dengue infection rely primarily on alleviating symptoms rather than assisting host immune responses against the virus.

A need therefore exists for improved dengue virus diagnostic tools, and agents which aid host immune responses against dengue virus infection.

Summary of the Invention

The present inventors have identified a series of binding molecules beneficial for the diagnosis, prevention and treatment of dungue virus infection.

The present ~~invention~~ disclosure relates at least to the following ~~embodiment~~examples:

1. A human monoclonal antibody capable of specifically binding to an envelope (E) protein of at least one dengue virus serotype, wherein the antibody comprises a light chain variable domain sequence comprising the first, second, and third complementarity determining region (CDR) sequences of a single clone designated in Figure 20, 21 or 22.

2. A cross-reactive human monoclonal antibody derived from a memory B lymphocyte capable of specifically binding to an E protein of at least one dengue virus serotype, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202: SEQ ID NOs: 203 and 204; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; or SEQ ID NOs: 215 and 216.

3. A cross-reactive human monoclonal antibody derived from a plasmablast capable of specifically binding to an E protein of at least one dengue virus serotype, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NOs: 113 and 114; SEQ ID NOs: 115 and 116; SEQ ID NOs: 121 and 122; SEQ ID NOs: 123 and 124; SEQ ID NOs: 127 and 128; SEQ ID NOs: 129 and 130; SEQ ID NOs: 131 and 132; SEQ ID NOs: 133 and 134; SEQ ID NOs: 135 and 136; SEQ ID NOs: 137 and 138; SEQ ID NOs: 139 and 140; SEQ ID NOs: 141 and 142; SEQ ID NOs: 143 and 144; SEQ ID NOs: 145 and 146; SEQ ID NOs: 147 and 148; SEQ ID NOs: 151 and 152; SEQ ID NOs: 153 and 154; SEQ ID NOs: 155 and 156; SEQ ID NOs: 157 and 158; SEQ ID NOs: 159 and 160; SEQ ID NOs: 161 and 162; SEQ ID NOs: 163 and 164; SEQ ID NOs: 165 and 166; SEQ ID NOs: 169 and 170; SEQ ID NOs: 171 and 172; SEQ ID NOs: 173 and 174; SEQ ID NOs: 177 and 178; SEQ ID NOs: 179 and 180; SEQ ID NOs: 181 and 182; SEQ ID NOs: 183 and 184; SEQ ID NOs: 187 and 188; SEQ ID NOs: 189 and 190; SEQ ID NOs: 191

and 192; SEQ ID NOs: 193 and 104: SEQ ID NOs: 195 and 196; SEQ ID NOs: 197 and 198; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202; SEQ ID NOs: 203 and 204; SEQ ID NOs: 205 and 206; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; or SEQ ID NOs: 215 and 216.

4. A serotype-specific human monoclonal antibody derived from a plasmablast capable of specifically binding to an E protein of one or two dengue virus serotypes with higher affinity compared to E proteins of other dengue virus serotypes, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NO: 109 and SEQ ID NO: 110; SEQ ID NO: 111 and SEQ ID: NO 112; SEQ ID NO: 119 and SEQ ID NO: 120: SEQ ID NO: 125 and SEQ ID NO: 126; SEQ ID NO: 149 and SEQ ID NO: 150; SEQ ID NO: 153 and SEQ ID NO: 154; SEQ ID NO: 167 and SEQ ID NO: 168; SEQ ID NO: 175 and SEQ ID NO: 176;SEQ ID NO: 185 or SEQ ID NO: 186.

5. A serotype-specific human monoclonal antibody derived from a memory B lymphocyte capable of specifically binding to an E protein of one or two dengue virus serotypes with higher affinity compared to E proteins of other dengue virus serotypes, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NO: 193 and SEQ ID NO: 194; SEQ ID NO: 195 and SEQ ID NO: 196; SEQ ID NO: 197 or 198; or SEQ ID NO: 205 and SEQ ID NO: 206

6. The monoclonal antibody of any one of ~~embodiments~~examples 1 to 5, wherein the antibody comprises full heavy and light chain variable domain sequences from said pair.

7. A bi-specific antibody comprising a variable domain of a first monoclonal antibody linked to a variable domain of a second monoclonal antibody, wherein the first and second antibody each comprise all CDR sequences from one pair of heavy and light chain variable domain peptide sequences according to any one of ~~embodiments~~examples 1 to 6.

