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 ~~OF THE INVENTION~~

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

In ~~some embodiments~~one aspect, there is provided an isolated anti-hemagglutinin antibody ~~of the present invention comprises~~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.

In some embodiments, the disclosure~~invention~~ 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: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.

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

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

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

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

In some embodiments, the disclosure~~invention~~ 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:178;

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

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

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

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

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

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

In some embodiments, the disclosure~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three heavy chain hypervariable region (HVR) sequences, 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; and

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

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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.

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

In ~~some embodiments~~one aspect, there is provided an isolated anti-hemagglutinin antibody ~~of the present invention comprises~~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 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 amino acid sequence selected from the group consisting of SEQ ID NOs:197, 198, and 199.

In some embodiments, the disclosure~~invention~~ 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 an 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 amino acid sequence selected from the group consisting of SEQ ID NOs:197, 198, and 199.

In some embodiments, the disclosure~~invention~~ 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:195;

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

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

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

(a) HVR-H1 comprises an 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; and

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

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

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

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

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

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

(a) HVR-H1 comprises an 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; and

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

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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:134, 138, 142, 148, and 234, and the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:136, 140, 144, 146, 150, 152, and 235.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 136, 140, 144, 146, 150, 152, and 235.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 134, 138, 142, 148, and 234.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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:133, 137, 141, and 147, and the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:135, 139, 143, 145, 149, and 151.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 135, 139, 143, 145, 149, and 151.

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

In ~~some embodiments~~one aspect, there is provided an isolated anti-hemagglutinin antibody ~~of the present invention comprises~~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~~invention~~ 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~~invention~~ 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~~invention~~ 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;

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

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

In some embodiments, the disclosure~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three light chain hypervariable region (HVR) sequences, 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~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three heavy chain 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; and

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

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:156.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure ~~invention~~ comprises a heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 154 and 158.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure ~~invention~~ 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.

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

In ~~some embodiments~~one aspect, there is provided an isolated anti-hemagglutinin antibody ~~of the present invention comprises~~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~~invention~~ 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~~invention~~ 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

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

In some embodiments, the disclosure~~invention~~ 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:206;

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

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

In some embodiments, the disclosure~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three light chain hypervariable region (HVR) sequences, 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

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

In some embodiments, the disclosure~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three heavy chain 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; and

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

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:162.

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

In ~~some embodiments~~one aspect, there is provided an isolated anti-hemagglutinin antibody ~~of the present invention comprises~~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~~invention~~ 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, the disclosure~~invention~~ 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:215;

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

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

In some embodiments, the disclosure~~invention~~ 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:212;

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

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

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

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

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

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

In some embodiments, the disclosure~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three heavy chain 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; and

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

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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.

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

In ~~some embodiments~~one aspect, there is provided an isolated anti-hemagglutinin antibody ~~of the present invention comprises~~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~~invention~~ 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;

(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~~invention~~ 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:221;

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

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

In some embodiments, the disclosure~~invention~~ 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:218;

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

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

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

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

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

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

In some embodiments, the disclosure~~invention~~ provides an isolated anti-hemagglutinin antibody comprising: at least one, two, and/or three heavy chain 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; and

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

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure ~~invention~~ 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.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:170.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure ~~invention~~ comprises a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 168.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ 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.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure~~invention~~ comprises a light chain comprising the amino acid sequence of SEQ ID NO:169.

In some embodiments, an isolated anti-hemagglutinin antibody of the present disclosure ~~invention~~ comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:167.

The disclosure~~invention~~ also provides isolated nucleic acids encoding an anti-hemagglutinin antibody of the present disclosure~~invention~~. In one aspect, there is provided an isolated nucleic acid encoding the antibody as defined herein. The disclosure~~invention~~ also provides vectors comprising a nucleic acid encoding an anti-hemagglutinin antibody of the present disclosure~~invention~~. The disclosure~~invention~~ also provides host cells comprising a nucleic acid or a vector of the present disclosure~~invention~~. A vector can be of any type, for example, a recombinant vector such as an expression vector. In one aspect, there is provided a host cell comprising the nucleic acid as defined herein. Any of a variety of host cells can be used. In one embodiment, a host cell is a prokaryotic cell, for example, *E. coli*. In another embodiment, a host cell is a eukaryotic cell, for example, a mammalian cell, such as a Chinese Hamster Ovary (CHO) cell.

