CLAIMS

1. A T cell derived from an induced pluripotent stem cell (iPSC), wherein the iPSC comprises: one or more polynucleotides encoding a rearranged γδ T cell receptor (TCR) and an exogenous polynucleotide encoding a chimeric antigen receptor (CAR); and one or more of:

a. an exogenous polynucleotide encoding an artificial cell death polypeptide;
b. a deletion or reduced expression of one or more of B2M, TAP 1, TAP 2, Tapasin, RFXANK, CIITA, RFX5 and RFXAP genes;
c. a deletion or reduced expression of RAG1 and RAG2 genes;
d. an exogenous polynucleotide encoding a non-naturally occurring variant of FcγRIII (CD16);
e. an exogenous polynucleotide encoding interleukin 15 (IL-15) and/or IL-15 receptor or a variant or truncation thereof;
f. an exogeneous polynucleotide encoding a constitutively active interleukin 7 (IL-7) receptor or variant thereof;
g. an exogenous polynucleotide encoding interleukin 12 (IL-12) or interleukin 21 (IL-21) or a variant thereof;
h. an exogenous polynucleotide encoding human leukocyte antigen E (HLA-E) and/or human leukocyte antigen G (HLA-G);
i. an exogenous polynucleotide encoding leukocyte surface antigen cluster of differentiation CD47 (CD47) and/or CD24; and
j. an exogenous polynucleotide encoding one or more imaging or reporter proteins.

2. The T cell according to claim 1, wherein the T cell with the rearranged γδ TCR enables increased expansion of the T cell after mitogenic stimulation than a T cell without the rearranged TCR.

3. The T cell according to claim 2, wherein the iPSC is reprogrammed from peripheral blood mononuclear cells (PBMCs).

4. The T cell according to claim 1, wherein the rearranged γδ TCR is activated by one or more phospho-antigens selected from isopentenyl pyrophosphate (IPP), dimethylallyl diphosphate (DMAPP), and (E)-4-hydroxy-3-methyl-but-2-enylpyrophosphate (HMBPP), or chemically similar molecules, wherein the phospho-antigens are naturally-occurring in cells as part of normal metabolic processes or the phospho-antigens are caused to accumulate in cells at higher

levels due to treatment with bisphosphonate chemicals, wherein the activity of phospho-antigens is through direct interaction with the γδ TCR or wherein the activity of phospho-antigens is through interactions with butyrophilin (BTN) proteins BTN2A1, BTN3A1, BTN3A2, or BTN3A3.

5. The T cell according to claim 1, wherein the rearranged γδ TCR is not activated by phospho-antigens.

6. The T cell according to any one of claims 1-5, comprising an exogenous polynucleotide encoding a human leukocyte antigen E (HLA-E) and/or human leukocyte antigen G (HLA-G).

7. The T cell according to any one of claims 1-6, wherein one or more of the exogenous polynucleotides are integrated at one or more loci on the chromosome of the cell selected from the group consisting of AAVS1, CCR5, ROSA26, collagen, HTRP, Hl l, GAPDH, RUNX1, B2M, TAPI, TAP2, Tapasin, NLRC5, CIITA, RFXANK, CIITA, RFX5, RFXAP, TRAC, TRBC1, TRBC2, RAG1, RAG2, NKG2A, NKG2D, CD38, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT genes, provided at least one of the exogenous polynucleotides is integrated at a locus of a gene selected from the group consisting of B2M, TAP 1, TAP 2, Tapasin, RFXANK, CIITA, RFX5 and RFXAP genes to thereby result in a deletion or reduced expression of the gene.

8. The T cell according to claim 7, wherein one or more of the exogenous polynucleotides are integrated at the loci of the CIITA, AAVS1 and B2M genes.

9. The T cell according to claim 8 having a deletion or reduced expression of one or more of B2M or CIITA genes.

10. The T cell according to any one of claims 1-9, wherein one or more of the exogenous polynucleotides are integrated at a CD38 locus to thereby result in a deletion or reduced expression of the CD38 gene.

