Summary

According to a first aspect, there is provided isolated IL-1β specific antigen binding protein comprises the following binding units:(i) a binding unit L1 comprising Kabat residues 23-35 of SEQ ID NO: 3; (ii) a binding unit L2 comprising Kabat residues 51-57 of SEQ ID NO: 3;(iii) a binding unit L3 comprising Kabat residues 92-102 of SEQ ID NO: 3;(iv) a binding unit H1 comprising Kabat residues 31-35 of SEQ ID NO: 1;(v) a binding unit H2 comprising Kabat residues 50-66 of SEQ ID NO: 1; and(vi) a binding unit H3 comprising Kabat residues 99-114 of SEQ ID NO: 1; or (i) a binding unit L1 comprising Kabat residues 24-33 of SEQ ID NO: 4, 15 or 16; (ii) a binding unit L2 comprising Kabat residues 49-55 of SEQ ID NO: 4, 15 or 16; (iii) a binding unit L3 comprising Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16; (iv) a binding unit H1 comprising Kabat residues 31-35 of SEQ ID NO: 2 or 14;(v) a binding unit H2 comprising Kabat residues 50-65 of SEQ ID NO: 2 or 14; and (vi) a binding unit H3 comprising Kabat residues 98-108 of SEQ ID NO: 2 or 14; or a variant of (A) or (B) which one arginine and one serine residues are substituted by lysine residues in positions 75 and 81 of the heavy chain variable region.

Also disclosed is an isolated IL-1β specific antigen binding protein comprising one or more binding units selected from the group consisting of the following binding units:

(i) a binding unit L1 comprising Kabat residues 23-35 of SEQ ID NO: 3 or Kabat residues 24-33 of SEQ ID NO: 4, 15 or 16, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit L1;

(ii) a binding unit L2 comprising Kabat residues 51-57 of SEQ ID NO: 3 or Kabat residues 49-55 of SEQ ID NO: 4, 15 or 16, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit L2;

(iii) a binding unit L3 comprising Kabat residues 92-102 of SEQ ID NO: 3 or Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit L3;

(iv) a binding unit H1 comprising Kabat residues 31-35 of SEQ ID NO: 1 or Kabat residues 31-35 of SEQ ID NO: 2 or 14, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit H1;

(v) a binding unit H2 comprising Kabat residues 50-66 of SEQ ID NO: 1 or Kabat residues 50-65 of SEQ ID NO: 2 or 14, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit H2; and

(vi) a binding unit H3 comprising Kabat residues 99-114 of SEQ ID NO: 1 or Kabat residues 98-108 of SEQ ID NO: 2 or 14, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit H3.

Also provided herein is an isolated, IL-1β specific antigen binding protein that neutralizes IL-1β in a cell stimulation assay at an IC50 value of less than 20nM, less than 15nM, less than 10 nM, less than 5nM, less than 3nM, less than 1nM, less than 0.5nM or less than 0.2nM.

Claims

1. An isolated IL-1β specific antigen binding protein comprises the following binding units:

(A) (i) a binding unit L1 comprising Kabat residues 23-35 of SEQ ID NO: 3;

(ii) a binding unit L2 comprising Kabat residues 51-57 of SEQ ID NO: 3;

(iii) a binding unit L3 comprising Kabat residues 92-102 of SEQ ID NO: 3;

(iv) a binding unit H1 comprising Kabat residues 31-35 of SEQ ID NO: 1;

(v) a binding unit H2 comprising Kabat residues 50-66 of SEQ ID NO: 1; and

(vi) a binding unit H3 comprising Kabat residues 99-114 of SEQ ID NO: 1;

or

(B) (i) a binding unit L1 comprising Kabat residues 24-33 of SEQ ID NO: 4, 15 or 16;

(ii) a binding unit L2 comprising Kabat residues 49-55 of SEQ ID NO: 4, 15 or 16;

(iii) a binding unit L3 comprising Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16;

(iv) a binding unit H1 comprising Kabat residues 31-35 of SEQ ID NO: 2 or 14;

(v) a binding unit H2 comprising Kabat residues 50-65 of SEQ ID NO: 2 or 14; and

(vi) a binding unit H3 comprising Kabat residues 98-108 of SEQ ID NO: 2 or 14; or

(C) a variant of (A) or (B) which one arginine and one serine residues are substituted by lysine residues in positions 75 and 81 of the heavy chain variable region.

