The different serotypes of dengue virus differ at the amino acid level by about 25-40% and have antigenic differences, and this variation has hindered efforts to produce a therapy effective against all serotypes.

All four dengue virus serotypes display an E (envelope) protein on the viral surface. The E protein contributes to the attachment of the virus to a host cell. The E protein comprises a DI domain (a nine-stranded beta-barrel) a DII domain (a domain implicated in fusion with the host cell), and a DIII domain (an immunoglobulin-like domain). The humoral response to E protein in humans generally targets the DI and DII regions, with much of the antibodies exhibiting high cross-serotype reactivity but low neutralization activity.

There is a need in the art for new prophylactic and therapeutic treatments for dengue virus, and especially for treatments that are effective against all four serotypes of the virus.

SUMMARY

This disclosure provides, at least in part, antibody molecules that bind to the dengue virus, for example, the dengue virus E protein, and which comprise functional and structural properties disclosed herein. In some embodiments, the antibody molecules bind to the "A" beta-strand of EDIII (the E protein DIII domain). In some embodiments, the antibody molecules bind to and/or neutralize at least 1, 2, 3, or 4 dengue virus serotypes, *e.g.,* DV-1, DV-2, DV-3, and DV-4. In some embodiments, the antibody molecule is selected from Table 1. In some embodiments, the antibody molecules comprise a deletion of VH S26 and/or a VH T33V substitution compared to antibody A11. These mutations, in some embodiments, may improve one or more properties, *e.g.,* improve antibody affinity for one or more dengue virus serotypes, for example serotype DV-4. In some embodiments, the antibody molecule targets a site on EDIII that is conserved across all four dengue serotypes. Nucleic acid molecules encoding the antibody molecules, expression vectors, host cells, pharmaceutical compositions, and methods for making the antibody molecules are also provided. The anti-dengue antibody molecules disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose dengue virus, *e.g.,* DV-1, DV-2, DV-3, or DV-4.

Accordingly, in certain ~~aspects~~embodiments, this disclosure provides an antibody molecule (*e.g.,* an isolated, recombinant, or humanized antibody molecule) having one or more (*e.g.,* 1, 2, 3, 4, 5, 6,

sequence of Table 2. In some embodiments, an antibody molecule has a structural feature discussed in this paragraph and one or more advantageous properties such as an improved (*e.g.*, relative to A11) affinity for or neutralization activity towards dengue virus, *e.g.*, DV-4. In some embodiments, the advantageous property is a property of List 1, *e.g.*, one or more (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all) of properties (a), (b), (c), (d), (e), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), or (x).

In ~~aspects~~ embodiments, the antibody molecule has a VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 selected from Table 3. The six CDRs may all be Kabat-defined, all Chothia-defined, or some Kabat- and some Chothia-defined. For instance, VHCDR1 may be selected from SEQ ID NO: 3, 9, 14, 15, 22, 24, 26, 28, or 30; VHCDR2 may be selected from SE$Q ID NO: 4, 10, or 35; VHCDR3 may be SEQ ID NO: 5; VLCDR1 may be SEQ ID NO: 6; VLCDR2 may be SEQ ID NO: 7; and VLCDR3 may be SEQ ID NO: 8.

In certain embodiments, the light or the heavy chain variable framework of the anti-dengue antibody can be chosen from: (a) a light or heavy chain variable framework including at least 80%, 85%, 87% 90%, 92%, 93%, 95%, 97%, 98%, or preferably 100% of the amino acid residues from a human light or heavy chain variable framework, *e.g.*, a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (b) a light or heavy chain variable framework including from 20% to 80%, 40% to 60%, 60% to 90%, or 70% to 95% of the amino acid residues from a human light or heavy chain variable framework, *e.g.*, a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (c) a non-human framework (*e.g.*, a rodent framework); or (d) a non-human framework that has been modified, *e.g.*, to remove antigenic or cytotoxic determinants, *e.g.*, deimmunized, or partially humanized. In some embodiments, the light or heavy chain variable framework region includes a light or heavy chain variable framework sequence at least 70, 75, 80, 85, 87, 88, 90, 92, 94, 95, 96, 97, 98, 99% identical or identical to the frameworks of a VH or VL segment of a human germline gene. In some embodiments, an antibody molecule has a structural feature discussed in this paragraph and one or more advantageous properties such as an improved (*e.g.*, relative to A11) affinity for or neutralization activity towards dengue virus, *e.g.*, DV-4. In some embodiments, the advantageous property is a property of List 1, *e.g.*, one or more (*e.g.*, two,

herein. This application also discloses the heavy or light chain variable region, or both, of the anti-dengue antibody molecule includes an amino acid sequence encoded by a nucleic acid sequence of Table 4, or its complement, *e.g.*, under low stringency, medium stringency, or high stringency, or other hybridization condition described herein. In some embodiments, the nucleic acid is at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical to a sequence of Table 4 or a portion thereof. In some embodiments, an antibody molecule has a structural feature discussed in this paragraph and one or more advantageous properties such as an improved (*e.g.*, relative to A11) affinity for or neutralization activity towards dengue virus, *e.g.*, DV-4. In some embodiments, the advantageous property is a property of List 1, *e.g.*, one or more (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all) of properties (a), (b), (c), (d), (e), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), or (x).

In certain embodiments, the anti-dengue antibody molecule comprises at least one, two, three, or four antigen-binding regions, *e.g.*, variable regions, having an amino acid sequence as set forth in Table 2, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the sequences shown in Table 2). In certain embodiments, the anti-dengue antibody molecule includes a VH and/or VL domain encoded by a nucleic acid having a nucleotide sequence that encodes an antibody of Table 1, *e.g.*, D88, A48, F38, F108, or C88, or a sequence substantially identical to any one of the nucleotide sequences (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from any one of the nucleotide sequences). In some embodiments, an antibody molecule has a structural feature discussed in this paragraph and one or more advantageous properties such as an improved (*e.g.*, relative to A11) affinity for or neutralization activity towards dengue virus, *e.g.*, DV-4. In some embodiments, the advantageous property is a property of List 1, *e.g.*, one or more (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all) of properties (a), (b), (c), (d), (e), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), or (x).

