HLA CLASS II–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. 62/560,930, filed September 20, 2017, which is incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under project number BC010984 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 59,753 Byte ASCII (Text) file named "739664_ST25.txt," dated September 5, 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 T-cell receptor (TCR), wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence presented by a human leukocyte antigen (HLA) Class II molecule, 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 and the TCR comprises: an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

[0005a] In another aspect, the present disclosure provides an isolated or purified polypeptide comprising a functional portion of a TCR, wherein the functional portion comprises an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

[0005b] In another aspect, the present disclosure provides an isolated or purified protein comprising a first polypeptide chain comprising an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3 and a second polypeptide chain comprising a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

[0005c] In another aspect, the present disclosure provides a pharmaceutical composition comprising the TCR as described herein, and a pharmaceutically acceptable carrier. In yet another aspect, the present disclosure provides an isolated or purified TCR that results from expression of a nucleotide sequence encoding the isolated or purified TCR as described herein. In yet another aspect, the present disclosure provides an isolated or purified host cell comprising the TCR as described herein.

[0005d] In another aspect, the present disclosure provides a method of detecting the presence of a KRAS G12V-expressing cancer in a mammal, the method comprising:

(a) contacting a sample comprising cells of the cancer with the TCR as described herein, thereby forming a complex; and (b) detecting the complex, wherein detection of the complex is indicative of the presence of the KRAS G12V-expressing cancer in the mammal.

[0005e] In another aspect, the present disclosure provides a use of the TCR as described herein in the manufacture of a pharmaceutical composition for treating a KRAS G12V-expressing cancer in a mammal. In another aspect, the present disclosure provides a use of the isolated or purified TCR as described herein in the manufacture of a pharmaceutical composition for treating a KRAS G12V-expressing cancer in a mammal.

[0005f] An ~~embodiment~~example of the ~~invention~~disclosure provides an isolated or purified T-cell receptor (TCR), wherein the TCR has antigenic specificity for a mutated human Ras amino acid sequence presented by a human leukocyte antigen (HLA) Class II molecule, 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 ~~embodiment~~example of the ~~invention~~disclosure 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, (c) all of SEQ ID NOs: 7-9, (d) all of SEQ ID NOs: 10-12, (e) all of SEQ ID NOs: 1-6, or (f) all of SEQ ID NOs: 7-12.

[0007] Still another ~~embodiment~~example of the ~~invention~~disclosure provides an isolated or purified protein comprising at least one of the inventive polypeptides.

[0008] ~~Embodiment~~Examples of the ~~invention~~disclosure further 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 ~~embodiment~~examples of the ~~invention~~disclosure.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

[0010] Figure 1 depicts experimental data (dot plots) illustrating the detection of cells stained for isotype (control) or cells stained for PD-1 and/or OX40 expression by flow cytometry. The numbers in the histograms represent the percentage of cells expressing PD-1.

[0011] Figure 2 is a graph showing the number of interferon gamma (IFNg) positive spots per well detected upon co-culture of pooled cultures of effector autologous T cells (culture numbers W1-W16) with target DCs pulsed with the indicated pools of 25-mer peptides (PP) or pools of peptide encoded by 25-mer tandem minigenes (TMGs) encompassing various tumor-specific mutations. Autologous T cells cultured alone, with dimethyl sulfoxide (DMSO), or OKT3 antibody served as controls. The boxed symbol (▼) indicates the pooled cultures (7 and 8) from which the TCR was isolated.

[0012] Figure 3 is a graph showing the number of IFNγ positive spots per 2 x 10^4 (2E4) cells detected upon co-culture of autologous T cells of culture number 7 (W7) with autologous DCs pulsed with each of peptides 1-17 (P1-P17) from peptide pool 1 (PP1). Autologous T cells cultured with dimethyl sulfoxide (DMSO) or OKT3 antibody served as controls.

[0013] Figure 4 is a graph showing the percentage of effector T cells transduced with the TCR of Example 2 which expressed 4-1BB upon co-culture with target autologous APCs

CLAIM(S):

1. An isolated or purified T-cell receptor (TCR), wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence presented by a human leukocyte antigen (HLA) Class II molecule,

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 and the TCR comprises:

an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

2. The isolated or purified TCR according to claim 1, comprising:

(i) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 13;

(ii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 14;

(iii) an amino acid sequence at least 99% identical to amino acids 21-131 of SEQ ID NO: 13;

(iv) an amino acid sequence at least 99% identical to amino acids 17-132 of SEQ ID NO: 14; or

(v) both (i) and (ii); both (i) and (iv); both (ii) and (iii); or both (iii) and (iv).

