

Claims

1. A specific binding member which binds to lymphocyte-activation gene 3 (LAG-3), comprising a LAG-3 antigen-binding site located in ~~a antibody~~ CH3 domain of the specific binding member, wherein the LAG-3 binding site comprises the amino acid sequences WDEPWGED (SEQ ID NO: 1) and PYDRWVWPDE (SEQ ID NO: 3), and wherein the amino acid sequence WDEPWGED is located in ~~a first structural~~ the AB loop of the CH3 domain and the amino acid sequence PYDRWVWPDE is located in ~~a second structural~~ the EF loop of the CH3 domain.

2. A specific binding member according to claim 1, wherein the LAG-3 antigen-binding site further comprises ~~the amino acid sequence set forth in SEQ ID NO: 1 in the AB loop, and the amino acid sequence set forth in SEQ ID NO: 3 in the EF~~ one of the following sequences in the CD loop of the CH3 domain.

(i) SNGQPENNY (SEQ ID NOS 2, 8 and 18);

(ii) SNGQPEDNY (SEQ ID NO: 13);

(iii) SNGYPEIEF (SEQ ID NO: 23);

(iv) SNGIPEWNY (SEQ ID NO: 28);

(v) SNGYAEYNY (SEQ ID NO: 33);

(vi) SNGYKEENY (SEQ ID NO: 38);

(vii) SNGVPELNV (SEQ ID NO: 43); or

(viii) SNGYQEDNY (SEQ ID NO: 48).

3. A specific binding member according to claim ~~1 or 2~~, wherein:—

~~(i) the amino acid sequence set forth in SEQ ID NO: 1 is located at residues 11 to 18 of the CH3 domain; and/or~~

~~(ii) the amino acid sequence set forth in SEQ ID NO: 3 is located at residues 92 to 101 of the CH3 domain;~~

~~wherein the amino acid residue numbering is according to the ImMunoGeneTics (IMGT) numbering scheme. the LAG-3 antigen-binding site comprises the amino acid sequence set forth in SEQ ID NO: 2 in the CD loop of the CH3 domain.~~

4. A specific binding member according to ~~any one of claims 1 to 32~~, wherein the LAG-3 antigen-binding site ~~further comprises one of the following sequences:~~ the amino acid sequence set forth in SEQ ID NO: 2 in the CD loop of the CH3 domain.

- (i) ~~SNGQPENNY (SEQ ID NOS 2, 8 and 18);~~
- (ii) ~~SNGQPEDNY (SEQ ID NO: 13);~~
- (iii) ~~SNGYPEIEF (SEQ ID NO: 23);~~
- (iv) ~~SNGIPEWNY (SEQ ID NO: 28);~~
- (v) ~~SNGYAEYNY (SEQ ID NO: 33);~~
- (vi) ~~SNGYKEENY (SEQ ID NO: 38);~~
- (vii) ~~SNGVPELNV (SEQ ID NO: 43); or~~
- (viii) ~~SNGYQEDNY (SEQ ID NO: 48).~~

5. A specific binding member according to claim 4, wherein the ~~LAG-3 antigen-specific binding site member~~ comprises the amino acid sequence set forth in SEQ ID NO: 2, 8, 13, 18, 23, 28, 33, 38, 43, or 48 in the CD loop of the CH3 domain set forth in SEQ ID NO: 5.

6. A specific binding member according to any one of claims 1 to 5, wherein the ~~LAG-3 antigen-specific binding site~~ comprises the amino acid sequence set forth in SEQ ID NO: 2, 28, or 38 in the CD loop of the CH3 an antibody CH2 domain.

7. A specific binding member according to claim 46, wherein the ~~LAG-3 antigen-binding site~~ comprises the amino acid sequence set forth in SEQ ID NO: 2 in the CD loop of the CH3 ~~CH2-domain-~~ has the sequence set forth in SEQ ID NO: 53 or SEQ ID NO: 54.