In certain ~~aspects~~embodiments, the present disclosure provides an antibody molecule, optionally capable of binding dengue virus, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence D**V**YMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that **V** is unchanged),

a CDR2 comprising the sequence RIDPENGDTKYDPK**L**QG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **L** is unchanged), and

a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom);

(b) a light chain variable region segment comprising:

a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom),

a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and

a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

In an aspect, the present disclosure provides an antibody molecule capable of binding dengue virus, comprising: (a) a heavy chain immunoglobulin variable region segment comprising: a CDR1 comprising the sequence DVYMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, provided that V is unchanged), a CDR2 comprising the sequence RIDPENGDTKYDPKLQG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that L is unchanged), and a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and (b) a light chain immunoglobulin variable region segment comprising: a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom), a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

In another aspect, the present disclosure provides an antibody molecule capable of binding dengue virus, comprising: (a) a heavy chain immunoglobulin variable region segment comprising: a CDR1 comprising the sequence DVYMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that V is unchanged), a CDR2 comprising the sequence RIDPENGDTKYDPKLQG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, provided that L is unchanged), and a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and (b) a light chain immunoglobulin variable region segment comprising: a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom), a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

In some embodiments, V of HCDR1 is unchanged; in some embodiments, L of HCDR2 is unchanged, and in some embodiments, both V of HCDR1 and L of HCDR2 are unchanged.

In certain embodiments, the antibody molecule comprises a VH FR1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 11.

In certain embodiments, the antibody molecule comprises a VH FR2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 84. In certain embodiments, the antibody molecule comprises a VH FR2 having the sequence WVRQAPEQGLEWMG (SEQ ID NO: 85), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 85.

In certain ~~aspects~~embodiments, the present disclosure provides an antibody molecule capable of binding dengue virus, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a FW1 comprising a deletion of position 26 relative to SEQ ID NO: 33;

a CDR1 comprising the sequence D**T**YMS (SEQ ID NO: 14) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that **T** is unchanged), or a CDR1 comprising the sequence D**V**YMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that **V** is unchanged),

a CDR2 comprising the sequence RIDPENGDTKYDPK**L**QG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **L** is unchanged), and

a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and

(b) a light chain variable region segment comprising:

a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom),

a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and

a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

In an aspect, the present disclosure provides an antibody molecule capable of binding dengue virus, comprising: (a) a heavy chain immunoglobulin variable region segment comprising: a FR1 comprising a deletion of position 26 relative to SEQ ID NO: 33; a CDR1 comprising the sequence DVYMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that V is unchanged), a CDR2 comprising the sequence RIDPENGDTKYDPKLQG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that L is unchanged), and a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and (b) a light chain immunoglobulin variable region segment comprising: a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom), a

CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

In certain embodiments, the antibody molecule comprises a VH FR2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 84. In certain embodiments, the antibody molecule comprises a VH FR2 having the sequence WVRQAPEQGLEWMG (SEQ ID NO: 85), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 85.

In certain ~~aspects~~embodiments, the present disclosure provides an antibody molecule, optionally capable of binding dengue virus, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence D**V**YMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that **V** is unchanged),

a CDR2 comprising the sequence RIDPENGDTKYDPK**L**QG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **L** is unchanged), and

In some embodiments, the antibody molecule is capable of binding to dengue virus EDIII with a dissociation constant (K_D) of less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, or 0.1 nM. The antibody molecule may be capable of binding to dengue virus serotype DV-4 EDIII with a dissociation constant (K_D) of less than about 10, 8, 6, 5, 4, or 3 nM. The antibody molecule may be capable of binding to DV-3 or DV-4 EDIII domain with at least a 2, 3, 4, 5, 6, 8, 10, 12, 100, 1,000-fold greater affinity than antibody A11 or antibody 4E11. The antibody molecule may be capable of binding to a dengue virus strain chosen from one or more of DENV-4 BC2, DENV-4-Sing10, DENV-4 NewCal09, DENV-4 *Phil56*, DENV-3 *Sing09*, DENV-3 *Nic10*, DENV-3 *H87*, DENV-2 Peru95, DENV-2 Sing08, DENV-2 NGC, DENV-1 Hawaii/1944, DENV-2 New Guinea/1944 (NGC), DENV-3 *Philippines/1956 (H87)*, DENV-4 *Mexico/1997 (BC287/97)*, and DENV-4 *H241*, with at least 2, 3, 4, 5, 6, 8, 10, 12, 25, 50, 75, 100, or 1,000-fold greater affinity than antibody A11 or antibody 4E11. The antibody molecule may be capable of neutralizing dengue virus in a focus reduction neutralization test or a related test for evaluating neutralization of viral activity. The antibody molecule may be capable of neutralizing dengue virus with an IC50 that is at least 2, 3, 4, 5, 6, 8, 10, 12, 50, 75, or 100-fold lower than antibody A11 or antibody 4E11 in a focus reduction neutralization test or a related test for evaluating neutralization of viral activity.

In some aspects, the present disclosure provides a pharmaceutical composition comprising the antibody molecule as described herein~~of any of the above claims~~ and a pharmaceutically acceptable carrier, excipient, or stabilizer.

In an aspect, t~~T~~he present disclosure also provides~~, e.g.,~~ a nucleic acid encoding the antibody heavy or light chain variable region of an antibody molecule as described herein. In another aspect, t~~T~~he disclosure also provides~~, for example,~~ an expression vector comprising such a nucleic acid. In another aspect, t~~T~~he disclosure also provides~~, for example,~~ a host cell comprising such a nucleic acid. In another aspect, t~~T~~he present disclosure additionally provides~~, e.g.,~~ a method of producing an antibody molecule or fragment thereof as described herein, comprising culturing the host cell under conditions suitable for gene expression.

