

Interleukin-9 Signaling in Chimeric Antigen Receptor (CAR) Immune Cells

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 63/245,400, filed September 17, 2021, and to U.S. Provisional Patent Application No. 63/245,386, filed September 17, 2021, which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

10 Current immunotherapy advances have been revolutionary for the treatment of hematologic malignancies as evident by the FDA approvals of CD19-targeting chimeric antigen receptor T cells (CAR-T cells) for the treatment of acute lymphoblastic leukemia and diffuse-large B-cell lymphoma. However, the greatest unmet burden for cancer treatment is
15 solid tumors. CAR-T cells have lacked efficacy in the fight against solid tumors due to a number of challenges, including the lack of tumor-specific antigens, overcoming obstacles of therapeutic resistance, tumor heterogeneity, poor expansion and persistence, and extrinsic dysfunction and physical barriers to T cell infiltration caused by the dense, immunosuppressive tumor microenvironment (TME). One major limitation is the poor *in vivo*
20 expansion and persistence of adoptively transferred T cells, necessitating lymphodepleting conditioning chemotherapy – a toxic regimen that limits patient eligibility. Even those T cells that do expand and persist become terminally differentiated and dysfunctional. T cells with a stem-like phenotype can overcome these limitations and exhibit superior antitumor activity in mouse models and humans, but therapeutic manipulations to select or expand stem-like T
25 cells are limited to the cell manufacturing phase and cannot be made *in vivo*. There is a need in the art for novel cell-based therapies that overcome these obstacles and challenges. The present invention addresses this need.

SUMMARY OF THE INVENTION

30 In some aspects, the invention provides a chimeric cytokine receptor, comprising:
 (a) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an

interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb);

- (b) a transmembrane domain; and
- (c) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least

90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

In some embodiments, there is provided an isolated nucleic acid comprising a
 5 nucleotide sequence encoding the chimeric cytokine receptor of any one of the preceding embodiments.

In some embodiments, there is provided a vector comprising the isolated nucleic acid of embodiment 6.

In some embodiments, the vector is a retroviral vector or a lentiviral vector.

10 In some aspects, there is provided an isolated nucleic acid comprising:

- a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising
 - (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha
 15 (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 20
 - b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human
 25 IL9Ra intracellular signaling domain;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 30 (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- 5 (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

In some embodiments of the isolated nucleic acid of any one of the preceding embodiments, the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

In some embodiments of the isolated nucleic acid of any one of the preceding embodiments, the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

30 In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific

antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;

- 5 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 10 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 15 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

20 In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

25 In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

30 In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some aspects, there is provided a vector comprising the isolated nucleic acid of any one of the preceding embodiments.

In some embodiments, the vector is a retroviral vector or a lentiviral vector.

In some aspects, there is provided a modified cell comprising the chimeric cytokine receptor of any one of the embodiments comprising the chimeric cytokine receptor, the
5 embodiments comprising the isolated nucleic acid, and/or the embodiments comprising the vector, wherein the cell is an immune cell or precursor cell thereof.

In some embodiments, the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

10 In some embodiments, the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express:

- a) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2
15 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen
20 binding domain, a second transmembrane domain, and a second intracellular domain.

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- 25 (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human
30 IL9Ra intracellular signaling domain;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 5 (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid
 10 sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

15 In some embodiments, the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

In some embodiments of the modified cell, the tumor antigen is selected from the group consisting of alpha fetoprotein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA,
 25 claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRA)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to
 30 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

- 10 In some embodiments, the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95
 - 15 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - 20 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
 - 25 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%,
 - 30

at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;

- 5 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 10 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 15 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
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In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, 25 NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based 30 activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some embodiments, the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

In some embodiments, the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.

In other aspects, there is provided a pharmaceutical composition comprising a population of the modified cell of any one of the embodiments comprising a modified cell, and at least one pharmaceutically acceptable carrier.

In other aspects, there is provide a system for enabling IL9 signaling in a cell, the system comprising:

- (a) a modified immune cell engineered to express:
 - (i) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and
- (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

In some embodiments, the vector is an adenoviral vector.

In some embodiments, the vector is a serotype 5 adenoviral vector.

In some embodiments, the vector is an oncolytic adenoviral vector.

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- 5 (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a
10 murine IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18; or
- 15 (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least
20 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

In some embodiments, the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least
25 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

In some embodiments, the tumor antigen is selected from the group consisting of
30 alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate

binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3),
HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1,
MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1,
Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16,
5 PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any
combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2,
TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group
10 consisting of a full length antibody or antigen-binding fragment thereof, a monospecific
antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable
fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic
(such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an
affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin,
15 and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable
fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- 20 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least
80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,
at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least
97%, at least 98%, at least 99%, or at least 100% sequence identity to a
sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 25 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at
least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%,
at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least
92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at
least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO:
30 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at
least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%,
at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least

92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;

- 5 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 10 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 15 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 20 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
- 25

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

30

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some embodiments:

- (a) the IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 25 and SEQ ID NO: 61;
- (b) the IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 27 and SEQ ID NO: 63;
- (c) the IL13 is an IL13-TQM variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29;
- (d) the IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 31 and SEQ ID NO: 67;

- 5 (e) the IL2 is an IL2 F42A variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 33; or
- 10 (f) the IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 35 and SEQ ID NO: 71.

In some embodiments, the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

- 15 In some embodiments, the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.

In other aspects, there is provide a method of treating cancer in a subject in need thereof, the method comprising administering to the subject:

- 20 (a) a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express:
- 25 (i) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- 30 (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and
- (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

In some embodiments, the vector is an adenoviral vector.

In some embodiments, the vector is a serotype 5 adenoviral vector.

In some embodiments, the vector is an oncolytic adenoviral vector.

In some embodiments, the transmembrane domain is an IL9Ra transmembrane
5 domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human
10 IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a
15 murine IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine
20 IL9Ra intracellular signaling domain, and the cytokine is an IL18; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least
25 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

In some embodiments, the first nucleotide sequence is a sequence having at least
30 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100%

sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

In some embodiments, the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%,

- at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 5 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 10 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 15 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 20 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 25 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 130;
- 30

97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some embodiments:

- (a) the IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 25 and SEQ ID NO: 61;
- (b) the IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 27 and SEQ ID NO: 63;
- (c) the IL13 is an IL13-TQM variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,

at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29;

- 5 (d) the IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 31 and SEQ ID NO: 67;
- 10 (e) the IL2 is an IL2 F42A variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 33; or
- 15 (f) the IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 35 and SEQ ID NO: 71.
- 20

In some embodiments, the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.

In some embodiments, the population of cells is capable of activating STAT1, STAT3, STAT5, or any combination thereof.

- 25 In some embodiments, the subject is a human.

In some embodiments, the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer,

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cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

In other aspects, there is provided a modified cell, wherein the cell is an immune cell or precursor cell thereof, wherein the cell is engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an
 5 intracellular domain, and further wherein expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA.

In some embodiments, the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory
 10 interspaced short palindromic repeats (CRISPR)/Cas9 system.

In some embodiments, the inhibitory RNA comprises an siRNA or an shRNA.

In some embodiments, the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b,
 15 CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRA)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1,
 20 Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an
 30 affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- 5 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 10 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 15 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 20 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 25 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 30 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least

86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and

- 5 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID
10 NO: 131.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS,
15 NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based
20 activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

25 In some embodiments, the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

In some embodiments, STAT1, STAT3, STAT5, or any combination thereof, is/are activated in the cell.

In other aspects, there is provided a pharmaceutical composition comprising a
30 population of the modified cell of the preceding embodiments and at least one pharmaceutically acceptable carrier.

In other aspects, there is provided a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a population of modified cells,

wherein the cells are immune cells or precursor cells thereof, wherein the cells are engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cells is reduced and/or eliminated via a genetic engineering technique or by
 5 introduction of an inhibitory RNA.

In some embodiments, the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system.

In some embodiments, the inhibitory RNA comprises an siRNA or an shRNA.

10 In some embodiments, the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate
 15 binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any
 20 combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific
 25 antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

30 In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- 5 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 10 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 15 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 20 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 25 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 30 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at

least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and

- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some embodiments, the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.

In some embodiments, STAT1, STAT3, STAT5, or any combination thereof, is/are activated in the population of cells.

In some embodiments, the subject is a human.

In some embodiments, the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus

cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

5 In other aspects, there is provided a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).

10 In some embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-
15 lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- 20 (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a
25 human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 30 (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

- (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 5 (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 10 (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 15 (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

25 In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

In other aspects, there is provided an isolated nucleic acid comprising a nucleotide sequence encoding the chimeric cytokine receptor of any one of the preceding embodiments.

In other aspects, there is provided a vector comprising the isolated nucleic acid of the invention.

In some embodiments, the vector is a retroviral vector or a lentiviral vector.

In some aspects, there is provided an isolated nucleic acid comprising:

- 5 a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- 10 b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In some embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a
 15 Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

20 In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 25 (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human
 30 IL9Ra intracellular signaling domain;
- (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 5 (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 10 (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain
- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 15 (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- 20 (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least
 25 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

In some embodiments, the first nucleotide sequence is a sequence having at least
 30 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100%

sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

In some embodiments, the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, 5 CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, 10 MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, 15 TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic 20 (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

25 In some embodiments, the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 30 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%,

- at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 5 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 10 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 15 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 20 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 25 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 130;
- 30

97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some aspects, there is provided a vector comprising the isolated nucleic acid of the preceding embodiments.

In some embodiments, the vector is a retroviral vector or a lentiviral vector.

In other aspects, there is provided a modified cell comprising the chimeric cytokine receptor of the preceding embodiments, the isolated nucleic acid of the preceding embodiments, and/or the vector of the preceding embodiments, wherein the cell is an immune cell or precursor cell thereof.

In some embodiments, the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

In some embodiments, the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express:

- a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and

- b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In some embodiments, the inhibitory immunoreceptor is selected from a Programmed
 5 Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a
 Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig
 and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3
 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-
 lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and
 10 a Programmed Death Ligand-1 (PD-L1).

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human
 15 IL9Ra intracellular signaling domain;
- (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human
 IL9Ra intracellular signaling domain;
- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a
 human IL9Ra intracellular signaling domain;
- 20 (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human
 IL9Ra intracellular signaling domain;
- (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human
 IL9Ra intracellular signaling domain;
- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine
 25 IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a
 murine IL9Ra intracellular signaling domain;
- (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a
 murine IL9Ra intracellular signaling domain;
- 30 (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine
 IL9Ra intracellular signaling domain;
- (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine
 IL9Ra intracellular signaling domain;

- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 5 (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- 10 (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 15 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

In some embodiments, the first nucleotide sequence is a sequence having at least 20 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

25 In some embodiments, the tumor antigen is selected from the group consisting of alpha fetoprotein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRA)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), 30 HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16,

PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

- 5 In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- 15 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 20 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 25 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 30

- 5 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 10 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 15 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 20 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

25 In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a
30 killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based

activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a
5 CD3 zeta, or any combination thereof.

In some embodiments, the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

In some embodiments, the chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.

10 In other aspects, there is provided a pharmaceutical composition comprising a population of the modified cell of the preceding embodiments and at least one pharmaceutically acceptable carrier.

In other aspects, there is provided a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a population of modified cells,
15 wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express:

- a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an
20 intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

25 In some embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-
30 lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In some embodiments, the transmembrane domain is an IL9Ra transmembrane domain.

In some embodiments, the chimeric cytokine receptor comprises:

- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 5 (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 10 (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 15 (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 20 (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 25 (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 30 (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

In some embodiments, the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

In some embodiments, the tumor antigen is selected from the group consisting of alpha fetoprotein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSMA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

In some embodiments, the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

In some embodiments, the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

In some embodiments, the tumor antigen binding domain is a single-chain variable fragment (scFv).

In some embodiments, the tumor antigen binding domain is selected from:

- 5 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 10 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO:
15 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at
20 least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at
25 least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least
30 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;

- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

In some embodiments, the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

In some embodiments, the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

In some embodiments, the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.

In some embodiments, the chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cells.

In some embodiments, the subject is a human.

In some embodiments, the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer,

Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the present invention will be more fully understood from the following detailed description of illustrative embodiments taken in conjunction with the accompanying drawings.

FIG. 1A – FIG. 1D provides schematics illustrating various embodiments of the cytokine receptors of the invention. **FIG. 1A** is a schematic illustrating a wild type IL9Ra cytokine receptor co-expressed with an exemplary CAR. **FIG. 1B** is a schematic illustrating an IL13Ra2-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR. **FIG. 1C** is a schematic illustrating an IL2Rb-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR. **FIG. 1D** is a schematic illustrating an IL18R-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR.

FIG. 2A – FIG. 2F provides schematics illustrating various exemplary expression constructs for cytokine receptors, CARs, and ligands disclosed herein. **FIG. 2A** is a schematic of two lentiviral constructs for expression of human IL9Ra and a human CAR. The top and bottom constructs show that the nucleotide sequence encoding the cytokine receptor and the nucleotide sequence encoding the CAR are linked by a nucleotide sequence encoding either a 2A self-cleaving peptide (2A) or an internal ribosome entry site (IRES), respectively. **FIG. 2B** is a schematic of an Ad5 adenoviral construct for expression of human IL-9 under control of a CMV promoter. **FIG. 2C** is a schematic of an Ad5 adenoviral construct for expression of murine IL-9 under control of a CMV promoter. **FIG. 2D** is a schematic of an Ad5 adenoviral construct for expression of an IL-13 TQM mutant under control of a CMV promoter. **FIG. 2E** is a schematic of an Ad5 adenoviral construct for expression of an IL-2 F42A mutant under control of a CMV promoter. **FIG. 2F** is a schematic of an Ad5 adenoviral construct for expression of IL-18 under control of a CMV promoter.

FIG. 3A – FIG. 3D provide data relating to a wild type murine IL9Ra cytokine receptor co-expressed with an exemplary CAR on transduced murine CD3+ T cells. **FIG. 3A** provides data illustrating co-expression of murine IL9Ra and a murine CAR on transduced murine CD3+ T cells compared to untransduced (UTD) cells. **FIG. 3B** provides flow cytometry analysis of surface markers CD44, C62L, and Fas (CD95) illustrating the finding that the transduced cells display Tscm phenotype 24 h after stimulation with 100 ng/mL of wild type mIL9 or wild type mIL2. **FIG. 3C** provides global gene expression profile data in transduced murine CAR T cells expressing mIL9Ra 24 h after stimulation with wild type mIL9 or wild type mIL2. Total RNA was extracted from transduced T cells cultured in the presence of mIL-2 or mIL-9 for 24h. RNA was analyzed with Nanostring nCounter Mouse Immunology Panel (562 genes) and plotted using nSolver 4.0 software. **FIG. 3D** provides a graph illustrating in vitro expression of mIL9 via adenoviral vector construct Ad-mIL9 as shown in **FIG. 2C**. Murine pancreatic cancer cell line PDA7940b (10,000 cells/well) was infected with 100 viral particles/cell of Ad-mIL9 and cell culture supernatants were analyzed for mIL-9 by ELISA at indicated time points.

FIG. 4A – FIG. 4B provide data related to a human IL13Ra2-IL9Ra chimeric cytokine receptor. **FIG. 4A** provides flow cytometry data illustrating expression of the human IL13Ra2-IL9Ra chimeric cytokine receptor on lentivirally transduced human T cells compared to untransduced cells (UTD). **FIG. 4B** provides Western blots from four donors illustrating pSTAT1/pSTAT3/pSTAT5 expression in hIL13Ra2-IL9Ra expressing T cells. 10x10⁶ lentivirally transduced T cells were starved overnight in RPMI with 0.1% FBS and were left untreated or treated with hIL-13 (100 ng/mL) for 30 minutes. Western blot detection of phosphorylated STAT1, STAT3 and STAT5 with GAPDH as loading control.

FIG. 5 provides flow cytometry data illustrating expression of chimeric hIL2Rb-IL9Ra receptor on lentivirally transduced human T cells. UTD, untransduced.

FIG. 6A – FIG. 6D provide schematics illustrating the chimeric IL-9R cytokine receptor of the invention. **FIG. 6A** is a schematic illustrating a PD1-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR. **FIG. 6B** is a schematic illustrating a TGFbRII-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR. **FIG. 6C** is a schematic illustrating a TIGIT-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR. **FIG. 6D** is a schematic illustrating a TIM3-IL9Ra chimeric cytokine receptor co-expressed with an exemplary CAR. **FIG. 6E** is a schematic illustrating a chimeric cytokine receptor comprising an anti-CTLA4 (H+L) antigen binding domain and an IL9Ra

ICD, co-expressed with an exemplary CAR. **FIG. 6F** is a schematic illustrating a chimeric cytokine receptor comprising an anti-CTLA4 scFv antigen binding domain and an IL9Ra ICD, co-expressed with an exemplary CAR.

FIG. 7 provides flow cytometry data illustrating co-expression of a murine PD1-IL9Ra chimeric cytokine receptor and a murine anti-mesothelin CAR comprising the A03 scFv on transduced murine T cells compared to untransduced (UTD) cells.

FIG. 8 provides flow cytometry data illustrating expression of a murine TGFbRII-IL9Ra chimeric cytokine receptor on transduced murine T cells compared to untransduced (UTD) cells.

FIG. 9A provides a schematic of a gene expression construct for expressing human IL9Ra and a human anti-mesothelin CAR (M5), and flow cytometry data showing co-expression of the IL9Ra and the CAR in human T cells.

FIG. 9B provides a schematic of a gene expression construct for expressing murine IL9Ra and a murine anti-mesothelin CAR (A03), and flow cytometry data showing co-expression of the IL9Ra and the CAR in murine cells on Day 5 post transduction.

FIG. 10 provides flow cytometry data illustrating the finding that IL9Ra signaling in T cells leads to a Tscm phenotype.

FIG. 11 provides phospho flow cytometry data illustrating the finding that IL9Ra signaling in T induces phosphorylation of STAT1, STAT3, and STAT5. Shown is the $\log_2(\text{fold change})$ of MFI.

FIG. 12 provides quantified cytokine secretion data for the indicated cytokines in murine T cells incubated with IL9. The T cells were transduced to express the A03 CAR (left side of each panel) or the A03 CAR and IL9Ra (right side of each panel).

FIG. 13 illustrates the finding that IL9Ra signaling in murine T cells enhances tumor cell killing.

FIGs. 14A – 14C illustrate the finding that IL9a signaling induces similar gene expression profiles in T cells engineered to express the anti-meso CAR and IL9Ra or anti-meso CAR and an orthogonal chimeric cytokine receptor (ortho-IL2R β -IL9Ra chimeric cytokine receptor (o9R)). **FIG. 14A** shows top 20 up-regulated and down-regulated genes for T cells expressing anti-meso CAR and IL9Ra pre-incubated with either IL9 or IL2. **FIG. 14B** shows top 20 up-regulated and down-regulated genes for T cells expressing anti-meso CAR and o9R pre-incubated with ortho-IL2 or IL-2. **FIG. 14C** shows the shared up-regulated and down-regulated genes.

FIGs. 15A – 15F show gene set variation analysis (GSVA) and gene set enrichment analysis (GSEA) data for T cells expressing anti-meso CAR and IL9Ra pre-incubated with either IL9 or IL2 and for T cells expressing anti-meso CAR and an ortho-IL2R β -IL9Ra chimeric cytokine receptor (o9R) pre-incubated with ortho-IL2 or IL-2. **FIG. 15A** data compares the pathways significantly enriched in the CAR T cells stimulated with IL9 vs IL2. **FIG. 15B** provides a table of the enriched pathways together with the GSEA statistics. **FIG. 15C** provides enrichment plots and analyses for interferon gamma response in T cells expressing anti-meso CAR and IL9Ra pre-incubated with IL9 vs. IL2. **FIG. 15D** provides enrichment plots and analyses for interferon alpha response in T cells expressing anti-meso CAR and IL9Ra pre-incubated with IL9 vs. IL2. **FIG. 15E** provides enrichment plots and analyses for interferon gamma response in T cells expressing anti-meso CAR and ortho-IL2R β -IL9Ra chimeric cytokine receptor (o9R) pre-incubated with ortho-IL2 vs. IL-2. **FIG. 15F** provides enrichment plots and analyses for interferon alpha response in T cells expressing anti-meso CAR and ortho-IL2R β -IL9Ra chimeric cytokine receptor (o9R) pre-incubated with ortho-IL2 vs. IL-2.

FIGs. 16A – 16D relate to establishment of an *in vivo* syngenic murine model of PDA. **FIG. 16A** shows a schematic of the protocol, charts of the tumor volume, and mesothelin expression data for the PDA7940b cells. **FIG. 16B** shows the experimental plan for dose titration of an adenoviral vector expressing mL9 (Ad-mIL9) in the syngenic PDA murine model. **FIG. 16C** provides transduction efficiency data for the Ad-mIL9. **FIG. 16D** provides dose titration tumor growth data for the indicated conditions in the syngenic PDA murine model.

DETAILED DESCRIPTION

The present disclosure provides several approaches to enable IL-9 signaling in chimeric antigen receptor (CAR)-expressing immune cells, thereby enhancing the efficacy of CAR immune cell therapy. In one aspect, IL9Ra receptors or chimeric cytokine receptors comprising IL9Ra intracellular signaling domain (ICD), along with adenoviral delivery of cytokine ligand at a tumor site, and uses thereof, are provided. This approach improves chimeric antigen receptor (CAR) cell immunotherapy for treating cancer by (1) enabling IL-9 signaling in the immune cells to improve effector functions *in situ*, (2) expressing the cytokine ligand in tumor cells selectively, thereby obtaining higher intratumoral

concentration of cytokine compared to systemic administration, and (3) promoting tumor antigen spreading via viral oncolysis.

In an alternative approach to enable IL-9 signaling in CAR-expressing immune cells, an immune cell expressing a CAR, in which expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA, is provided.

The present disclosure also provides chimeric cytokine receptors and uses thereof to improve chimeric antigen receptor (CAR) cell immunotherapy for treating cancer by (1) exploiting naturally existing molecules (*i.e.*, ligands and tumor antigens) in tumors and checkpoint inhibitors in T cells to convert immunosuppressive signals into immunostimulatory signals in immune cells (*e.g.*, T cells), (2) altering the phenotype of immune cells expressing the chimeric cytokine receptor and the CAR upon ligand and/or checkpoint inhibitor binding at a tumor site, and (3) enabling IL-9 signaling in the immune cells expressing the chimeric cytokine receptor and the CAR to improve effector functions *in situ* and/or to down regulate immune cell exhaustion.

By repurposing IL-9R signaling in CAR T cells, these cells gain new functions through concomitant activation of STAT1, STAT3 and STAT5. Such T cells assume stem cell memory (Tscm) features with improved trafficking and effector function, thereby resulting in improved antitumor activity for hard-to-treat solid tumors.

It is contemplated herein that a receptor comprising an IL-9 intracellular domain (ICD) of the present disclosure is distinguished from a receptor comprising an IL-4R ICD, an IL-7R ICD, or an IL-21R ICD because an orthogonal chimeric cytokine receptor comprising the IL-9R ICD resulted in a potent activation (*e.g.*, phosphorylation) of STAT1, STAT3 and STAT5 in T cells expressing the orthogonal chimeric cytokine receptor. *See*, Kalbasi, *et al.*, *Nature*, 607: 360–365 (2022). Indeed, CAR T cells expressing the oIL2R β -IL9R α chimeric cytokine receptor assumed characteristics of stem cell memory and effector T cells and exhibited superior anti-tumor efficacy in two recalcitrant syngeneic mouse solid tumour models of melanoma and pancreatic cancer when compared to, for example, a cell expressing an orthogonal receptor comprising an IL-2R ICD. Furthermore, the anti tumor efficacy of a receptor comprising the IL-9R ICD was effective in the absence of conditioning lymphodepletion. In addition, the CAR T cells expressing the orthogonal chimeric cytokine receptor comprising the IL-9R ICD proliferated less than, *e.g.*, a cell expressing an IL-2R ICD.

Accordingly, the present disclosure provides novel CAR-expressing cells (e.g., CAR T cells) expressing IL9Ra or a chimeric cytokine receptor comprising an IL9Ra ICD, and a novel process for engineering CAR T cells with a stem-like phenotype that does not require administration of an orthogonal cytokine or, in some embodiments, does not require administration of any exogenous cytokine. It is contemplated herein that the cells of the present invention will exhibit superior antitumor activity. The stem-like phenotype in a T cell was demonstrated herein by expressing wild-type IL9Ra together with a CAR, which resulted in activation of STAT1, STAT3, and STAT5 and enrichment for a CD62L⁺ population and higher expression of Fas (CD95) and Sca-1. CD62L⁺ are known for their superior anti-tumour activity in adoptive cell therapy (ACT).

The novelty of the chimeric cytokine receptors and CAR-expressing cells which co-express IL9Ra or a chimeric cytokine receptor disclosed herein is heightened by the fact that IL-9 naive T cells are insensitive to IL-9 and T cell development is unimpaired in IL-9-deficient mice. Mouse T cells do not express an IL-9R receptor. Thus, IL-9 may not be a critical natural cytokine in T cell biology. Indeed, IL-9R is naturally expressed by mast cells, memory B cells, innate lymphoid cells and haematopoietic progenitors. Although T cell subsets that produce IL-9 have been described. However, the effects of IL-9R signaling on T cells are not well characterized. The identification of IL-9 (a lesser-known cytokine among the γc cytokine receptor family) unique signaling properties in T cells, such as the unique STAT signalling profile (e.g., potent activation), and the acquisition of features of stem cell memory T (T_{SCM}) cells were surprising and unexpected.

Accordingly, in one aspect, the invention provides a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb); a transmembrane domain; and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).

In another aspect, the invention provides an isolated nucleic acid comprising a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular

signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In another aspect, the invention provides a modified cell, wherein the cell is an
5 immune cell or precursor cell thereof, and wherein the cell is engineered to express a) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a
10 first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In another aspect, the invention provides a system for enabling IL9 signaling in a cell,
15 the system comprising: (a) a modified immune cell engineered to express: (i) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane
20 domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

In another aspect, the invention provides a method of treating cancer in a subject in
25 need thereof, comprising administering to the subject (a) a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express (i) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a
30 receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and

(ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

5 In another aspect, the invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, wherein the cell is engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an
10 inhibitory RNA.

 In another aspect, the invention provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, wherein the cells are engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a
15 transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cells is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA.

 In one aspect, the invention provides a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or
20 an anti-checkpoint inhibitor antigen binding domain, a transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra). In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell
25 Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

 In another aspect, the invention provides an isolated nucleic acid comprising a) a first
30 nucleotide sequence encoding a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor

alpha (IL9Ra); and b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In another aspect, the invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In another aspect, the invention provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding

domain, a second transmembrane domain, and a second intracellular domain. In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In other aspects, provided herein are related compositions (*e.g.*, pharmaceutical compositions) and kits.

It is to be understood that the methods described in this disclosure are not limited to particular methods and experimental conditions disclosed herein as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

Furthermore, the experiments described herein, unless otherwise indicated, use conventional molecular and cellular biological and immunological techniques within the skill of the art. Such techniques are well known to the skilled worker, and are explained fully in the literature. See, *e.g.*, Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, N.Y. (1987-2008), including all supplements, Molecular Cloning: A Laboratory Manual (Fourth Edition) by MR Green and J. Sambrook and Harlow et al., Antibodies: A Laboratory Manual, Chapter 14, Cold Spring Harbor Laboratory, Cold Spring Harbor (2013, 2nd edition).

Methods and techniques using immune cells with chimeric antigen receptors (*e.g.*, CAR T cells) are described in *e.g.*, Ruella, *et al.*, J. Clin. Invest., 126(10):3814-3826 (2016) and Kalos, *et al.*, 3 (95), 95ra73:1-11 (2011), the contents of which are hereby incorporated by reference in their entireties.

A. Definitions

Unless otherwise defined, scientific and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of “or” means “and/or” unless

stated otherwise. The use of the term “including,” as well as other forms, such as “includes” and “included,” is not limiting.

Generally, nomenclature used in connection with cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein is well-known and commonly used in the art. The methods and techniques provided herein are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

That the disclosure may be more readily understood, select terms are defined below.

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

“About” as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 1\%$, and still more preferably $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

“Activation,” as used herein, refers to the state of a T cell that has been sufficiently stimulated to induce detectable cellular proliferation. Activation can also be associated with induced cytokine production, and detectable effector functions. The term “activated T cells” refers to, among other things, T cells that are undergoing cell division.

As used herein, to “alleviate” a disease means reducing the severity of one or more symptoms of the disease.

The term “antigen” as used herein is defined as a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen.

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. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to elicit the desired immune response. 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. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a biological fluid.

As used herein, the term “autologous” is meant to refer to any material derived from the same individual to which it is later to be re-introduced into the individual.

A “co-stimulatory molecule” refers to the cognate binding partner on a T cell that specifically binds with a co-stimulatory ligand, thereby mediating a co-stimulatory response by the T cell, such as, but not limited to, proliferation. Co-stimulatory molecules include, but are not limited to an MHC class I molecule, BTLA and a Toll ligand receptor.

A “co-stimulatory signal”, as used herein, refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to T cell proliferation and/or upregulation or downregulation of key molecules.

A “disease” is a state of health of an animal wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal’s health continues to deteriorate. In contrast, a “disorder” in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal’s state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal’s state of health.

The term “downregulation” as used herein refers to the decrease or elimination of gene expression of one or more genes.

“Effective amount” or “therapeutically effective amount” are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result or provides a therapeutic or prophylactic benefit. Such results may include, but are not limited to an amount that when

administered to a mammal, causes a detectable level of immune suppression or tolerance compared to the immune response detected in the absence of the composition of the invention. The immune response can be readily assessed by a plethora of art-recognized methods. The skilled artisan would understand that the amount of the composition administered herein varies and can be readily determined based on a number of factors such as the disease or condition being treated, the age and health and physical condition of the mammal being treated, the severity of the disease, the particular compound being administered, and the like.

“Encoding” refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (i.e., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

As used herein “endogenous” refers to any material from or produced inside an organism, cell, tissue or system.

The term “epitope” as used herein is defined as a small chemical molecule on an antigen that can elicit an immune response, inducing B and/or T cell responses. An antigen can have one or more epitopes. Most antigens have many epitopes; i.e., they are multivalent. In general, an epitope is roughly about 10 amino acids and/or sugars in size. Preferably, the epitope is about 4-18 amino acids, more preferably about 5-16 amino acids, and even more most preferably 6-14 amino acids, more preferably about 7-12, and most preferably about 8-10 amino acids. One skilled in the art understands that generally the overall three-dimensional structure, rather than the specific linear sequence of the molecule, is the main criterion of antigenic specificity and therefore distinguishes one epitope from another. Based on the present disclosure, a peptide used in the present invention can be an epitope.

As used herein, the term “exogenous” refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term “expand” as used herein refers to increasing in number, as in an increase in the number of T cells. In one embodiment, the T cells that are expanded *ex vivo* increase in number relative to the number originally present in the culture. In another embodiment, the T cells that are expanded *ex vivo* increase in number relative to other cell types in the culture.

- 5 The term “*ex vivo*,” as used herein, refers to cells that have been removed from a living organism, (e.g., a human) and propagated outside the organism (e.g., in a culture dish, test tube, or bioreactor).

The term “expression” as used herein is defined as the transcription and/or translation of a particular nucleotide sequence driven by its promoter.

- 10 “Expression vector” refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an *in vitro* expression system. Expression vectors include all those known in the art, such as cosmids, plasmids
15 (e.g., naked or contained in liposomes) and viruses (e.g., Sendai viruses, lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

- “Identity” as used herein refers to the subunit sequence identity between two polymeric molecules particularly between two amino acid molecules, such as, between two
20 polypeptide molecules. When two amino acid sequences have the same residues at the same positions; e.g., if a position in each of two polypeptide molecules is occupied by an arginine, then they are identical at that position. The identity or extent to which two amino acid sequences have the same residues at the same positions in an alignment is often expressed as a percentage. The identity between two amino acid sequences is a direct function of the
25 number of matching or identical positions; e.g., if half (e.g., five positions in a polymer ten amino acids in length) of the positions in two sequences are identical, the two sequences are 50% identical; if 90% of the positions (e.g., 9 of 10), are matched or identical, the two amino acids sequences are 90% identical.

- The term “immune response” as used herein is defined as a cellular response to an
30 antigen that occurs when lymphocytes identify antigenic molecules as foreign and induce the formation of antibodies and/or activate lymphocytes to remove the antigen.

The term “immunosuppressive” is used herein to refer to reducing overall immune response.

“Isolated” means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not “isolated,” but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is “isolated.” An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

A “lentivirus” as used herein refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses. Vectors derived from lentiviruses offer the means to achieve significant levels of gene transfer *in vivo*.

By the term “modified” as used herein, is meant a changed state or structure of a molecule or cell of the invention. Molecules may be modified in many ways, including chemically, structurally, and functionally. Cells may be modified through the introduction of nucleic acids.

By the term “modulating,” as used herein, is meant mediating a detectable increase or decrease in the level of a response in a subject compared with the level of a response in the subject in the absence of a treatment or compound, and/or compared with the level of a response in an otherwise identical but untreated subject. The term encompasses perturbing and/or affecting a native signal or response thereby mediating a beneficial therapeutic response in a subject, preferably, a human.

In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. “A” refers to adenosine, “C” refers to cytosine, “G” refers to guanosine, “T” refers to thymidine, and “U” refers to uridine.

The term “oligonucleotide” typically refers to short polynucleotides. It will be understood that when a nucleotide sequence is represented by a DNA sequence (i.e., A, T, C, G), this also includes an RNA sequence (i.e., A, U, C, G) in which “U” replaces “T.”

Unless otherwise specified, a “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or an RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

“Parenteral” administration of an immunogenic composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, or infusion techniques.

The term “polynucleotide” as used herein is defined as a chain of nucleotides.

5 Furthermore, nucleic acids are polymers of nucleotides. Thus, “nucleic acid” and “polynucleotide” as used herein are interchangeable. One skilled in the art has the general knowledge that nucleic acids are polynucleotides, which can be hydrolyzed into the monomeric “nucleotides” and which comprise one or more “nucleotide sequence(s)”. The monomeric nucleotides can be hydrolyzed into nucleosides. As used herein polynucleotides
10 include, but are not limited to, all nucleic acid sequences (i.e., “nucleotide sequences”) which are obtained by any means available in the art, including, without limitation, recombinant means, i.e., the cloning of nucleic acid sequences from a recombinant library or a cell genome, using ordinary cloning technology and PCR, and the like, and by synthetic means.

As used herein, the terms “peptide,” “polypeptide,” and “protein” are used
15 interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein’s or peptide’s sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both
20 short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. “Polypeptides” include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion
25 proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

By the term “specifically binds,” as used herein with respect to an antibody, is meant an antibody which recognizes a specific antigen, but does not substantially recognize or bind other molecules in a sample. For example, an antibody that specifically binds to an antigen
30 from one species may also bind to that antigen from one or more species. But, such cross-species reactivity does not itself alter the classification of an antibody as specific. In another example, an antibody that specifically binds to an antigen may also bind to different allelic forms of the antigen. However, such cross reactivity does not itself alter the classification of

an antibody as specific. In some instances, the terms “specific binding” or “specifically binding,” can be used in reference to the interaction of an antibody, a protein, or a peptide with a second chemical species, to mean that the interaction is dependent upon the presence of a particular structure (e.g., an antigenic determinant or epitope) on the chemical species; for example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody is specific for epitope “A”, the presence of a molecule containing epitope A (or free, unlabeled A), in a reaction containing labeled “A” and the antibody, will reduce the amount of labeled A bound to the antibody.

By the term “stimulation,” is meant a primary response induced by binding of a 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, such as downregulation of TGF-beta, and/or reorganization of cytoskeletal structures, and the like.

A “stimulatory molecule,” as the term is used herein, means a molecule on a T cell that specifically binds with a cognate stimulatory ligand present on an antigen presenting cell.

A “stimulatory ligand,” as used herein, means a ligand that when present on an antigen presenting cell (e.g., an aAPC, a dendritic cell, a B-cell, and the like) can specifically bind with a cognate binding partner (referred to herein as a “stimulatory molecule”) on a T cell, thereby mediating a primary response by the T cell, including, but not limited to, activation, initiation of an immune response, proliferation, and the like. Stimulatory ligands are well-known in the art and encompass, inter alia, an MHC Class I molecule loaded with a peptide, an anti-CD3 antibody, a superagonist anti-CD28 antibody, and a superagonist anti-CD2 antibody.

The term “subject” is intended to include living organisms in which an immune response can be elicited (e.g., mammals). A “subject” or “patient,” as used herein, may be a human or non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals, as well as simian and non-human primate mammals. Preferably, the subject is human.

A “target site” or “target sequence” refers to a nucleic acid sequence that defines a portion of a nucleic acid to which a binding molecule may specifically bind under conditions sufficient for binding to occur. In some embodiments, a target sequence refers to a genomic nucleic acid sequence that defines a portion of a nucleic acid to which a binding molecule may specifically bind under conditions sufficient for binding to occur.

As used herein, the term “T cell receptor” or “TCR” refers to a complex of membrane proteins that participate in the activation of T cells in response to the presentation of antigen. The TCR is responsible for recognizing antigens bound to major histocompatibility complex molecules. TCR is composed of a heterodimer of an alpha (α) and beta (β) chain, although in
5 some cells the TCR consists of gamma and delta (γ/δ) chains. TCRs may exist in alpha/beta and gamma/delta forms, which are structurally similar but have distinct anatomical locations and functions. Each chain is composed of two extracellular domains, a variable and constant domain. In some embodiments, the TCR may be modified on any cell comprising a TCR, including, for example, a helper T cell, a cytotoxic T cell, a memory T cell, regulatory T cell,
10 natural killer T cell, and gamma delta T cell.

The term “therapeutic” as used herein means a treatment and/or prophylaxis. A therapeutic effect is obtained by suppression, remission, or eradication of a disease state.

The term “transfected” or “transformed” or “transduced” as used herein refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A
15 “transfected” or “transformed” or “transduced” cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

To “treat” a disease as the term is used herein, means to reduce the frequency or severity of at least one sign or symptom of a disease or disorder experienced by a subject.

20 A “vector” is a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term “vector” includes an autonomously replicating plasmid or a virus. The term
25 should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are not limited to, Sendai viral vectors, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

30 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. This applies regardless of the breadth of the range.

B. Chimeric Cytokine Receptors

The present invention provides a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb); a transmembrane domain; and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra). In various embodiments, the transmembrane domain is derived from the IL9Ra.

In some embodiments, the chimeric cytokine receptor comprises a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a murine IL9Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

In some embodiments, the chimeric cytokine receptor comprises a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

The chimeric cytokine receptor of the present invention may also comprise a leader sequence, a hinge domain, and/or one or more spacers or linker sequences as described herein which serve to link one domain of the chimeric cytokine receptor to the next domain. The chimeric cytokine receptor may also comprise a tag (*e.g.*, a chemical tag or a biological tag) or may be fused to another protein (*e.g.*, a fluorescent protein such as GFP). Such tags may be present, *e.g.*, at the N-terminus or the C-terminus, or may be incorporated between two domains of the chimeric cytokine receptor. Techniques for post-transcriptional site selective tagging of polypeptides are also well-known in the art. One of skill in the art would be able to select such sequences and tags as appropriate to include in the chimeric cytokine receptor of the invention.

Amino acid and nucleotide sequences for certain embodiments of the chimeric cytokine receptor and domains thereof are described as follows:

Human IL9Ra ICD
(SEQ ID NO: 1)

KLSPRVKRIFYQNVPS PAMFFQPLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCVQ
EATALITCGPARPWKSVALEEEQEGPGTRLPGNLSSDVLPA GCTEWRVQTLAYLPQEDWAP
TSLTRPAPPDSEGSRSSSSSSSSNNNNYCALGCYGGWHL SALPGNTQSSGPI PALACGLSCD
HQGLETTQQGVAWVL AGHCQRPG LHEDLQGMLLPSVLSKARSWTF

Human IL9Ra ICD
(SEQ ID NO: 2)

AAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCAGCCCCGCCATGTTCTT
CCAGCCCCCTGTACAGCGTGCACAACGGCAACTTCCAGACCTGGATGGGCGCCACGGCGCCG

CGCTGCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTGCGTGCAG
GAGGCCACCGCCCTGCTGACCTGCGGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGAGGA
GGAGCAGGAGGGCCCCGGCACCCAGGCTGCCCCGGCAACCTGAGCAGCGAGGACGTGCTGCCCCG
CCGGCTGCACCGAGTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCCCCC
5 ACCAGCCTGACCAGGCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAG
CAGCAGCAACAACAACAACCTACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCC
TGCCCCGGCAACACCCAGAGCAGCGGCCCCATCCCCGCCCTGGCCTGCGGCCCTGAGCTGCGAC
CACCAGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAGGCC
CGGCCTGCACGAGGACCTGCAGGGCATGCTGCTGCCCAGCGTCTGAGCAAGGCCAGGAGCT
10 GGACCTTC

Human IL9Ra ICD

(SEQ ID NO: 73)

AAGCTGAGCCCTAGAGTGAAAAGAATCTTCTACCAGAACGTGCCTTCTCCAGCCATGTTCTT
15 CCAGCCTCTGTACAGCGTGCAACGGCAACTTCCAGACCTGGATGGGCGCTCACGGCGCCG
GCGTTCTGCTGAGCCAGGATTGCGCCGGAACACCTCAAGGCGCTCTGGAACCTTGCGTGCAG
GAGGCCACCGCCCTGCTGACCTGTGGCCCTGCTCGGCCCTGGAAGTCCGTGGCCCTAGAGGA
AGAGCAGGAAGGCCCCGGGACCAGACTGCCTGGCAACCTGAGCAGCGAGGACGTGCTGCCTG
CCGGATGTACTGAGTGGCGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCTCCA
20 ACATCTCTGACCAGACCGGCCCTCCAGACAGCGAAGGCAGCAGATCTAGCAGCAGCAGCAG
TTCTTCTAATAACAACAACCTACTGTGCCCTCGGCTGTTACGGCGGCTGGCACCTGAGCGCCC
TCCCTGGAAATACACAGTCTAGCGGCCCTATCCCCGCCCTGGCTTGTGGACTGAGCTGCGAC
CACCAGGGCCTGGAAACACAGCAGGGCGTGGCCTGGGTCTGGCCGGCCACTGCCAGAGACC
TGGCCTGCACGAGGACCTGCAGGGAATGCTGCTGCCCAGCGTCTGAGCAAGGCCAGAAGCT
25 GGACCTTT

Human IL9Ra TM

(SEQ ID NO: 3)

GNTLVAVSIFLLLTGPTYLLF

30

Human IL9Ra TM

(SEQ ID NO: 4)

GGCAACACCCTGGTGGCCGTGAGCATCTTCCTGCTGCTGACCGGCCCCACCTACCTGCTGTT
C

Human IL9Ra TM

(SEQ ID NO: 74)

GGCAATACCCCTGGTCGCAGTGTCCATCTTTTTGCTGCTGACCGGCCCAACCTACCTGCTGTT
5 T

Human IL9Ra LBD

(SEQ ID NO: 5)

MGLGRCIWEGWTLSEALRRDMGTWLLACICICTCVCLGVSVTGEGQGPRSRFTFTCLTNNIL
10 RIDCHWSAPELGQSSPWLLFTSNQAPGGTHKCILRGSECTVVLPEAVLVPSDNFTITFHH
MSGREQVSLVDPEYLPRRHVKLDPPSDLQSNISSGHCILTWSISPALPMTTLLSYELAFK
KQEEAWEQAQHRDHIVGVTWLILEAFELDPGFIHEARLRVQMATLEDDVVEEERYTGQWSEW
SQPVCFQAPQRQGPLIPPWGWP

15 Human IL9Ra LBD

(SEQ ID NO: 6)

ATGGGCCTGGGCAGGTGCATCTGGGAGGGCTGGACCCTGGAGAGCGAGGCCCTGAGGAGGGA
CATGGGCACCTGGCTGCTGGCCTGCATCTGCATCTGCACCTGCGTGTGCCTGGGCGTGAGCG
TGACCGGCGAGGGCCAGGGCCCCAGGAGCAGGACCTTCACCTGCCTGACCAACAACATCCTG
20 AGGATCGACTGCCACTGGAGCGCCCCCGAGCTGGGCCAGGGCAGCAGCCCCCTGGCTGCTGTT
CACCAGCAACCAGGCCCCCGGCGGCACCCACAAGTGCATCCTGAGGGGCAGCGAGTGCACCG
TGGTGCTGCCCCCGAGGCCGTGCTGGTGCCAGCGACAACCTTCACCATCACCTTCCACCAC
TGCATGAGCGGCAGGGAGCAGGTGAGCCTGGTGGACCCCGAGTACCTGCCCAGGAGGCACGT
GAAGCTGGACCCCCCAGCGACCTGCAGAGCAACATCAGCAGCGGCCACTGCATCCTGACCT
25 GGAGCATCAGCCCCGCCCTGGAGCCCATGACCACCCTGCTGAGCTACGAGCTGGCCTTCAAG
AAGCAGGAGGAGGCCTGGGAGCAGGCCCAGCACAGGGACCACATCGTGGGCGTGACCTGGCT
GATCCTGGAGGCCTTCGAGCTGGACCCCGGCTTCATCCACGAGGCCAGGCTGAGGGTGCAGA
TGGCCACCCTGGAGGACGACGTGGTGGAGGAGGAGGTACACCGGCCAGTGGAGCGAGTGG
AGCCAGCCCGTGTGCTTCCAGGCCCCCAGAGGCAGGGCCCCCTGATCCCCCCTGGGGCTG
30 GCCC

Human IL13Ra2 LBD

(SEQ ID NO: 7)

MAFVCLAIGCLYTFLISTTFGCTSSSDTEIKVNPPQDFEIVDPGYLGYYLQWQPPLSLDHF
KECTVEYELKYRNIGSETWKTIIITKNLHYKDGFDLNKGIEAKIHTLLPWQCTNGSEVQSSWA
ETTYWISPQGIPEKVKQDMDCVYYNWQYLLCSWKPGIGVLLDTNYNLFYWYEGLDHALQCVD
YIKADGQNIQGRFPYLEASDYKDFYICVNGSSENKPIRSSYFTFQLQNIVKPLPPVYLTFTFR
5 ESSCEIKLKWSIPLGPIPARCFDYEIEIREDDTTTLVTATVENETYTLKTTNETRQLCFVVR
KVNIYCSDDGIWSEWSKQCEGEDLSKKTLLR

Human IL13Ra2 LBD**(SEQ ID NO: 8)**

10 ATGGCCTTCGTGTGCCTGGCCATCGGCTGCCTCTACACCTTCCTGATCAGCACAACCTTCGG
CTGCACCAGCAGCAGCGATACCGAGATCAAAGTGAATCCTCCTCAGGACTTCGAGATCGTGG
ACCCCGGATACCTGGGCTACCTGTACCTGCAGTGGCAACCTCCACTGTCTCTGGATCATTTT
AAGGAATGCACAGTGAATACGAGCTGAAGTACCGGAACATCGGATCCGAGACATGGAAGAC
CATCATCACCAAGAACCTGCACTACAAGGACGGCTTCGACCTCAACAAGGGCATCGAGGCCA
15 AGATCCACACCCTGCTGCCTTGGCAGTGTACAAACGGCAGCGAGGTGCAGAGCTCCTGGGCC
GAGACAACATACTGGATCTCCCCCAGGGCATCCCCGAGACCAAAGTGCAAGATATGGACTG
CGTGTACTACAACCTGGCAGTACCTGCTGTGCAGCTGGAAACCTGGAATCGGCGTGCTGCTGG
ACACCAACTACAACCTGTTCTACTGGTATGAGGGCCTGGACCACGCCCTGCAGTGCGTCGAC
TACATCAAGGCCGATGGCCAGAACATCGGCTGCAGATTCCCCTACCTGGAAGCCTCCGATTA
20 TAAGGACTTCTACATCTGCGTGAACGGCAGCTCTGAGAACAAACCAATCCGGAGCAGCTACT
TCACATTTCAACTGCAAAACATCGTGAAGCCCCCTGCCTCCTGTGTATCTGACATTACCAGG
GAAAGCTCCTGCGAGATCAAGCTGAAGTGGTCTATCCCTCTGGGCCCCATTCCCTGCTCGCTG
CTTCGACTACGAGATCGAGATTAGAGAAGATGACACCACCCTGGTGACCGCCACAGTGGAAA
ACGAAACCTATACACTGAAAACCAACCAATGAGACTCGGCAGCTCTGTTTTGTGGTGCGGAGC
25 AAGGTGAATATCTACTGCAGCGACGACGGCATTTGGAGCGAATGGTCCGATAAGCAGTGCTG
GGAAGGCGAGGATCTTTCTAAGAAGACACTGCTGAGA

Human IL2Rb LBD**(SEQ ID NO: 9)**

30 MAAPALSWRLPLLILLPLATSWASAAVNGTSQFTCFYNSRANISCVWSQDQALQDTSCQVH
AWPDRRRWNQTELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVLCREGVRWRVMAIQDF
KPFENLRMAPISLQVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGHTWEEAPLLTL
KQKQEWICLETILTPDTQYEFQVRVKPLQGEFTTWS PWSQPLAFRTKPAALGKDT

Human IL2Rb LBD**(SEQ ID NO: 10)**

ATGGCCGCCCCGCCCCCTGAGCTGGAGGCTGCCCCCTGCTGATCCTGCTGCTGCCCCCTGGCCAC
CAGCTGGGCCAGCGCCGCGCGTGAACGGCACCAGCCAGTTCACCTGCTTCTACAACAGCAGGG
5 CCAACATCAGCTGCGTGTGGAGCCAGGACGGCGCCCTGCAGGACACCAGCTGCCAGGTGCAC
GCCTGGCCCCGACAGGAGGAGGTGGAACCAGACCTGCGAGCTGCTGCCCCGTGAGCCAGGCCAG
CTGGGCCTGCAACCTGATCCTGGGCGCCCCGACAGCCAGAAGCTGACCACCGTGGACATCG
TGACCCTGAGGGTGTGTGTCAGGGAGGGCGTGAGGTGGAGGGTGATGGCCATCCAGGACTTC
AAGCCCTTCGAGAACCTGAGGCTGATGGCCCCCATCAGCCTGCAGGTGGTGCACGTGGAGAC
10 CCACAGGTGCAACATCAGCTGGGAGATCAGCCAGGCCAGCCACTACTTCGAGAGGCACCTGG
AGTTCGAGGCCAGGACCCTGAGCCCCGCCACACCTGGGAGGAGGCCCCCTGCTGACCCTG
AAGCAGAAGCAGGAGTGGATCTGCCTGGAGACCCTGACCCCCGACACCCAGTACGAGTTCCA
GGTGAGGGTGAAGCCCCGTCAGGGCGAGTTCACCACCTGGAGCCCCCTGGAGCCAGCCCCCTGG
CCTTCAGGACCAAGCCCCGCCGCGCTGGGCAAGGACACC

15

Human IL18Ra LBD**(SEQ ID NO: 11)**

MNCRELPLTLWVLISVSTAESCTSRPHITVVEGEPFYLKHCSCSLAHEIETTTKSWYKSSGS
QEHVELNPRSSSRIALHDCVLEFWPVELNDTGSYFFQMKNYTQKWKLNVIRRNKHSCFTRQ
20 VTSKIVEVKFFQITCENSYYQTLVNSTSLYKNCKLLENNKNPTIKKNAEFEDQGYYSVCV
HFLHHNGKLFNITKTFNITIVEDRSNIVPVLGPKLNHVAVELGKNVRLNCSALLNEEDVIY
WMFGEENGSDPNIHEEKEMRIMTPEGKWHASKVLRIENIGESNLNVLYNCTVASTGGTDTKS
FILVRKADMADIPGHVFTR

25 **Human IL18Ra LBD****(SEQ ID NO: 12)**

ATGAACTGCAGGGAGCTGCCCCTGACCCTGTGGGTGCTGATCAGCGTGAGCACCGCCGAGAG
CTGCACCAGCAGGCCCCACATCACCGTGGTGGAGGGCGAGCCCTTCTACCTGAAGCACTGCA
GCTGCAGCCTGGCCCACGAGATCGAGACCACCACCAAGAGCTGGTACAAGAGCAGCGGCAGC
30 CAGGAGCACGTGGAGCTGAACCCCAGGAGCAGCAGCAGGATCGCCCTGCACGACTGCGTGCT
GGAGTTCTGGCCCGTGGAGCTGAACGACACCGGCAGCTACTTCTTCCAGATGAAGAACTACA
CCCAGAAGTGGAAGCTGAACGTGATCAGGAGGAACAAGCACAGCTGCTTCACCGAGAGGCAG
GTGACCAGCAAGATCGTGGAGGTGAAGAAGTTCTTCCAGATCACCTGCGAGAACAGCTACTA
CCAGACCCTGGTGAACAGCACCAGCCTGTACAAGAAGCTGCAAGAAGCTGCTGCTGGAGAACA

ACAAGAACCCACCATCAAGAAGAACGCCGAGTTCGAGGACCAGGGCTACTACAGCTGCGTG
CACTTCCTGCACCACAACGGCAAGCTGTTCAACATCACCAAGACCTTCAACATCACCATCGT
GGAGGACAGGAGCAACATCGTGCCCGTGCTGCTGGGCCCCAAGCTGAACCACGTGGCCGTGG
AGCTGGGCAAGAACGTGAGGCTGAACTGCAGCGCCCTGCTGAACGAGGAGGACGTGATCTAC
5 TGGATGTTTCGGCGAGGAGAACGGCAGCGACCCCAACATCCACGAGGAGAAGGAGATGAGGAT
CATGACCCCCGAGGGCAAGTGGCAGGCCAGCAAGGTGCTGAGGATCGAGAACATCGGCGAGA
GCAACCTGAACGTGCTGTACAACCTGCACCGTGGCCAGCACCGGCGGCACCGACACCAAGAGC
TTCATCCTGGTGAGGAAGGCCGACATGGCCGACATCCCCGGCCACGTGTTTACCAGG

10 Human IL18Rb LBD

(SEQ ID NO: 13)

MLCLGWIFLWLVAGERIKGFNISGCSTKKLLWITYSTRSEEEFVLFCDLPEPQKSHFCHNRNL
SPKQVPEHLPMFGSNDLSDVQWYQQPSNGDPLEDIRKSYPHIIQDKCTLHFLTPGVNNSGSY
ICRPMIKSPYDVACCVKMLEVKPQTNASCEYSASHKQDLLLGSTGSI SCPSLSCQSDAQS
15 PAVTWYKNGKLLSVERSNRIVVDEVYDYHQGT YVC DYTQSDTVSSWTVRAVVQVRTIVGDTK
LKPDIILDPVEDTLEVELGKPLTISCKARFGFERVFNPNVIKWYIKDS DLEWEVSVPEAKSIKS
TLKDEIIERNIILEKVTQRDLRRKFVCFVQNSIGNTTQSVQLKEKR

