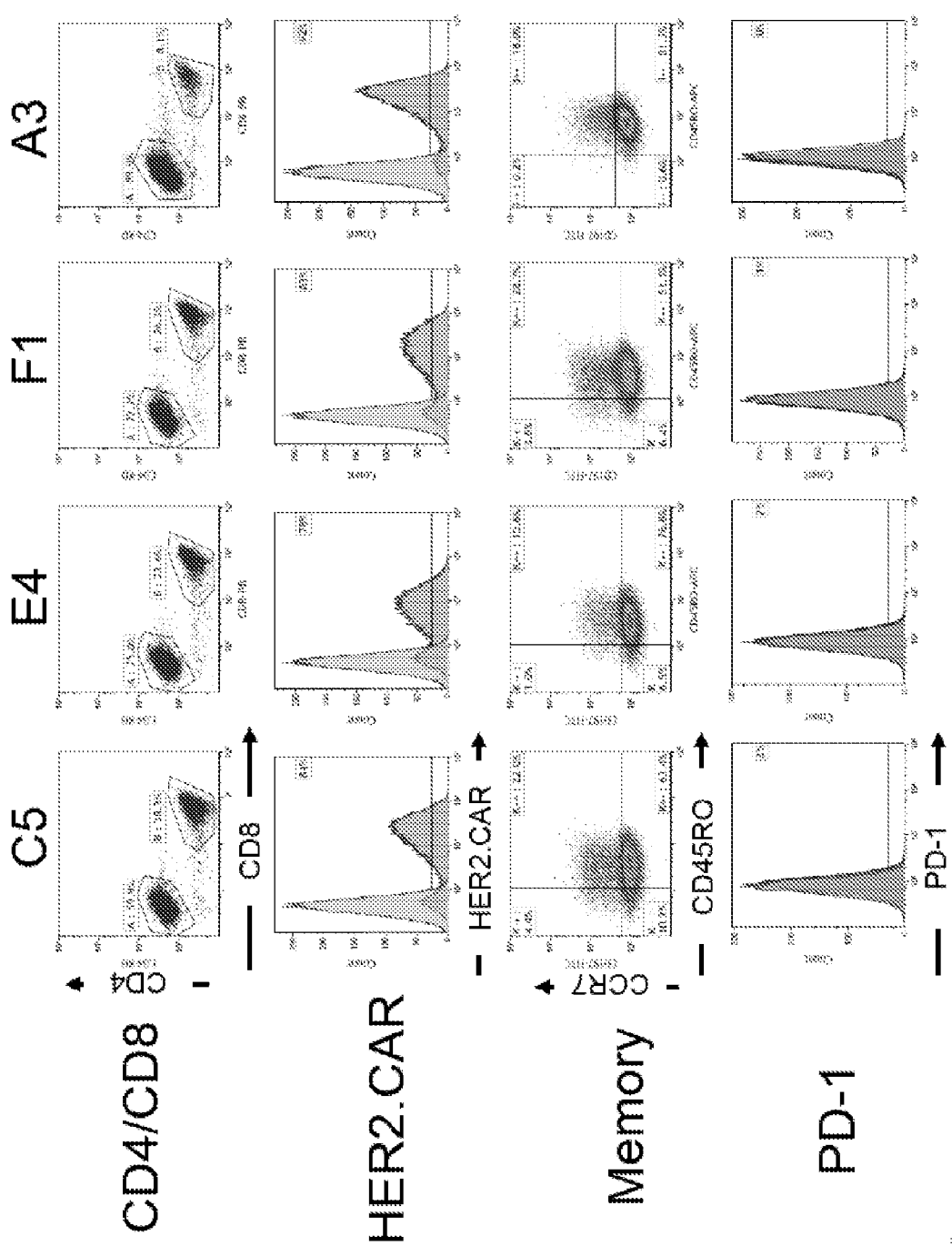


Figure 2

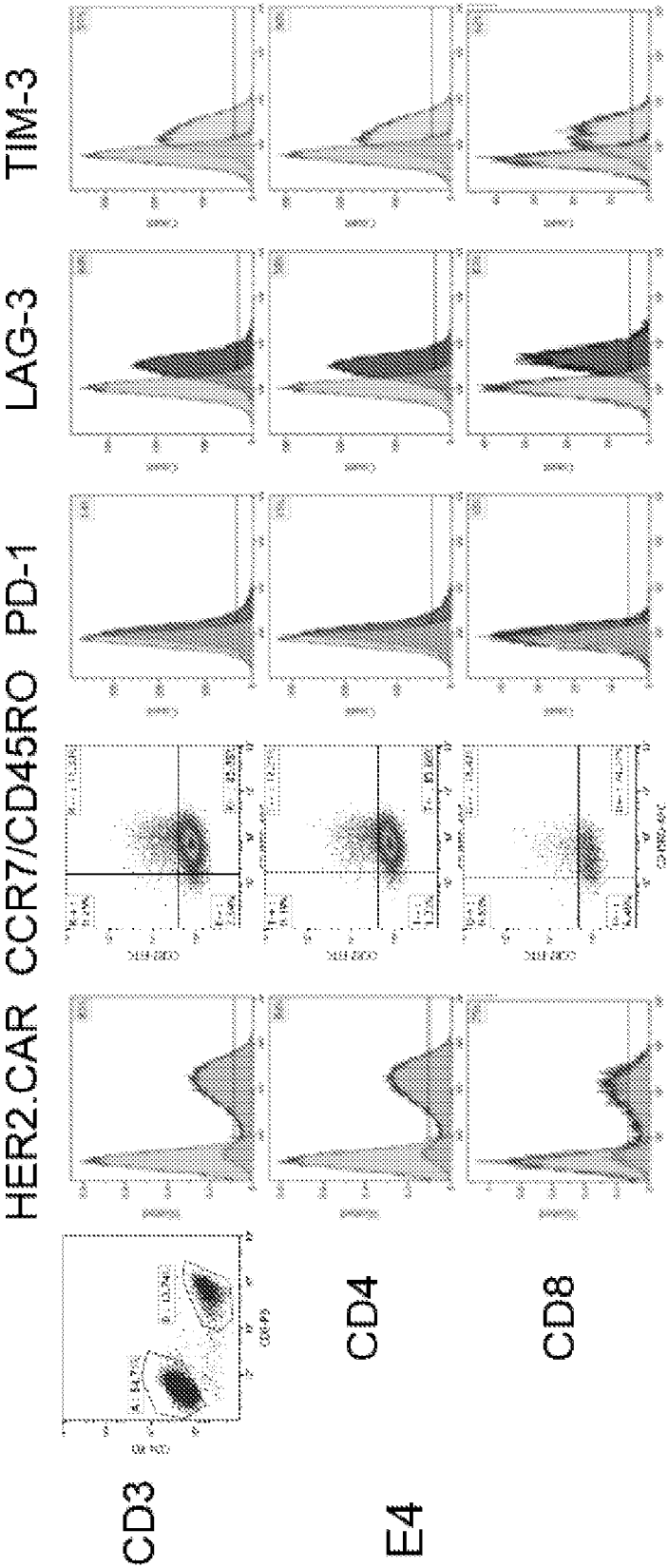


Figure 3

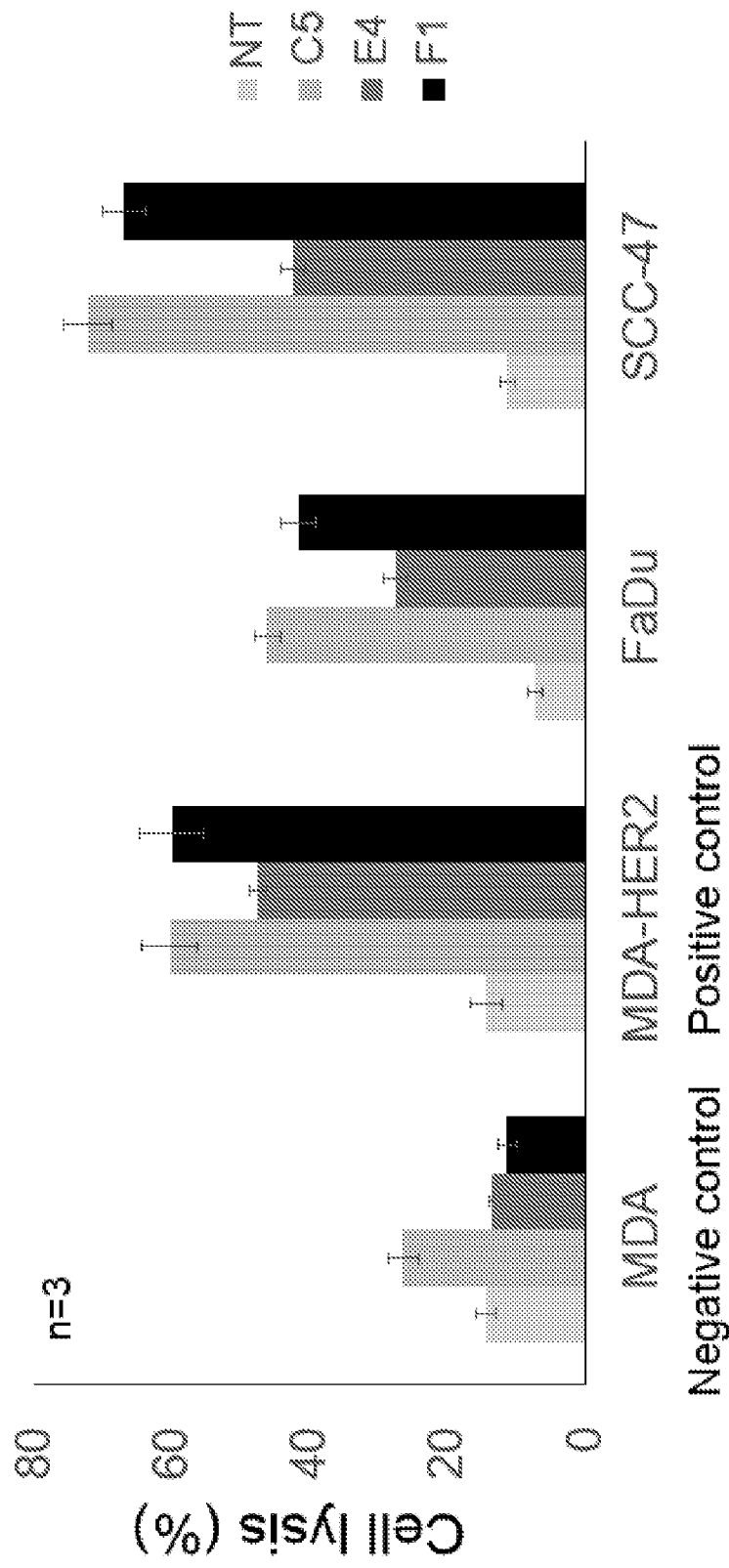


Figure 4A

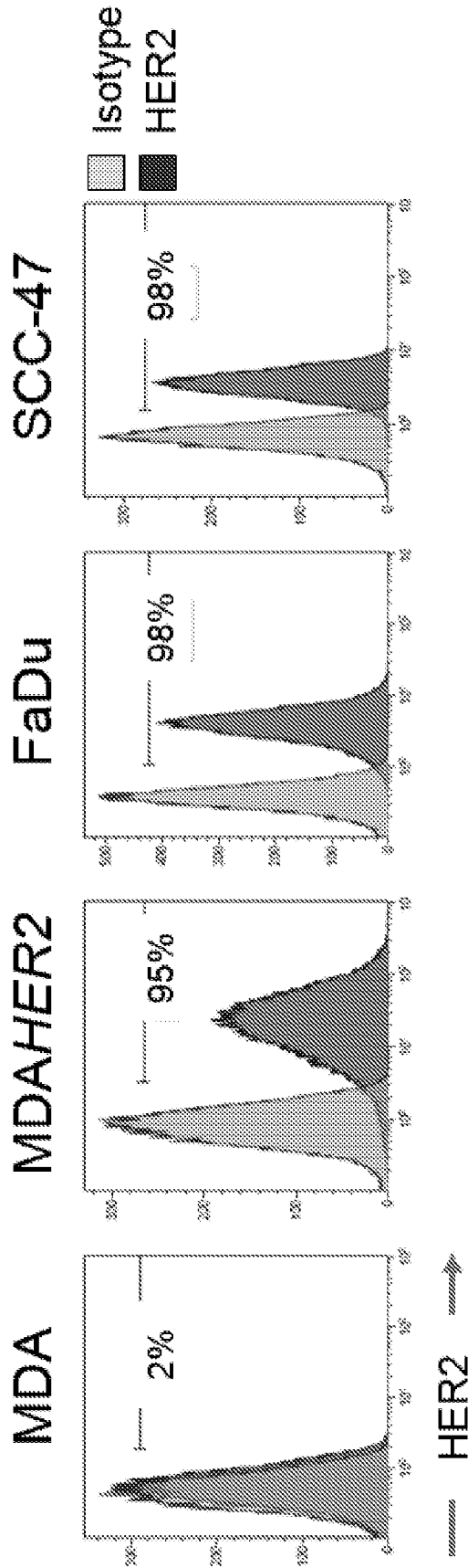


Figure 4B

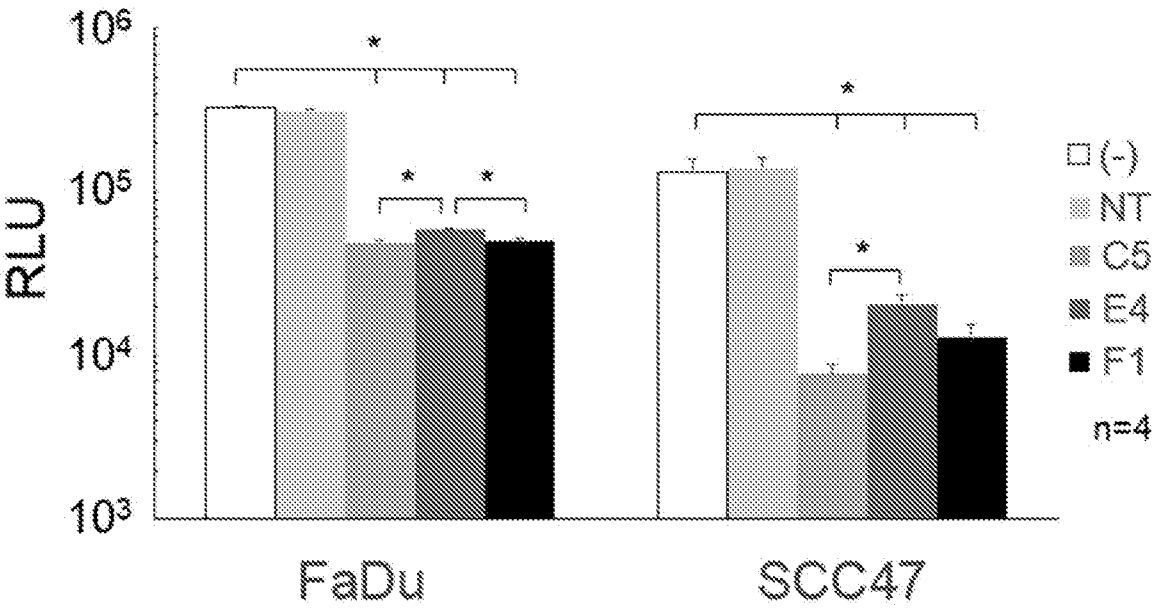


Figure 5

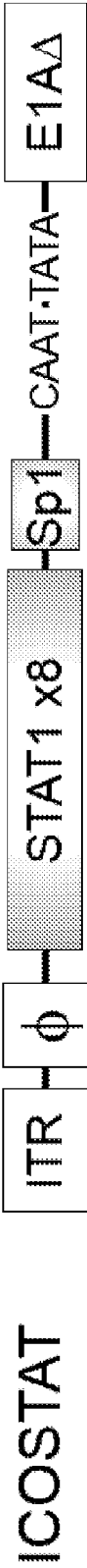


Figure 6

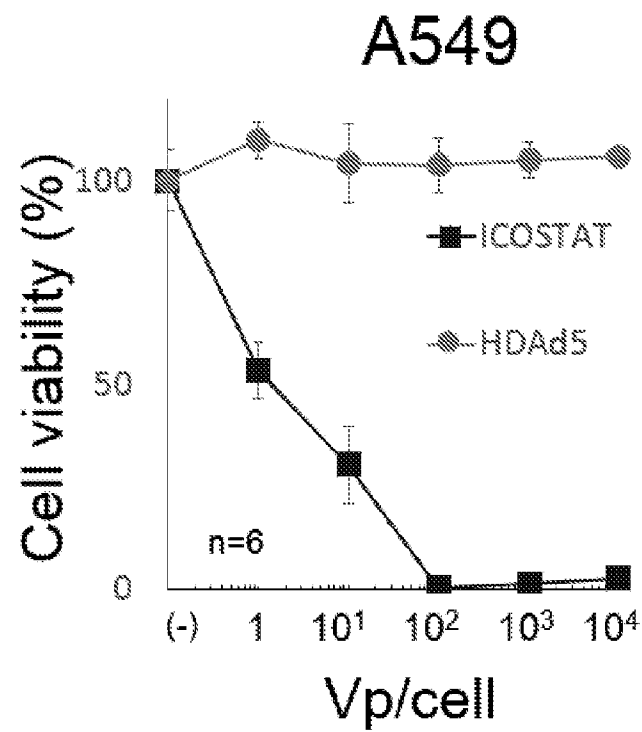


Figure 7A

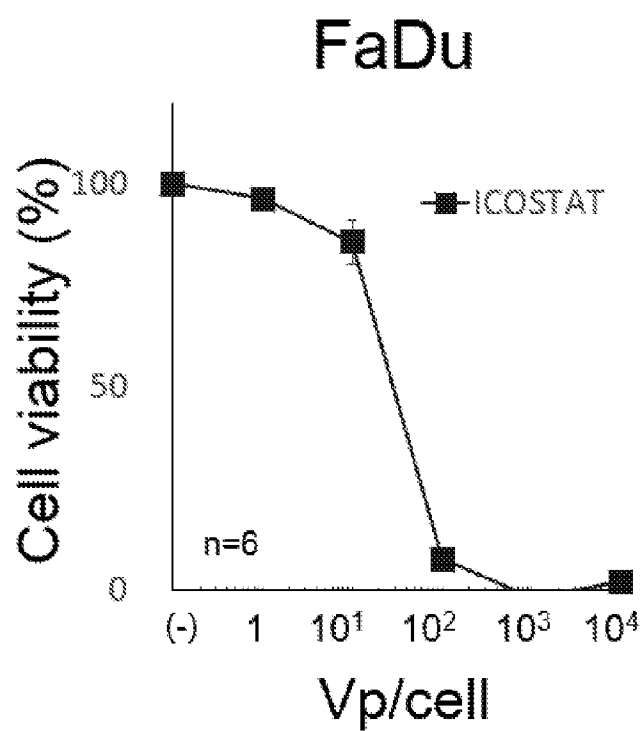


Figure 7B

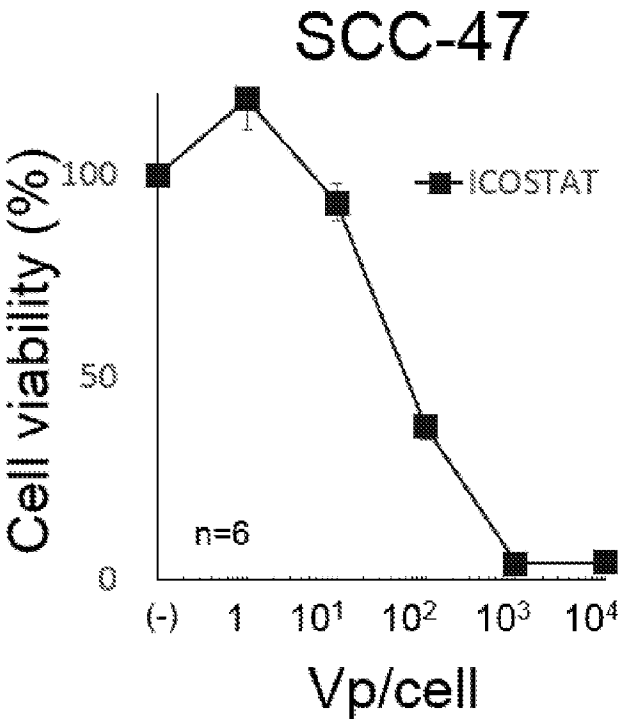


Figure 7C

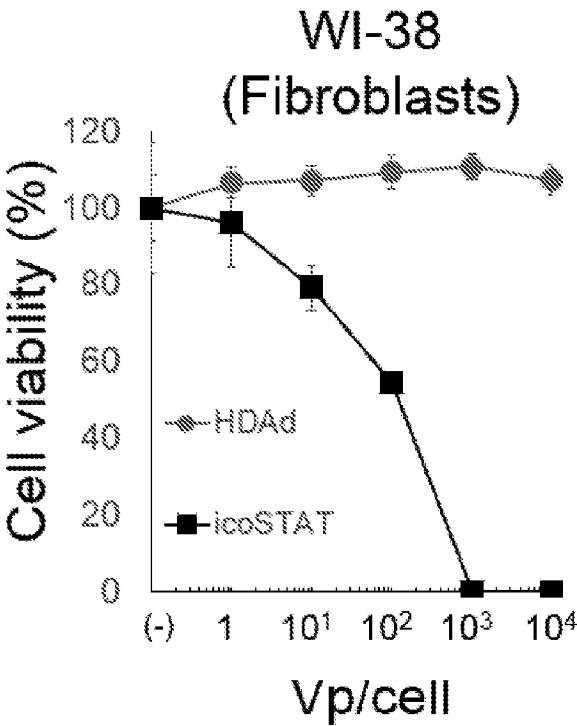


