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(54) **RECOMBINANT ANTIBODIES AGAINST H1N1 INFLUENZA**

(76) Inventors: **Jens Wrammert**, Decatur, GA (US); **Rafi Ahmed**, Atlanta, GA (US); **Patrick Wilson**, Chicago, IL (US)

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(57) **ABSTRACT**

Antibodies that bind with high affinity to swine H1N1 virus are described. In vivo experiments showed that one such antibody is able to fully protect mice challenged with a lethal dose of swine H1N1 virus. The antibody is also able to cure mice in a therapeutic setting when treated as late as up to 60 hours (2.5 days) after infection with swine H1N1 virus. Also described are recombinant forms of this antibody.

Figure 1

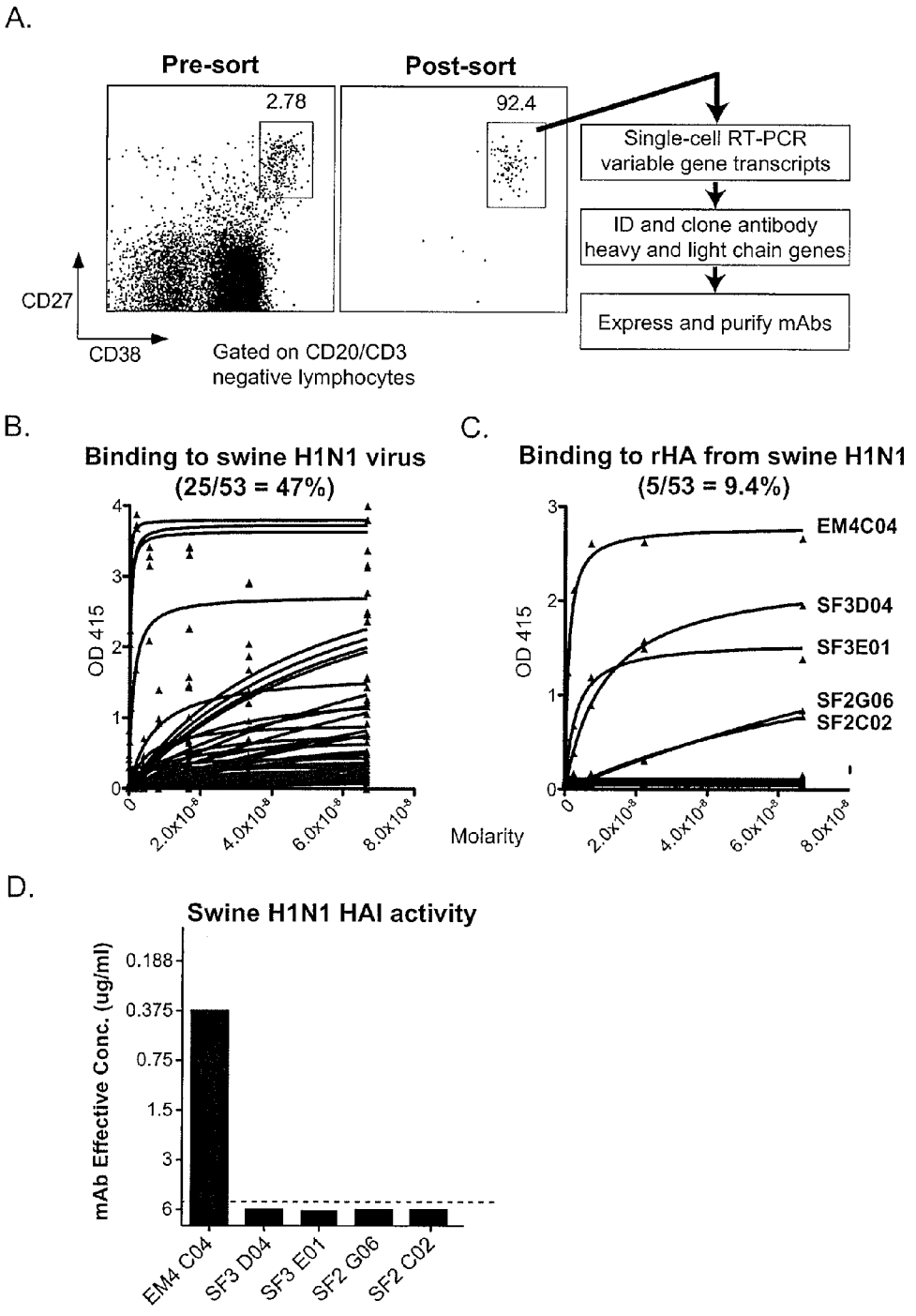

A.
Pre-sort
Post-sort
2.78
92.4
CD27
CD38
Gated on CD20/CD3 negative lymphocytes
Single-cell RT-PCR variable gene transcripts
ID and clone antibody heavy and light chain genes
Express and purify mAbs
B.
Binding to swine H1N1 virus (25/53 = 47%)
OD 415
Molarity
C.
Binding to rHA from swine H1N1 (5/53 = 9.4%)
EM4C04
SF3D04
SF3E01
SF2G06
SF2C02
D.
Swine H1N1 HAI activity
mAb Effective Conc. (ug/ml)
0.188
0.375
0.75
1.5
3
6
EM4 C04
SF3 D04
SF3 E01
SF2 G06
SF2 C02

Figure 2

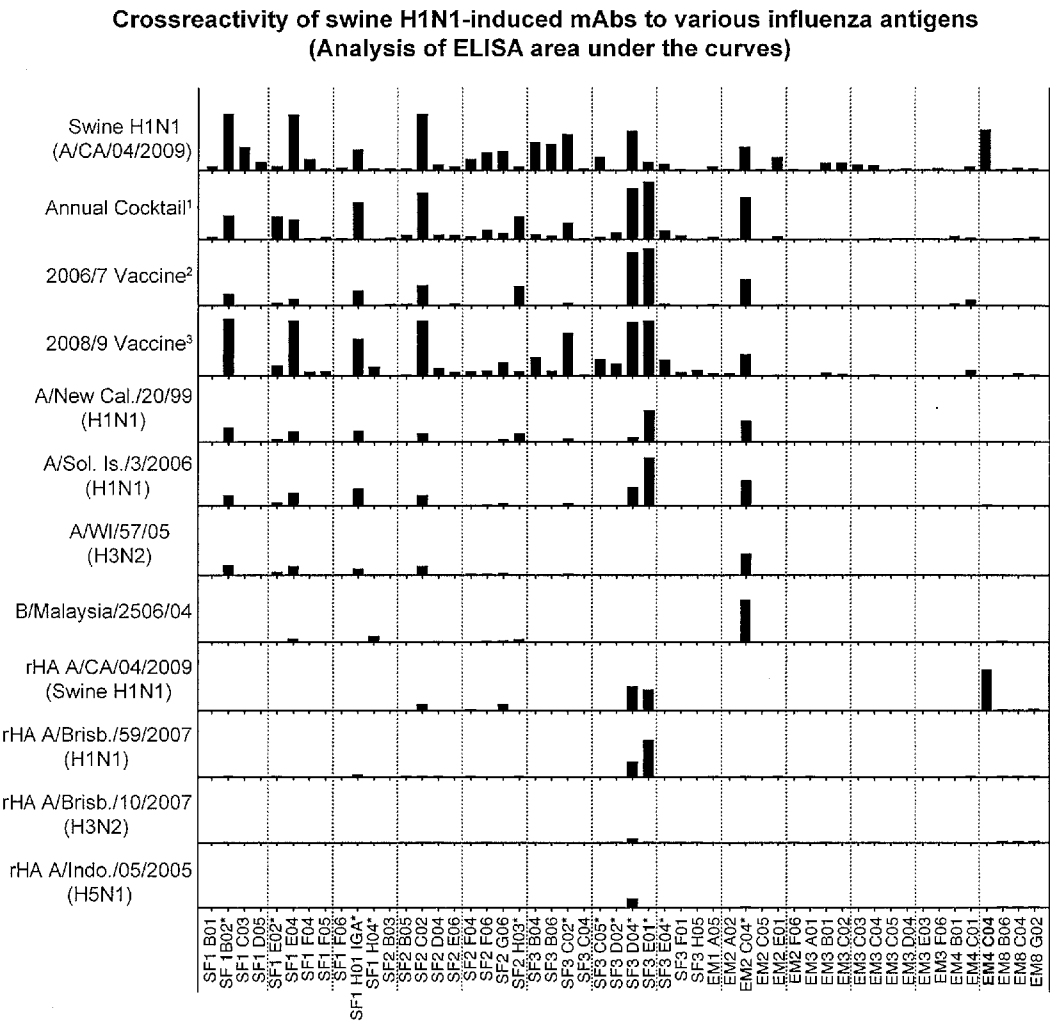
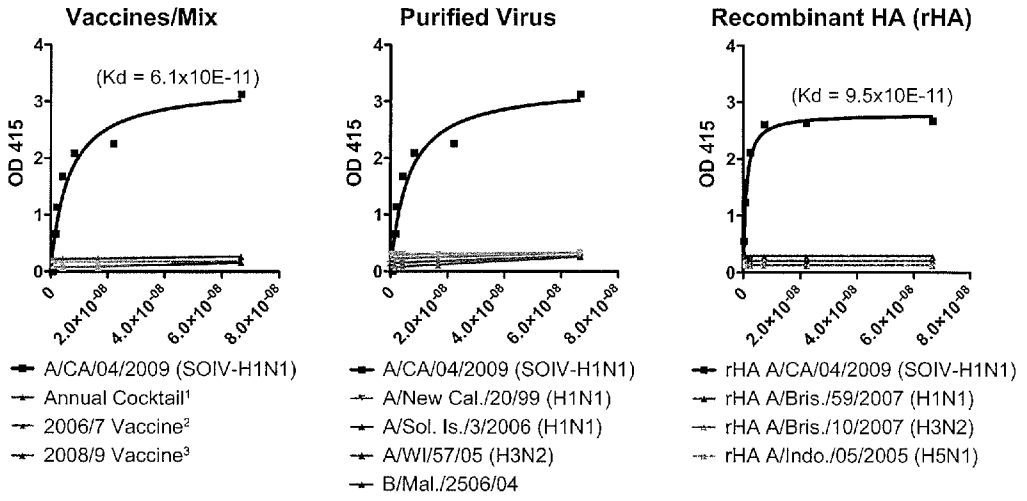
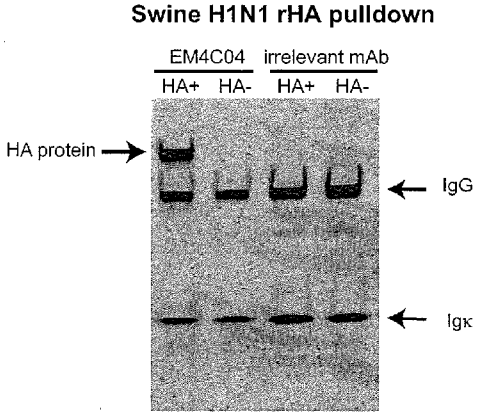

Crossreactivity of swine H1N1-induced mAbs to various influenza antigens
(Analysis of ELISA area under the curves)
Swine H1N1 (A/CA/04/2009)
Annual Cocktail[1]
2006/7 Vaccine[2]
2008/9 Vaccine[3]
A/New Cal./20/99 (H1N1)
A/Sol. Is./3/2006 (H1N1)
A/WI/57/05 (H3N2)
B/Malaysia/2506/04
rHA A/CA/04/2009 (Swine H1N1)
rHA A/Brisb./59/2007 (H1N1)
rHA A/Brisb./10/2007 (H3N2)
rHA A/Indo./05/2005 (H5N1)
SF1 B01
SF 1B02*
SF1 C03
SF1 D05
SF1 E02*
SF1 E04
SF1 F04
SF1 F05
SF1 F06
SF1 H01 IGA*
SF1 H04*
SF2 B03
SF2 B05
SF2 C02
SF2 D04
SF2 E06
SF2 F04
SF2 F06
SF2 G06
SF2 H03*
SF3 B04
SF3 B06
SF3 C02*
SF3 C04
SF3 C05*
SF3 D02*
SF3 D04*
SF3 E01*
SF3 E04*
SF3 F01
SF3 H05
EM1 A05
EM2 A02
EM2 C04*
EM2 C05
EM2 E01
EM2 F06
EM3 A01
EM3 B01
EM3 C02
EM3 C03
EM3 C04
EM3 C05
EM3 D04
EM3 E03
EM3 F06
EM4 B01
EM4 C01
EM4 C04
EM8 B06
EM8 C04
EM8 G02

Figure 3

A.


