

CLAIMS

1. A chimeric antigen receptor (CAR) comprising an extracellular spacer which comprises at least part of the extracellular domain of human low affinity nerve growth factor (LNGFR) or a derivative thereof.
2. A CAR according to claim 1 wherein said at least part of the LNGFR is suitable for facilitating immunoselection and identification of cells transduced with said CAR.
3. A CAR according to claim 1 or 2 wherein the spacer lacks the intracellular domain of LNGFR.
4. A CAR according to any preceding claim wherein the extracellular spacer comprises the first three TNFR-Cys domains of LNGFR or fragments or derivatives thereof.
5. A CAR according to claim 4 wherein spacer comprises all four TNFR-Cys domains of LNGFR or fragments or derivatives thereof.
6. A CAR according to any preceding claim wherein the spacer comprises the fourth TNFR-Cys domain (TNFR-Cys 4) but wherein the following amino acid sequence is removed from said domain: NHVDPCLPCTVCEDTERQLRECTRW and replaced with the following amino acid sequence: ARA.
7. A CAR according to any preceding claim wherein the spacer comprises the serine /threonine-rich stalk of LNGFR.
8. A CAR according to claims 1 to 6 wherein the spacer lacks the serine /threonine-rich stalk of LNGFR.
9. A CAR according to any one of claims 1 to 3 wherein said spacer comprises the entire extracellular domain of LNGFR.
10. A CAR according to any one of claims 1 to 3 wherein the spacer comprises the extracellular domain of LNGFR with the exception of the serine /threonine-rich stalk of said domain.
11. A CAR according to any one of claims 1 to 3 wherein the spacer comprises the sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 or a sequence at least 90% identical thereto.
12. A CAR according to any one of claims 1 to 3 wherein the spacer consists of a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 or a sequence at least 90% identical thereto.
13. A chimeric antigen receptor (CAR) comprising

- (i) an antigen-specific targeting domain;
 - (ii) an extracellular spacer domain as defined in any one of claims 1 to 12;
 - (iii) a transmembrane domain;
 - (iv) optionally at least one costimulatory domain; and
 - (v) an intracellular signaling domain.
14. A CAR according to claim 13 wherein the antigen-specific targeting domain comprises an antibody or fragment thereof.
15. A CAR according to claim 14 wherein the antigen-specific targeting domain is a single chain variable fragment.
16. A CAR according to any one of claims 13 to 15 wherein the antigen-specific targeting domain targets a tumour antigen.
17. A CAR according to claim 16 wherein the tumour antigen is selected from the group consisting of CD44, CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, mesothelin, c-Met, PSMA, Her2, GD-2, CEA, MAGE A3 TCR and combinations thereof.
18. A CAR according to claim 16 wherein the tumour antigen is isoform 6 of CD44 (CD44v6).
19. A CAR according to any one of claims 13 to 18 wherein the transmembrane domain comprises any one or more of a transmembrane domain of a zeta chain of a T cell receptor complex, CD28, CD8a, and combinations thereof.
20. A CAR according to claim 13 or 19 wherein the costimulatory domain comprises a costimulating domain from any one or more of CD28, CD137 (4-1BB), CD134 (OX40), Dap10, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40 and combinations thereof.
21. A CAR according to any one of claims 13 to 20 wherein the intracellular signaling domain comprises an intracellular signaling domain of one or more of a human CD3 zeta chain, FcγRIII, FcεRI, a cytoplasmic tail of a Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptors, and combinations thereof.
22. A CAR according to any one of claims 13 to 21 wherein the antigen-specific targeting domain targets CD44v6, the transmembrane domain comprises a transmembrane domain of CD28, the intracellular signaling domain comprises an intracellular signaling domain of human CD3 zeta chain and the costimulatory domain comprises a CD28 endo-costimulating domain.
23. A polynucleotide encoding a CAR of any one of claims 1 to 22.
24. A vector comprising the polynucleotide of claim 23.
25. A vector according to claim 24 wherein the vector is a viral vector.

26. A cell comprising a CAR according to any one of claims 1 to 22, a polynucleotide according to claim 23 or a vector according to claim 24 or 25.
27. A cell according to claim 26 wherein the cell is a T-cell.
28. A pharmaceutical composition comprising the cell of claim 26 or 27.
29. A CAR according to any one of claims 13 to 22, or a polynucleotide according to claim 23, a vector according to claim 24 or 25 or a cell according to claim 26 or 27, for use in treating cancer.
30. A CAR according to claim 22, a polynucleotide encoding said CAR, a vector comprising said polynucleotide or a host cell comprising said CAR, polynucleotide or vector, for use in treating tumours that express CD44.