8. A bispecific antibody comprising a variable domain of a first monoclonal antibody linked to a variable domain of a second monoclonal antibody, wherein first and second antibodies are a combination as defined in Table 5 or Table 6.

9. A pharmaceutical composition or kit comprising the antibody of any one of ~~embodiments~~ examples 1 to 8.

10. An isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the heavy chain variable domain of a single clone designated in Figure 20, 21 or 22.

11. An isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the light chain heavy chain variable domain of a single clone designated in Figure 20, 21 or 22.

12. An isolated polynucleotide encoding an antibody according to any one of ~~embodiments~~examples 1 to 8.

13. Use of the antibody according to any one of ~~embodiments~~examples 1 to 8 for prevention, treatment or diagnosis of dengue virus infection.

14. Use of the antibody according to any one of ~~embodiments~~examples 1 to 8 in the preparation of a medicament for prevention or treatment of dengue virus infection.

15. The use according to ~~embodiment~~ example 13 or ~~embodiment~~ example 14, wherein the antibody comprises:

all CDR sequences from any one or more of the following pairs of heavy and light chain variable domain peptide sequences (SEQ ID NOs: 109 and 110; SEQ ID NOs: 111 and 112; SEQ ID NOs: 117 and 118; SEQ ID NOs: 119 and 120; SEQ ID NOs: 125 and 126; SEQ ID NOs: 149 and 150; SEQ ID NOs: 153 and 154; SEQ ID NOs: 167 and 168; SEQ ID NOs: 175 and 176; SEQ ID NOs: 185 and 186; SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 193 and 194; SEQ ID NOs: 195 and 196; SEQ ID NOs: 197 and 198; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202: SEQ ID NOs: 203 and 204; SEQ ID NOs: 205 and 206; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; SEQ ID NOs: 215 and 216; or

a series of heavy and light chain variable domain CDR sequences in accordance with any one clone as designated in **Figure 22** herein.

16. An antibody according to any one of ~~embodiments~~examples 1 to 8 for use in the prevention or treatment of dengue virus infection.

17. The antibody according to ~~embodiment~~ example 16, wherein the antibody comprises:

all CDR sequences from any one or more of the following pairs of heavy and light chain variable domain peptide sequences (SEQ ID NOs: 109 and 110; SEQ ID NOs: 111 and 112; SEQ ID NOs: 117 and 118; SEQ ID NOs: 119 and 120; SEQ ID NOs: 125 and 126; SEQ ID NOs: 149 and 150; SEQ ID NOs: 153 and 154; SEQ ID NOs: 167 and 168; SEQ ID NOs: 175 and 176; SEQ ID NOs: 185 and 186; SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 193 and 194; SEQ ID NOs: 195 and 196; SEQ ID NOs: 197 and 198; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202: SEQ ID NOs: 203 and 204; SEQ ID NOs: 205 and 206; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209

and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; SEQ ID NOs: 215 and 216; or

a series of heavy and light chain variable domain CDR sequences in accordance with any one clone as designated in **Figure 22** herein.

18. The use according to any one of ~~embodiments~~examples 13 to 15, or the antibody according to claim 16 or claim 17, wherein said antibody comprises full heavy and light chain variable domain sequences from said pair

19. A method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a dengue virus E protein,

contacting the E protein coated to the support with a first antibody comprising:

an antibody according to any one of ~~embodiments~~examples 1 to 8; and

the biological sample of the subject;

and detecting a presence or absence of competitive binding to the E protein between the first antibody and an antibody specific to the E protein that may be present in the sample,

wherein detection of said competitive binding indicates pre-existing immunity to dengue virus in the subject.

20. The method according to ~~embodiment~~ example 19, comprising:

coating four of said insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated to each said isolated insoluble support with said first antibody and said biological sample; and

determining the amount of first antibody bound to the E protein coated on each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

21. The method according to ~~embodiment~~ example 20, comprising:

coating four of said insoluble supports with E protein, wherein each said support is coated with E protein from the same dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated to each said isolated insoluble support with said first antibody, said biological sample and soluble E protein of a specific dengue virus serotype,

wherein each said isolated insoluble support is contacted with soluble E protein from a different dengue virus serotype; and

determining the amount of first antibody bound to the E protein of each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the soluble E protein contacted with the E protein to which less first antibody is bound.

