

related adverse events that result from their use at higher, potentially efficacious doses. In particular, current antibodies are either too potent, leading to adverse events, or display sub-optimal efficacy.

The anti-human CD137 agonistic antibodies described herein are fully human,
5 Fcγ-receptor-mediated effector null antibodies that bind human CD137 and cynomolgus monkey CD137, stimulate T cell activation *in vitro*, promote human CD137 cell surface expression, enhance NF-kappa B activity, inhibit tumor growth in murine tumor models of non-small cell lung cancer as a monotherapy, inhibit T-regulatory cell mediated suppression *in vitro*, activate immune gene signatures, increase the frequency of
10 intratumoral CD3⁺ T cells, compete with human CD137-Ligand for binding to human CD137, and bind to unique amino acid residues on human CD137.

Summary

In one aspect, the present disclosure refers to an anti-human CD137 (SEQ ID NO:1)
15 antibody comprising HCDR1 having the amino acid sequence of SEQ ID NO: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO:6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

20 In another aspect, the present disclosure refers to a mammalian cell capable of expressing an antibody comprising HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the
25 amino acid sequence of SEQ ID NO:7.

In a further aspect, the present disclosure refers to a mammalian cell capable of expressing an antibody comprising a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11 or the amino acid sequence of SEQ ID NO: 13.

In another aspect, the present disclosure refers to a process for producing an antibody comprising cultivating a mammalian cell capable of expressing the antibody and recovering the antibody; wherein the antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

In a further aspect, the present disclosure refers to a process for producing an antibody comprising cultivating a mammalian cell capable of expressing the antibody and recovering the antibody; wherein the antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11 or the amino acid sequence of SEQ ID NO: 13.

In another aspect, the present disclosure refers to an antibody produced by the process disclosed herein.

In a further aspect, the present disclosure refers to a DNA molecule comprising a polynucleotide having the sequence of SEQ ID NO:14 and one of SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.

In another aspect, the present disclosure refers to a DNA molecule comprising a polynucleotide having the sequence of SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.

In a further aspect, the present disclosure refers to a mammalian cell comprising a DNA molecule disclosed herein.

In another aspect, the present disclosure refers to a pharmaceutical composition, comprising an antibody disclosed herein and an acceptable carrier, diluent, or excipient.

In a further aspect, the present disclosure refers to an antibody disclosed herein, for use in therapy.

In another aspect, the present disclosure refers to an antibody disclosed herein, for use in the treatment of cancer.

In a further aspect, the present disclosure refers to a use of an antibody disclosed herein for the manufacture of a medicament for the treatment of cancer.

Description

The present disclosure provides an anti-human CD137 (SEQ ID NO:1) antibody comprising HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO:6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

The present disclosure provides an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9. The present disclosure provides an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 12.

The present disclosure provides an antibody comprising a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11. The present disclosure provides an antibody comprising a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 13.

The present disclosure provides a mammalian cell capable of expressing an antibody comprising HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid

WE CLAIM:

1. An anti-human CD137 (SEQ ID NO:1) antibody comprising HCDR1 having the amino acid sequence of SEQ ID NO: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO:6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.
2. The antibody of claim 1, comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.
3. The antibody of claim 1, comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 12.
4. The antibody of claim 1, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.
5. The antibody of claim 1, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 13.
6. A mammalian cell capable of expressing an antibody comprising HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO:7.
7. A mammalian cell capable of expressing an antibody comprising a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11 or the amino acid sequence of SEQ ID NO: 13.
8. A process for producing an antibody comprising cultivating a mammalian cell capable of expressing the antibody and recovering the antibody; wherein the antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2

having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

9. A process for producing an antibody comprising cultivating a mammalian cell capable of expressing the antibody and recovering the antibody; wherein the antibody
5 comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11 or the amino acid sequence of SEQ ID NO: 13.
10. The antibody produced by the process of any one of Claims 8-9.
11. A DNA molecule comprising a polynucleotide having the sequence of SEQ ID NO:14
10 and one of SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.
12. A DNA molecule comprising a polynucleotide having the sequence of SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.
13. A mammalian cell comprising the DNA molecule of Claim 11 or Claim 12.
14. A pharmaceutical composition, comprising the antibody of any one of Claims 1-5 and
15 10 and an acceptable carrier, diluent, or excipient.
15. The antibody of any one of Claims 1-5 and 10, for use in therapy.

16. The antibody of any one of Claims 1-5 and 10, for use in the treatment of cancer.
17. The antibody for use of Claim 16, wherein the cancer is bladder cancer, breast cancer, biliary tract cancer, colon cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, non-small cell lung cancer, prostate cancer, rectal cancer, or thyroid cancer.
18. The antibody for use of Claim 16, wherein the cancer is cholangiocarcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, clear cell renal carcinoma, or head and neck squamous cell carcinoma.
19. The antibody for use of Claim 16, wherein the cancer is bladder cancer, head and neck squamous cell carcinoma, or renal cell carcinoma.
20. The antibody for use of any one of Claims 16-19, wherein the antibody is to be administered in simultaneous, separate, or sequential combination with ionizing radiation.
21. The antibody for use of any one of Claims 16-20, wherein the antibody is to be administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.
22. Use of the antibody of any one of Claims 1-5 and 10 for the manufacture of a medicament for the treatment of cancer.
23. The use of Claim 22, wherein the cancer is bladder cancer, breast cancer, biliary tract cancer, colon cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, non-small cell lung cancer, prostate cancer, rectal cancer, or thyroid cancer.
24. The use of Claim 22, wherein the cancer is cholangiocarcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, clear cell renal carcinoma, or head and neck squamous cell carcinoma.
25. The use of Claim 22, wherein the cancer is bladder cancer, head and neck squamous cell carcinoma, or renal cell carcinoma.
26. The use of any one of Claims 22-25, wherein the antibody is to be administered in simultaneous, separate, or sequential combination with ionizing radiation.

27. The use of any one of Claims 22-26, wherein the antibody is to be administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.

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