

CLAIMS

1. A chimeric transmembrane protein comprising:

a dimerization domain; and

a cytokine receptor endodomain.

5 2. A chimeric transmembrane protein according to Claim 1, in which the dimerization domain comprises the dimerization portion of a heavy chain constant domain (C_H) and a light chain constant domain (C_L).

3. A chimeric transmembrane protein according to Claim 1 or 2, which comprises two polypeptides:

10 (i) a first polypeptide which comprises:

(a) a first dimerisation domain; and

(b) a first chain of the cytokine receptor endodomain; and

(ii) a second polypeptide which comprises:

15 (a) a second dimerization domain, which dimerises with the first dimerization domain; and

(b) a second chain of the cytokine-receptor endodomain.

4. A chimeric transmembrane protein according to Claim 3, in which the first and second dimerization domains either dimerise spontaneously, or in the presence of a chemical inducer of dimerization (CID).

20 5. A chimeric transmembrane protein according to Claim 2, 3 or 4 which comprises two polypeptides:

(i) a first polypeptide which comprises:

(a) a heavy chain constant domain (C_H)

(b) a first chain of the cytokine receptor endodomain; and

25 (ii) a second polypeptide which comprises:

(a) a light chain constant domain (CL)

(b) a second chain of the cytokine-receptor endodomain.

6. A chimeric transmembrane protein according to Claim 5, in which the first and second chains for the cytokine receptor endodomains are different and are selected from type I
5 cytokine receptor endodomain α -, β -, and γ -chains.

7. A chimeric transmembrane protein according to Claim 5, in which the first and second chains for the cytokine receptor endodomains are the same and are selected from type I cytokine receptor endodomain α -, β -, and γ -chains.

8. A chimeric transmembrane protein according to any preceding claim, in which the
10 cytokine receptor endodomain comprises:

(i) IL-2 receptor β -chain endodomain

(ii) IL-7 receptor α -chain endodomain; or

(iii) IL-15 receptor α -chain endodomain; and/or

(iv) common γ -chain receptor endodomain.

15 9. A chimeric transmembrane protein according to Claim 5, in which the first polypeptide comprises a heavy chain variable domain (VH) and a heavy chain constant domain (CH); and the second polypeptide comprises a light chain variable domain (VL) and a light chain constant domain (CL).

10. A chimeric transmembrane protein according to Claim 9 which comprises a Fab
20 exodomain.

11. A cell which comprises a chimeric transmembrane protein according to any preceding claim.

12. A cell according to Claim 11, which also comprises a chimeric antigen receptor.

13. A cell according to Claim 12, in which the chimeric antigen receptor binds a tumour-
25 associated cell surface antigen.

14. A nucleic acid sequence encoding a chimeric transmembrane protein according to any of Claims 1 to 10.

15. A nucleic acid construct which comprises a first nucleic acid sequence encoding a first polypeptide as defined in Claim 3 and a second nucleic acid sequence encoding a second polypeptide as defined in Claim 3, the nucleic acid construct having the structure:

Dim1 -TM1-endo1-coexpr-Dim2 -TM2-endo2

in which

Dim1 is a nucleic acid sequence encoding the first dimerisation domain;

TM1 is a nucleic acid sequence encoding the transmembrane domain of the first polypeptide;

endo 1 is a nucleic acid sequence encoding the endodomain of the first polypeptide;

coexpr is a nucleic acid sequence enabling co-expression of both CCRs

Dim2 is a nucleic acid sequence encoding the second dimerization domain;

TM2 is a a nucleic acid sequence encoding the transmembrane domain of the second polypeptide;

endo 2 is a nucleic acid sequence encoding the endodomain of the second polypeptide.

16. A nucleic acid construct according to Claim 15 which also encodes a chimeric antigen receptor (CAR).

17. A nucleic acid construct according to Claim 15 or 16, in which coexpr encodes a sequence comprising a self-cleaving peptide.

18. A nucleic acid construct according to any of Claims 15 to 17, in which alternative codons are used in regions of sequence encoding the same or similar amino acid sequences, in order to avoid homologous recombination.