2. The isolated IL-1β specific antigen binding protein of claim 1, comprising a heavy chain and/or a light chain, in which the heavy chain comprises or consists of an amino

acid sequence selected from SEQ ID NO:1 or SEQ ID NO: 2 or 14 and in which the light chain comprises or consists of an amino acid sequence selected from SEQ ID NO:3 or SEQ ID NO: 4, 15 or 16.

3. The isolated IL-1β specific antigen binding protein of claim 1, wherein said Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16 are selected from residues consisting of the group selected from amino acids 1-9 of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12 or SEQ ID NO: 13.

4. The isolated, IL-1β specific antigen binding protein as claimed in any one of the preceding claims, wherein the IL-1β is human, murine or simian IL-1β.

5. The isolated antigen binding protein of any one of the preceding claims, comprising a heavy chain and/or a light chain, in which the heavy chain comprises or consists of an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO: 2 or 14 and in which the light chain comprises or consists of an amino acid sequence selected from SEQ ID NO:3 or SEQ ID NO: 4, 15 or 16.

6. The isolated antigen binding protein of any one of the preceding claims, wherein said isolated antigen binding protein specifically binds to IL-1β.

7. The isolated antigen binding protein as claimed in claim 6, wherein the IL-1β is human, murine or simian IL-1β.

8. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β specific antigen binding protein neutralizes human IL-1β.

9. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β specific antigen binding protein neutralizes murine IL-1β.

10. The isolated antigen binding protein of any preceding claim, comprising or consisting of:

(i) a heavy chain sequence of SEQ ID NO:1 and a light chain encoded by the nucleotide sequence of SEQ ID NO:3; or

(ii) a heavy chain sequence of SEQ ID NO:2 or 14 and a light chain encoded by the nucleotide sequence of SEQ ID NO:4, 15 or 16.

11. The isolated IL-1β specific antigen binding protein of any one of the preceding claims, wherein said Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16 are selected from residues consisting of the group selected from amino acids 1-9 of SEQ ID 9, SEQ ID 10, SEQ ID 11, SEQ ID 12 or SEQ ID NO: 13.

12. The isolated antigen binding protein of any one of the preceding claims, wherein said protein is an antibody.

13. The isolated antigen binding protein of claim 12, wherein said antibody is monoclonal, polyclonal, bispecific, multispecific or heteroconjugate.

14. The isolated antigen binding protein of claim 12 or 11, wherein said antibody is fully human.

15. The isolated antigen binding protein of any one of claims 12-14, wherein said antibody is of the subtype IgG1, of the subtype IgG2, of the subtype IgG4, or of the subtype IgG3

16. The isolated antigen binding protein of any one of claims 1-15, wherein said protein is a single variable domain, a domain antibody, an antigen binding fragment, an immunologically effective fragment, a single chain Fv, a diabody or a tetravalent bispecific antibody (Tandab).

17. The isolated antigen binding protein of claim 16, wherein said fragment comprises or consists of (i) a heavy chain sequence of SEQ ID NO: 1 and a light chain sequence of SEQ ID NO:3; or (ii) a heavy chain sequence of SEQ ID NO:2 or 14 and a light chain sequence of SEQ ID NO:4, 15 or 16.

18. The isolated antigen binding protein of any preceding claim, wherein the protein is recombinant.

19. The isolated antigen binding protein of any one of the preceding claims, wherein said binding protein further comprises an agent selected from the group consisting of an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

20. The binding protein of claim 19, wherein said agent is an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

21. The binding protein of claim 19, wherein said agent is a therapeutic or cytotoxic agent selected from the group consisting of an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin and an apoptotic agent.