Vaccines/Mix
(Kd = 6.1x10E-11)
OD 415
A/CA/04/2009 (SOIV-H1N1)
Annual Cocktail[1]
2006/7 Vaccine[2]
2008/9 Vaccine[3]
Purified Virus
A/CA/04/2009 (SOIV-H1N1)
A/New Cal./20/99 (H1N1)
A/Sol. Is./3/2006 (H1N1)
A/WI/57/05 (H3N2)
B/Mal./2506/04
Recombinant HA (rHA)
(Kd = 9.5x10E-11)
rHA A/CA/04/2009 (SOIV-H1N1)
rHA A/Bris./59/2007 (H1N1)
rHA A/Bris./10/2007 (H3N2)
rHA A/Indo./05/2005 (H5N1)

B.


Swine H1N1 rHA pulldown
EM4C04
irrelevant mAb
HA+
HA-
HA+
HA-
HA protein
IgG
Igκ

C.

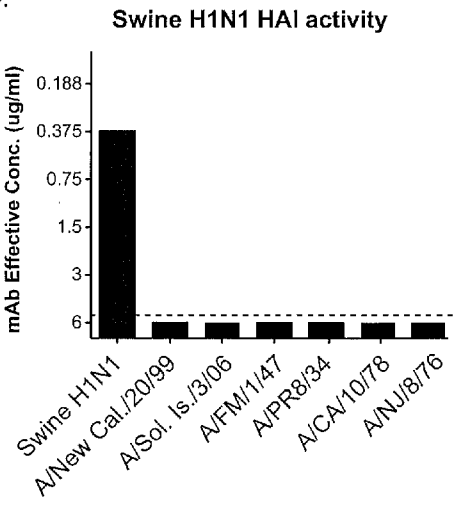
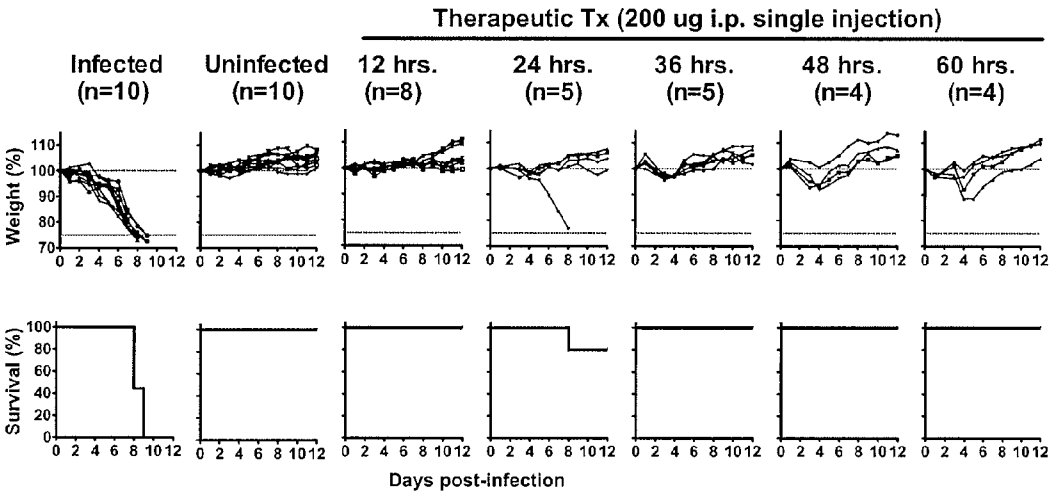

Swine H1N1 HAI activity
mAb Effective Conc. (ug/ml)
0.188
0.375
0.75
1.5
3
6
Swine H1N1
A/New Cal./20/99
A/Sol. Is./3/06
A/FM/1/47
A/PR8/34
A/CA/10/78
A/NJ/8/76

Figure 4




97% (30/31) of the mice lethally infected with pandemic swine H1N1 were rescued by EM4C04 treatment

Figure 5

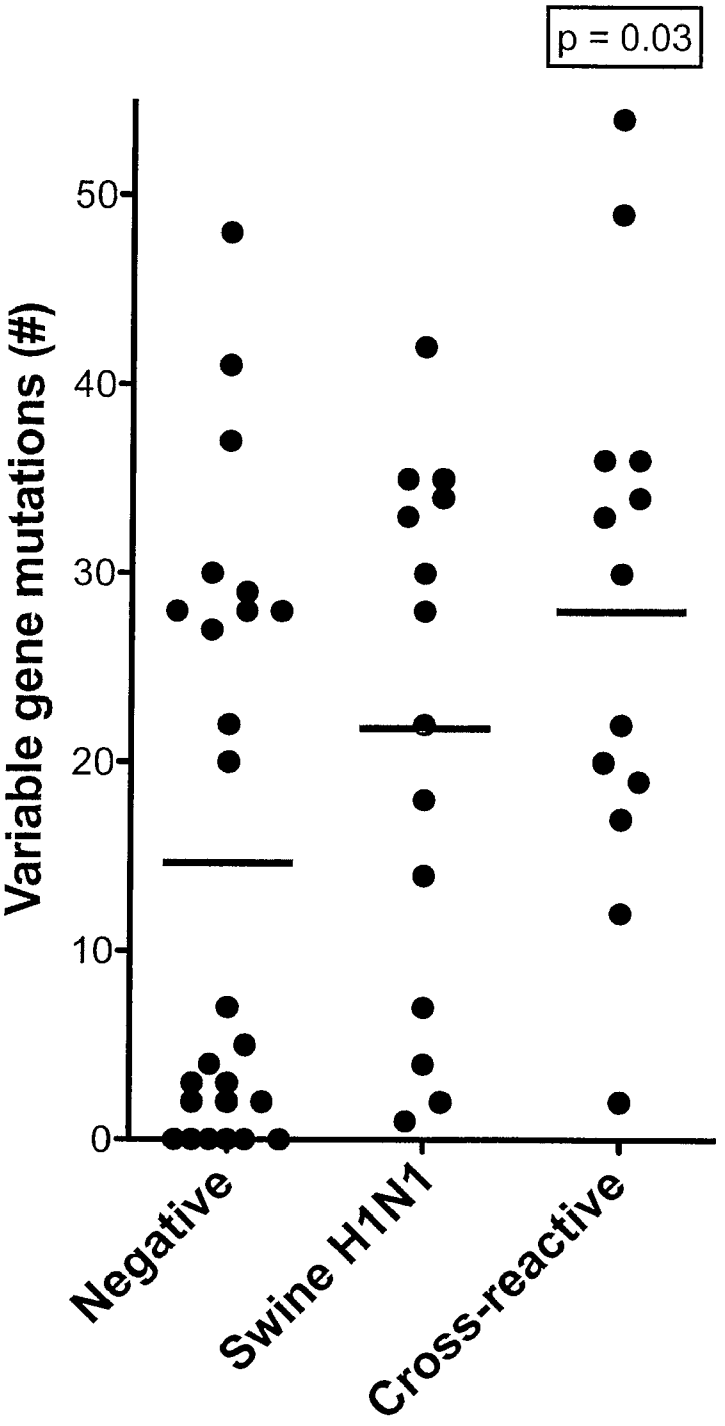
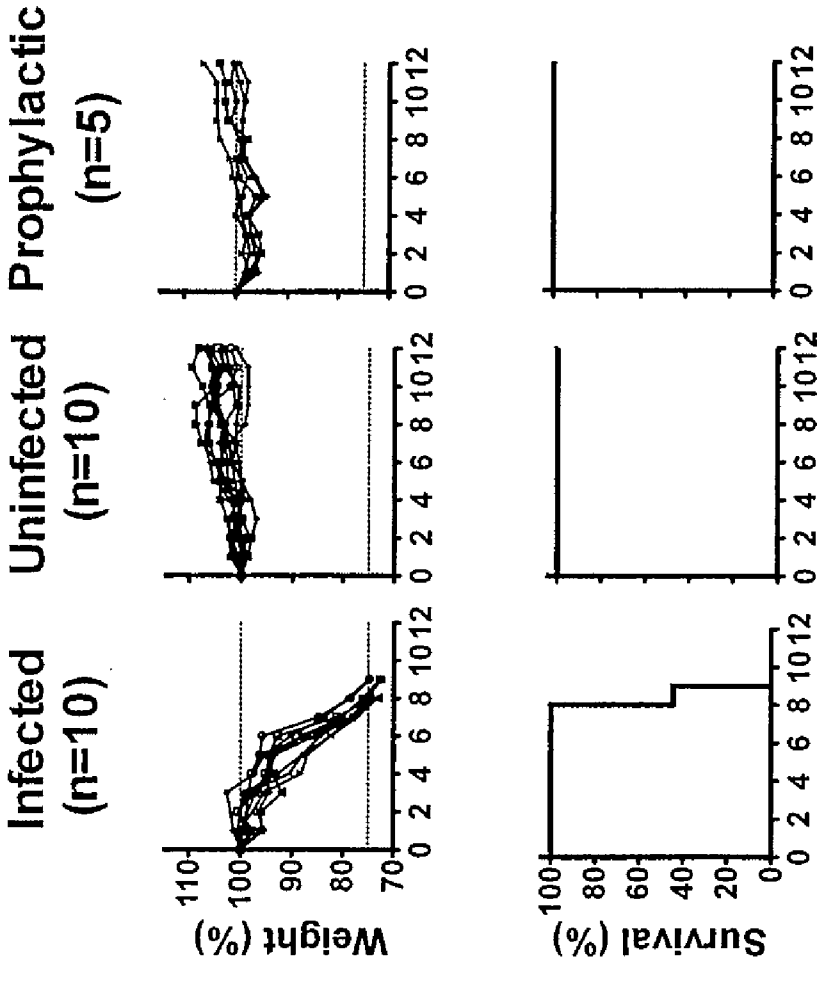

p = 0.03
Variable gene mutations (#)
50
40
30
20
10
0
Negative
Swine H1N1
Cross-reactive

Figure 6


Infected (n=10)
Uninfected (n=10)
Prophylactic (n=5)
Weight (%)
Survival (%)
110
100
90
80
70
100
80
60
40
20
0
0 2 4 6 8 10 12

# RECOMBINANT ANTIBODIES AGAINST H1N1 INFLUENZA

## BACKGROUND

**[0001]** The swine H1N1 influenza virus is currently causing a world-wide pandemic associated with substantial morbidity and mortality[1-5]. This newly emergent strain is immunologically distinct from other influenza viruses including recent H1N1 strains[6] thus leaving a large population of the world highly susceptible to infection by this pandemic virus[7]. Although there is some B cell cross-reactivity with the seasonal influenza viruses the protective epitopes of the swine H1N1 virus appear to be quite distinct.

## SUMMARY

**[0002]** Described herein are recombinant antibodies (e.g., human monoclonal antibodies) against the swine H1N1 influenza virus.

**[0003]** Described herein are antibodies derived from plasmablasts isolated from patients during (or shortly after) infection with the novel influenza virus. Among the antibodies described herein is an antibody that binds with particularly high affinity, is highly specific to swine H1N1 virus, and is able to mediate hemagglutination-inhibition at low concentrations. In vivo experiments showed that this antibody is able to fully protect mice challenged with a lethal dose of swine H1N1 virus. The antibody is also able to cure mice in a therapeutic setting when treated as late as up to 60 hours (2.5 days) after infection with swine H1N1 virus. Such antibodies have great potential as a human therapeutic or prophylactic agent against the novel swine H1N1 influenza.

**[0004]** In one aspect, the recombinant antibodies described herein include all or part of the amino acid sequence of SEQ ID NO:1 (light chain) and/or all or part of the amino acid sequence of SEQ ID NO:2 (heavy chain). Within the light chain, the variable domain includes all or part of the sequence of SEQ ID NO:9 and can include one or more of CDR1-light (SEQ ID NO:3), CDR2-light (SEQ ID NO:4) and CDR3-light (SEQ ID NO:5). Within the heavy chain, the variable domain includes all or part of the sequence of SEQ ID NO:10 and can include one or more of CDR1-heavy (SEQ ID NO:6), CDR2-heavy (SEQ ID NO:7) and CDR3-heavy (SEQ ID NO:8).