Figure 7D

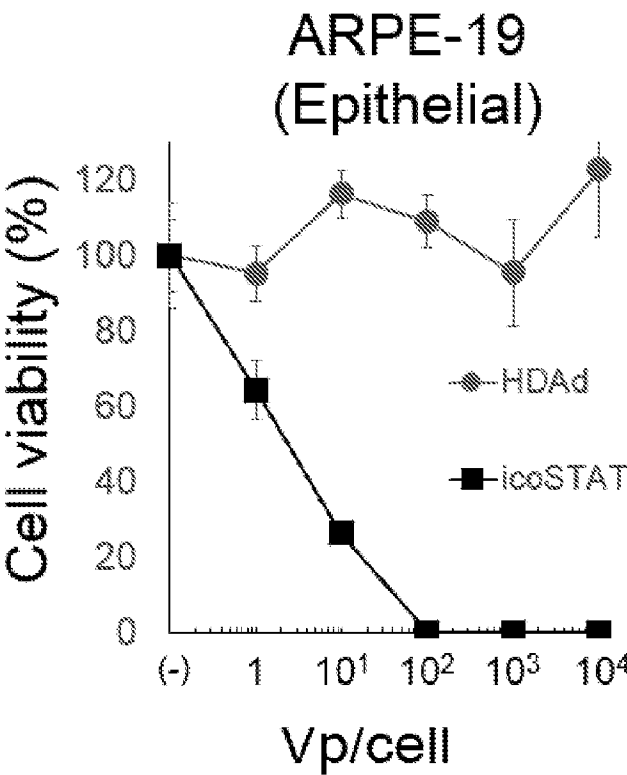


Figure 7E

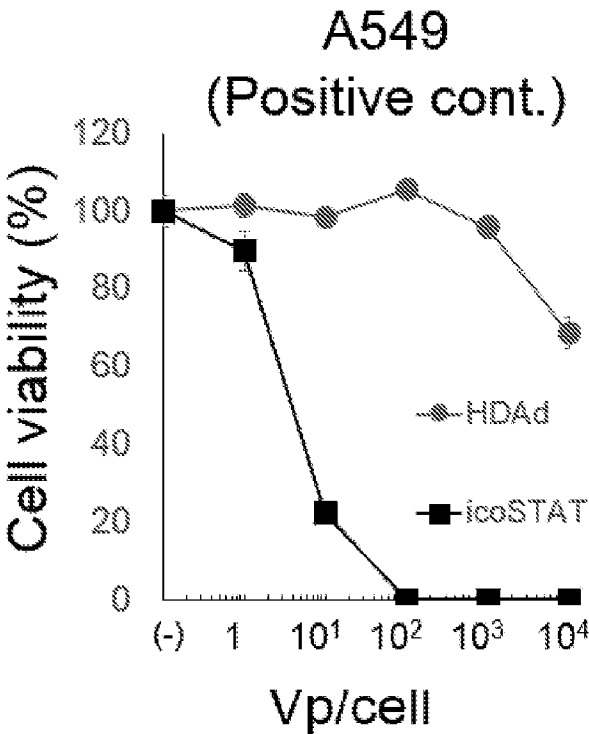


Figure 7F

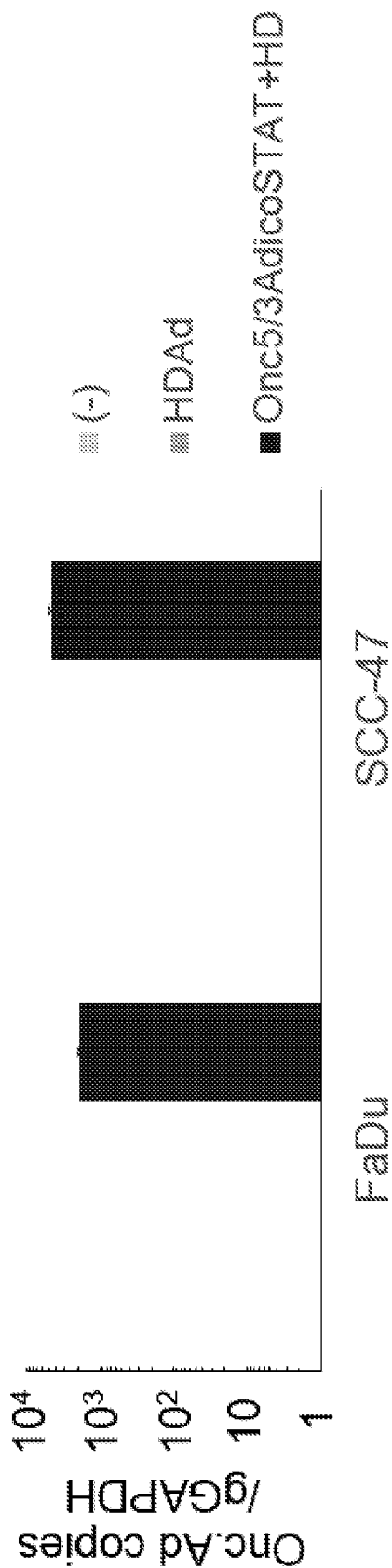


Figure 8A

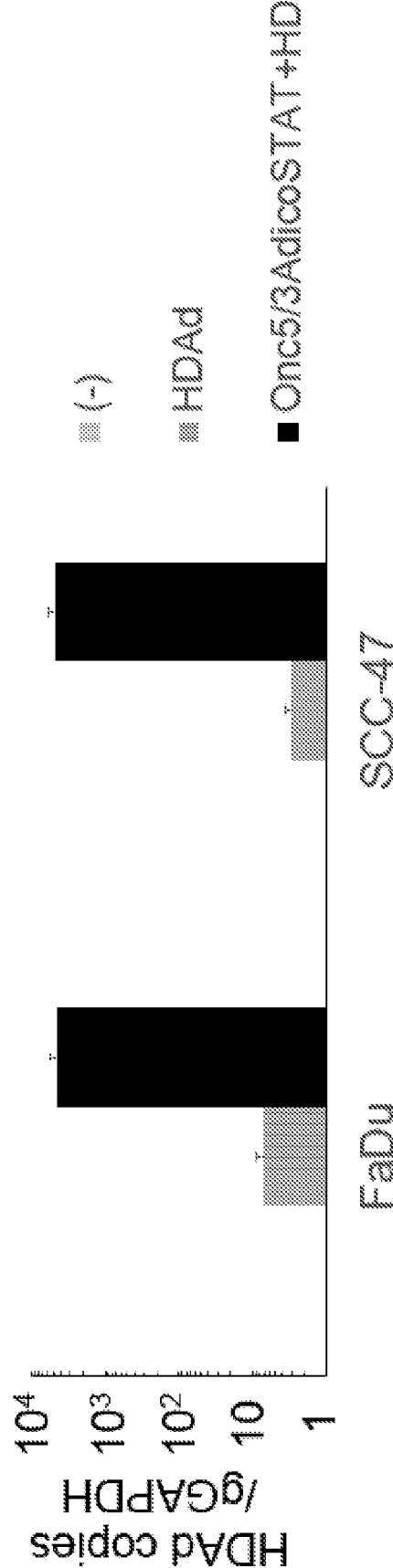


Figure 8B

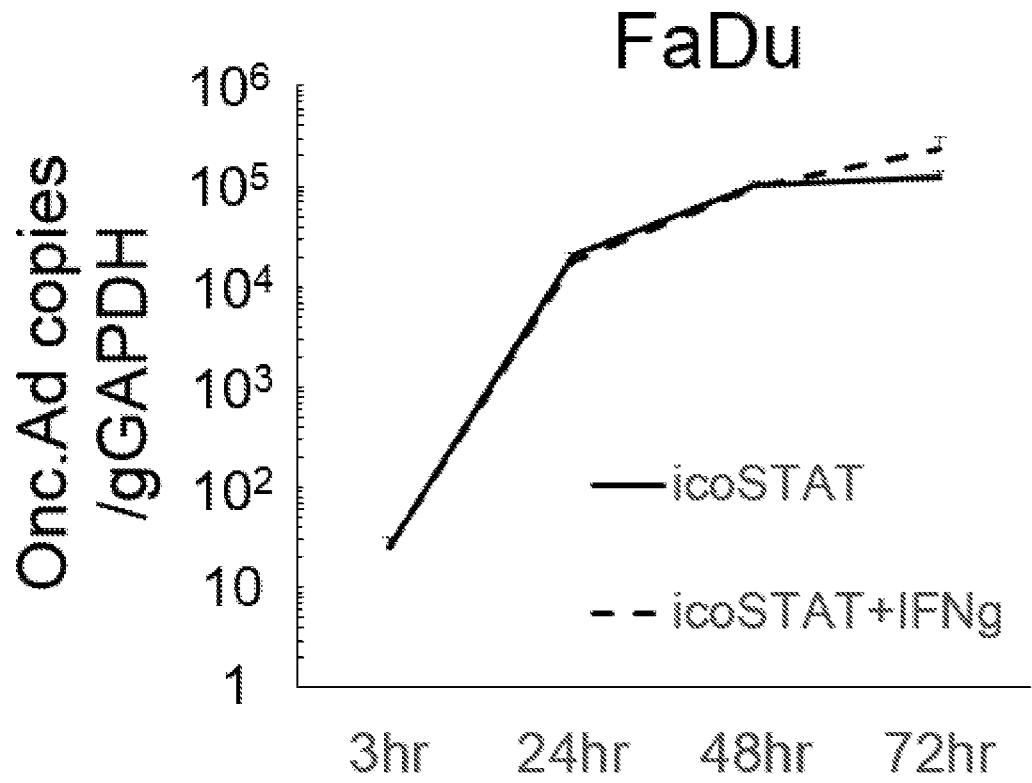


Figure 9A

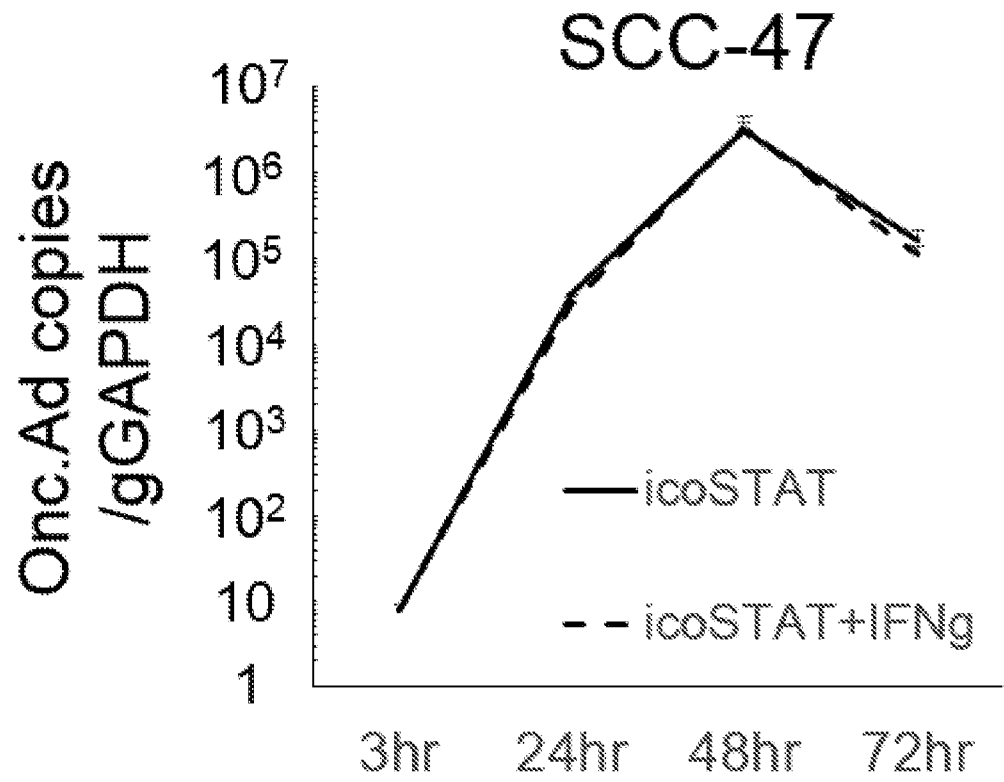


Figure 9B

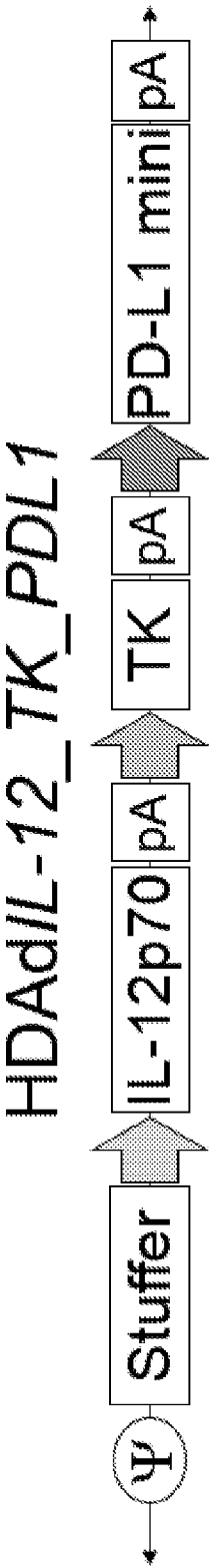


Figure 10A

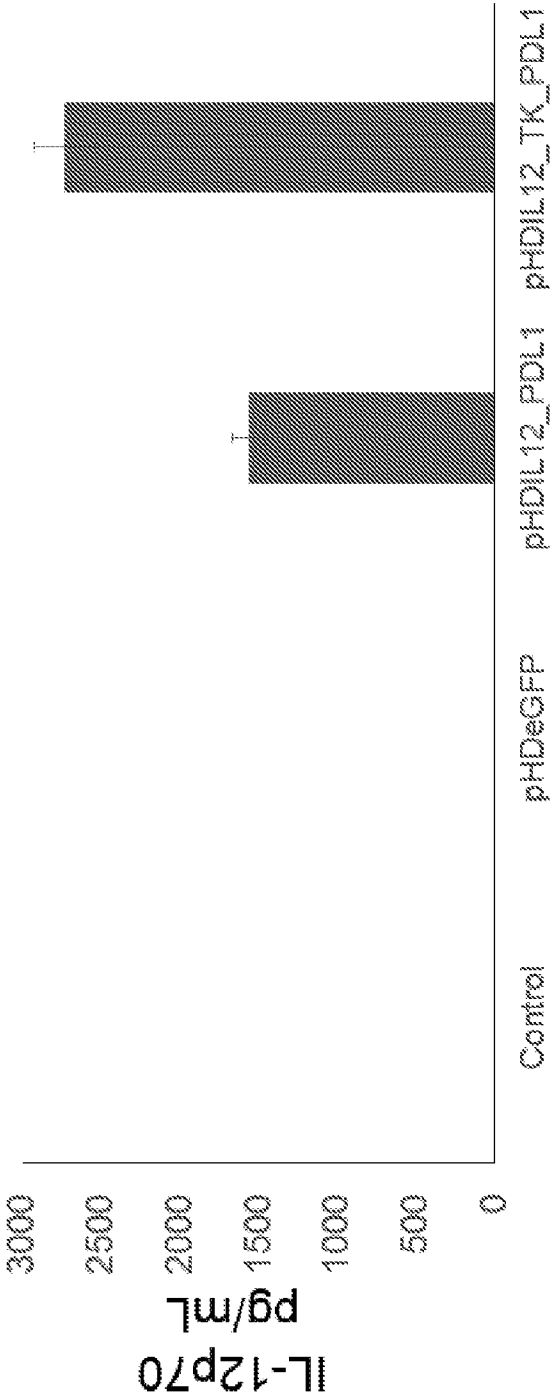


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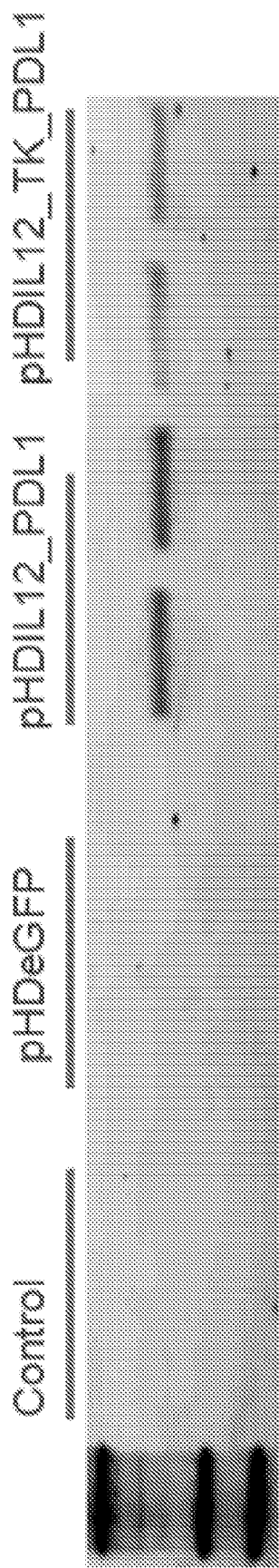


