

WHAT IS CLAIMED IS:

1. 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, wherein the encoded VH domain comprises the amino acid sequence of SEQ ID NO: 120, 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, andwherein 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.
2. The polynucleotide of Claim 1, wherein the 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 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. 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,
 - 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 comprises an amino acid sequence having at least 95% sequence identity to 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 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.

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

7. The polynucleotide 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.

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.

20. 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, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 120, 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.

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

26. The immune cell 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. The immune cell of Claim 30, wherein the immune cell comprises a Natural Killer 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.