**[0005]** Described herein is an isolated antibody or an antigen-binding fragment thereof that specifically binds the antigen bound by an H1N1 antibody having a light chain consisting of the amino acid sequence of SEQ ID NO:1 and a heavy chain consisting of the amino acid sequence of SEQ ID NO:2. In various embodiments: the antibody or antigen-binding fragment thereof binds H1N1 (e.g., A/CA/04/2009 H1N1) with a Kd of equal to or less than $10^{-9}$, $10^{-10}$ or $6\times10^{-11}$); the antibody or antigen-binding fragment thereof binds recombinat HA from H1N1 (e.g., A/CA/04/2009 H1N1) with a Kd equal to or less than $10^{-9}$, $10^{-10}$ or $9\times10^{-11}$); the antibody comprises a light chain variable region comprising the amino acids sequences of SEQ ID NOs: 3, 4, and 5; the antibody comprises a heavy chain variable region comprising the amino acids sequences of SEQ ID NOs: 6, 7, and 8; the antibody is a human antibody; the antibody is an IgG antibody; the antibody is an IgG1 antibody; the antibody is an IgG1, kappa antibody; the antibody is an IgG1, lambda antibody; the antibody is selected from an IgM, IgA, IgD and IgE antibody; the antigen-binding fragment is selected from a Fab, a F(ab')2 fragment, a Fd fragment, an Fv fragment, and a dAb fragment; the antibody is a scFv.

**[0006]** Also described is an isolated antibody or antigen-binding fragment thereof wherein the antibody comprises: (a) polypeptide comprising the amino acid sequences of one or more of SEQ ID NOs: 3, 4, and 5; and (b) polypeptide comprising the amino acid sequences of one or more of SEQ ID NOs: 6, 7, and 8. In various embodiments: the isolated antibody or antigen-binding fragment thereof comprises: (a) polypeptide comprising the amino acid sequences of two or more of SEQ ID NOs: 3, 4, and 5; and (b) polypeptide comprising the amino acid sequences of two or more of SEQ ID NOs: 6, 7, and 8; the isolated antibody or antigen-binding fragment thereof comprises: (a) polypeptide comprising the amino acid sequences of SEQ ID NOs: 3, 4, and 5; and (b) polypeptide comprising the amino acid sequences of SEQ ID NOs: 6, 7, and 8; the isolated antibody or antigen-binding fragment thereof comprises a first polypeptide comprising, in the amino terminal to carboxy terminal direction amino acid sequences of two or more of SEQ ID NOs: 3, 4, and 5, wherein there are 10-20 amino acids between SEQ ID NOs: 3 and 4 and between SEQ ID NOs: 4 and 5; and a second polypeptide comprising, in the amino terminal to carboxy terminal direction amino acid sequences of two or more of SEQ ID NOs: 6, 7, and 8, wherein there are 10-20 amino acids between SEQ ID NOs: 6 and 7 and between SEQ ID NOs: 7 and 8: the antibody or antigen-binding fragment thereof binds H1N1 (e.g., A/CA/04/2009 H1N1) with a Kd of equal to or less than $10^{-9}$, $10^{-10}$ or $6\times10^{-11}$); the antibody or antigen-binding fragment thereof binds recombinat HA from H1N1 (e.g., A/CA/04/2009 H1N1) with a Kd equal to or less than $10^{-9}$, $10^{-10}$ or $9\times10^{-11}$); the antibody comprises a light chain variable region comprising the amino acids sequences of SEQ ID NOs: 3, 4, and 5; the antibody comprises a heavy chain variable region comprising the amino acids sequences of SEQ ID NOs: 6, 7, and 8; the antibody is a human antibody; the antibody is an IgG antibody; the antibody is an IgG1 antibody; the antibody is an IgG1, kappa antibody; the antibody is an IgG1, lambda antibody; the antibody is selected from an IgM, IgA, IgD and IgE antibody; the antigen-binding fragment is selected from a Fab, a F(ab')2 fragment, a Fd fragment, an Fv fragment, and a dAb fragment; the antibody is a scFv.

**[0007]** Also described is an isolated antibody or antigen-binding fragment thereof comprising a light chain variable region comprising SEQ ID NOs: 3, 4, and 5 and a heavy chain variable region comprising SEQ ID NOs: 6, 7, and 8. In various embodiments: In various embodiments: the antibody or antigen-binding fragment thereof binds H1N1 (e.g., A/CA/04/2009 H1N1) with a Kd of equal to or less than $10^{-9}$, $10^{-10}$ or $6\times10^{-11}$); the antibody or antigen-binding fragment thereof binds recombinat HA from H1N1 (e.g., A/CA/04/2009 H1N1) with a Kd equal to or less than $10^{-9}$, $10^{-10}$ or $9\times10^{-11}$); the antibody comprises a light chain variable region comprising the amino acids sequences of SEQ ID NOs: 3, 4, and 5; the antibody comprises a heavy chain variable region comprising the amino acids sequences of SEQ ID NOs: 6, 7, and 8; the antibody is a human antibody; the antibody is an IgG antibody; the antibody is an IgG1 antibody; the antibody is an IgG1, kappa antibody; the antibody is an IgG1, lambda antibody; the antibody is selected from an IgM, IgA, IgD and IgE antibody; the antigen-binding frag-

ment is selected from a Fab, a F(ab')2 fragment, a Fd fragment, an Fv fragment, and a dAb fragment; the antibody is a scFv.

**[0008]** Also described is a composition comprising an antibody or antigen binding fragment thereof described herein and a pharmaceutically acceptable carrier.

**[0009]** Also described is a method for treating or reducing one or more symptoms of infection with H1N1 in a human subject, the method comprising administering an antibody or antigen binding fragment thereof described herein.

**[0010]** Also described is a method of reducing the risk of becoming infected with H1N1, the method comprising administering an antibody described herein.

**[0011]** Naturally-occurring antibodies are immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, called complementarity determining regions (CDR), interspersed with regions that are more conserved, called framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

**[0012]** CDRs and FRs may be defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991)). Amino acid numbering of antibodies or antigen binding fragments is also according to that of Kabat.

**[0013]** Each CDR can included amino acid residues from a complementarity determining region as defined by Kabat (i.e. about residues 24-34 (CDR-L1), 50-56 (CDR-L2) and 89-97 (CDR-L3) in the light chain variable domain (SEQ ID NO:1) and 31-35 (CDR-H1), 50-65 (CDR-H2) and 95-102 (CDR-H3) in the heavy chain variable domain (SEQ ID NO:2); Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) and/or those residues from a hypervariable loop (i.e. about residues 26-32 (CDR-L1), 50-52 (CDR-L2) and 91-96 (CDR-L3) in the light chain variable domain (SEQ ID NO:1) and 26-32 (CDR-H1), 53-55 (CDR-H2) and 96-101 (CDR-H3) in the heavy chain variable domain (SEQ ID NO:2); Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)). In some instances, a complementarity determining region can include amino acids from both a CDR region defined according to Kabat and a hypervariable loop.

**[0014]** Framework regions are those variable domain residues other than the CDR residues. Each variable domain typically has four FRs identified as FR1, FR2, FR3 and FR4. If the CDRs are defined according to Kabat, the light chain FR residues are positioned at about residues 1-23 (LCFR1), 35-49 (LCFR2), 57-88 (LCFR3), and 98-107 (LCFR4) of SEQ ID NO:1) and the heavy chain FR residues are positioned about at residues 1-30 (HCFR1), 36-49 (HCFR2), 66-94 (HCFR3), and 103-113 (HCFR4) of SEQ ID NO:2. If the CDRs comprise amino acid residues from hypervariable loops, the light chain FR residues are positioned about at residues 1-25 (LCFR1), 33-49 (LCFR2), 53-90 (LCFR3), and 97-107 (LCFR4) in the light chain (SEQ ID NO:1) and the heavy chain FR residues are positioned about at residues 1-25 (HCFR1), 33-52 (HCFR2), 56-95 (HCFR3), and 102-113 (HCFR4) in the heavy chain (SEQ ID NO:2). In some instances, when the CDR comprises amino acids from both a CDR as defined by Kabat and those of a hypervariable loop, the FR residues will be adjusted accordingly.

**[0015]** An Fv fragment is an antibody fragment which contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in tight association, which can be covalent in nature, for example in scFv. It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the VH-VL dimer. Collectively, the six CDRs or a subset thereof confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although usually at a lower affinity than the entire binding site.

**[0016]** The Fab fragment contains a variable and constant domain of the light chain and a variable domain and the first constant domain (CH1) of the heavy chain. F(ab')2 antibody fragments comprise a pair of Fab fragments which are generally covalently linked near their carboxy termini by hinge cysteines between them. Other chemical couplings of antibody fragments are also known in the art.

**[0017]** Single-chain Fv or (scFv) antibody fragments comprise the VH and VL domains of antibody, wherein these domains are present in a single polypeptide chain. Generally the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains, which enables the scFv to form the desired structure for antigen binding.

**[0018]** Diabodies are small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (VH and VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites.).

**[0019]** Linear antibodies comprise a pair of tandem Fd segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

**[0020]** The antibodies herein specifically include chimeric antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity.

**[0021]** An antigen binding portion of an antibody specifically binds to an antigen (e.g., H1N1). It has been shown that the antigen-binding function of an antibody can be performed by portions of a full-length antibody, all of which are encompassed by the general term antibody, including: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the

VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al, (1989) Nature 341:544 546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423 426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879 5883). Single chain Fv and other forms of single chain antibodies, such as diabodies are also encompassed by the general term antibody. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:6444; Poljak et al. (1994) *Structure* 2:1121).

**[0022]** An antibody or antigen-binding portion thereof may be part of a larger immunoadhesion molecules, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov et al. (1995) *Human Antibodies and Hybridomas* 6:93) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov et al. (1994) *Mol. Immunol.* 31:1047). Antibody portions, such as Fab and $F(ab')_2$ fragments, can be prepared from whole antibodies using conventional techniques, such as papain or pepsin digestion, respectively, of whole antibodies. Moreover, antibodies, antibody portions and immunoadhesion molecules can be obtained using standard recombinant DNA techniques.

**[0023]** Human antibodies include antibodies having variable and constant regions derived from (or having the same amino acid sequence as those derived from) human germline immunoglobulin sequences. Human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3.

**[0024]** Recombinant antibodies are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (Taylor et al. (1992) Nucl. Acids Res. 20:6287) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences or variants thereof to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences or variants thereof. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that may not naturally exist within the human antibody germline repertoire in vivo.

## DESCRIPTION OF THE DRAWINGS

**[0025]** FIG. **1**. Generation of human monoclonal antibodies against swine H1N1 influenza virus from plasmablasts of infected patients. (a) Antibody-secreting B cells in the PBMC of swine influenza virus infected patients were isolated by flow cytometry sorting based on their cell surface phenotype ($CD19^+$, $CD20^-$, $CD3^-$, $CD38^{high}$ and $CD27^{high}$). RT-PCR was used to isolate the variable genes from sorted single plasmablasts, which were then cloned into expression vectors and expressed in 293 cells as we have previously described[11, 12]. (b) Forty-seven percent (25/53) of the monoclonal antibodies generated bound to purified swine H1N1 (A/CA/04/2009) virus as determined by ELISA. (c) Five of 53 antibodies bound to recombinant swine H1N1 hemagglutinin (rHA), but only one of these mAbs (EM4C04) could inhibit hemagglutination (HAI+) of erythrocytes by the swine H1N1 influenza strain (d).

**[0026]** FIG. **2**. A majority of the antibodies induced by swine H1N1 infection are crossreactive to seasonal influenza strains. Antibodies generated during active infection with the swine H1N1 strain (top line) were screened by ELISA for reactivity to various influenza antigens (indicated within the figure). Bars indicate the area under the curve, thus providing insight into both the maximal binding (Bmax) and persistence of binding with decreasing dilutions (affinity or Kd). Note that only a few antibodies were specific just to the swine H1N1 strain alone and that a number of antibodies bound to annual influenza vaccine strains either solely or with higher affinity (indicated with asterisks). In total 47% (25/52) bound swine H1N1 and 58% (30/52) bound influenza antigens at levels detectable by ELISA assay[12]. The mAb EM4C04 (bold) had the highest and most specific affinity against swine H1N1. Cocktail: A/Sal. Is./3/2006 (H1N1), A/WI/57/05 (H3N2), and B/Mal./2506/04, 2006/7 Vaccine: A/New Cal./20/90 (H1N1), A/WI/57/05 (H3N2), and B/Mal./2506/04, 2008/9 Vaccine: A/Brisb./59/2007 (H1N1), A/Brisb./10/2007 (H3N2),and B/FL/4/2006.

