
arthromeningitis and is mostly accompanied by organ and tissue damages of different degrees. Its main manifestations are fever, rash, and arthralgia, and it has poor prognosis such as low long-term remission rate, high dysfunction rate and disability rate, and high mortality rate. (Woerner A *et al. Expert Rev Clin Immunol.* 11(5):575-88. (2015)). It is generally accepted that the sJIA is an autoinflammatory disease instead of an autoimmune disease (Sun Juan *et al. Progress in Modern Biomedicine.* 8:1584-1588 (2016)). Clinical studies have demonstrated that the anti-human IL-1 β monoclonal antibody canakinumab can effectively treat active sJIA accompanied by fever and reduce steroid doses, and significantly reduces the recurrence of sJIA (Orrock JE *et al. Expert Rev Clin Pharmacol.* 9:1015-24. (2016)). Therefore the anti-IL-1 β monoclonal antibody canakinumab is approved for treating systemic juvenile idiopathic arthritis by FDA and the like.

There is still a need to develop new anti-IL-1 β antibodies.

SUMMARY

In one aspect, the present disclosure refers to an anti-IL-1 β antibody or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment thereof comprises a heavy chain variable region comprising HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, respectively; and the antibody or the antigen-binding fragment thereof comprises a light chain variable region comprising LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively.

In another aspect, the present disclosure refers to a bispecific antibody comprising a first protein functional region and a second protein functional region, wherein the first protein functional region targets IL-1 β , and the second protein functional region targets a target other than IL-1 β , wherein the first protein functional region is the antibody or the antigen-binding fragment thereof as disclosed herein.

In another aspect, the present disclosure refers to an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody heavy chain variable region and a nucleotide sequence encoding an antibody light chain variable region, wherein the antibody heavy chain variable region comprises HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, respectively, and the antibody light chain variable region comprises LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively.

In yet another aspect, the present disclosure refers to a use of the antibody or the antigen-binding fragment thereof as disclosed herein, the antibody-drug conjugate as disclosed herein, or the bispecific antibody as disclosed herein in preparing a medicament for the treatment and/or prevention of rheumatoid arthritis or cryopyrin-associated periodic syndromes in children and adults.

After intensive study and creative effort, the inventors used mammalian cell expression systems to express recombinant IL-1 β -His as an antigen to immunize mice, and obtained hybridoma cells by fusion of mouse spleen cells and myeloma cells. The inventors acquired the following hybridoma cell line by screening a large number of the samples:

the hybridoma cell line LT010 deposited at China Center for Type Culture Collection (CCTCC) on June 21, 2018 with an accession number of CCTCC NO: C2018133.

The inventors surprisingly found:

the hybridoma cell line LT010 may secrete and produce a specific monoclonal antibody (named as 3H6) that specifically binds to human IL-1 β , and the monoclonal antibody can block the binding of IL-1 β to IL-1R1 very effectively;

CLAIMS

1. An anti-IL-1 β antibody or an antigen-binding fragment thereof, wherein

the antibody or the antigen-binding fragment thereof comprises a heavy chain variable region comprising HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, respectively; and

the antibody or the antigen-binding fragment thereof comprises a light chain variable region comprising LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively.

2. The antibody or the antigen-binding fragment thereof according to claim 1, wherein

the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 10, and SEQ ID NO: 14; and

the light chain variable region comprises an amino acid sequence selected from SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, and SEQ ID NO: 16.

3. The antibody or the antigen-binding fragment thereof according to claim 1, wherein

the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 2, and the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 4;

the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 6, and the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 8;

the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 12; or

the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 14, and the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 16.

4. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the antibody or the antigen-binding fragment thereof is selected from Fab, Fab', F(ab')₂, Fv, a single chain antibody, a humanized antibody, a chimeric antibody, and a diabody.

5. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the antibody or the antigen-binding fragment thereof binds to IL-1 β protein with a K_D less than 10⁻⁵ M, wherein the K_D is measured by a Biacore molecular interaction instrument.

6. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein

the antibody or the antigen-binding fragment thereof comprises a non-CDR region derived from a species other than murine.

7. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the antibody or the antigen-binding fragment thereof comprises a non-CDR region derived from a human.

8. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein

the antibody or antigen-binding fragment thereof comprises a constant region selected from constant regions of human IgG1, IgG2, IgG3, and IgG4.

9. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the antibody or the antigen-binding fragment thereof comprises an IgG1 or IgG4 heavy chain constant region and an Ig kappa light chain constant region.

10. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the antibody is a monoclonal antibody produced by a hybridoma cell line LT010 deposited at China Center for Type Culture Collection (CCTCC) with an accession number of CCTCC NO: C2018133.

11. An antibody-drug conjugate comprising an antibody or an antigen-binding fragment thereof and a small molecule drug, wherein the antibody or the antigen-binding fragment thereof is the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10.

12. The antibody-drug conjugate according to claim 11, wherein the small molecule drug is a small molecule cytotoxic drug.

13. The antibody-drug conjugate according to claim 11, wherein the small molecule drug is a tumor chemotherapeutic drug.

14. The antibody-drug conjugate according to any one of claims 11 to 13, wherein the antibody or the antigen-binding fragment thereof is linked to the small molecule drug via a linker.

