

CLAIMS

What is claimed is:

1. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which comprises (i) an antigen binding molecule, (ii) a costimulatory domain, and (iii) an activating domain, wherein the costimulatory domain comprises an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a truncated hinge domain consisting essentially of or consisting of (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1 and, optionally, (ii) one to six amino acids.
2. The polynucleotide of claim 1, wherein the one to six amino acids are heterologous amino acids.
3. The polynucleotide of claim 1 or 2, wherein the truncated hinge domain consists essentially of or consists of an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1.
4. The polynucleotide of claim 1 or 2, wherein the amino acid sequence is encoded by a nucleotide sequence at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 2.
5. The polynucleotide of claim 1 or 2, wherein the transmembrane domain is a transmembrane domain of 4-1BB/CD137, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, CD3 epsilon, CD4, CD5, CD8 alpha, CD9, CD16, CD19, CD22, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD154, or a zeta chain of a T cell receptor, or any combination thereof.
6. The polynucleotide of claim 1 or 2, wherein the transmembrane domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%,

at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 5.

7. The polynucleotide of claim 6, wherein the transmembrane domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 4.

8. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises a signaling region of 4-1BB/CD137, activating NK cell receptors, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CD11a, CD11b, CD11c, CD11d, CDS, CEACAM1, CRT AM, cytokine receptors, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHT), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL2R beta, IL2R gamma, IL7R alpha, Immunoglobulin-like proteins, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, LFA-1, a ligand that specifically binds with CD83, LIGHT, LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1 (CD11a/CD18), MHC class I molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), signaling lymphocytic activation molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Lyl08), SLAMF7, SLP-76, TNF receptor proteins, TNFR2, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a combination thereof.

9. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises a 4-1BB/CD137 signaling region.

10. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 7.

11. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises an amino acid sequence encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 6.
- 5 12. The polynucleotide of claim 1 or 2, wherein the antigen binding molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises 3 complementarity determining regions (CDRs) and the VL comprises 3 CDRs.
- 10 13. The polynucleotide of claim 1 or 2, wherein the antigen binding molecule specifically binds an antigen selected from the group consisting of 5T4, alphafetoprotein, B cell maturation antigen (BCMA), CA-125, carcinoembryonic antigen, CD19, CD20, CD22, CD23, CD30, CD33, CD56, CD123, CD138, c-Met, CSPG4, C-type lectin-like molecule 1 (CLL-1), EGFRvIII, epithelial tumor antigen, ERBB2, FLT3, folate binding protein, GD2, GD3, HER1-HER2 in combination, HER2-HER3 in combination, HER2/Neu, HERV-K, HIV-1 envelope glycoprotein gp41, HIV-1 envelope glycoprotein gpl20, IL-11Ralpha, kappa chain, lambda chain, melanoma-associated antigen, mesothelin, MUC-1, mutated p53, mutated ras, prostate-specific antigen, ROR1, or VEGFR2, or a combination thereof.
- 15 14. The polynucleotide of claim 1 or 2, wherein the antigen binding molecule specifically binds BCMA, CLL-1, or FLT3.
- 20 15. The polynucleotide of claim 1 or 2, wherein the activation domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 9 or SEQ ID NO: 251.
- 25 16. The polynucleotide of claim 1 or 2, wherein the activation domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 8.
17. The polynucleotide of any one of claims 1 to 16, wherein the CAR or TCR further comprises a leader peptide.

18. The polynucleotide of claim 17, wherein the leader peptide comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 11.

5 19. The polynucleotide of claim 17, wherein the leader peptide is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 10.

20. A vector comprising the polynucleotide of any one of claims 1 to 19.

10 21. The vector of claim 20, wherein the vector is an adenoviral vector, an adenovirus-associated vector, a DNA vector, a lentiviral vector, a plasmid, a retroviral vector, or an RNA vector, or any combination thereof.

22. A polypeptide encoded by the polynucleotide of any one of claims 1 to 19 or the vector of claim 20 or 21.

15 23. A cell comprising the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, or any combination thereof.

24. The cell of claim 23, wherein the cell is a T cell.

25. The cell of claim 24, wherein the T cell is an allogeneic T cell, an autologous T cell, an engineered autologous T cell (eACT), or a tumor-infiltrating lymphocyte (TIL).

20 26. The cell of claim 24 or 25, wherein the T cell is a CD4⁺ T cell.

27. The cell of claim 24 or 25, wherein the T cell is a CD8⁺ T cell.

28. The cell of claim 24 or 25, wherein the T cell is an *in vitro* cell.

29. The cell of claim 24 or 25, wherein the T cell is an autologous T cell.

25 30. A composition comprising the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, or the cell of any one of claims 23 to 29.

31. The composition of claim 30, which is formulated to be delivered to a subject, optionally, comprising at least one pharmaceutically-acceptable excipient.

32. A method of making a cell expressing a CAR or TCR comprising transducing a cell with the polynucleotide of any one of claims 1 to 19 under suitable conditions.

5 33. The method of claim 32, further comprising isolating the cell.

34. A method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, or any combination thereof.

10 35. Use of the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, the cell of any one of claims 23 to 29, or the composition of claim 30 or 31 for the manufacture of a medicament for treating a cancer in a subject in need thereof.

36. The use of claim 35, wherein the cancer is a hematologic cancer.

37. The use of claim 35, wherein the cancer is of the white blood cells.

15 38. The use of claim 35, wherein the cancer is of the plasma cells.

39. The use of any one of claims 35 to 38, wherein the cancer is leukemia, lymphoma, or myeloma.

40. The use of any one of claims 35 to 38, wherein the cancer is acute lymphoblastic leukemia (ALL) (including non T cell ALL), acute myeloid leukemia, B cell prolymphocytic
20 leukemia, B-cell acute lymphoid leukemia ("BALL"), blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloid leukemia, chronic or acute leukemia, diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), hairy cell leukemia, Hodgkin's Disease, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma,
25 Marginal zone lymphoma, monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma (NHL), plasma cell proliferative disorder (including asymptomatic myeloma (smoldering

- multiple myeloma or indolent myeloma), plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, plasmacytomas (including plasma cell dyscrasia; solitary myeloma; solitary plasmacytoma; extramedullary plasmacytoma; and multiple plasmacytoma), POEMS syndrome (also known as Crow-Fukase syndrome; Takatsuki disease; and PEP syndrome),
- 5 primary mediastinal large B cell lymphoma (PMBC), small cell- or a large cell-follicular lymphoma, splenic marginal zone lymphoma (SMZL), systemic amyloid light chain amyloidosis, T-cell acute lymphoid leukemia ("TALL"), T-cell lymphoma, transformed follicular lymphoma, or Waldenstrom macroglobulinemia, or a combination thereof.