```
                                ▼(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
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```
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    NLLWLTEKE-------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 PLTTPTKSH  FANLKGTQTR
                                                  ▲(Arg50)

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

101   RTKIRQLPNL LRGYENIRLS ARNVTNAETA PGGPYTVGTS GSCPNVTNGN
                                                  ▲(Cys143)

151   GEFATMAWAV 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

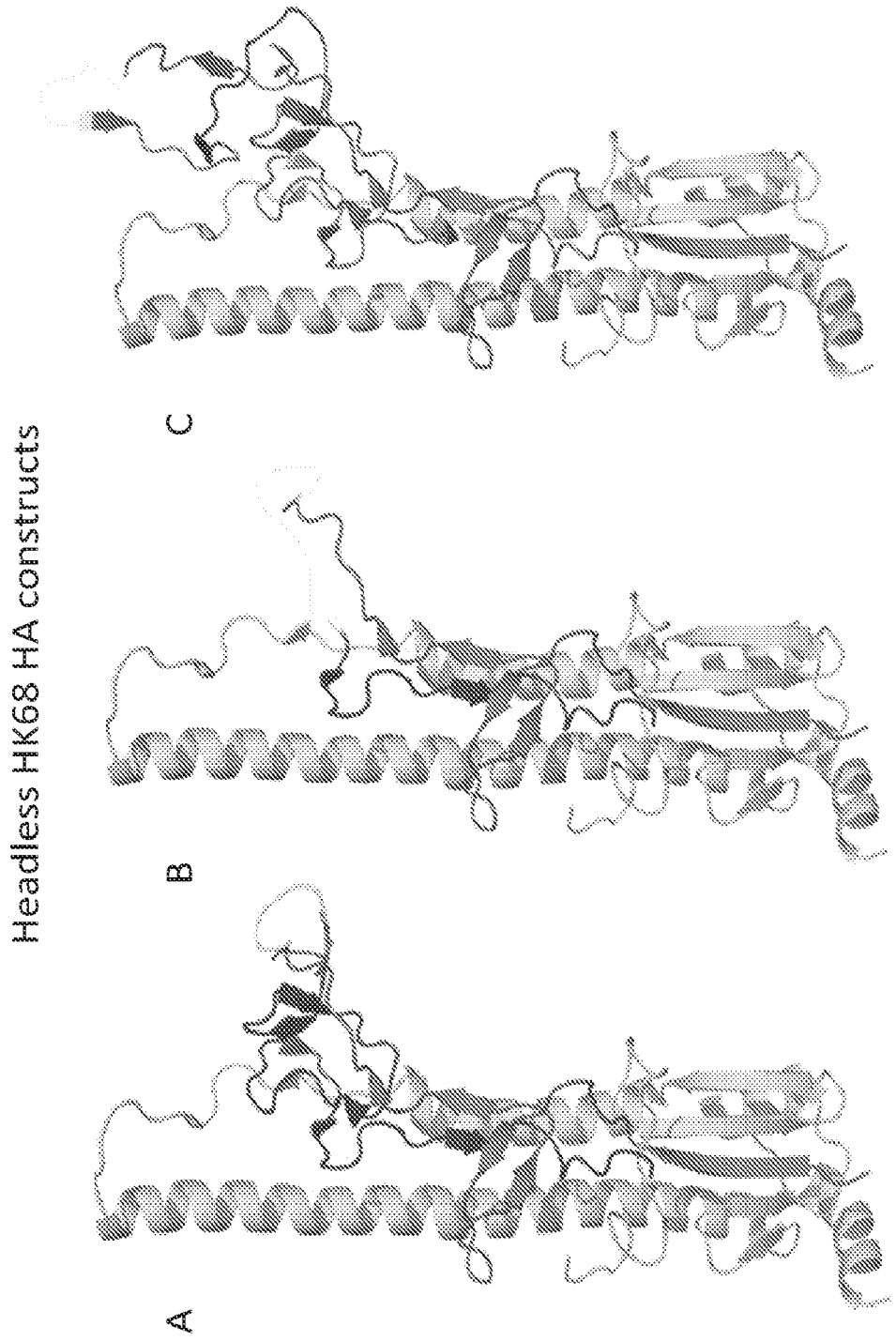


FIG. 4

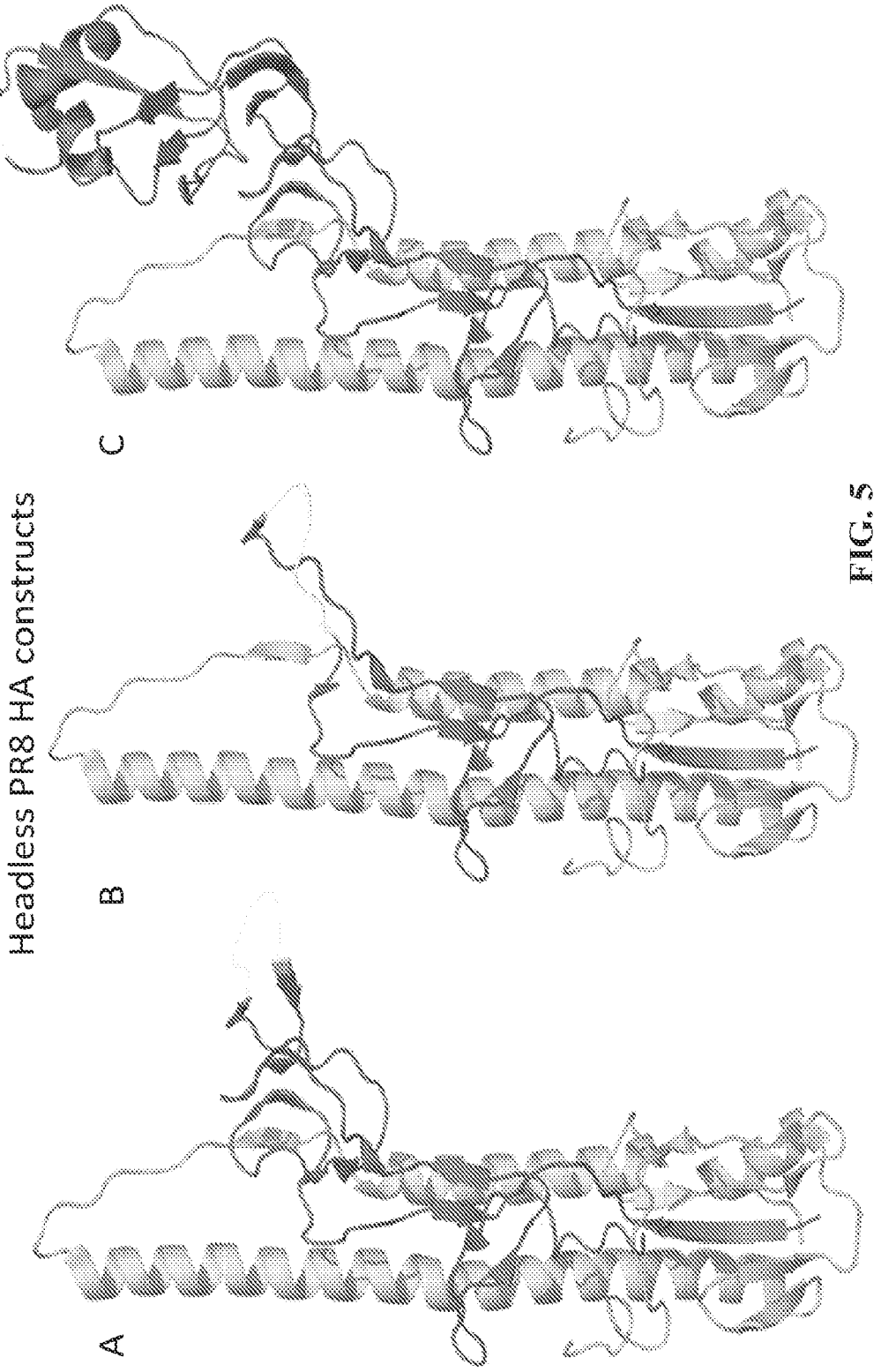


FIG. 5

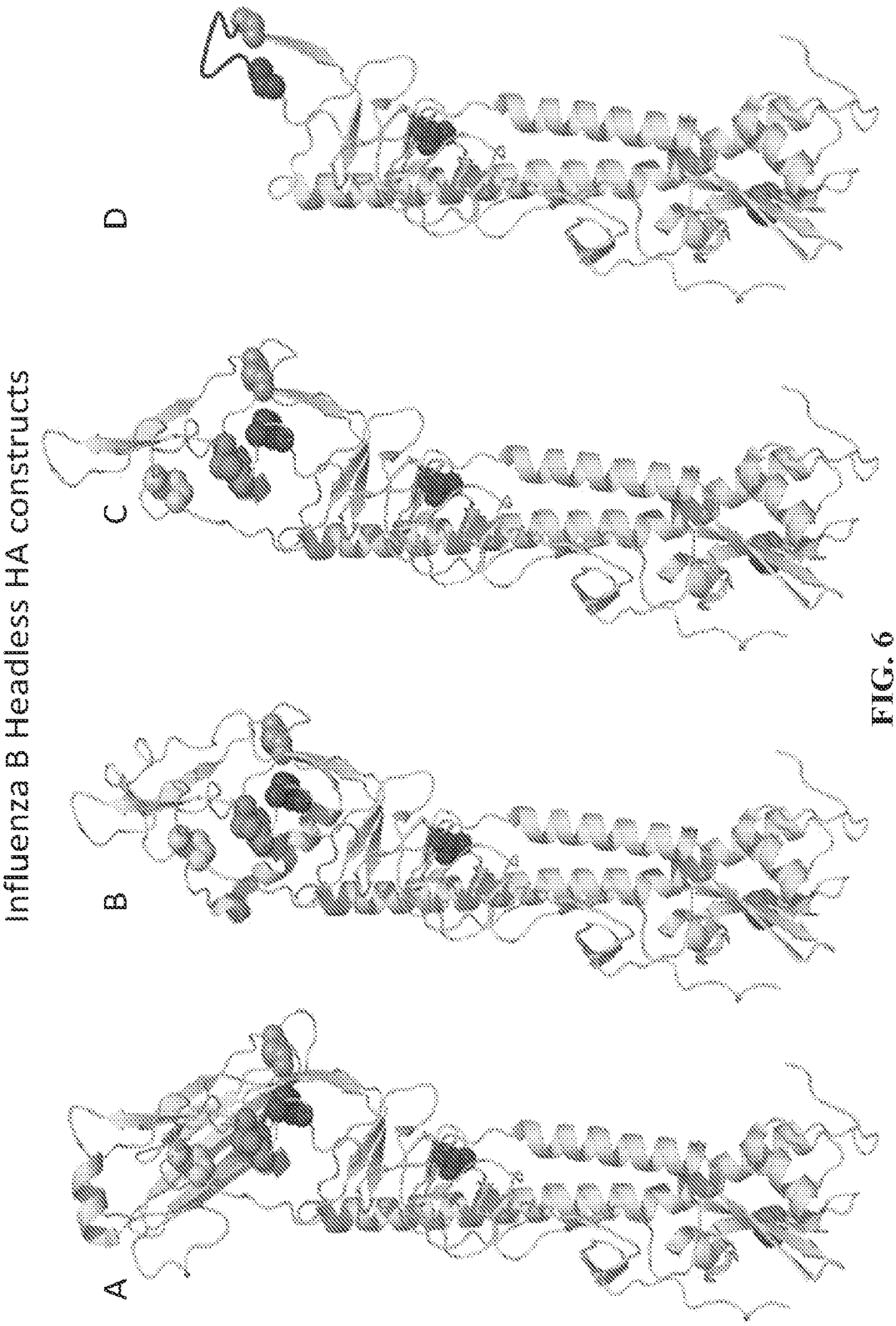


FIG. 6

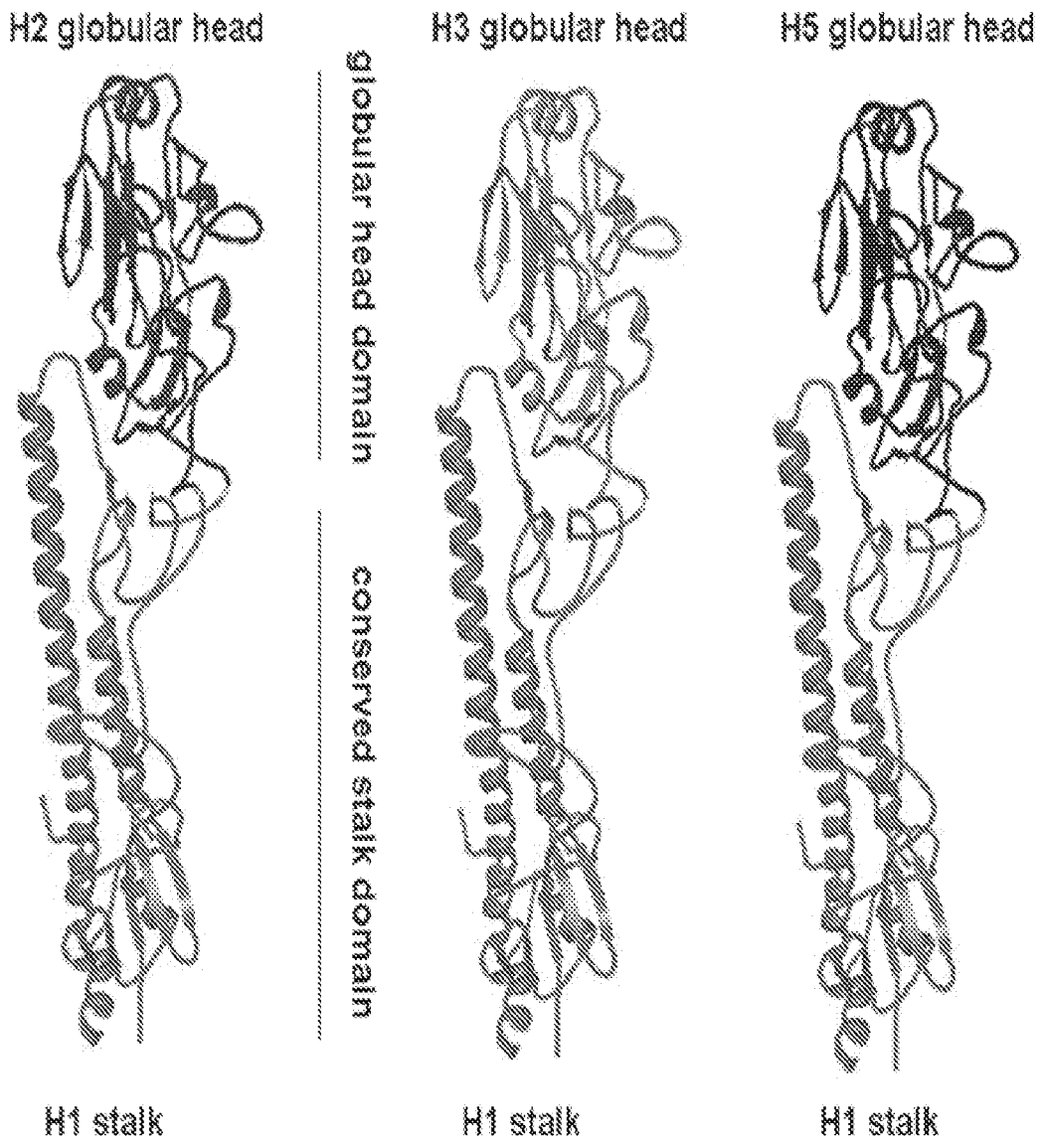

H2 globular head
H3 globular head
H5 globular head
globular head domain
conserved stalk domain
H1 stalk
H1 stalk
H1 stalk

FIG. 7

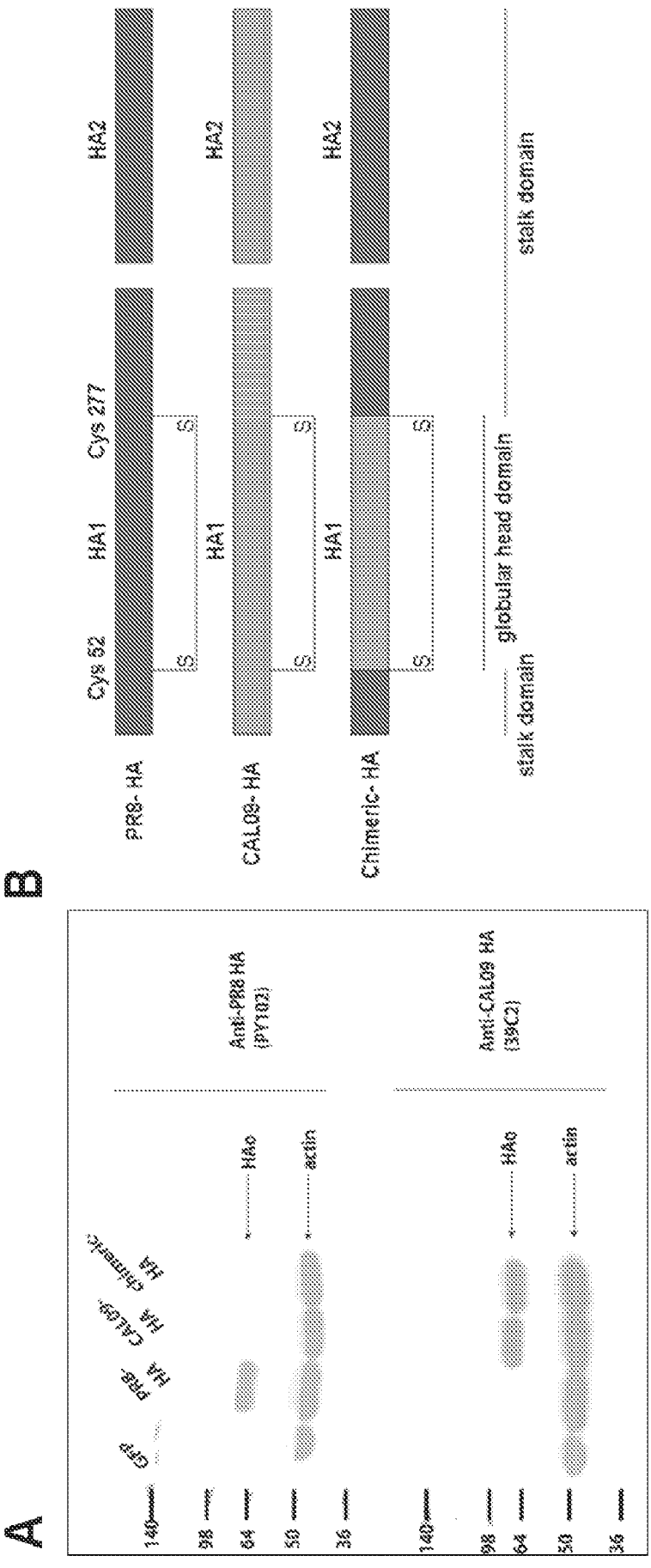

A
GFP
PR8-HA
CAL09-HA
Chimeric-HA
140
98
64
50
36
Anti-PR8 HA (PY102)
HAo
actin
Anti-CAL09 HA (39C2)
B
Cys 52
HA1
Cys 277
HA2
S
PR8- HA
CAL09- HA
Chimeric- HA
stalk domain
globular head domain

Fig. 8

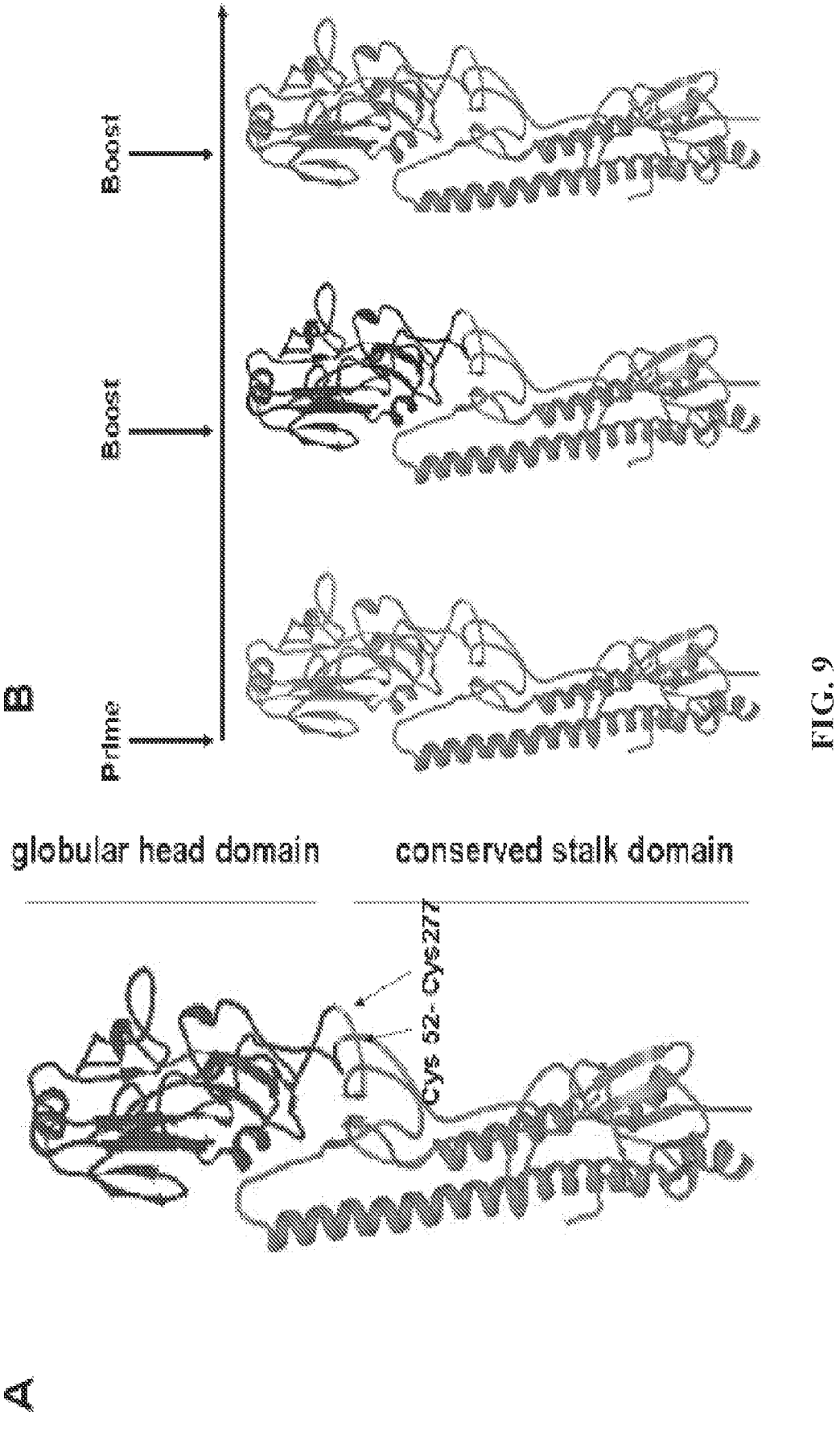

B
Prime
Boost
Boost
globular head domain
conserved stalk domain
Cys 52- Cys277
A

FIG. 9

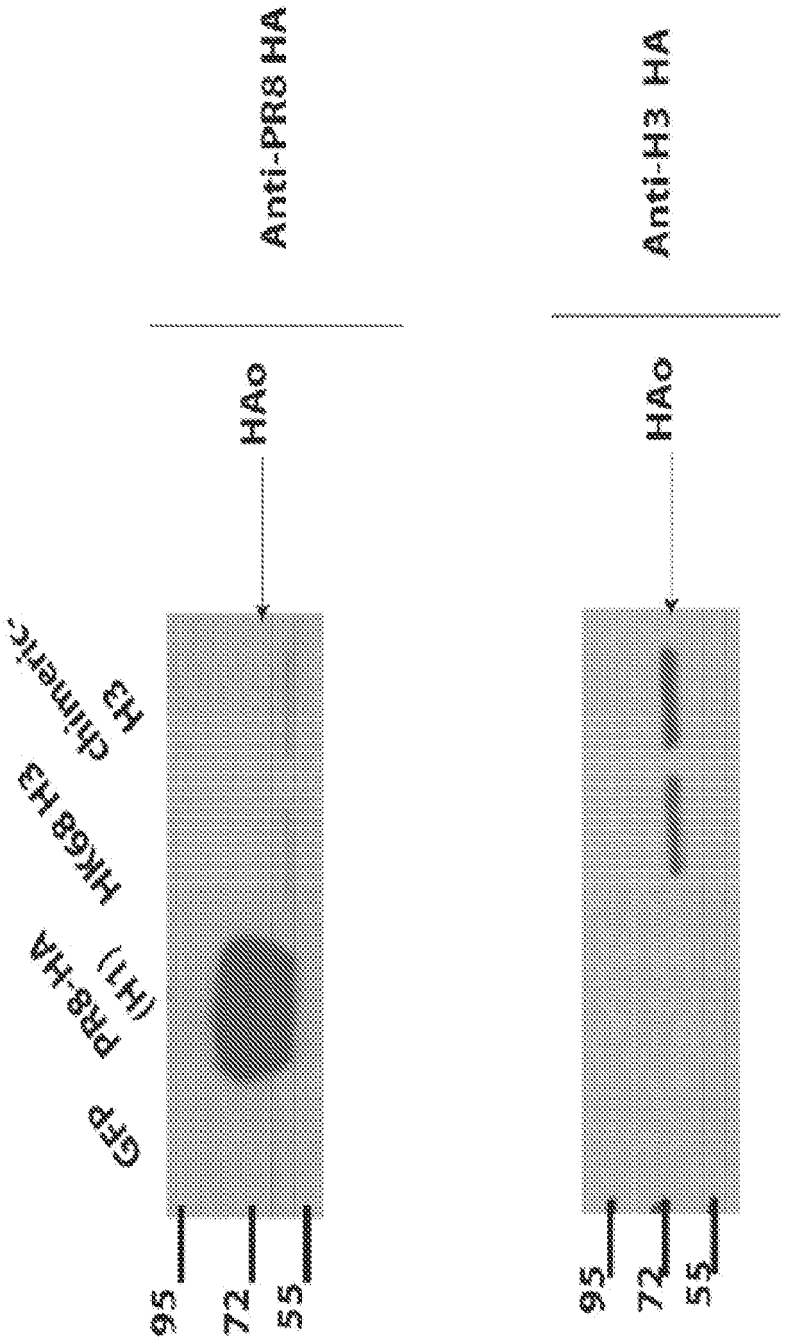

Anti-PR8 HA
Anti-H3 HA
HAo
HAo
95
72
55
95
72
55
GFP
PR8-HA (H1)
HK68 H3
chimeric H3

FIG. 10

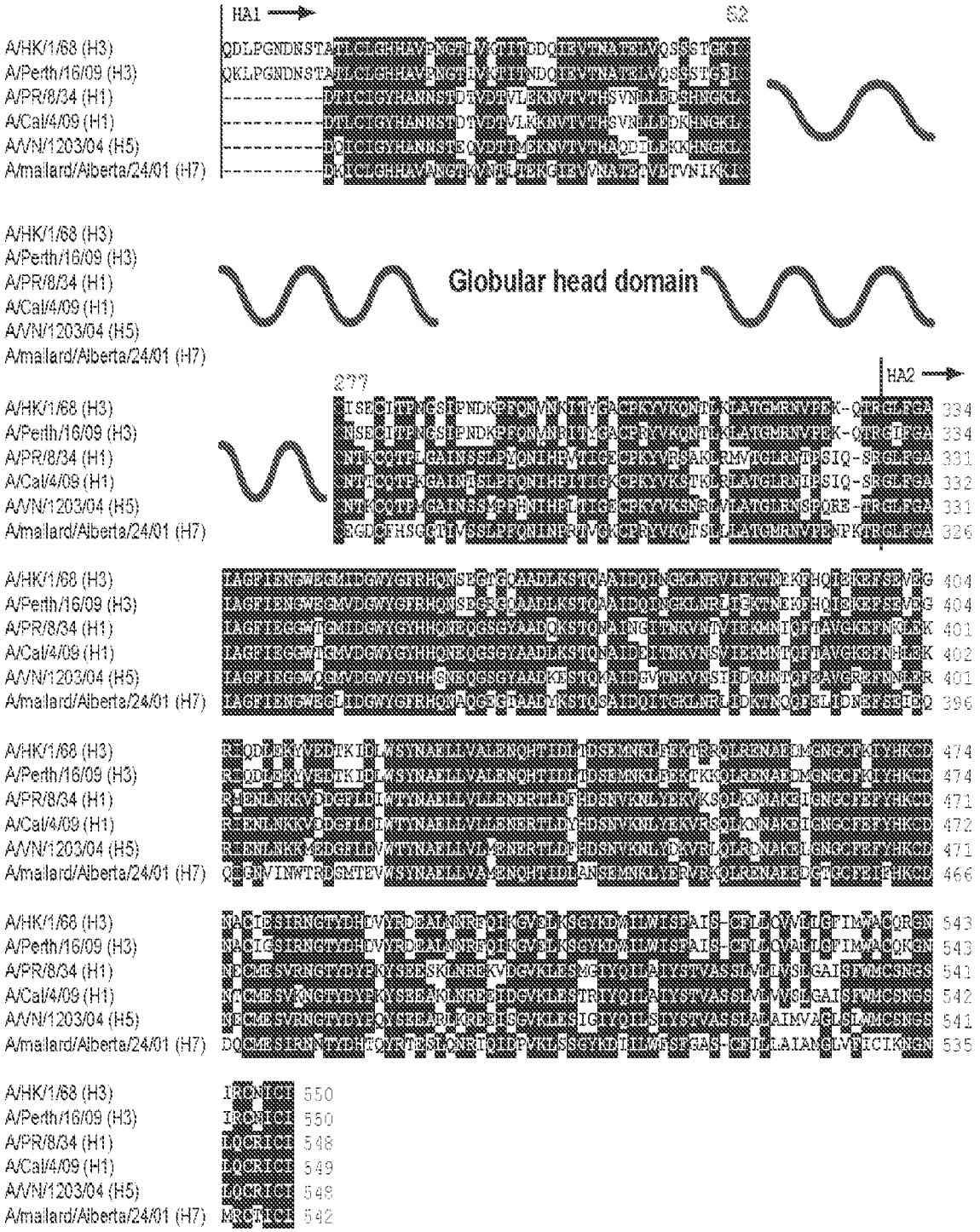

HA1
52
A/HK/1/68 (H3)
A/Perth/16/09 (H3)
A/PR/8/34 (H1)
A/Cal/4/09 (H1)
A/VN/1203/04 (H5)
A/mallard/Alberta/24/01 (H7)
Globular head domain
277
HA2
334
334
331
332
331
