CLAIMS

1. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an antibody or fragment thereof, which specifically binds to a Vγ4 chain of a γδ T cell receptor (TCR) and not to a gamma variable 2 (Vγ2) chain of a γδ TCR, to a cell population comprising Vγ4 T cells.

2. The method as defined in claim 1, wherein the Vγ4 chain of the γδ TCR is human Vγ4 and the Vγ2 chain of the γδ TCR is human Vγ2.

3. The method as defined in claim 1 or 2, wherein the antibody or fragment thereof binds to an epitope of the Vγ4 chain of the γδ TCR comprising one or more amino acid residues within amino acid region 67-82 of SEQ ID NO: 1.

4. The method as defined in claim 3, wherein the epitope comprises at least one of amino acid residues 71, 73, 75, 76, 79 of SEQ ID NO: 1.

5. The method as defined in any one of claims 1 to 4, wherein the epitope comprises or consists of K76 and/or M80 of SEQ ID NO: 1.

6. The method as defined in any one of claims 1 to 5, wherein the epitope is an activating epitope of a γδ T cell.

7. The method as defined in claim 6, wherein binding of the activating epitope: (i) downregulates the γδ TCR; (ii) activates degranulation of the γδ T cell; (iii) activates γδ T cell-mediated killing; and/or (iv) activates or increases Vγ4 chain-mediated cell signalling.

8. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an anti-Vγ4 antibody or fragment thereof, which comprises one or more of:

a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-47, preferably with SEQ ID NO: 10 and/or 33;

a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 48-70 and SEQUENCES: A1-A23 (of Figure 1), preferably with SEQ ID NO: 56 and/or SEQUENCE A9; and/or

a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 71-116, preferably with SEQ ID NO: 79 and/or 102,

to a cell population comprising Vγ4 T cells.

9. The method as defined in claim 8, wherein the antibody of fragment thereof comprises a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-24, such as SEQ ID NOs: 10, 4, 14, 15, 17, 19 or 23.

10. The method as defined in claim 8 or claim 9, wherein the antibody of fragment thereof comprises a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 25-47, such as SEQ ID NOs: 33, 27, 37, 38, 40, 42 or 46.

11. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an anti-Vγ4 antibody or fragment thereof, which comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 117-162 or 261-283, to a cell population comprising Vγ4 T cells.

12. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an anti-Vγ4 antibody or fragment thereof comprises one or more of:

(a) a VH comprising a HCDR1 having SEQ ID NO: 79, a HCDR2 having SEQ ID NO: 56 and a HCDR3 having SEQ ID NO: 10, optionally wherein the VH comprises SEQ ID NO: 125; and
a VL comprising a LCDR1 having SEQ ID NO: 102, a LCDR2 having SEQUENCE A9 (of Figure 1) and a LCDR3 having SEQ ID NO: 33, optionally wherein the VL comprises SEQ ID NO: 148 or 269;

(b) a VH comprising a HCDR1 having SEQ ID NO: 86, a HCDR2 having SEQ ID NO: 63 and a HCDR3 having SEQ ID NO: 17, optionally wherein the VH comprises SEQ ID NO: 132; and
a VL comprising a LCDR1 having SEQ ID NO: 109, a LCDR2 having SEQUENCE A16 (of Figure 1) and a LCDR3 having SEQ ID NO: 40, optionally wherein the VL comprises SEQ ID NO: 155 or 276;

(c) a VH comprising a HCDR1 having SEQ ID NO: 73, a HCDR2 having SEQ ID NO: 50 and a HCDR3 having SEQ ID NO: 4, optionally wherein the VH comprises SEQ ID NO: 119; and
a VL comprising a LCDR1 having SEQ ID NO: 96, a LCDR2 having SEQUENCE A3 (of Figure 1) and a LCDR3 having SEQ ID NO: 27, optionally wherein the VL comprises SEQ ID NO: 142 or 263;

(d) a VH comprising a HCDR1 having SEQ ID NO: 83, a HCDR2 having SEQ ID NO: 60 and a HCDR3 having SEQ ID NO: 14, optionally wherein the VH comprises SEQ ID NO: 129; and

a VL comprising a LCDR1 having SEQ ID NO: 106, a LCDR2 having SEQUENCE A13 (of Figure 1) and a LCDR3 having SEQ ID NO: 37, optionally wherein the VL comprises SEQ ID NO: 152 or 273;

