Improved CD19-binding molecules and engineered CD19-targeting cells are needed. For example, there is a need for molecules and cells with reduced immunogenicity and/or human antibodies, including antibody fragments that specifically bind to CD19 and chimeric receptors expressing such human antibodies for use in adoptive cell therapy. Provided are embodiments that meet such needs.

Summary

[0005] Provided are CD19-binding molecules, including polypeptides, such as anti-CD19 antibodies, including antigen-binding antibody fragments such as single-chain fragments including scFv fragments, and polypeptides containing such antibodies, including fusion proteins, receptors, e.g., recombinant receptors, including chimeric receptors such as chimeric antigen receptors (CARs) containing the antibody as an antigen-recognition component. In particular examples, the antibodies are human antibodies, such as human single-chain fragments including scFvs.

[0006] Provided are antibodies or antigen-binding fragments thereof, including those that specifically bind to CD19. In some examples, the antibodies contain particular complementarity determining regions (CDRs), including heavy chain CDRs (CDR-Hs) and light chain CDRs (CDR-Ls). In some examples, the CDRs have or include amino acid sequences of CDRs of a reference antibody or chain or sequence thereof.

[0006a] Disclosed is an anti-CD19 antibody or antigen-binding fragment thereof, said antibody or antigen-binding fragment 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 3 (CDR-H3) comprising the amino acid sequence set forth as SEQ ID NO: 20; or said VH region comprises at least 90 % sequence identity to the VH region amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63 62, 167 or 185.

[0007] In some examples, the antibody or antigen-binding fragment thereof includes a heavy chain variable (VH) region and a light chain variable (VL) region. In some examples, the antibody, e.g., the VH region thereof, includes a heavy chain complementarity determining region 3 (CDR-H3) comprising the amino acid sequence set forth as SEQ ID NO: 20. In some examples, the VH region comprises at least at or about 90 % sequence identity to the VH region amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63,

or 62, e.g., at least at or about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some examples, the antibody or fragment includes a CDR-H1 of SEQ ID NO: 18 and a CDR-H3 of SEQ ID NO: 20. In some examples, the antibody or fragment further includes a CDR-H2 sequence comprising SEQ ID NO: 81, 82, 19 or 72.

[0007a] In one aspect, the present invention provides a chimeric antigen receptor comprising: i) an extracellular portion comprising an anti-CD19 antibody or antigen-binding fragment thereof, said antibody or antigen-binding fragment comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein: the VH region comprises at least 90 % sequence identity to the VH region amino acid sequence set forth in SEQ ID NO: 11 or 12; and the VL region comprises at least 90% sequence identity to the VL region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16 or 17; ii) an intracellular signaling domain; and iii) a transmembrane domain between the extracellular portion and the intracellular signaling domain.

[0007b] In another aspect, the present invention provides a chimeric antigen receptor comprising: i) an extracellular portion comprising an anti-CD19 antibody or antigen-binding fragment thereof, said anti-CD19 antibody or antigen-binding fragment comprising: a heavy chain variable (VH) region comprising a heavy chain complementarity determining region 1 (CDR-H1) 1, a CDR-H2, and a CDR-H3, respectively, comprising the amino acid sequences of CDR-H1, CDR-H2, and CDR-H3 sequences contained within the VH region amino acid sequence set forth in SEQ ID NO: 11 or 12; and a light chain variable (VL) region comprising a light chain complementarity determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, respectively, comprising the amino acid sequences of CDR-L1, CDR-L2, and CDR-L3 sequences contained within the VL region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, or 17; and ii) an intracellular signaling domain; and iii) a transmembrane domain between the extracellular portion and the intracellular signaling domain

[0007c] In yet another aspect, the present invention provides 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 comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 81, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20;

and a light chain variable (VL) region comprising a CDR-L1 comprising the amino acid sequence set forth in any one of SEQ ID NO: 21, 25, 28 or 31; a CDR-L2 comprising the amino acid sequence set forth in any one of SEQ ID NO: 22, 26, 29, or 32; and a CDR-L3 comprising the amino acid sequence set forth in any one of SEQ ID NO: 23, 24, 27, 30, or 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 invention provides a nucleic acid encoding the chimeric antigen receptor disclosed herein.