22. The isolated antigen binding protein of any one of the preceding claims, for use in treating cancer, an inflammatory disease or an autoimmune disease selected from the group consisting of arthritis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, gout, diabetes, uveitis, cryopyrin-associated periodic syndromes and inflammatory acne.

23. Use of the isolated antigen binding protein of any one of claims 1 to 22, in the preparation of a medicament for the treatment of cancer, an inflammatory disease or an autoimmune disease selected from the group consisting of arthritis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, gout, diabetes, uveitis, cryopyrin-associated periodic syndromes and inflammatory acne.

24. A composition comprising the antigen binding protein of any one of claims 1 to 22 and a pharmaceutically acceptable carrier.

25. The composition of claim 24, further comprising one or more therapeutic agents.

26. An isolated cell line producing the antigen binding protein of any one of claims 1 to 22.

27. An isolated nucleic acids encoding polypeptide with amino acid sequences comprising or consisting of sequences selected from SEQ ID NO: 1 or SEQ ID NO:2 or 14, or fragments thereof.

28. An isolated nucleic acids encoding polypeptide with amino acid sequences comprising or consisting of sequences selected from SEQ ID NO:3 or SEQ ID NO:4, 15 or 16, or fragments thereof.

29. An isolated nucleic acid molecule according to claim 27 or 28, in which the fragment comprises or consists of a nucleotide sequence encoding polypeptide with amino acid sequences having an identity of at least 70% to SEQ ID NO:1, 2, 14, 3, 4, 15 or 16.

30. An isolated nucleic acid molecule according to claim 27 or 28, in which the fragment comprises or consists of a nucleotide sequence encoding polypeptide with amino acid sequences having an identity of at least 80% to SEQ ID NO:1, 2, 14, 3, 4, 15 or 16.

31. An isolated nucleic acid molecule according to claim 27 or 28, in which the fragment comprises or consists of a nucleotide sequence encoding polypeptide with amino acid sequences having an identity of at least 90% to SEQ ID NO:1, 2, 14, 3, 4, 15 or 16.

32. A vector comprising the nucleic acid molecule according to claim 27, or 28.

33. A vector comprising the nucleic acid molecule according to claim 29.

34. A vector comprising the nucleic acid molecule according to claim 30.

35. A vector comprising the nucleic acid molecule according to claim 31.

36. A vector of any one of claims 32 to 35, wherein the vector comprises an expression control sequence operably linked to said nucleic acid molecule.

37. A host cell comprising the nucleic acid molecule according to any one of claims 27 to 29.

38. A host cell comprising the vector of any one of claims 32 to 36.

39. A method of producing an antigen binding protein of any one of claims 1-22, comprising culturing the host cell according to claim 37 or 38 under suitable conditions and recovering said protein therefrom.

Claims

1. An isolated IL-1β specific antigen binding protein comprising one or more binding units selected from the group consisting of the following binding units:

(i) a binding unit L1 comprising Kabat residues 23-35 of SEQ ID NO: 3 or Kabat residues 24-33 of SEQ ID NO: 4, 15 or 16, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit L1;

(ii) a binding unit L2 comprising Kabat residues 51-57 of SEQ ID NO: 3 or Kabat residues 49-55 of SEQ ID NO: 4, 15 or 16, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit L2;

(iii) a binding unit L3 comprising Kabat residues 92-102 of SEQ ID NO: 3 or Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit L3;

(iv) a binding unit H1 comprising Kabat residues 31-35 of SEQ ID NO: 1 or Kabat residues 31-35 of SEQ ID NO: 2 or 14, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit H1;

(v) a binding unit H2 comprising Kabat residues 50-66 of SEQ ID NO: 1 or Kabat residues 50-65 of SEQ ID NO: 2 or 14, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit H2; and

(vi) a binding unit H3 comprising Kabat residues 99-114 of SEQ ID NO: 1 or Kabat residues 98-108 of SEQ ID NO: 2 or 14, or a variant thereof which contains at least one amino acid substitution, insertion or deletion in the binding unit H3.

