(2011), and HER2 CARs for sarcoma (4 of 17 patients showing stable disease) (Ahmed et al, J Clin Oncol (33), (2015).

[0008] It has been suggested that poor trafficking, limited persistence and T-cell inhibitory activity in patients' serum contributed to the observed lack of efficacy (Kershaw, et al. Clin. Cancer Res (12), (2006). Some armored CAR-T designs (constitutive secretion of immune-checkpoint inhibitors, IL-12, etc.) were expected to enhance antitumor efficacy by better T cell activity or better cell trafficking to the tumor (Oladapo et al, Nature scientific reports, (2017). While, new designs to improve the comprehensive functions of CAR T cells with better cell-killing effect, persistence in vivo and better tolerance to tumor microenvironments still core requirements.

[0009] T-cell mediated immunity is an adaptive process of developing antigen (Ag) – specific T lymphocytes to eliminate malignant cells. In recently years, fundamental advances in immunology and tumor biology have led to significant progress in the field of cell-based immunotherapy. For example, one promising approach has been developed in recent years to engage T cells for targeted cancer immunotherapy. This new approach is called Chimeric Antigen Receptor T cell Therapy (CAR-T). T cells equipped with CARs can be redirected to attack a broad variety of cells, including those that do not match the major histocompatibility complex (MHC) type of the T cell receptors (TCRs) on the T cells but express the target cell-surface antigens. Several attempts have also been made to engineer TCR molecules having antibody specificity. See, for example, WO2015/117229 and WO2016/187349.

[0010] One most notable adverse effect of current CAR-T and TCR-T approach is cytokine release syndrome (CRS) or cytokine storm. The basal signaling in the absence of a tumor antigen (tonic signaling) of current CAR-T and TCR-T can be substantial, which can increase differentiation and exhaustion of T cells and limit their potency. Due to tonic signaling, CAR-T and TCR-T cells exhibit cytokine production even in the absence of stimulation.

[0011] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

SUMMARY

[0012] The present disclosure in one example provides a chimeric receptor polypeptide (also referred to herein as "STS polypeptides") comprising: a) an extracellular target binding domain

(*e.g.*, anti-BCMA sdAb); b) an extracellular TCR binding domain (*e.g.*, anti-CD3 scFv or sdAb, or anti-TCR scFv); c) a transmembrane domain; and d) optionally an intracellular domain, wherein the transmembrane domain and/or intracellular domain comprises a transmembrane and/or intracellular domain of a TCR subunit selected from the group consisting of CD3ε, CD3γ, CD3δ, TCRα, TCRβ, TCRγ, and TCRδ. In some examples, there is provided a chimeric receptor polypeptide comprising: a) an extracellular target binding domain (*e.g.*, anti-BCMA sdAb); b) an extracellular TCR binding domain (*e.g.*, anti-CD3 scFv or sdAb, or anti-TCR scFv); c) a transmembrane domain comprising a transmembrane domain of a first TCR subunit; and d) optionally an intracellular domain comprising an intracellular domain of a second TCR subunit, wherein the first TCR subunit and the second TCR subunit are both selected from the group consisting of CD3ε, CD3γ, CD3δ, TCRα, TCRβ, TCRγ, and TCRδ. In one aspect, the present disclosure refers to a chimeric receptor polypeptide comprising: a) an extracellular target binding domain; b) an extracellular T-cell receptor (TCR) binding domain; c) a transmembrane domain comprising a transmembrane domain of a first TCR subunit; and d) optionally an intracellular domain comprising an intracellular domain of a second TCR subunit, wherein the first TCR subunit and the second TCR subunit are each independently selected from the group consisting of CD3ε, CD3γ, CD3δ, TCRα, TCRβ, TCRγ, and TCRδ.