Figure 10C

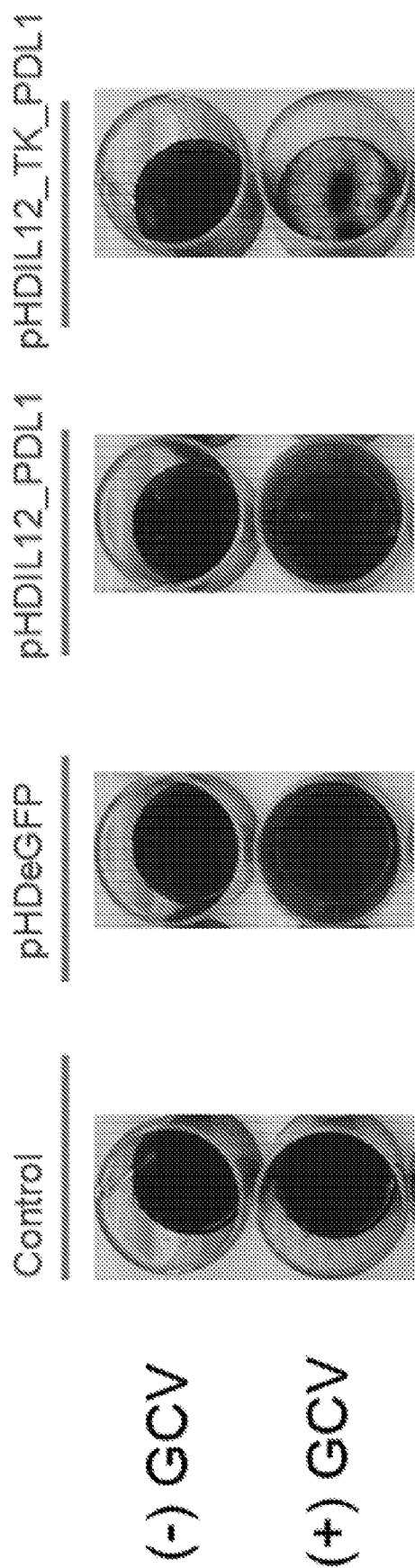


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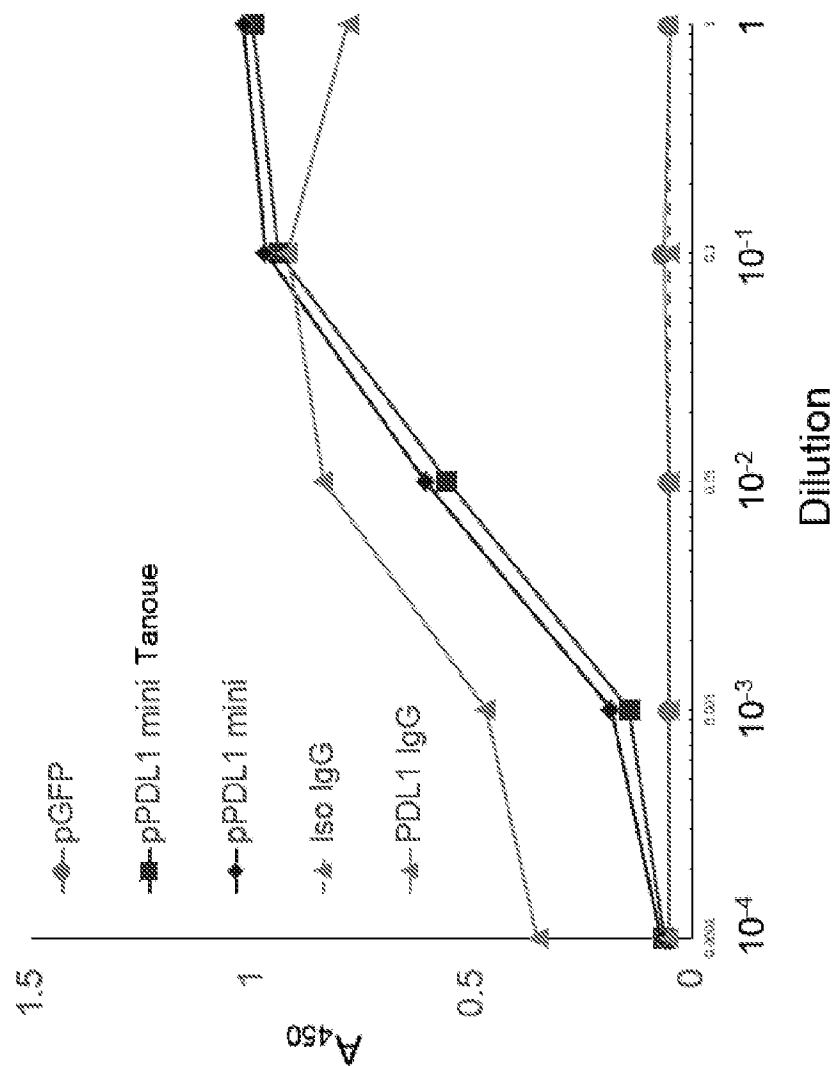


