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(54) Title: ANTIBODIES USEFUL IN PASSIVE INFLUENZA IMMUIZATION

(57) Abstract: Monoclonal antibodies and fragments thereof that are crossreactive with multiple clades of influenza virus including both Group 1 and Group 2 representatives are disclosed. These antibodies are useful in controlling influenza epidemics and pandemics as well as in providing prophylactic or therapeutic protection against seasonal influenza.

ANTIBODIES USEFUL IN PASSIVE INFLUENZA IMMUNIZATION

Related Applications

[0001] This application claims priority to United States Provisional Patent Application Serial No. 61/445,455 filed on 22 February 2011, United States Provisional Patent Application Serial No. 61/443,103 filed on 15 February 2011, and United States Provisional Patent Application Serial No. 61/355,978 filed on 17 June 2010 the contents of which are incorporated in their entirety by reference herein.

Reference to Sequence Listing Submitted Via EFS-WEB

[0002] The entire content of the following electronic submission of the sequence listing via the USPTO EFS-WEB server, as authorized and set forth in MPEP §1730 II.B.2(a)(C), is incorporated herein by reference in its entirety for all purposes. The sequence listing is identified on the electronically filed text file as follows:

File Name	Date of Creation	Size (bytes)
388512012840seqlist.txt	June 17, 2011	85,437 bytes

Technical Field

[0003] The invention relates to the field of passive immunization against influenza. More particularly, antibodies that bind near to the HA_0 maturation cleavage site consensus sequence of influenza hemagglutinin A, including antibodies secreted by human cells.

Background Art

[0004] The hemagglutinin protein of influenza virus has a globular head domain which is highly heterogeneous among flu strains and a stalk region containing a fusion site which is needed for entry into the cells. The hemagglutinin protein (HA_0) is activated to permit the fusion site to effect virulence by cleavage into HA_1 and HA_2 portions which remain coupled using disulfide bonds but undergo a conformational change. This cleavage site contains a consensus sequence which is shared both by influenza A and influenza B and by the various strains of influenza A and B.

[0005] Bianchi, E., *et al., J. Virol.* (2005) 79:7380-7388 describe a "universal" influenza B vaccine based on the consensus sequence of this cleavage site which was able to raise antibodies in mice when conjugated to the outer membrane protein complex of *Neisseria meningitidis*. Monoclonal antibodies which appear to bind to the consensus sequence were also described. In addition, successful passive transfer of antiserum was observed in mice. Prior vaccines, such as those described in WO2004/080403 comprising peptides derived from the M2 and/or HA proteins of influenza are subject to inducing antibodies that are either of weak efficacy or are not effective across strains.

Disclosure of the Invention

[0006] The invention provides monoclonal antibodies that bind an epitope shared across multiple strains of influenza, and more particularly that bind representatives of either or both Group 1 and Group 2 influenza A. Such antibodies are able to confer passive immunity in the event of a pandemic caused, for example, by a previously unidentified influenza strain or a strain against which protection is not conferred by the seasonal vaccines currently available. Since the antibodies bind across many strains, indicative of targeting an essential site and thus likely to be included even in previously unencountered strain, such a vaccine would be effective in such circumstances. Such antibodies are also useful to ameliorate or prevent infection in subjects for whom vaccination failed to produce a fully protective response or who are at high risk due to a weak immune system (*e.g.*, the very young, the elderly, transplant patients, cancer or HIV chemotherapy treated patients).

[0007] Thus, in one aspect, the invention is directed to monoclonal antibodies or immunoreactive fragments thereof that are broadly crossreactive with influenza A virus of Group 1 including H1, H2, H5, H6, H8, H9, H11, H13, H16 or Group 2 including H3 and H7 as type specimens, or that show cross-Group reactivity. The antibodies bind specifically to an epitope contained in the HA_0 protein of the influenza virus and recognize the native trimeric form of HA. As is well understood in the art, non-immunoglobulin based proteins may have similar epitope recognition properties as an antibody and can also provide suitable embodiments, including binding agents based on fibronectin, transferrin, lipocalin, or nucleic acid based aptamers.

[0008] In other aspects, the invention is directed to methods to use the antibodies and fragments of the invention for passively inhibiting viral infection in subjects. The invention is also directed to recombinant materials and methods to produce these antibodies or fragments.

Brief Description of the Drawings

[0009] Figures 1A and 1B show the results of binding by MAB53 and MAB8 with respect to HA_0 protein from various influenza clades tested by ELISA. Figure 1C shows that MAB53 binds to native trimer, expressed in HEK293 cells.

[0010] Figures 2A and 2B show the results of binding of MAB53 and MAB8 *versus* HA_0 protein from various clades as tested by FortéBio® biosensor.

[0011] Figure 3A shows the extent of binding as tested by ELISA of MAB53 with respect to HA_0 as an intact protein and the cleavage fragment HA_1. Figure 3B shows the extent of binding of MAB53 to a peptide denoted CP from HA_2.

[0012] Figures 4A and 4B show the results of a FortéBio® assay demonstrating that MAB53 competes with MAB8, but not with MAB30.

[0013] Figures 5A and 5B show CDR mapping according to Kabat number of MAB53 heavy and light chain variable regions. IGHV1-69*01 is SEQ ID NO:83 and IGKV3-20*01 is SEQ ID NO:84.

[0014] Figure 6 shows neutralization of H1N1 by various amounts of MAB53, as measured by in vitro plaque assay.

[0015] Figures 7A and 7B show survival times for mice challenged with H1N1 (panel A) or H5N1 (panel B) as a function of administration of various amounts of MAB53.

[0016] Figure 8 shows the effect of post-infection treatment of H5N1 with MAB53.

Modes of Carrying Out the Invention

[0017] The present invention provides useful antibodies including providing effective means to identify cells that secrete such antibodies so that the relevant coding sequences can be retrieved and stored for subsequent and facile recombinant production of such antibodies. The method includes a binary logic based design of a screening procedure.

[0018] Such a procedure can readily be applied to human cells using, in particular, the CellSpot™ method described in U.S. patent 7,413,868, the contents of which are incorporated herein by reference. Briefly, the method is able to screen individual cells obtained from human

(or other) subjects in high throughput assays taking advantage of labeling with particulate labels and microscopic observation. In one illustrative embodiment, even a single cell can be analyzed for antibodies it secretes by allowing the secreted antibodies to be adsorbed on, or coupled to, a surface and then treating the surface with desired antigens each coupled to a distinctive particulate label. The footprint of a cell can therefore be identified with the aid of a microscope. Using this technique, millions of cells can be screened for desirable antibody secretions and even rare antibodies, such as those herein desirable for passive influenza immunization across strains can be recovered. Since human subjects have existing antibodies to at least some influenza strains, and since the antibodies obtained by the method of the invention bind a conserved sequence, these antibodies serve the purpose of addressing new strains as well as strains with which human populations have experience.

[0019] The invention provides a method to identify a monoclonal antibody that binds to a location near the hemagglutinin (HA_0) cleavage site consensus sequence. The method comprises contacting candidate monoclonal antibodies or fragments with: i) a peptide consisting essentially of an amino acid sequence upstream of or downstream of said consensus sequence, but lacking said consensus sequence; ii) a peptide consisting essentially of an amino acid sequence upstream of said consensus sequence and including said consensus sequence; and iii) a peptide consisting essentially of an amino acid sequence downstream of said consensus sequence and including said consensus sequence; wherein a monoclonal antibody that binds to the peptide of ii) and iii) but not to the peptide of i) is identified as a peptide that binds specifically to the HA_0 cleavage site consensus sequence. Other combinations could also be used, as will be evident to the skilled artisan, as long as binary logic is followed. For example, i) could be a peptide consisting essentially of an amino acid upstream of the consensus sequence of a first strain and lacking the consensus sequence , with ii) being the whole HA_0 sequence from the first strain and iii) being the whole HA_0 sequence from a second strain. Shorter portions could also be used. For further confirmation, an isolated peptide from the conserved region can also be used, although the information derived from the larger protein domains is believed to be more informative regarding recognition of the intact antigen.

[0020] This method is not limited to employing the CellSpot™ technique, nor is it limited to human antibodies. The binary logic of this method can be employed in any alternative screening

method. Likewise, it can be applied to other diversity libraries besides natural immunoglobulins.

[0021] The method of the invention relies on binary logic wherein peptides that contain the desired consensus sequence and additional upstream and/or downstream portions are used as test peptides and their ability to complex antibodies as compared to regions lacking the consensus sequence is assessed. Thus, patterns are obtained whereby cells secreting the appropriate antibodies can be instantly identified.

[0022] In one illustrative embodiment, three antigens are used to assess the secreted antibody population. The first peptide is all or substantially all of the amino acid sequence upstream of the consensus sequence contained in HA_0 and is coupled to a particulate label of, say, red. A second test antigen contains these upstream sequences, but contains also the consensus sequence and is labeled with particle of a different color, for example, blue. A third test peptide contains the consensus sequence and all or substantially all of the downstream regions of the HA_0 protein and is labeled with a third color particulate, for example, green. (By upstream portion is meant toward the N-terminus from the consensus sequence and by downstream portion the continuation of the amino acid sequence from the consensus sequence toward the C-terminus. By "substantially all" is meant lacking only one or a few non-essential amino acids.) Antibodies that bind to the consensus sequence will bind both the green and blue particulate labeled peptides but will not bind the red labeled upstream sequence lacking the consensus sequence. If desired, the specificity can be confirmed by adding a fourth peptide representing only the downstream portion without the consensus sequence bound, for example, to a yellow particulate label, wherein the yellow particulate label will not be bound to the antibody. Of course, it does not matter whether the upstream or downstream portion is chosen as the negative control.

[0023] The cleavage site for various strains of influenza A and influenza B is known. For example, the above cited article by Bianchi, *et al.,* shows in Table 1 the sequence around the cleavage site of several such strains:

Table 1 Consensus sequence of the solvent-exposed region of the influenza A and B virus maturational cleavage sites

Virus/subtype	Strain	Sequence[a]
A/H3/HA_0	Consensus	NVPEKQTR ↓ GIFGAIAGFIE (SEQ ID NO:1) (SEQ ID NO: 2)
A/H1/HA_0	Consensus	NIPSIQSR ↓ GLFGAIAGFIE (SEQ ID NO:3) (SEQ ID NO: 4)
B/HA_0	Consensus[b]	PAKLLKER ↓ GFFGAIAGFLE (SEQ ID NO:5) (SEQ ID NO: 6)

[a] The position of cleavage between HA_1 and HA_2 is indicated by the arrow.
[b] The consensus is the same for both the Victoria and Yamagata lineages.

[0024] As indicated, strict consensus occurs starting with the arginine residue upstream of the cleavage site and thus preferred consensus sequences included in the test peptides of the invention have the sequence RGI/L/F FGAIAGFLE (SEQ ID NO:7). It may be possible to use only a portion of this sequence in the test peptides.

[0025] Once cells that secrete the desired antibodies have been identified, it is straightforward to retrieve the nucleotide sequences encoding them and to produce the desired antibodies on a large scale recombinantly. This also enables manipulation of the antibodies so that they can be produced, for example, as single-chain antibodies or in terms of their variable regions only.

[0026] The retrieved nucleic acids may be physically stored and recovered for later recombinant production and/or the sequence information as to the coding sequence for the antibody may be retrieved and stored to permit subsequent synthesis of the appropriate nucleic acids. The availability of the information contained in the coding sequences and rapid synthesis and cloning techniques along with known methods of recombinant production permits rapid production of needed antibodies in the event of a pandemic or other emergency.

[0027] Applicants have recovered multiple monoclonal antibodies that are immunoreactive with HA_0 protein of influenza from multiple clades (SEQ ID NOS:9-23, 26-40, 42-56, and 59-73). Other sequences include the amino acid sequence for the human IgG1 heavy chain constant region (SEQ ID NO:8), the amino acid sequence for the human light chain constant kappa region (SEQ ID NO:24), the amino acid sequence for the human light chain constant lambda region (SEQ ID NO:25), the nucleotide sequence for the human heavy chain constant

region (SEQ ID NO:41), the nucleotide sequence for the human light chain constant kappa region (SEQ ID NO:57), and the nucleotide sequence for the human light chain constant lambda region (SEQ ID NO:58).

[0028] Two of these mAbs, MAB53 and MAB8, have substantial crossreactivity among important, distantly related influenza clades. As shown in Figures 1A and B, each of these binds to three different clades with reasonable or high affinity. MAB53 binds to HA_0 from the H1, H9 and H7 clades and MAB8 binds to HA_0 protein from H1, H7 and H3 clades. The results shown in Figure 1 were obtained by ELISA assay against HA_0 protein, and imply that the affinities are in the nanomolar range. Reactivity to native trimer of HA from all the Group 1 clades was verified using HA expressed in HEK293 cells with antibody binding measured by flow cytometry.

[0029] These results were confirmed using an alternative assay system, the biolevel interferometry based binding assay designated FortéBio® biosensor, as shown in Figures 2A and 2B. As measured by this more accurate assay, the affinities are as follows:

MAB53 / H1 = 60 pM, H5 = 6 nM, H7 = 70 pM, H9 = 30 pM;

MAB8 / H1 = 9 nM, H3 = 16 nM, H5 = 0.2 nM.

