CLAIMS

1. An induced pluripotent stem cell (iPSC) or a derivative cell thereof comprising:

(i) a first exogenous polynucleotide encoding a chimeric antigen receptor (CAR);

(ii) a second exogenous polynucleotide encoding an inactivated cell surface receptor that comprises a monoclonal antibody-specific epitope and an interleukin 15 (IL-15), wherein the inactivated cell surface receptor and the IL-15 are operably linked by an autoprotease peptide; and

(iii) a deletion or reduced expression of one or more of B2M, TAP 1, TAP 2, Tapasin, RFXANK, CIITA, RFX5 and RFXAP genes.

2. The iPSC or the derivative cell according to claim 1, further comprising a third exogenous polynucleotide encoding a human leukocyte antigen E (HLA-E) and/or human leukocyte antigen G (HLA-G),

optionally 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;

optionally wherein the third exogenous polynucleotide comprises the polynucleotide sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 67.

3. The iPSC or the derivative cell according to claim 1 or 2, wherein one or more of the exogenous polynucleotides are integrated at:

(i) 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, RFXANK, CIITA, RFX5, RFXAP, TCR a or b constant region, NKG2A, NKG2D, CD38, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and 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, or

(ii) the loci of the CIITA, AAVS1 and B2M genes.

4. The iPSC or the derivative cell according to any one of claims 1-3, wherein the CAR comprises:

(i) a signal peptide,

(ii) an extracellular domain comprising a binding domain that specifically binds an antigen,

(iii) a hinge region,

(iv) a transmembrane domain,

(iv) an intracellular signaling domain, and

(v) a co-stimulatory domain;

optionally wherein:

(a) the signal peptide comprises a GMCSFR signal peptide, or

(b) the extracellular domain comprises a VHH domain that specifically binds the antigen, or

(c) the hinge region comprises a CD28 hinge region, or

(d) the transmembrane domain comprises a CD28 transmembrane domain, or

(e) the intracellular signaling domain comprises a CD3ζ intracellular domain, or the co-stimulatory domain comprises a CD28 signaling domain; optionally

optionally wherein the CAR comprises:

(A)

(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 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,

(iii) 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,

(iv) 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

(v) 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, or

(B)

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

(ii) an extracellular domain comprising a scFV or a VHH domain that specifically binds the antigen;

(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.

5. The iPSC or the derivative cell according to any one of the preceding claims, wherein:

(i) the inactivated cell surface receptor is 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, and ustekinumab; and/or

comprises a truncated epithelial growth factor (tEGFR) variant, optionally 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; and/or

(ii) the autoprotease peptide comprises a porcine tesehovirus-1 2A (P2A) peptide, optionally wherein the autoprotease peptide 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: 73; and/or

(iii) the IL-15 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: 72;

optionally wherein the second exogenous polynucleotide comprises the polynucleotide sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 75.

6. The iPSC or the derivative cell according to any one of the preceding claims, wherein:

(i) the first exogenous polynucleotide is integrated at a locus of AAVS1 gene;

(ii) the second exogenous polynucleotide is integrated at a locus of CIITA gene; and

(iii) the third exogenous polynucleotide is integrated at a locus of B2M gene;

wherein integration of the exogenous polynucleotides deletes or reduces expression of CIITA and B2M, preferably, the first exogenous polynucleotide comprises the polynucleotide sequence of SEQ ID NO: 62, the second exogenous polynucleotide comprises the polynucleotide sequence of SEQ ID NO: 75, and the third exogenous polynucleotide comprises the polynucleotide sequence of SEQ ID NO: 67.

7. The iPSC or the derivative cell of any one of the preceding claims, wherein the derivative cell is CD34+ hematopoietic progenitor cell (HPC), a natural killer (NK) cell or a T cell.

8. The iPSC or the derivative cell according to any of the preceding claims, wherein the first exogenous polynucleotide encoding the CAR targets a CD19 antigen; optionally wherein:

a. the extracellular domain comprises an scFv derived from an antibody that specifically binds the CD19 antigen;
b. 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 the 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;
c. the inactivated cell surface receptor is a truncated epithelial growth factor (tEGFR) variant; and/or
d. the first exogenous polynucleotide comprises the polynucleotide sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 62; the second exogenous polynucleotide comprises the polynucleotide sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 75; and the third exogenous polynucleotide comprises the polynucleotide sequence having at least 90%, 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO: 67.

9. The iPSC or derivative cell according to any one of the preceding claims comprising:

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

(ii) a second exogenous polynucleotide encoding a truncated epithelial growth factor (tEGFR) variant having the amino acid sequence of SEQ ID NO: 71, an autoprotease peptide having the amino acid sequence of SEQ ID NO: 73, and interleukin 15 (IL-15) having the amino acid sequence of SEQ ID NO: 72; and

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

wherein the first, second and third exogenous polynucleotides are integrated at loci of AAVS1, CIITA and B2M genes, to thereby delete or reduce expression of CIITA and B2M;

wherein the derivative cell is a natural killer (NK) cell or a T cell.

10. A composition comprising the iPSC or derivative cell according to any one of the preceding claims,

optionally further comprising 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).

11. The iPSC or derivative cell according to any one of claims 1-9 or the composition according to claim 10 for use in a method of treating cancer in a subject in need thereof.

12. A method of manufacturing a derivative cell from the iPSC according to any one of claims 1-9, comprising differentiating the iPSC under conditions for cell differentiation to thereby obtain the derivative cell,

optionally wherein the iPSC is obtained by genomic engineering an unmodified iPSC, wherein the genomic engineering comprises targeted editing, optionally wherein the targeted editing comprises deletion, insertion, or in/del carried out by CRISPR, ZFN, TALEN, homing nuclease, homology recombination, or any other functional variation of these methods.

13. A method of differentiating the iPSC according to any one of claims 1-9 into an NK cell, comprising subjecting the iPSC to a differentiation protocol including culturing the cell in a medium comprising a recombinant human IL-12p70 for the final 24 hours of culturing under the differentiation protocol.

14. A polynucleotide encoding an inactivated cell surface receptor that comprises a monoclonal antibody-specific epitope and an interleukin 15 (IL-15), wherein the monoclonal antibody-specific epitope and the IL-15 are operably linked by an autoprotease peptide;

optionally wherein:

(i) the inactivated cell surface receptor comprises an epitope 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, or ustekinumab; and/or

the inactivated cell surface receptor comprises a truncated epithelial growth factor (tEGFR) variant, optionally 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 or consists of the amino acid sequence of SEQ ID NO: 71; and/or

(ii) the autoprotease peptide comprises a porcine tesehovirus-1 2A (P2A) peptide, optionally wherein the autoprotease peptide 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: 73 or consists of the amino acid sequence of SEQ ID NO: 73; and/or

(iii) the IL-15 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: 72 or consists of the amino acid sequence of SEQ ID NO: 72.

15. A protein encoded by the polynucleotide according to claim 14.