On average 41,400 people died each year in the United States between 1979 and 2001 from influenza.

SUMMARY

The disclosure is based, at least in part, on the discovery of human anti-HA antibodies comprising functional and structural properties disclosed herein, e.g., antibodies that bind a conserved region or epitope on influenza virus and uses thereof.

Accordingly, the disclosure features binding agents, e.g., antibody molecules, or preparations, or isolated preparations thereof, that bind hemagglutinin (HA) from influenza viruses. In an embodiment, a binding agent, e.g., an antibody molecule, is broad spectrum, and binds more than one HA, e.g., an HA from one or both of Group 1 or Group 2 strains of influenza A viruses and/or one or more strains of influenza B viruses. Therefore, in some examples, a binding agent, e.g., an antibody molecule, featured in the disclosure can treat or prevent infection by a Group 1 influenza virus and a Group 2 influenza virus. In other examples, a binding agent, e.g., an antibody molecule, featured in the disclosure can treat or prevent infection by an influenza A virus and an influenza B virus. The binding agents, e.g, antibody molecules, share sufficient structural similarity with antibodies or variable regions disclosed herein such that they possess functional attributes of the antibodies disclosed herein. In examples the structural similarity can be in terms of three dimensional structure or linear amino acid sequence or both.

In an aspect, there is provide an isolated antibody molecule comprising:

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

a CDR1 comprising the sequence [S/T]-Y-[A/G]-M-H (SEQ ID NO:1);

a CDR2 comprising the sequence V-[I/V/L]-S-[Y/F]-D-G-[S/N]-[Y/N]-[K/R]-Y-Y-A-D-S-V-Q-G (SEQ ID NO:2); and

a CDR3 comprising the sequence D-[S/T]-[R/K/Q]-L-R-[S/T]-L-L-Y-F-E-W-L-S-[Q/S]-G-[Y/L/V]-[F/L]-[N/D]-[P/Y] (SEQ ID NO:3); and

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

a CDR1 comprising the sequence Q-[S/T]-[V/L/I]-[T/S]-[Y/F/W]-[N/S/D/Q/R/E]-Y-K-N-Y-L-A (SEQ ID NO:170);

a CDR2 comprising the sequence W-[A/G]-S-[T/A/Y/H/K/D]-[R/L]-E-[S/T] (SEQ ID NO:5); and

a CDR3 comprising the sequence Q-Q-[Y/H]-Y-R-T-P-P-[T/S] (SEQ ID NO:6).

In another aspect, there is provide the antibody molecule as defined above for use in preventing or treating an influenza virus infection in a human subject.

In another aspect, there is provided the use of the antibody molecule as defined above in the manufacture of a medicament for preventing or treating an influenza virus infection in a human subject.

In another aspect, there is provided a pharmaceutical composition comprising the antibody molecule as defined above and a pharmaceutically acceptable carrier.

In another aspect, there is provided a kit comprising the antibody molecule as defined above; and a pharmaceutically acceptable delivery vehicle or buffer, a delivery device, or both.

In another aspect, there is provided an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment and/or a nucleotide sequence that encodes a light chain immunoglobulin variable region segment of the antibody molecule as defineda above.

In another aspect, there is provided a recombinant vector comprising the nucleic acid molecule as defined above.

In another aspect, there is provided an isolated cell comprising the vector as defined above.

In another aspect, there is provided a method of making the antibody molecule as defined above, the method comprising providing a host cell as defined above and expressing the nucleic acids in the host cell, thereby making the antibody molecule.

In another aspect, there is provided a method of detecting an influenza virus in a biological sample, the method comprising contacting the sample with an antibody molecule as defined above, and detecting the binding of the antibody molecule to the sample, thereby detecting the influenza virus in the sample.

In one example, the disclosure features an anti-hemagglutinin (anti-HA) binding agent, e.g., a specific binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising one or more or all of the following properties:

(a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004;

(p) it binds an epitope which comprises or consists of the hemagglutinin trimer interface; and

(q) it binds an epitope other than that bound by a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., as determined by structural analysis, e.g., by X-ray crystallography or NMR spectroscopy;

(r) in an example it binds to an epitope, e.g., it has an epitope that overlaps with or is the same as, of an antibody disclosed herein, e.g., as determined by mutational analysis or crystal structure analysis

In one example, the binding agent, e.g., an anti-HA antibody molecule, has one or more of the following characteristics: the anti-HA antibody molecule prevents infection by at least 1, 2, 3, 4 or 5 influenza subtypes of Group 1, and by at least 1, 2, 3, 4 or 5 influenza subtypes of Group 2; the concentration of the anti-HA antibody molecule required for 50% neutralization of influenza A virus is less than 10 μg/mL; or the anti-HA antibody molecule binds an epitope that comprises or consists of the hemagglutinin trimer interface.

In one example, the binding agent, e.g., an anti-HA antibody molecule, featured in the disclosure treats or prevents infection by a Group 1 virus, such as where the virus is an H1, H2, H5, H6, H8, H9, H12, H11, H13, H16, or H17 virus; and treats or prevents infection by a Group 2 virus, such as where the virus is an H3, H4, H7, H10 or H15 virus.

In one example, the binding agent, e.g., an anti-HA antibody molecule, featured in the disclosure prevents infection by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 influenza subtypes of Group 1, and by at least 1, 2, 3, 4, 5 or 6 influenza subtypes of Group 2.

In one example, the binding agent, e.g., an anti-HA antibody molecule, featured in the disclosure treats or prevents infection by one or more of H1N1, H2N2,

H5N1, and H9N2, and also treats or prevents infection by one or more of H3N2 and H7N7.

In an example, a binding agent, e.g., antibody molecule, binds, and in examples, neutralizes:

at least one strain from the Group 1 H1, e.g., H1 a or H1b, cluster and at least one strain from the Group 2 H3 or H7 cluster.

In an example, a binding agent, e.g., antibody molecule, binds, and in examples, neutralizes:

at least one strain from the Group 1 H1, e.g., H1 a or H1b, cluster and at least one influenza B strain, e.g., B/Wisconsin/1/2010.

In an example, a binding agent, e.g., antibody molecule, binds, and in examples, neutralizes:

at least one strain from the Group 2 H3 or H7 cluster and at least one influenza B strain, e.g., B/Wisconsin/1/2010.

In an example, a binding agent, e.g., antibody molecule, binds, and in examples, neutralizes:

at least one strain from the Group 1 H1, e.g., H1 a or H1b, cluster, at least one strain from the Group 2 H3 or H7 cluster, and at least one influenza B strain, e.g., B/Wisconsin/1/2010.

In one example, the binding agent, e.g., an anti-HA antibody molecule, featured in the disclosure treats or prevents infection by one or more of influenza B viruses, e.g., B/Wisconsin/1/2010.

In one example, the anti-HA antibody molecule is not an anti-HA antibody molecule previously described in the art. For example, the anti-HA antibody molecule is other than one or more or all of Ab 67-11 (U.S. Provisional Application No. 61/645,453), FI6 (FI6, as used herein, refers to any specifically disclosed FI6

sequence in U.S. Published Application No. 2010/0080813, US published application No. 2011/0274702, WO2013/011347 or Corti et al., Science 333:850-856, 2011, published online July 28, 2011; FIGs. 12A to 12C), FI28 (U.S. Published Application No. 2010/0080813), C179 (Okuno et al., J. Virol. 67:2552-1558, 1993), F10 (Sui et al., Nat. Struct. Mol. Biol. 16:265, 2009), CR9114 (Dreyfus et al., Science. 2012; 337(6100):1343-1348; published online August 9, 2012), or CR6261 (Ekiert et al., Science 324:246-251, 2009; published online February 26, 2009).

In one example, the binding agent, e.g., an anti-HA antibody molecule, neutralizes infection with H1N1 and H3N2 in vitro. In another example, binding agent, e.g., an anti-HA antibody molecule, neutralizes infection with H1N1 and H3N2 in vivo.

In one example, the binding agent, e.g., an anti-HA antibody molecule, neutralizes infection with H5N1 in vitro. In another example, binding agent, e.g., an anti-HA antibody molecule, neutralizes infection with H5N1 in vivo.

In one example, the binding agent, e.g., an anti-HA antibody molecule, neutralizes infection with an influenza B virus, e.g., B/Wisconsin/1/2010, in vitro. In another example, the binding agent, e.g., an anti-HA antibody molecule neutralizes infection with an influenza B virus, e.g., B/Wisconsin/1/2010, in vivo.

In another example, the concentration of the binding agent, e.g., an anti-HA antibody molecule, required for 50% neutralization of influenza A virus is 10 μg/mL or less, such as 9 μg/mL or less, 8 μg/mL or less, 7 μg/mL or less, 6 μg/mL or less, or 5 μg/mL or less.

In another example, the concentration of the binding agent, e.g., an anti-HA antibody molecule, required for 60% neutralization of influenza A virus, 50% neutralization of influenza A virus, or 40% neutralization of influenza A virus is 10 μg/mL or less, such as 9 μg/mL or less, 8 μg/mL or less, 7 μg/mL or less, 6 μg/mL or less, or 5 μg/mL or less.

In yet another example, the binding agent, e.g., an anti-HA antibody molecule, is effective for prevention or treatment of infection, e.g., in humans or mice, with H1N1 and H3N2, such as when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6.0 mg/kg, 5.0 mg/kg, 4.0 mg/kg, 3.0 mg/kg, 2.0 mg/kg, 1.0 mg/kg or less.

In still another example, the binding agent, e.g., an the anti-HA antibody molecule, is effective for prevention or treatment of infection, e.g., in humans or mice, with H5N1, such as when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6.0 mg/kg, 5.0 mg/kg, 4.0 mg/kg, 3.0 mg/kg, 2.0 mg/kg, 1.0 mg/kg or less.

In another example, a binding agent, e.g., an anti-HA antibody molecule, is effective for the treatment or prevention of a Group 1 virus, where the Group 1 virus is H1, H5, or H9, and in another example, the binding agent, e.g., an anti-HA antibody molecule, is effective for the treatment or prevention of a Group 2 virus, where the Group 2 virus is H3 or H7.

In another example, the concentration of the binding agent, e.g., an anti-HA antibody molecule, required for 50% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, is 10 μg/mL or less, such as 9 μg/mL or less, 8 μg/mL or less, 7 μg/mL or less, 6 μg/mL or less, or 5 μg/mL or less.

In another example, the concentration of the binding agent, e.g., an anti-HA antibody molecule, required for 60% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, 50% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, or 40% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, is 10 μg/mL or less, such as 9 μg/mL or less, 8 μg/mL or less, 7 μg/mL or less, 6 μg/mL or less, or 5 μg/mL or less.

In another example, the binding agent, e.g., an anti-HA antibody molecule, is a full length tetrameric antibody, a single chain antibody (scFv), a $F(ab')_2$ fragment, a Fab fragment, or an Fd fragment. In another example, the heavy chain of the antibody molecule is a γ1 heavy chain, and in yet another example, the light chain of the antibody molecule is a κ light chain or a λ light chain. In yet another

example, the anti-HA antibody molecule featured in the disclosure is an IgG1 antibody.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

In an example the antibody molecule has properties: a; and b.

In an example the antibody molecule has properties: c; and d.

In an example the antibody molecule has properties: a; and c or d.

In an example the antibody molecule has properties: b; and c or d.

In an example the antibody molecule has properties: c; and a or b.

In an example the antibody molecule has properties: d; and a or b.

In an example the antibody molecule has properties: a, b, c and d.