[0030] Both MAB53 and MAB8 are fully human antibodies, but similar antibodies characteristic of other species are also included in the invention. In the context of the invention, "antibodies" and their fragments include those portions of the molecule that are relevant for binding; thus, fragments would include variable regions only and "antibodies" as a general term would also be considered to include such fragments. Thus, F_{ab} fragments, $F_{(ab')_2}$, and Fv fragments are included as well as recombinantly produced single chain antibodies, and fusions of such constructs to create bispecific agents. Chimeric, humanized and human antibodies are all within the scope of the present invention as are antibody mimics based on other protein scaffolds such as fibronectin, transferrin, or lipocalin. Likewise, multiple technologies now exist for making a single antibody-like molecule that incorporates antigen specificity domains from two separate antibodies (bi-specific antibody). Thus, a single antibody with very broad strain reactivity can be constructed using the Fab domains of individual antibodies with broad reactivity to Group 1 and Group 2 respectively. Suitable technologies have been described by Macrogenics (Rockville, MD), Micromet (Bethesda, MD) and Merrimac (Cambridge, MA). (See, *e.g.*, Orcutt KD, Ackerman ME, Cieslewicz M, Quiroz E, Slusarczyk AL, Frangioni JV,

Wittrup KD. A modular IgG-scFv bispecific antibody topology, *Protein Eng Des Sel.* (2010) 23:221-228; Fitzgerald J, Lugovskoy A. Rational engineering of antibody therapeutics targeting multiple oncogene pathways. *MAbs.* (2011) 1:3(3); Baeuerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy. *Cancer Res.* (2009) 69:4941-4944.)

[0031] To identify the epitope to which MAB53 binds, ELISA assays were conducted with respect to uncleaved HA_0 protein, the HA_1 fragment, and the HA_2 fragment. As shown in Figures 3A and B, while MAB53 binds with high affinity to HA_0, it does not bind HA_1 implying binding to the complementary HA2 fragment. To confirm this hypothesis, a peptide derived from HA_2 was immobilized on a streptavidin coated plate using a C-terminal biotin. Specifically, the sequence tested was RGLFGAIAGFIENGW (SEQ ID NO:74). Irrelevant flanking portions were also used. MAB53 was confirmed as capable of binding to this peptide. As MAB53 does not bind to HA_0 when tested by Western blot, it is assumed that the dominant epitope is at least in part conformational in nature.

[0032] It has also been found that MAB8 and MAB53 bind to the same or nearby epitopes as demonstrated by their ability to compete with each other for binding to the HA_0 protein of the H1 clade. This was shown using a FortéBio® assay using 2 μg/ml of antibody and 50 nM HA_0 from H1. As shown in Figure 4A, the signal obtained from MAB53 bound to the FortéBio® surface is augmented when 50 nM HA_0 solution is added. However, when MAB8 is then added, no further signal occurs. Thus, MAB53 blocks the epitope bound by MAB8. As shown in Figure 4B, however, another antibody that is immunoreactive with HA_0, MAB30, binds, apparently, to a different epitope as the signal is enhanced when it is added to the coupled MAB53-HA_0.

[0033] Importantly, MAB53 and MAB8 differ in that MAB8 is released from the HA_0 protein when the pH is lowered to 6, whereas MAB53 is not. This difference is significant as this appears predictive of neutralizing capability. In tests for the ability of MAB8 to neutralize H1N1 viral infection in a plaque reduction assay in MDCK target cells, low doses of MAB53 of 1-5 μg/ml neutralized infection by H1N1, by H7N3, H5N1 and H9N2. However, MAB8 does not neutralize infection by these strains. Thus, neutralizing strains may be preferentially selected by washing bound MAB or fragment at pH 6 during the primary screen, thus removing from HA_0 MAB's that are unlikely to remain bound as the antibody-virus complex enters the

cell via the endosomal compartment and thus will be expected to have reduced ability to neutralize the virus.

[0034] For example, in the CellSpot method HA_0 may be bound to solid support (fluorescent beads) and captured by the MAB or a mixture of MAB's, then washed at pH 6.

[0035] MAB53 is produced recombinantly and has been sequenced. The full-length sequences of the heavy chain and light chain are as follows:

Heavy Chain: **QVQLVQSGAEVRKPGSSVKVSCKVSGGIIRKYAINWVRQAPGQ GLEWMGGIIAIFNTANYAQKFQGRVTITADESTSTVYMELSSLRSEDTALYYCARG MNYYSDYFDYWGQGSLVTVSP**ASTKGPSVFPLVPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:75); and

Light Chain: **EIVLTQSPGTLSLSPGERATLSCRASQSVRSNNLAWYQHKPGQA PRLLIFGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPALTFGG GTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:76).

[0036] The bold sequences are variable domains, and the un-bolded sequences represent the IgG1 constant chain for the heavy chain and the kappa constant chain for the light chain.

[0037] In addition, these variable regions have been analyzed according to the Kabat CDR assessment based on matching framework regions. As shown in Figure 5A, CDR1, CDR2, and CDR3 of the IGHV1-69*01 heavy chain (SEQ ID NO:83) are GGIIRKYAIN (SEQ ID NO:77), GGIIAIFNTANYAQKFQG (SEQ ID NO:78) and ARGMNYYSDYFDY (SEQ ID NO:79), respectively. As shown in Figure 5B, CDR1, CDR2, and CDR3 of the IGKV3-20*01 light chain (SEQ ID NO:84) are RASQSVRSNNLA (SEQ ID NO:80), GASSRAT (SEQ ID NO:81) and QQYGSSPALT (SEQ ID NO:82), respectively.

[0038] As shown in Figure 6, MAB53 neutralizes H1N1 *in vitro* in a plaque assay.

[0039] It has also been shown that mice pretreated with graded doses of MAB53 survive challenge with otherwise lethal titers of H1N1 and H5N1 viruses with 100% protection against H1N1 challenge, as shown in Figure 7. The potency is comparable to a prior art antibody described by Crucell which does not show activity against Group 2 strains. Throsby M., *et al.*, *PLoS One*. (2008) 3:e3942. Epub 2008 Dec 16. These are heterosubtypic neutralizing monoclonal antibodies cross-protective against H5N1 and H1N1 recovered from human IgM+ memory B cells.

[0040] As shown in Figure 7A, MAB53 provided full protection at 10 mg/kg; 90% survived at 2 mg/kg and 50% survived at 0.4 mg/kg. In comparison, the prior art antibody from Crucell gave full protection at 2 mg/kg, but only 20% survived when 0.7 mg/kg were administered. This is despite the fact that the lethality of the viral dose was less than that in the experiment shown in Figure 7A; only 90% of the mice died after infection, whereas in the experiment shown in Figure 7A, all the mice died at day 6. This demonstrates that MAB53 is highly potent.

[0041] Where challenge by H5N1 was substituted for challenge by H1N1, for MAB53 shown in Figure 7B, 10 mg/kg gave 80% survival; 2 mg/kg gave 60% survival and 0.4 mg/kg gave 50% survival. In comparison, for the prior art antibody, 100% survival was obtained at 5 mg/kg and 60% survival at 1.7 mg/kg. Thus, the survival rates at 1.7 mg/kg and 2 mg/kg were comparable. In this case, the viral dose itself was slightly less potent in the mice tested with MAB53.

[0042] As shown in Figure 8, MAB53 (10 mg/kg) was administered as a post-infection treatment at day +3 against the high pathology H5N1 strain. The control antibody is isotype matched but does not recognize any flue antigen. The infection and treatment protocol is the same as that for Figure 7A, but given at day +3 instead of day -1.

[0043] Pepscan analysis was performed, establishing that MAB53 and CR6261 bind to similar regions of HA, but different epitopes (data not shown). This is consistent with the different activity of the two antibodies.

[0044] Thus, MAB53 and antibodies that bind to the same epitope under the same conditions are effective as passive vaccines suitable for protection of populations against epidemics and pandemics, and for prophylactic or therapeutic use against seasonal influenza for patients with a weakened immune system.

SEQUENCE LISTING

NVPEKQTR (SEQ ID NO:1)

GIFGAIAGFIE (SEQ ID NO:2)

NIPSIQSR (SEQ ID NO:3)

GLFGAIAGFIE (SEQ ID NO:4)

PAKLLKER (SEQ ID NO:5)

GFFGAIAGFLE (SEQ ID NO:6)

RGI/L/F FGAIAGFLE (SEQ ID NO:7).

Human IgG1 HC amino acid sequence of constant region (SEQ ID NO:8)

ASTKGPSVFPLVPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

MAB1 HC amino acid sequence of variable domain (SEQ ID NO:9)

QVQLQESGPGLVKPSETLSLICRVSGGSISSHYWSWIRQPPGKGLEWIGYISYRGRS
NHNPSLGRRVSMSIDTSENQFSLNLSSVIAADTAVYYCARDATGIREINALDIWGQG
TTVTVSS

MAB8 HC amino acid sequence of variable domain (SEQ ID NO:10)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYTMSWVRQAPGQGLEWVSSITRTSSN
IYYADSVEGRFTISRDNAKNSLYLQMHSLRVEDTAVYYCARISGVVGPVPFDYWGQG
TLITVSS

MAB30 HC amino acid sequence of variable domain (SEQ ID NO:11)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGRIRNKAAI
YTTEYAASVKGRFTISRDDLKSSVYLQMNSLKTDDTAIYYCARSYGYFDYWGQGTLV
TVSS

MAB42 HC amino acid sequence of variable domain (SEQ ID NO:12)

QVQLVQSGAEVKKPGASVKVSCKASGYSFNGYYMHWVRQAPGQGLEWMGWINLSSGG
TDYAQKFQGWVTLTRDTSITTAYMELSSLRSNDTAVYYCARIRPRTGGLDSWGQGTL
VIVSS

MAB48 HC amino acid sequence of variable domain (SEQ ID NO:13)

QVQLVQSGAEVKKPGSSVKVSCKASGVTFTAYAISWVRQAPGRGLEWMGGISPLFGI
VNFGQNFQGRVTITADKSTGAAYMELSSLSSEDTAMYYCARGPYYYDRSHLDYWGQG
TLVTVSS

MAB49 HC amino acid sequence of variable domain (SEQ ID NO:14)

QVQLVQSGAEVKRPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIGMFGT
TNYAQKFQGRVTITADEFTSTAYMELTSLRSDDTAMYYCARDRNYYASGTYDHWGQG
TLVTVSS

MAB52 HC amino acid sequence of variable domain (SEQ ID NO:15)

QVLLVQSGAEVKKPGSSVNISCKASGGTFSNYAISWVRQAPGQGLDWMGRIIPIFGT
ANYAQKFQGRLTITADESTSTAYMELSSLRSEDTAVFYCAITKPGSVYALDVWGQGT
TVTVSS

MAB53 HC amino acid sequence of variable domain (SEQ ID NO:16)

QVQLVQSGAEVRKPGSSVKVSCKVSGGIIRKYAINWVRQAPGQGLEWMGGIIAIFNT
ANYAQKFQGRVTITADESTSTVYMELSSLRSEDTALYYCARGMNYYSDYFDYWGQGS
LVTVSP

MAB285 HC amino acid sequence of variable domain (SEQ ID NO:17)

QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMQWVRQAPGQGLEWMGFINANTGV
TNFAQKFQGRVTLTRDTSISTAYMELRRLTSADTAVYYCARAPQWLSYSFDIWGQGT
MVTVSS

MAB321 HC amino acid sequence of variable domain (SEQ ID NO:18)

EVQLVESGAEVRSPGASVKLSCKASAYTFINYYLHWVRQAPGQRLEWMGWINPDSGV
TEYAQTFQGRVTMTRDTSINTAYLDLERLTSDDTAVYYCARGFIPWGGKYFYLDYWG
QGTLVTVSS

MAB322 HC amino acid sequence of variable domain (SEQ ID NO:19)

QVQLQQSGPGLVKPSQTLSLTCSVSGSFIRSGDYNWSWIRQPPGKGLEWIGYIDNSG
STHYNPSLKSRVSISVDTSKNHLSLKLSFVTDADTGVYYCAGEQASDSRGNYYYYAM
DVWGQGTPVTVSS

MAB375 HC amino acid sequence of variable domain (SEQ ID NO:20)

QVQLQQSGPGLMKPSETLSLSCTVSGDSVSSFYWSWIRQSPGKGLEWIGYLLYSGNT
KYNPSLKSRATISRDTSKNQLSLELTSLTAADTAVYYCARVVRWRHGGDLDVWGQGT
MVTVSS

MAB376 HC amino acid sequence of variable domain (SEQ ID NO:21)

QVQLVQSGGDLVQPGGSLRLSCAVSGFIFRKYIMSWVRQAPGKGPEWVAVISSSGDR
TFYADSVEGRFIVSRDNSKDTLFLQMNSLRTEDTAMYYCAKDLLGFCSGGDCLKVFD
LWGRGTMVTVSS

MAB377 HC amino acid sequence of variable domain (SEQ ID NO:22)

QVQLLQSGPGLIKASETLSLSCSVSNDSVSNYYWSWIRQSPEKGLEWIGYLLYSGNT
KYNPSLKSRAIISRDMSKNQLSLRVTSVTAADTAIYYCARVVRWRFGGDMDVWGQGT
AVTVST

MAB378 HC amino acid sequence of variable domain (SEQ ID NO:23)

QVQLQQSGPGLIKPSETLSLSCSVSGDSVNNYYWSWIRQPPEKGLEWIGYLQYSGST
KYNPSLKSRVTISRDTSKNQLSLKLTSVTAADTAIYYCARVVRWRHGGDMDVWGQGT
AVTVSS

Human LC amino acid sequence of constant kappa region (SEQ ID NO:24)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT
EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Human LC amino acid sequence of constant lambda region (SEQ ID NO:25)

GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT
PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVVPAECS

MAB1 LC amino acid sequence (SEQ ID NO:26)

DIQMTQSPSSLSASGGDRVTITCRASQSVSTYLNWYQQKPGKAPNLLVYAVSNLQRG
VPSRFSGSGSGTHFTLTISSLQPEDFATYYCQQSYSDPLTFGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB8 LC amino acid sequence (SEQ ID NO:27)

