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] In one aspect, there is provided 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.

[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] In another aspect, there is provided 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] In yet another aspect, there is provided 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

A; X_3 is I, T, D or S; X_4 is S, R, T or Q; X_5 is null or S; X_6 is null, D, N or G; X_7 is null, V or L; X_8 is X or null; X_9 is X or null; X_{10} is X; X_{11} is X; X_{12} is Y, F, D or W; X_{13} is V, A or L and X_{14} is S, N or A. For example, in some examples, the antibody has 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: 111), wherein X_1 is T, Q, S, or R; X_2 is G or A; X_3 is I, T, D, or S; X_4 is S, R, T, or Q; X_5 is null or S; X_6 is G, D, N, or null; X_7 is null, V, or L; X_8 is D, G, I, L, S, or null; X_9 is S, G, A, I, R, or null; X_{10} is H, Y, F, S, or N; X_{11} is R, N, D, H, or Y; X_{12} is Y, F, D, or W; X_{13} is V, A, or L; and X_{14} is S, N, or A; and/or

[0014] a CDR-L2 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 112), wherein X_1 is D or S; 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/or

[0015] 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: 115), wherein X_1 is X; 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 X; X_6 is X; X_7 is S, P, L, Y, G; X_8 is X or null; X_9 is X or null; X_{10} is L or null; X_{11} is X; and X_{12} is V, T, or L. For example, in some examples, the antibody has a CDR-L3 comprising the amino acid sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 114), 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, 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 or null; X_{10} is L or null; X_{11} is Y, W, F, V, A or L; and X_{12} is V, T, or L.

[0016] In some such examples, in said CDR-L1, X_3 is I, T, or S; X_4 is S, T, or Q; X_8 is D, G, I, S, or null; X_9 is S, G, I, or null; X_{10} is H, Y, S, or N; X_{11} is R, N, D, or H; X_{12} is Y or D; and X_{13} is V or L; and/or in said CDR-L2, X_1 is D; X_4 is K, V, N, Q, or R; X_6 is P, K, or A; and X_7 is S, A, or T ; and/or in said CDR-L3, X_1 is S, G, T, A, Q, C, or N; X_5 is A, S, P, G, N, or D; X_6 is I, S, G, T, A, L, H, R, or N; X_8 is P, T, S, Q, M, R, N, or null; X_9 is S, L, N, A, M or null; and X_{11} is Y, W, F, V, A, or L. In some examples, in said CDR-L3, X_1 is S, G, Q, or N; X_2 is S, Q, or T; X_4 is A, D, T, or Y; X_5 is A, S, or G; and X_6 is I, S, N, R, A, H, or T.

[0017] In some examples, the CDR-H2 comprises the amino acid sequence set forth in SEQ ID NO: 19 (GISWNSGRIGYADSVKG); or the CDR-H2 comprises the amino acid sequence set forth in SEQ ID NO: 72 (GISWNSGSIGYADSVKG).

[0018] In some examples, the CDR-L1 comprises the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 75, 79, 78, 76, 21, 25, 28, or 31. In some examples, the CDR-L1 comprises the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 78, 21, or 28.

[0019] In some examples, the CDR-L2 comprises the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 95, 99, 98, 96, 22, 26, 29, or 32. In some examples, the CDR-L2 comprises the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 98, 22, or 29.

[0020] In some examples, the CDR-L3 comprises the amino acid sequence set forth in SEQ ID NO: 109, 106, 103, 101, 104, 108, 107, 105, 102, 23, 24, 27, 30, or 33. In some examples, the CDR-L3 comprises the amino acid sequence set forth in SEQ ID NO: 109, 106, 103, 101, 107, 24 or 30.

[0021] In some examples, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 23, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 24 or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 25, 26, and 27, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 29 and 30, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 31, 32, and 33, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 80, 100, and 109, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs:77, 97, and 106, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence

identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 74, 94, and 103, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 73, 93, and 101, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs:75, 95, and 104, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 79, 99, and 108, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 78, 98, and 107, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 76, 96, and 105, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 73, 93, and 102, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; or the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 77, 97, and 106, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto.

[0022] In some examples, the CDR-L3 comprises the amino acid sequence set forth as SEQ ID NO: 116, 117, 118, 119, 120, or 121, 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, respectively, thereto.

[0023] In some examples, the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 81, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 19, and 20,

respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 82, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; or the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 72, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto.

