

WHAT IS CLAIMED IS: **CLAIMS**

~~1. A method for the treatment or prevention of an NLRC4 inflammasomopathy in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a bispecific antibody, wherein the antibody comprises~~

~~1. Use of a bispecific antibody comprising~~

- ~~a. a first part which is an immunoglobulin with a first variable light chain of (VL1) and a first variable heavy chain (VH1), that binds specifically to a IL1 β , and a first constant heavy chain (CH1) with a hetero-dimerization modification, and~~
- ~~b. a second part which is an immunoglobulin with a second variable light chain (VL2) and a second variable heavy chain (VH2), that binds specifically to IL-18 and a second constant heavy chain (CH2) with a hetero-dimerization modification which is complementary to the hetero-dimerization modification of the first constant heavy chain, in the manufacture of a medicament for the treatment or prevention of an NLRC4 inflammasomopathy in a subject in need thereof.~~

~~2. A method for slowing, arresting, or reducing the development of an NLRC4 inflammasomopathy in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a bispecific antibody, wherein the antibody comprises~~

- ~~a. a first part which is an immunoglobulin with a first variable light chain of (VL1) and a first variable heavy chain (VH1), that binds specifically to a IL1 β , and a first constant heavy chain (CH1) with a hetero-dimerization modification, and~~
- ~~b. a second part which is an immunoglobulin with a second variable light chain (VL2) and a second variable heavy chain (VH2), that binds specifically to IL-18 and a second constant heavy chain (CH2) with a hetero-dimerization modification which is complementary to the hetero-dimerization modification of the first constant heavy chain.~~

~~3. The method according to claim 1 or 22. The use according to claim 1, wherein the first and second constant heavy chain of the bispecific antibody are human IgA, IgD, IgE, IgG, or IgM, preferably IgD, IgE or IgG, such as human IgG1, IgG2, IgG3, or IgG4, preferably IgG1.~~

~~3. The method use according to claim 1 or 2, wherein the first and second constant heavy chains of the bispecific antibody are IgG1, and wherein~~

- ~~a. the first constant heavy chain has point mutations generating a knob structure and the second constant heavy has point mutations generating a hole structure, or~~
- ~~b. the first constant heavy chain has point mutations generating a hole structure and the second constant heavy has point mutations generating a knob structure, and optionally the first and second constant heavy chains have mutations resulting in a disulfide bridge.~~

~~4. The method use according to any one of claims 1-43, wherein:~~

~~a. the first immunoglobulin VH1 domain of the bispecific antibody comprises~~

~~i. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:76, said CDR2 having the amino acid sequence SEQ ID NO:77, and said CDR3 having the amino acid sequence SEQ ID NO:78; or~~

~~ii. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:79, said CDR2 having the amino acid sequence SEQ ID NO:80, and said CDR3 having the amino acid sequence SEQ ID NO:81; and~~

b. the first immunoglobulin VL1 domain of the bispecific antibody comprises

i. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:92, said CDR2 having the amino acid sequence SEQ ID NO:93, and said CDR3 having the amino acid sequence SEQ ID NO:94 or

ii. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:95, said CDR2 having the amino acid sequence SEQ ID NO:96, and said CDR3 having the amino acid sequence SEQ ID NO:97; and

c. the second immunoglobulin VH2 domain of the bispecific antibody comprises

i. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:44, said CDR2 having the amino acid sequence SEQ ID NO:45, and said CDR3 having the amino acid sequence SEQ ID NO:46; or

ii. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:47, said CDR2 having the amino acid sequence SEQ ID NO:48, and said CDR3 having the amino acid sequence SEQ ID NO:49; and

d. the second immunoglobulin VL2 domain of the bispecific antibody comprises

i. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:60, said CDR2 having the amino acid sequence SEQ ID NO:61, and said CDR3 having the amino acid sequence SEQ ID NO:62 or

ii. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:63, said CDR2 having the amino acid sequence SEQ ID NO:64, and said CDR3 having the amino acid sequence SEQ ID NO:65.

