

HLA CLASS I-RESTRICTED T CELL RECEPTORS AGAINST MUTATED RAS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/594,244, filed December 4, 2017, which is incorporated by reference in its entirety herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH AND
DEVELOPMENT

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

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED
ELECTRONICALLY

[0003] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 37,098 Byte ASCII (Text) file named "741039_ST25.txt," dated December 3, 2018.

BACKGROUND OF THE INVENTION

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

BRIEF SUMMARY ~~OF THE INVENTION~~

[0005] In one aspect, the present disclosure provides an isolated or purified nucleic acid comprising a nucleotide sequence encoding a T-cell receptor (TCR) comprising the amino acid sequences of (i) SEQ ID NOs: 1-3, (ii) SEQ ID NOs: 4-6, or (iii) SEQ ID NOs: 1-6.

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

[0005b] In another aspect, the present disclosure provides a method of detecting the presence of cancer in mammal, the method comprising: (a) contacting a sample comprising cells of the cancer with the host cell as described herein, thereby forming a complex; and (b) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal. In yet another aspect, the present disclosure provides a use of the population of cells as described herein in the manufacture of a medicament for treating cancer in a mammal.

[0005c] In a further aspect, the present disclosure provides an isolated or purified TCR encoded by the nucleic acid as described herein. In another aspect, the present disclosure provides an isolated or purified nucleic acid comprising a nucleotide sequence encoding a polypeptide, wherein the polypeptide comprises a functional portion of the TCR encoded by the nucleic acid as described herein, wherein the functional portion comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, or (c) all of SEQ ID NOs: 1-6. In a further aspect, the present disclosure provides an isolated or purified nucleic acid comprising a nucleotide sequence encoding a protein, wherein the protein comprises the polypeptide as described herein.

[0005d] An ~~embodiment~~example of the ~~invention~~disclosure provides an isolated or purified T-cell receptor (TCR) comprising the amino acid sequences of (i) SEQ ID NOs: 1-3, (ii) SEQ ID NOs: 4-6, or (iii) SEQ ID NOs: 1-6, wherein the TCR has antigenic specificity for a mutated human

RAS amino acid sequence presented by a human leukocyte antigen (HLA) Class I molecule, and wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS), a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS), or a mutated human Neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.

[0006] Another embodimentexample of the inventiondisclosure provides an isolated or purified polypeptide comprising a functional portion of the inventive TCR, wherein the functional portion comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, or (c) all of SEQ ID NOs: 1-6.

[0007] Still another embodimentexample of the inventiondisclosure provides an isolated or purified protein comprising at least one of the inventive polypeptides.

[0008] Further embodimentexamples of the inventiondisclosure provide nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the inventive TCRs, polypeptides, and proteins.

[0009] Methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal are further provided by embodimentexamples of the inventiondisclosure.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0010] Figure 1A depicts graphs illustrating CD137 expression by peripheral blood CD8+ T cells following co-culture with dimethyl sulfoxide (DMSO) or autologous DCs pulsed with the KRAS WT 24-mer peptide or the KRAS G12V 24-mer peptide. The numbers in the boxes indicate the percentages of T cells expressing CD137 in each co-culture condition.

[0011] Figure 1B is a graph showing the number of IFN- γ spots per 2×10^4 cells following co-culture of T cells with autologous DCs pulsed with DMSO, the KRAS WT 24-mer peptide or the KRAS G12V 24-mer peptide. T cells cultured with PMA:ionomycin and T cells cultured with DCs pulsed with DMSO served as controls.

[0012] Figure 2 shows graphs depicting experimental data (dot plots) illustrating the percentage of CD8+ peripheral blood cells, which already underwent IVS with the KRAS G12V 24-mer peptide, which bound to KRAS G12V tetramer-allophycocyanin (APC) or KRAS G12V tetramer-phycoerythrin (PE) (right plot). The left plot shows T cells which had been modified to express a TCR which recognized a KRAS G12D 10-mer in the context of HLA-A*11:01, which bound to KRAS G12V tetramer-APC or KRAS G12V tetramer-PE.