In some aspects, this disclosure provides a kit comprising an antibody molecule as described herein. The kit ~~may~~ comprises a container, and the container ~~may have~~ has the antibody molecule disposed therein. The kit ~~may~~ also comprises a pharmaceutically acceptable carrier,

excipient, or stabilizer, optionally admixed with the antibody molecule. The kit may also comprise a delivery device, *e.g.*, one comprising a syringe or needle. The kit may also comprise instructions for use.

In certain aspects, the present disclosure provides a method of neutralizing dengue virus, comprising: contacting the dengue virus with an antibody molecule as described herein. In some embodiments, the dengue virus is of serotype DV-1, DV-2, DV-3, or DV-4.

In some ~~aspects~~embodiments, the present disclosure provides a method of treating a dengue virus infection, comprising administering to a subject in need thereof an isolated antibody molecule as described herein, in an amount effective to treat the virus. The method may further comprise administering an anti-viral agent to the subject, *e.g.*, an anti-viral agent chosen from one or more of balapiravir, chloroquine, celgosivir, ivermectin, or Carica folia. In certain embodiments, the antiviral agent is a second anti-dengue antibody molecule, *e.g.*, an anti-dengue antibody molecule described herein different from a first anti-dengue antibody molecule. In other embodiments, the antiviral agent is selected from an alpha-glucosidase I inhibitor (*e.g.*, celgosivir), an adenosine nucleoside inhibitor (*e.g.*, NITD008); an RNA-dependent RNA polymerase (RdRp) inhibitor (*e.g.*, NITD107), an inhibitor of host pyrimidine biosynthesis, *e.g.*, host dihydroorotate dehydrogenase (DHODH) (*e.g.*, NITD-982 and brequinar), an inhibitor of viral NS4B protein (*e.g.*, NITD-618), and an iminosugar (*e.g.*, UV-4). The method may further comprise administering a vaccine to the subject, *e.g.*, a dengue virus vaccine. In some embodiments, administration of the antibody molecule is parenteral or intravenous. In an aspect, the present disclosure provides the use of an isolated antibody molecule as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating dengue virus in a subject.

The disclosure also provides prophylactic methods. In some embodiments, a method of preventing a dengue virus infection by administering an antibody molecule as disclosed herein to a subject who is not, at the time, infected with dengue virus. For instance, in certain ~~aspects~~embodiments, the present disclosure provides a method of reducing a patient's risk of contracting dengue virus, comprising administering to a subject in need thereof an isolated antibody molecule as described herein, in an amount effective to reduce the risk of contracting the virus. For example the risk of contracting dengue virus may be reduced by, *e.g.*, at least 25%, 50%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or more. In some embodiments, the antibody molecule is provided to a patient who is not infected with dengue virus, with the result that if infection occurs, the course of the disease is likely to be milder than the course of disease in a similar patient who has not

received the antibody molecule. For instance, the antibody molecule may reduce the risk of dengue fever developing (*e.g.*, the patient is more likely to experience an asymptomatic infection). The risk of dengue fever developing may be reduced, *e.g.*, by at least 25%, 50%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or more compared to a patient that did not receive the antibody molecule. In some embodiments, the risk of dengue fever progressing into dengue hemorrhagic fever may be reduced, *e.g.*, by at least 25%, 50%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or more compared to a patient that did not receive the antibody molecule. In an aspect, the present disclosure provides the use of an isolated antibody molecule as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for preventing dengue virus infection in a subject. In another aspect, the present disclosure provides the use of an isolated antibody molecule as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for reducing a patient's risk of contracting dengue virus. In another aspect, the present disclosure provides the use of an isolated antibody molecule as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for reducing transmission of dengue virus between a subject and a mosquito.

The disclosure also provides methods of reducing or preventing transmission of dengue virus (e.g., reducing or preventing transmission between a subject (*e.g.*, a human) and a mosquito. In certain embodiments, the subject is infected with dengue virus. In other embodiments, the subject is not, at the time, infected with dengue virus, but is at risk of dengue viral infection. For instance, in certain ~~aspects~~embodiments, the present disclosure provides a method of reducing or preventing transmission of dengue virus (*e.g.*, reducing or preventing transmission of dengue virus between a subject (*e.g.*, human) and a mosquito), comprising administering to a subject an isolated antibody molecule as described herein, in an amount effective to reduce the transmission of dengue virus. For example, the transmission of dengue virus, *e.g.*, from a subject to a mosquito, can be reduced by, *e.g.*, at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%, compared to the transmission from a subject that did not receive the antibody molecule, *e.g.*, as measured by a mosquito model described herein. As a result, in some embodiments, the transmission of dengue virus from an infected mosquito to an

uninfected subject (*e.g.*, human) can be further reduced, *e.g.*, at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

In certain aspects, this disclosure provides a method of detecting dengue virus in a biological sample, comprising (i) contacting the sample or the subject (and optionally, a reference sample or subject) with an antibody molecule described herein under conditions that allow interaction of the antibody molecule and the polypeptide to occur, and (ii) detecting formation of a complex between the antibody molecule and the sample or the subject (and optionally, the reference sample or subject).

In some ~~aspects~~embodiments, this disclosure provides an anti-dengue antibody molecule comprising a VH region that has a deletion of position 26 relative to the VH of antibody A11. For instance,

the anti-dengue antibody molecule of claim may have a VH region with between about 1-30, 5-30, 10-30, 15-30, or 20-25 mutations relative to a VH of antibody A11.

In some embodimentsaspects, this disclosure provides an antibody molecule capable of binding to dengue virus, which comprises a VH CDR1 having the sequence of SEQ ID NO: 3, or an amino acid sequence having no more than 1, 2, 3, 4, 5, 10, or 15 mutations relative to SEQ ID NO: 3. In some embodiments, the mutations are substitutions, *e.g.*, conservative substitutions.

