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(54) **Title**: NOVEL PD-1 IMMUNE MODULATING AGENTS

(57) **Abstract**: The present application provides constructs comprising an anti-PD-1 antigen-binding protein or a fragment thereof, as well as nucleic acids or CAR T cells expressing such antigen-binding protein or fragment. Also provided are methods of regulating T cells or treating patients using such constructs or cells.

NOVEL PD-1 IMMUNE MODULATING AGENTS

Cross Reference to Related Applications

[001] This application claims priority to U.S. provisional application no. 62/183,297 filed June 23, 2015 and U.S. provisional application no. 62/266,398 filed December 11, 2015; the contents of each are hereby incorporated by reference into the present disclosure.

Sequence Listing

[002] This application contains a Sequence Listing, created on June 16, 2016; the file, in ASCII format, is designated 3314070AWO_SequenceListing_ST25.txt and is 104 kilobytes in size. The file is hereby incorporated by reference in its entirety into the present application.

Technical Field

[003] The present disclosure relates generally to antigen-binding proteins involved in immune function. More particularly, the present disclosure relates to recombinant antibodies, chimeric antigen receptors and fragments thereof with specificity for PD-1.

Background of the Disclosure

[004] The goal of cancer immunotherapy is to treat malignant disease by modulating cancer specific immune responses. A prime target is the programmed cell death (PD-1) receptor, which is expressed on the surface of activated T cells and leads to an intracellular inhibitory signal when bound to one of its ligands, PD-L1 and PD-L2.

[005] PD-1 has been shown to play a role in cancer. In humans, expression of PD-1 and/or PD-L1 has been found in a number of primary tumor biopsies assessed by immunohistochemistry. Such tissues include cancers of the lung, liver, ovary, cervix, skin, colon, glioma, bladder, breast, kidney, esophagus, stomach, oral squamous cell, urothelial cell, and pancreas as well as tumors of the head and neck. Furthermore, PD-ligand expression on tumor cells has been correlated to poor prognosis of cancer patients across multiple tumor types.

[006] There is an ongoing need for new therapeutics, including antibodies and other antigen-binding proteins that target PD-1 and function either as agonists of PD-1 or antagonists thereof.

Summary of the Disclosure

[007] The present disclosure describes antigen-binding proteins such as antibodies and chimeric antigen receptors that are able to specifically bind a protein receptor associated with programmed cell death, PD-1, on T cells, thereby modulating immune response by the T cells. By inhibiting the binding of PD-1 to its ligand, PD-L1, blockade of the PD-1 signaling pathway inhibits apoptosis of the T cells.

[008] In one aspect, therefore, the disclosure relates to recombinant antigen-binding proteins, antibodies and chimeric antigen receptors or antigen-binding portions thereof that bind specifically to PD-1 and prevent binding of its ligand.

[009] In one aspect, therefore, the disclosure relates to a recombinant antigen-binding protein or antigen-binding fragment thereof comprising one of:

(A) an antigen binding region having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, SEQ ID NO: 21, SEQ ID NO: 32, SEQ ID NO: 43, SEQ ID NO: 53, SEQ ID NO: 61, SEQ ID NO: 72, SEQ ID NO: 83, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 114, SEQ ID NO: 125, SEQ ID NO: 133, SEQ ID NO: 142; a fragment thereof, and a homologous sequence thereof;

(B) an antigen binding region comprising a variable light chain (VL) and variable heavy chain (VH), respectively, with amino acid sequences selected from SEQ ID NOS: 6 and 8; SEQ ID NOS: 17 and 19; SEQ ID NOS: 28 and 30; SEQ ID NOS: 39 and 41; SEQ ID NOS: 49 and 51; SEQ ID NOS: 57 and 59; SEQ ID NOS: 68 and 70; SEQ ID NOS: 79 and 81; SEQ ID NOS: 90 and 92; SEQ ID NOS: 99 and 101; SEQ ID NOS: 110 and 112; SEQ ID NOS: 121 and 123; SEQ ID NOS: 129 and 131; SEQ ID NOS: 138 and 140; fragments thereof, and homologous sequences thereof; or

(C) an antigen binding region comprising:
(i) a light chain (LC) comprising light chain complementarity determining regions (LCCDR) LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence QSISSY (SEQ ID NO: 1), AAS and QQSYSTPLT (SEQ ID NO: 2) and a heavy chain (HC) comprising heavy chain complementarity determining regions (HCCDR) HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTSSSYW (SEQ ID NO: 4), IKQDGSEK (SEQ ID NO. 5) and ARGGWSYDM (SEQ ID NO: 6); fragments thereof or homologous sequences thereof;

(ii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGAGYA (SEQ ID NO: 12), TNN and QSYDSSLSGVI (SEQ ID NO: 13) and a heavy chain (HC) comprising

HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTLTELS (SEQ ID NO: 14), FDPEDGET (SEQ ID NO. 15) and ARAYYGFDQ (SEQ ID NO: 16); fragments thereof or homologous sequences thereof;

(iii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGNNA (SEQ ID NO: 23), YND and AAWDDSVNGYV (SEQ ID NO: 24) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTRFG (SEQ ID NO: 25), ISVNNGNT (SEQ ID NO. 26) and ARYMYGRRDS (SEQ ID NO: 27); fragments thereof or homologous sequences thereof;

(iv) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDNHSDVV (SEQ ID NO: 35) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences RNKFSSYA (SEQ ID NO: 36), ISGSGGTT (SEQ ID NO. 37) and ARWYSSYYDV (SEQ ID NO: 38); fragments thereof or homologous sequences thereof;

(v) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDYV (SEQ ID NO: 45) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARNYISMFDS (SEQ ID NO: 48); fragments thereof or homologous sequences thereof;

(vi) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDHV (SEQ ID NO: 55) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARGYSSYYDA (SEQ ID NO: 56); fragments thereof or homologous sequences thereof;

(vii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence RSNIGENT (SEQ ID NO: 63), SNN and AAWDDRLNGYV (SEQ ID NO: 64) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTNYG (SEQ ID NO: 65), IGAQKGDT (SEQ ID NO. 66) and ARSQGVPFDS (SEQ ID NO: 67); fragments thereof or homologous sequences thereof;

(viii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence RSNIGSNT (SEQ ID NO: 74), NNN and ATWDDSLNEYV (SEQ ID NO: 75) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTRYG (SEQ ID NO: 76), ISGYNGNT (SEQ ID NO. 77) and ARHGYGYHGD (SEQ ID NO: 78); fragments thereof or homologous sequences thereof;

(ix) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGAGYV (SEQ ID NO: 85), HNN and QSYDSSLSGWV (SEQ ID NO: 86) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFKDYY (SEQ ID NO: 87), ISTSGNSV (SEQ ID NO. 88) and

ARSPGHSDYDS (SEQ ID NO: 89); fragments thereof or homologous sequences thereof;

(x) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGDKS (SEQ ID NO: 96), YDS and QVWASGTDHPYVI (SEQ ID NO: 97) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARMYGSYTDM (SEQ ID NO: 98); and a fragment or homologous sequence thereof;

(xi) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGYNY (SEQ ID NO: 105), RNN and TSWDDSLSGYV (SEQ ID NO: 106) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GNAFTNFY (SEQ ID NO: 107), INPSGTDLT (SEQ ID NO. 108) and ARQYAYGYSGFDM (SEQ ID NO: 109); fragments thereof or homologous sequences thereof;

(xii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence QSVSNW (SEQ ID NO: 116), AAS and QQSYSTPIT (SEQ ID NO: 117) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTSYY (SEQ ID NO: 118), INPNTGGS (SEQ ID NO. 119) and ARGDVTYDE (SEQ ID NO: 120); fragments thereof or homologous sequences thereof;

(xiii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDD and QVWDINDHYV (SEQ ID NO: 127) and a heavy chain (HC) comprising

HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARSQASFMDI (SEQ ID NO: 128); fragments thereof or homologous sequences thereof; or

(xiv) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), DDS and QVWDSSSDQGV (SEQ ID NO: 135) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), IGTGGGT (SEQ ID NO. 136) and ARGTGYDGDQ (SEQ ID NO: 137) and fragments thereof or homologous sequences thereof.

[0009a] In one aspect, the disclosure relates to a recombinant antigen-binding protein comprising one of:

(A) an antigen binding region comprising an amino acid sequence of SEQ ID NO: 53;

(B) an antigen binding region comprising a variable light chain (VL) and variable heavy chain (VH), with amino acid sequences selected from SEQ ID NOS: 49 and 51, respectively; and

(C) an antigen binding region comprising:
a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDYV (SEQ ID NO: 45) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARNYISMFDS (SEQ ID NO: 48).

[0010] In some embodiments, the recombinant antigen-binding protein or antigen-binding fragment thereof comprises a fragment of at least one of the recited SEQ ID NOS that is at least 40%, 45%, 50%, 55%, 60%, 65%,

70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the entire length of the at least one recited SEQ ID NO. In some embodiments, the recombinant antigen-binding protein or antigen-binding fragment thereof comprises a sequence homologous to at least one of the recited SEQ ID NOS that has at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity to the at least one recited SEQ ID NO.

[0011] In a related aspect, the disclosure relates to recombinant antigen-binding proteins or antigen-binding fragments thereof, wherein the recombinant antigen-binding protein is an antibody, chimeric antigen receptor (CAR), fusion protein or conjugate thereof. In an embodiment, the recombinant antigen-binding protein or antigen-binding fragment thereof is

conjugated to a therapeutic agent, for example, a drug, toxin or cytotoxic moiety, radioisotope, protein or peptide.

[0012] An antibody of the disclosure is a full-length antibody, an intact antibody, fragments and homologous sequences thereof, including but not limited to, an Fab fragment, an $F(ab')_2$ fragment or a single chain variable fragment (scFv).

[0013] In the recombinant antigen-binding protein, the antigen-binding region specifically binds to an epitope of human PD-1 and blocks binding of PD-1 to its ligand(s).

[0014] In a related aspect, the disclosure relates to nucleic acids encoding an antigen-binding protein of the disclosure as well as vectors and cells comprising such nucleic acids or antigen-binding proteins.

[0015] In yet another aspect, the disclosure relates to a method of increasing a T cell response in a subject comprising administering a therapeutically effective amount of an antigen-binding protein or an antigen binding fragment thereof. The administration of a therapeutically effective amount of the antigen-binding protein or antigen binding fragment thereof inhibits, reduces, modulates or abolishes signal transduction mediated by PD-1.

[0016] In yet another related aspect, the disclosure relates to a method for treatment of a subject having a PD1-positive disease comprising administering to the subject a therapeutically effective amount of an antigen-binding protein or antigen binding fragment thereof. In an embodiment, a pharmaceutical composition comprising the antigen-binding protein or antigen binding fragment thereof is administered.

[0017] In another aspect of the invention, the disclosure relates to a vector comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

[0018] In yet another aspect, the disclosure relates to a cell comprising the vector described herein. In a related aspect, the disclosure relates to a cell comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor. In another related aspect, the disclosure relates to a cell comprising a recombinant anti-PD-1 antigen-binding protein and a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

[0019] In some embodiments of the vectors or the cells described herein, the chimeric antigen receptor does not specifically bind to PD-1.

[0020] In another aspect of the invention, the disclosure provides a method of increasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of a recombinant anti-PD-1 antigen-binding protein, a vector, a cell, or a pharmaceutical composition described herein, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 antagonist.

[0021] In yet another aspect of the invention, the disclosure provides a method of decreasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of a recombinant anti-PD-1

antigen-binding protein, a vector, a cell, or a pharmaceutical composition described herein, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 agonist.

[0022] In another aspect of the invention, the disclosure provides a method for treatment of a subject having a PD1-positive disease, comprising administering to the subject a therapeutically effective amount of a recombinant anti-PD-1 antigen-binding protein, a vector, a cell, or a pharmaceutical composition described herein.

[0023] In a related aspect, the disclosure provides a method for treatment of a subject having a PD1-positive disease, comprising transducing at least one T cell of the subject with a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

[0024] In some embodiments of the methods described herein, the chimeric antigen receptor does not specifically bind to PD-1. In some embodiments, the PD1-positive disease is a cancer. In some embodiments, the PD1-positive disease is an autoimmune disease.

Brief Description of the Drawings

[0025] **Figure 1** shows relative binding affinity of scFv-Fc clones to PD-1 monomer. The ability of scFv-Fc clones to bind PD-1 was determined by detecting level of binding to PD-1 monomer. Binding affinity of the scFv-Fc clones was ranked where clone 31 bound weakly and clones 26 and 27 bound the most (31 < 23 < 40 < 18 < 16 = 27 < 26.)

[0026] **Figures 2A** and **B** show disruption of the interaction of PD-1 with its ligand, PD-L1. **A**. is a schematic of the competitive binding assay used to measure the ability of the scFv-Fc to disrupt the PD-1/PD-L1 interaction. (1) biotinylated PD-1-Fc was mixed with serially diluted ET901 ScFv-Fc (negative control) or anti-PD1 ScFv-Fcs; and (2) then added into a PD-L1-Fc coated plate. In step (3) PD-1-Fc binding towards coated PD-L1 was visualized via HRP-conjugated streptavidin. **B**. In order to compare the competitive binding assay results, points where the concentration of the scFv was 1.7-5.25 ug/ml are circled. Clones 40 and 23 had the weakest ability to disrupt the interaction and clone 26 had the strongest (26 > 27 = 16 > 18 > 31 > 23 = 40).

[0027] **Figure 3** is a schematic of the construct used. A secreteable scFv was designed to include a murine kappa leader sequence to allow exportation of the scFv from the cell. A serine glycine linker (G_4S) was used to link the variable heavy chain and variable light chain. A HIS/HA tag was included to allow detection of the scFv. The schematic of SFG-1928z/scFv retroviral construct depicting the 5' and 3' long terminal repeats (LTR), splice donor (SD), splice acceptor (SA), packaging element (ψ), CD8 leader sequence (CD8), variable heavy (VH) and variable light (VL) chains of the single chain variable fragment (scFv), transmembrane domain (TM), human CD28 signaling domain (hCD28), human zeta chain signaling domain (hζ chain) and position of the anti-PD-1 scFv.

[0028] **Figure 4** Expansion of human peripheral blood T cells modified to express the 1928z CAR alone or with a PD-1 scFv. Transduced T cells were cultured in 50 IU/ml recombinant human IL-2 and expansion was monitored. T cells modified to express the CAR and secrete anti-PD-1 scFv clone 23 or 27 had expansion that was at least equivalent to T cells

expressing the CAR alone. Cells modified to express the 1928z CAR and secrete anti-PD-1 scFv clones 16, 18, 26, 31 or 40 did not expand *in vitro*. Data shown is representative of two independent experiments.

[0029] **Figure 5** INF-γ secretion (pg/ml) from tumor targeted T cells that secrete an anti-PD-1 scFv. T cells expressing the CAR or CAR and secreting an anti-PD-1 scFv were cocultured with CD19+ Raji tumor cells. Supernatants were analysed with Luminex technology to detect the levels of cytokines secreted from the T cells. T cells modified to express the 1928z CAR and secrete anti-PD-1scFv clones 23 and 27 had increased secretion of IFN-γ compared to cells modified to express the CAR alone. Cells modified to express the 1928z CAR and secrete anti-PD-1 scFv clones 16, 18, 2, 31 or 40 secreted less IFN-γ compared to cells modified with the CAR alone.

[0030] **Figure 6** shows the results of transduction of human T cells with 1928z CAR and Eureka anti-PD-1 scFvs. (Upper panel) Following transduction, human T cells were assessed by flow cytometry to detect CAR expression using antibody specific for the 1928z CAR (19E3). Transduction efficiency was greater than 55% for all contructs tested and reproducible. (Lower panel) Constructs containing Eureka anti-PD-1 scFv clones 26, 27 and 40 had significantly lower transductions efficiency, *$p<0.05$. Transduction efficiency from 4 independent experiments, data shown is average +/- SEM.

[0031] **Figure 7** shows the effect of the presence of anti-PD-1 scFv in T cells modified to express the 1928z CAR and Eureka anti-PD-1 scFv. Human T cells transduced to express the CAR and the Eureka anti-PD-1 scFvs were incubated with golgi inhibitors for 4 hours prior to preparation of western blot lysates. Western blot analysis was used to detect anti-PD-1 scFv by probing

the membrane with anti-HA antibody. Membranes were probed with anti-GAPDH antibody as loading control.

[0032] **Figure 8** shows the expansion of human T cells modified to express the 1928z CAR and anti-PD-1 scFv in the presence/absence of PD-L1/L2. Human T cells modified to express the CAR and secrete anti-PD-1 scFv clones 23, 26, 27,and 40 were placed on artificial antigen presenting cells (aAPCs, murine 3T3 fibroblasts) expressing human PD-1L1/L2 or not. After 24 hours incubation with aAPCs, CD3/CD28 activating beads were added to the cells to stimulate proliferation (1:2 bead:T cell ratio). After 3 days, T cells were enumerated using trypan blue exclusion. T cells modified to express the 1928zCAR and anti-PD-1 scFv clone 26 and 23 had decreased proliferation on aAPCs expressing PD-L1/L2 to aAPCs not expressing inhibitory ligands. In contrast, T cells modified to express the 1928zCAR and anti-PD-1 scFv clone 27 had increased expansion on aAPCs expressing PD-L1/L2. Data shown is representative of one experiment.

[0033] **Figure 9** shows the amino acid sequences for the complementarity determining regions (CDR) for light and heavy variable chains of some antigen-binding proteins of the disclosure.

[0034] **Figure 10** shows that monoclonal antibodies generated from the anti-PD-1 specific scFvs bind to PD-1 on human T cells. Human monoclonal antibodies from the PD-1 specific scFvs were generated and incubated with human T cells modified to overexpress human PD-1 (1µg/ml). Flow cytometry was used to detect bound antibody using a goat anti-human Ig FITC conjugated antibody. Clones 23, 26 and 27 monoclonal antibodies bound P-1 human T cells at 51%, 78% and 67% respectively. Control antibody (clone

901) did not bind human PD-1 on T cells. Data shown is representative of one experiment.

[0035] Figure 11 shows that T cells modified to express a first generation CAR incubated on aAPCs expressing PD-L1/L2 expand when anti-PD-1 clone 27 monoclonal antibody is present. Human T cells modified to express the first generation CD19-specific CAR (19z1) were incubated with anti-PD-1 monoclonal antibodies for 24 hours then placed on aAPCs expressing PD-L1/L2 or not. After 24 hours stimulation with aAPCs, the cells were then stimulated with CD3/CD28 beads. After three days, the cells were enumerated. 19z1 T cells incubated with no monoclonal antibody (stippled bar), control antibody, 901 (checkered bar) and clones 23 (horizontal striped bar) and 26 (vertical striped bar) monoclonal antibody expanded much less on aAPCs expressing PD-1 ligands (corresponding open bars) compared to aAPCs with no inhibitory ligand. However, 19z1 T cells incubated with anti-PD-1 clone 27 monoclonal antibody (diagonally striped bar) expanded on PD-L1/L2 aAPCs to a greater extent. Data shown is representative of one experiment.

[0036] Figures 12A-12D show the generation of CAR T cells further modified to secrete PD-1 blocking scFv, E27. **A**. Bicistronic retroviral constructs were generated encoding a CD19-specific CAR (termed 1928z) or an ovarian tumor antigen specific CAR (termed 4H1128z) and the PD-1 blocking scFv, E27. The E27 was preceded by a signal peptide, mouse IgK, to allow secretion of the scFv. A HA/His tag was also included to detect the scFv once secreted from the T cells. **B**. Human peripheral blood T cells were transduced with the retroviral constructs encoding the CAR, 1928z, or the CAR and the E27 PD-1 blocking scFv, 1928z-E27. Following transduction, flow cytometry was used to detect expression of the CAR, using an antibody that specifically binds the

CD19-targeted CAR, termed 19E3. **C**. Western blot analysis of supernatant from transduced human T cells was utilized to detect the PD-1 blocking scFv with an anti-HA antibody. We also investigated scFv secretion from T cells modified to express the CAR and a control scFv, B6, which was detected using an anti-c-myc tag antibody. **D**. A standard ^{51}Cr release assay against two $CD19^{+}$ tumor targets was performed to ensure that secretion of an scFv did not interrupt the ability of the CAR to redirect T cells cytolytic capacity. CAR T cells expressing either the CAR alone (1928z or 4H1128z control CAR), the CAR and the E27 scFv (1928z-E27 or 4H1128z-E27), or the CAR and a control scFv (1928z-B6H12.2 or 4H1128z-B6H12.2) were incubated with ^{51}Cr labeled tumor cells (Raji or Nalm6) for 4 hrs. T cells expressing the CD19 specific CAR were able to lyse the tumor targets at equivalent levels, and the ovarian-targeted CAR T cells were unable to lyse Raji or Nalm6. Therefore, we conclude that secretion of the scFv did not interrupt the ability of the CAR to redirect T cell lytic capacity.

[0037] Figures 13A-13D show that T cells modified to express the CAR and secrete a PD-1 blocking scFv resist inhibition from PD-L1-PD-1 interactions, *in vitro*. **A**. T cells expressing the CAR alone (1928z), or the CAR and the PD-1 blocking scFv (1928z-E27) were cultured on 3T3 cells empty cells or 3T3 cells modified to express human PD-L1. Following 24 hours on the 3T3 feeder cells, cells were stimulated with CD3/CD28 beads added to the cultures at a 1:3 bead: T cell ratio. Expansion of T cells was determined with trypan blue enumeration and fresh beads were added twice to the cultures (indicated by the arrows). 1928z T cells expanded on 3T3 empty feeder cells, however did not expand on the 3T3-PD-L1 feeder cells. In contrast, 1928z-E27 T cells expanded on both the 3T3 Empty and 3T3-PD-L1 feeder cells, indicating a resistance to PD-L1-PD-1 mediated suppression. **B**. T cells incubated on 3T3 empty or 3T3-PD-L1 cells as shown in **Figure 13A** were analyzed by flow

cytometry to detect expression on inhibitory receptors, PD-1, 2B4 and LAG3. 1928z cells expressed increased levels of PD-1 than 1928z-E27 cells (not shown). When gated on PD-1$^+$ cells, analysis of 2B4 and LAG3 revealed that 1928z cells had a higher proportion of PD-1$^+$, 2B4$^+$ and LAG3$^+$ cells compared to 1928z-E27 cells. **C**. Transduced T cells were cultured with Raji-PDL1 or Nalm6-PDL1 tumor cells at varying effector to target (E:T) ratios (1:1, 1:3, 1:5) for 72 hours. Flow cytometry following staining with anti-CD3 and anti-CD19 antibodies and enumeration beads were used to monitor lysis of tumor targets and expansion of T cells over time. 1928z-E27 cells (upper curves) continued to expand to greater levels compared to 1928z T cells (lower curves) when cultured with PDL1$^+$ tumor cells. **D**. Transduced T cells were stimulated with Nalm6-PDL1 tumor cells as shown in Figure 3C were re-stimulated with Nalm6-PDL1 tumor cells at the 1:5 T E:T ratio. After 48 hours co-culture flow cytometry was used to determine lysis of tumor targets. 1928z-E27 retained ability to lyse PD-L1 tumor targets upon re-stimulation compared to 1928z cells.

[0038] Figure 14 shows *in vivo* anti-tumor efficacy of T cells modified to express the CAR and secrete the PD-1 blocking scFv. A. SCID-beige mice were inoculated with Raji-PD-L1 tumor cells via intravenous infusion on Day 0. On Day 1, mice were infused intravenously with 10^6 CAR+ T cells and survival was monitored clinically. Mice were euthanized upon development of hind limb paralysis.

[0039] Figures 15A-15D relate to the selection of PD-1 blocking scFv, E27. **A** PD-1 blocking mAb candidates E27, E26 and E23 were used in a competitive binding assay to detect interruption of PD-1 binding to PD-L1 at varying concentrations, compared to a control mAb, targeted to a hapten not present in humans. E23, E26 and E27 mAbs all prevented PD-1 binding to PD-L1. **B**

Schematic of design of PD-1 blocking scFv designed from the E23, E26 and E27 mAbs used in **A**, where the signal peptide was linked to the variable heavy sequence and a serine glycine linker and the the variable light sequence. This HIS/HA tag was included for detection of the scFv. **C** Western blot on SN from 293Glv9 packaging cells transduced to express the secretable scFvs with the 1928z CAR, stained with anti-HA antibody. The E27 scFv was detected at the highest levels and therefore was used in the remainder of the publication. **D** Western blot on SN from PBMCs + 4H1128z and PBMCs +4H1128z stained with anti-HA mAb.

[0040] Figures 16A-16E show that T cells can be co-modified to express CAR and secrete PD-1 blocking scFv, E27. **A** Representative flow cytometry plot demonstrating equivalent CAR expression following transduction with the 1928z CAR alone (1928z) or the 1928z CAR and the E27 PD-1 blocking scFv (1928z-E27), following stainting with 19E3 mAb that specifically binds the 1928z CAR. **B** Western blot on SN from 1928z and 1928z-E27 T cells stained with anti-HA mAb, showing only a ~30 kDa protein in the 1928z-E27 cells, demonstrating that the E27 scFv is secreted from the 1928z-E27 transduced T cells and not those transduced with the CAR alone. **C** Representative flow cytometry demonstrating lower levels of PD-1 expression on 1928z-E27 T cells compared to 1928z T cells following transduction. **D** Expression of PD-1 was statistically significantly lower on 1928z-E27 T cells compared to 1928z T cells, data shown is mean +/- SEM from 4 independent experiments. **E** 4 hr ^{51}Cr release assay demonstrating that lysis of Raji tumor cells was unaffected by secretion of the E27 scFv. 1928z and 1928z-E27 T cells lysed Raji tumor cells equivalently. Control 4H1128z-E27 T cells mediated no increase in lysis of Raji cells compared to 4H1128z T cells. Data shown is representative of two independent experiments.

[0041] Figures 17A-17G show that expression of CAR and E27 protects proliferative and lytic capacity of T cells in the context of $CD19^+$ $PD\text{-}L1^+$ tumor cells. **A** Raji tumor cells were retrovirally modified to express human PD-L1 (Raji-PDL1) and were stained with mAb specific for PD-L1. Parental Raji tumor (Raji) express no PD-L1 and Raji-PDL1 tumor cells expressed high levels of PD-L1. **B** Representative flow cytometry plots showing1928z-E27 T cells lyse more Raji-PDL1 tumor cells compared to 1928z T cells as determined with flow cytometry following 72 hrs co-culture. **C** 1928z-E27 T cells lyse statistically significantly more Raji-PDL1 tumor cells compared to 1928z T cells, data shown the mean +/- SEM from 4 independent experiments. **D** 1928z-E27 T cells expand to greater numbers following co-culture with Raji-PDL1 tumor cells as determined by flow cytometry and enumeration beads, data shown is the average total number of T cells +/- SEM from 4 independent experiments. **E** Representative flow cytometry plot showing increased PD-1 expression on 1928z T cells compared to 1928z-E27 T cells following 7 days co-culture with Raji-PDL1 tumor cells. **F** 1928z T cells express significantly more PD-1 compared to 1928z-E27 T cells, with regard to percentage positive cells and mean fluorescence intensity (MFI) of PD-1 staining. Data show in the mean +/- SEM from 4 independent experiments. **G** Representative flow cytometry plots showing increased percentage of 2B4+PD-1+ 1928z T cells compared to 1928z-E27 cells following coculture with Raji-PDL1 for 7 days. 1928z-E27 T cells also express less BTLA and TIM3 on the 2B4+PD-1+ population. Data shown is representative of 3 independent experiments.

[0042] Figures 18A-18C show that E27 protects proliferative capacity of CD3/CD28 stimulated T cells in the context of PD-L1. **A** NIH3T3 cells were retrovirally modified to express human PD-L1 (3T3-PDL1) and were stained with mAb specific for PD-L1. Parental NIH3T3 (3T3-EMPTY) express no PD-

L1 and 3T3-PDL1 tumor cells expressed high levels of PD-L1. **B** 1928z and 1928z-E27 T cells were cultured with 3T3-EMPTY or 3T3-PDL1 cells and stimulated with CD3/CD28 beads. Cells were enumerated and re-plated on new 3T3 cells on days 3, 6, 9 and 12. 1928z T cells had reduced expansion when cultured with 3T3-PDL1 cells compared to 3T3-EMPTY cells. 1928z-E27 cells had equivalent expansion when cultured on 3T3-EMPTY or 3T3-PDL1 cells. Data shown is the mean fold expansion +/- SEM from 4 independent experiments. **C** Representative flow cytometry plots showing increased expression of 2B4, PD-1, BTLA and TIM3 on 1928z T cells cultured with 3T3-PDL1 compared to1928z T cells cultured on 3T3-EMPTY cells. 1928z-E27 cells had equivalent expression of 2B4, PD-1, BTLA-4 and TIM3 when cultured with 3T3-EMPTY and 3T3-PDL1. Data shown is representative of 3 independent experiments.

[0043] Figure 19 shows that CAR T cells secreting E27 scFv have increased anti-tumor function in vivo. SCID-Beige mice were inoculated with Raji-PDL1 tumor cells intravenously, and the following day were infused intravenously with CAR T cells. Mice treated with 1928z-E27 T cells had enhanced survival compared to mice treated with 1928z T cells. Mice treated with 1928z T cells survived longer than untreated mice, and mice treated with CAR T cells targeted to an irrelevant antigen, 4H1128z and 4H1128z-E27 T cells. Data shown is from 2 independent experiments.

[0044] Figure 20 shows the results of a PD1/PDL1 blocking ELISA using the anti-PD-1 antibodies, ET130-23, ET130-26 and ET130-27. ET901 (negative control) showed no binding, while ET130-23, ET130-26 and ET130-27 showed a blocking effect to PD1/PDL1 binding over a range of concentrations between 0.031 and 10 µg/ml.

[0045] Figure 21 shows the results of a PD1/PDL2 blocking ELISA using the anti-PD-1 antibodies, ET130-23, ET130-26 and ET130-27. ET901 (negative control) showed no binding, while ET130-23, ET130-26 and ET130-27 showed a blocking effect to PD1/PDL1 binding over a range of concentrations between 0.031 and 10 μg/ml.

Detailed Description of the Disclosure

[0046] All publications, patents and other references cited herein are incorporated by reference in their entirety into the present disclosure.

[0047] In practicing the present disclosure, many conventional techniques in molecular biology, microbiology, cell biology, biochemistry, and immunology are used, which are within the skill of the art. These techniques are described in greater detail in, for example, Molecular Cloning: a Laboratory Manual 3rd edition, J.F. Sambrook and D.W. Russell, ed. Cold Spring Harbor Laboratory Press 2001; Recombinant Antibodies for Immunotherapy, Melvyn Little, ed. Cambridge University Press 2009; "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987, and periodic updates); "PCR: The Polymerase Chain Reaction", (Mullis et al., ed., 1994); "A Practical Guide to Molecular Cloning" (Perbal Bernard V., 1988); "Phage Display: A Laboratory Manual" (Barbas et al., 2001). The contents of these references and other references containing standard protocols, widely known to and relied upon by those of skill in the art, including manufacturers' instructions are hereby incorporated by reference as part of the present disclosure.

[0048] In the description that follows, certain conventions will be followed as regards the usage of terminology. Generally, terms used herein are intended to be interpreted consistently with the meaning of those terms as they are known to those of skill in the art.

[0049] An “antigen-binding protein” is a protein or polypeptide that comprises an antigen-binding region or antigen-binding portion, that is, has a strong affinity to another molecule to which it binds. Antigen-binding proteins encompass antibodies, chimeric antigen receptors and fusion proteins.

[0050] "Antibody" and "antibodies" as those terms are known in the art refer to antigen binding proteins of the immune system. The term "antibody" as referred to herein includes whole, full length antibodies and any fragment thereof in which the "antigen-binding portion" or "antigen-binding region" is retained, or single chains thereof. A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant (CH) region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant CL region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies

may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

[0051] The term "antigen-binding portion" or "antigen-binding region" of an antibody, as used herein, refers to that region or portion of the antibody that confers antigen specificity; fragments of antigen-binding proteins, for example, antibodies therefore, includes one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., an HLA-peptide complex). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of antigen-binding fragments encompassed within the term "antibody fragments" of an antibody include a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a Fab fragment (Ward et al., 1989 Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR).

[0052] Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules. These are known as single chain Fv (scFv); see e.g., Bird et al., 1988 Science 242:423-426; and Huston et al., 1988 Proc. Natl. Acad. Sci. 85:5879-5883. Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques known to

those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0053] A "recombinant antibody" or “recombinant antigen-binding protein” is one which has an antigen binding portion that has been identified and selected based on binding characteristics for inclusion in a recombinantly generated antigen-binding protein, for example an antibody.

[0054] The term “homologous sequence thereof” refers to amino acid and nucleotide sequences that are between 60 and 99.9% identical to the sequences shown in Tables 1-14. In some embodiments, a homologous sequence has at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity. In an embodiment, a homologous sequence has 95-99.9% identity; in another embodiment the homologous sequence has 98-99.9%.

[0055] In one embodiment, single chain variable fragments (scFv) that specifically bind to human PD-1 were selected and tested. scFvs were isolated from a phage display library that is a proprietary fully human antibody scFv phage library (Eureka Therapeutics, Emeryville CA). The library is composed of human antibody repertoires from more than 100 Caucasian and Asian healthy donors, and from donors with autoimmune disease, such as systemic lupus erythematosus, scleroderma, etc.

[0056] The antigen used for antibody phage panning was a recombinant fusion protein, PD-1 extracellular domain fused to human IgG1 Fc (PD-1 ECD-Fc domain. DNA sequences encoding PD-1 ECD and hIgG1 Fc were synthesized by Genewiz, Inc. (South Plainfield, NJ). The DNA sequences were then subcloned into Eureka’s proprietary mammalian expression vector, which was then transfected into HEK293 cells for fusion protein expression.

PD-1 ECD-Fc fusion protein was purified by standard FPLC method from HEK293 cell culture medium after the cells died off.

[0057] A human scFv antibody phage display library is used for the selection of mAb clones. In brief, biotinylated antigens (PD-1 ECD-Fc fusion protein) can be first mixed with the human scFv phage library, then the antigen-scFv antibody complexes can be pulled down by streptavidin-conjugated Dynabeads M-280 through a magnetic rack. Bound clones can then be eluted and used to infect *E.Coli* XL1 -Blue. The scFv phage clones expressed in the bacteria can be purified (Yasmina NA, et al. *Probing the binding mechanism and affinity of tanezumab, a recombinant humanized anti-NGF monoclonal antibody, using a repertoire of biosensors*. Protein Science 2008; 17(8): 1326-1335; Roberts WK, et al. *Vaccination with CD20 peptides induces a biologically active, specific immune response in mice*. Blood 2002: 99 (10): 3748-3755). Panning can be performed for 3-4 cycles to enrich scFv phage clones that bind to PD-1 specifically. Positive clones can be determined by standard ELISA method against biotinylated single chain PD-1. Positive clones can be further tested for their binding to PD-1 on live cell surfaces by flow cytometry, using a PD-1$^+$ cell line, for example a 3T3 cell line.

[0058] Some clones encompassed by the disclosure are referred to herein as clones 14, 16, 18, 19, 23, 26, 27, 31, 36, 37, 40, 42, 46, and 47. Variable light (VL) and variable heavy (VH) chain amino acid sequences and the nucleotide sequences that code for these embodiments are shown in Tables 1-14 below. In some embodiments, the VL and VH sequences were linked with a serine glycine linker to form an scFv. In some embodiments, a HA/His tag can be included to allow for detection of the scFv.

