CLAIMS

1. A method of generating iPSCs comprising at least one targeted genomic editing at one or more selected sites in genome, the method comprising (I), (II) or (III):

(I): genetically engineering iPSCs comprising one or both of (i) and (ii), in any order:

(i) introducing into iPSCs one or more constructs, each comprising one or more exogenous polynucleotides of interest, to allow targeted integration at selected site;

(ii)(a) introducing into iPSCs one or more double strand break at the selected sites using one or more endonuclease capable of selected site recognition; and

(b) culturing the iPSCs of step (I)(ii)(a) to allow endogenous DNA repair to generate targeted in/dels at the selected sites;

(II): genetically engineering reprogramming non-pluripotent cells to obtain the genome-engineered iPSCs comprising:

(i) contacting non-pluripotent cells with one or more reprogramming factors, and optionally a small molecule composition comprising a TGFβ receptor/ALK inhibitor, a MEK inhibitor, a GSK3 inhibitor and/or a ROCK inhibitor to initiate reprogramming of the non-pluripotent cells; and

(ii) introducing into the reprogramming non-pluripotent cells of step (II)(i) one or both of (a) and (b), in any order:

(a) one or more constructs, each comprising one or more exogenous polynucleotides of interest, to allow targeted integration at a selected site;

(b) one or more double strand break at a selected site using at least one endonuclease capable of selected site recognition,

in which the cells of step (II)(ii)(b) are cultured to allow endogenous DNA repair to generate targeted in/dels at the selected sites;

and,

(III): genetically engineering non-pluripotent cells for reprogramming to obtain genome-engineered iPSCs comprising (i) and (ii):

(i) introducing into non-pluripotent cells one or both of (a) and (b), in any order:

(a) one or more constructs, each comprising one or more exogenous polynucleotides of interest, to allow targeted integration at a selected site;

(b) one or more double strand break at a selected site using at least one endonuclease capable of selected site recognition,

in which the cells of step (III)(i)(b) are cultured to allow endogenous DNA repair to generate targeted in/dels at the selected sites; and,

(ii) contacting the cells of step (III)(i) with one or more reprogramming factors, and optionally a small molecule composition comprising a TGFβ receptor/ALK inhibitor, a MEK inhibitor, a GSK3 inhibitor and/or a ROCK inhibitor, to obtain genome-engineered iPSCs comprising targeted editing at selected sites;

thereby obtaining genome-engineered iPSCs comprising at least one functional targeted genomic editing, and in which the genome-engineered iPSCs are capable of being differentiated into partially differentiated cells or fully-differentiated cells.

2. A method according to Claim 1, in which the genome-engineered iPSCs comprise at least one targeted genomic editing at one or more selected sites comprising: (i) insertion of one or more exogenous polynucleotides; or (ii) in/del at one or more endogenous genes,

in which the one or more exogenous polynucleotides encode safety switch proteins, targeting modalities, receptors, signaling molecules, transcription factors, pharmaceutically active proteins and peptides, drug target candidates, immune response regulation and modulation, or proteins promoting or suppressing engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the iPSCs or derivative cells thereof.

3. A method according to Claim 2, in which:

(i) the exogenous polynucleotides are operatively linked to (1) one or more exogenous promoters comprising CMV, EF1α, PGK, CAG, UBC, or other constitutive, inducible, temporal-, tissue-, or cell type- specific promoters; or (2) one or more

endogenous promoters comprised in the selected sites comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1;

(ii) the exogenous polynucleotides encode proteins comprising caspase, thymidine kinase, cytosine deaminase, modified EGFR, B-cell CD20, or any combinations thereof, in which the exogenous polynucleotides are integrated in different safe harbor locus comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1; and/or

(iii) the endogenous gene comprises at least one of B2M, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, and any gene in the chromosome 6p21 region; and/or

(iv) the genome-engineered iPSCs comprise a caspase encoding exogenous polynucleotide at AAVS1 locus, and a thymidine kinase encoding exogenous polynucleotide at H11 locus; and/or

(v) the genome engineered iPSCs comprise at least one targeted genomic editing are functional, are differentiation potent, and are capable of differentiating into non-pluripotent cells comprising the same functional genomic editing.

