CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein:

(i) the cell is (a) an induced pluripotent cell (iPSC); or (b) a derivative effector cell obtained from differentiating the iPSC; and

(ii) the cell comprises:

an exogenous polynucleotide encoding a CXCR2; and optionally

a chimeric antigen receptor (CAR).

2. 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 (i) 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, or a derivative B lineage cell; or (ii) the derivative cell comprises 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.

3. The cell or population thereof of claim 1, 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;

(iv) an exogenous CD16 or variant thereof;

(v) a cytokine 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 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, an engager, and surface triggering receptor for coupling with an agonist.

4. The cell or population thereof of claim 3, 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).

5. The cell or population thereof of claim 3, 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.

6. The cell or population thereof of any one of claims 1-5, 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 cytokine signaling complex comprising 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;

(xi) specific to at least one of CD19, BCMA, CD20, CD22, CD38, CD123, HER2, CD52, EGFR, GD2, MICA/B, MSLN, VEGF-R2, PSMA and PDL1; and/or

(xii) specific 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, Mucin 1 (Muc-1), Mucin 16 (Muc-16), Mesothelin (MSLN), NKCSI, NKG2D ligands, c-Met, cancer-testis antigen

NY-ESO-1, oncofetal antigen (h5T4), PRAME, prostate stem cell antigen (PSCA), PRAME prostate-specific membrane antigen (PSMA), tumor-associated glycoprotein 72 (TAG-72), TIM-3, TRBCI, 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 (xii) is inserted at a TCR locus, and/or is driven by an endogenous promoter of the TCR, and/or the TCR is knocked out by the CAR insertion.

7. The cell or population thereof of claim 3, wherein the cytokine signaling complex:

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

(b) comprises at least one of:

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

(ii) a fusion protein of IL15 and IL15Rα;

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

(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) is optionally co-expressed with a CAR in separate constructs or in a bi-cistronic expression cassette;

and optionally,

(d) is transiently expressed.

8. The cell or population thereof of claim 1, wherein the cell is an NK lineage cell or a T lineage cell, wherein:

(i) the NK lineage cell or the T lineage cell has improved infiltration and/or retention at tumor sites;

(ii) the NK lineage cell is capable of recruiting, and/or migrating T cells to tumor sites; or

(iii) the NK lineage cell or the T lineage cell is capable of reducing tumor immunosuppression in the presence of one or more checkpoint inhibitors.

9. The cell or population thereof of claim 6 or 8, wherein the checkpoint inhibitors are antagonists 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, or inhibitory KIR.

10. The cell or population thereof of any one of claims 1-5, 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 population thereof of claim 10, wherein the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; or 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, CD69, CD71, 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 population thereof of claim 11, wherein the TCR locus is a constant region of TCR alpha and/or TCR beta.

13. A method for improving T lineage cell migration and/or tumor cell control and clearance, the method comprising:

obtaining a T lineage cell comprising an exogenous polynucleotide encoding a CXCR2, and

expanding the T lineage cell, thereby producing a T lineage cell population having improved cell migration and/or tumor cell control and clearance as compared to counterpart cells without the exogenous polynucleotide encoding the CXCR2,

wherein the T lineage cell: (i) is derived from an iPSC, or (ii) further comprises a chimeric antigen receptor (CAR).

14. The method of claim 13, wherein the step of obtaining comprises (I) or (II):

(I)

(i) engineering an induced pluripotent cell (iPSC) to produce a genomically edited iPSC that comprises one or more exogenous polynucleotides encoding the CXCR2 and optionally a CAR; and

(ii) differentiating the genomically edited iPSC to a derivative T lineage cell comprising the CXCR2 and optionally the CAR; or

(II)

engineering a T lineage cell by introducing a polynucleotide encoding the CXCR2 to the T lineage cell to produce a genomically edited T lineage cell that comprises the CXCR2 and the CAR.

15. The method of claim 14, wherein the genomically edited iPSC further comprises one or more edits resulting in:

(i) CD38 knockout;

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

(iii) introduction of HLA-G or non-cleavable HLA-G;

(iv) introduction of an exogenous CD16 or a variant thereof;

(v) a cytokine 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, an engager, and surface triggering receptor for coupling with an agonist,

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

16. A composition comprising the cell or population thereof of any one of the claims 1-12.

17. The composition of claim 16, further comprising one or more therapeutic agents.

18. The composition of claim 17, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, an effector, 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).

19. The composition of claim 18, 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 therapeutic agents comprise one or more of venetoclax, azacitidine, and pomalidomide.

20. The composition of claim 18, wherein the antibody, or functional variant or fragment thereof comprises:

(a) an anti-CD20, an anti-HER2, an anti-CD52, an anti-EGFR, an anti-CD123, an anti-GD2, an anti-PDL1, and/or an 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 an expression of CD16 or a variant thereof.