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

[0007f] In yet another aspect, the present invention provides a composition, comprising the chimeric antigen receptor disclosed herein, or the engineered cell disclosed herein.

[0007g] In yet another aspect, the present invention provides use of the chimeric antigen receptor disclosed herein, or the engineered cell disclosed herein for the manufacture of a medicament for treating a disease or disorder associated with CD19.

[0007h] In yet another aspect, the present invention provides use of a composition disclosed herein for the manufacture of a medicament for treating a disease or disorder associated with CD19.

[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

heavy chain variable (V_H) region of a reference antibody. In some examples, the VH region of the reference antibody has the amino acid sequence set forth in SEQ ID NO: 11 or 12. In some examples, it has the amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62.

[0008a] Also disclosed an anti-CD19 antibody or antigen-binding fragment thereof comprising: a heavy chain variable (VH) region comprising a heavy chain complementarity determining region 1 (CDR-H1) 1, a CDR-H2, and a CDR-H3, respectively, comprising the amino acid sequences of CDR-H1, CDR-H2, and CDR-H3 sequences contained within the VH region amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63 62, 167 or 185; and/or a light chain variable (VL) region comprising a light chain complementarity determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, respectively, comprising the amino acid sequences of CDR-L1, CDR-L2, and CDR-L3 sequences contained within the VL region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, 17, 71, 65, 64, 66, 70, 69, 67, 90, 91 or 187-205.

[0009] In some examples, the antibody has, e.g., further includes, a CDR-L1, a CDR-L2, and/or a CDR-L3, respectively comprising the amino acid sequences of CDR 1, 2, and 3 sequences contained within the light chain variable (V_L) region of a reference antibody. In some examples, the V_L of the reference antibody has the amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, or 17. In some examples, the VL of the reference antibody has the amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, 17, 71, 65, 64, 66, 70, 69, 67, 90 or 91.

[0010] In some examples, the CDR within the reference antibody, VH, or VL refers to the CDR as defined by any numbering scheme, e.g., those defined herein. In some examples, the CDR in the reference antibody or VH or VL refers to the CDR as defined by Kabat numbering scheme as described herein, the CDR as defined by the Chothia scheme as described herein, or the Contact scheme as described herein.

[0011] In some examples, the antibody contains a VH chain that includes a CDR-H1, CDR-H2 and/or CDR-H3 in which the CDR-H1 comprises the amino acid sequence of DYAMH (SEQ ID NO: 18) or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 18; the CDR-H2

comprises the amino acid sequence of SEQ ID NO: 81 or 82 or 19 or 72 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 81 or to SEQ ID NO: 82 or to SEQ ID NO: 19 or to SEQ ID NO: 72; and/or the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 20 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 20.

[0012] In some examples, the antibody comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 81 or 82, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20.

[0012a] Also disclosed is an antibody or antigen-binding fragment thereof comprising: a heavy chain variable (VH) region comprising: a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 81 or 82, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20; and/or a CDR-L1 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 226), wherein X_1 is T, Q, S, or R; X_2 is G, A or E; X_3 is I, T, A, D, or S; X_4 is S, R, T Q, G or I; X_5 is null, S, R or T; X_6 is G, D, N, or null; X_7 is null, V, L or I; X_8 is D, G, I, L, S, or null; X_9 is S, G, A, I, D, R, or null; X_{10} is H, Y, F, S, or N; X_{11} is R, N, D, H, Y or T; X_{12} is Y, F, D, W, H, T or S; X_{13} is V, A, or L; and X_{14} is S, N, or A; a CDR-L2 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 227), wherein X_1 is D,S or G; X_2 is F, V, N, K, or A; X_3 is S, T, D, or N; X_4 is K, V, N, Q, or R; X_5 is R, V, or L; X_6 is P, K, A, or E; and X_7 is S, P, A, or T, and a CDR-L3 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 228), wherein X_1 is S, G, T, A, Q, C, or N; X_2 is S, Q, A, or T; X_3 is Y, S, W, R; X_4 is A, D, R, T, or Y; X_5 is A, S, P, G, N, or D; X_6 is I, S, G, T, A, L, H, R, or N; X_7 is S, P, L, Y, G; X_8 is P, T, S, Q, M, R, N or null; X_9 is S, L, N, A, M, R or null; X_{10} is L, D or null; X_{11} is Y, W, F, V, A, or L; and X_{12} is V, T, P or L.

