

Claims:

1. A T cell receptor (TCR) having the property of binding to SLLMWITQC (SEQ ID NO: 1) HLA-A*02 complex and comprising a TCR alpha chain variable domain and/or a TCR beta chain variable domain,
- 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 amino acids 1-117 of SEQ ID NO: 2, and/or
- 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
- 10 amino acids 1-115 of SEQ ID NO: 3.
2. A TCR that binds to a SLLMWITQC (SEQ ID NO: 1) HLA-A*02 complex with an affinity greater than 50 μ M, wherein: the alpha chain CDRs 1, 2 and 3 comprise SEQ ID NO: 41, 42 and 43 respectively, and/or the beta chain CDRs 1, 2 and 3 comprise SEQ ID NO: 44, 45 and 46
- 15 respectively; and/or at least one of the CDRs contains one or more conservative substitutions with respect to SEQ ID NO: 41 to 46; and/or at least one of the CDRs contains up to three tolerated substitutions with respect to SEQ ID NO: 41 to 46.
3. A TCR as claimed in claim 1 or claim 2, wherein the alpha chain variable domain has at
- 20 least one of the following mutations with reference to the numbering of SEQ ID NO: 2:

Residue no.	
I51	L
T52	G
G53	D
D54	S
N55	A
D95	S
I96	S
N97	D or R
S98	Q
G99	H

and/or the beta chain variable domain has at least one of the following mutations with reference to the numbering of SEQ ID NO: 3:

Residue no.	
S27	K
Q28	R
V29	L
T30	A
M31	L
N50	W

Q51	T
S53	G
G100	A

4. A TCR as claimed in any one of claims 1 to 3 wherein the alpha chain variable domain has between 2 and 6 of the following mutations with reference to the numbering of SEQ ID NO: 2:

Residue no.	
I51	L
T52	G
G53	D
D54	S
N55	A
D95	S
I96	S
N97	D or R
S98	Q
G99	H

5 and / or the beta chain variable domain has between 3 and 9 of the following mutations with reference to SEQ ID NO: 3:

Residue no.	
S27	K
Q28	R
V29	L
T30	A
M31	L
N50	W
Q51	T
S53	G
G100	A

5. A TCR as claimed in any one of claims 1 to 4 wherein the alpha chain variable domain has at least one of the following groups of mutations

- 10 Group 1: I51L, T52G, G53D, D54S, N55A
 Group 2: I51L, T52G, G53D, D54S, N55A, N97D
 Group 3: I51L, T52G, G53D, D54S, N55A, N97R
 Group 4: I96S, N97D, S98Q, G99H
 Group 5: D95S, I96S, N97R, S98Q, G99H

15 Group 6: I51L, G53D

and/or the beta chain variable domain has at least one of the following groups of mutations

- Group 1: N50W, Q51T, S53G
 Group 2: S27K, Q28R, V29L, T30A, M31L, N50W, Q51T, S53G
 Group 3: S27K, Q28R, V29L, T30A, M31L, N50W, Q51T, S53G, G100A

Group 4: S27K, Q28R, V29L, T30A, N50W, Q51T

Group 5: S27K, Q28R, V29L, T30A, N50W, Q51T S53G

Group 6: S27K, Q28R, V29L, T30A, N50W, Q51T S53G, G100A.

Group 7: S27K, Q28R, V29L, T30A, M31L, N50W, Q51T

5 Group 8: T30A, N50W, G100A

6. A TCR as claimed in any one of the preceding claims wherein the alpha chain variable domain and beta chain variable domain have the following groups of mutations, respectively:

alpha chain		beta chain	
Group 1	I51L, T52G, G53D, D54S, N55A	Group 3	S27K, Q28R, V29L, T30A, M31L, N50W, Q51T, S53G, G100A
Group 1	I51L, T52G, G53D, D54S, N55A	Group 7	S27K, Q28R, V29L, T30A, M31L, N50W, Q51T
Group 3	I51L, T52G, G53D, D54S, N55A, N97R	Group 3	S27K, Q28R, V29L, T30A, M31L, N50W, Q51T, S53G, G100A
Group 3	I51L, T52G, G53D, D54S, N55A, N97R	Group 7	S27K, Q28R, V29L, T30A, M31L, N50W, Q51T

