Summary

According to a first example, there is provided 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.

According to the second example, there is provided 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.

According to a third example, there is provided an isolated IL-1β specific antigen binding protein that 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 or less than 0.4nM.

According to a fourth example, there is provided an isolated, IL-1β specific antigen binding protein that binds IL-1β with a K_D value of less than 10nM, less than 5nM, less than 2nM, less than 1nM, less than 0.5nM, or less than 0.1nM.

According to a fifth example, there is provided an isolated, IL-1β specific antigen binding protein that neutralizes human IL-1β at an IC50 value of from 1pM to 100pM.

According to a sixth example, there is provided an isolated, IL-1β specific antigen binding protein that neutralizes murine IL-1β at an IC50 value of from 100pM to 1000pM.

According to a seventh example, there is provided an isolated, IL-1β specific antigen binding protein wherein said binding protein has an affinity (KD) to human IL-1β of from 1pM to 100pM.

According to an eighth example, there is provided an isolated, IL-1β specific antigen binding protein wherein said binding protein has an affinity (KD) to murine IL-1β of from 5pM to 200pM.

According to a ninth example, there is provided an 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.

According to a tenth example, there is provided a use of the isolated antigen binding protein as defined above, 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.

According to an eleventh example, there is provided a composition comprising the antigen binding protein as defined above and a pharmaceutically acceptable carrier.

According to a twelfth example, there is provided an isolated cell line that is capable of producing the antigen binding protein as defined above.

According to a thirteenth example, there is provided 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.

According to a fourteenth example, there is provided 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.

According to a fifteenth example, there is provided a vector comprising the nucleic acid molecule as defined above.

According to a sixteenth example, there is provided a host cell comprising the nucleic acid molecule as defined above.

According to a seventeenth example, there is provided a host cell comprising the vector as defined above.

According to an eighteenth example, there is provided a method of producing an antigen binding protein as defined above, comprising culturing the host cell as defined above under suitable conditions and recovering said protein therefrom.

According to a nineteenth example, there is provided a method of 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, wherein the isolated antigen binding protein as defined above is administered to a subject.

In one aspect, there is provided an isolated monoclonal antibody which specifically binds to IL-1β, or an antigen binding fragment thereof, wherein said antibody or fragment thereof comprises:

(i) Complementarity Determining Regions (CDRs) according to the Kabat numbering convention of a light chain comprising the amino acid sequence of SEQ ID NO: 17; and

(ii) CDRs according to the Kabat numbering convention of a heavy chain comprising the amino acid sequence of SEQ ID NO: 14.

In another aspect, there is provided an isolated monoclonal antibody which specifically binds to IL-1β, or an antigen binding fragment thereof, wherein said antibody or fragment thereof comprises the following Complementarity Determining Regions (CDRs):

(i) a heavy chain variable region CDR H1 comprising the amino acid sequence DYYWS,

(ii) a heavy chain variable region CDR H2 comprising the amino acid sequence EIDHSGSTNYNPSLKS,

(iii) a heavy chain variable region CDR H3 comprising the amino acid sequence ASPSSGWTLDY,

(iv) a light chain variable region CDR L1 comprising the amino acid sequence GDKLGDKFAF,

(v) a light chain variable region CDR L2 comprising the amino acid sequence LDNKRPS, and

(vi) a light chain variable region CDR L3 comprising an amino acid sequence selected from the group consisting of: YAWADTYEV, QAWADSFEV, YAWDNAYEV, EAWDAAAEV, and EAWADTYEV.

In another aspect, there is provided an isolated monoclonal antibody which specifically binds to IL-1β, or an antigen binding fragment thereof, wherein said antibody or fragment thereof comprises:

(i) a light chain sequence comprising the amino acid sequence of SEQ ID NO: 17; and

(ii) a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 18 or SEQ ID NO:2.

In another aspect, there is provided a composition comprising the isolated antibody or fragment thereof as described herein and a pharmaceutically acceptable carrier.

In another aspect, there is provided an isolated nucleic acid encoding the isolated monoclonal antibody or fragment thereof as described herein, wherein the nucleic acid comprises: a first sequence encoding the light chain or the light chain variable region of said antibody or fragment, and a second sequence encoding the heavy chain or the heavy chain variable region of said antibody or fragment.

In another aspect, there is provided a set of two isolated nucleic acids which together encode the isolated antibody or fragment thereof as described herein, wherein: the first nucleic acid comprises a sequence encoding the light chain or the light chain variable region of said antibody or fragment, and the second nucleic acid comprises a sequence encoding the heavy chain or the heavy chain variable region of said antibody or fragment.

In another aspect, there is provided a vector comprising the isolated nucleic acid molecule as described herein, or the set of two isolated nucleic acids as described hereni.

In another aspect, there is provided a host cell comprising the isolated nucleic acid as described herein, or the set of two isolated nucleic acids as described herein.

In another aspect, there is provided a method of producing the isolated monoclonal antibody or fragment thereof as described herein, comprising culturing the host cell as described herein under suitable conditions and recovering said antibody or fragment therefrom.

In another aspect, there is provided an isolated cell line that is capable of producing the isolated monoclonal antibody or fragment thereof as described herein.

In another aspect, there is provided an isolated monoclonal antibody or fragment thereof as described herein or the composition as described herein for use in therapy.

In another aspect, there is provided a use of the isolated monoclonal antibody or fragment thereof as described herein or the composition as described herein, in the preparation of a medicament for the treatment of 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.

In another aspect, there is provided a use of the isolated monoclonal antibody or fragment thereof as described herein or the composition as described herein, in the preparation of a medicament for the treatment of an inflammatory disease.

In another aspect, there is provided a use of the isolated monoclonal antibody or fragment thereof as described herein or the composition as described herein, in the preparation of a medicament for the treatment of cancer.

