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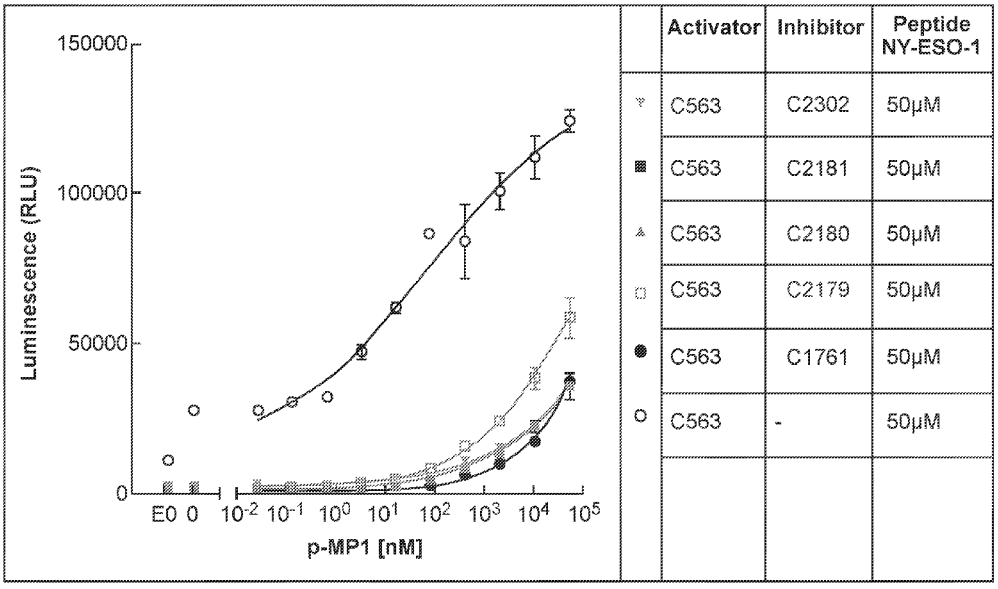

	Activator	Inhibitor	Peptide NY-ESO-1
▽	C563	C2302	50μM
■	C563	C2181	50μM
△	C563	C2180	50μM
□	C563	C2179	50μM
●	C563	C1761	50μM
○	C563	-	50μM

FIG. 8

(57) Abstract: Provided are chimeric antigen receptors having the hinge, transmembrane region, and/or intracellular domain of LILRB1, or functional fragments or variants thereof. Also provided herein are cells comprising the LILRB1 based receptors, and methods of making and using same.

[Continued on next page]

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LILRB1-BASED CHIMERIC ANTIGEN RECEPTOR

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent applications 62/946,888, filed on December 11, 2019, and 63/085,969 filed on August 30, 2020, the contents of each of which are incorporated herein by reference in their entireties.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] This application contains a Sequence Listing which has been submitted in ASCII format via EFS-WEB and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 11, 2020 is named A2BI-015-01WO_SeqList.txt and is 228 KB in size.

BACKGROUND

[0003] Chimeric antigen receptor (CAR) T cell therapy, and T Cell Receptor (TCR) therapy, is proving to be an effective therapeutic approach to various diseases, particularly hematological malignancies but also other cancers. CAR NK cells may also have clinical applications. Conventional CARs provide a stimulatory signal to the engineered immune cell (*e.g.* a T cell or an NK cell). In CAR-T cells, this results in killing activity towards the target cell identified by the antigen-binding domain of the CAR. Inhibitory CARs (iCARs) have been developed as a means to control cell activity or restrict the activity of an activator CAR to specific cell types. Fedorov et al. *Sci. Transl. Med.* 5(215):215ra172 (2013). The inhibitory CAR generally has the intracellular domain of an inhibitory signaling molecule (such as PD-1 or CTLA-4) fused to an antigen-binding domain (*e.g.*, a single-chain variable fragment, scFv) through a transmembrane region and optionally a hinge region.

[0004] Numerous alternative iCAR architectures have been described in the art. However, there remains an unmet need for novel alternative inhibitory receptors and identification of particular inhibitory receptor architectures having superior performance, along with associated compositions and methods of use thereof.

SUMMARY

[0005] In one aspect, the disclosure provides chimeric antigen receptors having the hinge, transmembrane region, and/or intracellular domain of LILRB1, or functional fragments or variants

thereof. The chimeric antigen receptor may include single polypeptide, or more than one polypeptide. The receptors may include one or more, or all of the following: (a) an LILRB1 hinge domain or functional fragment or variant thereof; (b) an LILRB1 transmembrane domain or a functional variant thereof; and (c) an LILRB1 intracellular domain or a functional variant thereof, such as an LILRB1 intracellular domain and/or an intracellular domain comprising at least one immunoreceptor tyrosine-based inhibitory motif (ITIM) found in the polypeptide sequence of LILRB1. In some embodiments, the receptor comprises at least two ITIMS found in the polypeptide sequence of LILRB1. The ITIMs of LILRB1 are NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). The receptor may include one, two, three, four, five, six, or more of these ITIMs, in any combination including multiple copies of the same ITIM.

[0006] In some embodiments of the receptors of the disclosure, the intracellular domain comprises both ITIMs NLYAAV (SEQ ID NO: 8) and VTYAEV (SEQ ID NO: 9). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 12. In some embodiments, the intracellular domain comprises both ITIMs VTYAEV (SEQ ID NO: 9) and VTYAQL (SEQ ID NO: 10). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 13. In some embodiments, the intracellular domain comprises both ITIMs VTYAQL (SEQ ID NO: 10) and SIYATL (SEQ ID NO: 11). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 14. In some embodiments, the polypeptide comprises an intracellular domain comprising at least three immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In some embodiments, the intracellular domain comprises the ITIMs NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), and VTYAQL (SEQ ID NO: 10). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 15. In some embodiments, the intracellular domain comprises the ITIMs VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 16. In some embodiments, the intracellular domain comprises the ITIMs NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ

ID NO: 17. In some embodiments, the intracellular domain comprises a sequence at least 95% identical to the LILRB1 intracellular domain (SEQ ID NO: 7). In some embodiments, the intracellular domain comprises a sequence of SEQ ID NOS: 12-17.

[0007] In some embodiments of the receptors of the disclosure, the polypeptide comprises the LILRB1 transmembrane domain or a functional variant thereof. In some embodiments, the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 5. In some embodiments, the LILRB1 transmembrane domain comprises SEQ ID NO: 5.

[0008] In some embodiments of the receptors of the disclosure, the polypeptide comprises the LILRB1 hinge domain or functional fragment or variant thereof. In some embodiments, the LILRB1 hinge domain or functional fragment or variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84 or SEQ ID NO: 93. In some embodiments, the LILRB1 hinge domain comprises a sequence identical to SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84 or SEQ ID NO: 93. In some embodiments, the LILRB1 hinge domain or functional fragment or variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 80, SEQ ID NO:81, SEQ ID NO: 82, SEQ ID NO: 83 or SEQ ID NO: 84. In some embodiments, the LILRB1 hinge domain comprises a sequence identical to SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83 or SEQ ID NO: 84.

[0009] In some embodiments of the receptors of the disclosure, the polypeptide comprises: (a) an LILRB1 hinge domain or functional fragment or variant thereof, and (b) the LILRB1 transmembrane domain or a functional variant thereof. In some embodiments, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 20.

[0010] In some embodiments of the receptors of the disclosure, the polypeptide comprises: (a) the LILRB1 transmembrane domain or a functional variant thereof, and (b) an LILRB1 intracellular domain and/or an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In some embodiments, the polypeptide comprises a sequence at least

95% identical to SEQ ID NO: 21. In some embodiments, the polypeptide comprises a sequence of SEQ ID NO: 21.

[0011] In some embodiments of the receptors of the disclosure, the polypeptide comprises: (a) an LILRB1 hinge domain or functional fragment or variant thereof; (b) an LILRB1 transmembrane domain or a functional variant thereof; and (c) an LILRB1 intracellular domain and/or an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0012] In some embodiments of the receptors of the disclosure, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 2 or SEQ ID NO: 3. In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 20. In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 21. In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 2 or SEQ ID NO: 3. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 20. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 21. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 2 or SEQ ID NO: 3.

[0013] In some embodiments of the receptors of the disclosure, the polypeptide comprises antigen-binding domain. In some embodiments, the antigen-binding domain is an antigen-binding domain other than the LILRB1 extracellular ligand binding protein. In some embodiments, the polypeptide comprises two or more antigen-binding domains. In some embodiments, the antigen-binding domain comprises a single chain variable fragment (scFv). In some embodiments, the receptor comprises a second polypeptide. In some embodiments, the first polypeptide comprises a first chain of an antibody and the second polypeptide comprise a second chain of said antibody. In some embodiments, the receptor comprises a Fab fragment of an antibody. In some embodiments, (a) the first polypeptide comprises an antigen-binding fragment of the heavy chain of the antibody, and (b) the second polypeptide comprises an antigen-binding fragment of the light chain of the antibody. In some embodiments, (a) the first polypeptide comprises an antigen-binding fragment of the light chain of the antibody, and (b) the second polypeptide comprises an antigen-binding fragment of the heavy chain of the antibody. In some embodiments, the first polypeptide comprises a first chain of a T-cell receptor (TCR) and the second polypeptide comprises a second chain of

said TCR. In some embodiments, in the receptor comprises an extracellular fragment of a T cell receptor (TCR). In some embodiments, (a) the first polypeptide comprises an antigen-binding fragment of an alpha chain of the TCR, and (b) the second polypeptide comprises an antigen-binding fragment of the beta chain of the TCR. In some embodiments, (a) the first polypeptide comprises an antigen-binding fragment of the beta chain of the TCR, and (b) the second polypeptide comprises an antigen-binding fragment of the alpha chain of the TCR. In some embodiments, the receptor comprises a single-chain TCR. In some embodiments, the scFv comprises the complementarity determined regions (CDRs) of any one of SEQ ID NOS: 22-33. In some embodiments, the scFv comprises a sequence at least 95% identical to any one of SEQ ID NOS: 35-46 or 125. In some embodiments, the scFv comprises a sequence at least 95% identical to any one of SEQ ID NOS: 35, 39, 46 or 125. In some embodiments, the scFv comprises a sequence identical to any one of SEQ ID NOS: 35-46 or 125. In some embodiments, the scFv comprises a sequence identical to any one of SEQ ID NOS: 35, 39, 46 or 125. In some embodiments, the heavy chain of the antibody comprises the heavy chain CDRs of any one of SEQ ID NOS: 25-27 or 31-33, and wherein the light chain of the antibody comprises the light chain CDRs of any one of SEQ ID NOS: 22-24 or 28-30. In some embodiments, the heavy chain of the antibody comprises a sequence at least 95% identical to the heavy chain portion of any one of SEQ ID NOS: 35-46 or 125, and wherein the light chain of the antibody comprises a sequence at least 95% identical to the light chain portion of any one of SEQ ID NOS: 35-46 or 125. In some embodiments, the heavy chain of the antibody comprises a sequence identical to the heavy chain portion of any one of SEQ ID NOS: 35-46 or 125, and wherein the light chain of the antibody comprises a sequence identical to the light chain portion of any one of SEQ ID NOS: 35-46 or 125. In some embodiments, the heavy chain of the antibody comprises a sequence identical to the heavy chain portion of any one of SEQ ID NOS: 35, 39, 46 or 125, and wherein the light chain of the antibody comprises a sequence identical to the light chain portion of any one of SEQ ID NOS: 35, 39, 46 or 125.

[0014] In some embodiments of the receptors of the disclosure, the receptor comprises an amino acid sequence at least 95% identical to any one of SEQ ID NOS: 47-71, 77-79, 89-92, 120 or 122. In some embodiments, the receptor comprises an amino acid sequence of SEQ ID NOS: 47-71, 77-79, 89-92, 120 or 122.

[0015] In some embodiments of the receptors of the disclosure, the receptor is an inhibitory receptor.

[0016] The disclosure provides a polynucleotide comprising a nucleic acid sequence encoding the receptor or polypeptide of the disclosure.

[0017] The disclosure provides a vector comprising the polynucleotide of the disclosure. In some embodiments, the vector further comprises a sequence encoding a promoter operably linked to the polynucleotide.

[0018] The disclosure provides an immune cell comprising the receptor, polynucleotide, polypeptide or receptor of the disclosure. In some embodiments, the immune cell activation is reduced when the cell is contacted with the antigen or a cell expressing the antigen on its surface. In some embodiments, immune cell activation comprises expression of a gene operatively linked to an NFAT promoter. In some embodiments, the immune cell is a T cell. In some embodiments, further comprises an activator receptor. In some embodiments, the activator receptor is a chimeric antigen receptor or a T cell receptor.

[0019] The disclosure provides methods making an immune cell, comprising introducing the polynucleotide or vector of the disclosure into the immune cell. In some embodiments, the immune cell expresses the receptor. In some embodiments, the cell is an immune cell. In some embodiments, the immune cell is a T cell. In some embodiments, immune cell activation is reduced when the cell is contacted with an antigen specific to the chimeric antigen receptor, or a cell expressing the antigen on its surface. In some embodiments, immune cell activation comprises expression of a gene operatively linked to an NFAT promoter.

[0020] The disclosure provides methods of treating a subject with a disease or a disorder, comprising administering to the subject a plurality of the immune cells of the disclosure. In some embodiments, the disease or disorder is cancer.

[0021] The disclosure provides a kit, comprising the receptor, polypeptide, polynucleotide, vector or immune cell of the disclosure.

[0022] The disclosure provides an immune cell comprising a chimeric antigen receptor comprising a polypeptide, wherein the polypeptide sequence shares at least 95% identity or at least 100% identity to SEQ ID NO: 21.

[0023] In some embodiments of the immune cells of the disclosure, the polypeptide sequence shares at least 95% identity or at least 100% identity to SEQ ID NO: 3. In some embodiments,

the polypeptide sequence shares at least 95% identity or at least 100% identity to SEQ ID NO: 2. In some embodiments, the chimeric antigen receptor comprises an antigen-binding domain comprising CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 22-27, respectively. In some embodiments, the chimeric antigen receptor comprises an antigen-binding domain comprising CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 28-33, respectively. In some embodiments, the polypeptide sequence shares at least 95% identity or at least 100% identity to SEQ ID NO: 122. In some embodiments, the polypeptide sequence shares at least 95% identity or at least 100% identity with any one of SEQ ID NOS: 35, 39, 46 or 125 in combination with SEQ ID NO: 2.

[0024] In some embodiments, the immune cell is a T cell. In some embodiments, the T cell comprises a chimeric antigen receptor or T cell receptor that specifically binds to a target expressed on tumor cells. In some embodiments, the T cell comprises a chimeric antigen receptor or T cell receptor that specifically binds to a target selected from etiolate receptor, αvββ integrin, BCMA, B7-H3, B7-H6, CAIX, CD19, CD20, CD22, CD30, CD33, CD37, CD44, CD44v6, CD44v7/8, CD70, CD123, CD138, CD171, CEA, DLL4, EGP-2, EGP-40, CSPG4, EGFR, EGFR family including ErbB2 (HER2), EGFRvIII, EPCAM, EphA2, EpCAM, FAP, FBP, fetal acetylcholine receptor, Fzd7, GD2, GD3, Glypican-3 (GPC3), h5T4, IL-11R , IL13R-a2, KDR, κ light chain, λ light chain, LeY, LI CAM, MAGE-A1, mesothelin, MHC presented peptides, MUC1, MUC16, NCAM, NKG2D ligands, Notchl, Notch2/3, NY-ESO-1, PRAME, PSCA, PSMA, Survivin, TAG-72, TEMs, TERT, VEGFR2, and ROR1.

[0025] The disclosure provide methods of treating and/or preventing cancer in a subject in need thereof, comprising administering to the subject the immune cells of the disclosure. In some embodiments, the method comprises treating and/or preventing cancer in a subject in need thereof, comprising administering to the subject the immune cells of the disclosure.

[0001] Illustrative CARs provided herein include, without limitation, antibody-based CARs such as single-chain variable fragment (scFv) CARs, Fab CARs, or others; and T cell receptor (TCR)-based CARs.

[0002] In other aspects, the disclosure provides polynucleotides encoding such receptors; vectors for delivery of such polynucleotides; and immune cells with such polynucleotide and receptors.

[0003] In further aspects, the disclosure provides methods of introducing polynucleotide or vectors encoding such receptors into a cell. Advantageously, immune cell activation is reduced when the cell is contacted with the antigen or a cell expressing the antigen on its surface.

[0004] Yet further aspects and embodiments of the invention are provided in the detailed description that follows.

BRIEF DESCRIPTION OF DRAWINGS

[0005] FIG. 1 shows an illustrative diagram of domain arrangement in an embodiment having a ligand binding domain (LBD), hinge, transmembrane (TM), and intracellular signaling domain (ICD).

[0006] FIGS. 2A-2B show illustrative diagrams of domain arrangements in embodiments having a ligand binding domain (LBD), hinge, transmembrane (TM), and intracellular signaling domain (ICD). When the ligand binding domain comprises two peptides, for example a heterodimeric LDB from a T Cell Receptor, each peptide may be fused with a hinge, TM and intracellular domain (FIG. 2A). Alternatively, only one peptide of the ligand binding domain may be fused to the hinge, TM and intracellular domain (FIG. 2B).

[0007] FIG. 3 shows four illustrative embodiments of immune cells having an activator scFv-based chimeric antigen receptor (CAR) [**101** and **102**] or activator T cell receptor [**103** and **104**] and an inhibitory scFv based CAR [**101** and **103**] or inhibitory TCR-based CAR [**102** and **104**].

[0008] FIG. 4 shows a chart of luminescence in an NFAT-based reporter assay (relative luminescence units, RLU) at varying concentrations of MAGE-A3 activating peptide 1 (MP1, microliters, μM) for the indicated constructs in the presence of 50 μM NY-ESO-1 peptide.

[0009] FIG. 5 shows a chart of luminescence in an NFAT-based reporter assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of various concentrations (μM) of NY-ESO-1 peptide.

[0010] FIG. 6 shows a chart of luminescence in an NFAT-based reporter assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of various concentrations (μM) of NY-ESO-1 peptide.

[0011] FIG. 7 shows a chart of luminescence in an NFAT-based reporter assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of 50 μM NY-ESO-1 peptide.

[0012] FIG. 8 shows a chart of luminescence in an NFAT-based reporter assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of 50 μM NY-ESO-1 peptide.

[0013] FIG. 9 shows a chart of luminescence in an NFAT-based reporter assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of 5 μM NY-ESO-1 peptide.

[0014] FIG. 10 shows a chart of luminescence in an NFAT-based reporter assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of 50 μM NY-ESO-1 peptide.

[0015] FIG. 11 shows a chart of luminescence in an NFAT-based report assay (RLU) at varying concentrations of MAGE-A3 peptide 1 (MP1, nM) for the indicated constructs in the presence of 50 μM NY-ESO-1 peptide.

[0016] FIG. 12A is a plot showing the effect of LIR-1 hinge on the ability of an HLA-A*02 scFv inhibitory receptor to block activation of Jurkat cells by a KRAS TCR. H: hinge, T: transmembrane domain, ICD: intracellular domain, s: short. LIR-1 constructs are described in more detail in FIG. 12B. Humanized PA2.1 and humanized BB7.2 with shorter LIR-1 hinge block similarly to original, longer hinge.

[0017] FIG. 12B is a plot and a table showing EC50 shift (+/- HLA-A*02 target cells) for Jurkat cells expressing a KRAS TCR activator and the HLA-A*02 scFv LIR-1 inhibitory receptor shown in the table at bottom.

[0018] FIG. 13A is a plot showing the effect of LIR-1 hinge on the ability of an HLA-A*02 inhibitory receptor to block activation of Jurkat cells by a KRAS TCR. H: hinge, TM: transmembrane domain, ICD: intracellular domain, s: short; tr: truncated. LIR-1 constructs are described in more detail in FIG. 13B. Mouse PA2.1 with slightly longer hinges function similarly to original LIR-1 hinge in T2-Jurkat assay.

[0019] FIG. 13B is a plot and a pair of tables showing EC50 shift (+/- HLA-A*02 target cells) for Jurkat cells expressing a KRAS TCR activator and the HLA-A*02 scFv LIR-1 inhibitory receptors shown in the table at bottom, with hinge lengths shown in the table at left.

[0020] FIG. 14A is a diagram showing a schematic of T2-Jurkat experiments to evaluate blocker constructs.

[0021] FIG. 14B is a plot, table and diagram showing the effect of various NY-ESO-1 scFv LBD blocker modules (PD-1, CTLA-4, LIR-1) on EC50 of MAGE-A3 CAR activator (MP1-LBD 1-CAR), measured by MAGE peptide titration of cells loaded with a fixed (50 μM) NY-ESO-1 blocker peptide concentration. In each of FIGS. 14B-14F, NFAT-luciferase signal of Jurkat cells transfected with either activator CAR alone or in combination with each blocker receptor after 6 hours of co-culture with activator and blocker peptide-loaded T2 cells was assayed. The baseline (Jurkat only) varies with different activator alone constructs and can be especially high with CARs; in most cases expression of the blocker receptor absent its ligand suppresses the baseline. Activator peptide concentrations range from 0 then 10^{-6} to 10^{2} μM and luminescence measurements ranged from 0 to 80000 RLU.

[0022] FIG. 14C is a plot, table and diagram showing the effect of LIR-1 blocker receptor with various scFv LBDs (ESO, MP1 LBD 1, MP1 LBD 2, HPV E6 LBD 1, HPV E6 LBD 2, HPV E7) on EC50 of MAGE-A3 CAR activator (MP1-CAR) when loaded with corresponding blocker peptide at fixed (50 μM) peptide concentration, as in FIG. 14B. RLU = relative light units; error bars indicate ± SD (n=2). Activator peptide concentrations range from 0 then 10^{-3} to 10^{2} μM and luminescence measurements ranged from 0 to 100000 RLU.

[0023] FIG. 14D is a plot, table and diagram showing the effect of LIR-1 blocker receptor with NY-ESO-1 scFv LBD on EC50 of different MAGE-A3 CAR activators (MP1-LBD 1-CAR or MP2-CAR) when loaded with 50uM NY-ESO-1 blocker peptide. Activator peptide concentrations range from 0 then 10^{-4} to 10^{2} μM and luminescence measurements ranged from 0 to 80000 RLU.

[0024] FIG. 14E is a plot, table and diagram showing the effect of LIR-1 blocker receptor with NY-ESO-1 scFv LBD on EC50 of different TCR activators (MP1-TCR, MP2-TCR, HPV E6-TCR) when loaded with 50uM NY-ESO-1 blocker peptide. Activator peptide concentrations range from 0 then 10^{-4} to 10^{2} μM and normalized luminescence measurements ranged from 0 to 150 RLU.

[0025] FIG. 14F is a plot, table and diagram showing the effect of LIR-1 blocker receptor with NY-ESO-1 TCR LBDs on EC50 of MAGE-A3 CAR and TCR activators (MP1-LBD 1-CAR, MP1-TCR) when loaded with 50uM NY-ESO-1 blocker peptide. RLU = relative light units; error bars indicate ± SD (n=2). Activator peptide concentrations range from 0 then 10^{-7} to 10^{1} μM and normalized luminescence measurements ranged from 0 to 150 RLU.

[0026] FIG. 15 is a plot showing the effect of blocker peptide loading (50 μM each of NY-ESO-1, MAGE-A3, HPV E6, and HPV E7) on activating MAGE-A3 CAR. MP2-CAR [0 μM], EC50 = 44 nM; MP2-CAR [50 μM HPVp2], EC50 = 495 nM. RLU = relative light units; error bars indicate ± SD (n = 2).

[0027] FIG. 16A is a series of plots showing NFAT-luciferase signal of Jurkat cells transfected with either activator MAGE-A3 CAR alone or in combination with various amounts of NY-ESO-1 scFv LBD blocker (DNA ratios of activator and blocker receptors components shown on left as A:B, activator receptor: blocker receptor after 6 h of co-culture with activator and blocker peptide-loaded T2 cells. T2 cells were loaded with titrated amounts of activator MAGE-A3 peptide and a fixed amount of blocker NY-ESO-1 peptide concentration. Activator and/or blocker peptide concentrations range from 0 then 10^{-6} to 10^{2} μM and luminescence measurements ranged from 0 to 200000 RLU.

[0028] FIG. 16B is a series of plots showing NFAT-luciferase signal of Jurkat cells transfected with either activator MAGE-A3 CAR alone or in combination with various amounts of NY-ESO-1 scFv LBD blocker. T2 cells were loaded with titrated amounts of blocker NY-ESO-1 peptide and a fixed amount of activator MAGE-A3 peptide concentration above the Emax concentration (~0.1 mM). Activator and/or blocker peptide concentrations range from 10^{-5} to 10^{2} μM and luminescence measurements ranged from 0 to 200000 RLU.

[0029] FIG. 16C is a series of plots and two tables showing NFAT-luciferase signal of Jurkat cells transfected with either activator MAGE-A3 CAR alone or in combination with various amounts of NY-ESO-1 scFv LBD blocker. The x-value blocker NY-ESO-1 peptide concentrations from FIG. 16B were normalized to the constant activator MAGE peptide concentrations used for each curve and plotted on the x-axis. The ratio of blocker peptide to activator peptide required for 50 % blocking (IC50) are indicated for each curve. For all DNA ratios, the B:A peptide ratio required is less than 1 indicating that, for this pair of activator CAR and blocker, similar (or fewer) blocker pMHC antigens are required on target cells to block activator pMHC antigens. Activator and/or blocker peptide concentrations range from 10^{-10} to 10^{4} μM and luminescence measurements ranged from 0 to 200000 RLU.

[0030] FIG. 16D is a table and a plot showing that blocking CD19-CAR activator is possible with pMHC blockers at blocker pMHC antigen densities similar to those required to activate pMHC CARs. NFAT-luciferase signal of Jurkat cells transfected with either activator CD19 CAR alone

or in combination with various amounts of NY-ESO-1 blocker (DNA ratios shown) after 6 h of co-culture with blocker peptide-loaded T2 cells which express endogenous levels of CD19 antigen. The IC50 is estimated from the inhibition curves to range from 0.1-1.0 mM, corresponding to ~1,500 - 3,500 pMHCs/cell. RLU = relative light units; error bars indicate ± SD (n = 2).

[0031] FIG. 17A is a plot showing the effect of NY-ESO-1-LIR-1 blocker on EC50 of activating MAGE-A3 CAR (MP1-CAR) when loaded with various concentrations of NY-ESO-1 blocker peptide. The EC50 shifts are greater as the concentration of blocker peptide (NY-ESO-1) increases. The shift in the presence of a negative-control HPV peptide (binds HLA-A*02 but not NY-ESO-1 blocker scFv) is routinely seen and believed to be caused by competition of the control peptide for binding sites on the T2 HLA-A*02 molecules, reducing the number of activator targets. Activator concentrations range from 0 then 10^{-4} to 10^{2} μM and luminescence measurements ranged from 0 to 140000 RLU.

[0032] FIG. 17B is a plot showing the effect of modified LIR-1 blocker receptors containing no ICD or a mutated ICD with NY-ESO-1 scFv LBD on EC50 of MAGE-A3 CAR activator (MP2-CAR) when loaded with 10 μM of NY-ESO-1 blocker peptide. Activator concentrations range from 0 then 10^{-4} to 10^{2} μM and luminescence measurements ranged from 0 to 140000 RLU.

[0033] FIGS. 17C-17E are a series of plots showing the effect of various NY-ESO-1 scFv LBD blocker receptors (CTLA-4 (FIG. 17C), PD-1 (FIG. 17D) and LIR-1 (FIG. 17E)) on EC50 of MAGE-A3 CAR activator (MP1-LBD 1-CAR) when blockers are stimulated or unstimulated. NFAT-luciferase signal of Jurkat cells transfected with either activator CAR alone or in combination with each blocker after 6 h of co-culture with peptide-loaded T2 cells. T2 cells were loaded with titrated amounts of activating MAGE peptide and tested with and without loading additional constant amount (50 μM) of NY-ESO-1 blocker peptide. RLU = relative light units; error bars indicate ± SD (n = 2). Activator concentrations range from 0 then 10^{-6} to 10^{2} μM and luminescence measurements ranged from 0 to 100000 RLU.

[0034] FIG. 18A is a diagram and a pair of plots showing that Jurkat cells transfected with either HPV E7-CAR or HPV E7-CAR & A2-LIR-1 co-cultured with beads displaying various ratios of activator (HPV E7) and blocker (NY-ESO-1) antigen demonstrates blocking in cis but not trans.

[0035] FIG. 18B is a plot showing that HLA-A*02-LIR-1 blocker receptor blocks CD19-CAR activator at various activator to blocker ratios. Ratios ranged from 0 to 10 and luminescence (RLU) ranged from 0 to 70000.

[0036] FIG. 18C is a plot showing surface expression of titrated HLA-A*02 (A2) LIR-1 blocker receptor.

[0037] FIG. 18D is a plot showing that an scFv against HLA-A*02 can also serve as an activator when fused to activator CAR. T2 cells expressing endogenous HLA-A*02 serve as the target. RLU = relative light units; error bars indicate ± SD (n=2).

[0038] FIG. 19A is a plot showing the effect of LIR-1 blocker receptor with NY-ESO-1 scFv LBD on EC50 of different TCR activators (MP1-TCR, MP2-TCR, HPV E6-TCR) when loaded with NY-ESO-1 blocker peptide. For FIG. 14E each set was normalized to the Emax of the curve showing response of the activator only. Activator concentrations range from 0 then 10^{-4} to 10^{2} μM and luminescence measurements ranged from 0 to 140000 RLU.

[0039] FIG. 19B is a plot showing the effect of LIR-1 blocker receptor with NY-ESO-1 TCR LBDs on EC50 of MAGE-A3 CAR and TCR activators (MP1-LBD 1-CAR, MP1-TCR). Each set was normalized to the Emax of the curve showing response of the activator only. RLU = relative light units; error bars indicate ± SD (n = 2). Activator concentrations range from 0 then 10^{-7} to 10^{1} μM and luminescence measurements ranged from 0 to 140000 RLU.

[0040] FIG. 20A is a plot showing primary T cells (donor 1) transduced with HPV E7-TCR activator and ESO-LIR-1 blocker shifts EC50 ~25x in primary T cell killing assay (HPV E7 TCR EC50 = 0.044 nM; HPV E7 TCR + ESO-LIR-1, EC50 = 1.1 nM). The assay was performed using peptide-loaded MCF7 target cells at a 3:1 E:T. Luciferase measurement represents live target cells at 48 hours.

[0041] FIG. 20B is a plot showing that HLA-A*02-LIR-1 blocks NY-ESO-1 CAR activator at various activator:blocker DNA ratios in Jurkat cells using NY-ESO-1 peptide-loaded T2 target cells. RLU = relative light units; error bars indicate ± SD (n=2).

[0042] FIG. 21A is a series of images and plots showing that primary T cells (donor 1) transduced with CD19 CAR activator and HLA-A*02 blocker distinguish "tumor" cells from "normal" cells in in vitro cytotoxicity assay and demonstrate selective killing of "tumor" cells in mixed target cell assay at 3:1 E:T. Images shown were captured at 72 hours. Shown are Untransduced, CD19-CAR T cells, and CD19-CAR T + A2-LIR-1. Measurements were taken between 0 and 150 hours and normalized fluorescent protein intensity (GFP or RFP) ranged from 0 to 10.

[0043] FIG. 21B is a series of plots showing that primary T cells (donor 1) selectively kill tumor cells similarly at various tumor to "normal" cell ratios at 3:1 E:T ratios in Incucyte imaging

assay. RLU values were normalized against target cell mixtures grown in the absence of primary T cells. Shown are Untransduced, CD19-CAR T cells, and CD19-CAR T + A2-LIR-1. Measurements were taken between 0 and 150 hours and normalized fluorescent protein intensity (GFP or RFP) ranged from, on the top row, from left to right: 0 to 3×10^7, 0 to 2×10^7, 0 to 1.6×10^7, 0 to 7×10^6, 0 to 2×10^6; bottom row, from left to right: 0 to 7×10^5, 0 to 2×10^5, 0 to 4×10^5, 0 to 6×10^5, 0 to 7×10^5.

[0044] FIG. 21C is a series of plots showing that primary T cells (donor 1) selectively kill tumor cells similarly at various tumor to "normal" cell ratios at 3:1 E:T ratios in quantitative target cell lysis and IFNγ secretion. Shown are Untransduced, CD19-CAR T cells, and CD19-CAR T + A2-LIR-1.

[0045] FIG. 22A is a pair of plots showing that Jurkat cells transfected with MSLN LBD1-CAR or MSLN LBD1-CAR & A2-LIR-1 co-cultured with K562 cells expressing either MSLN or MSLN & HLA-A*02 shows blocking of activation by a high-density antigen with A2-LIR-1 blocker only in the presence of HLA-A*02.

[0046] FIG. 22B is a pair of plots showing that killing of endogenous MSLN+ HeLa cells by MLSN LBD1-CAR T cells is blocked in the presence of HLA-A*02 with the A2-LIR-1 blocker.

[0047] FIG. 22C is a pair of plots showing killing of endogenous MSLN+ HeLa cells by MLSN LBD2-CAR T cells. The effect of A2-LIR-1 blocker on T cell killing is in part controlled by the activator LBD.

[0048] FIG. 23 is a plot showing that LIR-1 blocker receptors have little effect on killing efficacy of activator in absence of blocker antigen. In the absence of NY-ESO-1 blocker antigen, primary T cells (donor 1) transduced with HPV E7-TCR activator and ESO-LIR-1 blocker display similar killing efficacy to primary T cells transduced with only the HPV E7-TCR activator. Luciferase measurement represents live target cells. RLU = relative light units; error bars indicate ± SD (n = 2).

[0049] FIG. 24A is a pair of plots showing that A2-LIR-1 blocks Jurkat activation in A2+ Raji cells but not WT Raji cells. Histograms show Raji WT "tumor" cells and Raji A2+ "normal" cells have identical CD19 surface expression while HLA-A*02 is expressed only in Raji A2 "normal" cells.

[0050] FIG. 24B is a plot showing that A2-LIR-1 blocks Jurkat activation in A2+ Raji cells but not WT Raji cells. Jurkat cells transfected with either CD19 or CD19 + A2-LIR-1 were co-cultured

with either WT (A2-) Raji cells or A2+ Raji cells at various cell ratios. RLU = relative light units; error bars indicate ± SD (n = 2).

[0051] FIGS. 25A-25B are each a series of images showing the reversibility of blockade by LIR-1 inhibitory receptors. Primary T cells (donor 2) transduced with CD19 CAR activator and HLA-A*02 blocker demonstrate reversible blockade (FIG. 25A) and activation (FIG. 25B) after 3 rounds of antigen exposure (AB–A–AB and A–AB–A) in in vitro cytotoxicity assay at 3:1 E:T. Primary T cell cytotoxicity assay was reproduced with three HLA-A*02-negative donors. Images shown were captured at 72 hours.

[0052] FIGS. 25C-25D are each a pair of plots showing quantification of target cell lysis (FIG. 25C) and IFNγ (FIG. 25D) in response to repeated exposure to multiple rounds of normal and target cells, 3:1 E:T (T cells from donor 2). Shown conditions are Untransduced, CD19-CAR T cells, and CD19-CAR T + A2-LIR-1. Error bars indicate ± SEM (n=2). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, determined using a two-way ANOVA followed by Tukey's multiple-comparisons test. In this experiment, IFNγ response diminished over time, while cytotoxicity remained robust.

[0053] FIGS. 26A-26B are each a pair of plots showing cytotoxic T cell killing and secretion of IFNγ in co-culture with a separate donor (donor 3). Cytotoxic CD19 CAR activator and HLA-A*02 blocker transduced T cells demonstrate reversible blocking after multiple rounds of antigen exposure in cytotoxic assays and IFNγ at 9:1 E:T. We noted that this donor's T cells survival and activity tailed off over time in culture. Shown conditions are Untransduced, CD19-CAR T cells, and CD19-CAR T + A2-LIR-1. Cytotoxicity (FIG. 26A) and IFNγ (FIG. 26B) results correspond to FIGS. 25C-25D. Error bars indicate ± SEM (n = 2). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, determined using a two-way ANOVA followed by Tukey's multiple-comparisons test.

[0054] FIG. 27A is a plot showing primary T cells transduced with CD19 CAR activator and HLA-A*02 blocker demonstrates ~20-fold expansion with CD3/28 stimulation over 10 days.

[0055] FIG. 27B is a diagram showing an experiment to show that CAR-T cells expressing a LIR-1 blocker receptor selectively kill tumors in a xenograft model. HLA-A*02 NSG mice were administered either "tumor cells" (A2-negative Raji cells) or "normal cells" (A2-positive Raji cells) subcutaneously and primary T cells (human, HLA-A*02-negative donor 4) were injected into the tail vein when Raji xenografts averaged ~70 mm^3.

[0056] FIGS. 27C-27E are each a pair of plots that show readouts by caliper measurement (FIG. 27C), human T cell counts in peripheral blood by flow cytometry (FIG. 27D), and survival (FIG. 27E). Error bars in C-D indicate ± SEM (n=7). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, determined using a two-way ANOVA followed by Tukey's multiple-comparisons test.

[0057] FIG. 28A is a series of plots showing flow cytometry analysis of primary T cell post-enrichment and expansion prepared for mouse tail vein injection. Tumor volume was measured at the number of days from T cell injection, starting 10 days prior to T cell injection (-10) to 40 days following T cell injection (40). Tumor volumes ranged from 0 to 2500 mm^3.

[0058] FIG. 28B is a series of plots showing tumor measurement by caliper plotted for individual mice in each group.

[0059] FIG. 28C is a series of plots showing correlation of huCD3+ T cells in mouse blood to tumor growth. Graph of huCD3+ T cells compared to tumor volume 10 days and 17 days after T cell injection.

[0060] FIG. 28D is a pair of plots showing huCD4+ and huCD8+ T cell counts in peripheral blood by flow cytometry. Open circles, mice grafted with "normal" cells; closed circle, mice grafted with tumor cells. Samples with fewer than 100 cells were excluded from the analysis. Error bars indicate ± SEM (n = 7 in all groups except n = 6 in CD19+/A2- Raji group treated with CD19-CAR + A2-LIR-1 T cells).

[0061] FIG. 29A is a series of images showing histological analysis of T cell infiltration in tumors. Representative images of tumor samples collected at study termination, sectioned and stained for huCD3 are shown.

[0062] FIG. 29B is a plot showing quantification of T cell infiltration using ImageJ. T cell infiltration was significantly higher for T cells with CD19-CAR or CD19-CAR + A2-LIR-1 in CD19+/A2- tumors compared to untransduced cells. However, in CD19+/A2+ tumors, CD19-CAR + A2-LIR-1 T cells were not significantly different compared to untransduced cells. There was also a significant drop in infiltration of CD19-CAR + A2-LIR-1 T cells between CD19+/A2- and CD19+/A2+ tumors. Qualitatively, CD19-CAR + A2-LIR-1 T cells were less prevalent in CD19+/A2+ tumors compared to CD19-CAR only T cells; however, this difference was not statistically significant. Saline samples were similarly quantified to show background staining levels. Groups of data were analyzed using an ordinary one-way ANOVA, while individual pairs

between "tumor" and "normal" were analyzed using an unpaired t test. ns = not significant, *p < 0.05, **p < 0.01.

DETAILED DESCRIPTION

[0063] The present disclosure describes receptors having one or more domains from Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1, sometimes referred to as LIR1 or LIR-1). Numerous receptors, engineered cells, and uses thereof are contemplated herein. The inventors have found that chimeric receptors comprising an antigen-binding domain and one or more LILRB1 domains, including the LILRB1 intracellular domain, can inhibit immune cell signaling even in the presence of activatory chimeric antigen receptors (CARs) or T cell receptors (TCRs).

[0064] The term “chimeric antigen receptors” or “CARs” as used herein, may refer to artificial T-cell receptors, chimeric T-cell receptors, or chimeric immunoreceptors, for example, and encompass engineered receptors that graft an artificial specificity onto a particular immune effector cell, such as a helper T cell (CD4+), cytotoxic T cell (CD8+) or NK cell. CARs may be employed to impart the specificity of a monoclonal antibody onto a T cell, thereby allowing a large number of specific T cells to be generated, for example, for use in adoptive cell therapy. In specific embodiments, CARs direct specificity of the cell to a tumor associated antigen. In some embodiments, CARs comprise an intracellular signaling domain, a transmembrane domain, and an extracellular domain comprising an antigen-binding region. In some embodiments, CARs comprise fusions of single-chain variable fragments (scFvs) or scFabs derived from monoclonal antibodies, fused to a transmembrane domain and intracellular signaling domain(s). The fusion may also comprise a hinge. Either heavy-light (H-L) and light-heavy (L-H) scFvs may be used. The specificity of CAR designs may be derived from ligands of receptors (*e.g.*, peptides). Depending on the type of intracellular domain, a CAR can be an activatory receptor or an inhibitory receptor. In some embodiments, for example when the CAR is an activatory receptor, the CAR comprises domains for additional co-stimulatory signaling, such as CD3, FcR, CD27, CD28, CD137, DAP10, and/or 0X40. In some embodiments, molecules can be co-expressed with the CAR, including co-stimulatory molecules, reporter genes for imaging (*e.g.*, for positron emission tomography), gene products that conditionally ablate the T cells upon addition of a pro-drug, homing receptors, cytokines, and cytokine receptors. As used herein, characteristics

attributed to a chimeric antigen receptor may be understood to refer to the receptor itself or to a host cell comprising the receptor.

[0065] As used herein, a "TCR", sometimes also called a "TCR complex" or "TCR/CD3 complex" refers to a protein complex comprising a TCR alpha chain, a TCR beta chain, and one or more of the invariant CD3 chains (zeta, gamma, delta and epsilon), sometimes referred to as subunits. The TCR alpha and beta chains can be disulfide-linked to function as a heterodimer to bind to peptide-MHC complexes. Once the TCR alpha/beta heterodimer engages peptide-MHC, conformational changes in the TCR complex in the associated invariant CD3 subunits are induced, which leads to their phosphorylation and association with downstream proteins, thereby transducing a primary stimulatory signal. In an exemplary TCR complex, the TCR alpha and TCR beta polypeptides form a heterodimer, CD3 epsilon and CD3 delta form a heterodimer, CD3 epsilon and CD3 gamma for a heterodimer, and two CD3 zeta form a homodimer.

[0066] The term "stimulation" refers to a primary response induced by binding of a stimulatory domain or stimulatory molecule (*e.g.*, a TCR/CD3 complex) with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3 complex. Stimulation can mediate altered expression of certain molecules, and/or reorganization of cytoskeletal structures, and the like.

[0067] The term "stimulatory molecule" or "stimulatory domain" refers to a molecule or portion thereof that, when natively expressed by a T-cell, provides the primary cytoplasmic signaling sequence(s) that regulate activation of the TCR complex in a stimulatory way for at least some aspect of the T-cell signaling pathway. TCR alpha and/or TCR beta chains of wild type TCR complexes do not contain stimulatory domains and require association with CD3 subunits such as CD3 zeta to initiate signaling. In one aspect, the primary stimulatory signal is initiated by, for instance, binding of a TCR/CD3 complex with an a major histocompatibility complex (MHC) bound to peptide, and which leads to mediation of a T-cell response, including, but not limited to, proliferation, activation, differentiation, and the like. One or more stimulatory domains, as described herein, can be fused to the intracellular portion of any one or more subunits of the TCR complex, including TCR alpha, TCR beta, CD3 delta, CD3 gamma and CD3 epsilon.

[0068] As used herein, a "domain capable of providing a stimulatory signal" refers to any domain that, either directly or indirectly, can provide a stimulatory signal that enhances or increases the effectiveness of signaling mediated by the TCR complex to enhance at least some

aspect of T-cell signaling. The domain capable of providing a stimulatory signal can provide this signal directly, for example with the domain capable of providing the stimulatory signal is a primary stimulatory domain or co-stimulatory domain. Alternatively, or in addition, the domain capable of providing the stimulatory signal can act indirectly. For example, the domain can be a scaffold that recruits stimulatory proteins to the TCR, or provide an enzymatic activity, such as kinase activity, that acts through downstream targets to provide a stimulatory signal.

[0069] As used herein, a "domain capable of providing an inhibitory signal" refers to any domain that, either directly or indirectly, can provide an inhibitory signal that inhibits or decreases the effectiveness signaling mediated by the TCR complex. The domain capable of providing an inhibitory signal can reduce, or block, totally or partially, at least some aspect of T-cell signaling or function. The domain capable of providing an inhibitory signal can provide this signal directly, for example with the domain capable of providing the inhibitory signal provides a primary inhibitory signal. Alternatively, or in addition, the domain capable of providing the stimulatory signal can act indirectly. For example, the domain can recruit additional inhibitory proteins to the TCR, or can provide an enzymatic activity that acts through downstream targets to provide an inhibitory signal.

[0070] Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. As another example, a range such as 95-99% identity, includes something with 95%, 96%, 97%, 98% or 99% identity, and includes subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98% and 98-99% identity. This applies regardless of the breadth of the range.

[0071] In general, "sequence identity" or "sequence homology" refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Typically, techniques for determining sequence identity include determining the nucleotide sequence of a polynucleotide and/or determining the amino acid

sequence encoded thereby and comparing these sequences to a second nucleotide or amino acid sequence. Two or more sequences (polynucleotide or amino acid) can be compared by determining their "percent identity." The percent identity of two sequences, whether nucleic acid or amino acid sequences, is the number of exact matches between two aligned sequences divided by the length of the shorter sequences and multiplied by 100. Percent identity may also be determined, for example, by comparing sequence information using the advanced BLAST computer program, including version 2.2.9, available from the National Institutes of Health. The BLAST program is based on the alignment method of Karlin and Altschul, Proc. Natl. Acad. Sci. USA 87:2264-2268 (1990) and as discussed in Altschul, et al., J. Mol. Biol. 215:403-410 (1990); Karlin And Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5877 (1993); and Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997). Briefly, the BLAST program defines identity as the number of identical aligned symbols (generally nucleotides or amino acids), divided by the total number of symbols in the shorter of the two sequences. The program may be used to determine percent identity over the entire length of the proteins being compared. Default parameters are provided to optimize searches with short query sequences in, for example, with the blastp program. Ranges of desired degrees of sequence identity are approximately 80% to 100% and integer values therebetween. Typically, the percent identities between a disclosed sequence and a claimed sequence are at least 80%, at least 85%, at least 90%, at least 95%, or at least 98%.

[0072] As used herein, a "subsequence" refers to a length of contiguous amino acids or nucleotides that form a part of a sequence described herein. A subsequence may be identical to a part of a full length sequence when aligned to the full length sequence, or less than 100% identical to the part of the full length sequence to which it aligns (e.g., 90% identical to 50% of the full sequence, or the like).

[0073] The term "exogenous" is used herein to refer to any molecule, including nucleic acids, protein or peptides, small molecular compounds, and the like that originate from outside the organism. In contrast, the term "endogenous" refers to any molecule that originates from inside the organism (*i.e.*, naturally produced by the organism).

[0074] A polynucleotide is "operably linked" to another polynucleotide when it is placed into a functional relationship with the other polynucleotide. For example, a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. A peptide is

"operably linked" to another peptide when the polynucleotides encoding them are operably linked, preferably they are in the same open reading frame.

[0075] A “promoter” is a sequence of DNA needed to turn a gene on or off. Promoters are located immediately upstream and/or overlapping the transcription start site, and are usually between about one hundred to several hundred base pairs in length.

[0076] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

[0077] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. The term “about”, when immediately preceding a number or numeral, means that the number or numeral ranges plus or minus 10%.

[0078] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1)

[0079] The present disclosure describes receptors having one or more domains from Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1, or LIR1). Numerous receptors, engineered cells, and uses thereof are contemplated herein.

[0080] Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1), also known as Leukocyte immunoglobulin-like receptor B1, as well as ILT2, LIR1, MIR7, PIRB, CD85J, ILT-2 LIR-1, MIR-7 and PIR-B, is a member of the leukocyte immunoglobulin-like receptor (LIR) family. The LILRB1 protein belongs to the subfamily B class of LIR receptors. These receptors contain two to four extracellular immunoglobulin domains, a transmembrane domain, and two to four cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs).

The LILRB1 receptor is expressed on immune cells, where it binds to MHC class I molecules on antigen-presenting cells and transduces a negative signal that inhibits stimulation of an immune response. LILRB1 is thought to regulate inflammatory responses, as well as cytotoxicity, and to play a role in limiting auto-reactivity. Multiple transcript variants encoding different isoforms of LILRB1 exist, all of which are contemplated as within the scope of the instant disclosure.

[0081] In some embodiments of the receptors having one or domains of LILRB1, the one or more domains of LILRB1 comprise an amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or is identical to a sequence or subsequence of SEQ ID NO: 1. In some embodiments, the one or more domains of LILRB1 comprise an amino acid sequence that is identical to a sequence or subsequence of SEQ ID NO: 1. In some embodiments, the one or more domains of LILRB1 consist of an amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or is identical to a sequence or subsequence of SEQ ID NO: 1. In some embodiments, the one or more domains of LILRB1 consist of an amino acid sequence that is identical to a sequence or subsequence of SEQ ID NO: 1.

[0082] In some embodiments of the receptors having one or domains of LILRB1, the one or more domains of LILRB1 are encoded by a polynucleotide sequence that is at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or is identical to a sequence or subsequence of SEQ ID NO: 34.

[0083] In some embodiments of the receptors having one or domains of LILRB1, the one or more domains of LILRB1 are encoded by a polynucleotide sequence that is identical to a sequence or subsequence of SEQ ID NO: 34.

Receptors

[0084] In various embodiments, a chimeric antigen receptor is provided, comprising a polypeptide, wherein the polypeptide comprises one or more of: an LILRB1 hinge domain or functional fragment or variant thereof; an LILRB1 transmembrane domain or a functional variant thereof; and an LILRB1 intracellular domain or an intracellular domain comprising at least one, or at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

Intracellular Domain

[0085] The disclosure provides chimeric antigen receptors, the chimeric antigen receptors comprising a polypeptide. In some embodiments, the polypeptide comprises an intracellular domain. In some embodiments, the intracellular domain is an LILRB1 intracellular domain or a functional variant thereof.

[0086] As used herein, "intracellular domain" refers to the cytoplasmic or intracellular domain of a protein, such as a receptor, that interacts with the interior of the cell, and carries out a cytosolic function. As used herein, "cytosolic function" refers to a function of a protein or protein complex that is carried out in the cytosol of a cell. For example, intracellular signal transduction cascades are cytosolic functions.

[0087] As used herein an "immunoreceptor tyrosine-based inhibitory motif" or "ITIM" refers to a conserved sequence of amino acids with a consensus sequence of S/I/V/LxYxxI/V/L (SEQ ID NO: 124), or the like, that is found in the cytoplasmic tails of many inhibitory receptors of the immune system. After ITIM-possessing inhibitory receptors interact with their ligand, the ITIM motif is phosphorylated, allowing the inhibitory receptor to recruit other enzymes, such as the phosphotyrosine phosphatases SHP-1 and SHP-2, or the inositol-phosphatase called SHIP.

[0088] In some embodiments, the polypeptide comprises an intracellular domain comprising at least one immunoreceptor tyrosine-based inhibitory motif (ITIM), at least two ITIMs, at least 3 ITIMs, at least 4 ITIMs, at least 5 ITIMs or at least 6 ITIMs. In some embodiments, the intracellular domain has 1, 2, 3, 4, 5, or 6 ITIMs.

[0089] In some embodiments, the polypeptide comprises an intracellular domain comprising at least one ITIM selected from the group of ITIMs consisting of NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0090] In further particular embodiments, the polypeptide comprises an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0091] In some embodiments, the intracellular domain comprises both ITIMs NLYAAV (SEQ ID NO: 8) and VTYAEV (SEQ ID NO: 9). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 12. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 12.

[0092] In some embodiments, the intracellular domain comprises both ITIMs VTYAEV (SEQ ID NO: 9) and VTYAQL (SEQ ID NO: 10). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 13. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 13.

[0093] In some embodiments, the intracellular domain comprises both ITIMs VTYAQL (SEQ ID NO: 10) and SIYATL (SEQ ID NO: 11). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 14. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 14.

[0094] In some embodiments, the intracellular domain comprises the ITIMs NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), and VTYAQL (SEQ ID NO: 10). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 15. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 15.

[0095] In some embodiments, the intracellular domain comprises the ITIMs VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 16. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 16.

[0096] In some embodiments, the intracellular domain comprises the ITIMs NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 17. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 17.

[0097] In some embodiments, the intracellular domain comprises a sequence at least 95% identical to the LILRB1 intracellular domain (SEQ ID NO: 7). In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to the LILRB1 intracellular domain (SEQ ID NO: 7).

[0098] LILRB1 intracellular domains or functional variants thereof of the disclosure can have at least 1, at least 2, at least 4, at least 4, at least 5, at least 6, at least 7, or at least 8 ITIMs. In some embodiments, the LILRB1 intracellular domain or functional variant thereof has 2, 3, 4, 5, or 6 ITIMs.

[0099] In particular embodiments, the polypeptide comprises an intracellular domain comprising two, three, four, five, or six immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0100] In particular embodiments, the polypeptide comprises an intracellular domain comprising at least three immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0101] In particular embodiments, the polypeptide comprises an intracellular domain comprising three immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0102] In particular embodiments, the polypeptide comprises an intracellular domain comprising four immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0103] In particular embodiments, the polypeptide comprises an intracellular domain comprising five immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0104] In particular embodiments, the polypeptide comprises an intracellular domain comprising six immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0105] In particular embodiments, the polypeptide comprises an intracellular domain comprising at least seven immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0106] In some embodiments, the intracellular domain comprises a TCR alpha intracellular domain. In some embodiments, the intracellular domain comprises a TCR alpha intracellular domain and an LILRB1 intracellular domain, as described herein. In some embodiments, a TCR

alpha intracellular domain comprises Ser-Ser. In some embodiments, a TCR alpha intracellular domain is encoded by a sequence of TCCAGC.

[0107] In some embodiments, the intracellular domain comprises a TCR beta intracellular domain. In some embodiments, the intracellular domain comprises a TCR beta intracellular domain and an LILRB1 intracellular domain, as described herein. In some embodiments, the TCR beta intracellular domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, or is identical to a sequence of: MAMVKRKDSR (SEQ ID NO: 94). In some embodiments, the TCR beta intracellular domain comprises, or consists essentially of MAMVKRKDSR (SEQ ID NO: 94). In some embodiments, the TCR beta intracellular domain is encoded by a sequence of ATGGCCATGGTCAAGAGAAAGGATTCCAGA (SEQ ID NO: 95).

Transmembrane Domain

[0108] The disclosure provides chimeric antigen receptors the receptors comprising a polypeptide. In some embodiments, the polypeptide comprises a transmembrane domain. In some embodiments, the transmembrane domain is a LILRB1 transmembrane domain or a functional variant thereof.

[0109] A "transmembrane domain", as used herein, refers to a domain of a protein that spans membrane of the cell. Transmembrane domains typically consist predominantly of non-polar amino acids, and may traverse the lipid bilayer once or several times. Transmembrane domains usually comprise alpha helices, a configuration which maximizes internal hydrogen bonding.

[0110] Transmembrane domains isolated or derived from any source are envisaged as within the scope of the fusion proteins of the disclosure.

In particular embodiments, the polypeptide comprises an LILRB1 transmembrane domain or a functional variant thereof.

[0111] In some embodiments, the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical or at least 99% to SEQ ID NO: 5. In some embodiments, the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 5. In some embodiments, the LILRB1 transmembrane domain comprises a sequence identical to SEQ ID NO: 5. In embodiments, the LILRB1 transmembrane domain consists essentially of a sequence identical to SEQ ID NO: 5.

[0112] In some embodiments of the chimeric antigen receptors of the disclosure, the transmembrane domain is not a LILRB1 transmembrane domain. In some embodiments, the transmembrane domain is one that is associated with one of the other domains of the fusion protein, or isolated or derived from the same protein as one of the other domains of the fusion protein.

[0113] The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. Exemplary transmembrane domains may include at least the transmembrane region(s) of *e.g.*, the alpha, beta or zeta chain of the TCR, CD3 delta, CD3 epsilon or CD3 gamma, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154.

[0114] In some embodiments, the transmembrane comprises a TCR alpha transmembrane domain. In some embodiments, the TCR alpha transmembrane domain comprises an amino acid sequence having at least 85% identity, at least 90% identity, at least 95% identity, at least 96% identity, at least 97% identity, at least 98% identity, at least 99% identity or is identical to a sequence of: VIGFRILLLKVAGFNLLMTLRLW (SEQ ID NO: 96). In some embodiments, the TCR alpha transmembrane domain comprises, or consists essentially of, VIGFRILLLKVAGFNLLMTLRLW (SEQ ID NO: 96). In some embodiments, the TCR alpha transmembrane domain is encoded by a sequence of: GTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACG CTGCGGCTGTGG (SEQ ID NO: 97).

[0115] In some embodiments, the transmembrane comprises a TCR beta transmembrane domain. In some embodiments, the TCR beta transmembrane domain comprises an amino acid sequence having at least 85% identity, at least 90% identity, at least 95% identity, at least 96% identity, at least 97% identity, at least 98% identity, at least 99% identity or is identical to a sequence of: TILYEILLGKATLYAVLVSALVL (SEQ ID NO: 98). In some embodiments, the TCR beta transmembrane domain comprises, or consists essentially of TILYEILLGKATLYAVLVSALVL (SEQ ID NO: 98). In some embodiments, the TCR beta transmembrane domain is encoded by a sequence of ACCATCCTCTATGAGATCTTGCTAGGGAAGGCCACCTTGTATGCCGTGCTGGTCAGT GCCCTCGTGCTG (SEQ ID NO: 99).

[0116] In some embodiments, the TCR alpha and/or TCR beta transmembrane domain comprises one or more mutations that attenuate or abolish interaction of the TCR with the TCR CD3 subunit. In some embodiments, the TCR alpha transmembrane domain comprises a R253L mutation. In some embodiments, the TCR beta transmembrane domain comprises a K288L mutation.

