

CLAIMS

1. A T cell receptor (TCR) having the property of binding to GLYDGMEHL (SEQ ID No: 1) in complex with HLA-A*02 with a dissociation constant of from 0.05 μ M to 10.0 μ 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, 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 Y3 and E7 of GLYDGMEHL (SEQ ID No: 1), 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 1-111 of SEQ ID No: 4 and the beta chain variable domain comprises an amino acid sequence that has at least 80% identity to the sequence of amino acid residues 1-111 of SEQ ID No: 5.
2. A TCR according to Claim 1, which is an alpha-beta heterodimer, having an alpha chain TRAC constant domain sequence and a beta chain TRBC1 or TRBC2 constant domain sequence.
3. A TCR according to Claim 2, in which the alpha and beta chain constant domain sequences are modified by truncation or substitution to delete the native disulfide bond between Cys4 of exon 2 of TRAC and Cys2 of exon 2 of TRBC1 or TRBC2.
4. A TCR according to Claim 2 or 3, in which the alpha and beta chain constant domain sequences are modified by substitution of cysteine residues for Thr 48 of TRAC and Ser 57 of TRBC1 or TRBC2, the cysteines forming a disulfide bond between the alpha and beta constant domains of the TCR.
5. 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 α -L- $V\beta$, or $V\alpha$ -L- $V\beta$ -C β , in which $V\alpha$ and $V\beta$ are TCR α and β variable regions respectively, C α and C β are TCR α and β constant regions respectively, and L is a linker sequence.
6. A TCR according to any preceding claim, which is associated with a detectable label, a therapeutic agent or a PK modifying moiety.
7. A TCR according to any preceding claim, having the following mutation in the alpha chain:

Q31	A or S
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with reference to the numbering shown in SEQ ID No: 4, and/or at least one of the following mutations in the beta chain:

E30	D
G51	S, A or F

with reference to the numbering shown in SEQ ID No: 5.

- 5 8. A TCR according to any preceding claim, in which the alpha chain variable domain comprises the amino acid sequence of amino acid residues 1-111 of SEQ ID No: 6 or 12 or
an amino acid sequence in which amino acid residues 1-26, 33-49, 55-89 and 94-111 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-26, 33-49, 55-89 and 94-111 respectively of SEQ ID No: 6 or 12 and in which amino acid
10 residues 27-32, 50-54 and 90-93 have at least 90% or 95% identity to the sequence of amino acid residues 27-32, 50-54 and 90-93 respectively of SEQ ID No: 6 or 12.
9. A TCR according to any of Claims 1 to 7, in which the alpha chain variable domain comprises the amino acid sequence of amino acid residues 1-111 of SEQ ID No: 7 or 13 or
an amino acid sequence in which amino acid residues 1-26, 33-49, 55-89 and 94-111
15 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-26, 33-49, 55-89 and 94-111 respectively of SEQ ID No: 7 or 13 and in which amino acid residues 27-32, 50-54 and 90-93 have at least 90% or 95% identity to the sequence of amino acid residues 27-32, 50-54 and 90-93 respectively of SEQ ID No: 7 or 13.
10. A TCR according to any preceding claim, in which in the alpha chain variable domain
20 the sequence of
 - (i) amino acid residues 1-26 thereof has (a) at least 90% identity to the sequence of amino acid 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 27-32 is DRGSQS, DRGSAS or DRGSSS;

(iii) amino acid residues 33-49 thereof has (a) at least 90% identity to the sequence of amino acid residues 33-49 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 50-54 is IYSNG

5 (v) amino acid residues 55-89 thereof has at least 90% identity to the sequence of amino acid residues 55-89 of SEQ ID No: 4 or has one, two or three insertions, deletions or substitutions relative thereto;

(vi) amino acids 90-93 is AVRG; and

10 (vii) amino acid residues 94-111 thereof has at least 90% identity to the sequence of amino acid residues 94-111 of SEQ ID No: 4 or has one, two or three insertions, deletions or substitutions relative thereto.

