interaction with OX40L. This interaction is mediated by the binding of trimeric OX40L to CD134. In current anti-cancer therapies, the use of trimerized OX40 ligand is proposed as a more effective agent than anti-OX40 antibodies (Morris et al. Mol Immunol 2007; 44: 3112-3121).

Summary

The present disclosure provides a binding molecule comprising

(a) a heavy chain variable region comprising the amino acid sequence of figure 27, or a variant of that sequence having 1, 2 or 3 amino acid substitutions; and/or

(b) a light chain variable region comprising the amino acid sequence of figure 27, or a variant of that sequence having 1, 2 or 3 amino acid substitutions.

The disclosure further provides a binding molecule comprising

(a) a heavy chain variable region comprising the amino acid sequence of figure 26, or a variant of that sequence having 1, 2 or 3 amino acid substitutions; and/or

(b) a light chain variable region comprising the amino acid sequence of figure 26 or a variant of that sequence having 1, 2 or 3 amino acid substitutions.

In some embodiments, the isolated binding, molecules bind to human CD134. The binding molecules of the disclosure may not prevent human CD134 (OX40) receptor binding to OX40 ligand (OX40L).

Such binding molecules include suitable anti-CD134 antibodies, antigen-binding fragments of the anti-CD134 antibodies, and derivatives of the anti-CD134 antibodies.

In one aspect, there is provided an isolated antibody that binds human CD134, comprising a light chain variable region (VL) of SEQ ID NO: 98 and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3~~, optionally having 1, 2 or 3 amino acid substitutions in the VL of SEQ ID NO: 98~~.

~~In another aspect, there is provided an isolated antibody that binds human CD134, comprising a light chain variable region (VL) of SEQ ID NO: 100 and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, optionally having 1, 2 or 3 amino acid substitutions in the VL of SEQ ID NO: 100.~~

~~In another aspect, there is provided an isolated agonistic antibody that binds human CD134, comprising a light chain variable region (VL) and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, and light chain complementarity determining regions (LCDR)s LCDR1, LCDR2 and LCDR3, wherein~~

~~a. the HCDR1 comprises the amino acid sequence of SEQ ID NO: 14;~~

~~b. the HCDR2 comprises the amino acid sequence of SEQ ID NOs:15, 141, 142 or 143;~~

~~c. the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 16, 144 or 145;~~

~~d. the LCDR1 comprises the amino acid sequence of SEQ ID NO: 17;~~

~~e. the LCDR2 comprises the amino acid sequence of SEQ ID NO: 18; and~~

~~f. the LCDR3 comprises the amino acid sequence of SEQ ID NO: 19;~~

~~with the proviso that the antibody does not comprise the VH comprising the HCDR1,the HCDR2 and the HCDR3 amino acid sequences of SEQ ID NOs: 14, 15 and 16, and the VL comprising the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 17, 18 and 19.~~

In another aspect, there is provided an isolated agonistic antibody that binds human CD134, comprising a light chain variable region (VL) and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, and light chain complementarity determining regions (LCDR)s LCDR1, LCDR2 and LCDR3, wherein

a. the HCDR1 comprises the amino acid sequence of SEQ ID NO: 6;

b. the HCDR2 comprises the amino acid sequence of SEQ ID NOs:7, 135, 136, 137 or 138;

Claims

1. An isolated antibody that binds human CD134, comprising a light chain variable region (VL) of SEQ ID NO: 98 and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3.
2. The antibody of claim 1, wherein the VH comprises the amino acid sequence of SEQ ID NO: 134.
3. The antibody of claim 2, wherein the VH comprises the amino acid sequence of SEQ ID NO: 97.
4. The antibody of claim 1, wherein the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 8, 139 or 140.
5. The antibody of claim 4, wherein the HCDR2 comprises the amino acid sequence of SEQ ID NOs: 7, 135, 136, 137 or 138.
6. The antibody of claim 5, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 6.
7. The antibody of claim 2, wherein:
    a. the VL comprises the amino acid sequence of SEQ ID NOs: 62 or 63; and the VH comprises the amino acid sequence of SEQ ID NOs: 64, 65, 66, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 149, 150 or 151; or
    b. the VL and the VH comprise the amino acid sequences of
        i. SEQ ID NOs: 62 and 64, respectively;
        ii. SEQ ID NOs: 62 and 65, respectively;
        iii. SEQ ID NOs: 62 and 66, respectively;
        iv. SEQ ID NOs: 63 and 64, respectively;
        v. SEQ ID NOs: 63 and 65, respectively; or
        vi. SEQ ID NOs: 63 and 66, respectively.
8. The antibody of claim 7, wherein the VL comprises SEQ ID NO:63 and the VH comprises SEQ ID NO:66.
9. The antibody of any one of claims 1-8, wherein the antibody is humanized or DeImmunized™.
10. The antibody of any one claims 1-9, wherein the antibody is an agonist of CD134.
11. The antibody of claim 10, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.

