

Various antibodies against CD137 are already known (see, for example, WO 00/29445 and WO 2004/010947), and at least two anti-CD137 antibodies are currently in the clinic: urelumab (Bristol-Myers Squibb), a fully humanized IgG4 mAb, and utomilumab (PF-05082566, Pfizer), a fully human IgG2 mAb (Chester C., et al., *Cancer Immunol Immunother* Oct;65(10):1243-8 (2016)). Although utilization of therapeutic antibodies agonizing CD137 is a very promising treatment strategy, it is coupled to such difficulties 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(115S):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 higher affinity, improved efficacy, lower toxicities, and improved biophysical properties, such as 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 provides for an isolated antibody having a binding specificity for human CD137, which comprises an HCDR1, HCDR2, HCDR3 sequences of SEQ ID NOs: 1, 2 and 3, respectively, and an LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 18, 19 and 20, respectively.

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

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

In yet another aspect, the present disclosure provides for use of the antibody as disclosed herein or the composition as disclosed herein in the manufacture of a medicament for the treatment of a cancer.

In yet another aspect, the present disclosure provides for a nucleic acid encoding the antibody as disclosed herein.

In yet another aspect, the present disclosure provides for a method of producing the antibody as disclosed herein, the method comprising the step of culturing a host cell comprising the nucleic acid as disclosed herein.

In one example, the present disclosure relates to a novel CD137 antibody.

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

In another example, the present disclosure relates to the antibody of the disclosure, or the composition of the disclosure for use as a medicament

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

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

In another example, the present disclosure relates to 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 example, the present disclosure relates to a nucleic acid encoding the antibody of the disclosure. In a further example, the present disclosure relates to a vector comprising said nucleic acid. In a further example, the present disclosure relates to a host cell comprising said nucleic acid or said vector.

In another example, the present disclosure relates to a method of producing the antibody of the disclosure, the method comprising the step of culturing a host cell comprising the nucleic acid or the vector of the disclosure.

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. An isolated antibody having a binding specificity for human CD137, which comprises: (a) a heavy chain variable region CDR1 comprising, preferably consisting of, an amino acid sequence selected from any one of SEQ ID NOs: 1, 4, 5, 8 and 11, preferably SEQ ID NO: 1; (b) a heavy chain variable region CDR2 comprising, preferably consisting of, an amino acid sequence selected from any of SEQ ID NOs: 2, 6, 9 and 12, preferably SEQ ID NO: 2; (c) a heavy chain variable region CDR3 comprising, preferably consisting of, an amino acid sequence selected from any of SEQ ID NOs: 3, 7, 10 and 13, preferably SEQ ID NO: 3; (d) a light chain variable

- a) 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 is formulated in 50 mM phosphate-citrate buffer at pH 6.4, 150 mM NaCl;
 - b) 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 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 is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
 - c) 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 is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.
14. The isolated antibody of any of the previous items, wherein the isolated antibody is selected from the group consisting of: a monoclonal antibody, a chimeric antibody, a Fab, an Fv, an scFv, dsFv, a 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 TechnologyTM), preferably Fv or scFv.
 15. The antibody of any one of the preceding items, which is a single-chain variable fragment (scFv).
 16. The antibody of item 15, wherein said scFv has the amino acid sequence selected from the group consisting of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35, preferably SEQ ID NO: 32 and SEQ ID NO: 35, more preferably SEQ ID NO: 35.
 17. The isolated antibody of item 14, wherein the antibody is an IgG selected from the group consisting of an IgG1, an IgG2, an IgG3 and an IgG4, preferably IgG4.
 18. The isolated antibody of any of the previous items, wherein the antibody is chimeric or humanized.

