CLAIMS

1. A cell or a population thereof, in which

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

(ii) the cell is TCR^{neg}, and comprises one or more polynucleotide encoding one or more exogenous protein to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed.

2. A cell or population thereof according to Claim 1, in which the cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3):

(i) is associated with a non-binding recombinant TCR (nb-rTCR);

(ii) is associated with a defined recombinant TCR (d-rTCR);

(iii) is associated with a recombinant pre-TCR (p-rTCR);

(iv) is anchored to a non-binding recombinant TCR (nb-rTCR-CD3); or

(v) is a CD3 chimeric chain (ccCD3).

3. A cell or population thereof according to Claim 1, in which the one or more polynucleotide encodes exogenous protein comprising one or more of:

(i) a transgenic TCRα constant region (tgTRAC);

(ii) a transgenic TCRβ constant region (tgTRBC);

(iii) a transgenic TCRα (tgTCRα);

(iv) a transgenic TCRβ (tgTCRβ);

(v) a transgenic pre-TCRα (tgpTCRα);

(vi) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3δ, and a full or partial TCRα constant region (tgCD3(ε-δ)-TRAC);

(vii) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3γ, and a full or partial TCRβ constant region (tgCD3(ε-γ)-TRBC);

(viii) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3γ, and a full or partial TCRα constant region (tgCD3(ε-γ)-TRAC);

(ix) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3δ, and a full or partial TCRβ constant region (tgCD3(ε-δ)-TRBC);

(x) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3γ, and a full or partial length of endodomain of CD3ζ (tgCD3(ε-γ)-ζ);

(xi) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3δ, and a full or partial length of endodomain of CD3ζ (tgCD3(ε-δ)-ζ);

(xii) a transgenic fusion protein comprising a full or partial length of ectodomain of CD3ε, a transgenic fusion protein comprising a full or partial length of ectodomain of CD3γ or CD3δ, a full or partial length of endodomain of CD3ζ, and a signaling domain of CD28 (tgCD3(ε- γ/δ)-28ζ);

(xiii) a transgenic fusion protein comprising a full or partial length of ectodomain of CD3ε, a transgenic fusion protein comprising a full or partial length of ectodomain of CD3γ or CD3δ, a full or partial length of endodomain of CD3ζ, and a signaling domain of 41BB (tgCD3(ε- γ/δ)-BBζ); and/or

(xiv) a transgenic fusion protein comprising a full or partial length of ectodomain of CD3γ or CD3δ, a full or partial length of endodomain of CD3ζ, a signaling domain of CD28, and a signaling domain of 41BB (tgCD3(ε- γ/δ)-(28-BB)ζ).

4. A cell or population thereof according to Claim 3,

in which the one or more polynucleotide encoding tgTRAC, tgTCRα, tgpTCRα, tgCD3(ε-δ)-TRAC, tgCD3(ε-γ)-TRAC, tgCD3(ε-γ)-ζ, tgCD3(ε-δ)-ζ, tgCD3(ε- γ/δ)-28ζ, tgCD3(ε- γ/δ)-BBζ, or tgCD3(ε- γ/δ)-(28-BB)ζ is inserted in a TRAC locus, and optionally upon insertion, is operatively linked to endogenous promoter of TRAC; or

in which the one or more polynucleotide encoding tgTRBC, tgTCRβ, tgCD3(ε-γ)-TRBC, tgCD3(ε-δ)-TRBC, tgCD3(ε-γ)-ζ, tgCD3(ε-δ)-ζ, tgCD3(ε- γ/δ)-28ζ, tgCD3(ε-γ/δ)-BBζ, and/or tgCD3(ε- γ/δ)-(28-BB)ζ is inserted in a TRBC locus, and optionally upon insertion, is operatively linked to endogenous promoter of TRBC.

5. A cell or population thereof according to Claim 4,

in which the polynucleotide encoding tgTRAC comprises a sequence encoding a full or partial length of the constant region of TCRα, and optionally an N-terminal signal peptide; or

in which the polynucleotide encoding tgTRAC comprises a sequence encoding a full length of the constant region of TCRα and a poly A tail at C-terminal, and optionally an N-terminal signal peptide; or

in which the polynucleotide encoding tgTRAC comprises a sequence encoding a partial length of the constant region of TCRα, and optionally an N-terminal signal peptide; and in which the insertion of the polynucleotide is in an exon of the constant region and is in frame; or

in which the polynucleotide encoding tgTRBC comprises a sequence encoding a full or partial length of the constant region of TCRβ, and optionally an N-terminal signal peptide; or

in which the polynucleotide encoding tgTRBC comprises a sequence encoding a full length of the constant region of TCRβ and a poly A tail at C-terminal, and optionally an N-terminal signal peptide; or

in which the polynucleotide encoding tgTRBC comprises a sequence encoding a partial length of the constant region of TCRβ, and optionally an N-terminal signal peptide; and in which the insertion of the polynucleotide is in an exon of the constant region and is in frame.

