

COMPOSITIONS AND METHODS FOR MODULATING THE IMMUNE SYSTEM

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/438106, filed December 22, 2016, which is hereby incorporated by reference in its entirety.

BACKGROUND

There are many compositions and methods to manipulate the immune system to treat cancer. However, there is still a need for improved compositions and methods to treat cancer. The presently disclosed subject matter fulfills these needs and others that would be evident to one of skill in the art

SUMMARY

Embodiments disclosed herein provide for proteins comprising an extracellular domain of PD-1; a transmembrane domain selected from the group consisting of: 4- IBB transmembrane domain, CD28 transmembrane domain, CD27 transmembrane domain, and ICOS transmembrane domain; and an intracellular signaling domain selected from the group consisting of 4- IBB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain, and any combination thereof.

Embodiments disclosed herein also provide for nucleic acid molecules encoding the proteins provided herein.

In some embodiments, recombinant cells comprising the proteins or the nucleic acid molecules described herein are provided.

Disclosed herein is a recombinant cell comprising a chimeric transmembrane protein comprising: an extracellular domain of PD-1; a transmembrane domain selected from the group consisting of 4-1BB transmembrane domain, CD28 transmembrane domain, CD27 transmembrane domain, and ICOS transmembrane domain; and an intracellular signaling domain selected from the group consisting of 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain, and any combination thereof; wherein the recombinant cell is a marrow infiltrating lymphocyte (MIL).

In some embodiments, methods of making the recombinant cells are provided.

Disclosed herein is a method for making the recombinant cell as defined herein, comprising transfecting or infecting a subject's cell extracted from a bone marrow sample with a nucleic acid molecule that is able to encode the chimeric transmembrane protein.

Embodiments for increasing an immune response or treating a neoplasm are also provided.

Disclosed herein is the use of a recombinant cell as defined herein in the manufacture of a medicament for increasing an immune response in a subject having leukemia, lymphoma, or multiple myeloma.

Disclosed herein is the use of a recombinant cell as defined herein in the manufacture of a medicament for treating a neoplasm in a subject, wherein the neoplasm is leukemia, lymphoma, or multiple myeloma.

DETAILED DESCRIPTION

As used herein, terms such as "a," "an," and "the" include singular and plural referents unless the context clearly demands otherwise.

What is claimed is:

1. A recombinant cell comprising a chimeric transmembrane protein comprising:
an extracellular domain of PD-1;
a transmembrane domain selected from the group consisting of 4-1BB transmembrane domain, CD28 transmembrane domain, CD27 transmembrane domain, and ICOS transmembrane domain; and
an intracellular signaling domain selected from the group consisting of 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain, and any combination thereof;
wherein the recombinant cell is a marrow infiltrating lymphocyte (MIL).
2. The recombinant cell of claim 1, wherein the transmembrane domain is the 4-1BB transmembrane domain.
3. The recombinant cell of claim 2, wherein the intracellular signaling domain is selected from the group consisting of: 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.
4. The recombinant cell of claim 2, wherein the intracellular signaling domain is the intracellular domain of 4-1BB and an intracellular domain selected from the group consisting of: CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.
5. The recombinant cell of claim 1, wherein the transmembrane domain is the CD28 transmembrane domain.
6. The recombinant cell of claim 5, wherein the intracellular signaling domain is selected from the group consisting of: 4-1BB transmembrane domain, CD28 transmembrane domain, CD27 transmembrane domain, and ICOS transmembrane domain.
7. The recombinant cell of claim 5, wherein the intracellular signaling domain is the

intracellular domain of 4-1BB and an intracellular domain selected from the group consisting of: CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.

8. The recombinant cell of claim 1, wherein the transmembrane domain is the CD27 transmembrane domain.

9. The recombinant cell of claim 8, wherein the intracellular signaling domain is selected from the group consisting of: 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.

10. The recombinant cell of claim 8, wherein the intracellular signaling domain is the intracellular domain of 4-1BB and an intracellular domain selected from the group consisting of: CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.

11. The recombinant cell of claim 1, wherein the transmembrane domain is the ICOS transmembrane domain.

12. The recombinant cell of claim 11, wherein the intracellular signaling domain is selected from the group consisting of: 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.