DIQMTQSPSSLSASVGDRVTITCRASQTISKYLNWYQQKPGRAPKLLIYSASSLQSG
VPSRFTGSGSGTDFTLTITSLQPEDFATYYCQQSYRPSQITFGPGTKVDIKR

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB30 LC amino acid sequence (SEQ ID NO:28)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGNAPNLLIYKASSLESG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDTYSPTFGQGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB42 LC amino acid sequence (SEQ ID NO:29)

QSALTQPASVSGSAGQSITISCTGTSSDVGAYNFVSWYQHHPGKAPKLMIYDVDNRP
SGVSNRFSGSKSGDTASLTISGLQAEDEADYYCSSYRRNGPWVFGGGTKLTVLGQPK
AAPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ
SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVVPAECS

MAB48 LC amino acid sequence (SEQ ID NO:30)

EIVLTQSPGTLSLSPGERATLSCRASQSVGSSDLAWYQQKPGQAPRLLIYGASSRAT
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYVSSPLTFGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB49 LC amino acid sequence (SEQ ID NO:31)

DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYSASSLQSG
VPSRFGGSGSGTDFTLTISSLQPEDFALYYCQQTYSIPITFGQGTRLDFKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB52 LC amino acid sequence (SEQ ID NO:32)

DIQMTQSPSSLSASVGDRVTITCRASQTISTYLNWYQQKPGKAPNLLIYTASSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYDAPTWTFGPGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB53 LC amino acid sequence (SEQ ID NO:33)

EIVLTQSPGTLSLSPGERATLSCRASQSVRSNNLAWYQHKPGQAPRLLIFGASSRAT
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPALTFGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB285 LC amino acid sequence (SEQ ID NO:34)

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNPVNWYQQLPGTAPRLLIYSNNQRPS
GVPDRFSGSKSGTSASLAISGLRSEDEADYYCTSWDDSLNAWVFGGGTRLTVLGQPK
AAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ
SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVVPAECS

MAB321 LC amino acid sequence (SEQ ID NO:35)

DIVLTQSPPSLSASVGDRVTITCRASQSINNYLNWYQQKPGNAPRILIYGASSLVSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRPLYTFGPGTQLDVKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB322 LC amino acid sequence (SEQ ID NO:36)

DIVMTQSPSSLSASVGDRVTITCRASESISAYLNWYQHTPGRAPKLLIYAASSLETG
VPSRFSGSGSGTEFTLTISGLQPEDFVTYYCQQTYNTPRTFGQGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB375 LC amino acid sequence (SEQ ID NO:37)

DIQMTQSPSFLSASVGDRVTFTCRASQGIASSLAWYQQKAGKAPKLLIYAASTLEDG
VPSRFSGSGFGTEFTLTITSLQPEDFATYYCHQVNSYPRTFGPGTTVDINR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB376 LC amino acid sequence (SEQ ID NO:38)

DIQMTQSPSTLSASVGDTVTITCRASQSISTWLAWFQQKPGRAPKLLIYQASSLEGG
VPSRFSGSGSGTDFNLTISGLQPDDFATYYCLQYNTYSKSFGQGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB377 LC amino acid sequence (SEQ ID NO:39)

DIQMTQSPSFLSASVGDRVTITCRASQGIATSLAWYQQKPGKAPRLLIYAASTLESG
VPSRFSGGGSGTDFTLTISSLQPEDFAVYYCQQVNSYPRTFGPGTKLDVKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB378 LC amino acid sequence (SEQ ID NO:40)

DIQMTQSPSFLSASVGDRVTMTCRASQGISSYLAWYQQKPGKAPKLLIYAASTLESG
VPSRFSGSGSGTEFTLTISSLQPEDFAIYYCQQVNGYPRTFGPGTKVDIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Human IgG1 HC nucleotide sequence of constant region (introns are underlined) (SEQ ID NO:41)

GCCTCCACCAAGGGCCCATCAGTCTTCCCCCTGGCACCCTCTACCAAGAGCACCTCT
GGGGGCACAACGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG
GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA
CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG
GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
AAGAGAGTTGGTGAGAGGCCAGCACAGGGAGGGAGGGTGTCTGCTGGAAGCCAGGCT
CAGCGCTCCTGCCTGGACGCATCCCGGCTATGCAGTCCCAGTCCAGGGCAGCAAGGC
AGGCCCCGTCTGCCTCTTCACCCGGAGGCCTCTGCCCGCCCCACTCATGCTCAGGGA
GAGGGTCTTCTGGCTTTTTCCCCAGGCTCTGGGCAGGCACAGGCTAGGTGCCCCTAA
CCCAGGCCCTGCACACAAAGGGGCAGGTGCTGGGCTCAGACCTGCCAAGAGCCATAT
CCGGGAGGACCCTGCCCCTGACCTAAGCCCACCCCAAAGGCCAAACTCTCCACTCCC
TCAGCTCGGACACCTTCTCTCCTCCCAGATTCCAGTAACTCCCAATCTTCTCTCTGC
AGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGGTAAGCCAGC
CCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTAGCCTGCATCCA
GGGACAGGCCCCAGCCGGGTGCTGACACGTCCACCTCCATCTCTTCCTCAGCACCTG
AACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA
TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAA
AGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCC
TGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGTGGGACCCGTGGGGTGC
GAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCCTGAGAGTGACCGCT
GTACCAACCTCTGTCCCTACAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC
CCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC
TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
TACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAG
CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG
CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCCCCGGGTAAA
TGA

MAB1 HC variable domain nucleotide sequence (SEQ ID NO:42)

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCC
CTCATCTGCAGAGTCTCTGGTGGCTCGATCAGTAGTCATTACTGGAGCTGGATCCGG
CAGCCCCCAGGGAAGGGACTGGAGTGGATTGGATATATTTCTTATAGGGGGAGAAGC
AACCACAATCCTTCCCTTGGGAGACGAGTCTCTATGTCAATAGACACGTCGGAGAAC
CAGTTCTCCCTGAACCTGAGCTCTGTGATCGCTGCGGACACGGCCGTATATTACTGT
GCGAGAGATGCTACTGGGATCAGAGAAATCAATGCTCTTGATATCTGGGGCCAAGGG
ACAACGGTCACCGTCTCTTCA

MAB8 HC variable domain nucleotide sequence (SEQ ID NO:43)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGTTTCACTTTCAGTACCTATACTATGAGTTGGGTCCGC
CAGGCTCCAGGGCAGGGGCTAGAGTGGGTCTCGTCCATTACTAGGACTAGTAGTAAT
ATATACTACGCAGACTCAGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCACTGTATCTGCAGATGCATAGCCTGAGAGTCGAAGACACGGCTGTGTATTAC
TGTGCGAGAATCAGCGGGGTAGTGGGACCTGTCCCCTTTGACTACTGGGGCCAGGGA
ACCCTGATCACCGTCTCCTCT

MAB30 HC variable domain nucleotide sequence (SEQ ID NO:44)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGAGGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACCACTACATGGACTGGGTCCGC
CAGGCTCCAGGGAAGGGGCTGGAGTGGGTTGGCCGTATTAGAAATAAAGCTGCCATT
TACACCACAGAATACGCCGCGTCTGTGAAAGGCAGATTCACCATCTCAAGAGATGAT
TTAAAGAGCTCAGTGTATCTGCAAATGAACAGTCTGAAAACCGACGACACGGCCATA
TATTACTGTGCTAGGAGCTATGGATACTTTGACTACTGGGGCCAGGGAACCCTGGTC
ACCGTCTCCTCA

MAB42 HC variable domain nucleotide sequence (SEQ ID NO:45)

CAGGTGCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAG
GTCTCCTGCAAGGCTTCTGGATATTCCTTCAACGGCTACTATATGCACTGGGTGCGA
CAGGCCCCTGGACAAGGGCTTGAGTGGATGGGTTGGATCAACCTGAGCAGTGGTGGC
ACAGATTATGCACAGAAATTTCAGGGGTGGGTCACTTTGACCAGGGACACGTCCATC
ACCACAGCCTACATGGAGTTGAGCAGCCTGAGATCGAACGACACGGCCGTGTATTAC
TGTGCGAGAATTAGACCTCGCACTGGTGGACTTGACTCCTGGGGCCAGGGAACCCTG
GTCATCGTCTCCTCA

MAB48 HC variable domain nucleotide sequence (SEQ ID NO:46)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAA
GTCTCCTGCAAGGCTTCTGGAGTCACCTTCACCGCCTATGCTATCAGTTGGGTGCGA

CAGGCCCCTGGACGAGGGCTTGAGTGGATGGGAGGGATCAGCCCTTTGTTTGGAATA
GTAAATTTCGGACAGAACTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACG
GGCGCAGCCTACATGGAGCTGAGCAGCCTGAGCTCTGAGGACACGGCCATGTATTAC
TGTGCGAGAGGACCCTATTATTACGATAGAAGTCACCTAGACTACTGGGGCCAGGGA
ACCCTGGTCACCGTCTCCTCA

MAB49 HC variable domain nucleotide sequence (SEQ ID NO:47)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAGGCCTGGGTCCTCGGTGAAG
GTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGTTATGCTATTAGCTGGGTGCGA
CAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCGGTATGTTTGGAACA
ACAAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATTCACG
AGCACAGCCTACATGGAGCTGACCAGCCTGAGATCTGACGACACGGCCATGTATTAC
TGTGCGAGAGACCGAAATTACTATGCTTCGGGGACTTATGACCACTGGGGCCAGGGA
ACCCTGGTCACCGTCTCCTCA

MAB52 HC variable domain nucleotide sequence (SEQ ID NO:48)

CAAGTGCTGCTGGTGCAGTCTGGGGCTGAAGTGAAGAAGCCTGGGTCCTCGGTGAAT
ATCTCTTGCAAGGCTTCTGGAGGCACTTTCAGCAACTATGCTATCTCCTGGGTGCGA
CAGGCCCCTGGACAAGGTCTTGACTGGATGGGAAGGATCATCCCTATCTTTGGAACA
GCAAACTACGCACAGAAATTCCAGGGCAGACTCACCATTACCGCGGACGAATCCACG
AGCACAGCCTACATGGAACTGAGCAGCCTGAGATCTGAAGACACGGCCGTGTTTTAC
TGTGCGATTACTAAACCGGGGTCTGTCTACGCTTTGGACGTCTGGGGCCAAGGGACC
ACGGTCACCGTCTCCTCA

MAB53 HC variable domain nucleotide sequence (SEQ ID NO:49)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAGGAAGCCGGGGTCCTCGGTGAAG
GTCTCCTGCAAGGTTTCTGGAGGCATCATTAGGAAATATGCTATCAACTGGGTGCGA
CAGGCCCCCGGACAAGGGCTTGAGTGGATGGGAGGGATCATCGCTATCTTTAATACA
GCAAACTATGCACAGAAATTCCAGGGCAGAGTCACGATTACCGCGGACGAGTCCACG
AGCACAGTCTACATGGAGCTGAGCAGCCTGAGATCTGAAGACACGGCCCTTTATTAC
TGTGCGAGAGGAATGAATTACTACAGTGACTACTTTGACTACTGGGGCCAGGGAAGC
CTTGTCACCGTCTCCCCA

MAB285 HC variable domain nucleotide sequence (SEQ ID NO:50)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAG
GTCTCCTGCCGGGCTTCTGGATACACCTTCACCGGCTACTATATGCAGTGGGTGCGG
CAGGCCCCTGGCCAAGGGCTTGAGTGGATGGGATTCATCAATGCTAACACTGGTGTC
ACAAACTTTGCTCAGAAGTTTCAGGGCAGGGTCACCTTGACCAGGGACACGTCCATC
AGCACAGCCTACATGGAGCTGAGGAGGCTGACATCTGCCGACACGGCCGTGTATTAC

TGTGCGAGAGCGCCCCAGTGGTTATCGTATTCTTTTGATATCTGGGGCCAAGGGACA
ATGGTCACCGTCTCCTCA

MAB321 HC variable domain nucleotide sequence (SEQ ID NO:51)

GAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAGGAGCCCTGGGGCCTCAGTGAAG
CTCTCCTGCAAGGCTTCTGCATACACCTTCATCAACTACTATCTGCACTGGGTGCGA
CAGGCCCCTGGACAAAGGCTTGAGTGGATGGGATGGATCAACCCTGACAGTGGTGTC
ACAGAATATGCACAGACATTTCAGGGCAGGGTCACCATGACCAGGGACACGTCCATC
AATACAGCCTACCTGGACCTGGAGAGACTGACATCTGACGACACGGCCGTATATTAC
TGTGCGAGAGGTTTTATTCCTTGGGGTGGGAAGTACTTCTACCTTGACTACTGGGGC
CAGGGAACCCTGGTCACCGTCTCCTCA

MAB322 HC variable domain nucleotide sequence (SEQ ID NO:52)

CAGGTACAGCTGCAGCAGTCAGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCC
CTCACCTGCAGTGTATCTGGTAGTTTCATCAGAAGTGGAGATTATAATTGGAGTTGG
ATCCGCCAGCCCCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCGATAATAGCGGG
AGCACCCACTACAACCCGTCCCTCAAGAGTCGAGTTAGCATATCAGTGGACACGTCC
AAGAACCACTTGTCCCTGAAGCTGAGTTTTGTGACTGACGCAGACACGGGCGTGTAT
TACTGTGCCGGAGAACAAGCGTCTGATAGTCGTGGTAATTACTACTACTACGCTATG
GACGTCTGGGGCCAAGGGACCCCGGTCACCGTCTCCTCA

MAB375 HC variable domain nucleotide sequence (SEQ ID NO:53)

