CLAIMS

1. A bispecific antibody of any one of bispecific antibodies (A) to (D) that specifically bind to human TNF alpha (TNFα) and to the P19 subunit of human IL-23 (IL23p19), wherein bispecific antibody (A) comprises:

(1) a first light chain (LC1) comprising a first light chain variable domain (VL1) and a first heavy chain constant domain 1 (CH1);

(2) a first heavy chain (HC1) comprising a first heavy chain variable domain (VH1), a first light chain constant (CL) region, and a Knob-Fc region;

(3) a second light chain (LC2) comprising a second light chain variable domain (VL2) and a second CL region; and

(4) a second heavy chain (HC2) comprising a second heavy chain variable domain (VH2), a second CH1 domain, and a Hole-Fc region;

wherein

(i) the VL1/VH1 pair and the VL2/VH2 pair specifically bind to human TNFα and human IL23p19, respectively, or to human IL23p19 and human TNFα, respectively; and

(ii) the Knob-Fc region is a human IgG Fc region variant having a T366W substitution (numbered according to the EU Index); and the Hole-Fc region is a human IgG Fc region variant having a Y407V substitution (numbered according to the EU Index);

bispecific antibody (B) comprises:

(1) a light chain (LC) comprising a first light chain variable domain (VL1) and a CL region; and

(2) a heavy chain (HC) comprising a first heavy chain variable domain (VH1), a heavy chain constant region (CH), a second light chain variable domain (VL2); and a second heavy chain variable domain (VH2);

wherein the VL1/VH1 pair and VL2/VH2 pair specifically bind to human TNFα and human IL23p19, respectively, or to human IL23p19 and human TNFα, respectively;

bispecific antibody (C) comprises:

(1) a light chain (LC) comprising a first light chain variable domain (VL1), a second light chain variable domain (VL2), and a CL region; and

(2) a heavy chain (HC) comprising a first heavy chain variable domain (VH1), a second heavy chain variable domain (VH2), and a CH region;

wherein the VL1/VH1 pair and VL2/VH2 pair specifically bind to human TNFα and human IL23p19, respectively, or to human IL23p19 and human TNFα, respectively;

and bispecific antibody (D) comprises:

(1) a light chain (LC) comprising a light chain variable domain (VL) and a CL region; and

(2) a heavy chain (HC) comprising a heavy chain variable domain (VH) and a CH region;

wherein

(1) the VL/VH pair specifically binds to human IL23p19; and (2) the HC further comprises a single heavy chain variable domain antibody (VHH) that specifically binds to human TNFα.

2. The bispecific antibody of claim 1, wherein

for bispecific antibody (A):

(1) the first CL region is kappa CL (Cκ; SEQ ID NO: 68) or lambda CL (Cλ, SEQ ID NO: 69); and the second CL region is Cκ (SEQ ID NO: 68) or Cλ (SEQ ID NO: 69);

(2) the first CH1 domain and the second CH1 domain are both human IgG1 CH1 domain (SEQ ID NO: 61); or

(3) the Knob-Fc region has the amino acid sequence of SEQ ID NO: 66; and the Hole-Fc region has the amino acid sequence of SEQ ID NO: 67; or any combination of (1)-(3);

for bispecific antibody (B),

(1) the CL region is Cκ (SEQ ID NO: 68) or Cλ (SEQ ID NO: 69); or

(2) the CH region is human IgG1 CH region (SEQ ID NO: 58); or both (1) and (2);

for bispecific antibody (C),

(1) the CL region is Cκ (SEQ ID NO: 68) or Cλ (SEQ ID NO: 69); or

(2) the CH region is human IgG1 CH region (SEQ ID NO: 58); or both (1) and (2);

for bispecific antibody (D),

(1) the CL region is Cκ (SEQ ID NO: 68) or Cλ (SEQ ID NO: 69); or

(2) the CH region is human IgG1 CH region (SEQ ID NO: 58); or both (1) and (2).