19. A vector comprising a nucleic acid construct according to any of Claims 15 to 18.

20. A retroviral vector or a lentiviral vector or a transposon according to Claim 19.

21. A kit which comprises:

(i) a vector comprising a nucleic acid sequence encoding a first polypeptide as defined in Claim 3; and

(ii) a vector comprising a nucleic acid sequence encoding a second polypeptide as defined in Claim 3.

5 22. A kit according to Claim 21 which also comprises a vector comprising a nucleic acid sequence encoding a chimeric antigen receptor.

23. A kit which comprises:

(i) a vector comprising a nucleic acid sequence encoding a chimeric transmembrane protein as defined in any of Claims 1 to 10; and

10 (ii) a vector comprising a nucleic acid sequence encoding a chimeric antigen receptor.

24. A method for making a cell according to any of Claims 11 to 13, which comprises the step of introducing: a nucleic acid sequence according to Claim 14; a nucleic acid construct according to any of Claims 15 to 18; a vector according to Claim 19 or 20; or a kit of vectors according to any Claims 21 to 23, into a cell.

15 25. A method according to Claim 24, in which the cell is from a sample isolated from a subject.

26. A pharmaceutical composition comprising a plurality of cells according to any of Claims 11 to 13.

20 27. A method for treating and/or preventing a disease, which comprises the step of administering a pharmaceutical composition according to Claim 26 to a subject.

28. A method according to Claim 27, which comprises the following steps:

(i) isolation of a cell-containing sample from a subject;

25 (ii) transduction or transfection of the cells with: a nucleic acid sequence according to Claim 14; a nucleic acid construct according to any of Claims 15 to 18; a vector according to Claim 19 or 20; or a kit of vectors according to any of Claims 21 to 23;; and

(iii) administering the cells from (ii) to a the subject.

29. A method according to Claim 28, in which the sample is a T-cell containing sample.
30. A method according to Claim 28 or 29, in which the disease is a cancer.
31. A pharmaceutical composition according to Claim 26 for use in treating and/or preventing a disease.
- 5 32. Use of a cell according to any of Claims 11 to 13 in the manufacture of a medicament for treating and/or preventing a disease.

CLAIMS

1. A chimeric transmembrane protein which comprises two polypeptides:
 - (i) a first polypeptide which comprises:
 - (a) a heavy chain constant domain (CH)
 - 5 (b) a first chain of the cytokine receptor endodomain; and
 - (ii) a second polypeptide which comprises:
 - (a) a light chain constant domain (CL)
 - (b) a second chain of the cytokine-receptor endodomain, in which the cytokine receptor endodomain comprises:
 - 10 (i) IL-2 receptor β -chain endodomain
 - (ii) IL-7 receptor α -chain endodomain; or
 - (iii) IL-15 receptor α -chain endodomain; and
 - (iv) common γ -chain receptor endodomain.
2. A cell which comprises a chimeric transmembrane protein according to Claim 1.
- 15 3. A cell which comprises a chimeric antigen receptor (CAR) and a chimeric transmembrane protein which comprises two polypeptides:
 - (i) a first polypeptide which comprises:
 - (a) a heavy chain constant domain (CH)
 - (b) a first chain of a type I cytokine receptor endodomain; and
 - 20 (ii) a second polypeptide which comprises:
 - (a) a light chain constant domain (CL)
 - (b) a second chain of a type I cytokine-receptor endodomain.
4. A cell according to Claim 3, in which the cytokine receptor endodomain of the chimeric transmembrane protein comprises:
 - 25 (i) IL-2 receptor β -chain endodomain

- (ii) IL-7 receptor α -chain endodomain; or
- (iii) IL-15 receptor α -chain endodomain; and
- (iv) common γ -chain receptor endodomain.