CAGGTGCAGCTGCAGCAGTCGGGCCCCGGACTGATGAAGCCTTCGGAGACCCTGTCC
CTCAGCTGCACTGTCTCTGGTGACTCCGTCAGTAGTTTTTATTGGAGTTGGATTCGG
CAGTCTCCAGGAAAGGGACTGGAGTGGATTGGGTATTTGCTTTACAGTGGGAATACC
AAGTATAATCCGTCCCTCAAGAGTCGAGCCACCATATCAAGAGACACGTCCAAGAAC
CAGTTGTCCCTGGAGTTGACCTCTCTGACCGCTGCGGACACGGCCGTCTACTATTGT
GCGAGAGTGGTGAGATGGCGACATGGTGGCGATTTGGACGTCTGGGGCCAAGGGACC
ACGGTCACCGTCTCCTCA

MAB376 HC variable domain nucleotide sequence (SEQ ID NO:54)

CAGGTGCAGCTGGTGCAGTCCGGGGGGGGACTTGGTCCAGCCGGGGGGGTCCCTGAGA
CTGTCATGTGCAGTCTCTGGATTCATCTTTAGAAAATATATCATGAGTTGGGTCCGG
CAGGCTCCAGGGAAGGGGCCGGAGTGGGTCGCAGTTATTAGTTCTAGTGGTGACCGG
ACATTCTACGCCGACTCCGTGGAGGGCCGCTTCATCGTCTCCAGAGACAATTCCAAG
GACACACTGTTTCTGCAAATGAACAGCCTGAGAACCGAGGACACGGCCATGTATTAC
TGTGCGAAAGACCTTTTGGGATTTTGTAGTGGTGGTGATTGCCTGAAGGTCTTCGAT
CTCTGGGGCCGAGGCACCATGGTCACTGTCTCCTCA

MAB377 HC variable domain nucleotide sequence (SEQ ID NO:55)

CAGGTGCAGCTGCTGCAGTCGGGCCCAGGACTGATAAAGGCTTCGGAGACCCTGTCT
CTCAGCTGCAGTGTCTCTAATGACTCCGTCAGTAATTATTATTGGAGTTGGATCCGG
CAGTCCCCAGAGAAGGGACTGGAGTGGATTGGGTATTTGCTTTATAGTGGGAATACC
AAGTACAATCCCTCCCTCAAGAGTCGAGCCATCATATCAAGAGACATGTCCAAAAAT
CAGTTGTCCCTCAGAGTGACTTCTGTGACCGCTGCGGACACGGCCATATATTATTGT
GCGCGAGTGGTGAGATGGCGATTTGGTGGTGATATGGACGTCTGGGGTCAAGGGACC
GCGGTCACCGTCTCCACA

MAB378 HC variable domain nucleotide sequence (SEQ ID NO:56)

CAGGTGCAGCTGCAGCAGTCGGGCCCAGGACTGATAAAGCCTTCGGAGACCCTGTCT
CTCAGCTGCTCTGTCTCTGGTGACTCCGTCAATAATTATTATTGGAGTTGGATCCGG
CAGCCCCCAGAGAAGGGACTGGAGTGGATTGGGTATCTGCAGTATAGTGGGAGTACA
AAGTACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAAGAGACACGTCCAAAAAC
CAGTTGTCCCTGAAGCTGACCTCTGTGACCGCTGCGGACACGGCCATATATTATTGT
GCGAGAGTGGTGAGATGGCGACATGGTGGGGATATGGACGTCTGGGGCCAAGGGACC
GCGGTCACCGTCTCCTCT

Human LC nucleotide sequence of constant kappa region (SEQ ID NO:57)

CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA
TCTGGAACTGCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA
GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAA
GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC
TCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

Human LC nucleotide sequence of constant lambda region (SEQ ID NO:58)

GGTCAGCCCAAGGCTGCCCCCTCTGTCACTCTGTTCCCGCCCTCTAGCGAGGAGCTT
CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTG
ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACA
CCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCT
GAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACC
GTGGAGAAGACAGTGGTCCCTGCAGAATGCTCT

MAB1 LC variable domain nucleotide sequence (SEQ ID NO:59)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGGAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGTGTTAGTACGTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAACCTCCTGGTCTATGCTGTATCCAATTTACAACGTGGC
GTGCCATCAAGGTTCAGTGGCAGTGGATCTGGGACACATTTCACTCTCACAATCAGC

AGTCTGCAACCTGAGGATTTCGCAACTTACTACTGTCAACAGAGTTACAGTGACCCT
CTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

MAB8 LC variable domain nucleotide sequence (SEQ ID NO:60)

GACATCCAGATGACCCAGTCTCCATCTTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGACCATTAGCAAGTATTTAAATTGGTATCAGCAG
AAGCCAGGGAGAGCCCCTAAACTCCTGATCTACTCTGCGTCCAGTTTGCAAAGTGGG
GTCCCATCAAGGTTCACTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCACC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGACCCTCC
CAGATCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA

MAB30 LC variable domain nucleotide sequence (SEQ ID NO:61)

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGTTGGTTGGCCTGGTATCAGCAG
AAACCAGGGAACGCCCCTAACCTCCTGATCTATAAGGCGTCTAGTTTAGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGTATGATACTTATTCT
CCGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA

MAB42 LC variable domain nucleotide sequence (SEQ ID NO:62)

CAGTCTGCCCTGACTCAGCCTGCCTCCGGGTCTGGGTCTGCTGGACAGGCGATCACC
ATCTCCTGCACTGGAACCGGCACTGACGTCTGTGCTTATAACTTTGTCTCCTGGTAC
CAACACCACCCCGGCGAAGCCCCCAAACTCATGATTTATGATGTCGATAATCGGCCC
TCATGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGTAACACGGCCTCCCTGACC
ATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTACTACTGCAGCTCATATAGAAGG
AACGGCCCTTGCTTGTTCGGCGGAGGGACCAAGCTGACCGTCCTG

MAB48 LC variable domain nucleotide sequence (SEQ ID NO:63)

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCAGCAGCGACTTAGCCTGGTACCAG
CAGAAACCTGGCCAGGCTCCCAGGCTCCTCATATATGGTGCATCCAGCCGGGCCACT
GGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATC
AGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGTCAGTTCA
CCCCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAG

MAB49 LC variable domain nucleotide sequence (SEQ ID NO:64)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGGTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAACTCCTGATCTATTCTGCATCCAGTTTGCAAAGTGGG

GTCCCATCAAGGTTCGGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCACTTTACTACTGTCAACAGACTTACAGTATCCCG
ATCACCTTCGGCCAAGGGACACGACTGGACTTTAAA

MAB52 LC variable domain nucleotide sequence (SEQ ID NO:65)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACTATCACTTGCCGGGCAAGTCAGACCATTAGCACCTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAACCTCCTGATCTATACTGCATCCAGTTTGCAAAGCGGG
GTCCCATCAAGATTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTATTACTGTCAACAGAGTTACGATGCCCCC
ACGTGGACCTTCGGCCCAGGGACCAAGGTGGAAATCAAA

MAB53 LC variable domain nucleotide sequence (SEQ ID NO:66)

GAAATTGTGTTGACACAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGAAGCAACAACTTAGCCTGGTACCAG
CACAAACCTGGCCAGGCTCCCAGGCTCCTCATCTTTGGTGCATCCAGCAGGGCCACT
GGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATC
AGCAGACTGGAGCCTGAAGATTTTGCAGTATATTACTGTCAGCAGTATGGTAGCTCA
CCTGCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

MAB285 LC variable domain nucleotide sequence (SEQ ID NO:67)

CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATCCTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAGACTTCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATC
AGTGGGCTCCGGTCCGAGGATGAGGCTGATTACTACTGTACATCATGGGATGACAGC
CTGAATGCTTGGGTGTTCGGCGGGGGGACCAGGCTGACCGTCCTA

MAB321 LC variable domain nucleotide sequence (SEQ ID NO:68)

GATATCGTGTTGACTCAGTCTCCACCCTCCCTGTCTGCATCTGTGGGGGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGCATTAATAACTACTTAAATTGGTATCAACAG
AAACCAGGGAACGCCCCAAGAATACTAATCTATGGTGCATCCAGTTTGGTAAGTGGG
GTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACCCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACCGGCCCCTG
TACACTTTTGGCCCGGGGACCCAGCTGGATGTCAAA

MAB322 LC variable domain nucleotide sequence (SEQ ID NO:69)

GATATCGTGATGACCCAGTCTCCATCTTCCCTGTCTGCATCTGTGGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTGAGAGCATTAGCGCTTATTTAAATTGGTATCAGCAC

ACACCAGGGAGAGCCCCTAAGCTCCTGATCTATGCTGCCTCCAGTTTGGAAACTGGG
GTCCCATCAAGGTTCAGTGGCAGTGGATCTGGCACAGAATTCACTCTCACCATCAGC
GGTCTGCAACCTGAAGATTTTGTCACTTACTACTGTCAACAGACTTACAATACCCCT
CGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

MAB375 LC variable domain nucleotide sequence (SEQ ID NO:70)

GATATCCAGATGACCCAGTCTCCATCCTTCTTGTCTGCATCTGTGGGAGACAGAGTC
ACCTTCACTTGCCGGGCCAGTCAGGGCATTGCCAGTTCTTTAGCCTGGTATCAGCAA
AAAGCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCTTCTACTTTGGAAGATGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATTTGGGACAGAATTCACTCTCACAATCACC
AGCCTGCAGCCTGAAGATTTTGCAACCTATTACTGTCATCAGGTGAATAGTTACCCT
CGGACTTTCGGCCCTGGGACCACAGTGGATATCAAC

MAB376 LC variable domain nucleotide sequence (SEQ ID NO:71)

GATATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTGGGAGACACAGTC
ACCATCACTTGCCGGGCCAGTCAGAGTATTAGTACTTGGTTGGCCTGGTTTCAGCAG
AAACCAGGGAGAGCCCCTAAACTCCTGATCTATCAGGCGTCTAGTTTGGAAGGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGGTCTGGGACAGACTTCAACCTCACCATCAGC
GGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCTACAATATAACACTTATTCG
AAGTCATTCGGCCAAGGGACCAAGGTGGAAATCAAAC

MAB377 LC variable domain nucleotide sequence (SEQ ID NO:72)

GATATCCAGATGACCCAGTCTCCATCCTTCTTGTCTGCATCTGTCGGAGACAGAGTC
ACCATCACCTGCCGGGCCAGTCAGGGCATTGCCACTTCTTTAGCCTGGTATCAGCAA
AAACCTGGGAAAGCCCCGAGGCTCCTGATCTATGCTGCATCCACTTTGGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCGGTGGATCTGGGACAGACTTCACTCTCACAATCAGC
AGTCTGCAGCCCGAAGATTTTGCTGTTTATTACTGTCAACAGGTTAACTCCTATCCT
CGGACTTTCGGCCCTGGGACCAAACTGGATGTCAAAC

MAB378 LC variable domain nucleotide sequence (SEQ ID NO:73)

GATATCCAGATGACCCAGTCTCCATCCTTCTTGTCTGCATCTGTAGGAGACAGAGTC
ACCATGACCTGCCGGGCCAGTCAGGGCATTAGCAGTTATTTAGCCTGGTATCAGCAA
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCGACTTTGGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCAGC
AGCCTGCAGCCCGAAGATTTTGCAATTTATTACTGTCAACAGGTTAATGGTTACCCT
CGGACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC

RGLFGAIAGFIENGW (SEQ ID NO:74).

MAB53 Heavy Chain (SEQ ID NO:75)

QVQLVQSGAEVRKPGSSVKVSCKVSGGIIRKYAINWVRQAPGQGLEWMGGIIAIFNT
ANYAQKFQGRVTITADESTSTVYMELSSLRSEDTALYYCARGMNYYSDYFDYWGQGS
LVTVSPASTKGPSVFPLVPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

MAB53 Light Chain (SEQ ID NO:76)

EIVLTQSPGTLSLSPGERATLSCRASQSVRSNNLAWYQHKPGQAPRLLIFGASSRAT
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPALTFGGGTKVEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

GGIIRKYAIN (SEQ ID NO:77)

GGIIAIFNTANYAQKFQG (SEQ ID NO:78)

ARGMNYYSDYFDY (SEQ ID NO:79)

RASQSVRSNNLA (SEQ ID NO:80)

GASSRAT (SEQ ID NO:81)

QQYGSSPALT (SEQ ID NO:82)

IGHV1-69*01 (SEQ ID NO:83)

QVQLVQSGAEVRK PGSSVKVSCKVSGGIIRKYAINWVRQAPGQG
LEWMGGIIAIFNTANYAQKFQGRVTITADESTSTVYMELSSLRSEDTALYYCARGMN
YYSDYFDYWGQGSLVTTVS

IGKV3-20*01 (SEQ ID NO:84)

EIVLTQSPGTLSLSPGERATLSCRASQSVRSNNLAWYQHKPGQAPRLLIFGASSRAT
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPALTFGGGTKVEIK

Claims

1. The binding moiety which is a monoclonal antibody or immunoreactive fragment thereof, or which is an antibody mimic or a bi-specific antibody, which binding moiety crossreacts with HA_0 protein stalk region from influenza viral clades that include both Group 1 and Group 2 representatives of influenza A.

2. A binding moiety of claim 1 that crossreacts with HA_0 protein stalk region from influenza viral clades H1, H7 and H9 or with influenza viral clades H1, H7 and H3.

3. The binding moiety of claim 1 or 2, that binds to the same epitope as MAB53.

4. The binding moiety of any of claims 1 - 3 that remains bound to influenza HA_0 protein at pH 6 *in vitro* or that remains bound to the virus following uptake via the endosomal pathway.

5. The binding moiety of any of claims 1 - 4 which is an antibody or fragment thereof which is human or humanized or chimerized.

6. The binding moiety of any of claims 1 - 5 that neutralizes infection by H1N1, H7N3 or H5N1 virus in MDCK cells.

7. The binding moiety of any of claims 1 - 6 that is protective in mice against challenge with otherwise lethal titers of H1N1 or H5N1 at a single dose of 1-10 mg/kg.

