WHAT IS CLAIMED IS:

1. A polynucleotide encoding a CD19-directed chimeric antigen receptor (CAR), the ~~chimeric antigen receptor~~CAR comprising:

a) an extracellular anti-CD19 binding moiety comprising a single chain variable fragment (scFv) comprising~~Fragment variable (scFv), wherein the scFv comprises~~:

a variable heavy (VH) domain domain comprising the CDR-H1, CDR-H2, and CDR-H3 of the VH domain sequence of SEQ ID NO. 120, ~~wherein the encoded VH domain comprises the amino acid sequence of SEQ ID NO: 120,~~ and

~~-~~a variable light (VL) domain comprising the CDR-L1, CDR-L2, and CDR-L3 of the VL domain sequence of SEQ ID NO. 118;

b) a ~~hinge, wherein the hinge is a~~ CD8 alpha hinge;

c) a ~~transmembrane domain, wherein the transmembrane domain comprises a~~ CD8 alpha transmembrane domain; and

d) an intracellular signaling domain comprising an OX40 subdomain and a CD3 zeta subdomain, ~~wherein the intracellular signaling domain comprises:~~

~~an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,~~

~~a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and~~

wherein the polynucleotide also encodes a membrane-bound interleukin-15 (mbIL15)~~, wherein the mbIL15 comprises a sequence~~ having at least 95% sequence identity to SEQ ID NO. 12.

2. The polynucleotide of Claim 1, wherein the VH domain comprises the amino acid sequence of SEQ ID NO. 120~~OX40 subdomain is encoded by SEQ ID NO. 5, and wherein the CD3 zeta subdomain is encoded by SEQ ID NO. 7~~.

3. The polynucleotide of Claim 1 or 2, wherein the VL domain comprises the amino acid sequence of SEQ ID NO. 118~~encoded OX40 subdomain comprises the amino acid sequence of SEQ ID NO: 6~~.

~~4. The polynucleotide according to any one of Claims 1-3, wherein the encoded CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO: 8.~~

~~5.~~4. A polynucleotide encoding a CD19-directed chimeric antigen receptor (CAR), the ~~chimeric antigen receptor~~CAR comprising:

a) an extracellular anti-CD19 binding moiety comprising a single chain variable fragment (scFv) comprising ~~Fragment variable (scFv), wherein the scFv comprises~~:

a variable heavy (VH) domain comprising the amino acid sequence of SEQ ID NO. 120,

~~wherein the encoded VH domain comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 120;~~ and

a variable light (VL) domain,

wherein the encoded VL domain comprising the amino acid sequence of SEQ ID NO. 118~~comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 118~~;

b) a CD8 alpha hinge;

c) a CD8 alpha transmembrane domain; and

an intracellular signaling domain comprising an OX40 subdomain and a CD3 zeta subdomain~~,~~

~~wherein the intracellular signaling domain comprises:~~

~~an OX40 subdomain,~~

~~a CD3 zeta subdomain; and~~

wherein the polynucleotide also encodes a membrane-bound interleukin-15 (mbIL15)~~, wherein the mbIL15 comprises~~ comprising a sequence having at least 95% sequence identity to SEQ ID NO. 12.

~~6.~~5. The polynucleotide of any one of claims 1 to 5~~Claim 5~~, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5.

~~7.~~6. The polynucleotide of any one of claims 1 to 5~~according to Claim 5 or 6~~, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7.

7. The polynucleotide of any one of Claims 1-6, wherein the OX40 subdomain comprises the amino acid sequence of SEQ ID NO. 6.

8. The polynucleotide of any one of Claims 1-7, wherein the CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO. 8.

9. The polynucleotide of any one of Claims 1-8, wherein the mbIL15 comprises the amino acid sequence of SEQ ID NO. 12.

10. A vector comprising the polynucleotide of any one of Claims 1-9.

11. The vector of Claim 10, wherein the vector is a retroviral vector.

8. The polynucleotide according to any one of Claims 5 to 7, wherein the polynucleotide does not encode SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, or SEQ ID NO: 116.

9. The polynucleotide according to any one of Claims 5 to 8, wherein the encoded VH domain comprises the amino acid sequence of SEQ ID NO: 120.

