

- [NPL 1] Hanahan, Cell, 2011, 144, 646-74
- [NPL 2] Prieto, Clin Cancer Res. 2012, 18, 2039-47
- [NPL 3] Hamid, Expert Opin. Biol. Ther., 2013, 6, 847-61
- [NPL 4] Summers, Nat Rev Immunol, 2012, 12, 339-51
- [NPL 5] Vinay, Cellular & Molecular Immunology, 2011, 8, 281-284
- [NPL 6] Houot, Blood, 2009, 114, 3431-8
- [NPL 7] Ascierto, Semin Oncol, 2010, 37, 508-16
- [NPL 8] Dubrot, Cancer Immunol Immunother, 2010, 59, 1223-33
- [NPL 9] Schabowsky, Vaccine, 2009, 28, 512-22
- [NPL 10] Li, Proc Natl Acad Sci U S A. 2013, 110(48), 19501-6

[Summary of Invention]

[Technical Problem]

The present disclosure relates to anti-CD137 antigen-binding molecules and methods of using the same.

[Solution to Problem]

In order to provide anti-CD137 antigen-binding molecules which have immunocyte-activating effect, cytotoxic activity, or antitumor activity and meanwhile have reduced effect on non-tumor tissues such as normal tissues and have less side effects, and provide methods of using the same, the present disclosure provides anti-CD137 antigen-binding molecules characterized in that their binding activity to CD137 varies depending on various compounds (e.g. small molecule compounds) in target tissues (e.g. tumor tissues), and provides methods of using the same, pharmaceutical formulations, and such. In one embodiment, the anti-CD137 antigen-binding molecules of the present disclosure have low side effects, and thus the dosage can be increased without concerns about side effects, and as a result, they can exhibit stronger drug efficacy (cytotoxic activity or antitumor activity).

In one aspect, the present disclosure refers to an anti-CD137 antibody comprising any combination of HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 selected from (a) to (i) below:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;

(b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 9, HVR-H3 comprising the amino

acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 22, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;

(c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 22, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;

(d) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 11, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;

(e) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 12, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28;

(f) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 13, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 29;

(g) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 24, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;

(h) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27; and

(i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 14, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 19, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 24, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27.

In another aspect, the present disclosure refers to an isolated nucleic acid encoding the anti-CD137 antibody as disclosed herein. In yet another aspect, the present disclosure refers to a vector into which the nucleic acid as disclosed herein is introduced. In yet a further aspect, the present disclosure refers to a host cell comprising the nucleic acid as disclosed herein or the vector as disclosed herein. In still another aspect, the present disclosure refers to a method for producing an anti-CD137 antibody, which

comprises culturing the host cell as disclosed herein such that the anti-CD137 antibody is produced. In a further aspect, the present disclosure refers to an immunoconjugate comprising the anti-CD137 antibody as disclosed herein and an cytotoxic agent.

Specifically, the present disclosure provides anti-CD137 antigen-binding molecules, methods of using the same, pharmaceutical formulations, and such, as exemplarily described below.

[1]

An anti-CD137 antigen-binding molecule which has CD137-binding activity dependent on a small molecule compound.

[2]

- [illegible]

amino acid sequence of SEQ ID NO: 27.

2. The anti-CD137 antibody of claim 1, which is a human antibody, humanized antibody, or chimeric antibody, or an antigen-binding fragment thereof.
3. The anti-CD137 antibody of claim 1 or 2, which comprises a heavy chain constant region comprising any one of the amino acid sequences of SEQ ID NOs: 64 to 85.
4. An isolated nucleic acid encoding the anti-CD137 antibody of any one of claims 1 to 3.
5. A vector into which the nucleic acid of claim 4 is introduced.
6. A host cell comprising the nucleic acid of claim 4 or the vector of claim 5.
7. A method for producing an anti-CD137 antibody, which comprises culturing the host cell of claim 6 such that the anti-CD137 antibody is produced.
8. An immunoconjugate comprising the anti-CD137 antibody of any one of claims 1 to 3 and an cytotoxic agent.