In an example the antibody molecule has properties: a, b, c, d, e, and f.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

a) H3 HA1 residues N38, I278, or D291;

b) H3 HA2 residue N12;

c) H3 HA1 residues T318, R321, or V323; or

d) H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56, or E57.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

c) H3 HA1 residues Q327, T328, or R329; or

d) H3 HA2 residues G1, L2, F3, G4, or D46.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

aa) it includes one, two, or all of, H1 HA1 residues H31, N279, and S292;

bb) it includes H1 HA2 residue G12;

cc) it does not include one or both of H1 HA1 residues Q328 and S329;

dd) it does not include one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

ee) it includes one, two, or all of, H1 HA1 residues T319, R322, and I324 are bound by both Ab 044 and FI6; or

ff) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57

In an example the antibody molecule has properties: aa; and bb.

In an example the antibody molecule has properties: cc; and dd.

In an example the antibody molecule has properties: aa; and cc or dd.

In an example the antibody molecule has properties: bb; and cc or dd.

In an example the antibody molecule has properties: cc; and aa or bb.

In an example the antibody molecule has properties: dd; and aa or bb.

In an example the antibody molecule has properties: aa, bb, cc and dd.

In an example the antibody molecule has properties: aa, bb, cc, dd, ee, and ff.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324 ; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329 ; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an example the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an example the molecule has properties c, cc, d, and dd.

In an example the binding agent, e.g., a specific binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least, or more than, 60, 65, 70, 75, 80, 85, 87, 90, 95, 98 or 99 percent homology with a heavy chain variable region from Table 3, Table 4A, Table 4B, Fig.2, Fig 13 or Fig.17; and

a light chain variable region comprising at least, or more than, 60, 65, 70, 75, 80, 85, 87, 90, 95, 98 or 99 percent homology with light chain variable region from Table 3, Table 4A, Table 4B, Fig.3, Fig. 14 or Fig 17.

In an example, the antibody molecule comprises a heavy chain variable region 25 (SEQ ID NO:25), or a structurally or functionally related variable heavy chain region as described herein.

In an example, the antibody molecule comprises a light chain variable region 52 (SEQ ID NO:52), 155 (SEQ ID NO:155), or 45 (SEQ ID NO:45), or a structurally or functionally related variable light chain region as described herein.

In an example, the antibody molecule comprises:

a heavy chain variable region 25 (SEQ ID NO:25), or a structurally or functionally related variable heavy chain region as described herein; and

a light chain variable region 52 (SEQ ID NO:52), 155 (SEQ ID NO:155), or 45 (SEQ ID NO:45), or a structurally or functionally related variable light chain region as described herein.

In an example, the antibody molecule comprises a heavy chain variable region comprising one, two, or all of CDR1, CDR2, and CDR3, from heavy chain variable region 25 (SEQ ID NO:25), or a structurally or functionally related variable heavy chain region as described herein.

In an example, the antibody molecule comprises a light chain variable region comprising one, two, or all of CDR1, CDR2, and CDR3, from light chain variable region 52 (SEQ ID NO:52), 155 (SEQ ID NO:155), or 45 (SEQ ID NO:45), or a structurally or functionally related sequence as described herein.

In an example, the antibody molecule comprises:

a heavy chain variable region comprising one, two, or all of CDR1, CDR2, and CDR3, from heavy chain variable region 25 (SEQ ID NO:25), or a structurally or functionally related variable heavy chain region as described herein; and

a light chain variable region comprising one, two, or all of CDR1, CDR2, and CDR3, from light chain variable region 52 (SEQ ID NO:52), 155 (SEQ ID NO:155), or 45 (SEQ ID NO:45), or a structurally or functionally related variable light chain region as described herein.

In an example the antibody molecule comprises a heavy chain variable region from Fig 2 or Fig 13 or a structurally or functionally related variable heavy chain region as described herein.

In an example the antibody molecule comprises a light chain variable region from Fig 3 or Fig 14 or a structurally or functionally related variable light chain region as described herein.

In an example the antibody molecule comprises one, two, or all of, a CDR1, CDR2, and CDR3 from a heavy chain variable region from Fig 2 or Fig 13, or a structurally or functionally related sequences as described herein.

In an example the antibody molecule comprises one, two, or all of, a CDR1, CDR2, and CDR3 from a light chain variable region from Fig 3 or Fig 14, or a structurally or functionally related sequences as described herein.

In an example the antibody molecule comprises one, two or all of, HC CDR1, HC CDR2, and HC CDR3 and one, two or all of, LC CDR1, LC CDR2, and LC CDR3 from an antibody disclosed in Table 3, or a structurally or functionally related sequences as described herein.

In another example, the antibody molecule comprises the light chain LC45 (SEQ ID NO: 45). In yet another example, the antibody comprises the light chain LC45, and the heavy chain HC25 (SEQ ID NO: 25) or 24 (SEQ ID NO: 24). In one example, the antibody molecule comprises the light chain Ab032(SEQ ID NO: 45) and the heavy chain 25 (SEQ ID NO: 25). In yet another example, the antibody molecule comprises light chain LC52(SEQ ID NO: 52) and heavy chain HC25 (SEQ ID NO: 25).

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from heavy chain disclosed herein. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or FR sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from a heavy chain disclosed herein; and

b) one or more framework regions (FRs) from light chain disclosed herein. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or FR

sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from light chain disclosed herein.

In one example, an anti-HA antibody molecule featured in the disclosure, or preparation, or isolated preparation thereof, comprises

(a) a heavy chain immunoglobulin variable domain comprising a sequence at least 60, 70, 80, 85, 87, 90, 95, 97, 98, or 99, e.g., 90%, homologous, to a heavy chain consensus sequence provided herein, e.g., the heavy chain consensus sequence provided in Fig. 2 or Fig 13, e.g., the heavy chain consensus sequence provided in Fig. 2, SEQ ID NO:161; and

(b) a light chain immunoglobulin variable domain comprising a sequence at least 60, 70, 80, 85, 87, 90, 95, 97, 98, or 99, e.g., 95%, homologous, to a light chain consensus sequence provided herein, e.g., the light chain consensus sequence provided in Fig. 3 or Fig 14, e.g., the light chain consensus sequence provided in Fig. 3, SEQ ID NO:62.

For example, in one example, the anti-HA antibody molecule featured in the disclosure comprises one or both of:

(a) a heavy chain immunoglobulin variable domain comprising the sequence of SEQ ID NO:161, or a sequence at least 87% identical to SEQ ID NO:161; and

(b) a light chain immunoglobulin variable domain comprising the sequence SEQ ID NO:62, or a sequence at least 95% identical to SEQ ID NO:62.

In another example the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable domain comprising the sequence of SEQ ID NO:161, or a sequence at least 87% identical to SEQ ID NO:161; and

(b) a light chain immunoglobulin variable domain comprising the sequence SEQ ID NO:62, or a sequence at least 95% identical to SEQ ID NO:62, wherein said antibody molecule:

(i) fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an

influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); and

(ii) produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, such as when tested by the method described in (i).

In an example, the disclosure features an antibody molecule comprising one or both of:

(a) a heavy chain immunoglobulin variable region comprising the sequence of SEQ ID NO:161, or a sequence that differs from SEQ ID NO:161 by not more than 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15 or 16 , e.g., by no more than 2, 3, 4, or 5 amino acids, e.g., conservative amino acids; and

(b) a light chain immunoglobulin variable domain comprising the sequence SEQ ID NO:62, or a sequence that differs from SEQ ID NO:62 that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids.

In one example, the 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15 or 16 amino acid differences, e.g., conservative amino acid differences, in the heavy chain immunoglobulin variable region are in the FR regions of the heavy chain immunoglobulin variable domain. In another example, the 1, 2, 3, 4 or 5 amino acid differences, e.g., conservative amino acid differences, in the light chain immunoglobulin variable domain are in the FR regions of the light chain immunoglobulin variable domain. In one example, the amino acid differences in the heavy chain immunoglobulin variable region, or in the light chain immunoglobulin variable region, are conservative amino acid changes.

In an example the binding agent, e.g., an antibody molecule, binds to an epitope, e.g., it has an epitope that overlaps with or is the same as, of an antibody disclosed herein, e.g., as determined by mutational analysis or crystal structure analysis.

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from heavy chain consensus sequence disclosed herein. e.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from heavy chain consensus sequence disclosed herein; and

b) one or more framework regions (FRs) from light chain consensus sequence disclosed herein. e.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from light chain consensus disclosed herein.

In an example the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In another example, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 044.

In an example, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (ii) a light chain variable region segment comprising SEQ ID NO:52; or

c) Ab 044.

The HA can be from a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecules or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; and

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the antibody molecule binds to the same epitope, or a portion thereof, which the reference antibody molecule binds. In an example the antibody molecule does not bind to the same epitope, or a portion thereof, which the reference antibody molecule binds.

In an example the antibody molecule binds to the same epitope, or a portion thereof, on HA, as does a reference antibody molecule, e.g. an antibody molecule disclosed herein. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (ii) a light chain variable region segment comprising SEQ ID NO:52; or

c) Ab 044.

The HA can be HA1 or HA5, e.g., from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004Binding to the same epitope, or a portion thereof, can be shown by one or more of:

a) mutational analysis, e.g., binding to HA, or binding affinity for HA, is decreased or abolished if a residue is mutated;

b) analysis, e.g., comparison, of the crystal structure of the antibody molecule and HA and the crystal structure of a reference antibody and HA, e.g., to determine the touch points of each;

c) competition of the two antibodies for binding to HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004; and

d) (c) and one or both of (a) and (b).

Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004.

Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; or

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 52.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 52,

wherein, each HC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 25 and each LC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 52.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 52,

wherein the antibody molecule comprises 1, 2, 3, 4, 5, or all of:

(i) a HC CDR1 comprising: S at the 1st position and A at the 3rd position in HC CDR1;

(ii) a HC CDR2 comprising one or both, e.g., one of: V at the 2nd position; or N at the 7th position and Q at the 16th position in HC CDR2;

(iii) a HC CDR3 comprising: R at the 3rd position (and optionally, L at the 3rd position);

(iv) a LC CDR1 comprising one or both of, e.g., one of: I at the 3rd position; or D at the 6th position in LC CDR1;

(v) a LC CDR2 comprising one, two, or three of, e.g., one of: G at the 2nd position; Y at the 4th position; or L at the 5th position in LC CDR2;

(vi) a LC CDR3 comprising: S at the 9th position in LC CDR3;

In an example, the binding agent, e.g., an antibody molecule, comprises:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO:25 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising SEQ ID NO:52 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom).

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence:

Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom).

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a) LC CDR1-3, that collectively, differ from the AB 044 LC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids; and

b) HC CDR1-3, that collectively, differ from the AB 044 HC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids.

In one example, the antibody molecule comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (b) a light chain variable region segment comprising SEQ ID NO:52.

In an example, the binding agent is an antibody molecule comprising one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence **S**-Y-**A**-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, or 3, e.g., 1 or 2, amino acids, e.g., conservative amino acids, there from, optionally provided that at least 1 or 2 of the highlighted residue are not changed, e.g., both **S** and **A** are not changed);

a CDR2 comprising the sequence V-**V**-S-Y-D-G-**N**-Y-K-Y-Y-A-D-S-V-**Q**-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1, 2, or 3 of the highlighted residues are not changed, e.g., **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** are not changed);

a CDR3 comprising the sequence D-S-**R**-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that **R** is not changed); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence:

Q-S-**I**-T-**F**-**D**-Y-K-N-Y-L-A (SEQ ID NO:145) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1or 2 of the highlighted residues are not changed, e.g., **I** or **D** is not changed);

a CDR2 comprising the sequence W-**G**-S-**Y-L**-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided thatat least 1, 2 or 3 of the highlighted residues are not changed, e.g., 1, 2 or all of **G**, **Y**, and **L** are not changed);

a CDR3 comprising the sequence Q-Q-**H**-Y-R-T-P-P-**S** (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1 or both of the highlighted residues are not changed, e.g., **S** is not changed).

