CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein the cell comprises a polynucleotide encoding a CAR targeting a B7H3 tumor antigen, wherein the CAR comprises a binding domain comprising:

(i) an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 36, 37, 38, 39, 40, or 41;

(ii) an amino acid sequence represented by a variant of SEQ ID NO: 36, and wherein the variant has one or more mutations at positions comprising 1, 40, 46, 79, 87, 88, 89, 97, 98, and 117 of SEQ ID NO: 36;

(iii) an amino acid sequence represented by a variant of SEQ ID NO: 36, wherein the variant has one or more substitutions comprising Q1E, T40A, E46V, G79L, K87R, P88A, D89E, V97A, S98R, and Q117L according to SEQ ID NO: 36; or

(iv) an amino acid sequence represented by any of SEQ ID NOs: 36, 37, 38, 39, 40, and 41; and

wherein the cell is an eukaryotic cell, an animal cell, a human cell, an immune cell, an induced pluripotent cell (iPSC), or a derivative cell differentiated therefrom.

2. The cell or a population thereof of claim 1, wherein the cell further comprises one or more polynucleotides encoding an engager, and optionally a CFR (chimeric fusion receptor), wherein the engager has a tumor antigen targeting specificity that is not B7H3.

3. The cell or a population thereof of claim 2, wherein

(i) the engager comprises a first binding domain having a tumor targeting specificity to any one of ADGRE2, 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 glycoprotein-2 (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, NY-ESO-1, 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;

(ii) the engager comprises a second binding domain having specificity that is different from the specificity of the first binding domain and is to an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof; or the second binding domain of the engager is specific to an ectodomain of the CFR; or

(iii) the engager comprises a cytokine or a variant thereof between the first and the second binding domains, wherein the cytokine comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, and IL21.

4. The cell or a population thereof of claim 2, wherein

(i) 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;

(ii) the CFR comprises an ectodomain that 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;

(iii) the CFR comprises an ectodomain that initiates signal transduction upon binding to a selected agonist;

(iv) the CFR comprises an endodomain that 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 any combination 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; or

(iv) the CFR is co-expressed with the engager or the CAR in separate constructs or in a bicistronic expression cassette.

5. The cell or a population thereof of any of claims 1-4, wherein the cell further comprises one or more of:

(i) CD38 knockout;

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

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

(iv) an exogenous CD16 or a variant thereof;

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

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

(vii) 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

(viii) introduction of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, antigen-specific TCR, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, and

surface triggering receptor for coupling with an agonist, in comparison to its counterpart primary cell.

6. The cell or a population thereof of any of claims 1-5, 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.

7. The cell or a population thereof of claim 6, wherein the exogenous 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.

8. The cell or a population thereof of claim 7, 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) is optionally 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) is optionally co-expressed with a CAR in separate constructs or in a bi-cistronic expression cassete;

and optionally,

(d) is transiently expressed.

9. The cell or a population thereof of claim 7, 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 inhibitory KIR.

10. The cell or a population thereof of claim 1, wherein the cell comprises:

(i) one or more exogenous polynucleotides integrated in a safe harbor locus or a selected gene locus; or

(ii) more than two exogenous polynucleotides integrated in different safe harbor loci or two or more selected gene loci.

11. The cell or a population thereof of claim 10, wherein the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; and wherein 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, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and/or wherein the integration of the exogenous polynucleotides knocks out expression of the gene in the locus.

12. The cell or a population thereof of claim 11, wherein the TCR locus is a constant region of TCR alpha and/or TCR beta (TRAC and/or TRBC).

13. The cell or a population thereof of claim 1, wherein the iPSC is a clonal iPSC, a single cell dissociated iPSC, an iPSC cell line cell, or an iPSC master cell bank (MCB) cell; or 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.

14. A composition comprising the cell or population thereof of any one of claims 1-13.

15. A composition ~~for therapeutic use~~ comprising the derivative cell of any one of claims 1-13, and one or more therapeutic agents.

16. The composition of claim 15, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, 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, an

antibody, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

17. The composition of claim 16, wherein:

(i) the checkpoint inhibitor comprises:

(a) one or more antagonists to 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 inhibitory KIR;

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

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

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

18. The composition of claim 16, wherein the antibody comprises:

(a) anti-CD20, 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, 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 hematopoietic cells comprise derivative NK cells or derivative T cells comprising a CD38 knockout, and optionally an expression of exogenous CD16 or a variant thereof.