[0059] In some embodiments, the disclosure includes anti-bodies that have the scFv sequence fused to one or more constant domains of the heavy chain to form an antibody with an Fc region of a human immunoglobulin to yield a bivalent protein, increasing the overall avididty and stability of the antibody. In addition, the Fc portion allows the the direct conjugation of other molecules, including but not limited to fluorescent dyes, cytotoxins, radioisotopes etc. to the antibody for example, for use in antigen quantitation studies, to immobilize the antibody for affinity measurements, for targeted delivery of a therapeutic agent, to test for Fc-mediated cytotoxicity using immune effector cells and many other applications.

[0060] In some embodiments, the anti-PD-1 antigen-binding proteins may comprise one or more framework region amino acid substitutions designed to improve protein stability, antibody binding, expression levels or to introduce a site for conjugation of therapeutic agents. These scFv are then used to produce recombinant human monoclonal Igs in accordance with methods known to those of skill in the art.

[0061] In some embodiments, the antigen-binding protein is a chimeric antigen receptor (CAR). Chimeric antigen receptor therapy (CAR-T therapy) is a new form of targeted immunotherapy. It merges the exquisite targeting specificity of monoclonal antibodies with the potent cytotoxicity and long-term persistence provided by cytotoxic T cells. This technology enables T cells to acquire long-term novel antigenic specificity independent of the endogenous TCR. Clinical trials have shown clinically significant antitumor activity of CAR-T therapy in neuroblastoma (Louis C.U. *et al.*, *Blood* 118(23):6050-6056), B-ALL (Maude S.L. *et al.*, *N. Engl. J. Med.* 371(16):1507-1517, 2014), CLL (Brentjens R.J. *et al.*, *Blood* 118(18):4817-4828, 2011), and B cell lymphoma (Kochenderfer J.N. *et al.*, Blood. 116(20):4099-4102, 2010). In one study,

a 90% complete remission rate in 30 patients with B-ALL treated with CD19-CAR T therapy was reported (Maude S.L. *et al.*, *supra*).

[0062] In some embodiments, the chimeric antigen receptor comprises an extracellular domain comprising the antibody moiety, a transmembrane domain, and an intracellular signaling domain. In some embodiments, the intracellular signaling domain comprises a CD3ζ intracellular signaling sequence and a co-stimulatory signaling sequence. In some embodiments, the co-stimulatory signaling sequence is a CD28 intracellular signaling sequence.

[0063] Other aspects of the disclosure include without limitation, the use of antigen-binding proteins and nucleic acids that encode them for treatment of PD1 associated disease, for diagnostic and prognostic applications as well as use as research tools for the detection of PD1 in cells and tissues. Pharmaceutical compositions comprising the disclosed antigen-binding proteins and nucleic acids are encompassed by the disclosure. Vectors comprising the nucleic acids of the disclosure for antibody-based treatment by vectored immunotherapy are also contemplated by the present disclosure. Vectors include expression vectors which enable the expression and secretion of antibodies, as well as vectors which are directed to cell surface expression of the antigen binding proteins, such as chimeric antigen receptors (CAR).

[0064] Cells comprising the nucleic acids, for example cells that have been transfected with the vectors of the disclosure are also encompassed by the disclosure.

[0065] For use in diagnostic and research applications, kits are also provided that contain a PD1 antibody or nucleic acids of the disclosure, assay reagents, buffers, and the like.

Table 1: PD1-16

Antigen	PD1 ECD-hIgG1 Fc fusion		
CDRs:	1	2	3
VL	QSISSY (SEQ ID NO: 1)	AAS	QQSYSTPLT (SEQ ID NO: 2)
VH	GFTSSSYW (SEQ ID NO: 3)	IKQDGSEK (SEQ ID NO: 4)	ARGGWSYDM (SEQ ID NO: 5)
Full VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRSR (SEQ ID NO: 6)		
DNA	gacatccagatgacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgccgggcaag tcagagcattagcagctatttaaattggtatcagcagaaaccagggaaagcccctaagctcctgatctatgctgcatc cagtttgcaaagtggggtcccatcaaggttcagtggcagtggatctgggacagatttcactctcaccatcagcagtct gcaacctgaagattttgcaacttactactgtcaacagagttacagtaccccgctcactttcggcggagggaccaagg tggagatcaaacgt (SEQ ID NO: 7)		
Full VH	EVQLVESGGGLVQPGGSLRLSCAASGFTSSSYWMSWVRQAPGRGLEWVANIKQ DGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGGWSYDMW GQGTLVTVSS (SEQ ID NO: 8)		
DNA	gaggtgcagctggtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctgg attcacctctagtagctattggatgagctgggtccgccaggctccagggagagggctggagtgggtggccaacata aagcaagatggaagtgagaagtactatgtggactctgtgaagggccgattcaccatctccagagacaacgccaa gaactcactgtatctgcaaatgaacagcctgagagccgaggacactgccgtgtattactgtgcgcgcggtggttggt cttacgatatgtggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 9)		
scFv PD1-16	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRSRG GGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTSSSYWMSWVR QAPGRGLEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGWSYDMWGQGTLVTVSS HHHHHHGAYPYDVPDYAS* (SEQ ID NO: 10)		
DNA (5' -3')	gacatccagatgacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgccgggcaag tcagagcattagcagctatttaaattggtatcagcagaaaccagggaaagcccctaagctcctgatctatgctgcatc cagtttgcaaagtggggtcccatcaaggttcagtggcagtggatctgggacagatttcactctcaccatcagcagtct gcaacctgaagattttgcaacttactactgtcaacagagttacagtaccccgctcactttcggcggagggaccaagg tggagatcaaacgtggtggtggtggtagcggcggcggcggctctggtggtggtggatccgaggtgcagctggtgga gtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcacctctagtagctatt ggatgagctgggtccgccaggctccagggagagggctggagtgggtggccaacataaagcaagatggaagtga gaagtactatgtggactctgtgaagggccgattcaccatctccagagacaacgccaagaactcactgtatctgcaa atgaacagcctgagagccgaggacactgccgtgtattactgtgcgcgcggtggttggtcttacgatatgtggggtca aggtactctggtgaccgtctcctca (SEQ ID NO: 11)		

Table 2: PD1-18

Antigen	PD1 ECD-hIgG1 Fc fusion		
CDRs:	1	2	3
VL	SSNIGAGYA (SEQ ID NO: 12)	TNN	QSYDSSLSGVI SEQ ID NO: 13)
VH	GYTLTELS (SEQ ID NO: 14)	FDPEDGET (SEQ ID NO: 15)	ARAYYGFDQ (SEQ ID NO: 16)
Full VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYAVNWYQLLPGTAPKLLISTNNNR PSGVPDRFSGSQFGASASLAITGLQAEDEADYYCQSYDSSLSGVIFGGGTKLTVLG (SEQ ID NO: 17)		
DNA	cagtctgtgttgacgcagccgccctcagtgtctggggccccagggcagagggtcaccatctcctgcactgggagcag ctccaacatcggggcaggttatgctgtaaattggtaccagcttcttccaggaacagcccccaaactcctcatctctacta acaacaatcggccctcaggggtccctgaccgattctctggctcccagtttggcgcctctgcctccctggccatcactgg actccaggctgaggatgaggctgattattactgccagtcctatgacagtagtctgagtggtgtgatattcggcggaggg accaagctgaccgtcctaggt (SEQ ID NO: 18)		
Full VH	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDP EDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCARAYYGFDQWG QGTLVTVSS (SEQ ID NO: 19)		
DNA	gaagtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggtttccgg atacaccctcactgaattatccatgcactgggtgcgacaggctcctggaaaagggcttgagtggatgggaggttttgat cctgaagatggtgaaacaatctacgcacagaagttccagggcagagtcaccatgaccgaggacacatctacagac acagcctacatggagctgagcagcctgaggtctgaggacactgccgtgtattactgtgcgcgcgcttactacggtttcg atcagtggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 20)		
scFv PD-1-18	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKR GGGGSGGGGSGGGGS EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDP EDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCARAYYGFDQWG QGTLVTVSSHHHHHHGAYPYDVPDYAS* (SEQ ID NO: 21)		
DNA (5' -3')	cagtctgtgttgacgcagccgccctcagtgtctggggccccagggcagagggtcaccatctcctgcactgggagcag ctccaacatcggggcaggttatgctgtaaattggtaccagcttcttccaggaacagcccccaaactcctcatctctacta acaacaatcggccctcaggggtccctgaccgattctctggctcccagtttggcgcctctgcctccctggccatcactgg actccaggctgaggatgaggctgattattactgccagtcctatgacagtagtctgagtggtgtgatattcggcggaggg accaagctgaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcc gaagtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggtttccgg atacaccctcactgaattatccatgcactgggtgcgacaggctcctggaaaagggcttgagtggatgggaggttttgat cctgaagatggtgaaacaatctacgcacagaagttccagggcagagtcaccatgaccgaggacacatctacagac acagcctacatggagctgagcagcctgaggtctgaggacactgccgtgtattactgtgcgcgcgcttactacggtttcg atcagtggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 22)		

Table 3: PD1-23

Antigen	PD1 ECD-hIgG1 Fc fusion		
CDRs:	1	2	3
VL	SSNIGNNA (SEQ ID NO: 23)	YND	AAWDDSVNGYV (SEQ ID NO: 24)
VH	GYTFTRFG (SEQ ID NO: 25)	ISVNNGNT (SEQ ID NO: 26)	ARYMYGRRDS (SEQ ID NO: 27)
Full VL	QAVLTQPPSMSEAPRQRVTISCSGSSSNIGNNAVNWYQQLPGKAPKLLIYYNDLLSS GVSDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSVNGYVFGTGTKVTVLG (SEQ ID NO: 28)		
DNA	caggctgtgctgactcagccaccctcgatgtctgaagcccccaggcagagggtcaccatctcctgttctggaagcagc tccaacatcggaaataatgctgtaaactggtaccagcagctcccaggaaaggctcccaaactcctcatctattataatg atctgctgtcctcaggggtctctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggctcc agtctgaggatgaggctgattattactgtgcagcatgggatgacagtgtgaatggttatgtcttcggaactgggaccaag gtcaccgtcctaggt (SEQ ID NO: 29)		
Full VH	EVQLVQSGAEVKKPGDSVKVSCKASGYTFTRFGFSWVRQAPGQGLEWMGWISVN NGNTKYAQKYQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARYMYGRRDSWG QGTLVTVSS (SEQ ID NO: 30)		
DNA	Gaggtccagctggtgcagtctggagctgaggtgaagaagcctggggactcagtgaaggtctcctgcaaggcttctgg ttacctttaccagatttggtttcagctgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcagc gttaataatggtaacacaaagtatgcacagaagtaccagggcagagtcaccatgaccacagacacatccacgagc acagcctacatggagctgaggagcctgaggtctgacgacactgccgtgtattactgtgcgcgctacatgtacggtcgtc gtgattcttggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 31)		
scFv PD-1-23	QAVLTQPPSMSEAPRQRVTISCSGSSSNIGNNAVNWYQQLPGKAPKLLIYYNDLLSS GVSDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSVNGYVFGTGTKVTVLG GSRGGGGSGGGGSGGGGS EVQLVQSGAEVKKPGDSVKVSCKASGYTFTRFGFSWVRQAPGQGLEWMGWISVN NGNTKYAQKYQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARYMYGRRDSWG QGTLVTVSS GQHHHHHHGAYPYDVPDYAS* (SEQ ID NO: 32)		
DNA (5' -3')	caggctgtgctgactcagccaccctcgatgtctgaagcccccaggcagagggtcaccatctcctgttctggaagcagc tccaacatcggaaataatgctgtaaactggtaccagcagctcccaggaaaggctcccaaactcctcatctattataatg atctgctgtcctcaggggtctctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggctcc agtctgaggatgaggctgattattactgtgcagcatgggatgacagtgtgaatggttatgtcttcggaactgggaccaag gtcaccgtcctaggtggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccgaggtccag ctggtgcagtctggagctgaggtgaagaagcctggggactcagtgaaggtctcctgcaaggcttctggttacacctttac cagatttggtttcagctgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcagcgttaataatggt aacacaaagtatgcacagaagtaccagggcagagtcaccatgaccacagacacatccacgagcacagcctacat ggagctgaggagcctgaggtctgacgacactgccgtgtattactgtgcgcgctacatgtacggtcgtcgtgattcttggg gtcaaggtactctggtgaccgtctcctcagccggccagcaccatcaccatcaccatggcgcatacccgtacgacgttc cggactacgcttcttag (SEQ ID NO: 33)		

Table 4: PD1-26

Antigen	PD1 ECD-hIgG1 Fc fusion		
CDRs:	1	2	3
VL	NIGSKS (SEQ ID NO: 34)	YDS	QVWDNHSDVV (SEQ ID NO: 35)
VH	RNKFSSYA (SEQ ID NO: 36)	ISGSGGTT (SEQ ID NO: 37)	ARWYSSYYDV (SEQ ID NO: 38)
Full VL	QSVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDSDRPSG IPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDNHSDVVFGGGTKLTVLG (SEQ ID NO: 39)		
DNA	Cagtctgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatagcg accggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcagggtc gaagccggggatgaggccgactattactgtcaggtctgggataatcatagtgatgtggtattcggcggagggaccaag ctgaccgtcctaggt (SEQ ID NO: 40)		
Full VH	QVQLVESGGGLVQPGGSLRLSCAASGYTRNKFSSYAMSWVRQAPGKGLEWVSGI SGSGGTTYYADSVKGRFTISRDNSKNTQYLQLDSLRAEDTAVYYCARWYSSYYDV WGQGTLVTVSS (SEQ ID NO: 41)		
DNA	Caggtgcagctggtggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctgga tacacccgtaacaaatttagcagctatgccatgagctgggtccgccaggctccagggaagggcctggaatgggtctc aggtattagtggtagtggtggtactacatactatgcagactccgtgaagggccggttcaccatctccagagacaattcca agaacacgcagtatctgcaattggacagcctgagagccgaggacacggccgtatattactgtgcgcgctggtactctt cttactacgatgtttggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 42)		
scFv PD1-26	QSVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDSDRPSG IPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDNHSDVVFGGGTKLTVLGGGG GSGGGGSGGGGS QVQLVESGGGLVQPGGSLRLSCAASGYTRNKFSSYAMSWVRQAPGKGLEWVSGI SGSGGTTYYADSVKGRFTISRDNSKNTQYLQLDSLRAEDTAVYYCARWYSSYYDV WGQGTLVTVSS HHHHHHGAYPYDVPDYAS* (SEQ ID NO: 43)		
DNA (5' -3')	cagtctgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatagcg accggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcagggtc gaagccggggatgaggccgactattactgtcaggtctgggataatcatagtgatgtggtattcggcggagggaccaag ctgaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcccaggtgcagctggtggag tctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggatacacccgtaacaaattta gcagctatgccatgagctgggtccgccaggctccagggaagggcctggaatgggtctcaggtattagtggtagtggtg gtactacatactatgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgcagtatctgc aattggacagcctgagagccgaggacacggccgtatattactgtgcgcgctggtactcttcttactacgatgtttggggtc aaggtactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttct tag (SEQ ID NO: 44)		

Table 5: PD-1-27

Antigen	PD1 ECD-hIgG1 Fc fusion		
CDRs:	1	2	3
VL	NIGSKS (SEQ ID NO: 34)	YDS	QVWDSSSDYV (SEQ ID NO: 45)
VH	GFTFSSYA (SEQ ID NO: 46)	ISGSGGST (SEQ ID NO: 47)	ARNYISMFDS (SEQ ID NO: 48)
Full VL	QSVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQRPGQAPVLVIYYDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDYVFGIGTKVTVLG (SEQ ID NO: 49)		
DNA	cagtctgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaggccaggccaggcccctgtgctggtcatctattatgatagc gaccggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcaggg tcgaagccggggatgaggccgactattactgtcaggtgtgggatagtagtagtgattatgtcttcggaattgggaccaa ggtcaccgtcctaggt (SEQ ID NO: 50)		
Full VH	EVQLVESGGGLIQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSG GSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNYISMFDSWGQG TLVTVSS (SEQ ID NO: 51)		
DNA	gaggtgcagctggtggagtctggaggaggcttgatccagcctgggggtccctgagactctcctgtgcagcctctgg attcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattag tggtagtggtggtagcacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaaca cgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgcaactacatctctatgtt cgattcttggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 52)		
scFv PD1- 27	QSVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQRPGQAPVLVIYYDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDYVFGIGTKVTVLG GGGGSGGGGSGGGGS EVQLVESGGGLIQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSG GSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNYISMFDSWGQG TLVTVSSHHHHHHGAYPYDVPDYAS*(SEQ ID NO: 53)		
DNA (5' -3')	cagtctgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaggccaggccaggcccctgtgctggtcatctattatgatagc gaccggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcaggg tcgaagccggggatgaggccgactattactgtcaggtgtgggatagtagtagtgattatgtcttcggaattgggaccaa ggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatccgaggtgcagctggtgg agtctggaggaggcttgatccagcctgggggtccctgagactctcctgtgcagcctctggattcacctttagcagctat gccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcac atactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatga acagcctgagagccgaggacacggccgtatattactgtgcgcgcaactacatctctatgttcgattcttggggtcaagg tactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttcttag (SEQ ID NO: 54)		

Table 6: PD-1-31

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	NIGSKS (SEQ ID NO: 34)	YDS	QVWDSSSDHV (SEQ ID NO: 55)
VH	GFTFSSYA (SEQ ID NO: 46)	ISGSGGST (SEQ ID NO: 47)	ARGYSSYYDA (SEQ ID NO: 56)
Full VL	QAVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVFGTGTKVTVLG (SEQ ID NO: 57)		
DNA	caggctgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaac aacattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatag cgaccggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcagg gtcgaagccggggatgaggccgactattactgtcaggtgtgggatagtagtagtgatcatgtcttcggaactgggacc aaggtcaccgtcctaggt (SEQ ID NO: 58)		
Full VH	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGYSSYYDAWG QGTLVTVSS (SEQ ID NO: 59)		
DNA	caggtgcagctggtggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctgg attcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattag tggtagtggtggtagcacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaaca cgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgcggttactcttcttacta cgatgcttggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 60)		
scFv PD-1- 31	QAVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVFGTGTKVTVLGGG GGSGGGGSGGGGS QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGYSSYYDAWG QGTLVTVSS HHHHHHGAYPYDVPDYAS* (SEQ ID NO: 61)		
DNA (5' -3')	caggctgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaac aacattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatag cgaccggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcagg gtcgaagccggggatgaggccgactattactgtcaggtgtgggatagtagtagtgatcatgtcttcggaactgggacc aaggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcccaggtgcagctggt ggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggattcacctttagcagc tatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagc acatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaat gaacagcctgagagccgaggacacggccgtatattactgtgcgcgcggttactcttcttactacgatgcttggggtcaa ggtactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttctta g (SEQ ID NO: 62)		

Table 7: PD-1-40

Antigen	PD1 ECD-hIgG1 Fc fusion		
CDRs:	1	2	3
VL	RSNIGENT (SEQ ID NO: 63)	SNN	AAWDDRLNGYV (SEQ ID NO: 64)
VH	GYTFTNYG (SEQ ID NO: 65)	IGAQKGDT (SEQ ID NO: 66)	ARSQGVPFDS (SEQ ID NO: 67)
Full VL	QSVLTQPPSASGTPGQRVTISCSGSRSNIGENTVNWYQQLPGTAPKLLIYSNNQRP SGVPDRFSGSKSGTSASLAISGLHSDDEADYFCAAWDDRLNGYVFGTGTKVTVLG (SEQ ID NO: 68)		
DNA	Cagtctgtgttgactcagccaccctcagcgtctgggacccccgggcagagagtcaccatctcttgttctggaagcaggt ccaacatcggagaaaatactgtcaactggtaccagcagctcccaggaacggcccccaaactcctcatctacagtaat aatcagcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggc ttcactctgacgatgaggctgactatttttgtgcagcatgggatgaccgcctcaatggttatgtcttcggaactgggaccaa ggtcaccgtcctaggt (SEQ ID NO: 69)		
Full VH	QVQLVQSGPEVKKPGASVKVSCKASGYTFTNYGFTWVRQAPGQGLEWMGWIGAQ KGDTEYAQKFQGRVTMTTDTSTSTVYLELRSLRSDDTAVYYCARSQGVPFDSWGQ GTLVTVSS (SEQ ID NO: 70)		
DNA	Caggtgcagctggtgcaatctggacctgaggtgaagaagcctggggcctcggtgaaggtctcctgcaaggcttctggt tacacctttaccaactatggtttcacctgggtgcgacaggcccctggacaaggtcttgagtggatgggatggatcggcg ctcaaaagggtgacacagagtatgcacaaaaattccagggcagagtcaccatgacgacagacacatccacgagc acagtctacttggagttgaggagcctgaggtctgacgacacggccgtgtattactgtgcgcgctctcagggtgttccgttc gattcttggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 71)		
scFv PD-1-40	QSVLTQPPSASGTPGQRVTISCSGSRSNIGENTVNWYQQLPGTAPKLLIYSNNQRP SGVPDRFSGSKSGTSASLAISGLHSDDEADYFCAAWDDRLNGYVFGTGTKVTVLG GGGGSGGGGSGGGGS QVQLVQSGPEVKKPGASVKVSCKASGYTFTNYGFTWVRQAPGQGLEWMGWIGAQ KGDTEYAQKFQGRVTMTTDTSTSTVYLELRSLRSDDTAVYYCARSQGVPFDSWGQ GTLVTVSSHHHHHHGAYPYDVPDYAS* (SEQ ID NO: 72)		
DNA (5' -3')	cagtctgtgttgactcagccaccctcagcgtctgggacccccgggcagagagtcaccatctcttgttctggaagcaggt ccaacatcggagaaaatactgtcaactggtaccagcagctcccaggaacggcccccaaactcctcatctacagtaat aatcagcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggc ttcactctgacgatgaggctgactatttttgtgcagcatgggatgaccgcctcaatggttatgtcttcggaactgggaccaa ggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcccaggtgcagctggtgca atctggacctgaggtgaagaagcctggggcctcggtgaaggtctcctgcaaggcttctggttacacctttaccaactatg gtttcacctgggtgcgacaggcccctggacaaggtcttgagtggatgggatggatcggcgctcaaaagggtgacaca gagtatgcacaaaaattccagggcagagtcaccatgacgacagacacatccacgagcacagtctacttggagttga ggagcctgaggtctgacgacacggccgtgtattactgtgcgcgctctcagggtgttccgttcgattcttggggtcaaggta ctctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttcttag (SEQ ID NO: 73)		

Table 8: PD-1-36

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	RSNIGSNT (SEQ ID NO: 74)	NNN	ATWDDSLNEYV (SEQ ID NO: 75)
VH	GYTFTRYG (SEQ ID NO: 76)	I SGYNGNT (SEQ ID NO: 77)	ARHGYGYHGD (SEQ ID NO: 78)
Full VL	QSVLTQPPSASATPGQRGTISCSGGRSNIGSNTVNWYQQLPGTAPKLLIYNNNLRP SGVPDRFSGSKSGTSASLAIRGLQSEDEADYYCATWDDSLNEYVFGTGTKVTVLG (SEQ ID NO: 79)		
DNA	Cagtctgtgttgactcagccaccctcagcgtctgcgacccccgggcagaggggcaccatttcgtgttctggaggcagg tccaacatcggaagtaacactgttaactggtaccagcagctcccaggaacggcccccaaactcctcatctataataat aatctgcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcaggggc tccagtctgaggatgaggctgattattactgtgcaacatgggatgacagcctgaatgaatatgtcttcggaactgggacc aaggtcaccgtcctaggt (SEQ ID NO: 80)		
Full VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQAPGQGLEWMGWISGY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARHGYGYHGDWG QGTLVTVSS (SEQ ID NO: 81)		
DNA	Caggtgcagctggtgcaatctggagctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggt tacacctttaccagatatggtatcagctgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcagc ggttacaacggtaacacaaactatgcacagaagctccagggcagagtcaccatgaccacagacacatccacgagc acagcctacatggagctgaggagcctgaggtctgacgacacggccgtgtattactgtgcgcgccatggttacggttac catggtgattggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 82)		
scFv PD-1-36	QSVLTQPPSASATPGQRGTISCSGGRSNIGSNTVNWYQQLPGTAPKLLIYNNNLRP SGVPDRFSGSKSGTSASLAIRGLQSEDEADYYCATWDDSLNEYVFGTGTKVTVLG GGGGSGGGGSGGGGS QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQAPGQGLEWMGWISGY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARHGYGYHGDWG QGTLVTVSS HHHHHHGAYPYDVPDYAS* (SEQ ID NO: 83)		
DNA (5' -3')	cagtctgtgttgactcagccaccctcagcgtctgcgacccccgggcagaggggcaccatttcgtgttctggaggcaggt ccaacatcggaagtaacactgttaactggtaccagcagctcccaggaacggcccccaaactcctcatctataataata atctgcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcaggggct ccagtctgaggatgaggctgattattactgtgcaacatgggatgacagcctgaatgaatatgtcttcggaactgggacc aaggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcc caggtgcagctggtgcaatctggagctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggt tacacctttaccagatatggtatcagctgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcagc ggttacaacggtaacacaaactatgcacagaagctccagggcagagtcaccatgaccacagacacatccacgagc acagcctacatggagctgaggagcctgaggtctgacgacacggccgtgtattactgtgcgcgccatggttacggttac catggtgattggggtcaaggtactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacg ttccggactacgcttcttag (SEQ ID NO: 84)		

Table 9: PD-1-37

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	SSNIGAGYV (SEQ ID NO: 85)	HNN	QSYDSSLSGWV (SEQ ID NO: 86)
VH	GFTFKDYY (SEQ ID NO: 87)	ISTSGNSV (SEQ ID NO: 88)	ARSPGHSDYDS (SEQ ID NO: 89)
Full VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYVVQWYQQLPGTAPKLLIYHNNDR PSGVPYRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTKLTVLG (SEQ ID NO: 90)		
DNA	Cagtctgtgctgacgcagccgccctcagtgtctggggccccagggcagagggtcaccatctcctgtactgggagcag ctccaacatcggggcaggttatgttgtacagtggtatcagcagcttccaggaacagcccccaaactcctcatctatcata acaacgatcggccctcaggggtcccttaccgattctctggctccaagtctggcacctcagcctccctggccatcactgg gctccaggctgaggatgaggctgattattactgccagtcctatgacagcagcctgagtggttgggtgttcggcggaggg accaagctgaccgtcctaggt (SEQ ID NO: 91)		
Full VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFKDYYMNWIRQAPGKGLEWISHISTSGN SVDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSPGHSDYDSWGQG TLVTVSS (SEQ ID NO: 92)		
DNA	gaggtgcagctggtggagtctgggggaggcctagtcaagcctggagggtccctgagactctcctgtgcagcctctgga ttcacctttaaagactactacatgaactggatccgccaggctccagggaagggcctggagtggatttcacacattagta ccagcggtaatagtgtagattatgcagactctgtcaagggccggttcaccatctccagggacaacgccaagaattcac tgtacctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgctctccgggtcattctgacta cgattcttggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 93)		
scFv PD-1-37	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYVVQWYQQLPGTAPKLLIYHNNDR PSGVPYRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTKLTVLG GGGGSGGGGSGGGGS EVQLVESGGGLVKPGGSLRLSCAASGFTFKDYYMNWIRQAPGKGLEWISHISTSGN SVDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSPGHSDYDSWGQG TLVTVSS HHHHHHGAYPYDVPDYAS*(SEQ ID NO: 94)		
DNA (5' -3')	cagtctgtgctgacgcagccgccctcagtgtctggggccccagggcagagggtcaccatctcctgtactgggagcag ctccaacatcggggcaggttatgttgtacagtggtatcagcagcttccaggaacagcccccaaactcctcatctatcata acaacgatcggccctcaggggtcccttaccgattctctggctccaagtctggcacctcagcctccctggccatcactgg gctccaggctgaggatgaggctgattattactgccagtcctatgacagcagcctgagtggttgggtgttcggcggaggg accaagctgaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcc gaggtgcagctggtggagtctgggggaggcctagtcaagcctggagggtccctgagactctcctgtgcagcctctgga ttcacctttaaagactactacatgaactggatccgccaggctccagggaagggcctggagtggatttcacacattagta ccagcggtaatagtgtagattatgcagactctgtcaagggccggttcaccatctccagggacaacgccaagaattcac tgtacctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgctctccgggtcattctgacta cgattcttggggtcaaggtactctggtgaccgtctcctca caccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttcttag (SEQ ID NO: 95)		

Table 10: PD-1-19

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	NIGDKS (SEQ ID NO: 96)	YDS	QVWASGTDHPYVI (SEQ ID NO: 97)
VH	GFTFSSYA (SEQ ID NO: 46)	ISGSGGST (SEQ ID NO: 47)	ARMYGSYTDM (SEQ ID NO: 98)
Full VL	SYVLTQPPSVSVAPGKTARITCGGNNIGDKSVHWYQQKPGQAPVLVIYYDSDRPSGI PERFSGSNSGNTATLTISRVEAGDEADYYCQVWASGTDHPYVIFGGGTKVTVLG (SEQ ID NO: 99)		
DNA	Tcctatgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaaca acattggagataaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatagcg accggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcagggtc gaagccggggacgaggccgactattactgtcaggtgtgggctagtggtactgatcatccctatgtgatattcggcggag gaccaaggtcaccgtcctaggt (SEQ ID NO: 100)		
Full VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSG GSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARMYGSYTDMWGQG TLVTVSS (SEQ ID NO: 101)		
DNA	Gaggtgcagctggtggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctgga ttcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtg gtagtggtggtagcacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacg ctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgcatgtacggttcttacactg atatgtggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 102)		
scFv PD-1-19	SYVLTQPPSVSVAPGKTARITCGGNNIGDKSVHWYQQKPGQAPVLVIYYDSDRPSGI PERFSGSNSGNTATLTISRVEAGDEADYYCQVWASGTDHPYVIFGGGTKVTVLGGG GGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARMYGSYTDMWGQGTLVTVSS HHHHHHGAYPYDVPDYAS*(SEQ ID NO: 103)		
DNA (5' -3')	tcctatgtgctgactcagccaccctcagtgtcagtggccccaggaaagacggccaggattacctgtgggggaaacaa cattggagataaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatagcga ccggccctcagggatccctgagcgattctctggctccaactctgggaacacggccaccctgaccatcagcagggtcg aagccggggacgaggccgactattactgtcaggtgtgggctagtggtactgatcatccctatgtgatattcggcggagg gaccaaggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcc gaggtgcagctggtggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggat tcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtgg tagtggtggtagcacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgc tgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgcatgtacggttcttacactgat atgtggggtcaaggtactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccgg actacgcttcttag (SEQ ID NO: 104)		

Table 11: PD-1-14

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	SSNIGYNY (SEQ ID NO: 105)	RNN	TSWDDSLSGYV (SEQ ID NO: 106)
VH	GNAFTNFY (SEQ ID NO: 107)	INPSGTDLT (SEQ ID NO: 108)	ARQYAYGYSGFDM (SEQ ID NO: 109)
Full VL	QSVLTQPPSASGTPGQRVTISCSGSSSNIGYNYVYWYQQLPGTAPKLLISRNNQRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCTSWDDSLSGYVFGPGTKVTVLG (SEQ ID NO: 110)		
DNA	cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatctcttgttctggaagcagct ccaacatcggatataattatgtatactggtaccagcagctcccaggaacggcccccaaactcctcatctctagaaataa tcagcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggctc cggtccgaggatgaggctgactattactgtacatcgtgggatgacagcctgagtggttatgtcttcggacctgggacca aggtcaccgtcctaggt (SEQ ID NO: 111)		
Full VH	EVQLVQSGAEVKKPGASVKVSCKASGNAFTNFYIHWVRQAPGQGLEWMGLINPSG TDLTRYAQKFQGRVTMTRDTPTSTVYMELSSLRSDDTAVYYCARQYAYGYSGFDM WGQGTLVTVSS (SEQ ID NO: 112)		
DNA	Gaagtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaaggcatctgg aaacgccttcaccaacttctatatacactgggtgcgacaggcccctggacaagggcttgagtggatgggattaatcaa ccctagtggtactgacctcacaaggtacgcacagaagttccagggcagagtcaccatgaccagggacacgcccac gagcacagtctacatggagctgagcagcctgaggtctgacgacacggctgtgtattactgtgcgcgccagtacgctta cggttactctggtttcgatatgtggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 113)		
scFv PD-1-14	QSVLTQPPSASGTPGQRVTISCSGSSSNIGYNYVYWYQQLPGTAPKLLISRNNQRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCTSWDDSLSGYVFGPGTKVTVLGG GGGSGGGGSGGGGS EVQLVQSGAEVKKPGASVKVSCKASGNAFTNFYIHWVRQAPGQGLEWMGLINPSG TDLTRYAQKFQGRVTMTRDTPTSTVYMELSSLRSDDTAVYYCARQYAYGYSGFDM WGQGTLVTVSS HHHHHHGAYPYDVPDYAS*(SEQ ID NO: 114)		
DNA (5' -3')	cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatctcttgttctggaagcagct ccaacatcggatataattatgtatactggtaccagcagctcccaggaacggcccccaaactcctcatctctagaaataa tcagcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggctc cggtccgaggatgaggctgactattactgtacatcgtgggatgacagcctgagtggttatgtcttcggacctgggacca aggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatccgaagtgcagctggtgc agtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaaggcatctggaaacgccttcaccaact tctatatacactgggtgcgacaggcccctggacaagggcttgagtggatgggattaatcaaccctagtggtactgacct cacaaggtacgcacagaagttccagggcagagtcaccatgaccagggacacgcccacgagcacagtctacatgg agctgagcagcctgaggtctgacgacacggctgtgtattactgtgcgcgccagtacgcttacggttactctggtttcgata tgtggggtcaaggtactctggtgaccgtctcctca caccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttcttag (SEQ ID NO: 115)		