[0013] In some examples according to any of the examples described above, the extracellular TCR binding domain comprises a TCR antigen binding domain (e.g., sdAb, scFv) specifically recognizing a TCR subunit (e.g., extracellular domain of a TCR subunit) selected from the group consisting of TCRα, TCRβ, TCRγ, TCRδ, CD3ε, CD3δ, CD3γ, and CD3ζ, such as CD3ε or TCRγ/δ. In some examples, the TCR antigen binding domain is a single chain Fv (scFv; *e.g.*, anti-CD3 scFv or anti-TCR scFv) or a single domain antibody (sdAb; e.g., anti-CD3 sdAb). In some examples, the extracellular TCR binding domain comprises two or more TCR antigen binding domains (e.g., scFv, sdAb), such as two or more TCR antigen binding domains arranged in tandem. In some examples, the TCR antigen binding domain is an anti-CD3 sdAb comprising the amino acid sequence of SEQ ID NO: 22 or 23. In some examples, the TCR antigen binding domain is an anti-CD3 scFv comprising the amino acid sequence of SEQ ID NO: 24. In some examples, the TCR antigen binding domain is an anti-TCR scFv comprising the amino acid sequence of SEQ ID NO: 27.

[0014] In some examples according to any of the examples described above, the first TCR subunit and the second TCR subunit are both selected from the group consisting of TCRα, TCRβ, TCRγ, and TCRδ, and the chimeric receptor polypeptide does not comprise a variable region of the extracellular domain of the first TCR subunit or the second TCR subunit. In some examples, the chimeric receptor polypeptide does not comprise a variable region of the extracellular domain of any of TCRα, TCRβ, TCRγ, and TCRδ.

[0015] In some examples according to any of the examples described above, the chimeric receptor polypeptide does not comprise an extracellular domain of the first TCR subunit or the second TCR subunit. In some examples, the chimeric receptor polypeptide does not comprise an extracellular domain of any TCR subunit.

[0016] In some examples according to any of the examples described above, the chimeric receptor polypeptide does not comprise an intracellular co-stimulatory domain.

[0017] In some examples according to any of the examples described above, the first TCR subunit and the second TCR subunit are different. In some examples, the first TCR subunit is CD3ε. In some examples, the second TCR subunit is CD3ε.

[0018] In some examples according to any of the examples described above, the first TCR subunit and the second TCR subunit are the same. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of CD3ε and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of CD3ε. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of CD3γ and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of CD3γ. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of CD3δ and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of CD3δ. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRα and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRα. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRβ and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRβ. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRγ and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRγ. In some examples, the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRδ and the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRδ.

[0019] In some examples according to any of the examples described above, the extracellular target binding domain is N-terminal to the extracellular TCR binding domain. In some examples, the extracellular target binding domain is C-terminal to the extracellular TCR binding domain.

[0020] In some examples according to any of the examples described above, the extracellular target binding domain comprises a target antigen binding domains specifically recognizing a target antigen (e.g., BCMA). In some examples, the target antigen binding domain is an scFv, an sdAb (e.g., anti-BCMA sdAb), or a designed ankyrin repeat protein (DARPin). In some examples, the extracellular target binding domain comprises two or more target antigen binding domains (e.g., anti-BCMA sdAb), such as two or more target antigen binding domains arranged in tandem. In some examples, the two or more target antigen binding domains each specifically recognizes a same epitope on a same target antigen (e.g., same anti-BCMA sdAbs). In some examples, the two or more target antigen binding domains each specifically recognizes a different epitope on a same target antigen. In some examples, the two or more target antigen binding domains each specifically recognizes a different target antigen.

[0021] In some examples according to any of the examples described above, the target antigen is selected from the group consisting of BCMA, NY-ESO-1, VEGFR2, MAGE-A3, AFP, CD4, CD19, CD20, CD22, CD30, CD33, CD38, CD70, CD123, CEA, EGFR (such as EGFRvIII), GD2, GPC-2, GPC-3, HER2, LILRB4, IL-13Rα2, IGF1R, mesothelin, PSMA, ROR1, WT1, NKG2D, CLL1, Mesothelin, TGFaRII, TGFbRII, CCR5, CXCR4, CCR4, HPV related antigen, EBV related antigen (such as LMP1 and LMP2). In some examples, the target antigen is BCMA. In some examples, the target antigen binding domain is an anti-BCMA sdAb comprising the amino acid sequence of SEQ ID NO: 26.

