Antibodies which target intracellular targets abnormally expressed by MHC class I molecules during cancer have been developed by different groups. However, these antibodies focus mostly on HLA*A02 which is the predominant allele in Caucasians, for instance among the 14 most common HLA*A types in Europe HLA*A02 represent ~30%. HLA-A distribution in Asia is more scattered, and HLA*A24 and HLA*A11 are common alleles too.

Summary

In one aspect, the present disclosure refers to an antibody or antigen binding fragment, optionally isolated, which is capable of binding to a peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele;

wherein the antibody or antigen binding fragment comprises:

(i) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)

LC-CDR2: GNTNRPS (SEQ ID NO:18)

LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWS (SEQ ID NO:32)

HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)

HC-CDR3: ENFGAFDH (SEQ ID NO:34); or

(ii) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)

LC-CDR2: GNTNRPS (SEQ ID NO:18)

LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWA (SEQ ID NO:35)

HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)

HC-CDR3: ENFGAFDH (SEQ ID NO:34); or

(iii) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: SGGYYWS (SEQ ID NO:32)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGSYDY (SEQ ID NO:36); or
(iv) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: SGGYYWA (SEQ ID NO:35)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGSYDY (SEQ ID NO:36); or
(v) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: AGSYSNIGDDYETH (SEQ ID NO:20)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: SGGYYWS (SEQ ID NO:32)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGAFDH (SEQ ID NO:34); or
(vi) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: AGSYSNIGDDYETH (SEQ ID NO:20)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: SGGYYWA (SEQ ID NO:35)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGSYDY (SEQ ID NO:36); or
(vii) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: RASQSIGTDLA (SEQ ID NO:21)
LC-CDR2: DASNRAT (SEQ ID NO:22)
LC-CDR3: QQRSNWPPT (SEQ ID NO:23); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: GYYMH (SEQ ID NO:37)
HC-CDR2: WINPNSAGTNYAQKFQG (SEQ ID NO:38)
HC-CDR3: EGADGIYYFDY (SEQ ID NO:39); or
(viii) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: TGSSSNIGAGYDVH (SEQ ID NO:24)
LC-CDR2: GNNNRPS (SEQ ID NO:25)
LC-CDR3: QSYDSNLSDTWV (SEQ ID NO:26); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: SGGYYWS (SEQ ID NO:40)

HC-CDR2: YIYYSGTTYYNPSLKS (SEQ ID NO:41)
HC-CDR3: ENFGAFDY (SEQ ID NO:42); or
(ix) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: TGSSSNIGAGYDVN (SEQ ID NO:27)
LC-CDR2: GNNNRPS (SEQ ID NO:25)
LC-CDR3: QSYDSSLSAWV (SEQ ID NO:28); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: SGGYYWS (SEQ ID NO:32)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGAFDH (SEQ ID NO:34); or
(x) at least one light chain variable region incorporating the following CDRs:
LC-CDR1: TGTSSDVGGYNYVS (SEQ ID NO:29)
LC-CDR2: DVSSRPS (SEQ ID NO:30)
LC-CDR3: SSYTVFSTLV (SEQ ID NO:31); and
at least one heavy chain variable region incorporating the following CDRs:
HC-CDR1: DYYIH (SEQ ID NO:43)
HC-CDR2: WMSPDSGATYYAQKFQG (SEQ ID NO:44)
HC-CDR3: DTYGHDY (SEQ ID NO:45).

In yet another aspect, there is provided a chimeric antigen receptor (CAR) comprising an antigen binding fragment as disclosed herein. In yet another aspect, there is provided an *in vitro* complex, optionally isolated, comprising an antibody, antigen binding fragment or CAR as disclosed herein bound to a peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele. In a further aspect, the present disclosed refers to a composition comprising the antibody, antigen binding fragment or CAR according to the present disclosure and at least one pharmaceutically-acceptable carrier. In still another aspect, the present disclosure refers to an isolated nucleic acid encoding the antibody, antigen binding fragment or CAR as disclosed herein. In another aspect, there is also provided a vector comprising the nucleic acid as disclosed herein. In another aspect, there is also provided a cell comprising the nucleic acid or the vector as disclosed herein. In yet another aspect, the present invention refers to a method for making an antibody, antigen binding fragment or CAR according to the present disclosure, comprising culturing the cell as disclosed herein under conditions suitable for the expression of the antibody or antigen binding fragment or CAR. In a further aspect, there is also provided an antibody, antigen binding fragment, CAR or composition according to the present disclosure for use in therapy, or in a method of medical treatment. Another aspect of the present disclosure refers to the use of an antibody, antigen binding fragment, CAR or composition according to the present invention in the manufacture of a medicament for treating or preventing a cancer. In yet another aspect, there is provided a method comprising: modifying at least one immune cell isolated from a subject to express or comprise the antibody, antigen binding fragment, CAR, nucleic acid or vector according to the present disclosure, wherein the subject is in need of treatment or prevention of a cancer; and wherein the modified at least one immune cell is to be administered to a subject. In still another aspect, the present disclosure refers to a method comprising: introducing into at least one immune cell isolated from a subject the nucleic acid according to the present disclosure, wherein

