CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein

(i) the cell is (a) an induced pluripotent cell (iPSC), a clonal iPSC, or an iPS cell line cell; or (b) a derivative cell obtained from differentiating the cell of (a); and

(ii) the cell comprises a CD38 knockout or a polynucleotide encoding an IL15/IL15Rα fusion protein without an intracellular domain (IL15Δ).

2. The cell or population thereof of claim 1, wherein the derivative cell of (i)(b) is a hematopoietic cell, and comprises longer telomeres in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues.

3. The cell or population thereof of claim 1, wherein the cell further comprises one or more of:

(i) B2M null or low;

(ii) CIITA null or low;

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

(iv) a high affinity non-cleavable CD16 (hnCD16) or a variant thereof;

(v) a chimeric antigen receptor (CAR),

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

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

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

(ix) introduced or increased expression in at least one of HLA-E, 41BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, CAR, TCR, Fc receptor, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers.

4. The cell or population thereof of claim 1 or 3, wherein the cell is a derivative NK or a derivative T cell, and has at least one of the following characteristics comprising:

(i) improved persistency and/or survival;

(ii) increased resistance to native immune cells;

(iii) increased cytotoxicity;

(iv) improved tumor penetration;

(v) enhanced or acquired ADCC;

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

(vii) enhanced ability to reduce tumor immunosuppression;

(viii) improved ability in rescuing tumor antigen escape; and

(ix) reduced fratricide,

in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues.

5. The cell or population thereof of claim 3, wherein the cell further comprises a high affinity non-cleavable CD16 (hnCD16) or a variant thereof.

6. The cell or population thereof of claim 5, wherein the high affinity non-cleavable CD16 (hnCD16) or a variant thereof comprises at least one of:

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

(b) a full or partial ectodomain originated from 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.

7. The cell or population thereof of claim 6, 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 (41BB), 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.

8. The cell or population thereof of claim 3, wherein the cell further comprises a chimeric antigen receptor (CAR), and wherein the CAR is:

(i) T cell specific or NK cell specific;

(ii) 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;

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

(xii) specific to CD19 or BCMA; and/or

(xiii) specific to any one of ADGRE2, carbonic anhydrase IX (CAlX), CCRI, 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, TRBCI, TRBC2, vascular endothelial growth factor R2 (VEGF- R2), Wilms tumor protein (WT-1), and a pathogen antigen;

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

9. The cell or population thereof of claim 3, wherein the cell comprising a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof, the exogenous cytokine or a receptor thereof

(a) comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, and its respective receptor; 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, wherein the common receptor γC is native or modified; 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.

10. The cell or population thereof of claim 3, wherein the cell is a derivative NK or a derivative T cell, wherein the derivative NK cell is capable of recruiting, and/or migrating T cells to tumor sites, and wherein the derivative NK or the derivative T cell is capable of reducing tumor immunosuppression in the presence of one or more checkpoint inhibitors.

11. The cell or population thereof of claim 8 or 10, 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, A2aR, 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.

12. The cell or population thereof of claim 11, wherein the checkpoint inhibitors comprise:

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

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

13. The cell or population thereof of claim 2, wherein the derivative cell comprises derivative CD34 cell, derivative hematopoietic stem and progenitor cell, derivative hematopoietic multipotent progenitor cell, derivative T cell progenitor, derivative NK cell progenitor, derivative T cell, derivative NKT cell, derivative NK cell, or derivative B cell.

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

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

(ii) more than two exogenous polynucleotides integrated in different safe harbor loci; or

(iii) a polynucleotide encoding an IL15Δ comprising an amino acid sequence of at least 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NOs: 17, 19 or 21.

15. The cell or population thereof of claim 14, wherein the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1.

16. The cell or population thereof of claim 15, wherein the safe harbor locus TCR is a constant region of TCR alpha.

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

18. A composition for therapeutic use comprising the derivative cell of any one of the claims 1-16, and one or more therapeutic agents.

19. The composition of claim 18, wherein the 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).

20. The composition of claim 19, wherein

(1) the checkpoint inhibitor comprises:

(a) one or more antagonists checkpoint molecules comprising PD-1, PDL-1, TIM-3, TIGIT, LAG-3, CTLA-4, 2B4, 4-1BB, 4-1BBL, A2aR, 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

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

21. The composition of claim 19, 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, certuximab, 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 hnCD16 or a variant thereof.