10. The polynucleotide according to any one of Claims 5 to 9, wherein the encoded VL domain comprises the amino acid sequence of SEQ ID NO: 118.

11. A polynucleotide encoding a CD19-directed chimeric antigen receptor, the chimeric antigen receptor comprising:

an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:

a variable heavy (VH) domain, and

a variable light (VL) domain, wherein the encoded VL domain comprises the amino acid sequence of SEQ ID NO: 118;

a hinge, wherein the hinge is a CD8 alpha hinge;

a transmembrane domain, wherein the transmembrane domain comprises a CD8 alpha transmembrane domain; and

an intracellular signaling domain, wherein the intracellular signaling domain comprises:

an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,

a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and

wherein the polynucleotide also encodes membrane-bound interleukin-15 (mbIL15), wherein the mbIL15 comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12.

12. The polynucleotide of Claim 11, wherein the OX40 subdomain is encoded by SEQ ID NO. 5, and wherein the CD3 zeta subdomain is encoded by SEQ ID NO. 7.

13. The polynucleotide according to Claim 11 or 12, wherein the encoded OX40 subdomain comprises the amino acid sequence of SEQ ID NO: 6 and wherein the encoded CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO: 8.

14. A polynucleotide encoding a CD19-directed chimeric antigen receptor, the chimeric antigen receptor comprising:

an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:

a variable heavy (VH) domain, and

a variable light (VL) domain;

a hinge, wherein the hinge is a CD8 alpha hinge;

a transmembrane domain, wherein the transmembrane domain comprises a CD8 alpha transmembrane domain; and

an intracellular signaling domain, wherein the intracellular signaling domain comprises:

an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,

a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and

wherein the polynucleotide also encodes membrane-bound interleukin-15 (mbIL15), wherein the comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12, and

wherein the encoded CD19-directed chimeric antigen receptor and mbIL15 have at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 187.

15. The polynucleotide of Claim 14, wherein the OX40 subdomain is encoded by SEQ ID NO. 5, and wherein the CD3 zeta subdomain is encoded by SEQ ID NO. 7.

16. The polynucleotide according to Claim 14 or 15, wherein the encoded OX40 subdomain comprises the amino acid sequence of SEQ ID NO: 6 and wherein the encoded CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO: 8.

17. A polynucleotide encoding a CD19-directed chimeric antigen receptor, the chimeric antigen receptor comprising:

an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:

a variable heavy (VH) domain, and

a variable light (VL) domain;

a hinge, wherein the hinge is a CD8 alpha hinge;

a transmembrane domain, wherein the transmembrane domain comprises a CD8 alpha transmembrane domain; and

an intracellular signaling domain, wherein the intracellular signaling domain comprises:

an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,

a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and

wherein the polynucleotide also encodes membrane-bound interleukin-15 (mbIL15), wherein the mbIL15 comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12, and

~~wherein the encoded CD19-directed chimeric antigen receptor and mbIL15 are encoded by the amino acid sequence set forth in SEQ ID NO: 187.~~

~~18. The polynucleotide of Claim 17, wherein the OX40 subdomain is encoded by SEQ ID NO. 5, and wherein the CD3 zeta subdomain is encoded by SEQ ID NO. 7.~~

~~19. The polynucleotide according to Claim 17 or 18, wherein the encoded OX40 subdomain comprises the amino acid sequence of SEQ ID NO: 6 and wherein the encoded CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO: 8.~~

12. A CD19-directed chimeric antigen receptor (CAR) comprising:

(a) an extracellular anti-CD19 binding moiety comprising a single chain variable fragment (scFv) comprising a variable heavy (VH) domain comprising the CDR-H1, CDR-H2, and CDR-H3 of the VH domain sequence of SEQ ID NO. 120, and a variable light (VL) domain comprising the CDR-L1, CDR-L2, and CDR-L3 of the VL domain sequence of SEQ ID NO. 118;

(b) a CD8 alpha hinge;

(c) a CD8 alpha transmembrane domain; and

(d) an intracellular signaling domain comprising an OX40 subdomain and a CD3 zeta subdomain.

13. The CD19-directed CAR of Claim 12, wherein the VH domain comprises the amino acid sequence of SEQ ID NO. 120 and the VL domain comprises the amino acid sequence of SEQ ID NO. 118.

