

05082566), or the anti-PDL1 antibody pembrolizumab, and combinations thereof, at inducing INF γ or mediating CD8⁺ T-cell proliferation and activation (WO 2017/123650). Additionally, WO 2016/149201 discloses certain antibodies directed against PDL1 and suggests creating bispecific antibody constructs further comprising a T-cell engaging antibody, with CD137 being contained in a non-exclusive list of more than 20 potential T-cell targets.

In spite of numerous treatment options for patients suffering from cancer, there remains a need for effective and safe therapeutic agents and a need for their preferential use in a more targeted manner. Immune-modulating biologics offer promising approaches in treatment of cancers due to their modes of actions, however global immunostimulation and lack of any restriction of this immunomodulation to pathologically relevant cells and sites causes numerous side effects and significant toxicities, which potentially may lead to increased morbidity and mortality of patients. It is therefore an object of the present invention to provide a medicament to improve treatment of a proliferative disease, particularly a cancer.

SUMMARY

It is an object of the present invention to provide a medicament to improve treatment of a proliferative disease, particularly a cancer. The present invention addresses the need for precision therapeutics for immuno-oncology that target only the disease-colocalized T cells for upregulation.

In one aspect, the present disclosure provides for a multispecific antibody comprising:

- a) at least one CD137 binding domain (CD137-BD); and
- b) at least one PDL1 binding domain (PDL1-BD),

wherein said CD137-BD binds to human CD137 with a dissociation constant (KD) of at least at least 5 times, preferably at least 10 times, e.g., at least 50, at least 100, at least 200, at least 300, at least 400, more preferably at least 500 times, e.g., at least 600, at least 700, at least 800, at least 900, at least 1,000 times higher relative to a dissociation constant (KD) of binding to human PDL1 of said PDL1-BD.

In another aspect, the present disclosure provides for a pharmaceutical composition comprising the multispecific antibody disclosed herein and a pharmaceutically acceptable carrier.

In yet another aspect, the present disclosure provides for the multispecific antibody disclosed herein or the pharmaceutical composition disclosed herein for use as a medicament.

In yet another aspect, the present disclosure provides for a method of producing the multispecific antibody disclosed herein, the method comprising the step of culturing a host cell comprising a nucleic acid or a vector encoding the multispecific antibody disclosed herein or a binding domain thereof or a fragment thereof.

In one example, the present disclosure relates to a multispecific antibody comprising at least one CD137 binding domain and at least one PDL1 binding domain. The present disclosure further relates to a multispecific antibody comprising at least one CD137 binding domain, at least one PDL1 binding domain, and at least one human serum albumin domain.

In one example, the present disclosure relates to a pharmaceutical composition comprising the multispecific antibody of the disclosure and a pharmaceutically acceptable carrier.

In a further example, the present disclosure provides the multispecific antibody of the disclosure or the pharmaceutical composition of the disclosure for use as a medicament.

In a further example, the present disclosure provides the multispecific antibody of the disclosure or the pharmaceutical composition of the disclosure for use in treatment of cancer in a subject in need thereof.

In one example, the present disclosure provides use of the multispecific antibody of the

disclosure or the pharmaceutical composition of the disclosure for treating cancer in a subject in need thereof.

In one example, the present disclosure provides use of the multispecific antibody of the disclosure or the pharmaceutical composition of the disclosure in the manufacture of a medicament for treatment of a cancer, in a subject in need thereof.

In yet another example, the present disclosure provides a method of treating a cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the multispecific antibody of the disclosure or the pharmaceutical composition of the disclosure.

In a further example, the present disclosure provides a nucleic acid comprising a nucleotide sequence encoding the multispecific antibody of the disclosure. In a further example, the present disclosure provides a vector comprising said nucleic acid. In a further example, the present disclosure provides a host cell comprising said nucleic or said vector.

In yet another example, the present disclosure provides a method of producing the multispecific antibody of the disclosure or a binding domain thereof or a fragment thereof, the method comprising the step of culturing a host cell comprising a nucleic acid or a vector encoding the multispecific antibody of the disclosure or a binding domain thereof or a fragment thereof.

