

A SEROTYPE CROSS-REACTIVE, DENGUE NEUTRALIZING ANTIBODY AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 [0001] This application claims the benefit of priority of Singapore patent application No. 10201502068V, filed 17 March 2015, the contents of it being hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

- 10 [0002] The present invention relates to a preparation for medical purpose or specific therapeutic activity of a preparation. In particular, the present invention relates to antibodies and other agents that bind to dengue virus (or DENV), as well as to methods of using the antibodies or other agents for the treatment of diseases.

BACKGROUND OF THE INVENTION

- 15 [0003] Dengue fever is the most common arthropod-borne viral disease in the world. The virus causing dengue (i.e. DENV) can be divided into four different infective serotypes such as DENV-1, DENV-2, DENV-3, and DENV-4. Symptoms of dengue infection include fever, muscle pain, headache, low platelet numbers and low white blood cell numbers,
20 coagulopathy, bleeding and vascular leakage that can lead to dengue shock syndrome. When a person is exposed to the dengue virus after a previous dengue infection, antiviral antibodies may enhance the uptake of virus into host cells and the patient is at higher risk to develop a severe form of dengue. Severe forms of dengue can, however, also occur during a first infection.
- 25 [0004] Whilst being the most common arthropod-borne viral disease, to date, there is no drug for dengue. Approaches with regards to dengue have mainly been towards the prevention of the infection and/or treatment to alleviate symptoms.
- [0005] Thus, there is a need to provide agents capable of neutralizing and/or binding to at least one dengue serotype.

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SUMMARY OF THE INVENTION

[0005a] In one aspect, there is provided an isolated antibody, or antigen binding fragment thereof, wherein the antibody comprises:

a heavy chain amino acid sequence comprising all of the CDRs of

- (a) a CDRH1 as shown in SEQ ID NO: 3,
- 5 (b) a CDRH2 as shown in SEQ ID NO: 4,
- (c) a CDRH3 as shown in SEQ ID NO: 5, and

light chain amino acid sequence comprising all of the CDR selected from the group consisting of:

- (a) a CDRL1 as shown in SEQ ID NO: 6,
- 10 (b) a CDRL2 as shown in SEQ ID NO: 7,
- (c) a CDRL3 as shown in SEQ ID NO: 8,

wherein the antibody, or antigen binding fragment thereof recognizes a whole dengue virus particle.

- [0005b] In another aspect, there is provided the use of the isolated antibody, or antigen binding fragment thereof as disclosed herein in the manufacture of a medicament for treatment of a dengue virus infection in a subject.

[0005c] In another aspect, there is provide an isolated nucleic acid molecule comprising: a nucleic acid sequence encoding an isolated antibody, or antibody fragment thereof, as disclosed herein, or a nucleic acid sequence complementary thereto.

- 20 [0006] In one example, there is provided an isolated antibody, or antigen binding fragment thereof, wherein the antibody comprises at least: one heavy chain amino acid sequences

comprising at least one CDR selected from the group consisting of (a) a CDRH1 as shown in SEQ ID NO: 3, or a CDRH1 sequence having at least 70% sequence identity to SEQ ID NO: 3 therefrom, (b) a CDRH2 as shown in SEQ ID NO: 4, or a CDRH2 sequence having at least 70% sequence identity to SEQ ID NO: 4 therefrom, (c) a CDRH3 as shown in SEQ ID NO: 5, or a CDRH3 sequence having at least 70% sequence identity to SEQ ID NO: 5 therefrom, or an antibody, or antigen binding fragment thereof.

[0007] In another example there is provided an isolated antibody, or antigen binding fragment thereof, wherein the antibody comprises at least: one light chain amino acid sequences comprising at least one CDR selected from the group consisting of: (a) a CDRL1 as shown in SEQ ID NO: 6, or a CDRL1 sequence having at least 70% sequence identity to SEQ ID NO: 6 therefrom, (b) a CDRL2 as shown in SEQ ID NO: 7, or a CDRL2 sequence having at least 70% sequence identity to SEQ ID NO: 7 therefrom, (c) a CDRL3 as shown in SEQ ID NO: 8, or a CDRL3 sequence having at least 70% to SEQ ID NO: 8 therefrom, or an antibody, or antigen binding fragment thereof.

[0008] In yet another example, there is provided an isolated antibody, or antigen binding fragment thereof, wherein the antibody comprises at least: one heavy chain amino acid sequences comprising at least one CDR selected from the group consisting of (a) a CDRH1 as shown in SEQ ID NO: 3, or a CDRH1 sequence differing 1 or 2 amino acids therefrom, (b) a CDRH2 as shown in SEQ ID NO: 4, or a CDRH2 sequence differing 1 or 2 amino acids therefrom, (c) a CDRH3 as shown in SEQ ID NO: 5, or a CDRH3 sequence differing 1 or 2 amino acids therefrom, and/or at least one light chain amino acid sequences comprising at least one CDR selected from the group consisting of (a) a CDRL1 as shown in SEQ ID NO: 6, or a CDRL1 sequence differing 1 or 2 amino acids therefrom, (b) a CDRL2 as shown in SEQ ID NO: 7, or a CDRL2 sequence differing 1 or 2 amino acids therefrom, (c) a CDRL3 as shown in SEQ ID NO: 8, or a CDRL3 sequence differing 1 or 2 amino acids therefrom, or an antibody, or antigen binding fragment thereof, recognizing a whole dengue virus particle.

[0009] In yet another example there is provided a composition comprising the isolated antibody, or antigen binding fragment thereof, as described herein.

[0010] In yet another example there is provided a kit comprising the isolated antibody as described herein.