Table 12: PD-1-47

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	QSVSNW (SEQ ID NO: 116)	AAS	QQSYSTPIT (SEQ ID NO: 117)
VH	GYTFTSYY (SEQ ID NO: 118)	INPNTGGS (SEQ ID NO: 119)	ARGDVTYDE (SEQ ID NO: 120)
Full VL	DIQMTQSPSSVSASVGDRVTITCRASQSVSNWLAWYQLKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGGGTKVEIKR (SEQ ID NO: 121)		
DNA	Gacatccagatgacccagtctccatcttccgtgtctgcatctgtaggagacagagtcaccatcacttgtcgggcgagtc agagtgttagcaactggttagcctggtatcaactgaaaccagggaaagcccctaagctcctgatctatgctgcatccag tttgcaaagtggggtcccatcaaggttcagtggcagtggatctgggacagatttcactctcaccatcagcagtctgcaac ctgaagattttgcaacttactactgtcaacagagttacagtaccccgatcaccttcggcggagggaccaaggtggagat caaacgt (SEQ ID NO: 122)		
Full VH	QVQLVQSGAEVKKPGTSVKVSCKASGYTFTSYYIHWVRQAPGQGLEWMGWINPNT GGSNFAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARGDVTYDEWGQGT LVTVSS (SEQ ID NO: 123)		
DNA	Caggtccagctggtacagtctggggctgaggtgaagaagcctgggacctcagtgaaggtctcctgcaaggcttctgg atacaccttcacctcctactatatacactgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcaa ccctaacactggtggctcaaactttgcacagaagtttcagggcagggtcaccatgaccagggacacgtccatcagca cagcctacatggagctgaacaggctgaggtctgacgacacggccgtgtattactgtgcgcgcggtgacgttacttacg atgaatggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 124)		
scFv PD-1-47	DIQMTQSPSSVSASVGDRVTITCRASQSVSNWLAWYQLKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGGGTKVEIKR GGGGSGGGGSGGGGS QVQLVQSGAEVKKPGTSVKVSCKASGYTFTSYYIHWVRQAPGQGLEWMGWINPNT GGSNFAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARGDVTYDEWGQGT LVTVSS HHHHHHGAYPYDVPDYAS*(SEQ ID NO: 125)		
DNA (5' -3')	gacatccagatgacccagtctccatcttccgtgtctgcatctgtaggagacagagtcaccatcacttgtcgggcgagtca gagtgttagcaactggttagcctggtatcaactgaaaccagggaaagcccctaagctcctgatctatgctgcatccagtt tgcaaagtggggtcccatcaaggttcagtggcagtggatctgggacagatttcactctcaccatcagcagtctgcaacc tgaagattttgcaacttactactgtcaacagagttacagtaccccgatcaccttcggcggagggaccaaggtggagatc aaacgtggtggtggtggtagcggcggcggcggctctggtggtggtggatcc caggtccagctggtacagtctggggctgaggtgaagaagcctgggacctcagtgaaggtctcctgcaaggcttctgga tacaccttcacctcctactatatacactgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcaac cctaacactggtggctcaaactttgcacagaagtttcagggcagggtcaccatgaccagggacacgtccatcagcac agcctacatggagctgaacaggctgaggtctgacgacacggccgtgtattactgtgcgcgcggtgacgttacttacgat gaatggggtcaaggtactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccg gactacgcttcttag (SEQ ID NO: 126)		

Table 13: PD-1-46

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	NIGSKS (SEQ ID NO: 34)	YDD	QVWDINDHYV (SEQ ID NO: 127)
VH	GFTFSSYA (SEQ ID NO: 46)	ISGSGGST (SEQ ID NO: 47)	ARSQASFMDI (SEQ ID NO: 128)
Full VL	SYELTQPPSVSVAPGKTASITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDDMRPSG IPERFSGSSSGNTATLTISPVEAGDEADYYCQVWDINDHYVFASGTKVTVLG (SEQ ID NO: 129)		
DNA	Tcctatgagctgactcagccaccctcagtgtcagtggccccaggaaagacggccagcattacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatgacat gcggccctcaggtatccctgagcgattctctggctccagctctgggaacacggccaccctgaccatcagcccggtcga agccggggatgaggccgactattactgtcaggtgtgggatattaatgatcattatgtcttcgcatcggggaccaaggtca ccgtcctaggt (SEQ ID NO: 130)		
Full VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSG GSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSQASFMDIWGQGT LVTVSS (SEQ ID NO: 131)		
DNA	Gaggtgcagctggtggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctgga ttcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtg gtagtggtggtagcacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacg ctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgctctcaggcttctttcatgga tatctggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 132)		
scFv PD-1-46	SYELTQPPSVSVAPGKTASITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDDMRPSG IPERFSGSSSGNTATLTISPVEAGDEADYYCQVWDINDHYVFASGTKVTVLGGGGG SGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSG GSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSQASFMDIWGQGT LVTVSS HHHHHHGAYPYDVPDYAS* (SEQ ID NO: 133)		
DNA (5' -3')	tcctatgagctgactcagccaccctcagtgtcagtggccccaggaaagacggccagcattacctgtgggggaaacaa cattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcatctattatgatgacatg cggccctcaggtatccctgagcgattctctggctccagctctgggaacacggccaccctgaccatcagcccggtcgaa gccggggatgaggccgactattactgtcaggtgtgggatattaatgatcattatgtcttcgcatcggggaccaaggtcac cgtcctaggtggtggtggtagcggcggcggcggctctggtggtggtggatccgaggtgcagctggtggagtctgg gggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggattcacctttagcagctatgccatga gctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacg cagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctg agagccgaggacacggccgtatattactgtgcgcgctctcaggcttctttcatggatatctggggtcaaggtactctggtg accgtctcctca caccatcaccatcaccatggcgcatacccgtacgacgttccggactacgcttcttag (SEQ ID NO: 134)		

Table 14: PD-1-42

Antigen	PD1 ECD hIgG1 Fc fusion		
CDRs:	1	2	3
VL	NIGSKS (SEQ ID NO: 34)	DDS	QVWDSSSDQGV (SEQ ID NO: 135)
VH	GFTFSSYA (SEQ ID NO: 46)	IGTGGGT (SEQ ID NO: 136)	ARGTGYDGDQ (SEQ ID NO: 137)
Full VL	LPVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDQGVFGTGTKVTVLG (SEQ ID NO: 138)		
DNA	Ctgcctgtgctgactcagccaccctcggtgtcagtggccccaggacagacggccaggatcacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcgtctatgatgatagcg accggccctcagggatccctgagcgattctctggctccaattctgggaacacggccaccctgaccatcagcagggtcg aagccggggatgaggccgactattactgtcaggtgtgggatagtagtagtgatcagggcgtcttcggaactgggacca aggtcaccgtcctaggt (SEQ ID NO: 139)		
Full VH	EVQLVQSGGGLVQPRGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWVSAIGTG GGTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAMYYCARGTGYDGDQWGQ GTLVTVSS (SEQ ID NO: 140)		
DNA	Gaagtgcagctggtgcagtctgggggaggcttggtacagcctaggggtccctgagactctcctgtgcaggctctgga ttcaccttcagtagctatgctatgcactgggttcgccaggctccaggaaaaggtctggagtgggtatcagctattggtact ggtggtggcacatactatgcagactccgtgaagggccgattcaccatctccagggacaatgccaagaactccttgtat cttcaaatgaacagcctgagagccgaggacaccgccatgtattactgtgcgcgcggtactggttacgacggtgatcag tggggtcaaggtactctggtgaccgtctcctca (SEQ ID NO: 141)		
scFv PD-1-42	LPVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDQGVFGTGTKVTVLG GGGGSGGGGSGGGGS EVQLVQSGGGLVQPRGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWVSAIGTG GGTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAMYYCARGTGYDGDQWGQ GTLVTVSS HHHHHHGAYPYDVPDYAS* (SEQ ID NO: 142)		
DNA (5' -3')	ctgcctgtgctgactcagccaccctcggtgtcagtggccccaggacagacggccaggatcacctgtgggggaaaca acattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggcccctgtgctggtcgtctatgatgatagcg accggccctcagggatccctgagcgattctctggctccaattctgggaacacggccaccctgaccatcagcagggtcg aagccggggatgaggccgactattactgtcaggtgtgggatagtagtagtgatcagggcgtcttcggaactgggacca aggtcaccgtcctaggtggtggtggtggtagcggcggcggcggctctggtggtggtggatcc gaagtgcagctggtgcagtctgggggaggcttggtacagcctaggggtccctgagactctcctgtgcaggctctggat tcaccttcagtagctatgctatgcactgggttcgccaggctccaggaaaaggtctggagtgggtatcagctattggtactg gtggtggcacatactatgcagactccgtgaagggccgattcaccatctccagggacaatgccaagaactccttgtatct tcaaatgaacagcctgagagccgaggacaccgccatgtattactgtgcgcgcggtactggttacgacggtgatcagtg ggtcaaggtactctggtgaccgtctcctcacaccatcaccatcaccatggcgcatacccgtacgacgttccggactac gcttcttag (SEQ ID NO: 143)		

[0066] In an embodiment in which the antigen-binding protein is a full length antibody, the heavy and light chains of an antibody of the disclosure may be full-length (e.g., an antibody can include at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains) or may include an antigen-binding portion (a Fab, $F(ab')_2$, Fv or a single chain Fv fragment ("scFv")). In other embodiments, the antibody heavy chain constant region is chosen from, e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE. In some embodiments, the immunoglobulin isotype is selected from IgG1, IgG2, IgG3, and IgG4, more particularly, IgG1 (e.g., human IgG1). The choice of antibody type will depend on the immune effector function that the antibody is designed to elicit.

[0067] In constructing a recombinant immunoglobulin, appropriate amino acid sequences for constant regions of various immunoglobulin isotypes and methods for the production of a wide array of antibodies are known to those of skill in the art.

[0068] Nucleic acids that encode the antigen binding proteins identified herein can be used to engineer recombinant immune effector cells. Methods and vectors to generate genetically modified T-cells, for example, are known in the art (See Brentjens et al., Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias in Blood 118(18):4817-4828, November 2011).

[0069] Other embodiments of the disclosure include cells and expression vectors comprising nucleic acids encoding the antigen-binding proteins or antigen-binding fragments thereof of the disclosure. The cells may be

recombinant immune effector cells, such as T-cells genetically modified to express a chimeric antigen receptor comprising an antigen binding region in accordance with the present disclosure. Cells which have been engineered to produce antibodies in accordance with the disclosure are also encompassed by the disclosure.

[0070] Further, the disclosure comprises a method of producing an antibody or antibody fragment of the disclosure comprising: (a) culturing the recombinant cell comprising a nucleic acid encoding an antibody or antibody fragment of the disclosure in culture medium under conditions wherein the nucleic acid sequence is expressed, thereby producing polypeptides comprising the light and heavy chain variable regions; and (b) recovering the polypeptides from the host cell or culture medium.

[0071] Some embodiments of the antigen-binding protein of the disclosure encompass antagonistic anti-PD1 antibodies as well as anti-PD1 antibodies that function as agonists of PD1. While some anti-PD1 antibodies are antagonists, that is, they block binding of PD1 by its ligand, others are agonists, antibodies that have the effect of enhancing the immunosuppressive signal of PD-1, making them useful in the treatment of autoimmunity, for example. Antibodies of the disclosure that exhibit antagonist activity include clones 23 and 27 while clones 16, 18, 26, 31 and 40 appear to function as agonists.

[0072] The disclosure also comprises the use of an anti-PD-1 antibody or antibody fragment of the disclosure for the preparation of a medicament to increase immune response as well as the use of an anti-PD-1 antibody or antibody fragment of the disclosure for the preparation of a medicament to treat cancer.

[0073] Pharmaceutical compositions comprising the antigen binding protein, antibodies, nucleic acids, vectors or cells comprising the nucleic acids or antigen binding proteins of disclosed herein along with a pharmaceutically acceptable carrier are also encompassed by the disclosure.

[0074] The disclosure also comprises the use of an anti-PD-1 antibody or antibody fragment of the disclosure as a vaccine adjuvant.

[0075] In another aspect, the disclosure relates to an immunoconjugate comprising a first component which is an antigen-binding protein, antibody or antigen-binding fragment thereof as disclosed herein. The immunoconjugate comprises a second component that is a cytotoxin, a detectable label, a radioisotope, a therapeutic agent, a binding protein or a molecule having a second amino acid sequence. Where the second component is a binding protein or second antibody, the binding protein or second antibody has binding specificity for a target that is different from the HLA-peptide complex for which the first is specific.

[0076] The disclosure also relates to methods for treatment of a subject having a PD-1 associated disease, comprising administering to the subject a therapeutically effective amount of an antigen binding protein, antibody or antigen binding fragment thereof, a chimeric antigen receptor (CAR), a nucleic acid encoding the antigen binding protein or a cell comprising the nucleic acids or proteins as disclosed herein.

[0077] Those skilled in the art will recognize that several embodiments are possible within the scope and spirit of this invention. The invention will now be described in greater detail by reference to the following non-limiting examples. The following examples further illustrate the invention but, of course, should not be construed as in any limiting its scope.

Examples

Example 1

[0078] To test the ability of the scFvs to inhibit PD-1 ligation, scFv-Fc domain (scFv-Fc) fusion proteins were generated, where the scFvs were linked to a murine Fc (mouse IgG1a) domain. The scFv-Fc clones were then analyzed for the ability to bind PD-1 by coating an ELISA plate with human PD-1 monomer. Binding of the scFvs to PD-1 was quantified using a HRP-conjugated anti-mouse IgG1 Fc secondary antibody. All seven antibodies showed binding activity with respect to the PD1 monomer in a dose dependent manner (**Figure 1**). ET901 ScFv-Fc (mouse IgG1 Fc) served as the negative control. Binding affinity of the scFv-Fc clones was ranked where clone 31 bound weakly and clones 26 and 27 bound the most strongly (31 < 23 < 40 < 18 < 16 = 27 < 26).

Example 2

[0079] To test the ability of the scFv-Fc to inhibit PD-1 interacting with PD-L1, a competitive ligand-binding assay as shown schematically in **Figure 2A** was performed. In this assay, PD-L1-Fc was coated onto ELISA plates. Biotinylated-PD1-Fc was mixed with serially diluted ET901 ScFv-Fc (negative control) or anti-PD1 ScFv-Fcs and then added into the PD-L1-Fc coated plate. PD-1-Fc binding to PD-L1 coated on the plates was visualized via HRP-conjugated streptavidin (**Figure 2B**). When comparing similar concentrations of scFv-Fc (circled), the ability to disrupt the PD-1-PDL1 interaction was ranked where clones 40 and 23 had the weakest and clone 26 had the strongest ability to do so (26 > 27 = 16 > 18 > 31 > 23 = 40, **Figure 2B**).

Example 3

[0080] These clones were then investigated for their ability to regulate specific T cell function. We have previously generated tumor-targeted T cells, wherein T cells are retrovirally transduced to express a tumor-specific chimeric antigen receptor (CAR). We have previously demonstrated that expression of a CAR has redirected T cell function to target a given antigen (Brentjens, Santos et al. 2007). In our lab, we target B cell malignancies using a CAR specific for CD19, termed 1928z (Brentjens, Santos et al. 2007). We have previously demonstrated that CAR modified T cells have demonstrated significant anti-tumor activity *in vitro* and *in vivo* and in clinical studies (Brentjens, Latouche et al. 2003; Brentjens, Davila et al. 2013; Davila, Riviere et al. 2014). To determine whether the 7 scFv clones are agonistic (stimulate PD-1), antagonistic (block PD-1) or have no significant effect on PD-1, we generated a secretable scFv by including the murine Kappa leader sequence proximal to the anti-PD-1 scFv gene (**Figure 3**). We then generated a bicistronic retroviral vector to induce expression of the 1928z CAR and secretion of an anti PD-1 scFv from transduced human peripheral blood T cells.

Example 4

[0081] Given the ability of PD-1 stimulation to inhibit T cell proliferation and function, we subsequently sought to characterize the effect of the anti-PD-1 scFvs on T cell proliferation. To achieve this, human T cells were isolated from peripheral blood of healthy donors and modified through retroviral transduction to express the CAR and secrete a PD-1-specific scFv, using methodology that has been previously described (Brentjens, Santos et al. 2007). Following transduction, modified T cells were monitored for expansion *in vitro* (**Figure 4**). Expansion of T cells expressing the 1928z CAR and secreting PD-1 specific scFv clones 23 and 27 expanded as well as T cells

modified to express the 1928z CAR alone. Cells modified to express the CAR and secrete PD-1-specific scFv clones 16, 18, 26, 31 or 40 did not proliferate, suggesting that these PD-1-specific scFv clones were agonistic, potentially stimulating PD-1 and in turn, resulting in decreased T cell proliferation.

Example 5

[0082] In addition to expansion studies, we co-cultured T cells (expressing the CAR or CAR and secreting a PD-1-specific scFv) with the $CD19^+$ Burket's lymphoma tumor cell line, Raji, and determined the level of cytokine secretion from the T cells. As shown in **Figure 5**, T cells modified to express the 1928z CAR and secrete the PD-1-specific scFv clones 23 or 27 had increased secretion of IFN-γ compared to cells modified to express the CAR alone, suggesting that these scFv clones were antagonistic to PD-1 signaling. Cells modified to express the 1928z CAR and secrete the PD-1-specific scFv clones 16, 18, 2, 31 or 40 secreted less IFN-γ compared to cells modified with the CAR alone, suggesting that these scFvs were agonistic to PD-1 and inhibited T cell function.

Example 6

[0083] Human T cells modified to express the 1928 CAR and a PD-1 blocking scFv were analyzed by flow cytometry. Following verification of expression of the CAR (**Figure 6**) the presence of the scFvs was determined using western blot (using an antibody specific for an HA tag incorporated in the scFv design) on lysates prepared from human T cells treated with golgi inhibitors to allow detection in the cell lysates. Human T cells modified to express 1928z CAR and clone 23 had significantly less scFv protein compared to the other clones (**Figure 7**). These cells were then placed on 3T3 murine fibroblasts (artificial antigen presenting cells, a APCs) that do or do not express PD-1 ligands, PD-L1/L2. Following 24 hour culture with the aAPCs, CD3/D28 beads were added to the cultures to activate the human T cells.

Three days following culture of human T cells, aAPCs and beads the human T cells were enumerated to determine if the presence of PD-1 ligands inhibited the bead-driven expansion of human T cells, or if the anti-PD-1 scFvs prevented the PD-1 ligand mediated inhibition of T cell expansion. T cells modified to express the 1928z CAR and anti-PD-1 scFv clone 26 and 23 have decreased proliferation on aAPCs expressing PD-L1/L2 to aAPCs not expressing inhibitory ligands (**Figure 8**). In contrast, T cells modified to express the 1928z CAR and anti-PD-1 scFv clone 27 have increased expansion on aAPCs expressing PD-L1/L2.

Example 7

[0084] Using recombinant technology know in the art, recombinant human monoclonal antibodies were generated from the PD-1 specific scFvs, that is, fully human Ig molecules were made with the same variable heavy and light chains found in the corresponding scFvs (see Tables 1-14 above and **Figure 9**). The binding of these monoclonal antibodies to PD-1 was demonstrated using flow cytometry (see **Figure 10**).

[0085] Human T cells were modified to overexpress human PD-1, then incubated with 1µg/ml of antibody. Clone 27 mAb bound to the PD-1 T cells the most, followed by clone 26 and then clone 23 (**Figure 9**). The control monoclonal antibody, 901, did not bind to the PD-1 T cells. T cells incubated with these antibodies were then placed on artificial antigen presenting cells (aAPCs) with beads to determine the impact of PD-1 ligands on the expansion of the T cells and the ability of the monoclonal antibodies to prevent this interaction. 19z1 T cells incubated with anti-PD-1 clone 27 monoclonal antibody expanded on PD-L1/L2 aAPCs to a greater extent.

Example 8

[0086] T cells modified to express a first generation CAR incubated on aAPCs expressing PD-L1/L2 expand when anti-PD-1 clone 27 monoclonal antibody is present. Human T cells modified to express the first generation CD19-specific CAR (19z1) were incubated with anti-PD-1 monoclonal antibodies for 24 hours then placed on aAPCs expressing PD-L1/L2 or not. After 24 hours stimulation with aAPCs, the cells were then stimulated with CD3/CD28 beads. After three days, the cells were enumerated. 19z1 T cells incubated with no monoclonal antibody, control antibody (901) and clones 23 and 26 monoclonal antibody expanded much less on aAPCs expressing PD-1 ligands (**Figure 11** open bars) compared to aAPCs with no inhibitory ligands (**Figure 11** closed bars). However, 19z1 T cells incubated with anti-PD-1 clone 27 monoclonal antibody expanded on PD-L1/L2 aAPCs to a greater extent. Data shown is representative of one experiment.

Example 9

[0087] Generation of CAR T cells further modified to secrete PD-1 blocking scFv, E27. Bicistronic retroviral constructs were generated encoding a CD19-specific CAR (termed 1928z) or an ovarian tumor antigen specific CAR (termed 4H1128z) and the PD-1 blocking scFv, E27 (**Figure 12A**). The E27 was preceded by a signal peptide, mouse IgK, to allow secretion of the scFv. A HA/His tag was also included to detect the scFv once secreted from the T cells. Human peripheral blood T cells were transduced with the retroviral constructs encoding the CAR, 1928z, or the CAR and the E27 PD-1 blocking scFv, 1928z-E27. Following transduction, flow cytometry was used to detect expression of the CAR, using an antibody that specifically binds the CD19-targeted CAR, termed 19E3 (**Figure 12 B**). Western blot analysis of supernatant from transduced human T cells was utilized to detect the PD-1 blocking scFv with an anti-HA antibody (**Figure 12C**). We also investigated

scFv secretion from T cells modified to express the CAR and a control scFv, B6, which was detected using an anti-c-myc tag antibody. A standard ^{51}Cr release assay against two $CD19^{+}$ tumor targets was performed to ensure that secretion of an scFv did not interrupt the ability of the CAR to redirect T cells cytolytic capacity. CAR T cells expressing either the CAR alone (1928z or 4H1128z control CAR), the CAR and the E27 scFv (1928z-E27 or 4H1128z-E27), or the CAR and a control scFv (1928z-B6H12.2 or 4H1128z-B6H12.2) were incubated with ^{51}Cr labeled tumor cells (Raji or Nalm6) for 4 hrs. T cells expressing the CD19 specific CAR were able to lyse the tumor targets at equivalent levels, and the ovarian-targeted CAR T cells were unable to lyse Raji or Nalm6 (**Figure 12D**). Therefore, we conclude that secretion of the scFv did not interrupt the ability of the CAR to redirect T cell lytic capacity.

Example 10

[0088] T cells modified to express the CAR and secrete a PD-1 blocking scFv resist inhibition from PD-L1-PD-1 interactions, *in vitro*. T cells expressing the CAR alone (1928z), or the CAR and the PD-1 blocking scFv (1928z-E27) were cultured on 3T3 cells empty cells or 3T3 cells modified to express human PD-L1. Following 24 hours on the 3T3 feeder cells, cells were stimulated with CD3/CD28 beads added to the cultures at a 1:3 bead: T cell ratio. Expansion of T cells was determined with trypan blue enumeration and fresh beads were added twice to the cultures (indicated by the arrows). 1928z T cells expanded on 3T3 empty feeder cells, however did not expand on the 3T3-PD-L1 feeder cells. In contrast, 1928z-E27 T cells expanded on both the 3T3 Empty and 3T3-PD-L1 feeder cells, indicating a resistance to PD-L1-PD-1 mediated suppression (**Figure 13A**). T cells incubated on 3T3 empty or 3T3-PD-L1 cells as shown in **Figure 13A** were analyzed by flow cytometry to detect expression on inhibitory receptors, PD-1, 2B4 and LAG3. 1928z cells expressed increased levels of PD-1 than 1928z-E27 cells (not shown). When

gated on PD-1$^+$ cells, analysis of 2B4 and LAG3 revealed that 1928z cells had a higher proportion of PD-1$^+$, 2B4$^+$ and LAG3$^+$ cells compared to 1928z-E27 cells (**Figure 13B**). Transduced T cells were cultured with Raji-PDL1 or Nalm6-PDL1 tumor cells at varying effector to target (E:T) ratios (1:1, 1:3, 1:5) for 72 hours. Flow cytometry following staining with anti-CD3 and anti-CD19 antibodies and enumeration beads were used to monitor lysis of tumor targets and expansion of T cells over time. 1928z-E27 cells continued to expand to greater levels compared to 1928z T cells when cultured with PDL1$^+$ tumor cells (**Figure 13C**). Transduced T cells were stimulated with Nalm6-PDL1 tumor cells as shown in Figure 3C were re-stimulated with Nalm6-PDL1 tumor cells at the 1:5 T E:T ratio. After 48 hours co-culture flow cytometry was used to determine lysis of tumor targets. 1928z-E27 retained ability to lyse PD-L1 tumor targets upon re-stimulation compared to 1928z cells (**Figure 13D**).

Example 11

[0089] *In vivo* anti-tumor efficacy of T cells modified to express the CAR and secrete the PD-1 blocking scFv is shown in **Figure 14**. SCID-beige mice were inoculated with Raji-PD-L1 tumor cells via intravenous infusion on Day 0. On Day 1, mice were infused intravenously with 10^6 CAR+ T cells and survival was monitored clinically. Mice were euthanized upon development of hind limb paralysis.

Example 12

[0090] PD-1 blocking mAb candidates E27, E26 and E23 were used in a competitive binding assay to detect interruption of PD-1 binding to PD-L1 at varying concentrations, compared to a control mAb, targeted to a hapten not present in humans. E23, E26 and E27 mAbs all prevented PD-1 binding to PD-L1 (**Figure 15A**). Western blot on SN from 293Glv9 packaging cells transduced to express the secretable scFvs with the 1928z CAR, stained with

anti-HA antibody. The E27 scFv was detected at the highest levels and therefore was used in the remainder of the study (**Figure 15C**).

Example 13

[0091] T cells can be co-modified to express CAR and secrete PD-1 blocking scFv, E27. **Figure 16A** is a representative flow cytometry plot demonstrating equivalent CAR expression following transduction with the 1928z CAR alone (1928z) or the 1928z CAR and the E27 PD-1 blocking scFv (1928z-E27), following staining with 19E3 mAb that specifically binds the 1928z CAR. **Figure 16B** shows a Western blot on SN from 1928z and 1928z-E27 T cells stained with anti-HA mAb, showing only a ~30 kDa protein in the 1928z-E27 cells, demonstrating that the E27 scFv is secreted from the 1928z-E27 transduced T cells and not those transduced with the CAR alone. **Figure 16C** is a representative flow cytometry demonstrating lower levels of PD-1 expression on 1928z-E27 T cells compared to 1928z T cells following transduction. Expression of PD-1 was statistically significantly lower on 1928z-E27 T cells compared to 1928z T cells, data shown is mean +/- SEM from 4 independent experiments (**Figure 16D**). A 4 hr ^{51}Cr release assay demonstrating that lysis of Raji tumor cells was unaffected by secretion of the E27 scFv. 1928z and 1928z-E27 T cells lysed Raji tumor cells equivalently. Control 4H1128z-E27 T cells mediated no increase in lysis of Raji cells compared to 4H1128z T cells (**Figure 16 E**). Data shown is representative of two independent experiments.

Example 14

[0092] Expression of CAR and E27 protects proliferative and lytic capacity of T cells in the context of $CD19^+$ $PD\text{-}L1^+$ tumor cells. Raji tumor cells were retrovirally modified to express human PD-L1 (Raji-PDL1) and were stained with mAb specific for PD-L1. Parental Raji tumor (Raji) express no PD-L1 and

Raji-PDL1 tumor cells expressed high levels of PD-L1 (**Figure 17A**). **Figure 17B** shows representative flow cytometry plots showing1928z-E27 T cells lyse more Raji-PDL1 tumor cells compared to 1928z T cells as determined with flow cytometry following 72 hrs co-culture. 1928z-E27 T cells lyse statistically significantly more Raji-PDL1 tumor cells compared to 1928z T cells, data shown the mean +/- SEM from 4 independent experiments (**Figure 17C**). 1928z-E27 T cells expand to greater numbers following co-culture with Raji-PDL1 tumor cells as determined by flow cytometry and enumeration beads, data shown is the average total number of T cells +/- SEM from 4 independent experiments (**Figure 17D**). **Figure 17E** shows a representative flow cytometry plot showing increased PD-1 expression on 1928z T cells compared to 1928z-E27 T cells following 7 days co-culture with Raji-PDL1 tumor cells. 1928z T cells express significantly more PD-1 compared to 1928z-E27 T cells, with regard to percentage positive cells and mean fluorescence intensity (MFI) of PD-1 staining. Data show in the mean +/- SEM from 4 independent experiments (**Figure 17F**). **Figure 17G** shows representative flow cytometry plots showing increased percentage of 2B4+PD-1+ 1928z T cells compared to 1928z-E27 cells following coculture with Raji-PDL1 for 7 days. 1928z-E27 T cells also express less BTLA and TIM3 on the 2B4+PD-1+ population. Data shown is representative of 3 independent experiments.

Example 15

[0093] E27 protects proliferative capacity of CD3/CD28 stimulated T cells in the context of PD-L1. NIH3T3 cells were retrovirally modified to express human PD-L1 (3T3-PDL1) and were stained with mAb specific for PD-L1. Parental NIH3T3 (3T3-EMPTY) express no PD-L1 and 3T3-PDL1 tumor cells expressed high levels of PD-L1 (**Figure 18A**). 1928z and 1928z-E27 T cells were cultured with 3T3-EMPTY or 3T3-PDL1 cells and stimulated with CD3/CD28 beads. Cells were enumerated and re-plated on new 3T3 cells on

days 3, 6, 9 and 12. 1928z T cells had reduced expansion when cultured with 3T3-PDL1 cells compared to 3T3-EMPTY cells. 1928z-E27 cells had equivalent expansion when cultured on 3T3-EMPTY or 3T3-PDL1 cells (**Figure 18B**). Data shown is the mean fold expansion +/- SEM from 4 independent experiments. **Figure 18C** are representative flow cytometry plots showing increased expression of 2B4, PD-1, BTLA and TIM3 on 1928z T cells cultured with 3T3-PDL1 compared to1928z T cells cultured on 3T3-EMPTY cells. 1928z-E27 cells had equivalent expression of 2B4, PD-1, BTLA-4 and TIM3 when cultured with 3T3-EMPTY and 3T3-PDL1. Data shown is representative of 3 independent experiments.

Example 16

[0094] CAR T cells secreting E27 scFv have increased anti-tumor function in vivo. SCID-Beige mice were inoculated with Raji-PDL1 tumor cells intravenously, and the following day were infused intravenously with CAR T cells. As shown in **Figure 19** mice treated with 1928z-E27 T cells had enhanced survival compared to mice treated with 1928z T cells. Mice treated with 1928z T cells survived longer than untreated mice, and mice treated with CAR T cells targeted to an irrelevant antigen, 4H1128z and 4H1128z-E27 T cells. Data shown is from 2 independent experiments.

Example 17

[0095] Anti-PD-1 antibodies ET130-23, ET130-26 and ET130-27 were tested by ELISA to check the blocking effect to PD1/PDL1 binding. As shown in **Figure 20**, ET901 (negative control) showed no binding, while ET130-23, ET130-26 and ET130-27 showed a blocking effect to PD1/PDL1 binding over a range of concentrations between 0.031 and 10 μg/ml.

[0096] Similarly, ET130-23, ET130-26 and ET130-27 were tested by ELISA to check the blocking effect to PD1/PDL2 binding. As shown in **Figure 21**, ET901 (negative control) showed no binding, while ET130-23, ET130-26 and ET130-27 showed a blocking effect to PD1/PDL2 binding over the same range of concentrations. ET130-26 showed the highest blocking effect against PD1/PDL2, while ET130-23 showed the lowest effect. The blocking pattern is parallel to PD1/PDL1 binding.

Example 18

[0097] The application of the anti-PD-1 scFvs or monoclonal antibodies is investigated for the ability of the scFvs or monoclonal antibodies to dampen the immune response and subvert autoimmune diseases. This can also be investigated using murine models of GVHD. Infusion of human T cells into irradiated NOD.SCID.IL-2Rγ$^{-/-}$ results in engraftment of human cells and severe GVHD, where the human T cells attack the murine tissues. T cells secreting an anti-PD-1 scFv (or T cells augmented with injection of monoclonal antibodies) are infused into a subject and the development of GVHD is assessed. When the anti-PD-1 scFv/mAb is agonistic, the GVHD response is inhibited due to suppression of the human T cells.

[0097a] The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

[0097b] Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

Exemplary Embodiments

1. A recombinant antigen-binding protein or antigen-binding fragment thereof comprising one of:

(A) an antigen binding region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 10, SEQ ID NO: 21, SEQ ID NO: 32, SEQ ID NO: 43, SEQ ID NO: 53, SEQ ID NO: 61, SEQ ID NO: 72, SEQ ID NO: 83, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 114, SEQ ID

NO: 125, SEQ ID NO: 133, SEQ ID NO: 142; a fragment thereof and a homologous sequence thereof;

(B) an antigen binding region comprising a variable light chain (VL) and variable heavy chain (VH), respectively, with amino acid sequences selected from SEQ ID NOS: 6 and 8; SEQ ID NOS: 17 and 19; SEQ ID NOS: 28 and 30; SEQ ID NOS: 39 and 41; SEQ ID NOS: 49 and 51; SEQ ID NOS: 57 and 59; SEQ ID NOS: 68 and 70; SEQ ID NOS: 79 and 81; SEQ ID NOS: 90 and 92; SEQ ID NOS: 99 and 101; SEQ ID NOS: 110 and 112; SEQ ID NOS: 121 and 123; SEQ ID NOS: 129 and 131; SEQ ID NOS: 138 and 140; fragments thereof and homologous sequences thereof;

(C) an antigen binding region comprising:
(i) a light chain (LC) comprising light chain complementarity determining regions (LCCDR) LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence QSISSY (SEQ ID NO: 1), AAS and QQSYSTPLT (SEQ ID NO: 2) and a heavy chain (HC) comprising heavy chain complementarity determining regions (HCCDR) HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTSSSYW (SEQ ID NO: 4), IKQDGSEK (SEQ ID NO. 5) and ARGGWSYDM (SEQ ID NO: 6); fragments thereof and homologous sequences thereof;

(ii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGAGYA (SEQ ID NO: 12), TNN and QSYDSSLSGVI (SEQ ID NO: 13) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTLTELS (SEQ ID NO: 14), FDPEDGET (SEQ ID NO. 15) and ARAYYGFDQ (SEQ ID NO: 16); fragments thereof and homologous sequences thereof;

(iii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGNNA (SEQ ID NO: 23), YND and AAWDDSVNGYV (SEQ ID NO: 24) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTRFG (SEQ ID NO: 25), ISVNNGNT (SEQ ID NO. 26) and ARYMYGRRDS (SEQ ID NO: 27); fragments thereof and homologous sequences thereof;

(iv) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDNHSDVV (SEQ ID NO: 35) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences RNKFSSYA (SEQ ID NO: 36), ISGSGGTT (SEQ ID NO. 37) and ARWYSSYYDV (SEQ ID NO: 38); fragments thereof and homologous sequences thereof;

(v) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDYV (SEQ ID NO: 45) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARNYISMFDS (SEQ ID NO: 48); fragments thereof and homologous sequences thereof;

(vi) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDHV (SEQ ID NO: 55) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and

ARGYSSYYDA (SEQ ID NO: 56); fragments thereof and homologous sequences thereof;

(vii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence RSNIGENT (SEQ ID NO: 63), SNN and AAWDDRLNGYV (SEQ ID NO: 64) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTNYG (SEQ ID NO: 65), IGAQKGDT (SEQ ID NO. 66) and ARSQGVPFDS (SEQ ID NO: 67); fragments thereof and homologous sequences thereof;

(viii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence RSNIGSNT (SEQ ID NO: 74), NNN and ATWDDSLNEYV (SEQ ID NO: 75) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTRYG (SEQ ID NO: 76), ISGYNGNT (SEQ ID NO. 77) and ARHGYGYHGD (SEQ ID NO: 78); fragments thereof and homologous sequences thereof;

(ix) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGAGYV (SEQ ID NO: 85), HNN and QSYDSSLSGWV (SEQ ID NO: 86) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFKDYY (SEQ ID NO: 87), ISTSGNSV (SEQ ID NO. 88) and ARSPGHSDYDS (SEQ ID NO: 89); fragments thereof and homologous sequences thereof;

(x) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGDKS (SEQ ID NO: 96), YDS and QVWASGTDHPYVI (SEQ ID NO: 97) and a heavy chain (HC) comprising

HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARMYGSYTDM (SEQ ID NO: 98); fragments thereof and homologous sequences thereof;

(xi) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGYNY (SEQ ID NO: 105), RNN and TSWDDSLSGYV (SEQ ID NO: 106) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GNAFTNFY (SEQ ID NO: 107), INPSGTDLT (SEQ ID NO. 108) and ARQYAYGYSGFDM (SEQ ID NO: 109); fragments thereof and homologous sequences thereof;

(xii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence QSVSNW (SEQ ID NO: 116), AAS and QQSYSTPIT (SEQ ID NO: 117) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTSYY (SEQ ID NO: 118), INPNTGGS (SEQ ID NO. 119) and ARGDVTYDE (SEQ ID NO: 120); fragments thereof and homologous sequences thereof;

(xiii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDD and QVWDINDHYV (SEQ ID NO: 127) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARSQASFMDI (SEQ ID NO: 128); fragments thereof and homologous sequences thereof; or

(xiv) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), DDS and QVWDSSSDQGV (SEQ ID NO: 135) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), IGTGGGT (SEQ ID NO. 136) and ARGTGYDGDQ (SEQ ID NO: 137); fragments thereof and homologous sequences thereof.