Figure 11

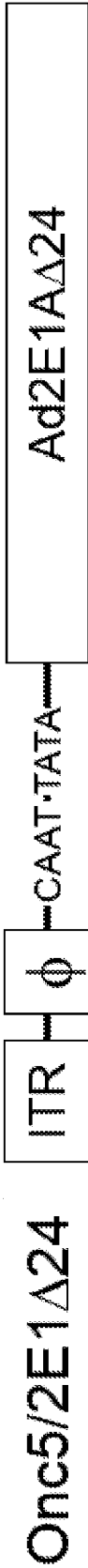


Figure 12A

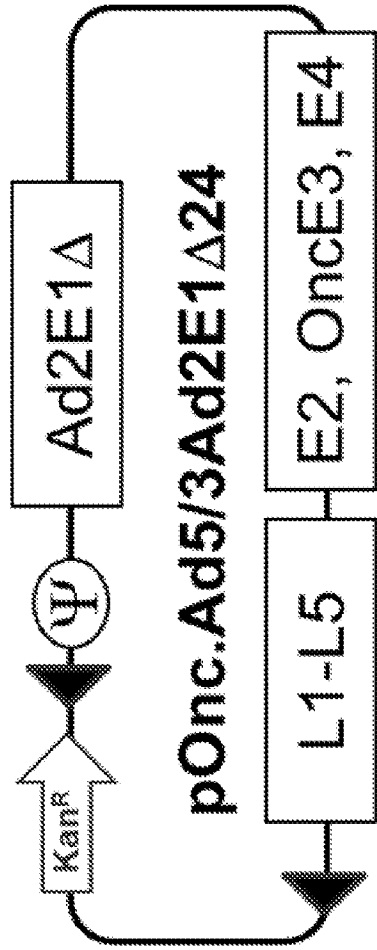


Figure 12B

17/44

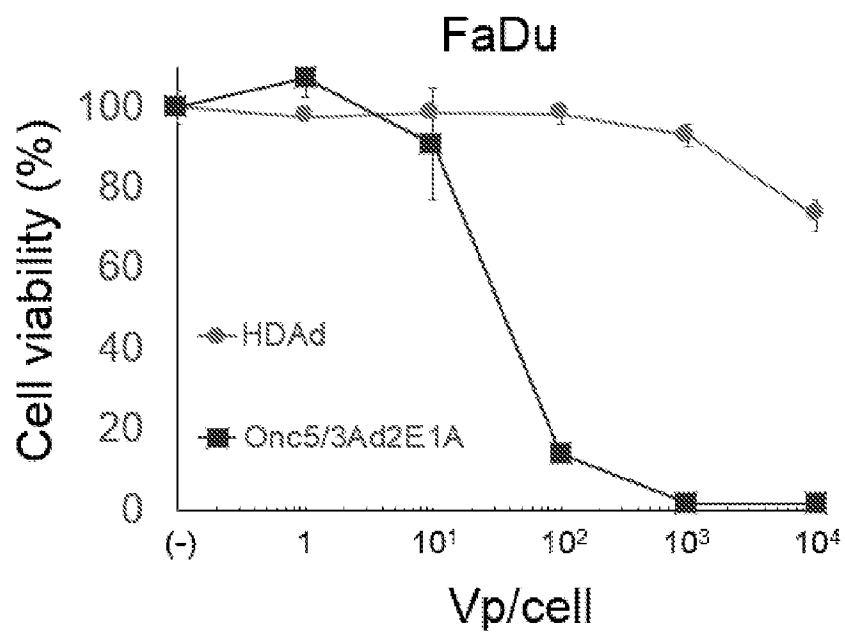


Figure 13A

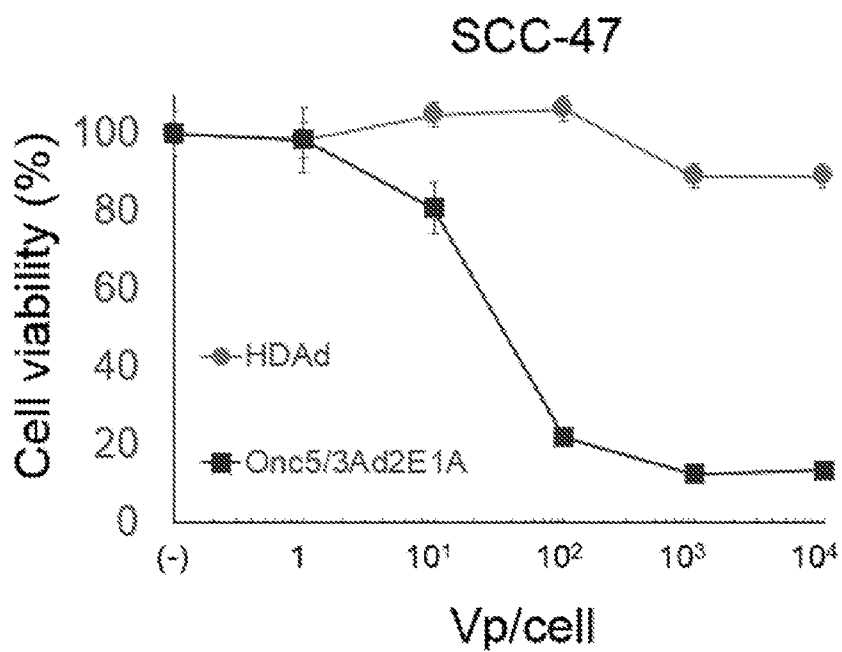


Figure 13B

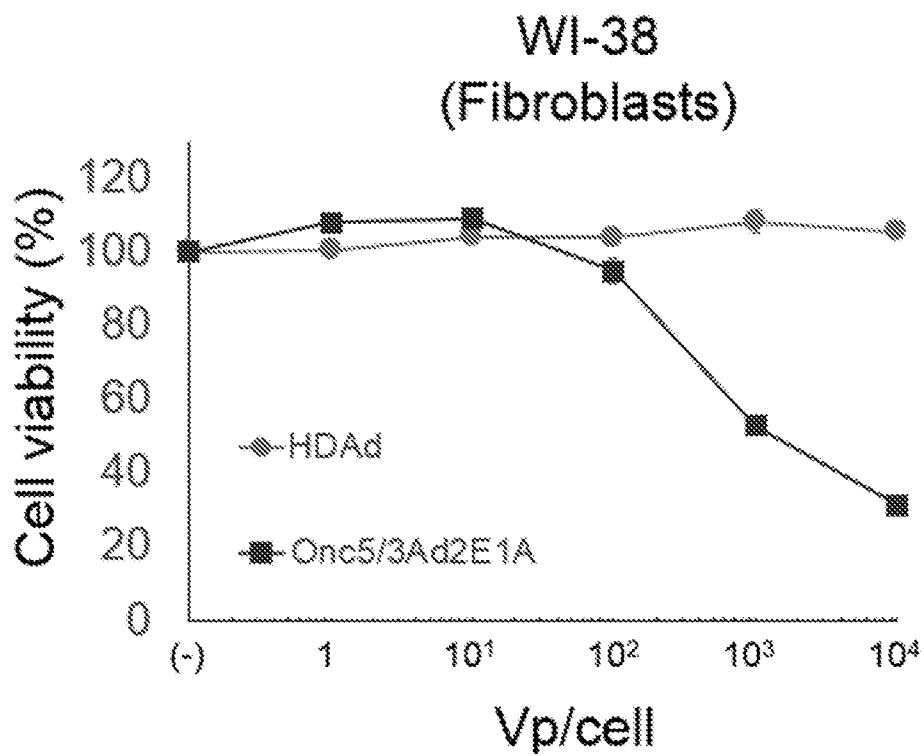


Figure 13C

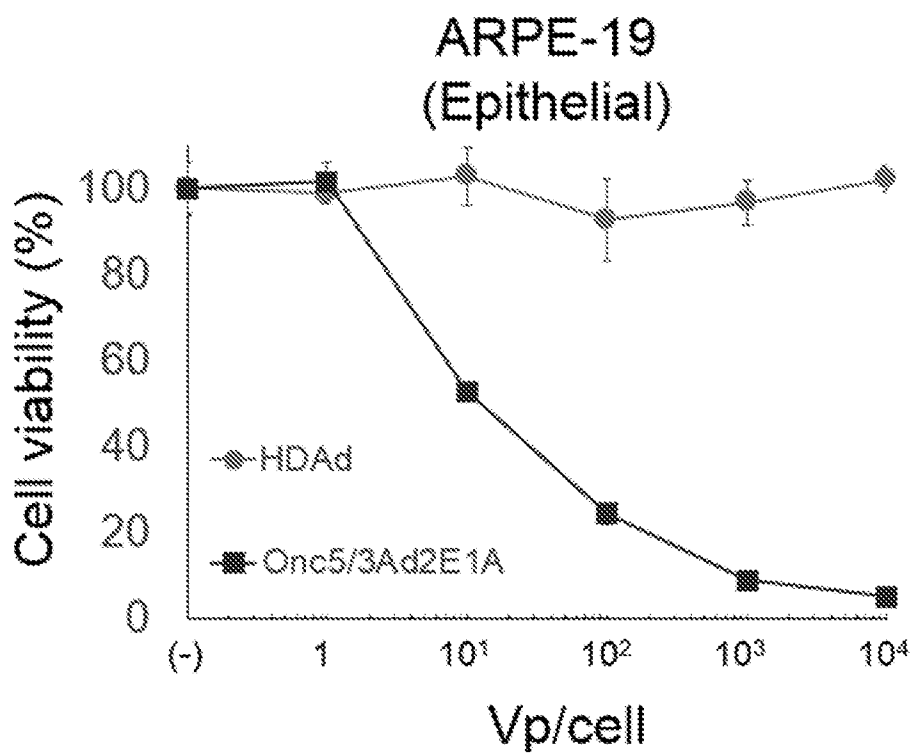


Figure 13D

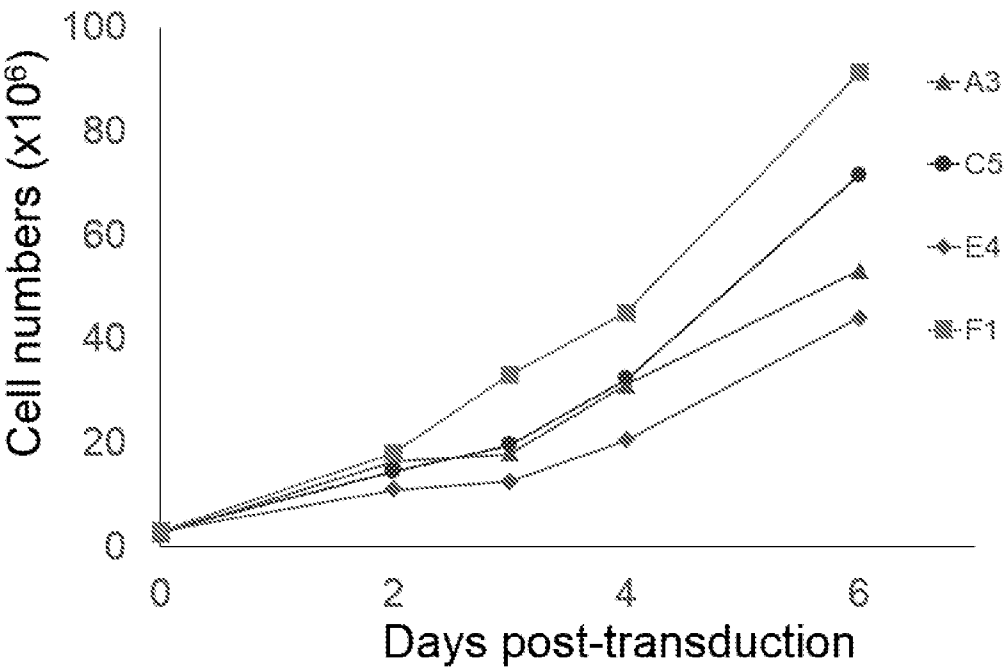


Figure 14

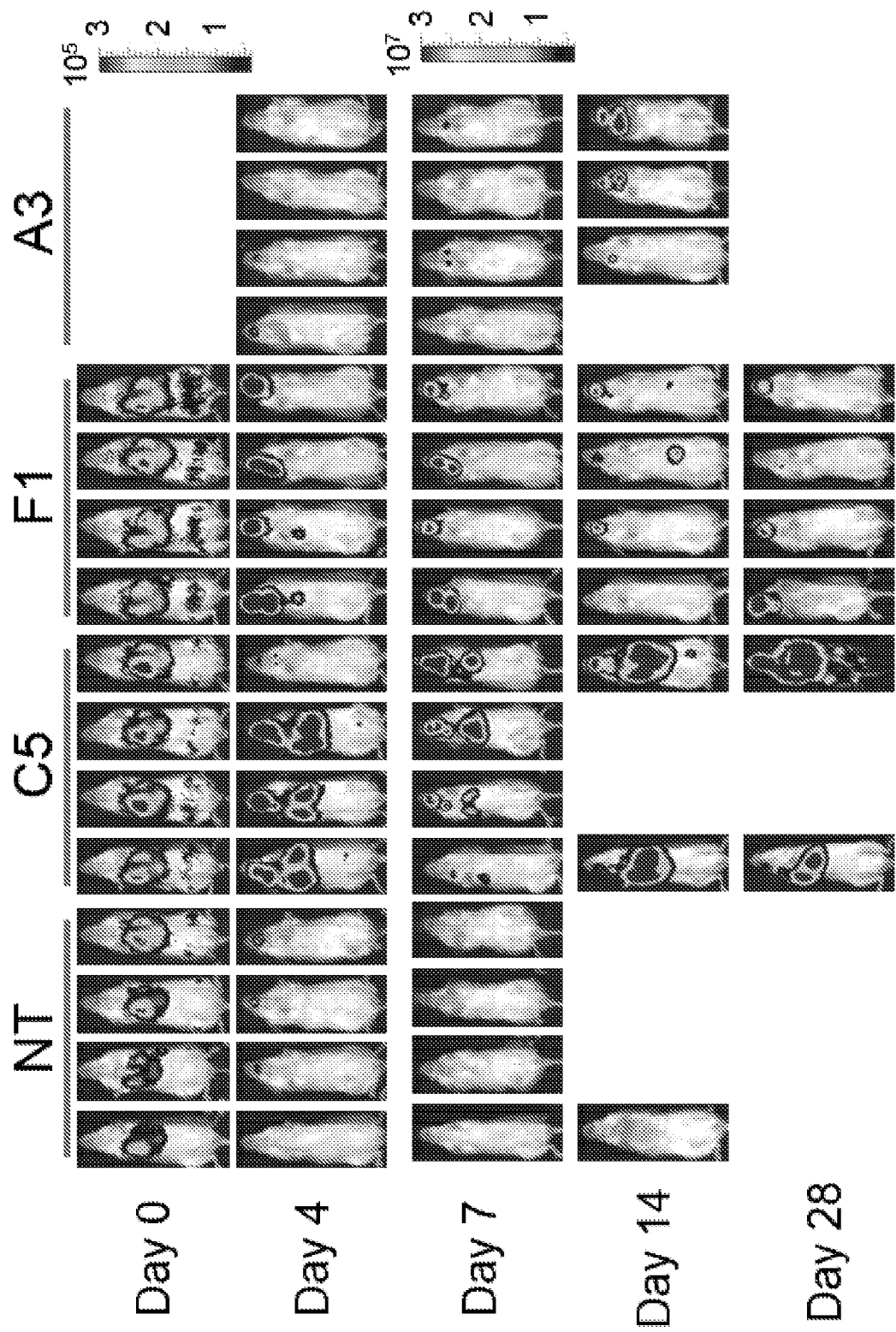


Figure 15A

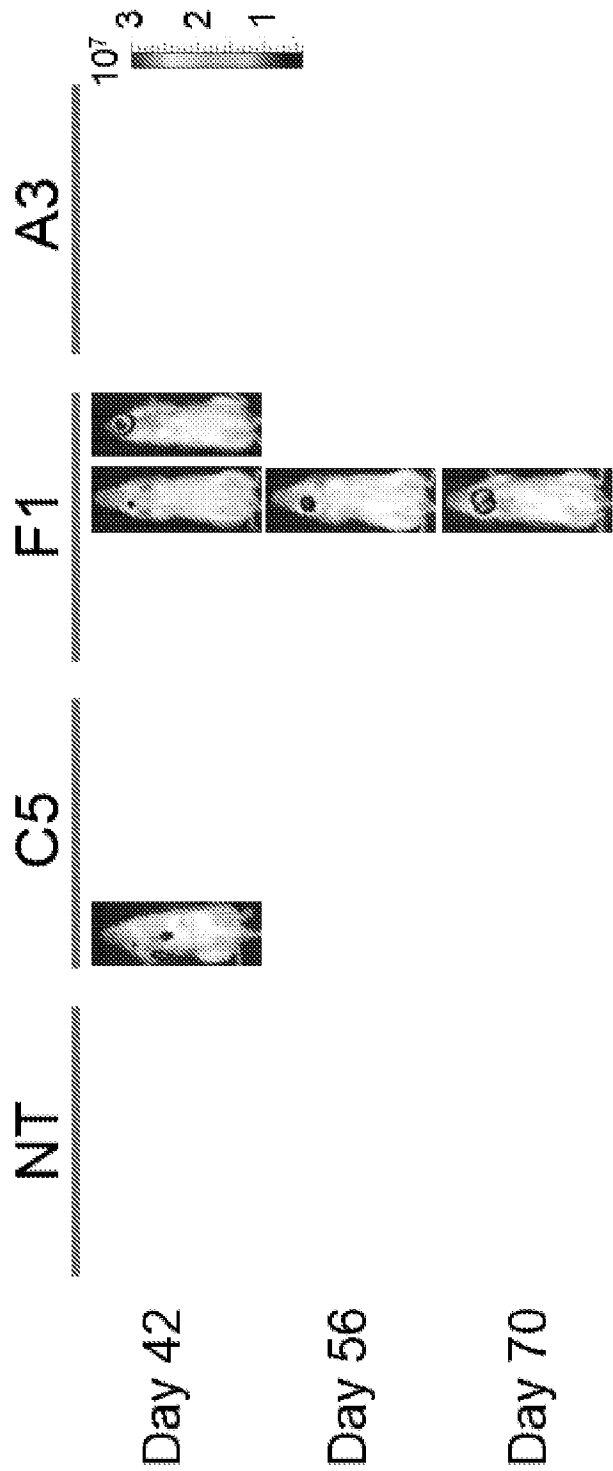


Figure 15B

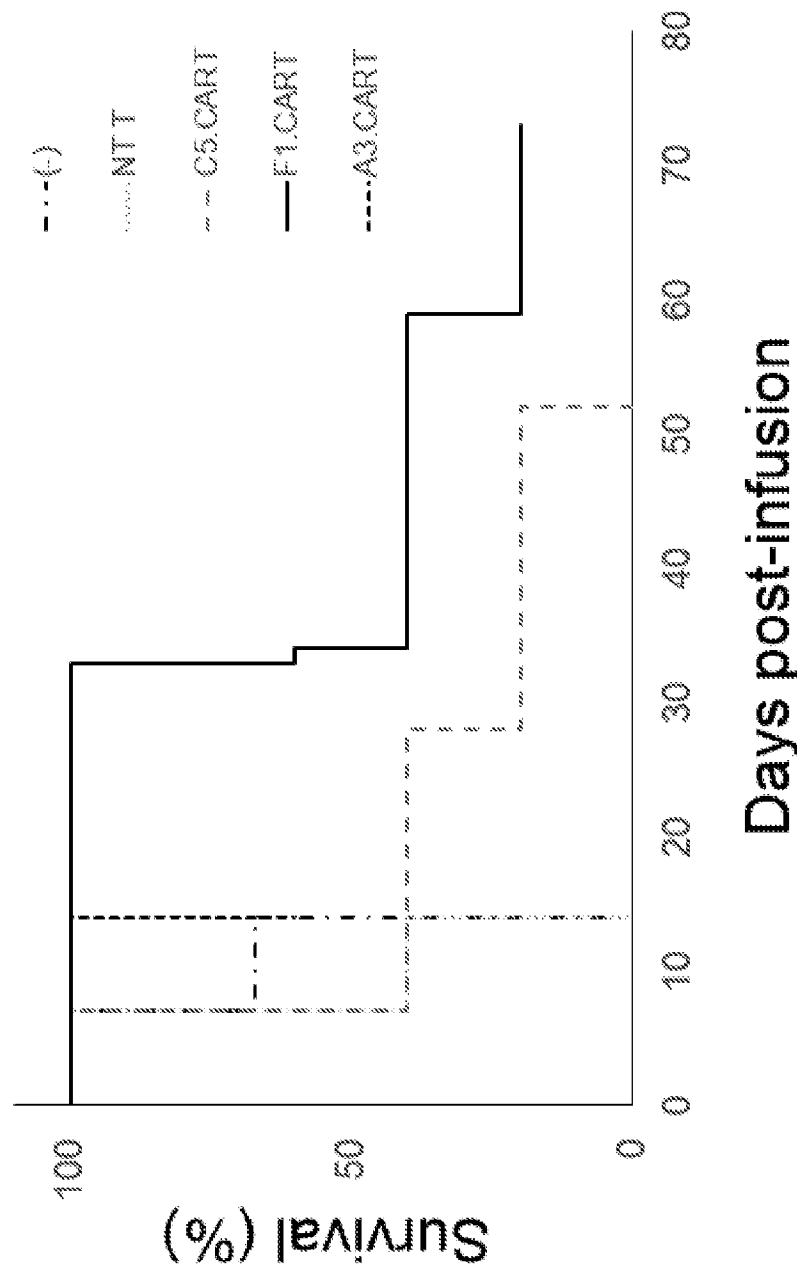


Figure 15C

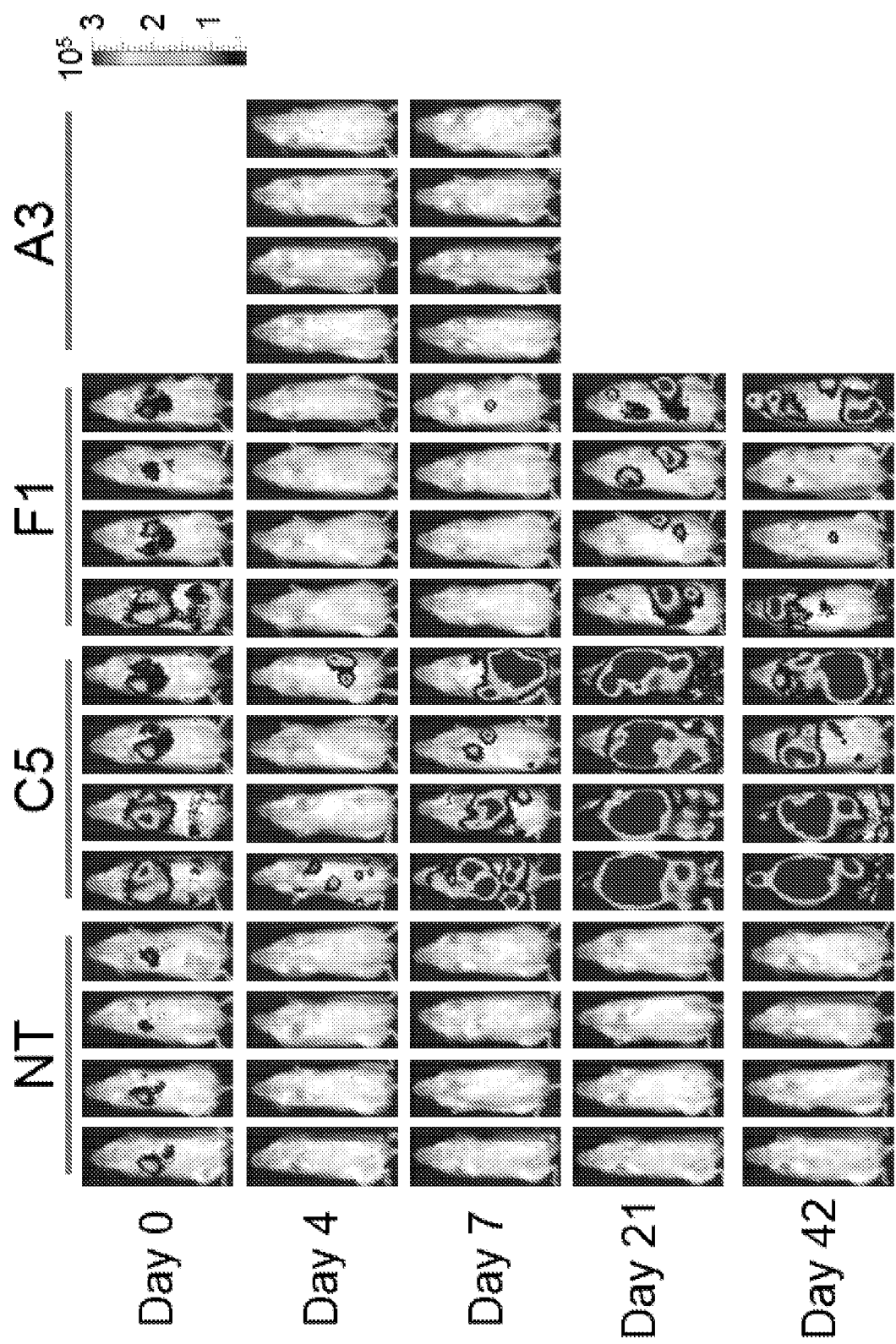


Figure 16A

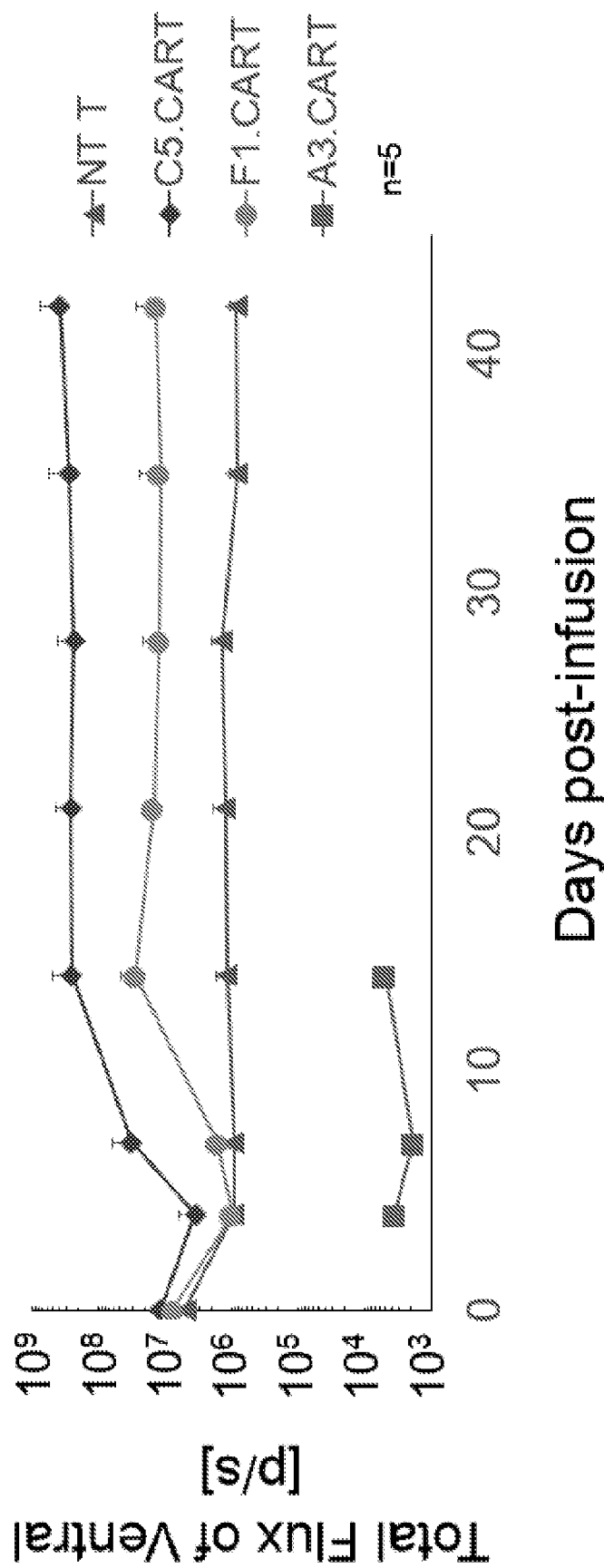


Figure 16B

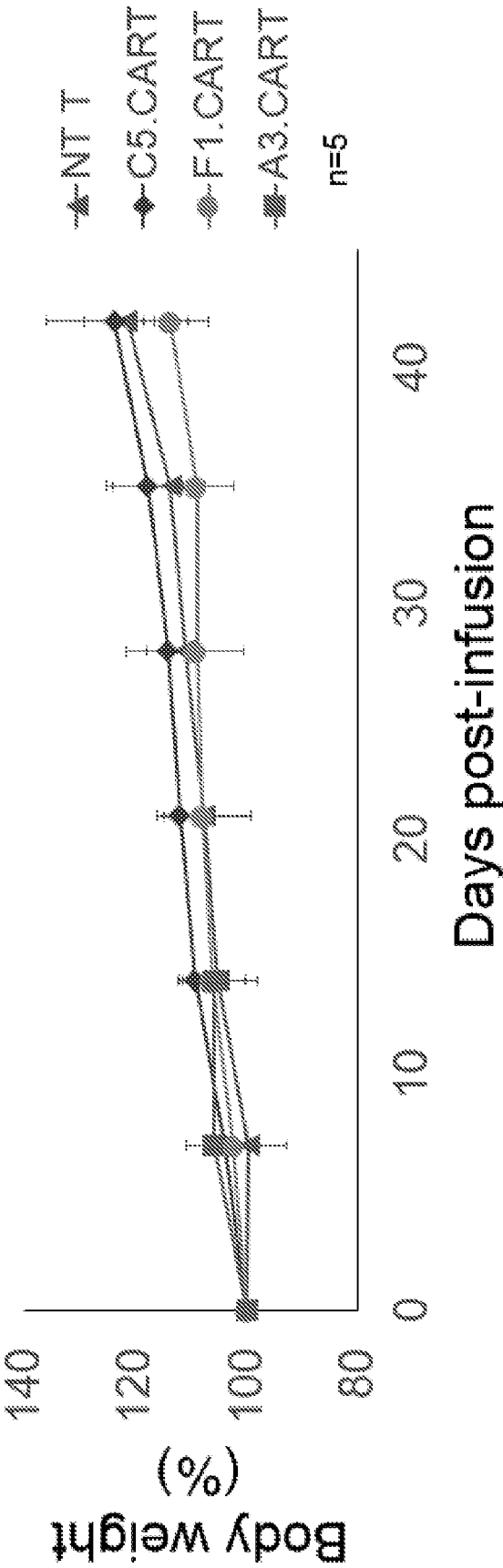


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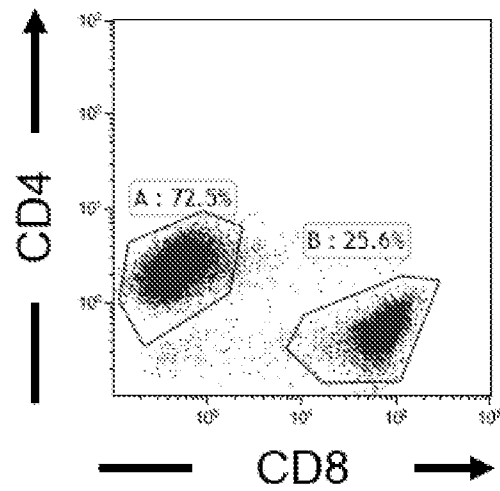


