WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises a single chain antibody or a single chain antibody fragment comprising an anti-CD19 binding domain, a transmembrane domain, a costimulatory, and an intracellular signaling domain; and

wherein the anti-CD19 binding domain comprises:

(a) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1) of SEQ ID NO: 1, a light chain complementary determining region 2 (LC CDR2) of SEQ ID NO: 2, and a light chain complementary determining region 3 (LC CDR3) of SEQ ID NO: 3; and

a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1) of SEQ ID NO: 4, a heavy chain complementary determining region 2 (HC CDR2) of SEQ ID NO: 5, and a heavy chain complementary determining region 3 (HC CDR3) of SEQ ID NO: 6; or

(b) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) disclosed in Table 2; and

a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) disclosed in Table 2.

2. The isolated nucleic acid molecule of claim 1, wherein:

(a) the light chain variable region comprises the amino acid sequence of SEQ ID NO: 7 or 199; or an amino acid sequence having at least about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to the amino acid sequence of SEQ ID NO: 7 or 199;

(b) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 8 or 200, or an amino acid sequence having at least about 90%, about 91%, about 92%,

about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to the amino acid sequence of SEQ ID NO: 8 or 200;

(c) the light chain variable region comprises the amino acid sequence of SEQ ID NO: 7 and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 8; or

(d) the light chain variable region comprises the amino acid sequence of SEQ ID NO: 199 and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 200.

3. The isolated nucleic acid molecule of claim 1, wherein the anti-CD19 binding domain:

(a) is a scFv;

(b) comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9, 226, and 201, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 9, 226, and 201;

(c) comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 116, SEQ ID NO: 225, and SEQ ID NO: 216;

(d) comprises a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 21, SEQ ID NO: 116, SEQ ID NO: 225, or SEQ ID NO: 216;

(e) comprises a light chain variable region or a heavy chain variable region encoded by a nucleic acid sequence selected from a group consisting of SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 116, SEQ ID NO:203, SEQ ID NO: 202, SEQ ID NO: 225, and SEQ ID NO: 216; or

(f) comprises a light chain variable region or a heavy chain variable region encoded by a nucleic acid sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 19-21, SEQ ID NO: 116, SEQ ID NO: 203, SEQ ID NO: 202, SEQ ID NO: 225, or SEQ ID NO: 216; or

(g) is connected to the transmembrane domain by a hinge region.

4. The isolated nucleic acid molecule of claim 1, wherein:

(a) the transmembrane domain comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD2, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134 (OX-40), CD137 (4-1BB), CD154 (CD40L), CD278 (ICOS), CD357 (GITR), Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, and TLR9;

(b) the transmembrane domain comprises an amino acid sequence selected from SEQ ID NO: 29, 31, or 33, or an amino acid sequence or an amino acid sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 29, 31, or 33;

(c) the transmembrane domain comprises a nucleic acid sequence selected from SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34 or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 30, 32, or 34;

(d) the transmembrane domain comprises a CD8 transmembrane domain, and/or an amino acid sequence of SEQ ID NO: 29; or an amino acid sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 29;

(e) the transmembrane domain comprises a nucleic acid sequence of SEQ ID NO: 30, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 30;

(f) the costimulatory domain is a functional signaling domain of a protein selected from the group consisting of a TNFR superfamily member, OX40 (CD134), CD2, CD5, CD7, CD27, CD28, CD30, CD40, PD-1, CD8, ICAM-1, lymphocyte function-associated antigen-1 (LFA-1), CD11a, CD18, ICOS (CD278), LIGHT, NKG2C, B7-H3, a ligand that specifically binds to CD83, DAP10, DAP12, Lck, Fas and 4-1BB (CD137);

(g) the costimulatory domain comprises an amino acid sequence selected from SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 46, SEQ ID NO: 48, or SEQ ID NO: 50, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 37, 39, 41, 43, 46, 48, or 50;

(h) the costimulatory domain is encoded by a nucleic acid sequence selected from SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 47, or SEQ ID NO: 49, or a nucleic acid sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 38, 40, 42, 44, 45, 47, or 49;

(i) the intracellular signaling domain comprises a signaling domain of a protein selected from the group consisting of CD3 zeta, FcyRIII, FcsRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d;

(j) the intracellular signaling domain comprises the intracellular signaling domain of CD3 zeta, the amino acid sequence of SEQ ID NO: 52 or 54, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 52 or 54;

(k) the intracellular signaling domain comprises the intracellular signaling domain of CD3 zeta, the amino acid sequence of SEQ ID NO: 52 or 54, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 52 or 54; or

(l) the intracellular signaling domain comprises the nucleic acid sequence of SEQ ID NO: 53 or 55, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 53 or 55.