In another aspect, there is provided a use of the isolated monoclonal antibody or fragment thereof as described herein or the composition as described herein, in the preparation of a medicament for reducing tumor growth.

Claims

1. An isolated monoclonal antibody which specifically binds to IL-1β, or an antigen binding fragment thereof, wherein said antibody or fragment thereof comprises:

(i) Complementarity Determining Regions (CDRs) according to the Kabat numbering convention of a light chain comprising the amino acid sequence of SEQ ID NO: 17; and

(ii) CDRs according to the Kabat numbering convention of a heavy chain comprising the amino acid sequence of SEQ ID NO: 14.

2. An isolated monoclonal antibody which specifically binds to IL-1β, or an antigen binding fragment thereof, wherein said antibody or fragment thereof comprises the following Complementarity Determining Regions (CDRs):

(i) a heavy chain variable region CDR H1 comprising the amino acid sequence DYYWS,

(ii) a heavy chain variable region CDR H2 comprising the amino acid sequence EIDHSGSTNYNPSLKS,

(iii) a heavy chain variable region CDR H3 comprising the amino acid sequence ASPSSGWTLDY,

(iv) a light chain variable region CDR L1 comprising the amino acid sequence GDKLGDKFAF,

(v) a light chain variable region CDR L2 comprising the amino acid sequence LDNKRPS, and

(vi) a light chain variable region CDR L3 comprising an amino acid sequence selected from the group consisting of: YAWADTYEV, QAWADSFEV, YAWDNAYEV, EAWDAAAEV, and EAWADTYEV.

3. The isolated monoclonal antibody or fragment thereof of claim 2, wherein the light chain variable region CDR L3 comprises the amino acid sequence YAWADTYEV.

4. The isolated monoclonal antibody or fragment thereof of claim 2, wherein the light chain variable CDR3 comprises the amino acid sequence QAWADSFEV.

5. The isolated monoclonal antibody or fragment thereof of claim 2, wherein the light chain variable CDR3 comprises the amino acid sequence YAWDNAYEV.

6. The isolated monoclonal antibody or fragment thereof of claim 2, wherein the light chain variable CDR3 comprises the amino acid sequence EAWDAAAEV.

7. The isolated monoclonal antibody or fragment thereof of claim 2, wherein the light chain variable CDR3 comprises the amino acid sequence EAWADTYEV.

8. An isolated monoclonal antibody which specifically binds to IL-1β, or an antigen binding fragment thereof, wherein said antibody or fragment thereof comprises:

(i) a light chain sequence comprising the amino acid sequence of SEQ ID NO: 17; and

(ii) a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 18 or SEQ ID NO:2.

9. The isolated monoclonal antibody or fragment thereof of claim 8, wherein the heavy chain sequence comprises the amino acid sequence of SEQ ID NO: 18.

10. The isolated monoclonal antibody or fragment thereof of claim 9, wherein the heavy chain sequence comprises the amino acid sequence of SEQ ID NO: 14.

11. The isolated monoclonal antibody or fragment thereof of claim 8, wherein the heavy chain sequence comprises the amino acid sequence of SEQ ID NO:2.

12. The isolated monoclonal antibody or fragment thereof of any one of claims 1–11, which is fully human.

13. The isolated monoclonal antibody or fragment thereof of any one of claims 1–12, wherein the IL–1β is human.

14. The isolated monoclonal antibody or fragment thereof of any one of claims 1–13, which is the antibody of the subtype IgG1, IgG2, IgG3 or IgG4.

15. The isolated monoclonal antibody or fragment thereof of claim 14, wherein the antibody is of the subtype IgG4.

16. A composition comprising the isolated antibody or fragment thereof of any one of claims 1–15 and a pharmaceutically acceptable carrier.

17. An isolated nucleic acid encoding the isolated monoclonal antibody or fragment thereof of any one of claims 1–15, wherein the nucleic acid comprises: a first sequence encoding the light chain or the light chain variable region of said antibody or fragment, and a second sequence encoding the heavy chain or the heavy chain variable region of said antibody or fragment.

18. A set of two isolated nucleic acids which together encode the isolated antibody or fragment thereof of any one of claims 1–15, wherein: the first nucleic acid comprises a sequence encoding the light chain or the light chain variable region of said antibody or fragment, and the second nucleic acid comprises a sequence encoding

the heavy chain or the heavy chain variable region of said antibody or fragment.

19. A vector comprising the isolated nucleic acid molecule of claim 17, or the set of two isolated nucleic acids of claim 18.

20. A host cell comprising the isolated nucleic acid of claim 17, or the set of two isolated nucleic acids of claim 18.

21. A method of producing the isolated monoclonal antibody or fragment thereof of any one of claims 1–15, comprising culturing the host cell of claim 20 under suitable conditions and recovering said antibody or fragment therefrom.

22. An isolated cell line that is capable of producing the isolated monoclonal antibody or fragment thereof of any one of claims 1–15.

23. The isolated monoclonal antibody or fragment thereof of any one of claims 1–15 or the composition of claim 16 for use in therapy.

24. Use of the isolated monoclonal antibody or fragment thereof of any one of claims 1–15 or the composition of claim 16, in the preparation of a medicament for the treatment of 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.

25. Use of the isolated monoclonal antibody or fragment thereof of any one of claims 1–15 or the composition of claim 16, in the preparation of a medicament for the treatment of an inflammatory disease.

26. Use of the isolated monoclonal antibody or fragment thereof of any one of claims 1-15 or the composition of claim 16, in the preparation of a medicament for the treatment of cancer.

27. Use of the isolated monoclonal antibody or fragment thereof of any one of claims 1-15 or the composition of claim 16, in the preparation of a medicament for reducing tumor growth.