3. The bispecific antibody of claim 1 or 2, wherein

for bispecific antibody (A), the VL1/VH1 pair specifically binds to human TNFα and the VL2/VH2 pair specifically binds to human IL23p19;

for bispecific antibody (B), the VL1/VH1 pair specifically binds to human TNFα and the VL2/VH2 pair specifically binds to human IL23p19;

for bispecific antibody (C), the VL1/VH1 pair specifically binds to human TNFα and the VL2/VH2 pair specifically binds to human IL23p19;

for bispecific antibody (D), the VL and VH have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively; and/or, the VHH has the amino acid sequence of SEQ ID NO: 9; and/or, the VHH is linked to the N-terminus of the VH; and/or, the VHH is linked to the C-terminus of the Fc domain.

4. The bispecific antibody of claim 3, wherein

for bispecific antibody (A), the VL1 and VH1 have the amino acid sequences of (1) SEQ ID NOs: 1 and 2, respectively; or (2) SEQ ID NOs: 5 and 6, respectively; or wherein the VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively; or,

the VL1, VH1, VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 1, 2, 10, and 11, respectively; (2) SEQ ID NOs: 1, 2, 14, and 15, respectively; (3) SEQ ID NOs: 5, 6, 10, and 11, respectively; or (4) SEQ ID NOs: 5, 6, 14, and 15, respectively; or,

LC1, HC1, LC2, and HC2 each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 24, 25, 12, and 26, respectively; (2) SEQ ID NOs: 27, 28, 12, and 26, respectively; (3) SEQ ID NOs: 24, 25, 16, and 29, respectively; or (4) SEQ ID NOs: 27, 28, 16, and 29, respectively;

for bispecific antibody (B),

the VL1 and VH1 have the amino acid sequences of (1) SEQ ID NOs: 1 and 2, respectively; or (2) SEQ ID NOs: 5 and 6, respectively; or wherein the VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively; or (3) SEQ ID NOs: 93 and 94, respectively;

or, the VL1, VH1, VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 1, 2, 10, and 11, respectively; (2) SEQ ID NOs: 1, 2, 14, and 15, respectively; (3) SEQ ID NOs: 1, 2, 93, and 94, respectively; (4) SEQ ID NOs: 5, 6, 10, and 11, respectively; or (5) SEQ ID NOs: 5, 6, 14, and 15, respectively; (6) SEQ ID NOs: 5, 6, 93, and 94, respectively;

or, the LC and HC each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 3 and 30, respectively; (2) SEQ ID NOs: 3 and 31 respectively; (3) SEQ ID NOs: 7 and 32,

respectively; (4) SEQ ID NOs: 7 and 33, respectively; or (5) SEQ ID NOs: 7 and 92, respectively;

for bispecific antibody (C),

the VL1 and VH1 have the amino acid sequences of (1) SEQ ID NOs: 1 and 2, respectively; or (2) SEQ ID NOs: 5 and 6, respectively; or wherein VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively;

or, the VL1, VH1, VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 1, 2, 10, and 11, respectively; (2) SEQ ID NOs: 1, 2, 14, and 15, respectively; (3) SEQ ID NOs: 5, 6, 10, and 11, respectively; or (4) SEQ ID NOs: 5, 6, 14, and 15, respectively;

or, the LC and HC each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 46 and 47, respectively; (2) SEQ ID NOs: 48 and 49 respectively; (3) SEQ ID NOs: 50 and 51, respectively; or (4) SEQ ID NOs: 52 and 53, respectively;

for bispecific antibody (D),

the LC and HC each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 12 and 54, respectively; or (2) SEQ ID NOs: 16 and 56 respectively; and/or, when the VHH is linked to the C-terminus of the Fc domain, the LC and the HC each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 12 and 55, respectively; or (2) SEQ ID NOs: 16 and 57, respectively.

5. The bispecific antibody of claim 1 or 2, wherein

for bispecific antibody (A), the VL1/VH1 pair specifically binds to human IL23p19 and the VL2/VH2 pair specifically binds to human TNFα;

for bispecific antibody (B), the VL1/VH1 pair specifically binds to human IL23p19 and the VL2/VH2 pair specifically binds to human TNFα;
for bispecific antibody (C), the VL1/VH1 pair specifically binds to human IL23p19 and the VL2/VH2 pair specifically binds to human TNFα.

