CLAIMS

1. A cell or a population thereof, in which the cell is an induced pluripotent cell (iPSC) or a derivative cell obtained from differentiating the iPSC; and in which the cell comprises a CD38 knockout.

2. A cell or population thereof according to Claim 1, in which the cell has at least one of the genotypes listed in Table 1 and comprises one or more of:

(i) B2M null or low;

(ii) CIITA null or low;

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

(iv) a CD16 or a variant thereof;

(v) a chimeric antigen receptor (CAR),

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

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

(viii) 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, or surface triggering receptor for coupling with bi- or multi-specific or universal engagers.

3. A cell or population thereof according to Claim 1, 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 immune rejection;

(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; or

(ix) reduced fratricide,

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

4. A cell or population thereof according to Claim 2, in which the CD16 comprises:

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

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

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

(iv) a non-native (or non-CD16) transmembrane domain, intracellular domain stimulatory domain, and/or signaling domain from a same or different polypeptide.

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

6. A cell or population thereof according to Claim 2, in which the cell further comprises a chimeric antigen receptor (CAR), and optionally, in which the CAR is:

(i) T cell specific or NK cell specific;

(ii) co-expressed with a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof, optionally in separate constructs or in a bi-cistronic construct;

(iii) inserted at one of the loci comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR, CD38, or RUNX1a; or

(iv) inserted at a T cell receptor (TCR) locus, or CD38 locus, and in which the TCR or CD38 is knocked out by the CAR insertion.

7. A cell or population thereof according to Claim 2, in which the cell comprises a partial or full peptide of a cell surface expressed exogenous cytokine and/or a partial or full peptide of its receptor thereof, and optionally, in which the partial or full peptide of cytokine and/or a receptor is (i) at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18 or IL21, or its respective receptor; or (ii) transiently expressed.

8. A cell or population thereof according to Claim 2, in which the cell comprises at least one of:

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

(ii) a partial or full peptide of IL15 fused with a partial or full peptide of IL15Rα;

(iii) a partial or full peptide of IL15 fused with a partial IL15Rα, in which the IL15Rα has its intracellular domain truncated;

(iv) a partial or full peptide of IL15 fused with a Sushi domain of IL15Rα;

(v) a partial or full peptide of IL15 fused with a partial or full peptide of IL15Rβ;

(vi) a partial or full peptide of IL15 fused with a partial or full peptide of common receptor γC, in which the common receptor γC is native or modified; or

(vii) a homodimer of a partial or full peptide of IL15Rβ.

9. A cell or population thereof according to Claim 3, (a) in which the derivative cell is an immune effector cell in the presence of one or more checkpoint inhibitors, (b) in which the immune effector cell is capable of recruiting, and/or migrating T cells to tumor sites, and (c)

in which the immune effector cell is capable of reducing tumor immunosuppression in the tumour site.

10. A cell or population thereof according to Claim 9, in which the immune effector cell expresses the one or more checkpoint inhibitors.

11. A cell or population thereof according to Claim 10, in which the one or more checkpoint inhibitors:

(i) 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; or

(ii) comprise:

(a) one or more of atezolizumab, avelumab, durvalumab, ipilimumab, IPH4102, IPH43, IPH33, lirimumab, monalizumab, nivolumab, pembrolizumab, or a derivative; or

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

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

(i) derivative CD34 cell, or

(ii) derivative hematopoietic cell that comprises

(a) derivative hematopoietic multipotent progenitor cell, derivative T cell progenitor, derivative NK cell progenitor, derivative T lineage cell, derivative NKT lineage cell, or derivative NK lineage cell;

(b) derivative B lineage cell; or

(c) longer telomeres in comparison to its 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 comprises a polynucleotide encoding a fusion protein of IL15 and a truncated IL15Rα, and in which the

fusion protein comprises an amino acid sequence of at least 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NOs: 17, 19 or 21.