**[0027]** FIG. **3**. The monoclonal antibody EM4C04 is highly specific for the swine H1N1 influenza hemagglutinin and displays HAI activity only to the swine H1N1 virus. (a) ELISA binding curves of the mAb EM4C04, comparing binding to whole virus with reactivity to viral mixtures or the annual vaccines as indicated, to purified virions or to recombinant hemagglutinin (rHA) from swine H1N1 versus other influenza strains. Calculated Kd values are shown in parenthesis above the graphs. Cocktail: A/Sal.Is./3/2006 (H1N1), A/WI/57/05 (H3N2), and B/Mal./2506/04, 2006/7 Vaccine: A/New Cal./20/90 (H1N1), A/WI/57/05 (H3N2), and B/Mal./2506/04, 2008/9 Vaccine: A/Brisb./59/2007 (H1N1), A/Brisb./10/2007 (H3N2),and B/FL/4/2006. (b) EM4C04 is able to immuno-precipitate recombinant from swine H1N1 HA protein. (c) EM4C04 displays HAI activity toward swine H1N1 but not to several other H1N1 strains tested as indicated.

**[0028]** FIG. **4**. EM4C04 has therapeutic efficacy in mice challenged with a lethal dose of mouse-adapted 2009 swine H1N1 influenza. 6-8 week old Balb/c mice were infected with a 3×LD50 dose of highly pathogenic, mouse-adapted 2009 swine H1N1 influenza (A/California/04/09). Subsequently, they were treated with 200 mg (10 mg/kg of body weight)

EM4C04 human monoclonal antibody intraperitoneally at various time points (12, 24, 36, 48 and 60 hours) after infection. All mice were monitored daily for body weight changes and any signs of morbidity and mortality. Infected, untreated mice showed clear signs of sickness around day 4-5 post infection and perished by day 8-9. Upper panels show body weight change and the lower panels show survival curves.

**[0029]** FIG. **5**. Plasmablasts expressing antibodies that cross-react to annual influenza strains have accumulated more somatic hypermutations. The higher frequency of mutations in the more crossreactive antibodies indicate that they were derived from a recall response of memory B cells, originally induced by annual influenza viruses. It is also notable that a number of IgG+ plasmablasts that had no detectable binding to influenza by ELISA were from cells that had no mutations of the variable genes. The origin and specificity of these cells is unknown but they may be cells activated during a primary response against swine H1N1 epitopes that had affinities below the threshold of detection. The frequency of point mutations was determined from the variable gene sequences of the VH and Vκ sequences that were generated for the cloning and expression of the antibodies. Points represent the sum of heavy and light chain mutations. Statistical significance was determined by students t test.

**[0030]** FIG. **6**. Prophylactic treatment with EM4C04 can protect mice from a lethal challenge with mouse-adapted swine H1N1 influenza. 6-8 week old Balb/c mice were treated with 200 μg (10 mg/kg of body weight) EM4C04 human monoclonal antibody intraperitoneally 12 hours prior to infection with a 3×LD50 dose of highly pathogenic mouse adapted swine H1N1 influenza. All mice were monitored daily for body weight changes and any signs of morbidity and mortality. Upper panels show body weight change and the lower panels show survival curves.

## DETAILED DESCRIPTION

**[0031]** The studies described below analyzed the B cell responses in patients infected with swine H1N1 virus. As part of these studies we generated a panel of virus specific human monoclonal antibodies. These antibodies were isolated from plasmablasts that were activated by infection providing a means to directly evaluate the breadth and repertoire of the antibody response elicited by swine H1N1 virus. Interestingly, a majority of these antibodies also reacted with seasonal influenza viruses. In fact, several of the antibodies bound with higher affinity to past influenza strains than to the current swine H1N1 virus. These findings suggest that the swine H1N1 virus predominantly activated memory B cells previously generated against cross-reactive but non-protective epitopes present in annual influenza strains. Of the influenza specific antibodies generated five bound to recombinant hemagglutinin (HA) protein and of these only one antibody showed hemagglutination-inhibition (HAI) activity against the swine H1N1 influenza virus. In contrast to most of the other antibodies generated, this neutralizing antibody was highly specific for the swine H1N1 virus and did not cross-react with the other H1N1 influenza viruses, confirming that the critical HA active-site epitopes in this new virus are quite unique. In vivo experiments showed that this antibody was able to protect mice challenged with a lethal dose of mouse-adapted swine H1N1 influenza virus. Moreover, it was effective therapeutically even when administered 60 hours after infection and could thus potentially be developed as a therapeutic agent against the swine H1N1 influenza virus pandemic.

**[0032]** The novel 2009 pandemic swine H1N1 influenza virus is characterized by a unique genetic make-up[1,2,8] that results in little or no pre-existing serum antibody mediated protection against infection[7,9]. It is currently unclear what effect this has on the repertoire of responding B cells in infected patients and whether infection with this novel virus leads to activation of cross-reactive memory B cells or if the response is dominated by newly induced naive B cells. To analyze the repertoire of the responding B cells after infection and to generate monoclonal antibodies (mAbs) against the swine H1N1 influenza strain, we examined the B cell responses in five patients infected with swine H1N1 virus. The clinical details about these patients are given in the supplemental methods section. Blood samples were taken 1-2 weeks after onset of clinical symptoms and were used to isolate infection-induced plasmablasts ($CD19^+$, $CD20^-$, $CD3^-$, $CD38^{high}$ and $CD27^{high}$ cells) by flow cytometry based cell sorting (FIG. **1***a* shows a representative donor). Using an adapted single cell multiplex RT-PCR approach[10,11,12], we then identified the heavy and light chain immunoglobulin genes from each individual plasmablast from two of the five patients. These heavy and light chain fragment pairs were then used to express fully human monoclonal antibodies. In total, 25 out of the 53 (47%) antibodies generated in this fashion bound to purified whole swine H1N1 influenza (A/CA/04/2009) virus by ELISA (FIG. **1***b*). It is notable that the majority of antibodies induced by infection were low affinity; only five of the 53 isolated antibodies, had affinities $>10^{-9}$ by non-linear regression analysis of ELISA data. Further, as indicated in FIG. **1***c*, five of the 53 antibodies bound to recombinant hemagglutinin (rHA) from swine H1N1 influenza by ELISA, but only one of these mAbs (EM4C04) displayed HAI activity (FIG. **1***d*). We conclude from this analysis that a large proportion of virus specific plasmablasts in these patients were not producing neutralizing antibodies, and that the majority of the B cell response was in fact directed at non-HA proteins.

**[0033]** In order to determine how specific the antibody response was to the swine H1N1 virus strain, the 53 monoclonal antibodies were screened by ELISA for reactivity to various influenza antigens (FIG. **2**). The bars in FIG. **2** indicate the area under the curve of ELISA binding data (FIG. **1***a*), thus providing an overview of both the maximal binding ($B_{max}$) and the persistence of binding with decreasing dilutions (affinity or $K_d$), allowing a relative comparison of each antibody to all antigens by column. It is notable that most of the antibodies were indeed cross-reactive with past strains of influenza virus, suggesting that they arose through the activation of cross-reactive memory B cells. In total, 47% ($^{25}/_{52}$) of the antibodies bound to swine H1N1 and 58% ($^{30}/_{52}$) bound to antigens from any of the influenza strains tested. In fact, 23% of the antibodies bound to past annual influenza strains with higher affinity than to the swine H1N1 strain (FIG. **2**, asterisks). The plasmablasts expressing antibodies that were cross-reactive to past annual influenza strains had also accumulated significantly more mutations in the variable genes on average than the swine H1N1-specific B cells (FIG. **5**). These findings suggest that the swine H1N1 strain predominantly activated memory B cells previously generated against cross-reactive but non-protective epitopes present in annual influenza virus strains.

**[0034]** It is worth noting that the sole HAI$^+$mAb, EM4C04 (FIG. **2**) was also the most specific against swine H1N1, demonstrating that the critical HA active-site epitopes are quite unique, as predicted by analyses of the HA amino acid sequences by several other groups[1,2,7,13]. The high specificity of EM4C04 demonstrates that this antibody could be valuable for diagnostic purposes for the pandemic swine H1N1 influenza virus (FIG. **3***a*). This antibody was also able to immunoprecipitate recombinant HA protein derived from swine H1N1 (FIG. **3***b*). In addition, while EM4C04 efficiently inhibited the agglutination of red blood cells by swine H1N1 virus, it had no HAI activity against several other influenza strains (FIG. **3***c*). The high affinity ($6.1x^{10-11}$ to purified virus and $9x^{10-11}$ to rHA) for the HA active site suggested that this antibody could be used for passive immunization to treat swine H1N1 influenza infection. We therefore tested the prophylactic and therapeutic potential of EM4C04 in mice infected with a lethal dosage of highly pathogenic, mouse-adapted swine H1N1 strain.

**[0035]** As indicated in FIG. **4** (and FIG. **6**), the EM4C04 antibody is highly effective at either providing prophylactic protection against infection or to treat and facilitate clearance of a lethal dose of mouse-adapted swine H1N1 from 6-8 week old Balb/c mice. For the prophylactic experiments mice were pretreated with 200 μg EM4C04 human monoclonal antibody intraperitoneally and then challenged 12 hours later with a 3×LD50 dose of mouse-adapted novel H1N1 influenza (FIG. **6**). To determine the therapeutic potential of EM4C04, mice were first challenged and then treated with antibody at various times after infection (FIG. **4**). While untreated mice died 8-9 days after the infection, mice treated even as late as 60 hours after challenge survived. Infected mice treated at later time points were already showing measurable weight loss that was reversed by administration of the antibody, demonstrating therapeutic potential even after the onset of symptoms. Overall, 30 of 31 infected mice that were treated with EM4C04, irrespective of when they were treated, made a complete recovery from infection. It is likely that the therapeutic effects of EM4C04 treatment involve both direct viral neutralization as well as facilitation of endogenous cell-mediated immunity[14]. It is possible that the antibody treatment may reduce viral titers and thus allow the endogenous immune responses to catch up and subsequently clear the infection.

**[0036]** The studies show that the antibody responses induced in patients infected with the novel swine H1N1 influenza appear to be dominated by a recall response of non-protective memory B cells that are cross-reactive to annual influenza strains. Of the 25 virus-specific monoclonal antibodies generated herein only one displayed HAI activity against the swine H1N1 virus. This low frequency of cells producing protective antibodies after infection differs significantly as compared to previous work on seasonal influenza vaccines[12], where 40% of the virus specific antibodies bound with high affinity to HA and half of those antibodies had HAI activity against the influenza vaccine viral strains. As the novel swine H1N1 vaccine is now becoming widely available[15-18], it will be of interest to compare the vaccine induced antibody responses to the responses induced by infection as described herein. Finally, the in vivo protection experiments presented here demonstrate that the human monoclonal antibody EM4C04 has impressive prophylactic and therapeutic activity in mice and shows potential for development as a therapeutic agent against the pandemic swine H1N1 influenza virus in humans.

## METHODS

**[0037]** Patients were recruited with IRB approval and had ongoing or recent verified swine H1N1 infections. HAI titers, inhibiting antibody concentrations, and viral neutralization were determined by standard procedures as previously described[12,19]. The ASCs were identified herein as CD3$^-$/CD20$^-$/$^{low}$/CD19$^+$/CD27$^{hi}$/CD38$^{hi}$ cells as previously described[11,12]. The single cell RT-PCR methods and the procedures for production of recombinant mAbs were as previously describee[10-12]. Monoclonal antibodies were screened against fresh influenza virions grown in chicken eggs. ELISA was performed on starting concentrations of 10 ug/ml of virus or rHA and on 1:20 dilution of the vaccines and antibody affinities (Kd) were calculated by nonlinear regression analysis as previously described[12]. For immunoprecipitation, 1 μg each of recombinant HA protein and antibody were incubated at 4° C. overnight in 100 μl NP40 Buffer prior to precipitation with Protein G-Sepharose. The samples were denatured for 5 min at 95° C. in Laemmli gel sample buffer followed by centrifugation to remove the Protein GSepharose and analysis on 12% Tris-Glycine polyacrylamide gels. Precipitated protein bands were identified by staining with Sypro-orange and Fluorescence imaging. For the challenge experiments, female Balb/c mice (8 weeks old) were challenged intranasally with $3\times xLD_{50}$ of a highly pathogenic, mouse-adapted swine H1N1 influenza virus (A/California/04/09) that was passaged in mice for five generations. Mice were treated intraperitoneally with 200 ug (10 mg/kg of body weight) of the specific mAb EM4C04 at all time points. All mice were monitored daily for morbidity and body weight changes.