326
404
404
401
402
401
396
474
474
471
472
471
466
543
543
541
542
541
535
550
550
548
549
548
542

FIG. 11

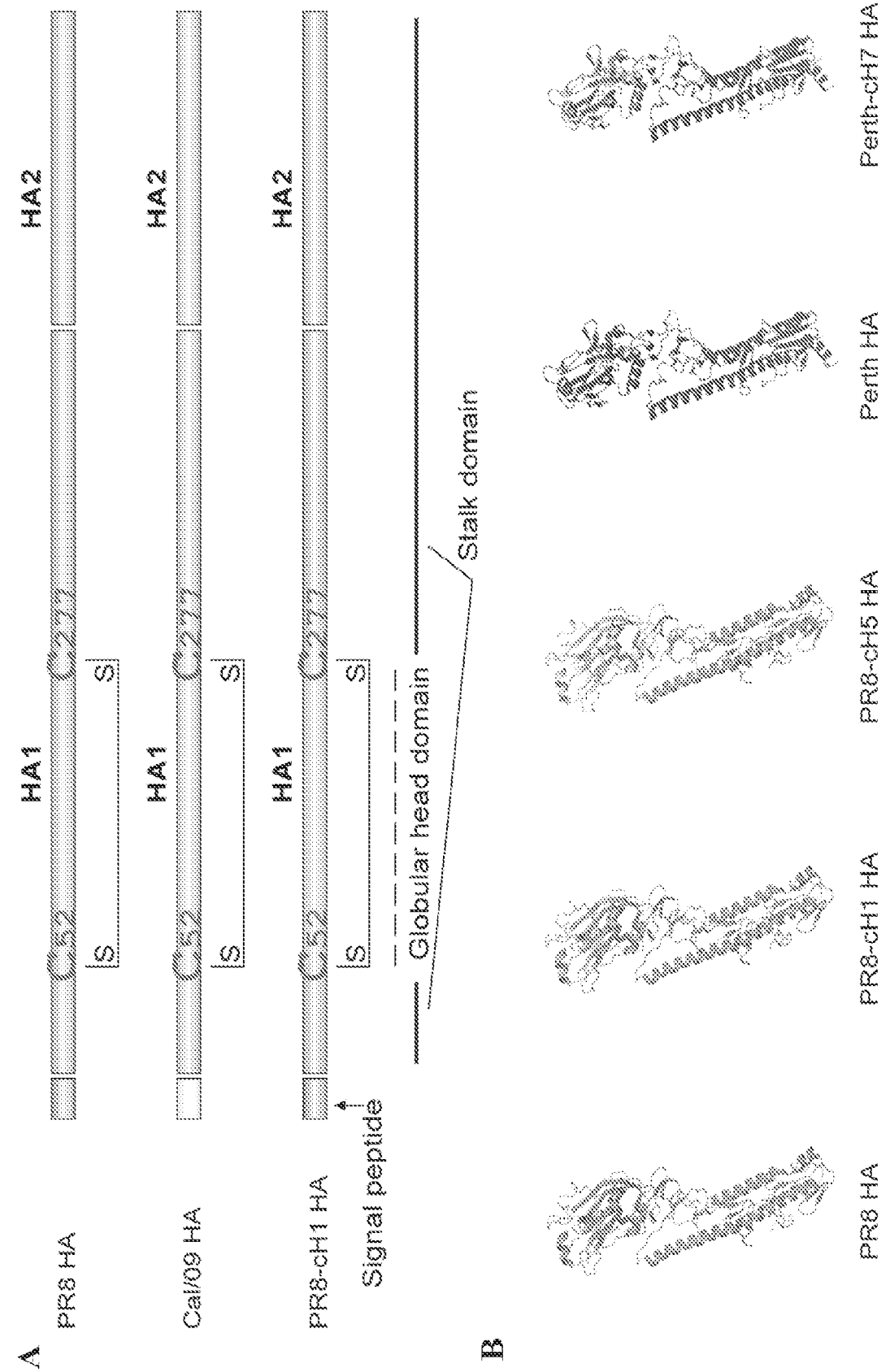

A
HA1
HA2
PR8 HA
Cal/09 HA
PR8-cH1 HA
Signal peptide
Globular head domain
Stalk domain
B
PR8 HA
PR8-cH1 HA
PR8-cH5 HA
Perth HA
Perth-cH7 HA

FIG. 12A - 12B

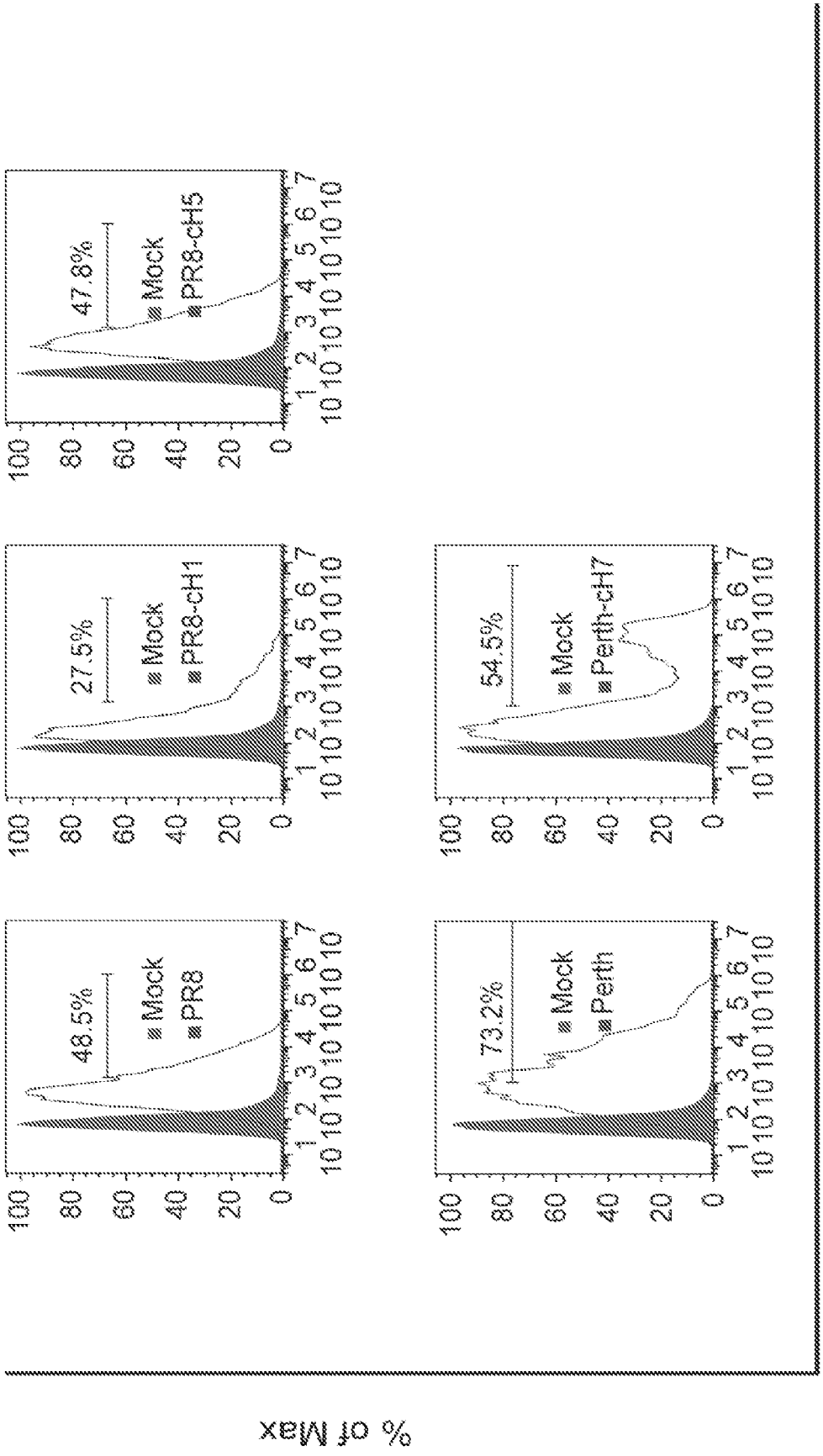

% of Max
Hemagglutinin
48.5%
Mock
PR8
27.5%
Mock
PR8-cH1
47.8%
Mock
PR8-cH5
73.2%
Mock
Perth
54.5%
Mock
Perth-cH7

FIG. 13A

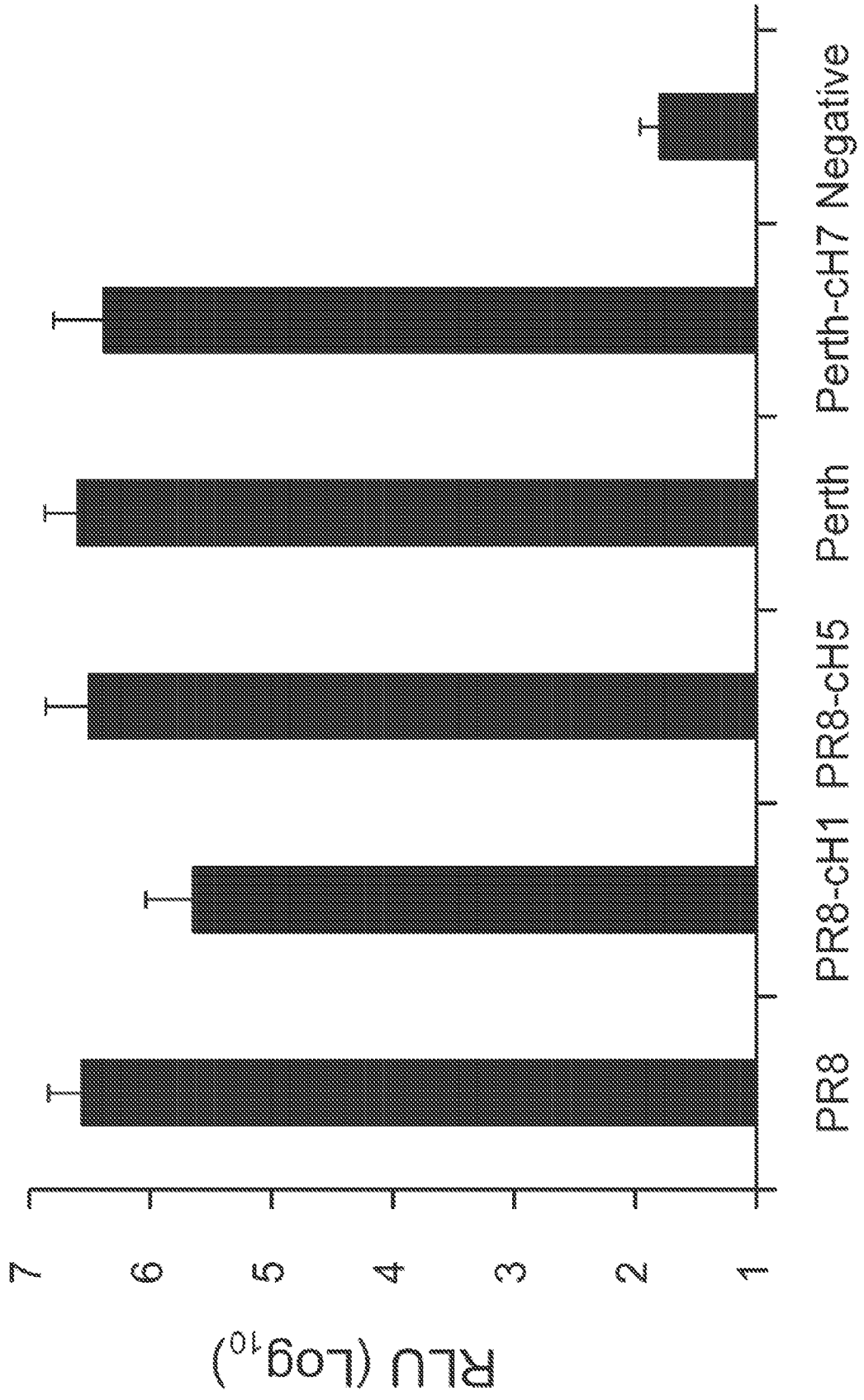

RLU (Log10)
7
6
5
4
3
2
1
PR8
PR8-cH1
PR8-cH5
Perth
Perth-cH7
Negative

FIG. 13B

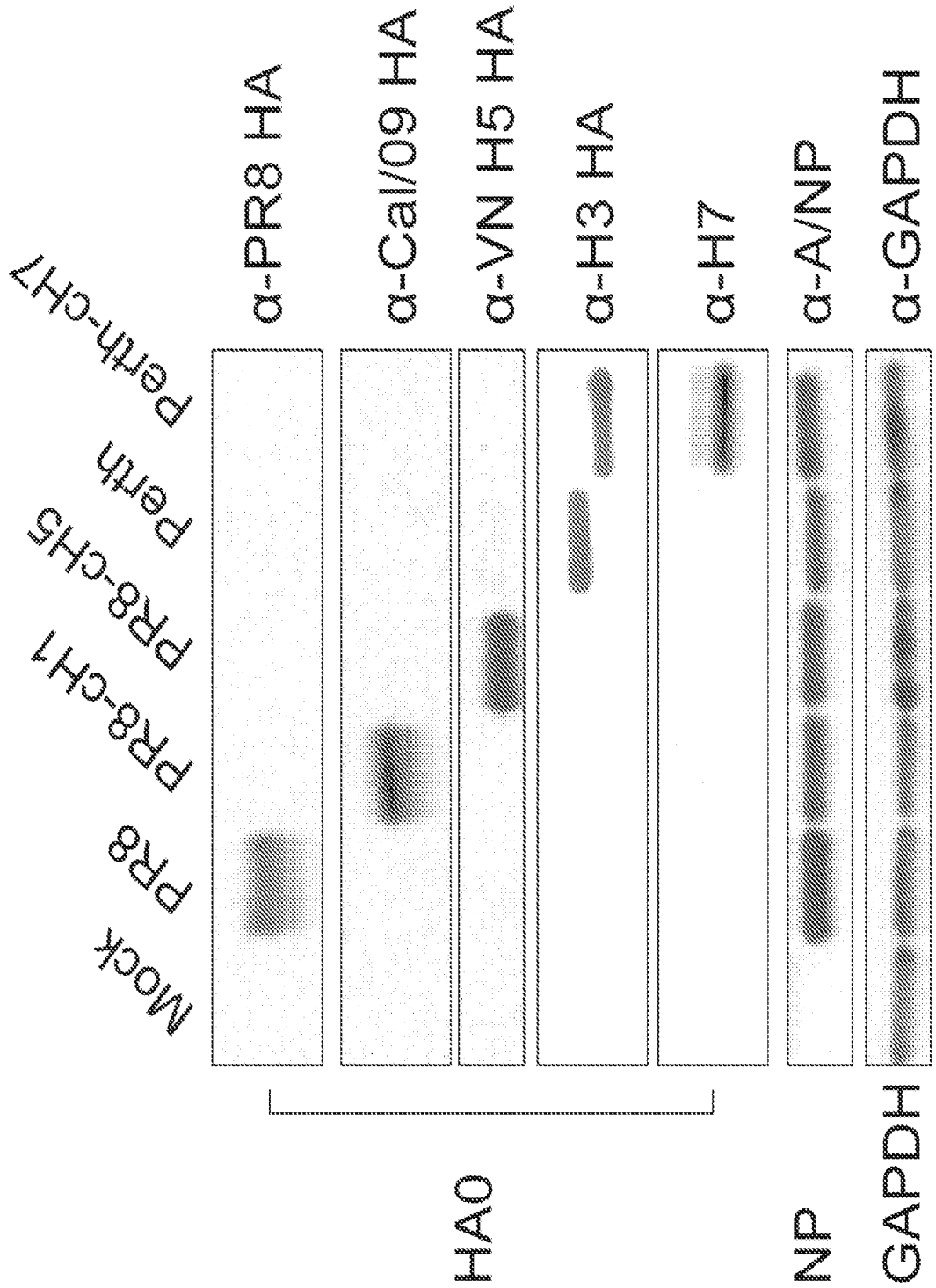

Mock
PR8
PR8-cH1
PR8-cH5
Perth
Perth-cH7
α-PR8 HA
α-Cal/09 HA
α-VN H5 HA
α-H3 HA
α-H7
α-A/NP
α-GAPDH
HA0
NP
GAPDH

FIG. 14A

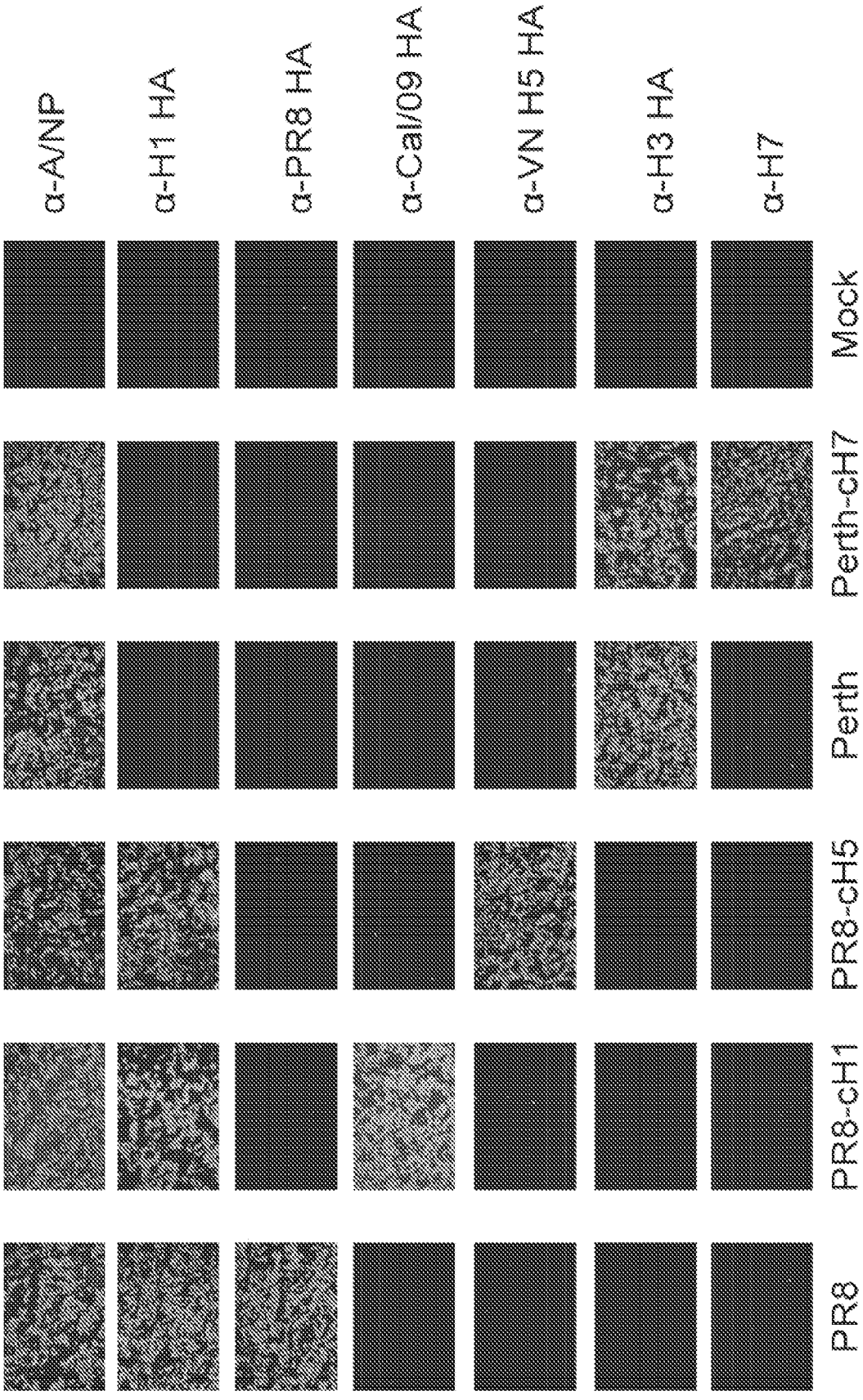

α-A/NP
α-H1 HA
α-PR8 HA
α-Cal/09 HA
α-VN H5 HA
α-H3 HA
α-H7
Mock
Perth-cH7
Perth
PR8-cH5
PR8-cH1
PR8

FIG. 14B

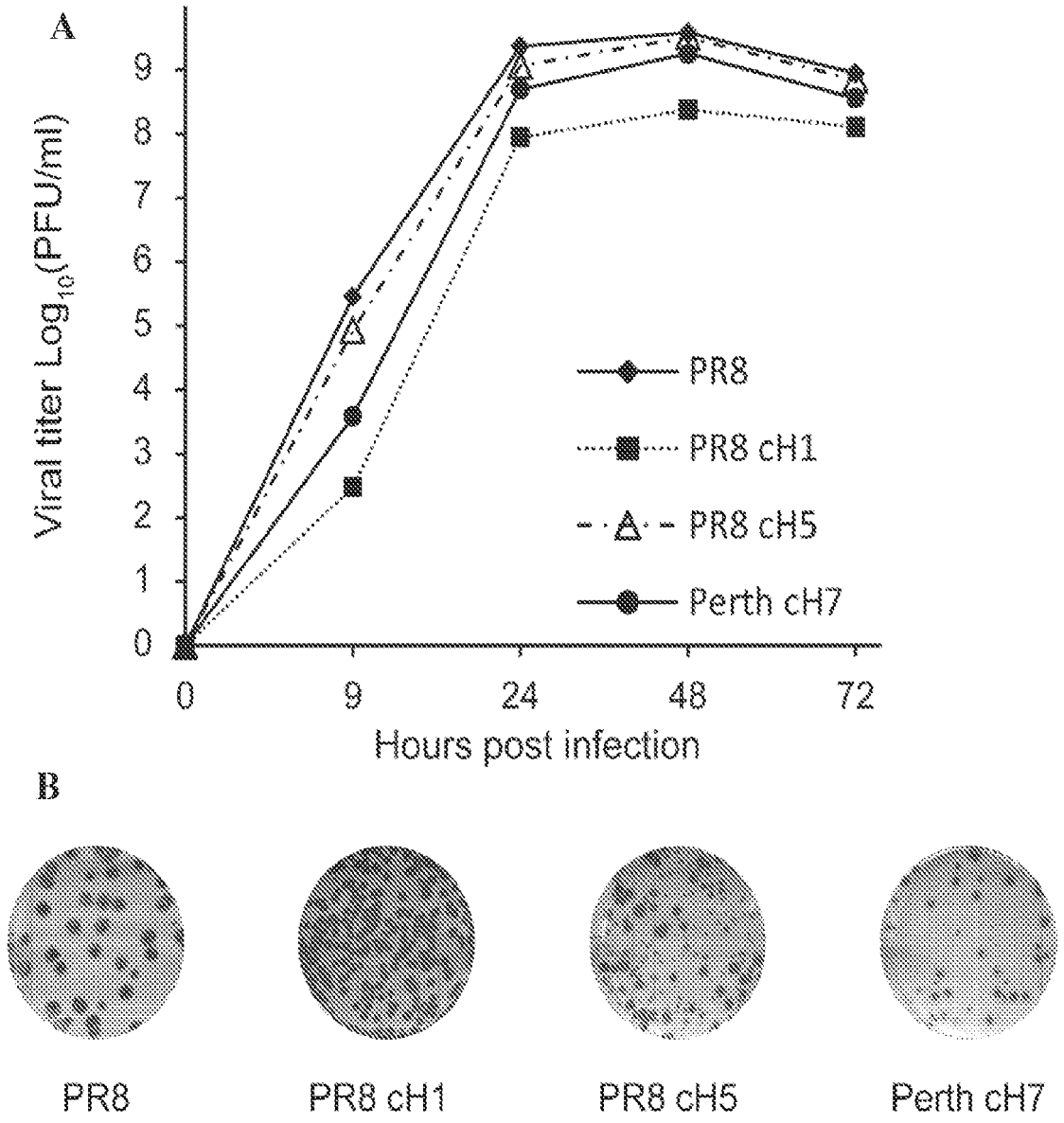

A
Viral titer Log10(PFU/ml)
0
1
2
3
4
5
6
7
8
9
0
9
24
48
72
Hours post infection
PR8
PR8 cH1
PR8 cH5
Perth cH7
B
PR8
PR8 cH1
PR8 cH5
Perth cH7

FIG. 15 A - 15B

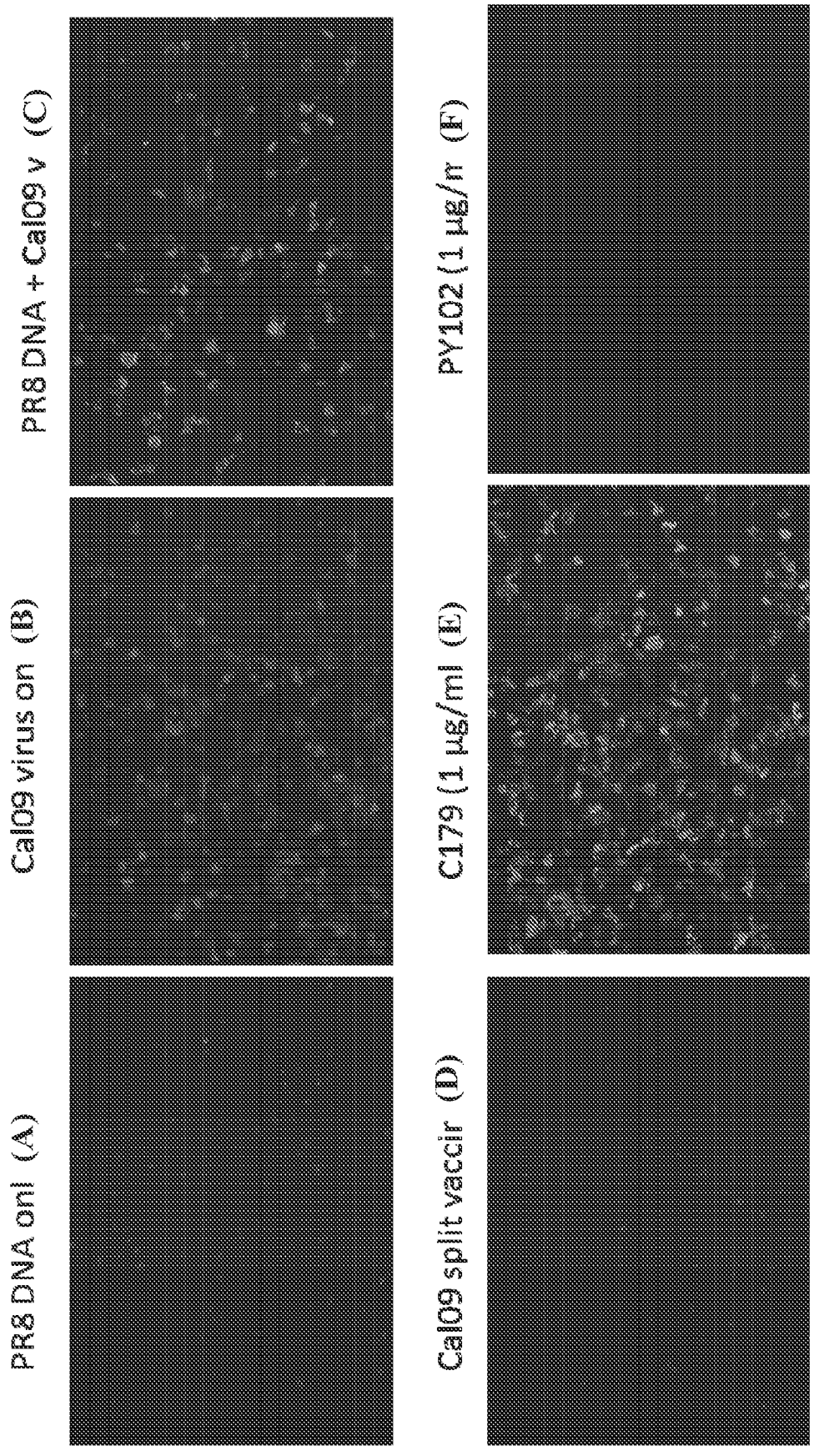

PR8 DNA onl (A)
Cal09 virus on (B)
PR8 DNA + Cal09 v (C)
Cal09 split vaccir (D)
C179 (1 µg/ml (E)
PY102 (1 µg/m (F)

FIG. 16A - 16F

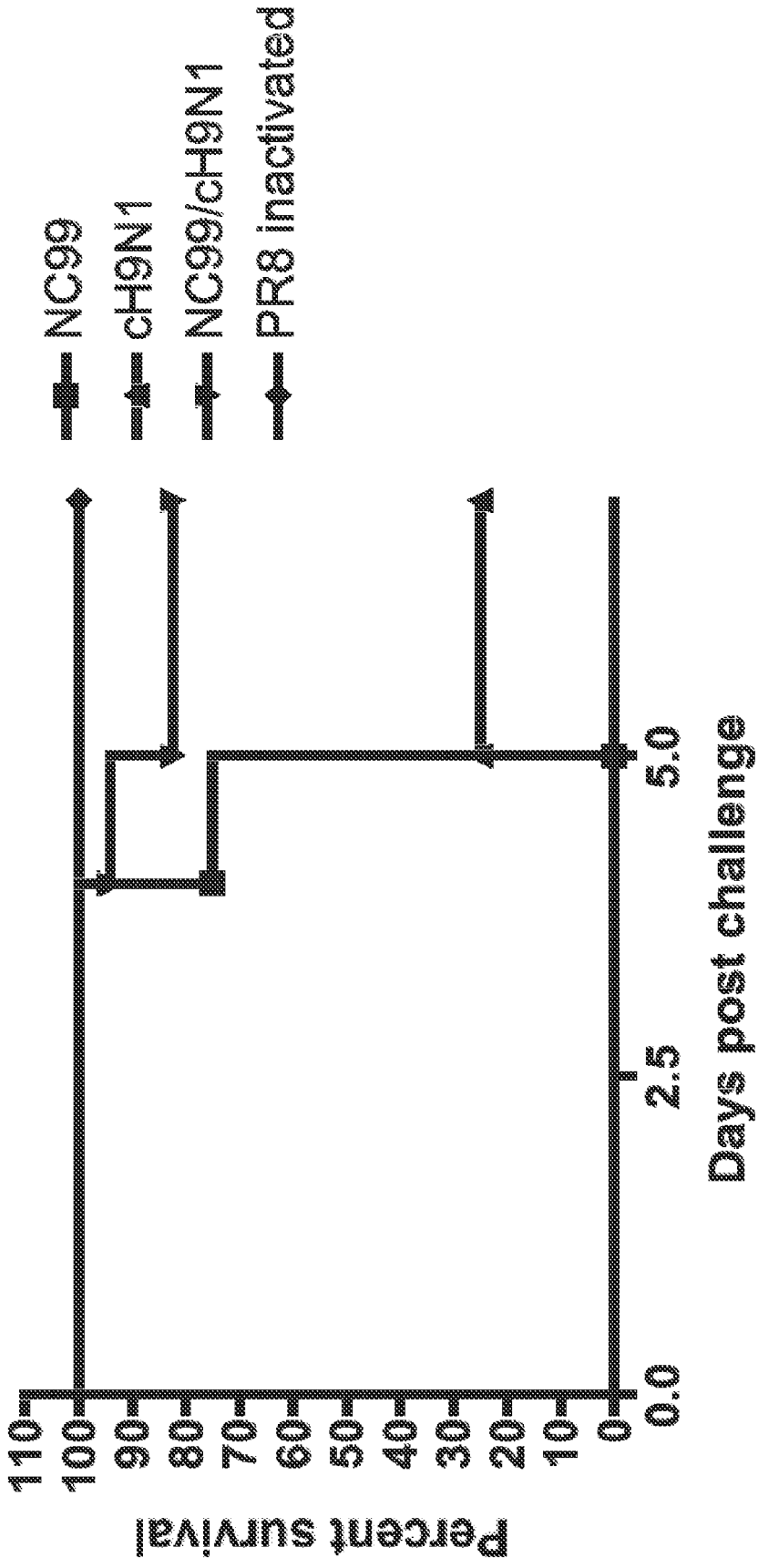

NC99
cH9N1
NC99/cH9N1
PR8 inactivated
Percent survival
110
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
Days post challenge

FIG. 17

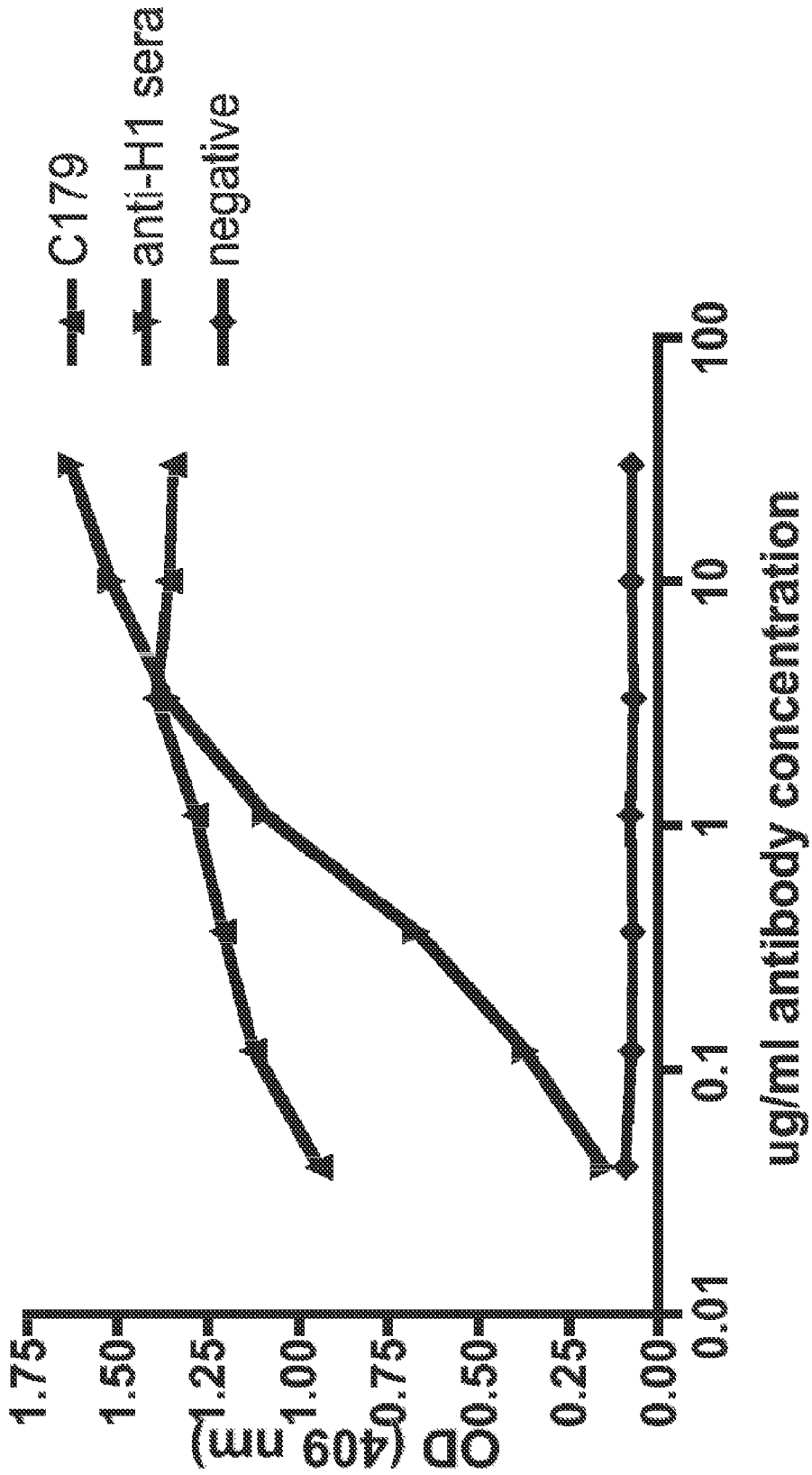

C179
anti-H1 sera
negative
OD (409 nm)
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0.01
0.1
1
10
100
ug/ml antibody concentration