In certain embodimentsaspects, this disclosure provides an antibody molecule capable of binding to dengue virus, which comprises a VH FR1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11), or an amino acid sequence having no more than 1, 2, 3, 4, 5, 10, or 15 mutations relative to SEQ ID NO: 11. In some embodiments, the mutations are independently selected from deletions and substitutions, *e.g.*, conservative substitutions. An antibody molecule of this paragraph may also have the features described throughout this application, *e.g.*, in the previous paragraph.

In some embodimentsaspects, this disclosure provides antibody molecules capable of binding to dengue virus, which comprises a VH CDR2 having the sequence of SEQ ID NO: 4, or an amino acid sequence having no more than 1, 2, 3, 4, 5, 10, or 15 mutations relative to SEQ ID NO: 4. In some embodiments, the mutations are substitutions, *e.g.*, conservative substitutions. An antibody molecule of this paragraph may also have the features described throughout this application, *e.g.*, in the previous two paragraphs.

In certain embodimentsaspects, this disclosure provides an antibody molecule capable of binding to dengue virus, which comprises a VH FR2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85), or an amino acid sequence having no more than 1, 2, 3, 4, 5, or 10 mutations relative to SEQ ID NO: 84 or SEQ ID NO: 85. In some embodiments, the mutations are independently selected from deletions and substitutions, *e.g.*, conservative substitutions. An antibody molecule of this paragraph may also have the features described throughout this application, *e.g.*, in the previous paragraph.

In some embodiments, the antibody molecule is capable of binding to EDIII of two or more, *e.g.*, three or four, dengue virus serotypes, *e.g.*, selected from DV-1, DV-2, DV-3, and DV-4, with a dissociation constant (K_D) of less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, or 0.01 nM for each of said two or more serotypes.

one or more (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all) of properties (a), (b), (c), (d), (e), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), or (x).

This disclosure also provides nucleic acid sequences, *e.g.*, a nucleic acid that hybridizes to a nucleic acid sequence that encodes an antibody of Table 1, *e.g.*, D88, A48, F38, F108, or C88, and its complement, *e.g.*, under low stringency, medium stringency, or high stringency, or other hybridization condition described herein. This application also discloses nucleic acid sequences of Table 4, and their complements, *e.g.*, under low stringency, medium stringency, or high stringency, or other hybridization condition described herein. In some embodiments, the nucleic acid is at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical to a sequence of Table 4, its complement, or a portion of any of the aforementioned sequences. In some embodiments, a nucleic acid having a structural feature discussed in this paragraph encodes an antibody molecule or portion thereof having one or more advantageous properties such as an improved (*e.g.*, relative to A11) affinity for or neutralization activity towards dengue virus, *e.g.*, DV-4. In some embodiments, the advantageous property is a property of List 1, *e.g.*, one or more (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all) of properties (a), (b), (c), (d), (e), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), or (x).

In certain embodimentsaspects, this disclosure features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell. The host cell can be a eukaryotic cell, *e.g.*, a mammalian cell, an insect cell, a yeast cell, or a prokaryotic cell, *e.g.*, *E. coli*. For example, the mammalian cell can be a cultured cell or a cell line. Exemplary mammalian cells include human cells *e.g.*, HEK293 cells, lymphocytic cell lines (*e.g.*, NS0), Chinese hamster ovary cells (CHO), COS cells, oocyte cells, and cells from a transgenic animal.

In some embodimentsaspects, the present disclosure provides a method of providing an antibody molecule described herein. The method may include: providing an antibody molecule that specifically binds to an EDIII antigen; making one or more mutations to the antibody (*e.g.*, to the constant region, framework, and/or CDRs) and evaluating if the antibody molecule specifically binds to the EDIII antigen, or evaluating efficacy of the antibody molecule in inhibiting dengue

virus function. The method can further include purifying the antibody molecule. For example, the antibody molecule can be purified by one or more chromatography steps comprising, *e.g.,* affinity chromatography, *e.g.,* Protein A chromatography. The method can further include administering the antibody molecule to a subject, *e.g.,* a human or non-human animal.

In certain embodiments~~aspects~~, *the disclosure provides, compositions, e.g.,* pharmaceutical compositions, which include a pharmaceutically acceptable carrier, excipient or stabilizer, and at least one of the anti-dengue antibody molecules described herein. In some embodiments, the antibody molecule is conjugated to a label or a therapeutic agent. In some embodiments, the compositions, *e.g.,* the pharmaceutical compositions, comprise a *combination of the antibody molecule and a second agent, e.g., a therapeutic agent, or two or* more of the aforesaid antibody molecules, as further described herein.

The antibody molecules disclosed herein can inhibit one or more activities of dengue virus. For instance, the antibody molecules may disrupt the native structure of the E protein on the surface of the virion, *e.g.,* causing inactivation of the virus. As a result, the antibody molecule may neutralize the virus, inhibit its ability to enter a host cell, or reduce viral stability. In some embodiments, an antibody molecule neutralizes dengue virus (*e.g.,* in a focus reduction neutralization test or a related test for evaluating neutralization of viral activity) with an EC50 or FRNT50 of less than or equal to 1400, 1000, 800, 600, 550, 500, 450, 400, 350, 300, 350, 200, 150, 100, 50, or 25 ng/ml. In some embodiments, the antibody neutralizes dengue virus (*e.g.,* in a focus reduction neutralization test or a related test for evaluating neutralization of viral activity) with an IC50 of less than or equal to 20, 17.6, 15, 10, 5, 4, 2, 1.4, 1, or 0.50 μg/mL. In some embodiments, neutralization of DV-4 is tested, and in some embodiments, neutralization of one of DV-1, DV-2, or DV-3 is tested.

