

Claims

1. An isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 (ganglioside GD2), comprising:

(a) a heavy chain variable domain comprising:

CDR1 with an amino acid sequence selected from the group of SEQ ID NO: 1 or SEQ ID NO: 2,

CDR2 with the amino acid sequence of SEQ ID NO: 3,

CDR3 with an amino acid sequence selected from the group of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7; and

(b) a light chain variable domain comprising:

(i) CDR1 with an amino acid sequence selected from the group of SEQ ID NO: 8 or SEQ ID NO: 9,

(ii) CDR2 with an amino acid sequence selected from the group of SEQ ID NO: 10 or SEQ ID NO: 11,

(iii) CDR3 with an amino acid sequence selected from the group of SEQ ID NO: 12 or SEQ ID NO: 13.

2. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises:

(i) FR1 with the amino acid sequence of SEQ ID NO: 42,

(ii) FR2 with the amino acid sequence of SEQ ID NO: 43,

(iii) FR3 with the amino acid sequence of SEQ ID NO: 44 and

(iv) FR4 with the amino acid sequence of SEQ ID NO: 45.

3. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises:

(i) FR1 with the amino acid sequence of SEQ ID NO: 46,

(ii) FR2 with an amino acid sequence selected from the group of SEQ ID NO: 47 or SEQ ID NO: 48,

(iii) FR3 with the amino acid sequence of SEQ ID NO: 49 and

(iv) FR4 with the amino acid sequence of SEQ ID NO: 50.

4. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein

a) the heavy chain variable domain comprises:

(i) FR1 with the amino acid sequence of SEQ ID NO: 42,

(ii) FR2 with the amino acid sequence of SEQ ID NO: 43,

(iii) FR3 with the amino acid sequence of SEQ ID NO: 44 and

- (iv) FR4 with the amino acid sequence of SEQ ID NO: 45, and, wherein
 - b) the light chain variable domain comprises:
 - (i) FR1 with the amino acid sequence of SEQ ID NO: 46,
 - (ii) FR2 with an amino acid sequence selected from the group of SEQ ID NO: 47 or SEQ ID NO: 48,
 - (iii) FR3 with the amino acid sequence of SEQ ID NO: 49 and
 - (iv) FR4 with the amino acid sequence of SEQ ID NO: 50.
- 5. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises:
 - (i) CDR1 with the amino acid sequence of SEQ ID NO: 2, CDR2 with the amino acid sequence of SEQ ID NO: 3, CDR3 with the amino acid sequence of SEQ ID NO: 5; or
 - (ii) CDR1 with the amino acid sequence of SEQ ID NO: 2, CDR2 with the amino acid sequence of SEQ ID NO: 3, CDR3 with the amino acid sequence of SEQ ID NO: 4.
- 6. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises:
 - (i) CDR1 with the amino acid sequence of SEQ ID NO: 9, CDR2 with the amino acid sequence of SEQ ID NO: 11, CDR3 with the amino acid sequence of SEQ ID NO: 12; or
 - (ii) CDR1 with the amino acid sequence of SEQ ID NO: 8, CDR2 with the amino acid sequence of SEQ ID NO: 10, CDR3 with the amino acid sequence of SEQ ID NO: 12.
- 7. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17.
- 8. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises an amino acid sequence that is selected from the group of SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17.
- 9. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21.
- 10. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises an amino acid sequence that is

selected from the group of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

11. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein:

(a) the heavy chain variable domain comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17;

(b) the light chain variable domain comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21.

12. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein:

(a) the heavy chain variable domain comprises an amino acid sequence that is selected from the group of SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

(b) the light chain variable domain comprises an amino acid sequence that is selected from the group of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

13. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 14, wherein:

(i) (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 16; and

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19; or

(ii) (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 17;

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 21.

14. The isolated monoclonal antibody according to any of claims 1-13, wherein the antibody that specifically binds to GD2 is a full-length IgG antibody.

15. The isolated monoclonal antibody according to claim 14, wherein the full-length IgG antibody belongs to the human IgG1, IgG2, IgG3 or IgG4 isotype.

16. The isolated monoclonal antibody according to claim 1, wherein the antibody comprises YTE mutations (M252Y, S254T, T256E) and/or K322A mutation in the Fc fragment as compared to the natural sequence of the Fc fragment.

