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) of SEQ ID NO:97.

Also disclosed is 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.

In some embodiments the binding molecule binds to human CD134 with a K_d of 1×10^{-7} M or less. The binding molecule has agonist activity on human CD134 on T- effector cells and/or antagonistic activity on human CD134 on T-regulator cells. In some further embodiments, the binding molecule is a human monoclonal antibody that specifically binds human CD134 with a K_d of 100 nM or less, for example less than 50nM, or less than 20 nM.

The present disclosure also provides a composition that comprises one or more of the binding molecules and a pharmaceutically acceptable carrier. In some embodiments, the binding molecule is a human monoclonal anti-CD134 antibody or

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) of SEQ ID NO: 97.
2. The antibody of claim1, 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.
3. The antibody of claim 2, wherein the VL comprises SEQ ID NO:63 and the VH comprises SEQ ID NO:66.
4. The antibody of any one of claims 1-3, wherein the antibody is humanized or DeImmunized™.
5. The antibody of any one claims 1-4, wherein the antibody is an agonist of CD134.
6. The antibody of claim 5, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.
7. The antibody of claim 6, wherein the antibody comprises a substitution in an Fc region.
8. The antibody of claim 7, wherein the substitution modulates binding of the antibody to an Fc gamma receptor (FcγR) or to a neonatal Fc receptor (FcRn).
9. The antibody of claim 8, 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.
10. An isolated nucleic acid molecule encoding the VH or the VL of claim 1.
11. An isolated nucleic acid molecule encoding the VH or the VL of claim 3.

12. A vector comprising the nucleic acid molecule of claim 10 or 11.
13. A host cell comprising the vector of claim 12.
14. Use of an antibody of any one of claims 1-3 in the manufacture of a medicament for enhancing an immune response.
15. Use of an antibody of any one of claims 1-3 in the manufacture of a medicament for the treatment of cancer.
16. The use of claim 15, wherein the cancer is prostate cancer, colon cancer, lung cancer, hematological malignancy, melanoma or bladder cancer.
17. A pharmaceutical composition comprising the antibody of any one of claims 1-3 and a pharmaceutically acceptable carrier.