CLAIMS

1. A cell or a population thereof, in which

(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; and

(ii) the cell comprises:

(1) an exogenous CD16 or a variant thereof; and

(2) one or both of a chimeric antigen receptor (CAR), and a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof, or a combination thereof.

2. 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.

3. 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) at least one of the genotypes listed in Table 1;

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

(vi) 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. A cell or population thereof according to Claim 1 or 3, in which the derivative cell is an immune effector 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, in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues, and

(ix) acquired dual targeting capability.

5. A cell or population thereof according to Claim 1, in which the exogenous CD16 or a variant thereof comprises at least one of:

(a) a high affinity non-cleavable CD16 (hnCD16);

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

(c) a full or partial ectodomain originated from CD64;

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

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

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

(g) a non-native stimulatory domain; and

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

6. A cell or population thereof according to Claim 5, in which

(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.

7. A cell or population thereof according to Claim 1, 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 peptide of a cell surface expressed exogenous cytokine or a receptor, or a combination 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, 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; 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.

8. A cell or population thereof according to Claim 1, in which the cell further comprises a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor, or a combination thereof, and in which 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 respective receptor thereof; or

(b) comprises at least one of:

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

(ii) a fusion protein of IL15 and IL15Rα;

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

(iv) a fusion protein of IL15 and membrane bound Sushi domain of IL15Rα;

(v) a fusion protein of IL15 and IL15Rβ;

(vi) a fusion protein of IL15 and common receptor γC, 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.

9. A cell or population thereof according to Claim 3, in which the cell is a derivative cell, in which

(i) the derivative cell is an immune effector cell capable of recruiting, and/or migrating T cells to tumor sites;

(ii) the derivative cell is an immune effector cell capable of reducing tumor immunosuppression in the presence of one or more checkpoint inhibitors.

10. A cell or population thereof according to Claim 7 or 9, 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.

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

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

13. 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.

14. A cell or population thereof according to Claim 13, in which the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1.

15. A cell or population thereof according to Claim 14, in which the safe harbor locus TCR is a constant region of TCR.

16. A composition comprising a cell or population thereof according to any preceding claim.

17. A composition for therapeutic use comprising a derivative cell according to any preceding claim, and one or more therapeutic agents.

18. A composition according to Claim 17, 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 or functional variant or fragment thereof, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

19. A composition according to Claim 18, in which 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.

20. A composition according to Claim 18, in which the antibody comprises:

(a) anti-CD20, anti-HER2, anti-CD52, anti-EGFR, anti-CD123, anti-GD2, anti-PDL1, and/or anti-CD38 antibody;

(b) one or more of retuximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, trastuzumab, pertuzumab, alemtuzumab, certuximab, dinutuximab, avelumab, daratumumab, isatuximab, MOR202, 7G3, CSL362, elotuzumab, and their humanized or Fc modified variants or fragments and their functional equivalents and biosimilars; or

(c) daratumumab.

21. Use of the composition according to any of Claims 16 to 20, in which in the manufacture of a medicament for the treatment of an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection.

22. A method of manufacturing a derivative cell according to any of Claims 1 to 15 comprising differentiating an iPSC, in which the iPSC comprises exogenous polynucleotides encoding:

(i) CD16 or a variant thereof; and

(ii) one or both of a chimeric antigen receptor (CAR), and a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor or a combination thereof; and optionally one or more of:

(1) HLA-I deficiency;

(2) HLA-II deficiency;

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

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

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

(6) introduced or increased expression in at least one of HLA-E, 41BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, A2AR, CAR, TCR, Fc receptor, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers.

23. A method of manufacturing a derivative cell according to Claim 22, further comprising genomically engineering a clonal iPSC to introduce

(i) an exogenous polynucleotide encoding a CD16 or a variant thereof; and

(ii) an exogenous polynucleotide encoding one or both of a chimeric antigen receptor (CAR), and a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor or a combination thereof; and optionally to

(1) knock out B2M null;

(2) knock out CIITA; or

(3) introduce expression of HLA-G or non-cleavable HLA-G;

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

24. A method of manufacturing a derivative cell according to Claim 22, in which the genomic engineering comprises targeted editing.

25. A method of manufacturing a derivative cell according to Claim 24, in which the targeted editing comprising 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.

26. CRISPR mediated editing of clonal iPSCs, in which the edited clonal iPSCs comprise:

(a) (i) an exogenous polynucleotide encoding a CD16 or a variant thereof; and

(ii) an exogenous polynucleotide encoding a chimeric antigen receptor (CAR), and optionally a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof; or

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

in which the CAR is optionally inserted at a constant region of TCR locus, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion.

27. Use of immune effector cells in the preparation of a medicament for preventing or reducing tumor antigen escape and/or tumor relapse, in which the immune effector cells comprise:

(a) (i) an exogenous CD16 or a variant thereof; and

(ii) a chimeric antigen receptor (CAR), and optionally a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof; or

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

an antigen specific monoclonal antibody, or any of the humanized or Fc modified variants or fragments, functional equivalents and biosimilars thereof, in which the antigen targeted by the antibody is different from tumor antigen recognized by the CAR.

28. Use according to Claim 27, in which the exogenous CD16 or a variant thereof comprises at least one of:

(a) a high affinity non-cleavable CD16 (hnCD16);

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

(c) a full or partial ectodomain originated from CD64;

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

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

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

(g) a non-native stimulatory domain; and

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

29. An engineered protein comprising at least one of:

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

(ii) a fusion protein of IL15 and membrane bound Sushi domain of IL15Rα;

(iii) a fusion protein of IL15 and IL15Rβ;

(iv) a fusion protein of IL15 and common receptor γC, in which the common receptor γC is native or modified; and

(v) a homodimer of IL15Rβ;

in which any one of (i)-(v) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct.

30. A cell or a population thereof, in which

(1) 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; and

(2) the cell comprises a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor, or a combination thereof, and

in which 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 respective receptor thereof; or

(b) comprises at least one of:

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

(ii) a fusion protein of IL15 and IL15Rα;

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

(iv) a fusion protein of IL15 and membrane bound Sushi domain of IL15Rα;

(v) a fusion protein of IL15 and IL15Rβ;

(vi) a fusion protein of IL15 and common receptor γC, 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.