Figure 17A

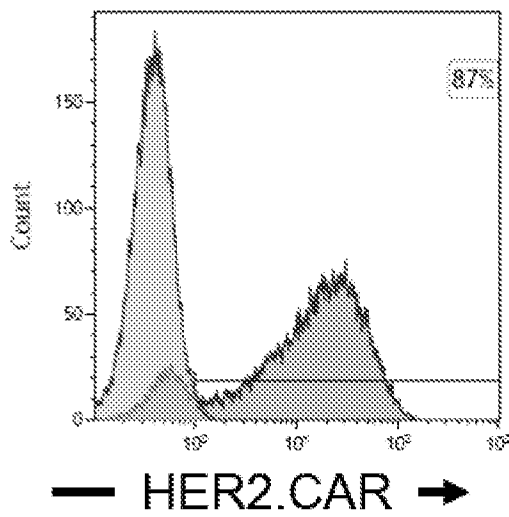


Figure 17B

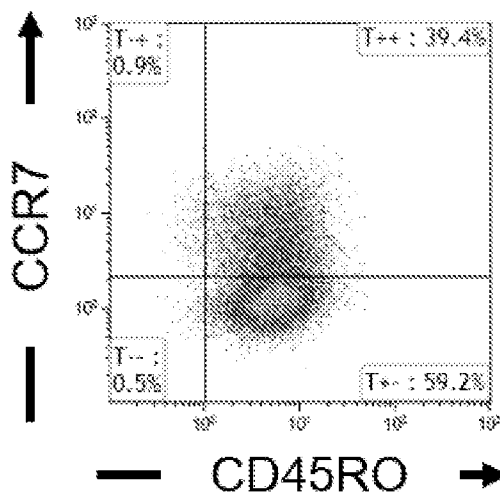


Figure 17C

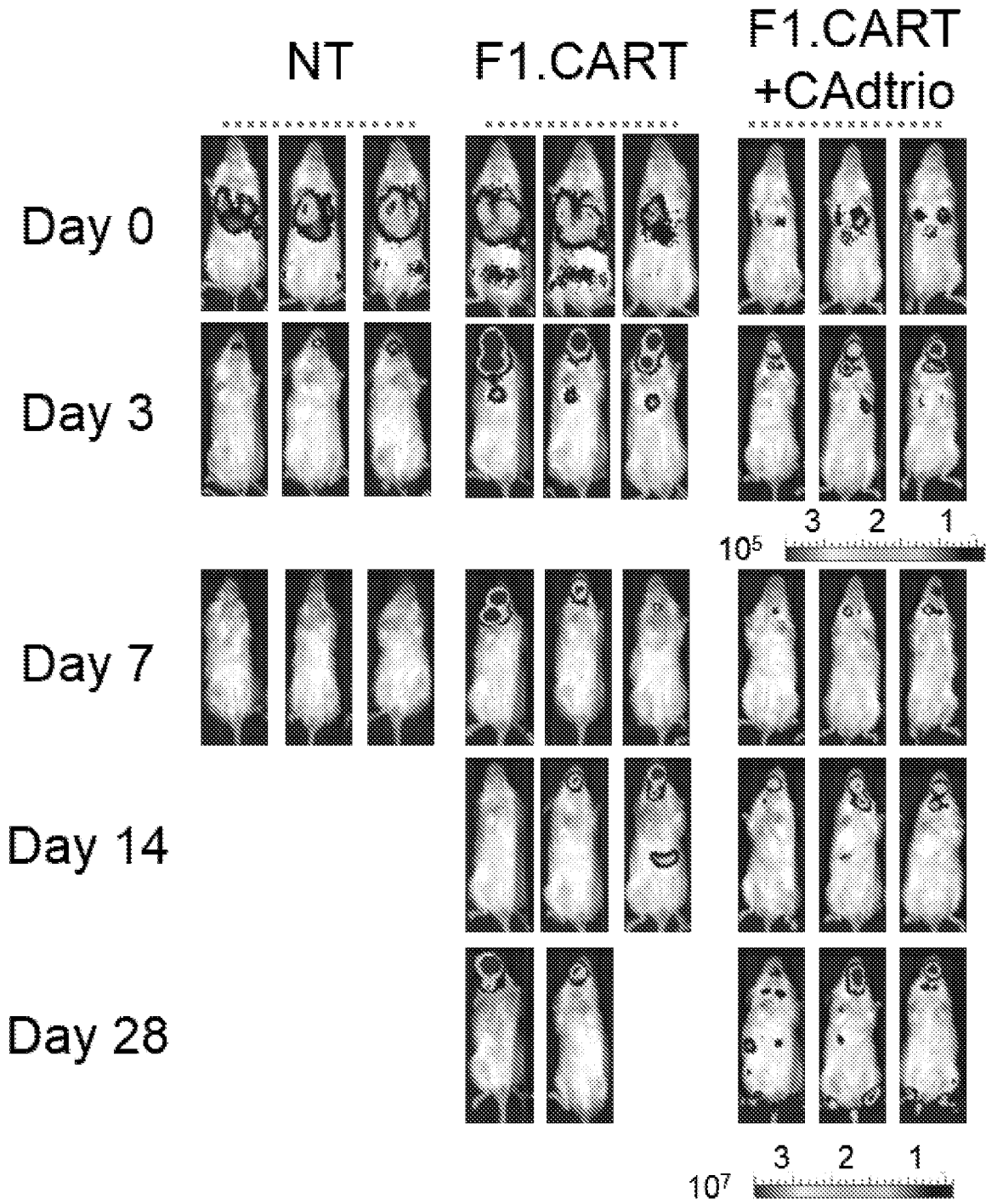


Figure 18A

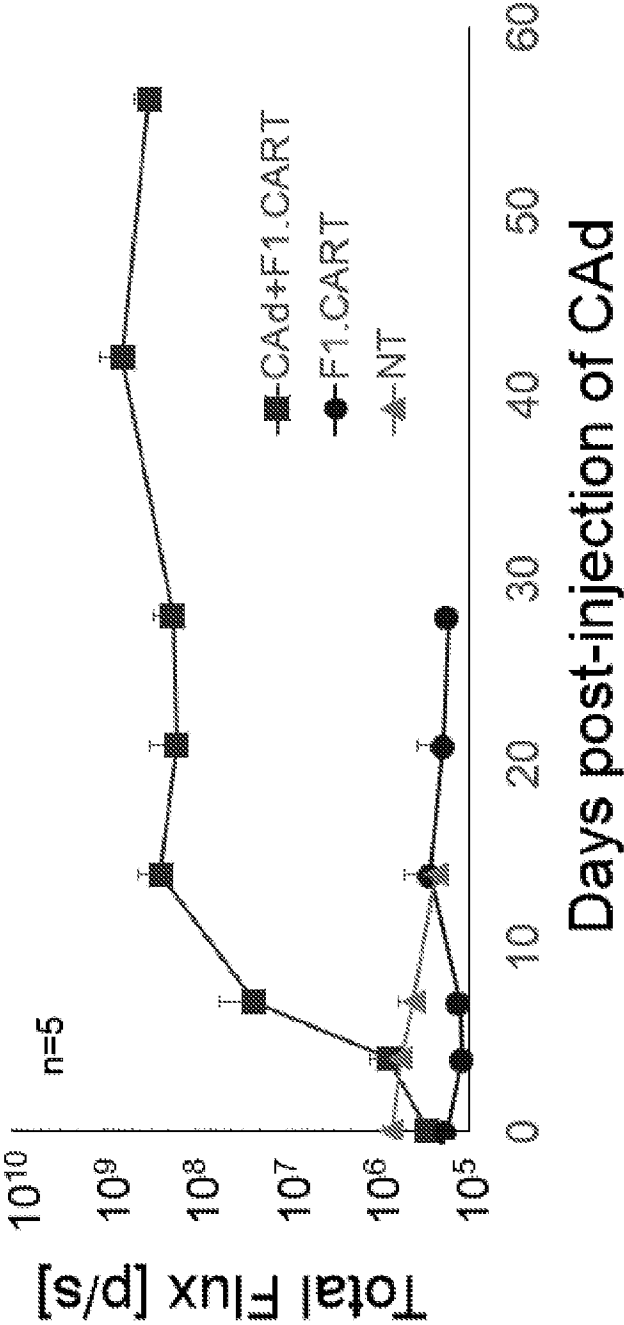


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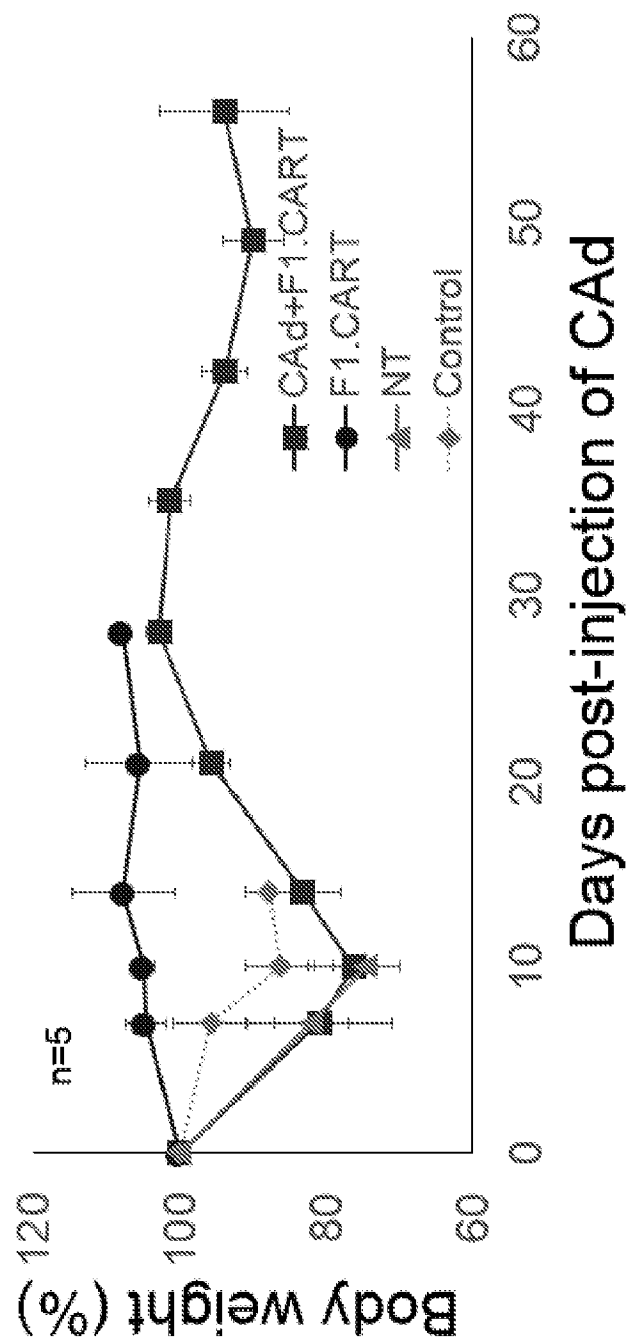


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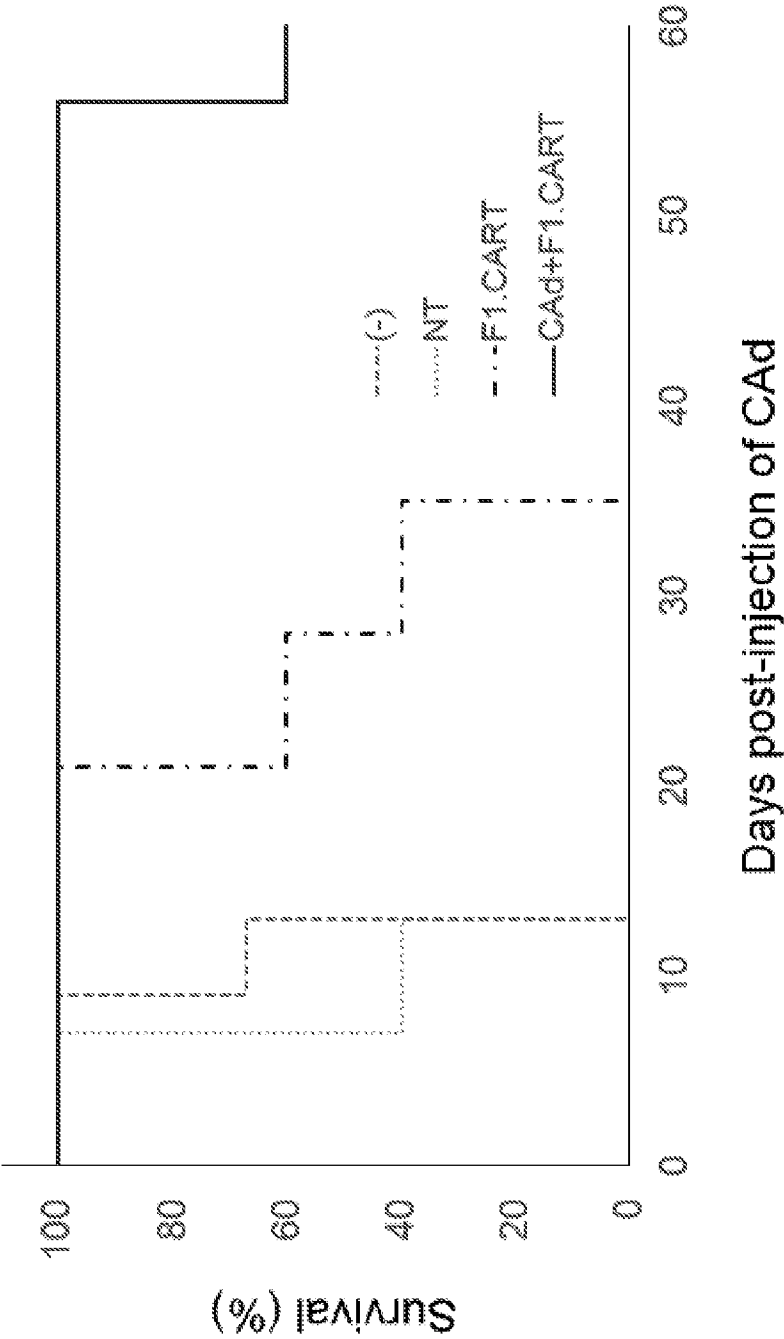


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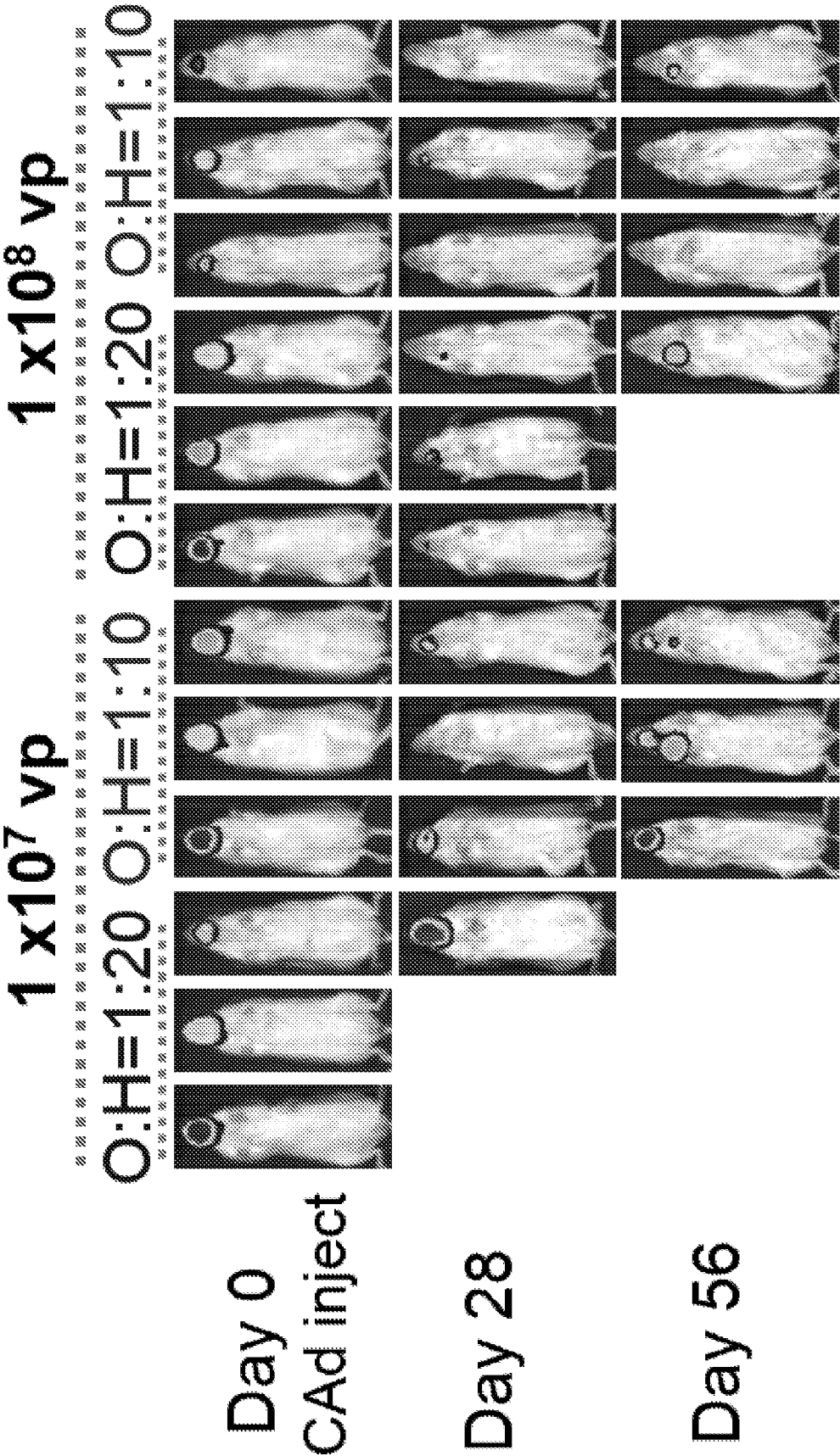