Human IL18Rb LBD

20 (SEQ ID NO: 14)

ATGCTGTGCCTGGGCTGGATCTTCCTGTGGCTGGTGGCCGGCGAGAGGATCAAGGGCTTCAA
CATCAGCGGCTGCAGCACCAAGAAGCTGCTGTGGACCTACAGCACCGAGGAGCGAGGAGGAGT
TCGTGCTGTTCTGCGACCTGCCCCGAGCCCCAGAAGAGCCACTTCTGCCACAGGAACAGGCTG
AGCCCCAAGCAGGTGCCCCGAGCACCTGCCCTTCATGGGCAGCAACGACCTGAGCGACGTGCA
25 GTGGTACCAGCAGCCCAGCAACGGCGACCCCCCTGGAGGACATCAGGAAGAGCTACCCCCACA
TCATCCAGGACAAGTGCACCTGCACTTCCTGACCCCCGGCGTGAACAACAGCGGCAGCTAC
ATCTGCAGGCCCAAGATGATCAAGAGCCCCCTACGACGTGGCCTGCTGCGTGAAGATGATCCT
GGAGGTGAAGCCCCAGACCAACGCCAGCTGCGAGTACAGCGCCAGCCACAAGCAGGACCTGC
TGCTGGGCAGCACCGGCAGCATCAGCTGCCCCAGCCTGAGCTGCCAGAGCGACGCCAGAGC
30 CCCGCCGTGACCTGGTACAAGAACGGCAAGCTGCTGAGCGTGGAGAGGAGCAACAGGATCGT
GGTGGACGAGGTGTACGACTACCACCAGGGCACCTACGTGTGCGACTACACCCAGAGCGACA
CCGTGAGCAGCTGGACCGT GAGGGCCGTGGTGCAGGTGAGGACCATCGTGGCGACACCAAG
CTGAAGCCCCGACATCCTGGACCCCGTGGAGGACACCCTGGAGGTGGAGCTGGGCAAGCCCCCT
GACCATCAGCTGCAAGGCCAGGTTTCGGCTTCGAGAGGGTGTTC AACCCCGTGATCAAGTGGT

ACATCAAGGACAGCGACCTGGAGTGGGAGGTGAGCGTGCCCGAGGCCAAGAGCATCAAGAGC
 ACCCTGAAGGACGAGATCATCGAGAGGAACATCATCCTGGAGAAGGTGACCCAGAGGGACCT
 GAGGAGGAAGTTCGTGTGCTTCGTGCAGAACAGCATCGGCAACACCACCCAGAGCGTGCAGC
 TGAAGGAGAAGAGG

5

Human IL9Ra (hIL9Ra LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 15)

MGLGRCIWEGWTLSEALRRDMGTWLLACICICTCVCLGVSVTGEGQGPRSRFTTCLTNNIL
 RIDCHWSAPELGQGSSPWLLFTSNQAPGGTHKCILRGSECTVVLPPPEAVLVPDNTFTITFHH
 10 CMSSGREQVSLVDPEYLP RRHV KLDPPSDLQSNISSGHCILTWSISPALPMTTLLSYELAFK
 KQEEAWEQAQHRDHIVGVTWLILEAFELDPGFIHEARLRVQMATLEDDVVEEERYTGQWSEW
 SQPVCFAQPQRQGPLIPPWGWPGNTLVAVSIFLLLTGPTYLLFKLSPRVKRIFYQNVPSAM
 FFQPLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCVQEATALLTCGPAPWKSVALL
 EEEQEGPGTRLPGNLSSDVLPA GCTEWRVQTLAYLPQEDWAPTSLTRPAPPDSEGSRSSSS
 15 SSSSNNNNYCALGCYGGWHL SALPGNTQSSGPI PALACGLSCDHQGLETTQQGVAVVLAGHCQ
 RPGLHEDLQGM LLPSVLSKARSWTF

Human IL9Ra (hIL9Ra LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 16)

20 ATGGGCCTGGGCAGGTGCATCTGGGAGGGCTGGACCCTGGAGAGCGAGGCCCTGAGGAGGGA
 CATGGGCACCTGGCTGCTGGCCTGCATCTGCATCTGCACCTGCGTGTGCCTGGGCGTGAGCG
 TGACCGGCGAGGGCCAGGGCCCCAGGAGCAGGACCTTCACCTGCCTGACCAACAACATCCTG
 AGGATCGACTGCCACTGGAGCGCCCCGAGCTGGGCGAGGGCAGCAGCCCCCTGGCTGCTGTT
 CACCAGCAACCAGGCCCCCGGCGGCACCCACAAGTGCATCCTGAGGGGCAGCGAGTGCACCG
 25 TGGTGCTGCCCCCGAGGCCGTGCTGGTGCCAGCGACAACCTTCACCATCACCTTCCACCAC
 TGCATGAGCGGCAGGGAGCAGGTGAGCCTGGTGACCCCGAGTACCTGCCAGGAGGCACGT
 GAAGCTGGACCCCCCAGCGACCTGCAGAGCAACATCAGCAGCGGCCACTGCATCCTGACCT
 GGAGCATCAGCCCCGCCCTGGAGCCCATGACCACCCTGCTGAGCTACGAGCTGGCCTTCAAG
 AAGCAGGAGGAGGCCTGGGAGCAGGCCCAGCACAGGGACCACATCGTGGGCGTGACCTGGCT
 30 GATCCTGGAGGCCTTCGAGCTGGACCCCGGCTTCATCCACGAGGCCAGGCTGAGGGTGCAGA
 TGGCCACCCTGGAGGACGACGTGGTGAGGAGGAGAGGTACACCGGCCAGTGGAGCGAGTGG
 AGCCAGCCCCTGTGCTTCCAGGCCCCCAGAGGCAGGGCCCCCTGATCCCCCCTGGGGCTG
 GCCCGGCAACACCCTGGTGCCGTGAGCATCTTCCTGCTGCTGACCGGCCACCTACCTGC
 TGTTCAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCAGCCCCGCCATG

TTCTTCCAGCCCCTGTACAGCGTGCACAACGGCAACTTCCAGACCTGGATGGGCGCCACGG
 CGCCGGCGTGTCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTGCG
 TGCAGGAGGCCACCGCCCTGCTGACCTGCGGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTG
 GAGGAGGAGCAGGAGGGCCCCGGCACAGGCTGCCCCGGCAACCTGAGCAGCGAGGACGTGCT
 5 GCCCCCGGCTGCACCGAGTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTGGG
 CCCCCACCAGCCTGACCAGGCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGC
 AGCAGCAGCAGCAACAACAACAATACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAG
 CGCCCTGCCCCGGCAACACCCAGAGCAGCGGCCCATCCCCGCCCTGGCCTGCGGCCTGAGCT
 GCGACCACCAGGGCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAG
 10 AGGCCCGGCTGCACGAGGACCTGCAGGGCATGCTGCTGCCAGCGTGTGAGCAAGGCCAG
 GAGCTGGACCTTC

Human hIL13Ra2-hIL9Ra (hIL13Ra2 LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 17)

15 MAFVCLAIGCLYTFLISTTFGCTSSSDTEIKVNPPQDFEIVDPGYLGYYLQWQPPLSLDHF
 KECTVEYELKYRNIGSETWKTIIITKNLHYKDGFDLNKGIEAKIHTLLPWQCTNGSEVQSSWA
 ETTYWISPQGIPEKTVQDMDCVYYNWQYLLCSWKPGIGVLLDTNYNLFYWYEGLDHALQCVD
 YIKADGQNIQCRFPYLEASDYKDFYICVNGSSSENKPIRSSYFTFQLQNIVKPLPPVYLTFTTR
 ESSCEIKLKWSIPLGPIPARCFDYEIEIREDDTTLVTATVENETYTLKTTNETRQLCFVVR
 20 KVNIIYCSDDGIWSEWSKQCEGEDLSKKTLLRGNTLVAVSI~~FLLLTGPTYLLFKLS~~PRVKR
 IFYQNVPSAMFFQPLYSVHNGNFQTMGAHAGVLLSQDCAGTPQGALEPCVQEATALLTC
 GPARPWKSVALEEEQEGPGTRLPGNLSSDVLPAAGCTEWRVQTLAYLPQEDWAPTSLTRPAP
 PDSEGSRSSSSSSSSNNNNYALGCGYGGWHLALPGNTQSSGPIPALACGLSCDHQGLTQQ
 GVAWVLGHCQRPLHEDLQGMLLPSVLSKARSWTF

25

Human hIL13Ra2-hIL9Ra (hIL13Ra2 LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 18)

ATGGCCTTCGTGTGCCTGGCCATCGGCTGCCTCTACACCTTCCTGATCAGCACAACTTCGG
 CTGCACCAGCAGCAGCGATACCGAGATCAAAGTGAATCCTCCTCAGGACTTCGAGATCGTGG
 30 ACCCCGGATACCTGGGCTACCTGTACCTGCAGTGGCAACCTCCACTGTCTCTGGATCATTTT
 AAGGAATGCACAGTGAATACGAGCTGAAGTACCGGAACATCGGATCCGAGACATGGAAGAC
 CATCATCACCAAGAACCTGCACTACAAGGACGGCTTCGACCTCAACAAGGCATCGAGGCCA
 AGATCCACACCCTGCTGCCTTGGCAGTGTACAAACGGCAGCGAGGTGCAGAGCTCCTGGGCC
 GAGACAACATACTGGATCTCCCCCAGGGCATCCCCGAGACCAAAGTGCAAGATATGGACTG

CGTGTACTACAACCTGGCAGTACCTGCTGTGCAGCTGGAAACCTGGAATCGGCGTGCTGCTGG
 ACACCAACTACAACCTGTTCTACTGGTATGAGGGCCTGGACCACGCCCTGCAGTGCGTCGAC
 TACATCAAGGCCGATGGCCAGAACATCGGCTGCAGATTCCCCTACCTGGAAGCCTCCGATTA
 TAAGGACTTCTACATCTGCGTGAACGGCAGCTCTGAGAACAAACCAATCCGGAGCAGCTACT
 5 TCACATTTCAACTGCAAAACATCGTGAAGCCCCTGCCCTCCTGTGTATCTGACATTCACCAGG
 GAAAGCTCCTGCGAGATCAAGCTGAAGTGGTCTATCCCTCTGGGCCCCATTCTCTGCTCGCTG
 CTTTCGACTACGAGATCGAGATTAGAGAAGATGACACCACCCTGGTGACCGCCACAGTGAAAA
 ACGAAACCTATACACTGAAAACCACCAATGAGACTCGGCAGCTCTGTTTTGTGGTGCGGAGC
 AAGGTGAATATCTACTGCAGCGACGACGGCATTTGGAGCGAATGGTCCGATAAGCAGTGCTG
 10 GGAAGGCGAGGATCTTTCTAAGAAGACACTGCTGAGAGGCAATACCCCTGGTCGCAGTGTCCA
 TCTTTTTGCTGCTGACCGGCCCAACCTACCTGCTGTTTAAGCTGAGCCCTAGAGTGAAAAGA
 ATCTTCTACCAGAACGTGCCTTCTCCAGCCATGTTCTTCCAGCCTCTGTACAGCGTGACAAA
 CGGCAACTTCCAGACCTGGATGGGCGCTCACGGCGCCGGCGTTCTGCTGAGCCAGGATTGCG
 CCGGAACACCTCAAGGCGCTCTGGAACCTTGCGTGCAGGAGGCCACCGCCCTGCTGACCTGT
 15 GGCCCTGCTCGGCCCTGGAAGTCCGTGGCCCTAGAGGAAGAGCAGGAAGGCCCCGGGACCAG
 ACTGCCTGGCAACCTGAGCAGCGAGGACGTGCTGCCTGCCGGATGTACTGAGTGGCGGGTGC
 AGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCTCCAACATCTCTGACCAGACCGGCCCTT
 CCAGACAGCGAAGGCAGCAGATCTAGCAGCAGCAGCAGTTCTTCTAATAACAACAACCTACTG
 TGCCCTCGGCTGTTACGGCGGCTGGCACCTGAGCGCCCTCCCTGGAAATACACAGTCTAGCG
 20 GCCCTATCCCCGCCCTGGCTTGTGGACTGAGCTGCGACCACCAGGGCCTGGAAACACAGCAG
 GCGGTGGCCTGGGTCTGGCCGGCCACTGCCAGAGACCTGGCCTGCACGAGGACCTGCAGGG
 AATGCTGCTGCCAGCGTCTGAGCAAGGCCAGAAGCTGGACCTTT

Human hIL2Rb-hIL9Ra (hIL2Rb LBD – hIL9Ra TM – hIL9Ra ICD)

25 (SEQ ID NO: 19)

MAAPALSWRLPLLILLPLATSWASAAVNGTSQFTCFYNSRANISCVWSQDQALQDTSCQVH
 AWPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVLCREGVRWRVMAIQDF
 KPFENLRMAPISLQVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGHTWEEAPLLTL
 KQKQEWICLETLPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAALGKDTGNTLVAVS
 30 IFLLLTGPTYLLFKLSPRVKRIFYQNVPSPAMFFQPLYSVHNGNFQTMGAHGAGVLLSQDC
 AGTPQGALEPCVQEATALLTCGPAPWKSVALEEEQEGPGTRLPGNLSSSEDLVPAGCTEWRV
 QTLAYLPQEDWAPTSLTRPAPPDSEGSRSSSSSSSSNNNNYCALGCYGGWHLALPGNTQSS
 GPIPALACGLSCDHQGLETTQQGVAWVLAGHCQRPLHEDLQGMLLPSVLSKARSWTF

Human hIL2Rb-hIL9Ra (hIL2Rb LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 20)

ATGGCCGCCCCGCCCCCTGAGCTGGAGGCTGCCCCCTGCTGATCCTGCTGCTGCCCCCTGGCCAC
CAGCTGGGCCAGCGCCCGCCGTGAACGGCACCAGCCAGTTTACCTGCTTCTACAACAGCAGGG
5 CCAACATCAGCTGCGTGTGGAGCCAGGACGGCGCCCTGCAGGACACCAGCTGCCAGGTGCAC
GCCTGGCCCCGACAGGAGGAGGTGGAACCAGACCTGCGAGCTGCTGCCCCGTGAGCCAGGCCAG
CTGGGCCTGCAACCTGATCCTGGGCGCCCCGACAGCCAGAAGCTGACCACCGTGGACATCG
TGACCCTGAGGGTGTGTGTCAGGGAGGGCGTGAGGTGGAGGGTGATGGCCATCCAGGACTTC
AAGCCCTTCGAGAACCTGAGGCTGATGGCCCCCATCAGCCTGCAGGTGGTGCACGTGGAGAC
10 CCACAGGTGCAACATCAGCTGGGAGATCAGCCAGGCCAGCCACTACTTCGAGAGGCACCTGG
AGTTCGAGGCCAGGACCCTGAGCCCCGCCACACCTGGGAGGAGGCCCCCTGCTGACCCTG
AAGCAGAAGCAGGAGTGGATCTGCCTGGAGACCCTGACCCCCGACACCCAGTACGAGTTCCA
GGTGAGGGTGAAGCCCCCTGCAGGGCGAGTTCACCACCTGGAGCCCCCTGGAGCCAGCCCCCTGG
CCTTCAGGACCAAGCCCCGCCGCCCTGGGCAAGGACACCGGCAACACCCTGGTGGCCGTGAGC
15 ATCTTCTGCTGCTGACCGGCCCCACCTACCTGCTGTTCAAGCTGAGCCCCAGGGTGAAGAG
GATCTTCTACCAGAACGTGCCCAGCCCCGCCATGTTCTTCCAGCCCCGTACAGCGTGCACA
ACGGCAACTTCCAGACCTGGATGGGCGCCACGGCGCCGGCGTGCTGCTGAGCCAGGACTGC
GCCGGCACCCCCCAGGGCGCCCTGGAGCCCTGCGTGCAGGAGGCCACCGCCCTGCTGACCTG
CGGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGAGGAGGAGCAGGAGGGCCCCGGCACCA
20 GGCTGCCCCGGCAACCTGAGCAGCGAGGACGTGCTGCCCCGCCGGCTGCACCGAGTGGAGGGTG
CAGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCCCCCACCAGCCTGACCAGGCCCGCCCC
CCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAGCAGCAACAACAACACTACT
GCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCCTGCCCGGCAACACCCAGAGCAGC
GGCCCCATCCCCGCCCTGGCCTGCGGCCTGAGCTGCGACCACCAGGGCCTGGAGACCCAGCA
25 GGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAGGCCCGGCCTGCACGAGGACCTGCAGG
GCATGCTGCTGCCAGCGTGTGAGCAAGGCCAGGAGCTGGACCTTC

Human hIL18Ra-IL9Ra (hIL18Ra LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 21)

30 MNCRELPLTLWVLISVSTAESCTSRPHITVVEGEPFYLKHCSCSLAHEIETTTKSWYKSSGS
QEHVELNPRSSSRIALHDCVLEFWPVELNDTGSYFFQMKNYQKWKLNVIIRRNKHSCFTERQ
VTSKIVEVKFFQITCENSYYQTLVNSTSLYKNCKLLENNKNPTIKKNAEFEDQGYYSKV
HFLHHNGKLFNITKTFTNITIVEDRSNIVPVLGPKLNHVAVELGKNVRLNCSALLNEEDVIY
WMFGEENGSDPNIHEEKEMRIMTPEGKWHASKVLRIENIGESNLNVLYNCTVASTGGTDTKS

FILVRKADMADIPGHVFTRGNTLVAVSIFLLLTGPTYLLFKLSPRVKRIFYQNVPSAMFFQ
 PLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCVQEATALLTCGPAPRWKSVALEEE
 QEGPGTRLPGNLSSDVLPAAGCTEWRVQTLAYLPQEDWAPTSLTRPAPPDSEGSRSSSSSSSS
 SNNNNYCALGCYGGWHLALPGNTQSSGPIPALACGLSCDHQGLETTQQGVAVWLAGHCQRPG
 5 LHEDLQGMMLPSVLSKARSWTF

Human hIL18Ra-IL9Ra (hIL18Ra LBD – hIL9Ra TM – hIL9Ra ICD)

(SEQ ID NO: 22)

ATGAACTGCAGGGAGCTGCCCCTGACCCTGTGGGTGCTGATCAGCGTGAGCACCGCCGAGAG
 10 CTGCACCAGCAGGCCCCACATCACCGTGGTGGAGGGCGAGCCCTTCTACCTGAAGCACTGCA
 GCTGCAGCCTGGCCACGAGATCGAGACCACCACCAAGAGCTGGTACAAGAGCAGCGGCAGC
 CAGGAGCACGTGGAGCTGAACCCAGGAGCAGCAGCAGGATCGCCCTGCACGACTGCGTGCT
 GGAGTTCTGGCCCGTGGAGCTGAACGACACCGGCAGCTACTTCTTCCAGATGAAGAACTACA
 CCCAGAAGTGGAAGCTGAACGTGATCAGGAGGAACAAGCACAGCTGCTTCACCGAGAGGCAG
 15 GTGACCAGCAAGATCGTGGAGGTGAAGAAGTTCTTCCAGATCACCTGCGAGAACAGCTACTA
 CCAGACCCCTGGTGAACAGCACCAGCCTGTACAAGAAGCTGCAAGAAGCTGCTGCTGGAGAACA
 ACAAGAACCCCAACATCAAGAAGAAGCGCCGAGTTTCGAGGACCAGGGCTACTACAGCTGCGTG
 CACTTCTGCAACACAACGGCAAGCTGTTCAACATCACCAAGACCTTCAACATCACCATCGT
 GGAGGACAGGAGCAACATCGTGCCCGTGCTGCTGGGCCCCAAGCTGAACCACGTGGCCGTGG
 20 AGCTGGGCAAGAAGCTGAGGCTGAACTGCAGCGCCCTGCTGAACGAGGAGGACGTGATCTAC
 TGGATGTTTCGGCGAGGAGAACGGCAGCGACCCCAACATCCACGAGGAGAAGGAGATGAGGAT
 CATGACCCCCGAGGGCAAGTGGCAGCCAGCAAGGTGCTGAGGATCGAGAACATCGGCGAGA
 GCAACCTGAACGTGCTGTACAACCTGCACCGTGGCCAGCACCGGCGGCACCGACACCAAGAGC
 TTCATCCTGGTGAGGAAGGCCGACATGGCCGACATCCCCGGCCACGTGTTTACCAGGGGCAA
 25 CACCTGGTGGCCGTGAGCATCTTCTGCTGCTGACCGGCCCCACCTACCTGCTGTTCAAGC
 TGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCAGCCCCGCCATGTTCTTCCAG
 CCCCTGTACAGCGTGCACAACGGCAACTTCCAGACCTGGATGGGCGCCACGGCGCCGGCGT
 GCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTGCGTGCCAGGAGG
 CCACCGCCCTGCTGACCTGCGGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGAGGAGGAG
 30 CAGGAGGGCCCCGGCACCAGGCTGCCCGGCAACCTGAGCAGCGAGGACGTGCTGCCCGCCGG
 CTGCACCGAGTGGAGGGTGCAGACCTGGCCCTACCTGCCCCAGGAGGACTGGGCCCCACCA
 GCCTGACCAGGCCCCCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAGCAGC
 AGCAACAACAACAACCTACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCCTGCC
 CGGCAACACCCAGAGCAGCGGCCCCATCCCCGCCCTGGCCTGCGGCCTGAGCTGCGACCACC

AGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAGGCCCGGC
CTGCACGAGGACCTGCAGGGCATGCTGCTGCCAGCGTGCTGAGCAAGGCCAGGAGCTGGAC
CTTC

5 Human hIL18Rb-IL9Ra (hIL18Rb LBD – hIL9Ra TM – hIL9Ra ICD)
(SEQ ID NO: 23)

MLCLGWIFLWLVAGERIKGFNISGCSTKKLLWTYSTRSEEEFVLFCDLPEPQKSHFCHNRNL
SPKQVPEHLPMFGSNDLSDVQWYQQPSNGDPLEDIRKSYPHIIQDKCTLHFLTPGVNNSGSY
ICRPKMIKSPYDVACCVKMLEVKPQTNASCEYSASHKQDLLLGSTGSI SCPSLSCQSDAQ
10 PAVTWYKNGKLLSVERSNRIVDEVYDYHQGTIVCDYTQSDTVSSWTVRAVVQVRTIVGDTK
LKPDIIDLPVEDTLEVELGKPLTISCKARFGFERVFNPFVIKWKDSDLEWEVSVPEAKSIKS
TLKDEIIERNIILEKVTQRDLRRKFVCFVQNSIGNTTQSVQLKEKRGNTLVAVSI FLLLTG
TYLLFKLSPRVKRIFYQNVPSAMFFQPLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGAL
EPCVQEATALLTCGPAPRWKSVALEEEQEGPGTRLPGNLSSDVLPA GCTEWRVQTLAYLPQ
15 EDWAPTSLTRPAPPDSEGSRSSSSSSSSNNNNYCALGCYGGWHL SALPGNTQSSGPI PALAC
GLSCDHQGLETTQQGVAVVLAGHCQRPLHEDLQGMLLPSVLSKARSWTF

Human hIL18Rb-IL9Ra (hIL18Rb LBD – hIL9Ra TM – hIL9Ra ICD)
(SEQ ID NO: 24)

20 ATGCTGTGCCTGGGCTGGATCTTCCTGTGGCTGGTGGCCGGCGAGAGGATCAAGGGCTTCAA
CATCAGCGGCTGCAGCACCAAGAAGCTGCTGTGGACCTACAGCACCAGGAGCGAGGAGGAGT
TCGTGCTGTTCTGCGACCTGCCCAGCCCCAGAAGAGCCACTTCTGCCACAGGAACAGGCTG
AGCCCCAAGCAGGTGCCCAGCACCTGCCCTTCATGGGCAGCAACGACCTGAGCGACGTGCA
GTGGTACCAGCAGCCCAGCAACGGCGACCCCCCTGGAGGACATCAGGAAGAGCTACCCCCACA
25 TCATCCAGGACAAGTGCACCCTGCACTTCCTGACCCCCGGCGTGAACAACAGCGGCAGCTAC
ATCTGCAGGCCCAAGATGATCAAGAGCCCCCTACGACGTGGCCTGCTGCGTGAAGATGATCCT
GGAGGTGAAGCCCCAGACCAACGCCAGCTGCGAGTACAGCGCCAGCCACAAGCAGGACCTGC
TGCTGGGCAGCACCGGCAGCATCAGCTGCCCCAGCCTGAGCTGCCAGAGCGACGCCAGAGC
CCCCCGTGACCTGGTACAAGAACGGCAAGCTGCTGAGCGTGGAGAGGAGCAACAGGATCGT
30 GGTGGACGAGGTGTACGACTACCACCAGGGCACCTACGTGTGCGACTACACCCAGAGCGACA
CCGTGAGCAGCTGGACCGTGAGGGCCGTGGTGCAGGTGAGGACCATCGTGGGCGACACCAAG
CTGAAGCCCCGACATCCTGGACCCCGTGAGGACACCCTGGAGGTGGAGCTGGGCAAGCCCCCT
GACCATCAGCTGCAAGGCCAGGTTGGGCTTCGAGAGGGTGTTCAACCCCGTGATCAAGTGGT
ACATCAAGGACAGCGACCTGGAGTGGGAGGTGAGCGTGCCCAGGCCAAGAGCATCAAGAGC

ACCCTGAAGGACGAGATCATCGAGAGGAACATCATCCTGGAGAAGGTGACCCAGAGGGACCT
GAGGAGGAAGTTCGTGTGCTTCGTGCAGAACAGCATCGGCAACACCACCCAGAGCGTGCAGC
TGAAGGAGAAGAGGGGCAACACCCTGGTGGCCGTGAGCATCTTCCTGCTGCTGACCGGCCCC
ACCTACCTGCTGTTCAAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCAG
5 CCCCCCATGTTCTTCCAGCCCCGTACAGCGTGCACAACGGCAACTTCCAGACCTGGATGG
GCGCCACGGCGCCGGCGTGCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTG
GAGCCCTGCGTGCAGGAGGCCACCGCCCTGCTGACCTGCGGCCCCGCCAGGCCCTGGAAGAG
CGTGGCCCTGGAGGAGGAGCAGGAGGGCCCCGGCACAGGCTGCCCGGCAACCTGAGCAGCG
AGGACGTGCTGCCCGCCGGCTGCACCGAGTGGAGGGTGCAGACCTGGCCTACCTGCCCCAG
10 GAGGACTGGGCCCCCACCAGCCTGACCAGGCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAG
CAGCAGCAGCAGCAGCAGCAGCAACAACAACAATACTGCGCCCTGGGCTGCTACGGCGGCT
GGCACCTGAGCGCCCTGCCCGGCAACACCAGAGCAGCGGCCCCATCCCCGCCCTGGCCTGC
GGCCTGAGCTGCGACCACCAGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGG
CCACTGCCAGAGGCCCGGCCTGCACGAGGACCTGCAGGGCATGCTGCTGCCAGCGTGCTGA
15 GCAAGGCCAGGAGCTGGACCTTC

Human IL9

(SEQ ID NO: 25)

MLLAMVLTSALLLCSVAGQGCPFLAGILDINFLINKMQEDPASKCHCSANVTSCLCLGIPSD
20 NCTRPCFSERLSQMTNTTMQTRYPLIFSRVKKSVEVLKNNKCPYFSCEQPCNQTTAGNALTF
LKSLLEIFQKEKMRGMRGKI

Human IL9

(SEQ ID NO: 26)

ATGCTGCTGGCCATGGTGCTGACCAGCGCCCTGCTGCTGTGCAGCGTGGCCGGCCAGGGCTG
CCCCACCCTGGCCGGCATCCTGGACATCAACTTCCTGATCAACAAGATGCAGGAGGACCCCG
CCAGCAAGTGCCACTGCAGCGCCAACGTGACCAGCTGCCTGTGCCTGGGCATCCCCAGCGAC
AACTGCACCAGGCCCTGCTTCAGCGAGAGGCTGAGCCAGATGACCAACACCACCATGCAGAC
CAGGTACCCCTGATCTTCAGCAGGGTGAAGAAGAGCGTGGAGGTGCTGAAGAACAACAAGT
30 GCCCCTACTTCAGCTGCGAGCAGCCCTGCAACCAGACCACCGCCGGCAACGCCCTGACCTTC
CTGAAGAGCCTGCTGGAGATCTTCCAGAAGGAGAAGATGAGGGGCATGAGGGGCAAGATC

Human IL13

(SEQ ID NO: 27)

MHPLLNPLLLALGLMALLLTTVIALTCLGGFASPGPVPPSTALRELIEELVNITQNQKAPLC
NGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIE
VAQFVKDLLLLHLKKLFREGRFN

5 Human IL13

(SEQ ID NO: 28)

ATGCACCCCTGCTGAACCCCTGCTGCTGGCCCTGGGCCTGATGGCCCTGCTGCTGACCAC
CGTGATCGCCCTGACCTGCCTGGGCGGCTTCGCCAGCCCCGGCCCCGTGCCCCCAGCACCG
CCCTGAGGGAGCTGATCGAGGAGCTGGTGAACATCACCCAGAACCAGAAGGCCCCCTGTGC
10 AACGGCAGCATGGTGTGGAGCATCAACCTGACCGCCGGCATGTACTGCGCCGCCCTGGAGAG
CCTGATCAACGTGAGCGGCTGCAGCGCCATCGAGAAGACCCAGAGGATGCTGAGCGGCTTCT
GCCCCACAAGGTGAGCGCCGGCCAGTTCAGCAGCCTGCACGTGAGGGACACCAAGATCGAG
GTGGCCCAGTTCGTGAAGGACCTGCTGCTGCACCTGAAGAAGCTGTTTCAGGGAGGGCAGGTT
CAAC

15

Human IL13 TQM

(SEQ ID NO: 29)

MHPLLNPLLLALGLMALLLTTVIALTCLGGFASPGPVPPSTALRKLIEELVNITQNQKAPLC
NGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQDMLDGFCPHKVSAGQFSSLHVRDTKIE
20 VAQFVKDLLLLHLRKLFREGRFN

Human IL13 TQM

(SEQ ID NO: 30)

ATGCACCCCTGCTGAACCCCTGCTGCTGGCCCTCGGCCTGATGGCCCTGCTGCTGACAAC
25 CGTGATCGCCCTGACCTGTCTGGGCGGATTTGCCAGCCCTGGACCTGTGCCACCTAGCACCG
CCCTGAGAAAAGTATTGAGGAACTGGTGAACATCACCCAGAATCAGAAAGCCCCCTCTGTGC
AACGGCAGCATGGTCTGGTCCATCAATCTGACAGCCGGCATGTACTGCGCCGCTCTGGAAAG
CCTGATCAACGTGTCCGGCTGCAGCGCTATCGAGAAGACCCAAGATATGCTGGACGGCTTCT
GCCCCACAAGGTGTCTGCTGGCCAGTTCAGCTCTCTGCACGTGCGGGACACCAAGATCGAG
30 GTGGCCCAGTTCGTGAAGGACCTGCTGCTTCATCTGCGGAAGCTGTTTCAGAGAGGGCAGATT
CAAC

Human IL2

(SEQ ID NO: 31)

MYRMQLLSICIALSLALVTNSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTF
KFYMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM
CEYADETATIVEFLNRWITFCQSIISTLT

5 Human IL2

(SEQ ID NO: 32)

ATGTACAGGATGCAGCTGCTGAGCTGCATCGCCCTGAGCCTGGCCCTGGTGACCAACAGCGC
CCCCACCAGCAGCAGCACCAAGAAGACCCAGCTGCAGCTGGAGCACCTGCTGCTGGACCTGC
AGATGATCCTGAACGGCATCAACAACATAAGAACCCCAAGCTGACCAGGATGCTGACCTTC
10 AAGTTCTACATGCCCAAGAAGGCCACCGAGCTGAAGCACCTGCAGTGCCTGGAGGAGGAGCT
GAAGCCCCCTGGAGGAGGTGCTGAACCTGGCCCAGAGCAAGAACTTCCACCTGAGGCCAGGG
ACCTGATCAGCAACATCAACGTGATCGTGCTGGAGCTGAAGGGCAGCGAGACCACCTTCATG
TGCGAGTACGCCGACGAGACCGCCACCATCGTGGAGTTCCTGAACAGGTGGATCACCTTCTG
CCAGAGCATCATCAGCACCCCTGACC

15

Human IL2 F42A

(SEQ ID NO: 33)

MYRMQLLSICIALSLALVTNSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTA
KFYMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM
20 CEYADETATIVEFLNRWITFCQSIISTLT

Human IL2 F42A

(SEQ ID NO: 34)

ATGTATAGAATGCAGCTGCTGAGCTGCATCGCCCTGTCTCTGGCTCTGGTGACCAACAGCGC
25 CCCTACAAGCAGCTCCACCAAGAAAACCCAGCTGCAGCTCGAGCACCTGCTGCTTGATCTGC
AGATGATCCTGAACGGCATCAACAACATAAGAACCCCAAGCTGACCAGAATGCTGACAGCC
AAGTTCTACATGCCTAAGAAGGCCACCGAGCTGAAGCACCTGCAATGTCTGGAAGAAGAGCT
GAAACCTCTGGAAGAGGTGCTGAATCTGGCCCAGAGCAAGAATTTCCACCTGAGACCACGGG
ACCTGATCAGCAACATCAACGTGATCGTCCTGGAACCTGAAGGGCAGCGAGACAACCTTTATG
30 TGCGAGTACGCCGACGAGACAGCTACCATCGTGGAAATTCCTGAACCGGTGGATCACCTTCTG
CCAGTCCATCATTTCTACACTGACC

Human IL18

(SEQ ID NO: 35)

MAAEPVEDNCINFMVKFIDNTLYFIAEDDENLESDFGKLESKLSVIRNLNDQVLFIDQGN
RPLFEDMTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNP
PDNIKDTKSDIIFQRSVPGHDNKMQFESSYEGYFLACEKERDLFKLILKKEDELGDRSIM
FTVQNE

5

Human IL18**(SEQ ID NO: 36)**

ATGGCCGCCGAGCCCGTGGAGGACAACCTGCATCAACTTCGTGGCCATGAAGTTCATCGACAA
CACCCTGTACTTCATCGCCGAGGACGACGAGAACCTGGAGAGCGACTACTTCGGCAAGCTGG
10 AGAGCAAGCTGAGCGTGATCAGGAACCTGAACGACCAGGTGCTGTTTCATCGACCAGGGCAAC
AGGCCCCGTTCGAGGACATGACCGACAGCGACTGCAGGGACAACGCCCCCAGGACCATCTT
CATCATCAGCATGTACAAGGACAGCCAGCCAGGGGCATGGCCGTGACCATCAGCGTGAAGT
GCGAGAAGATCAGCACCCCTGAGCTGCGAGAACAAGATCATCAGCTTCAAGGAGATGAACCCC
CCCACAACATCAAGGACACCAAGAGCGACATCATCTTCTTCCAGAGGAGCGTGCCCGGCCA
15 CGACAACAAGATGCAGTTCGAGAGCAGCAGCTACGAGGGCTACTTCCTGGCCTGCGAGAAGG
AGAGGGACCTGTTCAAGCTGATCCTGAAGAAGGAGGACGAGCTGGGCGACAGGAGCATCATG
TTCACCGTGCAGAACGAGGAC

Murine IL9Ra ICD20 **(SEQ ID NO: 37)**

KLSPLRLKRIFYQNI PSPEAFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESSIW
EAVATLTYS PACPVQFACLKWEATAPGFPGLP GSEHVL PAGCLELEGQPSAYLPQEDWAPLG
SARPPPPDS DSGSSDYCMLDCCEECHLSAFP GHTE SPELT LAQPVALPVSSRA

25 **Murine IL9Ra ICD****(SEQ ID NO: 38)**

AAGCTGTCACCCAGGCTGAAGAGAATCTTTTACCAGAACATTCATCTCCCAGGCGTTCTT
CCATCCTCTCTACAGTGTGTACCATGGGACTTCCAGAGTTGGACAGGGGCCCGCAGAGCCG
GACCACAAGCAAGACAGAATGGTGTCAGTACTTCATCAGCAGGCTCAGAGTCCAGCATCTGG
30 GAGGCCGTCGCCACACTCACCTATAGCCCGGCATGCCCTGTGCAGTTTGCCTGCCTGAAGTG
GGAGGCCACAGCCCCGGGCTTCCCAGGGCTCCCAGGCTCAGAGCATGTGCTGCCGGCAGGGT
GTCTGGAGTTGGAAGGACAGCCATCTGCCTACCTGCCCCAGGAGGACTGGGCCCCACTGGGC
TCTGCCAGGCCCCCTCCTCCAGACTCAGACAGCGGCAGCAGCGACTATTGCATGTTGGACTG

CTGTGAGGAATGCCACCTCTCAGCCTTCCCAGGACACACCGAGAGTCCTGAGCTCACGCTAG
CTCAGCCTGTGGCCCTTCCTGTGTCCAGCAGGGCC

Murine IL9Ra ICD

5 (SEQ ID NO: 75)

AAGCTGTCACCTCGCCTTAAACGAATCTTCTACCAGAATATCCCGTCGCCTGAGGCTTTCTT
CCACCCTCTCTATAGTGTCTACCACGGAGACTTCCAATCGTGGACTGGTGCAAGGCGGGCCG
GCCCACAAGCCAGGCAAAATGGTGTGTCAACAAGCAGCGCAGGCAGTGAGTCTTCCATCTGG
GAAGCGGTGCGCCACCTTGACTTACAGTCCAGCTTGTCCAGTCCAGTTTGCCTGCCTAAAGTG
10 GGAGGCAACAGCCCCCGGATTCCCCGGTCTGCCCCGGCAGTGAACATGTACTACCTGCAGGAT
GTTTGGAGTTAGAAGGCCAACCTTCAGCATACTTGCCTCAGGAAGACTGGGCTCCACTGGGC
TCTGCTAGACCACCCCTCCAGACTCCGACTCAGGGTCCTCAGACTACTGCATGCTGGACTG
CTGTGAGGAGTGTACCTGAGCGCTTTCCCTGGGCACACTGAATCTCCAGAACTGACTCTGG
CCCAGCCCGTGGCCCTGCCAGTATCAAGCCGAGCC

15

Murine IL9Ra ICD

(SEQ ID NO: 76)

AAGCTGAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCCCGAGGCCTTCTT
CCACCCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCGCCAGGAGGGCCG
20 GCCCCAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAGAGCAGCATCTGG
GAGGCCGTGGCCACCTGACCTACAGCCCCGCTGCCCCGTGCAGTTGCTGCCTGCTGAAGTG
GGAGGCCACCGCCCCCGGCTTCCCCGGCCTGCCCCGGCAGCGAGCACGTGCTGCCCCCGGCT
GCCTGGAGCTGGAGGGCCAGCCCAGCGCTACCTGCCCCAGGAGGACTGGGCCCCCTGGGC
AGCGCCAGGCCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTGCATGCTGGACTG
25 CTGCGAGGAGTGCCACCTGAGCGCTTCCCCGGCCACACCGAGAGCCCCGAGCTGACCCTGG
CCCAGCCCGTGGCCCTGCCCCTGAGCAGCAGGGCC

Murine IL9Ra TM

(SEQ ID NO: 39)

30 ASILVVVPIFLLLTGFVHLLF

Murine IL9Ra TM

(SEQ ID NO: 40)

GCCAGCATCCTTGTAGTTGTGCCCATCTTTCTTCTGCTGACTGGCTTTGTCCACCTTCTGTT
C

Murine IL9Ra TM

5 (SEQ ID NO: 77)

GCTTCAATACTAGTTGTGGTTCCAATCTTTTTACTGTAACTGGTTTTGTCCATCTCCTCTT
C

Murine IL9Ra TM

10 (SEQ ID NO: 78)

GCCAGCATCCTGGTGGTGGTGCCCATCTTCCTGCTGCTGACCGGCTTCGTGCACCTGCTGTT
C

Murine IL9Ra LBD

15 (SEQ ID NO: 41)

MALGRCIAEGWTLERVAVKQVSWFLIYSWVCSGVCRGVSVPEQGGGGQKAGAF TCLSNSIYR
IDCHWSAPELGQESRAWLLEFTSNQVTEIKHKCTFWDSMCTLVLPKEEVFLPFDFNFTITLHRC
IMGQEQVSLVDSQYLPRRHIKLDPPSDLQSNVSSGRCVLTWGINLALEPLITSLSYELAFKR
QEEAWEQARHKDRIVGVTWLILEAVELNPGSIYEARLRVQMTLESYEDKTEGEYYKSHWSEW
20 SQPVSFPSQRRQGLLVPRWQWS

Murine IL9Ra LBD

(SEQ ID NO: 42)

ATGGCCCTGGGAAGATGCATTGCGGAAGGTTGGACCTTGGAGAGAGTGGCGGTGAAACAGGT
25 CTCCTGGTTCCTGATCTACAGCTGGGTCTGCTCTGGAGTCTGCCGGGGAGTCTCGGTCCCAG
AGCAAGGAGGAGGAGGGCAGAAGGCTGGAGCATTCACCTGTCTCAGCAACAGTATTTACAGG
ATCGACTGCCACTGGTCGGCTCCAGAGCTGGGCCAGGAATCCAGGGCCTGGCTCCTCTTTAC
CAGTAACCAGGTGACTGAAATCAAACACAAATGCACCTTCTGGGACAGTATGTGTACCCTGG
TGCTGCCTAAAGAGGAGGTGTTCTTACCTTTTGACAACTTCACCATCACACTTCACCGCTGC
30 ATCATGGGACAGGAACAGGTCAGCCTGGTGGACTCACAGTACCTGCCCAGGAGACACATCAA
GTTGGACCCACCCTCTGATCTGCAGAGCAATGTGAGCTCTGGGCGTTGTGTCTGACCTGGG
GTATCAATCTTGCCCTGGAGCCATTGATCACATCCCTCAGCTACGAGCTGGCCTTCAAGAGG
CAGGAAGAGGCCTGGGAGCAGGCCCGGCACAAGGACCGTATCGTTGGAGTGACCTGGCTCAT
CCTTGAAGCCGTGAACTGAATCCTGGTTCATCTACGAGGCCAGGCTGCGTGTCCAGATGA

CTTTGGAGAGTTATGAGGACAAGACAGAGGGGGAATATTATAAGAGCCATTGGAGTGAGTGG
AGCCAGCCCCGTGTCCTTTCTCTCCCCAGAGGAGACAGGGCCTCCTGGTCCCACGCTGGCA
ATGGTCA

5 Murine IL13Ra2 LBD

(SEQ ID NO: 43)

MAFVHIRCLCFILLCTITGYSLEIKVNPPQDFEILDPLGGLGYLYLQWKPPVIEKFKGCTLE
YELKYRNVDSDSWKTIIITRNLIYKDGFDLNKGIEGKIRTHLSEHCTNGSEVQSPWIEASYGI
SDEGSLETKIQDMKCIYYNWQYLVCSWKPGKTVYSNTNYTMFFWYEGLDHALQCADYLQHDE
10 KNVGCKLSNLDSSDYKDFICVNGSSKLEPIRSSYTVFQLQNIVKPLPPEFLHISVENSIDI
RMKWSTPGGPPIPPRCYTYEIVIREDDISWESATDKNDMKLKRANESDLCCFFVRCKVNIYC
ADDGIWSEWSEEECWEGYTGPDSK

Murine IL13Ra2 LBD

15 (SEQ ID NO: 44)

ATGGCATTGTGCACATTCGCTGCCTGTGTTTCATCTTGCTTTGTACCATCACCGGTTACAG
CCTAGAGATCAAGGTGAACCCCTCCCCAGGACTTTGAAATACTGGACCCTGGGCTGCTTGGCT
ACTTGTACCTCCAGTGGAAACCCCACTGGTGATCGAGAAGTTTAAGGGCTGCACCTTGGAA
TATGAGCTGAAGTACCGTAACGTGGATTAGATAGCTGGAAGACAATCATAACTAGAAACCT
20 CATTTATAAGGACGGGTTTGACCTGAATAAGGGAATAGAAGGAAAAATTAGAACACATCTGT
CCGAGCACTGTACAAATGGAAGTGAAGTTCAGAGTCCCTGGATCGAGGCATCCTATGGCATC
TCCGATGAAGGCTCCTTAGAGACCAAGATCCAGGATATGAAGTGCATTTACTACAACCTGGCA
GTATCTTGTGTGTTTCTGGAAGCCTGGTAAAACAGTTTATAGTGACACCAACTACACCATGT
TCTTCTGGTACGAGGGGCTTGATCATGCGCTCCAGTGCGCCGACTATCTGCAGCATGACGAG
25 AAAAATGTGGGATGCAAGCTTTCTAACCTGGACTCTAGTGATTACAAGGATTTTTTTCATTTG
CGTGAATGGGAGCAGCAAATTAGAGCCCATACGTAGCTCTTATACCGTGTTCAGCTGCAGA
ACATTGTAAAGCCGCTCCCCCGGAATTCCTCCACATTTCTGTGGAGAACAGTATTGATATA
AGGATGAAATGGAGCACACCGGGAGGCCCATCCACCTCGCTGTTACACGTATGAGATCGT
CATTAGGGAGGATGACATCTCCTGGGAGTCTGCCACAGACAAAAATGATATGAAACTCAAGA
30 GACGGGCTAATGAAAGCGAAGATCTGTGCTTTTTTGTTCGGTGTAAAGTCAACATTTATTTGT
GCTGATGATGGAATCTGGTCCGAGTGGTCTGAGGAAGAGTGTGGGAAGGGTATACGGGGCC
CGATTCGAAA

Murine IL2Rb LBD

(SEQ ID NO: 45)

MATIALPWSLSLYVFLLLLATPWASAAVKNC SHLECFYNSRANVSCMWSHEEALNVTTCCHVH
 AKSNLRHWNKTCELTTLVRQASWACNLILGSPESQSLTSVDLLDINVVCWEEKGWRRVKTCD
 FHPFDNLRVLVAPHS LQVLHIDTQRCNISWKVSQVSHYIEPYLEFEARRRLLGHSWEDASVLS
 5 LKQRQQWLFLEMLIPSTSYEVQVRVKAQRNNTGTWSPWSQPLTFRTRPADPMKE

Murine IL2Rb LBD

(SEQ ID NO: 46)

ATGGCCACCATCGCCCTGCCCTGGAGCCTGAGCCTGTACGTGTTCCCTGCTGCTGCTGGCCAC
 10 CCCCTGGGCCAGCGCCGCCGTGAAGAACTGCAGCCACCTGGAGTGCTTCTACAACAGCAGGG
 CCAACGTGAGCTGCATGTGGAGCCACGAGGAGGCCCTGAACGTGACCACCTGCCACGTGCAC
 GCCAAGAGCAACCTGAGGCACTGGAACAAGACCTGCGAGCTGACCCTGGTGAGGCAGGCCAG
 CTGGGCCTGCAACCTGATCCTGGGCAGCTTCCCCGAGAGCCAGAGCCTGACCAGCGTGGACC
 TGCTGGACATCAACGTGGTGTGCTGGGAGGAGAAGGGCTGGAGGAGGGTGAAGACCTGCGAC
 15 TTCCACCCCTTCGACAACCTGAGGCTGGTGGCCCCCACAGCCTGCAGGTGCTGCACATCGA
 CACCCAGAGGTGCAACATCAGCTGGAAGGTGAGCCAGGTGAGCCACTACATCGAGCCCTACC
 TGGAGTTCGAGGCCAGGAGGAGGCTGCTGGGCCACAGCTGGGAGGACGCCAGCGTGCTGAGC
 CTGAAGCAGAGGCAGCAGTGGCTGTTCCCTGGAGATGCTGATCCCCAGCACCAGCTACGAGGT
 GCAGGTGAGGGTGAAGGCCAGAGGAACAACACCGGCACCTGGAGCCCCTGGAGCCAGCCCC
 20 TGACCTTCAGGACCAGGCCCGCCGACCCCATGAAGGAG

Murine IL18Ra LBD

(SEQ ID NO: 47)

MHHEELILTLCILIVKSASKSCIHR SQIHVVEGEPFYLKPCGISAPVHRNETATMRWFKGSA
 25 SHEYRELNNRSSPRVTFHDHTLEFWPVEMEDEGTYISQVGNDRRNWTLNVTKRKNHSCFSDK
 LVTSRDVEVNKSLHITCKNP NYEELIQDTWLYKNCKEISKTPRILKDAEFGDEGYYS CVFSV
 HHNGTRYNITKTVNITVIEGRSKVTPAILGPKCEKVGVELGKDVELNCSASLNKDDL FYWSI
 RKEDSSDPNVQEDRKETTTWIS EGGLEHASKILRFQKITENYLNVLNCTVANEEAIDTKSFV
 LVRKEIPDIPGHVFTG

30

Murine IL18Ra LBD

(SEQ ID NO: 48)

ATGCACCACGAGGAGCTGATCCTGACCCTGTGCATCCTGATCGTGAAGAGCGCCAGCAAGAG
 CTGCATCCACAGGAGCCAGATCCACGTGGTGGAGGGCGAGCCCTTCTACCTGAAGCCCTGCG

GCATCAGCGCCCCGTGCACAGGAACGAGACCGCCACCATGAGGTGGTTCAAGGGCAGCGCC
AGCCACGAGTACAGGGAGCTGAACAACAGGAGCAGCCCCAGGGTGACCTTCCACGACCACAC
CCTGGAGTTCTGGCCCCGTGGAGATGGAGGACGAGGGCACCTACATCAGCCAGGTGGGCAACG
ACAGGAGGAACTGGACCCTGAACGTGACCAAGAGGAACAAGCACAGCTGCTTCAGCGACAAG
5 CTGGTGACCAGCAGGGACGTGGAGGTGAACAAGAGCCTGCACATCACCTGCAAGAACCCCAA
CTACGAGGAGCTGATCCAGGACACCTGGCTGTACAAGAACTGCAAGGAGATCAGCAAGACCC
CCAGGATCCTGAAGGACGCCGAGTTCGGCGACGAGGGCTACTACAGCTGCGTGTTCAGCGTG
CACCACAACGGCACCAGGTACAACATCACCAAGACCGTGAACATCACCGTGATCGAGGGCAG
GAGCAAGGTGACCCCCGCCATCCTGGGCCCCAAGTGCGAGAAGGTGGGCGTGGAGCTGGGCA
10 AGGACGTGGAGCTGAACTGCAGCGCCAGCCTGAACAAGGACGACCTGTTCTACTGGAGCATC
AGGAAGGAGGACAGCAGCGACCCCAACGTGCAGGAGGACAGGAAGGAGACCACCACCTGGAT
CAGCGAGGGCAAGCTGCACGCCAGCAAGATCCTGAGGTTCCAGAAGATCACCGAGAACTACC
TGAACGTGCTGTACAACCTGCACCGTGGCCAACGAGGAGGCCATCGACACCAAGAGCTTCGTG
CTGGTGAGGAAGGAGATCCCCGACATCCCCGGCCACGTGTTACCCGGC

15

Murine IL18Rb LBD**(SEQ ID NO: 49)**

MLCLGWVFLWFVAGEKTTGFNHSACATKKLLWTYSARGAENFVLFCDLQELQEQKFSSHASQL
SPTQSPAHPKPCSGSQKDLSDVQWYMQPRSGSPLEEISRNSPHMQSEGMLHILAPQTNSIWSY
20 ICRPRIIRSPQDMACCIKTVLEVQPKQRNVSCGNTAQDEQVLLLGSTGSIHCPSLSCQSDVQSP
EMTWYKDGRLPLEHKKNPIEMADIYVFNQGLYVCDYTQSDNVSSWTVRAVVKVRTIGKDINV
KPEILDPIITDLDVELGKPLTLPCRQVQFGFQRLSKPVIKQYVKESTQEWEMSVFEEKRIQST
FKNEVIERTIFLREVTQRDLRSKFVCFQAQNSIGNTTTRTIRLRKKEE

25 Murine IL18Rb LBD**(SEQ ID NO: 50)**

ATGCTGTGCCTGGGCTGGGTGTTCCCTGTGGTTCGTGGCCGGCGAGAAGACCACCGGCTTCAA
CCACAGCGCCTGCGCCACCAAGAAGCTGCTGTGGACCTACAGCGCCAGGGGCGCCGAGAAGT
TCGTGCTGTTCTGCGACCTGCAGGAGCTGCAGGAGCAGAAGTTCAGCCACGCCAGCCAGCTG
30 AGCCCCACCCAGAGCCCCGCCACAAGCCCTGCAGCGGCAGCCAGAAGGACCTGAGCGACGT
GCAGTGGTACATGCAGCCAGGAGCGGCAGCCCCCTGGAGGAGATCAGCAGGAACAGCCCCC
ACATGCAGAGCGAGGGCATGCTGCACATCCTGGCCCCCAGACCAACAGCATCTGGAGCTAC
ATCTGCAGGCCCAGGATCAGGAGCCCCAGGACATGGCCTGCTGCATCAAGACCGTGCTGGA
GGTGAAGCCCCAGAGGAACGTGAGCTGCGGCAACACCGCCCAGGACGAGCAGGTGCTGCTGC

TGGGCAGCACCGGCAGCATCCACTGCCCCAGCCTGAGCTGCCAGAGCGACGTGCAGAGCCCC
 GAGATGACCTGGTACAAGGACGGCAGGCTGCTGCCCCGAGCACAAGAAGAACCCCATCGAGAT
 GGCCGACATCTACGTGTTCAACCAGGGCCTGTACGTGTGCGACTACACCCAGAGCGACAACG
 TGAGCAGCTGGACCGTGAGGGCCGTGGTGAAGGTGAGGACCATCGGCAAGGACATCAACGTG
 5 AAGCCCGAGATCCTGGACCCCATCACCGACACCCTGGACGTGGAGCTGGGCAAGCCCCCTGAC
 CCTGCCCTGCAGGGTGCAGTTCGGCTTCCAGAGGCTGAGCAAGCCCGTGATCAAGTGGTACG
 TGAAGGAGAGCACCCAGGAGTGGGAGATGAGCGTGTTTCGAGGAGAAGAGGATCCAGAGCACC
 TTCAAGAACGAGGTGATCGAGAGGACCATCTTCCTGAGGGAGGTGACCCAGAGGGACCTGAG
 CAGGAAGTTCGTGTGCTTCGCCCAGAACAGCATCGGCAACACCACCAGGACCATCAGGCTGA
 10 GGAAGAAGGAGGAG

Murine IL9Ra (mIL9Ra LBD – mIL9Ra TM – mIL9Ra ICD)

