

SUMMARY

In one aspect, the present disclosure relates to a T cell receptor (TCR) capable of binding to a polypeptide comprising an amino acid sequence according to amino acid sequence LYVDSLFFL (SEQ ID NO: 2) wherein not more than 4 amino acids have been substituted, or to a portion of said polypeptide, or to the respective HLA-A bound form of said polypeptide or portion thereof, wherein the TCR comprises:

(A) a CDR3

(Aa) of the TCR alpha chain comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 12, and/or

(Ab) of the TCR beta chain comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 14,

or

(B) a CDR3

(Ba) of the TCR alpha chain comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 40, and/or

(Bb) of the TCR beta chain comprising of an amino acid sequence being at least 80 % similar to SEQ ID NO: 42.

In another aspect, the present disclosure relates to a nucleic acid molecule encoding the TCR as described herein. In yet another aspect, the present disclosure relates to a vector comprising the nucleic acid molecule as described herein. In yet another aspect, the present disclosure relates to a host cell comprising the TCR as described herein, the nucleic acid molecule as described herein or the vector as described herein.

In a further aspect, the present disclosure relates to a pharmaceutical or diagnostic composition comprising one or more of:

(i) the TCR as described herein;

(ii) the nucleic acid molecule as described herein;

(iii) the vector as described herein; and/or

(iv) the host cell as described herein,

and, optionally, pharmaceutically excipient(s).

In a further aspect, the present disclosure relates to the TCR as described herein, the nucleic acid molecule as described herein, the vector as described herein and/or the host cell as described herein for use as a medicament.

In a further aspect, the present disclosure relates to a use of the TCR as described herein, the nucleic acid molecule as described herein, the vector as described herein and/or the host cell as described herein in the manufacture of a medicament for the detection, diagnosis, prognosis, prevention and/or treatment of cancer.

The present invention relates to a T cell receptor (TCR) capable of binding to a polypeptide comprising or consisting of an amino acid sequence according to amino acid sequence LYVDSLFFL (SEQ ID NO: 2) wherein not more than 4 amino acids have been substituted, or

to a portion of said polypeptide, or

to the respective HLA-A bound form of said polypeptide or portion thereof,

wherein the TCR comprises:

(A) a CDR3

(Aa) of the TCR alpha chain comprising or consisting of an amino acid sequence being at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similar or identical (preferably identical), or preferably being 100% similar or identical (preferably identical) to SEQ ID NO: 12, and/or

(Ab) of the TCR beta chain comprising or consisting of an amino acid sequence being at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similar or identical, or preferably being 100% similar or identical (preferably identical) to SEQ ID NO: 14,

or

(B) a CDR3

(Ba) of the TCR alpha chain comprising or consisting of an amino acid sequence being at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similar or identical (preferably identical), or preferably being 100% similar or identical (preferably identical) to SEQ ID NO: 40, and/or

(Bb) of the TCR beta chain comprising or consisting of an amino acid sequence being at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similar or identical, or preferably being 100% similar or identical (preferably identical) to SEQ ID NO: 42.

As has surprisingly been found in context with the present invention, a portion of the PRAME peptide, i.e. a polypeptide comprising or consisting of an amino acid sequence according to amino acid sequence LYVDSLFFL (SEQ ID NO: 2; PRAME₃₀₁₋₃₀₉) wherein not more than 4 amino acids have been substituted, is presented by cells via human leukocyte antigen class A (HLA-A) and effectively recognized by a TCR as described and provided herein. Binding of a cell comprising a TCR of the present invention to said polypeptide leads to significant IFN-gamma (IFN- γ) secretion and effective killing of such polypeptide-loaded cells by T-cells transduced with a TCR of the present invention. The polypeptide comprising or consisting of an amino acid sequence according to amino acid sequence LYVDSLFFL (SEQ ID NO: 2;