2. The recombinant antigen-binding protein of embodiment 1, wherein said protein is an antibody.

3. The recombinant antigen-binding protein of embodiment 2, wherein the antibody is a human antibody.

4. The recombinant antigen-binding protein of embodiment 2, wherein said antibody or antigen-binding fragment thereof is intact Ig, Fab, $F(ab')_2$, Fv, or scFv.

5. The antigen-binding protein of embodiment 1, wherein said antigen-binding protein is a PD-1 agonist.

6. The antigen-binding protein of embodiment 1, wherein said antigen-binding protein is a PD-1 antagonist.

7. The antigen-binding protein of embodiment 1, wherein said antigen-binding protein is a chimeric antigen receptor (CAR).

8. A nucleic acid encoding an antigen-binding protein of any one of embodiments 1-7.

9. A vector comprising a nucleic acid of embodiment 8.

10. A cell comprising an antigen-binding protein of any one of embodiments 1-7, a nucleic acid of embodiment 8 or a vector of embodiment 9.

11. An antigen-binding protein of any one of embodiments 1-7 conjugated to a therapeutic agent.

12. The antigen-binding protein of embodiment 11, wherein said therapeutic agent is a drug, toxin, radioisotope, protein, or peptide.

13. A pharmaceutical composition comprising an antigen-binding protein of any one of embodiments 1-7, a nucleic acid of embodiment 8, a vector of embodiment 9, a cell of embodiment 10 or an antigen-binding protein of embodiment 11 or 12.

14. The pharmaceutical composition of embodiment 13 further comprising a pharmaceutically acceptable carrier.

15. A method of increasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of an antigen-binding protein or an antigen binding fragment thereof of any one of embodiments 1-7, a nucleic acid of embodiment 8, a vector of embodiment 9, a cell of embodiment 10, an antigen-binding protein of either of embodiments 11 or 12 or a pharmaceutical composition of either of embodiments 13 or 14.

16. The method of embodiment 15, wherein the antigen-binding protein or antigen binding fragment thereof inhibits, reduces, modulates or abolishes signal transduction mediated by PD-1.

17. A method for treatment of a subject having a PD1-positive disease, comprising administering to the subject a therapeutically effective amount of an antigen-binding protein or antigen binding fragment thereof of any one of embodiments 1-7, a nucleic acid of embodiment 8, a vector of embodiment 9, a cell of embodiment 10, an antigen-binding protein of either of embodiments 11 or 12 or a pharmaceutical composition of either of embodiments 13 or 14.

18. The method of embodiment 17, wherein said antigen-binding protein or antigen binding fragment thereof is a conjugate having a cytotoxic moiety linked thereto.

19. The method of embodiment 17 or 18, wherein the PD-1 positive disease is cancer.

20. Use of a recombinant anti-PD1 antigen-binding protein or antigen-binding fragment thereof of any one of embodiments 1-7, a nucleic acid of embodiment 8, a vector of embodiment 9, a cell of embodiment 10, an antigen-binding protein of either of embodiments 11 or 12 or a pharmaceutical composition of either of embodiments 13 or 14 for the treatment of PD1-positive disease by inhibiting PD1 binding to a PD1 ligand.

21. The use of embodiment 20, wherein the PD1-positive disease is a cancer.

22. Use of a recombinant anti-PD1 antigen-binding protein or antigen-binding fragment thereof of any one of embodiments 1-7, a nucleic acid of embodiment 8, a vector of embodiment 9, a cell of embodiment 10, an antigen-binding protein of either of embodiments 11 or 12 or a pharmaceutical composition of either of embodiments 13 or 14 for immunomodulation by inhibiting the PD-1 signaling pathway.

23. A vector comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

24. A cell comprising the vector of embodiment 23.

25. A cell comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

26. A cell comprising a recombinant anti-PD-1 antigen-binding protein and a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

27. The vector or the cell of any one of embodiments 23-26, wherein the chimeric antigen receptor does not specifically bind to PD-1.

28. The vector or the cell of any one of embodiments 23-27, wherein the recombinant anti-PD-1 antigen-binding protein is an antibody.

29. The vector or the cell of any one of embodiments 23-28, wherein the recombinant anti-PD-1 antigen-binding protein is a human antibody.

30. The vector or the cell of any one of embodiments 23-29, wherein the recombinant anti-PD-1 antigen-binding protein is an intact Ig, Fab, $F(ab')_2$, Fv, or scFv.

31. The vector or the cell of any one of embodiments 23-30, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 agonist.

32. The vector or the cell of any one of embodiments 23-30, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 antagonist.

33. The vector or the cell of any one of embodiments 23-32, wherein the recombinant anti-PD-1 antigen-binding protein is a secretable protein.

34. The vector or the cell of any one of embodiments 23-33, wherein the recombinant anti-PD-1 antigen-binding protein comprises an antigen binding region recited in embodiment 1.

35. The vector or the cell of any one of embodiments 23-34, wherein the chimeric antigen receptor specifically binds to CD-19.

36. The vector or the cell of any one of embodiments 23-35, wherein the chimeric antigen receptor can be inserted in a human T cell membrane.

37. The cell of any one of embodiments 24-36, wherein the cell is a T cell.

38. A pharmaceutical composition comprising a vector or a cell of any one of embodiments 23-37.

39. The pharmaceutical composition of embodiment 38 further comprising a pharmaceutically acceptable carrier.

40. A method of increasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of a vector or cell of any one of embodiments 23-37, or a pharmaceutical composition of embodiment 38 or 39, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 antagonist.

41. The method of embodiment 40, wherein the recombinant anti-PD-1 antigen-binding protein inhibits, reduces, modulates or abolishes signal transduction mediated by PD-1.

42. A method of decreasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of a vector or cell of any one of embodiments 23-37, or a pharmaceutical composition of embodiment 38 or 39, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 agonist.

43. A method for treatment of a subject having a PD1-positive disease, comprising administering to the subject a therapeutically effective amount of a vector or cell of any one of embodiments 23-37, or a pharmaceutical composition of embodiment 38 or 39.

44. A method for treatment of a subject having a PD1-positive disease, comprising transducing at least one T cell of the subject with a

nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

45. The method of embodiment 44, wherein the chimeric antigen receptor does not specifically bind to PD-1.

46. The method of any one of embodiments 42-45, wherein the PD1-positive disease is a cancer.

47. Use of a vector or cell of any one of embodiments 23-37, or a pharmaceutical composition of embodiment 38 or 39 for the treatment of PD1-positive disease by inhibiting PD1 binding to a PD1 ligand.

48. The use of embodiment 47, wherein the PD1-positive disease is a cancer.

49. Use of a vector or cell of any one of embodiments 23-37, or a pharmaceutical composition of embodiment 38 or 39 for immunomodulation by inhibiting the PD-1 signaling pathway.

50. Use of an antigen-binding protein of embodiment 5, a vector or cell of any one of embodiments 23-37, or a pharmaceutical composition of embodiment 38 or 39, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 agonist, for the treatment of an autoimmune disease.

51. The vector or the cell of any one of embodiments 23-37, wherein at least one of the anti-PD-1 antigen-binding protein and chimeric antigen receptor is conjugated to a therapeutic agent.

52. The vector or the cell of embodiment 51, wherein said therapeutic agent is a drug, toxin, radioisotope, protein, or peptide.

53. The method of any one of embodiments 17 and 42-45, wherein the antigen-binding protein or the recombinant anti-PD-1 antigen-binding protein is a PD-1 agonist, and wherein the PD1-positive disease is an autoimmune disease.

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Brentjens, R. J., J. B. Latouche, et al. (2003). "Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15." Nat Med 9(3): 279-286.

Brentjens, R. J., E. Santos, et al. (2007). "Genetically targeted T cells eradicate systemic acute lymphoblastic leukemia xenografts." Clin Cancer Res **13** (18 Pt 1): 5426-5435.

Davila, M. L., **I.** Riviere, et al. (2014). "Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia." Sci Transl Med 6(224): 224ra225.

2016281641 14 Dec 2021

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A recombinant antigen-binding protein comprising one of:

(A) an antigen binding region comprising an amino acid sequence of SEQ ID NO: 53;

(B) an antigen binding region comprising a variable light chain (VL) and variable heavy chain (VH), with amino acid sequences selected from SEQ ID NOS: 49 and 51, respectively; and

(C) an antigen binding region comprising:
a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDYV (SEQ ID NO: 45) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARNYISMFDS (SEQ ID NO: 48).

2. The recombinant antigen-binding protein of claim 1, wherein said protein is an antibody.

3. The recombinant antigen-binding protein of claim 2, wherein the antibody is a human antibody.

4. The recombinant antigen-binding protein of claim 2, wherein said antibody or antigen-binding fragment thereof is intact Ig, Fab, $F(ab')_2$, Fv, or scFv.

5. The antigen-binding protein of claim 1, wherein said antigen-binding protein is a PD-1 antagonist.

6. The antigen-binding protein of claim 1, wherein said antigen-binding protein is a chimeric antigen receptor (CAR).

7. A nucleic acid encoding an antigen-binding protein of any one of claims 1-6.

8. A vector comprising a nucleic acid of claim 7.

9. A cell comprising an antigen-binding protein of any one of claims 1-6, a nucleic acid of claim 7 or a vector of claim 8.

10. A pharmaceutical composition comprising an antigen-binding protein of any one of claims 1-6, a nucleic acid of claim 7, a vector of claim 8, a cell of claim 9.

11. A method of increasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of an antigen-binding protein or an antigen binding fragment thereof of any one of claims 1-6, a nucleic acid of claim 7, a vector of claim 8, a cell of claim 9, or a pharmaceutical composition of claim 10.

12. The method of claim 11, wherein the antigen-binding protein or antigen binding fragment thereof inhibits, reduces, modulates or abolishes signal transduction mediated by PD-1.

13. A method for treatment of a subject having a PD1-positive disease, comprising administering to the subject a therapeutically effective amount of an antigen-binding protein or antigen binding fragment thereof of any one of claims 1-6, a nucleic acid of claim 7, a vector of claim 8, a cell of claim 9, or a pharmaceutical composition of claim 10.

14. A vector comprising a nucleic acid encoding the recombinant anti-PD-1 antigen-binding protein of any one of claims 1-5 and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

15. A cell comprising the vector of claim 14.

16. A cell comprising a nucleic acid encoding the recombinant antigen-binding protein of any one of claims 1-5 and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant antigen-binding protein is not identical to said chimeric antigen receptor.

17. A cell comprising the recombinant antigen-binding protein of any one of claims 1-5 and a chimeric antigen receptor, wherein said recombinant antigen-binding protein is not identical to said chimeric antigen receptor.

18. The vector or the cell of any one of claims 14-17, wherein the chimeric antigen receptor does not specifically bind to PD-1.

19. The vector or the cell of any one of claims 14-18, wherein the recombinant antigen-binding protein is a secretable protein.

20. The vector or the cell of any one of claims 14-19, wherein the chimeric antigen receptor specifically binds to CD-19.

21. The cell of any one of claims 14-20, wherein the cell is a T cell.

22. A pharmaceutical composition comprising a vector or a cell of any one of claims 14-21.

23. A method of increasing a T cell response in a subject comprising administering to the subject a therapeutically effective amount of a vector or cell of any one of claims 14-21, or a pharmaceutical composition of claim 22.

24. A method for treatment of a subject having a PD1-positive disease, comprising administering to the subject a therapeutically effective amount of a vector or cell of any one of claims 14-21, or a pharmaceutical composition of claim 22.

25. A method for treatment of a subject having a PD1-positive disease, comprising transducing at least one T cell of the subject with a nucleic acid encoding the recombinant antigen-binding protein of any one of claims 1-5 and a nucleic acid encoding a chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said chimeric antigen receptor.

26. The method of claim 25, wherein the chimeric antigen receptor does not specifically bind to PD-1.

27. The method of any one of claims 23-26, wherein the PD-1-positive disease is a cancer.

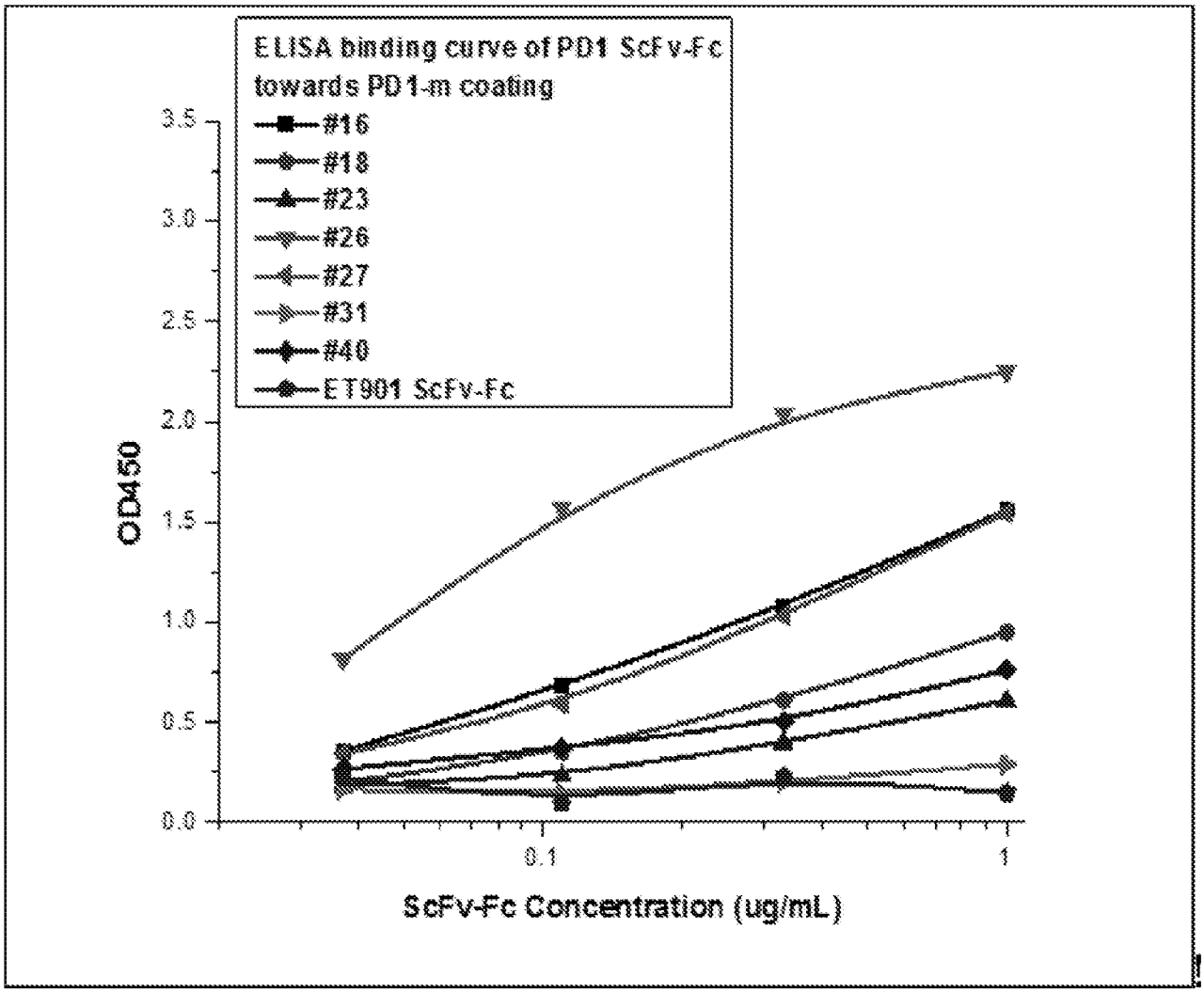
ELISA binding curve of PD1 ScFv-Fc towards PD1-m coating
#16
#18
#23
#26
#27
#31
#40
ET901 ScFv-Fc
OD450
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.1
1
ScFv-Fc Concentration (ug/mL)

FIGURE 1

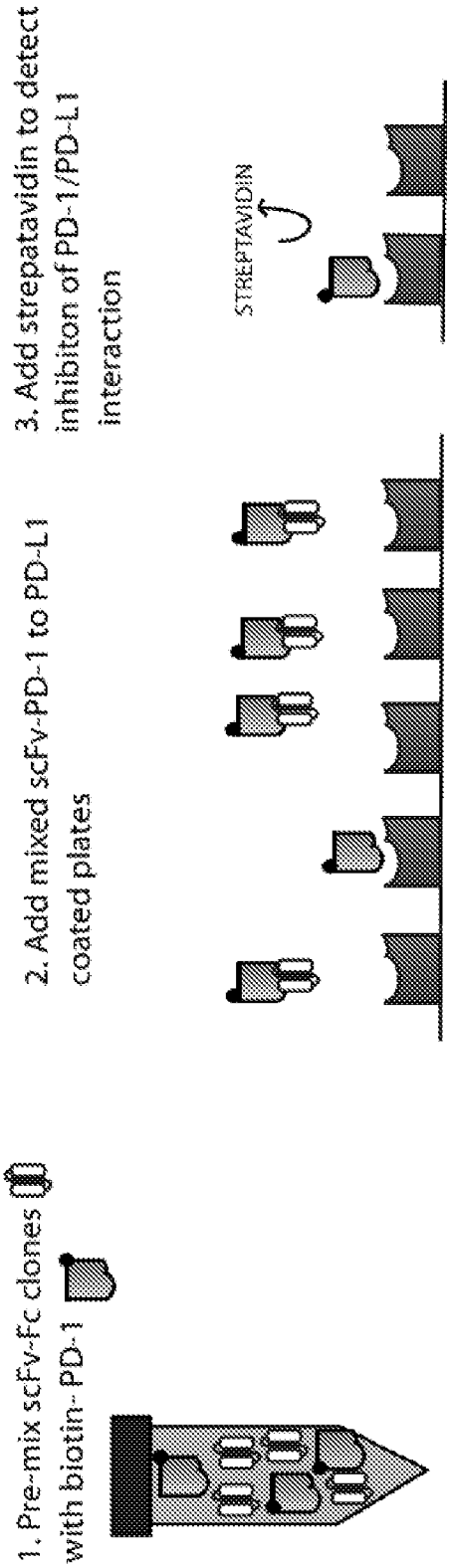
1. Pre-mix scFv-Fc clones with biotin- PD-1
2. Add mixed scFv-PD-1 to PD-L1 coated plates
3. Add strepatavidin to detect inhibiton of PD-1/PD-L1 interaction
STREPTAVIDIN

FIGURE 2A

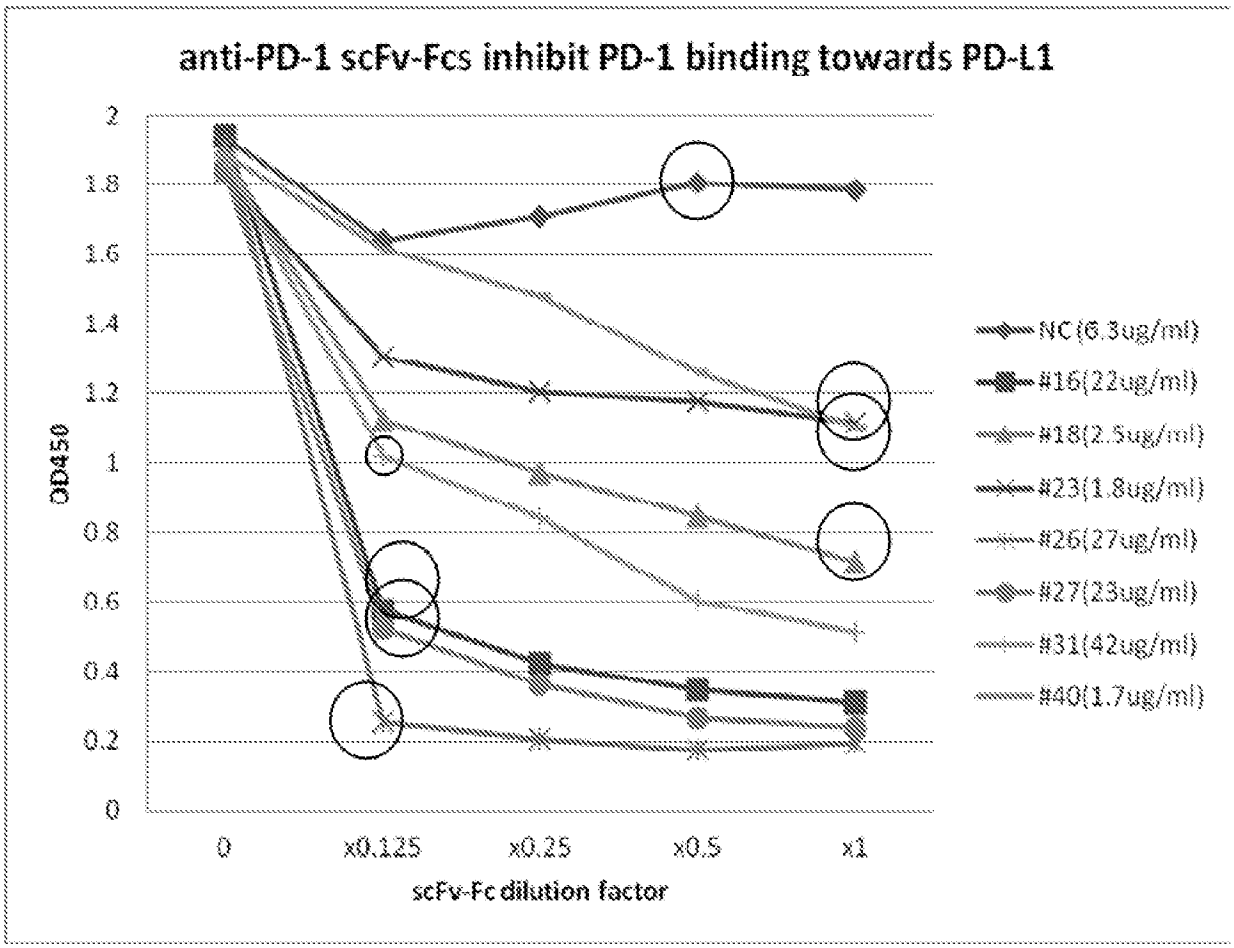
anti-PD-1 scFv-Fcs inhibit PD-1 binding towards PD-L1
OD450
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
x0.125
x0.25
x0.5
x1
scFv-Fc dilution factor
NC(6.3ug/ml)
#16(22ug/ml)
#18(2.5ug/ml)
#23(1.8ug/ml)
#26(27ug/ml)
#27(23ug/ml)
#31(42ug/ml)
#40(1.7ug/ml)

FIGURE 2B

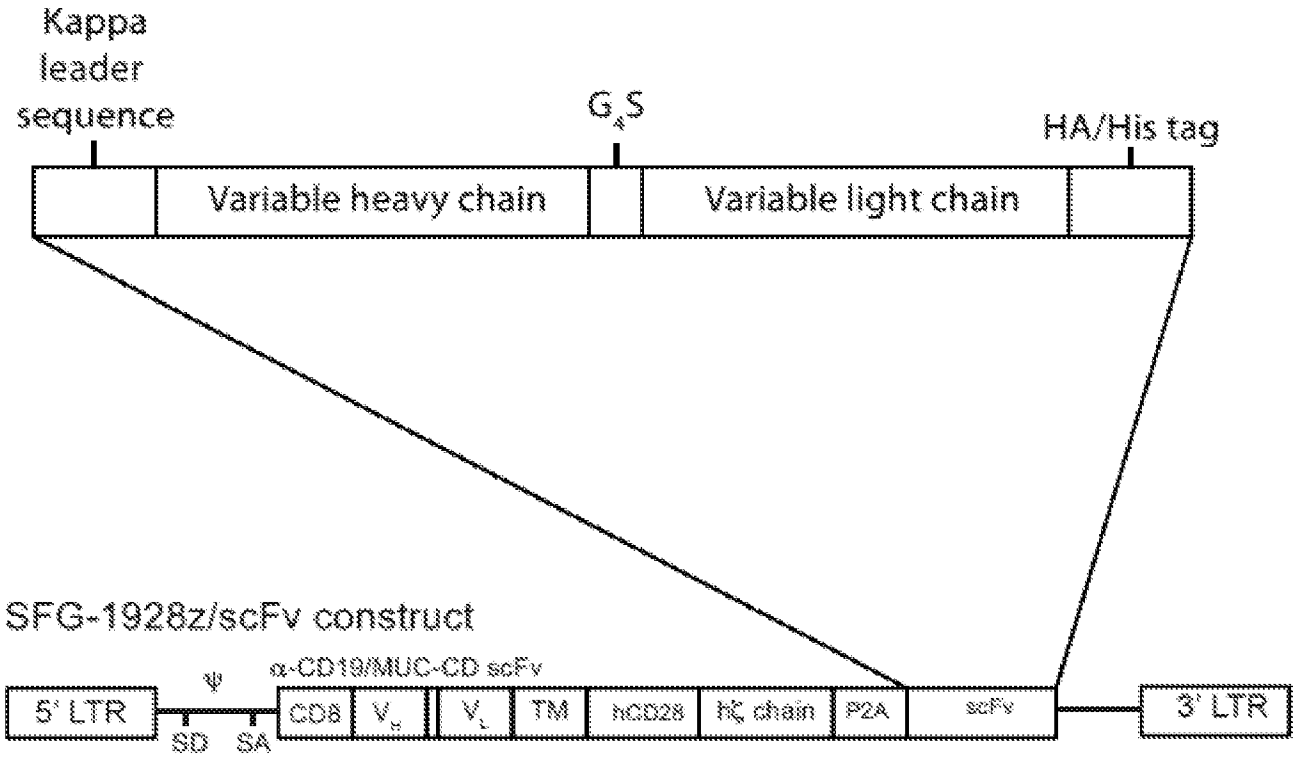
Kappa leader sequence
G4S
HA/His tag
Variable heavy chain
Variable light chain
SFG-1928z/scFv construct
Ψ
α-CD19/MUC-CD scFv
5' LTR
SD
SA
CD8
TM
hCD28
hζ chain
P2A
scFv
3' LTR

FIGURE 3

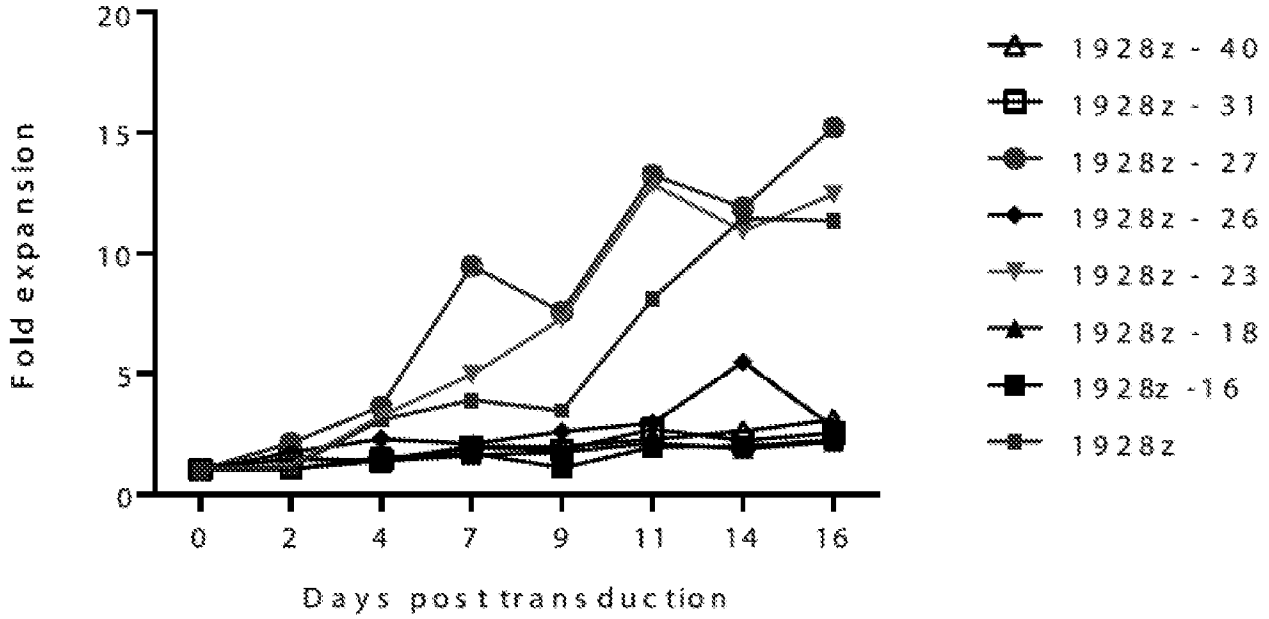
Fold expansion
20
15
10
5
0
0
2
4
7
9
11
14
16
Days post transduction
1928z - 40
1928z - 31
1928z - 27
1928z - 26
1928z - 23
1928z - 18
1928z -16
1928z

FIGURE 4

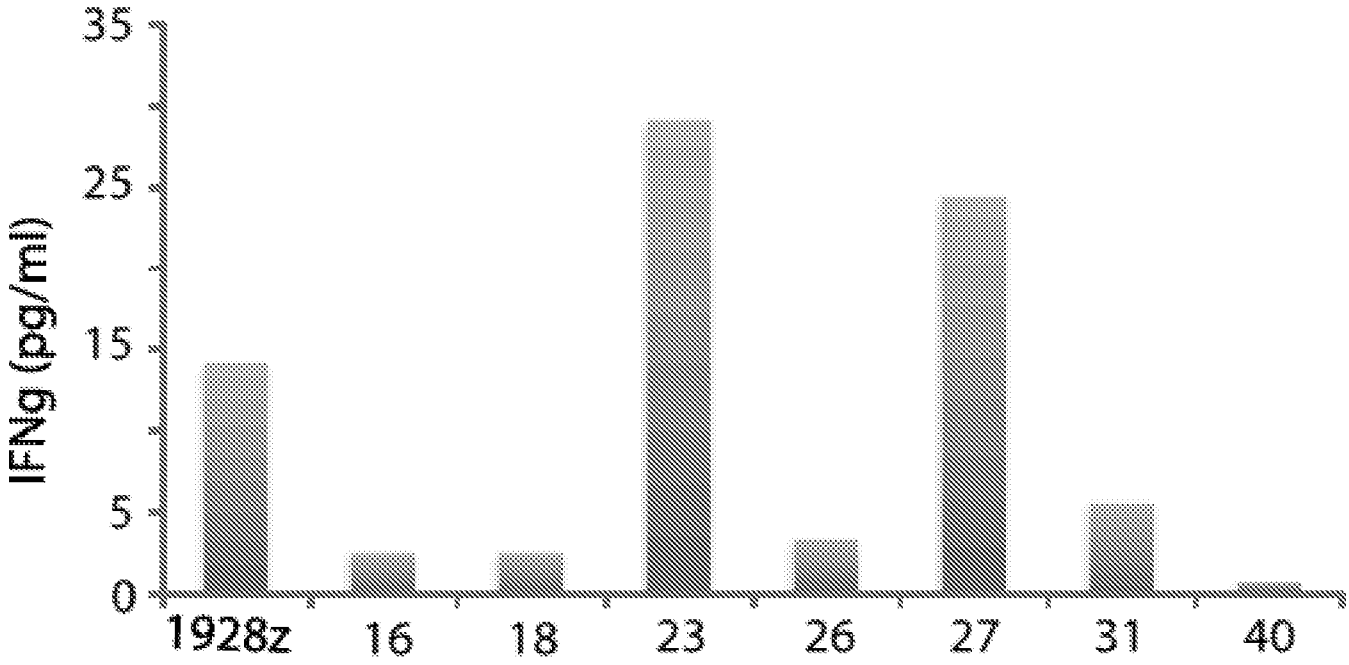

FIGURE 5

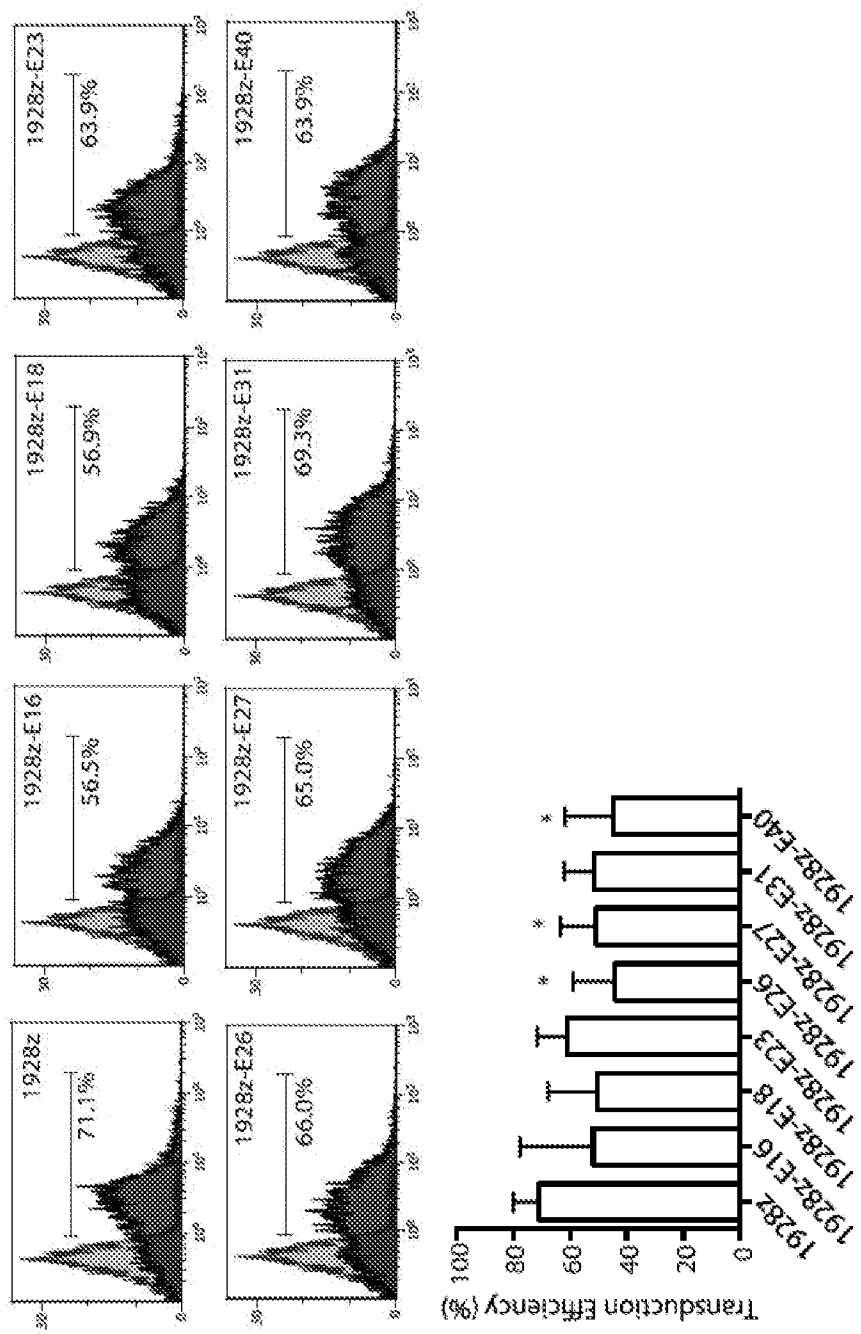
1928z
71.1%
1928z-E16
56.5%
1928z-E18
56.9%
1928z-E23
63.9%
1928z-E26
66.0%
1928z-E27
65.0%
1928z-E31
69.3%
1928z-E40
63.9%
Transduction Efficiency (%)
100
80
60
40
20
0
1928z
1928z-E16
1928z-E18
1928z-E23
1928z-E26
1928z-E27
1928z-E31
1928z-E40
*
*
*

