

T CELL RECEPTORS RECOGNIZING R273C OR Y220C MUTATIONS IN P53

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Patent Application No. 63/074,747, filed on September 4, 2020, which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under project number BC010985 awarded 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 222,016 Byte ASCII (Text) file named "757042_ST25.txt," dated August 18, 2021.

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 OF THE INVENTION

[0005] An embodiment of the invention provides an isolated or purified T cell receptor (TCR) having antigenic specificity for a human p53^{R273C} or human p53^{Y220C} amino acid sequence, wherein the TCR comprises the amino acid sequences of: (1) all of SEQ ID NOs: 2-7; (2) all of SEQ ID NOs: 21-26; (3) all of SEQ ID NOs: 40-45; (4) all of SEQ ID NOs: 59-64; or (5) all of SEQ ID NOs: 78-83.

[0006] Further embodiments of the invention provide polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the TCRs of the invention.

[0007] Still further embodiments of the invention provide methods of detecting the presence of cancer in a mammal, methods of inducing an immune response against a cancer in a mammal, and methods of treating or preventing cancer in a mammal.

[0008] Additional embodiments of the invention provide methods of producing a host cell expressing the TCR and methods of producing the TCR, polypeptide, or protein.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0009] Figure 1A is a graph showing the number of IFN- γ spots (per 2e4 cells) measured following co-culture of Patient 4343 tumor fragment numbers F1-F7 and F9-F24 with autologous DCs pulsed with DMSO (vehicle) or mutant p53-Y220C (Fig. 1A). Fragments with mutant p53 reactivity are boxed.

[0010] Figure 1B is a graph showing the number of IFN- γ spots (per 2e4 cells) measured following co-culture of Patient 4386 tumor fragment numbers F1-F24 with autologous DCs pulsed with DMSO (vehicle) or mutant p53-R273C (Fig. 1B). Fragments with mutant p53 reactivity are boxed.

[0011] Figure 1C is a graph showing the number of IFN- γ spots (per 2e4 cells) measured following co-culture of sorted T cells from fresh tumor digest (of Tumor 1A or Tumor 1B) of Patient 4386 with autologous DCs pulsed with DMSO (vehicle) or mutant p53-R273C. The T cells were sorted based on expression of the indicated cell surface markers. Sorted T cell populations with mutant p53 reactivity are boxed.

[0012] Figure 1D shows the percentages of T cells expressing OX40 and 4-1BB following co-culture of TILs from patient 4386 with autologous DCs pulsed with DMSO (vehicle) or mutant p53-R273C peptide, as measured by flow cytometry.

[0013] Figure 2A is a graph showing the percentage of murine TCR constant region positive cells expressing 4-1BB upon co-culture of target cells with effector cells. The effector cells were transduced with the 4343-D TCR. The target cells were COS7 cells transfected with one of the HLA Class II heterodimers shown and pulsed with the p53-Y220C 25-mer peptide.

[0014] Figure 2B is a graph showing the percentage of CD3 positive cells expressing 4-1BB upon co-culture of target cells with effector cells. The effector cells were TIL that

contain T cells recognizing p53-R273C. The target cells were COS7 cells transfected with one of the HLA Class II heterodimers shown and pulsed with the p53-R273C 25-mer peptide.

[0015] Figure 3A is a graph showing IFN- γ secretion (number of spots/2e4 cells) measured following co-culture of target cells with effector cells. The effector cells were T cells transduced with the 4343-D TCR. The target cells were autologous DCs pulsed with p53-Y220C 25-mer peptide (squares) or the corresponding WT 25-mer peptide (circles) at the concentrations ($\mu\text{g/mL}$) shown.

[0016] Figures 3B-3C are graphs showing the percentage of murine TCR constant region positive cells expressing 4-1BB following co-culture of target cells with effector cells. The effector cells were T cells from Donor C (3B) or Donor H (3C) transduced with the 4343-D TCR. The target cells were autologous B cells pulsed with the mutated p53-Y220C 25-mer peptide with alpha-aminobutyric acid (AABA) substitutions (squares) over the corresponding WT 25-mer peptide with AABA substitution (circles) at the concentrations ($\mu\text{g/mL}$) shown.

[0017] Figures 3D-3G are graphs showing IFN- γ secretion (pg/mL) measured following co-culture of target cells with effector cells. The effector cells were T cells independently transduced with the 4386-F TCR (Fig. 3D), the 4386-G TCR (Fig. 3E), the 4386-H TCR (Fig. 3F), or the 4386-O TCR (Fig. 3G). The target cells were autologous DCs pulsed with p53-R273C 25-mer peptide (squares) or the corresponding WT 25-mer peptide (circles) at the concentrations (ng/mL) shown.

[0018] Figure 4 shows an alignment of the amino acid sequences of the nine p53 splice variants. SP|P04637|P53_HUMAN (SEQ ID NO: 1); SP|P04637-2|P53_HUMAN (SEQ ID NO: 101); SP|P04637-3|P53_HUMAN (SEQ ID NO: 102); SP|P04637-4|P53_HUMAN (SEQ ID NO: 103); SP|P04637-5|P53_HUMAN (SEQ ID NO: 104); SP|P04637-6|P53_HUMAN (SEQ ID NO: 105); SP|P04637-7|P53_HUMAN (SEQ ID NO: 106); SP|P04637-8|P53_HUMAN (SEQ ID NO: 107); and SP|P04637-9|P53_HUMAN (SEQ ID NO: 108).

DETAILED DESCRIPTION OF THE INVENTION

[0019] Tumor Protein P53 (also referred to as “TP53” or “p53”) acts as a tumor suppressor by, for example, regulating cell division. The p53 protein is located in the nucleus of the cell, where it binds directly to DNA. When DNA becomes damaged, the p53 protein is involved in determining whether the DNA will be repaired, or the damaged cell will undergo apoptosis. If the DNA can be repaired, p53 activates other genes to fix the damage. If the

DNA cannot be repaired, the p53 protein prevents the cell from dividing and signals it to undergo apoptosis. By stopping cells with mutated or damaged DNA from dividing, p53 helps prevent the development of tumors. WT (normal) full-length p53 comprises the amino acid sequence of SEQ ID NO: 1.

{0020} Mutations in the p53 protein may reduce or eliminate the p53 protein's tumor suppressor function. Alternatively, or additionally, a p53 mutation may be a gain-of-function mutation by interfering with WT p53 in a dominant negative fashion. Mutated p53 protein may be expressed in any of a variety of human cancers such as, for example, 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.

{0021} An embodiment of the invention provides an isolated or purified T cell receptor (TCR) having antigenic specificity for mutated human p53^{R273C} or human p53^{Y220C} amino acid sequence (hereinafter, "mutated p53"). Hereinafter, references to a "TCR" also refer to functional portions and functional variants of the TCR, unless specified otherwise. Mutations of p53 are defined herein by reference to the amino acid sequence of full-length, WT p53 (SEQ ID NO: 1). Mutations of p53 are described herein by reference to the amino acid residue present at a particular position, followed by the position number, followed by the amino acid with which that residue has been replaced in the particular mutation under discussion. A p53 amino acid sequence (e.g., a p53 peptide) may comprise fewer than all of the amino acid residues of the full-length, WT p53 protein. Accordingly, the position numbers are defined herein by reference to the WT full-length p53 protein (namely, SEQ ID NO: 1) with the understanding that the actual position of the corresponding residue in a particular example of a p53 amino acid sequence may be different. Because the positions are as defined by SEQ ID NO: 1, the term "R273C" indicates that the arginine present at position 273 of SEQ ID NO: 1 is replaced by cysteine, while "Y220C" indicates that the tyrosine present at position 220 of SEQ ID NO: 1 has been replaced with cysteine. For example, when a particular example of a p53 amino acid sequence is, e.g.,

SGNLLGRNSFEVRVCACPGRDRRTE (SEQ ID NO: 116) (an exemplary WT p53 peptide corresponding to contiguous amino acid residues 261 to 285 of SEQ ID NO: 1), "R273C" refers to a substitution of the underlined arginine in SEQ ID NO: 116 with cysteine, even though the actual position of the underlined arginine in SEQ ID NO: 116 is 13. Human p53 amino acid sequences with the R273C mutation are hereinafter referred to as "R273C" or

“p53^{R273C}.” Human p53 amino acid sequences with the Y220C mutation are hereinafter referred to as “Y220C” or “p53^{Y220C}.” As used herein, “mutated p53” refers to human p53^{R273C} or human p53^{Y220C}.

[0022] P53 has nine known splice variants. The p53 mutations described herein are conserved over all nine p53 splice variants. An alignment of the nine p53 splice variants is shown in Figure 4. Accordingly, the inventive TCRs may have antigenic specificity for any mutated p53 amino acid sequence described herein encoded by any of the nine p53 splice variants. Because the positions are as defined by SEQ ID NO: 1, the actual positions of the amino acid sequence of a particular splice variant of p53 are defined relative to the corresponding positions of SEQ ID NO: 1, and the positions as defined by SEQ ID NO: 1 may be different than the actual positions in a particular splice variant. Thus, for example, mutations refer to a replacement of an amino acid residue in the amino acid sequence of a particular splice variant of p53 corresponding to the indicated position of the 393-amino acid sequence of SEQ ID NO: 1 with the understanding that the actual positions in the splice variant may be different.

[0023] In an embodiment of the invention, the TCR has antigenic specificity for human p53 with a mutation at position 273, as defined by SEQ ID NO: 1. The p53 mutation at position 273 may be any missense mutation. Accordingly, the mutation at position 273 may be a substitution of the native (WT) arginine residue present at position 273 with any amino acid residue other than arginine. In an embodiment of the invention, the TCR has antigenic specificity for a human p53^{R273C} amino acid sequence. For example, the TCR may have antigenic specificity for the human p53^{R273C} amino acid sequence of SGNLLGRNSFEVCVACPGRRRTE (SEQ ID NO: 117). In an embodiment of the invention, the TCR does not have antigenic specificity for the wild-type human p53 amino acid sequence of SGNLLGRNSFEVRVACPGRRRTE (SEQ ID NO: 116).

[0024] In an embodiment of the invention, the TCR has antigenic specificity for human p53 with a mutation at position 220, as defined by SEQ ID NO: 1. The p53 mutation at position 220 may be any missense mutation. Accordingly, the mutation at position 220 may be a substitution of the native (WT) tyrosine residue present at position 220 with any amino acid residue other than tyrosine. In an embodiment of the invention, the TCR has antigenic specificity for a human p53^{Y220C} amino acid sequence. For example, the TCR may have antigenic specificity for the human p53^{Y220C} amino acid sequence of DRNTFRHSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115). In an embodiment of the

invention, the TCR does not have antigenic specificity for the wild-type human p53 amino acid sequence of DRNTFRHSVVVPYEPPEVGSDCTTI (SEQ ID NO: 114).

[0025] In an embodiment of the invention, the inventive TCRs may be able to recognize mutated p53 in an HLA (human leukocyte antigen)-molecule-dependent manner. “HLA-molecule-dependent manner,” as used herein, means that the TCR elicits an immune response upon binding to mutated p53 within the context of an HLA molecule, which HLA molecule is expressed by the patient from which the TCR was isolated. The inventive TCRs may be able to recognize mutated p53 that is presented by the applicable HLA molecule and may bind to the HLA molecule in addition to mutated p53.

[0026] In an embodiment of the invention, the inventive TCRs are able to recognize R273C presented by an HLA Class II molecule. In this regard, the TCR may elicit an immune response upon binding to R273C within the context of an HLA Class II molecule. The inventive TCRs are able to recognize R273C that is presented by an HLA Class II molecule and may bind to the HLA Class II molecule in addition to R273C.

[0027] In an embodiment of the invention, the HLA Class II molecule is an HLA-DP molecule. The HLA-DP molecule is a heterodimer of an α chain (DPA) and β chain (DPB). The HLA-DPA chain may be any HLA-DPA chain. The HLA-DPB chain may be any HLA-DPB chain. In an embodiment of the invention, the HLA Class II molecule is a heterodimer of an HLA-DPA1 chain and an HLA-DPB1 chain. Examples of HLA-DPA1 molecules may include, but are not limited to, those encoded by the HLA-DPA1*01:03, HLA-DPA1*01:04, HLA-DPA1*01:05, HLA-DPA1*01:06, HLA-DPA1*01:07, HLA-DPA1*01:08, HLA-DPA1*01:09, HLA-DPA1*01:10, HLA-DPA1*02:01, HLA-DPA1*02:02, HLA-DPA1*02:03, HLA-DPA1*02:04, HLA-DPA1*03:01, HLA-DPA1*03:02, HLA-DPA1*03:03, and HLA-DPA1*04:01 alleles. Examples of HLA-DPB1 molecules may include, but are not limited to, those encoded by the HLA-DPB1*01:01, HLA-DPB1*02:01, HLA-DPB1*02:02, HLA-DPB1*03:01, HLA-DPB1*04:01, HLA-DPB1*04:02, HLA-DPB1*05:01, HLA-DPB1*06:01, HLA-DPB1*07:01, HLA-DPB1*08:01, HLA-DPB1*09:01, and HLA-DPB1*10:01 alleles. Preferably, the HLA Class II molecule is a heterodimer of an HLA-DPA1*01:03 chain and an HLA-DPB1*04:02 chain.

[0028] In an embodiment of the invention, one of the inventive TCRs is able to recognize Y220C presented by an HLA Class II molecule. In this regard, the TCR may elicit an immune response upon binding to Y220C within the context of an HLA Class II molecule.

The inventive TCR is able to recognize Y220C that is presented by an HLA Class II molecule and may bind to the HLA Class II molecule in addition to Y220C.

[0029] In an embodiment of the invention, the HLA Class II molecule is an HLA-DR heterodimer. The HLA-DR heterodimer is a cell surface receptor including an α chain and a β chain. The HLA-DR α chain is encoded by the HLA-DRA gene. In an embodiment, the alpha chain of the HLA Class II molecule is expressed by the HLA-DRA1*01:01:01 allele. The HLA-DR β chain is encoded by the HLA-DRB1 gene, the HLA-DRB3 gene, HLA-DRB4 gene, or the HLA-DRB5 gene. Examples of molecules encoded by the HLA-DRB1 gene may include, but are not limited to, HLA-DR1, HLA-DR2, HLA-DR3, HLA-DR4, HLA-DR5, HLA-DR6, HLA-DR7, HLA-DR8, HLA-DR9, HLA-DR10, HLA-DR11, HLA-DR12, HLA-DR13, HLA-DR14, HLA-DR15, HLA-DR16, and HLA-DR17. The HLA-DRB3 gene encodes HLA-DR52. The HLA-DRB4 gene encodes HLA-DR53. The HLA-DRB5 gene encodes HLA-DR51. In an embodiment of the invention, the HLA Class II molecule is an HLA-DRB3:HLA-DRA heterodimer. The beta chain of the HLA Class II molecule may be expressed by the HLA-DRB3*01:01, HLA-DRB3*02:02, or HLA-DRB3*03:01 allele. Preferably, the beta chain of the HLA Class II molecule is expressed by the HLA-DRB3*02:02:01 allele. In a preferred embodiment, the HLA Class II molecule is a heterodimer of an HLA-DRA1*01:01:01 chain and an HLA-DRB3*02:02:01 chain.

[0030] The TCRs of the invention may provide any one or more of many advantages, including when expressed by cells used for adoptive cell transfer. Mutated p53 is expressed by cancer cells and is not expressed by normal, noncancerous cells. Without being bound to a particular theory or mechanism, it is believed that the inventive TCRs advantageously target the destruction of cancer cells while minimizing or eliminating the destruction of normal, non-cancerous cells, thereby reducing, for example, by minimizing or eliminating, toxicity. Moreover, the inventive TCRs may, advantageously, successfully treat or prevent mutated p53-positive cancers that do not respond to other types of treatment such as, for example, chemotherapy, surgery, or radiation. Additionally, the inventive TCRs may provide highly avid recognition of mutated p53, which may provide the ability to recognize unmanipulated tumor cells (e.g., tumor cells that have not been treated with interferon (IFN)- γ , transfected with a vector encoding one or both of mutated p53 and the applicable HLA molecule, pulsed with a p53 peptide with the p53 mutation, or a combination thereof). Roughly half of all tumors harbor a mutation in p53, about half of which will be a missense mutation. The R273C mutation is expressed by about 2.8% of all cancers, and the HLA-DPB1*04:02 allele

is expressed by about 24% of the U.S. Caucasian population and about 60% to about 80% of the U.S. Hispanic population. The Y220C mutation occurs in about 1.5% of all cancers, and the HLA-DRB3*02:02 allele is expressed by about 33% of the U.S. Caucasian population. The R273C and Y220C mutations arise in many cancer histologies, suggesting that a diverse group of patients could benefit from the inventive TCRs. Accordingly, the inventive TCRs may increase the number of patients who may be eligible for treatment with immunotherapy.

{0031} The phrase “antigenic specificity,” as used herein, means that the TCR can specifically bind to and immunologically recognize mutated p53 with high avidity. For example, a TCR may be considered to have “antigenic specificity” for mutated p53 if about 1×10^4 to about 1×10^5 T cells expressing the TCR secrete at least about 200 pg/mL or more (e.g., 200 pg/mL or more, 300 pg/mL or more, 400 pg/mL or more, 500 pg/mL or more, 600 pg/mL or more, 700 pg/mL or more, 1,000 pg/mL or more, 5,000 pg/mL or more, 7,000 pg/mL or more, 10,000 pg/mL or more, 20,000 pg/mL or more, or a range defined by any two of the foregoing values) of IFN- γ upon co-culture with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with a low concentration of mutated p53 peptide (e.g., about 0.05 ng/mL to about 5 ng/mL, 0.05 ng/mL, 0.1 ng/mL, 0.5 ng/mL, 1 ng/mL, 5 ng/mL, or a range defined by any two of the foregoing values) or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding mutated p53 has been introduced such that the target cell expresses mutated p53. Cells expressing the inventive TCRs may also secrete IFN- γ upon co-culture with antigen-negative, applicable HLA molecule positive target cells pulsed with higher concentrations of mutated p53 peptide.

{0032} Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for mutated p53 if T cells expressing the TCR secrete at least twice as much IFN- γ upon co-culture with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with a low concentration of mutated p53 peptide or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding mutated p53 has been introduced such that the target cell expresses mutated p53 as compared to the amount of IFN- γ expressed by a negative control. The negative control may be, for example, (i) T cells expressing the TCR, co-cultured with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with the same concentration of an irrelevant peptide (e.g., some other peptide with a different sequence from the mutated p53 peptide) or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding an irrelevant peptide has been introduced such that the target cell

expresses the irrelevant peptide, or (ii) untransduced T cells (e.g., derived from PBMC, which do not express the TCR) co-cultured with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with the same concentration of mutated p53 peptide or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding mutated p53 has been introduced such that the target cell expresses mutated p53. IFN- γ secretion may be measured by methods known in the art such as, for example, enzyme-linked immunosorbent assay (ELISA).