10

7. A TCR as claimed in any of the preceding claims wherein the alpha chain variable domain has at least one of the following mutations with reference to the numbering of SEQ ID NO: 2:

Residue no.	
Q10	L

and/or the beta chain variable domain has at least one of the following mutations with reference to

15 the numbering of SEQ ID NO: 3:

Residue no.	
C13	K
L43	P

8. A TCR as claimed in any of the preceding claims wherein in the alpha chain variable domain the sequence of amino acid residues 27 - 32, 50 - 57 and 91 - 107 is selected from the following:

Residues 27 - 32	Residues 50 - 57	Residues 91 - 107
VSGNPY	YITGDNLV	CAVRDSDQHAGSYQLTF
VSGNPY	YLGDSALV	CAVRDINSAGSYQLTF
VSGNPY	YITGDNLV	CAVRSSRQHAGSYQLTF
VSGNPY	YLGDSALV	CAVRDIDSGAGSYQLTF

VSGNPY	YLGDSALV	CAVRDIRSGAGSYQLTF
VSGNPY	YLTDDNLV	CAVRDINSAGAGSYQLTF

9. A TCR as claimed in claim 8 wherein 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.

5

10. A TCR as claimed in any of the preceding claims wherein in the beta chain variable domain the sequence of amino acid residues 27 - 31, 49 - 55 and 93 - 106 is selected from the following:

Residues 27 - 31	Residues 49 - 55	Residues 93 - 106
KRLAL	AWTGGEA	CSVGGSGGADTQYF
KRLAL	AWTGGEA	CSVGGSGAADTQYF
KRLAM	AWTGGEA	CSVGGSGGADTQYF
KRLAL	AWTGSEA	CSVGGSGGADTQYF
KRLAM	AWTGGEA	CSVGGSGAADTQYF
KRLAM	AWTGSEA	CSVGGSGGADTQYF
SQVTM	AWTGGEA	CSVGGSGGADTQYF
SQVAM	AWQGSEA	CSVGGSGAADTQYF

10 11. A TCR as claimed in claim 10 wherein 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 ID NO: 15.

12. A TCR as claimed in any preceding claim, wherein the alpha chain variable domain sequence of amino acids residues 27-32, 50-57 and 91-107 and the beta chain variable domain sequence of amino acid residues 27-31, 49-55 and 93-106 is selected from the following:

15

Alpha chain			Beta Chain		
27-32	50-57	91-107	27-31	49-55	93-106
VSGNPY	YLGDSALV	CAVRDINSAGAGSYQLTF	KRLAL	AWTGGEA	CSVGGSGAADTQYF
VSGNPY	YLGDSALV	CAVRDINSAGAGSYQLTF	KRLAL	AWTGSEA	CSVGGSGGADTQYF
VSGNPY	YLGDSALV	CAVRDIRSGAGSYQLTF	KRLAL	AWTGGEA	CSVGGSGAADTQYF
VSGNPY	YLGDSALV	CAVRDIRSGAGSYQLTF	KRLAL	AWTGSEA	CSVGGSGGADTQYF

13. A TCR as claimed in claim 12, wherein 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%,

20 98% or 100% identity to SEQ ID NO: 12 and 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 ID NO: 15.

14. A TCR as claimed in any of the preceding claims wherein the alpha chain variable domain
5 is selected from the amino acid sequence of SEQ ID NO: 6-12 or 51 and the beta chain variable domain is selected from the amino acid sequence of SEQ ID NO: 13-23 or 52.

15. 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

- 10 16. 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.

17. The TCR of claim 16, 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
15 of TRAC and Cys2 of exon 2 of TRBC1 or TRBC2.

18. The TCR of claim 16 or claim 17 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.

- 20 19. The TCR of 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.

20. The TCR of any preceding claim associated with a detectable label, a therapeutic agent or a PK modifying moiety.

- 25 21. 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.

22. The TCR anti-CD3 fusion of claim 21, comprising an alpha chain variable domain selected from SEQ ID NO: 6-12 or 51 and comprising a beta chain variable domain selected from SEQ ID NO: 13-23 or 52.

23. The TCR anti-CD3 fusion of claim 22, wherein the beta chain is linked to the anti-CD3 antibody sequence via a linker sequence.

24. The TCR anti-CD3 fusion of claim 23, wherein the linker sequence is selected from the group consisting of GGGGS (SEQ ID NO: 24), GGGSG (SEQ ID NO: 25), GSGGG (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).