17. The isolated monoclonal antibody according to claim 1, including a heavy chain comprising an amino acid sequence selected from the group of SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID

NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37.

18. The isolated monoclonal antibody according to claim 1, including a light chain comprising an amino acid sequence selected from the group of SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

19. The isolated monoclonal antibody according to claim 1, including:

(a) a heavy chain comprising an amino acid sequence selected from the group of SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37, and

(b) a light chain comprising an amino acid sequence selected from the group of SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

20. The isolated monoclonal antibody according to claim 1, including:

(i) (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 32, and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 39; or

(ii) (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 33, and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 41.

21. An isolated nucleic acid that encodes the antibody or antigen-binding fragment thereof according to any of claims 1-20.

22. The isolated nucleic acid according to claim 21, wherein the nucleic acid is DNA.

23. An expression vector comprising the nucleic acid according to any of claims 21-22.

24. A method for obtaining a host cell to obtain the antibody or antigen-binding fragment thereof according to any of claims 1-20, including cell transformation by the expression vector according to claim 23.

25. A host cell for obtaining the antibody or antigen-binding fragment thereof according to any of claims 1-20, comprising the nucleic acid according to any of claims 21-22.

26. A method for obtaining the antibody or antigen-binding fragment thereof according to any of claims 1-20, comprising culturing the host cell according to claim 25 in a growth medium under conditions sufficient to produce said antibody, if necessary, followed by isolation and purification of the resulting antibody.

27. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any of claims 1-20 in combination with one or more pharmaceutically acceptable excipients.

28. The pharmaceutical composition according to claim 27 for treating a disease or disorder mediated by GD2.

29. The pharmaceutical composition according to claim 28, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

30. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any of claims 1-20 and at least one other therapeutically active compound.

31. The pharmaceutical composition according to claim 30 for treating a disease or disorder mediated by GD2.

32. The pharmaceutical composition according to claim 31, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

33. The pharmaceutical composition according to claim 30, wherein the other therapeutically active compound is an antibody, chemotherapeutic agent, hormone therapy agent or an immune checkpoint inhibitor, or the other therapeutically active compound is selected from the group of IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

34. The pharmaceutical composition according to claim 33, wherein the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor or CTLA-4 inhibitor.

35. The pharmaceutical composition according to claim 34, wherein the PD-1 inhibitor is an antibody that specifically binds to PD-1.

36. The pharmaceutical composition according to claim 35, wherein the antibody that specifically binds to PD-1 is selected from the group of prolgolimab, pembrolizumab, nivolumab.

37. The pharmaceutical composition according to claim 34, wherein the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

38. The pharmaceutical composition according to claim 37, wherein the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

39. The pharmaceutical composition according to claim 34, wherein the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

40. The pharmaceutical composition according to claim 39, wherein the antibody that specifically binds to PD-L1 is selected from the group of durvalumab, avelumab, atezolizumab, manelimumab.

41. Use of the antibody or antigen-binding fragment thereof according to any of claims 1-20 or the pharmaceutical composition according to any of claims 27 or 30 for treating a disease or disorder mediated by GD2 in a subject in need of such treatment.

42. The use according to claim 41, wherein the use of the antibody or antigen-binding fragment thereof according to any of claims 1-20 or the pharmaceutical composition according to any of claims 27 or 30 and at least one of the group of:

- a) other therapeutically active compound,
 - b) radiotherapy,
 - c) hematopoietic stem cell transplantation or
 - d) surgical treatment and, if necessary, adjuvant therapy,
- for treating a disease or disorder mediated by GD2.

43. The use according to claim 41, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

44. The use according to claim 42 wherein the other therapeutically active compound is an immune checkpoint inhibitor or

the other therapeutically active compound is selected from the group of IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

45. The use according to claim 44, wherein the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor or CTLA-4 inhibitor.

46. The use according to claim 45, wherein the PD-1 inhibitor is an antibody that specifically binds to PD-1.

47. The use according to claim 46, wherein the antibody that specifically binds to PD-1 is selected from the group of prololimumab, pembrolizumab, nivolumab.

48. The use according to claim 45, wherein the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

49. The use according to claim 48, wherein the antibody that specifically binds to CTLA-4 is ipilimumab or nivorolumab.

50. The use according to claim 45, wherein the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

51. The use according to claim 50, wherein the antibody that specifically binds to PD-L1 and is selected from the group of durvalumab, avelumab, atezolizumab, manelimab.