Claims

What is claimed is:

1. An antibody agent specific to Dengue virus, wherein the antibody agent binds to and neutralizes each of Dengue Virus serotypes D1, D2, D3, and D4.

2. The antibody agent according to claim 1, wherein the antibody agent binds to an epitope that is or comprises an amino acid sequence within: SEQ ID NO. 17 (EDIII-DV1), SEQ ID NO. 18 (EDIII-DV2), SEQ ID NO. 19 (EDIII-DV3), SEQ ID NO. 20 (EDIII-DV4), or combinations thereof.

3. The antibody agent according to claim 1, wherein the agent binds to an epitope in the A-strand region of envelope glycoprotein of Dengue virus.

4. The antibody agent according to claim 2, wherein the epitope comprises one or more residues corresponding to that at a position selected from the group consisting of: 305, 306, 307, 308, 309, 310, 311, 312, 323, 325, 327, 329, 360, 361, 362, 363, 364, 385, 387, 388, 389, 390, 391, and combinations thereof, of any one of SEQ ID NOs. 17-20.

5. The antibody agent according to claim 4, wherein the epitope comprises one or more residues corresponding to that at a position selected from the group consisting of: 305, 310, 311, 323, 327, 329, and combinations thereof, of any one of SEQ ID NOs. 17-20.

6. The antibody agent according to claim 4, wherein the epitope comprises a residue corresponding to that at position 305 of any one of SEQ ID NOs. 17-20.

7. The antibody agent according to claim 4, wherein the epitope comprises a residue corresponding to that at position 310 of any one of SEQ ID NOs. 17-20.

8. The antibody agent according to claim 4, wherein the epitope comprises a residue corresponding to that at position 311 of any one of SEQ ID NOs. 17-20.

9. The antibody agent according to claim 4, wherein the epitope comprises a residue corresponding to that at position 323 of any one of SEQ ID NOs. 17-20.

10. The antibody agent according to claim 4, wherein the epitope comprises a residue corresponding to that at position 327 of any one of SEQ ID NOs. 17-20.

11. The antibody agent according to claim 4, wherein the epitope comprises a residue corresponding to that at position 329 of any one of SEQ ID NOs. 17-20.

12. The antibody agent according to claim 6, wherein the corresponding residue is selected from the group consisting of: serine, lysine, and threonine.

13. The antibody agent according to claim 7, wherein the corresponding residue is lysine.

14. The antibody agent according to claim 8, wherein the corresponding residue is lysine.

15. The antibody agent according to claim 9, wherein the corresponding residue is selected from the group consisting of: arginine, lysine, and glutamine.

16. The antibody agent according to claim 10, wherein the corresponding residue is selected from the group consisting of: lysine and glutamate.

17. The antibody agent according to claim 11, wherein the corresponding residue is selected from the group consisting of: arginine, aspartate, glutamate, and threonine.

18. The antibody agent according to claim 1, whose heavy chain variable region and/or light chain variable region includes at least one complementarity determining region (CDR) sharing at least 80% sequence identity with a reference CDR of antibody 4E11, but differs by substitution of at least one amino residue within the CDR, so that the antibody agent potently neutralizes all four DV serotypes.

19. The antibody agent according to claim 18, which antibody agent includes at least one CDR that is substantially identical to a reference CDR of antibody 4E11 in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference CDR.

20. The antibody agent according to claim 19, wherein the reference CDR is selected from the group consisting of:

one found between residues 27 and 33 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 53 and 58 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 100 and 106 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 24 and 38 of the 4E11 light chain (SEQ ID NO. 2);
one found between residues 54 and 60 of the 4E11 light chain (SEQ ID NO. 2);
one found between residues 93 and 101 of the 4E11 light chain (SEQ ID NO. 2); and
combinations thereof.

21. The antibody agent according to claim 19, which antibody agent includes at least one CDR that is substantially identical to a reference CDR set forth below, in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference CDR:

reference CDRs: GFNIKDT (SEQ ID NO. 7), DPANGD (SEQ ID NO. 8), GWEGFAY (SEQ ID NO. 9), RASENVDRYGNSFMH (SEQ ID NO. 14), RASNLES (SEQ ID NO. 15), and/or QRSNEVPWT (SEQ ID NO. 16).

