CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein the cell is an eukaryotic cell, an animal cell, a human cell, an immune cell, an induced pluripotent cell (iPSC), a clonal iPSC or a derivative cell differentiated therefrom, and wherein the cell comprises:

(i) a polynucleotide encoding a transgenic TCRα chain (tgTCRα); and

(ii) a polynucleotide encoding a transgenic TCRβ chain (tgTCRβ), wherein the tgTCRα chain and the tgTCRβ chain form an exogenous TCR complex (TCR^{exo}) that recognizes a first tumor antigen; and optionally,

(iii) one or more additional exogenous polynucleotides comprising a polynucleotide encoding a chimeric antigen receptor (CAR) or an engager targeting at least a second tumor antigen.

2. The cell or population thereof of claim 1, wherein:

(i) the polynucleotide encoding the tgTCRα chain and the polynucleotide encoding the tgTCRβ chain are comprised in a bi-cistronic construct, and optionally wherein:

(a) the construct is inserted at a constant region of TCRα or TCRβ (TRAC or TRBC);

(b) the insertion of the construct disrupts expression of endogenous TCRα or TCRβ at the insertion site; and/or

(c) expression of the construct is driven by an endogenous promoter of TCR or an exogenous promoter; or

(ii) the polynucleotide encoding the CAR or the engager is inserted at TRAC or TRBC, and optionally wherein:

(a) the insertion of the polynucleotide encoding the CAR or the engager disrupts expression of the endogenous TCRα or TCRβ at the insertion site; and/or

(b) expression of the CAR or the engager is driven by an endogenous promoter of TCR or an exogenous promoter; or

(iii) the polynucleotides encoding the tgTCRα chain and the tgTCRβ chain, the CAR or the engager, or the one or more additional polynucleotides are inserted in one, or more safe harbor loci or selected gene loci.

3. The cell or population thereof of claim 2, (I) wherein the construct and the polynucleotide encoding the CAR or the engager are each inserted at a constant region of TCRα or TCRβ (TRAC or TRBC), but not at the same constant region, thereby disrupting expression of both endogenous TCRα and TCRβ, knocking out the endogenous TCR, and avoiding a mis-paired TCR comprising:

(a) the transgenic TCRα and the endogenous TCRβ, or

(b) the transgenic TCRβ and the endogenous TCRα;

or (II) wherein the construct and the polynucleotide encoding the CAR or the engager are each integrated at a locus comprising a safe harbor locus or a selected gene locus.

4. The cell or population thereof of claim 3, wherein:

(i) the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1;

(ii) the selected gene locus is one of B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD25, CD69, CD44, CD58, CD54, CD56, CD69, CD71, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and/or

(iii) the integration of the exogenous polynucleotides knocks out expression of the gene in the locus.

5. The cell or population thereof of claim 1, wherein the first tumor antigen and the second tumor antigen each comprises at least one of:

(i) MR1, NYESO1, MICA/B, EpCAM, EGFR, B7H3, Muc1, Muc16, CD19, BCMA, CD20, CD22, CD38, CD123, HER2, CD52, GD2, MSLN, VEGF-R2, PSMA and PDL1; or

(ii) ADGRE2, B7H3, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD44V6, CD49f, CD56, CD70,

