

**CLAIMS**

1. A T cell receptor (TCR) having the property of binding to GGYDGEHHSV (SEQ ID No: 1) in complex with HLA-A\*0201 with a dissociation constant of from about 0.05  $\mu$ M to about 20.0  $\mu$ M when measured with surface plasmon resonance at 25°C and at a pH between 7.1 and 7.5 using a soluble form of the TCR, and has at least a ten-fold selectivity of binding to SEQ ID No:1 in complex with HLA-A\*0201 over binding to GGYDGREHTV (SEQ ID No 2) in complex with HLA-A\*0201 in which the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain, and in which the TCR variable domains form contacts with at least residues V2, Y3 and D4 of GGYDGEHHSV (SEQ ID No: 1).
2. A TCR according to Claim 1, which is an alpha-beta heterodimer, having an alpha chain TRAV10 + TRAC constant domain sequence and a beta chain TRBV24-1 + TRBC-2 constant domain sequence.
3. A TCR according to Claim 1, which is in single chain format of the type V $\alpha$ -L-V $\beta$ , V $\beta$ -L-V $\alpha$ , V $\alpha$ -C $\alpha$ -L-V $\beta$ , or V $\alpha$ -L-V $\beta$ -C $\beta$ , in which V $\alpha$  and V $\beta$  are TCR  $\alpha$  and  $\beta$  variable regions respectively, C $\alpha$  and C $\beta$  are TCR  $\alpha$  and  $\beta$  constant regions respectively, and L is a linker sequence.
4. A TCR according to Claim 1, 2 or 3, which is associated with a detectable label, a therapeutic agent or a PK modifying moiety.
5. A TCR according to any preceding claim, in which the alpha chain variable domain comprises an amino acid sequence that has at least 80% identity to the sequence of amino acid residues 1-105 of SEQ ID No: 3 and has the following mutation:

|         |   |
|---------|---|
| CDR2 I3 | R |
|---------|---|

with reference to the numbering shown in SEQ ID No: 3, and/or the beta chain variable domain comprises an amino acid sequence that has at least 80% identity to the sequence of amino acid residues 1-123 of SEQ ID No: 4 and has at least one of the following mutations:

|          |   |
|----------|---|
| CDR1 H3  | R |
| CDR3 N10 | E |
| CDR3 N10 | R |

with reference to the numbering shown in SEQ ID No: 4.

6. A TCR according to any preceding claim, in which the alpha chain variable domain comprises the amino acid sequence of amino acid residues 1-105 of SEQ ID No: 3 or 5 or 7 or an amino acid sequence in which amino acid residues 1-27, 34-47, and 54-90 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-27, 34-47, and 54-90 respectively of SEQ ID No: 3 or 5 or 7 and in which amino acid residues 28-34, 48-53 and 91-105 have at least 90% or 95% identity to the sequence of amino acid residues 28-33, 48-53 and 91-105 respectively of SEQ ID No 3 or 5 or 7.

7. A TCR according to any preceding claim, in which the alpha chain variable domain comprises the amino acid sequence of amino acid residues 1-105 of SEQ ID No: 3 or 7 or an amino acid sequence in which amino acid residues 1-27, 34-47 and 55-89 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-27, 34-47, and 55-89 respectively of SEQ ID No: 3 or 7 and in which amino acid residues 28-33, 48-53 and 91-105 have at least 90% or 95% identity to the sequence of amino acid residues 28-33, 48-53 and 91-105 respectively of SEQ ID No: 3 or 7.

8. A TCR according to any preceding claim, in which in the alpha chain variable domain the sequence of:

(i) amino acid residues 1-27 thereof has:

(a) at least 90% identity to the sequence of amino acid residues 1-26 of SEQ ID No: 3; or

(b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

(ii) amino acid residues 28-33 is VSPFSN;

(iii) amino acid residues 34-47 thereof has (a) at least 90% identity to the sequence of amino acid residues 34-47 of SEQ ID NO: 3 or (b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

(iv) amino acid residues 48-53 is LTIMTF or LTRMTF;

(v) amino acid residues 54-90 thereof has at least 90% identity to the sequence of amino acid residues 55-89 of SEQ ID No: 3 or has one, two or three insertions, deletions or substitutions relative thereto; and

(vi) amino acids 91-105 is CVVSGGTDSWGKLQF.

5 9. A TCR according to any preceding claim, in which the beta chain variable domain comprises the amino acid sequence of SEQ ID No: 4 or 8-10 or an amino acid sequence in which amino acid residues 1-45, 51-67, and 74-109 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-45, 51-67, and 74-109 respectively of SEQ ID No: 4 or 8-10 and in which amino acid residues 46-50, 68-73 and 109-123 have at least 90% or 95%  
10 identity to the sequence of amino acid residues 46-50, 68-73 and 109-123 respectively of SEQ ID No: 4 or 8-10.

10. A TCR according to any preceding claim, in which in the beta chain variable domain the sequence of:

(i) amino acid residues 1-45 thereof has:

15 (a) at least 90% identity to the amino acid sequence of residues 1-26 of SEQ ID No: 4; or

(b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

(ii) amino acid residues 46-50 is KGHDR or KGRDR;

20 (iii) amino acid residues 51-67 thereof has (a) at least 90% identity to the sequence of amino acid residues 51-67 of SEQ ID NO: 4 or (b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

(iv) amino acid residues 68-73 is SFDVK;

25 (v) amino acid residues 54-90 thereof has (a) at least 90% identity to the sequence of amino acid residues 54-90 of SEQ ID NO: 4 or (b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a); and

(vi) amino acids 109-123 is CATSGQGAYNEQFF or CATSGQGAYREQFF or CATSGQGAYKEQFF.

11. A nucleic acid encoding a TCR according to any preceding claim.

12. An isolated or non-naturally occurring cell, especially a T-cell, presenting a TCR according to any preceding claim.
13. A cell harbouring:
- 5 (a) a TCR expression vector which comprises nucleic acid according to Claim 12 in a single open reading frame, or two distinct open reading frames encoding the alpha chain and the beta chain respectively; or
- (b) a first expression vector which comprises nucleic acid encoding the alpha chain of a TCR according to any preceding claim, and a second expression vector which comprises nucleic acid encoding the beta chain of a TCR according to any preceding claim.
- 10 14. A pharmaceutical composition comprising a TCR according to any of Claims 1 to 10, nucleic acid according to Claim 11 or a cell according to Claim 12 or 13, together with one or more pharmaceutically acceptable carriers or excipients.
- 15 15. A TCR according to any of Claims 1 to 12, a nucleic acid according to Claim 13 or cell according to Claim 14 or 15 for use in medicine.
16. A TCR, nucleic acid or cell for use according to Claim 15, for use in a method of treating cancer.