the subject is in need of treatment or prevention of a cancer, thereby modifying the at least one immune cell; and wherein the modified at least one immune cell is to be administered to a subject. In yet another aspect, there is also provided a kit of parts comprising a predetermined quantity of the antibody, antigen binding fragment, CAR, composition, nucleic acid, vector or cell as disclosed herein. In yet another aspect, the present disclosure refers to a method of diagnosing a disease or a condition in a subject, the method comprising contacting a sample containing, or suspected to contain, peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele with an antibody or antigen binding fragment as disclosed herein and

Claims:

1. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to a peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele;

wherein the antibody or antigen binding fragment comprises:

(i) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWS (SEQ ID NO:32)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGAFDH (SEQ ID NO:34); or

(ii) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWA (SEQ ID NO:35)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGAFDH (SEQ ID NO:34); or

(iii) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWS (SEQ ID NO:32)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGSYDY (SEQ ID NO:36); or

(iv) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGADYETH (SEQ ID NO:17)
LC-CDR2: GNTNRPS (SEQ ID NO:18)
LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWA (SEQ ID NO:35)
HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)
HC-CDR3: ENFGSYDY (SEQ ID NO:36); or

(v) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: AGSYSNIGDDYETH (SEQ ID NO:20)
LC-CDR2: GNTNRPS (SEQ ID NO:18)

LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWS (SEQ ID NO:32)

HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)

HC-CDR3: ENFGAFDH (SEQ ID NO:34); or

(vi) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: AGSYSNIGDDYETH (SEQ ID NO:20)

LC-CDR2: GNTNRPS (SEQ ID NO:18)

LC-CDR3: QSYDSNLSAWV (SEQ ID NO:19); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWA (SEQ ID NO:35)

HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)

HC-CDR3: ENFGSYDY (SEQ ID NO:36); or

(vii) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: RASQSIGTDLA (SEQ ID NO:21)

LC-CDR2: DASNRAT (SEQ ID NO:22)

LC-CDR3: QQRSNWPPT (SEQ ID NO:23); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: GYYMH (SEQ ID NO:37)

HC-CDR2: WINPNSAGTNYAQKFQG (SEQ ID NO:38)

HC-CDR3: EGADGIYYFDY (SEQ ID NO:39); or

(viii) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGAGYDVH (SEQ ID NO:24)

LC-CDR2: GNNNRPS (SEQ ID NO:25)

LC-CDR3: QSYDSNLSDTWV (SEQ ID NO:26); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWS (SEQ ID NO:40)

HC-CDR2: YIYYSGTTYYNPSLKS (SEQ ID NO:41)

HC-CDR3: ENFGAFDY (SEQ ID NO:42); or

(ix) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGSSSNIGAGYDVN (SEQ ID NO:27)

LC-CDR2: GNNNRPS (SEQ ID NO:25)

LC-CDR3: QSYDSSLSAWV (SEQ ID NO:28); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SGGYYWS (SEQ ID NO:32)

HC-CDR2: YIYYSGSTYYNPSLKS (SEQ ID NO:33)

HC-CDR3: ENFGAFDH (SEQ ID NO:34); or

(x) at least one light chain variable region incorporating the following CDRs:

LC-CDR1: TGTSSDVGGYNYVS (SEQ ID NO:29)

LC-CDR2: DVSSRPS (SEQ ID NO:30)

LC-CDR3: SSYTVFSTLV (SEQ ID NO:31); and

at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: DYYIH (SEQ ID NO:43)

HC-CDR2: WMSPDSGATYYAQKFQG (SEQ ID NO:44)
HC-CDR3: DTYGHDY (SEQ ID NO:45).

