CLAIMS

What is claimed is:

1. A composition comprising a cell or population thereof, wherein the cell is an immune cell, an induced pluripotent cell (iPSC) or a derivative cell obtained from differentiating the iPSC; and wherein the cell comprises a MICA/B tumor antigen targeting specificity; wherein the cell optionally comprises one or more exogenous polynucleotides encoding a MICA/B-CAR (chimeric antigen receptor), a CD16 or a variant thereof that mediates ADCC when in combination with an anti-MICA/B antibody, an exogenous TCR targeting a MICA/B tumor antigen, or any combination thereof; and wherein:

(i) the cell or population thereof further comprises a CAR having a tumor antigen targeting specificity other than MICA/B, or

(ii) the composition further comprises a sensitizing agent, wherein the sensitizing agent increases tumor cell surface levels of MICA/B.

2. The composition of claim 1, wherein the iPSC is a clonal iPSC, a single cell dissociated iPSC, an iPSC cell line cell, or an iPSC master cell bank (MCB) cell; or wherein the derivative cell is a hematopoietic cell, and comprises longer telomeres in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues; or wherein the MICA/B-CAR has at least one of the following characteristics:

(i) being T cell specific;

(ii) being NK cell specific;

(iii) binding to surface MICA/B;

(iv) comprising a scFV (single chain variable fragment) binding to the conserved α3 domain of MICA/B;

(v) 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 SEQ ID NO: 1;

(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 SEQ ID NO: 2;

(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 SEQ ID NOs: 3 or 4;

(viii) comprising a heavy chain variable region of a MICA/B binding scFV functionally linked to a first constant region of a T cell receptor (TCR), and a light chain variable region of a MICA/B binding scFV functionally linked to a second constant region of a T cell receptor (TCR); and

(ix) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD38, CD25, CD44, CD58, CD54, CD56, CD69, CD71, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and, optionally, wherein the insertion knocks out expression of the gene in the locus.

3. The composition of claim 1 or 2, wherein the cell further comprises one or more of:

(i) CD38 knockout;

(ii) HLA-I deficiency and/or HLA-II deficiency;

(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 MICA/B;

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

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

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

(ix) introduction of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, antigen-specific TCR, Fc receptor, 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 composition of claim 3, wherein the exogenous CD16 comprises a high affinity non-cleavable CD16 (hnCD16) or a variant thereof.

5. The composition of claim 1, wherein the sensitizing agent comprises at least one of external beam radiation, brachytherapy, a radiopharmaceutical and a chemotherapeutic agent.

6. The composition of claim 1 or 5, further comprising one or more therapeutic agents.

7. The composition of any one of claims 1-6, further comprising a multi-specific engager; optionally wherein the multi-specific engager is at least one of: (i) a T cell engager; (ii) an NK cell engager; (iii) a bi-specific T cell engager (BiTE); (iv) a bi-specific killer cell engager (BiKE); (v) a tri-specific killer cell engager (TriKE); (vi) a MICA/B engager; or (vii) a CD16 engager.

8. The composition of any one of claims 1-7, 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.

9. The composition of claim 1, wherein the CAR having a tumor antigen targeting specificity other than MICA/B is:

(i) T cell specific or NK cell specific;
(ii) a 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) a recombinant TCR;

(ix) co-expressed with another CAR;

(x) co-expressed with a cytokine signaling complex comprising 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;

(xi) co-expressed with a checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct;

(xii) specific to at least one of CD19, BCMA, 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, CD33, CD34, CD38, CD41, CD44, CD44V6, CD49f, CD56, CD70, CD74, CD99, CD123, CD133, CD138, CDS, CLEC12A, an antigen of a cytomegalovirus (CMV) infected cell, epithelial glycoprotein2 (EGP-2), epithelial glycoprotein-40 (EGP-40), epithelial cell adhesion molecule (EpCAM), EGFRvIII, receptor tyrosine-protein kinases erb- B2,3,4, EGFIR, EGFR-VIII, ERBB folate-binding protein (FBP), fetal acetylcholine receptor (AChR), folate receptor-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 A1 (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;

wherein the CAR of any one of (i) to (xiii) is optionally inserted at TRAC locus, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion.

10. The composition of claim 9, wherein the CAR having a tumor antigen targeting specificity other than MICA/B is specific to BCMA.