5. ~~The method use~~ according to any one of the ~~preceding~~ claims 1-4, wherein:

a. the first immunoglobulin VH1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 85,

b. the first immunoglobulin VL1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 101,

c. the second immunoglobulin VH2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 53, and

d. the second immunoglobulin VL2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 69.

6. ~~The method use~~ according to any one of the ~~preceding~~ claims, 1-5, wherein:

a. the first immunoglobulin heavy chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 87,

b. the first immunoglobulin light chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 103,

c. the second immunoglobulin heavy chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 55, and

d. the second immunoglobulin light chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 71.

87. The ~~method use~~ according to any one of the ~~preceding~~ claims 1-6, wherein said subject has an NLRC4-GOF inflammasomopathy.

98. The method use according to any one of the preceding claims 1-7, wherein said subject has an NLRC4-GOF mutation in the nucleotide binding domain or the winged helix domain of the NLRC4 gene.

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~~40. —~~ The method use according to any one of the preceding claims 1-8, wherein said subject has macrophage activation syndrome (MAS).

10. _____

~~41. —~~ The method use according to any one of the preceding claims 1-9, wherein said subject has autoinflammation with infantile enterocolitis (AIFEC).

~~42~~11. The method use according to any one of the preceding claims 1-10, wherein said subject has hyper elevated levels of serum IL-18 and serum IL-1 β as compared to a control population of subjects that does not have an NLRC4 inflammasomopathy.

~~43~~12. The method use according to any one of the preceding claims 1-11, wherein said subject has a serum ferritin level of > 600 ng/mL or a serum C-reactive protein (CRP) of > 20 mg/L.

~~44~~13. The method use according to any one of the preceding claims, wherein said NLRC4 inflammasomopathy is resistant to treatment with cyclosporin, anti-TNF α treatments, systemic glucocorticoids and anti-IL-1 β therapies as a monotherapy, or as a combination thereof claims 1-12.

~~45. —~~ A bispecific antibody comprising

a. — a first part which is an immunoglobulin with a first variable light chain of (VL1) and a first variable heavy chain (VH1), that binds specifically to a IL1 β , and a first constant heavy chain (CH1) with a hetero-dimerization modification, and

b. — a second part which is an immunoglobulin with a second variable light chain (VL2) and a second variable heavy chain (VH2), that binds specifically to IL-18 and a second constant heavy chain (CH2) with a hetero-dimerization modification which is complementary to the hetero-dimerization modification of the first constant heavy chain, for use in the treatment or prevention of an NLRC4 inflammasomopathy in a subject in need thereof.

~~46. —~~ The bispecific antibody for the use in the treatment of or prevention of of an NLRC4 inflammasomopathy in a subject in need thereof according to claim 15, wherein the first and second constant heavy chain of the bispecific antibody are human IgA, IgD, IgE, IgG, or IgM, preferably IgD, IgE or IgG, such as human IgG1, IgG2, IgG3, or IgG4, preferably IgG1.

~~47. —~~ The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to claim 15 or 16, wherein the first and second constant heavy chains of the bispecific antibody are IgG1, and wherein

a. — the first constant heavy chain has point mutations generating a knob structure and the second constant heavy has point mutations generating a hole structure, or

- b. ~~the first constant heavy chain has point mutations generating a hole structure and the second constant heavy has point mutations generating a knob structure, and optionally~~
- c. ~~the first and second constant heavy chains have mutations resulting in a disulfide bridge.~~

18. ~~The bispecific antibody for the use in the treatment of or prevention of an NLR4 inflammasomopathy in a subject in need thereof according to any one of claims 15-17, wherein:~~

a. ~~the first immunoglobulin VH1 domain of the bispecific antibody comprises~~

i. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:76, said CDR2 having the amino acid sequence SEQ ID NO:77, and said CDR3 having the amino acid sequence SEQ ID NO:78; or~~

ii. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:79, said CDR2 having the amino acid sequence SEQ ID NO:80, and said CDR3 having the amino acid sequence SEQ ID NO:81; and~~

b. ~~the first immunoglobulin VL1 domain of the bispecific antibody comprises~~

iii. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:92, said CDR2 having the amino acid sequence SEQ ID NO:93, and said CDR3 having the amino acid sequence SEQ ID NO:94 or~~