4. A method according to Claim 1, in which group (I), (II) and/or (III) further comprising: contacting the genome-engineered iPSCs with a small molecule composition comprising a MEK inhibitor, a GSK3 inhibitor and a ROCK inhibitor.

5. A method according to Claim 1, in which the method has at least one of the following characteristics:

(i) in which the one or more exogenous polynucleotides of interest are operatively linked to one or more exogenous promoters comprised in the construct, or to an endogenous promoter comprised in a selected site upon integration;

(ii) in which the constructs further comprise a pair of homology arms specific to the selected site and flanking the exogenous polynucleotides of interest;

(iii) in which the one or more exogenous polynucleotides remain integrated and functional in subsequently expanded iPSCs, differentiated cells derived from the iPSCs, and/or dedifferentiated cells derived therefrom;

(iv) in which the one or more exogenous polynucleotides are linked to each other by a linker sequence; or in which the one or more exogenous polynucleotides expresses under same or different promoters;

(v) in which the constructs further comprise at least one polynucleotide encoding a marker;

(vi) the constructs further comprise a polynucleotide encoding a marker that is driven by the endogenous promoter at the selected site; and

(vii) in which the one or more exogenous polynucleotides of interest encodes safety switch protein and is operatively linked to CAG.

6. A method according to Claim 5, in which the method has at least one of the following characteristics:

(i) in which the linker sequence (a) encodes a self-cleaving peptide; or (b) provides an Internal Ribosome Entry Sequence (IRES);

(ii) in which the selected site is a safe harbor locus, highly expressive locus, temporally expressed locus, or a gene locus for interruption, in which at least one of the exogenous polynucleotides operatively linked to an exogenous promoter comprising CMV, EF1α, PGK, CAG, UBC, or other constitutive, inducible, temporal-, tissue-, or cell type- specific promoters;

(iii) in which the selected site comprises AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1, loci meeting the criteria of a genome safe harbor, B2M, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, and any gene in the chromosome 6p21 region;

7. A method of generating genome-engineered non-pluripotent cells, the method comprising:

(i) obtaining genome-engineered iPSCs according to any preceding claim, in which the iPSC comprises at least one functional genomic editing; and

(ii) differentiating the genome-engineered iPSCs to obtain derived non-pluripotent cells comprising the same functional targeted genomic editing comprised in the genome-engineered iPSCs.

8. A method according to Claim 7, in which the derived non-pluripotent cells comprise hematopoietic lineage cells; and in which the differentiating step (ii) is without formation of embryoid bodies.

9. A method according to Claim 7, in which the derived non-pluripotent cells comprise mesodermal cells, CD34 cells, hemogenic endothelium cells, hematopoietic stem and progenitor cells, hematopoietic multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NKT cells, NK cells, or B cells.

10. A method of generating genome-engineered non-pluripotent cells from iPSCs, the method comprising:

(i) subjecting iPSCs under condition sufficient for initiating lineage specific differentiation; and

(ii) genetically engineering the differentiating cells of step (i) to obtain the genome-engineered non-pluripotent cells by one or both of (a) and (b), in any order:

(a) introducing into the differentiating cells of step (i) one or more construct, each comprising one or more exogenous polynucleotides of interest, to allow targeted integration at selected site;

(b)(1) introducing into the differentiating cells of step (i) one or more double strand break at the selected sites using at least one endonuclease capable of selected site recognition; and

(2) culturing the cells from step (ii)(b)(1) to allow endogenous DNA repair to generate targeted in/dels at the selected sites;

thereby obtaining genome-engineered non-pluripotent cells comprising one or more functional targeted editing in one or more selected sites.

11. A method according to Claim 10, in which the genome-engineered non-pluripotent cells comprise

(i) hematopoietic lineage cells;

(ii) mesodermal cells, CD34 cells, hemogenic endothelium cells, hematopoietic stem and progenitor cells, hematopoietic multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NKT cells, NK cells, or B cells.

