

CLAIMS

1. A T cell receptor (TCR) having the property of binding to GGYDGREHTV (SEQ ID No: 1) in complex with HLA-A*0201 with a dissociation constant of from about 0.05 μ M to about 20.0 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, and has at least a ten-fold selectivity of binding to SEQ ID No:1 in complex with HLA-A*0201 over binding to GGYDGEHHSV (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 GGYDGREHTV (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 α -L-V β , V β -L-V α , V α -C α -L-V β , or V α -L-V β -C β , in which V α and V β 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.
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 CDR mutation:

M4	V or L
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with reference to the numbering of the CDRs 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 1-105 of SEQ ID No: 4 and has at least one of the following CDR mutations:

N10	E
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with reference to the numbering of the CDRs shown in SEQ ID No: 4.

6. A TCR according to any preceding claim, in which the alpha chain variable domain is the alpha chain variable domain sequence set forth in SEQ ID No. 3 and the beta chain variable domain is the beta chain variable domain sequence set forth in SEQ ID No. 9; or the alpha chain variable domain is the alpha chain variable domain sequence set forth in SEQ ID No. 7 and the beta chain variable domain is the beta chain variable domain sequence set forth in SEQ ID No. 9; or the alpha chain variable domain is the alpha chain variable domain sequence set forth in SEQ ID No. 8 and the beta chain variable domain is the beta chain variable domain sequence set forth in SEQ ID No. 9.

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 5 or 7 to 8 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 to 8 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 to 8.

8. A TCR according to any preceding claim, in which the alpha chain variable domain comprises the amino acid sequence of amino acid residues 1-105 of SEQ ID No: 7 or 8 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: 7 or 8 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: 7 or 8.

9. 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 or LTIVTF or LTILTF

5 (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

10. A TCR according to any preceding claim, in which the beta chain variable domain
10 comprises the amino acid sequence of SEQ ID No: 4 or 6 or 9 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 6 or 9 and in which amino acid residues 46-50, 68-73 and 109-123 have at least 90% or 95% identity to the sequence of amino acid residues 46-50, 68-73 and 109-123 respectively of
15 SEQ ID No: 4 or 6 or 9.

11. 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:

20 (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;

25 (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;

(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

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

13. An isolated or non-naturally occurring cell, especially a T-cell, presenting a TCR according to any preceding claim.

14. A cell harbouring:

10 (a) a TCR expression vector which comprises nucleic acid as claimed in claim 13 in a single open reading frame, or two distinct open reading frames encoding the alpha chain and the beta chain respectively; or

15 (b) a first expression vector which comprises nucleic acid encoding the alpha chain of a TCR as claimed in any of claims 1 to 12, and a second expression vector which comprises nucleic acid encoding the beta chain of a TCR as claimed in any of claims 1 to 12.

15. A pharmaceutical composition comprising a TCR according to any of Claims 1 to 11, a nucleic acid according to Claim 12 or a cell according to Claim 13 or 14, together with one or more pharmaceutically acceptable carriers or excipients.

20 16. A TCR according to any of Claims 1 to 13, a nucleic acid according to Claim 14 or a cell according to Claim 15 or 16 for use in medicine.

17. A TCR, nucleic acid or cell for use according to Claim 16, for use in a method of treating cancer.

CLAIMS

1. A T cell receptor (TCR) having the property of binding to GGYDGREHTV (SEQ ID No: 1) in complex with HLA-A*0201 with a dissociation constant of from 0.05 μ M to 20.0 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, and has at least a ten-fold selectivity of binding to SEQ ID No:1 in complex with HLA-A*0201 over binding to GGYDGEEHSV (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 GGYDGREHTV (SEQ ID No: 1), in which:
 - 10 (A) 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 1-27 of SEQ ID No: 3 or (b) one, two or three amino acid insertions, deletions or substitutions relative to the sequence of (a);
 - (ii) amino acid residues 28-33 is VSPFSN;
 - 15 (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) one, two or three amino acid insertions, deletions or substitutions relative to the sequence of (a);
 - (iv) amino acid residues 48-53 is LTIMTF or LTIVTF or LTILTF
 - (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: 3 or (b) one, two or three amino acid insertions, deletions or substitutions relative to the sequence of (a); and
 - 20 (vi) amino acids 91-105 is CVVSGGTDSWGKLQF; and
 - (B) in the beta chain variable domain, the sequence of
 - (i) amino acid residues 1-45 thereof has (a) at least 90% identity to the amino acid sequence of residues 1-45 of SEQ ID No: 4; or (b) one, two or three amino acid insertions, deletions or substitutions relative to the sequence of (a);
 - 25 (ii) amino acid residues 46-50 is KGHDR;

(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) one, two or three amino acid insertions, deletions or substitutions relative to the sequence of (a);

(iv) amino acid residues 68-72 is SFDVK;

5 (v) amino acid residues 73-109 thereof has (a) at least 90% identity to the sequence of amino acid residues 73-109 of SEQ ID NO: 4 or (b) one, two or three amino acid insertions, deletions or substitutions relative to the sequence of (a); and

(vi) amino acids 110-123 are CATSGQGAYEEQFF.

10 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.

15 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 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.

4. A TCR according to Claim 1, 2 or 3, which is associated with a detectable label, a therapeutic agent or a pharmacokinetic (PK) modifying moiety.

20 5. A TCR according to any preceding claim, in which the alpha chain variable domain is the alpha chain variable domain sequence set forth in SEQ ID No. 3 and the beta chain variable domain is the beta chain variable domain sequence set forth in SEQ ID No. 9; or the alpha chain variable domain is the alpha chain variable domain sequence set forth in SEQ ID No. 7 and the beta chain variable domain is the beta chain variable domain sequence set forth in SEQ ID No. 9; or the alpha chain variable domain is the alpha chain variable domain sequence set forth in SEQ ID No. 8 and the beta chain variable domain is the beta chain variable domain sequence set forth in SEQ ID No. 9.

6. A TCR according to any preceding claim, in which the alpha chain variable domain comprises the amino acid sequence of SEQ ID No: 3 or 7 or 8.

30 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: 7 or 8.

8. A TCR according to any preceding claim, in which the beta chain variable domain comprises the amino acid sequence of SEQ ID No: 9.
9. A nucleic acid encoding a TCR according to any preceding claim.
10. An isolated or non-naturally occurring cell presenting a TCR according to any preceding claim.
11. An isolated or non-naturally occurring cell according to Claim 10, in which the cell is a T-cell.
12. A cell harbouring:
 - (a) a TCR expression vector which comprises a nucleic acid as claimed in Claim 9 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 as claimed in any of Claims 1 to 8, and a second expression vector which comprises nucleic acid encoding the beta chain of a TCR as claimed in any of Claims 1 to 8.
13. A pharmaceutical composition comprising a TCR according to any of Claims 1 to 8, a nucleic acid according to Claim 9 or a cell according to Claims 10, 11 or 12, together with one or more pharmaceutically acceptable carriers or excipients.
14. A cell according to Claim 11 for use in medicine.
15. A cell for use according to Claim 14, for use in a method of treating cancer.