[0117] In some embodiments the transmembrane domain comprise a CD28 transmembrane domain. In some embodiments, the CD28 transmembrane domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of FWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO: 100). In some embodiments, the CD28 transmembrane domain comprises or consists essentially of FWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO: 100). In some embodiments, the CD28 transmembrane domain is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of

TTCTGGGTGCTGGTCGTTGTGGGCGGCGTGCTGGCCTGCTACAGCCTGCTGGTGACAGTGGCCTTCATCATCTTTTG GGTG (SEQ ID NO: 101).

[0118] In some embodiments, the transmembrane domain can be attached to the extracellular region chimeric antigen receptor, *e.g.*, the antigen-binding domain or ligand binding domain, via a hinge, *e.g.*, a hinge from a human protein. For example, in some embodiments, the hinge can be a human immunoglobulin (Ig) hinge, *e.g.*, an IgG4 hinge, a CD8a hinge or an LILRB1 hinge.

Hinge Domain

[0119] The disclosure provides chimeric antigen receptors, the receptors comprising a polypeptide. In some embodiments, the polypeptide comprises a hinge domain. In some embodiments, the hinge domain is a LILRB1 hinge domain or a functional variant thereof.

[0120] The LILRB1 protein has four immunoglobulin (Ig) like domains termed D1, D2, D3 and D4. In some embodiments, the LILRB1 hinge domain comprises an LILRB1 D3D4 domain or a functional variant thereof. In some embodiments, the LILRB1 D3D4 domain comprises a sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or identical to SEQ ID NO: 18. In some embodiments, the LILRB1 D3D4 domain comprises or consists essentially of SEQ ID NO: 18.

[0121] In some embodiments, the polypeptide comprises the LILRB1 hinge domain or functional fragment or variant thereof. In embodiments, the LILRB1 hinge domain or functional

fragment or variant thereof comprises a sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical or identical to SEQ ID NO: 4, SEQ ID NO: 18, or SEQ ID NO: 19. In embodiments, the LILRB1 hinge domain or functional fragment or variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 4, SEQ ID NO: 18, or SEQ ID NO: 19.

[0122] In some embodiments, the LILRB1 hinge domain comprises a sequence identical to SEQ ID NO: 4, SEQ ID NO: 18, or SEQ ID NO: 19.

[0123] In some embodiments, the LILRB1 hinge domain consists essentially of a sequence identical to SEQ ID NO: 4, SEQ ID NO: 18, or SEQ ID NO: 19.

[0124] In some embodiments the chimeric antigen receptors of the disclosure, the polypeptide comprises a hinge that is not isolated or derived from LILRB1.

[0125] In some embodiments, the hinge is isolated or derived from CD8α or CD28. In some embodiments, the CD8α hinge comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 102). In some embodiments, the CD8α hinge comprises TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 102). In some embodiments, the CD8α hinge consists essentially of TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 102). In some embodiments, the CD8α hinge is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of accacgacgccagcgccgcgaccaccaacaccggcgcccaccatcgcgtcgcagcccctgtccc tgcgcccagaggcgtgccggccagcggcgggggcgcagtgcacacgaggggctggacttcgc ctgtgat (SEQ ID NO: 103).

[0126] In some embodiments, the CD28 hinge comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of CTIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP (SEQ ID NO: 104). In some embodiments, the CD28 hinge comprises or consists essentially of CTIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP (SEQ ID NO: 104). In some embodiments, the CD28 hinge is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of

tgtaccattgaagttatgtatcctcctccttacctagacaatgagaagagcaatggaaccattatccatg tgaaagggaaacacctttgtccaagtcccctatttcccggaccttctaagccc (SEQ ID NO: 105).

Combinations of LILRB1 Domains

[0127] In some embodiments, the chimeric antigen receptors of the disclosure comprise a polypeptide comprising more than one LILRB1 domain or functional equivalent thereof. For example, in some embodiments, the polypeptide comprises an LILRB1 transmembrane domain and intracellular domain, or an LILRB1 hinge domain, transmembrane domain and intracellular domain.

[0128] In particular embodiments, the polypeptide comprises an LILRB1 hinge domain or functional fragment or variant thereof, and the LILRB1 transmembrane domain or a functional variant thereof. In some embodiments, the polypeptide comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical or identical to SEQ ID NO: 20. In some embodiments, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 20. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 20.

[0129] In further embodiments, the polypeptide comprises: the LILRB1 transmembrane domain or a functional variant thereof, and an LILRB1 intracellular domain and/or an intracellular domain comprising at least one immunoreceptor tyrosine-based inhibitory motif (ITIM), wherein the ITIM is selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11). In some embodiments, the polypeptide comprises the LILRB1 transmembrane domain or a functional variant thereof, and an LILRB1 intracellular domain and/or an intracellular domain comprising at least two ITIM, wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0130] In some embodiments, the polypeptide comprises a LILRB1 transmembrane domain and intracellular domain. In some embodiments, the polypeptide comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical or identical to SEQ ID NO: 21. In some embodiments, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 21. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 21.

[0131] In preferred embodiments, the polypeptide comprises: an LILRB1 hinge domain or functional fragment or variant thereof; an LILRB1 transmembrane domain or a functional variant thereof; and an LILRB1 intracellular domain and/or an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from LYAAV (SEQ ID NO: 8), VTYAE (SEQ ID NO:9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).

[0132] In some embodiments, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 2 or SEQ ID NO: 3, or at least 99% identical to SEQ ID NO: 2 or SEQ ID NO: 3, or identical to SEQ ID NO: 2 or SEQ ID NO: 3.

[0133] In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 20, or at least 99% identical to SEQ ID NO: 20, or identical to SEQ ID NO: 20.

[0134] In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 21, or at least 99% identical to SEQ ID NO: 21, or identical to SEQ ID NO: 21.

Extracellular Domains

[0135] The disclosure provides chimeric antigen receptors comprising a polypeptide. In some embodiments, the polypeptide comprises a ligand binding domain, such as an antigen-binding domain. Suitable antigen-binding domains include, but are not limited to antigen-binding domains from antibodies, antibody fragments, scFv, antigen-binding domains derived from T cell receptors, and the like. All forms of antigen-binding domains known in the art are envisaged as within the scope of the disclosure.

[0136] An "extracellular domain", as used herein, refers to the extracellular portion of a protein. For example, the TCR alpha and beta chains each comprise an extracellular domain, which comprise a constant and a variable region involved in peptide-MHC recognition. The "extracellular domain" can also comprise a fusion domain, for example of fusions between additional domains capable of binding to and targeting a specific antigen and the endogenous extracellular domain of the TCR subunit.

[0137] The term "antibody," as used herein, refers to a protein, or polypeptide sequences derived from an immunoglobulin molecule, which specifically binds to an antigen. Antibodies can be intact immunoglobulins of polyclonal or monoclonal origin, or fragments thereof and can be derived from natural or from recombinant sources.

[0138] The terms "antibody fragment" or "antibody binding domain" refer to at least one portion of an antibody, or recombinant variants thereof, that contains the antigen-binding domain, *i.e.*, an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen and its defined epitope. Examples of antibody fragments include, but are not limited to, Fab, Fab′, F(ab′)2, and Fv fragments, single-chain (sc)Fv ("scFv") antibody fragments, linear antibodies, single domain antibodies (abbreviated "sdAb") (either VL or VH), camelid VHH domains, and multi-specific antibodies formed from antibody fragments.

[0139] The term "scFv" refers to a fusion protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single polypeptide chain, and wherein the scFv retains the specificity of the intact antibody from which it is derived.

[0140] "Heavy chain variable region" or "VH" (or, in the case of single domain antibodies, *e.g.*, nanobodies, "VHH") with regard to an antibody refers to the fragment of the heavy chain that contains three CDRs interposed between flanking stretches known as framework regions, these framework regions are generally more highly conserved than the CDRs and form a scaffold to support the CDRs.

[0141] Unless specified, as used herein a scFv may have the VL and VH variable regions in either order, *e.g.*, with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

[0142] The term "antibody light chain," refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa ("K") and lambda ("λ") light chains refer to the two major antibody light chain isotypes.

[0143] The term "recombinant antibody" refers to an antibody that is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage or yeast expression system. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the

DNA or amino acid sequence has been obtained using recombinant DNA or amino acid sequence technology which is available and well known in the art.

[0144] In some embodiments, for example those embodiments wherein the receptor comprises a first and a second polypeptide, the antigen-binding domain is isolated or derived from a T cell receptor (TCR) extracellular domain or an antibody.

[0145] In preferred embodiments, the polypeptide comprises antigen-binding domain, *e.g.*, an antigen-binding domain other than the LILRB1 antigen-binding protein. An illustrative embodiments of receptor having a single antigen-binding domain is depicted in **FIG. 1**. The disclosure contemplated chimeric antigen receptors have two, three, four or more antigen-binding domains. The antigen-binding domains may be provided on the same or a different chain of the chimeric antigen receptor. In embodiments, the chimeric antigen receptor is a DARIC as described, for example in Leung et al. *JCI Insight.* 2019 Jun 6; 4(11):e124430, WO2015017214A1; and WO2017156484A1.

[0146] In some embodiments, the receptor is an inhibitory chimeric antigen receptor (iCAR). Various methods and composition suitable for use with the embodiments disclosure herein include those provided in US2018/0044399A1; WO2018148454A1; and WO2017087723A1, each of which is incorporated herein for all purposes.

[0147] In some embodiments, the antigen-binding domain comprises a single chain variable fragment (scFv).

[0148] In some embodiments, the receptor comprises a second polypeptide. The disclosure provides receptors having two polypeptides each having a part of a ligand-binding domain (*e.g.* cognates of a heterodimeric LDB, such as a TCRα/β- or Fab-based LBD) and each having an intracellular domain, as depicted in **FIG. 2A**. The disclosure further provides receptors having two polypeptides, each having a part of a ligand-binding domain (*e.g.* cognates of a heterodimeric LDB, such as a TCRα/β- or Fab-based LBD) and one part of the ligand binding domain is fused to a hinge or transmembrane domain, while the other part of the ligand binding domain has no intracellular domain, as depicted in **FIG. 2B**. Further variations include receptors where each polypeptide has a hinge domain, and where each polypeptide has a hinge and transmembrane domain. In some embodiments, the hinge domain is absent. In other embodiments, the hinge domain is a membrane proximal extracellular region (MPER), such as the LILRB1 D3D4 domain.

In any of the embodiments disclosed herein, the domains may be fused adjacent to one another with linkers between them.

[0149] In some embodiments, the first polypeptide comprises a first chain of an antibody and the second polypeptide comprise a second chain of said antibody.

[0150] In some embodiments, the receptor comprises a Fab fragment of an antibody. In embodiments, an antigen-binding fragment of the heavy chain of the antibody, and the second polypeptide comprises an antigen-binding fragment of the light chain of the antibody. In embodiments, the first polypeptide comprises an antigen-binding fragment of the light chain of the antibody, and the second polypeptide comprises an antigen-binding fragment of the heavy chain of the antibody.

[0151] In some embodiments, the first polypeptide comprises a first chain of a T-cell receptor (TCR) and the second polypeptide comprises a second chain of said TCR. In embodiments, the receptor comprises an extracellular fragment of a T cell receptor (TCR). In embodiments, the first polypeptide comprises an antigen-binding fragment of the alpha chain of the TCR, and the second polypeptide comprises an antigen-binding fragment of the beta chain of the TCR. In some embodiments, the first polypeptide comprises an antigen-binding fragment of the beta chain of the TCR, and the second polypeptide comprises an antigen-binding fragment of the alpha chain of the TCR.

[0152] In some embodiments, the receptor comprises a single-chain TCR, such as, without limitation, those disclosed in WO2017091905A1.

Illustrative Antigen-Binding Domains

[0153] Various single variable domains known in the art or disclosed herein are suitable for use in embodiments. Such scFv's include, for example and without limitation the following mouse and humanized scFv antibodies that bind HLA-A*02 in a peptide-independent way (complementarity determining regions underlined):

C-001765

MMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRFSG VPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPRTSGGGTKLEIKGGGGSGGGG SGGGGSGGQVQLQQSGPELVKPGASVRISCKASGYTFTSYHIHWVKQRPGQGLEWIGWI YPGNVNTEYNEKFKGKATLTADKSSSTAYMHLSSLTSEDSAVYFCAREEITYAMDYWG QGTSVTVSSYG (SEQ ID NO: 35); or

DVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPRTSGGGTKLEIKGGGGSGG GGSGGGGSGGQVQLQQSGPELVKPGASVRISCKASGYTFTSYHIHWVKQRPGQGLEWI GWIYPGNVNTEYNEKFKGKATLTADKSSSTAYMHLSSLTSEDSAVYFCAREEITYAMD YWGQGTSVTVSS (SEQ ID NO: 125, the corresponding polynucleotide sequence is provided as SEQ ID NO: 127)

C-002159
QLVQSGAEVKKPGSSVKVSCKASGYTFTSYHIHWVRQAPGQGLEWMGWIYPGNVNTE YNEKFKGKATITADKSTSTAYMELSSLRSEDTAVYYCAREEITYAMDYWGQGTTVTVS SGGGGSGGGGSGGGGSGGEIVLTQSPGTLSLSPGERATLSCRSSQSIVHSNGNTYLEWYQ QKPGQAPRLLIYKVSNRFSGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCFQGSHVPRTF GGGTKVEIK (SEQ ID NO: 36)

C-002160
QLVQSGAEVKKPGSSVKVSCKASGYTFTSYHIHWVRQAPGQGLEWMGWIYPGNVNTE YNEKFKGKATITADKSTSTAYMELSSLRSEDTAVYYCAREEITYAMDYWGQGTTVTVS SGGGGSGGGGSGGGGSGGDIVMTQTPLSLPVTPGEPASISCRSSQSIVHSNGNTYLEWYL QKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPRT FGGGTKVEIK (SEQ ID NO: 37)

C-002161
QLVESGGGLVKPGGSLRLSCAASGYTFTSYHIHWVRQAPGKGLEWVGWIYPGNVNTEY NEKFKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCAREEITYAMDYWGQGTTVTVSS GGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRSSQSIVHSNGNTYLEWYQ QKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCFQGSHVPRTF GGGTKVEIK (SEQ ID NO: 38)

C-002162
QLVQSGAEVKKPGSSVKVSCKASGYTFTSYHIHWVRQAPGQGLEWIGWIYPGNVNTEY NEKFKGKATITADESTNTAYMELSSLRSEDTAVYYCAREEITYAMDYWGQGTLVTVSS GGGGSGGGGSGGGGSGGDIQMTQSPSTLSASVGDRVTITCRSSQSIVHSNGNTYLEWYQ QKPGKAPKLLIYKVSNRFSGVPARFSGSGSGTEFTLTISSLQPDDFATYYCFQGSHVPRTF GQGTKVEVK (SEQ ID NO: 39)

C-002163
QLVQSGAEVKKPGSSVKVSCKASGYTFTSYHMHWVRQAPGQGLEWIGYIYPGNVNTE YNEKFKGKATLTADKSTNTAYMELSSLRSEDTAVYFCAREEITYAMDYWGQGTLVTVS

SGGGGSGGGGSGGGGSGGDVQMTQSPSTLSASVGDRVTITCSSSQSIVHSNGNTYMEW
YQQKPGKAPKLLIYKVSNRFSGVPDRFSGSGSGTEFTLTISSLQPDDFATYYCHQGSHVP
RTFGQGTKVEVK (SEQ ID NO: 40)

C-002164
QVQLQQSGPELVKPGASVKMSCKASGYTFTSYHIQWVKQRPGQGLEWIGWIYPGDGST
QYNEKFKGKTTLTADKSSSTAYMLLSSLTSEDSAIYFCAREGTYYAMDYWGQGTSVTV
SSGGGGSGGGGSGGGGSGGDVLMTQTPLSLPVSLGDQVSISCRSSQSIVHSNGNTYLEW
YLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVP
RTFGGGTKLEIK (SEQ ID NO: 41)

C-002165
QLQLQESGPGLVKPSETLSLTCTVSGYTFTSYHIQWIRQPPGKGLEWIGWIYPGDGSTQY
NEKFKGRATISVDTSKNQFSLNLDSVSAADTAIYYCAREGTYYAMDYWGKGSTVTVSS
GGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRSSQSIVHSNGNTYLEWYQ
QKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCFQGSHVPRTF
GPGTKVDIK (SEQ ID NO: 42)

C-002166
EVQLVQSGAELKKPGSSVKVSCKASGYTFTSYHIQWVKQAPGQGLEWIGWIYPGDGST
QYNEKFKGKATLTVDKSTNTAYMELSSLRSEDTAVYYCAREGTYYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSGGDIQMTQSPSTLSASVGDRVTITCRSSQSIVHSNGNTYLE
WYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCFQGSHV
PRTFGQGTKVEVK (SEQ ID NO: 43)

C-002167
QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYHIQWVRQAPGQGLEWMGWIYPGDGS
TQYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCAREGTYYAMDYWGQGTTV
TVSSGGGGSGGGGSGGGGSGGEIVLTQSPGTLSLSPGERATLSCRSSQSIVHSNGNTYLE
WYQQKPGQAPRLLIYKVSNRFSGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCFQGSHV
PRTFGGGTKVEIK (SEQ ID NO: 44)

C-002168
QVTLKQSGAEVKKPGSSVKVSCTASGYTFTSYHVSWVRQAPGQGLEWLGRIYPGDGST
QYNEKFKGKVTITADKSMDTSFMELTSLTSEDTAVYYCAREGTYYAMDLWGQGTLVT
VSSGGGGSGGGGSGGGGSGGEIVLTQSPGTLSLSPGERATLSCRSSQSIVHSNGNTYLAW
YQQKPGQAPRLLISKVSNRFSGVPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSHVP
RTFGGGTKVEIK (SEQ ID NO: 45)

C-002169
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYHMHWVRQAPGQRLEWMGWIYPGDG STQYNEKFKGKVTITRDTSASTAYMELSSLRSEDTAVYYCAREGTYYAMDYWGQGTLV TVSSGGGGSGGGGSGGGGSGGDIVMTQTPLSLPVTPGEPASISCRSSQSIVHSNGNTYLD WYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGSH VPRTFGGGTKVEIK (SEQ ID NO: 46)

CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
RSSQSIVH SNGNTYLE (SEQ ID NO: 22)	KVSNRFSG VPDR (SEQ ID NO: 23)	FQGSHVPR T (SEQ ID NO: 24)	ASGYTFTS YHIH (SEQ ID NO: 25)	WIYPGNVN TEYNEKFK GK (SEQ ID NO: 26)	EEITYAMD Y (SEQ ID NO: 27)
RSSQSIVH SNGNTYLD (SEQ ID NO: 28)	KVSNRFSG VPDR (SEQ ID NO: 29)	MQGSHVPR T (SEQ ID NO: 30)	SGYTFTSY HMH (SEQ ID NO: 31)	WIYPGDGS TQYNEKFK G (SEQ ID NO: 32	EGTYYAM DY (SEQ ID NO: 33)

[0154] In some embodiments, the scFv comprises the complementarity determined regions (CDRs) of any one of SEQ ID NOS: 22-33. In some embodiments, the scFv comprises a sequence at least 95% identical to any one of SEQ ID NOS: 22-33. In some embodiments, the scFv comprises a sequence identical to any one of SEQ ID NOS: 22-33. In some embodiments, the heavy chain of the antibody comprises the heavy chain CDRs of any one of SEQ ID NOS: 25-27 or 31-33, and the light chain of the antibody comprises the light chain CDRs of any one of SEQ ID NOS: 22-24 or 28-30. In some embodiments, the heavy chain of the antibody comprises a sequence at least 95% identical to the heavy chain portion of any one of SEQ ID NOS: 35-46 or 125, and wherein the light chain of the antibody comprises a sequence at least 95% identical to the light chain portion of any one of SEQ ID NOS: 35-46 or 125. In some embodiments, the heavy chain comprises all of SEQ ID NOS: 25-27, and the light chain comprises all of SEQ ID NOS: 22-24. In some embodiments, the heavy chain comprises all of SEQ ID NOS: 31-33, and the light chain comprises all of SEQ ID NOS: 28-30.

[0155] In some embodiments, the heavy chain of the antibody comprises a sequence identical to the heavy chain portion of any one of SEQ ID NOS: 35-46 or 125, and wherein the light chain

of the antibody comprises a sequence identical to the light chain portion of any one of SEQ ID NOS: 35-46 or 125.

[0156] In some embodiments, the ScFv comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical or identical to any one of SEQ ID NOS: 35-46 or 125.

B- and T-lymphocyte attenuator (BTLA) Domains

[0157] In some embodiments, the polypeptide comprises a B- and T-lymphocyte attenuator (BTLA) hinge domain, transmembrane domain, intracellular domain or a functional variant, derivative or combination thereof.

[0158] In some embodiments, the polypeptide comprises a BTLA intracellular domain. In some embodiments, the BTLA intracellular domain comprises a sequence of RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQ EGSEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAPTEYASICVRS (SEQ ID NO: 87). In some embodiments, the BTLA intracellular domain comprises SEQ ID NO: 87, or a sequence with at least 95% identity thereto. In some embodiments, the BTLA intracellular domain consists essentially SEQ ID NO: 87.

[0159] In some embodiments, the BTLA transmembrane domain and intracellular domain comprises a sequence at least 95% identical to a sequence of LLPLGGLPLLITTCFCLFCCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQ VLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKE APTEYASICVRS (SEQ ID NO: 88). In some embodiments, the BTLA transmembrane domain and intracellular domain comprises or consists essentially of a sequence of SEQ ID NO: 88.

[0160] *Signal Peptides*

[0161] In some embodiments, the polypeptide comprises a signal peptide. For example, the polypeptide comprises a VK1 signal peptide. In some embodiments, the signal peptide is an N-terminal signal peptide. In some embodiments, the signal peptide comprises a sequence at least 95% identical to a sequence of MDMRVPAQLLGLLLLWLRGARC (SEQ ID NO: 128). In some embodiments, the signal peptide comprises a sequence of MDMRVPAQLLGLLLLWLRGARC (SEQ ID NO: 128). In some embodiments, the signal peptide is encoded by a sequence at least 95% identical to a sequence of

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTACTCTGGCTCCGAGGT GCCAGATGT (SEQ ID NO: 129), or a sequence identical thereto.

Antigens

[0162] The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen for the LILRB1-based receptors described herein. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. Moreover, a skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a fluid with other biological components.

[0163] In some embodiments, the antigen-binding domain specifically binds to a target selected from etiolate receptor, αvββ integrin, TNF receptor superfamily member 17 (BCMA), CD276 molecule (B7-H3), natural killer cell cytotoxicity receptor 3 ligand 1 (B7-H6), carbonic anhydrase 9 (CAIX), CD19 molecule (CD19), membrane spanning 4-domains A1 (CD20), CD22 molecule (CD22), TNF receptor superfamily member 8 (CD30), CD33 molecule (CD33), CD37 molecule (CD37), CD44 molecule (CD44), CD44v6, CD44v7/8, CD70 molecule (CD70), interleukin 3 receptor subunit alpha (CD123), syndecan 1 (CD138), L1 cell adhesion molecule (CD171), CEA cell adhesion molecule (CEA), delta like canonical Notch ligand 4 (DLL4), epithelial cell adhesion molecule (EGP-2), epithelial cell adhesion molecule (EGP-40), chondroitin sulfate proteoglycan 4 (CSPG4), epidermal growth factor receptor (EGFR), EGFR family including ErbB2 (HER2), EGFRvIII, epithelial cell adhesion molecule (EPCAM), EPH receptor A2 (EphA2), EpCAM, fibroblast activation protein alpha (FAP), folate receptor alpha (FBP), fetal acetylcholine receptor, frizzled class receptor 7 (Fzd7), diganglioside GD2 (GD2), ganglioside GD3 (GD3), Glypican-3 (GPC3), trophoblast glycoprotein (h5T4), interleukin 11 receptor subunit alpha (IL-11R), interleukin 13 receptor subunit alpha 2 (IL13R-a2), kinase insert domain receptor (KDR), κ light chain, λ light chain, LeY, L1 cell adhesion molecule (L1 CAM),

MAGE-A1, mesothelin, MHC presented peptides, mucin 1, cell surface associated (MUC1), mucin 16, cell surface associated (MUC16), neural cell adhesion molecule 1 (NCAM), killer cell lectin like receptor K1 (NKG2D) ligands, Notch1, Notch2/3, NY-ESO-1, PRAME nuclear receptor transcriptional regulator (PRAME), prostate stem cell antigen (PSCA), folate hydrolase 1 (PSMA), Survivin, TAG-72, TEMs, telomerase reverse transcriptase (TERT), kinase insert domain receptor (VEGFR2), and receptor tyrosine kinase like orphan receptor 1(ROR1).

[0164] In some embodiments, the antigen-binding domain specifically binds to a target selected from CD33, CD38, a human leukocyte antigen (HLA), an organ specific antigen, a blood-brain barrier specific antigen, an Epithelial-mesenchymal transition (EMT) antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), cell surface carbohydrate and mucin type O-glycan.

[0165] In some embodiments, the extracellular domain of the LILRB1-based receptors described herein comprises an antigen-binding domain specific to an antigen that is lost through loss of heterozygosity in cells of a subject.

[0166] As used herein, "loss of heterozygosity (LOH)" refers to a genetic change that occurs at high frequency in cancers, whereby one of the two alleles is deleted, leaving a single mono-allelic (hemizygous) locus.

[0167] In some embodiments, the LILRB1-based receptor comprises an antigen-binding domain specific to a minor histocompatibility antigen (MiHA). MiHAs are peptides derived from proteins that contain nonsynonymous differences between alleles and are displayed by common HLA alleles. The non-synonymous differences can arise from SNPs, deletions, frameshift mutations or insertions in the coding sequence of the gene encoding the MiHA. Exemplary MiHAs can be about 9-12 amino acids in length and can bind to MHC class I and MHC class II proteins. Binding of the TCR to the MHC complex displaying the MiHA can activate T cells. The genetic and immunological properties of MiHAs will be known to the person of ordinary skill in the art, and specific MiHas described in PCT/US2020/045228, the contents of which are incorporated by reference.

[0168] In some embodiments, the LILRB1-based receptor comprises an antigen-binding domain specific to an antigen that is lost in cancer cells of a subject through loss of Y chromosome.

[0169] In some embodiments, the LILRB1-based receptor comprises an antigen-binding domain specific to an HLA class I allele. The major histocompatibility complex (MHC) class I is a protein complex that displays antigens to cells of the immune system, triggering immune response. The Human Leukocyte Antigens (HLAs) corresponding to MHC class I are HLA-A, HLA-B and HLA-C. HLA-E is known in the art as a non-classical MHC class I molecule. In some embodiments, the antigen for the LILR1-based receptor comprises an HLA class I allele. In some embodiments, allele of HLA class I is lost in a target cell, such as a cancer cell, through loss of heterozygosity (LOH).

[0170] HLA-A is a group of human leukocyte antigens (HLA) of the major histocompatibility complex (MHC) that are encoded by the HLA-A locus. HLA-A is one of three major types of human MHC class I cell surface receptors. The receptor is a heterodimer comprising a heavy α chain and smaller β chain. The α chain is encoded by a variant of HLA-A, while the β chain (β2-microglobulin) is invariant. There are several thousand HLA-A variants, all of which fall within the scope of the instant disclosure.

[0171] In some embodiments, the LILRB1-based receptor comprises an antigen-binding domain specific to an HLA-B allele. The HLA-B gene has many possible variations (alleles). Hundreds of versions (alleles) of the HLA-B gene are known, each of which is given a particular number (such as HLA-B27).

[0172] In some embodiments, the LILRB1-based receptor comprises an antigen-binding domain specific to an HLA-C allele. HLA-C belongs to the HLA class I heavy chain paralogues. This class I molecule is a heterodimer consisting of a heavy chain and a light chain (beta-2 microglobulin).

[0173] In some embodiments, the HLA class I allele has broad or ubiquitous RNA expression.

[0174] In some embodiments, the HLA class I allele has a known, or generally high minor allele frequency.

[0175] In some embodiments, the HLA class I allele does not require a peptide-MHC antigen, for example when the HLA class I allele is recognized by a pan-HLA ligand binding domain.

[0176] In some embodiments, the LILRB1-based receptor comprises an antigen-binding domain specific to an HLA-A allele. In some embodiments the HLA-A allele comprises HLA-A*02. Various single variable domains known in the art or disclosed herein that bind to and recognize HLA-A*02 are suitable for use in embodiments, and are described herein.

[0177] In some embodiments, the antigen-binding domain specifically binds to an HLA-A*02 antigen. In some embodiments, the antigen-binding domain specifically binds to an HLA-A*02 antigen in a peptide-independent manner.

Polynucleotides and Vectors

[0178] In other aspects, the disclosure provides polynucleotides comprising a nucleic acid sequence encoding receptors of the disclosure. In some embodiments, the polynucleotides encode one or more of an LILRB1 hinge domain, an LILRB1 transmembrane domain and an LILRB1 intracellular domain or a functional derivative or fragment thereof.

[0179] In some embodiments, the polynucleotide comprises a nucleic acid sequence that encodes a polypeptide that is at least 95% identical to any one of SEQ ID NOS: 1-7 or 12-21. In some embodiments, the polynucleotide comprises a nucleic acid sequence that encodes a polypeptide that is at least 95% identical to any one of SEQ ID NOS: 47-71, 77-79, 89-92, 120 or 122. In some embodiments, the polynucleotide comprises a nucleic acid sequence that encodes a polypeptide that is at least 95% identical to the heavy chain portion or the light chain portion of any one of SEQ ID NOS: 35-46 or 125. In some embodiments, the polynucleotide comprises a nucleic acid sequence that encodes a polypeptide that is at least 95% identical to the heavy chain portion or the light chain portion of any one of SEQ ID NOS: 35, 39, 46 or 125. In some embodiments, the polynucleotide comprises a nucleic acid sequence that encodes a polypeptide that is identical to the heavy chain portion or the light chain portion of any one of SEQ ID NOS: 35, 39, 46 or 125. In another aspect, the disclosure provides vectors comprising the polynucleotides encoding receptors of the disclosure.

[0180] In some embodiments, the polynucleotide comprises a sequence at least 95% identical to SEQ ID NO: 121 or 123. In some embodiments, the polynucleotide comprises SEQ ID NO: 121 or 123.

[0181] In some embodiments, the polynucleotide comprises a sequence of a LILRB1 hinge, transmembrane and intracellular domain. In some embodiments, the polynucleotide comprises a sequence at least 95% identical to SEQ ID NO: 126. In some embodiments, the polynucleotide comprises a sequence of SEQ ID NO: 126.

[0182] Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its

propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity.

[0183] The expression of natural or synthetic nucleic acids encoding receptors is typically achieved by operably linking a nucleic acid encoding receptor or portions thereof to a promoter, and incorporating the construct into an expression vector. The vectors can be suitable for replication and integration eukaryotes. Typical cloning vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

[0184] The polynucleotides encoding the receptors can be cloned into a number of types of vectors. For example, the polynucleotides can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

[0185] Further, the expression vector may be provided to cells, such as immune cells, in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (*e.g.*, WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

[0186] A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either *in vivo* or *ex vivo*. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art. In one embodiment, lentivirus vectors are used.

[0187] In some embodiments, the vector comprises a promoter. Vectors can also include additional regulatory elements. Additional regulatory elements, e.g., enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 basepairs (bp) upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription.

[0188] One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. Another example of a suitable promoter is Elongation Growth Factor-1α (EF-1α). However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the invention should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the invention. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

[0189] In order to assess the expression of receptor the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co-transfection procedure. Both selectable markers and

reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

[0190] Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, e.g., mammalian, bacterial, yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

[0191] Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York). One method for the introduction of a polynucleotide into a host cell is calcium phosphate transfection.

[0192] Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, e.g., human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

[0193] Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g., an artificial membrane vesicle).

[0194] Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present invention, in order to confirm the presence of the recombinant DNA sequence in the host cell, a variety of assays may be performed. Such assays include, for example, "molecular biological" assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the presence or absence of a particular peptide, e.g., by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the invention.

Engineered cells

[0195] In another aspect, the disclosure provides immune cells comprising a nucleic acid sequence or vector encoding receptors of the disclosure and/or expressing receptors of the disclosure.

[0196] In embodiments, immune cell activation is reduced when the cell is contacted with the antigen of the LILRB1 based receptors of the disclosure, or a cell expressing the antigen on its surface. In embodiments, immune cell activation comprises expression of a gene operatively linked to an NFAT promoter. Immune cell activation and/or inhibition of activation can be measured by various other methods known in the art. In some embodiments, the immune cell comprises an additional exogenous receptor, for example an activator receptor such as a chimeric antigen receptor (CAR) or TCR.

[0197] In embodiments, the immune cell is a T cell.

[0198] As used herein, the term "immune cell" refers to a cell involved in the innate or adaptive (acquired) immune systems. Exemplary innate immune cells include phagocytic cells such as neutrophils, monocytes and macrophages, Natural Killer (NK) cells, polymophonuclear leukocytes such as neutrophils eosinophils and basophils and mononuclear cells such as monocytes, macrophages and mast cells. Immune cells with roles in acquired immunity include lymphocytes such as T-cells and B-cells.

[0199] As used herein, a "T-cell" refers to a type of lymphocyte that originates from a bone marrow precursor that develops in the thymus gland. There are several distinct types of T-cells which develop upon migration to the thymus, which include, helper CD4+ T-cells, cytotoxic CD8+ T cells, memory T cells, regulatory CD4+ T-cells and stem memory T-cells. Different types of T-cells can be distinguished by the ordinarily skilled artisan based on their expression of markers. Methods of distinguishing between T-cell types will be readily apparent to the ordinarily skilled artisan.

Method of making engineered cells

[0200] In another aspect, the disclosure provides methods comprising introducing a polynucleotide of the disclosure into cells, optionally using vectors of the disclosure. In

embodiments, the resulting cell expresses LILRB1 based receptor encoded by the polynucleotide. In embodiments, the cell is an immune cell. In embodiments, the immune cell is a T cell.

[0201] Methods of transforming populations of immune cells, such as T cells, with the vectors of the instant disclosure will be readily apparent to the person of ordinary skill in the art. For example, CD3+ T cells can be isolated from PBMCs using a CD3+ T cell negative isolation kit (Miltenyi), according to manufacturer's instructions. T cells can be cultured at a density of 1 x 10^6 cells/mL in X-Vivo 15 media supplemented with 5% human A/B serum and 1% Pen/strep in the presence of CD3/28 Dynabeads (1:1 cell to bead ratio) and 300 Units/mL of IL-2 (Miltenyi). After 2 days, T cells can be transduced with viral vectors, such as lentiviral vectors using methods known in the art. In some embodiments, the viral vector is transduced at a multiplicity of infection (MOI) of 5. Cells can then be cultured in IL-2 or other cytokines such as combinations of IL-7/15/21 for an additional 5 days prior to enrichment. Methods of isolating and culturing other populations of immune cells, such as B cells, or other populations of T cells, will be readily apparent to the person of ordinary skill in the art. Although this method outlines a potential approach it should be noted that these methodologies are rapidly evolving. For example excellent viral transduction of peripheral blood mononuclear cells can be achieved after 5 days of growth to generate a >99% CD3+ highly transduced cell population.

[0202] Methods of activating and culturing populations of T cells comprising the receptors, polynucleotides or vectors of the disclosure will be readily apparent to the person of ordinary skill in the art.

[0203] Whether prior to or after genetic modification, T cells can be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041, 10040846; and U.S. Pat. Appl. Pub. No. 2006/0121005.

[0204] In some embodiments, T cells of the instant disclosure are expanded and activated in vitro. Generally, the T cells of the instant disclosure are expanded in vitro by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a co-stimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the

accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

[0205] In some embodiments, the primary stimulatory signal and the co-stimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (i.e., in "cis" formation) or to separate surfaces (i.e., in "trans" formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In some embodiments, the agent providing the co-stimulatory signal is bound to a cell surface and the agent providing the primary activation signal is in solution or coupled to a surface. In certain embodiments, both agents can be in solution. In another embodiment, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for example, U.S. Patent Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present invention.

[0206] In some embodiments, the two agents are immobilized on beads, either on the same bead, i.e., "cis," or to separate beads, i.e., "trans." By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the co-stimulatory signal is an anti-CD28 antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In one embodiment, a 1:1 ratio of each antibody bound to the beads for CD4+ T cell expansion and T cell growth is used. In some embodiments, the ratio of CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In one aspect of the present invention, more anti-CD28 antibody is bound to the particles than anti-CD3 antibody, i.e., the ratio of CD3:CD28 is less than one. In certain embodiments of the invention, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1.

[0207] Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In certain embodiments the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values in-between and in further embodiments the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. In some embodiments, a ratio of 1:1 cells to beads is used. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present invention. In particular, ratios will vary depending on particle size and on cell size and type.

[0208] In further embodiments of the present invention, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In an alternative embodiment, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In a further embodiment, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

[0209] By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached to contact the T cells. In one embodiment the cells (for example, CD4+ T cells) and beads (for example, DYNABEADS CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer. Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. In certain embodiments, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and particles. For example, in one embodiment, a concentration of about 2 billion cells/ml is used. In another embodiment, greater than 100 million cells/ml is used. In a further embodiment, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet another embodiment, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further embodiments, concentrations of 125 or 150 million cells/ml can be used. In some embodiments, cells that are cultured at a density of $1x10^6$ cells/mL are used.

[0210] In some embodiments, the mixture may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. In another embodiment, the beads and T

cells are cultured together for 2-3 days. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 15, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, and TNF-α or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, AIM-V, DMEM, MEM, α-MEM, F-12, X-Vivo 15, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. In some embodiments, the media comprises X-VIVO-15 media supplemented with 5% human A/B serum, 1% penicillin/streptomycin (pen/strep) and 300 Units/ml of IL-2 (Miltenyi).

[0211] The T cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (*e.g.*, 37° C.) and atmosphere (e.g., air plus 5% CO2).

[0212] In some embodiments, the T cells comprising receptors of the disclosure are autologous. Prior to expansion and genetic modification, a source of T cells is obtained from a subject. Immune cells such as T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art, may be used. In certain embodiments of the present invention, T cells can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as Ficoll™ separation.

[0213] In some embodiments, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In some embodiments, the cells collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent processing steps. In some embodiments, the cells are washed with phosphate buffered saline (PBS). In alternative embodiments, the wash solution lacks calcium and may lack magnesium or may lack many if not

all divalent cations. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the Haemonetics Cell Saver 5) according to the manufacturer's instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca2+-free, Mg2+-free PBS, PlasmaLyte A, or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

[0214] In some embodiments, immune cells such as T cells are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLL™ gradient or by counterflow centrifugal elutriation. Specific subpopulations of immune cells, such as T cells, B cells, or CD4+ T cells can be further isolated by positive or negative selection techniques. For example, in one embodiment, T cells are isolated by incubation with anti-CD4 -conjugated beads, for a time period sufficient for positive selection of the desired T cells.

[0215] Enrichment of an immune cell population, such as a T cell population, by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immune-adherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD 14, CD20, CD 11b, CD 16, HLA-DR, and CD8.

[0216] For isolation of a desired population of immune cells by positive or negative selection, the concentration of cells and surface (e.g., particles such as beads) can be varied. In certain embodiments, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and beads.

[0217] In some embodiments, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10° C or at room temperature.

[0218] T cells for stimulation, or PBMCs from which immune cells such as T cells are isolated, can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and

subsequent thaw step provides a more uniform product by removing granulocytes and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to −80° C. at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at −20° C. or in liquid nitrogen.

Assaying Signaling

[0219] In some embodiments, immune cell activation is reduced when the cell is contacted with the antigen corresponding to the LILRB1 based receptor of the disclosure, or a cell expressing the antigen on its surface. In some embodiments, immune cell activation comprises expression of a gene operatively linked to an NFAT promoter. Nuclear factor of activated T-cells (NFAT) is a family of transcription factors shown to be important in immune response. The NFAT transcription factor family consists of five members NFATc1, NFATc2, NFATc3, NFATc4, and NFAT5. NFAT plays a role in regulating inflammation.

[0220] As used herein, an NFAT promoter is a promoter that is regulated (i.e., activated or repressed) when NFAT is expressed in a cell. NFAT target promoters are described in Badran, B. M. et al.(2002) J. Biological Chemistry Vol. 277: 47136-47148, and contain NFAT consensus sequences such as GGAAA.

[0221] Methods of assessing the effects of receptor activation on gene expression are known in the art, and include the use of reporter genes, whose expression can be quantified. Reporter genes are used for identifying potentially transfected or transduced cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells.

Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (e.g., Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5′ flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription. In exemplary embodiments, an NFAT promoter operably linked to a reporter gene is used to evaluate the expression of the receptors of the disclosure on NFAT signaling.

Pharmaceutical Compositions

[0222] The disclosure provides pharmaceutical compositions comprising immune cells comprising the LILRB1-based receptors of the disclosure a pharmaceutically acceptable diluent, carrier or excipient.

[0223] Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; and preservatives.

Methods of Treating Disease

[0224] Provided herein are methods of treating a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition comprising a plurality of immune cells comprising the LILRB1-based receptors described herein. In some embodiments, the immune cells further comprise an activator receptor, such as an activator CAR or TCR.

[0225] Additional methods of treating subjects, and activator receptors combination combined with inhibitory receptors, are described in PCT/US2020/045228, the contents of which are incorporated by reference herein in their entirety.

[0226] In some embodiments, the subject in need thereof has cancer. In some embodiments, the methods of treating the subject comprise administering to the subject a plurality of immune cells comprising the LILRB1-receptors of the disclosure. In some embodiments, the plurality of immune cells further comprises an activator receptor, such as a CAR or a TCR. In some

embodiments, the CAR or TCR comprises an antigen-binding domain specific to a cancer antigen. Activator receptors specific for cancer antigens can comprise antigen-binding domains isolated or derived from any antibody or antigen-binding domain known in the art, including, but not limited to, urelumab, utomilumab, oleclumab, naptumomab, ascrinvacumab, tacatuzumab, nesvacumab, vanucizumab, belimumab, tabalumab, tibulizumab, belantamab, igovomab, oregovomab, sofituzumab, mogamulizumab, talacotuzumab, tavolimab, vonlerolizumab, ipilimumab, duvortuxizumab, blinatumomab, coltuximab, denintuzumab, inebilizumab, loncastuximab, taplitumomab, ibritumomab, obinutuzumab, ocaratuzumab, ocrelizumab, ofatumumab, rituximab, tositumomab, veltuzumab, samalizumab, bectumomab, epratuzumab, inotuzumab, moxetumomab, pinatuzumab, gomiliximab, lumiliximab, camidanlumab, basiliximab, inolimomab, daclizumab, varlilumab, enoblituzumab, omburtamab, brentuximab, iratumumab, gemtuzumab, lintuzumab, vadastuximab, lilotomab, otlertuzumab, tetulomab, daratumumab, isatuximab, bivatuzumab, abituzumab, intetumumab, lorvotuzumab, itolizumab, cusatuzumab, vorsetuzumab, milatuzumab. polatuzumab, iladatuzumab, galixima, altumomab, arcitumomab, labetuzumab, cibisatamab, zolbetuximab, lacnotuzumab, cabiralizumab, emactuzumab, gimsilumab,lenzilumab, otilimab, mavrilimumab, tremelimumab, ulocuplumab, tepoditamab, rovalpituzumab, demcizumab, drozitumab, parsatuzumab, cetuximab, depatuxizumab, futuximab, imgatuzumab, laprituximab, matuzumab, necitumumab, nimotuzumab, panitumumab, zalutumumab, modotuximab, amivantamab, tomuzotuximab, losatuxizumab, adecatumumab, citatuzumab, edrecolomab, oportuzumab, solitomab, tucotuzumab, catumaxomab, ifabotuzumab, duligotuzumab, elgemtumab, lumretuzumab, patritumab, seribantumab, zenocutuzumab, aprutumab, bemarituzumab, vantictumab, dinutuximab, ecromeximab, mitumomab, codrituzumab, glembatumumab, zatuximab, ertumaxomab, margetuximab, timigutuzumab, gancotamab, pertuzumab, trastuzumab, ficlatuzumab, rilotumumab, telisotuzumab, emibetuzumab, cixutumumab, dalotuzumab, figitumumab, ganitumab, robatumumab, teprotumumab, flotetuzumab, bermekimab, cergutuzumab, volociximab, etaracizumab, relatlimab, carlumab, amatuximab, clivatuzumab, gatipotuzumab, pemtumomab, cantuzumab, pankomab, racotumomab, brontictuzumab, tarextumabm vesencumab, camrelizumab, cetrelimab, nivolumab,pembrolizumab, pidilizumab, cemiplimab, spartalizumab, atezolizumab, avelumab, durvalumab, cirmtuzumab, tenatumomab, fresolimumab, brolucizumab, bevacizumab, ranibizumab, varisacumab, faricimab, icrucumab, alacizumab, and ramucirumab.

[0227] In some embodiments, the LILRB1-based receptor of the disclosure comprises an antigen-binding domain specific to an antigen that is lost in the cancer cells through loss of heterozygosity. In some embodiments, the antigen is a minor histocompatibility antigen (MiHA). In some embodiments, the antigen is an HLA class I allele. In some embodiments, the HLA class I allele comprises HLA-A, HLA-B or HLA-C. In some embodiments, the HLA class I allele comprises HLA-E. In some embodiments, the HLA class I allele is an HLA-A*02 allele. In some embodiments, the antigen is not expressed in the target cell due to loss of Y chromosome. In some embodiments, the antigen specific to the LILRB1-based receptor is an HLA-A*02 antigen.

[0228] In some embodiments, the subject in need thereof has cancer. Cancer is a disease in which abnormal cells divide without control and spread to nearby tissue. In some embodiments, the cancer comprises a liquid tumor or a solid tumor. Exemplary liquid tumors include leukemias and lymphomas. Further cancers that are liquid tumors can be those that occur, for example, in blood, bone marrow, and lymph nodes, and can include, for example, leukemia, myeloid leukemia, lymphocytic leukemia, lymphoma, Hodgkin's lymphoma, melanoma, and multiple myeloma. Leukemias include, for example, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), and hairy cell leukemia. Exemplary solid tumors include sarcomas and carcinomas. Cancers can arise in virtually an organ in the body, including blood, bone marrow, lung, breast, colon, bone, central nervous system, pancreas, prostate and ovary. Further cancers that are solid tumors include, for example, prostate cancer, testicular cancer, breast cancer, brain cancer, pancreatic cancer, colon cancer, thyroid cancer, stomach cancer, lung cancer, ovarian cancer, Kaposi's sarcoma, skin cancer, squamous cell skin cancer, renal cancer, head and neck cancers, throat cancer, squamous carcinomas that form on the moist mucosal linings of the nose, mouth, throat, bladder cancer, osteosarcoma, cervical cancer, endometrial cancer, esophageal cancer, liver cancer, and kidney cancer. In some embodiments, the condition treated by the methods described herein is metastasis of melanoma cells, prostate cancer cells, testicular cancer cells, breast cancer cells, brain cancer cells, pancreatic cancer cells, colon cancer cells, thyroid cancer cells, stomach cancer cells, lung cancer cells, ovarian cancer cells, Kaposi's sarcoma cells, skin cancer cells, renal cancer cells, head or neck cancer cells, throat cancer cells, squamous carcinoma cells, bladder cancer cells, osteosarcoma cells, cervical cancer cells, endometrial cancer cells, esophageal cancer cells, liver cancer cells, or kidney cancer cells.

[0229] Any cancer wherein a plurality of the cancer cells express the first, activator ligand and do not express the second, inhibitor ligand is envisaged as within the scope of the instant disclosure. For example, CEA positive cancers that can be treated using the methods described herein include colorectal cancer, pancreatic cancer, esophageal cancer, gastric cancer, lung adenocarcinoma, head and neck cancer, diffuse large B cell cancer or acute myeloid leukemia cancer.

[0230] Treating cancer can result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as "tumor regression". Preferably, after treatment, tumor size is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor size is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0231] Treating cancer can result in a reduction in tumor volume. Preferably, after treatment, tumor volume is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0232] Treating cancer results in a decrease in number of tumors. Preferably, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0233] Treating cancer can result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; more preferably, the

number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0234] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population receiving carrier alone. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0235] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0236] Treating cancer can result in increase in average survival time of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the average survival time is increased by more than 30 days; more

preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0237] Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving carrier alone. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present invention, or 1a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the mortality rate is decreased by more than 2%; more preferably, by more than 5%; more preferably, by more than 10%; and most preferably, by more than 25%. A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. A decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with an active compound.

[0238] Treating cancer can result in a decrease in tumor growth rate. Preferably, after treatment, tumor growth rate is reduced by at least 5% relative to number prior to treatment; more preferably, tumor growth rate is reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Tumor growth rate may be measured by any reproducible means of measurement. Tumor growth rate can be measured according to a change in tumor diameter per unit time.

[0239] Treating cancer can result in a decrease in tumor regrowth. Preferably, after treatment, tumor regrowth is less than 5%; more preferably, tumor regrowth is less than 10%; more preferably, less than 20%; more preferably, less than 30%; more preferably, less than 40%; more preferably, less than 50%; even more preferably, less than 50%; and most preferably, less than 75%. Tumor regrowth may be measured by any reproducible means of measurement. Tumor regrowth is measured, for example, by measuring an increase in the diameter of a tumor after a prior tumor shrinkage that followed treatment. A decrease in tumor regrowth is indicated by failure of tumors to reoccur after treatment has stopped.

[0240] Treating or preventing a cell proliferative disorder can result in a reduction in the rate of cellular proliferation. Preferably, after treatment, the rate of cellular proliferation is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. The rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

[0241] Treating or preventing a cell proliferative disorder can result in a reduction in the proportion of proliferating cells. Preferably, after treatment, the proportion of proliferating cells is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The proportion of proliferating cells may be measured by any reproducible means of measurement. Preferably, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample. The proportion of proliferating cells can be equivalent to the mitotic index.

[0242] Treating or preventing a cell proliferative disorder can result in a decrease in size of an area or zone of cellular proliferation. Preferably, after treatment, size of an area or zone of cellular proliferation is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of

measurement. The size of an area or zone of cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

[0243] Treating or preventing a cell proliferative disorder can result in a decrease in the number or proportion of cells having an abnormal appearance or morphology. Preferably, after treatment, the number of cells having an abnormal morphology is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. An abnormal cellular appearance or morphology may be measured by any reproducible means of measurement. An abnormal cellular morphology can be measured by microscopy, e.g., using an inverted tissue culture microscope. An abnormal cellular morphology can take the form of nuclear pleiomorphism.

Kits and Articles of Manufacture

[001] The disclosure provides kits and articles of manufacture comprising the polynucleotides and vectors encoding the receptors described herein. In some embodiments, the kit comprises articles such as vials, syringes and instructions for use.

[002] In some embodiments, the kit comprises a polynucleotide or vector comprising a sequence encoding one or more chimeric antigen receptors of the disclosure. For example, the polynucleotide or vector comprises a sequence one or more LILRB1 domains as described herein.

[003] In some embodiments, the kit comprises a plurality of immune cells comprising a chimeric antigen receptor as described herein. In some embodiments, the plurality of immune cells comprises a plurality of T cells.