[0024] In some examples, the antibody has a CDR-L1 comprising the amino acid sequence $X_1GX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}S$ (SEQ ID NO: 36), wherein X1 is T, S, or Q, X3 is T, S, or D, X4 is T or S, X5 is null or S, X6 is null, D, or N, X7 is null or V, X8 is null, G, or I, X9 is null, G, or R, X10 is S, Y, or N, X11 is D or N, X12 is D or Y, X13 is V or A; the CDR-L2 comprises the amino acid sequence $X_1X_2X_3X_4RPS$ (SEQ ID NO: 37), wherein X1 is D or S, X2 is V, N, or K, X3 is S, N, or D, and X4 is K, Q, or N; and/or the CDR-L3 comprises the amino acid sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 113), wherein X1 is C, S, A, G, or N; X2 is S, A, or T; X3 is Y, W, or R; X4 is A or D; X5 is G, D, or S; X6 is R, S, or N; X7 is Y, L, or G; X8 is N or S; X9 is S, N, or null; X10 is null; X11is V, A, or W; and X12 is L or V.

[0025] In some examples, the antibody has a CDR-L1 comprising the amino acid sequence $X_1GX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}S$ (SEQ ID NO: 36), wherein X1 is T, S, or Q, X3 is T, S, or D, X4 is T or S, X5 is null or S, X6 is null, D, or N, X7 is null or V, X8 is null, G, or I, X9 is null, G, or R, X10 is S, Y, or N, X11 is D or N, X12 is D or Y, X13 is V or A; the CDR-L2 comprises the amino acid sequence $X_1X_2X_3X_4RPS$ (SEQ ID NO: 37), wherein X1 is D or S, X2 is V, N, or K, X3 is S, N, or D, and X4 is K, Q, or N; and/or the CDR-L3 comprises the amino acid sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 38), wherein X1 is C, S, A, G, or N; X2 is S, A, or T; X3 is Y, W, or R; X4 is A or D; X5 is G, D, or S; X6 is R, S, or N; X7 is Y, L, or G; X8 is N or S; X9 is S or null; X10 is V, A or N; X11 is W or null; and X12 is L or V.

[0026] In some such examples, in the CDR-L1, X1 is T or S, X3 is T or S, X11 is D or N, and X13 is V; and/or in the CDR-L2, X2 is V or N and X4 is K or Q.

[0027] In some examples, the CDR-H2 comprises the amino acid sequence set forth in SEQ ID NO: 19 (GISWNSGRIGYADSVKG) 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: 19.

[0028] In some examples, the CDR-L1 comprises the sequence set forth in SEQ ID NO: 21, 25, 28, or 31 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 thereto; and/or the CDR-L2 comprises the sequence set forth in SEQ ID NO: 22, 26, 29, or 32 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 thereto; and/or the CDR-L3 comprises the sequence set forth in SEQ ID NO: 23, 24, 27, 30, or 33 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 thereto.

[0029] In some examples, the CDR-L1, CDR-L2, and/or CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and/or 23, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0030] In some examples, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 24, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0031] In some examples, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 25, 26, and 27, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0032] In some examples, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 29, and 30, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively. In some examples, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 31, 32, and 33, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0033] In some examples, the heavy and light chain CDRs are any combination of the aforementioned CDR-L and CDR-H sequences, including sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0034] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 11 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 thereto.

[0035] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 12 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 thereto.

[0036] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 13 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 thereto.

[0037] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 14 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 thereto.

[0038] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 15 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 thereto.

[0039] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 16 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 thereto.

[0040] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 17 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 thereto.

[0041] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 63 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 thereto.

[0042] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 60 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 thereto.

[0043] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 61 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 thereto.

[0044] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 63 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 thereto.

[0045] In particular examples, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 62 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 thereto.

[0046] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 71 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 thereto.

[0047] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 90 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 thereto.

[0048] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 91 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 thereto.

[0049] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 68 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 thereto.

[0050] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 65 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 thereto.

[0051] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 64 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 thereto.

[0052] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 66 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 thereto.

[0053] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 70 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 thereto.

[0054] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 69 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 thereto.

[0055] In particular examples, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 67 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 thereto.

[0056] In particular examples, the VH region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 11, 60, 63, or 62 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 thereto; and/or the VL region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 14, 16, 71, 90, 65, 64, or 69 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 thereto.