[0022] In some examples according to any of the examples described above, the TCR subunit recognized by the TCR antigen binding domain, the first TCR subunit, and the second TCR subunit are all the same. In some examples, the TCR subunit recognized by the TCR antigen binding domain is different from the first TCR subunit or the second TCR subunit.

[0023] In some examples according to any of the examples described above, the chimeric receptor polypeptide further comprises a first linker connecting the extracellular target binding domain with the extracellular TCR binding domain. In some examples, the chimeric

receptor polypeptide further comprise a second linker connecting the extracellular target binding domain and/or the extracellular TCR binding domain with the transmembrane domain. In some examples, the first linker and/or the second linker is a GS linker, an α-helical linker, a glycine-alanine polymer linker, an alanine-serine polymer linker, or an IgG4-Fc linker.

[0024] In some examples according to any of the examples described above, the chimeric receptor polypeptide further comprises a signal peptide at the N-terminus of the extracellular target binding domain or the extracellular TCR binding domain.

[0025] In some examples according to any of the examples described above, the chimeric receptor polypeptide further comprises a hinge region (e.g., CD8 hinge region) N-terminal to the transmembrane domain of the chimeric receptor polypeptide. In some examples, the hinge region comprises the amino acid sequence of SEQ ID NO: 31.

[0026] In some examples according to any of the examples described above, the chimeric receptor polypeptide comprises (or consists essentially of or consists of), from the N-terminus to the C-terminus: a) optional signal peptide – extracellular target binding domain – optional first linker – extracellular TCR binding domain – optional second linker – optional hinge region – transmembrane domain – intracellular domain; or b) optional signal peptide – extracellular TCR binding domain – optional first linker – extracellular target binding domain – optional second linker – optional hinge region – transmembrane domain – intracellular domain.

[0027] In some examples according to any of the examples described above, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – full length CD3ε without CD3ε signal peptide. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – full length CD3γ without CD3γ signal peptide. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – full length CD3δ without CD3δ signal peptide. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – CD8 hinge region – CD3ε transmembrane domain – CD3ε intracellular

domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – CD8 hinge region – – CD3γ transmembrane domain – CD3γ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – CD8 hinge region – CD3δ transmembrane domain – CD3δ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRα constant region – TCRα transmembrane domain – TCRα intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRβ constant region – TCRβ transmembrane domain – TCRβ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRγ constant region – TCRγ transmembrane domain – TCRγ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRδ constant region – TCRδ transmembrane domain – TCRδ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRα transmembrane domain – TCRα intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRβ transmembrane domain – TCRβ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRγ transmembrane domain – TCRγ intracellular domain. In some examples, the chimeric

receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRδ transmembrane domain – TCRδ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRα constant region – TCRα transmembrane domain – TCRα intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRβ constant region – TCRβ transmembrane domain – TCRβ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRγ constant region – TCRγ transmembrane domain – TCRγ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRδ constant region – TCRδ transmembrane domain – TCRδ intracellular domain. In some examples, the chimeric receptor polypeptide comprises (or consists essentially of or consists of) from the N-terminus to the C-terminus: optional signal peptide – first anti-BCMA sdAb – first linker – second anti-BCMA sdAb – second linker – anti-CD3ε scFv – third linker – full length CD3ε without CD3ε signal peptide.

[0028] In some examples according to any of the examples described above, the first, second, and/or third linker comprises the sequence of any of SEQ ID NOs: 1-21, 67, and 68.

