

**WHAT IS CLAIMED IS:**

1. An immune cell comprising a chimeric antigen receptor (CAR), wherein the (CAR) comprises:
  - (a) an extracellular domain comprising an antigen-binding domain;
  - 5 (b) a transmembrane domain; and
  - (c) an intracellular domain comprising a costimulatory endodomain, wherein the costimulatory endodomain comprises an intracellular signaling domain from 4-1BB/CD137 and five additional amino acids.
- 10 2. The immune cell of claim 1, wherein the chimeric antigen receptor is a single polypeptide.
3. The immune cell of claim 1, wherein the chimeric antigen receptor is comprised of two polypeptides.
- 15 4. The immune cell of any one of claims 1-3, wherein the costimulatory endodomain comprises an intracellular signaling domain from 4-1BB/CD137 and five additional amino acids, wherein the five additional amino acids are encoded by SEQ ID NO: 1.
- 20 5. The immune cell of claim 4, wherein the costimulatory endodomain comprises SEQ ID NO: 2.
6. The immune cell of any one of claims 1-5, wherein the antigen-binding domain is humanized.
- 25 7. The immune cell of any one of claims 1-6, wherein the antigen-binding domain is human.
8. The immune cell of any one of claims 1-7, wherein the antigen-binding domain is an scFv.

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9. The immune cell of any one of claims 1-8, wherein the antigen-binding domain specifically binds an antigen associated with a disease.
10. The immune cell of any one of claims 1-9, wherein the antigen-binding domain specifically binds a tumor antigen.
11. The immune cell of any one of claims 1-10, wherein the antigen-binding domain specifically binds to an antigen selected from the group consisting of: glypican-3 (GPC3), malignancy variant receptor (MVR), and CD19.
12. The immune cell of any one of claims 1-11, wherein the transmembrane domain is a transmembrane domain selected from a protein selected from the group consisting of: 4-1BB/CD137, an activating NK cell receptor, an immunoglobulin protein, B7-H3, BAFRR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD3 zeta, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8, CD8alpha, CD8beta, CD96 (Tactile), CD11a, CD11b, CD11c, CD11d, CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), an integrin, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, a ligand that specifically binds with CD83, LIGHT, LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1), an MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), a Signaling Lymphocytic Activation Molecule (a SLAM protein), SLAM (SLAMF1), SLAMF4 (CD244), SLAMF6 (NTB-A), SLAMF7, SLP-76, a TNF receptor protein, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, and VLA-6.
13. The immune cell of any one of claims 1-12, wherein the transmembrane domain is a transmembrane domain from CD8 $\alpha$ .

14. The immune cell of any one of claims 1-13, wherein the intracellular domain further comprises an intracellular domain from CD3 $\zeta$ .
- 5 15. The immune cell of any one of claims 1-14, wherein the chimeric antigen receptor further comprises a signal peptide or leader sequence.
16. The immune cell of any one of claims 1-15, wherein the chimeric antigen receptor further comprises a hinge region.
- 10 17. The immune cell of claim 16, wherein the hinge region is a CD8 $\alpha$  hinge.
18. The immune cell of any one of claims 1-17, wherein the chimeric antigen receptor further comprises an additional antigen-binding domain.
- 15 19. The immune cell of claim 18, wherein the additional antigen-binding domain is an scFv.
20. The immune cell of any one of claims 1-19, wherein the immune cell is a human immune cell.
- 20 21. The immune cell of claim 20, wherein the human immune cell is an autologous human immune cell.
22. The immune cell of claims 20, wherein the human immune cell is an allogenic human
- 25 immune cell.
23. The immune cell of any one of claims 1-22, wherein the immune cell is a T cell.
24. The immune cell of any one of claims 1-23, wherein the immune cell is an NK cell.
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25. A nucleic acid encoding a chimeric antigen receptor (CAR), wherein the chimeric antigen receptor comprises:
- (a) an extracellular domain comprising an antigen-binding domain;
  - (b) a transmembrane domain; and
  - 5 (c) an intracellular domain comprising a costimulatory endodomain, wherein the costimulatory endodomain comprises an intracellular signaling domain from 4-1BB/CD137 and five additional amino acids.
- 10 26. The nucleic acid of claim 25, wherein the chimeric antigen receptor is a single polypeptide.
27. The nucleic acid of claim 25, wherein the chimeric antigen receptor is comprised of two polypeptides.
- 15 28. The nucleic acid of any one of claims 25-27, wherein the costimulatory endodomain comprises an intracellular signaling domain from 4-1BB/CD137 and five additional amino acids, wherein the five additional amino acids are encoded by a nucleotide sequence of SEQ ID NO: 1.
- 20 29. The nucleic acid of claim 28, wherein the costimulatory endodomain comprises SEQ ID NO: 2.
30. The nucleic acid of any one of claims 25-29, wherein the antigen-binding domain is humanized.
- 25 31. The nucleic acid of any one of claims 25-30, wherein the antigen-binding domain is human.
- 30 32. The nucleic acid of any one of claims 25-31, wherein the antigen-binding domain is an scFv.