[0033] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for mutated p53 if at least twice as many of the numbers of T cells expressing the TCR secrete IFN- γ upon co-culture with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with a low concentration of mutated p53 peptide or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding mutated p53 has been introduced such that the target cell expresses mutated p53 as compared to the numbers of negative control T cells that secrete IFN- γ . The concentration of peptide and the negative control may be as described herein with respect to other aspects of the invention. The numbers of cells secreting IFN- γ may be measured by methods known in the art such as, for example, enzyme-linked immunospot (ELISpot) assay.

[0034] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for mutated p53 if at least twice as many spots are detected by ELISpot for the T cells expressing the TCR upon co-culture with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with a low concentration of mutated p53 peptide or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding mutated p53 has been introduced such that the target cell expresses mutated p53 as compared to the number of spots detected by ELISpot for negative control T cells co-cultured with the same target cells. The concentration of peptide and the negative control may be as described herein with respect to other aspects of the invention.

[0035] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for mutated p53 if greater than about 50 spots are detected by ELISpot for the T cells expressing the TCR upon co-culture with (a) antigen-negative, applicable HLA molecule positive target cells pulsed with a low concentration of mutated p53 peptide or (b) antigen-negative, applicable HLA molecule positive target cells into which a nucleotide sequence encoding mutated p53 has been introduced such that the target cell expresses

mutated p53. The concentration of peptide may be as described herein with respect to other aspects of the invention.

[0036] Alternatively, or additionally, a TCR may be considered to have “antigenic specificity” for mutated p53 if T cells expressing the TCR upregulate expression of one or both of 4-1BB and OX40 as measured by, for example, flow cytometry after stimulation with target cells expressing mutated p53.

[0037] An embodiment of the invention provides a TCR comprising two polypeptides (i.e., polypeptide chains), such as an alpha (α) chain of a TCR, a beta (β) chain of a TCR, a gamma (γ) chain of a TCR, a delta (δ) chain of a TCR, or a combination thereof. The polypeptides of the inventive TCR can comprise any amino acid sequence, provided that the TCR has antigenic specificity for mutated p53.

[0038] In an embodiment of the invention, the TCR comprises two polypeptide chains, each of which comprises a variable region comprising a complementarity determining region (CDR)1, a CDR2, and a CDR3 of a TCR. In an embodiment of the invention, the TCR comprises a first polypeptide chain comprising an α chain CDR1 (CDR1 α), an α chain CDR2 (CDR2 α), and an α chain CDR3 (CDR3 α), and a second polypeptide chain comprising a β chain CDR1 (CDR1 β), a β chain CDR2 (CDR2 β), and a β chain CDR3 (CDR3 β). In an embodiment of the invention, the TCR comprises the amino acid sequences of: (1) all of SEQ ID NOs: 2-7; (2) all of SEQ ID NOs: 21-26; (3) all of SEQ ID NOs: 40-45; (4) all of SEQ ID NOs: 59-64; or (5) all of SEQ ID NOs: 78-83. Each one of the foregoing five collections of amino acid sequences in this paragraph sets forth the six CDR regions of each of five different TCRs having antigenic specificity for mutated human p53. The six amino acid sequences in each collection correspond to the CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β of a TCR, respectively.

[0039] In an embodiment of the invention, the TCR comprises an α chain variable region amino acid sequence and a β chain variable region amino acid sequence, which together comprise one of the collections of CDRs set forth above. In this regard, the TCR can, e.g., comprise the amino acid sequence of any one of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 27, 28, 29, 30, 31, 32, 46, 47, 48, 49, 50, 51, 65, 66, 67, 68, 69, 70, 84, 85, 86, 87, 88, 89, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, and 138. For example, the TCR can comprise the amino acid sequences of: (1) both of SEQ ID NOs: 8 and 9; (2) both of SEQ ID NOs: 10 and 11; (3) both of SEQ ID NOs: 12 and 13; (4) both of SEQ ID NOs: 12 and 11; (5) both of SEQ ID NOs: 121 and 13; (6) both of SEQ ID NOs: 121 and

122; (7) both of SEQ ID NOs: 8 and 120; (8) both of SEQ ID NOs: 119 and 9; (9) both of SEQ ID NOs: 119 and 120; (10) both of SEQ ID NOs: 27 and 28; (11) both of SEQ ID NOs: 29 and 30; (12) both of SEQ ID NOs: 31 and 32; (13) both of SEQ ID NOs: 31 and 30; (14) both of SEQ ID NOs: 125 and 32; (15) both of SEQ ID NOs: 125 and 126; (16) both of SEQ ID NOs: 27 and 124; (17) both of SEQ ID NOs: 123 and 28; (18) both of SEQ ID NOs: 123 and 124; (19) both of SEQ ID NOs: 46 and 47; (20) both of SEQ ID NOs: 48 and 49; (21) both of SEQ ID NOs: 50 and 51; (22) both of SEQ ID NOs: 50 and 49; (23) both of SEQ ID NOs: 129 and 51; (24) both of SEQ ID NOs: 129 and 130; (25) both of SEQ ID NOs: 46 and 128; (26) both of SEQ ID NOs: 127 and 47; (27) both of SEQ ID NOs: 127 and 128; (28) both of SEQ ID NOs: 65 and 66; (29) both of SEQ ID NOs: 67 and 68; (30) both of SEQ ID NOs: 69 and 70; (31) both of SEQ ID NOs: 69 and 68; (32) both of SEQ ID NOs: 133 and 70; (33) both of SEQ ID NOs: 133 and 134; (34) both of SEQ ID NOs: 65 and 132; (35) both of SEQ ID NOs: 131 and 66; (36) both of SEQ ID NOs: 131 and 132; (37) both of SEQ ID NOs: 84 and 85; (38) both of SEQ ID NOs: 86 and 87; (39) both of SEQ ID NOs: 88 and 89; (40) both of SEQ ID NOs: 88 and 87; (41) both of SEQ ID NOs: 137 and 89; (42) both of SEQ ID NOs: 137 and 138; (43) both of SEQ ID NOs: 84 and 136; (44) both of SEQ ID NOs: 135 and 85; or (45) both of SEQ ID NOs: 135 and 136. Each one of the foregoing collections of amino acid sequences in this paragraph sets forth the two variable regions of each of the different TCRs having antigenic specificity for mutated human p53. The two amino acid sequences in each collection correspond to the variable region of the α chain and the variable region of the β chain of a TCR, respectively.

[0040] The inventive TCRs may further comprise a constant region. The constant region may be derived from any suitable species such as, e.g., human or mouse. In an embodiment of the invention, the TCRs further comprise a murine constant region. As used herein, the term “murine” or “human,” when referring to a TCR or any component of a TCR described herein (e.g., complementarity determining region (CDR), variable region, constant region, alpha chain, and/or beta chain), means a TCR (or component thereof) which is derived from a mouse or a human, respectively, i.e., a TCR (or component thereof) that originated from or was, at one time, expressed by a mouse T cell or a human T cell, respectively. In an embodiment of the invention, the TCR may comprise a murine α chain constant region and a murine β chain constant region. The murine α chain constant region may be modified or unmodified. A modified murine α chain constant region may be, e.g., cysteine-substituted, LVL-modified, or both cysteine-substituted and LVL-modified, as described, for example, in

U.S. Patent No. 10,174,098. The murine β chain constant region may be modified or unmodified. A modified murine β chain constant region may be, e.g., cysteine-substituted, as described, for example, in U.S. Patent No. 10,174,098. In some embodiments of the invention, the TCR comprises a cysteine-substituted, LVL-modified murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments of the invention, the TCR comprises a cysteine-substituted, LVL-modified murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 98. In some embodiments of the invention, the TCR comprises a cysteine-substituted, LVL-modified murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 143. In some embodiments of the invention, the TCR comprises an LVL-modified murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 144. In some embodiments of the invention, the TCR comprises an LVL-modified murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 145. In some embodiments of the invention, the TCR comprises an LVL-modified murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 146. In some embodiments of the invention, the TCR comprises a cysteine-substituted murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 147. In some embodiments of the invention, the TCR comprises a cysteine-substituted murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 148. In some embodiments of the invention, the TCR comprises a cysteine-substituted murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 149. In an embodiment of the invention, the TCR comprises a D1 murine α chain constant region comprising the amino acid sequence of SEQ ID NO: 139. In some embodiments of the invention, the TCR comprises a murine α chain constant region described in the degenerate amino acid sequence comprising the amino acid sequence of SEQ ID NO: 141. In an embodiment of the invention, the TCR comprises a cysteine-substituted murine β chain constant region comprising the amino acid sequence of SEQ ID NO: 99. In an embodiment of the invention, the TCR comprises a wild-type murine β chain constant region comprising the amino acid sequence of SEQ ID NO: 140. In some embodiments of the invention, the TCR comprises a murine β chain constant region described in the degenerate amino acid sequence comprising the amino acid sequence of SEQ ID NO: 142.

[0041] Exemplary C α region sequences and C β region sequences are shown in Tables 1 and 2.

TABLE 1

Amino acid sequences of TCR C α regions.

Description	Sequence	SEQ ID NO:
C α (D1 variant)	DIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKTVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVSVGLRILLKLVAGFNLLMTLRLWSS	139
C α (degenerate)	XIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKXVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVXXLRILLKLVAGFNLLMTLRLWSS X at position 1 is Asn, Asp, His, or Tyr; X at position 48 is Thr or Cys; X at position 112 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; X at position 114 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; X at position 115 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp	141
C α (cysteine- and LVL-modified, substituted w/X at amino acid 1)	XIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS X at position 1 is Asn, Asp, His, or Tyr	143
C α (cysteine- and LVL-modified, substituted w/N at amino acid 1)	NIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS	97
C α (cysteine- and LVL-modified, substituted w/D at amino acid 1)	DIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS	98
C α (LVL-modified, w/X at amino acid 1)	XIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKTVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS X at position 1 is Asn, Asp, His, or Tyr	144
C α (LVL-modified w/N at amino acid 1)	NIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKTVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS	145
C α (LVL-modified, w/D at amino acid 1)	DIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKTVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS	146
C α (cysteine-substituted, w/X at amino acid 1)	XIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVSVGLRILLKLVAGFNLLMTLRLWSS X at position 1 is Asn, Asp, His, or Tyr	147
C α (cysteine-substituted, w/N at amino acid 1)	NIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVSVGLRILLKLVAGFNLLMTLRLWSS	148
C α (cysteine-substituted, w/D at amino acid 1)	DIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDM NLNFQNLVSVGLRILLKLVAGFNLLMTLRLWSS	149

TABLE 2

Amino acid sequences of TCR C β regions.

Description	Sequence	SEQ ID NO:
C β (cysteine-substituted)	EDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFFPDHVELSWVNGKEV HSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDK WPEGSPKPVTQNI SAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYA VLVSTLVVMAMVKRKNS	99
C β (wild-type)	EDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFFPDHVELSWVNGKEV HSGVSTDQPAYKESNYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDK WPEGSPKPVTQNI SAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYA VLVSTLVVMAMVKRKNS	140
C β (degenerate)	EDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFFPDHVELSWVNGKEV HSGVXTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDK WPEGSPKPVTQNI SAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYA VLVSTLVVMAMVKRKNS X at position 57 is Ser or Cys	142

[0042] In an embodiment of the invention, the inventive TCR can comprise an α chain of a TCR and a β chain of a TCR. The α chain of the TCR may comprise a variable region of an α chain and a constant region of an α chain. An α chain of this type can be paired with any β chain of a TCR. The β chain may comprise a variable region of a β chain and a constant region of a β chain.

[0043] In some embodiments, the amino acid sequence of any of the α chains and/or β chains disclosed herein further comprises the amino acid sequence RAKR (SEQ ID NO: 118) at the C-terminal end.

[0044] In an embodiment of the invention, the TCR comprises the amino acid sequence of any one of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 33, 34, 35, 36, 37, 38, 52, 53, 54, 55, 56, 57, 71, 72, 73, 74, 75, 76, 90, 91, 92, 93, 94, and 95. For example, the TCR can comprise the amino acid sequences of: (1) both of SEQ ID NOs: 14 and 15; (2) both of SEQ ID NOs: 16 and 17; (3) both of SEQ ID NOs: 18 and 19; (4) both of SEQ ID NOs: 33 and 34; (5) both of SEQ ID NOs: 35 and 36; (6) both of SEQ ID NOs: 37 and 38; (7) both of SEQ ID NOs: 52 and 53; (8) both of SEQ ID NOs: 54 and 55; (9) both of SEQ ID NOs: 56 and 57; (10) both of SEQ ID NOs: 71 and 72; (11) both of SEQ ID NOs: 73 and 74; (12) both of SEQ ID NOs: 75 and 76; (13) both of SEQ ID NOs: 90 and 91; (14) both of SEQ ID NOs: 92 and 93; or (15) both of SEQ ID NOs: 94 and 95. Each one of the foregoing collections of amino acid sequences in this paragraph sets forth the α chain and β chain of each of different TCRs having antigenic specificity for mutated human p53. The two amino acid sequences in each collection correspond to the α chain and the β chain of a TCR, respectively.

[0045] Included in the scope of the invention are functional variants of the inventive TCRs described herein. The term “functional variant,” as used herein, refers to a TCR, polypeptide, or protein having substantial or significant sequence identity or similarity to a parent TCR, polypeptide, or protein, which functional variant retains the biological activity of the TCR, polypeptide, or protein of which it is a variant. Functional variants encompass, for example, those variants of the TCR, polypeptide, or protein described herein (the parent TCR, polypeptide, or protein) that retain the ability to specifically bind to mutated p53 for which the parent TCR has antigenic specificity or to which the parent polypeptide or protein specifically binds, to a similar extent, the same extent, or to a higher extent, as the parent TCR, polypeptide, or protein. In reference to the parent TCR, polypeptide, or protein, the functional variant can, for instance, be at least about 30%, at least about 50%, at least about 75%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or more identical in amino acid sequence to the parent TCR, polypeptide, or protein, respectively.

[0046] The functional variant can, for example, comprise the amino acid sequence of the parent TCR, polypeptide, or protein with at least one conservative amino acid substitution. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same chemical or physical properties. For instance, the conservative amino acid substitution can be an acidic amino acid substituted for another acidic amino acid (e.g., Asp or Glu), an amino acid with a nonpolar side chain substituted for another amino acid with a nonpolar side chain (e.g., Ala, Gly, Val, Ile, Leu, Met, Phe, Pro, Trp, Val, etc.), a basic amino acid substituted for another basic amino acid (Lys, Arg, etc.), an amino acid with a polar side chain substituted for another amino acid with a polar side chain (Asn, Cys, Gln, Ser, Thr, Tyr, etc.), etc.

[0047] Alternatively, or additionally, the functional variants can comprise the amino acid sequence of the parent TCR, polypeptide, or protein with at least one non-conservative amino acid substitution. In this case, it is preferable for the non-conservative amino acid substitution to not interfere with or inhibit the biological activity of the functional variant. Preferably, the non-conservative amino acid substitution enhances the biological activity of the functional variant, such that the biological activity of the functional variant is increased as compared to the parent TCR, polypeptide, or protein.

[0048] The TCR, polypeptide, or protein can consist essentially of the specified amino acid sequence or sequences described herein, such that other components of the TCR, polypeptide, or protein, e.g., other amino acids, do not materially change the biological activity of the TCR, polypeptide, or protein.

[0049] Also provided by the invention is a polypeptide comprising a functional portion of any of the TCRs described herein. The term “polypeptide,” as used herein, includes oligopeptides and refers to a single chain of amino acids connected by one or more peptide bonds.

[0050] With respect to the inventive polypeptides, the functional portion can be any portion comprising contiguous amino acids of the TCR of which it is a part, provided that the functional portion specifically binds to mutated p53. The term “functional portion,” when used in reference to a TCR, refers to any part or fragment of the TCR of the invention, which part or fragment retains the biological activity of the TCR of which it is a part (the parent TCR). Functional portions encompass, for example, those parts of a TCR that retain the ability to specifically bind to mutated p53 (e.g., in an applicable HLA molecule-dependent manner), or detect, treat, or prevent cancer, to a similar extent, the same extent, or to a higher extent, as the parent TCR. In reference to the parent TCR, the functional portion can comprise, for instance, about 10%, about 25%, about 30%, about 50%, about 70%, about 80%, about 90%, about 95%, or more, of the parent TCR.

[0051] The functional portion can comprise additional amino acids at the amino or carboxy terminus of the portion, or at both termini, which additional amino acids are not found in the amino acid sequence of the parent TCR. Desirably, the additional amino acids do not interfere with the biological function of the functional portion, e.g., specifically binding to mutated p53; and/or having the ability to detect cancer, treat or prevent cancer, etc. More desirably, the additional amino acids enhance the biological activity, as compared to the biological activity of the parent TCR.

[0052] The polypeptide can comprise a functional portion of either or both of the α and β chains of the TCRs of the invention, such as a functional portion comprising one or more of CDR1, CDR2, and CDR3 of the variable region(s) of the α chain and/or β chain of a TCR of the invention. In an embodiment of the invention, the polypeptide can comprise the amino acid sequences of: (1) all of SEQ ID NOs: 2-7; (2) all of SEQ ID NOs: 21-26; (3) all of SEQ ID NOs: 40-45; (4) all of SEQ ID NOs: 59-64; or (5) all of SEQ ID NOs: 78-83.

[0053] In an embodiment of the invention, the inventive polypeptide can comprise, for instance, the variable region of the inventive TCR comprising a combination of the CDR regions set forth above. In this regard, the polypeptide can comprise, e.g., the amino acid sequences of: (1) both of SEQ ID NOs: 8 and 9; (2) both of SEQ ID NOs: 10 and 11; (3) both of SEQ ID NOs: 12 and 13; (4) both of SEQ ID NOs: 12 and 11; (5) both of SEQ ID NOs: 121 and 13; (6) both of SEQ ID NOs: 121 and 122; (7) both of SEQ ID NOs: 8 and 120; (8) both of SEQ ID NOs: 119 and 9; (9) both of SEQ ID NOs: 119 and 120; (10) both of SEQ ID NOs: 27 and 28; (11) both of SEQ ID NOs: 29 and 30; (12) both of SEQ ID NOs: 31 and 32; (13) both of SEQ ID NOs: 31 and 30; (14) both of SEQ ID NOs: 125 and 32; (15) both of SEQ ID NOs: 125 and 126; (16) both of SEQ ID NOs: 27 and 124; (17) both of SEQ ID NOs: 123 and 28; (18) both of SEQ ID NOs: 123 and 124; (19) both of SEQ ID NOs: 46 and 47; (20) both of SEQ ID NOs: 48 and 49; (21) both of SEQ ID NOs: 50 and 51; (22) both of SEQ ID NOs: 50 and 49; (23) both of SEQ ID NOs: 129 and 51; (24) both of SEQ ID NOs: 129 and 130; (25) both of SEQ ID NOs: 46 and 128; (26) both of SEQ ID NOs: 127 and 47; (27) both of SEQ ID NOs: 127 and 128; (28) both of SEQ ID NOs: 65 and 66; (29) both of SEQ ID NOs: 67 and 68; (30) both of SEQ ID NOs: 69 and 70; (31) both of SEQ ID NOs: 69 and 68; (32) both of SEQ ID NOs: 133 and 70; (33) both of SEQ ID NOs: 133 and 134; (34) both of SEQ ID NOs: 65 and 132; (35) both of SEQ ID NOs: 131 and 66; (36) both of SEQ ID NOs: 131 and 132; (37) both of SEQ ID NOs: 84 and 85; (38) both of SEQ ID NOs: 86 and 87; (39) both of SEQ ID NOs: 88 and 89; (40) both of SEQ ID NOs: 88 and 87; (41) both of SEQ ID NOs: 137 and 89; (42) both of SEQ ID NOs: 137 and 138; (43) both of SEQ ID NOs: 84 and 136; (44) both of SEQ ID NOs: 135 and 85; or (45) both of SEQ ID NOs: 135 and 136.

