

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 a fragment of NKG2D,
 - wherein the fragment of NKG2D is encoded by: (i) a polynucleotide comprising a fragment of SEQ ID NO: 1, (ii) 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 CD3zeta, and
 - wherein the CD3zeta is encoded by a polynucleotide having at least 95% homology to SEQ ID NO. 13.
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 fragment of NKG2D coupled to CD8a, 4-1BB and CD3z.

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 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.

10. The composition for use of claim 9, wherein said NK cells are autologous cells isolated from a patient having a cancer or an infectious disease.

11. The composition for use of claim 9, wherein said NK cells are allogenic cells isolated from a donor.

12. Use of NK cells expressing the mbIL15 and chimeric receptor encoded by a polynucleotide according to any one of Claims 1 to 8 in the manufacture of a medicament for enhancing NK cell cytotoxicity.

13. Use of NK cells expressing the mbIL15 and chimeric receptor encoded by a polynucleotide according to any one of Claims 1 to 8 in the manufacture of a medicament for treating cancer or an infectious disease.

14. 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 a fragment of NKG2D,

wherein the fragment of NKG2D is encoded by: (i) a polynucleotide comprising a fragment of SEQ ID NO: 1, (ii) 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 CD3zeta,

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

wherein the mbIL15 is encoded by a polynucleotide having at least 95% homology to SEQ ID NO: 16.

15. The polynucleotide of Claim 14, wherein the transmembrane region of the effector domain comprises a CD8a transmembrane domain.

16. The polynucleotide of Claim 14 or 15, wherein the transmembrane region of the effector domain further comprises a CD8a hinge region.

17. The polynucleotide of Claim 16, wherein the CD8a hinge region is encoded by a polynucleotide comprising SEQ ID NO: 5.

18. The polynucleotide of any one of Claims 14 to 17, wherein mbIL15 comprises an amino acid sequence having at least 95% homology to SEQ ID NO: 17.

19. The polynucleotide of any one of Claims 14 to 18, wherein the effector domain further comprises an OX-40 domain.

20. The polynucleotide of Claim 19, wherein the chimeric receptor comprises the fragment of NKG2D coupled to a CD8a hinge, a CD8a transmembrane domain, the OX-40 domain, the CD3zeta.

21. The polynucleotide of Claim 20, wherein the chimeric receptor is encoded by a nucleic acid sequence having at least 95% homology to SEQ ID NO: 90 coupled to the mbIL15 encoded by a nucleic acid sequence having at least 95% homology to SEQ ID NO. 16.

22. The polynucleotide of Claim 20 or 21, 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.

23. The polynucleotide of Claim 19, wherein the chimeric receptor comprises the fragment 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 nucleic acid sequence having at least 95% homology to SEQ ID NO: 100 coupled to the mbIL15 encoded by a nucleic acid sequence 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.

24. 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 14 to 23.

25. The composition for use of claim 24, wherein said NK cells are autologous cells isolated from a patient having a cancer.

26. The composition for use of claim 24, wherein said NK cells are allogenic cells isolated from a donor.

27. Use of NK cells expressing the mbIL15 and chimeric receptor encoded by a polynucleotide according to any one of Claims 14 to 23 in the manufacture of a medicament for enhancing NK cell cytotoxicity.

28. Use of NK cells expressing the mbIL15 and chimeric receptor encoded by a polynucleotide according to any one of Claims 14 to 23 in the manufacture of a medicament for treating cancer or an infectious disease.

29. 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 a fragment of NKG2D,

wherein the fragment of NKG2D is encoded by: (i) a polynucleotide comprising a fragment of SEQ ID NO: 1, (ii) 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.

30. 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 a fragment of NKG2D,

wherein the fragment of NKG2D is encoded by: (i) a polynucleotide comprising a fragment of SEQ ID NO: 1, (ii) 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.

31. An engineered cell comprising the vector of Claim 30.

32. The engineered cell of Claim 31, wherein the cell is an NK cell, and wherein the NK cell is configured for use in allogeneic therapy.

33. 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 a fragment of NKG2D,

wherein the fragment of NKG2D is encoded by: (i) a polynucleotide comprising a fragment of SEQ ID NO: 1, (ii) 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; and

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

34. The genetically engineered immune cell of Claim 33, wherein the genetically engineered immune cell is a Natural Killer (NK) cell.

35. The genetically engineered NK cell of Claim 34 for use in allogeneic treatment for cancer.

36. The genetically engineered natural killer cell for use according to Claim 35 for enhancing NK cell cytotoxicity in a mammal.