22. A method for detecting immunity to dengue virus in a subject, comprising:

coating four insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated on each said isolated support with a biological sample from the subject, and, a first antibody according to any one of claims 1 to 8;

wherein the first antibody contacted with the E protein coated on each said isolated insoluble support binds specifically to that said E protein, and cannot bind to an E protein coated to any other of said supports;

determining the amount of first antibody bound to the E protein of each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

23. The method according to ~~embodiment~~ example 22, wherein said first antibody is an antibody according to claim 4.

24. The method according to any one of ~~embodiments~~examples 19 to 23, wherein any one or more of said insoluble supports is a bead or a well in culture plate.

25. The method according to any one of ~~embodiments~~examples 19 to 24, wherein the first antibody is labelled with a detectable marker.

26. A method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a first antibody comprising all heavy and light chain variable domain CDR sequences from an antibody according to any one of ~~embodiments~~ examples 1 to 8;

contacting the first antibody coated on the support with dengue virus particles to thereby allow said virus particles to bind to said first antibody;

contacting the virus particles with a biological sample from the subject to thereby allow any dengue virus-specific antibodies that may be present in said sample to bind to said virus particles; and

detecting whether said virus particles are bound by any said dengue virus-specific antibodies to thereby determine whether immunity to dengue virus exists in the subject.

27. The method according to ~~embodiment~~ example 26, wherein the first antibody is only capable of binding to an E protein from one dengue virus serotype.

28. The method according to any one of ~~embodiments~~ examples 19 to 25, or embodiment 27, wherein the E protein is E domain III (EDIII) protein.

In one aspect, the present invention refers to a human monoclonal antibody capable of specifically binding to an envelope (E) protein of at least one dengue virus serotype, wherein the antibody comprises a light chain variable domain sequence comprising the first, second, and third complementarity determining region (CDR) sequences of clone 11E1 defined in Figure 20 or 22.

In another aspect, the present invention refers to a serotype-specific human monoclonal antibody derived from a plasmablast capable of specifically binding to an E protein of one or two dengue virus serotypes with higher affinity compared to E proteins of other dengue virus serotypes, wherein the antibody comprises all CDR sequences from the following heavy and light chain variable domain peptide sequences: SEQ ID NO: 109 and SEQ ID NO: 110.

In another aspect, the present invention refers to a bi-specific antibody comprising a variable domain of a first monoclonal antibody as defined in claim 1 linked to a variable domain of a second monoclonal antibody, wherein the first and second antibody each comprise all CDR sequences from one pair of heavy and light chain variable domain peptide sequences as described above.

In another aspect, the present invention refers to a bi-specific antibody comprising a variable domain of a first monoclonal antibody linked to a variable domain of a second monoclonal antibody, wherein first and second antibodies are a combination as defined in Table 5 or Table 6.

In another aspect, the present invention refers to a pharmaceutical composition or kit comprising the antibody as described above.

In another aspect, the present invention refers to an isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the heavy chain variable domain of the clone defined in claim 1.

In another aspect, the present invention refers to an isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the light chain heavy chain variable domain of the clone defined in claim 1.

In another aspect, the present invention refers to an isolated polynucleotide encoding an antibody.

In another aspect, the present invention refers to use of the antibody in the manufacture of a medicament for prevention or treatment of dengue virus infection.

In another aspect, the present invention refers to an antibody for use in the prevention or treatment of dengue virus infection.

In another aspect, the present invention refers to an *in vitro* method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a dengue virus E protein,

contacting the E protein coated to the support with a first antibody comprising:

an antibody according to the present invention; and

the biological sample of the subject;

and detecting a presence or absence of competitive binding to the E protein between the first antibody and an antibody specific to the E protein that may be present in the sample,

wherein detection of said competitive binding indicates pre-existing immunity to dengue virus in the subject.