FIGURE 6

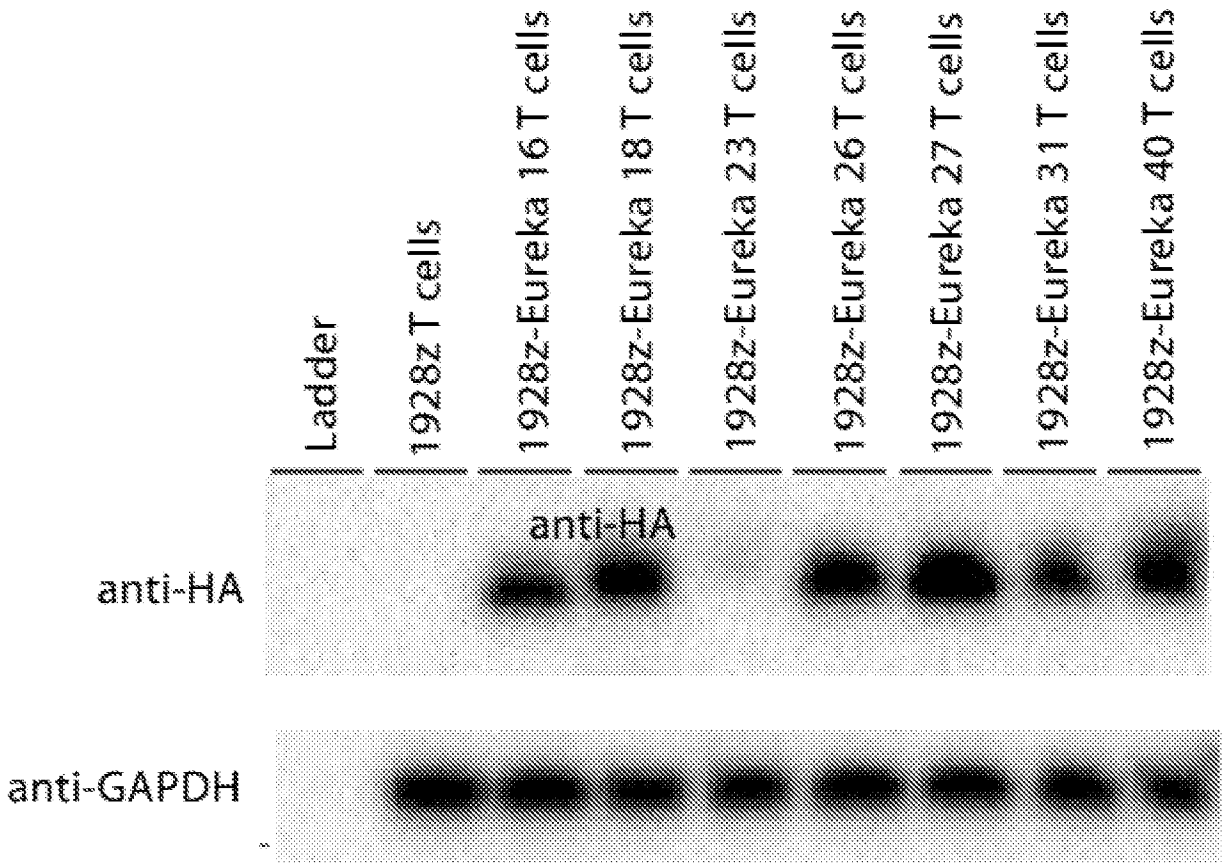
Ladder
1928z T cells
1928z-Eureka 16 T cells
1928z-Eureka 18 T cells
1928z-Eureka 23 T cells
1928z-Eureka 26 T cells
1928z-Eureka 27 T cells
1928z-Eureka 31 T cells
1928z-Eureka 40 T cells
anti-HA
anti-HA
anti-GAPDH

FIGURE 7

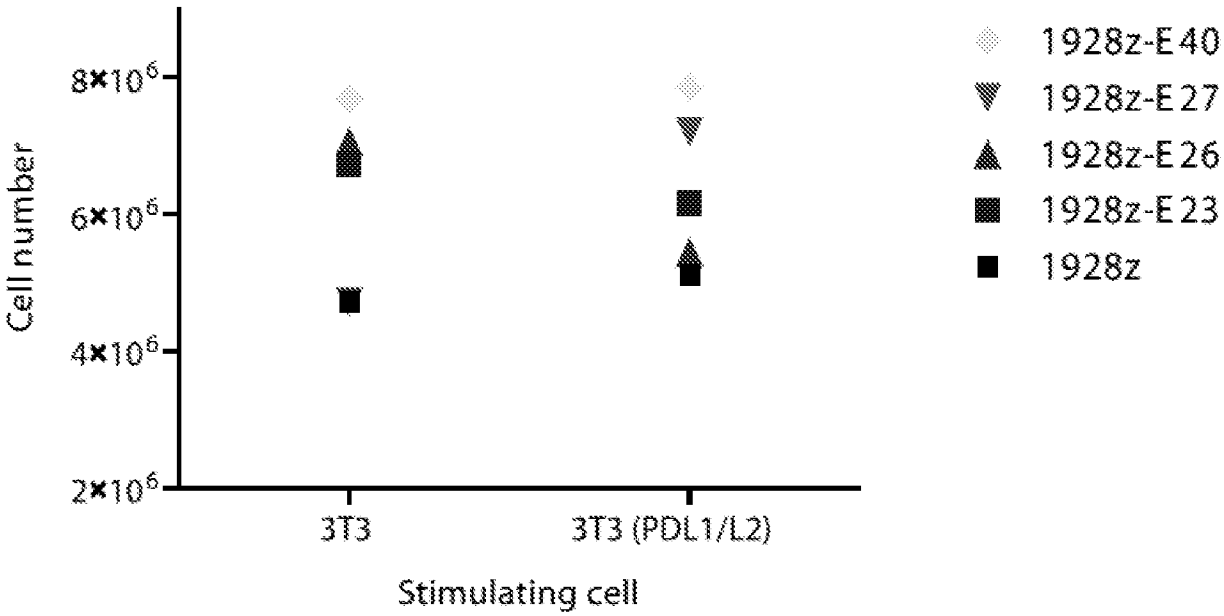
Cell number
8×10^6
6×10^6
4×10^6
2×10^6
3T3
3T3 (PDL1/L2)
Stimulating cell
1928z-E40
1928z-E27
1928z-E26
1928z-E23
1928z

FIGURE 8

	LV					HV					
	CDR1		CDR2	CDR3		CDR1		CDR2		CDR3	
#16	QSISSY	1	AAS	QQSYSTPLT	2	GFTSSSYW	3	IKQDGSEK	4	ARGGWSYDM	5
#18	SSNIGAGYA	12	TNN	QSYDSSLSGVI	13	GYTLTELS	14	FDPEDGET	15	ARAYYGFDQ	16
#23	SSNIGNNA	23	YND	AAWDDSVNGYV	24	GYTFTRFG	25	ISVNNGNT	26	ARYNYGSRDS	27
#26	NIGSKS	34	YDS	QVWDNHSDVV	35	RNKFSSYA	36	ISGSGGTT	37	ARWYSSYYDV	38
#27	NIGSKS	34	YDS	QVWDSSDYV	45	GFTFSSYA	46	ISGSGGST	47	ARNYISMFDS	48
#31	NIGSKS	34	YDS	QVWDSSSDHV	55	GFTFSSYA	46	ISGSGGST	47	ARGYSSYYDA	56
#40	RSNIGENT	63	SNN	AAWDDRLNGYV	64	GYTFTNYG	65	IGAQNGDT	66	ARSQGVPFDS	67
#36	RSNIGSNT	74	NNN	ATWDDSLNEYV	75	GYTFTRYG	76	ISGYNGNT	77	ARHGYGYHGD	78
#37	SSNIGAGYV	85	HNN	QSYDSSLSGWV	86	GFTFKDYY	87	ISTSGNSV	88	ARSPGHSDYDS	89
#19	NIGDKS	96	YDS	QVWASGTDHPYVI	97	GFTFSSYA	46	ISGSGGST	47	ARMYGSYTDM	98
#14	SSNIGYNY	105	RNN	TSWDDSLSGYV	106	GNAFTNFY	107	INPSGTDLT	108	ARQYAYGYSGFDM	109
#47	QSVSNW	116	AAS	QQSYSTPIT	117	GYTFTSYY	118	INPNTGGS	119	ARGDVTYDE	120
#46	NIGSKS	34	YDD	QVWDINDHVV	127	GFTFSSYA	46	ISGSGGST	47	ARSQASFMDI	128
#42	NIGSKS	34	DDS	QVWDSSSDQGV	135	GFTFSSYA	46	IGTGGGT	136	ARGTGYDGDQ	137

FIGURE 9

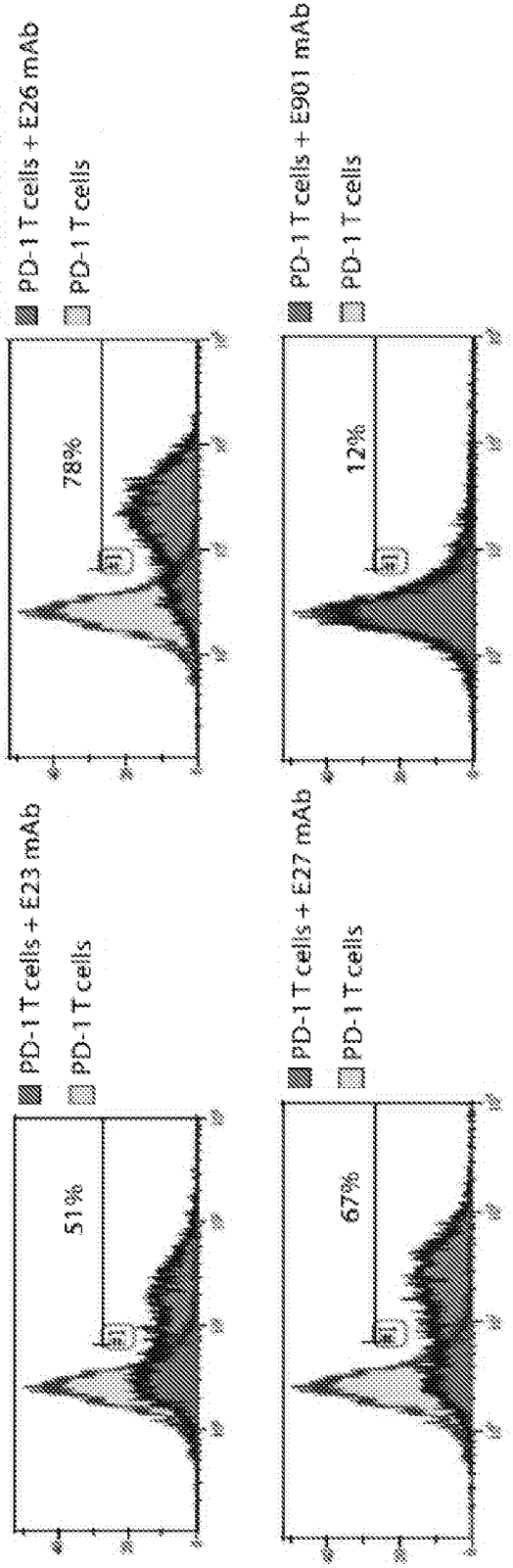
PD-1 T cells + E26 mAb
PD-1 T cells
78%
PD-1 T cells + E901 mAb
PD-1 T cells
12%
PD-1 T cells + E23 mAb
PD-1 T cells
51%
PD-1 T cells + E27 mAb
PD-1 T cells
67%

FIGURE 10

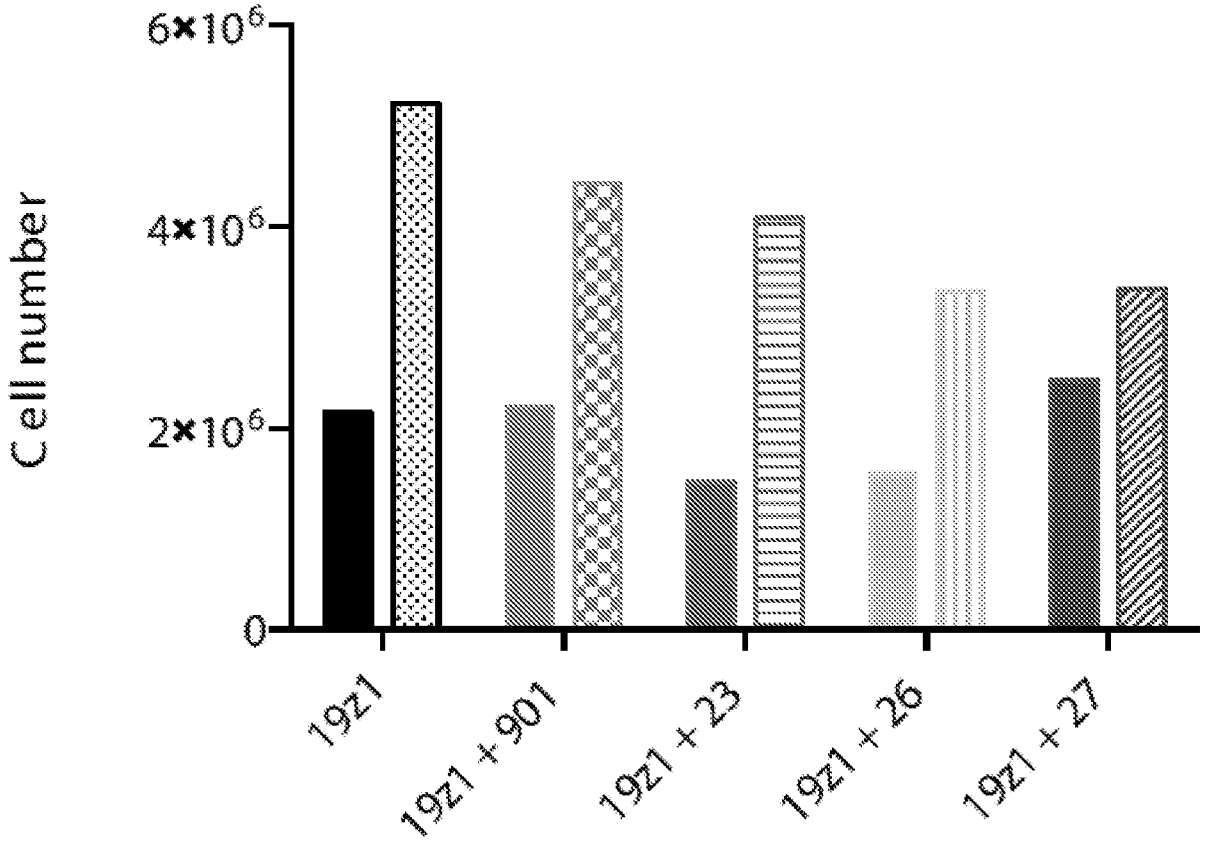
6×10^6
4×10^6
2×10^6
0
Cell number
19z1
19z1 + 901
19z1 + 23
19z1 + 26
19z1 + 27

FIGURE 11

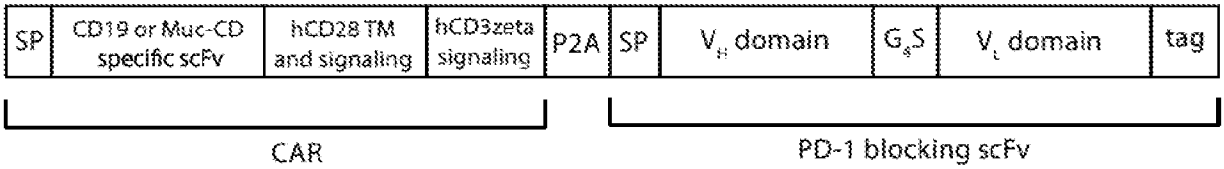

FIGURE 12A

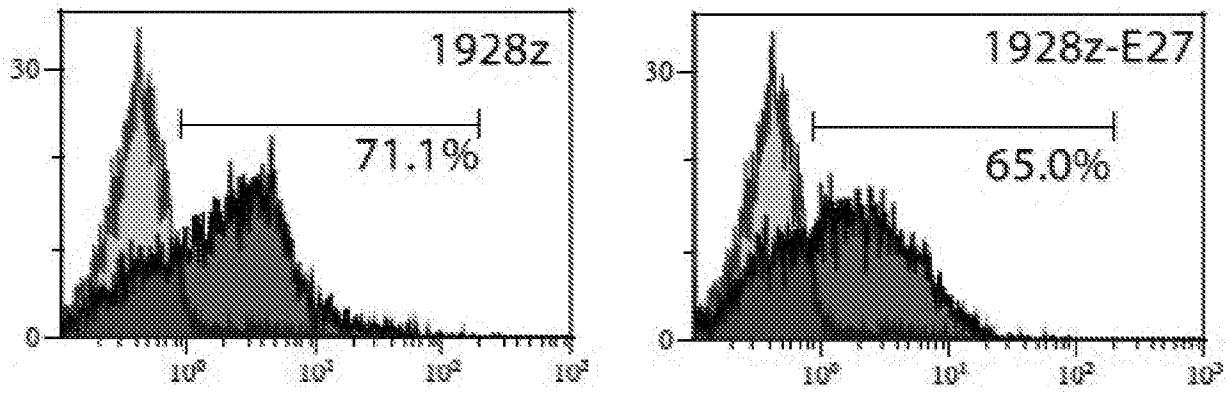

FIGURE 12B

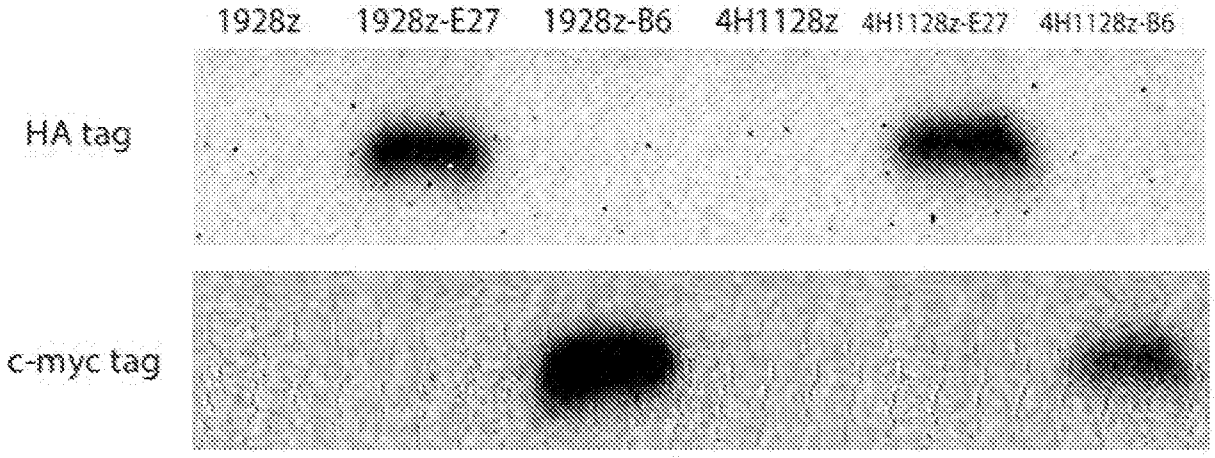

FIGURE 12C

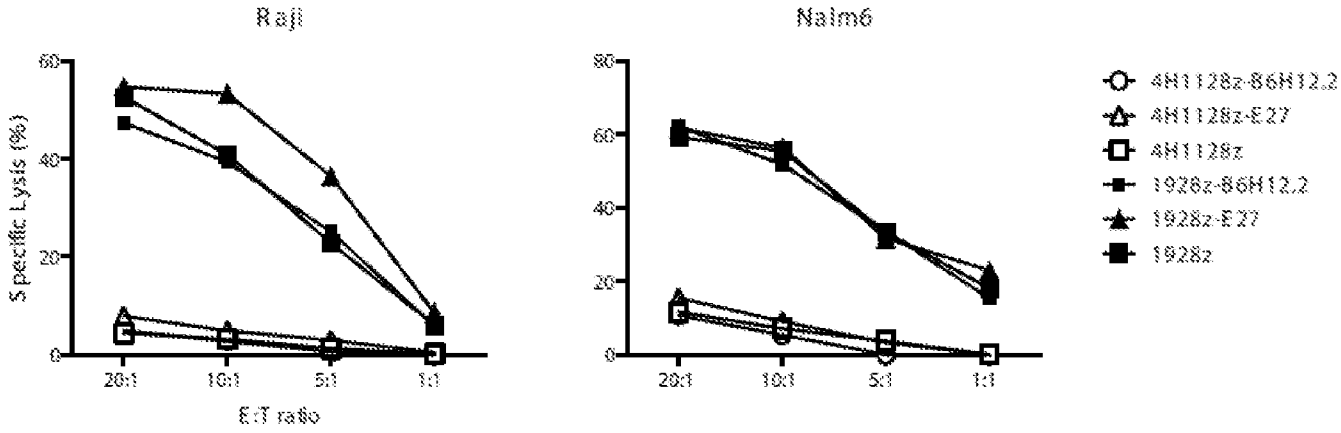

FIGURE 12D

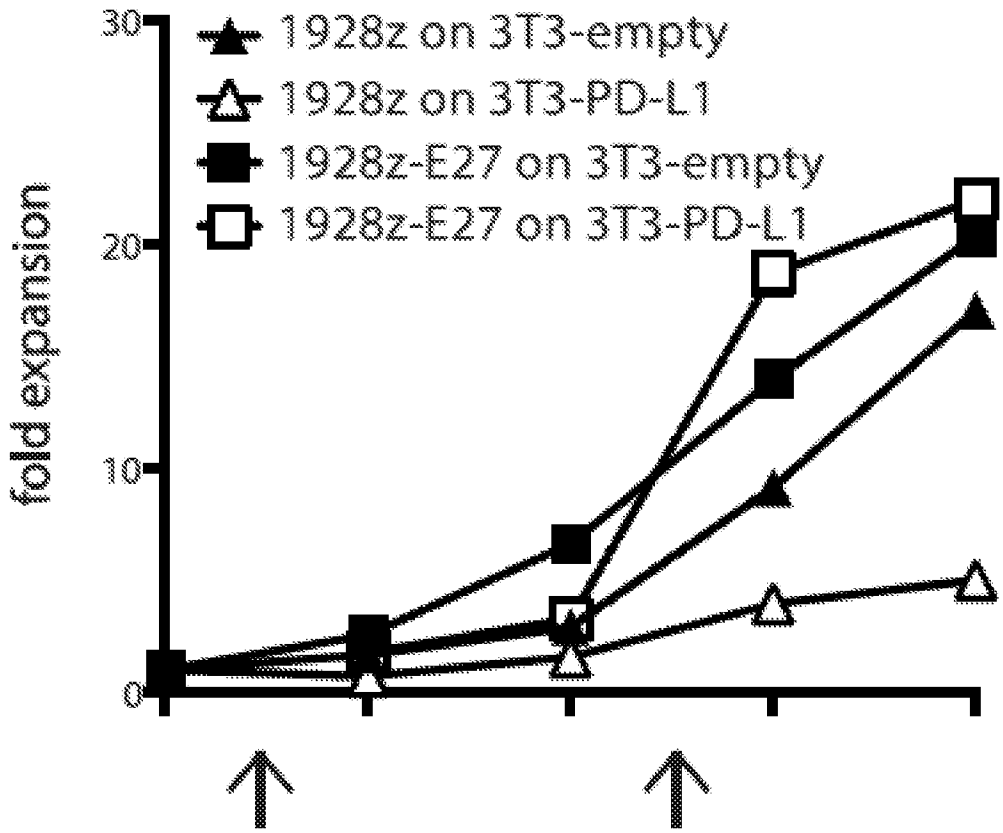
30
20
10
0
fold expansion
1928z on 3T3-empty
1928z on 3T3-PD-L1
1928z-E27 on 3T3-empty
1928z-E27 on 3T3-PD-L1

FIGURE 13A

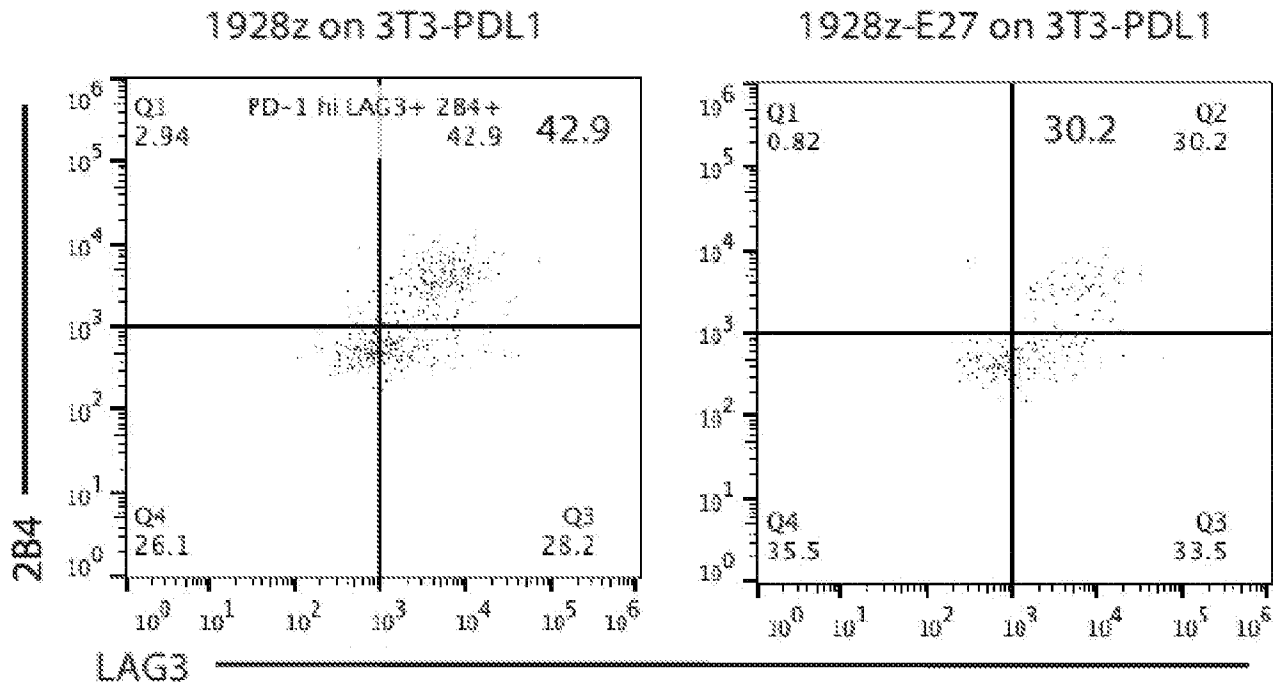
1928z on 3T3-PDL1
1928z-E27 on 3T3-PDL1
Q1
2.94
PD-1 hi LAG3+ 284+
42.9
42.9
Q4
26.1
Q3
28.2
Q1
0.82
30.2
Q2
30.2
Q4
35.5
Q3
33.5
284
LAG3

FIGURE 13B

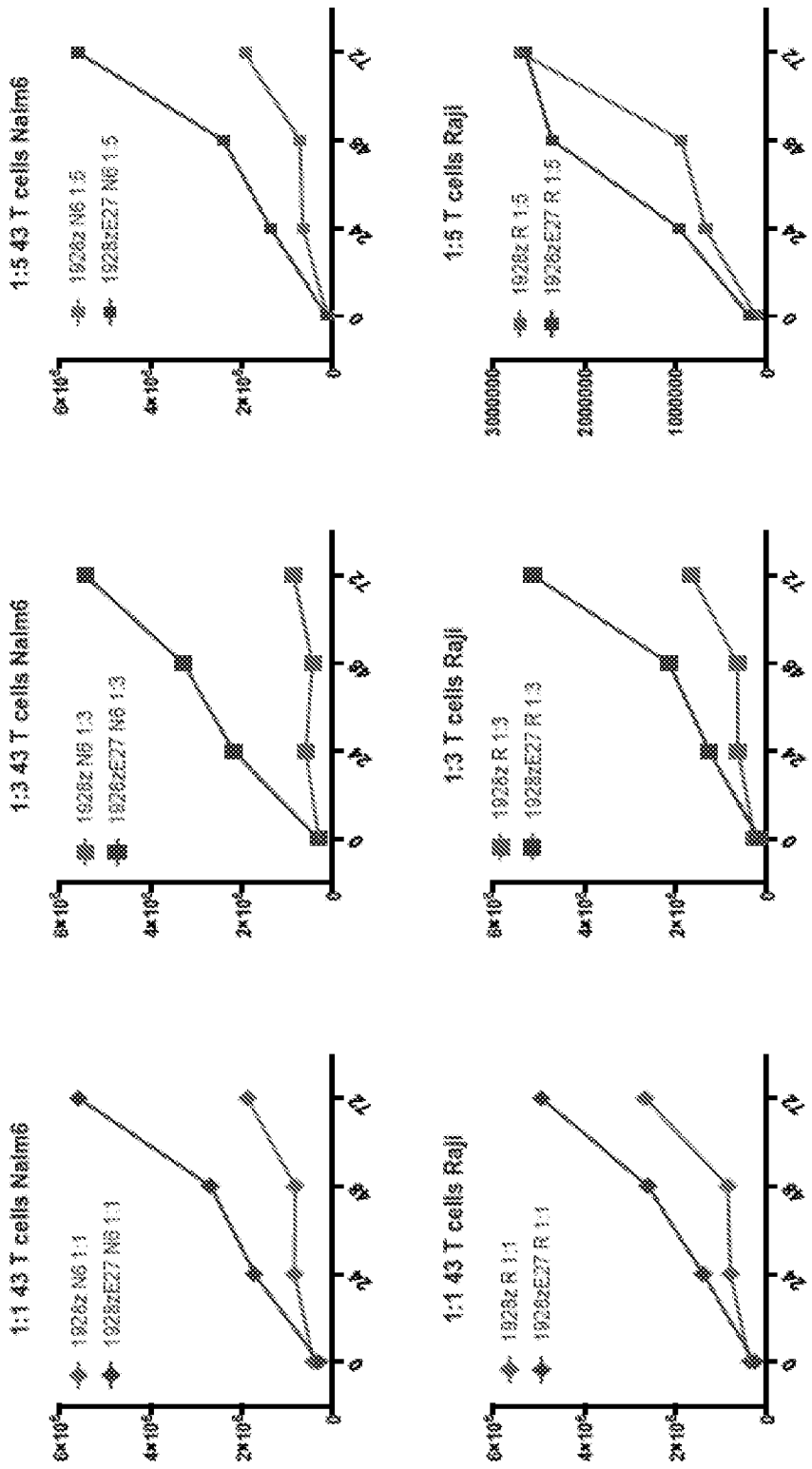
1:1 43 T cells Nalm6
1928z NB 1:1
1928zE27 NB 1:1
1:3 43 T cells Nalm6
1928z NB 1:3
1928zE27 NB 1:3
1:5 43 T cells Nalm6
1928z NB 1:5
1928zE27 NB 1:5
1:1 43 T cells Raji
1928z R 1:1
1928zE27 R 1:1
1:3 T cells Raji
1928z R 1:3
1928zE27 R 1:3
1:5 T cells Raji
1928z R 1:5
1928zE27 R 1:5

FIGURE 13C

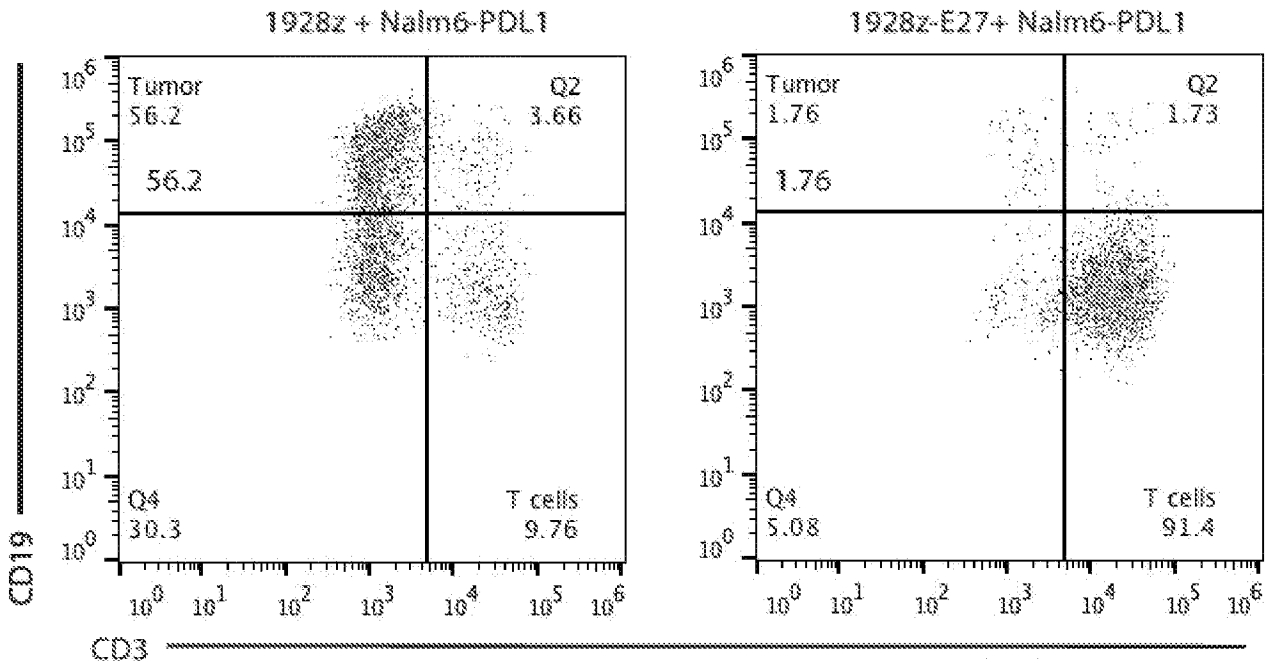
1928z + Nalm6-PDL1
1928z-E27+ Nalm6-PDL1
Tumor
56.2
Q2
3.66
56.2
Q4
30.3
T cells
9.76
Tumor
1.76
Q2
1.73
1.76
Q4
5.08
T cells
91.4
CD19
CD3

