ANTI-HEMAGGLUTININ ANTIBODIES AND METHODS OF USE

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/725,859, filed on 13 November 2012~~, which is incorporated by reference herein in its entirety~~.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 31, 2013, is named P4982R1WO_PCTSequenceListing.txt and is 227,598 bytes in size.

FIELD OF THE INVENTION

The present invention provides anti-hemagglutinin antibodies, compositions comprising anti-hemagglutinin antibodies, and methods of using the same.

BACKGROUND

Influenza virus infection causes between three and five million cases of severe illness and between 250,000 and 500,000 deaths every year around the world. In the United States alone, 5% to 20% of the population becomes infected with influenza virus each year, with the majority of these infections caused by the influenza A virus. (See, *e.g.*, Dushoff *et al.*, (2006) Am J Epidemiology 163:181-187; Thompson *et al.*, (2004) JAMA 292:1333-1340; Thompson *et al.*, (2003) JAMA 289:179-186.) Approximately 200,000 people in the United States become hospitalized with influenza-related complications every year, resulting in 7,000 to 30,000 deaths annually. The burden associated with influenza virus infection on health care costs and lost productivity is extensive. Hospitalization and deaths mainly occur in high-risk groups, such as the elderly, children, and chronically ill.

Influenza viruses are segmented membrane-enveloped negative-strand RNA viruses belonging to the *Orthomyxoviridae* family. Influenza A virus consists of 9 structural proteins and 1 non-structural protein, which include three virus surface proteins: hemagglutinin (HA or H), neuraminidase (NA or N), and matrix protein 2 (M2). The segmented nature of the influenza viral genome allows the mechanism of genetic reassortment (*i.e.*, exchange of genome

treatment window at the time of seeking treatment. Therefore, significant focus has recently been placed on identifying influenza virus therapeutics to treat hospitalized influenza virus infected patients. One strategy has focused on development of human monoclonal antibodies (mAbs) that target a highly conserved epitope on the stalk of influenza A virus hemagglutinin. (See, *e.g.*, Corti et al., (2011) Science 333:850-856; Ekiert *et al.*, (2009) Science 324:246-251; Ekiert *et al.*, (2011) Science 333:843-850; Sui *et al.*, (2009) Nature Structural & Molecular Biology 16:265-273; Dreyfus *et al.*, (2012) Science 337:1343-1348; Wu *et al.*, (2012) J Virology 2012.09.034; Clementi *et al.*, (2011) PLoS One 6:1-10. See also International Patent Application Publication Nos: WO2009/115972, WO2011/117848, WO2008/110937, WO2010/010466, WO2008/028946, WO2010/130636, WO2012/021786, WO2010/073647, WO2011/160083, WO2011/111966, WO2002/46235, and WO2009/053604; U.S. Patent Nos: 5,631,350 and 5,589,174.)

Several reports have described monoclonal antibodies (mAb) that bind hemagglutinin and broadly neutralize influenza A virus. For example, Corti *et al.* (*supra*) described antibody FI6v3, which was cloned from a human plasma cell and shown to neutralize human influenza A viruses belonging to both Group1 and Group2 hemagglutinin subtypes. The FI6v3 mAb was discovered as a result of a heroic effort of analyzing approximately 104,000 human plasma cells. Additionally, Dreyfus *et al.* (*supra*) recently described the identification of antibody CR9114 by phage display panning; antibody CR9114 was shown to bind to a highly conserved stalk epitope shared between influenza A virus and influenza B virus hemagglutinin.

Despite these reports, a need still exists in the art for novel influenza A virus therapies effective against Group1 and Group2 influenza A virus subtypes. The present invention meets this need and provides other benefits for the treatment of influenza A virus infection.

SUMMARY

The present disclosure provides anti-hemagglutinin antibodies, compositions comprising anti-hemagglutinin antibodies, and methods of using the same.

In one ~~aspect~~embodiment, there is provided an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:178;

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:111 and 115.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:110, 114, and 120, and the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:112, 116, 118, 121, 123, 125, 127, 129, and 131.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:112, 116, 118, 121, 123, 125, 127, 129, and 131.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:110, 114, and 120.

In one aspect, there is provided an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:191 ~~and 192~~;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:193;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:194;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:195;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:196; and

(f) HVR-L3 comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:197 ~~, 198, and 199~~.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising: at least one, two, three, four, five and/or six hypervariable region (HVR) sequences, wherein:

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 133, 137, 141, and 147.