In another aspect, the present invention refers to an *in vitro* method for detecting immunity to dengue virus in a subject, comprising:

coating four insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated on each said isolated support with a biological sample from the subject, and, a first antibody according to the present invention;

wherein the first antibody contacted with the E protein coated on each said isolated insoluble support binds specifically to that said E protein, and cannot bind to an E protein coated to any other of said supports;

determining the amount of first antibody bound to the E protein of each said isolated insoluble support; wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

In another aspect, the present invention refers to an *in vitro* method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a first antibody comprising all heavy and light chain variable domain CDR sequences from an antibody according to the present invention;

contacting the first antibody coated on the support with dengue virus particles to thereby allow said virus particles to bind to said first antibody;

contacting the virus particles with a biological sample from the subject to thereby allow any dengue virus-specific antibodies that may be present in said sample to bind to said virus particles; and

detecting whether said virus particles are bound by any said dengue virus-specific antibodies to thereby determine whether immunity to dengue virus exists in the subject.

Brief Description of the Drawings

Preferred embodiments of the present invention will now be described, by way of example only, with reference to the accompanying figures wherein:Figure 1 shows cross-reactive plasmablasts after secondary dengue infection. A) Experimental setup: individual plasmablasts were sorted into 96 well plates for Ig variable gene sequencing, cloning and expression of antibodies. B) ELISA to test DENV-specificity of recombinantly expressed mAbs. For each mAb clone (x axes), the OD450 values for DENV1, 2, 3 and 4 are represented by an individual data bar. Serum pooled from several dengue-immune individuals was used as a positive control. C) Representative clone 1B-H1L1 is shown for immunohistology with DENV-infected BHK-21 cells. Serum pooled from several dengue-immune individuals was used as a positive control and chikungunya-specific 5C-RF was used as a negative control. Clones showing a staining intensity and frequency comparable to the positive control were considered positive. D) 77% of the mAbs derived from patient 10/63 bound to DENV1, 2, 3, or 4 (as assessed by ELISA and/or histology). Cells were sorted at day 4 after onset of fever. Similarly, 60% of mAbs derived from patient 10/50 bound to DENV1, 2, 3, or 4 (as assessed by ELISA and/or histology). Cells were sorted at day 6 after onset of fever.

CLAIMS:

1. A human monoclonal antibody capable of specifically binding to an envelope (E) protein of at least one dengue virus serotype, wherein the antibody comprises a light chain variable domain sequence comprising the first, second, and third complementarity determining region (CDR) sequences of clone 11E1 defined in Figure 20 or 22.

2. A serotype-specific human monoclonal antibody derived from a plasmablast capable of specifically binding to an E protein of one or two dengue virus serotypes with higher affinity compared to E proteins of other dengue virus serotypes, wherein the antibody comprises all CDR sequences from the following heavy and light chain variable domain peptide sequences: SEQ ID NO: 109 and SEQ ID NO: 110.

3. The monoclonal antibody of any one of claims 1 to 2, wherein the antibody comprises full heavy and light chain variable domain sequences from said pair.

4. A bi-specific antibody comprising a variable domain of a first monoclonal antibody as defined in claim 1 linked to a variable domain of a second monoclonal antibody, wherein the first and second antibody each comprise all CDR sequences from one pair of heavy and light chain variable domain peptide sequences according to any one of claims 1 to 3.

5. A bi-specific antibody comprising a variable domain of a first monoclonal antibody as defined in claim 1 linked to a variable domain of a second monoclonal antibody, wherein first and second antibodies are a combination as defined in Table 5 or Table 6.

6. A pharmaceutical composition or kit comprising the antibody of any one of claims 1 to5.

7. An isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the heavy chain variable domain of the clone defined in claim 1.

8. An isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the light chain heavy chain variable domain of the clone defined in claim 1.

9. An isolated polynucleotide encoding an antibody according to any one of claims 1 to 5.

10. Use of the antibody according to any one of claims 1 to 5 in the manufacture of a medicament for prevention or treatment of dengue virus infection.

11. The use according to claim 10, wherein the antibody comprises:

all CDR sequences from the following pair of heavy and light chain variable domain peptide sequences SEQ ID NOs: 109 and 110.

12. An antibody according to any one of claims 1 to 5 for use in the prevention or treatment of dengue virus infection.

13. The antibody according to claim 12, wherein the antibody comprises:

all CDR sequences from the following pair of heavy and light chain variable domain peptide sequences SEQ ID NOs: 109 and 110.

14. The use according to any one of claims 10 to 11, or the antibody according to claim 12 or claim 13, wherein said antibody comprises full heavy and light chain variable domain sequences from said pair.