22. The antibody agent according to claim 19, wherein the reference CDR is a heavy chain CDR.

23. The antibody agent according to claim 19, wherein the reference CDR is a light chain CDR.

24. The antibody agent according to claim 19, wherein the antibody agent includes at least one heavy chain CDR that is substantially identical to a heavy chain reference CDR and also includes at least one light chain CDR that is identical to a light chain reference CDR.

25. The antibody agent according to claim 19, wherein each of the CDRs in the antibody agent is substantially identical to one of the reference CDRs.

26. The antibody agent according to claim 1, whose heavy chain variable region and/or light chain variable region includes at least one complementarity determining region (CDR) sharing at least 95% sequence identity with a reference CDR of antibody 4E11, but differs by substitution of at least one amino acid residue within the CDR, so that the antibody agent potently neutralizes all four DV serotypes.

27. The antibody agent according to claim 26, which antibody agent includes at least one CDR that is substantially identical to a reference CDR of antibody 4E11 in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference CDR.

28. The antibody agent according to claim 27, wherein the reference CDR is selected from the group consisting of:

one found between residues 27 and 33 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 53 and 58 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 100 and 106 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 24 and 38 of the 4E11 light chain (SEQ ID NO. 2);
one found between residues 54 and 60 of the 4E11 light chain (SEQ ID NO. 2);
one found between residues 93 and 101 of the 4E11 light chain (SEQ ID NO. 2); and
combinations thereof.

29. The antibody agent according to claim 27, which antibody agent includes at least one CDR that is substantially identical to a reference CDR set forth below, in that it is either identical

to such reference CDR or includes between 1-5 substitutions of amino acids within such reference CDR:

reference CDRs: GFNIKDT (SEQ ID NO. 7), DPANGD (SEQ ID NO. 8), GWEGFAY (SEQ ID NO. 9), RASENVDRYGNSFMH (SEQ ID NO. 14), RASNLES (SEQ ID NO. 15), and/or QRSNEVPWT (SEQ ID NO. 16).

30. The antibody agent according to claim 27, wherein the reference CDR is a heavy chain CDR.

31. The antibody agent according to claim 27, wherein the reference CDR is a light chain CDR.

32. The antibody agent according to claim 27, wherein the antibody agent includes at least one heavy chain CDR that is substantially identical to a heavy chain reference CDR and also includes at least one light chain CDR that is identical to a light chain reference CDR.

33. The antibody agent according to claim 27, wherein each of the CDRs in the antibody agent is substantially identical to one of the reference CDRs.

34. The antibody agent according to any one of claims 18 or 26, wherein the heavy chain variable region CDR has substitution of the amino acid residue at position 55.

35. The antibody agent according to claim 34, wherein the substitute amino acid residue at position 55 is selected from the group consisting of: glutamate and aspartate.

36. The antibody agent according to claim 34, wherein the substitute amino acid residue at position 55 is glutamate.

37. The antibody agent according to any one of claims 18 or 26, wherein the light chain variable region CDR has substitution of the amino acid residue at positions selected from the group consisting of: 31, 57, 59, 60, and combinations thereof.

38. The antibody agent according to claim 37, wherein the light chain variable region CDR has substitution of the amino acid residue at position 31.

39. The antibody agent according to claim 38, wherein the substitute amino acid residue at position 31 is lysine.

40. The antibody agent according to claim 37, wherein the light chain variable region CDR has substitution of the amino acid residue at position 57.

41. The antibody agent according to claim 40, wherein the substitute amino acid residue at position 57 is selected from the group consisting of: glutamate and serine.

42. The antibody agent according to claim 40, wherein the substitute amino acid residue at position 57 is glutamate.

43. The antibody agent according to claim 37, wherein the light chain variable region CDR has substitution of the amino acid residue at position 59.

44. The antibody agent according to claim 43, wherein the substitute amino acid residue at position 59 is selected from the group consisting of: glutamine and asparagine.

45. The antibody agent according to claim 43, wherein the substitute amino acid residue at position 59 is glutamine.

46. The antibody agent according to claim 37, wherein the light chain variable region CDR has substitution of the amino acid residue at position 60.