iv. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:95, said CDR2 having the amino acid sequence SEQ ID NO:96, and said CDR3 having the amino acid sequence SEQ ID NO:97; and~~

c. ~~the second immunoglobulin VH2 domain of the bispecific antibody comprises~~

v. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:44, said CDR2 having the amino acid sequence SEQ ID NO:45, and said CDR3 having the amino acid sequence SEQ ID NO:46; or~~

vi. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:47, said CDR2 having the amino acid sequence SEQ ID NO:48, and said CDR3 having the amino acid sequence SEQ ID NO:49; and~~

d. ~~the second immunoglobulin VL2 domain of the bispecific antibody comprises~~

vii. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:60, said CDR2 having the amino acid sequence SEQ ID NO:61, and said CDR3 having the amino acid sequence SEQ ID NO:62 or~~

viii. ~~hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:63, said CDR2 having the amino acid sequence SEQ ID NO:64, and said CDR3 having the amino acid sequence SEQ ID NO:65.~~

19. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-18, wherein:

- a. the first immunoglobulin VH1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 85,
- b. the first immunoglobulin VL1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 101,
- c. the second immunoglobulin VH2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 53, and
- d. the second immunoglobulin VL2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 69.

20. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-19, wherein:

- a. the first immunoglobulin heavy chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 87,
- b. the first immunoglobulin light chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 103,
- c. the second immunoglobulin heavy chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 55, and
- d. the second immunoglobulin light chain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 71.

21. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-20, wherein said subject has an NLRC4-GOF inflammasomopathy.

22. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-21, wherein said subject has an NLRC4-GOF mutation in the nucleotide binding domain or the winged helix domain of the NLRC4 gene.

23. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-22, wherein said subject has macrophage activation syndrome (MAS).

24. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-23, wherein said subject has autoinflammation with infantile enterocolitis (AIEC).

25. — The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-24, wherein

said subject has hyper-elevated levels of serum IL-18 and serum IL-1 β as compared to a control population of subjects that does not have an NLR4 inflammasomopathy.

~~26. The bispecific antibody for the use in the treatment of or prevention of an NLR4 inflammasomopathy in a subject in need thereof according to any one of claims 15-25, wherein said subject has a serum ferritin level of > 600 ng/mL or a serum C-reactive protein (CRP) of > 20 mg/L.~~

~~27. The method according to any one of claims 1-14, comprising administering about 1 mg/kg to about 35 mg/kg of the bispecific antibody to the subject.~~

~~28. The method according to claim 27, comprising administering about 10 mg/kg of the bispecific antibody to said subject.~~

~~29. The method according to claim 28, wherein the bispecific antibody is be administered to the subject.~~

~~14. The use according to claim 13, comprising 10 mg/kg intravenously or subcutaneously.~~

~~30. The method according to claim 29, wherein the dose of the of the bispecific antibody to be administered to said subject.~~

~~15. The use according to any one of claims 1-12, wherein the bispecific antibody is about 10 mg/kg to be administered intravenously, optionally wherein the bispecific antibody is administered every other week.~~

~~31. The method according to claim 29, wherein the dose of the administered bispecific antibody is at a dose of about 50 mg to about 900 mg administered subcutaneously.~~

32

~~16. The method use according to claim 30 or 31 any one of claims 13-15, wherein the bispecific antibody is to be administered intravenously or subcutaneously to the patient on day 1; or wherein the bispecific antibody is to be administered intravenously every other week.~~

~~3317. The method use according to any one of the claims 26-31 13-16, comprising administering at least one further therapeutic agent to be administered.~~

~~34-18. The bispecific antibody for the use in the treatment of or prevention of an NLR4 inflammasomopathy in a subject in need thereof according to any one of the claims 15-26, comprising administering 1 mg/kg to 35 mg/kg of the bispecific antibody to the subject.~~

~~35. The bispecific antibody for the use in the treatment of or prevention of an NLR4 inflammasomopathy in a subject in need thereof according to claim 34, comprising administering 10 mg/kg intravenously of the bispecific antibody to said subject.~~

