ANTI-KRAS-G12D T CELL RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/369,883, filed August 2, 2016, which is incorporated by reference in its entirety herein.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 60,828 Byte ASCII (Text) file named "728242_ST25.txt" dated July 26, 2017.

BACKGROUND OF THE INVENTION

[0003] 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

[0004] In one aspect, the present disclosure provides an isolated or purified TCR comprising the amino acid sequences of: (a) SEQ ID NOs: 9-14; (b) SEQ ID NOs: 17-22; (c) SEQ ID NOs: 25-30; or (d) SEQ ID NOs: 33-38.

[0005] In another aspect, the present disclosure provides an isolated or purified polypeptide comprising the amino acid sequences of: (a) SEQ ID NOs: 9-14; (b) SEQ ID NOs: 17-22; (c) SEQ ID NOs: 25-30; or (d) SEQ ID NOs: 33-38.

[0006] In another aspect, the present disclosure provides an isolated or purified protein comprising: (a) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 9-11 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 12-14; (b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 17-19 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 20-22; (c) a first polypeptide chain comprising the amino acid sequences of SEQ ID

NOs: 25-27 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 28-30; or (d) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 33-35 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 36-38.

[0006a] In a further aspect, the present disclosure provides an isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR, the polypeptide, or the protein as disclosed herein.

[0007] The present disclosure further provides related nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the TCRs, polypeptides, and proteins of the invention.

[0007a] In one aspect, the present disclosure provides a recombinant expression vector comprising the nucleic acid as disclosed herein.

[0007b] In another aspect, the present disclosure provides an isolated or purified host cell comprising the recombinant expression vector as disclosed herein.

[0007c] In another aspect, the present disclosure provides a population of cells comprising at least one isolated or purified host cell as disclosed herein.

[0007d] In another aspect, the present disclosure provides a pharmaceutical composition comprising the TCR, the polypeptide, the protein, the nucleic acid, the recombinant expression vector, the host cell, or the population of host cells as disclosed herein, and a pharmaceutically acceptable carrier.

[0008] Methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal are further provided by the present disclosure.

[0008a] In one aspect, the present disclosure provides a method of detecting the presence of cancer in a mammal, the method comprising: (a) contacting a sample comprising cells of the cancer with the TCR, the polypeptide, the protein, the nucleic acid, the recombinant expression vector, the host cell, the population of host cells, or the pharmaceutical composition as disclosed 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.

[0008b] In another aspect, the present disclosure provides the use of the TCR, the polypeptide, the protein, the nucleic acid, the recombinant expression vector, the host cell, the population of host cells, or the pharmaceutical composition, in the manufacture of a medicament for the treatment or prevention of cancer in a mammal.

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

[0009] Figure 1A is a graph showing IFN-γ production (spots/2e4 cells) as determined by ELISPOT assay of 24 individual TIL cultures after co-culture with autologous dendritic cells transfected with an irrelevant tandem minigene (TMG) RNA (closed circles), or the indicated TMG construct encoding the 61 mutations identified by whole-exomic and transcriptome sequencing (TMG-1 (stars), TMG-2 (△), TMG-3 (▽), TMG-4 (open diamond), TMG-5 (closed diamond)).

[0010] Figure 1B is a graph showing IFN-γ production (spots/2e4 cells) as determined by ELISPOT assay (left axis; unshaded bars), and flow cytometric analysis of 4-1BB expression on CD8+ T cells (%) (right axis; shaded bars) of TIL culture #6 after co-culture with dendritic cells (DCs) transfected with an irrelevant TMG RNA or TMG-1, or incubated overnight with the mutated long peptides encoded by TMG-1.

[0011] Figure 1C is a graph showing IFN-γ production as determined by ELISPOT assay (left axis; unshaded bars), and flow cytometric analysis of 4-1BB expression on CD8+ T cells (%) (right axis; shaded bars) of the infusion product (TIL culture #6 after undergoing clinical scale rapid expansion) after co-culture with DCs transfected with the indicated TMG RNA, or incubated overnight with the 24-AA long KRAS-wild type (WT) or $KRAS^{G12D}$ peptides.

[0012] Figures 2A-2D are graphs showing the results of a TCR-Vβ deep sequencing analysis quantitating the frequency of each of the four identified $KRAS^{G12D}$-reactive T-cell clones in the infusion product (Rx1, filled bar), three metastatic lung samples prior to cell transfer (Tu-1, diamond; Tu-2A, square; and Tu-2B, triangle), the one progressing lesion after cell transfer (Tu-Pro, inverted triangle), and the peripheral blood of the patient before and at various times after cell infusion (circles). Numbers in parentheses indicate the rank of

of claim 13, the recombinant expression vector of claim 14, the host cell of claim 15, or the population of host cells of claim 16, and a pharmaceutically acceptable carrier.

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

(a) contacting a sample comprising cells of the cancer with the TCR of any one of claims 1-4, the polypeptide of any one of claims 5-8, the protein of any one of claims 9-12, the nucleic acid of claim 13, the recombinant expression vector of claim 14, the host cell of claim 15, the population of host cells of claim 16, or the pharmaceutical composition of claim 17, thereby forming a complex; and

(b) detecting the complex,

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

19. The method of claim 18, wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

20. Use of the TCR of any one of claims 1-4, the polypeptide of any one of claims 5-8, the protein of any one of claims 9-12, the nucleic acid of claim 13, the recombinant expression vector of claim 14, the host cell of claim 15, the population of host cells of claim 16, or the pharmaceutical composition of claim 17, in the manufacture of a medicament for the treatment or prevention of cancer in a mammal.

21. The use of claim 20, wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.