8. The binding moiety of claim 1 which is an antibody or fragment thereof and which comprises:

a heavy chain CDR1 of the sequence GGIIRKYAIN (SEQ ID NO:77);

a heavy chain CDR2 of the sequence GGIIAIFNTANYAQKFQG (SEQ ID NO:78);

a heavy chain CDR3 of the sequence ARGMNYYSDYFDY (SEQ ID NO:79);

a light chain CDR1 of the sequence RASQSVRSNNLA (SEQ ID NO:80);

a light chain CDR2 of the sequence GASSRAT (SEQ ID NO:81); or

a light chain CDR3 of the sequence QQYGSSPALT (SEQ ID NO:82); or combinations thereof.

9. The antibody or fragment of claim 8 which comprises a heavy chain comprising CDR1 of the sequence GGIIRKYAIN (SEQ ID NO:77), CDR2 of the sequence GGIIAIFNTANYAQKFQG (SEQ ID NO:78), and CDR3 of the sequence ARGMNYYSDYFDY (SEQ ID NO:79).

10. The antibody or fragment of claim 8 which comprises a light chain comprising CDR1 of the sequence RASQSVRSNNLA (SEQ ID NO:80), a CDR2 of the sequence GASSRAT (SEQ ID NO:81), and a CDR3 of the sequence QQYGSSPALT (SEQ ID NO:82).

11. The antibody or fragment of claim 9 which comprises a light chain comprising CDR1 of the sequence RASQSVRSNNLA (SEQ ID NO:80), a CDR2 of the sequence GASSRAT (SEQ ID NO:81) and a CDR3 of the sequence QQYGSSPALT (SEQ ID NO:82).

12. The antibody or fragment of claim 8 which comprises a heavy chain comprising the sequence QVQLVQSGAEVRKPGSSVKVSCKVSGGIIRKYAINWVRQAPGQGLEWMG GIIAIFNTANYAQKFQGRVTITADESTSTVYMELSSLRSEDTALYYCARGMNYYSDYFD YWGQGSLVTVSP (amino acids 1-120 of SEQ ID NO:75).

13. The antibody or fragment of claim 8 which comprises a light chain comprising the sequence EIVLTQSPGTLSLSPGERATLSCRASQSVRSNNLAWYQHKPGQAPRLLIFGA SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPALTFGGGTKVEIK (amino acids 1-109 of SEQ ID NO:76).

14. The antibody or fragment of claim 12 which comprises a light chain comprising the sequence EIVLTQSPGTLSLSPGERATLSCRASQSVRSNNLAWYQHKPGQAPRLLIFGA SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPALTFGGGTKVEIK (amino acids 1-109 of SEQ ID NO:76).

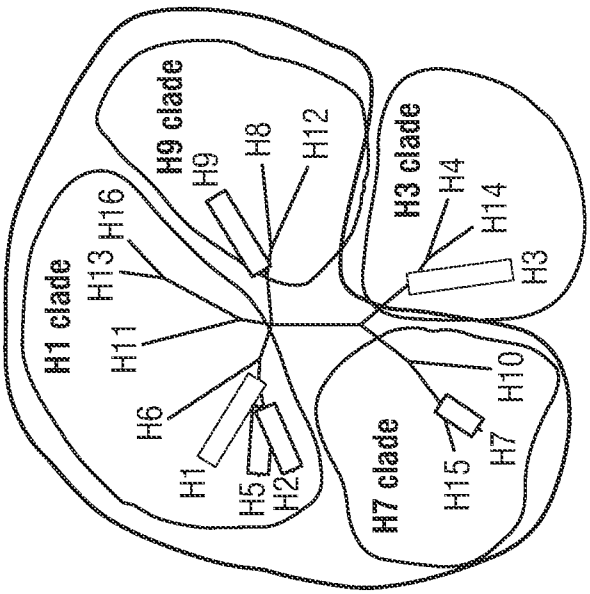
15. A pharmaceutical composition comprising the binding moiety of any of claims 1-14.

16. A method for the treatment or prophylaxis of influenza infection in a subject which method comprises administering to a subject an effective amount of the composition of claim 15.

17. A recombinant expression system that comprises a nucleotide sequence encoding the heavy chain or light chain variable region of the antibody or fragment of any of claims 8-14 operably linked to control sequences for expression.

18. Recombinant host cells modified to contain the expression system of claim 17.

19. A method to produce a monoclonal antibody or fragment immunoreactive with influenza virus which method comprises culturing the cells of claim 18 under conditions wherein said nucleotide sequence is expressed.


H1 clade
H9 clade
H3 clade
H7 clade
H1
H2
H3
H4
H5
H6
H7
H8
H9
H10
H11
H12
H13
H14
H15
H16

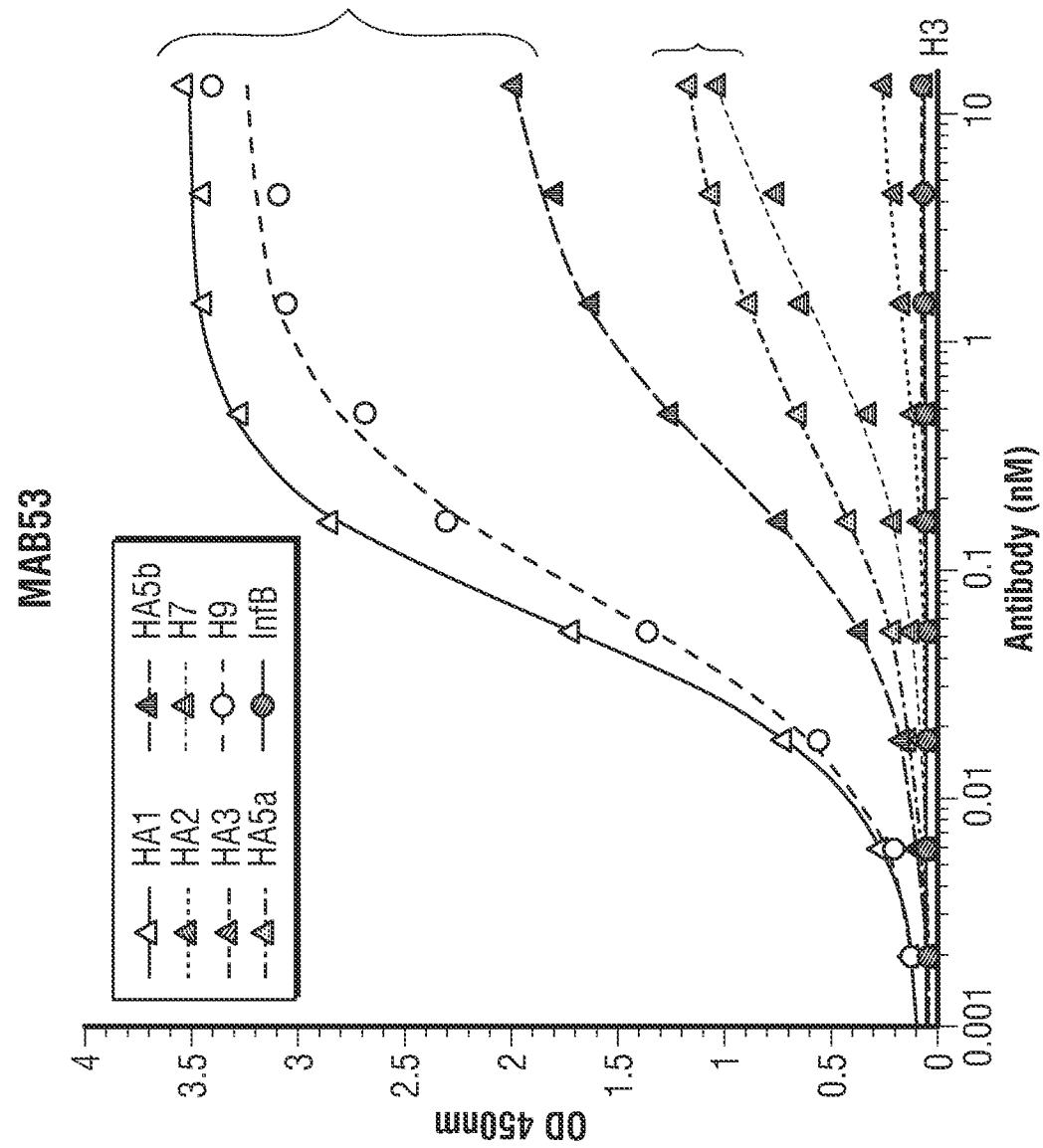
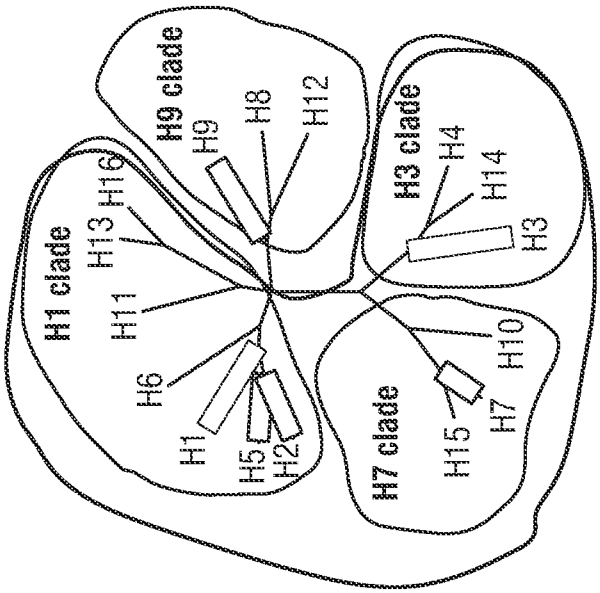

MAB53
HA1
HA2
HA3
HA5a
HA5b
H7
H9
InfB
OD 450nm
0
0.5
1
1.5
2
2.5
3
3.5
4
0.001
0.01
0.1
1
10
Antibody (nM)
H3

FIG. 1A


H9 clade
H9
H8
H12
H3 clade
H4
H14
H3
H1 clade
H13
H16
H11
H6
H1
H5
H2
H7 clade
H15
H7
H10

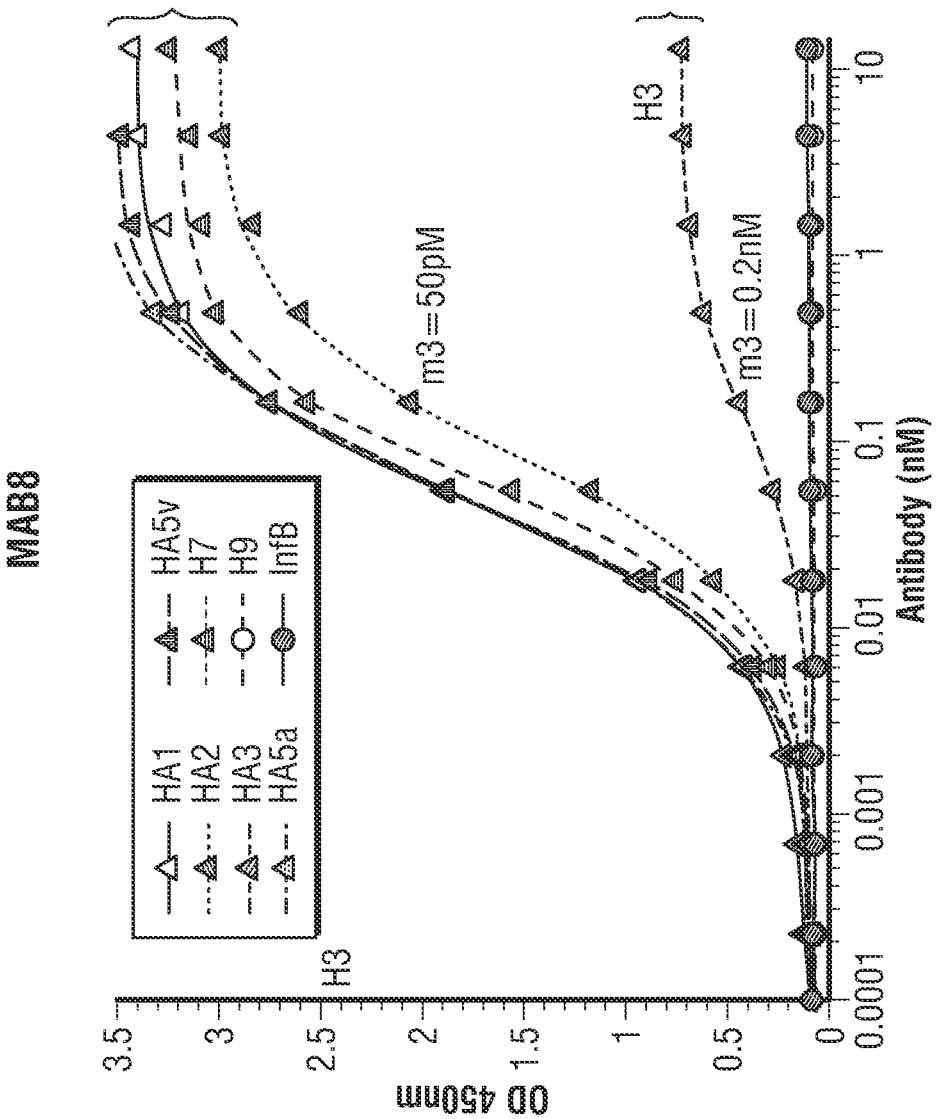

MAB8
HA1
HA2
HA3
HA5a
HA5v
H7
H9
InfB
H3
m3=50pM
m3=0.2nM
H3
OD 450nm
Antibody (nM)
0.0001
0.001
0.01
0.1
1
10
0
0.5
1
1.5
2
2.5
3
3.5