In an example a CDR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR, (i.e., while other residues in that CDR might be changed, the highlighted residue or combination of residues, are not changed). E.g., in an example, **V** or both **N** and **Q**, for heavy chain CDR2 are not changed.

In an example a CDR of the light and a CDR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of two CDRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of the three CDRs in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the three CDRs in the light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the six CDRs in the heavy and light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In one example, the binding agent is an antibody molecule that comprises one or more or all of the following properties:

(a) both **S** and **A** in HC CDR1 are unchanged;

(b) **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** in HC CDR2 are unchanged;

(c) **R** in HC CDR3 is unchanged;

(d) One or both of **I** and **D** in LC CDR1 are unchanged.

(e) 1, 2 or 3 of **G**, **Y**, and **L** in LC CDR2 are unchanged; OR

(f) **S** in LC CDR3 is unchanged.

In an example the antibody molecule comprises 1, 2, 3, 4, 5, or all 6 properties selected from (a) to (f).

In an example, the antibody molecule comprises a heavy chain having a one or more properties selected from (a), (b), and (c) and a light chain having one or more properties selected from (d), (e), and (f).

In one example, the binding agent, e.g., an antibody molecule, comprises one or both of:

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

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

In some examples, the antibody molecule comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an

H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); and (ii) it produces fewer escape mutants than does a reference anti-HA antibody molecule, such as Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, such as when tested by the method described in (i).

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from SEQ ID NO: 25 e.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 25; and

b) one or more framework regions (FRs) from SEQ ID NO: 52. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 52.

In one example, the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable region segment that further comprises one or more or all of:

an FR1 comprising the sequence Q-V-Q-L-L-E-T-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-***T*** (SEQ ID NO:74) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***T*** is not changed);

an FR2 comprising the sequence W-V-R-Q-P-P-G-K-G-L-E-***W***-V-A (SEQ ID NO:75) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***W*** is not changed, or that if changed, is other than R);

an FR3 comprising the sequence R-F-T-***I***-S-***R***-D-N-S-K-N-T-***L***-Y-L-Q-M-N-S-L-R-A-E-D-T-A-V-Y-Y-C-A-K (SEQ ID NO:76) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that one, two or three of ***I***, ***R***, or ***L*** is not changed, or that if ***I*** is changed it is other than G, if ***R*** is changed it is other than P. or if ***L*** is changed it is other than A); and

an FR4 comprising the sequence W-G-Q-G-T-T-L-T-V-S-S (SEQ ID NO:77) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom) or W-G-Q-G-T-T-V-T-V-S-S(SEQ ID NO:171) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain immunoglobulin variable region segment comprising one or more or all of:

an FR1 comprising the sequence D-I-Q-M-T-Q-S-P-S-S-L-S-A-S-V-G-D-R-V-T-I-T-C-***R***-S-S (SEQ ID NO:78) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***R*** is not changed);

an FR2 comprising the sequence W-Y-Q-Q-K-P-G-K-A-P-K-L-L-I-Y (SEQ ID NO:79) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

an FR3 comprising the sequence G-V-P-S-R-F-S-G-S-G-S-G-T-D-F-T-L-T-I-S-S-L-Q-P-E-D-F-A-T-Y-Y-***C*** (SEQ ID NO:80) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***C*** is not changed, or if changed, is other than P); and

an FR4 comprising the sequence F-G-Q-G-T-K-V-E-I-K (SEQ ID NO:81) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom).

In an example a FR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR, (i.e., while other residues in that FR might be changed, the highlighted residue or combination of residues, are not changed). E.g., in an example, one, two or three of ***I***, ***R***, or ***L*** for heavy chain FR3 is not changed.

In an example a FR of the light and a FR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of two FRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of FR2 and FR3 in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of FR1 and FR2 in the heavy and light chain includes one of the h ighlighted residues for that FR.

In an example all of the highlighted residues in heavy chain FR1-4 are unchanged.

In an example all of the highlighted residues in light chain FR1-4 are unchanged.

In an example all of the highlighted residues in both heavy and light chain FR1-4 are unchanged.

In an example, sequence of FR1 of the heavy chain variable region segment is Q-V-Q-L-L-E-T-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-*T* (SEQ ID NO:74).

In an example, sequence of FR1 of the heavy chain variable region segment is E-V-Q-L-L-E-S-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-*T* (SEQ ID NO:173).

In another example, the binding agent, e.g., an antibody molecule, comprises one or more or all of the following properties: (a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); (b) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g.,

In an example the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

In an example the antibody molecule has properties: a; and b.

In an example the antibody molecule has properties: c; and d.

In an example the antibody molecule has properties: a; and c or d.

In an example the antibody molecule has properties: b; and c or d.

In an example the antibody molecule has properties: c; and a or b.

In an example the antibody molecule has properties: d; and a or b.

In an example the antibody molecule has properties: a, b, c and d.

In an example the antibody molecule has properties: a, b, c, d, e, and f.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

a) H3 HA1 residues N38, I278, or D291;

b) H3 HA2 residue N12;

c) H3 HA1 residues T318, R321, or V323; or

d) H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56, or E57.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

c) H3 HA1 residues Q327, T328, or R329; or

d) H3 HA2 residues G1, L2, F3, G4, or D46.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

aa) it includes one, two, or all of, H1 HA1 residues H31, N279, and S292;

bb) it includes H1 HA2 residue G12;

cc) it does not include one or both of H1 HA1 residues Q328 and S329;

dd) it does not include one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

ee) it includes one, two, or all of, H1 HA1 residues T319, R322, and I324 are bound by both Ab 044 and FI6; or

ff) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example the antibody molecule has properties: aa; and bb.

In an example the antibody molecule has properties: cc; and dd.

In an example the antibody molecule has properties: aa; and cc or dd.

In an example the antibody molecule has properties: bb; and cc or dd.

In an example the antibody molecule has properties: cc; and aa or bb.

In an example the antibody molecule has properties: dd; and aa or bb.

In an example the antibody molecule has properties: aa, bb, cc and dd.

In an example the antibody molecule has properties: aa, bb, cc, dd, ee, and ff.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324 ; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329 ; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an example the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an example the molecule has properties c, cc, d, and dd.

In another example, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 069.

In an example, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G
(SEQ ID NO:69); and
a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:
a CDR1 comprising the sequence Q-S-I-T-F-E-Y-K-N-Y-L-A (SEQ ID NO:172);;
a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and
a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (ii) a light chain variable region segment comprising SEQ ID NO:155; or

c) Ab 069.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay;

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more. In an example

the antibody molecule binds to the same epitope, or a portion thereof, which the reference antibody molecule binds. In an example the antibody molecule does not bind to the same epitope, or a portion thereof, which the reference antibody molecule binds.

In an example the antibody molecule binds to the same epitope, or a portion thereof, on HA, as does a reference antibody molecule, e.g. an antibody molecule disclosed herein. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-E-Y-K-N-Y-L-A (SEQ ID NO:172);;

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (ii) a light chain variable region segment comprising SEQ ID NO:155; or

c) Ab 069.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Binding to the same epitope, or a portion thereof, can be shown by one or more of:

a) mutational analysis, e.g., binding or lack thereof to mutant HA, e.g., if a residue is mutated;

b) analysis, e.g., comparison, of the crystal structure of the antibody molecule and HA and the crystal structure of a reference antibody and HA, e.g., to determine the touch points of each;

c) competition of the two antibodies for binding to HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004; or

d) (c) and one or both of (a) and (b);

Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay;

c) flow cytometry. The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 155.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 155,

wherein each HC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 25 and each LC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 155.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising at least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 155,

wherein the antibody molecule comprises 1, 2, 3, 4, 5, or all of:

(i) a HC CDR1 comprising: S at the 1st position and A at the 3rd position in HC CDR1;

(ii) a HC CDR2 comprising one or both, e.g., one of: V at the 2nd position; or N at the 7^{th} position and Q at the 16^{th} position in HC CDR2;

(iii) a HC CDR3 comprising: R at the 3rd position (and optionally, L at the 3^{rd} position);

(iv) a LC CDR1 comprising one or both of, e.g., one of: ; I at the 3rd position; or E at the 6th position in LC CDR1;

(v) a LC CDR2 comprising one, two or three of, e.g., one of: G at the 2nd position; Y at the 4^{th} position; or L at the 5^{th} position in LC CDR2;

(vi) a LC CDR3 comprising: S at the 9^{th} position in LC CDR3;

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO:25 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising SEQ ID NO:155 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom).

In one example, the antibody molecule comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and

(b) a light chain variable region segment comprising SEQ ID NO:155.

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence:

Q-S-I-T-F-E-Y-K-N-Y-L-A (SEQ ID NO: 172) or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom).

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a) LC CDR1-3, that collectively, differ from the AB 069 LC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids; and

b) HC CDR1-3, that collectively, differ from the AB 069 HC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids.

In an example, the binding agent is an antibody molecule comprising one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence **S**-Y-**A**-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, or 3, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1 or 2 of the highlighted residues are not changed, e.g., both **S** and **A** are not changed);

a CDR2 comprising the sequence V-**V**-S-Y-D-G-**N**-Y-K-Y-Y-A-D-S-V-**Q**-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom , optionally provided that at least 1, 2, or 3 of the highlighted residues are not changed, e.g., **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** are not changed);

a CDR3 comprising the sequence D-S-**R**-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom optionally provided that, **R** is not changed); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence:

Q-S-**I**-T-**F-E**-Y-K-N-Y-L-A (SEQ ID NO: 172) or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1 or 2 of the highlighted residues are not changed, e.g., **I** or **E** is not changed);

a CDR2 comprising the sequence W-**G**-S-**Y-L**-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided thatat least 1, 2, or 3 of the highlighted residues are not changed, e.g., 1, 2 or all of **G**, **Y**, and **L** are not changed);

a CDR3 comprising the sequence Q-Q-**H**-Y-R-T-P-P-**S** (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that, at least one or both of the highlighted residues are not changed, e.g., **S** is not changed).

In an example a CDR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR, (i.e., while other residues in that CDR might be changed, the highlighted residue or combination of residues, are not changed).

In an example a CDR of the light and a CDR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of two CDRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of the three CDRs in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the three CDRs in the light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the six CDRs in the heavy and light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In one example, the binding agent is an antibody molecule that comprises one or more or all of the following properties:

(a) both **S** and **A** in HC CDR1 are unchanged.

(b) **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** in HC CDR2 are unchanged.

(c) **R** in HC CDR3 is unchanged.

(d) one or both of **I** and **E** in LC CDR1 are unchanged.

(e) 1, 2 or 3 of **G**, **Y**, and **L** in LC CDR2 are unchanged;

(f) **S** in LC CDR3 is unchanged.

In an example the antibody molecule comprises 1, 2, 3, 4, 5, or all 6 properties selected from (a) to (f).

In an example, the antibody molecule comprises a heavy chain having a one or more properties selected from (a), (b), and (c) and a light chain having one or more properties selected from (d), (e), and (f).

In one example, the antibody molecule comprises one or both of:

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

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-E-Y-K-N-Y-L-A (SEQ ID NO:172);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

In some examples, the antibody molecule comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); and (ii) it produces fewer escape mutants than does a reference anti-HA antibody molecule, such as Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, such as when tested by the method described in (i).