3. The isolated or purified TCR according to claim 1, comprising:

(i) the amino acid sequence of SEQ ID NO: 13;

(ii) the amino acid sequence of SEQ ID NO: 14;

(v) amino acids 21-131 of SEQ ID NO: 13;

(vi) amino acids 17-132 of SEQ ID NO: 14; or

(v) both (i) and (ii); both (i) and (iv); both (ii) and (iii); or both (iii) and (iv).

4. The isolated or purified TCR according to claim 1, further comprising:

(a) an α chain constant region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain constant region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or

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

5. The isolated or purified TCR according to claim 1, further comprising:

(a) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 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: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or

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

6. The isolated or purified TCR according to claim 1, comprising:

(a) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 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: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) an α chain comprising an amino acid sequence at least 99% identical to amino acids 21-268 of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising an amino acid sequence at least 99% identical to amino acids 17-305 of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys; or

(e) both (a) and (b); both (a) and (d); both (b) and (c); or both (c) and (d).

7. The isolated or purified TCR according to claim 1, comprising:

(a) an α chain comprising the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain comprising the amino acid sequence of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) an α chain comprising amino acids 21-268 of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising amino acids 17-305 of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys; or

(e) both (a) and (b); both (a) and (d); both (b) and (c); or both (c) and (d).

8. An isolated or purified polypeptide comprising a functional portion of a TCR, wherein the functional portion comprises an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

9. The isolated or purified polypeptide according to claim 8, wherein the functional portion comprises:

(i) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 13,

(ii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 14,

(iii) an amino acid sequence at least 99% identical to amino acids 21-131 of SEQ ID NO: 13;

(iv) an amino acid sequence at least 99% identical to amino acids 17-132 of SEQ ID NO: 14; or

(v) both (i) and (ii); both (i) and (iv); both (ii) and (iii); or both (iii) and (iv).

10. The isolated or purified polypeptide according to claim 8, wherein the functional portion comprises:

(i) the amino acid sequence of SEQ ID NO: 13,

(ii) the amino acid sequence of SEQ ID NO: 14,

(iii) amino acids 21-131 of SEQ ID NO: 13;

(iv) amino acids 17-132 of SEQ ID NO: 14; or

(v) both (i) and (ii); both (i) and (iv); both (ii) and (iii); or both (iii) and (iv).

11. The isolated or purified polypeptide according to claim 8, further comprising:

(a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 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: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or

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

12. The isolated or purified polypeptide according to claim 8, further comprising:

(a) the amino acid sequence of SEQ ID NO: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or

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

13. The isolated or purified polypeptide according to claim 8, comprising:

(a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 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: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) an amino acid sequence at least 99% identical to amino acids 21-268 of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) an amino acid sequence at least 99% identical to amino acids 17-305 of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys; or

(e) both (a) and (b); both (a) and (d); both (b) and (c); or both (c) and (d).

14. The isolated or purified polypeptide according to claim 8, comprising:

(a) the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) amino acids 21-268 of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) amino acids 17-305 of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys; or

(e) both (a) and (b); both (a) and (d); both (b) and (c); or both (c) and (d).

15. An isolated or purified protein comprising a first polypeptide chain comprising an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3 and a second polypeptide chain comprising a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

16. The isolated or purified protein according to claim 15, comprising:

(i) a first polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 13, and a second polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 14;

(ii) a first polypeptide chain comprising an amino acid sequence at least 99% identical to amino acids 21-131 of SEQ ID NO: 13, and a second polypeptide chain comprising an amino acid sequence at least 99% identical to amino acids 17-132 of SEQ ID NO: 14;

(iii) a first polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 13, and a second polypeptide chain comprising an amino acid sequence at least 99% identical to amino acids 17-132 of SEQ ID NO: 14; or

(iv) a first polypeptide chain comprising an amino acid sequence at least 99% identical to amino acids 21-131 of SEQ ID NO: 13, and a second polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 14.

