# Supporting Online Material

# A Highly Conserved Neutralizing Epitope on Group 2 Influenza A Viruses

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## Materials and Methods

**Generation and selection of influenza-specific BCR$^+$ B cell lines.** Antigen-specific immortalized B cell clones were generated from PBMCs of donors vaccinated 7 days earlier with the trivalent inactivated influenza vaccine for the 2006-2007 season (containing A/New Caledonia/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004) essentially as described by Kwakkenbos *et al. (S1)*. Immortalized IgM memory cells ($CD19^+CD27^+IgD^+$) were stained with APC-labeled H3 HA (Insect cell produced recombinant soluble H3 HA (A/Wisconsin/67/2005; Protein Sciences, CT, USA) and single cells sorted into limiting dilution culture. After recovery and cell expansion, the supernatants of the H3 HA sorted cells were measured by solid phase ELISA for H1, H3 and H7 immunoreactivity and neutralization.

**IgG expression.** Fully human IgG1 antibodies CR8020, CR6261, CR8057 (binding to the globular head of recent H3 HAs), and CR8011 (binding to the globular head of H7 HAs) were constructed by cloning the heavy ($V_H$) and light ($V_L$) chain variable regions into a single IgG1 expression vector. PER.C6® cells were transfected with the IgG1 expression constructs and the expressed antibodies were purified from serum-free culture supernatants using POROS Mabcapture A chromatography (Applied Biosystems). Fab-CR8020 and Fab-CR6261 fragments were obtained by specific cleavage of CR8020 and CR6261 using Immobilized Papain (Pierce, cat # 20341). The Fabs were separated from the Fc fragment by protein A chromatography and then buffer exchanged to 50 mM NaAc, 50 mM NaCl, pH 5.5. The identity of the fragments was confirmed by western

blotting using a rabbit anti-human IgG κ-chain (anti λ-chain for CR6261), goat anti-rabbit/HRP antibody combination. The Fabs were then subjected to cation exchange chromatography (after dilution in 50mM sodium acetate buffer, pH 5.0, and separation over a gradient of 0-1M NaCl) and gel filtration. Fab concentration was measured by optical absorption at 280 nm. Fab quality was also confirmed by size exclusion chromatography, SDS-PAGE and isoelectric focusing. Fabs were >97 % monomeric, and displayed the correct heavy chain/light chain distribution and charge homogeneity.

**Viruses.** Wild-type influenza viruses A/Brisbane/10/2007 (H1N1), A/Wisconsin/67/2005 (H3N2), A/Hiroshima/52/2005 (H3N2), A/Panama/2007/1999 (H3N2), A/Johannesburg/33/1994 (H3N2), A/Hong Kong/1/1968 (H3N2), A/Hong Kong/1073/1999 (H9N2), A/New Caledonia/20/1999 (H1N1), A/NYMC/X-161B (high-growth reassortant of A/Wisconsin/67/2005 (H3N2)), A/WF/Hong Kong/MPA892/06 (H4), A/chicken/Germany/n/49 (H10N7) and recombinant viruses NIBRG-60 (6:2 reassortant A/mallard/Netherlands/12/2000 (H7N3, NIBSC code 07/204)) and NIBR-14 (6:2 reassortant A/Vietnam/1194/2004 (H5N1, NIBSC code 03/246)) were grown on PER.C6® cells using standard viral culturing techniques. Furthermore, a 7:1 recombinant virus with the HA of A/New York/107/2003 (H7N7) and A/PR/8/34 was rescued and propagated on PER.C6® cells as described previously (*S2*). For the challenge experiments, stocks of mouse-adapted A/Hong Kong/1/1968 (H3N2) (*S3*) and A/Ck/Netherlands/621557/2003 (H7N7) were grown in eggs.

***In vitro* neutralizing activity.** Microneutralization (MN) and hemagglutination inhibition (HAI) assays were performed as described before using full-length IgG (*S4*).

**Prophylactic and therapeutic efficacy studies in mice.** Female SPF 129 X1/SvJ (Jackson Laboratories) and BALB/c mice (Charles River Laboratories) aged 6–8 weeks were used in the H3N2 and H7N7 experiments, respectively. In the prophylactic studies, groups of 8 mice received a dose of 1, 3, 10, or – only in the H3N2 experiment – 30 mg/kg of full length CR8020 IgG, or 30 mg/kg control human mAb CR3014 (*S5*) i.v. in a volume of 200 μl one day prior to intranasal challenge with 25 $LD_{50}$ of either mouse-adapted A/Hong Kong/1/68 (H3N2) or A/Ck/Netherlands/621557/03 (H7N7). Twenty-five $LD_{50}$ of A/Hong Kong/1/68 (H3N2) and A/Ck/Netherlands/621557/03 (H7N7) equalled 2.8log $TCID_{50}$ and 3.1log $TCID_{50}$, respectively. In the therapeutic studies, groups of 10 and 8 mice received 15 mg/kg of CR8020 one day prior to, or at day 1, 2, 3, 4, 5, or 6 after, challenge with either 25 $LD_{50}$ of A/Hong Kong/1/68 (H3N2) or A/Ck/Netherlands/621557/03 (H7N7), respectively. Control IgG CR3014 (15 mg/kg) was administered at day 1 post challenge. Survival, weight loss, and clinical signs were monitored until 21 days after infection. Clinical signs were scored daily with a scoring system (0 = no clinical signs; 1 = rough coat; 2 = rough coat, less reactive, passive during handling; 3 = rough coat, rolled up, laboured breathing, passive during handling; 4 = rough coat, rolled up, laboured breathing, unresponsive). Animals with a score of 4 were euthanized. All experiments were approved prior to commencement by the Ethical Review Committee of the Central Veterinary Institute in accordance with Dutch law.

**Cloning, expression and purification of hemagglutinins.** Based on H3 numbering, cDNAs corresponding to residues 11-329 (HA1) and 1-176 (HA2) of the ectodomain of the HA were fused to an N-terminal gp67 signal peptide and to a C-terminal biotinylation site (amino acid sequence: GGGLNDIFEAQKIEWHE), trimerization domain, and His-tag by overlap PCR, essentially as previously described (*S6*). The trimerization domain and His-tag were separated from the HA ectodomain by a thrombin cleavage site. In the case of the HK68/H3 construct used for crystallization, the biotinylation site was omitted from the construct. The resulting PCR products were digested with SfiI and inserted into a custom baculovirus transfer vector (pDCE066 or pDCE198). Recombinant bacmid was generated using the Bac-to-Bac system (Invitrogen) and virus was rescued by transfecting purified bacmid DNA into Sf9 cells using Cellfectin II (Invitrogen). HA protein was produced by infecting suspension cultures of Hi5 cells (Invitrogen) with recombinant baculovirus at an MOI of 5-10 and incubating at 28°C shaking at 110 RPM. After 72 hours, the cultures were clarified by two rounds of centrifugation at 2000g and 10,000g at 4 °C. The supernatant, containing secreted, soluble HA was concentrated and buffer exchanged into 1x PBS, pH 7.4. After metal affinity chromatography using Ni-NTA resin, HAs for crystallography were digested with trypsin (New England Biolabs, 5mU trypsin per mg HA, 16 hours at 17°C) to produce uniformly cleaved (HA1/HA2), and to remove the trimerization domain and His-tag. After quenching the digests with 2mM PMSF, the digested material was further purified by anion exchange chromatography (10mM Tris, pH 9.0, 50-1M NaCl) and size exclusion chromatography (10mM Tris, pH

8.0, 150mM NaCl), essentially as previously described for other HAs (*S6-8*).

**Expression and purification of BirA.** *E. coli* biotin ligase (BirA enzyme) was expressed and purified in a manner similar to previous reports (*S9*), but with an N-terminal His tag. The *birA* gene was amplified from an *E. coli* colony (wild-type strain MG1655) using primers DE389 (5'-agtcactaggtcatatgcatcaccatcaccatcacaaggataacaccgtgccactg-3') and DE390 (5'-agtcactaggtaagcttttatttttctgcactacgcagggatatttc-3'). The PCR product was digested with NdeI and HindIII and ligated into similarly digested pET21a, yielding pDCE095. This vector was transformed into BL21(DE3) cells for protein expression. BL21(DE3)/pDCE095 cells were grown in shake flasks in low salt LB medium at 37°C to an OD (600nm) of ~0.7, then shifted to 23°C and induced with the addition of IPTG (isopropyl-beta-D-thiogalactopyranoside) to a final concentration of 1mM. The culture was incubated at 23°C for ~16 hours after induction, then harvested by centifugation (3000g, 10 minutes). The pellet from a 1L culture was resuspended in 50-100mL of lysis buffer (50mM Tris pH 8.0, 300mM potassium chloride, 10mM imidazole pH 8.0, with Roche EDTA-free protease inhibitor cocktail tablet) and the cells were lysed and homogenized by two passes through an EmulsiFlex C-3 cell disruptor (15kPSI). After clearing the lysates by centrifugation (25,000g, ~1 hour), the supernatant was incubated with NiNTA resin (Qiagen), washed with excess lysis buffer, and bound proteins were eluted (with 50mM Tris pH 8.0, 300mM potassium chloride, 250mM imidazole pH 8.0). After concentrating and buffer exchanging into 50mM potassium phosphate, pH6.5, 5% glycerol, 0.1mM dithiothreitol (DTT), the BirA was loaded onto a MonoQ column (GE

Healthcare) and eluted with a linear gradient of 0-1M potassium chloride. BirA containing fractions were pooled, concentrated, and subjected to gel filtration. The final yield of BirA protein was approximately 10mg/L and >95% pure as assessed by SDS-PAGE. Purified BirA protein was concentrated down to 5mg/mL in 50mM Tris, pH 7.5, 200mM potassium chloride, 5% glycerol, aliquoted, flash frozen in liquid nitrogen, and stored at -80°C.

**Biotinylation and purification of HAs for binding studies.** After expression and NiNTA purification as described above, HAs for binding studies were concentrated down to ~2-5mg/mL total protein. The HAs were biotinylated by the addition of 25μg BirA enzyme/mg total protein, in a buffer of the following composition: 100mM Tris pH 8.0, 10mM ATP, 10mM MgOAc, 50μM biotin, with less than 50mM NaCl. The biotinylation reactions were incubated at 37°C for 1-2 hours. Biotinylated HAs were purified by size exclusion chromatography, and concentrated to ~5-20 mg/mL.

**$K_D$ determination.** $K_D$'s were determined by bio-layer interferometry using an Octet Red instrument (ForteBio, Inc.). Bio-layer interferometry is conceptually similar to surface plasmon resonance experiments in that a protein of interest is immobilized on a surface and then exposed to potential binding partners in solution. The binding of analytes to the immobilized protein changes the optical properties of the biosensor's, leading to a shift in the wavelength of light reflected off the binding surface. This shift in wavelength can be measured in real-time, allowing the measurement of association and dissociation rates

and therefore, $K_D$. Biotinylated HAs, purified as described above, were used for these measurements. HAs at ~10-50 μg/mL in 1x kinetics buffer (1x PBS, pH 7.4, 0.01% BSA, and 0.002% Tween 20) were loaded onto streptavidin coated biosensors and incubated with varying concentrations of CR8020 Fab in solution. All binding data were collected at 30°C. The experiments comprised 5 steps: 1. Baseline acquisition (60 s); 2. HA loading onto sensor (600 s); 3. Second baseline acquisition (180-600 s); 4. Association of CR8020 for the measurement of $k_{on}$ (180-600 s); and 5. Dissociation of CR8020 for the measurement of $k_{off}$ (180-600 s). 4-6 concentrations of CR8020 were used, with the highest concentration being 50 nM. Baseline and dissociation steps were carried out in buffer only. The ratio of $k_{on}$ to $k_{off}$ determines the $K_D$ reported here. The sequences of all proteins used in this work are available in Fasta format at the end of this document. All binding traces and curves used for fitting $k_{on}$ and $k_{off}$ are reported in Figs. S10 and S11.

**Isolation of the CR8020-HK68/H3 HA complex.** To determine the optimal ratio of Fab to HA to saturate all of the CR8020 binding sites on HA, CR8020 at 1mg/mL was titrated into 10ug HK68/H3 HA. The reaction was allowed to incubate for ~30 minutes at room temperature and binding of the Fab CR8020 to HA was assayed by gel-shift using Blue Native PAGE (Invitrogen).

CR8020 Fab and purified HK68/H3 HA, in 10mM Tris pH 8.0, 150mM NaCl at ~1mg/mL, were mixed at the optimal ratio determined in the titrations described above (usually estimated to be ~3 Fabs per trimer). The mixtures were incubated overnight at

4°C to allow complex formation. Saturated complexes were then purified from unbound Fab by gel filtration.

**Crystallization and structure determination of the CR8020- HK68/H3 HA complex**

Gel filtration fractions containing the CR8020-HK68/H3 HA complex were concentrated to ~10mg/mL in 10mM Tris, pH 8.0 and 50mM NaCl. Initial crystallization trials were set up using the automated Rigaku Crystalmation robotic system at the Joint Center for Structural Genomics (www.jcsg.org). Several hits were obtained, with the most promising candidates grown in ~2.0-2.5M ammonium sulfate between pH 5 and 7. Optimization of these conditions resulted in diffraction quality crystals. The crystals used for data collection were grown by the sitting drop vapor diffusion method with a reservoir solution (1mL) containing 1.8M ammonium sulfate, 100mM sodium acetate 5.4, and 50mM NaCl. Drops consisting of 0.5μL protein + 0.5μL precipitant were set up at 4°C, and crystals appeared within 3-7 days. The resulting crystals were cryoprotected by soaking in well solution supplemented with increasing concentrations of ethylene glycol (5% steps, 1hr/step), to a final concentration of 20%, then flash cooled and stored in liquid nitrogen until data collection.

Diffraction data for the CR8020-HK68/H3 complex were collected on 9-2 beamline at the Stanford Synchrotron Radiation Lightsource (SSRL). The data were indexed in spacegroup $P2_13$, integrated using HKL2000 (HKL Research), and scaled using Xprep (Bruker). The structure was solved by molecular replacement to 2.85 Å resolution using Phaser (*S10*). A protomer from 2VIU (HK68/H3 HA) was used as the initial search

model and a single copy was found in the asymmetric unit (*S11*). Examination of the maps at this stage revealed clear positive electron density around the membrane proximal end of HA. A subsequent search with the variable and constant domains from PDB codes 1VGE and 1MIM, respectively yielded good solutions for a single Fab fragment (*S12, 13*). At this point, poorly defined regions of the model were trimmed and the Fab was mutated *in silico* to match the CR8020 sequence. Rigid body refinement, simulated annealing and restrained refinement (including TLS refinement, with one group for HA1, one for HA2, and one for each Ig domain) were carried out in Phenix (*S14*). Between rounds of refinement, the model was built and adjusted using Coot (*S15*). A total of 10 sulfate molecules (from the crystallization medium) were built in locations with very strong $F_O$-$F_C$ density in close proximity to positively charged residues. Additional positive electron density was observed near all 6 of the potential N-linked glycosylation sites, and a total of 20 sugar residues were built in at 5 sites (density at the remaining to site was too weak/diffuse to model reliably). Additional density was also observed around the glycan linked to Asn38 in HA2 suggesting that this glycan may adopt an alternate or even an ensemble of conformations. Nevertheless, the predominant conformation could be modeled well and is included in the final model. Refinement statistics can be found in Table S2.

**Structural analyses**. Hydrogen bonds and van der Waals' contacts between CR8020 and HK68/H3 HA were calculated using HBPLUS and CONTACSYM, respectively (*S16, 17*). Surface area buried upon Fab binding was calculated with MS (*S18*). MacPyMol

(DeLano Scientific) was used to render structure figures and for general manipulations. Kabat numbering was applied to the coordinates using the AbNum server (S*19*). The final coordinates were validated using the JCSG quality control server (v2.7), which includes Molprobity (S*20*).

**Sequence analysis of CR8020 epitope conservation**. All full-length, non-redundant, and non-lab strain influenza A HA sequences were downloaded from the NCBI FLU database (S*21*). At the time of download (August 7, 2010), the dataset included 8720 sequences encompassing all 16 influenza A subtypes, of which 5813 and 2907 sequences were from group 1 and group 2 viruses, respectively. The sequences were aligned using MUSCLE (S*22*) and analyzed using GCG (Accelrys) and custom shell scripts (available from the authors upon request). In this analysis, residues are considered conserved if substitutions are restricted to other amino acids in the same group: 1) Asp, Asn, Glu, Gln; 2) Val, Ile, Leu, Met; 3) Phe and Tyr; and 4) Ser and Thr. The values reported for percent conservation are the number to sequences with an identical or conservative change at a position divided by the total number of sequences.

**Generation of neutralization-resistant virus variants.** A/Hong Kong/1/1968 (H3N2) virus was cultured in the presence of CR8020 IgG for 4 passages. As a reference, control experiments without antibody were done in parallel. Serially diluted viruses were first incubated with 5 μg/ml antibody for 1 hour at 37 °C. This concentration of antibody was shown to reduce the viral infectious titre of A/Hong Kong/1/1968 by 3 log units (data not

shown). The incubated mixture was absorbed by MDCK cells for 1 hour. Infected cells were washed twice with PBS and replenished with infection medium complemented with 5 μg/ml antibody. CPE of infected cells was monitored 72 hours after infection. Supernatants from CPE positive wells infected with the lowest viral titre were harvested for a consecutive round of infection. The HA sequence of the viruses obtained after passage 4 were sequence analysed.

**FACS assay conformational change.** Full-length recombinant influenza A subtype H3 (A/Wisconsin/67/2005, A/Hong Kong/24/1985 or A/Hong Kong/1/1968), H7 (A/Netherlands/219/2003), and H10 A/Greater white fronted goose/California/HKWF446/2007 HA were expressed on the surface of PER.C6® cells by transient transfection using pcDNA-based vectors using Lipofectamine (Invitrogen). To measure mAb binding to different structural HA conformations, cells were detached from the plastic support using PBS-EDTA and subsequently treated with trypsin (TrypLE™Select, Gibco) for 5 min at RT, washed (1% BSA in PBS) and incubated for 15 min in citric acid–sodium phosphate buffer (pH 4.9), washed, and then incubated for 20 min in the presence of 50 mM DTT in PBS at RT. Cell samples were set aside after each processing step (untrypsinized/HA0; trypsinized/HA1-HA2; pH 4.9/fusion HA; post-reduction/tHA2) and fractions of each treatment were incubated with CR8020 and CR8057 (binding to the globular head of recent H3 HAs) or CR8011 (binding to the globular head of H7 HA) IgGs for 1 hour. Cells were then incubated for 30 min with phycoerythrin-conjugated anti-human IgG (Southern Biotech) in 1% BSA. Alternatively,

CR8020 IgG was added before the low pH step. Samples of consecutive treatments were split and stained with either phycoerythrin-conjugated anti-human IgG (Southern Biotech) or HA1 specific AlexaFluor488-conjugated CR8057 or CR8011. Stained cells were analysed using a FACS Canto with FACS Diva software (Becton Dickinson).