6. A cell or population thereof according to Claim 4, in which the one or more polynucleotide inserted in TRAC and/or TRBC locus disrupts expression of TRAC and TRBC, respectively, leading to TCR^{neg} cell.

7. A cell or population thereof according to Claim 6, in which the one or more polynucleotide inserted in TRAC and/or TRBC locus is driven by (i) an endogenous promoter of TRAC and TRBC respectively, or (ii) a heterologous promoter.

8. A cell or population thereof according to Claim 7, in which the heterologous promoter comprises: (i) at least one of constitutive, inducible, temporal-, tissue-, or cell type- specific promoters; or (ii) one of CMV, EF1α, PGK, CAG, and UBC; or (iii) CAG.

9. A cell or population thereof according to Claim 2, in which

(i) the nb-rTCR comprises one or both of a tgTRAC and a tgTRBC;

(ii) the d-rTCR comprises a tgTCRα, and optionally, a tgTCRβ, in which each of the tgTCRα and the tgTCRβ comprises a respective defined variable region;

(iii) the p-rTCR comprises a tgpTCRα, and optionally a tgTRBC or a tgTCRβ, in which the tgTCRβ comprises a defined variable region;

(iv) the nb-rTCR-CD3 comprises one or more of fusion proteins: (1) a tgCD3(ε-δ)-TRAC; (2) a tgCD3(ε-γ)-TRBC; (3) a tgCD3(ε-γ)-TRAC; and/or (4) a tgCD3(ε-δ)-TRBC, in which the fusion protein comprises full or partial length of ectodomains of CD3ε, CD3δ, CD3γ, and/or a full or partial length of TRAC or TRBC; or

(v) the ccCD3 comprises at least one of fusion proteins: tgCD3(ε-γ)-ζ, tgCD3(ε-δ)-ζ, tgCD3(ε- γ/δ)-28ζ, tgCD3(ε- γ/δ)-BBζ, and tgCD3(ε-γ/δ)-(28-BB)ζ, in which the fusion protein comprising full or partial length of ectodomains of CD3ε, CD3δ and/or CD3γ protein, further comprises a cytoplasmic domain comprising a full or partial length endodomain of CDζ protein, and optionally one or both of a CD28 signaling domain and a 41BB signaling domain.

10. A cell or population thereof according to Claim 9, in which the nb-rTCR-CD3 comprising fusion protein tgCD3(ε-δ)-TRAC further comprises tgTRBC or tgTCRβ; or in which the nb-rTCR-CD3 comprising fusion protein tgCD3(ε-γ)-TRBC further comprises tgTRAC or tgTCRα; or in which the d-rTCR comprising a tgTCRα and a tgTCRβ comprises TCRα and TCRβ of an invariant NKT cell.

11. A cell or population thereof according to Claim 9, in which

(i) the cell comprises one of the recombinant TCRs: nb-rTCR, d-rTCR, or the p-rTCR, in which the recombinant TCR complexes with endogenous CD3 subunits, thereby enabling cell surface presentation of endogenous CD3 subunits and signaling thereof; or in which

(ii) the cell comprises a nb-rTCR-CD3 or a ccCD3, thereby enabling cell surface presentation of exogenous CD3 subunits and signaling thereof.

12. A cell or population thereof according to Claim 1, in which the derivative cell 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.

13. A cell or population thereof according to Claim 1, in which the cell 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) an exogenous CD16

or a variant thereof;

(v) a chimeric antigen receptor (CAR),

(vi) a partial or full length 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 B2M, CD38, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, RAG1, and any gene in the chromosome 6p21 region; and

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

14. A cell or population thereof according to Claim 1 or 13, in which 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.

15. A cell or population thereof according to Claim 13, in which the cell further comprises an exogenous CD16 or a variant thereof.

16. A cell or population thereof according to Claim 15, in which the exogenous CD16 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.

17. A cell or population thereof according to Claim 16, in which

(a) the non-native transmembrane domain is derived from 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 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.

18. A cell or population thereof according to Claim 13, in which the cell further comprises a chimeric antigen receptor (CAR), and in which 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 length 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 (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD19, 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 (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, TRBC1, TRBC2, vascular endothelial growth factor R2 (VEGF- R2), Wilms tumor protein (WT-1), and a pathogen antigen;

in which 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.

19. A cell or population thereof according to Claim 13, in which the cell comprising a partial or full length 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, in which the common receptor γC is native or modified; and

(vii) a homodimer of IL15Rβ;

in which 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.

20. A cell or population thereof according to Claim 13, in which the cell is a derivative NK or a derivative T cell, in which the derivative NK cell is capable of recruiting, and/or migrating T cells to tumor sites, and in which the derivative NK or the derivative T cell is capable of reducing tumor immunosuppression in the presence of one or more checkpoint inhibitors.

21. A cell or population thereof according to Claim 18 or 20, in which 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.

22. A cell or population thereof according to Claim 21, in which 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.

23. A cell or population thereof according to Claim 1, in which 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 cell, a derivative NKT cell, a derivative NK cell, or a derivative B cell.