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from SEQ ID NO: 25. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 25; and

b) one or more framework regions (FRs) from SEQ ID NO: 155. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 155.

In one example, the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable region segment that further comprises one or more or all of:

In an example a FR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR, (i.e., while other residues in that FR might be changed, the highlighted residue or combination of residues, are not changed). E.g., in an example, one, two or three of ***I***, ***R***, or ***L*** for heavy chain FR3 is not changed.

In an example a FR of the light and a FR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of two FRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of FR2 and FR3 in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of FR1 and FR2 in the heavy and light chain includes one of the h ighlighted residues for that FR.

In an example all of the highlighted residues in heavy chain FR1-4 are unchanged.

In an example all of the highlighted residues in light chain FR1-4 are unchanged.

In an example all of the highlighted residues in both heavy and light chain FR1-4 are unchanged.

In another example, the binding agent, e.g., an antibody molecule, comprises one or more or all of the following properties: (a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); (b) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g.,

In an example the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

In an example the antibody molecule has properties: a; and b.

In an example the antibody molecule has properties: c; and d.

In an example the antibody molecule has properties: a; and c or d.

In an example the antibody molecule has properties: b; and c or d.

In an example the antibody molecule has properties: c; and a or b.

In an example the antibody molecule has properties: d; and a or b.

In an example the antibody molecule has properties: a, b, c and d.

In an example the antibody molecule has properties: a, b, c, d, e, and f.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

a) H3 HA1 residues N38, I278, or D291;

b) H3 HA2 residue N12;

c) H3 HA1 residues T318, R321, or V323; or

d) H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56, or E57.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

c) H3 HA1 residues Q327, T328, or R329; or

d) H3 HA2 residues G1, L2, F3, G4, or D46.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

aa) it includes one, two, or all of, H1 HA1 residues H31, N279, and S292;

bb) it includes H1 HA2 residue G12;

cc) it does not include one or both of H1 HA1 residues Q328 and S329;

dd) it does not include one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

ee) it includes one, two, or all of, H1 HA1 residues T319, R322, and I324 are bound by both Ab 044 and FI6; or

ff) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example the antibody molecule has properties: aa; and bb.

In an example the antibody molecule has properties: cc; and dd.

In an example the antibody molecule has properties: aa; and cc or dd.

In an example the antibody molecule has properties: bb; and cc or dd.

In an example the antibody molecule has properties: cc; and aa or bb.

In an example the antibody molecule has properties: dd; and aa or bb.

In an example the antibody molecule has properties: aa, bb, cc and dd.

In an example the antibody molecule has properties: aa, bb, cc, dd, ee, and ff.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329 ; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an example the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an example the molecule has properties c, cc, d, and dd.

In an example the molecule has properties c, cc, d, and dd.

In another example, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 032.

In an example, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO: 71);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (ii) a light chain variable region segment comprising SEQ ID NO:45; or

c) Ab 032.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; and

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the antibody molecule binds to the same epitope, or a portion thereof, which the reference antibody molecule binds. In an example the

antibody molecule does not bind to the same epitope, or a portion thereof, which the reference antibody molecule binds.

In an example the antibody molecule binds to the same epitope, or a portion thereof, on HA, as does a reference antibody molecule, e.g. an antibody molecule disclosed herein. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO: 71);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and (ii) a light chain variable region segment comprising SEQ ID NO:45; or

c) Ab 32.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Binding to the same epitope, or a portion thereof, can be shown by one or more of:

a) mutational analysis, e.g., binding to HA, or binding affinity for HA, is decreased or abolished if a residue is mutated;

b) analysis, e.g., comparison, of the crystal structure of the antibody molecule and HA and the crystal structure of a reference antibody and HA, e.g., to determine the touch points of each;

c) competition of the two antibodies for binding to HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004; and

d) (c) and one or both of (a) and (b);

Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; and

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 45.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 45,

wherein each HC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 25 and each LC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 45.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 45,

wherein the antibody molecule comprises 1, 2, 3, 4, 5, or all of:

(i) a HC CDR1 comprising: S at the 1st position and A at the 3rd position in HC CDR1;

(ii) a HC CDR2 comprising one or both, e.g., one of: V at the 2nd position; or N at the 7th position and Q at the 16th position in HC CDR2;

(iii) a HC CDR3 comprising: R at the 3rd position (and optionally, L at the 3rd position);

(iv) a LC CDR1 comprising: ; I at the 3rd position;;

(v) a LC CDR2 comprising one, two, or three of, e.g., one of: G at the 2nd position; Y at the 4th position; or L at the 5th position in LC CDR2;

(vi) a LC CDR3 comprising: S at the 9th position in LC CDR3;

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO:25 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising SEQ ID NO:155 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom).

In one example, the antibody molecule comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 25; and

(b) a light chain variable region segment comprising SEQ ID NO:155.

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence:

Q-S-I-T-F N-Y-K-N-Y-L-A (SEQ ID NO:71) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom).

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a) LC CDR1-3, that collectively, differ from the AB 032 LC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids; and

b) HC CDR1-3, that collectively, differ from the AB 032 HC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids.

In an example, the binding agent is an antibody molecule comprising one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence **S**-Y-**A**-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, or 3, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1 or 2 of the highlighted residues are not changed, e.g., both **S** and **A** are not changed);

a CDR2 comprising the sequence V-**V**-S-Y-D-G-**N**-Y-K-Y-Y-A-D-S-V-**Q**-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, provided that, e,g., at least 1, 2, or 3 of the highlighted residues are not changed, e.g., **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** are not changed);

a CDR3 comprising the sequence D-S-**R**-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that **R** is not changed); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence: Q-S-**I**-T-**F**-N-Y-K-N-Y-L-A (SEQ ID NO: 71) or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2

amino acids, e.g., conservative amino acids, therefrom, optionally provided thatat least 1 or 2 of the highlighted residues are not changed, e.g., **I** is not changed);

a CDR2 comprising the sequence W-**G**-S-**Y-L**-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1, 2, or 3 of the highlighted residues are not changed, e.g., 1, 2 or all of **G**, **Y**, and **L** are not changed);

a CDR3 comprising the sequence Q-Q-**H**-Y-R-T-P-P-**S** (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least one or both of the highlighted residues are not changed, e.g., **S** is not changed).

In an example a CDR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR, (i.e., while other residues in that CDR might be changed, the highlighted residue or combination of residues, are not changed).

In an example a CDR of the light and a CDR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of two CDRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of the three CDRs in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the three CDRs in the light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the six CDRs in the heavy and light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In one example, the binding agent is an antibody molecule that comprises one or more or all of the following properties:

(a) both **S** and **A** in HC CDR1 are unchanged.

(b) **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** in HC CDR2 are unchanged.

(c) **R** in HC CDR3 is unchanged.

(d) **I** in LC CDR1 is unchanged.

(e) 1, 2 or 3 of **G**, **Y**, and **L** in LC CDR2 are unchanged;

(f) **S** in LC CDR3 is unchanged.

In an example the antibody molecule comprises 1, 2, 3, 4, 5, or all 6 properties selected from (a) to (f).

In an example, the antibody molecule comprises a heavy chain having a one or more properties selected from (a), (b), and (c) and a light chain having one or more properties selected from (d), (e), and (f).

In one example, the antibody molecule comprises one or both of:

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

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO: 71);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

In some examples, the antibody molecule comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); and (ii) it produces fewer escape mutants than does a reference anti-HA antibody molecule, such as Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, such as when tested by the method described in (i).

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from SEQ ID NO: 25. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 25; and

b) one or more framework regions (FRs) from SEQ ID NO: 45. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 45.

In one example, the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable region segment that further comprises one or more or all of:

an FR1 comprising the sequence Q-V-Q-L-L-E-T-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-***T*** (SEQ ID NO:74) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***T*** is not changed);

an FR2 comprising the sequence W-V-R-Q-P-P-G-K-G-L-E-***W***-V-A (SEQ ID NO:75) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2, amino

In an example a FR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR, (i.e., while other residues in that FR might be changed, the highlighted residue or combination of residues, are not changed). E.g., in an example, one, two or three of ***I***, ***R***, or ***L*** for heavy chain FR3 is not changed.

In an example a FR of the light and a FR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of two FRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of FR2 and FR3 in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of FR1 and FR2 in the heavy and light chain includes one of the h ighlighted residues for that FR.

In an example all of the highlighted residues in heavy chain FR1-4 are unchanged.

In an example all of the highlighted residues in light chain FR1-4 are unchanged.

In an example all of the highlighted residues in both heavy and light chain FR1-4 are unchanged.

In another example, the binding agent, e.g., an antibody molecule, comprises one or more or all of the following properties: (a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); (b) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g.,

In an example the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

In an example the antibody molecule has properties: a; and b.

In an example the antibody molecule has properties: c; and d.

In an example the antibody molecule has properties: a; and c or d.

In an example the antibody molecule has properties: b; and c or d.

In an example the antibody molecule has properties: c; and a or b.

In an example the antibody molecule has properties: d; and a or b.

In an example the antibody molecule has properties: a, b, c and d.

In an example the antibody molecule has properties: a, b, c, d, e, and f.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

a) H3 HA1 residues N38, I278, or D291;

b) H3 HA2 residue N12;

c) H3 HA1 residues T318, R321, or V323; or

d) H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56, or E57.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

c) H3 HA1 residues Q327, T328, or R329; or

d) H3 HA2 residues G1, L2, F3, G4, or D46.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

aa) it includes one, two, or all of, H1 HA1 residues H31, N279, and S292;

bb) it includes H1 HA2 residue G12;

cc) it does not include one or both of H1 HA1 residues Q328 and S329;

dd) it does not include one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

ee) it includes one, two, or all of, H1 HA1 residues T319, R322, and I324 are bound by both Ab 044 and FI6; or

ff) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example the antibody molecule has properties: aa; and bb.

In an example the antibody molecule has properties: cc; and dd.

In an example the antibody molecule has properties: aa; and cc or dd.

In an example the antibody molecule has properties: bb; and cc or dd.

In an example the antibody molecule has properties: cc; and aa or bb.

In an example the antibody molecule has properties: dd; and aa or bb.

In an example the antibody molecule has properties: aa, bb, cc and dd.

In an example the antibody molecule has properties: aa, bb, cc, dd, ee, and ff.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an example the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an example the molecule has properties c, cc, d, and dd.

In another example, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 031.

In an example, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO:71);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 24; and (ii) a light chain variable region segment comprising SEQ ID NO:45; or

c) Ab 031.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; and

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the antibody molecule binds to the same epitope, or a portion thereof, which the reference antibody molecule binds.

In an example the antibody molecule does not bind to the same epitope, or a portion thereof, which the reference antibody molecule binds.

In an example the antibody molecule binds to the same epitope, or a portion thereof, on HA, as does a reference antibody molecule, e.g. an antibody molecule disclosed herein. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO:71);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

b) an antibody molecule comprises one or both of: (i) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 24; and (ii) a light chain variable region segment comprising SEQ ID NO:45; or

c) Ab 031.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Binding to the same epitope, or a portion thereof, can be shown by one or more of:

a) mutational analysis, e.g., binding to HA, or binding affinity for HA, is decreased or abolished if a residue is mutated;

b) analysis, e.g., comparison, of the crystal structure of the antibody molecule and HA and the crystal structure of a reference antibody and HA, e.g., to determine the touch points of each;

c) competition of the two antibodies for binding to HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004;

d) (c) and one or both of (a) and (b).

Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; and

c) flow cytometry.