**Protease susceptibility assay.** For A/Hong Kong/1/1968(H3N2) HA, each reaction contained ~2.5 μg HA or ~5 μg Fab-HA complex (complex purified by gel filtration, 1 Fab per HA protomer). For A/Netherlands/219/2003(H7N7), each reaction contained ~2.5 μg HA or ~2.5 μg HA and a 10-fold molar excess of Fab (~10 Fabs per HA protomer). For A/Netherlands/219/2003(H7N7), inhibition was only detected with a high ratio of Fab to HA, presumably due to the stringency of our assay (1 hour at 37°C at low pH) and the lower affinity of CR8020 for H7 compared with H3 (~30-fold lower); little protection was observed when the reaction contained approximated 1 Fab per HA protomer. All reactions contained 1% dodecylmaltoside (to prevent aggregation of the post-fusion HA). Reactions were set up at room temperature and the pH was lowered by adding 100 mM buffer to all samples except controls. Sodium acetate was used for pH ranges 4.9 to 6.1, and PIPES buffer was used for pH 6.2 to 7.4 and Tris was used for pH 7.5 and above. Reactions were thoroughly mixed, centrifuged at >12,000g for 30 seconds and allowed to incubate at 37 °C for one hour. After incubation, reactions were equilibrated to room temperature and the pH was neutralized by addition of 200 mM Tris, pH 8.5. The actual pH reached during the low pH-treatment was determined in parallel using larger buffer volumes, but no protein. Trypsin was added to all samples except

controls, at a final ratio of 1:1 by mass for H3, and 1:10 for H7, and digested overnight (~18 hours) at 22 °C. Reactions were quenched by addition of non-reducing SDS buffer and were boiled for ~2 min. Samples were analyzed by SDS-PAGE. To determine the pH required to convert 50% of the HK68/H3 HA to the post-fusion form in 1 hour, pH titrations were carried out using the assay described above to monitor conversion. Samples were exposed to a range of pH, then neutralized and processed as described above. The resulting SDS-PAGE gels were quantified using ImageJ (S*23*) and analyzed using Prism (GraphPad).

**Trypsin cleavage inhibition assay.** Recombinant soluble H3 HA (A/Wisconsin/67/2005; Protein Sciences, CT, USA; 0.4 μg) was incubated in the presence of 2.5 μg CR8020 IgG, control "α-head" mAb CR8057, or in the absence of antibody in 4 mM Tris HCl buffer at pH 8.0 containing 6.7 μg/ml Trypsin-EDTA (Gibco) and 1% N-dodecyl-β-maltoside (Sigma). Trypsin digestion was stopped at several time-points by addition of 1% BSA. Samples were run on SDS-page gel (reduced) and blotted according to standard methods. HA0 bands were detected using a rabbit anti-H3 HA polyclonal antibody (Protein Sciences, CT, USA).

**Statistical analyses.** Statistical analysis of bodyweight was based on Area Under the Curve (AUC) analysis. For the purpose of this analysis, the last observed bodyweight was carried forward if a mouse died / was euthanized during follow-up of the study. Briefly, the weight per mouse at day 0 was used as baseline and weight change was determined relative to baseline. The AUC was defined as the summation of the area above and below

the baseline. Mean AUC values were compared using analysis of variance with Dunnett's T3 adjustment for multiple comparisons. In addition, bodyweight expressed as change from baseline was calculated at the end of study (or at death if earlier) and compared to baseline using a T-test. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, USA) and PASW Statistics version 17.0.3 (SPSS Inc, USA). Statistical significance level was set at $\alpha$=0.05.

**Immunogold electron microscopy.** Supernatant of PER.C6® cells infected for 3 days with A/NYMC/X-161B was cleared by centrifugation (10 min, 1000 g), filtered (0.45µm, Corning), and concentrated by ultracentrifugation (30 ml supernatant, 5 ml 25% sucrose cushion, 2 hours, 27000 rpm, SW28, Beckman Coulter). Virus pellet was dissolved overnight at 4 °C in 200 µl NTE buffer (100 mM NaCl, 10 mM Tris-HCl, 1 mM EDTA, pH 7.4). Purified virus (5 µl, ~$10^9$ pfu/ml diluted 1:4 in IAD buffer, 1 mM PBS, 2% BSA, 0.1% Tween 20) was incubated with the primary antibody (5 µl, 0.2 mg/ml IgG or PBS (Gibco) for 60 min at room temperature. Next, 10 µl virus–antibody complex was transferred to formvar-coated mesh copper grids (Storck-Veco), washed before and after incubation with 10 nm gold-labeled protein A (1 hour, Aurion, diluted 1:80 in IAD buffer) for 2 min with IAD buffer, and fixed with 1.5% glutaraldehyde in cacodylate buffer (5 min, Sigma-Aldrich). Virus–antibody–protein A complexes were stained with 2% STA (Tungsto-silicic acid in water, Electron Microscopy Sciences) and examined in a transmission electron microscope at 120 kV (Tecnai12 Biotwin equipped with a 4K

Eagle CCD Camera, FEI company). At least 5 randomly chosen fields per grid were imaged.

**Structural differences in the H3 HA in the low pH structure.** It is interesting to note two further subtle changes in the HA in this low pH structure of the complex with CR8020. First, the heads of the HA have opened up slightly compared to other HA structures determined at high pH (Fig. S9A). The motion is consistent with a rigid body rotation of the receptor binding domains about a point at the interface with the vestigial esterase domain, leading to a maximal Cα displacement of ~2.5Å for residues near the receptor binding site, in the region most distal from the point of rotation. This observation suggests that the heads have been "unlatched" to initiate the complex refolding of HA2 to its post-fusion state, but CR8020 is able to block the subsequent steps in the process. A similar observation was noted in the structure of the 1918 H1 HA in complex with the fusion-inhibiting antibody CR6261, in which the crystals were grown below the fusion pH (*S6*). Second, the B-loop of HA2 adopts multiple conformations and appears to be much more flexible than in H3 neutral-pH structures (Fig. S9B). The B-loop adopts an extended conformation in the pre-fusion ectodomain, and connects helix A to the top of the long, central, C/D helix. Upon exposure to low pH, this loop is converted to an extension of the central helix, yielding the continuous A/B/C helix observed in the post-fusion conformation. While the B-loop is usually well ordered and associated with the inner surface of the HA1 heads, the opening of the heads appears to have released this loop at low pH or vice-versa, allowing it to sample potential

intermediate conformations along the folding pathway towards the post-fusion state. A similar increase in B-loop mobility was also recently reported in a low pH crystal structure of an H2 fusion mutant (S*24*).

**Presence of Asp19Asn escape mutant in circulating H7 viruses.** Due to the nature of the sequence data available, the analyses presented here can only give a rough picture of the natural variation present in the CR8020 epitope. Biased sampling of viruses for sequencing can profoundly alter the apparent frequency of particular mutations. In the case of H7 viruses, a total of 460 H7 sequences are available and 113 have Asn at position 19. This analysis would appear to suggest that ~25% of all H7 viruses will be resistant to CR8020. However, 108 of these 113 Asp19Asn isolates were sampled from1997-2006 in the northeastern USA (NE-USA). During 1997-2006, a total of 142 strains were sequenced from the NE-USA, out of only 276 isolates globally. Thus, while Asp19Asn may be relatively common in the NE-USA (108/142 or ~76%), it is rare elsewhere (5/310 or ~1.6% of sequences from 1900-1996 (global), 1997-2006 (outside NE-USA), and 2007-2010 (global)). A crude correction based upon the surface area of the NE-USA relative to global land surface area suggests that the overall frequency of Asp19Asn may, therefore, be approximated worldwide as only around 2%.

**Fig. S1**. **Binding of CR8020 to intact virions.** TEM images of purified A/NYMC/X-161B (H3N2) virus incubated with control mAb + ProtA-10nm-Gold (left panel), or mAb CR8020 + ProtA-10nm-Gold (right panel). Scale bars 100 nm.

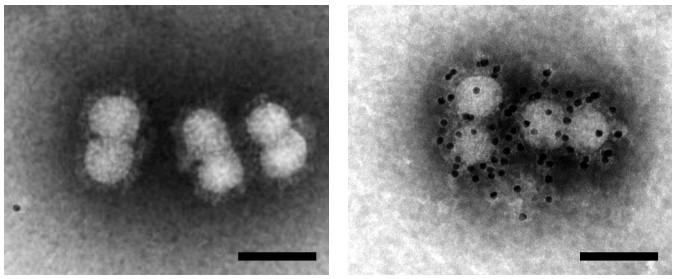
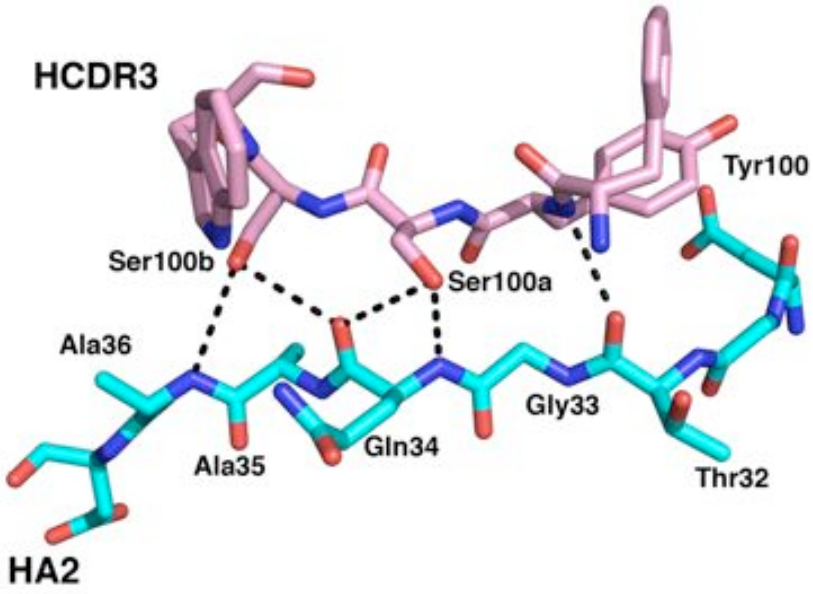


**Fig. S2**. **Sequence-independent recognition of the edge of the outermost strand of the small β-sheet by HCDR3.** HCDR3 of CR8020 interacts with the backbone atoms of the edge of the small β-sheet, explaining the antibody's tolerance for numerous substitutions in this region. HCDR3 is colored in pink and the β-strand from HA2 is colored cyan.



F**ig. S3**. **Alignment of the fusion peptide consensus sequence of each of the 16 influenza A hemagglutinin subtypes**. Identity across most subtypes is indicated in black blocks. Conservation across most subtypes is indicated in gray blocks. Residues conserved within group 1 versus group 2 are highlighted in orange and cyan, respectively. Note that while the asparagines at position 19 in H11, H13, and H16 in group 2 would generally be regarded as conservative substitutions relative to aspartate (both residues having roughly the same size, shape, and hydrogen bonding potential), they are bolded and boxed in light gray here to highlight that, in the context of CR8020 binding, they are non-conservative, since D19N escapes antibody neutralization.

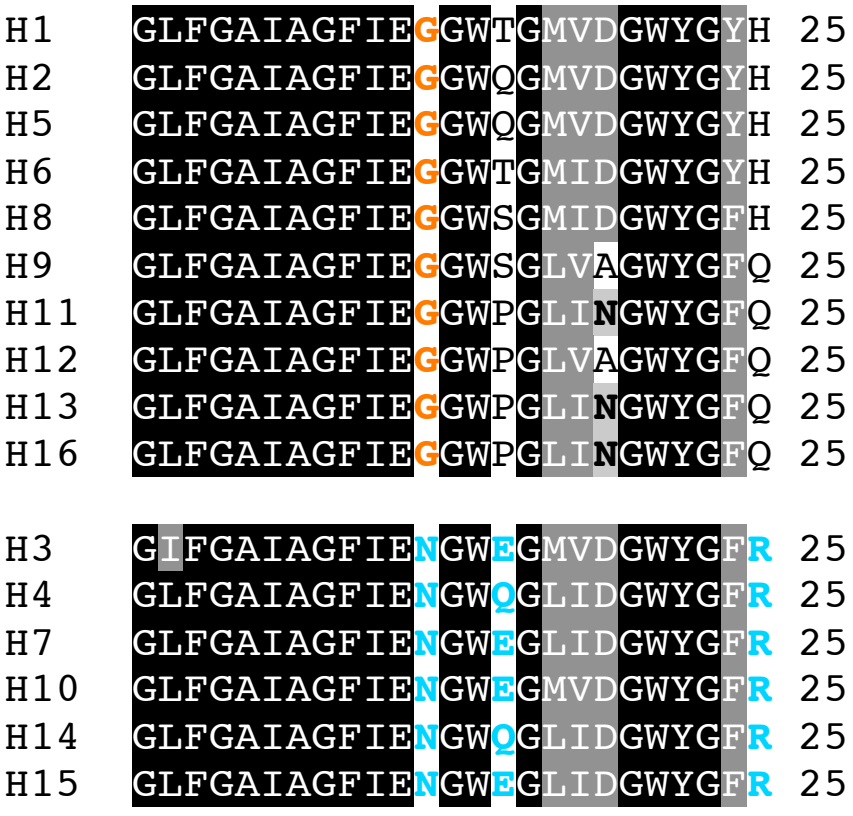


**Fig. S4. CR8020 contact residues map to key elements of the membrane fusion machinery**. A) HA2 positions 15, 16, 18, and 19 all reside within the fusion peptide, which is highly conserved across most of the 16 influenza A subtypes. Note that while Glu15 is well conserved within group 2 HAs, the fusion peptide structure is derived from a group 1 (H1) hemagglutinin, where Thr15 is most common. B) Epitope residues 32-38 form the N cap motif in the post-fusion state. Formation of the cap may provide some of the necessary free-energy to drive the membrane fusion process.

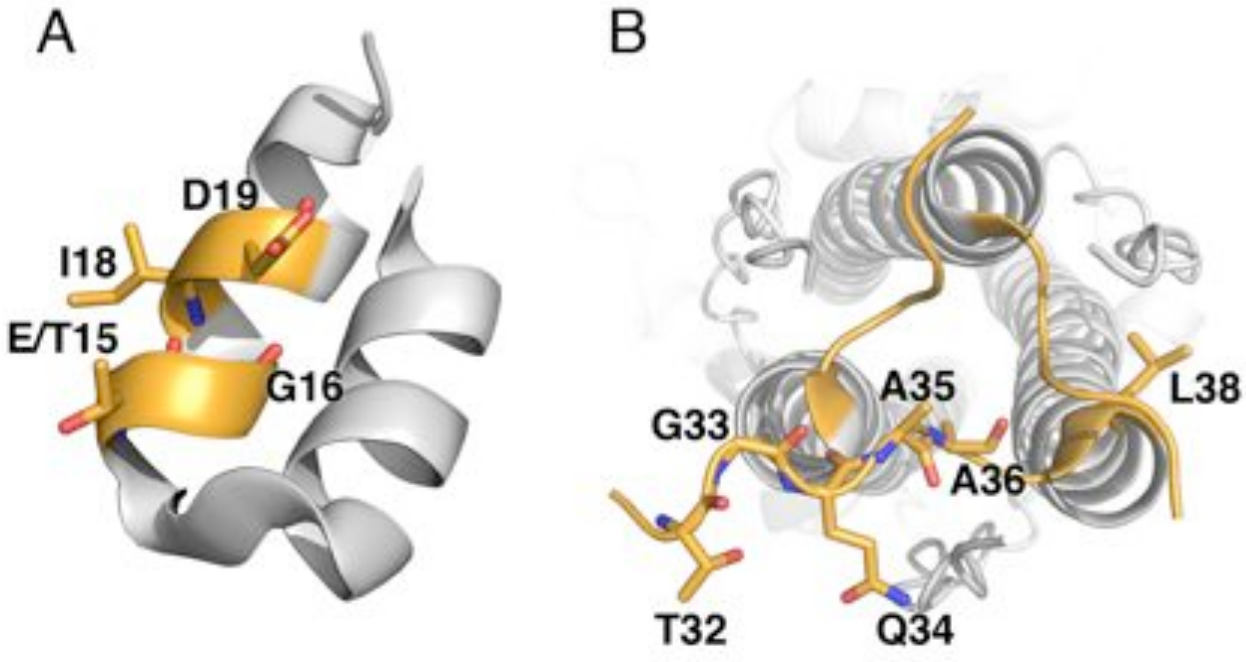


**Fig. S5**. **Frequency of CR8020 escape mutations in group 2 subtypes.** Fraction of all sequences in the dataset (see Materials and Methods) with possible escape mutations at HA2 positions 19 and 33. All strains bound with high affinity and/or neutralized by CR8020 have Asp19 and Gly33. Any substitution away from this consensus is reported as a possible escape. Nearly all of these substitutions are Asp19Asn. Note that the frequency plotted for Asp19Asn in H7 reflects our best estimate of the true frequency for this mutation, as discussed above.

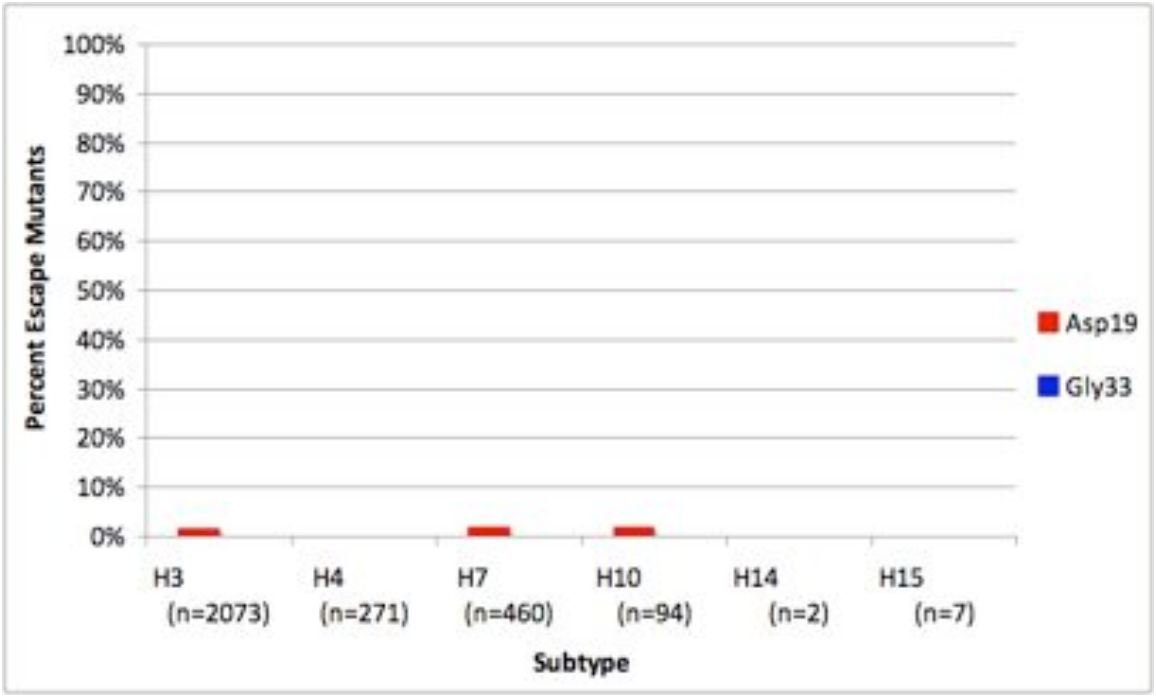


**Fig. S6. Glycosylation of HA1:Asn21 blocks the CR8020 epitope in group 1HAs .** A complex glycan modeled onto the CR8020-HK68 structure at HA1 position 21 projects directly into the middle of the Fab variable domains and is expected to completely abolish binding to all HA subtypes that have a glycosylation site at this position (all group 1 HAs).