[0029] In another example, there is provided an isolated nucleic acid encoding any of the chimeric receptor polypeptides described above. Also provided are nucleic acid vectors comprising any of the chimeric receptor polypeptide-encoding nucleic acids described herein. In some examples, the nucleic acid vector comprises two or more any of the chimeric receptor polypeptide-encoding nucleic acids described herein connected via one or more linking sequences. In some examples, the linking sequence is selected from the group consisting of nucleic acids encoding P2A, T2A, E2A, F2A, BmCPV 2A, and BmIFV 2A, and internal ribosome entry site (IRES) sequence. In some examples, the nucleic acid vector comprises a

nucleic acid encoding from the N-terminus to the C-terminus: optional first signal peptide – first anti-BCMA sdAb – first linker – first anti-CD3ε scFv – second linker – TCRα constant region – TCRα transmembrane domain – TCRα intracellular domain – P2A – optional second signal peptide – second anti-BCMA sdAb – third linker – second anti-CD3ε scFv – fourth linker – TCRβ constant region – TCRβ transmembrane domain – TCRβ intracellular domain. In some examples, the nucleic acid vector comprises a nucleic acid encoding from the N-terminus to the C-terminus: optional first signal peptide – first anti-BCMA sdAb – first linker – first anti-CD3ε scFv – second linker – TCRγ constant region – TCRγ transmembrane domain – TCRγ intracellular domain – P2A – optional second signal peptide – second anti-BCMA sdAb – third linker – second anti-CD3ε scFv – fourth linker – TCRδ constant region – TCRδ transmembrane domain – TCRδ intracellular domain. In some examples, the nucleic acid vector comprises a nucleic acid encoding from the N-terminus to the C-terminus: optional first signal peptide – first anti-BCMA sdAb – first linker – first anti-CD3ε scFv – second linker – TCRα transmembrane domain – TCRα intracellular domain – P2A – optional second signal peptide – second anti-BCMA sdAb – third linker – second anti-CD3ε scFv – fourth linker – TCRβ transmembrane domain – TCRβ intracellular domain. In some examples, the nucleic acid vector comprises a nucleic acid encoding from the N-terminus to the C-terminus: optional first signal peptide – first anti-BCMA sdAb – first linker – first anti-CD3ε scFv – second linker – TCRγ transmembrane domain – TCRγ intracellular domain – P2A – optional second signal peptide – second anti-BCMA sdAb – third linker – second anti-CD3ε scFv – fourth linker – TCRδ transmembrane domain – TCRδ intracellular domain. In some examples, the nucleic acid vector comprises a nucleic acid encoding from the N-terminus to the C-terminus: optional first signal peptide – first anti-BCMA sdAb – first linker – first anti-TCR scFv – second linker – TCRγ constant region – TCRγ transmembrane domain – TCRγ intracellular domain – P2A – optional second signal peptide – second anti-BCMA sdAb – third linker – second anti-TCR scFv – fourth linker – TCRδ constant region – TCRδ transmembrane domain – TCRδ intracellular domain. In one aspect, the present disclosure refers to an isolated nucleic acid encoding the chimeric receptor polypeptide as disclosed herein. In one aspect, the present disclosure refers to a vector comprising one or more isolated nucleic acids as disclosed herein; optionally wherein the vector comprises two or more isolated nucleic acids connected via one or more linking sequences; optionally wherein the linking sequence is an internal ribosome entry site (IRES) sequence, or a nucleic acid encoding any of P2A, T2A, E2A, F2A, BmCPV 2A, and BmIFV 2A.