47. The antibody agent according to claim 46, wherein the substitute amino acid residue at position 60 is selected from the group consisting of: tryptophan, tyrosine, and arginine.

48. ~~The antibody agent according to claim 46, wherein the substitute amino acid residue at~~ position 60 is tryptophan.

49. The antibody agent according to claim 1, which is an IgG.

50. The antibody agent according to claim 1, which is a monoclonal antibody.

51. The antibody agent according to claim 1, wherein the antibody agent is selected from the group consisting of: a mouse antibody, humanized antibody, a human antibody, a purified antibody, an isolated antibody, a chimeric antibody, a polyclonal antibody, and combinations thereof.

52. The antibody agent according to claim 1, wherein the antibody agent is selected from the group consisting of: a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment, a Fd fragment, a Fd' fragment, a Fv fragment, a dAb fragment, a scFv fragment, an isolated CDR region, a dsFv diabody, a single chain antibody, and combinations thereof.

53. A cell line expressing an antibody agent according to claim 1.

54. A pharmaceutical composition comprising:
one or more antibody agents according to claim 1; and
a pharmaceutically acceptable carrier or excipient.

55. The pharmaceutical composition of claim 54, further comprising at least one additional antiviral agent.

56. ~~A method of treating a subject in need thereof, comprising administering~~Use of an antibody agent according to claim 1 in the manufacture of a medicament for treatment or prevention of Dengue virus infection in a subject in need thereof.

57. A kit comprising:

at least one antibody agent according to claim 1;

a syringe, needle, or applicator for administration of the at least one antibody or fragment to a subject; and instructions for use.

58. A method of manufacturing a pharmaceutical composition, the method comprising steps of:

providing an antibody agent according to claim 1; and

formulating the antibody agent with at least one pharmaceutically acceptable carrier or excipient,

so that a pharmaceutical composition is generated.

59. The method of claim 58, wherein the pharmaceutical composition is a liquid composition.

60. The method of claim 58, wherein the pharmaceutical composition is formulated for parenteral administration.

61. The method of claim 60, wherein the pharmaceutical composition is formulated for intravenous administration.

62. The method of claim 61, wherein the pharmaceutical composition is formulated for intravenous administration to a child.

63. An antibody agent whose heavy chain is or comprises an amino acid sequence within SEQ ID NO.: 21 and whose light chain is or comprises an amino acid sequence within SEQ ID NO.: 22.

64. An antibody agent with at least one CDR that has a sequence selected from the group consisting of: SEQ ID NO.: 23, SEQ ID NO.: 24, SEQ ID NO.: 25, SEQ ID NO.: 26, SEQ ID NO.: 27, SEQ ID NO.: 28.

Claims

What is claimed is:

1. An antibody agent specific to Dengue virus, wherein the antibody agent binds to and neutralizes each of Dengue Virus serotypes D1, D2, D3, at least as effectively as does antibody 4E11 and neutralizes D4 more effectively than does antibody 4E11.

2. The antibody agent according to claim 1, wherein the antibody agent binds to an epitope that is or comprises an amino acid sequence within: SEQ ID NO. 17 (EDIII-DV1), SEQ ID NO. 18 (EDIII-DV2), SEQ ID NO. 19 (EDIII-DV3), SEQ ID NO. 20 (EDIII-DV4), or combinations thereof.

3. The antibody agent according to claim 1, whose heavy chain variable region and/or light chain variable region includes at least one complementarity determining region (CDR) sharing at least 80% sequence identity with a reference CDR of antibody 4E11, but differs by substitution of at least one amino acid residue within the CDR, so that the antibody agent neutralizes all four DV serotypes.

4. The antibody agent according to claim 3, which antibody agent further includes at least one CDR that is substantially identical to a reference CDR of antibody 4E11 in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference CDR.

5. The antibody agent according to claim 4, wherein the reference CDR is selected from the group consisting of:

one found between residues 27 and 33 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 53 and 58 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 100 and 106 of the 4E11 heavy chain (SEQ ID NO. 1);
one found between residues 24 and 38 of the 4E11 light chain (SEQ ID NO. 2);
one found between residues 54 and 60 of the 4E11 light chain (SEQ ID NO. 2);

one found between residues 93 and 101 of the 4E11 light chain (SEQ ID NO. 2); and combinations thereof.