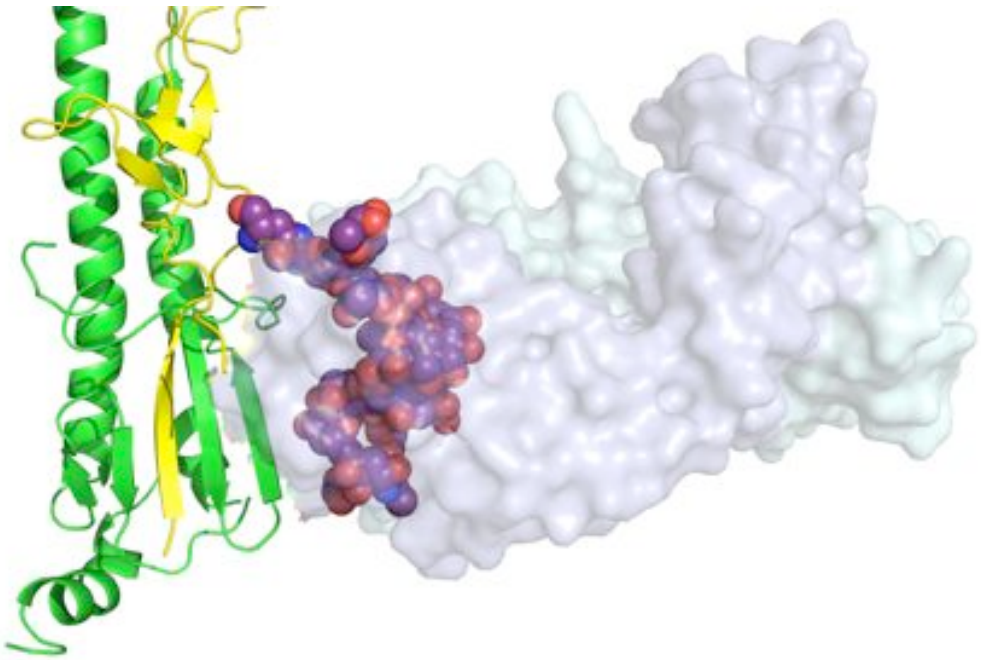


**Fig. S7. Blocking of conformational change of H7 and H10 HAs by CR8020.** (A) FACS binding of CR8020 (open bars) and CR8011 – binding to the globular head of H7 HA – (closed bars) to various conformations – uncleaved precursor (HA0); neutral pH, cleaved (HA); fusion pH, cleaved (fusion pH); trimeric HA2 (tHA2) – of surface-expressed rHA of A/Netherlands/219/2003 (H7) and A/Greater white fronted goose/California/HKWF446/2007 (H10). Binding is expressed as the percentage of binding to untreated rHA (HA0). Error bars represent SD of data obtained in 3 independent experiments. (B) FACS binding of CR8020 (open bars) and CR8011 (closed bars) to surface-expressed HA as above, except that mAb CR8020 was added before exposure of the cleaved HAs to a pH of 4.9. Please note that due to the presence of poly-basic amino acids in the cleavage site of A/Netherlands/219/2003 (H7) part of the untreated HA (designated HA0) is, in fact, likely to be cleaved. However, CR8020 binds with high affinity to both cleaved H7 HA and uncleaved H7 HA0. No monoclonal antibody specific for the globular head of H10 HA was available.

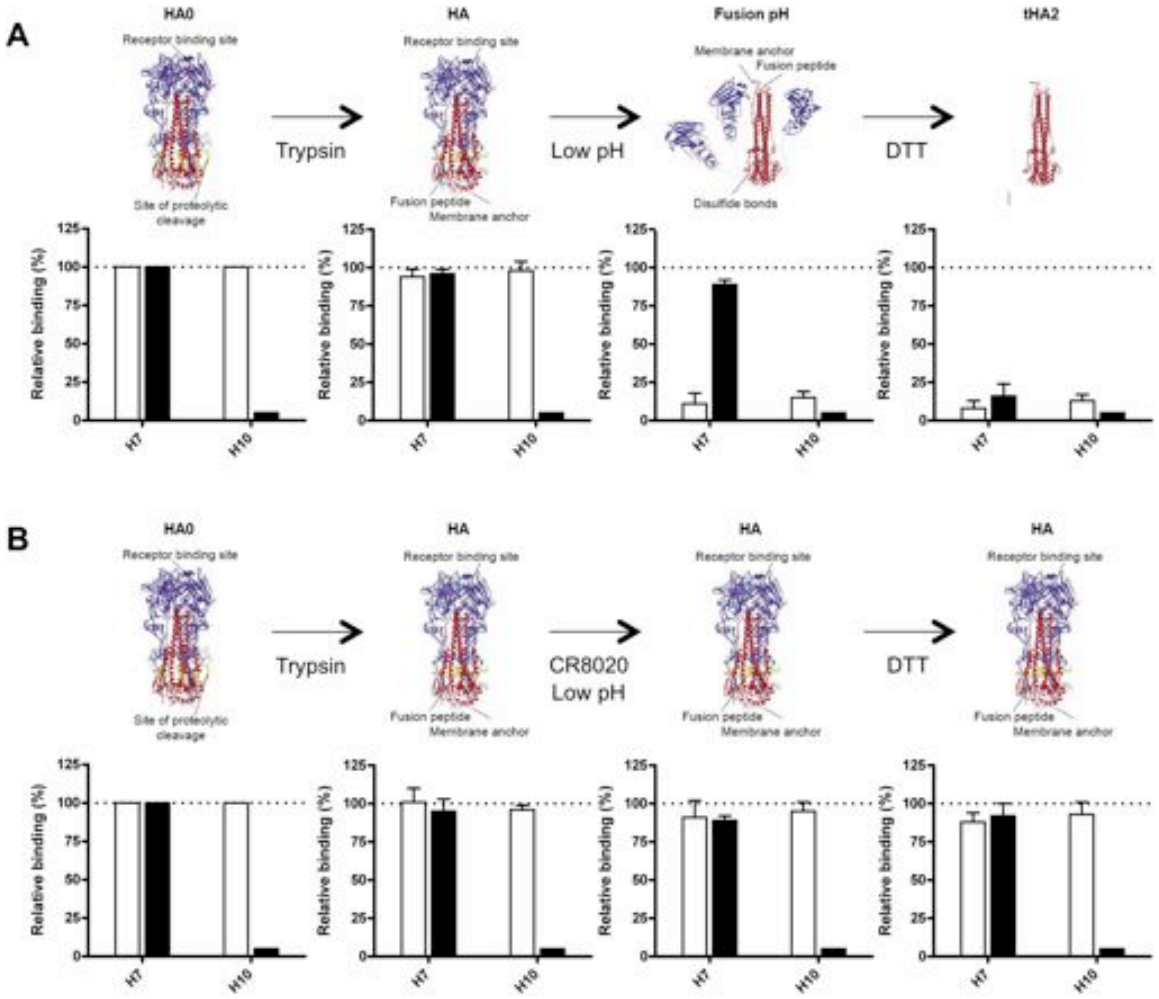

A
HA0
Receptor binding site
Site of proteolytic cleavage
Trypsin
HA
Receptor binding site
Fusion peptide
Membrane anchor
Low pH
Fusion pH
Membrane anchor
Fusion peptide
Disulfide bonds
DTT
tHA2
Relative binding (%)
125
100
75
50
25
0
H7
H10
B
HA0
Receptor binding site
Site of proteolytic cleavage
Trypsin
HA
Receptor binding site
Fusion peptide
Membrane anchor
CR8020
Low pH
HA
Receptor binding site
Fusion peptide
Membrane anchor
DTT
HA
Receptor binding site
Fusion peptide
Membrane anchor
Relative binding (%)
H7
H10

**Fig. S8. pH Titration of HK68/H3 HA to determine fusion pH.** HK68/H3 HA was exposed a range of pHs (4.9-8.0) and subjected to trypsin digestion as described above. The pH resulting in 50% conversion of the HA to the post-fusion state under these conditions was ~5.4.

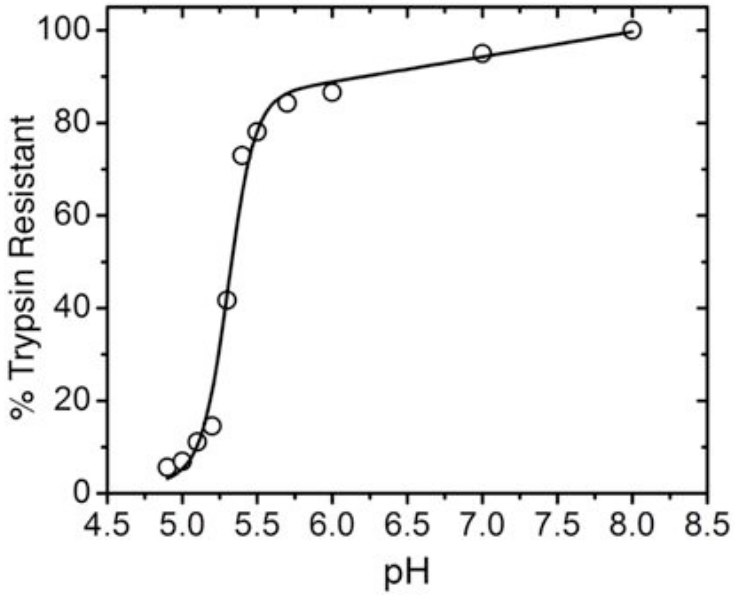


**Fig. S9. pH-induced conformational changes in HK68 HA in the CR8020-H3 crystal structure.** A) In the low pH environment of the crystal, the HA1 heads have opened up slightly. The neutral pH H3 structure (PDB code 2VIU) is shown in blue and the low pH H3 from the CR8020 complex is in pink. B) The predominant conformation of loop B is different in the neutral and low pH structures. Coloring is as in A.

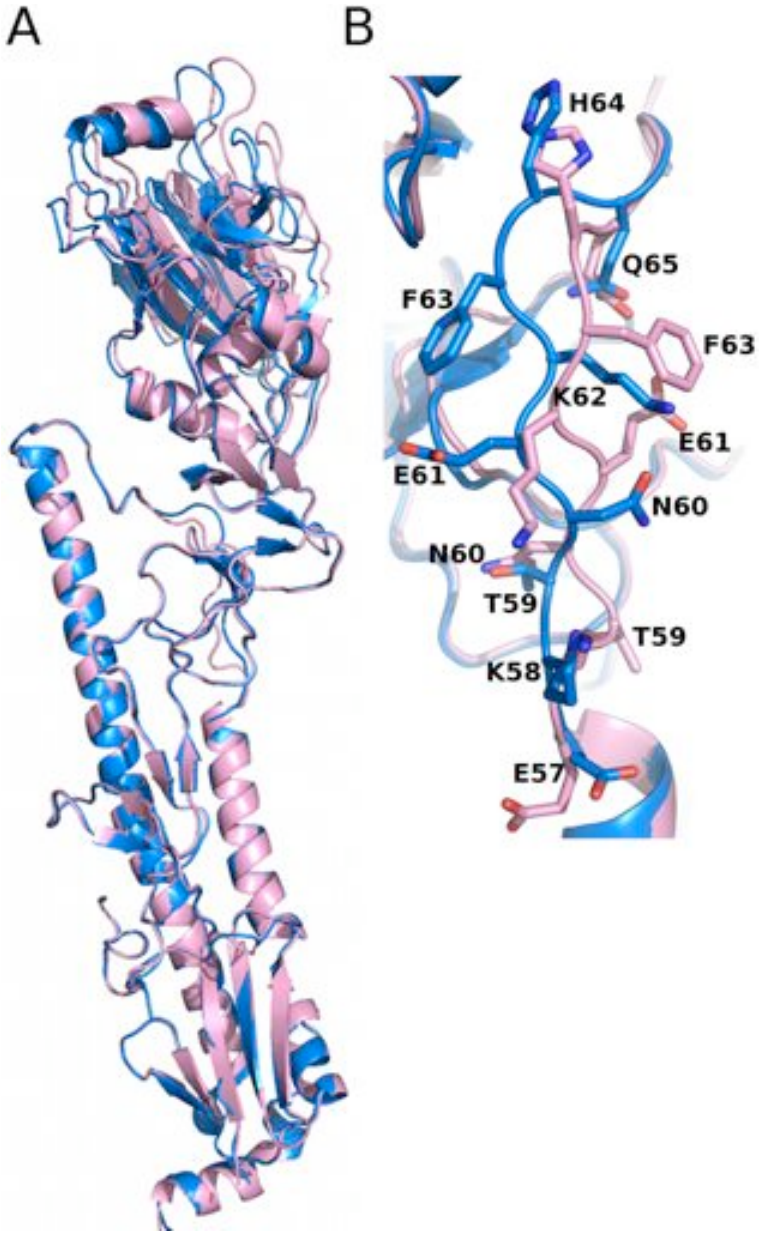
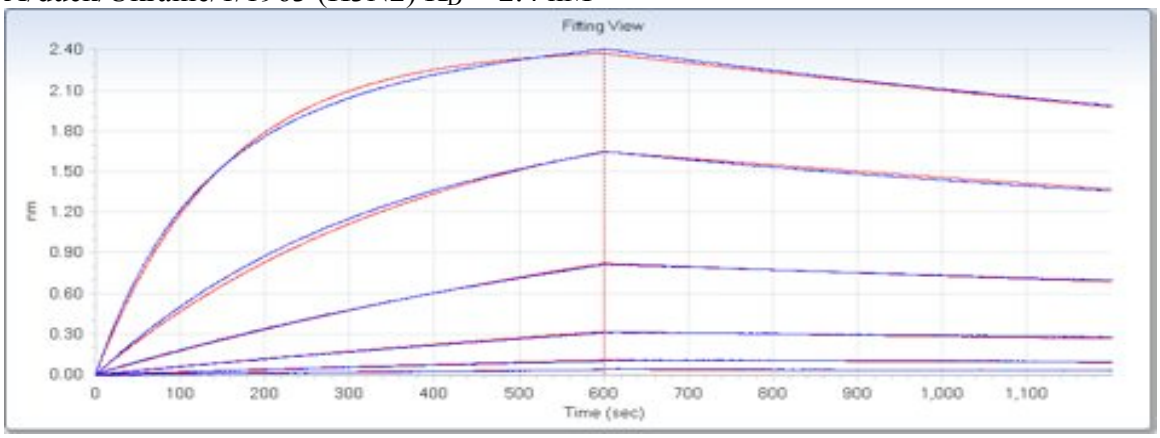
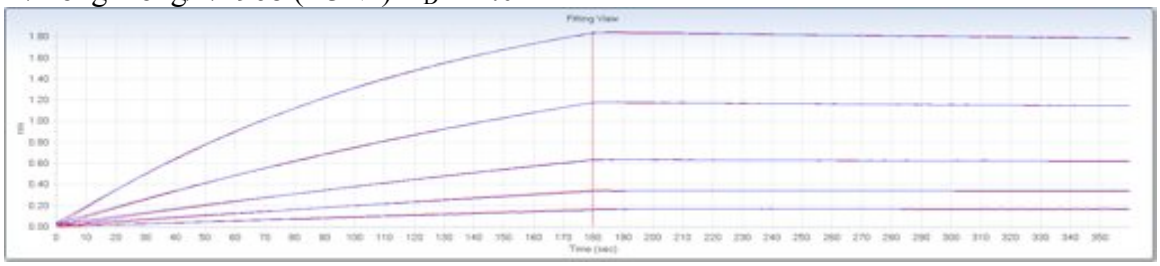


**Fig. S10. Binding curves for reported $K_d$ values.** Blue curves are the experimental trace obtained from biolayer interferometry experiments, and red curves are the best global fits to the data used to calculate the $K_D$'s.

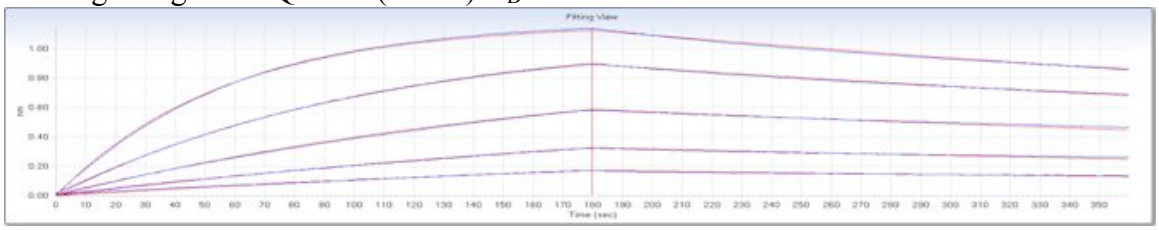
A/duck/Ukraine/1/1963 (H3N2) $K_D$ = 2.4 nM



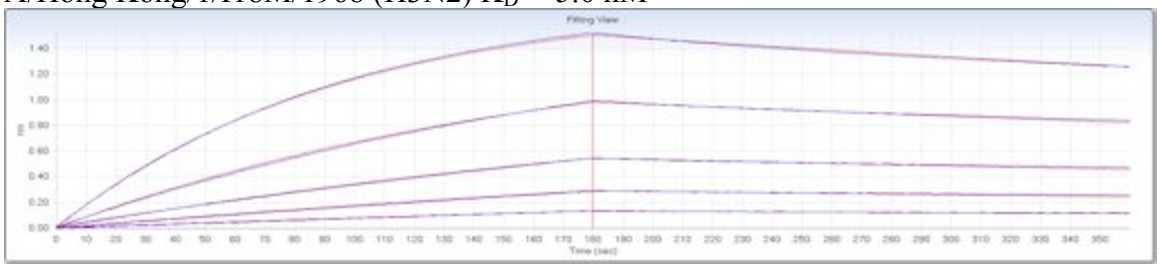

A/Hong Kong/1/1968 (H3N2) $K_D$ = 1.0 nM



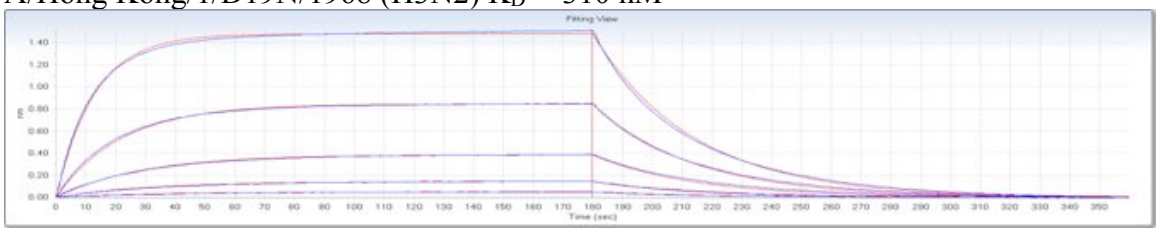
A/Hong Kong/1/E15Q/1968 (H3N2) $K_D$ = 9.3 nM