15. The antibody-drug conjugate according to claim 14, wherein the linker is a hydrazone bond, a disulfide bond or a peptide bond.

16. The antibody-drug conjugate according to any one of claims 11 to 15, wherein a molar ratio of the antibody or the antigen-binding fragment thereof to the small molecule drug is 1:1–1:4.

17. A bispecific antibody comprising a first protein functional region and a second protein functional region, wherein

the first protein functional region targets IL-1 β , and

the second protein functional region targets a target other than IL-1 β ,

wherein the first protein functional region is the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10.

18. The bispecific antibody according to claim 17, wherein the bispecific antibody is in an IgG-scFv form.

19. The bispecific antibody according to claim 17, wherein the first protein functional region is the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10, and the second protein functional region is a single chain antibody.

20. The bispecific antibody according to claim 17, wherein the first protein functional region is the single chain antibody according to claim 4, and the second protein functional region is an antibody.

21. The bispecific antibody according to any one of claims 17 to 20, wherein the first and second protein functional regions are linked directly or via a linker.

22. The bispecific antibody according to claim 21, wherein the linker is (GGGGS)_m, wherein m is 1, 2, 3, 4, 5, or 6.

23. The bispecific antibody according to claim 21, wherein the linker is SS(GGGGS)_n, wherein n is 1, 2, 3, 4, 5, or 6.

24. The bispecific antibody according to any one of claims 17 to 23, wherein a number of the first protein functional region and a number of the second protein functional region are each independently 1, 2 or more.

25. The bispecific antibody according to any one of claims 19 to 24, wherein the single chain antibody is linked to the C-terminus of the heavy chain of the antibody or the antigen-binding fragment thereof.

26. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody heavy chain variable region and a nucleotide sequence encoding an antibody light chain variable region, wherein the antibody heavy chain variable region comprises HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, respectively, and the antibody light chain variable region comprises LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively.

27. The isolated nucleic acid molecule according to claim 26, wherein the amino acid sequence of the antibody heavy chain variable region is selected from SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 10, and SEQ ID NO: 14, and the amino acid sequence of the antibody light chain variable region is selected from SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, and SEQ ID NO: 16.

28. The isolated nucleic acid molecule according to claim 26 or 27, wherein the amino acid sequence of the antibody heavy chain variable region is set forth in SEQ ID NO: 2, and the amino acid sequence of the antibody light chain variable region is set forth in SEQ ID NO: 4; the amino acid sequence of the antibody heavy chain variable region is set forth in SEQ ID NO: 6, and the amino acid sequence of the antibody light chain variable region is set forth in SEQ ID NO: 8; the amino acid sequence of the antibody heavy chain variable region is set forth in SEQ ID NO: 10, and the amino acid sequence of the antibody light chain variable region is set forth in SEQ ID NO: 12; or the amino acid sequence of the antibody heavy chain variable region is set forth in SEQ ID NO: 14, and the amino acid sequence of the antibody light chain variable region is set forth in SEQ ID NO: 16.

**29. The isolated nucleic acid molecule according to any one of claims 26 to 28, wherein the isolated nucleic acid molecule comprises:
nucleotide sequences set forth in SEQ ID NO: 1 and SEQ ID NO: 3,
nucleotide sequences set forth in SEQ ID NO: 5 and SEQ ID NO: 7,**

nucleotide sequences set forth in SEQ ID NO: 9 and SEQ ID NO: 11, or nucleotide sequences set forth in SEQ ID NO: 13 and SEQ ID NO: 15.

30. A recombinant vector comprising the isolated nucleic acid molecule according to any one of claims 26 to 29.

31. A host cell comprising the isolated nucleic acid molecule according to any one of claims 26 to 29 or the recombinant vector according to claim 30.

32. A method for preparing the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10, comprising: cultivating the host cell according to claim 31 in a suitable condition, and isolating the antibody or the antigen-binding fragment thereof from the cell cultures.

33. A hybridoma cell line LT010 deposited at China Center for Type Culture Collection (CCTCC) with an accession number of CCTCC NO: C2018133.

34. A pharmaceutical composition comprising the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10, the antibody-drug conjugate according to any one of claims 11 to 16, or the bispecific antibody according to any one of claims 17 to 25; and a pharmaceutically acceptable carrier and/or excipient.

35. Use of the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10, the antibody-drug conjugate according to any one of claims 11 to 16, or the bispecific antibody according to any one of claims 17 to 25 in preparing a medicament for the treatment and/or prevention of rheumatoid arthritis or cryopyrin-associated periodic syndromes in children and adults.

36. The use according to claim 35, wherein the cryopyrin-associated periodic syndrome in children and adults is selected from familial cold auto-inflammatory syndrome, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease, chronic infantile neurological cutaneous and articular syndrome, and familial cold urticaria.

37. Use of the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 10, the antibody-drug conjugate according to any one of claims 11 to 16, or the bispecific antibody according to any one of claims 17 to 25 in preparing:

(i) a medicament for blocking the binding of human IL-1 β to human IL-1R1 and/or human IL-1R2,

(ii) a medicament for down-regulating the activity or level of human IL-1 β , or

(iii) a medicament for inhibiting the activation of downstream signaling pathways mediated by the binding of human IL-1 β to human IL-1R1 and/or human IL-1R2.