The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 24;

and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 45.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 24;

and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 45,

wherein, optionally, each HC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 24 and each LC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR of SEQ ID NO: 45.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 25;

and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with SEQ ID NO: 45,

wherein the antibody molecule comprises 1, 2, 3, 4, 5, or all of:

(i) a HC CDR1 comprising: S at the 1st position and A at the 3rd position in HC CDR1;

(ii) a HC CDR2 comprising one or both, e.g., one of: V at the 2nd position; or N at the 7^{th} position and Q at the 16^{th} position in HC CDR2;

(iii) a HC CDR3 comprising: R at the 3rd position (and optionally, L at the 3^{rd} position);

(iv) a LC CDR1 comprising: ; I at the 3rd position;;

(v) a LC CDR2 comprising one, two, or three of, e.g., one of: G at the 2nd position; Y at the 4^{th} position; or L at the 5^{th} position in LC CDR2;

(vi) a LC CDR3 comprising: S at the 9^{th} position in LC CDR3;

In an example, the binding agent comprises an antibody molecule comprising:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO:24(or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising SEQ ID NO:45 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom).

In one example, the antibody molecule comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO: 24; and

(b) a light chain variable region segment comprising SEQ ID NO:45.

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO:71) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO: 72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom).

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a) LC CDR1-3, that collectively, differ from the AB 031 LC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids; and

b) HC CDR1-3, that collectively, differ from the AB 031 HC CDR1-3 by no more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, e.g., 1, 2, 3, or 4, amino acids, e.g., conservative amino acids.

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence **S**-Y-**A**-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, or 3, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided thatat least 1 or 2 of the highlighted residues are not changed, e.g., both **S** and **A** are not changed);

a CDR2 comprising the sequence V-**V**-S-Y-D-G-**N**-Y-K-Y-Y-A-D-S-V-**Q**-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom , provided that, e,g., at least 1, 2, or 3 of the highlighted residues are not changed, e.g., **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** are not changed);

a CDR3 comprising the sequence D-S-**R**-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom optionally provided that, e.g., **R** is not changed); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-**I**-T-**F**-N-Y-K-N-Y-L-A (SEQ ID NO: 71) or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided thatat least 1 or 2 of the highlighted residues are not changed, e.g., **I** is not changed);

a CDR2 comprising the sequence W-**G**-S-**Y-L**-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least 1, 2, or 3 of

the highlighted residues are not changed, e.g., 1, 2 or all of **G**, **Y**, and **L** are not changed);

a CDR3 comprising the sequence Q-Q-**H**-Y-R-T-P-P-**S** (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that at least one or both of the highlighted residues are not changed, e.g., **S** is not changed).

In an example a CDR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR, (i.e., while other residues in that CDR might be changed, the highlighted residue or combination of residues, are not changed).

In an example a CDR of the light and a CDR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of two CDRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of the three CDRs in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the three CDRs in the light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In an example each of the six CDRs in the heavy and light chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

In one example, the binding agent is an antibody molecule that comprises one or more or all of the following properties:

(a) both **S** and **A** in HC CDR1 are unchanged.

(b) **V** or both **N** and **Q** or all three of **V**, **N**, and **Q** in HC CDR2 are unchanged.

(c) **R** in HC CDR3 is unchanged.

(d) **I** in LC CDR1 is unchanged.

(e) 1, 2 or 3 of **G**, **Y**, and **L** in LC CDR2 are unchanged;

(f) **S** in LC CDR3 is unchanged.

In an example the antibody molecule comprises 1, 2, 3, 4, 5, or all 6 properties selected from (a) to (f).

In an example, the antibody molecule comprises a heavy chain having a one or more properties selected from (a), (b), and (c) and a light chain having one or more properties selected from (d), (e), and (f).

In the example, the antibody molecule comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO:71);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

In some examples, the antibody molecule comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by

the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); and (ii) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by the method described in (i).

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from SEQ ID NO: 24. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 24; and

b) one or more framework regions (FRs) from SEQ ID NO: 45. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from SEQ ID NO: 45.

In one example, the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable region segment that further comprises one or more or all of:

an FR1 comprising the sequence E-V-Q-L-L-E-S-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-***T*** (SEQ ID NO:82) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***T*** is not changed);

an FR2 comprising the sequence W-V-R-Q-P-P-G-K-G-L-E-***W***-V-A (SEQ ID NO:75) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***W*** is not changed, or that if changed, is other than R);

an FR3 comprising the sequence R-F-T-***I***-S-***R***-D-N-S-K-N-T-***L***-Y-L-Q-M-N-S-L-R-A-E-D-T-A-V-Y-Y-C-A-K (SEQ ID NO:76) (or a sequence that differs by no

more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that one, two or three of ***I***, ***R***, or ***L*** is not changed, or that if ***I*** is changed it is other than G, if ***R*** is changed it is other than P. or if ***L*** is changed it is other than A); and

an FR4 comprising the sequence W-G-Q-G-T-T-L-T-V-S-S (SEQ ID NO:77) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom)or W-G-Q-G-T-T-V-T-V-S-S (SEQ ID NO:171) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom); and

(a) a light chain immunoglobulin variable region segment further comprises one or more or all of:

an FR1 comprising the sequence D-I-Q-M-T-Q-S-P-S-S-L-S-A-S-V-G-D-R-V-T-I-T-C-***R***-S-S (SEQ ID NO:78) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, , optionally provided that ***R*** is not changed);

an FR2 comprising the sequence W-Y-Q-Q-K-P-G-K-A-P-K-L-L-I-Y (SEQ ID NO:79) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom);

an FR3 comprising the sequence G-V-P-S-R-F-S-G-S-G-S-G-T-D-F-T-L-T-I-S-S-L-Q-P-E-D-F-A-T-Y-Y-***C*** (SEQ ID NO:80) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom, optionally provided that ***C*** is not changed, or if changed, is other than P); and

an FR4 comprising the sequence F-G-Q-G-T-K-V-E-I-K (SEQ ID NO:81) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids, therefrom).

In an example a FR of the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR, (i.e., while other residues in that FR might be changed, the highlighted residue or combination of residues, are not changed). E.g., in an example, one, two or three of ***I***, ***R***, or ***L*** for heavy chain FR3 is not changed.

In an example a FR of the light and a FR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of two FRs in the antibody molecule includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR. In examples both are in the light chain. In examples both are in the heavy chain.

In an example each of FR2 and FR3 in the heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that FR.

In an example each of FR1 and FR2 in the heavy and light chain includes one of the h ighlighted residues for that FR.

In an example all of the highlighted residues in heavy chain FR1-4 are unchanged.

In an example all of the highlighted residues in light chain FR1-4 are unchanged.

In an example all of the highlighted residues in both heavy and light chain FR1-4 are unchanged.

In one example, the antibody molecule comprises:

(a) the heavy chain immunoglobulin variable region segment comprises one or more or all of

an FR1 comprising the sequence E-V-Q-L-L-E-S-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-T (SEQ ID NO:82);

an FR2 comprising the sequence W-V-R-Q-P-P-G-K-G-L-E-W-V-A (SEQ ID NO:75);

an FR3 comprising the sequence R-F-T-I-S-R-D-N-S-K-N-T-L-Y-L-Q-M-N-S-L-R-A-E-D-T-A-V-Y-Y-C-A-K (SEQ ID NO:76); and

an FR4 comprising the sequence W-G-Q-G-T-T-L-T-V-S-S (SEQ ID NO:77) or W-G-Q-G-T-T-V-T-V-S-S (SEQ ID NO:171); and

(b) the light chain immunoglobulin variable region segment comprising one or more or all of

an FR1 comprising the sequence D-I-Q-M-T-Q-S-P-S-S-L-S-A-S-V-G-D-R-V-T-I-T-C-*R*-S-S (SEQ ID NO:78);

an FR2 comprising the sequence W-Y-Q-Q-K-P-G-K-A-P-K-L-L-I-Y (SEQ ID NO:79);

an FR3 comprising the sequence G-V-P-S-R-F-S-G-S-G-S-G-T-D-F-T-L-T-I-S-S-L-Q-P-E-D-F-A-T-Y-Y-C (SEQ ID NO:80); and

an FR4 comprising the sequence F-G-Q-G-T-K-V-E-I-K (SEQ ID NO:81).

In another example, the antibody molecule comprises one or more or all of the following properties: (a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); (b) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by the method described in (a); (c) it binds with high affinity to a hemagglutinin (HA) of at least 1, 2, 3, 4 or 5 influenza subtypes of Group 1 and at least 1, 2, 3, 4 or 5 influenza subtypes of Group 2; (d) it treats or prevents infection by at least 1, 2, 3, 4 or 5 influenza subtypes of Group 1, and by at least 1, 2, 3, 4 or 5 influenza subtypes of Group 2; (e) it inhibits fusogenic activity of the targeted HA; (f) it treats or prevents infection by a Group 1 virus, wherein the virus is an H1, H5, or H9 virus; and treats or prevents infection by a Group 2 virus, wherein the virus is an H3 or H7 virus; (g) it treats or prevents infection by influenza A strains H1N1 and H3N2; (h) it is effective for prevention or treatment of infection, e.g., in humans or mice, with H1N1 and H3N2 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (i) it treats or prevents infection by influenza A strains H5N1; (j) it is effective for prevention or treatment of infection, e.g., in humans or mice, with H5N1 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or

1 mg/kg; (k) it binds with high affinity to a hemagglutinin (HA) of an influenza B virus, e.g., B/Wisconsin/1/2010; (l) it treats or prevents infection by an influenza B virus, e.g., B/Wisconsin/1/2010; (m) it is effective for prevention or treatment of infection, e.g., in humans or mice, with an influenza B virus, e.g., B/Wisconsin/1/2010 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (n) the concentration of antibody molecule required for 50% neutralization of influenza A virus is less than 10 μg/mL; (o) the concentration of antibody molecule required for 50% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, is less than 10 μg/mL; (p) it prevents or minimizes secondary infection (e.g., secondary bacterial infection) or effects thereof on a subject; (q) it is effective for preventing or minimizing secondary infection (e.g., secondary bacterial infection) or effects thereof on a subject when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (r) it binds an epitope which comprises or consists of the hemagglutinin trimer interface; and (s) it binds an epitope other than that bound by a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by a method disclosed herein, e.g., by competition in an ELISA assay.

In another example, the disclosure features an antibody molecule comprising: (a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO:24 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom); and (b) a light chain variable region segment comprising SEQ ID NO:45 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom). In some examples, the antibody molecule comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza a virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004; and (ii) it produces fewer escape mutants than does a

reference anti-HA antibody molecule, such as Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, such as when tested by the method described in (i).

In an example the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

In an example the antibody molecule has properties: a; and b.

In an example the antibody molecule has properties: c; and d.

In an example the antibody molecule has properties: a; and c or d.

In an example the antibody molecule has properties: b; and c or d.

In an example the antibody molecule has properties: c; and a or b.

In an example the antibody molecule has properties: d; and a or b.

In an example the antibody molecule has properties: a, b, c and d.

In an example the antibody molecule has properties: a, b, c, d, e, and f.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

a) H3 HA1 residues N38, I278, or D291;

b) H3 HA2 residue N12;

c) H3 HA1 residues T318, R321, or V323; or

d) H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56, or E57.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

c) H3 HA1 residues Q327, T328, or R329; or

d) H3 HA2 residues G1, L2, F3, G4, or D46.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

aa) it includes one, two, or all of, H1 HA1 residues H31, N279, and S292;

bb) it includes H1 HA2 residue G12;

cc) it does not include one or both of H1 HA1 residues Q328 and S329;

dd) it does not include one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

ee) it includes one, two, or all of, H1 HA1 residues T319, R322, and I324 are bound by both Ab 044 and FI6; or

ff) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example the antibody molecule has properties: aa; and bb.