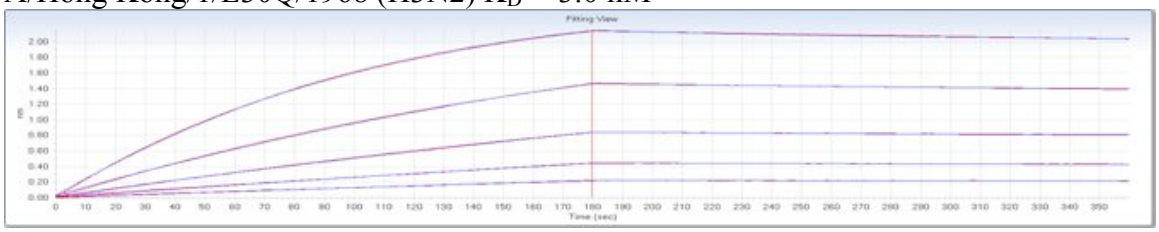
A/Hong Kong/1/I18M/1968 (H3N2) $K_D$ = 5.0 nM



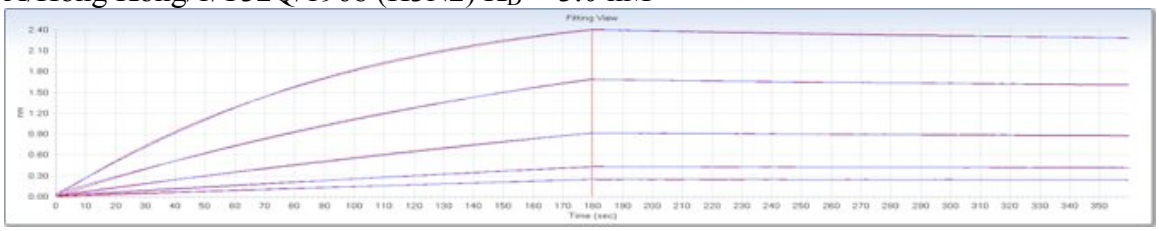
A/Hong Kong/1/D19N/1968 (H3N2) $K_D$ = 310 nM



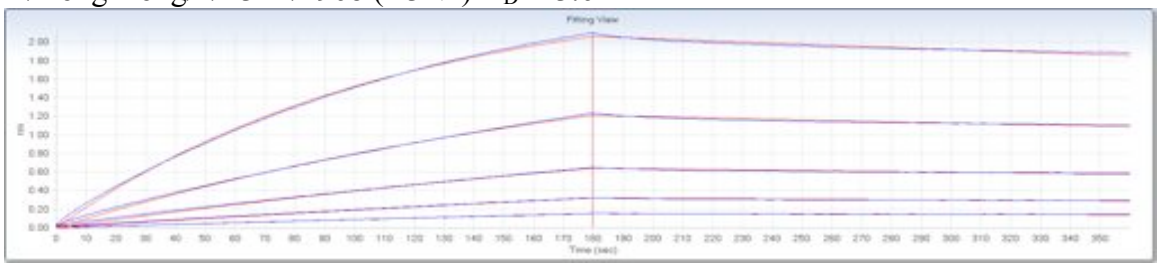
A/Hong Kong/1/E30Q/1968 (H3N2) $K_D$ = 3.0 nM



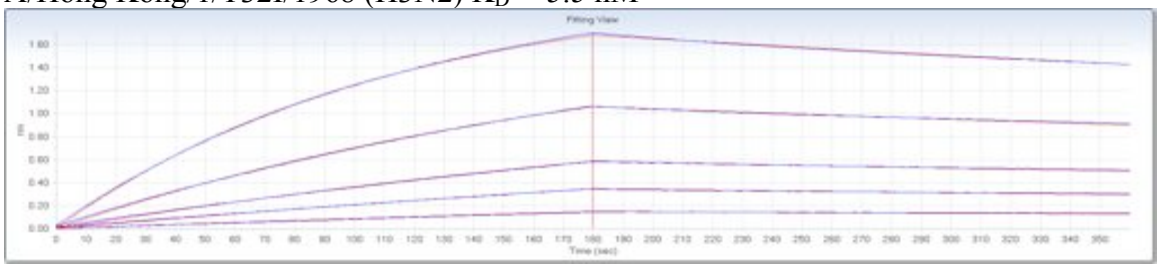
A/Hong Kong/1/T32Q/1968 (H3N2) $K_D$ = 3.0 nM



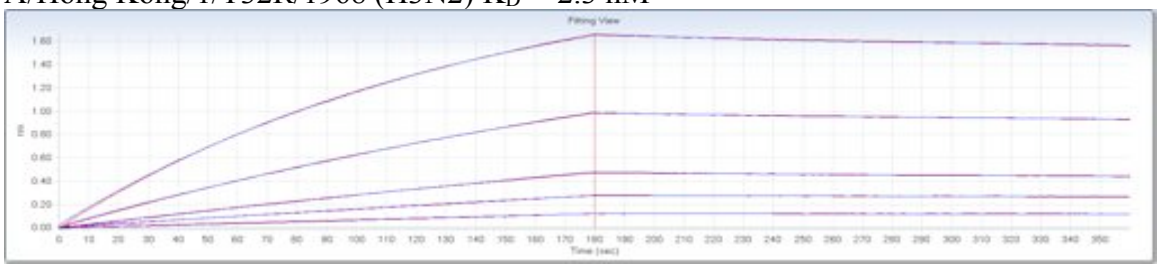
A/Hong Kong/1/T32E/1968 (H3N2) $K_D$ = 3.6 nM



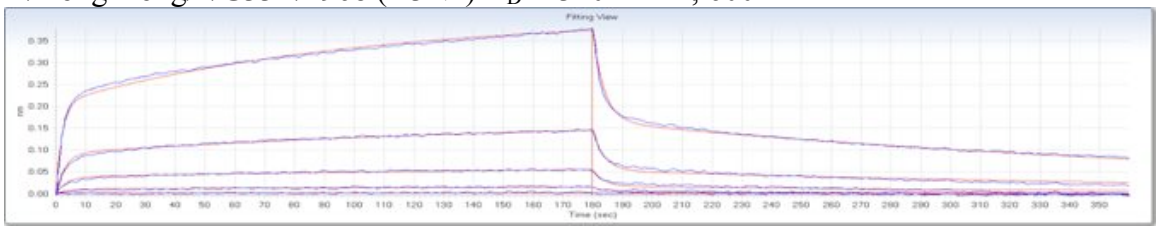
A/Hong Kong/1/T32I/1968 (H3N2) $K_D$ = 5.5 nM



A/Hong Kong/1/T32R/1968 (H3N2) $K_D$ = 2.3 nM

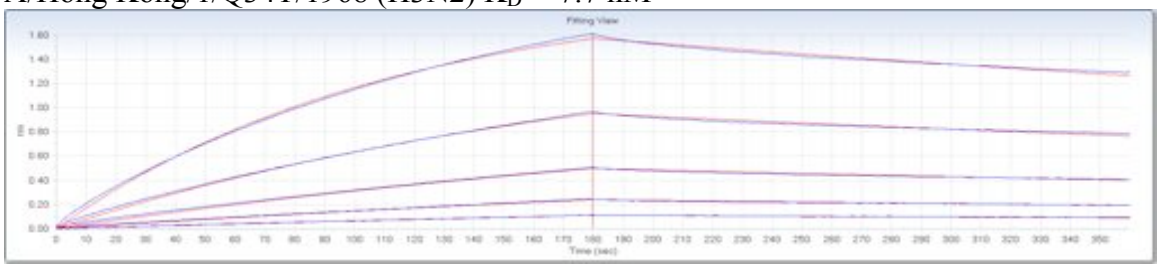


A/Hong Kong/1/G33E/1968 (H3N2) $K_D$ = 340 nM**, 600 nM**

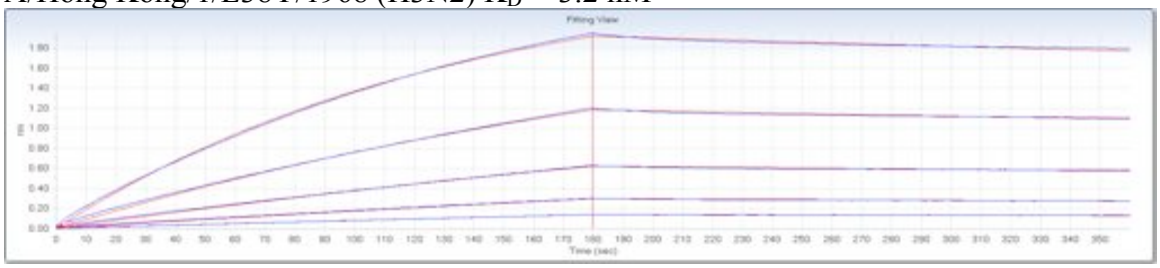


** Binding curves for the G33E mutant could only be fit with a 2:1 model, with apparent $K_{D1}$ = 600nM, $K_{D2}$ = 340nM. While most other experiments reported here used a maximum CR8020 Fab concentration of 50nM, the weak binding to this mutant necessitated the use of higher Fab concentrations (up to 500nM). At 250 and 500nM CR8020, a small degree of non-specific interaction of the Fab with the sensor was observed, while at lower concentrations this interaction was undetectable. One of these binding processes may reflect this non-specific interaction with the sensor. However, this analysis may also indicate multiple binding modes to this mutant. Due to this uncertainty, we report this $K_D$ as approximately 500 nM.

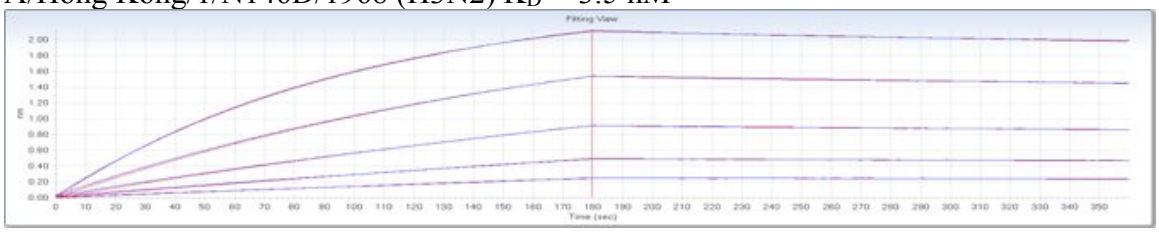
A/Hong Kong/1/Q34T/1968 (H3N2) $K_D$ = 7.7 nM



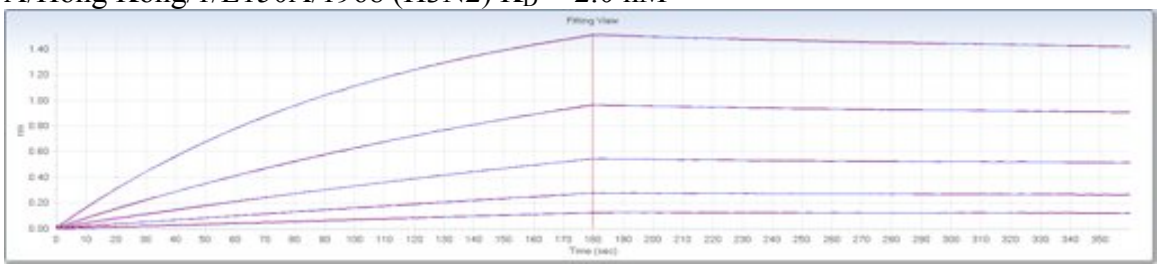
A/Hong Kong/1/L38Y/1968 (H3N2) $K_D$ = 3.2 nM



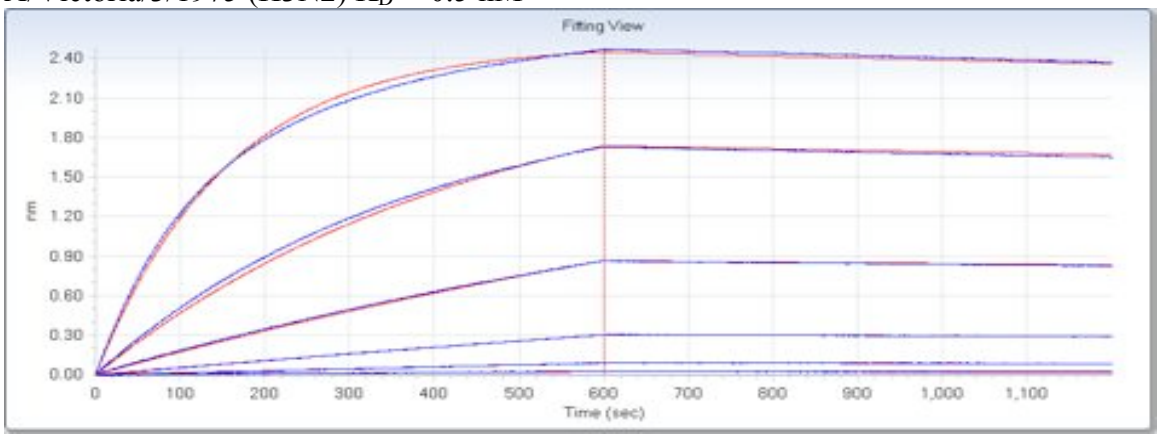
A/Hong Kong/1/N146D/1968 (H3N2) $K_D$ = 3.5 nM



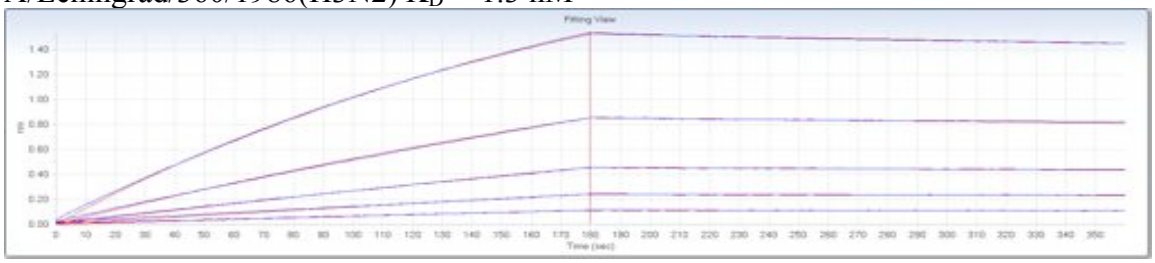
A/Hong Kong/1/E150A/1968 (H3N2) $K_D$ = 2.0 nM



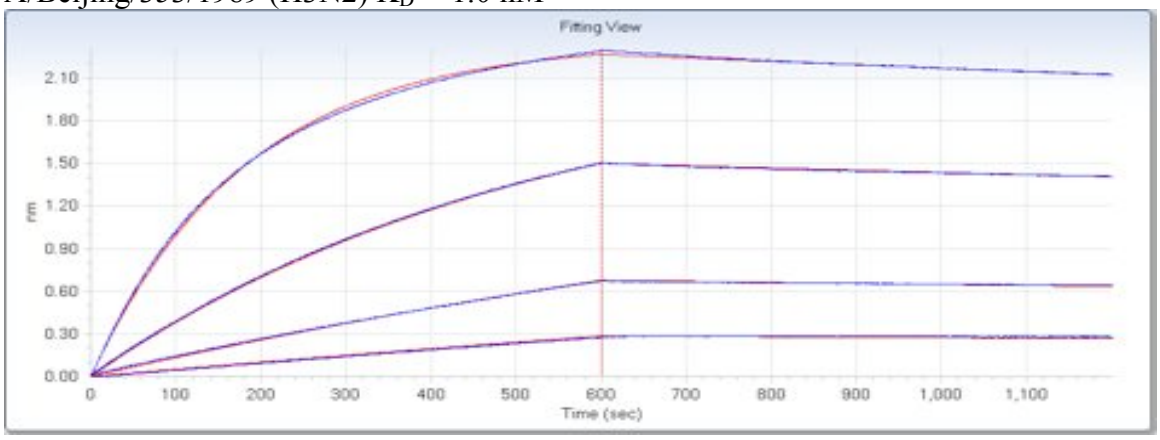
A/Victoria/3/1975 (H3N2) $K_D$ = 0.5 nM



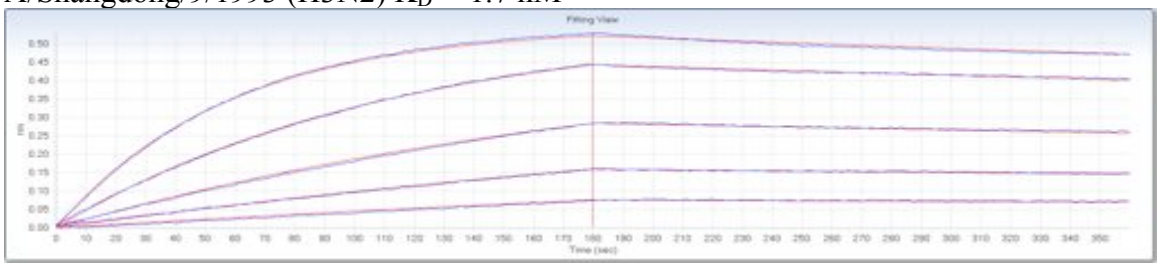
A/Leningrad/360/1986(H3N2) $K_D$ = 1.3 nM



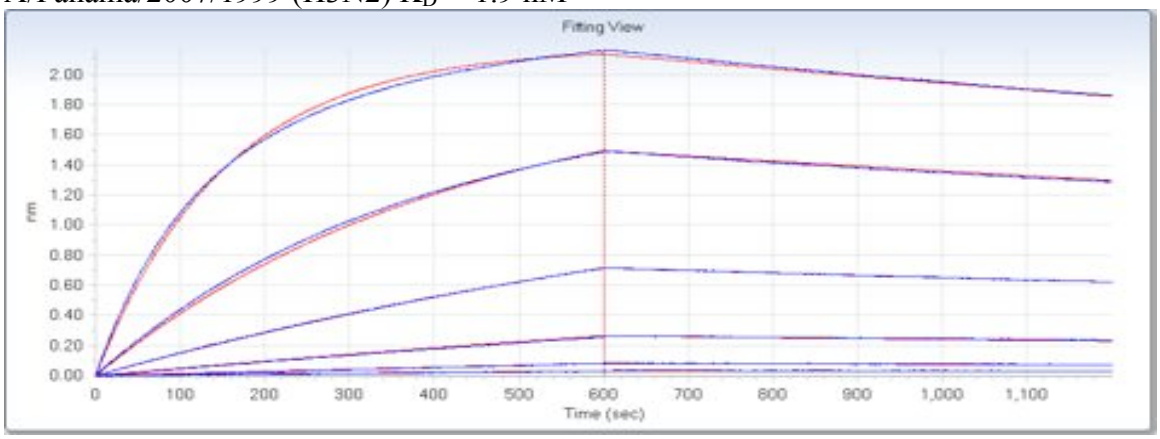
A/Beijing/353/1989 (H3N2) $K_D$ = 1.0 nM



