

CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein:
 - (i) the cell is an induced pluripotent cell (iPSC), or a derivative cell obtained from iPSC differentiation; and
 - (ii) the cell comprises a polynucleotide encoding at least a BCMA-CAR (chimeric antigen receptor).
2. The cell or population thereof of claim 1, wherein the derivative cell obtained from iPSC differentiation 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; or wherein the BCMA-CAR has at least one of the following characteristics:
 - (i) being T cell specific;
 - (ii) being NK cell specific;
 - (iii) binding to surface BCMA;
 - (iv) being inserted at one of the loci: AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; or
 - (v) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD58, CD54, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and wherein the insertion optionally knocks out expression of the gene in the locus.
3. The cell or population thereof of claim 1, wherein the cell further comprises one or more of:
 - (i) CD38 knockout;
 - (ii) B2M null or low, and optionally CIITA null or low, in comparison to its native counterpart cell;
 - (iii) introduced expression of HLA-G or non-cleavable HLA-G, or knockout in one or both of CD58 and CD54;
 - (iv) an exogenous CD16 or a variant thereof;
 - (v) a chimeric antigen receptor (CAR) with targeting specificity other than BCMA;
 - (vi) a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof;

- (vii) at least one of the genotypes listed in Table 1;
 - (viii) deletion or reduced expression in at least one of TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT, in comparison to its native counterpart cell; 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, an antigen-specific TCR, a Fc receptor, a checkpoint inhibitor, an antibody or functional fragments and variants thereof, an engager, and surface triggering receptor for coupling with bi- or multi-specific or universal engagers, in comparison to its native counterpart cell.
4. The cell or population thereof of claim 1, wherein the BCMA-CAR comprises at least:
- (a) a heavy chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;
 - (b) a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38; or
 - (c) a scFV represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39-44.
5. The cell or population thereof of claim 1, wherein 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;
 - (ix) ability to stabilize tumor antigen; and
 - (x) ability to avoid fratricide,

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

6. The cell or population thereof of claim 3, wherein the exogenous CD16 or a variant thereof comprises a high affinity non-cleavable CD16 (hnCD16).

7. The cell or population thereof of claim 3, wherein 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.

8. The cell or population thereof of claim 7, wherein

- (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.

9. The cell or population thereof of claim 3, wherein the cell further comprises a CAR with targeting specificity other than BCMA, and wherein 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 a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof, optionally in separate constructs or in a bi-cistronic construct;
 - (xi) co-expressed with an antibody or functional fragment or variant thereof, or a checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct;
 - (xii) specific to at least one of CD19, MICA/B, CD20, CD22, CD38, CD123, HER2, CD52, EGFR, GD2, MSLN, VEGF-R2, PSMA and PDL1; and/or
 - (xiii) specific to any one of ADGRE2, carbonic anhydrase IX (CAIX), CCRI, 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, EGFR, 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-13R α 2), 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.
10. The cell or population thereof of claim 3, wherein the cell comprises at least a CAR 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.
11. The cell or population thereof of claim 3, wherein the cell surface expressed protein complex:

(a) comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, or variants thereof; and their receptors or variants thereof; or

(b) comprises at least one of:

(i) co-expression of IL15 and IL15R α by using a self-cleaving peptide;

(ii) a fusion protein of IL15 and IL15R α ;

(iii) an IL15/IL15R α fusion protein with intracellular domain of IL15R α truncated;

(iv) a fusion protein of IL15 and membrane bound Sushi domain of IL15R α ;

(v) a fusion protein of IL15 and IL15R β ;

(vi) a fusion protein of IL15 and common receptor γ C, wherein the common receptor γ C is native or modified; and

(vii) a homodimer of IL15R β ;

wherein 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.

12. The cell or population thereof of claim 3, wherein the cell is a derivative NK or a derivative T cell, wherein the derivative NK cell is capable of recruiting, and/or migrating T cells to tumor sites, and wherein the derivative NK or the derivative T cell is capable of reducing tumor immunosuppression in the presence of one or more checkpoint inhibitors.