15. An *in vitro* method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a dengue virus E protein,

contacting the E protein coated to the support with a first antibody comprising:

an antibody according to any one of claims 1 to 5; and

the biological sample of the subject;

and detecting a presence or absence of competitive binding to the E protein between the first antibody and an antibody specific to the E protein that may be present in the sample,

wherein detection of said competitive binding indicates pre-existing immunity to dengue virus in the subject.

16. The method according to claim 15, comprising:

coating four of said insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated to each said isolated insoluble support with said first antibody and said biological sample; and

determining the amount of first antibody bound to the E protein coated on each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

17. The method according to claim 16, comprising:

coating four of said insoluble supports with E protein, wherein each said support is coated with E protein from the same dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated to each said isolated insoluble support with said first antibody, said biological sample and soluble E protein of a specific dengue virus serotype,

wherein each said isolated insoluble support is contacted with soluble E protein from a different dengue virus serotype; and

determining the amount of first antibody bound to the E protein of each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the soluble E protein contacted with the E protein to which less first antibody is bound.

18. An *in vitro* method for detecting immunity to dengue virus in a subject, comprising:

coating four insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated on each said isolated support with a biological sample from the subject, and, a first antibody according to any one of claims 1 to 5;

wherein the first antibody contacted with the E protein coated on each said isolated insoluble support binds specifically to that said E protein, and cannot bind to an E protein coated to any other of said supports;

determining the amount of first antibody bound to the E protein of each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

19. The method according to claim 18, wherein said first antibody is an antibody according to claim 4.

20. The method according to any one of claims 15 to 19, wherein any one or more of said insoluble supports is a bead or a well in culture plate.

21. The method according to any one of claims 15 to 20, wherein the first antibody is labelled with a detectable marker.

22. An *in vitro* method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a first antibody comprising all heavy and light chain variable domain CDR sequences from an antibody according to any one of claims 1 to 5;

contacting the first antibody coated on the support with dengue virus particles to thereby allow said virus particles to bind to said first antibody;

contacting the virus particles with a biological sample from the subject to thereby allow any dengue virus-specific antibodies that may be present in said sample to bind to said virus particles; and

detecting whether said virus particles are bound by any said dengue virus-specific antibodies to thereby determine whether immunity to dengue virus exists in the subject.

23. The method according to claim 22, wherein the first antibody is only capable of binding to an E protein from one dengue virus serotype.

24. The method according to any one of claims 15 to 21, or claim 23, wherein the E protein is E domain III (EDIII) protein.

CLAIMS:

1. A human monoclonal antibody capable of specifically binding to an envelope (E) protein of at least one dengue virus serotype, wherein the antibody comprises a light chain variable domain sequence comprising the first, second, and third complementarity determining region (CDR) sequences of a single clone designated in Figure 20, 21 or 22.

2. A cross-reactive human monoclonal antibody derived from a memory B lymphocyte capable of specifically binding to an E protein of at least one dengue virus serotype, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202; SEQ ID NOs: 203 and 204; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; or SEQ ID NOs: 215 and 216.

3. A cross-reactive human monoclonal antibody derived from a plasmablast capable of specifically binding to an E protein of at least one dengue virus serotype, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NOs: 113 and 114; SEQ ID NOs: 115 and 116; SEQ ID NOs: 121 and 122; SEQ ID NOs: 123 and 124; SEQ ID NOs: 127 and 128; SEQ ID NOs: 129 and 130; SEQ ID NOs: 131 and 132; SEQ ID NOs: 133 and 134; SEQ ID NOs: 135 and 136; SEQ ID NOs: 137 and 138; SEQ ID NOs: 139 and 140; SEQ ID NOs: 141 and 142; SEQ ID NOs: 143 and 144; SEQ ID NOs: 145 and 146; SEQ ID NOs: 147 and 148; SEQ ID NOs: 151 and 152; SEQ ID NOs: 153 and 154; SEQ ID NOs: 155 and 156; SEQ ID NOs: 157 and 158; SEQ ID NOs: 159 and 160; SEQ ID NOs: 161 and 162; SEQ ID NOs: 163 and 164; SEQ ID NOs: 165 and 166; SEQ ID NOs: 169 and 170; SEQ ID NOs: 171 and 172; SEQ ID NOs: 173 and 174; SEQ ID NOs: 177 and 178; SEQ ID NOs: 179 and 180; SEQ ID NOs: 181 and 182; SEQ ID NOs: 183 and 184; SEQ ID NOs: 187 and 188; SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 193 and 104: SEQ ID NOs: 195 and 196; SEQ ID NOs: 197 and 198; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202; SEQ ID NOs: 203 and 204; SEQ ID NOs: 205 and 206; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; or SEQ ID NOs: 215 and 216.