6. The antibody agent according to claim 4, which antibody agent includes at least one CDR that is substantially identical to a reference CDR set forth below, in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference CDR:

reference CDRs: GFNIKDT (SEQ ID NO. 7), DPANGD (SEQ ID NO. 8), GWEGFAY (SEQ ID NO. 9), RASENVDRYGNSFMH (SEQ ID NO. 14), RASNLES (SEQ ID NO. 15), and/or QRSNEVPWT (SEQ ID NO. 16).

7. The antibody agent according to claim 4, wherein the antibody agent includes at least one heavy chain CDR that is substantially identical to a heavy chain reference CDR and also includes at least one light chain CDR that is identical to a light chain reference CDR.

8. The antibody agent according to claim 3, wherein the heavy chain variable region CDR has substitution of the amino acid residue at position 55 relative to the reference 4E11 heavy chain variable region CDR.

9. The antibody agent according to claim 8, wherein the substitute amino acid residue at position 55 is selected from the group consisting of: glutamate and aspartate.

10. The antibody agent according to claim 8, wherein the substitute amino acid residue at position 55 is glutamate.

11. The antibody agent according to claim 3, wherein the light chain variable region CDR has an amino acid substitution at one or more positions selected from the group consisting of: 31, 57, 59, 60, and combinations thereof, relative to the reference 4E11 light chain variable region CDR.

12. The antibody agent according to claim 11, wherein the light chain variable region CDR has an amino acid substitution at position 31, relative to the reference 4E11 light chain variable region CDR.

13. The antibody agent according to claim 12, wherein the substitute amino acid residue at position 31 is lysine.

14. The antibody agent according to claim 11, wherein the light chain variable region CDR has an amino acid substitution at position 57, relative to the reference 4E11 light chain variable region CDR.

15. The antibody agent according to claim 14, wherein the substitute amino acid residue at position 57 is selected from the group consisting of: glutamate and serine.

16. The antibody agent according to claim 14, wherein the substitute amino acid residue at position 57 is glutamate.

17. The antibody agent according to claim 11, wherein the light chain variable region CDR has an amino acid substitution at position 59, relative to the reference 4E11 light chain variable region CDR.

18. The antibody agent according to claim 17, wherein the substitute amino acid residue at position 59 is selected from the group consisting of: glutamine and asparagine.

19. The antibody agent according to claim 17, wherein the substitute amino acid residue at position 59 is glutamine.

20. The antibody agent according to claim 11, wherein the light chain variable region CDR has an amino acid substitution at position 60, relative to the reference 4E11 light chain variable region CDR.

21. The antibody agent according to claim 20, wherein the substitute amino acid residue at position 60 is selected from the group consisting of: tryptophan, tyrosine, and arginine.

22. The antibody agent according to claim 20, wherein the substitute amino acid residue at position 60 is tryptophan.

23. The antibody agent according to claim 1, which is an IgG.

24. The antibody agent according to claim 1, which is a monoclonal antibody.

25. The antibody agent according to claim 1, wherein the antibody agent is selected from the group consisting of: a mouse antibody, a humanized antibody, a human antibody, a purified antibody, an isolated antibody, a chimeric antibody, a polyclonal antibody, and combinations thereof.

26. The antibody agent according to claim 1, wherein the antibody agent is selected from the group consisting of: a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment, a Fd fragment, a Fd' fragment, a Fv fragment, a dAb fragment, a scFv fragment, an isolated CDR region, a dsFv diabody, a single chain antibody, and combinations thereof.

27. Use of an antibody agent according to claim 1 in the manufacture of a medicament for treatment or prevention of Dengue virus infection in a subject in need thereof.

28. A kit comprising:

at least one antibody agent according to claim 1;

a syringe, needle, or applicator for administration of the at least one antibody or fragment to a subject; and instructions for use.

29. A method of manufacturing a pharmaceutical composition, the method comprising steps of:

providing an antibody agent according to claim 1; and

formulating the antibody agent with at least one pharmaceutically acceptable carrier or excipient,

so that a pharmaceutical composition is generated.

30. An antibody agent whose heavy chain has an amino acid sequence as set forth in SEQ ID NO.: 21 and whose light chain has an amino acid sequence as set forth in SEQ ID NO.: 22.

