```
                                ▼(Mature residue 1)
H1          -MKANLLVLLCALA--AAD--------ADTICIGYHANNSTDTVDTVLEKNVTVTHSVNL
H2          ---MAIIYLILLFT--AVR--------GDQICIGYHSNNSTEKVDTILERNVTVTHAQNI
H3          --MKTIIALSYIFCLALGQDLPGNDNSTATLCLGHHAVPNGTLVKTITDDQIEVTNATEL
H4          --MLSIVILFLLIAENS----SQNYTGNPVICMGHHAVANGTMVKTLADDQVEVVTAQEL
H5          --MERIVLLLAIVS--LVK--------SDQICIGYHANKSTKQVDTIMEKNVTVTHAQDI
H6          --MIAIIVVAILAT--AGR--------SDKICIGYHANNSTTQIDTILEKNVTVTHSVEL
H7          --MNTQILVFALVAVIPTN--------ADKICLGHHAVSNGTKVNTLTERGVEVVNATET
H8          --MEKFIAIAT-LASTNA---------YDRICIGYQSNNSTDTVNTLIEQNVPVTQTMEL
H9          --METKAIIAALLMVTAAN--------ADKICIGYQSTNSTETVDTLTESNVPVTHTKEL
H10         --MYKVVVIIALLGAVKG---------LDRICLGHHAVANGTIVKTLTNEQEEVTNATET
H11         --MEKTLLFAAIFL--CVK--------ADEICIGYLSNNSTDKVDTIIENNVTVTSSVEL
H12         --MEKFIILSTVLAASFA---------YDKICIGYQTNNSTETVNTLSEQNVPVTQVEEL
H13         -MALNVIATLTLIS-VCVH--------ADRICVGYLSTNSSERVDTLLENGVPVTSSIDL
H14         --MIALILVALALSHTAYSQITNGTTGNPIICLGHHAVENGTSVKTLTDNHVEVVSAKEL
H15         --MNTQIIVILVLGLSMVK--------SDKICLGHHAVANGTKVNTLTERGVEVVNATET
H16         -MMIKVLYFLIIVLGRYSK--------ADKICIGYLSNNSSDTVDTLTENGVPVTSSVDL
H17         MELIVLLILLNPYT--FVL--------GDRICIGYQANQNNQTVNTLLEQNVPVTGAQEI
                                ▲(Mature residue 1)
                    ▼(Residue Ap)                          (Residue Cp)▼
H1          LEDSHNGKLCRLKGIAPLQLGKCNIAGWLLGNPECDPLLPVRSWSYIVETPNSENGICYP
H2          LEKTHNGKLCKLNGIPPLELGDCSIAGWLLGNPECDRLLTVPEWSYIMEKENPRNGLCYP
H3          VQSSSTGKICNN-PHRILDGIDCTLIDALLGDPHCDVFQNET-WDLFVERSKAFS-NCYP
H4          VESQNLPELCPS-PLRLVDGQTCDIINGALGSPGCDHLNGAE-WDVFIERPNAVD-TCYP
H5          LERTHNGKLCSLNGVKPLILRDCSVAGWLLGNPMCDEFLNLPEWLYIVEKDNPINSLCYP
H6          LENQKEERFCKILKKAPLDLKGCTIEGWILGNPQCDLLLGDQSWSYIVERPTAQNGICYP
H7          VERTNIPKICSK-GKRTTDLGQCGLLGTITGPPQCDQFLEFS-ADLIIERREGND-VCYP
H8          VETEKHPAYCNTDLGAPLELRDCKIEAVIYGNPKCDIHLKDQGWSYIVERPSAPEGMCYP
H9          LHTEHNGMLCATDLGHPLILDTCTIEGLIYGNPSCDILLGGKEWSYIVERSSAVNGMCYP
H10         VESTNLNKLCMK-GRSYKDLGNCHPVGMLIGTPVCDPHLTGT-WDTLIERENAIA-HCYP
H11         VETEHTGSFCSINGKQPISLGDCSFAGWILGNPMCDELIGKTSWSYIVEKPNPTNGICYP
H12         VHRGIDPILCGTELGSPLVLDDCSLEGLILGNPKCDLYLNGREWSYIVERPKEMEGVCYP
H13         IETNHTGTYCSLNGVSPVHLGDCSFEGWIVGNPACTSNFGIREWSYLIEDPAAPHGLCYP
H14         VETNHTDELCPS-PLKLVDGQDCHLINGALGSPGCDRLQDTT-WDVFIERPTAVD-TCYP
H15         VEITGIDKVCTK-GKKAVDLGSCGILGTIIGPPQCDLHLEFK-ADLIIERRNSSD-ICYP
H16         VETNHTGTYCSLNGISPIHLGDCSFEGWIVGNPSCATNINIREWSYLIEDPNAPNKFCYP
H17         LETNHNGKLCSLNGVPPLDLQSCTLAGWLLGNPNCDSLLEAEEWSYIKINESAPDDLCFP
                    ▲(Residue Ap)                          (Residue Cp)▲

H1          GDFIDYEELREQLSSVSSFERFEIFPKESSWPNHNTNGVTAACSHE-GKSSFYRNLLWLT
H2          GSFNDYEELKHLLSSVTHFEKVKILPKDRWTQHTTTGG-SRACAVS-GNPSFFRNMVWLT
H3          YDVPDYASLRSLVASSGTLE--FITEGFTW-TGVTQNGGSNACKRG-PGNGFFSRLNWLT
H4          FDVPEYQSLRSILANNGKFE--FIAEEFQW-NTVKQNGKSGACKRA-NVDDFFNRLNWLV
H5          GDFNDYEELKYLLSSTNHFEKIRIIPRSSWSNHDASSGVSSACPYI-GRSSFLRNVVWLI
H6          GVLNEVEELKALIGSGERVERFEMFPKSTWTGVDTSSGVTRACPYN-SGSSFYRNLLWII
H7          GKFVNEEALRQILRGSGGID--KETMGFTY-SGIRTNGTTSACRRS-G-SSFYAEMEWLL
H8          GSVENLEELRFVFSSAASYKRIRLFDYSRWNVTRS--GTSKACNASTGGQSFYRSINWLT
H9          GNVENLEELRSLFSSAKSYKRIQIFPDKTWNVTYS--GTSRACSN-----SFYRSMRWLT
H10         GATINEEALRQKIMESGGIS--KMSTGFTYGSSITSAGTTKACMRN-GGDSFYAELKWLV
H11         GTLESEEELRLKFSGVLEFNKFEVFTSNGWGAVNSGVGVTAACKFG-GSNSFFRNMVWLI
H12         GSIENQEELRSLFSSIKKYERVKMFDFTKWNVTYT--GTSKACNNTSNQGSFYRSMRWLT
H13         GELNNNGELRHLFSGIRSFSRTELIPPTSWGEVLD--GTTSACRDNTGTNSFYRNLVWFI
H14         FDVPDYQSLRSILASSGSLE--FIAEQFTW-NGVKVDGSSSACLRG-GRNSFFSRLNWLT
H15         GRFTNEEALRQIIRESGGID--KESMGFRY-SGIRTDGATSACKRT-V-SSFYSEMKWLS
H16         GELDNNGELRHLFSGVNSFSRTELINPSKWGNVLD--GVTASCLDR-GASSFYRNLVWIV
H17         GNFENLQDLLLEMSGVQNFTKVKLFNPQSMTG-VTTNNVDQTCPFE-GKPSFYRNLNWIQ
```

FIG. 1A

```
H1          E-K-EGSYPKLKNSYVNKKGKEVLVLWGIHHPPNSKEQQNLYQNENAYVSVVTSNYNRRF
H2          K-K-GSNYPIAKGSYNNTSGEQMLIIWGVHHPNDETEQRTLYQNVGTYVSIGTSTLNKRS
H3          KS--GSTYPVLNVTMPNNDNFDKLYIWGVHHPSTNQEQTSLYVQESGRVTVSTRRSQQSI
H4          KSD-GNAYPLQNLTKINNGDYARLYIWGVHHPSTSTEQTNLYKNNPGRVTVSTKTSQTSV
H5          K-K-NNTYPTIKRSYNNTNQEDLLILWGIHHPNDAAEQTKLYQNPTTYVSVGTSTLNQRS
H6          KTK-SAAYSVIKGAYNNTGNQPILYFWGVHHPPDTNEQNTLYGSGDRYVRMGTESMNFAK
H7          SNTDNASFPQMTKSYKNTRRESALIVWGIHHSGSTTEQTKLYGSGNKLITVGSSKYHQSF
H8          KKE-PDTYDFNEGAYVNNEDGDIIFLWGIHHPPDTKEQTTLYKNANTLSSVTTNTINRSF
H9          HK--SNSYPFQNAHYTNNERENILFMWGIHHPPTDTEQTDLYKNADTTTSVTTEDINRTF
H10         SKTKGQNFPQTTNTYRNTDTAEHLIIWGIHHPSSTQEKNDLYGTQSLSISVESSTYQNNF
H11         H-Q-SGTYPVIKRTFNNTKGRDVLIVWGIHHPATLTEHQDLYKKDSSYVAVGSETYNRRF
H12         LK--SGQFPVQTDEYKNTRDSDIVFTWAIHHPPTSDEQVKLYKNPDTLSSVTTVEINRSF
H13         K-K-NTRYPVISKTYNNTTGRDVLVLWGIHHPVSVDETKTLYVNSDPYTLVSTKSWSEKY
H14         KAT-NGNYGPINVTKENTGSYVRLYLWGVHHPSSDNEQTDLYKVATGRVTVSTRSDQISI
H15         SSMNNQVFPQLNQTYRNTRKEPALIVWGVHHSSSLDEQNKLYGTGNKLITVGSSKYQQSF
H16         K-K-DEKYPVIKGDYNNTTGRDVLVLWGIHHPDTETTATNLYVNKNPYTLVSTKEWSKRY
H17         G----NSGLPFNIEIKNPTSNPLLLLWGIHNTKDAAQQRNLYGNDYSYTIFNFGEKSEEF

                                                    ▼(Residue Cq)
H1          TPEIAERPKVRDQAGRMNYYWTLLKPGDTIIFEANGNLIAPMYAFALSRGFG--------
H2          IPVIATRPKVNGQGGRMEFSWTILDIWDTINFESTGNLIAPEYGFRISKRGS--------
H3          IPNIGSRPWVRGQSSRISIYWTIVKPGDVLVINSNGNLIAPRGYFKMRTG---------K
H4          VPDIGSRPLVRGQSGRVSFYWTIVEPGDLIVFNTIGNLIAPRGHYKLNNQK--------K
H5          IPEIATRPKVNGQSGRMEFFWTILKPNDAINFESNGNFIAPRYAYKIVKKGD--------
H6          SPEIAARPAVNGQRGRIDYYWSILKPGETLNVESNGNLIAPWYAFRFVSTSNK-------
H7          VPSPGTRPQINGQSGRIDFHWLILDPNDTVTFSFNGAFIAPNRASFLR----------GK
H8          QPNIGPRPLVRGQQGRMDYYWGILKRGETLKIRTNGNLIAPEFGYLLKGESY--------
H9          KPVIGPRPLVNGQQGRIDYYWSVLKPGQTLRIRSNGNLIAPWYGHVLTGESH--------
H10         VPVVGARPQVNGQSGRIDFHWTLVQPGDNITFSDNGGLIAPSRVSKLT----------GR
H11         TPEINTRPRVNGQAGRMTFYWKIVKPGESITFESNGAFLAPRYAFEIVSVGN--------
H12         KPNIGPRPLVRGQQGRMDYYWAVLKPGQTVKIQTNGNLIAPEYGHLITGKSH--------
H13         KLETGVRPGYNGQRSWMKIYWSLIHPGEMITFESNGGFLAPRYGYIIEEYGK--------
H14         VPNIGSRPRVRNQSGRISIYWTLVNPGDSIIFNSIGNLIAPRGHYKISKST--------K
H15         SPSPGARPKVNGQAGRIDFHWMLLDPGDTVTFTFNGAFIAPDRATFLRSNAPSGIEYNGK
H16         ELEIGTRIG-DGQRSWMKLYWHLMHPGERIMFESNGGLIAPRYGYIIEKYGT--------
H17         RPEIGQRDEVKAHQDRIDYYWGSLPAQSTLRIESTGNLIAPEYGFYYKRKEGK-------
                                                    ▲(Residue Cq)

                            ▼(Residue Aq)           ▼(Residue Bq)
H1          SGIITS-NASMHECNTKCQTPLGAINSSLPYQNIHPVTIGECPKYVRSAKLRMVTGLRNN
H2          SGIMKT-EGTLENCETKCQTPLGAINTTLPFHNVHPLTIGECPKYVKSERLVLATGLRNV
H3          SSIMSSDAPIDT-CISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLATGMRNV
H4          STILNTAIPIGS-CVSKCHTDKGSLSTTKPFQNISRIAVGDCPRYVKQGSLKLATGMRNI
H5          SAIMKS-GLAYGNCDTKCQTPVGEINSSMPFHNIHPHTIGECPKYVKSDRLVLATGLRNV
H6          GAVFKS-NLPIENCDATCQTVAGVLRTNKTFQNVSPLWIGECPKYVKSESLRLATGLRNV
H7          SMGIQSDVQVDANCEGECYHSGGTITSRLPFQNINSRAVGKCPRYVKQESLLLATGMKNV
H8          GRIIQNEDIPIGNCNTKCQTYAGAINSSKPFQNASRHYMGECPKYVKKASLRLAVGLRNT
H9          GRILKT-DLNNGNCVVQCQTEKGGLNTTLPFHNISKYAFGNCPKYVGVKSLKLPVGLRNV
H10         DLGIQSEALIDNSCESKCFWRGGSINTKLPFQNLSPRTVGQCPKYVNQRSLLLATGMRNV
H11         GKLFRS-ELNIESCSTKCQTEIGGINTNKSFHNVHRNTIGDCPKYVNVKSLKLATGPRNV
H12         GRILKN-NLPMGQCVTECQLNEGVMNTSKPFQNTSKHYIGKCPKYIPSGSLKLAIGLRNV
H13         GRIFQS-RIRMSRCNTKCQTSVGGINTNRTFQNIDKNALGDCPKYIKSGQLKLATGLRNV
H14         STVLKSDKRIGS-CTSPCLTDKGSIQSDKPFQNVSRIAIGNCPKYVKQGSLMLATGMRNI
H15         SLGIQSDAQIDESCEGECFYSGGTINSPLPFQNIDSRAVGKCPRYVKQSSLPLALGMKNV
H16         GRIFQS-GVRMARCNTKCQTSLGGINTNKTFQNIERNALGDCPKYIKSGQLKLATGLRNV
H17         GGLMKS-KLPISDCSTKCQTPLGALNSTLPFQNVHQQTIGNCPKYVKATSLMLATGLRNN
                            ▲(Residue Aq)           ▲(Residue Bq)
```

FIG. 1B

```
                    ▼(HA2 domain starts)
H1          P----SIQSRGLFGAIAGFIEGGWTGMIDGWYGYHHQNEQGSGYAADQKSTQNAINGITN
H2          P----QIESRGLFGAIAGFIEGGWQGMIDGWYGYHHSNDQGSGYAADKESTQKAIDGITN
H3          P----EKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAIDQING
H4          P----EKASRGLFGAIAGFIENGWQGLIDGWYGFRHQNAEGTGTAADLKSTQAAIDQING
H5          P----QRKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSGYAADKESTQKAIDGITN
H6          P----QIETRGLFGAIAGFIEGGWTGMIDGWYGYHHENSQGSGYAADRESTQKAVDGITN
H7          PEPSKKRKKRGLFGAIAGFIENGWEGLVDGWYGFRHQNAQGEGTAADYKSTQSAIDQITG
H8          P----SVEPRGLFGAIAGFIEGGWSGMIDGWYGFHHSNSEGTGMAADQKSTQEAIDKITN
H9          P----AVSSRGLFGAIAGFIEGGWPGLVAGWYGFQHSNDQGVGMAADKGSTQKAIDKITS
H10         P---EVVQGRGLFGAIAGFIENGWEGMVDGWYGFRHQNAQGTGQAADYKSTQAAIDQITG
H11         P----AIASRGLFGAIAGFIEGGWPGLINGWYGFQHRDEEGTGIAADKESTQKAIDQITS
H12         P----QVQDRGLFGAIAGFIEGGWPGLVAGWYGFQHQNAEGTGIAADRDSTQRAIDNMQN
H13         P----AISNRGLFGAIAGFIEGGWPGLINGWYGFQHQNEQGTGIAADKESTQKAIDQITT
H14         P----GKQAKGLFGAIAGFIENGWQGLIDGWYGFRHQNAEGTGTAADLKSTQAAIDQING
H15         P---EKIRTRGLFGAIAGFIENGWEGLIDGWYGFRHQNAQGQGTAADYKSTQAAIDQITG
H16         P----SIGERGLFGAIAGFIEGGWPGLINGWYGFQHQNEQGTGIAADKASTQKAINEITT
H17         P----QMEGRGLFGAIAGFIEGGWQGMIDGWYGYHHENQEGSGYAADKEATQKAVDAITN
                    ▲(HA2 domain starts)

H1          KVNTVIEKMNIQFTAVGKEFNKLEKRMENLNKKVDDGFLDIWTYNAELLVLLENERTLDF
H2          RVNSVIEKMNTQFEAVGKEFSNLEKRLENLNKKMEDGFLDVWTYNAELLVLMENERTLDF
H3          KLNRVIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDL
H4          KLNRLIEKTNDKYHQIEKEFEQVEGRIQDLENYVEDTKIDLWSYNAELLVALENQHTIDV
H5          KVNSIIDKMNTRFEAVGKEFNNLERRVENLNKKMEDGFLDVWTYNVELLVLMENERTLDF
H6          KVNSIIDKMNTQFEAVDHEFSNLERRIDNLNKRMEDGFLDVWTYNAELLVLLENERTLDL
H7          KLNRLIEKTNQQFELIDNEFTEVEKQIGNLINWTKDSITEVWSYNAELIVAMENQHTIDL
H8          KVNNIVDKMNREFEVVNHEFSEVEKRINMINDKIDDQIEDLWAYNAELLVLLENQKTLDE
H9          KVNNIIDKMNKQYEVIDHEFNELEARLNMINNKIDDQIQDIWAYNAELLVLLENQKTLDE
H10         KLNRLIEKTNTEFESIESEFSETEHQIGNVINWTKDSITDIWTYNAELLVAMENQHTIDM
H11         KVNNIVDRMNTNFESVQHEFSEIEERINQLSKHVDDSVVDIWSYNAQLLVLLENEKTLDL
H12         KLNNVIDKMNKQFEVVNHEFSEVESRINMINSKIDDQITDIWAYNAELLVLLENQKTLDE
H13         KINNIIDKMNGNYDSIRGEFNQVEKRINMLADRIDDAVTDIWSYNAKLLVLLENDKTLDM
H14         KLNRLIEKTNEKYHQIEKEFEQVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDV
H15         KLNRLIEKTNKQFELIDNEFTEVEQQIGNVINWTRDSLTEIWSYNAELLVAMENQHTIDL
H16         KINNIIEKMNGNYDSIRGEFNQVEKRINMLADRVDDAVTDIWSYNAKLLVLLENDRTLDL
H17         KVNSIIDKMNSQFESNIKEFNRLELRIQHLSDRVDDALLDIWSYNTELLVLLENERTLDF


H1          HDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCDNECMESVRNGTYDYPKYSEESKLNR
H2          HDSNVKNLYDRVRMQLRDNAKELGNGCFEFYHKCDDECMNSVKNGTYDYPKYEEESKLNR
H3          TDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESIRNGTYDHDVYRDEALNNR
H4          TDSEMNKLFERVRRQLRENAEDKGNGCFEIFHKCDNNCIESIRNGTYDHDIYRDEAINNR
H5          HDSNVNNLYDKVRLQLKDNARELGNGCFEFYHKCDNECMESVRNGTYDYPQYSEEARLNR
H6          HDANVKNLYERVKSQLRDNAMILGNGCFEFWHKCDDECMESVKNGTYDYPKYQDESKLNR
H7          ADSEMNRLYERVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYREEAMQNR
H8          HDSNVKNLFDEVKRRLSANAIDAGNGCFDILHKCDNECMETIKNGTYDHKEYEEEAKLER
H9          HDANVNNLYNKVKRALGSNAVEDGNGCFELYHKCDDQCMETIRNGTYDRQKYQEESRLER
H10         ADSEMLNLYERVRKQLRQNAEEDGKGCFEIYHTCDDSCMESIRNNTYDHSQYREEALLNR
H11         HDSNVRNLHEKVRRMLKDNAKDEGNGCFTFYHKCDNKCIERVRNGTYDHKEFEEESKINR
H12         HDANVRNLHDRVRRVLRENAIDTGDGCFEILHKCDNNCMDTIRNGTYNHKEYEEESKIER
H13         HDANVKNLHEQVRRELKDNAIDEGNGCFELLHKCNDSCMETIRNGTYDHTEYAEESKLKR
H14         TDSEMNKLFERVRRQLRENAEDQGNGCFEIFHQCDNNCIESIRNGTYDHNIYRDEAINNR
H15         ADSEMNKLYERVRRQLRENAEEDGTGCFEIFHRCDDQCMESIRNNTYNHTEYRQEALQNR
H16         HDANVRNLHDQVKRALKSNAIDEGDGCFNLLHKCNDSCMETIRNGTYNHEDYREESQLKR
H17         HDANVKNLFEKVKAQLKDNAIDEGNGCFLLLHKCNNSCMDDIKNGTYKYMDYREESHIEK
```

FIG. 1C

```
H1          EKVDGVKLESMG-IYQILAIYSTVASSLVLLVSLGAISFWMCSNGSLQCRICI
H2          NEIKGVKLSNMG-VYQILAIYATVAGSLSLAIMIAGISLWMCSNGSLQCRICI
H3          FQIKGVELKSGY--KDWILWISFAISCFLLCVVLLGFIMWACQRGNIRCNICI
H4          FQIQGVKLTQGY--KDIILWISFSISCFLLVALLLAFILWACQNGNIRCQICI
H5          EEISGVKLESMG-VYQILSIYSTVASSLALAIMIAGLSFWMCSNGSLQCRICI
H6          QEIESVKLESLG-VYQILAIYSTVSSSLVLVGLIIAVGLWMCSNGSMQCRICI
H7          IQIDPVKLSSGY--KDVILWFSFGASCFLLLAIAMGLVFICVKNGNMRCTICI
H8          SKINGVKLEENT-TYKILSIYSTVAASLCLAILIAGGLILGMQNGSCRCMFCI
H9          QKIEGVKLESEG-TYKILTIYSTVASSLVLAMGFAAFLFWAMSNGSCRCNICI
H10         LNINPVKLSSGY--KDIILWFSFGESCFVLLAVVMGLVFFCLKNGNMRCTICI
H11         QEIEGVKLDSSGNVYKILSIYSCIASSLVLAALIMGFMFWACSNGSCRCTICI
H12         QKVNGVKLEENS-TYKILSIYSSVASSLVLLLMIIGGFIFGCQNGNVRCTFCI
H13         QEIDGIKLKSEDNVYKALSIYSCIASSVVLVGLILSFIMWACSSGNCRFNVCI
H14         IKINPVTLTMGY--KDIILWISFSMSCFVFVALILGFVLWACQNGNIRCQICI
H15         IMINPVKLSSGY--KDVILWFSFGASCVMLLAIAMGLIFMCVKNGNLRCTICI
H16         QEIEGIKLKTEDNVYKVLSIYSCIASSIVLVGLILAFIMWACSNGSCRFNVCI
H17         QKIDGVKLTDYS-RYYIMTLYSTIASSVVLGSLIIAAFLWGCQKGSIQCKICI
```

FIG. 1D

```
H1   MK--ANLLVLLCALAAADAD--------TICIGYHANNSTDTVDTVLEKNVTVTHSVNLLE
H3   MKTIIALSYIFCLALGQDLPGNDNSTATLCLGHHAVPNGTLVKTITDDQIEVTNATELVQ
HB   MK---AIIVILMVVTSNADR--------ICTGITSSNSPHVVKTATQGEVNVTGVIPLTT

           ▼(Cys52,HA1)
H1   DSHNGKLCRLKG------IAPLQLGKCNIAGWLLGNPECDPLLPVRSWSYIVETPNSENG-
H3   SSSTGKICNNP-------HRILDGIDCTLIDALLGDPHCD-VFQNETWDLFVERSKAFS--
HB   TPTKSHFANLKGTETRGKLCPKCLNCTDLDVALGRPKCTGKIPSARVSILHEVRPVTSGC
                      ▲(Arg50,B-HA1)  ▲(Ala66,B-HA1)▲(Arg80,B-HA1)

H1   ICYPGDFIDYEELREQLSSVSSF--ERFEIFPKESSWPNHNTNGVTAACS-HEGKSSFYR
H3   NCYPYDVPDYASLRSLVASSG-----T-LEFITEGFTWTGVTQNGGSNACK-RGPGNGFFS
HB   FPIMHDRTKIRQLPNLLRGYEHIRLSTHNVINAENAPGGPYKIGTSGSCPNITNGNGFFA

H1   NLLWLIEKE------GSYPKLKNSYVNKKGKEVLVLWGIHHPPNSKEQQNLYQNENAYVS
H3   RLNWLTKSG------STYPVLNVTMPNNDNFDKLYIWGVHHPSTNQEQTSLYVQESGRVT
HB   TMAWAVPKNDKNKTATNPLTIEVPYICTEGEDQITVWGFHSDSETQMAKLYGDSKPQKFT

H1   VVTSNYNRRFTPEIAERPKVRD-----QAGRMNYYWTLLKPGDTIIFEANGNLIAPMYAF
H3   VSTRRSQQSIIPNIGSRPWVRG-----QSSRISIYWTIVKPGDVLVINSNGNLIAPRGYF
HB   SSANGVTTHYVSQIGGFPNQTEDGGLPQSGRIVVDYMVQKSGKTGTITYQRGILLPQKVW

▲(Trp271)

H1   ALSRGFGSGIITSNASMHECNTKCQTPLGAINSSLPYQNIHPVTIGECPKYVRSAKLRMV
H3   KMRTGKSS-IMSSDAPIDTCISECITPNGSIPNDKPFQNVNKITYGACPKYVKQNTLKLA
HB   CASGRSKV-IKGSLPLIGEADCLHEKYGGLNKSKPYYTGEHAKAIGNCPIWVKTP-LKLA
          ▲(Ser277,B-HA1)
```

FIG. 2A

```
                    ▼(HA2 domain starts)
H1   TGLRNNP---SIQSRGLFGAIAGFIEGGWTGMIDGWYGYHHQNEQGSGYAADQKSTQNAI
H3   TGMRNVP---EKQTRGLFGAIAGFIENGWEGMIDGWYGFRHQNSEGTGQAADLKSTQAAI
HB   NGTKYRPPAKLLKERGFFGAIAGFLEGGWEGMIAGWHGYTSHGAHGVAVAADLKSTQEAI
                    ▲(B-HA2 domain starts)

H1   NGITNKVNTVIEKMNIQFTAVGKEFNKLEKRMENLNKKVDDGFLDIWTYNAELLVLLENE
H3   DQINGKLNRVIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQ
HB   NKITKNLNSLSELEVKNLQRLSGAMDELHNEILELDEKVDDLRADTISSQIELAVLLSNE

H1   RTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCDNECMESVRNGTYDYPKYSEE
H3   HTIDLTDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESIRNGTYDHDVYRDE
HB   GIINSEDEHLLALERKLKKMLGPSAVEIGNGCFETKHKCNQTCLDRIAAGTFDAGEFSLP

H1   SKLNR-EKVDGVKLESMGIYQILAIYSTVASSLVLLVSLGAISFWMCSNGSLQCRICI
H3   ALNNR-FQIKGVELKSGYKDWILWISFAISCFLLCVVLLGFI-MWACQRGNIRCNICI
HB   TFDSLNITAASLNDDGLDNHTILLYYSTAASSLAVTLMIAIFVVYMVSRDNVSCSICL
```

FIG. 2B

```
1          DRICTGITSS NSPHVVKTAT QGEVNVTGVI PLTTTPTKSH FANLKGTQTR
                                                          ▲(Arg50)

51         GKLCPNCLNC TDLDVALGRP KCMGTIPSAK ASILHEVKPV TSGCFPIMHD
             ▲(Cys54)      ▲(Ala66)       ▲(Arg/Lys80)     ▲(Cys94)

101        RTKIRQLPNL LRGYENIRLS ARNVTNAETA PGGPYIVGTS GSCPNVTNGN
                                                        ▲(Cys143)

151        GFFATMAWAV PKNKTATNPL TVEVPYICTK GEDQITVWGF HSDDETQMVK
                                    ▲(Cys178)

201        LYGDSKPQKF TSSANGVTTH YVSQIGGFPN QAEDEGLPQS GRIVVDYMVQ

                                          (Cys272)▼     ▼(Ser277)

251        KPGKTGTIAY QRGVLLPQKV WCASGRSKVI KGSLPLIGEA DCLHEKYGGL
                               ▲(Trp271)

301        NKSKPYYTGE HAKAIGNCPI WVKTPLKLAN GTKYRPPAKL LK
```