4. A serotype-specific human monoclonal antibody derived from a plasmablast capable of specifically binding to an E protein of one or two dengue virus serotypes with higher affinity compared to E proteins of other dengue virus serotypes, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light

chain variable domain peptide sequences: SEQ ID NO: 109 and SEQ ID NO: 110; SEQ ID NO: 111 and SEQ ID: NO 112; SEQ ID NO: 119 and SEQ ID NO: 120: SEQ ID NO: 125 and SEQ ID NO: 126; SEQ ID NO: 149 and SEQ ID NO: 150; SEQ ID NO: 153 and SEQ ID NO: 154; SEQ ID NO: 167 and SEQ ID NO: 168; SEQ ID NO: 175 and SEQ ID NO: 176;SEQ ID NO: 185 or SEQ ID NO: 186.

5. A serotype-specific human monoclonal antibody derived from a memory B lymphocyte capable of specifically binding to an E protein of one or two dengue virus serotypes with higher affinity compared to E proteins of other dengue virus serotypes, wherein the antibody comprises all CDR sequences from one pair of the following heavy and light chain variable domain peptide sequences: SEQ ID NO: 193 and SEQ ID NO: 194; SEQ ID NO: 195 and SEQ ID NO: 196; SEQ ID NO: 197 or 198; or SEQ ID NO: 205 and SEQ ID NO: 206

6. The monoclonal antibody of any one of claims 1 to 5, wherein the antibody comprises full heavy and light chain variable domain sequences from said pair.

7. A bi-specific antibody comprising a variable domain of a first monoclonal antibody linked to a variable domain of a second monoclonal antibody, wherein the first and second antibody each comprise all CDR sequences from one pair of heavy and light chain variable domain peptide sequences according to any one of claims 1 to 6.

8. A bispecific antibody comprising a variable domain of a first monoclonal antibody linked to a variable domain of a second monoclonal antibody, wherein first and second antibodies are a combination as defined in Table 5 or Table 6.

9. A pharmaceutical composition or kit comprising the antibody of any one of claims 1 to 8.

10. An isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the heavy chain variable domain of a single clone designated in Figure 20, 21 or 22.

11. An isolated polynucleotide encoding first, second, and third complementarity determining region (CDR) sequences in the light chain heavy chain variable domain of a single clone designated in Figure 20, 21 or 22.

12. An isolated polynucleotide encoding an antibody according to any one of claims 1 to 8.

13. Use of the antibody according to any one of claims 1 to 8 for prevention, treatment or diagnosis of dengue virus infection.

14. Use of the antibody according to any one of claims 1 to 8 in the preparation of a medicament for prevention or treatment of dengue virus infection.

15. The use according to claim 13 or claim 14, wherein the antibody comprises:

all CDR sequences from any one or more of the following pairs of heavy and light chain variable domain peptide sequences (SEQ ID NOs: 109 and 110; SEQ ID NOs: 111 and 112; SEQ ID NOs: 117 and 118; SEQ ID NOs: 119 and 120; SEQ ID NOs: 125 and 126; SEQ ID NOs: 149 and 150; SEQ ID NOs: 153 and 154; SEQ ID NOs: 167 and 168; SEQ ID NOs: 175 and 176; SEQ ID NOs: 185 and 186; SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 193 and 194; SEQ ID NOs: 195 and 196; SEQ ID NOs: 197 and 198; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202: SEQ ID NOs: 203 and 204; SEQ ID NOs: 205 and 206; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; SEQ ID NOs: 215 and 216; or

a series of heavy and light chain variable domain CDR sequences in accordance with any one clone as designated in **Figure 22** herein.

