

CLAIMS

1. An anti-CD40 antibody or an antigen-binding fragment thereof, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

a-1) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in any one of SEQ ID NOs: 67 and 68, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in any one of SEQ ID NOs: 63-66;

a-2) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 1, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 2;

a-3) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 3, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 4;

a-4) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 5, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 6;

b-1) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in any one of SEQ ID NOs: 81 and 82, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in any one of SEQ ID NOs: 77-80;

b-2) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 7, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 8;

b-3) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 9, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 10;

b-4) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 11, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 12;

b-5) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 13, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 14;

b-6) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 15, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 16;

b-7) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 17, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 18;

c) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 19, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 20; or

d) the VH comprises a HCDR1, a HCDR2 and a HCDR3 in a VH set forth in SEQ ID NO: 21, and the VL comprises a LCDR1, a LCDR2 and a LCDR3 in a VL set forth in SEQ ID NO: 22;

wherein the CDRs are defined according to the Kabat, IMGT, Chothia, AbM or Contact numbering scheme, preferably the Kabat numbering scheme.

2. The anti-CD40 antibody or the antigen-binding fragment thereof according to claim 1, comprising:

1) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 23, 24 and 25, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 74, 75 and 76, respectively;

2) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 88, 89 and 90, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 91, 37 and 92, respectively;

3) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 51, 52 and 53, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 54, 55 and 56, respectively; or

4) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 57, 58 and 59, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 60, 61 and 62, respectively;

wherein preferably, the anti-CD40 antibody or the antigen-binding fragment thereof in 1) comprises:

1-1) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 23, 24 and 25, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 29, 30 and 73, respectively;

1-2) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 23, 24 and 25, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 26, 27 and 28, respectively; or

1-3) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 23, 24 and 25, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 29, 27 and 32, respectively;

preferably, the anti-CD40 antibody or the antigen-binding fragment thereof in 2) comprises:

2-1) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 39, 47 and 49, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 87, 50 and 48, respectively;

2-2) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 33, 34 and 35, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the

sequences set forth in SEQ ID NOs: 36, 37 and 38, respectively;

2-3) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 39, 40 and 41, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 42, 37 and 43, respectively;

2-4) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 39, 44 and 35, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 45, 37 and 46, respectively; or

2-5) a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 39, 47 and 41, respectively; and a light chain LCDR1, a light chain LCDR2 and a light chain LCDR3, comprising the sequences set forth in SEQ ID NOs: 36, 37 and 48, respectively;

more preferably, the anti-CD40 antibody or the antigen-binding fragment thereof in 1-1) comprises:

a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 23, 24 and 25, respectively; a light chain LCDR1, comprising the sequence set forth in SEQ ID NO: 29; a light chain LCDR2, comprising the sequence set forth in SEQ ID NO: 30; and a light chain LCDR3, comprising the sequence set forth in any one of SEQ ID NOs: 69-72;

more preferably, the anti-CD40 antibody or the antigen-binding fragment thereof in 2-1) comprises:

a heavy chain HCDR1, a heavy chain HCDR2 and a heavy chain HCDR3, comprising the sequences set forth in SEQ ID NOs: 39, 47 and 49, respectively; a light chain LCDR1, comprising the sequence set forth in any one of SEQ ID NOs: 83-86; a light chain LCDR2, comprising the sequence set forth in SEQ ID NO: 50; and a light chain LCDR3, comprising the sequence set forth in SEQ ID NO: 48.

3. The anti-CD40 antibody or the antigen-binding fragment thereof according to claim 1 or 2, being a recombinant antibody, a rabbit antibody, a chimeric antibody, a humanized antibody, a fully human antibody or an antigen-binding fragment thereof.

4. The anti-CD40 antibody or the antigen-binding fragment thereof according to claim 3, wherein:

of the humanized antibody or the antigen-binding fragment thereof, heavy chain framework regions are derived from IGHV2-26*01, IGHV4-30-4*02, IGHV4-4*08 and IGHJ1*01, and/or light chain framework regions are derived from IGkV1-13*02, IGkV1-9*01, IGkV1-6*01 and IGKJ4*01;

preferably, heavy chain framework regions FR1-FR3 are derived from IGHV2-26*01, IGHV4-30-4*02 or IGHV4-4*08, and a heavy chain framework region FR4 is derived from IGHJ1*01; light chain framework regions FR1-FR3 are derived from IGkV1-13*02, IGkV1-9*01 or IGkV1-6*01, and a light chain framework region FR4 is derived from IGKJ4*01.