CD74, CD99, CD123, CD133, CD138, CDS, CLEC12A, an antigen of a cytomegalovirus (CMV) infected cell, epithelial glycoprotein2 (EGP-2), epithelial glycoprotein-40 (EGP-40), epithelial cell adhesion molecule (EpCAM), EGFRvIII, receptor tyrosine-protein kinases erb- B2,3,4, EGFIR, EGFR-VIII, ERBB folate-binding protein (FBP), fetal acetylcholine receptor (AChR), folate receptor-α, Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER2), human telomerase reverse transcriptase (hTERT), ICAM-1, Integrin B7, Interleukin-13 receptor subunit alpha-2 (IL-13Rα2), κ-light chain, kinase insert domain receptor (KDR), Lewis A (CA19.9), Lewis Y (LeY), L1 cell adhesion molecule (L1-CAM), LILRB2, melanoma antigen family A 1 (MAGE-A1), MICA/B, MR1, Mucin 1 (Muc-1), Mucin 16 (Muc-16), Mesothelin (MSLN), NKCSI, NKG2D ligands, c-Met, NYESO1, oncofetal antigen (h5T4), PDL1, PRAME, prostate stem cell antigen (PSCA), PRAME prostate-specific membrane antigen (PSMA), tumor-associated glycoprotein 72 (TAG-72), TIM-3, TRBC1, TRBC2, vascular endothelial growth factor R2 (VEGF-R2), Wilms tumor protein (WT-1), and a pathogen antigen; and

wherein the first tumor antigen and the second tumor antigen are the same or different.

6. The cell or population thereof of claim 1, wherein the first tumor antigen comprises at least one of MR1, NYESO1, and MICA/B; or

wherein:

(i) the tgTCRα comprises a variable alpha (Vα) fragment that has at least about 85% identity to SEQ ID NO: 7, and a TCRα constant fragment comprising a sequence having at least about 85% identity to SEQ ID NO: 8; and/or

(ii) the tgTCRβ comprises a variable alpha (Vβ) fragment that has at least about 85% identity to SEQ ID NO: 9, and a TCRβ constant fragment comprising a sequence having at least about 85% identity to SEQ ID NO: 10.

7. The cell of population thereof of claim 1, wherein the CAR is:

(i) T cell specific or NK cell specific;

(ii) a bi-specific antigen binding CAR;

(iii) a switchable CAR;

(iv) a dimerized CAR;

(v) a split CAR;

(vi) a multi-chain CAR;

(vii) an inducible CAR;

(viii) an inactivation CAR;

(ix) co-expressed with a partial or full peptide of a cell surface expressed exogenous cytokine and/or a receptor thereof, optionally in separate constructs or in a bi-cistronic construct; or

(x) co-expressed with a checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct.

8. The cell or population thereof of claim 1, wherein the engager comprises:

(i) a first binding domain recognizing an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof of the cell or a by-stander immune effector cell; and

(ii) a second binding domain targeting the second tumor antigen that is different from the first tumor antigen targeted by the exogenous TCR, and wherein the second binding domain of the engager is specific to any one of: B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, CD52, CD79a, CD79b, CD123, CD138, CD179b, CEA, CLEC12A, CS-1, DLL3, EGFR, EGFRvIII, EpCAM, FLT-3, FOLR1, FOLR3, GD2, gpA33, HER2, HM1.24, LGR5, MSLN, MCSP, MICA/B, Muc1, Muc16, PDL1, PSMA, PAMA, P-cadherin, ROR1, or VEGF-R2.

9. The cell or population thereof of any one of claims 1-8, wherein the cell further comprises one or more of:

(i) CD38 knockout;

(ii) HLA-I deficiency and/or HLA-II deficiency;

(iii) introduced HLA-G or non-cleavable HLA-G, or knockout of one or both of CD58 and CD54;

(iv) a CD16 or a variant thereof;

(v) a chimeric fusion receptor (CFR);

(vi) a signaling complex comprising a partial or full peptide of a cell surface expressed exogenous cytokine and/or a receptor thereof;

(vii) at least one of the genotypes listed in Table 1;

(viii) deletion or disruption of at least one of B2M, CIITA, TAP1, TAP2, Tapasin, NLRC5, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD25, CD69, CD44, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT; or

(ix) introduction or upregulation of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, and surface triggering receptor for coupling with an agonist.

