

(2016)). Although utilization of therapeutic antibodies agonizing CD137 is a very promising treatment strategy, it is coupled to difficulties such as low efficacy of anti-CD137 agonist antibodies, high toxicities and adverse events. CD137 agonist antibodies were shown to lead to alterations in immune system and organ function increasing risks of toxicities. High doses of CD137 agonist antibodies in naïve and tumor-bearing mice have been reported to induce T-cell infiltration to the liver and elevations of aspartate aminotransferase and alanine aminotransferase consistent with liver inflammation (Niu L, et al. *J Immunol* 178(7):4194–4213 (2007); Dubrot J, et al., *Int J Cancer* 128(1):105–118 (2011)). Initial clinical studies into the human therapeutic use of CD137 agonist antibody have also demonstrated elevations of liver enzymes and increased incidence of hepatitis (Sznol M., et al., *J Clin Oncol* 26(11S):3007 (2008); Ascierto PA, et al., *Semin Oncol* 37(5):508–516 (2010); Chester C., et al., *Cancer Immunol Immunother* Oct;65(10):1243-8 (2016)). Potentially fatal hepatitis was observed in a Bristol-Myers Squibb (BMS) phase II anti-CD137 study for previously treated stage III/IV melanoma, National Clinical Trial (NCT) 00612664. That study and several others (NCT00803374, NCT00309023, NCT00461110, NCT00351325) were terminated due to adverse events (Chester C., et al., *Cancer Immunol Immunother* Oct;65(10):1243-8 (2016)). Such adverse events are most probably due to systemic overstimulation of T-cells.

Thus, there is a need in the field to generate improved therapeutic anti-human CD137 antibodies having higher efficacy without the inherent side effects of general anti-proliferative drugs, in particular having lower toxicities comparable to the currently available CD137 antibodies.

SUMMARY

It is an object of the present disclosure to provide antibodies that specifically bind to human CD137 protein, and which have beneficial properties for use in therapies, such as improved affinity, efficacy, safety and improved biophysical properties, e.g. improved solubility, developability and stability. In particular, CD137 antibodies are yet to be found that do not directly and independent of other cell-surface molecules result in CD137 signaling upon binding.

In one aspect, the present disclosure refers to an isolated antibody having a binding specificity for human CD137, which comprises: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2, and 3, respectively, and LCDR1, LCDR 2 and LCDR3 sequences of SEQ ID NOs: 16, 17 and 18, respectively, wherein said antibody binds human CD137 extracellular domain at an epitope located in the distal part of the extracellular domain of CD137 within amino acid residues 24-86 of SEQ ID NO: 32, wherein said epitope is characterized by a set of critical residues, determined in accordance with Example 13, comprising the residues Ala33, Asn40, Arg 41, Gln43, Cys45, Cys48, Pro49, Ser52, and Ser80; provided that amino acid residue Asn42 of CD137 is not a critical residue for binding. In one example, the present disclosure describes a novel CD137 antibody.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier. In one example, there is disclosed a pharmaceutical composition comprising the isolated antibody of the disclosure, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure refers to the antibody of the disclosure, or the composition of the disclosure for use as a medicament.

In one example, the antibody of the disclosure, or the composition of the disclosure is described for use in the treatment of a cancer in a subject in need thereof.

In one aspect, the present disclosure refers to a use of the antibody as disclosed herein, or the composition as disclosed herein in the manufacture of a medicament in the treatment of a cancer.

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

In yet another aspect, the present disclosure refers to a nucleic acid encoding the antibody as disclosed herein. In a further example, the present disclosure describes a vector comprising said nucleic acid. In a further example, the present disclosure describes a host cell comprising said nucleic acid or said vector.

In another aspect, the present disclosure refers to a method of producing the antibody as disclosed herein, the method comprising the step of culturing a host cell comprising the nucleic acid or the vector as disclosed herein.

