

WHAT IS CLAIMED IS:

1. A polynucleotide encoding a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with a chimeric receptor, the chimeric receptor comprising:
 - (a) an extracellular receptor domain,
wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),
wherein the peptide that binds native ligands of NKG2D,
is encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and
 - (b) an effector domain comprising a transmembrane region and an intracellular signaling domain,
wherein the intracellular signaling domain comprises CD3zeta, and
wherein the CD3zeta is encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 13,
wherein the polynucleotide also encodes ambIL 15 in a bicistronic configuration with the chimeric receptor.
2. The polynucleotide of Claim 1, wherein the transmembrane region of the effector domain comprises a CD8a transmembrane domain.
3. The polynucleotide of Claim 1 or 2, wherein the transmembrane region of the effector domain further comprises a CD8a hinge region.
4. The polynucleotide of Claim 3, wherein the CD8a hinge region is encoded by a polynucleotide having at least 95% sequence identity to SEQ ID NO. 5.
5. The polynucleotide of Claim 1, wherein the intracellular signaling domain further comprises 4-1BB, wherein the 4-1BB is encoded by a polynucleotide having at least 95% sequence identity to SEQ ID NO. 12.
6. The polynucleotide of any one of Claims 1 to 5, wherein the chimeric receptor comprises the peptide that binds native ligands of NKG2D coupled to CD8a; 4-1BB; and CD3zeta.

7. The polynucleotide of Claim 6, wherein the chimeric receptor is encoded by a nucleic acid sequence having at least 95% homology to SEQ ID NO. 18 or by a nucleic sequence having at least 95% homology to SEQ ID NO. 108.

8. The polynucleotide of Claim 6, wherein the chimeric receptor comprises an amino acid sequence having at least 95% homology to SEQ ID NO. 19.

9. A chimeric receptor comprising:

(a) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D comprises an amino acid sequence encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain,

wherein the intracellular signaling domain comprises CD3zeta, and

wherein the CD3zeta comprises an amino acid sequence encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 13,

wherein the chimeric receptor is encoded by a polynucleotide that encodes a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with the chimeric receptor.

10. The chimeric receptor of Claim 9, wherein the transmembrane region of the effector domain comprises a CD8a transmembrane domain.

11. The chimeric receptor of Claim 9 or Claim 10, wherein the transmembrane region of the effector domain comprises a CD8a hinge region.

12. The chimeric receptor of any one of Claims 9 to 11, wherein the intracellular signaling domain comprises 4-1BB, wherein the 4-1BB comprises an amino

acid sequence encoded by a polynucleotide having at least 95% sequence identity to SEQ ID NO. 12.

13. The chimeric receptor of any one of Claims 9 to 12, wherein the chimeric receptor comprises the peptide that binds native ligands of NKG2D coupled to CD8a; 4-1BB; and CD3zeta.

14. The chimeric receptor of any one of Claims 9 to 13, wherein the chimeric receptor comprises an amino acid sequence having at least 95% homology to SEQ ID NO. 19.

15. A polynucleotide encoding a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with a chimeric receptor, the chimeric receptor comprising:

(a) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D is encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain,

wherein the intracellular signaling domain comprises CD3zeta,

wherein the CD3zeta is encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 13 and

wherein the polynucleotide also encodes a mbIL15 in a bicistronic configuration with the chimeric receptor, and the mbIL15 is encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 16.

16. The polynucleotide of Claim 15, wherein the transmembrane region of the effector domain comprises a CD8a transmembrane domain.

17. The polynucleotide of Claim 15 or Claim 16, wherein the transmembrane region of the effector domain further comprises a CD8a hinge region.

18. The polynucleotide of Claim 17, wherein the CD8a hinge region is encoded by a polynucleotide comprising SEQ ID NO. 5.

19. The polynucleotide of any one of Claims 15 to 18, wherein mbIL15 comprises an amino acid sequence having at least 95% homology to SEQ ID NO. 17.

20. The polynucleotide of any one of Claims 15 to 19, wherein the effector domain further comprises an OX-40 domain.

21. The polynucleotide of Claim 20, wherein the chimeric receptor comprises the peptide that binds ligands of NKG2D coupled to a CD8a hinge; a CD8a transmembrane domain; the OX-40 domain; and the CD3zeta.

22. The polynucleotide of Claim 21, wherein the chimeric receptor is encoded by a polynucleotide having at least 95% homology to SEQ ID NO: 90 coupled to the mbIL15 encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 16.

23. The polynucleotide of Claim 21 or Claim 22, wherein the chimeric receptor comprises an amino acid sequence at least 95% homologous to the amino acid sequence of SEQ ID NO. 109 coupled to the mbIL15 comprising an amino acid sequence at least 95% homologous to the amino acid sequence of SEQ ID NO. 17.

24. The polynucleotide of Claim 20, wherein the chimeric receptor comprises the peptide that binds native ligands of NKG2D coupled to a IgG4 hinge, a CD8a transmembrane domain, the OX-40 domain, the CD3zeta, wherein the chimeric receptor is encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 100 coupled to the mbIL15 encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 16, and wherein the chimeric receptor comprises an amino acid sequence having at least 95% homology to SEQ ID NO. 101 coupled to the mbIL15 comprising an amino acid sequence having at least 95% homology to SEQ ID NO. 17.