10. The cell or population thereof of claim 9, wherein the CD16 or a variant thereof comprises at least one of:

(a) a high affinity non-cleavable CD16 (hnCD16);

(b) F176V and S197P in ectodomain domain of CD16;

(c) a full or partial ectodomain originated from CD64;

(d) a non-native (or non-CD16) transmembrane domain;

(e) a non-native (or non-CD16) intracellular domain;

(f) a non-native (or non-CD16) signaling domain;

(g) a non-native stimulatory domain; and

(h) transmembrane, signaling, and stimulatory domains that are not originated from CD16, and are originated from a same or different polypeptide.

11. The cell or population thereof of claim 9, wherein the CFR comprises an ectodomain fused to a transmembrane domain, which is operatively connected to an endodomain, and wherein the ectodomain, transmembrane domain and the endodomain do not comprise any endoplasmic reticulum (ER) retention signals or endocytosis signals.

12. The cell or population thereof of claim 11, wherein:

(i) the ectodomain of the CFR comprises a full or partial length of an extracellular portion of a signaling protein comprising at least one of CD3ε, CD3γ, CD3δ,

CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, any functional variants, and a combination or a chimera thereof;

(ii) the ectodomain of the CFR initiates signal transduction upon binding to a selected agonist; or

(iii) the endodomain of the CFR comprises a cytotoxicity domain comprising at least a full length or a portion of CD3ζ, 2B4, DAP10, DAP12, DNAM1, CD137 (4-1BB), IL21, IL7, IL12, IL15, NKp30, NKp44, NKp46, NKG2C, or NKG2D polypeptide; and optionally wherein the endodomain further comprises one or more of:

(a) a co-stimulatory domain comprising a full length or a portion of CD2, CD27, CD28, CD40L, 4-1BB, OX40, ICOS, PD-1, LAG-3, 2B4, BTLA, DAP10, DAP12, CTLA-4, or NKG2D polypeptide, or any combination thereof;

(b) a co-stimulatory domain comprising a full length or a portion of CD28, 4-1BB, CD27, CD40L, ICOS, CD2, or combinations thereof;

(c) a persistency signaling domain comprising a full length or a portion of an endodomain of a cytokine receptor comprising IL7R, IL15R, IL18R, IL12R, IL23R, or combinations thereof; and/or

(d) a full or a partial intracellular portion of a receptor tyrosine kinase (RTK), a tumor necrosis factor receptor (TNFR), an EGFR or a FAS receptor.

13. The cell or population thereof of claim 12, wherein the selected agonist is (i) an antibody or a functional variant or fragment thereof; or (ii) an engager; and

wherein the selected agonist is encoded by a polynucleotide comprised in the cell or is comprised in a medium comprising the cell or population thereof.

14. The cell or population thereof of claim 9, wherein the cell surface expressed exogenous cytokine or receptor thereof:

(a) comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, and its respective receptor(s); or

(b) comprises at least one of:

(i) co-expression of IL15 and IL15Rα by using a self-cleaving peptide;

(ii) a fusion protein of IL15 and IL15Rα;

(iii) an IL15/IL15Rα fusion protein with intracellular domain of IL15Rα truncated or eliminated;

(iv) a fusion protein of IL15 and membrane bound Sushi domain of IL15Rα;

(v) a fusion protein of IL15 and IL15Rβ;

(vi) a fusion protein of IL15 and common receptor γC, wherein the common receptor γC is native or modified; and

(vii) a homodimer of IL15Rβ,

wherein any one of (b)(i)-(vii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct; or

(c) comprises at least one of:

(i) a fusion protein of IL7 and IL7Rα;

(ii) a fusion protein of IL7 and common receptor γC, wherein the common receptor γC is native or modified; and

(iii) a homodimer of IL7Rβ, wherein any one of (c)(i)-(iii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct;

and optionally,

(d) is transiently expressed.