### Patients

**[0038]** All studies were approved by the Emory University, University of Chicago and Columbia University institutional review boards (Emory IRB#22371 and 555-2000, U of C IRB# 16851E, CU IRB#AAAE1819). Patient 1 (EM) is a 30-year old healthy woman who developed fever, cough and progressive dyspnea over 8 days prior to hospital admission. She was diagnosed with acute respiratory syndrome (ARDS), which required mechanical ventilation. Her nasopharyngeal swab on admission was positive for influenza by RTPCR. She continued shedding virus (hospital day 13) despite treatment with oseltamivir, but had cleared the virus by day 15 with continued treatment. Her course was further complicated by bacterial pneumonia, pulmonary embolism, and a requirement for prolonged oscillatory ventilator support and tracheostomy. She gradually recovered and was discharged to home two months after becoming ill. Blood samples for PBMC preparation were collected 19 days and 29 days after the onset of symptoms. Patient 2 (SF) is a 37-year old man with a history of hypertension and interstitial lung disease of unknown etiology who was hospitalized with symptoms of fever, cough, shortness of breath, nausea and vomiting for 3 days. He was diagnosed with pneumonia, acute sinusitis and acute renal failure. His nasopharyngeal swab on admission was positive for influenza virus by culture and was confirmed as the swine H1N1 influenza virus by RTPCR. He was initially treated with oseltamivir for 5 days but was continuing to shed influenza virus and was discharged with a course of zanamivir. He was hospitalized for a total of 8 days and recovered. PBMCs were collected 18 days after the onset of symptoms. Patient 3 is a 25 year old male who developed cough and fever to 103° F. The diagnosis of 2009 H1N1 influenza was confirmed by RT-PCR. He was treated with oseltamivir and his symptoms lasted for 4 days. He recovered completely and blood samples were collected 9 days after the onset of symptoms. Patient 4 is a previously healthy, 40-year

old man who developed symptoms consistent with mild upper respiratory tract illness, including cough, rhinorrhea, and fever. MassTag PCR analysis of a nasopharyngeal swab specimen obtained 6 days after symptom onset identified H1N1 influenza virus; the presence of swine H1N1 influenza virus was subsequently confirmed by RT-PCR. Blood samples for PBMC isolation were obtained 13 days after the onset of symptoms. Patient 5 is a 52 year old female whose diagnosis of 2009 H1N1 influenza A was confirmed by RT-PCR. Her symptoms included fever, cough, pharyngitis, myalgias, nausea, headache, and gastrointestinal symptoms. She was treated with oseltamivir and her symptoms resolved after 6 days and she recovered completely. Blood samples were collected 10 days after the onset of symptoms.

Cell and Serum Isolation

**[0039]** All work with samples from infected patients was performed in a designated BSL2+ facility at Emory University. Peripheral blood mononuclear cells (PBMC) were isolated using Vacutainer tubes (Becton Dickinson, BD), washed, and resuspended in PBS with 2% FCS for immediate use or frozen for subsequent analysis. Plasma samples were saved in −80C.

Viruses and Antigens

**[0040]** The Swine H1N1 influenza virus (A/California/04/2009) was kindly provided by Dr. Richard J Webby at St. Jude Childrens Hospital. Influenza virus stocks used for the assays were freshly grown in eggs, prepared and purified as described[19] and the hemagglutination activity (HA) was determined using turkey red blood cells (Lampire Biological Laboratories, Pipersville, Pa.) as previously described[12,19] or purchased as inactivated preparations (ProSpec-Tany TechnoGene Ltd., Rehovot, Israel) and included: A/California/04/2009 (H1N1), A/FM/1/47 (H1N1), A/PR8/34 (H1N1), A/New Jersey/76 (H1N1), A/New Caledonia/20/9 (H1N1), A/Solomon Island/3/2006, A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. Vaccines tested included the 2006/7 vaccine from Chiron Vaccines Limited (Liverpool, UK) and the 2008/9 formulation from Sanofi Pasteur Inc. (Swiftwater, Pa.). Recombinant HA proteins were provided by the influenza reagent resource (IRR; influenza reagent resource.org) of the CDC (rHA from A/California/04/2009 (H1N1) (#FR-180), A/Brisbane/10/2007 (H1N1) (#FR-61), A/Brisbane/59/2007 (H3N2) (#FR-65)) or by Biodefense & Emerging Infections research repository (BEI; www.beiresources.org) (rHA from A/Indonesia/05/2005).

Flow Cytometry Analysis and Cell Sorting

**[0041]** Analytical flow cytometry analysis was performed on whole blood following lysis of erythrocytes and fixing in 2% PFA. All live cell sorting was performed on purifiedPBMCs in the BSL-3 facility at the Emory Vaccine Center. All antibodies for bothanalytical and cell sorting cytometry were purchased from Pharmingen, except anti-CD27 that was purchased from ebiosciences. Anti-CD3-PECy7 or PerCP, anti-CD20-PECy7 or PerCP, anti-CD38-PE, anti-CD27-APC and anti-CD19-FITC. ASCs were gated and isolated as $CD19^{+}CD3^{-}CD20^{low}CD27^{high}CD38^{high}$ cells. Flow cytometry data was analyzed using FlowJo software.

Generation of Monoclonal Antibodies

**[0042]** Identification of antibody variable region genes were done essentially as previously described[10,11]. Briefly, single ASCs were sorted into 96-well PCR plates containing RNase inhibitor (Promega). VH and Vic genes from each cell were amplified by RT-PCR and nested PCR reactions using cocktails of primers specific for both IgG and IgA as previously describee[10,11] and then sequenced. To generate recombinant antibodies, restriction sites were incorporated by PCR with primers to the particular variable and junctional genes. VH or Vκ genes amplified from each single cell were cloned into IgG1 or Igκ expression vectors as previously describee[10,11]. Heavy/light chain plasmids were co-transfected into the 293A cell line for expression and antibodies purified with protein A sepharose.

ELISA and HAI Assays

**[0043]** Whole virus, recombinant HA or vaccine-specific ELISA was performed on starting concentrations of 10 ug/ml of virus or rHA and on 1:20 dilution of the vaccine as previously described[12]. The hemagglutination inhibition (HAI) titers were determined as previously described[11,19]. Affinity estimates were calculated by nonlinear regression analysis of curves from 8 dilutions of antibody (10 to 0.125 μg/ml) using GraphPad Prism.

Immunoprecipitation

**[0044]** For immunoprecipitation, 100 μl NP40 Buffer (20 mM Tris-HCl PH8.0, 137 mM NaCl, 10% Glycerol, 1% NP-40, 2 mM EDTA) containing complete Protease Inhibitors (Roche) was mixed with 1 μg of recombinant HA protein and incubated on ice for 30 min. One microgram of monoclonal antibody was then added. The antibody and HA mixture was incubated at 4° C. overnight with constant agitation. On the next day, Protein G-Sepharose (GE Healthcare) was prepared in NP40 buffer at a volume of 10 μl/sample. Protein GSepharose was incubated with the antibody and HA mixture at 4C for 4 hrs with constant agitation. The protein G-Sepharose was centrifuged for 3 min at 3000 rpm and the pellet was washed with 400 μl of NP40 buffer for 3 times. Finally the pellet was resuspended into 25 μl of Laemmli gel sample buffer (Bio-Rad). The samples were then boiled for 5 min at 95C. The protein G was pelleted and **15** μ*l* of supernatant was loaded onto 12%Tris-Glycine polyacrylamide gels. The gels were run in 1×TGS at 70V for 30 min, followed by 120V till the frontline ran out of the gel. The gels were stained with 1× Sypro-orange (Invitrogen) in 7.5% acetic acid for 1 hr, and then gels were destained with 7.5% acetic acid for 3 min. Gels were finally scanned in a Typhoon 9410 Fluorescence imaging system (GE Healthcare).

**[0045]** In vivo Protection Experiments

**[0046]** Female Balb/c mice 6-8 weeks old were used for the challenge studies. Mice were inoculated intra-nasally with $3xLD_{50}$ of a highly pathogenic, mouse-adapted swine H1N1 influenza virus (A/California/04/09) that was passaged in mice five generations. The $LD_{50}$ was determined by the method of Reed and Muench. The experiments were conducted in accordance with ethical procedures and policies approved by the Emory University's Institutional Animal Care and Use Committee. In order to determine the prophy-

lactic efficacy of the mAb, mice were treated intraperitoneally with 200 μg (10 mg/kg of body weight) of the specific mAb EM4C04. Twelve hours later mice were challenged with $3xLD_{50}$ of the mouse adapted H1N1 virus. All mice were monitored daily for any signs of morbidity and mortality. Body weight changes were registered daily for a period of 14 days. All mice that lost more that 25% of their initial body weight were sacrificed according to the IACUC guideless. In order to determine the therapeutic efficacy of the EM4C04 mAb, mice were challenged with $3xLD_{50}$ of the mouse-adapted swine H1N1 virus. At various times post infection (12, 24, 36, 48, 60 hours) mice were treated intraperitoneally with 200 μg (10 mg/kg of body weight) of the specific mAb EM4C04. All mice were monitored daily and the body weight changes were registered daily as described above.

### Statistical Analysis

**[0047]** Data was collected and graphed using MS Excel and Graphpad Prism software. Efficacy of the therapeutic and challenge experiments was evaluated by ANOVA using Graphpad Prism software.

### Sequences of Antibodies

**[0048]** Described below are the sequences of the EM4C04 heavy chain and light chain

EM4C04 Heavy Chain Variable Region:
DNA
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCC

TGAGACTCTCCTGTTCAGCCTCTGGATTCACCTTCAATATCTATGCCATGAAC

TGGGTCCGCCAGGTTCCAGGAAAGGGGCTGGATTGGGTCTCATCCATTAGTA

GTAGGGGTGATTACATATACTACGCAGAGTCAGTGGAGGGCCGATTCACCAT

CTCCAGAGACAACGCCAAGAACTCACTGTATCTGGAAATGAACAGCCTGAGA

GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGCTGGGCTGGGTACAGTGG

ATTTAAGGTGGGGGGGGGCCTTCGACCACTGGGGCAAGGGAATCCTGGTCAC

CGTCTCCTCA

Amino Acid:

(SEQ ID NO: 2)

EVQLVESGGGLVKPGGSLRLSCSASGFTFNIYAMNWVRQVPGKGLDWVSSISSR

GDYIYYAESVEGRFTISRDNAKNSLYLEMNSLRAEDTAVYYCARAGLGTVDLR

WGGAFDHWGKGILVTVSS

Alignment:
Ig Sequence Name: EM-Swine1-4C04H-

V gene: Z14073_IGHV3-21*01

D Gene: None Found

D Gene 2: None Found

J Gene: X86355 IGHJ5*02

Clonal Pool: 0

CDR3 Length: 17

CDR3 AA: RAGLGTVDLRWGGAFDH

```
                1> Z14073_1GHV3-21*01    20          30          40
                 E   V   Q   L   V   E   S   G   G   G   L   V   K   P   G
Germline        GAG GTG CAG CTG GTG GAG TCT GGG GGA GGC CTG GTC AAG CCT GGG
EM-Swine1-4C04H- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

                     50          60          70          80          90
                 G   S   L   R   L   S   C   A   A   S   G   F   T   F   S
Germline        GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTC AGT
EM-Swine1-4C04H- --- --- --- --- --- --- --- T-- --- --- --- --- --- --- -A-
                                            S                           N

                         100         110         120         130
                 S   Y   S   M   N   W   V   R   Q   A   P   G   K   G   L
Germline        AGC TAT AGC ATG AAC TGG GTC CGC CAG GCT CCA GGG AAG GGG CTG
EM-Swine1-4C04H- -T- --- GC- --- --- --- --- --- --- -T- --- --A --- --- ---
                 I       A                           V
```

