

T CELL RECEPTORS RECOGNIZING MUTATED P53

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/565,383, filed September 29, 2017, which is incorporated by reference in its entirety herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under project number BC010985 by the National Institutes of Health, National Cancer Institute. The Government has certain rights in the invention.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0003] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 687,555 Byte ASCII (Text) file named “739980_ST25.txt,” dated September 7, 2018.

BACKGROUND OF THE INVENTION

[0004] Some cancers may have very limited treatment options, particularly when the cancer becomes metastatic and unresectable. Despite advances in treatments such as, for example, surgery, chemotherapy, and radiation therapy, the prognosis for many cancers, such as, for example, pancreatic, colorectal, lung, endometrial, ovarian, and prostate cancers, may be poor. Accordingly, there exists an unmet need for additional treatments for cancer.

BRIEF SUMMARY

[0005] In one aspect, the present disclosure provides an isolated or purified T cell receptor (TCR) having antigenic specificity for mutated human p53 with the R175H mutation, wherein the TCR comprises:

(1) the alpha chain complementarity determining region (CDR) 1 amino acid sequence of SEQ ID NO: 67, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 68, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 69, the beta chain CDR1 amino acid sequence of SEQ ID NO: 70, the beta chain CDR2 amino acid sequence of SEQ ID NO: 71, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 72;

2) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 77, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 78, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 79, the beta chain CDR1 amino acid sequence of SEQ ID NO: 80, the beta chain CDR2 amino acid sequence of SEQ ID NO: 81, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 82;

(3) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 87, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 88, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 89, the beta chain CDR1 amino acid sequence of SEQ ID NO: 90, the beta chain CDR2 amino acid sequence of SEQ ID NO: 91, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 92;

(4) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 487, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 488, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 489, the beta chain CDR1 amino acid sequence of SEQ ID NO: 490, the beta chain CDR2 amino acid sequence of SEQ ID NO: 491, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 492. An example of the disclosure provides an isolated or purified T cell receptor (TCR) having antigenic specificity for mutated human p53.

[0005a] In another aspect, the present disclosure provides an isolated or purified polypeptide comprising a functional portion of the TCR as described herein, wherein the functional portion comprises:

(1) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 67, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 68, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 69, the beta chain CDR1 amino acid sequence of SEQ ID NO: 70, the beta chain CDR2 amino acid sequence of SEQ ID NO: 71, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 72;

(2) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 77, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 78, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 79, the beta chain CDR1 amino acid sequence of SEQ ID NO: 80, the beta

chain CDR2 amino acid sequence of SEQ ID NO: 81, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 82;

(3) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 87, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 88, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 89, the beta chain CDR1 amino acid sequence of SEQ ID NO: 90, the beta chain CDR2 amino acid sequence of SEQ ID NO: 91, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 92; or

(4) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 487, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 488, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 489, the beta chain CDR1 amino acid sequence of SEQ ID NO: 490, the beta chain CDR2 amino acid sequence of SEQ ID NO: 491, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 492.

[0005b] In yet another aspect, the present disclosure provides an isolated or purified protein comprising a functional portion of a TCR having antigenic specificity for human p53 with the R175H mutation, wherein the functional portion comprises:

(1) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 67, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 68, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 69 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 70, the beta chain CDR2 amino acid sequence of SEQ ID NO: 71, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 72;

(2) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 77, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 78, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 79 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 80, the beta chain CDR2 amino acid sequence of SEQ ID NO: 81, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 82;

(3) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 87, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 88, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 89 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 90, the beta chain

CDR2 amino acid sequence of SEQ ID NO: 91, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 92; or

(4) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 487, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 488, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 489 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 490, the beta chain CDR2 amino acid sequence of SEQ ID NO: 491, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 492.

[0005c] In yet another aspect, the present disclosure provides an isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR as described herein, the polypeptide as described herein, or the protein as described herein. In yet another aspect, the present disclosure provides a recombinant expression vector comprising the nucleic acid as described herein. In a further aspect, the present disclosure provides an isolated or purified host cell comprising the recombinant expression vector as described herein. In a further aspect, the present disclosure provides an isolated or purified population of cells comprising the host cell as described herein.