24. A cell or population thereof according to Claim 1, in which 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.

25. A cell or population thereof according to Claim 24, in which the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, CD38, GAPDH, TCR, CD38, RUNX1, or TCR.

26. A cell or population thereof according to Claim 25, in which the safe harbor locus TCR is a constant region of TCR alpha or TCR beta.

27. A clonal master cell bank comprising clonal iPSC cell line cells according to any preceding claim.

28. A composition comprising a cell or population thereof according to any of Claims 1 to 26.

29. A composition for therapeutic use comprising a derivative cell according to any of Claims 1 to 26, and one or more therapeutic agents.

30. A composition according to Claim 29, in which 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).

31. A composition according to Claim 30, in which

(a) the checkpoint inhibitor comprises:

(i) 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;

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

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

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

32. A composition according to Claim 30, in which the antibody comprises:

(a) an anti-CD20, an anti-CD22, 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 in which 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.

33. Use of a composition according to any of Claims 28 to 31 in the manufacture of a medicament for adoptive cell therapy in a subject, in which the subject has an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

34. A method of manufacturing a cell according to any of Claims 1 to 26 comprising differentiating a TCR^{neg} iPSC, in which the iPSC comprises one or more polynucleotide encoding one or more exogenous protein to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed, and optionally the 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) an exogenous CD16 or a variant thereof;

(v) a chimeric antigen receptor (CAR);

(vi) a partial or full length 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 B2M, CD38, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, RAG1, 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.

35. A method of manufacturing a cell according to Claim 34, further comprising

(a) knocking out TCR of a clonal iPSC to obtain the genomically engineered TCR^{neg} iPSC, and knocking in, simultaneously or subsequently, one or more polynucleotide encoding one or more exogenous protein; or

(b) reprogramming an invariant NKT cell to iPSC to provide a clonal iPSC comprising iTCRαβ but not T cell-TCR,

to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed; and

(c) optionally genomically engineering the iPSC of (a) or (b) by

(i) knocking out B2M and CIITA, or

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

in which 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.

36. A method of manufacturing a cell according to Claim 35, in which the step (a), knocking in one or more polynucleotide encoding one or more exogenous protein to provide cs-CD3, further comprises introducing to the iPSC one of the following:

(i) one or both of a tgTRAC and a tgTRBC encoding polynucleotide, to provide a nb-rTCR when expressed;

(ii) a tgTCRα, and optionally a tgTCRβ, encoding polynucleotide, to provide a d-rTCR when expressed, in which each of the tgTCRα and the tgTCRβ comprises a respective defined variable region;

(iii) a tgpTCRα, and optionally a tgTRBC or a tgTCRβ, encoding polynucleotide, to provide a p-rTCR, in which the tgTCRβ comprises a defined variable region;

(iv) one or more polynucleotides encoding one or more of fusion proteins: (1) tgCD3(ε-δ)-TRAC, (2) tgCD3(ε-γ)-TRBC, (3) tgCD3(ε-γ)-TRAC, and/or (4) tgCD3(ε-δ)-TRBC, to provide a nb-rTCR-CD3; in which the fusion protein comprises full or partial length of ectodomains of CD3ε, CD3δ, CD3γ, and/or a full or partial length of TRAC or TRBC; or

(v) one or more polynucleotides encoding one or more of fusion proteins: (1) tgCD3(ε-γ)-ζ, (2) tgCD3(ε-δ)-ζ, (3) tgCD3(ε- γ/δ)-28ζ, (4) tgCD3(ε- γ/δ)-BBζ, and (5) tgCD3(ε-γ/δ)-(28-BB)ζ, to provide ccCD3; in which the fusion protein comprising full or partial length of ectodomains of CD3ε, CD3δ and/or CD3γ protein, further comprises a cytoplasmic domain comprising a full or partial length endodomain of CDζ protein, and optionally one or both of a CD28 signaling domain and a 41BB signaling domain.

37. A method of manufacturing a cell according to Claim 36, in which the step of introducing to the iPSC one or more polynucleotides encoding fusion protein tgCD3(ε-δ)-TRAC of (iv), further comprises introducing a polynucleotide encoding tgTRBC or tgTCRβ, to provide the nb-rTCR-CD3; or

in which the step of introducing to the iPSC one or more polynucleotides encoding fusion protein tgCD3(ε-γ)-TRBC of (iv) further comprises tgTRAC or tgTCRα, to provide the nb-rTCR-CD3; or

in which in the step of introducing to the iPSC the polynucleotide encoding tgTCRα, and optionally, the polynucleotide encoding tgTCRβ, to provide the d-rTCR, the tgTCRα and the tgTCRβ respectively comprise a TCRα and a TCRβ of an invariant NKT cell.

38. A method of manufacturing a cell according to Claim 35, in which the knocking out, the knocking in, or the genomically engineering comprises targeted editing.

