CLAIMS

WHAT IS CLAIMED IS:

1. A modular chimeric receptor comprising:

a synthetic receptor module comprising an extracellular domain fused to a first synthetic transmembrane domain;

a synthetic signaling module comprising an intracellular signaling domain fused to a second synthetic transmembrane domain;

wherein the synthetic receptor module and the synthetic signaling module form the modular chimeric receptor:

wherein the first synthetic transmembrane domain comprises:

a sequence having at least 40% identity with the sequence VLIGTSVVKLPFTILLFFL (SEQ ID NO:16),

wherein the lysine residue at position 9 of SEQ ID NO: 16 is replaced by an uncharged amino acid residue; and

(i) at least one of: the glycine residue at position 4, the threonine residue at position 5, or the serine residue at position 6 of SEQ ID NO: 16 is replaced by a positively charged amino acid; and/or

(ii) at least one of: the phenylalanine residue at position 12, the threonine residue at position 13, or the isoleucine residue at position 14 of SEQ ID NO: 16 is replaced by a positively charged amino acid;

wherein the second synthetic transmembrane domain comprises:

a sequence having at least 40% identity with the sequence VLAGIVMGDLVLTVLIALAVYFL (SEQ ID NO:26), wherein:

the aspartic acid residue at position 9 of SEQ ID NO: 26 is replaced by an uncharged amino acid residue; and

(i) at least one of: the glycine residue at position 4, the isoleucine residue at position 5, or the valine residue at position 6 is replaced by a negatively charged amino acid;

(ii) at least one of: the leucine residue at position 12, the threonine residue at position 13, or the valine residue at position 14 is replaced by a negatively charged amino acid; and/or

(iii) at least one of: the isoleucine residue at position 16, the alanine residue at position 17, or the leucine residue at position 18 is replaced by a negatively charged amino acid residue.

2. The modular chimeric receptor of claim 1, wherein the first synthetic transmembrane domain comprises a positively charged residue at position 13 in place of the threonine.

3. The modular chimeric receptor of claim 1, wherein the first synthetic transmembrane domain comprises the sequence selected from the group consisting of VLILLLLLTLLLKLLLFFLL (SEQ ID NO: 38), VLIGTSVVLLPFKILLFFLL (SEQ ID N0:32), VLIILLVGTSVVKLLLFFLL (SEQ ID N0:33), VLIGTSVVTLPFKILLFFLL (SEQ ID N0:34), VLILLLLLLLLLKLLLFFLL (SEQ ID N0:35), and VLILLLLGLLLLKLLLFFLL (SEQ ID N0:36), VLILLLLLALLLKLLLFFLL (SEQ ID N0:37).

4. The modular chimeric receptor of claim 1, wherein the second synthetic transmembrane domain comprises a negatively charged residue at position 13 in place of the threonine.

5. The modular chimeric receptor of claim 1, wherein the second synthetic transmembrane domain comprises the sequence of VLAGIVMGALVLDVLITLAVYFL (SEQ ID NO:39), VLALAVLGIVMGDVLITLAVYFL (SEQ ID NO:40) or VLAGDVMGTLVLIVLIALAVYFL (SEQ ID NO:41).

6. The modular chimeric receptor of claim 1, wherein the extracellular domain comprises one or more ligand-binding domains or antigen-binding domains.

7. The modular chimeric receptor of claim 1, wherein the synthetic receptor module further comprises a polypeptide linker or spacer between the extracellular domain and the first synthetic transmembrane domain.

8. The modular chimeric receptor of claim 1, wherein the synthetic receptor module further comprises an intracellular domain.

9. The modular chimeric receptor of claim 8, wherein the intracellular domain of the synthetic receptor module comprises a sequence of an intracellular domain of a costimulatory immune receptor.

10. The modular chimeric receptor of claim 9, wherein the costimulatory immune receptor is CD28, 4-IBB, OX40, or ICOS.

11. The modular chimeric receptor of claim 1, wherein the intracellular signaling domain of the

first synthetic signaling module comprises a sequence of an intracellular domain of an immune cell signaling protein and/or of a costimulatory immune receptor.

12. The modular chimeric receptor of claim 11, wherein the intracellular signaling domain of the first synthetic signaling module comprises a sequence of the intracellular domain of DAP12 or CD3 Zeta.

13. The modular chimeric receptor of claim 6, wherein the antigen-binding domain is a scFv.

14. The modular chimeric receptor of claim 13, wherein the scFv binds to CD19.

15. The modular chimeric receptor of claim 14, wherein the scFv that binds to CD19 comprises an amino acid sequence of SEQ ID NO: 65.

16. The modular chimeric receptor of claim 12, wherein the DAP12 domain comprises an amino acid sequence of SEQ ID NO: 70.

17. The modular chimeric receptor of claim 12, wherein the CD3 Zeta domain comprises an amino acid sequence of SEQ ID NO: 69.

18. The modular chimeric receptor of claim 1, wherein:

the synthetic receptor module comprises an extracellular domain that binds to CD19, a transmembrane domain comprising an amino acid sequence of SEQ ID NO: 38, and an intracellular domain comprising a CD28 costimulatory domain; and

the synthetic signaling module comprises a transmembrane domain comprising an amino acid sequence of SEQ ID NO: 39 and a CD3 zeta intracellular domain.

19. An immune cell comprising the modular chimeric receptor of claim 1.

20. The immune cell of claim 19, wherein the immune cell is a T cell or a NK cell.