[0005d] In yet another aspect, the present disclosure provides a pharmaceutical composition comprising (a) the TCR as described herein, the polypeptide as described herein, the protein as described herein, the nucleic acid as described herein, the recombinant expression vector as described herein, the host cell as described herein, or the population of cells as described herein and (b) a pharmaceutically acceptable carrier.

[0005e] In yet another aspect, the present disclosure provides a method of detecting the presence of cancer in mammal, the method comprising: (a) contacting a sample comprising cells of the cancer with the TCR as described herein, the polypeptide as described herein, the protein as described herein, the nucleic acid as described herein, the recombinant expression vector as described herein, the host cell as described herein, the population of cells as described herein, or the pharmaceutical composition as described herein, thereby forming a complex; and (b) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal.

[0005f] In yet another aspect, the present disclosure provides a use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing cancer in a

mammal, which comprises the TCR as described herein, the polypeptide as described herein, the protein as described herein, the nucleic acid as described herein, the recombinant expression vector as described herein, the host cell as described herein, or the population of cells as described herein.

[0006] Further examples of the disclosure provide related polypeptides and proteins, as well as related nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the TCRs of the disclosure.

[0007] Still further examples of the disclosure provide methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0008] Figure 1 is a graph showing the concentration of IFN- γ (pg/mL) measured following co-culture of autologous PBL transduced with one of the indicated TCRs from patient 4127 following co-culture with autologous dendritic cells (DCs) pulsed with either WT p53-G245 peptide (wt) (unshaded bars) or mutated p53-G245S peptide (mut) (shaded bars) at the indicated decreasing peptide concentrations (μ g/mL).

[0009] Figure 2 is a graph showing the percentage of 4-1BB positive cells (% of CD4+ mTCR β +) detected following co-culture of autologous PBL transduced with one of the indicated TCRs from patient 4127 with autologous DCs pulsed with either WT p53-G245 peptide (wt) (unshaded bars) or mutated p53-G245S peptide (mut) (shaded bars) at the indicated decreasing peptide concentrations (μ g/mL).

[0010] Figure 3 is a graph showing the percentage of 4-1BB positive cells (% of CD4+ mTCR β +) detected following co-culture of autologous PBL transduced with one of the indicated TCRs from patient 4127 with autologous DCs pulsed with one of the peptides shown in Table A.

[0011] Figure 4 is a graph showing the concentration of IFN- γ (pg/mL) measured following co-culture of TIL from patient 4127 or T cells transduced with one of the indicated TCRs with COS7 cells which were transduced with one of the indicated HLA alleles and pulsed with DMSO or one of the indicated peptides.

[0012] Figure 5 is a graph showing the percentage of 4-1BB positive cells (% of CD4+ mTCR β +) detected following co-culture of TIL from patient 4127 or T cells which were transduced with one of the indicated TCRs with COS7 cells which were transduced with one of the indicated HLA alleles and pulsed with DMSO or one of the indicated peptides.

[0013] Figure 6 is a graph showing the number of spots per 2×10^4 effector cells measured following co-culture of TIL from patient 4127 with allogeneic (DRB3*01:01:01 or DRB3*02:02:01) APCs which were (1) electroporated with TMG composed of irrelevant (IRR; left hatched open bars), WT p53 (p53-WT; left hatched gray bars) or mutated p53 (p53-MUT; gray bars) sequence or (2) pulsed with peptide vehicle (DMSO; right hatched open bars) or purified (>95% by HPLC) 25-amino acid peptides composed of WT p53-G245

CLAIMS

1. An isolated or purified T cell receptor (TCR) having antigenic specificity for mutated human p53 with the R175H mutation, wherein the TCR comprises:

(1) the alpha chain complementarity determining region (CDR) 1 amino acid sequence of SEQ ID NO: 67, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 68, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 69, the beta chain CDR1 amino acid sequence of SEQ ID NO: 70, the beta chain CDR2 amino acid sequence of SEQ ID NO: 71, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 72;

(2) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 77, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 78, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 79, the beta chain CDR1 amino acid sequence of SEQ ID NO: 80, the beta chain CDR2 amino acid sequence of SEQ ID NO: 81, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 82;

(3) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 87, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 88, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 89, the beta chain CDR1 amino acid sequence of SEQ ID NO: 90, the beta chain CDR2 amino acid sequence of SEQ ID NO: 91, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 92; or

(4) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 487, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 488, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 489, the beta chain CDR1 amino acid sequence of SEQ ID NO: 490, the beta chain CDR2 amino acid sequence of SEQ ID NO: 491, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 492.

2. The TCR of claim 1, wherein the TCR comprises:

(1) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 73, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(2) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 83, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84;

(3) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 93, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 94; or

(4) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 493, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 494;

(5) an amino acid sequence at least 95% identical to amino acids 21-131 of SEQ ID NO: 73, and an amino acid sequence at least 95% identical to amino acids 22-134 of SEQ ID NO: 74;

(6) an amino acid sequence at least 95% identical to amino acids 22-137 of SEQ ID NO: 83, and an amino acid sequence at least 95% identical to amino acids 22-133 of SEQ ID NO: 84;

(7) an amino acid sequence at least 95% identical to amino acids 22-131 of SEQ ID NO: 93, and an amino acid sequence at least 95% identical to amino acids 22-134 of SEQ ID NO: 94; or

(8) an amino acid sequence at least 95% identical to amino acids 23-134 of SEQ ID NO: 493, and an amino acid sequence at least 95% identical to amino acids 22-132 of SEQ ID NO: 494.

3. The TCR of claim 1 or 2, wherein the TCR comprises the amino acid sequences of:

(1) both of SEQ ID NOs: 73-74;

(2) both of SEQ ID NOs: 83-84;

(3) both of SEQ ID NOs: 93-94;

(4) both of SEQ ID NOs: 493-494;

(5) both of amino acids 21-131 of SEQ ID NO: 73 and amino acids 22-134 of SEQ ID NO: 74;

(6) both of amino acids 22-137 of SEQ ID NO: 83 and amino acids 22-133 of SEQ ID NO: 84;

(7) both of amino acids 22-131 of SEQ ID NO: 93 and amino acids 22-134 of SEQ ID NO: 94; or

(8) both of amino acids 23-134 of SEQ ID NO: 493 and amino acids 22-132 of SEQ ID NO: 494.

4. The TCR of any one of claims 1-3, wherein the TCR comprises:

(1) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 75, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 76;

(2) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(3) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 95, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 96;

(4) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 495, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 496;

(5) an amino acid sequence at least 95% identical to amino acids 21-268 of SEQ ID NO: 75, and an amino acid sequence at least 95% identical to amino acids 22-307 of SEQ ID NO: 76;

(6) an amino acid sequence at least 95% identical to amino acids 22-274 of SEQ ID NO: 85, and an amino acid sequence at least 95% identical to amino acids 22-306 of SEQ ID NO: 86;

(7) an amino acid sequence at least 95% identical to amino acids 22-268 of SEQ ID NO: 95, and an amino acid sequence at least 95% identical to amino acids 22-307 of SEQ ID NO: 96;
or

(8) an amino acid sequence at least 95% identical to amino acids 23-271 of SEQ ID NO: 495, and an amino acid sequence at least 95% identical to amino acids 22-305 of SEQ ID NO: 496.