FIG. 1B

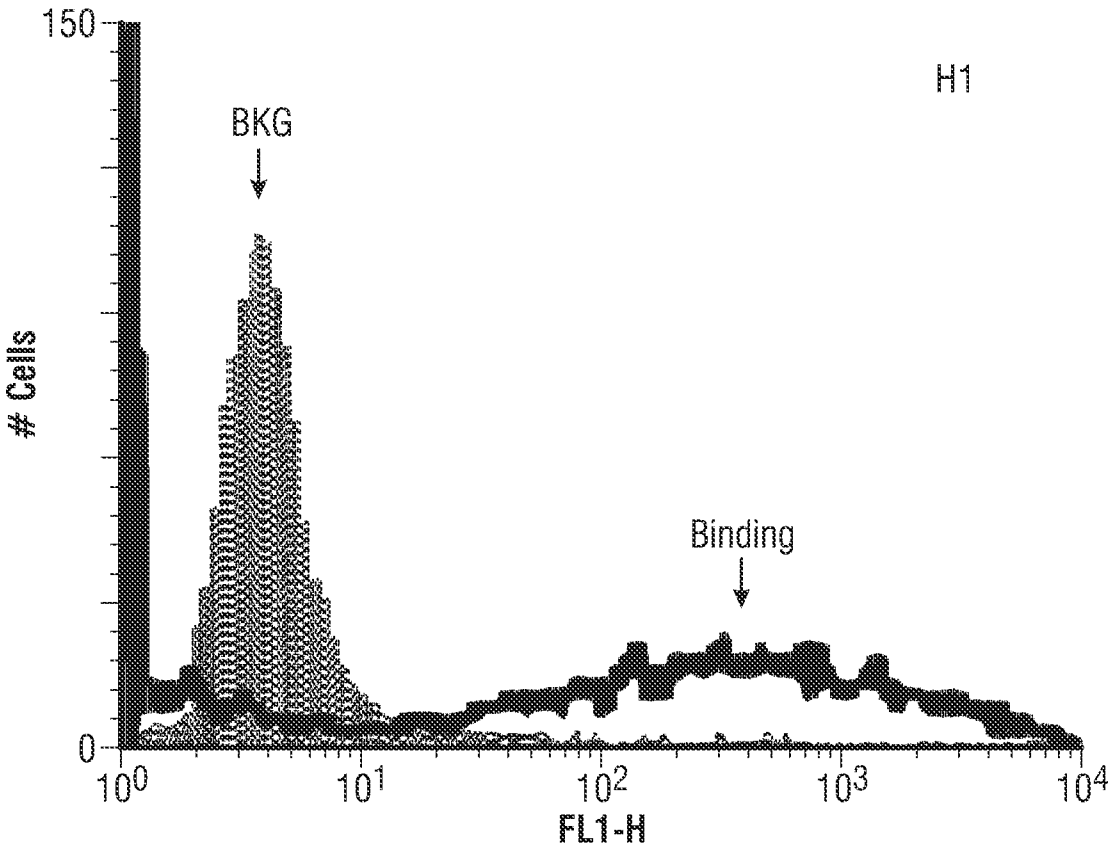


FIG. 1C

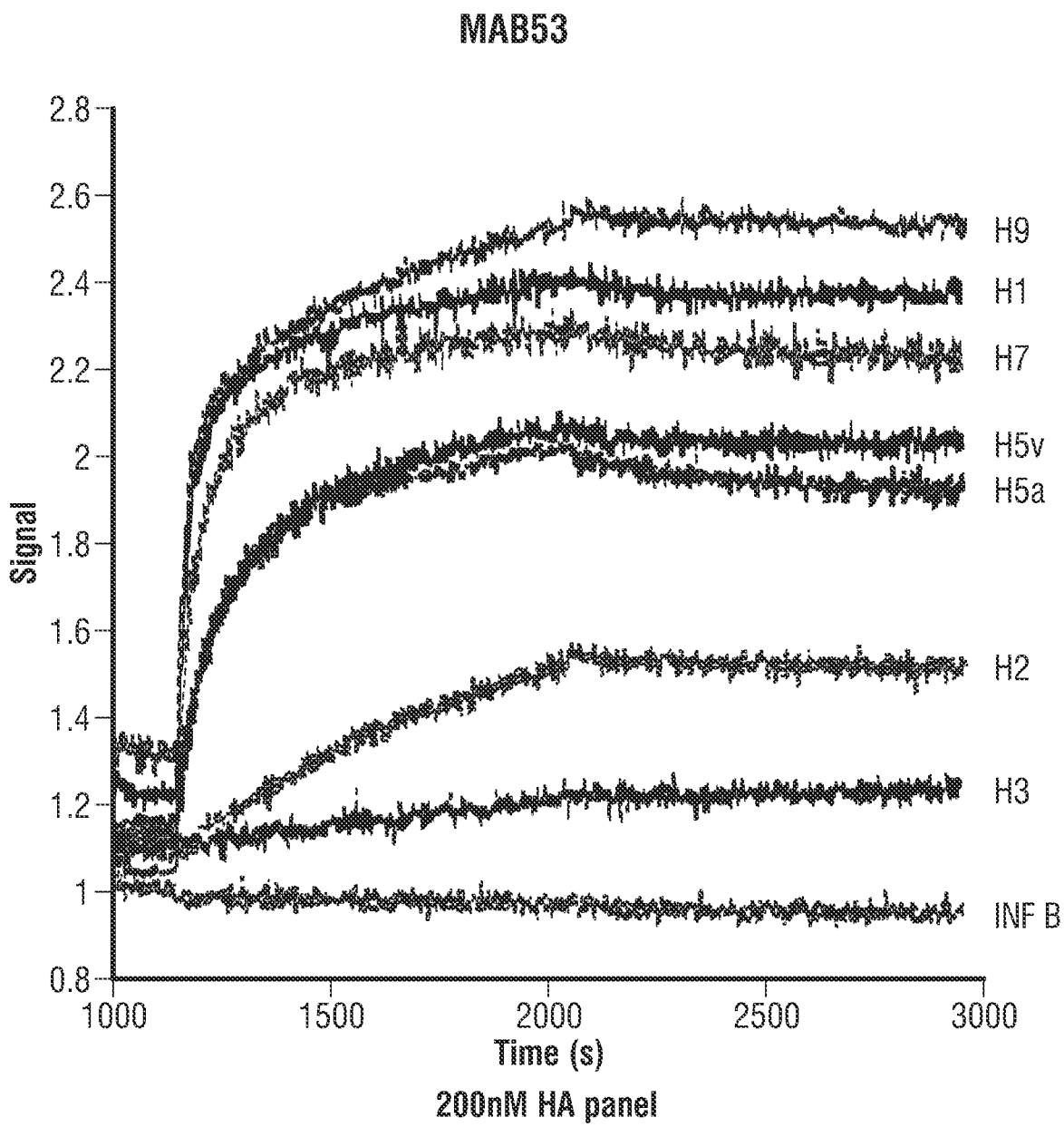

MAB53
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
Signal
1000
1500
2000
2500
3000
Time (s)
H9
H1
H7
H5v
H5a
H2
H3
INF B
200nM HA panel

FIG. 2A

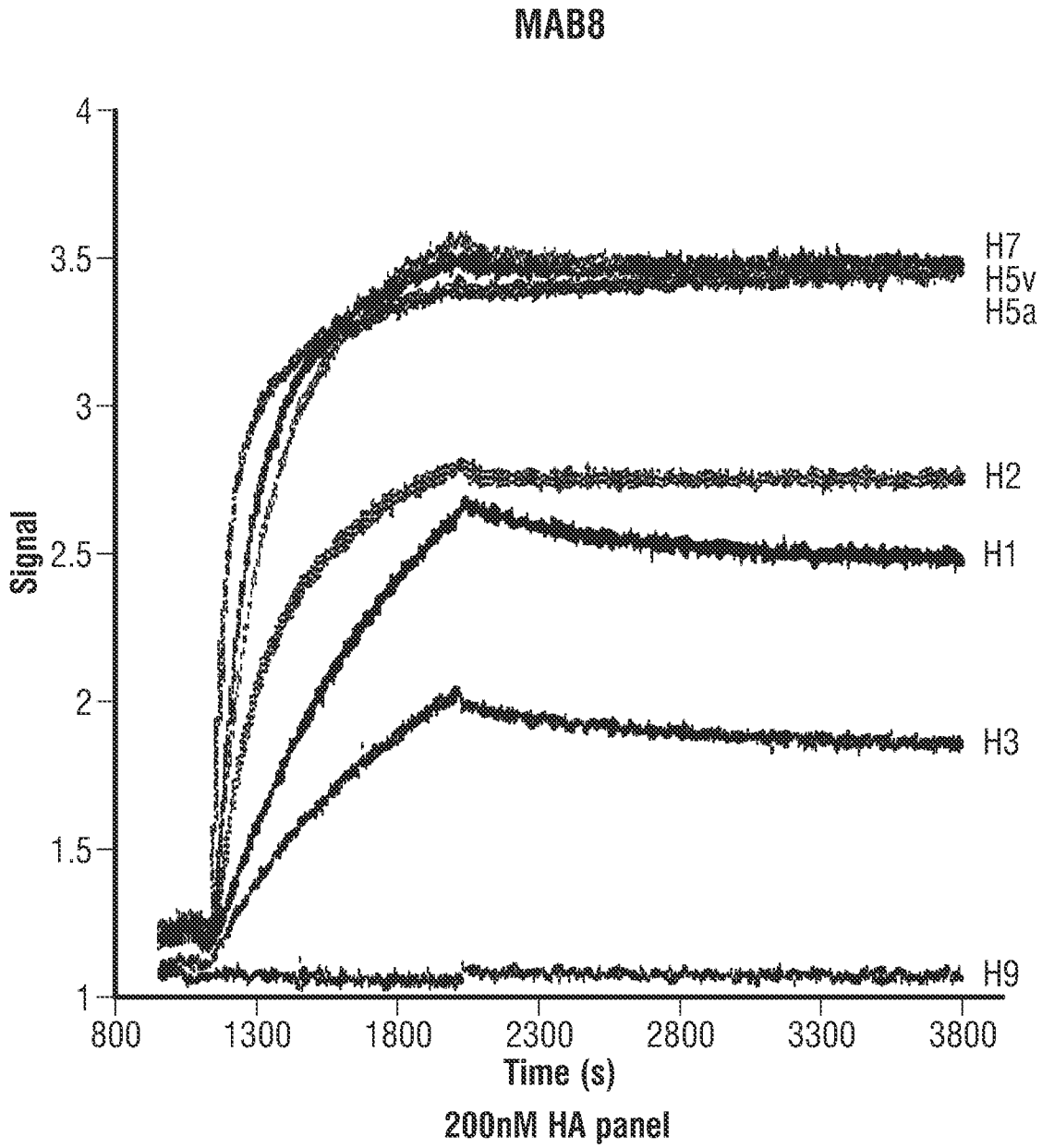

MAB8
4
3.5
3
2.5
2
1.5
1
Signal
800
1300
1800
2300
2800
3300
3800
Time (s)
H7
H5v
H5a
H2
H1
H3
H9
200nM HA panel

FIG. 2B

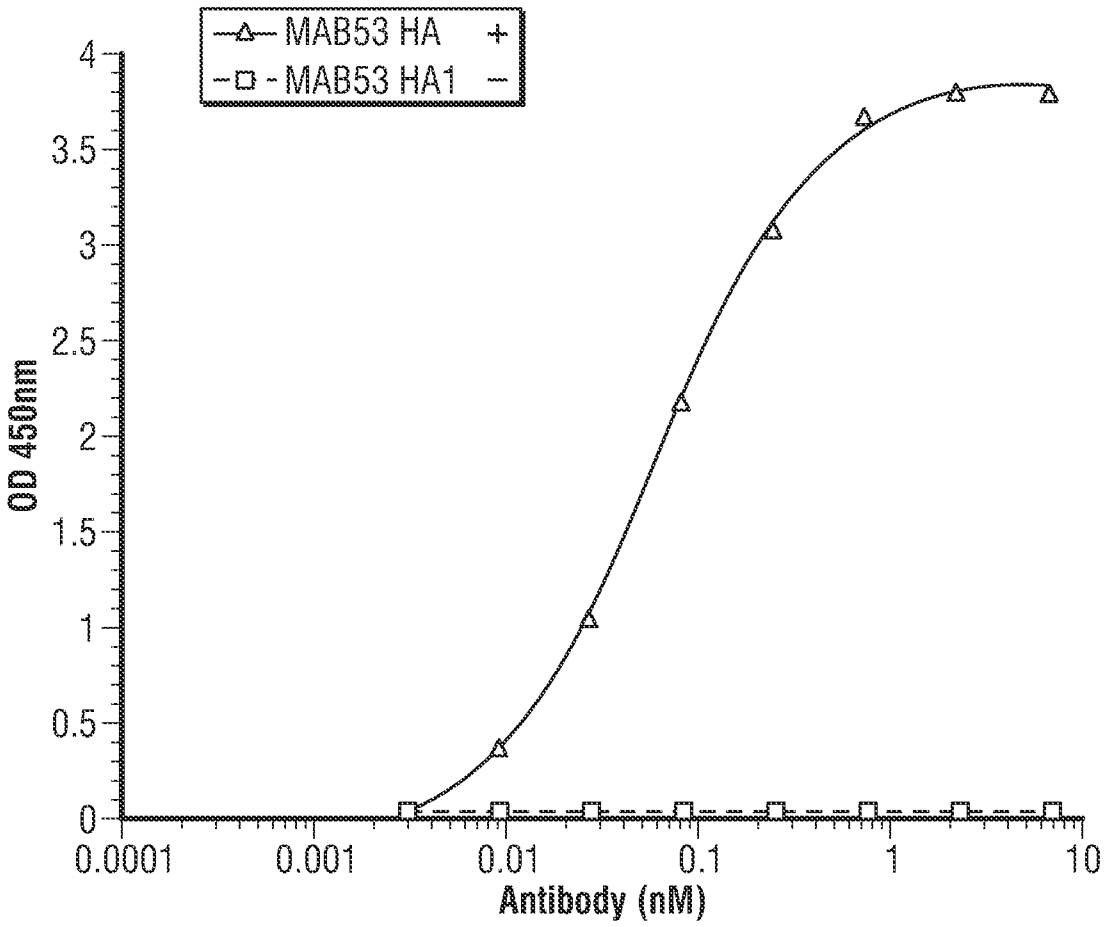

MAB53 HA
MAB53 HA1
OD 450nm
4
3.5
3
2.5
2
1.5
1
0.5
0
0.0001
0.001
0.01
0.1
1
10
Antibody (nM)