Figure 19A

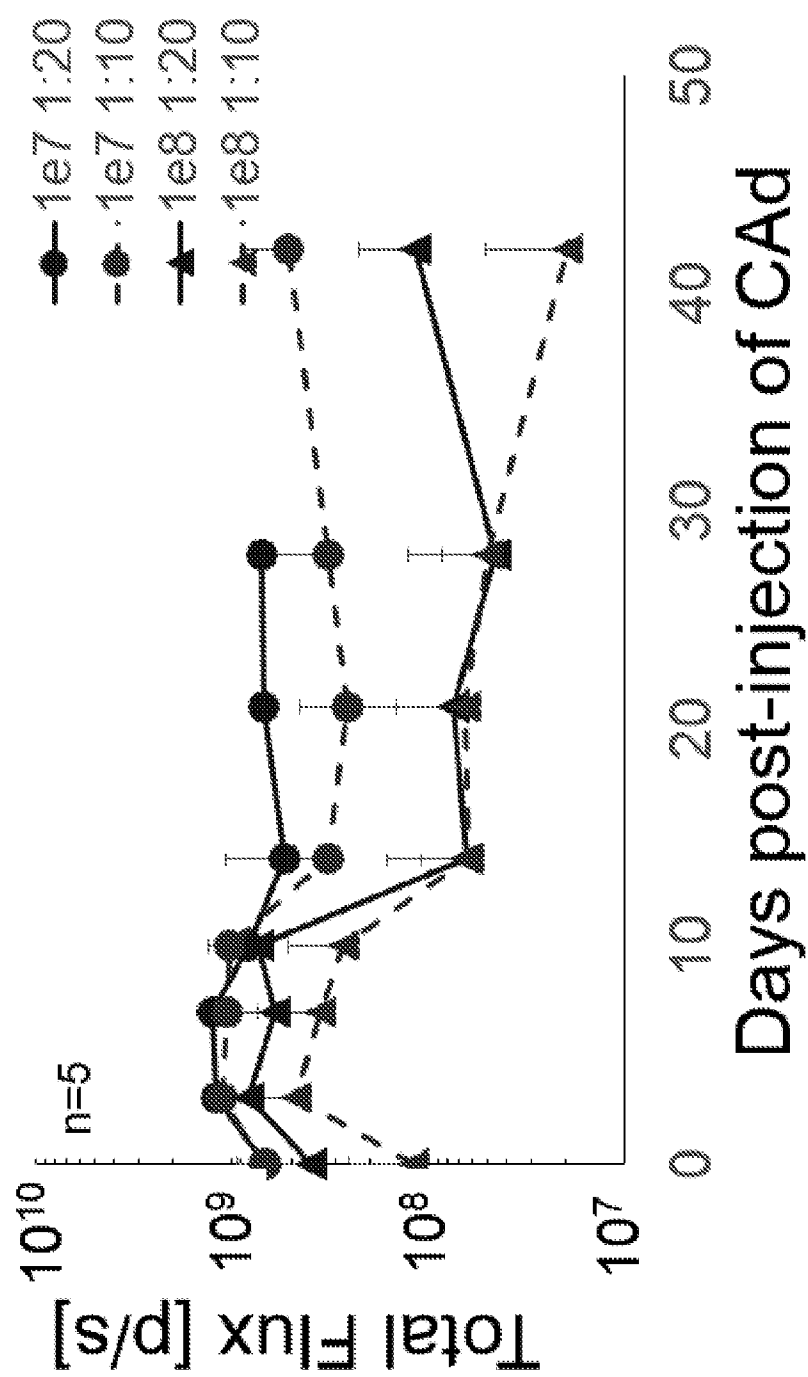


Figure 19B

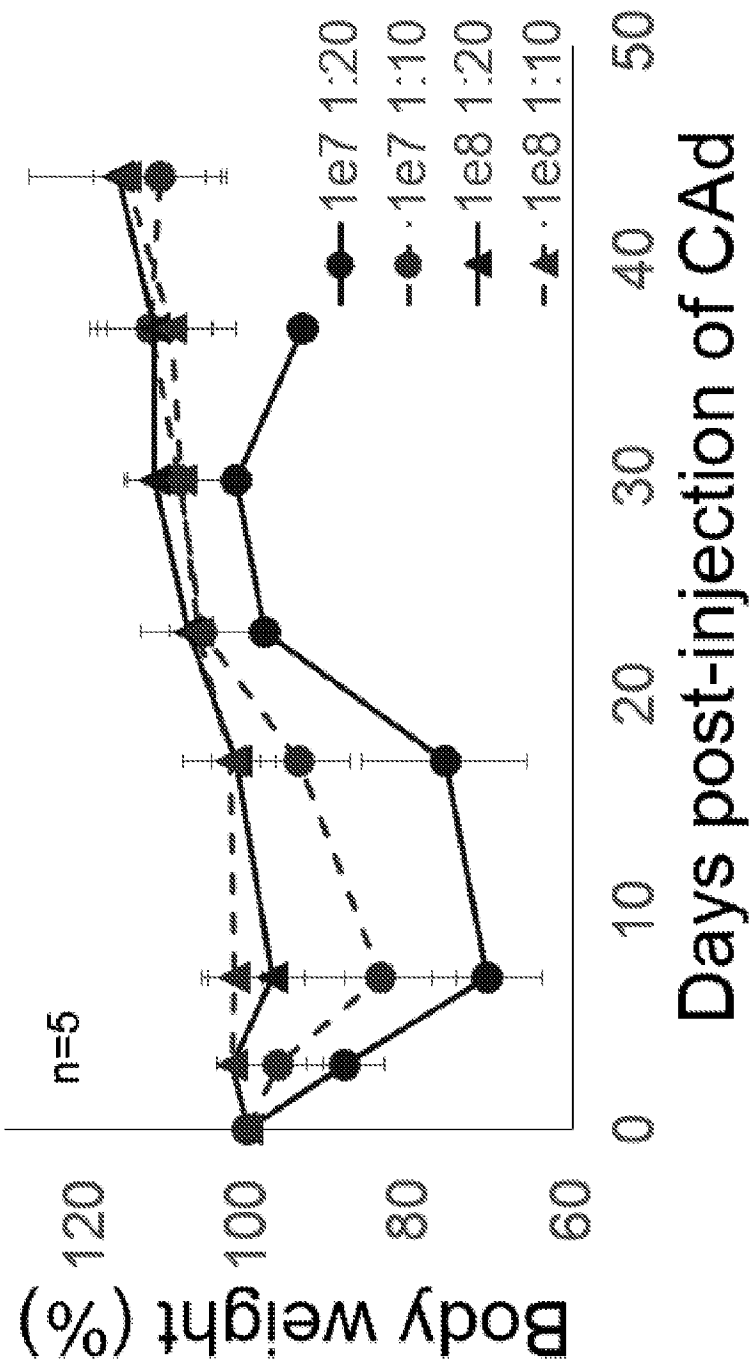


Figure 19C

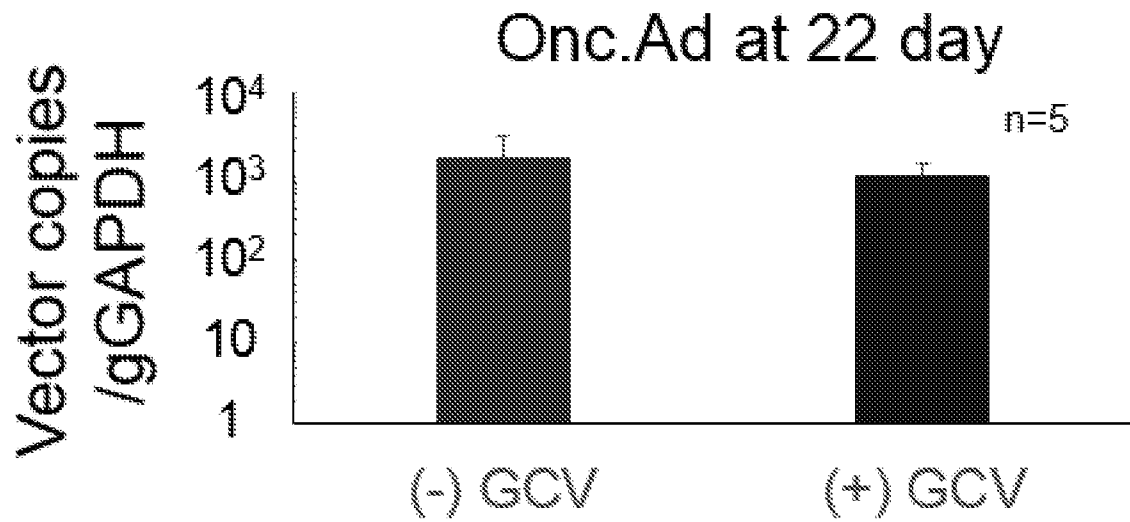


Figure 20A

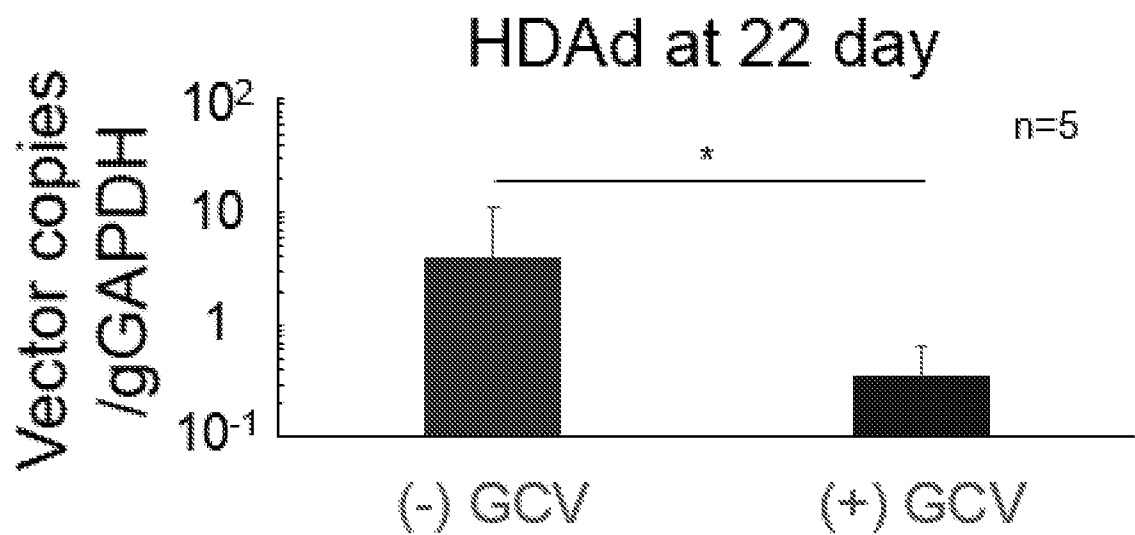


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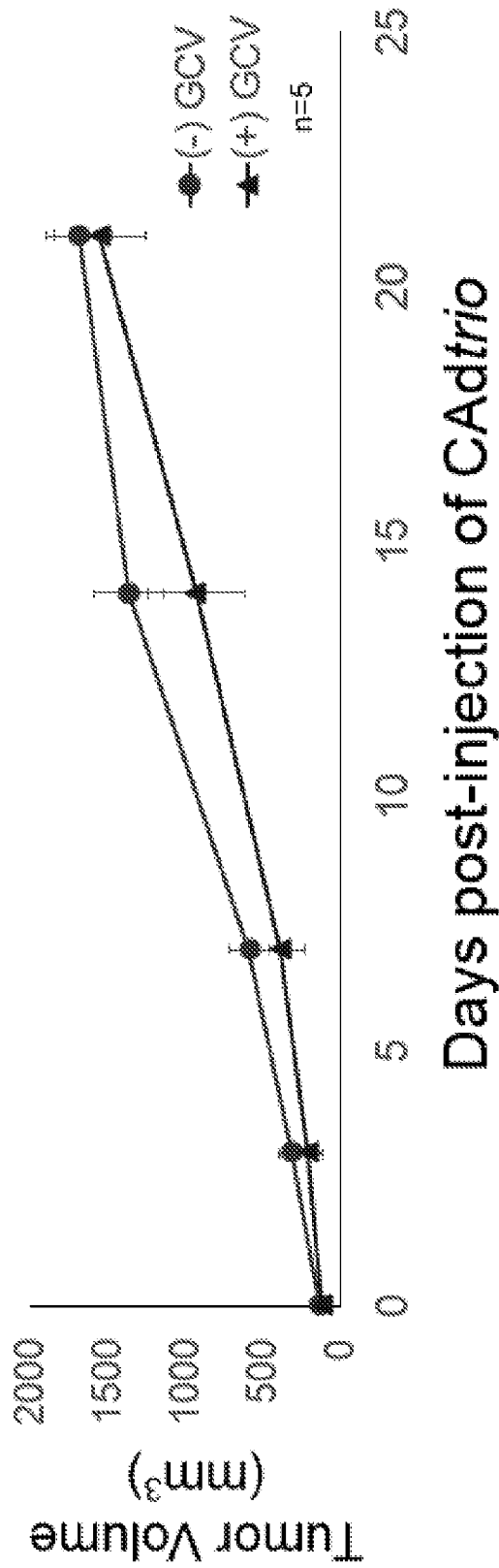


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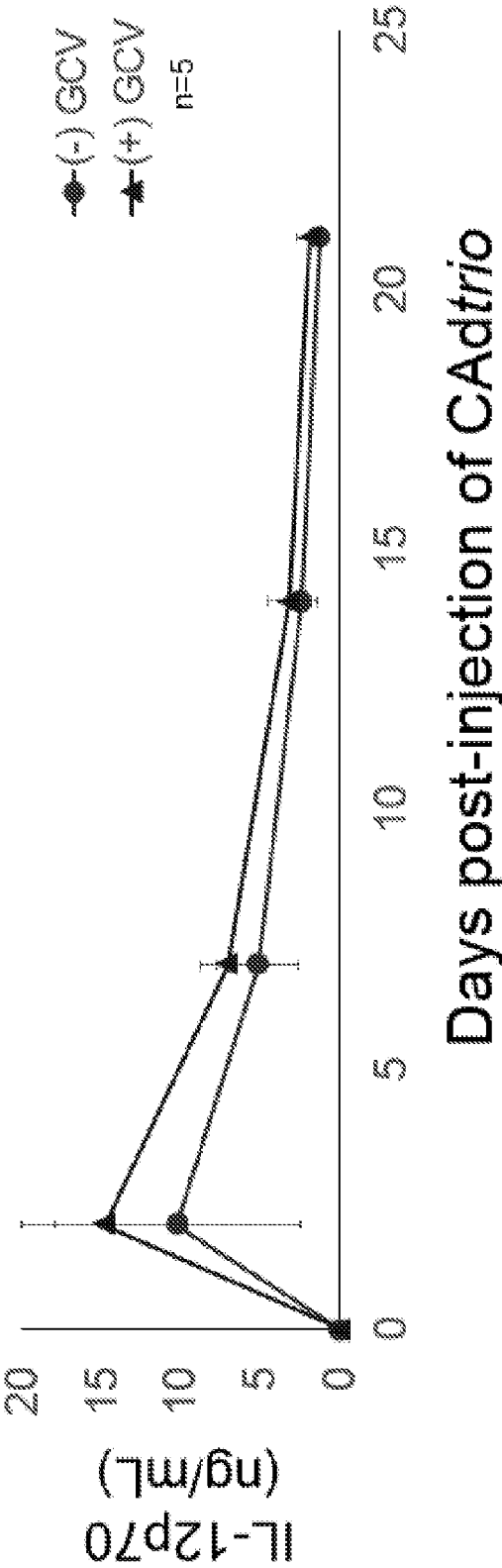


Figure 20D

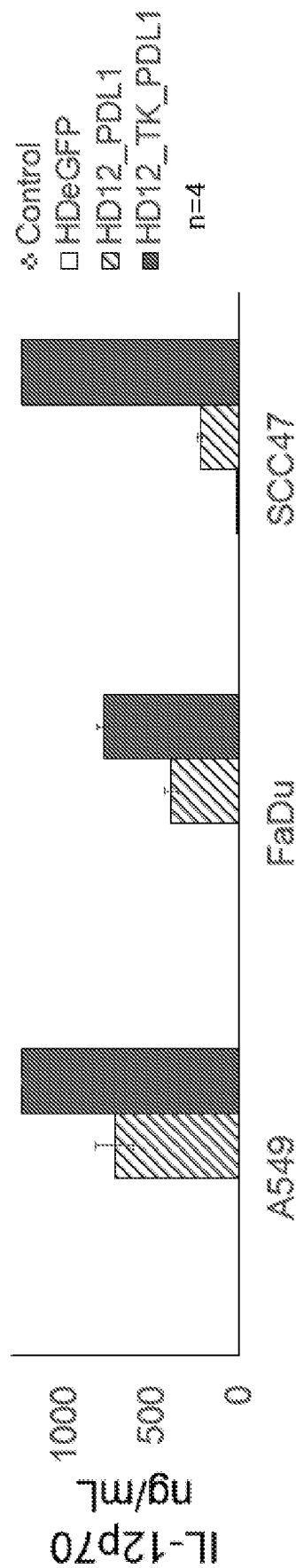


Figure 21A

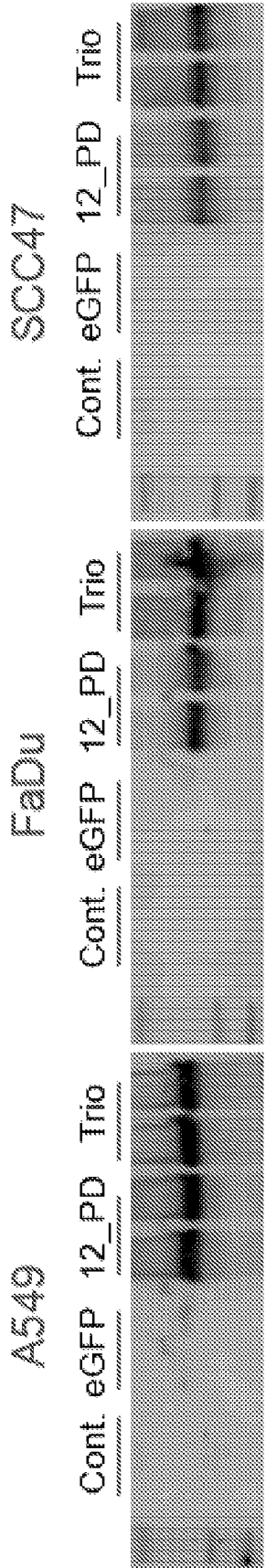


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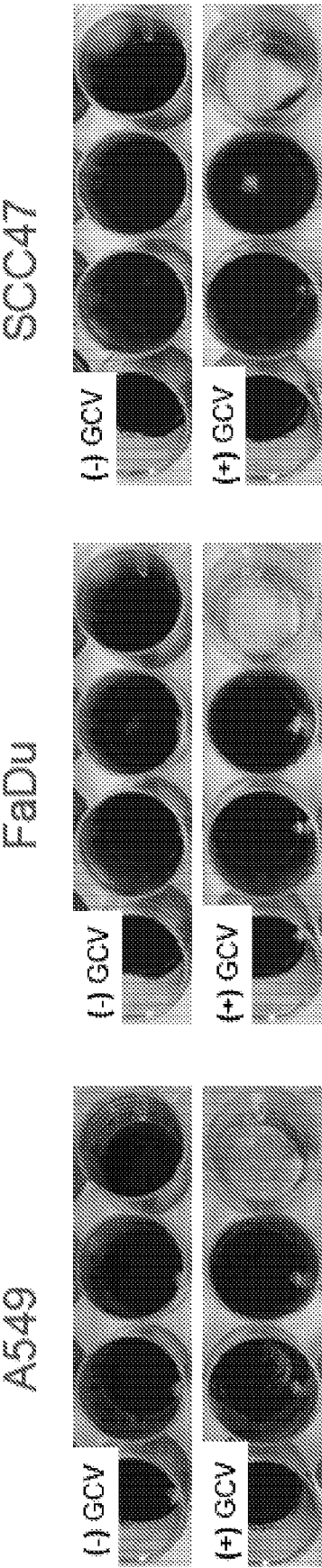


Figure 21C

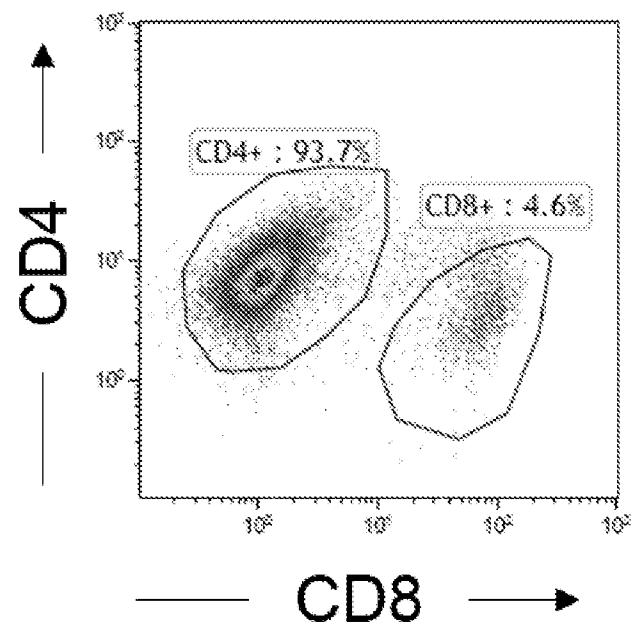


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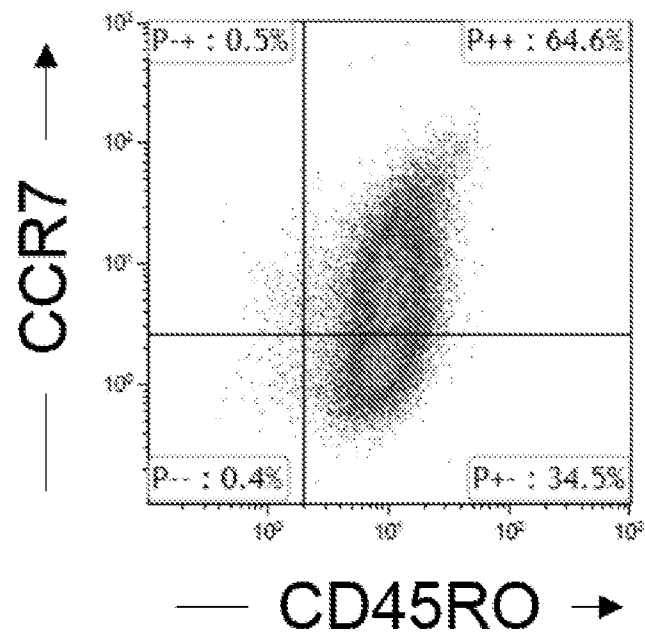