5. The TCR of any one of claims 1-3, wherein the TCR comprises the amino acid sequences of:

(1) both of SEQ ID NOs: 75-76;

(2) both of SEQ ID NOs: 85-86;

- (3) both of SEQ ID NOs: 95-96;
- (4) both of SEQ ID NOs: 495-496;
- (5) both of amino acids 21-268 of SEQ ID NO: 75 and amino acids 22-307 of SEQ ID NO: 76;
- (6) both of amino acids 22-274 of SEQ ID NO: 85 and amino acids 22-306 of SEQ ID NO: 86;
- (7) both of amino acids 22-268 of SEQ ID NO: 95 and amino acids 22-307 of SEQ ID NO: 96; or
- (8) both of amino acids 23-271 of SEQ ID NO: 495 and amino acids 22-305 of SEQ ID NO: 496.

6. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-5, wherein the functional portion comprises:

(1) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 67, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 68, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 69, the beta chain CDR1 amino acid sequence of SEQ ID NO: 70, the beta chain CDR2 amino acid sequence of SEQ ID NO: 71, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 72;

(2) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 77, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 78, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 79, the beta chain CDR1 amino acid sequence of SEQ ID NO: 80, the beta chain CDR2 amino acid sequence of SEQ ID NO: 81, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 82;

(3) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 87, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 88, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 89, the beta chain CDR1 amino acid sequence of SEQ ID NO: 90, the beta chain CDR2 amino acid sequence of SEQ ID NO: 91, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 92; or

(4) the alpha chain CDR1 amino acid sequence of SEQ ID NO: 487, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 488, the alpha chain CDR3 amino acid sequence of SEQ ID NO: 489, the beta chain CDR1 amino acid sequence of SEQ ID NO: 490, the beta chain

CDR2 amino acid sequence of SEQ ID NO: 491, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 492.

7. The polypeptide of claim 6, wherein the polypeptide comprises:

(1) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 73, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(2) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 83, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84;

(3) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 93, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 94;

(4) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 493, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 494;

(5) an amino acid sequence at least 95% identical to amino acids 21-131 of SEQ ID NO: 73, and an amino acid sequence at least 95% identical to amino acids 22-134 of SEQ ID NO: 74;

(6) an amino acid sequence at least 95% identical to amino acids 22-137 of SEQ ID NO: 83, and an amino acid sequence at least 95% identical to amino acids 22-133 of SEQ ID NO: 84;

(7) an amino acid sequence at least 95% identical to amino acids 22-131 of SEQ ID NO: 93, and an amino acid sequence at least 95% identical to amino acids 22-134 of SEQ ID NO: 94;
or

(8) an amino acid sequence at least 95% identical to amino acids 23-134 of SEQ ID NO: 493, and an amino acid sequence at least 95% identical to amino acids 22-132 of SEQ ID NO: 494.

8. The polypeptide of claim 6, wherein the polypeptide comprises the amino acid sequences of:

(1) both of SEQ ID NOs: 73-74;

(2) both of SEQ ID NOs: 83-84;

- (3) both of SEQ ID NOs: 93-94;
- (4) both of SEQ ID NOs: 493-494;
- (5) both of amino acids 21-131 of SEQ ID NO: 73 and amino acids 22-134 of SEQ ID NO: 74;
- (6) both of amino acids 22-137 of SEQ ID NO: 83 and amino acids 22-133 of SEQ ID NO: 84;
- (7) both of amino acids 22-131 of SEQ ID NO: 93 and amino acids 22-134 of SEQ ID NO: 94; or
- (8) both of amino acids 23-134 of SEQ ID NO: 493 and amino acids 22-132 of SEQ ID NO: 494.

9. The polypeptide of any one of claims 6-8, wherein the polypeptide comprises:

- (1) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 75, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 76;
 - (2) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 86;
 - (3) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 95, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 96;
 - (4) an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 495, and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 496;
 - (5) an amino acid sequence at least 95% identical to amino acids 21-268 of SEQ ID NO: 75, and an amino acid sequence at least 95% identical to amino acids 22-307 of SEQ ID NO: 76;
 - (6) an amino acid sequence at least 95% identical to amino acids 22-274 of SEQ ID NO: 85, and an amino acid sequence at least 95% identical to amino acids 22-306 of SEQ ID NO: 86;
 - (7) an amino acid sequence at least 95% identical to amino acids 22-268 of SEQ ID NO: 95, and an amino acid sequence at least 95% identical to amino acids 22-307 of SEQ ID NO: 96;
- or

(8) an amino acid sequence at least 95% identical to amino acids 23-271 of SEQ ID NO: 495, and an amino acid sequence at least 95% identical to amino acids 22-305 of SEQ ID NO: 496.