13. The recombinant cell of claim 11, wherein the intracellular signaling domain is the intracellular domain of 4-1BB and the intracellular domain selected from the group consisting of: CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain.

14. The recombinant cell of claim 1, wherein the chimeric transmembrane protein comprises a sequence of SEQ ID NO: 21, 23, 25, 27, 29, or 31.

15. The recombinant cell of claim 1, wherein the chimeric transmembrane protein comprises a leader sequence.
16. The recombinant cell of claim 15, wherein the chimeric transmembrane protein comprises a CD8 leader sequence.
17. The recombinant cell of claim 16, wherein the CD8 leader sequence comprises SEQ ID NO: 1.
18. The recombinant cell of claim 1, comprising a nucleic acid molecule that is able to encode the chimeric transmembrane protein.
19. The recombinant cell of claim 18, wherein the nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO: 22, 24, 26, 28, 30, and 32.
20. The recombinant cell of claim 1, wherein the nucleic acid molecule further comprises a leader sequence encoded by SEQ ID NO: 2.
21. The recombinant cell of claim 1, wherein the MIL is a hypoxic-activated MIL.
22. A method for making the recombinant cell of claim 1, comprising transfecting or infecting a subject's cell extracted from a bone marrow sample with a nucleic acid molecule that is able to encode the chimeric transmembrane protein.
23. The method of claim 22 further comprising incubating the subject's cell under hypoxic conditions prior to transfecting or infecting the cell with the nucleic acid molecule encoding the protein.
24. The method of claim 23, wherein the hypoxic conditions comprise 0.5% to 5% oxygen gas.

25. The method of claim 23, wherein the hypoxic conditions comprise 1% to 2% oxygen gas.
26. The method of claim 23, further comprising incubating the subject's cell under normoxic conditions after said incubating under hypoxic conditions.
27. The method of claim 22, further comprising contacting the cell with anti-CD3/anti-CD28 beads.
28. Use of a recombinant cell of claim 1 in the manufacture of a medicament for increasing an immune response in a subject having leukemia, lymphoma, or multiple myeloma.
29. The use of claim 28, wherein the recombinant cell is produced by transfecting or infecting a subject's cell extracted from a bone marrow sample with a nucleic acid molecule encoding a chimeric transmembrane protein comprising:
- an extracellular domain of PD-1;
 - a transmembrane domain selected from the group consisting of 4-1BB transmembrane domain, CD28 transmembrane domain, CD27 transmembrane domain, and ICOS transmembrane domain; and
 - an intracellular signaling domain selected from the group consisting of 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain, and any combination thereof.
30. The use of claim 29, wherein the subject's cell is isolated from the subject.
31. The method of claim 28, wherein the subject is a human.
32. Use of a recombinant cell of claim 1 in the manufacture of a medicament for treating a neoplasm in a subject, wherein the neoplasm is leukemia, lymphoma, or multiple myeloma.
33. The use of claim 32, wherein the recombinant cell is made by transfecting or infecting a subject's cell extracted from a bone marrow sample with a nucleic acid molecule encoding a

chimeric transmembrane protein comprising:

an extracellular domain of PD-1;

a transmembrane domain selected from the group consisting of 4-1BB transmembrane domain, CD28 transmembrane domain, CD27 transmembrane domain, and ICOS transmembrane domain; and

an intracellular signaling domain selected from the group consisting of 4-1BB intracellular signaling domain, CD28 intracellular signaling domain, CD27 intracellular signaling domain, and ICOS intracellular signaling domain, and any combination thereof.

34. The use of claim 33, wherein the subject's cell is isolated from the subject.

35. The use of claim 32, wherein the subject is a human.

36. The use of claim 32, further comprising:

contacting a cell extracted from a bone marrow sample with anti-CD3/anti-CD28 beads;
incubating the cell under hypoxic conditions; and
incubating the cell under normoxic conditions.

37. The use of claim 36, wherein the cell is incubated under hypoxic conditions for 0.5 to 4 days.

38. The use of claim 36, wherein the cell is incubated under normoxic conditions for 0.5 to 4 days.