The subject can be a mammal, e.g., a monkey, a primate, preferably a higher primate, *e.g.,* a human (*e.g.,* a patient having, or at risk of having, dengue virus).

This disclosure also provides a method of treating dengue virus in a subject, comprising administering to the subject an anti-dengue antibody molecule described herein, *e.g.,* a therapeutically effective amount of an anti-dengue antibody molecule, or an antigen-binding portion thereof. In some embodiments, the anti-dengue antibody molecule is administered to a patient suffering from dengue virus, resulting in the reduction of viral load and/or the reduction

of at least one symptom, *e.g.*, selected from sudden-onset fever, headache, muscle and joint pains, weight loss, central nervous system penetration, and/or rash. In some embodiments, the anti-dengue antibody molecule is administered to a patient at risk of being infected from dengue virus, resulting in the reduction of the risk of becoming infected or reduction of the severity of the infection if infection does occur.

The anti-dengue antibody molecule can be administered to the subject systemically (*e.g.*, orally, parenterally, subcutaneously, intravenously, rectally, intramuscularly, intraperitoneally, intranasally, transdermally, or by inhalation or intracavitary installation), topically, or by application to mucous membranes, such as the nose, throat and bronchial tubes.

The methods and compositions described herein can be used in combination with other therapeutic modalities. In some embodiments, the methods of described herein include administering to the subject an anti-dengue antibody molecule as described herein, in combination with a second treatment or prophylactic for dengue virus, in an amount effective to treat or prevent said disorder. The antibody molecule and the second agent can be administered simultaneously or sequentially.

Any combination and sequence of the anti-dengue antibody molecules and other therapeutic modalities can be used. The anti-dengue antibody molecule and/or other therapeutic modalities can be administered during periods of active infection, or during a period of remission or less active disease. The anti-dengue antibody molecule and other therapeutic modalities can be administered before treatment, concurrently with treatment, post-treatment, or during remission of the infection.

In some embodimentsaspects, the present disclosure provides methods for detecting the presence of dengue virus in a sample, *e.g.*, *in vitro* or *in vivo* (*e.g.*, a biological sample, *e.g.*, blood or serum). The methods herein can be used to evaluate (*e.g.*, monitor treatment or progression of, diagnose and/or stage a disorder described herein, *e.g.*, dengue virus, in a subject). The method may include: (i) contacting the sample with (and optionally, a reference, *e.g.*, a control sample), or administering to the subject, an anti-dengue antibody molecule as described herein, under conditions that allow interaction to occur, and (ii) detecting whether there is formation of a complex between the antibody molecule and the sample (and optionally, the reference, *e.g.*, control, sample). Formation of the complex is indicative of the presence of dengue virus, and

can indicate the suitability or need for a treatment described herein. The method can involve, *e.g.*, an immunohistochemistry, immunocytochemistry, FACS, antibody molecule-complexed magnetic beads, ELISA assays, or PCR-techniques (*e.g.*, RT-PCR).

Typically, the anti-dengue antibody molecule used in the *in vivo* and *in vitro* diagnostic methods is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound binding agent. Suitable detectable substances include various biologically active enzymes, prosthetic groups, fluorescent materials, luminescent materials, paramagnetic (*e.g.*, nuclear magnetic resonance active) materials, and radioactive materials.

In some embodimentsaspects, the present disclosure provides diagnostic or therapeutic kits that include the anti-dengue antibody molecules described herein and instructions for use.

The disclosure contemplates all combinations of any one or more of the foregoing aspects and/or embodiments, as well as combinations with any one or more of the embodiments set forth in the detailed description and examples.

Other features, objects, and advantages of the compositions and methods herein will be apparent from the description and drawings, and from the claims.

Figures and Tables are provided herewith.

BRIEF DESCRIPTION OF THE DRAWINGS

Each of the Figures is described herein in more detail.

Figures 1A-1I show the amino acid and nucleotide sequences of several anti-dengue EDIII antibodies. Kabat CDRs are underlined, and certain residues of interest are boxed (shown with a gray background in the priority documents).

Figure 2 depicts the results of a focus reduction neutralization test using live virus showing that antibody B11 improves upon mAb A11 neutralization of DV4.

Figure 3 shows a repeated assay of antibodies A11 and B11 neutralizing DV4.

Figure 4 is a functional assessment of frameworks of several humanized EDIII antibodies.

Figure 5 shows antibody affinity upon back-mutations of the N-terminus of anti-dengue antibodies. Heavy chain FW "04" refers to a type of framework that has the same heavy chain framework amino acid sequence as, *e.g.*, mAb B48. Light chain FW "08" refers to a type of

We claim:

1. An antibody molecule capable of binding dengue virus, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence D**V**YMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, provided that **V** is unchanged),

a CDR2 comprising the sequence RIDPENGDTKYDPK**L**QG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **L** is unchanged), and

a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and

(b) a light chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom),

a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and

a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

~~2. The antibody molecule of claim 1, which comprises a VH FW1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 11.~~

~~3. The antibody molecule of claim 1, which comprises a VH FW1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11).~~

~~4. The antibody molecule of claim 1, which comprises a VH FW2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 84 or 85.~~

~~5. The antibody molecule of claim 1, which comprises a VH FW2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85).~~

~~6~~2. An antibody molecule capable of binding dengue virus, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence D**V**YMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that **V** is unchanged),

a CDR2 comprising the sequence RIDPENGDTKYDPK**L**QG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, provided that **L** is unchanged), and

a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and

(b) a light chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom),

a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and

a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

3. The antibody molecule of claim 1 or 2, which comprises a VH FW1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 11, or a VH FW1 comprising a deletion of position 26 relative to SEQ ID NO: 33.