15. The cell or population thereof of claim 9, wherein the checkpoint inhibitor is an antagonist to one or more checkpoint molecules comprising PD-1, PDL-1, TIM-3, TIGIT, LAG-3, CTLA-4, 2B4, 4-1BB, 4-1BBL, $A_{2A}R$, BATE, BTLA, CD39, CD47, CD73, CD94, CD96, CD160, CD200, CD200R, CD274, CEACAM1, CSF-1R, Foxpl, GARP, HVEM, IDO, EDO, TDO, LAIR-1, MICA/B, NR4A2, MAFB, OCT-2, Rara (retinoic acid receptor alpha), TLR3, VISTA, NKG2A/HLA-E, and an inhibitory KIR.

16. The cell or population thereof of any one of claims 1-15, wherein the cell has therapeutic properties comprising one or more of:

(i) increased cytotoxicity;

(ii) improved persistency and/or survival;

(iii) enhanced ability in migrating, and/or activating or recruiting bystander immune cells, to tumor sites;

(iv) improved tumor penetration;

(v) enhanced ability to reduce tumor immunosuppression;

(vi) improved ability in rescuing tumor antigen escape;

(vii) controlled apoptosis;

(viii) enhanced or acquired ADCC; and

(ix) ability to avoid fratricide,

in comparison to its counterpart primary cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues without the same genetic edit(s).

17. The cell or population thereof of any one of claims 1-16, wherein the derivative cell comprises a derivative $CD34^+$ cell, a derivative hematopoietic stem and progenitor cell, a derivative hematopoietic multipotent progenitor cell, a derivative T cell progenitor, a derivative NK cell progenitor, a derivative T lineage cell, a derivative NKT lineage cell, a derivative NK lineage cell, a derivative B lineage cell, or a derivative effector cell having one or more functional features that are not present in a counterpart primary T, NK, NKT, and/or B cell.

18. The cell or population thereof of claim 17, wherein the derivative effector cell is a hematopoietic cell and comprises longer telomeres in comparison to its counterpart primary cell.

19. The cell or population thereof of any one of claims 1-18, wherein the cell comprises one of the genotypes listed in Table 1; or wherein the cell comprises:

(i) (1) a CD19-CAR at TRAC locus, (2) a TRAC knockout, and (3) a MR1-TCR or a NYESO1-TCR, and optionally (4) a TRBC knockout;

(ii) (1) a BCMA-CAR and hnCD16 insertion at TRAC locus, (2) a TRAC knockout, and (3) a MR1-TCR or NYESO1-TCR, and optionally (4) a TRBC knockout; or

(iii) (1) a MICA/B-CAR insertion at TRAC locus, (2) a TRAC knockout, (3) a hnCD16 insertion at CD38 locus, (4) a CD38 knockout, and (5) a MR1-TCR or NYESO1-TCR, and optionally (6) a TRBC knockout.

20. A composition comprising the cell or population thereof of any one of claims 1-19.

21. The composition of claim 20, wherein the cell or population thereof comprises a derivative effector cell differentiated from the iPSC, and wherein the composition further comprises one or more therapeutic agents.

22. The composition of claim 21, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, an antibody or functional variant or fragment thereof, an engager, a mitogen, a growth factor, a small RNA, a dsRNA (double stranded RNA), mononuclear blood cells, feeder cells, feeder cell components or replacement factors thereof, a vector comprising one or more polynucleic acids of interest, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

23. The composition of claim 22, wherein:

(a) the checkpoint inhibitor comprises:

(i) one or more antagonist checkpoint molecules comprising PD-1, PDL-1, TIM-3, TIGIT, LAG-3, CTLA-4, 2B4, 4-1BB, 4-1BBL, $A_{2A}R$, BATE, BTLA, CD39, CD47, CD73, CD94, CD96, CD160, CD200, CD200R, CD274, CEACAM1, CSF-1R, Foxpl, GARP, HVEM, IDO, EDO, TDO, LAIR-1, MICA/B, NR4A2, MAFB, OCT-2, Rara (retinoic acid receptor alpha), TLR3, VISTA, NKG2A/HLA-E, or an inhibitory KIR;

(ii) one or more of atezolizumab, avelumab, durvalumab, ipilimumab, IPH4102, IPH43, IPH33, lirimumab, monalizumab, nivolumab, pembrolizumab, and their derivatives or functional equivalents; or

(iii) at least one of atezolizumab, nivolumab, and pembrolizumab; or

(b) the one or more therapeutic agents comprise one or more of venetoclax, azacitidine, and pomalidomide.

