CLAIMS

1. A cell or a population thereof, in which

(i) the cell is (a) an induced pluripotent stem cell (iPSC), or (b) a derivative cell obtained from differentiating the iPSC;

(ii) the cell comprises one or more exogenous polynucleotides collectively encoding NKG2C, CD94 and DAP12; and

(iii) the one or more exogenous polynucleotides are stably integrated into the genome of the cell.

2. A cell or population thereof according to Claim 1, in which the iPSC is a clonal iPSC, a single cell dissociated iPSC, or an iPS cell line cell; or in which (i) the derivative cell comprises a hematopoietic cell, or (ii) the derivative cell comprises a derivative effector cell having one or more functional features that are not present in a counterpart primary T, NK, NKT, and/or B cell; or (iii) the derivative cell 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) a BiKE or a TriKE;

(ii) HLA-I deficiency;

(iii) HLA-II deficiency;

(iv) introduction of HLA-G or non-cleavable HLA-G;

(v) a chimeric antigen receptor (CAR);

(vi) an exogenous CD16;

(vii) a cell surface expressed exogenous cytokine or a receptor thereof;

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

(xi) disruption of at least one of B2M, TAP1, TAP2, tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD38, CIS,

CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, TIGIT, or any gene in the chromosome 6p21 region; and

(x) 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, 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 tumor targeting specificity,

(ii) improved persistency and/or survival,

(iii) increased resistance to native immune cells,

(iv) increased cytotoxicity,

(v) improved tumor penetration,

(vi) enhanced or acquired ADCC,

(vii) enhanced ability in migrating, and/or activating or recruiting bystander immune cells to tumor sites,

(viii) enhanced ability to reduce tumor immunosuppression,

(ix) improved ability in rescuing tumor antigen escape,

(x) acquired dual targeting capability, and

(xi) serves as an expandable source for engineered effector cells,in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues.

5. A cell or population thereof according to Claim 3, in which (a) the BiKE or the TriKE comprises a first component for CD16, CD64, or NKG2C binding, and a second component for CD30, CD33, BCMA or EPCAM binding; (b) the TriKE comprises a first component for NKG2C binding, a second component for tumor antigen binding, and an IL15 linker between the first and the second components; in which the tumor antigen is

(i) at least one of ADGRE2, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD20, CD22, CD30,

CD33, CD34, CD38, CD41, CD44, CD44V6, CD49f, CD56, CD70, CD74, CD99, CD123, CD133, CD138, CDS, CLEC12A, an antigen of a cytomegalovirus (CMV) infected cell, epithelial glycoprotein-2 (EGP-2), epithelial glycoprotein-40 (EGP-40), epithelial cell adhesion molecule (EpCAM), EGFRvIII, receptor tyrosine-protein kinases erb- B2,3,4, EGFIR, EGFR-VIII, ERBB folate-binding protein (FBP), fetal acetylcholine receptor (AChR), folate receptor-α, Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER2), human telomerase reverse transcriptase (hTERT), ICAM-1, Integrin B7, Interleukin-13 receptor subunit alpha-2 (IL-13Rα2), κ-light chain, kinase insert domain receptor (KDR), Lewis A (CA19.9), Lewis Y (LeY), L1 cell adhesion molecule (L1-CAM), LILRB2, melanoma antigen family A 1 (MAGE-A1), 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; or

(ii) CD33.

6. A cell or population thereof according to Claim 3, in which the exogenous CD16 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.

7. A cell or population thereof according to Claim 6, 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 (4-1BB), IL21, IL7, IL12, IL15, NKp30, NKp44, NKp46, NKG2C, or NKG2D polypeptide; or

(d) the non-native transmembrane domain is derived from NKG2D, the non-native stimulatory domain is derived from 2B4, and the non-native signaling domain is derived from CD3ζ.

