

CLAIMS

What is claimed is:

1. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises
a light chain variable region comprising an amino acid sequence of SEQ ID NO: 73 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 72, wherein the extracellular antigen-binding domain binds the G protein receptor family C group 5 member D (GPRC5D) antigen.
2. The CAR of claim 1, wherein the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv).
3. The CAR of claim 2, wherein the scFv comprises a linker polypeptide between the light chain variable region and the heavy chain variable region.
4. The CAR of claim 3, wherein the linker polypeptide comprises an amino acid sequence of SEQ ID NO: 7.
5. The CAR of any of claims 2-4, wherein the scFv comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 78 and 77. .
6. The CAR of any of claims 1-5, wherein the extracellular antigen-binding domain comprises a signal polypeptide.
7. The CAR of claims 6, wherein the signal polypeptide comprises an amino acid sequence of SEQ ID NO: 11.
8. The CAR of any of claims 1-7, wherein the intracellular signaling domain comprises a polypeptide component selected from the group consisting of a TNF receptor superfamily member 9 (CD137) component, a T-cell surface glycoprotein CD3 zeta chain (CD3z)

component, a cluster of differentiation (CD27) component, a cluster of differentiation superfamily member component, and a combination thereof.

9. The CAR of claim 8, wherein the CD137 component comprises an amino acid sequence of SEQ ID NO: 12.
10. The CAR of claim 8, wherein the CD3z component comprises an amino acid sequence of SEQ ID NO: 13.
11. The CAR of claim 8, wherein the intracellular signaling domain comprises an amino acid sequence of SEQ ID NO: 14.
12. The CAR of any of claims 1-11, wherein the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide.
13. The CAR of claim 12, wherein the CD8a-TM polypeptide comprises an amino acid sequence of SEQ ID NO: 15.
14. The CAR of any of claims 1-13, further comprising a hinge region linking the transmembrane domain to the extracellular antigen-binding domain.
15. The CAR of claim 14, wherein the hinge region is a CD8a-hinge region.
16. The CAR of claim 15, wherein the CD8a-hinge region comprises an amino acid sequence of SEQ ID NO: 16.
17. The CAR of any of claims 1-16, wherein the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 82 and 81.

18. The CAR of any of claims 1-17, wherein the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 86 and 85.
19. An isolated T cell expressing the CAR of any of claims 1-18.
21. The isolated T cell of claim 20, wherein the T cell is a naïve T cell.
22. The isolated T cell of claim 20, wherein the T cell is a memory stem T cell.
23. The isolated T cell of claim 20, wherein the T cell is a central memory T cell.
24. The isolated T cell of any of claims 20 to 23, wherein the T cell is CD4+.
25. The isolated T cell of any of claims 20 to 23, wherein the T cell is CD8+.
26. The isolated T cell of any of claims 20 to 23, wherein the T cell is CD4+ and CD8+.
27. An isolated nucleic acid molecule encoding the CAR of any of claims 1-18.
28. The isolated nucleic acid molecule of claim 27, wherein the nucleic acid molecule comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOS: 90 and 89.
29. The isolated nucleic acid molecule of claim 27, wherein the nucleic acid molecule comprises a nucleotide sequence that is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleotide sequence of SEQ ID NOS: 90 and 89.
30. A vector comprising the nucleic acid molecule of any of claims 27-29.
31. A cell expressing the nucleic acid molecule of any of claims 27-29.

32. A pharmaceutical composition, comprising
an effective amount of the T cell of any of claims 19-26.
33. A pharmaceutical composition, comprising
an effective amount of the T cell of any of claims 19-26 and a pharmaceutically acceptable excipient.
34. The CAR-expressing T cell any of claims 19-26, or the pharmaceutical composition of claims 32 or 33 for use in therapy.
35. The CAR-expressing T cell of any of claims 19-26, or the pharmaceutical composition of claims 32 or 33 for use in a method of treating a subject in need thereof, wherein the subject has cancer, wherein the method comprises a therapeutically effective amount of the T cell to be administered to the subject, whereby the T cell induces killing of cancer cells in the subject.
36. The CAR-expressing T cell of any of claims 19-26, or the pharmaceutical composition of claims 32 or 33 for use in a method of treating a subject in need thereof, wherein the subject has cancer, wherein the method comprises a therapeutically effective amount of the T cell to be administered to the subject, and wherein the T cell is selected from a CD4⁺ T cell, a CD8⁺ T cell, or a mixture thereof.
37. The CAR-expressing T cell, of claim 35 or 36, wherein the cancer is selected from the group consisting of a lung cancer, a gastric cancer, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a smoldering multiple myeloma (SMM), a multiple myeloma (MM), an acute myeloid leukemia (AML), and combinations thereof.

38. The CAR-expressing T cell, t of claims 35 or 37 for use in a method of claim 36, wherein the cancer is multiple myeloma.
39. An in vitro method of targeted killing of a cancer cell, the method comprising:
contacting the cancer cell with the T cell of any of claims 19-26, whereby the T cell induces killing of the cancer cell.
41. The method of claim 39, wherein the cancer cell is a multiple myeloma cell.
42. The CAR-expressing T cell of any of claims 39-26 for use in a method of detecting the presence of cancer in a subject, comprising:
- (a) contacting a cell sample obtained from the subject with the CAR of any of claims 1-18, thereby forming a CAR-cell complex, and
 - (b) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the subject.