~~7. The antibody molecule of claim 6, which comprises a VH FW1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 11.~~

~~8. The antibody molecule of claim 6, which comprises a VH FW1 having the sequence QVQLVQSGAEVKKPGASVKVSCKAGFNIK (SEQ ID NO: 11).~~

~~9. The antibody molecule of claim 6, which comprises a VH FW2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 84 or 85.~~

~~10. The antibody molecule of claim 6, which comprises a VH FW2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85).~~

~~11~~4. An antibody molecule capable of binding dengue virus, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a FR1 comprising a deletion of position 26 relative to SEQ ID NO: 33;

a CDR1 comprising the sequence D**V**YMS (SEQ ID NO: 3) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that **V** is unchanged),

a CDR2 comprising the sequence RIDPENGDTKYDPK**L**QG (SEQ ID NO: 4) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **L** is unchanged), and

a CDR3 comprising the sequence GWEGFAY (SEQ ID NO: 5) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom); and

(b) a light chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence RASENVDKYGNSFMH (SEQ ID NO: 6) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom),

a CDR2 comprising the sequence RASELQW (SEQ ID NO: 7) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom), and

a CDR3 comprising the sequence QRSNEVPWT (SEQ ID NO: 8) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

~~12~~5. The antibody molecule of any one of claims ~~11~~1-4, which comprises a VH FW2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85), or an amino acid sequence having no more than 1, 2, 3, 4, or 5 mutations relative to SEQ ID NO: 84 or 85.

~~13. The antibody molecule of claim 11, which comprises a VH FW2 having the sequence WVRQAPGQGLEWMG (SEQ ID NO: 84) or WVRQAPEQGLEWMG (SEQ ID NO: 85).~~

~~14~~6. The antibody molecule of any of ~~the above~~ claims 1-5, which is capable of binding to dengue virus EDIII (E protein domain III).

~~15~~7. ~~An~~ The antibody molecule of any of ~~the above~~ claims 1-6, which comprises one, two, three, four, five, or six ~~or more~~ CDRs having the sequence of any of SEQ ID NOS: 3-8, 14, ~~and~~ or 35 (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom).

~~16. The antibody molecule of any of the above claims, which comprises one or more CDRs having the sequence of any of SEQ ID NOS: 3-8, 14, and 35.~~

~~17. The antibody molecule of any of the above claims, which comprises at least two, three, four, five, or six CDRs having the sequence of any of SEQ ID NOS: 3-8, 14, and 35.~~

~~18~~8. The antibody molecule of any of ~~the above~~ claims 1-7, which comprises a VH CDR1 comprising the sequence of SEQ ID NO: 3 or 14, a VH CDR2 comprising the sequence of SEQ ID NO: 4 or 35, a VH CDR3 comprising the sequence of SEQ ID NO: 5, a VL CDR1 comprising the sequence of SEQ ID NO: 6, a VL CDR2 comprising the sequence of SEQ ID NO: 7, and a VL CDR3 comprising the sequence of SEQ ID NO: 8.

~~19~~9. The antibody molecule of any of ~~the above~~ claims 1-8, which comprises a VH CDR1 comprising the sequence of SEQ ID NO: 3 ~~or 14~~, a VH CDR2 of SEQ ID NO: 4 ~~or 35~~, a VH CDR3 of SEQ ID NO: 5, a VL CDR1 of SEQ ID NO: 6, a VL CDR2 of SEQ ID NO: 7, and a VL CDR3 of SEQ ID NO: 8.

~~20~~10. The antibody molecule of any of ~~the above~~ claims 1-9, which comprises a VH amino acid sequence at least 70% identical to SEQ ID NO: 1.

~~21~~11. The antibody molecule of any of ~~the above~~ claims 1-10, which comprises the VH amino acid sequence of SEQ ID NO: 1.

~~22~~12. The antibody molecule of any of ~~the above~~ claims 1-11, which comprises a VH amino acid sequence at least 70% identical to any of SEQ ID NOS:~~s~~ 16-21, 24, 25, 27, 29, 31, 32, 33, 36, 80, or 81, or the VH amino acid sequence of any of SEQ ID NOS: 16-21, 24, 25, 27, 29, 31, 32, 33, 36, 80, or 81.

~~23. The antibody molecule of any of the above claims, which comprises the VH amino acid sequence of SEQ ID NOs. 16-21, 24, 25, 27, 29, 31, 32, 33, 36, 80, or 81.~~

~~24~~13. The antibody molecule of any of ~~the above~~ claims 1-12, which comprises a VL amino acid sequence at least 70% identical to SEQ ID NO: 2.

~~25~~14. The antibody molecule of any of ~~the above~~ claims 1-13, which comprises the VL amino acid sequence of SEQ ID NO: 2.

15. The antibody molecule of any of claims 1-14, which comprises the VH amino acid sequence of SEQ ID NO: 1 and the VL amino acid sequence of SEQ ID NO: 2.

~~26~~16. The antibody molecule of any of ~~the above~~ claims 1-12, which comprises a VL amino acid sequence at least 70% identical to SEQ ID NO: 34 or the VL amino acid sequence of SEQ ID NO: 34.

~~27. The antibody molecule of any of the above claims, which comprises the VL amino acid sequence of SEQ ID NO: 34.~~

~~28~~17. The antibody molecule of any of ~~the above~~ claims 1-16, which is a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv).

~~29~~18. The antibody molecule of any of ~~the above~~ claims 1-16, which comprises (a) a heavy chain constant region selected from IgG1, IgG2, IgG3, and IgG4, (b) a light chain constant region chosen from the light chain constant regions of kappa or lambda, or both (a) and (b).

~~30. The antibody molecule of any of the above claims, which comprises a light chain constant region chosen from the light chain constant regions of kappa or lambda.~~

~~31~~19. The antibody molecule of any of ~~the above~~ claims 1-18, which is an isolated antibody molecule or a humanized antibody molecule, or comprises one or more framework regions derived from a human framework germline sequence.