10. The polypeptide of any one of claims 6-8, wherein the polypeptide comprises the amino acid sequences of:

- (1) both of SEQ ID NOs: 75-76;
- (2) both of SEQ ID NOs: 85-86;
- (3) both of SEQ ID NOs: 95-96;
- (4) both of SEQ ID NOs: 495-496;
- (5) both of amino acids 21-268 of SEQ ID NO: 75 and amino acids 22-307 of SEQ ID NO: 76;
- (6) both of amino acids 22-274 of SEQ ID NO: 85 and amino acids 22-306 of SEQ ID NO: 86;
- (7) both of amino acids 22-268 of SEQ ID NO: 95 and amino acids 22-307 of SEQ ID NO: 96; or
- (8) both of amino acids 23-271 of SEQ ID NO: 495 and amino acids 22-305 of SEQ ID NO: 496.

11. An isolated or purified protein comprising a functional portion of a TCR having antigenic specificity for human p53 with the R175H mutation, wherein the functional portion comprises:

- (1) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 67, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 68, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 69 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 70, the beta chain CDR2 amino acid sequence of SEQ ID NO: 71, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 72;
- (2) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 77, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 78, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 79 and a second polypeptide chain comprising

the beta chain CDR1 amino acid sequence of SEQ ID NO: 80, the beta chain CDR2 amino acid sequence of SEQ ID NO: 81, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 82;

(3) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 87, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 88, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 89 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 90, the beta chain CDR2 amino acid sequence of SEQ ID NO: 91, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 92;
or

(4) a first polypeptide chain comprising the alpha chain CDR1 amino acid sequence of SEQ ID NO: 487, the alpha chain CDR2 amino acid sequence of SEQ ID NO: 488, and the alpha chain CDR3 amino acid sequence of SEQ ID NO: 489 and a second polypeptide chain comprising the beta chain CDR1 amino acid sequence of SEQ ID NO: 490, the beta chain CDR2 amino acid sequence of SEQ ID NO: 491, and the beta chain CDR3 amino acid sequence of SEQ ID NO: 492.

12. The protein of claim 11, wherein the protein comprises:

(1) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 73 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(2) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 83 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84;

(3) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 93 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 94;

(4) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 493 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 494;

(5) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 21-131 of SEQ ID NO: 73 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-134 of SEQ ID NO: 74;

(6) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-137 of SEQ ID NO: 83 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-133 of SEQ ID NO: 84;

(7) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-131 of SEQ ID NO: 93 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-134 of SEQ ID NO: 94; or

(8) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 23-134 of SEQ ID NO: 493 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-132 of SEQ ID NO: 494.

13. The protein of claim 11, wherein the protein comprises:

(1) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 73 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 74;

(2) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 83 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 84;

(3) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 93 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 94;

(4) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 493 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 494;

(5) a first polypeptide chain comprising amino acids 21-131 of SEQ ID NO: 73 and a second polypeptide chain comprising amino acids 22-134 of SEQ ID NO: 74;

(6) a first polypeptide chain comprising amino acids 22-137 of SEQ ID NO: 83 and a second polypeptide chain comprising amino acids 22-133 of SEQ ID NO: 84;

(7) a first polypeptide chain comprising of amino acids 22-131 of SEQ ID NO: 93 and a second polypeptide chain comprising amino acids 22-134 of SEQ ID NO: 94; or

(8) a first polypeptide chain comprising amino acids 23-134 of SEQ ID NO: 493 and a second polypeptide chain comprising amino acids 22-132 of SEQ ID NO: 494.

