CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein:

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

(ii) the cell comprises (a) HLA-I deficiency; (b) CD38 knockout; and optionally, (c) an exogenous polynucleotide encoding a CD16 or a variant thereof.

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

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

(ii) an exogenous polynucleotide encoding a chimeric antigen receptor (CAR);

(iii) HLA-II deficiency; and

(iv) an exogenous polynucleotide encoding HLA-G, HLA-E, or a variant thereof;

wherein the cell has improved persistency in the presence of alloreactive host cells in an adoptive cell therapy incorporating CD38 conditioning.

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

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

(ii) comprises knockout of one or both of CD58 and CD54;

(iii) comprises 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;

(iv) comprises introduction of at least one of 4-1BBL, CD3, CD4, CD8, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, TCR, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers; and/or

(v) does not comprise an exogenous polynucleotide encoding HLA-G, HLA-E, or a variant thereof;

wherein the HLA-I deficiency comprises disruption of at least one of: B2M, TAP1, TAP2, and Tapasin; and/or

wherein the HLA-II deficiency comprises disruption of at least one of: CIITA, RFX5, RFXAP, and RFXANK.

4. The cell or population thereof of claim 1, wherein the derivative cell:

(a) 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 cell, a derivative NKT cell, a derivative NK cell, or a derivative B cell; or

(b) is used as an allogeneic effector cell, wherein the effector cell is a derivative NK cell or a derivative T cell having at least one of the following characteristics comprising:

(i) improved persistency and/or survival;

(ii) increased resistance to activated recipient 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 1, wherein the CD16 or variant thereof comprises at least one of:

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

(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 claim 5, wherein:

(a) the non-native transmembrane domain is derived from a CD3δ, CD3ε, CD3γ, 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 a 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 a 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.

7. The cell or population thereof of claim 2, 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 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;

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

(x) optionally inserted at:

(1) a TRAC or a TRBC locus, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion;

(2) a safe harbor locus; or

(3) a gene locus intended for disruption.

8. The cell or population thereof of claim 2, wherein the CAR is:

(i) specific to CD19, BCMA, B7H3, MICA/B, or MR1; and/or

(ii) 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), 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.

9. The cell or population thereof of claim 2, wherein the cytokine signaling complex comprises:

(a) a partial or full peptide of a cell surface expressed exogenous cytokine and/or receptor thereof comprising at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, or respective receptor(s) thereof; or

(b) at least one of:

(i) co-expression of IL15 and IL15Rα with a self-cleaving peptide in-between;

(ii) a fusion protein of IL15 and IL15Rα;

(iii) an IL15/IL15Rα fusion protein with intracellular domain of IL15Rα truncated (IL15Δ);

(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) is optionally 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 1, 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 cell 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 10, wherein the one or more 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.

12. The cell or population thereof of claim 10, wherein the one or more 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 1, wherein the cell comprises:

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

(ii) more than two exogenous polynucleotides integrated in different safe harbor loci or loci intended for disruption.

14. The cell or population thereof of claim 13, wherein the safe harbor locus or loci comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, TCR or RUNX1; or wherein the gene locus or loci intended for disruption comprises B2M, TAP1, TAP2, tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD38, CD25, CD69, CD71, CD44, CD58, CD54, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT.

15. The cell or population thereof of claim 2, wherein the CD38 conditioning:

(i) is through a CD38 antagonist comprising an anti-CD38 antibody or a CAR specifically binding to CD38 (CD38-CAR);

(ii) is through daratumumab, isatuximab, or MOR202;

(iii) is through daratumumab;

(iv) comprises a CD38 antagonist to be administered to a subject in need of the adoptive cell therapy prior to, during, or after infusion of the cell or population thereof for the therapy;

(v) comprises preloading a CD38 antagonist to the cell or population thereof *in vitro* prior to infusion of the preloaded cell or population thereof;

(vi) eliminates or reduces the number of alloreactive host cells;

(vii) delays host immune reconstitution; and/or

(viii) extends survival and persistence of the cell or population thereof in the presence of alloreactive host cells of a subject in need of the adoptive cell therapy.