14. A composition comprising a cell or population thereof according to Claim 1.

15. A composition according to Claim 14, further comprising one or more therapeutic agents.

16. A composition according to Claim 15, in which 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 polynucleotides of interest, an antibody, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

17. A composition according to Claim 16, in which:

(i) 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, or a derivative; or

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

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

(iii) the antibody comprises:

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

(b) daratumumab, isatuximab or MOR202, or a humanized or Fc modified variant or fragments thereof, and in which the derivative cell comprises an immune effector cell comprising a CD38 knockout, and optionally an expression of a CD16 or a variant thereof.

18. Use of a composition according to Claim 14 in the manufacture of a medicament for the treatment of an autoimmune disorder; a hematological malignancy; a solid tumor; or a virus infection, in which the cell or population thereof is autologous or allogeneic.

19. A method of making a cell or population thereof according to Claim 1, comprising disrupting CD38 expression of a pluripotent cell, and selecting a CD38 null pluripotent cell.

20. A method according to Claim 19, further comprising targeted editing simultaneously with, or sequentially to, disrupting CD38 expression, thereby obtaining pluripotent cells having at least one of the genotypes listed in Table 1 and comprising one or more of:

(i) B2M null or low;

(ii) CIITA null or low;

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

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

(v) a chimeric antigen receptor (CAR);

(vi) a partial or full peptide of IL15 fused with a partial or full peptide of its receptor;

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

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

21. A method according to Claim 19, further comprising differentiating the CD38 null pluripotent cell to a hematopoietic lineage cell, in which the hematopoietic lineage cell does not express CD38.

22. Use of a CD38 specific antagonist in the manufacture of a medicament for the treatment of allorejection against allogenic effector cells, in which the allogenic effector cells comprise CD38 knockout, in which the CD38 specific antagonist is capable of suppressing activated T and B cells in a recipient of the allogenic effector cells, and in which the CD38 specific antagonist is a CD38 antibody, a CD38 specific engager, a CD38 chimeric antigen receptor (CAR), daratumumab, isatuximab, MOR202, or a humanized or Fc modified variant or fragment of a CD38 antibody.

CLAIMS

1. A cell or a population thereof, in which the cell is an induced pluripotent cell (iPSC) or a derivative cell obtained from differentiating the iPSC; in which the cell comprises a CD38 knockout; and in which:

(A) the cell comprises a CD16, and in which the CD16 comprises:

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

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

(iii) an ectodomain of CD64; or

(iv) a non-native (or non-CD16) transmembrane domain, intracellular domain stimulatory domain, and/or signaling domain from a same or different polypeptide; or

(B) the cell comprises a functional partial or full peptide of a cell surface expressed exogenous cytokine and/or a functional partial or full peptide of its receptor thereof, in which the functional partial or full peptide of cytokine and/or receptor is at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18 or IL21, or its respective receptor.

2. A cell or population thereof according to Claim 1, in which the cell 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) a chimeric antigen receptor (CAR),

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

(vi) introduced expression of 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, or surface triggering receptor for coupling with bi- or multi- specific or universal engagers.

3. A cell or population thereof according to Claim 1, 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 immune rejection;

(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; or

(ix) reduced fratricide,

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

4. A cell or population thereof according to Claim 1, in which the cell comprises the CD16, and in which the CD16 comprises:

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

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

(iii) an ectodomain of CD64; or

(iv) a non-native (or non-CD16) transmembrane domain, intracellular domain stimulatory domain, and/or signaling domain from a same or different polypeptide.

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

6. A cell or population thereof according to Claim 2, in which the cell further comprises a chimeric antigen receptor (CAR), and optionally, in which the CAR is:

(i) T cell specific or NK cell specific;

(ii) co-expressed with a functional partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof, optionally in separate constructs or in a bi-cistronic construct;

(iii) inserted at one of the loci comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR, CD38, or RUNX1a; or

(iv) inserted at a T cell receptor (TCR) locus, or CD38 locus, and in which the TCR or CD38 is knocked out by the CAR insertion.