8. A cell or population thereof according to Claim 3, 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 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, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD44V6, CD49f, CD56, CD70, CD74, CD99, CD123, CD133, CD138, CDS, CLEC12A, an antigen of a cytomegalovirus (CMV) infected cell, epithelial glycoprotein-2 (EGP-2), epithelial glycoprotein-40 (EGP-40), epithelial cell adhesion molecule (EpCAM), EGFRvIII, receptor tyrosine-protein kinases erb- B2,3,4, EGFIR, EGFR-VIII, ERBB folate-binding protein (FBP), fetal acetylcholine receptor (AChR), folate receptor-α, Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER2), human telomerase reverse transcriptase (hTERT), ICAM-1, Integrin B7, Interleukin-13 receptor subunit alpha-2 (IL-13Rα2), κ-light chain, kinase insert domain receptor (KDR), Lewis A (CA19.9), Lewis Y (LeY), L1 cell adhesion molecule (L1-CAM), LILRB2, melanoma antigen family A 1 (MAGE-A1), 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 a TCR constant region, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion.

9. A cell or population thereof according to Claim 3, in which the cell further comprises a cell surface expressed exogenous cytokine or a receptor 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.

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

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

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

11. A cell or population thereof according to Claim 8 or 10, 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, $A_{2A}R$, BATE, BTLA, CD39, CD47, CD73, CD94, CD96, CD160, CD200, CD200R, CD274, CEACAM1, CSF-1R, Foxpl, GARP, HVEM, IDO, EDO, TDO, LAIR-1, MICA/B, NR4A2, MAFB, OCT-2, Rara (retinoic acid receptor alpha), TLR3, VISTA, NKG2A/HLA-E, or inhibitory KIR.

12. A cell or population thereof according to Claim 10, in which the checkpoint inhibitors comprise:

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

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

13. A cell or population thereof according to Claim 1, in which the derivative cell obtained from differentiating the iPSC 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 lineage cell, a derivative NKT lineage cell, a derivative NK lineage cell, or a derivative B lineage cell.

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

(i) one or more exogenous polynucleotides integrated in a selected genomic locus; or

(ii) more than two exogenous polynucleotides integrated in different selected genomic loci.

15. A cell or population thereof according to Claim 14, in which the selected genomic locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, RUNX1, B2M, TAP1, TAP2, tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD38, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, TIGIT, or any gene in the chromosome 6p21 region.

16. A cell or population thereof according to Claim 15, in which the selected genomic locus is a constant region of TCR α.

17. A composition comprising the cell or population thereof of any of Claims 1 to 16.

18. A composition for therapeutic use comprising the derivative cell of any of Claims 1 to 16, and one or more therapeutic agents; in which the derivative cell is an NK cell.

19. A composition according to Claim 18, 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, a vector comprising one or more polynucleic acids of interest, an antibody or antigen-binding fragment thereof, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

20. A composition according to Claim 19, 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, $A_{2A}R$, BATE, BTLA, CD39, CD47, CD73, CD94, CD96, CD160, CD200, CD200R, CD274, CEACAM1, CSF-1R, Foxpl, GARP, HVEM, IDO, EDO, TDO, LAIR-1, MICA/B, NR4A2, MAFB, OCT-2, Rara (retinoic acid receptor alpha), TLR3, VISTA, NKG2A/HLA-E, or inhibitory KIR;

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

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

21. A composition according to Claim 19, 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

(c) daratumumab.

22. Use of a composition according to any of Claims 17 to 21 in the manufacture of a medicament for the treatment of a hematological malignancy, a solid tumor; cancer, or a virus infection; in which (i) the medicament comprises the derivative cell, and (ii) the derivative cell is an NK cell.

23. A method of manufacturing a derivative cell according to any of Claims 1 to 16 comprising differentiating the iPSC comprising the one or more exogenous polynucleotides collectively encoding NKG2C, CD94 and DAP12.

24. A method of manufacturing derivative cells according to Claim 23, further comprising genomically engineering a clonal iPSC to obtain the iPSC, in which the iPSC has at least one genotype listed in Table 1.

25. A method of manufacturing a derivative cell according to Claim 24, in which the genomic engineering comprises targeted editing, in which the targeted editing comprises deletion or insertion at a pre-selected genomic site.

26. A method of manufacturing a derivative cell according to Claim 25, 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 or homology recombination.

27. A method of CRISPR mediated editing of clonal iPSCs, in which the edited clonal iPSCs comprise:

(a) one or more exogenous polynucleotides collectively encoding NKG2C, CD94 and DAP12; and optionally exogenous polynucleotides encoding one or more of:

(i) a BiKE or a TriKE;

(ii) a CD16; and

(iii) a chimeric antigen receptor (CAR); or

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

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