39. A method of manufacturing a cell according to Claim 38, in which the targeted editing comprises deletion, insertion, or in/del, and in which the targeted editing is carried out by CRISPR, ZFN, TALEN, homing nuclease, homology recombination, or any other functional variation of these methods.

40. CRISPR mediated editing of clonal iPSCs according to any of Claims 1 to 26, in which the edited iPSCs are TCR^{neg} and comprise one or more polynucleotide encoding one or more exogenous protein to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed, in which the edited clonal iPSCs comprise at least one of the genotypes listed in Table 1.

41. CRISPR mediated editing according to Claim 40, in which the editing further comprises an insertion of a CAR at a TRAC or a TRBC locus, and/or in which the CAR is driven by an endogenous promoter of TCR, and/or in which the TCR is knocked out by the CAR insertion.

42. Use of a composition comprising a cell or population thereof according to any of Claims 1 to 26 in the manufacture of a medicament, in which (a) the cell or population thereof comprises derivative cells comprising effector cells, and (b) the medicament is to be administered with a selected multi-specific engager.

43. Use according to Claim 42, in which the selected multi-specific engager is at least one of: (i) a T cell engager; (ii) an NK cell engager; (iii) a bispecific T cell engager (BiTE); (iv) a bispecific killer cell engager (BiKE); (v) a tri-specific killer cell engager (TriKE); (vi) a CD3 engager; or (vii) a CD16 engager.

44. Use according to Claim 42, in which the selected multispecific engager is a CD3 engager, in which the CD3 engager comprises a first variable segment that binds to a cs-CD3 and a second variable segment that binds to an antigen comprising at least one of:

(i) ADGRE2, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD19, 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 (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/or a pathogen antigen; or

(ii) BCMA, CD19, CD20, CD33, CD38, CD52, CD123, CEA, EGFR, EpCAM, GD2, GPA33, HER2, MICA/B, PDL1, and/or PSMA; or

(iii) CD19, CD33, CD123, CEA, EpCAM, GPA33, HER2, and/or PSMA;

or in which the CD3 engager comprises at least one of: blinatumomab, catumaxomab, ertumaxomab, RO6958688, AFM11, MT110/AMG 110, MT111/AMG211/MEDI-565, AMG330, MT112/BAY2010112, MOR209/ES414, MGD006/S80880, MGD007, and/or FBTA05.

45. Use according to Claim 44, in which the CD3 engager is to be administered to the subject simultaneously or subsequently with the effector cells.

46. Use according to Claim 42, in which the effector cells comprise derivative hematopoietic cells comprising derivative NK cells or derivative T cells, in which the derivative NK cells or derivative T cells comprise a CD38 knockout, an exogenous CD16 or a variant thereof, and optionally comprise:

(i) HLA-I deficiency and HLA-II deficiency;

(ii) introduced expression of HLA-G or non-cleavable HLA-G, a CAR, and/or a partial or full length peptide of a cell surface expressed exogenous cytokine or a receptor thereof; in which the CAR and a partial or full length 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.

47. Use of a composition comprising a cell or population thereof according to any of Claims 1 to 26 in the manufacture of a medicament for reducing or preventing allorejection by recipient T cells against effector cells in an adoptive cell treatment, in which (a) the cell or population thereof comprises derivative cells comprising effector cells, and (b) the medicament is to be administered with an anti-CD3 agent.

48. Use according to Claim 47, in which the anti-CD3 agent is CD3 antibody or a CD3-CAR, in which the CD3-CAR is comprised in a NK cell; and in which the anti-CD3 agent deactivates recipient T cells, thereby reducing or preventing allorejection.

49. Use according to Claim 47, in which the CD3 engager comprising a first variable segment that binds to a cs-CD3 of the effector cell, comprises a second variable segment that binds to an antigen related to an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

50. Use according to Claim 49, in which the CD3 engager comprises a second variable segment that binds to an antigen comprises at least one of:

(i) ADGRE2, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD19, 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 (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/or a pathogen antigen; or

(ii) BCMA, CD19, CD20, CD33, CD38, CD52, CD123, CEA, EGFR, EpCAM, GD2, GPA33, HER2, MICA/B, PDL1, and/or PSMA; or

(iii) CD19, CD33, CD123, CEA, EpCAM, GPA33, HER2, and/or PSMA;

or in which the CD3 engager comprises at least one of: blinatumomab, catumaxomab, ertumaxomab, RO6958688, AFM11, MT110/AMG 110, MT111/AMG211/MEDI-565, AMG330, MT112/BAY2010112, MOR209/ES414, MGD006/S80880, MGD007, and/or FBTA05.

CLAIMS

1. A cell or a population thereof, in which

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

(ii) the cell lacks expression of an endogenous TCR (TCR^{neg});

(iii) the cell comprises one or more polynucleotide encoding one or more exogenous protein to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed; and

(iv) expression of the one or more exogenous protein in the cell or a T cell derived therefrom induces formation of the cs-CD3 comprising (a) a CD3ζ endodomain, and (b) one or more of a CD3ε ectodomain, a CD3δ ectodomain, or a CD3γ ectodomain.