FIGURE 13D

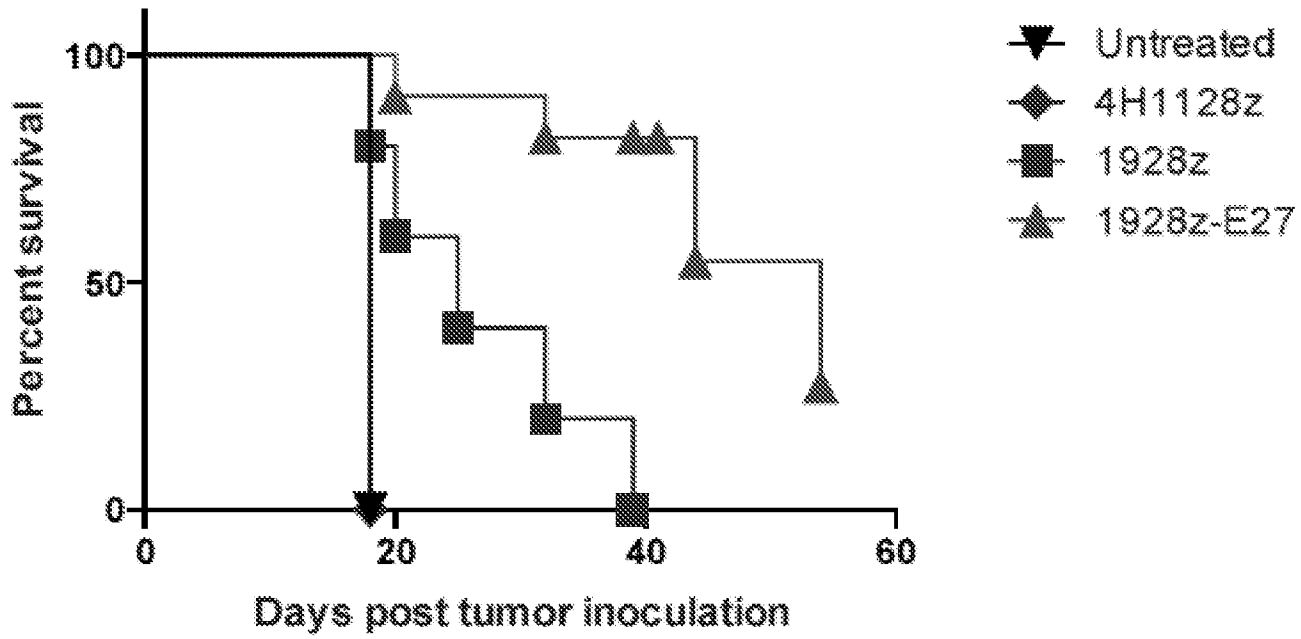
Percent survival
100
50
0
0
20
40
60
Days post tumor inoculation
Untreated
4H1128z
1928z
1928z-E27

FIGURE 14

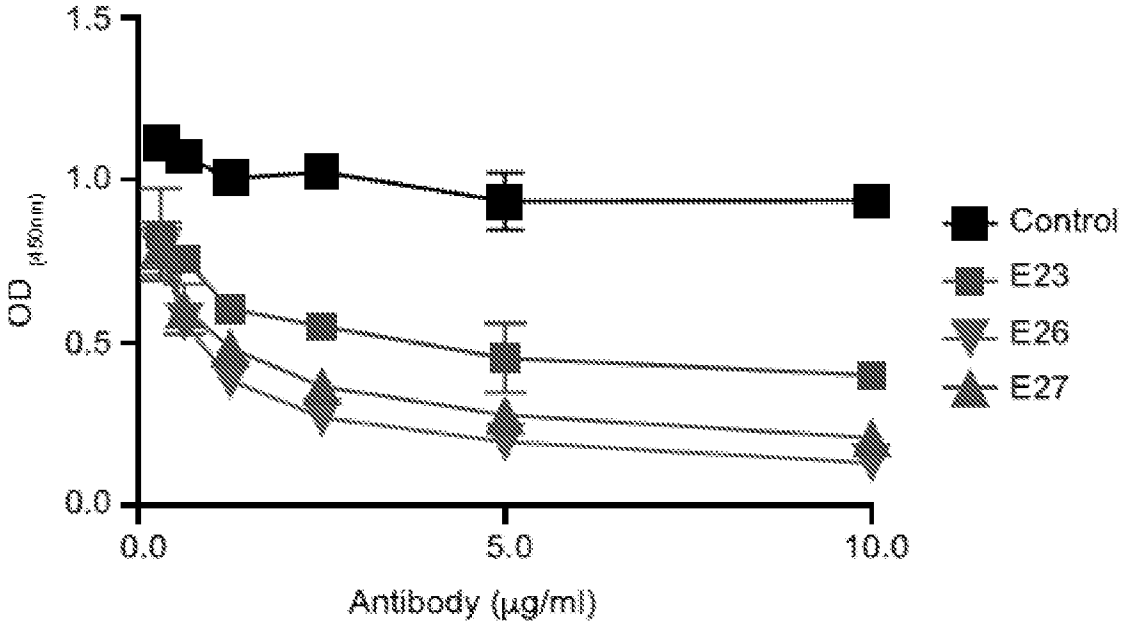

FIGURE 15A

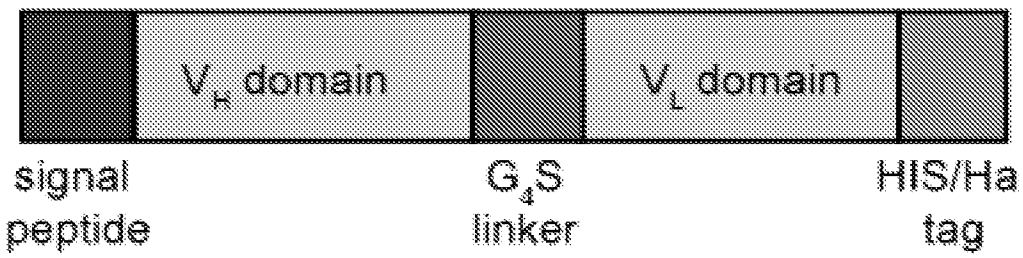

FIGURE 15B

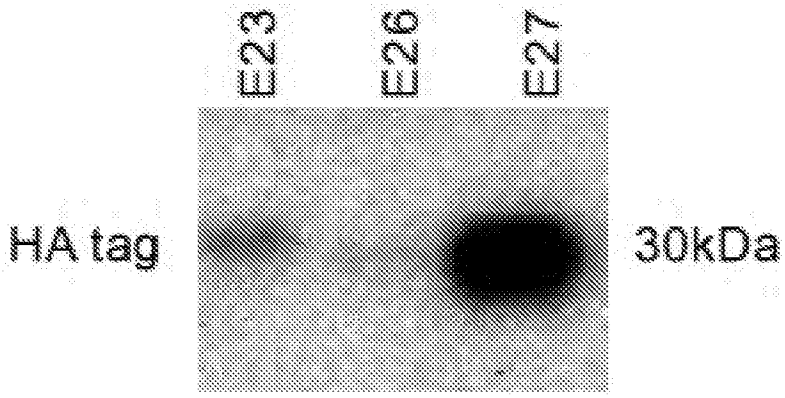

FIGURE 15C

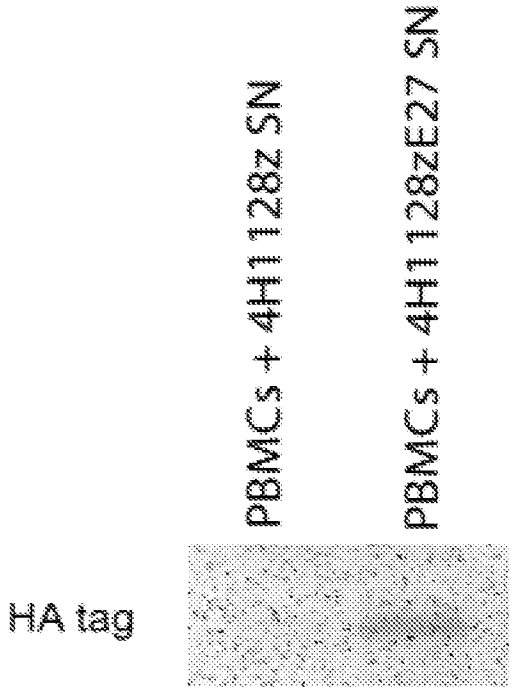

FIGURE 15D

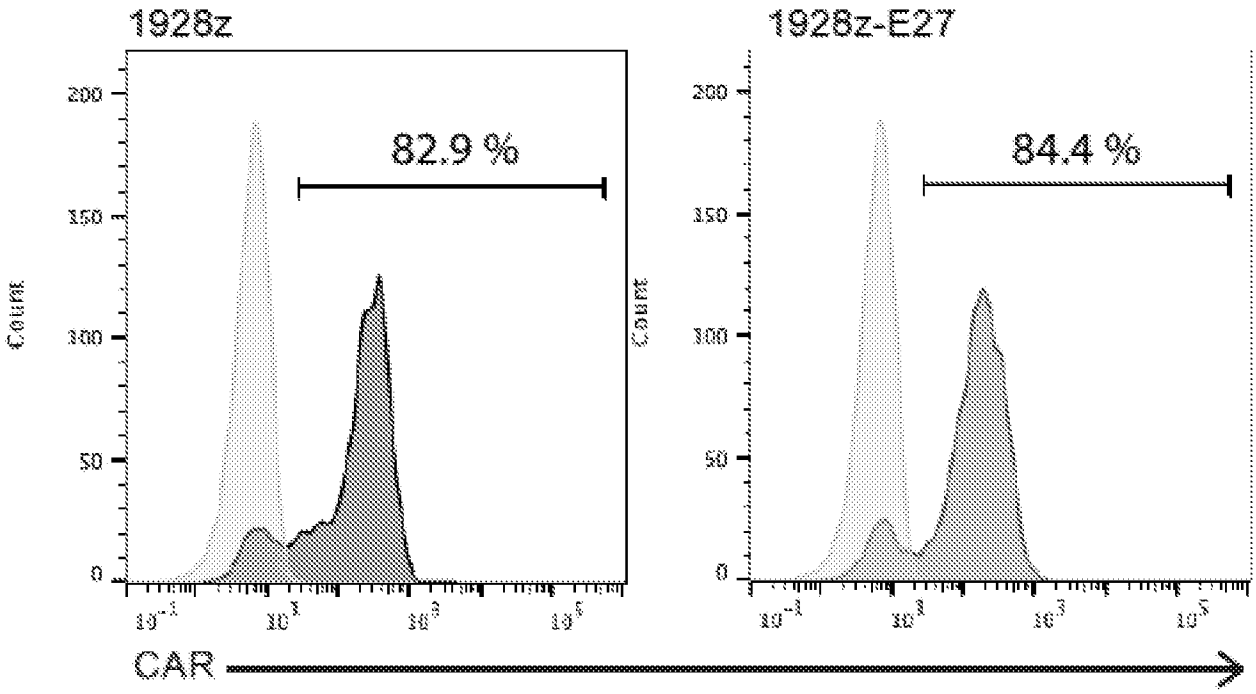

FIGURE 16A

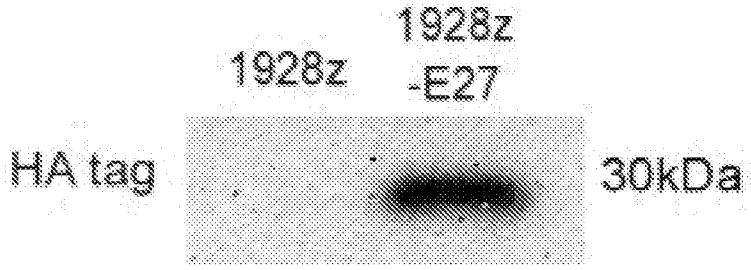

FIGURE 16B

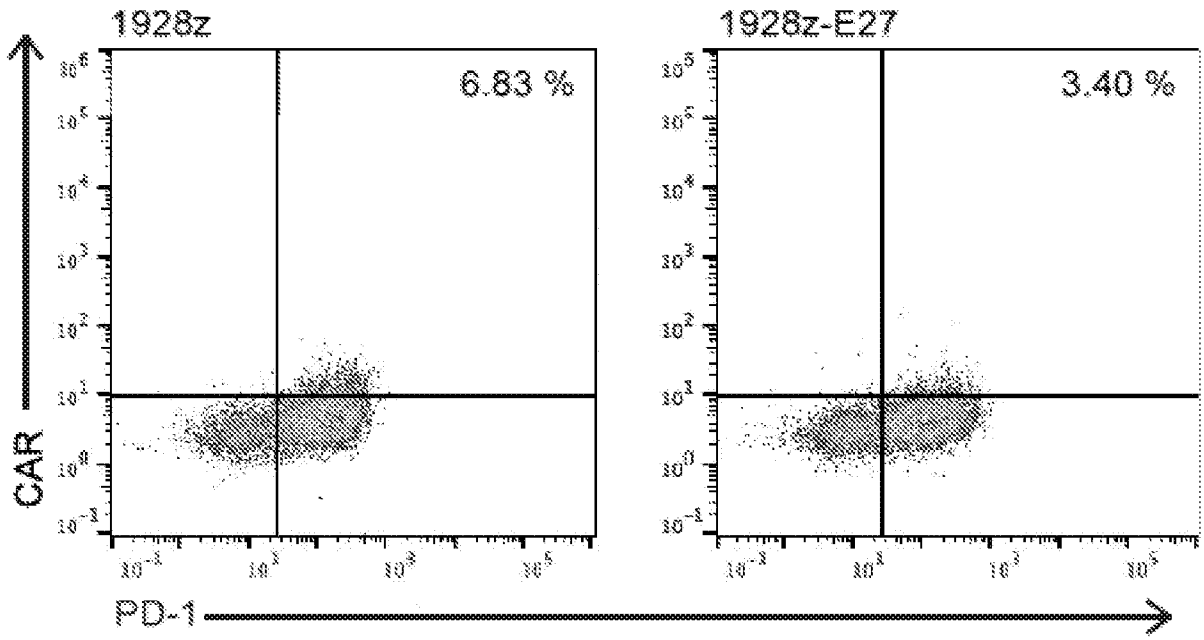

FIGURE 16C

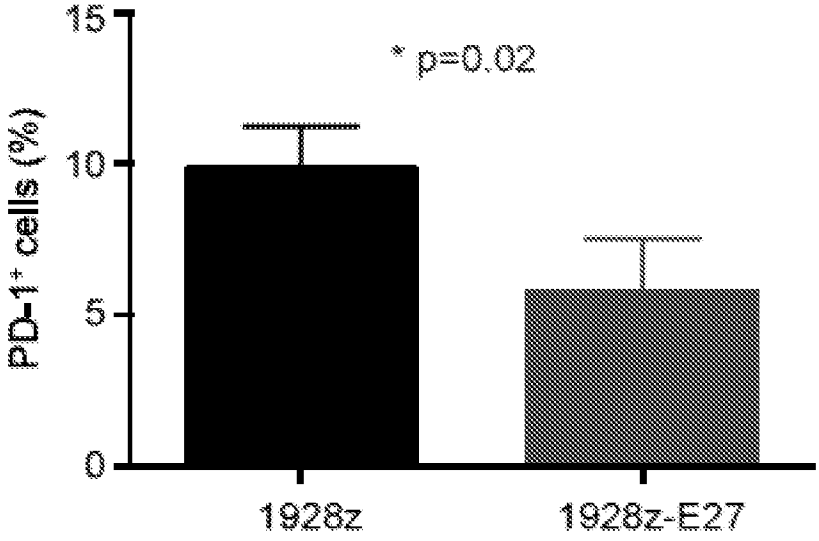

FIGURE 16D

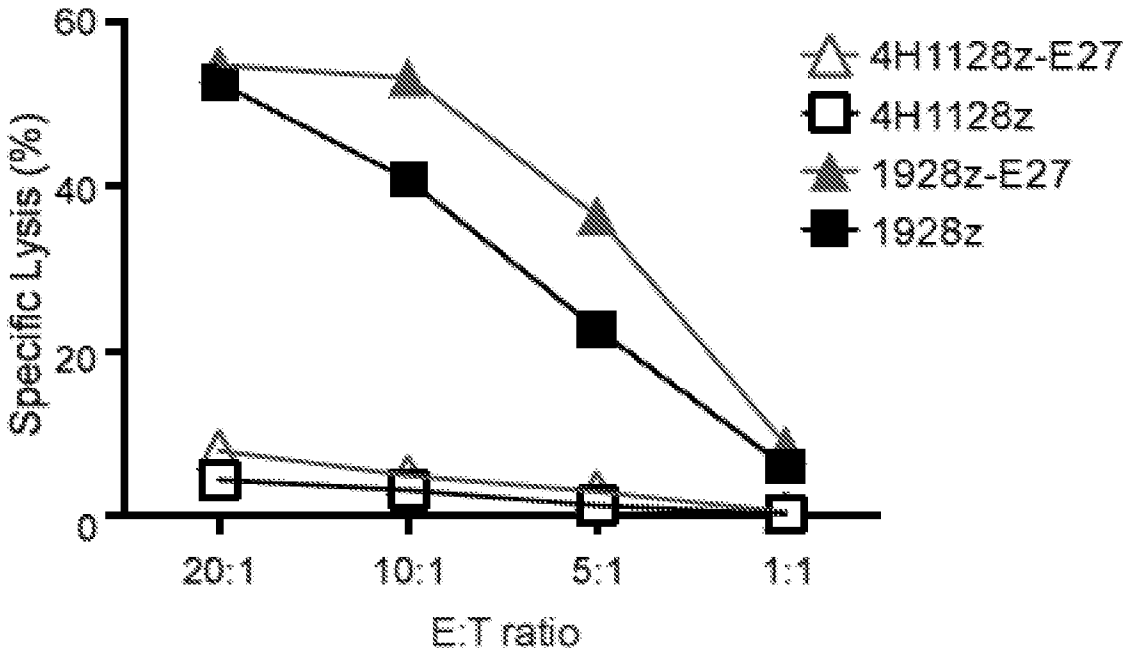
60
40
20
0
Specific Lysis (%)
20:1
10:1
5:1
1:1
E:T ratio
4H1128z-E27
4H1128z
1928z-E27
1928z

FIGURE 16E

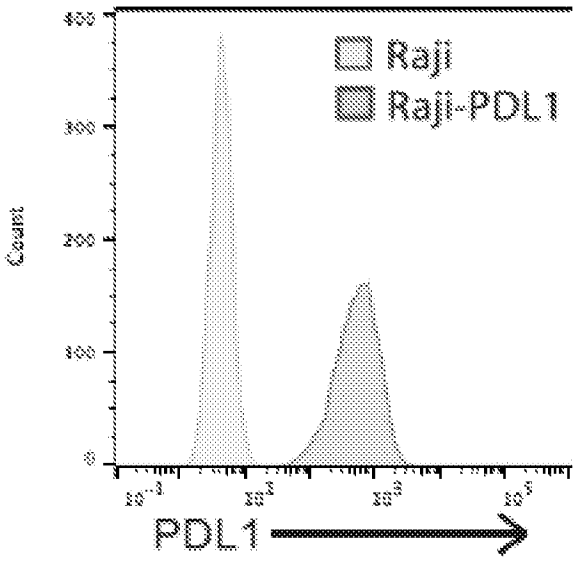

FIGURE 17A

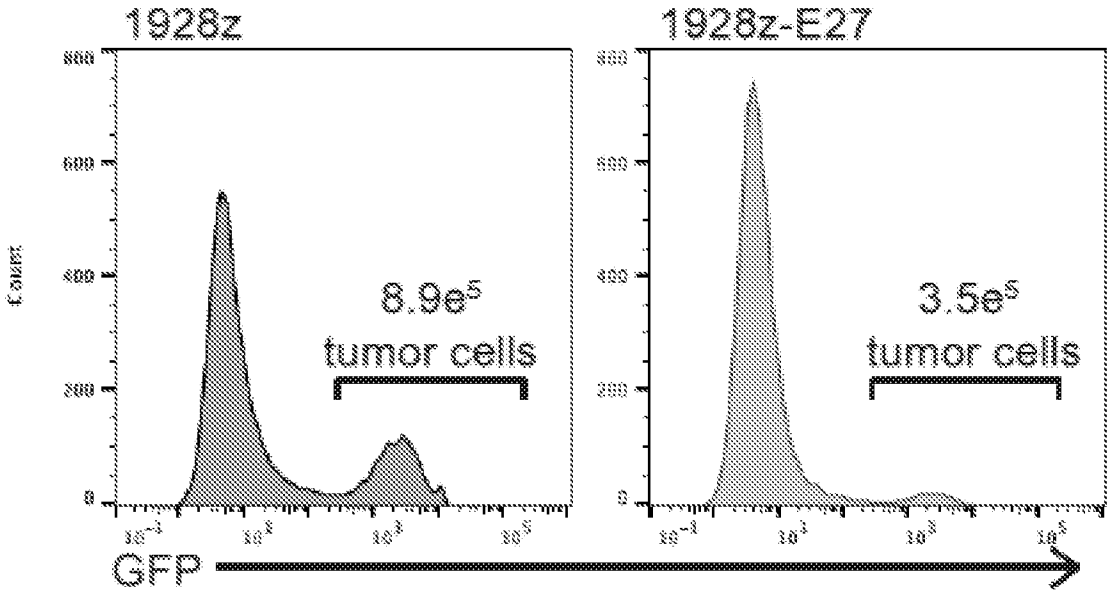

FIGURE 17B

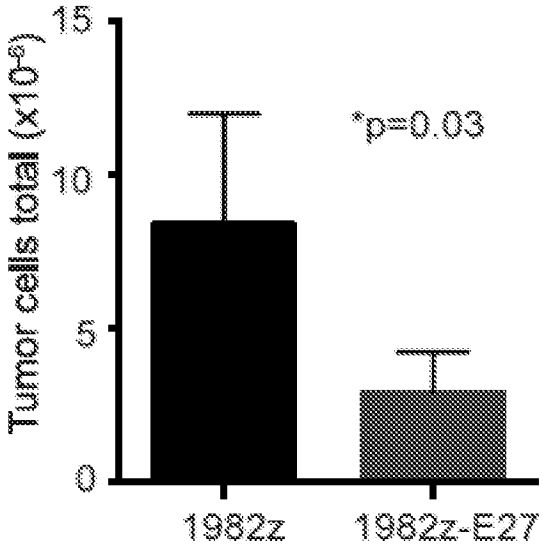

FIGURE 17C

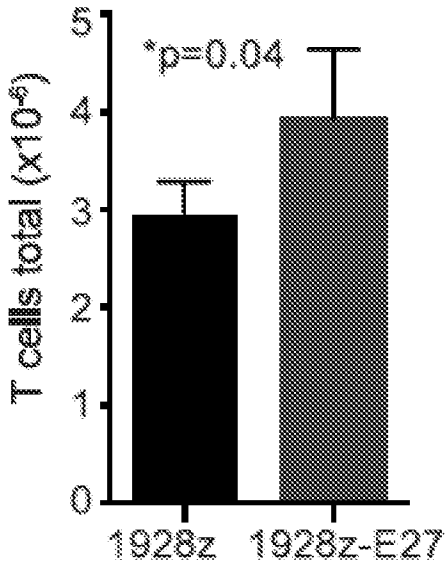

FIGURE 17D

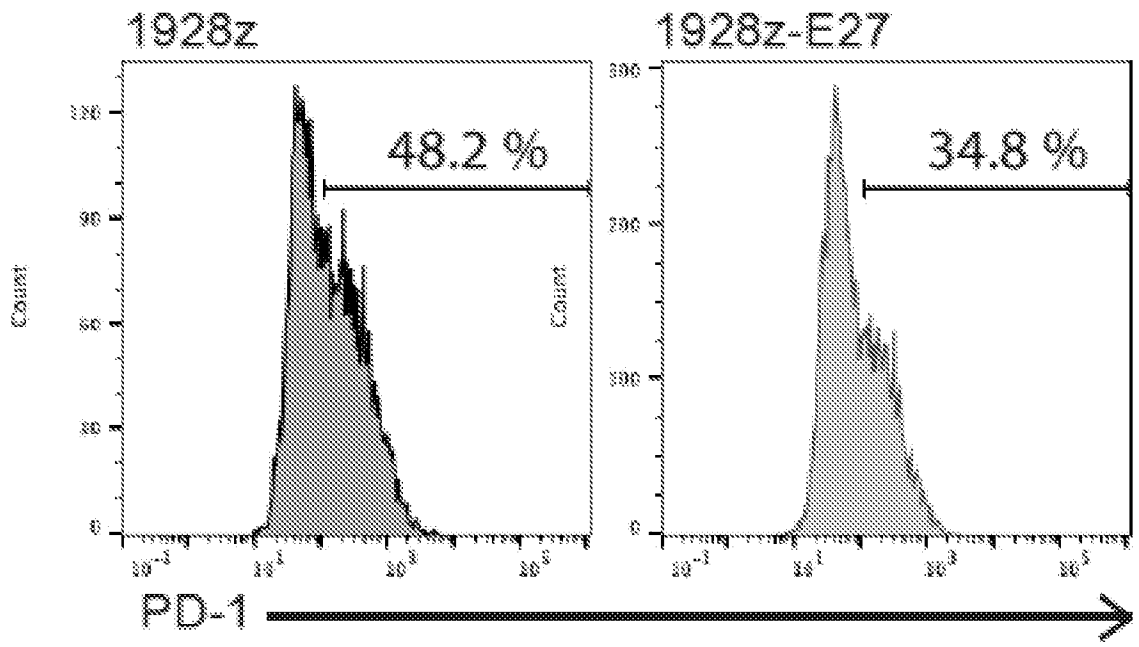

FIGURE 17E

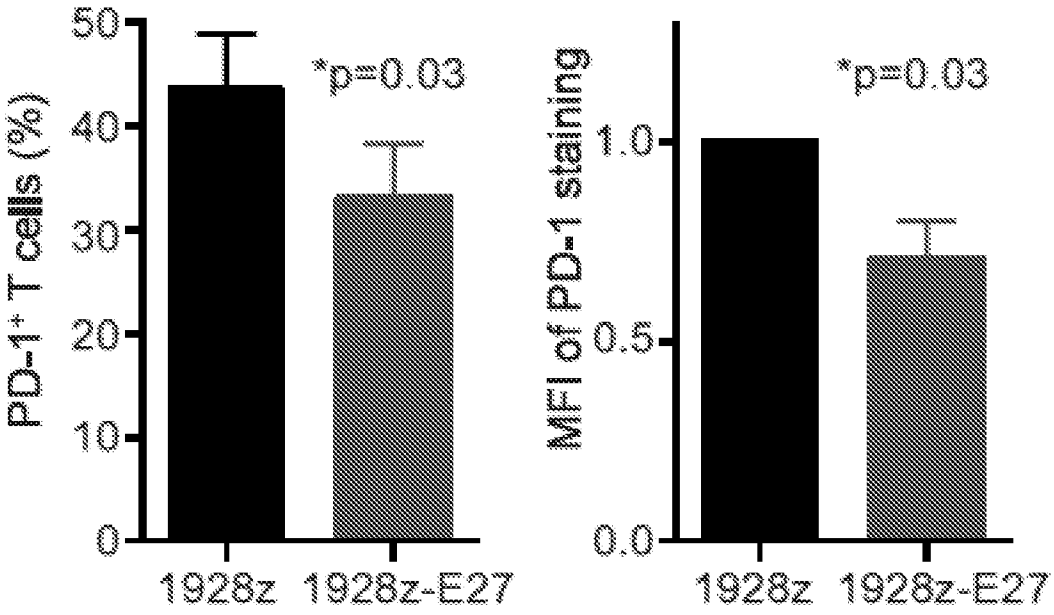
PD-1+ T cells (%)
50
40
30
20
10
0
*p=0.03
1928z
1928z-E27
MFI of PD-1 staining
1.0
0.5
0.0
*p=0.03
1928z
1928z-E27

FIGURE 17F

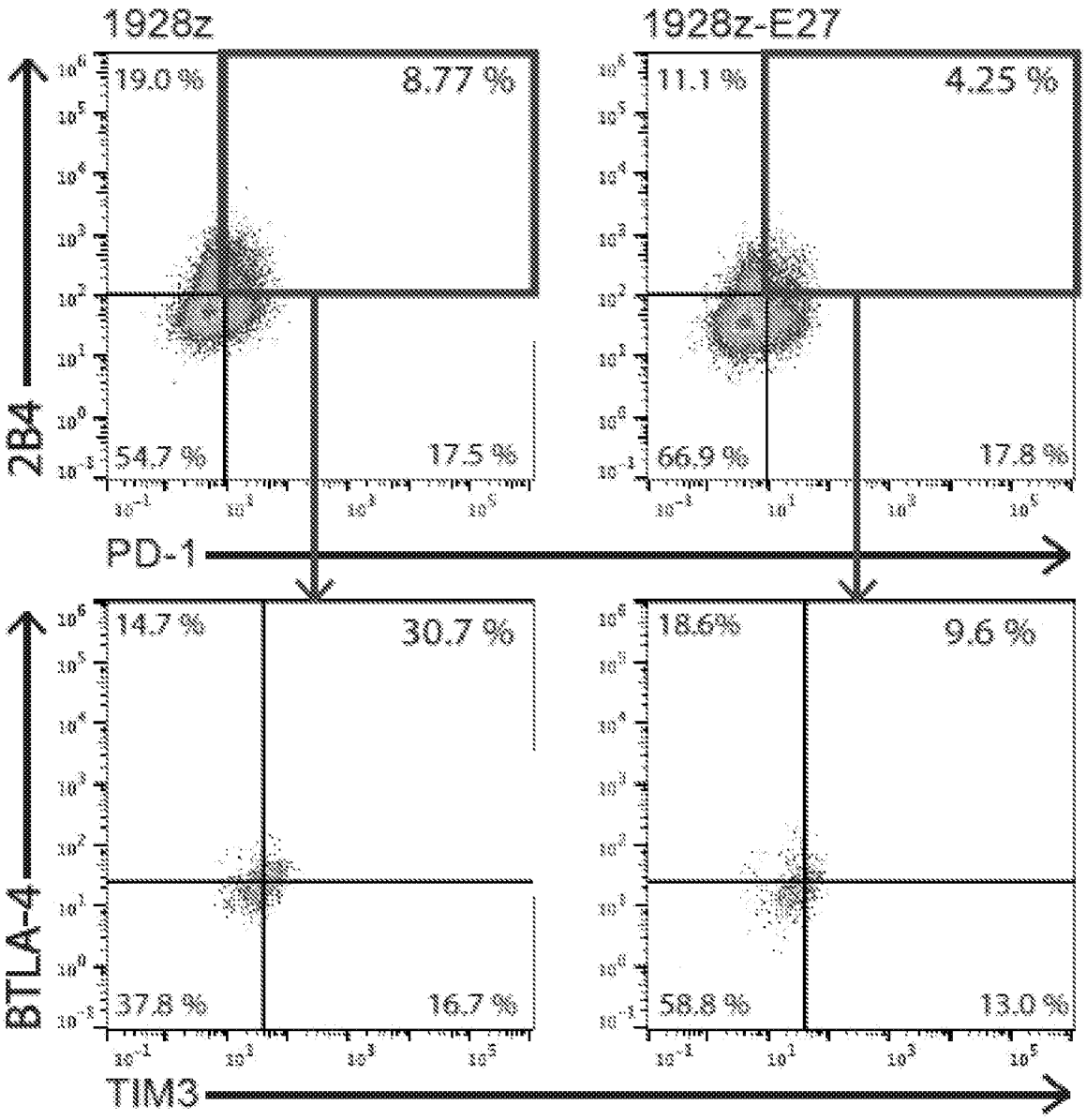
1928z
1928z-E27
19.0 %
8.77 %
54.7 %
17.5 %
11.1 %
4.25 %
66.9 %
17.8 %
2B4
PD-1
14.7 %
30.7 %
37.8 %
16.7 %
18.6%
9.6 %
58.8 %
13.0 %
BTLA-4
TIM3

FIGURE 17G

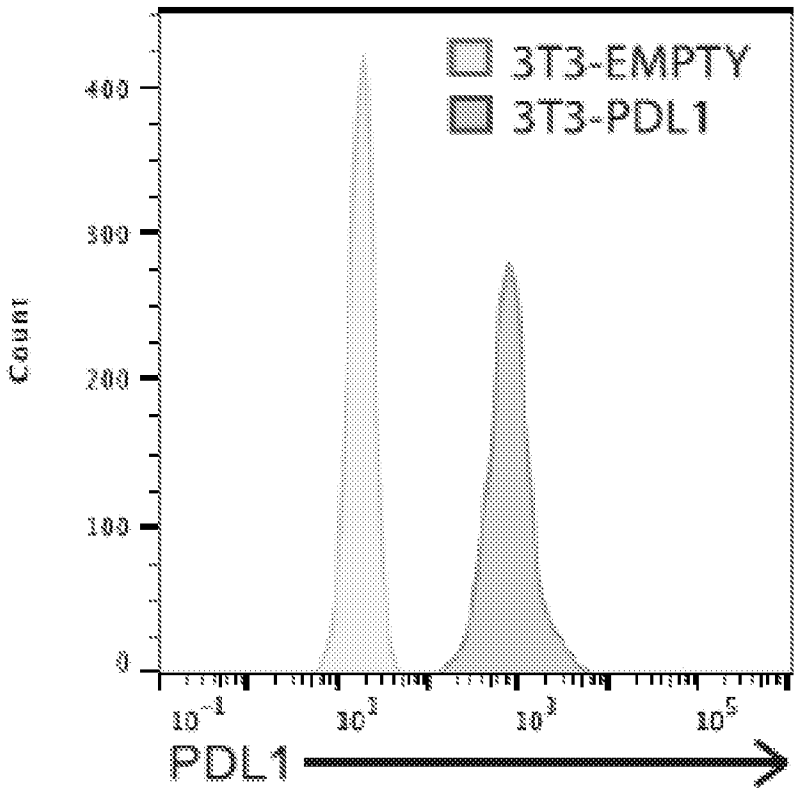

FIGURE 18A

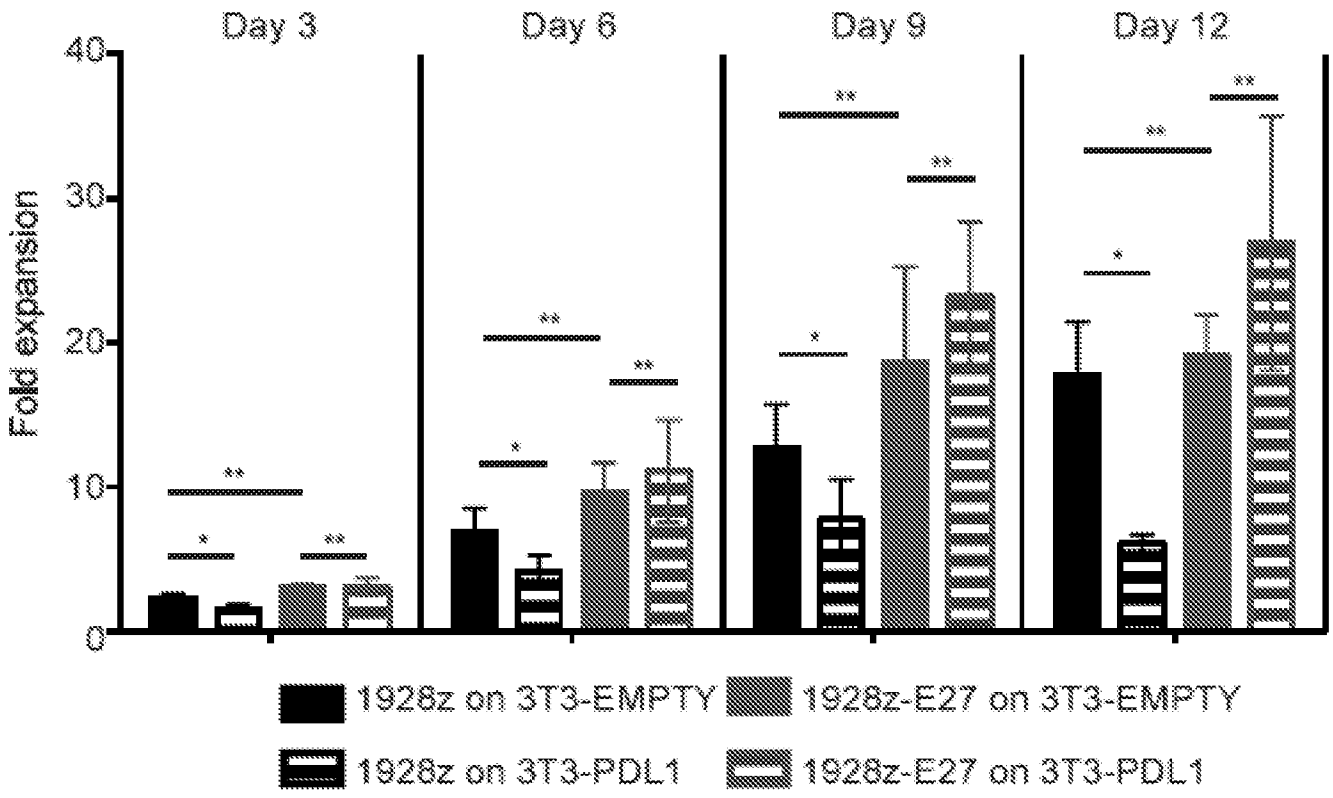
Day 3
Day 6
Day 9
Day 12
Fold expansion
0
10
20
30
40
*
**
1928z on 3T3-EMPTY
1928z-E27 on 3T3-EMPTY
1928z on 3T3-PDL1
1928z-E27 on 3T3-PDL1