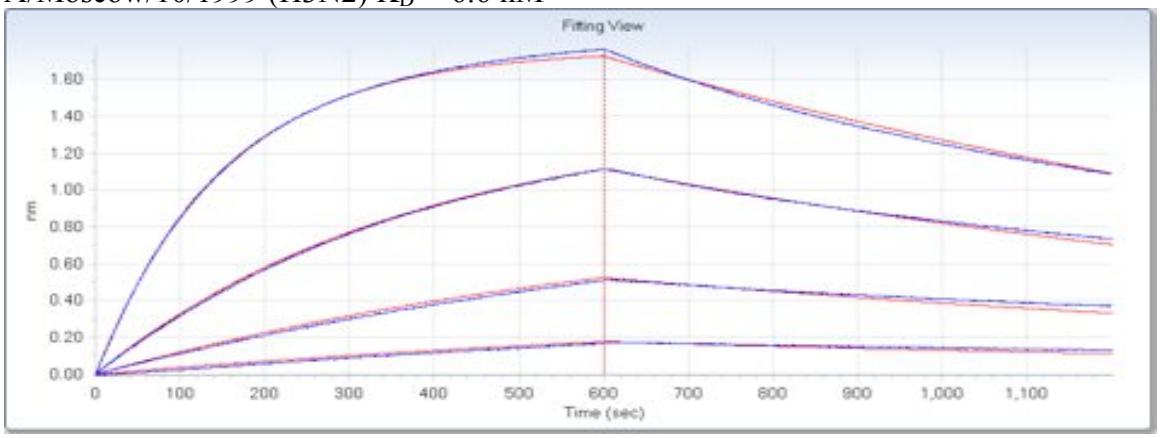

A/Shangdong/9/1993 (H3N2) $K_D$ = 1.7 nM



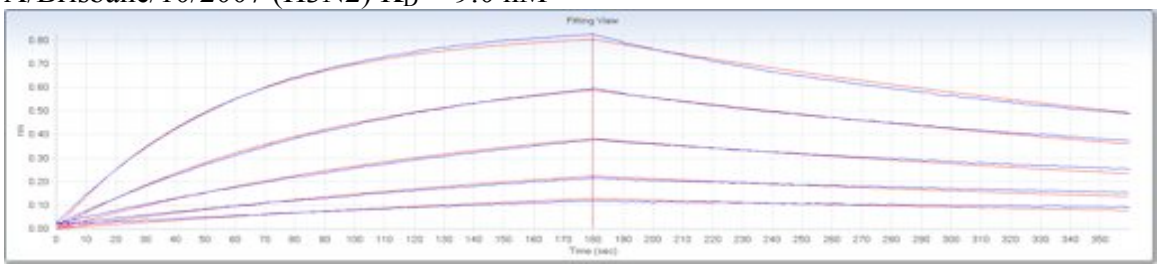
A/Panama/2007/1999 (H3N2) $K_D$ = 1.9 nM



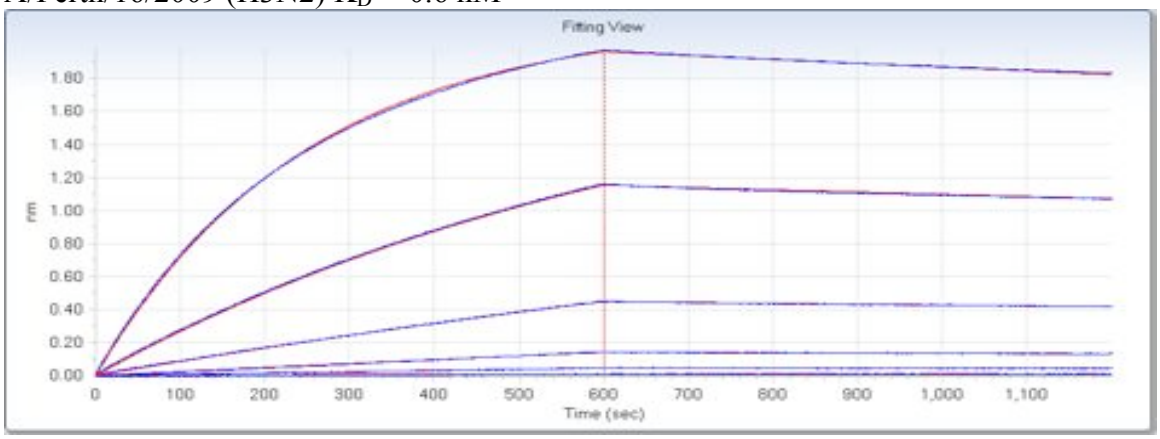
A/Moscow/10/1999 (H3N2) $K_D$ = 6.6 nM



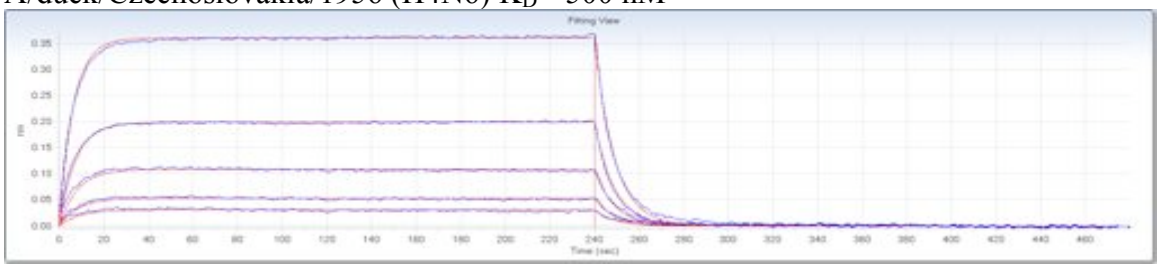

A/Brisbane/10/2007 (H3N2) $K_D$ = 9.0 nM



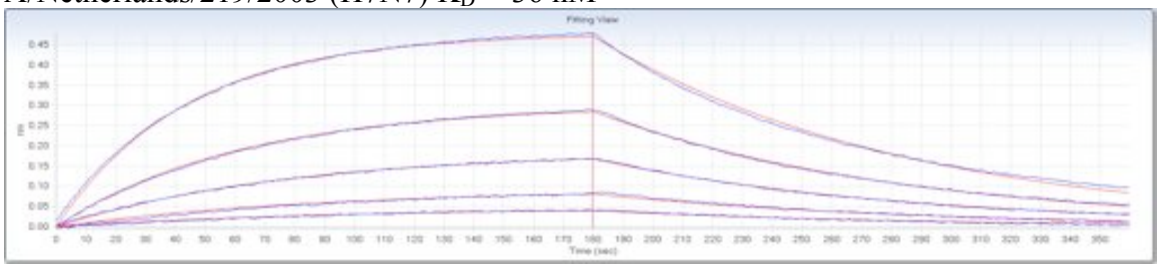
A/Perth/16/2009 (H3N2) $K_D$ = 0.6 nM



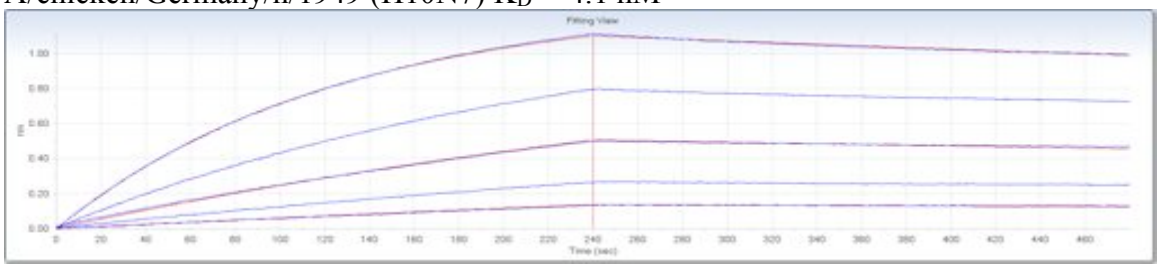

A/duck/Czechoslovakia/1956 (H4N6) $K_D$ =500 nM



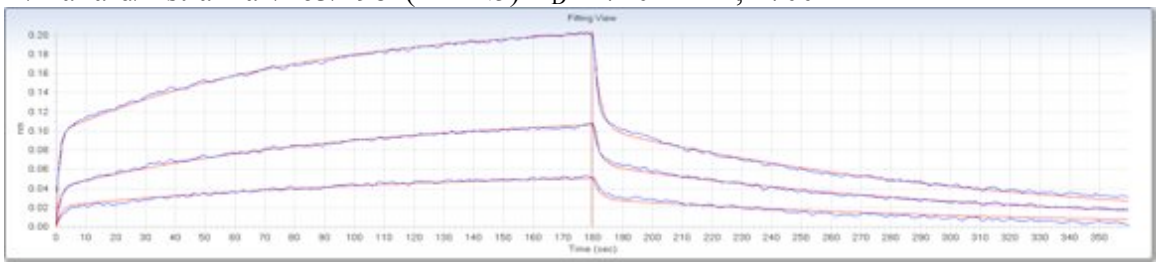
A/Netherlands/219/2003 (H7N7) $K_D$ = 36 nM



A/chicken/Germany/n/1949 (H10N7) $K_D$ = 4.1 nM

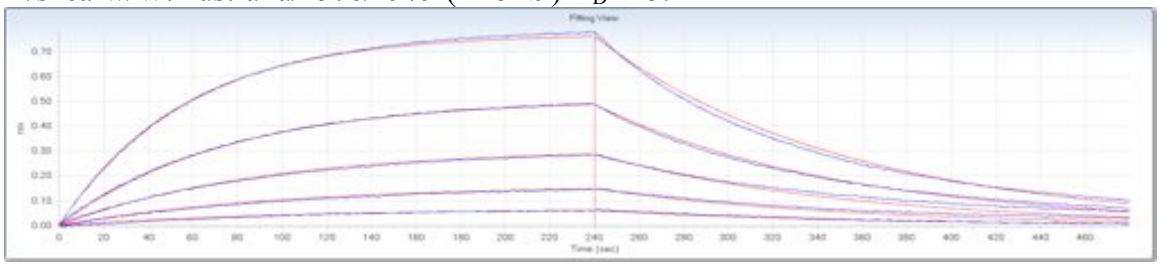


A/mallard/Astrakhan/263/1982(H14N5) $K_D$ = 720 nM**, 1700 nM**



** Binding curves for H14 could only be fit with a 2:1 model, with apparent $K_{D1}$ = 720nM, $K_{D2}$ = 1700nM. While most other experiments reported here used a maximum CR8020 Fab concentration of 50nM, the weak binding to this HA necessitated the use of higher Fab concentrations (up to 1000nM). At 250, 500, and 1000nM CR8020, some non-specific interaction of the Fab with the sensor was observed, while at lower concentrations this interaction was undetectable. One of these binding processes may reflect this non-specific interaction with the sensor. However, this analysis may also indicate multiple binding modes to this mutant. Due to this uncertainty, we report this $K_D$ as approximately 1000 nM.

A/shearw/W.Australia/2576/1979 (H15N9) $K_D$ = 87 nM

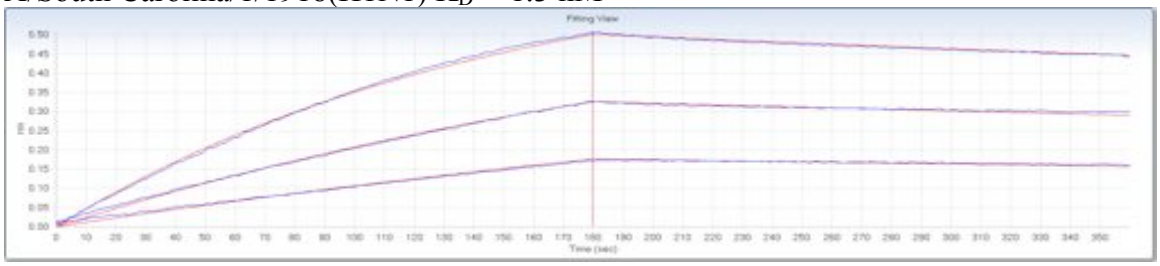


Additional strains tested with no significant binding to CR8020:

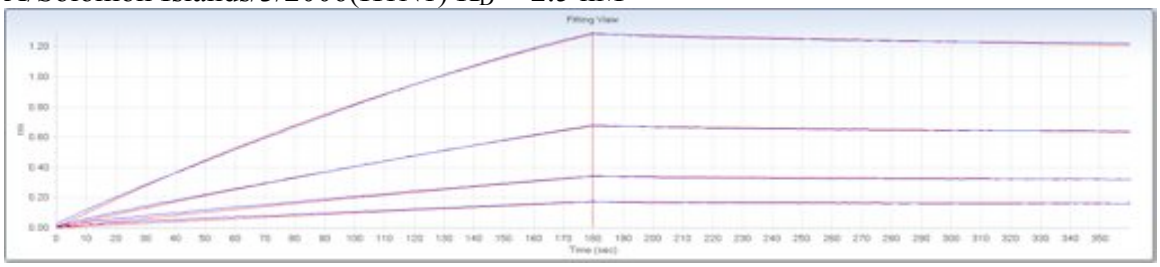
A/South Carolina/1/1918 (H1N1)
A/Solomon Islands/3/2006 (H1N1)
A/California/04/2009 (H1N1)
A/Vietnam/1203/2004 (H5N1)
A/turkey/Massachusetts/3740/1965 (H6N2)
A/turkey/Wisconsin/1/1966(H9N2)
A/gull/Maryland/704/1977 (H13N6)
A/black-headed gull/Sweden/4/99 (H16N3)

**Fig. S11. Binding curves for reported $K_D$ values for CR6261.** Blue curves are the experimental trace obtained from biolayer interferometry experiments, and red curves are the best global fits to the data used to calculate the $K_D$'s reported in Fig.1C.

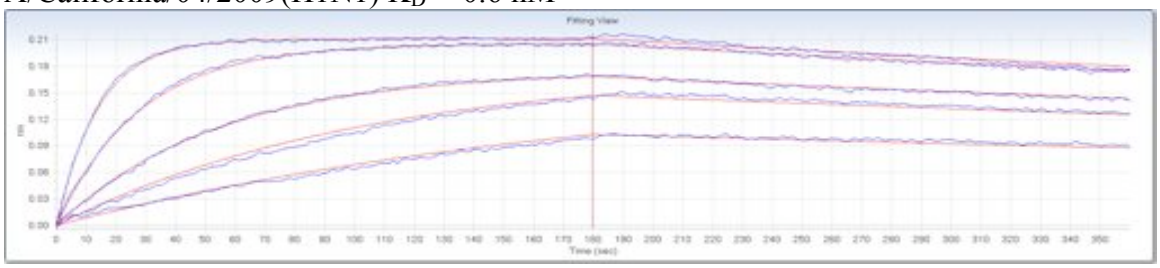
A/South Carolina/1/1918(H1N1) $K_D$ = 1.3 nM



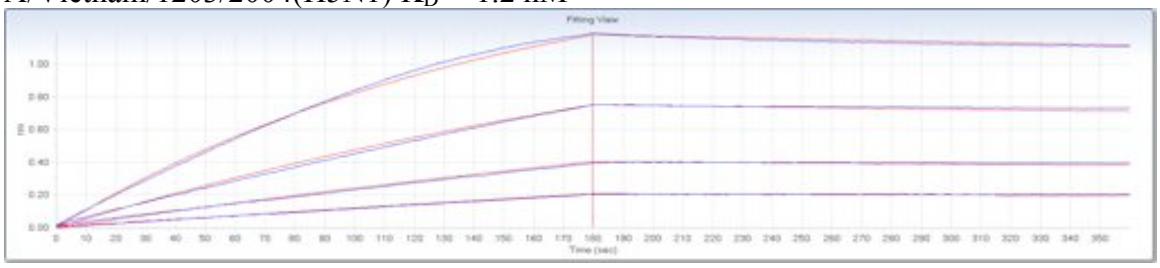
A/Solomon Islands/3/2006(H1N1) $K_D$ = 2.5 nM



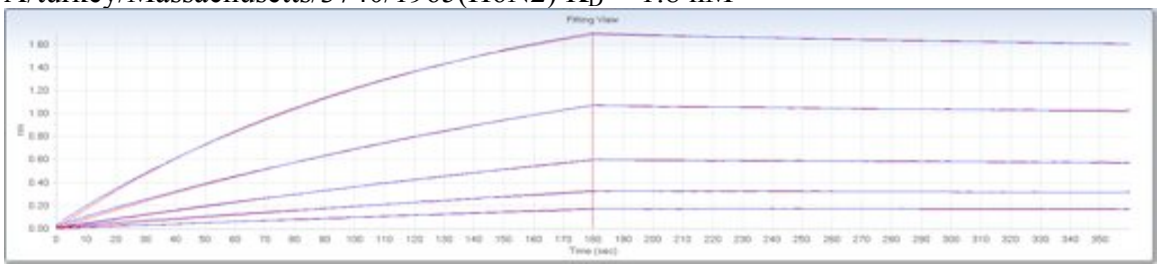
A/California/04/2009(H1N1) $K_D$ = 0.6 nM



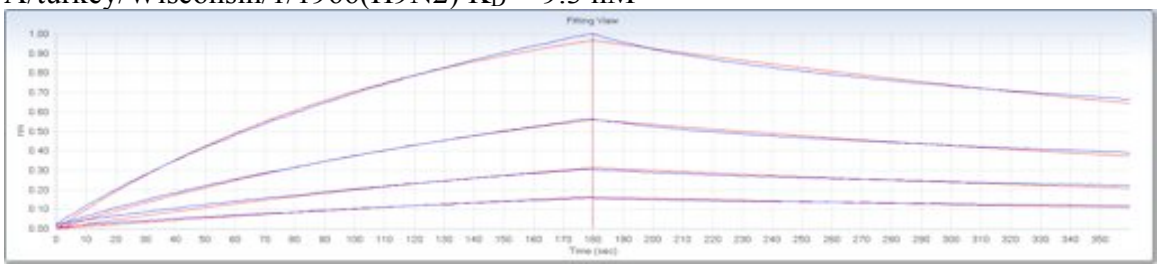
A/Vietnam/1203/2004(H5N1) $K_D$ = 1.2 nM



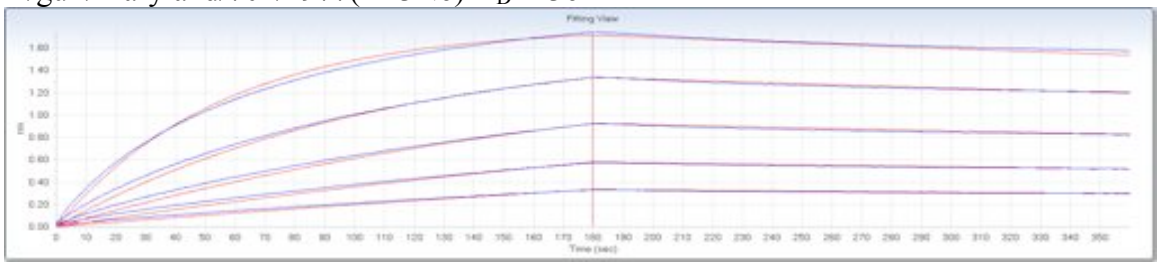
A/turkey/Massachusetts/3740/1965(H6N2) $K_D$ = 1.8 nM