[0054] In an embodiment of the invention, the inventive polypeptide can further comprise the constant region of the inventive TCR set forth above. In this regard, the polypeptide can comprise, e.g., the amino acid sequence of (i) one of SEQ ID NOs 97-99, and 139-149 or (ii) one of SEQ ID NOs: 99, 140, and 142 and one of SEQ ID NOs: 97, 98, 139, 141, and 143-149.

[0055] In an embodiment of the invention, the inventive polypeptide may comprise an α chain and a β chain of the inventive TCR. In this regard, the polypeptide can comprise, e.g., the amino acid sequences of: (1) both of SEQ ID NOs: 14 and 15; (2) both of SEQ ID NOs: 16 and 17; (3) both of SEQ ID NOs: 18 and 19; (4) both of SEQ ID NOs: 33 and 34; (5) both of SEQ ID NOs: 35 and 36; (6) both of SEQ ID NOs: 37 and 38; (7) both of SEQ ID NOs: 52

and 53; (8) both of SEQ ID NOs: 54 and 55; (9) both of SEQ ID NOs: 56 and 57; (10) both of SEQ ID NOs: 71 and 72; (11) both of SEQ ID NOs: 73 and 74; (12) both of SEQ ID NOs: 75 and 76; (13) both of SEQ ID NOs: 90 and 91; (14) both of SEQ ID NOs: 92 and 93; or (15) both of SEQ ID NOs: 94 and 95.

[0056] An embodiment of the invention further provides a protein comprising at least one of the polypeptides described herein. By “protein” is meant a molecule comprising one or more polypeptide chains. In an embodiment, the protein of the invention can comprise: (1) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 2-4 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 5-7; (2) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 21-23 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 24-26; (3) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 40-42 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 43-45; (4) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 59-61 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 62-64; or (5) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 78-80 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 81-83.

[0057] In an embodiment of the invention, the protein comprises: (1) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 8 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 9; (2) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 10 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 11; (3) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 12 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 13; (4) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 12 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 11; (5) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 121 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 13; (6) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 121 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 122; (7) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 8 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 120; (8) a first polypeptide chain

comprising the amino acid sequence of SEQ ID NO: 119 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 9; (9) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 119 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 120; (10) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 27 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 28; (11) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 29 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 30; (12) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 31 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 32; (13) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 31 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 30; (14) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 125 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 32; (15) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 125 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 126; (16) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 27 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 124; (17) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 123 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 28; (18) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 123 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 124; (19) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 46 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 47; (20) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 48 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 49; (21) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 50 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 51; (22) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 50 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 49; (23) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 129 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 51; (24) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 129 and a second polypeptide chain

comprising the amino acid sequence of SEQ ID NO: 130; (25) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 46 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 128; (26) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 127 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 47; (27) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 127 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 128; (28) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 65 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 66; (29) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 67 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 68; (30) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 69 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 70; (31) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 69 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 68; (32) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 133 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 70; (33) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 133 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 134; (34) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 65 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 132; (35) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 131 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 66; (36) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 131 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 132; (37) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 84 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 85; (38) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 86 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 87; (39) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 88 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 89; (40) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 88 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 87; (41) a first polypeptide chain

comprising the amino acid sequence of SEQ ID NO: 137 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 89; (42) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 137 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 138; (43) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 84 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 136; (44) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 135 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 85; or (45) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 135 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 136.

[0058] In an embodiment of the invention, the protein can further comprise the constant region of the inventive TCR set forth above. In this regard, the first polypeptide chain can comprise one of SEQ ID NOs: 99, 140, and 142 and the second polypeptide chain can comprise one of SEQ ID NOs: 97, 98, 139, 141, and 143-149.

[0059] In an embodiment of the invention, the protein comprises: (1) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 14 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 15; (2) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 16 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 17; (3) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 18 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 19; (4) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 33 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 34; (5) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 35 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 36; (6) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 37 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 38; (7) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 52 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 53; (8) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 54 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 55; (9) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 56 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 57; (10) a first polypeptide chain

comprising the amino acid sequence of SEQ ID NO: 71 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 72; (11) 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; (12) 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; (13) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 90 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 91; (14) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 92 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 93; or (15) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 94 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 95.

{0060} The protein of the invention may be a TCR. Alternatively, if the first and/or second polypeptide chain(s) of the protein further comprise(s) other amino acid sequences, e.g., an amino acid sequence encoding an immunoglobulin or a portion thereof, then the inventive protein can be a fusion protein. In this regard, an embodiment of the invention also provides a fusion protein comprising at least one of the inventive polypeptides described herein along with at least one other polypeptide. The other polypeptide can exist as a separate polypeptide of the fusion protein, or can exist as a polypeptide, which is expressed in frame (in tandem) with one of the inventive polypeptides described herein. The other polypeptide can encode any peptidic or proteinaceous molecule, or a portion thereof, including, but not limited to an immunoglobulin, CD3, CD4, CD8, an MHC molecule, a CD1 molecule, e.g., CD1a, CD1b, CD1c, CD1d, etc.

{0061} The fusion protein can comprise one or more copies of the inventive polypeptide and/or one or more copies of the other polypeptide. For instance, the fusion protein can comprise 1, 2, 3, 4, 5, or more, copies of the inventive polypeptide and/or of the other polypeptide. Suitable methods of making fusion proteins are known in the art, and include, for example, recombinant methods.

{0062} In some embodiments of the invention, the TCRs, polypeptides, and proteins of the invention may be expressed as a single protein comprising a linker peptide linking the α chain and the β chain. In this regard, the TCRs, polypeptides, and proteins of the invention may further comprise a linker peptide. The linker peptide may advantageously facilitate the expression of a recombinant TCR, polypeptide, and/or protein in a host cell. The linker

peptide may comprise any suitable amino acid sequence. For example, the linker peptide may comprise the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 100). Upon expression of the construct, including the linker peptide by a host cell, the linker peptide may be cleaved, resulting in separated α and β chains. In an embodiment of the invention, the TCR, polypeptide, or protein may comprise an amino acid sequence comprising a full-length α chain, a full-length β chain, and a linker peptide positioned between the α and β chains.

[0063] In some embodiments, the TCR, polypeptide or protein disclosed herein comprises an α chain and/or a β chain, as disclosed herein, comprising a signal peptide. In some embodiments, the sequence of the signal peptide of any of the α chains and/or β chains disclosed herein comprises an alanine or histidine residue substituted for the wild-type residue at position 2.

[0064] In some embodiments, the TCR, polypeptide or protein disclosed herein comprises a mature version of an α chain and/or a β chain, as disclosed herein, that lacks a signal peptide.

[0065] The protein of the invention can be a recombinant antibody, or an antigen binding portion thereof, comprising at least one of the inventive polypeptides described herein. As used herein, “recombinant antibody” refers to a recombinant (e.g., genetically engineered) protein comprising at least one of the polypeptides of the invention and a polypeptide chain of an antibody, or an antigen binding portion thereof. The polypeptide of an antibody, or antigen binding portion thereof, can be a heavy chain, a light chain, a variable or constant region of a heavy or light chain, a single chain variable fragment (scFv), or an Fc, Fab, or F(ab)₂’ fragment of an antibody, etc. The polypeptide chain of an antibody, or an antigen binding portion thereof, can exist as a separate polypeptide of the recombinant antibody. Alternatively, the polypeptide chain of an antibody, or an antigen binding portion thereof, can exist as a polypeptide, which is expressed in frame (in tandem) with the polypeptide of the invention. The polypeptide of an antibody, or an antigen binding portion thereof, can be a polypeptide of any antibody or any antibody fragment, including any of the antibodies and antibody fragments described herein.

[0066] The TCRs, polypeptides, and proteins of the invention can be of any length, i.e., can comprise any number of amino acids, provided that the TCRs, polypeptides, or proteins retain their biological activity, e.g., the ability to specifically bind to mutated p53; detect cancer in a mammal; or treat or prevent cancer in a mammal, etc. For example, the

polypeptide can be in the range of from about 50 to about 5,000 amino acids long, such as 50, 70, 75, 100, 125, 150, 175, 200, 300, 400, 500, 600, 700, 800, 900, 1000 or more amino acids in length. In this regard, the polypeptides of the invention also include oligopeptides.

[0067] The TCRs, polypeptides, and proteins of the invention of the invention can comprise synthetic amino acids in place of one or more naturally-occurring amino acids. Such synthetic amino acids are known in the art, and include, for example, aminocyclohexane carboxylic acid, norleucine, α -amino n-decanoic acid, homoserine, S-acetylaminoethyl-cysteine, trans-3- and trans-4-hydroxyproline, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β -phenylserine β -hydroxyphenylalanine, phenylglycine, α -naphthylalanine, cyclohexylalanine, cyclohexylglycine, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aminomalonic acid, aminomalonic acid monoamide, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α -aminocyclopentane carboxylic acid, α -aminocyclohexane carboxylic acid, α -aminocycloheptane carboxylic acid, α -(2-amino-2-norbornane)-carboxylic acid, α,γ -diaminobutyric acid, α,β -diaminopropionic acid, homophenylalanine, and α -tert-butylglycine.

[0068] The TCRs, polypeptides, and proteins of the invention can be, e.g., glycosylated, amidated, carboxylated, phosphorylated, esterified, N-acylated, cyclized via, e.g., a disulfide bridge, or converted into an acid addition salt and/or optionally dimerized or polymerized, or conjugated.

[0069] The TCR, polypeptide, and/or protein of the invention can be obtained by methods known in the art such as, for example, *de novo* synthesis. Also, polypeptides and proteins can be recombinantly produced using the nucleic acids described herein using standard recombinant methods. See, for instance, Green and Sambrook, Molecular Cloning: A Laboratory Manual, 4th ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (2012). Alternatively, the TCRs, polypeptides, and/or proteins described herein can be synthesized by any of a variety of commercial entities. In this respect, the inventive TCRs, polypeptides, and proteins can be synthetic, recombinant, isolated, and/or purified.

[0070] An embodiment of the invention provides a nucleic acid comprising a nucleotide sequence encoding any of the TCRs, polypeptides, or proteins described herein. "Nucleic acid," as used herein, includes "polynucleotide," "oligonucleotide," and "nucleic acid molecule," and generally means a polymer of DNA or RNA, which can be single-stranded or

double-stranded, which can contain natural, non-natural or altered nucleotides, and which can contain a natural, non-natural or altered internucleotide linkage, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified oligonucleotide. In an embodiment, the nucleic acid comprises complementary DNA (cDNA). It is generally preferred that the nucleic acid does not comprise any insertions, deletions, inversions, and/or substitutions. However, it may be suitable in some instances, as discussed herein, for the nucleic acid to comprise one or more insertions, deletions, inversions, and/or substitutions.

[0071] An embodiment of the invention provides an isolated or purified nucleic acid comprising, from 5' to 3', a first nucleic acid sequence and a second nucleotide sequence, wherein the first and second nucleotide sequence, respectively, encode the amino sequences of SEQ ID NOs: 8 and 9; 9 and 8; 10 and 11; 11 and 10; 12 and 13; 13 and 12; 12 and 11; 11 and 12; 121 and 13; 13 and 121; 121 and 122; 122 and 121; 8 and 120; 120 and 8; 119 and 9; 9 and 119; 119 and 120; 120 and 119; 14 and 15; 15 and 14; 16 and 17; 17 and 16; 18 and 19; 19 and 18; 27 and 28; 28 and 27; 29 and 30; 30 and 29; 31 and 32; 32 and 31; 31 and 30; 30 and 31; 125 and 32; 32 and 125; 125 and 126; 126 and 125; 27 and 124; 124 and 27; 123 and 28; 28 and 123; 123 and 124; 124 and 123; 33 and 34; 34 and 33; 35 and 36; 36 and 35; 37 and 38; 38 and 37; 46 and 47; 47 and 46; 48 and 49; 49 and 48; 50 and 51; 51 and 50; 50 and 49; 49 and 50; 129 and 51; 51 and 129; 129 and 130; 130 and 129; 46 and 128; 128 and 46; 127 and 47; 47 and 127; 127 and 128; 128 and 127; 52 and 53; 53 and 52; 54 and 55; 55 and 54; 56 and 57; 57 and 56; 65 and 66; 66 and 65; 67 and 68; 68 and 67; 69 and 70; 70 and 69; 69 and 68; 68 and 69; 133 and 70; 70 and 133; 133 and 134; 134 and 133; 65 and 132; 132 and 65; 131 and 66; 66 and 131; 131 and 132; 132 and 131; 71 and 72; 72 and 71; 73 and 74; 74 and 73; 75 and 76; 76 and 75; 84 and 85; 85 and 84; 86 and 87; 87 and 86; 88 and 89; 89 and 88; 88 and 87; 87 and 88; 137 and 89; 89 and 137; 137 and 138; 138 and 137; 84 and 136; 136 and 84; 135 and 85; 85 and 135; 135 and 136; 136 and 135; 90 and 91; 91 and 90; 92 and 93; 93 and 92; 94 and 95; or 95 and 94.

[0072] In an embodiment of the invention, the nucleic acid further comprises a third nucleotide acid sequence interposed between the first and second nucleotide sequence, wherein the third nucleotide sequence encodes a cleavable linker peptide. For example, the cleavable linker peptide may comprise the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 100). In an embodiment, of the invention, nucleic acid encodes an amino acid sequence selected from the group consisting

of: SEQ ID NOs: 20, 39, 58, 77, and 96. For example, the nucleic acid may comprise a nucleotide sequence selected from the group consisting of SEQ ID NOs: 109-113.

[0073] Preferably, the nucleic acids of the invention are recombinant. As used herein, the term “recombinant” refers to (i) molecules that are constructed outside living cells by joining natural or synthetic nucleic acid segments to nucleic acid molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above. For purposes herein, the replication can be *in vitro* replication or *in vivo* replication.

[0074] The nucleic acids can be constructed based on chemical synthesis and/or enzymatic ligation reactions using procedures known in the art. See, for example, Green and Sambrook et al., *supra*. For example, a nucleic acid can be chemically synthesized using naturally-occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed upon hybridization (e.g., phosphorothioate derivatives and acridine substituted nucleotides). Examples of modified nucleotides that can be used to generate the nucleic acids include, but are not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N⁶-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N⁶-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N⁶-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine. Alternatively, one or more of the nucleic acids of the invention can be purchased from any of a variety of commercial entities.

[0075] In an embodiment of the invention, the nucleic acid comprises a codon-optimized nucleotide sequence encoding any of the TCRs, polypeptides, or proteins described herein. Without being bound to any particular theory or mechanism, it is believed that codon optimization of the nucleotide sequence increases the translation efficiency of the mRNA transcripts. Codon optimization of the nucleotide sequence may involve substituting a native codon for another codon that encodes the same amino acid, but can be translated by tRNA

that is more readily available within a cell, thus increasing translation efficiency.

Optimization of the nucleotide sequence may also reduce secondary mRNA structures that would interfere with translation, thus increasing translation efficiency.

[0076] An embodiment of the invention also provides a nucleic acid comprising a nucleotide sequence which is complementary to the nucleotide sequence of any of the nucleic acids described herein or a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of any of the nucleic acids described herein.

[0077] The nucleotide sequence which hybridizes under stringent conditions preferably hybridizes under high stringency conditions. By “high stringency conditions” is meant that the nucleotide sequence specifically hybridizes to a target sequence (the nucleotide sequence of any of the nucleic acids described herein) in an amount that is detectably stronger than non-specific hybridization. High stringency conditions include conditions which would distinguish a polynucleotide with an exact complementary sequence, or one containing only a few scattered mismatches from a random sequence that happened to have a few small regions (e.g., 3-10 bases) that matched the nucleotide sequence. Such small regions of complementarity are more easily melted than a full-length complement of 14-17 or more bases, and high stringency hybridization makes them easily distinguishable. Relatively high stringency conditions would include, for example, low salt and/or high temperature conditions, such as provided by about 0.02-0.1 M NaCl or the equivalent, at temperatures of about 50-70 °C. Such high stringency conditions tolerate little, if any, mismatch between the nucleotide sequence and the template or target strand and are particularly suitable for detecting expression of any of the inventive TCRs. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide.

[0078] An embodiment of the invention also provides a nucleic acid comprising a nucleotide sequence that is at least about 70% or more, e.g., about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any of the nucleic acids described herein. In this regard, the nucleic acid may consist essentially of any of the nucleotide sequences described herein.

[0079] The nucleic acids of the invention can be incorporated into a recombinant expression vector. In this regard, an embodiment of the invention provides a recombinant expression vector comprising any of the nucleic acids of the invention. In an embodiment of the invention, the recombinant expression vector comprises a nucleotide sequence encoding the α chain, the β chain, and linker peptide.

[0080] For purposes herein, the term “recombinant expression vector” means a genetically-modified oligonucleotide or polynucleotide construct that permits the expression of an mRNA, protein, polypeptide, or peptide by a host cell, when the construct comprises a nucleotide sequence encoding the mRNA, protein, polypeptide, or peptide, and the vector is contacted with the cell under conditions sufficient to have the mRNA, protein, polypeptide, or peptide expressed within the cell. The vectors of the invention are not naturally-occurring as a whole. However, parts of the vectors can be naturally-occurring. The inventive recombinant expression vectors can comprise any type of nucleotide, including, but not limited to DNA and RNA, which can be single-stranded or double-stranded, synthesized or obtained in part from natural sources, and which can contain natural, non-natural or altered nucleotides. The recombinant expression vectors can comprise naturally-occurring, non-naturally-occurring internucleotide linkages, or both types of linkages. Preferably, the non-naturally-occurring or altered nucleotides or internucleotide linkages do not hinder the transcription or replication of the vector.

