

CLAIMS

1. A T cell which expresses a gamma-delta T cell receptor (TCR) and a chimeric antigen receptor (CAR), in which binding of a first antigen to the gamma-delta TCR results in signal 1 production and binding of a second antigen to an antigen binding domain of the CAR results
5 in signal 2 production, in which the CAR comprises;
 - (i) an antigen binding domain;
 - (ii) a transmembrane domain; and
 - (iii) a co-stimulatory intracellular signalling domain; in which the intracellular
10 signalling domain provides a co-stimulatory signal (signal 2) to the T cell following
binding of the second antigen to the antigen binding domain, in which the intracellular
signalling domain of the CAR comprises a DAP10, CD28, CD27, 41BB, OX40, CD30,
IL2-R, IL7-R, IL21-R, NKp30, NKp44 or DNAM-1 (CD226) signalling domain.
2. A cell according to Claim 1, in which the antigen binding domain is capable of binding
to a tumour-associated antigen (TAA).
- 15 3. A cell according to Claim 1, in which the antigen binding domain is capable of binding
to GD2, CD33, CD19 or EGFR.
4. A cell according to Claim 1, 2 or 3, in which the transmembrane domain comprises a
CD8 stalk or a CD28 transmembrane domain.
5. A cell according to any preceding claim, in which the intracellular signalling domain
20 comprises the DAP10 signalling domain.
6. A cell according to any preceding claim, in which 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.
7. A cell according to any preceding claim, in which the gamma-delta TCR is capable of
25 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; CD1 d; endothelial protein C receptor (EPCR); lipohexapeptide;
phycoreythrins or histidyl-tRNA-synthase.
8. A CAR comprising;

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

in which the intracellular signalling domain comprises a co-stimulatory intracellular signalling domain but does not comprise a CD3 endodomain, and in which 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.

9. A CAR according to Claim 8 comprising;

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

in which the intracellular signalling domain comprises a DAP10 signalling domain, and in which the intracellular signalling domain does not comprise a CD3 endodomain.

10. A CAR according to Claim 8 or 9, which is a CAR as defined in any of Claims 2 to 7.

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

12. A vector comprising a nucleic acid sequence as defined in Claim 11.

13. A vector according to Claim 12, which is a retroviral vector, a lentiviral vector or a transposon.

14. A method for making a cell according to any of Claims 1 to 7, which comprises the step of introducing: a nucleic acid sequence according to Claim 11 or a vector according to Claim 12 or 13 into a cell.

15. A method according to Claim 14, in which the cell is stimulated with a gamma delta T cell stimulating agent.

16. A method according to Claim 15, in which the gamma-delta T cell stimulating agent is selected from isopentenyl pyrophosphate (IPP); analogs of IPP; and inhibitors of farnesyl pyrophosphate synthase (FPPS).

17. A method according to Claim 15 or 16, in which the cell is from a sample isolated from a subject.
18. A pharmaceutical composition comprising a cell according to any of Claims 1 to 7, a CAR according to Claim 8 or 9, a nucleic acid sequence according to Claim 11 or a vector
5 according to Claim 12 or 13.
19. A pharmaceutical composition according to Claim 18, for use in a method of treating a disease.
20. A pharmaceutical composition for use according to Claim 19, in which a gamma-delta T cell stimulating agent is to be administered to the subject.
- 10 21. A pharmaceutical composition for use according to Claim 20, in which the gamma-delta T cell stimulating agent is selected from isopentenyl pyrophosphate (IPP); analogs of IPP; and inhibitors of farnesyl pyrophosphate synthase (FPPS).
22. A pharmaceutical composition for use according to Claims 19, 20 or 21, in which:
- (i) a cell-containing sample is isolated from a subject;
- 15 (ii) a nucleic acid according to Claim 11 or a vector according to Claim 12 or 13 is transduced or transfected into cells; and
- (iii) the cells from (ii) are to be administered to the subject.
23. A pharmaceutical composition according to Claim 18, for use in treating and/or preventing a disease.
- 20 24. Use of a cell according to any of Claims 1 to 7 in the manufacture of a medicament for treating and/or preventing a disease.
25. A pharmaceutical composition for use according to Claim 19, 21 or 22, in which the disease is cancer, microbial infection or viral infection.
26. A pharmaceutical composition for use according to Claim 19, 20 or 22, in which the
25 disease is cancer.