2. A cell or population thereof according to Claim 1, in which the cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) in the cell or T cell derived therefrom comprises:

(i) a non-binding recombinant TCR (nb-rTCR) characterized by (a) a transgenic TCRα constant region (tgTRAC) lacking a TCRα variable region, or (b) a transgenic TCRβ constant region (tgTRBC) lacking a TCRβ variable region;

(ii) a defined recombinant TCR (d-rTCR) characterized by (a) a transgenic TCRα (tgTCRα) having a defined TCRα variable region, or (b) a transgenic TCRβ (tgTCRβ) having a defined TCRβ variable region;

(iii) a recombinant pre-TCR (p-rTCR) comprising an intracellular domain of a pre-TCRα;

(iv) a non-binding recombinant TCR (nb-rTCR-CD3) comprising a fusion protein comprising: (a) a tgTRAC or a tgTRBC; (b) the CD3ε ectodomain; and (c) the CD3δ ectodomain or the CD3γ ectodomain; or

(v) a CD3 chimeric chain (ccCD3) comprising a fusion between (a) the CD3ε ectodomain and (b) the CD3δ ectodomain or the CD3γ ectodomain.

3. A cell or population thereof according to Claim 1, in which the one or more polynucleotide encodes exogenous protein comprising one or more of:

(i) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3δ, and a full or partial TCRα constant region (tgCD3(ε-δ)-TRAC);

(ii) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3γ, and a full or partial TCRβ constant region (tgCD3(ε-γ)-TRBC);

(iii) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3γ, and a full or partial TCRα constant region (tgCD3(ε-γ)-TRAC);

(iv) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3δ, and a full or partial TCRβ constant region (tgCD3(ε-δ)-TRBC);

(v) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3γ, and a full or partial length of endodomain of CD3ζ (tgCD3(ε-γ)-ζ);

(vi) a transgenic fusion protein comprising full or partial length of ectodomains of CD3ε and CD3δ, and a full or partial length of endodomain of CD3ζ (tgCD3(ε-δ)-ζ);

(vii) a transgenic fusion protein comprising a full or partial length of ectodomain of CD3ε, a transgenic fusion protein comprising a full or partial length of ectodomain of CD3γ or CD3δ, a full or partial length of endodomain of CD3ζ, and a signaling domain of CD28 (tgCD3(ε- γ/δ)-28ζ);

(viii) a transgenic fusion protein comprising a full or partial length of ectodomain of CD3ε, a transgenic fusion protein comprising a full or partial length of ectodomain of CD3γ or CD3δ, a full or partial length of endodomain of CD3ζ, and a signaling domain of 41BB (tgCD3(ε- γ/δ)-BBζ); and/or

(ix) a transgenic fusion protein comprising a full or partial length of ectodomain of CD3γ or CD3δ, a full or partial length of endodomain of CD3ζ, a signaling domain of CD28, and a signaling domain of 41BB (tgCD3(ε- γ/δ)-(28-BB)ζ).

4. A cell or population thereof according to Claim 3,

in which the one or more polynucleotide encoding tgCD3(ε-δ)-TRAC, tgCD3(ε-γ)-TRAC, tgCD3(ε-γ)-ζ, tgCD3(ε-δ)-ζ, tgCD3(ε- γ/δ)-28ζ, tgCD3(ε- γ/δ)-BBζ, or tgCD3(ε-γ/δ)-(28-BB)ζ is inserted in a TRAC locus, and optionally upon insertion, is operatively linked to endogenous promoter of TRAC; or

in which the one or more polynucleotide encoding tgCD3(ε-γ)-TRBC, tgCD3(ε-δ)-TRBC, tgCD3(ε-γ)-ζ, tgCD3(ε-δ)-ζ, tgCD3(ε- γ/δ)-28ζ, tgCD3(ε- γ/δ)-BBζ, and/or

tgCD3(ε- γ/δ)-(28-BB)ζ is inserted in a TRBC locus, and optionally upon insertion, is operatively linked to endogenous promoter of TRBC.

5. A cell or population thereof according to Claim 4,

in which the transgenic fusion protein comprises a full or partial length of the constant region of TCRα, and optionally an N-terminal signal peptide; or

in which the transgenic fusion protein comprises a full length of the constant region of TCRα and a poly A tail at C-terminal, and optionally an N-terminal signal peptide; or

in which the transgenic fusion protein comprises a partial length of the constant region of TCRα, and optionally an N-terminal signal peptide; and in which the insertion of the polynucleotide is in an exon of the constant region and is in frame; or

in which the transgenic fusion protein comprises a full or partial length of the constant region of TCRβ, and optionally an N-terminal signal peptide; or

in which the transgenic fusion protein comprises a full length of the constant region of TCRβ and a poly A tail at C-terminal, and optionally an N-terminal signal peptide; or

in which the transgenic fusion protein comprises a partial length of the constant region of TCRβ, and optionally an N-terminal signal peptide; and in which the insertion of the polynucleotide is in an exon of the constant region and is in frame.