11. The composition of claim 3, wherein the cytokine signaling complex:

(a) comprises a partial or full peptide of at least one of IL2, IL4, IL6, IL7, IL9, IL10, IL11, IL12, IL15, IL18, IL21, and its respective receptor; 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, wherein the common receptor γC is native or modified; and

(vii) a homodimer of IL15Rβ; wherein any one of (b)(i)-(vii) can be co-expressed with a CAR in separate constructs or in a bi-cistronic construct; or

(c) comprises at least one of:

(i) a fusion protein of IL7 and IL7Rα;

(ii) a fusion protein of IL7 and common receptor γC, wherein the common receptor γC is native or modified; and

(iii) a homodimer of IL7Rβ, wherein any one of (c)(i)-(iii) is optionally co-expressed with a CAR in separate constructs or in a bi-cistronic expression cassette;

and optionally,

(d) is transiently expressed.

12. The composition 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 composition of claim 3, 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.

14. The composition 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 locus.

15. The composition of claim 14, wherein the safe harbor locus is a constant region of TCR alpha or TCR beta.

16. Use of a cell or population thereof in the manufacture of a medicament for treating tumor cells in a subject, wherein:

(a) the cell or population thereof is to be administered to the subject;

(b) the cell is an immune cell or a derivative cell obtained from differentiating an iPSC;

(c) the cell comprises a MICA/B tumor antigen targeting specificity;

(d) the cell optionally comprises one or more exogenous polynucleotides encoding a MICA/B-CAR (chimeric antigen receptor), a CD16 or a variant thereof that mediates ADCC when in combination with an anti-MICA/B antibody, an exogenous TCR targeting a MICA/B tumor antigen, or any combination thereof;

(e) the subject has an autoimmune disorder; a hematological malignancy; a solid tumor; cancer, or a virus infection; and

(f) (i) the tumor cells comprise tumor cells preconditioned with a sensitizing agent;

and/or (ii) the cell comprises an exogenous polynucleotide encoding a CAR with targeting specificity other than MICA/B.

17. The use of claim 16, wherein the sensitizing agent increases MICA/B surface expression and/or MICA/B density on the tumor cells.

18. The use of claim 16, wherein the sensitizing agent comprises at least one of a chemotherapeutic agent, external beam radiation, brachytherapy, and a radiopharmaceutical.

19. The use of claim 18, wherein the sensitizing agent comprises:

(i) at least one of x-ray radiation, gamma radiation, photon radiation, proton radiation, and neutron radiation; or

(ii) at least one of calcium-47, carbon-11, carbon-14, chromium-51, cobalt-57, cobalt-58, erbium-169, fluorine-18, gallium-67, gallium-68, hydrogen-3, indium-111, iodine-123, iodine-125, iodine-131, iorn-59, krypton-81m, lutetium-177, nitrogen-13, oxygen-15, phosphorus-32, radium-223, rubidium-82, samarium-153, selenium-75, sodium-22, sodium-24, strontium-89, technetium-99m, thallium-201, xenon-133, and yttrium-90; or

(iii) paclitaxel.

20. The use of claim 18, wherein an antibody that binds to a MIC alpha 3-domain of MICA/B tumor cell surface antigen is to be further administered to the subject.

21. The use of claim 18, wherein the derivative cell is a hematopoietic cell, and comprises longer telomeres in comparison to its native counterpart cell obtained from peripheral blood, umbilical cord blood, or any other donor tissues; or wherein the MICA/B-CAR has at least one of the following characteristics:

(i) being T cell specific;

(ii) being NK cell specific;

(iii) binding to surface MICA/B;

(iv) comprising a scFV (single chain variable fragment) binding to the conserved α3 domain of MICA/B;

(v) 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 SEQ ID NO: 1;

(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 SEQ ID NO: 2;

(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 SEQ ID NOs: 3 or 4;

(viii) comprising a heavy chain variable region of a MICA/B binding scFV functionally linked to a first constant region of a T cell receptor (TCR), and a light chain variable region of a MICA/B binding scFV functionally linked to a second constant region of a T cell receptor (TCR); and

(ix) being inserted at one of the gene loci: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR α or β constant region, NKG2A, NKG2D, CD38, CD25, CD44, CD58, CD54, CD56, CD69, CD71, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and, optionally, wherein the insertion knocks out expression of the gene in the locus.