13. The cell or population thereof of claim 3 or 12, wherein the checkpoint inhibitor is an antagonist 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, Foxp1, 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.

14. The cell or population thereof of claim 13, wherein the checkpoint inhibitor comprises:

(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.

15. The cell or population thereof of claim 1, wherein 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.

16. The cell or population thereof of claim 1, wherein the cell comprises:

- (i) one or more exogenous polynucleotides integrated in one safe harbor locus or a selected gene locus; or
- (ii) more than two exogenous polynucleotides integrated in different safe harbor loci or two or more selected gene loci; or
- (iii) a polynucleotide encoding an IL15 Δ comprising an amino acid sequence of at least about 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NOs: 17, 19 or 21.

17. The cell or population thereof of claim 16, wherein the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; and wherein the selected gene locus is one of B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD58, CD54, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and wherein the integration of the exogenous polynucleotides optionally knocks out expression of the gene in the locus.

18. The cell or population thereof of claim 17, wherein the TCR locus is a constant region of TCR alpha or TCR beta.

19. A cell or population thereof comprising a BCMA-CAR, and one or more of: (i) a CD38 knockout, (ii) an exogenous CD16 or a variant thereof, and (iii) a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof; wherein the cell is an immune effector cell.

20. The cell or population thereof of claim 19, wherein the BCMA-CAR comprises at least:

- (a) a heavy chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;
- (b) a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38; or
- (c) a scFV represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39-44.

21. The cell or population thereof of claim 19, comprising at least one of the following characteristics:

- (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;
- (ix) ability to stabilize tumor antigen; and
- (x) ability to avoid fratricide,

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

22. The cell or population thereof of claim 19, wherein the immune effector cell is a T lineage or NK lineage cell.

23. A composition comprising the cell or population thereof of any one of the claims 1-22.

24. A composition for therapeutic use comprising the cell of any one of the claims 1-22, and one or more therapeutic agents.

25. The composition of claim 24, wherein 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 polynucleic acids of interest, an antibody or a functional variant or fragment thereof, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

26. The composition of claim 25, wherein:

- (1) 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, Foxp1, 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; or

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

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

(3) the therapeutic agents comprise a gamma secretase inhibitor (GSI).

27. The composition of claim 25, wherein 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 rituximab, 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.

28. Therapeutic use of the composition of any one of the claims 24-27 by introducing the composition to a subject suitable for adoptive cell therapy, wherein the subject has (i) an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection; (ii) an inflammatory autoimmune disease, a cancer of plasma cells, or a cancer of B lymphocytes; (iii) an autoimmune disease associated with autoreactive plasma cells and/or autoreactive memory B cells; (iv) systemic lupus erythematosus (SLE), or rheumatic arthritis, multiple myeloma, plasmacytoma, Waldenström macroglobulinemia, plasma cell leukemia or Hodgkin's disease; or (v) multiple myeloma.

29. A method of manufacturing the derivative cell of any one of the claims 1-18, comprising differentiating an iPSC, wherein the iPSC comprises a polynucleotide encoding a BCMA-CAR, and optionally one or more of:

(i) CD38 knockout;

(ii) B2M null or low, and optionally CIITA null or low, in comparison to its native counterpart cell;

(iii) introduced expression of HLA-G or non-cleavable HLA-G, or knockout in one or both of CD58 and CD54;

- (iv) a high affinity non-cleavable CD16 (hnCD16) or a variant thereof;
- (v) a chimeric antigen receptor (CAR) with targeting specificity other than BCMA;
- (vi) a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof;
- (vii) at least one of the genotypes listed in Table 1;
- (viii) deletion or reduced expression in at least one of TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT, in comparison to its native counterpart cell; 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, antigen-specific TCR, Fc receptor, a checkpoint inhibitor, an antibody or functional fragments or variants thereof, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers, in comparison to its native counterpart cell.