17. The isolated or purified protein according to claim 15, comprising:

(i) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 13 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 14;

(ii) a first polypeptide chain comprising amino acids 21-131 of SEQ ID NO: 13, and a second polypeptide chain comprising amino acids 17-132 of SEQ ID NO: 14;

(iii) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 13, and a second polypeptide chain comprising amino acids 17-132 of SEQ ID NO: 14; or

(iv) a first polypeptide chain comprising amino acids 21-131 of SEQ ID NO: 13, and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 14.

18. The isolated or purified protein according to claim 15, further comprising:

(a) a first polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 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: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or

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

19. The isolated or purified protein according to claim 15, wherein:

(a) the first polypeptide chain further comprises the amino acid sequence of SEQ ID NO: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the second polypeptide chain further comprises the amino acid sequence of SEQ ID NO: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or

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

20. The isolated or purified protein according to claim 15, comprising:

(a) a first polypeptide chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 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: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) a first polypeptide chain comprising an amino acid sequence at least 99% identical to amino acids 21-268 of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a second polypeptide chain comprising an amino acid sequence at least 99% identical to amino acids 17-305 of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys; or

(e) both (a) and (b); both (a) and (d); both (b) and (c); or both (c) and (d).

21. The isolated or purified protein according to claim 15, comprising:

(a) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 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: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) a first polypeptide chain comprising amino acids 21-268 of SEQ ID NO: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a second polypeptide chain comprising amino acids 17-305 of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys; or

(e) both (a) and (b); both (a) and (d); both (b) and (c); or both (c) and (d).

22. A pharmaceutical composition comprising the TCR according to claim 1, and a pharmaceutically acceptable carrier.

23. An isolated or purified TCR that results from expression of a nucleotide sequence encoding the isolated or purified TCR according to claim 1.

24. An isolated or purified host cell comprising the TCR according to claim 23.

25. A method of detecting the presence of a KRAS G12V-expressing cancer in a mammal, the method comprising:

(a) contacting a sample comprising cells of the cancer with the TCR according to claim 1, thereby forming a complex; and

(b) detecting the complex, wherein detection of the complex is indicative of the presence of the KRAS G12V-expressing cancer in the mammal.

26. The method according to claim 25, wherein the KRAS G12V-expressing cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

27. Use of the TCR according to claim 1 in the manufacture of a pharmaceutical composition for treating a KRAS G12V-expressing cancer in a mammal.

28. The use according to claim 27, wherein the KRAS G12V-expressing cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

29. Use of the isolated or purified TCR according to claim 23 in the manufacture of a pharmaceutical composition for treating a KRAS G12V-expressing cancer in a mammal.

30. The use according to claim 29, wherein the KRAS G12V-expressing cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

~~1. An isolated or purified T-cell receptor (TCR), wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence presented by a human leukocyte antigen (HLA) Class II molecule,~~

~~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 II molecule is an HLA-DR molecule.~~

~~3. The TCR according to claim 1, wherein the HLA Class II molecule is an HLA-DRB1 molecule.~~

~~4. The TCR according to claim 1, wherein the HLA Class II molecule is an HLA-DRB1*07:01 molecule or an HLA-DRB1*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 or cysteine.~~

~~7. The TCR according to any one of claims 1-6, comprising the amino acid sequences of:~~

~~(a) all of SEQ ID NOs: 1-3,~~

~~(b) all of SEQ ID NOs: 4-6,~~

~~(c) all of SEQ ID NOs: 7-9,~~

~~(d) all of SEQ ID NOs: 10-12,~~

~~(e) all of SEQ ID NOs: 1-6, or~~

~~(f) all of SEQ ID NOs: 7-12.~~

~~8. The TCR according to any one of claims 1-7, comprising the amino acid sequences of:~~

~~(i) SEQ ID NO: 13,~~

~~(ii) SEQ ID NO: 14,~~

~~(iii) SEQ ID NO: 15,~~

~~(iv) SEQ ID NO: 16,~~

~~(v) both of SEQ ID NO: 13-14, or~~

~~(vi) both of SEQ ID NO: 15-16.~~

~~9. The TCR of any one of claims 1-8, further comprising:~~

~~(a) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 30, wherein:~~

~~(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;~~

~~(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~

~~(iv) X at position 115 of SEQ ID NO: 30 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: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or~~