22. The use of any one of claims 16-21, wherein the cell further comprises one or more of:

(i) CD38 knockout;

(ii) HLA-I deficiency and/or HLA-II deficiency;

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

(iv) an exogenous CD16 or a variant thereof;

(v) a cytokine signaling complex comprising a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof;

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

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

(viii) introduction of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, $A_{2A}R$, antigen-specific TCR, Fc receptor, an engager, and surface triggering receptor for coupling with bi- or multi- specific or universal engagers, in comparison to its native counterpart cell.

23. The use of claim 22, wherein the exogenous CD16 comprises a high affinity non-cleavable CD16 (hnCD16) or a variant thereof.

24. The use of claim 23, wherein the high affinity non-cleavable CD16 (hnCD16) 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 stimulatory domain; and

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

25. The use of claim 16, wherein the chimeric antigen receptor (CAR) with targeting specificity other than MICA/B is:

(i) T cell specific or NK cell specific;

(ii) a 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) a recombinant TCR;

(ix) co-expressed with another CAR;

(x) co-expressed with a cytokine signaling complex comprising 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;

(xi) co-expressed with a checkpoint inhibitor, optionally in separate constructs or in a bi-cistronic construct;

(xii) specific to at least one of CD19, BCMA, 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, 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;

wherein the CAR of any one of (i) to (xiii) is optionally inserted at TRAC locus, and/or is driven by an endogenous promoter of TCR, and/or the TCR is knocked out by the CAR insertion.

26. The use of claim 16, wherein the CAR with targeting specificity other than MICA/B is specific to BCMA.

27. The use of claim 16, wherein one or more therapeutic agents is to be further administered to the subject.

28. The use of claim 27, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, an engager, an antibody, an antibody conjugate, 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, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

29. The use of claim 28, wherein:

(a) the checkpoint inhibitor comprises:

(i) 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;

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

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

(b) the therapeutic agents comprise one or more of venetoclax, azacitidine, and pomalidomide.

30. The use of claim 28, wherein the antibody comprises:

(a) an MICA/B antibody that binds to a MIC alpha 3-domain of a cell surface MICA/B antigen;

(b) an antibody triggering antibody-dependent cellular cytotoxicity (ADCC);

(c) an anti-CD20, an anti-CD22, an anti-HER2, an anti-CD52, an anti-EGFR, an anti-CD123, an anti-GD2, an anti-PDL1, and/or an anti-CD38 antibody; and/or

(d) one or more of rituximab, veltuzumab, ofatumumab, ublituximab, ocaratuzumab, obinutuzumab, ibritumomab, ocrelizumab, inotuzumab, moxetumomab, epratuzumab, trastuzumab, pertuzumab, alemtuzumab, cetuximab, amivantamab, dinutuximab, avelumab, daratumumab, isatuximab, MOR202, 7G3, CSL362, elotuzumab, and their humanized or Fc modified variants or fragments and their functional equivalents and biosimilars.

31. The use of any one of claims 16-30, wherein a multi-specific engager is to be further administered to the subject.

32. The use of claim 31, wherein the multi-specific engager is at least one of: (i) a T cell engager; (ii) an NK cell engager; (iii) a bi-specific T cell engager (BiTE); (iv) a b-ispecific killer cell engager (BiKE); (v) a tri-specific killer cell engager (TriKE); (vi) a MICA/B engager; or (vii) a CD16 engager.

33. The use of any one of claims 16-32, wherein the tumor cells comprise tumor cells preconditioned with the sensitizing agent.

34. The use of any one of claims 16-32, wherein the cell comprises the exogenous polynucleotide encoding the CAR with targeting specificity other than MICA/B.

35. A cell or population thereof for use in therapy, wherein:

(a) the cell is an immune cell or a derivative cell obtained from differentiating an iPSC;

(b) the cell comprises a MICA/B tumor antigen targeting specificity;

(c) the cell optionally comprises one or more exogenous polynucleotides encoding a MICA/B-CAR (chimeric antigen receptor), a CD16 or a variant thereof that mediates ADCC when in combination with an anti-MICA/B antibody, an exogenous TCR targeting a MICA/B tumor antigen, or any combination thereof; and

(d) the cell comprises an exogenous polynucleotide encoding a CAR with targeting specificity other than MICA/B.