6. A cell or population thereof according to Claim 4, in which the one or more polynucleotide inserted in TRAC and/or TRBC locus disrupts expression of TRAC and TRBC, respectively, leading to TCR^{neg} cell.

7. A cell or population thereof according to Claim 6, in which the one or more polynucleotide inserted in TRAC and/or TRBC locus is driven by (i) an endogenous promoter of TRAC and TRBC respectively, or (ii) a heterologous promoter.

8. A cell or population thereof according to Claim 7, in which the heterologous promoter comprises: (i) at least one of constitutive, inducible, temporal-, tissue-, or cell type- specific promoters; or (ii) one of CMV, EF1α, PGK, CAG, and UBC; or (iii) CAG.

9. A cell or population thereof according to Claim 2, in which

(i) the nb-rTCR comprises one or both of a tgTRAC and a tgTRBC;

(ii) the d-rTCR comprises a tgTCRα, and optionally, a tgTCRβ, in which each of the tgTCRα and the tgTCRβ comprises a respective defined variable region;

(iii) the p-rTCR comprises a tgpTCRα, and optionally a tgTRBC or a tgTCRβ, in which the tgTCRβ comprises a defined variable region;

(iv) the nb-rTCR-CD3 comprises one or more of fusion proteins: (1) a tgCD3(ε-δ)-TRAC; (2) a tgCD3(ε-γ)-TRBC; (3) a tgCD3(ε-γ)-TRAC; and/or (4) a tgCD3(ε-δ)-TRBC, in which the fusion protein comprises full or partial length of ectodomains of CD3ε, CD3δ, CD3γ, and/or a full or partial length of TRAC or TRBC; or

(v) the ccCD3 comprises at least one of fusion proteins: tgCD3(ε-γ)-ζ, tgCD3(ε-δ)-ζ, tgCD3(ε- γ/δ)-28ζ, tgCD3(ε- γ/δ)-BBζ, and tgCD3(ε-γ/δ)-(28-BB)ζ, in which the fusion protein comprising full or partial length of ectodomains of CD3ε, CD3δ and/or CD3γ protein, further comprises a cytoplasmic domain comprising a full or partial length endodomain of CDζ protein, and optionally one or both of a CD28 signaling domain and a 41BB signaling domain.

10. A cell or population thereof according to Claim 9, in which the nb-rTCR-CD3 comprising fusion protein tgCD3(ε-δ)-TRAC further comprises tgTRBC or tgTCRβ; or in which the nb-rTCR-CD3 comprising fusion protein tgCD3(ε-γ)-TRBC further comprises tgTRAC or tgTCRα; or in which the d-rTCR comprising a tgTCRα and a tgTCRβ comprises TCRα and TCRβ of an invariant NKT cell.

11. A cell or population thereof according to Claim 9, in which

(i) the cell comprises one of the recombinant TCRs: nb-rTCR, d-rTCR, or the p-rTCR, in which the recombinant TCR complexes with endogenous CD3 subunits, thereby enabling cell surface presentation of endogenous CD3 subunits and signaling thereof; or in which

(ii) the cell comprises a nb-rTCR-CD3 or a ccCD3, thereby enabling cell surface presentation of exogenous CD3 subunits and signaling thereof.

12. A cell or population thereof according to Claim 1, in which the derivative cell 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.

13. A cell or population thereof according to Claim 1, in which the cell 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) an exogenous CD16;

(v) a chimeric antigen receptor (CAR),

(vi) 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 B2M, CD38, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, RAG1, and any gene in the chromosome 6p21 region; and

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

14. A cell or population thereof according to Claim 1 or 13, in which 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.

15. A cell or population thereof according to Claim 13, in which the cell further comprises the exogenous CD16.

16. A cell or population thereof according to Claim 15, in which the exogenous CD16 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.

17. A cell or population thereof according to Claim 16, in which

(a) the non-native transmembrane domain is derived from 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 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.

18. A cell or population thereof according to Claim 13, in which the cell further comprises a chimeric antigen receptor (CAR), and in which 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 the cell surface expressed exogenous cytokine or the 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 (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD19, 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 (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, TRBC1, TRBC2, vascular endothelial growth factor R2 (VEGF- R2), Wilms tumor protein (WT-1), and a pathogen antigen;

in which 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.

19. A cell or population thereof according to Claim 13, in which the cell surface expressed exogenous cytokine or the 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, in which the common receptor γC is native or modified; and

(vii) a homodimer of IL15Rβ;

in which 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.

20. A cell or population thereof according to Claim 13, in which the cell is a derivative NK or a derivative T cell, in which the derivative NK cell is capable of recruiting, and/or

migrating T cells to tumor sites, and in which the derivative NK or the derivative T cell is capable of reducing tumor immunosuppression in the presence of one or more checkpoint inhibitors.

21. A cell or population thereof according to Claim 18 or 20, in which 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.

22. A cell or population thereof according to Claim 21, in which 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.

23. A cell or population thereof according to Claim 1, in which 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 cell, a derivative NKT cell, a derivative NK cell, or a derivative B cell.