FIG. 3

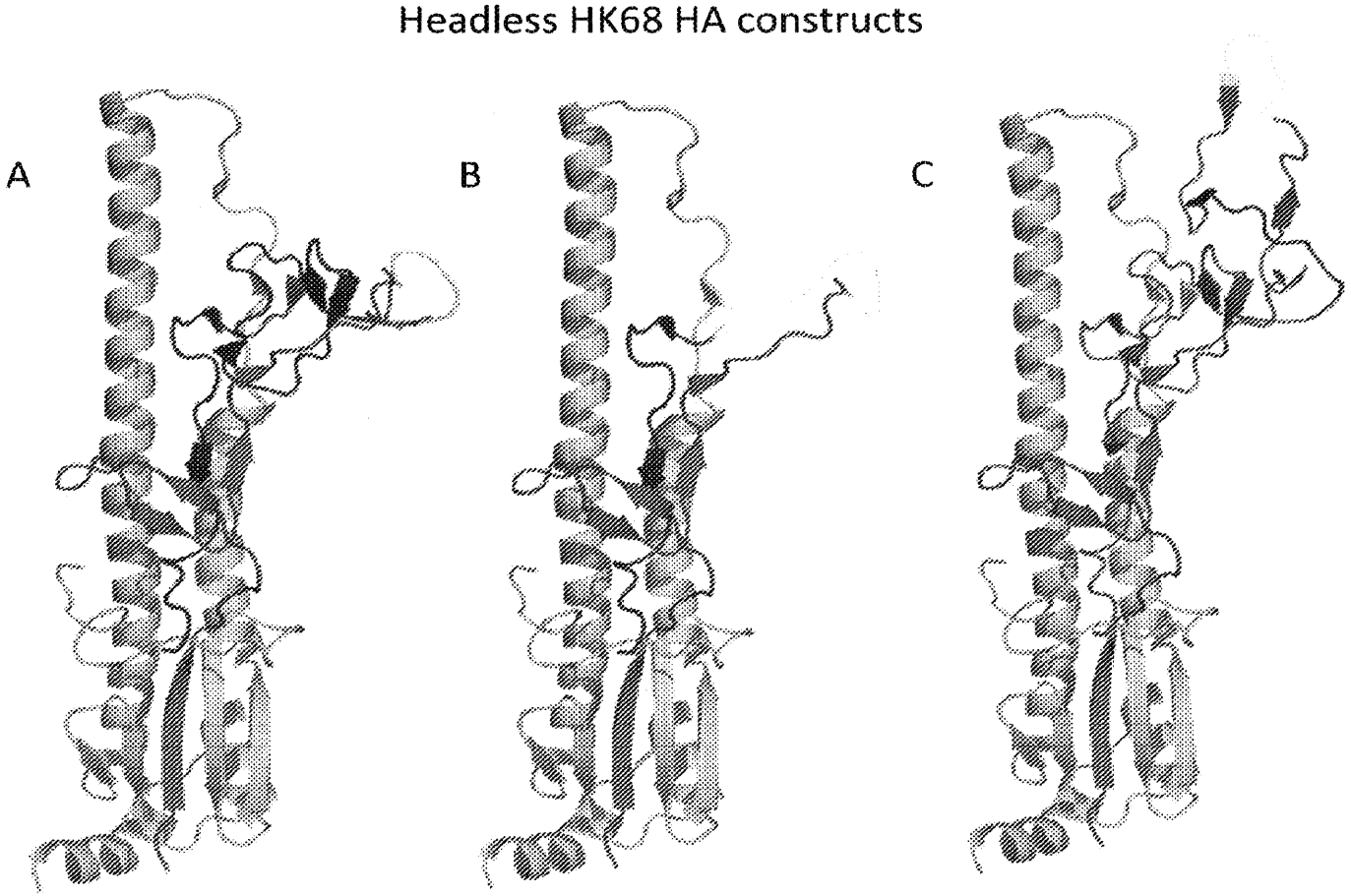


FIG. 4

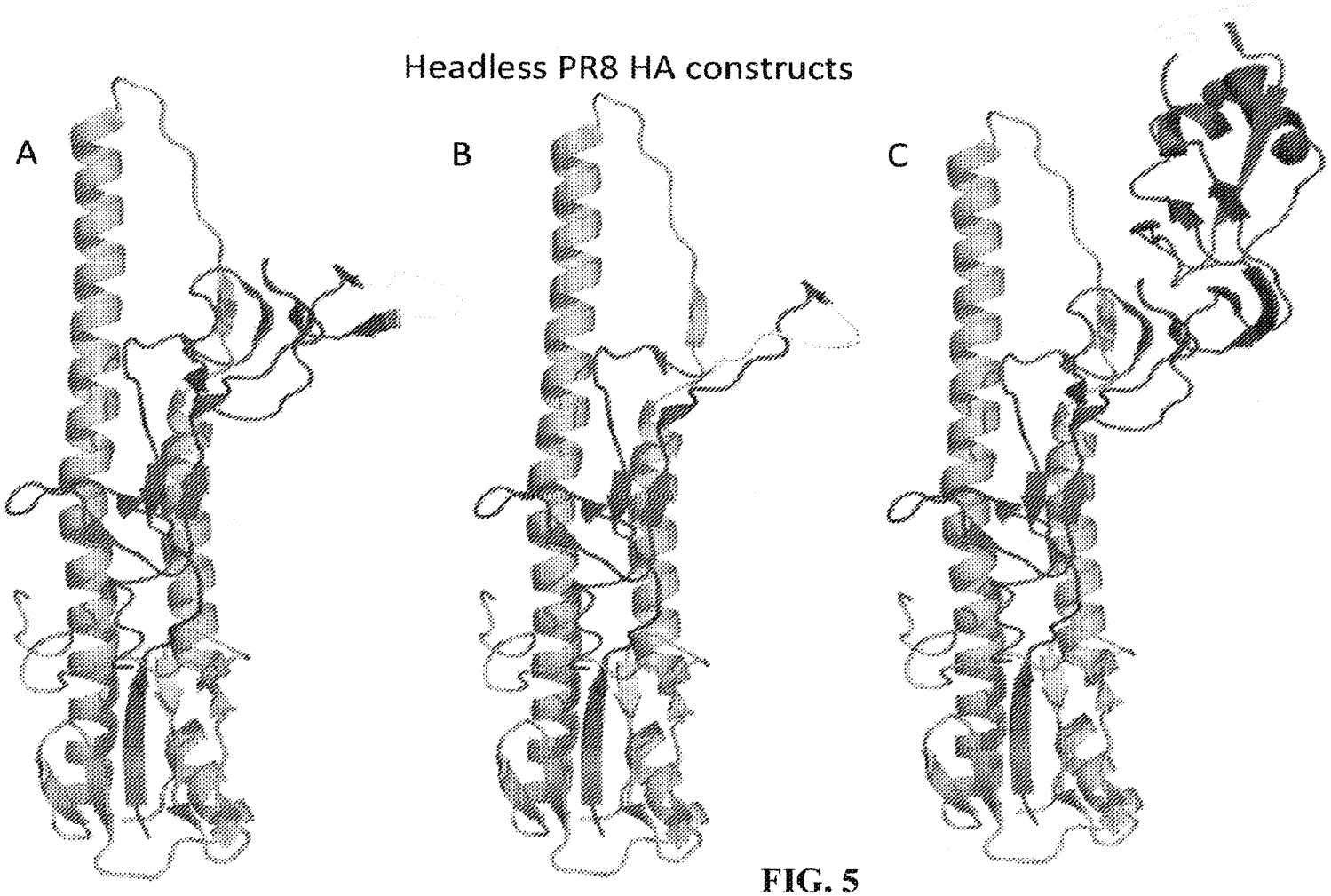


FIG. 5

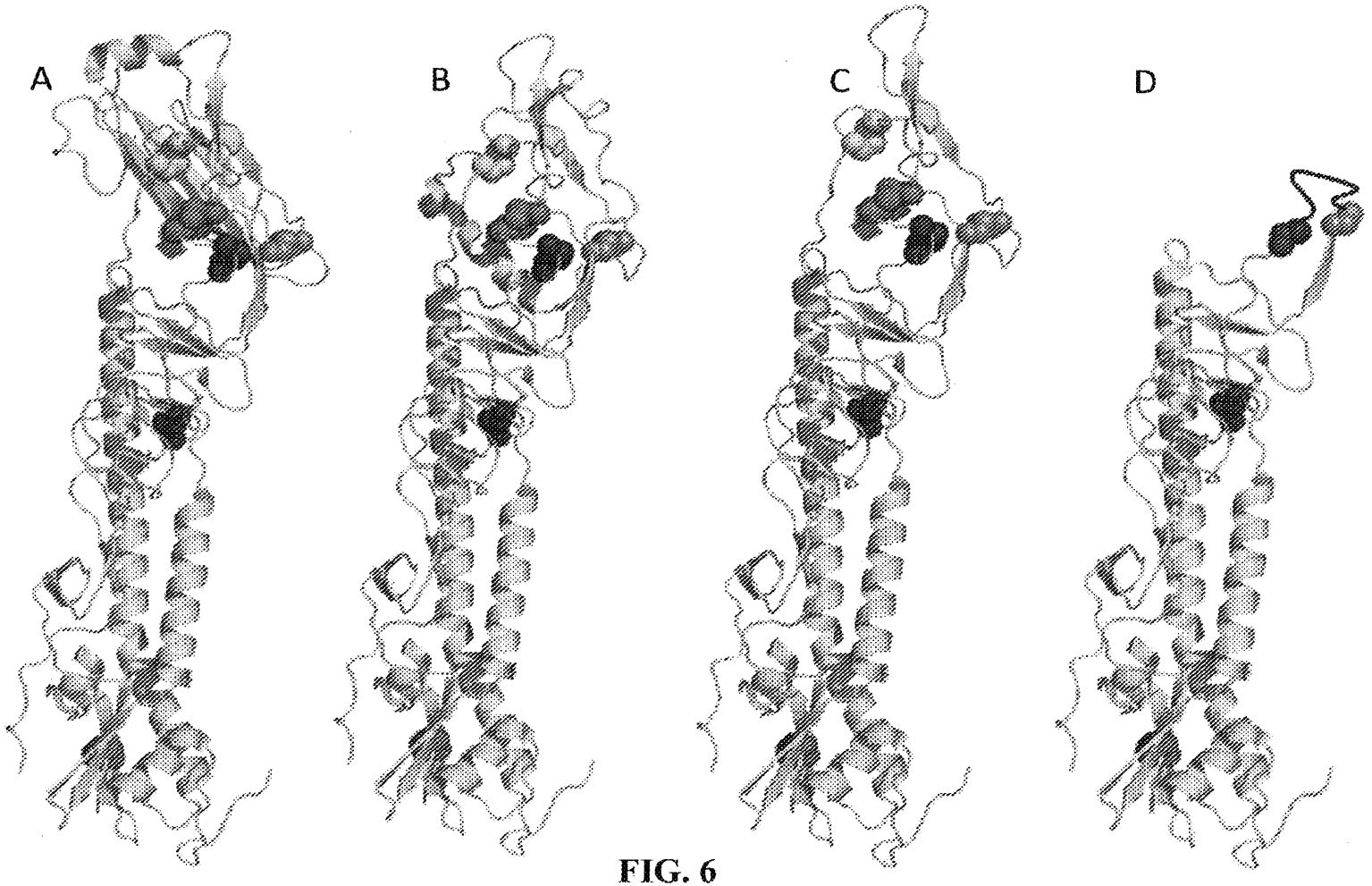


FIG. 6

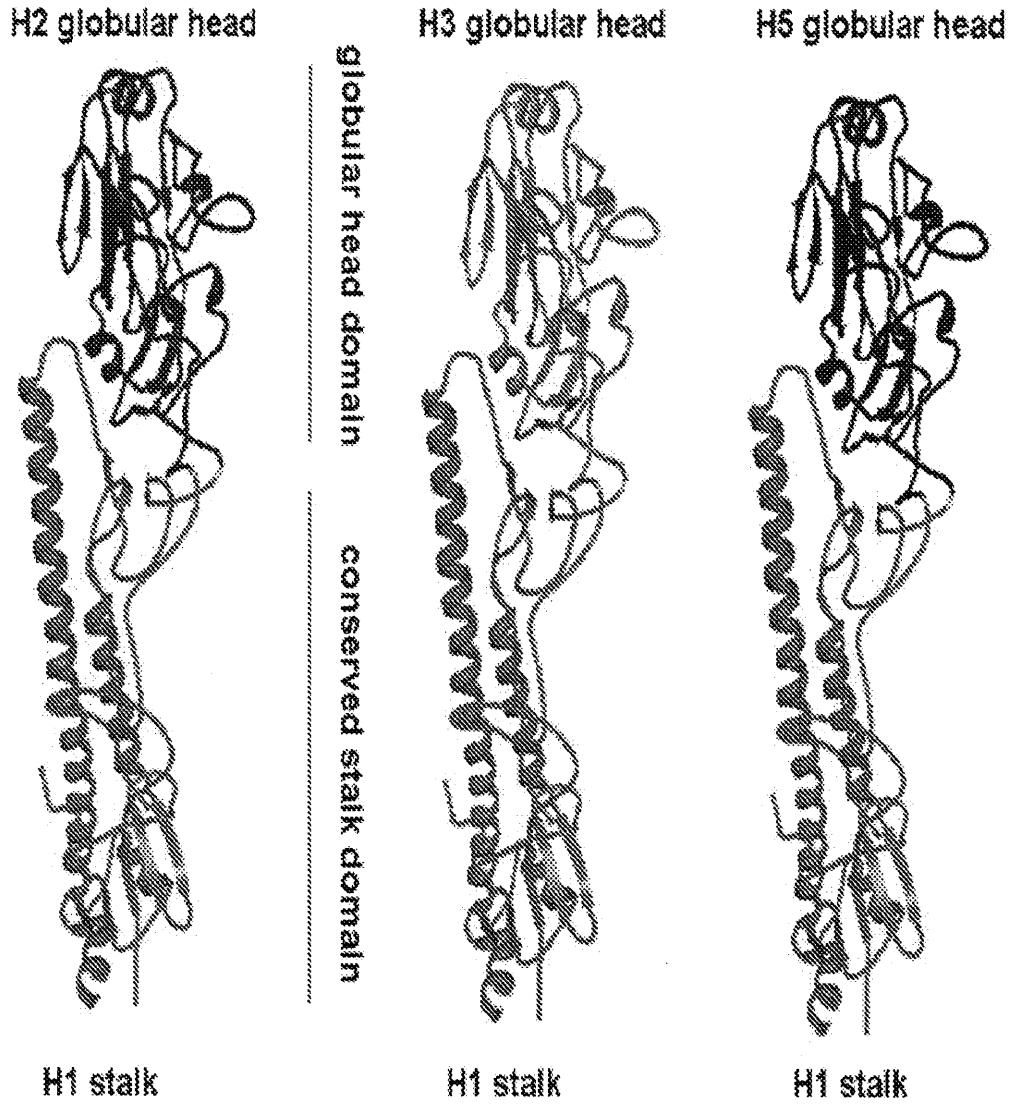

H2 globular head
H3 globular head
H5 globular head
globular head domain
conserved stalk domain
H1 stalk
H1 stalk
H1 stalk

FIG. 7

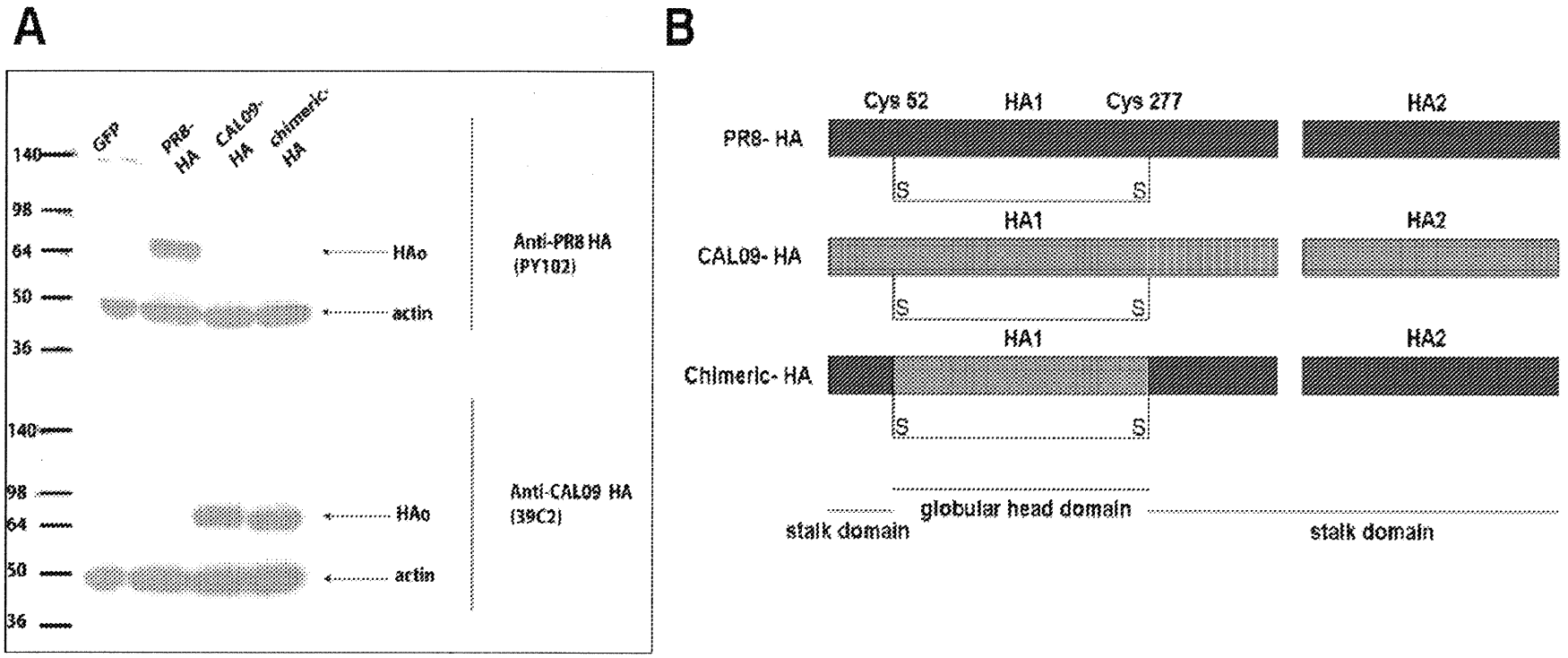

A
GFP
PR8-HA
CAL09-HA
chimeric-HA
140
98
64
50
36
HAo
actin
Anti-PR8 HA (PY102)
140
98
64
50
36
HAo
actin
Anti-CAL09 HA (39C2)
B
Cys 52
HA1
Cys 277
HA2
PR8- HA
S
S
HA1
HA2
CAL09- HA
S
S
HA1
HA2
Chimeric- HA
S
S
globular head domain
stalk domain
stalk domain

Fig. 8

A
Cys 52- Cys277
globular head domain
conserved stalk domain
B
Prime
Boost
Boost

FIG. 9

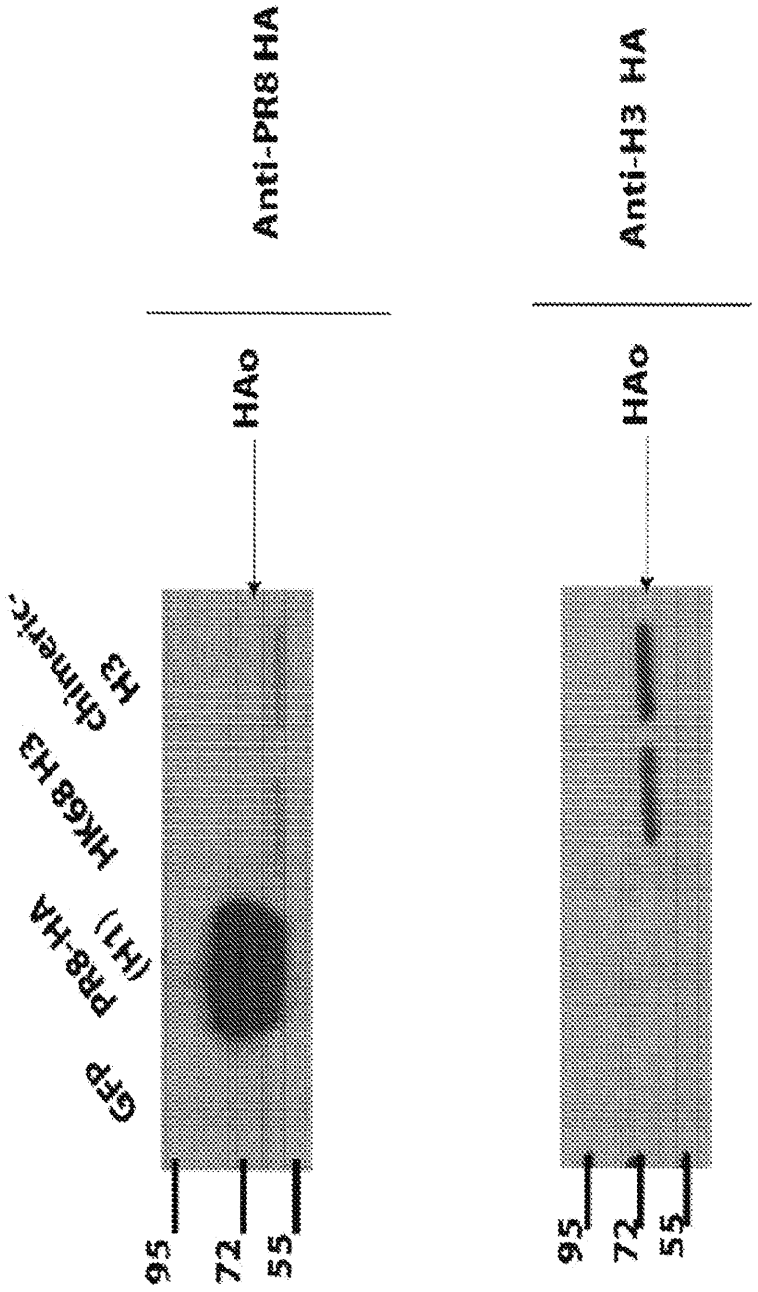

Anti-PR8 HA
Anti-H3 HA
HAo
HAo
GFP
PR8-HA (H1)
HK68 H3
Chimeric-H3
95
72
55
95
72
55

FIG. 10

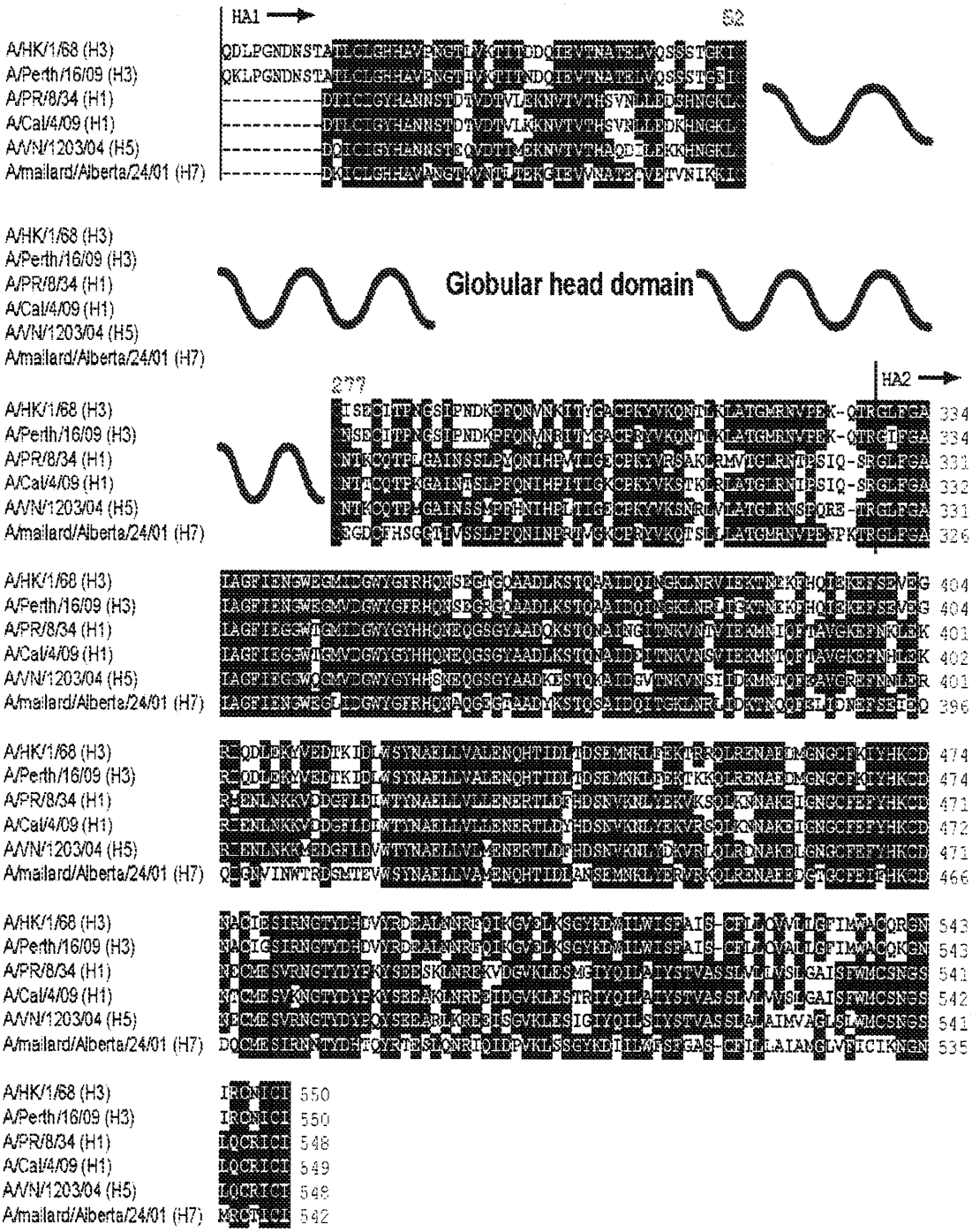
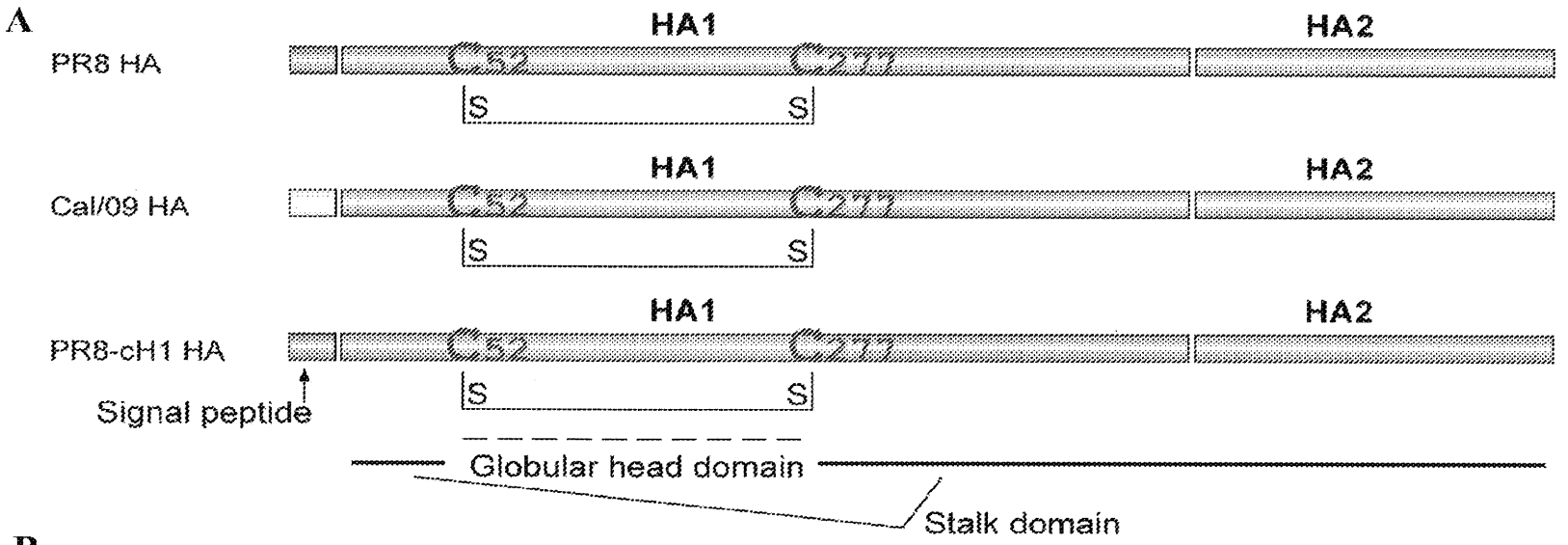

HA1
S2
A/HK/1/68 (H3)
A/Perth/16/09 (H3)
A/PR/8/34 (H1)
A/Cal/4/09 (H1)
A/VN/1203/04 (H5)
A/mallard/Alberta/24/01 (H7)
Globular head domain
277
HA2

FIG. 11


A
HA1
HA2
PR8 HA
C52
C277
S
S
HA1
HA2
Cal/09 HA
C52
C277
S
S
HA1
HA2
PR8-cH1 HA
C52
C277
S
S
Signal peptide
Globular head domain
Stalk domain

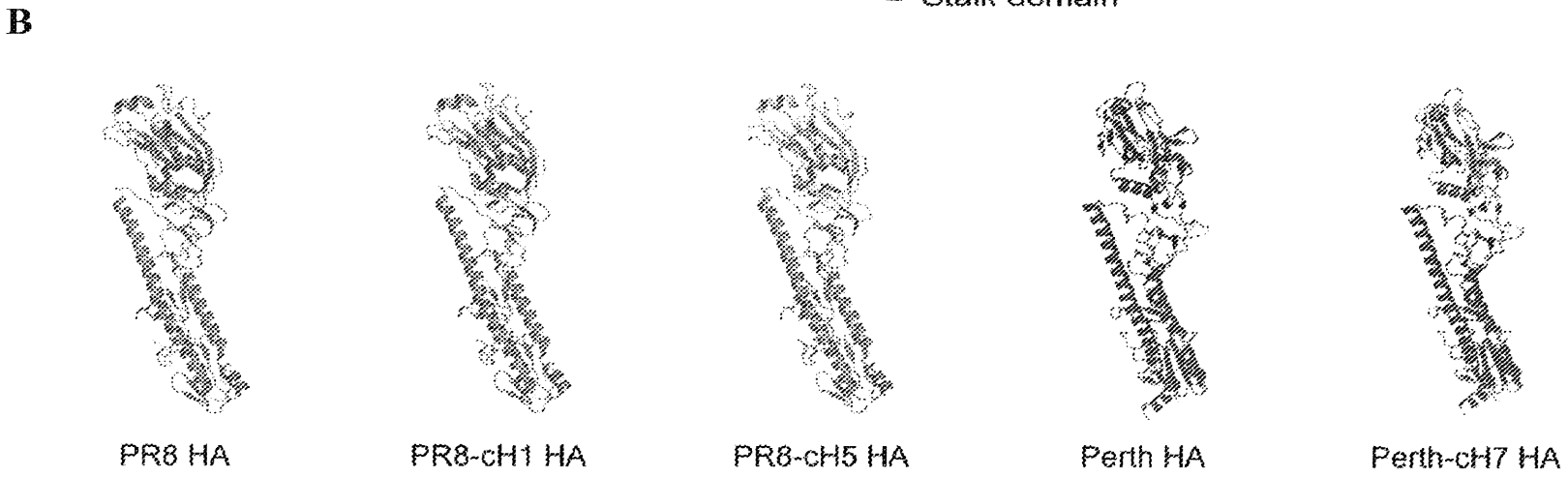

B
PR8 HA
PR8-cH1 HA
PR8-cH5 HA
Perth HA
Perth-cH7 HA

FIG. 12A - 12B

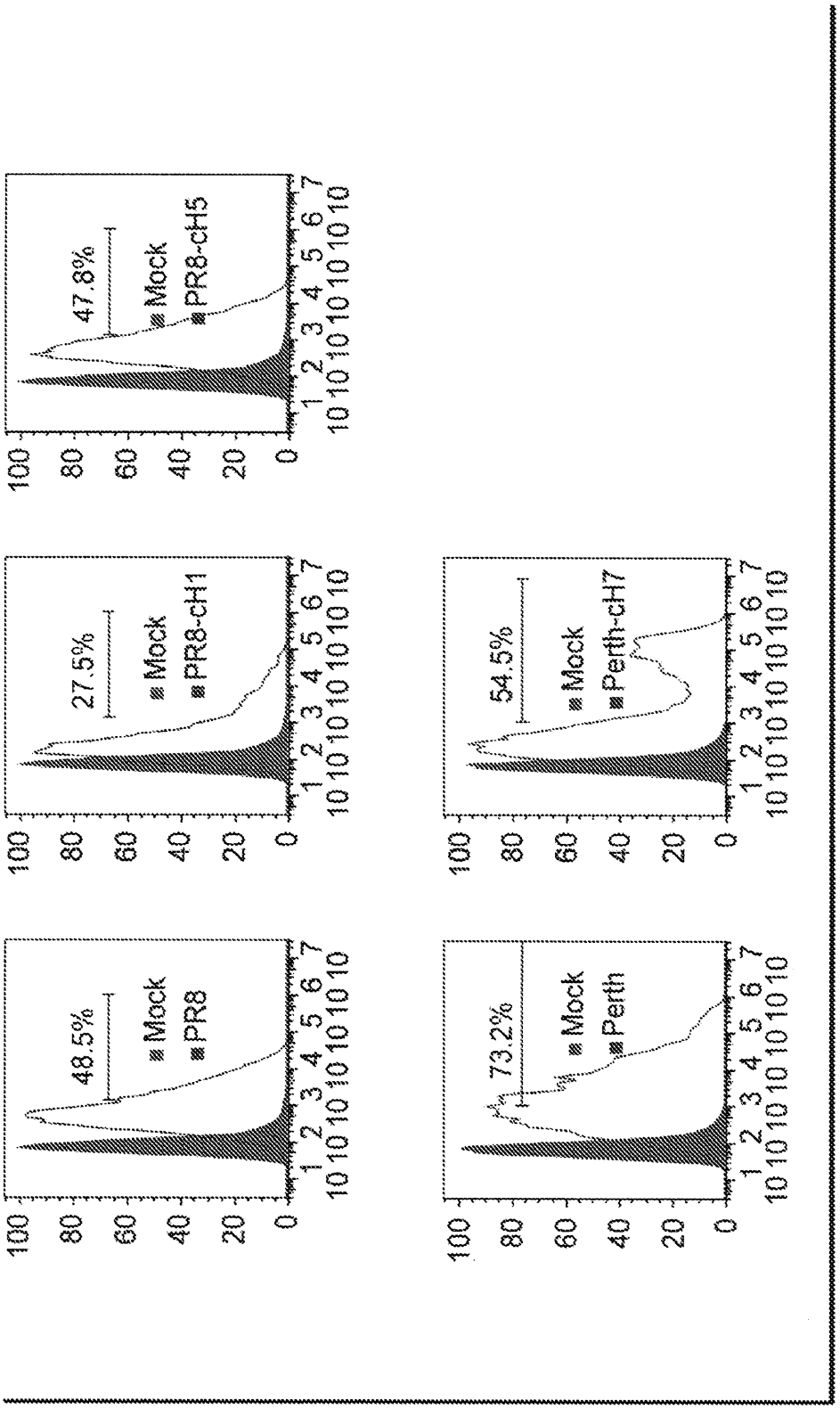

% of Max
Hemagglutinin
48.5%
Mock
PR8
27.5%
Mock
PR8-cH1
47.8%
Mock
PR8-cH5
73.2%
Mock
Perth
54.5%
Mock
Perth-cH7

FIG. 13A

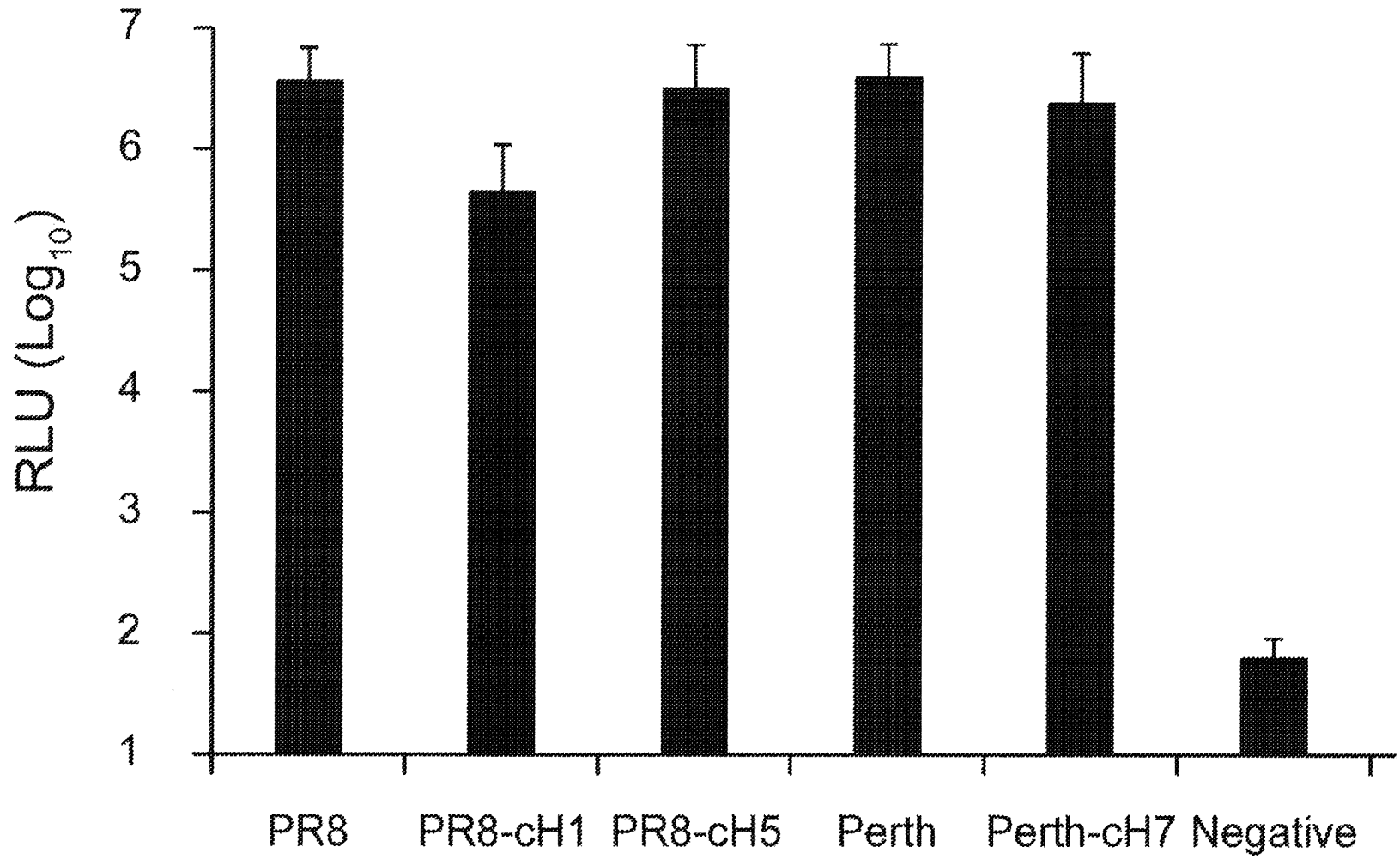

RLU (Log10)
7
6
5
4
3
2
1
PR8
PR8-cH1
PR8-cH5
Perth
Perth-cH7
Negative

FIG. 13B

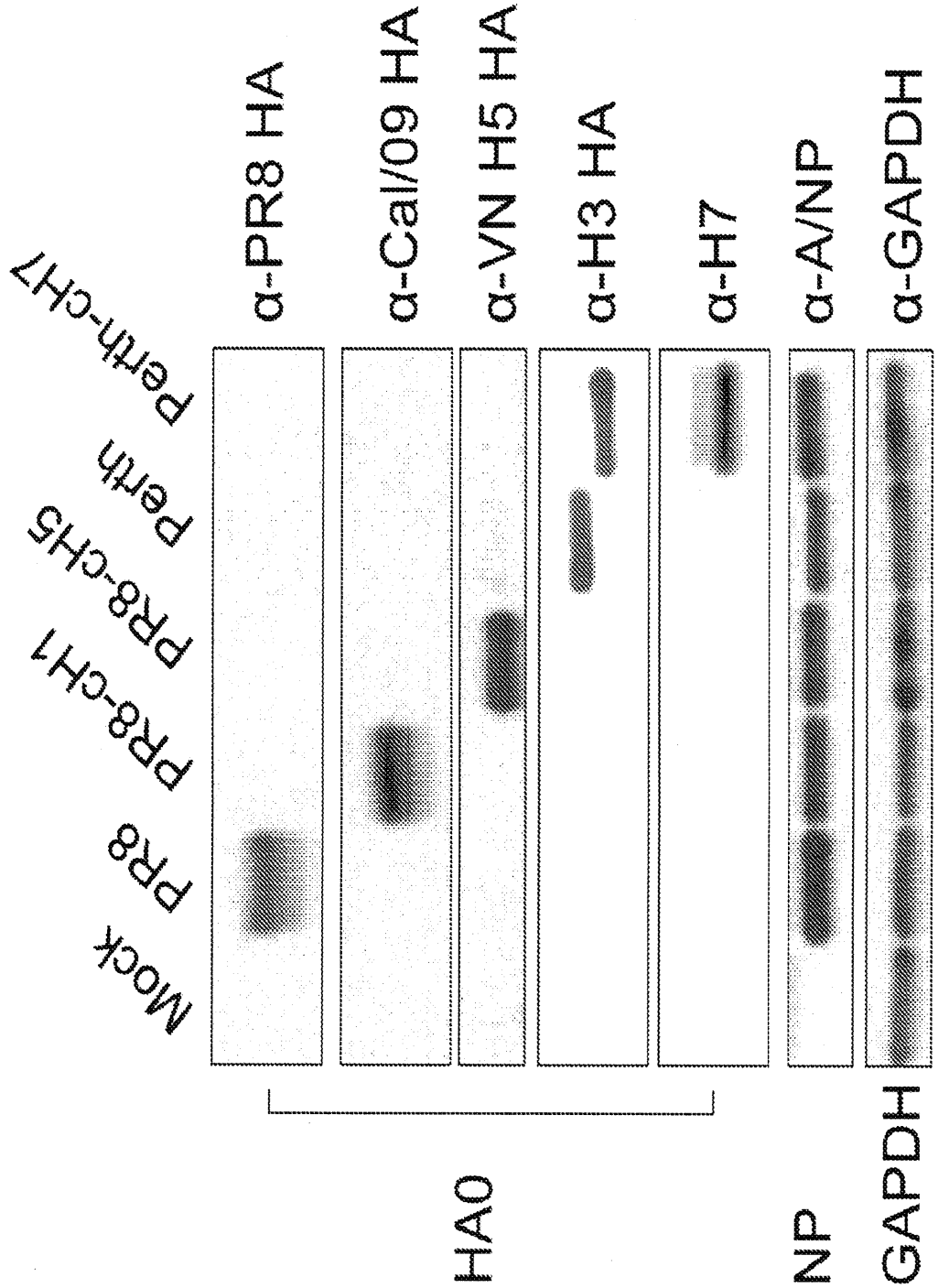

Mock
PR8
PR8-CH1
PR8-CH5
Perth
Perth-CH7
α-PR8 HA
α-Cal/09 HA
α-VN H5 HA
α-H3 HA
α-H7
α-A/NP
α-GAPDH
HA0
NP
GAPDH

FIG. 14A

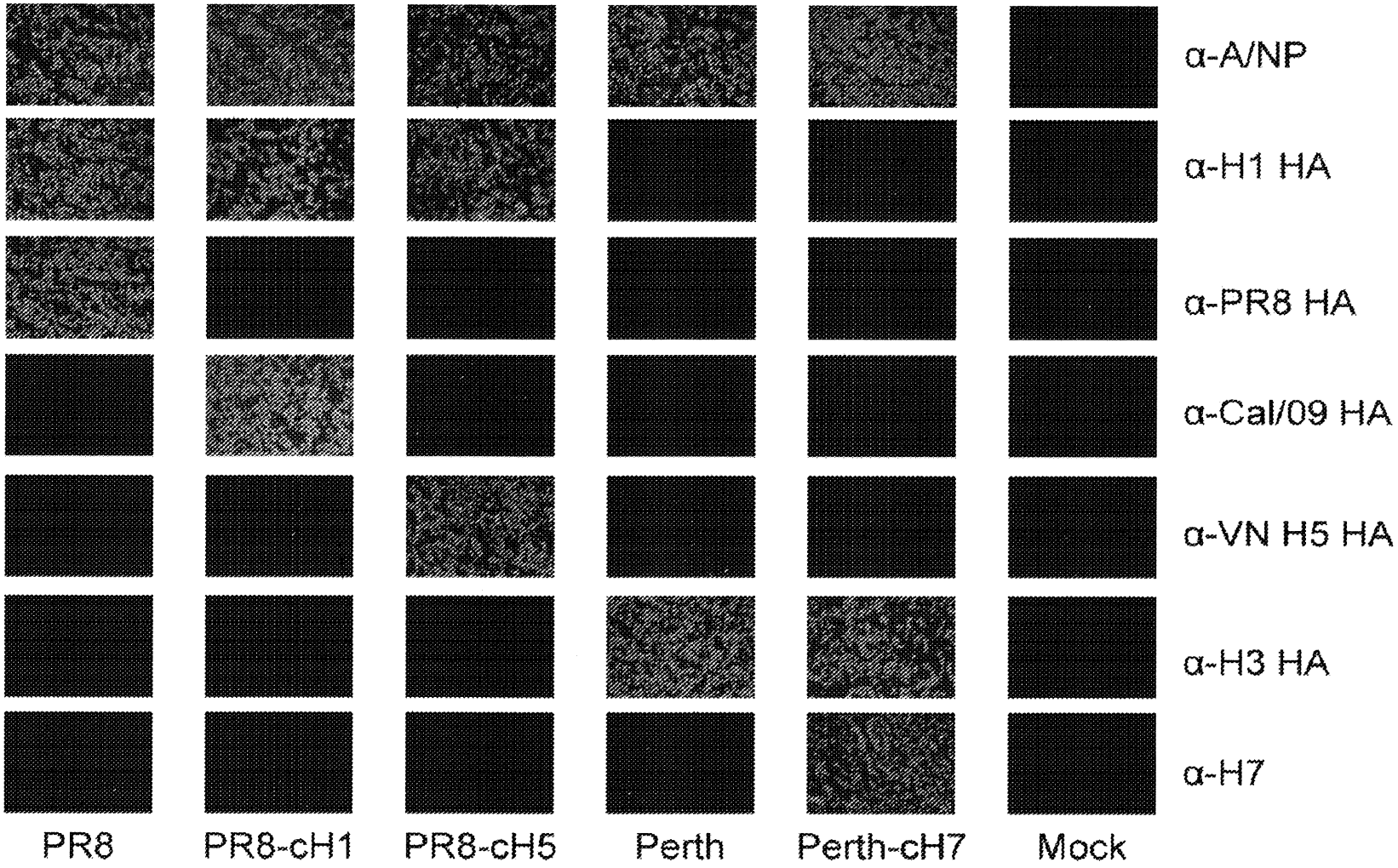

α-A/NP
α-H1 HA
α-PR8 HA
α-Cal/09 HA
α-VN H5 HA
α-H3 HA
α-H7
PR8
PR8-cH1
PR8-cH5
Perth
Perth-cH7
Mock