(SEQ ID NO: 51)

MALGRCIAEGWTLERVAVKQVSWFLIYSWVCSGVCRCVSVPEQGGGGQKAGAFITCLSNSIYR
 15 IDCHWSAPELGQESRAWLLEFTSNQVTEIKHKCTFWDSMCTLVLPKEEVFLPFDFNFTITLHRC
 IMGQEQVSLVDSQYLPRRHILKLDPPSDLQSNVSSGRCVLTWGINLALALEPLITSLSYELAFKR
 QEEAWEQARHKDRIVGVTWLILEAVELNPGSIYEALRVQMTLESYEDKTEGEYKSHWSEW
 SQPVSFPSPQRRQGLLVPRWQWSASILVVPIFLLLTGFVHLLFKLSPLKRIIFYQNIPSP
 AFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESIWEAVATLTYS PACPVQFAC
 20 LKWEATAPGFPGLPGSEHVLPAGCLELEGQPSAYLPQEDWAPLGSARPPPPDSGSSDYCM
 LDCCEECHLSAFPGHTEPELTLAQPVLPVSSRA

Murine IL9Ra (mIL9Ra LBD – mIL9Ra TM – mIL9Ra ICD)

(SEQ ID NO: 52)

25 ATGGCCCTGGGAAGATGCATTGCGGAAGGTTGGACCTTGGAGAGAGTGGCGGTGAAACAGGT
 CTCCTGGTTCCTGATCTACAGCTGGGTCTGCTCTGGAGTCTGCCGGGGAGTCTCGGTCCCAG
 AGCAAGGAGGAGGAGGGCAGAAGGCTGGAGCATTCACCTGTCTCAGCAACAGTATTTACAGG
 ATCGACTGCCACTGGTCGGCTCCAGAGCTGGGCCAGGAATCCAGGGCCTGGCTCCTCTTTAC
 CAGTAACCAGGTGACTGAAATCAAACACAAATGCACCTTCTGGGACAGTATGTGTACCCTGG
 30 TGCTGCCTAAAGAGGAGGTGTTCTTACCTTTTGACAACTTCACCATCACACTTCACCGCTGC
 ATCATGGGACAGGAACAGGTCAGCCTGGTGGACTCACAGTACCTGCCAGGAGACACATCAA
 GTTGGACCCACCCTCTGATCTGCAGAGCAATGTGAGCTCTGGGCGTTGTGTCTGACCTGGG
 GTATCAATCTTGCCCTGGAGCCATTGATCACATCCCTCAGCTACGAGCTGGCCTTCAAGAGG
 CAGGAAGAGGCCTGGGAGCAGGCCCGGCACAAGGACCGTATCGTTGGAGTGACCTGGCTCAT

CCTTGAAGCCGTCGAACTGAATCCTGGTTCCATCTACGAGGCCAGGCTGCGTGTCCAGATGA
 CTTTGGAGAGTTATGAGGACAAGACAGAGGGGAATATTATAAGAGCCATTGGAGTGAGTGG
 AGCCAGCCCGTGTCTTTCTCTCCCCAGAGGAGACAGGGCCTCCTGGTCCCACGCTGGCA
 ATGGTCAGCCAGCATCCTTGTAGTTGTGCCCATCTTTCTTCTGCTGACTGGCTTTGTCCACC
 5 TTCTGTTCAAGCTGTCAACCAGGCTGAAGAGAATCTTTTACCAGAACATTCCATCTCCCAG
 GCGTTCTTCCATCCTCTCTACAGTGTGTACCATGGGGACTTCCAGAGTTGGACAGGGGCCCC
 CAGAGCCGGACCACAAGCAAGACAGAATGGTGTGAGTACTTCATCAGCAGGCTCAGAGTCCA
 GCATCTGGGAGGCCGTCGCCACACTCACCTATAGCCCGGCATGCCCTGTGCAGTTTGCCTGC
 CTGAAGTGGGAGGCCACAGCCCCGGGCTTCCCAGGGCTCCCAGGCTCAGAGCATGTGCTGCC
 10 GGCAGGGTGTCTGGAGTTGGAAGGACAGCCATCTGCCTACCTGCCCCAGGAGGACTGGGCCC
 CACTGGGCTCTGCCAGGCCCCCTCCTCCAGACTCAGACAGCGGCAGCAGCGACTATTGCATG
 TTGGACTGCTGTGAGGAATGCCACCTCTCAGCCTTCCCAGGACACACCGAGAGTCCTGAGCT
 CACGCTAGCTCAGCCTGTGGCCCTTCTGTGTCCAGCAGGGCC

15 Murine mL13Ra2-mL9Ra (mL13Rb LBD – mL9Ra TM – mL9Ra ICD)

(SEQ ID NO: 53)

MAFVHIRCLCFILLCTITGYSLEIKVNPPQDFEILDPLLGYLYLQWKPPVIEKFKGCTLE
 YELKYRNVDSDSWKTIITRNLIYKDGFDLNGIEGKIRTHLSEHCTNGSEVQSPWIEASYGI
 SDEGSLETKIQDMKCIYYNWQYLVCWSWKPGKTVYSDTNYTMFFWYEGLDHALQCADYLQHDE
 20 KNVGCKLSNLDSSDYKDFICVNGSSKLEPIRSSYTVFQLQNIVKPLPPEFLHISVENSIDI
 RMKWSTPGGPIPPRCYTYEIVIREDDISWESATDKNDMKLKRRANESEDLCCFFVRCKVNIYC
 ADDGIWSEWSEEECWEGYTGPDSKASILVVVPIFLLLTGFVHLLFKLSPLRKIRIFYQNI P S P
 EAFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESSIWEAVATLTYS PACPVQFA
 CLKWEATAPGFPLPGSEHVLPA GCLELEGQPSAYLPQEDWAPLGSARPPPPDS DSGSSDYC
 25 MLDCCEECHLSAFPGHTE S PELTLAQPVALPVSSRA

Murine mL13Ra2-mL9Ra (mL13Rb LBD – mL9Ra TM – mL9Ra ICD)

(SEQ ID NO: 54)

ATGGCATTTGTGCACATTTCGCTGCCTGTGTTTCATCTTGCTTTGTACCATCACCGGTTACAG
 30 CCTAGAGATCAAGGTGAACCCCTCCCCAGGACTTTGAAATACTGGACCCCTGGGCTGCTTGGCT
 ACTTGTACCTCCAGTGAAACCCCACTGGTGATCGAGAAGTTTAAGGGCTGCACCTTGGAA
 TATGAGCTGAAGTACCGTAACGTGGATT CAGATAGCTGGAAGACAATCATAACTAGAAACCT
 CATTTATAAGGACGGGTTTGACCTGAATAAGGGAATAGAAGGAAAAATTAGAACACATCTGT
 CCGAGCACTGTACAAATGGAAGTGAAGTTCAGAGTCCCTGGATCGAGGCATCCTATGGCATC

TCCGATGAAGGCTCCTTAGAGACCAAGATCCAGGATATGAAGTGCATTTACTACAACCTGGCA
 GTATCTTGTGTGTTCCCTGGAAGCCTGGTAAAACAGTTTATAGTGACACCAACTACACCATGT
 TCTTCTGGTACGAGGGGCTTGATCATGCGCTCCAGTGCGCCGACTATCTGCAGCATGACGAG
 AAAAATGTGGGATGCAAGCTTTCTAACCTGGACTCTAGTGATTACAAGGATTTTTTTCATTTG
 5 CGTGAATGGGAGCAGCAAATTAGAGCCCATACGTAGCTCTTATACCGTGTTCAGCTGCAGA
 ACATTGTAAAGCCGCTCCCCCGGAATTCCTCCACATTTCTGTGGAGAACAGTATTGATATA
 AGGATGAAATGGAGCACACCGGGAGGCCCCATCCACCTCGCTGTTACACGTATGAGATCGT
 CATTAGGGAGGATGACATCTCCTGGGAGTCTGCCACAGACAAAAATGATATGAAACTCAAGA
 GACGGGCTAATGAAAGCGAAGATCTGTGCTTTTTTGTTCGGTGTAAGTCAACATTTATGT
 10 GCTGATGATGGAATCTGGTCCGAGTGGTCTGAGGAAGAGTGTGGGAAGGGTATACGGGGCC
CGATTCGAAAGCTTCAATACTAGTTGTGGTTCCAATCTTTTTACTGTAACTGGTTTTGTCC
ATCTCCTCTTCAAGCTGTCACCTCGCCTTAAACGAATCTTCTACCAGAATATCCCGTCGCT
 GAGGCTTTTCTTCCACCTCTCTATAGTGTCTACCACGGAGACTTCCAATCGTGGACTGGTGC
 AAGGCGGGCCGGCCACAAGCCAGGCAAATGGTGTGTCAACAAGCAGCGCAGGCAGTGAGT
 15 CTTCCATCTGGGAAGCGTCTGCCACCTTGACTTACAGTCCAGCTTGTCCAGTCCAGTTTGCC
 TGCCTAAAGTGGGAGGCAACAGCCCCCGGATTCCCCGGTCTGCCCCGAGTGAACATGTACT
 ACCTGCAGGATGTTTGGAGTTAGAAGGCCAACCTTCAGCATACTTGCCCTCAGGAAGACTGGG
 CTCCACTGGGCTCTGCTAGACCACCCCCTCCAGACTCCGACTCAGGGTCTCAGACTACTGC
 ATGCTGGACTGCTGTGAGGAGTGTACCTGAGCGCTTCCCTGGGCACACTGAATCTCCAGA
 20 ACTGACTCTGGCCCAGCCCGTGGCCCTGCCAGTATCAAGCCGAGCC

Murine mL2Rb-mL9Ra (mL2Rb LBD – mL9Ra TM – mL9Ra ICD)

(SEQ ID NO: 55)

MATIALPWSLSLYVFLLLLATPWASAAVKNCSHLECFYNSRANVSCMWSHEEALNVTTCVH
 25 AKSNLRHWNKTCELTIVRQASWACNLILGSFPESQSLTSVDLLDINVVCWEEKGWRRVKTCD
 FHPFDNLRIVAPHSLOVLHIDTQRCNISWKVSQVSHYIEPYLEFEARRRLGHWSWEDASVLS
 LKQRQQWLFLEMLIPSTSYEVQVRVKAQRNNTGTWSPWSQPLTFRTRPADPMKEASILVVVP
IFLLLTGFFVHLLFKLSPRLKRIFYQNIPSPEAFFHPLYSVYHGDFQSWTGARRAGPQARQNG
 VSTSSAGSESSIWEAVATLTYS PACPVQFACLKWEATAPGFPLPGSEHVLPA GCLELEGQP
 30 SAYLPQEDWAPLGSARPPPPDSGSSDYCMLDCCEECHLSAFPGHTEPELT LAQPVALPV
 SSRA

Murine IL2Rb-mL9Ra (mL2Rb LBD – mL9Ra TM – mL9Ra ICD)

(SEQ ID NO: 56)

ATGGCCACCATCGCCCTGCCCTGGAGCCTGAGCCTGTACGTGTTCCCTGCTGCTGCTGGCCAC
 CCCCTGGGCCAGCGCCGCGCTGAAGAACTGCAGCCACCTGGAGTGCTTCTACAACAGCAGGG
 CCAACGTGAGCTGCATGTGGAGCCACGAGGAGGCCCTGAACGTGACCACCTGCCACGTGCAC
 GCCAAGAGCAACCTGAGGCACTGGAACAAGACCTGCGAGCTGACCCTGGTGAGGCAGGCCAG
 5 CTGGGCCTGCAACCTGATCCTGGGCAGCTTCCCCGAGAGCCAGAGCCTGACCAGCGTGGACC
 TGCTGGACATCAACGTGGTGTGCTGGGAGGAGAAGGGCTGGAGGAGGGTGAAGACCTGCGAC
 TTCCACCCCTTCGACAACCTGAGGCTGGTGGCCCCCACAGCCTGCAGGTGCTGCACATCGA
 CACCCAGAGGTGCAACATCAGCTGGAAGGTGAGCCAGGTGAGCCACTACATCGAGCCCTACC
 TGGAGTTCGAGGCCAGGAGGAGGCTGCTGGGCCACAGCTGGGAGGACGCCAGCGTGCTGAGC
 10 CTGAAGCAGAGGCAGCAGTGGCTGTTCCCTGGAGATGCTGATCCCCAGCACCAGCTACGAGGT
 GCAGGTGAGGGTGAAGGCCAGAGGAACAACACCGGCACCTGGAGCCCCCTGGAGCCAGCCCC
 TGACCTTCAGGACCAGGCCCGCCGACCCCATGAAGGAGGCCAGCATCCTGGTGGTGGTGCCC
ATCTTCTGCTGCTGACCGGCTTCGTGCACCTGCTGTTCAAGCTGAGCCCCAGGCTGAAGAG
GATCTTCTACCAGAACATCCCCAGCCCCGAGGCCTTCTTCCACCCCTGTACAGCGTGTACC
 15 ACGGCGACTTCCAGAGCTGGACCGGCGCCAGGAGGGCCGGCCCCCAGGCCAGGCAGAACGGC
 GTGAGCACCAGCAGCGCCGGCAGCGAGAGCAGCATCTGGGAGGCCGTGGCCACCCTGACCTA
 CAGCCCCGCTGCCCCGTGCAGTTCGCCTGCCTGAAGTGGGAGGCCACCGCCCCGGCTTCC
 CCGGCCTGCCCCGGCAGCGAGCACGTGCTGCCCCCGGCTGCCTGGAGCTGGAGGGCCAGCCC
 AGCGCCTACCTGCCCCAGGAGGACTGGGCCCCCCTGGGCAGCGCCAGGCCCCCCCCCCCCGA
 20 CAGCGACAGCGGCAGCAGCGACTACTGCATGCTGGACTGCTGCGAGGAGTGCCACCTGAGCG
 CCTTCCCCGGCCACACCGAGAGCCCCGAGCTGACCCTGGCCCAGCCCGTGGCCCTGCCCCGTG
 AGCAGCAGGGCC

Murine mL18Ra-mL9Ra (mL18Ra LBD – mL9Ra TM – mL9Ra ICD)

25 (SEQ ID NO: 57)

MHHEELIILTLCLIVKSASKSCIHRSQIHVVEGEPFYLKPCGISAPVHRNETATMRWFKGSA
 SHEYRELNNRSSPRVTFHDHTLEFWPVEMEDEGTYISQVGNDRRNWTLNVTKRKNHSCFSDK
 LVTSRDVEVNKSLHITCKNPNYEELIQDTWLYKNCKEISKTPRILKDAEFGDEGYSCVFSV
 HHNGTRYNITKTVNITVIEGRSKVTPAILGPKCEKVGVELGKDVELNCSASLNKDDL FYWS I
 30 RKEDSSDPNVQEDRKETTTWISEGKLHASKILRFQKITENYLNVLNCTVANEEAIDTKSFV
LVRKEIPDIPGHVFTGASILVVVPIFLLLTGFVHLLFKLS PRLKRI FYQNI PSPEAFFHPLY
 SVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESSIWEAVATLTYS PACPVQFACLKWEATA
 PGFPLPGSEHVLPAGCLELEGQPSAYLPQEDWAPLGSARPPPPDS DSGSSDYCMLDCCEECEC
 HLSAFPGHTE SPELTLAQPVALPVSSRA

Murine mL18Ra-mL9Ra (mL18Ra LBD – mL9Ra TM – mL9Ra ICD)

(SEQ ID NO: 58)

ATGCACCACGAGGAGCTGATCCTGACCCTGTGCATCCTGATCGTGAAGAGCGCCAGCAAGAG
5 CTGCATCCACAGGAGCCAGATCCACGTGGTGGAGGGCGAGCCCTTCTACCTGAAGCCCTGCG
GCATCAGCGCCCCCGTGCACAGGAACGAGACCGCCACCATGAGGTGGTTC AAGGGCAGCGCC
AGCCACGAGTACAGGGAGCTGAACAACAGGAGCAGCCCCAGGGTGACCTTCCACGACCACAC
CCTGGAGTTCTGGCCCGTGGAGATGGAGGACGAGGGCACCTACATCAGCCAGGTGGGCAACG
ACAGGAGGAACCTGGACCCTGAACGTGACCAAGAGGAACAAGCACAGCTGCTTCAGCGACAAG
10 CTGGTGACCAGCAGGGACGTGGAGGTGAACAAGAGCCTGCACATCACCTGCAAGAACCCCAA
CTACGAGGAGCTGATCCAGGACACCTGGCTGTACAAGAAGTCAAGGAGATCAGCAAGACCC
CCAGGATCCTGAAGGACGCCGAGTTCGGCGACGAGGGCTACTACAGCTGCGTGTTCAGCGTG
CACCACAACGGCACCAGGTACAACATCACCAAGACCGTGAACATCACCGTGATCGAGGGCAG
GAGCAAGGTGACCCCCGCCATCCTGGGCCCCAAGTGCGAGAAGGTGGGCGTGGAGCTGGGCA
15 AGGACGTGGAGCTGAACTGCAGCGCCAGCCTGAACAAGGACGACCTGTTCTACTGGAGCATC
AGGAAGGAGGACAGCAGCGACCCCAACGTGCAGGAGGACAGGAAGGAGACCACCACCTGGAT
CAGCGAGGGCAAGCTGCACGCCAGCAAGATCCTGAGGTTCCAGAAGATCACCGAGAAGTACC
TGAACGTGCTGTACAACCTGCACCGTGGCCAACGAGGAGGCCATCGACACCAAGAGCTTCGTG
CTGGTGAGGAAGGAGATCCCCGACATCCCCGGCCACGTGTTACCGGCGCCAGCATCCTGGT
20 GGTGGTGCCCATCTTCTGCTGCTGACCGGCTTCGTGCACCTGCTGTTCAAGCTGAGCCCCA
GGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCCCGAGGCCTTCTTCCACCCCTGTAC
AGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCGCCAGGAGGGCCGCCCCCAGGCCAG
GCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAGAGCAGCATCTGGGAGGCCGTGGCCA
CCCTGACCTACAGCCCCGCCTGCCCCGTGCAGTTCGCCTGCCTGAAGTGGGAGGCCACCGCC
25 CCCGGCTTCCCCGGCCTGCCCCGCGAGCAGCACGTGCTGCCCCCGGCTGCCTGGAGCTGGA
GGGCCAGCCCAGCGCCTACCTGCCCCAGGAGGACTGGGCCCCCTGGGCAGCGCCAGGCCCC
CCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTGCATGCTGGACTGCTGCGAGGAGTGC
CACCTGAGCGCCTTCCCCGGCCACACCGAGAGCCCCGAGCTGACCTGGCCCAGCCCGTGGC
CCTGCCCCGTGAGCAGCAGGGCC

30

Murine mL18Rb-mL9Ra (mL18Rb LBD – mL9Ra TM – mL9Ra ICD)

(SEQ ID NO: 59)

MLCLGWVFLWFVAGEKTTGFNHSACATKLLWITYSARGAENFVLFCDLQELQE QKFSHASQL
SPTQSPAHPKPCSGSQKDLSDVQWYMQPRSGSPLEEISRNSPHMQSEGMLHILAPQTNSIWSY

ICRPRI RSPQDMACCIKTVLEV K PQ RNVSCGNTAQDEQVLLLGSTGSIHCPSLSCQSDVQSP
 EMTWYKDGRL LPEHKKNPIEMADIYVFNQGLYVCDYTQSDNVSSWTVRAVVKVRTIGKDINV
 KPEILDPI TD TLDVELGKPLTLPCR VQFGFQRLSKPVIK WYVKESTQEWEMSVFEEKRIQST
 FKNEVIERTI FLREVTQRDL SRKFVCFAQNSIGNTTRTIRLRKKEEASILVVVPIFLLLTGF
 5 VHLLFKLSPRLKRIFYQNIPSPEAFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGS
 ESSIWEAVATLTYS PACPVQFACLKWEATAPGFPLPGSEHVLPA GCLELEGQPSAYLPQED
 WAPLG SARPPPPDS DSGSSDYCMLDCCEECHLSAFPGHTE SPELT LAQPVALPVSSRA

Murine mL18Rb-mL9Ra (mL18Rb LBD – mL9Ra TM – mL9Ra ICD)

10 (SEQ ID NO: 60)

ATGCTGTGCCTGGGCTGGGTGTTCCCTGTGGTTCGTGGCCGGCGAGAAGACCACCGGCTTCAA
 CCACAGCGCCTGCGCCACCAAGAAGCTGCTGTGGACCTACAGCGCCAGGGGCGCCGAGAAGT
 TCGTGCTGTTCTGCGACCTGCAGGAGCTGCAGGAGCAGAAGTTCAGCCACGCCAGCCAGCTG
 AGCCCCACCCAGAGCCCCGCCCACAAGCCCTGCAGCGGCAGCCAGAAGGACCTGAGCGACGT
 15 GCAGTGGTACATGCAGCCCAGGAGCGGCAGCCCCCTGGAGGAGATCAGCAGGAACAGCCCCC
 ACATGCAGAGCGAGGGCATGCTGCACATCCTGGCCCCCAGACCAACAGCATCTGGAGCTAC
 ATCTGCAGGCCCAGGATCAGGAGCCCCAGGACATGGCCTGCTGCATCAAGACCGTGCTGGA
 GGTGAAGCCCCAGAGGAACGTGAGCTGCGGCAACACCGCCCAGGACGAGCAGGTGCTGCTGC
 TGGGCAGCACCGGCAGCATCCACTGCCCCAGCCTGAGCTGCCAGAGCGACGTGCAGAGCCCC
 20 GAGATGACCTGGTACAAGGACGGCAGGCTGCTGCCCCAGCACAAGAAGAACCCCATCGAGAT
 GGCCGACATCTACGTGTTCAACCAGGGCCTGTACGTGTGCGACTACACCCAGAGCGACAACG
 TGAGCAGCTGGACCGTGAGGGCCGTGGTGAAGGTGAGGACCATCGGCAAGGACATCAACGTG
 AAGCCCGAGATCCTGGACCCCATCACCGACACCCCTGGACGTGGAGCTGGGCAAGCCCCTGAC
 CCTGCCCTGCAGGGTGCAAGTTCGGCTTCCAGAGGCTGAGCAAGCCCGTGATCAAGTGGTACG
 25 TGAAGGAGAGCACCAGGAGTGGGAGATGAGCGTGTTCGAGGAGAAGAGGATCCAGAGCACC
 TTCAAGAACGAGGTGATCGAGAGGACCATCTTCCTGAGGGAGGTGACCCAGAGGGACCTGAG
 CAGGAAGTTCGTGTGCTTCGCCCAGAACAGCATCGGCAACACCACCAGGACCATCAGGCTGA
 GGAAGAAGGAGGAGGCCAGCATCCTGGTGGTGGTGCCCATCTTCCTGCTGCTGACCGGCTTC
GTGCACCTGCTGTTCAAGCTGAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAG
 30 CCCCAGAGCCTTCTTCCACCCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCG
 GCGCCAGGAGGGCCGGCCCCCAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGC
 GAGAGCAGCATCTGGGAGGCCGTGGCCACCCTGACCTACAGCCCCGCCCTGCCCCGTGCAGTT
 CGCCTGCCCTGAAGTGGGAGGCCACCGCCCCGGCTTCCCCGGCCTGCCCGGCAGCGAGCACG
 TGCTGCCCCGCCGGCTGCCTGGAGCTGGAGGGCCAGCCCAGCGCCTACCTGCCCCAGGAGGAC

TGGGCCCCCTGGGCAGCGCCAGGCCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTA
CTGCATGCTGGACTGCTGCGAGGAGTGCCACCTGAGCGCCTTCCCCGGCCACACCGAGAGCC
CCGAGCTGACCCTGGCCCAGCCCGTGGCCCTGCCCCTGAGCAGCAGGGCC

5 Murine IL9

(SEQ ID NO: 61)

MLVTYILASVLLFSSVLGQRCSTTWGIRDNYLIENLKDDPPSKSCSGNVTSCLCLSVPTD
DCTTPCYREGLLQLTNATQKSRLLPVFHRVKRIVEVLKNITCPSFSCEKPCNQTMAGNTLSF
LKSLLGTFQKTEMQRQKSRP

10

Murine IL9

(SEQ ID NO: 62)

ATGCTGGTGACCTACATCCTGGCCAGCGTGCTGCTGTTTACGACAGCGTGCTGGGCCAGAGGTG
CAGCACCACTGGGGCATCAGGGACACCAACTACCTGATCGAGAACCTGAAGGACGACCCCC
15 CCAGCAAGTGCAGCTGCAGCGGCAACGTGACCAGCTGCCTGTGCCTGAGCGTGCCACCGAC
GACTGCACCACCCCCTGCTACAGGGAGGGCCTGCTGCAGCTGACCAACGCCACCCAGAAGAG
CAGGCTGCTGCCCCTGTTCCACAGGGTGAAGAGGATCGTGGAGGTGCTGAAGAACATCACCT
GCCCCAGCTTCAGCTGCGAGAAGCCCTGCAACCAGACCATGGCCGGCAACACCCTGAGCTTC
CTGAAGAGCCTGCTGGGCACCTTCCAGAAGACCGAGATGCAGAGGCAGAAGAGCAGGCCC

20

Murine IL13

(SEQ ID NO: 63)

MALWVTAVLALACLGGLAAPGPVPRSVSLPLTLKELIEELSINITQDQTPLCNGSMVWSVDLA
AGGFCVALDSLNIISNCNAIYRTQRILHGLCNRKAPTTVSSLPDTKIEVAHFITKLLSYTKQ
25 LFRHGPF

Murine IL13

(SEQ ID NO: 64)

ATGGCCCTGTGGGTGACCGCCGTGCTGGCCCTGGCCTGCCTGGGCGGCCTGGCCGCCCCCGG
30 CCCCCTGCCCAGGAGCGTGAGCCTGCCCCTGACCCTGAAGGAGCTGATCGAGGAGCTGAGCA
ACATCACCCAGGACCAGACCCCCCTGTGCAACGGCAGCATGGTGTGGAGCGTGGACCTGGCC
GCCGGCGGCTTCTGCGTGGCCCTGGACAGCCTGACCAACATCAGCAACTGCAACGCCATCTA
CAGGACCCAGAGGATCCTGCACGGCCTGTGCAACAGGAAGGCCCCCACCACCGTGAGCAGCC

TGCCCCGACACCAAGATCGAGGTGGCCCACTTCATCACCAAGCTGCTGAGCTACACCAAGCAG
CTGTTTCAGGCACGGCCCCCTTC

P2A Linker(SEQ ID NO: 65)

5 ATNFSLLKQAGDVEENPGP

P2A Linker(SEQ ID NO: 66)

CGAGTGCGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACGTGGAGGAGAACCC

10 **Murine IL2**

(SEQ ID NO: 67)

MYSMQLASCVTLTILVLLVNSAPTSSSTSSSTAEEAQQQQQQQQQQHLEQLLMDLQELLSRM
ENYRNLKLPRLTTFKFYLPKQATELKDLCLEDELGPLRHVLDLTQSKSFQLEDAENFISNI
RVTVVKLKGSDNTFECQFDDDESATVVDLRRWIAFCQSIISTSPQ

15

Murine IL2

(SEQ ID NO: 68)

ATGTACAGCATGCAGCTGGCCAGCTGCGTGACCCTGACCCTGGTGCTGCTGGTGAACAGCGC
CCCCACCAGCAGCAGCACCAGCAGCAGCACCAGCGAGGCCAGCAGCAGCAGCAGCAGCAGC
20 AGCAGCAGCAGCAGCACCTGGAGCAGCTGCTGATGGACCTGCAGGAGCTGCTGAGCAGGATG
GAGAACTACAGGAACCTGAAGCTGCCCAGGATGCTGACCTTCAAGTTCTACCTGCCCCAAGCA
GGCCACCAGCTGAAGGACCTGCAGTGCCCTGGAGGACGAGCTGGGCCCCCTGAGGCACGTGC
TGGACCTGACCCAGAGCAAGAGCTTCCAGCTGGAGGACGCCGAGAACTTCATCAGCAACATC
AGGGTGACCGTGGTGAAGCTGAAGGGCAGCGACAACACCTTCGAGTGCCAGTTTCGACGACGA
25 GAGCGCCACCGTGGTGGACTTCCTGAGGAGGTGGATCGCCTTCTGCCAGAGCATCATCAGCA
CCAGCCCCCAG

Flexible Linker(SEQ ID NO: 69)

GGGSGGGSGGGSGGGSG

30

Flexible Linker(SEQ ID NO: 70)

GGCCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGG

Murine IL18

(SEQ ID NO: 71)

MAAMSEDSVCNFKEMMFIDNTLYFIPEENGDLSDNFGRLHCTTAVIRNINDQVLFVDKRQP
VFEDMTDIDQSASEPQTRLIIYMYKDSEVRGLAVTSLVKDSKMSTLSCKNKIISFEEMDPPE
NIDDIQSDLIFFQKRVPGHNKMEFESSLYEGHFLACQKEDDAFKLILKKKDENGDKSVMTL
5 TNLHQS

Murine IL18

(SEQ ID NO: 72)

ATGGCCGCCATGAGCGAGGACAGCTGCGTGAACCTCAAGGAGATGATGTTTCATCGACAACAC
10 CCTGTACTTCATCCCCGAGGAGAACGGCGACCTGGAGAGCGACAACCTTCGGCAGGCTGCACT
GCACCACCGCCGTGATCAGGAACATCAACGACCAGGTGCTGTTTCGTGGACAAGAGGCAGCCC
GTGTTTCGAGGACATGACCGACATCGACCAGAGCGCCAGCGAGCCCCAGACCAGGCTGATCAT
CTACATGTACAAGGACAGCGAGGTGAGGGGCTGGCCGTGACCCGTGAGCGTGAAGGACAGCA
AGATGAGCACCCCTGAGCTGCAAGAACAAGATCATCAGCTTCGAGGAGATGGACCCCCCGAG
15 AACATCGACGACATCCAGAGCGACCTGATCTTCTTCCAGAAGAGGGTGCCCGGCCACAACAA
GATGGAGTTCGAGAGCAGCCTGTACGAGGGCCACTTCCCTGGCCTGCCAGAAGGAGGACGACG
CCTTCAAGCTGATCCTGAAGAAGAAGGACGAGAACGGCGACAAGAGCGTGATGTTACCCCTG
ACCAACCTGCACCAGAGC

20 In some embodiments, an immune cell is engineered to expressed an IL-9Ra and a
CAR. In some embodiments, the IL9Ra is human IL9Ra. In some embodiments, the
intracellular signaling domain (ICD) of human IL9Ra comprises an amino acid sequence
havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at
25 least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
at least 100% sequence identity to SEQ ID NO: 1. As understood in the art, the genetic code
is degenerate and any nucleotide sequence which encodes an amino acid sequence having at
least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at
least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at
30 least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
100% sequence identity to SEQ ID NO: 1 may be used to encode the ICD of human IL9Ra.
In some embodiments, the ICD of human IL9Ra is encoded by a nucleic acid comprising a
nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at

least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 2 or SEQ ID NO:

73. In some embodiments, the ICD of human IL9Ra comprises SEQ ID NO: 1. In some
 5 embodiments, the ICD of human IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 2 or SEQ ID NO: 73.

- In some embodiments, an immune cell is engineered to expressed an IL-9Ra and a CAR. In some embodiments, the IL9Ra is human IL9Ra. In some embodiments, the transmembrane domain (TM) of human IL9Ra comprises an amino acid sequence havng at
 10 least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 3. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at
 15 least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 3 may be used to encode the TM of human IL9Ra. In some embodiments, the TM of human IL9Ra is encoded by a nucleic acid comprising a
 20 nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 4 or SEQ ID NO:
 74. In some embodiments, the TM of human IL9Ra comprises SEQ ID NO: 3. In some
 25 embodiments, the TM of human IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 4 or SEQ ID NO: 74.

- In some embodiments, an immune cell is engineered to expressed an IL-9Ra and a CAR. In some embodiments, the IL9Ra is human IL9Ra. In some embodiments, the ligand binding domain (LBD) of human IL9Ra comprises an amino acid sequence havng at least
 30 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 5. As understood in the art, the genetic code is degenerate

and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 5 may be used to encode the LBD of human IL9Ra. In some embodiments, the LBD of human IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 6. In some embodiments, the LBD of human IL9Ra comprises SEQ ID NO: 5. In some embodiments, the LBD of human IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 6.

In some embodiments, the IL13Ra2 is human IL13Ra2. In some embodiments, the ligand binding domain (LBD) of human IL13Ra2 comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 7. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 7 may be used to encode the LBD of human IL13Ra2. In some embodiments, the LBD of human IL13Ra2 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 8. In some embodiments, the LBD of human IL13Ra2 comprises SEQ ID NO: 7. In some embodiments, the LBD of human IL13Ra2 is encoded by a nucleic acid comprising SEQ ID NO: 8.

In some embodiments, the IL2Rb is human IL2Rb. In some embodiments, the ligand binding domain (LBD) of human IL2Rb comprises an amino acid sequence havng at least

80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 9. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 9 may be used to encode the LBD of human IL2Rb. In some embodiments, the LBD of human IL2Rb is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 10. In some embodiments, the LBD of human IL2Rb comprises SEQ ID NO: 9. In some embodiments, the LBD of human IL2Rb is encoded by a nucleic acid comprising SEQ ID NO: 10.

In some embodiments, the IL18Ra is human IL18Ra. In some embodiments, the ligand binding domain (LBD) of human IL18Ra comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 11. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 11 may be used to encode the LBD of human IL18Ra. In some embodiments, the LBD of human IL18Ra is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 12. In some embodiments, the LBD of human IL18Ra comprises SEQ ID NO: 11. In some

embodiments, the LBD of human IL18Ra is encoded by a nucleic acid comprising SEQ ID NO: 12.

In some embodiments, the IL18Rb is human IL18Rb. In some embodiments, the ligand binding domain (LBD) of human IL18Rb comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 13. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 13 may be used to encode the LBD of human IL18Rb. In some embodiments, the LBD of human IL18Rb is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 14. In some embodiments, the LBD of human IL18Rb comprises SEQ ID NO: 13. In some embodiments, the LBD of human IL18Rb is encoded by a nucleic acid comprising SEQ ID NO: 14.

In some embodiments, an immune cell is engineered to express a CAR and a human IL9Ra, wherein the human IL9Ra comprises a human IL9Ra LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the human IL9Ra comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 15. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 15 may be used to encode the

human IL9Ra. In some embodiments, the human IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 16. In some embodiments, the human IL9Ra comprises SEQ ID NO: 15. In some embodiments, the human IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 16.

In some embodiments, the chimeric cytokine receptor comprises a human IL13Ra2 LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 17. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 17 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 18. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 17. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 18.

In some embodiments, the chimeric cytokine receptor comprises a human IL2Rb LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

- to SEQ ID NO: 19. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 19 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 20. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 19. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 20.
- 15 In some embodiments, the chimeric cytokine receptor comprises a human IL18Ra LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 21. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 21 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 22. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 21. In some

embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 22.

In some embodiments, the chimeric cytokine receptor comprises a human IL18Rb LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 23. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 23 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 24. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 23. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 24.

In some embodiments, the IL9 is human IL9. In some embodiments, the human IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 25. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 25 may be used to encode the human IL9. In some embodiments, the human IL9 is encoded by a nucleic acid

comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 26.

- 5 In some embodiments, the human IL9 comprises SEQ ID NO: 25. In some embodiments, the human IL9 is encoded by a nucleic acid comprising SEQ ID NO: 26.

In some embodiments, the IL13 is human IL13. In some embodiments, the human IL13 comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 27.

As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 27 may be used to encode the human IL13. In some embodiments, the human IL13 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 28. In some embodiments, the human IL13 comprises SEQ ID NO: 27. In some embodiments, the human IL13 is encoded by a nucleic acid comprising SEQ ID NO: 28.

In some embodiments, the IL13 is human IL13-TQM. Human IL13-TQM is a IL13 variant comprising four point mutations (E13K, R66D, S69D, and K105R) that improve its binding affinity to the IL-13R α 2 receptor (Kd ~ 5 nM), while decreasing affinity to the IL-13 receptor α 1 subunit. In some embodiments, the human IL13-TQM comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least

85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29 may be used to encode the human IL13-TQM. In some embodiments, the human IL13-TQM is encoded by a nucleic acid

5 comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 30.

In some embodiments, the human IL13-TQM comprises SEQ ID NO: 29. In some
10 embodiments, the human IL13-TQM is encoded by a nucleic acid comprising SEQ ID NO:
30

In some embodiments, the IL2 is human IL2. In some embodiments, the human IL2 comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least
15 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 31. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
20 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 31 may be used to encode the human IL2. In some embodiments, the human IL2 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at
25 least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 32.

In some embodiments, the human IL2 comprises SEQ ID NO: 31. In some embodiments, the human IL2 is encoded by a nucleic acid comprising SEQ ID NO: 32.

In some embodiments, the IL2 is human IL2. In some embodiments, the IL2 is human
30 IL2 F42A. In some embodiments, the human IL2 F42A comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or

at least 100% sequence identity to SEQ ID NO: 33. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 33 may be used to encode the human IL2 F42A. In some embodiments, the human IL2 F42A is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 34. In some embodiments, the human IL2 F42A comprises SEQ ID NO: 33. In some embodiments, the human IL2 F42A is encoded by a nucleic acid comprising SEQ ID NO: 34.

In some embodiments, the IL18 is human IL18. In some embodiments, the human IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 35. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 35 may be used to encode the human IL18. In some embodiments, the human IL18 is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 36. In some embodiments, the human IL18 comprises SEQ ID NO: 35. In some embodiments, the human IL18 is encoded by a nucleic acid comprising SEQ ID NO: 36.

In some embodiments, an immune cell is engineered to express an IL-9Ra and a CAR. In some embodiments, the IL9Ra is murine IL9Ra. In some embodiments, the intracellular signaling domain (ICD) of murine IL9Ra comprises an amino acid sequence

- havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 37. As understood in the art, the genetic code
- 5 is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 37 may be used to encode the ICD of murine IL9Ra.
- 10 In some embodiments, the ICD of murine IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 38, SEQ ID NO:
- 15 75, or SEQ ID NO: 76. In some embodiments, the ICD of murine IL9Ra comprises SEQ ID NO: 37. In some embodiments, the ICD of murine IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 38, SEQ ID NO: 75, or SEQ ID NO: 76.

- In some embodiments, an immune cell is engineered to expressed an IL-9Ra and a CAR. In some embodiments, the IL9Ra is murine IL9Ra. In some embodiments, the
- 20 transmembrane domain (TM) of murine IL9Ra comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 39. As understood in the art, the genetic code is
- 25 degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 39 may be used to encode the TM of murine IL9Ra.
- 30 In some embodiments, the TM of murine IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 40, SEQ ID NO: 77, or SEQ ID NO: 78. In some embodiments, the TM of murine IL9Ra comprises SEQ ID NO: 39. In some embodiments, the TM of murine IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 40, SEQ ID NO: 77, or SEQ ID NO: 78.

5 In some embodiments, an immune cell is engineered to expressed an IL-9Ra and a CAR. In some embodiments, the IL9Ra is murine IL9Ra. In some embodiments, the ligand binding domain (LBD) of murine IL9Ra comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 41. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 41 may be used to encode the LBD of murine IL9Ra. In some 15 embodiments, the LBD of murine IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 42. In some 20 embodiments, the LBD of murine IL9Ra comprises SEQ ID NO: 41. In some embodiments, the LBD of murine IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 42.

In some embodiments, the IL13Ra2 is murine IL13Ra2. In some embodiments, the 25 ligand binding domain (LBD) of murine IL13Ra2 comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 43. As understood in the art, the genetic code is 30 degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least

- 100% sequence identity to SEQ ID NO: 43 may be used to encode the LBD of murine IL13Ra2. In some embodiments, the LBD of murine IL13Ra2 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 44. In some embodiments, the LBD of murine IL13Ra2 comprises SEQ ID NO: 43. In some embodiments, the LBD of murine IL13Ra2 is encoded by a nucleic acid comprising SEQ ID NO: 44.
- 10 In some embodiments, the IL2Rb is murine IL2Rb. In some embodiments, the ligand binding domain (LBD) of murine IL2Rb comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100%
- 15 sequence identity to SEQ ID NO: 45. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence
- 20 identity to SEQ ID NO: 45 may be used to encode the LBD of murine IL2Rb. In some embodiments, the LBD of murine IL2Rb is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at
- 25 least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 46. In some embodiments, the LBD of murine IL2Rb comprises SEQ ID NO: 45. In some embodiments, the LBD of murine IL2Rb is encoded by a nucleic acid comprising SEQ ID NO: 46.
- In some embodiments, the IL18Ra is murine IL18Ra. In some embodiments, the ligand binding domain (LBD) of murine IL18Ra comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 47. As understood in the art, the genetic code is

- degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
- 5 100% sequence identity to SEQ ID NO: 47 may be used to encode the LBD of murine IL18Ra. In some embodiments, the LBD of murine IL18Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 48.
- 10 In some embodiments, the LBD of murine IL18Ra comprises SEQ ID NO: 47. In some embodiments, the LBD of murine IL18Ra is encoded by a nucleic acid comprising SEQ ID NO: 48.
- In some embodiments, the IL18Rb is murine IL18Rb. In some embodiments, the
- 15 ligand binding domain (LBD) of murine IL18Rb comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 49. As understood in the art, the genetic code is
- 20 degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 49 may be used to encode the LBD of murine
- 25 IL18Rb. In some embodiments, the LBD of murine IL18Rb is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 50.
- 30 In some embodiments, the LBD of murine IL18Rb comprises SEQ ID NO: 49. In some embodiments, the LBD of murine IL18Rb is encoded by a nucleic acid comprising SEQ ID NO: 50.

In some embodiments, an immune cell is engineered to express a CAR and a murine IL9Ra, wherein the murine IL9Ra comprises a murine IL9Ra LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the murine IL9Ra comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 51. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 51 may be used to encode the murine IL9Ra. In some embodiments, the murine IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 52. In some embodiments, the murine IL9Ra comprises SEQ ID NO: 51. In some embodiments, the murine IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 52.

In some embodiments, the chimeric cytokine receptor comprises a murine IL13Ra2 LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 53. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 53 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at

least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 54. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 53. In some
5 embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 54.

 In some embodiments, the chimeric cytokine receptor comprises a murine IL2Rb LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least
10 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 55. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least
15 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 55 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a
20 nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 56. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 55. In some
25 embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 56.

 In some embodiments, the chimeric cytokine receptor comprises a murine IL18Ra LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least
30 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 57. As understood in the art, the genetic code is degenerate and any

nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 57 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 58. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 57. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 58.

In some embodiments, the chimeric cytokine receptor comprises a murine IL18Rb LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 59. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 59 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 60. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 59. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 60.

In some embodiments, the IL9 is murine IL9. In some embodiments, the murine IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 61. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 61 may be used to encode the murine IL9. In some embodiments, the murine IL9 is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 62. In some embodiments, the murine IL9 comprises SEQ ID NO: 61. In some embodiments, the murine IL9 is encoded by a nucleic acid comprising SEQ ID NO: 62.

In some embodiments, the IL13 is murine IL13. In some embodiments, the murine IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 63. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 63 may be used to encode the murine IL13. In some embodiments, the murine IL13 is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID

NO: 64. In some embodiments, the murine IL13 comprises SEQ ID NO: 63. In some embodiments, the murine IL13 is encoded by a nucleic acid comprising SEQ ID NO: 64.

In some embodiments, the IL2 is murine IL2. In some embodiments, the murine IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 67. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 67 may be used to encode the murine IL2. In some embodiments, the murine IL2 is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 68. In some embodiments, the murine IL2 comprises SEQ ID NO: 67. In some embodiments, the murine IL2 is encoded by a nucleic acid comprising SEQ ID NO: 68.

In some embodiments, the IL18 is murine IL18. In some embodiments, the murine IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 71. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 71 may be used to encode the murine IL18. In some embodiments, the murine IL18 is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 71.

96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 72. In some embodiments, the murine IL18 comprises SEQ ID NO: 71. In some embodiments, the murine IL18 is encoded by a nucleic acid comprising SEQ ID NO: 72.

In some embodiments, the IL9Ra or the chimeric cytokine receptor described herein is co-expressed on an immune cell (*e.g.*, a T cell) with any CAR targeting a tumor antigen, such as any of the CARs described herein.

The IL9Ra and the chimeric cytokine receptors of the invention enable IL9 signaling in an immune cell expressing a CAR. In some embodiments, the chimeric cytokine receptor of the invention is a switch receptor which switches the signal from the binding of a ligand to the ligand binding domain (LBD) to the immunostimulatory signal transduced by the intracellular signaling domain (ICD) of the IL9Ra. The ligand which binds to the LBD is a cytokine which is delivered intratumorally (*e.g.*, intratumoral injection) via an adenoviral vector. In some embodiments, the adenoviral vector is a serotype 5 adenoviral vector. In some embodiments, the adenoviral vector is an oncolytic adenoviral vector.

In some embodiments, an immune cell expresses a CAR and a human IL9Ra comprising a human IL9Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL9.

In some embodiments, the chimeric cytokine receptor comprises a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13.

In some embodiments, the chimeric cytokine receptor comprises a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL2.

In some embodiments, the chimeric cytokine receptor comprises a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18.

In some embodiments, the chimeric cytokine receptor comprises a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18.

In some embodiments, an immune cell expresses a CAR and a murine IL9Ra comprising a murine IL9Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL9.

In some embodiments, the chimeric cytokine receptor comprises a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL13.

5 In some embodiments, the chimeric cytokine receptor comprises a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2.

In some embodiments, the chimeric cytokine receptor comprises a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.

10 In some embodiments, the chimeric cytokine receptor comprises a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.

In some embodiments, a cytokine of the present disclosure is encoded by a nucleic acid sequence which is comprised within an oncolytic adenoviral vector such as a
15 conditionally replicating oncolytic adenoviral vector. One example of a conditionally replicating oncolytic adenoviral vector includes a serotype 5 adenoviral vector (Ad5) with modifications to the early genes E1A and E3 to enable cancer cell –specific replication and transgene expression, respectively. E1A is modified by deleting 24 base pairs of DNA from the CR2 region (aka D24 variant) to yield a virus capable of selectively replicating in cancer
20 cells harboring p16-Rb pathway mutations. The cytokine transgene may be placed in the E3 region. Furthermore, the virus capsid is modified to include a chimeric 5/3 fiber which enables improved transduction efficiency of tumor cells.

The present invention provides a chimeric cytokine receptor comprising an extracellular domain comprising a ligand binding domain (LBD) of an inhibitory
25 immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a transmembrane domain (TM), and an intracellular domain (ICD) comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra). In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II
30 (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4

(CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a PD1, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TGFbRI, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TGFbRII, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TIGIT, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TIM3, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-CTLA4 antigen binding domain, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-PD1 antigen binding domain, a transmembrane domain, and an intracellular signaling domain of an IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-PD-L1 antigen binding domain, a transmembrane domain, and an intracellular signaling domain of an IL9Ra.

The anti-checkpoint inhibitor antigen binding domain of the chimeric cytokine receptor can include any domain that binds to the checkpoint inhibitor and may include, but is not limited to, a monoclonal antibody (mAb), a polyclonal antibody, a synthetic antibody, a human antibody, a humanized antibody, a non-human antibody, a single-domain antibody, a full length antibody or any antigen-binding fragment thereof, a Fab, and a single-chain variable fragment (scFv). In some embodiments, the antigen binding domain comprises an aglycosylated antibody or a fragment thereof or scFv thereof. In some embodiments, the antigen binding domain is an scFv.

In some embodiments, the anti-checkpoint inhibitor antigen binding domain of the chimeric cytokine receptor comprises a light chain and a heavy chain, wherein the light chain comprises three light chain complementarity determining regions (LCDR1, LCDR2, and

LCDR3) and the heavy chain comprises three heavy chain complementarity determining regions (HCDR1, CDR2, and HCDR3). In some embodiments, the heavy chain lacks a CH3 region. In some embodiments, the light chain is encoded by a first nucleotide sequence and the heavy chain is encoded by a second nucleotide sequence. In some embodiments, the first
5 nucleotide sequence and the second nucleotide sequence are linked by a nucleotide sequence encoding a 2A self-cleaving peptide, such as a P2A sequence.

As used herein, the term “single-chain variable fragment” or “scFv” is a fusion protein of the variable regions of the heavy (VH) and light (VL) chains of an immunoglobulin (e.g., murine or human) covalently linked to form a VH:VL heterodimer.
10 The variable heavy (VH) and light (VL) chains are either joined directly or joined by a peptide linker, which connects the N-terminus of the VH with the C-terminus of the VL, or the C-terminus of the VH with the N-terminus of the VL. In some embodiments, the antigen binding domain (*e.g.*, tumor antigen binding domain) comprises an scFv having the configuration from N-terminus to C-terminus, VH – linker – VL. In some embodiments, the
15 antigen binding domain comprises an scFv having the configuration from N-terminus to C-terminus, VL – linker – VH or VH – linker – VL. Those of skill in the art would be able to select the appropriate configuration for use in the present invention.

The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility. The linker can link the heavy chain variable region and the light chain variable
20 region of the extracellular antigen-binding domain. Non-limiting examples of linkers are disclosed in Shen et al., Anal. Chem. 80(6):1910-1917 (2008) and WO 2014/087010, the contents of which are hereby incorporated by reference in their entireties. Various linker sequences are known in the art, including, without limitation, glycine serine (GS) linkers. Those of skill in the art would be able to select the appropriate linker sequence for use in the
25 present invention. In one embodiment, an antigen binding domain of the present invention comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL are separated by a linker sequence.

Despite removal of the constant regions and the introduction of a linker, scFv proteins retain the specificity of the original immunoglobulin. Single chain Fv polypeptide antibodies
30 can be expressed from a nucleic acid comprising VH- and VL-encoding sequences as described by Huston, et al. (Proc. Nat. Acad. Sci. USA, 85:5879-5883, 1988). See, also, U.S. Patent Nos. 5,091,513, 5,132,405 and 4,956,778; and U.S. Patent Publication Nos. 20050196754 and 20050196754. Antagonistic scFvs having inhibitory activity have been

described (see, e.g., Zhao et al., *Hybridoma (Larchmt)* 2008 27(6):455-51; Peter et al., *J Cachexia Sarcopenia Muscle* 2012 August 12; Shieh et al., *J Immunol* 2009 183(4):2277-85; Giomarelli et al., *Thromb Haemost* 2007 97(6):955-63; Fife et al., *J Clin Invest* 2006 116(8):2252-61; Brocks et al., *Immunotechnology* 1997 3(3):173-84; Moosmayer et al., *Ther Immunol* 1995 2(10):31-40). Agonistic scFvs having stimulatory activity have been described (see, e.g., Peter et al., *J Biol Chem* 2003 278(38):36740-7; Xie et al., *Nat Biotech* 1997 15(8):768-71; Ledbetter et al., *Crit Rev Immunol* 1997 17(5-6):427-55; Ho et al., *Biochim Biophys Acta* 2003 1638(3):257-66).

As used herein, “Fab” refers to a fragment of an antibody structure that binds to an antigen but is monovalent and does not have a Fc portion, for example, an antibody digested by the enzyme papain yields two Fab fragments and an Fc fragment (e.g., a heavy (H) chain constant region; Fc region that does not bind to an antigen).

As used herein, “F(ab')₂” refers to an antibody fragment generated by pepsin digestion of whole IgG antibodies, wherein this fragment has two antigen binding (ab') (bivalent) regions, wherein each (ab') region comprises two separate amino acid chains, a part of a H chain and a light (L) chain linked by an S—S bond for binding an antigen and where the remaining H chain portions are linked together. A “F(ab')₂” fragment can be split into two individual Fab' fragments.

In other embodiments, the antigen binding domain comprises an antibody mimetic protein such as, for example, designed ankyrin repeat protein (DARPin), affibody, monobody, (i.e., adnectin), affilin, affimer, affitin, alphabody, avimer, Kunitz domain peptide, or anticalin. Constructs with specific binding affinities can be generated using DPAPin libraries e.g., as described in Seeger, et al., *Protein Sci.*, 22:1239-1257 (2013).

In some embodiments, the antigen binding domain may be derived from the same species in which the CAR will ultimately be used. For example, for use in humans, the antigen binding domain of the CAR may comprise a human antibody or a fragment thereof. In some embodiments, the antigen binding domain may be derived from a different species in which the CAR will ultimately be used. For example, for use in humans, the antigen binding domain of the CAR may comprise a murine antibody or a fragment thereof, or a humanized murine antibody or a fragment thereof.

In certain embodiments, the antigen binding domain comprises a heavy chain variable region that comprises three heavy chain complementarity determining regions (HCDRs) and

a light chain variable region that comprises three light chain complementarity determining regions (LCDRs). In certain embodiments, the antigen binding domain comprises a linker.

In some embodiments, the anti-checkpoint inhibitor antigen binding domain binds CTLA4 and is derived from ipilimumab. In some embodiments, the anti-checkpoint inhibitor antigen binding domain binds PD1 and is derived from nivolumab, pembrolizumab, or cemiplimab. In some embodiments, the anti-checkpoint inhibitor antigen binding domain binds PD-L1 and is derived from atezolizumab, avelumab, or durvalumab.

The transmembrane domain (TM) of the chimeric cytokine receptor may be derived from the inhibitory immunoreceptor or from the IL9Ra, or may comprise any other suitable transmembrane domain. In various embodiments, the transmembrane domain is derived from the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a PD1, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TGFbRI, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TGFbRII, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TIGIT, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TIM3, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-CTLA4 antigen binding domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-PD1 antigen binding domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra. In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-PD-L1 antigen binding

domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a PD1, a transmembrane domain, and an intracellular signaling domain of an IL9Ra, and the ligand binding domain binds
5 Programmed Death Ligand 1 (PD-L1). PD-1 is a ligand expressed by tumor cells, including, but not limited to, tumor cells from non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, and triple-negative
10 breast cancer.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TGFbRI or a TGFbRII, a transmembrane domain, and an intracellular signaling domain of an IL9Ra, and the ligand binding domain binds Transforming Growth Factor-beta (TGF-beta). TGF-beta is a ligand expressed by
15 tumor cells, including, but not limited to, tumor cells from breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, lung cancer, kidney cancer, pancreas cancer, prostate cancer, brain cancer, and melanoma.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TIGIT, a transmembrane domain, and an intracellular signaling domain of an IL9Ra, and the ligand binding domain binds, and the
20 ligand binding domain binds CD155. CD155 is a ligand expressed by tumor cells, including, but not limited to, tumor cells from colon cancer, lung adenocarcinoma, melanoma, pancreatic cancer, glioblastoma, and hepatocellular carcinoma.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising a ligand-binding domain of a TIM3, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra, and the ligand binding domain binds Galectin-9. Galectin-9 is a ligand expressed by tumor cells, including, but not limited
25 to, tumor cells from breast cancer, gallbladder cancer, colon cancer, cervical squamous cell carcinoma, and hepatocellular carcinoma.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-CTLA4 antigen binding domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra, and the anti-CTLA4 antigen
30

binding domain binds CTLA4. CTLA4 is a checkpoint inhibitor expressed on the surface of T cells.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-PD1 antigen binding domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra, and the anti-PD1 antigen binding domain binds PD1. PD1 is a checkpoint inhibitor expressed on the surface of T cells.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-PD-L1 antigen binding domain, a transmembrane domain of an IL9Ra, and an intracellular signaling domain of the IL9Ra, and the anti-PD-L1 antigen binding domain binds PD-L1. PD-L1 is a checkpoint inhibitor expressed on the surface of T cells.