30. The method of manufacturing the derivative cell of claim 29, further comprising genomically engineering a clonal iPSC to knock in a polynucleotide encoding a BCMA-CAR; and optionally:

- (i) to knock out CD38; or
- (ii) to knock out B2M and CIITA, to knock out one or both CD58 and CD54, or to introduce expression of HLA-G or non-cleavable HLA-G, an exogenous CD16 or a variant thereof, a second CAR, and/or a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof.

31. The method of manufacturing the derivative cell of claim 30, wherein the genomic engineering comprises targeted editing.

32. The method of manufacturing the derivative cell of claim 31, wherein the targeted editing comprises deletion, insertion, or in/del, and wherein the targeted editing is carried out by CRISPR, ZFN, TALEN, homing nuclease, homology recombination, or any other functional variation of these methods.

33. CRISPR mediated editing of clonal iPSCs, wherein the editing comprises a knock-in of a polynucleotide encoding a BCMA-CAR, and wherein the edited clonal iPSCs comprise at least one of the genotypes listed in Table 1.

34. The CRISPR mediated editing of claim 33, wherein the editing further comprises knocking out CD38, or wherein the BCMA-CAR has at least one of the following characteristics:

- (i) being T cell specific;
- (ii) being NK cell specific;
- (iii) binding to surface BCMA;
- (iv) comprising a heavy chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;
- (vi) comprising a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38;
- (vii) comprising a scFV represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39, 40, 41, 42, 43, or 44; and
- (viii) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD58, CD54, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT, wherein the insertion knocks out expression of the gene in the locus.

35. The CRISPR mediated editing of claim 33, wherein the editing further comprises an insertion of the BCMA-CAR or a second CAR at a constant region of a TCR locus, and/or wherein the CAR is driven by an endogenous promoter of TCR, and/or wherein the TCR is knocked out by the CAR insertion.

36. A method of improving treatment of multiple myeloma comprising administering to a subject under the treatment effector cells comprising a BCMA-CAR, a CD38 knockout, and a high affinity non-cleavable CD16 or a variant thereof, wherein the BCMA-CAR has at least one of the following characteristics:

- (i) being T cell specific;
- (ii) being NK cell specific;
- (iii) binding to and stabilizing cell surface BCMA;

(iv) comprising a heavy chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;

(vi) comprising a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38;

(vii) comprising a scFV represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39, 40, 41, 42, 43 or 44; and

(viii) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD58, CD54, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT, wherein the insertion knocks out expression of the gene in the locus.

37. The method of claim 36, wherein the effector cells comprise derivative hematopoietic cells comprising derivative NK cells or derivative T cells, and wherein the derivative NK cells or derivative T cells further comprise one or more of:

- (i) B2M and CIITA knockout;
- (ii) introduced expression of HLA-G or non-cleavable HLA-G, or knockout of one or both of CD58 and CD54;
- (iii) introduced expression of a second CAR, and/or a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof; and/or
- (iii) at least one of the genotypes listed in Table 1.

38. The method of claim 36, further comprising administering an anti-CD38 antibody and/or a GSI.

39. The method of claim 36, wherein effector cells comprising a BCMA-CAR, a CD38 knockout, and a high affinity non-cleavable CD16 or a variant thereof, have been contacted, or are in contact, with a GSI.

40. The method of claim 36, wherein the multiple myeloma is a relapse or refractory type of multiple myeloma.

CLAIMS

1. A cell or a population thereof, in which:

(i) the cell is an induced pluripotent cell (iPSC), or a derivative cell obtained from iPSC differentiation; and

5 (ii) the cell comprises a polynucleotide encoding at least a BCMA-CAR (chimeric antigen receptor).

2. A cell or population thereof according to Claim 1, in which the derivative cell obtained from iPSC differentiation is a hematopoietic cell, and comprises longer telomeres in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood,
10 or any other donor tissues; or in which the BCMA-CAR has at least one of the following characteristics:

(i) being T cell specific;

(ii) being NK cell specific;

(iii) binding to surface BCMA;

15 (iv) being inserted at one of the loci: AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; or

(v) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and in which the insertion optionally
20 knocks out expression of the gene in the locus.