Polypeptide Sequences for Elements of Illustrative Chimeric Antigen Receptors

Name	Sequence
LILRB1	MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVITQ GSPVTLRCQGGQETQEYRLYREKKTALWITRIPQELVKKG QFPIPSITWEHAGRYRCYYGSDTAGRSESSDPLELVVTGA YIKPTLSAQPSPVVNSGGNVILQCDSQVAFDGFSLCKEGED EHPQCLNSQPHARGSSRAIFSVGPVSPSRRWWYRCYAYDS NSPYEWSLPSDLLELLVLGVSKKPSLSVQPGPIVAPEETLT

	LQCGSDAGYNRFVLYKDGERDFLQLAGAQPQAGLSQANF TLGPVSRSYGGQYRCYGAHNLSSEWSAPSDPLDILIAGQF YDRVSLSVQPGPTVASGENVTLLCQSQGWMQTFLLTKEG AADDPWRLRSTYQSQKYQAEFPMGPVTSAHAGTYRC**YG SQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSGPE DQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLLLFLI LRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWR SSPAADAQEEN**LYAAV**KHTQPEDGVEMDTRSPHDEDPQA **VTYAEV**KHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQD**VTYAQ**LHSLTLRREATEPPPSQEGPSP AVP**SIYAT**LAIHPSQEGPSPAVPSIYATLAIH SEQ ID NO: 1
LILRB1 hinge-transmembrane-intracellular domain (SEQ ID NO: 126 is the polynucleotide sequence)	**YGSQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLG**VVIGILVAVILLLLLLLLL FLIL**RHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQ WRSSPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDEDP QAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDR QMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPS PAVPSIYATLAIH SEQ ID NO: 2
LILRB1 hinge-transmembrane-intracellular domain (w/o YGSQSSKPYLLTHPSD PLEL, SEQ ID NO: 18)	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LG**VVIGILVAVILLLLLLLLLFLIL**RHRRQGKHWTSTQRK ADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAV KHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMA SPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYA QLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH SEQ ID NO: 3
LILRB1 hinge domain	**YGSQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLG SEQ ID NO: 4
LILRB1 transmembrane domain	**VVIGILVAVILLLLLLLLLFLIL** SEQ ID NO: 5
LILRB1 intracellular domain	RHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWRS SPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDEDPQAV TYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQM DTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSPA VPSIYATLAIH SEQ ID NO: 7
ITIM1	NLYAAV SEQ ID NO: 8
ITIM2	VTYAEV SEQ ID NO: 9
ITIM3	VTYAQL

	SEQ ID NO: 10
ITIM4	SIYATL SEQ ID NO: 11
ITIM1-2	**NLYAAV**KHTQPEDGVEMDTRSPHDEDPQA**VTYAEV** SEQ ID NO: 12
ITIM2-3	**VTYAEV**KHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQD**VTYAQL** SEQ ID NO: 13
ITIM3-4	**VTYAQL**HSLTLRREATEPPPSQEGPSPAVP**SIYATL** SEQ ID NO: 14
ITIM1-3	**NLYAAV**KHTQPEDGVEMDTRSPHDEDPQA**VTYAEV**KHS RPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEA PQD**VTYAQL** SEQ ID NO: 15
ITIM2-4	**VTYAEV**KHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQD**VTYAQL**HSLTLRREATEPPPSQEGPSP AVP**SIYATL** SEQ ID NO: 16
ITIM1-4	**NLYAAV**KHTQPEDGVEMDTRSPHDEDPQA**VTYAEV**KHS RPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEA PQD**VTYAQL**HSLTLRREATEPPPSQEGPSPAVP**SIYATL** SEQ ID NO: 17
D3D4 domain	**YGSQSSKPYLLTHPSDPLEL** SEQ ID NO: 18
Short hinge	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LG SEQ ID NO: 19
Hinge (iTIM hinge)	YGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGP EDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 80)
Short hinge 2	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LGV (SEQ ID NO: 81)
Long hinge 1	AGSGGSGGSGGSPVPSTPPTPSPSTPPTPSPSGGSGNSSGSG GSPVPSTPPTPSPSTPPTPSPSASV (SEQ ID NO: 82)
Long hinge 2	AGSGGSGGSGGSPVPSTPPTNSSSTPPTPSPSPVPSTPPTNSS STPPTPSPSPVPSTPPTNSSSTPPTPSPSASV (SEQ ID NO: 83)
2X short hinge	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LGV (SEQ ID NO: 84)
Hinge (truncated)	TTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 93)
Hinge-transmembrane	**YGSQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLG**VVIGILVAVILLLLLLLLL FLIL**

	SEQ ID NO: 20
Transmembrane-intracellular domain.	**VVIGILVAVILLLLLLLLLFLIL**RHRRQGKHWTSTQRKA DFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVK HTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMAS PPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYA QLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH SEQ ID NO: 21

Polypeptide Sequences for Illustrative Chimeric Antigen Receptors

Name	**Sequence**
C563 (SEQ ID NO: 47)	QVQLQESGPGLVKPSDTLSLTCAVSGYSISSSNWWGWIRQ PPGKGLEWIGYIYYSGSTYYNPSLKSRVTMSVDTSKNQFS LKLSSVTAVDTAVYYCARIPFGDWWYFDLWGRGTLVTVS SGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTIT CRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQSYSFVLTFGGGTKV EIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
C1759 (SEQ ID NO: 48)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSFGSFRALPCVWSNSSDPLLVSVTGNPSSSWPSPTEPSS KSGICRHLHVLIGTSVVIFLFILLLFFLLYRWCSNKKNAAV MDQEPAGDRTVNRQDSDEQDPQEVTYAQLDHCVFIQRKI SRPSQRPKTPLTDTSVYTELPNAEPRSKVVSCPRAPQSGLE GVF
C1760 (SEQ ID NO: 49)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSFGSFRALPHAWSDPSDPLPVSVTGNSRNLHVLIGTSVV IIPFAILLFFLLHRWCANKKNAVVMDQEPAGNRTVNREDS DEQDPQEVTYAQLNHCVFTQRKITRPSQRPKTPPTDTSV
C1761 (SEQ ID NO: 50)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF

	ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGL QWRSSPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDE DPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEE DRQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEG PSPAVPSIYATLAIH
C1762 (SEQ ID NO: 51)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSTERRAEVPTAHPSPSPRPAGQFQTLVVGVVGGLLGSL VLLVWVLAVICSRAARGTIGARRTGQPLKEDPSAVPVFSV DYGELDFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSP ARRGSADGPRSAQPLRPEDGHCSWPL
C2057 (SEQ ID NO: 52)	METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVL NCSFTDSAIYNLQWFRQDPGKGLTSLLLIQSSQREQTSGRL NASLDKSSGRSTLYIAASQPGDSATYLCAVRPLYGGSYIPT FGRGTSLIVHPYIQNPDPAVYQLRDSKSSDKSVCLFTDFDS QTNVSQSKDSDVYITDKCVLDMRSMDFKSNSAVAWSNKS DFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLN FQNLSVVIGILVAVILLLLLLLLLFLILRHRRQGKHWTSTQR KADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAV KHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMA SPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYA QLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH
C2058 (SEQ ID NO: 53)	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMT LQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQG EVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSYVGNT GELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA TLVCLATGFYPDHVELSWWVNGKEVHSGVCTDPQPLKEQ PALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSEN DEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSV VIGILVAVILLLLLLLLLFLILRHRRQGKHWTSTQRKADFQ HPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVKHTQP EDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMASPPSPL SGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYAQLHSL TLRREATEPPPSQEGPSPAVPSIYATLAIH
C2070 (SEQ ID NO: 54)	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMT LQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQG

	EVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSYVGNT GELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA TLVCLATGFYPDHVELSWWVNGKEVHSGVCTDPQPLKEQ PALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSEN DEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSA TILYEILLGKATLYAVLVSALVLMAMVKRKDSRGGGGGS GGGGSGGGGSRAARGTIGARRTGQPLKEDPSAVPVFSVD YGELDFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPA RRGSADGPRSAQPLRPEDGHCSWPL
C2071 (SEQ ID NO: 55)	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMT LQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQG EVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSYVGNT GELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA TLVCLATGFYPDHVELSWWVNGKEVHSGVCTDPQPLKEQ PALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSEN DEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSA TILYEILLGKATLYAVLVSALVLMAMVKRKDSRGGGGGS GGGGSGGGGSNKKNAAVMDQEPAGDRTVNRQDSDEQDP QEVTYAQLDHCVFIQRKISRPSQRPKTPLTDTSVYTELPNA EPRSKVVSCPRAPQSGLEGVF
C2072 (SEQ ID NO: 56)	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMT LQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQG EVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSYVGNT GELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA TLVCLATGFYPDHVELSWWVNGKEVHSGVCTDPQPLKEQ PALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSEN DEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSA TILYEILLGKATLYAVLVSALVLMAMVKRKDSRGGGGGS GGGGSGGGGSRHRRQGKHWTSTQRKADFQHPAGAVGPE PTDRGLQWRSSPAADAQEENLYAAVKHTQPEDGVEMDT RSPHDEDPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTK DRQAEEDRQMDTEAAASEAPQDVTYAQLHSLTLRREATE PPPSQEGPSPAVPSIYATLAIH
C2106 (SEQ ID NO: 57)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHDREKKPR QHSGDHENLMNVPSDKEMFSRSVTSLATDAPASSEQNGA LTNGDILSEDSTLTCMQHYEEVQTSASDLLDSQDSTGKPK CHQSRELPRIPPESAVDTMLTARSVDGDQGLGMEGPYEVL KDSSSQENMVEDCLYETVKEIKEVAAAAHLEKGHSGKAK STSASKELPGPQTEGKAEFAEYASVDRNKKCRQSVNVESI

	LGNSCDPEEEAPPPVPVKLLDENENLQEKEGGEAEESATD TTSETNKRFSSLSYKSREEDPTLTEEEISAMYSSVNKPGQL VNKSGQSLTVPESTYTSIQGDPQRSPSSCNDLYATVKDFEK TPNSTLPPAGRPSEEPEPDYEAIQTLNREEEKATLGTNGHH GLVPKENDYESISDLQQGRDITRL
C2107 (SEQ ID NO: 58)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDLWGSLAAVAIFFVITFLIFLCSSCDREKKPRQHS GDHENLMNVPSDKEMFSRSVTSLATDAPASSEQNGALTN GDILSEDSTLTCMQHYEEVQTSASDLLDSQDSTGKPKCHQ SRELPRIPPESAVDTMLTARSVDGDQGLGMEGPYEVLKDS SSQENMVEDCLYETVKEIKEVAAAAHLEKGHSGKAKSTS ASKELPGPQTEGKAEFAEYASVDRNKKCRQSVNVESILGN SCDPEEEAPPPVPVKLLDENENLQEKEGGEAEESATDTTSE TNKRFSSLSYKSREEDPTLTEEEISAMYSSVNKPGQLVNKS GQSLTVPESTYTSIQGDPQRSPSSCNDLYATVKDFEKTPNS TLPPAGRPSEEPEPDYEAIQTLNREEEKATLGTNGHHGLVP KENDYESISDLQQGRDITRL
C2153 (SEQ ID NO: 59)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDFWVLVVVGGVLACYSLLVTVAFIIFWVLRHRR QGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAA DAQEENLYAAVKHTQPEDGVEMDTRSPHDEDPQAVTYA EVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEA AASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSPAVPSIY ATLAIH
C2156 (SEQ ID NO:60)	METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVL NCSFTDSAIYNLQWFRQDPGKGLTSLLLIQSSQREQTSGRL NASLDKSSGRSTLYIAASQPGDSATYLCAVRPLYGGSYIPT FGRGTSLIVHPYIQNPDPAVYQLRDSKSSDKSVCLFTDFDS QTNVSQSKDSDVYITDKCVLDMRSMDFKSNSAVAWSNKS DFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLN FQNLSVIGFLILLLLVAGFNLLMTLLLWSSLILRHRRQGKH WTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEE NLYAAVKHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHS

	RPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEA PQDVTYAQLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH
C2157 (SEQ ID NO: 61)	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMT LQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQG EVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSYVGNT GELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA TLVCLATGFYPDHVELSWWVNGKEVHSGVCTDPQPLKEQ PALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSEN DEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSA TILYLILLGLATLYAVLVSALVLMLILRHRRQGKHWTSTQ RKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAA VKHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREM ASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTY AQLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH
C2158 (SEQ ID NO: 62)	QVQLQESGPGLVKPSDTLSLTCAVSGYSISSSNWWGWIRQ PPGKGLEWIGYIYYSGSTYYNPSLKSRVTMSVDTSKNQFS LKLSSVTAVDTAVYYCARIPFGDWWYFDLWGRGTLVTVS SGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTIT CRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQSYSFVLTFGGGTKV EIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDFWVLVVVGGVLACYSLLVTVAFIIFWVLRHRRQ GKHWTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAAD AQEENLYAAVKHTQPEDGVEMDTRSPHDEDPQAVTYAE VKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAA ASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSPAVPSIYA TLAIH
C2179 (SEQ ID NO: 63)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSP AVPSIYATLAIH
C2180 (SEQ ID NO: 64)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL

	LFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGL QWRSSPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDE DPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEE DRQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEG PSPAVPSIYATLAIHRPRREMASPPSPLSGEFLDTKDRQAEE DRQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEG PSPAVPSIYATLAIH
C2181 (SEQ ID NO: 65)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSP AVPSIYATLAIHRPRREMASPPSPLSGEFLDTKDRQAEEDR QMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPS PAVPSIYATLAIH
C2182 (SEQ ID NO: 66)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGL QWRSSPAADAQEENLFAAVKHTQPEDGVEMDTRSPHDED PQAVTFAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEED RQMDTEAAASEAPQDVTFAQLHSLTLRREATEPPPSQEGP SPAVPSIFATLAIH
C2183 (SEQ ID NO: 67)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGL QWRSSPAADAQEENLFAAVKHTQPEDGVEMDTRSPHDED PQAVTFAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEED RQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGP SPAVPSIYATLAIH

C2184 (SEQ ID NO: 68)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGL QWRSSPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDE DPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEE DRQMDTEAAASEAPQDVTFAQLHSLTLRREATEPPPSQEG PSPAVPSIFATLAIH
C2218 (SEQ ID NO: 69)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTR QNSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKP GIVYASLNHSVIGPNSRLARNVKEAPTEYASICVRS
C2219 (SEQ ID NO: 70)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVLLPLGGLPLLITTCFCL FCCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQ NSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPGI VYASLNHSVIGPNSRLARNVKEAPTEYASICVRS
C2220 (SEQ ID NO: 71)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSTDVKSASERPSKDEMASRPWLLYRLLPLGGLPLLITTC FCLFCCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEAS TRQNSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEEN KPGIVYASLNHSVIGPNSRLARNVKEAPTEYASICVRS

C2302 (SEQ ID NO: 77)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIKGGGGSGGGGSGGGGS GGEVQLVESGGGLVQPGGSLRLSCAASGFTVYDYMSWVR QAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARYSYYYYYMDVWGKGTTVT VSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTST SGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLL LFLILRHRRQRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSP AVPSIYATLAIHRPRREMASPPSPLSGEFLDTKDRQAEEDR QMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPS PAVPSIYATLAIHRPRREMASPPSPLSGEFLDTKDRQAEED RQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGP SPAVPSIYATLAIH
CT138 (SEQ ID NO: 78)	MGPVTCSVLVLLLMLRRSNGDGDSVTQTEGLVTLTEGLP VMLNCTYQTIYSNPFLFWYVQHLNESPRLLLKSFTDNKRT EHQGFHATLHKSSSSFHLQKSSAQLSDSALYYCAFDTNTY KVIFGKGTHLHVLPNIQNPEPAVYQLKDPRSQDSTLCLFTD FDSQINVPKTMESGTFITDKTVLDMKAMDSKSNGAIAWSN QTSFTCQDIFKETNTTYPSSDVPCDATLTEKSFETDMNLNF QNLSVMGLRILLLKVAGFNLLMTLRLWSSRAKRSGSGAT NFSLLKQAGDVEENPGPMRVRLISAVVLCSLGTGLVDMK VTQMPRYLIKRMGENVLLECGQDMSHETMYWYRQDPGL GLQLIYISYDVDSNSEGDIPKGYRVSRKKREHFSLILDSAK TNQTSVYFCASSSTNTEVFFGKGTRLTVVEDLRNVTPPKV SLFEPSKAEIANKQKATLVCLARGFFPDHVELSWWVNGK EVHSGVSTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHF RCQVQFHGLSEEDKWPEGSPKPVTQNISAEAWGRADCGIT SASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVK RKNS
CT139 (SEQ ID NO: 79)	MVLVTILLLSAFFSLRGNSAQSVDQPDAHVTLSEGASLELR CSYSYSAAPYLFWYVQYPGQSLQFLLKYITGDTVVKGTK GFEAEFRKSNSSFNLKKSPAHWSDSAKYFCALEGPDTGNY KYVFGAGTRLKVIAHIQNPEPAVYQLKDPRSQDSTLCLFT DFDSQINVPKTMESGTFITDKTVLDMKAMDSKSNGAIAWS NQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLN FQNLSVMGLRILLLKVAGFNLLMTLRLWSSRAKRSGSGAT NFSLLKQAGDVEENPGPMGIQTLCCVIFYVLIANHTDAGV TQTPRHEVAEKGQTIILKCEPVSGHNDLFWYRQTKIQGLE LLSYFRSKSLMEDGGAFKDRFKAEMLNSSFSTLKIQPTEPR DSAVYLCASSFGTASAETLYFGSGTRLTVLEDLRNVTPPK VSLFEPSKAEIANKQKATLVCLARGFFPDHVELSWWVNG KEVHSGVSTDPQAYKESNYSYCLSSRLRVSATFWHNPRN HFRCQVQFHGLSEEDKWPEGSPKPVTQNISAEAWGRADC

	GITSASYHQGVLSATILYEILLGKATLYAVLVSGLVLMAM VKKKNS
C1765 with signal peptide (SEQ ID NO: 120), LIR1 hinge, TM and ICD are underlined Polynucleotide sequence − SEQ ID NO: 121	MDMRVPAQLLGLLLLWLRGARCDVLMTQTPLSLPVSLGD QASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSN RFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSH VPRTSGGGTKLEIKGGGGSGGGGSGGGGSGGQVQLQQSG PELVKPGASVRISCKASGYTFTSYHIHWVKQRPGQGLEWI GWIYPGNVNTEYNEKFKGKATLTADKSSSTAYMHLSSLTS EDSAVYFCAREEITYAMDYWGQGTSVTVSSYGSQSSKPY LLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTG SDPQSGLGRHLGVVIGILVAVILLLLLLLLLFLILRHRRQGK HWTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQE ENLYAAVKHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHS RPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEA PQDVTYAQLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH
C1765 without signal peptide (SEQ ID NO: 122), LIR1 hinge, TM and ICD are underlined Polynucleotide sequence − SEQ ID NO: 123	DVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWY LQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISR VEAEDLGVYYCFQGSHVPRTSGGGTKLEIKGGGGSGGGG SGGGGSGGQVQLQQSGPELVKPGASVRISCKASGYTFTSY HIHWVKQRPGQGLEWIGWIYPGNVNTEYNEKFKGKATLT ADKSSSTAYMHLSSLTSEDSAVYFCAREEITYAMDYWGQ GTSVTVSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTT GPTSTSGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLL LLLLLLFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPT DRGLQWRSSPAADAQEENLYAAVKHTQPEDGVEMDTRS PHDEDPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDR QAEEDRQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPP SQEGPSPAVPSIYATLAIH

[0244] The present description sets forth numerous exemplary configurations, methods, parameters, and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure, but is instead provided as a description of exemplary embodiments.

EXAMPLES

Example 1: LILRB1-based Inhibitory scFv-CAR compared to PD-1, KIR3DL2, KIR3DL3

[0245] The NY-ESO-1-responsive inhibitory construct was created by fusing the NY-ESO-1 ligand binding scFv domain (C-266) to domains of receptors including hinge, transmembrane region, and/or intracellular domain of Leukocyte immunoglobulin-like receptor subfamily B member 1, LILRB1 (LILRB1); Killer cell immunoglobulin-like receptor 3DL2, KIR3DL2; Killer

cell immunoglobulin-like receptor 3DL3, KIR3DL3; and/or B- and T-lymphocyte attenuator, BTLA. Gene segments were combined using Golden Gate cloning and inserted downstream of an eF1α promoter contained in a lentiviral expression plasmid (pLenti1).

[0246] As reporter cells, Jurkat cells encoding an NFAT Luciferase reporter were maintained in RPMI media supplemented with 10% FBS, 1% Pen/Strep and 0.4mg/mL G418/Geneticin. T2 cells (ATCC CLR-1992) were maintained in IMDM media + 20% FBS and 1% Pen/Strep. For each construct to be evaluated, Jurkat cells were transfected via 100µL format Neon electroporation system (Thermo Fisher) according to manufacturer's protocol using the following settings: 3 pulses, 1500V, 10 msec.

[0247] Co-transfection was performed with 3µg of activating CAR construct (C-563) or TCR construct (CT-139) and 3µg of either inactivating CAR construct or empty vector (pLenti0) per 1 million cells and recovered in RPMI media supplemented with 20% heat-inactivated FBS and 0.1% Pen/Strep.

[0248] Peptides, MAGE-A3 (FLWGPRALV) (SEQ ID NO: 106) and modified NY-ESO-1 (SLLMWITQV) (SEQ ID NO: 107), were synthesized by Genscript. Activating peptide, MAGE-A3, was serially diluted 5-fold starting at 50µM. Inactivating peptide, NY-ESO-1, was diluted to 50 µM, 5 µM, 0.5 µM, or 0.05 uM and these constant amounts were added to the MAGE-A3 serial dilutions and subsequently loaded onto 10,000 T2 cells in 15µL of RPMI supplemented with 1% BSA and 0.1 % Pen/Strep and incubated in Corning® 384-well Low Flange White Flat Bottom Polystyrene TC-treated Microplates. The following day, 10,000 Jurkat cells were resuspended in 15uL of RPMI supplemented with 10% heat-inactivated FBS and 0.1% Pen/Strep, added to the peptide-loaded T2 cells and co-cultured for 6 hours. ONE-Step Luciferase Assay System (BPS Bioscience) was used to evaluate Jurkat luminescence. Assays were performed in technical duplicates.

LILRB1 compared to PD-1, KIR3DL2, KIR3DL3

[0249] **FIG. 4** shows testing of the constructs provided in **Table 1**. The data show scFv-LILRB1 inhibits CAR activation *in trans*. Because the construct with an LILRB1 domain demonstrates inhibition of signaling at higher concentrations of MAGE-A3 activator peptide, the data demonstrate that a CAR with hinge, transmembrane domain, and intracellular domain from LILRB1 is superior to CARs generated with the same domains from PD-1, KIR3DL2, or KIR3DL3.

Table 1

	LBD	Hinge	TM	ICD
C563	MAGE-A3 pep1 scFv	CD8[117-161]	CD28[135-161]	CD28[136-202] 41BB[197-238] CD3z[31-127]
C1761	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1
C1759	NY-ESO-1 scFv	KIR3DL2	KIR3DL2	KIR3DL2
C1760	NY-ESO-1 scFv	KIR3DL3	KIR3DL3	KIR3DL3
C1762	NY-ESO-1 scFv	PD1	PD1	PD1
CT139	MAGE-A3 pep1 TCR (both alpha and beta chains)			

Inhibition by LILRB1-based CAR requires antigen recognition by its ligand binding domain

[0250] **FIG. 5** shows testing of selected constructs from **Table 1**. The data show that LILRB1 inhibits signaling *in trans* in a dose-dependent fashion. At increasing concentrations of the inhibitory peptide NY-ESO-1 the response to activating peptide MAGE-A3 shifts downward. This shows that the inhibitory effect of the LILRB1-based CAR is dependent on engagement of the antigen to which the ligand binding domain is specific.

LILRB1 CAR inhibits signaling through the T-cell receptor (TCR)

[0251] **FIG. 6** shows testing of selected constructs from **Table 1**, in particular a TCR specific for activating peptide MAGE-A3 rather than the CARs used in previous experiments. The LILRB1-based inhibitory CAR inhibits TCR-mediated signaling in a dose-dependent fashion.

LIRLB1 CAR inhibition is preserved when two of the four native ITIMs are present

[0252] **FIG. 7** show testing of LILRB1 intracellular domains having inactivating mutations in the ITIM motifs of LILRB1. Mutation of tyrosine to phenylalanine (Y→F) was used to inactivate the ITIMs indicated by a starred number in **Table 2**.

Table 2

	LBD	Hinge	TM	ICD
C563	MAGE-A3 pep1 scFv	CD8[117-161]	CD28[135-161]	CD28[136-202] 41BB[197-238] CD3z[31-127]
C1761	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 1,2,3,4)

C2182	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 1*,2*,3*,4*)
C2183	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 1*,2*,3,4)
C2184	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 1,2,3*,4*)

[0253] Inactivation of all four ITIMs resulted in a non-functional inhibitory CAR (C2182). Inactivation of only two of the four ITIMs preserved the inhibitor function of the CAR at the concentrations tested (C1760 and C1762). Inactivation of all four ITIM (C1759) demonstrates that the ITIMs are necessary for inhibitory function. When all four ITIMs are mutated, the molecule loses inhibitory function. When only two of the four ITIMs are mutated, inhibitory activity is retained.

[0254] **FIG. 8** shows testing of LILRB1 ITIMs in combinations different from those of the native LILRB1 intracellular domain. As shown in **Table 3**, CARs having the third and fourth ITIMs of LILRB1 in four or six total copies achieve inhibitory activity comparable to the native LILRB1 intracellular domain. Inhibitory activity is also observed when only one copy each of the third and fourth ITIMs are used (C2179) or when two copies of each ITIM is used (C2180) or when multiple copies are used (C2302 or C2180).

Table 3

	LBD	Hinge	TM	ICD
C563	MAGE-A3 pep1 scFv	CD8[117-161]	CD28[135-161]	CD28[136-202] 41BB[197-238] CD3z[31-127]
C1761	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 1,2,3,4)
C2302	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 3,4,3,4,3,4)
C2181	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 3,4,3,4)
C2180	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs: 1,2,3,4,3,4)
C2179	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1 (ITIMs:3,4)

Example 2: LILRB1 hinge and transmembrane domains enhance the inhibitory activity of BTLA-based inhibitory CARs

BTLA-based CAR and LILRB1/BTLA-based CARs inhibit signaling via NFAT

[0255] B- and T-lymphocyte attenuator (BTLA), also known as CD272 (cluster of differentiation 272) interacts with B7 homology B7H4. Unlike CTLA-4 and PD-1, it is also a ligand for tumour necrosis factor (receptor) superfamily, member 14 (TNFRSF14). Inhibitory signaling through BTLA occurs in response to binding of B7H4 or TNFRSF14.

[0256] The full length BTLA protein was cloned into a construct having an extracellular scFv domain (C2220), a construct replacing the extracellular domain of BTLA with that of LILRB1 (C2219), and a construct replacing the extracell7ular and transmembrane domains of BTLA with those of LILRB1 (C2218) were generated and tested, as shown in **Table 4** and **FIG. 9**. The LILRB1-BTLA fusion exhibits inhibitory signaling comparable to the LILRB1-based CAR.

Table 4

	LBD	Hinge	TM	ICD
C563	MAGE-A3 pep1 scFv	CD8[117-161]	CD28[135-161]	CD28[136-202] 41BB[197-238] CD3z[31-127]
C1761	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1
C2218	NY-ESO-1 scFv	LILRB1	LILRB1	BTLA
C2219	NY-ESO-1 scFv	LILRB1	BTLA	BLTA
C2220	NY-ESO-1 scFv	BTLA	BTLA	BTLA

Example 3: LILRB1 hinge and transmembrane compared to CD8 or CD28

LILRB1-based CAR with LILRB1 hinge and transmembrane is superior to CD8 hinge and CD28 transmembrane region

[0257] The LILRB1-based CAR was compared to a CAR having the LILRB1 intracellular domain but CD8 hinge and CD28 transmembrane region, as shown in **Table 5** and **FIG. 10**.

Table 5

	LBD	Hinge	TM	ICD
C563	MAGE-A3 pep1 scFv	CD8[117-161]	CD28[135-161]	CD28[136-202] 41BB[197-238] CD3z[31-127]
C1761	NY-ESO-1 scFv	LILRB1	LILRB1	LILRB1
C2153	NY-ESO-1 scFv	CD8	C28	LILRB1

[0258] The LILRB1 hinge and transmembrane region generate results surprisingly superior to a construct having the CD8 hinge and CD28 transmembrane regions. Emin is decreased. Overall dynamic range is increased. Inhibitory potency is increased.

Table 6: Summary of results shown in Examples 1-3.

Inhibitor Construct	Activator Construct	uM Inhibitor peptide	E_{min}[RLU]	EC_{50}[nM]	E_{max}[RLU]
-	C563	50	30,000	10	100,000
-	CT139	50	0	20	100,000
C1761	C563	50	1,000	>10,000	NA
C1761	CT139	50	400	>1,000	NA
C1759	C563	50	20,000	200	100,000
C1760	C563	50	5,000	60	100,000
C1762	C563	50	5,000	600	90,000
C2184	C563	50	1,000	>1,000	NA
C2183	C563	50	4,000	>1,000	NA
C2182	C563	50	30,000	30	90,000
C2302	C563	50	0	>10,000	NA
C2181	C563	50	0	>10,000	NA
C2180	C563	50	0	>10,000	NA
C2179	C563	50	0	>10,000	NA
C2218	C563	50	1,000	>1,000	NA
C2219	C563	50	2,000	>1,000	NA
C2220	C563	50	3,000	>1,000	NA
C2153	C563	50	20,000	2,000	60,000

C2107	CT139	5	0	100	100,000
C2106	CT139	5	0	40	100,000

Example 4: TCR-based inhibitory chimeric antigen receptors

Construct design and cloning

[0259] The NY-ESO-1-responsive inhibitory constructs were created using the high affinity anti-HLA-A*02:01/NY-ESO-1 1G4α95:LY T cell receptor (TCR) variant. The charged residues in the TM of TCRα (R253 and K258) and TCRβ (K288) were mutated to leucine. Then, the LILRB1 ITIM (residues 484-650) was appended to the mutated TCRα or TCRβ. Anti-HLA-A*02:01/MAGE-A3 single chain variable fragment (scFv) was generated in-house. The anti-HLA-A2*02:01/MAGE-A3 chimeric antigen receptor (CAR) used in this study contains the anti-HLA-A*02:01/MAGE-A3 scFv, CD8 hinge, CD28 TM, and CD28, 41BB, and CD3ζ intracellular domains (ICDs). All fragments, including 5' and 3' BsmBI sites, were amplified using Q5 polymerase (New England Biolabs) and digested with DpnI (Thermo Scientific) at 37°C for 60 min. The generated PCR fragments were purified using the Nucleospin gel and PCR cleanup kit (Macherey-Nagel). The plasmids were Golden Gate assembled in a reaction containing BsmBI (Thermo Scientific), T4 DNA ligase (Thermo Scientific), 10 mM ATP, and 1x FastDigest buffer (Thermo Scientific).

Jurkat NFAT activation assay

[0260] Jurkat T lymphocytes that contain firefly luciferase gene under the control of the nuclear factor of activator T cells (NFAT) transcription factor (BPS Bioscience) were co-transfected with plasmids encoding TCR and/or scFv-fusion constructs using the Neon transfection system (Thermo Fisher). The electroporated cells were incubated in RPMI media supplemented with 20% fetal bovine serum (FBS) heat-inactivated at 56°C for 60 min (HIA-FBS) and 0.1% pencillin-streptomycin (P/S) (Gibco). TAP deficient T2 lymphoblasts (ATCC RL-1992) were loaded with varying amounts of a modified NY-ESO-1 peptide (SLLMWITQV) (SEQ ID NO: 107) alone, MAGE-A3 peptide (FLWGPRALV) (SEQ ID NO: 106) alone, or varying amounts of MAGE-A3 peptide in addition to 50 μM NY-ESO-1 peptide in RPMI supplemented with 1% BSA and 0.1% P/S (Gibco). Peptides used in the assay were synthesized to >95% purity assessed by mass spectrometry (Genscript). 18 hours post-transfection, Jurkats were resuspended at 0.8 x 10^6 cells per mL in RPMI supplemented with 10% HIA-FBS and 1% P/S. In a 384 well plate, 12000

Jurkats were co-cultured with 12000 peptide-loaded T2s per well at 37°C, 5% CO_2 for 6 hours. NFAT-mediated luciferase production was measured by adding 15 uL of ONE-Step luciferase assay reagent (BPS Bioscience). After 20 minutes, luminescence was detected using a plate reader (Tecan).

TCR-based inhibitory CARs using the LILRB1 intracellular domain

[0261] As shown in **Table 7** and **FIG. 11**, co-expression of TCR-based CARs having either only the extracellular domains of the TCR or also having the transmembrane regions of the TCRs with mutations to polar residues, yield functional inhibitory CARs.

Table 7

	LBD	Hinge	TM	ICD
C563	MAGE-A3 pep1 scFv	CD8[117-161]	CD28[135-161]	CD28[136-202] 41BB[197-238] CD3z[31-127]
C2057	TCR 1G4:α95LY α		LILRB1	LILRB1
C2058	TCR 1G4:α95LY α		LILRB1	LILRB1
C2156	TCR 1G4:α95LY α		TCR 1G4:α95LY α (R253L/K258L)	LILRB1
C2157	TCR 1G4:α95LY α		TCR 1G4:α95LY β (K288L)	LILRB1

[0262] TCR-base CARs inhibit the anti-HLA-A*02:01 MAGE-A3 CAR in *trans*. Jurkat-NFAT luciferase reporter cells were transfected with (1) anti-HLA-A*02:01/MAGE-A3 CAR alone (C563), (2) co-transfected with MAGE-A3 CAR (C563) and TCRα(R253L/K258L)-LILRB1 fusion and TCRβ(K288L)-LILRB1 ICD fusion TCR-inhibitory fusion construct (C2156 + C2157) or (3) co-transfected with MAGE-A3 CAR and TCRαECD/TCRβECD-LIRT1(TM+ICD) fusion (C2057 + C2058) TCR-inhibitory fusion construct. The effects of the two inhibitory variants on NFAT activation was measured by co-culturing transfected Jurkat cells with T2 cells loaded with 50 μM NY-ESO-1 peptide in combination with varying amounts of MAGE-A3 peptide. Data are summarized in **Table 8**.

Table 8: *Trans* effect of TCR-inhibitory fusion constructs on MAGE-A3 CAR

Inhibitor Construct	Activator Construct	μM Inhibitor peptide	E_{min}[RLU]	EC_{50}[nM]	E_{max}[RLU]
-	C563	50	19949	24.52	134443
C2057 + C2058	C563	50	2072	>10,000	NA
C2156 + C2157	C563	50	9198	7108	NA

[0263] Truncated TCR alpha or TCR beta extracellular domains (ECD)- with LILRB1 TM-ICD fusions inhibit CAR activation. TCR alpha or TCR beta extracellular domains (ECD)- with TCR TM- LILRB1 ICD fusions also acted as inhibitor CARs when the TCR transmembrane mutations abolish TCR-CD3 subunit interactions. The experiment demonstrates that the TCR α chain and β chains can be used to generate inhibitory chimeric antigen receptors by interfering with recruitment of stimulatory factors by CD3 subunits.

Example 5: Methods for Examples 6-14

[0264] Cell Culture

[0265] Jurkat cells encoding an NFAT luciferase reporter were obtained from BPS Bioscience. All other cell lines used in this study were obtained from ATCC. In culture, Jurkat cells were maintained in RPMI media supplemented with 10% FBS, 1% Pen/Strep and 0.4mg/mL G418/Geneticin. T2, MCF7, Raji, K562 and HeLa cells were maintained as suggested by ATCC. "Normal" Raji cells were made by transducing Raji cells with HLA-A*02 lentivirus (custom lentivirus, Alstem) at a MOI of 5. HLA-A*02-positive Raji cells were sorted using a FACSMelody Cell Sorter (BD).

[0266] Plasmid Construction

[0267] The NY-ESO-1-responsive inhibitory construct was created by fusing the NY-ESO-1 scFv LBD to domains of receptors including hinge, transmembrane region, and/or intracellular domain of leukocyte immunoglobulin-like receptor subfamily B member 1, LILRB1 (LIR-1), programmed cell death protein 1, PDCD1 (PD-1), or cytotoxic T-lymphocyte protein 4, CTLA4 (CTLA-4). All activating CAR constructs contained an scFv fused to the CD8α hinge, CD28 TM,

and CD28, 4-1BB and CD3zeta ICDs. The CD19-activating CAR scFv was derived from the FMC63 mouse hybridoma. MSLN-activating CAR scFvs were derived from human M5 (LBD1) as described and humanized SS1 (LBD2). Gene segments were combined using Golden Gate cloning and inserted downstream of a human EF1α promoter contained in a lentiviral expression plasmid.

[0268] Jurkat Cell Transfection

[0269] Jurkat cells were transiently transfected via 100uL format Neon electroporation system (Thermo Fisher Scientific) according to manufacturer's protocol using the following settings: 3 pulses, 1500V, 10 msec. Cotransfection was performed with 1-3ug of activator CAR or TCR construct and 1-3ug of either scFv or TCR alpha/TCR beta LIR-1 blocker constructs or empty vector per 1e6 cells and recovered in RPMI media supplemented with 20% heat-inactivated FBS and 0.1% Pen/Strep. To confirm blocker surface expression, Jurkat cells were stained 18-24 hours post-transfection with 10ug/mL streptavidin-PE-HLA-A*02-pMHC tetramer for 60 minutes at 4°C in PBS with 1% BSA and characterized by flow cytometry (BD FACSCanto II).

[0270] Jurkat-NFAT-luciferase activation studies

[0271] Peptides, MAGE-A3 (MP1; FLWGPRALV; SEQ ID NO: 106) , MAGE-A3 (MP2; MPKVAELVHFL; SEQ ID NO: 108), HPV E6 (TIHDIILECV; SEQ ID NO: 109), HPV E7 (YMLDLQPET; SEQ ID NO: 110) and modified NY-ESO-1 ESO (ESO; SLLMWITQV; SEQ ID NO: 107), were synthesized by Genscript. Activating peptide was serially diluted starting at 50uM. Blocker peptide, NY-ESO-1, was diluted to 50uM (unless otherwise indicated) which was added to the activating peptide serial dilutions and subsequently loaded onto 1e4 T2 cells in 15uL of RPMI supplemented with 1% BSA and 0.1 % Pen/Strep and incubated in Corning® 384-well Low Flange White Flat Bottom Polystyrene TC-treated Microplates. The following day, 1e4 Jurkat cells were resuspended in 15uL of RPMI supplemented with 10% heat-inactivated FBS and 0.1% Pen/Strep, added to the peptide-loaded T2 cells and co-cultured for 6 hours. ONE-Step Luciferase Assay System (BPS Bioscience) was used to evaluate Jurkat luminescence. For assays involving high density targets, Jurkat cells were similarly transfected and cocultured with tumor cells expressing target antigens at various Jurkat:tumor cell ratios. Assays were performed in technical duplicates.

[0272] Primary T cell transduction, expansion, and enrichment

[0273] Leukopaks were purchased from AllCells®. Collection protocols and donor informed consent were approved by an Institutional Review Board (IRB), with strict oversight. HIPAA compliance and approved protocols were also followed. Frozen PBMCs were thawed in 37°C water bath and cultured at 1e6 cells/mL in LymphoONE (Takara) with 1% human serum and activated using 1:100 of T cell TransAct (Miltenyi) supplemented with IL-15 (10ng/mL) and IL-21 (10ng/mL). After 24 hours, lentivirus was added to PBMCs at MOI = 5. Activator and blocker receptors were simultaneously co-transduced at a MOI = 5 for each lentivirus. PBMCs were cultured for 2-3 additional days to allow cells to expand under TransAct stimulation. Post expansion, activator and blocker transduced primary T cells were enriched for blocker-positive T cells by positive selection using anti-PE microbeads (Miltenyi) according to manufacturer's instructions. Briefly, primary T cells were incubated with 10ug/mL streptavidin-PE-HLA-A*02-pMHC tetramer for 60 minutes at 4°C in MACS buffer (0.5% BSA + 2mM EDTA in PBS). Cells were washed 3 times in MACS buffer and passed through the LS column (Miltenyi) to separate blocker-positive cells (a mix of blocker-only and activator + blocker cells) from untransduced and activator-only cells.

[0274] Primary T cell in vitro cytotoxicity studies

[0275] For cytotoxicity studies with pMHC targets, enriched primary T cells were incubated with 2e3 MCF7 cells expressing renilla luciferase (Biosettia) loaded with a titration of target peptide as described above at an effector:target ratio of 3:1 for 48 hours. Live luciferase-expressing MCF7 cells were quantified using a Renilla Luciferase Reporter Assay System (Promega). For cytotoxicity studies with non-pMHC targets, enriched primary T cells were incubated with 2e3 WT Raji cells ("tumor" cells) or HLA-A*02 transduced Raji cells ("normal" cells) at an effector:target ratio of 3:1 for up to 6 days. WT "tumor" Raji cells stably expressing GFP and renilla luciferase (Biosettia) or HLA-A*02 transduced "normal" Raji cells stably expressing RFP and firefly luciferase (Biosettia) were imaged together with unlabeled primary T cells using an IncuCyte live cell imager. Fluorescence intensity of live Raji cells over time was quantified using IncuCyte imaging software. For reversibility studies, enriched primary T cells were similarly cocultured with "normal" or "tumor" Raji cells for 3 days and imaged. After 3 days, T cells were separated from remaining Raji cells using CD19 negative selection and reseeded with fresh "normal" or "tumor" Raji cells as described. In separate wells, live luciferase-expressing Raji cells were quantified using a Dual-Luciferase Reporter Assay System (Promega) at 72 hours. For

studies in which IFNγ secretion was assessed, supernatants collected after 48 hours of co-culture were tested for IFNγ using a BD Human IFNγ flex kit following manufacturer's exact instructions.

[0276] Mouse Xenograft Study

[0277] Frozen PBMCs were thawed in 37°C water bath and rested overnight in serum-free TexMACS Medium (Miltenyi) prior to activation. PBMCs were activated in 1.5e6 cells/mL using T cell TransAct (Miltenyi) and TexMACS Medium supplemented with IL-15 (20ng/mL) and IL-21 (20ng/mL). After 24 hours, lentivirus was added to PBMCs at a MOI of 5. PBMCs were cultured for 8-9 additional days to allow cells to expand under TransAct stimulation. Post expansion, T cells were enriched on A2-LIR-1 using anti-PE microbeads (Miltenyi) against streptavidin-PE-HLA-A*02-pMHC for 2-5 additional days prior to in vivo injection. Enriched T cells were also validated by flow cytometry (BD FACSCanto II) for expression of CD19 scFv activator and HLA-A*02 LIR-1 blocker by sequential staining with CD19-Fc (1:100; R&D Systems) and goat anti-human IgG-FITC (1:200; Invitrogen) for activator and 10ug/mL streptavidin-APC-HLA-A*02-pMHC for blocker.

[0278] In vivo experiments were conducted by Explora BioLabs under Institutional Animal Care and Use Committee (IACUC)-approved protocols. 5-6 week old female NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(HLA-A/H2-D/B2M)1Dvs/SzJ (NSG-HLA-A2/HHD) mice were purchased from The Jackson Labs. Animals were acclimated to the housing environment for at least 3 days prior to the initiation of the study. Animals were injected with 2e6 WT Raji cells or HLA-A*02 transduced Raji cells in 100 uL volume subcutaneously in the right flank. When tumors reached an average of 70 mm3 (V = L x W x W/2), animals were randomized into 5 groups (n=7) and 2e6 or 1e7 T cells were administered via the tail vein. Post T cell injection, tumor measurements were performed 3 times per week and blood was collected 10 days and 17 days after for flow analysis. One animal from the WT Raji group receiving 1e7 CD19-CAR + A2-LIR-1 T cells was excluded from the study due to a failed tail vein injection, followed by flow cytometry confirmation of the absence of human T cells in the blood. At each time point, human T cells in the blood were quantified by flow cytometry (BD FACSCanto II) post RBC lysis. Cells were stained with anti-mouse CD45-FITC (clone 30-F11), anti-human CD3-PE (clone SK7), anti-human CD4-APC (clone OKT4), and anti-human CD8-PerCP-Cy5.5 (clone RPA-T8). All antibodies were obtained from Biolegend and used at a 1:100 dilution. DAPI (Invitrogen) was used to exclude dead cells

from analysis. For histopathological analysis, tumor samples were fixed, sectioned and stained for huCD3 (clone EP449E). Image quantification was done using ImageJ software.

[0279] Statistical Analysis

[0280] Statistical analyses were performed using GraphPad Prism software. All peptide and cell titration studies are shown as mean ± standard deviation (SD), while in vitro and in vivo studies using primary T cells are shown as mean ± standard error of the mean (SEM), unless otherwise noted. Peptide and cell titration curves were fit using a four-parameter non-linear regression analysis. EC50 values were calculated directly from the curves. All other groups of data were analyzed using an ordinary two-way ANOVA followed by a Tukey's multiple-comparisons test, unless otherwise noted.

Example 6: Assaying the Effect of the LIR-1 Hinge on Blocking Activity

[0281] The effects of different LIR-1 hinges on the ability of HLA-A*02 scFv LIR-1 inhibitory receptors to block killing by Jurkat cells expressing a KRAS TCR activator was assayed using the Jurkat NFat Luciferase assays described *supra*. A humanized PA2.1 scFv LIR-1 receptor and humanized BB7.2 scFv LIR-1 with a shorter LIR-1 hinge were assayed in Jurkat cells as previously described, and the results are shown in FIGS. 12A-12B. Jurkat cells were transfected with a KRAS TCR activator receptor and/or HLA-A*02 scFv LIR-1 inhibitory receptor (humanized PA2.1 or humanized BB7.2) with a variety of LIR-1 derived hinges, and co-cultured with T2 target cells that were either HLA:A11 positive, or HA:A11 and HLA:A02 positive. Inhibitory receptors with both the shorter and longer hinge behaved similarly (FIG. 12A-12B). An inhibitory receptor with a mouse PA2.1 scFv and slightly longer hinges was also assayed functioned similarly to shorter LIR-1 hinges in the T2-Jurkat assay (FIG. 13A-13B). Hinge sequences are shown in black in FIG. 12B and FIG. 13B, with the gray SS in the sequences in FIG. 13B representing a linker between the antigen-binding domain and the hinge, and the gray VIGIL the start of the LIR-1 transmembrane domain. Hinge, transmembrane domain and intracellular domain of the inhibitory receptors were all derived from LIR-1. FIGS. 12A-12B and 13A-13B show that LIR-1 hinge length can be varied without negatively effecting the LIR-1 inhibitory receptor. Shorter hinges can provide an advantage when packaging nucleic acid sequences encoding LIR-1 inhibitory receptors in lentiviral vectors for delivery.

[0282] Table 9. Sequences of constructs

Name	Amino Acid Sequence	Nucleotide Sequence
PA2.1.14 (VL:VH) scFv LIR1 sHTICD	TEFTLTISSLQPD DFATYYCFQGSHV PRTFGQGTKVEVK GGGGSGGGGSGGG GSGGQVQLVQSGA EVKKPGSSVKVSC KASGYTFTSYHIH WVRQAPGQGLEWI GWIYPGNVNTEYN EKFKGKATITADE STNTAYMELSSLR SEDTAVYYCAREE ITYAMDYWGQGTL VTVSSVVSGPSGG PSSPTTGPTSTSG PEDQPLTPTGSDP QSGLGRHLGVVIG ILVAVILLLLLLL LLFLILRHRRQGK HWTSTQRKADFQH PAGAVGPEPTDRG LQWRSSPAADAQE ENLYAAVKHTQPE DGVEMDTRSPHDE DPQAVTYAEVKHS RPRREMASPPSPL SGEFLDTKDRQAE EDRQMDTEAAASE APQDVTYAQLHSL TLRREATEPPPSQ EGPSPAVPSIYAT LAIH (SEQ ID NO: 92)	GACATTCAAATGACCCAGAGCCCATCCACCCTGAGCGCATCT GTAGGTGACCGGGTCACCATCACTTGTAGATCCAGTCAGAGT ATTGTACACAGTAATGGGAACACCTATTTGGAATGGTATCAG CAGAAACCAGGTAAAGCCCCAAAATTGCTCATCTACAAAGTC TCTAACAGATTTAGTGGTGTACCAGCCAGGTTCAGCGGTTCC GGAAGTGGTACTGAATTCACCCTCACGATCTCCTCTCTCCAG CCAGATGATTTCGCCACTTATTACTGTTTTCAAGGTTCACAT GTGCCGCGCACATTCGGTCAGGGTACTAAAGTAGAAGTCAAA GGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCGGCGGAGGA AGCGGAGGCCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTG AAGAAGCCTGGGTCCTCAGTGAAGGTTTCCTGCAAGGCTTCT GGATACACCTTCACTAGCTATCATATACATTGGGTGCGCCAG GCCCCCGGACAAGGGCTTGAGTGGATCGGATGGATCTACCCT GGCAATGTTAACACAGAATATAATGAGAAGTTCAAGGGCAAA GCCACCATTACCGCGGACGAATCCACGAACACAGCCTACATG GAGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTGTATTAC TGTGCGAGGGAGGAAATTACCTACGCTATGGACTACTGGGGC CAGGGAACCCTGGTCACCGTGTCCTCAGTGGTCTCAGGACCG TCTGGGGGCCCCAGCTCCCCGACAACAGGCCCCACCTCCACA TCTGGCCCTGAGGACCAGCCCCTCACCCCCACCGGGTCGGAT CCCCAGAGTGGTCTGGGAAGGCACCTGGGGGTTGTGATCGGC ATCTTGGTGGCCGTCATCCTACTGCTCCTCCTCCTCCTCCTC CTCTTCCTCATCCTCCGACATCGACGTCAGGGCAAACACTGG ACATCGACCCAGAGAAAGGCTGATTTCCAACATCCTGCAGGG GCTGTGGGGCCAGAGCCCACAGACAGAGGCCTGCAGTGGAGG TCCAGCCCAGCTGCCGATGCCCAGGAAGAAAACCTCTATGCT GCCGTGAAGCACACACAGCCTGAGGATGGGGTGGAGATGGAC ACTCGGAGCCCACACGATGAAGACCCCCAGGCAGTGACGTAT GCCGAGGTGAAACACTCCAGACCTAGGAGAGAAATGGCCTCT CCTCCTTCCCCACTGTCTGGGGAATTCCTGGACACAAAGGAC AGACAGGCGGAAGAGGACAGGCAGATGGACACTGAGGCTGCT GCATCTGAAGCCCCCCAGGATGTGACCTACGCCCAGCTGCAC AGCTTGACCCTCAGACGGGAGGCAACTGAGCCTCCTCCATCC CAGGAAGGGCCCTCTCCAGCTGTGCCCAGCATCTACGCCACT CTGGCCATCCACTAG (SEQ ID NO: 114)
PA2.1.14 (VL:VH) scFv LIR1 HTICD	DIQMTQSPSTLSA SVGDRVTITCRSS QSIVHSNGNTYLE WYQQKPGKAPKLL IYKVSNRFSGVPA RFSGSGSGTEFTL TISSLQPDDFATY YCFQGSHVPRTFG QGTKVEVKGGGGS GGGGSGGGGSGGQ VQLVQSGAEVKKP GSSVKVSCKASGY TFTSYHIHWVRQA PGQGLEWIGWIYP	GACATTCAAATGACCCAGAGCCCATCCACCCTGAGCGCATCT GTAGGTGACCGGGTCACCATCACTTGTAGATCCAGTCAGAGT ATTGTACACAGTAATGGGAACACCTATTTGGAATGGTATCAG CAGAAACCAGGTAAAGCCCCAAAATTGCTCATCTACAAAGTC TCTAACAGATTTAGTGGTGTACCAGCCAGGTTCAGCGGTTCC GGAAGTGGTACTGAATTCACCCTCACGATCTCCTCTCTCCAG CCAGATGATTTCGCCACTTATTACTGTTTTCAAGGTTCACAT GTGCCGCGCACATTCGGTCAGGGTACTAAAGTAGAAGTCAAA GGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCGGCGGAGGA AGCGGAGGCCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTG AAGAAGCCTGGGTCCTCAGTGAAGGTTTCCTGCAAGGCTTCT GGATACACCTTCACTAGCTATCATATACATTGGGTGCGCCAG GCCCCCGGACAAGGGCTTGAGTGGATCGGATGGATCTACCCT GGCAATGTTAACACAGAATATAATGAGAAGTTCAAGGGCAAA

	GNVNTEYNEKFKG KATITADESTNTA YMELSSLRSEDTA VYYCAREEITYAM DYWGQGTLVTVSS YGSQSSKPYLLTH PSDPLELVVSGPS GGPSSPTTGPTST SGPEDQPLTPTGS DPQSGLGRHLGVV IGILVAVILLLLL LLLLFLILRHRRQ GKHWTSTQRKADF QHPAGAVGPEPTD RGLQWRSSPAADA QEENLYAAVKHTQ PEDGVEMDTRSPH DEDPQAVTYAEVK HSRPRREMASPPS PLSGEFLDTKDRQ AEEDRQMDTEAAA SEAPQDVTYAQLH SLTLRREATEPPP SQEGPSPAVPSIY ATLAIH (SEQ ID NO: 91)	GCCACCATTACCGCGGACGAATCCACGAACACAGCCTACATG GAGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTGTATTAC TGTGCGAGGGAGGAAATTACCTACGCTATGGACTACTGGGGC CAGGGAACCCTGGTCACCGTGTCCTCATACGGCTCACAGAGC TCCAAACCCTACCTGCTGACTCACCCCAGTGACCCCCTGGAG CTCGTGGTCTCAGGACCGTCTGGGGGCCCCAGCTCCCCGACA ACAGGCCCCACCTCCACATCTGGCCCTGAGGACCAGCCCCTC ACCCCCACCGGGTCGGATCCCCAGAGTGGTCTGGGAAGGCAC CTGGGGGTTGTGATCGGCATCTTGGTGGCCGTCATCCTACTG CTCCTCCTCCTCCTCCTCCTCTTCCTCATCCTCCGACATCGA CGTCAGGGCAAACACTGGACATCGACCCAGAGAAAGGCTGAT TTCCAACATCCTGCAGGGGCTGTGGGGCCAGAGCCCACAGAC AGAGGCCTGCAGTGGAGGTCCAGCCCAGCTGCCGATGCCCAG GAAGAAAACCTCTATGCTGCCGTGAAGCACACACAGCCTGAG GATGGGGTGGAGATGGACACTCGGAGCCCACACGATGAAGAC CCCCAGGCAGTGACGTATGCCGAGGTGAAACACTCCAGACCT AGGAGAGAAATGGCCTCTCCTCCTTCCCCACTGTCTGGGGAA TTCCTGGACACAAAGGACAGACAGGCGGAAGAGGACAGGCAG ATGGACACTGAGGCTGCTGCATCTGAAGCCCCCCAGGATGTG ACCTACGCCCAGCTGCACAGCTTGACCCTCAGACGGGAGGCA ACTGAGCCTCCTCCATCCCAGGAAGGGCCCTCTCCAGCTGTG CCCAGCATCTACGCCACTCTGGCCATCCACTAG (SEQ ID NO: 113)
PA2.1.1 4 scFv LIR1 sHTICD	QVQLVQSGAEVKK PGSSVKVSCKASG YTFTSYHIHWVRQ APGQGLEWIGWIY PGNVNTEYNEKFK GKATITADESTNT AYMELSSLRSEDT AVYYCAREEITYA MDYWGQGTLVTVS SGGGGSGGGGSGG GGSGGDIQMTQSP STLSASVGDRVTI TCRSSQSIVHSNG NTYLEWYQQKPGK APKLLIYKVSNRF SGVPARFSGSGSG TEFTLTISSLQPD DFATYYCFQGSHV PRTFGQGTKVEVK VVSGPSGGPSSPT TGPTSTSGPEDQP LTPTGSDPQSGLG RHLGVVIGILVAV ILLLLLLLLLFLI LRHRRQGKHWTST QRKADFQHPAGAV GPEPTDRGLQWRS SPAADAQEENLYA	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCT GGGTCCTCAGTGAAGGTTTCCTGCAAGGCTTCTGGATACACC TTCACTAGCTATCATATACATTGGGTGCGCCAGGCCCCCGGA CAAGGGCTTGAGTGGATCGGATGGATCTACCCTGGCAATGTT AACACAGAATATAATGAGAAGTTCAAGGGCAAAGCCACCATT ACCGCGGACGAATCCACGAACACAGCCTACATGGAGCTGAGC AGCCTGAGATCTGAAGACACGGCTGTGTATTACTGTGCGAGG GAGGAAATTACCTACGCTATGGACTACTGGGGCCAGGGAACC CTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGA GGATCTGGCGGCGGAGGAAGCGGAGGCGACATTCAAATGACC CAGAGCCCATCCACCCTGAGCGCATCTGTAGGTGACCGGGTC ACCATCACTTGTAGATCCAGTCAGAGTATTGTACACAGTAAT GGGAACACCTATTTGGAATGGTATCAGCAGAAACCAGGTAAA GCCCCAAAATTGCTCATCTACAAAGTCTCTAACAGATTTAGT GGTGTACCAGCCAGGTTCAGCGGTTCCGGAAGTGGTACTGAA TTCACCCTCACGATCTCCTCTCTCCAGCCAGATGATTTCGCC ACTTATTACTGTTTTCAAGGTTCACATGTGCCGCGCACATTC GGTCAGGGTACTAAAGTAGAAGTCAAAGTGGTCTCAGGACCG TCTGGGGGCCCCAGCTCCCCGACAACAGGCCCCACCTCCACA TCTGGCCCTGAGGACCAGCCCCTCACCCCCACCGGGTCGGAT CCCCAGAGTGGTCTGGGAAGGCACCTGGGGGTTGTGATCGGC ATCTTGGTGGCCGTCATCCTACTGCTCCTCCTCCTCCTCCTC CTCTTCCTCATCCTCCGACATCGACGTCAGGGCAAACACTGG ACATCGACCCAGAGAAAGGCTGATTTCCAACATCCTGCAGGG GCTGTGGGGCCAGAGCCCACAGACAGAGGCCTGCAGTGGAGG TCCAGCCCAGCTGCCGATGCCCAGGAAGAAAACCTCTATGCT GCCGTGAAGCACACACAGCCTGAGGATGGGGTGGAGATGGAC ACTCGGAGCCCACACGATGAAGACCCCCAGGCAGTGACGTAT

	AVKHTQPEDGVEM DTRSPHDEDPQAV TYAEVKHSRPRRE MASPPSPLSGEFL DTKDRQAEEDRQM DTEAAASEAPQDV TYAQLHSLTLRRE ATEPPPSQEGPSP AVPSIYATLAIH (SEQ ID NO: 90)	GCCGAGGTGAAACACTCCAGACCTAGGAGAGAAATGGCCTCT CCTCCTTCCCCACTGTCTGGGGAATTCCTGGACACAAAGGAC AGACAGGCGGAAGAGGACAGGCAGATGGACACTGAGGCTGCT GCATCTGAAGCCCCCCAGGATGTGACCTACGCCCAGCTGCAC AGCTTGACCCTCAGACGGGAGGCAACTGAGCCTCCTCCATCC CAGGAAGGGCCCTCTCCAGCTGTGCCCAGCATCTACGCCACT CTGGCCATCCACTAG (SEQ ID NO: 112)
PA2.1.1 4 scFv LIR1 HTICD	QVQLVQSGAEVKK PGSSVKVSCKASG YTFTSYHIHWVRQ APGQGLEWIGWIY PGNVNTEYNEKFK GKATITADESTNT AYMELSSLRSEDT AVYYCAREEITYA MDYWGQGTLVTVS SGGGGSGGGGSGG GGSGGDIQMTQSP STLSASVGDRVTI TCRSSQSIVHSNG NTYLEWYQQKPGK APKLLIYKVSNRF SGVPARFSGSGSG TEFTLTISSLQPD DFATYYCFQGSHV PRTFGQGTKVEVK YGSQSSKPYLLTH PSDPLELVVSGPS GGPSSPTTGPTST SGPEDQPLTPTGS DPQSGLGRHLGVV IGILVAVILLLLL LLLLFLILRHRRQ GKHWTSTQRKADF QHPAGAVGPEPTD RGLQWRSSPAADA QEENLYAAVKHTQ PEDGVEMDTRSPH DEDPQAVTYAEVK HSRPRREMASPPS PLSGEFLDTKDRQ AEEDRQMDTEAAA SEAPQDVTYAQLH SLTLRREATEPPP SQEGPSPAVPSIY ATLAIH (SEQ ID NO: 89)	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCT GGGTCCTCAGTGAAGGTTTCCTGCAAGGCTTCTGGATACACC TTCACTAGCTATCATATACATTGGGTGCGCCAGGCCCCCGGA CAAGGGCTTGAGTGGATCGGATGGATCTACCCTGGCAATGTT AACACAGAATATAATGAGAAGTTCAAGGGCAAAGCCACCATT ACCGCGGACGAATCCACGAACACAGCCTACATGGAGCTGAGC AGCCTGAGATCTGAAGACACGGCTGTGTATTACTGTGCGAGG GAGGAAATTACCTACGCTATGGACTACTGGGGCCAGGGAACC CTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGA GGATCTGGCGGCGGAGGAAGCGGAGGCGACATTCAAATGACC CAGAGCCCATCCACCCTGAGCGCATCTGTAGGTGACCGGGTC ACCATCACTTGTAGATCCAGTCAGAGTATTGTACACAGTAAT GGGAACACCTATTTGGAATGGTATCAGCAGAAACCAGGTAAA GCCCCAAAATTGCTCATCTACAAAGTCTCTAACAGATTTAGT GGTGTACCAGCCAGGTTCAGCGGTTCCGGAAGTGGTACTGAA TTCACCCTCACGATCTCCTCTCTCCAGCCAGATGATTTCGCC ACTTATTACTGTTTTCAAGGTTCACATGTGCCGCGCACATTC GGTCAGGGTACTAAAGTAGAAGTCAAATACGGCTCACAGAGC TCCAAACCCTACCTGCTGACTCACCCCAGTGACCCCCTGGAG CTCGTGGTCTCAGGACCGTCTGGGGGCCCCAGCTCCCCGACA ACAGGCCCCACCTCCACATCTGGCCCTGAGGACCAGCCCCTC ACCCCCACCGGGTCGGATCCCCAGAGTGGTCTGGGAAGGCAC CTGGGGGTTGTGATCGGCATCTTGGTGGCCGTCATCCTACTG CTCCTCCTCCTCCTCCTCCTCTTCCTCATCCTCCGACATCGA CGTCAGGGCAAACACTGGACATCGACCCAGAGAAAGGCTGAT TTCCAACATCCTGCAGGGGCTGTGGGGCCAGAGCCCACAGAC AGAGGCCTGCAGTGGAGGTCCAGCCCAGCTGCCGATGCCCAG GAAGAAAACCTCTATGCTGCCGTGAAGCACACACAGCCTGAG GATGGGGTGGAGATGGACACTCGGAGCCCACACGATGAAGAC CCCCAGGCAGTGACGTATGCCGAGGTGAAACACTCCAGACCT AGGAGAGAAATGGCCTCTCCTCCTTCCCCACTGTCTGGGGAA TTCCTGGACACAAAGGACAGACAGGCGGAAGAGGACAGGCAG ATGGACACTGAGGCTGCTGCATCTGAAGCCCCCCAGGATGTG ACCTACGCCCAGCTGCACAGCTTGACCCTCAGACGGGAGGCA ACTGAGCCTCCTCCATCCCAGGAAGGGCCCTCTCCAGCTGTG CCCAGCATCTACGCCACTCTGGCCATCCACTAG (SEQ ID NO: 111)

Example 7: Comparison of LIR-1, CTLA-4 and PD-1 Inhibitory Receptors

[0283] An NY-ESO-1-responsive inhibitory construct was created by fusing the NY-ESO-1 scFv LBD to domains of receptors including hinge, transmembrane region, and/or intracellular domain of leukocyte immunoglobulin-like receptor subfamily B member 1, LILRB1 (LIR-1), programmed cell death protein 1, PDCD1 (PD-1), or cytotoxic T-lymphocyte protein 4, CTLA4 (CTLA-4). MAGE-A3 activating CAR constructs contained an scFv fused to the CD8α hinge, CD28 TM, and CD28, 4-1BB and CD 3zeta intracellular domains (ICDs). Gene segments were combined using Golden Gate cloning and inserted downstream of a human EF1α promoter contained in a lentiviral expression plasmid.