FIG. 14B

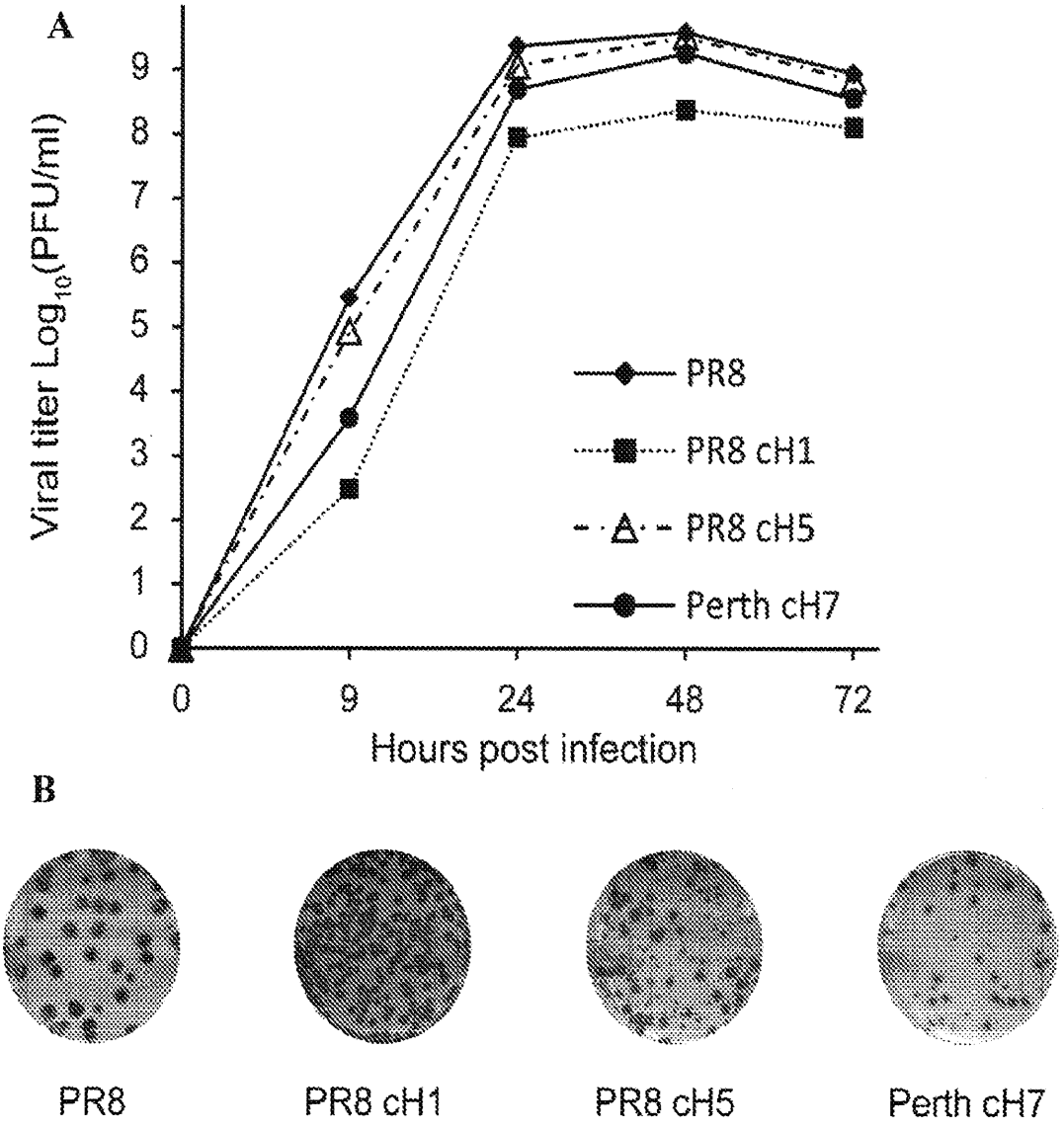

A
Viral titer Log_{10}(PFU/ml)
0
1
2
3
4
5
6
7
8
9
0
9
24
48
72
Hours post infection
PR8
PR8 cH1
PR8 cH5
Perth cH7
B
PR8
PR8 cH1
PR8 cH5
Perth cH7

FIG. 15 A - 15B

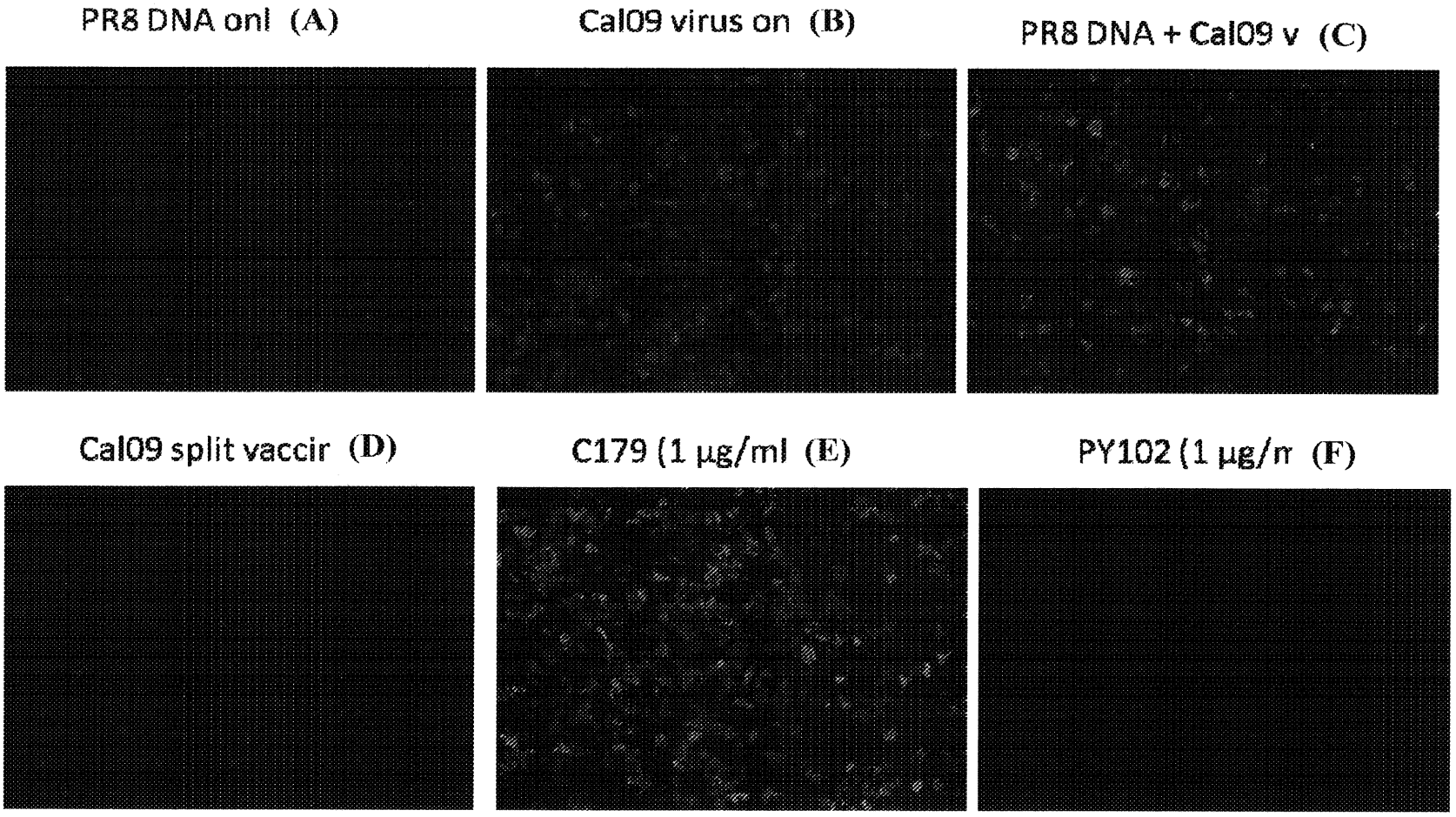

PR8 DNA onl (A)
Cal09 virus on (B)
PR8 DNA + Cal09 v (C)
Cal09 split vaccir (D)
C179 (1 µg/ml (E)
PY102 (1 µg/m (F)

FIG. 16A - 16F

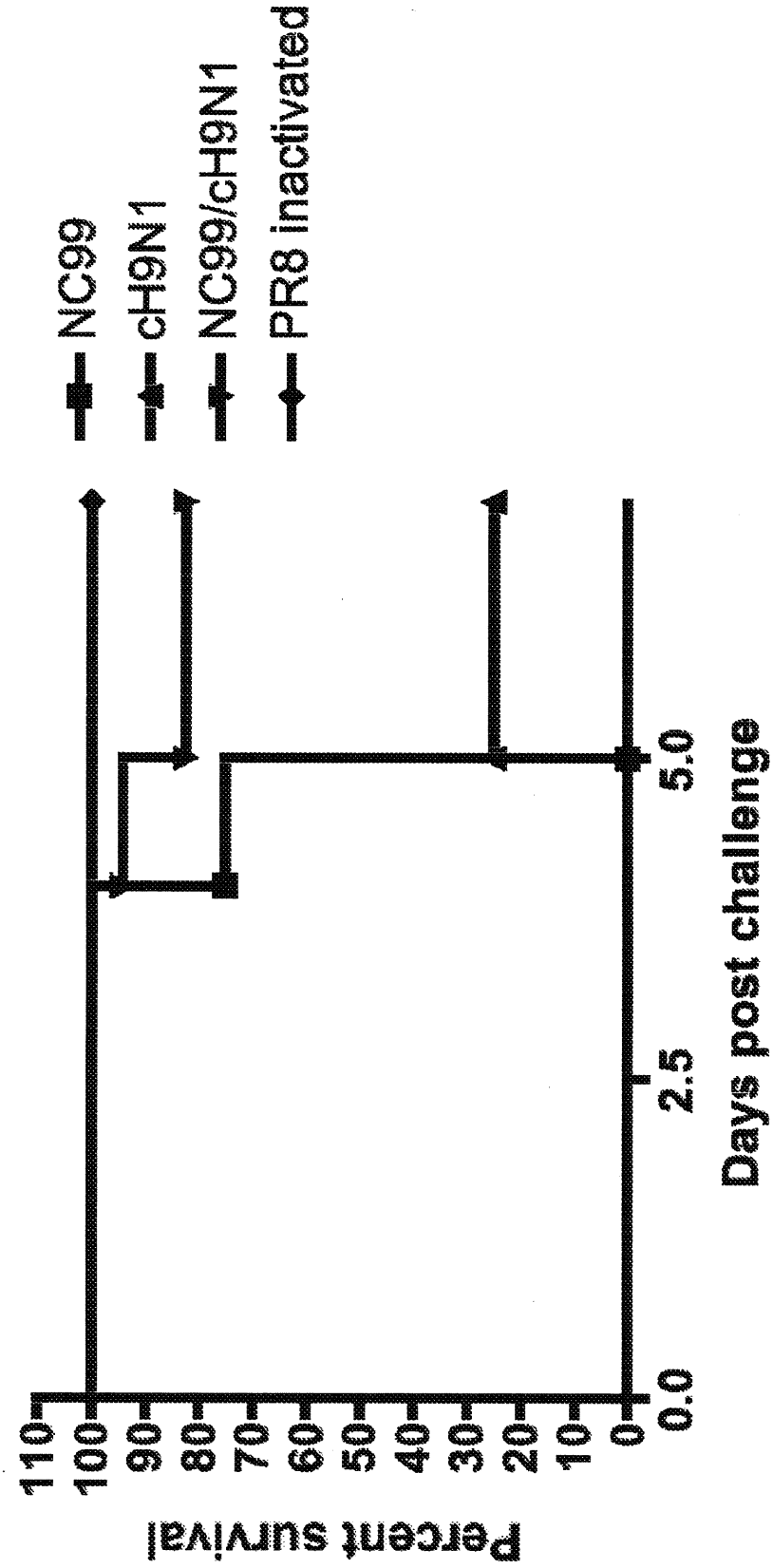

NC99
cH9N1
NC99/cH9N1
PR8 inactivated
Percent survival
110
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
Days post challenge

FIG. 17

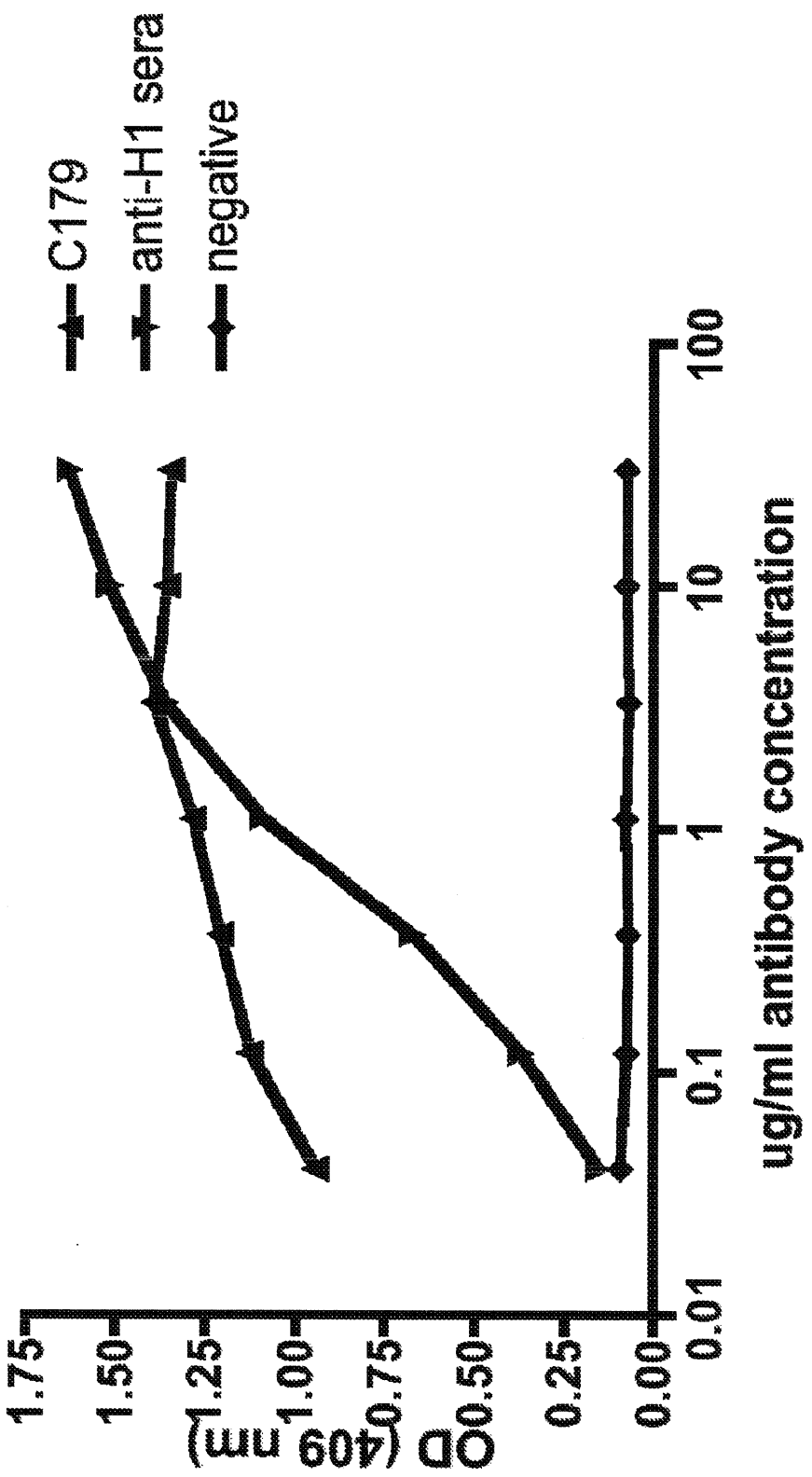

C179
anti-H1 sera
negative
OD (409 nm)
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0.01
0.1
1
10
100
ug/ml antibody concentration

FIG. 18

Fig. 19

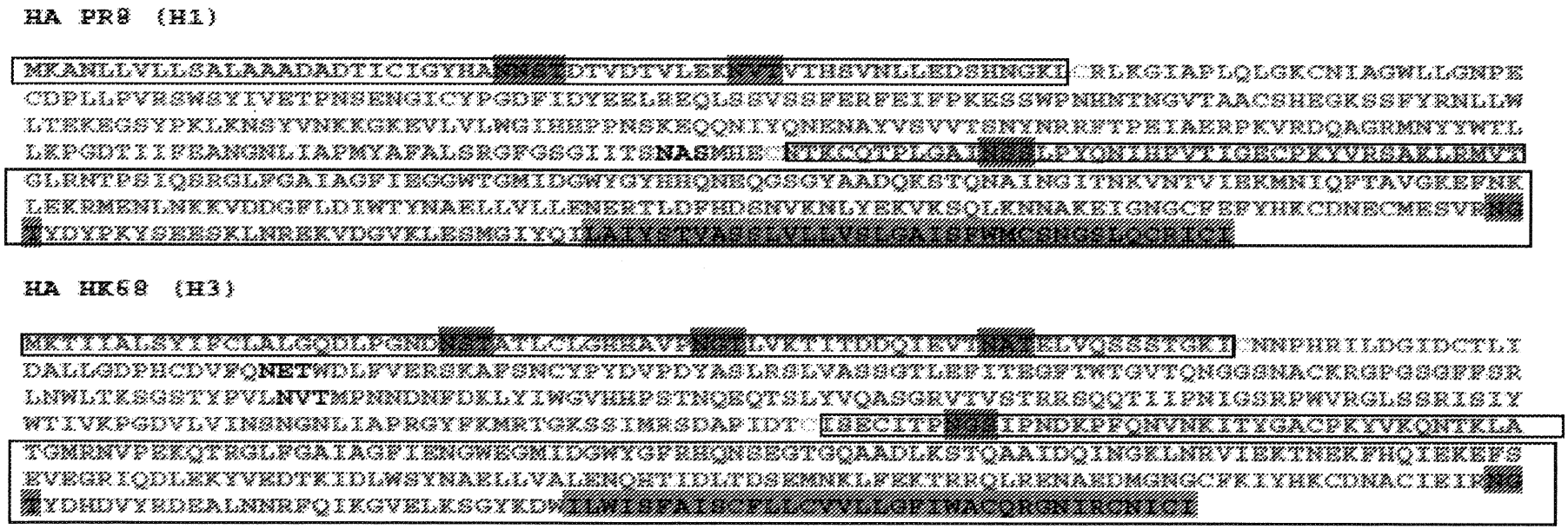
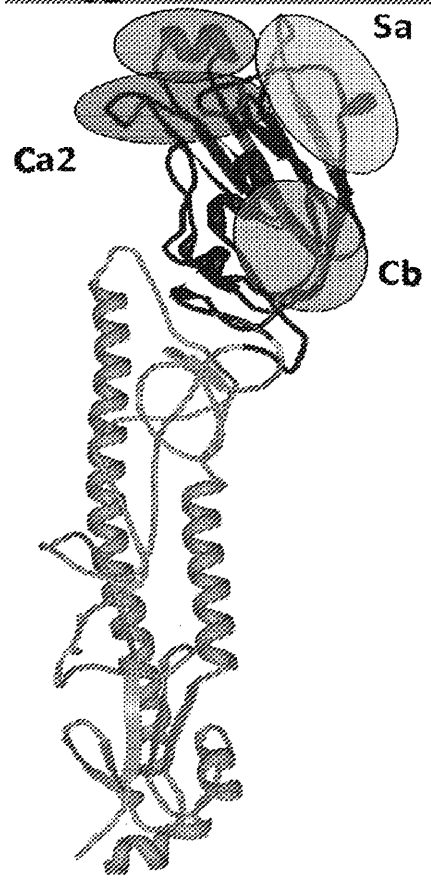


Fig. 20



B

	Cb		Sa	
Residue #	78		128	156
wt PR8	-LLPVRS-		-PN-	-EKEGS-PKLKNS-
Mutant	-...N..-		-.N.*S*-	-..N..-...N..-
	Ca_1			
Residue #	169	206	238	
wt PR8	-VNKKG-	-TSN-	-KPG-	
Mutant	-.N.S.-	-..N.*S*-	-...-	
	Ca_2		Sb	
Residue #	140	224	187	
wt PR8	-SHEGKS-	-RD-	-NSKDQQNIYQNE-	
Mutant	-...N..-	-..-	-N.T...N.S.N.*T*-	

Fig. 21

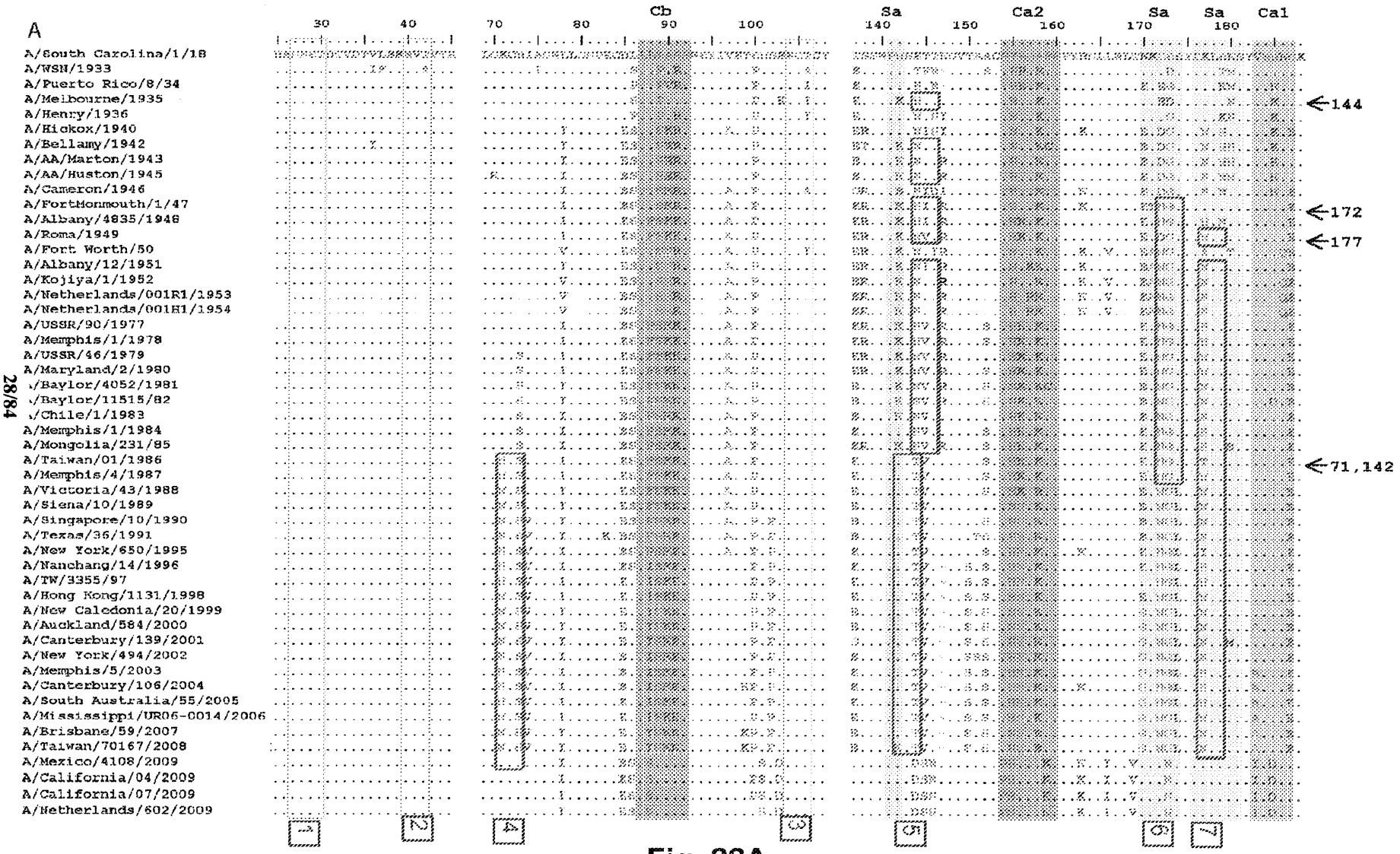

A
A/South Caxolina/1/18
A/WSN/1933
A/Puerto Rico/8/34
A/Melbourne/1935
A/Henry/1936
A/Hickox/1940
A/Bellamy/1942
A/AA/Marton/1943
A/AA/Huston/1945
A/Cameron/1946
A/FortMonmouth/1/47
A/Albany/4835/1948
A/Roma/1949
A/Fort Worth/50
A/Albany/12/1951
A/Kojiya/1/1952
A/Netherlands/001R1/1953
A/Netherlands/001H1/1954
A/USSR/90/1977
A/Memphis/1/1978
A/USSR/46/1979
A/Maryland/2/1980
A/Baylor/4052/1981
A/Baylor/11515/82
A/Chile/1/1983
A/Memphis/1/1984
A/Mongolia/231/85
A/Taiwan/01/1986
A/Memphis/4/1987
A/Victoria/43/1988
A/Siena/10/1989
A/Singapore/10/1990
A/Texas/36/1991
A/New York/650/1995
A/Nanchang/14/1996
A/TW/3355/97
A/Hong Kong/1131/1998
A/New Caledonia/20/1999
A/Auckland/584/2000
A/Canterbury/139/2001
A/New York/494/2002
A/Memphis/5/2003
A/Canterbury/106/2004
A/South Australia/55/2005
A/Mississippi/UR06-0014/2006
A/Brisbane/59/2007
A/Taiwan/70167/2008
A/Mexico/4108/2009
A/California/04/2009
A/California/07/2009
A/Netherlands/602/2009
30
40
70
80
90
100
140
150
160
170
180
Cb
Sa
Ca2
Sa
Sa
Ca1
144
172
177
71,142
1
2
4
5
3A
6
7

Fig. 22A

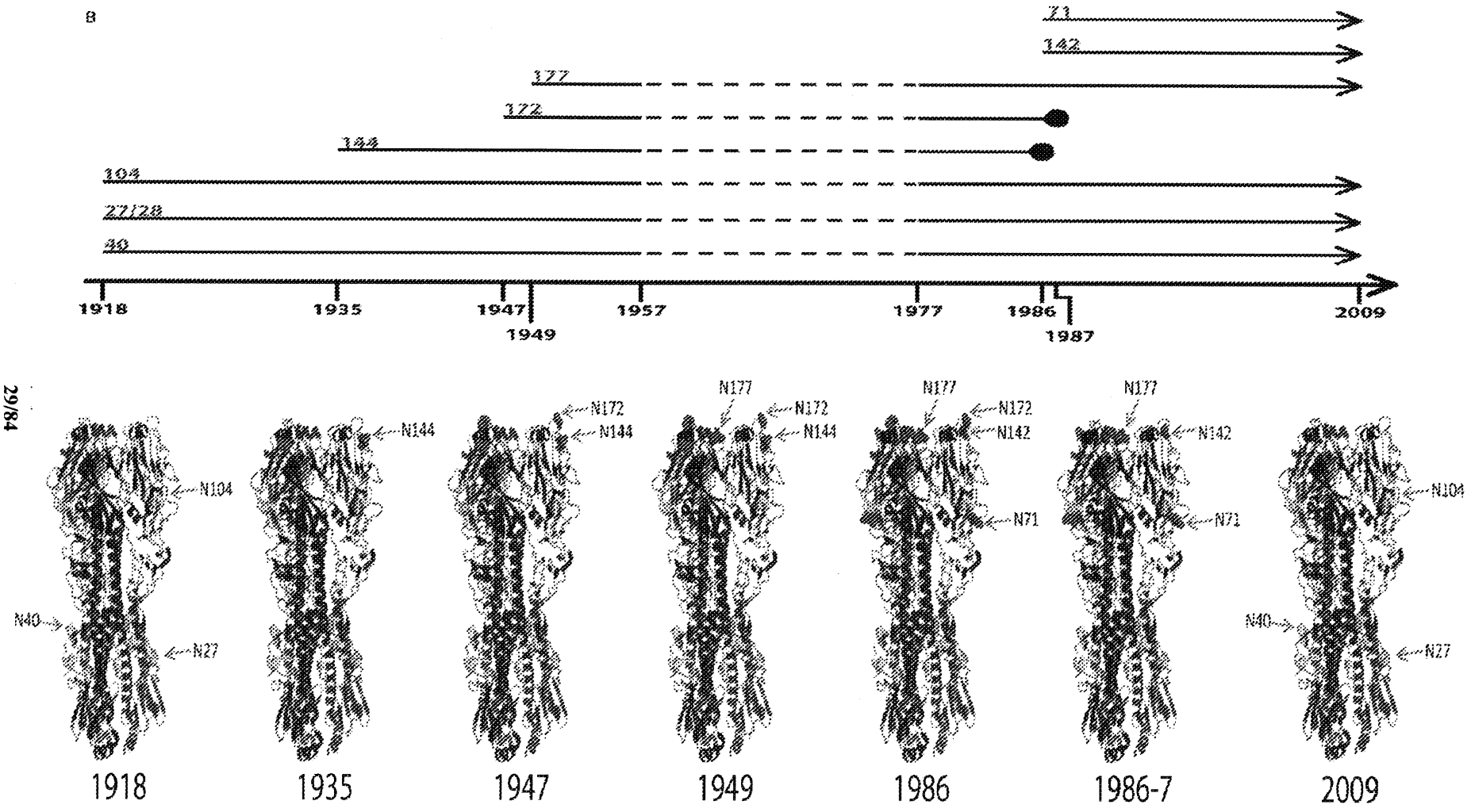

B
71
142
177
172
144
104
27128
40
1918
1935
1947
1949
1957
1977
1986
1987
2009
N177
N172
N144
N142
N104
N71
N40
N27
1918
1935
1947
1949
1986
1986-7
2009

Fig. 22B – 22C

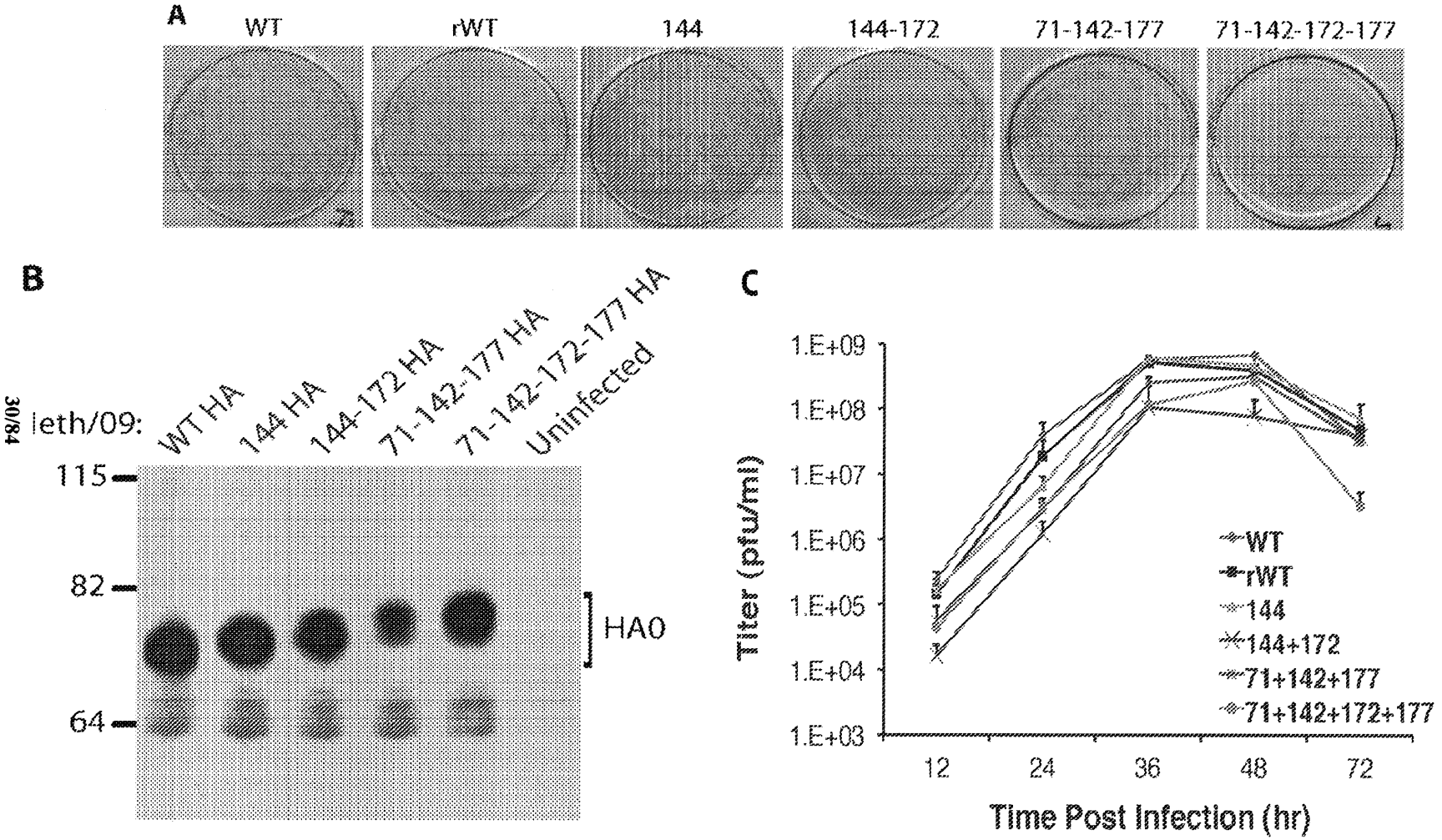

A
WT
rWT
144
144-172
71-142-177
71-142-172-177
B
30/84 leth/09:
WT HA
144 HA
144-172 HA
71-142-177 HA
71-142-172-177 HA
Uninfected
115
82
64
HA0
C
Titer (pfu/ml)
1.E+09
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
12
24
36
48
72
Time Post Infection (hr)
WT
rWT
144
144+172
71+142+177
71+142+172+177

Fig. 23

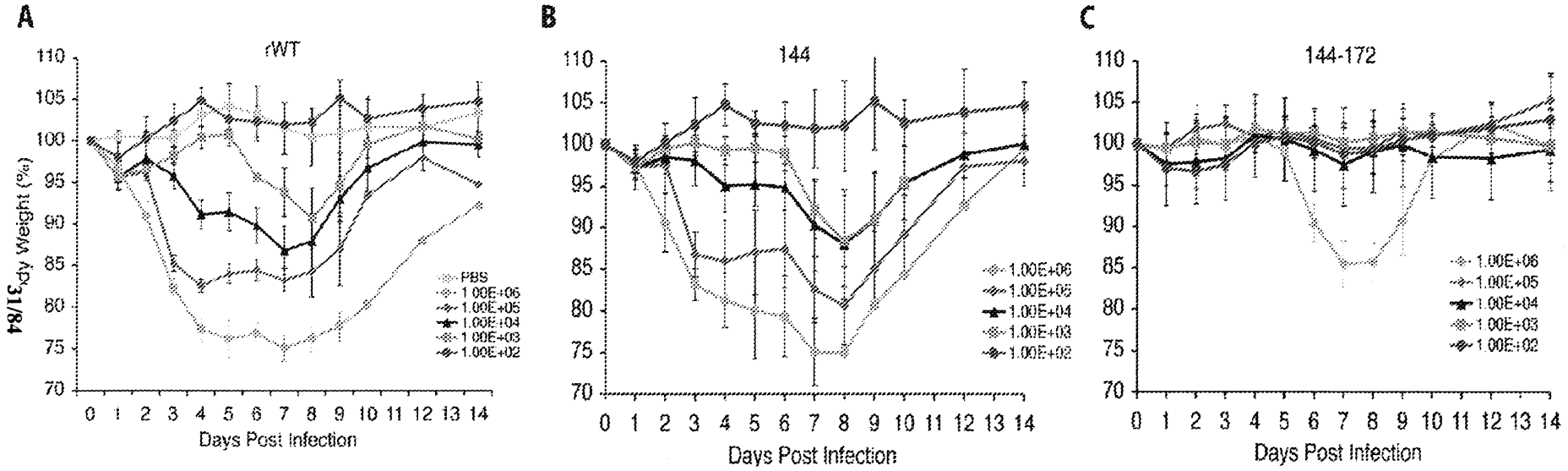

A
rWT
B
144
C
144-172
% Weight
Days Post Infection
PBS
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02