8. A specific binding member according to any one of claims 41 to 7, wherein the amino acid sequence set forth in SEQ ID NO: 2, 8, 13, 18, 23, 28, 33, 38, 43, or 48 is located at residues 43 to 78 of the CH3 domain of the specific binding member, wherein the residues are numbered according to the IMGT numbering scheme. comprises the sequence set forth in SEQ ID NO: 6, 7, 11, 12, 16, 17, 21, 22, 26, 27, 31, 32, 36, 37, 41, 42, 46, 47, 51, or 52.

9. A specific binding member according to ~~any one of~~ claims 1 to 8, wherein the CH3 domain is a human IgG1, IgG2, IgG3, or IgG4 CH3 domain. specific binding member comprises the sequence set forth in SEQ ID NO: 6 or 7.

10. A specific binding member according to claim 96 or 7, further comprising an immunoglobulin hinge region, or part thereof, at the N-terminus of the CH2 ~~wherein the CH3 domain is a human IgG1 CH3 domain.~~

11. A specific binding member according to ~~any one of claims 1 to 10~~, wherein the hinge region or part thereof has the sequence ~~specific binding member comprises the CH3 domain set forth in SEQ ID NO: 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50, 57 or SEQ ID NO: 58.~~

12. A specific binding member according to any one of claims 1 to 11, wherein the specific binding member further ~~comprises the CH3 domain set forth in SEQ ID NO: 5, 30, or 40,~~ a CDR-based antigen-binding site and is an antibody molecule.

13. ~~An specific binding member~~ antibody molecule according to claim 12, wherein the CDR-based ~~specific antigen-binding member comprises the CH3 domain set forth in SEQ ID NO: 5,~~ site of the antibody molecule binds to a molecule which is an immune system modulator.

14. A nucleic acid encoding a specific binding member or antibody molecule according to any one of claims 1 to 13, ~~wherein the~~ or a vector comprising a nucleic acid encoding a specific binding member further comprises a CH2 domain, or antibody molecule according to any one of claims 1 to 13.

15. ~~A specific binding member according to recombinant host cell comprising the nucleic acid or vector of claim 14, wherein the specific binding member comprises the CH2 domain of human IgG1, IgG2, IgG3, or IgG4.~~

16. A method of producing specific binding or antibody molecule ~~member~~ according to any one of claim 15 ~~1 to 13, wherein comprising culturing the recombinant host cell of claim 15 under conditions for production of the specific binding member or antibody molecule,~~ comprises the CH2 domain of human IgG1, optionally further comprising isolating and/or purifying the specific binding member or antibody molecule.

17. ~~A specific binding member according to claim 16, wherein the CH2 domain has the sequence set forth in SEQ ID NO: 53 or SEQ ID NO: 54.~~ A pharmaceutical composition comprising a specific binding member or antibody molecule according to any one of claims 1 to 13 and a pharmaceutically acceptable excipient.

18. ~~A specific binding member according to any one of claims 1 to 17, wherein the specific binding member comprises the sequence set forth in SEQ ID NO: 6, 7, 11, 12, 16, 17, 21, 22, 26, 27, 31, 32, 36, 37, 41, 42, 46, 47, 51, or 52.~~ A pharmaceutical composition for

treating cancer in a patient, comprising an antibody molecule according to any one of claims 12 to 13.

~~19. — A specific binding member according to claim 18, wherein the specific binding member comprises the sequence set forth in SEQ ID NO: 6, 7, 31, 32, 41, or 42.~~

~~20. — A specific binding member according to claim 19, wherein the specific binding member comprises the sequence set forth in SEQ ID NO: 6 or 7.~~

~~21. — A specific binding member according to any one of claims 1 to 20 further comprising an immunoglobulin hinge region, or part thereof, at the N-terminus of the CH2 domain.~~

~~22. — A specific binding member according to claim 21, wherein the hinge region, or part thereof, is a human IgG1, IgG2, IgG3 or IgG4 hinge region, or part thereof.~~

~~23. — A specific binding member according to claim 22, wherein the hinge region, or part thereof, is a human IgG1 hinge region, or part thereof.~~

~~24. — A specific binding member according to claim 23, wherein the hinge region or part thereof has the sequence set forth in SEQ ID NO:57 or SEQ ID NO:58.~~