FIG. 18

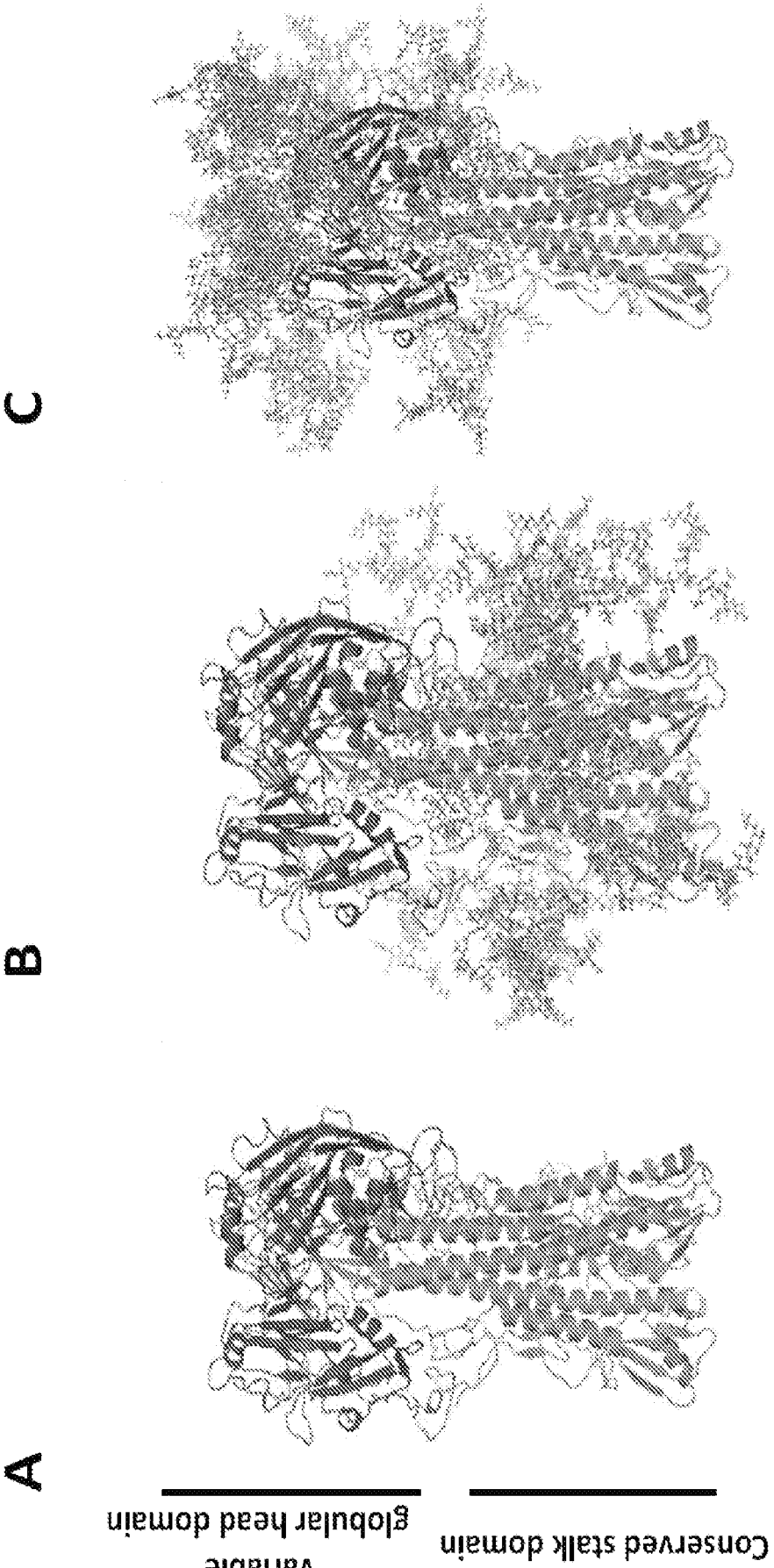


Fig. 19

Fig. 20

A
Sb
Sa
Cb
Ca2
B
Cb
Sa
Residue #
wt PR8
Mutant
78
128
156
-LLPVRS-
-PN-
-EKEGS-PKLKNS-
- - - N - - -
- - N . S -
- - - N . . - - - - N . . -
Ca1
Residue #
wt PR8
Mutant
160
206
238
-VNKKG-
-TSN-
-KPG-
- - N . S . -
- - - N . S -
- - - -
Ca2
Sb
Residue #
wt PR8
Mutant
140
224
187
-SHEGKS-
-RD-
-NSKDQQNIYQNE-
- - - N . . -
- - -
-N.T - - - N.S.N.T-

Fig. 21

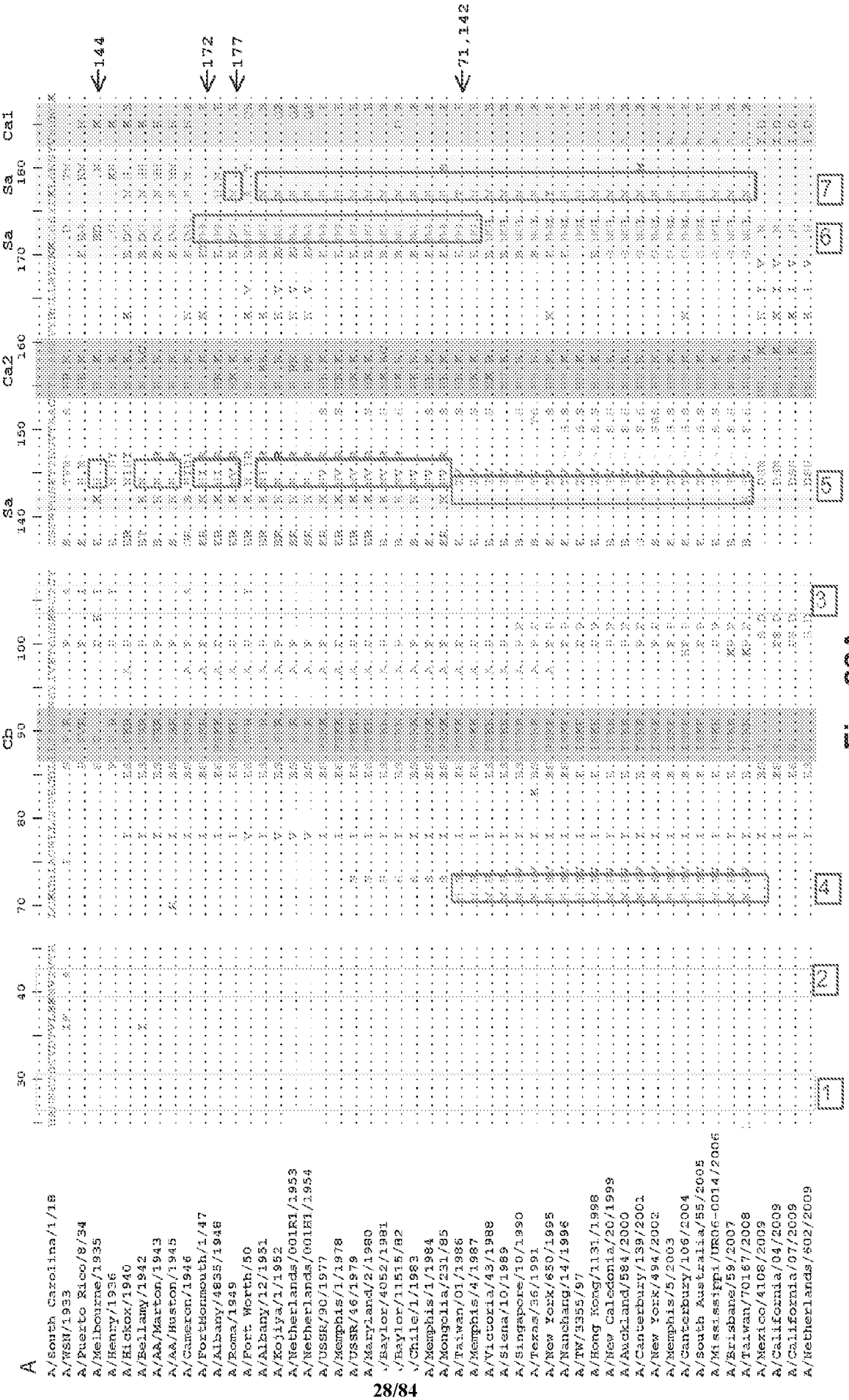


Fig. 22A

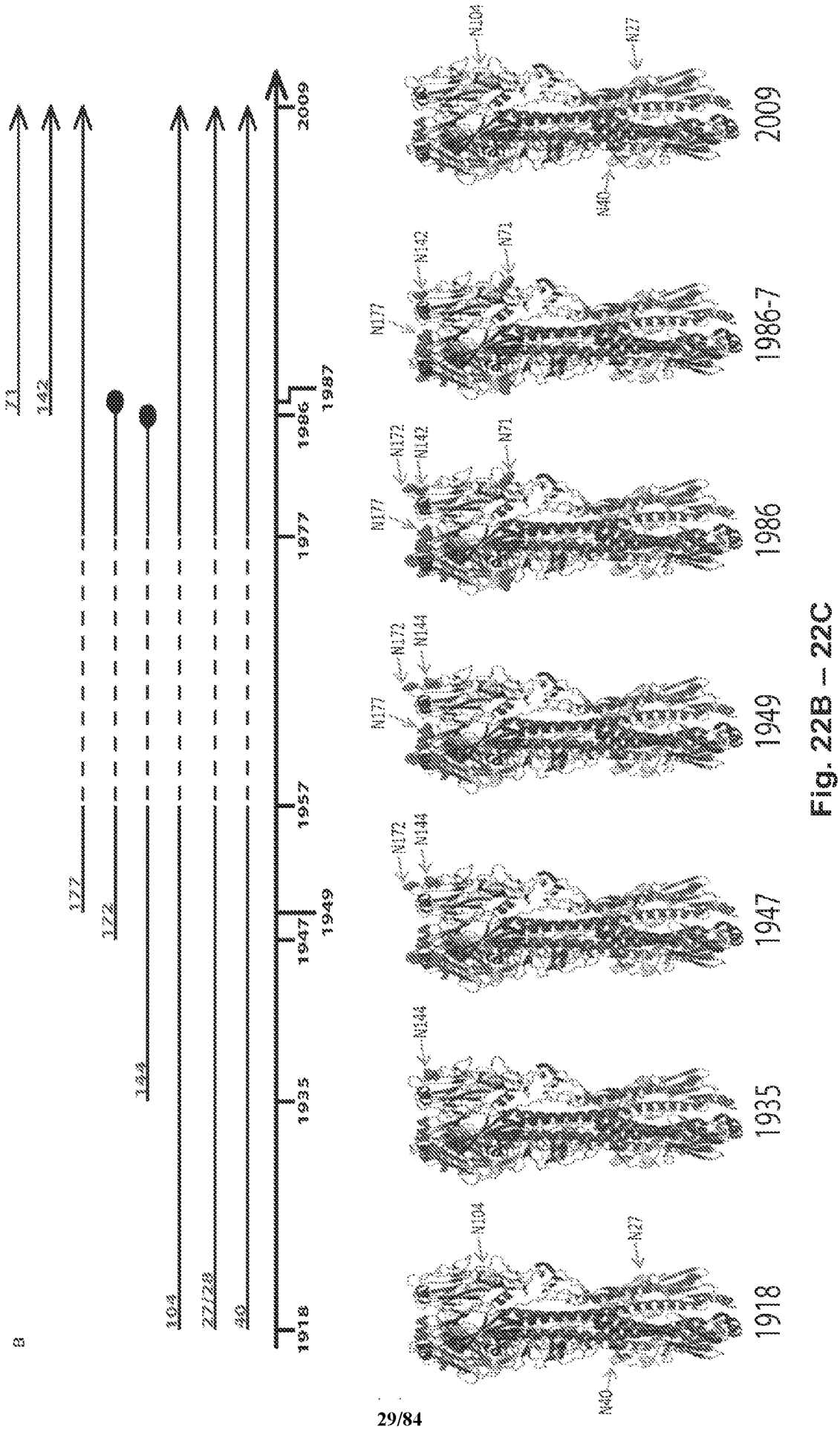

Z1
142
177
172
144
104
27/28
40
1918
1935
1947
1949
1957
1977
1986
1987
2009
N104
N27
N40
N144
N172
N177
N142
N71
1918
1935
1947
1949
1986
1986-7
2009

Fig. 22B – 22C

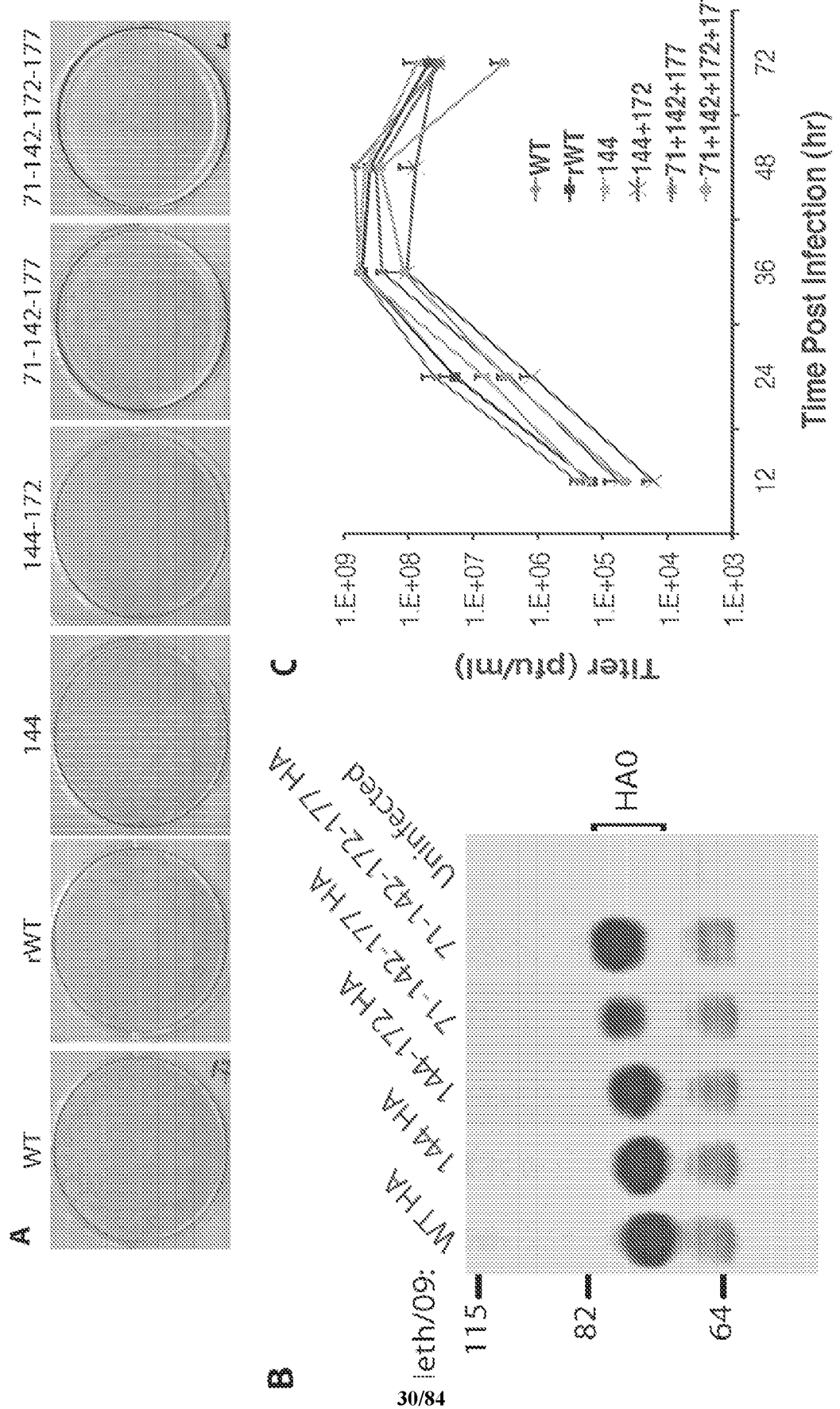

A
WT
rWT
144
144-172
71-142-177
71-142-172-177
B
eth/09:
WT HA
144HA
144-172 HA
71-142-177HA
71-142-172-177HA
Uninfected
115
82
64
HA0
C
Titer (pfu/ml)
1.E+09
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
12
24
36
48
72
Time Post Infection (hr)
WT
rWT
144
144+172
71+142+177
71+142+172+177

Fig. 23

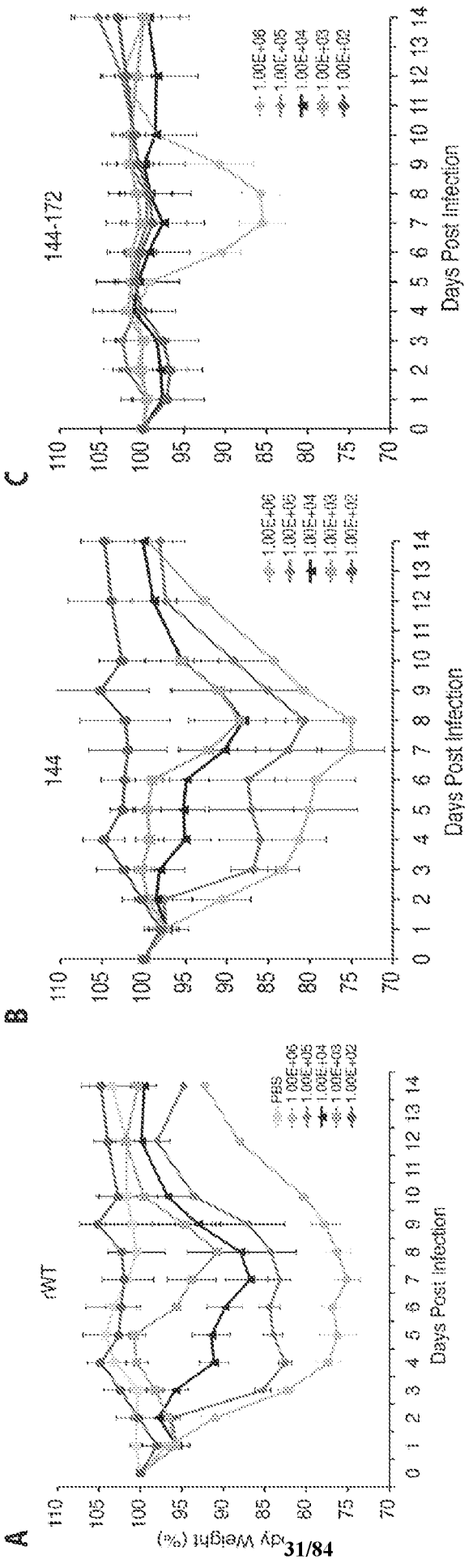

A
rWT
B
144
C
144-172
% Body Weight (%)
Days Post Infection
PBS
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02

Fig. 24A – 24C

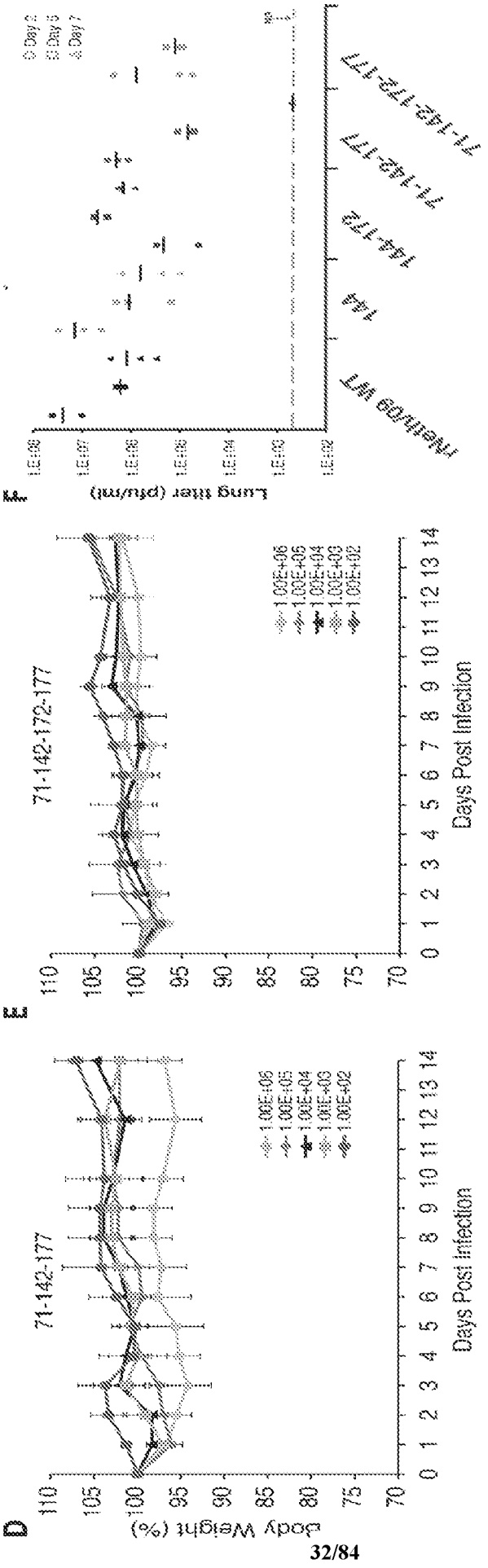

D
Body Weight (%)
71-142-177
Days Post Infection
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
E
71-142-172-177
Days Post Infection
F
Lung titer (pfu/ml)
Day 2
Day 5
Day 7
Infected WT
142
142-172
71-142-177
71-142-172-177

Fig. 24D – 24F

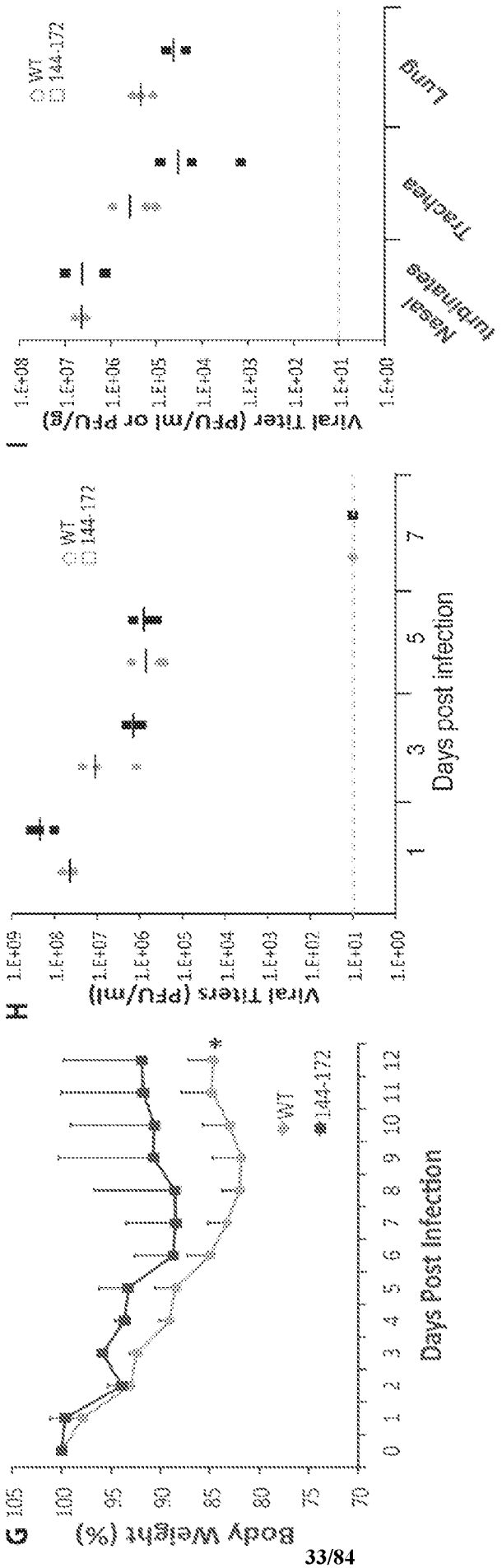

G
Body Weight (%)
105
100
95
90
85
80
75
70
0 1 2 3 4 5 6 7 8 9 10 11 12
Days Post Infection
WT