[0013] In some examples, the antibody has a CDR-1 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 110), wherein X_1 is T, W, S or R; X_2 is G or

For example, in some examples, the provided antibody or fragment contains one or more or all CDRs that are distinct from the corresponding CDRs in the antibody designated FMC63 or SJ25C1.

[0078a] Also disclosed is a human antibody fragment that specifically binds to the same or an overlapping epitope of a human CD19 as the epitope specifically bound by a reference antibody, wherein the reference antibody is the antibody or fragment thereof as disclosed herein or is an anti-CD19 antibody selected from the group consisting of FMC63 and SJ25C1, said human antibody fragment comprising heavy and light chain CDRs that are distinct from the CDRs present in FMC63 and SJ25C1.

[0078b] Also disclosed is a human antibody fragment that specifically binds to human CD19 and competes for binding to a human CD19 with a reference antibody, wherein the reference antibody is the antibody or fragment as disclosed herein or is an anti-CD19 antibody selected from the group consisting of FMC63 and SJ25C1, said human antibody fragment comprising heavy and light chain CDRs that are distinct from the CDRs present in FMC63 and SJ25C1.

[0079] For example, provided are human antibody and antigen-binding fragments that specifically bind to the same or an overlapping epitope of CD19 as the epitope specifically bound by the reference antibody, such as FMC63, SJ25C1, an antibody having a variable region sequence of SEQ ID NO: 39 and/or 40, or an antibody having a variable region sequence of SEQ ID NO: 41 and/or 42, and comprising heavy and light chain CDRs that are distinct from the CDRs present in the reference antibody.

[0080] In some examples, the antibody competes for binding with the reference antibody to at least the same degree as the reference antibody competes for binding with itself to CD19, or a degree of competition that is no more than 1.5-fold or 2-fold lower, 3-fold lower, 4-fold lower, 5-fold lower, or 10-fold lower than the competition by the reference antibody, and/or a measured IC50 that is no more than 1.5-fold or 2-fold or 3-fold or 4-fold or 5-fold or 10-fold higher than the IC50 of the reference antibody competing for binding with itself, for example, as measured in the same assay.

[0084] In some examples, the antibody or fragment further includes at least a portion of an immunoglobulin constant region. The constant region may include any one or more of CH1, CH2, CH3, and/or CH4, and/or CL, of a human or other antibody, and be of any class, including IgG, IgM, IgA, IgE, and IgD, for example, including human IgG, e.g., IgG1 or IgG4, constant region domains. In some examples, the constant region comprises or is an Fc region, such as a human IgG Fc region.

[0084a] Also disclosed is a conjugate, comprising the antibody or fragment as disclosed herein and a heterologous molecule or moiety.

[0085] Also provided are molecules such as chimeric and/or fusion molecules, including receptors, such as recombinant receptors, that include the antibody of any of the examples (e.g., contained in or part of an extracellular domain) and additional domains, such as intracellular signaling domains, spacers, linkers, and/or transmembrane domains. In some examples, the receptor is a chimeric antigen receptor, comprising an extracellular portion comprising the antibody or fragment of any of the examples and an intracellular signaling domain.

[0085a] Also disclosed is a chimeric antigen receptor (CAR) comprising an extracellular portion comprising the antibody or fragment as disclosed herein and an intracellular signaling domain.

[0086] In some examples, the antibody or fragment comprises an scFv. In some examples, the intracellular signaling domain comprises an ITAM and/or signaling domain capable of delivering a signal approximating that of natural ligation of an ITAM-containing molecule or receptor complex such as a TCR receptor complex. In some examples, the intracellular signaling domain comprises a signaling domain of a zeta chain of a CD3-zeta (CD3ζ) chain.