19. ~~Therapeutic use~~ Use of the composition of any one of the claims 14-18 in the manufacture of a medicament for the treatment of ~~by introducing the composition to a subject suitable for adoptive cell therapy, wherein the subject has~~ an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

20. A composition comprising a cell or a population thereof, wherein the cell comprises one or more polynucleotides encoding a chimeric antigen receptor (CAR), an engager, and optionally a CFR (chimeric fusion receptor), wherein the CFR is optionally for engager coupling, and wherein the cell is an eukaryotic cell, an animal cell, a human cell, an immune cell, an induced pluripotent cell (iPSC), or a derivative cell differentiated therefrom.

~~21. The composition of claim 20, wherein: (i) the engager has a different tumor targeting specificity from the CAR; or (ii) the engager is co-expressed with the CAR or the CFR.~~

~~22. The compostion of claim 20, 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) co-expressed with another CAR;~~

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

~~(x) co-expressed with a checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct; and/or~~

~~(xi) specific to any one of 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 glycoprotein-2 (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 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, NY-ESO-1, 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 CAR of any one of (i) to (xi) is optionally inserted at TRAC or TRBC locus, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion.~~

~~23~~21. The composition of claim 20, wherein the CAR comprises:

(i) an antigen recognition region specific to B7H3;

(ii) a binding domain comprising an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 36, 37, 38, 39, 40, or 41;

(iii) a binding domain comprising an amino acid sequence represented by a variant of SEQ ID NO: 36, wherein the variant has one or more mutations at positions comprising 1, 40, 46, 79, 87, 88, 89, 97, 98, and 117 of SEQ ID NO: 36;

(iv) a binding domain comprising an amino acid sequence represented by a variant of SEQ ID NO: 36, wherein the variant has one or more substitutions comprising Q1E, T40A, E46V, G79L, K87R, P88A, D89E, V97A, S98R, and Q117L according to SEQ ID NO:36; or

(v) a binding domain comprising an amino acid sequence represented by any of SEQ ID NOs: 36, 37, 38, 39, 40, and 41.

~~24. The composition of claim 20 or 21, wherein:~~

~~(i) the engager comprises a first binding domain having a different tumor targeting specificity from the CAR, and wherein the first binding domain is specific to any one of 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 glycoprotein-2 (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, NY-ESO-1, 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; or~~

~~(ii) the engager comprises a first binding domain having a different tumor targeting specificity from the CAR, and wherein the CAR comprises a binding domain specific to any one of B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, 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, PSMA, PAMA, P-cadherin, or ROR1; or~~

~~(iii) the engager comprises a second binding domain having specificity that is different from the specificity of the first binding domain and is to an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof; or~~

~~(iv) the engager comprises a cytokine or a variant thereof between the first and the second binding domains, wherein the cytokine comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, and IL21.~~

25. The composition of claim 20, wherein the cell further comprises one or more of:

(i) CD38 knockout;

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

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

(iv) an exogenous CD16 or a variant thereof;

(v) a chimeric fusion receptor (CFR);

(vi) an inactivation CAR;

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

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

(ix) 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

(x) introduction of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, antigen-specific TCR, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, and surface triggering receptor for coupling with an agonist, in comparison to its counterpart primary cell.

26. The composition of any one of claims 20-25, 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.~~

~~27. The composition of claim 25, wherein the exogenous 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.~~

~~28~~22. The composition of ~~any one of claims 20-25~~ claim 20 or 21, 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.

~~29~~23. The composition of claim ~~28~~22, 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;

(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; or

(iv) the CFR is co-expressed with the engager in separate constructs or in a bicistronic expression cassette, and optionally the engager has binding specificity to the ectodomain of the CFR.

~~30~~24. The composition of claim ~~29~~23, wherein the selected agonist is (i) an antibody or a functional variant or fragment thereof; (ii) an agonistic ligand; or (iii) an engager; and

wherein the selected agonist:

(a) is encoded by the polynucleotide comprised in the cell of the composition or is comprised in the composition;

(b) comprises at least a first binding domain that is specific to at least one tumor antigen comprising B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, 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, PSMA, PAMA, P-cadherin, or ROR1; and optionally,

(c) comprises a second binding domain that is specific to a cell surface protein of:

(1) the cell of the composition; or

(2) a bystander effector cell;

wherein the cell surface protein comprises an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof.

~~31. The composition of claim 25, wherein the inactivation CAR:~~

(i) targets an upregulated surface protein in activated recipient immune cells; or

(ii) comprises at least one of a CD38-CAR, a CD25-CAR, a CD69-CAR, a CD44-CAR, a 4-1BB-CAR, an OX40-CAR, and a CD40L-CAR.

32. The composition of claim 25, 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) is optionally 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) is optionally co-expressed with a CAR in separate constructs or in a bi-cistronic expression cassette;

and optionally,

(d) is transiently expressed.

33. The composition of claim 25, 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 inhibitory KIR.

34. The composition of claim 20, wherein the cell comprises:

(i) one or more exogenous polynucleotides integrated in a safe harbor locus or a selected gene locus; or

(ii) more than two exogenous polynucleotides integrated in different safe harbor loci or two or more selected gene loci.