Claims

1. A T cell receptor (TCR) capable of binding to
a polypeptide comprising an amino acid sequence according to amino acid sequence
LYVDSLFFL (SEQ ID NO: 2) wherein not more than 4 amino acids have been
substituted, or
to a portion of said polypeptide, or
to the respective HLA-A bound form of said polypeptide or portion thereof,
wherein the TCR comprises:
 - (A) a CDR3
 - (Aa) of the TCR alpha chain comprising an amino acid sequence being at
least 80 % similar to SEQ ID NO: 12, and/or
 - (Ab) of the TCR beta chain comprising an amino acid sequence being at least
80 % similar to SEQ ID NO: 14,
 - or
 - (B) a CDR3
 - (Ba) of the TCR alpha chain comprising an amino acid sequence being at
least 80 % similar to SEQ ID NO: 40, and/or
 - (Bb) of the TCR beta chain comprising of an amino acid sequence being at
least 80 % similar to SEQ ID NO: 42.
2. The TCR according to claim 1,
wherein said TCR comprising a CDR3 according to (A) further comprises
 - (Aa1) a CDR1 of the TCR alpha chain comprising an amino acid sequence being at
least 80 % similar to the amino acid sequence of SEQ ID NO: 4, and/or a CDR2
of the TCR alpha chain comprising an amino acid sequence being at least 80
% similar to the amino acid sequence of SEQ ID NO: 8,
and/or
 - (Ab1) a CDR1 of the TCR beta chain comprising an amino acid sequence being at
least 80 % similar to the amino acid sequence of SEQ ID NO: 6, and/or a CDR2
of the TCR beta chain comprising an amino acid sequence being at least 80 %
similar to the amino acid sequence of SEQ ID NO: 10,or wherein said TCR comprising a CDR3 according to (B) further comprises
 - (Ba1) a CDR1 of the TCR alpha chain comprising an amino acid sequence being at
least 80 % similar to the amino acid sequence of SEQ ID NO: 32, and/or a
CDR2 of the TCR alpha chain comprising an amino acid sequence being at
least 80 % similar to the amino acid sequence of SEQ ID NO: 36,

and/or

(Bb1) a CDR1 of the TCR beta chain comprising an amino acid sequence being at least 80 % similar to the amino acid sequence of SEQ ID NO: 34, and/or a CDR2 of the TCR beta chain comprising an amino acid sequence being at least 80 % similar to the amino acid sequence of SEQ ID NO: 38.

3. The TCR according to claims 1 or 2, wherein the HLA-A is an HLA-A*24, or HLA-A*02 encoded molecule.
4. The TCR according to any one of the preceding claims, wherein binding of said TCR to said polypeptide, or a portion thereof, or its HLA-A bound form, induces IFN-gamma secretion by cells comprising said TCR.
5. The TCR according to claim 4, wherein said induction of IFN-gamma secretion of cells comprising said TCR is at least 5-fold higher compared to control cells not comprising said TCR upon binding to a polypeptide comprising an amino acid sequence according to amino acid sequence LYVDSLFFL (SEQ ID NO: 2) wherein not more than 4 amino acids have been substituted, or to a portion of said polypeptide, or to the respective HLA-A bound form of said polypeptide or portion thereof.
6. The TCR according to any of the preceding claims, wherein said TCR comprising a CDR3 according to (A) comprises
 - (Aa2) a TCR alpha chain variable region
comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 16, and
comprising an amino acid sequence being at least 80% similar to positions 47 to 51 of SEQ ID NO: 16, and
comprising an amino acid sequence being at least 80% similar to positions 69 to 75 of SEQ ID NO: 16, and
comprising an amino acid sequence being at least 80% similar to positions 109 to 123 of SEQ ID NO: 16,
and/or
 - (Ab2) a TCR beta chain variable region
comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 18, and
comprising an amino acid sequence being at least 80% similar to positions 46 to 50 of SEQ ID NO: 18, and

comprising an amino acid sequence being at least 80% similar to positions 68 to 73 of SEQ ID NO: 18, and
comprising an amino acid sequence being at least 80% similar to positions 110 to 122 of SEQ ID NO: 18,

or

wherein said TCR comprising a CDR3 according to (B) comprises

(Ba2) a TCR alpha chain variable region

comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 44, and

comprising an amino acid sequence being at least 80% similar to positions 45 to 49 of SEQ ID NO: 44, and

comprising an amino acid sequence being at least 80% similar to positions 67 to 73 of SEQ ID NO: 44, and

comprising an amino acid sequence being at least 80% similar to positions 107 to 121 of SEQ ID NO: 44,

and/or

(Bb2) a TCR beta chain variable region

comprising the amino acid sequence being at least 80 % similar to SEQ ID NO: 46, and

comprising an amino acid sequence being at least 80% similar to positions 44 to 49 of SEQ ID NO: 46, and

comprising an amino acid sequence being at least 80% similar to positions 67 to 71 of SEQ ID NO: 46, and

comprising an amino acid sequence being at least 80% similar to positions 108 to 122 of SEQ ID NO: 46.

