CLAIMS

What is claimed is:

1. A composition comprising two or more cell populations, wherein the composition comprises:

(i) a first cell population comprising induced pluripotent stem cell (iPSC)-derived NK cells, wherein the iPSC-derived NK cells comprise:

(a) an exogenous CD16; and

(b) a first chimeric antigen receptor (CAR); and

(ii) a second cell population comprising iPSC-derived T cells, wherein the iPSC-derived T cells comprise: at least a second chimeric antigen receptor (CAR), and wherein the second CAR is expressed under control of an endogenous promoter of a TCR locus.

2. The composition of claim 1, wherein the exogenous CD16 is a high affinity non-cleavable exogenous CD16 (hnCD16); or wherein the exogenous CD16 comprises at least one of:

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

(b) an ectodomain of CD64;

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

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

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

(f) a non-native stimulatory domain; and

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

3. The composition of claim 2, wherein:

(a) the non-native transmembrane domain is derived from CD3D, CD3E, CD3G, CD3ζ, CD4, CD8, CD8a, CD8b, CD27, CD28, CD40, CD84, CD166, 4-1BB, OX40, ICOS, ICAM-1, CTLA-4, PD-1, LAG-3, 2B4, BTLA, CD16, IL7, IL12, IL15, KIR2DL4, KIR2DS1, NKp30, NKp44, NKp46, NKG2C, NKG2D, or T cell receptor (TCR) polypeptide;

(b) the non-native stimulatory domain is derived from CD27, CD28, 4-1BB, OX40, ICOS, PD-1, LAG-3, 2B4, BTLA, DAP10, DAP12, CTLA-4, or NKG2D polypeptide;

(c) the non-native signaling domain is derived from CD3ζ, 2B4, DAP10, DAP12, DNAM1, CD137 (4-1BB), IL21, IL7, IL12, IL15, NKp30, NKp44, NKp46, NKG2C, or NKG2D polypeptide; or

(d) the non-native transmembrane domain is derived from NKG2D, the non-native stimulatory domain is derived from 2B4, and the non-native signaling domain is derived from CD3ζ.

4. The composition of claim 1, wherein the first CAR and the second CAR are the same or are different in targeting specificity, and wherein the first CAR or the second 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 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 CD19 or BCMA; 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 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-a, Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER-2), 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, TRBC1, TRBC2, vascular endothelial growth factor R2 (VEGF- R2), Wilms tumor protein (WT-1), and a pathogen antigen.

5. The composition of claim 1, wherein the iPSC-derived NK cells comprise a cell surface expressed exogenous cytokine and/or a receptor thereof, and further wherein the cell surface expressed exogenous cytokine and/or a receptor thereof:

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

(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; and

(vii) a homodimer of IL15Rβ; wherein any one of (i)-(vii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct;

and optionally,

(c) is transiently expressed.

6. The composition of claim 1, wherein the iPSC-derived NK cells and/or the iPSC-derived T cells further comprise one or more of:

(i) HLA-I deficiency;

(ii) HLA-II deficiency;

(iii) introduced expression of HLA-G or non-cleavable HLA-G;

(iv) at least one of lig^-, inR^+, $cs\text{-}CD3^+$, En^+, and Ab^+; wherein

(1) lig^- is negative in an expressed alloantigen;

(2) inR^+ is positive in an expressed CAR specific to the negative alloantigen;

(3) $cs\text{-}CD3^+$ is positive in cell surface expressed CD3;

(4) En^+ is positive in at least one expressed engager, wherein the engager comprises a bi-specific T cell engager (BiTE), or a tri-specific killer cell engager (TriKE); and

(5) Ab^+ is positive in at least one expressed antibody or checkpoint inhibitor;

(v) deletion or reduced expression in at least one of B2M, CIITA, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, RFX5, RAG1, RFXAP, and any gene in the chromosome 6p21 region; and

(vi) introduced or increased expression in at least one of HLA-E, HLA-G, 41BBL, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, TCR, and Fc receptor.