12. Genome-engineered iPSCs generated from a method according to any of Claims 1 to 9.

13. Genome-engineered iPSCs according to Claim 12, in which the iPSCs comprise at least one of the following:

(i) one or more in/dels comprised in an endogenous gene associated with targeting modalities; receptors; signaling molecules; transcription factors; drug target candidates; immune response regulation and modulation; and proteins suppressing engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the iPSCs or derivative cells thereof;

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

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

(iv) deficiency in HLA class I and/or class II molecules;

(v) integrated or non-integrated exogenous polynucleotide encoding one or more of HLA-E, HLA-G, CD16, 41BBL and PDL1 proteins; or introduced expression of one or more of HLA-E, HLA-G, CD16, 41BBL and PDL1 proteins;

(vi) at least one exogenous polynucleotide encodes high affinity CD16 receptor; or at least one exogenous polynucleotide encodes non-cleavable CD16 receptor; or at least one exogenous polynucleotide encodes high affinity and non-cleavable CD16 receptor (hnCD16); or at least one exogenous polynucleotide encodes non-cleavable HLA-E; or at least one exogenous polynucleotide encodes non-cleavable HLA-G;

(vii) B2M null or low, TAP1 null or low, TAP2 null or low; Tapasin null or low; introduced expression of HLA-E or non-cleavable HLA-E; introduced expression of HLA-G or non-cleavable HLA-G; introduced expression of PDL1; high affinity non-cleavable CD16 (hnCD16); a Fc receptor; a T cell receptor (TCR); a chimeric antigen receptor (CAR); one or more suicide genes expressing safety switch protein; a bi-, multi-specific or universal engagers, or any combinations thereof; and

(viii) having improved persistency, increased resistance to immune cells, increased immune-resistance, or increased resistance to T and/or NK cells in comparison to iPSCs without the same genomic engineering; and maintain differentiation potential to non-pluripotent cells having the same functional genomic engineering.

14. Non-pluripotent cells generated using the method according to Claim 10 or 11, in which the non-pluripotent cells comprise one or more functional targeted genomic editing.

15. Non-pluripotent cells according to Claim 14, in which the non-pluripotent cells comprise at least one of the following:

(i) mesodermal cells, hemogenic endothelium cells, CD34 cells, hematopoietic stem and progenitor cells, hematopoietic multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NKT cells, NK cells, or B cells

(ii) one or more in/dels comprised in an endogenous gene associated with targeting modalities; receptors; signaling molecules; transcription factors; drug target candidates; immune response regulation and modulation; and proteins suppressing engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the iPSCs or derivative cells thereof;

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

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

(v) deficiency in HLA class I and/or class II molecules;

(vi) integrated or non-integrated exogenous polynucleotide encoding one or more of HLA-E, HLA-G, CD16, 41BBL and PDL1 proteins; or introduced expression of one or more of HLA-E, HLA-G, CD16, 41BBL and PDL1 proteins;

(vii) at least one exogenous polynucleotide encodes high affinity CD16 receptor; or at least one exogenous polynucleotide encodes non-cleavable CD16 receptor; or at least one exogenous polynucleotide encodes high affinity and non-cleavable CD16 receptor

(hnCD16); or at least one exogenous polynucleotide encodes non-cleavable HLA-E; or at least one exogenous polynucleotide encodes non-cleavable HLA-G;

(viii) B2M null or low, TAP1 null or low, TAP2 null or low; Tapasin null or low; introduced expression of HLA-E or non-cleavable HLA-E; introduced expression of HLA-G or non-cleavable HLA-G; introduced expression of PDL1; high affinity non-cleavable CD16 (hnCD16); a Fc receptor; a T cell receptor (TCR); a chimeric antigen receptor (CAR); one or more suicide genes expressing safety switch protein; a bi-, multi-specific or universal engagers, or any combinations thereof;

(ix) improved persistency, increased resistance to immune cells, increased immune-resistance, or increased resistance to T and/or NK cells in comparison to counterparts without the same genomic engineering;

(x) at least two exogenous polynucleotides each integrated in the same safe harbor locus, and in which the exogenous polynucleotides encode the same or different safety switch proteins;

(xi) at least two exogenous polynucleotides each integrated in different safe harbor locus, and in which the exogenous polynucleotides encode the same or different safety switch proteins;

(xii) being capable of being reprogrammed to iPSCs, and in which the iPSCs comprise the same functional exogenous polynucleotides comprised in the non-pluripotent cells; and/or

(xiii) being capable of being transdifferentiated to non-pluripotent cells of a different fate.