[0081] The recombinant expression vector of the invention can be any suitable recombinant expression vector and can be used to transform or transfect any suitable host cell. Suitable vectors include those designed for propagation and expansion or for expression or both, such as plasmids and viruses. The vector can be selected from the group consisting of the transposon/transposase series, pUC series (Fermentas Life Sciences), the pBluescript series (Stratagene, La Jolla, CA), the pET series (Novagen, Madison, WI), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, CA). Bacteriophage vectors, such as λ GT10, λ GT11, λ ZapII (Stratagene), λ EMBL4, and λ NM1149, also can be used. Examples of plant expression vectors include pBI01, pBI101.2, pBI101.3, pBI121 and pBIN19 (Clontech). Examples of animal expression vectors include pEUK-CI, pMAM and pMAMneo (Clontech). Preferably, the recombinant expression vector is a transposon or a viral vector, e.g., a lentiviral vector or a retroviral vector.

[0082] The recombinant expression vectors of the invention can be prepared using standard recombinant DNA techniques described in, for example, Green and Sambrook et al., *supra*. Constructs of expression vectors, which are circular or linear, can be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived, e.g., from ColEI, 2 μ plasmid, λ , SV40, bovine papillomavirus, and the like.

{0083} Desirably, the recombinant expression vector comprises regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host cell (e.g., bacterium, fungus, plant, or animal) into which the vector is to be introduced, as appropriate and taking into consideration whether the vector is DNA- or RNA-based.

{0084} The recombinant expression vector can include one or more marker genes, which allow for selection of transformed or transfected host cells. Marker genes include biocide resistance, e.g., resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host cell to provide prototrophy, and the like. Suitable marker genes for the inventive expression vectors include, for instance, neomycin/G418 resistance genes, hygromycin resistance genes, histidinol resistance genes, tetracycline resistance genes, and ampicillin resistance genes.

{0085} The recombinant expression vector can comprise a native or nonnative promoter operably linked to the nucleotide sequence encoding the TCR, polypeptide, or protein, or to the nucleotide sequence which is complementary to or which hybridizes to the nucleotide sequence encoding the TCR, polypeptide, or protein. The selection of promoters, e.g., strong, weak, inducible, tissue-specific, and developmental-specific, is within the ordinary skill of the artisan. Similarly, the combining of a nucleotide sequence with a promoter is also within the skill of the artisan. The promoter can be a non-viral promoter, e.g., a human elongation factor-1 α promoter, or a viral promoter, e.g., a cytomegalovirus (CMV) promoter, an SV40 promoter, an RSV promoter, and a promoter found in the long-terminal repeat of the murine stem cell virus.

{0086} The inventive recombinant expression vectors can be designed for either transient expression, for stable expression, or for both. Also, the recombinant expression vectors can be made for constitutive expression or for inducible expression.

{0087} Further, the recombinant expression vectors can be made to include a suicide gene. As used herein, the term "suicide gene" refers to a gene that causes the cell expressing the suicide gene to die. The suicide gene can be a gene that confers sensitivity to an agent, e.g., a drug, upon the cell in which the gene is expressed, and causes the cell to die when the cell is contacted with or exposed to the agent. Suicide genes are known in the art and include, for example, the Herpes Simplex Virus (HSV) thymidine kinase (TK) gene, cytosine deaminase, purine nucleoside phosphorylase, and nitroreductase.

{0088} Another embodiment of the invention provides an isolated or purified TCR, polypeptide, or protein encoded by any of the nucleic acids or vectors described herein with respect to other aspects of the invention.

{0089} Still another embodiment of the invention provides an isolated or purified TCR, polypeptide, or protein that results from expression of any of the nucleic acids or vectors described herein with respect to other aspects of the invention.

{0090} Another embodiment of the invention further provides a host cell comprising any of the nucleic acids or any of the recombinant expression vectors described herein. As used herein, the term “host cell” refers to any type of cell that can contain the inventive recombinant expression vector. The host cell can be a eukaryotic cell, e.g., plant, animal, fungi, or algae, or can be a prokaryotic cell, e.g., bacteria or protozoa. The host cell can be a cultured cell or a primary cell, i.e., isolated directly from an organism, e.g., a human. The host cell can be an adherent cell or a suspended cell, i.e., a cell that grows in suspension. Suitable host cells are known in the art and include, for instance, DH5 α *E. coli* cells, Chinese hamster ovarian cells, monkey VERO cells, COS cells, HEK293 cells, and the like. For purposes of amplifying or replicating the recombinant expression vector, the host cell is preferably a prokaryotic cell, e.g., a DH5 α cell. For purposes of producing a recombinant TCR, polypeptide, or protein, the host cell is preferably a mammalian cell. Most preferably, the host cell is a human cell. For example, the host cell may be a human lymphocyte. In an embodiment of the invention, the host cell is selected from the group consisting of a T cell, a natural killer T (NKT) cell, an invariant natural killer T (iNKT) cell, and a natural killer (NK) cell. While the host cell can be of any cell type, can originate from any type of tissue, and can be of any developmental stage, the host cell preferably is a peripheral blood lymphocyte (PBL) or a peripheral blood mononuclear cell (PBMC). More preferably, the host cell is a T cell.

{0091} For purposes herein, the T cell can be any T cell, such as a cultured T cell, e.g., a primary T cell, or a T cell from a cultured T cell line, e.g., Jurkat, SupT1, etc., or a T cell obtained from a mammal. If obtained from a mammal, the T cell can be obtained from numerous sources, including but not limited to blood, bone marrow, lymph node, the thymus, or other tissues or fluids. T cells can also be enriched for or purified. Preferably, the T cell is a human T cell. The T cell can be any type of T cell and can be of any developmental stage, including but not limited to, CD4⁺/CD8⁺ double positive T cells, CD4⁺ helper T cells, e.g., Th₁ and Th₂ cells, CD4⁺ T cells, CD8⁺ T cells (e.g., cytotoxic T cells), tumor infiltrating

lymphocytes (TILs), memory T cells (e.g., central memory T cells and effector memory T cells), naïve T cells, and the like.

[0092] Also provided by an embodiment of the invention is a population of cells comprising at least one host cell described herein. The population of cells can be a heterogeneous population comprising the host cell comprising any of the recombinant expression vectors described, in addition to at least one other cell, e.g., a host cell (e.g., a T cell), which does not comprise any of the recombinant expression vectors, or a cell other than a T cell, e.g., a B cell, a macrophage, a neutrophil, an erythrocyte, a hepatocyte, an endothelial cell, an epithelial cell, a muscle cell, a brain cell, etc. Alternatively, the population of cells can be a substantially homogeneous population, in which the population comprises mainly of host cells (e.g., consisting essentially of) comprising the recombinant expression vector. The population also can be a clonal population of cells, in which all cells of the population are clones of a single host cell comprising a recombinant expression vector, such that all cells of the population comprise the recombinant expression vector. In one embodiment of the invention, the population of cells is a clonal population comprising host cells comprising a recombinant expression vector as described herein.

[0093] In an embodiment of the invention, the numbers of cells in the population may be rapidly expanded. Expansion of the numbers of T cells can be accomplished by any of a number of methods as are known in the art as described in, for example, U.S. Patent 8,034,334; U.S. Patent 8,383,099; U.S. Patent Application Publication No. 2012/0244133; Dudley et al., *J. Immunother.*, 26:332-42 (2003); and Riddell et al., *J. Immunol. Methods*, 128:189-201 (1990). In an embodiment, expansion of the numbers of T cells is carried out by culturing the T cells with OKT3 antibody, IL-2, and feeder PBMC (e.g., irradiated allogeneic PBMC).

[0094] An embodiment of the invention provides a method of producing a host cell expressing a TCR that has antigenic specificity for the peptide of DRNTRHSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115) or SGNLLGRNSFEVCVCACPGRDRRTE (SEQ ID NO: 117), the method comprising contacting a cell with any of the vectors described herein under conditions that allow introduction of the vector into the cell.

[0095] The inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, and host cells (including populations thereof), can be isolated and/or purified. The term “isolated” as used herein means having been removed from its natural

environment. The term “purified” as used herein means having been increased in purity, wherein “purity” is a relative term, and not to be necessarily construed as absolute purity. For example, the purity can be at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or can be about 100%.

{0096} The inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, and host cells (including populations thereof), all of which are collectively referred to as “inventive TCR materials” hereinafter, can be formulated into a composition, such as a pharmaceutical composition. In this regard, an embodiment of the invention provides a pharmaceutical composition comprising any of the TCRs, polypeptides, proteins, nucleic acids, expression vectors, and host cells (including populations thereof), described herein, and a pharmaceutically acceptable carrier. The inventive pharmaceutical compositions containing any of the inventive TCR materials can comprise more than one inventive TCR material, e.g., a polypeptide and a nucleic acid, or two or more different TCRs. Alternatively, the pharmaceutical composition can comprise an inventive TCR material in combination with another pharmaceutically active agent(s) or drug(s), such as a chemotherapeutic agent, e.g., asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, vincristine, etc.

{0097} Preferably, the carrier is a pharmaceutically acceptable carrier. With respect to pharmaceutical compositions, the carrier can be any of those conventionally used for the particular inventive TCR material under consideration. Methods for preparing administrable compositions are known or apparent to those skilled in the art and are described in more detail in, for example, *Remington: The Science and Practice of Pharmacy*, 22nd Ed., Pharmaceutical Press (2012). It is preferred that the pharmaceutically acceptable carrier be one which has no detrimental side effects or toxicity under the conditions of use.

{0098} The choice of carrier will be determined in part by the particular inventive TCR material, as well as by the particular method used to administer the inventive TCR material. Accordingly, there are a variety of suitable formulations of the pharmaceutical composition of the invention. Suitable formulations may include any of those for parenteral, subcutaneous, intravenous, intramuscular, intraarterial, intrathecal, intratumoral, or intraperitoneal administration. More than one route can be used to administer the inventive TCR materials, and in certain instances, a particular route can provide a more immediate and more effective response than another route.

[0099] Preferably, the inventive TCR material is administered by injection, e.g., intravenously. When the inventive TCR material is a host cell expressing the inventive TCR, the pharmaceutically acceptable carrier for the cells for injection may include any isotonic carrier such as, for example, normal saline (about 0.90% w/v of NaCl in water, about 300 mOsm/L NaCl in water, or about 9.0 g NaCl per liter of water), NORMOSOL R electrolyte solution (Abbott, Chicago, IL), PLASMA-LYTE A (Baxter, Deerfield, IL), about 5% dextrose in water, or Ringer's lactate. In an embodiment, the pharmaceutically acceptable carrier is supplemented with human serum albumen.

[0100] The amount or dose (e.g., numbers of cells when the inventive TCR material is one or more cells) of the inventive TCR material administered should be sufficient to effect, e.g., a therapeutic or prophylactic response, in the subject or animal over a reasonable time frame. For example, the dose of the inventive TCR material should be sufficient to bind to a cancer antigen (e.g., mutated p53), or detect, treat, or prevent cancer in a period of from about 2 hours or longer, e.g., 12 to 24 or more hours, from the time of administration. In certain embodiments, the time period could be even longer. The dose will be determined by the efficacy of the particular inventive TCR material and the condition of the animal (e.g., human), as well as the body weight of the animal (e.g., human) to be treated.

[0101] Many assays for determining an administered dose are known in the art. For example, an assay, which comprises comparing the extent to which target cells are lysed or IFN- γ is secreted by T cells expressing the inventive TCR, polypeptide, or protein upon administration of a given dose of such T cells to a mammal among a set of mammals of which each is given a different dose of the T cells, could be used to determine a starting dose to be administered to a mammal. The extent to which target cells are lysed or IFN- γ is secreted upon administration of a certain dose can be assayed by methods known in the art.

[0102] The dose of the inventive TCR material also will be determined by the existence, nature and extent of any adverse side effects that might accompany the administration of a particular inventive TCR material. Typically, the attending physician will decide the dosage of the inventive TCR material with which to treat each individual patient, taking into consideration a variety of factors, such as age, body weight, general health, diet, sex, inventive TCR material to be administered, route of administration, and the severity of the cancer being treated. In an embodiment in which the inventive TCR material is a population of cells, the number of cells administered per infusion may vary, e.g., from about 1×10^6 to

about 1×10^{12} cells or more. In certain embodiments, fewer than 1×10^6 cells may be administered.

[0103] One of ordinary skill in the art will readily appreciate that the inventive TCR materials of the invention can be modified in any number of ways, such that the therapeutic or prophylactic efficacy of the inventive TCR materials is increased through the modification. For instance, the inventive TCR materials can be conjugated either directly or indirectly through a bridge to a chemotherapeutic agent. The practice of conjugating compounds to a chemotherapeutic agent is known in the art. One of ordinary skill in the art recognizes that sites on the inventive TCR materials, which are not necessary for the function of the inventive TCR materials, are ideal sites for attaching a bridge and/or a chemotherapeutic agent, provided that the bridge and/or chemotherapeutic agent, once attached to the inventive TCR materials, do(es) not interfere with the function of the inventive TCR materials, i.e., the ability to bind to mutated p53 or to detect, treat, or prevent cancer.

[0104] It is contemplated that the inventive pharmaceutical compositions, TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, or populations of cells can be used in methods of treating or preventing cancer. Without being bound to a particular theory, the inventive TCRs are believed to bind specifically to mutated p53, such that the TCR (or related inventive polypeptide or protein), when expressed by a cell, is able to mediate an immune response against a target cell expressing mutated p53. In this regard, an embodiment of the invention provides a method of treating or preventing cancer in a mammal, comprising administering to the mammal any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, in an amount effective to treat or prevent cancer in the mammal.

[0105] An embodiment of the invention provides any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, for use in the treatment or prevention of cancer in a mammal.

[0106] The terms “treat,” and “prevent” as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment or prevention. Rather, there are varying degrees of treatment or prevention of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment or prevention of cancer in a mammal. Furthermore, the treatment or prevention provided by the inventive method can include treatment or prevention of one or more conditions or symptoms of the cancer being treated or prevented. For example, treatment or prevention can include promoting the regression of a tumor. Also, for purposes herein, “prevention” can encompass delaying the onset of the cancer, or a symptom or condition thereof. Alternatively, or additionally, “prevention” may encompass preventing or delaying the recurrence of cancer, or a symptom or condition thereof.

[0107] It is also contemplated that the inventive pharmaceutical compositions, TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, or populations of cells can be used in methods of inducing an immune response against a cancer in a mammal. In this regard, an embodiment of the invention provides a method of inducing an immune response against a cancer in a mammal, comprising administering to the mammal any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, in an amount effective to induce an immune response against the cancer in the mammal.

[0108] An embodiment of the invention provides any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, for use in the inducement of an immune response against a cancer in a mammal.

[0109] Also provided by an embodiment of the invention is a method of detecting the presence of cancer in a mammal. The method comprises (i) contacting a sample comprising one or more cells from the mammal with any of the inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, populations of cells, or

pharmaceutical compositions described herein, thereby forming a complex, and (ii) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal.

[0110] With respect to the inventive method of detecting cancer in a mammal, the sample of cells can be a sample comprising whole cells, lysates thereof, or a fraction of the whole cell lysates, e.g., a nuclear or cytoplasmic fraction, a whole protein fraction, or a nucleic acid fraction.

[0111] For purposes of the inventive detecting method, the contacting can take place *in vitro* or *in vivo* with respect to the mammal. Preferably, the contacting is *in vitro*.

[0112] Also, detection of the complex can occur through any number of ways known in the art. For instance, the inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, or populations of cells, described herein, can be labeled with a detectable label such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles).

[0113] For purposes of the inventive methods, wherein host cells or populations of cells are administered, the cells can be cells that are allogeneic or autologous to the mammal. Preferably, the cells are autologous to the mammal.

[0114] With respect to the inventive methods, the cancer can be any cancer, including, e.g., any of acute lymphocytic cancer, acute myeloid leukemia, alveolar rhabdomyosarcoma, bone cancer, brain cancer, breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, cancer of the oral cavity, cancer of the vagina, cancer of the vulva, chronic lymphocytic leukemia, chronic myeloid cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, uterine cervical cancer, gastrointestinal carcinoid tumor, glioma, Hodgkin lymphoma, hypopharynx cancer, kidney cancer, larynx cancer, liver cancer, lung cancer, malignant mesothelioma, melanoma, multiple myeloma, nasopharynx cancer, non-Hodgkin lymphoma, cancer of the oropharynx, ovarian cancer, cancer of the penis, pancreatic cancer, peritoneum, omentum, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer, skin cancer, small intestine cancer, soft tissue cancer, stomach cancer, testicular cancer, thyroid cancer, cancer of the uterus, ureter cancer, and urinary bladder cancer. In a preferred embodiment, the cancer is a cancer which expresses mutated p53. The cancer may express

p53 with a mutation at one or both of positions 273 and 220, as defined by SEQ ID NO: 1. The cancer may express p53 with one or both of the following human p53 mutations: R273C and Y220C. In an embodiment of the invention, the cancer is an epithelial cancer. In an embodiment of the invention, 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. The cancer may be known to comprise an R273C or a Y220C mutation in human p53.

[0115] The mammal referred to in the inventive methods can be any mammal. As used herein, the term “mammal” refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Lagomorpha, such as rabbits. It is preferred that the mammals are from the order Carnivora, including Felines (cats) and Canines (dogs). It is more preferred that the mammals are from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perissodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simioids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human.

[0116] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0117] This example demonstrates the identification of anti-p53-Y220C T cell reactivity in the TIL of Patient 4343.

[0118] Resected tumors from Patient 4343 with a hormone-positive, HER2-positive metastatic breast cancer were cut into 23 fragments and were cultured in the presence of the cytokine IL-2 to grow TILs *ex vivo*. The fragments (numbered F1-F7 and F9-F24) were tested for tumor-specific neoantigen reactivity, including mutant p53, by co-culturing with autologous dendritic cells pulsed with DMSO (vehicle) or the mutant p53-Y220C peptide DRNTFRHSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115). IFN- γ production was measured by ELISpot assay. The results are shown in Fig. 1A. Fragment numbers F2, F3, F11, F21, and F23 were identified to contain TIL which recognized p53-Y220C.

EXAMPLE 2

[0119] This example demonstrates the identification of anti-p53-R273C T cell reactivity in the TIL of Patient 4386.

[0120] Resected tumors from Patient 4386's left breast axillary lymph node were cut into 24 fragments and were cultured in the presence of the cytokine IL-2 to grow TILs *ex vivo*. The fragments (numbered F1-F24) were tested for tumor-specific neoantigen reactivity, including mutant p53, by co-culturing with autologous dendritic cells pulsed with DMSO (vehicle) or mutant p53-R273C peptide SGNLLGRNSFEVCVCACPGRDRRTE (SEQ ID NO: 117). IFN- γ production was measured by ELISpot assay. The results are shown in Fig. 1B. Fragment number F7 was identified to contain TIL which recognized p53-R273C.