5. A cell according to Claim 3 or 4, in which the chimeric antigen receptor binds a tumour-associated cell surface antigen.
6. A nucleic acid sequence encoding a chimeric transmembrane protein according to Claim 1.
7. A nucleic acid construct encoding a chimeric transmembrane protein according to Claim 1, which comprises a first nucleic acid sequence encoding the first polypeptide and a second nucleic acid sequence encoding the second polypeptide, the nucleic acid construct having the structure:

CH -TM1-endo1-coexpr-CL -TM2-endo2

in which

CH is a nucleic acid sequence encoding the heavy chain constant domain of the first polypeptide;

TM1 is a nucleic acid sequence encoding the transmembrane domain of the first polypeptide;

endo 1 is a nucleic acid sequence encoding the endodomain of the first polypeptide;

coexpr is a nucleic acid sequence enabling co-expression of both the first and second polypeptide;

CL is a nucleic acid sequence encoding the light chain constant domain of the second polypeptide;

TM2 is a nucleic acid sequence encoding the transmembrane domain of the second polypeptide;

endo 2 is a nucleic acid sequence encoding the endodomain of the second polypeptide.

8. A nucleic acid construct encoding a chimeric transmembrane protein as defined in Claim 3, which comprises a first nucleic acid sequence encoding the first polypeptide and a

second nucleic acid sequence encoding the second polypeptide, the nucleic acid construct having the structure:

CH -TM1-endo1-coexpr-CL -TM2-endo2

in which

5 CH is a nucleic acid sequence encoding the heavy chain constant domain of the first polypeptide;

TM1 is a a nucleic acid sequence encoding the transmembrane domain of the first polypeptide;

endo 1 is a nucleic acid sequence encoding the endodomain of the first polypeptide;

10 coexpr is a nucleic acid sequence enabling co-expression of the first and second polypeptides

CL is a nucleic acid sequence encoding the light chain constant domain of the second polypeptide;

15 TM2 is a nucleic acid sequence encoding the transmembrane domain of the second polypeptide;

endo 2 is a nucleic acid sequence encoding the endodomain of the second polypeptide,

in which the nucleic acid construct also comprises a nucleic acid sequence which encodes a chimeric antigen receptor (CAR).

20 9. A nucleic acid construct according to Claim 7 or 8, in which coexpr encodes a sequence comprising a self-cleaving peptide.

10. A nucleic acid construct according to Claim 7, 8 or 9, in which alternative codons are used in regions of sequence encoding the same or similar amino acid sequences, in order to avoid homologous recombination.

25 11. A vector comprising a nucleic acid sequence according to Claim 6 or a nucleic acid construct according to any of Claims 7 to 10.

12. A retroviral vector or a lentiviral vector or a transposon according to Claim 11.

13. A kit which comprises:
- (i) a vector comprising a nucleic acid sequence encoding a first polypeptide as defined in Claim 1; and
 - (ii) a vector comprising a nucleic acid sequence encoding a second polypeptide as defined in Claim 1.
14. A kit which comprises:
- (i) a vector comprising a nucleic acid sequence encoding a first polypeptide as defined in Claim 3; and
 - (ii) a vector comprising a nucleic acid sequence encoding a second polypeptide as defined in Claim 3; and
 - (iii) a vector comprising a nucleic acid sequence encoding a chimeric antigen receptor.
15. A kit which comprises:
- (i) a vector comprising a nucleic acid sequence encoding a chimeric transmembrane protein as defined in Claim 3; and
 - (ii) a vector comprising a nucleic acid sequence encoding a chimeric antigen receptor.
16. A method for making a cell according to any of Claims 2 to 5, which comprises the step of introducing: a nucleic acid sequence according to Claim 6; a nucleic acid construct according to any of Claims 7 to 10; a vector according to Claim 11 or 12; or a kit of vectors according to any Claims 13 to 15, into a cell.
17. A method according to Claim 16, in which the cell is from a sample isolated from a subject.
18. A pharmaceutical composition comprising a plurality of cells according to any of Claims 2 to 5.
19. A pharmaceutical composition according to Claim 18 for use in treating a disease.
20. A pharmaceutical composition for use according to Claim 19, in which the disease is cancer.

21. Use of a cell according to any of Claims 2 to 5 in the manufacture of a medicament for treating a disease.