FIGURE 18B

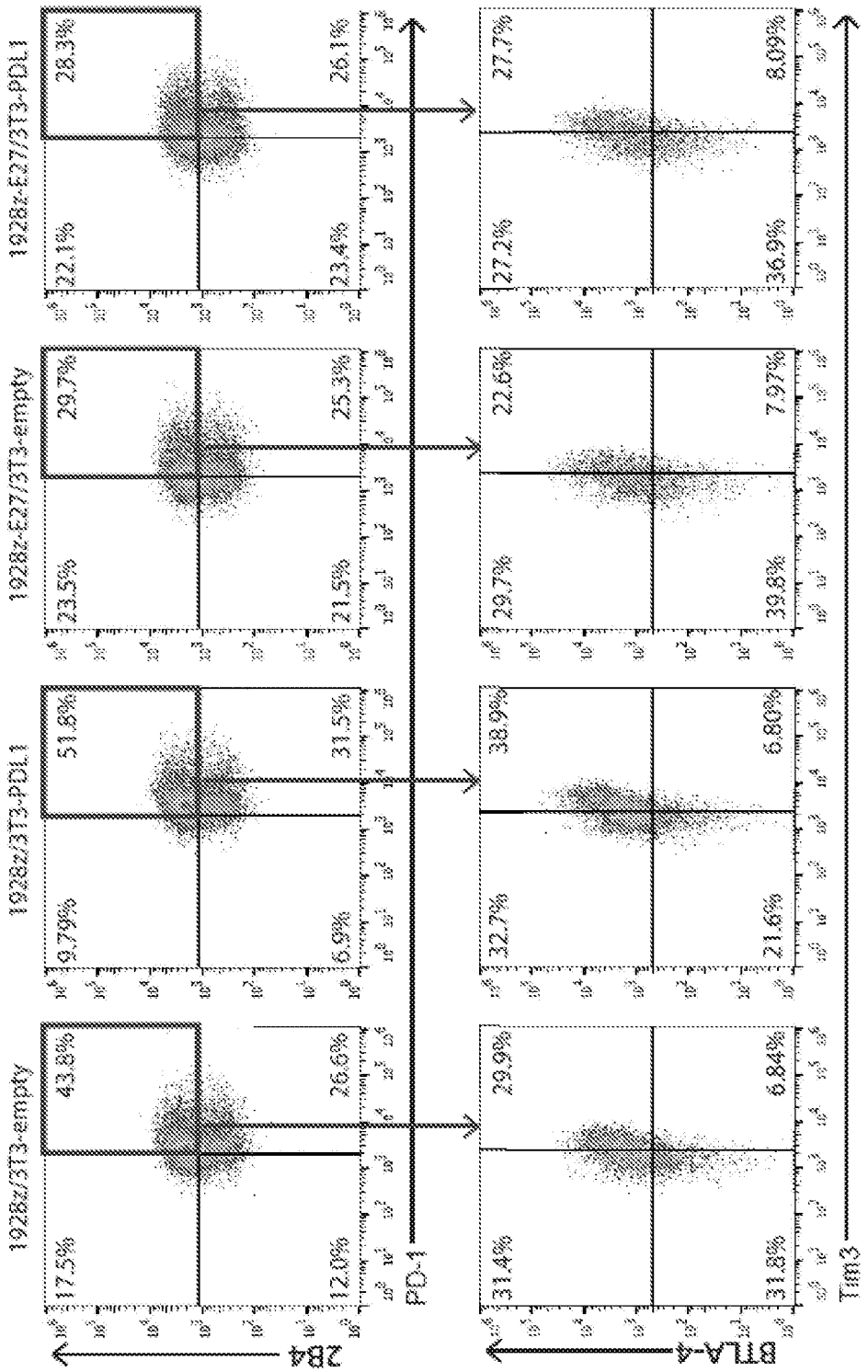
1928z-E27/3T3-PDL1
1928z-E27/3T3-empty
1928z/3T3-PDL1
1928z/3T3-empty
28.3%
22.1%
26.1%
23.4%
27.7%
27.2%
8.09%
36.9%
29.7%
23.5%
25.3%
21.5%
22.6%
29.7%
7.97%
39.8%
51.8%
9.79%
31.5%
6.9%
38.9%
32.7%
6.80%
21.6%
43.8%
17.5%
26.6%
12.0%
29.9%
31.4%
6.84%
31.8%
2B4
PD-1
BTLA-4
Tim3

FIGURE 18C

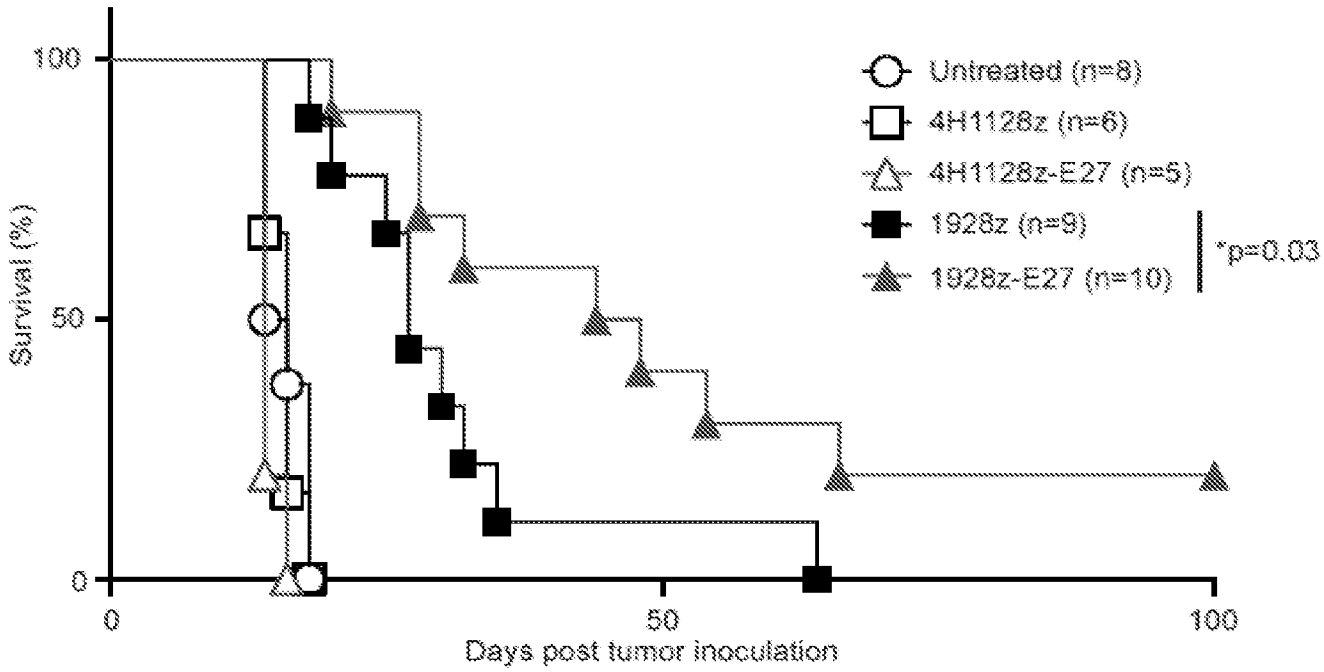
100
50
0
Survival (%)
0
50
100
Days post tumor inoculation
Untreated (n=8)
4H1128z (n=6)
4H1128z-E27 (n=5)
1928z (n=9)
1928z-E27 (n=10)
*p=0.03

FIGURE 19

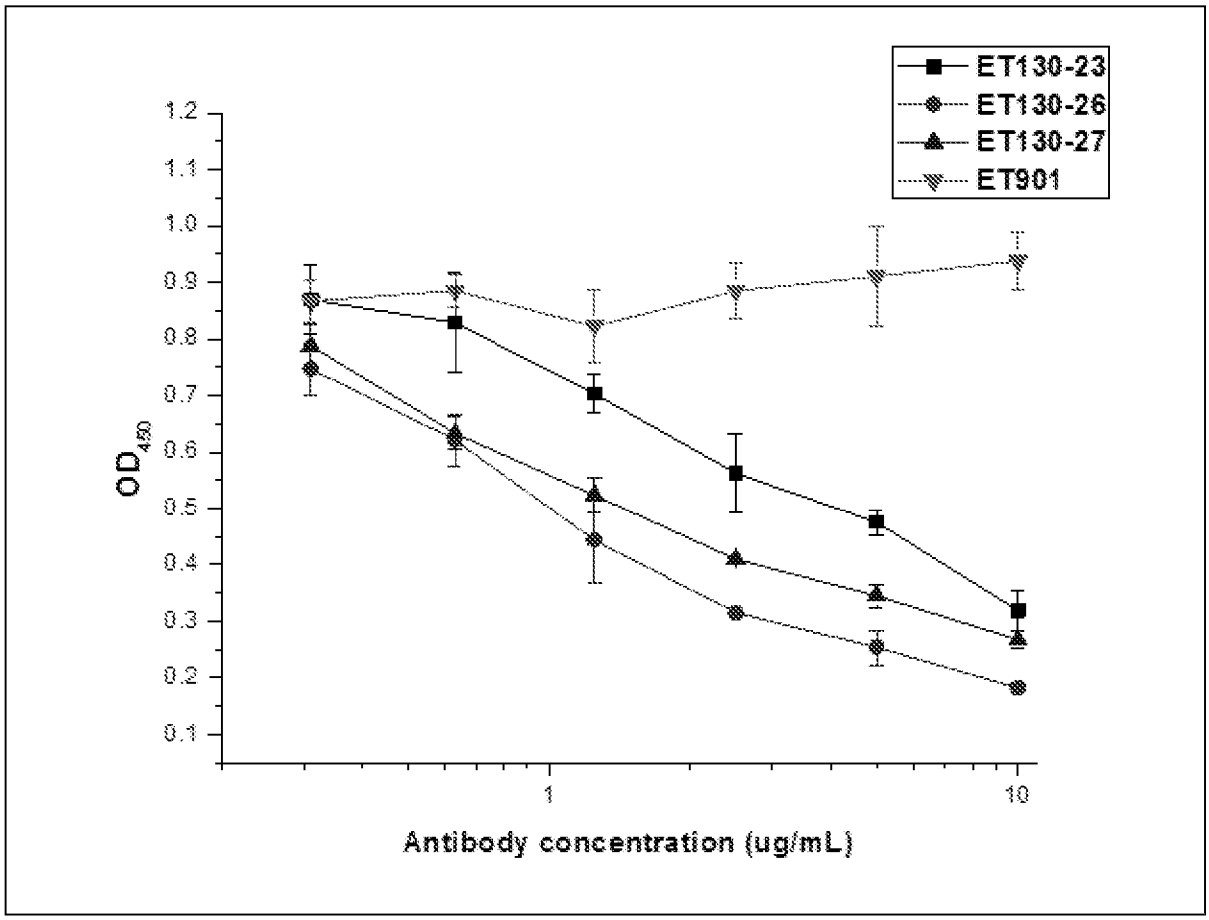
ET130-23
ET130-26
ET130-27
ET901
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
OD450
1
10
Antibody concentration (ug/mL)

FIGURE 20

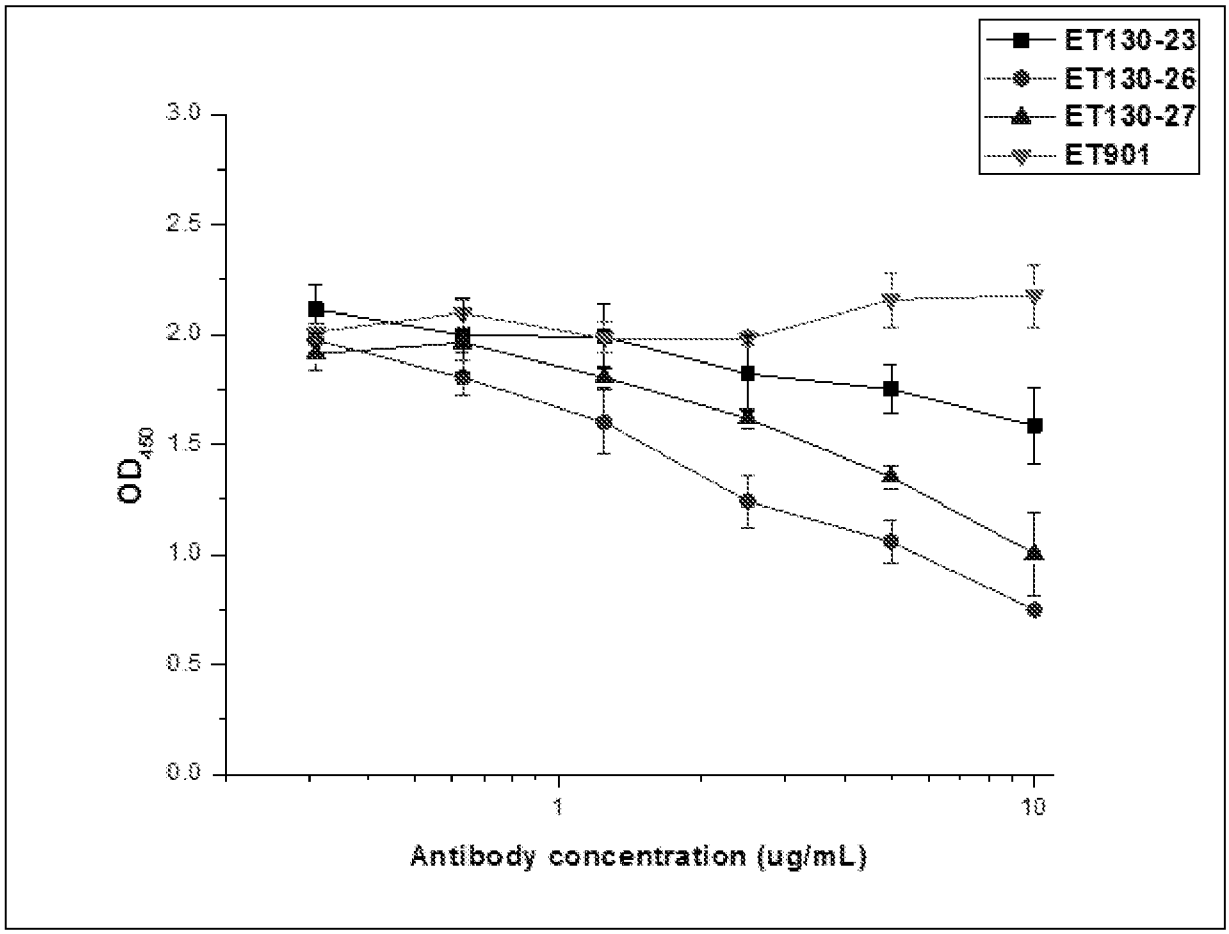
ET130-23
ET130-26
ET130-27
ET901
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD450
1
10
Antibody concentration (ug/mL)

FIGURE 21

SEQUENCE LISTING

<110> Memorial Sloan-Kettering Cancer Center
Eureka Therapeutics, Inc.
Brentjens, Renier J
Jackson, Hollie J
Liu, Cheng

<120> PD-1 Immune Modulating Agents

<130> 3314.070AWO

<150> 62/183,297
<151> 2015-06-23

<150> 62/266,389
<151> 2015-12-11

<160> 143

<170> PatentIn version 3.5

<210> 1
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Homo sapiens

<400> 1

Gln Ser Ile Ser Ser Tyr
1 5

<210> 2
<211> 9
<212> PRT
<213> Homo sapiens

<400> 2

Gln Gln Ser Tyr Ser Thr Pro Leu Thr
1 5

<210> 3
<211> 8
<212> PRT
<213> Homo sapiens

<400> 3

Gly Phe Thr Ser Ser Ser Tyr Trp
1 5

<210> 4
<211> 8
<212> PRT
<213> Homo sapiens

<400> 4

Ile Lys Gln Asp Gly Ser Glu Lys
1 5

<210> 5
<211> 9
<212> PRT
<213> Homo sapiens

<400> 5

Ala Arg Gly Gly Trp Ser Tyr Asp Met
1 5

<210> 6
<211> 110
<212> PRT
<213> Homo sapiens

<400> 6

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ser Arg
100 105 110

<210> 7
<211> 324
<212> DNA
<213> Homo sapiens

<400> 7
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccgctcac tttcggcgga 300

gggaccaagg tggagatcaa acgt 324

<210> 8
<211> 116

<212> PRT
<213> Homo sapiens

<400> 8

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

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

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Trp Ser Tyr Asp Met Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115
```

<210> 9
<211> 348
<212> DNA
<213> Homo sapiens

<400> 9

```
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc       60

tcctgtgcag cctctggatt cacctctagt agctattgga tgagctgggt ccgccaggct      120

ccagggagag ggctggagtg ggtggccaac ataaagcaag atggaagtga gaagtactat      180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat      240

ctgcaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gcgcggtggt      300

tggtcttacg atatgtgggg tcaaggtact ctggtgaccg tctcctca                  348
```

<210> 10
<211> 259
<212> PRT
<213> Homo sapiens

<400> 10

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
```

20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ser Arg Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln
115 120 125

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
130 135 140

Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser Ser Ser Tyr Trp Met Ser
145 150 155 160

Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val Ala Asn Ile
165 170 175

Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys Gly Arg
180 185 190

Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met
195 200 205

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly
210 215 220

Gly Trp Ser Tyr Asp Met Trp Gly Gln Gly Thr Leu Val Thr Val Ser
225 230 235 240

Ser His His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp
245 250 255

Tyr Ala Ser

<210> 11
<211> 717
<212> DNA
<213> Homo sapiens

<400> 11
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atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccgctcac tttcggcgga 300

gggaccaagg tggagatcaa acgtggtggt ggtggtagcg gcggcggcgg ctctggtggt 360

ggtggatccg aggtgcagct ggtggagtct gggggaggct tggtccagcc tgggggtcc 420

ctgagactct cctgtgcagc ctctggattc acctctagta gctattggat gagctgggtc 480

cgccaggctc agggagaggg gctggagtgg gtggccaaca taaagcaaga tggaagtgag 540

aagtactatg tggactctgt gaagggccga ttcaccatct ccagagacaa cgccaagaac 600

tcactgtatc tgcaaatgaa cagcctgaga gccgaggaca ctgccgtgta ttactgtgcg 660

cgcggtggtt ggtcttacga tatgtggggt caaggtactc tggtgaccgt ctcctca 717

<210> 12
<211> 9
<212> PRT
<213> Homo sapiens

<400> 12

Ser Ser Asn Ile Gly Ala Gly Tyr Ala
1 5

<210> 13
<211> 11
<212> PRT
<213> Homo sapiens

<400> 13

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

<210> 14
<211> 8
<212> PRT
<213> Homo sapiens

<400> 14

Gly Tyr Thr Leu Thr Glu Leu Ser
1 5

<210> 15
<211> 8
<212> PRT
<213> Homo sapiens

<400> 15

Phe Asp Pro Glu Asp Gly Glu Thr
1 5

<210> 16
<211> 9
<212> PRT
<213> Homo sapiens

<400> 16

Ala Arg Ala Tyr Tyr Gly Phe Asp Gln
1 5

<210> 17
<211> 112
<212> PRT
<213> Homo sapiens

<400> 17

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

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

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

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

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

<210> 18
<211> 336
<212> DNA
<213> Homo sapiens

<400> 18
cagtctgtgt tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg ctgtaaattg gtaccagctt 120

cttccaggaa cagcccccaa actcctcatc tctactaaca acaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc ccagtttggc gcctctgcct ccctggccat cactggactc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagtagtct gagtggtgtg 300

atattcggcg gagggaccaa gctgaccgtc ctaggt 336

<210> 19

<211> 116
<212> PRT
<213> Homo sapiens

<400> 19

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 Val Ser Gly Tyr Thr Leu Thr Glu Leu
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp 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 Ala Tyr Tyr Gly Phe Asp Gln Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 20
<211> 348
<212> DNA
<213> Homo sapiens

<400> 20
gaagtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg tttccggata caccctcact gaattatcca tgcactgggt gcgacaggct 120

cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aagatggtga aacaatctac 180

gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240

atggagctga gcagcctgag gtctgaggac actgccgtgt attactgtgc gcgcgcttac 300

tacggtttcg atcagtgggg tcaaggtact ctggtgaccg tctcctca 348

<210> 21
<211> 257
<212> PRT
<213> Homo sapiens

<400> 21

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
            100                 105                 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
        115                 120                 125

Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser
    130                 135                 140

Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu Leu Ser Met His Trp Val
145                 150                 155                 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met Gly Gly Phe Asp Pro
                165                 170                 175

Glu Asp Gly Glu Thr Ile Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr
            180                 185                 190

Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr Met Glu Leu Ser Ser
        195                 200                 205

Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Tyr Tyr
    210                 215                 220

Gly Phe Asp Gln Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser His
225                 230                 235                 240

His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
                245                 250                 255

Ser
```

<210> 22
<211> 729
<212> PRT
<213> Homo sapiens

<400> 22

```
Cys Ala Gly Thr Cys Thr Gly Thr Gly Thr Thr Gly Ala Cys Gly Cys
1               5                   10                  15

Ala Gly Cys Cys Gly Cys Cys Cys Thr Cys Ala Gly Thr Gly Thr Cys
            20                  25                  30

Thr Gly Gly Gly Gly Cys Cys Cys Cys Ala Gly Gly Gly Cys Ala Gly
        35                  40                  45

Ala Gly Gly Gly Thr Cys Ala Cys Cys Ala Thr Cys Thr Cys Cys Thr
    50                  55                  60

Gly Cys Ala Cys Thr Gly Gly Gly Ala Gly Cys Ala Gly Cys Thr Cys
65                  70                  75                  80

Cys Ala Ala Cys Ala Thr Cys Gly Gly Gly Gly Cys Ala Gly Gly Thr
                85                  90                  95

Thr Ala Thr Gly Cys Thr Gly Thr Ala Ala Ala Thr Thr Gly Gly Thr
            100                 105                 110

Ala Cys Cys Ala Gly Cys Thr Thr Cys Thr Thr Cys Cys Ala Gly Gly
        115                 120                 125

Ala Ala Cys Ala Gly Cys Cys Cys Cys Cys Ala Ala Ala Cys Thr Cys
    130                 135                 140

Cys Thr Cys Ala Thr Cys Thr Cys Thr Ala Cys Thr Ala Ala Cys Ala
145                 150                 155                 160

Ala Cys Ala Ala Thr Cys Gly Gly Cys Cys Cys Thr Cys Ala Gly Gly
                165                 170                 175

Gly Gly Thr Cys Cys Cys Thr Gly Ala Cys Cys Gly Ala Thr Thr Cys
            180                 185                 190

Thr Cys Thr Gly Gly Cys Thr Cys Cys Cys Ala Gly Thr Thr Thr Gly
        195                 200                 205

Gly Cys Gly Cys Cys Thr Cys Thr Gly Cys Cys Thr Cys Cys Cys Thr
    210                 215                 220

Gly Gly Cys Cys Ala Thr Cys Ala Cys Thr Gly Gly Ala Cys Thr Cys
225                 230                 235                 240

Cys Ala Gly Gly Cys Thr Gly Ala Gly Gly Ala Thr Gly Ala Gly Gly
                245                 250                 255

Cys Thr Gly Ala Thr Thr Ala Thr Thr Ala Cys Thr Gly Cys Cys Ala
```

260 265 270

Gly Thr Cys Cys Thr Ala Thr Gly Ala Cys Ala Gly Thr Ala Gly Thr
275 280 285

Cys Thr Gly Ala Gly Thr Gly Gly Thr Gly Thr Gly Ala Thr Ala Thr
290 295 300

Thr Cys Gly Gly Cys Gly Gly Ala Gly Gly Gly Ala Cys Cys Ala Ala
305 310 315 320

Gly Cys Thr Gly Ala Cys Cys Gly Thr Cys Cys Thr Ala Gly Gly Thr
325 330 335

Gly Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Thr Ala Gly Cys Gly
340 345 350

Gly Cys Gly Gly Cys Gly Gly Cys Gly Gly Cys Thr Cys Thr Gly Gly
355 360 365

Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Thr Cys Cys Gly Ala Ala
370 375 380

Gly Thr Gly Cys Ala Gly Cys Thr Gly Gly Thr Gly Cys Ala Gly Thr
385 390 395 400

Cys Thr Gly Gly Gly Gly Cys Thr Gly Ala Gly Gly Thr Gly Ala Ala
405 410 415

Gly Ala Ala Gly Cys Cys Thr Gly Gly Gly Gly Cys Cys Thr Cys Ala
420 425 430

Gly Thr Gly Ala Ala Gly Gly Thr Cys Thr Cys Cys Thr Gly Cys Ala
435 440 445

Ala Gly Gly Thr Thr Thr Cys Cys Gly Gly Ala Thr Ala Cys Ala Cys
450 455 460

Cys Cys Thr Cys Ala Cys Thr Gly Ala Ala Thr Thr Ala Thr Cys Cys
465 470 475 480

Ala Thr Gly Cys Ala Cys Thr Gly Gly Gly Thr Gly Cys Gly Ala Cys
485 490 495

Ala Gly Gly Cys Thr Cys Cys Thr Gly Gly Ala Ala Ala Ala Gly Gly
500 505 510

Gly Cys Thr Thr Gly Ala Gly Thr Gly Gly Ala Thr Gly Gly Gly Ala
515 520 525

Gly Gly Thr Thr Thr Thr Gly Ala Thr Cys Cys Thr Gly Ala Ala Gly

530 535 540

Ala Thr Gly Gly Thr Gly Ala Ala Ala Cys Ala Ala Thr Cys Thr Ala
545 550 555 560

Cys Gly Cys Ala Cys Ala Gly Ala Ala Gly Thr Thr Cys Cys Ala Gly
565 570 575

Gly Gly Cys Ala Gly Ala Gly Thr Cys Ala Cys Cys Ala Thr Gly Ala
580 585 590

Cys Cys Gly Ala Gly Gly Ala Cys Ala Cys Ala Thr Cys Thr Ala Cys
595 600 605

Ala Gly Ala Cys Ala Cys Ala Gly Cys Cys Thr Ala Cys Ala Thr Gly
610 615 620

Gly Ala Gly Cys Thr Gly Ala Gly Cys Ala Gly Cys Cys Thr Gly Ala
625 630 635 640

Gly Gly Thr Cys Thr Gly Ala Gly Gly Ala Cys Ala Cys Thr Gly Cys
645 650 655

Cys Gly Thr Gly Thr Ala Thr Thr Ala Cys Thr Gly Thr Gly Cys Gly
660 665 670

Cys Gly Cys Gly Cys Thr Thr Ala Cys Thr Ala Cys Gly Gly Thr Thr
675 680 685

Thr Cys Gly Ala Thr Cys Ala Gly Thr Gly Gly Gly Gly Thr Cys Ala
690 695 700

Ala Gly Gly Thr Ala Cys Thr Cys Thr Gly Gly Thr Gly Ala Cys Cys
705 710 715 720

Gly Thr Cys Thr Cys Cys Thr Cys Ala
725

<210> 23
<211> 8
<212> PRT
<213> Homo sapiens

<400> 23

Ser Ser Asn Ile Gly Asn Asn Ala
1 5

<210> 24
<211> 11
<212> PRT
<213> Homo sapiens

<400> 24

```
Ala Ala Trp Asp Asp Ser Val Asn Gly Tyr Val
1               5                   10
```

<210> 25
<211> 8
<212> PRT
<213> Homo sapiens

<400> 25

```
Gly Tyr Thr Phe Thr Arg Phe Gly
1               5
```

<210> 26
<211> 8
<212> PRT
<213> Homo sapiens

<400> 26

```
Ile Ser Val Asn Asn Gly Asn Thr
1               5
```

<210> 27
<211> 10
<212> PRT
<213> Homo sapiens

<400> 27

```
Ala Arg Tyr Met Tyr Gly Arg Arg Asp Ser
1               5                   10
```

<210> 28
<211> 111
<212> PRT
<213> Homo sapiens

<400> 28

```
Gln Ala Val Leu Thr Gln Pro Pro Ser Met Ser Glu Ala Pro Arg Gln
1               5                   10                  15

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

Ala Val Asn Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Lys Leu Leu
        35                  40                  45

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Val
                85                  90                  95
```

```
Asn Gly Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
            100                 105                 110


<210>  29
<211>  333
<212>  DNA
<213>  Homo sapiens

<400>  29
caggctgtgc tgactcagcc accctcgatg tctgaagccc ccaggcagag ggtcaccatc       60

tcctgttctg gaagcagctc caacatcgga aataatgctg taaactggta ccagcagctc      120

ccaggaaagg ctcccaaact cctcatctat tataatgatc tgctgtcctc aggggtctct      180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag      240

tctgaggatg aggctgatta ttactgtgca gcatgggatg acagtgtgaa tggttatgtc      300

ttcggaactg ggaccaaggt caccgtccta ggt                                   333


<210>  30
<211>  117
<212>  PRT
<213>  Homo sapiens

<400>  30

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


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


Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Ser Val Asn Asn Gly Asn Thr Lys Tyr Ala Gln Lys Tyr
    50                  55                  60


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


Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Met Tyr Gly Arg Arg Asp Ser Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  31
<211>  351
<212>  DNA
<213>  Homo sapiens
```

<400> 31
gaggtccagc tggtgcagtc tggagctgag gtgaagaagc ctggggactc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agatttggtt tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgtta ataatggtaa cacaaagtat 180

gcacagaagt accagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag gtctgacgac actgccgtgt attactgtgc gcgctacatg 300

tacggtcgtc gtgattcttg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 32
<211> 266
<212> PRT
<213> Homo sapiens

<400> 32

Gln Ala Val Leu Thr Gln Pro Pro Ser Met Ser Glu Ala Pro Arg Gln
1 5 10 15

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

Ala Val Asn Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Val
85 90 95

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

Ser Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly
130 135 140

Asp Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg
145 150 155 160

Phe Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
165 170 175

Met Gly Trp Ile Ser Val Asn Asn Gly Asn Thr Lys Tyr Ala Gln Lys
180 185 190

```
Tyr Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala
        195                 200                 205

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

Cys Ala Arg Tyr Met Tyr Gly Arg Arg Asp Ser Trp Gly Gln Gly Thr
225                 230                 235                 240

Leu Val Thr Val Ser Ser Gly Gln His His His His His His Gly Ala
                245                 250                 255

Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ser
            260                 265
```

<210> 33
<211> 804
<212> DNA
<213> Homo sapiens

<400> 33

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caggctgtgc tgactcagcc accctcgatg tctgaagccc ccaggcagag ggtcaccatc       60

tcctgttctg gaagcagctc caacatcgga aataatgctg taaactggta ccagcagctc      120

ccaggaaagg ctcccaaact cctcatctat tataatgatc tgctgtcctc aggggtctct      180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag      240

tctgaggatg aggctgatta ttactgtgca gcatgggatg acagtgtgaa tggttatgtc      300

ttcggaactg ggaccaaggt caccgtccta ggtggttcta gaggtggtgg tggtagcggc      360

ggcggcggct ctggtggtgg tggatccgag gtccagctgg tgcagtctgg agctgaggtg      420

aagaagcctg gggactcagt gaaggtctcc tgcaaggctt ctggttacac ctttaccaga      480

tttggtttca gctgggtgcg acaggcccct ggacaagggc ttgagtggat gggatggatc      540

agcgttaata atggtaacac aaagtatgca cagaagtacc agggcagagt caccatgacc      600

acagacacat ccacgagcac agcctacatg gagctgagga gcctgaggtc tgacgacact      660

gccgtgtatt actgtgcgcg ctacatgtac ggtcgtcgtg attcttgggg tcaaggtact      720

ctggtgaccg tctcctcagc cggccagcac catcaccatc accatggcgc atacccgtac      780

gacgttccgg actacgcttc ttag                                             804
```

<210> 34
<211> 6
<212> PRT
<213> Homo sapiens

<400> 34

```
Asn Ile Gly Ser Lys Ser
1               5
```

<210> 35

<211> 10
<212> PRT
<213> Homo sapiens

<400> 35

Gln Val Trp Asp Asn His Ser Asp Val Val
1 5 10

<210> 36
<211> 8
<212> PRT
<213> Homo sapiens

<400> 36

Arg Asn Lys Phe Ser Ser Tyr Ala
1 5

<210> 37
<211> 8
<212> PRT
<213> Homo sapiens

<400> 37

Ile Ser Gly Ser Gly Gly Thr Thr
1 5

<210> 38
<211> 10
<212> PRT
<213> Homo sapiens

<400> 38

Ala Arg Trp Tyr Ser Ser Tyr Tyr Asp Val
1 5 10

<210> 39
<211> 108
<212> PRT
<213> Homo sapiens

<400> 39

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

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

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

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

```
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Asn His Ser Asp Val
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105
```