7. A cell or population thereof according to Claim 1, in which the cell comprises the functional partial or full peptide of a cell surface expressed exogenous cytokine and/or the functional partial or full peptide of its receptor thereof, and optionally, in which the functional partial or full peptide of cytokine and/or receptor is transiently expressed.

8. A cell or population thereof according to Claim 1, in which the cell comprises at least one of:

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

(ii) a functional partial or full peptide of IL15 fused with a functional partial or full peptide of IL15Rα;

(iii) a functional partial or full peptide of IL15 fused with a IL15Rα, in which the IL15Rα has its intracellular domain truncated;

(iv) a functional partial or full peptide of IL15 fused with a Sushi domain of IL15Rα;

(v) a functional partial or full peptide of IL15 fused with a functional partial or full peptide of IL15Rβ;

(vi) a functional partial or full peptide of IL15 fused with a functional partial or full peptide of common receptor γC, in which the common receptor γC is native or modified; or

(vii) a homodimer of a functional partial or full peptide of IL15Rβ.

9. A cell or population thereof according to Claim 1, in which the derivative cell is an immune effector cell.

10. A cell or population thereof according to Claim 9, in which the immune effector cell expresses one or more checkpoint inhibitors.

11. A cell or population thereof according to Claim 10, in which the one or more checkpoint inhibitors:

(i) 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; or

(ii) comprise:

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

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

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

(i) a derivative $CD34^+$ cell obtained from differentiating the iPSC, or

(ii) a derivative hematopoietic cell obtained from differentiating the iPSC, in which the derivative hematopoietic cell comprises

(a) a hematopoietic multipotent progenitor cell, a T cell progenitor, an NK cell progenitor, a T cell, an NKT cell, or an NK cell;

(b) a B cell; or

(c) longer telomeres in comparison to its 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 comprises a polynucleotide encoding a fusion protein of IL15 and an IL15Rα comprising a truncated intracellular domain.

14. A composition comprising a cell or population thereof according to Claim 1.

15. A composition according to Claim 14, further comprising one or more therapeutic agents.

16. A composition according to Claim 15, in which 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 polynucleotides of interest, an antibody, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

17. A composition according to Claim 16, in which:

(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, 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 or pembrolizumab; or

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

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

(iii) the antibody comprises:

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

(b) daratumumab, isatuximab or MOR202, or a humanized or Fc modified variant or functional fragments thereof, and in which the derivative cell comprises an immune effector cell comprising a CD38 knockout, and optionally an expression of a CD16 or a variant thereof.

18. Use of a composition according to Claim 14 in the manufacture of a medicament for the treatment of an autoimmune disorder; a hematological malignancy; a solid tumor; or a virus infection, in which the cell or population thereof is autologous or allogeneic, and in which the cell is an immune effector cell obtained from differentiating the iPSC.

19. A method of making a cell or population thereof according to Claim 1, comprising disrupting CD38 expression of a pluripotent cell, and selecting a CD38 null pluripotent cell.

20. A method according to Claim 19, further comprising targeted editing simultaneously with, or sequentially to, disrupting CD38 expression, thereby obtaining pluripotent cells and comprising one or more of:

(i) HLA-I deficiency;

(ii) HLA-II deficiency;

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

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

(v) a chimeric antigen receptor (CAR);

(vi) a functional partial or full peptide of IL15 fused with a functional partial or full peptide of its receptor;

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

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

21. A method according to Claim 19, further comprising differentiating the CD38 null pluripotent cell to a hematopoietic lineage cell, in which the hematopoietic lineage cell does not express CD38.

22. Use of a CD38 specific antagonist in the manufacture of a medicament for the treatment of allorejection against allogenic effector cells, in which the allogenic effector cells obtained from differentiating an iPSC according to Claim 1, and in which the CD38 specific antagonist is a CD38 antibody, a CD38 specific engager, a CD38 chimeric antigen receptor (CAR), daratumumab, isatuximab, MOR202, or a humanized or Fc modified variant or functional fragment of a CD38 antibody.