2. The isolated IL-1β specific antigen binding protein of claim 1, comprising a heavy chain and/or a light chain, in which the heavy chain comprises or consists of an amino acid sequence encoded by the nucleotide sequence selected from SEQ ID NO:1 or SEQ ID NO: 2 or 14 and in which the light chain comprises or consists of an amino acid sequence

encoded by the nucleotide sequence selected from SEQ ID NO:3 or SEQ ID NO: 4, 15 or 16.

3. The isolated IL-1β specific antigen binding protein of claim 1, wherein said Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16 are selected from residues consisting of the group selected from amino acids 1-9 of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12 or SEQ ID NO: 13.

4. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β specific antigen binding protein neutralizes IL-1β in a cell function neutralization assay at an IC50 value of less than 20nM, less than 15nM, less than 10 nM, less than 5nM, less than 3nM, less than 1nM, less than 0.5nM, less than 0.2nM, less than 100pM, less than 50pM, less than 10pM or less than 5pM.

5. The isolated, IL-1β specific antigen binding protein as claimed in any one of the preceding claims, wherein the IL-1β is human, murine or simian IL-1β.

6. The isolated IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β specific antigen binding protein inhibits IL-1β induced IL-6 production in a cell inhibition assay at an IC50 value of less than 20nM, less than 15nM, less than 10 nM, less than 5nM, less than 4nM, less than 3nM, less than 1nM, less than 0.5nM, less than 0.4nM, less than about 300pM, less than about 200pM, less than about 100pM, less than about 50pM, less than about 10pM or less than about 5pM.

7. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β

specific antigen binding protein binds IL-1β with an affinity (K_D value) of less than 10nM, less than 5nM, less than 2nM, less than 1nM, less than 0.5nM, less than about 200pM, less than about 100pM, or less than about 5pM.

8. The isolated antigen binding protein of any one of the preceding claims, comprising a heavy chain and/or a light chain, in which the heavy chain comprises or consists of an amino acid sequence encoded by the nucleotide sequence selected from SEQ ID NO:1 or SEQ ID NO: 2 or 14 and in which the light chain comprises or consists of an amino acid sequence encoded by the nucleotide sequence selected from SEQ ID NO:3 or SEQ ID NO: 4, 15 or 16.

9. The isolated antigen binding protein of any one of the preceding claims, wherein said isolated antigen binding protein is capable of specifically binding to IL-1β.

10. The isolated antigen binding protein as claimed in claim 9, wherein the IL-1β is human, murine or simian IL-1β.

11. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β specific antigen binding protein neutralizes human IL-1β at an IC50 value of from 1pM to 5nM.

12. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein the isolated, IL-1β specific antigen binding protein neutralizes murine IL-1β at an IC50 value of from 100pM to 15nM.

13. The isolated antigen binding protein of any preceding claim, comprising or consisting of:

(i) a heavy chain encoded by the nucleotide sequence of SEQ ID NO:1 and a light chain encoded by the nucleotide sequence of SEQ ID NO:3; or

(ii) a heavy chain encoded by the nucleotide sequence of SEQ ID NO:2 or 14 and a light chain encoded by the nucleotide sequence of SEQ ID NO:4, 15 or 16.

14. The isolated IL-1β specific antigen binding protein of any one of the preceding claims, wherein said Kabat residues 88-96 of SEQ ID NO: 4, 15 or 16 are selected from residues consisting of the group selected from amino acids 1-9 of SEQ ID 9, SEQ ID 10, SEQ ID 11, SEQ ID 12 or SEQ ID NO: 13.