[0284] Initially, peptide-MHC (pMHC) targets for both the activator and blocker receptors were used, because pMHCs allow convenient quantification of the pharmacology of the system (FIG. 14A). Specifically, a single-chain fragment variable (scFv) that binds HLA-A*02-NY-ESO-$1_{(SLLMWITQC/V)}$ was used as the inhibitor receptor ligand-binding domain (LBD), and a second scFv against HLA-A*02-MAGE-$A3_{(FLWGPRALV)}$ pMHC (Gallo, unpublished) was as part of an activator receptor third-generation CAR. Jurkat effector cells that express luciferase upon NFAT activation were used to readout activator sensitivity, with EC50 values reporting the half-maximum activator peptide concentration required for a response. Both PD-1 and CTLA-4 intracellular domains (ICD) mediated a shift in EC50 of activation in Jurkat cells of less than ~10x, measured by titration of peptides loaded on T2 cells as stimulus (FIG. 14B).

[0285] A variety of potential inhibitor (blocker) receptor constructs were screened, and the LIR-1 blocker constructed was discovered to have stronger blocking properties than PD-1 and CTLA-4. This blocker receptor includes the intracellular, transmembrane (TM) and hinge domains of the LIR-1 (LILRB1) receptor, one of several LIR-family molecules encoded by the human genome. The LIR-1 blocker (henceforth referred to as LIR-1) fused to the NY-ESO-1 LBD mediated an EC50 shift of >5,000x (FIG. 14B, FIGS. 17A-17D). A control, titration of unrelated HLA-A*02-binding peptides provided an estimate of the shift caused by competition of loaded peptides on T2 cells for available HLA molecules, a contribution to the total shift typically less than ~10x (FIG. 15). For the EC50 shift values reported here, comparisons were typically to EC50s of activator-only constructs. Further, for a given pair of activator/blocker receptors, the mid-point of titration for inhibition was approximately constant and depended on the ratio of activating to

blocking peptide, presumably directly correlated with the target-antigen ratio (FIGS. 16A-16D). The target concentration explored in the majority of these experiments is estimated to have ranged from ~1,000-10,000 copies/cell.

Example 8: LIR-1 Inhibitory Receptors with Multiple scFv Ligand Binding Domains

[0286] The activity of the LIR-1 inhibitory receptor was tested with a variety of antigen-binding domains specific to other pMHC targets. For four different pMHC targets, a total of six different scFvs grafted onto the LIR-1 mediated dramatic shifts in EC50, ranging from 10 to 1,000x (FIG. 14C). With respect to its interaction with activator receptors, the LIR-1 receptor was also robust; its blocking behavior was applicable to multiple targets and scFvs (FIG. 14D). The blockade was ligand-dependent (FIG. 17A), although many LIR-1 constructs produced lower basal/tonic signaling when paired with specific activator receptors. The EC50 shifts depended on the presence of a fused ICD, as LIR-1 constructs completely lacking ICD, or containing mutations in key elements of the ICD, had no effect (FIG. 17B). The ligand-independent blocker activity, however, had little effect on the activation EC50 absent ligand (FIG. 16A-16D). LIR-1 inhibitory receptors are a modular, adaptable, ligand-gated system that functions across multiple targets and antigen-binding domains.

Example 9: LIR-1 Inhibitory Domains Fused to TCR alpha and TCR beta

[0287] The LIR-1 inhibitory receptor was tested when fused to TCRalpha and TCR beta subunits, or when in combination with a TCR activator receptor. TCRs directed against 3 different pMHC targets, 2 from MAGE-A3 and one from HPV (see Methods, *supra*). In every case, LIR-1 shifted the activation EC50 by large amounts, estimated to range >1,000x (FIG. 14E; FIG. 19A). Furthermore, an NY-ESO-1 TCR LBD, when fused to LIR-1, also produced substantial EC50 shifts (Fig. 14F; FIG. 19B). Indeed, all combinations of a MAGE-A3$_{(FLWGPRALV)}$ CAR or TCR with an NY-ESO-1$_{(SLLMWITQV)}$ scFv or TCR displayed large shifts. Thus, the LIR-1 inhibitory receptor exhibited modularity that encompassed both CARs and TCRs.

Example 10: LIR-1 Inhibitory Receptors Respond to Target Antigen Present in *cis* to Activator Receptor Target Antigen

[0288] The ability of the LIR-1 blocker receptor to inhibit activation by an activator receptor when activator and inhibitor targets were presented in cis was assayed. In a first assay, a simplified stimulus consisting of target-loaded beads roughly the size of cells (*d* ~2.8 um) was used. Jurkat cells expressing activator and blocker receptors were activated only by beads that contained the A (activator) target, not by beads with dual A/B (activator/blocker) targets (FIG. 18A). Interestingly, the effector cells were activated by a mixture of A+ and B+ beads, even when the A+ beads comprised only 20% of the total. This demonstrated that the cells expressing the activator and blocker receptors are: (i) blocked from activation by the blocker receptor when the targets are present in *cis* on the same surface; and, (ii) activated by individual A+ beads among an excess of B+ beads.

Example 11: LIR-1 Inhibitory Receptors and Cell Surface Antigens

[0289] The ability of the LIR-1 inhibitor receptor to block activation in response to non-pMHC targets, representing surface antigens that can extend into the realm of 100,000 epitopes/cell, was assayed. scFvs that bind either the B-cell marker CD19, the solid-tumor antigen mesothelin (MSLN), or HLA-A*02 in a peptide-independent fashion were tested. In these cases, the target antigen concentration was not controlled, as with exogenous peptide as with pMHCs. Instead, the ratio of activator to blocker expression was varied using different DNA concentrations in transient transfection assays. Though assay sensitivity prevented exploration of the full range of EC50 shifts, shifts in Emax over 10x were observed. These experiments showed that the properties of the LIR-1 receptor in a dual receptor system were generally the same for high-density targets (FIG. 18B;FIGS. 16-16D, FIG. 21A) and that the blocker receptor blocked activation of the A receptor to an extent reflected by its relative surface level on the effector cells (FIG. 18C). The LIR-1 receptor also behaved in a modular manner in this high-antigen-density setting. An scFv against HLA-A*02 acted either as activator (FIG. 18D) or blocker when fused to either an activator or blocker receptor, respectively. The LIR-1 receptor is flexible enough to accommodate low and high target densities, in principle allowing optimization for pMHC targets as well as non-pMHC surface antigens.

Example 12: LIR-1 Inhibitory Receptors in Primary T Cells

[0290] The ability of the LIR-1 receptor to block activation of primary T cells was assayed. pMHC targets were used initially. After enrichment for transduced T cells via physical selection, engineered T cells expressing activator and blocker receptors were assayed using target cells engineered to express luciferase as the readout for viable cells. With an HPV TCR as activator, the NY-ESO-1 scFv fused to LIR-1 shifted the cell-count vs. peptide-concentration curve in peptide-loaded MCF7 tumor cells by ~25x (FIG. 20A; FIG. 23). Thus, the behavior of LIR-1 receptor demonstrated in Jurkat cell activation assays was extended to primary T cell functions, including cytotoxicity.

[0291] To establish proof of concept, the HLA-A*02 LIR-1 construct was shown to function as a blocker in the presence of pMHC-dependent activators in Jurkat cells with T2 target cells (FIG. 20B). For the activator, a CD19 scFv was used as a CAR. This activator/blocker pair was shown to function together as robustly as other pairs previously tested in Jurkat cells (FIG. 18B). T model tumor cells that differentially express the LIR-1 receptor ligand, CD19-positive, HLA-A*02-negative Raji cells were used. To model the corresponding normal cells, the same cell line stably expressing the HLA-A*02 gene was used (FIG. 24A). The cell lines activated Jurkat cells if the target cells expressed CD19 only, but not if they expressed both CD19 and HLA-A*02; i.e., the HLA-A*02 blocker receptor blocked activation by CD19-CAR in a ligand-dependent way (FIG. 24B).

[0292] The CD19/HLA-A*02 receptor pair also worked in primary T cells (FIG. 21). Engineered T cells killed CD19-expressing Raji cells in the absence of HLA-A*02 expression. Raji cells that expressed both CD19 and HLA-A*02 were blocked from cytotoxicity. Importantly, primary T cells bearing the receptor pairs distinguished CD19+ “tumor” from CD19+/HLA-A*02+ “normal” cells in a mixed culture. These findings mirrored results from the above-mentioned bead experiment, but in a more complex cellular setting where the effector cells’ cytotoxicity focused on “tumor” targets, even when surrounded by “normal” cells. The degree of selectivity was impressive given that neither receptor had been subjected to deliberate optimization for maximal selectivity. This behavior was confirmed with a second antigen, MSLN (FIG. 22B).

Example 13: Reversibility of Inhibition by LIR-1 Inhibitory Receptors

[0293] The LIR-1 inhibitory receptor was tested for its ability to function reversibly; that is, to cycle from a state of blockade to activation and back to blockade. Effector T cells expressing the LIR-1 receptor and activator receptor were tested to see if they could function reversibly and iteratively. The effector cells were co-cultured with Raji cells, either to mimic tumor (CD19+) or normal (CD19+/HLA-A*02+) cell encounter. After each round of exposure to target cells, the Raji cells were removed from the culture and a new population of target cells was introduced. Cytotoxicity and gamma-interferon (IFNγ) were measured at the end of each round. In both permutations, block-kill-block and kill-block-kill, the T cells functioned as required by a cell therapeutic of this type (FIGS. 25A-25D). They reversibly cycled from a state of block to cytotoxicity and back, depending on the target cells to which they were exposed. This result demonstrates that a T cell expressing an activator receptor and the LIR-1 inhibitory receptor do not get stuck in one state (blockade or activation), but rather can switch back and forth as it integrates signals from normal and tumor cells. Additionally, these experiments were reproduced in primary T cells from multiple donors (FIGS. 21A-D, FIGS. 25A-25D; FIGS. 26A-26B), despite their complexity, heterogeneity and donor-to-donor variability, demonstrating the robust functions of the LIR-1 inhibitory receptor.

Example 14: Human T Cells expressing an Activator Receptor and LIR-1 Blocker Receptor Selectively Target Cancer Cells in a Mouse Model

[0294] The ability of the CD19/HLA-A*02 activator/blocker pair engineered in primary T cells to allow expansion of the T cells *in vitro* to large numbers using standard CD3/CD28 stimulation was assayed (FIG. 27A; FIG. 28A). Thus, T cells expressing the activator and LIR-1 receptors c can be scaled up to sufficient numbers for animal experiments and ultimately for patients.

[0295] The CD19/HLA-A*02 activator/blocker combination was tested *in vitro* to demonstrate selective killing of CD19+ tumor cells, while sparing CD19+/HLA-A*02+ cells in a mouse xenograft cancer model (FIG. 27B). The same two Raji cell lines described above, one CD19+ and the other CD19+/HLA-A*02+, were injected into the flanks of immunocompromised (NGS-HLA-A2.1) mice. T cells engineered with the test constructs were injected at two doses, 2e6

(not shown) or 1e7 T cells. The growth of the tumor, as well as the persistence of the implanted T cells, were analyzed over time. Only the CD19+ tumor cells were killed in the mouse and the tumor control tracked with transferred T cell numbers, promoting survival of the host mice (FIGS. 27C-27E; FIGS. 28B-28C). The CD19+/HLA-A*02+ cells designed to model normal cells were unaffected. Human CD4+/CD8+ cell ratios in the blood of mice bearing engineered cells tracked with their control counterpart; i.e., in "tumor"-grafted mice, CD4+ > CD8+ cells, as in the CD19 CAR positive control mice; and, in "normal"-grafted mice, CD4+ < CD8+ cells, similar to mice harboring untransduced T cells (FIG. 28D). Moreover, huCD3+ cells in the tumor (FIGS. 29A-29B) correlated inversely with tumor volume, and engineered T cells expressing the two receptors behaved like untransduced T cells in "normal" grafts (low infiltrate), and like the CD19 CAR in "tumor" grafts (high infiltrate). Finally, the mice appeared normal with regard to typical clinical observations (Table 10). Together, these results demonstrated that the LIR-1 inhibitory receptor can function *in vivo* to inhibit an activator receptor, in a simplified setting devised to mimic the different normal and tumor cell types that will be encountered in patients.

Table 10. Clinical observations of mice during in vivo experiment

	Study Day:	6	8	10	13	15	17	20	22	24	28	29
Group	Animal ID	CO	CO	CO	CO	CO	CO	CO	CO	CO	CO	CO
Tumor Untreated	59	N	N	N	N	N	N	N	N	N	N	N, EUT
	100	N	N	N	N	N	N	N	N	N	N	N
	61	N	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)
	285	N	N	N	N	N	N	N	N	N	N	N, EUT
	289	N	N	N	N	N	N	N	N	19AN(1)	N	N, EUT
	87	N	N	N	N	N	N	N	N	N	N	N, EUT
	60	N	N	N	N	N	N	N	N	N	N	N
Tumor Untransduced	286	N	N	N	N	N	N	N	N	N	19AN(1)	19AN(1), EUT
	78	N	N	N	N	N	N	N	N	N	N	N
	76	N	N	N	N	N	N	N	N	N	N	N
	89	N	N	N	N	N	N	N	N	N	N	N, EUT
	90	N	N	N	N	N	N	N	N	N	N	N

	275	N	N	N	N	N	N	N	N	N	N	N
	83	N	N	N	N	N	N	N	N	N	19AN(1)	19AN(1), EUT
Tumor CD19-CAR only	280	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)	19AN(1)	N	N
	99	N	N	N	N	N	N	N	N	N	N	N
	284	N	N	N	N	N	N	N	N	N	N	N
	71	N	N	N	N	N	N	N	N	N	N	N
	279	N	N	N	N	N	N	N	N	N	N	N
	77	N	N	N	N	N	N	N	N	N	N	N
	94	N	N	N	N	N	N	N	N	N	N	N
Tumor CD19-CAR + A2-LIR1	64	N	N	N	N	N	N	N	N	N	N	N
	69	N	N	N	N	N	N	N	N	N	N	N
	274	N	N	N	N	N	N	N	N	N	N	N
	96	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)
	277	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)
	97	N	N	N	N	N	N	N	N	N	N	N
"Normal" Untreated	66	N	N	N	N	N	N	N	N	19AN(1)	19AN(2)	19AN(2), EUT
	294	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(2)	19AN(2), EUT
	293	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(2)	19AN(2), EUT
	91	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(2)	19AN(2), EUT
	287	N	N	N	N	N	N	N	N	19AN(1)	19AN(2)	19AN(2), EUT
	281	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(2)	19AN(2), EUT
	282	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1), EUT
"Normal" Untransduced	290	N	N	N	N	N	N	N	N	N	19AN(1)	19AN(1), EUT

	25	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1), EUT
	93	N	N	N	N	N	N	N	N	N	N	N, EUT
	84	N	N	N	N	N	N	N	N	N	N	N, EUT
	292	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)
	65	N	N	N	N	N	N	N	N	N	19AN(1)	19AN(1), EUT
	79	N	N	N	N	N	N	N	N	N	N	N
"Normal" CD19-CAR only	270	N	N	N	N	N	N	N	N	N	N	N
	283	N	N	N	N	N	N	N	N	N	N	N
	82	N	N	N	N	N	N	N	N	N	N	N
	92	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)	19AN(1)	19AN(1)	19AN(1)
	95	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)	19AN(1)
	80	N	N	N	N	N	N	N	N	N	N	N
	297	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)	19AN(1)
"Normal" CD19-CAR + A2-LIR1	86	N	N	N	N	N	N	N	N	N	N	N
	74	N	N	N	N	N	N	N	N	N	N	N
	288	N	N	N	N	N	N	N	N	N	N	N
	273	N	N	N	N	N	N	N	N	N	N	N
	70	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)
	73	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1)
	72	N	N	N	N	N	N	N	N	19AN(1)	19AN(1)	19AN(1), EUT

[0296] Tumor and "normal" cells were injected on study day 0 and treatment started on study day 10. Clinical observation (CO) were performed 3x/week focusing on poor health, stress and pain. Per IACUC guidelines, mice were euthanized if tumors reached > 2000 mm^3. Codes: N = normal; 19A = Abnormal Tumor [N = Necrotic, O = Open], EUT = Euthanized. Severity codes: 0 = Not present, 1 = Moderate, 2 = Severe.

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The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

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

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CLAIMS:

1. A chimeric antigen receptor comprising a polypeptide, wherein the polypeptide comprises:
    a) an LILRB1 hinge domain;
    b) an LILRB1 transmembrane domain; and
    c) an LILRB1 intracellular domain and/or an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIM), wherein each ITIM is selected from NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11).
2. The receptor of claim 1, wherein the intracellular domain comprises:
    i.) both ITIMs NLYAAV (SEQ ID NO: 8) and VTYAEV (SEQ ID NO: 9);
    ii.) both ITIMs VTYAEV (SEQ ID NO: 9) and VTYAQL (SEQ ID NO: 10);
    iii.) both ITIMs VTYAQL (SEQ ID NO: 10) and SIYATL (SEQ ID NO: 11);
    iv.) the ITIMs NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), and VTYAQL (SEQ ID NO: 10);
    v.) the ITIMs VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11); or
    vi.) the ITIMs NLYAAV (SEQ ID NO: 8), VTYAEV (SEQ ID NO: 9), VTYAQL (SEQ ID NO: 10), and SIYATL (SEQ ID NO: 11);
3. The receptor of claim 1 or claim 2, wherein the intracellular domain comprises: a sequence at least 95% identical to any one of SEQ ID NOs: 7 or 12-17.
4. The receptor of any one of claims 1-3, wherein the LILRB1 transmembrane domain comprises a sequence at least 95% identical to SEQ ID NO: 5.
5. The receptor of any one of claims 1-4, wherein the LILRB1 hinge domain comprises a sequence at least 95% identical to SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84 or SEQ ID NO: 93.
6. The receptor of any one of claims 1-5, wherein the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 2, or SEQ ID NO: 3.

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7. The receptor of any one of claims 1-6, wherein the polypeptide comprises:
    a) the first polypeptide comprising an antigen-binding fragment of the heavy chain of an antibody, and
    b) a second polypeptide comprising an antigen-binding fragment of the light chain of an antibody.
8. The receptor of any one of claims 1-7, wherein the antigen-binding domain comprises a single chain variable fragment (scFv) comprising:
    i.) complementarity determining regions CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 22-27, respectively; or
    ii.) complementarity determining regions CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 28-33, respectively.
9. The receptor of claim 8, wherein the scFv comprises a sequence at least 95% identical to any one of SEQ ID NOS: 35-46 or 125.
10. The receptor of claim 8, wherein the receptor comprises an amino acid sequence at least 95% identical to any one of SEQ ID NOS: 47-71, 77-79, 89-92, 120 or 122, and wherein the receptor comprises an antigen-binding domain comprising:
    i.) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 22-27, respectively; or
    ii.) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 28-33, respectively.
11. The receptor of any one of claims 1-10, wherein the receptor is an inhibitory receptor.
12. A polynucleotide comprising a nucleic acid sequence encoding the receptor of any one of claims 1-11.
13. A vector comprising the polynucleotide of claim 12.
14. An immune cell comprising the receptor of any one of claims 1-11, the polynucleotide of claim 12, or the vector of claim 13.
15. An immune cell comprising a chimeric antigen receptor comprising a polypeptide, wherein the polypeptide sequence shares at least 95% identity to SEQ ID NO: 122, SEQ ID NO: 21, SEQ ID NO: 3, or SEQ ID NO: 2,

wherein the chimeric antigen receptor comprises an antigen-binding domain comprising:

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i.) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 22-27, respectively; or

ii.) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 sequences according to SEQ ID NO: 28-33, respectively.

16. The immune cell of claim 14 or claim 15, wherein the immune cells is a T cell.

17. A method of making an immune cell, comprising introducing the polynucleotide of claim 12, or the vector of claim 13 into the immune cell.

18. A method of treating a subject with a cancer, comprising administering to the subject a plurality of the immune cells of claim 14 or claim 15.

19. Use of the immune cell of claim 14 or claim 15 in the manufacture of a medicament for treating a subject with a cancer.

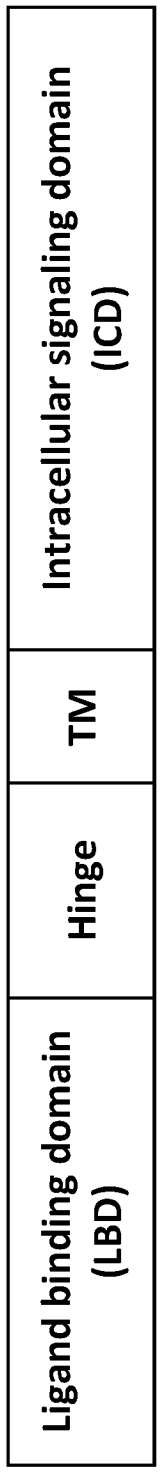

Ligand binding domain (LBD)
Hinge
TM
Intracellular signaling domain (ICD)

FIG. 1

FIG. 2A

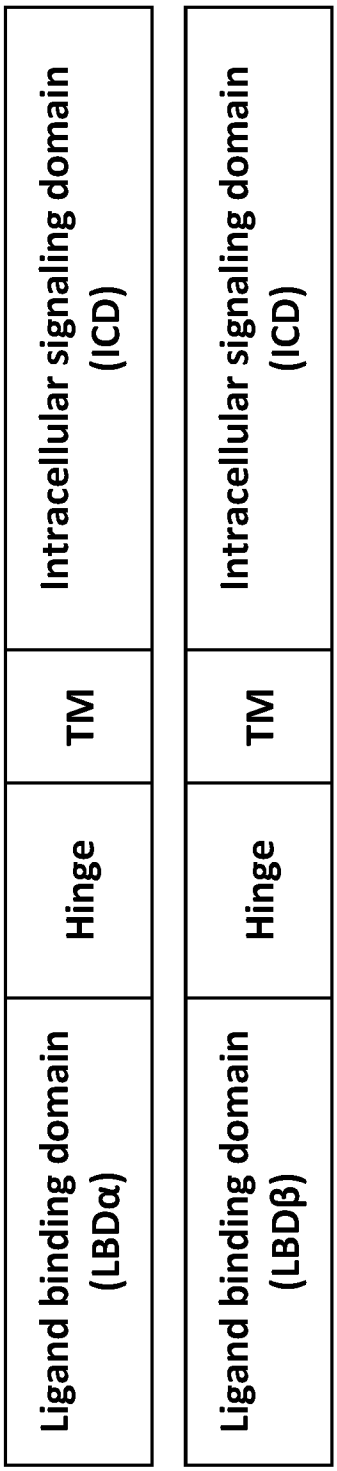
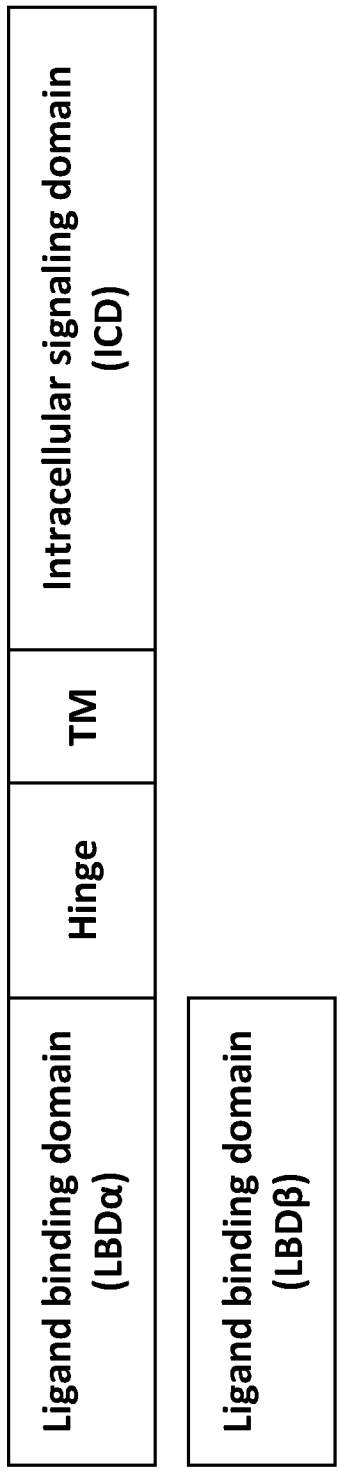

Ligand binding domain (LBDα)
Hinge
TM
Intracellular signaling domain (ICD)
Ligand binding domain (LBDβ)
Hinge
TM
Intracellular signaling domain (ICD)

FIG. 2B


Ligand binding domain (LBDα)
Hinge
TM
Intracellular signaling domain (ICD)
Ligand binding domain (LBDβ)

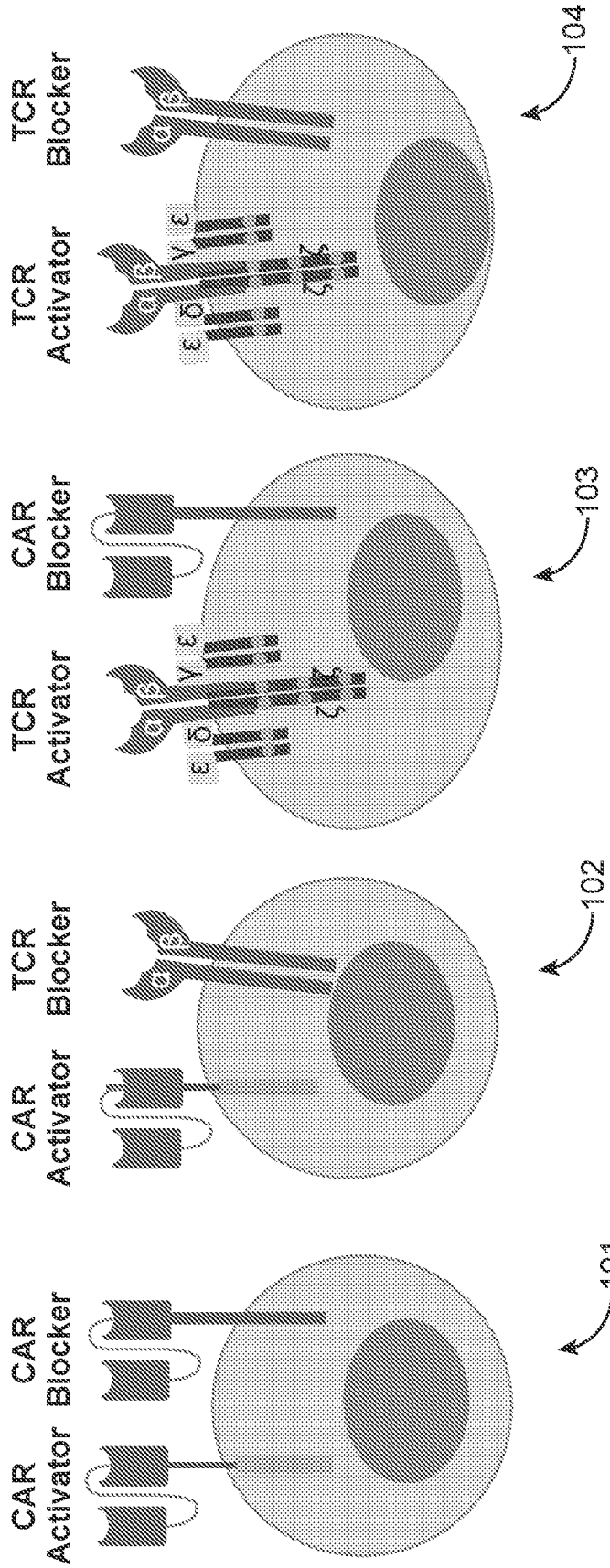

CAR Activator
CAR Blocker
101
CAR Activator
TCR Blocker
102
TCR Activator
CAR Blocker
103
TCR Activator
TCR Blocker
104

FIG. 3

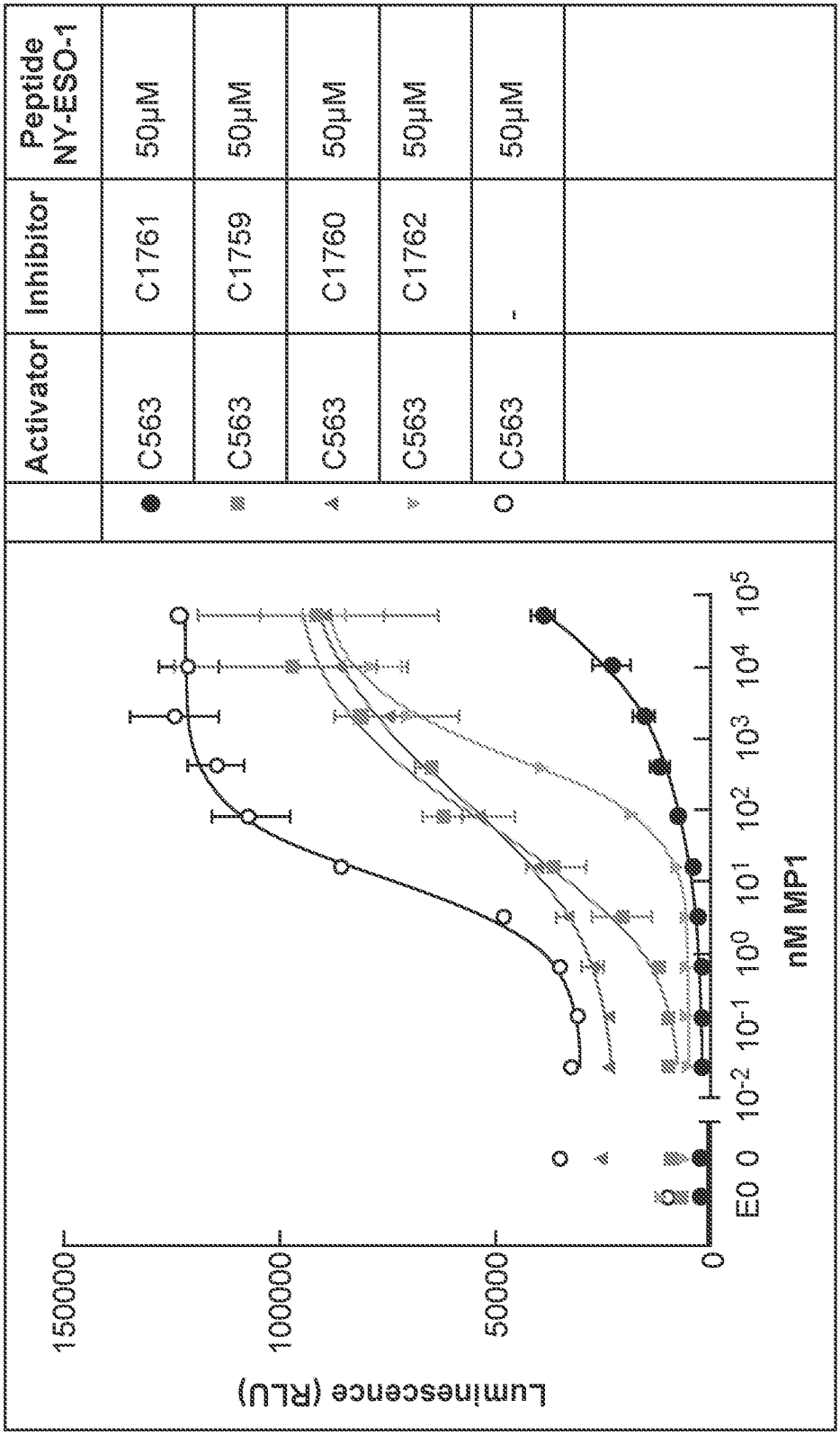

Activator
Inhibitor
Peptide NY-ESO-1
C563
C1761
50µM
C563
C1759
50µM
C563
C1760
50µM
C563
C1762
50µM
C563
-
50µM
Luminescence (RLU)
150000
100000
50000
0
E0 0 10-2 10-1 100 101 102 103 104 105
nM MP1

FIG. 4

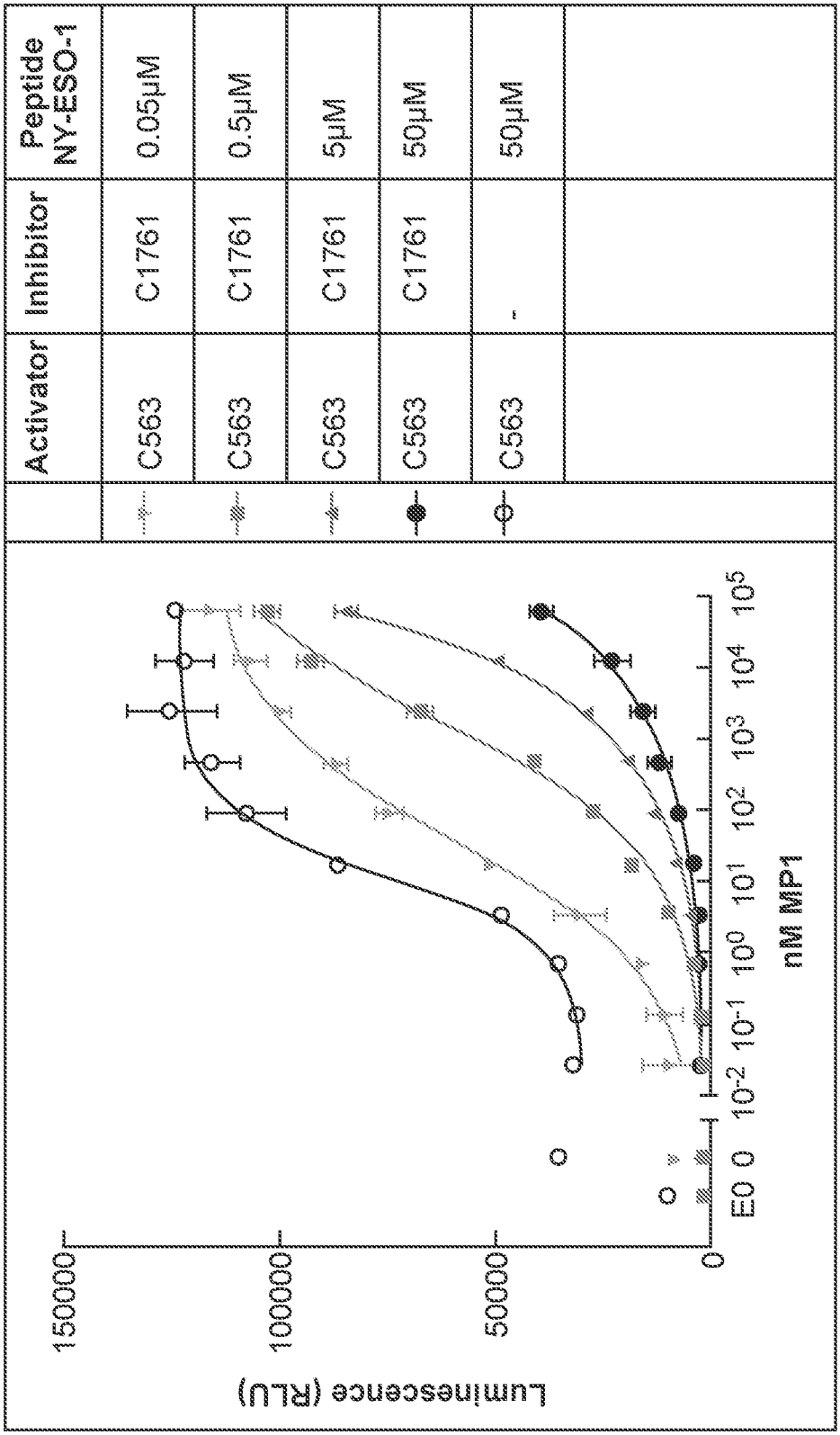

Activator
Inhibitor
Peptide NY-ESO-1
C563
C1761
0.05μM
C563
C1761
0.5μM
C563
C1761
5μM
C563
C1761
50μM
C563
-
50μM
Luminescence (RLU)
150000
100000
50000
0
E0 0
10-2 10-1 100 101 102 103 104 105
nM MP1

FIG. 5

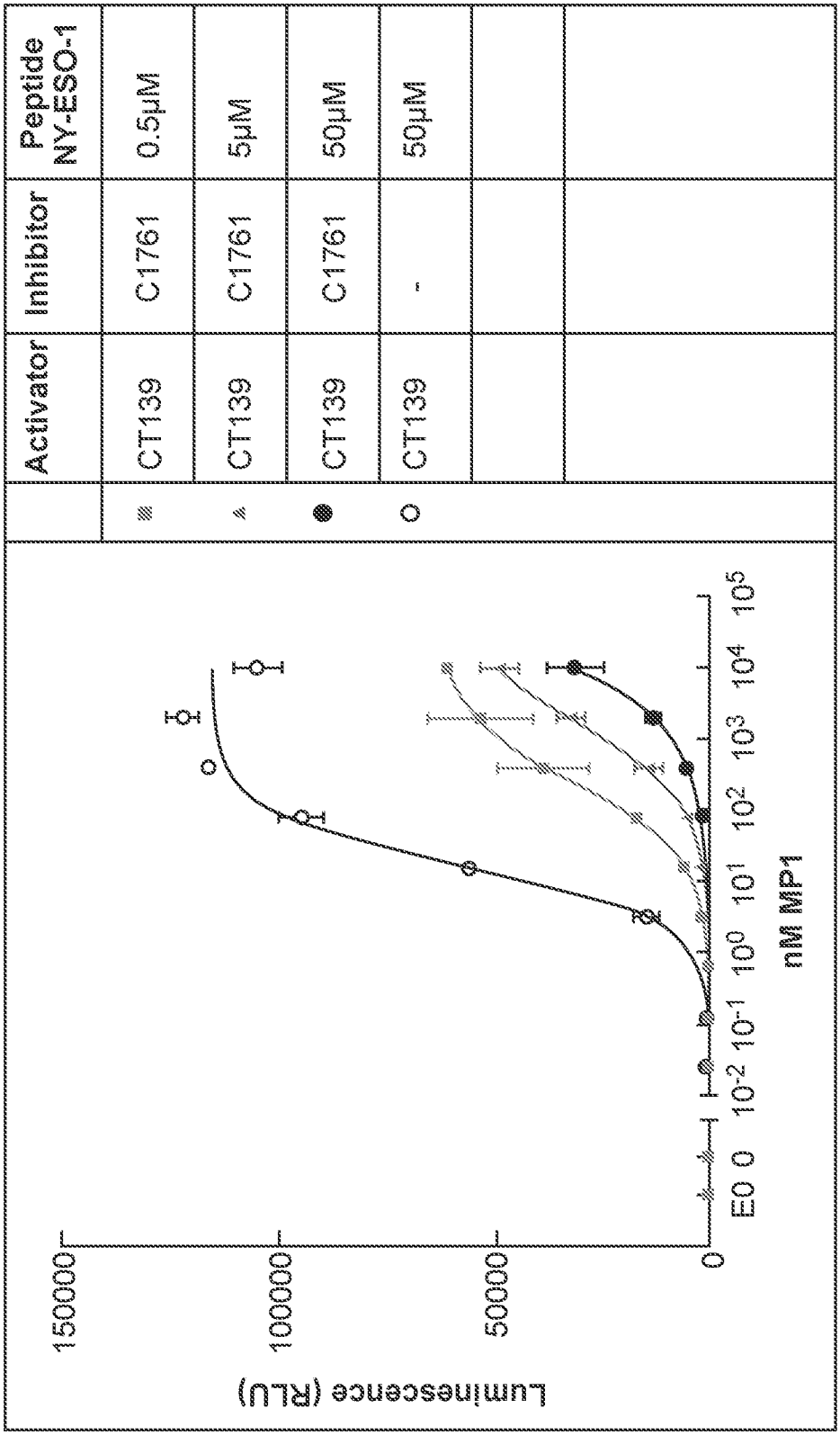

Activator
Inhibitor
Peptide NY-ESO-1
CT139 C1761 0.5µM
CT139 C1761 5µM
CT139 C1761 50µM
CT139 - 50µM
Luminescence (RLU)
150000
100000
50000
0
E0 0 10-2 10-1 100 101 102 103 104 105
nM MP1

FIG. 6

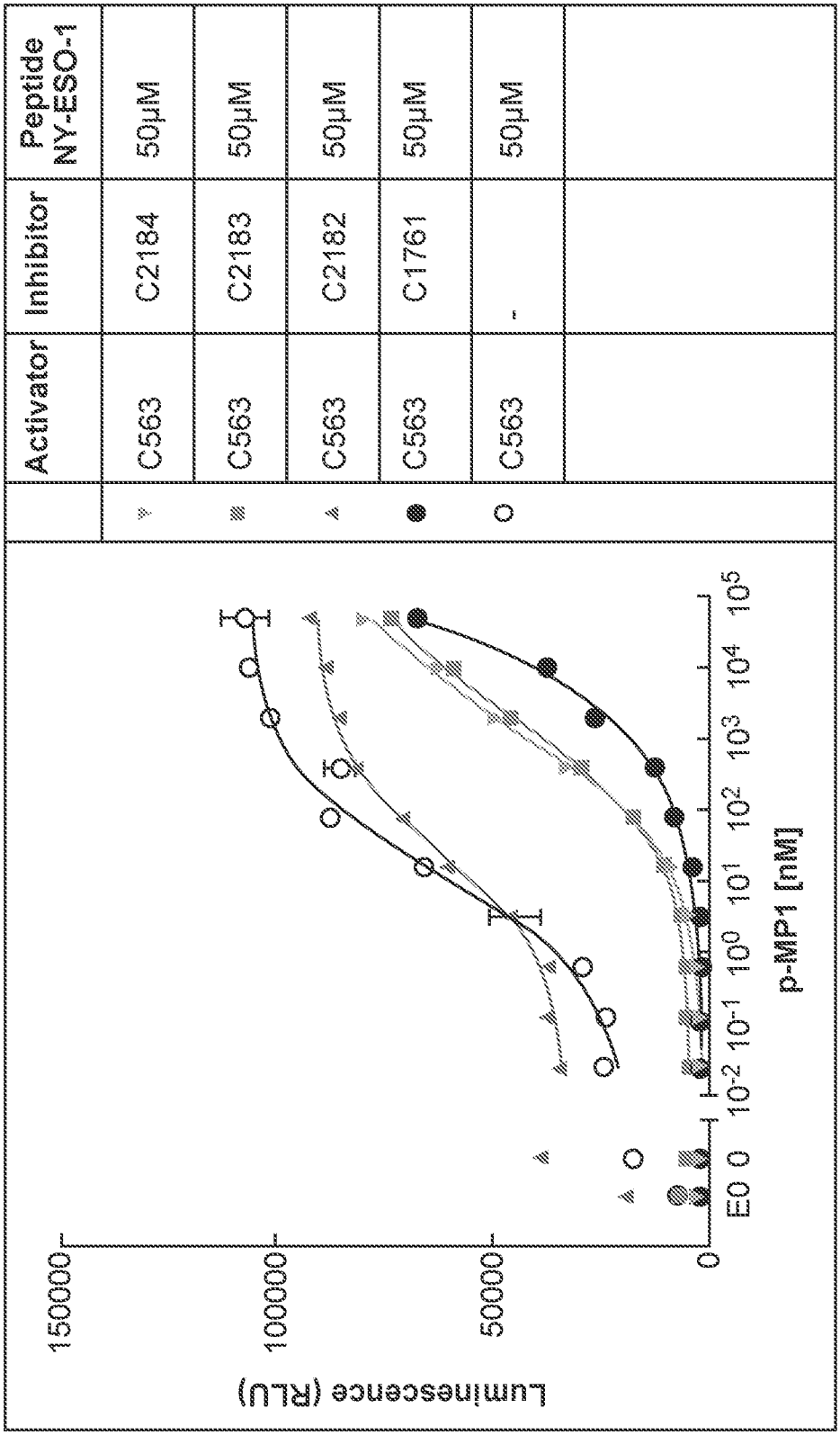

Activator
Inhibitor
Peptide NY-ESO-1
C563
C2184
50μM
C563
C2183
50μM
C563
C2182
50μM
C563
C1761
50μM
C563
-
50μM
Luminescence (RLU)
150000
100000
50000
0
E0 0 10-2 10-1 100 101 102 103 104 105
p-MP1 [nM]

FIG. 7

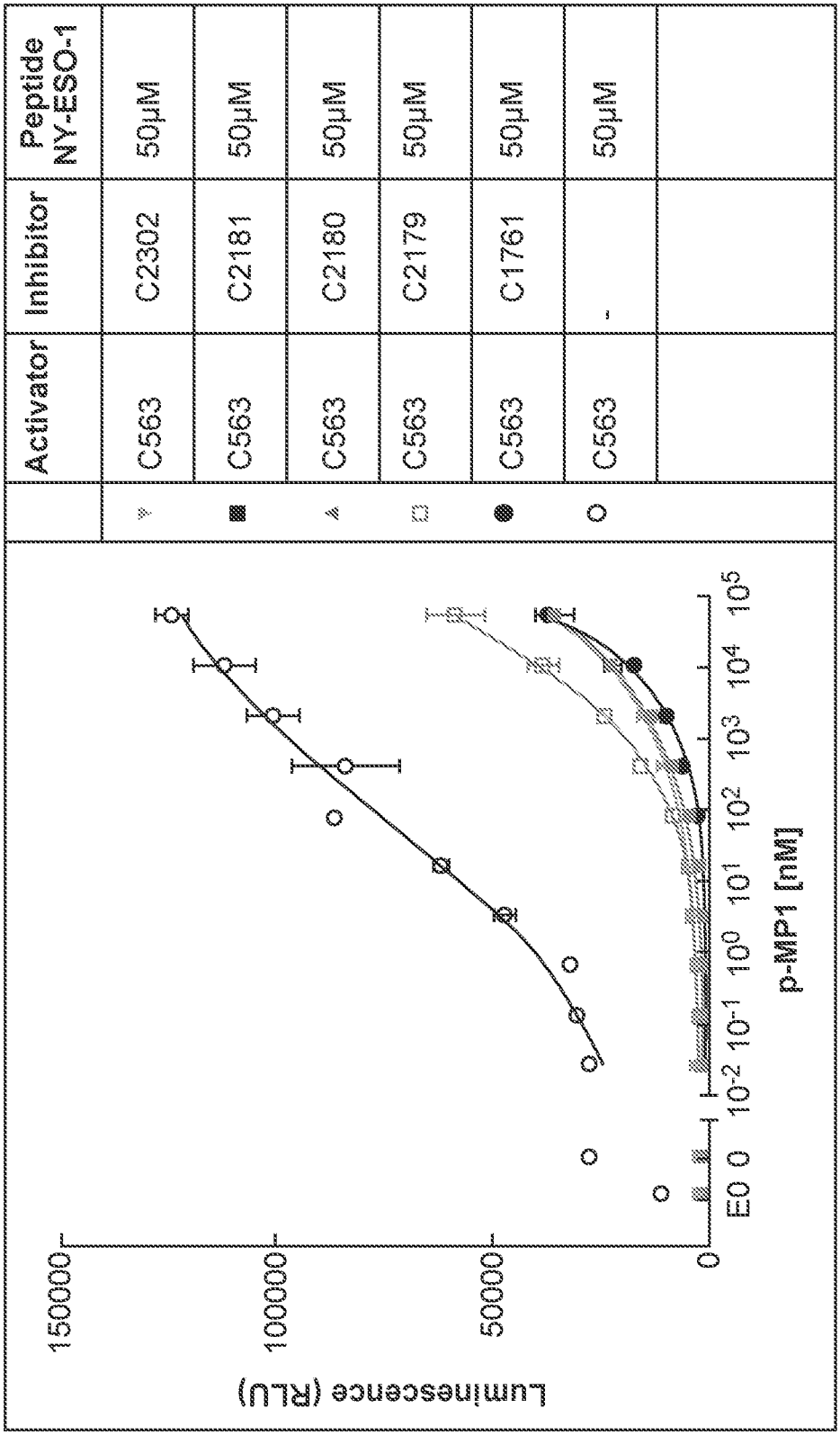

Activator
Inhibitor
Peptide NY-ESO-1
C563
C2302
50μM
C563
C2181
50μM
C563
C2180
50μM
C563
C2179
50μM
C563
C1761
50μM
C563
-
50μM
Luminescence (RLU)
150000
100000
50000
0
E0 0 10-2 10-1 100 101 102 103 104 105
p-MP1 [nM]

FIG. 8

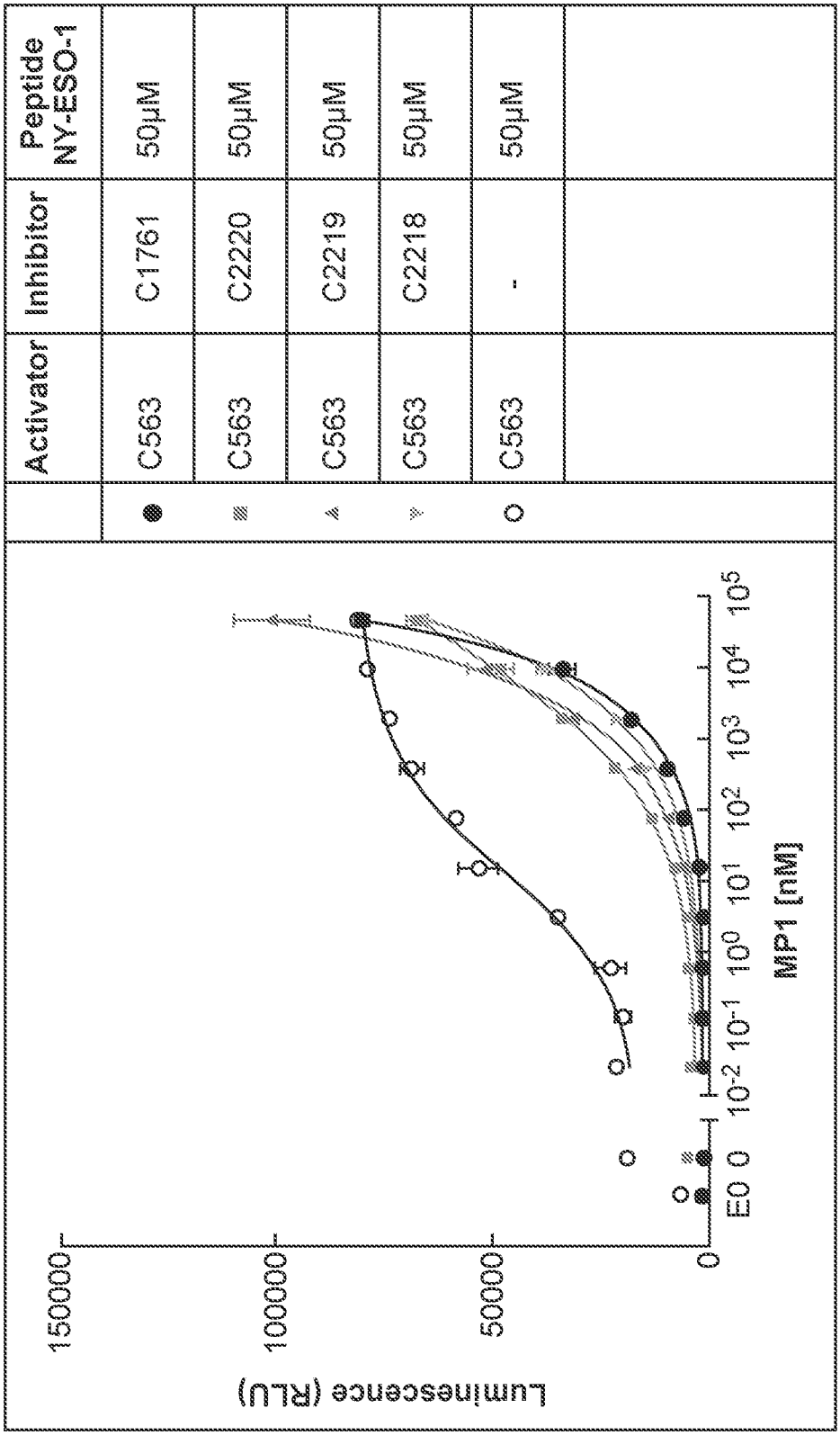

Activator
Inhibitor
Peptide NY-ESO-1
C563
C1761
50µM
C563
C2220
50µM
C563
C2219
50µM
C563
C2218
50µM
C563
-
50µM
Luminescence (RLU)
150000
100000
50000
0
E0 0 10-2 10-1 100 101 102 103 104 105
MP1 [nM]

FIG. 9

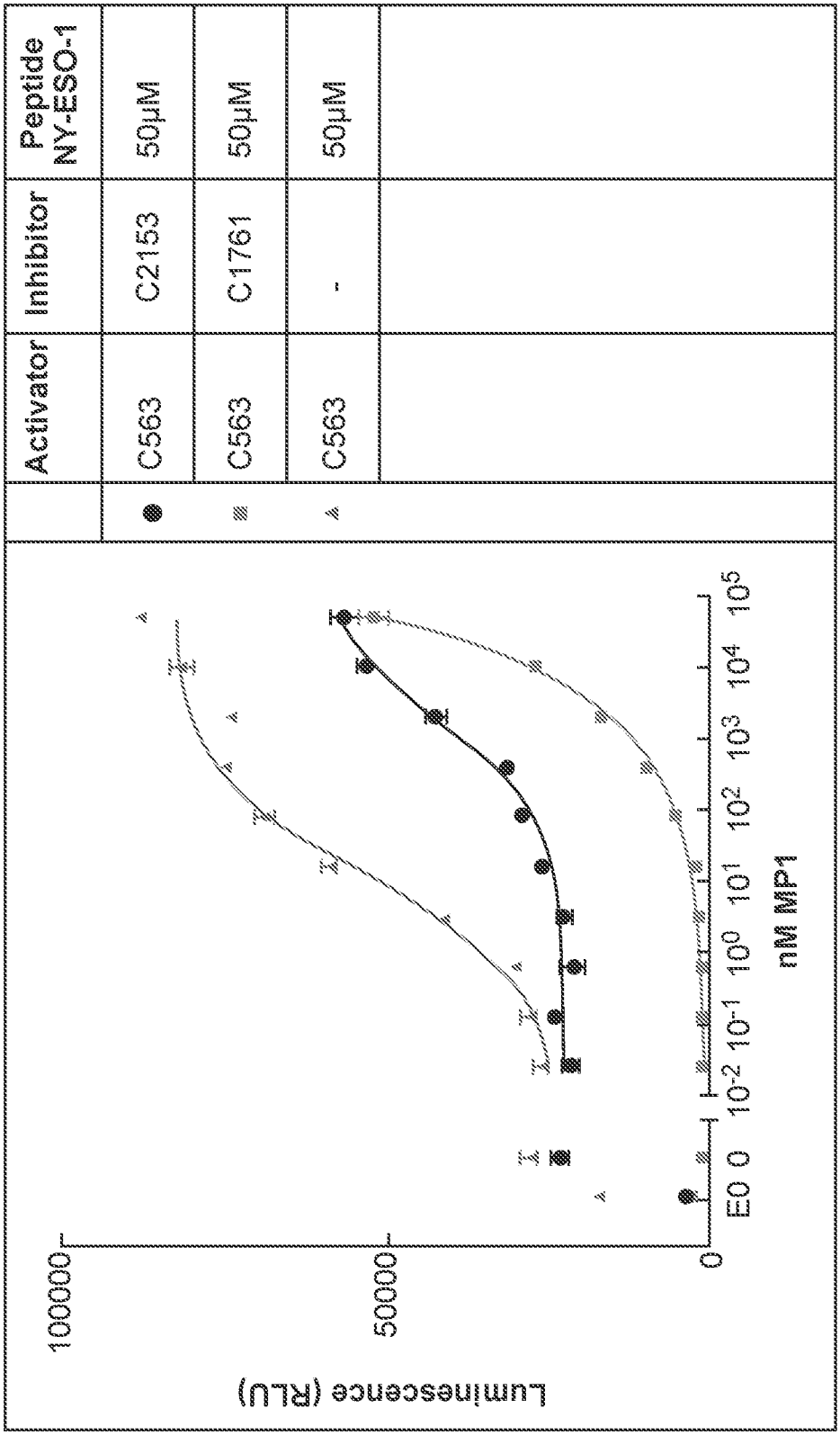

Activator
Inhibitor
Peptide NY-ESO-1
C563
C2153
50µM
C563
C1761
50µM
C563
-
50µM
Luminescence (RLU)
100000
50000
0
E0 0 10-2 10-1 100 101 102 103 104 105
nM MP1