The chimeric cytokine receptor of the present invention may also comprise a leader sequence, a hinge domain, and/or one or more spacers or linker sequences as described herein which serve to link one domain of the chimeric cytokine receptor to the next domain. The chimeric cytokine receptor may also comprise a tag (*e.g.*, a chemical tag or a biological tag) or may be fused to another protein (*e.g.*, a fluorescent protein such as GFP). Such tags may be present, *e.g.*, at the N-terminus or the C-terminus, or may be incorporated between two domains of the chimeric cytokine receptor. Techniques for post-transcriptional site selective tagging of polypeptides are also well-known in the art. One of skill in the art would be able to select such sequences and tags as appropriate to include in the chimeric cytokine receptor of the invention.

Amino acid and nucleotide sequences for certain embodiments of the chimeric cytokine receptor and domains thereof are described as follows:

Human IL9Ra ICD
(SEQ ID NO: 1)

KLSPRVKRIIFYQNVPS PAMFFQPLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCVQ
EATALLTCGPAPRWKSVALEEEQEGPGTRLPGNLSSDVLPA GCTEWRVQTLAYLPQEDWAP
TSLTRPAPPDSEGSRSSSSSSSSNNNNYCALGCYGGWHL SALPGNTQSSGPI PALACGLSCD
HQGLETQQGVAVWVL AGHCQRPG LHEDLQGMLLPSVLSKARSWTF

Human IL9Ra ICD
(SEQ ID NO: 2)

AAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCCAGCCCCGCCATGTTCTT
CCAGCCCCCTGTACAGCGTGCACAACGGCAACTTCCAGACCTGGATGGGCGCCACGGCGCCG
GCGTGCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTGCGTGACG
GAGGCCACCGCCCTGCTGACCTGCGGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGAGGA
5 GGAGCAGGAGGGCCCCGGCACCCAGGCTGCCC GGCAACCTGAGCAGCGAGGACGTGCTGCCCCG
CCGGCTGCACCGAGTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCCCCC
ACCAGCCTGACCAGGCCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAG
CAGCAGCAACAACAACAATACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCC
TGCCCCGGCAACACCCAGAGCAGCGGCCCCATCCCCGCCCTGGCCTGCGGCCCTGAGCTGCGAC
10 CACCAGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAGGCC
CGGCCTGCACGAGGACCTGCAGGGCATGCTGCTGCCAGCGTGCTGAGCAAGGCCAGGAGCT
GGACCTTC

Human IL9Ra TM

15 (SEQ ID NO: 3)
GNTLVAVSIFLLLTGPTYLLF

Human IL9Ra TM

(SEQ ID NO: 4)
20 GGCAACACCCCTGGTGGCCGTGAGCATCTTCCTGCTGCTGACCGGCCCCACCTACCTGCTGTT
C

Human PD1 LBD

(SEQ ID NO: 205)
25 MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPTFSPALLVVTEGDNATFTCSFSNTSES
FVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGYLCG
AISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSRPAGQFQTLV

Human PD1 LBD

30 (SEQ ID NO: 206)
ATGCAGATCCCCCAGGCCCCCTGGCCCGTGGTGTGGGCCGTGCTGCAGCTGGGCTGGAGGCC
CGGCTGGTTCCTGGACAGCCCCGACAGGCCCTGGAACCCCCCACCTTCAGCCCCGCCCTGC
TGGTGGTGACCGAGGGCGACAACGCCACCTTCACCTGCAGCTTCAGCAACACCAGCGAGAGC
TTCGTGCTGAACTGGTACAGGATGAGCCCCAGCAACCAGACCGACAAGCTGGCCGCCTTCCC

CGAGGACAGGAGCCAGCCCCGGCCAGGACTGCAGGTTGAGGGTGACCCAGCTGCCCCAACGGCA
 GGGACTTCCACATGAGCGTGGTGAGGGCCAGGAGGAACGACAGCGGCACCTACCTGTGCGGC
 GCCATCAGCCTGGCCCCCAAGGCCAGATCAAGGAGAGCCTGAGGGCCGAGCTGAGGGTGAC
 CGAGAGGAGGGCCGAGGTGCCCCACCGCCCACCCAGCCCCAGCCCCAGGGCCGCCGGCCAGT
 5 TCCAGACCCTGGTG

Human TGFbRI LBD

(SEQ ID NO: 207)

MEAAVAAPRPRLLLLVLAAAAAAAALLPGATALQCFCHLCTKDNFTCVTDGLCFVSVTETTT
 10 DKVIHNSMCIAEIDLIPDRPFVCAPSSKTGSVTTTYCCNQDHCNKIELPTTVKSSPGLGPV
 EL

Human TGFbRI LBD

(SEQ ID NO: 208)

ATGGAGGCCGCCGTGGCCGCCCCAGGCCAGGCTGCTGCTGCTGGTGCTGGCCGCCGCCGC
 CGCCGCCGCCGCCGCGCTGCTGCCCCGGCGCCACCGCCCTGCAGTGCTTCTGCCACCTGTGCA
 CCAAGGACAACCTTACCTGCGTGACCGACGGCCTGTGCTTCGTGAGCGTGACCGAGACCACC
 GACAAGGTGATCCACAACAGCATGTGCATCGCCGAGATCGACCTGATCCCCAGGGACAGGCC
 CTTCGTGTGCGCCCCCAGCAGCAAGACCGGCAGCGTGACCACCACCTACTGCTGCAACCAGG
 20 ACCACTGCAACAAGATCGAGCTGCCCCACCACCGTGAAGAGCAGCCCCGGCCTGGGCCCCGTG
 GAGCTG

Human TGFbRII LBD

(SEQ ID NO: 209)

MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCD
 NQKSCMSNCSITSICEKPQEVCAVVRKNDENITLETVCHDPKLPYHDFILEDAAAPKCIMK
 EKKKPGETFFMCSSSDECNDNIIIFSEYNTSNPDLLLVI FQ

Human TGFbRII LBD

(SEQ ID NO: 210)

ATGGGCAGGGGCCCTGCTGAGGGGCCCTGTGGCCCCCTGCACATCGTGCTGTGGACCAGGATCGC
 CAGCACCATCCCCCCCCACGTGCAGAAGAGCGTGAACAACGACATGATCGTGACCGACAACA
 ACGGCGCCGTGAAGTTCCCCCAGCTGTGCAAGTTCTGCGACGTGAGGTTTCAGCACCTGCGAC
 AACCAGAAGAGCTGCATGAGCAACTGCAGCATCACCAGCATCTGCGAGAAGCCCCAGGAGGT

5 AG

(SEQ ID NO: 211)

10 DQLLAICNADLGWHISPSFKDRVAPGPGGLGLTLQSLTVNDTGEYFCIYHTYPDGTYTGRIFL
EVLESSVAEHGARFQIP

(SEQ ID NO: 212)

CATGATGACCGGCACCATCGAGACCACGGCAACATCAGCGCCGAGAAGGGCGGCAGCATCA
 TCCTGCAGTGCCACCTGAGCAGCACCACGCCCAGGTGACCCAGGTGAACTGGGAGCAGCAG
 GACCAGCTGCTGGCCATCTGCAACGCCGACCTGGGCTGGCACATCAGCCCCAGCTTCAAGGA
 CAGGGTGGCCCCCGCCCCGGCCTGGGCCTGACCCTGCAGAGCCTGACCGTGAACGACACCG
 20 GCGAGTACTTCTGCATCTACCACACCTACCCCGACGGCACCTACACCGGCAGGATCTTCCTG
 GAGGTGCTGGAGAGCAGCGTGGCCGAGCACGGCGCCAGGTTCCAGATCCCC

(SEQ ID NO: 213)

CGNVVLRTDERDVNYWTSRYWLNQDFRKGDVSLTIENVTLADSGIYCCRIQIPGIMNDEKFN
LKLVIKPAKVTPAPTRQRDFTAAPRMLTTRGHGPAETQTLGSLPDINLTQISTLANELRDS
RLANDLRDSGATIRIG

(SEQ ID NO: 214)

CAGCGAGGTGGAGTACAGGGCCGAGGTGGGCCAGAACGCCTACCTGCCCTGCTTCTACACC
CCGCCGCCCCCGGCAACCTGGTGCCCGTGTGCTGGGGCAAGGGCGCTGCCCGTGTTCGAG

TGCGGCAACGTGGTGCTGAGGACCGACGAGAGGGACGTGAACTACTGGACCAGCAGGTACTG
 GCTGAACGGCGACTTCAGGAAGGGCGACGTGAGCCTGACCATCGAGAACGTGACCCTGGCCG
 ACAGCGGCATCTACTGCTGCAGGATCCAGATCCCCGGCATCATGAACGACGAGAAGTTCAAC
 CTGAAGCTGGTGATCAAGCCCCCAAGGTGACCCCCGCCCCACCAGGCAGAGGGACTTCAC
 5 CGCCGCCTTCCCCAGGATGCTGACCACCAGGGGCCACGGCCCCGCCGAGACCCAGACCCTGG
 GCAGCCTGCCCCGACATCAACCTGACCCAGATCAGCACCCCTGGCCAACGAGCTGAGGGACAGC
 AGGCTGGCCAACGACCTGAGGGACAGCGGCGCCACCATCAGGATCGGC

Human PD1-IL9Ra (hPD1-hIL9Ra) (*hPD1 LBD* - hIL9Ra TM - hIL9Ra ICD)

10 (SEQ ID NO: 215)

MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPTFS PALLVVTEGDNATFTCSFSNTSES
FVLNWMYRMSPSNQTDKLAAPEDRSQPGQDCRFRTQLPNGRDFHMSVVRARRNDSTYL
LCG ATSLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLVGNTLVAVSIFLLLTGE
TYLLEFKLSPRVKRIFYQNVPSPAMFFQPLYSVHNGNFQTWMGAHGAGVLLSQDCAGTPQAL
 15 EPCVQEATALLTCGPARPWKSVALEEEQEGPTRLPGNLSSEDVLPAGCTEWRVQTLAYLPQ
EDWAPTSLTRPAPPDSEGRSSSSSSSSNNNNYCALGCYGGWHSALPGNTQSSGPIPALAC
GLSCDHQGLETQQGVAWVLAGHCQRPLHEDLQGMLLPSVLSKARSWTF

20 **Human PD1-IL9Ra (hPD1-hIL9Ra) (*hPD1 LBD* - hIL9Ra TM - hIL9Ra ICD)**

(SEQ ID NO: 216)

ATGCAGATCCCCAGGCCCCCTGGCCCGTGGTGTGGGCCGTGCTGCAGCTGGGCTGGAGGCC
CGGCTGGTTCTTGGACAGCCCCGACAGGCCCTGGAACCCCCCACCTTCAGCCCCGCCCTGC
TGGTGGTGACCGAGGGCGACAACGCCACCTTCACCTGCAGCTTCAGCAACACCAGCGAGAGC
 25 *TTCGTGCTGAACTGGTACAGGATGAGCCCCAGCAACCAGACCGACAAGCTGGCCGCCTTCCC*
CGAGGACAGGAGCCAGCCCGGCCAGGACTGCAGGTTAGGGTGACCCAGCTGCCCAACGGCA
GGGACTTCCACATGAGCGTGGTGAGGGCCAGGAGGAACGACAGCGGCACCTACCTGTGCGGC
GCCATCAGCCTGGCCCCCAAGGCCAGATCAAGGAGAGCCTGAGGGCCGAGCTGAGGGTGAC
CGAGAGGAGGGCCGAGGTGCCCCACCGCCCACCCAGCCCCAGCCCCAGGCCCCCGGCCAGT
 30 *TCCAGACCCTGGTGGCAACACCCCTGGTGGCCGTGAGCATCTTCCTGCTGCTGACCGGCCCC*
ACCTACCTGCTGTTCAAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCAG
CCCCGCCATGTTCTTCCAGCCCCGTACAGCGTGCACAACGGCAACTTCCAGACCTGGATGG
GCGCCACGCGCCGCGCTGCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTG
GAGCCCTGCGTGCAGGAGGCCACCGCCCTGCTGACCTGCGGCCCGCCAGGCCCTGGAAGAG

- CGTGGCCCTGGAGGAGGAGCAGGAGGGCCCCGGCACCAGGCTGCCCCGCAACCTGAGCAGCG
 AGGACGTGCTGCCCCGGGCTGCACCGAGTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAG
 GAGGACTGGGCCCCCACCAGCCTGACCAGGCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAG
 CAGCAGCAGCAGCAGCAGCAGCAACAACAACAACACTACTGCGCCCTGGGCTGCTACGGCGGCT
 5 GGCACCTGAGCGCCCTGCCCCGGCAACACCCAGAGCAGCGGCCCATCCCCGCCCTGGCCTGC
 GGCCTGAGCTGCGACCACCAGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGG
 CCACTGCCAGAGGCCCGGCCCTGCACGAGGACCTGCAGGGCATGCTGCTGCCCAGCGTGCTGA
 GCAAGGCCAGGAGCTGGACCTTC
- 10 Human TGFbRI-IL9Ra (hTGFbRI-hIL9Ra) (*hTGFbRI LBD* - ~~hIL9Ra TM~~ - hIL9Ra ICD)
 (SEQ ID NO: 217)
 MEAAVAAPRPRLLLLVLAAAAAAAALLPGATALQCFCHLCTKDNFTCVTDGLCFVSVTETT
 DKVIHNSMCIAEIDLIPRDRPFVCAPSSKTGSVTTTYCCNQDHCNKIELPTTVKSSPGLGPV
 ELGNTLVAVSIFLLLTGPTYLLFKLSPRVKRIFYQNVPSAMFFQPLYSVHNGNFQTMGAH
 15 GAGVLLSQDCAGTPQGALEPCVQEATALLTCGPAPWKSVALEEEQEGPGTRLPGNLSSEDV
 LPAGCTEWRVQTLAYLPQEDWAPTSLTRPAPPDSEGSRSSSSSSSSNNNNYCALGCYGGWHL
 SALPGNTQSSGPIPALACGLSCDHQGLETTQQGVAVWLAGHCQRPLHEDLQGMLLPSVLSKA
 RSWTF
- 20 Human TGFbRI-IL9Ra (hTGFbRI-hIL9Ra) (*hTGFbRI LBD* - ~~hIL9Ra TM~~ - hIL9Ra ICD)
 (SEQ ID NO: 218)
 ATGGAGGCCGCCGTGGCCGCCCCAGGCCAGGCTGCTGCTGCTGGTGCTGGCCGCCGCCGC
 CGCCGCCGCCGCCCTGCTGCCCGGCGCCACCGCCCTGCAGTGCTTCTGCCACCTGTGCA
 CCAAGGACAACCTTACCTGCGTGACCGACGGCCTGTGCTTCGTGAGCGTGACCGAGACCACC
 25 GACAAGGTGATCCACAACAGCATGTGCATCGCCGAGATCGACCTGATCCCAGGGACAGGCC
 CTTCTGTGCGCCCCCAGCAGCAAGACCGGCAGCGTGACCACCACCTACTGCTGCAACCAGG
 ACCACTGCAACAAGATCGAGCTGCCCACCACCGTGAAGAGCAGCCCCGGCCTGGGCCCCGTG
 GAGCTGGGCAACACCCTGGTGGCCGTGAGCATCTTCTGCTGCTGACCGGCCCCACCTACCT
 GCTGTTCAAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCCAGCCCCGCCA
 30 TGTTCCTCCAGCCCCTGTACAGCGTGACAACGGCAACTTCCAGACCTGGATGGGCGCCAC
 GCGCCCGGCGTGCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTG
 CGTGCAGGAGGCCACCGCCCTGCTGACCTGCGGCCCGCCAGGCCCTGGAAGAGCGTGGCCC
 TGGAGGAGGAGCAGGAGGGCCCCGGCACCAGGCTGCCCCGCAACCTGAGCAGCGAGGACGTG
 CTGCCCGCCGGCTGCACCGAGTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTG

GGCCCCACCAGCCTGACCAGGCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCA
 GCAGCAGCAGCAGCAACAACAACAACACTACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTG
 AGCGCCCTGCCCCGGCAACACCCAGAGCAGCGGCCCATCCCCGCCCTGGCCTGCGGCCTGAG
 CTGCGACCACCAGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCC
 5 AGAGGCCCGGCCTGCACGAGGACCTGCAGGGCATGCTGCTGCCAGCGTGCTGAGCAAGGCC
 AGGAGCTGGACCTTC

Human TGFbRII-IL9Ra (hTGFbRII-hIL9Ra) (*hTGFbRII LBD* - ~~hIL9Ra TM~~ - hIL9Ra ICD)
 (SEQ ID NO: 219)

10 MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCD
 NQKSCMSNCSITSICEKPQEVCAVVRKNDENITLETVCHDPKLPYHDFILEDAAAPKCIMK
 EKKKPGETFFMCSSSDECNDNIIFSEEYNTSNPDLILLVIFQ~~GNTLVAVSIFLLLTGPTYLL~~
~~EKLS~~PRVKRIFYQNVPSAMFFQPLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCV
 QEATALLTCGPARPWKSVALEEEQEGPGTRLPGNLSSDVLPAAGCTEWRVQTLAYLPQEDWA
 15 P~~TS~~LT~~R~~PAPPDSEGSRSSSSSSSSNNNNYCALGCYGGWHL~~S~~ALPGNTQSSGPIPALACGLSC
 DHQGLE~~T~~QQGVAVVL~~A~~GH~~C~~QR~~P~~GLHEDLQGM~~L~~LP~~S~~VLSKARS~~W~~TF

Human TGFbRII-IL9Ra (hTGFbRII-hIL9Ra) (*hTGFbRII LBD* - ~~hIL9Ra TM~~ - hIL9Ra ICD)
 (SEQ ID NO: 220)

20 ATGGGCAGGGGCTGCTGAGGGGCTGTGGCCCCTGCACATCGTGCTGTGGACCAGGATCGC
 CAGCACCATCCCCCCCCACGTGCAGAAGAGCGTGAACAACGACATGATCGTGACCGACAACA
 ACGGCGCCGTGAAGTTCCCCCAGCTGTGCAAGTTCTGCGACGTGAGGTTACGACCTGCGAC
 AACCAGAAGAGCTGCATGAGCAACTGCAGCATCACCAGCATCTGCGAGAAGCCCCAGGAGGT
 GTGCGTGGCCGTGTGGAGGAAGAACGACGAGAACATCACCCCTGGAGACCGTGTGCCACGACC
 25 CCAAGCTGCCCTACCACGACTTCATCTGGAGGACGCCGCCAGCCCCAAGTGCATCATGAAG
 GAGAAGAAGAAGCCCGGCGAGACCTTCTTCATGTGCAGCTGCAGCAGCGACGAGTGAACGA
 CAACATCATCTTCAGCGAGGAGTACAACACCAGCAACCCCGACCTGCTGCTGGTGATCTTCC
 AGGGCAACACCCTGGTGGCCGTGAGCATCTTCCTGCTGCTGACCGGCCCCACCTACCTGCTG
 TTCAAGCTGAGCCCCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCCAGCCCCGCCATGTT
 30 CTTCAGCCCCTGTACAGCGTGACAACGGCAACTTCCAGACCTGGATGGGCGCCACGGCG
 CCGGCGTGCTGCTGAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTGCGTG
 CAGGAGGCCACCGCCCTGCTGACCTGCGGCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGA
 GGAGGAGCAGGAGGGCCCCGGCACAGGCTGCCCGGCAACCTGAGCAGCGAGGACGTGCTGC
 CCGCCGGCTGCACCGAGTGGAGGGTGCAGACCTGGCCTACCTGCCCCAGGAGGACTGGGCC

CCCACCAGCCTGACCAGGCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAG
 CAGCAGCAGCAACAACAACAACACTACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCG
 CCCTGCCCCGGCAACACCCAGAGCAGCGGCCCATCCCCGCCCTGGCCTGCGGCCTGAGCTGC
 GACCACCAGGGCCTGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAG
 5 GCGCGGCCTGCACGAGGACCTGCAGGGCATGCTGCTGCCAGCGTGCTGAGCAAGGCCAGGA
 GCTGGACCTTC

Human TIGIT-IL9Ra (hTIGIT-hIL9Ra) (*hTIGIT LBD* - hIL9Ra TM - hIL9Ra ICD)
 (SEQ ID NO: 221)

10 MRWCLLLIWAQGLRQAPLASGMMTGTIETGNI~~SAEKGGS~~IILQCHLSSTTAQVTQVNWEQQ
 DQLLAICNADLGWHISPSFKDRVAPGPGGLGLTLQSLTVNDTGEYFCIYHTYPDGTYTGRIFL
 EVLESSVAEHGARFQIPGNTLVAVSIFLLLTGPTYLLFKLSPRVKRIFYQNVPSAMFFQPL
 YSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCVQEATALLTCGPAPRWKSVALEEEQE
 GPGTRLPGNLSSEDLVLPAGCTEWRVQTLAYLPQEDWAPTSLTRPAPPDSEGSRSSSSSSSN
 15 NNNYCALGCYGGWHL~~SALPGNTQSSGPI~~PALACGLSCDHQGLETTQQGVAWVL~~AGHCQRPGLH~~
 EDLQGMLLPSVLSKARSWTF

Human TIGIT-IL9Ra (hTIGIT-hIL9Ra) (*hTIGIT LBD* - hIL9Ra TM - hIL9Ra ICD)
 (SEQ ID NO: 222)

20 ATGAGGTGGTGCCTGCTGCTGATCTGGGCCCAGGGCCTGAGGCAGGCCCCCTGGCCAGCGG
 CATGATGACCGGCACCATCGAGACCACCGGCAACATCAGCGCCGAGAAGGGCGGCAGCATCA
 TCCTGCAGTGCCACCTGAGCAGCACCACCGCCCAGGTGACCCAGGTGAACGGGAGCAGCAG
 GACCAGCTGCTGGCCATCTGCAACGCCGACCTGGGCTGGCACATCAGCCCCAGCTTCAAGGA
 CAGGGTGGCCCCCGGCCCGGCTGGGCTGACCCTGCAGAGCCTGACCGTGAACGACACCG
 25 GCGAGTACTTCTGCATCTACCACACCTACCCGACGGCACCTACACCGGCAGGATCTTCCTG
 GAGGTGCTGGAGAGCAGCGTGGCCGAGCACGGCGCCAGGTTCAGATCCCCGGCAACACCCCT
 GGTEGGCCGTGAGCATCTTCCTGCTGCTGACCGGCCCCACCTACCTGCTGTTCAGCTGAGCC
 CCAGGGTGAAGAGGATCTTCTACCAGAACGTGCCAGCCCCGCCATGTTCTTCCAGCCCCCTG
 TACAGCGTGACAAACGGCAACTTCCAGACCTGGATGGGCGCCACGGCGCCGGCTGCTGCT
 30 GAGCCAGGACTGCGCCGGCACCCCCAGGGCGCCCTGGAGCCCTGCGTGCAAGAGGCCACCG
 CCCTGCTGACCTGCGGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGAGGAGGAGCAGGAG
 GGCCCCGGCACACAGGCTGCCCGGCAACCTGAGCAGCGAGGACGTGCTGCCCGCCGGCTGCAC
 CGAGTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCCCCACCAGCCTGA
 CCAGGCCCCGCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAGCAGCAGCAAC

AACAACAAC TACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCCTGCCCCGGCAA
CACCCAGAGCAGCGGCCCCATCCCCGCCCTGGCCTGCGGCCCTGAGCTGCGACCACCAGGGCC
TGGAGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAGGCCCCGGCCTGCAC
GAGGACCTGCAGGGCATGCTGCTGCCCAGCGTGCTGAGCAAGGCCAGGAGCTGGACCTTC

5

Human TIM3-IL9Ra (hTIM3-hIL9Ra) (*hTIM3 LBD* - *hIL9Ra TM* - *hIL9Ra ICD*)
(SEQ ID NO: 223)

MFSHLPFDCVLLLLLLLLLTSRSEVEYRAEVGNAYLPCFYTPAAPGNLVPVCWGKGACPVFE
 CGNVVLRTDERDVNYWTSRYWLNGDFRKGDVSLTIENVTLADSGIYCCRIQIPGIMNDEKFN
 10 LKLVIKPAKVTPAPTRQRDFTAAFPRLMTTRGHGPAETQTLGSLPDINLTQISTLANELRDS
 RLANDLRDSGATIRIGNTLVAVSIFLLLTGPTYLLFKLSPRVKRIFYQNVPSAMFFQPLY
 SVHNGNFQTWMGAHGAGVLLSQDCAGTPQGALEPCVQEATAALLTCGPARPWKSVALEEEQEG
 PGTRLPGNLSSSEDLVPAGCTEWRVQTLAYLPQEDWAPTSLTRPAPPDSEGRSSSSSSSSNN
 NNYCALGCYGGWHSALPGNTQSSGPIPALACGLSCDHQGLTQQGVAVWVLAGHCQRPGLHE
 15 DLQGMLLPSVLSKARSWTF

Human TIM3-IL9Ra (hTIM3-hIL9Ra) (*hTIM3 LBD* - ~~hIL9Ra TM~~ - hIL9Ra ICD)
(SEQ ID NO: 224)

[illegible]

GTGGAGGGTGCAGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCCCCCACCAGCCTGACCA
 GGCCCCCCCCCCCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAGCAGCAACAAC
 AACAACTACTGCGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCCTGCCCGGCAACAC
 CCAGAGCAGCGGCCCCATCCCCGCCCTGGCCTGCGGCCTGAGCTGCGACCACCAGGGCCTGG
 5 AGACCCAGCAGGGCGTGGCCTGGGTGCTGGCCGGCCACTGCCAGAGGCCCGGCCTGCACGAG
 GACCTGCAGGGCATGCTGCTGCCAGCGTGTGAGCAAGGCCAGGAGCTGGACCTTC

Murine IL9Ra ICD

(SEQ ID NO: 225)

10 KLSPLRLKRIFYQNI PSPEAFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESSIW
 EAVATLTYS PACPVQFACLKWEATAPGFPLPGSEHVL PAGCLELEGQPSAYLPQEDWAPLG
 SARPPPPDS DSGSSDYCMLDCCEECHLSAFPGHTE SPELT LAQPVALPVSSRA

Murine IL9Ra ICD

15 (SEQ ID NO: 226)

AAGCTGAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCCCGAGGCCTTCTT
 CCACCCCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCCAGGAGGGCCG
 GCCCCAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAGAGCAGCATCTGG
 GAGGCCGTGGCCACCCTGACCTACAGCCCCGCTGCCCCGTGCAGTTTCGCTGCCTGAAGTG
 20 GGAGGCCACCGCCCCCGGCTTCCCCGGCCTGCCCCGGCAGCGAGCACGTGCTGCCCCCGGCT
 GCCTGGAGCTGGAGGGCCAGCCCAGCGCCTACCTGCCCCAGGAGGACTGGGCCCCCTGGGC
 AGCGCCAGGCCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTGCATGCTGGACTG
 CTGCGAGGAGTGCCACCTGAGCGCCTTCCCCGGCCACACCGAGAGCCCCGAGCTGACCCTGG
 CCCAGCCCGTGGCCCTGCCCCGTGAGCAGCAGGGCC

25

Murine IL9Ra ICD

(SEQ ID NO: 302)

AAACCTATCTCCACGGCTCAAACGGATCTTCTACCAGAACATCCCTTCTCCTGAAGCATTTCTT
 CCATCCCCTGTATTTCAGTTTATCATGGAGACTTCCAGTCCTGGACTGGGGCCCGCAGAGCTG
 30 GGCCACAAGCTCGACAGAATGGCGTGTCCACCAGCTCTGCAGGGTCCGAGTCTTCCATTTGG
 GAGGCAGTGGCAACTCTGACTTACTCCCCAGCATGCCCTGTGCAGTTTGCCTGTCTGAAATG
 GGAAGCCACTGCCCCGGGCTTCCCAGGATTGCCGGGCAGTGAGCATGTCTGCCTGCAGGCT
 GCCTCGAACTCGAGGGCCAGCCATCTGCCTACCTGCCCCAAGAAGACTGGGCCCCACTCGGC
 TCAGCTAGACCTCCCCCCCCAGATAGTGACTCCGGGTCGTCTGACTATTGCATGCTGGATTG

CTGTGAAGAGTGCCACCTGAGTGCCTTCCCTGGCCACACAGAGAGTCCCGAGCTGACCTTGG
CTCAGCCAGTAGCCCTCCCTGTCAGCTCCCGGGCC

Murine IL9Ra TM

5 (SEQ ID NO: 227)

ASILVVVPIFLLLTGFVHLLF

Murine IL9Ra TM

(SEQ ID NO: 228)

10 GCCAGCATCCTGGTGGTGGTGGCCATCTTCCTGCTGCTGACCGGCTTCGTGCACCTGCTGTT
C

Murine PD1 LBD

(SEQ ID NO: 229)

15 MWVRQVPWSFTWAVLQLSWQSGWLLEVPNGPWRSLTFYPAWLTVSEGANATFTCSLSNWS
ED
LMLNWNRLSPSNQTEKQAAFCNGLSQPVQDARFQIIQLPNRHDFHNMNILDTRRND
SGIYLCG
AISLHPKAKIEESPGAELVVTERILETSTRYPSPSPKPEGRFQGM

Murine PD1 LBD

20 (SEQ ID NO: 230)

ATGTGGGTGAGGCAGGTGCCCTGGAGCTTCACCTGGGCCGTGCTGCAGCTGAGCTGGCAGAG
CGGCTGGCTGCTGGAGGTGCCCAACGGCCCCCTGGAGGAGCCTGACCTTCTACCCCGCCTGGC
TGACCGTGAGCGAGGGCGCCAACGCCACCTTCACCTGCAGCCTGAGCAACTGGAGCGAGGAC
CTGATGCTGAACTGGAACAGGCTGAGCCCCAGCAACCAGACCGAGAAGCAGGCCGCTTCTG
25 CAACGGCCTGAGCCAGCCCCTGCAGGACGCCAGGTTCAGATCATCCAGCTGCCCCAACAGGC
ACGACTTCCACATGAACATCCTGGACACCAGGAGGAACGACAGCGGCATCTACCTGTGCGGC
GCCATCAGCCTGCACCCCAAGGCCAAGATCGAGGAGAGCCCCGGCGCCGAGCTGGTGGTGAC
CGAGAGGATCCTGGAGACCAGCACCAGGTACCCAGCCCCAGCCCCAAGCCGAGGGCAGGT
TCCAGGGCATG

30

Murine TGFbRI LBD

(SEQ ID NO: 231)

MEAAAAAPRRPQLLIVLVAAATLLPGAKALQCFCHLCTKDNFTCETDGLCFVSVTETTDKVI
HNSMCIAEIDLIPDRPFVFCAPSSKTGAVTTTYCCNQDHCNKIELPTTGPFSEKQSAGLGPV
EL

5 Murine TGFbRI LBD

(SEQ ID NO: 232)

ATGGAGGCCGCCGCCGCCGCCGCCAGGAGGCCCCAGCTGCTGATCGTGCTGGTGGCCGCCGC
CACCCTGCTGCCCCGGCGCCAAGGCCCTGCAGTGCTTCTGCCACCTGTGCACCAAGGACAAC
TCACCTGCGAGACCGACGGCCTGTGCTTCGTGAGCGTGACCGAGACCACCGACAAGGTGATC
10 CACAACAGCATGTGCATCGCCGAGATCGACCTGATCCCCAGGGACAGGCCCTTCGTGTGCGC
CCCCAGCAGCAAGACCGGCGCCGTGACCACCACCTACTGCTGCAACCAGGACCACTGCAACA
AGATCGAGCTGCCACCACCGGCCCTTCAGCGAGAAGCAGAGCGCCGGCCTGGGCCCCGTG
GAGCTG

15 Murine TGFbRII LBD

(SEQ ID NO: 233)

MGRGLLRGLWPLHIVLWTRIASTIPPHVPKSDVEMEAQKDASIHLSNRTIHPLKHFNSDVM
ASDNGGAVKLPQLCKFCDVRLSTCDNQKSCMSNCSITAICEKPHEVCVAVWRKNDKNITLET
VCHDPKLTYPHFTLEDAASPKCVMKEKKRAGETFFMCACNMEECNDYIIFSEEYTTSSPD

20

Murine TGFbRII LBD

(SEQ ID NO: 234)

ATGGGCAGGGGCCTGCTGAGGGGCCTGTGGCCCCTGCACATCGTGCTGTGGACCAGGATCGC
CAGCACCATCCCCCCCCACGTGCCCAAGAGCGACGTGGAGATGGAGGCCCAGAAGGACGCCA
25 GCATCCACCTGAGCTGCAACAGGACCATCCACCCCCTGAAGCACTTCAACAGCGACGTGATG
GCCAGCGACAACGGCGGCGCCGTGAAGCTGCCCCAGCTGTGCAAGTTCTGCGACGTGAGGCT
GAGCACCTGCGACAACCAGAAGAGCTGCATGAGCAACTGCAGCATCACCGCCATCTGCGAGA
AGCCCCACGAGGTGTGCGTGGCCGTGTGGAGGAAGAACGACAAGAACATCACCTGGAGACC
GTGTGCCACGACCCCAAGCTGACCTACCACGGCTTCACCTGGAGGACGCCGCCAGCCCCAA
30 GTGCGTGATGAAGGAGAAGAAGAGGGCCGGCGAGACCTTCTTCATGTGCGCCTGCAACATGG
AGGAGTGCAACGACTACATCATCTTCAGCGAGGAGTACACCACCAGCAGCCCCGAC

Murine TIGIT LBD

(SEQ ID NO: 235)

MHGWLLLVWVQGLIQAAFLATAIGATAGTIDTKRNISAEEGGSVILQCHFSSDTAEVTQVDW
KQQDQLLAIYSVDLGWHVASVFSRVPVPGPSLGLTFQSLTMNDTGEYFCTYHTYPGGIYKGR
IFLKVQESSDDRNGLAQFQTAPLG

5 Murine TIGIT LBD
(SEQ ID NO: 236)

ATGCACGGCTGGCTGCTGCTGGTGTGGGTGCAGGGCCTGATCCAGGCCGCCTTCCTGGCCAC
CGCCATCGGCGCCACCGCCGGCACCATCGACACCAAGAGGAACATCAGCGCCGAGGAGGGCG
GCAGCGTGATCCTGCAGTGCCACTTCAGCAGCGACACCGCCGAGGTGACCCAGGTGGACTGG
10 AAGCAGCAGGACCAGCTGCTGGCCATCTACAGCGTGGACCTGGGCTGGCACGTGGCCAGCGT
GTTTCAGCGACAGGGTGGTGCCCGGCCCCAGCCTGGGCCTGACCTTCCAGAGCCTGACCATGA
ACGACACCGGCGAGTACTTCTGCACCTACCACACCTACCCCGGCGGCATCTACAAGGGCAGG
ATCTTCCTGAAGGTGCAGGAGAGCAGCGACGACAGGAACGGCCTGGCCCAGTTCCAGACCGC
CCCCCTGGGCGCCAGCATCCTGGTGGTGGTGCCCATCTTCCTGCTGCTGACCGGCTTCGTGC
15 ACCTGCTGTTT

Murine TIM3 LBD
(SEQ ID NO: 237)

MFSGTLTNCVLLLLQLLLARSLNAYVFEVGKNAYLPCSYTLSTPGALVPMCWGKGFCPWSQ
20 CTNELLRTDERNVITYQKSSRYQLKGDNLKGDVSLIIKNVTLDDHGTYYCCRIQFPGLMNDKKL
ELKLDIKAARKVTPAQTAHGDSTTASPRTLTTERNGETQTLVTLHNNNGTKISTWADEIKDS
GETIRTA

Murine TIM3 LBD
(SEQ ID NO: 238)

ATGTTTCAGCGGCCTGACCCTGAACTGCGTGCTGCTGCTGCTGCTGCTGCTGCTGCTGGCCAGGAG
CCTGGAGAACGCCTACGTGTTTCGAGGTGGGCAAGAACGCCTACCTGCCCTGCAGCTACACCC
TGAGCACCCCCGGCGCCCTGGTGCCCATGTGCTGGGGCAAGGGCTTCTGCCCTGGAGCCAG
TGCACCAACGAGCTGCTGAGGACCGACGAGAGGAACGTGACCTACCAGAAGAGCAGCAGGTA
30 CCAGCTGAAGGGCGACCTGAACAAGGGCGACGTGAGCCTGATCATCAAGAAGCTGACCCTGG
ACGACCACGGCACCTACTGCTGCAGGATCCAGTTCCCCGGCCTGATGAACGACAAGAAGCTG
GAGCTGAAGCTGGACATCAAGGCCGCCAAGGTGACCCCCGCCAGACCGCCACGGCGACAG
CACCACCGCCAGCCCCAGGACCCTGACCACCGAGAGGAACGGCAGCGAGACCCAGACCCTGG

TGACCCTGCACAACAACAACGGCACCAAGATCAGCACCTGGGCCGACGAGATCAAGGACAGC
GGCGAGACCATCAGGACCGCC

Murine PD1-IL9Ra (mPD1-mIL9Ra) (*mPD1 LBD* – *mIL9Ra TM* – *mIL9Ra ICD*)

5 (SEQ ID NO: 239)

MWVRQVPWSFTWAVLQLSWQSGWLLEVPNGPWRS�TFYPAWLTVSEGANATFTCSLSNWS
LMLNWNRLSPSNQTEKQAAFCNGLSQPVQDARFQIIQLPNRHDFHMNILDTRRNDSGIYLCG
AISLHPKAKIEESPGAELVVTERILETSTRYPSPSPKPEGRFQGMASILVVPIFLLLTGFV
HLLFKLSPRĲKRIFYQNIPSPFAFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSE
10 SSIWEAVATLTYS PACPVQFACLKWEATAPGFPLPGSEHVL PAGCLELEGQPSAYLPQEDW
APĲGSARPPPPDSGSSDYCMLDCCEECHLSAFPGHTESPELTĲAQPVALPVSSRA

Murine PD1-IL9Ra (mPD1-mIL9Ra) (*mPD1 LBD* – *mIL9Ra TM* – *mIL9Ra ICD*)

(SEQ ID NO: 240)

15 ATGTGGGTGAGGCAGGTGCCCTGGAGCTTCACCTGGGCCGTGCTGCAGCTGAGCTGGCAGAG
CGGCTGGCTGCTGGAGGTGCCCAACGGCCCCCTGGAGGAGCCTGACCTTCTACCCCGCCTGGC
TGACCGTGAGCGAGGGCGCCAACGCCACCTTCACCTGCAGCCTGAGCAACTGGAGCGAGGAC
CTGATGCTGAACTGGAACAGGCTGAGCCCCAGCAACCAGACCGAGAAGCAGGCCGCTTCTG
CAACGGCCTGAGCCAGCCCCTGCAGGACGCCAGGTTCCAGATCATCCAGCTGCCCAACAGGC
20 ACGACTTCCACATGAACATCTTGGACACCAGGAGGAACGACAGCGGCATCTACCTGTGCGGC
GCCATCAGCCTGCACCCCAAGGCCAAGATCGAGGAGAGCCCCGGCGCCGAGCTGGTGGTGAC
CGAGAGGATCTTGGAGACCAGCACCAGGTACCCAGCCCCAGCCCCAAGCCCGAGGGCAGGT
TCCAGGGCATGĲCCAGCATCCTGGTGGTGGTGGCCATCTTCTGCTGCTGACCGGCTTCTGTG
CACCTGCTGTTC AAGCTGAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCC
25 CGAGGCCTTCTTCCACCCCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCG
CCAGGAGGGCCGGCCCCCAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAG
AGCAGCATCTGGGAGGCCGTGGCCACCCTGACCTACAGCCCCGCTGCCCGTGAGTTCGC
CTGCCTGAAGTGGGAGGCCACCGCCCCCGGCTTCCCCGGCCTGCCCGGCAGCGAGCACGTGC
TGCCCCGCCGGCTGCCTGGAGCTGGAGGGCCAGCCAGCGCCTACCTGCCCCAGGAGGACTGG
30 GCCCCCTGGGCAGCGCCAGGCCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTG
CATGCTGGACTGCTGCGAGGAGTGCCACCTGAGCGCCTTCCCCGGCCACACCGAGAGCCCCG
AGCTGACCCTGGCCCAGCCCCTGGCCCTGCCCGTGAGCAGCAGGGCC

Murine TGFbRI-IL9Ra (mTGFbRI-mIL9Ra) (*mTGFbRI LBD* – mIL9Ra TM – mIL9Ra ICD)

(SEQ ID NO: 241)

MEAAAAAPRRPQLLIVLVAAATLLPGAKALQCFCHLCTKDNFTCETDGLCFVSVTETTDKVI
 5 HNSMCIAEIDLIPDRPFVVCAPSSKTGAVTTTYCCNQDHCNKIELPTTGPFSEKQSAGLGPV
ELASILVVVPIFLLLTGFEVHLLFKLS PRLKRIFYQNI PSPEAFFHPLYSVYHGDFQSWTGAR
RAGPQARQNGVSTSSAGSESSIWEAVATLTYS PACPVQFACLKWEATAPGFPGLPGSEHVLP
AGCLELEGQPSAYLPQEDWAPLGSARPPPPDS DSGSSDYCMLDCCEECHLSAFPGHTESPEL
TLAQPVALPVSSRA

10

Murine TGFbRI-IL9Ra (mTGFbRI-mIL9Ra) (*mTGFbRI LBD* – mIL9Ra TM – mIL9Ra ICD)

(SEQ ID NO: 242)

ATGGAGGCCGCCGCCGCCGCCGCCAGGAGGCCCCAGCTGCTGATCGTGCTGGTGGCCGCCGC
 15 CACCCGTGCTGCCCCGGCGCCAAGGCCCTGCAGTGCTTCTGCCACCTGTGCACCAAGGACAAC
 TCACCTGCGAGACCGACGGCCTGTGCTTCGTGAGCGTGACCGAGACCACCGACAAGGTGATC
 CACAACAGCATGTGCATCGCCGAGATCGACCTGATCCCCAGGGACAGGCCCTTCGTGTGCGC
 CCCCAGCAGCAAGACCGGCGCCGTGACCACCACCTACTGCTGCAACCAGGACCACTGCAACA
 AGATCGAGCTGCCCACCACCGGCCCTTCAGCGAGAAGCAGAGCGCCGGCCTGGGCCCCGTG
 20 GAGCTGCCAGCATCCTGGTGGTGGTGCCCATCTTCCTGCTGCTGACCGGCTTCGTGCACCT
GCTGTTCAAGCTGAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCCCGAGG
CCTTCTTCCACCCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCGCCAGG
AGGGCCGGCCCCCAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAGAGCAG
CATCTGGGAGGCCGTGGCCACCCTGACCTACAGCCCCGCCTGCCCCGTGCAGTTTCGCCTGCC
 25 TGAAGTGGGAGGCCACCGCCCCCGGCTTCCCCGGCCTGCCCCGCGAGCAGCACGTGCTGCCC
GCCGGCTGCCTGGAGCTGGAGGGCCAGCCAGCGCCTACCTGCCCCAGGAGGACTGGGCCCC
CCTGGGCAGCGCCAGGCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTGCATGC
TGGACTGCTGCGAGGAGTGCCACCTGAGCGCCTTCCCCGGCCACACCGAGAGCCCCGAGCTG
ACCCTGGCCCAGCCCGTGGCCCTGCCCCGTGAGCAGCAGGGCC

30

Murine TGFbRII -IL9Ra (mTGFbRII-mIL9Ra) (*mTGFbRII LBD* – mIL9Ra TM – mIL9Ra ICD)

(SEQ ID NO: 243)

MGRGLLRGLWPLHIVLWTRIASTIPPHVPKSDVEMEAQKDAS IHLSCNRTIHPLKHFNSDVM
 ASDNGGAVKLPQLCKFCDVRLSTCDNQKSCMSNCSITAICEKPHEVCVAVWRKNDKNITLET
 VCHDPKLT YHGFTLEDAAS PKCVMKEKKRAGETFFMCACNMEECNDYIIFSEEYTTSSPDAS
 ILVVPIFLLLTGFFVHLLFKLS PRLKRI FYQNI PSPEAFFHPLYSVYHGDFQSWTGARRAGP
 5 QARQNGVSTSSAGSESSIWEAVATLTYS PACPVQFACLKWEATAPGFPLPGSEHVL PAGCL
ELEGQPSAYLPQEDWAPLGSARPPPPDS DSGSSDYCMLDCCEECHLSAFPGHTESELT LAQ
PVALPVSSRA

Murine TGFbRII -IL9Ra (mTGFbRII-mIL9Ra) (*mTGFbRII LBD* – mIL9Ra TM – mIL9Ra
 10 ICD)
 (SEQ ID NO: 244)
 ATGGGCAGGGGCGCTGCTGAGGGGCGCTGTGGCCCCCTGCACATCGTGCTGTGGACCAGGATCGC
 CAGCACCATCCCCCCCCACGTGCCCAAGAGCGACGTGGAGATGGAGGCCCAGAAGGACGCCA
 GCATCCACCTGAGCTGCAACAGGACCATCCACCCCCTGAAGCACTTCAACAGCGACGTGATG
 15 GCCAGCGACAACGGCGGCGCCGTGAAGCTGCCCCAGCTGTGCAAGTTCTGCGACGTGAGGCT
GAGCACCCTGCGACAACCAGAAGAGCTGCATGAGCAACTGCAGCATCACCGCCATCTGCGAGA
AGCCCCACGAGGTGTGCGTGGCCGTGTGGAGGAAGAACGACAAGAACATCACCTGGAGACC
GTGTGCCACGACCCCAAGCTGACCTACCACGGCTTCACCTGGAGGACGCCGCCAGCCCCAA
GTGCGTGATGAAGGAGAAGAAGAGGGCCGGCGAGACCTTCTTCATGTGCGCCTGCAACATGG
 20 AGGAGTGCAACGACTACATCATCTTCAGCGAGGAGTACACCACCAGCAGCCCCGACGCCAGC
ATCCTGGTGGTGGTGCCCATCTTCCTGCTGCTGACCGGCTTCGTGCACCTGCTGTTCAAGCT
GAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCCCGAGGCCTTCTTCCACC
CCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCGCCAGGAGGGCCGGCCCC
CAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAGAGCAGCATCTGGGAGGC
 25 CGTGGCCACCCTGACCTACAGCCCCGCCTGCCCCGTGCAGTTTCGCCTGCCTGAAGTGGGAGG
CCACCGCCCCCGGCTTCCCCGGCCTGCCCCGGCAGCGAGCACGTGCTGCCCGCCGGCTGCCTG
GAGCTGGAGGGCCAGCCCAGCGCCTACCTGCCCCAGGAGGACTGGGCCCCCTGGGCAGCGC
CAGGCCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTGCATGCTGGACTGCTGCG
AGGAGTGCCACCTGAGCGCCTTCCCCGGCCACACCGAGAGCCCCGAGCTGACCTGGCCCCAG
 30 CCCGTGGCCCTGCCCCGTGAGCAGCAGGGCC

Murine TIGIT-IL9Ra (mTIGIT-mIL9Ra) (*mTIGIT LBD* – mIL9Ra TM – mIL9Ra ICD)
 (SEQ ID NO: 245)

MHGWLLLWVWQGLIQAAFLATAIGATAGTIDTKRNISAEEGGSVILQCHFSSDTAEVTQVDW
 KQQDQLLAIYSVDLGWHVASVFSRVPVPGPSLGLTFQSLTMNDTGEYFCTYHTYPGGIYKGR
 IFLKVQESSDDRNGLAQFQTAPLGASILVVPVIFLLLTGTFVHLLFKLSPRLKRIFYQNI P S P
 EAFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESSIWEAVATLTYS PACPVQFA
 5 CLKWEATAPGFPLPGSEHVLPA G C L E L E G Q P S A Y L P Q E D W A P L G S A R P P P P D S D S G S S D Y C
 M L D C C E E C H L S A F P G H T E S P E L T L A Q P V A L P V S S R A

Murine TIGIT-IL9Ra (mTIGIT-mIL9Ra) (*mTIGIT LBD* – *mIL9Ra TM* – *mIL9Ra ICD*)
 (SEQ ID NO: 246)

10 ATGCACGGCTGGCTGCTGCTGGTGTGGGTGCAGGGCCTGATCCAGGCCGCTTCTGGCCAC
 CGCCATCGGCGCCACCGCCGGCACCATCGACACCAAGAGGAACATCAGCGCCGAGGAGGGCG
 GCAGCGTGATCCTGCAGTGCCACTTCAGCAGCGACACCGCCGAGGTGACCCAGGTGGACTGG
 AAGCAGCAGGACCAGCTGCTGGCCATCTACAGCGTGGACCTGGGCTGGCACGTGGCCAGCGT
 GTTCAGCGACAGGGTGGTGCCCGGCCCCAGCCTGGGCCTGACCTTCCAGAGCCTGACCATGA
 15 ACGACACCGGCGAGTACTTCTGCACCTACCACACCTACCCCGGCGGCATCTACAAGGGCAGG
 ATCTTCTTGAAGGTGCAGGAGAGCAGCGACGACAGGAACGGCCTGGCCCAGTTCCAGACCGC
 CCCCCGCGGCCAGCATCCTGGTGGTGGTGCCCATCTTCTGCTGCTGACCGGCTTCGTGC
 ACCTGCTGTTCAAGCTGAGCCCCAGGCTGAAGAGGATCTTCTACCAGAACATCCCCAGCCCC
 GAGGCCTTCTTCCACCCCTGTACAGCGTGTACCACGGCGACTTCCAGAGCTGGACCGGCGC
 20 CAGGAGGGCCGGCCCCCAGGCCAGGCAGAACGGCGTGAGCACCAGCAGCGCCGGCAGCGAGA
 GCAGCATCTGGGAGGCCGTGGCCACCCTGACCTACAGCCCCGCCTGCCCCGTGCAGTTCGCC
 TGCCCTGAAGTGGGAGGCCACCGCCCCCGGCTTCCCCGGCCTGCCCGGCAGCGAGCACGTGCT
 GCCCGCCGGCTGCCTGGAGCTGGAGGGCCAGCCAGCGCCTACCTGCCCCAGGAGGACTGGG
 CCCCCCTGGGCAGCGCCAGGCCCCCCCCCCCCGACAGCGACAGCGGCAGCAGCGACTACTGC
 25 ATGCTGGACTGCTGCGAGGAGTGCCACCTGAGCGCCTTCCCCGGCCACACCGAGAGCCCCGA
 GCTGACCCTGGCCAGCCCGTGGCCCTGCCCGTGCAGCAGGGCC

Murine TIM3-IL9Ra (mTIM3-mIL9Ra) (*mTIM3 LBD* – *mIL9Ra TM* – *mIL9Ra ICD*)
 (SEQ ID NO: 247)

30 MFSGLTLNCLVLLLLQLLLARSLNAYVFEVGKNAYLPCSYTLSTPGALVPMCWGKGFCPWSQ
 CTNELLRTDERNVITYQKSSRYQLKGDNLKGDVSLIIKNVTLDDHGTYYCCRIQFPGLMNDKKL
 ELKLDIKA AKVTPAQTAHGDS TTASPRTL TTERNGETQTLVTLHNNNGTKISTWADEIKDS
 GETIRTAASILVVPVIFLLLTGTFVHLLFKLSPRLKRIFYQNI P S P E A F F H P L Y S V Y H G D F Q S
 WTGARRAGPQARQNGVSTSSAGSESSIWEAVATLTYS PACPVQFA CLKWEATAPGFPLPGS

EHVLPAGCLELEGQPSAYLPLQEDWAPLGSARPPPPDSGSSDYCMLDCCEECHLSAFPGHT
ESPELTLAQPVLPVSSRA

Murine TIM3-IL9Ra (mTIM3-mIL9Ra) (*mTIM3 LBD* – *mIL9Ra TM* – *mIL9Ra ICD*)

5 (SEQ ID NO: 248)

[illegible]

25

Anti-CTLA4 antigen binding domain – light chain (light chain of ipilimumab)

(SEQ ID NO: 289)

30 EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDR
FSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC

Anti-CTLA4 antigen binding domain – heavy chain (heavy chain of ipilimumab without CH3)

(SEQ ID NO: 290)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYAD
 SVKGRFTISRDN SKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTTLVTVSSASTKGP
 SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
 5 VTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
 KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
 HQDWLNGKEYKCKVSNKALPAPIEKTISKAK

P2A linker

10 (SEQ ID NO: 291)

ATNFSLLKQAGDVEENPGP

Flexible linker

(SEQ ID NO: 292)

15 GGGGSGGGGSGGGGS

Anti-CTLA4 antigen binding domain (H+L)

(SEQ ID NO: 293)

MEIVLTQSPGTLTSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPD
 20 RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
DYEKHKVYACEVTHQGLSSPVTKSFNRGECATNFSLLKQAGDVEENPGPQVQLVESGGGVVQ
 PGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYADSVKGRFTISRDN
 SKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTTLVTVSSASTKGPSVFPLAPSSKSTS
 25 GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY
ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAK

30 Anti-CTLA4 light chain CDR1 (LCDR1)

(SEQ ID NO: 294)

QSVGSSY

Anti-CTLA4 light chain CDR2 (LCDR2)

(SEQ ID NO: 295)

GAF

Anti-CTLA4 light chain CDR3 (LCDR3)

5 (SEQ ID NO: 296)

QQYGSSPWT

Anti-CTLA4 heavy chain CDR1 (HCDR1)

(SEQ ID NO: 297)

10 GFTFSSYT

Anti-CTLA4 heavy chain CDR2 (HCDR2)

(SEQ ID NO: 298)

TFISYDGNNK

15

Anti-CTLA4 heavy chain CDR3 (HCDR3)

(SEQ ID NO: 299)

ARTGWLGPFDY

20 Anti-CTLA4 (H+L) chimeric cytokine receptor

(SEQ ID NO: 300)

MEIVLTQSPGTLSSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPD

RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSD

EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKA

25 DYEKHKVYACEVTHQGLSSPVTKSFNRGECATNFSLLKQAGDVEENPGPQVQLVESGGGVVQ

PGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYADSVKGRFTISRDN

KNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGGQTLVTVSSASTKGPSVFPLAPSSKSTS

GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT

30 CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK

VSNNKALPAPIEKTISKAKGSGGGSGGGSGGGSGNTLVAVSIFLLLTGPTYLLFKLSPRVKR

IFYQNVPSPAMFFQPLYSVHNGNFQTMGAHGAGVLLSQDCAGTPQGALEPCVQEATALLTC

GPARPWKSVALEEEQEGPGTRLPGNLSSDVLPAAGCTEWRVQTLAYLPQEDWAPTSLTRPAP

PDSEGRSSSSSSSSNNNNYCALGCGGWHLSALPGNTQSSGPIPALACGLSCDHQGLTQQ
GVAWVLAGHCQRPLHEDLQGMLLPSVLSKARSWTF

Anti-CTLA4 (H+L) chimeric cytokine receptor

5 (SEQ ID NO: 301)

ATGGAGATCGTGCTGACCCAGAGCCCCGGCACCCCTGAGCCTGAGCCCCGGCGAGAGGGCCAC
CCTGAGCTGCAGGGCCAGCCAGAGCGTGGGCAGCAGCTACCTGGCCTGGTACCAGCAGAAGC
CCGGCCAGGCCCCCAGGCTGCTGATCTACGGCGCCTTCAGCAGGGCCACCGGCATCCCCGAC
AGGTTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGGCTGGAGCCCGA
10 GGACTTCGCCGTGTACTACTGCCAGCAGTACGGCAGCAGCCCCCTGGACCTTCGGCCAGGGCA
CCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGAC
GAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACCTTCTACCCCAGGGA
GGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGA
CCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCC
15 GACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGT
GACCAAGAGCTTCAACAGGGGCGAGTGCGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCG
ACGTGGAGGAGAACCCCGGCCCCCAGGTGCAGCTGGTGGAGAGCGGCGGCGGTGGTGCAG
CCCGGCAGGAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACACCAT
GCACTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGACCTTCATCAGCTACGACG
20 GCAACAACAAGTACTACGCCGACAGCGTGAAGGGCAGGTTTACCATCAGCAGGGACAACAGC
AAGAACACCCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCATCTACTACTG
CGCCAGGACCGGCTGGCTGGGCCCCCTTCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGA
GCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCCTGGCCCCCAGCAGCAAGAGCACCAGC
GGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAG
25 CTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCG
GCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTAC
ATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGAG
CTGCGACAAGACCCACACCTGCCCCCCCCCTGCCCCGCCCCGAGCTGCTGGGCGGCCCCAGCG
TGTTCTGTTCCTTCCCCCCCCAAGCCCCAAGGACACCCCTGATGATCAGCAGGACCCCCGAGGTGACC
30 TGCGTGGTGGTGGACGTGAGCCACGAGGACCCCCGAGGTGAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACAGGG
TGGTGAGCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAG
GTGAGCAACAAGGCCCTGCCCCCCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCGGCGG
CGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCAACACCCTGGTGGCCGTGAGCA

TCTTCCTGCTGCTGACCGGCCCCACCTACCTGCTGTTCAAGCTGAGCCCCAGGGTGAAGAGG
 ATCTTCTACCAGAACGTGCCCAGCCCCGCCATGTTCTTCCAGCCCCGTACAGCGTGCACAA
 CGGCAACTTCCAGACCTGGATGGGCGCCCCACGGCGCCGGCGTGCTGCTGAGCCAGGACTGCG
 CCGGCACCCCCAGGGCGCCCTGGAGCCCTGCGTGAGGAGGCCACCGCCCTGCTGACCTGC
 5 GGCCCCGCCAGGCCCTGGAAGAGCGTGGCCCTGGAGGAGGAGCAGGAGGGCCCCGGCACCAG
 GCTGCCCGGCAACCTGAGCAGCGAGGACGTGCTGCCCGCCGGCTGCACCGAGTGGAGGGTGC
 AGACCCTGGCCTACCTGCCCCAGGAGGACTGGGCCCCCACCAGCCTGACCAGGCCCCGCCCC
 CCCGACAGCGAGGGCAGCAGGAGCAGCAGCAGCAGCAGCAGCAACAACAACAACTACTG
 CGCCCTGGGCTGCTACGGCGGCTGGCACCTGAGCGCCCTGCCCGGCAACACCCAGAGCAGCG
 10 GCCCCATCCCCGCCCTGGCCTGCGGCCCTGAGCTGCGACCACCAGGGCCTGGAGACCCAGCAG
 GCGTGCCCTGGGTGCTGGCCGGCCACTGCCAGAGGCCCGGCCTGCACGAGGACCTGCAGGG
 CATGCTGCTGCCCAGCGTGCTGAGCAAGGCCAGGAGCTGGACCTTC

- 15 In some embodiments, the IL9Ra is human IL9Ra. In some embodiments, the intracellular signaling domain (ICD) of human IL9Ra comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
- 20 at least 100% sequence identity to SEQ ID NO: 1. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
- 25 100% sequence identity to SEQ ID NO: 1 may be used to encode the ICD of human IL9Ra. In some embodiments, the ICD of human IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at
- 30 least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 2. In some embodiments, the ICD of human IL9Ra comprises SEQ ID NO: 1. In some embodiments, the ICD of human IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 2.

