

ANTI-B-CELL MATURATION ANTIGEN CHIMERIC ANTIGEN RECEPTORS WITH HUMAN DOMAINS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/527,556, filed June 30, 2017, which is incorporated by reference in its entirety herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under project number ZIABC01143905 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 67,061 Byte ASCII (Text) file named "739534_ST25.TXT," dated June 25, 2018.

BACKGROUND OF THE INVENTION

[0004] Cancer is a public health concern. Despite advances in treatments such as chemotherapy, the prognosis for many cancers may be poor. For example, therapies for multiple myeloma (MM) may cause remissions, but many patients eventually relapse and die. Accordingly, there exists an unmet need for additional treatments for cancer.

BRIEF SUMMARY

[0005] An aspect of the disclosure provides a chimeric antigen receptor (CAR) comprising an antigen recognition domain, a transmembrane © domain, and a T cell activation domain, wherein the CAR has antigen specificity for B-cell maturation antigen (BCMA), wherein the antigen recognition domain comprises the amino acid sequences of: (a) SEQ ID Nos: 1-3; (b) SEQ ID Nos: 4-6; (c) SEQ ID Nos: 7-9; or (d) SEQ ID Nos: 10-12.

[0005a] In another aspect, the present disclosure provides a nucleic acid comprising a nucleotide sequence encoding the CAR as described herein. In yet another aspect, the present disclosure provides a vector comprising the nucleic acid as described herein. In yet another aspect, the present disclosure provides an isolated host cell comprising the vector as described herein. In yet another aspect, the present disclosure provides a population of cells comprising at least one host cell as described herein. In yet another aspect, the present disclosure provides a pharmaceutical composition comprising (a) the CAR as described herein, the nucleic acid as described herein, the vector as described herein, the host cell as described herein, or the population as described herein and (b) a pharmaceutically acceptable carrier.

[0005b] In a further aspect, the present disclosure provides a use of the CAR as described herein, the nucleic acid as described herein, the vector as described herein, the host cell as described herein, or the population as described herein, in the manufacture of a medicament for treating or preventing cancer in a mammal, optionally wherein the cancer is multiple myeloma or Hodgkin's lymphoma.

[0006] Further examples of the disclosure provide related nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the CARs of the disclosure.

[0007] Additional examples of the disclosure provide related methods of treating or preventing cancer in a mammal.

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

[0008] Figures 1A-1D are diagrams depicting a CAR comprising the fully-human heavy-chain-only antigen-recognition domains of FHVH74 (A), FHVH32 (B), FHVH33 (C), or FHVH93 (D), in combination with the hinge and transmembrane regions of the CD8 α molecule, the cytoplasmic portion of the CD28 costimulatory molecule, and the cytoplasmic portion of the CD3 ζ T- cell activation domain.

[0009] Figures 1E-1H are diagrams depicting a CAR comprising the fully-human heavy-chain-only antigen recognition domains of FHVH74 (E), FHVH32 (F), FHVH33 (G), or FHVH93 (H), in combination with the hinge and transmembrane regions of the CD8 α molecule, the cytoplasmic portion of the 4-1BB costimulatory molecule, and the cytoplasmic portion of the CD3 ζ T- cell activation domain.

[0010] Figures 1I-1L are diagrams depicting a CAR comprising the fully-human heavy-chain-only antigen recognition domains of FHVH74 (I), FHVH32 (J), FHVH33 (K), or FHVH93 (L), in combination with the hinge and transmembrane regions of the CD8 α molecule, the cytoplasmic portion of the inducible T-cell costimulatory protein (ICOS), and the cytoplasmic portion of the CD3 ζ T- cell activation domain.

[0011] Figure 2 is a series of graphs which depict experimental data illustrating that the four FHVH CARs shown were expressed by primary human T cells, as described in Example 2. Untransduced (UT) T cells are included as a negative control and 11D5-3-CD828Z is provided as a positive control CAR. The T cells were transduced on day 2 of culture, and the cells were stained with a BCMA-Fc protein reagent on day 7 of culture. The plots are gated on live lymphocytes. The numbers on the plots are the percentages of CD3 $^{+}$ cells expressing the CAR (top) or not expressing the CAR (bottom).

CLAIMS

1. A chimeric antigen receptor (CAR) comprising an antigen recognition domain, a transmembrane (TM) domain, and a T cell activation domain, wherein the CAR has antigen specificity for B-cell maturation antigen (BCMA), wherein the antigen recognition domain comprises the amino acid sequences of:

- (a) SEQ ID NOs: 1-3;
- (b) SEQ ID NOs: 4-6;
- (c) SEQ ID NOs: 7-9; or
- (d) SEQ ID NOs: 10-12.

2. The CAR of claim 1, wherein all domains of the CAR are human.

3. The CAR of claim 1 or 2, wherein the antigen recognition domain does not comprise a linker peptide having a length of about 8 to about 40 amino acid residues.

4. The CAR of any one of claims 1-3, wherein the CAR does not comprise an antibody light chain variable region.

5. The CAR of any one of claims 1-4, wherein the antigen recognition domain comprises the amino acid sequence of:

- (a) SEQ ID NO: 13;
- (b) SEQ ID NO: 14;
- (c) SEQ ID NO: 15; or
- (d) SEQ ID NO: 16.

6. The CAR of any one of claims 1-5, wherein the T-cell activation domain comprises a T-cell signaling domain of any one of the following proteins: a human CD28 protein, a human CD3-zeta protein, a human FcR γ protein, a CD27 protein, an OX40 protein, a human 4-1BB protein, a human inducible T-cell costimulatory protein (ICOS), modified versions of any of the foregoing, or any combination of the foregoing.

7. The CAR of any one of claims 1-6 comprising the amino acid sequence of any one of SEQ ID NOs: 17-28.
8. A nucleic acid comprising a nucleotide sequence encoding the CAR of any one of claims 1-7.
9. The nucleic acid of claim 8 comprising the nucleotide sequence of any one of SEQ ID NOs: 29-40.
10. A vector comprising the nucleic acid of claim 8 or 9.
11. An isolated host cell comprising the vector of claim 10.
12. The isolated host cell of claim 11, wherein the host cell is a T-cell or a natural killer (NK) cell.
13. A population of cells comprising at least one host cell of claim 11 or 12.
14. A pharmaceutical composition comprising (a) the CAR of any one of claims 1-7, the nucleic acid of claim 8 or 9, the vector of claim 10, the host cell of claim 11 or 12, or the population of claim 13 and (b) a pharmaceutically acceptable carrier.
15. Use of the CAR of any one of claims 1-7, the nucleic acid of claim 8 or 9, the vector of claim 10, the host cell of claim 11 or 12, or the population of claim 13, in the manufacture of a medicament for treating or preventing cancer in a mammal, optionally wherein the cancer is multiple myeloma or Hodgkin's lymphoma.