24. A cell or population thereof according to Claim 1, in which 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 the amino acid sequence of SEQ ID NOs: 17, 19 or 21.

25. A cell or population thereof according to Claim 24, in which the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, CD38, GAPDH, TCR, CD38, RUNX1, or TCR.

26. A cell or population thereof according to Claim 25, in which the safe harbor locus TCR is a constant region of TCR alpha or TCR beta.

27. A clonal master cell bank comprising clonal iPSC cell line cells according to any preceding claim.

28. A composition comprising a cell or population thereof according to any of Claims 1 to 26.

29. A composition for therapeutic use comprising a derivative cell according to any of Claims 1 to 26, and one or more therapeutic agents.

30. A composition according to Claim 29, in which 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).

31. A composition according to Claim 30, in which

(a) the checkpoint inhibitor comprises:

(i) 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;

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

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

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

32. A composition according to Claim 30, in which the antibody comprises:

(a) an anti-CD20, an anti-CD22, 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 in which the derivative hematopoietic cells comprise derivative NK cells or derivative T cells comprising a CD38 knockout, and optionally an expression of exogenous CD16.

33. Use of a composition according to any of Claims 28 to 31 in the preparation of a medicament for the treatment of an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

34. A method of manufacturing a cell according to any of Claims 1 to 26 comprising differentiating a TCR^{neg} iPSC, in which the iPSC comprises one or more polynucleotide encoding one or more exogenous protein to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed, and optionally the 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) an exogenous CD16;

(v) a chimeric antigen receptor (CAR);

(vi) 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 B2M, CD38, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, RAG1, 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.

35. A method according to Claim 34, further comprising

(a) knocking out TCR of a clonal iPSC to obtain the genomically engineered TCR^{neg} iPSC, and knocking in, simultaneously or subsequently, the one or more polynucleotide encoding the one or more exogenous protein; or

(b) reprogramming an invariant NKT cell to iPSC to provide a clonal iPSC comprising iTCRαβ but not T cell-TCR,

to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed; and

(c) optionally genomically engineering the iPSC of (a) or (b) by

(i) knocking out B2M and CIITA, or

(ii) introducing expression of HLA-G or non-cleavable HLA-G, an exogenous CD16, a CAR, and/or a cell surface expressed exogenous cytokine or a receptor thereof;

in which the CAR and the cell surface expressed exogenous cytokine or the receptor thereof are co-expressed in separate constructs or in a bi-cistronic construct.

36. A method according to Claim 35, in which the step (a), knocking in one or more polynucleotide encoding the one or more exogenous protein, further comprises introducing to the iPSC one of the following:

(i) one or both of a tgTRAC and a tgTRBC encoding polynucleotide, to provide a nb-rTCR when expressed, characterized by (a) the tgTRAC lacking a TCRα variable region, or (b) the tgTRBC lacking a TCRβ variable region;

(ii) a tgTCRα, and optionally a tgTCRβ, encoding polynucleotide, to provide a d-rTCR when expressed, in which each of the tgTCRα and the tgTCRβ comprises a respective defined variable region;

(iii) a tgpTCRα, and optionally a tgTRBC or a tgTCRβ, encoding polynucleotide, to provide a p-rTCR;

(iv) one or more polynucleotides encoding one or more of fusion proteins: (1) tgCD3(ε-δ)-TRAC, (2) tgCD3(ε-γ)-TRBC, (3) tgCD3(ε-γ)-TRAC, and/or (4) tgCD3(ε-δ)-TRBC, to provide a nb-rTCR-CD3; in which the fusion protein comprises full or partial length of ectodomains of CD3ε, CD3δ, CD3γ, and/or a full or partial length of TRAC or TRBC; or

(v) one or more polynucleotides encoding one or more of fusion proteins: (1) tgCD3(ε-γ)-ζ, (2) tgCD3(ε-δ)-ζ, (3) tgCD3(ε- γ/δ)-28ζ, (4) tgCD3(ε- γ/δ)-BBζ, and (5) tgCD3(ε-γ/δ)-(28-BB)ζ, to provide ccCD3; in which the fusion protein comprising full or partial length of ectodomains of CD3ε, CD3δ and/or CD3γ protein, further comprises a cytoplasmic domain comprising a full or partial length endodomain of CDζ protein, and optionally one or both of a CD28 signaling domain and a 41BB signaling domain.

37. A method according to Claim 36, in which the step of introducing to the iPSC one or more polynucleotides encoding fusion protein tgCD3(ε-δ)-TRAC, further comprises introducing a polynucleotide encoding tgTRBC or tgTCRβ, to provide the nb-rTCR-CD3; or

in which the step of introducing to the iPSC one or more polynucleotides encoding fusion protein tgCD3(ε-γ)-TRBC further comprises tgTRAC or tgTCRα, to provide the nb-rTCR-CD3; or

in which in the step of introducing to the iPSC the polynucleotide encoding tgTCRα, and optionally, the polynucleotide encoding tgTCRβ, to provide the d-rTCR, the tgTCRα and the tgTCRβ respectively comprise a TCRα and a TCRβ of an invariant NKT cell.