FIG. 10

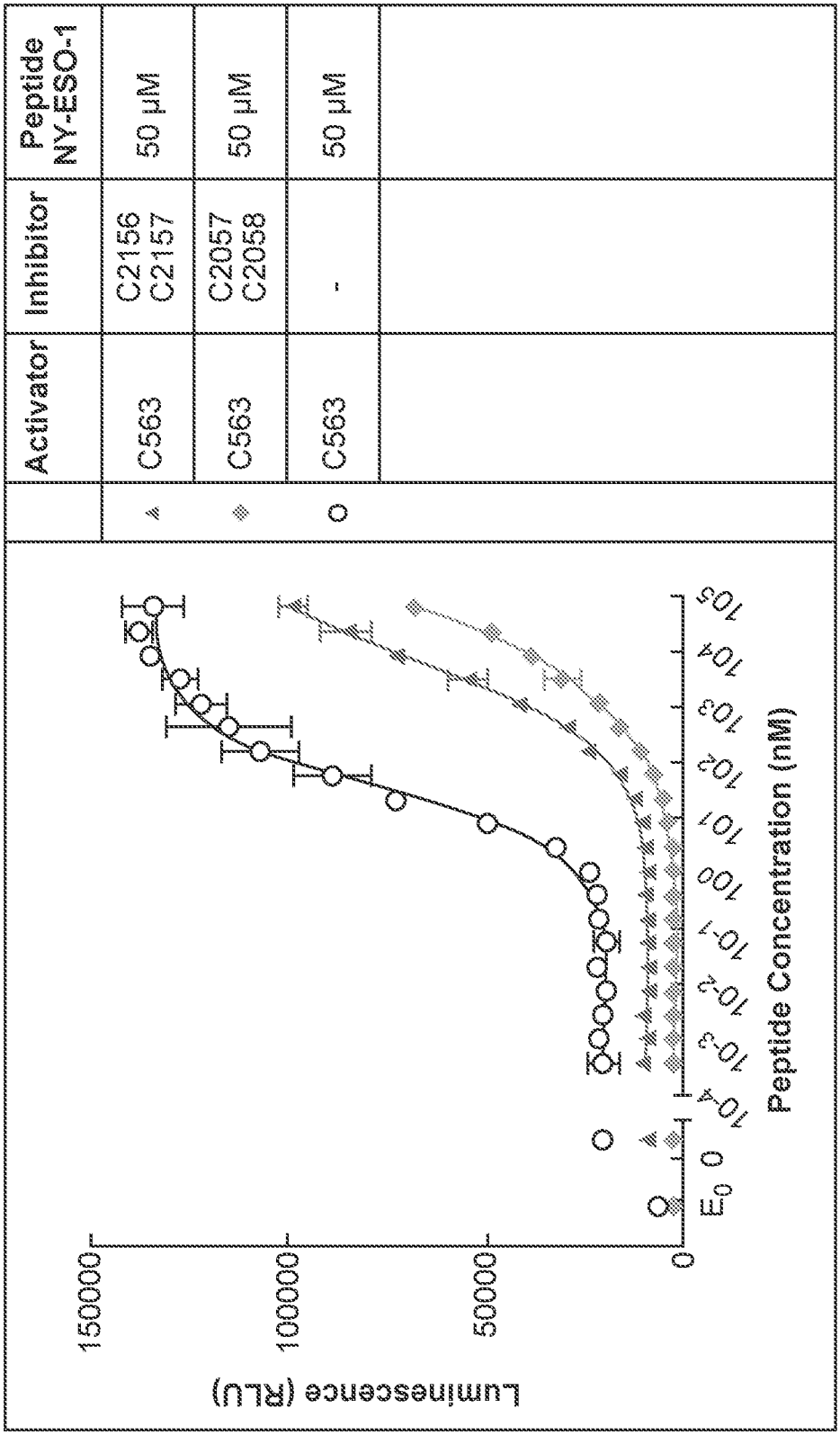
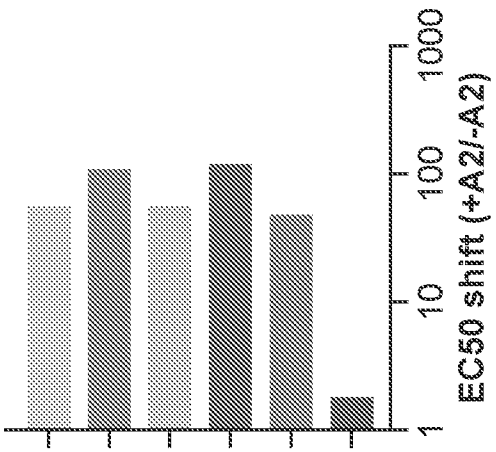

Activator
Inhibitor
Peptide NY-ESO-1
C563
C2156 C2157
50 µM
C563
C2057 C2058
50 µM
C563
-
50 µM
Luminescence (RLU)
150000
100000
50000
0
E0
Peptide Concentration (nM)

FIG. 11


pLenti [T2 A11]
KRAS TCR [T2 A11]
KRAS TCR + mPA2.1 LIR H,TM,ICD [T2 A11]
KRAS TCR + hPA2.1 LIR1 ITIM (SEQ ID NO: 89) [T2 A11]
KRAS TCR + hBB7.2 LIR1 H,TM,ICD [T2 A11]
KRAS TCR + hPA2.1 LIR1 short H, TM, ICD (SEQ ID NO: 90) [T2 A11]
KRAS TCR + hBB7.2 LIR1 short H, TM, ICD [T2 A11]
pLenti [T2 A11 A2]
KRAS TCR [T2 A11 A2]
KRAS TCR + mPA2.1 LIR H,TM,ICD [T2 A11 A2]
KRAS TCR + hPA2.1 LIR1 ITIM (SEQ ID NO: 89) [T2 A11 A2]
KRAS TCR + hBB7.2 LIR1 H,TM,ICD [T2 A11 A2]
KRAS TCR + hPA2.1 LIR1 short H, TM, ICD (SEQ ID NO: 90) [T2 A11 A2]
KRAS TCR + hBB7.2 LIR1 short H, TM, ICD [T2 A11 A2]
Luminescence (RLU)
80000
60000
40000
20000
0
10-5 10-4 10-3 10-2 10-1 100 101 102 103
uM KRAS pep14

FIG. 12A



PA2.1 scFv LIR1 HTICD	Mouse PA2.1	YGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 80)
BB7.2.6 scFv LIR1 HTICD	hPBB7.2.6	YGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 80)
BB7.2.6 scFv LIR1 sHTICD	hPBB7.2.6	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 81)
PA2.1.14 scFv LIR1 iTIM	hPA2.1.14	YGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 80)
PA2.1.14 scFv LIR1 sHTICD	hPA2.1.14	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 81)

FIG. 12B

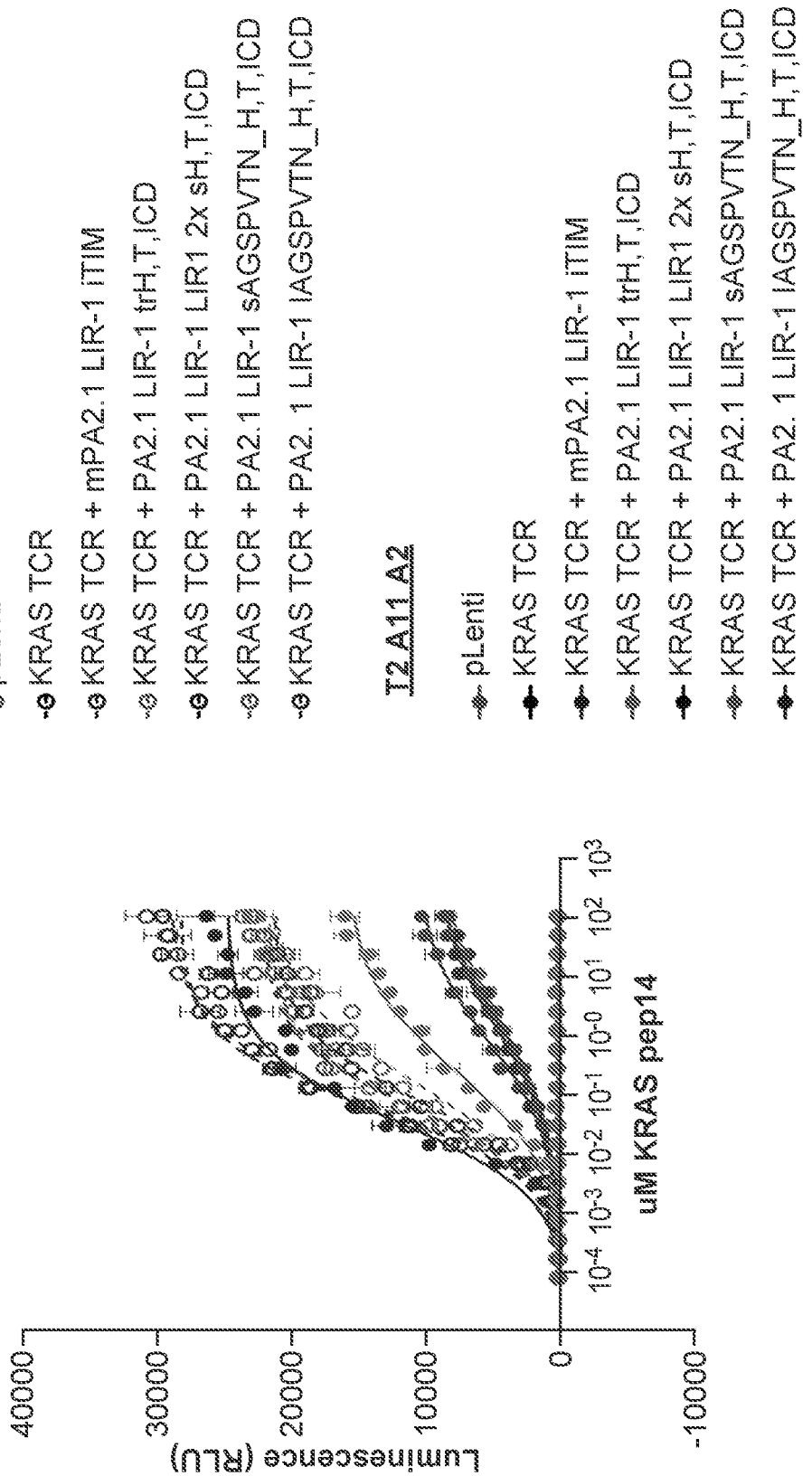
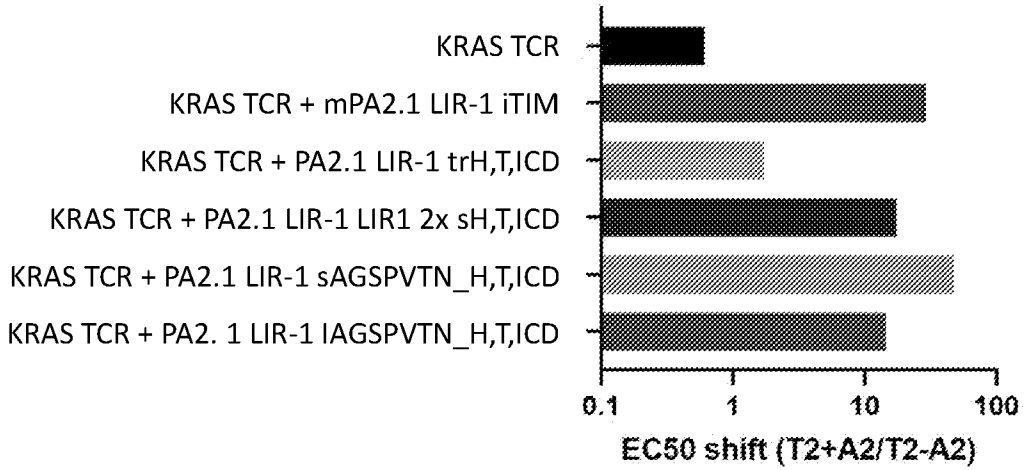

T2.A11
pLenti
KRAS TCR
KRAS TCR + mPA2.1 LIR-1 iTIM
KRAS TCR + PA2.1 LIR-1 trH,T,ICD
KRAS TCR + PA2.1 LIR-1 LIR1 2x sH,T,ICD
KRAS TCR + PA2.1 LIR-1 sAGSPVTN_H,T,ICD
KRAS TCR + PA2. 1 LIR-1 IAGSPVTN_H,T,ICD
T2.A11.A2
pLenti
KRAS TCR
KRAS TCR + mPA2.1 LIR-1 iTIM
KRAS TCR + PA2.1 LIR-1 trH,T,ICD
KRAS TCR + PA2.1 LIR-1 LIR1 2x sH,T,ICD
KRAS TCR + PA2.1 LIR-1 sAGSPVTN_H,T,ICD
KRAS TCR + PA2. 1 LIR-1 IAGSPVTN_H,T,ICD
Luminescence (RLU)
40000
30000
20000
10000
0
-10000
10-4 10-3 10-2 10-1 10-0 101 102 103
uM KRAS pep14

FIG. 13A

SUBSTITUTE SHEET (RULE 26)

FIG. 13B



blocker	hinge	length
mPA2.1_scFv LIR1 iTIM	LIR1	64
PA2.1_scFv LIR1 trHTICD	LIR1 trunc	32
PA2.1_scFv LIR1 2x sH TICD	2x LIR1 short	85
PA2.1_scFv sAGSPVTN_H LIR1 TICD	sAGSPVTN	67
PA2.1_scFv lAGSPVTN_H LIR1 TICD	lAGSPVTN	75

mPA2.1_scFv LIR1 iTIM	SSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGVVIGIL (SEQ ID NO: 115)
PA2.1_scFv LIR1 trHTICD	SSTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGVVIGIL (SEQ ID NO: 116)
PA2.1_scFv sAGSPVTN_H LIR1 TICD	SSAGSGGSGGSGGSPVPSTPPTPSPSTPPTPSPSGGSGNSSGSGGSPVPSTPPTPSPSTPPTPSPSASVVIGIL (SEQ ID NO: 117)
PA2.1_scFv lAGSPVTN_H LIR1 TICD	SSAGSGGSGGSGGSPVPSTPPTNSSSTPPTPSPSPVPSTPPTNSSSTPPTPSPSPVPSTPPTNSSSTPPTPSPSASVVIGIL (SEQ ID NO: 118)
PA2.1_scFv LIR1 2x sH TICD	SSVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGVVIGIL (SEQ ID NO: 119)

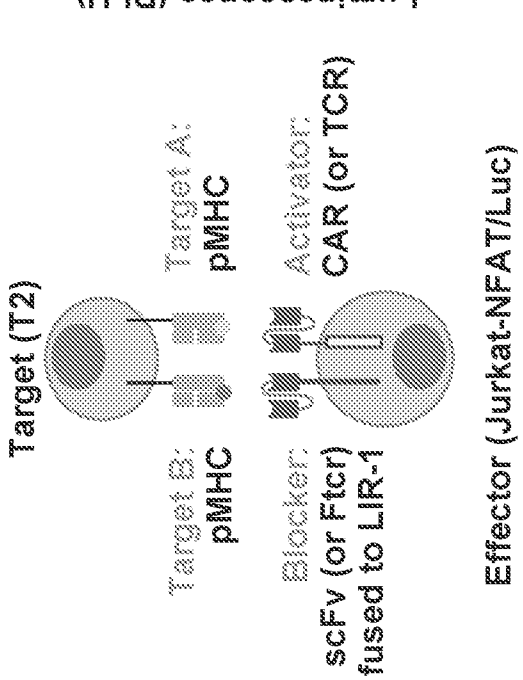


FIG. 14A

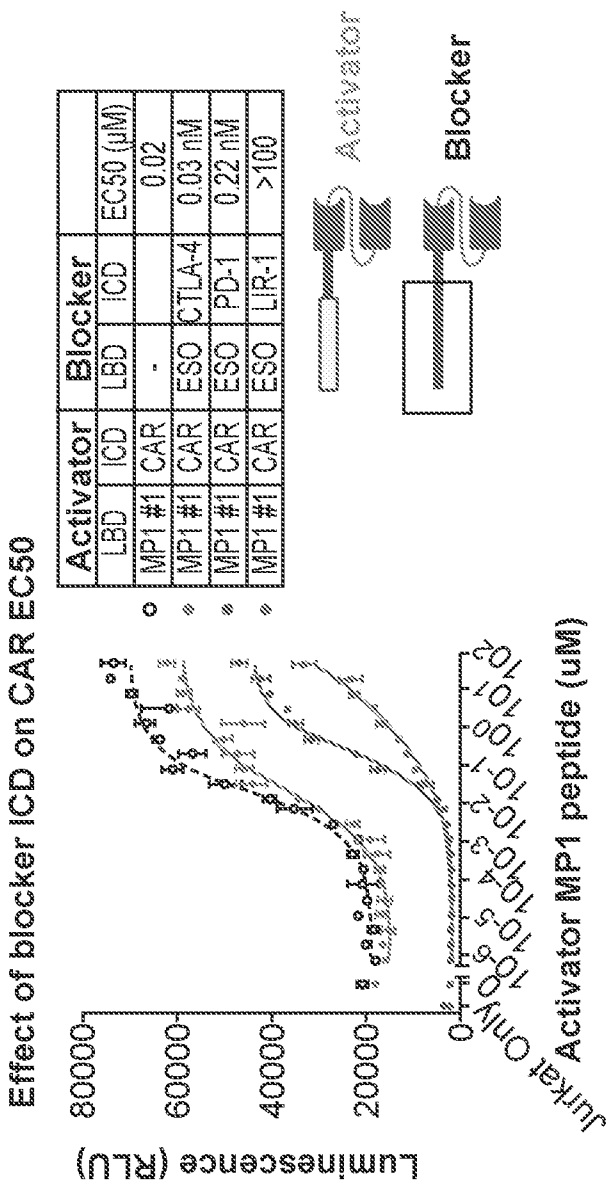
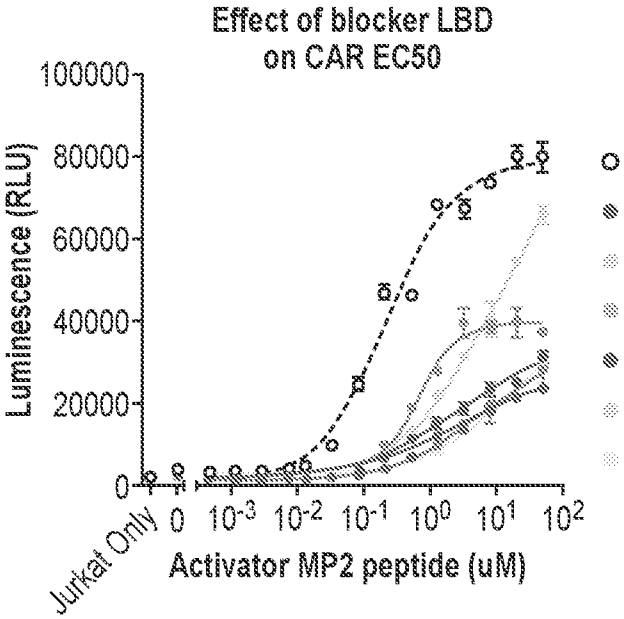


FIG. 14B



Activator		Blocker	
LBD	ICD	LBD	ICD
MP2	CAR	-	-
MP2	CAR	MP1 #1	LIR-1
MP2	CAR	HPV E6 #2	LIR-1
MP2	CAR	MP1 #2	LIR-1
MP2	CAR	HPV E6 #1	LIR-1
MP2	CAR	ESO	LIR-1
MP2	CAR	HPV E7	LIR-1

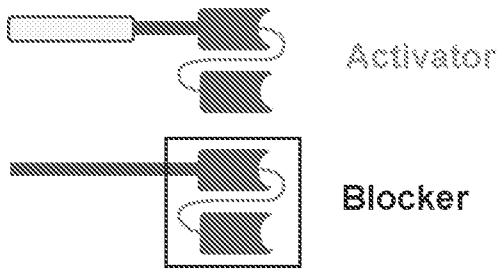
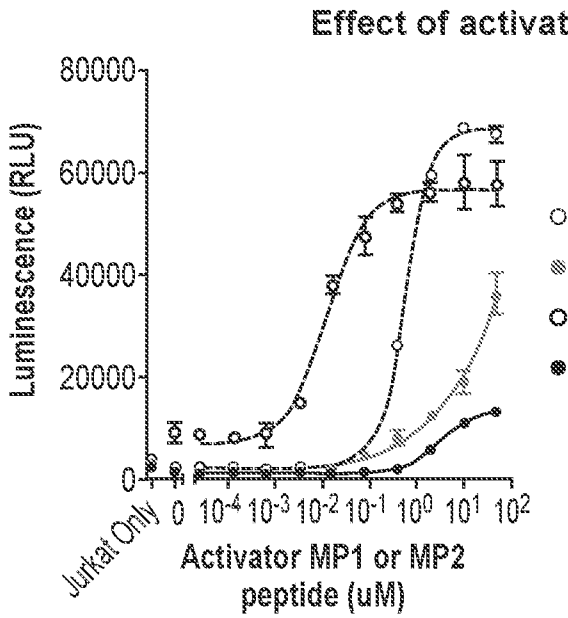


FIG. 14C



Activator		Blocker	
LBD	ICD	LBD	ICD
MP1 #1	CAR	-	
MP1 #1	CAR	ESO	LIR-1
MP2	CAR	-	
MP2	CAR	ESO	LIR-1

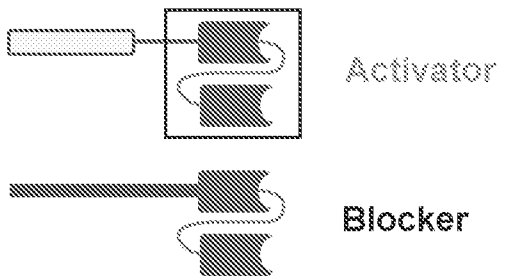
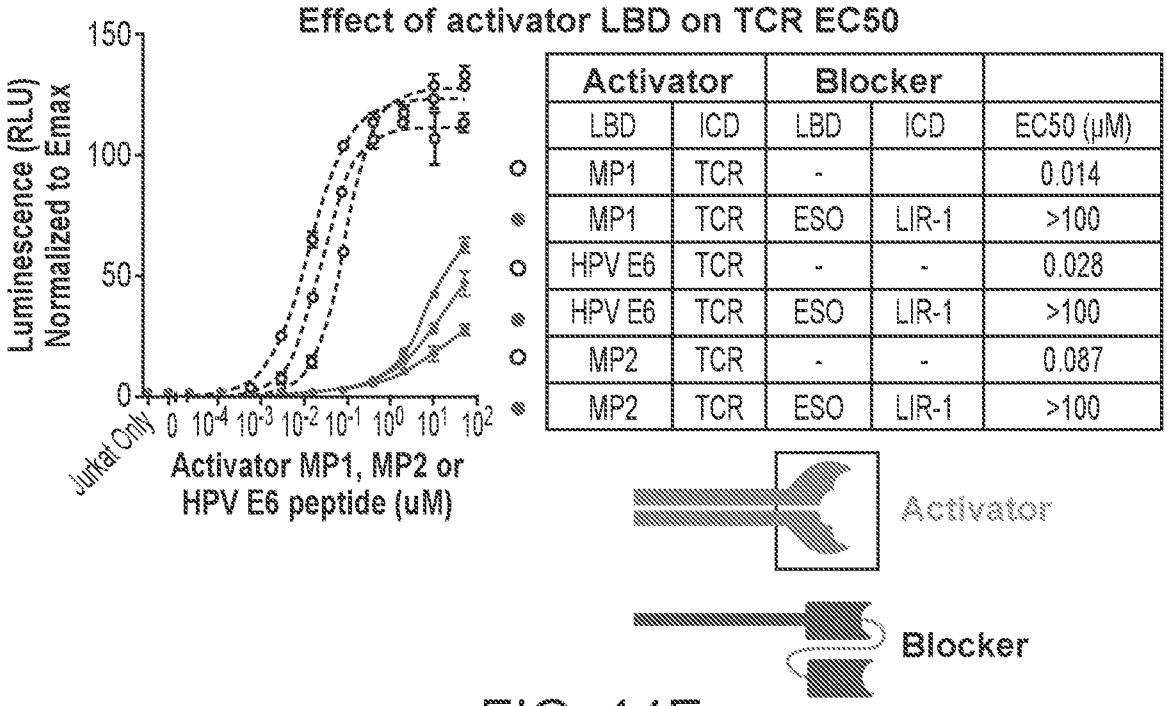
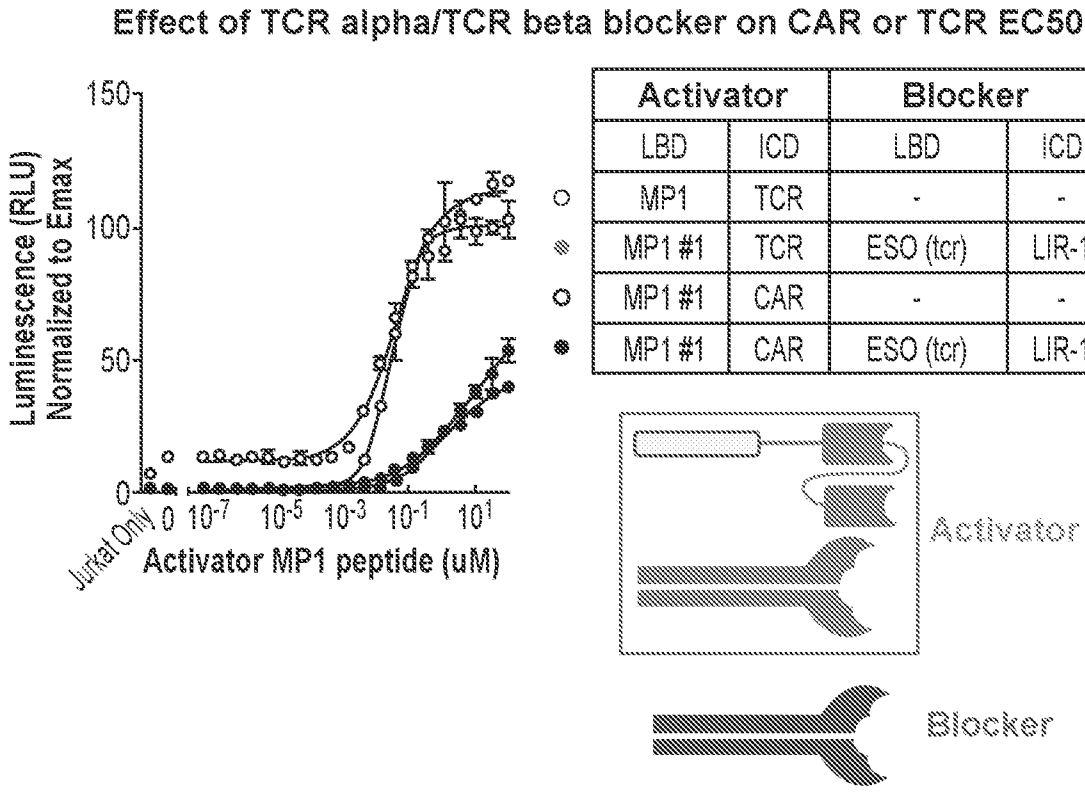


FIG. 14D



Activator		Blocker		
LBD	ICD	LBD	ICD	EC50 (μM)
MP1	TCR	-		0.014
MP1	TCR	ESO	LIR-1	>100
HPV E6	TCR	-	-	0.028
HPV E6	TCR	ESO	LIR-1	>100
MP2	TCR	-	-	0.087
MP2	TCR	ESO	LIR-1	>100

FIG. 14E



Activator		Blocker	
LBD	ICD	LBD	ICD
MP1	TCR	-	-
MP1 #1	TCR	ESO (tcr)	LIR-1
MP1 #1	CAR	-	-
MP1 #1	CAR	ESO (tcr)	LIR-1

FIG. 14F

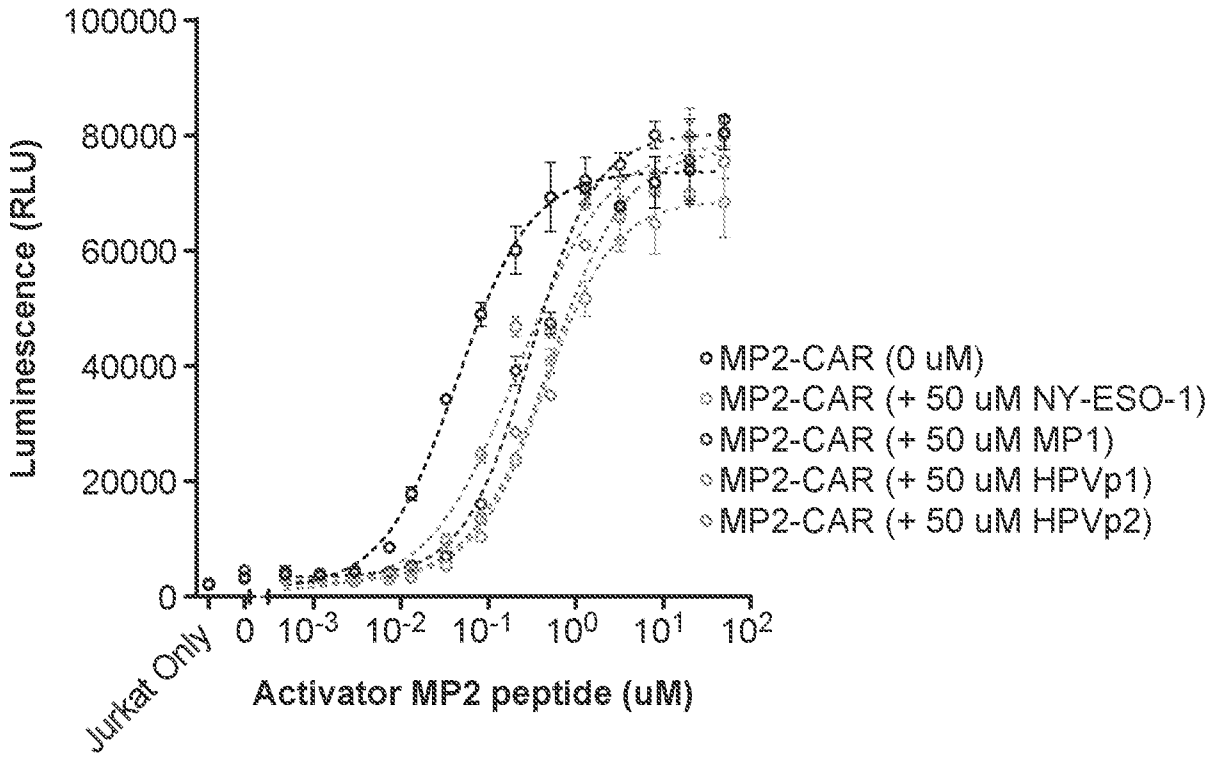

100000
80000
60000
40000
20000
0
Luminescence (RLU)
Jurkat Only
0
10-3
10-2
10-1
100
101
102
Activator MP2 peptide (uM)
MP2-CAR (0 uM)
MP2-CAR (+ 50 uM NY-ESO-1)
MP2-CAR (+ 50 uM MP1)
MP2-CAR (+ 50 uM HPVp1)
MP2-CAR (+ 50 uM HPVp2)

FIG. 15

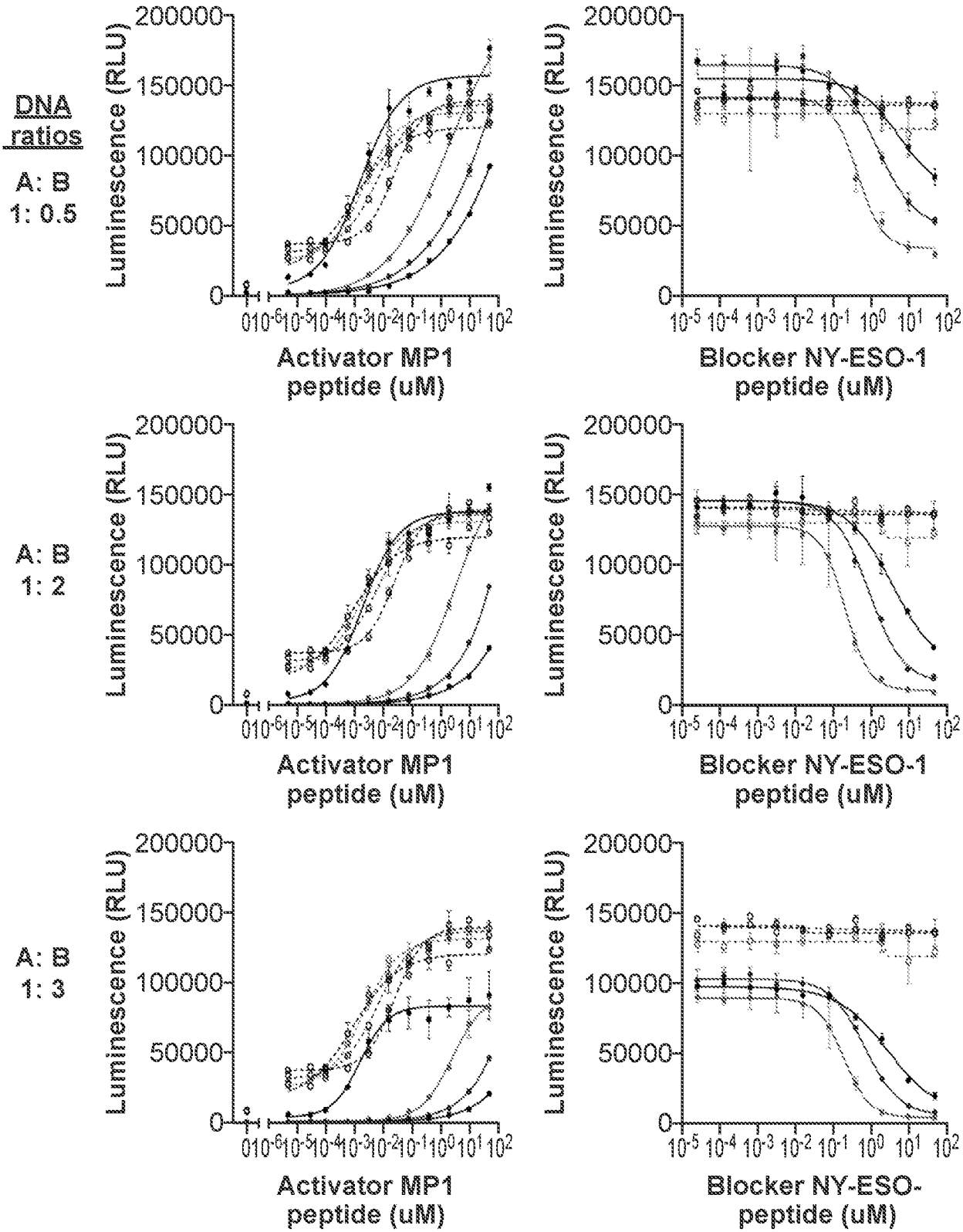
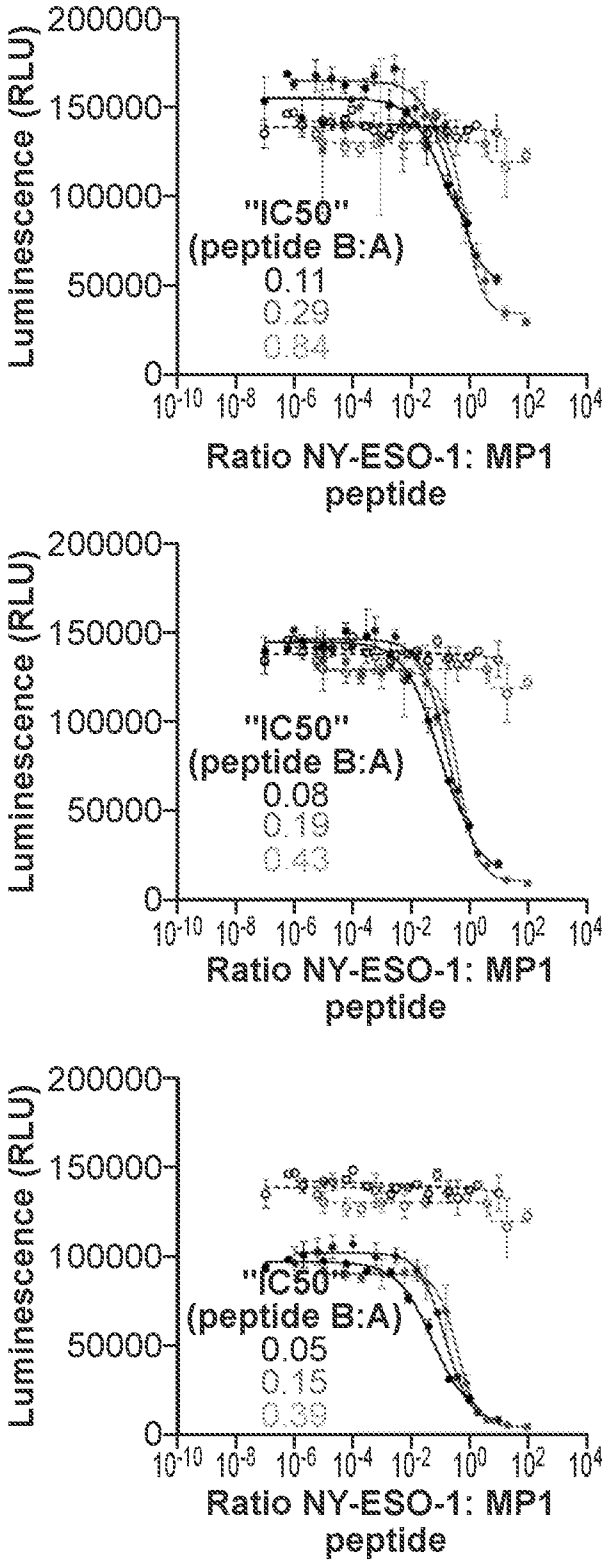


FIG. 16A FIG. 16B



Activator	Blocker	Blocker ESO peptide (uM)
MP1-CAR	-	50
MP1-CAR	-	5
MP1-CAR	-	0.5
MP1-CAR	-	0
MP1-CAR	ESO-LIR-1	50
MP1-CAR	ESO-LIR-1	5
MP1-CAR	ESO-LIR-1	0.5
MP1-CAR	ESO-LIR-1	0

Activator	Blocker	Activator MP1 peptide (uM)
MP1-CAR	-	50
MP1-CAR	-	5
MP1-CAR	-	0.5
MP1-CAR	ESO-LIR-1	50
MP1-CAR	ESO-LIR-1	5
MP1-CAR	ESO-LIR-1	0.5

FIG. 16C

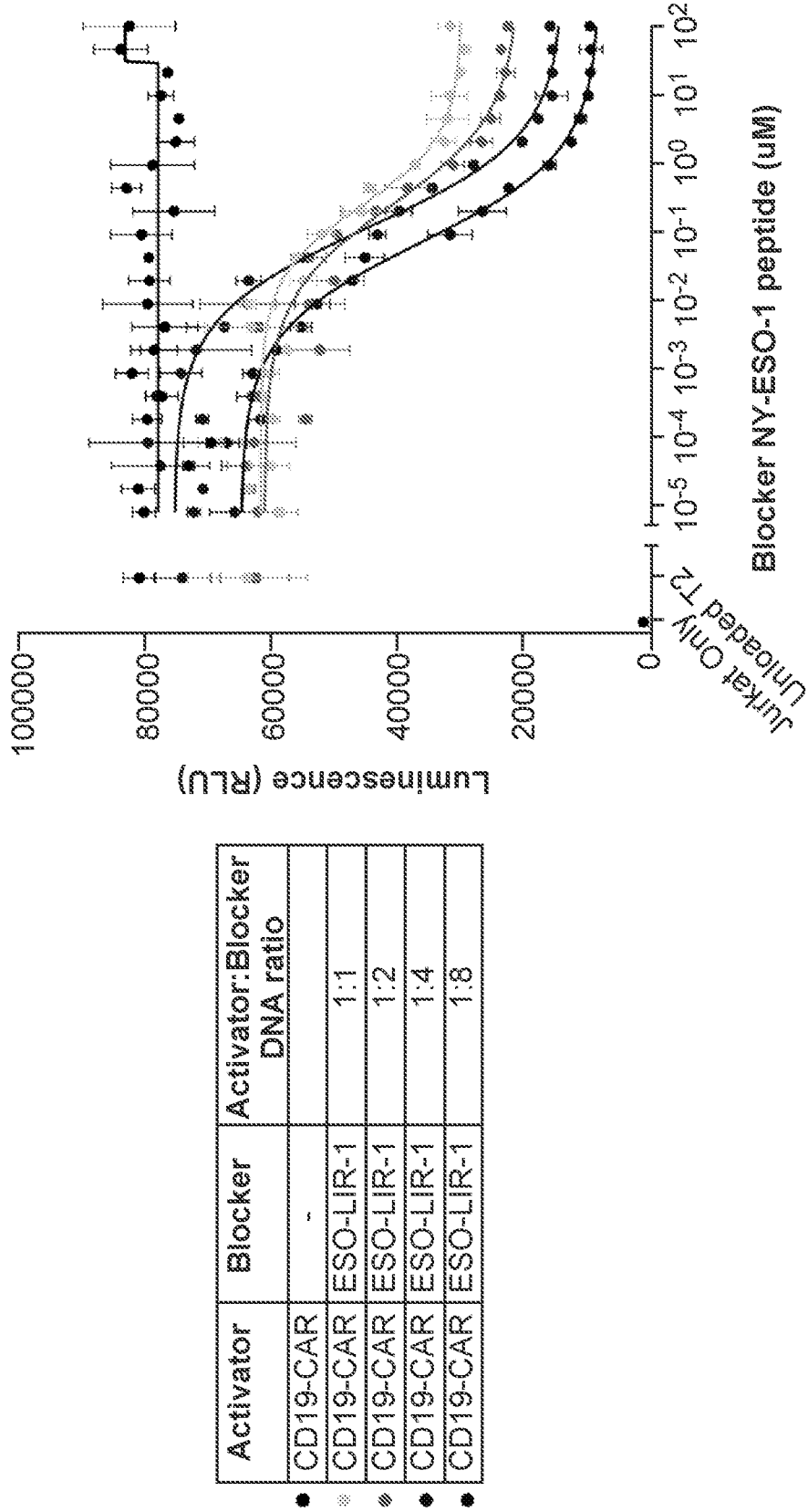

Luminescence (RLU)
100000
80000
60000
40000
20000
0
Jurkat Only Untoaded T2
10-5 10-4 10-3 10-2 10-1 100 101 102
Blocker NY-ESO-1 peptide (uM)
Activator
Blocker
Activator:Blocker DNA ratio
CD19-CAR -
CD19-CAR ESO-LIR-1 1:1
CD19-CAR ESO-LIR-1 1:2
CD19-CAR ESO-LIR-1 1:4
CD19-CAR ESO-LIR-1 1:8

FIG. 16D

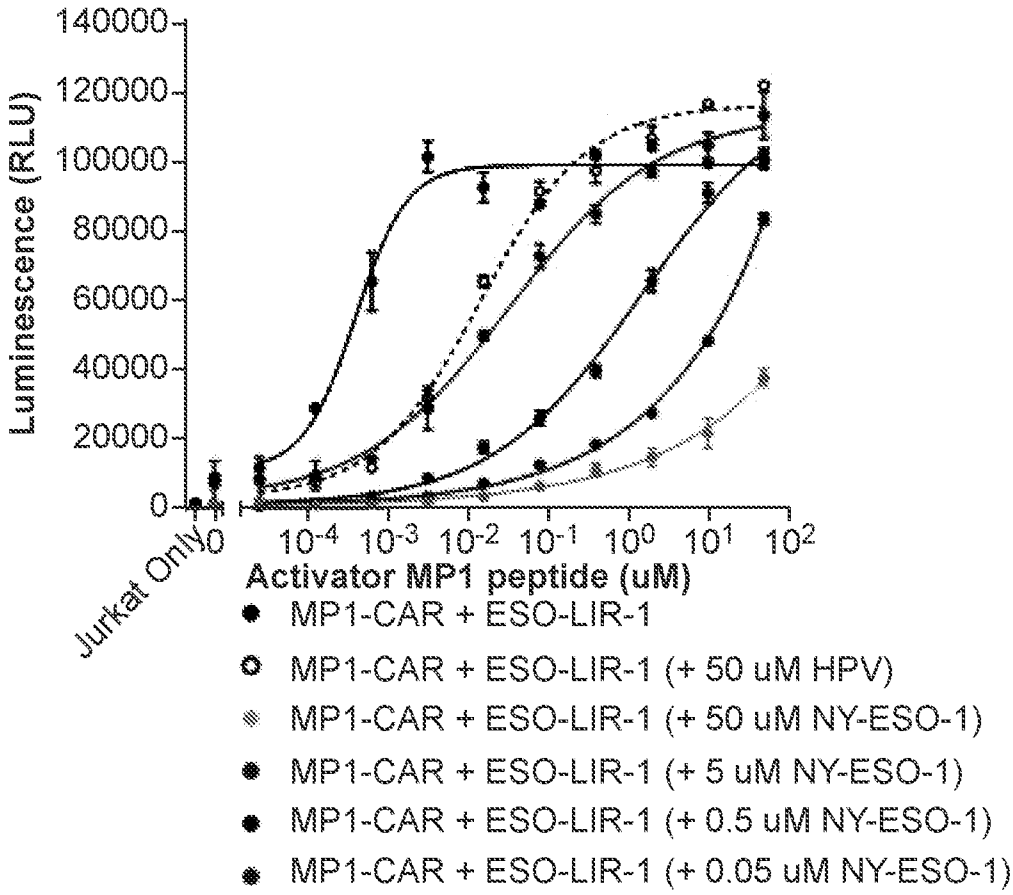


FIG. 17A

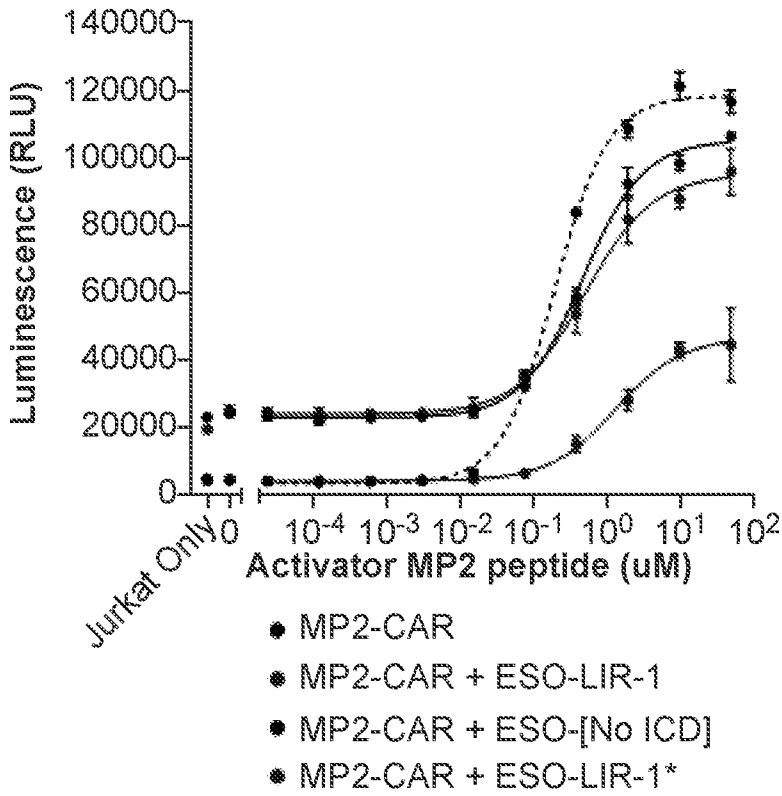


FIG. 17B

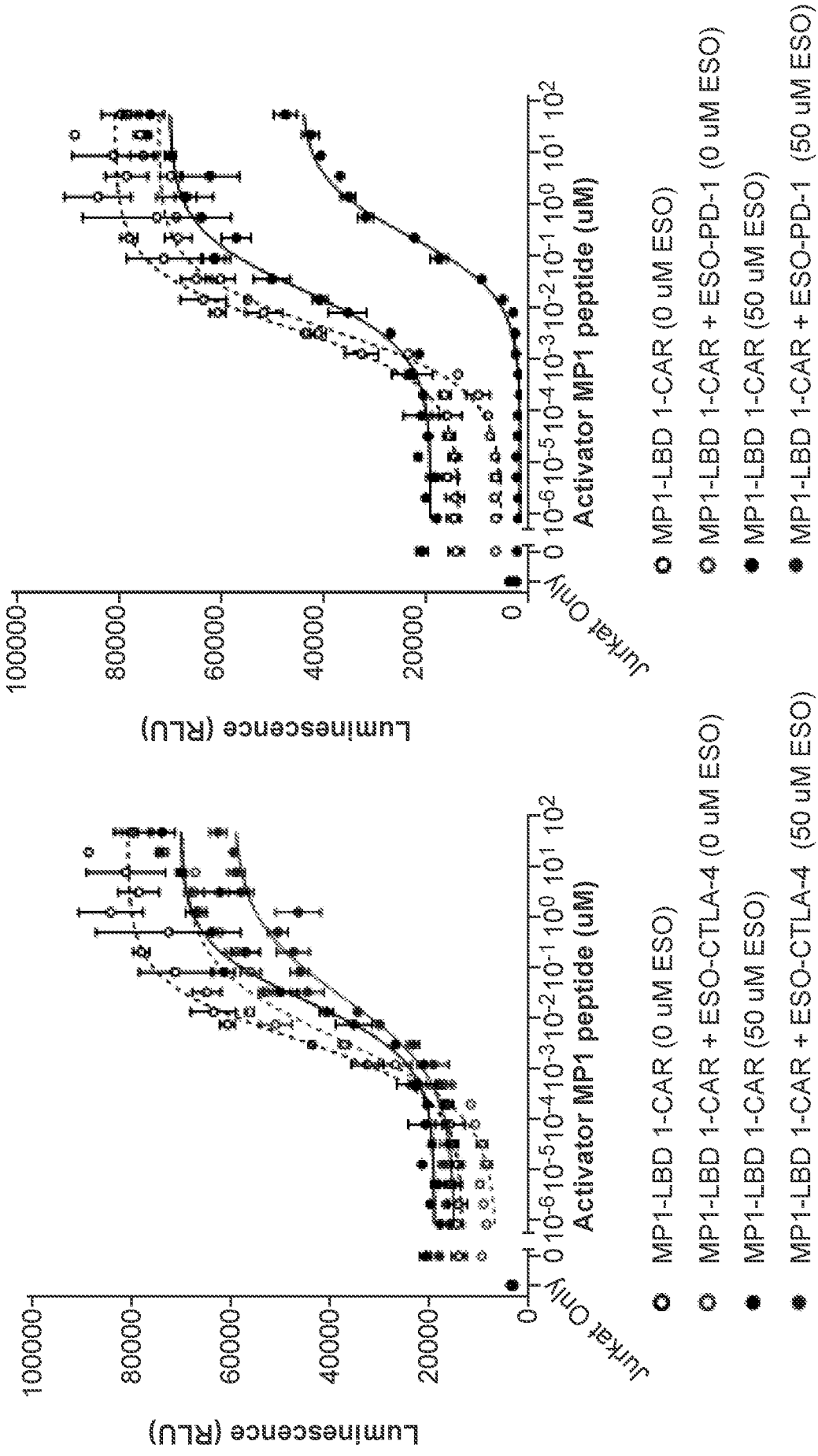


FIG. 17C

FIG. 17D

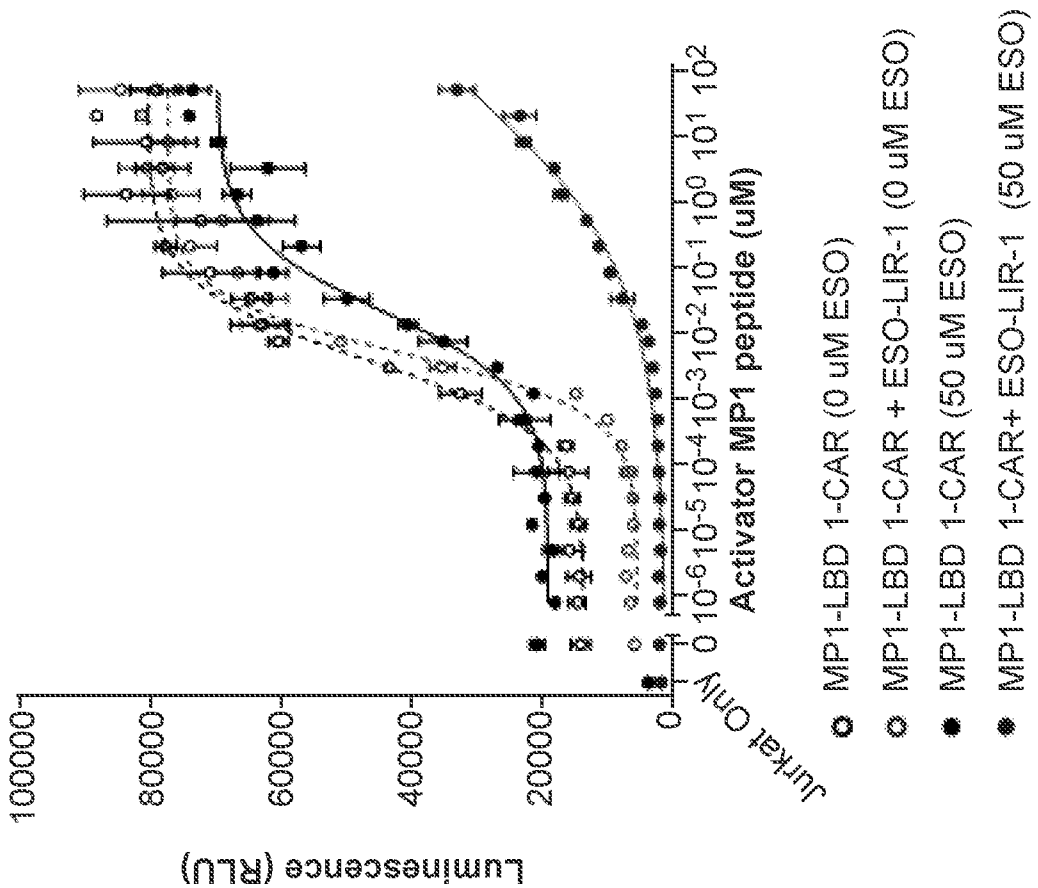

Luminescence (RLU)
100000
80000
60000
40000
20000
0
Jurkat Only
0 10-6 10-5 10-4 10-3 10-2 10-1 100 101 102
Activator MP1 peptide (uM)
MP1-LBD 1-CAR (0 uM ESO)
MP1-LBD 1-CAR + ESO-LIR-1 (0 uM ESO)
MP1-LBD 1-CAR (50 uM ESO)
MP1-LBD 1-CAR+ ESO-LIR-1 (50 uM ESO)

FIG. 17E

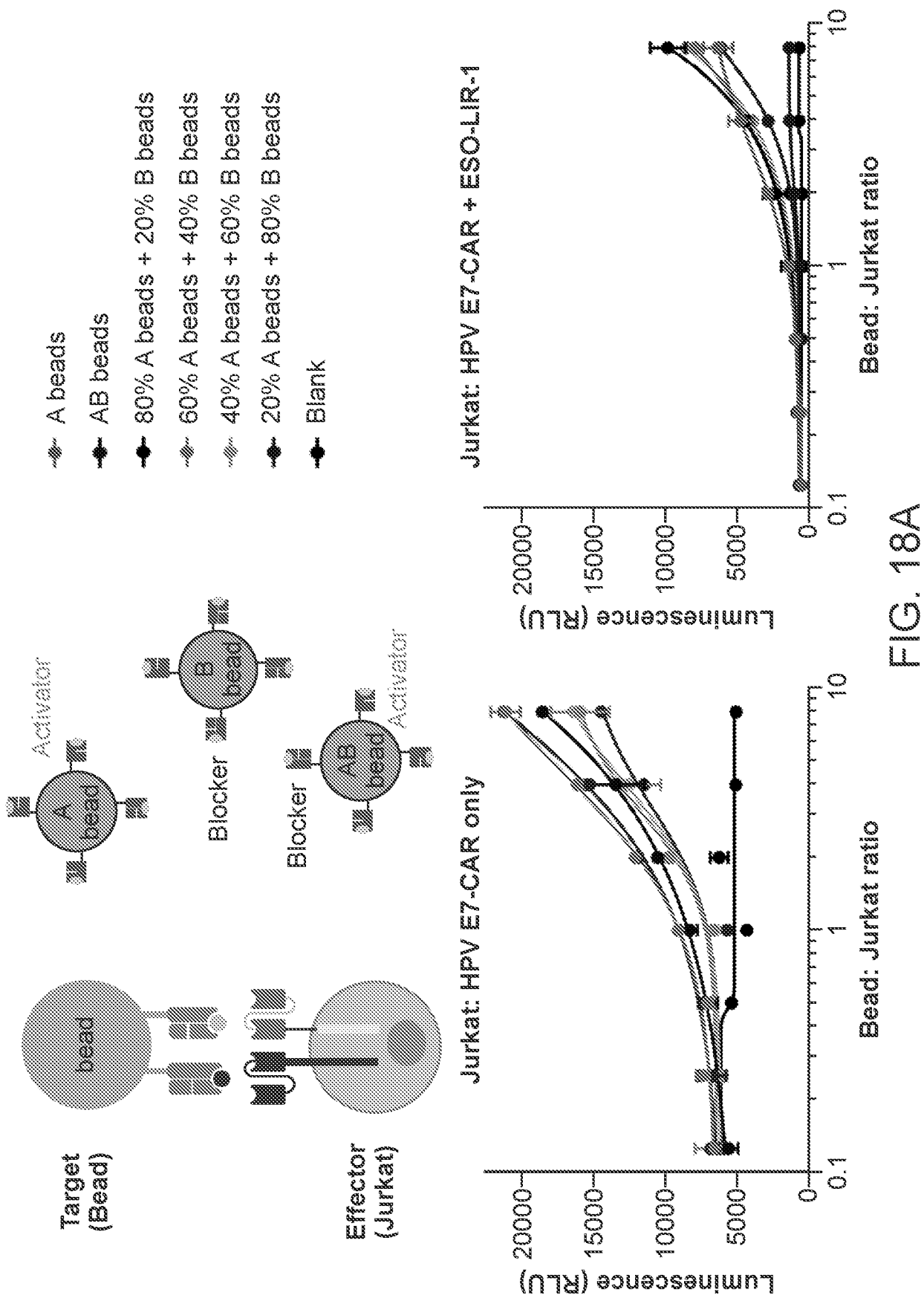

A beads
AB beads
80% A beads + 20% B beads
60% A beads + 40% B beads
40% A beads + 60% B beads
20% A beads + 80% B beads
Blank
Activator
A bead
Blocker
B bead
Blocker
AB bead
Activator
bead
Target (Bead)
Effector (Jurkat)
Jurkat: HPV E7-CAR + ESO-LIR-1
Jurkat: HPV E7-CAR only
Luminescence (RLU)
20000
15000
10000
5000
0
0.1
1
10
Bead: Jurkat ratio