33. The nucleic acid of any one of claims 25-32, wherein the antigen-binding domain specifically binds an antigen associated with a disease.
34. The nucleic acid of any one of claims 25-33, wherein the antigen-binding domain specifically binds a tumor antigen.
35. The nucleic acid of any one of claims 25-34, wherein the antigen-binding domain specifically binds to an antigen selected from the group consisting of: glycan-3 (GPC3), malignancy variant receptor (MVR), and CD19.
36. The nucleic acid of any one of claims 25-35, wherein the transmembrane domain is a transmembrane domain selected from a protein selected from the group consisting of: 4-1BB/CD137, an activating NK cell receptor, an immunoglobulin protein, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD3 zeta, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8, CD8 alpha, CD8 beta, CD96 (Tactile), CD11a, CD11b, CD11c, CD11d, CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), an integrin, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, a ligand that specifically binds with CD83, LIGHT, LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1), an MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), a Signaling Lymphocytic Activation Molecule (a SLAM protein), SLAM (SLAMF1), SLAMF4 (CD244), SLAMF6 (NTB-A), SLAMF7, SLP-76, a TNF receptor protein, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, and VLA-6.
37. The nucleic acid of any one of claims 25-36, wherein the transmembrane domain is a transmembrane domain from CD8 alpha.

38. The nucleic acid of any one of claims 25-37, wherein the intracellular domain further comprises an intracellular domain from CD3 $\zeta$ .
- 5 39. The nucleic acid of any one of claims 25-38, wherein the chimeric antigen receptor further comprises a signal peptide or leader sequence.
40. The nucleic acid of any one of claims 25-39, wherein the chimeric antigen receptor further comprises a hinge region.
- 10 41. The nucleic acid of claim 40, wherein the hinge region is a CD8 $\alpha$  hinge.
42. A vector comprising the nucleic acid of any one of claims 25-41.
- 15 43. The vector of claim 42 further comprising a promoter operationally linked to the nucleic acid.
44. The vector of claim 43, wherein the promoter is a constitutive promoter.
- 20 45. The vector of claim 43, wherein the promoter is an inducible promoter.
46. The vector of any one of claims 42-45, wherein the vector is a viral vector.
47. The vector of claim 46, wherein the viral vector is a lentiviral vector.
- 25 48. A method of producing an engineered immune cell, the method comprising:  
introducing into an immune cell a nucleic acid of any one of claims 25-41 or a vector of  
any one of claims 42-47, thereby producing the engineered immune cell.
- 30 49. The method of claim 48, further comprising, after the introducing step, culturing the  
engineered immune cell.

50. The method of any one of claims 48-49, wherein the immune cell is a T cell.
51. The method of any one of claims 48-50, wherein the immune cell is a NK cell.
52. The method of any one of claims 48-51, further comprising, before the introducing step, obtaining the immune cell from a subject.
53. The method of claim 52, wherein the method further comprises administering the engineered immune cell to the subject.
54. The method of claim 52 or 53, wherein the subject has been diagnosed or identified as having a cancer.
55. An engineered immune cell produced by the method of any one of claims 48-54.
56. A pharmaceutical composition comprising the engineered immune cell of claim 55 and a pharmaceutically acceptable carrier.
57. A method of treating a cancer in a subject, the method comprising administering to the subject an engineered immune cell of claim 55 or a pharmaceutical composition of claim 56.
58. The method of claim 57, wherein the cancer is an anti-glypican-3-associated cancer, an anti-CD19-associated cancer, or an anti-MVR-associated cancer.
59. The method of claim 57, wherein the cancer is carcinoma, lymphoma (e.g., Hodgkin's and non-Hodgkin's lymphomas), blastoma, sarcoma, leukemia, squamous cell carcinoma, small cell lung cancer, non-small cell lung cancer, lung adenocarcinoma, squamous cell carcinoma of the lung, peritoneal cancer, hepatocellular carcinoma, gastric cancer, pancreatic cancer, glioma, cervical cancer, ovarian cancer, liver cancer, bladder cancer,

breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary carcinoma, kidney cancer, prostate cancer, vulvar cancer, thyroid cancer, liver carcinoma, other lymphoproliferative disorders, and various types of head and neck cancer.

- 5        60. The method of any of claims 57-59, wherein the subject has previously been administered one or more additional anticancer therapies selected from the group consisting of: ionizing radiation, a chemotherapeutic agent, a therapeutic antibody, and a checkpoint inhibitor.
- 10       61. The method of any one of claims 57-60, wherein the subject has been identified or diagnosed as having the cancer.