~~25. — A specific binding member according to any one of claims 1 to 24, wherein the specific binding member further comprises a second antigen-binding site.~~

~~26. — A specific binding member according to claim 25, wherein the second antigen-binding site is a CDR-based antigen-binding site.~~

~~27. — A specific binding member according to claim 25 or 26, wherein the specific binding member is an antibody molecule.~~

~~28. — An antibody molecule according to claim 27, wherein the antibody molecule is a human IgG1, IgG2, IgG3 or IgG4 molecule.~~

~~29. — An antibody molecule according to claim 28, wherein the antibody molecule is a human IgG1 molecule.~~

~~30. — An antibody molecule according to any one of claims 27 to 29, wherein the CDR-based antigen-binding site of the antibody molecule binds to a molecule which is an immune system modulator.~~

~~31. — An antibody molecule according to claim 30, wherein the immune system modulator is an immunomodulatory receptor or a ligand for an immunomodulatory receptor.~~

~~32. — An antibody molecule according to claim 30, wherein the CDR-based antigen-binding site is specific for a molecule which is an immune system inhibitor or activator.~~

~~33. — An antibody molecule according to claim 32, wherein the CDR-based antigen-binding site is specific for a molecule which is an immune system inhibitor.~~

~~34. — An antibody molecule according to any one of claims 30 to 33, wherein the CDR-based antigen-binding site is specific for an antigen selected from the group consisting of: cytotoxic T lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), CD73 and Colony stimulating factor 1 receptor (CSF1R).~~

~~35. — A specific binding member or antibody molecule according to any one of claims 1 to 34, wherein the specific binding member or antibody molecule is conjugated to an immune system modulator, cytotoxic molecule, radioisotope, or detectable label.~~

~~36. — A specific binding member or antibody molecule according to claim 35, wherein the immune system modulator or cytotoxic molecule is a cytokine.~~

~~37. — A nucleic acid encoding a specific binding member or antibody molecule according to any one of claims 1 to 36.~~

~~38. — A vector comprising the nucleic acid of claim 37.~~

~~39. — A recombinant host cell comprising the nucleic acid of claim 32, or the vector of claim 38.~~

~~40. — A method of producing a specific binding member or antibody molecule according to any one of claims 1 to 36, comprising culturing the recombinant host cell of claim 39 under conditions for production of the specific binding member or antibody molecule.~~

~~41. — The method of claim 40 further comprising isolating and/or purifying the specific binding member or antibody molecule.~~

~~42. — A pharmaceutical composition comprising a specific binding member or antibody molecule according to any one of claims 1 to 36 and a pharmaceutically acceptable excipient.~~

~~43. — A specific binding member or antibody molecule according to any one of claims 1 to 36, for use in a method of treating cancer in a patient.~~

~~44. — A method of treating cancer in a patient, wherein the method comprises administering to the patient a therapeutically effective amount of a specific binding member or antibody molecule according to any one of claims 1 to 36.~~

~~45. — A specific binding member or antibody molecule for use according to claim 43, or a method according to claim 44, wherein the cancer is selected from the group consisting of: Hodgkin's lymphoma, non-Hodgkin's lymphoma, ovarian cancer, prostate cancer, colorectal cancer, fibrosarcoma, renal cell carcinoma, melanoma, pancreatic cancer, breast cancer, glioblastoma multiforme, lung cancer, head and neck cancer, stomach cancer, bladder cancer, cervical cancer, uterine cancer, vulvar cancer, testicular cancer, penile cancer, leukemia, multiple myeloma, squamous cell cancer, testicular cancer, esophageal cancer, Kaposi's sarcoma, and central nervous system (CNS) lymphoma, hepatocellular carcinoma, nasopharyngeal cancer, Merkel cell carcinoma, and mesothelioma.~~

~~46. — A specific binding member or antibody molecule for use, or a method, according to any one of claims 43 to 45, wherein the method further comprises administering an anti-tumour vaccine to the patient.~~

~~47. — A specific binding member or antibody molecule for use, or a method, according to any one of claims 43 to 45, wherein the method further comprises administering a chemotherapeutic agent to the patient.~~