FIG. 18A

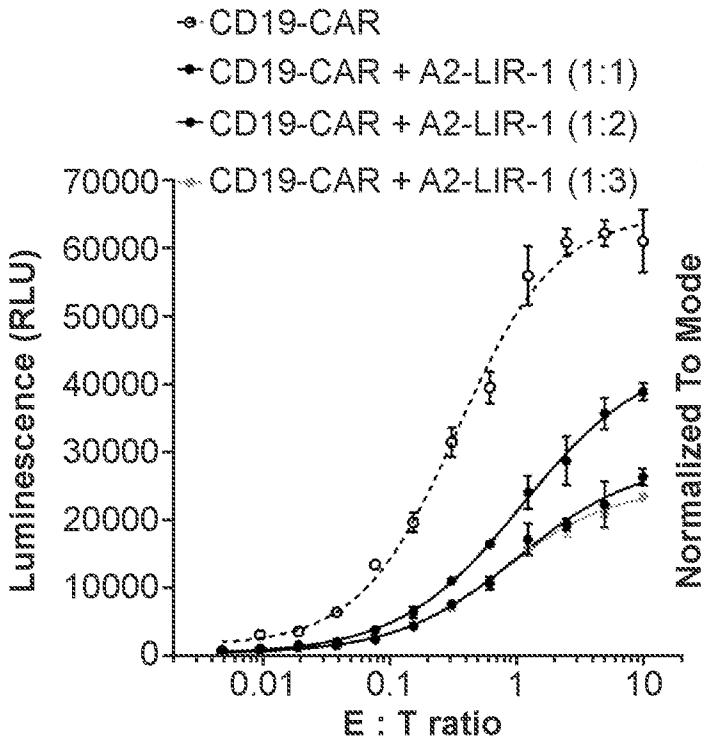


FIG. 18B

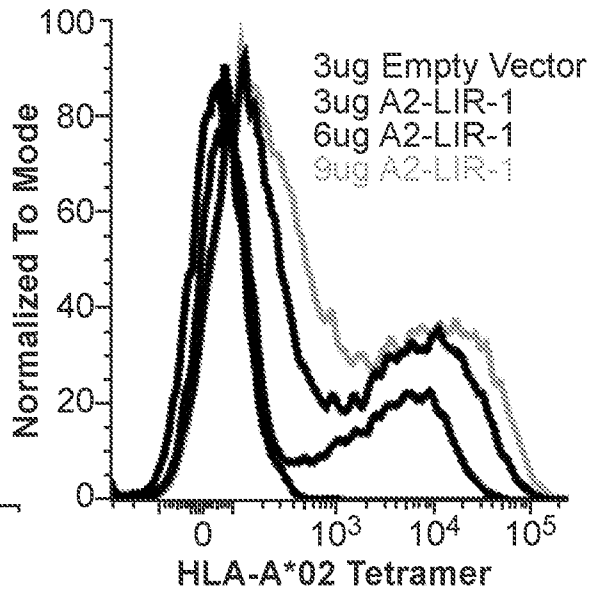


FIG. 18C

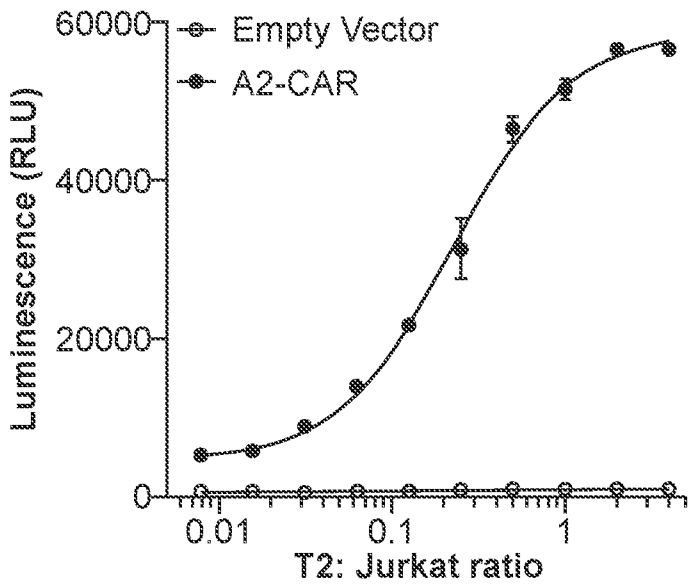


FIG. 18D

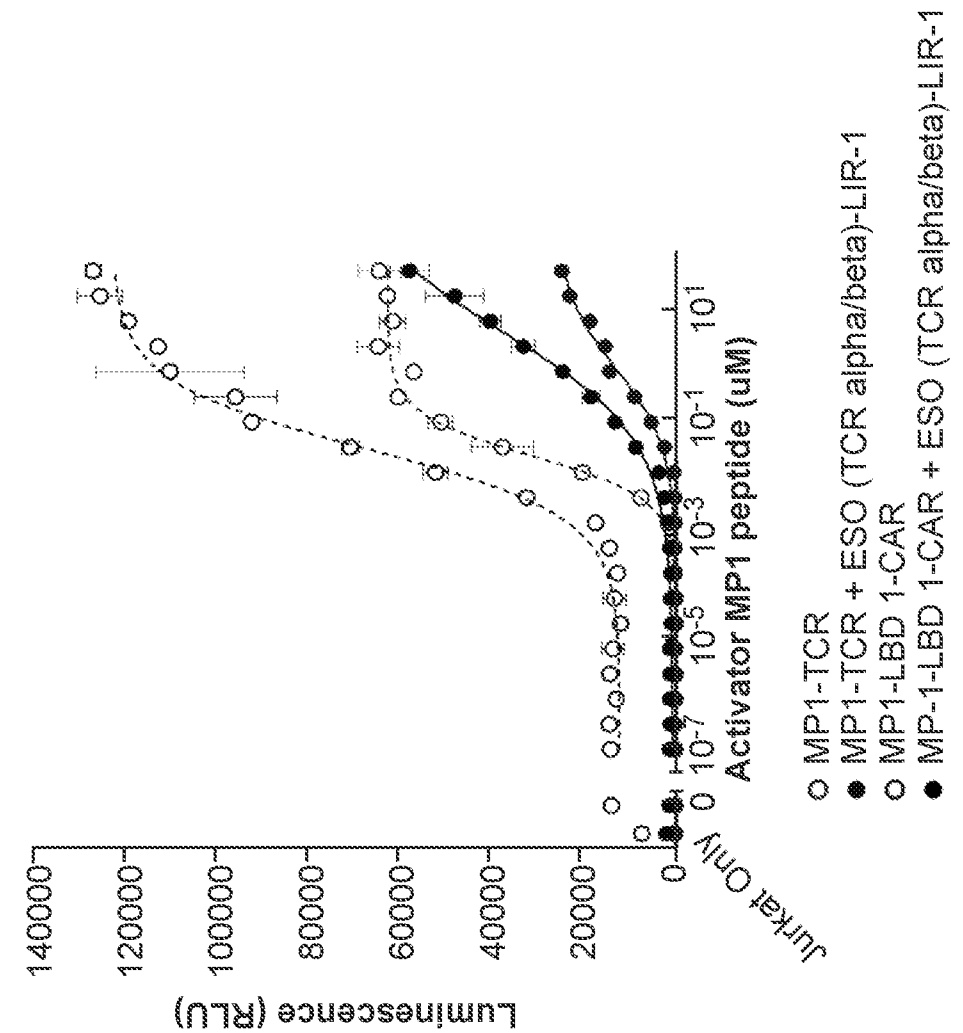


FIG. 19B

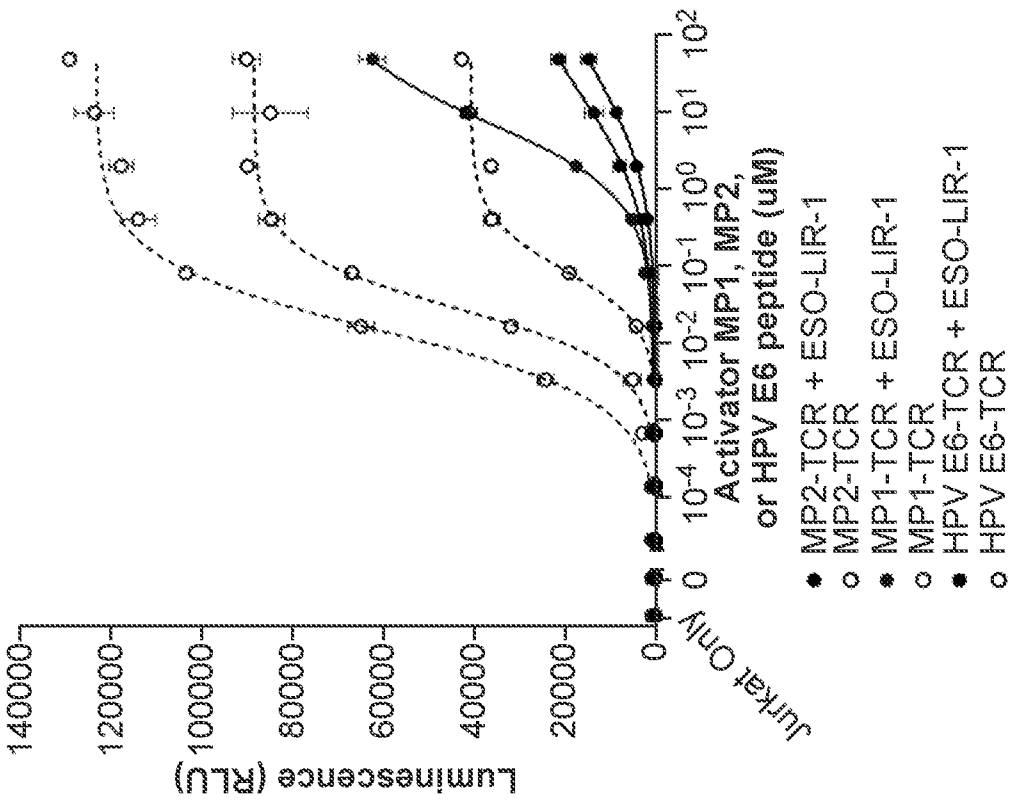


FIG. 19A

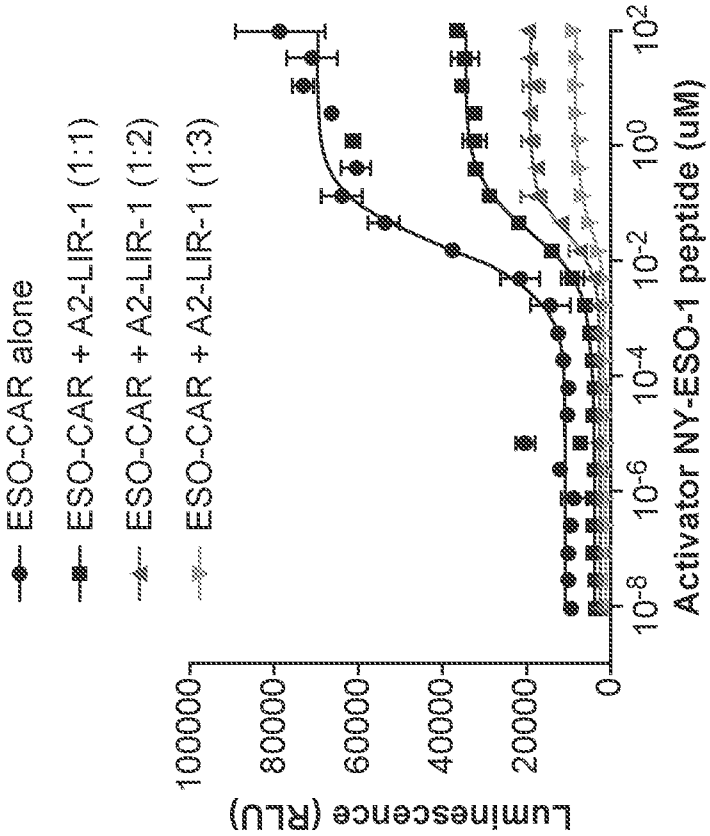


FIG. 20B

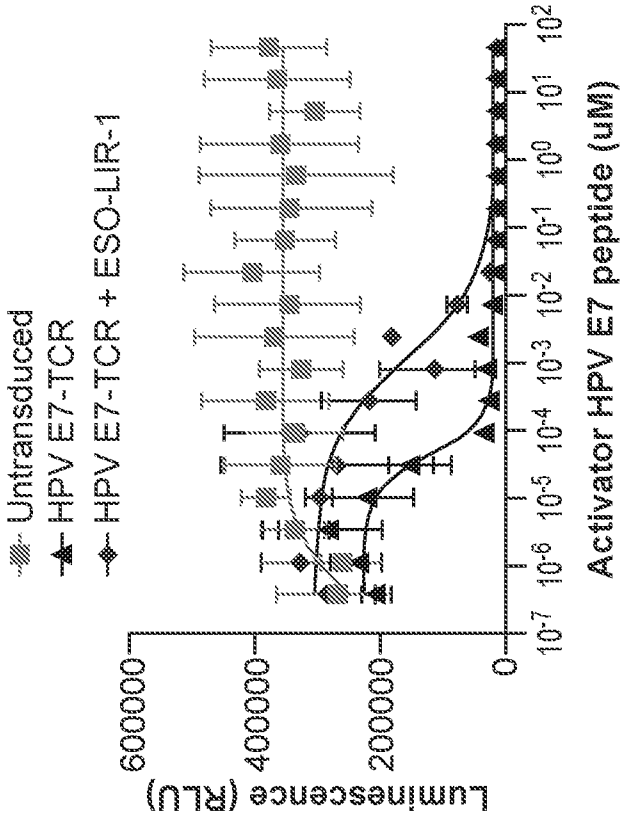


FIG. 20A

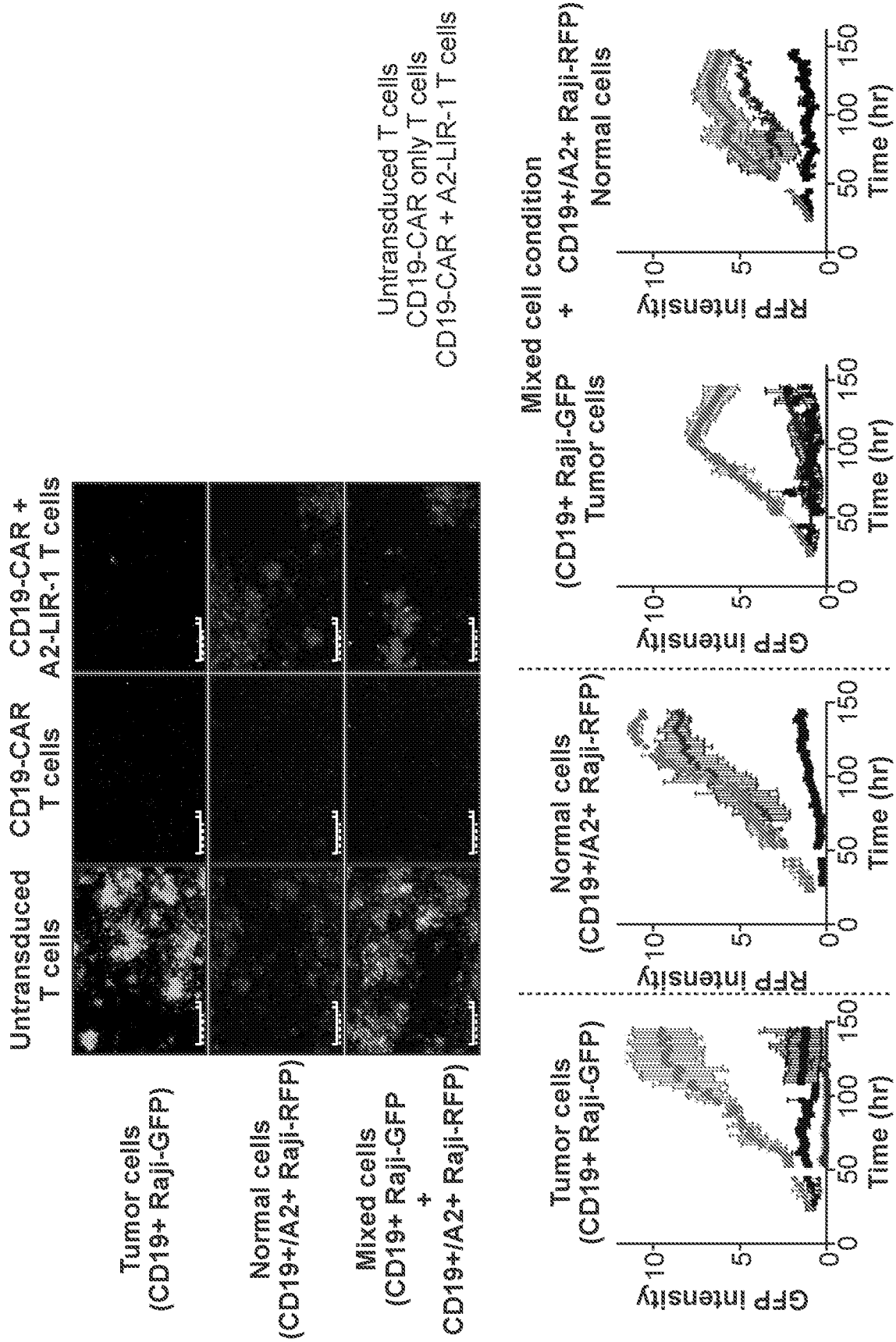

Untransduced T cells
CD19-CAR T cells
CD19-CAR + A2-LIR-1 T cells
Tumor cells (CD19+ Raji-GFP)
Normal cells (CD19+/A2+ Raji-RFP)
Mixed cells (CD19+ Raji-GFP + CD19+/A2+ Raji-RFP)
Untransduced T cells
CD19-CAR only T cells
CD19-CAR + A2-LIR-1 T cells
Mixed cell condition
(CD19+ Raji-GFP + CD19+/A2+ Raji-RFP)
Tumor cells
Normal cells
GFP intensity
RFP intensity
Time (hr)
0
5
10
50
100
150

FIG. 21A

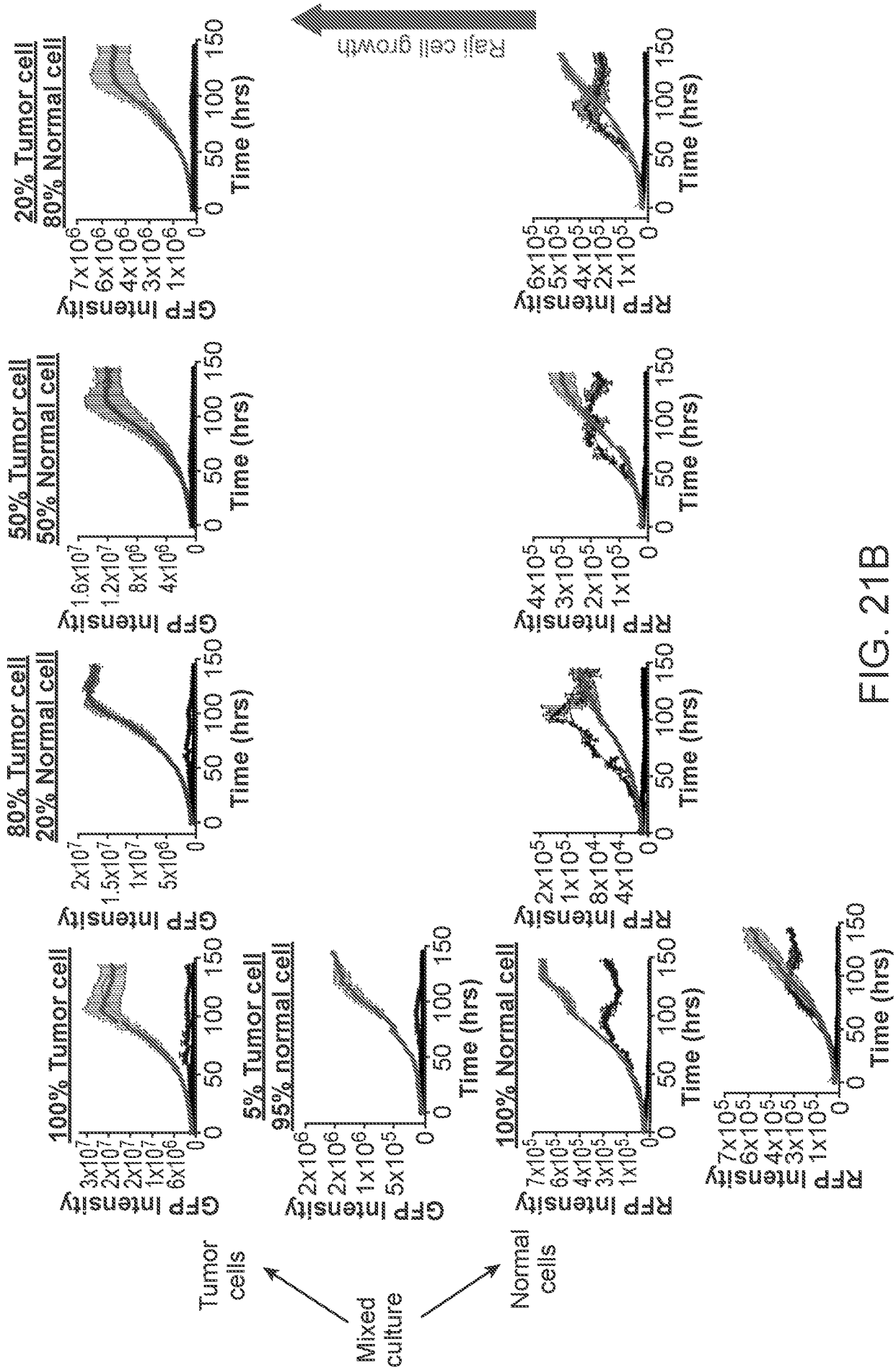

Tumor cells
Mixed culture
Normal cells
100% Tumor cell
5% Tumor cell
95% normal cell
100% Normal cell
80% Tumor cell
20% Normal cell
50% Tumor cell
50% Normal cell
20% Tumor cell
80% Normal cell
GFP Intensity
RFP Intensity
Time (hrs)
Rall cell growth

FIG. 21B

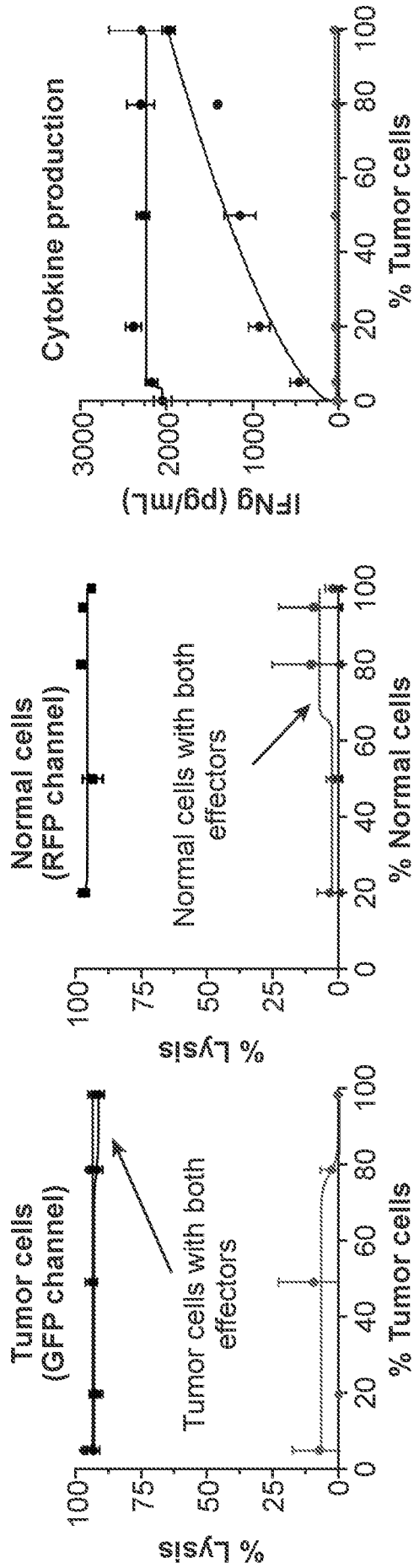

Cytokine production
IFNg (pg/mL)
3000
2000
1000
0
0 20 40 60 80 100
% Tumor cells
Normal cells
(RFP channel)
Normal cells with both
effectors
% Lysis
100
75
50
25
0
0 20 40 60 80 100
% Normal cells
Tumor cells
(GFP channel)
Tumor cells with both
effectors
% Lysis
100
75
50
25
0
0 20 40 60 80 100
% Tumor cells

FIG. 21C

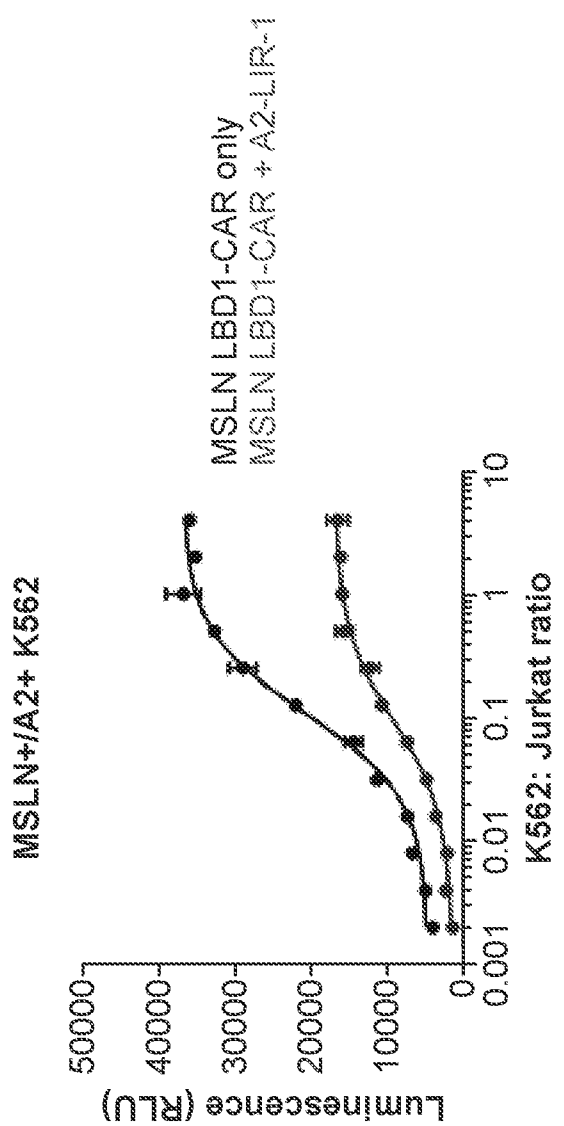


FIG. 22A

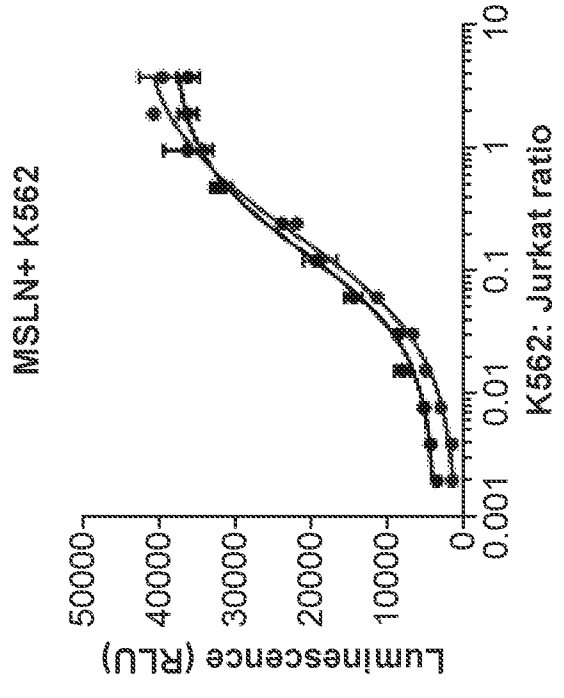


FIG. 22B

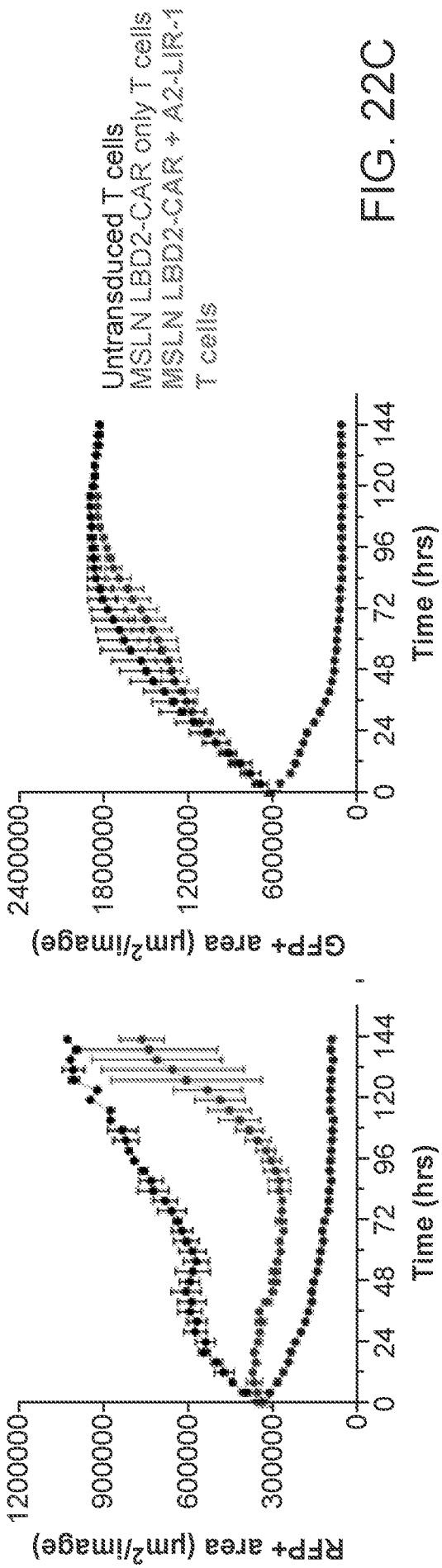

Untransduced T cells
MSLN LBD2-CAR only T cells
MSLN LBD2-CAR + A2-LIR-1
T cells
GFP+ area (µm²/image)
2400000
1800000
1200000
600000
0
0 24 48 72 96 120 144
Time (hrs)
RFP+ area (µm²/image)
1200000
900000
600000
300000
0
0 24 48 72 96 120 144
Time (hrs)

FIG. 22C

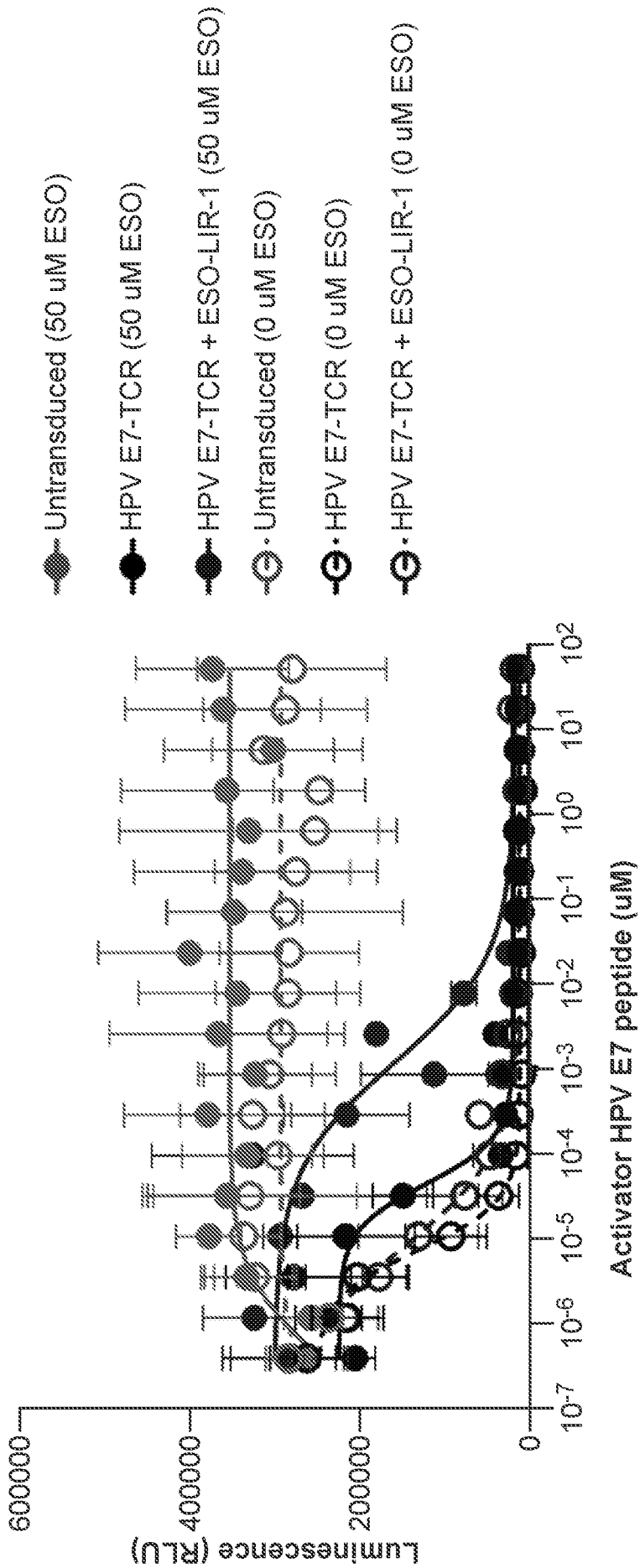

Untransduced (50 uM ESO)
HPV E7-TCR (50 uM ESO)
HPV E7-TCR + ESO-LIR-1 (50 uM ESO)
Untransduced (0 uM ESO)
HPV E7-TCR (0 uM ESO)
HPV E7-TCR + ESO-LIR-1 (0 uM ESO)
Luminescence (RLU)
600000
400000
200000
0
Activator HPV E7 peptide (uM)
10-7
10-6
10-5
10-4
10-3
10-2
10-1
100
101
102

FIG. 23

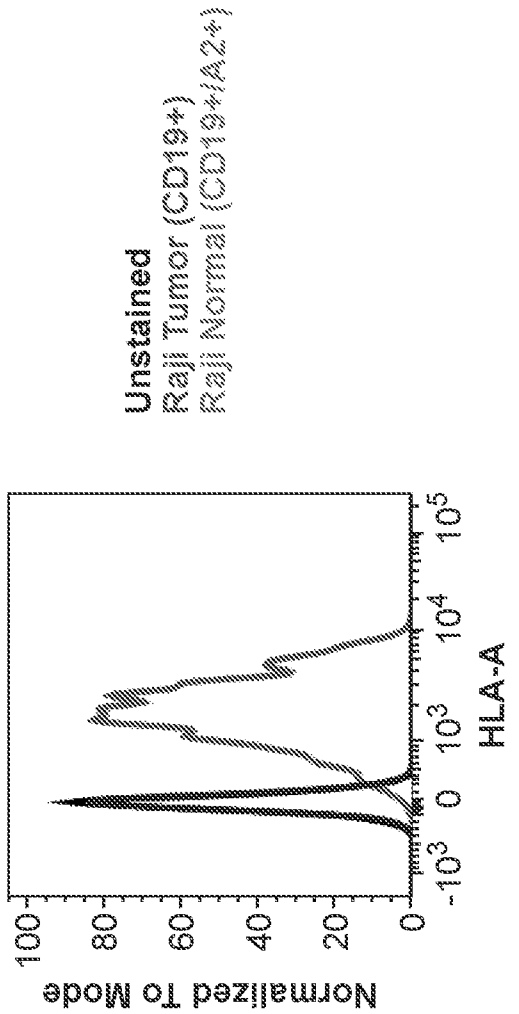


FIG. 24A

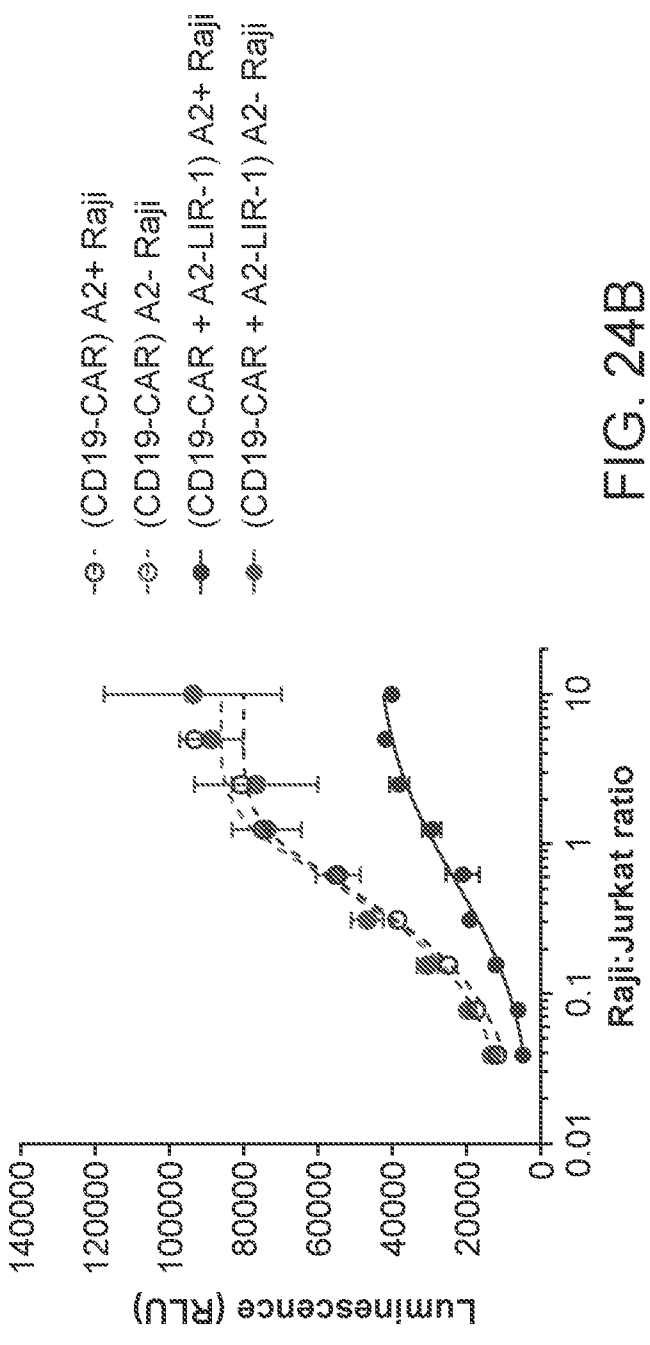


FIG. 24B

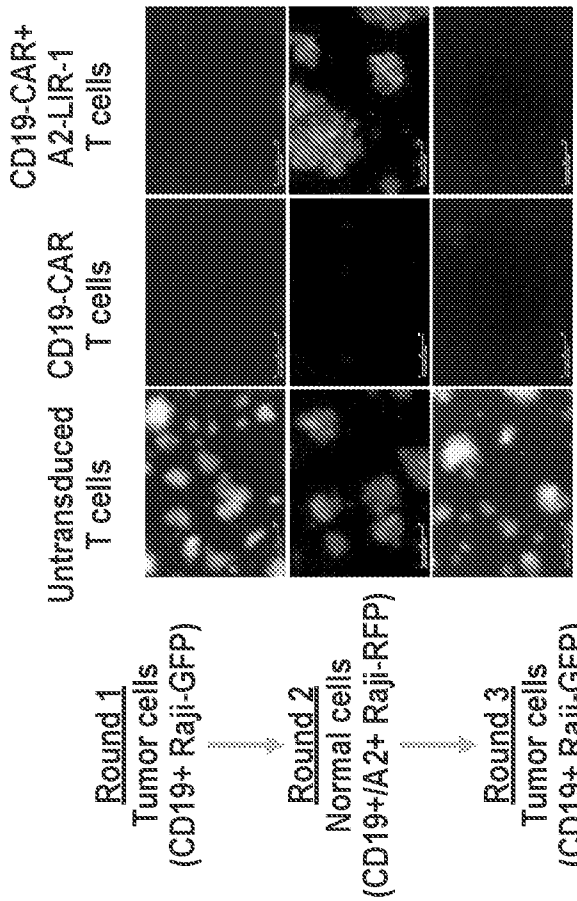


FIG. 25B

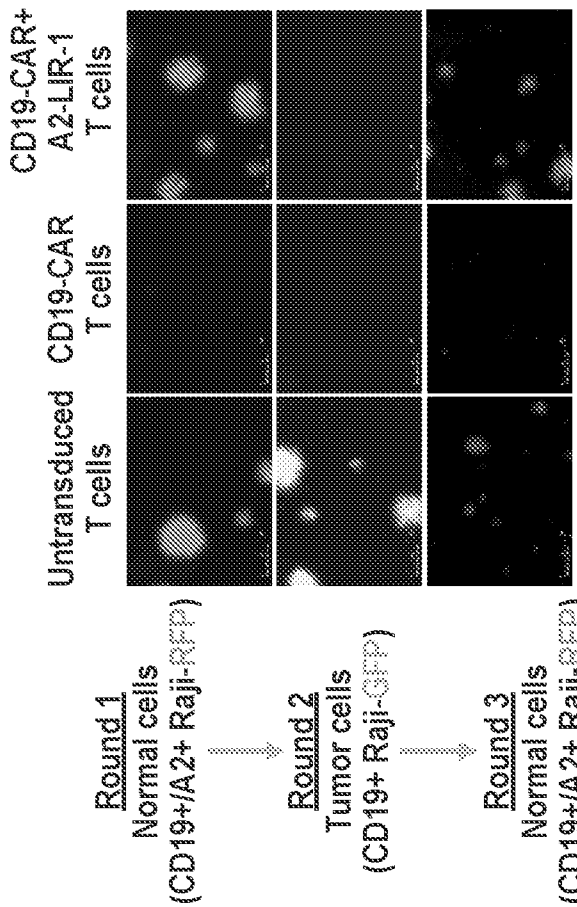


FIG. 25A

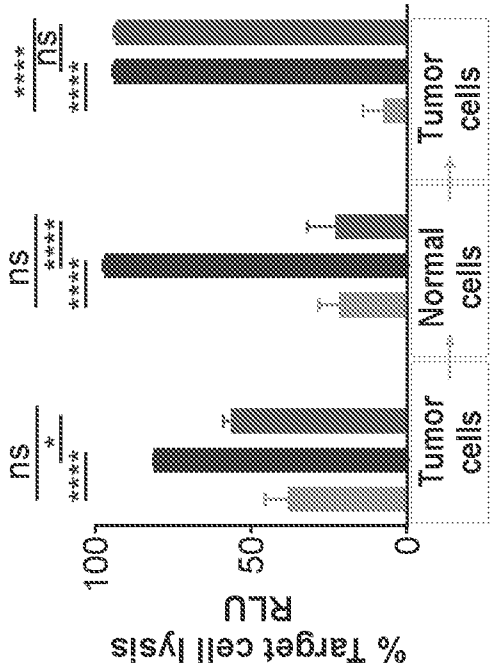


FIG. 25C

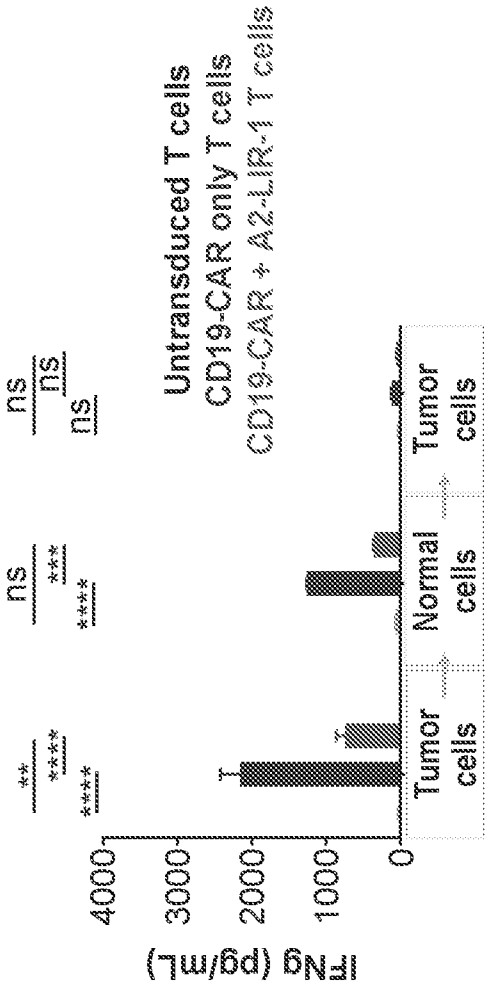


FIG. 25D

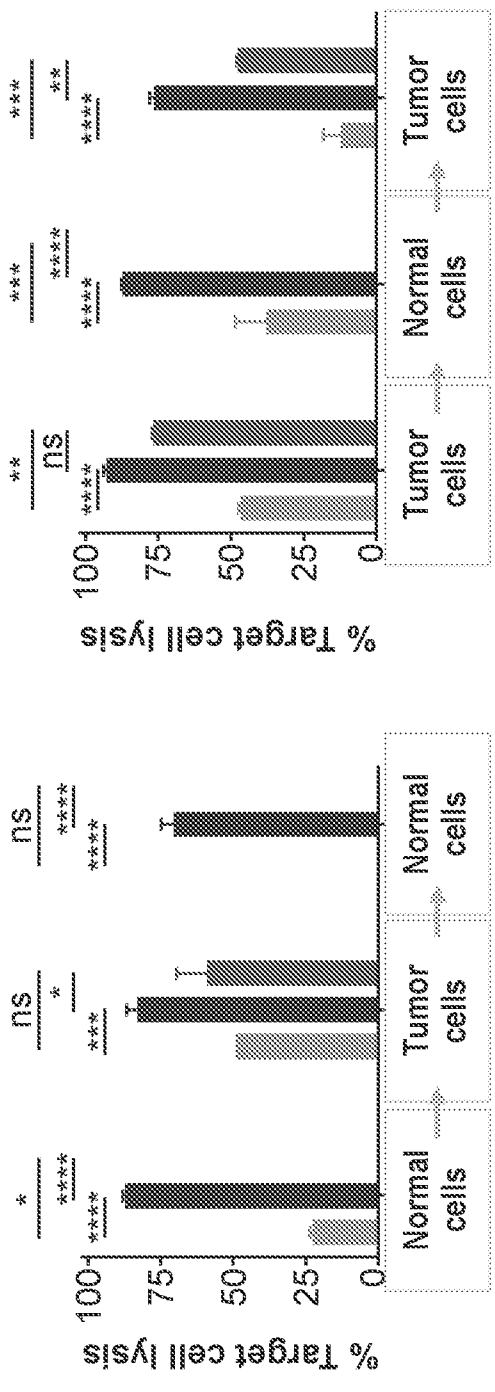


FIG. 26A

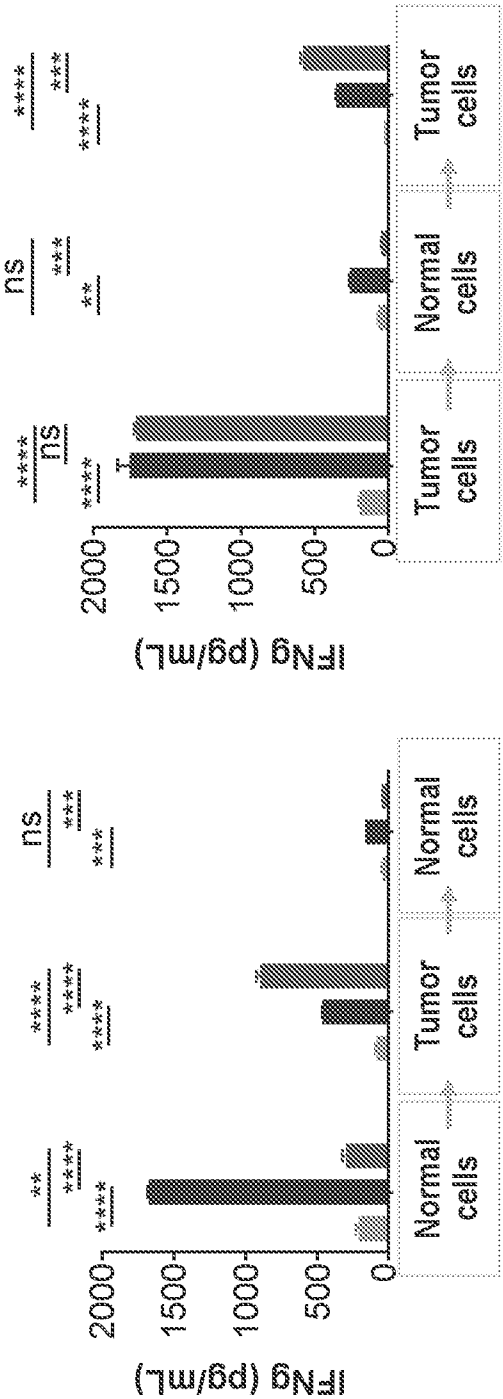


FIG. 26B

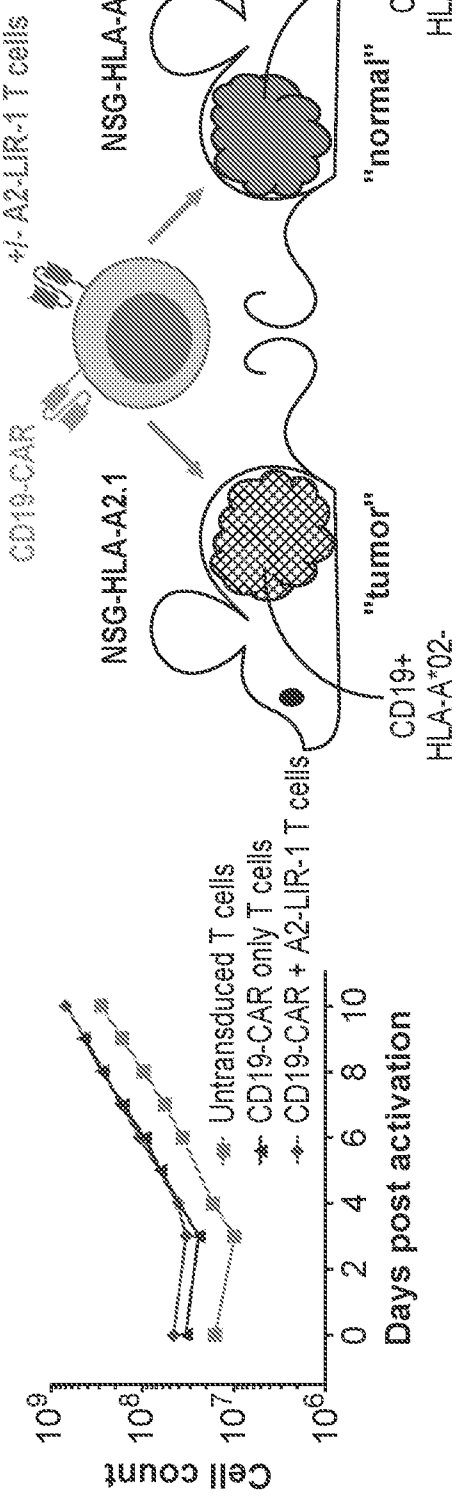


FIG. 27A

FIG. 27B

FIG. 27C

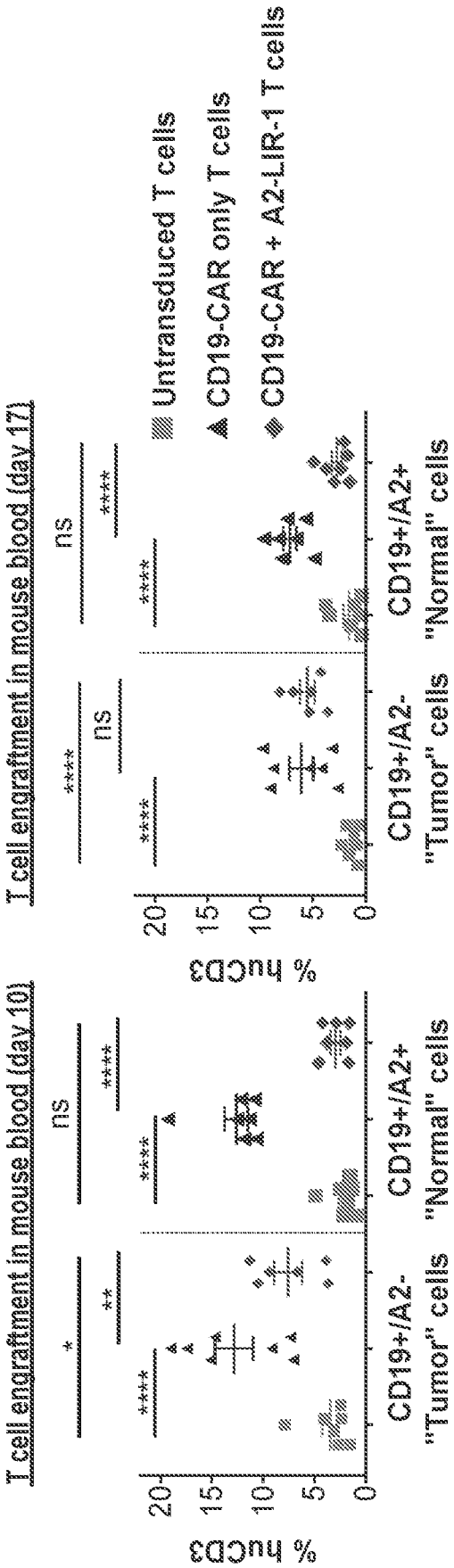


FIG. 27D

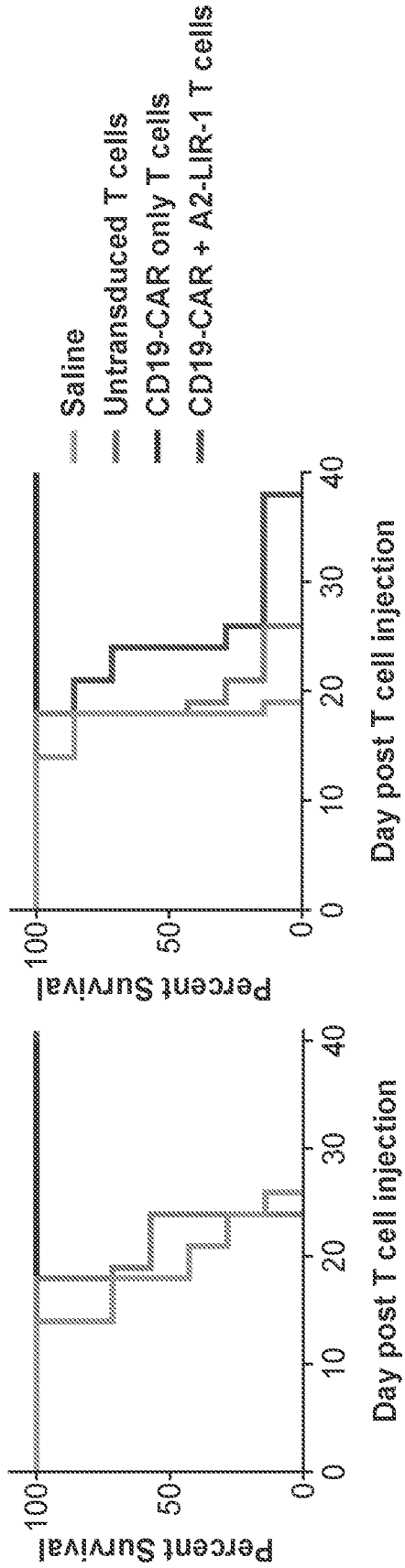


FIG. 27E

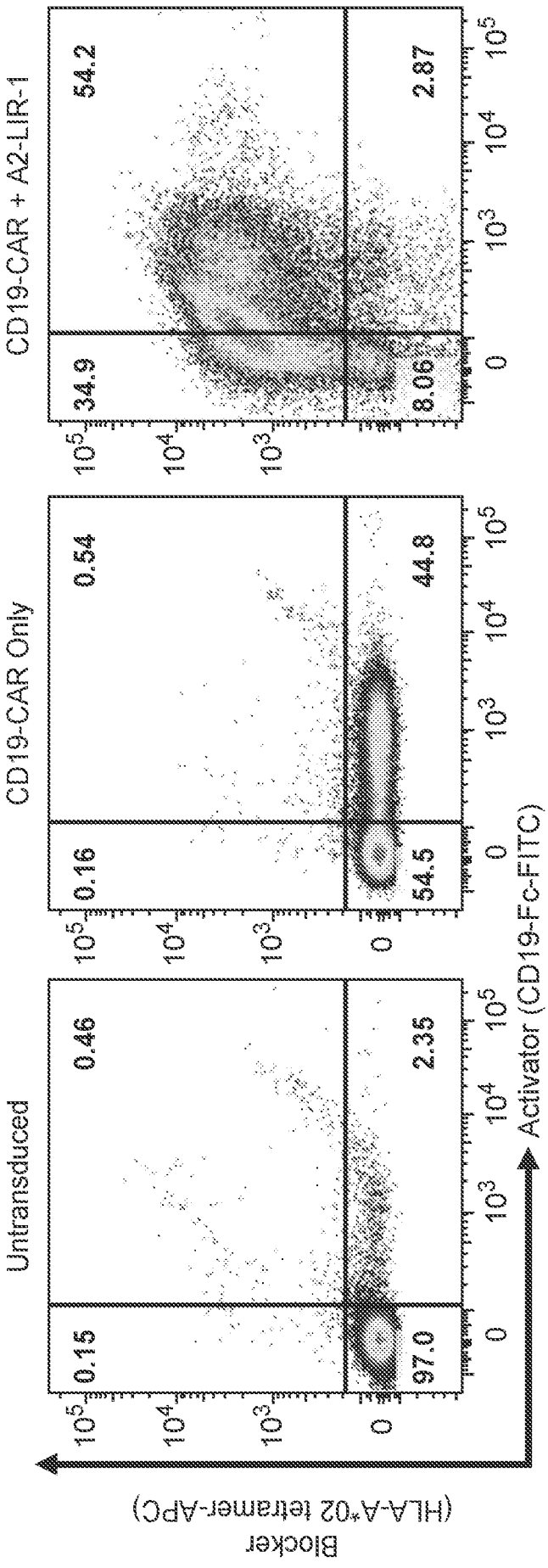

Untransduced
CD19-CAR Only
CD19-CAR + A2-LIR-1
Blocker
(HLA-A*02 tetramer-APC)
Activator (CD19-Fc-FITC)
0.15
0.46
97.0
2.35
0.16
0.54
54.5
44.8
34.9
54.2
8.06
2.87
0
10^3
10^4
10^5