12. The antibody of claim 11, wherein the antibody comprises a substitution in an Fc region.
13. The antibody of claim 12, wherein the substitution modulates binding of the antibody to an Fc gamma receptor (FcγR) or to a neonatal Fc receptor (FcRn).
14. The antibody of claim 13, wherein the substitution comprises a S267E/L328F substitution, an E233D/G237D/H268D/P271G/A330R substitution, a V234A/G237A/P238S/H268A/V309L/A330S/P331S substitution, or a M252Y/S254T/T256E substitution, wherein residue numbering is according to the EU Index.
15. An isolated nucleic acid molecule encoding the VH or the VL of claim 2.
16. An isolated nucleic acid molecule encoding the VH or the VL of claim 7.
17. A vector comprising the nucleic acid molecule of claim 15 or 16.
18. A host cell comprising the vector of claim 17.
19. Use of an antibody of any one of claims 2-14 in the manufacture of a medicament for enhancing an immune response.
20. Use of an antibody of any one of claims 2-14 in the manufacture of a medicament for the treatment of cancer.
21. The use of claim 20, wherein the cancer is prostate cancer, colon cancer, lung cancer, hematological malignancy, melanoma or bladder cancer.
22. A pharmaceutical composition comprising the antibody of any one of claims 2-14 and a pharmaceutically acceptable carrier.
23. An isolated agonistic antibody that binds human CD134, comprising a light chain variable region (VL) and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, and light chain complementarity determining regions (LCDR)s LCDR1, LCDR2 and LCDR3, wherein
    a. the HCDR1 comprises the amino acid sequence of SEQ ID NO: 6;
    b. the HCDR2 comprises the amino acid sequence of SEQ ID NOs:7, 135, 136, 137 or 138;
    c. the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 8, 139 or 140;
    d. the LCDR1 comprises the amino acid sequence of SEQ ID NO: 9;
    e. the LCDR2 comprises the amino acid sequence of SEQ ID NO: 10; and
    f. the LCDR3 comprises the amino acid sequence of SEQ ID NO: 11;

g. with the proviso that the antibody does not comprise the VH comprising the HCDR1, the HCDR2 and the HCDR3 amino acid sequences of SEQ ID NO:s 6, 7 and 8, and the VL comprising the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 9, 10 and 11.

Claims

1. An isolated antibody that binds human CD134, comprising a light chain variable region (VL) of SEQ ID NO: 98 and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, optionally having 1, 2 or 3 amino acid substitutions in the VL of SEQ ID NO: 98.
2. The antibody of claim 1, wherein the VH comprises the amino acid sequence of SEQ ID NO: 134, optionally having 1, 2 or 3 amino acid substitutions in the VH of SEQ ID NO: 134.
3. The antibody of claim 2, wherein the VH comprises the amino acid sequence of SEQ ID NO: 97, optionally having 1, 2 or 3 amino acid substitutions in the VH of SEQ ID NO: 97.
4. The antibody of claim 1, wherein the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 8, 139 or 140.
5. The antibody of claim 4, wherein the HCDR2 comprises the amino acid sequence of SEQ ID NOs: 7, 135, 136, 137 or 138.
6. The antibody of claim 5, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 6.
7. The antibody of claim 2, wherein:
    a. the VL comprises the amino acid sequence of SEQ ID NOs: 62 or 63; and the VH comprises the amino acid sequence of SEQ ID NOs: 64, 65, 66, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 149, 150 or 151, optionally having 1, 2 or 3 amino acid substitutions at the VH linear amino acid residue positions 11, 56 or 106; or
    b. the VL and the VH comprise the amino acid sequences of
        i. SEQ ID NOs: 62 and 64, respectively;
        ii. SEQ ID NOs: 62 and 65, respectively;
        iii. SEQ ID NOs: 62 and 66, respectively;
        iv. SEQ ID NOs: 63 and 64, respectively;
        v. SEQ ID NOs: 63 and 65, respectively; or
        vi. SEQ ID NOs: 63 and 66, respectively.
8. The antibody of claim 7, wherein the 1, 2 or 3 amino acid substitutions at the VH linear amino acid residue positions are V11L, D56G, D56A, D56S, D56E, M106L or M106I.