[0030] In another example, there is provided an isolated immune cell comprising one or more chimeric receptor polypeptides described above, one or more nucleic acids described above, or one or more nucleic acid vectors described above. In some examples, the isolated immune cell comprises two or more chimeric receptor polypeptides described above. In some examples, there is provided an isolated immune cell comprising any of the nucleic acids or

nucleic acid vectors described above. In some examples, the isolated immune cell is selected from the group consisting of Tαβ cells, Tγδ cells, effector T cells, memory T cells, cytotoxic T cells, T helper cells, Natural Killer T (NKT) cells, regulatory T cells (Tregs), tumor infiltrating lymphocytes (TILs). In some examples, the isolated immune cell is a T cell (*e.g.*, effector T cell). In some examples, the isolated immune cell further comprises a chimeric antigen receptor (CAR) and/or an engineered TCR. In one aspect, the present disclosure refers to an isolated immune cell comprising: (i) one or more chimeric receptor polypeptides as disclosed herein; optionally wherein the isolated immune cell comprises two or more chimeric receptor polypeptides; (ii) an isolated nucleic acid as disclosed herein; or (iii) a vector as disclosed herein.

[0031] In another example, there is provided a pharmaceutical composition comprising any of the immune cells described above, and an optional pharmaceutically acceptable excipient. In some examples, there is provided a method of treating a disease in an individual (e.g., human), comprising administering to the individual an effective amount of any of the immune cells described above, or any of the pharmaceutical compositions described above. In some examples, the pharmaceutical composition is administered intravenously, intratumorally, or subcutaneously. In some examples, the disease is cancer. In some examples, the cancer is selected from the group consisting of acute leukemias (including but not limited to acute myeloid leukemia (AML), B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), and acute lymphoid leukemia (ALL)), chronic leukemias (including but not limited to chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL)), multiple myeloma (MM), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPNs), chronic myeloid leukemia (CML), and blastic plasmacytoid dendritic cell neoplasm (BPDCN). In one aspect, the present disclosure refers to a pharmaceutical composition comprising the isolated immune cell as disclosed herein, and an optional pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to use of an effective amount of the isolated immune cell as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a disease in an individual; optionally wherein the individual is a human; optionally wherein the disease is a cancer, an infectious disease, or an autoimmune disease.

[0032] Also provided are methods of making any of the constructs described herein, articles of manufacture, and kits that are suitable for the methods described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 shows an exemplary configuration of a chimeric receptor polypeptide expressed on the surface of a T cell, comprising a target antigen binding domain, a TCR antigen binding domain, and CD3ε. As illustrated in FIG. 1, without being bound by the theory, the chimeric receptor polypeptide may transduce TCR signaling via another TCR complex.

[0034] FIG. 2 shows an exemplary configuration of a chimeric receptor polypeptide expressed on the surface of a T cell, comprising a target antigen binding domain, a TCR antigen binding domain, and CD3γ. As illustrated in FIG. 2, without being bound by the theory, the chimeric receptor polypeptide may transduce TCR signaling via another TCR complex.

CLAIMS

What is claimed is:

1. A chimeric receptor polypeptide comprising:

a) an extracellular target binding domain;

b) an extracellular T-cell receptor (TCR) binding domain;

c) a transmembrane domain comprising a transmembrane domain of a first TCR subunit; and

d) optionally an intracellular domain comprising an intracellular domain of a second TCR subunit,

wherein the first TCR subunit and the second TCR subunit are each independently selected from the group consisting of CD3ε, CD3γ, CD3δ, TCRα, TCRβ, TCRγ, and TCRδ.

2. The chimeric receptor polypeptide of claim 1, wherein the extracellular TCR binding domain comprises a TCR antigen binding domain specifically recognizing a TCR subunit selected from the group consisting of TCRα, TCRβ, TCRγ, TCRδ, CD3ε, CD3δ, CD3γ, and CD3ζ, optionally wherein the TCR antigen binding domain specifically recognizes an extracellular domain of CD3ε, CD3δ, CD3γ, TCRγ, or TCRδ.

3. The chimeric receptor polypeptide of claim 2, wherein the TCR antigen binding domain is a single chain Fv (scFv) or a single domain antibody (sdAb).

4. The chimeric receptor polypeptide of claim 2 or 3, wherein the extracellular TCR binding domain comprises two or more TCR antigen binding domains arranged in tandem.