[0121] T cells from fresh tumor digest of Patient 4386 (Tumor 1A or Tumor 1B) were sorted based on expression of CD3 and one or more of the cell surface markers CD4, CD8, CD39, PD-1 and TIGIT. The sorted cell populations were expanded and tested for reactivity against the mutant p53-R273C peptide or DMSO. IFN- γ production was measured by ELISpot assay. The results are shown in Fig. 1C. Two cell populations from Tumor 1A were identified to contain T cells which recognized p53-R273C: CD3⁺CD4⁺CD39⁺PD-1⁺TIGIT⁺ and CD3⁺CD4⁺CD39⁺PD-1⁺TIGIT⁻.

[0122] TIL from patient 4386 were subjected to *in vitro* sensitization to enrich for neoantigen-reactive T cells, followed by testing against DMSO or the mutant p53-R273C peptide. T cell activation markers, 4-1BB and OX40, were measured by flow cytometry. The results are shown in Fig. 1D.

EXAMPLE 3

[0123] This example demonstrates the isolation of an anti-p53-Y220C TCR from the reactive TIL of Example 1.

[0124] Reactive TIL were re-stimulated and sorted by 4-1BB upregulation into 96 well plates for single-cell T cell receptor (TCR) sequencing. A TCR was found, namely 4343-D TCR (TRAV12-3 / TRBV27).

[0125] The sequences of the TCR alpha and beta chain variable regions were identified by single-cell TCR sequencing. The amino acid sequences of the alpha and beta chain variable regions are shown in Table 3. The CDRs are underlined. The N-terminal signal peptides are in bold font.

TABLE 3

TCR name	TCR chain	Amino acid sequence
4343-D TCR	Variable α (Predicted sequence without N-terminal signal peptide SignalP)	QOKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSR KGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSA TYLCAGGSYGKLTFTGQGTILTVHP (SEQ ID NO: 8)
	Variable α (Predicted sequence without N-terminal signal peptide IMGT)	QKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSRK GPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSAT YLCAGGSYGKLTFTGQGTILTVHP (SEQ ID NO: 119)
	Variable β (Predicted sequence without N-terminal signal peptide SignalP)	QVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGL RQIYYSMNVEVTDKGDVPEGYKVSRRKEKRNFLILESPSPNQ TSLYFCASSFISNQPHFGDGTRLSIL (SEQ ID NO: 9)
	Variable β (Predicted sequence without N-terminal signal peptide IMGT)	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGL GLRQIYYSMNVEVTDKGDVPEGYKVSRRKEKRNFLILESPSP NQTSLYFCASSFISNQPHFGDGTRLSIL (SEQ ID NO: 120)
	Variable α (With N-terminal signal peptide with H at position 2)	MHKSRLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRF TAQVDKSSKYISLFIRDSQPSDSATYLCAGGSYGKLTFTGQGTIL TVHP (SEQ ID NO: 10)
	Variable α (With N-terminal signal peptide with A at position 2)	MAKSRLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRF TAQVDKSSKYISLFIRDSQPSDSATYLCAGGSYGKLTFTGQGTIL TVHP (SEQ ID NO: 121)
	Variable β (With N-terminal signal peptide with A at position 2)	MAPQLLGYYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVT CSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTDKGDVPEG YKVSRRKEKRNFLILESPSPNQTSLYFCASSFISNQPHFGDGTR LSIL (SEQ ID NO: 11)
	Variable β (With N-terminal signal peptide with H at position 2)	MHPQLLGYYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVT CSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTDKGDVPEG YKVSRRKEKRNFLILESPSPNQTSLYFCASSFISNQPHFGDGTR LSIL (SEQ ID NO: 122)
	Variable α (With WT N-terminal signal peptide)	MMKSRLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDG RFTAQVDKSSKYISLFIRDSQPSDSATYLCAGGSYGKLTFTGQGT ILTVHP (SEQ ID NO: 12)
	Variable β	MGPQLLGYYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVT CSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTDKGDVPEG

TCR name	TCR chain	Amino acid sequence
	(With WT N-terminal signal peptide)	YKVS ~~RKEKRN~~ FPLILESPSPNQTSLYFCASSFISNQPHFGDGTRLSIL (SEQ ID NO: 13)

EXAMPLE 4

[0126] This example demonstrates the isolation of an anti-p53-R273C TCR from the reactive TIL of Example 2.

[0127] Reactive TIL were re-stimulated and sorted by 4-1BB upregulation into 96 well plates for single-cell T cell receptor (TCR) sequencing. Four TCRs were found, namely 4386-F TCR (TRAV13-2 / TRBV4-3), 4386-G TCR (TRAV3 / TRBV20-1), 4386-H TCR (TRAV23 / TRBV7-2), and 4386-O TCR (TRAV13-2 / TRBV7-3).

[0128] The sequences of the TCR alpha and beta chain variable regions were identified by single-cell TCR sequencing. The amino acid sequences of the alpha and beta chain variable regions are shown in Table 4. The CDRs are underlined. The N-terminal signal peptides are in bold font.

TABLE 4

TCR Name	TCR chain	Amino acid sequence
4386-F TCR	Variable α (Predicted sequence without N-terminal signal peptide SignalP)	ESVGLHLP ~~TL~~ SVQEGDNSIINCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDK ~~RQ~~ QQRVTVLLNKTVKHL ~~SL~~ QIAATQPGDSAVYFCAEKSTGNQFYFGTGTSLTVIP (SEQ ID NO: 27)
	Variable α (Predicted sequence without N-terminal signal peptide IMGT)	GESVGLHLP ~~TL~~ SVQEGDNSIINCAYSNSASDYFIWYKQESGKGKQFIIDIRSNMDK ~~RQ~~ QQRVTVLLNKTVKHL ~~SL~~ QIAATQPGDSAVYFCAEKSTGNQFYFGTGTSLTVIP (SEQ ID NO: 123)
	Variable β (Predicted sequence without N-terminal signal peptide SignalP)	METGVTQT ~~PRHL~~ VMGMTNKKSLKCEQHLGH ~~N~~ AMYWYKQSAKKPLELMFVYSLEERVENNSVPSRFSPECN ~~SSH~~ FLHLHTLQPEDSALYL ~~CASSR~~ VEGSDTQYFGPGTRLTVL (SEQ ID NO: 28)
	Variable β (Predicted sequence without N-terminal signal peptide IMGT)	ETGVTQT ~~PRHL~~ VMGMTNKKSLKCEQHLGH ~~N~~ AMYWYKQSAKKPLELMFVYSLEERVENNSVPSRFSPECN ~~SSH~~ FLHLHTLQPEDSALYL ~~CASSR~~ VEGSDTQYFGPGTRLTVL (SEQ ID NO: 124)
	Variable α (With N-terminal signal peptide)	MHGIRALFMYLWLQLDWVSR GESVGLHLP ~~TL~~ SVQEGDNSIINCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDK ~~RQ~~ QQRVTVLLNKTVKHL ~~SL~~ QIAATQPGDSAVYFCAEKSTGNQFYFGTGTSLTVIP (SEQ ID NO: 29)

TCR Name	TCR chain	Amino acid sequence
	with H at position 2)	
	Variable α (With N-terminal signal peptide with A at position 2)	MAGIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSII NCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDKRQGRVTV LLNKTVKHLSLQIAATQPGDSAVYFCAEKSTGNQFYFGTGTSL TVIP (SEQ ID NO: 125)
	Variable β (With N-terminal signal peptide with A at position 2)	MACRLLCCAVLCLLGAVPMETGVTQTTPRHLVMGMTNKKSL KCEQHLGHNAMYWYKQSAKKPLELMFVYSLEERVENNSVPS RFSPECNSSLFLHLHTLQPEDSALYLCASSRVEGSDTQYFGP GTRLTVL (SEQ ID NO: 30)
	Variable β (With N-terminal signal peptide with H at position 2)	MHCRLCCAVLCLLGAVPMETGVTQTTPRHLVMGMTNKKSL KCEQHLGHNAMYWYKQSAKKPLELMFVYSLEERVENNSVPS RFSPECNSSLFLHLHTLQPEDSALYLCASSRVEGSDTQYFGP GTRLTVL (SEQ ID NO: 126)
	Variable α (With WT N-terminal signal peptide)	MAGIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSII NCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDKRQGRVTV LLNKTVKHLSLQIAATQPGDSAVYFCAEKSTGNQFYFGTGTSL TVIP (SEQ ID NO: 31)
	Variable β (With WT N-terminal signal peptide)	MGCRLCCAVLCLLGAVPMETGVTQTTPRHLVMGMTNKKSL KCEQHLGHNAMYWYKQSAKKPLELMFVYSLEERVENNSVPS RFSPECNSSLFLHLHTLQPEDSALYLCASSRVEGSDTQYFGP GTRLTVL (SEQ ID NO: 32)
	Variable α (Predicted sequence without N-terminal signal peptide SignalP)	QSVAPQEDQVNVAEGNPLTVKCTYSVSGNPYLFWYVQYPNR GLQFLKYYITGDNLYKGSYGFEAEFNKSQTSFHLKKPSALVSD SALYFCAVRDPTVSGTYKYIFGTGTRLK VLA (SEQ ID NO: 46)
4386-G TCR	Variable α (Predicted sequence without N-terminal signal peptide IMGT)	AQSVAPQEDQVNVAEGNPLTVKCTYSVSGNPYLFWYVQYPN RGLQFLKYYITGDNLYKGSYGFEAEFNKSQTSFHLKKPSALVS DSALYFCAVRDPTVSGTYKYIFGTGTRLK VLA (SEQ ID NO: 127)
	Variable β (Predicted sequence without N-terminal signal peptide SignalP)	AVVSQHPSRVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSL MLMATSNESKATYEQGVEKDKFLINHASLTLSTLTVTSAHPE DSSFYICSAIRDRSGGETQYFGPGTRLVL (SEQ ID NO: 47)
	Variable β (Predicted sequence without N-terminal signal peptide IMGT)	GAVVSQHPSRVICKSGTSVKIECRSLDFQATTMFWYRQFPKQS LMLMATSNESKATYEQGVEKDKFLINHASLTLSTLTVTSAHP EDSSFYICSAIRDRSGGETQYFGPGTRLVL (SEQ ID NO: 128)
	Variable α	MHSAPISMLAMLFTLSGLRAQSVAPQEDQVNVAEGNPLTVK CTYSVSGNPYLFWYVQYPNRGLQFLKYYITGDNLYKGSYGFE

TCR Name	TCR chain	Amino acid sequence
	(With N-terminal signal peptide with H at position 2)	AEFNKSQTSFHLKKPSALVSDSALYFCAVRDPTVSGTYKYIFG TGTRLKVLA (SEQ ID NO: 48)
	Variable α (With N-terminal signal peptide with A at position 2)	MASAPISMLAMLFTLSGLRAQSV AQPEDQVNVAEGNPLTVK CTYSVSGNPYLFWYVQYPNRLQFLK YITGDNLVKGSYGFE AEFNKSQTSFHLKKPSALVSDSALYFCAVRDPTVSGTYKYIFG TGTRLKVLA (SEQ ID NO: 129)
	Variable β (With N-terminal signal peptide with A at position 2)	MALLLLLLGPGSGLGAVVSQHPSRVICKSGTSVKIECRSLDF QATTMFWYRQFPKQSLMLMAT\$NEGSKATYEQGVEKDKFLI NHASLTSTLTVTSAHPEDSSFYICSAIRDRSGGETQYFGPGTR LLVL (SEQ ID NO: 49)
	Variable β (With N-terminal signal peptide with H at position 2)	MHLLLLLLGPGSGLGAVVSQHPSRVICKSGTSVKIECRSLDF QATTMFWYRQFPKQSLMLMAT\$NEGSKATYEQGVEKDKFLI NHASLTSTLTVTSAHPEDSSFYICSAIRDRSGGETQYFGPGTR LLVL (SEQ ID NO: 130)
	Variable α (With WT N-terminal signal peptide)	MASAPISMLAMLFTLSGLRAQSV AQPEDQVNVAEGNPLTVK CTYSVSGNPYLFWYVQYPNRLQFLK YITGDNLVKGSYGFE AEFNKSQTSFHLKKPSALVSDSALYFCAVRDPTVSGTYKYIFG TGTRLKVLA (SEQ ID NO: 50)
	Variable β (With WT N-terminal signal peptide)	MLLLLLLLGPGSGLGAVVSQHPSRVICKSGTSVKIECRSLDFQ ATTMFWYRQFPKQSLMLMAT\$NEGSKATYEQGVEKDKFLIN HASLTSTLTVTSAHPEDSSFYICSAIRDRSGGETQYFGPGTRLL VL (SEQ ID NO: 51)
	Variable α (Predicted sequence without N-terminal signal peptide SignalP)	QQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWY QQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDS QPGDSATYFCAAKROGGSEKLVFGKGTKLTVNP (SEQ ID NO: 65)
4386-H TCR	Variable α (Predicted sequence without N-terminal signal peptide IMGT)	QQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPGK PALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSATY FCAAKROGGSEKLVFGKGTKLTVNP (SEQ ID NO: 131)
	Variable β (Predicted sequence without N-terminal signal peptide SignalP)	GVSQSPSNKVTEKGKDVELRCDPISGHTALYWYRQSLGQGLE FLIYFQGN\$APDKSGLPSDRFSAERTGGSVSTLTIQRTQQEDSA VYLCASSLGG\$SETQYFGPGTRLLVL (SEQ ID NO: 66)
	Variable β (Predicted sequence without N-terminal signal peptide IMGT)	GAGVSQSPSNKVTEKGKDVELRCDPISGHTALYWYRQSLGQG LEFLIYFQGN\$APDKSGLPSDRFSAERTGGSVSTLTIQRTQQED SAVYLCASSLGG\$SETQYFGPGTRLLVL (SEQ ID NO: 132)

TCR Name	TCR chain	Amino acid sequence
	Variable α (With N-terminal signal peptide with H at position 2)	MHKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLI VQKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSE KKEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAKRQGGSE KLVFGKGTKLTVNP (SEQ ID NO: 67)
	Variable α (With N-terminal signal peptide with A at position 2)	MAKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIV QKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEK KEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAKRQGGSEK LVFGKGTKLTVNP (SEQ ID NO: 133)
	Variable β (With N-terminal signal peptide with A at position 2)	MATRLFWVAFCLLGADHTGAGVSQSPSNKVTEKGKDVEL RCDPISGHTALYWYRQSLGQGLEFLIYFQGNAPDKSGLPSDR FSAERTGGSVSTLTIQRTQQEDSAVYLCASSLGGSSETQYFGPG TRLLVL (SEQ ID NO: 68)
	Variable β (With N-terminal signal peptide with H at position 2)	MHTRLLFWVAFCLLGADHTGAGVSQSPSNKVTEKGKDVEL RCDPISGHTALYWYRQSLGQGLEFLIYFQGNAPDKSGLPSDR FSAERTGGSVSTLTIQRTQQEDSAVYLCASSLGGSSETQYFGPG TRLLVL (SEQ ID NO: 134)
	Variable α (With WT N-terminal signal peptide)	MDKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIV QKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEK KEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAKRQGGSEK LVFGKGTKLTVNP (SEQ ID NO: 69)
	Variable β (With WT N-terminal signal peptide)	MGTRLLFWVAFCLLGADHTGAGVSQSPSNKVTEKGKDVEL RCDPISGHTALYWYRQSLGQGLEFLIYFQGNAPDKSGLPSDR FSAERTGGSVSTLTIQRTQQEDSAVYLCASSLGGSSETQYFGPG TRLLVL (SEQ ID NO: 70)
4386-O TCR	Variable α (Predicted sequence without N-terminal signal peptide SignalP)	ESVGLHLP T LSVQEGD NSIINCAY SNSASDYFIWYKQESGKGP QFIIDIRSNMDKRQGRVTVLLNKTVKHL SLQIAATQPGDSAV YFCAEKRRGGSEKLVFGKGTKLTVNP (SEQ ID NO: 84)
	Variable α (Predicted sequence without N-terminal signal peptide IMGT)	GESVGLHLP T LSVQEGD NSIINCAY SNSASDYFIWYKQESGKG PQFIIDIRSNMDKRQGRVTVLLNKTVKHL SLQIAATQPGDSA VYFCAEKRRGGSEKLVFGKGTKLTVNP (SEQ ID NO: 135)
	Variable β (Predicted sequence without N-terminal signal peptide SignalP)	GVSQTPSNKVTEKGKYVELRCDPISGHTALYWYRQSLGQGP FLIYFOGTGAADDSGLPNDRFFAVRPEGSVSTLKIQRTERGDSA VYLCASSPGGSQETQYFGPGTRLLVL (SEQ ID NO: 85)
	Variable β (Predicted sequence without N-terminal signal peptide IMGT)	GAGVSQTPSNKVTEKGKYVELRCDPISGHTALYWYRQSLGQGP PEFLIYFOGTGAADDSGLPNDRFFAVRPEGSVSTLKIQRTERGD SAVYLCASSPGGSQETQYFGPGTRLLVL (SEQ ID NO: 136)

TCR Name	TCR chain	Amino acid sequence
	N-terminal signal peptide (IMGT)	
	Variable α (With N-terminal signal peptide with H at position 2)	MHGIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSII NCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDKRQGRVTV LLNKTVKHLSLQIAATQPGDSAVYFCAEKRRGGSEKLVFGKG TKLTVNP (SEQ ID NO: 86)
	Variable α (With N-terminal signal peptide with A at position 2)	MAGIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSII NCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDKRQGRVTV LLNKTVKHLSLQIAATQPGDSAVYFCAEKRRGGSEKLVFGKG TKLTVNP (SEQ ID NO: 137)
	Variable β (With N-terminal signal peptide with A at position 2)	MATRLLCWAALCLLGADHTGAGVSQTPSNKVTEKGKYVEL RCDPISGHTALYWYRQSLGQGPEFLIYFOGTGAADDSGLPNDR FFAVRPEGSVSTLKIQRTERGDSAVYLCASSPGGSQETQYFGPG TRLLVL (SEQ ID NO: 87)
	Variable β (With N-terminal signal peptide with H at position 2)	MHTRLLCWAALCLLGADHTGAGVSQTPSNKVTEKGKYVEL RCDPISGHTALYWYRQSLGQGPEFLIYFOGTGAADDSGLPNDR FFAVRPEGSVSTLKIQRTERGDSAVYLCASSPGGSQETQYFGPG TRLLVL (SEQ ID NO: 138)
	Variable α (With WT N-terminal signal peptide)	MAGIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSII NCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDKRQGRVTV LLNKTVKHLSLQIAATQPGDSAVYFCAEKRRGGSEKLVFGKG TKLTVNP (SEQ ID NO: 88)
	Variable β (With WT N-terminal signal peptide)	MGTRLLCWAALCLLGADHTGAGVSQTPSNKVTEKGKYVEL RCDPISGHTALYWYRQSLGQGPEFLIYFOGTGAADDSGLPNDR FFAVRPEGSVSTLKIQRTERGDSAVYLCASSPGGSQETQYFGPG TRLLVL (SEQ ID NO: 89)

EXAMPLE 5

[0129] This example demonstrates the construction of retroviral vectors encoding the respective TCRs of Examples 3-4.

