**CLAIMS**

**WHAT IS CLAIMED IS:**

1. A modular chimeric receptor for expression in a target immune cell comprising:

a synthetic receptor module comprising an extracellular domain fused to a first synthetic transmembrane domain comprising a first positively charged amino acid;

a first synthetic signaling module comprising an intracellular signaling domain fused to a second synthetic transmembrane domain comprising a first negatively charged amino acid; wherein the first positively charged amino acid and first negatively charged amino acid are positioned so that the electrostatic interactions between the first synthetic transmembrane domain and the second synthetic transmembrane domains in the target immune cell membrane are stronger than the electrostatic interactions with native transmembrane domains from immune receptors and/or native transmembrane domains from immune cell signaling proteins expressed by said target immune cell.

2. The modular chimeric receptor of claim 1, wherein the first synthetic transmembrane domain is a variant of a native transmembrane domain from an immune receptor and/or wherein the second synthetic transmembrane domain is a variant of a native transmembrane domain from an immune cell signaling protein.

3. The modular chimeric receptor of claim 2, wherein the first positively charged amino acid is located at a position that is 3 to 5 residues or 7 to 9 residues amino- or carboxy terminal relative to the position of a positively charged amino acid in the native transmembrane domain from the immune receptor.

4. The modular chimeric receptor of claim 3, wherein the first positively charged amino acid is located at a position that is 4 residues amino- or carboxy terminal relative to the position of a positively charged amino acid in the native transmembrane domain from the immune receptor.

5. The modular chimeric receptor of any one of claims 2 to 4, wherein the first negatively charged amino acid is located at a position that is 3 to 5 residues or 7 to 9 residues amino- or carboxy- terminal relative to the position of the negatively charged amino acid in the native transmembrane domain from the immune cell signaling protein.

6. The modular chimeric receptor of claim 5, wherein the first negatively charged amino acid is located at a position that is 4 residues amino- or carboxy-terminal relative to the position of the negatively charged amino acid in the native transmembrane domain from the immune cell signaling protein.

~~7. The modular chimeric receptor of any one of claims 1 to 6, wherein the first synthetic transmembrane domain comprises a threonine located at a position that is 4 residues amino- or carboxy-terminal relative to the position of the first positively charged amino acid.~~

~~8. The modular chimeric receptor of any one of claims 1 to 7, wherein the second synthetic transmembrane domain comprises a threonine located at a position that is 4 residues amino- or carboxy-terminal relative to the position of the first negatively charged amino acid.~~

~~9. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the transmembrane domain (TM) of TRDC and comprises a sequence having at least 40% identity with the sequence VLGLRMLFAKTVAVNFLLTAKLFF (SEQ ID NO:1), wherein the K residue at position 10 and/or the K residue at position 21 is/are replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the A residue at position 13, the V residue at position 14, or the N residue at position 15 is replaced by a positively charged amino acid; or (ii) at least one of: the F residue at position 16, the L residue at position 17, or the L residue at position 18 is replaced by a positively charged amino acid.~~

~~10. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of TRAC and comprises a sequence having at least 40% identity with the sequence VIGFRILLLKVAGFNLLMTLRLW (SEQ ID NO:2), wherein the R residue at position 5, the K residue at position 10 and/or the R residue at position 21 is/are replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 8 or the L residue at position 9 is replaced by a positively charged amino acid; (ii) at least one of: the I residue at position 6 or the L residue at position 7 is replaced by a positively charged amino acid; (iii) at least one of: the G residue at position 13, the F residue at position 14, or the N residue at position 15 is replaced by a positively charged amino acid; and/or (iv) at least one of: the L residue at position 16, the L residue at position 17, or the M residue at position 18 is replaced by a positively charged amino acid.~~

~~11. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of TRBC1 or TRBC2 and comprises a sequence having at least 40% identity with the sequence ILLGKATLYAVLVSALVLMAMV (SEQ ID NO:3), wherein the K residue at position 5 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 8, the Y residue at position 9, or the A residue at position 10 is replaced by a positively charged amino acid; (ii) at least one of: the L~~

residue at position 12, the V residue at position 13, or the S residue at position 14 is replaced by a positively charged amino acid; and/or (iii) at least one of: the L residue at position 16, the V residue at position 17, or the L residue at position 18 is replaced by a positively charged amino acid.

12. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of TRGC1 and comprises a sequence having at least 40% identity with the sequence YYMYLLLLLKSVVYFAIITCCLL (SEQ ID NO:4), wherein the K residue at position 10 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 5, the L residue at position 6, or the L residue at position 7 is replaced by a positively charged amino acid; (ii) at least one of: the V residue at position 13, the Y residue at position 14, or the F residue at position 15 is replaced by a positively charged amino acid; and/or (iii) at least one of: the I residue at position 17, the I residue at position 18, or the T residue at position 19 is replaced by a positively charged amino acid.

13. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of TRGC2 and comprises a sequence having at least 40% identity with the sequence YYTYLLLLLKSVVYFAIITCCLL (SEQ ID NO:5), wherein the K residue at position 10 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 5, the L residue at position 6, or the L residue at position 7 is replaced by a positively charged amino acid; (ii) at least one of: the V residue at position 13, the Y residue at position 14, or the F residue at position 15 is replaced by a positively charged amino acid; and/or (iii) at least one of: the I residue at position 17, the I residue at position 18, or the T residue at position 19 is replaced by a positively charged amino acid.

14. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NCTR1 and comprises a sequence having at least 40% identity with the sequence LLRMGLAFLVLVALVWFLV (SEQ ID NO:6), wherein the R residue at position 3 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 6, the A residue at position 7, or the F residue at position 8 is replaced by a positively charged amino acid; (ii) at least one of: the V residue at position 10, the L residue at position 11, or the V residue at position 12 is replaced by a positively charged amino acid; and/or (iii) at least one of: the V residue at position 14, the W residue at position 15, or the F residue at position 16 is replaced by a positively charged amino acid.

15. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NCTR2 and comprises a sequence having at least 40% identity with the sequence LVPVFCGLLVAKSLVLSALLV (SEQ ID NO:7),

wherein the K residue at position 12 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 7, the L residue at position 8, or the L residue at position 9 is replaced by a positively charged amino acid; and/or (ii) at least one of: the V residue at position 11, the L residue at position 12, or the S residue at position 13 is replaced by a positively charged amino acid.

16. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NCTR3 and comprises a sequence having at least 40% identity with the sequence AGTVLLLRAGFYAVSFLSVAV (SEQ ID NO:8), wherein the R residue at position 8 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the T residue at position 3, the V residue at position 4, or the L residue at position 5 is replaced by a positively charged amino acid; (ii) at least one of: the F residue at position 11, the Y residue at position 12, or the A residue at position 13 is replaced by a positively charged amino acid; and/or (iii) at least one of: the S residue at position 15, the F residue at position 16, or the L residue at position 17 is replaced by a positively charged amino acid.

17. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of KI2L4 and comprises a sequence having at least 40% identity with the sequence AVIRYSVAIILFTILPFFLLH (SEQ ID NO:9), wherein the R residue at position 4 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the V residue at position 7, the A residue at position 8, or the I residue at position 9 is replaced by a positively charged amino acid; (ii) at least one of: the L residue at position 11, the F residue at position 12, or the T residue at position 13 is replaced by a positively charged amino acid; and/or (iii) at least one of: the L residue at position 15, the P residue at position 16, or the F residue at position 18 is replaced by a positively charged amino acid.

18. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NKG2F and comprises a sequence having at least 40% identity with the sequence VLGIICIVLMATVLKTIVLIP (SEQ ID NO: 10), wherein the K residue at position 15 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the M residue at position 10, the A residue at position 11, or the T residue at position 12 is replaced by a positively charged amino acid; and/or (ii) at least one of: the C residue at position 6, the I residue at position 7, or the V residue at position 8 is replaced by a positively charged amino acid.

19. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NKG2E and comprises a sequence having

at least 40% identity with the sequence LTAEVLGIICIVLMATVLKTIVL (SEQ ID NO:11), wherein the K residue at position 19 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the M residue at position 14, the A residue at position 15, or the T residue at position 16 is replaced by a positively charged amino acid; (ii) at least one of: the C residue at position 10, the I residue at position 11, or the V residue at position 12 is replaced by a positively charged amino acid; and/or (iii) at least one of: the L residue at position 6, the G residue at position 7, or the I residue at position 8 is replaced by a positively charged amino acid.

20. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NKG2D and comprises a sequence having at least 40% identity with the sequence PFFFCCFIAVAMGIRFIIMVA (SEQ ID NO:12), wherein the R residue at position 15 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the V residue at position 10, the A residue at position 11, or the M residue at position 12 is replaced by a positively charged amino acid; and/or (ii) at least one of: the C residue at position 6, the F residue at position 7, or the I residue at position 8 is replaced by a positively charged amino acid.

21. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of NKG2C and comprises a sequence having at least 40% identity with the sequence VLGIICIVLMATVLKTIVLIPFL (SEQ ID NO:13), wherein the K residue at position 15 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the M residue at position 10, the A residue at position 11, or the T residue at position 12 is replaced by a positively charged amino acid; and/or (ii) at least one of: the C residue at position 6, the I residue at position 7, or the V residue at position 8 is replaced by a positively charged amino acid.

22. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of KI2S1 and comprises a sequence having at least 50% identity with the sequence VLIGTSWKIPFTILLFFL (SEQ ID NO:14), wherein the K residue at position 9 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 4, the T residue at position 5, or the S residue at position 6 is replaced by a positively charged amino acid; and/or (ii) at least one of: the F residue at position 12, the T residue at position 13, or the I residue at position 14 is replaced by a positively charged amino acid.

23. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of KI2S2 or KI2S4 and comprises a sequence having at least 40% identity with the sequence VLIGTSVVKIPFTILLFFLL (SEQ ID NO:15),

wherein the K residue at position 9 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 4, the T residue at position 5, or the S residue at position 6 is replaced by a positively charged amino acid; and/or (ii) at least one of: the F residue at position 12, the T residue at position 13, or the I residue at position 14 is replaced by a positively charged amino acid.

24. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of KI2S3 or KI2S5 and comprises a sequence having at least 40% identity with the sequence VLIGTSVVKLPFTILLFFL (SEQ ID NO: 16), wherein the K residue at position 9 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 4, the T residue at position 5, or the S residue at position 6 is replaced by a positively charged amino acid; and/or (ii) at least one of: the F residue at position 12, the T residue at position 13, or the I residue at position 14 is replaced by a positively charged amino acid.

25. The modular chimeric receptor of claim 24, wherein the first synthetic transmembrane domain comprises the amino acid sequence VLIGTSVVLLPFKILLFFLL (SEQ ID NO:32), VLIILLVGTSVVKLLLFFLL (SEQ ID NO:33), VLIGTSVVTLPFKILLFFLL (SEQ ID NO:34), VLILLLLLLLLLKLLLFFLL (SEQ ID NO:35), VLILLLLGLLLLKLLLFFLL (SEQ ID NO:36), VLILLLLLALLLKLLLFFLL (SEQ ID NO:37) or VLILLLLLTLLLKLLLFFLL (SEQ ID NO:38), preferably SEQ ID NO:38.

26. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of KI3S1 and comprises a sequence having at least 40% identity with the sequence ILIGTSVVKIPFTILLFFLL (SEQ ID NO: 17), wherein the K residue at position 9 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 4, the T residue at position 5, or the S residue at position 6 is replaced by a positively charged amino acid; and/or (ii) at least one of: the F residue at position 12, the T residue at position 13, or the I residue at position 14 is replaced by a positively charged amino acid.

27. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of TREM1 and comprises a sequence having at least 40% identity with the sequence IVILLAGGFLSKSLVFSVLFA (SEQ ID NO:18), wherein the K residue at position 12 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 7, the G residue at position 8, or the F residue at position 9 is replaced by a positively charged amino acid; and/or (ii) at least one of: the V residue at position 15, the F residue at position 16, or the S residue at position 17 is replaced by a positively charged amino acid.

28. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of TREM2 and comprises a sequence having at least 40% identity with the sequence ILLLLACIFLIKILAASALWA (SEQ ID NO:19), wherein the K residue at position 12 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the C residue at position 7, the I residue at position 8, or the F residue at position 9 is replaced by a positively charged amino acid; and/or (ii) at least one of: the A residue at position 15, the A residue at position 16, or the S residue at position 17 is replaced by a positively charged amino acid.

29. The modular chimeric receptor of any one of claims 1 to 8, wherein the first synthetic transmembrane domain is a variant of the TM of GPVI and comprises a sequence having at least 40% identity with the sequence GNLVRICLGAVILIILAGFLA (SEQ ID NO:20), wherein the R residue at position 5 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 8, the G residue at position 9, or the A residue at position 10 is replaced by a positively charged amino acid; and/or (ii) at least one of: the I residue at position 12, the L residue at position 13, or the I residue at position 14 is replaced by a positively charged amino acid; and/or (iii) at least one of: the L residue at position 16, the A residue at position 17, or the G residue at position 18 is replaced by a positively charged amino acid.

30. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of CD3D and comprises a sequence having at least 40% identity with the sequence GIIVTDVIATLLLALGVFCFA (SEQ ID NO:21), wherein the D residue at position 6 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the A residue at position 9, the T residue at position 10, or the L residue at position 11 is replaced by a negatively charged amino acid; and/or (ii) at least one of: the L residue at position 13, the A residue at position 14, or the L residue at position 15 is replaced by a negatively charged amino acid.

31. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of CD3E and comprises a sequence having at least 40% identity with the sequence VSVATIVIVDICITGGLLLLVYYWS (SEQ ID NO:22), wherein the D residue at position 10 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the T residue at position 5, the I residue at position 6, or the V residue at position 7 is replaced by a negatively charged amino acid; (ii) at least one of: the I residue at position 13, the T residue at position 14, or the G residue at position 15 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the L residue at position 17, the L residue at position 18, or the L residue at position 19 is replaced by a negatively charged amino acid.

32. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of CD3G and comprises a sequence having at least 40% identity with the sequence GFLFAEIVSIFVLAVGVYFIA (SEQ ID NO:23), wherein the E residue at position 6 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the S residue at position 9, the I residue at position 10, or the F residue at position 11 is replaced by a negatively charged amino acid; and/or (ii) at least one of: the L residue at position 13, the A residue at position 14, or the V residue at position 15 is replaced by a negatively charged amino acid.

33. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of CD3Z and comprises a sequence having at least 40% identity with the sequence LCYLLDGILFIYGVILTALFL (SEQ ID NO:24), wherein the D residue at position 6 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 9, the F residue at position 10, or the I residue at position 11 is replaced by a negatively charged amino acid; and/or (ii) at least one of: the G residue at position 13, the V residue at position 14, or the I residue at position 15 is replaced by a negatively charged amino acid.

34. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of HCST/DAP10 and comprises a sequence having at least 40% identity with the sequence LLAGLVAADAVASLLIVGAVF (SEQ ID NO:25), wherein the D residue at position 9 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 4, the L residue at position 5, or the V residue at position 6 is replaced by a negatively charged amino acid; (ii) at least one of: the A residue at position 12, the S residue at position 13, or the L residue at position 14 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the I residue at position 16, the V residue at position 17, or the G residue at position 18 is replaced by a negatively charged amino acid.

35. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of TYROBP/DAP12 and comprises a sequence having at least 40% identity with the sequence VLAGIVMGDLVLTVLIALAVYFL (SEQ ID NO:26), wherein the D residue at position 9 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the G residue at position 4, the I residue at position 5, or the V residue at position 6 is replaced by a negatively charged amino acid; (ii) at least one of: the L residue at position 12, the T residue at position 13, or the V residue at position 14 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the I residue at position 16, the A residue at position 17, or the L residue at position 18 is replaced by a negatively charged amino acid.

36. The modular chimeric receptor of claim 35, wherein the second synthetic transmembrane domain comprises the sequence VLAGIVMGALVLDVLITLAVYFL (SEQ ID NO:39), VLALAVLGIVMGDVLITLAVYFL (SEQ ID NQ:40) or VLAGDVMGTLVLIVLIALAVYFL (SEQ ID NO:41).

The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic

transmembrane domain is a variant of the TM of CD79A and comprises a sequence having at least 40% identity with the sequence IITAEGIILLFCAVVPGTLLLF (SEQ ID NO:27), wherein the E residue at position 5 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the I residue at position 8, the L residue at position 9, or the L residue at position 10 is replaced by a negatively charged amino acid; (ii) at least one of: the C residue at position 12, the A residue at position 13, or the V residue at position 14 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the G residue at position 16, the T residue at position 17, or the L residue at position 18 is replaced by a negatively charged amino acid.

37. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of FCERG and comprises a sequence having at least 40% identity with the sequence LCYILDAILFLYGIVLTLLYC (SEQ ID NO:28), wherein the D residue at position 6 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 9, the F residue at position 10, or the L residue at position 11 is replaced by a negatively charged amino acid; (ii) at least one of: the G residue at position 13, the I residue at position 14, or the V residue at position 15 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the T residue at position 17, the L residue at position 18, or the L residue at position 19 is replaced by a negatively charged amino acid.

38. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of FCERA and comprises a sequence having at least 40% identity with the sequence FFIPLLVVILFAVDTGLFI (SEQ ID NO:29), wherein the D residue at position 14 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the I residue at position 9, the L residue at position 10, or the F residue at position 11 is replaced by a negatively charged amino acid; and/or (ii) at least one of: the L residue at position 5, the L residue at position 6, or the V residue at position 7 is replaced by a negatively charged amino acid.

39. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of FCG3A and comprises a sequence having at least 40% identity with the sequence VSFCLVMVLLFAVDTGLYFSV (SEQ ID NO:30),

wherein the D residue at position 14 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 9, the L residue at position 10, or the F residue at position 11 is replaced by a negatively charged amino acid; (ii) at least one of: the L residue at position 5, the V residue at position 6, or the M residue at position 7 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the L residue at position 17, the Y residue at position 18, or the F residue at position 19 is replaced by a negatively charged amino acid.

40. The modular chimeric receptor of any one of claims 1 to 29, wherein the second synthetic transmembrane domain is a variant of the TM of FCRL1 and comprises a sequence having at least 50% identity with the sequence GVIEGLLSTLGPATVALLFCY (SEQ ID NO:31), wherein the E residue at position 4 is replaced by an uncharged amino acid, preferably a hydrophobic amino acid, and (i) at least one of: the L residue at position 7, the S residue at position 8, or the T residue at position 9 is replaced by a negatively charged amino acid; (ii) at least one of: the G residue at position 11, the P residue at position 12, or the A residue at position 13 is replaced by a negatively charged amino acid; and/or (iii) at least one of: the V residue at position 15, the A residue at position 16, or the L residue at position 17 is replaced by a negatively charged amino acid.

41. The modular chimeric receptor of any one of claims 1 to 41, wherein the first synthetic transmembrane domain is a variant of the TM of KI2S3 and the second synthetic transmembrane domain is a variant of the TM of DAP12 or CD3Z.