144-172
*
H
Viral Titers (PFU/ml)
1.E+09
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
1
3
5
7
Days post infection
WT
144-172
I
Viral Titer (PFU/ml or PFU/g)
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04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

Fig. 24G – 24I

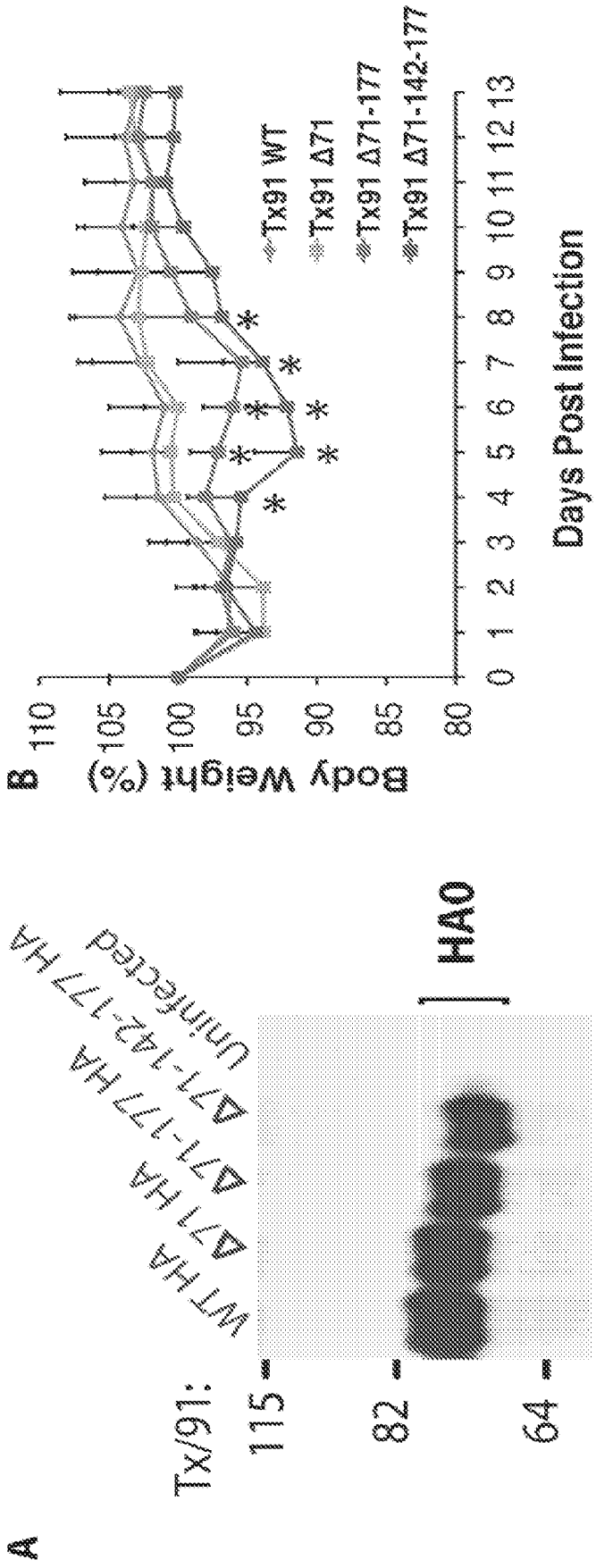

A
Tx/91:
WT HA
Δ71 HA
Δ71-177 HA
Δ71-142-177 HA
Uninfected
115
82
64
HA0
B
Body Weight (%)
110
105
100
95
90
85
80
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Days Post Infection
Tx91 WT
Tx91 Δ71
Tx91 Δ71-177
Tx91 Δ71-142-177

Fig. 25A – 25B

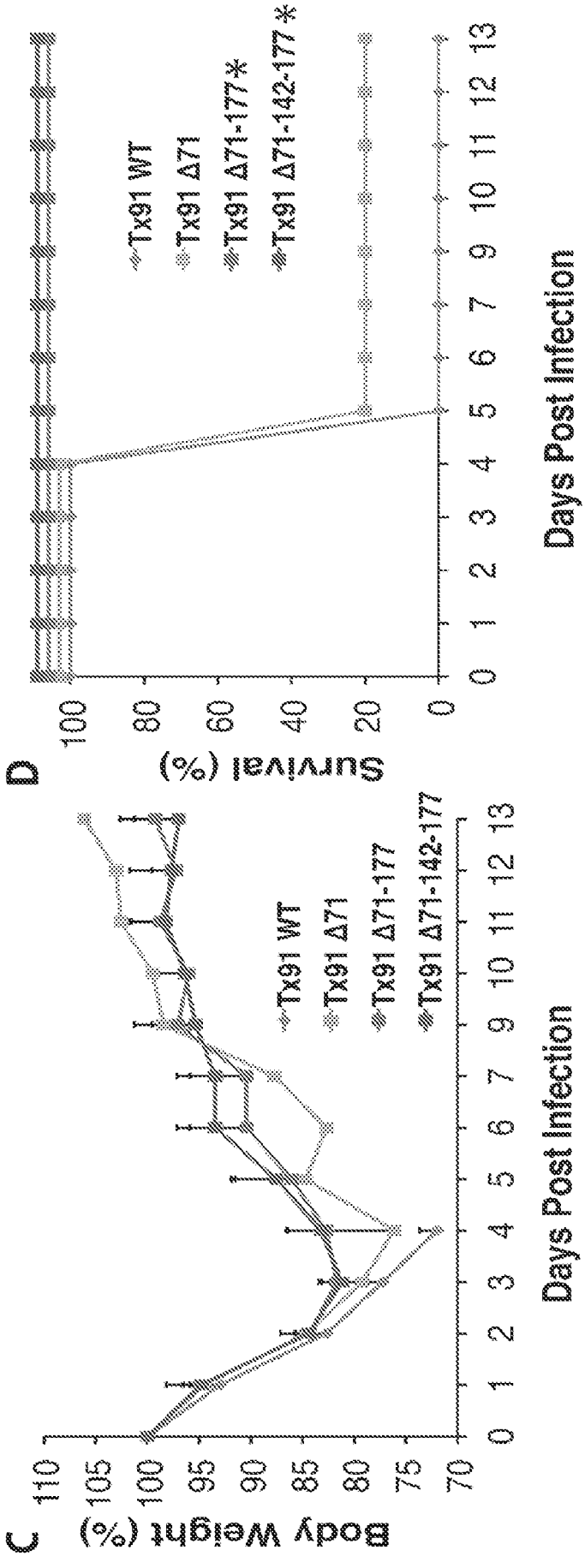
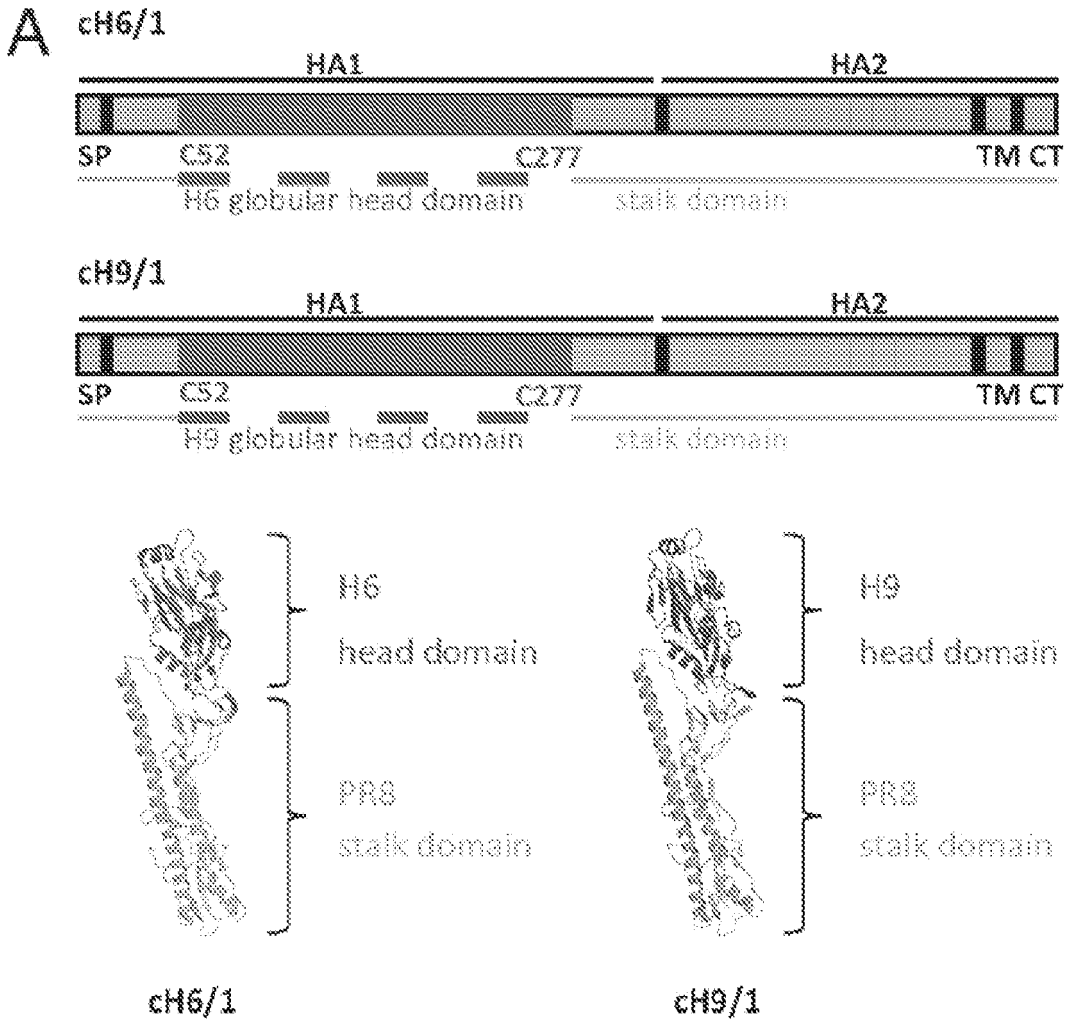

C
Body Weight (%)
110
105
100
95
90
85
80
75
70
0 1 2 3 4 5 6 7 9 10 11 12 13
Days Post Infection
Tx91 WT
Tx91 Δ71
Tx91 Δ71-177
Tx91 Δ71-142-177
D
Survival (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 9 10 11 12 13
Days Post Infection
Tx91 WT
Tx91 Δ71
Tx91 Δ71-177*
Tx91 Δ71-142-177*

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

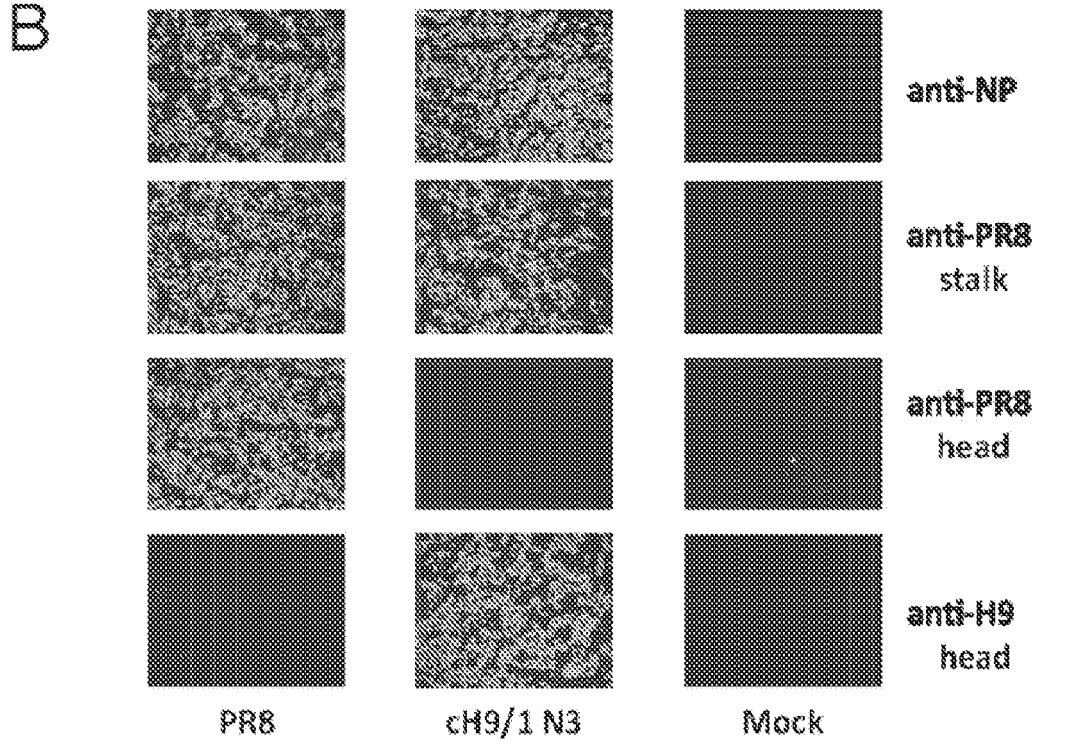

B
anti-NP
anti-PR8
stalk
anti-PR8
head
anti-H9
head
PR8
cH9/1 N3
Mock

Fig. 26

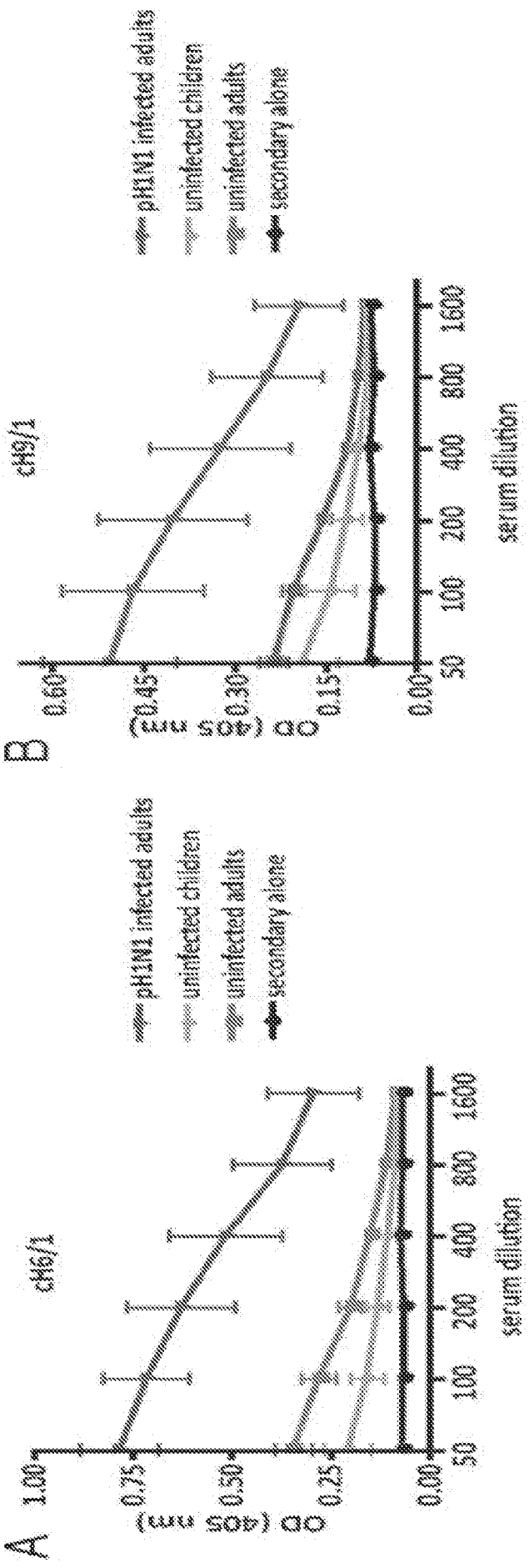

A
cH6/1
OD (405 nm)
1.00
0.75
0.50
0.25
0.00
50
100
200
400
800
1600
serum dilution
pH1N1 infected adults
uninfected children
uninfected adults
secondary alone
B
cH9/1
OD (405 nm)
0.60
0.45
0.30
0.15
0.00
50
100
200
400
800
1600
serum dilution
pH1N1 infected adults
uninfected children
uninfected adults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

Fig. 27A – 27B

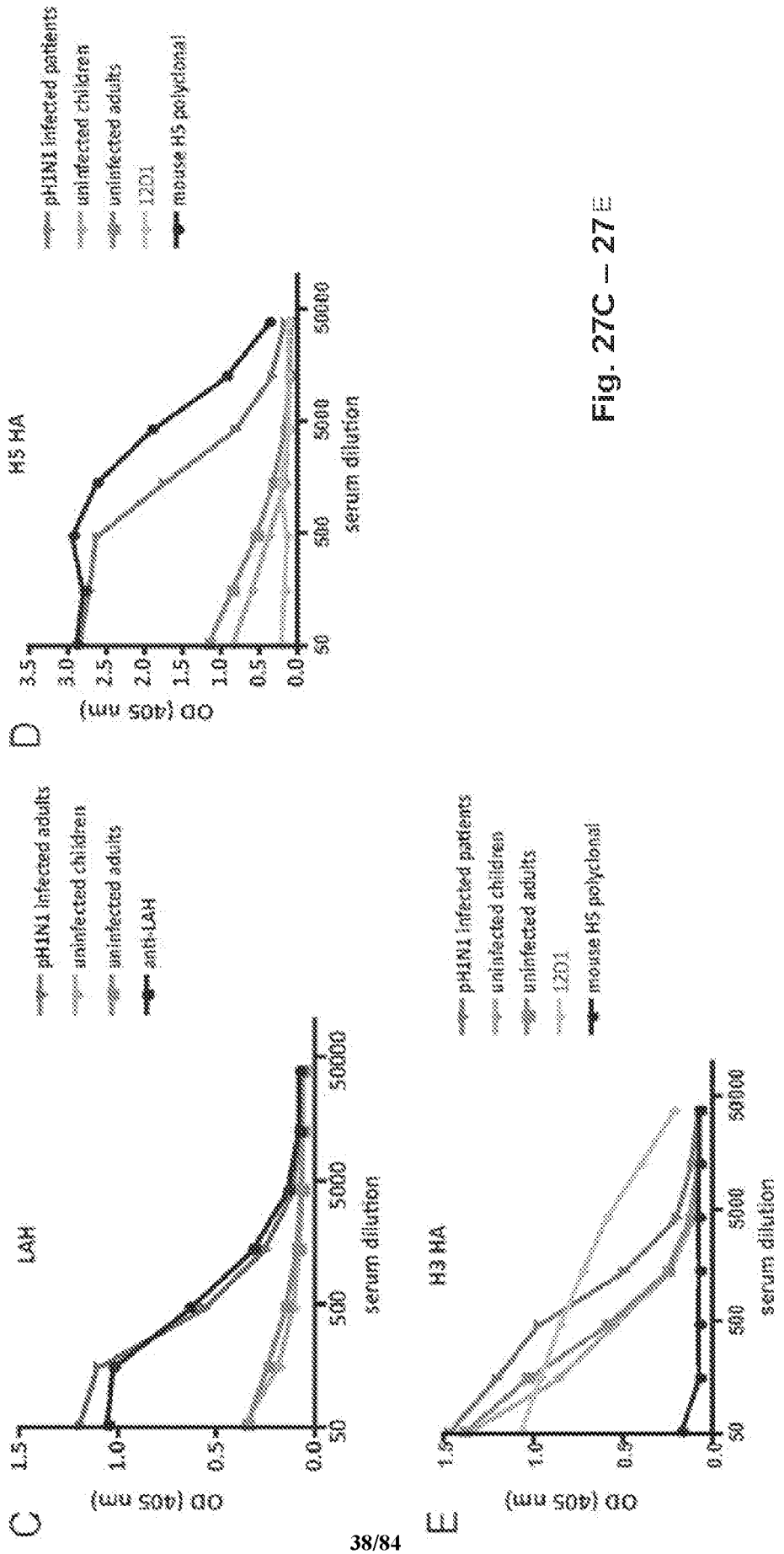
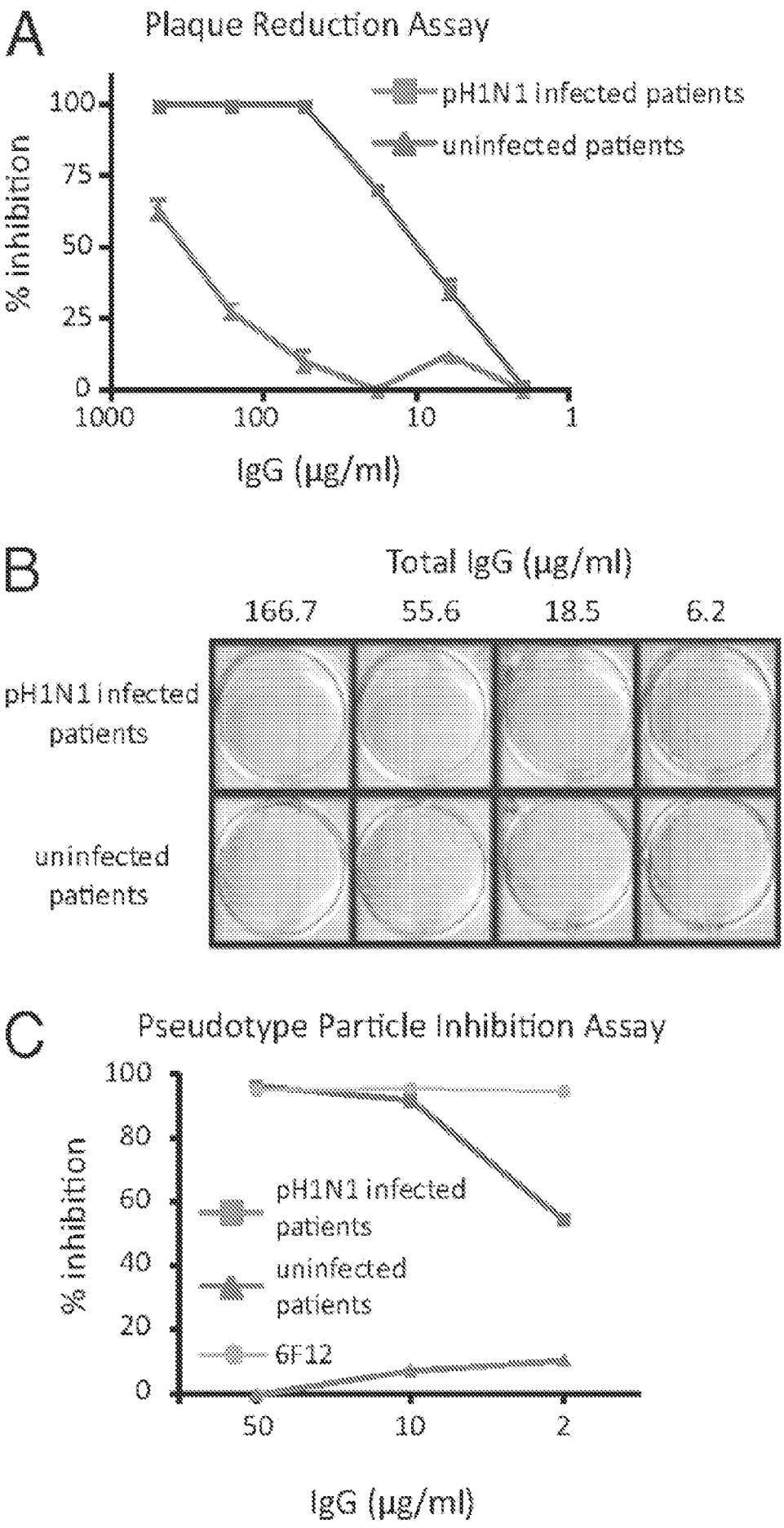

C
LAH
OD (405 nm)