7. The composition of claim 6, wherein:

(i) the alloantigen comprises CD40L, OX40, or 4-1BB;

(ii) the CAR specific to the negative alloantigen comprises CD40L-CAR, OX40-CAR, or 4-1BB-CAR;

(iii) the BiTE or the TriKE recognizes (a) an immune cell surface molecule comprising CD3, CD28, CD5, CD16, NKG2D, CD64, CD32, CD89, NKG2C, or a chimeric Fc receptor thereof; and (b) a tumor surface molecule comprising B7H3, BCMA, 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;

(iv) the BiTE comprises CD3-CD19, CD16-CD30, CD64-CD30, CD16-BCMA, CD64-BCMA, or CD3-CD33;

(v) the TriKE comprises CD16-IL15-EPCAM, CD64-IL15-EPCAM, CD16-IL15-CD33, CD64-IL15-CD33, or NKG2C-IL15-CD33;

(vi) the antibody comprises an anti-CD20, anti-HER2, anti-CD52, anti-EGFR, anti-CD123, anti-GD2, anti-PDL1, or anti-CD38 antibody; or

(vii) the checkpoint inhibitor comprises (a) an antagonist to a checkpoint molecule 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 of atezolizumab, avelumab, durvalumab, ipilimumab, IPH4102,

IPH43, IPH33, lirimumab, monalizumab, nivolumab, and pembrolizumab; or (c) one of atezolizumab, nivolumab, and pembrolizumab.

8. The composition of claim 1, wherein the iPSC-derived NK cells or the iPSC-derived T cells comprise:

(i) one or more exogenous polynucleotides integrated in one desired integration site; or

(ii) more than two exogenous polynucleotides integrated in different desired integration sites.

9. The composition of claim 8, wherein the desired integration site comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, RUNX1, B2M, TAP1, TAP2, tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD25, CD38, CD40L, CD44, CD54, CD56, CD58, CD69, CD71, OX40, 4-1BB, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT.

10. The composition of claim 8, wherein the desired integration site comprises TCR α or β constant region, CD25, CD38, CD40L, CD44, CD54, CD58, CD69, CD71, OX40 or 4-1BB; and optionally, wherein the TCRα or TCRβ, CD25, CD38, CD40L, CD44, CD54, CD58, CD69, CD71, OX40 or 4-1BB is knocked out as a result of integrating said one or more exogenous polynucleotides at the respective integration site.

11. The composition of claim 1, wherein the iPSC-derived NK cells or the iPSC-derived T cells comprise longer telomeres in comparison to their respective native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues.

12. The composition of claim 1, wherein the iPSC-derived NK cells comprise type I NKT cells, and/or adaptive NK cells; or wherein the iPSC-derived T cells comprise naïve T cells, stem cell memory T cells, and/or central memory T cells.

13. The composition of claim 1, wherein

(i) the iPSC-derived NK cells and the iPSC-derived T cells are in a ratio ranging from 100:1 to 1:100;

(ii) the composition further comprises one or more additional cell populations; or

(iii) the composition further comprises one or more therapeutic agents.

14. The composition of claim 13, wherein the additional cell population comprises regulatory cells.

15. The composition of claim 14, wherein the regulatory cells are iPSC-derived immune regulatory cells or myeloid derived suppressor cells (MDSCs).

16. The composition of claim 13, 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, 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 the checkpoint inhibitor comprises:

(a) one or more antagonist 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, and pembrolizumab; or

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

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 retuximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, trastuzumab, pertuzumab, alemtuzumab, certuximab, dinutuximab, avelumab, daratumumab, isatuximab, MOR202, 7G3, CSL362, and elotuzumab; or

(c) daratumumab.

19. The composition of any one of the claims 1-18 for use in treating a subject, wherein the subject has an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

20. A method of improving tumor killing and/or clearance activity of a population of CAR-T cells, the method comprising:

contacting a cell population comprising iPSC-derived NK cells to the population of CAR-T cells *in vitro* to obtain a combined cell population,

wherein the iPSC-derived NK cells comprise:

(a) an exogenous CD16; and

(b) a first chimeric antigen receptor (CAR); and wherein the first CAR of the iPSC-derived NK cells comprise a CAR targeting specificity that is same or different from that of the CAR-T cell.