In one ~~aspect~~embodiment, there is provided an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:200;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:201;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:202;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:203;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:204; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:205.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising: at least one, two, three, four, five and/or six hypervariable region (HVR) sequences, wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:200;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:201;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:202;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:203;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:204; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:205.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising three light chain hypervariable regions (HVR-L1, HVR-L2, and LVR-L3), wherein:

(a) HVR-L1 comprises the amino acid sequence of SEQ ID NO:203;

(b) HVR-L2 comprises the amino acid sequence of SEQ ID NO:204; and

(c) HVR-L3 comprises the amino acid sequence of SEQ ID NO:205.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:200;

sequence selected from the group consisting of SEQ ID NOs:153 and 157, and the light chain comprises the amino acid sequence of SEQ ID NO:155.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a light chain comprising the amino acid sequence of SEQ ID NO:155.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:153 and 157.

In one embodimentaspect, there is provided an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:206;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:207;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:208;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:209;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:210; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:211.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising: at least one, two, three, four, five and/or six hypervariable region (HVR) sequences, wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:206;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:207;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:208;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:209;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:210; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:211.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising three light chain hypervariable regions (HVR-L1, HVR-L2, and LVR-L3), wherein:

(a) HVR-L1 comprises the amino acid sequence of SEQ ID NO:209;

(b) HVR-L2 comprises the amino acid sequence of SEQ ID NO:210; and

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 160.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:159, and the light chain comprises the amino acid sequence of SEQ ID NO:161.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a light chain comprising the amino acid sequence of SEQ ID NO:161.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:159.

In one embodiment~~aspect~~, there is provided an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:212;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:213;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:214;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:215;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:216; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:217.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising: at least one, two, three, four, five and/or six hypervariable region (HVR) sequences, wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:212;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:213;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:214;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:215;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:216; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:217.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:166.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 164.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:163, and the light chain comprises the amino acid sequence of SEQ ID NO:165.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a light chain comprising the amino acid sequence of SEQ ID NO:165.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:163.

In one embodimentaspect, there is provided an isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:218;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:219;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:220;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:221;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:222; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:223.

In some embodiments, the disclosure provides an isolated anti-hemagglutinin antibody comprising: at least one, two, three, four, five and/or six hypervariable region (HVR) sequences, wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:218;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:219;

thereof), the method comprising expressing in a suitable host cell a recombinant vector of the disclosure encoding the anti-hemagglutinin antibody or fragments thereof so that the antibody or fragments thereof are produced. In some embodiments, the method comprises culturing a host cell comprising nucleic acid encoding an anti-hemagglutinin antibody of the present disclosure (or fragments thereof) so that the nucleic acid is expressed. The method may further comprise recovering the anti-hemagglutinin antibody or fragments thereof from the host cell culture or the host cell culture medium.

In one aspect, there is provided a method of producing an antibody comprising culturing the host cell as defined herein so that the antibody is produced.

In one aspect, there is provided a pharmaceutical composition comprising the antibody as defined herein and a pharmaceutically acceptable carrier.

The disclosure also provides a pharmaceutical formulation comprising an anti-hemagglutinin antibody of the present disclosure and a pharmaceutically acceptable carrier. The pharmaceutical formulation may further comprise an additional therapeutic agent (*e.g.*, a neuraminidase inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In one aspect, there is provided a composition comprising the antibody as defined herein.

The disclosure also provides compositions comprising an anti-hemagglutinin antibody of the present disclosure. The composition may further comprise an additional therapeutic agent (*e.g.*, a neuraminidase inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In one aspect, there is provided an anti-hemagglutinin antibody as defined herein for use as a medicament. In another aspect, there is provided an anti-hemagglutinin antibody as defined herein for use in treating, inhibiting, or preventing influenza A virus infection.

The disclosure also provides a composition comprising an anti-hemagglutinin antibody of the present disclosure for use in preventing influenza A virus infection. In some embodiments, the disclosure provides a pharmaceutical composition comprising an anti-hemagglutinin antibody of the present disclosurefor use in preventing influenza A virus infection. The disclosure further provides a composition comprising an anti-hemagglutinin antibody of the present disclosure for use in treating influenza A virus infection. In some embodiments, the disclosure provides a pharmaceutical composition comprising an anti-hemagglutinin antibody of the present disclosure for use in treating influenza A virus infection. The disclosure further provides a composition comprising an anti-hemagglutinin antibody of the present disclosure for use in inhibiting influenza A virus infection. In some embodiments, the disclosure provides a pharmaceutical composition comprising an anti-hemagglutinin antibody of the present disclosure for use in inhibiting influenza A virus infection.