Fig. 24A – 24C

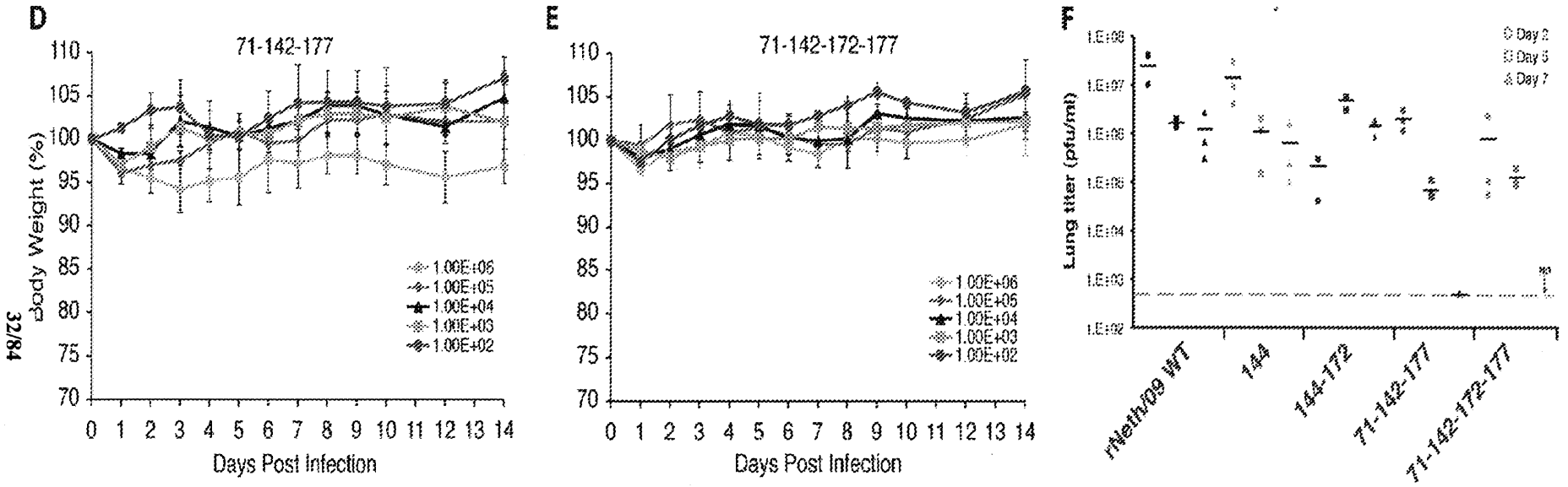

D
71-142-177
Body Weight (%)
Days Post Infection
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
E
71-142-172-177
Days Post Infection
F
Lung titer (pfu/ml)
Day 2
Day 5
Day 7
rNetherlands/09 WT
144
144-172
71-142-177
71-142-172-177

Fig. 24D – 24F

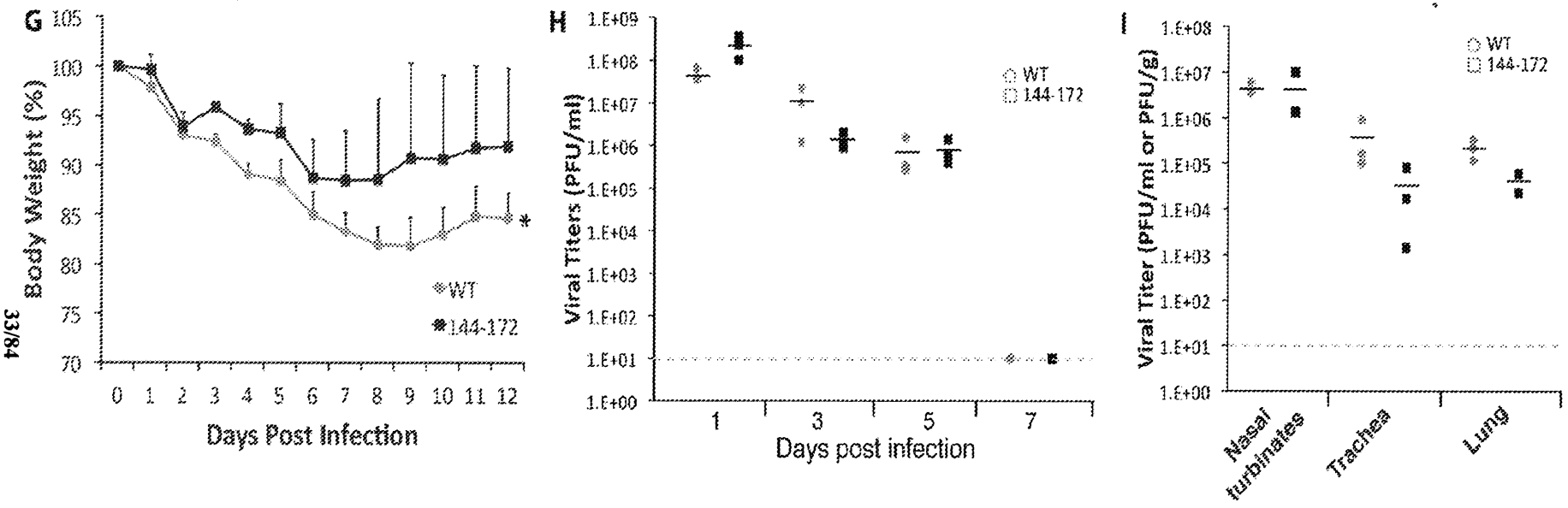

G
Body Weight (%)
105
100
95
90
85
80
75
70
0 1 2 3 4 5 6 7 8 9 10 11 12
Days Post Infection
WT
144-172
*
H
Viral Titers (PFU/ml)
1.E+09
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
1 3 5 7
Days post infection
WT
144-172
I
Viral Titer (PFU/ml or PFU/g)
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
Nasal turbinates
Trachea
Lung
WT
144-172

Fig. 24G – 24I

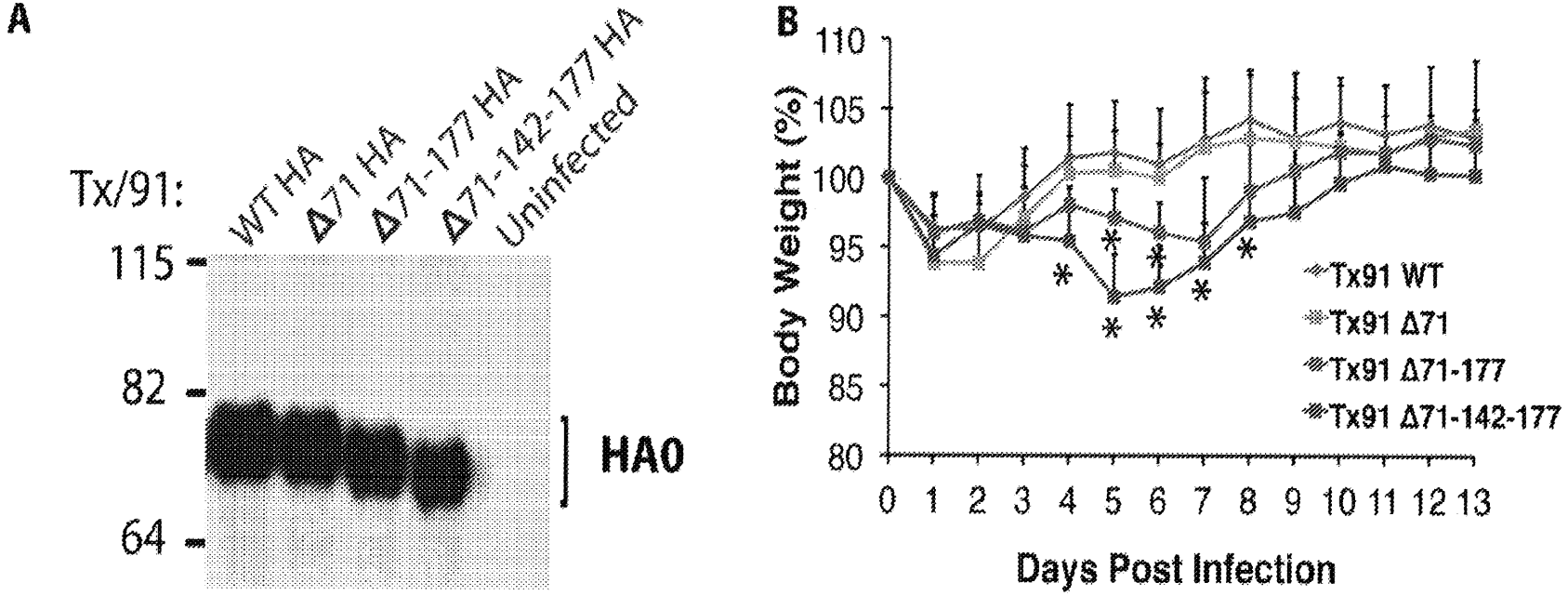

A
Tx/91:
WT HA
Δ71 HA
Δ71-177 HA
Δ71-142-177 HA
Uninfected
115
82
64
HA0
B
Body Weight (%)
110
105
100
95
90
85
80
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Days Post Infection
Tx91 WT
Tx91 Δ71
Tx91 Δ71-177
Tx91 Δ71-142-177

Fig. 25A – 25B

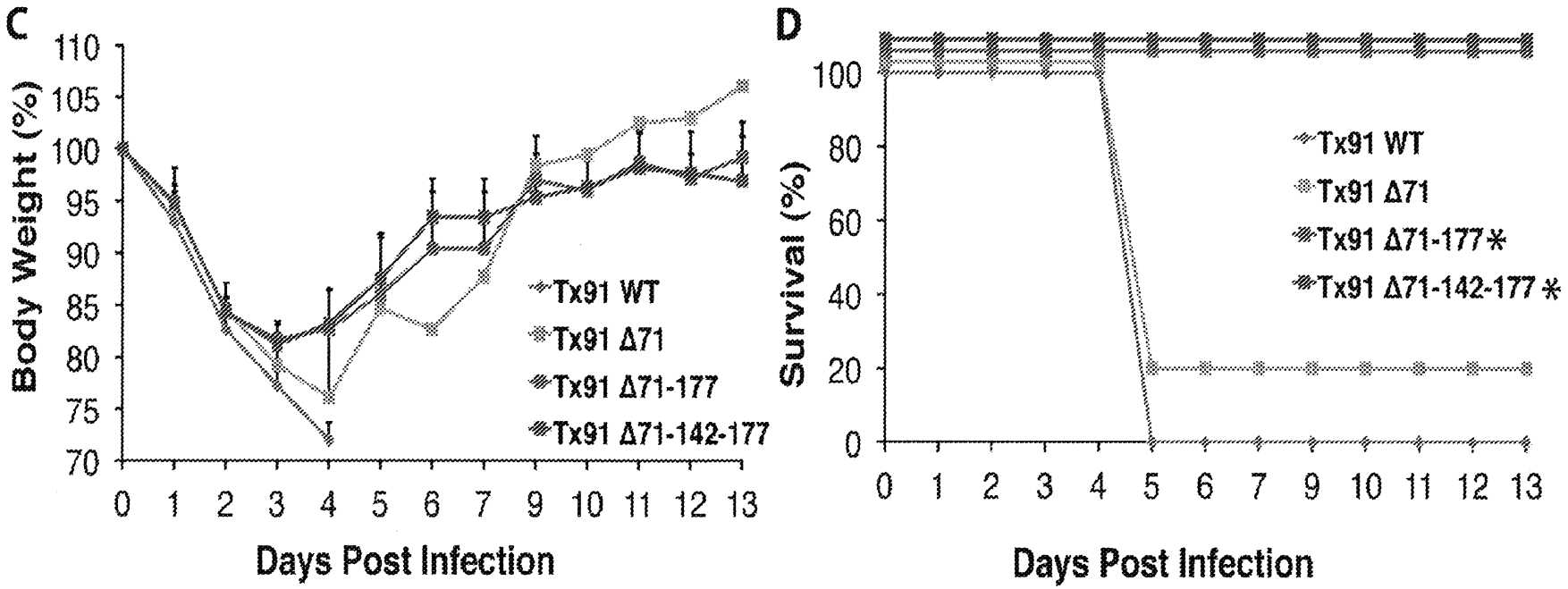
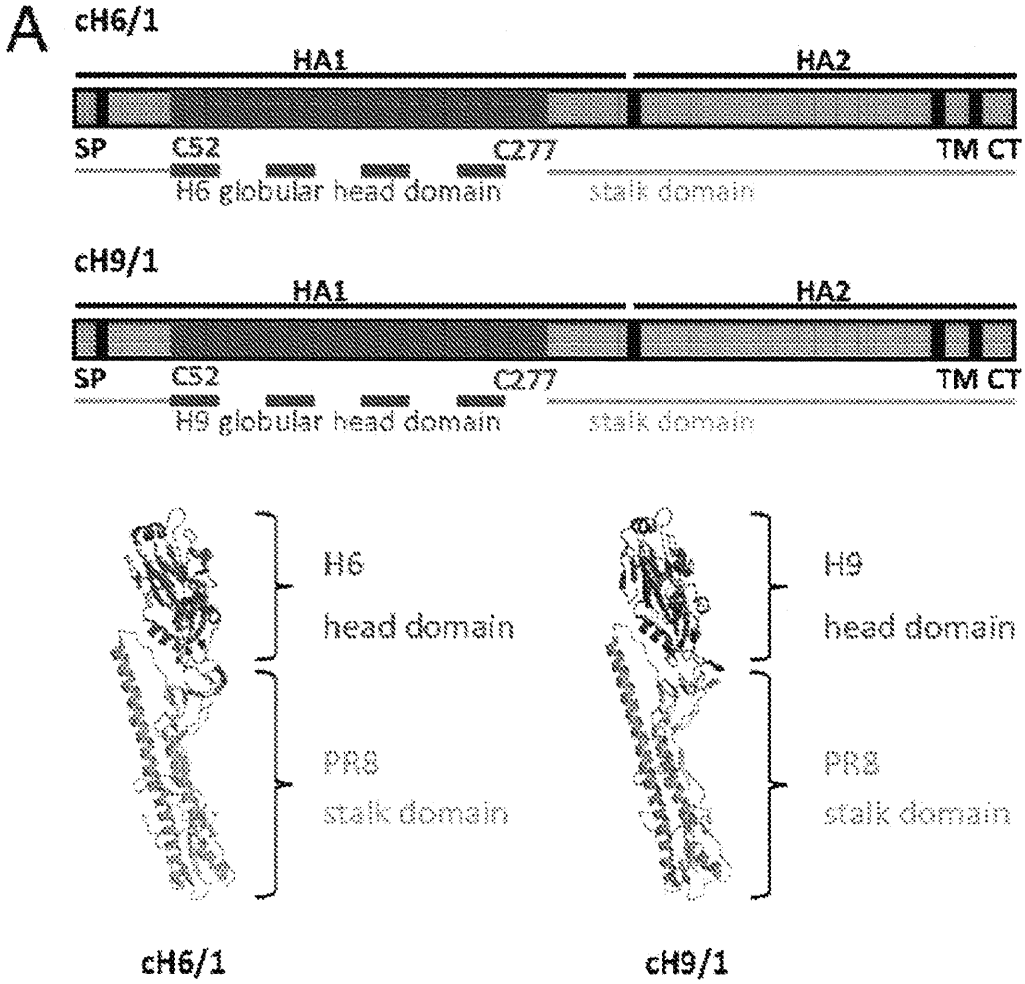

C
Body Weight (%)
110
105
100
95
90
85
80
75
70
0 1 2 3 4 5 6 7 9 10 11 12 13
Days Post Infection
Tx91 WT
Tx91 Δ71
Tx91 Δ71-177
Tx91 Δ71-142-177
D
Survival (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 9 10 11 12 13
Days Post Infection
Tx91 WT
Tx91 Δ71
Tx91 Δ71-177*
Tx91 Δ71-142-177*

Fig. 25C – 25D


A
cH6/1
HA1
HA2
SP
C52
C277
TM CT
H6 globular head domain
stalk domain
cH9/1
HA1
HA2
SP
C52
C277
TM CT
H9 globular head domain
stalk domain
H6
head domain
PR8
stalk domain
H9
head domain
PR8
stalk domain
cH6/1
cH9/1

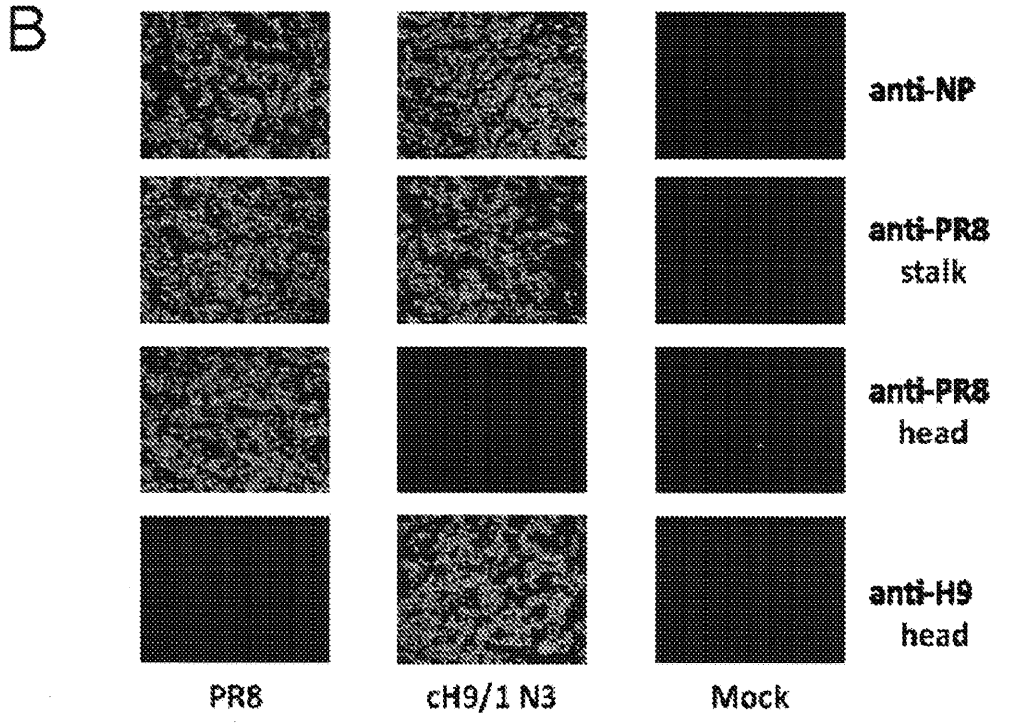

B
anti-NP
anti-PR8
stalk
anti-PR8
head
anti-H9
head
PR8
cH9/1 N3
Mock

Fig. 26

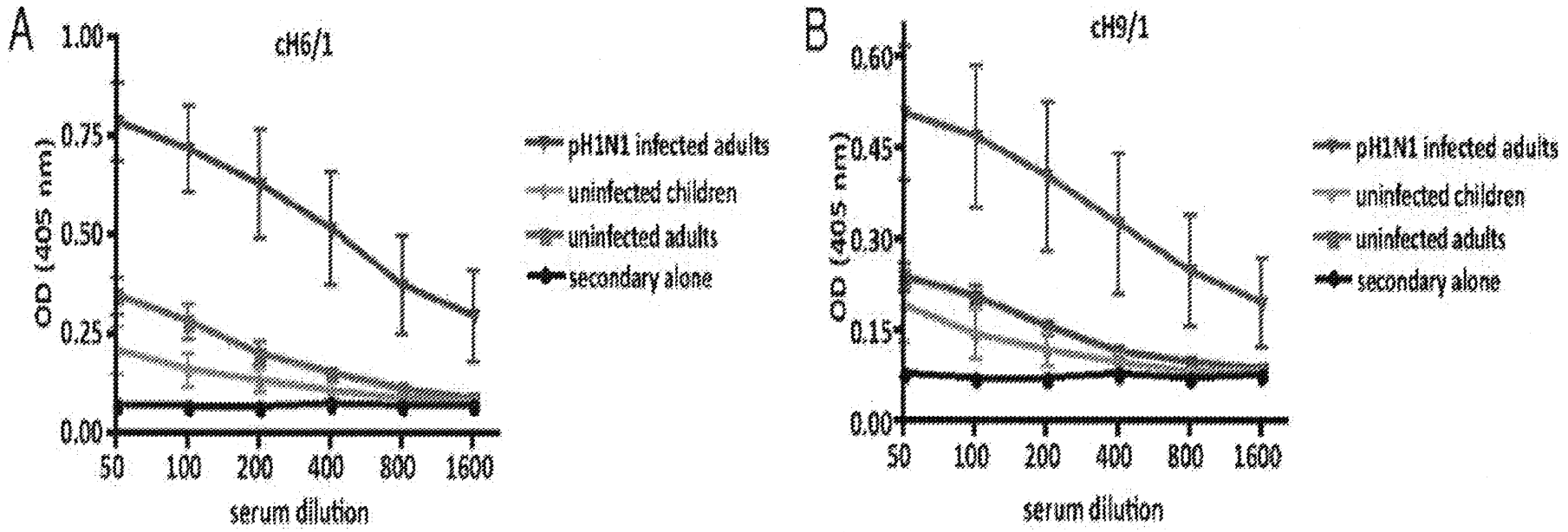

A
cH6/1
1.00
0.75
0.50
0.25
0.00
OD (405 nm)
50
100
200
400
800
1600
serum dilution
pH1N1 infected adults
uninfected children
uninfected adults
secondary alone
B
cH9/1
0.60
0.45
0.30
0.15
0.00
OD (405 nm)
50
100
200
400
800
1600
serum dilution
pH1N1 infected adults
uninfected children
uninfected adults
secondary alone

Fig. 27A – 27B

SUBSTITUTE SHEET (RULE 26)

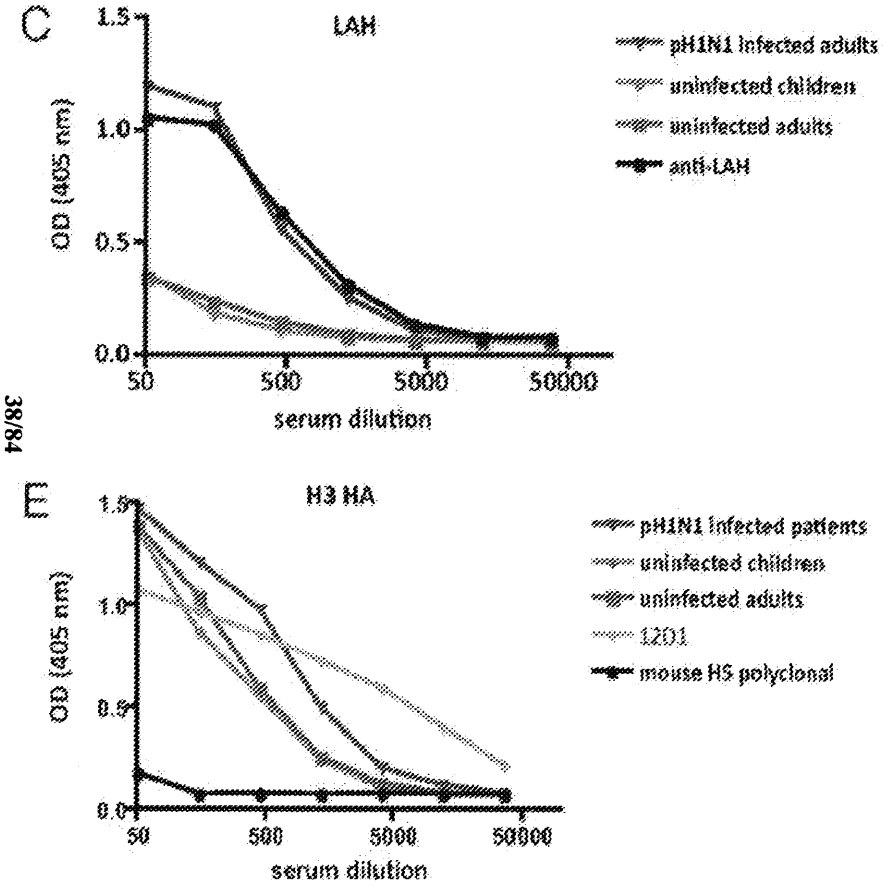
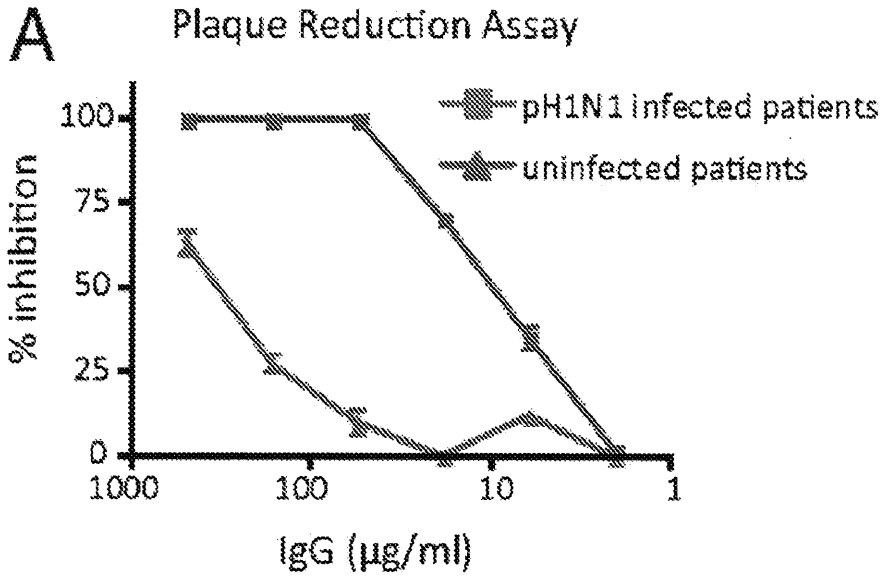
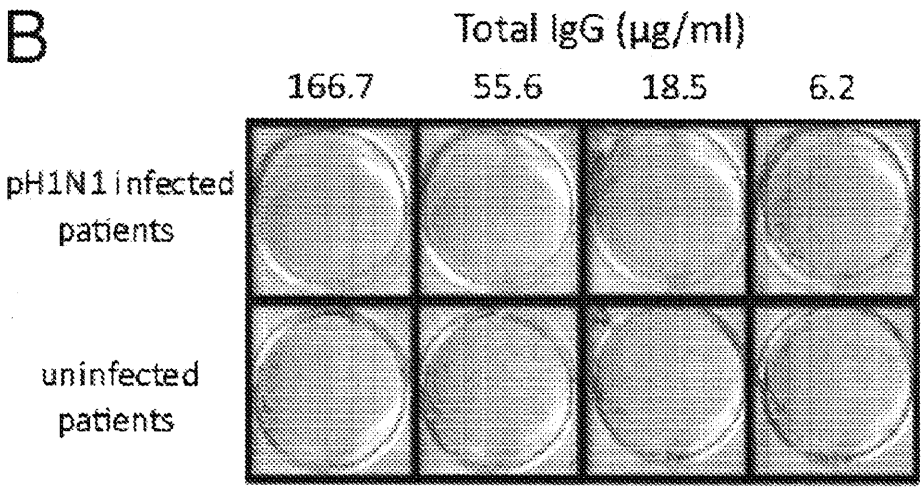
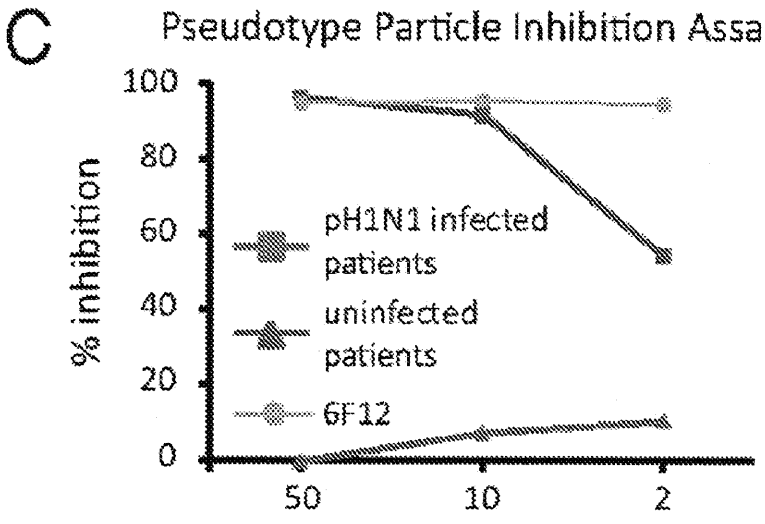


Fig. 27C – 27E


A
Plaque Reduction Assay
pH1N1 infected patients
uninfected patients
% inhibition
100
75
50
25
0
1000
100
10
1
IgG (µg/ml)


B
Total IgG (µg/ml)
166.7
55.6
18.5
6.2
pH1N1 infected patients
uninfected patients


C
Pseudotype Particle Inhibition Assay
% inhibition
100
80
60
40
20
0
pH1N1 infected patients
uninfected patients
6F12
50
10
2
IgG (µg/ml)

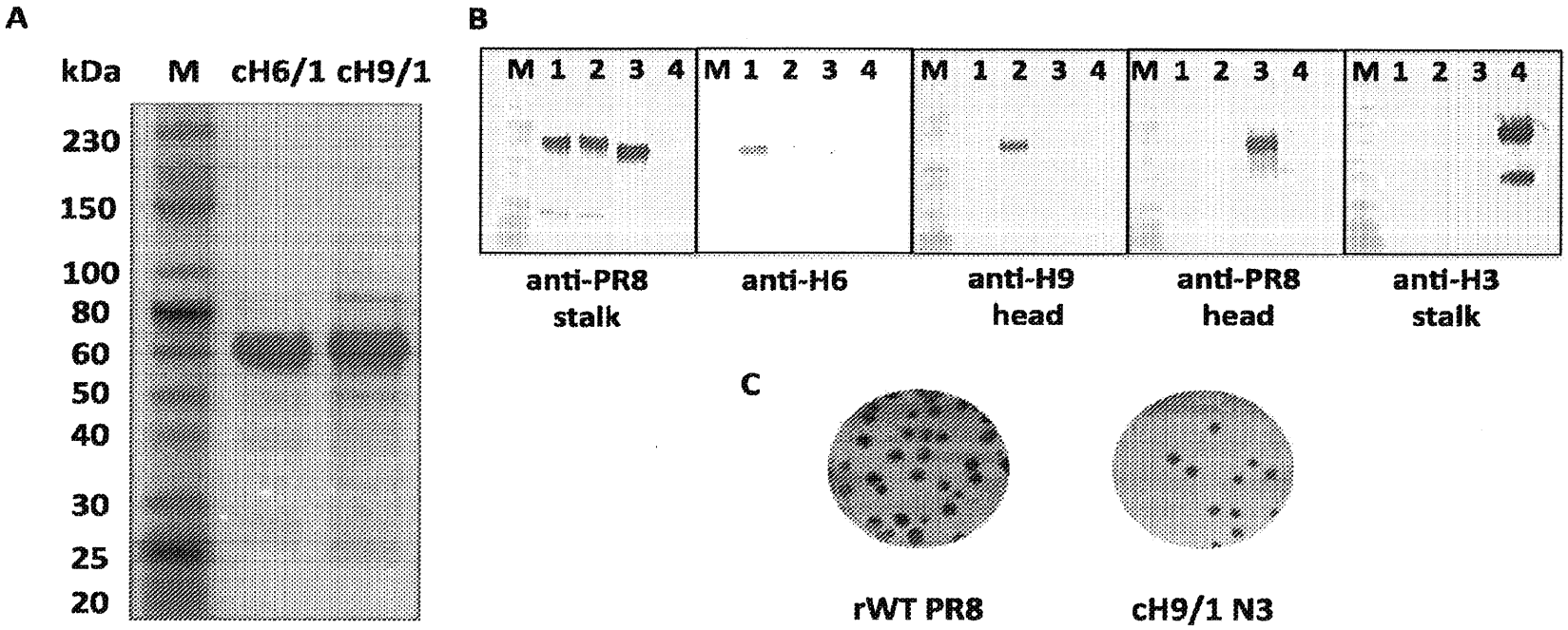

A
kDa
M
cH6/1
cH9/1
230
150
100
80
60
50
40
30
25
20
B
M 1 2 3 4
M 1 2 3 4
M 1 2 3 4
M 1 2 3 4
M 1 2 3 4
anti-PR8 stalk
anti-H6
anti-H9 head
anti-PR8 head
anti-H3 stalk
C
rWT PR8
cH9/1 N3

Fig. 29

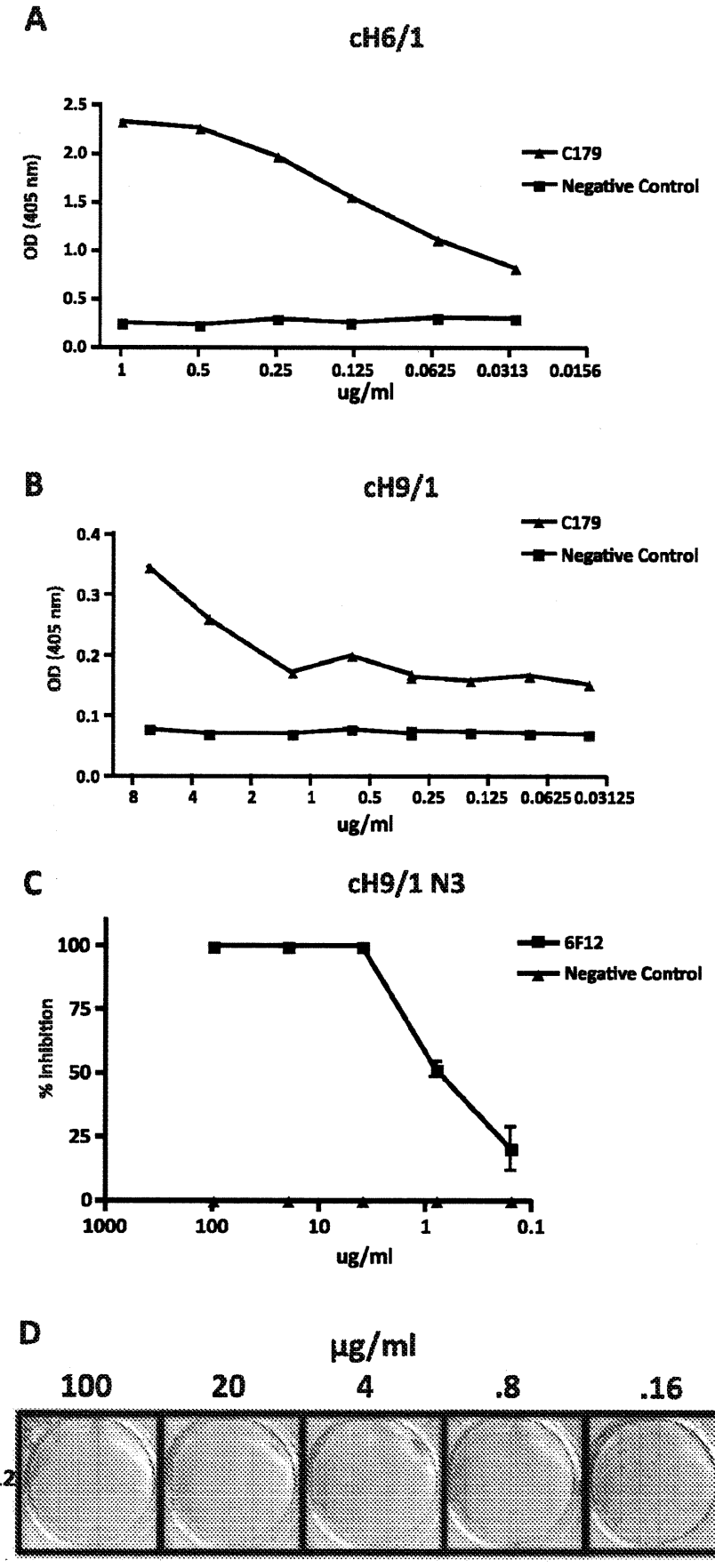
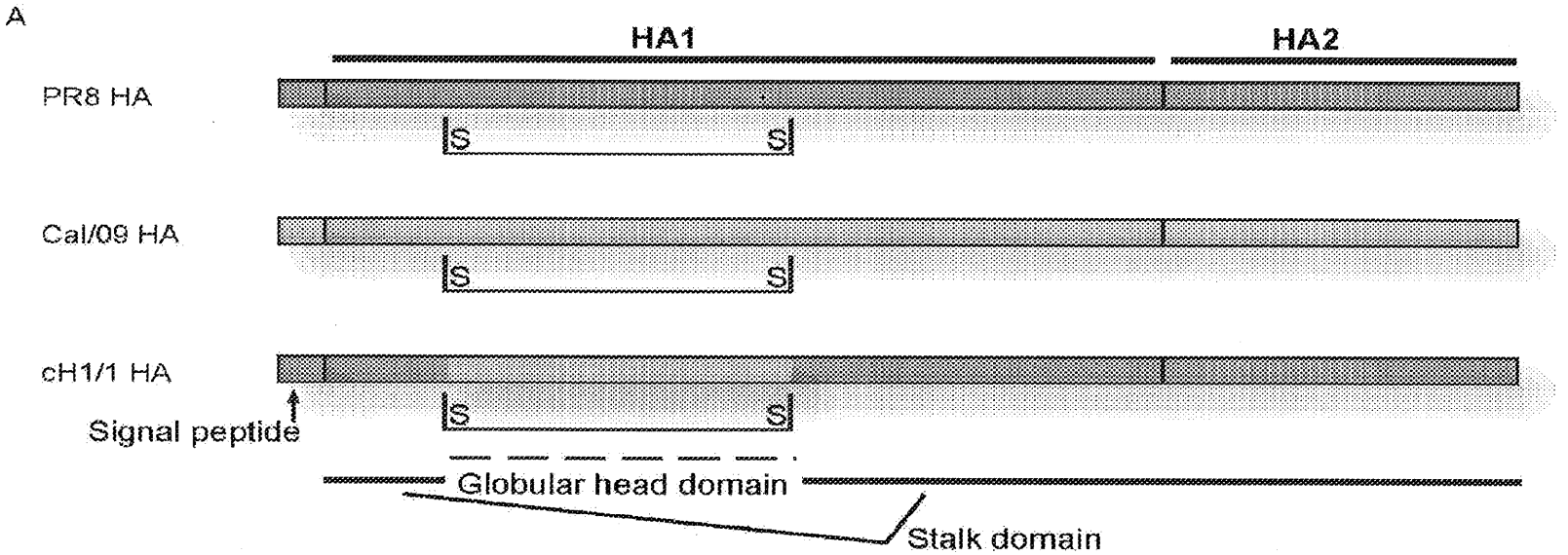

A
cH6/1
OD (405 nm)
2.5
2.0
1.5
1.0
0.5
0.0
1
0.5
0.25
0.125
0.0625
0.0313
0.0156
ug/ml
C179
Negative Control
B
cH9/1
OD (405 nm)
0.4
0.3
0.2
0.1
0.0
8
4
2
1
0.5
0.25
0.125
0.0625
0.03125
ug/ml
C179
Negative Control
C
cH9/1 N3
% Inhibition
100
75
50
25
0
1000
100
10
1
0.1
ug/ml
6F12
Negative Control
D
µg/ml
100
20
4
.8
.16
6F12