3. A cell or population thereof according to Claim 1, in which the cell further comprises one or more of:

(i) CD38 knockout;

25 (ii) HLA-I deficiency, and optionally HLA-II deficiency, in comparison to its native counterpart cell;

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

(iv) an exogenous CD16 or a variant thereof;

(v) a chimeric antigen receptor (CAR) with targeting specificity other than BCMA;

(vi) a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof;

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

5 (viii) deletion or disruption in at least one of B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT, in comparison to its native counterpart cell; and

10 (ix) introduction or upregulation of at least one of HLA-E, 41BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, A_{2A}R, an antigen-specific TCR, a Fc receptor, a checkpoint inhibitor, an antibody or functional fragments and variants thereof, an engager, and surface triggering receptor for coupling with bi- or multi-specific or universal engagers, in comparison to its native counterpart cell.

4. A cell or population thereof according to Claim 1, in which the BCMA-CAR comprises at least:

15 (a) a heavy chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;

20 (b) a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38; or

(c) a scFV represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39-44.

5. A cell or population thereof according to Claim 1, in which the cell is a derivative NK or a derivative T cell, and has at least one of the following characteristics comprising:

- 25 (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;

5 (ix) ability to stabilize tumor antigen; and

(x) ability to avoid fratricide,

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

10 6. A cell or population thereof according to Claim 3, in which the exogenous CD16 or a variant thereof comprises a high affinity non-cleavable CD16 (hnCD16).

7. A cell or population thereof according to Claim 3, 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;

15 (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

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

8. A cell or population thereof according to Claim 7, in which

25 (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 CD3 ζ , 2B4, DAP10, DAP12, DNAM1, CD137 (41BB), IL21, IL7, IL12, IL15, NKp30, NKp44, NKp46, NKG2C, or NKG2D polypeptide; or

5 (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 CD3 ζ .

9. A cell or population thereof according to Claim 3, in which the cell further comprises a CAR with targeting specificity other than BCMA, and in which the CAR is:

- (i) T cell specific or NK cell specific;
- 10 (ii) bi-specific antigen binding CAR;
- (iii) a switchable CAR;
- (iv) a dimerized CAR;
- (v) a split CAR;
- (vi) a multi-chain CAR;
- 15 (vii) an inducible CAR;
- (viii) co-expressed with a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof, optionally in separate constructs or in a bi-cistronic construct;
- (xi) co-expressed with an antibody or functional fragment or variant thereof, or a
- 20 checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct;
- (xii) specific to at least one of CD19, MICA/B, CD20, CD22, CD38, CD123, HER2, CD52, EGFR, GD2, MSLN, VEGF-R2, PSMA and PDL1; 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,
- 25 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, EGFR, 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-13R α 2), 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.

10. A cell or population thereof according to Claim 3, in which the cell comprises at least a CAR 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.

11. A cell or population thereof according to Claim 3, in which the cell surface expressed protein complex:

(a) comprises at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, or variants thereof; and their receptors or variants thereof; or

(b) comprises at least one of:

(i) co-expression of IL15 and IL15R α by using a self-cleaving peptide;

(ii) a fusion protein of IL15 and IL15R α ;

(iii) an IL15/IL15R α fusion protein with intracellular domain of IL15R α truncated;

(iv) a fusion protein of IL15 and membrane bound Sushi domain of IL15R α ;

(v) a fusion protein of IL15 and IL15R β ;

(vi) a fusion protein of IL15 and common receptor γ C, in which the common receptor γ C is native or modified; and

(vii) a homodimer of IL15R β ;

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.

5 12. A cell or population thereof according to Claim 3, 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.

10 13. A cell or population thereof according to Claim 3 or 12, in which the checkpoint inhibitor is an antagonist 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, Foxp1, 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.