21. The method of claim 20, wherein the exogenous CD16 is a high affinity non-cleavable exogenous CD16 (hnCD16); or wherein the exogenous CD16 comprises at least one of:

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

(b) an ectodomain of CD64;

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

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

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

(f) a non-native stimulatory domain; and

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

22. The method of claim 21, wherein

(a) the non-native transmembrane domain is derived from CD3D, CD3E, CD3G, CD3ζ, CD4, CD8, CD8a, CD8b, CD27, CD28, CD40, CD84, CD166, 4-1BB, OX40, ICOS, ICAM-1, CTLA-4, PD-1, LAG-3, 2B4, BTLA, CD16, IL7, IL12, IL15, KIR2DL4, KIR2DS1, NKp30, NKp44, NKp46, NKG2C, NKG2D, or T cell receptor (TCR) polypeptide;

(b) the non-native stimulatory domain is derived from CD27, CD28, 4-1BB, OX40, ICOS, PD-1, LAG-3, 2B4, BTLA, DAP10, DAP12, CTLA-4, or NKG2D polypeptide;

(c) the non-native signaling domain is derived from CD3ζ, 2B4, DAP10, DAP12, DNAM1, CD137 (4-1BB), IL21, IL7, IL12, IL15, NKp30, NKp44, NKp46, NKG2C, or NKG2D polypeptide; or

(d) the non-native transmembrane domain is derived from NKG2D, the non-native stimulatory domain is derived from 2B4, and the non-native signaling domain is derived from CD3ζ.

23. The method of claim 20, wherein the iPSC-derived NK cells comprise a cell surface expressed exogenous cytokine and/or a receptor thereof, and further wherein the cell surface expressed exogenous cytokine and/or a receptor thereof:

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

(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; and

(vii) a homodimer of IL15Rβ; wherein any one of (i)-(vii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct;

and optionally,

(c) is transiently expressed.

24. The method of claim 20, wherein the CAR-T cells are differentiated from an engineered iPSC, and/or wherein the CAR-T cells comprise a CAR having 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 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-a, Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER-2), 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, TRBC1, TRBC2, vascular endothelial growth factor R2 (VEGF- R2), Wilms tumor protein (WT-1), and a pathogen antigen.

25. The method of claim 20, wherein the iPSC-derived NK cells and/or the CAR-T cells further comprise one or more of:

(i) HLA-I deficiency;

(ii) HLA-II deficiency;

(iii) introduced expression of HLA-G or non-cleavable HLA-G;

(iv) at least one of lig^-, inR^+, $cs\text{-}CD3^+$, En^+, and Ab^+; wherein

(1) lig^- is negative in an expressed alloantigen;

(2) inR^+ is positive in an expressed CAR specific to the negative alloantigen;

(3) $cs\text{-}CD3^+$ is positive in cell surface expressed CD3;

(4) En^+ is positive in at least one expressed engager, wherein the engager comprises a bi-specific T cell engager (BiTE), or a tri-specific killer cell engager (TriKE); and

(5) Ab^+ is positive in at least one expressed antibody or checkpoint inhibitor;

(v) deletion or reduced expression in at least one of B2M, CIITA, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, RFX5, RAG1, RFXAP, and any gene in the chromosome 6p21 region; and

(vi) introduced or increased expression in at least one of HLA-E, HLA-G, 4-1BBL, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, TCR, Fc receptor, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers.

26. The method of claim 25, wherein

(i) the alloantigen comprises CD40L, OX40, or 4-1BB;

(ii) the CAR specific to the negative alloantigen comprises CD40L-CAR, OX40-CAR, or 4-1BB-CAR;

(iii) the BiTE or the TriKE recognizes (a) an immune cell surface molecule comprising CD3, CD28, CD5, CD16, NKG2D, CD64, CD32, CD89, NKG2C, or a chimeric Fc receptor thereof; and (b) a tumor surface molecule comprising B7H3, BCMA, 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;

(iv) the BiTE comprises CD3-CD19, CD16-CD30, CD64-CD30, CD16-BCMA, CD64-BCMA, or CD3-CD33;

(v) the TriKE comprises CD16-IL15-EPCAM, CD64-IL15-EPCAM, CD16-IL15-CD33, CD64-IL15-CD33, or NKG2C-IL15-CD33;

(vi) the antibody comprises an anti-CD20, anti-HER2, anti-CD52, anti-EGFR, anti-CD123, anti-GD2, anti-PDL1, or anti-CD38 antibody; or

(vii) the checkpoint inhibitor comprises (a) an antagonist to a checkpoint molecule 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 of atezolizumab, avelumab, durvalumab, ipilimumab, IPH4102, IPH43, IPH33, lirimumab, monalizumab, nivolumab, and pembrolizumab; or (c) one of atezolizumab, nivolumab, and pembrolizumab.

