

CLAIMS

1. A T cell which expresses a gamma-delta T cell receptor (TCR) and a chimeric antigen receptor (CAR), wherein the CAR comprises;

- 5 (i) an antigen binding domain;
(ii) a transmembrane domain; and
(iii) a co-stimulatory intracellular signalling domain;

wherein the intracellular signalling domain provides a co-stimulatory signal to the T cell following binding of antigen to the antigen binding domain.

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2. A cell according to claim 1 wherein the antigen binding domain is capable of binding to a tumour-associated antigen (TAA).

3. A cell according to claim 1 wherein the antigen binding domain is capable of
15 binding to GD2, CD33, CD19 or EGFR.

4. A cell according to any preceding claim wherein the transmembrane domain comprises a CD8 stalk or a CD28 transmembrane domain.

20 5. A cell according to any of claims 1 to 4 wherein the intracellular signalling domain comprises the DAP10, CD28, CD27, 41BB, OX40, CD30, IL2-R, IL7-R, IL21-R, NKp30, NKp44 or DNAM-1 (CD226) signalling domain.

6. A cell according to any of claims 1 to 4 wherein the intracellular signalling
25 domain comprises the DAP10 signalling domain.

7. A cell according to any preceding claim wherein the binding of a first antigen to the gamma-delta TCR results in signal 1 production and binding of a second antigen to the antigen binding domain of the CAR results in signal 2 production.

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8. A cell according to any preceding claim wherein the CAR further comprises a spacer domain between the antigen binding domain and the transmembrane domain, for example a CD8 stalk or an Fc region.

35 9. A cell according to any preceding claim wherein the gamma-delta TCR is capable of binding to a phosphoantigen; major histocompatibility complex class I chain-related A (MICA); major histocompatibility complex class I chain-related B

(MICB); NKG2D ligand 1-6 (ULBP 1-6); CD1c; CD1d; endothelial protein C receptor (EPCR); lipohexapeptide; phycoreythrins or histidyl-tRNA-synthase.

10. A CAR comprising;

- 5 (i) an antigen-binding domain;
(ii) a transmembrane domain; and
(iii) an intracellular signalling domain;

wherein the intracellular signalling domain comprises a co-stimulatory intracellular signalling domain but does not comprise a CD3 endodomain.

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11. A CAR according to claim 10 wherein the co-stimulatory intracellular signalling domain is selected from a DAP10, CD28, CD27, 41BB, OX40, CD30, IL2-R, IL7-R, IL21-R, NKp30, NKp44 or DNAM-1 (CD226) signalling domain.

15 12. A CAR comprising;

- (i) an antigen-binding domain;
(ii) a transmembrane domain; and
(iii) an intracellular signalling domain;

wherein the intracellular signalling domain comprises a DAP10 signalling domain.

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13. A CAR according to claim 12 wherein the intracellular signalling domain does not comprise a CD3 endodomain.

14. A CAR according to any of claims 10 to 13 which is a CAR as defined in any
25 of claims 2 to 9.

15. A nucleic acid sequence encoding a CAR as defined in any preceding claim.

16. A vector comprising a nucleic acid sequence as defined in claim 15.

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17. A vector according to claim 16 which is a retroviral vector, a lentiviral vector or a transposon.

18. A method for making a cell according to any of claims 1 to 9, which comprises
35 the step of introducing: a nucleic acid sequence according to claim 15 or a vector according to claim 16 or 17 into a cell.

19. A method according to claim 18 wherein the cell is stimulated with a gamma delta T cell stimulating agent.

20. A method according to claim 19 wherein the gamma-delta T cell stimulating agent is selected from isopentenyl pyrophosphate (IPP); analogs of IPP; and inhibitors of farnesyl pyrophosphate synthase (FPPS).

21. A method according to claim 19 or 20, wherein the cell is from a sample isolated from a subject.

22. A pharmaceutical composition comprising a cell according to any of claims 1 to 9, a CAR according to any of claims 10 to 14, a nucleic acid sequence according to claim 15 or a vector according to claim 16 or 17.

23. A method for treating a disease, which comprises the step of administering a pharmaceutical composition according to claim 22 to a subject.

24. A method according to claim 23 which comprises the step of administering a gamma-delta T cell stimulating agent to the subject.

25. A method according to claim 24 wherein the gamma-delta T cell stimulating agent is selected from isopentenyl pyrophosphate (IPP); analogs of IPP; and inhibitors of farnesyl pyrophosphate synthase (FPPS).

26. A method according to any of claims 23 to 25, which comprises the following steps:

- (i) isolation of a cell-containing sample from a subject;
- (ii) transduction or transfection of cells with: a nucleic acid according to claim 15 or a vector according to claim 16 or 17; and
- (iii) administering the cells from (ii) to the subject.

27. A pharmaceutical composition according to claim 22 for use in treating and/or preventing a disease.

28. The use of a cell according to any of claims 1 to 9 in the manufacture of a medicament for treating and/or preventing a disease.

29. A method according to any of claims 23 to 26 or a use according to claim 24 or 25 wherein the disease is cancer, microbial infection or viral infection.

30. A method according to any of claims 23 to 26 or a use according to claim 27
5 or 28 wherein the disease is cancer.