11. The T cell according to any one of claims 1-10, wherein the CAR comprises:

(i) a signal peptide;

(ii) an extracellular domain comprising a binding domain that specifically binds an antigen on a target cell;

(iii) a hinge region;

(iv) a transmembrane domain;

(v) an intracellular signaling domain; and

(vi) a co-stimulatory domain.

12. The T cell according to claim 11, wherein the signal peptide is a GMCSFR signal peptide.

13. The T cell according to claim 11, wherein the extracellular domain comprises an scFv or V_HH derived from an antibody that specifically binds an antigen that is expressed on cancer cells.

14. The T cell according to claim 11, wherein the hinge region comprises a CD28 hinge region, a CD8 hinge region, or an IgG hinge region.

15. The T cell according to claim 11, wherein the transmembrane domain comprises a CD28 transmembrane domain or a CD8 transmembrane domain.

16. The T cell according to claim 11, wherein the intracellular signaling domain is derived from DAP10, DAP12, Fc epsilon receptor I γ chain (FCER1G), FcR β, NKG2D, CD3δ, CD3ε, CD3γ, CD3ζ, CD5, CD22, CD226, CD66d, CD79A, or CD79B.

17. The T cell according to claim 11, wherein the co-stimulatory domain is a co-stimulatory signaling domains are derived from CD28, 41BB, IL2Rb, CD40, OX40 (CD134), CD80, CD86, CD27, ICOS, NKG2D, DAP10, DAP12, or 2B4 (CD244).

18. The T cell according to claim 11, wherein the CAR comprises:

(i) the signal peptide comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 1;

(ii) the extracellular domain comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 7;

(iii) the hinge region comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 22;

(iv) the transmembrane domain comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 24;

(v) the intracellular signaling domain comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 6; and

(vi) the co-stimulatory domain comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 20.

19. The T cell according to claim 21, wherein the CAR comprises:

(i) the signal peptide comprising the amino acid sequence of SEQ ID NO: 1;

(ii) the extracellular domain comprising the amino acid sequence of SEQ ID NO: 7;

(iii) the hinge region comprising an amino acid sequence of SEQ ID NO: 22;

(iv) the transmembrane domain comprising the amino acid sequence of SEQ ID NO: 24;

(v) the intracellular signaling domain comprising the amino acid sequence of SEQ ID NO: 6; and

(vi) the co-stimulatory domain comprising the amino acid sequence of SEQ ID NO: 20.

20. The T cell according to any one of claims 1-19, comprising the exogenous polynucleotide encoding the artificial cell death polypeptide, wherein the mechanism of action of the artificial cell death polypeptide is metabolic, dimerization-inducing or therapeutic monoclonal antibody-mediated.

21. The T cell according to claim 20, wherein the artificial cell death polypeptide is an inactivated cell surface protein selected from the group of monoclonal antibody specific epitopes selected from epitopes specifically recognized by ibritumomab, tiuxetan, muromonab-CD3, tositumomab, abciximab, basiliximab, brentuximab vedotin, cetuximab, infliximab, rituximab, alemtuzumab, bevacizumab, certolizumab pegol, daclizumab, eculizumab, efalizumab, gemtuzumab, natalizumab, omalizumab, palivizumab, polatuzumab vedotin, ranibizumab, tocilizumab, trastuzumab, vedolizumab, adalimumab, belimumab, canakinumab, denosumab, golimumab, ipilimumab, ofatumumab, panitumumab, daratumumab, or ustekinumab.

22. The T cell according to claim 21, wherein the inactivated cell surface protein is a truncated epithelial growth factor receptor (tEGFR) variant.

23. The T cell according to claim 22, wherein the tEGFR variant consists of an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 71.

24. The T cell according to claim 6, wherein the HLA-E comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 66 or the HLA-G comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 69.