[0130] Nucleotide sequences encoding the variable regions of the α and β chains of the TCRs of Tables 3-4 were obtained and codon optimized. The TCR β VDJ regions were fused to the mouse TCR β constant chain. The TCR α VJ regions were fused to the mouse TCR α constant chain. Without being bound to a particular theory or mechanism, it is believed that replacing the constant regions of the human TCR α and TCR β chains with the corresponding murine constant regions improves TCR expression and functionality (Cohen et al., *Cancer Res.*, 66(17): 8878-86 (2006)).

[0131] In addition, the murine TCR α and TCR β constant chains were cysteine-modified. Transmembrane hydrophobic mutations were introduced into the murine TCR α constant chain. Without being bound to a particular theory or mechanism, it is believed that these modifications result in preferential pairing of the introduced TCR chains and enhanced TCR surface expression and functionality (Cohen et al., *Cancer Res.*, 67(8):3898-903 (2007); Haga-Friedman et al., *J. Immu.*, 188: 5538–5546 (2012)).

[0132] To facilitate cloning of the TCR expression cassette into the MSGV1 vector 5'NcoI site, and to introduce a Kozak sequence, the second amino acid in the N-terminal signal peptide of the TCRV α chain was changed to an histidine (H), and the second amino acid in the N-terminal signal peptide of the TCRV β chain was changed to an alanine (A).

[0133] The full length α and β chains of each of the five TCRs, including these modifications to the constant region, are shown in Table 5. In Table 5, the CDRs are underlined, the constant region is in italics, and the modified amino acid residues of the constant region are underlined and in bold.

TABLE 5

TCR Name	TCR chain	Amino acid sequence
4343-D TCR	Cys-substituted, LVL-modified α chain with N-terminal signal peptide	MHKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAIVSLNCTY <u>SNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKY</u> ISLFIRDSQPSDSATYLCAGGSYGKLTFGQGTLTVHPNIQNPEPAVYQL KDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMDSSKNGA IAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNLIV IVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 14)
	Cys-substituted, LVL-modified β chain with N-terminal signal peptide	MAPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVTCSQNM NHEYMSWYRQDPGLGLRQIYYSMNVEVTDKGDVPEGYKVSKEKR NFPLILESPSPNQTSLYFCASSFISNQPHFGDGTRLSEDLRNVTPPKV SLFEPСКАELANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQ AYKESNYSYCLSSRLRVSATFWHNPRNHFRQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVV MAMVKRKNS (SEQ ID NO: 15)
	Cys-substituted, LVL-modified α chain with WT N-terminal signal peptide	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAIVSLNCTY <u>SNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKY</u> ISLFIRDSQPSDSATYLCAGGSYGKLTFGQGTLTVHPNIQNPEPAVYQL KDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMDSSKNGA IAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNLIV IVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 16)
	Cys-substituted, LVL-modified β chain with WT N-terminal signal peptide	MGPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVTCSQNM NHEYMSWYRQDPGLGLRQIYYSMNVEVTDKGDVPEGYKVSKEKR NFPLILESPSPNQTSLYFCASSFISNQPHFGDGTRLSEDLRNVTPPKV SLFEPСКАELANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQ AYKESNYSYCLSSRLRVSATFWHNPRNHFRQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVV MAMVKRKNS (SEQ ID NO: 17)

TCR Name	TCR chain	Amino acid sequence
	Cys-substituted, LVL-modified α chain predicted sequence without N-terminal signal peptide	QQKEVEQDPGLSVPEGAIIVSLNCTYSNSAFQYFMWYRQYSRKGPGL LMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAGGSY <u>GKLTFGQGTILTVHPNIQNPEPAVYQLKDPQRSQDSTLCFLTDFDSQINVP</u> <u>KTMEGTFITDKCVLDMKAMD</u> SKSNGALAWSNQTSTFCQDIFKETNATYP SSDVPCDATLTEKSFETDMNLFQNL <u>LVI</u> LRILLKLVAGFNLLMTLRLWS S (SEQ ID NO: 18)
	Cys-substituted, LVL-modified β chain predicted sequence without N-terminal signal peptide	QVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYY <u>SMNVEVTDKGDVPEGYKVS</u> RKEKRNFLILESPSPNQTSLYFCASSFIS <u>NQPQHFGDGTRLSILEDLRNVT</u> PPKVSLEFESKAEIANKQKATLVCLARG FFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFWHN PRNHFRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQ QGVLSATILYEILLGKATLYAVLVSTLVMMAMVKRKNS (SEQ ID NO: 19)
4386-F	Cys-substituted, LVL-modified α chain with N-terminal signal peptide	MHGIRALFMYLWLQLDWVSRGESVGLHPLTVSVQEGDNSINCAYSN <u>SASDYFIWYKQESGKG</u> PQFIIDIRSNMDKRRQGRVTVLLNKTVKHLSL QIAATQPGDSAVYFCAEKSTGNQFYFGTGTSLTVIPNIQNPEPAVYQLK DPRSQDSTLCFLTDFDSQINVPKTMEGTFITDKCVLDMKAMDSKSNGAI AWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <u>LVI</u> <u>LRILLKLVAGFNLLMTLRLWS</u> (SEQ ID NO: 33)
	Cys-substituted, LVL-modified β chain with N-terminal signal peptide	MACRLCCAVLCLLGAVPMETGVTQTPRHLVMGMTNKKSLKCEQH <u>LGH</u> NAMYWYKQSAKKPLELMFVYSLEERVENNSVPSRFSPECNSSH LFLHLHTLQPEDSALYLCASSRVEGSDTOYFGPGTRLTVLEDLRNVTTP KVSLEFESKAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGVCTD PQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGS PKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTL VMMAMVKRKNS (SEQ ID NO: 34)
	Cys-substituted, LVL-modified α chain with WT N-terminal signal peptide	MAGIRALFMYLWLQLDWVSRGESVGLHPLTVSVQEGDNSINCAYSN <u>SASDYFIWYKQESGKG</u> PQFIIDIRSNMDKRRQGRVTVLLNKTVKHLSL QIAATQPGDSAVYFCAEKSTGNQFYFGTGTSLTVIPNIQNPEPAVYQLK DPRSQDSTLCFLTDFDSQINVPKTMEGTFITDKCVLDMKAMDSKSNGAI AWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <u>LVI</u> <u>LRILLKLVAGFNLLMTLRLWS</u> (SEQ ID NO: 35)
	Cys-substituted, LVL-modified β chain with WT N-terminal signal peptide	MGCRLLCCAVLCLLGAVPMETGVTQTPRHLVMGMTNKKSLKCEQH <u>LGH</u> NAMYWYKQSAKKPLELMFVYSLEERVENNSVPSRFSPECNSSH LFLHLHTLQPEDSALYLCASSRVEGSDTOYFGPGTRLTVLEDLRNVTTP KVSLEFESKAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGVCTD PQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGS PKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTL VMMAMVKRKNS (SEQ ID NO: 36)
	Cys-substituted, LVL-modified α chain predicted sequence without N-terminal signal peptide	ESVGLHPLTVSVQEGDNSINCAYSNSASDYFIWYKQESGKGQPFIIIDIR SNMDKRRQGRVTVLLNKTVKHLSLQIAATQPGDSAVYFCAEKSTGN QFYFGTGTSLTVIPNIQNPEPAVYQLKDPQRSQDSTLCFLTDFDSQINVPKT MESGTFITDKCVLDMKAMDSKSNGALAWSNQTSTFCQDIFKETNATYPSS DVPCDATLTEKSFETDMNLFQNL <u>LVI</u> LRILLKLVAGFNLLMTLRLWS (SEQ ID NO: 37)
	Cys-substituted, LVL-modified β chain predicted sequence without N-terminal signal peptide	METGVTQTPRHLVMGMTNKKSLKCEQH <u>LGH</u> NAMYWYKQSAKKPLE LMFVYSLEERVENNSVPSRFSPECNSSHFLHLHTLQPEDSALYLCAS <u>SRVEGSDTOYFGPGTRLTVLEDLRNVT</u> PPKVSLEFESKAEIANKQKATLV CLARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSA TFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGI TSASYQQGVLSATILYEILLGKATLYAVLVSTLVMMAMVKRKNS (SEQ ID NO: 38)
4386-G	Cys-substituted, LVL-modified α chain with N-	MHSAPISMLAMLFTLSGLRAQSVAQPEDQVNAEGNPLTVKCTYSYS GNPYLFWYVQYPNRGLQFLK ~~Y~~ ITGDNLVKGSGYGFEEFNKSQTSFH LKKPSALVSDSALYFCAVRDPTVSGTYKYIFGTGTRLKVLANIQNPEP AVYQLKDPQRSQDSTLCFLTDFDSQINVPKTMEGTFITDKCVLDMKAMDS

TCR Name	TCR chain	Amino acid sequence
	terminal signal peptide	<i>KSN</i> GALAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <i>LVL</i> RLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 52)
	Cys-substituted, LVL-modified β chain with N-terminal signal peptide	MALLLLLLGPGSGLGAVVSQHPSRVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSKATYEQGVKDKFLINHASLTLSTLTV TSAHPEDSSFYICSAIRDRSGGETQYFGPGTRLLVLEDLRNVTTPPKVSLF EPKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAY KESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMA MVRKNS (SEQ ID NO: 53)
	Cys-substituted, LVL-modified α chain with WT N-terminal signal peptide	MASAPISMLAMLFTLSGLRAQSVAPEDQVNVAEGNPLTVKCTYSVSGNPYLFWYVQYPNRLQFLFKYITGDNLYKGSYGFEAEFNKSQTSFHLKKPSALVSDSALYFCAVRDPTVSGTYKYIFGTGTRLLKVLANIQNPEP AVYQKDPKPRSDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMDS KSNALAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <i>LVL</i> RLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 54)
	Cys-substituted, LVL-modified β chain with WT N-terminal signal peptide	MLLLLLLLGPGSGLGAVVSQHPSRVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSKATYEQGVKDKFLINHASLTLSTLTV TSAHPEDSSFYICSAIRDRSGGETQYFGPGTRLLVLEDLRNVTTPPKVSLF EPKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAY KESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMA MVRKNS (SEQ ID NO: 55)
	Cys-substituted, LVL-modified α chain predicted sequence without N-terminal signal peptide	QSVAPEDQVNVAEGNPLTVKCTYSVSGNPYLFWYVQYPNRLQFL LKYITGDNLYKGSYGFEAEFNKSQTSFHLKKPSALVSDSALYFCAVRD PTVSGTYKYIFGTGTRLLKVLANIQNPEP AVYQKDPKPRSDSTLCLFTDF DSQINVPKTMESGTFITDKCVLDMKAMDSKSNALAWSNQTSTFCQDIFK ETNATYPSSDVPCDATLTEKSFETDMNLFQNL <i>LVL</i> RLILLKVAGFNLL MTLRLWSS (SEQ ID NO: 56)
	Cys-substituted, LVL-modified β chain predicted sequence without N-terminal signal peptide	AVVSQHPSRVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMA TSNEGSKATYEQGVKDKFLINHASLTLSTLTV TSAHPEDSSFYICSAI RDRSGGETQYFGPGTRLLVLEDLRNVTTPPKVSLFEPKAEIANKQKATLV CLARGFFPDHVELSWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSA FWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGI TSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMA MVRKNS (SEQ ID NO: 57)
4386-H	Cys-substituted, LVL-modified α chain with N-terminal signal peptide	MHKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIVQKGGIS IINCA YENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNK SAKQFSLHIMDSQPGDSATYFCAAKRQGGSEKLVFGKGTKLTVNPNI QNPEP AVYQKDPKPRSDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNALAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETD MNLFQNL <i>LVL</i> RLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 71)
	Cys-substituted, LVL-modified β chain with N-terminal signal peptide	MATRLLFWVAFCLLGADHTGAGVSQSPSNKVTEKGDVELRCDPISG HTALYWYRQSLGQGLEFLIYFQGNAPDKSGLPSDRFSAERTGGSVST LTIQRTQQEDSAVYL CASSLGGSSETQYFGPGTRLLVLEDLRNVTTPPKV SLFEPKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQ AYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVV MAMVRKNS (SEQ ID NO: 72)
	Cys-substituted, LVL-modified α chain with WT N-terminal signal peptide	MDKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIVQKGGIS IINCA YENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNK SAKQFSLHIMDSQPGDSATYFCAAKRQGGSEKLVFGKGTKLTVNPNI QNPEP AVYQKDPKPRSDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDM KAMDSKSNALAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETD MNLFQNL <i>LVL</i> RLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 73)
	Cys-substituted, LVL-modified β	MGTRLLFWVAFCLLGADHTGAGVSQSPSNKVTEKGDVELRCDPISG HTALYWYRQSLGQGLEFLIYFQGNAPDKSGLPSDRFSAERTGGSVST

TCR Name	TCR chain	Amino acid sequence
	chain with WT N-terminal signal peptide	LTIQRTQQEDSAVYLCASSLGGSSSETQYFGPGTRLLVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMV KRKNS (SEQ ID NO: 74)
	Cys-substituted, LVL-modified α chain predicted sequence without N-terminal signal peptide	QQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPKGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSATYFC AAKRQGGSEKLVFGKGTCLTVNPNIONPEPAVYQLKDPQRSQDSTLCFLTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGALAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL LVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 75)
	Cys-substituted, LVL-modified β chain predicted sequence without N-terminal signal peptide	GVSQSPSNKVTEKGKDELRCDPISGHTALYWYRQSLGQGLEFLIYFQ GNSAPDKSGLPSDRFSAERTGGSVSTLTIQRTQQEDSAVYLCASSLGG SSETQYFGPGTRLLVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMV KRKNS (SEQ ID NO: 76)
4386-O	Cys-substituted, LVL-modified α chain with N-terminal signal peptide	MHGIRALFMYLWLQLDWVSRGESVGLHPLTVSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPOFIIDIRSNMDKRRQGQRVTVLLNKT VKHLSLQIAATQPGDSAVYFCAEKRRGGSEKLVFGKGTCLTVNPNIONPEPAVYQLKDPQRSQDSTLCFLTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGALAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL LVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 90)
	Cys-substituted, LVL-modified β chain with N-terminal signal peptide	MATRLLCWAALCLLGADHTGAGVSQTPSNKVTEKGKYVELRCDPISGHTALYWYRQSLGQGPFLIYFQGTGAADDSGLPNDRFFAVRPEGSVSTLKIQRTERGDSAVYLCASSPGGSQETQYFGPGTRLLVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMV KRKNS (SEQ ID NO: 91)
	Cys-substituted, LVL-modified α chain with WT N-terminal signal peptide	MAGIRALFMYLWLQLDWVSRGESVGLHPLTVSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPOFIIDIRSNMDKRRQGQRVTVLLNKT VKHLSLQIAATQPGDSAVYFCAEKRRGGSEKLVFGKGTCLTVNPNIONPEPAVYQLKDPQRSQDSTLCFLTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGALAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL LVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 92)
	Cys-substituted, LVL-modified β chain with WT N-terminal signal peptide	MGTRLLCWAALCLLGADHTGAGVSQTPSNKVTEKGKYVELRCDPISGHTALYWYRQSLGQGPFLIYFQGTGAADDSGLPNDRFFAVRPEGSVSTLKIQRTERGDSAVYLCASSPGGSQETQYFGPGTRLLVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMV KRKNS (SEQ ID NO: 93)
	Cys-substituted, LVL-modified α chain predicted sequence without N-terminal signal peptide	ESVGLHPLTVSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPOFIIDIRSNMDKRRQGQRVTVLLNKT VKHLSLQIAATQPGDSAVYFCAEKRRGGSEKLVFGKGTCLTVNPNIONPEPAVYQLKDPQRSQDSTLCFLTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGALAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL LVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 94)
	Cys-substituted, LVL-modified β chain predicted sequence without N-terminal signal peptide	GVSQTPSNKVTEKGKYVELRCDPISGHTALYWYRQSLGQGPFLIYFQGTGAADDSGLPNDRFFAVRPEGSVSTLKIQRTERGDSAVYLCASSPGGSQETQYFGPGTRLLVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPK PVTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMV KRKNS (SEQ ID NO: 95)

[0134] Nucleotide sequences encoding the variable regions of the α and β chains of the TCRs of Table 5 were cloned into an MSGV1-based retroviral vector with the following expression cassette configuration: 5'NcoI-VDJ β -mC β -Furin/SerGly/P2A-VJ α -mC α -EcoRI3'.

[0135] The TCR β and TCR α chains were separated by a Furin Ser/Gly P2A linker RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 100). Without being bound to a particular theory or mechanism, it is believed that the linker provides comparable expression efficiency of the two chains (Szymczak et al., *Nat. Biotechnol.*, 22(5):589-94 (2004)).

[0136] The TCR expression cassette of the retroviral vector encoded, from 5' to 3', the TCR β and TCR α chains separated by the linker. The nucleotide sequences of the TCR expression cassettes are shown in Table 6.

TABLE 6

TCR Name	TCR Expression Cassette
4343-D	SEQ ID NO: 109
4386-F	SEQ ID NO: 110
4386-G	SEQ ID NO: 111
4386-H	SEQ ID NO: 112
4386-O	SEQ ID NO: 113

[0137] The amino acid sequences encoded by each respective TCR expression cassette is shown in Table 7. In Table 7, the CDRs are underlined, the constant regions are italicized, and the linker is shown in bold.