serum dilution
pH1N1 infected adults
uninfected children
uninfected adults
anti-LAH
D
H5 HA
OD (405 nm)
serum dilution
pH1N1 infected patients
uninfected children
uninfected adults
1201
mouse H5 polyclonal
E
H3 HA
OD (405 nm)
serum dilution
pH1N1 infected patients
uninfected children
uninfected adults
1201
mouse H3 polyclonal

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)

F'39/84 28

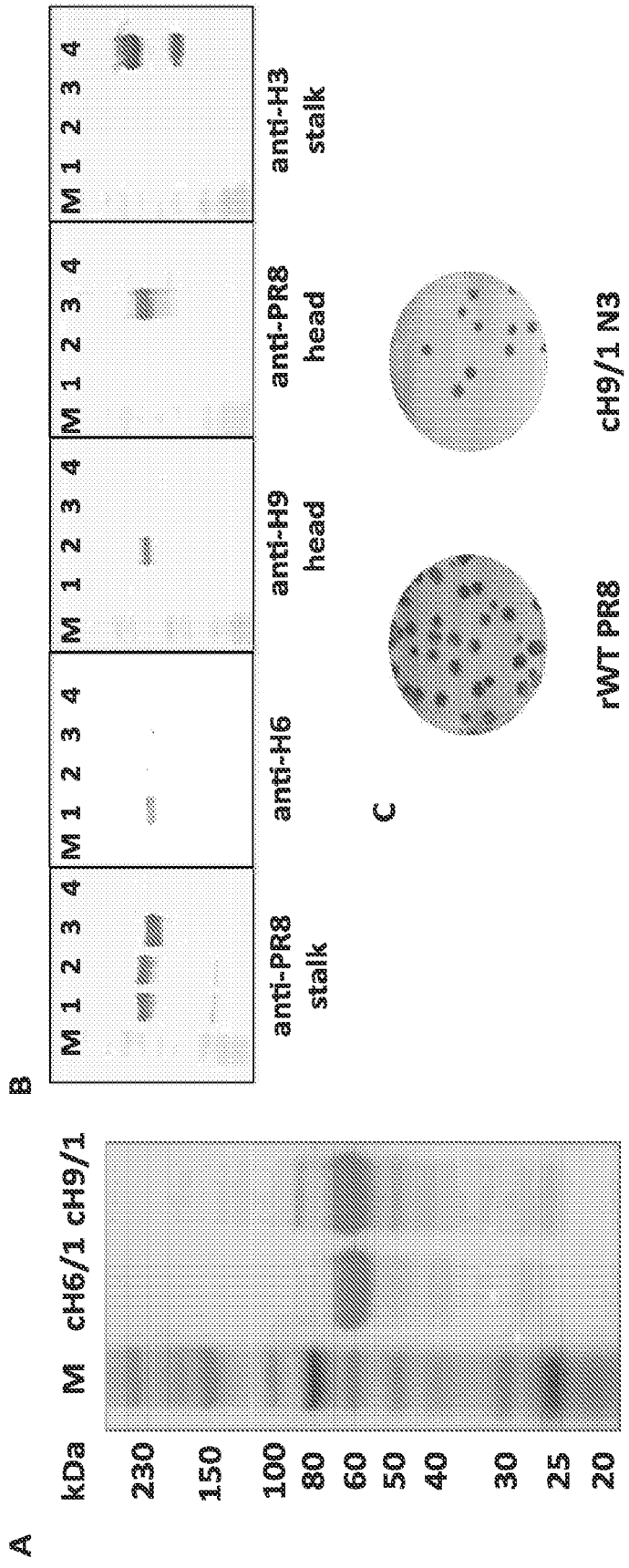

A
kDa
M
cH6/1
cH9/1
230
150
100
80
60
50
40
30
25
20
B
M 1 2 3 4
anti-PR8 stalk
anti-H6
anti-H9 head
anti-PR8 head
anti-H3 stalk
C
rWT PR8
cH9/1 N3

Fig. 29

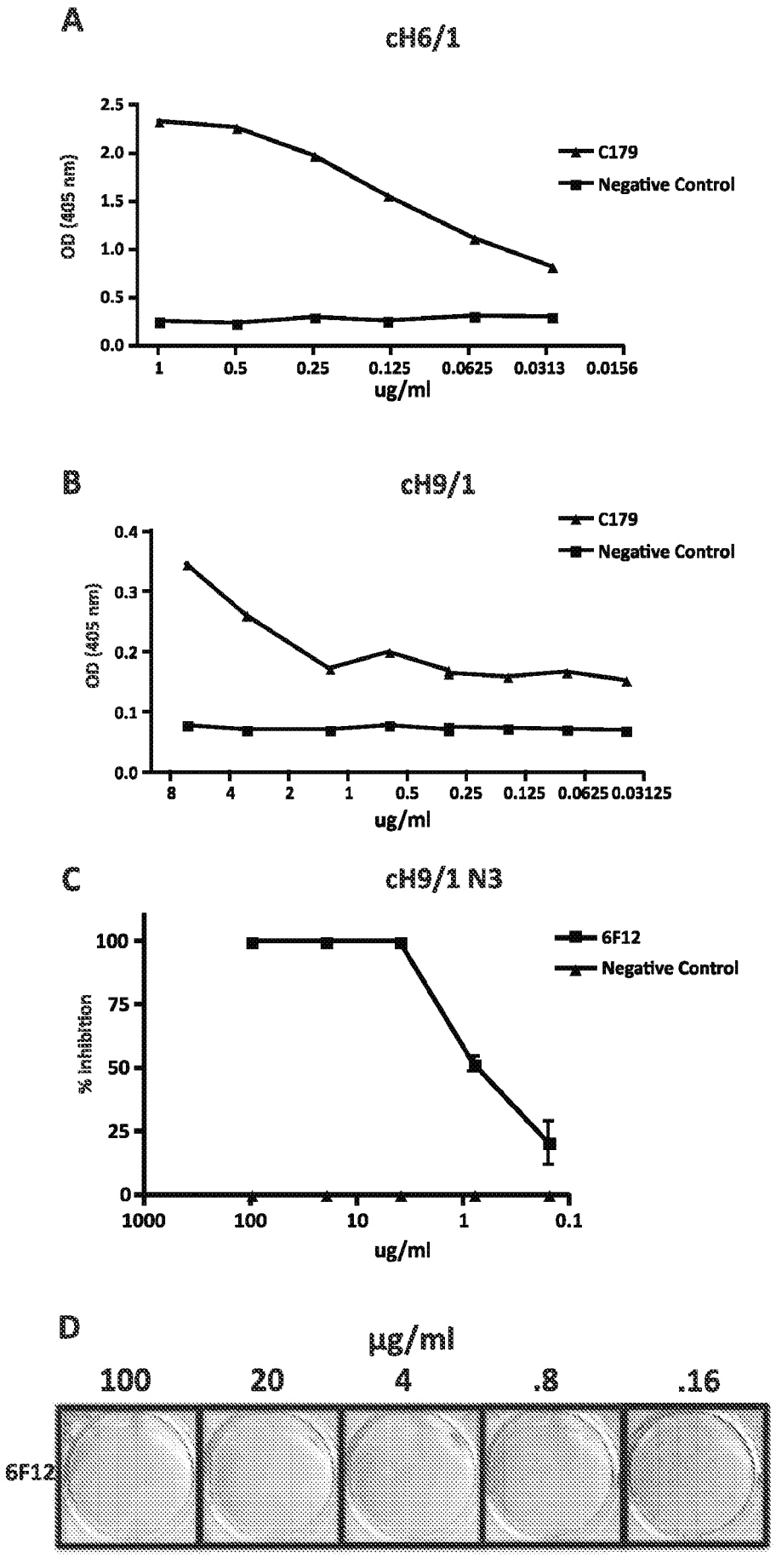

A
cH6/1
OD (405 nm)
2.5
2.0
1.5
1.0
0.5
0.0
C179
Negative Control
1
0.5
0.25
0.125
0.0625
0.0313
0.0156
ug/ml
B
cH9/1
OD (405 nm)
0.4
0.3
0.2
0.1
0.0
C179
Negative Control
8
4
2
1
0.5
0.25
0.125
0.0625
0.03125
ug/ml
C
cH9/1 N3
% Inhibition
100
75
50
25
0
6F12
Negative Control
1000
100
10
1
0.1
ug/ml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

Fig 30

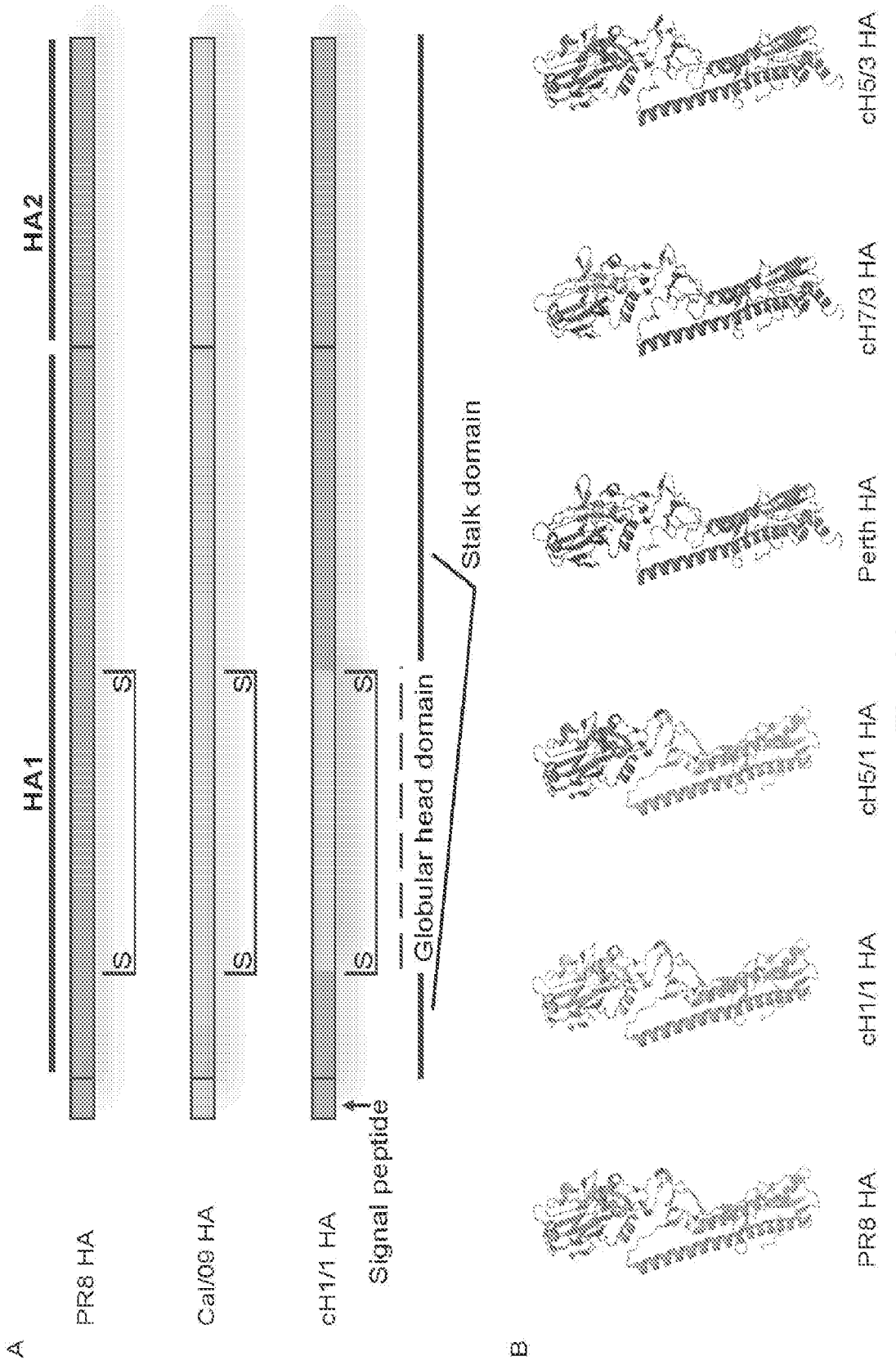

A
HA1
HA2
PR8 HA
Cal/09 HA
cH1/1 HA
S
S
S
S
S
S
Signal peptide
Globular head domain
Stalk domain
B
PR8 HA
cH1/1 HA
cH5/1 HA
Perth HA
cH7/3 HA
cH5/3 HA

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

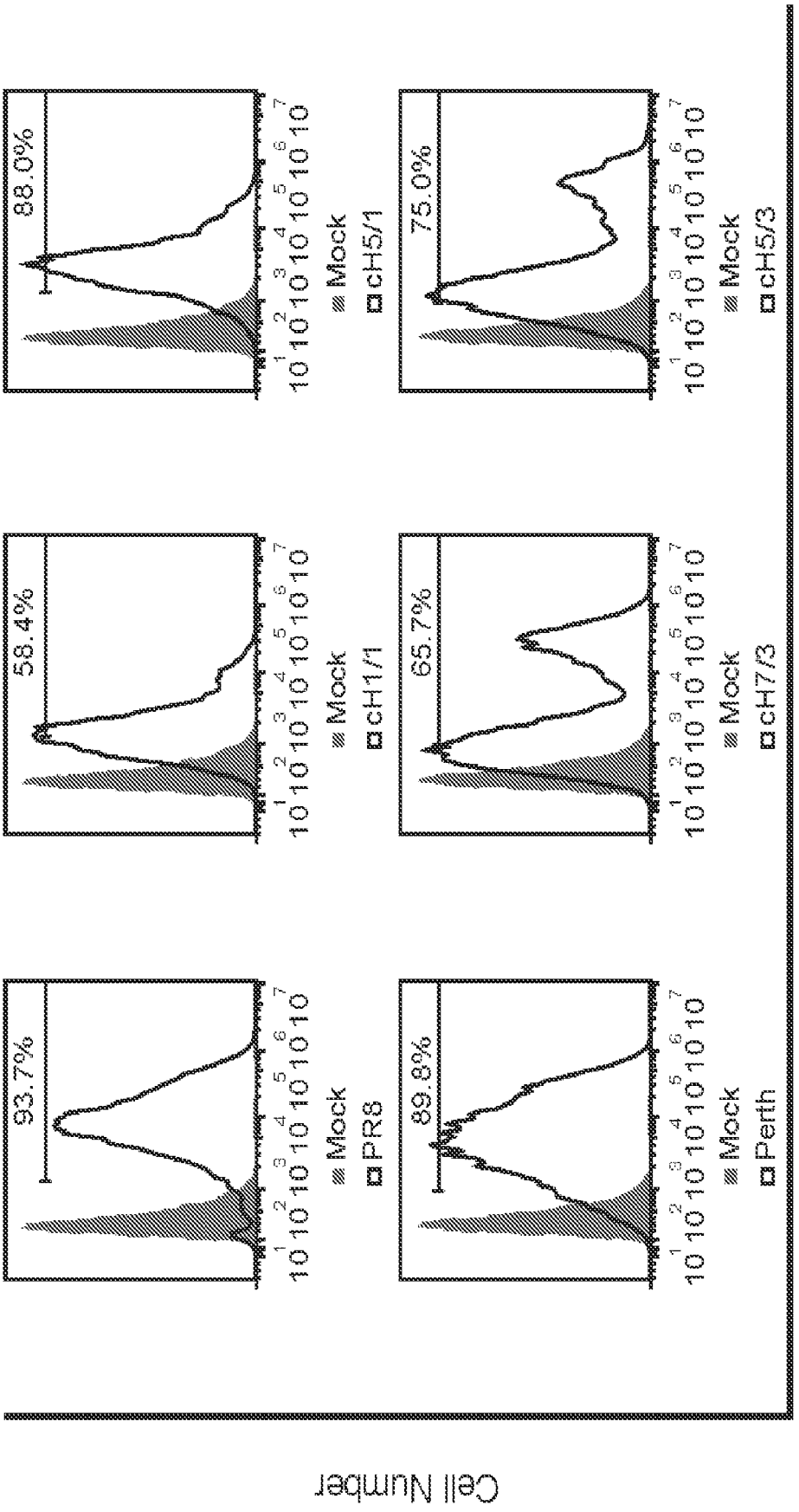

93.7%
89.8%
58.4%
65.7%
88.0%
75.0%
Mock
PR8
Perth
cH1/1
cH7/3
cH5/1
cH5/3
Cell Number
Hemagglutinin

Fig. 33

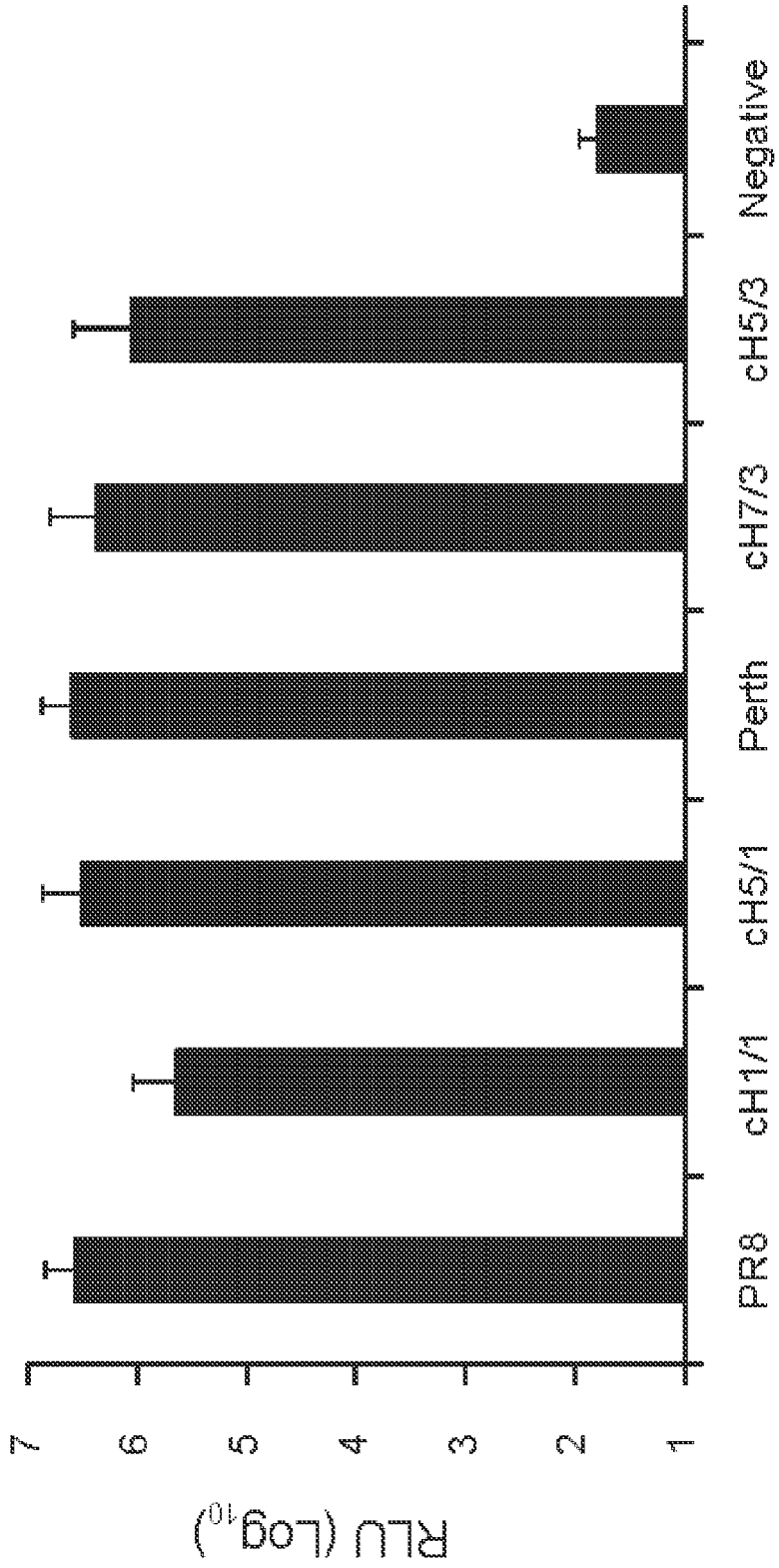


Fig. 34

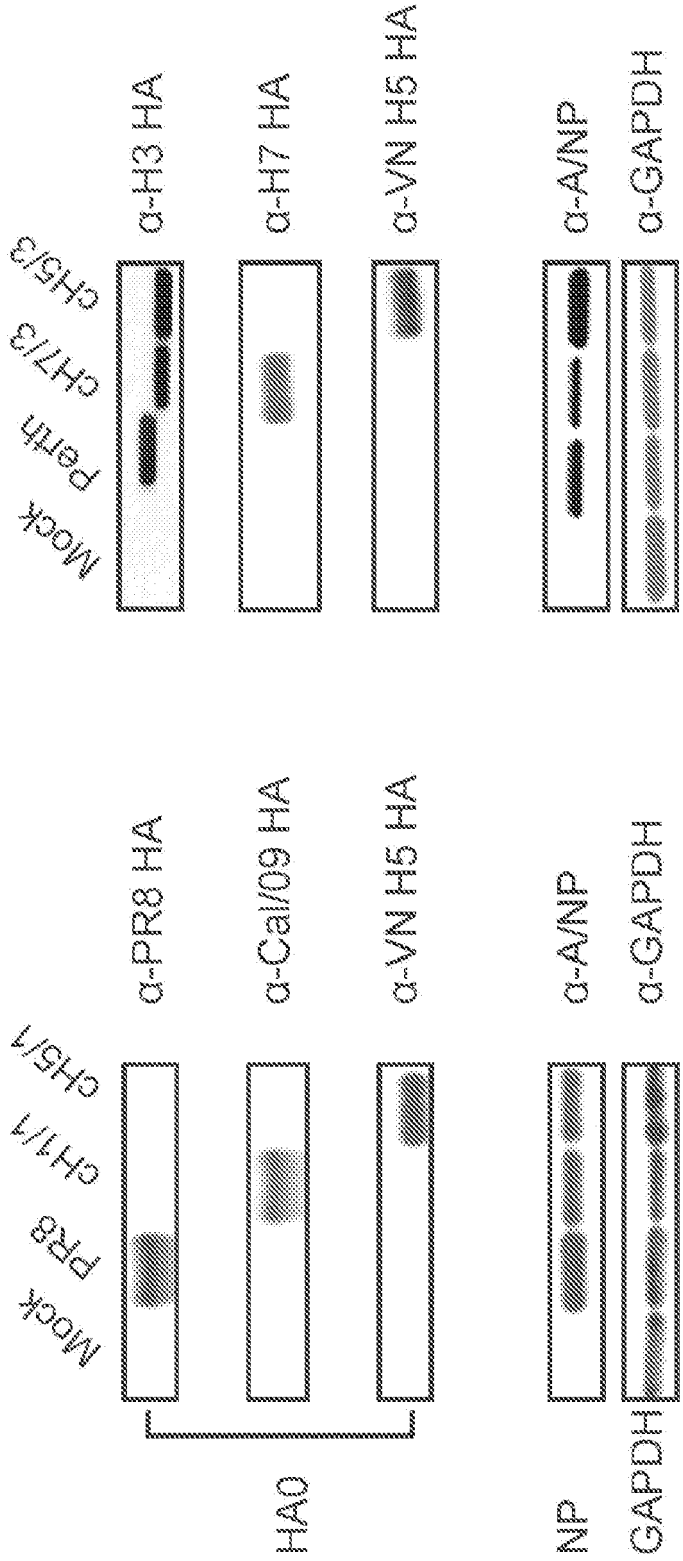

Mock
PR8
CH1/1
CH5/1
α-PR8 HA
α-Cal/09 HA
α-VN H5 HA
α-A/NP
α-GAPDH
HA0
NP
GAPDH
Mock
Perth
CH7/3
CH5/3
α-H3 HA
α-H7 HA
α-VN H5 HA
α-A/NP
α-GAPDH

Fig. 35

