Claims

1. A vector for preparing a dendritic cell tumor vaccine, comprising:

(a) a first polynucleotide encoding a chimeric antigen receptor (CAR) capable of activating a dendritic cell, wherein the CAR comprises (1) an extracellular antigen-binding domain, (2) a transmembrane domain and (3) an intracellular signaling domain, and

(b) a second polynucleotide encoding one or more tumor antigens, the tumor antigen is a tumor associated antigen (TAA) or tumor specific antigen (TSA),

wherein the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv), the scFv is specific for a tumor surface marker,

wherein the intracellular signaling domain comprises the cytoplasmic domain of Dectin-1 and the cytoplasmic domain of FcγR, wherein the cytoplasmic domain of Dectin-1 comprises an amino acid sequence set forth in SEQ ID NO: 1, wherein the cytoplasmic domain of FcγR comprises an amino acid sequence set forth in SEQ ID NO: 2,

wherein the CAR and the tumor antigen when expressed in the dendritic cell is capable of activating the dendritic cell in an immune suppressive tumor microenvironment, and

wherein the vector is a DNA or RNA.

2. The vector of claim 1, wherein the immune suppressive tumor microenvironment comprises 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 vector of claim 1, wherein the intracellular signaling domain comprises an amino acid sequence set forth in SEQ ID NO: 3.

4. The vector of claim 1, wherein the intracellular signaling domain comprises an amino acid sequence encoded by a nucleic acid sequence set forth in SEQ ID NO: 4.

5. The vector of claim 1, 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, IL13Ra2, HER2, MDC1, PMSA (prostate membrane specific antigen), ROR1, B7-H3, CAIX, CEA, GPC3, MUC1, and NKG2D.

6. The vector of claim 1, wherein the CAR further comprises a signal peptide, the signal peptide comprises a signal peptide of CD8 alpha.

7. The vector of claim 6, wherein the signal peptide of CD8 alpha comprises a sequence set forth in SEQ ID NO: 5.

8. The vector of claim 1, wherein the transmembrane domain comprises a transmembrane domain of CD8 alpha.

9. The vector of claim 8, wherein the transmembrane domain of CD8 alpha comprises a sequence set forth in SEQ ID NO: 6.

10. The vector 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.

11. The vector of claim 10, wherein the hinge region of CD8 alpha comprises a sequence set forth in SEQ ID NO: 7.

12. The vector of claim 1, wherein the second polynucleotide is a mutated tumor gene or a fragment thereof, wherein the tumor gene is selected from p53, ras, beta-catenin, BRCA1/2, CDK4, CML66, fibronectin, MART-2, TGF-betaRII.

13. The vector of claim 1, wherein the tumor antigen is selected from CEA, immature laminin receptor, TAG-72, HPV E6, HPV E7, BING-4, calcium-activated chloride channel 2, cyclin-B1, 9D7, Ep-Cam, EphA3, GPC3, Her2/neu, telomerase, mesothelin, SAP-2, and survivin.

14. The vector of claim 1, wherein the tumor antigen is selected from a p53 R273H mutated peptide, a p53 R175H mutated peptide, a p53 R248Q mutated peptide, a p53 R249S mutated peptide, a p53-R175H-R248Q-R249S-R273H mutated peptide, a KRAS G12V mutated peptide, a KRAS G12C mutated peptide or combination thereof.

15. The vector of claim 14, wherein the p53 R273H mutated peptide has a sequence set forth in SEQ ID NO: 29, the p53-R175H-R248Q-R249S-R273H mutated peptide has a sequence set forth in SEQ ID NO: 37, the KRAS G12V mutated peptide has a sequence set forth in SEQ ID NO: 31, or the KRAS G12C mutated peptide has a sequence set forth in SEQ ID NO: 30.

16. An engineered cell comprising the vector of any one of the preceding claims.

17. A method of producing the engineered cells, comprising introducing to a starting cell the one or more vector of any one of claims 1-15 under conditions suitable for expression of the CAR and the tumor antigen.

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

19. The method of claim 17, wherein the dendritic cell or a precursor or a progenitor cell thereof is derived from a peripheral blood cell, a bone marrow cell, an embryonic stem cell, or an induced pluripotent stem cell.

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

21. A pharmaceutical composition comprising (i) the vector of any one of claims 1-15, or the population of the engineered cells of claim 16 or the population of cells of claim 20, and (ii) a pharmaceutically acceptable medium.

22. Use of the pharmaceutical composition of claim 21 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the cancer expressing the tumor antigen.

23. The use of claim 22, wherein the cancer is a solid cancer selected from the group consisting of adrenal cancer, bone cancer, brain cancer, breast cancer, colorectal cancer, esophageal cancer, eye cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, mesothelioma, head and neck cancer, squamous cell carcinoma, melanoma, oral cancer, ovarian cancer, cervical cancer, penile cancer, prostate cancer, pancreatic cancer, skin cancer, sarcoma, testicular cancer, thyroid cancer, uterine cancer, vaginal cancer.