16. The cell or population thereof of claim 2, wherein the alloreactive host cells:

(i) comprise primary T, B and/or NK cells that are allogeneic to the cell or population thereof;

(ii) are sensitized to CD38 conditioning by the cell or population thereof; and/or

(iii) are eliminated by CD38 conditioning via a CD38 antagonist in a dose-dependent manner.

17. A composition comprising a CD38 antagonist and the cell or population thereof of any one of the claims 1-16.

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

19. The composition of claim 18, 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).

20. The composition of claim 19, 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, Foxp1, GARP, HVEM, IDO, EDO, TDO, LAIR-1, MICA/B, NR4A2, MAFB, OCT-2, retinoic acid receptor alpha (Rara), 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.

21. The composition of claim 19, wherein the antibody comprises:

(a) an anti-CD20 antibody, an anti-HER2 antibody, an anti-CD52 antibody, an anti-EGFR antibody, an anti-CD123 antibody, an anti-GD2 antibody, an anti-PDL1 antibody, an anti-CD25 antibody, an anti-CD69 antibody, an anti-CD71 antibody, or an anti-CD44 antibody; or

(b) one or more of rituximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, trastuzumab, pertuzumab, alemtuzumab, cetuximab, dinutuximab, avelumab, daclizumab, basiliximab, M-A251, 2A3, BC69, 24204, 22722, 24212, MAB23591, FN50, 298614, AF2359, CY1G4, DF1513, bivatuzumab, RG7356, G44-26, 7G3, CSL362, elotuzumab, and their humanized or Fc modified variants or fragments and their functional equivalents and biosimilars thereof.

22. The composition of claim 17, wherein the CD38 antagonist:

(i) comprises an anti-CD38 antibody or a CD38-CAR;

(ii) comprises daratumumab, isatuximab, or MOR202;

(iii) comprises daratumumab; or

(iv) is to be provided to the subject in need of adoptive cell therapy prior to, during, or after infusion of the cell or population thereof.

23. Use of the composition of any one of the claims 17-22 in the manufacture of a medicament for an adoptive cell therapy for the treatment of an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a virus infection.

24. Use of the cell or population thereof of any one of the claims 1-16 in the manufacture of a medicament for reducing or preventing alloreactivity of host cells against allogeneic effector cells in an adoptive cell therapy to be provided to a subject in need thereof, wherein the medicament is to be used in combination with CD38 conditioning.

25. The use of claim 24, wherein the host cells comprise alloreactive immune cells comprising primary T cells, B cells, and/or NK cells.

26. The use of claim 24, wherein the CD38 conditioning:

(i) comprises use of a CD38 antagonist; or

(ii) comprises preloading a CD38 antagonist to the allogeneic effector cells *in vitro*;

wherein the CD38 conditioning (a) eliminates or reduces the number of alloreactive host cells; (b) extends survival and persistence of the allogeneic effector cells to an extent controllable by a given dose of the CD38 antagonist; and/or (c) delays host immune reconstitution.

27. The use of claim 26, wherein the CD38 antagonist comprises:

(i) an anti-CD38 antibody or a CD38-CAR;

(ii) daratumumab, isatuximab, or MOR202; and/or

(iii) daratumumab.

28. The use of claim 26, wherein the alloreactive host cells comprise upregulated CD38 expression.

29. The use of claim 24, wherein a therapeutic agent is to be further administered.

30. The use of claim 29, wherein the therapeutic agent comprises 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).

31. The use of claim 30, 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, Foxp1, 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; or

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

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

32. The use of claim 24, wherein the medicament is to be used without or with minimal need of lymphodepeletion with a combination of cyclophosphamide and fludarabine (Cy/Flu).

33. The cell or population thereof of any one the claims 1-16 or the composition of any one of the claims 17-22 for use in therapy.