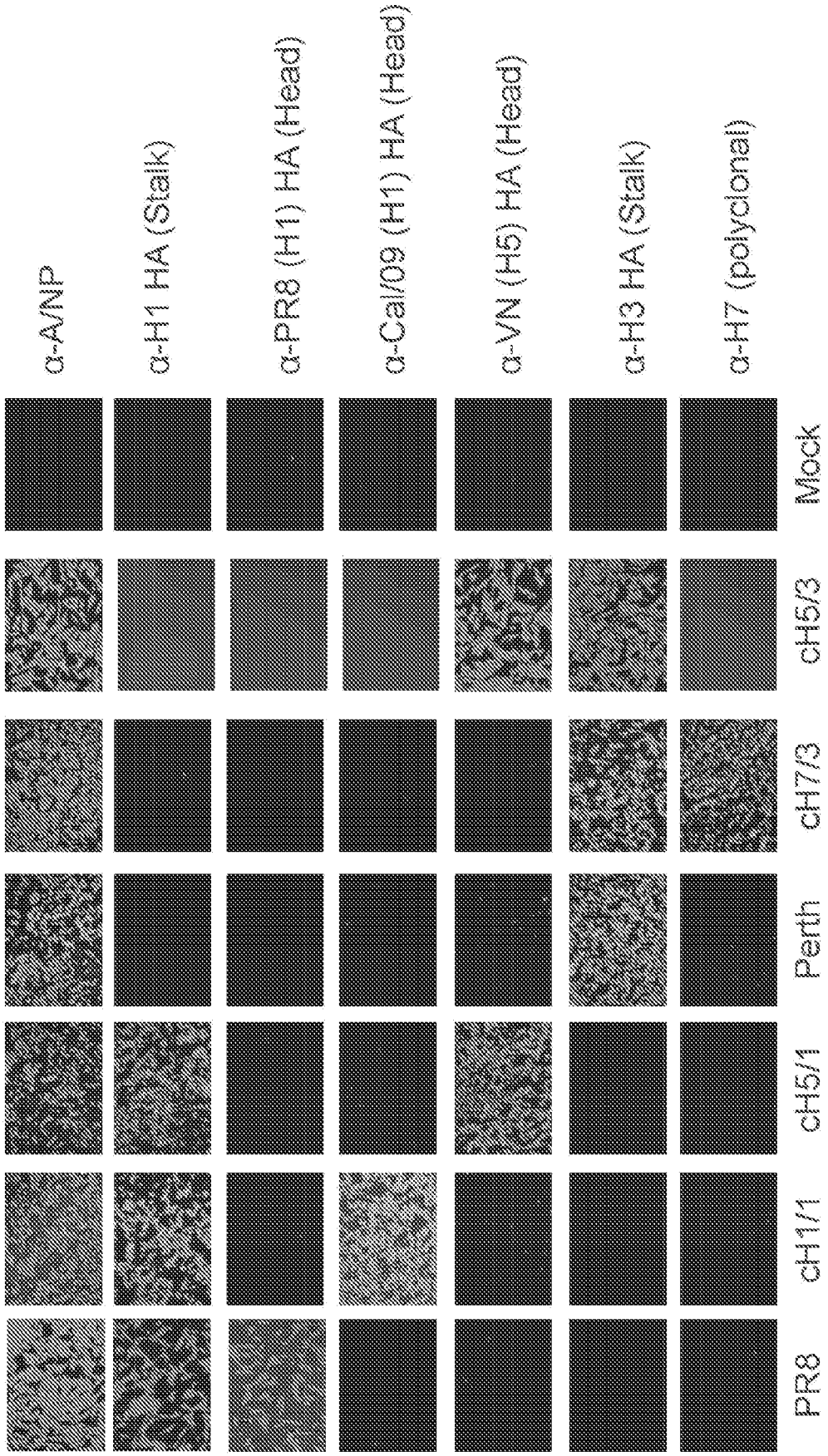

α-A/NP
α-H1 HA (Stalk)
α-PR8 (H1) HA (Head)
α-Cal/09 (H1) HA (Head)
α-VN (H5) HA (Head)
α-H3 HA (Stalk)
α-H7 (polyclonal)
PR8
cH1/1
cH5/1
Perth
cH7/3
cH5/3
Mock

Fig. 36

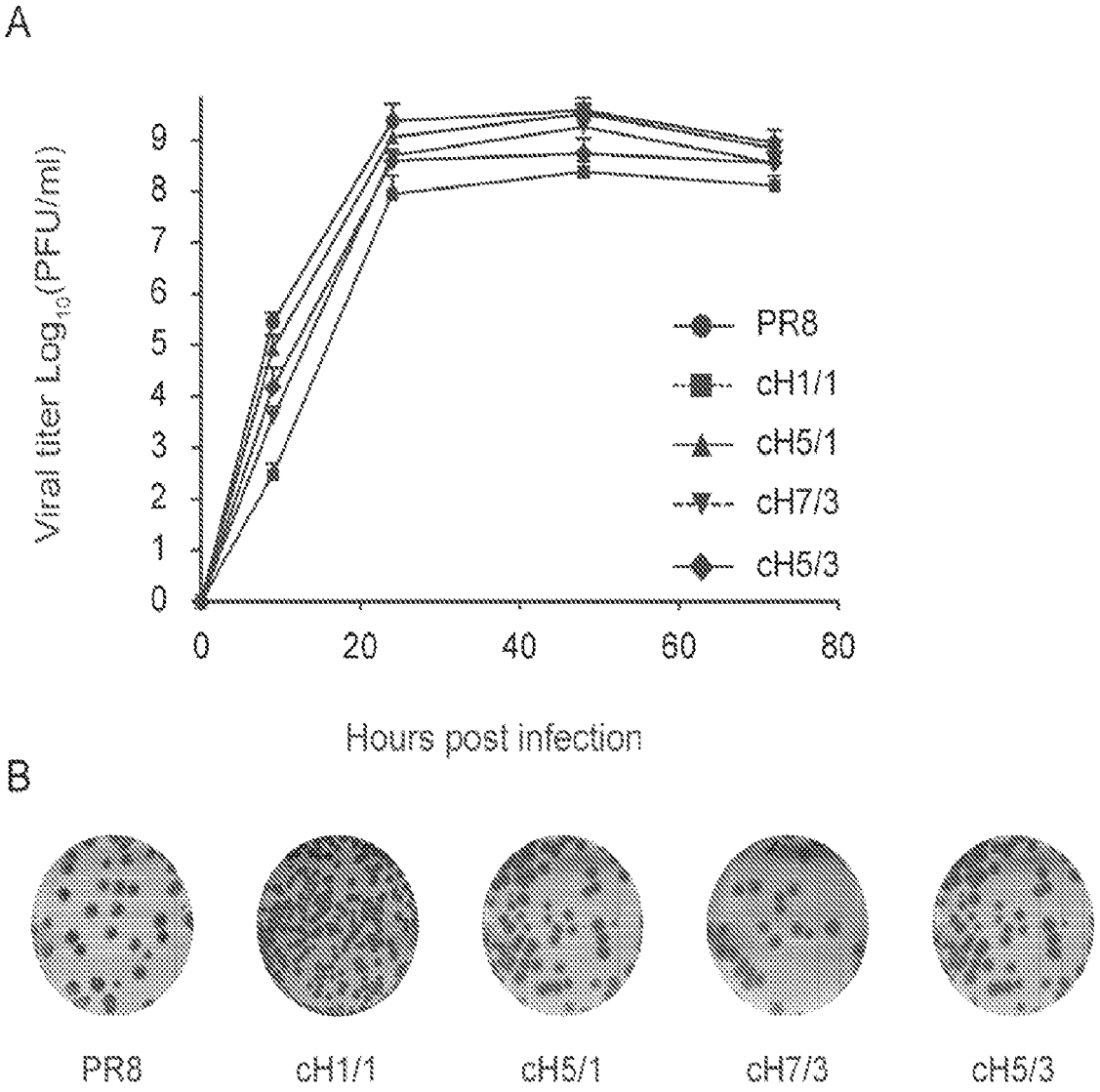

A
Viral liter Log10(PFU/ml)
0
1
2
3
4
5
6
7
8
9
0
20
40
60
80
Hours post infection
PR8
cH1/1
cH5/1
cH7/3
cH5/3
B
PR8
cH1/1
cH5/1
cH7/3
cH5/3

Fig. 37

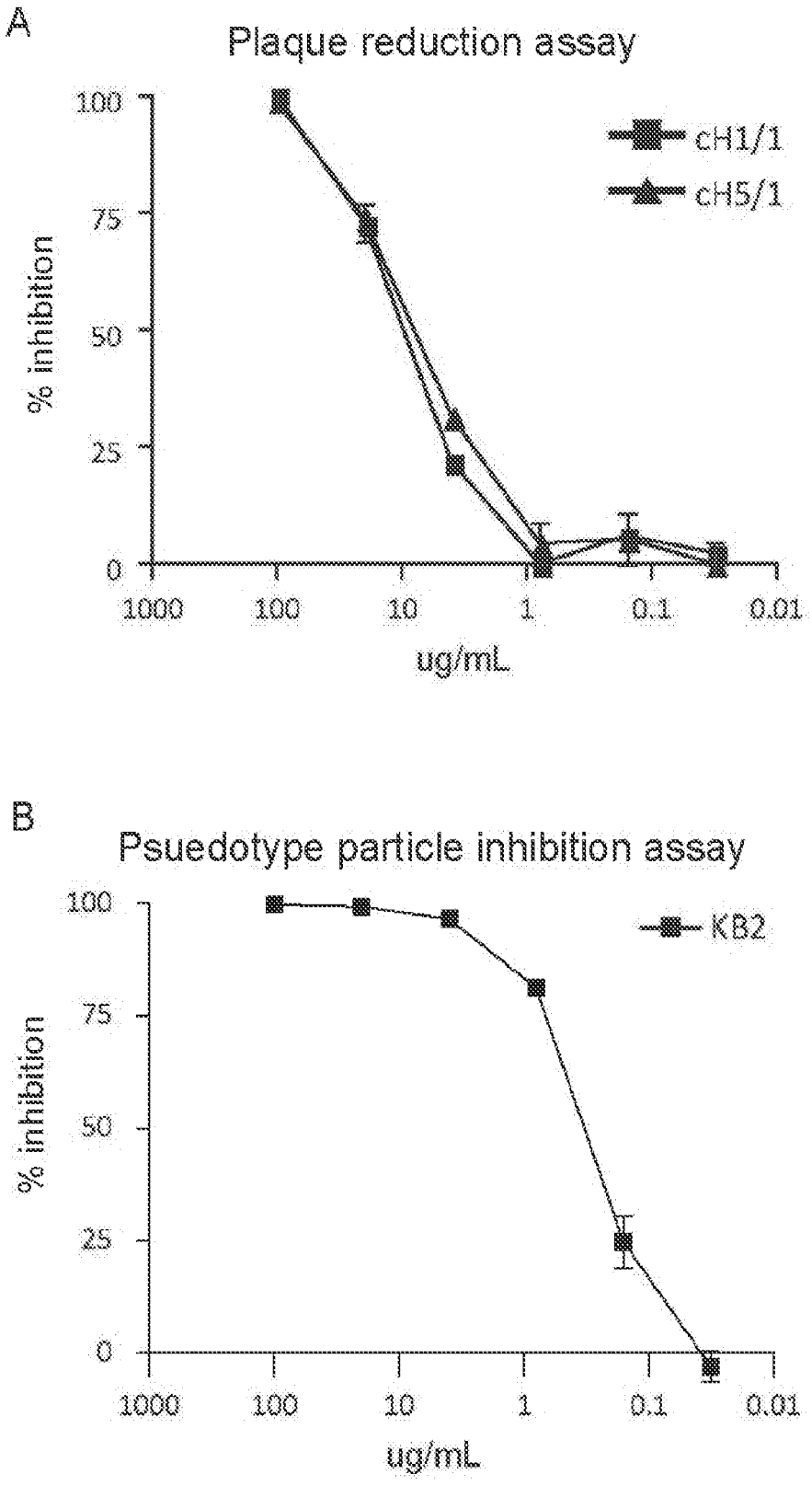

A
Plaque reduction assay
100
75
50
25
0
% inhibition
cH1/1
cH5/1
1000
100
10
1
0.1
0.01
ug/mL
B
Psuedotype particle inhibition assay
100
75
50
25
0
% inhibition
KB2
1000
100
10
1
0.1
0.01
ug/mL

Fig. 38

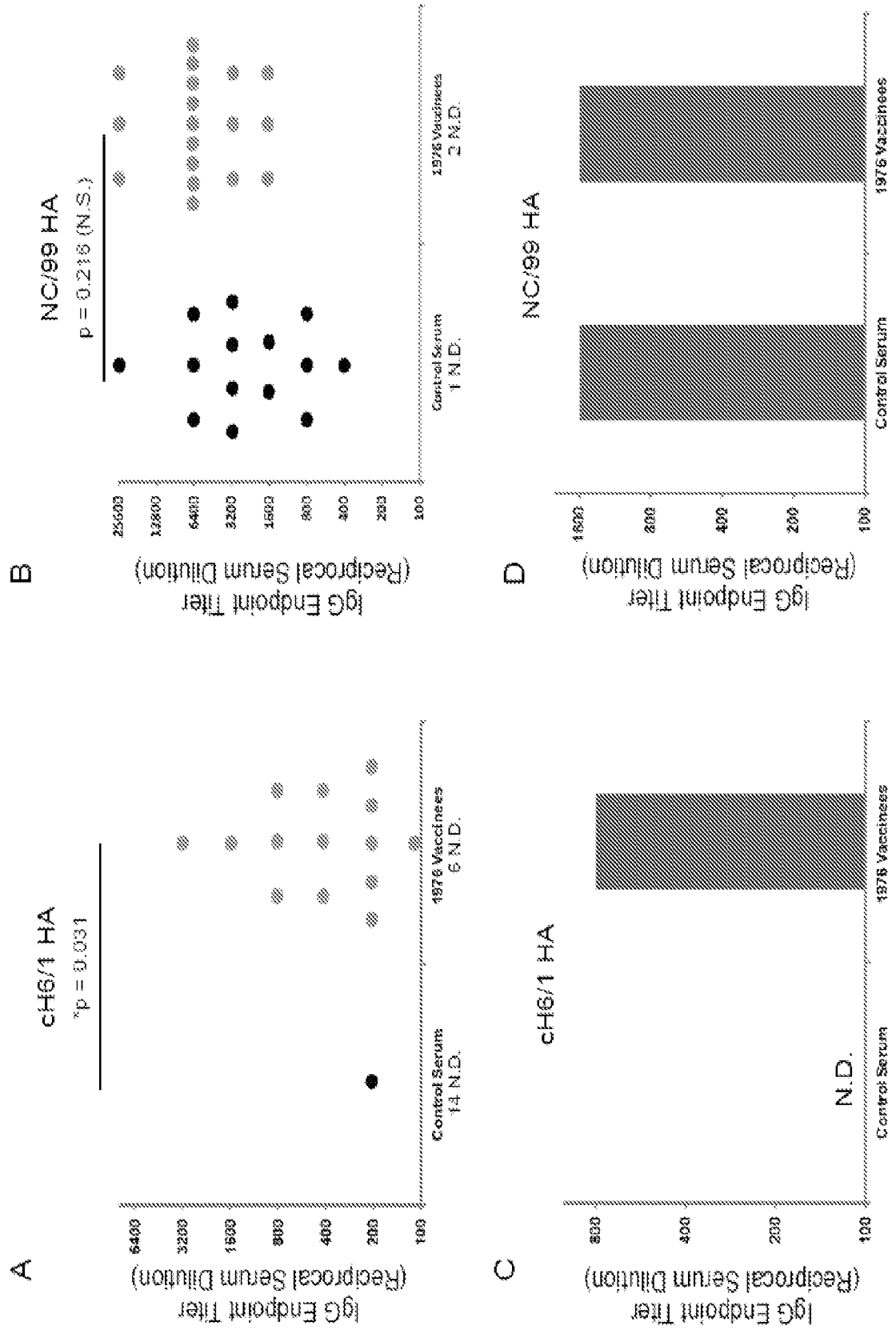

A
cH6/1 HA
*p = 0.031
IgG Endpoint Titer
(Reciprocal Serum Dilution)
6400
3200
1600
800
400
200
100
Control Serum
14 N.D.
1976 Vaccinees
6 N.D.
B
NC/99 HA
p = 0.218 (N.S.)
IgG Endpoint Titer
(Reciprocal Serum Dilution)
25600
12800
6400
3200
1600
800
400
200
100
Control Serum
1 N.D.
1976 Vaccinees
2 N.D.
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

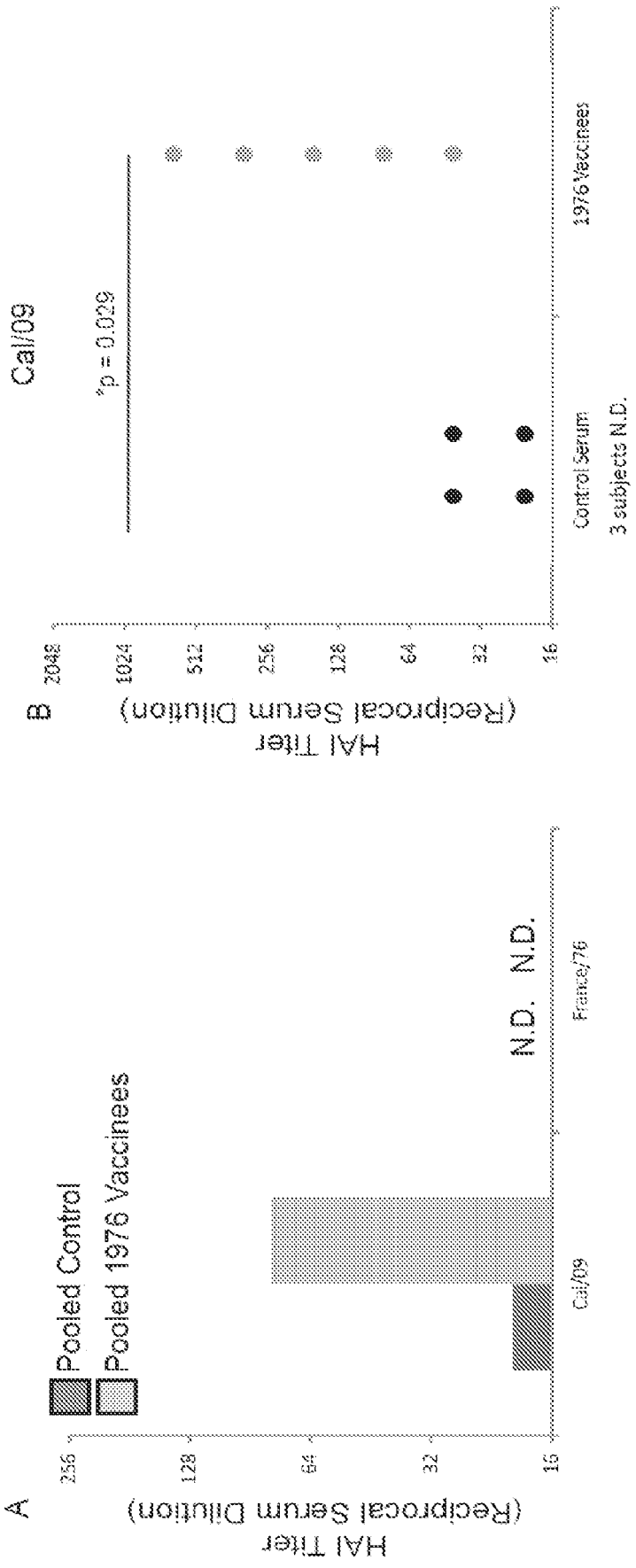

A
HAI Titer
(Reciprocal Serum Dilution)
256
128
64
32
16
Pooled Control
Pooled 1976 Vaccinees
N.D.
N.D.
Cal/09
France/76
B
HAI Titer
(Reciprocal Serum Dilution)
2048
1024
512
256
128
64
32
16
Cal/09
*p = 0.029
Control Serum
3 subjects N.D.
1976 Vaccinees

Fig. 40

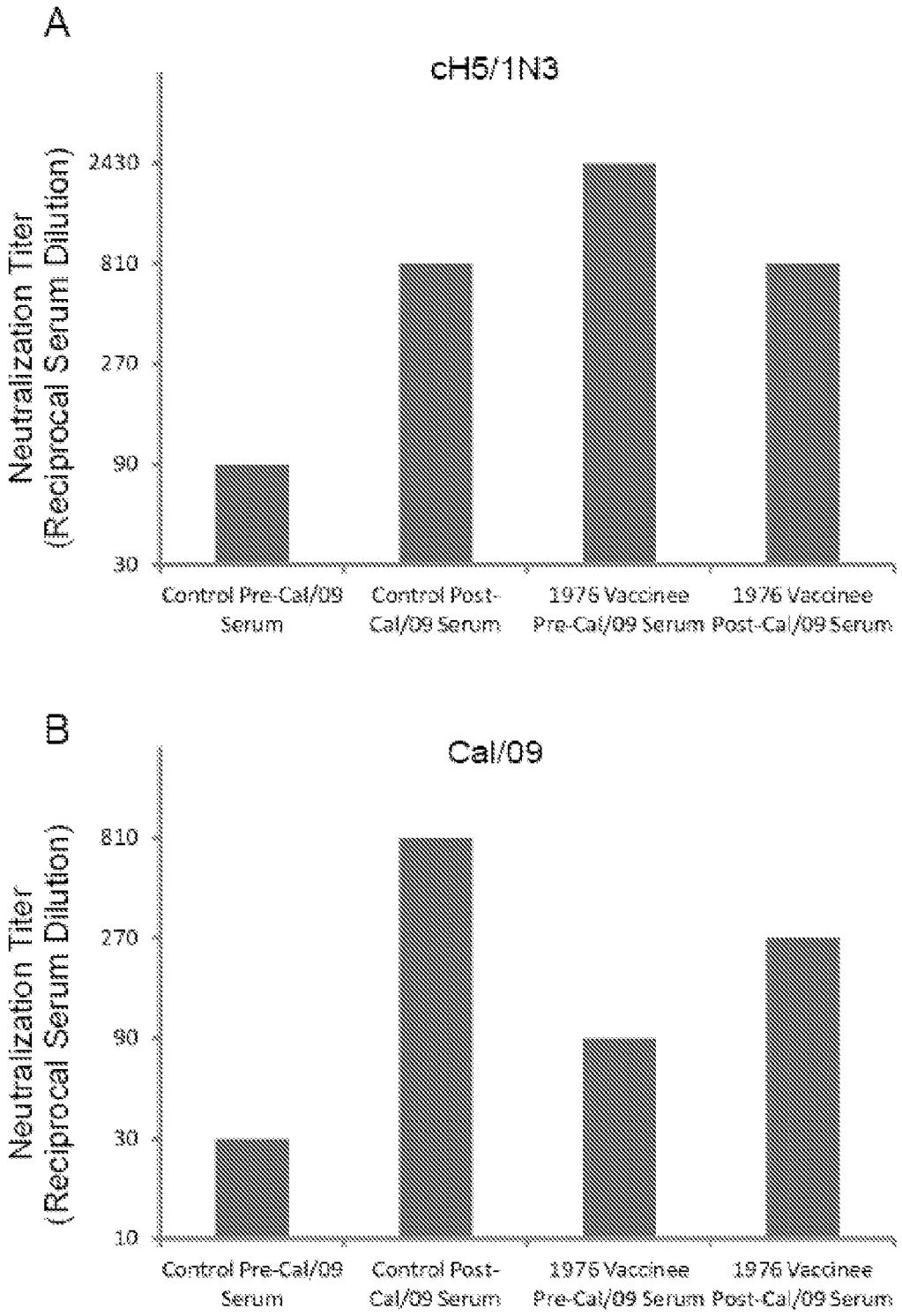

A
cH5/1N3
Neutralization Titer
(Reciprocal Serum Dilution)
2430
810
270
90
30
Control Pre-Cal/09 Serum
Control Post-Cal/09 Serum
1976 Vaccinee Pre-Cal/09 Serum
1976 Vaccinee Post-Cal/09 Serum
B
Cal/09
Neutralization Titer
(Reciprocal Serum Dilution)
810
270
90