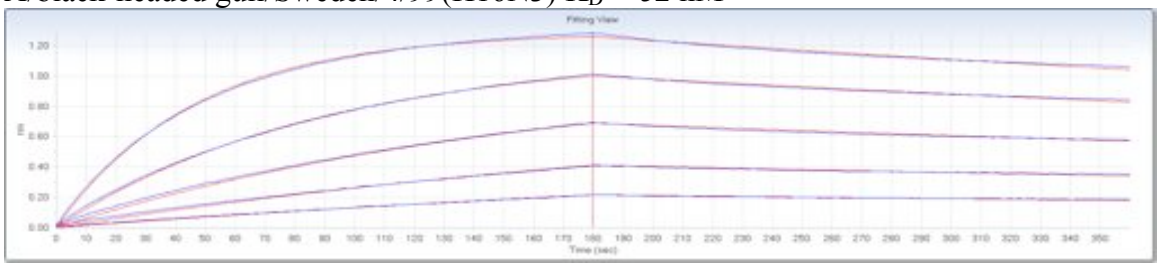
A/turkey/Wisconsin/1/1966(H9N2) $K_D$ = 9.3 nM



A/gull/Maryland/704/1977(H13N6) $K_D$ = 36 nM



A/black-headed gull/Sweden/4/99(H16N3) $K_D$ = 52 nM



Additional strains tested with no significant binding to CR6261:

A/duck/Ukraine/1/1963 (H3N2)
A/Hong Kong/1/1968 (H3N2)
A/Victoria/3/1975 (H3N2)
A/Leningrad/360/1986 (H3N2)
A/Beijing/353/1989 (H3N2)

A/Shangdong/9/1993 (H3N2)
A/Panama/2007/1999 (H3N2)
A/Moscow/10/1999 (H3N2)
A/Brisbane/10/2007 (H3N2)
A/Perth/16/2009 (H3N2)
A/duck/Czechoslovakia/1956 (H4N6)
A/Netherlands/219/2003 (H7N7)
A/chicken/Germany/N/1949 (H10N7)
A/mallard duck/Astrakhan/263/1982 (H14N5)
A/shearwater/West Australia/2576/79 (H15N9)

**Table S1. *In vitro* neutralization of H3 viruses by CR8020 and CR8057**. Fifty percent inhibiting concentrations ($IC_{50}$) as determined in microneutralization (MN) and hemagglutination inhibition (HAI) assays.

| Isolate | $IC_{50}$ (μg/ml) | | | |
|---|---|---|---|---|
| | CR8020 | | CR8057 | |
| | MN | HAI | MN | HAI |
| A/Hong Kong/1/68 | 1.8 | >10 | >40 | >10 |
| A/Johannesburg/33/1994 | 2.0 | >10 | >40 | >10 |
| A/Panama/2007/1999 | 5.0 | >10 | 0.01 | 0.028 |
| A/Hiroshima/52/2005 | 3.5 | >10 | 0.003 | 0.055 |
| A/Wisconsin/67/2005 | 3.5 | >10 | 0.005 | 0.005 |

**Table S2. Data collection and refinement statistics.**

| | |
|---|---|
| Data collection | CR8020-HK68 H3 Complex |
| Beamline | SSRL 9-2 |
| Wavelength (Å) | 0.97946 |
| Space group | $P2_13$ |
| Unit cell parameters | a = b = c = 197.75 Å<br>$\alpha = \beta = \gamma = 90.0^\circ$ |
| Resolution (Å) | 50 - 2.85 (2.95 – 2.85)[a] |
| Observations | 1,616,282 |
| Unique reflections | 60,239 (5,320) [a] |
| Redundancy | 20.4 (19.4) [a] |
| Completeness (%) | 100.0 (100.0) [a] |
| $\langle I/\sigma_I \rangle$ | 27.7 (2.2) [a] |
| $R_{sym}$[b] | 0.15 (0.99) [a, b] |
| $R_{pim}$[b] | 0.03 (0.23) [a, b] |
| $Z_a$[c] | 1 |
| Refinement statistics | |
| Resolution (Å) | 50 - 2.85 |
| Reflections (work) | 53,024 |
| Reflections (test) | 2,660 |
| $R_{cryst}$(%)[d] | 19.8 [d] |
| $R_{free}$(%)[e] | 23.1 [e] |
| Average B-value (Å$^2$) | 97.5 |
| Wilson B-value (Å$^2$) | 73.1 |
| Protein atoms | 7,159 |
| Carbohydrate atoms | 248 |
| Waters | 0 |
| Other | 50 |
| RMSD from ideal geometry | |
| Bond length (Å) | 0.014 |
| Bond angles (°) | 1.36 |
| Ramachandran statistics (%)[f] | |
| Favored | 97.3 |
| Outliers | 0.0 |
| PDB ID | 3SDY |

[a] Numbers in parentheses refer to the highest resolution shell.

[b] $R_{sym} = \Sigma_{hkl} \Sigma_i | I_{hkl,i} - \langle I_{hkl} \rangle | / \Sigma_{hkl} \Sigma_i I_{hkl,I}$ and $R_{pim} = \Sigma_{hkl} (1/(n\text{-}1))^{1/2} \Sigma_i | I_{hkl,i} - \langle I_{hkl} \rangle | / \Sigma_{hkl} \Sigma_i I_{hkl,I}$, where $I_{hkl,i}$ is the scaled intensity of the $i^{th}$ measurement of relection h, k, l, $\langle I_{hkl} \rangle$ is the average intensity for that reflection, and $n$ is the redundancy (S*25*). Note that despite the high $R_{sym}$ in the highest resolution shell, the high redundancy enables the average F's to be well determined (assuming measurement errors are randomly

distributed), as reflected by the redundancy-independent measure of the quality of intensity measurements $R_{pim}$.

[c] $Z_a$ is the number of HA monomer-Fab complexes per crystallographic asymmetric unit.

[d] $R_{cryst} = \Sigma_{hkl} | F_o - F_c | / \Sigma_{hkl} | F_o | \times 100$

[e] $R_{free}$ was calculated as for $R_{cryst}$, but on a test set comprising 5% of the data excluded from refinement.

[f] Calculated using Molprobity (S*20*).

**Table S3. Conservation of CR8020 epitope by subtype.**

| Res | Consensus [a] | HK68/H3 Sequence | Grp 2 Percent Conservation (Simple) [b] | Grp 2 Percent Conservation (Weighted) [c] | Percent Conservation by Subtype | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | H3 (2073) [d] | H4 (271) [d] | H7 (460) [d] | H10 (94) [d] | H14 (2) [d] | H15 (7) [d] |
| 325 | E | E | 99.7 | 83.1 | 99.8 | 100.0 | 99.8 | 98.9 | 0.0 (G) [e] | 100.0 |
| 15 | E | E | 99.9 | 100.0 | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 16 | G | G | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 18 | V | I | 99.9 | 100.0 | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 19 | D | D | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 25 | R | R | 100.0 | 99.9 | 100.0 | 99.6 | 100.0 | 100.0 | 100.0 | 100.0 |
| 30 | E | E | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 32 | T | T | 62.0 | 61.4 | 69.3 | 100.0 | 0.0 (E) [e] | 98.9 | 100.0 | 0.0 (Q) [e] |
| 33 | G | G | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 34 | Q | Q | 74.5 | 33.2 | 100.0 | 0.0 (T) [e] | 0.2 (T) [e] | 98.9 | 0.0 (T) [e] | 0.0 (T) [e] |
| 35 | A | A | 99.9 | 100.0 | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 36 | A | A | 99.7 | 99.9 | 99.5 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 38 | L | L | 80.5 | 49.9 | 99.7 | 100.0 | 0.0 (Y) [e] | 0.0 (Y) [e] | 100.0 | 0.0 (Y) [e] |
| 146 | N | N | 100.0 | 99.9 | 100.0 | 99.6 | 100.0 | 100.0 | 100.0 | 100.0 |
| 150 | G | E | 56.9 | 13.3 | 79.7 | 0.0 (E) [e] | 0.2 (E/A) [e] | 0.0 (E) [e] | 0.0 (E) [e] | 0.0 (E) [e] |

[a] Most common residue at position by simple majority across all group 2 sequences.
[b] Percent of all group 2 sequences that are identical to the consensus or have conservative substitutions.
[c] Percent of all group 2 sequences that are identical to the consensus or have conservative substitutions, but weighted to correct for the under/over-representation of some subtypes in the dataset (the mean of the percent conservation values for each individual subtype).
[d] Number of sequences available for subtype at time of download.
[e] Most common residue in this subtype.

**Table S4. Conservation of CR8020 epitope by subtype.**

| Res | Group 2 Consensus [a] | Percent Conservation by Subtype | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | H1 (2420) [d] | H2 (168) [d] | H5 (2023) [d] | H6 (427) [d] | H8 (40) [d] | H9 (521) [d] | H11 (112) [d] | H12 (46) [d] | H13 (41) [d] | H16 (15) [d] |
| 325 | E | 0.0 (S) [e] | 99.4 | 91.3 | 97.7 | 0.0 (S) [e] | 0.2 (A/S) [e] | 0.0 (A) [e] | 100.0 | 0.0 (A) [e] | 0.0 (S) [e] |
| 15 | E | 0.0 (T) [e] | 100.0 | 99.8 | 0.0 (T) [e] | 0.0 (S) [e] | 0.0 (S/P) [e] | 0.0 (P) [e] | 0.0 (P) [e] | 0.0 (P) [e] | 0.0 (P) [e] |
| 16 | G | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 18 | V | 99.6 | 100.0 | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 19 | D | 100.0 | 100.0 | 99.8 | 100.0 | 100.0 | 0.0 (A) [e] | 100.0 | 0.0 (A) [e] | 100.0 | 100.0 |
| 25 | R | 0.0 (H) [e] | 0.0 (H) [e] | 0.1 (H) [e] | 0.0 (H) [e] | 0.0 (H) [e] | 0.0 (Q) [e] | 0.0 (Q) [e] | 0.0 (Q) [e] | 0.0 (Q) [e] | 0.0 (Q) [e] |
| 30 | E | 99.9 | 100.0 | 99.7 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 32 | T | 99.9 | 98.2 | 99.7 | 100.0 | 100.0 | 9.0 (V) [e] | 100.0 | 100.0 | 43.9 | 100.0 |
| 33 | G | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 99.8 | 100.0 | 100.0 | 100.0 | 100.0 |
| 34 | Q | 0.0 (Y) [e] | 0.0 (Y) [e] | 0.0 (Y) [e] | 0.0 (Y) [e] | 0.0 (M) [e] | 0.0 (M/I) [e] | 0.0 (I) [e] | 0.0 (I/M) [e] | 0.0 (I/M) [e] | 0.0 (I) [e] |
| 35 | A | 100.0 | 100.0 | 99.8 | 100.0 | 100.0 | 100.0 | 100.0 | 97.8 | 100.0 | 100.0 |
| 36 | A | 100.0 | 100.0 | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| 38 | L | 46.2 | 0.0 (K) [e] | 0.0 (K) [e] | 0.0 (K/R) [e] | 0.0 (Q) [e] | 0.0 (R) [e] | 0.0 (K) [e] | 0.0 (R) [e] | 0.0 (K) [e] | 0.0 (K) [e] |
| 146 | N | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 99.8 | 100.0 | 100.0 | 100.0 | 100.0 |
| 150 | G | 0.1 (E) [e] | 0.0 (N) [e] | 0.0 (E) [e] | 0.0 (Q/N) [e] | 0.0 (E) [e] | 0.6 (E) [e] | 0.0 (E) [e] | 0.0 (D/E) [e] | 0.0 (E) [e] | 0.0 (E) [e] |

[a] Most common residue at position by simple majority across all group 2 sequences.
[b] Percent of all group 2 sequences that are identical to the consensus or have conservative substitutions.
[c] Percent of all group 2 sequences that are identical to the consensus or have conservative substitutions, but weighted to correct for the under/over-representation of some subtypes in the dataset (the mean of the percent conservation values for each individual subtype).
[d] Number of sequences available for subtype at time of download.
[e] Most common residue in this subtype.

**Table S5**. ***In vitro*** **neutralizing activity of CR8020 against H3N2 escape mutants and H7 viruses**. Amino-acid residues at positions 19 and 33 of HA2 and fifty percent inhibiting concentrations ($IC_{50}$) as determined in microneutralization (MN) assays. The bottom row shows the amino-acid residues at these positions in all H7 sequences.

| Subtype | Isolate | HA2 position | | $IC_{50}$ (μg/ml) |
|---|---|---|---|---|
| | | 19 | 33 | |
| H3N2 | A/HK/1/68 wt | D | G | 1.8 |
| H3N2 | CR8020 escape 1 | **N** | G | >40 |
| H3N2 | CR8020 escape 2 | D | **E** | >40 |
| | | | | |
| H7N7 | A/Ck/Neth/621557/2003 | D | G | 13.1 |
| H7N7 | A/New York/107/2003[a] | **N** | G | >40 |
| H7N3 | A/Mallard/Neth/12/2000 [b] | D | G | 2.5 |
| | All H7 HAs[c] | D (77%)<br>N (23%) | G (100%) | |

[a] Recombinant virus with the HA segment of A/New York/107/2003 (H7N2) and the remaining 7 segments of A/PR/8/34

[b] Recombinant virus (NIBRG-60) with the HA and NA segments of A/mallard/Netherlands/12/2000 (H7N3) and the internal segments of A/PR/8/34

[c] All 488 full-length, non-redundant H7 HA sequences available in the NCBI FLU database (S*21*) at time of download (November 4, 2010).

**Table S6. Effect of escape mutants on binding of CR8020 to HK68/H3 HA.**

| Subtype | Isolate | Mutation [a] | $K_D$ (nM) | HA1 | | HA2 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | NX(T/S) [b] | 325 | 15 | 16 | 18 | 19 | 25 | 30 | 32 | 33 | 34 | 35 | 36 | 38 | 146 | 150 |
| H3N2 | A/Hong Kong/1/1968 | wt | 1.0 | - | E | E | G | I | D | R | E | T | G | Q | A | A | L | N | E |
| H3N2 | A/Hong Kong/1/1968 | D19N | 310 | - | E | E | G | I | N | R | E | T | G | Q | A | A | L | N | E |
| H3N2 | A/Hong Kong/1/1968 | G33E | ~500 | - | E | E | G | I | D | R | E | T | E | Q | A | A | L | N | E |

[a] Indicates whether HA tested is wild-type (wt) or a mutant

[b] Presence (+) or absence (-) of an NX(T/S) glycosylation motif on Asn21. Glycosylation of this site is predicted to block CR8020 binding in group 1 HAs. The glycosylation site is absent from all group 2 HAs analyzed, including those tested above.

**Table S7. Sequence of CR8020 epitope positions in Group1 HAs tested for binding.** Dissociation constants ($K_D$), presence of a glycosylation site at HA1 position 21 (predicted to block binding in group 1 HAs), and protein sequence of CR8020 contact residues. Residues that differ from the HK68 sequence are in black boxes.

| Subtype | Isolate | $K_D$ (nM) | HA1 | | HA2 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | NX(T/S)[a] | 325 | 15 | 16 | 18 | 19 | 25 | 30 | 32 | 33 | 34 | 35 | 36 | 38 | 146 | 150 |
| H3N2 | A/Hong Kong/1/1968 | **1.0** | - | E | E | G | I | D | R | E | T | G | Q | A | A | L | N | E |
| H1N1 | A/South Carolina/1/1918 | **>10,000** | + | **S** | **T** | G | I | D | **H** | **Q** | **S** | G | **Y** | A | A | **Q** | **D** | E |
| H1N1 | A/Solomon Islands/3/2006 | **>10,000** | + | **S** | **T** | G | **V** | D | **H** | **Q** | **S** | G | **Y** | A | A | **Q** | **D** | E |
| H1N1 | A/California/04/2009 | **>10,000** | + | **S** | **T** | G | **V** | D | **H** | **Q** | **S** | G | **Y** | A | A | L | N | E |
| H5N1 | A/Vietnam/1203/2004 | **>10,000** | + | **Q** | **Q** | G | **V** | D | **H** | **Q** | **S** | G | **Y** | A | A | **K** | N | E |
| H6N2 | A/turkey/Massachusetts/3740/1965 | **>10,000** | + | **Q** | **T** | G | I | D | **H** | **Q** | **S** | G | **Y** | A | A | **K** | **D** | **N** |
| H9N2 | A/turkey/Wisconsin/1/1966 | **>10,000** | + | **A** | **P** | G | **V** | **A** | **Q** | **Q** | **V** | G | **M** | A | A | **K** | **D** | E |
| H13N6 | A/gull/Maryland/704/1977 | **>10,000** | + | **A** | **P** | G | I | **N** | **Q** | **Q** | T | G | **I** | A | A | **K** | **D** | E |
| H16N3 | A/black-headed gull/Sweden/4/99 | **>10,000** | + | **S** | **P** | G | I | **N** | **Q** | **Q** | T | G | **I** | A | A | **K** | **D** | E |

[a] Presence (+) or absence (-) of an NX(T/S) glycosylation motif on Asn21. Glycosylation of this site is predicted to block CR8020 binding in group 1 hemagglutinins. The glycosylation site is absent from all group 2 hemagglutinins analyzed.

**Sequences of HA proteins used in binding studies**. The sequences listed below represent the full-length ORF as cloned in the baculovirus transfer vector. Most of the N-terminal signal peptide (MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFA) is presumably removed during secretion, leaving four non-native residues (ADPG) at the N-terminus of HA1. The C-terminal biotinylation site, trimerization domain, and His-tag are retained on all proteins.