5. The anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-4, wherein:

A-1) the amino acid sequence of the VH is set forth in SEQ ID NO: 67 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in any one of SEQ ID NOs: 63-66 or has at least 90% identity thereto;

A-2) the amino acid sequence of the VH is set forth in SEQ ID NO: 68 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in any one of SEQ ID NOs: 63-66 or has at least 90% identity thereto;

A-3) the amino acid sequence of the VH is set forth in SEQ ID NO: 1 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 2 or has at least 90% identity thereto;

A-4) the amino acid sequence of the VH is set forth in SEQ ID NO: 3 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 4 or has at least 90% identity thereto;

A-5) the amino acid sequence of the VH is set forth in SEQ ID NO: 5 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 6 or has at least 90% identity thereto;

B-1) the amino acid sequence of the VH is set forth in SEQ ID NO: 81 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in any one of SEQ ID NOs: 77-80 or has at least 90% identity thereto;

B-2) the amino acid sequence of the VH is set forth in SEQ ID NO: 82 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in any one of SEQ ID NOs: 77-80 or has at least 90% identity thereto;

B-3) the amino acid sequence of the VH is set forth in SEQ ID NO: 7 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 8 or has at least 90% identity thereto;

B-4) the amino acid sequence of the VH is set forth in SEQ ID NO: 9 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 10 or has at least 90% identity thereto;

B-5) the amino acid sequence of the VH is set forth in SEQ ID NO: 11 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 12 or has at least 90% identity thereto;

B-6) the amino acid sequence of the VH is set forth in SEQ ID NO: 13 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 14 or has at least 90% identity thereto;

B-7) the amino acid sequence of the VH is set forth in SEQ ID NO: 15 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 16 or has at least 90% identity thereto;

B-8) the amino acid sequence of the VH is set forth in SEQ ID NO: 17 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 18 or has at least 90% identity thereto;

C) the amino acid sequence of the VH is set forth in SEQ ID NO: 19 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 20 or has at least 90% identity thereto; or

D) the amino acid sequence of the VH is set forth in SEQ ID NO: 21 or has at least 90% identity thereto, and the amino acid sequence of the VL is set forth in SEQ ID NO: 22 or has at least 90% identity thereto.

6. The anti-CD40 antibody or the antigen-binding fragment thereof according to any one of the preceding claims, further comprising an Fc region of an IgG antibody, wherein preferably, the IgG antibody is an IgG1, IgG2 or IgG4 antibody; more preferably, the Fc region is an Fc region of IgG1 containing the mutation N297A, or an Fc region of IgG1 having any one or more of the mutations L234A, L235A, M252Y, S254T and T256E.

7. The anti-CD40 antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein the antigen-binding fragment is an scFv, Fv, Fab or Fab' fragment.

8. The anti-CD40 antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein:

the full-length amino acid sequence of a heavy chain is set forth in SEQ ID NO: 93 or 97 or has at least 90% identity thereto, and the full-length amino acid sequence of a light chain is set forth in SEQ ID NO: 94 or has at least 90% identity thereto; or

the full-length amino acid sequence of a heavy chain is set forth in SEQ ID NO: 95 or 98 or has at least 90% identity thereto, and the full-length amino acid sequence of a light chain is set forth in SEQ ID NO: 96 or has at least 90% identity thereto.

9. The anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-8, having at least one of the following:

- i) binding to human CD40 with a K_D of 10 nM or lower; and
- ii) having no significant agonistic activity.

10. An isolated polynucleotide, encoding the anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-9.

11. A vector, comprising the polynucleotide according to claim 10.

12. A host cell, comprising the polynucleotide according to claim 10 or the vector according to claim 11.

13. A CD40-binding molecule, comprising the anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-9.

14. A pharmaceutical composition, comprising the anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-9, and at least one pharmaceutically acceptable excipient, diluent or carrier.

15. The pharmaceutical composition according to claim 14, further comprising

tacrolimus.

16. Use of the anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-9, or the pharmaceutical composition according to claim 14 for the preparation of a medicament for treating an autoimmune disease, wherein the autoimmune disease is preferably Sjögren's syndrome, multiple sclerosis or lupus erythematosus, and is more preferably systemic lupus erythematosus.

17. Use of the anti-CD40 antibody or the antigen-binding fragment thereof according to any one of claims 1-9, or the pharmaceutical composition according to any one of claims 14-15 for the preparation of a medicament for treating graft-versus-host disease or alleviating graft rejection, wherein the graft is preferably a solid organ graft, and is more preferably a liver, kidney, heart or lung graft.