35. The composition of claim 34, wherein the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; and wherein 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, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and/or wherein the integration of the exogenous polynucleotides knocks out expression of the gene in the locus.

36. The composition of claim 35, wherein the TCR locus is a constant region of TCR alpha and/or TCR beta (TRAC and/or TRBC).

37. The composition of claim 20, wherein the derivative cell comprises a derivative $CD34^{\pm}$ 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.

38. The composition of claim 20, further comprising one or more therapeutic agents.

39. The composition of claim 38, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, an antibody or functional variant or fragment thereof, 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).~~

~~40. The composition of claim 39, 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 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.~~

~~41. The composition of claim 39, 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.~~

~~42. Therapeutic use of the composition of any one of claims 20-41 by introducing the composition to a subject suitable for adoptive cell therapy, wherein the subject has an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a viral infection.~~

~~43~~25. A method of manufacturing a derivative effector cell comprising a first polynucleotide encoding a chimeric antigen receptor (CAR) and one or more additional polynucleotides encoding one or both of an engager and a CFR, wherein the engager has a different tumor targeting specificity from the CAR, wherein the method comprises:

differentiating a genetically engineered iPSC, wherein the iPSC comprises the first and the one or more additional polynucleotides and optionally one or more genomic edits comprising:

(i) CD38 knockout;

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

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

(iv) an exogenous CD16 or a variant thereof;

(v) a chimeric fusion receptor (CFR);

(vi) an inactivation CAR;

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

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

(ix) 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

(x) introduction of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, antigen-specific TCR, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, and surface triggering receptor for coupling with an agonist, in comparison to its counterpart primary cell.

~~44. The method of claim 43, wherein:~~

~~(i) the engager comprises a first binding domain having a different tumor targeting specificity from the CAR, and wherein the binding domain is specific to any one of 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 glycoprotein-2 (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, NY-ESO-1, 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; or~~

~~(ii) the engager comprises a first binding domain having a different tumor targeting specificity from the CAR, and wherein the binding domain is specific to any one of B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, 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, PSMA, PAMA, P-cadherin, or ROR1; or~~

~~(iii) the engager comprises a second binding domain having specificity that is different from the specificity of the first binding domain and is to an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof; or~~

~~(iv) the engager comprises a cytokine or a variant thereof between the first and the second binding domains, wherein the cytokine comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, and IL21.~~

~~45. The method of claim 43, 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) co-expressed with another 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;~~

~~(x) co-expressed with a checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct; and/or~~

~~(xi) specific to any one of 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 glycoprotein-2 (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 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, NY-ESO-1, 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 optionally,~~

~~wherein the CAR of any one of (i) to (xi) is optionally inserted at a TCR locus, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion.~~

~~46~~26. The method of claim ~~43~~25, wherein the CAR comprises an antigen recognition region specific to B7H3.

~~47. The method of claim 43, wherein the exogenous 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.~~

~~48~~27. The method of claim ~~43~~25, 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.

~~49~~28. The method of claim ~~48~~27, 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.

~~50~~29. The method of claim ~~49~~28, wherein the selected agonist is (i) an antibody or a functional variant or fragment thereof; (ii) an agonistic ligand; or (iii) an engager; and

wherein the selected agonist:

(a) is encoded by the polynucleotide comprised in the cell of the composition or is comprised in the composition;

(b) comprises at least a first binding domain that is specific to at least one tumor antigen comprising B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, 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, PSMA, PAMA, P-cadherin, or ROR1; and optionally,

(c) comprises a second binding domain that is specific to a cell surface protein of:

(1) the cell of the composition; or

(2) a bystander effector cell;

wherein the cell surface protein comprises an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof.

~~51. The method of claim 43, wherein the inactivation CAR:~~

~~(i) targets an upregulated surface protein in activated recipient immune cells; or~~

~~(ii) comprises at least one of a CD38-CAR, a CD25-CAR, a CD69-CAR, a CD44-CAR, a 4-1BB-CAR, an OX40-CAR, and a CD40L-CAR.~~

52. The method of claim 43, 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 inhibitory KIR.

53. The method of claim of claim 43, wherein the iPSC comprises:

(i) one or more exogenous polynucleotides integrated in a safe harbor locus or a selected gene locus; or

(ii) more than two exogenous polynucleotides integrated in different safe harbor loci or two or more selected gene loci.

54. The method of claim 53, wherein the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; and wherein 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, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and/or wherein the integration of the exogenous polynucleotides knocks out expression of the gene in the locus.