**>A/South Carolina/1/1918 (H1N1)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDTICIGYHANNSTDTVDTVLEKNVTVTHS
VNLLEDSHNGKLCKLKGIAPLQLGKCNIAGWLLGNPECDLLLTASSWSYIVETSNSENGTCYPGDFIDYEE
LREQLSSVSSFEKFEIFPKTSSWPNHETTKGVTAACSYAGASSFYRNLLWLTKKGSSYPKLSKSYVNNKGK
EVLVLWGVHHPPTGTDQQSLYQNADAYVSVGSSKYNRRFTPEIAARPKVRDQAGRMNYYWTLLEPGDTITF
EATGNLIAPWYAFALNRGSGSGIITSDAPVHDCNTKCQTPHGAINSSLPFQNIHPVTIGECPKYVRSTKLR
MATGLRNIPSIQSRGLFGAIAGFIEGGWTGMIDGWYGYHHQNEQGSGYAADQKSTQNAIDGITNKVNSVIE
KMNTQFTAVGKEFNNLERRIENLNKKVDDGFLDIWTYNAELLVLLENERTLDFHDSNVRNLYEKVKSQLKN
NAKEIGNGCFEFYHKCDDACMESVRNGTYDYPKYSEESKLNREEIDGVSGGGGLNDIFEAQKIEWHERLVP
RGSPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Solomon Islands/3/2006 (H1N1)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDTICIGYHANNSTDTVDTVLEKNVTVTHS
VNLLEDSHNGKLCRLKGIAPLQLGNCSVAGWILGNPECELLISRESWSYIVEKPNPENGTCYPGHFADYEE
LREQLSSVSSFERFEIFPKESSWPNHTTTGVSASCSHNGESSFYKNLLWLTGKNGLYPNLSKSYANNKEKE
VLVLWGVHHPPNIGDQRALYHKENAYVSVVSSHYSRKFTPEIAKRPKVRDQEGRINYYWTLLEPGDTIIFE
ANGNLIAPRYAFALSRGFGSGIINSNAPMDECDAKCQTPQGAINSSLPFQNVHPVTIGECPKYVRSAKLRM
VTGLRNIPSIQSRGLFGAIAGFIEGGWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNKVNSVIEK
MNTQFTAVGKEFNKLERRMENLNKKVDDGFIDIWTYNAELLVLLENERTLDFHDSNVKNLYEKVKSQLKNN
AKEIGNGCFEFYHKCNDECMESVKNGTYDYPKYSEESKLNREKIDSGGGGLNDIFEAQKIEWHERLVPRGS
PGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/California/04/2009 (H1N1)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDTLCIGYHANNSTDTVDTVLEKNVTVTHS
VNLLEDKHNGKLCKLRGVAPLHLGKCNIAGWILGNPECESLSTASSWSYIVETPSSDNGTCYPGDFIDYEE
LREQLSSVSSFERFEIFPKTSSWPNHDSNKGVTAACPHAGAKSFYKNLIWLVKKGNSYPKLSKSYINDKGK
EVLVLWGIHHPSTSADQQSLYQNADTYVFVGSSRYSKKFKPEIAIRPKVRDQEGRMNYYWTLVEPGDKITF
EATGNLVVPRYAFAMERNAGSGIIISDTPVHDCNTTCQTPKGAINTSLPFQNIHPITIGKCPKYVKSTKLR
LATGLRNIPSIQSRGLFGAIAGFIEGGWTGMVDGWYGYHHQNEQGSGYAADLKSTQNAIDEITNKVNSVIE
KMNTQFTAVGKEFNHLEKRIENLNKKVDDGFLDIWTYNAELLVLLENERTLDYHDSNVKNLYEKVRSQLKN
NAKEIGNGCFEFYHKCDNTCMESVKNGTYDYPKYSEEAKLNREEIDSGGGGLNDIFEAQKIEWHERLVPRG
SPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/duck/Ukraine/1/1963 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTIVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGRACTLIDALLGDPHCDVFQNETWDLFVERSNAFSNCYPYDIPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSSACKRGPANGFFSRLNWLTKSESAYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTDLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGQPGRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PGKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINRKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLADSEMNKLFEKTRRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDIYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/E15Q/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWQGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/I18M/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMMDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/D19N/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMINGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/E30Q/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSQGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/T32Q/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGQGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/T32E/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGEGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/T32I/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGIGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/T32R/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGRGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/G33E/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTEQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/Q34T/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGTAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/L38Y/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADYKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/N146D/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDDACIESIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Hong Kong/1/E150A/1968 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITDDQIEVTNA
TELVQSSSTGKICNNPHRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFITEGFTWTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWG
VHHPSTNQEQTSLYVQASGRVTVSTRRSQQTIIPNIGSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTGRQLRENAEDMGNG
CFKIYHKCDNACIASIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Victoria/3/1975 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITNDQIEVTNA
TELVQSSSTGKICNNPHRILDGINCTLIDALLGDPHCDGFQNEKWDLFVERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFINEGFNWTGVTQNGGSSACKRGPDSGFFSRLNWLYKSGSTYPVQNVTMPNNDNSDKLYIWG
VHHPSTDKEQTNLYVQASGKVTVSTKRSQQTIIPNVGSRPWVRGLSSRISIYWTIVKPGDILVINSNGNLI
APRGYFKMRTGKSSIMRSDAPIGTCSSECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTRRQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Leningrad/360/1986 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITNDQIEVTNA
TELVQSSSTGRICDSPHRILDGKNCTLIDALLGDPHCDGFQNEKWDLFIERSKAFSNCYPYDVPDYASLRS
LVASSGTLEFINEGFNWTGVTQSGGSYTCKRGSVNSFFSRLNWLYESEYKYPALNVTMPNNGKFDKLYIWG
VHHPSTEKEQTNLYVRASGRVTVSTKRSQQTVIPNIGSRPWVRGLSSRISIYWTIVKPGDILLINSTGNLI
APRGYFKIRTGKSSIMRSDAPIGTCSSECITPNGSIPNDKPFQNVNKITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRLIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQYTIDLTDSEMNKLFEKTRKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Beijing/353/1989 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITNDQIEVTNA
TELVQSSSTGRICDSPHRILDGKNCTLIDALLGDPHCDGFQNKEWDLFVERSKAYSNCYPYDVPDYASLRS
LVASSGTLEFINEDFNWTGVAQSGESYACKRGSVKSFFSRLNWLHESEYKYPALNVTMPNNGKFDKLYIWG
VHHPSTDREQTNLYVRASGRVTVSTKRSQQTVIPNIGSRPWVRGLSSRISIYWTIVKPGDILLINSTGNLI
APRGYFKIRTGKSSIMRSDAPIGTCSSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRLIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTRKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Shangdong/9/1993 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITNDQIEVTNA
TELVQSSSTGRICGSPHRILDGKNCTLIDALLGDPHCDGFQNKEWDLFVERSKAYSNCYPYDVPDYASLRS
LVASSGTLEFINEDFNWTGVAQDGGSYACKRGSVNSFFSRLNWLHKLEYKYPALNVTMPNNGKFDKLYIWG
VHHPSTDSDQTSLYVRASGRVTVSTKRSQQTVTPNIGSRPWVRGQSSRISIYWTIVKPGDILLINSTGNLI
APRGYFKIRNGKSSIMRSDAPIGNCSSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRLIEKTNEKFQQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTRKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Panama/2007/1999 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVSNGTLVKTITNDQIEVTNA
TELVQSSSTGRICDSPHQILDGENCTLIDALLGDPHCDGFQNKEWDLFVERSKAYSNCYPYDVPDYASLRS
LVASSGTLEFNNESFNWTGVAQNGTSSACKRRSNKSFFSRLNWLHQLKYKYPALNVTMPNNEKFDKLYIWG
VLHPSTDSDQISLYAQASGRVTVSTKRSQQTVIPNIGSRPWVRGVSSRISIYWTIVKPGDILLINSTGNLI
APRGYFKIRSGKSSIMRSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAINQINGKLNRLIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Moscow/10/1999 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTLVKTITNDQIEVTNA
TELVQSSSTGRICDSPHQILDGENCTLIDALLGDPHCDGFQNKEWDLFVERSKAYSNCYPYDVPDYASLRS
LVASSGTLEFNNESFNWTGVAQNGTSSACKRRSINSFFSRLNWLHQLKYRYPALNVTMPNNDKFDKLYIWG
VHHPSTDSDQTSLYTQASGRVTVSTKRSQQTVIPNIGSRPWVRGISSRISIYWTIVKPGDILLIKSTGNLI
APRGYFKIRSGKSSIMRSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMMDGWYGFRHQNSEGTGQAADLKSTQAAINQINGKLNRLIEKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTRKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Brisbane/10/2007 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTIVKTITNDQIEVTNA
TELVQSSSTGEICDSPHQILDGENCTLIDALLGDPQCDGFQNKKWDLFVERSKAYSNCYPYDVPDYASLRS
LVASSGTLEFNNESFNWTGVTQNGTSSACIRRSNNSFFSRLNWLTHLKFKYPALNVTMPNNEKFDKLYIWG
VHHPGTDNDQIFPYAQASGRITVSTKRSQQTVIPNIGSRPRVRNIPSRISIYWTIVKPGDILLINSTGNLI
APRGYFKIRSGKSSIMRSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAIDQINGKLNRLIGKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTKKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Perth/16/2009 (H3N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGATLCLGHHAVPNGTIVKTITNDQIEVTNA
TELVQSSSTGEICDSPHQILDGKNCTLIDALLGDPQCDGFQNKKWDLFVERSKAYSNCYPYDVPDYASLRS
LVASSGTLEFNNESFNWTGVTQNGTSSACIRRSKNSFFSRLNWLTHLNFKYPALNVTMPNNEQFDKLYIWG
VHHPGTDKDQIFLYAQASGRITVSTKRSQQTVSPNIGSRPRVRNIPSRISIYWTIVKPGDILLINSTGNLI
APRGYFKIRSGKSSIMRSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNV
PEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGRGQAADLKSTQAAIDQINGKLNRLIGKTNEKFHQ
IEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTKKQLRENAEDMGNG
CFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIKGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/duck/Czechoslovakia/1956 (H4N6)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGPVICMGHHAVANGTMVKTLADDQVEVVTA
QELVESQNLPELCPSPLRLVDGQTCDIINGALGSPGCDHLNGAEWDVFIERPNAVDTCYPFDVPEYQSLRS
ILANNGKFEFIAEEFQWNTVKQNGKSGACKRANVNDFFNRLNWLVKSDGNAYPLQNLTKINNGDYARLYIW
GVHHPSTDTEQTNLYKNNPGRVTVSTKTSQTSVVPNIGSRPLVRGQSGRVSFYWTIVEPGDLIVFNTIGNL
IAPRGHYKLNNQKKSTILNTAIPIGSCVSKCHTDKGSLSTTKPFQNISRIAVGDCPRYVKQGSLKLATGMR
NIPEKASRGLFGAIAGFIENGWQGLIDGWYGFRHQNAEGTGTAADLKSTQAAIDQINGKLNRLIEKTNDKY
HQIEKEFEQVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDVTDSEMNKLFERVRRQLRENAEDKG
NGCFEIFHKCDNNCIESIRNGTYDHDIYRDEAINNRFQIQGVSGGGGLNDIFEAQKIEWHERLVPRGSPGS
GYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Vietnam/1203/2004 (H5N1)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDQICIGYHANNSTEQVDTIMEKNVTVTHA
QDILEKKHNGKLCDLDGVKPLILRDCSVAGWLLGNPMCDEFINVPEWSYIVEKANPVNDLCYPGDFNDYEE
LKHLLSRINHFEKIQIIPKSSWSSHEASLGVSSACPYQGKSSFFRNVVWLIKKNSTYPTIKRSYNNTNQED
LLVLWGIHHPNDAAEQTKLYQNPTTYISVGTSTLNQRLVPRIATRSKVNGQSGRMEFFWTILKPNDAINFE
SNGNFIAPEYAYKIVKKGDSTIMKSELEYGNCNTKCQTPMGAINSSMPFHNIHPLTIGECPKYVKSNRLVL
ATGLRNSPQRERRRKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSGYAADKESTQKAIDGVTNKVNS
IIDKMNTQFEAVGREFNNLERRIENLNKKMEDGFLDVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRLQ
LRDNAKELGNGCFEFYHKCDNECMESVRNGTYDYPQYSEEARLKREEISSGGGGLNDIFEAQKIEWHERLV
PRGSPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/turkey/Massachusetts/3740/1965 (H6N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDKICIGYHANNSTTQVDTILEKNVTVTHS
VELLESQKEERFCRVLNKTPLDLKGCTIEGWILGNPQCDILLGDQSWSYIVERPGAQNGICYPGVLNEVEE
LKAFIGSGEKVQRFEMFPKSTWTGVDTNSGVTRACPYTTSGSSFYRNLLWIIKTRSAAYPVIKGTYNNTGS
QPILYFWGVHHPPNTDEQNTLYGSGDRYVRMGTESMNFAKSPEIAARPAVNGQRGRIDYYWSVLKPGETLN
VESNGNLIAPWYAYKFTSSNNKGAIFKSNLPIENCDAVCQTVAGALKTNKTFQNVSPLWIGECPKYVKSES
LRLATGLRNVPQAETRGLFGAIAGFIEGGWTGMIDGWYGYHHENSQGSGYAADKESTQKAIDGITNKVNSI
IDKMNTQFEAVEHEFSNLERRIDNLNKRMEDGFLDVWTYNAELLVLLENERTLDLHDANVKNLYEKVKSQL
RDNAKDLGNGCFEFWHKCDDECINSVKNGTYDYPKYQDESKLNRQEIDSVSGGGGLNDIFEAQKIEWHERL
VPRGSPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/Netherlands/219/2003 (H7N7)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDKICLGHHAVSNGTKVNTLTERGVEVVNA
TETVERTNVPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEFSADLIIERREGSDVCYPGKFVNEEALRQ
ILRESGGIDKETMGFTYSGIRTNGTTSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKDPALIIW
GIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPSPGARPQVNGQSGRIDFHWLILNPNDTVTFSFNGAF
IALDRASFLRGKSMGIQSEVQVDANCEGDCYHSGGTIISNLPFQNINSRAVGKCPRYVKQESLLLATGMKN
VPEIPKRRRRGLFGAIAGFIENGWEGLIDGWYGFRHQNAQGEGTAADYKSTQSAIDQITGKLNRLIEKTNQ
QFELIDNEFTEVERQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSEMNKLYERVKRQLRENAEE
DGTGCFEIFHKCDDDCMASIRNNTYDHSKYREEAIQNRIQIDPVSGGGGLNDIFEAQKIEWHERLVPRGSP
GSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/turkey/Wisconsin/1/1966 (H9N2)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDKICIGYQSTNSTETVDTLTESNVPVTHT
KELLHTEHNGMLCATDLGHPLILDTCTIEGLIYGNPSCDILLGGKEWSYIVERSSAVNGMCYPGNVENLEE
LRSLFSSAKSYKRIQIFPDKTWNVTYSGTSRACSNSFYRSMRWLTHKSNSYPFQNAHYTNNERENILFMWG
IHHPPTDTEQTDLYKNADTTTSVTTEDINRTFKPVIGPRPLVNGQQGRIDYYWSVLKPGQTLRIRSNGNLI
APWYGHVLTGESHGRILKTDLNNGNCVVQCQTEKGGLNTTLPFHNISKYAFGNCPKYVGVKSLKLAVGLRN
VPAVSSRGLFGAIAGFIEGGWPGLVAGWYGFQHSNDQGVGMAADKGSTQKAIDKITSKVNNIIDKMNKQYE
VIDHEFNELEARLNMINNKIDDQIQDIWAYNAELLVLLENQKTLDEHDANVNNLYNKVKRALGSNAVEDGN
GCFELYHKCDDQCMETIRNGTYDRQKYQEESRLERQKIEGVSGGGGLNDIFEAQKIEWHERLVPRGSPGSG
YIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/chicken/Germany/n/1949 (H10N7)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDRICLGHHAVANGTIVKTLTNEQEEVTNA
TETVESTNLNKLCMKGRSYKDLGNCHPVGMLIGTPVCDPHLTGTWDTLIERENAIAHCYPGATINEEALRQ
KIMESGGISKMSTGFTYGSSINSAGTTKACMRNGGDSFYAELKWLVSKTKGQNFPQTTNTYRNTDTAEHLI
IWGIHHPSSTQEKNDLYGTQSLSISVESSTYQNNFVPVVGARPQVNGQSGRIDFHWTLVQPGDNITFSHNG
GLIAPSRVSKLTGRGLGIQSEALIDNSCESKCFWRGGSINTKLPFQNLSPRTVGQCPKYVNQRSLLLATGM
RNVPEVVQGRGLFGAIAGFIENGWEGMVDGWYGFRHQNAQGTGQAADYKSTQAAIDQITGKLNRLIEKTNT
EFESIESEFSETEHQIGNVINWTKDSITDIWTYQAELLVAMENQHTIDMADSEMLNLYERVRKQLRQNAEE
DGKGCFEIYHTCDDSCMESIRNNTYDHSQYREEALLNRLNINSVSGGGGLNDIFEAQKIEWHERLVPRGSP
GSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/gull/Maryland/704/1977 (H13N6)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDRICVGYLSTNSSERVDTLLENGVPVTSS
IDLIETNHTGTYCSLNGVSPVHLGDCSFEGWIVGNPACTSNFGIREWSYLIEDPAAPHGLCYPGELNNNGE
LRHLFSGIRSFSRTELIPPTSWGEVLDGTTSACRDNTGTNSFYRNLVWFIKKNNRYPVISKTYNNTTGRDV
LVLWGIHHPVSVDETKTLYVNSDPYTLVSTKSWSEKYKLETGVRPGYNGQRSWMKIYWSLIHPGEMITFES
NGGFLAPRYGYIIEEYGKGRIFQSRIRMSRCNTKCQTSVGGINTNRTFQNIDKNALGDCPKYIKSGQLKLA
TGLRNVPAISNRGLFGAIAGFIEGGWPGLINGWYGFQHQNEQGTGIAADKESTQKAIDQITTKINNIIDKM
NGNYDSIRGEFNQVEKRINMLADRIDDAVTDIWSYNAKLLVLLENDKTLDMHDANVKNLHEQVRRELKDNA
IDEGNGCFELLHKCNDSCMETIRNGTYDHTEYAEESKLKRQEIDGISGGGGLNDIFEAQKIEWHERLVPRG
SPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/mallard/Astrakhan/263/1982 (H14N5)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGPIICLGHHAVENGTSVKTLTDNHVEVVSA
KELVETNHTDELCPSPLKLVDGQDCDLINGALGSPGCDRLQDTTWDVFIERPTAVDTCYPFDVPDYQSLRS
ILASSGSLEFIAEQFTWNGVKVDGSSSACLRGGRNSFFSRLNWLTKATNGNYGPINVTKENTGSYVRLYLW
GVHHPSSDNEQTDLYKVATGRVTVSTRSDQISIVPNIGSRPRVRNQSGRISIYWTLVNPGDSIIFNSIGNL
IAPRGHYKISKSTKSTVLKSDKRIGSCTSPCLTDKGSIQSDKPFQNVSRIAIGNCPKYVKQGSLMLATGMR
NIPGKQAKGLFGAIAGFIENGWQGLIDGWYGFRHQNAEGTGTAADLKSTQAAIDQINGKLNRLIEKTNEKY
HQIEKEFEQVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDVTDSEMNKLFERVRRQLRENAEDQG
NGCFEIFHQCDNNCIESIRNGTYDHNIYRDEAINNRIKINPVSGGGGLNDIFEAQKIEWHERLVPRGSPGS
GYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/shearwater/Western Australia/2576/1979 (H15N9)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDKICLGHHAVANGTKVNTLTERGVEVVNA
TETVEITGIDKVCTKGKKAVDLGSCGILGTIIGPPQCDLHLEFKADLIIERRNSSDICYPGRFTNEEALRQ
IIRESGGIDKESMGFRYSGIRTDGATSACKRTVSSFYSEMKWLSSSMNNQVFPQLNQTYRNTRKEPALIVW
GVHHSSSLDEQNKLYGTGNKLITVGSSKYQQSFSPSPGARPKVNGQAGRIDFHWMLLDPGDTVTFTFNGAF
IAPDRATFLRSNAPSGIEYNGKSLGIQSDAQIDESCEGECFYSGGTINSPLPFQNIDSRAVGKCPRYVKQS
SLPLALGMKNVPEKIRTRGLFGAIAGFIENGWEGLIDGWYGFRHQNAQGQGTAADYKSTQAAIDQITGKLN
RLIEKTNKQFELIDNEFTEVEQQIGNVINWTRDSLTEIWSYNAELLVAMENQHTIDLADSEMNKLYERVRR
QLRENAEEDGTGCFEIFHRCDDQCMESIRNNTYNHTEYRQEALQNRIMINPVSGGGGLNDIFEAQKIEWHE
RLVPRGSPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**>A/black-headed gull/Sweden/4/99 (H16N3)**
MVLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFAADPGDKICIGYLSNNSTDTVDTLTENGVPVTSS
IDLVETNHTGTYCSLNGVSPIHLGDCSFEGWIVGNPSCASNINIREWSYLIEDPNAPHKLCFPGEVDNNGE
LRHLFSGVNSFSRTELIPPSKWGDILEGTTASCQNRGANSFYRNLIWLVNKLNKYPVVKGEYNNTTGRDVL
VLWGIHHPDTEATANKLYVNKNPYTLVSTKEWSRRYELEIGTRIGDGQRSWMKIYWHLMHPGERITFESSG
GLLAPRYGYIIEKYGTGRIFQSGVRLAKCNTKCQTSMGGINTNKTFQNIERNALGDCPKYIKSGQLKLATG
LRNVPSIVERGLFGAIAGFIEGGWPGLINGWYGFQHQNEQGTGIAADKTSTQKAINEITTKINNIIEKMNG
NYDSIRGEFNQVEKRINMIADRVDDAVTDIWSYNAKLLVLIENDRTLDLHDANVRNLHEQIKRALKDNAID
EGDGCFSILHKCNDSCMETIRNGTYNHEDYKEESQLKRQEIEGISGGGGLNDIFEAQKIEWHERLVPRGSP
GSGYIPEAPRDGQAYVRKDGEWVLLSTFLGHHHHHH