Compositions comprising an anti-hemagglutinin antibody of the present disclosure may also be used in the manufacture of a medicament. The medicament may be for use in the inhibition,

treatment, or prevention of influenza A virus infection. In certain embodiments, the medicament may further comprise an additional therapeutic agent (*e.g.*, a neuraminidase inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

The disclosure also provides a method for inhibiting influenza A virus infection, the method comprising administering to a patient in need thereof an effective amount of a composition comprising an anti-hemagglutinin antibody of the present disclosure, thereby inhibiting influenza A virus infection. The disclosure also provides a method for treating influenza A virus infection, the method comprising administering to a patient in need thereof an effective amount of a composition comprising an anti-hemagglutinin antibody of the present disclosure, thereby treating influenza A virus infection. The disclosure also provides a method for preventing influenza A virus infection, the method comprising administering to a patient in need thereof an effective amount of a composition comprising an anti-hemagglutinin antibody of the present disclosure, thereby preventing influenza A virus infection.

The disclosure also provides a method for inhibiting, treating, or preventing influenza A virus infection, the method comprising administering to a patient in need thereof an effective amount of a composition comprising an anti-hemagglutinin antibody of the present disclosure, and administering to the patient an effective amount of an additional therapeutic agent, thereby inhibiting, treating, or preventing influenza A virus infection. In some embodiments, the additional therapeutic agent is a neuraminidase inhibitor, such as oseltamivir or zanamivir. In other embodiments, the additional therapeutic agent is another anti-hemagglutinin antibody. In yet other embodiments, the additional therapeutic agent is an anti-M2 antibody. In various ~~aspects~~ embodiments of such combination treatments, the therapeutic agents are administered at about the same time, are administered together, or are administered sequentially or consecutively. In particular embodiments, an anti-neuraminidase inhibitor is administered prior to the administration of an anti-hemagglutinin antibody of the present disclosure.

In one aspect, there is provided use of the anti-hemagglutinin antibody as defined herein, in the manufacture of a medicament for treating, inhibiting, or preventing influenza A virus infection ~~in an individual in need thereof~~.

In another embodiment, the disclosure provides use of an anti-hemagglutinin antibody of the present disclosure in the manufacture of a medicament. The medicament may be for use in the inhibition, treatment, or prevention of influenza A virus infection. In certain embodiments, the medicament may further comprise an additional therapeutic agent (*e.g.*, a neuraminidase

Phage library sorting and screening to identify anti-hemagglutinin antibodies

Influenza A virus hemagglutinin H1 and H3 proteins (produced as described below in Example 2) were used as antigens for phage library sorting. Hemagglutinin H1 and H3 antigens were coated onto a high-binding 96-well maxisorp plate. The plates and phage libraries were pre-blocked with phage blocking buffer (phosphate-buffered saline (PBS), 1% (w/v) bovine serum albumin (BSA), and 0.05% (v/v) tween-20 (PBS-T)) and incubated for 2 hours at room temperature. The blocked phage library (100 µl) was added to the hemagglutinin-coated wells and incubated for 3 hours. The unbound phage were washed off the plates using 0.05% PBS–Tween, and bound phage were eluted with 100 µL 50 mM HCl and 500 mM NaCl for 30 minutes followed by neutralization with 100 µL of 1 M Tris base (pH 7.5). Recovered phage were amplified in *E. coli* XL-1 Blue cells. The resulting phage were precipitated and subjected another round of panning/selection against the hemagglutinin proteins. During subsequent panning/selection rounds, antibody phages were incubated with same or different hemagglutinin antigens. The stringency of plate washing was gradually increased from washing 15x to washing 40x.

After 2-3 rounds of panning and selection, significant enrichment of hemagglutinin-specific phage was observed. 96 phage clones were picked from the library sorting to determine whether they specifically bound to hemagglutinin H1 and/or H3. The variable regions of the phage clones displaying specific binding to the hemagglutinin proteins were sequenced to identify phage clones containing unique immunoglobulin nucleic acid sequences. Unique phage antibodies that bound hemagglutinin H1 and/or H3 with at least 5x above background were further characterized. Phage-derived clones of interest were reformatted into IgGs by cloning V_L and V_H regions of individual clones into the LPG3 and LPG4 expression vectors, respectively, transiently expressed in mammalian 293 cells, and purified using a protein A column. Two antibodies (mAb9 and mAb23) were identified for further analysis. (See Example 5 below.)

