

CLAIMS

1. A modified $\gamma\delta$ T cell comprising at least one co-stimulatory chimeric antigen receptor in which the co-stimulatory chimeric antigen receptor is a synthetic receptor to recognise and target a cell surface target, connected to a transmembrane domain which traverses the cell membrane and connects to an intracellular co-stimulatory immunoreceptor tyrosine-based activation motif capable of providing a signal 2 in which the $\gamma\delta$ T cell is provided with a tuneable response such that the $\gamma\delta$ T cell is provided with stimulating signal from the co-stimulatory chimeric antigen receptor (signal 2) to permit activation of the $\gamma\delta$ T cell only to cells which exhibit the cell surface target of the co-stimulatory CAR and cause $\gamma\delta$ T cell receptor stimulation (signal 1).
2. A modified $\gamma\delta$ T cell according to Claim 1, in which V γ 9V δ 2 TCR mediated recognition provides a CAR independent targeting strategy such that a stimulatory signal from the CAR will translate into a functional response only in the context of V γ 9V δ 2 T cell receptor stimulation.
3. A modified $\gamma\delta$ T cell according to Claim 1 or 2, further comprising an inhibitory chimeric antigen receptor (ICAR), in which the binding of an antigen by the inhibitory chimeric antigen receptor will cause the signal provided by any binding to a disease antigen of a chimeric antigen receptor comprising an extracellular antigen binding domain with binding specificity to the disease antigen, a hinge, a transmembrane domain, and one or more co-stimulatory signalling regions (tuneable) to be inhibited to minimise activation of the $\gamma\delta$ T cell in off-target cells.
4. A modified $\gamma\delta$ T cell according to Claim 1, 2 or 3, in which the chimeric antigen receptor is capable of binding to a cell surface target or natural ligand found in or associated with bacterial infection, fungal infection or protozoan infection; an active or inactivated viral fragment; a peptide; a protein; an antigenic segment from a virus; a tumour-specific antigen or tumour associated antigen.
5. A modified $\gamma\delta$ T cell according to any preceding claim for use in treatment of cancer or infection, optionally in which the infection is selected from a viral, bacterial, fungal or protozoan infection.

6. A modified $\gamma\delta$ T cell for use in the treatment of cancer or infection according to Claim 5 in which the modified $\gamma\delta$ T cell is co-administered to a subject with an aminobisphosphonate, or a substitute thereof, in which the substitute is capable of enhancing the levels of phosphoantigens present on target cells *via* dysregulation of the physiological mevalonate pathway.
7. A nucleic acid sequence encoding a chimeric antigen receptor (CAR), in which the CAR comprises an extracellular antigen recognition domain, a hinge, a transmembrane domain, and one or more co-stimulatory signalling regions to provide signal 2 in which the functional signal 1 providing domain is absent (tunable).
8. A nucleic acid sequence encoding a chimeric antigen receptor (CAR), in which the CAR comprises an extracellular antigen recognition domain, a hinge, a transmembrane domain, and one or more co-stimulatory signalling regions to provide signal 2 in which the functional signal 1 providing domain is absent (tuneable), comprising the nucleotide sequence SEQ ID NO: 7 which encodes the amino acid sequences SEQ ID NOs: 8 to 11.
9. A process to provide a CAR modified $\gamma\delta$ T cell comprising a step of incorporating or transducing a nucleic acid according to Claim 7 or 8 into a $\gamma\delta$ T cell to genetically modify the $\gamma\delta$ T cell.
10. A method to detect between a CAR comprising one or more co-stimulatory signalling regions and a CD3 zeta domain and a CAR in which a CD3 zeta domain is absent comprising a step of binding a primer pair selected from the group SEQ ID NO: 12 and SEQ ID NO: 13, and SEQ ID NO: 14 and SEQ ID NO: 15 to a nucleic acid encoding a CAR to be tested

Forward (SEQ ID NO: 12)	5'-GCTCCTGCACAGTGACTACAT-3'
Reverse (SEQ ID NO: 13)	5'-GGAGTTTCTTTCTGCCCCGT-3'

Forward (SEQ ID NO: 14)	5'-CTGTAGCTGCCGATTCCAGA-3'
Reverse (SEQ ID NO: 15)	5'-CATCGTACTCCTCTCTTCGTCC-3'

11. A kit comprising a $\gamma\delta$ T cell according to any of Claims 1 to 4 and a pyrophosphate/phosphonate drug for use in combination to treat a subject by autologous or allogeneic transfer.

5 12. A pharmaceutical composition comprising a $\gamma\delta$ T cell according to any of Claims 1 to 4.

13 A pharmaceutical composition according to Claim 12 and an antibody immunotherapy for use in the treatment of cancer, optionally further comprising a cytokine, interferon gamma, IL-2, chemotherapeutic, biologic or combination thereof for use in the treatment of cancer.

14. A pharmaceutical composition according to Claim 12 or 13 and a therapeutic for use in
10 the treatment of virus.

15. A method of preparing a treatment comprising; processing donor cells collected from a donor subject to allow a therapeutically effective amount of $\gamma\delta$ T cells to be allogeneically administered to a recipient subject, in which the processing includes the step of modifying the $\gamma\delta$ T cells to incorporate a chimeric antigen receptor to provide modified $\gamma\delta$ T cells according
15 to Claim 1 in which the modified $\gamma\delta$ T cell is provided with a tuneable response to the level of cell surface target which is expressed on a target cell recognised by the co-stimulatory CAR and optionally in which the $\gamma\delta$ T cells are to be administered to the recipient subject.

16. A method of preparing a treatment comprising processing donor cells collected from a donor subject to allow a therapeutically effective amount of $\gamma\delta$ T cells to be administered to
20 the donor subject, in which the processing includes the step of modifying the $\gamma\delta$ T cells to incorporate a chimeric antigen receptor to provide modified $\gamma\delta$ T cells according to Claim 1 in which the chimeric antigen receptor comprises an extracellular antigen binding domain with binding specificity to a disease antigen, a hinge, a transmembrane domain, one or more co-stimulatory signalling regions and a non-functional CD3 zeta domain and optionally in which
25 the $\gamma\delta$ T cells are to be administered to the donor subject in which the non-functional CD3 zeta domain is provided by the absence of a CD3 zeta domain in the chimeric antigen receptor.

17. A $\gamma\delta$ T-like cell, in which the $\gamma\delta$ T-like cell is a T cell genetically engineered to express a functional gamma delta T cell receptor comprising a chimeric antigen receptor in which the
30 chimeric antigen receptor comprises an extracellular antigen binding domain with binding

specificity to a disease antigen, a hinge, a transmembrane domain, and one or more co-stimulatory signalling regions in which a CD3 zeta domain is absent (tuneable), optionally in which the $\gamma\delta$ T-like cell is an $\alpha\beta$ T cell genetically engineered to express a functional gamma delta T cell receptor.

- 5 18. A T cell or T cell-like cell of defined antigen specificity, comprising a chimeric antigen receptor in which the chimeric antigen receptor comprises an extracellular antigen binding domain with binding specificity to a disease antigen, a hinge, a transmembrane domain, and
- one or more co-stimulatory signalling regions to provide signal 2 in which a CD3 zeta domain is absent (tuneable).
- 10 19. A T cell or T cell-like cell of defined antigen specificity according to Claim 18 selected from a NKT cell with specificity towards α -GalCer, and a mucosal-associated invariant T (MAIT) cell with specificity for vitamin B-related antigens.