The disclosure~~invention~~ further provides a method of producing an anti-hemagglutinin antibody of the present disclosure~~invention~~. For example, the disclosure~~invention~~ provides methods for making an anti-hemagglutinin antibody (which, as defined herein, includes full length antibody and fragments

thereof), the method comprising expressing in a suitable host cell a recombinant vector of the disclosure~~invention~~ 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~~invention~~ (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~~invention~~ also provides a pharmaceutical formulation comprising an anti-hemagglutinin antibody of the present disclosure~~invention~~ 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~~invention~~ also provides compositions comprising an anti-hemagglutinin antibody of the present disclosure~~invention~~. 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).

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

Compositions comprising an anti-hemagglutinin antibody of the present disclosure~~invention~~ 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~~invention~~ 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~~invention~~, thereby inhibiting influenza A virus infection. The ~~invention~~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 ~~invention~~disclosure, thereby treating influenza A virus infection. The ~~invention~~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 ~~invention~~disclosure, thereby preventing influenza A virus infection.

The ~~invention~~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 ~~invention~~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 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 ~~invention~~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 ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an anti-hemagglutinin antibody of the present ~~invention~~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

inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of a nucleic acid of the ~~invention~~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 inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an expression vector of the ~~invention~~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 inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of a host cell of the ~~invention~~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 inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an article of manufacture of the ~~invention~~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 inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of a kit of the ~~invention~~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 inhibitor, such as oseltamivir or zanamivir; another antibody, such as another anti-hemagglutinin antibody or an anti-M2 antibody; etc).

In various ~~aspect~~embodiments, an anti-hemagglutinin antibody of the present ~~invention~~disclosure binds hemagglutinin. In some ~~aspect~~embodiments, an anti-hemagglutinin antibody of the present ~~invention~~disclosure binds Group1 hemagglutinin, binds Group2 hemagglutinin, or binds Group1 and Group2 hemagglutinin. In other ~~aspect~~embodiments, an anti-hemagglutinin antibody of the present ~~invention~~disclosure binds hemagglutinin and neutralizes influenza A virus. In some embodiments, an anti-hemagglutinin antibody of the present ~~invention~~disclosure neutralizes influenza A virus *in vitro*, *in vivo*, or *in vitro* and *in vivo*.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A and1B sets forth data showing FACS analysis of anti-hemagglutinin-positive (hemagglutinin H3+ and hemagglutinin H1+) plasmablasts from day 7 post-vaccinated human peripheral blood mononuclear cells (PBMCs) prior to SCID/beige mouse enrichment (Figure 1A) and day 8 post-intrasplenic implantation after SCID/beige mouse enrichment with and without antigen premix (Figure 1B) in the upper and lower panels, respectively.

Figure 2 sets forth data showing analysis of splenocytes obtained from day 8 post-intrasplenic implantation of PBMCs from individual SCID/beige mice with no PBMC/antigen premix (circles) and with PBMC/antigen premix (squares), as percent hemagglutinin $(H1)^{+}/CD38^{high}$ plasmablasts. The rectangle indicates mice that presented hemagglutinin $H1^{+}$ plasmablasts.

Figure 3 sets for data showing *in vitro* neutralization of various influenza A Group1 and Group2 virus strains by anti-hemagglutinin antibodies of the present invention.

Figures 4A and 4B set forth data showing *in vitro* neutralization of various influenza A Group1 (Figure 4A) and Group2 (Figure 4B) virus strains by monoclonal antibody 39.29 NWPP ("NWPP" disclosed as SEQ ID NO: 177).

Figures 5A and 5B set forth data showing *in vitro* neutralization of various influenza A Group1 (Figure 5A) and Group2 (Figure 5B) virus strains by monoclonal antibody 81.39 SVSH-NYP ("SVSH" disclosed as SEQ ID NO: 171).

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. The isolated anti-hemagglutinin antibody of claims 1-42, wherein the antibody is a human antibody.

44. ~~A method for treating, inhibiting, or preventing influenza A virus infection in an individual in need thereof, the method comprising administering to the individual an effective amount of a composition comprising~~Use of the anti-hemagglutinin antibody of any one of claims 1-28, ~~thereby treating, inhibiting, or preventing influenza A virus infection~~in the manufacture of a medicament for treating, inhibiting, or preventing influenza A virus infection in an individual in need thereof.

45. The ~~method~~ use of claim 44, wherein the ~~method further comprises administering to the individual~~medicament is to be administered with an additional therapeutic agent.

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

47. A composition comprising the antibody of any one of claims 1-28.

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

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

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

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

~~52. Use of the anti-hemagglutinin antibody of any one of claims 1-28 in the manufacture of a medicament.~~

~~53. The use of claim 52, wherein the medicament is for treating, inhibiting, or preventing influenza A virus infection.~~