[0087] In some examples, the receptor further includes one or more domains, such as a transmembrane domain, linking the antibody transmembrane domain linking the extracellular domain and the intracellular signaling domain. In some examples, the transmembrane domain comprises a transmembrane portion of a costimulatory molecule, such as a T cell costimulatory molecule, e.g., CD28 and/or 41BB. In some examples, the T cell

[0088a] Also disclosed is a nucleic acid encoding the antibody or fragment as disclosed herein, conjugate as disclosed herein or the chimeric antigen receptor as disclosed herein.

[0089] Thus, also provided are cells and vectors for producing and expressing the molecules, including the antibodies and molecules such as receptors, e.g., chimeric antigen receptors (CARs). For example, provided are engineered cells expressing the chimeric antigen receptor of any of the examples. In some examples, the cell is a T cell. In some examples, the cell is an NK cell. In some examples, the cell is a stem cell.

[0089a] Also disclosed is an engineered cell expressing a receptor comprising the antibody or fragment as disclosed herein, conjugate as disclosed herein or the chimeric antigen receptor as disclosed herein.

[0090] Also provided are compositions comprising the antibodies, receptors, molecules, and/or cells, including pharmaceutical compositions, e.g., further including pharmaceutically acceptable substances such as carriers.

[0090a] Also disclosed is an a composition, comprising the antibody or fragment thereof as disclosed herein, conjugate as disclosed herein, the CAR as disclosed herein or the cell as disclosed herein.

[0091] Also provided are methods of administration, including methods of treatment, carried out by administering the cell, antibody, receptor, composition, or other molecule, of any of the examples, to a subject, for example, in an effective, e.g., therapeutically effective, amount. In some examples, the subject has or is suspected of having a disease or disorder associated with CD19, such as a B cell malignancy, such as 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, or Hodgkin lymphoma, or an autoimmune or inflammatory disease in which B cells are implicated.

[0091a] Also disclosed is use of an antibody or fragment thereof as disclosed herein, conjugate as disclosed herein, the CAR as disclosed herein or the cell as disclosed herein for the manufacture of a medicament for treating a disease or disorder associated with CD19.

[0091b] Also disclosed is use of a composition as disclosed herein for the manufacture of a medicament for treating a disease or disorder associated with CD19.

[0092] In some examples, administration of the antibody or receptor is associated with a lower degree of immunogenicity as compared to administration of a reference antibody (or receptor containing the reference antibody) that competes for binding with the antibody or binds to an overlapping epitope. In some examples, the reference antibody is a humanized, chimeric, or non-human antibody.

Brief Description of the Drawings

[0093] **Figure 1**: **Figures 1A** and **1B** show results from a binding assay comparing binding of exemplary human scFvs to CD19-expressing HEK293 cells as compared to binding to non-CD19-expressing HEK293 cells. MFI=mean fluorescence intensity.

CLAIMS

WHAT IS CLAIMED:

1. A chimeric antigen receptor comprising:

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

the VH region comprises at least 90 % sequence identity to the VH region amino acid sequence set forth in SEQ ID NO: 11 or 12; and

the VL region comprises at least 90% sequence identity to the VL region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16 or 17;

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 comprises at least 95% sequence to the VH region amino acid sequence set forth in SEQ ID NO: 11 or 12; and

the VL region comprises at least 95% sequence identity to the VL region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16 or 17.

3. A chimeric antigen receptor comprising:

i) an extracellular portion comprising an anti-CD19 antibody or antigen-binding fragment thereof, said anti-CD19 antibody or antigen-binding fragment comprising:

a heavy chain variable (VH) region comprising a heavy chain complementarity determining region 1 (CDR-H1) 1, a CDR-H2, and a CDR-H3, respectively, comprising the amino acid sequences of CDR-H1, CDR-H2, and CDR-H3 sequences contained within the VH region amino acid sequence set forth in SEQ ID NO: 11 or 12; and

a light chain variable (VL) region comprising a light chain complementarity determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, respectively, comprising the amino acid sequences of CDR-L1, CDR-L2, and CDR-L3 sequences contained

within the VL region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, or 17; and

ii) an intracellular signaling domain; and

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

4. The chimeric antigen receptor of any of claims 1-3, wherein the VH region comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 81, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20; and

the VL comprises a CDR-L1 comprising the amino acid sequence set forth in any one of SEQ ID NO: 21, 25, 28 or 31; a CDR-L2 comprising the amino acid sequence set forth in any one of SEQ ID NO: 22, 26, 29, or 32; and a CDR-L3 comprising the amino acid sequence set forth in any one of SEQ ID NO: 23, 24, 27, 30, or 33.