~~36. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 15-26, wherein the bispecific antibody is administered at a dose of about 50 mg to about 900 mg subcutaneously.~~

~~37. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 34-36, wherein the bispecific antibody is administered intravenously or subcutaneously to the patient on day 1; or wherein the bispecific antibody is administered intravenously every other week.~~

~~38. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy in a subject in need thereof according to any one of claims 34-37, comprising administering at least one further therapeutic agent.~~

~~39. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy (e.g., NLRC4-GOF inflammasomopathy) in a subject in need thereof according to any one of claims 34-3813-17, wherein the treatment increases the lifespan of the subject as compared to a control subject having an NLRC4 inflammasomopathy (e.g., NLRC4-GOF inflammasomopathy) and receiving the standard of care (SoC).~~

~~4019. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy (e.g., NLRC4-GOF inflammasomopathy) in a subject in need thereof according to any one of claims 34-3913-18, wherein the treatment reduces or prevents occurrence of disease flare compared with SoC after 14 days of treatment, e.g., for at least 1 week.~~

~~4120. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy (e.g., NLRC4-GOF inflammasomopathy) in a subject in need thereof according to any one of claims 34-4013-19, wherein the serum CRP level of patients is reduced after 7 days of treatment compared to standard of care.~~

~~4221. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy (e.g., NLRC4-GOF inflammasomopathy) in a subject in need thereof according to claim 4120, wherein the serum CRP level decreases by at least 1 mg/L, at least 2 mg/L, at least 3 mg/L, at least 4 mg/l or at least 5 mg/L.~~

~~4322. The bispecific antibody for the use in the treatment of or prevention of an NLRC4 inflammasomopathy (e.g., NLRC4-GOF inflammasomopathy) in a subject in need thereof according to claim 4120, wherein the serum CRP level decreases by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, after 7, or after 14, days of treatment.~~

~~44. A method of reducing the serum C-reactive protein (CRP) level in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a bispecific antibody comprising~~
~~a. a first immunoglobulin VH1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 85,~~

- ~~b. a first immunoglobulin VL1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 101,~~
- ~~c. a second immunoglobulin VH2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 53, and~~
- ~~d. a second immunoglobulin VL2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 69.~~

~~45. The method according to claim 44, wherein the serum CRP level decreases by at least 1 mg/l, at least 2 mg/l, at least 3 mg/l, at least 4 mg/l or at least 5 mg/l.~~

~~46. The method according to claim 44, wherein the serum CRP level decreases by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, after 7 days, 14 days, 3 weeks, or 29 days of treatment.~~

~~47. The method according to any one of claims 44-46, wherein the serum C reactive protein decreases after administration of bispecific antibody for at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 14 days, at least 3 weeks, or at least 29 days.~~

~~48. The method of any one of claims 44-46, wherein the subject has an NLRC4 inflammasomopathy, e.g., an NLRC4-GOF inflammasomopathy.~~

~~49. A method of reducing serum ferritin level in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a bispecific antibody comprising~~
~~a. a first immunoglobulin VH1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 85,~~

- ~~b. a first immunoglobulin VL1 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 101,~~
- ~~c. a second immunoglobulin VH2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 53, and~~
- ~~d. a second immunoglobulin VL2 domain of the bispecific antibody comprises the amino acid sequence SEQ ID NO: 69.~~

~~50. The method according to claim 49, wherein the serum ferritin level decreases by at least 100 ng/L, at least 200 ng/L, at least 300 ng/L, at least 400 ng/l or at least 500 ng/l.~~

~~51. The method according to claim 49, wherein the serum ferritin level decreases by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, after 7 days, 14 days, 3 weeks, or 29 days of treatment..~~

52. ~~The method according to any one of claims 49-51, wherein the serum ferritin decreases after administration of bispecific antibody for at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 14 days, at least 3 weeks, or at least 29 days.~~

53. ~~The method of any one of claims 49-51, wherein the subject has an NLRC4 inflammasomopathy, e.g., an NLRC4-GOF inflammasomopathy.~~