31. An antibody agent according to claim 1, whose heavy chain is or comprises an amino acid sequence within SEQ ID NO.: 21 and whose light chain is or comprises an amino acid sequence within SEQ ID NO.: 22.

32. An antibody agent:

whose heavy chain CDRs have amino acid sequences as set forth in SEQ ID NO.: 23, SEQ ID NO.: 24, SEQ ID NO.: 25; or

whose light chain CDRs have amino acid sequences as set forth in SEQ ID NO.: 26, SEQ ID NO.: 27, and SEQ ID NO.: 28; or

both.

33. The antibody agent of claim 1, which antibody agent:

includes at least one heavy chain variable region that:

(i) differs from but shows at least 90% overall sequence identity with a reference heavy chain variable region of SEQ ID NO. 1; and

(ii) includes heavy chain CDRs 1, 2, and 3, each of which is substantially identical to a reference heavy chain CDR selected from the group consisting of:

reference heavy chain CDR1: GFNIKDT (SEQ ID NO. 7);

reference heavy chain CDR2: DPANGD (SEQ ID NO. 8); and

reference heavy chain CDR3: GWEGFAY (SEQ ID NO. 9),

in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference heavy chain CDR

or

includes at least one light chain variable region that:

(i) differs from but shows at least 90% overall sequence identity with a reference light chain variable region of SEQ ID NO. 2; and

(ii) includes light chain CDRs 1, 2, and 3, each of which is substantially identical to a reference light chain CDR selected from the group consisting of:

reference light chain CDR1: RASENVDRYGNSFMH (SEQ ID NO. 14);

reference light chain CDR2: RASNLES (SEQ ID NO. 15); and

reference light chain CDR3: QRSNEVPWT (SEQ ID NO. 16),

in that it is either identical to such reference CDR or includes between 1-5 substitutions of amino acids within such reference light chain CDR.

34. The antibody agent according to claim 33, wherein at least one of the included heavy chain CDR1, CDR2, and CDR3 is identical to the corresponding reference chain CDR1, CDR2, or CDR3.

35. The antibody agent according to claim 34, wherein the included heavy chain CDR3 is identical to the reference heavy chain CDR3.

36. The antibody agent according to claim 34, wherein the included CDR1 has between 1-5 substitutions of amino acids relative to the reference CDR1.

37. The antibody agent according to claim 36 wherein the included CDR1 has one substitution of amino acids relative to the reference CDR1.

38. The antibody agent according to claim 34, wherein the included CDR2 has between 1-5 substitutions of amino acids relative to the reference CDR2.

39. The antibody agent according to claim 38, wherein the included CDR2 has one substitution of amino acids relative to the reference CDR2.

40. The antibody agent according to claim 34, wherein each of the included CDR1 and the CDR2 has between 1-5 substitutions of amino acids relative to the reference CDR1 and CDR2.

41. The antibody agent according to claim 33, wherein at least one of the included light chain CDR1, CDR2, and CDR3 is identical to the corresponding reference chain CDR1, CDR2, or CDR3.

42. The antibody agent according to claim 41, wherein the included CDR3 is identical to the reference light chain CDR3.

43. The antibody agent according to claim 41, wherein the included CDR1 has between 1-5 substitutions of amino acids relative to the reference CDR1.

44. The antibody agent according to claim 43, wherein the included CDR1 has one substitution of amino acids relative to the reference CDR1.

45. The antibody agent according to claim 41, wherein the included CDR2 has between 1-5 substitutions of amino acids relative to the reference CDR2.

46. The antibody agent according to claim 45, wherein the included CDR2 has four substitutions of amino acids relative to the reference CDR2.

47. The antibody agent according to claim 41, wherein each of the included CDR1 and the CDR2 has between 1-5 substitutions of amino acids relative to the reference CDR1 and CDR2.

48. The antibody agent according to claim 33, wherein:

the 1-5 substitutions of amino acids in at least one heavy chain CDR is a substitution of an amino acid at position 55; or

the 1-5 substitutions of amino acids in at least one light chain CDR are substitutions of amino acids at positions selected from the group consisting of: 31,57, 59, 60; or

both.