(e) a VH comprising a HCDR1 having SEQ ID NO: 84, a HCDR2 having SEQ ID NO: 61 and a HCDR3 having SEQ ID NO: 15, optionally wherein the VH comprises SEQ ID NO: 130; and
a VL comprising a LCDR1 having SEQ ID NO: 107, a LCDR2 having SEQUENCE A14 (of Figure 1) and a LCDR3 having SEQ ID NO: 38, optionally wherein the VL comprises SEQ ID NO: 153 or 274;

(f) a VH comprising a HCDR1 having SEQ ID NO: 88, a HCDR2 having SEQ ID NO: 65 and a HCDR3 having SEQ ID NO: 19, optionally wherein the VH comprises SEQ ID NO: 134; and
a VL comprising a LCDR1 having SEQ ID NO: 111, a LCDR2 having SEQUENCE A18 (of Figure 1) and a LCDR3 having SEQ ID NO: 42, optionally wherein the VL comprises SEQ ID NO: 157 or 278;

(g) a VH comprising a HCDR1 having SEQ ID NO: 92, a HCDR2 having SEQ ID NO: 69 and a HCDR3 having SEQ ID NO: 23, optionally wherein the VH comprises SEQ ID NO: 138; and
a VL comprising a LCDR1 having SEQ ID NO: 115, a LCDR2 having SEQUENCE A22 (of Figure 1) and a LCDR3 having SEQ ID NO: 46, optionally wherein the VL comprises SEQ ID NO: 161 or 282;

(h) a VH comprising a HCDR1 having SEQ ID NO: 71, a HCDR2 having SEQ ID NO: 48 and a HCDR3 having SEQ ID NO: 2, optionally wherein the VH comprises SEQ ID NO: 117; and
a VL comprising a LCDR1 having SEQ ID NO: 94, a LCDR2 having SEQUENCE A1 (of Figure 1) and a LCDR3 having SEQ ID NO: 25, optionally wherein the VL comprises SEQ ID NO: 140 or 261;

(i) a VH comprising a HCDR1 having SEQ ID NO: 72, a HCDR2 having SEQ ID NO: 49 and a HCDR3 having SEQ ID NO: 3, optionally wherein the VH comprises SEQ ID NO: 118; and
a VL comprising a LCDR1 having SEQ ID NO: 95, a LCDR2 having SEQUENCE A2 (of Figure 1) and a LCDR3 having SEQ ID NO: 26, optionally wherein the VL comprises SEQ ID NO: 141 or 262;

(j) a VH comprising a HCDR1 having SEQ ID NO: 74, a HCDR2 having SEQ ID NO: 51 and a HCDR3 having SEQ ID NO: 5, optionally wherein the VH comprises SEQ ID NO: 120; and

a VL comprising a LCDR1 having SEQ ID NO: 97, a LCDR2 having SEQUENCE A4 (of Figure 1) and a LCDR3 having SEQ ID NO: 28, optionally wherein the VL comprises SEQ ID NO: 143 or 264;

(k) a VH comprising a HCDR1 having SEQ ID NO: 75, a HCDR2 having SEQ ID NO: 52 and a HCDR3 having SEQ ID NO: 6, optionally wherein the VH comprises SEQ ID NO: 121; and

a VL comprising a LCDR1 having SEQ ID NO: 98, a LCDR2 having SEQUENCE A5 (of Figure 1) and a LCDR3 having SEQ ID NO: 29, optionally wherein the VL comprises SEQ ID NO: 144 or 265;

(l) a VH comprising a HCDR1 having SEQ ID NO: 76, a HCDR2 having SEQ ID NO: 53 and a HCDR3 having SEQ ID NO: 7, optionally wherein the VH comprises SEQ ID NO: 122; and

a VL comprising a LCDR1 having SEQ ID NO: 99, a LCDR2 having SEQUENCE A6 (of Figure 1) and a LCDR3 having SEQ ID NO: 30, optionally wherein the VL comprises SEQ ID NO: 145 or 266;

