

CLAIMS

1. A chimeric antigen receptor comprising:
 - i. an antigen binding region, wherein the antigen binding region specifically binds ROR-1 and wherein the antigen binding region comprises a light chain variable domain and a heavy chain variable domain;
 - (a) wherein the light chain variable domain comprises a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45; and the heavy chain variable domain comprises a CDR H1 as set forth in SEQ ID NO:46, a CDR H2 as set forth in SEQ ID NO:47, and a CDR H3 as set forth in SEQ ID NO:48; or
 - (b) wherein the light chain variable domain comprises a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51; and the heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:52, a CDR H2 as set forth in SEQ ID NO:53, and a CDR H3 as set forth in SEQ ID NO:54;
 - ii. a spacer domain, wherein the spacer domain comprises a spacer of between 10 and 240 amino acids in length;
 - iii. a transmembrane domain; and
 - iv. an intracellular domain.
2. The chimeric antigen receptor of claim 1, wherein the spacer domain is between 14 and 120 amino acids in length.
3. The chimeric antigen receptor of claim 1 or 2, wherein the light chain variable domain is coupled to the N-terminus or the C-terminus of the heavy chain variable domain.
4. The chimeric antigen receptor of claim 3, wherein the light chain variable domain is covalently coupled to the heavy chain variable domain through a polypeptide linker.
5. The chimeric antigen receptor of claim 4, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:24.

6. The chimeric antigen receptor of claim 1, wherein the spacer domain comprises an antibody domain.
7. The chimeric antigen receptor of claim 6, wherein the antibody domain comprises an immunoglobulin hinge domain, an immunoglobulin constant heavy chain 3 (CH3) domain, an immunoglobulin constant heavy chain 2 (CH2) domain, or a combination thereof.
8. The chimeric antigen receptor of claim 7, wherein the antibody domain consists of the immunoglobulin hinge domain.
9. The chimeric antigen receptor of claim 7, wherein the antibody domain consists of the immunoglobulin hinge domain and the immunoglobulin constant heavy chain 3 (CH3) domain.
10. The chimeric antigen receptor of claim 7, wherein the antibody domain consists of the immunoglobulin hinge domain, the immunoglobulin constant heavy chain 3 (CH3) domain and the immunoglobulin constant heavy chain 2 (CH2) domain.
11. The chimeric antigen receptor of claim 7, wherein the spacer domain comprises an amino acid sequence of SEQ ID NO:29, SEQ ID NO:41 or SEQ ID NO:42.
12. The chimeric antigen receptor of claim 7, wherein the spacer domain consists of an amino acid sequence of SEQ ID NO:29, SEQ ID NO:41 or SEQ ID NO:42.
13. The chimeric antigen receptor of claim 7, wherein the light chain variable domain comprises an amino acid sequence at least about 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO:21.
14. The chimeric antigen receptor of claim 7, wherein the light chain variable domain consists of an amino acid sequence of SEQ ID NO:21.
15. The chimeric antigen receptor of claim 7, wherein the heavy chain variable domain comprises an amino acid sequence at least about 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO:27.

16. The chimeric antigen receptor of claim 1, wherein the heavy chain variable domain consists of an amino acid sequence of SEQ ID NO:27.
17. The chimeric antigen receptor of claim 1, wherein the light chain variable domain comprises an amino acid sequence at least about 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO:19.
18. The chimeric antigen receptor of claim 1, wherein the light chain variable domain consists of an amino acid sequence of SEQ ID NO:19.
19. The chimeric antigen receptor of claim 1, wherein the light chain variable domain comprises an amino acid sequence at least about 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO:20.
20. The chimeric antigen receptor of claim 1, wherein the light chain variable domain consists of an amino acid sequence of SEQ ID NO:20.
21. The chimeric antigen receptor of claim 1, wherein the heavy chain variable domain comprises an amino acid sequence at least about 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO:25.
22. The chimeric antigen receptor of claim 1, wherein the heavy chain variable domain consists of an amino acid sequence of SEQ ID NO:25.
23. The chimeric antigen receptor of claim 1, wherein the heavy chain variable domain comprises an amino acid sequence at least about 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO:26.
24. The chimeric antigen receptor of claim 1, wherein the heavy chain variable domain consists of an amino acid sequence of SEQ ID NO:26.
25. The chimeric antigen receptor of claim 1, wherein the transmembrane domain comprises a CD8 α transmembrane domain, a CD28 transmembrane domain, a CD4 transmembrane domain, a CD3 ζ transmembrane domain, or any combination thereof.
26. The chimeric antigen receptor of claim 25, wherein the transmembrane domain is a CD28 transmembrane domain.