FIG. 3A

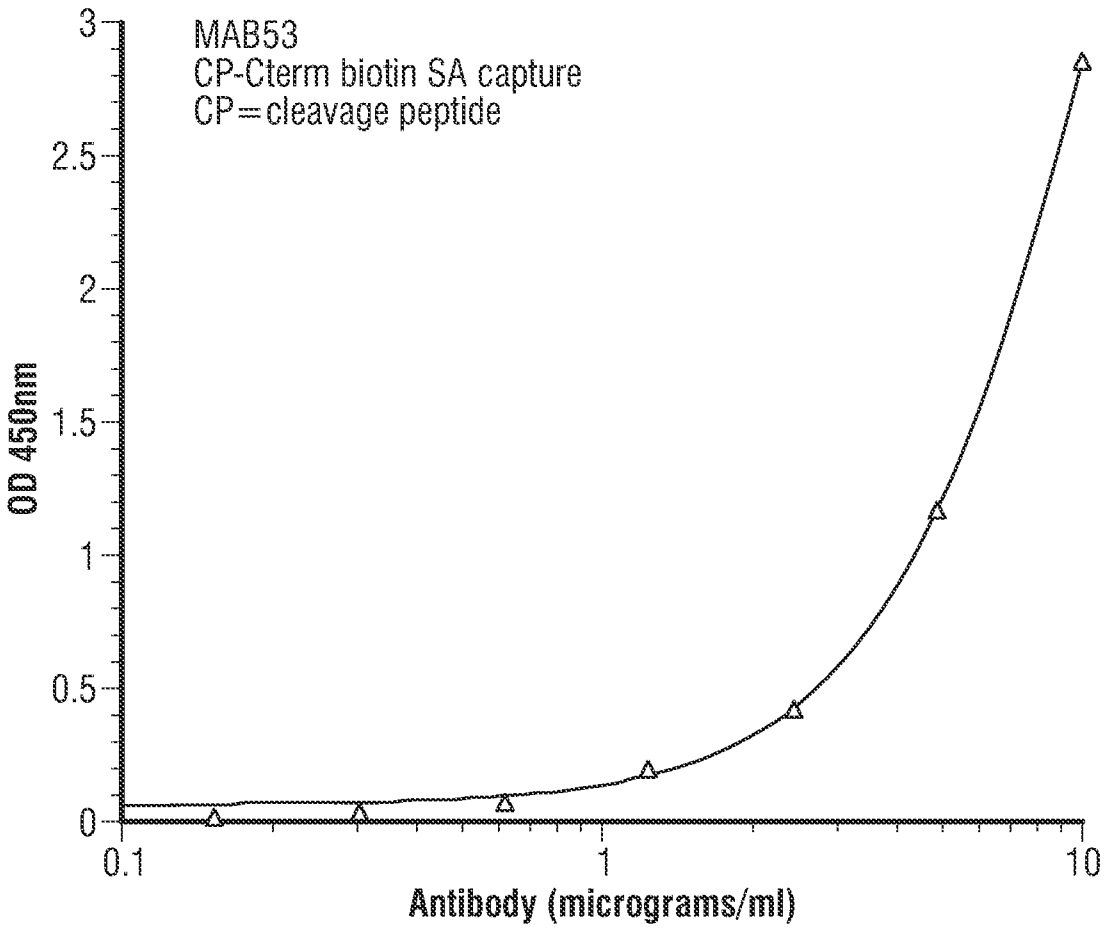

MAB53
CP-Cterm biotin SA capture
CP=cleavage peptide
OD 450nm
3
2.5
2
1.5
1
0.5
0
0.1
1
10
Antibody (micrograms/ml)

FIG. 3B

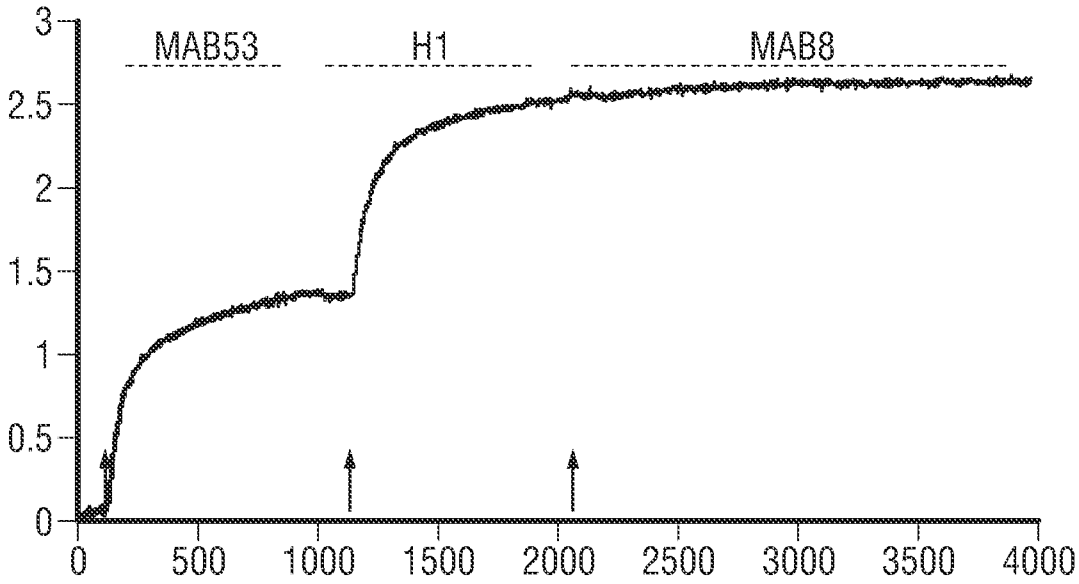

MAB53
H1
MAB8
3
2.5
2
1.5
1
0.5
0
0
500
1000
1500
2000
2500
3000
3500
4000

FIG. 4A

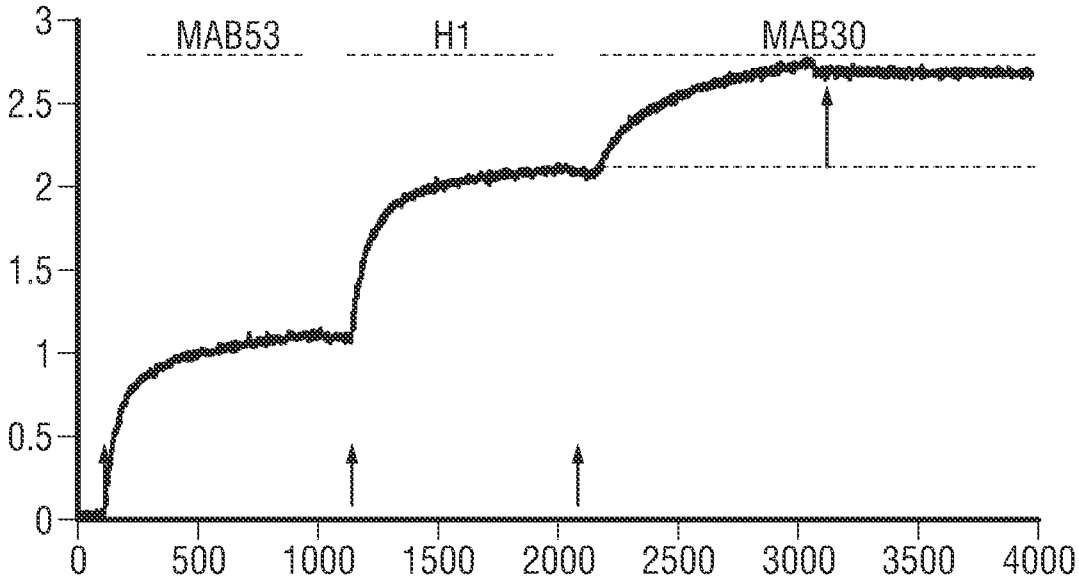

MAB53
H1
MAB30
3
2.5
2
1.5
1
0.5
0
0
500
1000
1500
2000
2500
3000
3500
4000

FIG. 4B

VH

Kabat - CDR H1

Kabat No. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 A B 36 37 38 39 40 41 42 43 44

IGHV1-69*01 Q V Q L V Q S G A E V R K P G S S V K V S C K V S G G I I R K Y A I N . . W V R Q A P G Q G

Kabat - CDR H2

45 46 47 48 49 50 51 52 A B C 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 A B C 83 84

L E W M G G I I A . . I F N T A N Y A Q K F Q G R V T I T A D E S T S T V Y M E L S S L R S

Kabat - CDR H3

85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 A B C D E F G H I J K 101 102 103 104 105 106 107 108 109 110 111 112 113

E D T A L Y Y C A R G M N Y Y S D Y . . . . F D Y W G Q G S L V T V S P

FIG. 5A

VL

Kabat - CDR L1

Kabat No. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 A B C D E F 28 29 30 31 32 33 34 35 36

IGKV3-20*01 E I V L T Q S P G T L S L S P G E R A T L S C R A S Q S . . . . . V R S N N L A W Y

Kabat - CDR L2

37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 A B C D E 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71

Q H K P G Q A P R L L I F G A S S R . . . . . A T G I P D R F S G S G S G T D F

Kabat - CDR L2

72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 A B C D E F 96 97 98 99 100 101 102 103 104 105 106 107

T L T I S R L E P E D F A V Y Y C Q Q Y G S S P A . . . . . L T F G G G T K V E I K

FIG. 5B

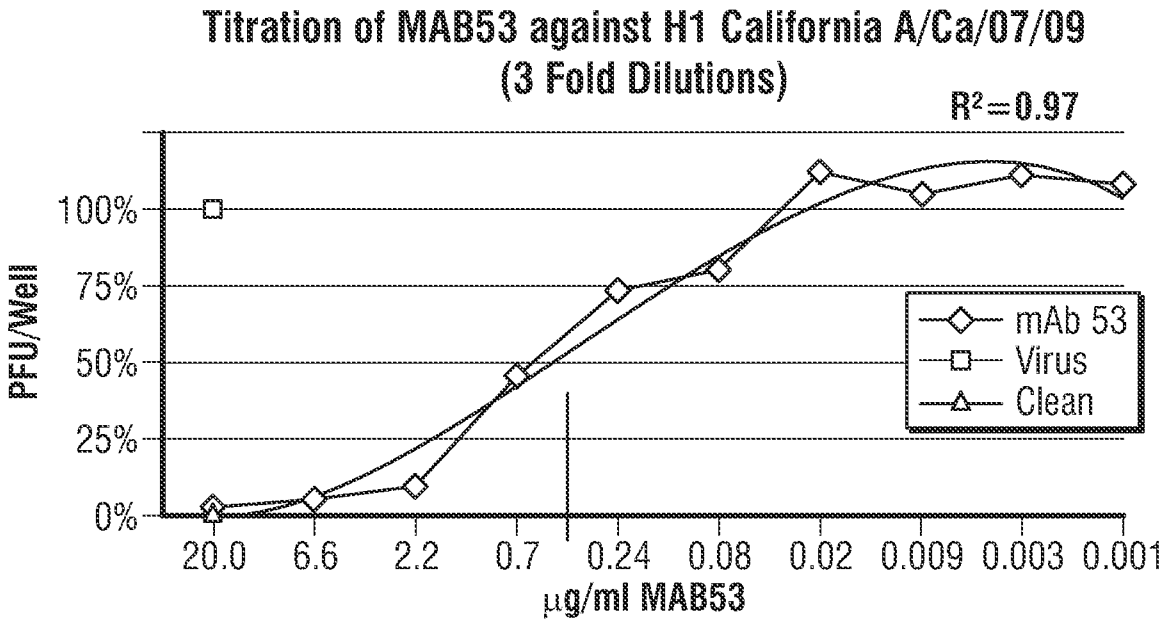

Titration of MAB53 against H1 California A/Ca/07/09
(3 Fold Dilutions)
R²=0.97
PFU/Well
100%
75%
50%
25%
0%
20.0
6.6
2.2
0.7
0.24
0.08
0.02
0.009
0.003
0.001
µg/ml MAB53
mAb 53
Virus
Clean