-continued

```
                    140          150          160          170          18
                     E   W   V   S   S   I   S   S   S   S   S   Y   I   Y   Y
Germline            GAG TGG GTC TCA TCC ATT AGT AGT AGT AGT AGT TAC ATA TAC TAC
EM-Swine1-4C04H- --T --- --- --- --- --- --- --- --G G-- GA- --- --- --- ---
                     D                              R   G   D

                    0           190          200          210          220
                     A   D   S   V   K   G   R   F   T   I   S   R   D   N   A
Germline            GCA GAC TCA GTG AAG GGC CGA TTC ACC ATC TCC AGA GAC AAC GCC
EM-Swine1-4C04H- --- --G --- --- G-- --- --- --- --- --- --- --- --- --- ---
                         E           E

                    230          240          250          260          27
                     K   N   S   L   Y   L   Q   M   N   S   L   R   A   E   D
Germline            AAG AAC TCA CTG TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC
EM-Swine1-4C04H- --- --- --- --- --- --- G-- --- --- --- --- --- --- --- ---
                                         E

                    0           280          290          300          310
                     T   A   V   Y   Y   C   A   ?   ?   ?   ?   ?   ?   ?   ?
Germline            ACG GCT GTG TAT TAC TGT GCG AGN NNN NNN NNN NNN NNN NNN NNN
EM-Swine1-4C04H- --- --- --- --- --- --- --- --A GCT GGG CTG GGT ACA GTG GAT
                                             R   A   G   L   G   T   V   D

                         320          330   1> X86355 IGHJ5*02   350          36
                     ?   ?   ?   ?   ?   ?   F   D   P   W   G   Q   G   T   L
Germline            NNN NNN NNN NNN NNN NNN TTC GAC CCC TGG GGC CAG GGA ACC CTG
EM-Swine1-4C04H- TTA AGG TGG GGG GGG GCC --- --- -A- --- --- A-- --- -T- ---
                     L   R   W   G   G   A           H            K       I

                    0           370
                     V   T   V   S   S   ?
Germline            GTC ACC GTC TCC TCA G
EM-Swine1-4C04H- --- --- --- --- --- -
```

EM4C04 kappa Variable Domain:

DNA

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGACAG

AGTCACCATCTCTTGCCAGGCGAGTCAGGATATTACCAACTTTTTAAATTGGT

ACCAGCAGAAATCTGGGGAAGCCCCTAAGCTCCTGATCTACGATGCATCCGA

TTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAGAT

TTTACTTTCACCATCAGCAGGCTGCAGCCTGAAGACACTGCAACATATTACTG

TCAACAGTATGACGATCTCCCGTATACTTTTGGCCAGGGGACCAAGGTGGAG

ATCAAA

Amino acid

(SEQ ID NO: 1)

DIQMTQSPSSLSASVGDRVTISCQASQDITNFLNWYQQKSGEAPKLLIYDASDLET

GVPSRFSGSGSGTDFTFTISRLQPEDTATYYCQQYDDLPYTFGQGTKVEIK

Alignment:

Ig Sequence Name: EM-Swine1-4C04K-

V gene: M64855_IGKV1D-33*01

D Gene: None Found

D Gene 2: None Found

J Gene: J00242 IGKJ2*01

Clonal Pool: 0

CDR3 Length: 8

-continued

```
CDR3 AA:          QYDDLPYT

                  1> M64855_IGKV1D-33*01   20           30           40
                   D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V
Germline          GAC ATC CAG ATG ACC CAG TCT CCA TCC TCC CTG TCT GCA TCT GTA
EM-Swine1-4C04K- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --T

                      50           60           70           80           90
                    G   D   R   V   T   I   T   C   Q   A   S   Q   D   I   S
Germline          GGA GAC AGA GTC ACC ATC ACT TGC CAG GCG AGT CAG GAC ATT AGC
EM-Swine1-4C04K- --- --- --- --- --- --- T-- --- --- --- --- --- --T --- -C-
                                          S                                 T

                              100          110          120          130
                    N   Y   L   N   W   Y   Q   Q   K   P   G   K   A   P   K
Germline          AAC TAT TTA AAT TGG TAT CAG CAG AAA CCA GGG AAA GCC CCT AAG
EM-Swine1-4C04K- --- -T- --- --- --- --C --- --- --- T-T --- G-- --- --- ---
                      F                                   S       E

                      140          150          160          170          18
                    L   L   I   Y   D   A   S   N   L   E   T   G   V   P   S
Germline          CTC CTG ATC TAC GAT GCA TCC AAT TTG GAA ACA GGG GTC CCA TCA
EM-Swine1-4C04K- --- --- --- --- --- --- --- G-- --- --- --- --- --- --- ---
                                            D

                  0           190          200          210          220
                    R   F   S   G   S   G   S   G   T   D   F   T   F   T   I
Germline          AGG TTC AGT GGA AGT GGA TCT GGG ACA GAT TTT ACT TTC ACC ATC
EM-Swine1-4C04K- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

                      230          240          250          260          27
                    S   S   L   Q   P   E   D   I   A   T   Y   Y   C   Q   Q
Germline          AGC AGC CTG CAG CCT GAA GAT ATT GCA ACA TAT TAC TGT CAA CAG
EM-Swine1-4C04K- --- --G --- --- --- --- --C -C- --- --- --- --- --- --- ---
                      R                       T

                  0           280         1> J00242 IGKJ2*01          310
                    Y   D   N   L   ?   ?   T   F   G   Q   G   T   K   L   E
Germline          TAT GAT AAT CTC CCN NNN ACT TTT GGC CAG GGG ACC AAG CTG GAG
EM-Swine1-4C04K- --- --C G-- --- --G TAT --- --- --- --- --- --- --- G-- ---
                          D       P   Y                                 V

                      320
                    I   K   ?
Germline          ATC AAA C
EM-Swine1-4C04K- --- --- -
```

CDR and FR of EM4C04 Heavy Chain:
Nucleotide:
FW1:
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCC

TGAGACTCTCCTGTTCAGCCTCTGGATTCACCTTCAAT

CDR1:
ATCTATGCCATGAAC

FW2:
TGGGTCCGCCAGGTTCCAGGAAAGGGGCTGGATTGGGTCTCA

CDR2:
TCCATTAGTAGTAGGGGTGATTACATATACTACGCAGAGTCAGTGGAGGGC

FW3:
CGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGGAAATGA

ACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGA

CDR3:
GCTGGGCTGGGTACAGTGGATTTAAGGTGGGGGGGGGCCTTCGACCAC

FW4:
TGGGGCAAGGGAATCCTGGTCACCGTCTCCTCA

-continued

Amino Acids:
FW1:
EVQLVESGGGLVKPGGSLRLSCSASGFTFN

CDR1:
(SEQ ID NO: 4)
IYAMN

FW2:
WVRQVPGKGLDWVS

CDR2:
(SEQ ID NO: 5)
SISSRGDYIYYAESVEG

FW3:
RFTISRDNAKNSLYLEMNSLRAEDTAVYYCAR

CDR3:
AGLGTVDLRWGGAFDH

FW4:
(SEQ ID NO: 6)
WGKGILVTVSS

CDR and FR of EM4C04 Light Chain:
Nucleotide:
FW1:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGACAG

AGTCACCATCTCTTGCCAGGCGAGT

CDR1:
CAGGATATTACCAACTTTTTAAAT

FW2:
TGGTACCAGCAGAAATCTGGGGAAGCCCCTAAGCTCCTGATCTAC

CDR2:
GATGCATCCGATTTGGAAACA

FW3:
GGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCA

CCATCAGCAGGCTGCAGCCTGAAGACACTGCAACATATTACTGT

CDR3:
CAACAGTATGACGATCTCCCGTATACT

FW4:
TTTGGCCAGGGGACCAAGGTGGAGATCAAA

Amino acids:
FW1:
DIQMTQSPSSLSASVGDRVTISC

CDR1:
(SEQ ID NO: 3)
QASQDITNFLN

FW2:
WYQQKSGEAPKLLIY

CDR2:
(SEQ ID NO: 4)
DASDLET

FW3:
GVPSRFSGSGSGTDFTFTISRLQPEDTATYYC

CDR3:
(SEQ ID NO: 5)
QQYDDLPYT

FW4:
FGQGTKVEIK

**[0049]** The CDR described herein can be grafted into the following vectors encoding human IgG and kappa chains, as well as others: Fully human IgG (GenBank® Accession No: FJ475055) and Fully human kappa (GenBank® Accession No: FJ475056).

GenBank ® FJ475055
RSTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA

VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP

PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV

EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI

SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN

YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS

PGK

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 121 ggctgaccgc ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta
 181 acgccaatag ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac
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 301 aaatggcccg cctggcatta tgcccagtac atgaccttat gggactttcc tacttggcag
 361 tacatctacg tattagtcat cgctattacc atggtgatgc ggttttggca gtacatcaat
 421 gggcgtggat agcggtttga ctcacgggga tttccaagtc tccaccccat tgacgtcaat
 481 gggagtttgt tttggcacca aaatcaacgg gactttccaa aatgtcgtaa caactccgcc
 541 ccattgacgc aaatgggcgg taggcgtgta cggtgggagg tctatataag cagagctcgt
 601 ttagtgaacc gtcagatcgc ctggagacgc catccacgct gttttgacct ccatagaaga
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 901 acctcggttc tatcgattga attccaccat gggatggtca tgtatcatcc tttttctagt
 961 agcaactgca accggtgtac actcgagcgt acggtcgacc aagggcccat cggtcttccc
1021 cctggcaccc tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa
1081 ggactacttc cccgaacctg tgacggtctc gtggaactca ggcgccctga ccagcggcgt
1141 gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca gcgtggtgac
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1261 caacaccaag gtggacaaga aagttgagcc caaatcttgt gacaaaactc acacatgccc
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1561 cgtcctgcac caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc
1621 cctcccagcc cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca
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1741 cctggtcaaa ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc

1801 ggagaacaac tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta

1861 cagcaagctc accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt

1921 gatgcatgag gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa

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2101 tgtccaaact catcaatgta tcttatcatg tctggatcga tcgggaatta attcggcgca

2161 gcaccatggc ctgaaataac ctctgaaaga ggaacttggt taggtacctt ctgaggcgga

2221 aagaaccagc tgtggaatgt gtgtcagtta gggtgtggaa agtccccagg ctccccagca

2281 ggcagaagta tgcaaagcat gcatctcaat tagtcagcaa ccaggtgtgg aaagtcccca

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2461 catggctgac taatttttt tatttatgca gaggccgagg ccgcctcggc ctctgagcta

2521 ttccagaagt agtgaggagg ctttttgga ggcctaggct tttgcaaaaa gctgttaaca

2581 gcttggcact ggccgtcgtt ttacaacgtc gtgactggga aaaccctggc gttacccaac

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2701 ccgatcgccc ttcccaacag ttgcgtagcc tgaatggcga atggcgcctg atgcggtatt

2761 ttctccttac gcatctgtgc ggtatttcac accgcatacg tcaaagcaac catagtacgc

2821 gccctgtagc ggcgcattaa gcgcggcggg tgtggtggtt acgcgcagcg tgaccgctac

2881 acttgccagc gccctagcgc ccgctccttt cgctttcttc ccttcctttc tcgccacgtt

2941 cgccggcttt ccccgtcaag ctctaaatcg ggggctccct ttagggttcc gatttagtgc

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3061 gccctgatag acggtttttc gccctttgac gttggagtcc acgttcttta atagtggact

3121 cttgttccaa actggaacaa cactcaaccc tatctcgggc tattcttttg atttataagg

3181 gattttgccg atttcggcct attggttaaa aaatgagctg atttaacaaa aatttaacgc

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3661 agacaataac cctgataaat gcttcaataa tattgaaaaa ggaagagtat gagtattcaa