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

1. An isolated antibody having a binding specificity for human CD137, comprising a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein the set of CDRs has 10 or fewer amino acid substitutions from a set of CDRs in which
HCDR1' is an amino acid sequence selected from any one of SEQ ID Nos: 1, 4, 7, and 10;
HCDR2' is an amino acid sequence selected from any one of SEQ ID Nos: 2, 5, 8, and 11;
HCDR3' is an amino acid sequence selected from any one of SEQ ID Nos: 3, 6, 9, and 12;
LCDR1' is an amino acid sequence selected from any one of SEQ ID Nos: 16, 19, and 22;
LCDR2' is an amino acid sequence selected from any one of SEQ ID Nos: 17, 20, and 23; and

CLAIMS

1. An isolated antibody having a binding specificity for human CD137, which comprises:
HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2, and 3, respectively,
and LCDR1, LCDR 2 and LCDR3 sequences of SEQ ID NOs: 16, 17 and 18,
5 respectively, wherein said antibody binds human CD137 extracellular domain at an
epitope located in the distal part of the extracellular domain of CD137 within amino
acid residues 24-86 of SEQ ID NO: 32, wherein said epitope is characterized by a set
of critical residues, determined in accordance with Example 13, comprising the
residues Ala33, Asn40, Arg 41, Gln43, Cys45, Cys48, Pro49, Ser52, and Ser80;
10 provided that amino acid residue Asn42 of CD137 is not a critical residue for binding.
2. The antibody of claim 1, wherein the antibody 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 consisting of SEQ ID NOs: 13, 14, and
15 15; and a light chain variable region comprising an amino acid sequence that is at least
90 percent identical to the amino acid sequence selected from the group consisting of
SEQ ID NOs: 25, 26, and 27.
3. The antibody of claim 2, comprising: (a) a VH sequence of SEQ ID NO: 13 and a VL
20 sequence of SEQ ID NO: 25; (b) a VH sequence of SEQ ID NO: 14 and a VL
sequence of SEQ ID NO: 26; or (c) a VH sequence of SEQ ID NO: 15 and a VL
sequence of SEQ ID NO: 27.
4. The antibody of claim 1, wherein said antibody does not inhibit the interaction
25 between CD137 and its ligand CD137L as measured by the competition ELISA.
5. The antibody of claim 1, wherein said antibody
 - (i) binds to human CD137 with a dissociation constant (KD) of less than 50 nM,
as measured by surface plasmon resonance;
 - 30 (ii) optionally, binds to Cynomolgus CD137 with a KD of less than 50 nM, as
measured by surface plasmon resonance;
 - (iii) optionally, does not bind to human CD40 and/or does not bind to human
OX40 as measured by SPR;

- (iv) when in scFv format, has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 50°C wherein said antibody is formulated in 50 mM phosphate-citrate buffer at pH 6.4, 150 mM NaCl;
- 5 (v) when in scFv format, has a loss in monomer content, after storage for at least two weeks at 4°C, of less than 7%, when the antibody of the invention is at a starting concentration of 10 mg/ml, and wherein the antibody in scFv format is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
- 10 (vi) when in scFv format, has a loss in monomer content, after five consecutive freeze-thaw cycles of less than 5%, when the antibody of the invention is at a starting concentration of 10 mg/ml, and wherein the antibody in scFv format is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.
- 15 6. The antibody of claim 1, wherein the isolated antibody is selected from the group consisting of: a monoclonal antibody, a chimeric antibody, a Fab, an Fv, an scFv, dsFv, an scAb, STAB, and binding domains based on alternative scaffolds including but limited to ankyrin-based domains, fynomers, avimers, anticalins, fibronectins, and binding sites being built into constant regions of antibodies (e.g. F-star's Modular Antibody Technology), preferably Fv or scFv.
- 20 7. The antibody of claim 6, wherein said antibody is an scFv having an amino acid sequence selected from the group consisting of SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31.
- 25 8. The isolated antibody of claim 1, wherein said epitope characterized by a set of critical residues, determined in accordance with Example 13, further comprises the residues Pro32, Gly34, Thr35, Ser46, Pro47, Pro50, Cys78, and Ser79.
- 30 9. The antibody of claim 1, wherein the antibody is a multispecific molecule having at least a second functional molecule.
10. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

11. The antibody of claim 1 or the composition of claim 10 for use as a medicament.

12. Use of the antibody of claim 1, or the composition of claim 10 in the manufacture of a medicament for the treatment of a cancer.

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13. A nucleic acid encoding the antibody of claim 1.

14. A method of producing the antibody of claim 1, the method comprising the step of culturing a host cell comprising a nucleic acid or a vector encoding the antibody of claim 1.

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