Fig 30


A
HA1
HA2
PR8 HA
S
S
Cal/09 HA
S
S
cH1/1 HA
S
S
Signal peptide
Globular head domain
Stalk domain

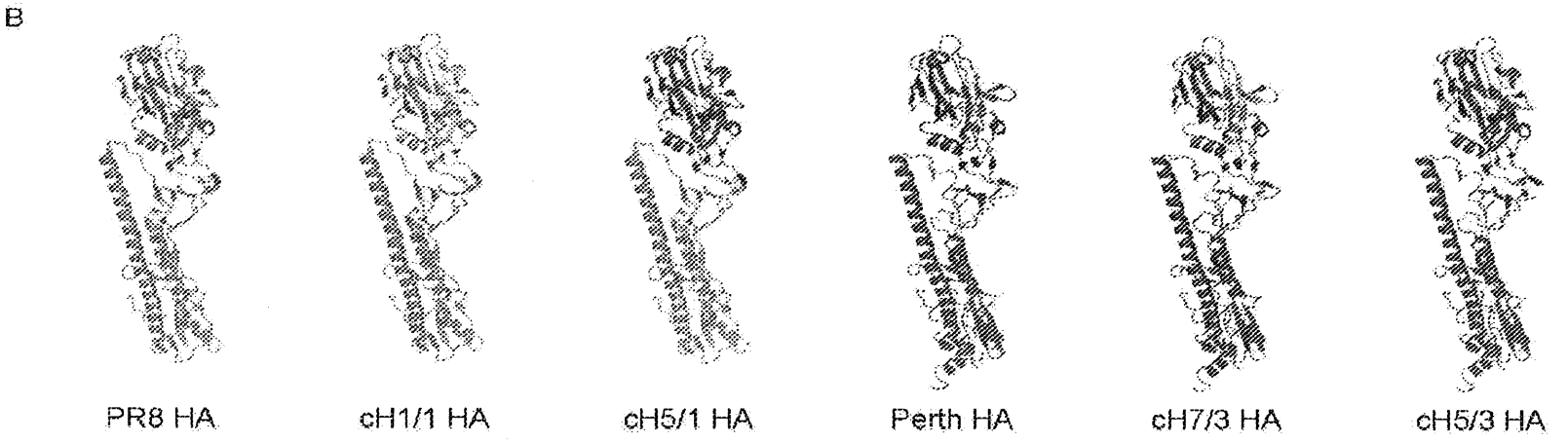

B
PR8 HA
cH1/1 HA
cH5/1 HA
Perth HA
cH7/3 HA
cH5/3 HA

Fig. 31

Percent amino acid identity in the globular head domain

	A/PR/8/34 (H1)	A/Cal/4/09 (H1)	A/VN/1203/04 (H5)	A/Perth/16/09 (H3)	A/mallard/Alb/24/01 (H7)
A/PR/8/34 (H1)		70	50	31	32
A/Cal/4/09 (H1)			46	31	27
A/VN/1203/04 (H5)				34	31
A/Perth/16/09 (H3)					30
A/mallard/Alb/24/01 (H7)					

Percent amino acid identity in the stalk domain

	A/PR/8/34 (H1)	A/Cal/4/09 (H1)	A/VN/1203/04 (H5)	A/Perth/16/09 (H3)	A/mallard/Alb/24/01 (H7)
A/PR/8/34 (H1)		90	77	47	47
A/Cal/4/09 (H1)			78	50	48
A/VN/1203/04 (H5)				46	49
A/Perth/16/09 (H3)					61
A/mallard/Alb/24/01 (H7)					

Percent amino acid identity of the full length hemagglutinin

	A/PR/8/34 (H1)	A/Cal/4/09 (H1)	A/VN/1203/04 (H5)	A/Perth/16/09 (H3)	A/mallard/Alb/24/01 (H7)
A/PR/8/34 (H1)		82	65	40	42
A/Cal/4/09 (H1)			65	42	40
A/VN/1203/04 (H5)				41	42
A/Perth/16/09 (H3)					49
A/mallard/Alb/24/01 (H7)					

Fig. 32

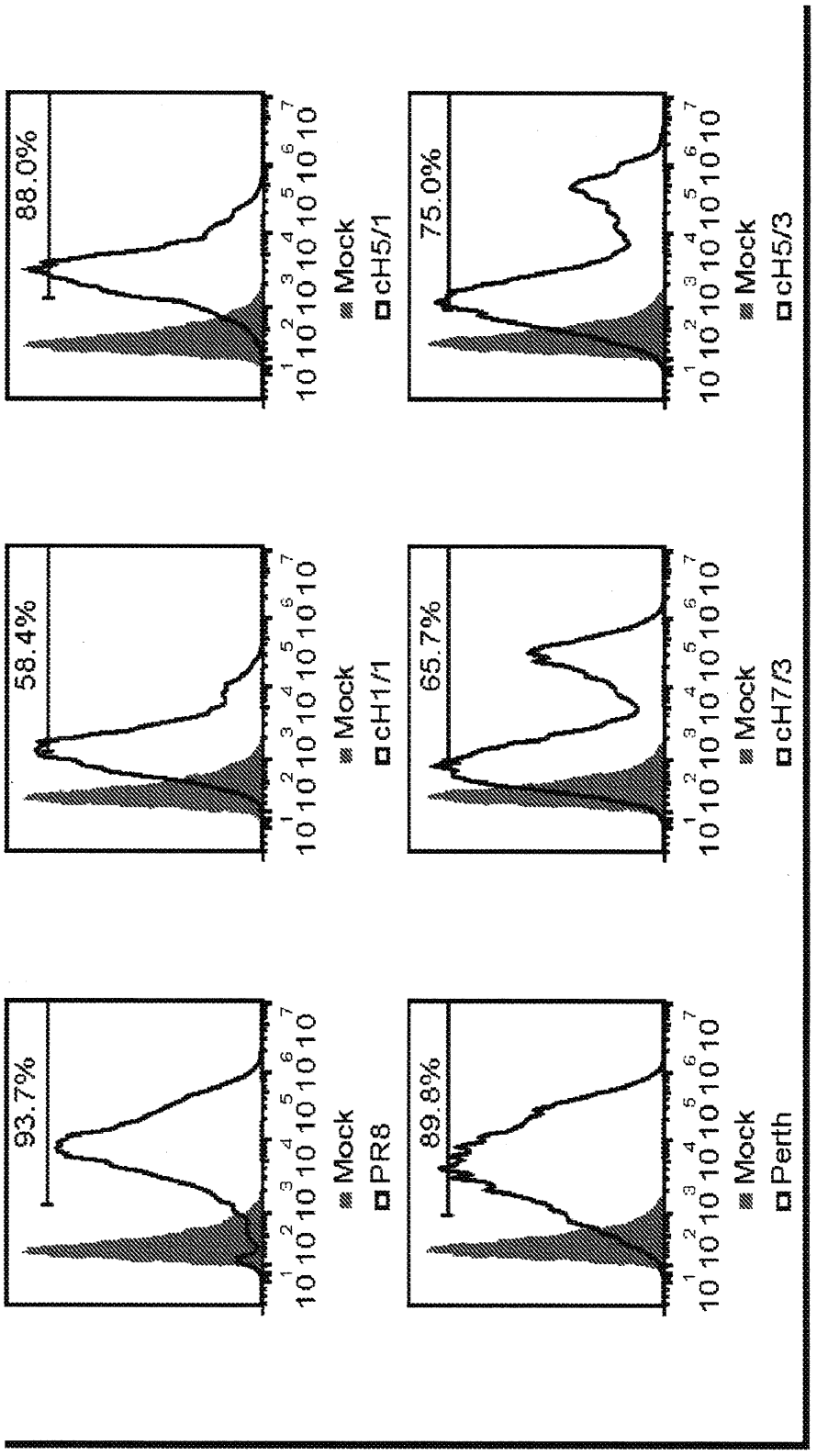

93.7%
Mock
PR8
89.8%
Mock
Perth
58.4%
Mock
cH1/1
65.7%
Mock
cH7/3
88.0%
Mock
cH5/1
75.0%
Mock
cH5/3
Cell Number
Hemagglutinin

Fig. 33

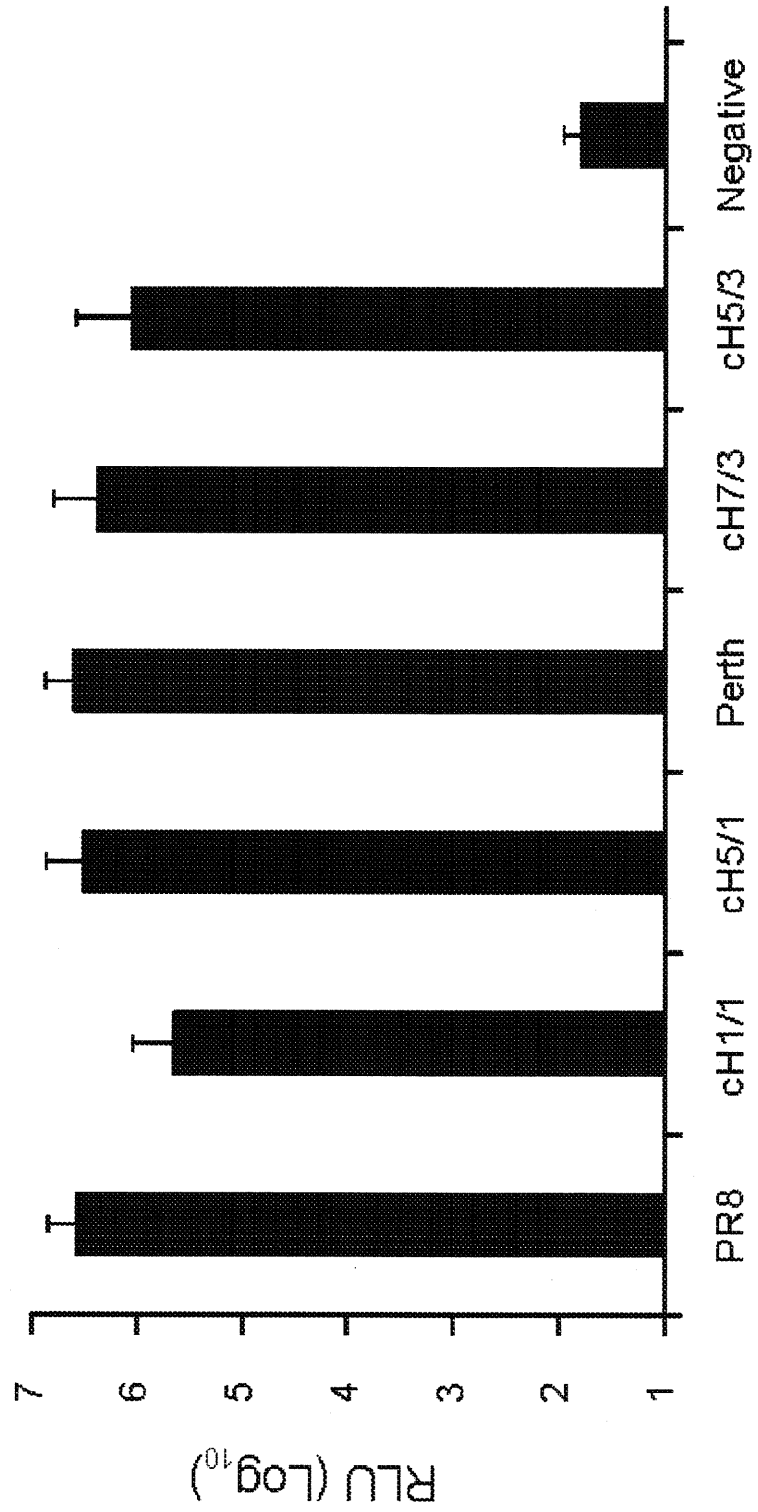


Fig. 34

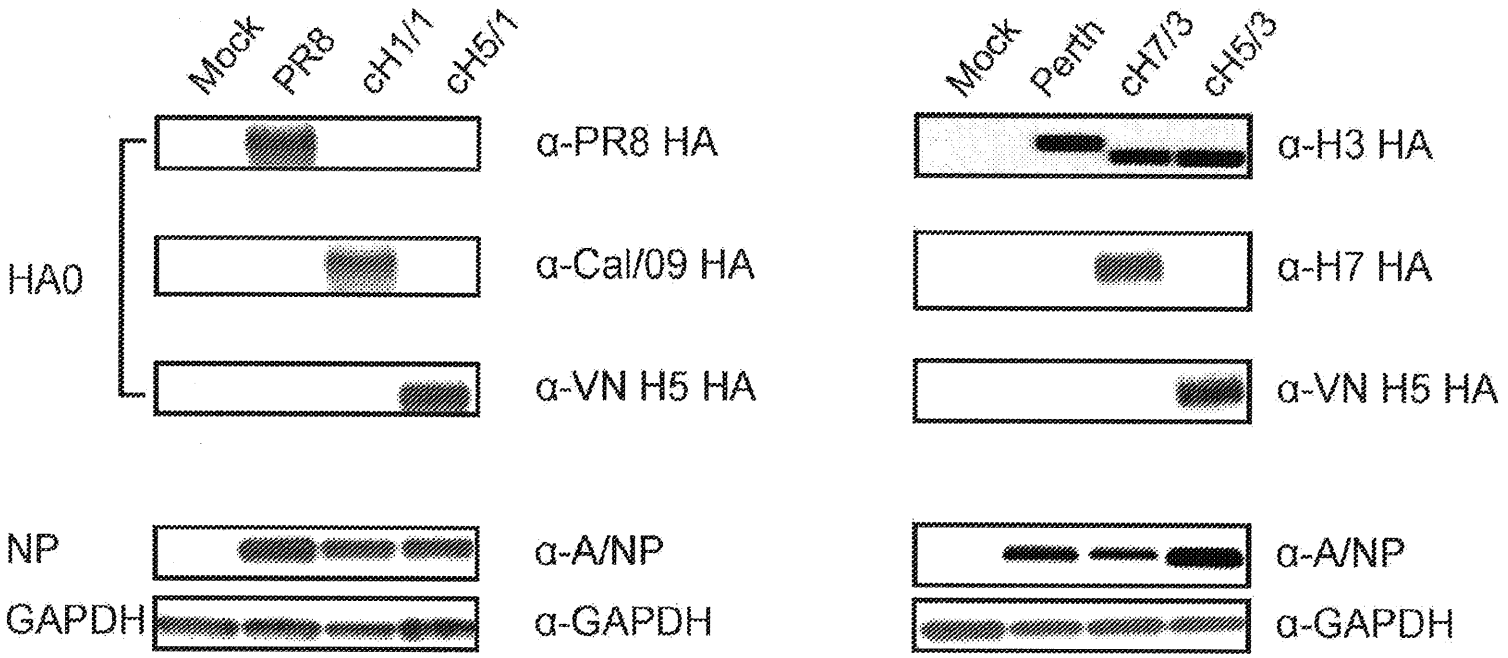

Mock
PR8
cH1/1
cH5/1
HA0
α-PR8 HA
α-Cal/09 HA
α-VN H5 HA
NP
α-A/NP
GAPDH
α-GAPDH
Mock
Perth
cH7/3
cH5/3
α-H3 HA
α-H7 HA
α-VN H5 HA
α-A/NP
α-GAPDH

Fig. 35

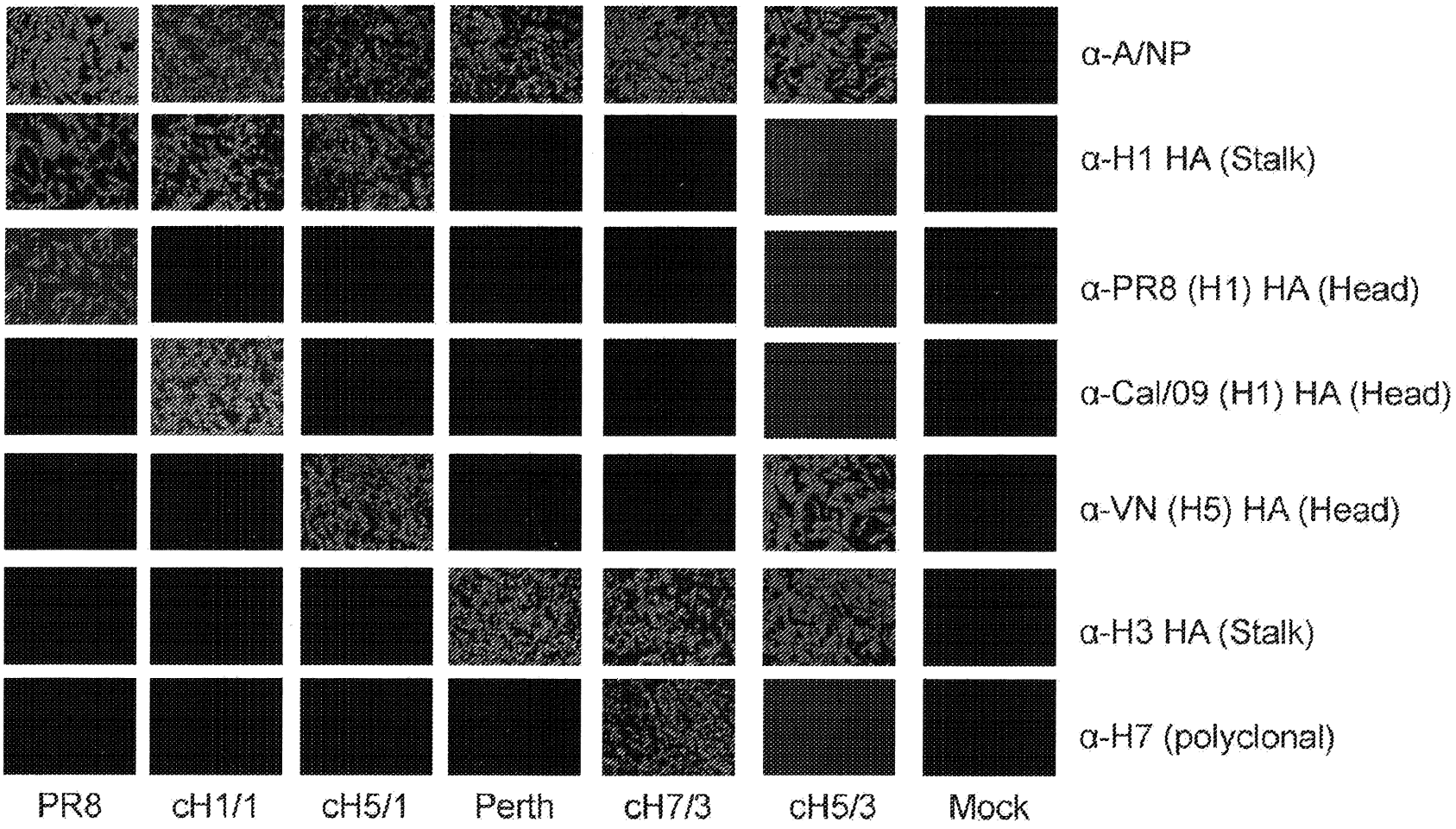
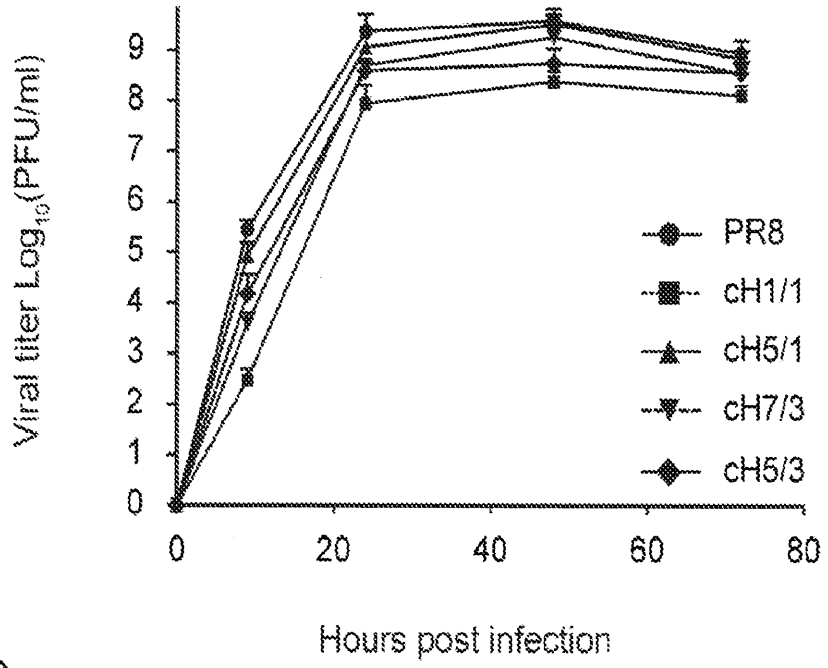

α-A/NP
α-H1 HA (Stalk)
α-PR8 (H1) HA (Head)
α-Cal/09 (H1) HA (Head)
α-VN (H5) HA (Head)
α-H3 HA (Stalk)
α-H7 (polyclonal)
PR8
cH1/1
cH5/1
Perth
cH7/3
cH5/3
Mock

Fig. 36

A


Viral titer Log_{10}(PFU/ml)
0
1
2
3
4
5
6
7
8
9
0
20
40
60
80
Hours post infection
PR8
cH1/1
cH5/1
cH7/3
cH5/3

B

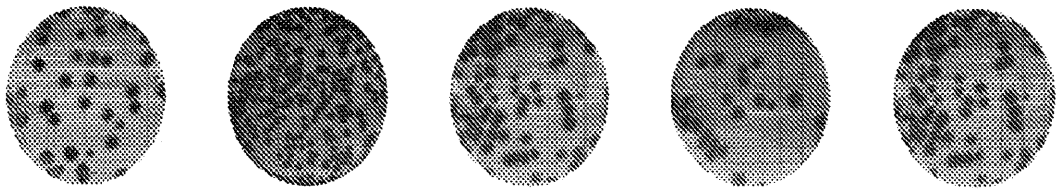
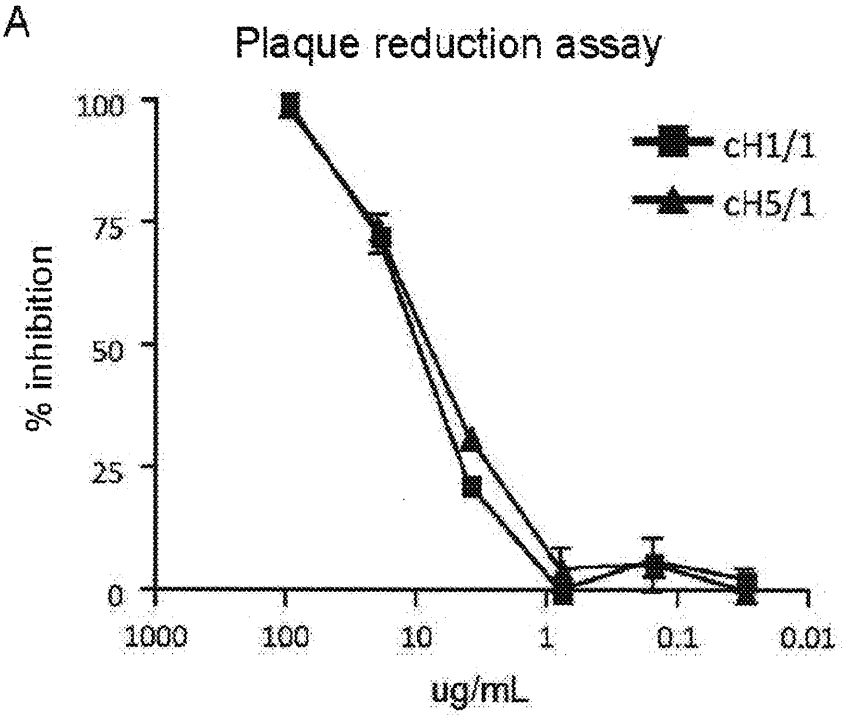

PR8
cH1/1
cH5/1
cH7/3
cH5/3

Fig. 37


A
Plaque reduction assay
100
75
50
25
0
% inhibition
cH1/1
cH5/1
1000
100
10
1
0.1
0.01
ug/mL

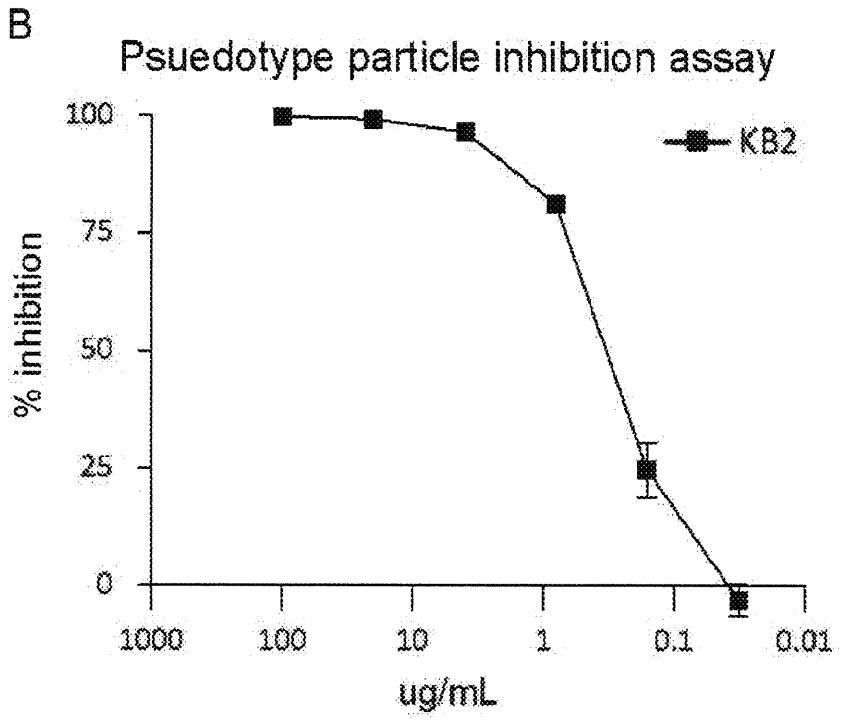

B
Psuedotype particle inhibition assay
100
75
50
25
0
% inhibition
KB2
1000
100
10
1
0.1
0.01
ug/mL

Fig. 38

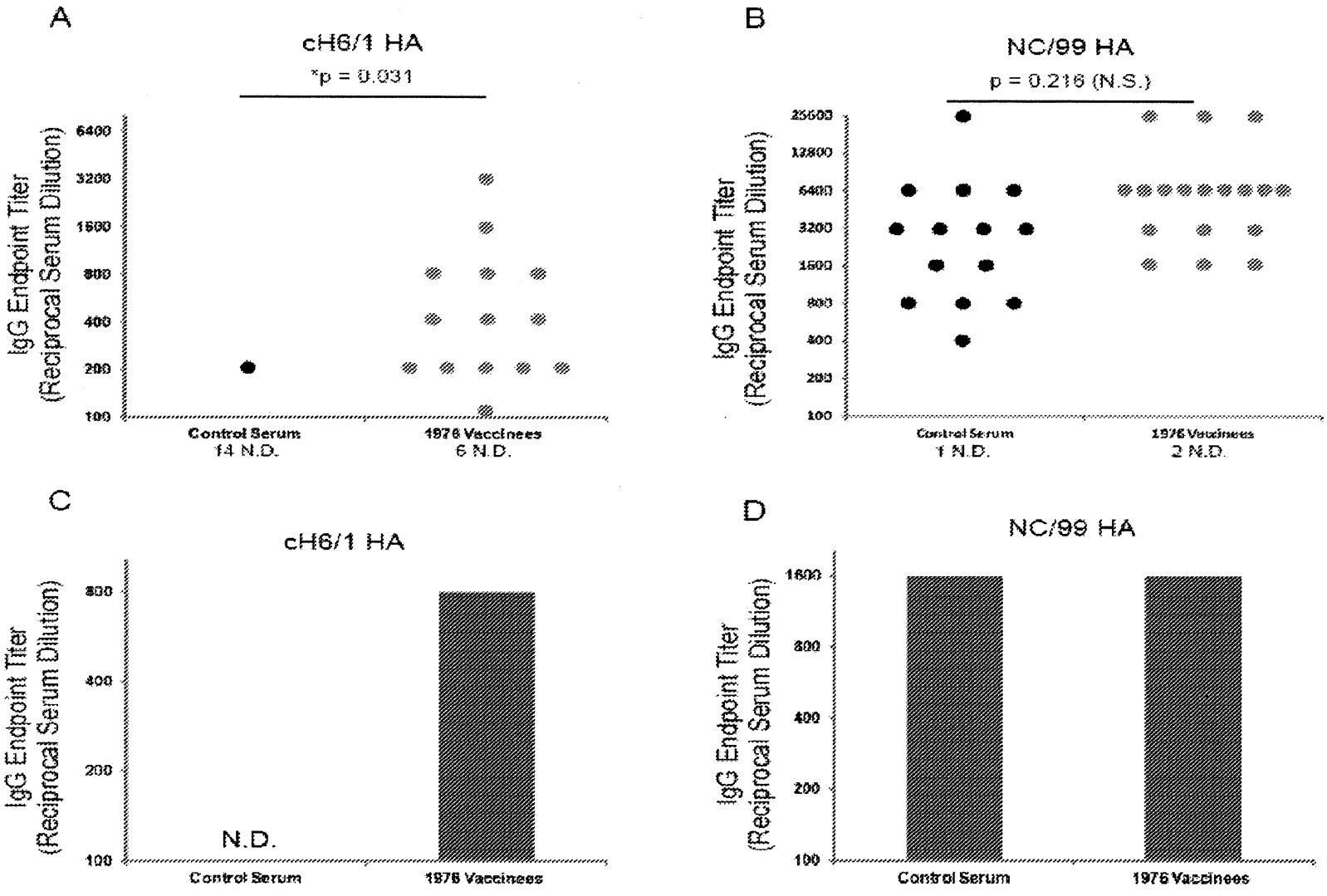

A
cH6/1 HA
*p = 0.031
IgG Endpoint Titer (Reciprocal Serum Dilution)
6400
3200
1600
800
400
200
100
Control Serum
14 N.D.
1976 Vaccinees
6 N.D.
B
NC/99 HA
p = 0.216 (N.S.)
IgG Endpoint Titer (Reciprocal Serum Dilution)
25600
12800
6400
3200
1600
800
400
200
100
Control Serum
1 N.D.
1976 Vaccinees
2 N.D.
C
cH6/1 HA
IgG Endpoint Titer (Reciprocal Serum Dilution)
800
400
200
100
N.D.
Control Serum
1976 Vaccinees
D
NC/99 HA
IgG Endpoint Titer (Reciprocal Serum Dilution)
1600
800
400
200
100
Control Serum
1976 Vaccinees

Fig. 39

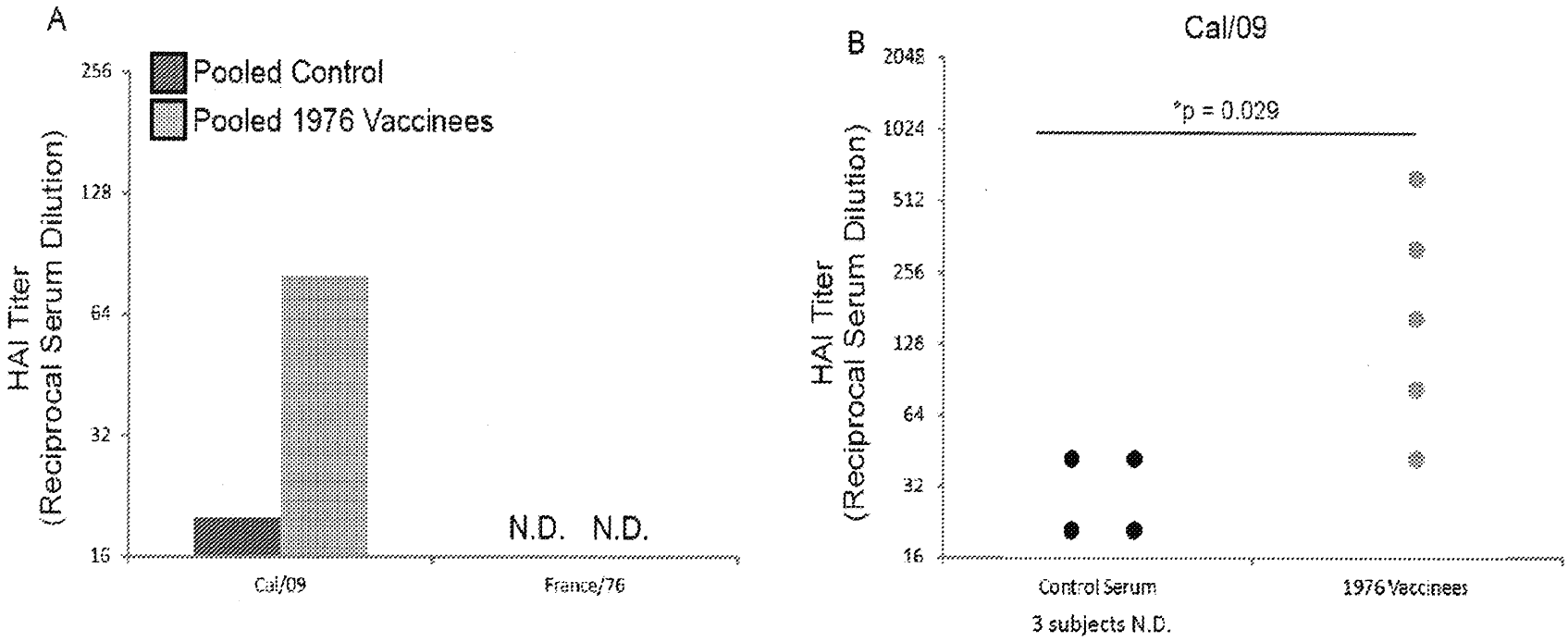

A
Pooled Control
Pooled 1976 Vaccinees
HAI Titer
(Reciprocal Serum Dilution)
256
128
64
32
16
N.D. N.D.
Cal/09
France/76
B
Cal/09
2048
1024
512
256
128
64
32
16
*p = 0.029
Control Serum
1976 Vaccinees
3 subjects N.D.