3721 catttccgtg tcgcccttat tcccttttt gcggcatttt gccttcctgt ttttgctcac

3781 ccagaaacgc tggtgaaagt aaaagatgct gaagatcagt tgggtgcacg agtgggttac

3841 atcgaactgg atctcaacag cggtaagatc cttgagagtt ttcgccccga agaacgtttt

3901 ccaatgatga gcacttttaa agttctgcta tgtggcgcgg tattatcccg tgatgacgcc

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4261 gcaacaacgt tgcgcaaact attaactggc gaactactta ctctagcttc ccggcaacaa

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GenBank ® FJ475056
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4381 ggctgaacgg ggggttcgtg cacacagccc agcttggagc gaacgaccta caccgaactg

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4861 ctccccgcgc gttggccgat tcattaatcc agctggcacg acaggtttcc cgactggaaa

4921 gcgggcagtg agcgcaacgc aattaatgtg agttacctca ctcattaggc accccaggct

4981 ttacacttta tgcttccggc tcgtatgttg tgtggaattg tgagcggata acaatttcac

5041 acaggaaaca gctatgacca tgattacgaa ttaa
```

## USE OF ANTIBODIES

**[0050]** Antibodies described herein can be used in any method that antibodies produced by other means cane be used. Thus, they can be used in passive therapy and diagnosis. Passive antibody immunization can provide a state of immediate immunity that can last for weeks and possibly months. Some human IgG isotypes have serum half-lives in excess of 30 days, which would confer long-lived protection to passively immunized persons. Where active vaccines are available, they may be administered together with antibodies to both immediate and long-lasting protection. In addition, the antibodies can be administered in conjunction with one or more therapeutic drugs for treatment or prevention of infection or for treatment of infection. Administration of antibodies produced as described herein will follow the general protocols for passive immunization. Antibodies for administration be prepare in a formulation suitable for administration to a host. Aqueous compositions comprise an effective amount of an antibody dispersed in a pharmaceutically acceptable carrier and/or aqueous medium. The phrases "pharmaceutically and/or pharmacologically acceptable" refer to compositions that do not produce an adverse, allergic and/or other untoward reaction when administered to an animal, and specifically to humans, as appropriate.

**[0051]** As used herein, "pharmaceutically acceptable carrier" includes any solvents, dispersion media, coatings, antibacterial and/or antifungal agents, isotonic and/or absorption delaying agents and the like. The use of such media or agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. For administration to humans, preparations should meet sterility, pyrogenicity, general safety and/or purity standards as required by FDA Office of Biologics standards.

**[0052]** Antibodies will generally be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, intralesional, or even intraperitoneal routes. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation or in such amount as is therapeutically effective. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

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SEQUENCE LISTING

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20 25 30

Leu Asn Trp Tyr Gln Gln Lys Ser Gly Glu Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asp Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Arg Leu Gln Pro
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35 40 45

Ser Ser Ile Ser Ser Arg Gly Asp Tyr Ile Tyr Tyr Ala Glu Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Gly

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1               5                   10                  15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt agc tat       96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

agc atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc      144
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

tca tcc att agt agt agt agt agt tac ata tac tac gca gac tca gtg      192
Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac tca ctg tat      240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

ctg caa atg aac agc ctg aga gcc gag gac acg gct gtg tat tac tgt      288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg agn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn ttc      336
Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe
            100                 105                 110

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            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe
            100                 105                 110

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        115                 120                 125
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tcc ctg aga ctc tcc tgt tca gcc tct gga ttc acc ttc aat atc tat       96
Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Asn Ile Tyr
            20                  25                  30

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Ala Met Asn Trp Val Arg Gln Val Pro Gly Lys Gly Leu Asp Trp Val
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tca tcc att agt agt agg ggt gat tac ata tac tac gca gag tca gtg      192
Ser Ser Ile Ser Ser Arg Gly Asp Tyr Ile Tyr Tyr Ala Glu Ser Val
    50                  55                  60

gag ggc cga ttc acc atc tcc aga gac aac gcc aag aac tca ctg tat      240
Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

ctg gaa atg aac agc ctg aga gcc gag gac acg gct gtg tat tac tgt      288
Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gct ggg ctg ggt aca gtg gat tta agg tgg ggg ggg gcc ttc      336
Ala Arg Ala Gly Leu Gly Thr Val Asp Leu Arg Trp Gly Gly Ala Phe
            100                 105                 110

gac cac tgg ggc aag gga atc ctg gtc acc gtc tcc tca g               376
Asp His Trp Gly Lys Gly Ile Leu Val Thr Val Ser Ser
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ggggaagccc ctaagctcct gatctacgat gcatccgatt tggaaacagg ggtcccatca    180

aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag gctgcagcct    240

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1 5 10 15

gac aga gtc acc atc act tgc cag gcg agt cag gac att agc aac tat 96
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

tta aat tgg tat cag cag aaa cca ggg aaa gcc cct aag ctc ctg atc 144
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Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
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gaa gat att gca aca tat tac tgt caa cag tat gat aat ctc ccn nnn 288
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<223> OTHER INFORMATION: Any amino acid

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20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

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```
        35                  40                  45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Xaa
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gac aga gtc acc atc tct tgc cag gcg agt cag gat att acc aac ttt       96
Asp Arg Val Thr Ile Ser Cys Gln Ala Ser Gln Asp Ile Thr Asn Phe
            20                  25                  30

tta aat tgg tac cag cag aaa tct ggg gaa gcc cct aag ctc ctg atc      144
Leu Asn Trp Tyr Gln Gln Lys Ser Gly Glu Ala Pro Lys Leu Leu Ile
        35                  40                  45

tac gat gca tcc gat ttg gaa aca ggg gtc cca tca agg ttc agt gga      192
Tyr Asp Ala Ser Asp Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

agt gga tct ggg aca gat ttt act ttc acc atc agc agg ctg cag cct      240
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Arg Leu Gln Pro
65                  70                  75                  80

gaa gac act gca aca tat tac tgt caa cag tat gac gat ctc ccg tat      288
Glu Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asp Leu Pro Tyr
                85                  90                  95

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            100                 105


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Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Asn
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 32

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgttggaga cagagtcacc 60

atctcttgcc aggcgagt 78

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<210> SEQ ID NO 33
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 33

caggatatta ccaacttttt aaat 24

<210> SEQ ID NO 34
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 34

tggtaccagc agaaatctgg ggaagcccct aagctcctga tctac 45

<210> SEQ ID NO 35
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 35

gatgcatccg atttggaaac a 21

<210> SEQ ID NO 36
<211> LENGTH: 96
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 36

ggggtcccat caaggttcag tggaagtgga tctgggacag attttacttt caccatcagc 60

aggctgcagc ctgaagacac tgcaacatat tactgt 96

<210> SEQ ID NO 37
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 37

caacagtatg acgatctccc gtatact 27

<210> SEQ ID NO 38
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 38

tttggccagg ggaccaaggt ggagatcaaa 30

<210> SEQ ID NO 39
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 39

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys
20

<210> SEQ ID NO 40
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 40

Trp Tyr Gln Gln Lys Ser Gly Glu Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 41
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 41

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Phe Thr Ile Ser Arg Leu Gln Pro Glu Asp Thr Ala Thr Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 42
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 42

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> SEQ ID NO 43
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Arg Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210> SEQ ID NO 44
<211> LENGTH: 5746
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

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ttagttcata gcccatatat ggagttccgc gttacataac ttacggtaaa tggcccgcct    120

ggctgaccgc ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta    180

acgccaatag ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac    240
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ttggcagtac atcaagtgta tcatatgcca agtacgcccc ctattgacgt caatgacggt 300

aaatggcccg cctggcatta tgcccagtac atgaccttat gggactttcc tacttggcag 360

tacatctacg tattagtcat cgctattacc atggtgatgc ggttttggca gtacatcaat 420

gggcgtggat agcggtttga ctcacgggga tttccaagtc tccaccccat tgacgtcaat 480

gggagtttgt tttggcacca aaatcaacgg gactttccaa aatgtcgtaa caactccgcc 540

ccattgacgc aaatgggcgg taggcgtgta cggtgggagg tctatataag cagagctcgt 600

ttagtgaacc gtcagatcgc ctggagacgc catccacgct gttttgacct ccatagaaga 660

caccgggacc gatccagcct ccgcggccgg gaacggtgca ttggaacgcg gattccccgt 720

gccaagagtg acgtaagtac cgcctataga gtctataggc ccaccccctt ggcttcgtta 780

gaacgcggct acaattaata cataacctta tgtatcatac acatacgatt taggtgacac 840

tatagaataa catccacttt gcctttctct ccacaggtgt ccactcccag gtccaactgc 900

acctcggttc tatcgattga attccaccat gggatggtca tgtatcatcc tttttctagt 960

agcaactgca accggtgtac actcgagcgt acggtcgacc aagggcccat cggtcttccc 1020

cctggcaccc tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa 1080

ggactacttc cccgaacctg tgacggtctc gtggaactca ggcgccctga ccagcggcgt 1140

gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca gcgtggtgac 1200

cgtgccctcc agcagcttgg gcacccagac ctacatctgc aacgtgaatc acaagcccag 1260

caacaccaag gtggacaaga aagttgagcc caaatcttgt gacaaaactc acacatgccc 1320

accgtgccca gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc 1380

caaggacacc ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag 1440

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cctcccagcc cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca 1680

ggtgtacacc ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg 1740

cctggtcaaa ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc 1800

ggagaacaac tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta 1860

cagcaagctc accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt 1920

gatgcatgag gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa 1980

atgaagcttg gccgccatgg cccaacttgt ttattgcagc ttataatggt tacaaataaa 2040

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ggcagaagta tgcaaagcat gcatctcaat tagtcagcaa ccaggtgtgg aaagtcccca 2340

ggctccccag caggcagaag tatgcaaagc atgcatctca attagtcagc aaccatagtc 2400

ccgcccctaa ctccgcccat cccgccccta actccgccca gttccgccca ttctccgccc 2460

catggctgac taatttttt tatttatgca gaggccgagg ccgcctcggc ctctgagcta 2520

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ccgatcgccc ttcccaacag ttgcgtagcc tgaatggcga atggcgcctg atgcggtatt 2760

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cttgttccaa actggaacaa cactcaaccc tatctcgggc tattcttttg atttataagg 3180

gattttgccg atttcggcct attggttaaa aaatgagctg atttaacaaa aatttaacgc 3240

gaattttaac aaaatattaa cgtttacaat tttatggtgc actctcagta caatctgctc 3300

tgatgccgca tagttaagcc aactccgcta tcgctacgtg actgggtcat ggctgcgccc 3360

cgacacccgc caacacccgc tgacgcgccc tgacgggctt gtctgctccc ggcatccgct 3420

tacagacaag ctgtgaccgt ctccgggagc tgcatgtgtc agaggttttc accgtcatca 3480

ccgaaacgcg cgaggcagta ttcttgaaga cgaaagggcc tcgtgatacg cctatttttа 3540

taggttaatg tcatgataat aatggtttct tagacgtcag gtggcacttt tcggggaaat 3600

gtgcgcggaa cccctatttg tttatttttc taaatacatt caaatatgta tccgctcatg 3660

agacaataac cctgataaat gcttcaataa tattgaaaaa ggaagagtat gagtattcaa 3720

catttccgtg tcgcccttat tccctttttt gcggcatttt gccttcctgt ttttgctcac 3780

ccagaaacgc tggtgaaagt aaaagatgct gaagatcagt tgggtgcacg agtgggttac 3840

atcgaactgg atctcaacag cggtaagatc cttgagagtt ttcgccccga agaacgtttt 3900

ccaatgatga gcacttttaa agttctgcta tgtggcgcgg tattatcccg tgatgacgcc 3960

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ataaccatga gtgataacac tgcggccaac ttacttctga caacgatcgg aggaccgaag 4140

gagctaaccg ctttttgca caacatgggg gatcatgtaa ctcgccttga tcgttgggaa 4200

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caggcaacta tggatgaacg aaatagacag atcgctgaga taggtgcctc actgattaag 4560

cattggtaac tgtcagacca agtttactca tatatacttt agattgattt aaaacttcat 4620

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taacgtgagt tttcgttcca ctgagcgtca gaccccgtag aaaagatcaa aggatcttct 4740

tgagatcctt ttttttctgcg cgtaatctgc tgcttgcaaa caaaaaaacc accgctacca 4800

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agcagagcgc agataccaaa tactgtcctt ctagtgtagc cgtagttagg ccaccacttc   4920

aagaactctg tagcaccgcc tacatacctc gctctgctaa tcctgttacc agtggctgct   4980

gccagtggcg ataagtcgtg tcttaccggg ttggactcaa gacgatagtt accggataag   5040

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gcggcctttt tacggttcct ggccttttgc tggccttttg ctcacatgtt ctttcctgcg   5400

ttatcccctg attctgtgga taaccgtatt accgcctttg agtgagctga taccgctcgc   5460

cgcagccgaa cgaccgagcg cagcgagtca gtgagcgagg aagcggaaga gcgcccaata   5520

cgcaaaccgc ctctccccgc gcgttggccg attcattaat ccagctggca cgacaggttt   5580

cccgactgga aagcgggcag tgagcgcaac gcaattaatg tgagttacct cactcattag   5640

gcaccccagg ctttacactt tatgcttccg gctcgtatgt tgtgtggaat tgtgagcgga   5700

taacaatttc acacaggaaa cagctatgac catgattacg aattaa                  5746
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<210> SEQ ID NO 45
<211> LENGTH: 286
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