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

~~10. The isolated or purified TCR of any one of claims 1-9, comprising:~~

~~(a) an α chain comprising the amino acid sequence of SEQ ID NO: 34, wherein:~~

~~(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;~~

~~(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~

~~(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

(b) a β chain comprising the amino acid sequence of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) an α chain comprising the amino acid sequence of SEQ ID NO: 36, wherein:

(i) X at position 180 of SEQ ID NO: 36 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 36 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 36 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 36 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising the amino acid sequence of SEQ ID NO: 37, wherein X at position 194 of SEQ ID NO: 37 is Ser or Cys;

(e) both (a) and (b); or

(f) both (c) and (d).

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,

(c) all of SEQ ID NOs: 7-9,

(d) all of SEQ ID NOs: 10-12,

(e) all of SEQ ID NOs: 1-6, or

(f) all of SEQ ID NOs: 7-12.

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: 13,

(ii) SEQ ID NO: 14,

(iii) SEQ ID NO: 15,

(iv) SEQ ID NO: 16,

(v) both of SEQ ID NO: 13-14, or

(vi) both of SEQ ID NO: 15-16.

~~13. The isolated or purified polypeptide of claim 11 or 12, further comprising:~~

~~(a) the amino acid sequence of SEQ ID NO: 30, wherein:~~

~~(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;~~

~~(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~

~~(iv) X at position 115 of SEQ ID NO: 30 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(b) the amino acid sequence of SEQ ID NO: 31, wherein X at position 57 of SEQ ID NO: 31 is Ser or Cys; or~~

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

~~14. The isolated or purified polypeptide of any one of claims 11-13, comprising:~~

~~(a) the amino acid sequence of SEQ ID NO: 34, wherein:~~

~~(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;~~

~~(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~

~~(iv) X at position 246 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(b) the amino acid sequence of SEQ ID NO: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;~~

~~(c) the amino acid sequence of SEQ ID NO: 36, wherein:~~

~~(i) X at position 180 of SEQ ID NO: 36 is Thr or Cys;~~

~~(ii) X at position 244 of SEQ ID NO: 36 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

~~(iii) X at position 246 of SEQ ID NO: 36 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and~~

~~(iv) X at position 247 of SEQ ID NO: 36 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;~~

(d) the amino acid sequence of SEQ ID NO: 37, wherein X at position 194 of SEQ ID NO: 37 is Ser or Cys;

(e) both (a) and (b); or

(f) both (c) and (d).

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) 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; or

(b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 7-9 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 10-12.

17. The isolated or purified protein according to claim 15 or 16, comprising:

(i) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 13 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 14; or

(ii) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 15 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 16.

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: 30, wherein:

(i) X at position 48 of SEQ ID NO: 30 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 30 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 30 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 30 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: 31, wherein X at position 57 of SEQ ID NO: 31 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: 34, wherein:

(i) X at position 179 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 243 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 245 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 246 of SEQ ID NO: 34 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: 35, wherein X at position 189 of SEQ ID NO: 35 is Ser or Cys;

(c) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 36, wherein:

(i) X at position 180 of SEQ ID NO: 36 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 36 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 36 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 36 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 37, wherein X at position 194 of SEQ ID NO: 37 is Ser or Cys;

(e) both (a) and (b); or

(f) both (c) and (d).

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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.

~~21. A recombinant expression vector comprising the nucleic acid according to claim 20.~~

~~22. An isolated or purified host cell comprising the recombinant expression vector according to claim 21.~~

~~23. An isolated or purified population of cells comprising the host cell according to claim 22.~~

~~24. 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 and (b) a pharmaceutically acceptable carrier.~~

~~25. 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 22, 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.~~

~~27. The method according to claim 25, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to 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.~~

~~28. The method according to claim 27, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to 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.~~

~~29. The method according to claim 28, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to claim 28, wherein the substitution is a substitution of glycine at position 12 with valine or cysteine.~~

~~30. The method according to any one of claims 27-29, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to 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.~~

~~31. The method according to any one of claims 27-29, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to 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.~~

~~32. The method according to any one of claims 27-29, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to 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.~~

~~33. The method according to any one of claims 25-32, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to any one of claims 26-32, wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.~~