5. The chimeric receptor polypeptide of any one of claims 1-4, wherein the chimeric receptor polypeptide

(i) does not comprise an extracellular domain of the first TCR subunit, the second TCR subunit, or any TCR subunit; and/or

(ii) does not comprise an intracellular co-stimulatory domain.

6. The chimeric receptor polypeptide of any one of claims 1-5, wherein the first TCR subunit and the second TCR subunit are different, optionally wherein the first TCR subunit or the second TCR subunit is CD3ε.

7. The chimeric receptor polypeptide of any one of claims 1-5, wherein the first TCR subunit and the second TCR subunit are the same; optionally

(i) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of CD3ε, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of CD3ε;

(ii) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of CD3γ, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of CD3γ;

(iii) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of CD3δ, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of CD3δ;

(iv) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRα, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRα;

(v) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRβ, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRβ;

(vi) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRγ, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRγ; or

(vii) wherein the transmembrane domain of the chimeric receptor polypeptide comprises a transmembrane domain of TCRδ, and wherein the intracellular domain of the chimeric receptor polypeptide comprises an intracellular domain of TCRδ.

8. The chimeric receptor polypeptide of any one of claims 1-7, wherein the extracellular target binding domain is N-terminal to the extracellular TCR binding domain.

9. The chimeric receptor polypeptide of any one of claims 1-7, wherein the extracellular target binding domain is C-terminal to the extracellular TCR binding domain.

10. The chimeric receptor polypeptide of any one of claims 1-9, wherein the extracellular target binding domain comprises a target antigen binding domain specifically recognizing a target antigen; optionally wherein the target antigen binding domain is an scFv, an sdAb, or a designed ankyrin repeat protein (DARPin).

11. The chimeric receptor polypeptide of claim 10, wherein the extracellular target binding domain comprises two or more target antigen binding domains arranged in tandem; optionally

wherein the two or more target antigen binding domains each specifically recognizes a same target antigen.

12. The chimeric receptor polypeptide of claim 10 or 11, wherein the target antigen is selected from the group consisting of BCMA, NY-ESO-1, VEGFR2, MAGE-A3, AFP, CD4, CD19, CD20, CD22, CD30, CD33, CD38, CD70, CD123, CEA, EGFR (such as EGFRvIII), GD2, GPC-2, GPC3, HER2, LILRB4, IL-13Rα2, IGF1R, mesothelin, PSMA, ROR1, WT1, NKG2D, CLL1, TGFaRII, TGFbRII, CCR5, CXCR4, CCR4, HPV related antigen, and EBV related antigen (such as LMP1 and LMP2); optionally wherein the target antigen is BCMA.

13. The chimeric receptor polypeptide of any one of claims 1-12,

(i) further comprising a first linker connecting the extracellular target binding domain with the extracellular TCR binding domain; and/or

(ii) further comprising a second linker connecting the extracellular target binding domain or the extracellular TCR binding domain with the transmembrane domain;

optionally wherein the first linker and/or the second linker is a GS linker, an α-helical linker, a glycine-alanine polymer linker, an alanine-serine polymer linker, or an IgG4-Fc linker;

optionally wherein the first and/or the second linker comprises the sequence of any of SEQ ID NOs: 1-21, 67, and 68.

14. The chimeric receptor polypeptide of any one of claims 1-13, comprising from the N-terminus to the C-terminus:

a) optional signal peptide – extracellular target binding domain – optional first linker – extracellular TCR binding domain – optional second linker – optional hinge region – transmembrane domain – intracellular domain; or

b) optional signal peptide – extracellular TCR binding domain – optional first linker – extracellular target binding domain – optional second linker – optional hinge region – transmembrane domain – intracellular domain.