In an example the antibody molecule has properties: cc; and dd.

In an example the antibody molecule has properties: aa; and cc or dd.

In an example the antibody molecule has properties: bb; and cc or dd.

In an example the antibody molecule has properties: cc; and aa or bb.

In an example the antibody molecule has properties: dd; and aa or bb.

In an example the antibody molecule has properties: aa, bb, cc and dd.

In an example the antibody molecule has properties: aa, bb, cc, dd, ee, and ff.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324 ; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an example the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an example the molecule has properties c, cc, d, and dd.

In another example, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of one or both a heavy chain variable region and a light chain variable region disclosed herein.

In an example, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising the heavy and light CDRs from :

a heavy chain variable region from Table 3, Table 4A, Table 4B, Fig.2, Fig 13, or Fig. 17; and

a light chain variable region from Table 3, Table 4A, Table 4B, Fig.3, Fig 14, or Fig 17.

b) an antibody molecule that comprises: (i) a heavy chain immunoglobulin variable region segment from Table 3, Table 4A, Table 4B, Fig.2, Fig 13, or Fig. 17; and (ii) a light chain variable region segment from Table 3, Table 4A, Table 4B, Fig.3, Fig 14, or Fig 17; or

c) an antibody disclosed herein.

The HA can be HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, e.g. from an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art. Reduction of the ability to bind can be evaluated, e.g., by one or more of:

a) BIAcore analysis;

b) ELISA assay; and

c) flow cytometry. The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more. In an example the antibody molecule binds to the same epitope, or a portion thereof, which the reference antibody molecule binds. In an example the antibody molecule does not bind to the same epitope, or a portion thereof, which the reference antibody molecule binds.

In an example the antibody molecule binds to the same epitope, or a portion thereof, on HA, as does a reference antibody molecule, e.g. an antibody molecule disclosed herein. The reference antibody molecule can be:

a) an antibody molecule comprising the heavy and light CDRs from :

a heavy chain variable region from Table 3, Table 4A, Table 4B, Fig.2, Fig 13, or Fig. 17; and

c) flow cytometry. The antibody molecule can compete with the reference antibody such that binding of the reference antibody is decreased by 50% or more.

d) competition of the two antibodies for binding to HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004; and

e) (c) and one or both of (a) and (b).

Competition between the antibody molecule and a reference antibody molecule can be determined by evaluating the ability of one of the antibody molecule or the reference antibody molecule to decrease binding of the other to a substrate, e.g., HA, e.g., HA1 or HA5, from, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004. Reduction of the ability to bind can be evaluated by methods in the art.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with a reference heavy chain from Table 3, Table 4A, Table 4B, Fig.2, Fig 13 or Fig.17; and

a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with reference light chain from Table 3, Table 4A, Table 4B, Fig.3, Fig. 14 or Fig 17,

wherein, optionally, each HC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding HC CDR from its reference heavy chain and each LC CDR differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., 1 or 2, e.g., conservative amino acids, from the corresponding CDR in its reference light chain.

In an example the binding agent, e.g., an antibody molecule, comprises: a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with a heavy chain from Table 3 and a light chain variable region

comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with the corresponding light chain from Table 3.

In an example the binding agent, e.g., an antibody molecule, comprises: a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with a heavy chain from Table 4A and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with the corresponding light chain from Table 4A.

In an example the binding agent, e.g., an antibody molecule, comprises: a heavy chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with a heavy chain from Table 4B and a light chain variable region comprising least 60, 70, 80, 85, 90, 95, 98 or 99 percent homology with the corresponding light chain from Table 4B.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

a heavy chain variable region from Table 3, Table 4A, Table 4B, Fig.2, Fig 13, or Fig. 17; and

a light chain variable region from Table 3, Table 4A, Table 4B, Fig.3, Fig 14, or Fig 17.

In an example the binding agent, e.g., an antibody molecule, comprises:

a heavy chain variable region from Table 3 and the corresponding light chain from Table 3;

a heavy chain from Table 4A and the corresponding light chain from Table 4A; or

a heavy chain from Table 4B and the corresponding light chain from Table 4B.

In an example, the binding agent, e.g., an antibody molecule, comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising a CDR1, a CDR2 and a CDR3 from a heavy chain sequence of Table 3, Table 4A, Table 4B, FIG. 2, FIG. 13, or FIG. 17 (or CDRs that, individually or collectively, differ therefrom by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids)); and

(b) a light chain immunoglobulin variable region segment comprising a CDR1, a CDR2 and a CDR3 from a light chain sequence of Table 3, Table 4A, Table 4B, FIG. 3, FIG. 14, or FIG. 17 (or CDRs that, individually or collectively, differ therefrom by no more than, 1, 2, 3, 4, or 5, e.g., 1 or 2 amino acids, e.g., conservative amino acids).

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

CDRs from a heavy chain of Table 3 and the light chain CDRs from the corresponding light chain from Table 3.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

CDRs from a heavy chain of Table 4A and the light chain CDRs from the corresponding light chain from Table 4A.

In an example the binding agent, e.g., an antibody molecule, comprises one or both of:

CDRs from a heavy chain of Table 4B and the light chain CDRs from the corresponding light chain from Table 4B.

In some examples, the binding agent, e.g., an antibody molecule, comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or

A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010); (ii) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by the method described in (i); and (iii) it is other than Ab 67-11 and FI6.

In one example, the antibody molecule comprises one or both of:

(a) a heavy chain immunoglobulin variable region segment comprising a CDR1, a CDR2; and a CDR3 from a heavy chain sequence of FIG. 2, FIG. 13, or FIG. 17; and

(b) a light chain immunoglobulin variable region segment comprising a CDR1, a CDR2 and a CDR3 from a light chain sequence of FIG. 3, FIG. 14, or FIG. 17.

In one example, the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable region segment from FIG. 2 or FIG. 17; and

(b) a light chain immunoglobulin variable region segment from FIG. 3 or FIG. 17.

In one example, the heavy chain immunoglobulin variable region further comprises an Isoleucine-Aspartate (Ile-Asp) dipeptide at the N-terminus. In another example, the light chain immunoglobulin variable region further comprises an Ile-Asp dipeptide at the N-terminus. In yet another example, both the heavy chain immunoglobulin variable region and the light chain immunoglobulin variable region or an antibody featured in the disclosure further comprises an Ile-Asp dipeptide at the N-terminus. In other example the Ile-Asp dipeptide is absent from one or both the heavy and light chain.

In one example, the binding agent, e.g., an antibody molecule, further comprises one or more or all of the following: (a) it treats or prevents infection by at least 1, 2, 3, 4 or 5 influenza subtypes of Group 1, and by at least 1, 2, 3, 4 or 5 influenza subtypes of Group 2; (b) it inhibits fusogenic activity of the targeted HA; (c) it treats or prevents infection by a Group 1 virus, wherein the virus is an H1, H5,

or H9 virus; and treats or prevents infection by a Group 2 virus, wherein the virus is an H3 or H7 virus; (d) it treats or prevents infection by influenza A strains H1N1 and H3N2; (e) it is effective for prevention or treatment of infection, e.g., in humans or mice, with H1N1 and H3N2 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (f) it treats or prevents infection by influenza A strains H5N1; (g) it is effective for prevention or treatment of infection, e.g., in humans or mice, with H5N1 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (h) it binds with high affinity to a hemagglutinin (HA) of an influenza B virus, e.g., B/Wisconsin/1/2010; (i) it treats or prevents infection by an influenza B virus, e.g., B/Wisconsin/1/2010; (j) it is effective for prevention or treatment of infection, e.g., in humans or mice, with an influenza B virus, e.g., B/Wisconsin/1/2010 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (k) the concentration of antibody molecule required for 50% neutralization of influenza A virus is less than 10 μg/mL; (l) the concentration of antibody molecule required for 50% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, is less than 10 μg/mL; (m) it prevents or minimizes secondary infection (e.g., secondary bacterial infection) or effects thereof on a subject; (n) it is effective for preventing or minimizing secondary infection (e.g., secondary bacterial infection) or effects thereof on a subject when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (o) it binds an epitope which comprises or consists of the hemagglutinin trimer interface; and (p) it binds an epitope other than that bound by a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by a method disclosed herein, e.g., by competition in an ELISA assay.

In an example the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from heavy chain disclosed herein. E.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from heavy chain disclosed herein; and

b) one or more framework regions (FRs) from light chain disclosed herein. E.g.,

the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from light chain disclosed herein.

In an example the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

In an example the antibody molecule has properties: a; and b.

In an example the antibody molecule has properties: c; and d.

In an example the antibody molecule has properties: a; and c or d.

In an example the antibody molecule has properties: b; and c or d.

In an example the antibody molecule has properties: c; and a or b.

In an example the antibody molecule has properties: d; and a or b.

In an example the antibody molecule has properties: a, b, c and d.

In an example the antibody molecule has properties: a, b, c, d, e, and f.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

a) H3 HA1 residues N38, I278, or D291;

b) H3 HA2 residue N12;

c) H3 HA1 residues T318, R321, or V323; or

d) H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56, or E57.

In an example, the antibody molecule has a K_D for H3 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

c) H3 HA1 residues Q327, T328, or R329; or

d) H3 HA2 residues G1, L2, F3, G4, or D46.

In an example, the antibody molecule binds an epitope that has one, two, three, four, five, or all of, the following properties a-f:

aa) it includes one, two, or all of, H1 HA1 residues H31, N279, and S292;

bb) it includes H1 HA2 residue G12;

cc) it does not include one or both of H1 HA1 residues Q328 and S329;

dd) it does not include one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

ee) it includes one, two, or all of, H1 HA1 residues T319, R322, and I324 are bound by both Ab 044 and FI6; or

ff) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example the antibody molecule has properties: aa; and bb.

In an example the antibody molecule has properties: cc; and dd.

In an example the antibody molecule has properties: aa; and cc or dd.

In an example the antibody molecule has properties: bb; and cc or dd.

In an example the antibody molecule has properties: cc; and aa or bb.

In an example the antibody molecule has properties: dd; and aa or bb.

In an example the antibody molecule has properties: aa, bb, cc and dd.

In an example the antibody molecule has properties: aa, bb, cc, dd, ee, and ff.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by at least 2, 5,10, or 100 fold, by a mutation or mutations in any of:

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an example, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an example the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an example the molecule has properties c, cc, d, and dd.