~~32. The antibody molecule of any of the above claims, which is a humanized antibody molecule.~~

~~33. The antibody molecule of any of the above claims, which contains one or more framework regions derived from a human framework germline sequence.~~

~~34~~20. The antibody molecule of any of ~~the above~~ claims 1-19, which is capable of one, two, three, four, five, or all of the following:

(a) binding to dengue virus EDIII with a dissociation constant (K_D) of less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, or 0.01 nM;

(b) binding to dengue virus serotype DV-4 EDIII with a dissociation constant (KD) of less than about 10, 8, 6, 5, 4, or 3 nM;

(c) binding to DV-3 or DV-4 EDIII domain with at least a 2, 3, 4, 5, 6, 8, 10, 12, 15, 25, 50, 75, 100, 1,000, 5,000, or 10,000-fold greater affinity than antibody A11 or antibody 4E11;

(d) binding to a dengue virus strain selected from DENV-4 BC2, DENV-4-Sing, DENV-4 NC, DENV-4 Phil, DENV-3 Sing, DENV-3 Nic, DENV-3 H87, DENV-2 Peru,

DENV-2 Sing, DENV-2 NGC, DENV-1 Hawaii/1944, DENV-2 New Guinea/1944 (NGC), DENV-3 Philippines/1956 (H87), DENV-4 Mexico/1997 (BC287/97), and DENV-4 H241, with at least 2, 3, 4, 5, 6, 8, 10, 12, 25, 50, 75, 100, or 1,000-fold greater affinity than antibody A11 or antibody 4E11;

(e) neutralizing dengue virus in a focus reduction neutralization test; or

(f) neutralizing dengue virus with an IC50 that is at least 2, 3, 4, 5, 6, 8, 10, 12, 25, 50, 75, or 100-fold lower than antibody A11 or antibody 4E11 in a focus reduction neutralization test.

~~35. The antibody molecule of any of the above claims, which is capable of binding to dengue virus serotype DV-4 EDIII with a dissociation constant (K_D) of less than about 10, 8, 6, 5, 4, or 3 nM.~~

~~36. The antibody molecule of any of the above claims, which is capable of binding to DV-3 or DV-4 EDIII domain with at least a 2, 3, 4, 5, 6, 8, 10, 12, 15, 25, 50, 75, 100, 1,000, 5,000, or 10,000-fold greater affinity than antibody A11 or antibody 4E11.~~

~~37. The antibody molecule of any of the above claims, which is capable of binding to a dengue virus strain selected from DENV-4 BC2, DENV-4 Sing, DENV-4 NC, DENV-4 Phil, DENV-3 Sing, DENV-3 Nic, DENV-3 H87, DENV-2 Peru, DENV-2 Sing, DENV-2 NGC, DENV-1 Hawaii/1944, DENV-2 New Guinea/1944 (NGC), DENV-3 Philippines/1956 (H87), DENV-4 Mexico/1997 (BC287/97), and DENV-4 H241, with at least 2, 3, 4, 5, 6, 8, 10, 12, 25, 50, 75, 100, or 1,000-fold greater affinity than antibody A11 or antibody 4E11.~~

~~38. The antibody molecule of any of the above claims, which is capable of neutralizing dengue virus in a focus reduction neutralization test.~~

~~39. The antibody molecule of any of the above claims, which is capable of neutralizing dengue virus with an IC50 that is at least 2, 3, 4, 5, 6, 8, 10, 12, 25, 50, 75, or 100-fold lower than antibody A11 or antibody 4E11 in a focus reduction neutralization test.~~

~~40~~21. A pharmaceutical composition comprising the antibody molecule of any of ~~the above~~ claims 1-20 and a pharmaceutically acceptable carrier, excipient, or stabilizer.

~~41~~22. A nucleic acid encoding the antibody heavy or light chain variable region of the antibody molecule of any of claims 1-~~39~~20.

~~42~~23. An expression vector comprising the nucleic acid of claim ~~41~~22.

~~43~~24. A host cell comprising the nucleic acid of claim ~~41~~22.

~~44~~25. A method of producing an antibody molecule or fragment thereof, comprising culturing the host cell of claim ~~43~~ 24 under conditions suitable for gene expression.

4526. A kit comprising a container having disposed therein an antibody molecule of any of claims 1-3920; a pharmaceutically acceptable carrier, excipient, or stabilizer; and optionally a delivery device, optionally wherein the delivery device comprises a syringe or needle, and optionally wherein the kit further comprises instructions for use.

~~46. The kit of claim 45, wherein the delivery device comprises a syringe or needle.~~

~~47. The kit of claim 45, further comprising instructions for use.~~

4827. A method of neutralizing dengue virus, comprising contacting the dengue virus with an antibody molecule of any of claims 1-3920.

4928. The method of claim 4827, wherein the dengue virus is of serotype DV-1, DV-2, DV-3, or DV-4.

5029. ~~A method of treating dengue virus, comprising administering to a subject in need thereof~~ Use of an isolated antibody molecule of any of claims 1-39-20, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for treating dengue virus in a subject~~in an amount effective to treat the virus~~.

5130. The use ~~method~~ of claim 5029, wherein the antibody molecule or pharmaceutical composition is used in combination with ~~further comprising administering~~ an anti-viral agent or vaccine~~to the subject~~.