Fig. 40

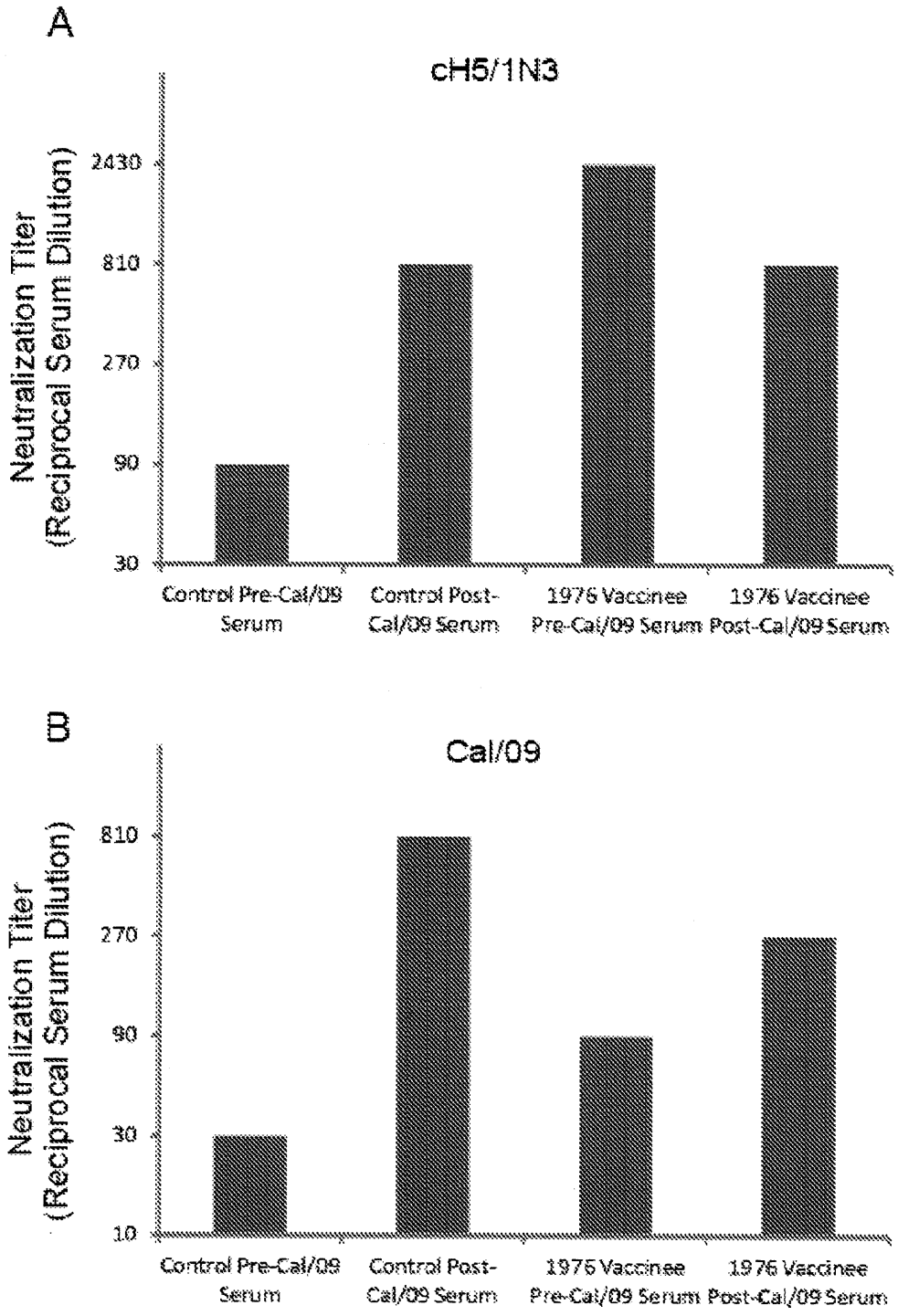

A
cH5/1N3
Neutralization Titer
(Reciprocal Serum Dilution)
2430
810
270
90
30
Control Pre-Cal/09 Serum
Control Post-Cal/09 Serum
1976 Vaccinee Pre-Cal/09 Serum
1976 Vaccinee Post-Cal/09 Serum
B
Cal/09
Neutralization Titer
(Reciprocal Serum Dilution)
810
270
90
30
10
Control Pre-Cal/09 Serum
Control Post-Cal/09 Serum
1976 Vaccinee Pre-Cal/09 Serum
1976 Vaccinee Post-Cal/09 Serum

Fig. 41

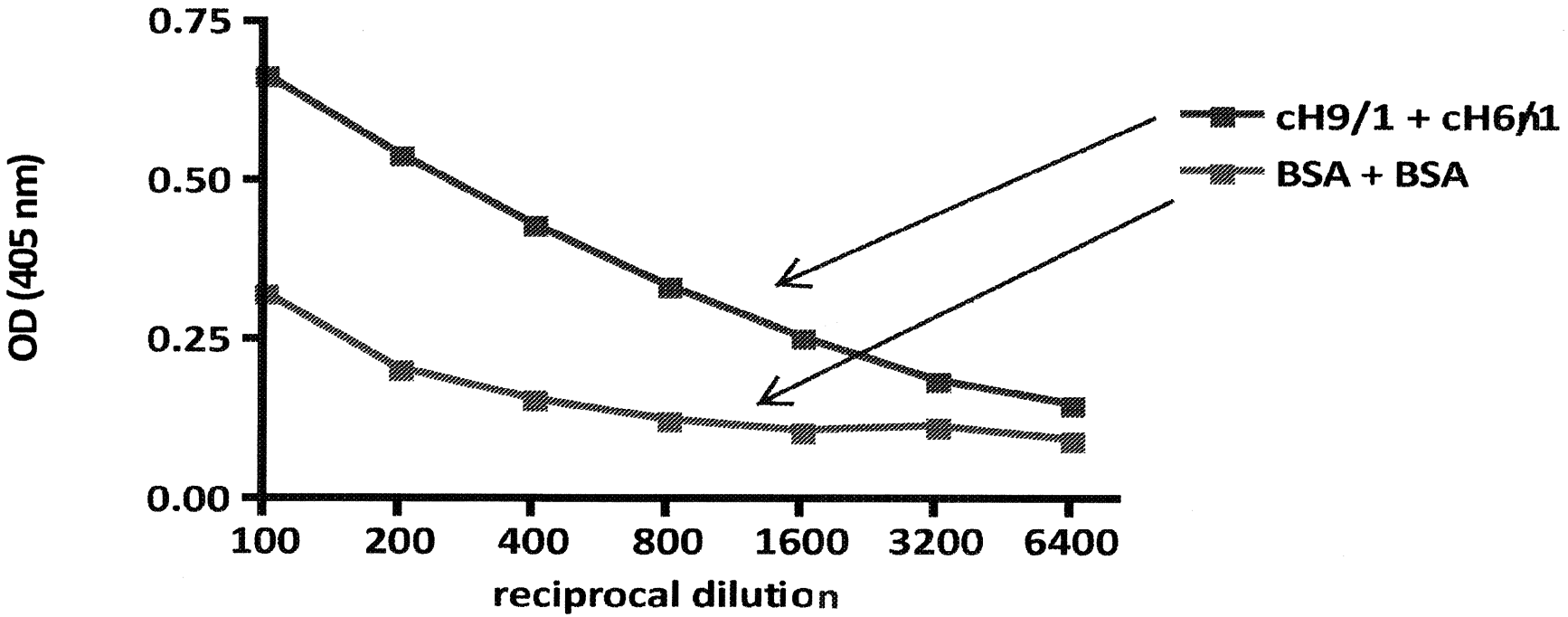

0.75
0.50
0.25
0.00
OD (405 nm)
100
200
400
800
1600
3200
6400
reciprocal dilution
cH9/1 + cH6/1
BSA + BSA

Fig. 42 A

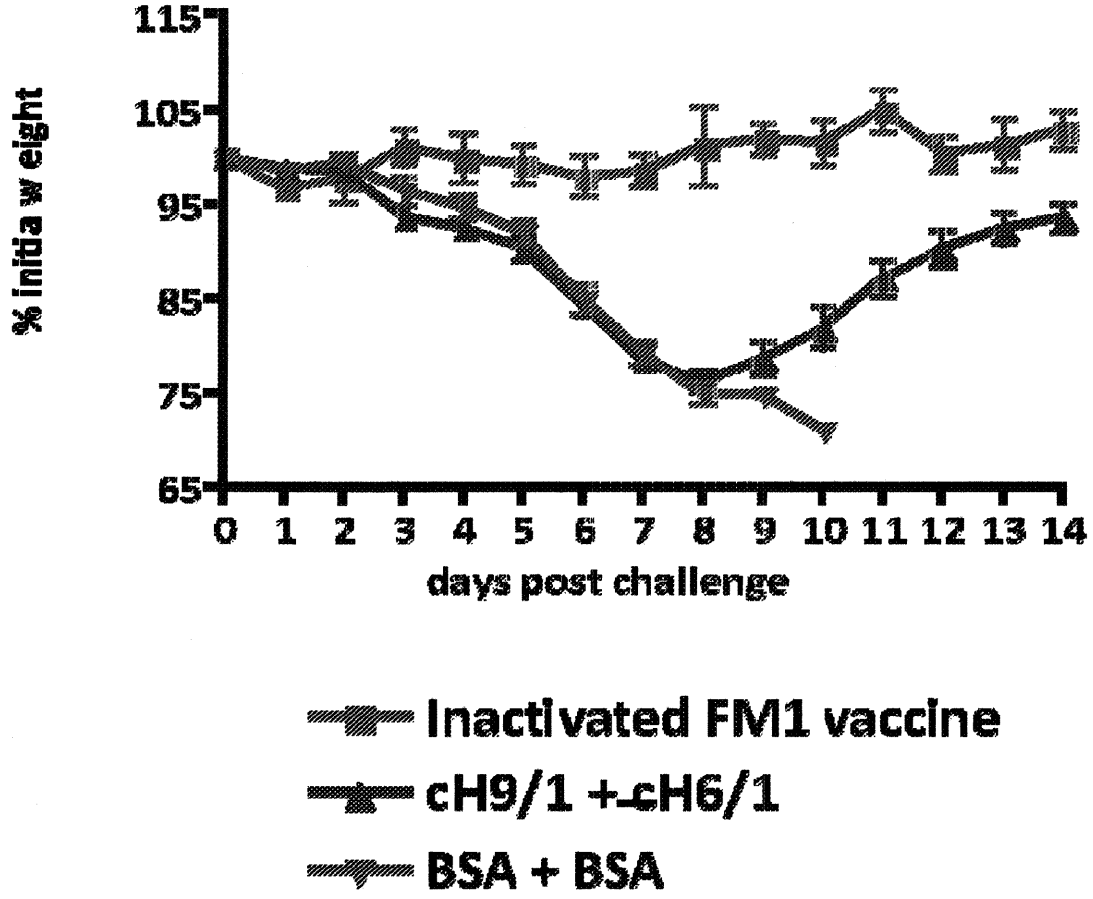

% initia w eight
115
105
95
85
75
65
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
days post challenge
Inactivated FM1 vaccine
cH9/1 + cH6/1
BSA + BSA

Fig. 42 B

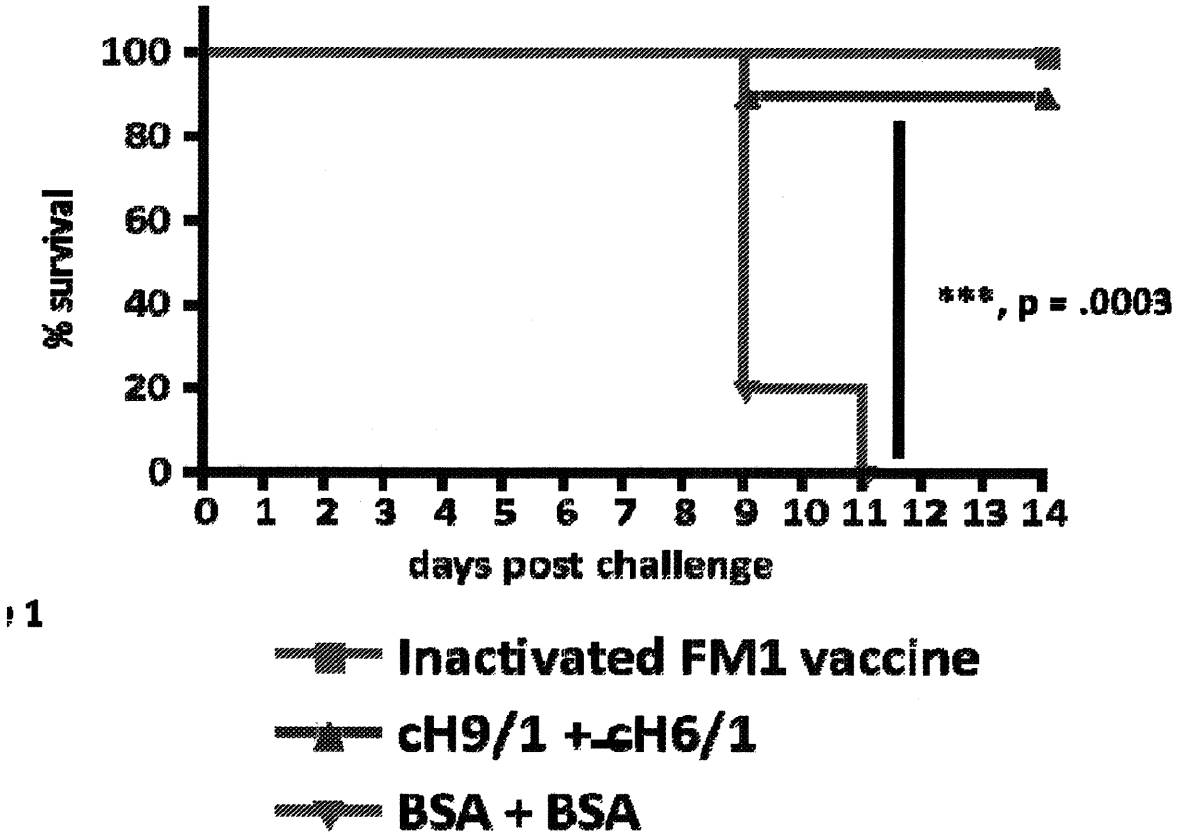

100
80
60
40
20
0
% survival
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
days post challenge
***, p = .0003
Inactivated FM1 vaccine
cH9/1 + cH6/1
BSA + BSA

Fig. 42 C

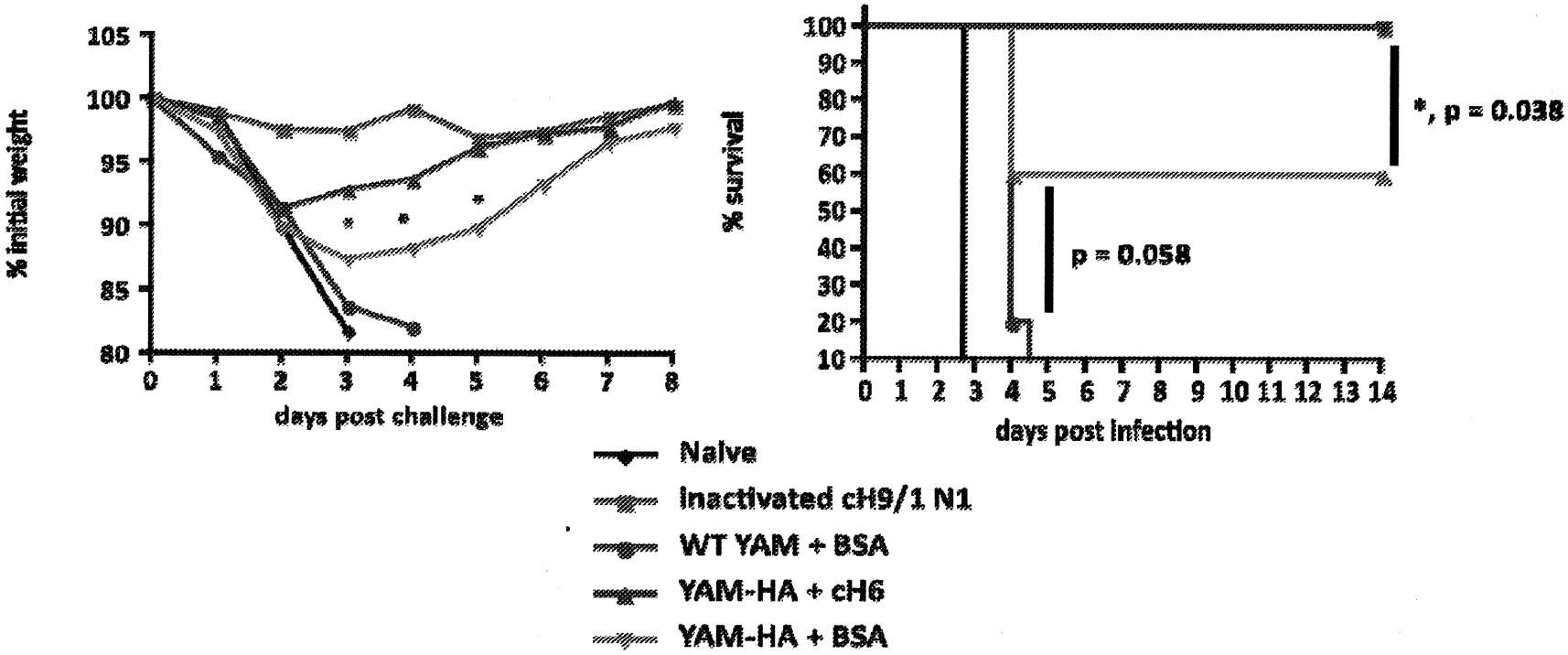

% initial weight
105
100
95
90
85
80
0 1 2 3 4 5 6 7 8
days post challenge
% survival
100
90
80
70
60
50
40
30
20
10
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
days post infection
*, p = 0.038
p = 0.058
Naive
Inactivated cH9/1 N1
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA

Fig. 43 A-B

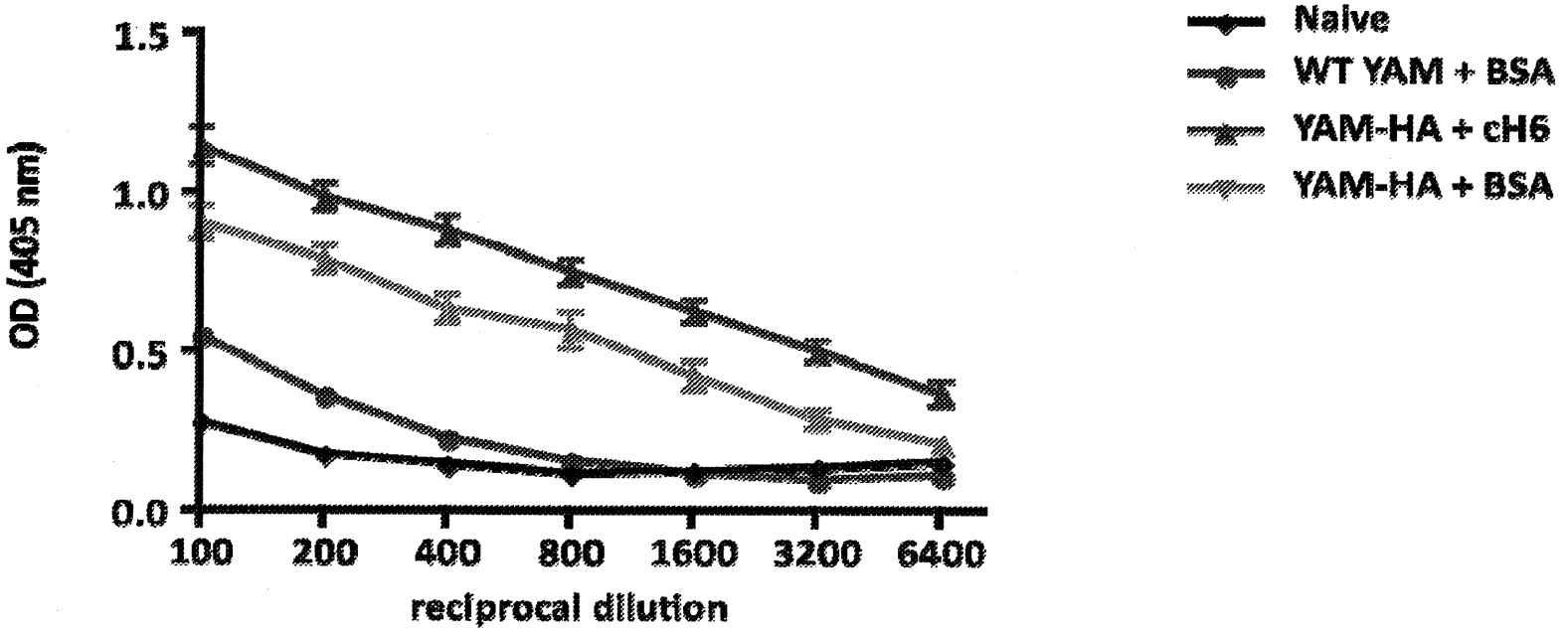

1.5
1.0
0.5
0.0
OD (405 nm)
100
200
400
800
1600
3200
6400
reciprocal dilution
Naive
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA

Fig. 43 C

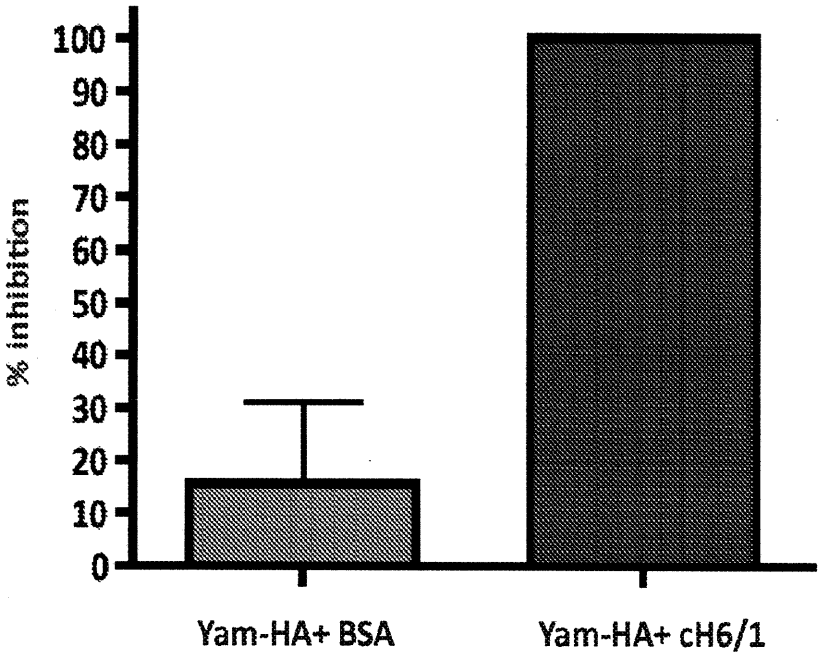


Fig. 43D

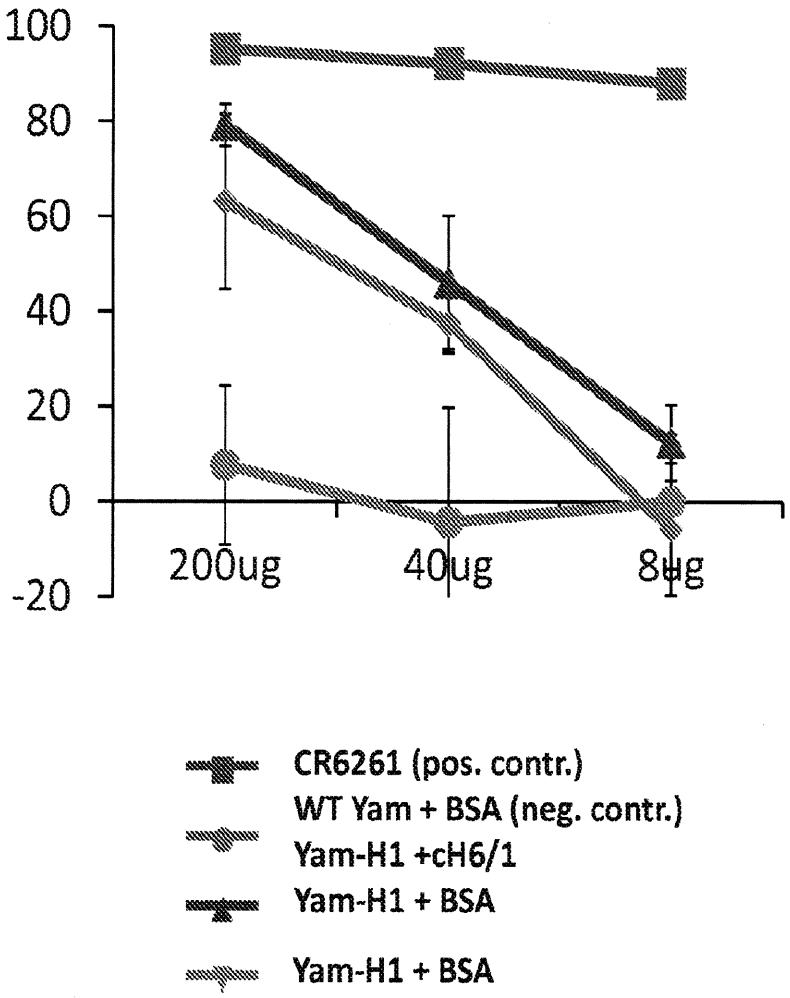

100
80
60
40
20
0
-20
200ug
40ug
8ug
CR6261 (pos. contr.)
WT Yam + BSA (neg. contr.)
Yam-H1 +cH6/1
Yam-H1 + BSA
Yam-H1 + BSA

Fig. 43E

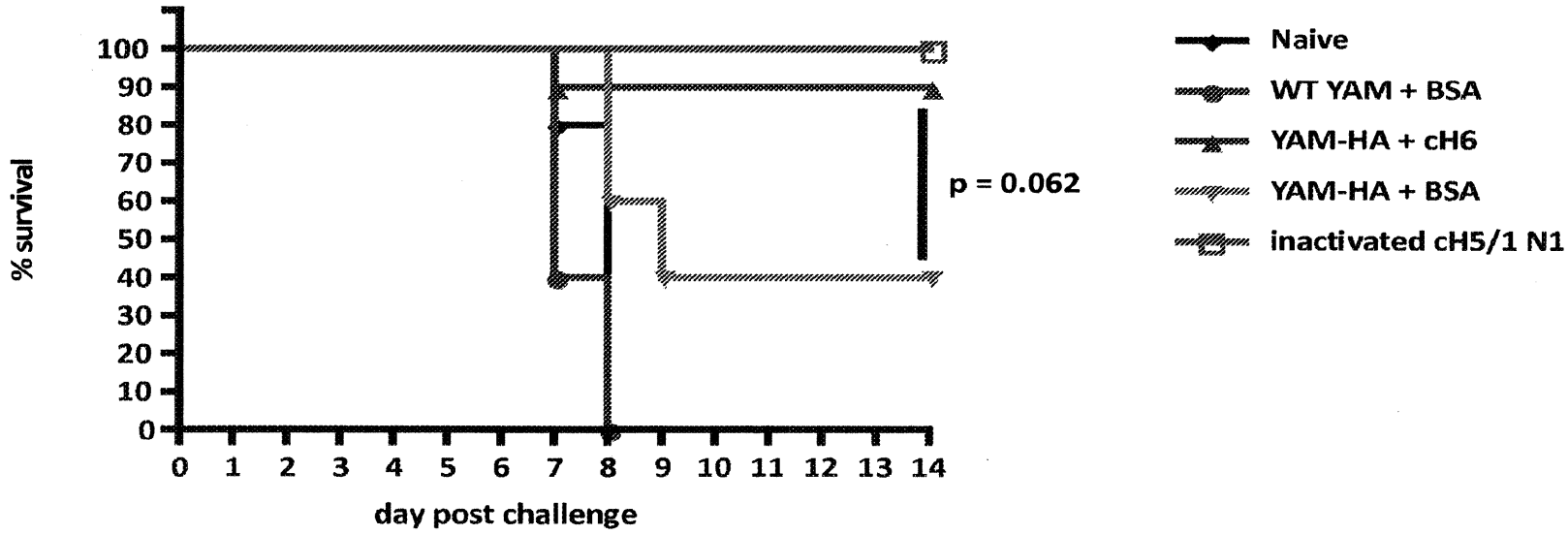

% survival
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
day post challenge
p = 0.062
Naive
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA
inactivated cH5/1 N1

Fig. 44A

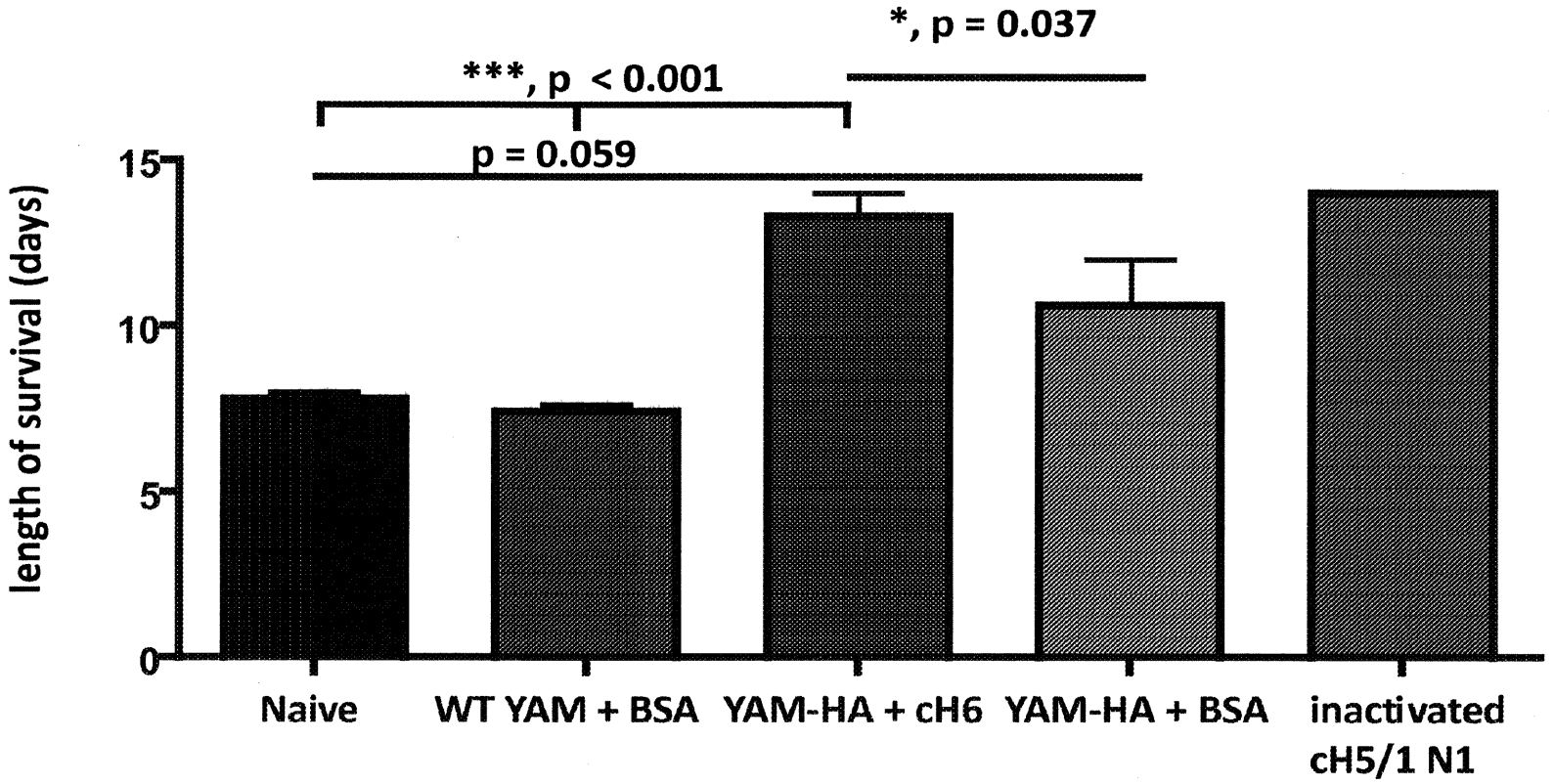

*, p = 0.037
***, p < 0.001
p = 0.059
length of survival (days)
15
10
5
0
Naive
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA
inactivated cH5/1 N1

Fig. 44B

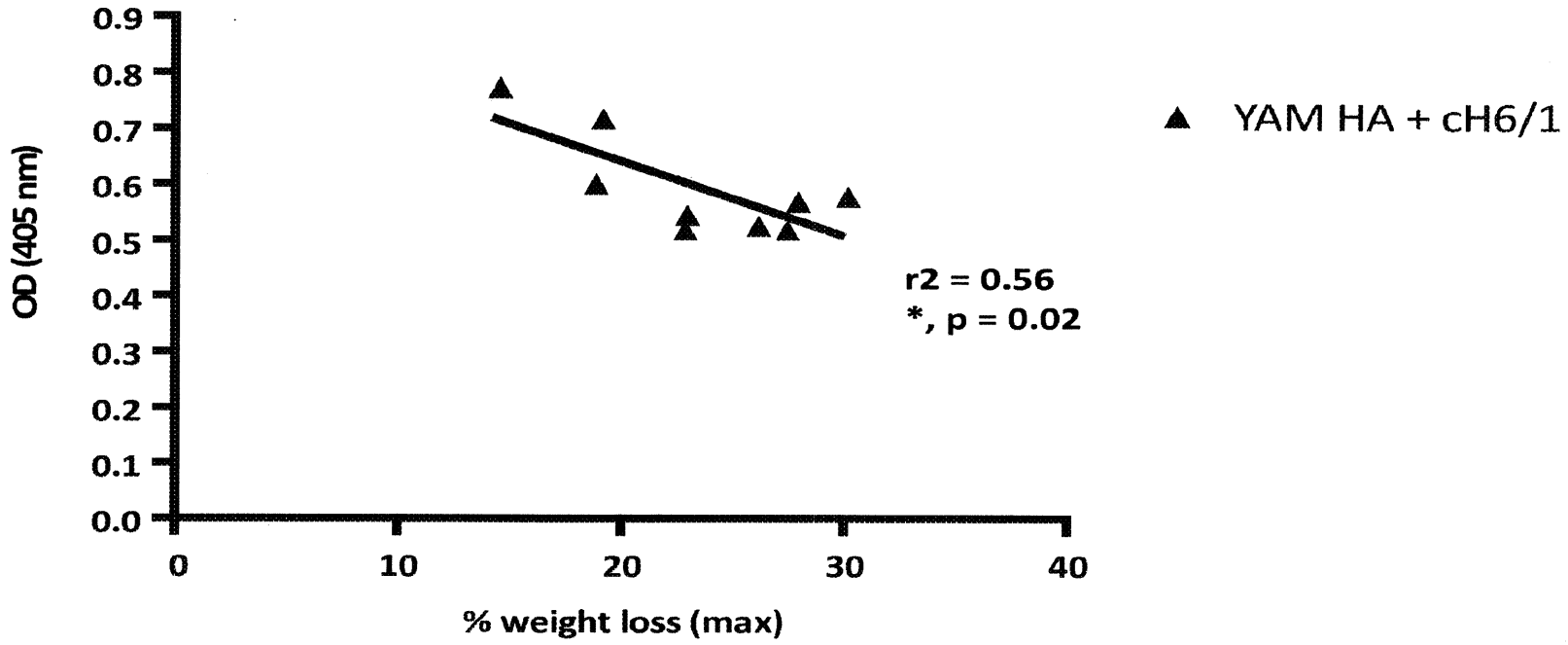

OD (405 nm)
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
% weight loss (max)
r2 = 0.56
*, p = 0.02
YAM HA + cH6/1

