

[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 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, wherein the T-cell receptor (TCR) comprises the amino acid sequences of SEQ ID NOs: 1-6; 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, wherein the population of cells is a population of peripheral blood lymphocytes (PBL), and wherein the TCR comprises the amino acid sequences of SEQ ID NOs: 1-6.

[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 example of the 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

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. The nucleic acid according to claim 1, wherein the TCR comprises a human variable region.
3. The nucleic acid according to claim 1, wherein 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.
4. The nucleic acid according to claim 1, wherein the TCR further 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).
5. The nucleic acid according to claim 1, wherein the TCR 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).

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 (HRAS), 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.
14. The nucleic acid according to claim 1, wherein the TCR 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 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 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 Cys; or
 - (c) both (a) and (b).
15. The nucleic acid according to claim 1, wherein the TCR 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 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) 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).
16. A recombinant expression vector comprising the nucleic acid according to claim 1.
17. An isolated or purified host cell comprising the recombinant expression vector according to claim 16.

18. An isolated or purified population of cells comprising the host cell according to claim 17.

19. A pharmaceutical composition comprising (a) the population of cells according to claim 18 and (b) a pharmaceutically acceptable carrier.

20. 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 according to claim 17, thereby forming a complex,

wherein the T-cell receptor (TCR) comprises the amino acid sequences of SEQ ID NOs: 1-6; and

(b) detecting the complex,

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

21. The method according to claim 20, 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.

22. The method according to claim 21, 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.

23. The method according to claim 22, wherein the substitution is a substitution of glycine at position 12 with valine.

24. The method according to claim 21, wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS) amino acid sequence.

25. The method according to claim 21, wherein the mutated human RAS amino acid sequence is a mutated human neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.

26. The method according to claim 21, wherein the mutated human RAS amino acid sequence is a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS) amino acid sequence.

27. The method according to claim 20, 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,
wherein the population of cells is a population of peripheral blood lymphocytes (PBL), and
wherein the TCR comprises the amino acid sequences of SEQ ID NOs: 1-6.

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 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 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).