16. A pharmaceutical composition comprising a pharmaceutically acceptable medium and

(a) genome-engineered iPSCs according to Claim 12 or 13; or

(b) genome-engineered non-pluripotent cells according to Claim 14 or 15.

17. A pharmaceutical composition according to Claim 16 for use in a method of treatment, in which the composition is to be administered to a subject in need of adoptive cell therapy, in which the subject has an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or an infection associated with HIV, RSV, EBV, CMV, adenovirus, or BK polyomavirus.

18. A method of manufacturing genome-engineered iPSCs according to any of Claims 1 to 9.

19. A method of manufacturing derived non-pluripotent cells from genome-engineered iPSCs according to Claim 10 or 11.

20. A composition for obtaining genome-engineered iPSCs, the composition comprising:

(i) non-pluripotent cells;

(ii) one or more constructs for targeted editing at one or more selected loci;

(iii) one or more reprogramming factors; and optionally,

(iv) a small molecule composition comprising a TGFβ receptor/ALK inhibitor, a MEK inhibitor, a GSK3 inhibitor and/or a ROCK inhibitor;

in which the composition is useful for obtaining iPSCs comprising targeted genomic editing, and thereby the genome-engineered iPSCs have improved persistency, increased resistance to immune cells, or increased immune-resistance; or in which the genome-engineered iPSCs have increased resistance to T and/or NK cells.

21. A composition according to Claim 20, further comprising (i) one or more endonuclease capable of selected site recognition for introducing double strand break at selected sites; or (ii) a small molecule composition comprising a MEK inhibitor, a GSK3 inhibitor and a ROCK inhibitor for maintaining pluripotency of the obtained genome-engineered iPSCs.

22. A composition according to Claim 20, in which the one or more constructs comprise one or more exogenous polynucleotides encoding safety switch proteins, targeting modality, receptors, signaling molecules, transcription factors, pharmaceutically active proteins and peptides, drug target candidates, or proteins promoting engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the non-pluripotent cell reprogrammed iPSCs or derivative cells thereof.

23. A composition according to Claim 22, in which

(i) the one or more exogenous polynucleotides is operatively linked to (1) one or more exogenous promoters comprising CMV, EF1α, PGK, CAG, UBC, or other constitutive, inducible, temporal-, tissue-, or cell type- specific promoters; or (2) one or

more endogenous promoters comprised in the selected sites comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1;

(ii) the one or more exogenous polynucleotides encode safety switch proteins comprising caspase, thymidine kinase, cytosine deaminase, modified EGFR, B-cell CD20, or any combinations thereof;

(iii) the one or more exogenous polynucleotides are integrated in different safe harbor loci comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1;

(iv) the exogenous polynucleotides encode a caspase at AAVS1 locus and a thymidine kinase at H11 locus;

(v) the targeted genomic editing further comprises one or more in/dels in an endogenous gene associated with targeting modalities; receptors; signaling molecules; transcription factors; drug target candidates; immune response regulation and modulation; and proteins suppressing engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the iPSCs or derivative cells thereof;

(vi) the targeted genomic editing further comprises one or more in/dels comprising one or more of B2M, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, and any gene in the chromosome 6p21 region;

(vii) the non-pluripotent cells comprise mesodermal cells, CD34 cells, hemogenic endothelium cells, hematopoietic stem and progenitor cells, hematopoietic multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NKT cells, NK cells, or B cells.

24. A composition comprising:

(i) genome-engineered iPSCs, in which the genome-engineered iPSCs are obtained from

(a) reprogramming genome-engineered non-pluripotent cells, in which the obtained iPSCs comprise the same targeted integration and/or in/del at selected sites in the genome-engineered non-pluripotent cells; or

(b) genomically engineering a clonal iPSC or a pool of iPSCs by introducing one or more targeted integration and/or in/del at one or more selected sites; or