Example 2. Plasmablast enrichment and expansion

To discover and identify rare antibodies against influenza A virus hemagglutinin, the following plasmablast enrichment and expansion technique was developed. (See co-pending patent application U.S. patent application serial number 61/725,764~~, which is incorporated by reference herein in its entirety~~.)

respiratory rate, or a reduction of time to normalization of oxygen saturation), reduction of time to return to normal oxygen saturation, *e.g.*, to an oxygen saturation of about 92% or greater, as measured over a 24 hour period without supplemental oxygen administration, or reduction of time to normalization of vital signs, such as heart rate, blood pressure, respiratory rate, and temperature.

Statistical analyses

Statistics were calculated using JMP version 9.0.2 software (SAS Institute). Survival experiments were compared using log-rank test. P values<0.05 were considered significant. IC_{50} curves and values were plotted and calculated using Graphpad Prism version 5.0 software.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. ~~The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.~~

WHAT IS CLAIMED IS:

1. An isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:191 ~~and 192~~;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:193;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:194;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:195;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:196; and

(f) HVR-L3 comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:197~~, 198, and 199~~.

2. The isolated anti-hemagglutinin antibody of claim 1, wherein the antibody comprises a light chain variable region comprising ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs: ~~136, 140, 144, 146, 150, 152, and~~ 235.

3. The isolated anti-hemagglutinin antibody of claim 1, wherein the antibody comprises a heavy chain variable region comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs: ~~134, 138, 142, 148, and~~ 234.

4. The isolated anti-hemagglutinin antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:~~134, 138, 142, 148, and~~ 234, and the light chain variable region comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:~~136, 140, 144, 146, 150, 152, and~~ 235.

5. The isolated anti-hemagglutinin antibody of claim 1, wherein the antibody comprises a light chain comprising ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs: ~~135,~~ 139~~, 143, 145, 149, and 151~~.

6. The isolated anti-hemagglutinin antibody of claim 1, wherein the antibody comprises a heavy chain comprising ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs: ~~133, 137, 141, and~~ 147.

7. The isolated anti-hemagglutinin antibody of claim 1, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:~~133, 137, 141, and~~ 147, and the light chain comprises ~~an~~ the amino acid sequence ~~selected from the group consisting~~ of SEQ ID NOs:~~135,~~ 139~~, 143, 145, 149, and 151~~.

~~8. An isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:~~

~~(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:178;~~

~~(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:179;~~

~~(c) HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:180 and 181;~~

~~(d) HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:182, 183, 184, 185, and 186;~~

~~(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:187; and~~

~~(f) HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:188, 189, and 190.~~

~~9. The isolated anti-hemagglutinin antibody of claim 8, wherein the antibody comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:113, 117, 119, 122, 124, 126, 128, 130, and 132.~~

~~10. The isolated anti-hemagglutinin antibody of claim 8, wherein the antibody comprises a heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:111 and 115.~~

~~11. The isolated anti-hemagglutinin antibody of claim 8, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID~~

NOs:111 and 115, and the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:113, 117, 119, 122, 124, 126, 128, 130, and 132.

12. The isolated anti-hemagglutinin antibody of claim 8, wherein the antibody comprises a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:112, 116, 118, 121, 123, 125, 127, 129, and 131.

13. The isolated anti-hemagglutinin antibody of claim 8, wherein the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:110, 114, and 120.

14. The isolated anti-hemagglutinin antibody of claim 8, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:110, 114, and 120, and the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:112, 116, 118, 121, 123, 125, 127, 129, and 131.

15. An isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:200;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:201;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:202;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:203;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:204; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:205.

16. The isolated anti-hemagglutinin antibody of claim 15, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:156.

17. The isolated anti-hemagglutinin antibody of claim 15, wherein the antibody comprises a heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 154 and 158.

~~18. The isolated anti-hemagglutinin antibody of claim 15, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:154 and 158, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:156.~~

~~19. The isolated anti-hemagglutinin antibody of claim 15, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:155.~~

~~20. The isolated anti-hemagglutinin antibody of claim 15, wherein the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:153 and 157.~~

~~21. The isolated anti-hemagglutinin antibody of claim 15, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:153 and 157, and the light chain comprises the amino acid sequence of SEQ ID NO:155.~~

~~22. An isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:~~

~~(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:206;~~

~~(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:207;~~

~~(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:208;~~

~~(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:209;~~

~~(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:210; and~~

~~(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:211.~~

~~23. The isolated anti-hemagglutinin antibody of claim 22, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:162.~~

~~24. The isolated anti-hemagglutinin antibody of claim 22, wherein the antibody comprises a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 160.~~

25. The isolated anti-hemagglutinin antibody of claim 22, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:160, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:162.