25. The T cell according to any one of claims 1-24, wherein:

(i) the exogenous polynucleotide encoding the chimeric antigen receptor (CAR) is integrated at a locus of AAVS1 gene;

(ii) the exogenous polynucleotide encoding the artificial cell death polypeptide is integrated at a locus of CIITA gene; and

(iii) the exogenous polynucleotide encoding the human leukocyte antigen E (HLA-E) and/or human leukocyte antigen G (HLA-G) is integrated at a locus of B2M gene;

wherein integration of the exogenous polynucleotides deletes or reduces expression of CIITA and B2M.

26. The T cell according to any one of claims 1-25, wherein the CAR specifically binds CD38.

27. A T cell derived from an induced pluripotent stem cell (iPSC), wherein the iPSC comprises:

(i) an exogenous polynucleotide encoding a chimeric antigen receptor (CAR) having the amino acid sequence of SEQ ID NO: 61;

(ii) an exogenous polynucleotide encoding an artificial cell death polypeptide comprising an apoptosis-inducing domain having the amino acid sequence of SEQ ID NO: 71;

(iii) a polynucleotide encoding a rearranged T cell receptor (TCR) locus comprising a γ TCR having the amino acid sequence of SEQ ID NO: 133, 135, or 150 and a δ TCR having the amino acid sequence of SEQ ID NO: 134, 136, or 151; and

(iv) optionally, an exogenous polynucleotide encoding a human leukocyte antigen E (HLA-E) having the amino acid sequence of SEQ ID NO: 66;

wherein one or more of the exogenous polynucleotides are integrated at loci of AAVS1, CIITA and B2M genes, to thereby delete or reduce expression of CIITA and B2M.

28. A composition comprising the T cell according to any one of the claims 1-27.

29. The composition according to claim 28, further comprising or being used in combination with, one or more therapeutic agents selected from the group consisting of a peptide, a cytokine, a checkpoint inhibitor, a mitogen, a growth factor, a small RNA, a dsRNA (double stranded RNA), siRNA, oligonucleotide, mononuclear blood cells, a vector comprising one or more polynucleic acids of interest, an antibody, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

30. The composition according to claim 29 comprising or being used in combination with the antibody, wherein the antibody is an anti-CD20 antibody.

31. The composition according to claim 29 comprising or being used in combination the antibody, wherein the antibody comprises one or more selected from the group consisting of ibritumomab, tiuxetan, muromonab-CD3, tositumomab, abciximab, basiliximab, brentuximab vedotin, cetuximab, infliximab, rituximab, alemtuzumab, bevacizumab, certolizumab pegol, daclizumab, eculizumab, efalizumab, gemtuzumab, natalizumab, omalizumab, palivizumab, polatuzumab vedotin, ranibizumab, tocilizumab, trastuzumab, vedolizumab, adalimumab, belimumab, canakinumab, denosumab, golimumab, ipilimumab, ofatumumab, panitumumab, obinutuzumab, daratumumab, or ustekinumab.

32. The composition according to claim 30 or 31, wherein the antibody comprises one or both of rituximab and obinutuzumab.

33. Use of the T cell according to any one of claims 1-27 or the composition according to any one of claims 28 and 29 in the manufacture of a medicament for treating cancer.

34. The use according to claim 33, wherein the cancer is non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM).

35. The use according to claim 33 or 34, further comprising administering one or more antibodies selected from the group consisting of ibritumomab, tiuxetan, muromonab-CD3, tositumomab, abciximab, basiliximab, brentuximab vedotin, cetuximab, infliximab, rituximab, alemtuzumab, bevacizumab, certolizumab pegol, daclizumab, eculizumab, efalizumab, gemtuzumab, natalizumab, omalizumab, palivizumab, polatuzumab vedotin, ranibizumab, tocilizumab, trastuzumab, vedolizumab, adalimumab, belimumab, canakinumab, denosumab, golimumab, ipilimumab, ofatumumab, panitumumab, obinutuzumab, daratumumab, or ustekinumab.