15. The chimeric receptor polypeptide of any one of claims 1-8 and 10-14, comprising from the N-terminus to the C-terminus:

(i) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – full length CD3ε without CD3ε signal peptide;

(ii) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – full length CD3γ without CD3γ signal peptide;

(iii) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – full length CD3δ without CD3δ signal peptide;

(iv) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – CD8 hinge region – CD3ε transmembrane domain – CD3ε intracellular domain;

(v) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – CD8 hinge region – CD3γ transmembrane domain – CD3γ intracellular domain;

(vi) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – CD8 hinge region – CD3δ transmembrane domain – CD3δ intracellular domain;

(vii) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRα constant region – TCRα transmembrane domain – TCRα intracellular domain;

(viii) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRβ constant region – TCRβ transmembrane domain – TCRβ intracellular domain;

(ix) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRγ constant region – TCRγ transmembrane domain – TCRγ intracellular domain;

(x) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRδ constant region – TCRδ transmembrane domain – TCRδ intracellular domain;

(xi) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRα transmembrane domain – TCRα intracellular domain;

(xii) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRβ transmembrane domain – TCRβ intracellular domain;

(xiii) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRγ transmembrane domain – TCRγ intracellular domain;

(xiv) anti-BCMA sdAb – first linker – anti-CD3ε scFv – second linker – TCRδ transmembrane domain – TCRδ intracellular domain;

(xv) anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRα constant region – TCRα transmembrane domain – TCRα intracellular domain;

(xvi) anti-BCMA sdAb – first linker – anti- TCR scFv – second linker – TCRβ constant region – TCRβ transmembrane domain – TCRβ intracellular domain;

(xvii) anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRγ constant region – TCRγ transmembrane domain – TCRγ intracellular domain;

(xviii) anti-BCMA sdAb – first linker – anti-TCR scFv – second linker – TCRδ constant region – TCRδ transmembrane domain – TCRδ intracellular domain; or

(xix) first anti-BCMA sdAb – first linker – second anti-BCMA sdAb – second linker – anti-CD3ε scFv – third linker – full length CD3ε without CD3ε signal peptide.

16. An isolated nucleic acid encoding the chimeric receptor polypeptide of any one of claims 1-15.

17. A vector comprising one or more isolated nucleic acids of claim 16; optionally wherein the vector comprises two or more isolated nucleic acids connected via one or more linking sequences; optionally wherein the linking sequence is an internal ribosome entry site (IRES) sequence, or a nucleic acid encoding any of P2A, T2A, E2A, F2A, BmCPV 2A, and BmIFV 2A.

18. An isolated immune cell comprising:

(i) one or more chimeric receptor polypeptides of any one of claims 1-15; optionally wherein the isolated immune cell comprises two or more chimeric receptor polypeptides;

(ii) an isolated nucleic acid of claim 16; or

(iii) a vector of claim 17.

19. The isolated immune cell of claim 18, wherein the isolated immune cell is selected from the group consisting of Tαβ cells, Tγδ cells, effector T cells, memory T cells, cytotoxic T cells, T helper cells, Natural Killer T (NKT) cells, regulatory T cells (Tregs), and tumor infiltrating lymphocytes (TILs); optionally wherein the isolated immune cell is a T cell.

20. The isolated immune cell of claim 18 or 19,

(i) further comprising a chimeric antigen receptor (CAR); and/or

(ii) further comprising an engineered TCR.

21. A pharmaceutical composition comprising the isolated immune cell of any one of claims 18-20, and an optional pharmaceutically acceptable excipient.

22. Use of an effective amount of the isolated immune cell of any one of claims 18-20, or the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a disease in an individual; optionally wherein the individual is a human; optionally wherein the disease is a cancer, an infectious disease, or an autoimmune disease.

23. The use of claim 22, wherein the cancer is selected from the group consisting of acute leukemias, chronic leukemias, multiple myeloma (MM), myelodysplastic syndrome (MDS),

myeloproliferative neoplasms (MPNs), and blastic plasmacytoid dendritic cell neoplasm (BPDCN);

optionally wherein the acute leukemia is acute myeloid leukemia (AML), B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), or acute lymphoid leukemia (ALL);

optionally wherein the chronic leukemia is chronic myelogenous leukemia (CML) or chronic lymphocytic leukemia (CLL).