<210> 40
<211> 324
<212> DNA
<213> Homo sapiens

<400> 40

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cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccaggatt       60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc      120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga      180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg      240

gatgaggccg actattactg tcaggtctgg gataatcata gtgatgtggt attcggcgga      300

gggaccaagc tgaccgtcct aggt                                             324
```

<210> 41
<211> 120
<212> PRT
<213> Homo sapiens

<400> 41

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Arg Asn Lys Phe
            20                  25                  30

Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
        35                  40                  45

Glu Trp Val Ser Gly Ile Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala
    50                  55                  60

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

Thr Gln Tyr Leu Gln Leu Asp Ser Leu Arg Ala Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Trp Tyr Ser Ser Tyr Tyr Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 42
<211> 360
<212> DNA
<213> Homo sapiens

<400> 42
caggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggata cacccgtaac aaatttagca gctatgccat gagctgggtc 120

cgccaggctc cagggaaggg cctggaatgg gtctcaggta ttagtggtag tggtggtact 180

acatactatg cagactccgt gaagggccgg ttcaccatct ccagagacaa ttccaagaac 240

acgcagtatc tgcaattgga gcctgaga gccgaggaca cggccgtata ttactgtgcg 300

cgctggtact cttcttacta cgatgtttgg ggtcaaggta ctctggtgac cgtctcctca 360

<210> 43
<211> 261
<212> PRT
<213> Homo sapiens

<400> 43

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

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

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

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Asn His Ser Asp Val
85 90 95

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val
115 120 125

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
130 135 140

Cys Ala Ala Ser Gly Tyr Thr Arg Asn Lys Phe Ser Ser Tyr Ala Met
145 150 155 160

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

Ile Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys Gly
180 185 190

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln Tyr Leu Gln
195 200 205

Leu Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
210 215 220

Trp Tyr Ser Ser Tyr Tyr Asp Val Trp Gly Gln Gly Thr Leu Val Thr
225 230 235 240

Val Ser Ser His His His His His His Gly Ala Tyr Pro Tyr Asp Val
245 250 255

Pro Asp Tyr Ala Ser
260

<210> 44
<211> 786
<212> DNA
<213> Homo sapiens

<400> 44
cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccaggatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtctgg gataatcata gtgatgtggt attcggcgga 300

gggaccaagc tgaccgtcct aggtggtggt ggtggtagcg gcggcggcgg ctctggtggt 360

ggtggatccc aggtgcagct ggtggagtct gggggaggct tggtacagcc tgggggtcc 420

ctgagactct cctgtgcagc ctctggatac acccgtaaca aatttagcag ctatgccatg 480

agctgggtcc gccaggctcc agggaagggc ctggaatggg tctcaggtat tagtggtagt 540

ggtggtacta catactatgc agactccgtg aagggccggt tcaccatctc cagagacaat 600

tccaagaaca cgcagtatct gcaattggac agcctgagag ccgaggacac ggccgtatat 660

tactgtgcgc gctggtactc ttcttactac gatgtttggg gtcaaggtac tctggtgacc 720

gtctcctcac accatcacca tcaccatggc gcatacccgt acgacgttcc ggactacgct 780

tcttag 786

<210> 45
<211> 10
<212> PRT
<213> Homo sapiens

<400> 45

Gln Val Trp Asp Ser Ser Ser Asp Tyr Val
1 5 10

<210> 46
<211> 8
<212> PRT
<213> Homo sapiens

<400> 46

Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 47
<211> 8
<212> PRT
<213> Homo sapiens

<400> 47

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 48
<211> 10
<212> PRT
<213> Homo sapiens

<400> 48

Ala Arg Asn Tyr Ile Ser Met Phe Asp Ser
1 5 10

<210> 49
<211> 108
<212> PRT
<213> Homo sapiens

<400> 49

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

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

His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

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

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

<210> 50
<211> 324
<212> DNA
<213> Homo sapiens

<400> 50
cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccaggatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaggccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgattatgt cttcggaatt 300

gggaccaagg tcaccgtcct aggt 324

<210> 51
<211> 117
<212> PRT
<213> Homo sapiens

<400> 51

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

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Tyr Ile Ser Met Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 52
<211> 351
<212> DNA
<213> Homo sapiens

<400> 52

gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gcgcaactac 300

atctctatgt tcgattcttg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 53
<211> 258
<212> PRT
<213> Homo sapiens

<400> 53

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

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

His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

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

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
115 120 125

Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly Ser Leu Arg Leu Ser
130 135 140

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val
145 150 155 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
165 170 175

Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
180 185 190

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
195 200 205

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asn Tyr Ile
210 215 220

Ser Met Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235 240

His His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
245 250 255

Ala Ser

<210> 54
<211> 777
<212> DNA
<213> Homo sapiens

<400> 54
cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccaggatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaggccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgattatgt cttcggaatt 300

gggaccaagg tcaccgtcct aggtggtggt ggtggtagcg gcggcggcgg ctctggtggt 360

ggtggatccg aggtgcagct ggtggagtct ggaggaggct tgatccagcc tgggggtcc 420

ctgagactct cctgtgcagc ctctggattc acctttagca gctatgccat gagctgggtc 480

cgccaggctc agggaaggg gctggagtgg gtctcagcta ttagtggtag tggtggtagc 540

acatactacg cagactccgt gaagggccgg ttcaccatct ccagagacaa ttccaagaac 600

acgctgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtata ttactgtgcg 660

cgcaactaca tctctatgtt cgattcttgg ggtcaaggta ctctggtgac cgtctcctca 720

caccatcacc atcaccatgg cgcatacccg tacgacgttc cggactacgc ttcttag 777

<210> 55
<211> 10
<212> PRT
<213> Homo sapiens

<400> 55

Gln Val Trp Asp Ser Ser Ser Asp His Val
1 5 10

<210> 56
<211> 10
<212> PRT
<213> Homo sapiens

<400> 56

Ala Arg Gly Tyr Ser Ser Tyr Tyr Asp Ala
1 5 10

<210> 57
<211> 108
<212> PRT
<213> Homo sapiens

<400> 57

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

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

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

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105

<210> 58
<211> 324
<212> DNA
<213> Homo sapiens

<400> 58
caggctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccaggatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatgt cttcggaact 300

gggaccaagg tcaccgtcct aggt 324

<210> 59
<211> 117
<212> PRT
<213> Homo sapiens

<400> 59

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

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Ser Ser Tyr Tyr Asp Ala Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 60
<211> 351
<212> DNA
<213> Homo sapiens

<400> 60
caggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gcgcggttac 300

tcttcttact acgatgcttg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 61
<211> 258
<212> PRT
<213> Homo sapiens

<400> 61

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

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

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

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val
115 120 125

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
130 135 140

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val
145 150 155 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
165 170 175

Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
180 185 190

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
195 200 205

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Tyr Ser
210 215 220

Ser Tyr Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235 240

His His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
245 250 255

Ala Ser

<210> 62
<211> 777
<212> DNA
<213> Homo sapiens

<400> 62
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acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatgt cttcggaact 300

gggaccaagg tcaccgtcct aggtggtggt ggtggtagcg gcggcggcgg ctctggtggt 360

ggtggatccc aggtgcagct ggtggagtct gggggaggct tggtacagcc tgggggtcc 420

ctgagactct cctgtgcagc ctctggattc acctttagca gctatgccat gagctgggtc 480

cgccaggctc agggaaggg gctggagtgg gtctcagcta ttagtggtag tggtggtagc 540

acatactacg cagactccgt gaagggccgg ttcaccatct ccagagacaa ttccaagaac 600

acgctgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtata ttactgtgcg 660

cgcggttact cttcttacta cgatgcttgg ggtcaaggta ctctggtgac cgtctcctca 720

caccatcacc atcaccatgg cgcatacccg tacgacgttc cggactacgc ttcttag 777

<210> 63
<211> 8
<212> PRT
<213> Homo sapiens

<400> 63

Arg Ser Asn Ile Gly Glu Asn Thr
1 5

<210> 64
<211> 11
<212> PRT
<213> Homo sapiens

<400> 64

Ala Ala Trp Asp Asp Arg Leu Asn Gly Tyr Val
1 5 10

<210> 65
<211> 8
<212> PRT
<213> Homo sapiens

<400> 65

Gly Tyr Thr Phe Thr Asn Tyr Gly
1 5

<210> 66
<211> 8
<212> PRT
<213> Homo sapiens

<400> 66

Ile Gly Ala Gln Lys Gly Asp Thr
1 5

<210> 67
<211> 10
<212> PRT
<213> Homo sapiens

<400> 67

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

<210> 68
<211> 111
<212> PRT
<213> Homo sapiens

<400> 68

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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

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

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

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

Ser Asp Asp Glu Ala Asp Tyr Phe Cys Ala Ala Trp Asp Asp Arg Leu
85 90 95

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

<210> 69
<211> 333
<212> DNA
<213> Homo sapiens

<400> 69
cagtctgtgt tgactcagcc accctcagcg tctgggaccc ccgggcagag agtcaccatc 60

tcttgttctg gaagcaggtc caacatcgga gaaaatactg tcaactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctac agtaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggcttcac 240

tctgacgatg aggctgacta tttttgtgca gcatgggatg accgcctcaa tggttatgtc 300

ttcggaactg ggaccaaggt caccgtccta ggt 333

<210> 70
<211> 117
<212> PRT

<213> Homo sapiens

<400> 70

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

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

Gly Phe Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Gly Ala Gln Lys Gly Asp Thr Glu Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Leu Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gln Gly Val Pro Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 71
<211> 351
<212> DNA
<213> Homo sapiens

<400> 71
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tcctgcaagg cttctggtta cacctttacc aactatggtt tcacctgggt gcgacaggcc 120

cctggacaag gtcttgagtg gatgggatgg atcggcgctc aaaagggtga cacagagtat 180

gcacaaaaat tccagggcag agtcaccatg acgacagaca catccacgag cacagtctac 240

ttggagttga ggagcctgag gtctgacgac acggccgtgt attactgtgc gcgctctcag 300

ggtgttccgt tcgattcttg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 72
<211> 261
<212> PRT
<213> Homo sapiens

<400> 72

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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

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

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

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

Ser Asp Asp Glu Ala Asp Tyr Phe Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
        115                 120                 125

Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Ala Ser Val
    130                 135                 140

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Phe
145                 150                 155                 160

Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp
                165                 170                 175

Ile Gly Ala Gln Lys Gly Asp Thr Glu Tyr Ala Gln Lys Phe Gln Gly
            180                 185                 190

Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr Leu Glu
        195                 200                 205

Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg
    210                 215                 220

Ser Gln Gly Val Pro Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser His His His His His His Gly Ala Tyr Pro Tyr Asp Val
                245                 250                 255

Pro Asp Tyr Ala Ser
            260
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<210> 73
<211> 786
<212> DNA
<213> Homo sapiens

<400> 73

cagtctgtgt tgactcagcc accctcagcg tctgggaccc ccgggcagag agtcaccatc 60

tcttgttctg gaagcaggtc caacatcgga gaaaatactg tcaactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctac agtaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggcttcac 240

tctgacgatg aggctgacta tttttgtgca gcatgggatg accgcctcaa tggttatgtc 300

ttcggaactg ggaccaaggt caccgtccta ggtggtggtg gtggtagcgg cggcggcggc 360

tctggtggtg gtggatccca ggtgcagctg gtgcaatctg gacctgaggt gaagaagcct 420

ggggcctcgg tgaaggtctc ctgcaaggct tctggttaca cctttaccaa ctatggtttc 480

acctgggtgc gacaggcccc tggacaaggt cttgagtgga tgggatggat cggcgctcaa 540

aagggtgaca cagagtatgc acaaaaattc cagggcagag tcaccatgac gacagacaca 600

tccacgagca cagtctactt ggagttgagg agcctgaggt ctgacgacac ggccgtgtat 660

tactgtgcgc gctctcaggg tgttccgttc gattcttggg gtcaaggtac tctggtgacc 720

gtctcctcac accatcacca tcaccatggc gcatacccgt acgacgttcc ggactacgct 780

tcttag 786

<210> 74
<211> 8
<212> PRT
<213> Homo sapiens

<400> 74

Arg Ser Asn Ile Gly Ser Asn Thr
1 5

<210> 75
<211> 11
<212> PRT
<213> Homo sapiens

<400> 75

Ala Thr Trp Asp Asp Ser Leu Asn Glu Tyr Val
1 5 10

<210> 76
<211> 8
<212> PRT
<213> Homo sapiens

<400> 76

Gly Tyr Thr Phe Thr Arg Tyr Gly
1 5

<210> 77
<211> 8
<212> PRT
<213> Homo sapiens

<400> 77

Ile Ser Gly Tyr Asn Gly Asn Thr
1 5

<210> 78
<211> 10
<212> PRT
<213> Homo sapiens

<400> 78

Ala Arg His Gly Tyr Gly Tyr His Gly Asp
1 5 10

<210> 79
<211> 111
<212> PRT
<213> Homo sapiens

<400> 79

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Ala Thr Pro Gly Gln
1 5 10 15

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

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

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Asp Ser Leu
85 90 95

Asn Glu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 80
<211> 333
<212> DNA
<213> Homo sapiens

<400> 80
cagtctgtgt tgactcagcc accctcagcg tctgcgaccc ccgggcagag gggcaccatt 60

tcgtgttctg gaggcaggtc caacatcgga agtaacactg ttaactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctat aataataatc tgcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag ggggctccag 240

tctgaggatg aggctgatta ttactgtgca acatgggatg acagcctgaa tgaatatgtc 300

ttcggaactg ggaccaaggt caccgtccta ggt 333

<210> 81
<211> 117
<212> PRT
<213> Homo sapiens

<400> 81

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

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

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Gly Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

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

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Gly Tyr Gly Tyr His Gly Asp Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 82
<211> 351
<212> DNA
<213> Homo sapiens

<400> 82
caggtgcagc tggtgcaatc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agatatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaacggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag gtctgacgac acggccgtgt attactgtgc gcgccatggt 300

tacggttacc atggtgattg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 83
<211> 261
<212> PRT
<213> Homo sapiens

<400> 83

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Ala Thr Pro Gly Gln

1 5 10 15

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

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

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Asp Ser Leu
85 90 95

Asn Glu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
115 120 125

Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val
130 135 140

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Gly Ile
145 150 155 160

Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp
165 170 175

Ile Ser Gly Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln Gly
180 185 190

Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
195 200 205

Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg
210 215 220

His Gly Tyr Gly Tyr His Gly Asp Trp Gly Gln Gly Thr Leu Val Thr
225 230 235 240

Val Ser Ser His His His His His His Gly Ala Tyr Pro Tyr Asp Val
245 250 255

Pro Asp Tyr Ala Ser
260

<210> 84

<211> 786
<212> DNA
<213> Homo sapiens

<400> 84
cagtctgtgt tgactcagcc accctcagcg tctgcgaccc ccgggcagag gggcaccatt 60

tcgtgttctg gaggcaggtc caacatcgga agtaacactg ttaactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctat aataataatc tgcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag ggggctccag 240

tctgaggatg aggctgatta ttactgtgca acatgggatg acagcctgaa tgaatatgtc 300

ttcggaactg ggaccaaggt caccgtccta ggtggtggtg gtggtagcgg cggcggcggc 360

tctggtggtg gtggatccca ggtgcagctg gtgcaatctg gagctgaggt gaagaagcct 420

ggggcctcag tgaaggtctc ctgcaaggct tctggttaca cctttaccag atatggtatc 480

agctgggtgc gacaggcccc tggacaaggg cttgagtgga tgggatggat cagcggttac 540

aacggtaaca caaactatgc acagaagctc cagggcagag tcaccatgac cacagacaca 600

tccacgagca cagcctacat ggagctgagg agcctgaggt ctgacgacac ggccgtgtat 660

tactgtgcgc gccatggtta cggttaccat ggtgattggg gtcaaggtac tctggtgacc 720

gtctcctcac accatcacca tcaccatggc gcatacccgt acgacgttcc ggactacgct 780

tcttag 786

<210> 85
<211> 9
<212> PRT
<213> Homo sapiens

<400> 85

Ser Ser Asn Ile Gly Ala Gly Tyr Val
1 5

<210> 86
<211> 11
<212> PRT
<213> Homo sapiens

<400> 86

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

<210> 87
<211> 8
<212> PRT
<213> Homo sapiens

<400> 87

Gly Phe Thr Phe Lys Asp Tyr Tyr
1 5

<210> 88

<211> 8
<212> PRT
<213> Homo sapiens

<400> 88

Ile Ser Thr Ser Gly Asn Ser Val
1 5

<210> 89
<211> 11
<212> PRT
<213> Homo sapiens

<400> 89

Ala Arg Ser Pro Gly His Ser Asp Tyr Asp Ser
1 5 10

<210> 90
<211> 112
<212> PRT
<213> Homo sapiens

<400> 90

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

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

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

Leu Ile Tyr His Asn Asn Asp Arg Pro Ser Gly Val Pro Tyr 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 Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 91
<211> 336
<212> DNA
<213> Homo sapiens

<400> 91
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tcctgtactg ggagcagctc caacatcggg gcaggttatg ttgtacagtg gtatcagcag 120

cttccaggaa cagcccccaa actcctcatc tatcataaca acgatcggcc ctcaggggtc 180

ccttaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttgg 300

gtgttcggcg gagggaccaa gctgaccgtc ctaggt 336

<210> 92
<211> 118
<212> PRT
<213> Homo sapiens

<400> 92

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Asp Tyr
20 25 30

Tyr Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser His Ile Ser Thr Ser Gly Asn Ser Val Asp Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Pro Gly His Ser Asp Tyr Asp Ser Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 93
<211> 354
<212> DNA
<213> Homo sapiens

<400> 93
gaggtgcagc tggtggagtc tgggggaggc ctagtcaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttaaa gactactaca tgaactggat ccgccaggct 120

ccagggaagg gcctggagtg gatttcacac attagtacca gcggtaatag tgtagattat 180

gcagactctg tcaagggccg gttcaccatc tccagggaca acgccaagaa ttcactgtac 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gcgctctccg 300

ggtcattctg actacgattc ttggggtcaa ggtactctgg tgaccgtctc ctca 354

<210> 94
<211> 263
<212> PRT

<213> Homo sapiens

<400> 94

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Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                  10                  15

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

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

Leu Ile Tyr His Asn Asn Asp Arg Pro Ser Gly Val Pro Tyr 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 Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Asp Tyr Tyr
145                 150                 155                 160

Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ser
                165                 170                 175

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

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
        195                 200                 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
    210                 215                 220

Arg Ser Pro Gly His Ser Asp Tyr Asp Ser Trp Gly Gln Gly Thr Leu
225                 230                 235                 240

Val Thr Val Ser Ser His His His His His His Gly Ala Tyr Pro Tyr
                245                 250                 255
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Asp Val Pro Asp Tyr Ala Ser
260

<210> 95
<211> 792
<212> DNA
<213> Homo sapiens

<400> 95
cagtctgtgc tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgtactg ggagcagctc caacatcggg gcaggttatg ttgtacagtg gtatcagcag 120

cttccaggaa cagcccccaa actcctcatc tatcataaca acgatcggcc ctcaggggtc 180

ccttaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttgg 300

gtgttcggcg gagggaccaa gctgaccgtc ctaggtggtg gtggtggtag cggcggcggc 360

ggctctggtg gtggtggatc cgaggtgcag ctggtggagt ctgggggagg cctagtcaag 420

cctggagggt ccctgagact ctcctgtgca gcctctggat tcacctttaa agactactac 480

atgaactgga tccgccaggc tccagggaag ggcctggagt ggatttcaca cattagtacc 540

agcggtaata gtgtagatta tgcagactct gtcaagggcc ggttcaccat ctccagggac 600

aacgccaaga attcactgta cctgcaaatg aacagcctga gagccgagga cacggccgta 660

tattactgtg cgcgctctcc gggtcattct gactacgatt cttggggtca aggtactctg 720

gtgaccgtct cctcacacca tcaccatcac catggcgcat acccgtacga cgttccggac 780

tacgcttctt ag 792

<210> 96
<211> 6
<212> PRT
<213> Homo sapiens

<400> 96

Asn Ile Gly Asp Lys Ser
1 5

<210> 97
<211> 13
<212> PRT
<213> Homo sapiens

<400> 97

Gln Val Trp Ala Ser Gly Thr Asp His Pro Tyr Val Ile
1 5 10

<210> 98
<211> 10
<212> PRT
<213> Homo sapiens

<400> 98

Ala Arg Met Tyr Gly Ser Tyr Thr Asp Met
1 5 10

<210> 99
<211> 111
<212> PRT
<213> Homo sapiens

<400> 99

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

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

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

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Ala Ser Gly Thr Asp His
85 90 95

Pro Tyr Val Ile Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 100
<211> 333
<212> DNA
<213> Homo sapiens

<400> 100
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acctgtgggg gaaacaacat tggagataaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gacgaggccg actattactg tcaggtgtgg gctagtggta ctgatcatcc ctatgtgata 300

ttcggcggag ggaccaaggt caccgtccta ggt 333

<210> 101
<211> 117
<212> PRT
<213> Homo sapiens

<400> 101

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

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Met Tyr Gly Ser Tyr Thr Asp Met Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 102
<211> 351
<212> DNA
<213> Homo sapiens

<400> 102
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gcgcatgtac 300

ggttcttaca ctgatatgtg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 103
<211> 261
<212> PRT
<213> Homo sapiens

<400> 103

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

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

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

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Ala Ser Gly Thr Asp His
85 90 95

Pro Tyr Val Ile Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val
115 120 125

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
130 135 140

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
145 150 155 160

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

Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly
180 185 190

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
195 200 205

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
210 215 220

Met Tyr Gly Ser Tyr Thr Asp Met Trp Gly Gln Gly Thr Leu Val Thr
225 230 235 240

Val Ser Ser His His His His His His Gly Ala Tyr Pro Tyr Asp Val
245 250 255

Pro Asp Tyr Ala Ser
260

<210> 104
<211> 786
<212> DNA
<213> Homo sapiens

<400> 104
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acctgtgggg gaaacaacat tggagataaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gacgaggccg actattactg tcaggtgtgg gctagtggta ctgatcatcc ctatgtgata 300

ttcggcggag ggaccaaggt caccgtccta ggtggtggtg gtggtagcgg cggcggcggc 360

tctggtggtg gtggatccga ggtgcagctg gtggagtctg ggggaggctt ggtacagcct 420

ggggggtccc tgagactctc ctgtgcagcc tctggattca cctttagcag ctatgccatg 480

agctgggtcc gccaggctcc agggaagggg ctggagtggg tctcagctat tagtggtagt 540

ggtggtagca catactacgc agactccgtg aagggccggt tcaccatctc cagagacaat 600

tccaagaaca cgctgtatct gcaaatgaac agcctgagag ccgaggacac ggccgtatat 660

tactgtgcgc gcatgtacgg ttcttacact gatatgtggg gtcaaggtac tctggtgacc 720

gtctcctcac accatcacca tcaccatggc gcatacccgt acgacgttcc ggactacgct 780

tcttag 786

<210> 105
<211> 8
<212> PRT
<213> Homo sapiens

<400> 105

Ser Ser Asn Ile Gly Tyr Asn Tyr
1 5

<210> 106
<211> 11
<212> PRT
<213> Homo sapiens

<400> 106

Thr Ser Trp Asp Asp Ser Leu Ser Gly Tyr Val
1 5 10

<210> 107
<211> 8
<212> PRT
<213> Homo sapiens

<400> 107

Gly Asn Ala Phe Thr Asn Phe Tyr
1 5

<210> 108
<211> 9
<212> PRT
<213> Homo sapiens

<400> 108

Ile Asn Pro Ser Gly Thr Asp Leu Thr
1 5

<210> 109
<211> 13

<212> PRT
<213> Homo sapiens

<400> 109

Ala Arg Gln Tyr Ala Tyr Gly Tyr Ser Gly Phe Asp Met
1 5 10

<210> 110
<211> 111
<212> PRT
<213> Homo sapiens

<400> 110

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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

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

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Thr Ser Trp Asp Asp Ser Leu
85 90 95

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

<210> 111
<211> 333
<212> DNA
<213> Homo sapiens

<400> 111
cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gaagcagctc caacatcgga tataattatg tatactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctct agaaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccgg 240

tccgaggatg aggctgacta ttactgtaca tcgtgggatg acagcctgag tggttatgtc 300

ttcggacctg ggaccaaggt caccgtccta ggt 333

<210> 112
<211> 121
<212> PRT
<213> Homo sapiens

<400> 112

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 Asn Ala Phe Thr Asn Phe
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Leu Ile Asn Pro Ser Gly Thr Asp Leu Thr Arg Tyr Ala Gln Lys
50 55 60

Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Pro Thr Ser Thr Val
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Gln Tyr Ala Tyr Gly Tyr Ser Gly Phe Asp Met Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 113
<211> 363
<212> DNA
<213> Homo sapiens

<400> 113
gaagtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctggaaa cgccttcacc aacttctata tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatta atcaacccta gtggtactga cctcacaagg 180

tacgcacaga agttccaggg cagagtcacc atgaccaggg acacgcccac gagcacagtc 240

tacatggagc tgagcagcct gaggtctgac gacacggctg tgtattactg tgcgcgccag 300

tacgcttacg gttactctgg tttcgatatg tggggtcaag gtactctggt gaccgtctcc 360

tca 363

<210> 114
<211> 265
<212> PRT
<213> Homo sapiens

<400> 114

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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

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

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Thr Ser Trp Asp Asp Ser Leu
                85                  90                  95

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val
        115                 120                 125

Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val
    130                 135                 140

Lys Val Ser Cys Lys Ala Ser Gly Asn Ala Phe Thr Asn Phe Tyr Ile
145                 150                 155                 160

His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Leu
                165                 170                 175

Ile Asn Pro Ser Gly Thr Asp Leu Thr Arg Tyr Ala Gln Lys Phe Gln
            180                 185                 190

Gly Arg Val Thr Met Thr Arg Asp Thr Pro Thr Ser Thr Val Tyr Met
        195                 200                 205

Glu Leu Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
    210                 215                 220

Arg Gln Tyr Ala Tyr Gly Tyr Ser Gly Phe Asp Met Trp Gly Gln Gly
225                 230                 235                 240

Thr Leu Val Thr Val Ser Ser His His His His His His Gly Ala Tyr
                245                 250                 255

Pro Tyr Asp Val Pro Asp Tyr Ala Ser
            260                 265
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<210> 115
<211> 798
<212> DNA
<213> Homo sapiens

<400> 115

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tcttgttctg gaagcagctc caacatcgga tataattatg tatactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctct agaaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccgg 240

tccgaggatg aggctgacta ttactgtaca tcgtgggatg acagcctgag tggttatgtc 300

ttcggacctg ggaccaaggt caccgtccta ggtggtggtg gtggtagcgg cggcggcggc 360

tctggtggtg gtggatccga agtgcagctg gtgcagtctg gggctgaggt gaagaagcct 420

ggggcctcag tgaaggtttc ctgcaaggca tctggaaacg ccttcaccaa cttctatata 480

cactgggtgc gacaggcccc tggacaaggg cttgagtgga tgggattaat caaccctagt 540

ggtactgacc tcacaaggta cgcacagaag ttccagggca gagtcaccat gaccagggac 600

acgcccacga gcacagtcta catggagctg agcagcctga ggtctgacga cacggctgtg 660

tattactgtg cgcgccagta cgcttacggt tactctggtt tcgatatgtg gggtcaaggt 720

actctggtga ccgtctcctc acaccatcac catcaccatg gcgcataccc gtacgacgtt 780

ccggactacg cttcttag 798

<210> 116
<211> 6
<212> PRT
<213> Homo sapiens

<400> 116

Gln Ser Val Ser Asn Trp
1 5

<210> 117
<211> 9
<212> PRT
<213> Homo sapiens

<400> 117

Gln Gln Ser Tyr Ser Thr Pro Ile Thr
1 5

<210> 118
<211> 8
<212> PRT
<213> Homo sapiens

<400> 118

Gly Tyr Thr Phe Thr Ser Tyr Tyr
1 5

<210> 119
<211> 8
<212> PRT
<213> Homo sapiens

<400> 119

Ile Asn Pro Asn Thr Gly Gly Ser
1 5

<210> 120
<211> 9
<212> PRT
<213> Homo sapiens

<400> 120

Ala Arg Gly Asp Val Thr Tyr Asp Glu
1 5

<210> 121
<211> 108
<212> PRT
<213> Homo sapiens

<400> 121

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Leu Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 122
<211> 324
<212> DNA
<213> Homo sapiens

<400> 122
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gagtgttagc aactggttag cctggtatca actgaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccgatcac cttcggcgga 300

gggaccaagg tggagatcaa acgt 324

<210> 123
<211> 116
<212> PRT
<213> Homo sapiens

<400> 123

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

Ser Val Lys Val Ser Cys Lys Ala 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

Gly Trp Ile Asn Pro Asn Thr Gly Gly Ser Asn Phe Ala Gln Lys Phe
50 55 60

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

Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Val Thr Tyr Asp Glu Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 124
<211> 348
<212> DNA
<213> Homo sapiens

<400> 124
caggtccagc tggtacagtc tggggctgag gtgaagaagc ctgggacctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc tcctactata tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaacccta acactggtgg ctcaaacttt 180

gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggagctga acaggctgag gtctgacgac acggccgtgt attactgtgc gcgcggtgac 300

gttacttacg atgaatgggg tcaaggtact ctggtgaccg tctcctca 348

<210> 125
<211> 257
<212> PRT
<213> Homo sapiens

<400> 125

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Leu Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
100 105 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val
115 120 125

Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Thr Ser Val Lys Val Ser
130 135 140

Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Tyr Ile His Trp Val
145 150 155 160

Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp Ile Asn Pro
165 170 175

Asn Thr Gly Gly Ser Asn Phe Ala Gln Lys Phe Gln Gly Arg Val Thr
180 185 190

Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Asn Arg
195 200 205

Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Asp Val
210 215 220

Thr Tyr Asp Glu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser His
225 230 235 240

His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
245 250 255

Ser

<210> 126

<211> 774
<212> DNA
<213> Homo sapiens

<400> 126
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gagtgttagc aactggttag cctggtatca actgaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccgatcac cttcggcgga 300

gggaccaagg tggagatcaa acgtggtggt ggtggtagcg gcggcggcgg ctctggtggt 360

ggtggatccc aggtccagct ggtacagtct ggggctgagg tgaagaagcc tgggacctca 420

gtgaaggtct cctgcaaggc ttctggatac accttcacct cctactatat acactgggtg 480

cgacaggccc ctggacaagg gcttgagtgg atgggatgga tcaaccctaa cactggtggc 540

tcaaactttg cacagaagtt tcagggcagg gtcaccatga ccagggacac gtccatcagc 600

acagcctaca tggagctgaa caggctgagg tctgacgaca cggccgtgta ttactgtgcg 660

cgcggtgacg ttacttacga tgaatggggt caaggtactc tggtgaccgt ctcctcacac 720

catcaccatc accatggcgc atacccgtac gacgttccgg actacgcttc ttag 774

<210> 127
<211> 10
<212> PRT
<213> Homo sapiens

<400> 127

Gln Val Trp Asp Ile Asn Asp His Tyr Val
1 5 10

<210> 128
<211> 10
<212> PRT
<213> Homo sapiens

<400> 128

Ala Arg Ser Gln Ala Ser Phe Met Asp Ile
1 5 10

<210> 129
<211> 108
<212> PRT
<213> Homo sapiens

<400> 129

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

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

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

Tyr Asp Asp Met Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Pro Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ile Asn Asp His Tyr
85 90 95

Val Phe Ala Ser Gly Thr Lys Val Thr Val Leu Gly
100 105

<210> 130
<211> 324
<212> DNA
<213> Homo sapiens

<400> 130
tcctatgagc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccagcatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctattatgat gacatgcggc cctcaggtat ccctgagcga 180

ttctctggct ccagctctgg gaacacggcc accctgacca tcagcccggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatattaatg atcattatgt cttcgcatcg 300

gggaccaagg tcaccgtcct aggt 324

<210> 131
<211> 117
<212> PRT
<213> Homo sapiens

<400> 131

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

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Ser Gln Ala Ser Phe Met Asp Ile Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 132
<211> 351
<212> DNA
<213> Homo sapiens

<400> 132
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gcgctctcag 300

gcttctttca tggatatctg gggtcaaggt actctggtga ccgtctcctc a 351

<210> 133
<211> 258
<212> PRT
<213> Homo sapiens

<400> 133

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

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

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

Tyr Asp Asp Met Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Pro Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ile Asn Asp His Tyr
85 90 95

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
115 120 125

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Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
    130                 135                 140

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val
145                 150                 155                 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
                165                 170                 175

Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
            180                 185                 190

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
        195                 200                 205

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Gln Ala
    210                 215                 220

Ser Phe Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235                 240

His His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
                245                 250                 255

Ala Ser
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<210> 134
<211> 777
<212> DNA
<213> Homo sapiens

<400> 134

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acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc      120

caggcccctg tgctggtcat ctattatgat gacatgcggc cctcaggtat ccctgagcga      180

ttctctggct ccagctctgg gaacacggcc accctgacca tcagcccggt cgaagccggg      240

gatgaggccg actattactg tcaggtgtgg gatattaatg atcattatgt cttcgcatcg      300

gggaccaagg tcaccgtcct aggtggtggt ggtggtagcg gcggcggcgg ctctggtggt      360

ggtggatccg aggtgcagct ggtggagtct gggggaggct tggtacagcc tgggggtcc       420

ctgagactct cctgtgcagc ctctggattc acctttagca gctatgccat gagctgggtc      480

cgccaggctc agggaaggg gctggagtgg gtctcagcta ttagtggtag tggtggtagc       540

acatactacg cagactccgt gaagggccgg ttcaccatct ccagagacaa ttccaagaac      600

acgctgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtata ttactgtgcg      660

cgctctcagg cttctttcat ggatatctgg ggtcaaggta ctctggtgac cgtctcctca      720

caccatcacc atcaccatgg cgcatacccg tacgacgttc cggactacgc ttcttag         777
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<210> 135
<211> 11
<212> PRT
<213> Homo sapiens

<400> 135

Gln Val Trp Asp Ser Ser Ser Asp Gln Gly Val
1 5 10

<210> 136
<211> 7
<212> PRT
<213> Homo sapiens

<400> 136

Ile Gly Thr Gly Gly Gly Thr
1 5

<210> 137
<211> 10
<212> PRT
<213> Homo sapiens

<400> 137

Ala Arg Gly Thr Gly Tyr Asp Gly Asp Gln
1 5 10

<210> 138
<211> 109
<212> PRT
<213> Homo sapiens

<400> 138

Leu Pro Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

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

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

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

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

Gly Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105

<210> 139
<211> 327
<212> DNA
<213> Homo sapiens

<400> 139
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acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaattctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcaggg cgtcttcgga 300

actgggacca aggtcaccgt cctaggt 327

<210> 140
<211> 116
<212> PRT
<213> Homo sapiens

<400> 140

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

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

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Thr Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

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

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Gly Thr Gly Tyr Asp Gly Asp Gln Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 141
<211> 348
<212> DNA
<213> Homo sapiens

<400> 141
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tcctgtgcag gctctggatt caccttcagt agctatgcta tgcactgggt tcgccaggct 120

ccaggaaaag gtctggagtg ggtatcagct attggtactg gtggtggcac atactatgca 180

gactccgtga agggccgatt caccatctcc agggacaatg ccaagaactc cttgtatctt 240

caaatgaaca gcctgagagc cgaggacacc gccatgtatt actgtgcgcg cggtactggt 300

tacgacggtg atcagtgggg tcaaggtact ctggtgaccg tctcctca 348

<210> 142
<211> 258
<212> PRT
<213> Homo sapiens

<400> 142

Leu Pro Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

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

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

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

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

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
115 120 125

Val Gln Ser Gly Gly Gly Leu Val Gln Pro Arg Gly Ser Leu Arg Leu
130 135 140

Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met His Trp
145 150 155 160

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Gly
165 170 175

Thr Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
180 185 190

Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser
195 200 205

Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Thr Gly
210 215 220

Tyr Asp Gly Asp Gln Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235 240

His His His His His His Gly Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
245 250 255

Ala Ser

<210> 143
<211> 777
<212> DNA
<213> Homo sapiens

<400> 143
ctgcctgtgc tgactcagcc accctcggtg tcagtggccc caggacagac ggccaggatc 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaattctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcaggg cgtcttcgga 300

actgggacca aggtcaccgt cctaggtggt ggtggtggta gcggcggcgg cggctctggt 360

ggtggtggat ccgaagtgca gctggtgcag tctgggggag gcttggtaca gcctaggggg 420

tccctgagac tctcctgtgc aggctctgga ttcaccttca gtagctatgc tatgcactgg 480

gttcgccagg ctccaggaaa aggtctggag tgggtatcag ctattggtac tggtggtggc 540

acatactatg cagactccgt gaagggccga ttcaccatct ccagggacaa tgccaagaac 600

tccttgtatc ttcaaatgaa cagcctgaga gccgaggaca ccgccatgta ttactgtgcg 660

cgcggtactg gttacgacgg tgatcagtgg ggtcaaggta ctctggtgac cgtctcctca 720

caccatcacc atcaccatgg cgcatacccg tacgacgttc cggactacgc ttcttag 777