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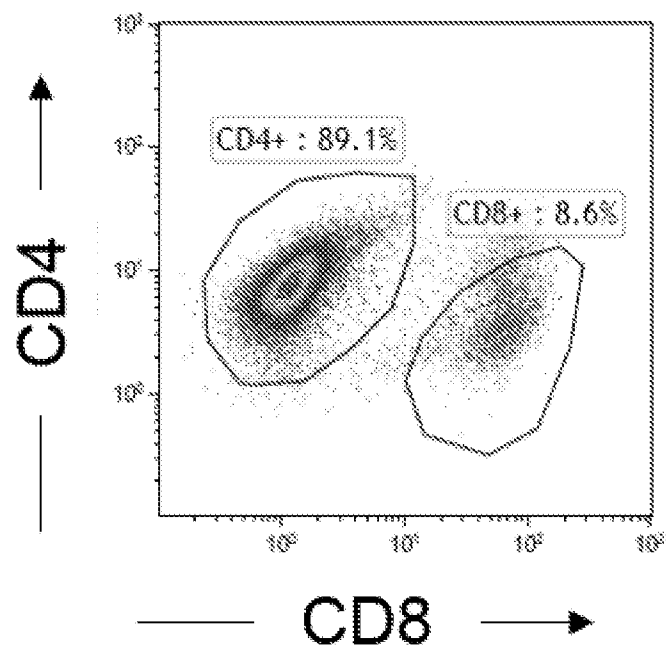


Figure 23A

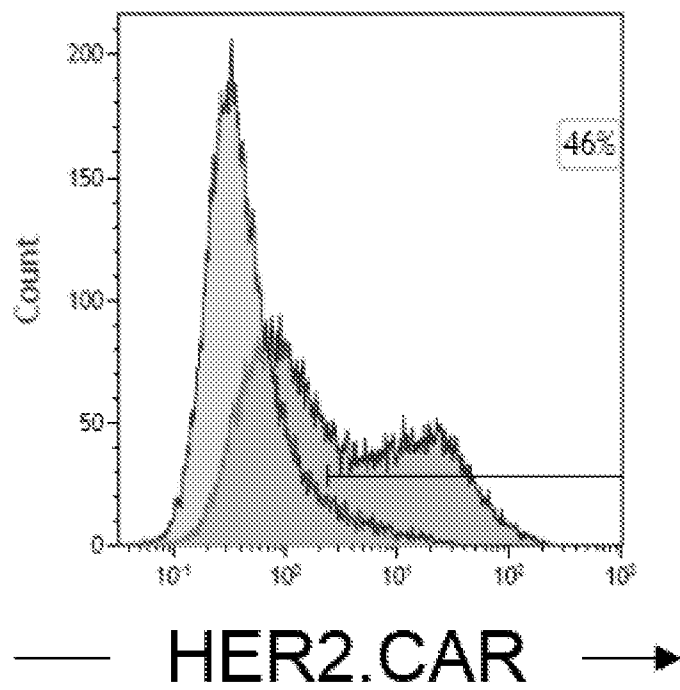


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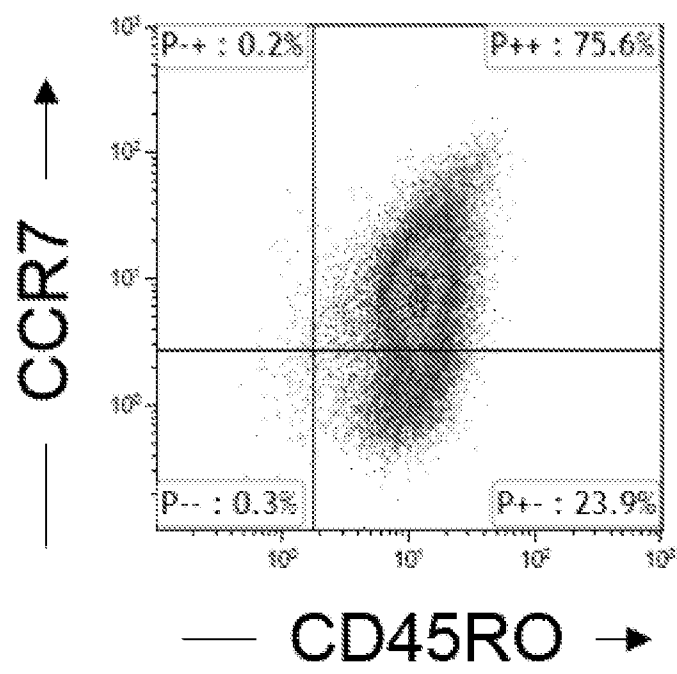


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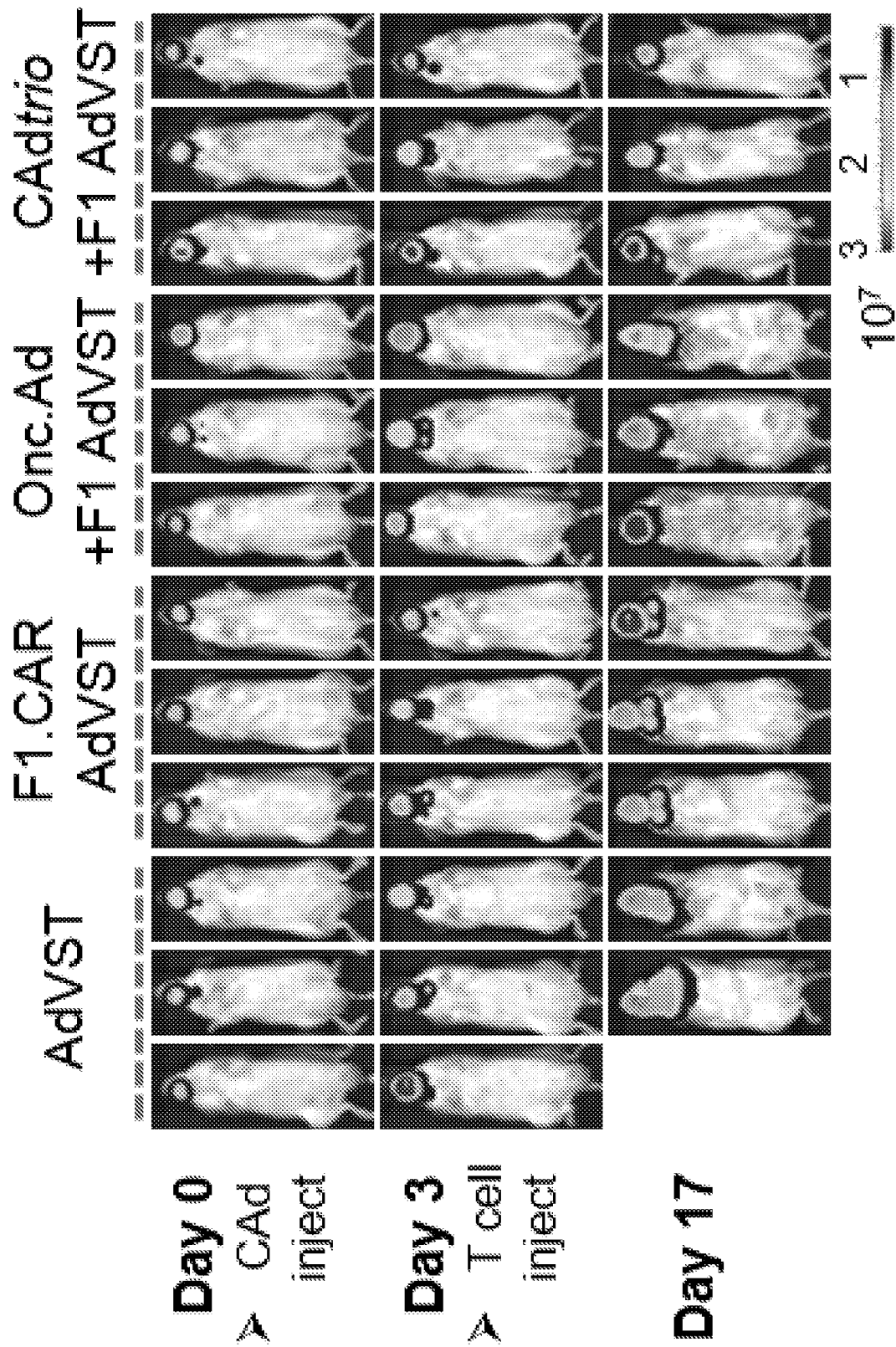


Figure 24A

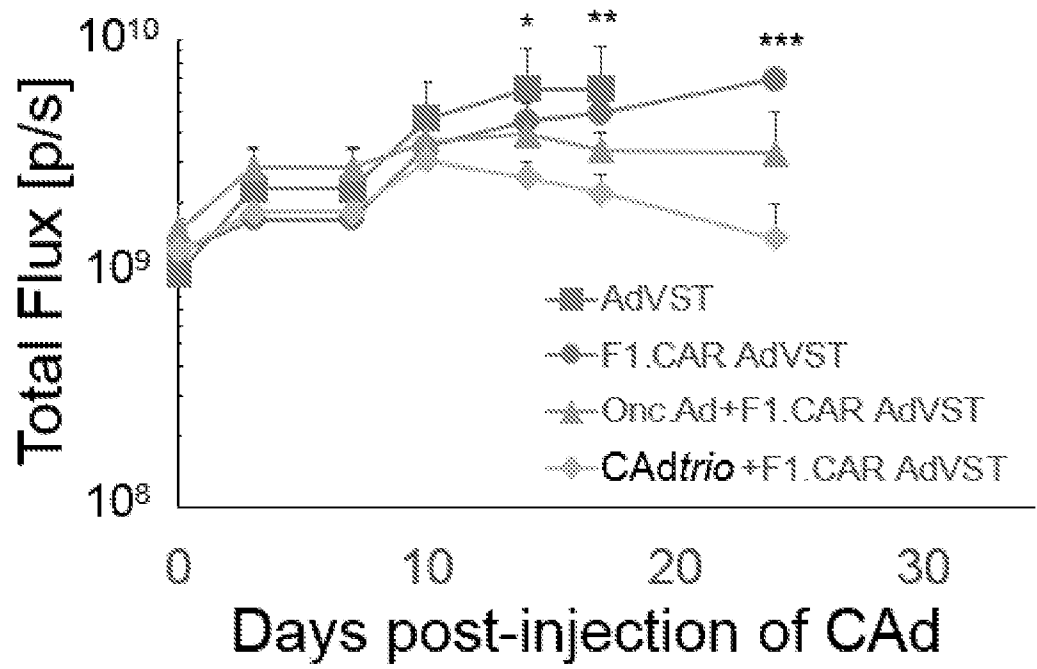


Figure 24B

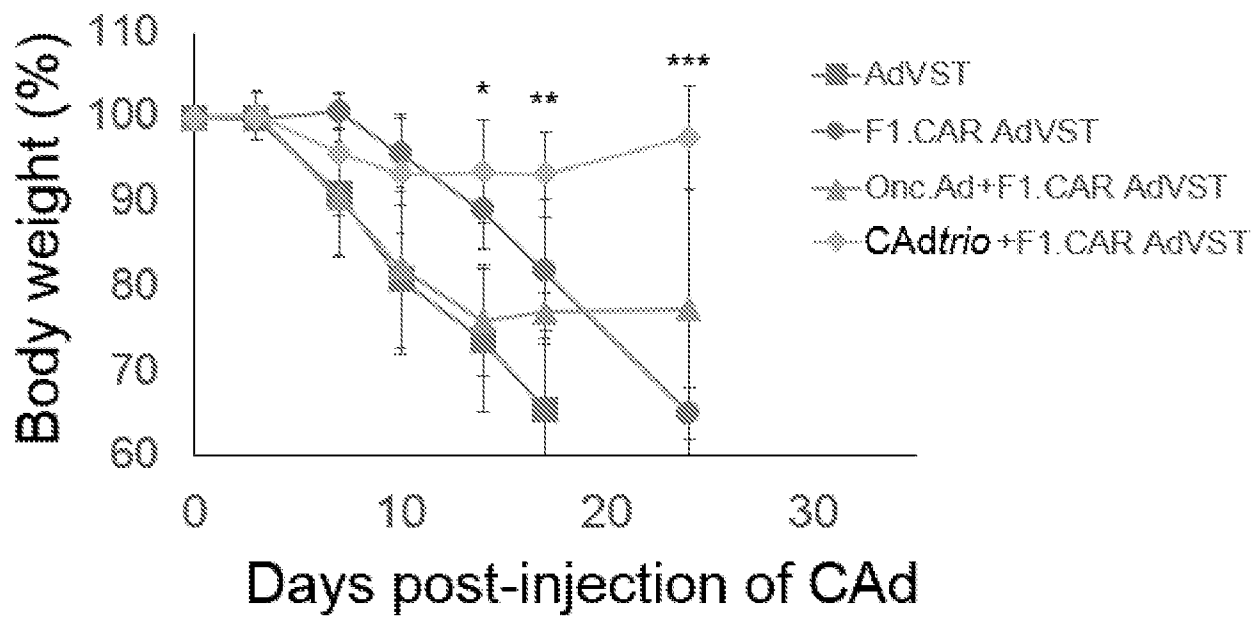


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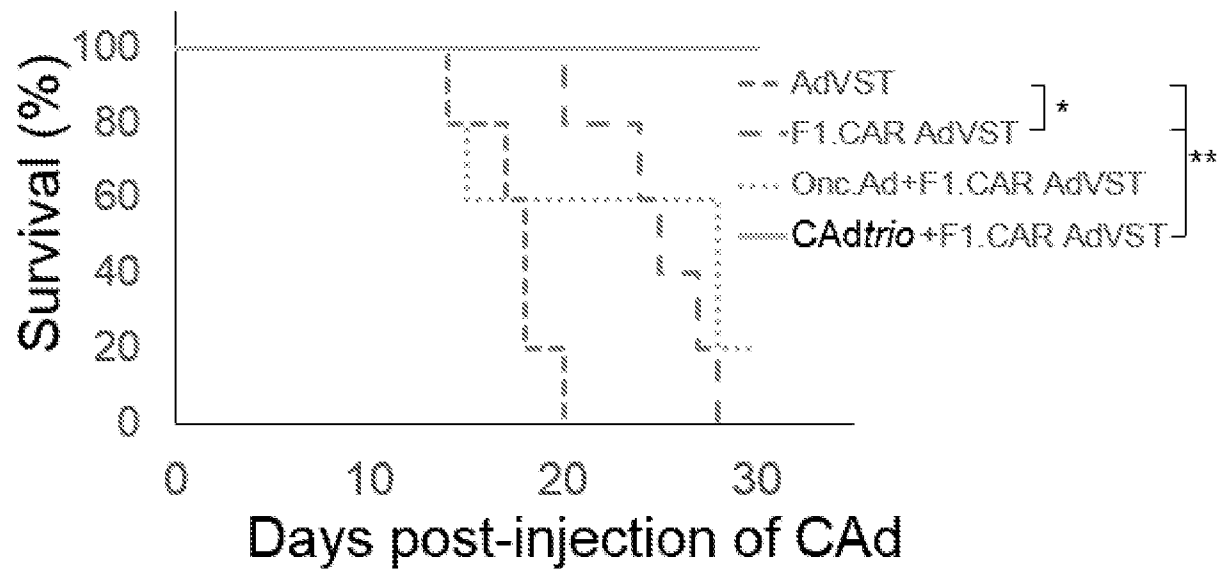


Figure 24D

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Gly Gly Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly Trp Ile Arg Gln
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Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly
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Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val
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Arg Phe Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr
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340 345 350

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
355 360 365

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
370 375 380

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
385 390 395 400

Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
405 410 415

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
420 425 430

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
435 440 445

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
450 455 460

Ala Leu Pro Pro Arg
465

<210> 2
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(E4)-CD28TM, ICD-CD3Z CAR

<400> 2

Met Thr Arg Ala Met Asp Trp Ile Trp Arg Ile Leu Phe Leu Val Gly
1 5 10 15

Sequence_Listing_BAYM_P0227.txt

Ala Ala Thr Gly Ala His Ser Gln Val Gln Leu Gln Gln Trp Gly Ala
20 25 30

Gly Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Tyr
35 40 45

Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro
50 55 60

Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn His Ser Gly Ser Thr
65 70 75 80

Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr
85 90 95

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Thr Ala Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Met Gly Ile Asn Ser Gly Gly Tyr
115 120 125

Leu Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
165 170 175

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
180 185 190

Tyr Tyr Pro Ser Trp Tyr Gln Gln Ile Pro Gly Gln Ala Pro Arg Thr
195 200 205

Leu Ile Tyr Thr Thr Asn Ile Arg Ser Ser Gly Val Pro Asp Arg Phe
210 215 220

Sequence_Listing_BAYM_P0227.txt

Gly Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
225 230 235 240

Gln Ala Glu Asp Glu Ser Asp Tyr Tyr Cys Met Leu Tyr Met Gly Ser
245 250 255

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser
260 265 270

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Thr Arg Phe Trp
275 280 285

Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val
290 295 300

Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu
305 310 315 320

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
325 330 335

Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
340 345 350

Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
355 360 365

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
370 375 380

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
385 390 395 400

Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
405 410 415

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
420 425 430

Sequence_Listing_BAYM_P0227.txt

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
435 440 445

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
450 455 460

Pro Pro Arg
465

<210> 3
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(F1)-CD28TM,ICD-CD3Z CAR

<400> 3

Met Thr Arg Ala Met Asp Trp Ile Trp Arg Ile Leu Phe Leu Val Gly
1 5 10 15

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

Gly Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala Val Ser
35 40 45

Gly Gly Ser Ile Ser Ser Ser Asn Trp Trp Ser Trp Val Arg Gln Pro
50 55 60

Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Tyr His Ser Gly Ser
65 70 75 80

Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp
85 90 95

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala
100 105 110

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Met Gly Ala Asn Ser Gly Gly
115 120 125