In some embodiments, the IL9Ra is human IL9Ra. In some embodiments, the transmembrane domain (TM) of human IL9Ra comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 3. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 3 may be used to encode the TM of human IL9Ra. In some embodiments, the TM of human IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 4. In some embodiments, the TM of human IL9Ra comprises SEQ ID NO: 3. In some embodiments, the TM of human IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 4.

In some embodiments, the PD1 is human PD1. In some embodiments, the ligand binding domain (LBD) of human PD1 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 205. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 205 may be used to encode the LBD of human PD1. In some embodiments, the LBD of human PD1 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 205.

99%, or at least 100% sequence identity to SEQ ID NO: 206. In some embodiments, the LBD of human PD1 comprises SEQ ID NO: 205. In some embodiments, the LBD of human PD1 is encoded by a nucleic acid comprising SEQ ID NO: 206.

In some embodiments, the TGFbRI is human TGFbRI. In some embodiments, the
5 ligand binding domain (LBD) of human TGFbRI comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
10 100% sequence identity to SEQ ID NO: 207. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
15 100% sequence identity to SEQ ID NO: 207 may be used to encode the LBD of human TGFbRI. In some embodiments, the LBD of human TGFbRI is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 208.
20 In some embodiments, the LBD of human TGFbRI comprises SEQ ID NO: 207. In some embodiments, the LBD of human TGFbRI is encoded by a nucleic acid comprising SEQ ID NO: 208.

In some embodiments, the TGFbRII is human TGFbRII. In some embodiments, the
ligand binding domain (LBD) of human TGFbRII comprises an amino acid sequence havng
25 at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
100% sequence identity to SEQ ID NO: 209. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at
30 least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least
100% sequence identity to SEQ ID NO: 209 may be used to encode the LBD of human

TGFbRII. In some embodiments, the LBD of human TGFbRII is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 210. In some embodiments, the LBD of human TGFbRII comprises SEQ ID NO: 209. In some embodiments, the LBD of human TGFbRII is encoded by a nucleic acid comprising SEQ ID NO: 210.

In some embodiments, the TIGIT is human TIGIT. In some embodiments, the ligand binding domain (LBD) of human TIGIT comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 211. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 211 may be used to encode the LBD of human TIGIT. In some embodiments, the LBD of human TIGIT is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 212. In some embodiments, the LBD of human TIGIT comprises SEQ ID NO: 211. In some embodiments, the LBD of human TIGIT is encoded by a nucleic acid comprising SEQ ID NO: 212.

In some embodiments, the TIM3 is human TIM3. In some embodiments, the ligand binding domain (LBD) of human TIM3 comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 213. As understood in the art, the genetic code is

degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least

5 100% sequence identity to SEQ ID NO: 213 may be used to encode the LBD of human TIM3. In some embodiments, the LBD of human TIM3 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at

10 least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 214. In some embodiments, the LBD of human TIM3 comprises SEQ ID NO: 213. In some embodiments, the LBD of human TIM3 is encoded by a nucleic acid comprising SEQ ID NO: 214.

In some embodiments, the chimeric cytokine receptor comprises a human PD1 LBD

15 fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

20 to SEQ ID NO: 215. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

25 to SEQ ID NO: 215 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

30 least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 216. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 215. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 216.

In some embodiments, the chimeric cytokine receptor comprises a human TGFRI LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 217. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 217 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 218. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 217. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 218.

In some embodiments, the chimeric cytokine receptor comprises a human TGFRII LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 219. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 219 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a

nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 220. In some
5 embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 219. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 220.

In some embodiments, the chimeric cytokine receptor comprises a human TIGIT LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the
10 chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 221. As understood in the art, the genetic code is degenerate and any
15 nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 221 may be used to encode the chimeric cytokine receptor. In some
20 embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 222. In some
25 embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 221. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 222.

In some embodiments, the chimeric cytokine receptor comprises a human TIM3 LBD fused to a human IL9Ra TM, fused to a human IL9Ra ICD. In some embodiments, the
30 chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

- to SEQ ID NO: 223. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 223 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 224. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 223. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 224.
- 15 In some embodiments, the IL9Ra is murine IL9Ra. In some embodiments, the intracellular signaling domain (ICD) of murine IL9Ra comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 225. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 225 may be used to encode the ICD of murine IL9Ra. In some embodiments, the ICD of murine IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 226 or SEQ ID NO: 302. In some embodiments, the ICD of murine IL9Ra comprises SEQ ID NO: 225. In some embodiments, the ICD of murine IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 226 or SEQ ID NO: 302.

In some embodiments, the IL9Ra is murine IL9Ra. In some embodiments, the transmembrane domain (TM) of murine IL9Ra comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 227. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 227 may be used to encode the TM of murine IL9Ra. In some embodiments, the TM of murine IL9Ra is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 228. In some embodiments, the TM of murine IL9Ra comprises SEQ ID NO: 227. In some embodiments, the TM of murine IL9Ra is encoded by a nucleic acid comprising SEQ ID NO: 228.

In some embodiments, the PD1 is murine PD1. In some embodiments, the ligand binding domain (LBD) of murine PD1 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 229. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 229 may be used to encode the LBD of murine PD1. In some embodiments, the LBD of murine PD1 is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 229.

99%, or at least 100% sequence identity to SEQ ID NO: 230. In some embodiments, the LBD of murine PD1 comprises SEQ ID NO: 229. In some embodiments, the LBD of murine PD1 is encoded by a nucleic acid comprising SEQ ID NO: 230.

- In some embodiments, the TGFbRI is murine TGFbRI. In some embodiments, the
- 5 ligand binding domain (LBD) of murine TGFbRI comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 231. As understood in the art, the genetic code is
- 10 degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 231 may be used to encode the LBD of murine
- 15 TGFbRI. In some embodiments, the LBD of murine TGFbRI is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 232.
- 20 In some embodiments, the LBD of murine TGFbRI comprises SEQ ID NO: 231. In some embodiments, the LBD of murine TGFbRI is encoded by a nucleic acid comprising SEQ ID NO: 232.

- In some embodiments, the TGFbRII is murine TGFbRII. In some embodiments, the
- ligand binding domain (LBD) of murine TGFbRII comprises an amino acid sequence havng
- 25 at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 233. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at
- 30 least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 233 may be used to encode the LBD of murine

TGFbRII. In some embodiments, the LBD of murine TGFbRII is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 234. In some embodiments, the LBD of murine TGFbRII comprises SEQ ID NO: 233. In some embodiments, the LBD of murine TGFbRII is encoded by a nucleic acid comprising SEQ ID NO: 234.

In some embodiments, the TIGIT is murine TIGIT. In some embodiments, the ligand binding domain (LBD) of murine TIGIT comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 235. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 235 may be used to encode the LBD of murine TIGIT. In some embodiments, the LBD of murine TIGIT is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 236. In some embodiments, the LBD of murine TIGIT comprises SEQ ID NO: 235. In some embodiments, the LBD of murine TIGIT is encoded by a nucleic acid comprising SEQ ID NO: 236.

In some embodiments, the TIM3 is murine TIM3. In some embodiments, the ligand binding domain (LBD) of murine TIM3 comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 237. As understood in the art, the genetic code is

degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least

5 100% sequence identity to SEQ ID NO: 237 may be used to encode the LBD of murine TIM3. In some embodiments, the LBD of murine TIM3 is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at

10 least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 238. In some embodiments, the LBD of murine TIM3 comprises SEQ ID NO: 237. In some embodiments, the LBD of murine TIM3 is encoded by a nucleic acid comprising SEQ ID NO: 238.

In some embodiments, the chimeric cytokine receptor comprises a murine PD1 LBD

15 fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

20 to SEQ ID NO: 239. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

25 to SEQ ID NO: 239 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

30 least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 240. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 239. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 240.

In some embodiments, the chimeric cytokine receptor comprises a murine TGF β RbI LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 241. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 241 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 242. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 241. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 242.

In some embodiments, the chimeric cytokine receptor comprises a murine TGF β RbII LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 243. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 243 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a

nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 244. In some
5 embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 243. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 244.

In some embodiments, the chimeric cytokine receptor comprises a murine TIGIT LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the
10 chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 245. As understood in the art, the genetic code is degenerate and any
15 nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 245 may be used to encode the chimeric cytokine receptor. In some
20 embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 246. In some
25 embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 245. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 246.

In some embodiments, the chimeric cytokine receptor comprises a murine TIM3 LBD fused to a murine IL9Ra TM, fused to a murine IL9Ra ICD. In some embodiments, the
30 chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity

- to SEQ ID NO: 247. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 247 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 248. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 247. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 248.
- 15 In some embodiments, the anti-checkpoint inhibitor antigen binding domain is an anti-CTLA4 antigen binding domain. In some embodiments, the anti-CTLA4 antigen binding domain is derived from ipilimumab and comprises an LCDR1 comprising SEQ ID NO: 294, an LCDR2 comprising SEQ ID NO: 295, an LCDR3 comprising SEQ ID NO: 296, an HCDR1 comprising SEQ ID NO: 297, an HCDR2 comprising SEQ ID NO: 298, and an
- 20 HCDR3 comprising SEQ ID NO: 299.
- In some embodiments, the anti-checkpoint inhibitor antigen binding domain is an anti-CTLA4 antigen binding domain. In some embodiments, the anti-CTLA4 antigen binding domain is derived from ipilimumab and comprises a light chain having an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 289. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 289 may be used to encode the anti-

CTLA4 light chain. In some embodiments, the anti-CTLA4 light chain comprises SEQ ID NO: 289.

In some embodiments, the anti-checkpoint inhibitor antigen binding domain is an anti-CTLA4 antigen binding domain. In some embodiments, the anti-CTLA4 antigen binding domain is derived from ipilimumab and comprises a heavy chain having an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 290. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 290 may be used to encode the anti-CTLA4 heavy chain. In some embodiments, the anti-CTLA4 heavy chain comprises SEQ ID NO: 290.

In some embodiments, the anti-checkpoint inhibitor antigen binding domain is an anti-CTLA4 antigen binding domain. In some embodiments, the anti-CTLA4 antigen binding domain is derived from ipilimumab and comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 293. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 293 may be used to encode the anti-CTLA4 antigen binding domain. In some embodiments, the anti-CTLA4 antigen binding domain comprises SEQ ID NO: 293.

In some embodiments, the chimeric cytokine receptor comprises an extracellular domain comprising an anti-CTLA4 antigen binding domain, an hIL9Ra transmembrane domain, and an hIL9Ra intracellular signaling domain. In some embodiments, the chimeric

cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ

- 5 ID NO: 300. As understood in the art, the genetic code is degenerate and any nucleotide sequence which encodes an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID
- 10 NO: 300 may be used to encode the chimeric cytokine receptor. In some embodiments, the chimeric cytokine receptor comprises SEQ ID NO: 300. In some embodiments, the chimeric cytokine receptor is encoded by a nucleic acid comprising SEQ ID NO: 301.

- In some embodiments, the chimeric cytokine receptor of the invention is a switch receptor which switches the signal from the binding of a ligand to the ligand-binding domain
- 15 (LBD) of the inhibitory immunoreceptor to the immunostimulatory signal transduced by the intracellular signaling domain (ICD) of the IL9Ra. The ligand which binds to the LBD is naturally expressed by tumor cells. In some embodiments, the chimeric cytokine receptor of the invention activates IL9Ra signaling in the immune cells upon binding of a checkpoint inhibitor to the anti-checkpoint inhibitor antigen binding domain. The checkpoint inhibitor is
- 20 expressed by T cells.

- In one aspect, the invention provides modified cells (*e.g.*, immune cells or precursor cells thereof) which are engineered to express a chimeric cytokine receptor and a chimeric antigen receptor (CAR). The chimeric cytokine receptor binds a ligand or an immune checkpoint inhibitor and the CAR binds a tumor antigen, where each of the ligand and the
- 25 tumor antigen is naturally expressed by tumor cells, and the checkpoint inhibitor is expressed by T cells. Accordingly, the chimeric cytokine receptors and uses thereof disclosed herein improve chimeric antigen receptor (CAR) cell immunotherapy for treating cancer by (1) exploiting naturally existing molecules (*i.e.*, ligands and tumor antigens) in tumors and/or checkpoint inhibitors in T cells to convert immunosuppressive signals into
- 30 immunostimulatory signals in immune cells (*e.g.*, T cells), (2) altering the phenotype of immune cells expressing the chimeric cytokine receptor and the CAR upon ligand and/or checkpoint inhibitor binding at a tumor site, and (3) enabling IL-9 signaling in the immune

cells expressing the chimeric cytokine receptor and the CAR to improve effector functions *in situ* and/or to down regulate immune cell exhaustion.

In some embodiments, the chimeric cytokine receptor described herein is co-expressed on an immune cell (*e.g.*, a T cell) with any CAR targeting a tumor antigen, such as
5 any of the CARs described herein.

C. Chimeric Antigen Receptors (CARs)

The present invention provides a modified immune cell or precursor cell thereof (*e.g.*, a modified T cell) engineered to express a CAR and an IL9Ra or a chimeric cytokine receptor
10 comprising an IL9Ra ICD. The present invention also provides a modified immune cell or precursor cell thereof (*e.g.*, a modified T cell), expressing a CAR, wherein expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA. In each aspect, the CAR comprises an extracellular tumor antigen binding domain, a transmembrane domain, and an intracellular domain. The
15 extracellular tumor antigen binding domain of the CAR is operably linked to another domain of the CAR, such as a hinge domain, the transmembrane domain, or the intracellular domain, each described elsewhere herein.

The tumor antigen binding domain described herein can be combined with any of the transmembrane domains described herein, any of the intracellular domains or cytoplasmic
20 domains described herein, or any of the other domains described herein that may be included in a CAR of the present invention, such as a hinge domain or a spacer sequence.

The CAR of the present invention may also include a leader sequence as described herein. The CAR of the present invention may also include a hinge domain as described herein. The CAR of the present invention may also include one or more spacer domains or
25 linkers as described herein which may serve to link one domain of the CAR to the next domain.

Antigen Binding Domain

The antigen binding domain of a CAR is an extracellular region of the CAR for
30 binding to a specific target antigen including proteins, carbohydrates, and glycolipids. The CAR of the invention comprises an antigen binding domain that is capable of binding a tumor antigen. Suitable tumor antigens are known in the art and include, but are not limited to, alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5,

CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3),

5 HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof. In some embodiments, the tumor antigen is selected from mesothelin,

10 GD2, HER2, GPC2, TnMuc1, CD70, PMSA, and EGFRvIII.

The antigen binding domain can include any domain that binds to the antigen (*e.g.*, tumor antigen) and may include, but is not limited to, a monoclonal antibody (mAb), a polyclonal antibody, a synthetic antibody, a human antibody, a humanized antibody, a non-human antibody, a single-domain antibody, a full length antibody or any antigen-binding

15 fragment thereof, a Fab, and a single-chain variable fragment (scFv). In some embodiments, the antigen binding domain comprises an aglycosylated antibody or a fragment thereof or scFv thereof. In some embodiments, the tumor antigen binding domain is an scFv.

As used herein, the term “single-chain variable fragment” or “scFv” is a fusion protein of the variable regions of the heavy (VH) and light (VL) chains of an

20 immunoglobulin (*e.g.*, mouse or human) covalently linked to form a VH::VL heterodimer. The variable heavy (VH) and light (VL) chains are either joined directly or joined by a peptide linker, which connects the N-terminus of the VH with the C-terminus of the VL, or the C-terminus of the VH with the N-terminus of the VL. In some embodiments, the antigen binding domain (*e.g.*, tumor antigen binding domain) comprises an scFv having the

25 configuration from N-terminus to C-terminus, VH – linker – VL. In some embodiments, the antigen binding domain comprises an scFv having the configuration from N-terminus to C-terminus, VL – linker – VH or VH – linker -VL. Those of skill in the art would be able to select the appropriate configuration for use in the present invention.

The linker is usually rich in glycine for flexibility, as well as serine or threonine for

30 solubility. The linker can link the heavy chain variable region and the light chain variable region of the extracellular antigen-binding domain. Non-limiting examples of linkers are disclosed in Shen et al., Anal. Chem. 80(6):1910-1917 (2008) and WO 2014/087010, the contents of which are hereby incorporated by reference in their entireties. Various linker

sequences are known in the art, including, without limitation, glycine serine (GS) linkers. Those of skill in the art would be able to select the appropriate linker sequence for use in the present invention. In one embodiment, an antigen binding domain of the present invention comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL are separated by a linker sequence.

Despite removal of the constant regions and the introduction of a linker, scFv proteins retain the specificity of the original immunoglobulin. Single chain Fv polypeptide antibodies can be expressed from a nucleic acid comprising VH- and VL-encoding sequences as described by Huston, et al. (Proc. Nat. Acad. Sci. USA, 85:5879-5883, 1988). See, also, U.S. Patent Nos. 5,091,513, 5,132,405 and 4,956,778; and U.S. Patent Publication Nos. 20050196754 and 20050196754. Antagonistic scFvs having inhibitory activity have been described (see, e.g., Zhao et al., Hybridoma (Larchmt) 2008 27(6):455-51; Peter et al., J Cachexia Sarcopenia Muscle 2012 August 12; Shieh et al., J Immunol 2009 183(4):2277-85; Giomarelli et al., Thromb Haemost 2007 97(6):955-63; Fife et al., J Clin Invest 2006 116(8):2252-61; Brocks et al., Immunotechnology 1997 3(3):173-84; Moosmayer et al., Ther Immunol 1995 2(10):31-40). Agonistic scFvs having stimulatory activity have been described (see, e.g., Peter et al., J Biol Chem 2003 278(38):36740-7; Xie et al., Nat Biotech 1997 15(8):768-71; Ledbetter et al., Crit Rev Immunol 1997 17(5-6):427-55; Ho et al., Biochim Biophys Acta 2003 1638(3):257-66).

As used herein, "Fab" refers to a fragment of an antibody structure that binds to an antigen but is monovalent and does not have a Fc portion, for example, an antibody digested by the enzyme papain yields two Fab fragments and an Fc fragment (e.g., a heavy (H) chain constant region; Fc region that does not bind to an antigen).

As used herein, "F(ab')₂" refers to an antibody fragment generated by pepsin digestion of whole IgG antibodies, wherein this fragment has two antigen binding (ab') (bivalent) regions, wherein each (ab') region comprises two separate amino acid chains, a part of a H chain and a light (L) chain linked by an S—S bond for binding an antigen and where the remaining H chain portions are linked together. A "F(ab')₂" fragment can be split into two individual Fab' fragments.

In other embodiments, the antigen binding domain comprises an antibody mimetic protein such as, for example, designed ankyrin repeat protein (DARPin), affibody, monobody, (i.e., adnectin), affilin, affimer, affitin, alphabody, avimer, Kunitz domain

peptide, or anticalin. Constructs with specific binding affinities can be generated using DARPIn libraries *e.g.*, as described in Seeger, et al., , Protein Sci., 22:1239-1257 (2013).

In some embodiments, the antigen binding domain may be derived from the same species in which the CAR will ultimately be used. For example, for use in humans, the antigen binding domain of the CAR may comprise a human antibody or a fragment thereof. In some embodiments, the antigen binding domain may be derived from a different species in which the CAR will ultimately be used. For example, for use in humans, the antigen binding domain of the CAR may comprise a murine antibody or a fragment thereof, or a humanized murine antibody or a fragment thereof.

In certain embodiments, the antigen binding domain comprises a heavy chain variable region that comprises three heavy chain complementarity determining regions (HCDRs) and a light chain variable region that comprises three light chain complementarity determining regions (LCDRs). In certain embodiments, the antigen binding domain comprises a linker.

In some embodiments, the light chain is encoded by a first nucleotide sequence and the heavy chain is encoded by a second nucleotide sequence. In some embodiments, the first nucleotide sequence and the second nucleotide sequence are linked by a nucleotide sequence encoding a 2A self-cleaving peptide, such as a P2A sequence. In some embodiments, the heavy chain lacks a CH3 region.

Transmembrane Domain

CARs of the present invention may comprise a transmembrane domain that connects the antigen binding domain of the CAR to the intracellular domain of the CAR. The transmembrane domain of the CAR is a region that is capable of spanning the plasma membrane of a cell (*e.g.*, an immune cell or precursor thereof). In some embodiments, the transmembrane domain is interposed between the antigen binding domain and the intracellular domain of a CAR.

In some embodiments, the transmembrane domain is naturally associated with one or more of the domains in the CAR. In some embodiments, the transmembrane domain can be selected or modified by one or more amino acid substitutions to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins, to minimize interactions with other members of the receptor complex.

The transmembrane domain may be derived either from a natural or a synthetic source. Where the source is natural, the domain may be derived from any membrane-bound

or transmembrane protein, *e.g.*, a Type I transmembrane protein. Where the source is synthetic, the transmembrane domain may be any artificial sequence that facilitates insertion of the CAR into a cell membrane, *e.g.*, an artificial hydrophobic sequence. Examples of the transmembrane domain of particular use in this invention include, without limitation,

5 transmembrane domains derived from (*i.e.* comprise at least the transmembrane region(s) of) the alpha, beta or zeta chain of the T cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD7, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134 (OX-40), CD137 (4-1BB), CD154 (CD40L), ICOS, CD278, Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 or a transmembrane domain derived from a killer

10 immunoglobulin-like receptor (KIR).

In certain embodiments, the transmembrane domain comprises a transmembrane domain of CD8. In certain embodiments, the transmembrane domain of CD8 is a transmembrane domain of CD8 α .

In some embodiments, the transmembrane domain may be synthetic, in which case it

15 will comprise predominantly hydrophobic residues such as leucine and valine. Preferably a triplet of phenylalanine, tryptophan and valine will be found at each end of a synthetic transmembrane domain.

The transmembrane domains described herein can be combined with any of the antigen binding domains described herein, any of the intracellular domains described herein,

20 or any of the other domains described herein that may be included in the CAR.

In some embodiments, the transmembrane domain further comprises a hinge region. The CAR of the present invention may also include a hinge region. The hinge region of the CAR is a hydrophilic region which is located between the antigen binding domain and the transmembrane domain. In some embodiments, this domain facilitates proper protein folding

25 for the CAR. The hinge region is an optional component for the CAR. The hinge region may include a domain selected from Fc fragments of antibodies, hinge regions of antibodies, CH2 regions of antibodies, CH3 regions of antibodies, artificial hinge sequences or combinations thereof. Examples of hinge regions include, without limitation, a CD8a hinge, artificial hinges made of polypeptides which may be as small as, three glycines (Gly), as well as CH1 and CH3 domains of IgGs (such as human IgG4).

30

In some embodiments, the CAR of the present disclosure includes a hinge region that connects the antigen binding domain with the transmembrane domain, which, in turn, connects to the intracellular domain. The hinge region is preferably capable of supporting the

antigen binding domain to recognize and bind to the target antigen on the target cells (see, e.g., Hudecek et al., *Cancer Immunol. Res.* (2015) 3(2): 125-135). In some embodiments, the hinge region is a flexible domain, thus allowing the antigen binding domain to have a structure to optimally recognize the specific structure and density of the target antigens on a cell such as tumor cell (Hudecek et al., *supra*). The flexibility of the hinge region permits the hinge region to adopt many different conformations.

In some embodiments, the hinge region is an immunoglobulin heavy chain hinge region. In some embodiments, the hinge region is a hinge region polypeptide derived from a receptor (e.g., a CD8-derived hinge region).

The hinge region can have a length of from about 4 amino acids to about 50 amino acids, e.g., from about 4 aa to about 10 aa, from about 10 aa to about 15 aa, from about 15 aa to about 20 aa, from about 20 aa to about 25 aa, from about 25 aa to about 30 aa, from about 30 aa to about 40 aa, or from about 40 aa to about 50 aa. In some embodiments, the hinge region can have a length of greater than 5 aa, greater than 10 aa, greater than 15 aa, greater than 20 aa, greater than 25 aa, greater than 30 aa, greater than 35 aa, greater than 40 aa, greater than 45 aa, greater than 50 aa, greater than 55 aa, or more.

Suitable hinge regions can be readily selected and can be of any of a number of suitable lengths, such as from 1 amino acid (e.g., Gly) to 20 amino acids, from 2 amino acids to 15 amino acids, from 3 amino acids to 12 amino acids, including 4 amino acids to 10 amino acids, 5 amino acids to 9 amino acids, 6 amino acids to 8 amino acids, or 7 amino acids to 8 amino acids, and can be 1, 2, 3, 4, 5, 6, or 7 amino acids. Suitable hinge regions can have a length of greater than 20 amino acids (e.g., 30, 40, 50, 60 or more amino acids).

For example, hinge regions include glycine polymers (G)_n, glycine-serine polymers, glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art. Glycine and glycine-serine polymers can be used; both Gly and Ser are relatively unstructured, and therefore can serve as a neutral tether between components. Glycine polymers can be used; glycine accesses significantly more phi-psi space than even alanine, and is much less restricted than residues with longer side chains (see, e.g., Scheraga, *Rev. Computational. Chem.* (1992) 2: 73-142). The hinge region can comprise an amino acid sequence of a human IgG1, IgG2, IgG3, or IgG4, hinge region (see, e.g., Yan et al., *J. Biol. Chem.* (2012) 287: 5891-5897). In one embodiment, the hinge region can comprise an amino acid sequence derived from human CD8, or a variant thereof.

Intracellular Signaling Domain

The CAR of the present invention also includes an intracellular signaling domain. The terms “intracellular signaling domain” and “intracellular domain” are used interchangeably herein. The intracellular signaling domain of the CAR is responsible for
 5 activation of at least one of the effector functions of the cell in which the CAR is expressed (*e.g.*, immune cell). The intracellular signaling domain transduces the effector function signal and directs the cell (*e.g.*, immune cell) to perform its specialized function, *e.g.*, harming and/or destroying a target cell.

Examples of an intracellular domain for use in the invention include, but are not
 10 limited to, the cytoplasmic portion of a surface receptor, co-stimulatory molecule, and any molecule that acts in concert to initiate signal transduction in the T cell, as well as any derivative or variant of these elements and any synthetic sequence that has the same functional capability.

Examples of the intracellular signaling domain include, without limitation, the ζ chain
 15 of the T cell receptor complex or any of its homologs, *e.g.*, η chain, Fc γ RI γ and β chains, MB 1 (Iga) chain, B29 (Ig) chain, etc., human CD3 zeta chain, CD3 polypeptides (Δ , δ and ϵ), syk family tyrosine kinases (Syk, ZAP 70, etc.), src family tyrosine kinases (Lck, Fyn, Lyn, etc.), and other molecules involved in T cell transduction, such as CD2, CD5 and CD28. In one
 20 embodiment, the intracellular signaling domain may comprise an intracellular signaling domain of a protein selected from human CD3 zeta chain, Fc γ RIII, Fc γ RI, DAP10, DAP12, cytoplasmic tails of Fc receptors, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptors, and combinations thereof.

In one embodiment, the intracellular signaling domain of the CAR includes any portion of one or more co-stimulatory molecules, such as at least one signaling domain from
 25 CD2, CD3, CD8, CD27, CD28, ICOS, 4-1BB, PD-1, any derivative or variant thereof, such as any synthetic sequence thereof, that has the same functional capability, and any combination thereof.

Other examples of the intracellular domain include a fragment or domain from one or more molecules or receptors including, but not limited to, TCR, CD3 zeta, CD3 gamma, CD3
 30 delta, CD3 epsilon, CD86, common FcR gamma, FcR beta (Fc Epsilon RIb), CD79a, CD79b, Fcgamma RIIa, DAP10, DAP12, T cell receptor (TCR), CD8, CD27, CD28, 4-1BB (CD137), OX9, OX40, CD30, CD40, PD-1, ICOS, a KIR family protein, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically

binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD127, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CDlib, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA- 1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, other co-stimulatory molecules described herein, any derivative, variant, or fragment thereof, any synthetic sequence of a co-stimulatory molecule that has the same functional capability, and any combination thereof.

Additional examples of intracellular domains include, without limitation, intracellular signaling domains of several types of various other immune signaling receptors, including, but not limited to, first, second, and third generation T cell signaling proteins including CD3, B7 family costimulatory, and Tumor Necrosis Factor Receptor (TNFR) superfamily receptors (see, *e.g.*, Park and Brentjens, J. Clin. Oncol. (2015) 33(6): 651-653). Additionally, intracellular signaling domains may include signaling domains used by NK and NKT cells (see, *e.g.*, Hermanson and Kaufman, Front. Immunol. (2015) 6: 195) such as signaling domains of NKp30 (B7-H6) (see, *e.g.*, Zhang et al., J. Immunol. (2012) 189(5): 2290-2299), and DAP 12 (see, *e.g.*, Topfer et al., J. Immunol. (2015) 194(7): 3201-3212), NKG2D, NKp44, NKp46, DAP10, and CD3z.

Intracellular signaling domains suitable for use in the CAR of the present invention include any desired signaling domain that provides a distinct and detectable signal (*e.g.*, increased production of one or more cytokines by the cell; change in transcription of a target gene; change in activity of a protein; change in cell behavior, *e.g.*, cell death; cellular proliferation; cellular differentiation; cell survival; modulation of cellular signaling responses; etc.) in response to activation of the CAR (*i.e.*, activated by antigen and dimerizing agent). In some embodiments, the intracellular signaling domain includes at least one (*e.g.*, one, two, three, four, five, six, etc.) ITAM motifs as described below. In some embodiments, the intracellular signaling domain includes DAP10/CD28 type signaling chains. In some embodiments, the intracellular signaling domain is not covalently attached to the membrane bound CAR, but is instead diffused in the cytoplasm.

Intracellular signaling domains suitable for use in the CAR of the present invention include immunoreceptor tyrosine-based activation motif (ITAM)-containing intracellular signaling polypeptides. In some embodiments, an ITAM motif is repeated twice in an intracellular signaling domain, where the first and second instances of the ITAM motif are
 5 separated from one another by 6 to 8 amino acids. In one embodiment, the intracellular signaling domain of the CAR comprises 3 ITAM motifs.

In some embodiments, intracellular signaling domains includes the signaling domains of human immunoglobulin receptors that contain immunoreceptor tyrosine based activation motifs (ITAMs) such as, but not limited to, FcγRI, FcγRIIA, FcγRIIC,
 10 FcγRIIIA, FcRL5 (see, *e.g.*, Gillis et al., *Front. Immunol.* (2014) 5:254).

A suitable intracellular signaling domain can be an ITAM motif-containing portion that is derived from a polypeptide that contains an ITAM motif. For example, a suitable intracellular signaling domain can be an ITAM motif-containing domain from any ITAM motif-containing protein. Thus, a suitable intracellular signaling domain need not contain the
 15 entire sequence of the entire protein from which it is derived. Examples of suitable ITAM motif-containing polypeptides include, but are not limited to: DAP12, FCER1G (Fc epsilon receptor I gamma chain), CD3D (CD3 delta), CD3E (CD3 epsilon), CD3G (CD3 gamma), CD3Z (CD3 zeta), and CD79A (antigen receptor complex-associated protein alpha chain).

In one embodiment, the intracellular signaling domain is derived from DAP12 (also
 20 known as TYROBP; TYRO protein tyrosine kinase binding protein; KARAP; PLOSL; DNAX-activation protein 12; KAR-associated protein; TYRO protein tyrosine kinase-binding protein; killer activating receptor associated protein; killer-activating receptor-associated protein; etc.). In one embodiment, the intracellular signaling domain is derived from FCER1G (also known as FCRG; Fc epsilon receptor I gamma chain; Fc receptor
 25 gamma-chain; fc-epsilon RI-gamma; fcRgamma; fceRI gamma; high affinity immunoglobulin epsilon receptor subunit gamma; immunoglobulin E receptor, high affinity, gamma chain; etc.). In one embodiment, the intracellular signaling domain is derived from T-cell surface glycoprotein CD3 delta chain (also known as CD3D; CD3-DELTA; T3D; CD3 antigen, delta subunit; CD3 delta; CD3d antigen, delta polypeptide (TiT3 complex); OKT3,
 30 delta chain; T-cell receptor T3 delta chain; T-cell surface glycoprotein CD3 delta chain; etc.). In one embodiment, the intracellular signaling domain is derived from T-cell surface glycoprotein CD3 epsilon chain (also known as CD3e, T-cell surface antigen T3/Leu-4 epsilon chain, T-cell surface glycoprotein CD3 epsilon chain, AI504783, CD3, CD3epsilon,

- T3e, etc.). In one embodiment, the intracellular signaling domain is derived from T-cell surface glycoprotein CD3 gamma chain (also known as CD3G, T-cell receptor T3 gamma chain, CD3-GAMMA, T3G, gamma polypeptide (TiT3 complex), etc.). In one embodiment, the intracellular signaling domain is derived from T-cell surface glycoprotein CD3 zeta chain (also known as CD3Z, T-cell receptor T3 zeta chain, CD247, CD3-ZETA, CD3H, CD3Q, T3Z, TCRZ, etc.). In one embodiment, the intracellular signaling domain is derived from CD79A (also known as B-cell antigen receptor complex-associated protein alpha chain; CD79a antigen (immunoglobulin-associated alpha); MB-1 membrane glycoprotein; ig-alpha; membrane-bound immunoglobulin-associated protein; surface IgM-associated protein; etc.).
- In some embodiments, the intracellular signaling domain includes a cytoplasmic signaling domain of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, or CD66d. In one embodiment, the intracellular signaling domain in the CAR includes a cytoplasmic signaling domain of human CD3 zeta.

While usually the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire molecule. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. The intracellular signaling domain includes any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

The intracellular domains described herein can be combined with any of the antigen binding domains described herein, any of the transmembrane domains described herein, or any of the other domains described herein that may be included in the CAR.

In certain embodiments, the intracellular domain comprises a costimulatory domain of 4-1BB. In certain embodiments, the intracellular domain comprises an intracellular domain of CD3 ζ or a variant thereof. In certain embodiments, the intracellular domain comprises a costimulatory domain of 4-1BB and an intracellular domain of CD3 ζ .

Tolerable variations of the individual CAR domain sequences (leader, antigen binding domain, hinge, transmembrane, and/or intracellular domains) will be known to those of skill in the art. For example, in certain embodiments the CAR domain comprises an amino acid sequence that has at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to any naturally-occurring or known sequence.

Amino acid and nucleotide sequences for certain embodiments of the CAR and domains thereof are described as follows:

Anti-human mesothelin (anti-hMSLN) scFv (M5)

5 (SEQ ID NO: 79)

MALPVTALLLPALALLHAARPQVQLVQSGAEVEKPGASVKVSKASGYTFSTDYYMHWVRQAP
GQGLEWMGWINPNSGGTNYAQKFQGRVTMTDRDTSISTAYMELSRLSDDTAVYYCASGWDFD
YWGQGTLLTVSSGGGGSGGGSGGGSGGGSDIVMTQSPSSLSASVGRVTITCRASQSIR
YYLSWYQQKPGKAPKLLIYTASILQNGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLQTY
10 TTPDFGPGTKVEIK

Anti-human mesothelin (anti-hMSLN) scFv (M5)

(SEQ ID NO: 80)

ATGGCCCTGCCCCTGACCGCCCTGCTGCTGCCCCTGGCCCTGCTGCTGCACGCCGCCAGGCC
15 CCAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGGAGAAGCCCGGCGCCAGCGTGAAGGTGA
GCTGCAAGGCCAGCGGCTACACCTTACCGACTACTACATGCACTGGGTGAGGCAGGCCCCC
GGCCAGGGCCTGGAGTGGATGGGCTGGATCAACCCCAACAGCGGCGGCACCAACTACGCCCA
GAAGTTCAGGGCAGGGTGACCATGACCAGGGACACCAGCATCAGCACCGCCTACATGGAGC
TGAGCAGGCTGAGGAGCGACGACACCGCCGTGTACTACTGCGCCAGCGGCTGGGACTTCGAC
20 TACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGGCGGCGGCAGCGGCGGCGGCGG
CAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCGTGATGACCCAGAGCCCCAGCA
GCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGG
TACTACCTGAGCTGGTACCAGCAGAAGCCCGCAAGGCCCCCAAGCTGCTGATCTACACCGC
CAGCATCCTGCAGAACGGCGTGCCCAGCAGGTTTCAGCGGCAGCGGCAGCGGCACCGACTTCA
25 CCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCTGCAGACCTAC
ACCACCCCCGACTTCGGCCCCGGCACCAAGGTGGAGATCAAG

Human CD8 Hinge

(SEQ ID NO: 81)

30 TTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

Human CD8 Hinge

(SEQ ID NO: 82)

ACCACCACCCCGCCCCAGGCCCCCACCACCCGCCCCCACCATCGCCAGCCAGCCCCCTGAG
CCTGAGGCCCCGAGGCCTGCAGGCCCCGCCGCCGGCGGCCGTGCACACCAGGGGCCTGGACT
TCGCCTGCGAC

5 Human CD8 TM

(SEQ ID NO: 83)

IYIWAPLAGTCGVLLLSLVITLYC

Human CD8 TM

10 (SEQ ID NO: 84)

ATCTACATCTGGGCCCCCTGGCCGGCACCTGCGGCGTGCTGCTGCTGAGCCTGGTGATCAC
CCTGTACTGC

Human CD8 Hinge and TM

15 (SEQ ID NO: 85)

TTTTAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS
LVITLYC

Human CD8 Hinge and TM

20 (SEQ ID NO: 86)

ACCACCACCCCGCCCCAGGCCCCCACCACCCGCCCCCACCATCGCCAGCCAGCCCCCTGAG
CCTGAGGCCCCGAGGCCTGCAGGCCCCGCCGCCGGCGGCCGTGCACACCAGGGGCCTGGACT
TCGCCTGCGACATCTACATCTGGGCCCCCCTGGCCGGCACCTGCGGCGTGCTGCTGCTGAGC
CTGGTGATCACCCCTGTACTGC

25

Human CD28 TM

(SEQ ID NO: 87)

FWVLVVVGGVLACYSLLVTVAFIIFWV

30 Human CD28 TM

(SEQ ID NO: 88)

TTCTGGGTGCTGGTGGTGGTGGGCGGCGTGCTGGCCTGCTACAGCCTGCTGGTGACCGTGGC
CTTCATCATCTTCTGGGTG

Human CD28 costimulatory domain (hCD28 ICD)

(SEQ ID NO: 89)

RSKRSRLLSHYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

5 Human CD28 costimulatory domain (hCD28 ICD)

(SEQ ID NO: 90)

AGGAGCAAGAGGAGCAGGCTGCTGCACAGCGACTACATGAACATGACCCCCAGGAGGCCCGG
CCCCACCAGGAAGCACTACCAGCCCTACGCCCCCCCCAGGGACTTCGCCGCCTACAGGAGC

10 Human 4-1BB costimulatory domain (h41BB ICD)

(SEQ ID NO: 91)

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL

Human 4-1BB costimulatory domain (h41BB ICD)

15 (SEQ ID NO: 92)

AAGAGGGGCAGGAAGAAGCTGCTGTACATCTTCAAGCAGCCCTTCATGAGGCCCCGTGCAGAC
CACCCAGGAGGAGGACGGCTGCAGCTGCAGGTTCCCCGAGGAGGAGGAGGGCGGCTGCGAGC
TG

20 Human CD3z stimulatory domain (hCD3z ICD)

(SEQ ID NO: 93)

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL
QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

25 Human CD3z stimulatory domain (hCD3z ICD)

(SEQ ID NO: 94)

AGGGTGAAGTTCAGCAGGAGCGCCGACGCCCCGCCTACAAGCAGGGCCAGAACCAGCTGTA
CAACGAGCTGAACCTGGGCAGGAGGGAGGAGTACGACGTGCTGGACAAGAGGAGGGGCAGGG
ACCCCAGATGGGCGGCAAGCCCAGGAGGAAGAACCCCAGGAGGGCCTGTACAACGAGCTG
30 CAGAAGGACAAGATGGCCGAGGCCTACAGCGAGATCGGCATGAAGGGCGAGAGGAGGAGGGG
CAAGGGCCACGACGGCCTGTACCAGGGCCTGAGCACCGCCACCAAGGACACCTACGACGCCC
TGCACATGCAGGCCCTGCCCCCAGG

Anti-murine mesothelin (anti-mMSLN) scFv (A03)

(SEQ ID NO: 95)

MASPLTRFLSLNLLLLGESIILGSGEATRAQVQLQESGPGLVKPSQTLSLTCTVSGGSISSG
 GYYWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV
 YYCARFDYGDFYDAFDIWGQGTMTVSSGGGSGGGGSGGGGSEIVLTQSPSSLSASVGDRTV
 5 TITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESQVPSRFSGSGSGTDFTLTISSLQPE
 DFATYYCQQFNSYPITFGQGTRLEIKRSG

Anti-murine mesothelin (anti-mMSLN) scFv (A03)

(SEQ ID NO: 96)

10 ATGGCTAGTCCGCTCACGAGGTTTTTGTCTCTGAACCTTCTCTTATTAGGGGAAAGCATAAT
 CCTGGGCAGCGGCGAGGCTACGCGGGCGCAGGTTTCTGCTGCAAGAGTCCGGACCCGGTCTGG
 TGAAGCCCAGCCAGACTTTGAGCCTGACCTGTACCGTATCTGGTGGCTCCATAAGTTCTGGA
 GGCTACTACTGGAGCTGGATAAGGCAGCACCCAGGGAAGGGCCTGGAGTGGATCGGCTATAT
 TTACTACAGCGGGAGCACTTATTATAATCCCTCATTTAAAGAGCAGGGTCACCATCTCAGTGG
 15 ACACATCCAAGAACCAGTTTCTGCTTGAACCTCTCTTCCGTAACAGCTGCTGACACTGCCGTT
 TACTATTGTGCCAGGTTTACTACGGAGATTTTTTACGATGCCCTTTGATATATGGGGCCAAGG
 CACCATGGTGACAGTCTCCTCAGGTGGAGGAGGCAGTGGGGGGGGGGGTCTGGGGGTGGTG
 GCTCTGAGATCGTTCTAAGCCAGAGCCGAGCAGCCTATCGGCGTCAGTGGGAGATAGAGTG
 ACCATTACCTGCAGGGCAAGTCAAGGCATAAGCAGCGCTCTGGCCTGGTACCAACAAAAGCC
 20 TGGAAGGCTCCTAAGCTGCTGATTTATGATGCTTCGAGTCTCGAAAGTGGTGTCCCGTCAA
 GGTTTTCTGGTAGTGGTTTCTGCTTACAGACTTACCTTACTATCAGCTCGCTCCAACAGAA
 GATTTCTGCAACATATTACTGCCAGCAGTTCAACAGCTACCCATTACATTTGGACAAGGAAC
 CCGGCTTGAAATTAAACGCTCAGGG

25 Murine CD8 Hinge

(SEQ ID NO: 97)

LQKVNSTTTKPVLRTSPVHPTGTSQPQRPEDCRPRGSVKGTGLDFACDIY

Murine CD8 Hinge

30 (SEQ ID NO: 98)

CTTCAGAAAGGTGAACAGCACAAACAAGCCAGTCTTGCGAACACCCAGTCTGTTCACCC
 TACGGGTACGTCTCAACCTCAGAGGCCTGAGGACTGTAGACCCCGTGGCTCTGTGAAAGGGA
 CAGGGCTGGACTTTGCTTGTGACATCTAC

Murine CD8 TM

(SEQ ID NO: 99)

IWAPLAGICVALLSLIITLI

5 Murine CD8 TM

(SEQ ID NO: 100)

ATCTGGGCACCCCTTAGCCGGTATCTGTGTGGCCTTGCTGCTTCCCTCATCATCACTCTAAT
T

10 Murine CD8 Hinge and TM

(SEQ ID NO: 101)

LQKVNSTTTKPVLRTPSPVHPTGTSQPQRPEDCRPRGSVKGTGLDFACDIYIWAPLAGICVA
LLLSLIITLI

15 Murine CD8 Hinge and TM

(SEQ ID NO: 102)

CTTCAGAAGGTGAACAGCACAAACAACCAAGCCAGTCTTGCGAACACCCAGTCCTGTTACCCC
TACGGGTACGTCTCAACCTCAGAGGCCTGAGGACTGTAGACCCCGTGGCTCTGTGAAAGGGA
CAGGGCTGGACTTTGCTTGTGACATCTACATCTGGGCACCCCTTAGCCGGTATCTGTGTGGCC
20 TTGCTGCTTCCCTCATCATCACTCTAATT

Murine CD28 TM

(SEQ ID NO: 103)

FWALVVVAGVLFYGLLVTVALCVIWT

25

Murine CD28 TM

(SEQ ID NO: 104)

TTCTGGGCCCTGGTGGTGGTGGCCGGCGTGCTGTTCTGCTACGGCCTGCTGGTGACCGTGGC
CCTGTGCGTGATCTGGACC

30

Murine CD28 costimulatory domain (mCD28 ICD)

(SEQ ID NO: 105)

NSRRNRLLQSDYMNMTPRRPLTRKPYQPYAPARDFAAAYRP

Murine CD28 costimulatory domain (mCD28 ICD)

(SEQ ID NO: 106)

AACAGCAGGAGGAACAGGCTGCTGCAGAGCGACTACATGAACATGACCCCCAGGAGGCCCGG
5 CCTGACCAGGAAGCCCTACCAGCCCTACGCCCCGCCAGGGACTTCGCCGCCTACAGGCC

Murine 4-1BB costimulatory domain (m41BB ICD)

(SEQ ID NO: 107)

KWIRKKFPHIFKQPFKKTGAAQEEDACSCRCPQEEEGGGGGYEL
10

Murine 4-1BB costimulatory domain (m41BB ICD)

(SEQ ID NO: 108)

AAGTGGATTTCGAAAAAGTTCCCCACATCTTTAAGCAGCCGTTCAAGAAAACCACTGGAGC
AGCCCAGGAGGAGGATGCTTGCAGCTGCCGCTGTCCCAGGAGGAAGAAGGCGCGGGGGCG
15 GATATGAGCTC

Murine CD3z stimulatory domain (mCD3z ICD)

(SEQ ID NO: 109)

KFSRSAETAANLQDPNQLYNELNLGRREEYDVLEKKRARDPEMGGKQRRRNPQEGVYNALQ
20 KDKMAEAYSEIGTKGERRRGKGHDGLYQGLSTATKDTYDALHMQTLAPR

Murine CD3z stimulatory domain (mCD3z ICD)

(SEQ ID NO: 110)

AAGTTTTTCACGCTCTGCAGAGACAGCTGCCAACCTGCAGGACCCCAATCAGCTGTACAATGA
25 ACTGAATCTCGGGCGGAGAGAAGAATATGATGTGTTGGAGAAGAAGCGTGCGAGAGACCCAG
AGATGGGCGGCAAACAGCAGAGAAGACGAAACCCACAGGAAGGAGTGTAACGCCCTGCAG
AAAGACAAGATGGCAGAGGCCTACTCAGAGATTGGAACCAAAGGAGAGAGGCGCCGTGGAAA
AGGACATGATGGGCTTTACCAGGGTTTAAGTACGGCCACTAAAGATACTTATGACGCGCTGC
ACATGCAGACACTGGCACCTCGA

30

Anti-hMSLN scFv M5 LCDR1

(SEQ ID NO: 111)

RASQSIRYYLS

Anti-hMSLN scFv M5 LCDR2

(SEQ ID NO: 112)

TASILQN

5 Anti-hMSLN scFv M5 LCDR3

(SEQ ID NO: 113)

LQTYTTPD

Anti-hMSLN scFv M5 HCDR1

10 (SEQ ID NO: 114)

GYTFTDYYMH

Anti-hMSLN scFv M5 HCDR2

(SEQ ID NO: 115)

15 WINPNSGGTNYAQKFQG

Anti-hMSLN scFv M5 HCDR3

(SEQ ID NO: 116)

GWDFDY

20

Anti-GD2 scFv

(SEQ ID NO: 117)

MALPVTALLLPLALLLHAARPGSDVMTQTPLSLPVSLGDQASISCRSSQSLVHRNGNTYLH
WYLQKPGQSPKLLIHKVSNRFGVDPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPP
25 LTFGAGTKLELKGGGGSGGGSGGGSGGGGSEVQLLQSGPELEKPSASVMISCKASGSSFT
GYNMNWVRQNIGKSLWIGAIDPYYGGTSYNQKFGRATLTVDKSSSTAYMHLKSLTSEDSV
YYCVSGMEYWGQGTSTVTVSSSG

Anti-GD2 scFv

30 (SEQ ID NO: 118)

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCGCCAGGCC
GGGATCCGATGTTGTGATGACCCAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAG
CCTCCATCTCTTGCAGATCTAGTCAGAGTCTTGTACACCGTAACGGAAACACCTATTTACAT

TGGTACCTGCAGAAGCCAGGCCAGTCTCCAAAGCTCCTGATTACAAAAGTTTCCAACCGATT
 TTCTGGGGTCCCAGACAGGTTTCAGTGGCAGTGGATCAGGGACAGATTTACACTCAAGATCA
 GCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTTCTGTTCTCAAAGTACACACGTTCCCTCCG
 CTCACGTTCCGGTGCTGGGACCAAGCTGGAGCTGAAAGGAGGTGGCGGGTCAGGGGGTGGCGG
 5 AAGCGGAGGCGGCGGTTTCAGGCGGAGGAGGCTCGGAGGTGCAGCTTCTGCAGTCTGGACCTG
 AGCTGGAGAAGCCTTCCGCTTCAGTGATGATATCCTGCAAGGCTTCTGGTTCCTCCTTCACT
 GGCTACAACATGAACTGGGTGAGGCAGAATATTGAAAGAGCCTTGAATGGATTGGAGCTAT
 TGATCCTTACTACGGTGGAACCTAGCTACAACCAGAAGTTCAAGGGCAGGGCCACATTGACTG
 TAGACAAATCGTCCAGCACAGCCTACATGCACCTCAAGAGCCTGACATCTGAGGACTCTGTC
 10 TATTACTGTGTAAGCGGAATGGAGTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCATC
 CGGA