In one example, the disclosure features an anti-hemagglutinin (anti-HA) binding agent, e.g., antibody molecule, or preparation, or isolated preparation thereof, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising one or more or all of a

CDR1 comprising the sequence G-F-T-F-[S/T]-[S/T]-Y-[A/G]-M-H (SEQ ID NO:1), or a sequence that differs from SEQ ID NO:1 by no more than 1 or 2 residues;

a CDR2 comprising the sequence V-[I/V/L]-S-[Y/F]-D-G-[S/N]-[Y/N]-[K/R]-Y-Y-A-D-S-V-Q-G (SEQ ID NO:2) or a sequence that differs from SEQ ID NO:2 by no more than 1 or 2 residues; and

a CDR3 comprising the sequence D-[S/T]-[R/K/Q]-L-R-[S/T]-L-L-Y-F-E-W-L-S-[Q/S]-G-[Y/L/V]-[F/L]-[N/D]-[P/Y] (SEQ ID NO:3), or a sequence that differs from SEQ ID NO:3 by no more than 1 or 2 residues; and

(b) a light chain variable region segment comprising one or more or all of a

CDR1 comprising the sequence [K/R]-S-S-Q-[S/T]-[V/L/I]-[T/S]-[Y/F/W]-[N/S/D]-Y-K-N-Y-L-A (SEQ ID NO:4) or a sequence that differs from SEQ ID NO:4 by no more than 1 or 2 residues, or comprising the sequence [K/R]-S-S-Q-[S/T]-

SEQ ID NO:6 is an S; (f) an FR1 wherein the amino residue at position 1 of SEQ ID NO:11 is a D; the amino residue at position 3 of SEQ ID NO:11 is a Q, the amino residue at position 9 of SEQ ID NO:11 is an S, the amino residue at position 10 of SEQ ID NO:11 is a T, the amino residue at position 11 of SEQ ID NO:11 is a V, the amino residue at position 12 of SEQ ID NO:11 is an S, the amino residue at position 13 of SEQ ID NO:11 is an A, the amino residue at position 14 of SEQ ID NO:11 is a T, the amino residue at position 15 of SEQ ID NO:11 is a V or an R, the amino residue at position 17 of SEQ ID NO:11 is a D, the amino residue at position 20 of SEQ ID NO:11 is an S, the amino residue at position 22 of SEQ ID NO:11 is a T, a Q, a D, or an R; (g) an FR2 wherein the amino residue at position 8 of SEQ ID NO:12 is a K; or the amino residue at position 9 of SEQ ID NO: 12 is an A; (h) an FR3 wherein the amino residue at position 4 of SEQ ID NO: 13 is an E or an S; the amino residue at position 24 of SEQ ID NO: 13 is a P, the amino residue at position 27 of SEQ ID NO: 13 is an F, a K, or a D, the amino residue at position 29 of SEQ ID NO: 13 is a T; (i) an FR4 wherein the amino residue at position 3 of SEQ ID NO:14 is a Q, a T, an S, or an N, the amino residue at position 7 of SEQ ID NO:14 is a V, or the amino residue at position 8 of SEQ ID NO:14 is an E; or (j) it produces fewer escape mutants than does a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by a method disclosed herein; and further provided that if the light chain variable region segment comprises: a CDR 1 comprising the sequence K-S-S-Q-S-V-T-F-N-Y-K-N-Y-L-A (SEQ ID NO:146); a CDR2 comprising the sequence W-A-S-A-R-E-S (SEQ ID NO:147); and a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-T (SEQ ID NO:148); then the heavy chain variable region segment comprises one or more of the following: CDRs other than the CDR's described at FIG. 12B; or FRs other than the FRs described at FIG. 12C.

In one example, the heavy chain CDR sequences, collectively, differ from the recited sequences by no more than 5, 4, 3, 2 or 1 amino acid residues; and the light chain CDR sequences, collectively, differ from the recited sequences by no more than 5, 4, 3, 2 or 1 amino acid residues.

In one example, the disclosure features an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment featured in the disclosure.

In another example, the disclosure features an isolated nucleic acid molecule that comprises a nucleotide sequence encoding a light chain immunoglobulin variable region segment featured in the disclosure.

In yet another example, the disclosure features an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment featured in the disclosure and a light chain immunoglobulin variable region segment featured in the disclosure.

In yet another example, the disclosure features a recombinant vector, such as an expression vector, that comprises a nucleic acid molecule that comprises a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment or nucleotide sequence that encodes a light chain immunoglobulin variable region segment featured in the disclosure.

In one example, the disclosure features a recombinant vector, such as an expression vector, that comprises a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment and a nucleotide sequence that encodes a light chain immunoglobulin variable region segment featured in the disclosure.

In one example, the nucleic acid molecules in the recombinant vector include a nucleotide sequence encoding (a) a heavy chain immunoglobulin variable region segment comprising the amino acid sequence of: S-Y-A-M-H (SEQ ID NO:68) in CDR1; V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) in CDR2; and D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) in CDR3; and (b) a light chain immunoglobulin variable region segment comprising the amino acid sequence of: Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145) in CDR1;

W-G-S-Y-L-E-S (SEQ ID NO:72) in CDR2; and Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73) in CDR3.

In one example, the disclosure features a cell containing a recombinant vector featured in the disclosure, such as a recombinant vector comprising a nucleic acid sequence that encodes a heavy chain immunoglobulin variable region, or a recombinant vector comprising a nucleic acid sequence that encodes a light chain immunoglobulin variable region. In one example, the cell contains a recombinant vector comprising a nucleic acid sequence that encodes a heavy chain immunoglobulin variable region, and a recombinant vector comprising a nucleic acid sequence that encodes a light chain immunoglobulin variable region. In yet another example, the cell contains a recombinant vector comprising a nucleic acid sequence that encodes a heavy chain immunoglobulin variable region, and a nucleic acid sequence that encodes a light chain immunoglobulin variable region.

In one example, the disclosure features a method of making an antibody molecule featured in the invention, such as by providing a host cell comprising a nucleic acid sequence expressing a heavy chain segment and a nucleic acid sequence expressing a light chain segment, and expressing the nucleic acids in the host cell.

In one example, the nucleic acid sequence expressing the heavy chain segment and the nucleic acid sequence expressing the light chain segment are on the same recombinant expression vector. In another example, the nucleic acid sequence expressing the heavy chain segment and the nucleic acid sequence expressing the light chain segment are on separate recombinant expression vectors.

In one example, the disclosure features a pharmaceutical composition containing an antibody molecule featured in the disclosure, and a pharmaceutically acceptable carrier.

In another example, the disclosure features a method of treating or preventing infection with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or

A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010), in a subject, e.g., a human subject, that comprises:

administering a binding agent, e.g., an antibody molecule, featured in the disclosure to a subject, e.g., human subject, in need thereof.

In one example, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In an example the administration results in, or correlates with, one or more of a reduction in the incidence or severity of a symptom or manifestation of an influenza infection, or the delay or onset of a symptom or manifestation of an influenza infection.

In an example the administration results in, or correlates with, one or more of a reduction in the incidence or severity of a symptom or manifestation of a secondary infection, or the delay or onset of a symptom or manifestation of a secondary infection.

In examples the subject, e.g., a human subject, has been administered, or the method comprises, administering, or recommending the administration of, a second or additional therapy.

In examples the antibody molecule is administered in combination with a second or additional agent or therapy.

In examples the second or additional therapy comprises administration of a vaccine or an anti-viral therapy, e.g., an anti-NA or an anti-M2 therapy.

In an example the second or additional therapy comprises a administration of a vaccine, e.g., a vaccine described herein or a mixture (a.k.a. a cocktail) of

influenza peptides to stimulate the patient's immune system to prevent infection with particular strains of influenza A.

In an example the second or additional agent comprises administering an anti-viral agent, a pain reliever, an anti-inflammatory, an antibiotic, a steroidal agent, a second therapeutic antibody molecule (e.g., an anti-HA antibody), an adjuvant, a protease or glycosidase (e.g., sialidase).

In an example the second or additional agent comprises, acyclovir, ribavirin, amantadine, remantidine, a neuraminidase inhibitor (e.g., zanamivir (Relenza®), oseltamivir (Tamiflu®), laninamivir, peramivir), or rimantadine.

In an example the second or additional agent comprises a second antibody molecule, e.g., Ab 67-11 (U.S. Provisional application number 61/645,453, FI6 (U.S. Published Application No. 2010/0080813), FI28 (U.S. Published Application No. 2010/0080813), C179 (Okuno et al., J. Virol. 67:2552-8, 1993), F10 (Sui et al., Nat. Struct. Mol. Biol. 16:265, 2009), CR9114 (Dreyfus et al., Science 337:1343, 2012), or CR6261 (see, e.g., Ekiert et al., Science 324:246, 2009). Thus, Ab 044 can be used in combination of any of those antibodies.

In an example the second or additional agent comprises a second or additional binding agent, e.g., antibody molecule, e.g., an anti-HA antibody, e.g., an disclosed herein. E.g., two or more of Ab 044, Ab 069, Ab 032, and Ab 031 can be administered. E.g., Ab 044 can be administered in combination with Ab 069 or Ab 032

In the case of combinations, two agents can be administered as part of the same dosage unit or administered separately. Other exemplary agents useful for treating the symptoms associated with influenza infection are acetaminophen, ibuprofen, aspirin, and naproxen.

In an example the binding agent, e.g., an antibody molecule, is administered to a human subject suffering from or susceptible to an influenza infection.

In an example the binding agent, e.g., an antibody molecule, is administered prior to known exposure to influenza, or to particular influenza substypes or strains.

In an example the binding agent, e.g., an antibody molecule, is administered prior to manifestation of effects or symptoms of influenza infection, or to one or more particular effects manifestation of effects or symptoms of influenza infection.

In an example the binding agent, e.g., an antibody molecule, is administered after known exposure to influenza, or to particular influenza substypes or strains.

In an example the binding agent, e.g., an antibody molecule, is administered after manifestation of effects or symptoms of influenza infection, or after observation of one or more particular effects manifestation of effects or symptoms of influenza infection.

In an example the binding agent, e.g., an antibody molecule, is administered in response to, or to treat or prevent, a manifestation of an effect or a symptom of influenza infection, e.g., inflammation, fever, nausea, weight loss, loss of appetite, rapid breathing, increase heart rate, high blood pressure, body aches, muscle pain, eye pain, fatigue, malaise, dry cough, runny nose, and/or sore throat.

In an example, the method further comprises, testing the human subject for the influenza virus, e.g., with a method disclosed herein. In examples, the administration is responsive to a positive test for influenza.

In yet another example, the disclosure features a method of treating a subject, e.g., a human subject, infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005

or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010) by administering a binding agent, e.g., an antibody molecule, featured in the disclosure. For example, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In one example, a binding agent, e.g., an anti-HA antibody, described herein is administered instead of a vaccine for prevention of influenza. In another example, the binding agent, e.g., anti-HA antibody molecule, is administered in combination with (simultaneously or sequentially with) a vaccine for prevention of the flu.

In yet another example, the disclosure features a method of detecting influenza (e.g., influenza A or influenza B) virions in a biological sample, such as by contacting the sample with a binding agent, e.g., an antibody molecule, featured in the disclosure, and then detecting the binding of the antibody molecule to the sample. In one example, the method of detecting the influenza virus (e.g., influenza A or influenza B virus) is performed in vitro.

In one example, the disclosure features a method of (a) providing a sample from a patient; (b) contacting the sample with a binding agent, e.g., an antibody molecule, featured in the disclosure, and (c) determining whether the binding agent, e.g., an antibody molecule, featured in the disclosure binds a polypeptide in the sample, where if the binding agent, e.g., an antibody molecule, binds a polypeptide in the sample, then the patient is determined to be infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., e.g., B/Wisconsin/1/2010). In one example, the patient is determined to be infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010), and the patient is further administered a binding agent, e.g., an antibody molecule, disclosed

herein, e.g., the binding agent, e.g., an antibody molecule, with which the test was performed.

In another example, the invention features, a method of inducing immunity to one or more influenza strains, or preventing, delaying or reducing infection with an influenza strain, or symptom thereof, in a vertebrate, e.g., a human. The method comprises administering to the vertebrate, e.g., a human, a broad range vaccine, or broad range immunogen, described herein.

In an example the broad range vaccine, or broad range immunogen, induces an immune response against, or confers protection against, one or more influenza strains.

In an example the broad range vaccine, or broad range immunogen, induces an immune response against, or confers protection against, two influenza strains.

In an example the broad range vaccine, or broad range immunogen, induces an immune response against, or confers protection against, two Group 1 influenza strains.