24. The composition of claim 22, wherein the antibody, or functional variant or fragment thereof comprises:

(a) anti-CD20, anti-CD22, anti-HER2, anti-CD52, anti-EGFR, anti-CD123, anti-GD2, anti-PDL1, and/or anti-CD38 antibody;

(b) one or more of rituximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, ibritumomab, ocrelizumab, inotuzumab, moxetumomab,

epratuzumab, trastuzumab, pertuzumab, alemtuzumab, cetuximab, dinutuximab, avelumab, daratumumab, isatuximab, MOR202, 7G3, CSL362, elotuzumab, and their humanized or Fc modified variants or fragments and their functional equivalents and biosimilars; or

(c) daratumumab, and wherein the derivative effector cell comprises a CD38 knockout, and optionally expresses CD16 or a variant thereof.

25. The composition of claim 22, wherein:

(a) the engager comprises:

(i) a bispecific T cell engager (BiTE);

(ii) a bispecific killer cell engager (BiKE); or

(iii) a tri-specific killer cell engager (TriKE); or

(b) the engager comprises:

(i) a first binding domain recognizing an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof of the cell or a by-stander immune effector cell; and

(ii) a second binding domain specific to an antigen comprising any one of: B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, CD52, CD79a, CD79b, CD123, CD138, CD179b, CEA, CLEC12A, CS-1, DLL3, EGFR, EGFRvIII, EpCAM, FLT-3, FOLR1, FOLR3, GD2, gpA33, HER2, HM1.24, LGR5, MSLN, MCSP, MICA/B, Muc1, Muc16, PDL1, PSMA, PAMA, P-cadherin, ROR1, or VEGF-R2.

26. Use of the composition of any one of claims 20-25 in the manufacture of a medicament for the treatment of an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a viral infection.

27. A master cell bank (MCB) comprising the clonal iPSC of any one of the claims 1-19.

28. A method of manufacturing a derivative cell of any one of the claims 1-19, wherein the derivative cell is a derivative effector cell, the method comprising:

differentiating a genetically engineered iPSC, wherein the iPSC comprises: (a) a polynucleotide encoding a transgenic TCRα chain (tgTCRα); (b) a polynucleotide encoding a

transgenic TCRβ chain (tgTCRβ); and optionally, (c) a polynucleotide encoding a chimeric antigen receptor (CAR) or an engager targeting a second tumor antigen; and optionally wherein the iPSC further comprises one or more of:

(i) CD38 knockout;

(ii) HLA-I deficiency and/or HLA-II deficiency;

(iii) introduced HLA-G or non-cleavable HLA-G, or knockout of one or both of CD58 and CD54;

(iv) a CD16 or a variant thereof;

(v) a chimeric fusion receptor (CFR);

(vi) a signaling complex comprising a partial or full peptide of a cell surface expressed exogenous cytokine and/or a receptor thereof;

(vii) at least one of the genotypes listed in Table 1;

(viii) deletion or disruption of at least one of B2M, CIITA, TAP1, TAP2, Tapasin, NLRC5, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD25, CD69, CD44, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT; or

(ix) introduction or upregulation of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, and surface triggering receptor for coupling with an agonist.