6. The bispecific antibody of claim 5, wherein for bispecific antibody (A),
VL1 and VH1 have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively; or wherein VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 1 and 2, respectively; or (2) SEQ ID NOs: 5 and 6, respectively; or,
VL1, VH1, VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 10, 11, 1, and 2, respectively; (2) SEQ ID NOs: 10, 11, 5, and 6, respectively; (3) SEQ ID NOs: 14, 15, 1, and 2, respectively; or (4) SEQ ID NOs: 14, 15, 5, and 6, respectively; or,
LC1, HC1, LC2, and HC2 each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 18, 19, 3, and 20, respectively; (2) SEQ ID NOs: 21, 22, 3, and 20 respectively; (3) SEQ ID NOs: 18, 19, 7 and 23, respectively; or (4) SEQ ID NOs: 21, 22, 7, and 23, respectively;
for bispecific antibody (B),
the VL1 and VH1 have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively; or wherein VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 1 and 2, respectively; or (2) SEQ ID NOs: 5 and 6, respectively;
or, the VL1, VH1, VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 10, 11, 1, and 2, respectively; (2) SEQ ID NOs: 10, 11, 5, and 6, respectively; (3) SEQ ID NOs: 14, 15, 1, and 2, respectively; or (4) SEQ ID NOs: 14, 15, 5, and 6, respectively;

or, the LC and HC each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 12 and 34, respectively; (2) SEQ ID NOs: 12 and 35, respectively; (3) SEQ ID NOs: 16 and 36, respectively; or (4) SEQ ID NOs: 16 and 37, respectively;

for bispecific antibody (C),

the VL1 and VH1 have the amino acid sequences of (1) SEQ ID NOs: 10 and 11, respectively; or (2) SEQ ID NOs: 14 and 15, respectively; or wherein VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 1 and 2, respectively; or (2) SEQ ID NOs: 5 and 6, respectively;

or, the VL1, VH1, VL2 and VH2 have the amino acid sequences of (1) SEQ ID NOs: 10, 11, 1, and 2, respectively; (2) SEQ ID NOs: 10, 11, 5, and 6, respectively; (3) SEQ ID NOs: 14, 15, 1, and 2, respectively, or (4) SEQ ID NOs: 14, 15, 5, and 6, respectively;

or, the LC and HC each has at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequences of (1) SEQ ID NOs: 38 and 39, respectively; (2) SEQ ID NOs: 40 and 41, respectively; (3) SEQ ID NOs: 42 and 43, respectively; or (4) SEQ ID NOs: 44 and 45, respectively.

7. A polynucleotide encoding the LC1, the LC2, the HC1, the HC2, or any combination thereof, of the bispecific antibody (A),

or encoding the LC, the HC, or both the LC and HC of any one of bispecific antibodies (B) to (D),

of any one of claims 1-6.

8. A vector comprising the polynucleotide of claim 7.

9. A cell comprising (a) a polynucleotide that encodes the LC1, LC2, HC1, and HC2, or (b) a plurality of the polynucleotides that collectively encode the LC1, LC2, HC1, and HC2;

or a cell comprising (a') a polynucleotide that encode both the LC and HC, or (b') a first polynucleotide that encodes the LC and a second polynucleotide that encodes the HC;

wherein the polynucleotide in (a), (b) and (a'), the first nucleotide and the second nucleotide in (b') are as defined in claim 7.

10. A pharmaceutical composition comprising the bispecific antibody of any one of claims 1 to 6, the polynucleotide of claim 7, and/or the cell of claim 9, and optionally a pharmaceutically acceptable carrier.

11. Use of the bispecific antibody of any one of claims 1 to 6, the polynucleotide of claim 7, or the cell of claim 9 for the preparation of a medicament for treating an autoimmune disease or an inflammatory disease.

12. A method of producing a bispecific antibody that specifically binds to human TNFα and to human IL23p19 by expressing the polynucleotide or the plurality of polynucleotides in the cell of claim 9.