(c) genome engineering by introducing one or more targeted integration and/or in/del at one or more selected sites to a pool of reprogramming non-pluripotent cells in contact with one or more reprogramming factors and optionally a small molecule composition comprising a TGFβ receptor/ALK inhibitor, a MEK inhibitor, a GSK3 inhibitor and/or a ROCK inhibitor;

and

(ii) a small molecule composition comprising a MEK inhibitor, a GSK3 inhibitor and a ROCK inhibitor,

in which the genome-engineered iPSCs comprise one or more exogenous polynucleotides encoding safety switch proteins, targeting modality, receptors, signaling molecules, transcription factors, pharmaceutically active proteins and peptides, drug target candidates, or proteins promoting engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the non-pluripotent cell reprogrammed iPSCs or derivative cells thereof; and /or in/dels at one or more endogenous genes associated with targeting modality, receptors, signaling molecules, transcription factors, drug target candidates, immune response regulation and modulation, or proteins suppressing engraftment, trafficking, homing, viability, self-renewal, persistence, and/or survival of the non-pluripotent cell reprogrammed iPSCs or derivative cells thereof.

25. A composition according to Claim 24, further comprising one or more endonuclease capable of selected site recognition for introducing double strand break at selected sites.

26. A composition according to Claim 24, in which the composition has at least one of the following characteristics:

(i) the one or more exogenous polynucleotides is operatively linked to (1) one or more exogenous promoters comprising CMV, EF1α, PGK, CAG, UBC, or other constitutive, inducible, temporal-, tissue-, or cell type- specific promoters; or (2) one or more endogenous promoters comprised in the selected sites comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1;

(ii) the genome-engineered iPSCs comprise one or more exogenous polynucleotides encoding safety switch proteins selected from caspase, thymidine kinase, cytosine deaminase, modified EGFR, B-cell CD20, and any combinations thereof;

(iii) the genome-engineered iPSCs comprise two or more same or different safety switch protein encoding exogenous polynucleotides integrated in different safe harbor loci comprising AAVS1, CCR5, ROSA26, collagen, HTRP, H11, H11, beta-2 microglobulin, GAPDH, TCR or RUNX1;

(iv) the genome-engineered iPSCs comprise a caspase encoding gene at AAVS1 locus, and a thymidine kinase encoding gene at H11 locus;

(v) the genome-engineered iPSCs comprise one or more in/dels comprising B2M, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP, and any gene in the chromosome 6p21 region; and in which the gene comprising the in/del has no or reduced expression;

(vi) the genome-engineered iPSCs comprise introduced or increased expression in at least one of HLA-E, HLA-G, CD16, 41BBL, CD3, CD4, CD8, 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;

(vii) the genome-engineered iPSCs are HLA class I and/or class II deficient;

(viii) the genome-engineered iPSCs comprise B2M null or low, TAP1 null or low and/or TAP2 null or low;

(ix) the genome-engineered iPSCs comprise integrated or non-integrated exogenous polynucleotide encoding one or more of HLA-E, HLA-G, CD16, 41BBL and PDL1 proteins; or in which the genome-engineered iPSCs comprise introduced expression of one or more of HLA-E, HLA-G, CD16, 41BBL and PDL1 proteins;

(x) the genome-engineered iPSCs comprise at least one exogenous polynucleotide encodes high affinity CD16 receptor; at least one exogenous polynucleotide encodes non-cleavable CD16 receptor; at least one exogenous polynucleotide encodes high affinity and non-cleavable CD16 receptor (hnCD16); at least one exogenous polynucleotide encodes non-cleavable HLA-E; or at least one exogenous polynucleotide encodes non-cleavable HLA-G;

(xi) the genome-engineered iPSCs have improved persistency, increased resistance to immune cells, or increased immune-resistance; or in which the genome-engineered iPSCs have increased resistance to T and/or NK cells;

(xii) the genome-engineered iPSCs have the potential to differentiate into non-pluripotent cells comprising hematopoietic lineage cells having the same functional targeted genomic editing;

(xiii) the genome-engineered iPSCs have the potential to differentiate into mesodermal cells, CD34 cells, hemogenic endothelium cells, hematopoietic stem and progenitor cells, hematopoietic multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NKT cells, NK cells, or B cells.

27. A cell or a population thereof, in which (i) the cell is an induced pluripotent stem cell (iPSC), a clonal iPSC, or an iPS cell line cell; and (ii) the cell comprises one or more exogenous polynucleotides at an endogenous T cell receptor (TCR) locus.

