

CLAIMS

1. A multispecific antibody comprising:

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

wherein said CD137-BD binds to human CD137 with a dissociation constant (KD) of at least 10 times higher relative to a dissociation constant (KD) of binding to human PDL1 of said PDL1-BD;

wherein said CD137-BD comprises:

- 1) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2 and 3, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 18, 19 and 20, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 15 and 17, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 28 and 30; or
- 2) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 35, 36 and 37, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 48, 49 and 50, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence of SEQ ID NO: 47, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence of SEQ ID NO: 57; or
- 3) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 59, 60 and 61, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 74, 75 and 76, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 72 and 73 and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 83, 84 and 85; and

wherein said PDL1-BD comprises:

- 1) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 89, 90 and 91, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 105, 106 and 107, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 102, 103 and 104, and a VL sequence that is at least 95, 96, 97, 98 or 99

percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 114 and 115; or

- 2) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 119, 120 and 121, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 135, 136 and 137, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 132, 133 and 134, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 144 and 145.

2. The multispecific antibody of claim 1, wherein said antibody is monovalent for CD137 specificity and, optionally, wherein said antibody is monovalent for PDL1 specificity.

3. The multispecific antibody of any one of claims 1 to 2, wherein said antibody further comprises at least one human serum albumin binding domain, preferably one human serum albumin binding domain.

4. The multispecific antibody of any one of claims 1 to 3, wherein said CD137-BD binds to human CD137 with a dissociation constant (KD) of at least 20 times higher relative to a dissociation constant (KD) of binding to human PDL1 of said PDL1-BD.

5. The multispecific antibody of claim of any of the preceding claims, wherein said CD137-BD is an agonist of CD137.

6. The multispecific antibody of claim 5, wherein said CD137-BD:

a) binds to human CD137 with a dissociation constant (KD) of less than 5 nM, particularly less than 1 nM, as measured by SPR, wherein said CD137-BD is an scFv;

b) binds to human CD137 with a K_{off} rate of 10^{-3} s^{-1} or less, as measured by SPR, wherein said CD137-BD is an scFv;

c) binds to human CD137 with a K_{on} rate of at least $10^5 \text{ M}^{-1}\text{s}^{-1}$ or greater, as measured by SPR, wherein said CD137-BD is an scFv;

d) does not cross-compete with urelumab;

- e) does not cross-compete with utomilumab; and/or
- f) is cross-reactive with *Macaca fascicularis* (Cynomolgus) CD137.

7. The multispecific antibody of any one of the preceding claims, wherein said CD137-BD comprises HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 59, 60 and 61, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 74, 75 and 76, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 71, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 83.

8. The multispecific antibody of any of the preceding claims, wherein said PDL1-BD is a blocker of PDL1.

9. The multispecific antibody of claim 8, wherein said PDL1-BD:

- a) binds to human PDL1 with a dissociation constant (KD) of less than 500 pM, more particularly less than 100 pM, as measured by SPR, wherein said PDL1-BD is an scFv;
- b) binds to human PDL1 with a K_{off} rate of 10^{-3} s^{-1} or less, or 10^{-4} s^{-1} or less, as measured by SPR, wherein said PDL1-BD is an scFv;
- c) binds to human PDL1 with a K_{on} rate of 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, wherein said PDL1-BD is an scFv;
- d) is cross-reactive with *Macaca fascicularis* (Cynomolgus) PDL1; and/or
- e) is non-cross reactive to *Mus musculus* PDL1.

10. The multispecific antibody of any one of the preceding claims, wherein said PDL1-BD comprises the HCDR1, HCDR2, and HCDR3 sequences of: SEQ ID NOs: 92, 93 and 94, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 108, 109 and 110, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 104, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 115.

11. The multispecific antibody of any one of claims 2 to 7, further comprising a HSA-binding domain (HSA-BD), wherein said HSA-BD comprises:

(a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 149, 150 and 151, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 162, 163 and 164, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 161, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 171; or

(b) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 173, 174 and 175, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 186, 187 and 188, respectively, a VH sequence that is at least 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 185, and a VL sequence that is at least 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 195.

12. The multispecific antibody of claim 1, wherein said multispecific antibody is selected from an antibody having the SEQ ID NOs: 229, 230 and 231.

13. A pharmaceutical composition comprising the multispecific antibody of anyone of the preceding claims and a pharmaceutically acceptable carrier.

14. The multispecific antibody of anyone of claims 1 to 12 or the pharmaceutical composition of claim 13 for use as a medicament.

15. A method of producing the multispecific antibody according to anyone of claims 1 to 12, the method comprising the step of culturing a host cell comprising one or more nucleic acids or one or more vectors encoding the multispecific antibody according to claims 1 to 12.