REPLACEMENT SHEETS

What is claimed is:

1. An antibody agent, which antibody agent:

includes at least one heavy chain variable region that includes:

a heavy chain CDR1 having the sequence GFNIKDT (SEQ ID NO. 35)

a heavy chain CDR2 having the sequence DPENGD (SEQ ID NO. 36); and

a heavy chain CDR3 having the sequence GWEGFAY (SEQ ID NO. 37);

or includes at least one light chain variable region that includes:

a light chain CDR1 having the sequence RASENVDKYGNSFMH (SEQ ID NO. 42)

a light chain CDR2 having the sequence RASELQW (SEQ ID NO. 43); and

a light chain CDR3 having the sequence QRSNEVPWT (SEQ ID NO. 44);

or both.

2. The antibody agent of claim 1, comprising a heavy chain variable region whose amino acid sequence contains at least one difference from but shows at least 80% overall sequence identity with that of reference antibody 4E5A, whose heavy chain is set forth in SEQ ID NO. 29.

3. The antibody of claim 2, wherein the at least one difference comprises or consists of a difference at a position corresponding to residue 26 or 27 of SEQ ID NO. 29.

4. The antibody of claim 2, wherein the at least one difference comprises or consists of a sequence element selected from the group consisting of:

Null at heavy chain residue 26 as found in SEQ ID NO. 29;

alanine at heavy chain residue 27 as found in SEQ ID NO. 29; and

Null at heavy chain residue 27 as found in SEQ ID NO. 29.

5. The antibody agent of claim 1, comprising a light chain variable region whose amino acid sequence contains at least one difference from but shows at least 80% overall sequence identity with that of reference antibody 4E5A, whose light chain is set forth in SEQ ID NO. 30.

6. The antibody agent of claim 1, comprising a heavy chain whose amino acid sequence comprises:

a heavy chain FR1 having the sequence EVKLLEQSGAELVKPGASVRLSCTAS (SEQ ID NO. 31),

a heavy chain FR2 having the sequence YMSWVKQRPEQGLEWIGRI (SEQ ID NO. 32),

a heavy chain FR3 having the sequence TKYDPKFQGKATITADTSSNTAYLHLSSLTSGDTAVYYCSR (SEQ ID NO. 33), and/or

a heavy chain FR4 having the sequence WGQGTLVTVSA (SEQ ID NO. 34).

7. The antibody agent of claim 1, comprising a light chain whose amino acid sequence comprises:

a light chain FR1 having the sequence ELVMTQTPASLAVSLGQRATISC (SEQ ID NO. 38),

a light chain FR2 having the sequence WYQQKAGQPPKLLIY (SEQ ID NO. 39),

a light chain FR3 having the sequence GIPARFSGSGSRTDFTLTINPVEADDVATYFC (SEQ ID NO. 40), and/or

a light chain FR4 having the sequence FGGGTKLEIKR (SEQ ID NO. 41).

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

9. The antibody agent according to claim 1, wherein the antigen binding fragment 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.

REPLACEMENT SHEETS

10. An antibody agent comprising two heavy chains and two light chains, wherein:

each of the heavy chains includes an amino acid sequence having a null at a position corresponding to residue 26 of the heavy chain of 4E11; and

wherein the amino substitutions in both heavy chains and both light chains total at least 1-5 amino acid substitutions, and wherein the antibody agent shows enhanced affinity for D4 when compared to that of 4E11.

11. 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, which antibody agent shows a KD with respect to each of D1, D2, D3, and D4 that is less than 45.

12. The antibody agent according to claim 11, 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 CDR of reference antibody selected from the group consisting of 4E11 and 4E5A, but differs by substitution of at least one amino residue within the CDR.

13. The antibody agent according to claim 12, 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.

14. The antibody agent according to claim 13, 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.

15. The antibody agent according to claim 13, 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).

16. The antibody agent according to claim 15, wherein the reference CDR is a heavy chain CDR.

17. The antibody agent according to claim 15, wherein the reference CDR is a light chain CDR.

18. The antibody agent according to claim 15, 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.

19. The antibody agent according to claim 15, wherein each of the CDRs in the antibody agent is substantially identical to one of the reference CDRs.

20. The antibody agent according to claim 11, 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 CDR of a reference antibody selected from the group consisting of 4E11 and 4E5A, but differs by substitution of at least one amino acid residue within the CDR.

21. The antibody agent according to claim 20, 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.

22. The antibody agent according to claim 21, 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.

23. The antibody agent according to claim 21, 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).

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

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

26. The antibody agent according to claim 23, 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.

27. The antibody agent according to claim 23, wherein each of the CDRs in the antibody agent is substantially identical to one of the reference CDRs.

28. The antibody agent according to claim 27, wherein the heavy chain variable region CDR has substitution of the amino acid residue at position 27.

29. The antibody agent according to claim 28, wherein the substitute amino acid residue at position 27 is selected from the group consisting of: null and alanine.

30. The antibody agent according to claim 28, wherein the substitute amino acid residue at position 27 is a null substitution.