CLAIM(S):

1. An isolated or purified nucleic acid comprising a nucleotide sequence encoding a T-cell receptor (TCR) comprising the amino acid sequences of (i) SEQ ID NOs: 1-3, (ii) SEQ ID NOs: 4-6, or (iii) SEQ ID NOs: 1-6;₂

~~wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence presented by a human leukocyte antigen (HLA) Class I molecule, and
 ——— wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS), a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS), or a mutated human Neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.~~

~~——— 2. ——— The TCR according to claim 1, wherein the HLA Class I molecule is an HLA-A molecule.~~

~~——— 3. ——— The TCR according to claim 1, wherein the HLA Class I molecule is an HLA-A11 molecule.~~

~~——— 4. ——— The TCR according to claim 1, wherein the HLA Class I molecule is an HLA-A*11:01 molecule.~~

~~——— 5. ——— The TCR according to any one of claims 1-4, wherein the mutated human RAS amino acid sequence comprises a wild-type human KRAS, a wild-type human HRAS, or a wild-type human NRAS amino acid sequence with a substitution of glycine at position 12, wherein position 12 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS protein, respectively.~~

~~——— 6. ——— The TCR according to claim 5, wherein the substitution is a substitution of glycine at position 12 with valine.~~

72. The nucleic acid~~TCR~~ according to ~~any one of claims 1-6, wherein the TCR comprising comprises~~ a human variable region.

~~83.~~ The nucleic acid~~TCR~~ according to ~~any one of~~ claims 1-7, wherein the TCR comprising comprises the amino acid sequences of:

- (i) the amino acid sequence of SEQ ID NO: 7,
- (ii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8, or
- (iii) both the amino acid sequence of SEQ ID NO: 7 and an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8~~of SEQ ID NO: 7-8.~~

~~94.~~ The nucleic acid~~TCR~~ according to ~~any one of~~ claims 1-8, wherein the TCR further comprising comprises:

- (a) an α chain constant region comprising ~~the an~~ amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:
 - (i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;
 - (ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
 - (iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
 - (iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (b) a β chain constant region comprising the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or
- (c) both (a) and (b).

~~105.~~ The nucleic acid according to isolated or purified TCR of any one of claims 1-9, wherein the TCR comprising comprises:

- (a) an α chain comprising ~~the an~~ amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:
 - (i) X at position 185 of SEQ ID NO: 21 is Thr or Cys;
 - (ii) X at position 249 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
 - (iii) X at position 251 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
 - (iv) X at position 252 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain comprising ~~the~~an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 190 of SEQ ID NO: 22 is Ser or Cys; or

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

6. The nucleic acid according to claim 1, wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence presented by a human leukocyte antigen (HLA) Class I molecule, and wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS), a mutated human Harvey rat sarcoma viral oncogene homolog (LIRAS), or a mutated human Neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.

7. The nucleic acid according to claim 6, wherein the amino acid sequence of the mutated human RAS amino acid sequence comprises or consists of SEQ ID NOs: 29 or 30.

8. The nucleic acid according to claim 6, wherein the HLA Class I molecule is an HLA-A molecule.

9. The nucleic acid according to claim 6, wherein the HLA Class I molecule is an HLA-A11 molecule.

10. The nucleic acid according to claim 6, wherein the HLA Class I molecule is an HLA-A*11:01 molecule.

11. The nucleic acid according to claim 6, wherein the mutated human RAS amino acid sequence comprises a wild-type human KRAS, a wild-type human HRAS, or a wild-type human NRAS amino acid sequence with a substitution of glycine at position 12, wherein position 12 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS protein, respectively.

12. The nucleic acid according to claim 11, wherein the substitution is a substitution of glycine at position 12 with valine.

13. The nucleic acid according to claim 1, wherein the TCR comprises the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, or both of SEQ ID NOs: 7 and 8.

~~11. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-10, wherein the functional portion comprises the amino acid sequences of:~~

- ~~(a) all of SEQ ID NOs: 1-3,~~
- ~~(b) all of SEQ ID NOs: 4-6, or~~
- ~~(c) all of SEQ ID NOs: 1-6.~~

~~12. The isolated or purified polypeptide according to claim 11, wherein the functional portion comprises the amino acid sequence(s) of:~~

- ~~(i) SEQ ID NO: 7,~~
- ~~(ii) SEQ ID NO: 8, or~~
- ~~(iii) both of SEQ ID NOs: 7-8.~~

~~1314. The nucleic acid according to isolated or purified polypeptide of claim 11 or 121, wherein the TCR further comprising comprises:~~

- (a) an α chain constant region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:
 - (i) X at position 48 of SEQ ID NO: 17 is ~~Thr or~~ Cys;
 - (ii) X at position 112 of SEQ ID NO: 17 is ~~Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~
 - (iii) X at position 114 of SEQ ID NO: 17 is ~~Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp;~~ and
 - (iv) X at position 115 of SEQ ID NO: 17 is ~~Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~
- (b) a β chain constant region comprising the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is ~~Ser or~~ Cys; or
- (c) both (a) and (b).