42. The modular chimeric receptor of any one of claims 1 to 41, wherein the first synthetic transmembrane domain is a variant of the TM of NKG2C and the second synthetic transmembrane domain is a variant of the TM of DAP12 or CD3Z.

43. The modular chimeric receptor of any one of claims 1 to 43, wherein the first synthetic transmembrane domain comprises two positively-charged residues and the modular chimeric receptor comprises a second signaling module comprising a third synthetic transmembrane domain, wherein the third synthetic transmembrane domain comprises a second negatively charged amino acid and is a variant of a native transmembrane domain from an immune cell signaling protein, and wherein the second negatively charged amino acid is positioned so that the electrostatic interactions between the third synthetic transmembrane domain and the first synthetic transmembrane domain in the target immune cell membrane are stronger than the electrostatic interactions between the third synthetic transmembrane domain and the native transmembrane domain from the immune receptor.

44. The modular chimeric receptor of any one of claims 1 to 44, wherein the extracellular domain of the synthetic receptor module comprises one or more ligand- or antigen-binding domains.

45. The modular chimeric receptor of claim 45, wherein the extracellular domain of the synthetic receptor module comprises two ligand- or antigen-binding domains.

46. The modular chimeric receptor of claim 45 or 46, wherein the extracellular domain of the synthetic receptor module comprises an antigen-binding portion of an antibody molecule.

47. The modular chimeric receptor of claim 47, wherein the extracellular domain of the synthetic receptor module comprises a single-chain antibody fragment (scFv) or a single-domain antibody (sdAb).

48. The modular chimeric receptor of claim 48, wherein the extracellular domain of the synthetic receptor module comprises two scFvs or sdAbs.

49. The modular chimeric receptor of any one of claims 45 to 49, wherein the antigen is a protein expressed at the surface of tumor cells.

50. The modular chimeric receptor of claim 50, wherein the protein expressed at the surface of tumor cells is CD19.

51. The modular chimeric receptor of claim 51, wherein the extracellular domain of the synthetic receptor module comprises the amino acid sequence of SEQ ID NO:65.

52. The modular chimeric receptor of any one of claims 1 to 52, wherein the synthetic receptor module further comprises a polypeptide linker or spacer between the extracellular domain and the first transmembrane domain.

53. The modular chimeric receptor of claim 53, wherein the polypeptide linker or spacer comprises a portion of the extracellular domain of human CD8alpha.

54. The modular chimeric receptor of claim 54, wherein the polypeptide linker or spacer comprises the amino acid sequence of SEQ ID NO:66.

55. The modular chimeric receptor of any one of claims 1 to 55, wherein the synthetic receptor module further comprises an intracellular domain.

56. The modular chimeric receptor of claim 56, wherein the intracellular domain of the synthetic receptor module comprises a sequence of an intracellular domain of a costimulatory immune receptor.

57. The modular chimeric receptor of claim 57, wherein the costimulatory immune receptor is CD28, 4-1BB, 0X40, or ICOS, preferably CD28.

58. The modular chimeric receptor of claim 58, wherein the intracellular domain of the synthetic receptor module comprises the amino acid sequence of SEQ ID NO:68.

59. The modular chimeric receptor of any one of claims 1 to 59, 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.

60. The modular chimeric receptor of claim 60, wherein the intracellular signaling domain of the first synthetic signaling module comprises a sequence of the intracellular domain of DAP12 or CD3Z.

61. The modular chimeric receptor of claim 61, wherein the intracellular signaling domain of the first synthetic signaling module comprises the amino acid sequence of SEQ ID NO:68, 69, 70 or 71.

62. A nucleic acid or a plurality of nucleic acids comprising nucleotide sequences encoding the receptor module and signaling module(s) defined in any one of claims 1 to 62.

63. The nucleic acid or plurality of nucleic acids of claim 63, wherein said nucleic acid or plurality of nucleic acids is/are present in one or more plasmids or vectors.

64. The nucleic acid or plurality of nucleic acids of claim 64, wherein said one or more plasmids or vectors is/are viral vectors such as lentiviral vectors.

