

Claims:

1. A T cell receptor (TCR) having the property of specifically binding to SLLMWITQC (SEQ ID NO: 1) HLA-A*02 complex and comprising a TCR alpha chain variable domain and a TCR beta chain variable domain, wherein
- 5 the alpha chain variable domain comprises an amino acid sequence that has at least 90% identity, such as 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity, to SEQ ID NO:12,
- the beta chain variable domain comprises an amino acid sequence that has at least 90% identity, such as 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity, to SEQ
- 10 ID NO:15, and
- the alpha chain variable domain sequence of amino acids residues 27-32 (CDR1), 50-57 (CDR2) and 91-107 (CDR3) and the beta chain variable domain sequence of amino acid residues 27-31 (CDR1), 49-55 (CDR2) and 93-106 (CDR3) are selected from the following:

Alpha chain			Beta Chain		
27-32 (CDR1)	50-57 (CDR2)	91-107 (CDR3)	27-31 (CDR1)	49-55 (CDR2)	93-106 (CDR3)
VSGNPY	YLGDSALV	CAVRDINSGAGSYQLTF	KRLAL	AWTGGEA	CSVGGSGAADTQYF
VSGNPY	YLGDSALV	CAVRDINSGAGSYQLTF	KRLAL	AWTGSEA	CSVGGSGGADTQYF
VSGNPY	YLGDSALV	CAVRDIRSGAGSYQLTF	KRLAL	AWTGGEA	CSVGGSGAADTQYF
VSGNPY	YLGDSALV	CAVRDIRSGAGSYQLTF	KRLAL	AWTGSEA	CSVGGSGGADTQYF

- 15 2. The TCR of claim 1 that binds to the SLLMWITQC (SEQ ID NO: 1) HLA-A*02 complex with a dissociation constant (K_D) stronger than 50 μ M.
3. The TCR of claim 2 that binds to the SLLMWITQC (SEQ ID NO:1) HLA-A*02 complex with a K_D of from 1 pM to 50 nM.
- 20 4. A TCR as claimed in any preceding claim, wherein the alpha chain variable domain and the beta chain variable domain are selected from the amino acid sequences of:

Alpha chain variable domain	Beta chain variable domain
SEQ ID NO: 7	SEQ ID NO: 15
SEQ ID NO: 7	SEQ ID NO: 18
SEQ ID NO: 12	SEQ ID NO: 15
SEQ ID NO: 12	SEQ ID NO: 18

5. A TCR as claimed in any preceding claim, which is an alpha-beta heterodimer, having an alpha chain TRAC constant domain sequence and a beta chain TRBC1 or TRBC2 constant domain sequence.
6. A TCR as claimed in claim 5, wherein the alpha and beta chain constant domain sequences are modified by truncation or substitution to delete the native disulphide bond between Cys4 of exon 2 of TRAC and Cys2 of exon 2 of TRBC1 or TRBC2.
7. A TCR as claimed in claim 5 or claim 6 wherein the alpha and/or beta chain constant domain sequence(s) are modified by substitution of cysteine residues for Thr 48 of TRAC and Ser 57 of TRBC1 or TRBC2, the said cysteines forming a non-native disulphide bond between the alpha and beta constant domains of the TCR.
8. A TCR as claimed in any preceding claim, which is in single chain format of the type $V\alpha$ -L- $V\beta$, $V\beta$ -L- $V\alpha$, $V\alpha$ -C α -L- $V\beta$, $V\alpha$ -L- $V\beta$ -C β , wherein $V\alpha$ 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.
9. A TCR as claimed in any preceding claim, associated with a detectable label, a therapeutic agent or a pharmacokinetics modifying moiety.
10. A TCR anti-CD3 fusion comprising the TCR of any preceding claim and an anti-CD3 antibody covalently linked to the C- or N-terminus of the alpha or beta chain of the TCR.
11. The TCR anti-CD3 fusion of claim 10, comprising an alpha chain variable domain selected from SEQ ID NO: 7 and 12 and comprising a beta chain variable domain selected from SEQ ID NO: 15 and 18.
12. The TCR anti-CD3 fusion of claim 10, wherein the beta chain is linked to the anti-CD3 antibody sequence via a linker sequence.
13. The TCR anti-CD3 fusion of claim 12, wherein the linker sequence is selected from the group consisting of GGGGS (SEQ ID NO: 24), GGGSG (SEQ ID NO: 25), GGSGG (SEQ ID NO: 26), GSGGG (SEQ ID NO: 27), GSGGGP (SEQ ID NO: 28), GGEPS (SEQ ID NO: 29), GGEGGGP (SEQ ID NO: 30), and GGEGGGSEGGGS (SEQ ID NO: 31).
14. The TCR anti-CD3 fusion of claim 11, comprising an alpha and beta chain that has at least 90% identity, such as 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity, to the amino acid sequences as set forth in the table below:

alpha chain SEQ ID NO:	beta chain SEQ ID NO:	Shown in
32	33	Figure 5

35	36	Figure 6
37	38	Figure 7
39	40	Figure 8

15. The TCR anti-CD3 fusion of any one of claims 10 to 14, comprising an alpha chain variable domain consisting of an amino acid sequence of SEQ ID NO: 12 and a beta chain variable domain consisting of an amino acid sequence of SEQ ID NO: 15 and wherein the beta chain is linked to an anti-CD3 antibody via a linker sequence, optionally wherein the beta chain is linked to an anti-CD3 antibody via the linker sequence of SEQ ID NO: 24 or wherein the alpha chain is linked to an anti-CD3 antibody via a linker sequence.
16. The TCR anti-CD3 fusion according to claim 15, having the alpha chain of SEQ ID NO: 32 and the beta chain of SEQ ID NO: 33.
17. The TCR anti-CD3 fusion according to claim 15, having the alpha chain of SEQ ID NO: 37 and the beta chain of SEQ ID NO: 38.
18. Nucleic acid encoding a TCR as claimed in any one of claims 1 to 9 or a TCR anti-CD3 fusion as claimed in any one of claims 10 to 17.
19. An expression vector comprising the nucleic acid of claim 18.
20. A non-naturally occurring and/or purified and/or engineered T cell, presenting a TCR as claimed in any one of claims 1 to 9 or a TCR anti-CD3 fusion as claimed in any one of claims 10 to 17.
21. A T cell, harbouring
- (a) a TCR expression vector as claimed in claim 19 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 9 or a TCR anti-CD3 fusion as claimed in any one of claims 10 to 17, and a second expression vector which comprises nucleic acid encoding the beta chain of a TCR as claimed in any of claims 1 to 9 or a TCR anti-CD3 fusion as claimed in any one of claims 10 to 17.
22. A pharmaceutical composition comprising a TCR as claimed in any one of claims 1 to 9 or a TCR anti-CD3 fusion as claimed in any one of claims 10 to 17, the nucleic acid of claim 18 or a cell as claimed in claims 20 or 21, together with one or more pharmaceutically acceptable carriers or excipients.

23. The TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion as claimed in any one of claims 10 to 17, the nucleic acid of claim 18 or cell of claim 20 or 21 for use in medicine, in a human subject.
- 5 24. Use of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21, for the manufacture of a medicament for the treatment of cancer in a human subject, wherein the cancer expresses NYESO-1 or LAGE-1A.
- 10 25. Use of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21 for the manufacture of a medicament for the treatment of a solid tumour expressing NYESO-1 or LAGE-1A in a human subject.
- 15 26. Use of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21 for the manufacture of a medicament for the treatment of non small cell lung cancer (NSCLC) in a human subject, wherein the cancer expresses NYESO-1 or LAGE-1A.
- 20 27. Use of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21 for the manufacture of a medicament for the treatment of bladder tumour in a human subject, wherein the tumour expresses NYESO-1 or LAGE-1A.
- 25 28. Use of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21 for the manufacture of a medicament for the treatment of melanoma in a human subject, wherein the melanoma expresses NYESO-1 or LAGE-1A.
- 30 29. Use of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21 for the manufacture of a medicament for the treatment of synovial sarcoma in a human subject, wherein the sarcoma expresses NYESO-1 or LAGE-1A.
- 35 30. Use according to any one of claims 24 to 29, wherein the human subject is a subject of HLA-A*02 subtype.
31. An injectable formulation suitable for administering to a human subject comprising the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion of any one of claims 10 to 17, the nucleic acid of claim 18, the cell of claim 20 or 21 or the pharmaceutical composition of claim 22.

32. The injectable formulation of claim 31, for use in medicine.

33. Use of the injectable formulation according to claim 31 for the manufacture of a medicament which is for administration by injection, such as intravenous or direct intratumoral injection.

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34. A method of producing the TCR according to any one of claims 1 to 9 or the TCR anti-CD3 fusion of any one of claims 10 to 17 comprising a) maintaining a host cell according to claim 21 under optimal conditions for expression of the nucleic acid and b) isolating the TCR or TCR anti-CD3 fusion encoded by the nucleic acid.

10

35. A combination of the TCR of any one of claims 1 to 9, the TCR anti-CD3 fusion as claimed in any one of claims 10 to 17, the nucleic acid of claim 18 or the cell of claim 20 or 21 and an anti-neoplastic agent for use in combination therapy.