

Claims

1. A T cell receptor (TCR) having the property of binding to GVDGREHTV (SEQ ID No: 1) in complex with HLA-A*0201 with a dissociation constant of from about 0.05 μM to about 20.0 μM 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 GVDGAYVSV (SEQ ID No 2) in complex with HLA-A*0201 wherein the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain, and wherein the TCR variable domains form contacts with at least residues V2, Y3 and D4 of GVDGKSDSV (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 as claimed in claim 1, which is in single chain format of the type Vα-L-Vβ, Vβ-L-Vα, Vα-Cα-L-Vβ, or Vα-L-Vβ-Cβ, wherein Vα and Vβ are TCR α and β variable regions respectively, Cα and Cβ are TCR α and β constant regions respectively, and L is a linker sequence.
4. A TCR as claimed in any preceding claim, which is associated with a detectable label, a therapeutic agent or a PK modifying moiety.
5. A TCR as claimed in any preceding claim, wherein 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:

M4	V or L
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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 1-105 of SEQ ID No: 4 and has at least one of the following mutations:

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

6. A TCR as claimed in any preceding claim, wherein 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.

7. A TCR as claimed in any one of claims 1-7, wherein 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.
8. A TCR as claimed in any preceding claim, wherein 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
 - (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;
 - (vi) amino acids 91-105 is CVVSGGTDSWGKLQF
9. A TCR as claimed in any preceding claim, wherein the beta chain variable domain 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 SEQ ID No: 4 or 6 or 9.
10. A TCR according to any preceding claim, wherein 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 1-26 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;
- 5 (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;
- 10 (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);
- (vi) amino acids 109-123 is CATSGQGAYNEQFF or CATSGQGAYREQFF
11. Nucleic acid encoding a TCR as claimed in any one of the preceding claims.
12. An isolated or non-naturally occurring cell, especially a T-cell, presenting a TCR as claimed
- 15 in any one of claims 1 to 12.
13. A cell harbouring
- (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
- 20 (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.
14. A pharmaceutical composition comprising a TCR as claimed in any one of claims 1 to 10, nucleic acid of claim 11 or a cell as claimed in claim 12 or claim 13, together with one or more
- 25 pharmaceutically acceptable carriers or excipients.
15. The TCR of any one of claims 1 to 12, nucleic acid of claim 13 or cell of claim 14 or claim 15 for use in medicine.
16. The TCR, nucleic acid or cell for use as claimed in claim 15, for use in a method of treating cancer.