65. An immune cell expressing the modular chimeric receptor of any one of claims 1 to 65.

66. The immune cell of claim 66, wherein the immune cell is a T cell, such as a $CD8^+$ T cell, or a natural killer (NK) cell.

67. A composition comprising the immune cell of claim 66 or 67 and at least one pharmaceutically acceptable carrier or excipient.

68. A method for treating a disease, condition or disorder in a subject, the method comprising administering the immune cell of claim 66 or 67 or the composition of claim 68 to the subject.

69. The method of claim 69, wherein the disease, condition or disorder is cancer, an autoimmune or inflammatory disease, or an infectious disease.

70. The method of claim 70, wherein the disease, condition or disorder is a hematologic cancer, such as a B cell-derived cancer.

71. The method of claim 70 or 71, wherein the cancer is B cell lymphoma (BCL), mantle cell lymphoma (MCL), multiple myeloma (MM), or acute lymphoblastic leukemia (ALL).

72. The method of any one of claims 70 to 72, wherein the cancer is a CD19-expressing cancer.

73. A method for inducing the suppression of a target cell, the method comprising contacting the target cell with the immune cell of claim 66 or 67, or with a composition comprising the immune

~~cell, wherein the target cell expresses at its surface an antigen recognizes by the extracellular domain of the receptor module of the modular chimeric receptor.~~

~~74. The method of claim 74, wherein the target cell is a tumor cell.~~

~~75. The method of claim 75, wherein the tumor cell is a B cell.~~

~~76. The immune cell of claim 66 or 67 or the composition of claim 68, for use in treating a disease, condition or disorder in a subject.~~

~~77. The immune cell or composition for use according to claim 77, wherein the disease, condition or disorder is cancer, an autoimmune or inflammatory disease, or an infectious disease.~~

~~78. The immune cell or composition for use according to claim 78, wherein the disease, condition or disorder is a hematologic cancer, such as a B cell-derived cancer.~~

~~79. The immune cell or composition for use according to claim 78 or 79, wherein the cancer is B- cell lymphoma (BCL), mantle cell lymphoma (MCL), multiple myeloma (MM), or acute lymphoblastic leukemia (ALL).~~

~~80. The immune cell or composition for use according to any one of claims 78 to 80, wherein the cancer is a CD19-expressing cancer.~~

~~81. The immune cell of claim 66 or 67 or a composition comprising the immune cell, for use in the suppression of a target cell expressing at its surface an antigen recognizes by the extracellular domain of the receptor module of the modular chimeric receptor.~~

~~82. The immune cell or composition for use according to claim 82, wherein the target cell is a tumor cell.~~

~~83. The immune cell or composition for use according to claim 83, wherein the tumor cell is a B cell.~~

~~84. Use of the immune cell of claim 66 or 67 or the composition of claim 68, for the manufacture of a medicament for treating a disease, condition or disorder in a subject.~~

~~85. The use according to claim 85, wherein the disease, condition or disorder is cancer, an autoimmune or inflammatory disease, or an infectious disease.~~

~~86. The use according to claim 85, wherein the disease, condition or disorder is a hematologic cancer, such as a B cell-derived cancer.~~

~~87. The use according to claim 86 or 87, wherein the cancer is B-cell lymphoma (BCL), mantle cell lymphoma (MCL), multiple myeloma (MM), or acute lymphoblastic leukemia (ALL).~~

~~88. The use according to any one of claims 86 to 88, wherein the cancer is a CD19-expressing cancer.~~

~~89. Use of the immune cell of claim 66 or 67 or a composition comprising the immune cell for the manufacture of a medicament for suppressing a target cell expressing at its surface an antigen recognizes by the extracellular domain of the receptor module of the modular chimeric receptor.~~

~~90. The use according to claim 90, wherein the target cell is a tumor cell.~~

~~91. The use according to claim 91, wherein the tumor cell is a B cell.~~

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.