5. The isolated nucleic acid molecule of claim 3, wherein the hinge region:

(a) is from a protein selected from the group consisting of an Fc fragment of an antibody, a hinge region of an antibody, a CH2 region of an antibody, a CH3 region of an antibody, an artificial spacer sequence, an IgG hinge, a CD8 hinge, and any combination thereof;

(b) comprises the amino acid sequence of SEQ ID NO: 27 or SEQ ID NO: 35, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 27 or 35;

(c) comprises a CD8 hinge region and/or the amino acid sequence of SEQ ID NO: 27, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 27; or

(d) comprises a nucleic acid sequence selected from SEQ ID NO: 28, or SEQ ID NO: 36 or a sequence having about 95%, about 96%, about 97%, about 98% or about 99% identity to SEQ ID NO: 28 or 36.

6. The isolated nucleic acid molecule of claim 1, wherein the CAR:

(a) comprises a functional 4-1BB costimulatory domain and a functional CD3 zeta intracellular signaling domain;

(b) comprises the amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 52, or SEQ ID NO: 54 or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to an amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 52 or SEQ ID NO: 54;

(c) comprises the amino acid sequence of SEQ ID NO: 37 and the sequence of SEQ ID NO: 52 or SEQ ID NO: 54, or a sequence having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 37, SEQ ID NO: 52 or SEQ ID NO: 54, and the sequences are expressed in the same frame and as a single polypeptide chain;

(d) further comprises a leader sequence; or

(e) further comprises a leader sequence comprising the amino acid of SEQ ID NO: 25.

7. An isolated nucleic acid molecule comprising:

(a) an scFv comprising an anti-CD19 binding domain, wherein the anti-CD19 binding domain comprises:

(i) LC CDR1 of SEQ ID NO: 1, LC CDR2 of SEQ ID NO: 2, and LC CDR3 of SEQ ID NO: 3, HC CDR1 of SEQ ID NO: 4, HC CDR2 of SEQ ID NO: 5, and HC CDR3 of SEQ ID NO: 6; or

(ii) any LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2, and HC CDR3 disclosed in Table 2;

(b) a transmembrane domain selected from CD28 or CD8 transmembrane domain,

(c) a costimulatory domain comprising an intracellular signaling domain of a protein selected from the group consisting of OX40, CD27, CD2, CD28, ICOS, and 4-1BB; and

(d) an intracellular signaling domain comprising of CD3-zeta or FcR gamma.

8. An isolated nucleic acid molecule comprising:

(a) an scFv comprising an anti-CD19 binding domain, wherein the anti-CD19 binding domain comprises the amino acid sequence of SEQ ID NO: 9, 226, or 201;

(b) a transmembrane domain selected from CD28 or CD8 transmembrane domain,

(c) a costimulatory domain comprising an intracellular signaling domain of a protein selected from the group consisting of OX40, CD27, CD2, CD28, ICOS, and 4-1BB; and

(d) an intracellular signaling domain comprising of CD3-zeta or FcR gamma.

9. An isolated nucleic acid molecule comprising:

(a) an scFv comprising an anti-CD19 binding domain, wherein the anti-CD19 binding domain comprises the amino acid sequence of SEQ ID NO: 9, 18, 64, 75, 86, 190, 157, 212, 201, 226, 179, 168, or 146;

(b) a transmembrane domain comprising the amino acid sequence of selected from the group consisting of SEQ ID NO: 29, 31, and 33;

(c) a costimulatory domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 46, SEQ ID NO: 48, and SEQ ID NO: 50; and

(d) an intracellular signaling domain comprising the amino acid sequence of SEQ ID NO: 52 or SEQ ID NO: 54.

10. An isolated nucleic acid molecule comprising:

(a) an anti-CD19 binding domain comprising the amino acid sequence of SEQ ID NO: 9, 18, 64, 75, 86, 190, 157, 212, 201, 226, 179, 168,or 146;

(b) a transmembrane domain comprising the amino acid sequence of SEQ ID NO: 29;

(c) a costimulatory domain comprising the amino acid sequence of SEQ ID NO: 37; and

(d) an intracellular signaling domain comprising of SEQ ID NO: 52 or 54.

11. The isolated nucleic acid molecule of any one of 1-34, wherein the isolated nucleic acid comprises:

(a) a nucleic acid sequence selected from the group consisting of SEQ ID NO: 20 and 203; and/or

(b) a nucleic acid sequence selected from the group consisting of SEQ ID NO: 19 and 202.

12. A vector comprising a nucleic acid molecule of any one of claims 1-11.

13. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1-11.

14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a sequence selected from the group consisting of SEQ ID NO: 7, 8, 199 and 200.

15. A chimeric antigen receptor (CAR) encoded by the nucleic acid molecule of any one of claims 1-11.

16. A chimeric antigen receptor (CAR) comprising a single chain antibody or a single chain antibody fragment comprising an anti-CD19 binding domain, a transmembrane domain, a costimulatory, and an intracellular signaling domain, and
wherein the anti-CD19 binding domain comprises:

(a) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1) of SEQ ID NO: 1, a light chain complementary determining region 2 (LC CDR2) of SEQ ID NO: 2, and a light chain complementary determining region 3 (LC CDR3) of SEQ ID NO: 3; and a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1) of SEQ ID NO: 4, a heavy chain complementary determining region 2 (HC CDR2) of SEQ ID NO: 5, and a heavy chain complementary determining region 3 (HC CDR3) of SEQ ID NO: 6; or

(b) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) disclosed in Table 2; and

a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) disclosed in Table 2.