FIG. 6

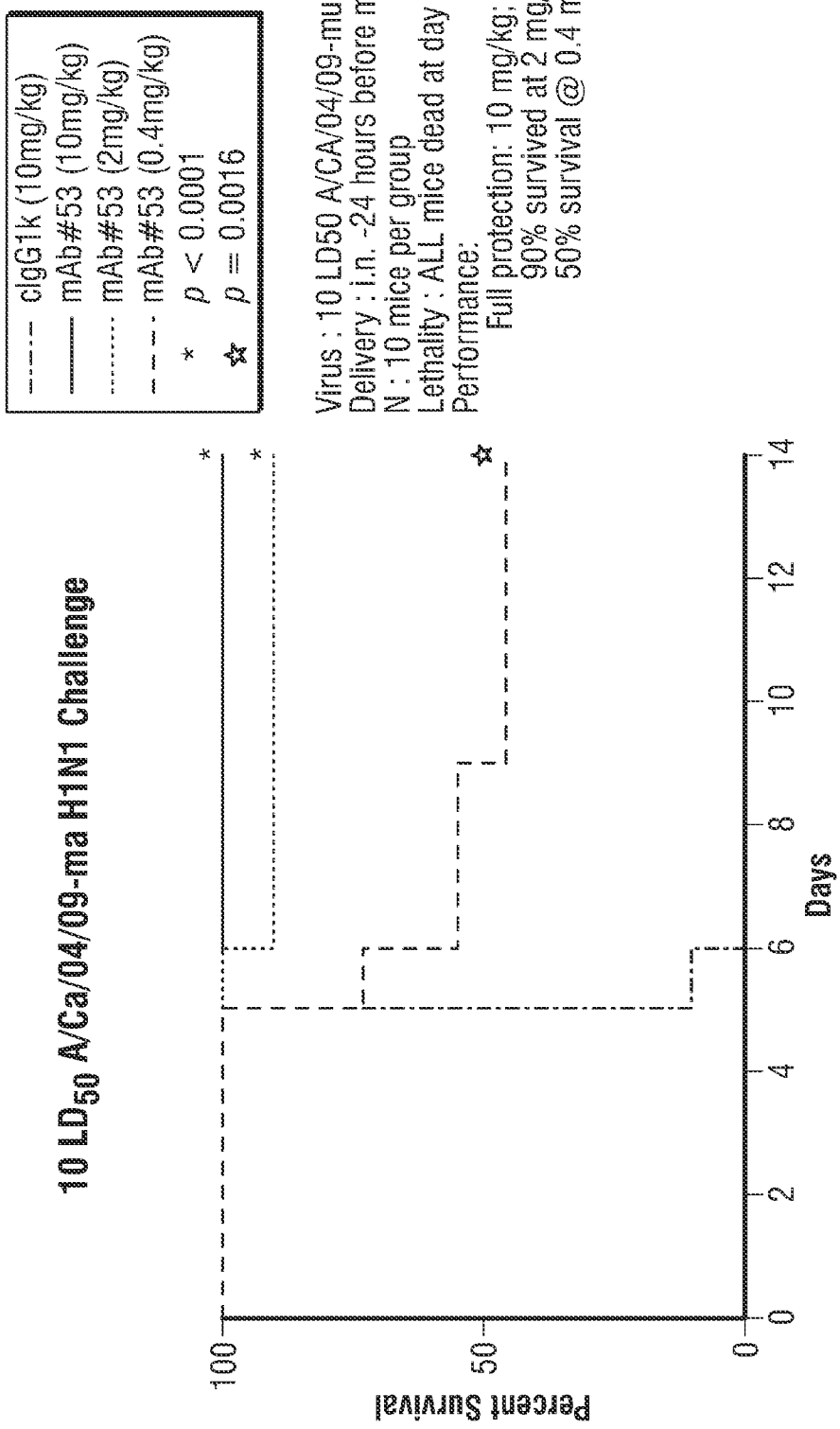

10 LD50 A/Ca/04/09-ma H1N1 Challenge
Percent Survival
Days
100
50
0
0
2
4
6
8
10
12
14
clgG1k (10mg/kg)
mAb#53 (10mg/kg)
mAb#53 (2mg/kg)
mAb#53 (0.4mg/kg)
* p < 0.0001
☆ p = 0.0016
Virus : 10 LD50 A/CA/04/09-murine adapted
Delivery : i.n. -24 hours before mAbs delivered i.p.
N : 10 mice per group
Lethality : ALL mice dead at day 6
Performance:
Full protection: 10 mg/kg;
90% survived at 2 mg/kg dose
50% survival @ 0.4 mg/kg

FIG. 7A

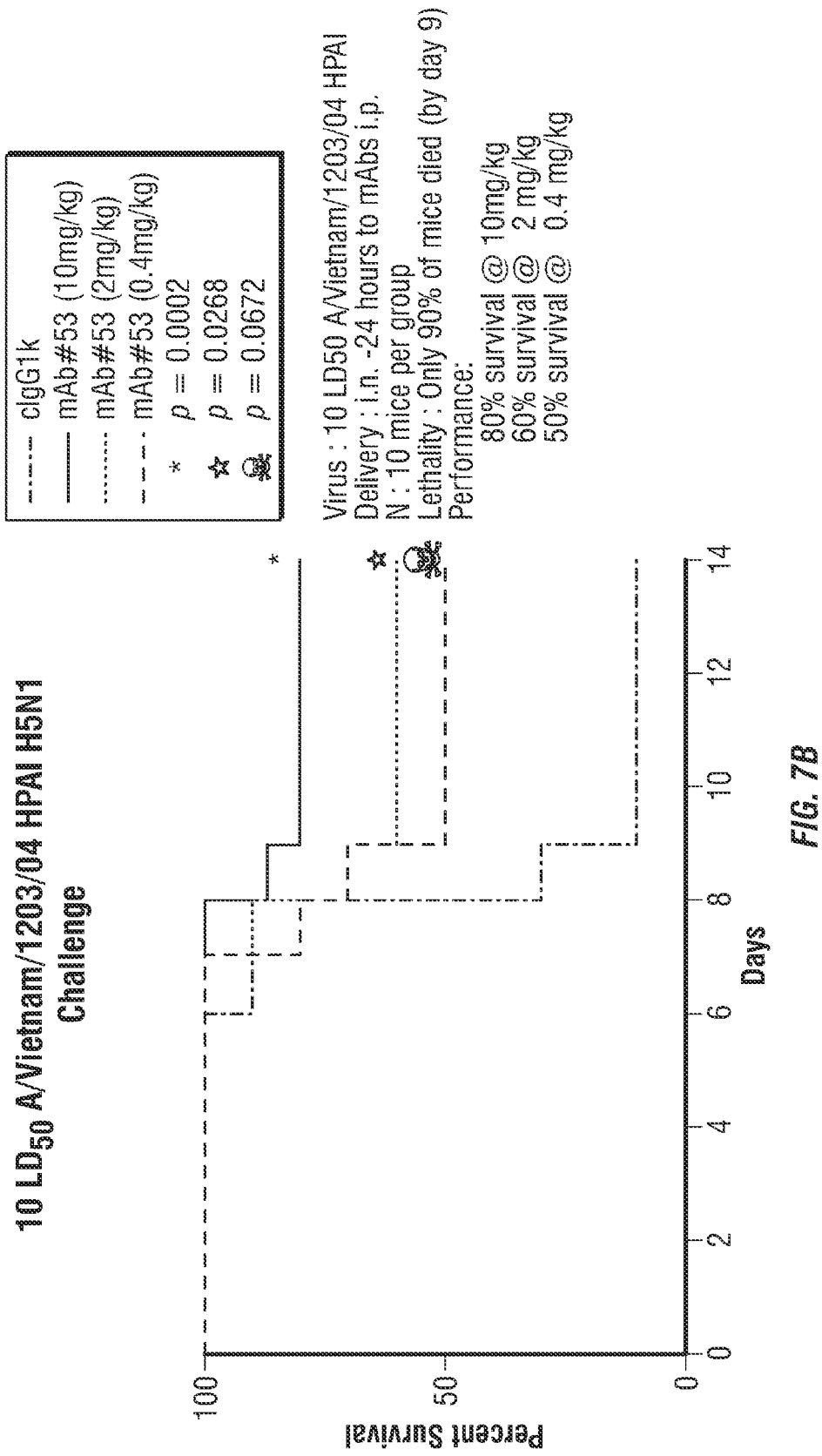

10 LD50 A/Vietnam/1203/04 HPAI H5N1
Challenge
Percent Survival
Days
100
50
0
0
2
4
6
8
10
12
14
cIgG1k
mAb#53 (10mg/kg)
mAb#53 (2mg/kg)
mAb#53 (0.4mg/kg)
* p = 0.0002
p = 0.0268
p = 0.0672
Virus : 10 LD50 A/Vietnam/1203/04 HPAI
Delivery : i.n. -24 hours to mAbs i.p.
N : 10 mice per group
Lethality : Only 90% of mice died (by day 9)
Performance:
80% survival @ 10mg/kg
60% survival @ 2 mg/kg
50% survival @ 0.4 mg/kg

FIG. 7B

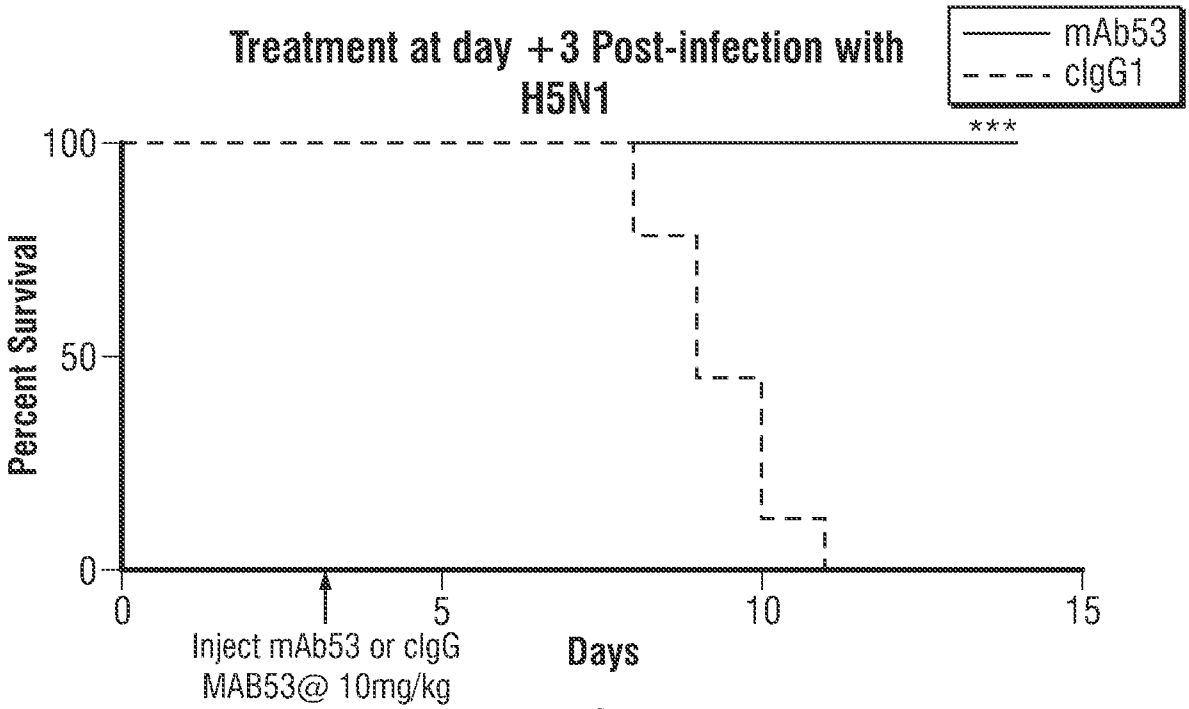

Treatment at day +3 Post-infection with H5N1
mAb53
clgG1
***
100
50
0
Percent Survival
0
5
10
15
Inject mAb53 or clgG
MAB53@ 10mg/kg
Days

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/40982

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/00; A61K 39/395 (2011.01)
USPC - 530/388.3; 514/13.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07K 16/00; A61K 39/395 (2011.01)
USPC: 530/388.3; 514/13.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (PGPB,USPT,EPAB,JPAB): antibody, influenza, HA, H1, H7, H9, H3, cross reaction, clade, stalk,
Google Scholar: monoclonal antibody influenza clades cross react HA protein stalk H1 H7 H9 mAb53
Google Web: monoclonal mAb53 epitope influenza; esp@cenet: Trellis, influenza, clade, monoclonal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	STEEL et al. Influenza Virus Vaccine Based on the Conserved Hemagglutinin Stalk Domain. MBio. April 2010, Vol 1, e00018-10, pgs. 1-9, especially pg 1, abstract; pg 6, right col, first para; pg 6, left col, third para; pg 7, Fig 6; pg 8, left col, third para.	1 --- 2, 8, 17-19
Y -- A	WO 2009/121004 A2 (HOROWITZ et al.) 1 October 2009 (01.10.2009), abstract; pg 1, ln 4-9; pg 4, ln 6-10; pg 34, ln 30-pg 25, ln 2; SEQ ID NO: 135	2 --- 10, 11
Y	WO 2009/079259 A2 (MARASCO et al.) 25 June 2009 (25.06.2009), abstract; pg 3, ln 13-15; pg 24, ln 29 - pg 25, ln 25; pg 26, ln 31-pg 27, ln 2.	8, 17-19
A	KUBOTA-KOKETSU et al. Broad neutralizing human monoclonal antibodies against influenza virus from vaccinated healthy donors. Biochemical and Biophysical Research Communications. 2009, Vol 387, pgs 180-185, especially pg 180, abstract.	3
A	US 7,696,330 B2 (MEULEN et al.) 13 April 2010 (13.04.2010), SEQ ID NO: 459.	9
A	US 2009/0311265 A1 (VAN DEN BRINK et al.) 17 December 2009 (17.12.2009), SEQ ID NO: 221.	9

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2011 (31.10.2011)	25 NOV 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/40982

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-7, 15, 16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without,effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/40982

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0086555 A1 (LANZAVECCHIA) 8 April 2010 (08.04.2010), SEQ ID NO: 51; SEQ ID NO: 60	9, 12
A	WO 2010/022120 A1 (MARTIN et al.) 25 February 2010 (25.02.2010), SEQ ID NO: 10.	10, 11
A	WO 2007/134327 A2 (BHATT et al.) 22 November 2007 (22.11.2007), claim 58; Fig 14.	13, 14
A	BRIGHT et al. Cross-Clade Protective Immune Responses to Influenza Viruses with H5N1 HA and NA Elicited by an Influenza Virus-Like Particle. PLos ONE, 2008, Vol 3, e1501, pgs. 1-14.	1