2. The antibody or antigen binding fragment according to claim 1, wherein the antibody or antigen binding fragment comprises:

(i) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:1, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:8; or

(ii) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:2, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:9; or

(iii) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:2, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:12; or

(iv) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:2, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:10; or

(v) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:2, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:11; or

(vi) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:3, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:9; or

(vii) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:3, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:12; or

(viii) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:5, and a heavy chain variable region having at

least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:14; or

(ix) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:4, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:13; or

(x) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:6, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:15; or

(xi) a light chain variable region having at least 70% amino acid sequence identity to the light chain variable region of SEQ ID NO:7, and a heavy chain variable region having at least 70% amino acid sequence identity to the heavy chain variable region of SEQ ID NO:16.

3. The antibody or antigen binding fragment according to claim 1 or claim 2, which displays antibody-dependent cell-mediated cytotoxicity (ADCC) to cells comprising or expressing peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele.

4. The antibody or antigen binding fragment according to any one of claims 1 to 3, which is internalised by cells comprising or expressing peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele.

5. The antibody or antigen binding fragment according to any one of claims 1 to 4, which is a fully human antibody or a fully human antibody fragment.

6. The antibody or antigen binding fragment according to any one of claims 1 to 5, conjugated to a drug moiety or a detectable moiety.

7. The antibody or antigen binding fragment according to any one of claims 1 to 6, further comprising an antibody or antigen binding fragment specific for a target other than a peptide-MHC complex.

8. The antibody or antigen binding fragment according to claim 7, wherein the target other than a peptide-MHC complex is an immune cell surface molecule.

9. A chimeric antigen receptor (CAR) comprising an antigen binding fragment according to any one of claims 1 to 8.

10. An *in vitro* complex, optionally isolated, comprising an antibody, antigen binding fragment or CAR according to any one of claims 1 to 9 bound to a peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele.

11. A composition comprising the antibody, antigen binding fragment or CAR according to any one of claims 1 to 9 and at least one pharmaceutically-acceptable carrier.

12. An isolated nucleic acid encoding the antibody, antigen binding fragment or CAR according to any one of claims 1 to 9.

13. A vector comprising the nucleic acid of claim 12.

14. A cell comprising the nucleic acid according to claim 12 or the vector according to claim 13.

15. A method for making an antibody, antigen binding fragment or CAR according to any one of claims 1 to 9, comprising culturing the cell of claim 14 under conditions suitable for the expression of the antibody or antigen binding fragment or CAR.

16. An antibody, antigen binding fragment, CAR or composition according to any one of claims 1 to 9 or 11, for use in therapy, or in a method of medical treatment.

17. Use of an antibody, antigen binding fragment, CAR or composition according to any one of claims 1 to 9 or 11, in the manufacture of a medicament for treating or preventing a cancer.

18. A method comprising: modifying at least one immune cell isolated from a subject to express or comprise the antibody, antigen binding fragment, CAR, nucleic acid or vector according to any one of claims 1 to 9, or 12 to 13, wherein the subject is in need of treatment or prevention of a cancer; and wherein the modified at least one immune cell is to be administered to a subject.

19. A method comprising: introducing into at least one immune cell isolated from a subject the nucleic acid according to claim 12 or the vector according to claim 13, wherein the subject is in need of treatment or prevention of a cancer, thereby modifying the at least one immune cell; and wherein the modified at least one immune cell is to be administered to a subject.

20. A kit of parts comprising a predetermined quantity of the antibody, antigen binding fragment, CAR, composition, nucleic acid, vector or cell according to any one of claims 1 to 9, or 11 to 14.

21. A method of diagnosing a disease or a condition in a subject, the method comprising contacting a sample containing, or suspected to contain, peptide-MHC complex comprising: (i) a peptide of p53 comprising or consisting of the amino acid sequence of SEQ ID NO:75, and (ii) an MHC class I molecule comprising an MHC class I α-chain encoded by an HLA-A*24 allele with an antibody or antigen binding fragment according to any one of claims 1 to 9 and detecting the formation of a complex of antibody, or antigen binding fragment, and the peptide-MHC complex.