Anti-HER2 scFv (high affinity)

(SEQ ID NO: 119)

15 MDFQVQIFSFLLISASVIMSRGDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP
 GKAPKLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGT
 KVEIKRTGSTSGSGKPGSGEGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA
 PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGD
 GFYAMDVWGQGTLLTVSS

20

Anti-HER2 scFv (high affinity)

(SEQ ID NO: 120)

ATGGATTTTCAGGTGCAGATTTTCAGCTTCTTGCTAATCAGTGCCTCAGTCATAATGTCCAG
 AGGAGATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCA
 25 CCATCACCTGCCGTGCCAGTCAGGATGTGAATACTGCTGTAGCCTGGTATCAACAGAAACCA
 GGAAAAGCTCCGAAACTACTGATTTACTCGGCATCCTTCTTTATTCTGGAGTCCCTTCTCG
 CTTCTCTGGATCTAGATCTGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAG
 ACTTCGCAACTTATTACTGTCAGCAACATTATACTACTCCTCCACGTTCCGGACAGGGTACC
 AAGGTGGAGATCAAACGCACTGGGTCTACATCTGGATCTGGGAAGCCGGGTCTGGTGAGGG
 30 TTCTGAGGTTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTT
 TGTCTGTGCAGCTTCTGGCTTCAACATTAAAGACACCTATATACACTGGGTGCGTCAGGCC
 CCGGGTAAGGGCCTGGAATGGGTGCAAGGATTTATCCTACGAATGGTTATACTAGATATGC
 CGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCAAAAACACAGCCTACCTGC

AGATGAACAGCCTGCGTGCTGAGGACACTGCCGTCTATTATTGTTCTAGATGGGGAGGGGAC
GGCTTCTATGCTATGGACGTGTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCG

Anti-HER2 scFv (low affinity)

5 (SEQ ID NO: 121)

MDFQVQIFSFLLISASVIMSRGDIQMTQSPSSLSASVGDRVITICRASQDVNTAVAWYQQKP
GKAPKLLIYSASFLESGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGT
KVEIKRTGSTSGSGKPGSGEGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA
PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGD
10 GFVAMDVWGQGTTLTVSS

Anti-HER2 scFv (low affinity)

(SEQ ID NO: 122)

ATGGATTTTCAGGTGCAGATTTTCAGCTTCCTGCTAATCAGTGCCTCAGTCATAATGTCCAG
15 AGGAGATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCCTCTGTGGGCGATAGGGTCA
CCATCACCTGCCGTGCCAGTCAGGATGTGAATACTGCTGTAGCCTGGTATCAACAGAAACCA
GGAAAAGCTCCGAACTACTGATTTACTCGGCATCCTTCCTTGAGTCTGGAGTCCCTTCTCG
CTTCTCTGGATCTAGATCTGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAG
ACTTCGCAACTTATTACTGTCAGCAACATTATACTACTCCTCCACGTTCCGGACAGGGTACC
20 AAGGTGGAGATCAAACGCACTGGGTCTACATCTGGATCTGGGAAGCCGGGTCTGGTGAGGG
TTCTGAGGTTCACTGGTGGAGTCTGGCGGTGGCTGGTGCAGCCAGGGGGCTCACTCCGTT
TGTCTGTGCAGCTTCTGGCTTCAACATTAAAGACACCTATATACACTGGGTGCGTCAGGCC
CCGGGTAAGGGCCTGGAATGGGTGCAAGGATTTATCCTACGAATGGTTATACTAGATATGC
CGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAACACAGCCTACCTGC
25 AGATGAACAGCCTGCGTGCTGAGGACACTGCCGTCTATTATTGTTCTAGATGGGGAGGGGAC
GGCTTCGTTGCTATGGACGTGTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCG

Anti-TnMuc1 scFv

(SEQ ID NO: 123)

30 QVQLQQSDAELVKPGSSVKISCKASGYTFDTHAIHWVKQKPEQGLEWIGHFSPGNTDIKYND
KFKGKATLTVDRSSSTAYMQLNSLTSEDSAVYFCKTSTFFFDYWGQGTTLTVSSGGGGSGGG
GSGGGGSELVMTQSPSSLTVTAGEKVTMICKSSQSLNSGDQKNYLTWYQQKPGQPPKLLIF
WASTRESGVPDRFTGSGSGTDFTLTISVQAEDLAVYYCQNDYSYPLTFGAGTKLELK

Anti-TnMuc1 scFv

(SEQ ID NO: 124)

CAGGTGCAGCTGCAGCAGTCTGATGCCGAGCTCGTGAAGCCTGGCAGCAGCGTGAAGATCAG
CTGCAAGGCCAGCGGCTACACCTTCACCGACCACGCCATCCACTGGGTCAAGCAGAAGCCTG
5 AGCAGGGCCTGGAGTGGATCGGCCACTTCAGCCCCGGCAACACCGACATCAAGTACAACGAC
AAGTTCAAGGGCAAGGCCACCCTGACCGTGGACAGAAGCAGCAGCACC GCCTACATGCAGCT
GAACAGCCTGACCAGCGAGGACAGCGCCGTGTACTTCTGCAAGACCAGCACCTTCTTTTTTCG
ACTACTGGGGCCAGGGCACAACCCTGACAGTGTCTAGCGGAGGCGGAGGATCTGGCGGCGGA
GGAAGTGGCGGAGGGGGATCTGAACTCGTGATGACCCAGAGCCCCAGCTCTCTGACAGTGAC
10 AGCCGGCGAGAAAGTGACCATGATCTGCAAGTCCTCCCAGAGCCTGCTGAACTCCGGCGACC
AGAAGAACTACCTGACCTGGTATCAGCAGAAACCCGGCCAGCCCCCAAGCTGCTGATCTTT
TGGGCCAGCACCCGGGAAAGCGGCGTGCCCGATAGATTACAGGCAGCGGCTCCGGCACCGA
CTTTACCCTGACCATCAGCTCCGTGCAGGCCGAGGACCTGGCCGTGTATTACTGCCAGAACG
ACTACAGCTACCCCTGACCTTCGGAGCCGGCACCAAGCTGGAAGTGAAG
15

Anti-CD70 scFv

(SEQ ID NO: 125)

MALPVTALLLPLALLLHAARPQAVVTQEPLTVSPGGTVTLTCLKSGSVTSDNFPTWYQQT
PGQAPRLLIYNTNTRHSGVPDRFSGSILGNKAALTITGAQADDEAEYFCALFISNPSVEFGG
20 GTQLTVLGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSVYYM
NWVRQAPGKGLEWVSDINNEGTTYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYC
ARDAGYSNHVPIFDSWGQGTILVTVSS

Anti-CD70 scFv

25 (SEQ ID NO: 126)

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCGCCAGGCC
GCAGGCCGTTGTACACAAGAGCCCTCTCTGACCGTGTACCCGGGGGACCGTGACCTGA
CATGTGGTTTGAAATCTGGAAGTGTAACATCCGACAACCTTCCCTACATGGTACCAGCAGACG
CCTGGTCAAGCGCCGCGATTGCTGATTTATAATACCAATACACGCCACAGCGGAGTACCTGA
30 CAGATTCAGTGGCAGCATCCTTGGAACAAAGCGGCACTGACCATAACAGGTGCCCCAAGCAG
ATGATGAAGCAGAGTACTTCTGTGCCCTCTTTATTAGTAATCCCTCAGTTGAATTTGGGGGT
GGTACACAACCTTACAGTTCTCGGTGGTGGCGGAGGATCAGGGGGGGGAGGAAGTGGTGGTGG
CGGCAGTGGCGGAGGTGGGAGTGAGGTTTCTAGCTCGTAGAATCAGGAGGAGGTTTGGTACAAC
CGGGCGGCTCTCTGAGACTTTCATGCGCTGCGAGCGGGTTTACTTTCTCTGTCTATTATATG

AATTGGGTGAGACAGGCGCCGGGAAAGGGGCTGGAATGGGTGAGTGATATTAACAATGAAGG
 AGGTACCACCTACTACGCGGACAGTGTAAAGGGCAGATTTACCATAAGCCGGGATAACAGTA
 AGAACAGTCTTTACTTGC AAATGAATTC ACTGCGAGCGGAGGATACCGCGGTATACTACTGT
 GCTAGGGACGCGGGTTACAGTAACCATGTGCCAATTTTCGATTCTTGGGGACAGGGAACCCCT
 5 CGTCACCGTGTCCAGC

Anti-CD70 tr27 CAR (tr27-h41BB-hCD3zeta)

(SEQ ID NO: 127)

ATGGCTCGGCCCCATCCCTGGTGGTTGTGTGTGCTGGGAACACTTGTCGGCCTGAGTGCTAC
 10 CCCTGCCCCATAAATCATGCCCGGAACGGCACTATTGGGCGCAGGGTAAACTGTGCTGCCAAA
 TGTGTGAACCAGGTACTTTTCTGGTCAAAGATTGCGATCAACACAGGAAGGCAGCTCAATGC
 GATCCTTGTATCCCTGGGGTGAGCTTCAGCCCCGACCATCATACTAGACCACATTGTGAAAG
 TTGCCGACACTGTAATAGCGGACTCTTGGTCCGCAATTGCACCATTACCGCTAATGCCGAAT
 GCGCCTGCCGCAATGGATGGCAGTGCCGGGACAAGGAGTGCACAGAGTGCAGCCCTCTCCCA
 15 AATCCAAGTCTCACGGCTCGGTCCAGTCAGGCGCTTAGCCCGCACCCACAACCTACTCACCT
 GCCCTACGTCTCTGAAATGTTGGAAGCGAGAACAGCAGGTCACATGCAAACACTTGCGGACT
 TTCGGCAGCTGCCTGCGCGCACACTTTCAACCCATTGGCCACCACAACGGAGTCTGTGTAGT
 TCCGACTTCATAAGAATCCTCGTTATCTTCTCTGGGATGTTCTTGGTATTACGTTGGCCGG
 CGCCCTGTTTCTCCGGTTCAGTGTAGTGAAACGGGGCAGAAAGAACTCCTGTATATATTCA
 20 AACAACCATTTATGAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTT
 CCAGAAGAAGAAGAAGGAGGATGTGAAGTGAAGTTCAGCAGGAGCGCAGACGCCCC
 CGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGT
 ACGATGTTTTTGGACAAGAGACGTGGCCGGGACCCCTGAGATGGGGGGAAAGCCGAGAAGGAAG
 AACCCTCAGGAAGGCCTGTACAATGAAGTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGA
 25 GATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCA
 GTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTAA

Anti-CD70 tr27 CAR (tr27-h41BB-hCD3zeta)

(SEQ ID NO: 128)

30 MARPHPWWLCVLGTLVGLSATPAPKSCPERHYWAQGKLCCQMCEPGTFLVKDCDQHRKAAQC
 DPCIPGVSFSPDHHTRPHCESCRHCNSGLLVNRNCTITANAECACRNGWQCRDKECTECDPLP
 NPSLTARSSQALSHPHPQPTHLPYVSEMLEARHTAGHMOTLADFRQLPARTLSTHWPPQRS LCS
 SDFIRILVIFSGMFLVFTLAGALFLRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF

PEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

Anti-PMSA scFv

5 (SEQ ID NO: 129)

MALPVTALLLPLALLLHAARPGSDIVMTQSHKFMSTSVGDRVSIICKASQDVGTAVDWYQQK
PGQSPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTITNVQSEDLADYFCQQNSYPLTFGAG
TMLDLKGGGSGGGGSSGGGSEVQLQQSGPELVKPGTSVRISCKTSGYTFTEYTIHWVKQSH
GKSLEWIGNINPNNGGTTYNQKFEDKATLTVDKSSSTAYMELRSLTSEDSAVYYCAAGWNFD
10 YWGQGTTLTVSSASSG

Anti-PMSA scFv

(SEQ ID NO: 130)

ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGCTGCTGCACGCCGCCAGACC
15 TGGATCTGACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAGTAGGAGACAGGG
TCAGCATCATCTGTAAGGCCAGTCAAGATGTGGGTACTGCTGTAGACTGGTATCAACAGAAA
CCAGGACAATCTCCTAACTACTGATTTATTGGGCATCCACTCGGCACACTGGAGTCCCTGA
TCGCTTCACAGGCAGTGGATCTGGGACAGACTTCACCTCTCACCATTACTAACGTTTCAGTCTG
AAGACTTGGCAGATTATTTCTGTCTAGCAATATAACAGCTATCCTCTCACGTTCCGTGCTGGG
20 ACCATGCTGGACCTGAAAGGAGGCGGAGGATCTGGCGGCGGAGGAAGTTCTGGCGGAGGCAG
CGAGGTGCAGCTGCAGCAGAGCGGACCCGAGCTCGTGAAGCCTGGAACAAGCGTGCAGGATCA
GCTGCAAGACCAGCGGCTACACCTTCACCGAGTACACCATCCACTGGGTCAAGCAGTCCCAC
GGCAAGAGCCTGGAGTGGATCGGCAATATCAACCCCAACAACGGCGGCACCACCTACAACCA
GAAGTTCGAGGACAAGGCCACCCTGACCGTGGACAAGAGCAGCAGCACCGCCTACATGGAAC
25 TGCGGAGCCTGACCAGCGAGGACAGCGCCGTGTACTATTGTGCCGCCGGTTGGAACCTCGAC
TACTGGGGCCAGGGCACAACCCTGACAGTGTCTAGCGCTAGCTCCGGA

Anti-EGFRvIII scFv

(SEQ ID NO: 131)

30 MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGESLRISCKGSGFNIEDYYIHWVRQMP
GKGLEWMGRIDPENDETKYGPIFQGHVTISADTSINTVYLQWSSLKASDTAMYYCAFRGGVY
WGQGTTVTVSSGGGSGGGGSGGGGSGGGGSDVMTQSPDSLAVSLGERATINCKSSQSLLD
SDGKTYLNWLQQKPGQPPKRLISLVSKLDSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC
WQGTHTFPGTFGGGTKEIK

Anti-EGFRvIII scFv

(SEQ ID NO: 132)

ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC
5 CGAGATTTCAGCTCGTGCAATCGGGAGCGGAAGTCAAGAAGCCAGGAGAGTCTTTCGGGATCT
CATGCAAGGGTAGCGGCTTTAACATCGAGGATTACTACATCCACTGGGTGAGGCAGATGCCG
GGGAAGGGACTCGAATGGATGGGACGGATCGACCCAGAAAACGACGAAACTAAGTACGGTCC
GATCTTCCAAGGCCATGTGACTATTAGCGCCGATACTTCAATCAATACCGTGTATCTGCAAT
GGTCTTCATTGAAAGCCTCAGATACCGCGATGTACTACTGTGCTTTCAGAGGAGGGGTCTAC
10 TGGGGACAGGGAACACCGTGAAGTGTCTCGTCCGGCGGAGGCGGGTCAGGAGGTGGCGGCAG
CGGAGGAGGAGGGTCCGGCGGAGGTGGGTCCGACGTGATGACCCAGAGCCCTGACAGCC
TGGCAGTGAGCCTGGGCGAAAGAGCTACCATTAAGTCAAATCGTCGCAGAGCCTGCTGGAC
TCGGACGGAAAAACGTACCTCAATTGGCTGCAGCAAAAGCCTGGCCAGCCACCGAAGCGCCT
TATCTCACTGGTGTGCAAGCTGGATTCCGGAGTGCCCGATCGCTTCTCCGGCTCGGGATCGG
15 GTACTGACTTCACCCCTCACTATCTCCTCGCTTCAAGCAGAGGACGTGGCCGTCTACTACTGC
TGGCAGGGAACCCACTTTCGGGAACCTTCGGCGGAGGGACGAAAGTGGAGATCAAG

Anti-EGFR₈₀₆ scFv

(SEQ ID NO: 133)

20 DILMTQSPSSMSVSLGDTVSI TCHSSQDINSNIGWLQQRPGKSFKGLIYHGTNLDDEV
PSRFSGSGSGADYSLTISSLESEDFADYYCVQYAQFPWTFGGGKLEIKRGGGSGG
GGSGGGGSDVQLQESGPSLVKPSQSLSLTCTVTGYSITSDFAWNWIRQFPGNKLEWM
GYISYSGNTRYNPSLKSRIITRDTSKNQFFLQLNSVTIEDTATYYCVTAGRGFPYWG
QGTLVTVSA

25

Anti-EGFR₈₀₆ scFv

(SEQ ID NO: 134)

GATATTCTGATGACTCAATCTCCGTCTTCTATGAGCGTGAGCTTGGGTGACACCG
TCAGCATCACCTGTCATTCCAGCCAGGATATAAACTCAAATATCGGCTGGCTCCA
30 GCAACGCCCAGGCAAGTCATTCAAGGGGCTTATTTATCATGGCACCAATCTTGAC
GATGAAGTCCCATCACGCTTCAGCGGATCAGGCTCAGGTGCGGACTATTCCTTGA
CTATAAGTTCCCTCGAATCTGAGGATTTGCCGACTATTATTGCGTACAATACGC
CCAGTTTCCCTGGACCTTCGGAGGCGGCACCAAATTGGAGATAAAAAGGGGTGG
AGGAGGATCAGGCGGGGTGGAAGCGGCGGAGGAGGCAGCGACGTACAACCTGC
35 AAGAATCCGGGCCGAGTTTGGTCAAGCCCTCTCAATCTCTTTCTCTCACTTGCAC
GGTCACCGGATACTCCATAACCAGCGATTTTGCCTGGAATTGGATTTCGACAATTT
CCAGGGAATAAATTGGAATGGATGGGATATATCAGTTATTCTGGTAATACCAGAT
ACAACCCGTCATTGAAAAGTCGCATCTCTATAACACGAGACACTTCAAAGAATC
AGTTCTTCCTTCAGCTCAATTCTGTAACCATCGAAGATACTGCTACTTATTACTGT
40 GTAACGGCGGGTCGAGGATTCCTTACTGGGGCCAGGGTACACTGGTTACTGTTT
CCGCC

Anti-IL13Ra2 (hu08) scFv

(SEQ ID NO: 135)

DIQMTQSPSSLSASVGDRVTITCKASQDVGTA VAWYQQIPGKAPKLLIYSASYRSTG
 5 VPDRFSGSGSGTDFSFIISSLPEDFATYYCQHHYSAPWTFGGGTKVEIKGGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSRNGMSWVRQTPDKRLEWV
 ATVSSGGSYIYYADSVKGRFTISRDNAKNSLYLQMSSLRAEDTAVYYCARQGTAL
 ATRFFDVWGQGLVTVSS

10 IL13Ra2 (hu08) scFv

(SEQ ID NO: 136)

GACATCCAAATGACTCAGAGCCCCCTCTAGCCTCAGTGCAAGCGTCGGAGACCGG
 GTGACCATCACCTGTAAAGCGTCCCAGGATGTTGGAACGGCAGTAGCTTGGTATC
 AACAAATCCCAGGGAAGGCTCCAAAGCTCCTTATATACTCTGCTAGTTACAGGTC
 15 CACCGGGGTGCCGACCGATTCTCTGGCTCCGGGAGCGGCACTGACTTTTCATTC
 ATCATTAGTAGTCTTCAACCTGAGGACTTTGCCACCTATTATTGCCAGCACCACT
 ACTCTGCGCCGTGGACTTTTCGGAGGAGGCACGAAGGTTGAAATTAAGGTGGAG
 GTGGGTCTGGCGGAGGTGGAAGTGGTGGAGGCGGGTCCGAGGTTTCAGTTGGTAG
 AGTCAGGCGGTGGTCTGGTGCAGCCAGGTGGGTCCCTGCGCCTCAGCTGTGCAG
 20 CTTCCGGCTTTACTTTCTCAAGGAATGGTATGTCCTGGGTACGGCAAACGCCGGA
 CAAACGCCTTGAGTGGGTAGCTACCGTATCCTCTGGGGGCTCTTACATATACTAT
 GCAGACTCTGTGAAAGGAAGATTTACAATTTACGCGACAATGCAAAAAATAGT
 TTGTACCTCCAAATGTCTAGTCTTAGGGCCGAGGATACTGCCGTCTACTACTGTG
 CACGCCAGGGAACGACGGCTCTTGCTACCCGATTTTCGACGTTTGGGGCCAAGG
 25 AACGTTGGTGACAGTTAGCAG

D. Nucleic Acids and Expression Vectors

In one aspect, the invention provides an isolated nucleic acid comprising a) a first
 30 nucleotide sequence encoding a chimeric cytokine receptor comprising (i) an extracellular
 domain comprising a ligand-binding domain (LBD) of a receptor selected from an
 interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an
 interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a
 first transmembrane domain, and (iii) an intracellular domain comprising an intracellular
 35 signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a second nucleotide
 sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor
 antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In another aspect, the invention provides an isolated nucleic acid comprising
 nucleotide sequence encoding a chimeric cytokine receptor comprising (i) an extracellular
 40 domain comprising a ligand-binding domain (LBD) of a receptor selected from an
 interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an
 interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a

first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).

In one aspect, the invention provides an isolated nucleic acid comprising a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In another aspect, the invention provides an isolated nucleic acid comprising a nucleotide sequence encoding any of the chimeric cytokine receptors described herein, *e.g.*, a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra). In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In certain embodiments, a nucleic acid of the present disclosure comprises a first nucleotide sequence and a second nucleotide sequence. The first and second nucleotide sequences may be separated by a linker. A linker for use in the present disclosure allows for

multiple proteins to be encoded by the same nucleic acid sequence (*e.g.*, a multicistronic or bicistronic sequence), which are translated as a polyprotein that is dissociated into separate protein components. In certain embodiments, the nucleic acid comprises from 5' to 3' the first nucleotide sequence, the linker, and the second nucleotide sequence. In certain
5 embodiments, the nucleic acid comprises from 5' to 3' the second nucleotide sequence, the linker, and the first nucleotide sequence.

 In some embodiments, the linker comprises a nucleic acid sequence that encodes an internal ribosome entry site (IRES). As used herein, "an internal ribosome entry site" or "IRES" refers to an element that promotes direct internal ribosome entry to the initiation
10 codon, such as ATG, of a protein coding region, thereby leading to cap-independent translation of the gene. Various internal ribosome entry sites are known to those of skill in the art, including, without limitation, IRES obtainable from viral or cellular mRNA sources, *e.g.*, immunoglobulin heavy-chain binding protein (BiP); vascular endothelial growth factor (VEGF); fibroblast growth factor 2; insulin-like growth factor; translational initiation factor
15 eIF4G; yeast transcription factors TFIID and HAP4; and IRES obtainable from, *e.g.*, cardiovirus, rhinovirus, aphthovirus, HCV, Friend murine leukemia virus (FrMLV), and Moloney murine leukemia virus (MoMLV). Those of skill in the art would be able to select the appropriate IRES for use in the present invention.

 In some embodiments, the linker comprises a nucleic acid sequence that encodes a
20 self-cleaving peptide. As used herein, a "self-cleaving peptide" or "2A peptide" refers to an oligopeptide that allow multiple proteins to be encoded as polyproteins, which dissociate into component proteins upon translation. Use of the term "self-cleaving" is not intended to imply a proteolytic cleavage reaction. Various self-cleaving or 2A peptides are known to those of skill in the art, including, without limitation, those found in members of the Picornaviridae
25 virus family, *e.g.*, foot-and-mouth disease virus (FMDV), equine rhinitis A virus (ERAV), Thosa assigna virus (TaV), and porcine tescho virus-1 (PTV-1); and carioviruses such as Theilovirus and encephalomyocarditis viruses. 2A peptides derived from FMDV, ERAV, PTV-1, and TaV are referred to herein as "F2A," "E2A," "P2A," and "T2A," respectively. Those of skill in the art would be able to select the appropriate self-cleaving peptide for use
30 in the present invention.

 In some embodiments, the construct includes a linker that optionally, further comprises a nucleic acid sequence that encodes a furin cleavage site. Furin is a ubiquitously expressed protease that resides in the trans-golgi and processes protein precursors before their

secretion. Furin cleaves at the COOH- terminus of its consensus recognition sequence. Various furin consensus recognition sequences (or “furin cleavage sites”) are known to those of skill in the art. Those of skill in the art would be able to select the appropriate Furin cleavage site for use in the present invention.

- 5 In some embodiments, the linker comprises a nucleic acid sequence encoding a combination of a Furin cleavage site and a 2A peptide. Examples include, without limitation, a linker comprising a nucleic acid sequence encoding a Furin cleavage site and F2A, a linker comprising a nucleic acid sequence encoding a Furin cleavage site and E2A, a linker comprising a nucleic acid sequence encoding a Furin cleavage site and P2A, a linker
10 comprising a nucleic acid sequence encoding a Furin cleavage site and T2A. Those of skill in the art would be able to select the appropriate combination for use in the present invention. In such embodiments, the linker may further comprise a spacer sequence between the Furin cleavage site and the 2A peptide. In some embodiments, the linker comprises a Furin cleavage site 5' to a 2A peptide. In some embodiments, the linker comprises a 2A peptide 5'
15 to a Furin cleavage site. Various spacer sequences are known in the art, including, without limitation, glycine serine (GS) spacers (also known as GS linkers). Those of skill in the art would be able to select the appropriate spacer sequence for use in the present invention.

 In some embodiments, a nucleotide sequence of the present disclosure may be operably linked to a transcriptional control element, *e.g.*, a promoter, and enhancer, etc.

- 20 Suitable promoter and enhancer elements are known to those of skill in the art.

 In certain embodiments, the promoter is selected from a phosphoglycerate kinase-1 (PGK) promoter, an EF-1a promoter, and a CMV promoter.

- For expression in a bacterial cell, suitable promoters include, but are not limited to, lacI, lacZ, T3, T7, gpt, lambda P and trc. For expression in a eukaryotic cell, suitable
25 promoters include, but are not limited to, light and/or heavy chain immunoglobulin gene promoter and enhancer elements; cytomegalovirus immediate early promoter; herpes simplex virus thymidine kinase promoter; early and late SV40 promoters; promoter present in long terminal repeats from a retrovirus; mouse metallothionein-I promoter; and various art-known tissue specific promoters. Suitable reversible promoters, including reversible inducible
30 promoters are known in the art. Such reversible promoters may be isolated and derived from many organisms, *e.g.*, eukaryotes and prokaryotes. Modification of reversible promoters derived from a first organism for use in a second organism, *e.g.*, a first prokaryote and a second a eukaryote, a first eukaryote and a second a prokaryote, etc., is well known in the art.

Such reversible promoters, and systems based on such reversible promoters but also comprising additional control proteins, include, but are not limited to, alcohol regulated promoters (*e.g.*, alcohol dehydrogenase I (*alcA*) gene promoter, promoters responsive to alcohol transactivator proteins (*AlcR*, etc.), tetracycline regulated promoters, (*e.g.*, promoter systems including TetActivators, TetON, TetOFF, etc.), steroid regulated promoters (*e.g.*, rat glucocorticoid receptor promoter systems, human estrogen receptor promoter systems, retinoid promoter systems, thyroid promoter systems, ecdysone promoter systems, mifepristone promoter systems, etc.), metal regulated promoters (*e.g.*, metallothionein promoter systems, etc.), pathogenesis-related regulated promoters (*e.g.*, salicylic acid regulated promoters, ethylene regulated promoters, benzothiadiazole regulated promoters, etc.), temperature regulated promoters (*e.g.*, heat shock inducible promoters (*e.g.*, HSP-70, HSP-90, soybean heat shock promoter, etc.), light regulated promoters, synthetic inducible promoters, and the like.

In some embodiments, the promoter is a CD8 cell-specific promoter, a CD4 cell-specific promoter, a neutrophil-specific promoter, or an NK-specific promoter. For example, a CD4 gene promoter can be used; see, *e.g.*, Salmon et al. Proc. Natl. Acad. Sci. USA (1993) 90:7739; and Marodon et al. (2003) Blood 101:3416. As another example, a CD8 gene promoter can be used. NK cell-specific expression can be achieved by use of an *Ncr1* (p46) promoter; see, *e.g.*, Eckelhart et al. Blood (2011) 117:1565.

For expression in a yeast cell, a suitable promoter is a constitutive promoter such as an *ADH1* promoter, a *PGK1* promoter, an *ENO* promoter, a *PYK1* promoter and the like; or a regulatable promoter such as a *GAL1* promoter, a *GAL10* promoter, an *ADH2* promoter, a *PHOS* promoter, a *CUP1* promoter, a *GALT* promoter, a *MET25* promoter, a *MET3* promoter, a *CYC1* promoter, a *HIS3* promoter, an *ADH1* promoter, a *PGK* promoter, a *GAPDH* promoter, an *ADC1* promoter, a *TRP1* promoter, a *URA3* promoter, a *LEU2* promoter, an *ENO* promoter, a *TP1* promoter, and *AOX1* (*e.g.*, for use in *Pichia*). Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. Suitable promoters for use in prokaryotic host cells include, but are not limited to, a bacteriophage T7 RNA polymerase promoter; a *trp* promoter; a *lac* operon promoter; a hybrid promoter, *e.g.*, a *lac/tac* hybrid promoter, a *tac/trc* hybrid promoter, a *trp/lac* promoter, a *T7/lac* promoter; a *trc* promoter; a *tac* promoter, and the like; an *araBAD* promoter; *in vivo* regulated promoters, such as an *ssaG* promoter or a related promoter (see, *e.g.*, U.S. Patent Publication No. 20040131637), a *pagC* promoter (Pulkkinen and Miller, J. Bacteriol. (1991)

173(1): 86-93; Alpuche-Aranda et al., Proc. Natl. Acad. Sci. USA (1992) 89(21): 10079-83), a nirB promoter (Harborne *et al.* Mol. Micro. (1992) 6:2805-2813), and the like (see, *e.g.*, Dunstan et al., Infect. Immun. (1999) 67:5133-5141; McKelvie et al., Vaccine (2004) 22:3243-3255; and Chatfield *et al.*, Biotechnol. (1992) 10:888-892); a sigma70 promoter, *e.g.*, a consensus sigma70 promoter (see, *e.g.*, GenBank Accession Nos. AX798980, AX798961, and AX798183); a stationary phase promoter, *e.g.*, a dps promoter, an spv promoter, and the like; a promoter derived from the pathogenicity island SPI-2 (see, *e.g.*, WO96/17951); an actA promoter (see, *e.g.*, Shetron-Rama et al., Infect. Immun. (2002) 70:1087-1096); an rpsM promoter (see, *e.g.*, Valdivia and Falkow Mol. Microbiol. (1996) 22:367); a tet promoter (see, *e.g.*, Hillen, W. and Wissmann, A. (1989) In Saenger, W. and Heinemann, U. (eds), Topics in Molecular and Structural Biology, Protein--Nucleic Acid Interaction. Macmillan, London, UK, Vol. 10, pp. 143-162); an SP6 promoter (see, *e.g.*, Melton *et al.*, Nucl. Acids Res. (1984) 12:7035); and the like. Suitable strong promoters for use in prokaryotes such as *Escherichia coli* include, but are not limited to Trc, Tac, T5, T7, and PLambda. Non-limiting examples of operators for use in bacterial host cells include a lactose promoter operator (LacI repressor protein changes conformation when contacted with lactose, thereby preventing the Lac repressor protein from binding to the operator), a tryptophan promoter operator (when complexed with tryptophan, TrpR repressor protein has a conformation that binds the operator; in the absence of tryptophan, the TrpR repressor protein has a conformation that does not bind to the operator), and a tac promoter operator (see, *e.g.*, deBoer et al., Proc. Natl. Acad. Sci. U.S.A. (1983) 80:21-25).

Other examples of suitable promoters include 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. Other constitutive promoter sequences may also be used, including, but not limited to a simian virus 40 (SV40) early promoter, a mouse mammary tumor virus (MMTV) or human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, a MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, the EF-1 alpha promoter, as well as human gene promoters such as, but not limited to, an actin promoter, a myosin promoter, a hemoglobin promoter, and a 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.

- 5 In some embodiments, the locus or construct or transgene containing the suitable promoter is irreversibly switched through the induction of an inducible system. Suitable systems for induction of an irreversible switch are well known in the art, *e.g.*, induction of an irreversible switch may make use of a Cre-lox-mediated recombination (see, *e.g.*, Fuhrmann-Benzakein, et al., Proc. Natl. Acad. Sci. USA (2000) 28:e99, the disclosure of which is
10 incorporated herein by reference). Any suitable combination of recombinase, endonuclease, ligase, recombination sites, etc. known to the art may be used in generating an irreversibly switchable promoter. Methods, mechanisms, and requirements for performing site-specific recombination, described elsewhere herein, find use in generating irreversibly switched promoters and are well known in the art, see, *e.g.*, Grindley *et al.* Annual Review of
15 Biochemistry (2006) 567-605; and Tropp, Molecular Biology (2012) (Jones & Bartlett Publishers, Sudbury, Mass.), the disclosures of which are incorporated herein by reference.

- In some embodiments, a nucleic acid of the present disclosure further comprises a nucleic acid sequence encoding a CAR inducible expression cassette. In one embodiment, the CAR inducible expression cassette is used for the production of a transgenic polypeptide
20 product that is released upon CAR signaling. See, *e.g.*, Chmielewski and Abken, Expert Opin. Biol. Ther. (2015) 15(8): 1145-1154; and Abken, Immunotherapy (2015) 7(5): 535-544. In some embodiments, a nucleic acid of the present disclosure further comprises a nucleic acid sequence encoding a cytokine operably linked to a T-cell activation responsive promoter. In some embodiments, the cytokine operably linked to a T-cell activation
25 responsive promoter is present on a separate nucleic acid sequence. In one embodiment, the cytokine is IL-12.

- A nucleic acid of the present disclosure may be present within an expression vector and/or a cloning vector. An expression vector can include a selectable marker, an origin of replication, and other features that provide for replication and/or maintenance of the vector.
30 Suitable expression vectors include, *e.g.*, plasmids, viral vectors, and the like. Large numbers of suitable vectors and promoters are known to those of skill in the art; many are commercially available for generating a subject recombinant construct. The following vectors are provided by way of example, and should not be construed in anyway as limiting:

Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene, La Jolla, Calif., USA); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia, Uppsala, Sweden). Eukaryotic: pWLneo, pSV2cat, pOG44, PXR1, pSG (Stratagene) pSVK3, pBPV, pMSG and pSVL (Pharmacia).

- 5 Expression vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences encoding heterologous proteins. A selectable marker operative in the expression host may be present. Suitable expression vectors include, but are not limited to, viral vectors (*e.g.* viral vectors based on vaccinia virus; poliovirus; adenovirus (see, *e.g.*, Li et al., Invest. Ophthalmol. Vis. Sci. (1994) 35: 2543-2549; Borras et al., Gene Ther. (1999) 6: 515-524; Li and Davidson, Proc. Natl. Acad. Sci. USA (1995) 92: 7700-7704; Sakamoto et al., H. Gene Ther. (1999) 5: 1088-1097; WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and WO 95/00655); adeno-associated virus (see, *e.g.*, Ali et al., Hum. Gene Ther. (1998) 9: 81-86, Flannery et al., Proc. Natl. Acad. Sci. USA (1997) 94: 6916-6921; Bennett et al., Invest. Ophthalmol. Vis. Sci. (1997) 38: 2857-2863; Jomary et al., Gene Ther. (1997) 4:683 690, Rolling et al., Hum. Gene Ther. (1999) 10: 641-648; Ali et al., Hum. Mol. Genet. (1996) 5: 591-594; Srivastava in WO 93/09239, Samulski et al., J. Vir. (1989) 63: 3822-3828; Mendelson et al., Virol. (1988) 166: 154-165; and Flotte et al., Proc. Natl. Acad. Sci. USA (1993) 90: 10613-10617); SV40; herpes simplex virus; human immunodeficiency virus (see, *e.g.*, Miyoshi et al., Proc. Natl. Acad. Sci. USA (1997) 94: 10319-23; Takahashi et al., J. Virol. (1999) 73: 7812-7816); a retroviral vector (*e.g.*, Murine Leukemia Virus, spleen necrosis virus, and vectors derived from retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, human immunodeficiency virus, myeloproliferative sarcoma virus, and mammary tumor virus); and the like.
- 25 Additional expression vectors suitable for use are, *e.g.*, without limitation, a lentivirus vector, a gamma retrovirus vector, a foamy virus vector, an adeno-associated virus vector, an adenovirus vector, a pox virus vector, a herpes virus vector, an engineered hybrid virus vector, a transposon mediated vector, and the like. Viral vector technology is well known in the art and is described, for example, in Sambrook et al., 2012, Molecular Cloning: A Laboratory Manual, volumes 1-4, Cold Spring Harbor Press, NY), 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.
- 30

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).

In some embodiments, an expression vector (*e.g.*, a lentiviral vector) may be used to
5 introduce the nucleic acid into an immune cell or precursor thereof (*e.g.*, a T cell). Accordingly, an expression vector (*e.g.*, a lentiviral vector) of the present invention may comprise a nucleic acid of the invention comprising one or more nucleotide sequences encoding an IL9Ra or a chimeric cytokine receptor and/or a CAR of the invention. In some
10 embodiments, the expression vector (*e.g.*, lentiviral vector) will comprise additional elements that will aid in the functional expression of the receptors encoded therein.

In some embodiments, an expression vector comprising a nucleic acid of the invention further comprises an elongation-factor-1-alpha promoter (EF-1 α promoter). Use of an EF-1 α promoter may increase the efficiency in expression of downstream transgenes (*e.g.*, a CAR encoding nucleotide sequence). Physiologic promoters (*e.g.*, an EF-1 α promoter) may
15 be less likely to induce integration mediated genotoxicity, and may abrogate the ability of the retroviral vector to transform stem cells. Other physiological promoters suitable for use in a vector (*e.g.*, lentiviral vector) are known to those of skill in the art and may be incorporated into a vector of the present invention. In some embodiments, the vector (*e.g.*, lentiviral vector) further comprises a non-requisite cis acting sequence that may improve titers and
20 gene expression. One non-limiting example of a non-requisite cis acting sequence is the central polypurine tract and central termination sequence (cPPT/CTS) which is important for efficient reverse transcription and nuclear import. Other non-requisite cis acting sequences are known to those of skill in the art and may be incorporated into a vector (*e.g.*, lentiviral vector) of the present invention. In some embodiments, the vector further comprises a
25 posttranscriptional regulatory element. Posttranscriptional regulatory elements may improve RNA translation, improve transgene expression and stabilize RNA transcripts. One example of a posttranscriptional regulatory element is the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). Accordingly, in some embodiments a vector for the present invention further comprises a WPRE sequence. Various posttranscriptional
30 regulator elements are known to those of skill in the art and may be incorporated into a vector (*e.g.*, lentiviral vector) of the present invention. A vector of the present invention may further comprise additional elements such as a rev response element (RRE) for RNA transport, packaging sequences, and 5' and 3' long terminal repeats (LTRs). The term "long terminal

repeat” or “LTR” refers to domains of base pairs located at the ends of retroviral DNAs which comprise U3, R and U5 regions. LTRs generally provide functions required for the expression of retroviral genes (*e.g.*, promotion, initiation and polyadenylation of gene transcripts) and to viral replication. In one embodiment, a vector (*e.g.*, lentiviral vector) of the present invention includes a 3’ U3 deleted LTR. Accordingly, a vector (*e.g.*, lentiviral vector) of the present invention may comprise any combination of the elements described herein to enhance the efficiency of functional expression of transgenes. For example, a vector (*e.g.*, lentiviral vector) of the present invention may comprise a WPRE sequence, cPPT sequence, RRE sequence, 5’LTR, 3’ U3 deleted LTR’ in addition to a nucleic acid encoding an IL9Ra or a chimeric cytokine receptor and/or CAR of the invention.

Vectors of the present invention may be self-inactivating vectors. As used herein, the term “self-inactivating vector” refers to vectors in which the 3’ LTR enhancer promoter region (U3 region) has been modified (*e.g.*, by deletion or substitution). A self-inactivating vector may prevent viral transcription beyond the first round of viral replication. Consequently, a self-inactivating vector may be capable of infecting and then integrating into a host genome (*e.g.*, a mammalian genome) only once, and cannot be passed further. Accordingly, self-inactivating vectors may greatly reduce the risk of creating a replication-competent virus.

In some embodiments, a nucleic acid of the present invention may be RNA, *e.g.*, *in vitro* synthesized RNA. Methods for *in vitro* synthesis of RNA are known to those of skill in the art; any known method can be used to synthesize RNA comprising a sequence encoding an IL9Ra or a chimeric cytokine receptor and/or CAR of the present disclosure. Methods for introducing RNA into a host cell are known in the art. See, *e.g.*, Zhao et al. Cancer Res. (2010) 15: 9053. Introducing RNA comprising a nucleotide sequence encoding an IL9Ra or a chimeric cytokine receptor and/or CAR of the present disclosure into a host cell can be carried out *in vitro*, *ex vivo* or *in vivo*. For example, a host cell (*e.g.*, an NK cell, a cytotoxic T lymphocyte, etc.) can be electroporated *in vitro* or *ex vivo* with RNA comprising a nucleotide sequence encoding an IL9Ra or a chimeric cytokine receptor and/or CAR of the present disclosure.

In order to assess the expression of a polypeptide or portions thereof, the expression vector to be introduced into a cell may 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 some

embodiments, 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, without limitation, antibiotic-resistance genes.

5 Reporter genes are used for identifying potentially transfected 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 assessed at a suitable time after the DNA has been
10 introduced into the recipient cells. Suitable reporter genes may include, without limitation, 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).

In some embodiments, a nucleic acid of the present disclosure is provided for the
15 production of an IL9Ra or a chimeric cytokine receptor and/or CAR as described herein, *e.g.*, in a mammalian cell. In some embodiments, a nucleic acid of the present disclosure provides for amplification of the nucleic acid.

Oncolytic Adenoviral Vectors

Oncolytic viruses represent highly promising agents for the treatment of solid tumors,
20 and an oncolytic herpes virus expressing GM-CSF was approved by the US FDA for the therapy of advanced melanoma based on therapeutic benefit demonstrated in a clinical study (Andtbacka RH, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015;33(25):2780–2788). Oncolytic adenoviruses (OAds) can be programmed to specifically target, replicate in, and kill cancer cells while
25 sparing normal cells. The release of virus progeny results in an exponential increase of the virus inoculum, which can cause direct tumor debulking while providing danger signals necessary to awaken the immune system (Lichty BD, Breitbach CJ, Stojdl DF, Bell JC. Going viral with cancer immunotherapy. Nat Rev Cancer. 2014;14(8):559–567). Importantly, OAds can be genetically modified to express therapeutic transgenes selectively in the TME
30 (Siurala M, et al. Adenoviral delivery of tumor necrosis factor- α and interleukin-2 enables successful adoptive cell therapy of immunosuppressive melanoma. Mol Ther. 2016;24(8):1435–1443; Nishio N, et al. Armed oncolytic virus enhances immune functions of chimeric antigen receptor-modified T cells in solid tumors. Cancer Res. 2014;74(18):5195–

- 5205; Tanoue K, et al. Armed oncolytic adenovirus-expressing PD-L1 mini-body enhances antitumor effects of chimeric antigen receptor T cells in solid tumors. *Cancer Res.* 2017;77(8):2040–2051; Rosewell Shaw A, et al. Adenovirotherapy delivering cytokine and checkpoint inhibitor augments CAR T cells against metastatic head and neck cancer. *Mol Ther.* 2017;25(11):2440–2451). The feasibility and safety of OAds in human patients have been demonstrated in clinical trials (Kim KH, et al. A phase I clinical trial of Ad5/3-Δ24, a novel serotype-chimeric, infectivity-enhanced, conditionally-replicative adenovirus (CRAd), in patients with recurrent ovarian cancer. *Gynecol Oncol.* 2013;130(3):518–524; Ranki T, et al. Phase I study with ONCOS-102 for the treatment of solid tumors - an evaluation of clinical response and exploratory analyses of immune markers. *J Immunother Cancer.* 2016;4:17). Their ability to revert tumor immunosuppression while locally expressing therapeutic transgenes provides a rational strategy for combination with adoptive T cell transfer.

In some embodiments, a cytokine of the present disclosure is encoded by a nucleic acid sequence which is comprised within an oncolytic adenoviral vector such as a conditionally replicating oncolytic adenoviral vector. One example of a conditionally replicating oncolytic adenoviral vector includes a serotype 5 adenoviral vector (Ad5) with modifications to the early genes E1A and E3 to enable cancer cell –specific replication and transgene expression, respectively. E1A is modified by deleting 24 base pairs of DNA from the CR2 region (aka D24 variant) to yield a virus capable of selectively replicating in cancer cells harboring p16-Rb pathway mutations. The cytokine transgene may be placed in the E3 region. Furthermore, the virus capsid is modified to include a chimeric 5/3 fiber which enables improved transduction efficiency of tumor cells.

25 **E. Modified Immune Cells**

The present invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express a) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a chimeric antigen

receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

In one aspect, the present invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express an interleukin-9 receptor alpha (IL9Ra), or any of the chimeric cytokine receptors disclosed herein, *e.g.*, a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).

In another aspect, the present invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, wherein the cell is engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA. In some embodiments, the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system. In some embodiments, the inhibitory RNA comprises an siRNA or an shRNA. Cullin 5 (Cul5) interacts with the SOCS-box protein CIS, a part of a CRL5 complex. CIS reduces IL-4 receptor signaling and limits Th2 and Th9 differentiation. Recently, it was shown that Cullin 5 associates with pJAK1 and promotes its ubiquitylation, and that Cullin 5 interacts with CIS and reduces levels of pJAK1 to limit IL-4 receptor signaling. Additionally, it was demonstrated that T cells lacking Cullin 5 are more likely to differentiate into Th2 and Th9 cells (and to deviate away from Treg differentiation) in vitro and in vivo, show a stronger Th9 gene expression program, show increased pSTAT6, and show reduced degradation of Jak1. Additionally, lungs from a mouse Cullin 5 knock out (Cul5^{fl/fl} CD4-Cre mice) have increased numbers of activated T cells, and the mice develop Th2 pathology as they age, show increased inflammation and airways resistance after HDM.

The present invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an

inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In one aspect, the present invention provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express any of the chimeric cytokine receptors disclosed herein, *e.g.*, a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra). In various embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

In certain embodiments, the modified immune cell or precursor cell thereof is selected from a T cell, a natural killer T (NKT) cell, a gamma-delta T cell, a natural killer (NK) cell, and a macrophage.

In certain embodiments, the modified cell comprises an isolated nucleic acid of the invention and/or a vector comprising an isolated nucleic acid of the present invention, such as an isolated nucleic acid comprising a) a first nucleotide sequence encoding an IL9Ra or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding

domain of an inhibitory immunoreceptor, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In some embodiments, the first nucleotide sequence encoding the IL9Ra or the chimeric cytokine receptor is linked to the second nucleotide sequence encoding the CAR via a nucleotide sequence encoding a 2A self-cleaving peptide as described herein, such as a P2A or T2A sequence.

In certain embodiments, the modified cell comprises an isolated nucleic acid of the invention and/or a vector comprising an isolated nucleic acid of the present invention, such as an isolated nucleic acid comprising a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In some embodiments, the first nucleotide sequence encoding the chimeric cytokine receptor is linked to the second nucleotide sequence encoding the CAR via a nucleotide sequence encoding a 2A self-cleaving peptide as described herein, such as a P2A or T2A sequence.

In certain embodiments, the modified cell is an autologous cell. In certain embodiments, the modified cell is an autologous T cell. In some embodiments, the cell is a human cell obtained from a human subject. In certain embodiments, the modified cell is a T cell.

F. Methods of Treatment

The present invention provides a method of treating cancer in a subject in need thereof, comprising administering to the subject: (a) a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express: (i) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta

(IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and (b) a vector comprising a
5 nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

The present invention also provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, wherein the cells are engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a
10 transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cells is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA. In some embodiments, the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system. In some
15 embodiments, the inhibitory RNA comprises an siRNA or an shRNA.

The present invention provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express a) a chimeric cytokine receptor comprising an extracellular domain comprising a
20 ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain. In various
25 embodiments, the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3). In various embodiments, the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-
30 Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

The modified cell (*e.g.*, T cells) described herein may be included in a composition for immunotherapy. The composition may include a pharmaceutical composition and further

include a pharmaceutically acceptable carrier. A therapeutically effective amount of the pharmaceutical composition comprising the modified T cells may be administered.

In one aspect, the invention includes a method for adoptive cell transfer therapy comprising administering to a subject in need thereof a population of modified cells of the present invention, wherein the cells are immune cells or precursor cells thereof (e.g., T cells).

Methods for administration of immune cells for adoptive cell therapy are known and may be used in connection with the provided methods and compositions. For example, adoptive immune cell therapy methods are described, e.g., in US Patent Application Publication No. 2003/0170238 to Gruenberg et al; US Patent No. 4,690,915 to Rosenberg; Rosenberg (2011) Nat Rev Clin Oncol. 8(10):577-85). See, e.g., Themeli et al. (2013) Nat Biotechnol. 31(10): 928-933; Tsukahara et al. (2013) Biochem Biophys Res Commun 438(1): 84-9; Davila et al. (2013) PLoS ONE 8(4): e61338; Lee et al., Int J. Mol Sci. (2021) 22(9):4590; Banerjee et al., JCO Clin Cancer Inform. (2021) 5:668-678; Robbins et al., Stem Cell Res Ther. (2021) 12(1):350; Wrona et al., Int J Mol Sci. (2021) 22(11):5899; Atrash and Moyo, Onco Targets Ther. (2021) 14:2185-2201; Martinez Bedoya et al., Front Immunol. (2021) 12:640082; Morgan et al., Front Immunol. (2020) 11:1965; Chicaybam et al., Cancers (Basel) (2020) 12(9):2360; and Rafiq et al., Nat Rev Clin Oncol. (2020) 17(3):147-167. In some embodiments, the cell therapy, e.g., adoptive T cell therapy is carried out by autologous transfer, in which the cells are isolated and/or otherwise prepared from the subject who is to receive the cell therapy, or from a sample derived from such a subject. Thus, in some aspects, the cells are derived from a subject, e.g., patient, in need of a treatment and the cells, following isolation and processing are administered to the same subject.

In some embodiments, the cell therapy, e.g., adoptive T cell therapy, is carried out by allogeneic transfer, in which the cells are isolated and/or otherwise prepared from a subject other than a subject who is to receive or who ultimately receives the cell therapy, e.g., a first subject. In such embodiments, the cells then are administered to a different subject, e.g., a second subject, of the same species. In some embodiments, the first and second subjects are genetically identical. In some embodiments, the first and second subjects are genetically similar. In some embodiments, the second subject expresses the same HLA class or supertype as the first subject.

In some embodiments, the subject has been treated with a therapeutic agent targeting the disease or condition, e.g. the tumor, prior to administration of the cells or composition containing the cells. In some aspects, the subject is refractory or non-responsive to the other

therapeutic agent. In some embodiments, the subject has persistent or relapsed disease, *e.g.*, following treatment with another therapeutic intervention, including chemotherapy, radiation, and/or hematopoietic stem cell transplantation (HSCT), *e.g.*, allogenic HSCT. In some embodiments, the administration effectively treats the subject despite the subject having
5 become resistant to another therapy.

In some embodiments, the subject is responsive to the other therapeutic agent, and treatment with the therapeutic agent reduces disease burden. In some aspects, the subject is initially responsive to the therapeutic agent, but exhibits a relapse of the disease or condition over time. In some embodiments, the subject has not relapsed. In some such embodiments,
10 the subject is determined to be at risk for relapse, such as at a high risk of relapse, and thus the cells are administered prophylactically, *e.g.*, to reduce the likelihood of or prevent relapse. In some aspects, the subject has not received prior treatment with another therapeutic agent.

In some embodiments, the subject has persistent or relapsed disease, *e.g.*, following treatment with another therapeutic intervention, including chemotherapy, radiation, and/or
15 hematopoietic stem cell transplantation (HSCT), *e.g.*, allogenic HSCT. In some embodiments, the administration effectively treats the subject despite the subject having become resistant to another therapy.

The modified immune cell of the present invention can be administered to an animal, preferably a mammal, even more preferably a human, to treat a cancer. In addition, the cells
20 of the present invention can be used for the treatment of any condition related to a cancer, especially a cell-mediated immune response against a tumor cell(s), where it is desirable to treat or alleviate the disease. The types of cancers to be treated with the modified cells or pharmaceutical compositions of the invention include certain leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies *e.g.*, sarcomas, carcinomas,
25 and melanomas. Exemplary cancers include but are not limited to B-cell malignancies (such as B-cell lymphomas and leukemias and the like), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer,
30 colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer. The cancers may be non-solid tumors (such as

hematological tumors) or solid tumors. Adult tumors/cancers and pediatric tumors/cancers are also included. In one embodiment, the cancer is a solid tumor or a hematological tumor.

The cells to be administered may be autologous, with respect to the subject undergoing therapy.

5 The administration of the cells of the invention may be carried out in any convenient manner known to those of skill in the art. The cells of the present invention may be administered to a subject by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient transarterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, 10 intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In other instances, the cells of the invention are injected directly into a site of inflammation in the subject, a local disease site in the subject, a lymph node, an organ, a tumor, and the like.

In some embodiments, the cells are administered at a desired dosage, which in some aspects includes a desired dose or number of cells or cell type(s) and/or a desired ratio of cell 15 types. Thus, the dosage of cells in some embodiments is based on a total number of cells (or number per kg body weight) and a desired ratio of the individual populations or sub-types, such as the CD4⁺ to CD8⁺ ratio. In some embodiments, the dosage of cells is based on a desired total number (or number per kg of body weight) of cells in the individual populations or of individual cell types. In some embodiments, the dosage is based on a combination of 20 such features, such as a desired number of total cells, desired ratio, and desired total number of cells in the individual populations.

In some embodiments, the populations or sub-types of cells, such as CD8⁺ and CD4⁺ T cells, are administered at or within a tolerated difference of a desired dose of total cells, such as a desired dose of T cells. In some aspects, the desired dose is a desired number of 25 cells or a desired number of cells per unit of body weight of the subject to whom the cells are administered, e.g., cells/kg. In some aspects, the desired dose is at or above a minimum number of cells or minimum number of cells per unit of body weight. In some aspects, among the total cells, administered at the desired dose, the individual populations or sub-types are present at or near a desired output ratio (such as CD4⁺ to CD8⁺ ratio), e.g., within a certain 30 tolerated difference or error of such a ratio.

