

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 signalling domain provides a co-stimulatory signal (signal 2) to the T cell following
10 binding of the second antigen to the antigen binding domain, and in the absence of antigen binding to the TCR a signal 1 is not generated and full $\gamma\delta$ T cell activation is not achieved and in the absence of antigen binding to the CAR, signal 2 is not generated and full $\gamma\delta$ T cell activation is not achieved, and in which the intracellular signalling domain of the CAR comprises a DAP10, CD28, CD27, 41BB, OX40, CD30, IL2-R, IL7-R,
15 IL21-R, NKp30, NKp44 or DNAM-1 (CD226) signalling domain;

in which the T cell is capable of killing a target cell(s) which expresses a first antigen capable of binding to the gamma delta TCR and a second antigen which is capable of binding to the CAR.
2. A cell according to Claim 1, in which the antigen binding domain is capable of binding
20 to a tumour-associated antigen (TAA).
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.
- 25 5. A cell according to any preceding claim, in which the intracellular signalling domain 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 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;
 - 5 phycoreythrins or histidyl-tRNA-synthase.
8. A method for making a cell according to any preceding claim, which comprises the step of introducing: a nucleic acid sequence encoding a CAR as defined in any preceding claim or a vector comprising a nucleic acid sequence encoding a CAR as defined in any preceding claim into a T cell expressing a gamma-delta TCR.
- 10 9. A method according to Claim 8, in which the vector is a retroviral vector, a lentiviral vector or a transposon.
10. A method according to Claim 8 or 9, in which the cell is stimulated with a gamma delta T cell stimulating agent.
11. A method according to Claim 10, in which the gamma-delta T cell stimulating agent is
 - 15 selected from isopentenyl pyrophosphate (IPP); analogs of IPP; and inhibitors of farnesyl pyrophosphate synthase (FPPS).
12. A method according to Claim 10 or 11, in which the cell is from a sample isolated from a subject.
13. A pharmaceutical composition comprising a cell according to any of Claims 1 to 7.
- 20 14. A pharmaceutical composition for use according to Claim 13, in which a gamma-delta T cell stimulating agent is to be administered to the subject.
15. A pharmaceutical composition for use according to Claim 14, 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).
- 25 16. A pharmaceutical composition for use according to Claim 13, 14 or 15, in which:
 - (i) a cell-containing sample is isolated from a subject;

(ii) a nucleic acid sequence encoding a CAR as defined in any of Claims 1 to 7 or a vector comprising a nucleic acid sequence encoding a CAR as defined in any of Claims 1 to 7 is transduced or transfected into cells; and

(iii) the cells from (ii) are to be administered to the subject.

5 17. A pharmaceutical composition according to Claim 13, for use in treating and/or preventing a disease.

18. 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, in which the disease is cancer, microbial infection or viral infection.

10 19. A pharmaceutical composition for use according to Claim 13, 15 or 16, in which the disease is cancer, microbial infection or viral infection.

20. A pharmaceutical composition for use according to Claim 13, 15 or 16, in which the disease is cancer.