The examples, advantageous features and preferred examples of the present disclosure summarized in the following items, respectively alone or in combination, further contribute to solving the object of the disclosure:

1. A multispecific antibody comprising:
 - a) at least one CD137 binding domain (CD137-BD); and
 - b) at least one PDL1 binding domain (PDL1-BD).
2. The multispecific antibody of item 1, wherein said antibody is monovalent, bivalent or multivalent for CD137 specificity, preferably monovalent.
3. The multispecific antibody of item 1 or 2, wherein said antibody is monovalent, bivalent or multivalent for PDL1 specificity, preferably monovalent.
4. The multispecific antibody of item 1, wherein said antibody comprises one CD137-BD and one PDL1-BD.
5. The multispecific antibody of item 1, wherein said antibody consists of one CD137-BD and one PDL1-BD.

- b) binds to human CD137 with a K_{off} rate of 10^{-3} s^{-1} or less, or 10^{-4} s^{-1} or less, or 10^{-5} s^{-1} or less as measured by SPR, particularly wherein said antibody is an scFv;
 - c) binds to human CD137 with a K_{on} rate of at least $10^4 \text{ M}^{-1}\text{s}^{-1}$ or greater, at least $10^5 \text{ M}^{-1}\text{s}^{-1}$ or greater, at least $10^6 \text{ M}^{-1}\text{s}^{-1}$ or greater, as measured by SPR, particularly wherein said antibody is an scFv;
 - d) optionally, does not cross-compete with urelumab;
 - e) optionally, does not cross-compete with utomilumab; and/or
 - f) is cross-reactive with *Macaca fascicularis* (Cynomolgus) CD137; and/or
 - g) when in scFv format, has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 50°C , preferably of at least 55°C , more preferably at least 60°C , in particular wherein said antibody or antigen-binding fragment thereof is formulated in phosphate-citrate buffer at pH 6.4, 150 mM NaCl, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
 - h) when in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C , of less than 7%, e.g. less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, preferably less than 1%, when the antibody of the disclosure is at a starting concentration of 10 mg/ml, and in particular wherein the antibody of the disclosure is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
 - i) when in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 40°C , of less than 5%, , e.g. less than 4%, less than 3%, less than 2%, preferably less than 1%, when the antibody of the disclosure is at a starting concentration of 10 mg/ml, and in particular wherein the antibody of the disclosure is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.
15. The multispecific antibody of item 13 or item 14, wherein said CD137-BD comprises a heavy chain variable region comprising a CDR having the sequence of SEQ ID NO: 1 for HCDR1, SEQ ID NO: 2 for HCDR2, and SEQ ID NO: 3 for HCDR3, and a light chain variable region comprising a CDR having the sequence SEQ ID NO: 18 for LCDR1, SEQ ID NO: 19 for LCDR2, and SEQ ID NO: 20 for LCDR3.

preferably at least 65°C, more preferably at least 70°C, in particular wherein said antibody or antigen-binding fragment thereof is formulated in phosphate-citrate buffer at pH 6.4, 150 mM NaCl, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;

- g) when in scFv format, has a loss in monomer content, after five consecutive freeze-thaw cycles, of less than 5%, preferably less than 3%, more preferably less than 1%, when the antibody of the disclosure is at a starting concentration of 10 mg/ml, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
- h) when in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C, of less than 15%, e.g. less than 12%, less than 10%, less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, preferably less than 1%, when the antibody of the disclosure is at a starting concentration of 10 mg/ml, and in particular wherein the antibody of the disclosure is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.

- 27. The multispecific antibody of item 25 or item 26, wherein said PDL1-BD comprises:
 - (a) a HCDR1 comprising the amino acid sequence of SEQ ID NO: 89; (b) a HCDR2 comprising the amino acid sequence of SEQ ID NO: 90; (c) a HCDR3 comprising the amino acid sequence of SEQ ID NO: 91; (d) a LCDR1 comprising the amino acid sequence of SEQ ID NO: 105; (e) a LCDR2 comprising the amino acid sequence of SEQ ID NO: 106; and (f) a LCDR3 comprising the amino acid sequence of SEQ ID NO: 107.
- 28. The multispecific antibody of item 25 or item 26, wherein said PDL1-BD comprises:
 - (a) a HCDR1 comprising the amino acid sequence of SEQ ID NO: 119; (b) a HCDR2 comprising the amino acid sequence of SEQ ID NO: 120; (c) a HCDR3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a LCDR1 comprising the amino acid sequence of SEQ ID NO: 135; (e) a LCDR2 comprising the amino acid sequence of SEQ ID NO: 136; and (f) a LCDR3 comprising the amino acid sequence of SEQ ID NO: 137.
- 29. The multispecific antibody of any one of items 25 to 28, wherein said PDL1-BD comprises: a heavy chain variable region comprising an amino acid sequence that is at least 90 percent identical to the amino acid sequence selected from the group