Claims

1. A polynucleotide encoding a chimeric antigen receptor (CAR), wherein the CAR comprising (1) an extracellular antigen-binding domain, (2) a transmembrane domain and (3) an intracellular signaling domain,

wherein the intracellular signaling domain comprises a cytoplasmic domain of a dendritic cell activating receptor selected from the group consisting of RIG-1, NLRP10, DEC-205, BDCA-2, CD86, 4-1BBL, OX40L, CD40, IFNAR, TLR4, TNFR (e.g., TNFR2), CD80, CD40L, CD367 (DCIR), CD207 (Langerin), CD371 (DCAL-2, CLEC12a), CD204, CD36, IFNγR, Dectin-1 and FcγR, or a combination thereof,

wherein the CAR is capable of activating dendritic cells in an immune suppressive tumor microenvironment,

wherein the polynucleotide is a DNA or RNA.

2. The polynucleotide of claim 1, wherein the immune suppressive tumor microenvironment comprises a tumor that has poor responsiveness to monotherapy of adoptive cell therapy (e.g., CAR-T monotherapy) or a tumor and/or tumor infiltrating immune cells that are: 1) expressing an immune inhibitory molecule, and/or 2) deficient in an immune stimulating cytokine,

wherein the immune inhibitory molecule is selected from the group consisting of PD-1, TIM-3, TIGIT, LAG-3, A2AR, BTLA (CD272), CTLA-4 (CD152), IDO1, IDO2, TDO, NOX2, VISTA, SIGLEC7 (CD328), PVR(CD155) and SIGLEC9 (CD329), PD-L1, PD-L2, B7-H3 (CD276), B7-H4 (VTCN1), PVR(CD155), HLA class I, sialoglycoprotein, CD112, CD113, Galectin9, CD24, and CD47,

wherein the immune stimulating cytokine is selected from TNF-a, IFN-β,

IFN-γ, IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-18, granulocyte-macrophage colony stimulating factor and a combination thereof.

3. The polynucleotide of claim 1, wherein the intracellular signaling domain comprises the cytoplasmic domain of Dectin-1 and the cytoplasmic domain of FcγR.

4. The polynucleotide of claim 3, wherein the cytoplasmic domain of Dectin-1 comprises an amino acid sequence set forth in SEQ ID NO: 1, or any functional forms thereof, or the cytoplasmic domain of FcγR comprises an amino acid sequence set forth in SEQ ID NO: 2 or any functional forms thereof.

5. The polynucleotide of claim 3, wherein the intracellular signaling domain comprises an amino acid sequence set forth in SEQ ID NO: 3 or any functional forms thereof or an amino acid sequence encoded by a nucleic acid sequence set forth in SEQ ID NO: 4 or any functional forms thereof.

6. The polynucleotide of claim 1, wherein the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv), the scFv is specific for a tumor surface marker (e.g., solid tumor surface marker).

7. The polynucleotide of claim 6, wherein the tumor surface marker is selected from the group consisting of: EphA2, CD19, CD70, CD133, CD147, CD171, DLL3, EGFRvIII, Mesothelin, ganglioside GD2, FAP (fibroblast activating protein), FBP (folate binding protein), Lewis Y, Claudin 18.2, IL13Rα2, HER2, MDC1, PMSA (prostate membrane specific antigen), ROR1, B7-H3, CAIX, CD133, CD171, CEA, GPC3, MUC1, NKG2D.

8. The polynucleotide of claim 1, wherein the CAR further comprises a

signal peptide, the signal peptide comprises a signal peptide of CD8 alpha.

9. The polynucleotide of claim 8, wherein the signal peptide of CD8 alpha comprises a sequence set forth in SEQ ID NO: 5 or any functional forms thereof.

10. The polynucleotide of claim 1, wherein the transmembrane domain comprises a transmembrane domain of CD8 alpha.

11. The polynucleotide of claim 10, wherein the transmembrane domain of CD8 alpha comprises a sequence set forth in SEQ ID NO: 6, or any functional forms thereof.

12. The polynucleotide of claim 1, wherein the extracellular antigen-binding domain is linked to the transmembrane domain by a hinge region, the hinge region comprises a hinge region of CD8 alpha.

13. The polynucleotide of claim 12, wherein the hinge region of CD8 alpha comprises a sequence set forth in SEQ ID NO: 7, or any functional forms thereof.

14. A polypeptide encoded by the polynucleotide of claim 1.

15. A vector comprising the polynucleotide of claim 1, wherein the polynucleotide encoding the CAR is operably linked to at least one regulatory polynucleotide element for expression of the CAR.

16. An engineered cell comprising the polypeptide of claim 14.

17. A method of producing the engineered cells of claim 16, comprising introducing to a starting cell the vector of claim 15 under conditions suitable for expression of the polynucleotide of claim 1.

18. The method of claim 17, wherein the starting cell is a dendritic cell or a precursor or a progenitor cell thereof which is derived from a peripheral

blood cell, a bone marrow cell, an embryonic stem cell, or an induced pluripotent stem cell.

19. A population of cells produced ex vivo by the method of claim 17.

20. A pharmaceutical composition comprising (i) the polynucleotide of claim 1, or the polypeptide of claim 14, or the vector of claim 15, or the population of the engineered cells of claim 16 or the population of cells of claim 19, and (ii) a pharmaceutically acceptable medium.

21. Use of the pharmaceutical composition of claim 20 in the manufacture of a medicament for improving efficacy of adoptive cell therapy in treating cancer in a subject in need thereof.

22. Use of the engineered cell of claim 16 in the manufacture of a medicament for inducing proliferation of immune cells, prolonging the survival of immune cells, and/or increasing expression and/or secretion of immune stimulating cytokines from immune cells in an immune suppressive microenvironment, wherein the immune cell is autologous or allogeneic.

23. Use of the pharmaceutical composition of claim 20 in the manufacture of a medicament for treating a disease or pathological condition in a subject in need thereof.

24. A method of selecting a CAR capable of activating dendritic cells, comprising:

(a) providing a non-human animal comprising an immune suppressive tumor microenvironment,

(b) administering a dendritic cell expressing a candidate CAR to the non-human animal,

(c) detecting a marker for the dendritic cell activation selected from

improved infiltration to the immune suppressive tumor microenvironment, improved survival rate, and enhanced function in inducing activation of an immune cell when compared to a reference dendritic cell, and

(d) selecting the candidate CAR as a CAR capable of activating dendric cells,

wherein the immune suppressive tumor microenvironment is clinically relevant, comprising a tumor and/or tumor infiltrating immune cells expressing an immune inhibitory molecule.

25. The method of claim 24, wherein the non-human animal comprises human fetal thymus and autologous human hematopoietic stem cells (e.g., human CD34+ hematopoietic stem cells).

26. The method of claim 24, wherein the immune inhibitory molecule is selected from the group consisting of PD-1, TIM-3, TIGIT, LAG-3, A2AR, BTLA (CD272), CTLA-4 (CD152), IDO1, IDO2, TDO, NOX2, VISTA, SIGLEC7 (CD328), PVR(CD155) and SIGLEC9 (CD329), PD-L1, PD-L2, B7-H3 (CD276), B7-H4 (VTCN1), PVR(CD155), HLA class I, sialoglycoprotein, CD112, CD113, Galectin9, CD24, and CD47.

27. The method of claim 24, wherein the immune cell is autologous or allogeneic and is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a NKT cell, a B cell, a macrophage cell, an eosinophil or a neutrophil.