21. The composition of claim 16, further comprising a sensitizing agent.

22. The composition of claim 21, wherein:

(i) the sensitizing agent comprises at least one of a chemotherapeutic agent, external beam radiation, brachytherapy, and a radiopharmaceutical;

(ii) the sensitizing agent increases chemokine secretion and/or surface expression by a tumor cell upon contact therewith;

(iii) the sensitizing agent comprises at least one of calcium-47, carbon-11, carbon-14, chromium-51, cobalt-57, cobalt-58, erbium-169, fluorine-18, gallium-67, gallium-68, hydrogen-3, indium-111, iodine-123, iodine-125, iodine-131, iorn-59, krypton-81m, lutetium-177, nitrogen-13, oxygen-15, phosphorus-32, radium-223, rubidium-82, samarium-153, selenium-75, sodium-22, sodium-24, strontium-89, technetium-99m, thallium-201, xenon-133, and yttrium-90;

(iv) the sensitizing agent comprises paclitaxel; or

(v) the sensitizing agent comprises cyclophosphamide and fludarabine (Cy/Flu).

23. A master cell bank (MCB) comprising a clonal iPSC of any one of the claims 1-12.

24. A method of manufacturing a derivative effector cell comprising a CXCR2, wherein the method comprises differentiating a genetically engineered iPSC to the derivative effector cell, wherein the genetically engineered iPSC comprises an exogenous polynucleotide encoding the CXCR2 and optionally one or more edits resulting in:

(i) a CAR;

(ii) exogenous CD16 or a variant thereof;

(iii) CD38 knockout;

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

(v) introduction of HLA-G or non-cleavable HLA-G;

(vi) a cytokine 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) disruption of 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 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, an engager, and surface triggering receptor for coupling with an agonist.

25. The method of claim 24, 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 (i) 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, or a derivative B lineage cell; or (ii) the derivative cell comprises 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.

26. The method of claim 24, wherein the exogenous CD16 or 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.

27. The method of claim 24, 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 cytokine signaling complex comprising 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;

(xi) specific to at least one of CD19, BCMA, CD20, CD22, CD38, CD123, HER2, CD52, EGFR, GD2, MICA/B, MSLN, VEGF-R2, PSMA and PDL1; and/or

(xii) specific 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 A1 (MAGE-A1), MICA/B, Mucin 1 (Muc-1), Mucin 16 (Muc-16), Mesothelin (MSLN), NKCSI, NKG2D ligands, c-Met, cancer-testis antigen NY-ESO-1, oncofetal antigen (h5T4), PRAME, prostate stem cell antigen (PSCA), PRAME prostate-specific membrane antigen (PSMA), tumor-associated glycoprotein 72 (TAG-72), TIM-3, TRBCI, 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 (xii) is 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.

28. The method of claim 24, further comprising genomically engineering a clonal iPSC to knock-in a polynucleotide encoding the CXCR2; and optionally:

(i) to knock out CD38,

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

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

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

29. A method of producing a clonal master engineered iPSC line using CRISPR, ZFN, or TALEN mediated editing of clonal iPSCs, wherein the editing comprises a knock-in of a polynucleotide encoding a CXCR2 and optionally a CAR, thereby producing the engineered iPSCs.

30. The composition of any one of claims 16-22 for use in therapy.

31. Use of the composition of any one of claims 16-22 in the manufacture of a medicament for treating a tumor of a subject, wherein the composition is to be administered to the subject, and wherein the tumor comprises tumor cells preconditioned with a sensitizing agent.

32. The use of claim 31, wherein one or more therapeutic agents is to be further administered to the subject.

33. The use of claim 31, wherein:

(i) the sensitizing agent comprises at least one of a chemotherapeutic agent, external beam radiation, brachytherapy, and a radiopharmaceutical;

(ii) the sensitizing agent increases secretion and/or surface expression of a chemokine that binds to CXCR2, by a tumor cell upon contact therewith;

(iii) the sensitizing agent comprises at least one of x-ray radiation, gamma radiation, photon radiation, proton radiation, and neutron radiation;

(iv) the sensitizing agent comprises at least one of calcium-47, carbon-11, carbon-14, chromium-51, cobalt-57, cobalt-58, erbium-169, fluorine-18, gallium-67, gallium-68, hydrogen-3, indium-111, iodine-123, iodine-125, iodine-131, iorn-59, krypton-81m, lutetium-177, nitrogen-13, oxygen-15, phosphorus-32, radium-223, rubidium-82, samarium-153, selenium-75, sodium-22, sodium-24, strontium-89, technetium-99m, thallium-201, xenon-133, and yttrium-90

(v) the sensitizing agent comprises paclitaxel; or

(vi) the sensitizing agent comprises cyclophosphamide and fludarabine (Cy/Flu).