

[0009] CD137 (4-1BB or TNFRSF9) is a member of the TNF Receptor Superfamily. CD137 expresses on both innate and adaptive immune cells. It plays a multifaceted role in the tumor microenvironment (TME). It is prevalently upregulated on T cells in TME and provides co-stimulation to CD8 and CD4 T cell activation, proliferation, and survival. It also modulates other cell functions in TME, such as promoting NK cells to interact with CD8 T cells, enhancing tumor antigen presentation on DC cells. A CD137 agonist can enhance the anti-tumor immune response and may work synergistically with other anti-tumor agents, including PD1/PD-L1 blocking antibodies.

[0010] Secretion of TGF β is another leading contributor to immune evasion and tumor progression. TGF β promotes tumor progression and immune-suppressing by preventing T cell proliferation and decrease the effector function of both T and NK cells. It also enhances the function of T regulatory cells and induces epithelial-to-mesenchymal transition (EMT).

[0011] Since PD1, CD137, and TGF β regulate independent immune suppression or immune stimulative pathway, it is possible that targeting PD1 and CD137, PD1 and TGF β , or targeting PD1, CD137 and TGF β will increase the anti-tumor efficacy, especially for immune-excluded and immune-desert tumors.

SUMMARY

[0011a] In one aspect, the present disclosure relates to an anti-CD137 antibody or antigen binding fragment thereof comprising:(i) a heavy chain variable region comprising CDR1: SEQ ID NO: 5, CDR2: SEQ ID NO: 22, and CDR3: SEQ ID NO: 23; and a light chain variable region comprising CDR1: SEQ ID NO: 24, CDR2: SEQ ID NO: 25, and CDR3: SEQ ID NO: 26.

[0011b] In another aspect, the present disclosure relates to a nucleic acid composition comprising one or more nucleic acids encoding the antibody or antigen binding fragment thereof as disclosed herein.

[0011c] In another aspect, the present disclosure relates to an expression vector composition comprising one or more expression vectors comprising the nucleic acid composition as disclosed herein.

[0011d] In another aspect, the present disclosure relates to a host cell comprising the nucleic acid composition as disclosed herein or the expression vector composition as disclosed herein.

[0011e] In another aspect, the present disclosure relates to a method for the production of the anti-CD137 antibody or antigen binding fragment thereof as disclosed herein, the method comprising culturing the host cell as disclosed herein.

[0011f] In another aspect, the present disclosure relates to a pharmaceutical composition comprising the anti-CD137 antibody or antigen binding fragment thereof as disclosed herein and a pharmaceutically acceptable carrier.

[0011g] In another aspect, the present disclosure relates to use of the antibody or antigen binding fragment thereof as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject.

[0012] The present disclosure addresses the above need by providing multispecific binding proteins including, for example, binding proteins that bind PD-L1 and CD137 (PD-L1/CD137 bispecific), binding proteins that bind PD-L1 and TGF β (PD-L1/TGF β bispecific), and binding proteins that bind PD-L1, TGF β , and CD137 (PD-L1/TGF β /CD137 trispecific). In an example, a PD-L1/CD137 bispecific is a binding protein that binds PD-L1 and CD137 and comprises: (a) an antibody scaffold module in an IgG format (e.g., a Y-shaped symmetrical or asymmetrical antibody comprising two heavy chains and two light chains) comprising a first antigen-binding site that binds PD-L1 and a second antigen-binding site that binds PD-L1; (b) at least one first binding module comprising a third antigen-binding site that binds CD137. In an example, a PD-L1/TGF β bispecific is a binding protein that binds PD-L1 and TGF β and comprises: (a) an antibody scaffold module in an IgG format comprising a first antigen-binding site that binds PD-L1 and a second antigen-binding site that binds PD-L1; (b) at least one

WHAT IS CLAIMED IS:

1. An anti-CD137 antibody or antigen binding fragment thereof comprising:
(i) a heavy chain variable region comprising CDR1: SEQ ID NO: 5, CDR2: SEQ ID NO: 22, and CDR3: SEQ ID NO: 23; and a light chain variable region comprising CDR1: SEQ ID NO: 24, CDR2: SEQ ID NO: 25, and CDR3: SEQ ID NO: 26.
2. The anti-CD137 antibody or antigen binding fragment thereof of claim 1, wherein the anti-CD137 antibody or antigen binding fragment thereof comprises:
(i) a heavy chain variable region comprising SEQ ID NO: 16; and a light chain variable region comprising SEQ ID NO: 17.
3. The anti-CD137 antibody or antigen binding fragment thereof of claim 1, wherein the binding protein or binding fragment thereof comprises a heavy chain constant region.
4. The anti-CD137 antibody or antigen binding fragment thereof of claim 3, wherein the constant region comprises SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, or SEQ ID NO: 64.
5. The anti-CD137 antibody of claim 1, wherein the anti-CD137 antibody comprises a heavy chain comprising SEQ ID NO: 75; and a light chain comprising SEQ ID NO: 76.
6. The anti-CD137 antibody or antigen binding fragment thereof of claim 1 comprising a light chain constant region comprising SEQ ID NO: 65 or SEQ ID NO: 66.
7. The anti-CD137 antibody of claim 1, wherein the anti-CD137 antibody is a multi-specific antibody, preferably a bispecific or tri-specific antibody.
8. The antigen binding fragment thereof of claim 1, wherein the binding fragment thereof is a Fab, a Fab', a F(ab)₂, a F(ab')₂, a Fd, a Fv, a scFv, a single-chain antibody, a minibody, or a diabody.

- 9.** A nucleic acid composition comprising one or more nucleic acids encoding the antibody or antigen binding fragment thereof of claim 1.
- 10.** An expression vector composition comprising one or more expression vectors comprising the nucleic acid composition of claim 9.
- 11.** A host cell comprising the nucleic acid composition of claim 9 or the expression vector composition of claim 10.
- 12.** A method for the production of the anti-CD137 antibody or antigen binding fragment thereof of claim 1, the method comprising culturing the host cell of claim 11.
- 13.** A pharmaceutical composition comprising the anti-CD137 antibody or antigen binding fragment thereof of claim 1 and a pharmaceutically acceptable carrier.
- 14.** Use of the antibody or antigen binding fragment thereof of any of claims 1-8 or the pharmaceutical composition of claim 13 in the manufacture of a medicament for treating cancer in a subject.