Fig. 44C

Fig. 45A

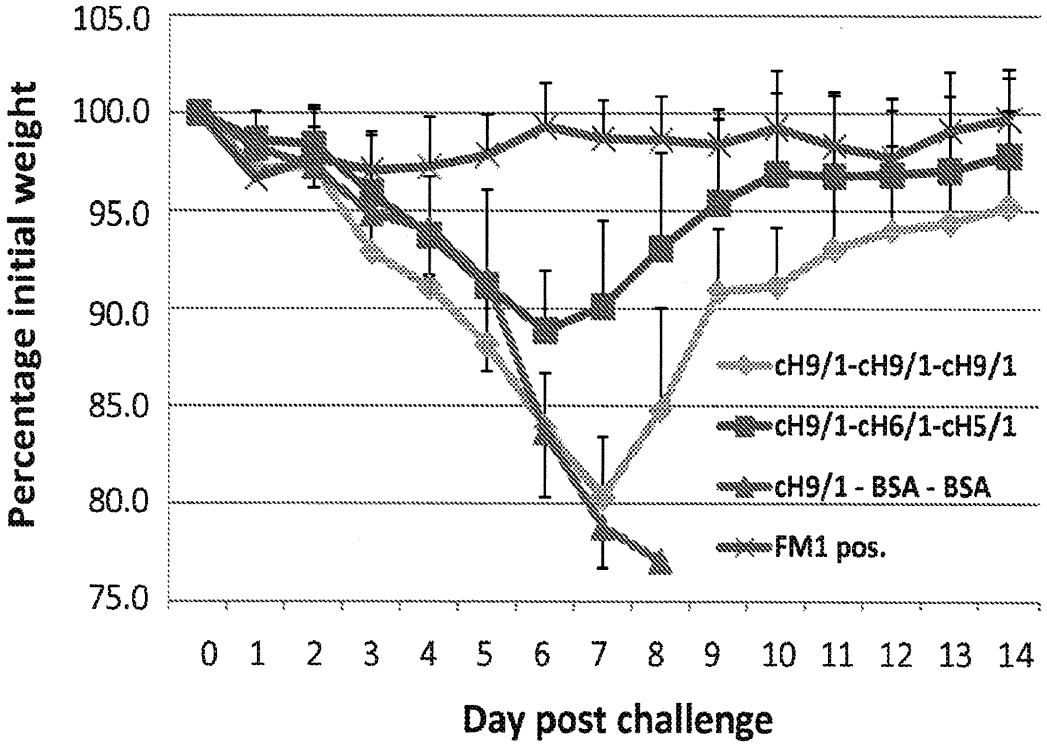


Fig. 45B

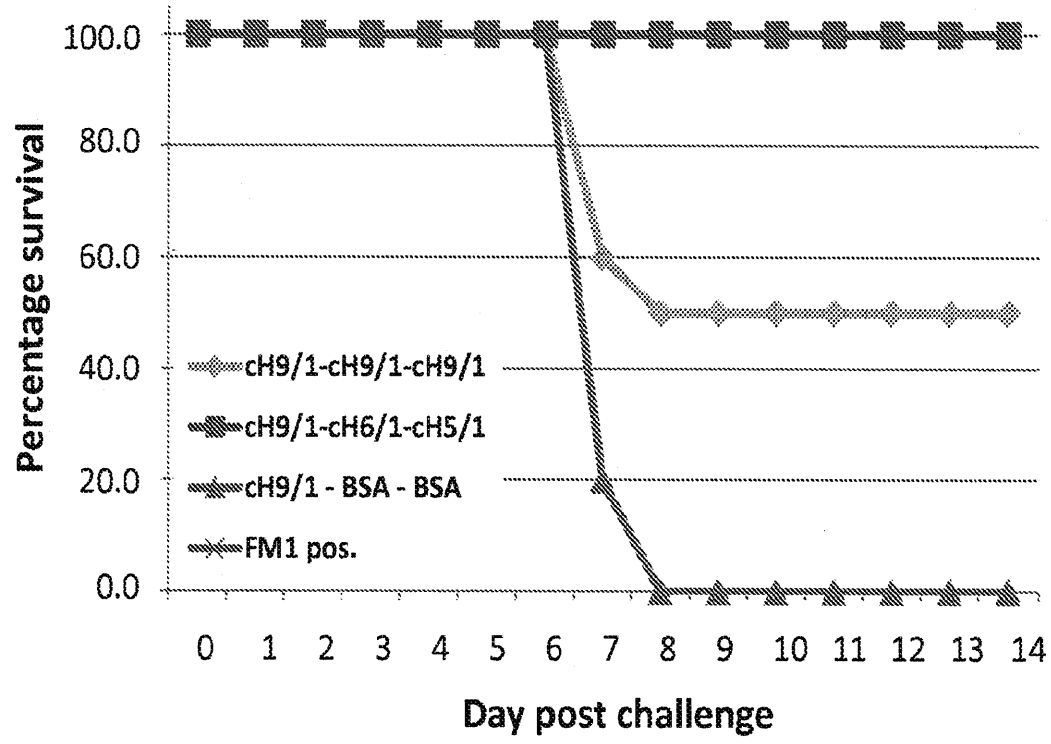


Fig. 45C

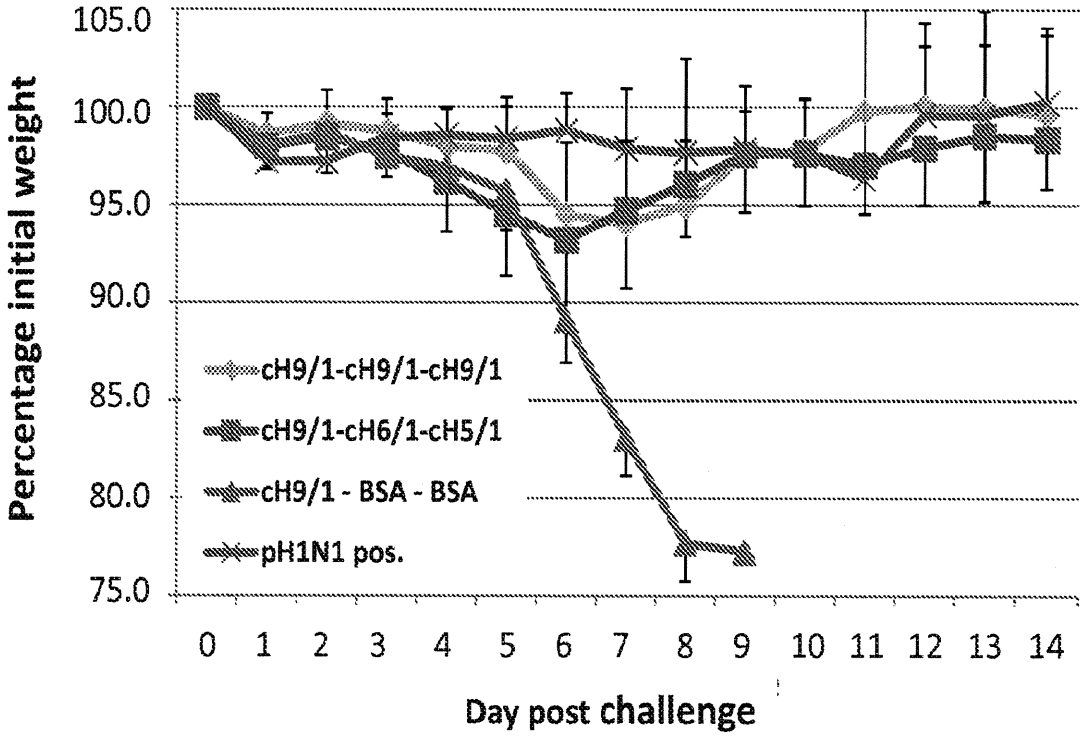


Fig. 45D

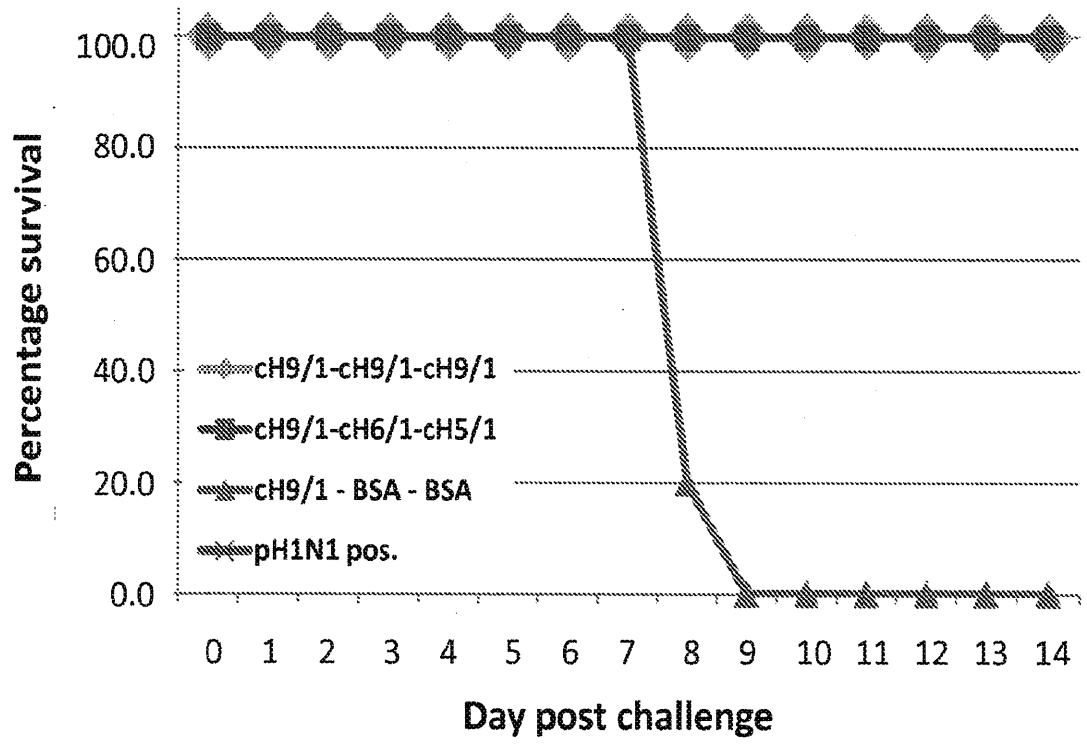


Fig. 45E

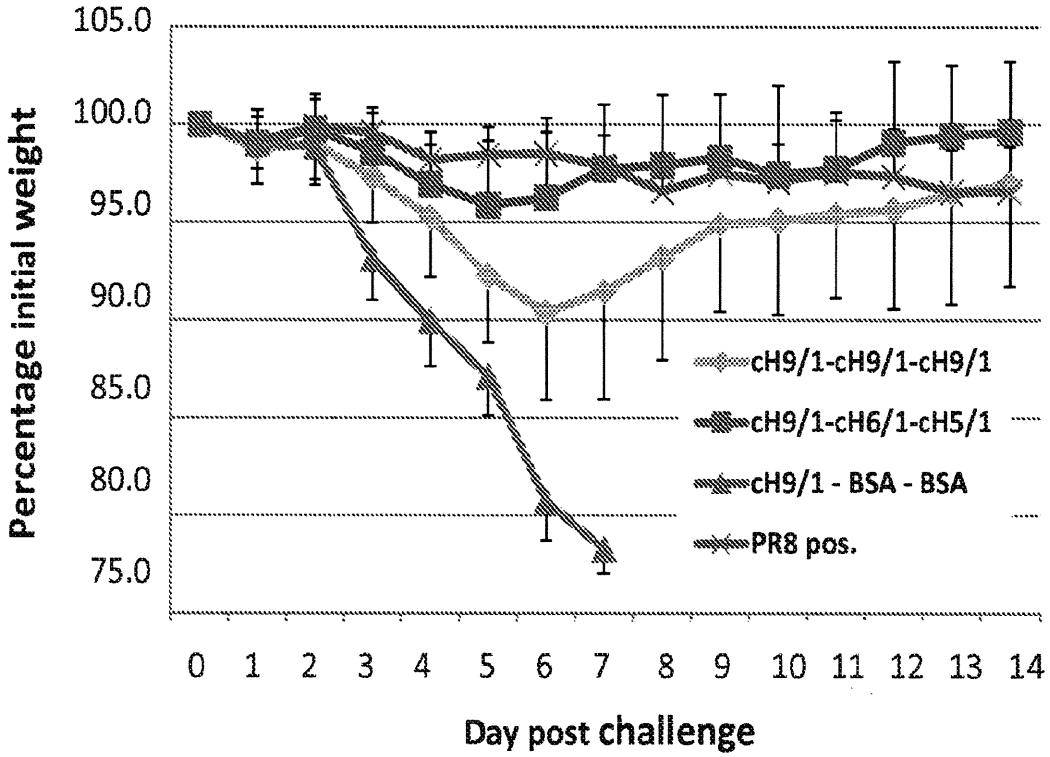
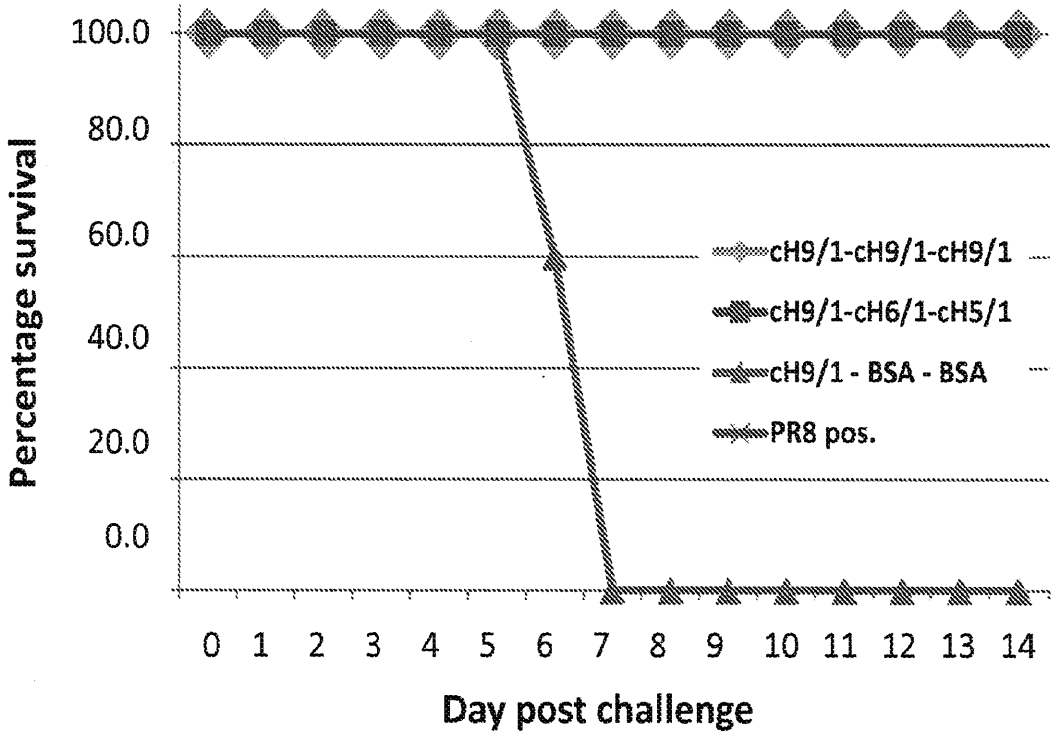


Fig. 45F



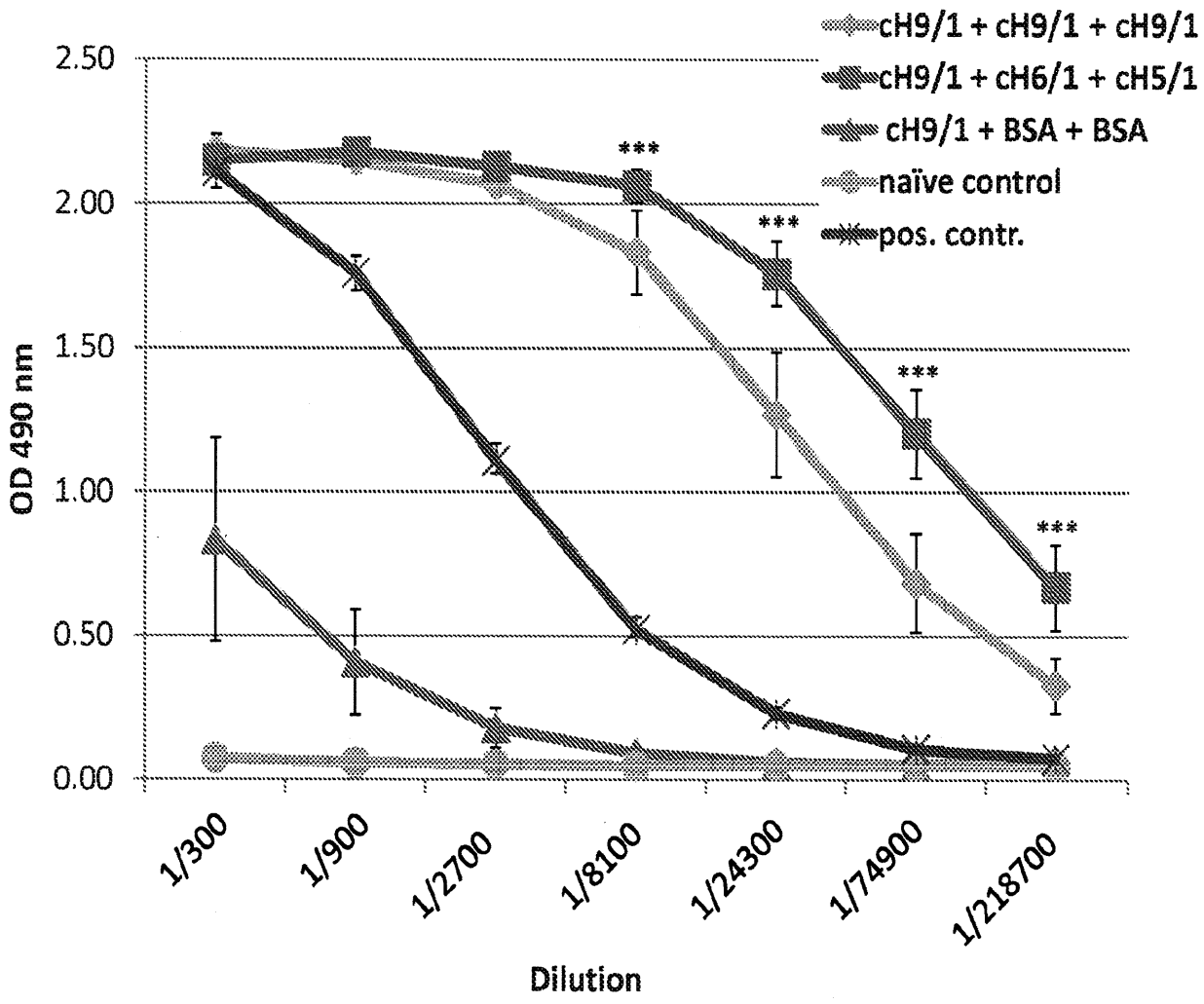

cH9/1 + cH9/1 + cH9/1
cH9/1 + cH6/1 + cH5/1
cH9/1 + BSA + BSA
naïve control
pos. contr.
2.50
2.00
1.50
1.00
0.50
0.00
OD 490 nm
***
***
***
***
1/300
1/900
1/2700
1/8100
1/24300
1/74900
1/218700
Dilution

Fig. 45G

Fig. 45H

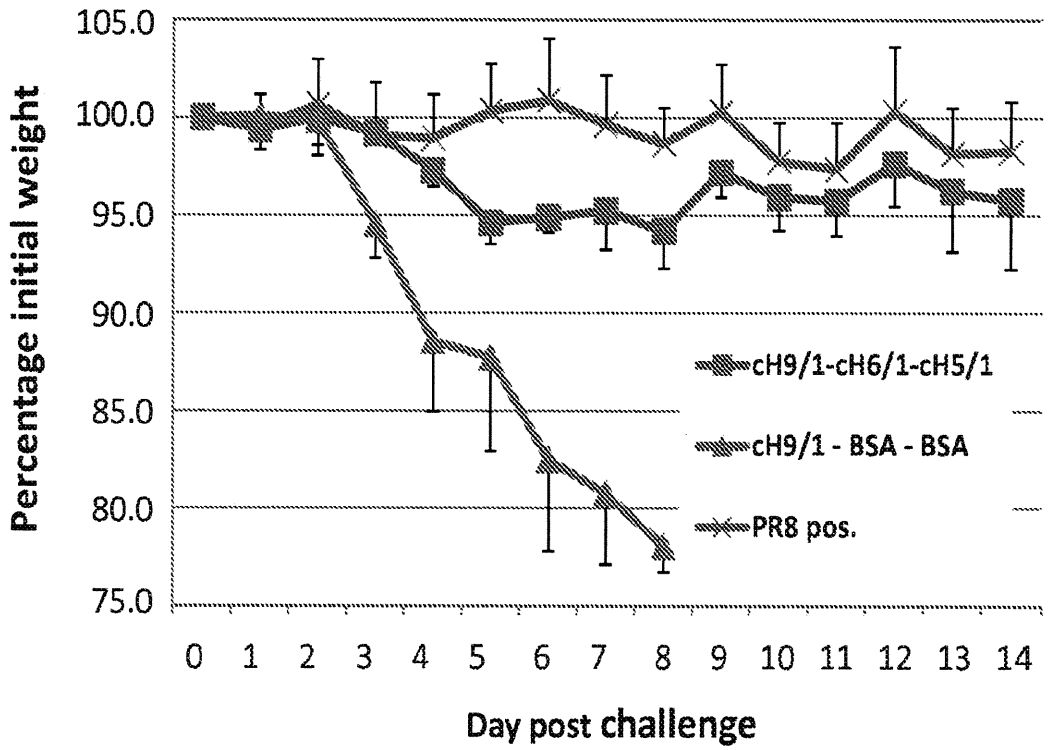
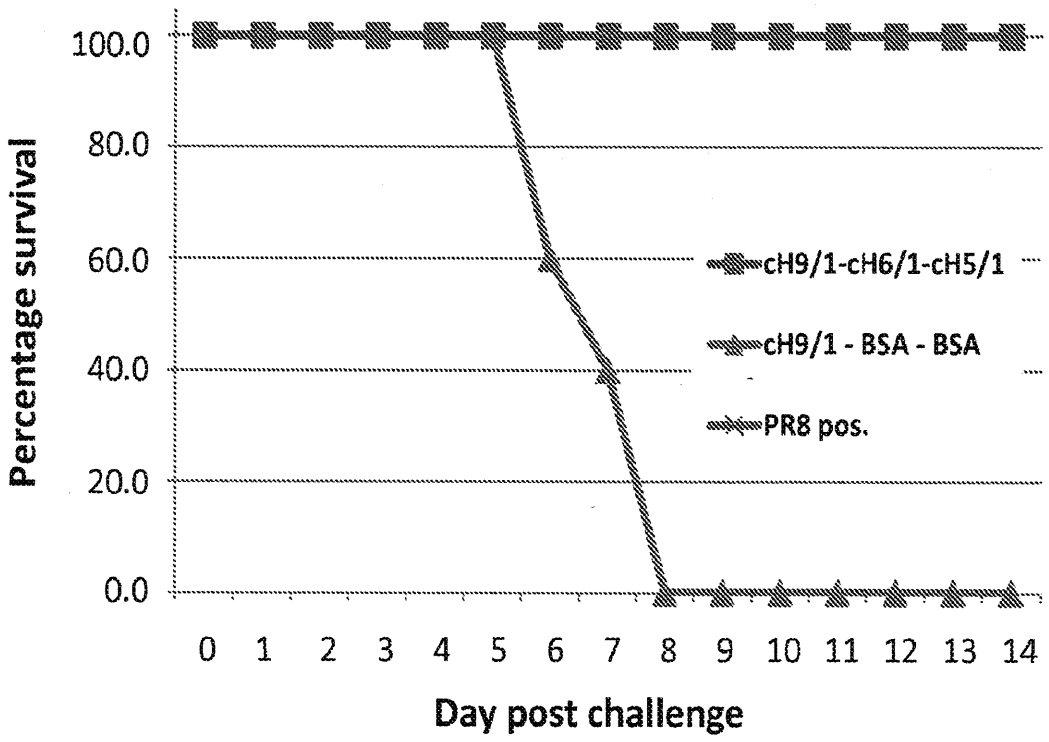


Fig. 45I



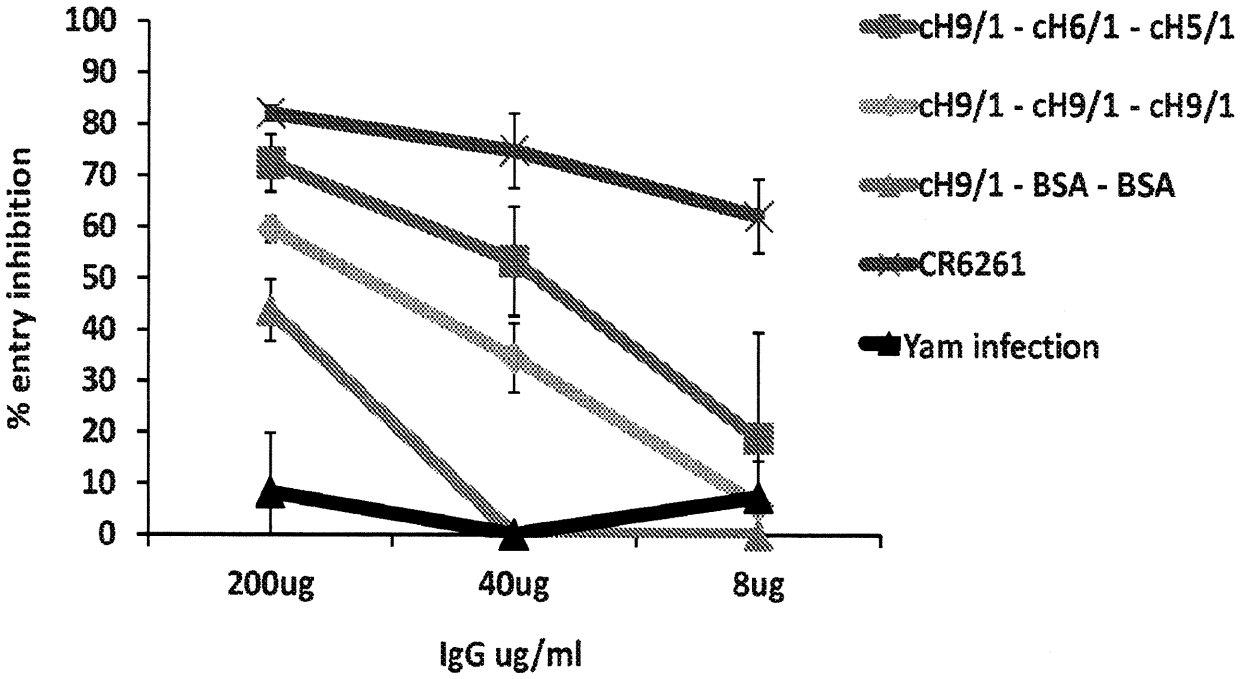

100
90
80
70
60
50
40
30
20
10
0
% entry inhibition
200ug
40ug
8ug
IgG ug/ml
cH9/1 - cH6/1 - cH5/1
cH9/1 - cH9/1 - cH9/1
cH9/1 - BSA - BSA
CR6261
Yam infection

Fig. 45J

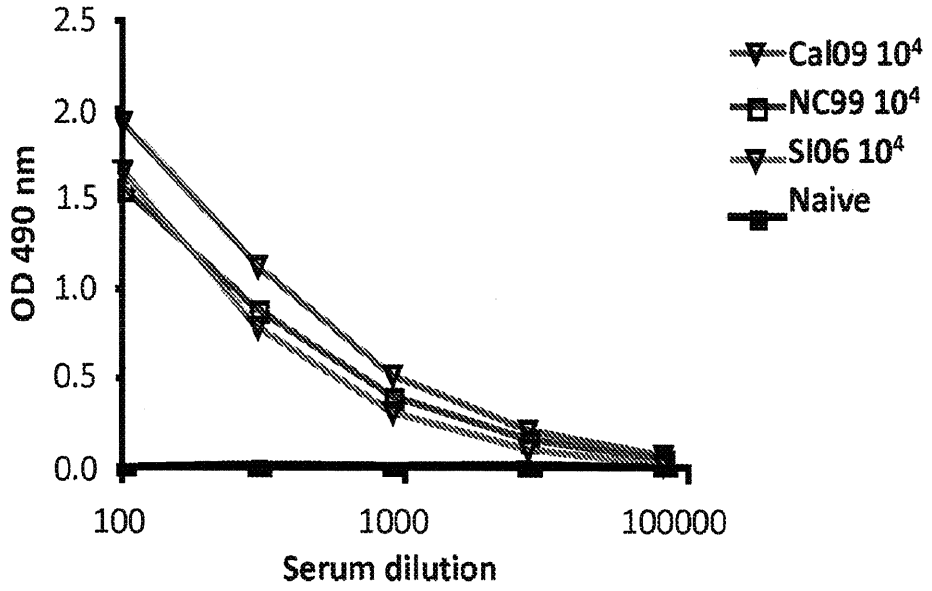

2.5
2.0
1.5
1.0
0.5
0.0
OD 490 nm
100
1000
100000
Serum dilution
Cal09 10⁴
NC99 10⁴
SI06 10⁴
Naive

Fig. 46

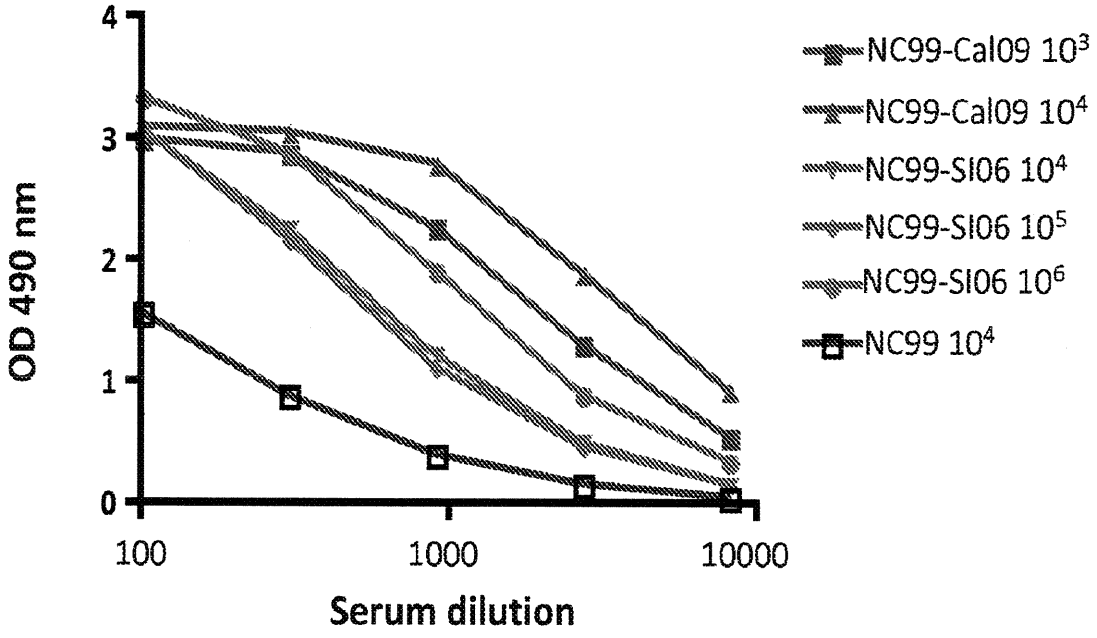

OD 490 nm
4
3
2
1
0
100
1000
10000
Serum dilution
NC99-Cal09 10^3
NC99-Cal09 10^4
NC99-SI06 10^4
NC99-SI06 10^5
NC99-SI06 10^6
NC99 10^4

Fig. 47

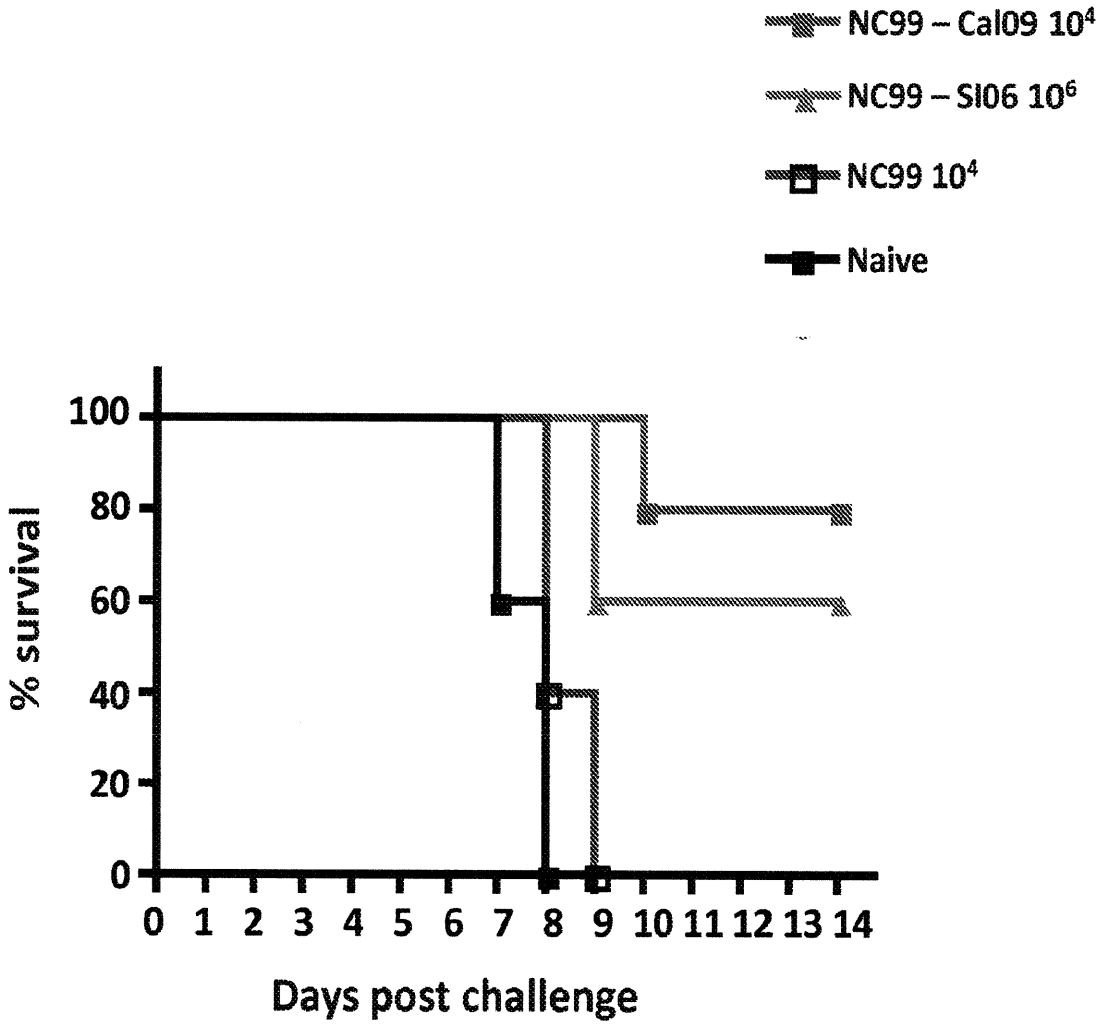
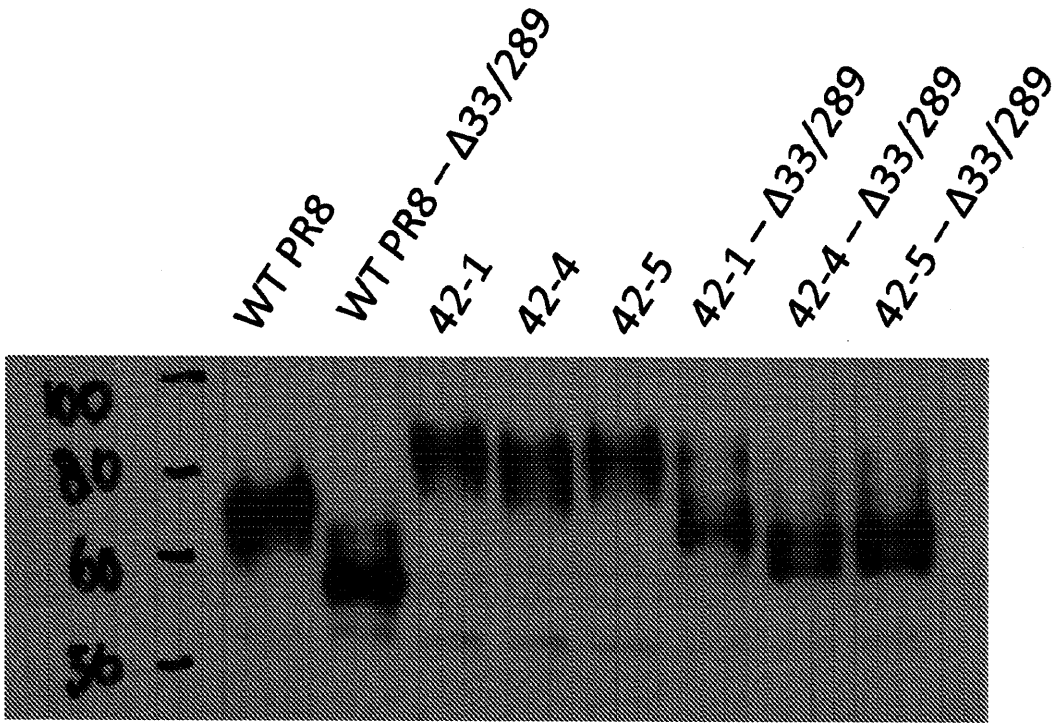

NC99 – Cal09 10⁴
NC99 – SI06 10⁶
NC99 10⁴
Naive
% survival
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days post challenge

Fig. 48



42-1: 81/131/158/165/189/172/210

42-4: 81/131/158/---/189/172/210

42-5: --/131/158/165/189/172/210

Fig. 49

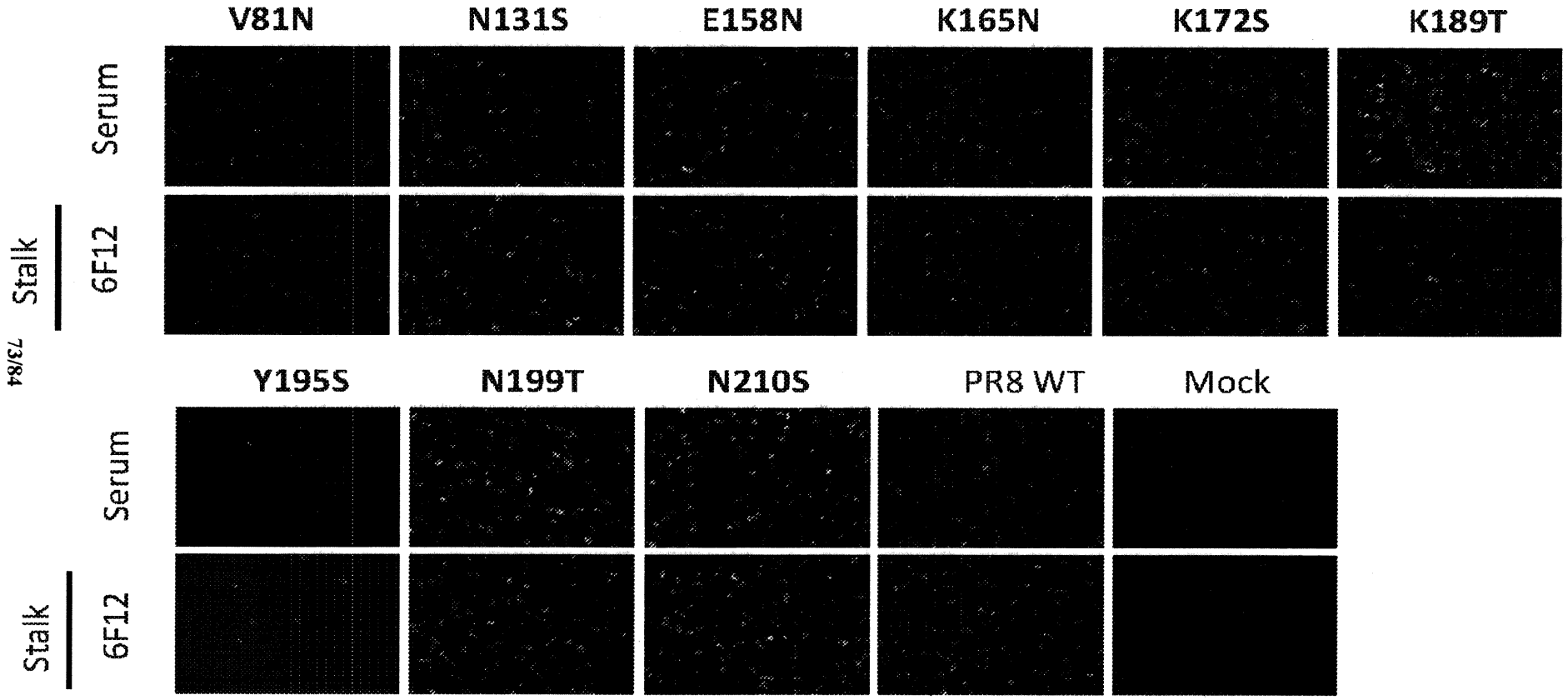

V81N
N131S
E158N
K165N
K172S
K189T
Serum
Stalk
6F12
Y195S
N199T
N210S
PR8 WT
Mock
Serum
Stalk
6F12

Fig. 50A

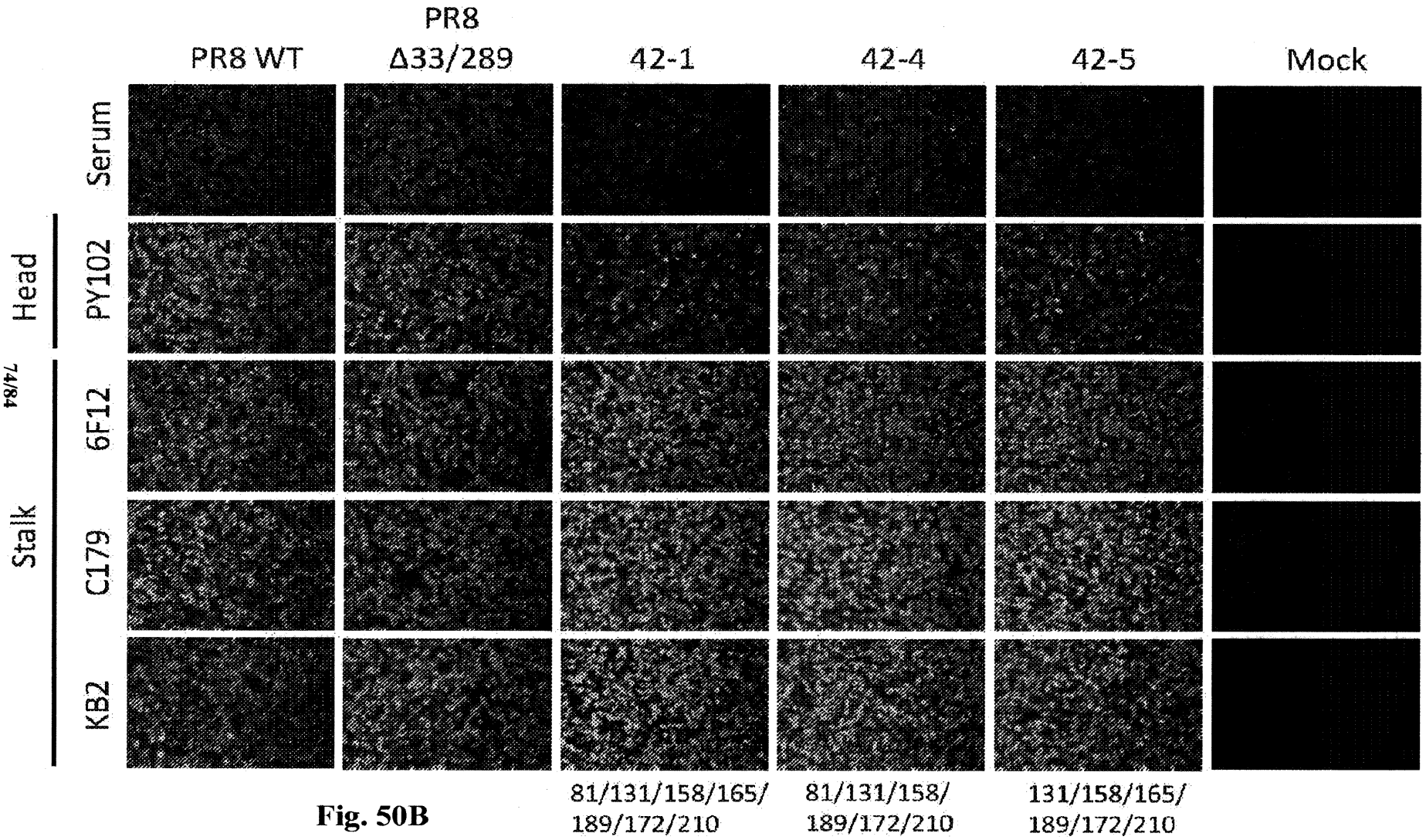

PR8 WT
PR8 Δ33/289
42-1
42-4
42-5
Mock
Serum
Head
PY102
Stalk
6F12
C179
KB2
81/131/158/165/ 189/172/210
81/131/158/ 189/172/210
131/158/165/ 189/172/210