15 14. A cell or population thereof according to Claim 13, in which the checkpoint inhibitor comprises:

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

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

15. 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
25 cell.

16. 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 a selected gene locus; or

(ii) more than two exogenous polynucleotides integrated in different safe harbor loci or two or more selected gene loci; or

(iii) a polynucleotide encoding an IL15 Δ comprising an amino acid sequence of at least about 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NOs: 17, 19 or 21.

5 17. A cell or population thereof according to Claim 16, in which the safe harbor locus comprises at least one of AAVS1, CCR5, ROSA26, collagen, HTRP, H11, GAPDH, or RUNX1; and in which the selected gene locus is one of B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and optionally in which the integration of the
10 exogenous polynucleotides knocks out expression of the gene in the locus.

18. A cell or population thereof according to Claim 17, in which the TCR locus is a constant region of TCR alpha or TCR beta.

19. A cell or population thereof comprising a BCMA-CAR, and one or more of: (i) a CD38 knockout, (ii) an exogenous CD16 or a variant thereof, and (iii) a cell surface expressed
15 protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof; in which the cell is an immune effector cell.

20. A cell or population thereof according to Claim 19, in which the BCMA-CAR comprises at least:

(a) a heavy chain variable region represented by an amino acid sequence that is of at
20 least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;

(b) a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38; or

(c) a scFV represented by an amino acid sequence that is of at least about 99%, 98%,
25 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39-44.

21. A cell or population thereof according to Claim 19, comprising at least one of the following characteristics:

(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;
 - 5 (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;
 - (ix) ability to stabilize tumor antigen; and
 - 10 (x) ability to avoid fratricide,
- in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues.
22. A cell or population thereof according to Claim 19, in which the immune effector cell is a T lineage or NK lineage cell.
- 15 23. A composition comprising a cell or population thereof according to any preceding claim.
24. A composition for therapeutic use comprising a cell according to any of Claims 1 to 22, and one or more therapeutic agents.
25. A composition according to Claim 24, in which the one or more therapeutic agents
- 20 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 a functional variant or fragment thereof, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).
- 25 26. A composition according to Claim 25, in which:
- (1) 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, A_{2A}R, BATE, BTLA,

CD39, CD47, CD73, CD94, CD96, CD160, CD200, CD200R, CD274, CEACAM1, CSF-1R, Foxp1, 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;

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

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

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

(3) the therapeutic agents comprise a gamma secretase inhibitor (GSI).

27. A composition according to Claim 25, 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;

15 (b) one or more of rituximab, 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

20 (c) daratumumab.

28. Use of a composition according to any of Claims 24 to 27 in the manufacture of a medicament for the treatment of (i) an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection; (ii) an inflammatory autoimmune disease, a cancer of plasma cells, or a cancer of B lymphocytes; (iii) an autoimmune disease associated with
25 autoreactive plasma cells and/or autoreactive memory B cells; (iv) systemic lupus erythematosus (SLE), or rheumatic arthritis, multiple myeloma, plasmacytoma, Waldenström macroglobulinemia, plasma cell leukemia or Hodgkin's disease; or (v) multiple myeloma.

29. A method of manufacturing a derivative cell according to any of Claims 1 to 18, comprising differentiating an iPSC, in which the iPSC comprises a polynucleotide encoding a
30 BCMA-CAR, and optionally one or more of:

- (i) CD38 knockout;
- (ii) HLA-I deficiency, and optionally HLA-II deficiency, in comparison to its native counterpart cell;
- (iii) introduction of HLA-G or non-cleavable HLA-G;
- 5 (iv) an exogenous CD16 or a variant thereof;
- (v) a chimeric antigen receptor (CAR) with targeting specificity other than BCMA;
- (vi) a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof;
- (vii) at least one of the genotypes listed in Table 1;
- 10 (viii) deletion or disruption in at least one of B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT, in comparison to its native counterpart cell; and
- (ix) introduction or upregulation of at least one of HLA-E, 41BBL, CD3, CD4, CD8, 15 CD16, CD47, CD113, CD131, CD137, CD80, PDL1, A_{2A}R, antigen-specific TCR, Fc receptor, a checkpoint inhibitor, an antibody or functional fragments or variants thereof, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers, in comparison to its native counterpart cell.
- 30. A method of manufacturing a derivative cell according to Claim 29, further comprising 20 genomically engineering a clonal iPSC to knock in a polynucleotide encoding a BCMA-CAR; and optionally:
 - (i) to knock out CD38; or
 - (ii) to knock out B2M or CIITA, or to introduce polynucleotides encoding HLA-G or non-cleavable HLA-G, an exogenous CD16 or a variant thereof, a second CAR, and/or a 25 cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof.
- 31. A method of manufacturing a derivative cell according to Claim 30, in which the genomic engineering comprises targeted editing.

32. A method of manufacturing a derivative cell according to Claim 31, 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.

5 33. CRISPR mediated editing of clonal iPSCs, in which the editing comprises a knock-in of a polynucleotide encoding a BCMA-CAR, and in which the edited clonal iPSCs comprise at least one of the genotypes listed in Table 1.

34. CRISPR mediated editing according to Claim 33, in which the editing further comprises knocking out CD38, or in which the BCMA-CAR has at least one of the following
10 characteristics:

- (i) being T cell specific;
- (ii) being NK cell specific;
- (iii) binding to surface BCMA;
- (iv) comprising a heavy chain variable region represented by an amino acid sequence
15 that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;
- (vi) comprising a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38;
- (vii) comprising a scFV represented by an amino acid sequence that is of at least about
20 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39, 40, 41, 42, 43, or 44; and
- (viii) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD56, CIS, CBL-
25 B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT, in which the insertion knocks out expression of the gene in the locus.

35. CRISPR mediated editing according to Claim 33, in which the editing further comprises an insertion of the BCMA-CAR or a second CAR at a constant region of a TCR locus, and/or in which the CAR is driven by an endogenous promoter of TCR, and/or in which the TCR is
30 knocked out by the CAR insertion.

36. Use of effector cells comprising a BCMA-CAR, a CD38 knockout, and an exogenous CD16 or a variant thereof in the manufacture of a medicament for the treatment of multiple myeloma, in which the BCMA-CAR has at least one of the following characteristics:

- (i) being T cell specific;
 - 5 (ii) being NK cell specific;
 - (iii) binding to and stabilizing cell surface BCMA;
 - (iv) comprising a heavy chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 33, 35, or 37;
 - 10 (vi) comprising a light chain variable region represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 34, 36, or 38;
 - (vii) comprising a scFV represented by an amino acid sequence that is of at least about 99%, 98%, 96%, 95%, 90%, 85%, or 80% identity to any one of SEQ ID NOs: 39, 40,
 - 15 41, 42, 43 or 44; and
 - (viii) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT, in which the insertion knocks out expression of the gene in the locus.
- 20 37. Use according to Claim 36, in which the effector cells comprise derivative hematopoietic cells comprising derivative NK cells or derivative T cells, and in which the derivative NK cells or derivative T cells further comprise one or more of:
- (i) B2M or CIITA knockout;
 - (ii) introduced expression of HLA-G or non-cleavable HLA-G;
 - 25 (iii) introduced expression of a second CAR, and/or a cell surface expressed protein complex comprising a partial or full length of a cytokine, a cytokine receptor, or any combination thereof; and/or
 - (iii) at least one of the genotypes listed in Table 1.

38. Use according to Claim 36, in which the medicament is for use in combination with an anti-CD38 antibody and/or a GSI.

39. Use according to Claim 36, in which effector cells comprising a BCMA-CAR, a CD38 knockout, and an exogenous CD16 or a variant thereof, have been contacted, or are in contact,
5 with a GSI.

40. Use according to Claim 36, in which the multiple myeloma is a relapse or refractory type of multiple myeloma.