25. A chimeric receptor comprising:

(a) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D comprises an amino acid sequence encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain,

wherein the intracellular signaling domain comprises CD3zeta,

wherein the CD3zeta comprises an amino acid sequence encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 13, and

wherein the chimeric receptor is encoded by a polynucleotide that encodes a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with the chimeric receptor, and the mbIL15 comprises an amino acid encoded by a polynucleotide at least 95% homologous to SEQ ID NO. 16.

26. The chimeric receptor of Claim 25, wherein the transmembrane region of the effector domain comprises a CD8a transmembrane domain.

27. The chimeric receptor of Claim 25 or Claim 26, wherein the transmembrane region of the effector domain further comprises a CD8a hinge region.

28. The chimeric receptor of any one of Claims 25 to 27, wherein the mbIL15 comprises an amino acid sequence having at least 95% homology to SEQ ID NO. 17.

29. The chimeric receptor of any one of Claims 25 to 28, wherein the effector domain comprises an OX-40 domain.

30. The chimeric receptor of any one of Claims 25 to 29, wherein the chimeric receptor comprises the peptide that binds native ligands of NKG2D coupled to a CD8a hinge; a CD8a transmembrane domain; the OX-40 domain, and the CD3zeta.

31. The chimeric receptor of any one of Claims 25 to 30, wherein the chimeric receptor comprises an amino acid sequence at least 95% homologous to the amino acid

sequence of SEQ ID NO. 109 coupled to the mbIL15 comprising an amino acid sequence at least 95% homologous to the amino acid sequence of SEQ ID NO. 17.

32. A composition for use in treating cancer, the composition comprising a Natural Killer (NK) cell expressing the chimeric receptor encoded by the polynucleotide of any one of Claims 1 to 8 or 15 to 24 or the chimeric receptor of any one of Claims 9 to 14 or 25 to 31.

33. The composition for use of Claim 32, wherein said NK cells are autologous cells isolated from a patient having a cancer.

34. The composition for use of Claim 32, wherein said NK cells are allogenic cells isolated from a donor.

35. Use of NK cells expressing the mbIL15 and chimeric receptor encoded by a polynucleotide of any one of Claims 1 to 8 or 15 to 24 or the chimeric receptor of any one of Claims 9 to 14 or 25 to 31 in the manufacture of a medicament for enhancing NK cell cytotoxicity.

36. Use of NK cells expressing the mbIL15 and chimeric receptor encoded by a polynucleotide of any one of Claims 1 to 8 or 15 to 24 or the chimeric receptor of any one of Claims 9 to 14 or 25 to 31 in the manufacture of a medicament for treating cancer or an infectious disease.

37. A polynucleotide encoding a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with a chimeric receptor, the chimeric receptor, comprising:

(a) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D is encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain

wherein the intracellular signaling domain comprises OX-40 and CD3zeta,

wherein the polynucleotide also encodes a mbIL15 in a bicistronic configuration with the chimeric receptor.

38. A chimeric receptor, comprising:

(a) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D is encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain

wherein the intracellular signaling domain comprises OX-40 and CD3zeta, and

wherein the chimeric receptor is encoded by a polynucleotide that encodes a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with the chimeric receptor.

39. A vector encoding a membrane-bound interleukin 15 (mbIL15) in a bicistronic configuration with a chimeric receptor, the chimeric receptor, comprising:

(a) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D is encoded by: (i) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (iii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain, wherein the intracellular signaling domain comprises OX-40 and CD3zeta.

40. An engineered cell comprising the polynucleotide of any one of Claims 1 to 8, 15 to 24, or 37, the chimeric receptor of any one of Claims 9 to 14, 25 to 31, or 38, or the vector of Claim 39.

41. The engineered cell of Claim 40, wherein the cell is an NK cell, and wherein the NK cell is configured for use in allogeneic therapy.

42. A genetically engineered immune cell expressing both membrane-bound interleukin 15 (mbIL15) and a chimeric receptor,

the chimeric receptor, comprising:

(b) an extracellular receptor domain,

wherein said extracellular receptor domain comprises a peptide that binds native ligands of Natural Killer Group 2 member D (NKG2D),

wherein the peptide that binds native ligands of NKG2D is encoded by: (i) (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 2, or (ii) a polynucleotide at least 95% homologous to SEQ ID NO. 3; and

(b) an effector domain comprising a transmembrane region and an intracellular signaling domain,

wherein the intracellular signaling domain comprises OX-40 and CD3zeta; and

wherein the mbIL15 is encoded bicistronically by a polynucleotide that also encodes the chimeric receptor.

43. The genetically engineered immune cell of any one of Claims 40 to 42, wherein the genetically engineered immune cell is a Natural Killer (NK) cell.

44. The genetically engineered immune cell of Claim 43 for use in allogeneic treatment for cancer.

45. The genetically engineered immune cell for use according to Claim 43 for enhancing NK cell cytotoxicity in a mammal.