FIG. 28A

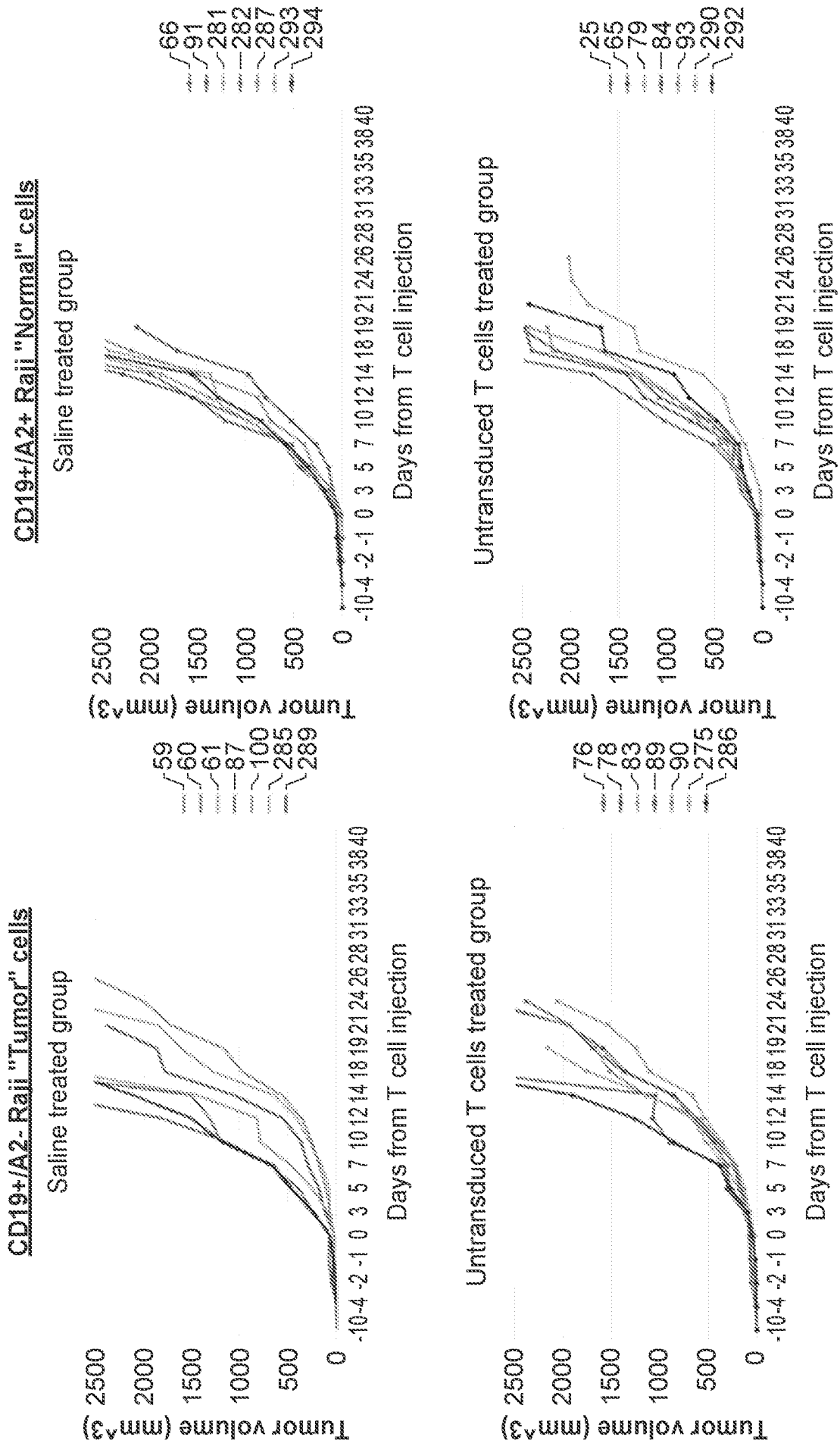

CD19+/A2- Raji "Tumor" cells
Saline treated group
Tumor volume (mm^3)
2500
2000
1500
1000
500
0
-10-4 -2 -1 0 3 5 7 10 12 14 18 19 21 24 26 28 31 33 35 38 40
Days from T cell injection
59
60
61
87
100
285
289
CD19+/A2+ Raji "Normal" cells
Saline treated group
66
91
281
282
287
293
294
Untransduced T cells treated group
76
78
83
89
90
275
286
Untransduced T cells treated group
25
65
79
84
93
290
292

FIG. 28B

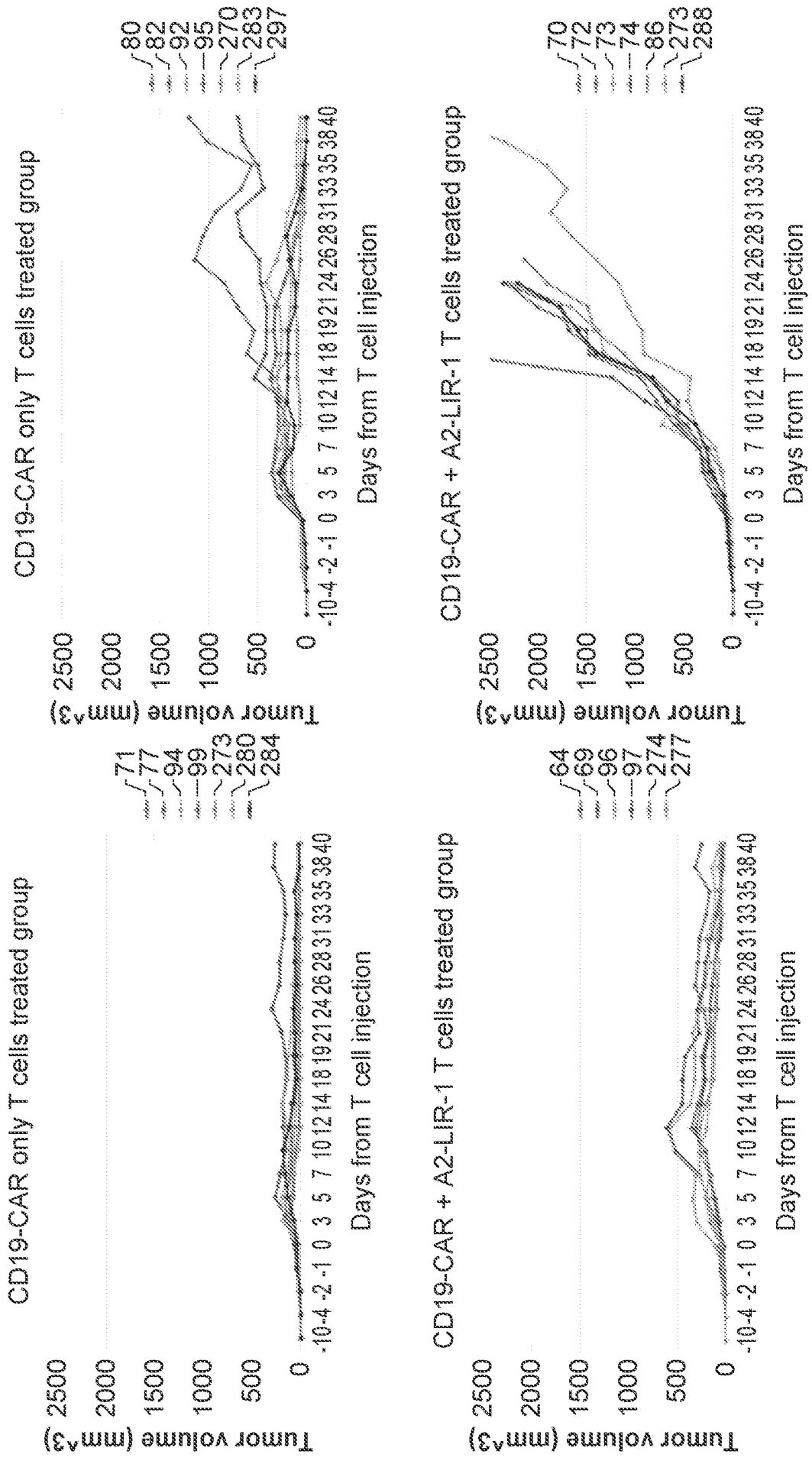

CD19-CAR only T cells treated group
Tumor volume (mm^3)
2500
2000
1500
1000
500
0
-10 -4 -2 -1 0 3 5 7 10 12 14 18 19 21 24 26 28 31 33 35 38 40
Days from T cell injection
80
82
92
95
270
283
297
CD19-CAR + A2-LIR-1 T cells treated group
70
72
73
74
86
273
288
CD19-CAR only T cells treated group
71
77
94
99
273
280
284
CD19-CAR + A2-LIR-1 T cells treated group
64
69
96
97
274
277

FIG. 28B (Cont.)

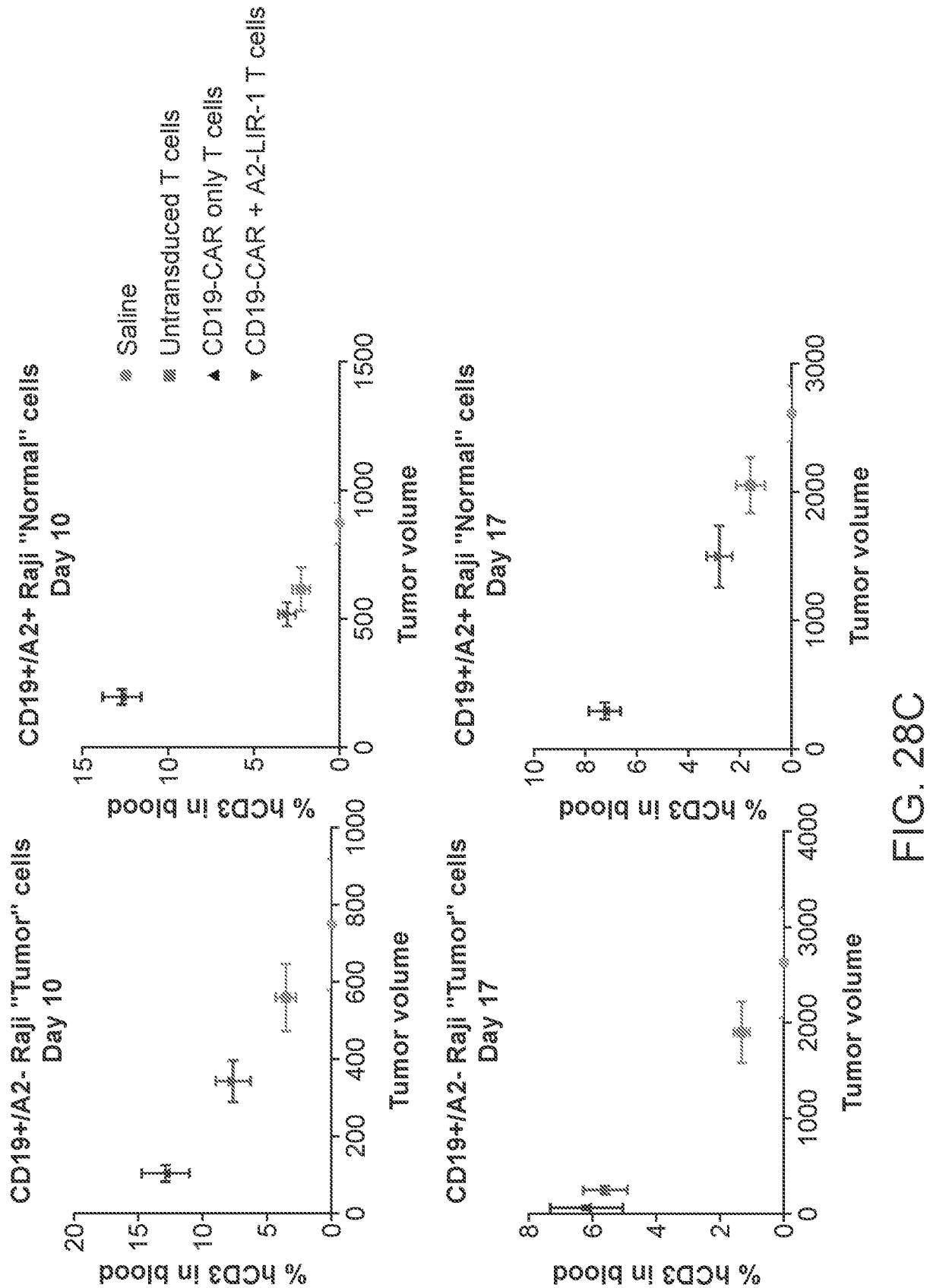

CD19+/A2- Raji "Tumor" cells
Day 10
% hCD3 in blood
Tumor volume
CD19+/A2+ Raji "Normal" cells
Day 10
Saline
Untransduced T cells
CD19-CAR only T cells
CD19-CAR + A2-LIR-1 T cells
CD19+/A2- Raji "Tumor" cells
Day 17
CD19+/A2+ Raji "Normal" cells
Day 17

FIG. 28C

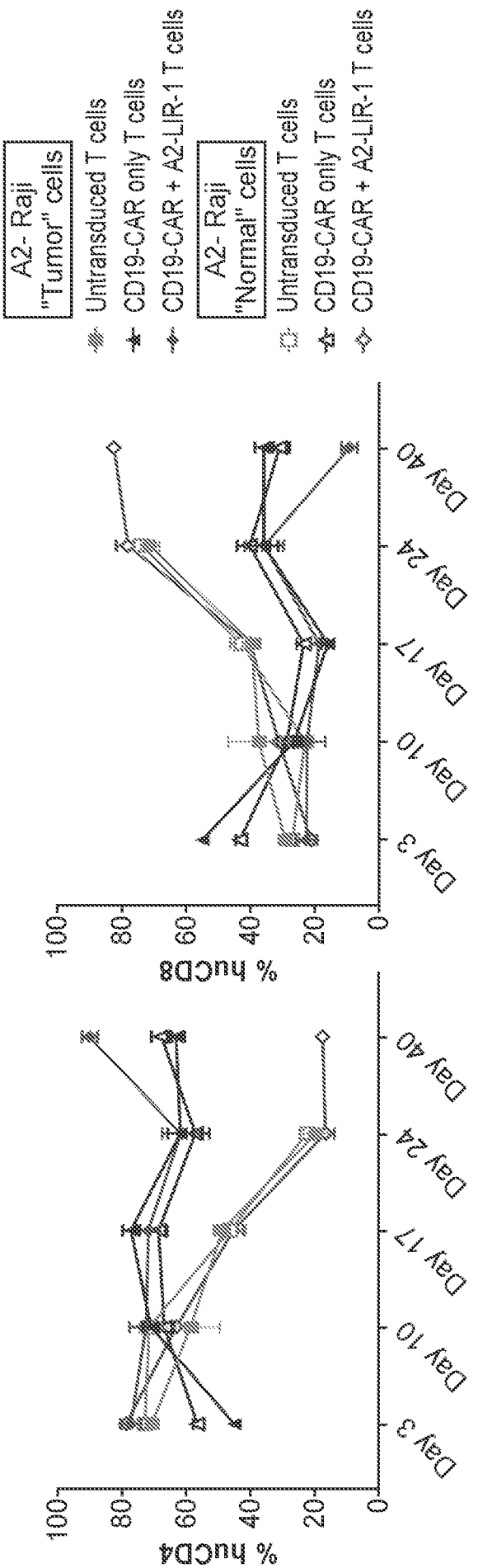

A2- Raji "Tumor" cells
Untransduced T cells
CD19-CAR only T cells
CD19-CAR + A2-LIR-1 T cells
A2- Raji "Normal" cells
Untransduced T cells
CD19-CAR only T cells
CD19-CAR + A2-LIR-1 T cells
% huCD8
% huCD4
0
20
40
60
80
100
Day 3
Day 10
Day 17
Day 24
Day 40

FIG. 28D

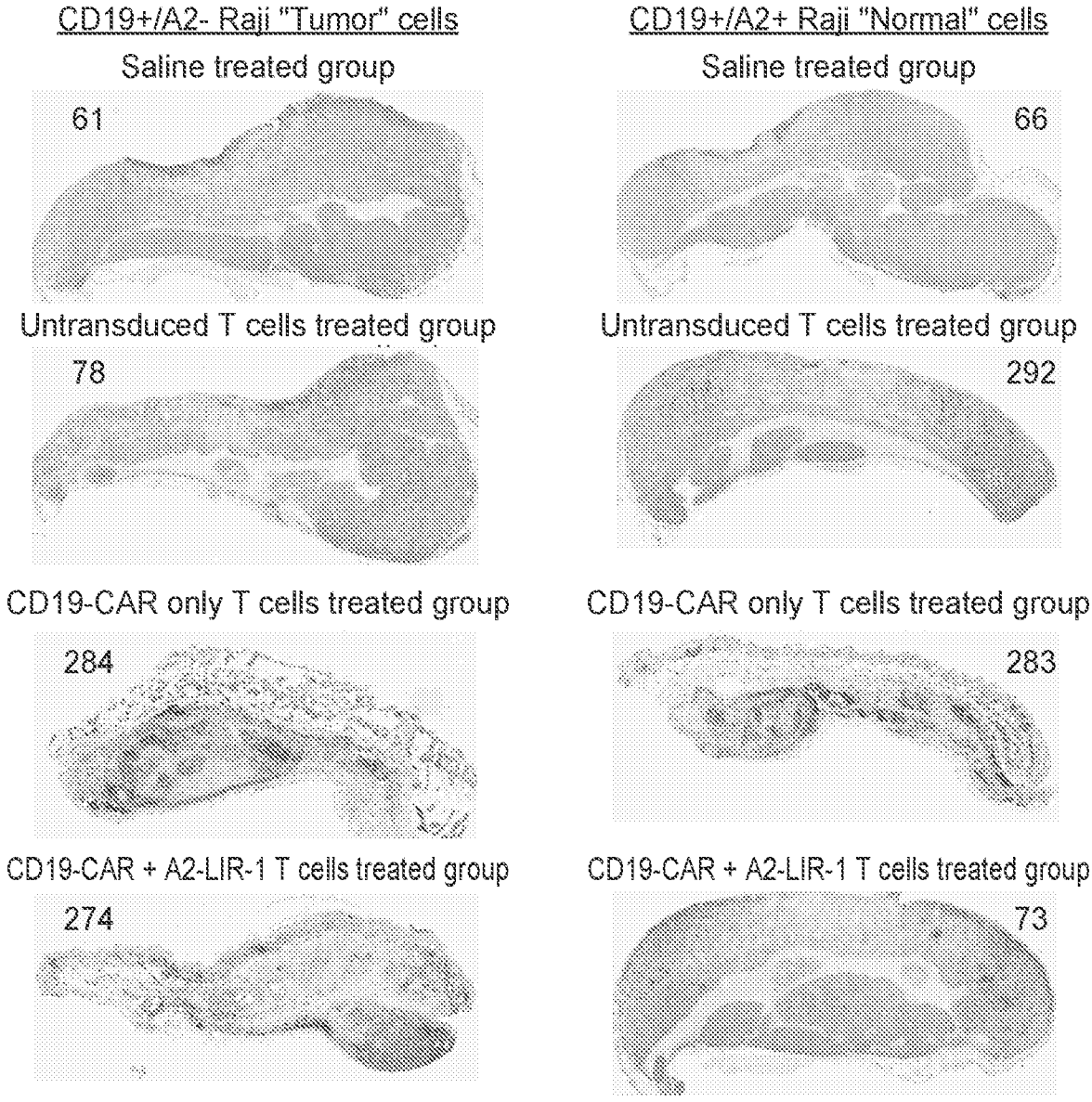

CD19+/A2- Raji "Tumor" cells
Saline treated group
61
Untransduced T cells treated group
78
CD19-CAR only T cells treated group
284
CD19-CAR + A2-LIR-1 T cells treated group
274
CD19+/A2+ Raji "Normal" cells
Saline treated group
66
Untransduced T cells treated group
292
CD19-CAR only T cells treated group
283
CD19-CAR + A2-LIR-1 T cells treated group
73

FIG. 29A

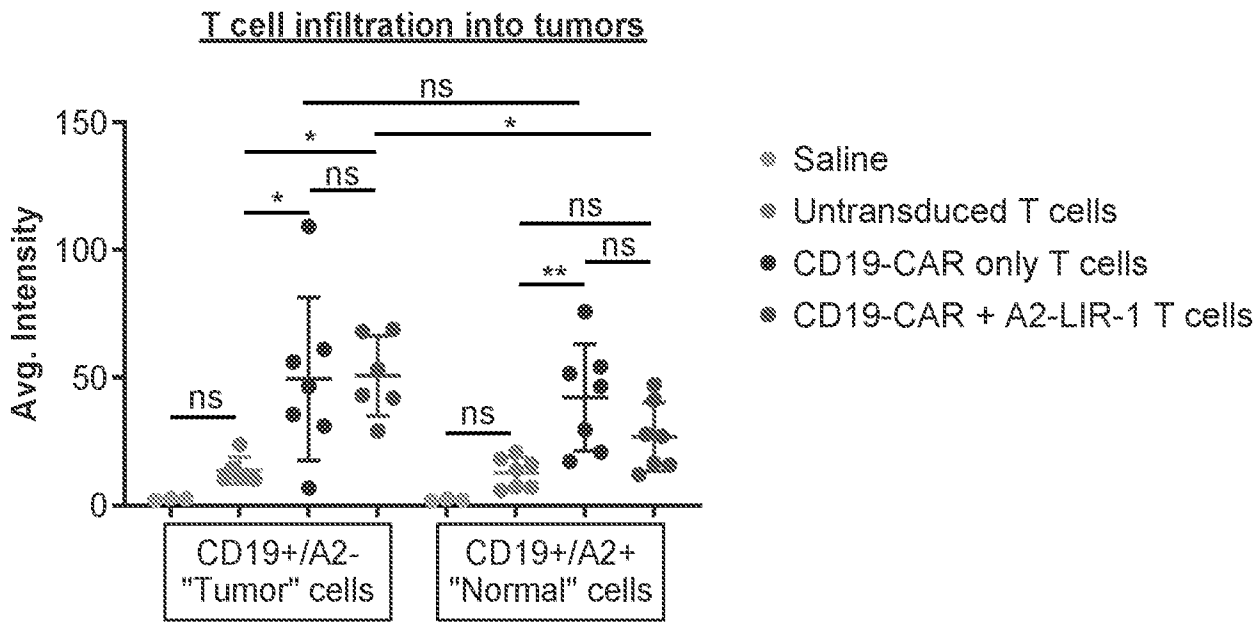

T cell infiltration into tumors
Avg. Intensity
150
100
50
0
ns
*
*
ns
*
ns
ns
**
ns
ns
CD19+/A2-
"Tumor" cells
CD19+/A2+
"Normal" cells
Saline
Untransduced T cells
CD19-CAR only T cells
CD19-CAR + A2-LIR-1 T cells

FIG. 29B

SEQUENCE LISTING

<110> A2 Biotherapeutics, Inc.
Kamb, Carl Alexander
Hamburger, Agnes E.
Diandreth, Breanna
Daris, Mark E.
Deshmukh, Kiran

<120> LILRB1-BASED CHIMERIC ANTIGEN RECEPTOR

<130> A2BI-015/04WO 331656-2036

<150> US 62/946,888
<151> 2019-12-11

<150> US 63/085,969
<151> 2020-08-30

<160> 129

<170> PatentIn version 3.5

<210> 1
<211> 670
<212> PRT
<213> Homo sapiens

<400> 1

Met Thr Pro Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly
1 5 10 15

Pro Arg Thr His Val Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp
20 25 30

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

Cys Gln Gly Gly Gln Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys
50 55 60

Lys Thr Ala Leu Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys
65 70 75 80

Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly Arg Tyr
85 90 95

Arg Cys Tyr Tyr Gly Ser Asp Thr Ala Gly Arg Ser Glu Ser Ser Asp
100 105 110

Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser
115 120 125

Ala Gln Pro Ser Pro Val Val Asn Ser Gly Gly Asn Val Ile Leu Gln
130 135 140

Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ser Leu Cys Lys Glu Gly
145 150 155 160

```
Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly
                165                 170                 175

Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg
            180                 185                 190

Trp Trp Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro Tyr Glu Trp
        195                 200                 205

Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Leu Gly Val Ser Lys
    210                 215                 220

Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro Glu Glu
225                 230                 235                 240

Thr Leu Thr Leu Gln Cys Gly Ser Asp Ala Gly Tyr Asn Arg Phe Val
                245                 250                 255

Leu Tyr Lys Asp Gly Glu Arg Asp Phe Leu Gln Leu Ala Gly Ala Gln
            260                 265                 270

Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
        275                 280                 285

Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser
    290                 295                 300

Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly
305                 310                 315                 320

Gln Phe Tyr Asp Arg Val Ser Leu Ser Val Gln Pro Gly Pro Thr Val
                325                 330                 335

Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Gln Gly Trp Met
            340                 345                 350

Gln Thr Phe Leu Leu Thr Lys Glu Gly Ala Ala Asp Asp Pro Trp Arg
        355                 360                 365

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

Gly Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser
385                 390                 395                 400

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

Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly
            420                 425                 430
```

```
Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly
        435                 440                 445

Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly
    450                 455                 460

Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe
465                 470                 475                 480

Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln
                485                 490                 495

Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro
            500                 505                 510

Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln
        515                 520                 525

Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly
    530                 535                 540

Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val
545                 550                 555                 560

Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser
                565                 570                 575

Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln
            580                 585                 590

Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala
        595                 600                 605

Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg
    610                 615                 620

Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val
625                 630                 635                 640

Pro Ser Ile Tyr Ala Thr Leu Ala Ile His Pro Ser Gln Glu Gly Pro
                645                 650                 655

Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
            660                 665                 670


<210>  2
<211>  253
<212>  PRT
<213>  Homo sapiens

<400>  2

Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp
```

```
1               5                   10                  15

Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro
            20                  25                  30

Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr
        35                  40                  45

Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val
    50                  55                  60

Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu
65                  70                  75                  80

Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr
                85                  90                  95

Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly
            100                 105                 110

Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala
        115                 120                 125

Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro
    130                 135                 140

Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro
145                 150                 155                 160

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

Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys
            180                 185                 190

Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala
        195                 200                 205

Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr
    210                 215                 220

Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser
225                 230                 235                 240

Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                245                 250
```

<210> 3
<211> 233
<212> PRT
<213> Homo sapiens

<400> 3

```
Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro
1               5                   10                  15

Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser
            20                  25                  30

Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly Ile
        35                  40                  45

Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe Leu
    50                  55                  60

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

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

Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu
            100                 105                 110

Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val
        115                 120                 125

Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr
    130                 135                 140

Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro
145                 150                 155                 160

Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala
                165                 170                 175

Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro
            180                 185                 190

Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu
        195                 200                 205

Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro
    210                 215                 220

Ser Ile Tyr Ala Thr Leu Ala Ile His
225                 230


<210>  4
<211>  63
<212>  PRT
<213>  Homo sapiens

<400>  4

Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp
```

1 5 10 15

Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro
20 25 30

Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr
35 40 45

Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
50 55 60

<210> 5
<211> 23
<212> PRT
<213> Homo sapiens

<400> 5

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Phe Leu Ile Leu
20

<210> 6

<400> 6
000

<210> 7
<211> 167
<212> PRT
<213> Homo sapiens

<400> 7

Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala
1 5 10 15

Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg
20 25 30

Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn
35 40 45

Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met
50 55 60

Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala
65 70 75 80

Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser
85 90 95

Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu
100 105 110

Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp
        115   120   125

Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr
    130   135   140

Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile
145   150   155   160

Tyr Ala Thr Leu Ala Ile His
                165

<210> 8
<211> 6
<212> PRT
<213> Homo sapiens

<400> 8

Asn Leu Tyr Ala Ala Val
1   5

<210> 9
<211> 6
<212> PRT
<213> Homo sapiens

<400> 9

Val Thr Tyr Ala Glu Val
1   5

<210> 10
<211> 6
<212> PRT
<213> Homo sapiens

<400> 10

Val Thr Tyr Ala Gln Leu
1   5

<210> 11
<211> 6
<212> PRT
<213> Homo sapiens

<400> 11

Ser Ile Tyr Ala Thr Leu
1   5

<210> 12
<211> 35
<212> PRT
<213> Homo sapiens

<400> 12

Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu

1 5 10 15

Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr
20 25 30

Ala Glu Val
35

<210> 13
<211> 58
<212> PRT
<213> Homo sapiens

<400> 13

Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala
1 5 10 15

Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg
20 25 30

Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu
35 40 45

Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu
50 55

<210> 14
<211> 36
<212> PRT
<213> Homo sapiens

<400> 14

Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr
1 5 10 15

Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile
20 25 30

Tyr Ala Thr Leu
35

<210> 15
<211> 87
<212> PRT
<213> Homo sapiens

<400> 15

Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu
1 5 10 15

Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr
20 25 30

Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro

```
        35                  40                  45

Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu
    50                  55                  60

Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln
65                  70                  75                  80

Asp Val Thr Tyr Ala Gln Leu
                85
```

<210> 16
<211> 88
<212> PRT
<213> Homo sapiens

<400> 16

```
Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala
1               5                   10                  15

Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg
            20                  25                  30

Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu
        35                  40                  45

Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg
    50                  55                  60

Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala
65                  70                  75                  80

Val Pro Ser Ile Tyr Ala Thr Leu
                85
```

<210> 17
<211> 117
<212> PRT
<213> Homo sapiens

<400> 17

```
Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu
1               5                   10                  15

Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr
            20                  25                  30

Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro
        35                  40                  45

Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu
    50                  55                  60
```

```
Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln
65                  70                  75                  80


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


Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser
            100                 105                 110


Ile Tyr Ala Thr Leu
        115


<210>  18
<211>  20
<212>  PRT
<213>  Homo sapiens

<400>  18

Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp
1               5                   10                  15


Pro Leu Glu Leu
            20


<210>  19
<211>  43
<212>  PRT
<213>  Homo sapiens

<400>  19

Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro
1               5                   10                  15


Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser
            20                  25                  30


Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
        35                  40


<210>  20
<211>  86
<212>  PRT
<213>  Homo sapiens

<400>  20

Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp
1               5                   10                  15


Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro
            20                  25                  30


Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr
        35                  40                  45
```

```
Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val
    50                  55                  60

Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu
65                  70                  75                  80

Leu Leu Phe Leu Ile Leu
                85
```

<210> 21
<211> 190
<212> PRT
<213> Homo sapiens

<400> 21

```
Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
1               5                   10                  15

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
            20                  25                  30

Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
        35                  40                  45

Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
    50                  55                  60

Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln
65                  70                  75                  80

Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp
                85                  90                  95

Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg
            100                 105                 110

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
        115                 120                 125

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
    130                 135                 140

Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
145                 150                 155                 160

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

Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
            180                 185                 190
```

<210> 22
<211> 16

<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR

<400> 22

Arg Ser Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu
1   5   10   15

<210> 23
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR

<400> 23

Lys Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg
1   5   10

<210> 24
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR

<400> 24

Phe Gln Gly Ser His Val Pro Arg Thr
1   5

<210> 25
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR

<400> 25

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr His Ile His
1   5   10

<210> 26
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR

<400> 26

Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys
1   5   10   15

Gly Lys

<210> 27
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR

<400> 27

Glu Glu Ile Thr Tyr Ala Met Asp Tyr
1   5

<210> 28
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR

<400> 28

Arg Ser Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Asp
1   5   10   15

<210> 29
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR

<400> 29

Lys Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg
1   5   10

<210> 30
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR

<400> 30

Met Gln Gly Ser His Val Pro Arg Thr
1   5

<210> 31
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR

<400> 31

Ser Gly Tyr Thr Phe Thr Ser Tyr His Met His
1   5   10

<210> 32
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR

<400> 32

Trp Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe Lys
1   5   10   15

Gly

<210> 33
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR

<400> 33

Glu Gly Thr Tyr Tyr Ala Met Asp Tyr
1   5

<210> 34
<211> 3229
<212> DNA
<213> Homo sapiens

<400> 34
aaatgagttt taaaaaggct tgtccaggaa gcacatatgg gagctggtca ctctgcattt   60

tgggccctcc tggaggtgtt tagaccttcc gagagagaaa ctgagacaca tgagagggaa   120

gaaatgactc agtggtgaga ccctgtggag tcccacccac aaccagcaca ctgtgaccca   180

ctgcacaaac ctctagccca cagctcactt cctcctttaa gaagagaaga gaaaagagga   240

gaggagagga ggaacagaaa agaaaagaaa agaaaaagtg ggaaacaaat aatctaagaa   300

tgaggagaaa gcaagaagag tgacccccct gtgggcactc cattggtttt atggcgcctc   360

tactttctgg agtttgtgta aaacaaaaat attatggtct ttgtgcacat ttacatcaag   420

ctcagcctgg gcggcacagc cagatgcgag atgcgtctct gctgatctga gtctgcctgc   480

agcatggacc tgggtcttcc ctgaagcatc tccagggctg gagggacgac tgccatgcac   540

cgagggctca tccatccaca gagcagggca gtgggaggag acgccatgac ccccatcctc   600

acggtcctga tctgtctcgg gctgagtctg ggcccccgga cccacgtgca ggcagggcac   660

ctccccaagc ccacctctg ggctgaacca ggctctgtga tcacccaggg gagtcctgtg   720

accctcaggt gtcaggggg ccaggagacc caggagtacc gtctatatag agaaaagaaa   780

acagcaccct ggattacacg gatcccacag gagcttgtga agaagggcca gttccccatc   840

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ccatccatca cctgggaaca cacagggcgg tatcgctgtt actatggtag cgacactgca      900

ggccgctcag agagcagtga ccccctggag ctggtggtga caggagccta catcaaaccc      960

accctctcag cccagcccag ccccgtggtg aactcaggag ggaatgtaac cctccagtgt     1020

gactcacagg tggcatttga tggcttcatt ctgtgtaagg aaggagaaga tgaacaccca     1080

caatgcctga actcccagcc ccatgcccgt gggtcgtccc gcgccatctt ctccgtgggc     1140

cccgtgagcc cgagtcgcag gtggtggtac aggtgctatg cttatgactc gaactctccc     1200

tatgagtggt ctctacccag tgatctcctg gagctcctgg tcctaggtgt ttctaagaag     1260

ccatcactct cagtgcagcc aggtcctatc gtggcccctg aggagaccct gactctgcag     1320

tgtggctctg atgctggcta caacagattt gttctgtata aggacgggga acgtgacttc     1380

cttcagctcg ctggcgcaca gccccaggct gggctctccc aggccaactt caccctgggc     1440

cctgtgagcc gctcctacgg gggccagtac agatgctacg gtgcacacaa cctctcctcc     1500

gagtggtcgg cccccagcga ccccctggac atcctgatcg caggacagtt ctatgacaga     1560

gtctccctct cggtgcagcc gggccccacg gtggcctcag gagagaacgt gaccctgctg     1620

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ccatggcgtc taagatcaac gtaccaatct caaaaatacc aggctgaatt ccccatgggt     1740

cctgtgacct cagcccatgc ggggacctac aggtgctacg gctcacagag ctccaaaccc     1800

tacctgctga ctcaccccag tgacccccctg gagctcgtgg tctcaggacc gtctgggggc     1860

cccagctccc cgacaacagg ccccacctcc acatctggcc ctgaggacca gcccctcacc     1920

cccaccgggt cggatcccca gagtggtctg ggaaggcacc tgggggttgt gatcggcatc     1980

ttggtggccg tcatcctact gctcctcctc ctcctcctcc tcttcctcat cctccgacat     2040

cgacgtcagg gcaaacactg gacatcgacc cagagaaagg ctgatttcca acatcctgca     2100

ggggctgtgg ggccagagcc cacagacaga ggcctgcagt ggaggtccag cccagctgcc     2160

gatgcccagg aagaaaacct ctatgctgcc gtgaagcaca cacagcctga ggatggggtg     2220

gagatggaca ctcggagccc acacgatgaa gacccccagg cagtgacgta tgccgaggtg     2280

aaacactcca gacctaggag agaaatggcc tctcctcctt ccccactgtc tggggaattc     2340

ctggacacaa aggacagaca ggcggaagag gacaggcaga tggacactga ggctgctgca     2400

tctgaagccc cccaggatgt gacctacgcc cagctgcaca gcttgaccct cagacgggag     2460

gcaactgagc ctcctccatc ccaggaaggg ccctctccag ctgtgcccag catctacgcc     2520

actctggcca tccactagcc cagggggga cgcagacccc acactccatg gagtctggaa     2580

tgcatgggag ctgccccccc agtggacacc attggacccc acccagcctg gatctacccc     2640

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tacaattttg aaataaagca acagacttct caataatcaa tgaagtagct gagaaaacta     2760

agtcagaaag tgcattaaac tgaatcacaa tgtaaatatt acacatcaag cgatgaaact     2820

ggaaaactac aagccacgaa tgaatgaatt aggaaagaaa aaaagtagga aatgaatgat     2880
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actttgggag gccgaggcgg gcagatcacg agttcaggag atcgagacca tcttggccaa 3000

catggtgaaa ccctgtctct cctaaaaata caaaaattag ctggatgtgg tggcagtgcc 3060

tgtaatccca gctatttggg aggctgaggc aggagaatcg cttgaaccag ggagtcagag 3120

gtttcagtga gccaagatcg caccactgct ctccagcctg gcgacagagg gagactccat 3180

ctcaaattaa aaaaaaaaaa aaaaaagaaa gaaaaaaaaa aaaaaaaaa 3229

<210> 35
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> C-001765 scFv antibody construct

<400> 35

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

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Asn Gly
20 25 30

Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys
35 40 45

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

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

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

Val Pro Arg Thr Ser Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly
100 105 110

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

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

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

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

Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys
180 185 190

```
Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met
        195                 200                 205


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


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


Val Thr Val Ser Ser Tyr Gly
                245
```

<210> 36
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002159 scFv antibody construct

<400> 36

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


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


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


Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys Gly
    50                  55                  60


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


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


Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val
            100                 105                 110


Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125


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


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln
145                 150                 155                 160


Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Gln Gln
```

```
                165                 170                 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190

Phe Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
    210                 215                 220

Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly Gly Thr
225                 230                 235                 240

Lys Val Glu Ile Lys
                245
```

<210> 37
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002160 scFv antibody construct

<400> 37

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

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

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

Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys Gly
    50                  55                  60

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

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

Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu
    130                 135                 140
```

```
Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
145                 150                 155                 160


Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln
                165                 170                 175


Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190


Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205


Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
    210                 215                 220


Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly Gly Thr
225                 230                 235                 240


Lys Val Glu Ile Lys
                245


<210>  38
<211>  245
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C-002161 scFv antibody construct

<400>  38

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


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


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


Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys Gly
    50                  55                  60


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


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


Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val
            100                 105                 110


Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125
```

```
Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130                 135                 140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln
145                 150                 155                 160

Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190

Phe Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
    210                 215                 220

Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly Gly Thr
225                 230                 235                 240

Lys Val Glu Ile Lys
                245
```

<210> 39
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002162 scFv antibody construct

<400> 39

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

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

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

Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys Gly
    50                  55                  60

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

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

Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
```

```
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125


Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu
    130                 135                 140


Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln
145                 150                 155                 160


Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Gln Gln
                165                 170                 175


Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190


Phe Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu
        195                 200                 205


Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr
    210                 215                 220


Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gln Gly Thr
225                 230                 235                 240


Lys Val Glu Val Lys
                245


<210>  40
<211>  245
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C-002163 scFv antibody construct

<400>  40

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


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


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


Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe Lys Gly
    50                  55                  60


Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Asn Thr Ala Tyr Met Glu
65                  70                  75                  80


Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
```

```
                85                  90                  95

Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Asp Val Gln Met Thr Gln Ser Pro Ser Thr Leu
    130                 135                 140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ser Ser Gln
145                 150                 155                 160

Ser Ile Val His Ser Asn Gly Asn Thr Tyr Met Glu Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190

Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr
    210                 215                 220

Tyr Cys His Gln Gly Ser His Val Pro Arg Thr Phe Gly Gln Gly Thr
225                 230                 235                 240

Lys Val Glu Val Lys
                245
```

<210> 41
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002164 scFv antibody construct

<400> 41

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

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

His Ile Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe
    50                  55                  60
```

```
Lys Gly Lys Thr Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


Met Leu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Ile Tyr Phe Cys
                85                  90                  95


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


Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Asp Val Leu Met Thr Gln Thr Pro Leu
    130                 135                 140


Ser Leu Pro Val Ser Leu Gly Asp Gln Val Ser Ile Ser Cys Arg Ser
145                 150                 155                 160


Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
                165                 170                 175


Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190


Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly
    210                 215                 220


Val Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly
225                 230                 235                 240


Gly Thr Lys Leu Glu Ile Lys
                245


<210>  42
<211>  247
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C-002165 scFv antibody construct

<400>  42

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


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


His Ile Gln Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe
    50                  55                  60

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

Leu Asn Leu Asp Ser Val Ser Ala Ala Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Thr Tyr Tyr Ala Met Asp Tyr Trp Gly Lys Gly Ser
            100                 105                 110

Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser
145                 150                 155                 160

Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190

Asn Arg Phe Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
    210                 215                 220

Thr Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Pro
225                 230                 235                 240

Gly Thr Lys Val Asp Ile Lys
                245
```

<210> 43
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002166 scFv antibody construct

<400> 43

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

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

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

Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Asn 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 Glu Gly Thr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser
145                 150                 155                 160

Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190

Asn Arg Phe Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala
    210                 215                 220

Thr Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Val Glu Val Lys
                245
```

<210> 44
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002167 scFv antibody construct

<400> 44

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
```

```
1               5                   10                  15

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

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

Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe
    50                  55                  60

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

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

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

Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

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

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser
145                 150                 155                 160

Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190

Asn Arg Phe Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala
    210                 215                 220

Val Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly
225                 230                 235                 240

Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 45
<211> 247
<212> PRT
<213> Artificial Sequence

<220>

<223> C-002168 scFv antibody construct

<400> 45

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


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


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


Gly Arg Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Gly Lys Val Thr Ile Thr Ala Asp Lys Ser Met Asp Thr Ser Phe
65                  70                  75                  80


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


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


Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


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


Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser
145                 150                 155                 160


Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Ala Trp Tyr
                165                 170                 175


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Ser Lys Val Ser
            180                 185                 190


Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala
    210                 215                 220


Val Tyr Tyr Cys Gln Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly
225                 230                 235                 240


Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 46

<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> C-002169 scFv antibody construct

<400> 46

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

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

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

Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe
    50   55   60

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

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

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

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115   120   125

Gly Gly Gly Gly Ser Gly Gly Asp Ile Val Met Thr Gln Thr Pro Leu
    130   135   140

Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser
145   150   155   160

Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Asp Trp Tyr
                165   170   175

Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser
            180   185   190

Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195   200   205

Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
    210   215   220

Val Tyr Tyr Cys Met Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly
225   230   235   240

Gly Thr Lys Val Glu Ile Lys
245

<210> 47
<211> 511
<212> PRT
<213> Artificial Sequence

<220>
<223> C563 chimeric antigen recetor constuct

<400> 47

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

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

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

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

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

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

Ala Arg Ile Pro Phe Gly Asp Trp Trp Tyr Phe Asp Leu Trp Gly Arg
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser
130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145 150 155 160

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys
165 170 175

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln
180 185 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
195 200 205

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210 215 220

```
Cys Gln Gln Ser Tyr Ser Phe Val Leu Thr Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
                245                 250                 255

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
            260                 265                 270

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
        275                 280                 285

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

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

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

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

Ala Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
        355                 360                 365

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
    370                 375                 380

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
385                 390                 395                 400

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
                405                 410                 415

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
            420                 425                 430

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
        435                 440                 445

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
    450                 455                 460

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
465                 470                 475                 480

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
                485                 490                 495
```

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
500 505 510

<210> 48
<211> 403
<212> PRT
<213> Artificial Sequence

<220>
<223> C1759 chimeric antigen recetor constuct

<400> 48

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro 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 Gly Gly Gly Gly Ser
100 105 110

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

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

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

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

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

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

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

```
Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
225                 230                 235                 240


Ser Phe Gly Ser Phe Arg Ala Leu Pro Cys Val Trp Ser Asn Ser Ser
                245                 250                 255


Asp Pro Leu Leu Val Ser Val Thr Gly Asn Pro Ser Ser Ser Trp Pro
            260                 265                 270


Ser Pro Thr Glu Pro Ser Ser Lys Ser Gly Ile Cys Arg His Leu His
        275                 280                 285


Val Leu Ile Gly Thr Ser Val Val Ile Phe Leu Phe Ile Leu Leu Leu
    290                 295                 300


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


Met Asp Gln Glu Pro Ala Gly Asp Arg Thr Val Asn Arg Gln Asp Ser
                325                 330                 335


Asp Glu Gln Asp Pro Gln Glu Val Thr Tyr Ala Gln Leu Asp His Cys
            340                 345                 350


Val Phe Ile Gln Arg Lys Ile Ser Arg Pro Ser Gln Arg Pro Lys Thr
        355                 360                 365


Pro Leu Thr Asp Thr Ser Val Tyr Thr Glu Leu Pro Asn Ala Glu Pro
    370                 375                 380


Arg Ser Lys Val Val Ser Cys Pro Arg Ala Pro Gln Ser Gly Leu Glu
385                 390                 395                 400


Gly Val Phe



<210>  49
<211>  358
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C1760 chimeric antigen recetor constuct

<400>  49

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 Gly Gly Gly Gly Ser
            100                 105                 110

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

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

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

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

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

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

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

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

Ser Phe Gly Ser Phe Arg Ala Leu Pro His Ala Trp Ser Asp Pro Ser
                245                 250                 255

Asp Pro Leu Pro Val Ser Val Thr Gly Asn Ser Arg Asn Leu His Val
            260                 265                 270

Leu Ile Gly Thr Ser Val Val Ile Ile Pro Phe Ala Ile Leu Leu Phe
        275                 280                 285

Phe Leu Leu His Arg Trp Cys Ala Asn Lys Lys Asn Ala Val Val Met
    290                 295                 300

Asp Gln Glu Pro Ala Gly Asn Arg Thr Val Asn Arg Glu Asp Ser Asp
305                 310                 315                 320
```

Glu Gln Asp Pro Gln Glu Val Thr Tyr Ala Gln Leu Asn His Cys Val
325 330 335

Phe Thr Gln Arg Lys Ile Thr Arg Pro Ser Gln Arg Pro Lys Thr Pro
340 345 350

Pro Thr Asp Thr Ser Val
355

<210> 50
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> C1761 chimeric antigen recetor constuct

<400> 50

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 Gly Gly Gly Gly Ser
100 105 110

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

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

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

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
                325                 330                 335

Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
            340                 345                 350

Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
        355                 360                 365

Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln
    370                 375                 380

Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp
385                 390                 395                 400

Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg
                405                 410                 415

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            420                 425                 430

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        435                 440                 445

Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
    450                 455                 460
```

```
Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro
465                 470                 475                 480


Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                485                 490


<210>  51
<211>  385
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C1762 chimeric antigen recetor constuct

<400>  51

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 Gly Gly Gly Gly Ser
            100                 105                 110


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


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


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


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


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


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

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

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

Ser Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser
245 250 255

Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly
260 265 270

Gly Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile
275 280 285

Cys Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln
290 295 300

Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr
305 310 315 320

Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val
325 330 335

Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser
340 345 350

Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro
355 360 365

Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro
370 375 380

Leu
385

<210> 52
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> C2057 chimeric antigen recetor constuct

<400> 52

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala

```
        35                  40                  45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
    50                  55                  60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65                  70                  75                  80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
                85                  90                  95

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

Pro Leu Tyr Gly Gly Ser Tyr Ile Pro Thr Phe Gly Arg Gly Thr Ser
        115                 120                 125

Leu Ile Val His Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
    130                 135                 140

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

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
                165                 170                 175

Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
            180                 185                 190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
        195                 200                 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro
    210                 215                 220

Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225                 230                 235                 240

Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Val Ile Gly Ile Leu Val
                245                 250                 255

Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe Leu Ile Leu
            260                 265                 270

Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala
        275                 280                 285

Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg
    290                 295                 300

Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn
305                 310                 315                 320
```

```
Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met
                325                 330                 335


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


Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser
        355                 360                 365


Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu
    370                 375                 380


Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp
385                 390                 395                 400


Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr
                405                 410                 415


Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile
            420                 425                 430


Tyr Ala Thr Leu Ala Ile His
        435


<210>  53
<211>  466
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C2058 chimeric antigen recetor constuct

<400>  53

Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1               5                   10                  15


Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
            20                  25                  30


Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
        35                  40                  45


Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
    50                  55                  60


Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro
65                  70                  75                  80


Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
                85                  90                  95


Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
```

```
            100                 105                 110

Ser Tyr Val Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
        115                 120                 125

Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
    130                 135                 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145                 150                 155                 160

Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser
                165                 170                 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro
            180                 185                 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
        195                 200                 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln
            260                 265                 270

Gly Val Leu Ser Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu
        275                 280                 285

Leu Leu Leu Leu Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln
    290                 295                 300

Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro
305                 310                 315                 320

Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg
                325                 330                 335

Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val
            340                 345                 350

Lys His Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro
        355                 360                 365

His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser
    370                 375                 380
```

```
Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu
385                 390                 395                 400


Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp
                405                 410                 415


Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln
            420                 425                 430


Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser
        435                 440                 445


Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala
    450                 455                 460


Ile His
465
```

<210> 54
<211> 421
<212> PRT
<213> Artificial Sequence

<220>
<223> C2070 chimeric antigen recetor constuct

<400> 54

```
Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1               5                   10                  15


Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
            20                  25                  30


Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
        35                  40                  45


Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
    50                  55                  60


Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro
65                  70                  75                  80


Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
                85                  90                  95


Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
            100                 105                 110


Ser Tyr Val Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
        115                 120                 125


Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
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    130                 135                 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145                 150                 155                 160

Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser
                165                 170                 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro
            180                 185                 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
        195                 200                 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln
            260                 265                 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
        275                 280                 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
    290                 295                 300

Lys Arg Lys Asp Ser Arg Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly
305                 310                 315                 320

Ser Gly Gly Gly Gly Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg
                325                 330                 335

Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe
            340                 345                 350

Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro
        355                 360                 365

Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile
    370                 375                 380

Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser
385                 390                 395                 400

Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His
                405                 410                 415
```

Cys Ser Trp Pro Leu
420

<210> 55
<211> 416
<212> PRT
<213> Artificial Sequence

<220>
<223> C2071 chimeric antigen recetor constuct

<400> 55

Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro
65 70 75 80

Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
85 90 95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
100 105 110

Ser Tyr Val Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
115 120 125

Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
130 135 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn

```
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln
            260                 265                 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
        275                 280                 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
    290                 295                 300

Lys Arg Lys Asp Ser Arg Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly
305                 310                 315                 320

Ser Gly Gly Gly Gly Ser Asn Lys Lys Asn Ala Ala Val Met Asp Gln
                325                 330                 335

Glu Pro Ala Gly Asp Arg Thr Val Asn Arg Gln Asp Ser Asp Glu Gln
            340                 345                 350

Asp Pro Gln Glu Val Thr Tyr Ala Gln Leu Asp His Cys Val Phe Ile
        355                 360                 365

Gln Arg Lys Ile Ser Arg Pro Ser Gln Arg Pro Lys Thr Pro Leu Thr
    370                 375                 380

Asp Thr Ser Val Tyr Thr Glu Leu Pro Asn Ala Glu Pro Arg Ser Lys
385                 390                 395                 400

Val Val Ser Cys Pro Arg Ala Pro Gln Ser Gly Leu Glu Gly Val Phe
                405                 410                 415


<210>  56
<211>  493
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C2072 chimeric antigen recetor constuct

<400>  56

Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1               5                   10                  15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
            20                  25                  30
```

```
Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
        35                  40                  45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
    50                  55                  60

Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro
65                  70                  75                  80

Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
                85                  90                  95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
            100                 105                 110

Ser Tyr Val Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
        115                 120                 125

Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
    130                 135                 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145                 150                 155                 160

Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser
                165                 170                 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro
            180                 185                 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
        195                 200                 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln
            260                 265                 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
        275                 280                 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
    290                 295                 300

Lys Arg Lys Asp Ser Arg Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly
```

305 310 315 320

Ser Gly Gly Gly Gly Ser Arg His Arg Arg Gln Gly Lys His Trp Thr
325 330 335

Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly
340 345 350

Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala
355 360 365

Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro
370 375 380

Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro
385 390 395 400

Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu
405 410 415

Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys
420 425 430

Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala
435 440 445

Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr
450 455 460

Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser
465 470 475 480

Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
485 490

<210> 57
<211> 704
<212> PRT
<213> Artificial Sequence

<220>
<223> C2106 chimeric antigen recetor constuct

<400> 57

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 Gly Gly Gly Gly Ser
            100                 105                 110

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

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

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

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

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

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

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

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

Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
                245                 250                 255

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
            260                 265                 270

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
        275                 280                 285

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
    290                 295                 300

Val Ile Thr Leu Tyr Cys Asn His Asp Arg Glu Lys Lys Pro Arg Gln
305                 310                 315                 320

His Ser Gly Asp His Glu Asn Leu Met Asn Val Pro Ser Asp Lys Glu
```

```
                325                 330                 335

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

Ser Glu Gln Asn Gly Ala Leu Thr Asn Gly Asp Ile Leu Ser Glu Asp
        355                 360                 365

Ser Thr Leu Thr Cys Met Gln His Tyr Glu Glu Val Gln Thr Ser Ala
    370                 375                 380

Ser Asp Leu Leu Asp Ser Gln Asp Ser Thr Gly Lys Pro Lys Cys His
385                 390                 395                 400

Gln Ser Arg Glu Leu Pro Arg Ile Pro Pro Glu Ser Ala Val Asp Thr
                405                 410                 415

Met Leu Thr Ala Arg Ser Val Asp Gly Asp Gln Gly Leu Gly Met Glu
            420                 425                 430

Gly Pro Tyr Glu Val Leu Lys Asp Ser Ser Ser Gln Glu Asn Met Val
        435                 440                 445

Glu Asp Cys Leu Tyr Glu Thr Val Lys Glu Ile Lys Glu Val Ala Ala
    450                 455                 460

Ala Ala His Leu Glu Lys Gly His Ser Gly Lys Ala Lys Ser Thr Ser
465                 470                 475                 480

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

Ala Glu Tyr Ala Ser Val Asp Arg Asn Lys Lys Cys Arg Gln Ser Val
            500                 505                 510

Asn Val Glu Ser Ile Leu Gly Asn Ser Cys Asp Pro Glu Glu Glu Ala
        515                 520                 525

Pro Pro Pro Val Pro Val Lys Leu Leu Asp Glu Asn Glu Asn Leu Gln
    530                 535                 540

Glu Lys Glu Gly Gly Glu Ala Glu Glu Ser Ala Thr Asp Thr Thr Ser
545                 550                 555                 560

Glu Thr Asn Lys Arg Phe Ser Ser Leu Ser Tyr Lys Ser Arg Glu Glu
                565                 570                 575

Asp Pro Thr Leu Thr Glu Glu Glu Ile Ser Ala Met Tyr Ser Ser Val
            580                 585                 590

Asn Lys Pro Gly Gln Leu Val Asn Lys Ser Gly Gln Ser Leu Thr Val
        595                 600                 605
```

Pro Glu Ser Thr Tyr Thr Ser Ile Gln Gly Asp Pro Gln Arg Ser Pro
610 615 620

Ser Ser Cys Asn Asp Leu Tyr Ala Thr Val Lys Asp Phe Glu Lys Thr
625 630 635 640

Pro Asn Ser Thr Leu Pro Pro Ala Gly Arg Pro Ser Glu Glu Pro Glu
645 650 655

Pro Asp Tyr Glu Ala Ile Gln Thr Leu Asn Arg Glu Glu Glu Lys Ala
660 665 670

Thr Leu Gly Thr Asn Gly His His Gly Leu Val Pro Lys Glu Asn Asp
675 680 685

Tyr Glu Ser Ile Ser Asp Leu Gln Gln Gly Arg Asp Ile Thr Arg Leu
690 695 700

<210> 58
<211> 702
<212> PRT
<213> Artificial Sequence

<220>
<223> C2107 chimeric antigen recetor constuct

<400> 58

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 Gly Gly Gly Gly Ser
100 105 110

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

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu

```
    130                 135                 140

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

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

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

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

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

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

Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
                245                 250                 255

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
            260                 265                 270

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Leu Trp
        275                 280                 285

Gly Ser Leu Ala Ala Val Ala Ile Phe Phe Val Ile Thr Phe Leu Ile
    290                 295                 300

Phe Leu Cys Ser Ser Cys Asp Arg Glu Lys Lys Pro Arg Gln His Ser
305                 310                 315                 320

Gly Asp His Glu Asn Leu Met Asn Val Pro Ser Asp Lys Glu Met Phe
                325                 330                 335

Ser Arg Ser Val Thr Ser Leu Ala Thr Asp Ala Pro Ala Ser Ser Glu
            340                 345                 350

Gln Asn Gly Ala Leu Thr Asn Gly Asp Ile Leu Ser Glu Asp Ser Thr
        355                 360                 365

Leu Thr Cys Met Gln His Tyr Glu Glu Val Gln Thr Ser Ala Ser Asp
    370                 375                 380

Leu Leu Asp Ser Gln Asp Ser Thr Gly Lys Pro Lys Cys His Gln Ser
385                 390                 395                 400

Arg Glu Leu Pro Arg Ile Pro Pro Glu Ser Ala Val Asp Thr Met Leu
                405                 410                 415
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```
Thr Ala Arg Ser Val Asp Gly Asp Gln Gly Leu Gly Met Glu Gly Pro
            420                 425                 430

Tyr Glu Val Leu Lys Asp Ser Ser Ser Gln Glu Asn Met Val Glu Asp
        435                 440                 445

Cys Leu Tyr Glu Thr Val Lys Glu Ile Lys Glu Val Ala Ala Ala Ala
    450                 455                 460

His Leu Glu Lys Gly His Ser Gly Lys Ala Lys Ser Thr Ser Ala Ser
465                 470                 475                 480

Lys Glu Leu Pro Gly Pro Gln Thr Glu Gly Lys Ala Glu Phe Ala Glu
                485                 490                 495

Tyr Ala Ser Val Asp Arg Asn Lys Lys Cys Arg Gln Ser Val Asn Val
            500                 505                 510

Glu Ser Ile Leu Gly Asn Ser Cys Asp Pro Glu Glu Glu Ala Pro Pro
        515                 520                 525

Pro Val Pro Val Lys Leu Leu Asp Glu Asn Glu Asn Leu Gln Glu Lys
    530                 535                 540

Glu Gly Gly Glu Ala Glu Glu Ser Ala Thr Asp Thr Thr Ser Glu Thr
545                 550                 555                 560

Asn Lys Arg Phe Ser Ser Leu Ser Tyr Lys Ser Arg Glu Glu Asp Pro
                565                 570                 575

Thr Leu Thr Glu Glu Glu Ile Ser Ala Met Tyr Ser Ser Val Asn Lys
            580                 585                 590

Pro Gly Gln Leu Val Asn Lys Ser Gly Gln Ser Leu Thr Val Pro Glu
        595                 600                 605

Ser Thr Tyr Thr Ser Ile Gln Gly Asp Pro Gln Arg Ser Pro Ser Ser
    610                 615                 620

Cys Asn Asp Leu Tyr Ala Thr Val Lys Asp Phe Glu Lys Thr Pro Asn
625                 630                 635                 640

Ser Thr Leu Pro Pro Ala Gly Arg Pro Ser Glu Glu Pro Glu Pro Asp
                645                 650                 655

Tyr Glu Ala Ile Gln Thr Leu Asn Arg Glu Glu Glu Lys Ala Thr Leu
            660                 665                 670

Gly Thr Asn Gly His His Gly Leu Val Pro Lys Glu Asn Asp Tyr Glu
        675                 680                 685
```