7. The TCR according to any of the preceding claims,
wherein said TCR comprising a CDR3 according to (A) comprises

(Aa3) a TCR alpha chain

comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 20, and

comprising an amino acid sequence being at least 80% similar to positions 47 to 51 of SEQ ID NO: 20, and

comprising an amino acid sequence being at least 80% similar to positions 69 to 75 of SEQ ID NO: 20, and

comprising an amino acid sequence being at least 80% similar to positions 109 to 123 of SEQ ID NO: 20,
and/or

(Ab3) a TCR beta chain

comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 22, and

comprising an amino acid sequence being at least 80% similar to positions 46 to 50 of SEQ ID NO: 22, and

comprising an amino acid sequence being at least 80% similar to positions 68 to 73 of SEQ ID NO: 22, and

comprising an amino acid sequence being at least 80% similar to positions 110 to 122 of SEQ ID NO: 22,

or

wherein said TCR comprising a CDR3 according to (B) comprises

(Ba3) a TCR alpha chain

comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 48, and

comprising an amino acid sequence being at least 80% similar to positions 45 to 49 of SEQ ID NO: 48, and

comprising an amino acid sequence being at least 80% similar to positions 67 to 73 of SEQ ID NO: 48, and

comprising an amino acid sequence being at least 80% similar to positions 107 to 121 of SEQ ID NO: 48,

and/or

(Bb3) a TCR beta chain

comprising an amino acid sequence being at least 80 % similar to SEQ ID NO: 50, and

comprising an amino acid sequence being at least 80% similar to positions 44 to 49 of SEQ ID NO: 50, and

comprising an amino acid sequence being at least 80% similar to positions 67 to 71 of SEQ ID NO: 50, and

comprising an amino acid sequence being at least 80% similar to positions 108 to 122 of SEQ ID NO: 50.

8. The TCR according to any of the preceding claims, comprising

(A) at least one TCR alpha chain or subregion thereof according to (Aa), (Aa1), (Aa2) or (Aa3), and

- at least one TCR beta chain or subregion thereof according to (Ab), (Ab1), (Ab2) or (Ab3),
covalently linked to each other to form a TCR heterodimer or multimer,
- or
- (B) at least one TCR alpha chain or subregion thereof according to (Ba), (Ba1), (Ba2) or (Ba3), and
at least one TCR beta chain or subregion thereof according to (Bb), (Bb1), (Bb2) or (Bb3),
covalently linked to each other to form a TCR heterodimer or multimer.
9. A nucleic acid molecule encoding the TCR according to any one of the preceding claims.
 10. The nucleic acid according to claim 9, comprising the nucleic acid sequence being at least 80% identical to the nucleic acid sequence of any one of SEQ ID NOs: 3, 5, 7, 9, 11, 13, 15, 17, 19, or 21; or being at least 80% identical to the nucleic acid sequence of any one of SEQ ID NOs: 31, 33, 35, 37, 39, 41, 43, 45, 47, or 49.
 11. A vector comprising the nucleic acid molecule according to claims 9 or 10.
 12. A host cell comprising the TCR according to any one of claims 1 to 8, the nucleic acid molecule according to claim 9 or 10 or the vector according to claim 11.
 13. A pharmaceutical or diagnostic composition comprising one or more of:
 - (i) the TCR according to any one of claims 1 to 8;
 - (ii) the nucleic acid molecule according to claim 9 or 10;
 - (iii) the vector according to claim 11; and/or
 - (iv) the host cell according to claim 12,
 and, optionally, pharmaceutically excipient(s).
 14. The TCR according to any one of claims 1 to 8, the nucleic acid molecule according to claim 9 or 10, the vector according to claim 11 and/or the host cell according to claim 12 for use as a medicament.
 15. Use of tThe TCR according to any one of claims 1 to 8, the nucleic acid molecule according to claim 9 or 10, the vector according to claim 11 and/or the host cell

according to claim 12 in the manufacture of a medicament for ~~use in~~the detection, diagnosis, prognosis, prevention and/or treatment of cancer.