In some embodiments, the cells are administered at or within a tolerated difference of a desired dose of one or more of the individual populations or sub-types of cells, such as a desired dose of CD4⁺ cells and/or a desired dose of CD8⁺ cells. In some aspects, the desired

dose is a desired number of cells of the sub-type or population, or a desired number of such cells per unit of body weight of the subject to whom the cells are administered, e.g., cells/kg. In some aspects, the desired dose is at or above a minimum number of cells of the population or subtype, or minimum number of cells of the population or sub-type per unit of body weight. Thus, in some embodiments, the dosage is based on a desired fixed dose of total cells and a desired ratio, and/or based on a desired fixed dose of one or more, e.g., each, of the individual sub-types or sub-populations. Thus, in some embodiments, the dosage is based on a desired fixed or minimum dose of T cells and a desired ratio of CD4⁺ to CD8⁺ cells, and/or is based on a desired fixed or minimum dose of CD4⁺ and/or CD8⁺ cells.

10 In certain embodiments, the cells, or individual populations of sub-types of cells, are administered to the subject at a range of about one million to about 100 billion cells, such as, e.g., 1 million to about 50 billion cells (e.g., about 5 million cells, about 25 million cells, about 500 million cells, about 1 billion cells, about 5 billion cells, about 20 billion cells, about 30 billion cells, about 40 billion cells, or a range defined by any two of the foregoing values), such as about 10 million to about 100 billion cells (e.g., about 20 million cells, about 30 million cells, about 40 million cells, about 60 million cells, about 70 million cells, about 80 million cells, about 90 million cells, about 10 billion cells, about 25 billion cells, about 50 billion cells, about 75 billion cells, about 90 billion cells, or a range defined by any two of the foregoing values), and in some cases about 100 million cells to about 50 billion cells (e.g., about 120 million cells, about 250 million cells, about 350 million cells, about 450 million cells, about 650 million cells, about 800 million cells, about 900 million cells, about 3 billion cells, about 30 billion cells, about 45 billion cells) or any value in between these ranges.

In some embodiments, the dose of total cells and/or dose of individual sub-populations of cells is within a range of between at or about 1×10^5 cells/kg to about 1×10^{11} cells/kg 10^4 and at or about 10^{11} cells/kilograms (kg) body weight, such as between 10^5 and 10^6 cells / kg body weight, for example, at or about 1×10^5 cells/kg, 1.5×10^5 cells/kg, 2×10^5 cells/kg, or 1×10^6 cells/kg body weight. For example, in some embodiments, the cells are administered at, or within a certain range of error of, between at or about 10^4 and at or about 10^9 T cells/kilograms (kg) body weight, such as between 10^5 and 10^6 T cells / kg body weight, for example, at or about 1×10^5 T cells/kg, 1.5×10^5 T cells/kg, 2×10^5 T cells/kg, or 1×10^6 T cells/kg body weight. In other exemplary embodiments, a suitable dosage range of modified cells for use in a method of the present disclosure includes, without limitation, from about 1×10^5 cells/kg to about 1×10^6 cells/kg, from about 1×10^6 cells/kg to about 1×10^7

cells/kg, from about 1×10^7 cells/kg about 1×10^8 cells/kg, from about 1×10^8 cells/kg about 1×10^9 cells/kg, from about 1×10^9 cells/kg about 1×10^{10} cells/kg, from about 1×10^{10} cells/kg about 1×10^{11} cells/kg. In an exemplary embodiment, a suitable dosage for use in a method of the present disclosure is about 1×10^8 cells/kg. In an exemplary embodiment, a suitable dosage for use in a method of the present disclosure is about 1×10^7 cells/kg. In other embodiments, a suitable dosage is from about 1×10^7 total cells to about 5×10^7 total cells. In some embodiments, a suitable dosage is from about 1×10^8 total cells to about 5×10^8 total cells. In some embodiments, a suitable dosage is from about 1.4×10^7 total cells to about 1.1×10^9 total cells. In an exemplary embodiment, a suitable dosage for use in a method of the present disclosure is about 7×10^9 total cells.

In some embodiments, the cells are administered at or within a certain range of error of between at or about 10^4 and at or about 10^9 CD4⁺ and/or CD8⁺ cells/kilograms (kg) body weight, such as between 10^5 and 10^6 CD4⁺ and/or CD8⁺ cells / kg body weight, for example, at or about 1×10^5 CD4⁺ and/or CD8⁺ cells/kg, 1.5×10^5 CD4⁺ and/or CD8⁺ cells/kg, 2×10^5 CD4⁺ and/or CD8⁺ cells/kg, or 1×10^6 CD4⁺ and/or CD8⁺ cells/kg body weight. In some embodiments, the cells are administered at or within a certain range of error of, greater than, and/or at least about 1×10^6 , about 2.5×10^6 , about 5×10^6 , about 7.5×10^6 , or about 9×10^6 CD4⁺ cells, and/or at least about 1×10^6 , about 2.5×10^6 , about 5×10^6 , about 7.5×10^6 , or about 9×10^6 CD8⁺ cells, and/or at least about 1×10^6 , about 2.5×10^6 , about 5×10^6 , about 7.5×10^6 , or about 9×10^6 T cells. In some embodiments, the cells are administered at or within a certain range of error of between about 10^8 and 10^{12} or between about 10^{10} and 10^{11} T cells, between about 10^8 and 10^{12} or between about 10^{10} and 10^{11} CD4⁺ cells, and/or between about 10^8 and 10^{12} or between about 10^{10} and 10^{11} CD8⁺ cells.

In some embodiments, the cells are administered at or within a tolerated range of a desired output ratio of multiple cell populations or sub-types, such as CD4⁺ and CD8⁺ cells or sub-types. In some aspects, the desired ratio can be a specific ratio or can be a range of ratios, for example, in some embodiments, the desired ratio (e.g., ratio of CD4⁺ to CD8⁺ cells) is between at or about 5: 1 and at or about 5: 1 (or greater than about 1:5 and less than about 5: 1), or between at or about 1:3 and at or about 3: 1 (or greater than about 1:3 and less than about 3: 1), such as between at or about 2: 1 and at or about 1:5 (or greater than about 1:5 and less than about 2: 1, such as at or about 5: 1, 4.5: 1, 4: 1, 3.5: 1, 3: 1, 2.5: 1, 2: 1, 1.9: 1, 1.8: 1, 1.7: 1, 1.6: 1, 1.5: 1, 1.4: 1, 1.3: 1, 1.2: 1, 1.1: 1, 1: 1, 1: 1.1, 1: 1.2, 1: 1.3, 1:1.4, 1: 1.5, 1: 1.6, 1: 1.7, 1: 1.8, 1: 1.9, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5, or 1:5. In some aspects, the

tolerated difference is within about 1%, about 2%, about 3%, about 4% about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50% of the desired ratio, including any value in between these ranges.

In some embodiments, a dose of modified cells is administered to a subject in need thereof, in a single dose or multiple doses. In some embodiments, a dose of modified cells is administered in multiple doses, e.g., once a week or every 7 days, once every 2 weeks or every 14 days, once every 3 weeks or every 21 days, once every 4 weeks or every 28 days. In an exemplary embodiment, a single dose of modified cells is administered to a subject in need thereof. In an exemplary embodiment, a single dose of modified cells is administered to a subject in need thereof by rapid intravenous infusion.

For the prevention or treatment of disease, the appropriate dosage may depend on the type of disease to be treated, the type of cells or recombinant receptors, the severity and course of the disease, whether the cells are administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the cells, and the discretion of the attending physician. The compositions and cells are in some embodiments suitably administered to the subject at one time or over a series of treatments.

In some embodiments, the cells are administered as part of a combination treatment, such as simultaneously with or sequentially with, in any order, another therapeutic intervention, such as an antibody or engineered cell or receptor or agent, such as a cytotoxic or therapeutic agent. The cells in some embodiments are co-administered with one or more additional therapeutic agents or in connection with another therapeutic intervention, either simultaneously or sequentially in any order. In some contexts, the cells are co-administered with another therapy sufficiently close in time such that the cell populations enhance the effect of one or more additional therapeutic agents, or vice versa. In some embodiments, the cells are administered prior to the one or more additional therapeutic agents. In some embodiments, the cells are administered after the one or more additional therapeutic agents. In some embodiments, the one or more additional agents includes a cytokine, such as IL-2, for example, to enhance persistence. In some embodiments, the methods comprise administration of a chemotherapeutic agent.

In certain embodiments, the modified cells of the invention (e.g., a modified cell comprising a CAR) may be administered to a subject in combination with an immune checkpoint antibody (e.g., an anti-PD1, anti-CTLA-4, or anti-PDL1 antibody). For example, the modified cell may be administered in combination with an antibody or antibody fragment

targeting, for example, PD-1 (programmed death 1 protein). Examples of anti-PD-1 antibodies include, but are not limited to, pembrolizumab (KEYTRUDA®, formerly lambrolizumab, also known as MK-3475), and nivolumab (BMS-936558, MDX-1106, ONO-4538, OPDIVA®) or an antigen-binding fragment thereof. In certain embodiments, the modified cell may be administered in combination with an anti-PD-L1 antibody or antigen-binding fragment thereof. Examples of anti-PD-L1 antibodies include, but are not limited to, BMS-936559, MPDL3280A (TECENTRIQ®, Atezolizumab), and MEDI4736 (Durvalumab, Imfinzi). In certain embodiments, the modified cell may be administered in combination with an anti-CTLA-4 antibody or antigen-binding fragment thereof. An example of an anti-CTLA-4 antibody includes, but is not limited to, Ipilimumab (trade name Yervoy). Other types of immune checkpoint modulators may also be used including, but not limited to, small molecules, siRNA, miRNA, and CRISPR systems. Immune checkpoint modulators may be administered before, after, or concurrently with the modified cell comprising the CAR. In certain embodiments, combination treatment comprising an immune checkpoint modulator may increase the therapeutic efficacy of a therapy comprising a modified cell of the present invention.

Following administration of the cells, the biological activity of the engineered cell populations in some embodiments is measured, *e.g.*, by any of a number of known methods. Parameters to assess include specific binding of an engineered or natural T cell or other immune cell to antigen, *in vivo*, *e.g.*, by imaging, or *ex vivo*, *e.g.*, by ELISA or flow cytometry. In certain embodiments, the ability of the engineered cells to destroy target cells can be measured using any suitable method known in the art, such as cytotoxicity assays described in, for example, Kochenderfer et al., *J. Immunotherapy*, 32(7): 689-702 (2009); Herman et al. *J. Immunological Methods*, 285(1): 25-40 (2004); Kiesgen et al., *Nat Protoc.* (2021) 16(3):1331-1342; and Maldini et al., *J Immunol Methods* (2020) 484-485:112830. In certain embodiments, the biological activity of the cells is measured by assaying expression and/or secretion of one or more cytokines, such as CD 107a, IFN γ , IL-2, and TNF. In some aspects the biological activity is measured by assessing clinical outcome, such as reduction in tumor burden or load.

In certain embodiments, the subject is provided a secondary treatment. Secondary treatments include but are not limited to chemotherapy, radiation, surgery, and medications.

In some embodiments, the subject can be administered a conditioning therapy prior to CAR T cell therapy. In some embodiments, the conditioning therapy comprises administering

an effective amount of cyclophosphamide to the subject. In some embodiments, the conditioning therapy comprises administering an effective amount of fludarabine to the subject. In preferred embodiments, the conditioning therapy comprises administering an effective amount of a combination of cyclophosphamide and fludarabine to the subject.

- 5 Administration of a conditioning therapy prior to CAR T cell therapy may increase the efficacy of the CAR T cell therapy. Methods of conditioning patients for T cell therapy are described in U.S. Patent No. 9,855,298, which is incorporated herein by reference in its entirety.

- 10 In some embodiments, a specific dosage regimen of the present disclosure includes a lymphodepletion step prior to the administration of the modified T cells. In an exemplary embodiment, the lymphodepletion step includes administration of cyclophosphamide and/or fludarabine.

- In some embodiments, the lymphodepletion step includes administration of cyclophosphamide at a dose of between about 200 mg/m²/day and about 2000 mg/m²/day (e.g., 200 mg/m²/day, 300 mg/m²/day, or 500 mg/m²/day). In an exemplary embodiment, the dose of cyclophosphamide is about 300 mg/m²/day. In some embodiments, the lymphodepletion step includes administration of fludarabine at a dose of between about 20 mg/m²/day and about 900 mg/m²/day (e.g., 20 mg/m²/day, 25 mg/m²/day, 30 mg/m²/day, or 60 mg/m²/day). In an exemplary embodiment, the dose of fludarabine is about 30 mg/m²/day.

- In some embodiment, the lymphodepletion step includes administration of cyclophosphamide at a dose of between about 200 mg/m²/day and about 2000 mg/m²/day (e.g., 200 mg/m²/day, 300 mg/m²/day, or 500 mg/m²/day), and fludarabine at a dose of between about 20 mg/m²/day and about 900 mg/m²/day (e.g., 20 mg/m²/day, 25 mg/m²/day, 30 mg/m²/day, or 60 mg/m²/day). In an exemplary embodiment, the lymphodepletion step includes administration of cyclophosphamide at a dose of about 300 mg/m²/day, and fludarabine at a dose of about 30 mg/m²/day.

In an exemplary embodiment, the dosing of cyclophosphamide is 300 mg/m²/day over three days, and the dosing of fludarabine is 30 mg/m²/day over three days.

- 30 Dosing of lymphodepletion chemotherapy may be scheduled on Days -6 to -4 (with a -1 day window, i.e., dosing on Days -7 to -5) relative to T cell (e.g., CAR-T, TCR-T, a modified T cell, etc.) infusion on Day 0.

In an exemplary embodiment, for a subject having cancer, the subject receives lymphodepleting chemotherapy including 300 mg/m² of cyclophosphamide by intravenous infusion 3 days prior to administration of the modified T cells. In an exemplary embodiment, for a subject having cancer, the subject receives lymphodepleting chemotherapy including
5 300 mg/m² of cyclophosphamide by intravenous infusion for 3 days prior to administration of the modified T cells.

In an exemplary embodiment, for a subject having cancer, the subject receives lymphodepleting chemotherapy including fludarabine at a dose of between about 20 mg/m²/day and about 900 mg/m²/day (*e.g.*, 20 mg/m²/day, 25 mg/m²/day, 30 mg/m²/day, or
10 60 mg/m²/day). In an exemplary embodiment, for a subject having cancer, the subject receives lymphodepleting chemotherapy including fludarabine at a dose of 30 mg/m² for 3 days.

In an exemplary embodiment, for a subject having cancer, the subject receives lymphodepleting chemotherapy including cyclophosphamide at a dose of between about 200
15 mg/m²/day and about 2000 mg/m²/day (*e.g.*, 200 mg/m²/day, 300 mg/m²/day, or 500 mg/m²/day), and fludarabine at a dose of between about 20 mg/m²/day and about 900 mg/m²/day (*e.g.*, 20 mg/m²/day, 25 mg/m²/day, 30 mg/m²/day, or 60 mg/m²/day). In an exemplary embodiment, for a subject having cancer, the subject receives lymphodepleting chemotherapy including cyclophosphamide at a dose of about 300 mg/m²/day, and
20 fludarabine at a dose of 30 mg/m² for 3 days.

Cells of the invention can be administered in dosages and routes and at times to be determined in appropriate pre-clinical and clinical experimentation and trials. Cell compositions may be administered multiple times at dosages within these ranges. Administration of the cells of the invention may be combined with other methods useful to
25 treat the desired disease or condition as determined by those of skill in the art.

It is known in the art that one of the adverse effects following infusion of CAR T cells is the onset of immune activation, known as cytokine release syndrome (CRS). CRS is immune activation resulting in elevated inflammatory cytokines. CRS is a known on-target toxicity, development of which likely correlates with efficacy. Clinical and laboratory
30 measures range from mild CRS (constitutional symptoms and/or grade-2 organ toxicity) to severe CRS (sCRS; grade ≥ 3 organ toxicity, aggressive clinical intervention, and/or potentially life threatening). Clinical features include: high fever, malaise, fatigue, myalgia, nausea, anorexia, tachycardia/hypotension, capillary leak, cardiac dysfunction, renal

impairment, hepatic failure, and disseminated intravascular coagulation. Dramatic elevations of cytokines including interferon-gamma, granulocyte macrophage colony-stimulating factor, IL-10, and IL-6 have been shown following CAR T-cell infusion. One CRS signature is elevation of cytokines including IL-6 (severe elevation), IFN-gamma, TNF-alpha (moderate), and IL-2 (mild). Elevations in clinically available markers of inflammation including ferritin and C-reactive protein (CRP) have also been observed to correlate with the CRS syndrome. The presence of CRS generally correlates with expansion and progressive immune activation of adoptively transferred cells. It has been demonstrated that the degree of CRS severity is dictated by disease burden at the time of infusion as patients with high tumor burden experience a more sCRS.

Accordingly, the invention provides for, following the diagnosis of CRS, appropriate CRS management strategies to mitigate the physiological symptoms of uncontrolled inflammation without dampening the antitumor efficacy of the engineered cells (*e.g.*, CAR T cells). CRS management strategies are known in the art. For example, systemic corticosteroids may be administered to rapidly reverse symptoms of sCRS (*e.g.*, grade 3 CRS) without compromising initial antitumor response.

In some embodiments, an anti-IL-6R antibody may be administered. An example of an anti-IL-6R antibody is the Food and Drug Administration-approved monoclonal antibody tocilizumab, also known as atilizumab (marketed as Actemra, or RoActemra). Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Administration of tocilizumab has demonstrated near-immediate reversal of CRS.

CRS is generally managed based on the severity of the observed syndrome and interventions are tailored as such. CRS management decisions may be based upon clinical signs and symptoms and response to interventions, not solely on laboratory values alone.

Mild to moderate cases generally are treated with symptom management with fluid therapy, non-steroidal anti-inflammatory drug (NSAID) and antihistamines as needed for adequate symptom relief. More severe cases include patients with any degree of hemodynamic instability; with any hemodynamic instability, the administration of tocilizumab is recommended. The first-line management of CRS may be tocilizumab, in some embodiments, at the labeled dose of 8 mg/kg IV over 60 minutes (not to exceed 800 mg/dose); tocilizumab can be repeated Q8 hours. If suboptimal response to the first dose of tocilizumab, additional doses of tocilizumab may be considered. Tocilizumab can be administered alone or in combination with corticosteroid therapy. Patients with continued or

progressive CRS symptoms, inadequate clinical improvement in 12-18 hours or poor response to tocilizumab, may be treated with high-dose corticosteroid therapy, generally hydrocortisone 100 mg IV or methylprednisolone 1-2 mg/kg. In patients with more severe hemodynamic instability or more severe respiratory symptoms, patients may be administered high-dose corticosteroid therapy early in the course of the CRS. CRS management guidance may be based on published standards (Lee et al. (2019) *Biol Blood Marrow Transplant*, doi.org/10.1016/j.bbmt.2018.12.758; Neelapu et al. (2018) *Nat Rev Clin Oncology*, 15:47; Teachey et al. (2016) *Cancer Discov*, 6(6):664-679).

Features consistent with Macrophage Activation Syndrome (MAS) or Hemophagocytic lymphohistiocytosis (HLH) have been observed in patients treated with CAR-T therapy (Henter, 2007), coincident with clinical manifestations of the CRS. MAS appears to be a reaction to immune activation that occurs from the CRS, and should therefore be considered a manifestation of CRS. MAS is similar to HLH (also a reaction to immune stimulation). The clinical syndrome of MAS is characterized by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly. It is associated with high serum ferritin, soluble interleukin-2 receptor, and triglycerides, and a decrease of circulating natural killer (NK) activity.

In one aspect, the invention includes a method of treating cancer in a subject in need thereof, comprising administering to the subject any one of the modified immune or precursor cells disclosed herein. Yet another aspect of the invention includes a method of treating cancer in a subject in need thereof, comprising administering to the subject a modified immune or precursor cell generated by any one of the methods disclosed herein.

G. Sources of Immune Cells

In certain embodiments, a source of immune cells (*e.g.* T cells) is obtained from a subject for *ex vivo* manipulation and/or *in vivo* transduction. Sources of target cells for *ex vivo* manipulation may also include, *e.g.*, autologous or heterologous donor blood, cord blood, or bone marrow. For example the source of immune cells may be from the subject to be treated with the modified immune cells of the invention, *e.g.*, the subject's blood, the subject's cord blood, or the subject's bone marrow. Non-limiting examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof. Preferably, the subject is a human. Methods for *in vivo* transduction of immune cells for CAR expression are described, *e.g.*, in Pfeiffer et al., *EMBO Mol Med*. (2018) 10(11):e9158; Weidner et al., *Nat Protoc*. (2021)

16(7):3210-3240; Frank et al., Blood Advances (2020) 4(22):5702-5715; Nawaz et al., Blood Cancer J. (2021) 11(6):119.

Immune cells can be obtained from a number of sources, including blood, peripheral blood mononuclear cells, bone marrow, lymph node tissue, spleen tissue, umbilical cord, lymph, or lymphoid organs. Immune cells are cells of the immune system, such as cells of the innate or adaptive immunity, *e.g.*, myeloid or lymphoid cells, including lymphocytes, typically T cells and/or NK cells. Other exemplary cells include stem cells, such as multipotent and pluripotent stem cells, including induced pluripotent stem cells (iPSCs). In some aspects, the cells are human cells. With reference to the subject to be treated, the cells may be allogeneic and/or autologous. The cells typically are primary cells, such as those isolated directly from a subject and/or isolated from a subject and frozen.

In certain embodiments, the immune cell is a T cell, *e.g.*, a CD8⁺ T cell (*e.g.*, a CD8⁺ naive T cell, central memory T cell, or effector memory T cell), a CD4⁺ T cell, a natural killer T cell (NKT cells), a regulatory T cell (Treg), a stem cell memory T cell, a lymphoid progenitor cell, a hematopoietic stem cell, a natural killer cell (NK cell), a macrophage, or a dendritic cell. In some embodiments, the cells are monocytes or granulocytes, *e.g.*, myeloid cells, macrophages, neutrophils, dendritic cells, mast cells, eosinophils, and/or basophils. In an embodiment, the target cell is an induced pluripotent stem (iPS) cell or a cell derived from an iPS cell, *e.g.*, an iPS cell generated from a subject, manipulated to alter (*e.g.*, induce a mutation in) or manipulate the expression of one or more target genes, and differentiated into, *e.g.*, a T cell, *e.g.*, a CD8⁺ T cell (*e.g.*, a CD8⁺ naive T cell, central memory T cell, or effector memory T cell), a CD4⁺ T cell, a stem cell memory T cell, a lymphoid progenitor cell, or a hematopoietic stem cell.

In some embodiments, the cells include one or more subsets of T cells or other cell types, such as whole T cell populations, CD4⁺ cells, CD8⁺ cells, and subpopulations thereof, such as those defined by function, activation state, maturity, potential for differentiation, expansion, recirculation, localization, and/or persistence capacities, antigen- specificity, type of antigen receptor, presence in a particular organ or compartment, marker or cytokine secretion profile, and/or degree of differentiation. Among the sub-types and subpopulations of T cells and/or of CD4⁺ and/or of CD8⁺ T cells are naive T (TN) cells, effector T cells (TEFF), memory T cells and sub-types thereof, such as stem cell memory T (TSCM), central memory T (TCM), effector memory T (TEM), or terminally differentiated effector memory T cells, tumor-infiltrating lymphocytes (TIL), immature T cells, mature T cells, helper T cells,

cytotoxic T cells, mucosa-associated invariant T (MAIT) cells, naturally occurring and adaptive regulatory T (Treg) cells, helper T cells, such as TH1 cells, TH2 cells, TH3 cells, TH17 cells, TH9 cells, TH22 cells, follicular helper T cells, alpha/beta T cells, and delta/gamma T cells. In certain embodiments, any number of T cell lines available in the art, 5 may be used.

In some embodiments, the methods include isolating immune cells from the subject, preparing, processing, culturing, and/or engineering them. In some embodiments, preparation of the engineered cells includes one or more culture and/or preparation steps. The cells for engineering as described may be isolated from a sample, such as a biological sample, e.g., 10 one obtained from or derived from a subject. In some embodiments, the subject from which the cell is isolated is one having the disease or condition or in need of a cell therapy or to which cell therapy will be administered. The subject in some embodiments is a human in need of a particular therapeutic intervention, such as the adoptive cell therapy for which cells are being isolated, processed, and/or engineered. Accordingly, the cells in some embodiments 15 are primary cells, e.g., primary human cells. The samples include tissue, fluid, and other samples taken directly from the subject, as well as samples resulting from one or more processing steps, such as separation, centrifugation, genetic engineering (e.g. transduction with viral vector), washing, and/or incubation. The biological sample can be a sample obtained directly from a biological source or a sample that is processed. Biological samples 20 include, but are not limited to, body fluids, such as blood, plasma, serum, cerebrospinal fluid, synovial fluid, urine and sweat, tissue and organ samples, including processed samples derived therefrom.

In some aspects, the sample from which the cells are derived or isolated is blood or a blood-derived sample, or is or is derived from an apheresis or leukapheresis product. 25 Exemplary samples include whole blood, peripheral blood mononuclear cells (PBMCs), leukocytes, bone marrow, thymus, tissue biopsy, tumor, leukemia, lymphoma, lymph node, gut associated lymphoid tissue, mucosa associated lymphoid tissue, spleen, other lymphoid tissues, liver, lung, stomach, intestine, colon, kidney, pancreas, breast, bone, prostate, cervix, testes, ovaries, tonsil, or other organ, and/or cells derived therefrom. Samples include, in the 30 context of cell therapy, e.g., adoptive cell therapy, samples from autologous and allogeneic sources.

In some embodiments, the cells are derived from cell lines, e.g., T cell lines. The cells in some embodiments are obtained from a xenogeneic source, for example, from mouse, rat,

non-human primate, and pig. In some embodiments, isolation of the cells includes one or more preparation and/or non-affinity based cell separation steps. In some examples, cells are washed, centrifuged, and/or incubated in the presence of one or more reagents, for example, to remove unwanted components, enrich for desired components, lyse or remove cells sensitive to particular reagents. In some examples, cells are separated based on one or more property, such as density, adherent properties, size, sensitivity and/or resistance to particular components.

In some examples, cells from the circulating blood of a subject are obtained, *e.g.*, by apheresis or leukapheresis. The samples, in some aspects, contain lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and/or platelets, and in some aspects contains cells other than red blood cells and platelets. In some embodiments, the blood cells collected from the subject are washed, *e.g.*, 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 some aspects, a washing step is accomplished by tangential flow filtration (TFF) according to the manufacturer's instructions. In some embodiments, the cells are resuspended in a variety of biocompatible buffers after washing. In certain embodiments, components of a blood cell sample are removed and the cells directly resuspended in culture media. In some embodiments, the methods include density-based cell separation methods, such as the preparation of white blood cells from peripheral blood by lysing the red blood cells and centrifugation through a Percoll or Ficoll gradient.

In one embodiment, immune are obtained cells from the circulating blood of an individual are obtained by apheresis or leukapheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. The cells collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media, such as phosphate buffered saline (PBS) or wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations, for subsequent processing steps. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca-free, Mg-free PBS. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

In some embodiments, the isolation methods include the separation of different cell types based on the expression or presence in the cell of one or more specific molecules, such

as surface markers, *e.g.*, surface proteins, intracellular markers, or nucleic acid. In some embodiments, any known method for separation based on such markers may be used. In some embodiments, the separation is affinity- or immunoaffinity-based separation. For example, the isolation in some aspects includes separation of cells and cell populations based on the cells' expression or expression level of one or more markers, typically cell surface markers, for example, by incubation with an antibody or binding partner that specifically binds to such markers, followed generally by washing steps and separation of cells having bound the antibody or binding partner, from those cells having not bound to the antibody or binding partner.

Such separation steps can be based on positive selection, in which the cells having bound the reagents are retained for further use, and/or negative selection, in which the cells having not bound to the antibody or binding partner are retained. In some examples, both fractions are retained for further use. In some aspects, negative selection can be particularly useful where no antibody is available that specifically identifies a cell type in a heterogeneous population, such that separation is best carried out based on markers expressed by cells other than the desired population. The separation need not result in 100% enrichment or removal of a particular cell population or cells expressing a particular marker. For example, positive selection of or enrichment for cells of a particular type, such as those expressing a marker, refers to increasing the number or percentage of such cells, but need not result in a complete absence of cells not expressing the marker. Likewise, negative selection, removal, or depletion of cells of a particular type, such as those expressing a marker, refers to decreasing the number or percentage of such cells, but need not result in a complete removal of all such cells.

In some examples, multiple rounds of separation steps are carried out, where the positively or negatively selected fraction from one step is subjected to another separation step, such as a subsequent positive or negative selection. In some examples, a single separation step can deplete cells expressing multiple markers simultaneously, such as by incubating cells with a plurality of antibodies or binding partners, each specific for a marker targeted for negative selection. Likewise, multiple cell types can simultaneously be positively selected by incubating cells with a plurality of antibodies or binding partners expressed on the various cell types.

In some embodiments, one or more of the T cell populations is enriched for or depleted of cells that are positive for (marker⁺) or express high levels (marker^{high}) of one or

more particular markers, such as surface markers, or that are negative for (marker⁻) or express relatively low levels (marker^{low}) of one or more markers. For example, in some aspects, specific subpopulations of T cells, such as cells positive or expressing high levels of one or more surface markers, *e.g.*, CD28⁺, CD62L⁺, CCR7⁺, CD27⁺, CD127⁺, CD4⁺, CD8⁺, CD45RA⁺, and/or CD45RO⁺ T cells, are isolated by positive or negative selection techniques. In some cases, such markers are those that are absent or expressed at relatively low levels on certain populations of T cells (such as non-memory cells) but are present or expressed at relatively higher levels on certain other populations of T cells (such as memory cells). In one embodiment, the cells (such as the CD8⁺ cells or the T cells, *e.g.*, CD3⁺ cells) are enriched for (*i.e.*, positively selected for) cells that are positive or expressing high surface levels of CD45RO, CCR7, CD28, CD27, CD44, CD 127, and/or CD62L and/or depleted of (*e.g.*, negatively selected for) cells that are positive for or express high surface levels of CD45RA. In some embodiments, cells are enriched for or depleted of cells positive or expressing high surface levels of CD 122, CD95, CD25, CD27, and/or IL7-Ra (CD 127). In some examples, CD8⁺ T cells are enriched for cells positive for CD45RO (or negative for CD45RA) and for CD62L. For example, CD3⁺, CD28⁺ T cells can be positively selected using CD3/CD28 conjugated magnetic beads (*e.g.*, DYNABEADS® M-450 CD3/CD28 T Cell Expander).

In some embodiments, T cells are separated from a PBMC sample by negative selection of markers expressed on non-T cells, such as B cells, monocytes, or other white blood cells, such as CD14. In some aspects, a CD4⁺ or CD8⁺ selection step is used to separate CD4⁺ helper and CD8⁺ cytotoxic T cells. Such CD4⁺ and CD8⁺ populations can be further sorted into sub-populations by positive or negative selection for markers expressed or expressed to a relatively higher degree on one or more naive, memory, and/or effector T cell subpopulations. In some embodiments, CD8⁺ cells are further enriched for or depleted of naive, central memory, effector memory, and/or central memory stem cells, such as by positive or negative selection based on surface antigens associated with the respective subpopulation. In some embodiments, enrichment for central memory T (TCM) cells is carried out to increase efficacy, such as to improve long-term survival, expansion, and/or engraftment following administration, which in some aspects is particularly robust in such sub-populations. In some embodiments, combining TCM-enriched CD8⁺ T cells and CD4⁺ T cells further enhances efficacy.

In some embodiments, memory T cells are present in both CD62L⁺ and CD62L⁻ subsets of CD8⁺ peripheral blood lymphocytes. PBMC can be enriched for or depleted of CD62L⁻CD8⁺ and/or CD62L⁺CD8⁺ fractions, such as using anti-CD8 and anti-CD62L antibodies. In some embodiments, a CD4⁺ T cell population and a CD8⁺ T cell sub-population, e.g., a sub-population enriched for central memory (TCM) cells. In some embodiments, the enrichment for central memory T (TCM) cells is based on positive or high surface expression of CD45RO, CD62L, CCR7, CD28, CD3, and/or CD 127; in some aspects, it is based on negative selection for cells expressing or highly expressing CD45RA and/or granzyme B. In some aspects, isolation of a CD8⁺ population enriched for TCM cells is carried out by depletion of cells expressing CD4, CD 14, CD45RA, and positive selection or enrichment for cells expressing CD62L. In one aspect, enrichment for central memory T (TCM) cells is carried out starting with a negative fraction of cells selected based on CD4 expression, which is subjected to a negative selection based on expression of CD 14 and CD45RA, and a positive selection based on CD62L. Such selections in some aspects are carried out simultaneously and in other aspects are carried out sequentially, in either order. In some aspects, the same CD4 expression-based selection step used in preparing the CD8⁺ cell population or subpopulation, also is used to generate the CD4⁺ cell population or subpopulation, such that both the positive and negative fractions from the CD4-based separation are retained and used in subsequent steps of the methods, optionally following one or more further positive or negative selection steps.

CD4⁺ T helper cells are sorted into naive, central memory, and effector cells by identifying cell populations that have cell surface antigens. CD4⁺ lymphocytes can be obtained by standard methods. In some embodiments, naive CD4⁺ T lymphocytes are CD45RO⁻, CD45RA⁺, CD62L⁺, CD4⁺ T cells. In some embodiments, central memory CD4⁺ cells are CD62L⁺ and CD45RO⁺. In some embodiments, effector CD4⁺ cells are CD62L⁻ and CD45RO⁻. In one example, to enrich for CD4⁺ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In some embodiments, the antibody or binding partner is bound to a solid support or matrix, such as a magnetic bead or paramagnetic bead, to allow for separation of cells for positive and/or negative selection.

In some embodiments, the cells are incubated and/or cultured prior to or in connection with genetic engineering. The incubation steps can include culture, cultivation, stimulation, activation, and/or propagation. In some embodiments, the compositions or cells are incubated

in the presence of stimulating conditions or a stimulatory agent. Such conditions include those designed to induce proliferation, expansion, activation, and/or survival of cells in the population, to mimic antigen exposure, and/or to prime the cells for genetic engineering, such as for the introduction of a recombinant antigen receptor. The conditions can include one or more of particular media, temperature, oxygen content, carbon dioxide content, time, agents, *e.g.*, nutrients, amino acids, antibiotics, ions, and/or stimulatory factors, such as cytokines, chemokines, antigens, binding partners, fusion proteins, recombinant soluble receptors, and any other agents designed to activate the cells. In some embodiments, the stimulating conditions or agents include one or more agent, *e.g.*, ligand, which is capable of activating an intracellular signaling domain of a TCR complex. In some aspects, the agent turns on or initiates TCR/CD3 intracellular signaling cascade in a T cell. Such agents can include antibodies, such as those specific for a TCR component and/or costimulatory receptor, *e.g.*, anti-CD3, anti-CD28, for example, bound to solid support such as a bead, and/or one or more cytokines. Optionally, the expansion method may further comprise the step of adding anti-CD3 and/or anti CD28 antibody to the culture medium (*e.g.*, at a concentration of at least about 0.5 ng/ml). In some embodiments, the stimulating agents include IL-2 and/or IL-15, for example, an IL-2 concentration of at least about 10 units/mL.

In another embodiment, T cells are isolated from peripheral blood by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLL™ gradient. Alternatively, T cells can be isolated from an umbilical cord. In any event, a specific subpopulation of T cells can be further isolated by positive or negative selection techniques.

The cord blood mononuclear cells so isolated can be depleted of cells expressing certain antigens, including, but not limited to, CD34, CD8, CD14, CD19, and CD56. Depletion of these cells can be accomplished using an isolated antibody, a biological sample comprising an antibody, such as ascites, an antibody bound to a physical support, and a cell bound antibody.

Enrichment of a T cell population by negative selection can be accomplished using a combination of antibodies directed to surface markers unique to the negatively selected cells. A preferred method is cell sorting and/or selection via negative magnetic immunoadherence 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 CD14, CD20, CD11b, CD16, HLA-DR, and CD8.

For isolation of a desired population of cells by positive or negative selection, the concentration of cells and surface (*e.g.*, particles such as beads) can be varied. In certain
5 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. For example, in one embodiment, a concentration of 2 billion cells/ml is used. In one embodiment, a concentration of 1 billion cells/ml is used. In a further embodiment, greater than 100 million cells/ml is used. In a further embodiment, a
10 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. Using high concentrations can result in increased cell yield, cell activation, and cell expansion.

15 T cells can also be frozen after the washing step, which does not require the monocyte-removal step. While not wishing 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
20 parameters are known in the art and will be useful in this context, in a non-limiting example, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or other suitable cell freezing media. The cells are then frozen to -80°C at a rate of 1°C 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
25 liquid nitrogen.

In one embodiment, the population of T cells is comprised within cells such as peripheral blood mononuclear cells, cord blood cells, a purified population of T cells, and a T cell line. In another embodiment, peripheral blood mononuclear cells comprise the population of T cells. In yet another embodiment, purified T cells comprise the population of T cells.

30 In certain embodiments, T regulatory cells (Tregs) can be isolated from a sample. The sample can include, but is not limited to, umbilical cord blood or peripheral blood. In certain embodiments, the Tregs are isolated by flow-cytometry sorting. The sample can be enriched for Tregs prior to isolation by any means known in the art. The isolated Tregs can be

cryopreserved, and/or expanded prior to use. Methods for isolating Tregs are described in U.S. Patent Numbers: 7,754,482, 8,722,400, and 9,555,105, and U.S. Patent Application No. 13/639,927, contents of which are incorporated herein in their entirety.

5 **H. Expansion of Immune Cells**

Whether prior to or after modification of cells to express an IL9Ra or a chimeric cytokine receptor and/or CAR of the invention, the cells can be activated and expanded in number using methods as described, for example, in U.S. Patent 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; 10 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Publication No. 20060121005. For example, the T cells of the invention may be expanded 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 by contact with an anti-CD3 antibody, or 15 antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (*e.g.*, bryostatin) in conjunction with a calcium ionophore. 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, T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating 20 proliferation of the T cells. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diacclone, Besancon, France) and these can be used in the invention, as can other methods and reagents known in the art (see, *e.g.*, ten Berge et al., Transplant Proc. (1998) 30(8): 3975-3977; Haanen et al., J. Exp. Med. (1999) 190(9): 1319-1328; and Garland et al., J. Immunol. Methods (1999) 227(1-2): 53-63).

25 Expanding T cells by the methods disclosed herein can be multiplied by about 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, 1000 fold, 2000 fold, 3000 fold, 4000 fold, 5000 fold, 6000 fold, 7000 fold, 8000 fold, 9000 fold, 10,000 fold, 100,000 fold, 1,000,000 fold, 10,000,000 fold, or greater, and any and all whole or partial 30 integers therebetween. In one embodiment, the T cells expand in the range of about 20 fold to about 50 fold.

Following culturing, the T cells can be incubated in cell medium in a culture apparatus for a period of time or until the cells reach confluency or high cell density for

optimal passage before passing the cells to another culture apparatus. The culturing apparatus can be of any culture apparatus commonly used for culturing cells *in vitro*. Preferably, the level of confluence is 70% or greater before passing the cells to another culture apparatus. More preferably, the level of confluence is 90% or greater. A period of time can be any time suitable for the culture of cells *in vitro*. The T cell medium may be replaced during the culture of the T cells at any time. Preferably, the T cell medium is replaced about every 2 to 3 days. The T cells are then harvested from the culture apparatus whereupon the T cells can be used immediately or cryopreserved to be stored for use at a later time. In one embodiment, the invention includes cryopreserving the expanded T cells. The cryopreserved T cells are thawed prior to introducing nucleic acids into the T cell.

In another embodiment, the method comprises isolating T cells and expanding the T cells. In another embodiment, the invention further comprises cryopreserving the T cells prior to expansion. In yet another embodiment, the cryopreserved T cells are thawed for electroporation with the RNA encoding the chimeric membrane protein.

Another procedure for *ex vivo* expansion cells is described in U.S. Pat. No. 5,199,942 (incorporated herein by reference). Expansion, such as described in U.S. Pat. No. 5,199,942 can be an alternative or in addition to other methods of expansion described herein. Briefly, *ex vivo* culture and expansion of T cells comprises the addition to the cellular growth factors, such as those described in U.S. Pat. No. 5,199,942, or other factors, such as flt3-L, IL-1, IL-3 and c-kit ligand. In one embodiment, expanding the T cells comprises culturing the T cells with a factor selected from the group consisting of flt3-L, IL-1, IL-3 and c-kit ligand.

The culturing step as described herein (contact with agents as described herein or after electroporation) can be very short, for example less than 24 hours such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 hours. The culturing step as described further herein (contact with agents as described herein) can be longer, for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or more days.

Various terms are used to describe cells in culture. Cell culture refers generally to cells taken from a living organism and grown under controlled condition. A primary cell culture is a culture of cells, tissues or organs taken directly from an organism and before the first subculture. Cells are expanded in culture when they are placed in a growth medium under conditions that facilitate cell growth and/or division, resulting in a larger population of the cells. When cells are expanded in culture, the rate of cell proliferation is typically

measured by the amount of time required for the cells to double in number, otherwise known as the doubling time.

Each round of subculturing is referred to as a passage. When cells are subcultured, they are referred to as having been passaged. A specific population of cells, or a cell line, is sometimes referred to or characterized by the number of times it has been passaged. For example, a cultured cell population that has been passaged ten times may be referred to as a P10 culture. The primary culture, *i.e.*, the first culture following the isolation of cells from tissue, is designated P0. Following the first subculture, the cells are described as a secondary culture (P1 or passage 1). After the second subculture, the cells become a tertiary culture (P2 or passage 2), and so on. It will be understood by those of skill in the art that there may be many population doublings during the period of passaging; therefore the number of population doublings of a culture is greater than the passage number. The expansion of cells (*i.e.*, the number of population doublings) during the period between passaging depends on many factors, including but is not limited to the seeding density, substrate, medium, and time between passaging.

In one embodiment, the cells may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. 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-gamma, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGF-beta, 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. Antibiotics, *e.g.*, penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target 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).

The medium used to culture the T cells may include an agent that can co-stimulate the T cells. For example, an agent that can stimulate CD3 is an antibody to CD3, and an agent that can stimulate CD28 is an antibody to CD28. A cell isolated by the methods disclosed herein can be expanded approximately 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, 1000 fold, 2000 fold, 3000 fold, 4000 fold, 5000 fold, 6000 fold, 7000 fold, 8000 fold, 9000 fold, 10,000 fold, 100,000 fold, 1,000,000 fold, 10,000,000 fold, or greater. In one embodiment, the T cells expand in the range of about 20 fold to about 50 fold, or more. In one embodiment, human T regulatory cells are expanded via anti-CD3 antibody coated KT64.86 artificial antigen presenting cells (aAPCs). Methods for expanding and activating T cells can be found in U.S. Patent Numbers: 7,754,482, 8,722,400, and 9,555,105, contents of which are incorporated herein in their entirety.

In one embodiment, the method of expanding the T cells can further comprise isolating the expanded T cells for further applications. In another embodiment, the method of expanding can further comprise a subsequent electroporation of the expanded T cells followed by culturing. The subsequent electroporation may include introducing a nucleic acid encoding an agent, such as a transducing the expanded T cells, transfecting the expanded T cells, or electroporating the expanded T cells with a nucleic acid, into the expanded population of T cells, wherein the agent further stimulates the T cell. The agent may stimulate the T cells, such as by stimulating further expansion, effector function, or another T cell function.

I. Pharmaceutical compositions and Formulations

Also provided are populations of immune cells of the invention, compositions containing such cells and/or enriched for such cells, such as in which cells expressing an IL9Ra or a chimeric cytokine receptor and/or CAR make up at least 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more of the total cells in the composition or cells of a certain type such as T cells or CD8⁺ or CD4⁺ cells. Among the compositions are pharmaceutical compositions and formulations for administration, such as for adoptive cell therapy. Also provided are therapeutic methods for administering the cells and compositions to subjects, *e.g.*, patients.

Also provided are compositions including the cells for administration, including pharmaceutical compositions and formulations, such as unit dose form compositions

including the number of cells for administration in a given dose or fraction thereof. The pharmaceutical compositions and formulations generally include one or more optional pharmaceutically acceptable carrier or excipient. In some embodiments, the composition includes at least one additional therapeutic agent.

- 5 The term “pharmaceutical formulation” or “pharmaceutical composition” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation,
10 other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative. In some aspects, the choice of carrier is determined in part by the particular cell and/or by the method of administration. Accordingly, there are a variety of suitable formulations. For example, the pharmaceutical composition can contain preservatives. Suitable preservatives may include,
15 for example, methylparaben, propylparaben, sodium benzoate, and benzalkonium chloride. In some aspects, a mixture of two or more preservatives is used. The preservative or mixtures thereof are typically present in an amount of about 0.0001% to about 2% by weight of the total composition. Carriers are described, e.g., by Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980). Pharmaceutically acceptable carriers are generally nontoxic to
20 recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol;
25 cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as
30 sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG).

Buffering agents in some aspects are included in the compositions. Suitable buffering agents include, for example, citric acid, sodium citrate, phosphoric acid, potassium phosphate, and various other acids and salts. In some aspects, a mixture of two or more buffering agents is used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition. Methods for preparing administrable pharmaceutical compositions are known. Exemplary methods are described in more detail in, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins; 21st ed. (May 1, 2005).

The formulations can include aqueous solutions. The formulation or composition may also contain more than one active ingredient useful for the particular indication, disease, or condition being treated with the cells, preferably those with activities complementary to the cells, where the respective activities do not adversely affect one another. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended. Thus, in some embodiments, the pharmaceutical composition further includes other pharmaceutically active agents or drugs, such as chemotherapeutic agents, *e.g.*, asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, and/or vincristine. The pharmaceutical composition in some embodiments contains the cells in amounts effective to treat or prevent the disease or condition, such as a therapeutically effective or prophylactically effective amount. Therapeutic or prophylactic efficacy in some embodiments is monitored by periodic assessment of treated subjects. The desired dosage can be delivered by a single bolus administration of the cells, by multiple bolus administrations of the cells, or by continuous infusion administration of the cells.

Formulations include those for oral, intravenous, intraperitoneal, subcutaneous, pulmonary, transdermal, intramuscular, intranasal, buccal, sublingual, or suppository administration. In some embodiments, the cell populations are administered parenterally. The term "parenteral," as used herein, includes intravenous, intramuscular, subcutaneous, rectal, vaginal, and intraperitoneal administration. In some embodiments, the cells are administered to the subject using peripheral systemic delivery by intravenous, intraperitoneal, or subcutaneous injection. Compositions in some embodiments are provided as sterile liquid preparations, *e.g.*, isotonic aqueous solutions, suspensions, emulsions, dispersions, or viscous compositions, which may in some aspects be buffered to a selected pH. Liquid preparations are normally easier to prepare than gels, other viscous compositions, and solid compositions.

Additionally, liquid compositions are somewhat more convenient to administer, especially by injection. Viscous compositions, on the other hand, can be formulated within the appropriate viscosity range to provide longer contact periods with specific tissues. Liquid or viscous compositions can comprise carriers, which can be a solvent or dispersing medium containing, for example, water, saline, phosphate buffered saline, polyoi (for example, glycerol, propylene glycol, liquid polyethylene glycol) and suitable mixtures thereof.

Sterile injectable solutions can be prepared by incorporating the cells in a solvent, such as in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose, dextrose, or the like. The compositions can contain auxiliary substances such as wetting, dispersing, or emulsifying agents (*e.g.*, methylcellulose), pH buffering agents, gelling or viscosity enhancing additives, preservatives, flavoring agents, and/or colors, depending upon the route of administration and the preparation desired. Standard texts may in some aspects be consulted to prepare suitable preparations.

Various additives which enhance the stability and sterility of the compositions, including antimicrobial preservatives, antioxidants, chelating agents, and buffers, can be added. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, and sorbic acid. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

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

The contents of the articles, patents, and patent applications, and all other documents and electronically available information mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference. Applicants reserve the right to physically incorporate into this application any and all materials and information from any such articles, patents, patent applications, or other physical and electronic documents.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the methods described herein may be made using suitable

equivalents without departing from the scope of the embodiments disclosed herein. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims
5 appended hereto. Having now described certain embodiments in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting.

EXPERIMENTAL EXAMPLES

10 The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only, and the invention is not limited to these Examples, but rather encompasses all variations that are evident as a result of the teachings provided herein.

15 Materials and Methods

Retroviruses encoding chimeric antigen receptors and an IL9Ra or chimeric cytokine receptors were produced utilizing Plat-E packaging cells (Cell Biolabs) by transfection with pMSGV vectors using Lipofectamine 2000 (ThermoFisher). Culture media was replaced 24 h later and after an additional 24 h the media was collected, clarified by centrifugation, and
20 passed through a 0.45 um filter before storage at -80 degrees celsius.

Retroviral transduction of mouse CAR T cells was achieved by enriching donor CD45.1+ mouse bulk splenocytes for CD3+ cells by magnetic bead separation (Stemcell Technologies). T cells were activated with mouse CD3/CD28 Dynabeads (ThermoFisher) in the presence of 50 U/ml recombinant human IL-2 (Peprotech) for 48 h before spinfection (1
25 h) with retroviral supernatant on retronectin-coated (Takara Bio) plates. Cells were harvested for flow cytometry two days after spinfection.

Flow cytometric detection of murine IL9Ra or chimeric cytokine receptors and chimeric antigen receptors was performed by incubating retrovirally transduced mouse T cells with antibodies specific for A03 CAR, PD1, TGFbRII, mIL9Ra, mCD44, mCD62L, or
30 mFas for 20 minutes in room temperature in the dark followed by acquisition of at least 10,000 events on LSR II flow cytometer (BD Biosciences). Data were analyzed with FlowJo software (BD Biosciences).

Lentiviruses for transduction of primary human CD4⁺ and CD8⁺ T cells were produced in 293T cells, and purified by ultracentrifugation. T cells activated with human CD3/CD28 Dynabeads (3:1 beads to cell ratio) were infected with lentiviruses one day after activation, de-beaded on Day 5, and expanded until cell volume reached 300 femtoliters.

- 5 Transduction efficiency was evaluated by flow cytometry with antibodies against hIL13Ra2 or hIL2Rb.

For RNA expression studies, total RNA was extracted from transduced mouse T cells cultured in the presence of mIL-2 or mIL-9 for 24 h. RNA was analyzed with Nanostring nCounter Mouse Immunology Panel (562 genes) and plotted using nSolver 4.0 software.

- 10 For Western blot experiments, IL-2 and serum-starved T cells were stimulated for 20 min with cytokines and lysed with ice-cold RIPA buffer supplemented with protease/phosphatase inhibitor cocktail (Halt, ThermoFisher) to extract protein. 30 ug of total protein was loaded into SDS-PAGE gels (NuPage Bis-Tris, ThermoFisher) and subsequently transferred to PVDF membranes (Immobilon-FL, Millipore). Detection of
- 15 pSTAT1/pSTAT3/pSTAT5 and GAPDH was performed with respective primary antibodies followed by IRDye-labelled secondary antibodies. Membranes were imaged on Odyssey CLx (LI-COR Biosciences).

Replication-deficient E1/E3 –deleted adenovirus vector Ad5-CMV-mIL9 (Ad-mIL9) was constructed. mIL-9 expression from PDA7940b cells (10,000 cells/well, 96 well plate)

20 was evaluated by mouse IL-9 ELISA (Abcam) in cell culture supernatants at various timepoints following infection with Ad-mIL9 (100 viral particles/cell).

The results of the experiments are now described.

25 Example 1: Cytokine Receptors Comprising IL9Ra ICD for Co-Expression with a CAR

Adoptively transferred gene engineered T cell therapies have demonstrated significant antitumor activity in patients with hematopoietic malignancies, but have limited benefit in patients with solid tumors (Rosenberg and Restifo, *Science* (2015) 348:62-68). One major limitation is the poor *in vivo* expansion and persistence of adoptively transferred T cells,

30 necessitating lymphodepleting conditioning chemotherapy – a toxic regimen that limits patient eligibility (Goff et al., *J Clin Oncol.* (2016) 34:2389-2397; Dudley et al., *J Clin Oncol.* (2008) 26:5233-5239; Dutcher et al., *Journal for ImmunoTherapy of Cancer* (2014) 2:26). Even those T cells that do expand and persist become terminally differentiated and

dysfunctional (Philip et al., *Nature* (2017) 545:452-456; Schietinger et al., *Immunity* (2016) 45:389-401). T cells with a stem-like phenotype can overcome these limitations and exhibit superior antitumor activity in mouse models and humans (Gattinoni et al., *Nature Reviews Cancer* (2012) 12:671-684; Krishna et al., *Science* (2020) 370:1328-1334), but therapeutic manipulations to select or expand stem-like T cells are limited to the cell manufacturing phase and cannot be made *in vivo*.

The IL-9 receptor (CD129) is a less-studied member of γc cytokine receptor family and binds to IL-9, forming a heterodimeric receptor signaling complex with γc that can result in pSTAT1, pSTAT3 and pSTAT5 activation (Demoulin et al., *Mol Cell Biol.* (1996) 16:4710-4716; Knoop et al., *Growth Factors* (2004) 22:207-215; Bauer et al., *J Biol Chem.* (1998) 273:9255-9260). IL-9R is naturally expressed by mast cells, memory B cells, innate lymphoid cells, and hematopoietic progenitors (Knoop et al., *Growth Factors* (2004) 22:207-215; Takatsuka et al., *Nature Immunology* (2018) 19:1025-1034; Townsend et al., *Immunity* (2000) 13:573-583; Williams et al., *Blood* (1990) 76:906-911; Turner et al., *J Exp Med* (2013) 210:2951-2965). While T cell subsets that produce IL-9 have been described (Lu et al., *J Clin Invest* (2012) 122:4160-4171; Lu et al., *Proc Natl Acad Sci USA* (2014) 111:2265; Purwar et al., *Nat Med* (2012) 18:1248-1253), the effects of IL-9R signaling on T cells are not well characterized (Elyaman et al., *Proc Natl Acad Sci USA* (2009) 106:12885-12890; Nowak et al., *J Exp Med* (2009) 206:1653-1660; Li et al., *Eur J Immunol* (2011) 41:2197-2206; Houssiau et al., *J Immunol* (1993) 150:2634-2640; Louahed et al., *J Immunol* (1995) 154:5061-5070; Lehrnbecher et al., *Cytokine* (1994) 6:279-284). For example, it has been well-documented that naïve T cells are insensitive to IL-9 and T cell development is unimpaired in IL-9 deficient mice suggesting that IL-9 is not a critical natural cytokine in T cell biology (Townsend et al., *Immunity* (2000) 13:573-583; Houssiau et al., *J Immunol* (1993) 150:2634-2640). More recently, common gamma chain (γc) cytokine receptor signaling with STAT1, STAT3 and STAT5 activation was observed in T cells engineered to express orthogonal chimeric cytokine receptors (WO 2021/050752; Kalbasi, et al., *Nature*, 2022, 607:360-365). These T cells assume characteristics of stem cell memory and effector T cells.