29. The method of claim 28, further comprising:

genomically engineering a clonal iPSC to knock in: (a) the polynucleotide encoding the transgenic TCRα chain (tgTCRα); (b) the polynucleotide encoding the transgenic TCRβ chain (tgTCRβ); and optionally, (c) the polynucleotide encoding the chimeric antigen receptor (CAR) or the engager targeting the second tumor antigen; and optionally further comprising genomically engineering the clonal iPSC:

(i) to knock out CD38,

(ii) to knock out B2M and/or CIITA,

(iii) to knock out one or both of CD58 and CD54, and/or

(iv) to introduce HLA-G or non-cleavable HLA-G, the CD16 or a variant thereof, the CFR, and/or the signaling complex comprising the partial or full peptide of the cell surface expressed exogenous cytokine and/or receptor thereof.

30. The method of claim 29, wherein the genomic engineering comprises targeted editing.

31. The method of claim 30, wherein the targeted editing comprises deletion, insertion, or in/del, and wherein the targeted editing is carried out by CRISPR, ZFN, TALEN, homing nuclease, homology recombination, or any other functional variation of these methods.

32. A chimeric antigen receptor (CAR) specific to tumor cell surface antigen MR1, wherein the MR1-CAR comprises:

(i) an ectodomain comprising at least one antigen recognition domain, wherein the antigen recognition domain comprises:

(a) a variable alpha (Vα) fragment that has at least about 85% identity to SEQ ID NO: 7 (MR1Vα), and a variable beta (Vβ) fragment that has at least about 85% identity to SEQ ID NO: 8 (MR1Vβ); or

(b) an extracellular domain of MR1 TCRα that has at least about 85% identity to SEQ ID NO: 15, and an extracellular domain of MR1 TCRβ that has at least about 85% identity to SEQ ID NO: 16;

(ii) a transmembrane domain; and

(iii) an endodomain comprising at least a first signaling domain, wherein the first signaling domain is originated from a cytoplasmic domain of a signal transducing protein specific to T and/or NK cell activation or functioning; and

wherein the tumor cell surface antigen MR1 is non-polymorphic.

33. The chimeric antigen receptor of claim 32, wherein the signal transducing protein comprises any one of: 2B4 (Natural killer Cell Receptor 2B4), 4-1BB (Tumor necrosis factor receptor superfamily member 9), CD16 (IgG Fc region Receptor III-A), CD2 (T-cell surface antigen CD2), CD28 (T-cell-specific surface glycoprotein CD28), CD28H (Transmembrane and immunoglobulin domain-containing protein 2), CD3ζ (T-cell surface glycoprotein CD3 zeta chain), CD3ζ1XX (CD3ζ variant), DAP10 (Hematopoietic cell signal transducer), DAP12 (TYRO protein tyrosine kinase-binding protein), DNAM1 (CD226 antigen), FcERIγ (High affinity immunoglobulin epsilon receptor subunit gamma), IL21R (Interleukin-21 receptor), IL-2Rβ/IL-15RB (Interleukin-2 receptor subunit beta), IL-2Rγ (Cytokine receptor common subunit gamma), IL-7R (Interleukin-7 receptor subunit alpha), KIR2DS2 (Killer cell immunoglobulin-

like receptor 2DS2), NKG2D (NKG2-D type II integral membrane protein), NKp30 (Natural cytotoxicity triggering receptor 3), NKp44 (Natural cytotoxicity triggering receptor 2), NKp46 (Natural cytotoxicity triggering receptor 1), CS1(SLAM family member 7), and CD8 (T-cell surface glycoprotein CD8 alpha chain).

34. The chimeric antigen receptor of claim 32, wherein the endodomain further comprises a second signaling domain, and optionally a third signaling domain; and wherein the first, second and third signaling domains are different.

35. The chimeric antigen receptor of claim 34, wherein the second or the third signaling domain comprises a cytoplasmic domain, or a portion thereof, of 2B4, 4-1BB, CD16, CD2, CD28, CD28H, CD3ζ, DAP10, DAP12, DNAM1, FcERIγ IL21R, IL-2Rβ (IL-15Rβ), IL-2Rγ, IL-7R, KIR2DS2, NKG2D, NKp30, NKp44, NKp46, CD3ζ1XX, CS1, or CD8.