9. The antibody of claim 8, wherein the antibody binds to an epitope of the extracellular domain of human CD134 comprising the amino acid sequence of SEQ ID NO: 34, SEQ ID NO: 35; SEQ ID NO: 36, SEQ ID NO: 38 or SEQ ID NO: 92.
10. The antibody of claim 1, wherein the antibody is humanized or DeImmunized™.
11. The antibody of claim 1, wherein the antibody is an agonist of CD134.
12. The antibody of claim 11, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.
13. The antibody of claim 12, wherein the antibody comprises a substitution in an Fc region.
14. The antibody of claim 13, wherein the substitution modulates binding of the antibody to an Fc gamma receptor (FcγR) or to a neonatal Fc receptor (FcRn).
15. The antibody of claim 14, wherein the substitution comprises a S267E/L328F substitution, an E233D/G237D/H268D/P271G/A330R substitution, a V234A/G237A/P238S/H268A/V309L/A330S/P331S substitution, or a M252Y/S254T/T256E substitution, wherein residue numbering is according to the EU Index.
16. An isolated nucleic acid molecule encoding the VH or the VL of claim 2.
17. A vector comprising the nucleic acid molecule of claim 16.
18. A host cell comprising the vector of claim 17.
19. Use of an antibody of claim 2 in the manufacture of a medicament for enhancing an immune response.
20. Use of an antibody of claim 2 in the manufacture of a medicament for the treatment of cancer.
21. The use of claim 20, wherein the cancer is prostate cancer, colon cancer, lung cancer, hematological malignancy, melanoma or bladder cancer.
22. A pharmaceutical composition comprising the antibody of claim 2 and a pharmaceutically acceptable carrier.
23. An isolated antibody that binds human CD134, comprising a light chain variable region (VL) of SEQ ID NO: 100 and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, optionally having 1, 2 or 3 amino acid substitutions in the VL of SEQ ID NO: 100.
24. The antibody of claim 23, wherein the VH comprises the amino acid sequence of SEQ ID NO: 152, optionally having 1, 2 or 3 amino acid substitutions in the VH of SEQ ID NO: 152.

25. The antibody of claim 24, wherein the VH comprises the amino acid sequence of SEQ ID NO: 99, optionally having 1, 2 or 3 amino acid substitutions in the VH of SEQ ID NO: 99.
26. The antibody of claim 23, wherein the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 16, 144 or 145.
27. The antibody of claim 26, wherein the HCDR2 comprises the amino acid sequence of SEQ ID NOs: 15, 141, 142 or 143.
28. The antibody of claim 27, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 14.
29. The antibody of claim 24, wherein:
    a. the VL comprises the amino acid sequence of SEQ ID NOs: 67 or 68; and the VH comprises the amino acid sequence of SEQ ID NOs: 69, 70, 71, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 146, 147 or 148, optionally having 1, 2 or 3 amino acid substitutions at the VH linear amino acid residue positions 11, 55 or 99; or
    b. the VL and the VH comprise the amino acid sequences of
        i. SEQ ID NOs: 67 and 69, respectively;
        ii. SEQ ID NOs: 67 and 70, respectively;
        iii. SEQ ID NOs: 67 and 71, respectively;
        iv. SEQ ID NOs: 68 and 69, respectively;
        v. SEQ ID NOs: 68 and 70, respectively; or

vi. SEQ ID NOs: 68 and 71, respectively.

30. The antibody of claim 29, wherein the 1, 2 or 3 amino acid substitutions at the VH linear amino acid residue positions are V11L, N55Q, N55A, N55E, M99L or M99I.
31. The antibody of claim 30, wherein the binding molecule binds to an epitope of the extracellular domain of human CD134 comprising the amino acid sequence of SEQ ID NO: 34, SEQ ID NO: 35; SEQ ID NO: 36, SEQ ID NO: 38 or SEQ ID NO: 92.
32. The antibody of claim 23, wherein the antibody is humanized or DeImmunized™.
33. The antibody of claim 23, wherein the antibody is an agonist of CD134.
34. The antibody of claim 33, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.
35. The antibody of claim 34, wherein the antibody comprises a substitution in an Fc region.
36. The antibody of claim 35, wherein the substitution modulates binding of the antibody to an Fc gamma receptor (FcγR) or to a neonatal Fc receptor (FcRn).
37. The antibody of claim 36, wherein the substitution comprises a S267E/L328F substitution, an E233D/G237D/H268D/P271G/A330R substitution, a V234A/G237A/P238S/H268A/V309L/A330S/P331S substitution, or a M252Y/S254T/T256E substitution, wherein residue numbering is according to the EU Index.
38. An isolated nucleic acid molecule encoding the VH or the VL of claim 24.
39. A vector comprising the nucleic acid molecule of claim 38.
40. A host cell comprising the vector of claim 39.
41. Use of an antibody of claim 24 in the manufacture of a medicament for enhancing an immune response.
42. Use of an antibody of claim 24 in the manufacture of a medicament for the treatment of cancer.
43. The use of claim 42, wherein the cancer is prostate cancer, colon cancer, lung cancer, hematological malignancy, melanoma or bladder cancer.