```
Met Ser Ile Gln His Phe Arg Val Ala Leu Ile Pro Phe Phe Ala Ala
1               5                   10                  15

Phe Cys Leu Pro Val Phe Ala His Pro Glu Thr Leu Val Lys Val Lys
            20                  25                  30

Asp Ala Glu Asp Gln Leu Gly Ala Arg Val Gly Tyr Ile Glu Leu Asp
        35                  40                  45

Leu Asn Ser Gly Lys Ile Leu Glu Ser Phe Arg Pro Glu Glu Arg Phe
    50                  55                  60

Pro Met Met Ser Thr Phe Lys Val Leu Leu Cys Gly Ala Val Leu Ser
65                  70                  75                  80

Arg Asp Asp Ala Gly Gln Glu Gln Leu Gly Arg Arg Ile His Tyr Ser
                85                  90                  95

Gln Asn Asp Leu Val Glu Tyr Ser Pro Val Thr Glu Lys His Leu Thr
            100                 105                 110

Asp Gly Met Thr Val Arg Glu Leu Cys Ser Ala Ala Ile Thr Met Ser
        115                 120                 125

Asp Asn Thr Ala Ala Asn Leu Leu Leu Thr Thr Ile Gly Gly Pro Lys
    130                 135                 140

Glu Leu Thr Ala Phe Leu His Asn Met Gly Asp His Val Thr Arg Leu
145                 150                 155                 160

Asp Arg Trp Glu Pro Glu Leu Asn Glu Ala Ile Pro Asn Asp Glu Arg
                165                 170                 175

Asp Thr Thr Met Pro Ala Ala Met Ala Thr Thr Leu Arg Lys Leu Leu
            180                 185                 190
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Thr Gly Glu Leu Leu Thr Leu Ala Ser Arg Gln Gln Leu Ile Asp Trp
        195                 200                 205

Met Glu Ala Asp Lys Val Ala Gly Pro Leu Leu Arg Ser Ala Leu Pro
    210                 215                 220

Ala Gly Trp Phe Ile Ala Asp Lys Ser Gly Ala Gly Glu Arg Gly Ser
225                 230                 235                 240

Arg Gly Ile Ile Ala Ala Leu Gly Pro Asp Gly Lys Pro Ser Arg Ile
                245                 250                 255

Val Val Ile Tyr Thr Thr Gly Ser Gln Ala Thr Met Asp Glu Arg Asn
            260                 265                 270

Arg Gln Ile Ala Glu Ile Gly Ala Ser Leu Ile Lys His Trp
        275                 280                 285


<210> SEQ ID NO 46
<211> LENGTH: 5074
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

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ggctgaccgc ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta    180

acgccaatag ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac    240

ttggcagtac atcaagtgta tcatatgcca agtacgcccc ctattgacgt caatgacggt    300

aaatggcccg cctggcatta tgcccagtac atgaccttat gggactttcc tacttggcag    360

tacatctacg tattagtcat cgctattacc atggtgatgc ggttttggca gtacatcaat    420

gggcgtggat agcggtttga ctcacgggga tttccaagtc tccaccccat tgacgtcaat    480

gggagtttgt tttggcacca aaatcaacgg gactttccaa aatgtcgtaa caactccgcc    540

ccattgacgc aaatgggcgg taggcgtgta cggtgggagg tctatataag cagagctcgt    600

ttagtgaacc gtcagatcgc ctggagacgc catccacgct gttttgacct ccatagaaga    660

caccgggacc gatccagcct ccgcggccgg gaacggtgca ttggaacgcg gattccccgt    720

gccaagagtg acgtaagtac cgcctataga gtctataggc ccaccccctt ggcttcgtta    780

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agcaactgca accggtgtac actcgagcgt acggtggctg caccatctgt cttcatcttc   1020

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac   1080

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac   1140

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc   1200

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat   1260

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta gaagcttggc   1320

cgccatggcc caacttgttt attgcagctt ataatggtta caaataaagc aatagcatca   1380

caaatttcac aaataaagca ttttttttcac tgcattctag ttgtggtttg tccaaactca   1440

tcaatgtatc ttatcatgtc tggatcgatc gggaattaat tcggcgcagc accatggcct   1500
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gaaataacct ctgaaagagg aacttggtta ggtaccttct gaggcggaaa gaaccagctg 1560

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caaagcatgc atctcaatta gtcagcaacc aggtgtggaa agtccccagg ctccccagca 1680

ggcagaagta tgcaaagcat gcatctcaat tagtcagcaa ccatagtccc gcccctaact 1740

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tgaggaggct tttttggagg cctaggcttt tgcaaaaagc tgttaacagc ttggcactgg 1920

ccgtcgtttt acaacgtcgt gactgggaaa accctggcgt tacccaactt aatcgccttg 1980

cagcacatcc ccccttcgcc agctggcgta atagcgaaga ggcccgcacc gatcgccctt 2040

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cgcattaagc gcggcgggtg tggtggttac gcgcagcgtg accgctacac ttgccagcgc 2220

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cctatttgtt tatttttcta aatacattca aatatgtatc cgctcatgag acaataaccc 3000

tgataaatgc ttcaataata ttgaaaaagg aagagtatga gtattcaaca tttccgtgtc 3060

gcccttattc cctttttgc ggcattttgc cttcctgttt ttgctcaccc agaaacgctg 3120

gtgaaagtaa aagatgctga agatcagttg ggtgcacgag tgggttacat cgaactggat 3180

ctcaacagcg gtaagatcct tgagagtttt cgccccgaag aacgttttcc aatgatgagc 3240

acttttaaag ttctgctatg tggcgcggta ttatcccgtg atgacgccgg gcaagagcaa 3300

ctcggtcgcc gcatacacta ttctcagaat gacttggttg agtactcacc agtcacagaa 3360

aagcatctta cggatggcat gacagtaaga gaattatgca gtgctgccat aaccatgagt 3420

gataacactg cggccaactt acttctgaca acgatcggag gaccgaagga gctaaccgct 3480

tttttgcaca acatgggggga tcatgtaact cgccttgatc gttgggaacc ggagctgaat 3540

gaagccatac caaacgacga gcgtgacacc acgatgccag cagcaatggc aacaacgttg 3600

cgcaaactat taactggcga actacttact ctagcttccc ggcaacaatt aatagactgg 3660

atggaggcgg ataaagttgc aggaccactt ctgcgctcgg cccttccggc tggctggttt 3720

attgctgata aatctggagc cggtgagcgt gggtctcgcg gtatcattgc agcactgggg 3780

-continued

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ccagatggta agccctcccg tatcgtagtt atctacacga cggggagtca ggcaactatg   3840

gatgaacgaa atagacagat cgctgagata ggtgcctcac tgattaagca ttggtaactg   3900

tcagaccaag tttactcata tatactttag attgatttaa aacttcattt ttaatttaaa   3960

aggatctagg tgaagatcct ttttgataat ctcatgacca aaatccctta acgtgagttt   4020

tcgttccact gagcgtcaga ccccgtagaa aagatcaaag gatcttcttg agatcctttt   4080

tttctgcgcg taatctgctg cttgcaaaca aaaaaaccac cgctaccagc ggtggtttgt   4140

ttgccggatc aagagctacc aactcttttt ccgaaggtaa ctggcttcag cagagcgcag   4200

ataccaaata ctgtccttct agtgtagccg tagttaggcc accacttcaa gaactctgta   4260

gcaccgccta catacctcgc tctgctaatc ctgttaccag tggctgctgc cagtggcgat   4320

aagtcgtgtc ttaccgggtt ggactcaaga cgatagttac cggataaggc gcagcggtcg   4380

ggctgaacgg ggggttcgtg cacacagccc agcttggagc gaacgaccta caccgaactg   4440

agatacctac agcgtgagca ttgagaaagc gccacgcttc ccgaagggag aaaggcggac   4500

aggtatccgg taagcggcag ggtcggaaca ggagagcgca cgagggagct tccaggggga   4560

aacgcctggt atctttatag tcctgtcggg tttcgccacc tctgacttga gcgtcgattt   4620

ttgtgatgct cgtcaggggg gcggagccta tggaaaaacg ccagcaacgc ggccttttta   4680

cggttcctgg ccttttgctg gccttttgct cacatgttct ttcctgcgtt atcccctgat   4740

tctgtggata accgtattac cgcctttgag tgagctgata ccgctcgccg cagccgaacg   4800

accgagcgca gcgagtcagt gagcgaggaa gcggaagagc gcccaatacg caaaccgcct   4860

ctccccgcgc gttggccgat tcattaatcc agctggcacg acaggtttcc cgactggaaa   4920

gcgggcagtg agcgcaacgc aattaatgtg agttacctca ctcattaggc accccaggct   4980

ttacacttta tgcttccggc tcgtatgttg tgtggaattg tgagcggata acaatttcac   5040

acaggaaaca gctatgacca tgattacgaa ttaa                               5074
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**1**. (canceled)

**2**. An isolated antibody or an antigen-binding fragment thereof, wherein the antibody comprises a light chain variable region and a heavy chain variable region, wherein the light chain variable region comprises the amino acid sequences of SEQ ID NOs: 3, 4, and 5 and wherein the heavy chain variable region comprises the amino acid sequences of SEQ ID NOs: 6, 7, and 8, and wherein the antibody or antigen-binding fragment specifically binds H1N1.

**3**. (canceled)

**4**. The isolated antibody of claim **2** wherein the antibody is a human antibody.

**5**. The isolated antibody of claim **2** wherein the antibody is an IgG antibody.

**6**. The isolated antibody of claim **5** wherein the antibody is an IgG1 antibody.

**7**. The isolated antibody of claim **6** wherein the antibody is an IgG1, kappa antibody.

**8**. The isolated antibody of claim **6** wherein the antibody is an IgG1, lambda antibody.

**9**. The isolated antibody of claim **2** wherein the antibody is selected from an IgM, IgA, IgD and IgE antibody.

**10**. The isolated antibody of claim **1** wherein the antigen-binding fragment is selected from a Fab, a F(ab')2 fragment, a Fd fragment, an Fv fragment, and a dAb fragment.

**11**. The isolated antibody of claim **1** wherein the antibody is a scFv.

**12-24**. (canceled)

**25**. The isolated antibody of claim **2** wherein the antibody has Kd for purified H1N1 that is less than $1\times10^{-9}$.

**26**. (canceled)

**27**. A composition comprising the antibody of claim **2** and a pharmaceutically acceptable carrier.

**28**. A method for reducing the risk of infection with H1N1 in a human subject, the method comprising

administering the antibody of claim **2** to the human subject thereby reducing the risk of infection of H1N1 in the human subject.

**29**. A method for treating a patient infected with H1N1 virus, the method comprising

administering the antibody of claim **2** to the patient infected with the H1N1 virus, thereby treating the patient.

**29**. The isolated antibody of claim **2**, or the antigen binding fragment thereof, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 2 and the

light chain variable region comprises the amino acid sequence of SEQ ID NO: 1.

**30**. The isolated antibody of claim **2**, or the antigen binding fragment thereof, wherein the heavy chain variable region consists of the amino acid sequence of SEQ ID NO: 2.

**31**. The isolated antibody of claim **2**, or antigen binding fragment thereof, wherein the light chain variable region consists of the amino acid sequence of SEQ ID NO: 1.

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