14. A CD19-directed chimeric antigen receptor (CAR) comprising:

(a) an extracellular anti-CD19 binding moiety comprising a single chain variable fragment (scFv) comprising a variable heavy (VH) domain comprising the amino acid sequence of SEQ ID NO. 120, and a variable light (VL) domain comprising the VL domain sequence of SEQ ID NO. 118;

(b) a CD8 alpha hinge;

(c) a CD8 alpha transmembrane domain; and

(d) an intracellular signaling domain comprising an OX40 subdomain and a CD3 zeta subdomain.

15. The CD19-directed CAR of any one of Claims 12 to 14, wherein the CD8 alpha hinge comprises the amino acid sequence of SEQ ID NO. 2.

16. The CD19-directed CAR of any one of Claims 12 to 15, wherein the CD8 transmembrane domain comprises the amino acid sequence of SEQ ID NO. 4.

17. The CD19-directed CAR of any one of Claims 12 to 16, wherein the OX40 subdomain comprises the amino acid sequence of SEQ ID NO. 6.

18. The CD19-directed CAR of any one of Claims 12 to 17, wherein the CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO. 8.

19. The CD19-directed CAR of any one of Claims 12 to 18, wherein the CAR comprises an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO. 187.

20. An immune cell comprising the polynucleotide of any one of Claims 1 to 9, the vector of Claim 10 or Claim 11, or the CD19-directed CAR of any one of Claims 12 to 19.

~~20.~~21. An immune cell that expresses a CD19-directed chimeric antigen receptor (CAR), the CAR~~chimeric antigen receptor~~ comprising:

a) an extracellular anti-CD19 binding moiety comprising a single chain variable fragment (scFv) comprising~~Fragment variable (scFv), wherein the scFv comprises~~:

a variable heavy (VH) domain comprising the CDR-H1, CDR-H2, and CDR-H3 of the VH domain sequence of SEQ ID NO. 120, ~~wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 120,~~ and

~~-~~a variable light (VL) domain comprising the CDR-L1, CDR-L2, and CDR-L3 of the VL domain sequence of SEQ ID NO. 118;

b) a ~~hinge, wherein the hinge is a~~ CD8 alpha hinge;

c) a ~~transmembrane domain, wherein the transmembrane domain comprises a~~ CD8 alpha transmembrane domain; and

d) an intracellular signaling domain comprising an OX40 subdomain and a CD3 zeta subdomain, ~~wherein the intracellular signaling domain comprises:~~

~~an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,~~

~~a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and~~

wherein the immune cell also expresses membrane-bound interleukin-15 (mbIL15) ~~, wherein the mbIL15 comprises a sequence~~ having at least 95% sequence identity to SEQ ID NO. 12.

~~21.~~22. The immune cell of Claim ~~20~~21, wherein the VH domain comprises the amino acid sequence of SEQ ID NO. 120~~immune cell is a Natural Killer (NK) cell, wherein the OX40 subdomain is encoded by SEQ ID NO. 5, wherein the CD3 zeta subdomain is encoded by SEQ ID NO. 7, and wherein the mbIL15 comprises SEQ ID NO. 12~~.

~~22. The immune cell of Claim 20, wherein the immune cell comprises a Natural Killer cell.~~

23. The immune cell ~~according to any one~~ of Claim~~s~~ ~~20~~21 or Claim ~~to~~ 22, wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 118.

24. The immune cell ~~according to any one~~ of any one of Claims ~~20~~21 to 23, wherein the ~~encoded~~ OX40 subdomain comprises the amino acid sequence of SEQ ID NO: 6.

25. The immune cell ~~according to any one~~ of any one of Claims ~~20~~21 to 24, wherein the ~~encoded~~ CD3 zeta subdomain comprises the amino acid sequence of SEQ ID NO: 8.

26. The immune cell of any one of Claims 21-25, wherein the CD19-directed CAR comprises an amino acid sequence that has at least 95% sequence identity to ~~according to any one of Claims 20 to 25, wherein the CD19-directed CAR and mbIL15 are encoded by the amino acid sequence set forth in~~ SEQ ID NO: 187.