17. The CAR of claim 16, wherein:

(a) the light chain variable region comprises the amino acid sequence of SEQ ID NO: 7 or 199; or an amino acid sequence having at least about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 7 or 199; or

(b) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 8 or 200, or an amino acid sequence having at least about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to SEQ ID NO: 8 or 200.

18. A chimeric antigen receptor (CAR) comprising:

(a) an scFv comprising an anti-CD19 binding domain, wherein the anti-CD19 binding domain comprises:

(i) LC CDR1 of SEQ ID NO: 1, LC CDR2 of SEQ ID NO: 2, and LC CDR3 of SEQ ID NO: 3, HC CDR1 of SEQ ID NO: 4, HC CDR2 of SEQ ID NO: 5, and HC CDR3 of SEQ ID NO: 6; or

(ii) any LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2, and HC CDR3 disclosed in Table 2;

(b) a transmembrane domain selected from CD28 or CD8 transmembrane domain;

(c) a costimulatory domain comprising an intracellular signaling domain of a protein selected from the group consisting of OX40, CD27, CD2, CD28, ICOS, and 4-1BB; and

(d) an intracellular signaling domain comprising of CD3-zeta or FcR gamma.

19. A chimeric antigen receptor (CAR) comprising:

(a) an anti-CD19 binding domain comprising the amino acid sequence of SEQ ID NO: 9, 226, or 201;

(b) a transmembrane domain selected from CD28 or CD8 transmembrane domain;

(c) a costimulatory domain comprising an intracellular signaling domain of a protein selected from the group consisting of OX40, CD27, CD2, CD28, ICOS, and 4-1BB; and

(d) an intracellular signaling domain comprising of CD3-zeta or FcR gamma.

20. A chimeric antigen receptor (CAR) comprising:

(a) an anti-CD19 binding domain comprising the amino acid sequence of SEQ ID NO: 9, 18, 64, 75, 86, 190, 157, 212, 201, 226, 179, 168, or 146;

(b) a transmembrane domain comprising the amino acid sequence of selected from the group consisting of SEQ ID NO: 29, 31, and 33;

(c) a costimulatory domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 46, SEQ ID NO: 48, and SEQ ID NO: 50; and

(d) an intracellular signaling domain comprising the amino acid sequence of SEQ ID NO: 52 or SEQ ID NO: 54.

21. A chimeric antigen receptor (CAR) comprising:

(a) an anti-CD19 binding domain comprising the amino acid sequence of SEQ ID NO: 9, 18, 64, 75, 86, 190, 157, 212, 201, 226, 179, 168, or 146;

(b) a transmembrane domain comprising the amino acid sequence of SEQ ID NO: 29;

(c) a costimulatory domain comprising the amino acid sequence of SEQ ID NO: 37; and

(d) an intracellular signaling domain comprising of SEQ ID NO: 52 or 54.

22. A chimeric antigen receptor comprising:

(a) an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 66, 77, 88, 148, 170, 181, 203, 214, 159, 192, 23, and 20; and/or

(b) an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 65, 76, 87, 147, 169, 180, 202, 213, 158, 191, 22, and 19.

23. A chimeric antigen receptor comprising a sequence selected from the group consisting of SEQ ID NO: 63, 74, 85, 145, 167, 178, 200, 211, 156, 189, 17, 8, 62, 73, 84, 144, 166, 177, 199, 210, 155, 188, 16, and 7.

24. An anti-CD19 binding domain comprising:

(a) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1) of SEQ ID NO: 1, a light chain complementary determining region 2 (LC CDR2) of SEQ ID NO: 2, and a light chain complementary determining region 3 (LC CDR3) of SEQ ID NO: 3; and a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1) of SEQ ID NO: 4, a heavy chain complementary determining region 2 (HC CDR2) of SEQ ID NO: 5, and a heavy chain complementary determining region 3 (HC CDR3) of SEQ ID NO: 6; or

(b) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1) of SEQ ID NO: 193, a light chain complementary determining region 2 (LC CDR2) of SEQ ID NO: 194, and a light chain complementary determining region 3 (LC CDR3) of SEQ ID NO: 195; and a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1) of SEQ ID NO: 196, a heavy chain complementary determining region 2 (HC CDR2) of SEQ ID NO: 197, and a heavy chain complementary determining region 3 (HC CDR3) of SEQ ID NO: 198; or

(c) a light chain variable domain comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC

CDR2), and a light chain complementary determining region 3 (LC CDR3) disclosed in Table 2; and

a heavy chain variable domain comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) disclosed in Table 2.

25. The anti-CD19 binding domain of claim 24, wherein the anti-CD19 binding domain is a scFv comprising:

(a) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 or 199, or a sequence having about 90% to about 99% identity to SEQ ID NO: 7 or 199; and/or

(b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8, or 200, or a sequence having about 90% to about 99% identity to SEQ ID NO: 8 or 200.