26. The isolated anti-hemagglutinin antibody of claim 22, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:161.

27. The isolated anti-hemagglutinin antibody of claim 22, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:159.

28. The isolated anti-hemagglutinin antibody of claim 22, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:159, and the light chain comprises the amino acid sequence of SEQ ID NO:161.

29. An isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:

(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:212;

(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:213;

(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:214;

(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:215;

(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:216; and

(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:217.

30. The isolated anti-hemagglutinin antibody of claim 29, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:166.

31. The isolated anti-hemagglutinin antibody of claim 29, wherein the antibody comprises a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 164.

32. The isolated anti-hemagglutinin antibody of claim 29, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable

~~region comprises the amino acid sequence of SEQ ID NO:164, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:166.~~

~~33. The isolated anti-hemagglutinin antibody of claim 29, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:165.~~

~~34. The isolated anti-hemagglutinin antibody of claim 29, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:163.~~

~~35. The isolated anti-hemagglutinin antibody of claim 29, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:163, and the light chain comprises the amino acid sequence of SEQ ID NO:165.~~

~~36. An isolated anti-hemagglutinin antibody comprising three heavy chain hypervariable regions (HVR-H1, HVR-H2, and HVR-H3) and three light chain hypervariable regions (HVR-L1, HVR-L2, and HVR-L3), wherein:~~

~~(a) HVR-H1 comprises the amino acid sequence of SEQ ID NO:218;~~

~~(b) HVR-H2 comprises the amino acid sequence of SEQ ID NO:219;~~

~~(c) HVR-H3 comprises the amino acid sequence of SEQ ID NO:220;~~

~~(d) HVR-L1 comprises the amino acid sequence of SEQ ID NO:221;~~

~~(e) HVR-L2 comprises the amino acid sequence of SEQ ID NO:222; and~~

~~(f) HVR-L3 comprises the amino acid sequence of SEQ ID NO:223.~~

~~37. The isolated anti-hemagglutinin antibody of claim 36, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:170.~~

~~38. The isolated anti-hemagglutinin antibody of claim 36, wherein the antibody comprises a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 168.~~

~~39. The isolated anti-hemagglutinin antibody of claim 36, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:168, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:170.~~

~~40. The isolated anti-hemagglutinin antibody of claim 36, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:169.~~

~~41. The isolated anti-hemagglutinin antibody of claim 36, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:167.~~

~~42. The isolated anti-hemagglutinin antibody of claim 36, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:167, and the light chain comprises the amino acid sequence of SEQ ID NO:169.~~

~~43~~8. The isolated anti-hemagglutinin antibody of any one of claims 1-~~42~~ to 7, wherein the antibody is a human antibody.

9. Anti-hemagglutinin antibody of any one of claims 1 to 8 for use as a medicament.

~~44~~10. Anti-hemagglutinin antibody of any one of claims 1 to 8 for use in~~Use of the anti-hemagglutinin antibody of any one of claims 1-28, in the manufacture of a medicament for~~ treating, inhibiting, or preventing influenza A virus infection~~ in an individual in need thereof~~.

~~45~~11. The anti-hemagglutinin antibody for use of claim ~~44~~9 or 10, wherein the anti-hemagglutinin antibody~~medicament~~ is ~~to be administered~~used in combination with an additional therapeutic agent.

~~46~~12. The anti-hemagglutinin antibody for use of claim ~~45~~11, wherein the additional therapeutic agent is a neuraminidase inhibitor, an anti-hemagglutinin antibody, or an anti-M2 antibody.

~~47~~13. A composition comprising the antibody of any one of claims 1-~~28~~ to 8.

~~48~~14. A pharmaceutical composition comprising the antibody of any one of claims 1-~~28~~ to 8 and a pharmaceutically acceptable carrier.

~~49~~15. An isolated nucleic acid encoding the antibody of any one of claims 1-~~28~~ to 8.

~~50~~16. A host cell comprising the nucleic acid of claim ~~49~~15.

~~51~~17. A method of producing an antibody comprising culturing the host cell of claim ~~50~~ 16 so that the antibody is produced.

18. Use of the anti-hemagglutinin antibody of any one of claims 1 to 8 in the manufacture of a medicament for treating, inhibiting, or preventing influenza A virus infection.