and said VL region comprises: a light chain complementarity determining region 1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 21; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 22; and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 23; or

a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 21, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 22, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 24; or
a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 25, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 26, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 27; or
a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 28, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 29, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 30; or
a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 31, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 32, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 33; ii) an intracellular signaling domain; and iii) a transmembrane domain between the extracellular portion and the intracellular signaling domain.

[0007d] In yet another aspect, the present disclosure refers to a nucleic acid encoding the chimeric antigen receptor disclosed herein.

[0007e] In yet another aspect, the present disclosure refers to an engineered cell expressing the chimeric antigen receptor disclosed herein.

[0007f] In yet another aspect, the present disclosure refers to a composition, comprising the engineered cell disclosed herein.

[0007g] In yet another aspect, the present disclosure refers to use of the engineered cell disclosed herein for the manufacture of a medicament for treating a B cell malignancy associated with CD19 expression.

[0007h] In yet another aspect, the present disclosure refers to use of a composition disclosed herein for the manufacture of a medicament for treating a B cell malignancy associated with CD19 expression.

[0008] In some examples, the antibody has a CDR-H1, a CDR-H2, and/or a CDR-H3 that respectively include the amino acid sequences of CDR 1, 2, and 3 sequences contained within the

CLAIMS

WHAT IS CLAIMED:

1. A chimeric antigen receptor comprising:

i) an extracellular portion comprising an anti-CD19 antibody or antigen-binding fragment thereof comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

said VH region comprises a heavy chain complementarity determining region 1 (CDR-H1) comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20; and

said VL region comprises:

a light chain complementarity determining region 1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 21; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 22; and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 23; or

a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 21, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 22, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 24; or

a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 25, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 26, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 27; or

a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 28, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 29, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 30; or

a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 31, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 32, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 33;

ii) an intracellular signaling domain; and

iii) a transmembrane domain between the extracellular portion and the intracellular signaling domain.

2. The chimeric antigen receptor of claim 1, wherein:

the VH region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 11 or 12; and

the VL region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 13, 14, 15, 16 or 17.

3. The chimeric antigen receptor of claim 1 or claim 2, wherein:

the VH and VL regions of the antibody or fragment comprise amino acid sequences that have at least 90% identity to the sequences set forth in SEQ ID NOs: 12 and 17, respectively;

the VH and VL regions of the antibody or fragment comprise amino acid sequences that have at least 90% identity to the sequences set forth in SEQ ID NOs: 12 and 15, respectively;

the VH and VL regions of the antibody or fragment comprise amino acid sequences that have at least 90% identity to the sequences set forth in SEQ ID NOs: 11 and 13, respectively;

the VH and VL regions of the antibody or fragment comprise amino acid sequences that have at least 90% identity to the sequences set forth in SEQ ID NOs: 11 and 14, respectively; or

the VH and VL regions of the antibody or fragment comprise amino acid sequences that have at least 90% identity to the sequences set forth in SEQ ID NOs: 11 and 16, respectively.

4. The chimeric antigen receptor of any of claims 1-3, wherein:

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 17, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 15, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 13, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 14, respectively; or

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 16, respectively.

5. The chimeric antigen receptor of any of claims 1-4, wherein the anti-CD19 antibody or antigen binding fragment thereof specifically binds to human CD19.

6. The chimeric antigen receptor of claim 5, wherein the anti-CD19 antibody or antigen binding fragment specifically binds to the same or an overlapping epitope of CD19 as the epitope specifically bound by a reference anti-CD19 antibody selected from the group consisting of FMC63 and SJ25C1.

7. The chimeric antigen receptor of claim 6, wherein the anti-CD19 antibody or antigen binding fragment competes for binding to CD19 with a reference anti-CD19 antibody selected from the group consisting of FMC63 and SJ25C1.

8. The chimeric antigen receptor of any of claims 1-7, wherein the binding affinity (EC50) and/or the dissociation constant of the antibody to human CD19 is at or about or less than at or about 100 nM, 50 nM, 40 nM, 30 nM, 25 nM, 20 nM, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 nM.

9. The chimeric antigen receptor of any of claims 1-8, wherein the antibody or fragment is human.

10. The chimeric antigen receptor of any of claims 1-9, wherein the antibody or fragment is a single chain fragment.

11. The chimeric antigen receptor of claim 10, wherein the single chain fragment comprises the variable regions joined by a flexible linker.

12. The chimeric antigen receptor of claim 10 or claim 11, wherein the single chain fragment comprises an scFv.

13. The chimeric antigen receptor of claim 12, wherein the scFv is in the VH-VL orientation.

14. The chimeric antigen receptor of claim 12 or claim 13, wherein the scFv comprises a linker comprising the sequence set forth SEQ ID NO: 34.

15. The chimeric antigen receptor of any of claims 12-14, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10 or a sequence that exhibits at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10.

16. The chimeric antigen receptor of any of claims 12-15, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10.

17. The chimeric antigen receptor of any of claims 1-16, wherein the intracellular signaling domain comprises an ITAM.

18. The chimeric antigen receptor of any of claims 1-17, wherein the intracellular signaling domain comprises a signaling domain of a CD3-zeta (CD3ζ) chain.

19. The chimeric antigen receptor of any of claims 1-18, wherein the transmembrane domain comprises a transmembrane portion of CD28.

20. The chimeric antigen receptor of any of claims 1-19, wherein the intracellular signaling domain further comprises an intracellular signaling domain of a T cell costimulatory molecule.

21. The chimeric antigen receptor of claim 20, wherein the T cell costimulatory molecule is selected from the group consisting of CD28 and 41BB.

22. A nucleic acid encoding the chimeric antigen receptor of any of claims 1-21.

23. An engineered cell expressing the chimeric antigen receptor of any of claims 1-21.

24. The engineered cell of claim 23, that is a T cell.

25. A composition, comprising the engineered cell of claim 24.

26. The composition of claim 25, further comprising a pharmaceutically acceptable excipient.

27. Use of the engineered cell of claim 24 for the manufacture of a medicament for treating a B cell malignancy associated with CD19 expression.

28. Use of a composition of claim 25 or claim 26 for the manufacture of a medicament for treating a B cell malignancy associated with CD19 expression.

29. The use of claim 27 or claim 28, wherein the B cell malignancy is selected from the group consisting of B cell chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), pro-lymphocytic leukemias, hairy cell leukemias, common acute lymphocytic leukemias, Null-acute lymphoblastic leukemias, non-Hodgkin lymphomas, diffuse large B cell lymphomas (DLBCLs), multiple myelomas,

follicular lymphoma, splenic, marginal zone lymphoma, mantle cell lymphoma, indolent B cell lymphoma, and Hodgkin lymphoma.