30
10
Control Pre-Cal/09 Serum
Control Post-Cal/09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

Fig. 41

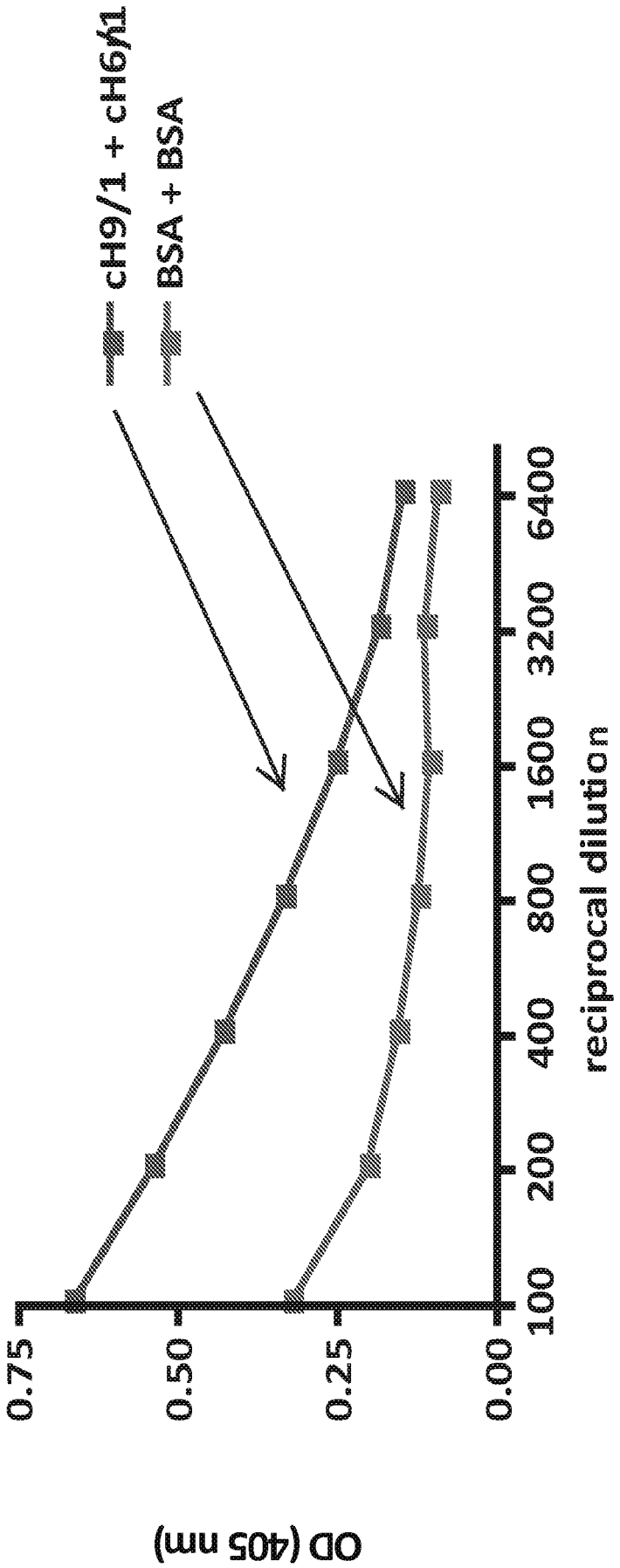

cH9/1 + cH6/l1
BSA + BSA
OD (405 nm)
0.75
0.50
0.25
0.00
100
200
400
800
1600
3200
6400
reciprocal dilution

Fig. 42 A

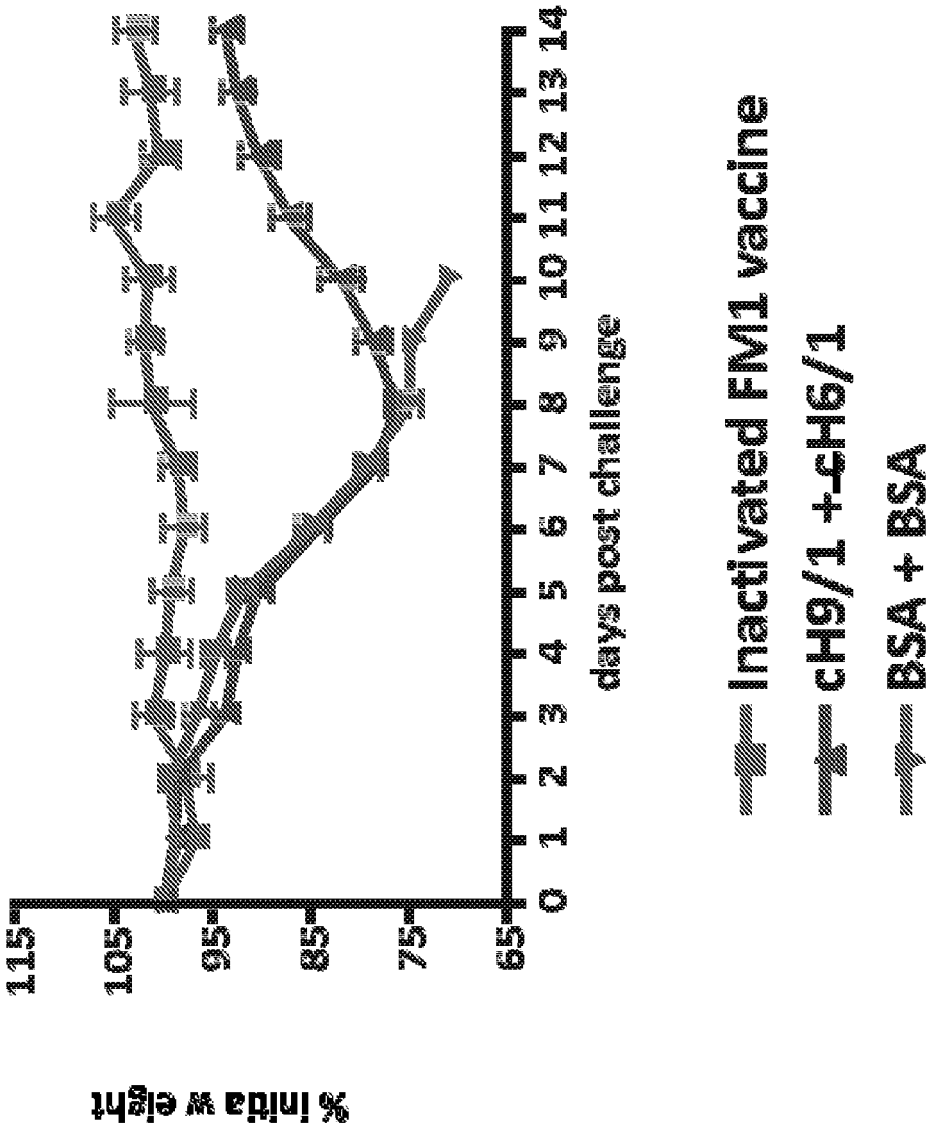

% initia w eight
115
105
95
85
75
65
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
days post challenge
Inactivated FM1 vaccine
cH9/1 +cH6/1
BSA + BSA

Fig. 42 B

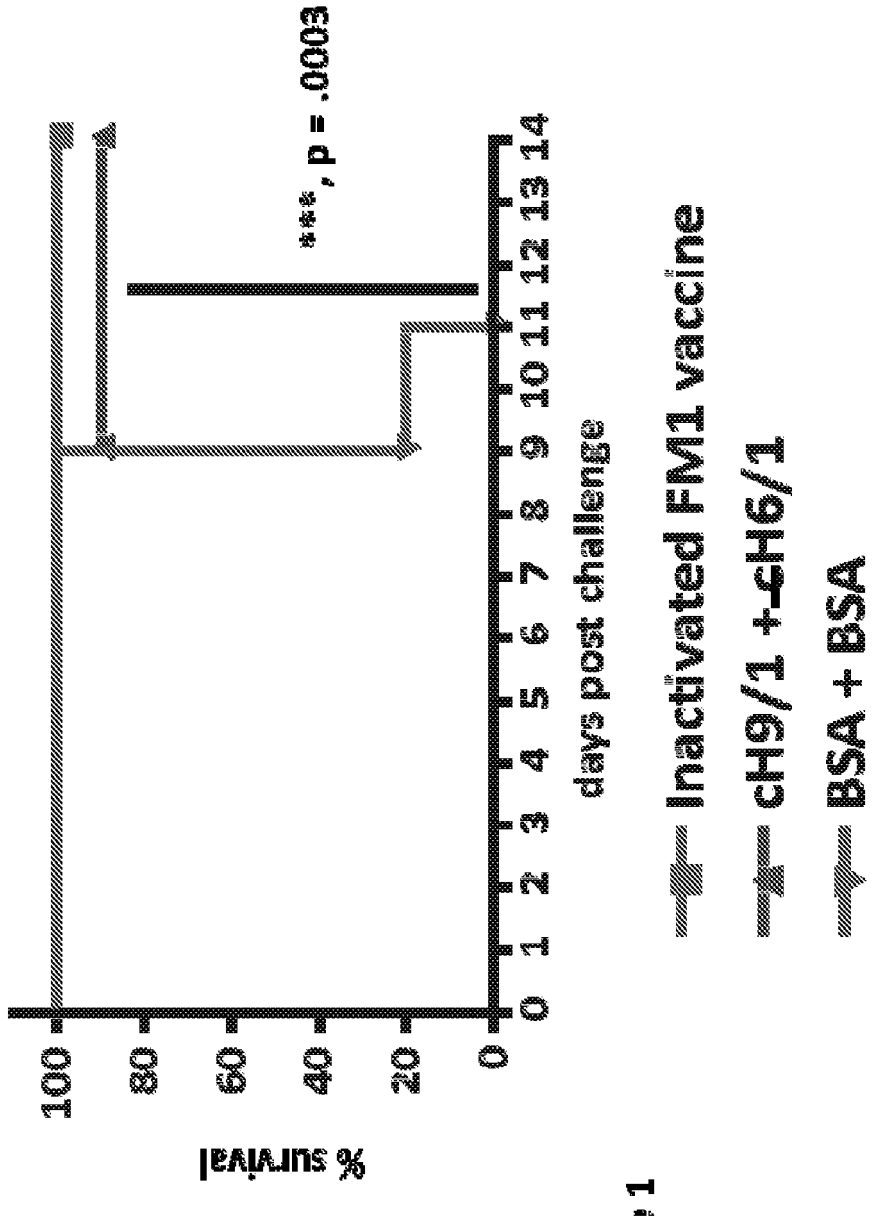

% survival
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
days post challenge
***, p = .0003
Inactivated FM1 vaccine
cH9/1 +cH6/1
BSA + BSA

Fig. 42 C

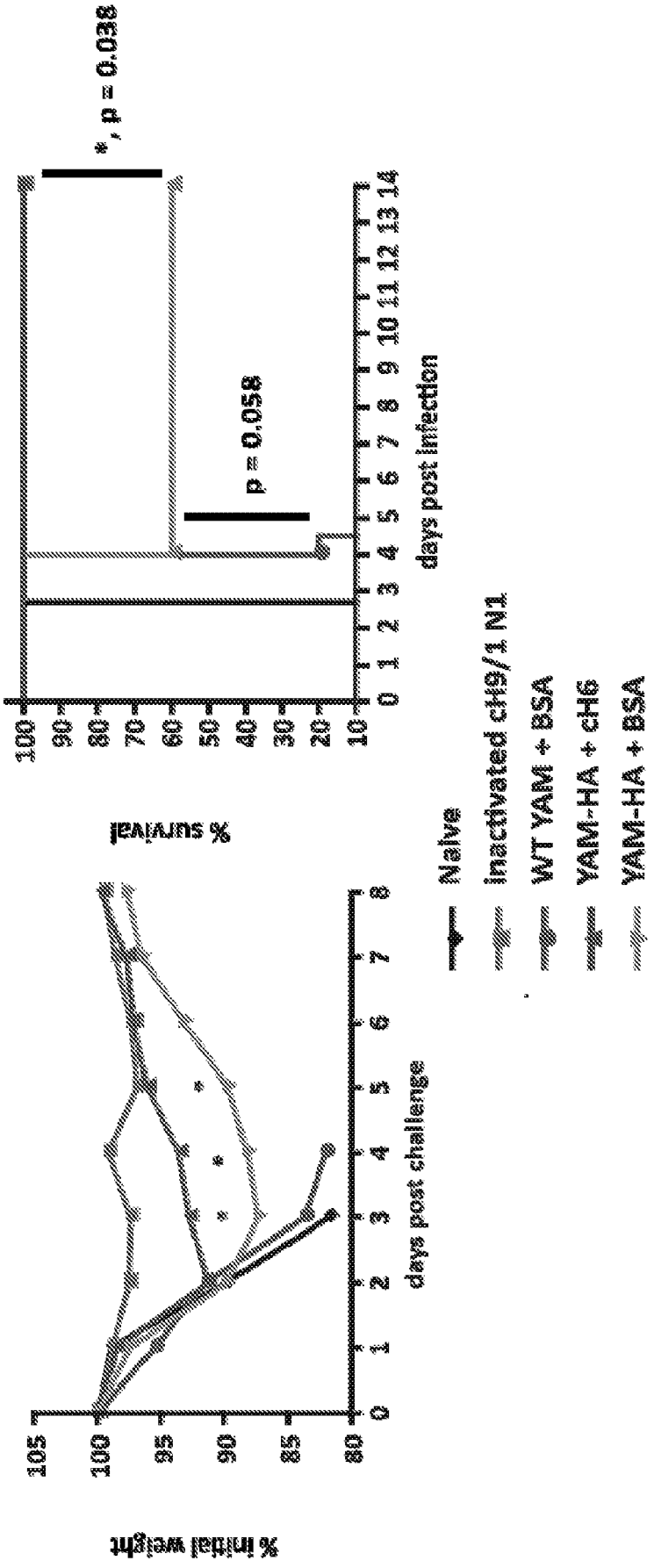

% initial weight
105
100
95
90
85
80
0 1 2 3 4 5 6 7 8
days post challenge
% survival
100 90 80 70 60 50 40 30 20 10
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
days post infection
*, p = 0.038
p = 0.058
Naïve
inactivated cH9/1 N1
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA

Fig. 43 A-B

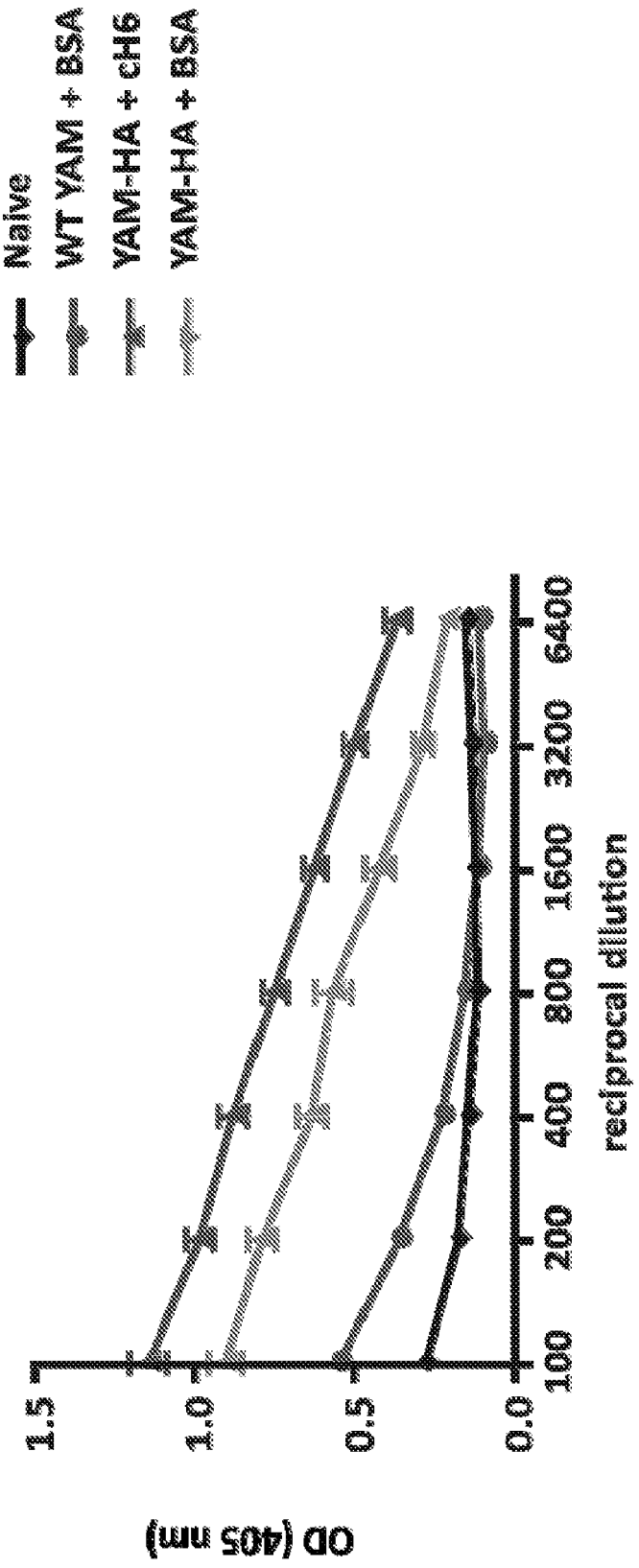

Naive
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA
OD (405 nm)
1.5
1.0
0.5
0.0
100
200
400
800
1600
3200
6400
reciprocal dilution

Fig. 43 C

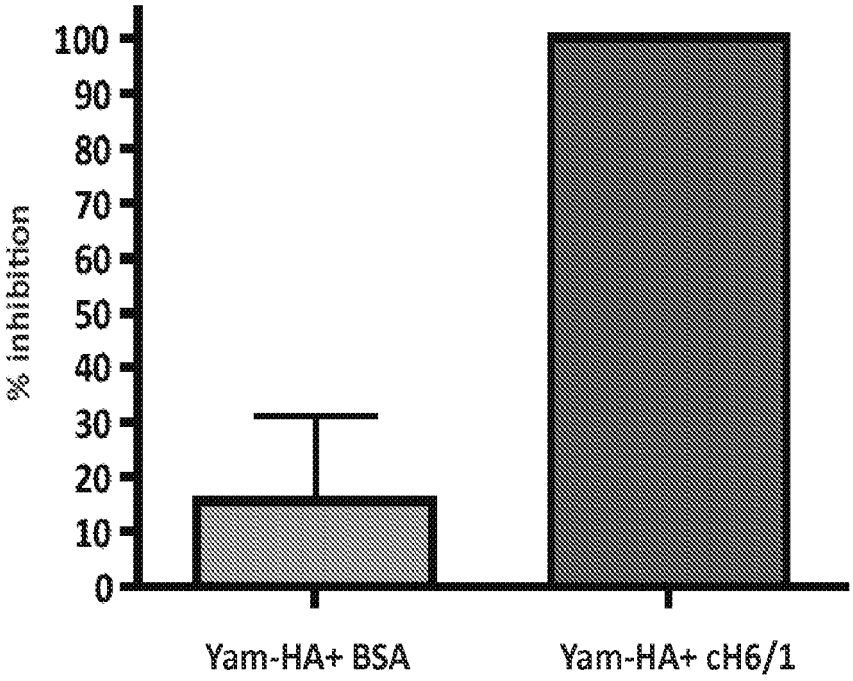


Fig. 43D

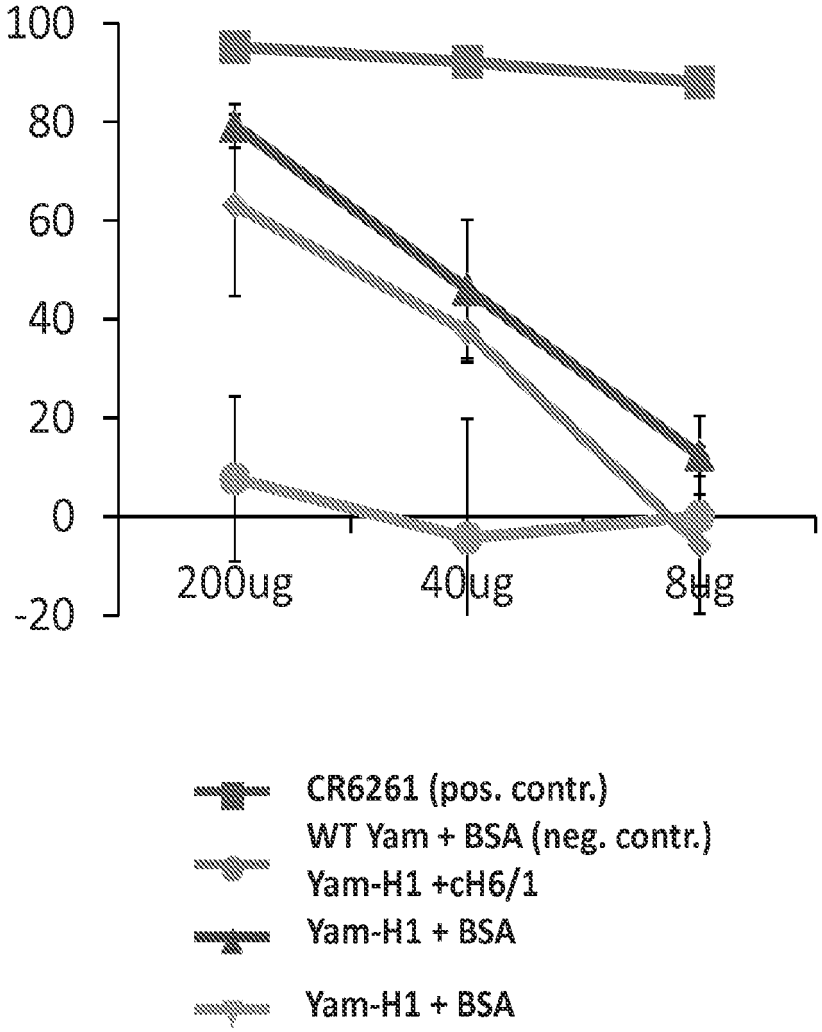

100
80
60
40
20
0
-20
200ug
40ug
8ug
CR6261 (pos. contr.)
WT Yam + BSA (neg. contr.)
Yam-H1 +cH6/1
Yam-H1 + BSA
Yam-H1 + BSA

Fig. 43E

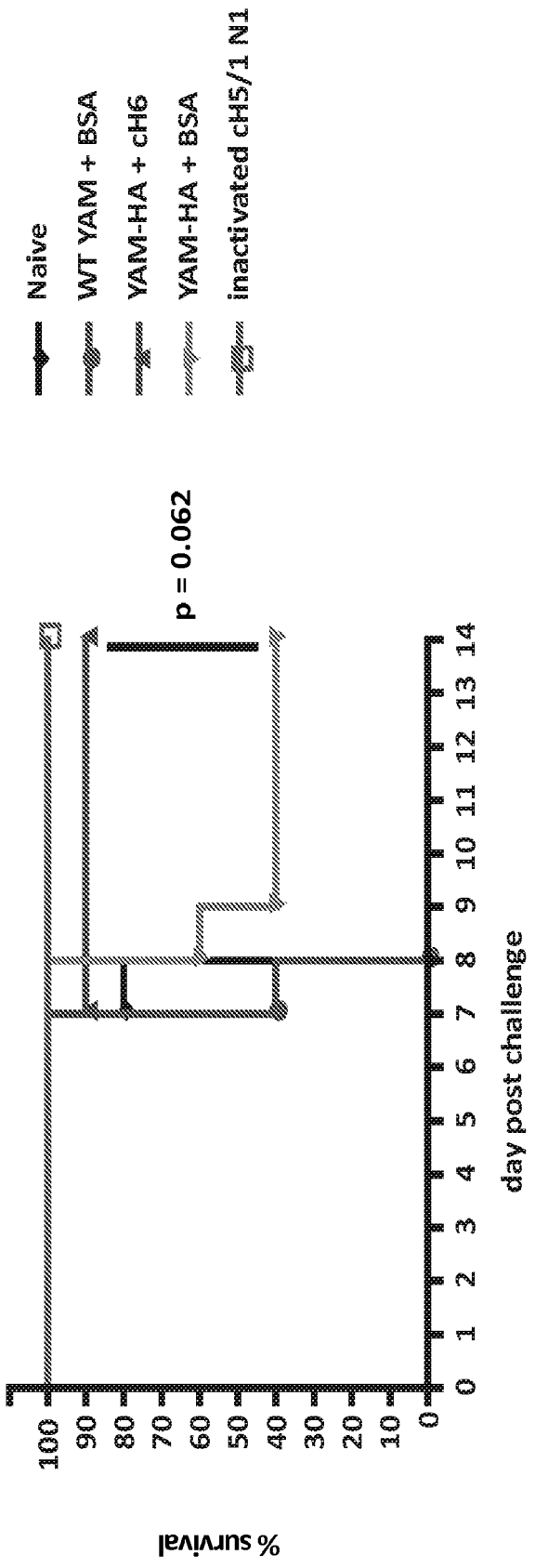

Naive
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA
inactivated cH5/1 N1
p = 0.062
% survival
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