**HA sequences used in the FACS assay for conformational change.**

**>A/Hong Kong/1/68 (H3N2)**
MKTIIALSYIFCLALGQDLPGNDNSTATLCLGHHAVPNGTLVKTITDDQIEVTNATELVQSSSTGKICNNP
HRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRSLVASSGTLEFITEGFT
WTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWGVHHPSTNQEQTSLYVQ
ASGRVTVSTRRSQQTIIPNIWSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLIAPRGYFKMRTGKSSIM
RSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNVPEKQTRGLFGAIAGFI
ENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESI
RNGNYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQRGNIRCNICI

**>A/Hong Kong/24/1985 (H3N2)**
MKTIIALSYIFCLVFAQKLPGNDNSTATLCLGHHAVPNGTLVKTITNDQIEVTNATELVQSSSTGRICDSP
HRILDGKNCTLIDALLGDPHCDGFQNEKWDLFVERSKAFSNCYPYDVPDYASLRSLVASSGTLEFINEGFN
WTGVTQSGGSYACKRGSVNSFFSRLNWLYKSEYKYPALNVTMPNNGKFDKLYIWGVHHPSTEKEQTNLYVR
ASGRVTVSTKRSQQTVIPNIGSIPWVRGLSSRISIYWTIVKPGDILLINSTGNLIAPRGYFKIRTGKSSIM
RSDAPIGTCSSECITPNGSIPNDKPFQNVNKITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRLIEKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTRKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQKGNIRCNICI

**>A/Wisconsin/67/05 (H3N2)**
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATELVQSSSTGGICDSP
HQILDGENCTLIDALLGDPQCDGFQNKKWDLFVERSKAYSNCYPYDVPDYASLRSLVASSGTLEFNDESFN
WTGVTQNGTSSSCKRRSNNSFFSRLNWLTQLKFKYPALNVTMPNNEKFDKLYIWGVHHPVTDNDQIFLYAQ
ASGRITVSTKRSQQTVIPNIGSRPRIRNIPSRISIYWTIVKPGDILLINSTGNLIAPRGYFKIRSGKSSIM
RSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAINQINGKLNRLIGKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

**>A/Netherlands/219/2003 (H7N7)**
MNTQILVFALVASIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATETVERTNVPRICSKGKRTVDLGQ
CGLLGTITGPPQCDQFLEFSADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTYSGIRTNG
TTSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKDPALIIWGIHHSGSTTEQTKLYGSGNKLITV
GSSNYQQSFVPSPGARPQVNGQSGRIDFHWLILNPNDTVTFSFNGAFIAPDRASFLRGKSMGIQSEVQVDA
NCEGDCYHSGGTIISNLPFQNINSRAVGKCPRYVKQESLLLATGMKNVPEIPKRRRRGLFGAIAGFIENGW
EGLIDGWYGFRHQNAQGEGTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFTEVERQIGNVINWTR
DSMTEVWSYNAELLVAMENQHTIDLADSEMNKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT
YDHSKYREEAIQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLVFICVKNGNMRCTICI

**>A/Greater white fronted goose/California/HKWF446/2007 (H10N7)**
MYKIVPVLALLGAVHGLDKICLGHHAVPNGTIVKTLTNEKEEVTNATETVESRSLDKLCMKSRNYKDLGNC
HPIGMVIGTPACDLHLTGTWDTLIERDNSIAYCYPGATVNEEALRQKIMESGGIDKIGTGFTYGSSINSAG
DTKACMRNGGNSFYAELKWLVSKTKGQNFPQTTNTYRNTDSAEHLIIWGIHHPSSTKEKNELYGTQSLSIS
VGSSTYQNNFVPVVGARPQVNGQSGRIDFHWTMVQPGDNITFSHNGGLIAPSRVSKLKGRGLGIQSGASID
NDCESKCFWKGGSINTKLPFQNLSPRTVGQCPKYVNKRSLLLATGMRNVPEVVQGRGLFGAIAGFIENGWE
GMVDGWYGFRHQNAQGTGQAADYKSTQAAVDQITGKLNRLIEKTNTEFESIESEFSEIEHQIGNVINWTKD
SITDIWTYQAELLVAMENQHTIDMADSEMLNLYERVRKQLRQNAEEDGKGCFEIYHKCDDNCMESIRNNTY
DHAQYREEALLNRLNINPVKLSSGYKDVILWFSFGASCFVLLAVIMGLVFFCLKNGNMRCTICI

## HA sequences of viruses used in neutralization studies

**>A/New Caledonia/20/99 (H1N1)**
MKAKLLVLLCTFTATYADTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLEDSHNGKLCLLKGIAPLQLGN
CSVAGWILGNPECELLISKESWSYIVETPNPENGTCYPGYFADYEELREQLSSVSSFERFEIFPKESSWPN
HTVTGVSASCSHNGKSSFYRNLLWLTGKNGLYPNLSKSYVNNKEKEVLVLWGVHHPPNIGDQRALYHTENA
YVSVVSSHYSRRFTPEIAKRPKVRDQEGRINYYWTLLEPGDTIIFEANGNLIAPWYAFALSRGFGSGIITS
NAPMDECDAKCQTPQGAINSSLPFQNVHPVTIGECPKYVRSAKLRMVTGLRNIPSIQSRGLFGAIAGFIEG
GWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNKVNSVIEKMNTQFTAVGKEFNKLERRMENLNKK
VDDGFLDIWTYNAELLVLLENERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNNECMESVKN
GTYDYPKYSEESKLNREKIDGVKLESMGVYQILAIYSTVASSLVLLVSLGAISFWMCSNGSLQCRICI

**>A/Hong Kong/1/68 (H3N2)**
MKTIIALSYIFCLALGQDLPGNDNSTATLCLGHHAVPNGTLVKTITDDQIEVTNATELVQSSSTGKICNNP
HRILDGIDCTLIDALLGDPHCDVFQNETWDLFVERSKAFSNCYPYDVPDYASLRSLVASSGTLEFITEGFT
WTGVTQNGGSNACKRGPGSGFFSRLNWLTKSGSTYPVLNVTMPNNDNFDKLYIWGVHHPSTNQEQTSLYVQ
ASGRVTVSTRRSQQTIIPNIWSRPWVRGLSSRISIYWTIVKPGDVLVINSNGNLIAPRGYFKMRTGKSSIM
RSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNVPEKQTRGLFGAIAGFI
ENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRVIEKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESI
RNGNYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQRGNIRCNICI

**>A/Johannesburg/33/94 (H3N2)**
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTLVKTITNDQIEVTNATELVQSSPTGRICDSP
HRILDGKNCTLIDALLGDPHCDGFQNKEWDLFVERSKAYSNCYPYDVPDYASLRSLVASSGTLEFINENFN
WTGVAQDGKSYACKRGSVNSFFSRLNWLHKLEYKYPALNVTMPNNGKFDKLYIWGVHHPSTDSDQTSLYVR
ASGRVTVSTKRSQQTVIPDIGYRPWVRGQSSRISIHWTIVKPGDILLINSTGNLIAPRGYFKIRNGKSSIM
RSDAPIGNCSSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAIDQINGKLNRLVEKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTRKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQKGNIRCNICI

**>A/Panama/2007/99 (H3N2)**
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVSNGTLVKTITNDQIEVTNATELVQSSSTGRICDSP
HQILDGENCTLIDALLGDPHCDGFQNKEWDLFVERSKAYSNCYPYDVPDYASLRSLVASSGTLEFNNESFN
WTGVAQNGTSSACKRRSNKSFFSRLNWLHQLKYKYPALNVTMPNNEKFDKLYIWGVHHPSTDSDQISIYAQ
ASGRVTVSTKRSQQTVIPNIGSSPWVRGVSSRISIYWTIVKPGDILLINSTGNLIAPRGYFKIRSGKSSIM
RSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGTGQAADLKSTQAAINQINGKLNRLIEKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQKGNIRCNICI

**>A/Hiroshima/52/05 (H3N2)**
MKTIIALSYILCLAFAQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATELVQSSSTGGICDSP
HQILDGENCTLIDALLGDPQCDGFQNKKWDLFVERSKAYSNCYPYDVPDYASLRSLVASSGTLEFNNESFN
WTGVTQNGTSSACKRRSNNSFFSRLNWLTQLKFKYPALKVTMPNNEKFDKLYIWGVHHPVTDNDQIFLYAQ
ASGRITVSTKRSQQTVIPNIGSRPRVRNIPSRISIYWTIVKPGDILLINSTGNLIAPRGYFKIRSGKSSIM
RSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAINQINGKLNRLIGKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDIKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

**>A/Wisconsin/67/05 (H3N2)**
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATELVQSSSTGGICDSP
HQILDGENCTLIDALLGDPQCDGFQNKKWDLFVERSKAYSNCYPYDVPDYASLRSLVASSGTLEFNDESFN
WTGVTQNGTSSSCKRRSNNSFFSRLNWLTQLKFKYPALNVTMPNNEKFDKLYIWGVHHPVTDNDQIFLYAQ
ASGRITVSTKRSQQTVIPNIGSRPRIRNIPSRISIYWTIVKPGDILLINSTGNLIAPRGYFKIRSGKSSIM
RSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAINQINGKLNRLIGKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

**>A/Brisbane/10/07 (H3N2)**
MKTIIALSYILCLVFTQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATELVQSSSTGEICDSP
HQILDGENCTLIDALLGDPQCDGFQNKKWDLFVERSKAYSNCYPYDVPDYASLRSLVASSGTLEFNNESFN
WTGVTQNGTSSACIRRSNNSFFSRLNWLTHLKFKYPALNVTMPNNEKFDKLYIWGVHHPGTDNDQIFPYAQ
ASGRITVSTKRSQQTVIPNIGSRPRVRNIPSRISIYWTIVKPGDILLINSTGNLIAPRGYFKIRSGKSSIM
RSDAPIGKCNSECITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFI
ENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAIDQINGKLNRLIGKTNEKFHQIEKEFSEVEGRIQDLE
KYVEDTKIDLWSYNAELLVALENQHTIDLTDSEMNKLFEKTKKQLRENAEDMGNGCFKIYHKCDNACIGSI
RNGTYDHDVYRDEALNNRFQIKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

**>A/WF/HK/MPA892/06 (H4)**
MLSIVILFLLVAESSSQNYTGNPVICMGHHAVANGTMVKTLTDDQVEVVTAQELVESQNLPELCPSPLRLV
DGQTCDIINGALGSPGCDHLNGAEWDVFIERPNAMDTCYPFDVPDYQSLRSILANNGKFEFIAEEFQWATV
KQNGKSGACKRANVNDFFNRLNWLVKSDGNAYPLQNLTKVNNGDYARLYIWGVHHPSTDTEQTTLYKNNPG
RVTVSTKTSQTSVVPNIGSRPWVRGQSGRISFYWTIVEPGDLIVFNTIGNLIAPRGHYKLNNQKKSTILNT
AIPIGSCVSKCHTDKGSLSTTKPFQNISRIAIGDCPKYVKQGSLKLATGMRNIPEKASRGLFGAIAGFIEN
GWQGLIDGWYGFRHQNAEGTGTAADLKSTQAAIDQINGKLNRLIEKTNEKYHQIEKEFEQVEGRIQDLEKY
VEDTKIDLWSYNAELLVALENQHTIDVTDSEMNKLFERVRRQLRENAEDRGNGCFEIFHKCDNNCIESIRN
GTYDHDIYRDEAISNRFQIQGVKLTQGYKDIILWISFSISCFLLVALLLAFILWACQNGNIRCQICI

**>A/Vietnam/1194/04 (H5N1)**
MEKIVLLFAIVSLVKSDQICIGYHANNSTEQVDTIMEKNVTVTHAQDILEKTHNGKLCDLDGVKPLILRDC
SVAGWLLGNPMCDEFINVPEWSYIVEKANPVNDLCYPGDFNDYEELKHLLSRINHFEKIQIIPKSSWSSHE
ASLGVSSACPYQGKSSFFRNVVWLIKKNSTYPTIKRSYNNTNQEDLLVLWGIHHPKDAAEQTKLYQNPTTY
ISVGTSTLNQRLVPRIATRSKVNGQSGRMEFFWTILKPNDAINFESNGNFIAPEYAYKIVKKGDSTIMKSE
LEYGNCNTKCQTPMGAINSSMPFHNIHPLTIGECPKYVKSNRLVLATGLRNSPQRERRRKKRGLFGAIAGF
IEGGWQGMVDGWYGYHHSNEQGSGYAADKESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNNLERRIENL
NKKMEDGFLDVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNECMES
VRNGTYDYPQYSEEARLKREEISGVKLESIGIYQILSIYSTVASSLALAIMVAGLSLWMCSNGSLQCRICI

**>A/mallard/Netherlands/12/00 (H7N3)**
MNTQILVFALMAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATETVERTNVPRICSKGKRTVDLGQ
CGLLGTITGPPQCDQFLEFSADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTYSGIRTNG
ATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKDPALIIWGIHHSGSTTEQTKLYGSGNKLITV
GSSNYQQSFVPSPGARPQVNGQSGRIDFHWLILNPNDTVTFSFNGAFIAPDRASFLRGKSMGIQSGVQVDA
NCEGDCYHSGGTIISNLPFQNINSRAVGKCPRYVKQESLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEG
LIDGWYGFRHQNAQGEGTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFTEVEKQIGNVINWTRDS
MTEVWSYNAELLVAMENQHTIDLADSEMNKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYD
HSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLVFICVKNGNMRCTICI

**>A/chicken/Netherlands/621557/03 (H7N7)**
MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATETVERTNVPRICSKGKRTVDLGQ
CGLLGTITGPPQCDQFLEFSADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTYSGIRTNG
ATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKDPALIIWGIHHSGSTTEQTKLYGSGNKLITV
GSSNYQQSFVPSPGARPQVNGQSGRIDFHWLILNPNDTVTFSFNGAFIAPDRASFLRGKSMGIQSEVQVDA
NCEGDCYHSGGTIISNLPFQNINSRAVGKCPRYVKQESLLLATGMKNVPEIPKRRRRGLFGAIAGFIENGW
EGLIDGWYGFRHQNAQGEGTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFTEVEKQIGNVINWTR
DSMTEVWSYNAELLVAMENQHTIDLADSEMNKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT
YDHSKYREEAIQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLVFICVKNGNMRCTICI

**>A/New York/107/03 (H7N7)**
MNTQILAFIACVLTGVKGDKICLGHHAVANGTKVNTLTERGIEVVNATETVETTNIKKICTQGKRPTDLGQ
CGLLGTLIGPPQCDQFLEFSSDLIIERREGTDICYPGRFTNEESLRQILRRSGGIGKESMGFTYSGIRTNG
ATSACTRSGSSFYAEMKWLLSNSDNAAFPQMTKAYRNPRNKPALIIWGVHHSESVSEQTKLYGSGNKLITV
RSSKYQQSFTPNPGARRIDFHWLLLDPNDTVTFTFNGAFIAPDRTSFFRGESLGVQSDAPLDSSCRGDCFH
SGGTIVSSLPFQNINSRTVGKCPRYVKQKSLLLATGMRNVPEKPKPRGLFGAIAGFIENGWEGLINGWYGF
RHQNAQGEGTAADYKSTQSAIDQITGKLNRLIGKTNQQFELIDNEFNEIEQQIGNVINWTRDAMTEIWSYN
AELLVAMENQHTIDLADSEMSKLYERVKKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNTYDHTQYRTES
LQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAIAMGLVFICIKNGNMQCTICI

**>A/Hong Kong/1073/99 (H9N2)**
METISLITILLVVTASNADKICIGHQSTNSTETVDTLTETNVPVTHAKELLHTEHNGMLCATSLGHPLILD
TCTIEGLVYGNPSCDLLLGGREWSYIVERSSAVNGTCYPGNVENLEELRTLFSSASSYQRIQIFPDTTWNV
TYTGTSRACSGSFYRSMRWLTQKSGFYPVQDAQYTNNRGKSILFVWGIHHPPTYTEQTNLYIRNDTTTSVT
TEDLNRTFKPVIGPRPLVNGLQGRIDYYWSVLKPGQTLRVRSNGNLIAPWYGHVLSGGSHGRILKTDLKGG
NCVVQCQTEKGGLNSTLPFHNISKYAFGTCPKYVRVNSLKLAVGLRNVPARSSRGLFGAIAGFIEGGWPGL
VAGWYGFQHSNDQGVGMAADRDSTQKAIDKITSKVNNIVDKMNKQYEIIDHEFSEVETRLNMINNKIDDQI
QDVWAYNAELLVLLENQKTLDEHDANVNNLYNKVKRALGSNAMEDGKGCFELYHKCDDQCMETIRNGTYNR
RKYREESRLERQKIEGVKLESEGTYKILTIYSTVASSLVLAMGFAAFLFWAMSNGSCRCNICI

**>A/chicken/Germany/n/49 (H10N7)**
MYKVVVIIALLGAVKGLDRICLGHHAVANGTIVKTLTNEQEEVTNATETVESTNLNKLCMKGRSYKDLGNC
HPVGMLIGTPVCDPHLTGTWDTLIERENAIAHCYPGATINEEALRQKIMESGGISKMSTGFTYGSSINSAG
TTKACMRNGGDSFYAELKWLVSKTKGQNFPQTTNTYRNTDTAEHLIIWGIHHPSSTQEKNDLYGTQSLSIS
VESSTYQNNFVPVVGARPQVNGQSGRIDFHWTLVQPGDNITFSHNGGLIAPSRVSKLTGRGLGIQSEALID
NSCESKCFWRGGSINTKLPFQNLSPRTVGQCPKYVNQRSLLLATGMRNVPEVVQGRGLFGAIAGFIENGWE
GMVDGWYGFRHQNAQGTGQAADYKSTQAAIDQITGKLNRLIEKTNTEFESIESEFSETEHQIGNVINWTKD
SITDIWTYQAELLVAMENQHTIDMADSEMLNLYERVRKQLRQNAEEDGKGCFEIYHTCDDSCMESIRNNTY
DHSQYREEALLNRLNINSVKLSSGYKDIILWFSFGASCFVLLAVVMGLVFFCLKNGNMRCTICI

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