~~1415. The nucleic acid according to isolated or purified polypeptide of any one of claims 11-131, wherein the TCR comprising comprises:~~

- (a) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:
 - (i) X at position 185 of SEQ ID NO: 21 is ~~Thr or~~ Cys;
 - (ii) X at position 249 of SEQ ID NO: 21 is ~~Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

(iii) X at position 251 of SEQ ID NO: 21 is ~~Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp~~; and

(iv) X at position 252 of SEQ ID NO: 21 is ~~Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp~~;

(b) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 190 of SEQ ID NO: 22 is Ser or Cys; or

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

~~15.—An isolated or purified protein comprising at least one of the polypeptides of any one of claims 11-14.~~

~~16.—The isolated or purified protein according to claim 15, comprising a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 1-3 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 4-6.~~

~~17.—The isolated or purified protein according to claim 15 or 16, comprising a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 7 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 8.~~

~~18.—The isolated or purified protein of any one of claims 15-17, further comprising:~~
~~(a) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 17, wherein:~~
~~(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;~~
~~(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~
~~(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~
~~(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~
~~(b) a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 18,~~
~~wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or~~
~~(c) both (a) and (b).~~

~~19.—The isolated or purified protein of any one of claims 15-18, comprising:~~
~~(a) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 21, wherein:~~
~~(i) X at position 185 of SEQ ID NO: 21 is Thr or Cys;~~
~~(ii) X at position 249 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

(iii) ~~X at position 251 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~
 (iv) ~~X at position 252 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~
 (b) ~~a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 22,~~
~~wherein X at position 190 of SEQ ID NO: 22 is Ser or Cys; or~~
 (c) ~~both (a) and (b).~~

~~20. An isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR according to any one of claims 1-10, the polypeptide according to any one of claims 11-14, or the protein according to any one of claims 15-19.~~

2416. A recombinant expression vector comprising the nucleic acid according to claim 201.

2417. An isolated or purified host cell comprising the recombinant expression vector according to claim 2416.

2418. An isolated or purified population of cells comprising the host cell according to claim 2417.

2419. A pharmaceutical composition comprising (a) ~~the TCR according to any one of claims 1-10, the polypeptide according to any one of claims 11-14, the protein according to any one of claims 15-19, the nucleic acid according to claim 20, the recombinant expression vector according to claim 21, the host cell according to claim 22, or the population of cells according to claim 23-18~~ and (b) a pharmaceutically acceptable carrier.

2520. A method of detecting the presence of cancer in mammal, the method comprising:

(a) contacting a sample comprising cells of the cancer with ~~the TCR according to any one of claims 1-10, the polypeptide according to any one of claims 11-14, the protein according to any one of claims 15-19, the nucleic acid according to claim 20, the recombinant expression vector according to claim 21, the host cell according to claim 2417, the population of cells according to claim 23, or the pharmaceutical composition of claim 24,~~ thereby forming a complex; and

(b) detecting the complex,

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

~~26. — The TCR according to any one of claims 1–10, the polypeptide according to any one of claims 11–14, the protein according to any one of claims 15–19, the nucleic acid according to claim 20, the recombinant expression vector according to claim 21, the host cell according to claim 22, the population of cells according to claim 23, or the pharmaceutical composition of claim 24, for use in the treatment or prevention of cancer in a mammal.~~

2721. The method according to claim ~~2520~~, ~~or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition, for the use of claim 26~~, wherein the cancer expresses a mutated human RAS amino acid sequence, wherein the mutated human RAS amino acid sequence is a mutated human KRAS, a mutated human HRAS, or a mutated human NRAS amino acid sequence.

2822. The method according to claim 2721, ~~or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition, for the use of claim 27~~, wherein the mutated human RAS amino acid sequence comprises a wild-type human KRAS, a wild-type human HRAS, or a wild-type human NRAS amino acid sequence with a substitution of glycine at position 12, wherein position 12 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS amino acid sequence, respectively.

2823. The method according to claim 2822, ~~or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition, for the use of claim 28~~, wherein the substitution is a substitution of glycine at position 12 with valine.

3024. The method according to ~~any one of claims 27–2921~~, ~~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 27–29~~, wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS) amino acid sequence.

