

CLAIMS

1. An isolated antibody or fragment thereof, which specifically binds to a gamma variable 4 (V γ 4) chain of a $\gamma\delta$ T cell receptor (TCR) and not to a gamma variable 2 (V γ 2) chain of a $\gamma\delta$ TCR.
2. The isolated anti-V γ 4 antibody or fragment thereof as defined in claim 1, wherein the V γ 4 chain of the $\gamma\delta$ TCR is human V γ 4 and the V γ 2 chain of the $\gamma\delta$ TCR is human V γ 2.
3. The isolated anti-V γ 4 antibody or fragment thereof as defined in claim 1 or 2, which binds to an epitope of the V γ 4 chain of the $\gamma\delta$ TCR comprising one or more amino acid residues within amino acid region 67-82 of SEQ ID NO: 1.
4. The isolated anti-V γ 4 antibody or fragment thereof 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 isolated anti-V γ 4 antibody or fragment thereof 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 isolated anti-V γ 4 antibody or fragment thereof as defined in any one of claims 1 to 5, wherein the epitope is an activating epitope of a $\gamma\delta$ T cell.
7. The isolated anti-V γ 4 antibody or fragment thereof as defined in claim 6, wherein binding of the activating epitope: (i) downregulates the $\gamma\delta$ TCR; (ii) activates degranulation of the $\gamma\delta$ T cell; (iii) activates $\gamma\delta$ T cell-mediated killing; and/or (iv) activates or increases V γ 4 chain-mediated cell signalling.
8. An isolated anti-V γ 4 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.
9. The isolated anti-V γ 4 antibody or fragment thereof as defined in claim 8, which 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 isolated anti-V γ 4 antibody or fragment thereof as defined in claim 8 or claim 9, which 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 isolated anti-V γ 4 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.
12. An isolated anti-V γ 4 antibody or fragment thereof comprising 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.

13. An isolated anti-V γ 4 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.
14. An isolated anti-V γ 4 antibody which comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 233-255.
15. An isolated anti-V γ 4 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.
16. An isolated anti-V γ 4 antibody or fragment thereof, preferably as defined according to any one of claims 1-7, which binds to the same, or essentially the same, epitope as, or competes with, an antibody or fragment thereof as defined in any one of claims 8-15.
17. The isolated anti-V γ 4 antibody or fragment thereof as defined in any one of claims 1 to 16, which is:
 - (i) an scFv or a full length antibody; and/or
 - (ii) a human antibody or fragment thereof.
18. A polynucleotide sequence encoding the anti-V γ 4 antibody or fragment thereof as defined in any one of claims 1-17.
19. A polynucleotide sequence encoding the anti-V γ 4 antibody or fragment thereof comprising a sequence having at least 70% sequence identity with any of SEQ ID NOs: 187-232.
20. An expression vector comprising the polynucleotide sequence as defined in claim 18 or claim 19.
21. A cell comprising the polynucleotide sequence as defined in claim 18 or claim 19 or the expression vector as defined in claim 20.
22. A composition comprising the antibody or fragment thereof as defined in any one of claims 1 to 17.

23. A pharmaceutical composition comprising the antibody or fragment thereof as defined in any one of claims 1 to 17, together with a pharmaceutically acceptable diluent or carrier.
24. The isolated anti-V γ 4 antibody or fragment thereof as defined in any one of claims 1 to 17 or the pharmaceutical composition as defined in claim 23, for use as a medicament.
25. The isolated anti-V γ 4 antibody or fragment thereof or the pharmaceutical composition as defined in claim 24 for use in the treatment of cancer, an infectious disease or an inflammatory disease.
26. An isolated antigen comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 256-258 for use in generating an anti-V γ 4 antibody or fragment thereof.
27. A method of generating an anti-V γ 4 antibody or fragment thereof comprising:
- (i) designing a series of antigens comprising a TCR gamma variable 4 (V γ 4) amino acid sequence wherein the CDR3 sequence of the V γ 4 is the same for all antigens in the series;
 - (ii) exposing a first antigen designed in step (i) to an antibody library;
 - (iii) isolating the antibodies or fragments thereof which bind to the antigen;
 - (iv) exposing the isolated antibodies or fragments thereof to a second antigen designed in step (i); and
 - (v) isolating the antibodies or fragments thereof which bind to both the first and second antigen.
28. The method as defined in claim 27, which further comprises exposing the isolated antibodies or fragments thereof to a second series of antigens comprising a $\gamma\delta$ TCR with a different gamma variable chain, such as TCR gamma variable 2 (V γ 2) or TCR gamma variable 8 (V γ 8), and then deselecting the antibodies or fragments thereof which also bind to the second series of antigens.
29. An antibody obtained by the method as defined in claim 27 or claim 28.
30. A kit comprising an anti-V γ 4 antibody or fragment thereof according to any one of claims 1 to 17 or a pharmaceutical composition according to claim 23, optionally comprising instructions for use and/or an additional therapeutically active agent.