~~27. An immune cell that expresses a CD19-directed chimeric antigen receptor, the chimeric antigen receptor comprising:~~

~~an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:~~

~~a variable heavy (VH) domain,~~

~~wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 120;~~

~~and~~

~~a variable light (VL) domain,~~

~~wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 118;~~

~~a hinge;~~

~~a transmembrane domain; and~~

~~an intracellular signaling domain, wherein the intracellular signaling domain comprises:~~

~~an OX40 subdomain,~~

~~a CD3 zeta subdomain; and~~

~~wherein the immune cell also expresses membrane-bound interleukin-15 (mbIL15), wherein the mbIL15 comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12.~~

~~28. The immune cell of Claim 27, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5.~~

~~29. The immune cell according to Claim 27 or 28, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7.~~

~~30. An immune cell that expresses a CD19-directed chimeric antigen receptor (CAR), the chimeric antigen receptor comprising:~~

~~an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:~~

~~a variable heavy (VH) domain, and~~

~~a variable light (VL) domain, wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 118;~~

~~a hinge, wherein the hinge is a CD8 alpha hinge;~~

~~a transmembrane domain, wherein the transmembrane domain comprises a CD8 alpha transmembrane domain; and~~

~~an intracellular signaling domain, wherein the intracellular signaling domain comprises:~~

~~an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,~~

~~a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and~~

~~wherein the immune cell also expresses membrane-bound interleukin-15 (mbIL15), wherein the mbIL15 comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12.~~

~~31.~~27. The immune cell of any one of Claims 20 to 16~~30~~, wherein the immune cell ~~comprises~~ is a Natural Killer cell.

28. A composition comprising the immune cell of any one of Claims 20 to 27.

29. The composition of Claim 28 for use in treating a subject having a cancer.

30. The composition for use of Claim 29, wherein the cancer is a leukemia or a lymphoma.

31. The composition for use of Claim 29 or Claim 30, wherein the immune cell is a Natural Killer cell.

32. The composition for use of any one of Claims 29 to 31, wherein the immune cell is allogeneic to the subject.

33. Use of the polynucleotide of any one of Claims 1 to 9, the vector of Claim 10 or Claim 11, the CD19-directed CAR of any one of Claims 12 to 19, or the immune cell of any one of Claims 20 to 27 in the manufacture of a medicament for treating a subject having a cancer.

34. The Use of Claim 33, wherein the cancer is a leukemia or a lymphoma.

35. The use of Claim 33 or Claim 34, wherein the immune cell is a natural killer (NK) cell.

32. An immune cell that expresses a CD19-directed chimeric antigen receptor (CAR), the chimeric antigen receptor comprising:
an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:
a variable heavy (VH) domain, and
a variable light (VL) domain;
a hinge, wherein the hinge is a CD8 alpha hinge;
a transmembrane domain, wherein the transmembrane domain comprises a CD8 alpha transmembrane domain; and
an intracellular signaling domain, wherein the intracellular signaling domain comprises:
an OX40 subdomain, wherein the OX40 subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 5,
a CD3 zeta subdomain, wherein the CD3 zeta subdomain is encoded by a sequence having at least 95% sequence identity to SEQ ID NO. 7, and
wherein the immune cell also expresses membrane-bound interleukin-15 (mbIL15), wherein the mbIL15 comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12, and
wherein the CD19-directed CAR and mbIL15 are encoded by the amino acid sequence set forth in SEQ ID NO: 187.

33. The immune cell of Claim 23, wherein the immune cell comprises a Natural Killer cell.

34. An immune cell that expresses a CD19-directed chimeric antigen receptor, the chimeric antigen receptor comprising:
an extracellular anti-CD19 binding moiety comprising a single chain Fragment variable (scFv), wherein the scFv comprises:
a variable heavy (VH) domain,
wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 120; and
a variable light (VL) domain,
wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 118;
a hinge;
a transmembrane domain; and
an intracellular signaling domain, wherein the intracellular signaling domain comprises:
an OX40 subdomain,
a CD3 zeta subdomain; and
wherein the immune cell also expresses membrane-bound interleukin-15 (mbIL15), wherein the mbIL15 comprises a sequence having at least 95% sequence identity to SEQ ID NO. 12,

~~wherein the CD19-directed CAR and mbIL15 are encoded by the amino acid sequence set forth in SEQ ID NO: 187.~~

~~35. The immune cell of Claim 34, wherein the immune cell comprises a Natural Killer cell.~~