5231. The ~~method~~ use of claim 5029, wherein the anti-viral agent is:

(a) chosen from one or more of balapiravir, chloroquine, celgosivir, ivermectin, or Carica folia;

(b) an anti-dengue antibody different from the antibody molecule of any of claims 1-18;

(c) an anti-dengue antibody chosen from one or more of any of the antibodies listed in Table 1, 4E11, 14c10 (HM14c10), 1F4, 2D22, 5J7, DV1.1, DV1.6, DV3.7, DV4.4, DV5.1, DV6.1, DV7.5, DV8.1, DV10.16, DV13.4, DV13.8, DV14.5, DV14.5, DV15.7, DV16.5, DV16.8, DV17.6, DV18.21, DV18.4, DV19.3, DV20.1, DV21.1, DV21.5, DV22.3, DV22.3 LALA, DV23.13, DV25.5, DV27.2, DV28.1, DV28.8, DV34.4, DV35.3, DV38.1, DV51.6, DV52.1, DV53.4, DV54.7, DV55.1, DV56.12, DV54.7, DV57.4, DV59.3, DV60.3, DV61.2,

DV62.5, DV63.1, DV64.3, DV65.5, DV66.1, DV67.9, DV68.2, DV69.6, DV70.1, DV71.1, DV74.4, DV75.9, DV76.5, DV77.5, DV78.6, DV79.3, DV82.11, DV82.11 LALA, DV86.2, DV87.1, DV87.1 LALA, DV90.3, DV257.13, DV291.7, DV415.8, DV470.12, 3-147, 58/5, 2F5, 2G4, 5F9, 135.3, 2H12, 1A5, or 1C19; or

(d) chosen from one or more of an alpha-glucosidase I inhibitor, an adenosine nucleoside inhibitor, an inhibitor of NS3 and/or its cofactor NS2B, an RNA-dependent RNA polymerase (RdRp) inhibitor, an inhibitor of host pyrimidine biosynthesis, an inhibitor of viral NS4B protein, or an iminosugar.

~~53. The method of claim 50, wherein the anti-viral agent is an anti-dengue antibody chosen from one or more of any of the antibodies listed in Table 1, 4E11, 14c10 (HM14c10), 1F4, 2D22, 5J7, DV1.1, DV1.6, DV3.7, DV4.4, DV5.1, DV6.1, DV7.5, DV8.1, DV10.16, DV13.4, DV13.8, DV14.5, DV14.5, DV15.7, DV16.5, DV16.8, DV17.6, DV18.21, DV18.4, DV19.3, DV20.1, DV21.1, DV21.5, DV22.3, DV22.3 LALA, DV23.13, DV25.5, DV27.2,~~

~~DV28.1, DV28.8, DV34.4, DV35.3, DV38.1, DV51.6, DV52.1, DV53.4, DV54.7, DV55.1, DV56.12, DV54.7, DV57.4, DV59.3, DV60.3, DV61.2, DV62.5, DV63.1, DV64.3, DV65.5, DV66.1, DV67.9, DV68.2, DV69.6, DV70.1, DV71.1, DV74.4, DV75.9, DV76.5, DV77.5, DV78.6, DV79.3, DV82.11, DV82.11-LALA, DV86.2, DV87.1, DV87.1-LALA, DV90.3, DV257.13, DV291.7, DV415.8, DV470.12, 3-147, 58/5, 2F5, 2G4, 5F9, 135.3, 2H12, 1A5, or 1C19.~~

~~54. The method of claim 50, wherein the anti-viral agent is chosen from one or more of an alpha-glucosidase I inhibitor, an adenosine nucleoside inhibitor, an inhibitor of NS3 and/or its cofactor NS2B, an RNA-dependent RNA polymerase (RdRp) inhibitor, an inhibitor of host pyrimidine biosynthesis, an inhibitor of viral NS4B protein, or an iminosugar.~~

~~55~~32. The ~~method~~ use of claim ~~54~~31, wherein the alpha-glucosidase I inhibitor is celgosivir, the adenosine nucleoside inhibitor is NITD008, the inhibitor of NS3 and/or its cofactor NS2B is a [5-amino-1-(phenyl)sulfonyl-pyrazol-3-yl] compound, the RNA-dependent RNA polymerase (RdRp) inhibitor is NITD107, the inhibitor of host pyrimidine biosynthesis is an inhibitor of host dihydroorotate dehydrogenase (DHODH) selected from NITD-982 or brequinar, the inhibitor of viral NS4B protein is NITD-618, or the iminosugar is UV-4.

~~56. The method of claim 50, further comprising administering a vaccine to the subject.~~

~~57~~33. The ~~method~~ use of any of claims 30-32~~-50~~, wherein the antibody molecule or pharmaceutical composition is to be administered ~~administration is~~ parenterally or intravenously.

~~58. The method of claim 50, wherein administration is intravenous.~~

34. The use of any of claims 30-33, wherein the antibody molecule neutralizes one, two, three, or all of dengue virus serotypes DV-1, DV-2, DV-3, or DV-4.

35. The use of any of claims 30-34, wherein the subject is infected with dengue virus or is at risk of being infected with dengue virus.

36. The use of any of claims 30-35, wherein the antibody molecule or pharmaceutical composition is to be administered prior to the subject being exposed to dengue virus or prior to onset of one or more manifestation of dengue virus.

~~59~~37. ~~A method of preventing dengue virus infection, comprising administering to a subject in need thereof~~ Use of an isolated antibody molecule of any of claims 1-~~39~~ 20, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for preventing dengue virus infection in a subject~~in an amount effective to prevent infection.~~

~~6038~~. ~~A method of reducing a patient's risk of contracting dengue virus, comprising administering to a subject in need thereof~~ Use of an isolated antibody molecule of any of claims 1-~~39~~ 20, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for reducing a patient's risk of contracting dengue virus~~in an amount effective to reduce the risk of contracting the virus~~.

~~6139~~. ~~A method of reducing transmission of dengue virus between a subject and a mosquito, comprising administering to a subject prior or after infection with dengue virus~~ Use of an isolated antibody molecule of any of claims 1-~~39~~ 20, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for reducing transmission of dengue virus between a subject and a mosquito~~in an amount effective to reduce the transmission of dengue virus~~.

~~6240~~. A method of detecting dengue virus in a biological sample, comprising (i) contacting the sample or the subject (and optionally, a reference sample or subject) with an antibody molecule of any of claims 1-~~39~~ 20 under conditions that allow interaction of the antibody molecule and the polypeptide to occur, and (ii) detecting formation of a complex between the antibody molecule and the sample or the subject (and optionally, the reference sample or subject).