22. Therapeutic use of the therapeutic composition of any one of the claims 17-21 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.

23. A method of manufacturing the derivative cell of any one of the claims 1-16 comprising differentiating an iPSC, wherein the iPSC comprises CD38 knockout or a polynucleotide encoding an IL15/IL15Rα fusion protein with intracellular domain of IL15Rα truncated (IL15Δ), and optionally one or more of:

(i) B2M null or low;

(ii) CIITA null or low;

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

(iv) a high affinity non-cleavable CD16 (hnCD16) or a variant thereof;

(v) a chimeric antigen receptor (CAR);

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

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

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

(ix) introduced or increased expression in at least one of HLA-E, 41BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, CAR, TCR, Fc receptor, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers.

24. The method of manufacturing the derivative cells of claim 23, further comprising genomically engineering a clonal iPSC to knock out CD38 or to knock in a polynucleotide encoding an IL15/IL15Rα fusion protein without an intracellular domain (IL15Δ); and optionally

(i) to knock out B2M and CIITA, or

(ii) to introduce expression of HLA-G or non-cleavable HLA-G, a high affinity non-cleavable CD16 or a variant thereof, a CAR, and/or a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof;

wherein the CAR and the partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof are co-expressed in separate constructs or in a bi-cistronic construct.

25. The method of manufacturing the derivative cell of claim 23, wherein the genomic engineering comprises targeted editing.

26. The method of manufacturing the derivative cell of claim 25, 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.

27. CRISPR mediated editing of clonal iPSCs, wherein the editing comprises a CD38 knockout or a knock-in of a polynucleotide encoding an IL15/IL15Rα fusion protein without an intracellular domain (IL15Δ), wherein the edited clonal iPSCs comprise at least one of the genotypes listed in Table 1.

28. The CRISPR mediated editing of claim 27, wherein

(i) the CD38 knockout is bi-allelic; or

(ii) the CD38 knockout is a nucleic acid cleavage between a first and a second target sequence, and wherein the targeting sequences comprise SEQ ID NO: 3 and SEQ ID NO: 4, respectively; or

(iii) the polynucleotide encoding an IL15Δ comprising an amino acid sequence of at least 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NOs: 17, 19 or 21.

29. The CRISPR mediated editing of claim 27, wherein the editing further comprises an insertion of a CAR at TRAC locus, and/or wherein the CAR is driven by an endogenous promoter of TCR, and/or wherein the TCR is knocked out by the CAR insertion.

30. A method of improving anti-CD38 antibody treatment comprising administering to a subject under the treatment effector cells without CD38 expression.

31. The method of claim 30, wherein the anti-CD38 antibody is daratumumab, isatuximab, or MOR202, or any of the humanized or Fc modified variants or fragments, functional equivalents and biosimilars thereof.

32. The method of claim 30, wherein the effector cells comprise derivative hematopoietic cells comprising derivative NK cells or derivative T cells, wherein the derivative NK cells or derivative T cells comprise a CD38 knockout, a high affinity non-cleavable CD16 or a variant thereof, and optionally comprise:

(i) B2M and CIITA knockout;

(ii) introduced expression of HLA-G or non-cleavable HLA-G, a CAR, and/or a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof; wherein the CAR and a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof is co-expressed in separate constructs or in a bi-cistronic construct; and/or

(iii) at least one of the genotypes listed in Table 1.

33. The method of claim 30, wherein the method reduces the anti-CD38 antibody induced effector cell reduction in the subject under the treatment.

34. A method of reducing or preventing allorejection against allogenic effector cells by using a CD38 specific antagonist, wherein the allogenic effector cells comprise CD38 knockout, and wherein the CD38 specific antagonist is capable of suppressing activated T and B cells in a recipient of the allogenic effector cells.

35. The method of 34, wherein the CD38 specific antagonist is an anti-CD38 antibody, a CD38 specific engager, or a CD38 chimeric antigen receptor (CAR).

36. The method of 35, wherein the anti-CD38 antibody is daratumumab, isatuximab, or MOR202, or any of the humanized or Fc modified variants or fragments, functional equivalents and biosimilars thereof.