~~3125.~~ The method according to ~~any one of claims 27-2921, 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 27-29,~~ wherein the mutated human RAS amino acid sequence is a mutated human neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.

~~3226.~~ The method according to ~~any one of claims 27-2921, 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 27-29,~~ wherein the mutated human RAS amino acid sequence is a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS) amino acid sequence.

~~3327.~~ The method according to ~~any one of claims 25-3220, 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 26-32,~~ wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

28. Use of the population of cells according to claim 18 in the manufacture of a medicament for treating cancer in a mammal.

29. An isolated or purified TCR encoded by the nucleic acid according to claim 1.

30. An isolated or purified nucleic acid comprising a nucleotide sequence encoding a polypeptide, wherein the polypeptide comprises a functional portion of the TCR encoded by the nucleic acid according to claim 1, wherein the functional portion comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, or (c) all of SEQ ID NOs: 1-6.

31. The nucleic acid according to claim 30, wherein the functional portion of the TCR comprises: (i) the amino acid sequence of SEQ ID NO: 7, (ii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8, or (iii) both the amino acid sequence of SEQ ID NO: 7 and an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8.

32. The nucleic acid according to claim 30, wherein the functional portion of the TCR comprises:

(a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or (c) both (a) and (b).

33. The nucleic acid according to claim 30, wherein the functional portion of the TCR comprises:

(a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 185 of SEQ ID NO: 21 is Thr or Cys; (ii) X at position 249 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 251 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 252 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 190 of SEQ ID NO: 22 is Ser or Cys; or

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

34. An isolated or purified nucleic acid comprising a nucleotide sequence encoding a protein, wherein the protein comprises the polypeptide according to claim 30.

35. The nucleic acid according to claim 34, wherein the protein comprises a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 1-3 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 4-6.

36. The nucleic acid according to claim 34, wherein the protein comprises a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 7 and a second polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8.

37. The nucleic acid according to claim 34, wherein the protein further comprises:

(a) a first polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys; (ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

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

38. The nucleic acid according to claim 34, wherein the protein comprises:

(a) a first polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 185 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 249 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 251 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Tip; and

(iv) X at position 252 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a second polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 190 of SEQ ID NO: 22 is Ser or Cys; or

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

39. The nucleic acid according to claim 34, wherein the protein comprises a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 7 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 8.

40. The nucleic acid according to claim 34, wherein the protein comprises:

(a) an amino acid sequence at least 99% identical to a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Leu;

(iii) X at position 114 of SEQ ID NO: 17 is Ile; and

(iv) X at position 115 of SEQ ID NO: 17 is Val;

(b) a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Cys; or

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

_____ 41. The nucleic acid according to claim 34, wherein the protein comprises:

_____ (a) an amino acid sequence at least 99% identical to a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 21, wherein:

_____ (i) X at position 185 of SEQ ID NO: 21 is Cys;

_____ (ii) X at position 249 of SEQ ID NO: 21 is Leu;

_____ (iii) X at position 251 of SEQ ID NO: 21 is Ile; and

_____ (iv) X at position 252 of SEQ ID NO: 21 is Val;

_____ (b) an amino acid sequence at least 99% identical to a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 22, wherein X at position 190 of SEQ ID NO: 22 is Cys; or

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

_____ 42. The nucleic acid according to claim 30, wherein the functional portion of the TCR comprises the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, or both of SEQ ID NOs: 7 and 8.

_____ 43. The nucleic acid according to claim 30, wherein the functional portion of the TCR comprises:

_____ (a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:

_____ (i) X at position 48 of SEQ ID NO: 17 is Cys;

_____ (ii) X at position 112 of SEQ ID NO: 17 is Leu;

_____ (iii) X at position 114 of SEQ ID NO: 17 is Ile; and

_____ (iv) X at position 115 of SEQ ID NO: 17 is Val;

_____ (b) the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Cys; or

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

_____ 44. The nucleic acid according to claim 30, wherein the functional portion of the TCR comprises: _____

_____ (a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:

_____ (i) X at position 185 of SEQ ID NO: 21 is Cys;

_____ (ii) X at position 249 of SEQ ID NO: 21 is Leu;

_____ (iii) X at position 251 of SEQ ID NO: 21 is Ile; and

_____ (iv) X at position 252 of SEQ ID NO: 21 is Val;

_____ (b) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 190 of SEQ ID NO: 22 is Cys; or

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