31. The antibody agent according to claim 28, wherein the substitute amino acid residue at position 27 is a alanine.

32. The antibody agent according to claim 11, which antibody agent comprises a polypeptide whose amino acid sequence includes one or more of the following sequence elements:

no residue at a position corresponding to residue 26 of a reference 4E11 or 4E5A antibody heavy chain

alanine at a position corresponding to residue 27 of a reference 4E11 or 4E5A antibody heavy chain; and

no residue at a position corresponding to residue 27 of a reference 4E11 or 4E5A antibody heavy chain.

33. The antibody agent according to claim 11, which is an IgG.

34. The antibody agent according to claim 11, which is a monoclonal antibody.

REPLACEMENT SHEETS

35. The antibody agent according to claim 11, 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.

36. The antibody agent according to claim 11, wherein the antigen binding fragment 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.

37. A cell line expressing an antibody agent according to claim 11.

38. A pharmaceutical composition comprising:

one or more antibody agents according to claim 11; and

a pharmaceutically acceptable carrier or excipient.

39. The pharmaceutical composition of claim 38, further comprising at least one additional antiviral agent.

40. A method of treating a subject in need thereof, comprising administering an antibody agent according to claim 11.

41. A kit comprising:

at least one antibody agent according to claim 11;

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

instructions for use.

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

REPLACEMENT SHEETS

providing an antibody agent according to claim 11; and

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

so that a pharmaceutical composition is generated.

43. An antibody agent that is an antibody whose heavy chain is or comprises an amino acid sequence within SEQ ID NO. 29 and whose light chain is or comprises an amino acid sequence within SEQ ID NO. 30.

44. An antibody agent that is a polypeptide whose sequence includes at least one CDR that has a sequence selected from the group consisting of: SEQ ID NO. 35, 36, 37, 42, 43 and 44.

CLAIMS

1. An antibody agent comprising two heavy chains and two light chains, wherein:

the heavy chain CDRs are identical to reference CDRs found between residues 27 and 33, residues 53 and 58, and residues 100 and 106 of SEQ ID NO:29 except that at least one of the heavy chain CDRs differs by a single amino acid substitution relative to its reference CDR; and

the light chain CDRs are identical to reference CDRs found between residues 24 and 38, residues 54 and 60, and residues 93 and 101 of SEQ ID NO:30, or at least one of the light chain CDRs differs by a single amino acid substitution relative to its reference CDR.

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

3. A pharmaceutical composition comprising:

one or more antibody agents according to claim 1; and

a pharmaceutically acceptable carrier or excipient.

4. The pharmaceutical composition of claim 3, further comprising at least one additional antiviral agent.

5. The antibody agent according to claim 1 for use in treating a subject in need thereof.

6. The pharmaceutical composition according to claim 3 for use in treating a subject in need thereof.

7. 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.

8. 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.

9. The antibody agent according to claim 1, wherein the antibody agent is an IgG antibody.

10. 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, and a chimeric antibody.

11. The antibody agent according to claim 1, wherein the antibody agent is selected from the group consisting of: a purified antibody, and an isolated antibody.

12. The antibody agent according to claim 1, wherein the antibody agent is a monoclonal antibody.

13. The antibody agent according to claim 1, wherein the antibody agent is a polyclonal antibody.

14. The antibody agent according to claim 1, wherein the antigen binding fragment 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.

15. A vaccine composition comprising the antibody agent of claim 1.

16. The use of the vaccine composition of claim 15 in the manufacture of a medicament that is to be administered to a subject who is suffering from or susceptible to dengue virus infection.

17. A method of detecting dengue virus, the method comprising steps of:

contacting an environmental sample with an antibody agent of claim 1; and

detecting dengue virus by detecting binding of the antibody to the sample.

18. The method of claim 17, wherein the environmental sample is or comprises one or more of soil, water and flora.

19. A diagnostic method comprising steps of:

contacting a patient sample with an antibody agent of claim 1; and

diagnosing the patient as suffering from infection with dengue virus by detecting binding of the antibody to the sample.

20. The method of claim 19, wherein the sample from a patient is selected from the group consisting of blood, serum/plasma, peripheral blood mononuclear cells/peripheral blood lymphocytes (PBMC/PBL), sputum, urine, feces, throat swabs, dermal lesion swabs, cerebrospinal fluids, cervical smears, pus samples, food matrices, and tissues from various parts of the body such as brain, spleen, and liver.

21. The antibody agent according to claim 1, wherein the heavy chain CDRs include one of the following residues: 55Glu or 55Asp.

22. The antibody agent according to claim 1, wherein the light chain CDRs include one or more of the following residues:

31Lys;

57Glu or 57Ser;

59Gln or 59Ans; and

60Trp, 60Tyr, or 60Arg.

23. The antibody agent according to claim 1, wherein the heavy chain has a deletion of Ala25 relative to SEQ ID NO:29.

24. The antibody agent according to claim 1, wherein the heavy chain has a deletion of Ser26 relative to SEQ ID NO:29.

25. The antibody agent according to claim 1, wherein the heavy chain has a deletion of Gly27 relative to SEQ ID NO:29.

26. The antibody agent according to claim 1, wherein the heavy chain has one or more of the following residues:

27Ala or 27Pro, and

106Arg.