(m) a VH comprising a HCDR1 having SEQ ID NO: 77, a HCDR2 having SEQ ID NO: 54 and a HCDR3 having SEQ ID NO: 8, optionally wherein the VH comprises SEQ ID NO: 123; and

a VL comprising a LCDR1 having SEQ ID NO: 100, a LCDR2 having SEQUENCE A7 (of Figure 1) and a LCDR3 having SEQ ID NO: 31, optionally wherein the VL comprises SEQ ID NO: 146 or 267;

(n) a VH comprising a HCDR1 having SEQ ID NO: 78, a HCDR2 having SEQ ID NO: 55 and a HCDR3 having SEQ ID NO: 9, optionally wherein the VH comprises SEQ ID NO: 124; and

a VL comprising a LCDR1 having SEQ ID NO: 101, a LCDR2 having SEQUENCE A8 (of Figure 1) and a LCDR3 having SEQ ID NO: 32, optionally wherein the VL comprises SEQ ID NO: 147 or 268;

(o) a VH comprising a HCDR1 having SEQ ID NO: 80, a HCDR2 having SEQ ID NO: 57 and a HCDR3 having SEQ ID NO: 11, optionally wherein the VH comprises SEQ ID NO: 126; and

a VL comprising a LCDR1 having SEQ ID NO: 103, a LCDR2 having SEQUENCE A10 (of Figure 1) and a LCDR3 having SEQ ID NO: 34, optionally wherein the VL comprises SEQ ID NO: 149 or 270;

(p) a VH comprising a HCDR1 having SEQ ID NO: 81, a HCDR2 having SEQ ID NO: 58 and a HCDR3 having SEQ ID NO: 12, optionally wherein the VH comprises SEQ ID NO: 127; and

a VL comprising a LCDR1 having SEQ ID NO: 104, a LCDR2 having SEQUENCE A11 (of Figure 1) and a LCDR3 having SEQ ID NO: 35, optionally wherein the VL comprises SEQ ID NO: 150 or 271;

(q) a VH comprising a HCDR1 having SEQ ID NO: 82, a HCDR2 having SEQ ID NO: 59 and a HCDR3 having SEQ ID NO: 13, optionally wherein the VH comprises SEQ ID NO: 128; and
a VL comprising a LCDR1 having SEQ ID NO: 105, a LCDR2 having SEQUENCE A12 (of Figure 1) and a LCDR3 having SEQ ID NO: 36, optionally wherein the VL comprises SEQ ID NO: 151 or 272;

(r) a VH comprising a HCDR1 having SEQ ID NO: 85, a HCDR2 having SEQ ID NO: 62 and a HCDR3 having SEQ ID NO: 16, optionally wherein the VH comprises SEQ ID NO: 131; and
a VL comprising a LCDR1 having SEQ ID NO: 108, a LCDR2 having SEQUENCE A15 (of Figure 1) and a LCDR3 having SEQ ID NO: 39, optionally wherein the VL comprises SEQ ID NO: 154 or 275;

(s) a VH comprising a HCDR1 having SEQ ID NO: 87, a HCDR2 having SEQ ID NO: 64 and a HCDR3 having SEQ ID NO: 18, optionally wherein the VH comprises SEQ ID NO: 133; and
a VL comprising a LCDR1 having SEQ ID NO: 110, a LCDR2 having SEQUENCE A17 (of Figure 1) and a LCDR3 having SEQ ID NO: 41, optionally wherein the VL comprises SEQ ID NO: 156 or 277;

(t) a VH comprising a HCDR1 having SEQ ID NO: 89, a HCDR2 having SEQ ID NO: 66 and a HCDR3 having SEQ ID NO: 20, optionally wherein the VH comprises SEQ ID NO: 135; and
a VL comprising a LCDR1 having SEQ ID NO: 112, a LCDR2 having SEQUENCE A19 (of Figure 1) and a LCDR3 having SEQ ID NO: 43, optionally wherein the VL comprises SEQ ID NO: 158 or 279;