CLAIMS

1. An isolated antibody having a binding specificity for human CD137, which comprises an HCDR1, HCDR2, HCDR3 sequences of SEQ ID NOs: 1, 2 and 3, respectively, and an LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 18, 19 and 20, respectively.
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2. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region (VH), wherein said VH is VH3 or VH4, preferably VH3.
- 10 3. The antibody of claim 1 or claim 2, wherein the antibody comprises a light chain variable region (VL), wherein said VL comprises V κ frameworks FR1, FR2 and FR3, particularly V κ 1 or V κ 3 FR1 to FR3, preferably V κ 1 FR1 to FR3, and a framework FR4, which is selected from a V κ FR4, particularly V κ 1 FR4, V κ 3 FR4, and V λ FR4, particularly V λ FR4 comprising the amino acid sequence having at least 60, 70, 80, 90
15 percent identity to an amino acid sequence selected from any of SEQ ID NO: 62 to SEQ ID NO: 68, preferably V λ FR4 as set forth in any of SEQ ID NO: 62 to SEQ ID NO: 68, preferably V λ FR4 as set forth in SEQ ID NO: 62 or 63, more preferably V λ FR4 as set forth in SEQ ID NO: 62.
- 20 4. The antibody of any one of the preceding claims, 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: 14, 15, 16 and 17, preferably SEQ ID NO: 14 and 17, more preferably SEQ ID NO: 17; and a light chain variable region comprising an amino acid sequence
25 that is at least 90 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 28, 29 and 30, preferably SEQ ID NO: 27 and 30, more preferably SEQ ID NO: 30.
- 30 5. The antibody of claim 4, comprising: (a) a VH sequence of SEQ ID NO: 14 and a VL sequence of SEQ ID NO: 27; (b) a VH sequence of SEQ ID NO: 15 and a VL sequence of SEQ ID NO: 28; (c) a VH sequence of SEQ ID NO: 16 and a VL sequence of SEQ ID NO: 29; or (d) a VH sequence of SEQ ID NO: 17 and a VL

sequence of SEQ ID NO: 30.

6. The antibody of any one of the preceding claims, wherein said antibody:

(i) binds to human CD137 with a dissociation constant (KD) of less than 10 nM, particularly less than 5 nM, particularly less than 1 nM, in particular as measured by surface plasmon resonance (SPR), particularly wherein said antibody is an scFv;

(ii) 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;

(iii) binds to human CD137 with a K_{on} rate of at least $10^4 M^{-1}s^{-1}$ or greater, at least $10^5 M^{-1}s^{-1}$ or greater, at least $10^6 M^{-1}s^{-1}$ or greater, as measured by SPR, particularly wherein said antibody is an scFv;

(iv) is cross-reactive with *Macaca fascicularis* (Cynomolgus) CD137, in particular binds to Cynomolgus PDL1 with a KD of less than 15 nM, particularly less than 10 nM, particularly less than 5 nM as measured by SPR, particularly wherein said antibody is an scFv; and/or

(v) does not bind to human CD40 and/or human OX40, in particular as measured by SPR.

7. The antibody of any one of the preceding items, wherein said antibody:

(i) 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 is formulated in 50 mM phosphate-citrate buffer at pH 6.4, 150 mM NaCl;

(ii) 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 5%, e.g. less than 4%, less than 3%, less than 2%, preferably less than 1%, when the antibody of the invention is at a starting concentration of 10 mg/ml, and in particular wherein the antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or

(iii) 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 invention is at a starting concentration of 10 mg/ml, and in particular wherein the antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.

8. The antibody of any one of the previous claims, wherein the isolated antibody is selected from the group consisting of: a monoclonal antibody, a chimeric antibody, a Fab, an Fv, an scFv, dsFv, a 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 TechnologyTM), preferably Fv or scFv.

9. The antibody of claim 8, wherein said scFv has the amino acid sequence selected from the group consisting of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35, preferably SEQ ID NO: 32 and SEQ ID NO: 35, more preferably SEQ ID NO: 35.

10. The antibody of any one of claims 1 to 7, wherein said antibody is a multispecific molecule, in particular wherein said multispecific molecule comprises at least a second functional molecule.

11. A pharmaceutical composition comprising the antibody of any one of claims 1-10, and a pharmaceutically acceptable carrier.

12. The antibody of any one of claims 1 to 10, or the composition of claim 11 for use as a medicament.

13. Use of the antibody of any one of claims 1 to 10 or the composition of claim 11 in the manufacture of a medicament for the treatment of a cancer.

14. A nucleic acid encoding the antibody of any one of claims 1-10.

- 5 15. A method of producing the antibody of any one of claims 1-10, the method comprising the step of culturing a host cell comprising the nucleic acid of claims 1-8.