[0011] In yet another example there is a passive vaccine against at least one of the dengue virus serotypes comprising the isolated antibody as described herein, or the composition as described herein, or the kit as described herein.

[0012] In yet another example there is provided a method of treating a dengue virus infection in a subject comprising administering to the subject an effective amount of the isolated antibody, or antigen binding fragment thereof, as described herein, or the composition as described herein, or the vaccine as described herein.

[0013] In yet another example there is provided a use of the antibody, or antigen binding fragment thereof, as described herein or the composition as described herein, or the kit as described herein, or the vaccine as described herein, in the manufacture of a medicament for treating a dengue virus infection in a subject.

[0014] In yet another example there is provided a method for detecting at least one dengue virus serotype in a sample. In one example, the method comprises: (a) incubating the sample with at least one of the isolated antibody as described herein, or kit as described herein, and (b) detecting the antibody-dengue virus complex wherein the presence or absence of the complex indicates the presence or absence of dengue virus in the sample.

[0015] In yet another example there is provide an isolated nucleic acid molecule selected from the group consisting of: (a) a nucleic acid sequence encoding the isolated antibody, or antibody fragment thereof, as described herein, (b) a nucleic acid sequence as shown in SEQ ID NOs: 1 and 2, (c) a nucleic acid complementary to any one of the sequences in (a) or (b); and (d) a nucleic acid sequence capable of hybridizing to (a), (b), or (c) under stringent conditions.

[0016] In yet another example there is provided a vector comprising a nucleic acid sequence as described herein.

[0017] In yet another example there is provided a host transformed with the vector as described herein.

[0018] In yet another example there is provided a process of manufacturing an antibody, or antigen binding fragment, as described herein, comprising the step of obtaining the antibody from the host as described herein.

Claims

1. An isolated antibody, or antigen binding fragment thereof, wherein the antibody comprises:

a heavy chain amino acid sequence comprising all of the CDRs of

- 5 (a) a CDRH1 as shown in SEQ ID NO: 3,
 (b) a CDRH2 as shown in SEQ ID NO: 4,
 (c) a CDRH3 as shown in SEQ ID NO: 5, and

light chain amino acid sequence comprising all of the CDR selected from the group consisting of:

- 10 (a) a CDRL1 as shown in SEQ ID NO: 6,
 (b) a CDRL2 as shown in SEQ ID NO: 7,
 (c) a CDRL3 as shown in SEQ ID NO: 8,

wherein the antibody, or antigen binding fragment thereof recognizes a whole dengue virus particle.

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2. The antibody, or antigen binding fragment thereof according to claim 1, wherein said antibody is specific for an epitope comprising at least one of the amino acids of a dengue virus glycoprotein selected from the group consisting K122, I162, and S274.

20 3. The antibody, or antigen binding fragment thereof, of claim 2, wherein the epitope further comprises at least one of the amino acids of a dengue virus glycoprotein selected from the group consisting of G100, W101, K310, W391, and F392, when the epitope comprises at least one of the amino acids of the dengue virus glycoprotein selected from the group consisting K122, I162, and S274; or wherein the epitope comprises at least three of the amino
 25 acids of a dengue virus glycoprotein selected from the group consisting of G100, W101, K122, I162, S274, K310, W391 and F392.

4. The antibody, or antigen binding fragment thereof according to claim 1, wherein the antibody is capable of binding to a whole dengue virus particle better than binding to a
 30 dengue virus surface glycoprotein.

5. The antibody, or antigen binding fragment thereof according to claim 2, wherein the glycoprotein is an E protein.
6. The antibody, or antigen binding fragment thereof according to claim 1, wherein the
5 dengue virus particle is at least one dengue virus selected from the group consisting of DENV serotype 1 (DENV-1), DENV serotype 2 (DENV-2), DENV serotype 3 (DENV-3), and DENV serotype 4 (DENV-4).
7. The antibody, or antigen binding fragment thereof according to claim 1, wherein the
10 antibody comprises a heavy chain variable region encoded by a nucleotide sequence having at least 90% sequence identity to SEQ ID NO: 1.
8. The isolated antibody, or antigen binding fragment thereof according to claim 1, wherein the antibody comprises a heavy chain variable region encoded by the nucleotide
15 sequence SEQ ID NO: 1.
9. The isolated antibody, or antigen binding fragment thereof according to claim 1, wherein the antibody comprises a light chain variable region encoded by the nucleotide sequence having at least 90% sequence identity to SEQ ID NO: 2.
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10. The isolated antibody, or antigen binding fragment thereof according to claim 1, wherein the antibody comprises a light chain variable region encoded by the nucleotide sequence SEQ ID NO: 2.
11. The isolated antibody, or antigen binding fragment thereof according to claim 1, wherein the antibody, or antigen binding fragment thereof, comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 9, or an amino acid sequence having a sequence identity of at least 90% thereto.
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12. The isolated antibody, or antigen binding fragment thereof according to claim 1, wherein the antibody, or antigen binding fragment thereof, comprises of a light chain variable
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region comprising the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having a sequence identity of at least 90% thereto.

13. The isolated antibody, or antigen binding fragment thereof according to claim 1,
5 wherein said antibody is a monoclonal antibody.

14. The isolated antibody, or antigen binding fragment thereof according to claim 1,
wherein the antibody is a modified IgG1 antibody, a modified IgG2 antibody, a modified
IgG3 antibody, or a modified IgG4 antibody.
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15. Use of the isolated antibody, or antigen binding fragment thereof according to claim 1
in the manufacture of a medicament for treatment of a dengue virus infection in a subject.

16. An isolated nucleic acid molecule comprising:
15 a nucleic acid sequence encoding an isolated antibody, or antibody fragment thereof,
according to claim 1, or a nucleic acid sequence complementary thereto.