16. An antibody according to any one of claims 1 to 8 for use in the prevention or treatment of dengue virus infection.

17. The antibody according to claim 16, wherein the antibody comprises:

all CDR sequences from any one or more of the following pairs of heavy and light chain variable domain peptide sequences (SEQ ID NOs: 109 and 110; SEQ ID NOs: 111 and 112; SEQ ID NOs: 117 and 118; SEQ ID NOs: 119 and 120; SEQ ID NOs: 125 and 126; SEQ ID NOs: 149 and 150; SEQ ID NOs: 153 and 154; SEQ ID NOs: 167 and 168; SEQ ID NOs: 175 and 176; SEQ ID NOs: 185 and 186; SEQ ID NOs: 189 and 190; SEQ ID NOs: 191 and 192; SEQ ID NOs: 193 and 194; SEQ ID NOs: 195 and 196; SEQ ID NOs: 197 and 198; SEQ ID NOs: 199 and 200; SEQ ID NOs: 201 and 202: SEQ ID NOs: 203 and 204; SEQ ID NOs: 205 and 206; SEQ ID NOs: 207 and 208; SEQ ID NOs: 209 and 210; SEQ ID NOs: 211 and 212; SEQ ID NOs: 213 and 214; SEQ ID NOs: 215 and 216; or

a series of heavy and light chain variable domain CDR sequences in accordance with any one clone as designated in **Figure 22** herein.

18. The use according to any one of claims 13 to 15, or the antibody according to claim 16 or claim 17, wherein said antibody comprises full heavy and light chain variable domain sequences from said pair

19. A method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a dengue virus E protein,

contacting the E protein coated to the support with a first antibody comprising:

an antibody according to any one of claims 1 to 8; and

the biological sample of the subject;

and detecting a presence or absence of competitive binding to the E protein between the first antibody and an antibody specific to the E protein that may be present in the sample,

wherein detection of said competitive binding indicates pre-existing immunity to dengue virus in the subject.

20. The method according to claim 19, comprising:

coating four of said insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated to each said isolated insoluble support with said first antibody and said biological sample; and

determining the amount of first antibody bound to the E protein coated on each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

21. The method according to claim 20, comprising:

coating four of said insoluble supports with E protein, wherein each said support is coated with E protein from the same dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated to each said isolated insoluble support with said first antibody, said biological sample and soluble E protein of a specific dengue virus serotype,

wherein each said isolated insoluble support is contacted with soluble E protein from a different dengue virus serotype; and

determining the amount of first antibody bound to the E protein of each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the soluble E protein contacted with the E protein to which less first antibody is bound.

22. A method for detecting immunity to dengue virus in a subject, comprising:

coating four insoluble supports with E protein, wherein each said support is coated with E protein from a distinct dengue virus serotype, and each said support is isolated from all other said supports;

contacting the E protein coated on each said isolated support with a biological sample from the subject, and, a first antibody according to any one of claims 1 to 8;

wherein the first antibody contacted with the E protein coated on each said isolated insoluble support binds specifically to that said E protein, and cannot bind to an E protein coated to any other of said supports;

determining the amount of first antibody bound to the E protein of each said isolated insoluble support;

wherein detection of less first antibody bound to the E protein coated on one of said supports when compared to at least one other of said supports indicates pre-existing immunity to dengue virus in the subject,

and wherein said pre-existing immunity is specific to the dengue serotype of the E protein to which less first antibody is bound.

23. The method according to claim 22, wherein said first antibody is an antibody according to claim 4.

24. The method according to any one of claims 19 to 23, wherein any one or more of said insoluble supports is a bead or a well in culture plate.

25. The method according to any one of claims 19 to 24, wherein the first antibody is labelled with a detectable marker.

26. A method for detecting immunity to dengue virus in a subject, comprising:

coating at least one insoluble support with a first antibody comprising all heavy and light chain variable domain CDR sequences from an antibody according to any one of claims 1 to 8;

contacting the first antibody coated on the support with dengue virus particles to thereby allow said virus particles to bind to said first antibody;

contacting the virus particles with a biological sample from the subject to thereby allow any dengue virus-specific antibodies that may be present in said sample to bind to said virus particles; and

detecting whether said virus particles are bound by any said dengue virus-specific antibodies to thereby determine whether immunity to dengue virus exists in the subject.

27. The method according to claim 26, wherein the first antibody is only capable of binding to an E protein from one dengue virus serotype.

28. The method according to any one of claims 19 to 25, or claim 27, wherein the E protein is E domain III (EDIII) protein.