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 the group consisting of 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, optionally wherein the transmembrane domain is an IL9Ra 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 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;

optionally 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 any one of SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, or 59.

3. A nucleic acid comprising a nucleotide sequence encoding the chimeric cytokine receptor of claim 1 or claim 2, optionally wherein the nucleotide sequence 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%, at least 99%, or at least 100% sequence identity to any one of SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, or 60.

4. A vector comprising the nucleic acid of claim 3, optionally wherein the vector is a retroviral vector or a lentiviral vector.

5. A 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 the group consisting of 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, optionally wherein the transmembrane domain is an IL9Ra 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.

6. The nucleic acid of claim 5, 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;

optionally 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 any one of SEQ ID NOs: 15, 17, 19, 21, 23, 51, 53, 55, 57, or 59.

7. The nucleic acid of claim 5, wherein:

(a) 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 any one of SEQ ID NOs: 16, 18, 20, 22, 24, 52, 54, 56, 58, or 60;

(b) 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;

(c) the tumor antigen binding domain is a single-chain variable fragment (scFv);

(d) 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);

(e) 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, FcsRI, 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; and/or

(f) 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.

8. The nucleic acid of claim 5, wherein the tumor antigen binding domain is:

(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 SEQ ID NO: 79 or 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; or

(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.

9. A vector comprising the nucleic acid of claim 8, optionally wherein the vector is a retroviral vector or a lentiviral vector.

10. A modified cell comprising:

(a) the chimeric cytokine receptor of claim 1 or claim 2,

(b) the nucleic acid of any one of claims3 or 5-8, and/or

(c) the vector of any claim 4 or claim 9,

wherein the cell is an immune cell or precursor cell thereof.

11. The modified cell of claim 10, wherein the modified cell is a T cell, an autologous cell, a human cell, or any combination thereof.

12. A pharmaceutical composition comprising the modified cell of claim 10 for use in a method of treating cancer in a subject in need thereof.

13. 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 the group consisting of 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.

14. The modified cell of claim 13, wherein:

(a) 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; and/or

(b) the IL9Ra or chimeric cytokine receptor is capable of activating STAT1, STAT3, STAT5, or any combination thereof, in the cell; and/or

(c) the transmembrane domain in an IL9Ra transmembrane domain; and/or

(d) the chimeric cytokine receptor comprises:

(i) a human IL13Ra2 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(ii) a human IL2Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(iii) a human IL18Ra LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(iv) a human IL18Rb LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(v) a murine IL13Ra2 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(vi) a murine IL2Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(vii) a murine IL18Ra LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or

(viii) a murine IL18Rb LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain.

15. 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 the group consisting of 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 the group consisting of an IL9, an IL13, an IL2, and an IL18.

16. A composition comprising the system of claim 15 for use in a method of treating cancer in a subject in need thereof, optionally wherein:

(a) the subject is a human; and/or

(b) the cancer is selected from the group consisting of a B-cell malignancy, 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; and/or

(c) the cancer is a B-cell lymphomas or a leukemia.

17. 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), optionally wherein:

(a) the inhibitory immunoreceptor is selected from the group consisting of 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 the group consisting of a Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4), a Programmed Cell Death Protein 1 (PD1), and a Programmed Death Ligand-1 (PD-L1); and/or

(b) the transmembrane domain is an IL9Ra transmembrane domain; and/or

(c) the chimeric cytokine receptor comprises:

(i) a human PD1 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(ii) a human TGFbRI LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(iii) a human TGFbRII LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(iv) a human TIGIT LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(v) a human TIM3 LBD, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(vi) a murine PD1 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(vii) a murine TGFbRI LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(viii) a murine TGFbRII LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(ix) a murine TIGIT LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(x) a murine TIM3 LBD, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(xi) an anti-human CTLA4 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(xii) an anti-human PD1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(xiii) an anti-human PD-L1 antigen binding domain, a human IL9Ra transmembrane domain, and a human IL9Ra intracellular signaling domain;

(xiv) an anti-murine CTLA4 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

(xv) an anti-murine PD1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain; or

(xvi) an anti-murine PD-L1 antigen binding domain, a murine IL9Ra transmembrane domain, and a murine IL9Ra intracellular signaling domain;

and/or

(d) 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 any one of SEQ ID NOs: 215, 217, 219, 221, 223, 239, 241, 243, 245, 247, or 300.

18. A nucleic acid comprising:

(a) a nucleotide sequence encoding the chimeric cytokine receptor of claim 17, optionally wherein the nucleotide sequence 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%, at least 99%, or at least 100% sequence identity to any one of SEQ ID NOs: 216, 218, 220, 222, 224, 240, 242, 244, 246, 248, or 301; or

(b) (i) 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
(ii) 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.

19. A modified immune cell or precursor cell thereof comprising:

(a) the chimeric cytokine receptor of claim 17, and/or

(b) the nucleic acid of claim 18.

20. A pharmaceutical composition comprising the modified immune cell or precursor cell thereof of claim 19 for use in a method of treating cancer in a subject in need thereof.