38. A method according to Claim 35, in which the knocking out, the knocking in, or the genomically engineering comprises targeted editing.

39. A method according to Claim 38, in which the targeted editing comprises deletion, insertion, or in/del, and in which the targeted editing is carried out by CRISPR, ZFN, TALEN, homing nuclease, homology recombination, or any other functional variation of these methods.

40. CRISPR mediated editing of clonal iPSCs according to any of Claims 1 to 26, in which the edited iPSCs are TCR^{neg} and comprise one or more polynucleotide encoding one or more exogenous protein to provide a cell surface CD3 complex, or one or more subunits or subdomains thereof (cs-CD3) when expressed, in which the edited clonal iPSCs comprise at least one of the genotypes listed in Table 1.

41. CRISPR mediated editing according to Claim 40, in which the editing further comprises an insertion of a CAR at a TRAC or a TRBC locus, and/or in which the CAR is driven by an endogenous promoter of TCR, and/or in which the TCR is knocked out by the CAR insertion.

42. Use of a composition comprising a cell or population thereof according to any of Claims 1 to 26 in the preparation of a medicament, in which (a) the cell or population thereof comprises derivative cells comprising effector cells, and (b) the medicament is to be administered with a selected multi-specific engager.

43. Use according to Claim 42, in which the selected multi-specific engager is at least one of: (i) a T cell engager; (ii) an NK cell engager; (iii) a bispecific T cell engager (BiTE); (iv) a bispecific killer cell engager (BiKE); (v) a tri-specific killer cell engager (TriKE); (vi) a CD3 engager; or (vii) a CD16 engager.

44. Use according to Claim 42, in which the selected multispecific engager is a CD3 engager, in which the CD3 engager comprises a first variable segment that binds to a cs-CD3 and a second variable segment that binds to an antigen comprising at least one of:

(i) ADGRE2, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD19, 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 (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/or a pathogen antigen; or

(ii) BCMA, CD19, CD20, CD33, CD38, CD52, CD123, CEA, EGFR, EpCAM, GD2, GPA33, HER2, MICA/B, PDL1, and/or PSMA; or

(iii) CD19, CD33, CD123, CEA, EpCAM, GPA33, HER2, and/or PSMA;

or in which the CD3 engager comprises at least one of: blinatumomab, catumaxomab, ertumaxomab, RO6958688, AFM11, MT110/AMG 110, MT111/AMG211/MEDI-565, AMG330, MT112/BAY2010112, MOR209/ES414, MGD006/S80880, MGD007, and/or FBTA05.

45. Use according to Claim 44, in which the CD3 engager is to be administered to the subject simultaneously or subsequently with the effector cells.

46. Use according to Claim 42, in which the effector cells comprise derivative hematopoietic cells comprising derivative NK cells or derivative T cells, in which the derivative NK cells or derivative T cells comprise a CD38 knockout, an exogenous CD16, and optionally comprise:

(i) HLA-I deficiency and HLA-II deficiency;

(ii) introduced expression of HLA-G or non-cleavable HLA-G, a CAR, and/or a cell surface expressed exogenous cytokine or a receptor thereof; in which the CAR and the cell surface expressed exogenous cytokine or the 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.

47. Use of a composition comprising a cell or population thereof according to any of Claims 1 to 26 in the preparation of a medicament for reducing or preventing allorejection by recipient T cells against effector cells in an adoptive cell treatment, in which (a) the cell or population thereof comprises derivative cells comprising effector cells, and (b) the medicament is to be administered with an anti-CD3 agent.

48. Use according to Claim 47, in which the anti-CD3 agent is CD3 antibody or a CD3-CAR, in which the CD3-CAR is comprised in a NK cell; and in which the anti-CD3 agent deactivates recipient T cells, thereby reducing or preventing allorejection.

49. Use according to Claim 47, in which the CD3 engager comprising a first variable segment that binds to a cs-CD3 of the effector cell, comprises a second variable segment that binds to an antigen related to an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

50. Use according to Claim 49, in which the CD3 engager comprises a second variable segment that binds to an antigen comprises at least one of:

(i) ADGRE2, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD19, 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 (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/or a pathogen antigen; or

(ii) BCMA, CD19, CD20, CD33, CD38, CD52, CD123, CEA, EGFR, EpCAM, GD2, GPA33, HER2, MICA/B, PDL1, and/or PSMA; or

(iii) CD19, CD33, CD123, CEA, EpCAM, GPA33, HER2, and/or PSMA;

or in which the CD3 engager comprises at least one of: blinatumomab, catumaxomab, ertumaxomab, RO6958688, AFM11, MT110/AMG 110, MT111/AMG211/MEDI-565, AMG330, MT112/BAY2010112, MOR209/ES414, MGD006/S80880, MGD007, and/or FBTA05.