44. A pharmaceutical composition comprising the antibody of claim 24 and a pharmaceutically acceptable carrier.

45. An isolated agonistic antibody that binds human CD134, comprising a light chain variable region (VL) and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, and light chain complementarity determining regions (LCDR)s LCDR1, LCDR2 and LCDR3, wherein
    a. the HCDR1 comprises the amino acid sequence of SEQ ID NO: 14;
    b. the HCDR2 comprises the amino acid sequence of SEQ ID NOs:15, 141, 142 or 143;
    c. the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 16, 144 or 145;
    d. the LCDR1 comprises the amino acid sequence of SEQ ID NO: 17;
    e. the LCDR2 comprises the amino acid sequence of SEQ ID NO: 18; and
    f. the LCDR3 comprises the amino acid sequence of SEQ ID NO: 19;
    with the proviso that the antibody does not comprise the VH comprising the HCDR1,the HCDR2 and the HCDR3 amino acid sequences of SEQ ID NOs: 14, 15 and 16, and the VL comprising the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 17, 18 and 19.
46. The isolated antibody of claim 45, wherein the antibody comprises the HCDR1, the HCDR2 and the HCDR3 sequences of
    a. SEQ ID NOs: 14, 15, 144, respectively,
    b. SEQ ID NOs: 14, 141, 16, respectively;
    c. SEQ ID NOs: 14, 142, 16, respectively;
    d. SEQ ID NOs: 14, 141, 144, respectively; or
    e. SEQ ID NOs: 14, 142, 144, respectively.
47. The isolated antibody of claim 45, wherein the antibody is humanized, DeImmunized™ or human.
48. The isolated antibody of claim 47, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.

49. The isolated antibody of claim 48, wherein the antibody comprises a substitution in an Fc region that modulates binding of the antibody to an Fc gamma receptor (FcγR) or to a neonatal Fc receptor (FcRn), wherein the substitution comprises a S267E/L328F substitution, an E233D/G237D/H268D/P271G/A330R substitution, a V234A/G237A/P238S/H268A/V309L/A330S/P331S substitution, or a M252Y/S254T/T256E substitution, wherein residue numbering is according to the EU Index.
50. An isolated nucleic acid molecule encoding the VH or the VL of claim 45.
51. A vector comprising the nucleic acid molecule of claim 50.
52. A host cell comprising the vector of claim 51.
53. Use of an antibody of claim 45 in the manufacture of a medicament for enhancing an immune response.
54. Use of an antibody of claim 45 in the manufacture of a medicament for the treatment of cancer.
55. The use of claim 54, wherein the cancer is prostate cancer, colon cancer, lung cancer, hematological malignancy, melanoma or bladder cancer.
56. An isolated agonistic antibody that binds human CD134, comprising a light chain variable region (VL) and a heavy chain variable region (VH) comprising heavy chain complementarity determining regions (HCDR)s HCDR1, HCDR2 and HCDR3, and light chain complementarity determining regions (LCDR)s LCDR1, LCDR2 and LCDR3, wherein
    a. the HCDR1 comprises the amino acid sequence of SEQ ID NO: 6;
    b. the HCDR2 comprises the amino acid sequence of SEQ ID NOs:7, 135, 136, 137 or 138;
    c. the HCDR3 comprises the amino acid sequence of SEQ ID NOs: 8, 139 or 140;
    d. the LCDR1 comprises the amino acid sequence of SEQ ID NO: 9;
    e. the LCDR2 comprises the amino acid sequence of SEQ ID NO: 10; and
    f. the LCDR3 comprises the amino acid sequence of SEQ ID NO: 11;

g. with the proviso that the antibody does not comprise the VH comprising the HCDR1, the HCDR2 and the HCDR3 amino acid sequences of SEQ ID NO:s 6, 7 and 8, and the VL comprising the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 9, 10 and 11.