(u) a VH comprising a HCDR1 having SEQ ID NO: 90, a HCDR2 having SEQ ID NO: 67 and a HCDR3 having SEQ ID NO: 21, optionally wherein the VH comprises SEQ ID NO: 136; and
a VL comprising a LCDR1 having SEQ ID NO: 113, a LCDR2 having SEQUENCE A20 (of Figure 1) and a LCDR3 having SEQ ID NO: 44, optionally wherein the VL comprises SEQ ID NO: 159 or 280;

(v) a VH comprising a HCDR1 having SEQ ID NO: 91, a HCDR2 having SEQ ID NO: 68 and a HCDR3 having SEQ ID NO: 22, optionally wherein the VH comprises SEQ ID NO: 137; and

a VL comprising a LCDR1 having SEQ ID NO: 114, a LCDR2 having SEQUENCE A21 (of Figure 1) and a LCDR3 having SEQ ID NO: 45, optionally wherein the VL comprises SEQ ID NO: 160 or 281;

and/or

(w) a VH comprising a HCDR1 having SEQ ID NO: 93, a HCDR2 having SEQ ID NO: 70 and a HCDR3 having SEQ ID NO: 24, optionally wherein the VH comprises SEQ ID NO: 139; and

a VL comprising a LCDR1 having SEQ ID NO: 116, a LCDR2 having SEQUENCE A23 (of Figure 1) and a LCDR3 having SEQ ID NO: 47, optionally wherein the VL comprises SEQ ID NO: 162 or 283,

to a cell population comprising Vγ4 T cells.

13. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an anti-Vγ4 antibody or fragment thereof which comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 163-185, to a cell population comprising Vγ4 T cells.

14. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an anti-Vγ4 antibody which comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 233-255, to a cell population comprising Vγ4 T cells.

15. An *ex vivo* method of modulating gamma variable 4 (Vγ4) T cells comprising administering an anti-Vγ4 antibody or fragment thereof comprising a heavy chain amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 284-306 and/or a light chain amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 307-329, to a cell population comprising Vγ4 T cells.

16. The method as defined in any one of claims 1 to 15, wherein the anti-Vγ4 antibody or fragment thereof is:

(i) an scFv or a full length antibody; and/or

(ii) a human antibody or fragment thereof.

17. The method as defined in any one of claims 1 to 16, wherein the modulation comprises expansion of Vγ4 T cells.

18. The method as defined in claim 17, wherein the method provides an expanded population of Vγ4 T cells which contains greater than about 60% Vγ4 T cells, such as greater than about 70% Vγ4 T cells.

19. The method as defined in any one of claims 1 to 18, wherein the method comprises culturing the cell population for at least 5 days.

20. The method as defined in any one of claims 1 to 19, wherein the method comprises culturing the cell population in the presence of IL-2 and/or IL-15.

21. The method as defined in any one of claims 1 to 20, wherein the cell population is obtained from a haematopoietic sample or a fraction thereof.

22. The method as defined in claim 21, wherein the haematopoietic sample consists of peripheral blood mononuclear cells (PBMCs) or low density mononuclear cells (LDMCs).

23. The method as defined in any one of claims 1 to 20, wherein the cell population is obtained from a non-haematopoietic tissue sample, such as a skin, colon, gut, mammary gland, lung, prostate, liver, spleen, pancreas, uterus, vagina or other cutaneous, mucosal or serous membrane sample.

24. The method as defined in any one of claims 1 to 23, wherein the cell population is obtained from human or non-human animal tissue.

25. A Vγ4 T cell population obtained by the *ex vivo* method as defined in any one of claims 1 to 24.

26. A composition comprising the Vγ4 T cell population as defined in claim 25.

27. A pharmaceutical composition comprising the Vγ4 T cell population as defined in claim 25, together with a pharmaceutically acceptable diluent or carrier.

28. The pharmaceutical composition as defined in claim 27, for use as a medicament.

29. The pharmaceutical composition as defined in claim 27 for use in the treatment of cancer, an infectious disease or an inflammatory disease.

30. A method of treating a cancer, an infectious disease or an inflammatory disease in a subject in need thereof, comprising administering a therapeutically effective amount of the Vγ4 T cell population as defined in claim 25 or the pharmaceutical composition as defined in claim 27.