55. The method of claim 54, wherein the TCR locus is a constant region of TCR alpha and/or TCR beta (TRAC and/or TRBC).

56. The method of claim 43, wherein the derivative effector 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.

57. The method of claim 43, 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) is optionally co-expressed with the 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) is optionally co-expressed with the CAR in separate constructs or in a bi-cistronic construct;

and optionally,

(d) is transiently expressed.

58. The method of any one of claims 43-57, further comprising genomically engineering a clonal iPSC to knock in polynucleotides encoding the CAR and one or both of the engager and the CFR; and optionally:

(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, a high affinity non-cleavable CD16 or a variant thereof, and/or a partial or full peptide of a cell surface expressed exogenous cytokine and/or a receptor thereof.

59. The method of claim 58, wherein the genomic engineering comprises targeted editing.

60. The method of claim 59, 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.

6130. A method of improving tumor cell control and clearance comprising administering to a subject in need thereof Use of the composition of any one of claims 20-4124 in the manufacture of a medicament for treating a tumor of a subject, optionally wherein the tumor is a solid tumor or the tumor is heterogenous.

62. The method of claim 61, wherein the cells of the composition express an antibody or functional variant or fragment thereof, or an engager.

63. The method of claim 61, wherein the composition comprises an engager.

64. The method of any one of claims 61-63, wherein:

(i) the engager comprises a first binding domain having a different tumor targeting specificity from the CAR, and wherein the binding domain is specific to any one of 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 glycoprotein-2 (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, NY-ESO-1, 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; or

(ii) the engager comprises a first binding domain having a different tumor targeting specificity from the CAR, and wherein the binding domain is specific to any one of B7H3, CD10, CD19, CD20, CD22, CD24, CD30, CD33, CD34, CD38, CD44, 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, PSMA, PAMA, P-cadherin, or ROR1; or

(iii) the engager comprises a second binding domain having specificity that is different from the specificity of the first binding domain and is to an extracellular portion of CD3, CD28, CD5, CD16, CD64, CD32, CD33, CD89, NKG2C, NKG2D, or any functional variants thereof; or

(iv) the engager comprises a cytokine or a variant thereof between the first and the second binding domains, wherein the cytokine comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, and IL21.

65. The method of claim 61, wherein the cells of the composition are iPSC-derived effector cells further comprising one or more of:

(i) a CD38 knockout;

(ii) an exogenous CD16 or a variant thereof;

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

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

(v) a CFR;

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

(vii) an inactivation CAR;

~~(viii) 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; and/or~~

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

~~66. The method of claim 61, wherein administration of the cells of the composition results in 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 administration of their counterpart primary cells.~~

~~67~~31. A chimeric antigen receptor (CAR) comprising a binding domain that comprises:

(i) an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 36, 37, 38, 39, 40, or 41;

(ii) an amino acid sequence represented by a variant of SEQ ID NO: 36, and wherein the variant has one or more mutations at positions comprising 1, 40, 46, 79, 87, 88, 89, 97, 98, and 117 of SEQ ID NO: 36;

(iii) an amino acid sequence represented by a variant of SEQ ID NO: 36, wherein the variant has one or more substitutions comprising Q1E, T40A, E46V, G79L, K87R, P88A, D89E, V97A, S98R, and Q117L according to SEQ ID NO:36; or

(iv) an amino acid sequence represented by any of SEQ ID NOs: 36, 37, 38, 39, 40, and 41.

~~68~~32. The CAR of claim ~~67~~31, further comprising a hinge peptide that comprises no more than 80 amino acids, or comprises between 80 to 180 amino acids, or comprises no more than 229 amino acids.

~~69~~33. The CAR of claim ~~67~~31, wherein the CAR has at least one of the following characteristics:

(i) being T cell specific;

(ii) being NK cell specific;

(iii) binding to tumor cell surface B7H3;

(iv) reducing tumor cell surface shedding of B7H3 antigen; or

(v) increasing tumor cell surface B7H3 density.

~~70~~34. The CAR of claim ~~67~~31, wherein when the CAR is expressed in an effector cell, said effector cell has one or more of the following characteristics:

(i) enhancing effector cell activation and killing function compared to a corresponding effector cell lacking the chimeric receptor; and

(ii) capable of *in vivo* tumor progression control, tumor cell burden reduction, tumor clearance, and/or improving rate of survival of a subject carrying the tumor compared to a corresponding cell lacking the chimeric receptor.

~~71~~35. A method of manufacturing the derivative cell comprising a polynucleotide encoding the CAR of any one of claims ~~67-69~~ 31-34, wherein the method comprises differentiating an iPSC to obtain the derivative cells, wherein the polynucleotide encoding the CAR is introduced into the iPSC before differentiation or is introduced to the derivative cells after iPSC differentiation.

36. The composition of any one of claims 14-18 and 20-24 for use in therapy.