27. The chimeric antigen receptor of claim 25, wherein the CD28 transmembrane domain comprises an amino acid sequence of SEQ ID NO:32.
28. The chimeric antigen receptor of claim 25, wherein the CD28 transmembrane domain consists of an amino acid sequence of SEQ ID NO:32.
29. The chimeric antigen receptor of claim 1, wherein the intracellular domain comprises an intracellular co-stimulatory signaling domain, an intracellular T-cell signaling domain, or a combination thereof.
30. The chimeric antigen receptor of claim 29, wherein the intracellular co-stimulatory signaling domain is a 4-1BB intracellular co-stimulatory signaling domain, a CD28 intracellular co-stimulatory signaling domain, a ICOS intracellular co-stimulatory signaling domain, an OX-40 intracellular co-stimulatory signaling domain, or any combination thereof.
31. The chimeric antigen receptor of claim 29, wherein the intracellular costimulatory signaling domain comprises a 4-1BB intracellular co-stimulatory signaling domain.
32. The chimeric antigen receptor of claim 31, wherein the 4-1BB intracellular co-stimulatory signaling domain comprises an amino acid sequence of SEQ ID NO:33.
33. The chimeric antigen receptor of claim 31, wherein the 4-1BB intracellular co-stimulatory signaling domain consists of an amino acid sequence of SEQ ID NO:33.
34. The chimeric antigen receptor of claim 29, the intracellular costimulatory signaling domain comprises a CD28 intracellular co-stimulatory signaling domain and a 4-1BB intracellular co-stimulatory signaling domain.
35. The chimeric antigen receptor of any one of claims 29-34, wherein the intracellular costimulatory signaling domain further comprises an intracellular T-cell signaling domain.
36. The chimeric antigen receptor of claim 35, wherein the intracellular T-cell signaling domain is a CD3 ζ intracellular T-cell signaling domain.

37. The chimeric antigen receptor of claim 36, wherein the CD3 ζ intracellular T-cell signaling domain comprises an amino acid sequence of SEQ ID NO:34.
38. The chimeric antigen receptor of claim 36, wherein the CD3 ζ intracellular T-cell signaling domain consists of an amino acid sequence of SEQ ID NO:34.
39. The chimeric antigen receptor of claim 1, wherein the chimeric antigen receptor binds to a cell expressing ROR-1.
40. A nucleic acid encoding the chimeric antigen receptor of claim 1.
41. The nucleic acid of claim 40, wherein the nucleic acid is a viral vector.
42. The nucleic acid of claim 41, wherein the viral vector is a lentiviral vector.
43. A cell comprising the nucleic acid of claim 40.
44. A cell expressing the chimeric antigen receptor of claim 1.
45. The cell of claim 43 or 44, wherein the cell is a T lymphocyte.
46. The cell of claim 45, wherein the T lymphocyte is a CD4⁺ T lymphocyte or a CD8⁺ T lymphocyte.
47. The cell of claim 43 or 44, wherein the cell is a natural killer cell.
48. A pharmaceutical composition comprising a therapeutically effective amount of the cell of claim 43 and a pharmaceutically acceptable diluent, carrier, or excipient.
49. The pharmaceutical composition of claim 48, wherein the composition is formulated for intravenous injection.
50. The pharmaceutical composition of claim 48 for use in a method of treating cancer in an individual.
51. The pharmaceutical composition for the use of claim 50, wherein the cancer comprises a leukemia, a lymphoma, chronic lymphocytic leukemia, adult acute myeloid leukemia, acute lymphoblastic leukemia, a mantle cell lymphoma, ovarian

cancer, colon cancer, lung cancer, skin cancer, pancreatic cancer, testicular cancer, bladder cancer, uterine cancer, prostate cancer, or adrenal cancer.

52. The pharmaceutical composition for the use of claim 50, wherein the cancer is a CD19 negative cancer or has reduced CD19 expression as a result of a prior treatment that targets CD19.
53. The pharmaceutical composition for the use of claim 50, wherein the individual has previously been treated with a therapeutic that targets CD19.
54. The pharmaceutical composition for the use of claim 53, wherein the therapeutic that targets CD19 is an antibody that binds to CD19.
55. The pharmaceutical composition for the use of claim 53, wherein the therapeutic that targets CD19 is a chimeric antigen receptor T cell that targets CD19.
56. The pharmaceutical composition for the use of claim 53, wherein the therapeutic that targets CD19 is a chimeric antigen receptor NK cell that targets CD19.
57. The pharmaceutical composition for the use of any one of claims 50 to 56, wherein the cancer expresses ROR1.