Ser Ile Ser Asp Leu Gln Gln Gly Arg Asp Ile Thr Arg Leu
690 695 700

<210> 59
<211> 481
<212> PRT
<213> Artificial Sequence

<220>
<223> C2153 chimeric antigen recetor constuct

<400> 59

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 Gly Gly Gly Gly Ser
100 105 110

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

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

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

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

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

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

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

```
Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
225                 230                 235                 240

Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
                245                 250                 255

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
            260                 265                 270

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Trp
        275                 280                 285

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

Thr Val Ala Phe Ile Ile Phe Trp Val Leu Arg His Arg Arg Gln Gly
305                 310                 315                 320

Lys His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala
                325                 330                 335

Gly Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser
            340                 345                 350

Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys
        355                 360                 365

His Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His
    370                 375                 380

Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg
385                 390                 395                 400

Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe
                405                 410                 415

Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr
            420                 425                 430

Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu
        435                 440                 445

His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln
    450                 455                 460

Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile
465                 470                 475                 480

His
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<210> 60
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> C2156 chimeric antigen recetor constuct

<400> 60

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1   5   10   15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
        35   40   45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
    50   55   60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65   70   75   80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
                85   90   95

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

Pro Leu Tyr Gly Gly Ser Tyr Ile Pro Thr Phe Gly Arg Gly Thr Ser
        115   120   125

Leu Ile Val His Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
    130   135   140

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

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
                165   170   175

Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
            180   185   190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
        195   200   205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro
    210   215   220

Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225   230   235   240

Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Leu Ile Leu
245 250 255

Leu Leu Leu Val Ala Gly Phe Asn Leu Leu Met Thr Leu Leu Leu Trp
260 265 270

Ser Ser Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser
275 280 285

Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro
290 295 300

Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp
305 310 315 320

Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu
325 330 335

Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln
340 345 350

Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met
355 360 365

Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp
370 375 380

Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser
385 390 395 400

Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu
405 410 415

Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro
420 425 430

Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
435 440

<210> 61
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> C2157 chimeric antigen recetor constuct

<400> 61

Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu

```
            20                  25                  30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
        35                  40                  45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
    50                  55                  60

Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro
65                  70                  75                  80

Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
                85                  90                  95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
            100                 105                 110

Ser Tyr Val Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
        115                 120                 125

Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
    130                 135                 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145                 150                 155                 160

Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser
                165                 170                 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro
            180                 185                 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
        195                 200                 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln
            260                 265                 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Leu Ile Leu Leu Gly Leu Ala
        275                 280                 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Leu Ile Leu
    290                 295                 300
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```
Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala
305                 310                 315                 320

Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg
                325                 330                 335

Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn
            340                 345                 350

Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met
        355                 360                 365

Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala
    370                 375                 380

Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser
385                 390                 395                 400

Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu
                405                 410                 415

Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp
            420                 425                 430

Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr
        435                 440                 445

Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile
    450                 455                 460

Tyr Ala Thr Leu Ala Ile His
465                 470


<210>  62
<211>  484
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C2158 chimeric antigen recetor constuct

<400>  62

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

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

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

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

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

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

Ala Arg Ile Pro Phe Gly Asp Trp Trp Tyr Phe Asp Leu Trp Gly Arg
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln
            180                 185                 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        195                 200                 205

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
    210                 215                 220

Cys Gln Gln Ser Tyr Ser Phe Val Leu Thr Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
                245                 250                 255

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
            260                 265                 270

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
        275                 280                 285

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

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

Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln
                325                 330                 335
```

```
His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln
            340                 345                 350

Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala
        355                 360                 365

Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg
    370                 375                 380

Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys
385                 390                 395                 400

His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser
                405                 410                 415

Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln
            420                 425                 430

Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr
        435                 440                 445

Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro
    450                 455                 460

Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr
465                 470                 475                 480

Leu Ala Ile His
```

<210> 63
<211> 414
<212> PRT
<213> Artificial Sequence

<220>
<223> C2179 chimeric antigen recetor constuct

<400> 63

```
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 Gly Gly Gly Gly Ser
            100                 105                 110

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

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

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

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Arg Pro Arg Arg
                325                 330                 335

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            340                 345                 350
```

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        355   360   365

Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
    370   375   380

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

Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                405   410

<210> 64
<211> 576
<212> PRT
<213> Artificial Sequence

<220>
<223> C2180 chimeric antigen recetor constuct

<400> 64

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro 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 Gly Gly Gly Gly Ser
            100   105   110

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

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

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

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val Ile Tyr Ser

```
                165                 170                 175

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
                325                 330                 335

Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
            340                 345                 350

Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
        355                 360                 365

Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln
    370                 375                 380

Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp
385                 390                 395                 400

Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg
                405                 410                 415

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            420                 425                 430

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        435                 440                 445
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```
Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
    450                 455                 460

Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro
465                 470                 475                 480

Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His Arg Pro
                485                 490                 495

Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu
            500                 505                 510

Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu
        515                 520                 525

Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His
    530                 535                 540

Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu
545                 550                 555                 560

Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                565                 570                 575


<210>  65
<211>  496
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C2181 chimeric antigen recetor constuct

<400>  65

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 Gly Gly Gly Gly Ser
```

```
            100                 105                 110

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

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

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

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Arg Pro Arg Arg
                325                 330                 335

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            340                 345                 350

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        355                 360                 365

Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
    370                 375                 380
```

```
Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro
385                 390                 395                 400


Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His Arg Pro
                405                 410                 415


Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu
            420                 425                 430


Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu
        435                 440                 445


Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His
    450                 455                 460


Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu
465                 470                 475                 480


Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                485                 490                 495


<210>  66
<211>  494
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  C2182 chimeric antigen recetor constuct

<400>  66

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 Gly Gly Gly Gly Ser
            100                 105                 110


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Glu Val Gln Leu
```

```
        115                 120                 125

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

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

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
                325                 330                 335

Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
            340                 345                 350

Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
        355                 360                 365

Ala Asp Ala Gln Glu Glu Asn Leu Phe Ala Ala Val Lys His Thr Gln
    370                 375                 380

Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp
385                 390                 395                 400
```

Pro Gln Ala Val Thr Phe Ala Glu Val Lys His Ser Arg Pro Arg Arg
405 410 415

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
420 425 430

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
435 440 445

Ala Ser Glu Ala Pro Gln Asp Val Thr Phe Ala Gln Leu His Ser Leu
450 455 460

Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro
465 470 475 480

Ser Pro Ala Val Pro Ser Ile Phe Ala Thr Leu Ala Ile His
485 490

<210> 67
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> C2183 chimeric antigen recetor constuct

<400> 67

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 Gly Gly Gly Gly Ser
100 105 110

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

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu

```
    130                 135                 140

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

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
                325                 330                 335

Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
            340                 345                 350

Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
        355                 360                 365

Ala Asp Ala Gln Glu Glu Asn Leu Phe Ala Ala Val Lys His Thr Gln
    370                 375                 380

Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp
385                 390                 395                 400

Pro Gln Ala Val Thr Phe Ala Glu Val Lys His Ser Arg Pro Arg Arg
                405                 410                 415
```

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            420   425   430

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        435   440   445

Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
    450   455   460

Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro
465   470   475   480

Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                485   490

<210> 68
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> C2184 chimeric antigen recetor constuct

<400> 68

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 Gly Gly Gly Gly Ser
            100   105   110

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

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

Ser Cys Ala Ala Ser Gly Phe Thr Val Tyr Asp Tyr Met Ser Trp Val

```
145                 150                 155                 160

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
                325                 330                 335

Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
            340                 345                 350

Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
        355                 360                 365

Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln
    370                 375                 380

Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp
385                 390                 395                 400

Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg
                405                 410                 415

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            420                 425                 430
```

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        435   440   445

Ala Ser Glu Ala Pro Gln Asp Val Thr Phe Ala Gln Leu His Ser Leu
    450   455   460

Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro
465   470   475   480

Ser Pro Ala Val Pro Ser Ile Phe Ala Thr Leu Ala Ile His
                485   490

<210> 69
<211> 438
<212> PRT
<213> Artificial Sequence

<220>
<223> C2218 chimeric antigen recetor constuct

<400> 69

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 Gly Gly Gly Gly Ser
            100   105   110

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

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

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

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val Ile Tyr Ser

```
                165                 170                 175

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300

Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg Arg His Gln Gly Lys Gln Asn Glu
                325                 330                 335

Leu Ser Asp Thr Ala Gly Arg Glu Ile Asn Leu Val Asp Ala His Leu
            340                 345                 350

Lys Ser Glu Gln Thr Glu Ala Ser Thr Arg Gln Asn Ser Gln Val Leu
        355                 360                 365

Leu Ser Glu Thr Gly Ile Tyr Asp Asn Asp Pro Asp Leu Cys Phe Arg
    370                 375                 380

Met Gln Glu Gly Ser Glu Val Tyr Ser Asn Pro Cys Leu Glu Glu Asn
385                 390                 395                 400

Lys Pro Gly Ile Val Tyr Ala Ser Leu Asn His Ser Val Ile Gly Pro
                405                 410                 415

Asn Ser Arg Leu Ala Arg Asn Val Lys Glu Ala Pro Thr Glu Tyr Ala
            420                 425                 430

Ser Ile Cys Val Arg Ser
        435
```

<210> 70
<211> 437
<212> PRT
<213> Artificial Sequence

<220>
<223> C2219 chimeric antigen recetor constuct

<400> 70

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 Gly Gly Gly Gly Ser
            100   105   110

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

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

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

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

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

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

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

Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser

225 230 235 240

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
245 250 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
260 265 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
275 280 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
290 295 300

Val Leu Leu Pro Leu Gly Gly Leu Pro Leu Leu Ile Thr Thr Cys Phe
305 310 315 320

Cys Leu Phe Cys Cys Leu Arg Arg His Gln Gly Lys Gln Asn Glu Leu
325 330 335

Ser Asp Thr Ala Gly Arg Glu Ile Asn Leu Val Asp Ala His Leu Lys
340 345 350

Ser Glu Gln Thr Glu Ala Ser Thr Arg Gln Asn Ser Gln Val Leu Leu
355 360 365

Ser Glu Thr Gly Ile Tyr Asp Asn Asp Pro Asp Leu Cys Phe Arg Met
370 375 380

Gln Glu Gly Ser Glu Val Tyr Ser Asn Pro Cys Leu Glu Glu Asn Lys
385 390 395 400

Pro Gly Ile Val Tyr Ala Ser Leu Asn His Ser Val Ile Gly Pro Asn
405 410 415

Ser Arg Leu Ala Arg Asn Val Lys Glu Ala Pro Thr Glu Tyr Ala Ser
420 425 430

Ile Cys Val Arg Ser
435

<210> 71
<211> 397
<212> PRT
<213> Artificial Sequence

<220>
<223> C2220 chimeric antigen recetor constuct

<400> 71

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 Gly Gly Gly Gly Ser
            100                 105                 110

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

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

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

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

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

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

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

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

Ser Thr Asp Val Lys Ser Ala Ser Glu Arg Pro Ser Lys Asp Glu Met
                245                 250                 255

Ala Ser Arg Pro Trp Leu Leu Tyr Arg Leu Leu Pro Leu Gly Gly Leu
            260                 265                 270

Pro Leu Leu Ile Thr Thr Cys Phe Cys Leu Phe Cys Cys Leu Arg Arg
        275                 280                 285

His Gln Gly Lys Gln Asn Glu Leu Ser Asp Thr Ala Gly Arg Glu Ile
```

290 295 300

Asn Leu Val Asp Ala His Leu Lys Ser Glu Gln Thr Glu Ala Ser Thr
305 310 315 320

Arg Gln Asn Ser Gln Val Leu Leu Ser Glu Thr Gly Ile Tyr Asp Asn
325 330 335

Asp Pro Asp Leu Cys Phe Arg Met Gln Glu Gly Ser Glu Val Tyr Ser
340 345 350

Asn Pro Cys Leu Glu Glu Asn Lys Pro Gly Ile Val Tyr Ala Ser Leu
355 360 365

Asn His Ser Val Ile Gly Pro Asn Ser Arg Leu Ala Arg Asn Val Lys
370 375 380

Glu Ala Pro Thr Glu Tyr Ala Ser Ile Cys Val Arg Ser
385 390 395

<210> 72

<400> 72
000

<210> 73

<400> 73
000

<210> 74

<400> 74
000

<210> 75

<400> 75
000

<210> 76

<400> 76
000

<210> 77
<211> 578
<212> PRT
<213> Artificial Sequence

<220>
<223> C2302 chimeric antigen recetor constuct

<400> 77

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 Gly Gly Gly Gly Ser
            100                 105                 110

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

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

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

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

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

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

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

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

Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser
                245                 250                 255

Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser
            260                 265                 270

Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu
        275                 280                 285

Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly
    290                 295                 300
```

```
Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu
305                 310                 315                 320

Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Arg Pro Arg Arg
                325                 330                 335

Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr
            340                 345                 350

Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala
        355                 360                 365

Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu
    370                 375                 380

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

Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His Arg Pro
                405                 410                 415

Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu
            420                 425                 430

Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu
        435                 440                 445

Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His
    450                 455                 460

Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu
465                 470                 475                 480

Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
                485                 490                 495

Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu
            500                 505                 510

Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp
        515                 520                 525

Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln
    530                 535                 540

Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser
545                 550                 555                 560

Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala
                565                 570                 575

Ile His
```

<210> 78
<211> 600
<212> PRT
<213> Artificial Sequence

<220>
<223> CT138 chimeric antigen recetor constuct

<400> 78

Met Gly Pro Val Thr Cys Ser Val Leu Val Leu Leu Leu Met Leu Arg
1   5   10   15

Arg Ser Asn Gly Asp Gly Asp Ser Val Thr Gln Thr Glu Gly Leu Val
            20   25   30

Thr Leu Thr Glu Gly Leu Pro Val Met Leu Asn Cys Thr Tyr Gln Thr
        35   40   45

Ile Tyr Ser Asn Pro Phe Leu Phe Trp Tyr Val Gln His Leu Asn Glu
    50   55   60

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

His Gln Gly Phe His Ala Thr Leu His Lys Ser Ser Ser Ser Phe His
                85   90   95

Leu Gln Lys Ser Ser Ala Gln Leu Ser Asp Ser Ala Leu Tyr Tyr Cys
            100   105   110

Ala Phe Asp Thr Asn Thr Tyr Lys Val Ile Phe Gly Lys Gly Thr His
        115   120   125

Leu His Val Leu Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln
    130   135   140

Leu Lys Asp Pro Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp
145   150   155   160

Phe Asp Ser Gln Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe
                165   170   175

Ile Thr Asp Lys Thr Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser
            180   185   190

Asn Gly Ala Ile Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp
        195   200   205

Ile Phe Lys Glu Thr Asn Thr Thr Tyr Pro Ser Ser Asp Val Pro Cys
    210   215   220

```
Asp Ala Thr Leu Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn
225                 230                 235                 240

Phe Gln Asn Leu Ser Val Met Gly Leu Arg Ile Leu Leu Leu Lys Val
                245                 250                 255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser Arg Ala
            260                 265                 270

Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala
        275                 280                 285

Gly Asp Val Glu Glu Asn Pro Gly Pro Met Arg Val Arg Leu Ile Ser
    290                 295                 300

Ala Val Val Leu Cys Ser Leu Gly Thr Gly Leu Val Asp Met Lys Val
305                 310                 315                 320

Thr Gln Met Pro Arg Tyr Leu Ile Lys Arg Met Gly Glu Asn Val Leu
                325                 330                 335

Leu Glu Cys Gly Gln Asp Met Ser His Glu Thr Met Tyr Trp Tyr Arg
            340                 345                 350

Gln Asp Pro Gly Leu Gly Leu Gln Leu Ile Tyr Ile Ser Tyr Asp Val
        355                 360                 365

Asp Ser Asn Ser Glu Gly Asp Ile Pro Lys Gly Tyr Arg Val Ser Arg
    370                 375                 380

Lys Lys Arg Glu His Phe Ser Leu Ile Leu Asp Ser Ala Lys Thr Asn
385                 390                 395                 400

Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser Ser Thr Asn Thr Glu Val
                405                 410                 415

Phe Phe Gly Lys Gly Thr Arg Leu Thr Val Val Glu Asp Leu Arg Asn
            420                 425                 430

Val Thr Pro Pro Lys Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile
        435                 440                 445

Ala Asn Lys Gln Lys Ala Thr Leu Val Cys Leu Ala Arg Gly Phe Phe
    450                 455                 460

Pro Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His
465                 470                 475                 480

Ser Gly Val Ser Thr Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser
                485                 490                 495

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn
```

```
            500                 505                 510

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu
        515                 520                 525

Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile
    530                 535                 540

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser
545                 550                 555                 560

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
                565                 570                 575

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Thr Leu Val Val Met
            580                 585                 590

Ala Met Val Lys Arg Lys Asn Ser
        595                 600


<210>  79
<211>  605
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  CT139 chimeric antigen recetor constuct

<400>  79

Met Val Leu Val Thr Ile Leu Leu Leu Ser Ala Phe Phe Ser Leu Arg
1               5                   10                  15

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

Ser Glu Gly Ala Ser Leu Glu Leu Arg Cys Ser Tyr Ser Tyr Ser Ala
        35                  40                  45

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

Phe Leu Leu Lys Tyr Ile Thr Gly Asp Thr Val Val Lys Gly Thr Lys
65                  70                  75                  80

Gly Phe Glu Ala Glu Phe Arg Lys Ser Asn Ser Ser Phe Asn Leu Lys
                85                  90                  95

Lys Ser Pro Ala His Trp Ser Asp Ser Ala Lys Tyr Phe Cys Ala Leu
            100                 105                 110

Glu Gly Pro Asp Thr Gly Asn Tyr Lys Tyr Val Phe Gly Ala Gly Thr
        115                 120                 125
```

```
Arg Leu Lys Val Ile Ala His Ile Gln Asn Pro Glu Pro Ala Val Tyr
    130                 135                 140

Gln Leu Lys Asp Pro Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr
145                 150                 155                 160

Asp Phe Asp Ser Gln Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr
                165                 170                 175

Phe Ile Thr Asp Lys Thr Val Leu Asp Met Lys Ala Met Asp Ser Lys
            180                 185                 190

Ser Asn Gly Ala Ile Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln
        195                 200                 205

Asp Ile Phe Lys Glu Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro
    210                 215                 220

Cys Asp Ala Thr Leu Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu
225                 230                 235                 240

Asn Phe Gln Asn Leu Ser Val Met Gly Leu Arg Ile Leu Leu Leu Lys
                245                 250                 255

Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser Arg
            260                 265                 270

Ala Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln
        275                 280                 285

Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ile Gln Thr Leu
    290                 295                 300

Cys Cys Val Ile Phe Tyr Val Leu Ile Ala Asn His Thr Asp Ala Gly
305                 310                 315                 320

Val Thr Gln Thr Pro Arg His Glu Val Ala Glu Lys Gly Gln Thr Ile
                325                 330                 335

Ile Leu Lys Cys Glu Pro Val Ser Gly His Asn Asp Leu Phe Trp Tyr
            340                 345                 350

Arg Gln Thr Lys Ile Gln Gly Leu Glu Leu Leu Ser Tyr Phe Arg Ser
        355                 360                 365

Lys Ser Leu Met Glu Asp Gly Gly Ala Phe Lys Asp Arg Phe Lys Ala
    370                 375                 380

Glu Met Leu Asn Ser Ser Phe Ser Thr Leu Lys Ile Gln Pro Thr Glu
385                 390                 395                 400

Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala Ser Ser Phe Gly Thr Ala
```

405 410 415

Ser Ala Glu Thr Leu Tyr Phe Gly Ser Gly Thr Arg Leu Thr Val Leu
420 425 430

Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu Pro
435 440 445

Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys Leu
450 455 460

Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn
465 470 475 480

Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Ala Tyr Lys
485 490 495

Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
500 505 510

Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe
515 520 525

His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro
530 535 540

Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
545 550 555 560

Ile Thr Ser Ala Ser Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu
565 570 575

Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
580 585 590

Gly Leu Val Leu Met Ala Met Val Lys Lys Lys Asn Ser
595 600 605

<210> 80
<211> 64
<212> PRT
<213> Homo sapiens

<400> 80

Tyr Gly Ser Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp
1 5 10 15

Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro
20 25 30

Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr
35 40 45

Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val
    50   55   60

<210> 81
<211> 44
<212> PRT
<213> Homo sapiens

<400> 81

Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro
1   5   10   15

Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser
            20   25   30

Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val
        35   40

<210> 82
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - long hinge 1 sequence

<400> 82

Ala Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Pro Val Pro Ser
1   5   10   15

Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser
            20   25   30

Gly Gly Ser Gly Asn Ser Ser Gly Ser Gly Gly Ser Pro Val Pro Ser
        35   40   45

Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser
    50   55   60

Ala Ser Val
65

<210> 83
<211> 75
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - long hinge 2 sequence

<400> 83

Ala Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Pro Val Pro Ser
1   5   10   15

Thr Pro Pro Thr Asn Ser Ser Ser Thr Pro Pro Thr Pro Ser Pro Ser

```
            20                  25                  30

Pro Val Pro Ser Thr Pro Pro Thr Asn Ser Ser Ser Thr Pro Pro Thr
        35                  40                  45

Pro Ser Pro Ser Pro Val Pro Ser Thr Pro Pro Thr Asn Ser Ser Ser
    50                  55                  60

Thr Pro Pro Thr Pro Ser Pro Ser Ala Ser Val
65                  70                  75


<210>  84
<211>  85
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Made in Lab - 2x short hinge sequence

<400>  84

Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro
1               5                   10                  15

Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser
            20                  25                  30

Asp Pro Gln Ser Gly Leu Gly Arg His Val Val Ser Gly Pro Ser Gly
        35                  40                  45

Gly Pro Ser Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu
    50                  55                  60

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

Arg His Leu Gly Val
                85


<210>  85

<400>  85
000

<210>  86

<400>  86
000

<210>  87
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  87

Arg Arg His Gln Gly Lys Gln Asn Glu Leu Ser Asp Thr Ala Gly Arg
1               5                   10                  15
```

```
Glu Ile Asn Leu Val Asp Ala His Leu Lys Ser Glu Gln Thr Glu Ala
            20                  25                  30

Ser Thr Arg Gln Asn Ser Gln Val Leu Leu Ser Glu Thr Gly Ile Tyr
        35                  40                  45

Asp Asn Asp Pro Asp Leu Cys Phe Arg Met Gln Glu Gly Ser Glu Val
    50                  55                  60

Tyr Ser Asn Pro Cys Leu Glu Glu Asn Lys Pro Gly Ile Val Tyr Ala
65                  70                  75                  80

Ser Leu Asn His Ser Val Ile Gly Pro Asn Ser Arg Leu Ala Arg Asn
                85                  90                  95

Val Lys Glu Ala Pro Thr Glu Tyr Ala Ser Ile Cys Val Arg Ser
            100                 105                 110
```

<210> 88
<211> 132
<212> PRT
<213> Homo sapiens

<400> 88

```
Leu Leu Pro Leu Gly Gly Leu Pro Leu Leu Ile Thr Thr Cys Phe Cys
1               5                   10                  15

Leu Phe Cys Cys Leu Arg Arg His Gln Gly Lys Gln Asn Glu Leu Ser
            20                  25                  30

Asp Thr Ala Gly Arg Glu Ile Asn Leu Val Asp Ala His Leu Lys Ser
        35                  40                  45

Glu Gln Thr Glu Ala Ser Thr Arg Gln Asn Ser Gln Val Leu Leu Ser
    50                  55                  60

Glu Thr Gly Ile Tyr Asp Asn Asp Pro Asp Leu Cys Phe Arg Met Gln
65                  70                  75                  80

Glu Gly Ser Glu Val Tyr Ser Asn Pro Cys Leu Glu Glu Asn Lys Pro
                85                  90                  95

Gly Ile Val Tyr Ala Ser Leu Asn His Ser Val Ile Gly Pro Asn Ser
            100                 105                 110

Arg Leu Ala Arg Asn Val Lys Glu Ala Pro Thr Glu Tyr Ala Ser Ile
        115                 120                 125

Cys Val Arg Ser
    130
```

<210> 89

<211> 500
<212> PRT
<213> Artificial Sequence

<220>
<223> PA2.1.14 scFv LIR1 HTICD construct

<400> 89

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


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


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


Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Gly Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn 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 Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140


Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser
145                 150                 155                 160


Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
                165                 170                 175


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190


Asn Arg Phe Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala
    210                 215                 220


Thr Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gln
225                 230                 235                 240
```

```
Gly Thr Lys Val Glu Val Lys Tyr Gly Ser Gln Ser Ser Lys Pro Tyr
                245                 250                 255

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

Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly
        275                 280                 285

Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly
    290                 295                 300

Leu Gly Arg His Leu Gly Val Val Ile Gly Ile Leu Val Ala Val Ile
305                 310                 315                 320

Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe Leu Ile Leu Arg His Arg
                325                 330                 335

Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln
            340                 345                 350

His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln
        355                 360                 365

Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala
    370                 375                 380

Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg
385                 390                 395                 400

Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys
                405                 410                 415

His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser
            420                 425                 430

Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln
        435                 440                 445

Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr
    450                 455                 460

Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro
465                 470                 475                 480

Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr
                485                 490                 495

Leu Ala Ile His
            500
```

<210> 90

<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> PA2.1.14 scFv LIR1 sHTICD construct

<400> 90

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


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


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


Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Gly Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn 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 Glu Glu Ile Thr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140


Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser
145                 150                 155                 160


Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
                165                 170                 175


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190


Asn Arg Phe Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala
    210                 215                 220


Thr Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gln
225                 230                 235                 240
```

```
Gly Thr Lys Val Glu Val Lys Val Val Ser Gly Pro Ser Gly Gly Pro
                245                 250                 255

Ser Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln
            260                 265                 270

Pro Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His
        275                 280                 285

Leu Gly Val Val Ile Gly Ile Leu Val Ala Val Ile Leu Leu Leu Leu
    290                 295                 300

Leu Leu Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys
305                 310                 315                 320

His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly
                325                 330                 335

Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser
            340                 345                 350

Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys His
        355                 360                 365

Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ser Pro His Asp
    370                 375                 380

Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro
385                 390                 395                 400

Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu
                405                 410                 415

Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu
            420                 425                 430

Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His
        435                 440                 445

Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu
    450                 455                 460

Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
465                 470                 475                 480
```

<210> 91
<211> 500
<212> PRT
<213> Artificial Sequence

<220>
<223> PA2.1.14 (VL:VH) scFv LIR1 HTICD construct

<400> 91

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30

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

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

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

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

Ser His Val Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys
            100                 105                 110

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

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

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

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

Ile Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys
            180                 185                 190

Phe Lys Gly Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala
        195                 200                 205

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

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

Thr Leu Val Thr Val Ser Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr
                245                 250                 255

Leu Leu Thr His Pro Ser Asp Pro Leu Glu Leu Val Val Ser Gly Pro
            260                 265                 270
```

```
Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly
        275                 280                 285

Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly
    290                 295                 300

Leu Gly Arg His Leu Gly Val Val Ile Gly Ile Leu Val Ala Val Ile
305                 310                 315                 320

Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe Leu Ile Leu Arg His Arg
                325                 330                 335

Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln
            340                 345                 350

His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln
        355                 360                 365

Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala
    370                 375                 380

Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg
385                 390                 395                 400

Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys
                405                 410                 415

His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser
            420                 425                 430

Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln
        435                 440                 445

Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr
    450                 455                 460

Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro
465                 470                 475                 480

Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr
                485                 490                 495

Leu Ala Ile His
            500
```

<210> 92
<211> 407
<212> PRT
<213> Artificial Sequence

<220>
<223> PA2.1.14 (VL:VH) scFv LIR1 sHTICD construct

<400> 92

```
Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala
1               5                   10                  15

Thr Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gln
            20                  25                  30

Gly Thr Lys Val Glu Val Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
        35                  40                  45

Ser Gly Gly Gly Gly Ser Gly Gly Gln Val Gln Leu Val Gln Ser Gly
    50                  55                  60

Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala
65                  70                  75                  80

Ser Gly Tyr Thr Phe Thr Ser Tyr His Ile His Trp Val Arg Gln Ala
                85                  90                  95

Pro Gly Gln Gly Leu Glu Trp Ile Gly Trp Ile Tyr Pro Gly Asn Val
            100                 105                 110

Asn Thr Glu Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Ile Thr Ala
        115                 120                 125

Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser
    130                 135                 140

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Glu Ile Thr Tyr Ala
145                 150                 155                 160

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Val Val
                165                 170                 175

Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro Thr Ser
            180                 185                 190

Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser Asp Pro
        195                 200                 205

Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly Ile Leu Val
    210                 215                 220

Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe Leu Ile Leu
225                 230                 235                 240

Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala
                245                 250                 255

Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg
            260                 265                 270
```

```
Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn
        275                 280                 285

Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met
    290                 295                 300

Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala
305                 310                 315                 320

Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser
                325                 330                 335

Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu
            340                 345                 350

Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp
        355                 360                 365

Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr
    370                 375                 380

Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile
385                 390                 395                 400

Tyr Ala Thr Leu Ala Ile His
                405
```

<210> 93
<211> 32
<212> PRT
<213> Homo sapiens

<400> 93

```
Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr
1               5                   10                  15

Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val
            20                  25                  30
```

<210> 94
<211> 10
<212> PRT
<213> Homo sapiens

<400> 94

```
Met Ala Met Val Lys Arg Lys Asp Ser Arg
1               5                   10
```

<210> 95
<211> 30
<212> DNA
<213> Homo sapiens

<400> 95
atggccatgg tcaagagaaa ggattccaga 30

<210> 96
<211> 23
<212> PRT
<213> Homo sapiens

<400> 96

Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu
1   5   10   15

Leu Met Thr Leu Arg Leu Trp
            20

<210> 97
<211> 69
<212> DNA
<213> Homo sapiens

<400> 97
gtgattgggt tccgaatcct cctcctgaaa gtggccgggt ttaatctgct catgacgctg   60

cggctgtgg   69

<210> 98
<211> 23
<212> PRT
<213> Homo sapiens

<400> 98

Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val
1   5   10   15

Leu Val Ser Ala Leu Val Leu
            20

<210> 99
<211> 69
<212> DNA
<213> Homo sapiens

<400> 99
accatcctct atgagatctt gctagggaag gccaccttgt atgccgtgct ggtcagtgcc   60

ctcgtgctg   69

<210> 100
<211> 27
<212> PRT
<213> Homo sapiens

<400> 100

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

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

<210> 101
<211> 81
<212> DNA
<213> Homo sapiens

<400> 101
ttctgggtgc tggtcgttgt gggcggcgtg ctggcctgct acagcctgct ggtgacagtg 60

gccttcatca tcttttgggt g 81

<210> 102
<211> 45
<212> PRT
<213> Homo sapiens

<400> 102

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
            20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
        35 40 45

<210> 103
<211> 135
<212> DNA
<213> Homo sapiens

<400> 103
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggcg cagtgcacac gaggggctg 120

gacttcgcct gtgat 135

<210> 104
<211> 41
<212> PRT
<213> Homo sapiens

<400> 104

Cys Thr Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys
1 5 10 15

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
            20 25 30

Pro Leu Phe Pro Gly Pro Ser Lys Pro
        35 40

<210> 105
<211> 123
<212> DNA
<213> Homo sapiens

<400> 105
tgtaccattg aagttatgta tcctcctcct tacctagaca atgagaagag caatggaacc 60

attatccatg tgaaagggaa acacctttgt ccaagtcccc tatttcccgg accttctaag 120

ccc 123

<210> 106
<211> 9
<212> PRT
<213> Homo sapiens

<400> 106

Phe Leu Trp Gly Pro Arg Ala Leu Val
1 5

<210> 107
<211> 9
<212> PRT
<213> Homo sapiens

<400> 107

Ser Leu Leu Met Trp Ile Thr Gln Val
1 5

<210> 108
<211> 11
<212> PRT
<213> Homo sapiens

<400> 108

Met Pro Lys Val Ala Glu Leu Val His Phe Leu
1 5 10

<210> 109
<211> 10
<212> PRT
<213> Human papillomavirus

<400> 109

Thr Ile His Asp Ile Ile Leu Glu Cys Val
1 5 10

<210> 110
<211> 9
<212> PRT
<213> Human papillomavirus

<400> 110

Tyr Met Leu Asp Leu Gln Pro Glu Thr
1 5

<210> 111
<211> 1503
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide encoding PA2.1.14 scFv LIR1 HTICD construct

<400> 111
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc agtgaaggtt 60

tcctgcaagg cttctggata caccttcact agctatcata tacattgggt gcgccaggcc 120

cccggacaag ggcttgagtg gatcggatgg atctaccctg gcaatgttaa cacagaatat 180

aatgagaagt tcaagggcaa agccaccatt accgcggacg aatccacgaa cacagcctac 240

atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagggaggaa 300

attacctacg ctatggacta ctggggccag ggaaccctgg tcaccgtgtc ctcaggcgga 360

ggtggaagcg gaggggggagg atctggcggc ggaggaagcg gaggcgacat tcaaatgacc 420

cagagcccat ccaccctgag cgcatctgta ggtgaccggg tcaccatcac ttgtagatcc 480

agtcagagta ttgtacacag taatgggaac acctatttgg aatggtatca gcagaaacca 540

ggtaaagccc caaaattgct catctacaaa gtctctaaca gatttagtgg tgtaccagcc 600

aggttcagcg gttccggaag tggtactgaa ttcaccctca cgatctcctc tctccagcca 660

gatgatttcg ccacttatta ctgttttcaa ggttcacatg tgccgcgcac attcggtcag 720

ggtactaaag tagaagtcaa atacggctca cagagctcca aaccctacct gctgactcac 780

cccagtgacc ccctggagct cgtggtctca ggaccgtctg ggggccccag ctccccgaca 840

acaggcccca cctccacatc tggccctgag gaccagcccc tcacccccac cgggtcggat 900

ccccagagtg gtctgggaag gcacctgggg gttgtgatcg gcatcttggt ggccgtcatc 960

ctactgctcc tcctcctcct cctcctcttc ctcatcctcc gacatcgacg tcagggcaaa 1020

cactggacat cgacccagag aaaggctgat ttccaacatc ctgcaggggc tgtggggcca 1080

gagcccacag acagaggcct gcagtggagg tccagcccag ctgccgatgc ccaggaagaa 1140

aacctctatg ctgccgtgaa gcacacacag cctgaggatg gggtggagat ggacactcgg 1200

agcccacacg atgaagaccc ccaggcagtg acgtatgccg aggtgaaaca ctccagacct 1260

aggagagaaa tggcctctcc tccttcccca ctgtctgggg aattcctgga cacaaaggac 1320

agacaggcgg aagaggacag gcagatggac actgaggctg ctgcatctga agccccccag 1380

gatgtgacct acgcccagct gcacagcttg accctcagac gggaggcaac tgagcctcct 1440

ccatcccagg aagggccctc tccagctgtg cccagcatct acgccactct ggccatccac 1500

tag 1503

<210> 112
<211> 1443
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide encoding PA2.1.14 scFv LIR1 sHTICD construct

<400> 112
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc agtgaaggtt 60

tcctgcaagg cttctggata caccttcact agctatcata tacattgggt gcgccaggcc 120

cccggacaag ggcttgagtg gatcggatgg atctaccctg gcaatgttaa cacagaatat 180

aatgagaagt tcaagggcaa agccaccatt accgcggacg aatccacgaa cacagcctac 240

atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagggaggaa 300

attacctacg ctatggacta ctggggccag ggaaccctgg tcaccgtgtc ctcaggcgga 360

ggtggaagcg gaggggggagg atctggcggc ggaggaagcg gaggcgacat tcaaatgacc 420

cagagcccat ccaccctgag cgcatctgta ggtgaccggg tcaccatcac ttgtagatcc 480

agtcagagta ttgtacacag taatgggaac acctatttgg aatggtatca gcagaaacca 540

ggtaaagccc caaaattgct catctacaaa gtctctaaca gatttagtgg tgtaccagcc 600

aggttcagcg gttccggaag tggtactgaa ttcaccctca cgatctcctc tctccagcca 660

gatgatttcg ccacttatta ctgttttcaa ggttcacatg tgccgcgcac attcggtcag 720

ggtactaaag tagaagtcaa agtggtctca ggaccgtctg ggggccccag ctccccgaca 780

acaggcccca cctccacatc tggccctgag gaccagcccc tcacccccac cgggtcggat 840

ccccagagtg gtctgggaag gcacctgggg gttgtgatcg gcatcttggt ggccgtcatc 900

ctactgctcc tcctcctcct cctcctcttc ctcatcctcc gacatcgacg tcagggcaaa 960

cactggacat cgacccagag aaaggctgat ttccaacatc ctgcaggggc tgtggggcca 1020

gagcccacag acagaggcct gcagtggagg tccagcccag ctgccgatgc ccaggaagaa 1080

aacctctatg ctgccgtgaa gcacacacag cctgaggatg gggtggagat ggacactcgg 1140

agcccacacg atgaagaccc ccaggcagtg acgtatgccg aggtgaaaca ctccagacct 1200

aggagagaaa tggcctctcc tccttcccca ctgtctgggg aattcctgga cacaaaggac 1260

agacaggcgg aagaggacag gcagatggac actgaggctg ctgcatctga agccccccag 1320

gatgtgacct acgcccagct gcacagcttg accctcagac gggaggcaac tgagcctcct 1380

ccatcccagg aagggccctc tccagctgtg cccagcatct acgccactct ggccatccac 1440

tag 1443

<210> 113
<211> 1503
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide PA2.1.14 (VL:VH) scFv LIR1 HTICD construct

<400> 113
gacattcaaa tgacccagag cccatccacc ctgagcgcat ctgtaggtga ccgggtcacc 60

atcacttgta gatccagtca gagtattgta cacagtaatg ggaacaccta tttggaatgg 120

tatcagcaga aaccaggtaa agccccaaaa ttgctcatct acaaagtctc taacagattt 180

agtggtgtac cagccaggtt cagcggttcc ggaagtggta ctgaattcac cctcacgatc 240

tcctctctcc agccagatga tttcgccact tattactgtt ttcaaggttc acatgtgccg 300

cgcacattcg gtcagggtac taaagtagaa gtcaaaggcg gaggtggaag cggaggggga 360

ggatctggcg gcggaggaag cggaggccag gtgcagctgg tgcagtctgg ggctgaggtg 420

aagaagcctg ggtcctcagt gaaggtttcc tgcaaggctt ctggatacac cttcactagc 480

tatcatatac attgggtgcg ccaggccccc ggacaagggc ttgagtggat cggatggatc 540

taccctggca atgttaacac agaatataat gagaagttca agggcaaagc caccattacc 600

gcggacgaat ccacgaacac agcctacatg gagctgagca gcctgagatc tgaagacacg 660

gctgtgtatt actgtgcgag ggaggaaatt acctacgcta tggactactg gggccaggga 720

accctggtca ccgtgtcctc atacggctca cagagctcca aaccctacct gctgactcac 780

cccagtgacc ccctggagct cgtggtctca ggaccgtctg ggggccccag ctccccgaca 840

acaggcccca cctccacatc tggccctgag gaccagcccc tcacccccac cgggtcggat 900

ccccagagtg gtctgggaag gcacctgggg gttgtgatcg gcatcttggt ggccgtcatc 960

ctactgctcc tcctcctcct cctcctcttc ctcatcctcc gacatcgacg tcagggcaaa 1020

cactggacat cgacccagag aaaggctgat ttccaacatc ctgcaggggc tgtggggcca 1080

gagcccacag acagaggcct gcagtggagg tccagcccag ctgccgatgc ccaggaagaa 1140

aacctctatg ctgccgtgaa gcacacacag cctgaggatg gggtggagat ggacactcgg 1200

agcccacacg atgaagaccc ccaggcagtg acgtatgccg aggtgaaaca ctccagacct 1260

aggagagaaa tggcctctcc tccttcccca ctgtctgggg aattcctgga cacaaaggac 1320

agacaggcgg aagaggacag gcagatggac actgaggctg ctgcatctga agccccccag 1380

gatgtgacct acgcccagct gcacagcttg accctcagac gggaggcaac tgagcctcct 1440

ccatcccagg aagggccctc tccagctgtg cccagcatct acgccactct ggccatccac 1500

tag 1503

<210> 114
<211> 1443
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide encoding PA2.1.14 (VL:VH) scFv LIR1 sHTICD construct

<400> 114
gacattcaaa tgacccagag cccatccacc ctgagcgcat ctgtaggtga ccgggtcacc 60

atcacttgta gatccagtca gagtattgta cacagtaatg ggaacaccta tttggaatgg 120

tatcagcaga aaccaggtaa agccccaaaa ttgctcatct acaaagtctc taacagattt 180

agtggtgtac cagccaggtt cagcggttcc ggaagtggta ctgaattcac cctcacgatc 240

tcctctctcc agccagatga tttcgccact tattactgtt ttcaaggttc acatgtgccg 300

cgcacattcg gtcagggtac taaagtagaa gtcaaaggcg gaggtggaag cggaggggga 360

ggatctggcg gcggaggaag cggaggccag gtgcagctgg tgcagtctgg ggctgaggtg 420

aagaagcctg ggtcctcagt gaaggtttcc tgcaaggctt ctggatacac cttcactagc 480

tatcatatac attgggtgcg ccaggccccc ggacaagggc ttgagtggat cggatggatc 540

taccctggca atgttaacac agaatataat gagaagttca agggcaaagc caccattacc 600

gcggacgaat ccacgaacac agcctacatg gagctgagca gcctgagatc tgaagacacg 660

gctgtgtatt actgtgcgag ggaggaaatt acctacgcta tggactactg gggccaggga 720

accctggtca ccgtgtcctc agtggtctca ggaccgtctg ggggccccag ctccccgaca 780

acaggcccca cctccacatc tggccctgag gaccagcccc tcacccccac cgggtcggat 840

ccccagagtg gtctgggaag gcacctgggg gttgtgatcg gcatcttggt ggccgtcatc 900

ctactgctcc tcctcctcct cctcctcttc ctcatcctcc gacatcgacg tcagggcaaa 960

cactggacat cgacccagag aaaggctgat ttccaacatc ctgcaggggc tgtggggcca 1020

gagcccacag acagaggcct gcagtggagg tccagcccag ctgccgatgc ccaggaagaa 1080

aacctctatg ctgccgtgaa gcacacacag cctgaggatg gggtggagat ggacactcgg 1140

agcccacacg atgaagaccc ccaggcagtg acgtatgccg aggtgaaaca ctccagacct 1200

aggagagaaa tggcctctcc tccttcccca ctgtctgggg aattcctgga cacaaaggac 1260

agacaggcgg aagaggacag gcagatggac actgaggctg ctgcatctga agccccccag 1320

gatgtgacct acgcccagct gcacagcttg accctcagac gggaggcaac tgagcctcct 1380

ccatcccagg aagggccctc tccagctgtg cccagcatct acgccactct ggccatccac 1440

tag 1443

<210> 115
<211> 71
<212> PRT
<213> Homo sapiens

<400> 115

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

Ser Asp Pro Leu Glu Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser
20 25 30

Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro
35 40 45

Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu
50 55 60

Gly Val Val Ile Gly Ile Leu
65 70

<210> 116
<211> 39
<212> PRT
<213> Homo sapiens

<400> 116

Ser Ser Thr Thr Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro
1 5 10 15

Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu

```
            20                  25                  30

Gly Val Val Ile Gly Ile Leu
        35


<210>  117
<211>  74
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Made in Lab - hinge sequence

<400>  117

Ser Ser Ala Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Pro Val
1               5                   10                  15


Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro Ser
            20                  25                  30


Pro Ser Gly Gly Ser Gly Asn Ser Ser Gly Ser Gly Gly Ser Pro Val
        35                  40                  45


Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro Ser
    50                  55                  60


Pro Ser Ala Ser Val Val Ile Gly Ile Leu
65                  70


<210>  118
<211>  82
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Made in Lab - hinge sequence

<400>  118

Ser Ser Ala Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Pro Val
1               5                   10                  15


Pro Ser Thr Pro Pro Thr Asn Ser Ser Ser Thr Pro Pro Thr Pro Ser
            20                  25                  30


Pro Ser Pro Val Pro Ser Thr Pro Pro Thr Asn Ser Ser Ser Thr Pro
        35                  40                  45


Pro Thr Pro Ser Pro Ser Pro Val Pro Ser Thr Pro Pro Thr Asn Ser
    50                  55                  60


Ser Ser Thr Pro Pro Thr Pro Ser Pro Ser Ala Ser Val Val Ile Gly
65                  70                  75                  80


Ile Leu
```

<210> 119
<211> 92
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - hinge sequence

<400> 119

Ser Ser Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr
1   5   10   15

Gly Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr
            20   25   30

Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Val Val Ser Gly Pro
        35   40   45

Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly
    50   55   60

Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly
65   70   75   80

Leu Gly Arg His Leu Gly Val Val Ile Gly Ile Leu
                85   90

<210> 120
<211> 522
<212> PRT
<213> Artificial Sequence

<220>
<223> C1765 chimeric antigen recetor constuct with signal peptide

<400> 120

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1   5   10   15

Leu Arg Gly Ala Arg Cys Asp Val Leu Met Thr Gln Thr Pro Leu Ser
            20   25   30

Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser
        35   40   45

Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu
    50   55   60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn
65   70   75   80

Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85   90   95

```
Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val
            100                 105                 110

Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Ser Gly Gly Gly
        115                 120                 125

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

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

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

Gly Tyr Thr Phe Thr Ser Tyr His Ile His Trp Val Lys Gln Arg Pro
            180                 185                 190

Gly Gln Gly Leu Glu Trp Ile Gly Trp Ile Tyr Pro Gly Asn Val Asn
        195                 200                 205

Thr Glu Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp
    210                 215                 220

Lys Ser Ser Ser Thr Ala Tyr Met His Leu Ser Ser Leu Thr Ser Glu
225                 230                 235                 240

Asp Ser Ala Val Tyr Phe Cys Ala Arg Glu Glu Ile Thr Tyr Ala Met
                245                 250                 255

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Tyr Gly Ser
            260                 265                 270

Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp Pro Leu Glu
        275                 280                 285

Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly
    290                 295                 300

Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly
305                 310                 315                 320

Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly
                325                 330                 335

Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu Phe
            340                 345                 350

Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln
        355                 360                 365
```

```
Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro
    370                 375                 380

Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln
385                 390                 395                 400

Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly
                405                 410                 415

Val Glu Met Asp Thr Arg Ser Pro His Asp Glu Asp Pro Gln Ala Val
            420                 425                 430

Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala Ser
        435                 440                 445

Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln
    450                 455                 460

Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala
465                 470                 475                 480

Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg
                485                 490                 495

Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala Val
            500                 505                 510

Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
        515                 520
```

<210> 121
<211> 1569
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide encoding C1765 chimeric antigen recetor constuct
       with signal peptide

<400> 121

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atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc       60

agatgtgatg ttttgatgac ccaaactcca ctctccctgc ctgtcagtct tggagatcaa      120

gcctccatct cttgcagatc tagtcagagc attgtacata gtaatggaaa cacctattta      180

gaatggtacc tgcagaaacc aggccagtct ccaaagctcc tgatctacaa agtttccaac      240

cgattttctg gggtcccaga caggttcagt ggcagtggat cagggacaga tttcacactc      300

aagatcagta gagtggaggc tgaggatctg ggagtttatt actgctttca aggttcacat      360

gttcctcgga cgtccggtgg aggcaccaag ctggaaatca aaggcggagg tggaagcgga      420

gggggaggat ctggcggcgg aggaagcgga ggccaggtcc agctgcagca gtctggacct      480

gagctggtga agcctggggc ttcagtgagg atatcctgca aggcttctgg ctacaccttc      540

acaagttacc atatacattg ggtgaagcag aggcctggac agggacttga gtggattgga      600
```

tggatttatc ctggaaatgt taatactgag tacaatgaga agttcaaggg caaggccaca 660

ctgactgcag acaaatcgtc cagcacagcc tacatgcacc tcagcagcct gacctctgag 720

gactctgcgg tctatttctg tgccagagag gagattacct atgctatgga ctactggggt 780

caaggaacct cagtcaccgt gtcctcatac ggctcacaga gctccaaacc ctacctgctg 840

actcacccca gtgaccccct ggagctcgtg gtctcaggac cgtctggggg ccccagctcc 900

ccgacaacag gccccacctc cacatctggc cctgaggacc agcccctcac ccccaccggg 960

tcggatcccc agagtggtct gggaaggcac ctgggggttg tgatcggcat cttggtggcc 1020

gtcatcctac tgctcctcct cctcctcctc ctcttcctca tcctccgaca tcgacgtcag 1080

ggcaaacact ggacatcgac ccagagaaag gctgatttcc aacatcctgc aggggctgtg 1140

gggccagagc ccacagacag aggcctgcag tggaggtcca gcccagctgc cgatgcccag 1200

gaagaaaacc tctatgctgc cgtgaagcac acacagcctg aggatggggt ggagatggac 1260

actcggagcc cacacgatga agacccccag gcagtgacgt atgccgaggt gaaacactcc 1320

agacctagga gagaaatggc ctctcctcct tccccactgt ctggggaatt cctggacaca 1380

aaggacagac aggcggaaga ggacaggcag atggacactg aggctgctgc atctgaagcc 1440

ccccaggatg tgacctacgc ccagctgcac agcttgaccc tcagacggga ggcaactgag 1500

cctcctccat cccaggaagg gccctctcca gctgtgccca gcatctacgc cactctggcc 1560

atccactag 1569

<210> 122
<211> 500
<212> PRT
<213> Artificial Sequence

<220>
<223> C1765 chimeric antigen recetor constuct without signal peptide

<400> 122

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

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

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

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

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

```
Ser His Val Pro Arg Thr Ser Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

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

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

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

Tyr His Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp
                165                 170                 175

Ile Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys
            180                 185                 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
        195                 200                 205

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

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

Thr Ser Val Thr Val Ser Ser Tyr Gly Ser Gln Ser Ser Lys Pro Tyr
                245                 250                 255

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

Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly Pro Thr Ser Thr Ser Gly
        275                 280                 285

Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly Ser Asp Pro Gln Ser Gly
    290                 295                 300

Leu Gly Arg His Leu Gly Val Val Ile Gly Ile Leu Val Ala Val Ile
305                 310                 315                 320

Leu Leu Leu Leu Leu Leu Leu Leu Leu Phe Leu Ile Leu Arg His Arg
                325                 330                 335

Arg Gln Gly Lys His Trp Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln
            340                 345                 350

His Pro Ala Gly Ala Val Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln
        355                 360                 365
```

```
Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala
    370                 375                 380

Ala Val Lys His Thr Gln Pro Glu Asp Gly Val Glu Met Asp Thr Arg
385                 390                 395                 400

Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr Ala Glu Val Lys
                405                 410                 415

His Ser Arg Pro Arg Arg Glu Met Ala Ser Pro Pro Ser Pro Leu Ser
            420                 425                 430

Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu Asp Arg Gln
        435                 440                 445

Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr
    450                 455                 460

Ala Gln Leu His Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro
465                 470                 475                 480

Pro Ser Gln Glu Gly Pro Ser Pro Ala Val Pro Ser Ile Tyr Ala Thr
                485                 490                 495

Leu Ala Ile His
            500
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<210> 123
<211> 1503
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide encoding C1765 chimeric antigen recetor constuct
       without signal peptide

<400> 123

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atctcttgca gatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg      120

tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt      180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc      240

agtagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct      300

cggacgtccg gtggaggcac caagctggaa atcaaaggcg gaggtggaag cggaggggga      360

ggatctggcg gcggaggaag cggaggccag gtccagctgc agcagtctgg acctgagctg      420

gtgaagcctg gggcttcagt gaggatatcc tgcaaggctt ctggctacac cttcacaagt      480

taccatatac attgggtgaa gcagaggcct ggacagggac ttgagtggat tggatggatt      540

tatcctggaa atgttaatac tgagtacaat gagaagttca agggcaaggc cacactgact      600

gcagacaaat cgtccagcac agcctacatg cacctcagca gcctgacctc tgaggactct      660

gcggtctatt tctgtgccag agaggagatt acctatgcta tggactactg gggtcaagga      720
```

acctcagtca ccgtgtcctc atacggctca cagagctcca aaccctacct gctgactcac 780

cccagtgacc ccctggagct cgtggtctca ggaccgtctg ggggccccag ctccccgaca 840

acaggcccca cctccacatc tggccctgag gaccagcccc tcacccccac cgggtcggat 900

ccccagagtg gtctgggaag gcacctgggg gttgtgatcg gcatcttggt ggccgtcatc 960

ctactgctcc tcctcctcct cctcctcttc ctcatcctcc gacatcgacg tcagggcaaa 1020

cactggacat cgacccagag aaaggctgat ttccaacatc ctgcaggggc tgtggggcca 1080

gagcccacag acagaggcct gcagtggagg tccagcccag ctgccgatgc ccaggaagaa 1140

aacctctatg ctgccgtgaa gcacacacag cctgaggatg gggtggagat ggacactcgg 1200

agcccacacg atgaagaccc ccaggcagtg acgtatgccg aggtgaaaca ctccagacct 1260

aggagagaaa tggcctctcc tccttcccca ctgtctgggg aattcctgga cacaaaggac 1320

agacaggcgg aagaggacag gcagatggac actgaggctg ctgcatctga agccccccag 1380

gatgtgacct acgcccagct gcacagcttg accctcagac gggaggcaac tgagcctcct 1440

ccatcccagg aagggccctc tccagctgtg cccagcatct acgccactct ggccatccac 1500

tag 1503

<210> 124
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> immunoreceptor tyrosine-based inhibitory motif

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Ser, Ile, Val or Leu

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa = Any amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(5)
<223> Xaa = Any amino acid

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa = Ile, Val or Leu

<400> 124

Xaa Xaa Tyr Xaa Xaa Xaa
1 5

<210> 125
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> C-001765 scFv antibody construct

<400> 125

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


Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30


Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


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


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


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


Ser His Val Pro Arg Thr Ser Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


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


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


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


Tyr His Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp
                165                 170                 175


Ile Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Glu Tyr Asn Glu Lys
            180                 185                 190


Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
        195                 200                 205


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


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


Thr Ser Val Thr Val Ser Ser
                245
```

<210> 126
<211> 759
<212> DNA
<213> Homo sapiens

<400> 126
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gtggtctcag gaccgtctgg gggccccagc tccccgacaa caggccccac ctccacatct 120

ggccctgagg accagcccct caccccccacc gggtcggatc cccagagtgg tctgggaagg 180

cacctggggg ttgtgatcgg catcttggtg gccgtcatcc tactgctcct cctcctcctc 240

ctcctcttcc tcatcctccg acatcgacgt cagggcaaac actggacatc gacccagaga 300

aaggctgatt tccaacatcc tgcaggggct gtggggccag agcccacaga cagaggcctg 360

cagtggaggt ccagcccagc tgccgatgcc caggaagaaa acctctatgc tgccgtgaag 420

cacacacagc ctgaggatgg ggtggagatg gacactcgga gcccacacga tgaagacccc 480

caggcagtga cgtatgccga ggtgaaacac tccagaccta ggagagaaat ggcctctcct 540

ccttccccac tgtctgggga attcctggac acaaaggaca gacaggcgga agaggacagg 600

cagatggaca ctgaggctgc tgcatctgaa gccccccagg atgtgaccta cgcccagctg 660

cacagcttga ccctcagacg ggaggcaact gagcctcctc catcccagga agggccctct 720

ccagctgtgc ccagcatcta cgccactctg gccatccac 759

<210> 127
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<223> C-001765 scFv antibody construct polynucleotide

<400> 127
gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agtagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct 300

cggacgtccg gtggaggcac caagctggaa atcaaaggcg gaggtggaag cggaggggga 360

ggatctggcg gcggaggaag cggaggccag gtccagctgc agcagtctgg acctgagctg 420

gtgaagcctg gggcttcagt gaggatatcc tgcaaggctt ctggctacac cttcacaagt 480

taccatatac attgggtgaa gcagaggcct ggacagggac ttgagtggat tggatggatt 540

tatcctggaa atgttaatac tgagtacaat gagaagttca agggcaaggc cacactgact 600

gcagacaaat cgtccagcac agcctacatg cacctcagca gcctgacctc tgaggactct 660

gcggtctatt tctgtgccag agaggagatt acctatgcta tggactactg gggtcaagga 720

acctcagtca ccgtgtcctc a 741

<210> 128
<211> 22
<212> PRT
<213> Homo sapiens

<400> 128

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1   5   10   15

Leu Arg Gly Ala Arg Cys
            20

<210> 129
<211> 66
<212> DNA
<213> Homo sapiens

<400> 129
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc   60

agatgt   66