TABLE 7

TCR Name	Amino acid sequence encoded by TCR Expression Cassette
4343-D	MAPQLLGYYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVTC SQNMNHEYMSW YRQDPGLGLRQIYYSMNVEVTDKGDVPEGYKVS RKEKRNFLILESPSNQTSLY FCASSFISNQPHFGDGTRLSILEDLRNVT PPKVSLFEP SKAEIANKQKATLVCLARGF FPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRV SATFWHNPRNHFR CQ VQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKA TLYAVLVSTLVVMAMVKRKN S RAKRSGSGATNFSLLKQAGDVEENPGPMH SLR VLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAIVSLNCTYSNSAFAQYFMWYR QYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAGG SYGKLTFGQGTLTVHPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMES GTFTDKCVLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEK SFETDMNLNFQNLVIVLRILLK VAGFNLLMTLR LWSS (SEQ ID NO: 20)
4386-F	MACRLCCA V LCLLGAVPMETGVTQT PRHLVMGMTNKKSLKCEQHLGHNAMY WYKQSAKKPLELMFVYSLEERVENNSVPSRFSPEC PNSSHLFLHLHTLQPEDSAL YLCASSRVEGSDTQYFGPGTRLTVLEDLRNVT PPKVSLFEP SKAEIANKQKATLVCL ARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRV SATFWHNPRNH

TCR Name	Amino acid sequence encoded by TCR Expression Cassette
	<i>FRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEIL LGKATLYAVLVSTLVVMAMVKRKNS</i> RAKRSGSGATNFSLLKQAGDVEENPGPMH GIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWY KQESGKGPQFIIDIRSNMDKRGQQRVTVLLNKTKVHLSLQIAATQPGDSAVYFCA EKSTGNQFYFGTGTSLTVPNIQNPEPAVYQLKDPRSQDSTLCFLTDFDSQINVPKTM ESGTFITDKCVLDMKAMDSKSNGLAWSNQTSFTCQDIFKETNATYPSSDVPCDATLT EKSFETDMNLNFQNLIVLRLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 39)
4386-G	MALLLLLLGPGSGLGAVVSQHPSPRVICKSGTSVKIECRSLDFQATTMFYRQFPK QSLMLMATSNESGKATYEQGVEKDKFLINHASLTSLTSTVTSAPEDSSFYICSAI RDRSGGETQYFGPGTRLLVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFF PDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPNNHFR QFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKAT LYAVLVSTLVVMAMVKRKNS RAKRSGSGATNFSLLKQAGDVEENPGPMHSAPIS MLAMLFTLSGLRAQSVAPEDQVNVAEGNPLTVKCTYSVSGNPYLFWYVQYPN RGLQFLKYYITGDNLVKGSYGFEAEFNKSQTSFHLKKPSALVSDSALYFCAVRDP TVSGTYKYIFGTGTRLKVLANIQNPEPAVYQLKDPRSQDSTLCFLTDFDSQINVPKT MESGTFITDKCVLDMKAMDSKSNGLAWSNQTSFTCQDIFKETNATYPSSDVPCDATL TEKSFETDMNLNFQNLIVLRLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 58)
4386-H	MATRLLFWVAFCLLGADHTGAGVSQSPSNKVTEKGKDVELRCDPISGHTALYW YRQSLGQGLEFLIYFQGNAPDKSGLPSDRFSAERTGGSVSTLTQRTQQEDSAVY LCASSLGGSETQYFGPGTRLLVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLAR GFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPNNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKRKNS RAKRSGSGATNFSLLKQAGDVEENPGPMH LGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFD YFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSAT YFCAAKRQGGSEKLVFGKGTCLTVNPNQNPEPAVYQLKDPRSQDSTLCFLTDFDS QINVPKTMESGTFITDKCVLDMKAMDSKSNGLAWSNQTSFTCQDIFKETNATYPSSD VPCDATLTEKSFETDMNLNFQNLIVLRLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 77)
4386-O	MATRLLCWAALCLLGADHTGAGVSQTPSNKVTEKGKYVELRCDPISGHTALYW YRQSLGQGPFLIYFQGTGAADDSGLPNDRFFAVRPEGSVSTLKIQRTERGDSAV YLCASSPGGSQETOYFGPGTRLLVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCL ARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPNNH FRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEIL LGKATLYAVLVSTLVVMAMVKRKNS RAKRSGSGATNFSLLKQAGDVEENPGPMH GIRALFMYLWLQLDWVSRGESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWY KQESGKGPQFIIDIRSNMDKRGQQRVTVLLNKTKVHLSLQIAATQPGDSAVYFCA EKRRGGSEKLVFGKGTCLTVNPNQNPEPAVYQLKDPRSQDSTLCFLTDFDSQINVP KTMESGTFITDKCVLDMKAMDSKSNGLAWSNQTSFTCQDIFKETNATYPSSDVPCDA TLTEKSFETDMNLNFQNLIVLRLILLKVAGFNLLMTLRLWSS (SEQ ID NO: 96)

EXAMPLE 6

[0138] This example demonstrates the avidity of the anti-p53-Y220C TCR expressed by the retroviral vector of Example 5.

[0139] Allogeneic PBL were independently transduced with the retroviral vector encoding the 4343-D TCR of Example 5. Autologous DCs were pulsed for two hours with the mutated p53-Y220C 25-mer peptide DRNTFRHSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115) or the corresponding WT 25-mer peptide DRNTFRHSVVVPYEPPEVGSDCTTI (SEQ ID NO: 114) at one of the various concentrations shown in Figure 3A. The cells were washed twice and co-cultured for 16 hours with transduced T cells at a ratio of 1:1. IFN- γ

secretion was measured by ELISpot assay. As shown in Figure 3A, the TCR-transduced cells demonstrated specific and avid recognition of the DC pulsed with the p53-Y220C 25-mer peptide.

[0140] Without being bound to a particular theory or mechanism, it is believed that the cysteine residues present in the WT 25-mer peptide (SEQ ID NO: 114) and the mutated p53 Y220C 25-mer peptide (SEQ ID NO: 115) may be susceptible to oxidation and homo-dimerization, which may eventually lead to reduced T cell potency (Sachs et al, *J. Immunol.*, 205(2):539-549 (2020)). The Y220C mutation itself introduces an additional cysteine residue. It was hypothesized that the additional cysteine residue may affect the TCR's recognition of the mutant peptide.

[0141] This hypothesis was tested by modifying all of the cysteine residues in the original sequences of both the wild-type and mutant peptides into AABA, which no longer is susceptible to oxidation or dimerization. The modified peptides are shown in Table 8.

TABLE 8

Wild-type 25-mer with AABA substitution	DRNTFRHSVVVP<u>X</u>EPPEVGSDXTTI X at position 22 is AABA	SEQ ID NO: 150
Mutated 25-mer with AABA substitutions	DRNTFRHSVVVP<u>X</u>EPPEVGSDXTTI X at position 13 is AABA X at position 22 is AABA	SEQ ID NO: 151

[0142] Allogeneic PBL were independently transduced with the retroviral vector encoding the 4343-D TCR of Example 5. Autologous B cells were pulsed for two hours with the mutated p53-Y220C 25-mer peptide with AABA substitutions (SEQ ID NO: 151) or the corresponding WT 25-mer peptide with AABA substitution (SEQ ID NO: 150) at one of the various concentrations shown in Figures 3B-3C. The cells were washed twice and co-cultured for 16 hours with transduced T cells at a ratio of 1:1. Reactivity was tested by measuring the upregulation of the T cell activation marker 4-1BB in murine TCR constant region positive cells by flow cytometry.

[0143] As shown in Figures 3B-3C, the results validated the hypothesis described above in this Example. A log or greater TCR potency was observed with the mutated p53-Y220C

25-mer peptide with AABA substitutions over the corresponding WT 25-mer peptide with AABA substitution.

EXAMPLE 7

[0144] This example demonstrates the avidity of the anti-p53-R273C TCRs expressed by the retroviral vectors of Example 5.

[0145] Allogeneic PBL were independently transduced with the retroviral vector encoding the 4386-F TCR, 4386-G TCR, 4386-H TCR, or 4386-O TCR of Example 5. Autologous DCs were pulsed for two hours with the p53-R273C 25-mer peptide SGNLLGRNSFEVCVCACPGRDRRTE (SEQ ID NO: 117) or the corresponding WT 25-mer peptide SGNLLGRNSFEVRVCACPGRDRRTE (SEQ ID NO: 116) at one of the various concentrations shown in Figures 3D-3G. The cells were washed twice and co-cultured for 16 hours with transduced T cells at a ratio of 1:1. IFN- γ secretion was measured by ELISA (Figs. 3D-3G). As shown in Figures 3D-3G, the TCR-transduced cells demonstrated specific and avid recognition of the DC pulsed with the mutated p53-R273C 25-mer peptide.

EXAMPLE 8

[0146] This example demonstrates that the anti-p53-Y220C TCR expressed by the retroviral vector of Example 5 recognizes mutated p53 presented by an HLA-DRB3*02/HLA-DRA1*01 heterodimer.

[0147] The MHC Class II molecules expressed by Patient 4343 were determined using exome and mRNA sequencing. The expressed MHC Class II molecules are shown in Figure 2A.

[0148] Effector cells were allogeneic PBL transduced with the retroviral vector of Example 5 encoding the 4343-D TCR. Target cells were COS7 cells independently transfected with one of the HLA Class II heterodimers shown in Fig. 2A and pulsed with the p53-Y220C 25-mer peptide DRNTFRHSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115).

[0149] Reactivity was tested by measuring the upregulation of the T cell activation marker 4-1BB in murine TCR constant region positive cells by flow cytometry. The results are shown in Figure 2A. As shown in Figure 2A, reactivity was observed only upon co-culture of the 4343-D TCR-transduced cells with the p53-Y220C 25-mer-loaded target cells

which had been transduced with a nucleotide sequence encoding an HLA-DRA1*01:01:01 / HLA-DRB3*02:02:01 heterodimer.

EXAMPLE 9

[0150] This example demonstrates that the TIL of Example 2 recognized mutated p53 presented by an HLA-DPB1*04:02 / HLA-DPA1*01 heterodimer.

[0151] The MHC Class II molecules expressed by Patient 4386 were determined using exome and mRNA sequencing. The expressed MHC Class II molecules are shown in Figure 2B.

[0152] Effector cells were TIL that contain T cells recognizing p53-R273C identified in Example 2. Target cells were COS7 cells independently transfected with one of the HLA Class II heterodimers shown in Fig. 2B and pulsed with the p53-R273C 25-mer peptide SGNLLGRNSFEVCVCACPGRDRRTE (SEQ ID NO: 117).

[0153] Reactivity was tested by measuring the upregulation of the T cell activation marker 4-1BB in CD3 positive cells by flow cytometry. The results are shown in Figure 2B. As shown in Figure 2B, reactivity was observed only upon co-culture of the TIL with the p53-R273C 25-mer-loaded target cells which had been transduced with a nucleotide sequence encoding an HLA-DPA1*01:03 / HLA-DPB1*04:02 heterodimer.

[0154] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0155] The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a

shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0156] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. An isolated or purified T cell receptor (TCR) having antigenic specificity for a human p53^{R273C} or human p53^{Y220C} amino acid sequence, wherein the TCR comprises the amino acid sequences of:

- (1) all of SEQ ID NOs: 2-7;
- (2) all of SEQ ID NOs: 21-26;
- (3) all of SEQ ID NOs: 40-45;
- (4) all of SEQ ID NOs: 59-64; or
- (5) all of SEQ ID NOs: 78-83.

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

(1) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 8 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9;

(2) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 10 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 11;

(3) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 12 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 13;

(4) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 12 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 11;

(5) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 121 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 13;

(6) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 121 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 122;

(7) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 8 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 120;

(8) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 119 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9;

(9) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 119 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 120;

(10) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 27 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 28;

(11) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 29 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 30;

(12) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 31 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 32;

(13) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 31 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 30;

(14) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 125 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 32;

(15) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 125 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 126;

(16) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 27 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 124;

(17) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 123 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 28;

(18) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 123 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 124;

(19) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 46 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 47;

(20) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 48 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 49;

(21) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 50 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 51;

(22) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 50 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 49;

(23) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 129 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 51;

(24) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 129 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 130;

(25) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 46 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 128;

(26) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 127 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 47;

(27) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 127 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 128;

(28) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 65 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 66;

(29) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 67 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 68;

(30) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 69 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70;

(31) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 69 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 68;

(32) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 133 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70;

(33) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 133 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 134;

(34) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 65 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 132;

(35) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 131 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 66;

(36) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 131 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 132;

(37) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85;

(38) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 86 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 87;

(39) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 88 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 89;

(40) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 88 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 87;

(41) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 137 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 89;

(42) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 137 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 138;

(43) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 136;

(44) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 135 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85; or

(45) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 135 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 136.

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

- (1) both of SEQ ID NOs: 8 and 9;
- (2) both of SEQ ID NOs: 10 and 11;
- (3) both of SEQ ID NOs: 12 and 13;
- (4) both of SEQ ID NOs: 12 and 11;
- (5) both of SEQ ID NOs: 121 and 13;
- (6) both of SEQ ID NOs: 121 and 122;
- (7) both of SEQ ID NOs: 8 and 120;
- (8) both of SEQ ID NOs: 119 and 9;
- (9) both of SEQ ID NOs: 119 and 120;
- (10) both of SEQ ID NOs: 27 and 28;
- (11) both of SEQ ID NOs: 29 and 30;
- (12) both of SEQ ID NOs: 31 and 32;
- (13) both of SEQ ID NOs: 31 and 30;
- (14) both of SEQ ID NOs: 125 and 32;
- (15) both of SEQ ID NOs: 125 and 126;
- (16) both of SEQ ID NOs: 27 and 124;

- (17) both of SEQ ID NOs: 123 and 28;
- (18) both of SEQ ID NOs: 123 and 124;
- (19) both of SEQ ID NOs: 46 and 47;
- (20) both of SEQ ID NOs: 48 and 49;
- (21) both of SEQ ID NOs: 50 and 51;
- (22) both of SEQ ID NOs: 50 and 49;
- (23) both of SEQ ID NOs: 129 and 51;
- (24) both of SEQ ID NOs: 129 and 130;
- (25) both of SEQ ID NOs: 46 and 128;
- (26) both of SEQ ID NOs: 127 and 47;
- (27) both of SEQ ID NOs: 127 and 128;
- (28) both of SEQ ID NOs: 65 and 66;
- (29) both of SEQ ID NOs: 67 and 68;
- (30) both of SEQ ID NOs: 69 and 70;
- (31) both of SEQ ID NOs: 69 and 68;
- (32) both of SEQ ID NOs: 133 and 70;
- (33) both of SEQ ID NOs: 133 and 134;
- (34) both of SEQ ID NOs: 65 and 132;
- (35) both of SEQ ID NOs: 131 and 66;
- (36) both of SEQ ID NOs: 131 and 132;
- (37) both of SEQ ID NOs: 84 and 85;
- (38) both of SEQ ID NOs: 86 and 87;
- (39) both of SEQ ID NOs: 88 and 89;
- (40) both of SEQ ID NOs: 88 and 87;
- (41) both of SEQ ID NOs: 137 and 89;
- (42) both of SEQ ID NOs: 137 and 138;
- (43) both of SEQ ID NOs: 84 and 136;
- (44) both of SEQ ID NOs: 135 and 85; or
- (45) both of SEQ ID NOs: 135 and 136.

4. The TCR of any one of claims 1-3, further comprising:

- (a) an α chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 141, wherein:

(i) X at position 1 of SEQ ID NO: 141 is Asn, Asp, His, or Tyr;

(ii) X at position 48 of SEQ ID NO: 141 is Thr or Cys;

(iii) X at position 112 of SEQ ID NO: 141 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iv) X at position 114 of SEQ ID NO: 141 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(v) X at position 115 of SEQ ID NO: 141 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

wherein optionally the α chain constant region comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 97 or 145;

(b) a β chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 142, wherein X at position 57 of SEQ ID NO: 142 is Ser or Cys;

wherein optionally the β chain constant region comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 99 or 140; or

(c) both (a) and (b).

5. The TCR of any one of claims 1-3, further comprising:

(a) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 141, wherein:

(i) X at position 1 of SEQ ID NO: 141 is Asn, Asp, His, or Tyr;

(ii) X at position 48 of SEQ ID NO: 141 is Thr or Cys;

(iii) X at position 112 of SEQ ID NO: 141 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iv) X at position 114 of SEQ ID NO: 141 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(v) X at position 115 of SEQ ID NO: 141 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

wherein optionally the α chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 145;

(b) a β chain constant region comprising the amino acid sequence of SEQ ID NO: 142, wherein X at position 57 of SEQ ID NO: 142 is Ser or Cys;

wherein optionally the β chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 140; or

(c) both (a) and (b).

6. The TCR of any one of claims 1-5, wherein the TCR comprises:

(1) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 14 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 15;

(2) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 16 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 17;

(3) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 18 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 19;

(4) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 33 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 34;

(5) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 35 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 36;

(6) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 37 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 38;

(7) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 52 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 53;

(8) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 54 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 55;

(9) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 56 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 57;

(10) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 71 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 72;

(11) both 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;

(12) both 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;

(13) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 90 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 91;

(14) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 92 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 93; or

(15) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 94 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 95.

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

- (1) both of SEQ ID NOs: 14 and 15;
- (2) both of SEQ ID NOs: 16 and 17;
- (3) both of SEQ ID NOs: 18 and 19;
- (4) both of SEQ ID NOs: 33 and 34;
- (5) both of SEQ ID NOs: 35 and 36;
- (6) both of SEQ ID NOs: 37 and 38;
- (7) both of SEQ ID NOs: 52 and 53;
- (8) both of SEQ ID NOs: 54 and 55;
- (9) both of SEQ ID NOs: 56 and 57;
- (10) both of SEQ ID NOs: 71 and 72;
- (11) both of SEQ ID NOs: 73 and 74;
- (12) both of SEQ ID NOs: 75 and 76;

- (13) both of SEQ ID NOs: 90 and 91;
- (14) both of SEQ ID NOs: 92 and 93; or
- (15) both of SEQ ID NOs: 94 and 95.

8. The TCR of any one of claims 1-7, wherein the human p53^{R273C} amino acid sequence is SGNLLGRNSFEVCVCACPGRDRRTE (SEQ ID NO: 117).

9. The TCR of any one of claims 1-7, wherein the human p53^{Y220C} amino acid sequence is DRNTRHRSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115).

10. The TCR of any one of claims 1-8, wherein the TCR does not have antigenic specificity for the wild-type human p53 amino acid sequence of SGNLLGRNSFEVRVCACPGRDRRTE (SEQ ID NO: 116).

11. The TCR of any one of claims 1-7 and 9, wherein the TCR does not have antigenic specificity for the wild-type human p53 amino acid sequence of DRNTRHRSVVVPYEPPEVGSDCTTI (SEQ ID NO: 114).

12. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-11, wherein the polypeptide comprises the amino acid sequences of:

- (1) all of SEQ ID NOs: 2-7;
- (2) all of SEQ ID NOs: 21-26;
- (3) all of SEQ ID NOs: 40-45;
- (4) all of SEQ ID NOs: 59-64; or
- (5) all of SEQ ID NOs: 78-83.