28. A cell or population thereof according to Claim 27, the cell or population has at least one of the following characteristics: (i) in which the one or more exogenous polynucleotides is present in the constant region of the TCR locus; (ii) in which the TCR is knocked out; (iii) in which the one or more exogenous polynucleotides in the TCR locus comprise a polynucleotide encoding a chimeric antigen receptor (CAR), and in which the TCR locus is a TRAC locus; (iv) in which the cell is an iPSC obtained from reprogramming a T cell to a pluripotent state (TiPSC) and genomically editing the TiPSC; (v) in which the cell is an iPSC obtained from reprogramming a T cell comprising the one or more exogenous polynucleotides at the constant region of the TCR locus; (vi) in which the cell is capable of differentiating into derivative cells comprising the one or more exogenous polynucleotides at the TCR locus; (vii) in which the cell further comprises deletion or reduced expression in at least one of B2M, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP and any gene in the chromosome 6p21 region; and/or introduced or increased expression in at least one of HLA-E, HLA-G, CD16, 41BBL, CD3, CD4, CD8, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, Fc receptor, an engager, and a surface triggering receptor for coupling with bi-, multi- specific or universal engagers; and (ix) in which the cell further comprises introduced or increased expression of CD16, in which the CD16 is a high affinity non-cleavable CD16 (hnCD16).

29. A cell or population thereof according to Claim 28, the cell or population has at least one of the following characteristics: (i) in which the CAR is expressed under the control of a TCR endogenous promoter; (ii) in which the CAR is expressed at about the same level as an endogenous TCR in a cell in which TCR is not knocked out; (iii) in which the CAR is

expressed at about the same developmental stage as an endogenous TCR in a cell in which TCR is not knocked out; (iv) the CAR comprises a CD19 related CAR.

30. A cell or population thereof according to Claim 28, in which the derivative cells comprise: (i) hematopoietic lineage cells; (ii) mesodermal cells, CD34 cells, hemogenic endothelium cells, hematopoietic stem and progenitor cells, hematopoietic multipotent progenitor cells, T cell progenitors, or NK cell progenitors, T cells, NKT cells, NK cells, or B cells.

31. An iPSC-derived cell or a population thereof, in which (i) the iPSC-derived cell is a T cell, a T cell progenitor, a clonal cell, or a cell line cell; (ii) the iPSC-derived cell encodes at least one chimeric antigen receptor (CAR) at a constant region of a T cell receptor (TCR) locus; (iii) the TCR is knocked out; and (iv) expression of the CAR is under control of an endogenous TCR promoter.

32. An iPSC-derived cell or population thereof according to Claim 31, in which the cell or population has at least one of the following characteristics:

(i) in which the CAR is present at a constant region of the TCR locus, and the derivative cells comprise a T cell, a T cell progenitor, a clonal T cell, or a cell line T cell;

(ii) in which the CAR comprises a CD19 related CAR, and in which the constant region of TCR locus is a TRAC locus;

(iii) in which the cell further comprises deletion or reduced expression in at least one of B2M, TAP1, TAP2, Tapasin, NLRC5, PD1, LAG3, TIM3, RFXANK, CIITA, RFX5, RFXAP and any gene in the chromosome 6p21 region; and/or introduced or increased expression in at least one of HLA-E, HLA-G, CD16, 41BBL, CD3, CD4, CD8, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, Fc receptor, an engager, and a surface triggering receptor for coupling with bi-, multi- specific or universal engagers;

(iv) in which the cell further comprises introduced or increased expression of CD16, in which the CD16 is a high affinity non-cleavable CD16;

(v) in which the iPSC-derived cells comprise a T cell or T cell progenitor that has at least one of the following characteristics: (a) comprises a longer telomere length than a cell of the same type that is not derived from an iPSC; and (b) exhibits a greater

proliferative, survival and/or persistence potential, in comparison to a cell of the same type that is not derived from an iPSC;

(vi) in which the iPSC-derived cells further comprising one or more polynucleotides encoding one or more of (a) a CRISPR endonuclease, and (b) a guide RNA that directs cleavage within a target TCR locus by a CRISPR endonuclease;

(vii) in which the one or more exogenous polynucleotides is inserted at the endogenous T cell receptor (TCR) locus using a CRISPR endonuclease.