25. The TCR anti-CD3 fusion of claim 24 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

26. A TCR anti-CD3 fusion according to claim 25 comprising an alpha chain consisting of SEQ ID NO: 37 and a beta chain consisting of SEQ ID NO: 38

27. A TCR anti-CD3 fusion of any one of claims 21 to 24 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.

28. A TCR anti-CD3 fusion of any one of claims 21 to 24 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 alpha chain is linked to an anti-CD3 antibody via a linker sequence.

29. A TCR anti-CD3 fusion according to claim 28, wherein the alpha chain variable domain consists of the amino acid sequence of SEQ ID NO: 12 and the beta chain variable domain consists of the amino acid sequence of SEQ ID NO: 15 and wherein the beta chain is linked to an anti-CD3 antibody via the linker sequence of SEQ ID NO: 24.

30. Nucleic acid encoding a TCR or a TCR anti-CD3 fusion as claimed in any one of the preceding claims.

31. An expression vector comprising the nucleic acid of claim 30.

32. A non-naturally occurring and/or purified and/or engineered cell presenting a TCR as claimed in any one of claims 1 to 20 or a TCR anti-CD3 fusion as claimed in any one of claims 21-29.
33. A cell harbouring
- 5 (a) a TCR expression vector as claimed in claim 31 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 20 or a TCR anti-CD3 fusion as claimed in any one of claims 21-29, and a second expression vector which comprises nucleic acid encoding the beta
- 10 chain of a TCR as claimed in any of claims 1 to 20 or a TCR anti-CD3 fusion as claimed in any one of claims 21-29.
34. The cell according to claim 32 or 33 which is a T-cell.
- 15 35. A pharmaceutical composition comprising a TCR as claimed in any one of claims 1 to 20 or a TCR anti-CD3 fusion as claimed in any one of claims 21-29, the nucleic acid of claim 30 or a cell as claimed in any one of claims 32 to 34, together with one or more pharmaceutically acceptable carriers or excipients.
- 20 36. The TCR of any one of claims 1 to 20 or a TCR anti-CD3 fusion as claimed in any one of claims 21-29, nucleic acid of claim 30 or cell of any one of claims 32 to 34 for use in medicine, in a human subject.
- 25 37. A method of treating a human subject in need thereof comprising administering to said subject a pharmaceutically effective dose of a pharmaceutical composition according to claim 35.
- 30 38. The TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29, the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35, for use in a method of treating cancer in a human subject.
- 35 39. The TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29, the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35 for use according to claim 38, wherein the human subject has a tumour that expresses NY-ESO-1 and/or LAGE-1A.

40. The TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29, the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35 for use according to claim 39, wherein the tumour is a solid tumour.
- 5 41. The TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29, the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35 for use according to claim 39 or 40, wherein the tumour is selected from a synovial sarcoma, non small cell lung carcinoma (NSCLC), bladder tumour, gastric tumour, prostate tumour, colorectal tumour, breast tumour, ovarian tumour, oesophageal tumour, melanoma, multiple
10 myeloma, hepatocellular carcinoma and head and neck tumour.
42. The TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29, the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35 for use according to any one of claim 38 to 41, wherein the human subject is a subject of
15 HLA-A*02 subtype.
43. A method of treating a human subject according to claim 37 which further comprises administering separately, in combination or sequentially an anti-neoplastic agent.
- 20 44. An injectable formulation for administering to a human subject comprising a TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29, the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35.
45. A TCR of any one of claims 1 to 20, the TCR anti-CD3 fusion of any one of claims 21 to 29,
25 the nucleic acid of claim 30, the cell of any one of claims 32 to 34 or the pharmaceutical composition of claim 35 for use according to claim 36 or claims 38 to 42, wherein the TCR, TCR anti-CD3 fusion, the nucleic acid, the cell or the pharmaceutical composition is administered by injection, such as intravenous or direct intratumoral injection.
- 30 46. A method of producing a TCR according to any one of claims 1 to 20 or the TCR anti-CD3 fusion of any one of claims 21 to 29 comprising a) maintaining a host cell according to claim 33 under optimal conditions for expression of the nucleic acid and b) isolating the TCR or TCR anti-CD3 fusion encoded by the nucleic acid.