27. The method of claim 26, further comprising combining the population of CAR-T cells *in vitro* with one or more therapeutic agents, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, an antibody, a mitogen, a growth factor, a small RNA, a dsRNA (double stranded RNA), mononuclear blood cells, feeder cells, a vector comprising one or more polynucleic acids of interest, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

28. The method of claim 27, wherein the checkpoint inhibitor comprises:

(a) one or more antagonist 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, and pembrolizumab; or

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

29. The method of claim 27, 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 retuximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, trastuzumab, pertuzumab, alemtuzumab, certuximab, dinutuximab, avelumab, daratumumab, isatuximab, MOR202, 7G3, CSL362, and elotuzumab; or

(c) daratumumab.

30. A method of manufacturing the composition of claim 1, comprising:

(I) differentiating a first genetically engineered iPSC to obtain a first cell population comprising iPSC-derived NK cells, wherein the first iPSC comprises a polynucleotide encoding (a) an exogenous CD16; and (b) a first chimeric antigen receptor (CAR), wherein the iPSC-derived NK cells comprise (a) and (b);

(II) differentiating a second genetically engineered iPSC to obtain a second cell population comprising iPSC-derived T cells, wherein the second iPSC comprises a polynucleotide encoding at least a second chimeric antigen receptor (CAR), wherein the second CAR is expressed under the control of an endogenous promoter of a TCR locus, and wherein the iPSC-derived T cells comprise the second CAR; and

(III) combining the first cell population and the second cell population into a mixed population,

thereby manufacturing the composition of claim 1.

31. The method of claim 30, wherein the exogenous CD16 is a high affinity non-cleavable exogenous CD16 (hnCD16); or wherein the exogenous CD16 comprises at least one of:

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

(b) an ectodomain of CD64;

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

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

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

(f) a non-native stimulatory domain; and

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

32. The method of claim 31, wherein:

(a) the non-native transmembrane domain is derived from CD3D, CD3E, CD3G, CD3ζ, CD4, CD8, CD8a, CD8b, CD27, CD28, CD40, CD84, CD166, 4-1BB, OX40, ICOS, ICAM-1, CTLA-4, PD-1, LAG-3, 2B4, BTLA, CD16, IL7, IL12, IL15, KIR2DL4, KIR2DS1, NKp30, NKp44, NKp46, NKG2C, NKG2D, or T cell receptor (TCR) polypeptide;

(b) the non-native stimulatory domain is derived from CD27, CD28, 4-1BB, OX40, ICOS, PD-1, LAG-3, 2B4, BTLA, DAP10, DAP12, CTLA-4, or NKG2D polypeptide;

(c) the non-native signaling domain is derived from CD3ζ, 2B4, DAP10, DAP12, DNAM1, CD137 (4-1BB), IL21, IL7, IL12, IL15, NKp30, NKp44, NKp46, NKG2C, or NKG2D polypeptide; or

(d) the non-native transmembrane domain is derived from NKG2D, the non-native stimulatory domain is derived from 2B4, and the non-native signaling domain is derived from CD3ζ.

33. The method of claim 30, wherein the first CAR and the second CAR are the same in targeting specificity, and the first CAR or the second 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 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 CD19 or BCMA; 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 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-a, Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER-2), 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, TRBC1, TRBC2, vascular endothelial growth factor R2 (VEGF- R2), Wilms tumor protein (WT-1), and a pathogen antigen.

34. The method of claim 30, wherein the iPSC-derived NK cells comprise a cell surface expressed exogenous cytokine and/or a receptor thereof, and further wherein the cell surface expressed exogenous cytokine and/or a receptor thereof:

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

(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; and

(vii) a homodimer of IL15Rβ; wherein any one of (i)-(vii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct;

and optionally,

(c) is transiently expressed.