In an example the broad range vaccine induces, or broad range immunogen, an immune response against, or confers protection against, at least one Group 1 strain, and a second strain from Group 1, Group2 or an influenza B strain.

In one example, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In an example the administration results in, or correlates with, one or more of : a reduction in the chance of an infection, a reduction in the incidence or severity of a symptom or manifestation of an influenza infection, or the delay or onset of a symptom or manifestation of an influenza infection.

In an example the administration results in, or correlates with, one or more of: a reduction in the incidence or severity of a symptom or manifestation of a secondary infection, or the delay or onset of a symptom or manifestation of a secondary infection.

In examples the subject, e.g., a human subject, has been administered, or the method comprises, administering, or recommending the administration of, a second or additional therapy.

In examples the broad range vaccine is administered in combination with a second or additional agent or therapy.

In examples the second or additional agent comprises administration of another vaccine or another anti-viral therapy, e.g., an anti-NA or an anti-M2 therapy.

In an example the second or additional agent comprises administration of a vaccine comprising a mixture (a.k.a. a cocktail) of influenza peptides to stimulate the patient's immune system to prevent infection with particular strains of influenza A.

In an example the second or additional agent comprises administering an anti-viral agent, a pain reliever, an anti-inflammatory, an antibiotic, a steroidal agent, a second therapeutic antibody molecule (e.g., an anti-HA antibody), an adjuvant, a protease or glycosidase (e.g., sialidase).

In an example the second or additional agent comprises, acyclovir, ribavirin, amantadine, remantidine, a neuraminidase inhibitor (e.g., zanamivir (Relenza®), oseltamivir (Tamiflu®), laninamivir, peramivir), or rimantadine.

In an example the second or additional agent comprises an antibody molecule, e.g., Ab 67-11 (U.S. Provisional application number 61/645,453, FI6 (U.S.

Published Application No. 2010/0080813), FI28 (U.S. Published Application No. 2010/0080813), C179 (Okuno et al., J. Virol. 67:2552-8, 1993), F10 (Sui et al., Nat. Struct. Mol. Biol. 16:265, 2009), CR9114 (Dreyfus et al., Science 337:1343, 2012), or CR6261 (see, e.g., Ekiert et al., Science 324:246, 2009).

In an example the second or additional agent comprises an antibody molecule disclosed herein, e.g., an antibody molecule selected from Ab-044, Ab 069, Ab 032, and Ab 031 antibody molecules.

In the case of combinations, two agents can be administered as part of the same dosage unit or administered separately.

Other exemplary second or additional agents useful for treating the symptoms associated with influenza infection are acetaminophen, ibuprofen, aspirin, and naproxen.

In an example the broad range vaccine, or broad range immunogen, is administered to a human subject suffering from or susceptible to an influenza infection.

In an example the broad range vaccine, or broad range immunogen, is administered prior to known exposure to influenza, or to particular influenza substypes or strains.

In an example the broad range vaccine, or broad range immunogen, is administered prior to manifestation of effects or symptoms of influenza infection, or to one or more particular effects manifestation of effects or symptoms of influenza infection.

In an example the broad range vaccine, or broad range immunogen, is administered after known exposure to influenza, or to particular influenza substypes or strains.

In an example the broad range vaccine is administered after manifestation of effects or symptoms of influenza infection, or after observation of one or more particular effects manifestation of effects or symptoms of influenza infection.

In an example the broad range vaccine, or broad range immunogen, is administered in response to, or to treat or prevent, a manifestation of an effect or a symptom of influenza infection, e.g., inflammation, fever, nausea, weight loss, loss of appetite, rapid breathing, increase heart rate, high blood pressure, body aches, muscle pain, eye pain, fatigue, malaise, dry cough, runny nose, and/or sore throat.

In an example, the method further comprises, testing the human subject for the influenza virus, e.g., with a method disclosed herein. In examples, the administration is responsive to a positive test for influenza.

In yet another example, the disclosure features a method of treating a subject, e.g., a human subject, infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010) by administering a broad range vaccine featured in the disclosure. For example, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In another example, the invention features, a method of reducing the severity of influenza in a population. The method includes administering a broad range vaccine, or broad range immunogen, to sufficient individuals in the population to prevent or decrease the chance of influenza virus transmission to another individual in the population.

In another example, the invention features, a kit comprising one or more containers having disposed therein a broad range immunogen, a nucleic acid encoding the broad range epitope, or a broad range vaccine described herein. In an example the kit includes a container having adjuvant disposed therein. In an example the kit comprises a delivery device, e.g., an injection device or inhaler. In an example the broad range epitope described herein, or a nucleic acid encoding the broad range epitope or broad reange vaccine, is disposed in a delivery device.

In an example the kit comprises a delivery device, e.g., an injection device or inhaler. In an example the vaccine is disposed in a delivery device.

In another example, the invention features, a composition, e.g., a vaccine, comprising a broad range epitope described herein, packaged in a hermetically sealed container such as an ampoule. In an example, the composition a liquid. In an example, the composition is liquid a dry sterilized lyophilized powder or water free concentrate.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more examples featured in the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages featured in the disclosure will be apparent from the description and drawings, and from the claims.

We Claim:

1. An isolated antibody molecule comprising:

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

a CDR1 comprising the sequence [S/T]-Y-[A/G]-M-H (SEQ ID NO:1);

a CDR2 comprising the sequence V-[I/V/L]-S-[Y/F]-D-G-[S/N]-[Y/N]-[K/R]-Y-Y-A-D-S-V-Q-G (SEQ ID NO:2); and

a CDR3 comprising the sequence D-[S/T]-[R/K/Q]-L-R-[S/T]-L-L-Y-F-E-W-L-S-[Q/S]-G-[Y/L/V]-[F/L]-[N/D]-[P/Y] (SEQ ID NO:3); and

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

a CDR1 comprising the sequence Q-[S/T]-[V/L/I]-[T/S]-[Y/F/W]-[N/S/D/Q/R/E]-Y-K-N-Y-L-A (SEQ ID NO:170);

a CDR2 comprising the sequence W-[A/G]-S-[T/A/Y/H/K/D]-[R/L]-E-[S/T] (SEQ ID NO:5); and

a CDR3 comprising the sequence Q-Q-[Y/H]-Y-R-T-P-P-[T/S] (SEQ ID NO:6).

2. The antibody of claim 1, comprising:

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

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68), or a sequence that differs by 1 amino acid therefrom and comprises the sequence [S/T]-Y-[A/G]-M-H (SEQ ID NO:1);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) or a sequence that differs by 1 amino acid therefrom and comprises the sequence V-[I/V/L]-S-[Y/F]-D-G-[S/N]-[Y/N]-[K/R]-Y-Y-A-D-S-V-Q-G (SEQ ID NO:2);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) or a sequence that differs by 1 amino acid therefrom and

comprises the sequence D-[S/T]-[R/K/Q]-L-R-[S/T]-L-L-Y-F-E-W-L-S-[Q/S]-G-[Y/L/V]-[F/L]-[N/D]-[P/Y] (SEQ ID NO:3); and

(b) a light chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-N-Y-K-N-Y-L-A (SEQ ID NO:71) or a sequence that differs by 1 amino acid therefrom and comprises the sequence Q-[S/T]-[V/L/I]-[T/S]-[Y/F/W]-[N/S/D/Q/R/E]-Y-K-N-Y-L-A (SEQ ID NO:170);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72), or a sequence that differs by 1 amino acid therefrom, and comprises the sequence W-[A/G]-S-[T/A/Y/H/K/D]-[R/L]-E-[S/T] (SEQ ID NO:5);

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73), or a sequence that differs by 1 amino acid therefrom, and comprises the sequence Q-Q-[Y/H]-Y-R-T-P-P-[T/S] (SEQ ID NO:6).

3. The antibody molecule of claim 1 or 2, comprising:

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

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

4. The antibody molecule of any of claims 1-3, comprising:

i) a heavy chain immunoglobulin variable region segment that comprises SEQ ID NO: 25;

ii) a light chain immunoglobulin variable region segment that comprises SEQ ID NO:52;

iii) a heavy chain immunoglobulin variable region segment that comprises SEQ ID NO:25 and a light chain immunoglobulin variable region segment that comprises SEQ ID NO:52; or

(iv) a tetramer of two heavy chain immunoglobulin variable region segments, each comprising SEQ ID NO:25 and two light chain immunoglobulin variable region segments, each comprising SEQ ID NO:52.

5. The antibody molecule of any of claims 1-4, wherein said antibody molecule has one, two three, or all of the following:

(i) comprises a full length antibody or is a single chain antibody (scFv), a $F(ab')_2$ fragment, a Fab fragment, or an Fd fragment

(ii) comprises a humanized antibody molecule;

(iii) comprises two heavy chain immunoglobulin variable regions and two light chain immunoglobulin variable regions; or

(iv) is an IgG antibody.

6. The antibody molecule of any of claims 1-5 for use in preventing or treating an influenza virus infection in a human subject.

7. Use of the antibody molecule of any of claims 1-5 in the manufacture of a medicament for preventing or treating an influenza virus infection in a human subject.

8. The use of claim 7, wherein the human subject has one, two, three, or all of the following:

(i) is at high risk of exposure to influenza virus;

(ii) is immunocompromised, 65 years or older, 6 months to 18 years old, or has a chronic medical condition;

(iii) has or is at risk of having a secondary bacterial infection; or

(iv) is tested for the influenza virus.

9. The use of claim 7, further comprising a second agent to be administered.

10. The use of claim 9, wherein the second agent is selected from the group consisting of a vaccine, an anti-viral agent, a pain reliever, an anti-inflammatory agent, an antibiotic, a steroidal agent, a second antibody molecule, an adjuvant, a protease, a glycosidase, and a neuraminidase inhibitor,or the group consisting of acyclovir, ribavirin, amantadine, rimantadine, zanamivir, oseltamivir, laninamivir and peramivir.

11. The use of any of claims 7-10, wherein the influenza virus is:

(i) an influenza A virus;

(ii) an influenza A virus Group 1 strain

(iii) an influenza A virus Group 2 strain;

(iv) an influenza A virus selected from the group consisting of H1, H3, H5, H7 and H9 strains or;

(v) an influenza A virus H1N1, H3N2 or H5N1 strain.

12. The use of any of claims 7-11, wherein the antibody molecule is administered:

(i) at a dose of between 1 mg/kg and 50 mg/kg or between 25 mg/kg and 50 mg/kg; and/or

(ii) (a) prior to known exposure to the influenza virus infection or prior to manifestation of an effect or a symptom of the influenza virus infection; or

(b) after known exposure to the influenza virus infection or after manifestation of an effect or a symptom of the influenza virus infection.

13. A pharmaceutical composition comprising the antibody molecule of any of claims 1-5 and a pharmaceutically acceptable carrier.

14. A kit comprising the antibody molecule of any of claims 1-5; and a pharmaceutically acceptable delivery vehicle or buffer, a delivery device, or both.

15. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment and/or a nucleotide sequence that encodes a light chain immunoglobulin variable region segment of the antibody molecule of any of claims 1-5.

16. A recombinant vector comprising the nucleic acid molecule of claim 15.

17. An isolated cell comprising the vector of claim 16.

18. A method of making the antibody molecule of any of claims 1-5, the method comprising providing a host cell of claim 17 and expressing the nucleic acids in the host cell, thereby making the antibody molecule.

19. A method of detecting an influenza virus in a biological sample, the method comprising contacting the sample with an antibody molecule of any of claims 1-5, and detecting the binding of the antibody molecule to the sample, thereby detecting the influenza virus in the sample.