13. The polypeptide of claim 12, wherein the polypeptide comprises :

(1) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 8 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9;

(2) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 10 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 11;

(3) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 12 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 13;

(4) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 12 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 11;

(5) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 121 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 13;

(6) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 121 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 122;

(7) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 8 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 120;

(8) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 119 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9;

(9) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 119 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 120;

(10) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 27 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 28;

(11) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 29 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 30;

(12) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 31 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 32;

(13) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 31 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 30;

(14) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 125 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 32;

(15) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 125 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 126;

(16) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 27 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 124;

(17) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 123 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 28;

(18) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 123 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 124;

(19) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 46 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 47;

(20) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 48 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 49;

(21) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 50 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 51;

(22) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 50 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 49;

(23) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 129 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 51;

(24) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 129 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 130;

(25) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 46 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 128;

(26) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 127 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 47;

(27) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 127 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 128;

(28) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 65 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 66;

(29) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 67 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 68;

(30) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 69 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70;

(31) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 69 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 68;

(32) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 133 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70;

(33) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 133 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 134;

(34) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 65 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 132;

(35) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 131 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 66;

(36) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 131 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 132;

(37) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85;

(38) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 86 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 87;

(39) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 88 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 89;

(40) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 88 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 87;

(41) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 137 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 89;

(42) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 137 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 138;

(43) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 136;

(44) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 135 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85; or

(45) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 135 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 136.

14. The polypeptide of claim 12, wherein the polypeptide comprises the amino acid sequences of:

- (1) both of SEQ ID NOs: 8 and 9;
- (2) both of SEQ ID NOs: 10 and 11;
- (3) both of SEQ ID NOs: 12 and 13;
- (4) both of SEQ ID NOs: 12 and 11;
- (5) both of SEQ ID NOs: 121 and 13;
- (6) both of SEQ ID NOs: 121 and 122;
- (7) both of SEQ ID NOs: 8 and 120;
- (8) both of SEQ ID NOs: 119 and 9;
- (9) both of SEQ ID NOs: 119 and 120;
- (10) both of SEQ ID NOs: 27 and 28;
- (11) both of SEQ ID NOs: 29 and 30;
- (12) both of SEQ ID NOs: 31 and 32;
- (13) both of SEQ ID NOs: 31 and 30;
- (14) both of SEQ ID NOs: 125 and 32;
- (15) both of SEQ ID NOs: 125 and 126;
- (16) both of SEQ ID NOs: 27 and 124;
- (17) both of SEQ ID NOs: 123 and 28;
- (18) both of SEQ ID NOs: 123 and 124;
- (19) both of SEQ ID NOs: 46 and 47;
- (20) both of SEQ ID NOs: 48 and 49;
- (21) both of SEQ ID NOs: 50 and 51;
- (22) both of SEQ ID NOs: 50 and 49;
- (23) both of SEQ ID NOs: 129 and 51;
- (24) both of SEQ ID NOs: 129 and 130;
- (25) both of SEQ ID NOs: 46 and 128;
- (26) both of SEQ ID NOs: 127 and 47;
- (27) both of SEQ ID NOs: 127 and 128;
- (28) both of SEQ ID NOs: 65 and 66;
- (29) both of SEQ ID NOs: 67 and 68;
- (30) both of SEQ ID NOs: 69 and 70;
- (31) both of SEQ ID NOs: 69 and 68;
- (32) both of SEQ ID NOs: 133 and 70;
- (33) both of SEQ ID NOs: 133 and 134;

- (34) both of SEQ ID NOs: 65 and 132;
- (35) both of SEQ ID NOs: 131 and 66;
- (36) both of SEQ ID NOs: 131 and 132;
- (37) both of SEQ ID NOs: 84 and 85;
- (38) both of SEQ ID NOs: 86 and 87;
- (39) both of SEQ ID NOs: 88 and 89;
- (40) both of SEQ ID NOs: 88 and 87;
- (41) both of SEQ ID NOs: 137 and 89;
- (42) both of SEQ ID NOs: 137 and 138;
- (43) both of SEQ ID NOs: 84 and 136;
- (44) both of SEQ ID NOs: 135 and 85; or
- (45) both of SEQ ID NOs: 135 and 136.

15. The polypeptide of any one of claims 12-14, further comprising:

(a) an α chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 141, wherein:

- (i) X at position 1 of SEQ ID NO: 141 is Asn, Asp, His, or Tyr;
- (ii) X at position 48 of SEQ ID NO: 141 is Thr or Cys;
- (iii) X at position 112 of SEQ ID NO: 141 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iv) X at position 114 of SEQ ID NO: 141 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (v) X at position 115 of SEQ ID NO: 141 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

wherein optionally the α chain constant region comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 97 or 145;

(b) a β chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 142, wherein X at position 57 of SEQ ID NO: 142 is Ser or Cys;

wherein optionally the β chain constant region comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 99 or 140; or

(c) both (a) and (b).

16. The polypeptide of any one of claims 12-14, further comprising:

(a) an α chain constant region comprising the amino acid sequence of SEQ ID NO:

141, wherein:

(i) X at position 1 of SEQ ID NO: 141 is Asn, Asp, His, or Tyr;

(ii) X at position 48 of SEQ ID NO: 141 is Thr or Cys;

(iii) X at position 112 of SEQ ID NO: 141 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iv) X at position 114 of SEQ ID NO: 141 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(v) X at position 115 of SEQ ID NO: 141 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

wherein optionally the α chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 145;

(b) a β chain constant region comprising the amino acid sequence of SEQ ID NO:

142, wherein X at position 57 of SEQ ID NO: 142 is Ser or Cys;

wherein optionally the β chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 140; or

(c) both (a) and (b).

17. The polypeptide of any one of claims 12-16, wherein the polypeptide comprises:

(1) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 14 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 15;

(2) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 16 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 17;

(3) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 18 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 19;

(4) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 33 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 34;

(5) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 35 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 36;

(6) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 37 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 38;

(7) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 52 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 53;

(8) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 54 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 55;

(9) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 56 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 57;

(10) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 71 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 72;

(11) both 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;

(12) both 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;

(13) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 90 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 91;

(14) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 92 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 93; or

(15) both an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 94 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 95.

18. The polypeptide of any one of claims 12-16, wherein the polypeptide comprises the amino acid sequences of:

- (1) both of SEQ ID NOs: 14 and 15;
- (2) both of SEQ ID NOs: 16 and 17;
- (3) both of SEQ ID NOs: 18 and 19;
- (4) both of SEQ ID NOs: 33 and 34;
- (5) both of SEQ ID NOs: 35 and 36;
- (6) both of SEQ ID NOs: 37 and 38;
- (7) both of SEQ ID NOs: 52 and 53;
- (8) both of SEQ ID NOs: 54 and 55;
- (9) both of SEQ ID NOs: 56 and 57;
- (10) both of SEQ ID NOs: 71 and 72;
- (11) both of SEQ ID NOs: 73 and 74;
- (12) both of SEQ ID NOs: 75 and 76;
- (13) both of SEQ ID NOs: 90 and 91;
- (14) both of SEQ ID NOs: 92 and 93; or
- (15) both of SEQ ID NOs: 94 and 95.

19. An isolated or purified protein comprising:

- (1) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 2-4 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 5-7;
- (2) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 21-23 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 24-26;
- (3) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 40-42 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 43-45;
- (4) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 59-61 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 62-64; or

(5) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 78-80 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 81-83.

20. The protein of claim 19, wherein:

(1) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 8 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9;

(2) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 10 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 11;

(3) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 12 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 13;

(4) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 12 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 11;

(5) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 121 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 13;

(6) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 121 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 122;

(7) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 8 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 120;

(8) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 119 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9;

(9) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 119 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 120;

(10) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 27 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 28;

(11) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 29 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 30;

(12) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 31 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 32;

(13) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 31 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 30;

(14) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 125 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 32;

(15) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 125 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 126;

(16) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 27 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 124;

(17) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 123 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 28;

(18) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 123 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 124;

(19) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 46 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 47;

(20) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 48 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 49;

(21) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 50 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 51;

(22) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 50 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 49;

(23) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 129 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 51;

(24) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 129 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 130;

(25) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 46 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 128;

(26) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 127 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 47;

(27) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 127 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 128;

(28) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 65 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 66;

(29) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 67 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 68;

(30) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 69 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70;

(31) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 69 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 68;

(32) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 133 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70;

(33) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 133 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 134;

(34) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 65 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 132;

(35) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 131 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 66;

(36) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 131 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 132;

(37) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85;

(38) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 86 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 87;

(39) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 88 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 89;

(40) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 88 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 87;

(41) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 137 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 89;

(42) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 137 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 138;

(43) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 84 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 136;

(44) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 135 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 85; or

(45) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 135 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 136.

21. The protein of claim 19, wherein:

(1) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 8 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9;

(2) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 11;

(3) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 12 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13;

- (4) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 12 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 11;
- (5) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 121 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13;
- (6) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 121 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 122;
- (7) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 8 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 120;
- (8) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 119 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9;
- (9) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 119 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 120;
- (10) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 27 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 28;
- (11) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 29 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 30;
- (12) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 31 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 32;
- (13) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 31 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 30;
- (14) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 125 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 32;
- (15) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 125 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 126;
- (16) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 27 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 124;
- (17) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 123 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 28;
- (18) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 123 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 124;

(19) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 46 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 47;

(20) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 48 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 49;

(21) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 50 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 51;

(22) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 50 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 49;

(23) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 129 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 51;

(24) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 129 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 130;

(25) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 46 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 128;

(26) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 127 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 47;

(27) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 127 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 128;

(28) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 65 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 66;

(29) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 67 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68;

(30) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 70;

(31) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68;

(32) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 133 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 70;

(33) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 133 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 134;

(34) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 65 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 132;

(35) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 131 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 66;

(36) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 131 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 132;

(37) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 84 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85;

(38) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87;

(39) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 89;

(40) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87;

(41) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 137 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 89;

(42) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 137 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 138;

(43) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 84 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 136;

(44) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 135 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85; or

(45) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 135 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 136.

22. The protein of any one of claims 19-21, wherein:

(a) the first polypeptide chain comprises an α chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 141, wherein:

(i) X at position 1 of SEQ ID NO: 141 is Asn, Asp, His, or Tyr;

(ii) X at position 48 of SEQ ID NO: 141 is Thr or Cys;

(iii) X at position 112 of SEQ ID NO: 141 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iv) X at position 114 of SEQ ID NO: 141 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(v) X at position 115 of SEQ ID NO: 141 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

wherein optionally the first polypeptide chain comprises an α chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 97 or 145; and

(b) the second polypeptide chain comprises a β chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 142, wherein X at position 57 of SEQ ID NO: 142 is Ser or Cys;

wherein optionally the second polypeptide chain comprises a β chain constant region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 99 or 140.

23. The protein of any one of claims 19-21, further comprising:

(a) the first polypeptide chain comprises an α chain constant region comprising the amino acid sequence of SEQ ID NO: 141, wherein:

(i) X at position 1 of SEQ ID NO: 141 is Asn, Asp, His, or Tyr;

(ii) X at position 48 of SEQ ID NO: 141 is Thr or Cys;

(iii) X at position 112 of SEQ ID NO: 141 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iv) X at position 114 of SEQ ID NO: 141 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(v) X at position 115 of SEQ ID NO: 141 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

wherein optionally the first polypeptide chain comprises an α chain constant region comprising the amino acid sequence of SEQ ID NO: 97 or 145; and

(b) the second polypeptide chain comprises a β chain constant region comprising the amino acid sequence of SEQ ID NO: 142, wherein X at position 57 of SEQ ID NO: 142 is Ser or Cys;

wherein optionally the second polypeptide chain comprises a β chain constant region comprising the amino acid sequence of SEQ ID NO: 99 or 140.

24. The protein of any one of claims 19-23, wherein:

(1) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 14 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 15;

(2) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 16 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 17;

(3) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 18 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 19;

(4) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 33 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 34;

(5) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 35 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 36;

(6) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 37 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 38;

(7) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 52 and the second polypeptide chain

comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 53;

(8) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 54 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 55;

(9) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 56 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 57;

(10) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 71 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 72;

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

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

(13) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 90 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 91;

(14) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 92 and the second polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 93; or

(15) the first polypeptide chain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 94 and the second polypeptide chain

comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 95.

25. The protein of any one of claims 19-23, wherein:

(1) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 15;

(2) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 16 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17;

(3) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 19;

(4) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 33 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 34;

(5) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 35 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 36;

(6) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 37 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 38;

(7) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 52 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 53;

(8) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 54 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 55;

(9) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 56 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 57;

(10) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 71 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 72;

(11) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74;

(12) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 75 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 76;

(13) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 90 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 91;

(14) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 92 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 93; or

(15) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 94 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 95.

26. An isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR of any one of claims 1-11, the polypeptide of any one of claims 12-18, or the protein of any one of claims 19-25.

27. An isolated or purified nucleic acid comprising, from 5' to 3', a first nucleic acid sequence and a second nucleotide sequence, wherein the first and second nucleotide sequence, respectively, encode the amino sequences of SEQ ID NOs: 8 and 9; 9 and 8; 10 and 11; 11 and 10; 12 and 13; 13 and 12; 12 and 11; 11 and 12; 121 and 13; 13 and 121; 121 and 122; 122 and 121; 8 and 120; 120 and 8; 119 and 9; 9 and 119; 119 and 120; 120 and 119; 14 and 15; 15 and 14; 16 and 17; 17 and 16; 18 and 19; 19 and 18; 27 and 28; 28 and 27; 29 and 30; 30 and 29; 31 and 32; 32 and 31; 31 and 30; 30 and 31; 125 and 32; 32 and 125; 125 and 126; 126 and 125; 27 and 124; 124 and 27; 123 and 28; 28 and 123; 123 and 124; 124 and 123; 33 and 34; 34 and 33; 35 and 36; 36 and 35; 37 and 38; 38 and 37; 46 and 47; 47 and 46; 48 and 49; 49 and 48; 50 and 51; 51 and 50; 50 and 49; 49 and 50; 129 and 51; 51 and 129; 129 and 130; 130 and 129; 46 and 128; 128 and 46; 127 and 47; 47 and 127; 127 and 128; 128 and 127; 52 and 53; 53 and 52; 54 and 55; 55 and 54; 56 and 57; 57 and 56; 65 and 66; 66 and 65; 67 and 68; 68 and 67; 69 and 70; 70 and 69; 69 and 68; 68 and 69; 133 and 70; 70 and 133; 133 and 134; 134 and 133; 65 and 132; 132 and 65; 131 and 66; 66 and 131; 131 and 132; 132 and 131; 71 and 72; 72 and 71; 73 and 74; 74 and 73; 75 and 76; 76 and 75; 84 and 85; 85 and 84; 86 and 87; 87 and 86; 88 and 89; 89 and 88; 88 and 87; 87 and 88; 137 and 89; 89 and 137; 137 and 138; 138 and 137; 84 and 136; 136 and 84; 135 and 85; 85 and 135; 135 and 136; 136 and 135; 90 and 91; 91 and 90; 92 and 93; 93 and 92; 94 and 95; or 95 and 94.

28. The isolated or purified nucleic acid of claim 27, further comprising a third nucleotide sequence interposed between the first and second nucleotide sequence, wherein the third nucleotide sequence encodes a cleavable linker peptide.

29. The isolated or purified nucleic acid of claim 28, wherein the cleavable linker peptide comprises the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 100).

30. The isolated or purified nucleic acid of claim 29, which encodes an amino acid sequence selected from the group consisting of: SEQ ID NOs: 20, 39, 58, 77, and 96.

31. A recombinant expression vector comprising the nucleic acid of any one of claims 26-30.

32. The recombinant expression vector of claim 31, which is a transposon or a lentiviral vector.

33. An isolated or purified TCR, polypeptide, or protein encoded by the nucleic acid of any one of claims 26-30 or the vector of claim 31 or 32.

34. An isolated or purified TCR, polypeptide, or protein that results from expression of the nucleic acid of any one of claims 26-30 or the vector of claim 31 or 32 in a cell.

35. A method of producing a host cell expressing a TCR that has antigenic specificity for the peptide of DRNTFRHSVVVPCEPPEVGSDCTTI (SEQ ID NO: 115) or SGNLLGRNSFEVCVCACPGRDRRTE (SEQ ID NO: 117), the method comprising contacting a cell with the vector of claim 31 or 32 under conditions that allow introduction of the vector into the cell.

36. An isolated or purified host cell comprising the nucleic acid of any one of claims 26-30 or the recombinant expression vector of claim 31 or 32.

37. The host cell of claim 36, wherein the cell is a human lymphocyte.

38. The host cell of claim 36, wherein the cell is selected from the group consisting of a T cell, a natural killer T (NKT) cell, an invariant natural killer T (iNKT) cell, and a natural killer (NK) cell.

39. An isolated or purified population of cells comprising the host cell of any one of claims 36-38.

40. A method of producing the TCR of any one of claims 1-11, 33, or 34, the polypeptide of any one of claims 12-18, 33, or 34, or the protein of any one of claims 19-25, 33, or 34, the method comprising culturing the host cell of any one of claims 36-38, or the population of host cells of claim 39, so that the TCR, polypeptide, or protein is produced.

41. A pharmaceutical composition comprising (a) the TCR of any one of claims 1-11, 33, or 34, the polypeptide of any one of claims 12-18, 33, or 34, the protein of any one of claims 19-25, 33, or 34, the nucleic acid of any one of claims 26-30, the recombinant expression vector of claim 31 or 32, the host cell of any one of claims 36-38, or the population of cells of claim 39 and (b) a pharmaceutically acceptable carrier.

42. 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 of any one of claims 1-11, 33, or 34, the polypeptide of any one of claims 12-18, 33, or 34, the protein of any one of claims 19-25, 33, or 34, the nucleic acid of any one of claims 26-30, the recombinant expression vector of claim 31 or 32, the host cell of any one of claims 36-38, the population of cells of claim 39, or the pharmaceutical composition of claim 41, thereby forming a complex; and

(b) detecting the complex,

wherein detection of the complex is indicative of the presence of cancer in the mammal.

43. The TCR of any one of claims 1-11, 33, or 34, the polypeptide of any one of claims 12-18, 33, or 34, the protein of any one of claims 19-25, 33, or 34, the nucleic acid of any one of claims 26-30, the recombinant expression vector of claim 31 or 32, the host cell of

any one of claims 36-38, the population of cells of claim 39, or the pharmaceutical composition of claim 41, for use in inducing an immune response against a cancer in a mammal.

44. The TCR of any one of claims 1-11, 33, or 34, the polypeptide of any one of claims 12-18, 33, or 34, the protein of any one of claims 19-25, 33, or 34, the nucleic acid of any one of claims 26-30, the recombinant expression vector of claim 31 or 32, the host cell of any one of claims 36-38, the population of cells of claim 39, or the pharmaceutical composition of claim 41, for use in treating or preventing cancer in a mammal.

45. The population of cells or the pharmaceutical composition comprising the population of cells for the use of claim 43 or 44, wherein the population of cells is autologous to the mammal.

46. The population of cells or the pharmaceutical composition comprising the population of cells for the use of claim 43 or 44, wherein the population of cells is allogeneic to the mammal.

47. The method of claim 42 or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of any one of claims 43-46, wherein the cancer is an epithelial cancer.

48. The method of claim 42 or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of any one of claims 43-46, 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.

49. The method of claim 42 or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of any one of claims 43-48, wherein the cancer is known to comprise an R273C or a Y220C mutation in human p53.