35. The method of claim 30, wherein the first genetically engineered iPSC or the second genetically engineered iPSC further comprises one or more of:

(i) HLA-I deficiency;

(ii) HLA-II deficiency;

(iii) introduced expression of HLA-G or non-cleavable HLA-G;

(iv) at least one of lig^-, inR^+, $cs\text{-}CD3^+$, En^+, and Ab^+; wherein

(1) lig^- is negative in an expressed alloantigen;

(2) inR^+ is positive in an expressed CAR specific to the negative alloantigen;

(3) $cs\text{-}CD3^+$ is positive in cell surface expressed CD3;

(4) En^+ is positive in at least one expressed engager, wherein the engager comprises a bi-specific T cell engager (BiTE), or a tri-specific killer cell engager (TriKE); and

(5) Ab^+ is positive in at least one expressed antibody or checkpoint inhibitor;

(v) deletion or reduced expression in at least one of B2M, CIITA, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, RFX5, RAG1, RFXAP, and any gene in the chromosome 6p21 region; and

(vi) introduced or increased expression in at least one of HLA-E, HLA-G, 41BBL, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, TCR, Fc receptor, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers.

36. The method of claim 35, wherein

(i) the alloantigen comprises CD40L, OX40, or 4-1BB;

(ii) the CAR specific to the negative alloantigen comprises CD40L-CAR, OX40-CAR, or 4-1BB-CAR;

(iii) the BiTE or the TriKE is specific to (a) an immune cell surface molecule comprising CD3, CD28, CD5, CD16, NKG2D, CD64, CD32, CD89, NKG2C, or a chimeric Fc receptor thereof; and (b) a tumor surface molecule comprising B7H3, BCMA, 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;

(iv) the BiTE comprises CD3-CD19, CD16-CD30, CD64-CD30, CD16-BCMA, CD64-BCMA, or CD3-CD33;

(v) the TriKE comprises CD16-IL15-EPCAM, CD64-IL15-EPCAM, CD16-IL15-CD33, CD64-IL15-CD33, or NKG2C-IL15-CD33;

(vi) the antibody comprises an anti-CD20, anti-HER2, anti-CD52, anti-EGFR, anti-CD123, anti-GD2, anti-PDL1, or anti-CD38 antibody; or

(vii) the checkpoint inhibitor comprises (a) an antagonist to a checkpoint molecule 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 of atezolizumab, avelumab, durvalumab, ipilimumab, IPH4102, IPH43, IPH33, lirimumab, monalizumab, nivolumab, and pembrolizumab; or (c) one of atezolizumab, nivolumab, and pembrolizumab.

37. The method of claim 30, wherein the first genetically engineered iPSC or the second genetically engineered iPSC comprise:

(i) one or more exogenous polynucleotides integrated in one desired integration site; or

(ii) more than two exogenous polynucleotides integrated in different desired integration sites.

38. The method of claim 37, wherein the desired integration site comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, RUNX1, B2M, TAP1, TAP2, tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD25, CD38, CD40L, CD44, CD54, CD56, CD58, CD69, CD71, OX40, 4-1BB, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT.

39. The method of claim 37, wherein the desired integration site comprises TCR α or β constant region, CD25, CD38, CD40L, CD44, CD54, CD58, CD69, CD71, OX40 or 4-1BB; and optionally, wherein the TCRα or TCRβ, CD25, CD38, CD40L, CD44, CD54, CD58,

CD69, CD71, OX40 or 4-1BB is knocked out as a result of integrating said one or more exogenous polynucleotides at the respective integration site.

40. The method of claim 30, wherein the iPSC-derived NK cells comprise type I NKT cells, and/or adaptive NK cells; or wherein the iPSC-derived T cells comprise naïve T cells, stem cell memory T cells, and/or central memory T cells.

41. The method of claim 30, wherein:

(i) the iPSC-derived NK cells and the iPSC-derived T cells are in a ratio ranging from 100:1 to 1:100;

(ii) the method further comprises adding one or more additional cell populations to the produced first and second cell populations; or

(iii) the method further comprises adding one or more therapeutic agents to the produced first and second cell populations.

42. The method of claim 41, wherein the one or more additional cell populations comprise regulatory cells.

43. The method of claim 42, wherein the regulatory cells are iPSC-derived immune regulatory cells or myeloid derived suppressor cells (MDSCs).

44. The method of claim 41, 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, a vector comprising one or more polynucleic acids of interest, an antibody, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

45. The method of claim 44, wherein the checkpoint inhibitor comprises:

(a) one or more antagonist 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, and pembrolizumab; or

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

46. The method of claim 44, 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 retuximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, trastuzumab, pertuzumab, alemtuzumab, certuximab, dinutuximab, avelumab, daratumumab, isatuximab, MOR202, 7G3, CSL362, and elotuzumab; or

(c) daratumumab.