11. A TCR according to any preceding claim, in which the beta chain variable domain comprises the amino acid sequence of SEQ ID No: 8 or 14 or

15 an amino acid sequence in which amino acid residues 1-26, 32-48, 54-90 and 96-111 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-26, 32-48, 54-90 and 96-111 respectively of SEQ ID No: 8 or 14 and in which amino acid residues 27-31, 49-53 and 91-95 have at least 90% or 95% identity to the sequence of amino acid residues 27-31, 49-53 and 91-95 respectively of SEQ ID No: 8 or 14.

20 12. A TCR according to any of Claims 1 to 10, in which the beta chain variable domain comprises the amino acid sequence of SEQ ID No: 9 or 15 or

25 an amino acid sequence in which amino acid residues 1-26, 32-48, 54-90 and 96-111 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-26, 32-48, 54-90 and 96-111 respectively of SEQ ID No: 9 or 15 and in which amino acid residues 27-31, 49-53 and 91-95 have at least 90% or 95% identity to the sequence of amino acid residues 27-31, 49-53 and 91-95 respectively of SEQ ID No: 9 or 15.

13. A TCR according to any of Claims 1 to 10, in which the beta chain variable domain comprises the amino acid sequence of SEQ ID No: 10 or 16

30 or an amino acid sequence in which amino acid residues 1-26, 32-48, 54-90 and 96-111 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-26, 32-48, 54-90 and 96-111 respectively of SEQ ID No: 10 or 16 and in which amino acid

residues 27-31, 49-53 and 91-95 have at least 90% or 95% identity to the sequence of amino acid residues 27-31, 49-53 and 91-95 respectively of SEQ ID No: 10 or 16.

14. A TCR according to any of Claims 1 to 10, in which the beta chain variable domain comprises the amino acid sequence of SEQ ID No: 11 or 17 or

5 an amino acid sequence in which amino acid residues 1-26, 32-48, 54-90 and 96-111 thereof have at least 90% or 95% identity to the sequence of amino acid residues 1-26, 32-48, 54-90 and 96-111 respectively of SEQ ID No: 11 or 17 and in which amino acid residues 27-31, 49-53 and 91-95 have at least 90% or 95% identity to the sequence of amino acid residues 27-31, 49-53 and 91-95 respectively of SEQ ID No: 11 or 17.

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

(i) amino acid residues 1-26 thereof has (a) at least 90% identity to the amino acid sequence of residues 1-26 of SEQ ID No: 5 or (b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

15 (ii) amino acid residues 27-31 is MNHEY or MNHDY;

(iii) amino acid residues 32-48 thereof has (a) at least 90% identity to the sequence of amino acid residues 32-48 of SEQ ID NO: 5 or (b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

(iv) amino acid residues 49-53 is SVGEG, SVSEG, SVAEG or SVFEG;

20 (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: 5 or (b) has one, two or three amino acid residues inserted or deleted relative to the sequence of (a);

(vi) amino acids 91-95 is CASSF; and

25 (vii) amino acid residues 96-111 thereof has at least 90% identity to the sequence of amino acid residues 96-111 of SEQ ID No: 5 or has one, two or three insertions, deletions or substitutions relative thereto.

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

17. An isolated or non-naturally occurring cell, especially a T-cell, presenting a TCR according to any of Claims 1 to 15.

18. A cell harbouring
- (a) a TCR expression vector which comprises nucleic acid according to Claim 16 in a single open reading frame, or two distinct open reading frames encoding the alpha chain and the beta chain respectively; or
- 5 (b) a first expression vector which comprises nucleic acid encoding the alpha chain of a TCR according to any of Claims 1 to 15, and a second expression vector which comprises nucleic acid encoding the beta chain of a TCR according to any of Claims 1 to 15.
19. A pharmaceutical composition comprising a TCR according to any of Claims 1 to 15, a
10 nucleic acid according to Claim 16 or a cell according to Claim 17 or 18, together with one or more pharmaceutically acceptable carriers or excipients.
20. A TCR according to any of Claims 1 to 15, a nucleic acid according to Claim 16 or a cell according to Claim 17 or 18 for use in medicine.
21. A TCR, nucleic acid or cell for use according to Claim 20, for use in a method of
15 treating cancer.