[0057] In some examples, the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 17, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;

[0058] the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 15, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;

[0068] the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 69, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;

[0069] the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 67, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;

[0070] the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 91, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively; or

[0071] the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 90, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0072] In some examples, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 13; in some examples, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 14; in some examples, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 15; in some examples, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 16, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; in some examples, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 17, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0073] In some examples, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 13; in some examples, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 14; in some examples, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 15; in some examples, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 16, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; in some examples, the VH region comprises SEQ ID NO: 12 and the

VL region comprises SEQ ID NO: 16, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0074] In some examples, the antibody is a single chain fragment, such as one with two or more variable regions joined by one or more flexible immunoglobulin linker. In some examples, the antibody is an scFv. In some examples, the scFv comprises a linker that is rich in serine and/or glycine, such as a linker comprising GGGS (SEQ ID NO: 122) or GGGGS (SEQ ID NO:123) repeats, such as one comprising the sequence set forth SEQ ID NO: 34. In some examples the linker comprises a sequence of SEQ ID NO: 43.

[0075] In some examples, the antibody fragment, e.g., scFv, contains a V_H region or portion thereof, followed by a linker, followed by a V_L or portions thereof. In some examples, the antibody fragment, e.g., scFv, contains a V_L region or portion thereof followed by a linker, followed by a V_H region or portion thereof.

[0076] In some examples, the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10, 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 thereto.

[0077] In some examples, the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, or 89, or has a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0078] In some examples, the antibody or fragment specifically binds to the same, similar, and/or an overlapping epitope of CD19 as the epitope specifically bound by a reference antibody, and/or the antibody competes for binding to CD19 with the reference antibody. In some examples, the reference antibody is a murine or chimeric or human or humanized anti-CD19 antibody, 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. In some example, the reference antibody is an antibody including a sequence as described herein, including sequence(s) of any of the aforementioned examples. For example, in some examples, the reference antibody can be an scFv that contains the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, or 89. In some examples, the provided antibody or fragment contains one or more or all CDRs that are distinct from those in the reference antibody.

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] In yet another aspect, there is provided 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] In yet another aspect, there is provided 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.

[0081] In some examples, the antibody has a binding affinity that is at least as high or substantially as high as the binding affinity for CD19 of the reference antibody. In some examples, the antibody has a binding affinity of an EC50 that is about the same or lower than the EC50 reference antibody or no more than about 1.5-fold or no more than about 2-fold greater, no more than 3-fold greater, and/or no more than 10-fold greater, than the EC50 of the reference antibody. In some examples, binding affinity of the antibody is compared to the corresponding form of the reference antibody. Comparison is generally by the same or a similar assay.

[0082] In some of any such examples, CD19 is a human CD19. In some of any such examples, the antibody or fragment specifically binds, exhibits binding affinity and/or competes for binding to human CD19.

[0083] In some examples, the antibody is human. In some examples, the antibody is recombinant. In some examples, the antibody is monoclonal. In some examples, the antibody is isolated.

[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] In yet another aspect, there is provided 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] In yet another aspect, there is provided 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

costimulatory molecule is selected from the group consisting of CD28 and 41BB, and in some examples, the receptor includes signaling domains from CD28 and 41BB.

[0088] Also provided are nucleic acids encoding the antibody (including fragments) of any of examples or the receptor, e.g., chimeric antigen receptor of any of the examples, vectors including such nucleic acids, and cells containing the vectors and/or nucleic acids, for example, for expression of the antibodies and/or molecules.

[0088a] In yet another aspect, there is provided 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] In yet another aspect, there is provided 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] In yet another aspect, there is provided 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] In yet another aspect, there is provided 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] In yet another aspect, there is provided 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. 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.

2. The anti-CD19 antibody or antigen-binding fragment of claim 1, wherein the VH region comprises at least 90% sequence to the VH region amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63 or 62.

3. 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.

4. The antibody or antigen-binding fragment 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 or 82, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20.

5. 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.

6. The antibody or antigen-binding fragment of claim 5, wherein:

the CDR-L1 comprises 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: 111), wherein X_1 is T, Q, S, or R; X_2 is G or A; X_3 is I, T, D, or S; X_4 is S, R, T, or Q; X_5 is null or S; X_6 is G, D, N, or null; X_7 is null, V, or L; X_8 is D, G, I, L, S, or null; X_9 is S, G, A, I, R, or null; X_{10} is H, Y, F, S, or N; X_{11} is R, N, D, H, or Y; X_{12} is Y, F, D, or W; X_{13} is V, A, or L; and X_{14} is S, N, or A;

the CDR-L2 comprises the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 112), wherein X_1 is D or S; 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

the CDR-L3 comprises the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 114), 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 or null; X_{10} is L or null; X_{11} is Y, W, F, V, A, or L; and X_{12} is V, T, or L.