Fig. 50B

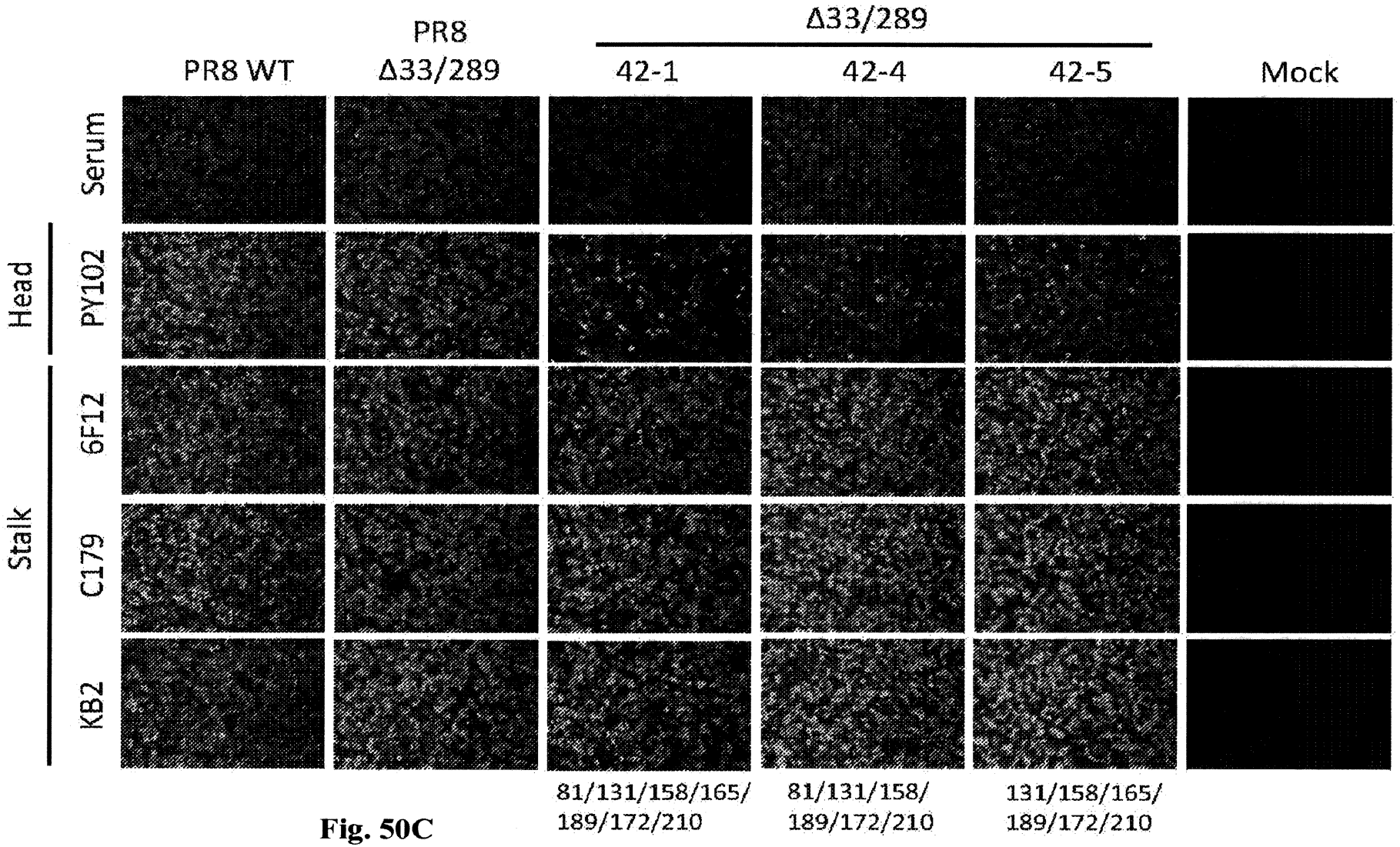

PR8 WT
PR8 Δ33/289
Δ33/289
42-1
42-4
42-5
Mock
Serum
Head
PY102
6F12
Stalk
C179
KB2
81/131/158/165/ 189/172/210
81/131/158/ 189/172/210
131/158/165/ 189/172/210

Fig. 50C

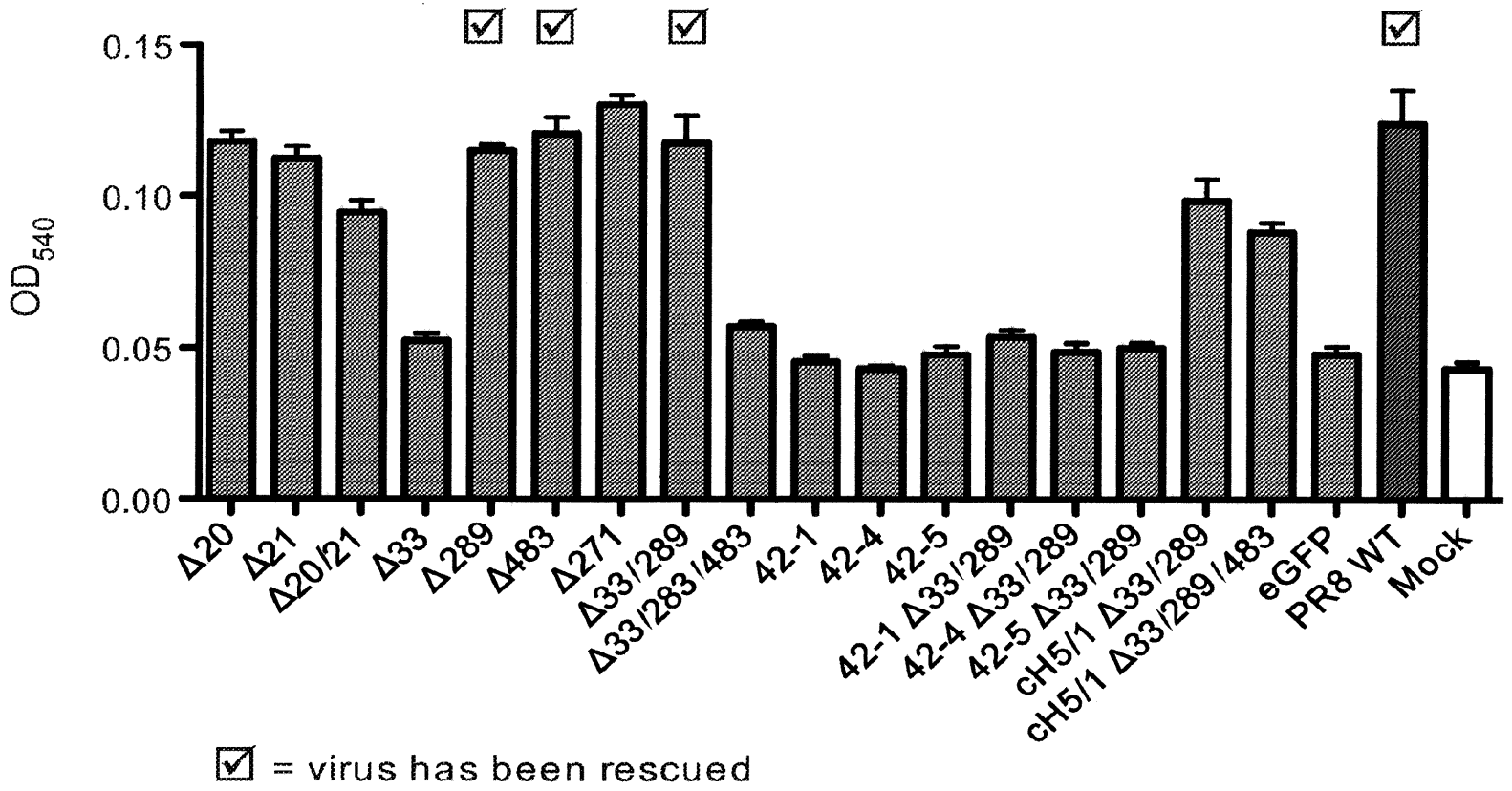

0.15
0.10
0.05
0.00
OD540
Δ20
Δ21
Δ20/21
Δ33
Δ289
Δ483
Δ271
Δ33/289
Δ33/283/483
42-1
42-4
42-5
42-1 Δ33/289
42-4 Δ33/289
42-5 Δ33/289
cH5/1 Δ33/289
cH5/1 Δ33/289/483
eGFP
PR8 WT
Mock
☑ = virus has been rescued

Fig. 51

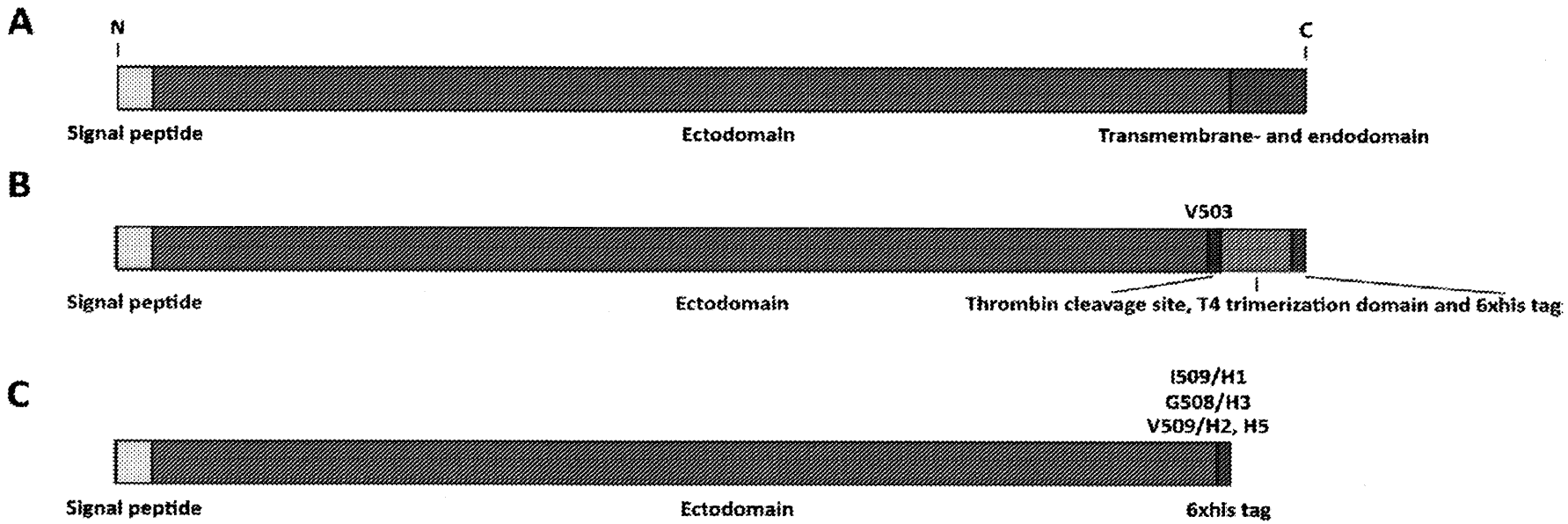

A
N
C
Signal peptide
Ectodomain
Transmembrane- and endodomain
B
V503
Signal peptide
Ectodomain
Thrombin cleavage site, T4 trimerization domain and 6xhis tag
C
I509/H1
G508/H3
V509/H2, H5
Signal peptide
Ectodomain
6xhis tag

FIG. 52A-C

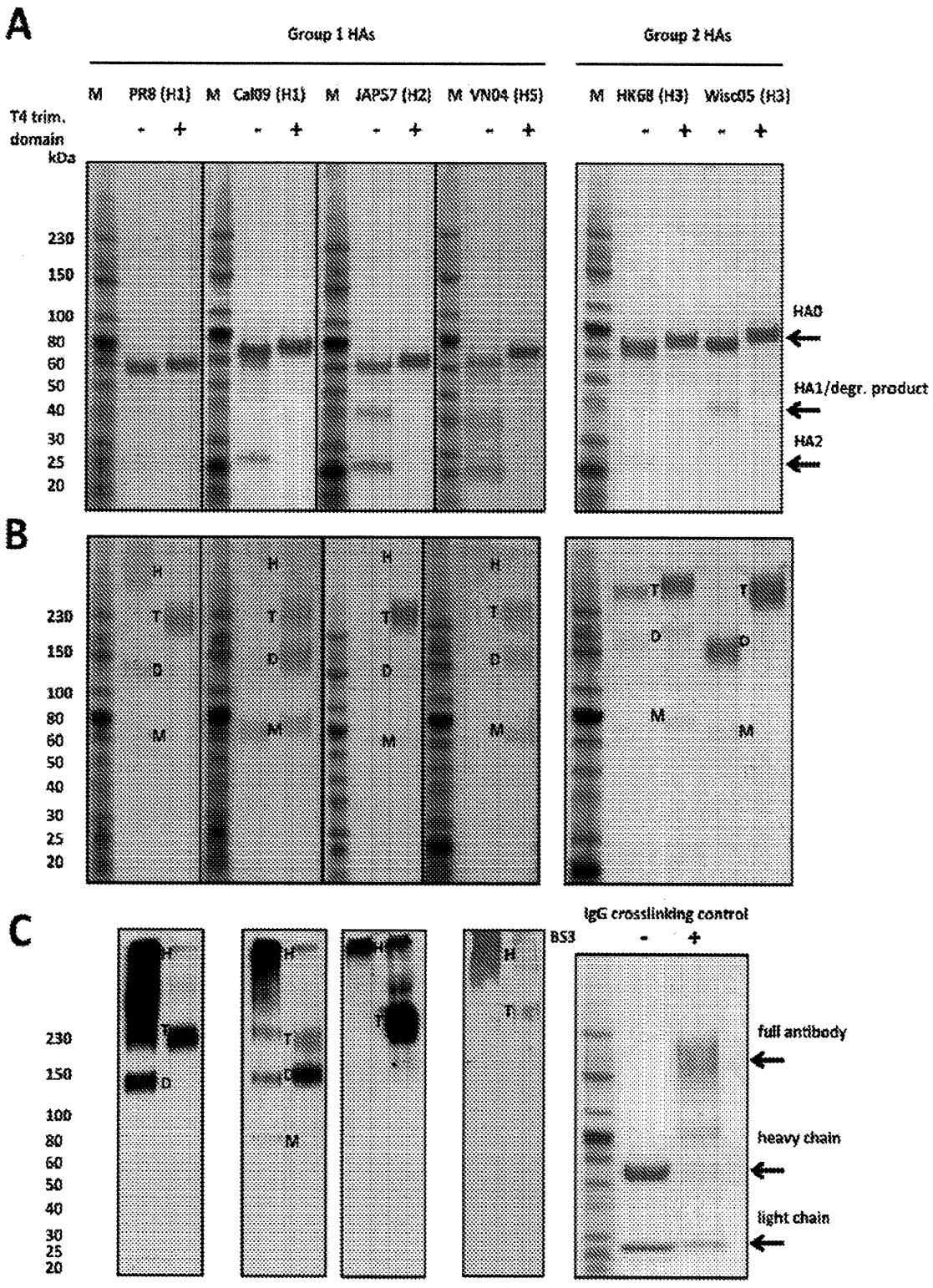

A
Group 1 HAs
Group 2 HAs
M PR8 (H1) M Cal09 (H1) M JAPS7 (H2) M VN04 (H5) M HK68 (H3) Wisc05 (H3)
T4 trim. domain
- + - + - + - + - + - +
kDa
230
150
100
80
60
50
40
30
25
20
HA0
HA1/degr. product
HA2
B
H
T
D
M
C
IgG crosslinking control
BS3 - +
full antibody
heavy chain
light chain

FIG. 53A-C

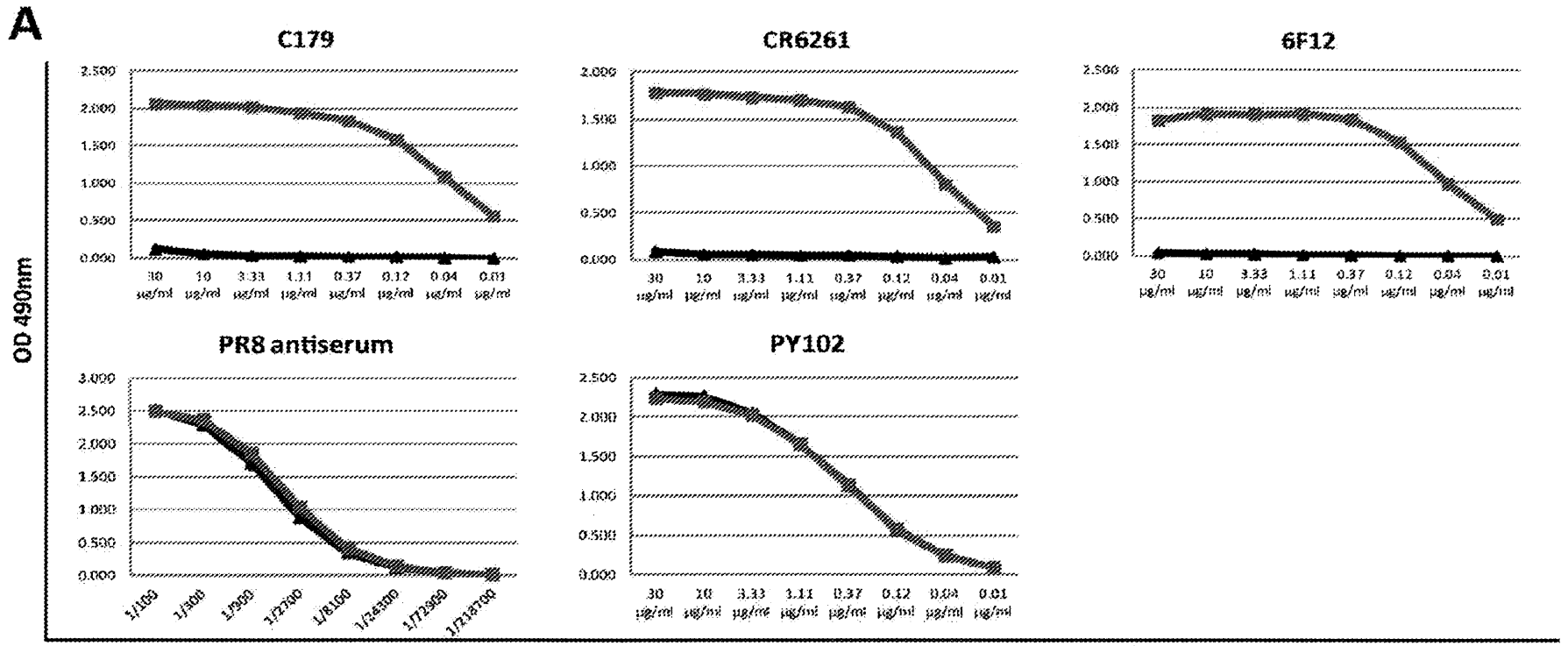

A
C179
CR6261
6F12
PR8 antiserum
PY102
OD 490nm
30 µg/ml
10 µg/ml
3.33 µg/ml
1.11 µg/ml
0.37 µg/ml
0.12 µg/ml
0.04 µg/ml
0.01 µg/ml
1/100
1/300
1/900
1/2700
1/8100
1/24300
1/72900
1/218700

FIG. 54A

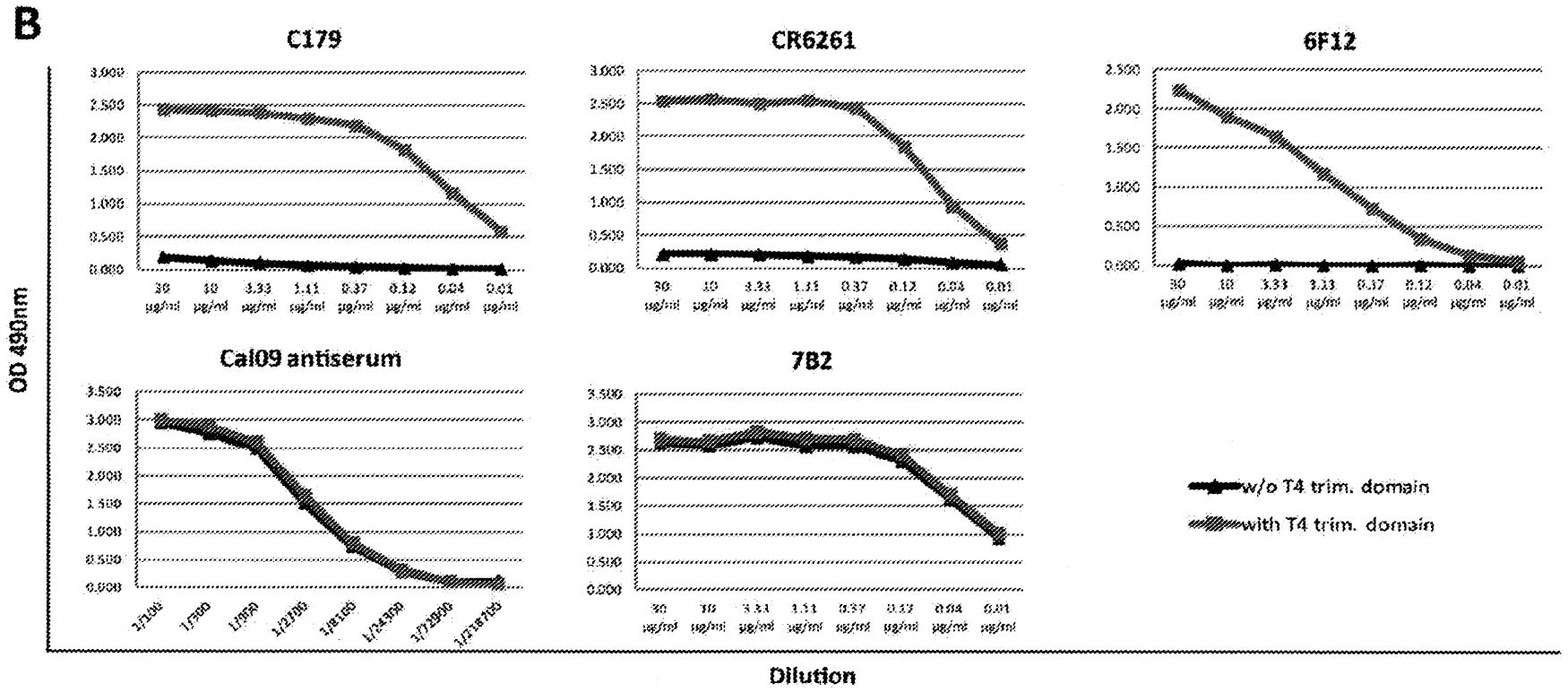

B
C179
CR6261
6F12
Cal09 antiserum
7B2
OD 490nm
Dilution
w/o T4 trim. domain
with T4 trim. domain

FIG. 54B

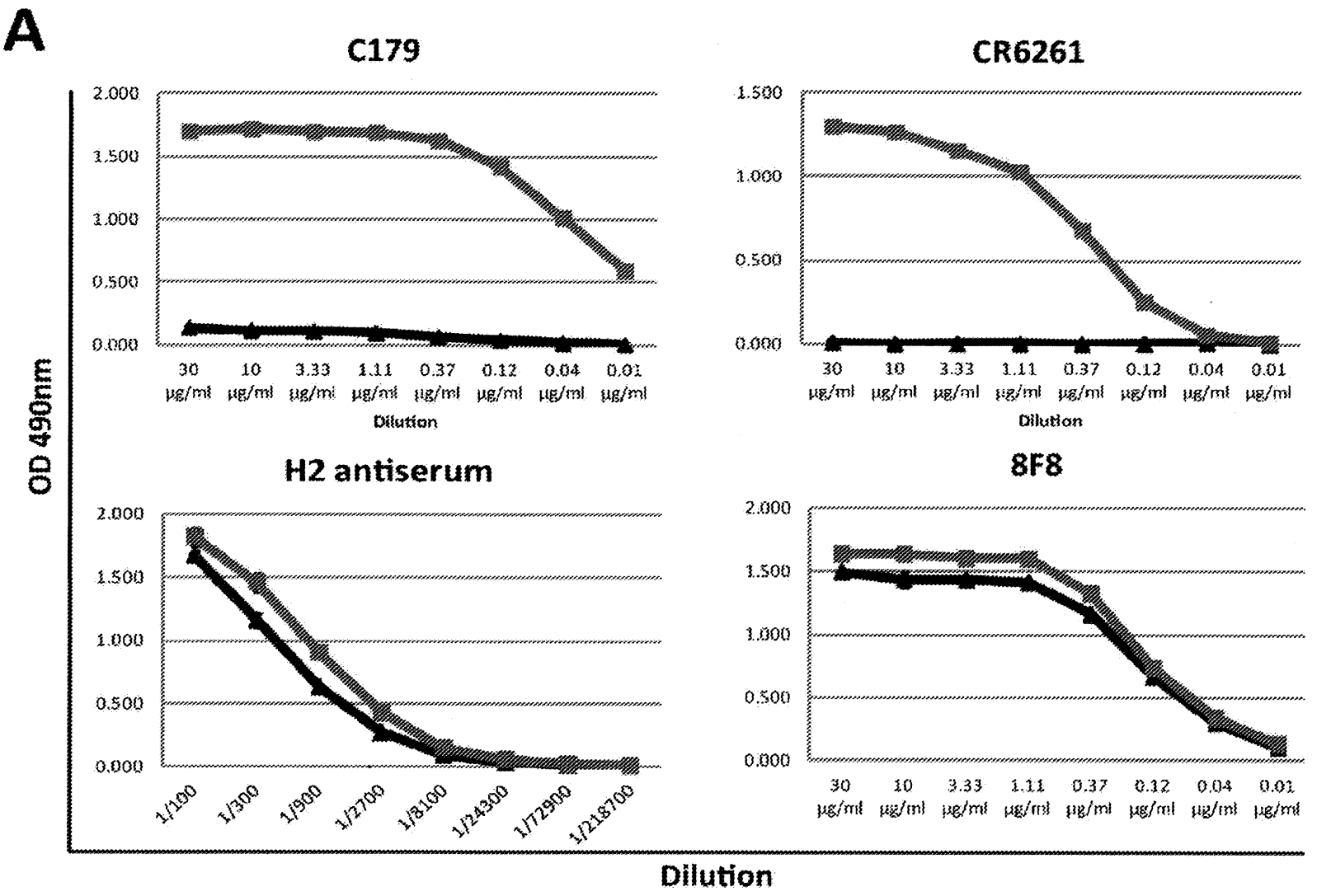

A
C179
CR6261
H2 antiserum
8F8
OD 490nm
2.000
1.500
1.000
0.500
0.000
30 µg/ml
10 µg/ml
3.33 µg/ml
1.11 µg/ml
0.37 µg/ml
0.12 µg/ml
0.04 µg/ml
0.01 µg/ml
Dilution
1/100
1/300
1/900
1/2700
1/8100
1/24300
1/72900
1/218700
Dilution

FIG. 55A

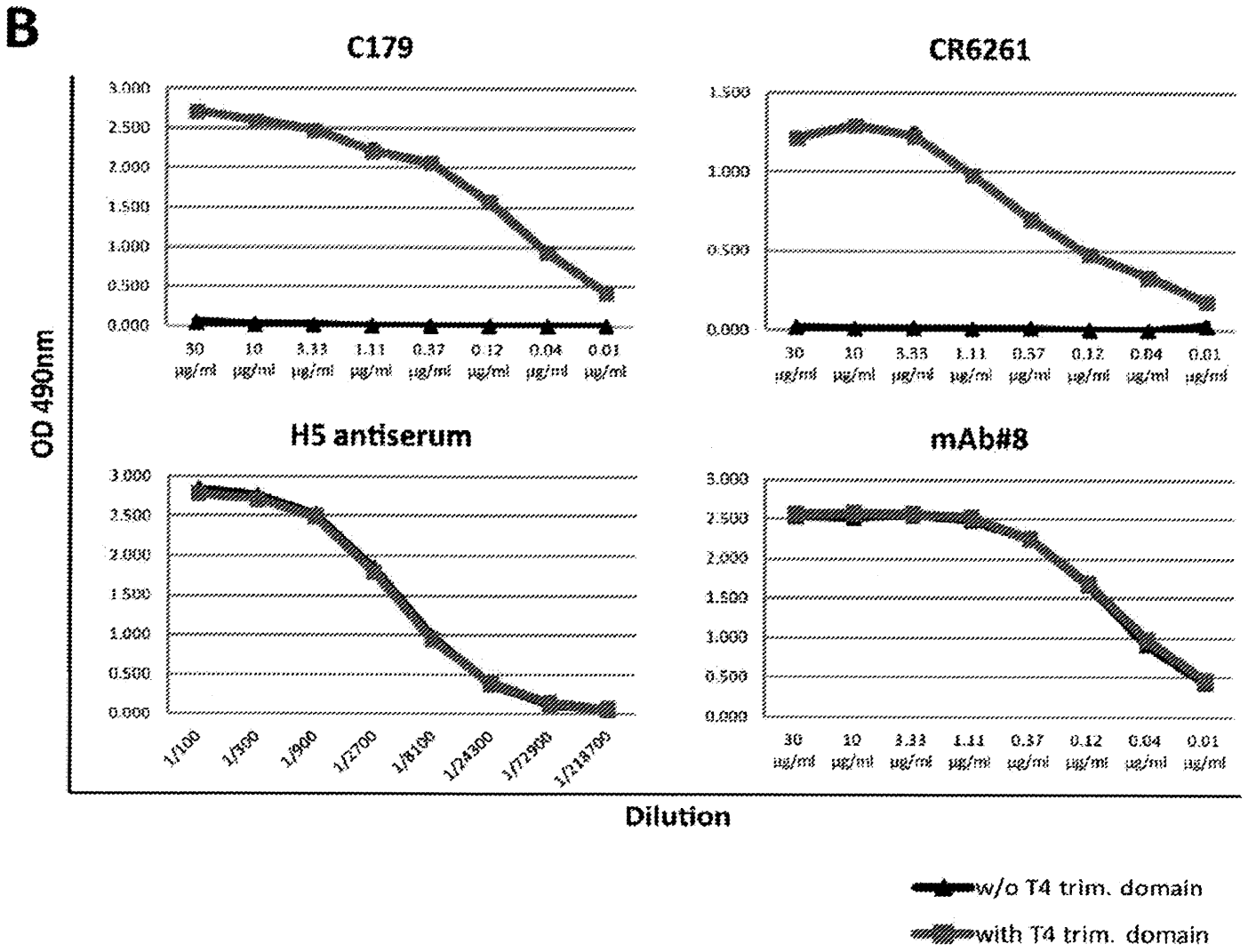

B
C179
CR6261
H5 antiserum
mAb#8
OD 490nm
Dilution
30 µg/ml
10 µg/ml
3.33 µg/ml
1.11 µg/ml
0.37 µg/ml
0.12 µg/ml
0.04 µg/ml
0.01 µg/ml
1/100
1/300
1/900
1/2700
1/8100
1/24300
1/72900
1/218700
w/o T4 trim. domain
with T4 trim. domain

FIG. 55B

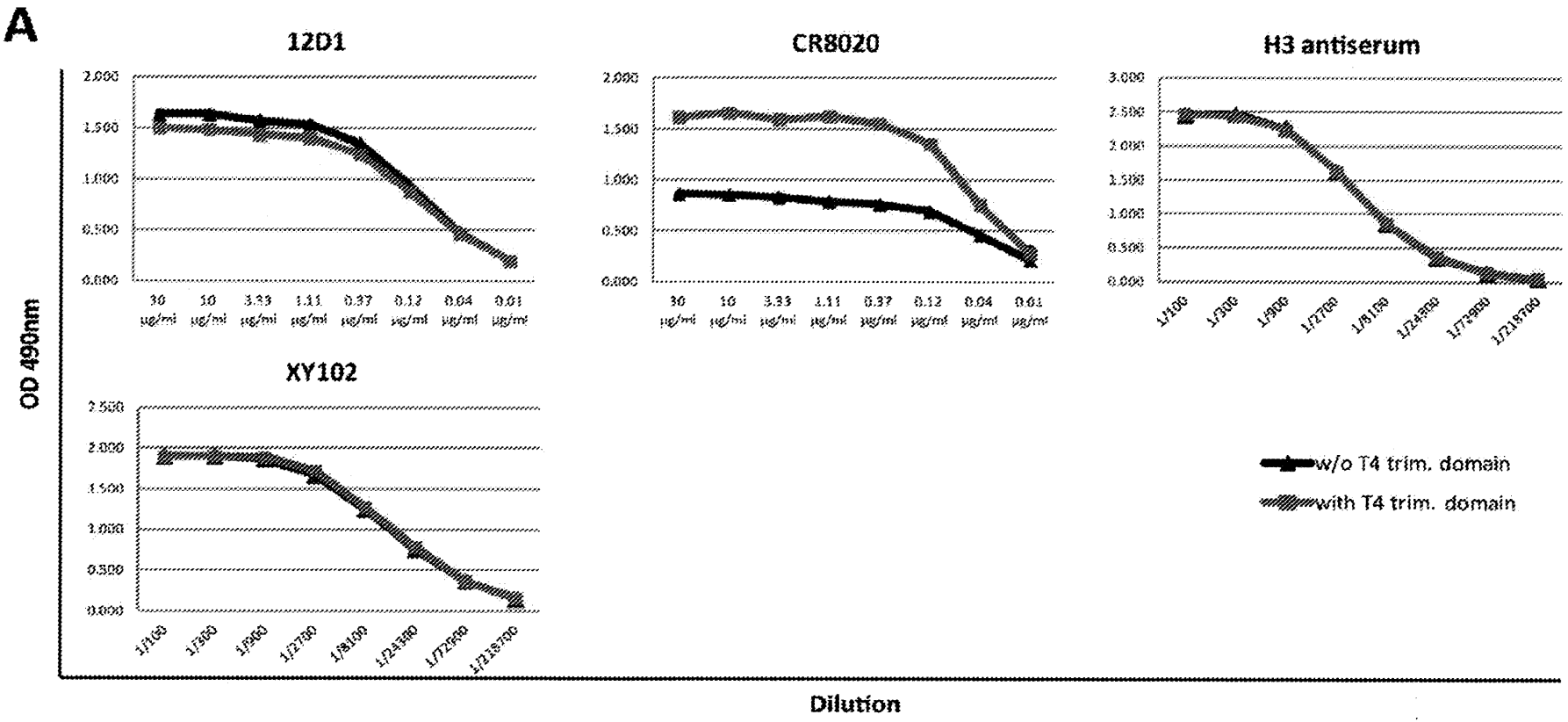

A
12D1
CR8020
H3 antiserum
XY102
OD 490nm
Dilution
w/o T4 trim. domain
with T4 trim. domain

FIG. 56A

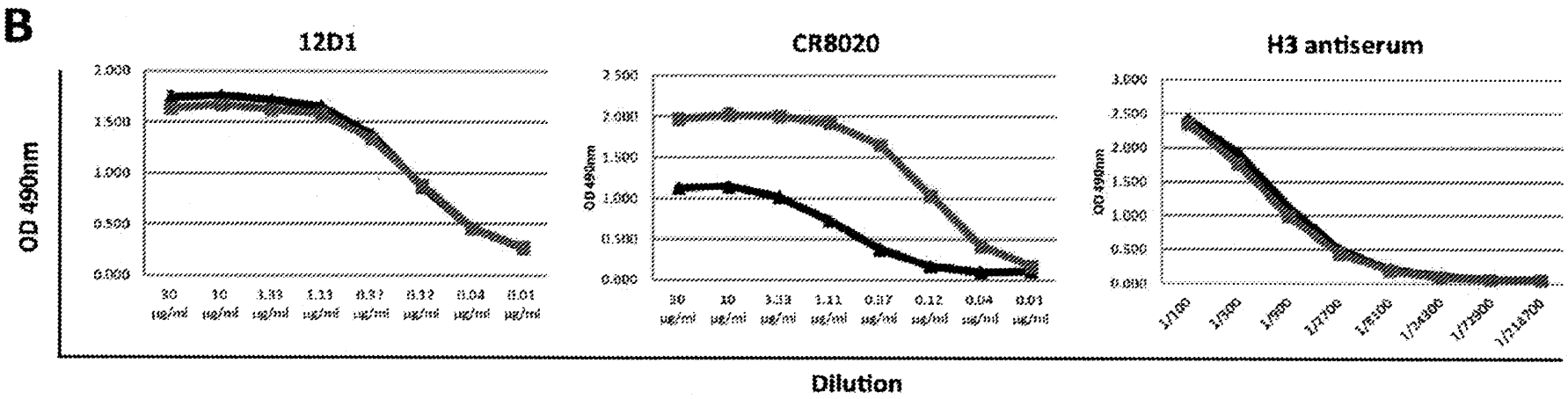


FIG. 56B