5. 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 comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 81, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20; and

a light chain variable (VL) region comprising a CDR-L1 comprising the amino acid sequence set forth in any one of SEQ ID NO: 21, 25, 28 or 31; a CDR-L2 comprising the amino acid sequence set forth in any one of SEQ ID NO: 22, 26, 29, or 32; and a CDR-L3 comprising the amino acid sequence set forth in any one of SEQ ID NO: 23, 24, 27, 30, or 33;

ii) an intracellular signaling domain; and

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

6. The chimeric antigen receptor of any of claims 1-5, wherein:

the VH region comprises a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 19 (GISWNSGRIGYADSVKG); or

the VH region comprises a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 72 (GISWNSGSIGYADSVKG).

7. The chimeric antigen receptor of any of claims 1-6, wherein:

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 21, 22, and 23, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 21, 22, and 24, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 25, 26, and 27, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 28, 29, and 30, respectively; or

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 31, 32, and 33, respectively.

8. The chimeric antigen receptor of any of claims 1-7, 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.

9. The chimeric antigen receptor of any of claims 1-8, 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.

10. The chimeric antigen receptor of any of claims 1-9, 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;

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

11. The chimeric antigen receptor of any of claims 1-10, wherein the anti-CD19 antibody or antigen binding fragment thereof specifically binds to human CD19.

12. The chimeric antigen receptor of claim 11, 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.

13. The chimeric antigen receptor of claim 12, 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.

14. The chimeric antigen receptor of any of claims 1-13, 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.

15. The chimeric antigen receptor of any of claims 1-14, wherein the antibody or fragment is human.

16. The chimeric antigen receptor of any of claims 1-15, wherein the antibody or fragment is a single chain fragment.

17. The chimeric antigen receptor of claim 16, wherein the single chain fragment comprises the variable regions joined by a flexible linker.

18. The chimeric antigen receptor of claim 16 or claim 17, wherein the single chain fragment comprises an scFv.

19. The chimeric antigen receptor of claim 18, wherein the scFv is in the VH-VL orientation.

20. The chimeric antigen receptor of claim 18 or claim 19, wherein the scFv comprises a linker comprising the sequence set forth SEQ ID NO: 34.

21. The chimeric antigen receptor of any of claims 18-20, 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.

22. The chimeric antigen receptor of any of claims 18-21, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10.

23. The chimeric antigen receptor of any of claims 1-22, wherein the intracellular signaling domain comprises an ITAM.

24. The chimeric antigen receptor of any of claims 1-23, wherein the intracellular signaling domain comprises a signaling domain of a CD3-zeta (CD3ζ) chain.

25. The chimeric antigen receptor of any of claims 1-24, wherein the transmembrane domain comprises a transmembrane portion of CD28.

26. The chimeric antigen receptor of any of claims 1-25, wherein the intracellular signaling domain further comprises an intracellular signaling domain of a T cell costimulatory molecule.

27. The chimeric antigen receptor of claim 26, wherein the T cell costimulatory molecule is selected from the group consisting of CD28 and 41BB.

28. A nucleic acid encoding the chimeric antigen receptor of any of claims 1-27.

29. An engineered cell expressing the chimeric antigen receptor of any of claims 1-27.

30. The engineered cell of claim 29, that is a T cell.

31. A composition, comprising the chimeric antigen receptor of any of claims 1-27, or the engineered cell of claim 29 or claim 30.

32. The composition of claim 31, further comprising a pharmaceutically acceptable excipient.

33. Use of the chimeric antigen receptor of any of claims 1-27, or the engineered cell of claim 29 or claim 30 for the manufacture of a medicament for treating a disease or disorder associated with CD19.

34. Use of a composition of claim 31 or claim 32 for the manufacture of a medicament for treating a disease or disorder associated with CD19.

35. The use of claim 33 or claim 34, wherein the disease or disorder is a B cell malignancy.

36. The use of claim 35, 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.