7. The antibody or antigen-binding fragment thereof of claim 5 or claim 6, wherein:

the CDR-L1 comprises the amino acid sequence $X_1GX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}S$ (SEQ ID NO: 36), wherein X_1 is T, S, or Q, X_3 is T, S, or D, X_4 is T or S, X_5 is null or S, X_6 is null, D, or N, X_7 is null or V, X_8 is null, G, or I, X_9 is null, G, or R, X_{10} is S, Y, or N, X_{11} is D or N, X_{12} is D or Y, X_{13} is V or A;

the CDR-L2 comprises the amino acid sequence $X_1X_2X_3X_4$RPS (SEQ ID NO: 37), wherein X_1 is D or S, X_2 is V, N, or K, X_3 is S, N, or D, and X_4 is K, Q, or N;

the CDR-L3 comprises the amino acid sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 38), wherein X_1 is C, S, A, G, or N, X_2 is S, A, or T, X_3 is Y, W, or R, X_4 is A or D, X_5 is G, D, or S, X_6 is R, S, or N, X_7 is Y, L, or G, X_8 is N or S, X_9 is S or null, X_{10} is V, A, or N, X_{11} is W or null, and X_{12} is L or V.

8. The antibody or fragment of any of claims 1-7, 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).

9. The antibody or fragment of any of claims 1-8, wherein the VL region comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 75, 79, 78, 76, 21, 25, 28, 31 or 146 to 152.

10. The antibody or fragment of any of claims 1-9, wherein the VL region comprises a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 95, 99, 98, 96, 22, 26, 29, 32 or 153 to 157.

11. The antibody or fragment of any of claims 1-10, wherein the VL region comprises a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 109, 106, 103, 101, 104, 108, 107, 105, 102, 23, 24, 27, 30, 33, 158 or 159.

12. The antibody or fragment of any of claims 1-11, 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;

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

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 80, 100, and 109, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs:77, 97, and 106, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 74, 94, and 103, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 73, 93, and 101, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs:75, 95, and 104, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 79, 99, and 108, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 78, 98, and 107, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 76, 96, and 105, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 73, 93, and 102, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 163, 164, and 165, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 80, 100, and 109, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 146, 97, and 106, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 28, 153 and 158, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 74, 94, and 103, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 147, 154 and 121, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 148, 94 and 103, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 75, 95 and 104, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 149, 155 and 119, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 150, 22, and 120, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 21, 22 and 159, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 151, 26 and 118, respectively;

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 28, 156 and 116, respectively; or

the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 152, 157 and 117, respectively.

13. The antibody or fragment of any of claims 1-12, wherein:

the VH region comprises a CDRH1, CDR-H2, and CDR-H3 comprising the sequences of SEQ ID NOs: 18, 81, and 20, respectively, and 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 VH region comprises a CDRH1, CDR-H2, and CDR-H3 comprising the sequences of SEQ ID NOs: 18, 81, and 20, respectively, and 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 VH region comprises a CDRH1, CDR-H2, and CDR-H3 comprising the sequences of SEQ ID NOs: 18, 81, and 20, respectively, and 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 VH region comprises a CDRH1, CDR-H2, and CDR-H3 comprising the sequences of SEQ ID NOs: 18, 81, and 20, respectively, and the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 28, 29, and 30, respectively;

the VH region comprises a CDRH1, CDR-H2, and CDR-H3 comprising the sequences of SEQ ID NOs: 18, 81, and 20, respectively, and the VL region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the sequences of SEQ ID NOs: 31, 32, and 33, respectively.

14. The antibody or fragment of any of claims 1-13, wherein:

the VH region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 11, 12, 60, 61, 63, 62, 167 or 185; and/or

the VL region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 13, 14, 15, 16, 17, 71, 90, 91, 68, 65, 64, 66, 70, 69, 67 or 187 to 205.

15. The antibody or fragment 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;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 71, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 68, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 65, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 60 and 64, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 61 and 66, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 70, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 69, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 67, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 91, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 90, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 167 and 207, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 168 or 63 and 208, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 169 or 11 and 209, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 170 or 61 and 210, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 171 or 61 and 211, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 172 and 212, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 173 or 11 and 213, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 174 or 11 and 214, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 175 or 11 and 215, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 176 or 61 and 216, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 177 or 61 and 217, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 178 or 61 and 218, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 179 or 61 and 219, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 180 or 12 and 220, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 181 or 12 and 221, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 182 or 11 and 222, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 183 or 60 and 223, respectively;

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 184 or 11 and 224, respectively; or

the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 185 and 225, respectively.