36. The chimeric antigen receptor of claim 32, wherein the transmembrane domain comprises an amino acid sequence of a transmembrane region, or a portion thereof, of CD2, CD3D, CD3E, CD3G, CD3ζ, CD4, CD8, CD8a, CD8b, CD16, CD27, CD28, CD28H, CD40, CD84, CD166, 4-1BB, OX40, ICOS, ICAM-1, CTLA4, PD1, LAG3, 2B4, BTLA, DNAM1, DAP10, DAP12, FcERIγ, IL7, IL12, IL15, KIR2DL4, KIR2DS1, KIR2DS2, NKp30, NKp44, NKp46, NKG2C, NKG2D, CS1, or a T cell receptor polypeptide.

37. The chimeric antigen receptor of claim 32, wherein the ectodomain further comprises:

(i) a signal peptide; and/or

(ii) a spacer/hinge/linker.

38. The chimeric antigen receptor of claim 32, wherein the CAR is comprised in a bi-cistronic construct co-expressing a partial or full length peptide of a cell surface expressed exogenous cytokine or a receptor thereof, wherein the exogenous cytokine or receptor thereof:

(a) comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, and its respective receptor(s); or

(b) comprises at least one of:

(i) co-expression of IL15 and IL15Rα by using a self-cleaving peptide;

(ii) a fusion protein of IL15 and IL15Rα;

(iii) an IL15/IL15Rα fusion protein with intracellular domain of IL15Rα truncated or eliminated;

(iv) a fusion protein of IL15 and membrane bound Sushi domain of IL15Rα;

(v) a fusion protein of IL15 and IL15Rβ;

(vi) a fusion protein of IL15 and common receptor γC, wherein the common receptor γC is native or modified; and

(vii) a homodimer of IL15Rβ,

wherein any one of (b)(i)-(vii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct; or

(c) comprises at least one of:

(i) a fusion protein of IL7 and IL7Rα;

(ii) a fusion protein of IL7 and common receptor γC, wherein the common receptor γC is native or modified; and

(iii) a homodimer of IL7Rβ.

39. The chimeric antigen receptor of claim 32, wherein the MR1-CAR is specific for one or more of colorectal cancer, lung cancer, kidney cancer, prostrate cancer, bladder cancer, cervical cancer, melanoma, bone cancer, breast cancer, ovarian cancer or blood cancer.

40. A cell or a population thereof, wherein the cell is an eukaryotic cell, an animal cell, a human cell, an immune cell, an induced pluripotent cell (iPSC), a clonal iPSC or a derivative cell differentiated therefrom, and wherein the cell comprises a polynucleotide encoding at least the chimeric antigen receptor (CAR) of any one of claims 32-39.

41. The cell or a population thereof of claim 40, wherein the cell further comprises:

(i) a polynucleotide encoding a transgenic TCRα chain (tgTCRα); and

(ii) a polynucleotide encoding a transgenic TCRβ chain (tgTCRβ), wherein the tgTCRα chain and the tgTCRβ chain form an exogenous TCR complex (TCR^{exo}) that recognizes a first tumor antigen other than MR1; and optionally,

(iii) one or more additional exogenous polynucleotides comprising a polynucleotide encoding an engager targeting at least a second tumor antigen.

42. The cell or population thereof of claim 41, wherein:

(i) the polynucleotide encoding the tgTCRα chain and the polynucleotide encoding the tgTCRβ chain are comprised in a bi-cistronic construct, and optionally wherein:

(a) the construct is inserted at a constant region of TCRα or TCRβ (TRAC or TRBC);

(b) the insertion of the construct disrupts expression of endogenous TCRα or TCRβ at the insertion site; and/or

(c) expression of the construct is driven by an endogenous promoter of TCR or an exogenous promoter; or

(ii) the polynucleotide encoding the CAR or the engager is inserted at TRAC or TRBC, and optionally wherein:

(a) the insertion of the polynucleotide encoding the CAR or the engager disrupts expression of the endogenous TCRα or TCRβ at the insertion site; and/or

(b) expression of the CAR or the engager is driven by an endogenous promoter of TCR or an exogenous promoter; or

(iii) the polynucleotides encoding the tgTCRα chain and the tgTCRβ chain, the CAR or the engager, or the one or more additional polynucleotides are inserted in one, or more safe harbor loci or selected gene loci.

