

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.

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).

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.