16. The antibody or fragment of any of claims 1-15, 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.

17. The antibody or fragment of any of claims 1-16, wherein the antibody specifically binds to human CD19.

18. The antibody or fragment of claim 17, wherein the antibody 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.

19. The antibody or fragment of claim 18, wherein the antibody competes for binding to CD19 with an anti-CD19 antibody selected from the group consisting of FMC63 and SJ25C1.

20. 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 of any of claims 1-19 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.

21. 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 of any of claims 1-19 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.

22. The antibody or fragment of claim 19 or 21, which 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 than the competition by the reference antibody.

23. The antibody or fragment of any of claims 1-22, wherein the antibody has a binding affinity that is at least as high or substantially as high as the binding affinity for CD19 of a reference antibody selected from the group consisting of FMC63 and SJ25C1.

24. The antibody or fragment of claim 23, which has a binding affinity of an EC_{50} that is about the same or lower than the EC_{50} of the reference antibody or no more than about 1.5-fold or no more than about 2-fold greater, no more than 3-fold greater, and/or no more than 10-fold greater, than the EC_{50} of the reference antibody.

25. The antibody or fragment of any of claims 1-24, 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.

26. The antibody or fragment of any of claims 1-25, wherein the antibody or fragment is human.

27. The antibody or fragment of any of claims 1-26, wherein the antibody or fragment is recombinant.

28. The antibody or fragment of any of claims 1-27, which is monoclonal.

29. The antibody or fragment of any of any of claims 1-28, which is a single chain fragment.

30. The antibody or fragment of any of claims 1-29, which is a fragment comprising antibody variable regions joined by a flexible immunoglobulin linker.

31. The antibody or fragment of claim 29 or 30, wherein the fragment comprises an scFv.

32. The antibody or fragment of claim 31, wherein the scFv comprises a linker comprising the sequence set forth SEQ ID NO: 34.

33. The antibody or fragment of claim 30 or claim 32, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, 89, or 207 to 225 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, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, 89, or 207 to 225.

34. The antibody or fragment of any of claims 31-33, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10.

35. The antibody or fragment of any of claims 1-34, which further comprises at least a portion of an immunoglobulin constant region.

36. The antibody or fragment of any of claims 1-35, wherein the at least a portion comprises a hinge region.

37. The antibody or fragment of claim 36 or 36, wherein the at least a portion of an immunoglobulin constant region comprises an Fc region.

38. The antibody or fragment of claim 37, wherein the Fc region is an Fc region of a human IgG.

39. A conjugate, comprising the antibody or fragment of any of claims 1-38 and a heterologous molecule or moiety.

40. A chimeric antigen receptor (CAR) comprising an extracellular portion comprising the antibody or fragment of any of claims 1-38 and an intracellular signaling domain.

41. The chimeric antigen receptor of claim 40, wherein the antibody or fragment comprises an scFv and the intracellular signaling domain comprises an ITAM.

42. The chimeric antigen receptor of claim 40 or 41, wherein the intracellular signaling domain comprises a signaling domain of a zeta chain of a CD3-zeta (CD3ζ) chain.

43. The chimeric antigen receptor of any of claims 40-42, further comprising a transmembrane domain linking the extracellular domain and the intracellular signaling domain.

44. The chimeric antigen receptor of claim 43, wherein the transmembrane domain comprises a transmembrane portion of CD28.

45. The chimeric antigen receptor of any of claims 40-44, further comprising an intracellular signaling domain of a T cell costimulatory molecule.

46. The chimeric antigen receptor of claim 45, wherein the T cell costimulatory molecule is selected from the group consisting of CD28 and 41BB.

47. A nucleic acid encoding the antibody or fragment of any of claims 1-38, conjugate of claim 39 or the chimeric antigen receptor of any of claims 40-46.

48. An engineered cell expressing a receptor comprising the antibody or fragment of any of claims 1-38, conjugate of claim 39 or the chimeric antigen receptor of any of claims 40-46.

49. The engineered cell of claim 48, which is a T cell.

50. A composition, comprising the antibody or fragment thereof of any of claims 1-38, conjugate of claim 39, the CAR of any of claims 40-46 or the cell of claim 48 or 49.

51. The composition of claim 50, further comprising a pharmaceutically acceptable excipient.

52. Use of an antibody or fragment thereof of any of claims 1-38, conjugate of claim 39, the CAR of any of claims 40-46 or the cell of claim 48 or 49 for the manufacture of a medicament for treating a disease or disorder associated with CD19.

53. Use of a composition of claim 50 or 51 for the manufacture of a medicament for treating a disease or disorder associated with CD19.

54. The use of claim 52 or claim 53 , wherein the disease or disorder is a B cell malignancy.

55. The use of claim 54, 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.