15. The isolated, IL-1β specific antigen binding protein of any one of the preceding claims, wherein said binding protein has an affinity (K_D) to human IL-1β of from 1pM to 200pM.

16. The isolated, IL-1β specific antigen binding protein wherein said binding protein has an affinity (K_D) to murine IL-1β of from 5pM to 500pM.

17. The isolated antigen binding protein of any one of the preceding claims, wherein said protein is an antibody.

18. The isolated antigen binding protein of claim 17, wherein said antibody is monoclonal, polyclonal, bispecific, multispecific or heteroconjugate.

19. The isolated antigen binding protein of claim 17 or 18, wherein said antibody is fully human.

20. The isolated antigen binding protein of any one of claims 17-19, wherein said antibody is of the subtype IgG1,

of the subtype IgG2, of the subtype IgG4, or of the subtype IgG3

21. The isolated antigen binding protein of any one of claims 1-20, wherein said protein is a single variable domain, a domain antibody, an antigen binding fragment, an immunologically effective fragment, a single chain Fv, a diabody or a tetravalent bispecific antibody (Tandab).

22. The isolated antigen binding protein of claim 21, wherein said fragment comprises or consists of (i) a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 1 and a light chain encoded by the nucleotide sequence of SEQ ID NO:3; or (ii) a heavy chain encoded by the nucleotide sequence of SEQ ID NO:2 or 14 and a light chain encoded by the nucleotide sequence of SEQ ID NO:4, 15 or 16.

23. The isolated antigen binding protein of any preceding claim, wherein the protein is recombinant.

24. The isolated antigen binding protein of any one of the preceding claims, wherein said binding protein further comprises an agent selected from the group consisting of an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

25. The binding protein of claim 24, wherein said agent is an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

26. The binding protein of claim 24, wherein said agent is a therapeutic or cytotoxic agent selected from the group consisting of an anti-metabolite, an alkylating agent, an

antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin and an apoptotic agent.

27. The isolated antigen binding protein of any one of the preceding claims, for use in treating cancer, an inflammatory disease or an autoimmune disease selected from the group consisting of arthritis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, gout, diabetes, uveitis, cryopyrin-associated periodic syndromes and inflammatory acne.

28. Use of the isolated antigen binding protein of any one of claims 1 to 27, in the preparation of a medicament for the treatment of cancer, an inflammatory disease or an autoimmune disease selected from the group consisting of arthritis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, gout, diabetes, uveitis, cryopyrin-associated periodic syndromes and inflammatory acne.

29. A composition comprising the antigen binding protein of any one of claims 1 to 27 and a pharmaceutically acceptable carrier.

30. The composition of claim 29, further comprising one or more therapeutic agents.

31. An isolated cell line that is capable of producing the antigen binding protein of any one of claims 1 to 27.

32. An isolated nucleic acid molecule comprising or consisting of sequences selected from SEQ ID NO: 1 or SEQ ID NO:2 or 14, or fragments thereof.

33. An isolated nucleic acid molecule comprising or consisting of sequences selected from SEQ ID NO:3 or SEQ ID NO:4, 15 or 16, or fragments thereof.

34. An isolated nucleic acid molecule according to claim 32 or 33, in which the fragment comprises or consists of a nucleotide sequence having an identity selected from the group consisting of from at least 50%, at least 60%, at least 70%, at least 80% and at least 90% to SEQ ID NO:1, 2, 14, 3, 4, 15 or 16.

35. A vector comprising the nucleic acid molecule according to claim 32, 33 or 34.

36. A vector of claim 35, wherein the vector comprises an expression control sequence operably linked to said nucleic acid molecule.

37. A host cell comprising the nucleic acid molecule according to claim 32, 33 or 34.

38. A host cell comprising the vector of claim 35 or 36.

39. A method of producing an antigen binding protein of any one of claims 1-27, comprising culturing the host cell according to claim 37 or 38 under suitable conditions and recovering said protein therefrom.