43. The cell or population thereof of claim 42, (I) wherein the construct and the polynucleotide encoding the CAR or the engager are each inserted at a constant region of TCRα or TCRβ (TRAC or TRBC), but not at the same constant region, thereby disrupting expression of both endogenous TCRα and TCRβ, knocking out the endogenous TCR, and avoiding a mispaired TCR comprising:

(a) the transgenic TCRα and the endogenous TCRβ, or

(b) the transgenic TCRβ and the endogenous TCRα;

or (II) wherein the construct and the polynucleotide encoding the CAR or the engager are each integrated at a locus comprising a safe harbor locus or a selected gene locus.

44. A composition comprising the cell or population thereof of any one of claims 40-43.

45. The composition of claim 44, wherein (i) the cell or population thereof comprises the derivative cell, (ii) the derivative cell is a derivative effector cell, and (iii) the composition further comprises one or more therapeutic agents.

46. Use of the composition of claim 44 or 45 in the manufacture of a medicament for the treatment of an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a viral infection.

47. The use of the composition of claim 46, wherein the subject has colorectal cancer, lung cancer, kidney cancer, prostrate cancer, bladder cancer, cervical cancer, stomach cancer, melanoma, bone cancer, breast cancer, ovarian cancer or blood cancer.

48. A method of enhancing a CAR-T cell function, wherein the CAR-T cell has a first tumor antigen specificity via a CAR, and wherein the method comprises introducing to the CAR-T cell:

(i) a polynucleotide encoding a transgenic TCRα chain (tgTCRα); and

(ii) a polynucleotide encoding a transgenic TCRβ chain (tgTCRβ), wherein the tgTCRα chain and the tgTCRβ chain form an exogenous TCR complex (TCR^{exo}) that has a second tumor antigen specificity;

wherein the CAR-induced tumor killing efficacy of the CAR-T cell is enhanced by expression of TCR^{exo}.

49. The method of claim 48, wherein the CAR-T cell comprises:

(i) an endogenous TCR knockout by disrupting expression of both endogenous TCRα and TCRβ; or

(ii) the CAR is inserted at a constant region of TCRα or TCRβ (TRAC or TRBC), thereby disrupting expression of endogenous TCRα or TCRβ of the CAR-T cell.

50. The method of claim 48 or 49, wherein the method further comprises activating TCR^{exo} using the second tumor antigen recognized by TCR^{exo}, wherein the first tumor antigen specificity and the second tumor antigen specificity are different.

51. The method of claim 48, wherein the step of introducing to the CAR-T cell a polynucleotide further comprises:

differentiating a genetically engineered iPSC to a T cell, wherein the iPSC comprises: (a) the polynucleotide encoding a transgenic TCRα chain (tgTCRα); (b) the polynucleotide encoding a transgenic TCRβ chain (tgTCRβ); and (c) a polynucleotide encoding the CAR having the first tumor antigen specificity, thereby obtaining the CAR-T cell having expression of the TCR^{exo}.

52. The method of claim 51, further comprising:

genomically engineering a clonal iPSC to knock in: (a) the polynucleotide encoding the transgenic TCRα chain (tgTCRα); (b) the polynucleotide encoding the transgenic TCRβ chain (tgTCRβ); and (c) the polynucleotide encoding the CAR having the first tumor antigen specificity, thereby obtaining an engineered iPSC for T cell differentiation.

53. The composition of any one of claims 20-25, 44 or 45 for use in therapy.