In order to enable specific, *in vivo* modulation of adoptively transferred T cells for cancer immunotherapy, the utility of common gamma chain (γc) cytokine receptor signals was explored by utilizing cytokine receptors having an intracellular signaling domain (ICD) of an interleukin-9 receptor alpha (IL9Ra) for co-expression with a CAR (**FIG. 1A – FIG.**

1D). One approach is to co-express wild type, full-length IL9Ra with a CAR targeting a tumor antigen in immune cells. Additionally, four chimeric cytokine receptors were designed, each in a human and a mouse version, having an LBD from IL13Ra2, IL2Rb, IL18Ra, and IL18Rb, respectively, fused to the transmembrane (TM) and ICD regions of IL9Ra, as outlined in **Table 1**. These chimeric cytokine receptors are designed to be switch receptors that switch the signal from the binding of a ligand to the LBD to the immunostimulatory signal transduced by IL9Ra. The ligands are cytokines IL9, IL13, IL2, and IL18, as shown in **Table 2**. A significant advantage of the chimeric cytokine receptors of the invention over orthogonal receptor systems is that they do not require administration of an orthogonal cytokine. This is also the case for expression of wild type, full-length IL9Ra together with a CAR.

Table 1: Cytokine Receptors

Receptor	LBD	TM	ICD	SEQ ID NOs
Human IL9Ra	hIL9Ra	hIL9Ra	hIL9Ra	SEQ ID NO: 15 – amino acid SEQ ID NO: 16 - nucleotide
Human IL13Ra2-IL9Ra	hIL13Ra2	hIL9Ra	hIL9Ra	SEQ ID NO: 17 – amino acid SEQ ID NO: 18 - nucleotide
Human IL2Rb-IL9Ra	hIL2Rb	hIL9Ra	hIL9Ra	SEQ ID NO: 19 – amino acid SEQ ID NO: 20 - nucleotide
Human IL18Ra-IL9Ra	hIL18Ra	hIL9Ra	hIL9Ra	SEQ ID NO: 21 – amino acid SEQ ID NO: 22 - nucleotide
Human IL18Rb-IL9Ra	hIL18Rb	hIL9Ra	hIL9Ra	SEQ ID NO: 23 – amino acid SEQ ID NO: 24 - nucleotide
Murine IL9Ra	mIL9Ra	mIL9Ra	mIL9Ra	SEQ ID NO: 51 – amino acid SEQ ID NO: 52 - nucleotide
Murine IL13Ra2-IL9Ra	mIL13Ra2	mIL9Ra	mIL9Ra	SEQ ID NO: 53 – amino acid SEQ ID NO: 54 - nucleotide
Murine IL2Rb-IL9Ra	mIL2Rb	mIL9Ra	mIL9Ra	SEQ ID NO: 55 – amino acid SEQ ID NO: 56 - nucleotide

Murine IL18Ra-IL9Ra	mIL18Ra	mIL9Ra	mIL9Ra	SEQ ID NO: 57 – amino acid SEQ ID NO: 58 - nucleotide
Murine IL18Rb-IL9Ra	mIL18Rb	mIL9Ra	mIL9Ra	SEQ ID NO: 59 – amino acid SEQ ID NO: 60 – nucleotide

Table 2: Cytokine Ligands for oncolytic adenoviral delivery

Receptor	Ligand	Ligand SEQ ID NOs
Human IL9Ra	Human IL9	SEQ ID NO: 25 – amino acid SEQ ID NO: 26 - nucleotide
Human IL13Ra2-IL9Ra	Human IL13	SEQ ID NO: 27 – amino acid SEQ ID NO: 28 - nucleotide
Human IL13Ra2-IL9Ra	Human IL13-TQM	SEQ ID NO: 29 – amino acid SEQ ID NO: 30 - nucleotide
Human IL2Rb-IL9Ra	Human IL2	SEQ ID NO: 31 – amino acid SEQ ID NO: 32 - nucleotide
Human IL2Rb-IL9Ra	Human IL2 F42A	SEQ ID NO: 33 – amino acid SEQ ID NO: 34 - nucleotide
Human IL18Ra-IL9Ra	Human IL18	SEQ ID NO: 35 – amino acid SEQ ID NO: 36 - nucleotide
Human IL18Rb-IL9Ra	Human IL18	SEQ ID NO: 35 – amino acid SEQ ID NO: 36 - nucleotide
Murine IL9Ra	Murine IL9	SEQ ID NO: 61 – amino acid SEQ ID NO: 62 - nucleotide
Murine IL13Ra2-IL9Ra	Murine IL13	SEQ ID NO: 63 – amino acid SEQ ID NO: 64 - nucleotide
Murine IL2Rb-IL9Ra	Murine IL2	SEQ ID NO: 67 – amino acid SEQ ID NO: 68 - nucleotide
Murine IL18Ra-IL9Ra	Murine IL18	SEQ ID NO: 71 – amino acid SEQ ID NO: 72 - nucleotide

Murine IL18Rb-IL9Ra	Murine IL18	SEQ ID NO: 71 – amino acid SEQ ID NO: 72 - nucleotide
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Lentiviral constructs were designed for expression of the cytokine receptors, and for co-expression of the cytokine receptors with a CAR targeting a tumor antigen, on transduced T cells. Serotype 5 oncolytic adenoviral vectors were designed for expression of the cytokine ligands. Examples of expression constructs are illustrated in **FIG. 2A – FIG. 2F**. The CAR in these initial constructs has an anti-mesothelin scFv.

Next, expression of the human IL13Ra2-IL9Ra chimeric cytokine receptor on lentivirally transduced human T cells was demonstrated (**FIG. 4A**). Western blot analysis revealed activation of STAT1, STAT3 and STAT5 in these cells (**FIG. 4B**). Briefly, 10×10^6 lentivirally transduced T cells were starved overnight in RPMI with 0.1% FBS and were left untreated or treated with hIL-13 (100 ng/mL) for 30 minutes. Phosphorylated STAT1, STAT3 and STAT5 were detected, with GAPDH as a loading control. Surprisingly, activation of STAT1, STAT3 and STAT5 appears to be constitutive in these cells.

In a further example, expression of chimeric hIL2Rb-IL9Ra receptor on lentivirally transduced human T cells was also demonstrated (**FIG. 5**).

The utility of common gamma chain (γ_c) cytokine receptor signals was further explored by designing chimeric cytokine receptors having an extracellular domain comprising a ligand binding domain (LBD) of an inhibitory immunoreceptor, or an anti-checkpoint inhibitor antigen binding domain, fused to an intracellular signaling domain (ICD) of an interleukin-9 receptor alpha (IL9Ra) (**FIG. 6A – FIG. 6F**). Five chimeric cytokine receptors were designed, each in a human and a mouse version, having an LBD from PD1, TGFbRI, TGFbRII, TIGIT, or TIM3, respectively, fused to the transmembrane (TM) and ICD regions of IL9Ra, as outlined in **Table 3**. These chimeric cytokine receptors are designed to be switch receptors that switch the signal from the binding of a ligand to the LBD of the inhibitory immunoreceptor to the immunostimulatory signal transduced by IL9Ra. The ligands are PD-L1 for PD1 LBD, TGFbeta for TGFbRI and TGFbRII LBDs, CD155 for TIGIT LBD, and Galectin-9 for TIM3 LBD, each of which is naturally expressed by various tumor cells (Wu, *et al.*, *Front in Immun.*, 2019; Haque, *et al.*, *Human Vaccines and Immunotherapeutics*, 2017; Lee, *et al.*, *Front in Immun.*, 2021; Ge, *et al.*, *Front in Immun.*, 2021). Additionally, a chimeric cytokine receptor having an anti-CTLA4 antigen binding domain (H+L) fused to an intracellular signaling domain (ICD) of an interleukin-9 receptor

alpha (IL9Ra) was designed comprising SEQ ID NO: 300 and encoded by SEQ ID NO: 301 (FIGs. 6E – 6F).

Table 3: Chimeric Cytokine Receptors

Receptor	LBD	TM	ICD	SEQ ID NOs
Human PD1-IL9Ra	hPD1	hIL9Ra	hIL9Ra	SEQ ID NO: 215 – amino acid SEQ ID NO: 216 - nucleotide
Human TGFbRI-IL9Ra	hTGFbRI	hIL9Ra	hIL9Ra	SEQ ID NO: 217 – amino acid SEQ ID NO: 218 - nucleotide
Human TGFbRII-IL9Ra	hTGFbRII	hIL9Ra	hIL9Ra	SEQ ID NO: 219 – amino acid SEQ ID NO: 220 - nucleotide
Human TIGIT-IL9Ra	hTIGIT	hIL9Ra	hIL9Ra	SEQ ID NO: 221 – amino acid SEQ ID NO: 222 - nucleotide
Human TIM3-IL9Ra	hTIM3	hIL9Ra	hIL9Ra	SEQ ID NO: 223 – amino acid SEQ ID NO: 224 - nucleotide
Murine PD1-IL9Ra	mPD1	mIL9Ra	mIL9Ra	SEQ ID NO: 239 – amino acid SEQ ID NO: 240 - nucleotide
Murine TGFbRI-IL9Ra	mTGFbRI	mIL9Ra	mIL9Ra	SEQ ID NO: 241 – amino acid SEQ ID NO: 242 - nucleotide
Murine TGFbRII-IL9Ra	mTGFbRII	mIL9Ra	mIL9Ra	SEQ ID NO: 243 – amino acid SEQ ID NO: 244 - nucleotide
Murine TIGIT-IL9Ra	mTIGIT	mIL9Ra	mIL9Ra	SEQ ID NO: 245 – amino acid SEQ ID NO: 246 - nucleotide
Murine TIM3-IL9Ra	mTIM3	mIL9Ra	mIL9Ra	SEQ ID NO: 247 – amino acid SEQ ID NO: 248 – nucleotide

5

Lentiviral constructs were designed for expression of the chimeric cytokine receptors, and for co-expression of the chimeric cytokine receptors with a CAR targeting a tumor antigen, on transduced T cells. The CAR in these initial constructs has an anti-mesothelin scFv. Co-expression of the murine PD1-IL9Ra chimeric cytokine receptor and anti-mesothelin

10 CAR on transduced murine T cells was tested and demonstrated (FIG. 7). Expression of the

murine TGFbRII-IL9Ra chimeric cytokine receptor on transduced T cells was also tested and demonstrated (**FIG. 8**).

Example 2: Co-Expression of WT IL9Ra and a CAR in T cells

5 It is contemplated herein that co-expressing an IL9Ra receptor, or a chimeric cytokine receptor comprising an IL9Ra ICD, together with a CAR targeting a tumor antigen on transduced T cells, will similarly activate STAT1, STAT3 and STAT5 in the T cells *in vivo*, and thereby convey the T cells with stem cell memory (Tscm) features with improved trafficking and effector function, resulting in improved antitumor activity for hard-to-treat
10 solid tumors in patients (as was previously shown using orthogonal chimeric cytokine receptors comprising an IL9Ra ICD).

 To demonstrate this, and to further investigate the mechanisms driving the unique phenotype and superior antitumor efficacy of CAR T cells engineered to receive an IL-9 signal, human and mouse lentiviral constructs for expression of WT IL9Ra and an anti-
15 mesothelin CAR were designed and generated. Human and mouse T cells were transduced with their respective constructs, and co-expression of the CAR and IL9Ra was demonstrated by flow cytometry post transduction. **FIG. 9A** shows the data for the human T cells.

 Co-expression of the mouse IL9Ra cytokine receptor and anti-mesothelin CAR on transduced mouse T cells was tested and demonstrated (**FIG. 3A** and **FIG. 9B**). Further,
20 these cells demonstrated stem cell memory (Tscm) phenotype, as shown by expression of surface markers CD44, CD62L, and Fas (CD95) 24 h after stimulation with 100 ng/mL of wild type mIL9 or wild type mIL2 (**FIG. 3B** and **FIG. 10**). Next, total RNA was extracted from the transduced T cells cultured in the presence of mIL-2 or mIL-9 for 24h. RNA was analyzed with Nanostring nCounter Mouse Immunology Panel (562 genes) and plotted using
25 nSolver 4.0 software to obtain a global gene expression profile (**FIG. 3C**). These data further demonstrate the Tscm phenotype of the transduced cells.

 The transduced T cells co-expressing IL9Ra and a CAR comprising a tumor antigen binding domain will be used together with the oncolytic adenoviral vector expressing IL9 to treat cancer in a subject. As such, expression of IL9 from the Ad5 vector was tested and
30 demonstrated in a murine pancreatic cancer cell line (**FIG. 3D**). Murine pancreatic cancer cell line PDA7940b (10,000 cells/well) was infected with 100 viral particles/cell of Ad-mIL9 and cell culture supernatants were analyzed for mIL-9 by ELISA at indicated time points.

Next, the murine T cells were starved from IL-2 for 24 hours and then incubated in increasing concentrations of IL-9 for 20 minutes. Cells were fixed, permeabilized, stained, and analyzed by phosphor flow cytometry. Cells coexpressing IL9Ra and the CAR showed a significant increase in phosphorylation of STAT1, STAT3, and STAT5 compared to cells expressing only the CAR (A03) or untransduced cells (**FIG. 11**). Cytokine secretion was analyzed by Luminex assay after incubating the cells with IL9 for 48 hours. Co-expression of the CAR and IL9Ra significantly increased secretion of IFN γ , TNF α , IL-10, IL-18, IL-1 β , IL-6, IL-17A, IL-9, IL-22, IL-23, IL-4, IL-5, IL-13, IL-12p70, and IL-27 (**FIG 12**, right side of each panel). For T cells expressing the CAR alone (without co-expression of IL9Ra), no significant increase was observed for IFN γ , TNF α , and IL-10, and the increases in IL-4 and IL-13 were less significant than that observed for cells co-expressing the CAR and IL9Ra (**FIG. 12**, left side of each panel).

Next, tumor cell killing was assessed by seeding 5000 PDA7940b (pancreatic tumor) cells. Primary mouse T cells were pre-incubated for 48 hours with IL-9 (100 nM) (or no IL9, as a control) and added at T cells:tumor cells ratios of 3:1, 1:1, and 1:3. Tumor cell killing was significantly enhanced for T cells expressing both IL9Ra and anti-mesothelin CAR (A03) in the presence of IL9 (**FIG. 13**).

Gene expression profiles were determined with Nanostring nCounter Mouse Immunology Panel for the mouse T cells expressing the CAR and IL9Ra pre-incubated with IL9 (or IL2 as a control) (**FIG. 14A**). To compare with the orthogonal chimeric cytokine receptor system (see, WO 2021/050752; Kalbasi, *et al.*, *Nature*, 2022, 607:360-365), gene expression profile was also determined for T cells expressing the CAR and an orthogonal chimeric cytokine receptor (ortho IL2R β -IL9Ra (“o9R”) pre-incubated with ortho-IL2 (or IL2 as a control) (**FIG. 14B**). The top 20 up-regulated and down-regulated genes for each are shown (p-adj<0.05) (**FIGs. 14A – 14B**). Gene expression profiles were similar for the two. The shared top up-regulated and down-regulated genes are shown in **FIG. 14C**.

Next, gene set variation analysis (GSVA) was performed for T cells expressing anti-meso CAR and IL9Ra pre-incubated with either IL9 or IL2 and for T cells expressing anti-meso CAR and an ortho-IL2R β -IL9Ra chimeric cytokine receptor (o9R) pre-incubated with ortho-IL2 or IL-2. The pathways significantly enriched in the CAR T cells stimulated with IL9 vs IL2 are shown in **FIGs. 15A – 15C**. Notably, the interferon gamma and interferon alpha pathways are significantly enriched in IL-9-stimulated CAR T cells (**FIGs. 15D – 15F**).

Next, an *in vivo* syngenic murine model of PDA was established (**FIG. 16A**) and a dose titration for Ad vector expressing IL-9 (Ad-mIL9) was performed (**FIG. 16B**). Transduction efficiency data are shown in **FIG. 16C**. *In vivo* tumor growth was determined at various doses of Ad-mIL9 in mice injected with T cells expressing the CAR and IL9Ra, as well as the indicated control conditions (**FIG. 16D**).

Enumerated Embodiments

The following enumerated embodiments are provided, the numbering of which is not to be construed as designating levels of importance.

- 10 Embodiment 1 provides a chimeric cytokine receptor, comprising:
 - (a) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb);
 - 15 (b) a transmembrane domain; and
 - (c) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).
- Embodiment 2 provides the chimeric cytokine receptor of embodiment 1, wherein the transmembrane domain is an IL9Ra transmembrane domain.
- 20 Embodiment 3 provides the chimeric cytokine receptor of any one of the preceding embodiments, wherein the chimeric cytokine receptor comprises:
 - (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - 25 (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - 30 (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

5 Embodiment 4 provides the chimeric cytokine receptor of any one of the preceding embodiments, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
10 at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

 Embodiment 5 provides the chimeric cytokine receptor of any one of the preceding embodiments, wherein the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least
15 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

 Embodiment 6 provides an isolated nucleic acid comprising a nucleotide sequence
20 encoding the chimeric cytokine receptor of any one of the preceding embodiments.

 Embodiment 7 provides a vector comprising the isolated nucleic acid of embodiment
6.

 Embodiment 8 provides the vector of embodiment 7, wherein the vector is a retroviral vector or a lentiviral vector.

25 Embodiment 9 provides an isolated nucleic acid comprising:

- a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising
 - (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first
30 transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and

- b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

Embodiment 10 provides the isolated nucleic acid of embodiment 9, wherein the
5 transmembrane domain is an IL9Ra transmembrane domain.

Embodiment 11 provides the isolated nucleic acid of any one of the preceding
embodiments, wherein the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human
IL9Ra intracellular signaling domain;
- 10 (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human
IL9Ra intracellular signaling domain;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human
IL9Ra intracellular signaling domain;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human
15 IL9Ra intracellular signaling domain;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a
murine IL9Ra intracellular signaling domain;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine
IL9Ra intracellular signaling domain;
- 20 (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine
IL9Ra intracellular signaling domain; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine
IL9Ra intracellular signaling domain.

Embodiment 12 provides the isolated nucleic acid of any one of the preceding
25 embodiments, wherein the chimeric cytokine receptor comprises an amino acid sequence
havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23,
30 51, 53, 55, 57, and 59.

Embodiment 13 provides the isolated nucleic acid of any one of the preceding
embodiments, wherein the first nucleotide sequence is a sequence having at least 80%, at
least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at

least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

Embodiment 14 provides the isolated nucleic acid of any one of the preceding
 5 embodiments, wherein the tumor antigen is selected from the group consisting of alpha fetoprotein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein
 10 (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

15 Embodiment 15 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 16 provides the isolated nucleic acid of any one of the preceding
 20 embodiments, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin,
 25 and a syntherin).

Embodiment 17 provides the isolated nucleic acid of any one of the preceding
 embodiments, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 18 provides the isolated nucleic acid of any one of the preceding
 30 embodiments, wherein the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

- at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 5 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 10 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 15 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 20 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 25 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 30

- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

Embodiment 19 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

Embodiment 20 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 21 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

Embodiment 22 provides a vector comprising the isolated nucleic acid of any one of embodiments 9-21.

Embodiment 23 provides the vector of embodiment 22, wherein the vector is a retroviral vector or a lentiviral vector.

Embodiment 24 provides a modified cell comprising the chimeric cytokine receptor of any one of embodiments 1-5, the isolated nucleic acid of any one of embodiments 6 or 9-21, and/or the vector of any one of embodiments 7-8 or 22-23, wherein the cell is an immune cell or precursor cell thereof.

Embodiment 25 provides the modified cell of embodiment 24, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

Embodiment 26 provides the a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express:

- a) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

Embodiment 27 provides the modified cell of embodiment 26, wherein the transmembrane domain is an IL9Ra transmembrane domain.

- Embodiment 28 provides the modified cell of any one of embodiments 26-27, wherein the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

Embodiment 29 provides the modified cell of any one of embodiments 26-28, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

Embodiment 30 provides the modified cell of any one of embodiments 26-29, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

Embodiment 31 provides the modified cell of any one of embodiments 26-30, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 32 provides the modified cell of any one of embodiments 26-31, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 33 provides the modified cell of any one of embodiments 26-32, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed

ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 34 provides the modified cell of any one of embodiments 26-33, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

5 Embodiment 35 provides the modified cell of any one of embodiments 26-34, wherein the tumor antigen binding domain is selected from:

- 10 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95
- 15 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 20 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 25 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 30 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least

92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;

- 5 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 10 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID
- 15 NO: 131.

Embodiment 36 provides the modified cell of any one of embodiments 26-35, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, 20 ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

Embodiment 37 provides the modified cell of any one of embodiments 26-36, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a 25 protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, Fc γ R gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 38 provides the modified cell of any one of embodiments 26-37, 30 wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

Embodiment 39 provides the modified cell of any one of embodiments 26-38, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

Embodiment 40 provides the modified cell of any one of embodiments 26-39, wherein the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3,
5 STAT5, or any combination thereof, in the cell.

Embodiment 41 provides a pharmaceutical composition comprising a population of the modified cell of any one of embodiments 24-40 and at least one pharmaceutically acceptable carrier.

Embodiment 42 provides a system for enabling IL9 signaling in a cell, the system
10 comprising:

- (a) a modified immune cell engineered to express:
 - (i) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2
15 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor
20 antigen binding domain, a second transmembrane domain, and a second intracellular domain; and
- (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

Embodiment 43 provides the system of embodiment 42, wherein the vector is an
25 adenoviral vector.

Embodiment 44 provides the system of embodiment 42 or embodiment 43, wherein the vector is a serotype 5 adenoviral vector.

Embodiment 45 provides the system of any one of embodiments 42-44, wherein the
30 vector is an oncolytic adenoviral vector.

Embodiment 46 provides the system of any one of embodiments 42-45, wherein the transmembrane domain is an IL9Ra transmembrane domain.

Embodiment 47 provides the system of any one of embodiments 42-46, wherein the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- 5 (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- 10 (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- 15 (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.

Embodiment 48 provides the system of any one of embodiments 42-47, wherein the
20 chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

25 Embodiment 49 provides the system of any one of embodiments 42-48, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence
30 selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

Embodiment 50 provides the system of any one of embodiments 42-49, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22,

CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 51 provides the system of any one of embodiments 42-50, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 52 provides the system of any one of embodiments 42-51, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 53 provides the system of any one of embodiments 42-52, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 54 provides the system of any one of embodiments 42-53, wherein the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

- least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 5 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 10 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 15 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 20 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 25 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
- 30

Embodiment 55 provides the system of any one of embodiments 42-54, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

Embodiment 56 provides the system of any one of embodiments 42-55, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 57 provides the system of any one of embodiments 42-56, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

Embodiment 58 provides the system of any one of embodiments 42-57, wherein:

- (a) the IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 25 and SEQ ID NO: 61;
- (b) the IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 27 and SEQ ID NO: 63;
- (c) the IL13 is an IL13-TQM variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at

least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29;

- 5 (d) the IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 31 and SEQ ID NO: 67;
- 10 (e) the IL2 is an IL2 F42A variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to
- 15 SEQ ID NO: 33; or
- (f) the IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%,
- 20 at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 35 and SEQ ID NO: 71.

Embodiment 59 provides the system of any one of embodiments 42-58, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

- 25 Embodiment 60 provides the system of any one of embodiments 42-59, wherein the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.

Embodiment 61 provides a method of treating cancer in a subject in need thereof, comprising administering to the subject:

- 30 (a) a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express:
- (i) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2

(IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra);
 5 and

(ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and

(b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.

Embodiment 62 provides the method of embodiment 61, wherein the vector is an adenoviral vector.

Embodiment 63 provides the method of embodiment 61 or embodiment 62, wherein the vector is a serotype 5 adenoviral vector.

Embodiment 64 provides the method of any one of embodiments 61-63, wherein the vector is an oncolytic adenoviral vector.

Embodiment 65 provides the method of any one of embodiments 61-64, wherein the transmembrane domain is an IL9Ra transmembrane domain.

Embodiment 66 provides the method of any one of embodiments 61-65, wherein the chimeric cytokine receptor comprises:

- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL2;
- 25 (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
- (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL13;
- 30 (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2;

- (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18; or
- (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.

5 Embodiment 67 provides the method of any one of embodiments 61-66, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity
10 to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

Embodiment 68 provides the method of any one of embodiments 61-67, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence
15 selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

Embodiment 69 provides the method of any one of embodiments 61-68, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22,
20 CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A,
25 mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 70 provides the method of any one of embodiments 61-69, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and
30 EGFRvIII.

Embodiment 71 provides the method of any one of embodiments 61-70, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an

Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

5 Embodiment 72 provides the method of any one of embodiments 61-71, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 73 provides the method of any one of embodiments 61-72, wherein the tumor antigen binding domain is selected from:

- 10 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 15 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 20 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 25 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 30

- 5 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 10 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 15 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

Embodiment 74 provides the method of any one of embodiments 61-73, wherein the
 20 intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor
 25 (KIR).

Embodiment 75 provides the method of any one of embodiments 61-74, wherein the
 intracellular domain of the CAR comprises an intracellular signaling domain of a protein
 selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a
 cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif
 30 (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 76 provides the method of any one of embodiments 61-75, wherein the
 intracellular domain of the CAR comprises a costimulatory domain of a CD28, a

costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

Embodiment 77 provides the method of any one of embodiments 61-76, wherein:

- 5 (a) the IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 25 and SEQ ID NO: 61;
- 10 (b) the IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from
- 15 SEQ ID NO: 27 and SEQ ID NO: 63;
- (c) the IL13 is an IL13-TQM variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
- 20 at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29;
- (d) the IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%,
- 25 at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 31 and SEQ ID NO: 67;
- (e) the IL2 is an IL2 F42A variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%,
- 30 at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 33; or

- (f) the IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 35 and SEQ ID NO: 71.

Embodiment 78 provides the method of any one of embodiments 61-77, wherein the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.

- Embodiment 79 provides the method of any one of embodiments 61-78, wherein the population of cells is capable of activating STAT1, STAT3, STAT5, or any combination thereof.

Embodiment 80 provides the method of any one of embodiments 61-79, wherein the subject is a human.

- Embodiment 81 provides the method of any one of embodiments 61-80, wherein the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

- Embodiment 82 provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, wherein the cell is engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA.

- Embodiment 83 provides the modified cell of embodiment 82, wherein the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system.

Embodiment 84 provides the modified cell of embodiment 82, wherein the inhibitory RNA comprises an siRNA or an shRNA.

Embodiment 85 provides the modified cell of any one of embodiments 82-84, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 86 provides the modified cell of any one of embodiments 82-85, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 87 provides the modified cell of any one of embodiments 82-86, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 88 provides the modified cell of any one of embodiments 82-87, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 89 provides the modified cell of any one of embodiments 82-88, wherein the tumor antigen binding domain is selected from:

(a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;

- 5 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 10 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 15 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 20 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 25 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 30 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

Embodiment 90 provides the modified cell of any one of embodiments 82-89,
5 wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer
10 immunoglobulin-like receptor (KIR).

Embodiment 91 provides the modified cell of any one of embodiments 82-90,
wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif
15 (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 92 provides the modified cell of any one of embodiments 82-91,
wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any
20 combination thereof.

Embodiment 93 provides the modified cell of any one of embodiments 82-92,
wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

Embodiment 94 provides the modified cell of any one of embodiments 82-93,
wherein STAT1, STAT3, STAT5, or any combination thereof, is/are activated in the cell.

25 Embodiment 95 provides a pharmaceutical composition comprising a population of the modified cell of any one of embodiments 82-94 and at least one pharmaceutically acceptable carrier.

Embodiment 96 provides a method of treating cancer in a subject in need thereof,
comprising administering to the subject a population of modified cells, wherein the cells are
30 immune cells or precursor cells thereof, wherein the cells are engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of

Cullin 5 in the cells is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA.

Embodiment 97 provides the method of embodiment 96, wherein the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system.

Embodiment 98 provides the method of embodiment 96, wherein the inhibitory RNA comprises an siRNA or an shRNA.

Embodiment 99 provides the method of any one of embodiments 96-98, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 100 provides the method of any one of embodiments 96-99, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 101 provides the method of any one of embodiments 96-100, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 102 provides the method of any one of embodiments 96-101, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 103 provides the method of any one of embodiments 96-102, wherein the tumor antigen binding domain is selected from:

- 5 (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- 10 (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- 15 (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- 20 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 25 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 30 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at

least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and

- 5 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

- 10 Embodiment 104 provides the method of any one of embodiments 96-103, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a
15 variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

- Embodiment 105 provides the method of any one of embodiments 96-105, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a
20 cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

- Embodiment 106 provides the method of any one of embodiments 96-105, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a
25 costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

Embodiment 107 provides the method of any one of embodiments 96-106, wherein the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.

- 30 Embodiment 108 provides the method of any one of embodiments 96-107, wherein STAT1, STAT3, STAT5, or any combination thereof, is/are activated in the population of cells.

Embodiment 109 provides the method of any one of embodiments 96-108, wherein the subject is a human.

Embodiment 110 provides the method of any one of embodiments 96-109, wherein the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

Embodiment 111 provides a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).

Embodiment 112 provides the chimeric cytokine receptor of embodiment 111, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

Embodiment 113 provides the chimeric cytokine receptor of embodiment 111 or embodiment 112, wherein the transmembrane domain is an IL9Ra transmembrane domain.

Embodiment 114 provides the chimeric cytokine receptor of any one of the preceding embodiments, wherein the chimeric cytokine receptor comprises:

- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 5 (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 10 (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 15 (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 20 (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 25 (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

Embodiment 115 provides the chimeric cytokine receptor of any one of the preceding
 30 embodiments, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or

at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

Embodiment 116 provides the chimeric cytokine receptor of any one of the preceding embodiments, wherein the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

Embodiment 117 provides an isolated nucleic acid comprising a nucleotide sequence encoding the chimeric cytokine receptor of any one of the preceding embodiments.

Embodiment 118 provides a vector comprising the isolated nucleic acid of embodiment 117.

Embodiment 119 provides the vector of embodiment 118, wherein the vector is a retroviral vector or a lentiviral vector.

Embodiment 120 provides an isolated nucleic acid comprising:

- a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

Embodiment 121 provides the isolated nucleic acid of embodiment 120, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

Embodiment 122 provides the isolated nucleic acid of embodiment 120 or embodiment 121, wherein the transmembrane domain is an IL9Ra transmembrane domain.

Embodiment 123 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the chimeric cytokine receptor comprises:

- 5 (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a
10 human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 15 (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a
20 murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain
- 25 (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane
30 domain, and a human IL9Ra intracellular signaling domain;
- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

- (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

5 Embodiment 124 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
10 at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

 Embodiment 125 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at
15 least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

 Embodiment 126 provides the isolated nucleic acid of any one of the preceding
20 embodiments, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein
25 (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

30 Embodiment 127 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 128 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 129 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 130 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least

86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;

5 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;

10 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and

15 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

Embodiment 131 provides the isolated nucleic acid of any one of the preceding

embodiments, wherein the intracellular domain of the CAR comprises a costimulatory

25 domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

30 Embodiment 132 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based

activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 133 provides the isolated nucleic acid of any one of the preceding embodiments, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

Embodiment 134 provides a vector comprising the isolated nucleic acid of any one of embodiments 120-133.

Embodiment 135 provides the vector of embodiment 134, wherein the vector is a retroviral vector or a lentiviral vector.

Embodiment 136 provides a modified cell comprising the chimeric cytokine receptor of any one of embodiments 111-116, the isolated nucleic acid of any one of embodiments 117 or 120-133, and/or the vector of any one of embodiments 118-119 or 134-135, wherein the cell is an immune cell or precursor cell thereof.

Embodiment 137 provides the modified cell of embodiment 136, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

Embodiment 138 provides a modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express:

- a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

Embodiment 139 provides the modified cell of embodiment 138, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4

(CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

Embodiment 140 provides the modified cell acid of embodiment 138 or embodiment 139, wherein the transmembrane domain is an IL9Ra transmembrane domain.

5 Embodiment 141 provides the modified cell of any one of embodiments 138-140, wherein the chimeric cytokine receptor comprises:

- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 10 (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 15 (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 20 (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 25 (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 30 (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- 5 (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

Embodiment 142 provides the modified cell of any one of embodiments 138-141, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 10 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

Embodiment 143 provides the modified cell of any one of embodiments 138-142, 15 wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 20 301.

Embodiment 144 provides the modified cell of any one of embodiments 138-143, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-IX, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, 25 CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D- 30 Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 145 provides the modified cell of any one of embodiments 138-144, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 146 provides the modified cell of any one of embodiments 138-145, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 147 provides the modified cell of any one of embodiments 138-146, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 148 provides the modified cell of any one of embodiments 138-147, wherein the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;

- 5 (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- 10 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 15 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 20 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

25 Embodiment 149 provides the modified cell of any one of embodiments 138-148, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3

30 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

Embodiment 150 provides the modified cell of any one of embodiments 138-149, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a

protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

- 5 Embodiment 151 provides the modified cell of any one of embodiments 138-150, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

- Embodiment 152 provides the modified cell of any one of embodiments 138-151,
10 wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

 Embodiment 153 provides the modified cell of any one of embodiments 138-152, wherein the chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.

- Embodiment 154 provides a pharmaceutical composition comprising a population of
15 the modified cell of any one of embodiments 136-153 and at least one pharmaceutically acceptable carrier.

 Embodiment 155 provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express:

- 20 a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
25 b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.

- Embodiment 156 provides the method of embodiment 155, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming
30 Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4

(CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

Embodiment 157 provides the method of embodiment 155 or embodiment 156, wherein the transmembrane domain is an IL9Ra transmembrane domain.

5 Embodiment 158 provides the method of any one of embodiments 155-157, wherein the chimeric cytokine receptor comprises:

- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human
10 IL9Ra intracellular signaling domain;
- (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- 15 (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a
20 murine IL9Ra intracellular signaling domain;
- (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- 25 (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
- (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane
30 domain, and a human IL9Ra intracellular signaling domain;
- (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

- (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
- (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
- 5 (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

Embodiment 159 provides the method of any one of embodiments 155-158, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 10 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.

Embodiment 160 provides the method of any one of embodiments 155-159, wherein 15 the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

Embodiment 161 provides the method of any one of embodiments 155-160, wherein 20 the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, 25 EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, 30 TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

Embodiment 162 provides the method of any one of embodiments 155-161, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

Embodiment 163 provides the method of any one of embodiments 155-162, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

Embodiment 164 provides the method of any one of embodiments 155-163, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

Embodiment 165 provides the method of any one of embodiments 155-164, wherein the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%,

at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;

- 5 (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- 10 (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- 15 (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
- 20

Embodiment 166 provides the method of any one of embodiments 155-165, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, 25 LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

Embodiment 167 provides the method of any one of embodiments 155-166, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein 30 selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, Fc γ gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

Embodiment 168 provides the method of any one of embodiments 155-167, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

- 5 Embodiment 169 provides the method of any one of embodiments 155-168, wherein the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.

- Embodiment 170 provides the method of any one of embodiments 155-169, wherein the chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any
10 combination thereof, in the cells.

Embodiment 171 provides the method of any one of embodiments 155-170, wherein the subject is a human.

- Embodiment 172 provides the method of any one of embodiments 155-171, wherein the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia),
15 lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma,
20 glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

Other Embodiments

- 25 The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS

What is claimed:

1. A chimeric cytokine receptor, comprising:
 - (a) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb);
 - (b) a transmembrane domain; and
 - (c) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).
2. The chimeric cytokine receptor of claim 1, wherein the transmembrane domain is an IL9Ra transmembrane domain.
3. The chimeric cytokine receptor of any one of the preceding claims, wherein the chimeric cytokine receptor comprises:
 - (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
 - (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

4. The chimeric cytokine receptor of any one of the preceding claims, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.
5. The chimeric cytokine receptor of any one of the preceding claims, wherein the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.
6. An isolated nucleic acid comprising a nucleotide sequence encoding the chimeric cytokine receptor of any one of the preceding claims.
7. A vector comprising the isolated nucleic acid of claim 6.
8. The vector of claim 7, wherein the vector is a retroviral vector or a lentiviral vector.
9. An isolated nucleic acid comprising:
 - a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising
 - (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and

- b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.
10. The isolated nucleic acid of claim 9, wherein the transmembrane domain is an IL9Ra transmembrane domain.
11. The isolated nucleic acid of any one of the preceding claims, wherein the chimeric cytokine receptor comprises:
- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
 - (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.
12. The isolated nucleic acid of any one of the preceding claims, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.

13. The isolated nucleic acid of any one of the preceding claims, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.
14. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
15. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
16. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an

affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).

17. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).
18. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen binding domain is selected from:
 - (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
 - (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;

- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
 - (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
 - (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
19. The isolated nucleic acid of any one of the preceding claims, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).
20. The isolated nucleic acid of any one of the preceding claims, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.

21. The isolated nucleic acid of any one of the preceding claims, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
22. A vector comprising the isolated nucleic acid of any one of claims 9-21.
23. The vector of claim 22, wherein the vector is a retroviral vector or a lentiviral vector.
24. A modified cell comprising the chimeric cytokine receptor of any one of claims 1-5, the isolated nucleic acid of any one of claims 6 or 9-21, and/or the vector of any one of claims 7-8 or 22-23, wherein the cell is an immune cell or precursor cell thereof.
25. The modified cell of claim 24, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.
26. A modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express:
 - a) an interleukin-9 receptor alpha (IL9Ra) or a chimeric cytokine receptor comprising (i) an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), (ii) a first transmembrane domain, and (iii) an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.
27. The modified cell of claim 26, wherein the transmembrane domain is an IL9Ra transmembrane domain.

28. The modified cell of any one of claims 26-27, wherein the chimeric cytokine receptor comprises:
- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
 - (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.
29. The modified cell of any one of claims 26-28, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.
30. The modified cell of any one of claims 26-29, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

31. The modified cell of any one of claims 26-30, wherein the tumor antigen is selected from the group consisting of alpha fetoprotein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
32. The modified cell of any one of claims 26-31, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
33. The modified cell of any one of claims 26-32, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
34. The modified cell of any one of claims 26-33, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).
35. The modified cell of any one of claims 26-34, wherein the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at

- least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%,

at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and

- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

36. The modified cell of any one of claims 26-35, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).
37. The modified cell of any one of claims 26-36, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, Fc γ R gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
38. The modified cell of any one of claims 26-37, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
39. The modified cell of any one of claims 26-38, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.

40. The modified cell of any one of claims 26-39, wherein the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.
41. A pharmaceutical composition comprising a population of the modified cell of any one of claims 24-40 and at least one pharmaceutically acceptable carrier.
42. A system for enabling IL9 signaling in a cell, the system comprising:
- (a) a modified immune cell engineered to express:
 - (i) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and
 - (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.
43. The system of claim 42, wherein the vector is an adenoviral vector.
44. The system of claim 42 or claim 43, wherein the vector is a serotype 5 adenoviral vector.
45. The system of any one of claims 42-44, wherein the vector is an oncolytic adenoviral vector.
46. The system of any one of claims 42-45, wherein the transmembrane domain is an IL9Ra transmembrane domain.

47. The system of any one of claims 42-46, wherein the chimeric cytokine receptor comprises:
- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13;
 - (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL2;
 - (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
 - (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
 - (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL13;
 - (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2;
 - (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18; or
 - (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.
48. The system of any one of claims 42-47, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.
49. The system of any one of claims 42-48, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%,

at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

50. The system of any one of claims 42-49, wherein the tumor antigen is selected from the group consisting of alpha fetoprotein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
51. The system of any one of claims 42-50, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
52. The system of any one of claims 42-51, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
53. The system of any one of claims 42-52, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).
54. The system of any one of claims 42-53, wherein the tumor antigen binding domain is selected from:

- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
- (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at

least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and

- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

55. The system of any one of claims 42-54, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).
56. The system of any one of claims 42-55, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3ζ), FcγRIII, FcεRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
57. The system of any one of claims 42-56, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
58. The system of any one of claims 42-57, wherein:
- (a) the IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at

- least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 25 and SEQ ID NO: 61;
- (b) the IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 27 and SEQ ID NO: 63;
- (c) the IL13 is an IL13-TQM variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29;
- (d) the IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 31 and SEQ ID NO: 67;
- (e) the IL2 is an IL2 F42A variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 33; or
- (f) the IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 35 and SEQ ID NO: 71.

59. The system of any one of claims 42-58, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.
60. The system of any one of claims 42-59, wherein the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.
61. A method of treating cancer in a subject in need thereof, comprising administering to the subject:
- (a) a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express:
 - (i) an interleukin-9 receptor alpha (IL9Ra), or a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of a receptor selected from an interleukin-13 receptor alpha type 2 (IL13Ra2), an interleukin-2 receptor beta (IL2Rb), an interleukin-18 receptor alpha (IL18Ra), and an interleukin-18 receptor beta (IL18Rb), a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - (ii) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain; and
 - (b) a vector comprising a nucleotide sequence encoding a cytokine selected from an IL9, an IL13, an IL2, and an IL18.
62. The method of claim 61, wherein the vector is an adenoviral vector.
63. The method of claim 61 or claim 62, wherein the vector is a serotype 5 adenoviral vector.
64. The method of any one of claims 61-63, wherein the vector is an oncolytic adenoviral vector.

65. The method of any one of claims 61-64, wherein the transmembrane domain is an IL9Ra transmembrane domain.
66. The method of any one of claims 61-65, wherein the chimeric cytokine receptor comprises:
- (a) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL13;
 - (b) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL2;
 - (c) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
 - (d) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain, and the cytokine is an IL18;
 - (e) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL13;
 - (f) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL2;
 - (g) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18; or
 - (h) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain, and the cytokine is an IL18.
67. The method of any one of claims 61-66, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, and 59.
68. The method of any one of claims 61-67, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at

least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, and 60.

69. The method of any one of claims 61-68, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
70. The method of any one of claims 61-69, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
71. The method of any one of claims 61-70, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
72. The method of any one of claims 61-71, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

73. The method of any one of claims 61-72, wherein the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
 - (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
 - (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;

- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
 - (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
74. The method of any one of claims 61-73, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).
75. The method of any one of claims 61-74, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
76. The method of any one of claims 61-75, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
77. The method of any one of claims 61-76, wherein:

- (a) the IL9 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 25 and SEQ ID NO: 61;
- (b) the IL13 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 27 and SEQ ID NO: 63;
- (c) the IL13 is an IL13-TQM variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 29;
- (d) the IL2 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 31 and SEQ ID NO: 67;
- (e) the IL2 is an IL2 F42A variant comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 33; or
- (f) the IL18 comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at

least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 35 and SEQ ID NO: 71.

78. The method of any one of claims 61-77, wherein the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.
79. The method of any one of claims 61-78, wherein the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the population of cells.
80. The method of any one of claims 61-79, wherein the subject is a human.
81. The method of any one of claims 61-80, wherein the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.
82. A modified cell, wherein the cell is an immune cell or precursor cell thereof, wherein the cell is engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cell is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA.
83. The modified cell of claim 82, wherein the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system.

84. The modified cell of claim 82, wherein the inhibitory RNA comprises an siRNA or an shRNA.
85. The modified cell of any one of claims 82-84, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
86. The modified cell of any one of claims 82-85, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
87. The modified cell of any one of claims 82-86, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
88. The modified cell of any one of claims 82-87, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

89. The modified cell of any one of claims 82-88, wherein the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
 - (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
 - (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;

- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
 - (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
90. The modified cell of any one of claims 82-89, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).
91. The modified cell of any one of claims 82-90, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
92. The modified cell of any one of claims 82-91, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

93. The modified cell of any one of claims 82-92, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.
94. The modified cell of any one of claims 82-93, wherein STAT1, STAT3, STAT5, or any combination thereof, is/are activated in the cell.
95. A pharmaceutical composition comprising a population of the modified cell of any one of claims 82-94 and at least one pharmaceutically acceptable carrier.
96. A method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, wherein the cells are engineered to express a chimeric antigen receptor (CAR) comprising a tumor antigen binding domain, a transmembrane domain, and an intracellular domain, and further wherein expression of Cullin 5 in the cells is reduced and/or eliminated via a genetic engineering technique or by introduction of an inhibitory RNA.
97. The method of claim 96, wherein the genetic engineering technique comprises a zinc finger nuclease, a transcription activator-like effector nuclease (TALEN), or a clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 system.
98. The method of claim 96, wherein the inhibitory RNA comprises an siRNA or an shRNA.
99. The method of any one of claims 96-98, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP,

NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

100. The method of any one of claims 96-99, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
101. The method of any one of claims 96-100, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
102. The method of any one of claims 96-101, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).
103. The method of any one of claims 96-102, wherein the tumor antigen binding domain is selected from:
 - (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;

- (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

104. The method of any one of claims 96-103, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group

consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

105. The method of any one of claims 96-105, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, Fc γ gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
106. The method of any one of claims 96-105, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
107. The method of any one of claims 96-106, wherein the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.
108. The method of any one of claims 96-107, wherein STAT1, STAT3, STAT5, or any combination thereof, is/are activated in the population of cells.
109. The method of any one of claims 96-108, wherein the subject is a human.
110. The method of any one of claims 96-109, wherein the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical

cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.

111. A chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain (LBD) of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra).
112. The chimeric cytokine receptor of claim 111, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).
113. The chimeric cytokine receptor of claim 111 or claim 112, wherein the transmembrane domain is an IL9Ra transmembrane domain.
114. The chimeric cytokine receptor of any one of the preceding claims, wherein the chimeric cytokine receptor comprises:
 - (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

- (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
 - (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.
115. The chimeric cytokine receptor of any one of the preceding claims, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.
116. The chimeric cytokine receptor of any one of the preceding claims, wherein the chimeric cytokine receptor is encoded by a nucleic acid comprising a nucleotide

sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

117. An isolated nucleic acid comprising a nucleotide sequence encoding the chimeric cytokine receptor of any one of the preceding claims.
118. A vector comprising the isolated nucleic acid of claim 117.
119. The vector of claim 118, wherein the vector is a retroviral vector or a lentiviral vector.
120. An isolated nucleic acid comprising:
 - a) a first nucleotide sequence encoding a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - b) a second nucleotide sequence encoding a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.
121. The isolated nucleic acid of claim 120, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).

122. The isolated nucleic acid of claim 120 or claim 121, wherein the transmembrane domain is an IL9Ra transmembrane domain.
123. The isolated nucleic acid of any one of the preceding claims, wherein the chimeric cytokine receptor comprises:
- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

- (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
 - (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.
124. The isolated nucleic acid of any one of the preceding claims, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.
125. The isolated nucleic acid of any one of the preceding claims, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.
126. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.

127. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
128. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
129. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).
130. The isolated nucleic acid of any one of the preceding claims, wherein the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%,

at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;

- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

131. The isolated nucleic acid of any one of the preceding claims, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1,

LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

132. The isolated nucleic acid of any one of the preceding claims, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
133. The isolated nucleic acid of any one of the preceding claims, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
134. A vector comprising the isolated nucleic acid of any one of claims 10-23.
135. The vector of claim 134, wherein the vector is a retroviral vector or a lentiviral vector.
136. A modified cell comprising the chimeric cytokine receptor of any one of claims 111-116, the isolated nucleic acid of any one of claims 117 or 120-133, and/or the vector of any one of claims 118-119 or 134-135, wherein the cell is an immune cell or precursor cell thereof.
137. The modified cell of claim 136, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.
138. A modified cell, wherein the cell is an immune cell or precursor cell thereof, and wherein the cell is engineered to express:
 - a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint

- inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
- b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.
139. The modified cell of claim 138, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).
140. The modified cell acid of claim 138 or claim 139, wherein the transmembrane domain is an IL9Ra transmembrane domain.
141. The modified cell of any one of claims 138-140, wherein the chimeric cytokine receptor comprises:
- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

- (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or
 - (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.
142. The modified cell of any one of claims 138-141, wherein the chimeric cytokine receptor comprises an amino acid sequence havng at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.
143. The modified cell of any one of claims 138-142, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at

least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.

144. The modified cell of any one of claims 138-143, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
145. The modified cell of any one of claims 28-34, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.
146. The modified cell of any one of claims 138-145, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
147. The modified cell of any one of claims 138-146, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).

148. The modified cell of any one of claims 138-147, wherein the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;
 - (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
 - (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;

- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
 - (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.
149. The modified cell of any one of claims 138-148, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).
150. The modified cell of any one of claims 138-149, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
151. The modified cell of any one of claims 138-150, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.

152. The modified cell of any one of claims 138-151, wherein the cell is a T cell, an autologous cell, a human cell, or any combination thereof.
153. The modified cell of any one of claims 138-152, wherein the chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell.
154. A pharmaceutical composition comprising a population of the modified cell of any one of claims 136-153 and at least one pharmaceutically acceptable carrier.
155. A method of treating cancer in a subject in need thereof, comprising administering to the subject a population of modified cells, wherein the cells are immune cells or precursor cells thereof, and wherein the cells are engineered to express:
- a) a chimeric cytokine receptor comprising an extracellular domain comprising a ligand-binding domain of an inhibitory immunoreceptor or an anti-checkpoint inhibitor antigen binding domain, a first transmembrane domain, and an intracellular domain comprising an intracellular signaling domain of an interleukin-9 receptor alpha (IL9Ra); and
 - b) a chimeric antigen receptor (CAR) comprising an extracellular tumor antigen binding domain, a second transmembrane domain, and a second intracellular domain.
156. The method of claim 155, wherein the inhibitory immunoreceptor is selected from a Programmed Cell Death Protein 1 (PD1), a Transforming Growth Factor Beta Receptor I (TGFbRI), a Transforming Growth Factor Beta Receptor II (TGFbRII), a T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), and a T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM3), and further wherein the checkpoint inhibitor is selected from a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1).
157. The method of claim 155 or claim 156, wherein the transmembrane domain is an IL9Ra transmembrane domain.

158. The method of any one of claims 155-157, wherein the chimeric cytokine receptor comprises:
- (a) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (b) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (c) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (d) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (e) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (f) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (g) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (h) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (i) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (j) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (k) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (l) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (m) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;
 - (n) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;
 - (o) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or

- (p) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.
159. The method of any one of claims 155-158, wherein the chimeric cytokine receptor comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, and 300.
160. The method of any one of claims 155-159, wherein the first nucleotide sequence is a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, and 301.
161. The method of any one of claims 155-160, wherein the tumor antigen is selected from the group consisting of alpha feto-protein (AFP)/HLA-A2, AXL, B7-H3, BCMA, CA-1X, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD30, CD33, CD38, CD44v6, CD70, CD79a, CD79b, CD80, CD86, CD117, CD123, CD133, CD147, CD171, CD276, CEA, claudin 18.2, c-Met, DLL3, DR5, EGFR, EGFRvIII, EpCAM, EphA2, FAP, folate receptor alpha (FRa)/folate binding protein (FBP), GD-2, Glycolipid F77, glypican-2 (GPC2), glypican-3 (GPC3), HER2, HLA-A2, ICAM1, IL3Ra, IL13Ra2, LAGE-1, Lewis Y, LMP1 (EBV), MAGE-A1, MAGE-A3, MAGE-A4, Melan A, mesothelin, MG7 (glycosylated CEA), MMP, MUC1, Nectin4/FAP, NKG2D-Ligands (MIC-A, MIC-B, and the ULBPs 1 to 6), NY-ESO-1, P16, PD-L1, PSCA, PSMA, ROR1, ROR2, TIM-3, TM4SF1, TnMuc1, VEGFR2, and any combination thereof.
162. The method of any one of claims 155-161, wherein the tumor antigen is selected from mesothelin, GD2, HER2, TnMuc1, CD70, PMSA, and EGFRvIII.

163. The method of any one of claims 155-162, wherein the tumor antigen binding domain is selected from the group consisting of a full length antibody or antigen-binding fragment thereof, a monospecific antibody, a bispecific antibody, an Fab, an Fab', an F(ab')₂, an Fv, a single-chain variable fragment (scFv), a linear antibody, a single-domain antibody (sdAb) and an antibody mimetic (such as a designed ankyrin repeat protein (DARPin), an affibody, a monobody (adnectin), an affilin, an affimer, an affitin, an alphabody, an avimer, a Kunitz domain peptide, an anticalin, and a syntherin).
164. The method of any one of claims 155-163, wherein the tumor antigen binding domain is a single-chain variable fragment (scFv).
165. The method of any one of claims 155-164, wherein the tumor antigen binding domain is selected from:
- (a) an anti-mesothelin scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to a sequence selected from SEQ ID NO: 79 and SEQ ID NO: 95;
 - (b) an anti-GD2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 117;
 - (c) an anti-HER2 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 119 or SEQ ID NO: 121;

- (d) an anti-TnMuc1 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 123;
- (e) an anti-CD70 scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 125;
- (f) an anti-PMSA scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 129; and
- (g) an anti-EGFRvIII scFv comprising an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 131.

166. The method of any one of claims 155-165, wherein the intracellular domain of the CAR comprises a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS, NKG2C, and B7-H3 (CD276), or a variant thereof, or an intracellular domain derived from a killer immunoglobulin-like receptor (KIR).

167. The method of any one of claims 155-166, wherein the intracellular domain of the CAR comprises an intracellular signaling domain of a protein selected from the group consisting of a CD3 zeta chain (CD3 ζ), Fc γ RIII, Fc ϵ RI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof.
168. The method of any one of claims 155-167, wherein the intracellular domain of the CAR comprises a costimulatory domain of a CD28, a costimulatory domain of a 4-1BB, an intracellular signaling domain of a CD3 zeta, or any combination thereof.
169. The method of any one of claims 155-168, wherein the population of cells comprises T cells, autologous cells, human cells, or any combination thereof.
170. The method of any one of claims 155-169, wherein the chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the population of cells.
171. The method of any one of claims 155-170, wherein the subject is a human.
172. The method of any one of claims 155-171, wherein the cancer is selected from a B-cell malignancy (such as a B-cell lymphomas or leukemia), lung cancer, non-small cell lung cancer, small cell lung cancer, Merkel cell carcinoma, melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, cutaneous squamous cell carcinoma, renal cell carcinoma, breast cancer, triple-negative breast cancer, colon cancer, esophagus cancer, stomach cancer, liver cancer, kidney cancer, pancreatic cancer, prostate cancer, brain cancer, lung adenocarcinoma, glioblastoma, hepatocellular carcinoma, gallbladder cancer, cervical cancer, cervical squamous cell carcinoma, colorectal cancer, ovarian cancer, and renal cancer.