Sequence_Listing_BAYM_P0227.txt

Tyr Leu Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly
165 170 175

Gly Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr
180 185 190

Ser Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg
195 200 205

Thr Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg
210 215 220

Phe Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly
225 230 235 240

Ala Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly
245 250 255

Ser Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
260 265 270

Ser Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Thr Arg Phe
275 280 285

Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu
290 295 300

Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg
305 310 315 320

Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro
325 330 335

Sequence_Listing_BAYM_P0227.txt

Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala
340 345 350

Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
355 360 365

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
370 375 380

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
385 390 395 400

Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
405 410 415

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
420 425 430

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
435 440 445

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
450 455 460

Leu Pro Pro Arg
465

<210> 4
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> CD28 TMD

<400> 4

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Sequence_Listing_BAYM_P0227.txt

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

<210> 5
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> CD28 ICD

<400> 5

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 6
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> CD3Z ICD

<400> 6

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
50 55 60

Sequence_Listing_BAYM_P0227.txt

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
65 70 75 80

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
85 90 95

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
100 105 110

Arg

<210> 7
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> (G4S)3 linker

<400> 7

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 8
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> huIgG H leader

<400> 8

Met Asp Trp Ile Trp Arg Ile Leu Phe Leu Val Gly Ala Ala Thr Gly
1 5 10 15

Ala His Ser

<210> 9
<211> 14
<212> PRT
<213> Artificial Sequence

Sequence_Listing_BAYM_P0227.txt

<220>

<223> Hinge

<400> 9

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Thr	Arg
1				5					10				

<210> 10

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(C5) LC-CDR1

<400> 10

Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Gly	Tyr	Tyr	Pro	Ser
1				5					10				

<210> 11

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(C5) LC-CDR2

<400> 11

Ser	Thr	Asn	Ser	Arg	Ser	Ser
1			5			

<210> 12

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(C5) LC-CDR3

<400> 12

Val	Leu	Tyr	Met	Gly	Ser	Gly	Ile	Ser	Val
1				5					10

Sequence_Listing_BAYM_P0227.txt

<210> 13
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(C5) HC-CDR1

<400> 13

Ser Ser Ser Tyr Tyr Trp Gly
 1 5

<210> 14
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(C5) HC-CDR2

<400> 14

Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
 1 5 10 15

<210> 15
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(C5) HC-CDR3

<400> 15

Tyr Ala Pro Asp Ser Ser Gly Tyr Leu Val Ala Phe Asp Ile
 1 5 10

<210> 16
 <211> 112
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(C5) VL

<400> 16

Sequence_Listing_BAYM_P0227.txt

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Gly
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Ser Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser
100 105 110

<210> 17
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(C5) VH

<400> 17

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Sequence_Listing_BAYM_P0227.txt

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

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

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 18
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(E4) LC-CDR1

<400> 18

Gly Leu Ser Ser Gly Ser Val Ser Thr Ser Tyr Tyr Pro Ser
1 5 10

<210> 19
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(E4) LC-CDR2

<400> 19

Thr Thr Asn Ile Arg Ser Ser
1 5

<210> 20
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> HER2(E4) LC-CDR3

<400> 20

Met	Leu	Tyr	Met	Gly	Ser	Gly	Ile	Trp	Val
1				5					10

<210> 21

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(E4) HC-CDR1

<400> 21

Ser	Gly	Tyr	Tyr	Trp	Ser
1				5	

<210> 22

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(E4) HC-CDR2

<400> 22

Glu	Ile	Asn	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	Lys	Ser
1				5					10					15	

<210> 23

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(E4) HC-CDR3

<400> 23

Met	Gly	Ile	Asn	Ser	Gly	Gly	Tyr	Leu	Tyr	Gly	Met	Asp	Val
1				5					10				

<210> 24

<211> 112

Sequence_Listing_BAYM_P0227.txt

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(E4) VL

<400> 24

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Ile Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Thr Thr Asn Ile Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Gly Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ser Asp Tyr Tyr Cys Met Leu Tyr Met Gly Ser
85 90 95

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser
100 105 110

<210> 25

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(E4) VH

<400> 25

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Sequence_Listing_BAYM_P0227.txt

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Thr Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Met Gly Ile Asn Ser Gly Gly Tyr Leu Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 26
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(F1) LC-CDR1

<400> 26

Gly Leu Ser Ser Gly Ser Val Ser Thr Ser Tyr Tyr Pro Ser
1 5 10

<210> 27
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> HER2(F1) LC-CDR2

<400> 27

Ser Thr Asn Thr Arg Ser Ser
1 5

Sequence_Listing_BAYM_P0227.txt

<210> 28
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(F1) LC-CDR3

<400> 28

Val Leu Tyr Met Gly Ser Gly Ile Trp Val
 1 5 10

<210> 29
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(F1) HC-CDR1

<400> 29

Ser Ser Asn Trp Trp Ser
 1 5

<210> 30
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(F1) HC-CDR2

<400> 30

Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
 1 5 10 15

<210> 31
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(F1) HC-CDR3

Sequence_Listing_BAYM_P0227.txt

<400> 31

Met Gly Ala Asn Ser Gly Gly Tyr Leu Tyr Gly Met Asp Val
1 5 10

<210> 32

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(F1) VL

<400> 32

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser
100 105 110

<210> 33

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(F1) VH

Sequence_Listing_BAYM_P0227.txt

<400> 33

Gln Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Met Gly Ala Asn Ser Gly Gly Tyr Leu Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 34

<211> 281

<212> PRT

<213> Artificial Sequence

<220>

<223> Ad2 E1Adelta24

<400> 34

Met Arg His Ile Ile Cys His Gly Gly Val Ile Thr Glu Glu Met Ala
1 5 10 15

Ala Ser Leu Leu Asp Gln Leu Ile Glu Glu Val Leu Ala Asp Asn Leu
20 25 30

Sequence_Listing_BAYM_P0227.txt

Pro Pro Pro Ser His Phe Glu Pro Pro Thr Leu His Glu Leu Tyr Asp
35 40 45

Leu Asp Val Thr Ala Pro Glu Asp Pro Asn Glu Glu Ala Val Ser Gln
50 55 60

Ile Phe Pro Glu Ser Val Met Leu Ala Val Gln Glu Gly Ile Asp Leu
65 70 75 80

Phe Thr Phe Pro Pro Ala Pro Gly Ser Pro Glu Pro Pro His Leu Ser
85 90 95

Arg Gln Pro Glu Gln Pro Glu Gln Arg Ala Leu Gly Pro Val Ser Met
100 105 110

Pro Asn Leu Val Pro Glu Val Ile Asp Pro Pro Ser Asp Asp Glu Asp
115 120 125

Glu Glu Gly Glu Glu Phe Val Leu Asp Tyr Val Glu His Pro Gly His
130 135 140

Gly Cys Arg Ser Cys His Tyr His Arg Arg Asn Thr Gly Asp Pro Asp
145 150 155 160

Ile Met Cys Ser Leu Cys Tyr Met Arg Thr Cys Gly Met Phe Val Tyr
165 170 175

Ser Pro Val Ser Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro
180 185 190

Ala Arg Pro Thr Arg Arg Pro Lys Leu Val Pro Ala Ile Leu Arg Arg
195 200 205

Pro Thr Ser Pro Val Ser Arg Glu Cys Asn Ser Ser Thr Asp Ser Cys
210 215 220

Asp Ser Gly Pro Ser Asn Thr Pro Pro Glu Ile His Pro Val Val Pro
225 230 235 240

Sequence_Listing_BAYM_P0227.txt

Leu Cys Pro Ile Lys Pro Val Ala Val Arg Val Gly Gly Arg Arg Gln
245 250 255

Ala Val Glu Cys Ile Glu Asp Leu Leu Asn Glu Ser Gly Gln Pro Leu
260 265 270

Asp Leu Ser Cys Lys Arg Pro Arg Pro
275 280

<210> 35
<211> 536
<212> PRT
<213> Artificial Sequence

<220>
<223> huIL-12p70

<400> 35

Met Gly 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

Sequence_Listing_BAYM_P0227.txt

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 Lys 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 Val Pro Gly Val Gly Val Pro Gly
325 330 335

Sequence_Listing_BAYM_P0227.txt

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

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

Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro Cys Thr Ser Glu
370 375 380

Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr Ser Thr Val Glu
385 390 395 400

Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser Cys Leu Asn Ser
405 410 415

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

Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile Tyr Glu Asp Leu
435 440 445

Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala Lys Leu Leu Met
450 455 460

Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met Leu Ala Val Ile
465 470 475 480

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

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

Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val Thr Ile Asp Arg
515 520 525

Val Met Ser Tyr Leu Asn Ala Ser
530 535

Sequence_Listing_BAYM_P0227.txt

<210> 36
 <211> 376
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HSV1 TK

<400> 36

Met Ala Ser Tyr Pro Gly His Gln His Ala Ser Ala Phe Asp Gln Ala
 1 5 10 15

Ala Arg Ser Arg Gly His Ser Asn Arg Arg Thr Ala Leu Arg Pro Arg
 20 25 30

Arg Gln Gln Glu Ala Thr Glu Val Arg Pro Glu Gln Lys Met Pro Thr
 35 40 45

Leu Leu Arg Val Tyr Ile Asp Gly Pro His Gly Met Gly Lys Thr Thr
 50 55 60

Thr Thr Gln Leu Leu Val Ala Leu Gly Ser Arg Asp Asp Ile Val Tyr
 65 70 75 80

Val Pro Glu Pro Met Thr Tyr Trp Arg Val Leu Gly Ala Ser Glu Thr
 85 90 95

Ile Ala Asn Ile Tyr Thr Thr Gln His Arg Leu Asp Gln Gly Glu Ile
 100 105 110

Ser Ala Gly Asp Ala Ala Val Val Met Thr Ser Ala Gln Ile Thr Met
 115 120 125

Gly Met Pro Tyr Ala Val Thr Asp Ala Val Leu Ala Pro His Ile Gly
 130 135 140

Gly Glu Ala Gly Ser Ser His Ala Pro Pro Pro Ala Leu Thr Leu Ile
 145 150 155 160

Sequence_Listing_BAYM_P0227.txt

Phe Asp Arg His Pro Ile Ala Ala Leu Leu Cys Tyr Pro Ala Ala Arg
165 170 175

Tyr Leu Met Gly Ser Met Thr Pro Gln Ala Val Leu Ala Phe Val Ala
180 185 190

Leu Ile Pro Pro Thr Leu Pro Gly Thr Asn Ile Val Leu Gly Ala Leu
195 200 205

Pro Glu Asp Arg His Ile Asp Arg Leu Ala Lys Arg Gln Arg Pro Gly
210 215 220

Glu Arg Leu Asp Leu Ala Met Leu Ala Ala Ile Arg Arg Val Tyr Gly
225 230 235 240

Leu Leu Ala Asn Thr Val Arg Tyr Leu Gln Gly Gly Gly Ser Trp Arg
245 250 255

Glu Asp Trp Gly Gln Leu Ser Gly Thr Ala Val Pro Pro Gln Gly Ala
260 265 270

Glu Pro Gln Ser Asn Ala Gly Pro Arg Pro His Ile Gly Asp Thr Leu
275 280 285

Phe Thr Leu Phe Arg Ala Pro Glu Leu Leu Ala Pro Asn Gly Asp Leu
290 295 300

Tyr Asn Val Phe Ala Trp Ala Leu Asp Val Leu Ala Lys Arg Leu Arg
305 310 315 320

Pro Met His Val Phe Ile Leu Asp Tyr Asp Gln Ser Pro Ala Gly Cys
325 330 335

Arg Asp Ala Leu Leu Gln Leu Thr Ser Gly Met Ile Gln Thr His Val
340 345 350

Thr Thr Pro Gly Ser Ile Pro Thr Ile Cys Asp Leu Ala Arg Thr Phe
355 360 365

Sequence_Listing_BAYM_P0227.txt

Ala Arg Glu Met Gly Glu Ala Asn
370 375

<210> 37
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> HA tag

<400> 37

Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
1 5

<210> 38
<211> 534
<212> PRT
<213> Artificial Sequence

<220>
<223> PD-L1(H12_g1) minibody

<400> 38

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Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe
35 40 45

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

Glu Trp Met Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala
65 70 75 80

Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
85 90 95

Sequence_Listing_BAYM_P0227.txt

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly His Gly Tyr Ser Tyr Gly Ala Phe Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr
145 150 155 160

Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser
165 170 175

Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp
180 185 190

Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn
195 200 205

Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser
210 215 220

Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu
225 230 235 240

Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Tyr
245 250 255

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Glu Ala Lys Ser
260 265 270

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

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

Sequence_Listing_BAYM_P0227.txt

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

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

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

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

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

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

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

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

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

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

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

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

Ser Pro Gly Lys Gly Gly Gly Gly Ser Tyr Pro Tyr Asp Val Pro Asp
500 505 510

Sequence_Listing_BAYM_P0227.txt

Tyr Ala Gly Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Gly Tyr Pro Tyr
515 520 525

Asp Val Pro Asp Tyr Ala
530

<210> 39
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> PD-L1(H12_g1) LC-CDR1

<400> 39

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His
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<210> 40
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> PD-L1(H12_g1) LC-CDR2

<400> 40

Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 41
<211> 13
<212> PRT
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<220>
<223> PD-L1(H12_g1) LC-CDR3

<400> 41

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Tyr Val Val
1 5 10

<210> 42
<211> 5

Sequence_Listing_BAYM_P0227.txt

<212> PRT
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<220>
<223> PD-L1(H12_g1) HC-CDR1

<400> 42

Ser Tyr Ala Ile Ser
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<210> 43
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> PD-L1(H12_g1) HC-CDR2

<400> 43

Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe Gln
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Gly

<210> 44
<211> 12
<212> PRT
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<220>
<223> PD-L1(H12_g1) HC-CDR3

<400> 44

Ser Gly His Gly Tyr Ser Tyr Gly Ala Phe Asp Tyr
1 5 10

<210> 45
<211> 113
<212> PRT
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<220>
<223> PD-L1(H12_g1) VL

Sequence_Listing_BAYM_P0227.txt

<400> 45

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Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Ser Tyr Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val
100 105 110

Leu

<210> 46

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> PD-L1(H12_g1) VH

<400> 46

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Sequence_Listing_BAYM_P0227.txt

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly His Gly Tyr Ser Tyr Gly Ala Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 47
<211> 3750
<212> DNA
<213> Artificial Sequence

<220>
<223> HER2(C5)-CD28TM, ICD-CD3Z CAR

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ccaaacagga tatctgtggt aagcagttcc tgccccggct cagggccaag aacagatggt 180
ccccagatgc ggtccagccc tcagcagttt ctagagaacc atcagatggt tccaggggtgc 240
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Sequence_Listing_BAYM_P0227.txt

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<210> 48

<211> 3744

<212> DNA

<213> Artificial Sequence

<220>

<223> HER2(E4)-CD28TM,ICD-CD3Z CAR

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Sequence_Listing_BAYM_P0227.txt

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Sequence_Listing_BAYM_P0227.txt

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 <212> DNA
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<220>
 <223> HER2(F1)-CD28TM,ICD-CD3Z CAR

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Sequence_Listing_BAYM_P0227.txt

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Sequence_Listing_BAYM_P0227.txt

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Sequence_Listing_BAYM_P0227.txt

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Sequence_Listing_BAYM_P0227.txt

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Sequence_Listing_BAYM_P0227.txt

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Sequence_Listing_BAYM_P0227.txt

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<211> 464

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(A3)-CD28TM,ICD-CD3Z CAR

<400> 56

Met	Thr	Arg	Ala	Met	Asp	Trp	Ile	Trp	Arg	Ile	Leu	Phe	Leu	Val	Gly
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Ala	Ala	Thr	Gly	Ala	His	Ser	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Thr
			20					25					30		

Sequence_Listing_BAYM_P0227.txt

Glu Val Lys Lys Pro Gly Ala Ser Val Arg Val Ser Cys Lys Ser Ser
35 40 45

Gly Tyr Thr Phe Thr Ser Tyr Tyr Ile His Trp Val Arg Gln Ala Pro
50 55 60

Gly Gln Gly Leu Glu Trp Met Ala Ile Ile Asn Pro Gly Asn Gly Asp
65 70 75 80

Thr Asn Tyr Ala Gln Arg Phe Gln Gly Arg Val Thr Met Thr Arg Asp
85 90 95

Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp
100 105 110

Asp Thr Ala Val Tyr Phe Cys Ala Arg Glu Ile Ala Ser Tyr Ser Gly
115 120 125

Ser Tyr Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
145 150 155 160

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

Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Gly His
180 185 190

Tyr Ala Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr Leu
195 200 205

Phe Tyr Asn Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Ile Val Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln
225 230 235 240

Sequence_Listing_BAYM_P0227.txt

Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Val Gly Asp Gly
245 250 255

Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Glu Pro Lys
260 265 270

Ser Cys Asp Lys Thr His Thr Cys Pro Thr Arg Phe Trp Val Leu Val
275 280 285

Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala
290 295 300

Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser
305 310 315 320

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
325 330 335

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg
340 345 350

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
355 360 365

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
370 375 380

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
385 390 395 400

Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
405 410 415

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
420 425 430

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
435 440 445

Sequence_Listing_BAYM_P0227.txt

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
 450 455 460

<210> 57
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(A3) LC-CDR1

<400> 57

Gly Leu Ser Ser Gly Ser Val Ser Thr Gly His Tyr Ala Ser
 1 5 10

<210> 58
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(A3) LC-CDR2

<400> 58

Asn Thr Asn Thr Arg Ser Ser
 1 5

<210> 59
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(A3) LC-CDR3

<400> 59

Val Leu Tyr Val Gly Asp Gly Ile Trp Val
 1 5 10

<210> 60
 <211> 10
 <212> PRT
 <213> Artificial Sequence

Sequence_Listing_BAYM_P0227.txt

<220>

<223> HER2(A3) HC-CDR1

<400> 60

Ser	Tyr	Tyr	Ile	His	Trp	Val	Arg	Gln	Ala
1				5				10	

<210> 61

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(A3) HC-CDR2

<400> 61

Ile	Ile	Asn	Pro	Gly	Asn	Gly	Asp	Thr	Asn	Tyr	Ala	Gln	Arg	Phe	Gln
1				5					10					15	

Gly

<210> 62

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(A3) HC-CDR3

<400> 62

Glu	Ile	Ala	Ser	Tyr	Ser	Gly	Ser	Tyr	Tyr	Asp	Tyr
1				5					10		

<210> 63

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> HER2(A3) VL

<400> 63

Gln Ala Val Val Leu Gln Glu Pro Ser Leu Ser Val Ser Pro Gly Gly

Sequence_Listing_BAYM_P0227.txt

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Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Gly
      20              25              30

His Tyr Ala Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
      35              40              45

Leu Phe Tyr Asn Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
      50              55              60

Ser Gly Ser Ile Val Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
      65              70              75              80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Val Gly Asp
      85              90              95

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100             105             110

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<210> 64
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HER2(A3) VH

<400> 64

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Glu Val Gln Leu Val Gln Ser Gly Thr Glu Val Lys Lys Pro Gly Ala
1           5           10           15

Ser Val Arg Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Ser Tyr
      20              25              30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35              40              45

Ala Ile Ile Asn Pro Gly Asn Gly Asp Thr Asn Tyr Ala Gln Arg Phe
      50              55              60

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Sequence_Listing_BAYM_P0227.txt

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Ile Ala Ser Tyr Ser Gly Ser Tyr Tyr Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120