14. The protein of any one of claims 11-13, wherein the protein comprises:

(1) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 75 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 76;

(2) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(3) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 95 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 96;

(4) a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 495 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 496;

(5) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 21-268 of SEQ ID NO: 75 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-307 of SEQ ID NO: 76;

(6) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-274 of SEQ ID NO: 85 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-306 of SEQ ID NO: 86;

(7) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-268 of SEQ ID NO: 95 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-307 of SEQ ID NO: 96; or

(8) a first polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 23-271 of SEQ ID NO: 495 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to amino acids 22-305 of SEQ ID NO: 496.

15. The protein of any one of claims 11-13, wherein the protein comprises:

(1) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 75 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 76;

(2) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 85 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 86;

(3) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 95 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 96;

(4) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 495 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 496;

(5) a first polypeptide chain comprising amino acids 21-268 of SEQ ID NO: 75 and a second polypeptide chain comprising amino acids 22-307 of SEQ ID NO: 76;

(6) a first polypeptide chain comprising amino acids 22-274 of SEQ ID NO: 85 and a second polypeptide chain comprising amino acids 22-306 of SEQ ID NO: 86;

(7) a first polypeptide chain comprising amino acids 22-268 of SEQ ID NO: 95 and a second polypeptide chain comprising amino acids 22-307 of SEQ ID NO: 96; or

(8) a first polypeptide chain comprising amino acids 23-271 of SEQ ID NO: 495 and a second polypeptide chain comprising amino acids 22-305 of SEQ ID NO: 496.

16. An isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR according to any one of claims 1-5, the polypeptide according to any one of claims 6-10, or the protein according to any one of claims 11-15.

17. A recombinant expression vector comprising the nucleic acid according to claim 16.

18. An isolated or purified host cell comprising the recombinant expression vector according to claim 17.

19. An isolated or purified population of cells comprising the host cell according to claim 18.

20. A pharmaceutical composition comprising (a) the TCR according to any one of claims 1-5, the polypeptide according to any one of claims 6-10, the protein according to any one of claims 11-15, the nucleic acid according to claim 16, the recombinant expression vector according to claim 17, the host cell according to claim 18, or the population of cells according to claim 19 and (b) a pharmaceutically acceptable carrier.

21. A method of detecting the presence of cancer in mammal, the method comprising:
(a) contacting a sample comprising cells of the cancer with the TCR according to any one of claims 1-5, the polypeptide according to any one of claims 6-10, the protein according to any one of claims 11-15, the nucleic acid according to claim 16, the recombinant expression vector according to claim 17, the host cell according to claim 18, the population of cells according to claim 19, or the pharmaceutical composition of claim 20, thereby forming a complex; and
(b) detecting the complex,
wherein detection of the complex is indicative of the presence of cancer in the mammal.

22. Use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing cancer in a mammal, which comprises the TCR according to any one of claims 1-5, the polypeptide according to any one of claims 6-10, the protein according to any one of claims 11-15, the nucleic acid according to claim 16, the recombinant expression vector according to claim 17, the host cell according to claim 18, or the population of cells according to claim 19.

23. The use according to claim 22, wherein the population of cells is autologous to the mammal.

24. The use according to claim 22, wherein the population of cells is allogeneic to the mammal.

25. The method according to claim 21, wherein the cancer is an epithelial cancer.

26. The method according to claim 21, wherein the cancer is cholangiocarcinoma, melanoma, colon cancer, rectal cancer, ovarian cancer, endometrial cancer, non-small cell lung cancer (NSCLC), glioblastoma, uterine cervical cancer, head and neck cancer, breast cancer, pancreatic cancer, or bladder cancer.

27. The use according to any one of claims 22-24, wherein the cancer is an epithelial cancer.

28. The use according to any one of claims 22-24, wherein the cancer is cholangiocarcinoma, melanoma, colon cancer, rectal cancer, ovarian cancer, endometrial cancer, non-small cell lung cancer (NSCLC), glioblastoma, uterine cervical cancer, head and neck cancer, breast cancer, pancreatic cancer, or bladder cancer.