day post challenge

Fig. 44A

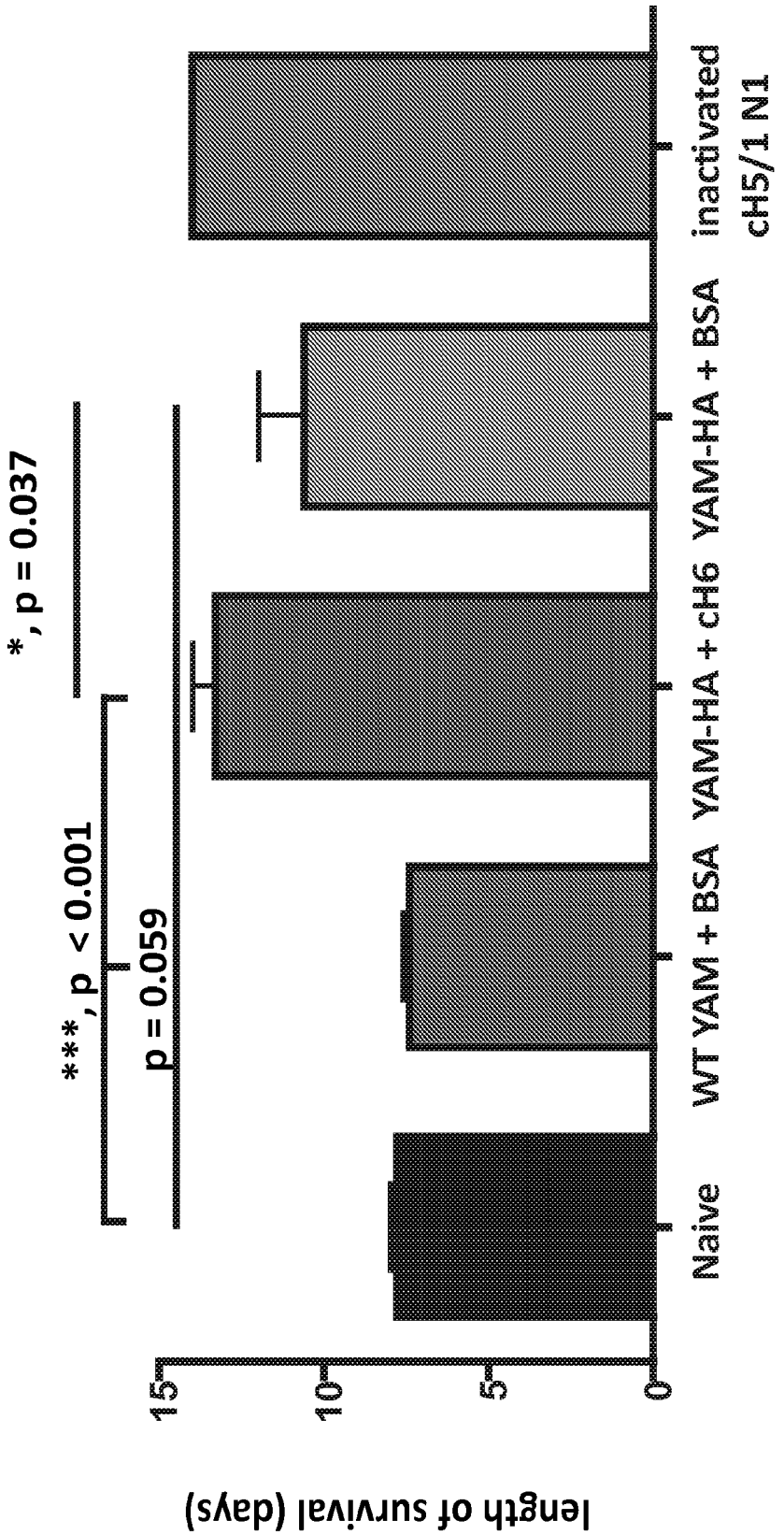

length of survival (days)
15
10
5
0
Naive
WT YAM + BSA
YAM-HA + cH6
YAM-HA + BSA
inactivated cH5/1 N1
*, p = 0.037
***, p < 0.001
p = 0.059

Fig. 44B

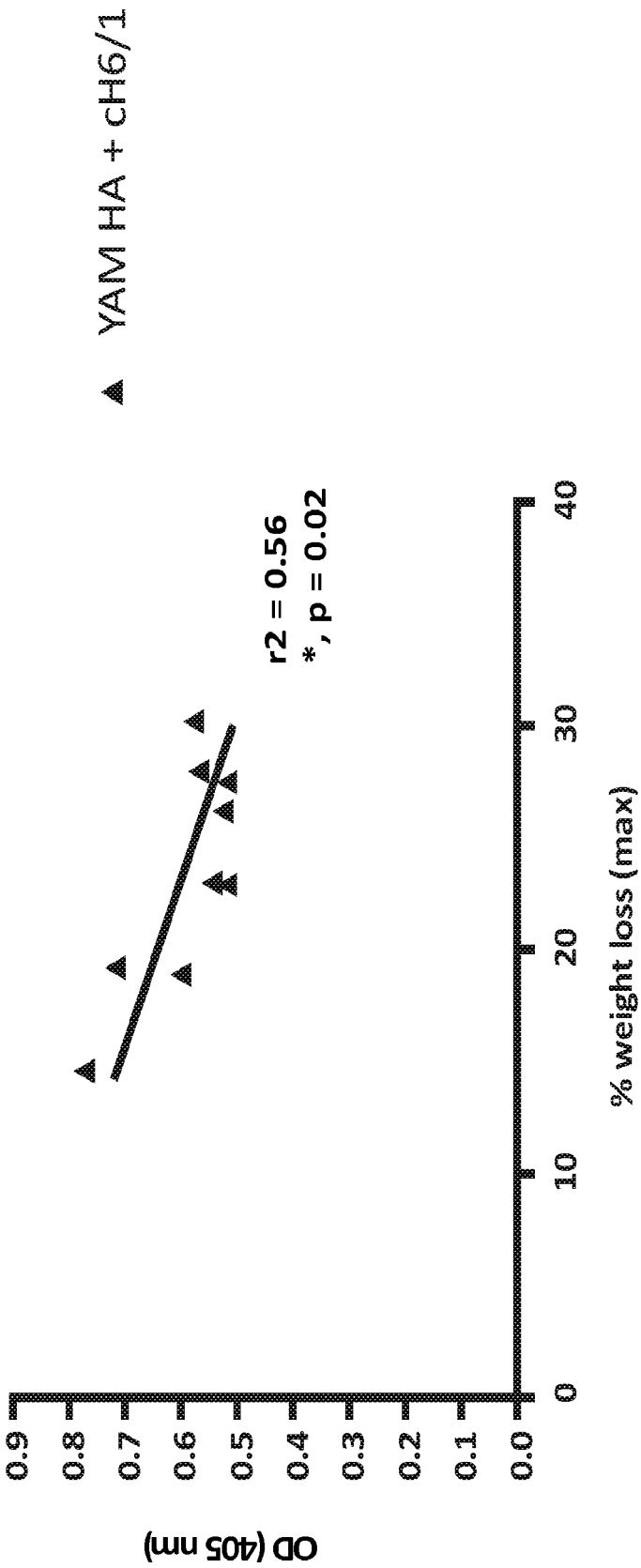

YAM HA + cH6/1
r2 = 0.56
*, p = 0.02
OD (405 nm)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
0
10
20
30
40
% weight loss (max)

Fig. 44C

Fig. 45A

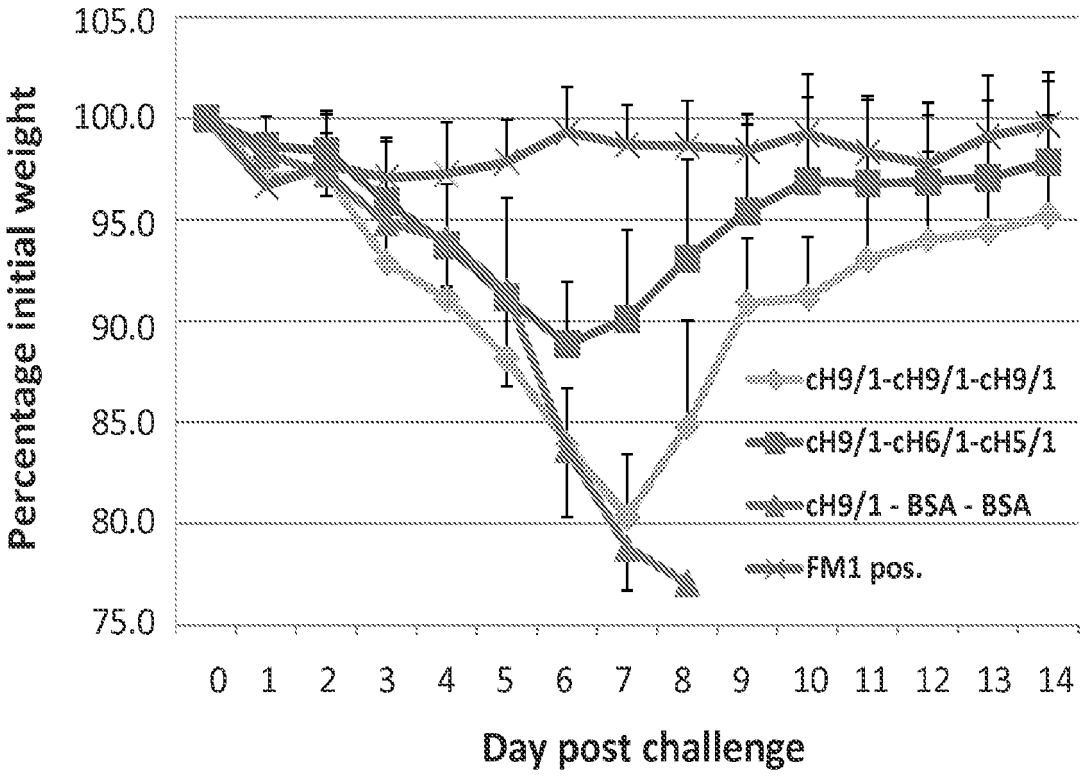


Fig. 45B

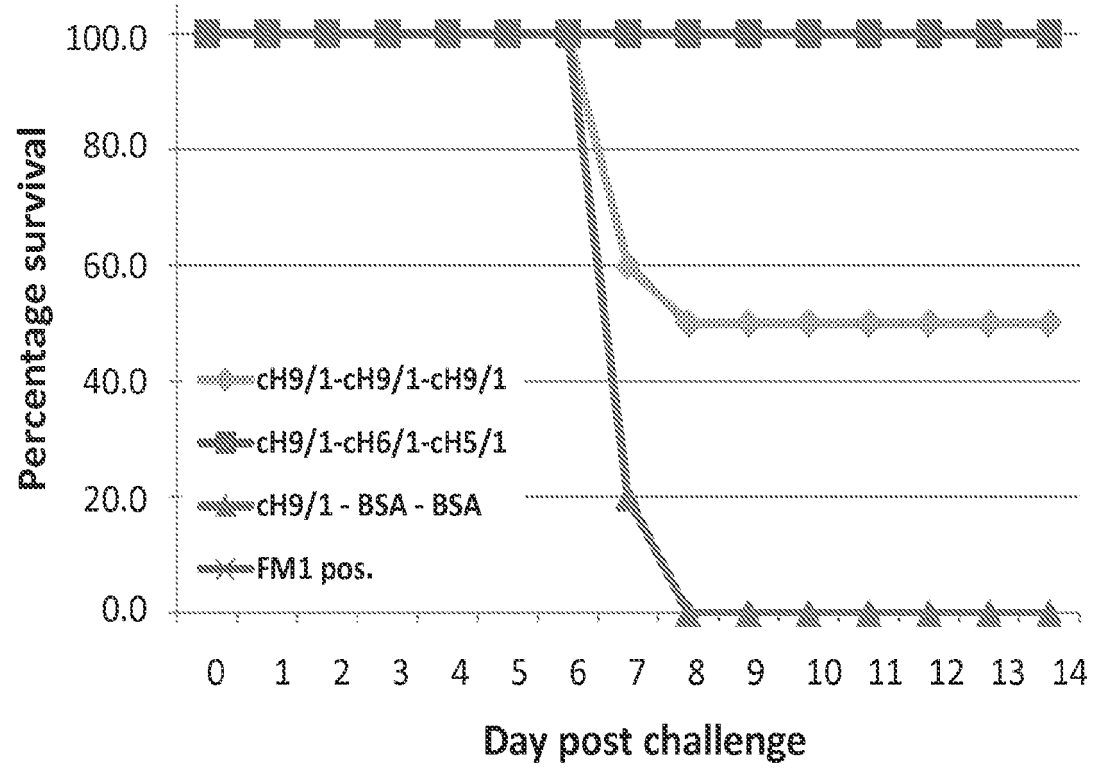


Fig. 45C

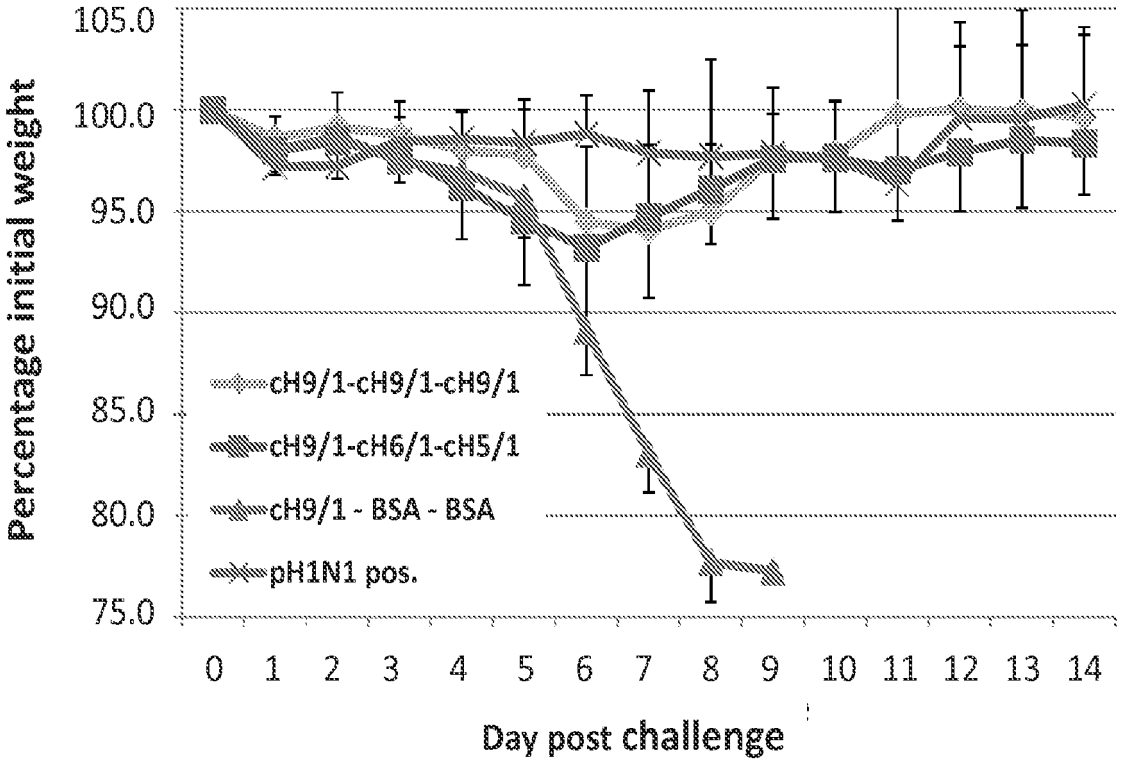


Fig. 45D

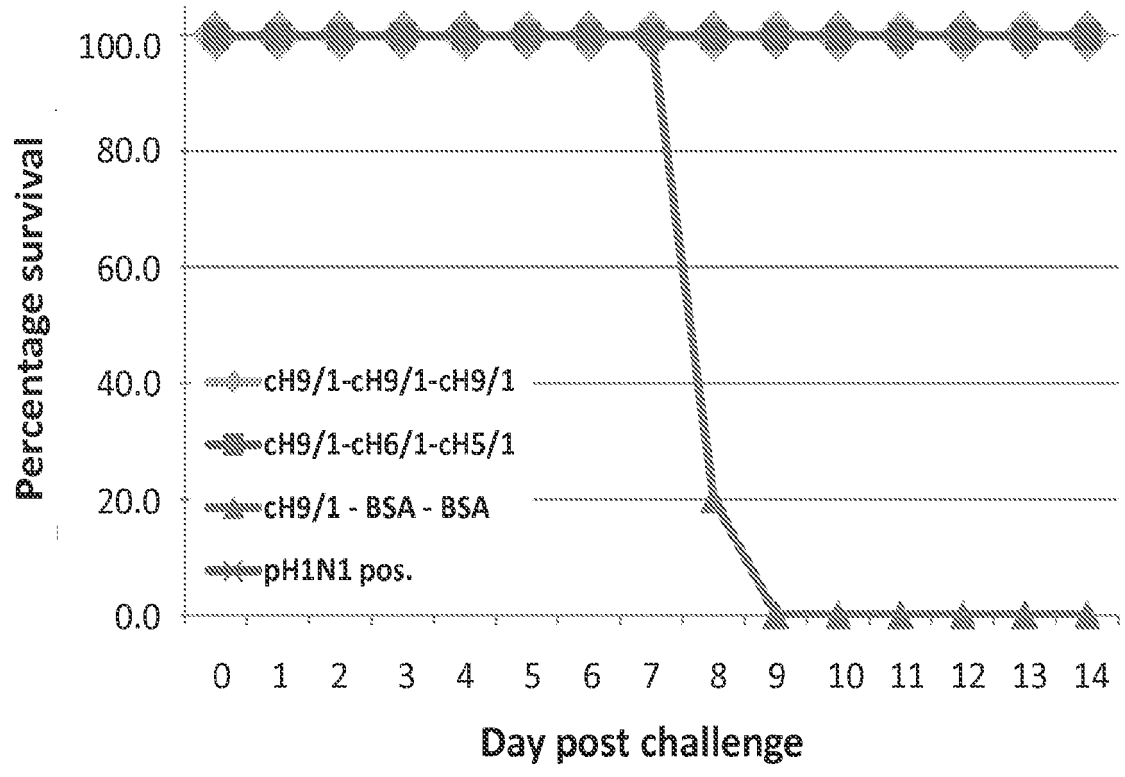


Fig. 45E

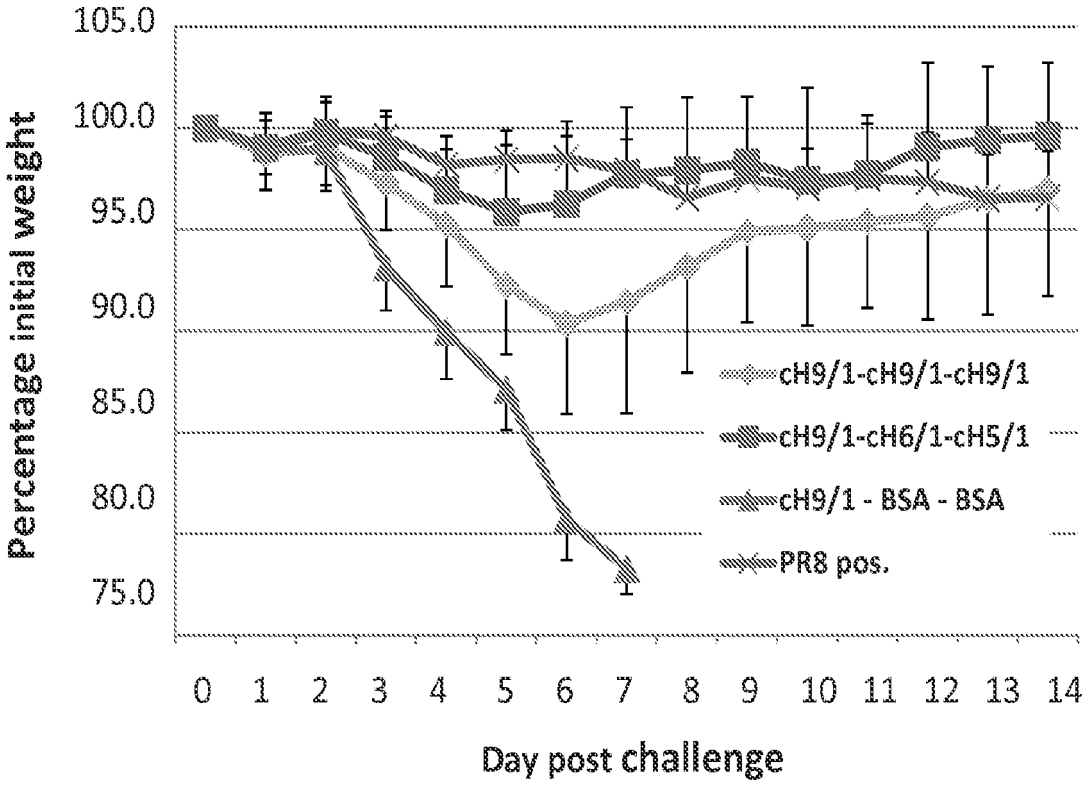
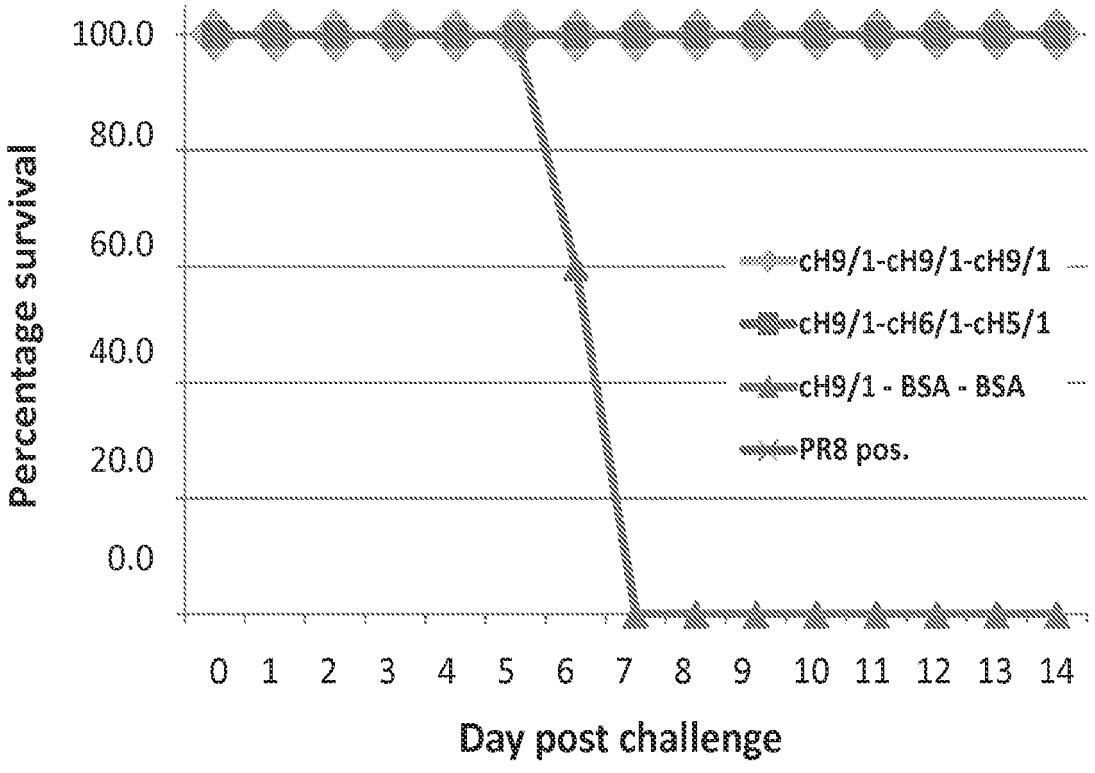


Fig. 45F



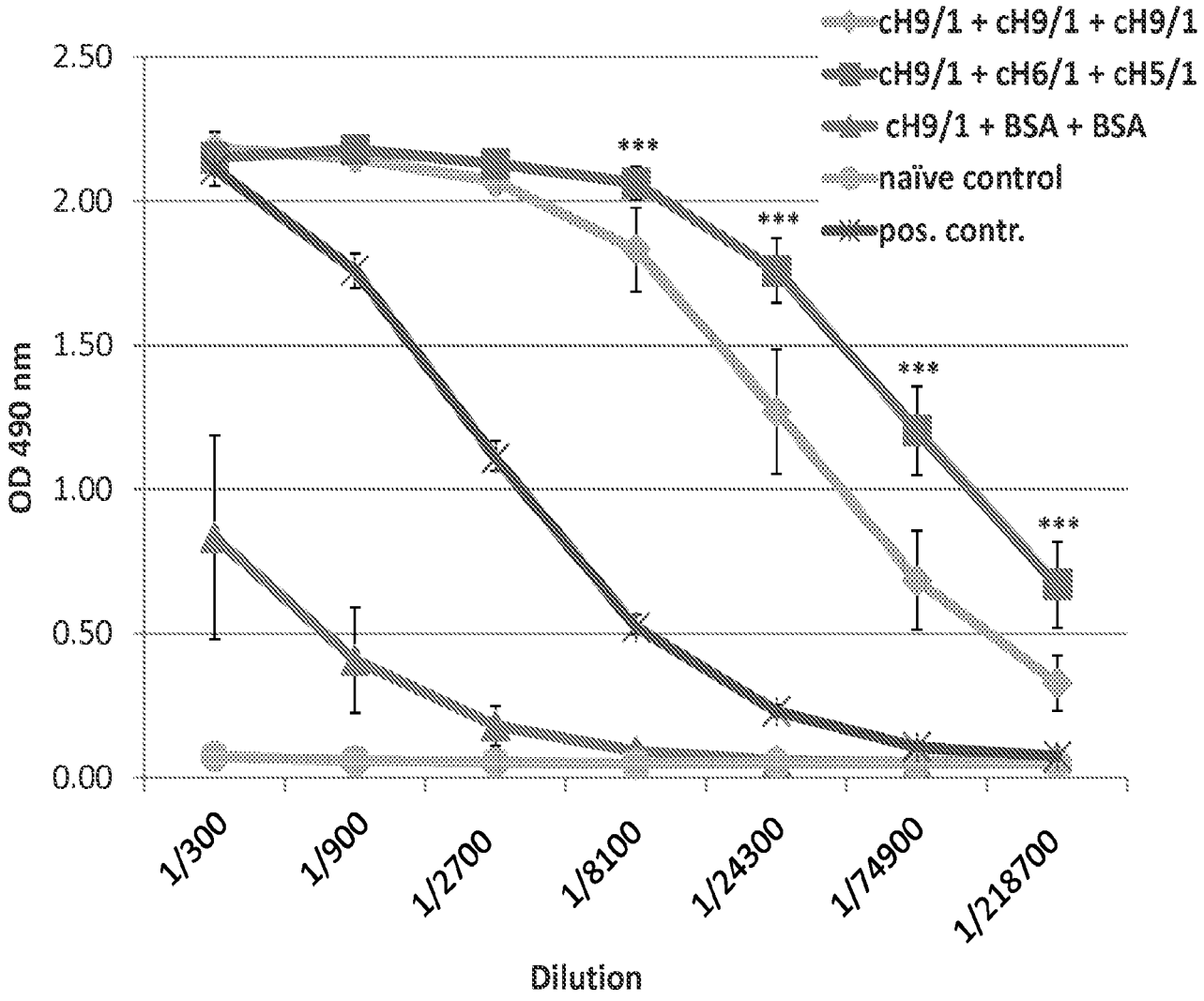

cH9/1 + cH9/1 + cH9/1
cH9/1 + cH6/1 + cH5/1
cH9/1 + BSA + BSA
naïve control
pos. contr.
2.50
2.00
1.50
1.00
0.50
0.00
OD 490 nm
***
***
***
***
1/300
1/900
1/2700
1/8100
1/24300
1/74900
1/218700
Dilution

Fig. 45G

Fig. 45H

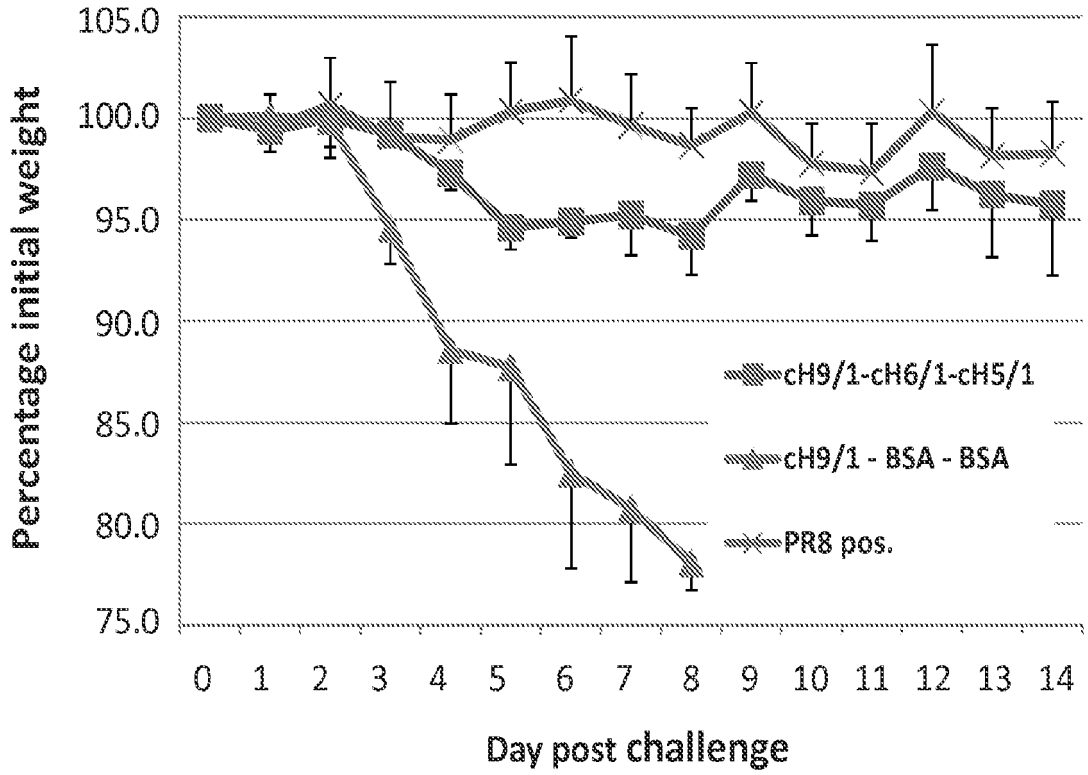
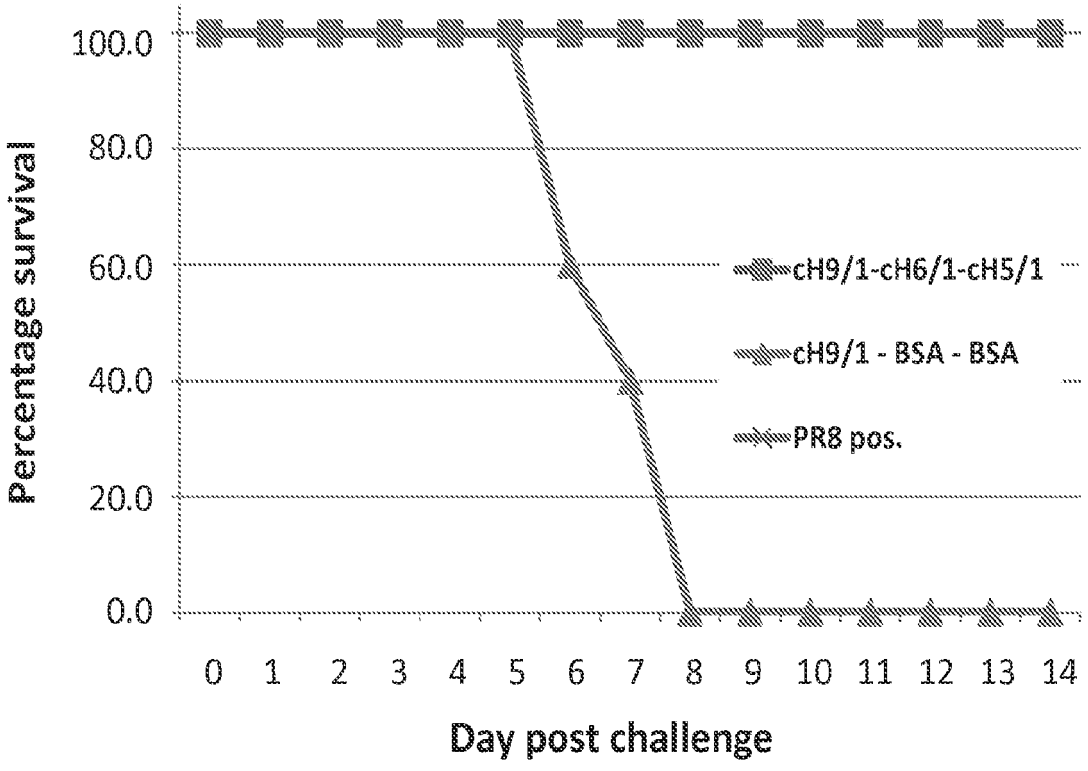


Fig. 45I



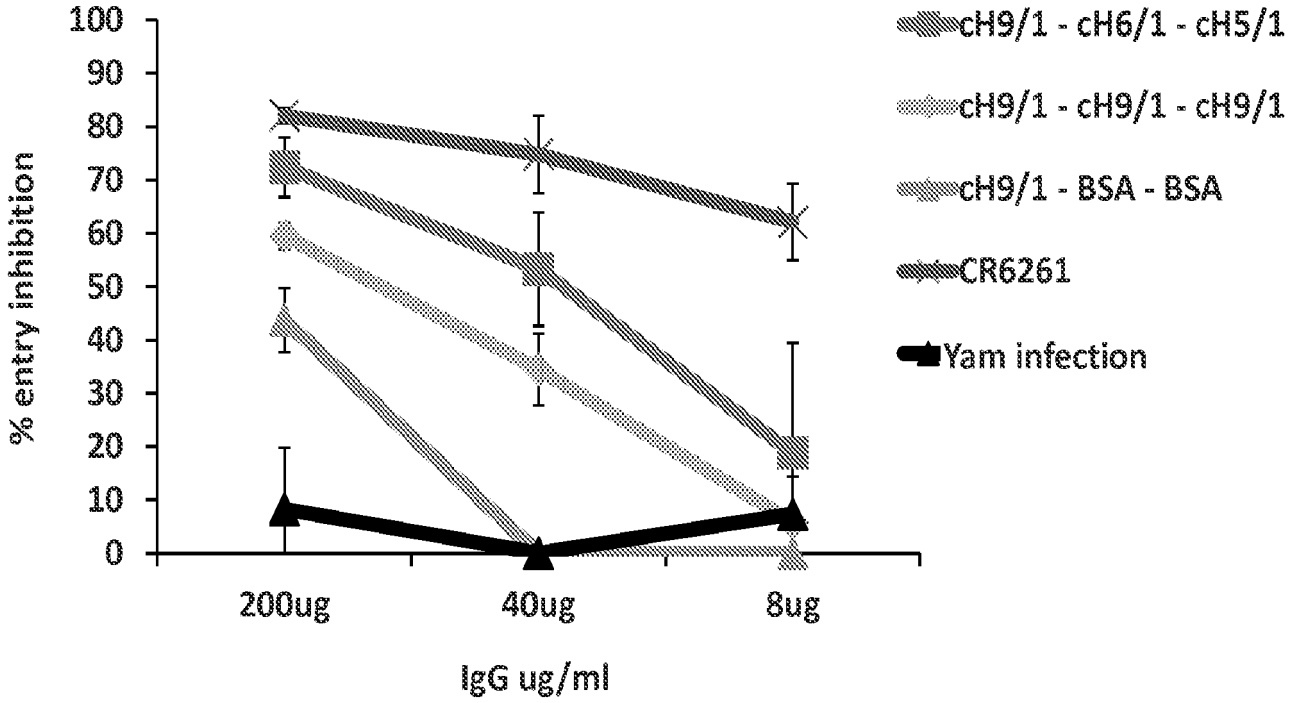

100
90
80
70
60
50
40
30
20
10
0
% entry inhibition
200ug
40ug
8ug
IgG ug/ml
cH9/1 - cH6/1 - cH5/1
cH9/1 - cH9/1 - cH9/1
cH9/1 - BSA - BSA
CR6261
Yam infection

Fig. 45J

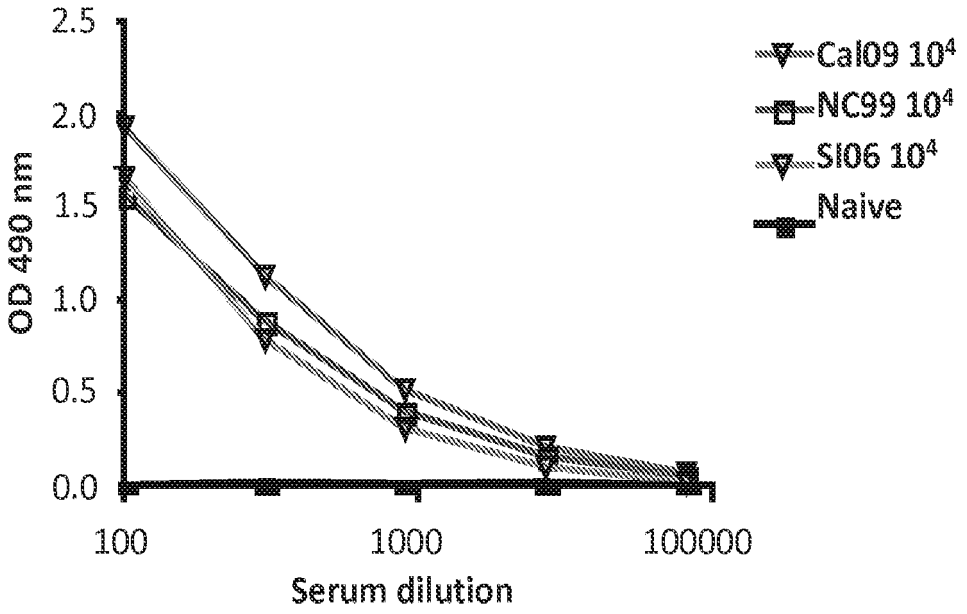

2.5
2.0
1.5
1.0
0.5
0.0
OD 490 nm
100
1000
100000
Serum dilution
Cal09 10^4
NC99 10^4
SI06 10^4
Naive

Fig. 46

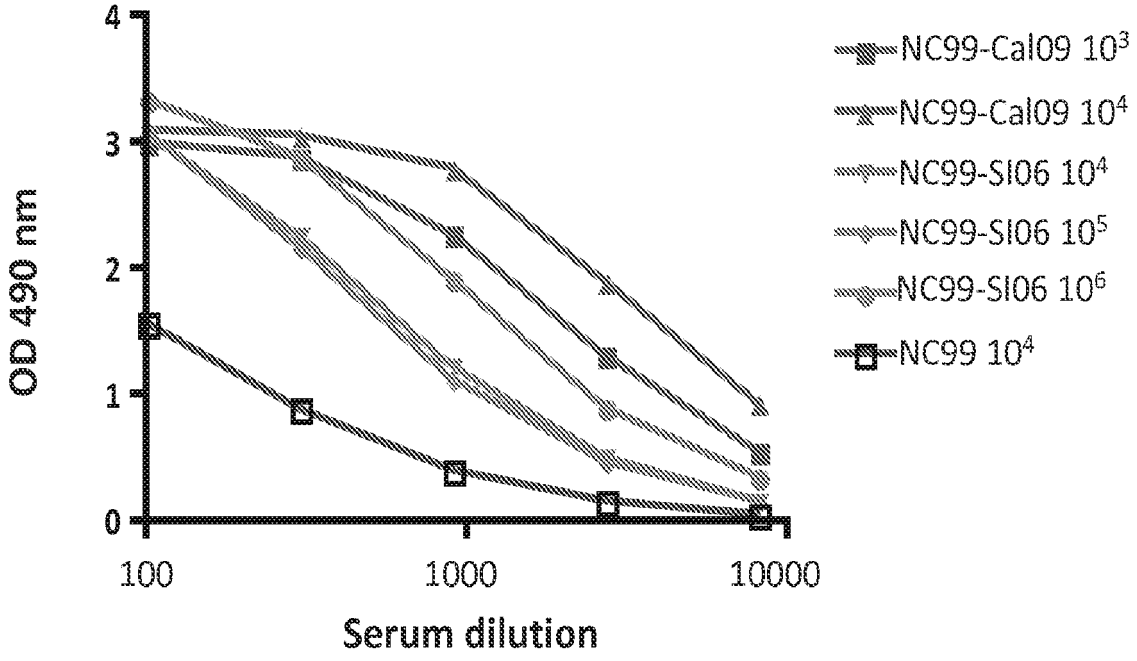

OD 490 nm
4
3
2
1
0
100
1000
10000
Serum dilution
NC99-Cal09 10^3
NC99-Cal09 10^4
NC99-SI06 10^4
NC99-SI06 10^5
NC99-SI06 10^6
NC99 10^4

Fig. 47

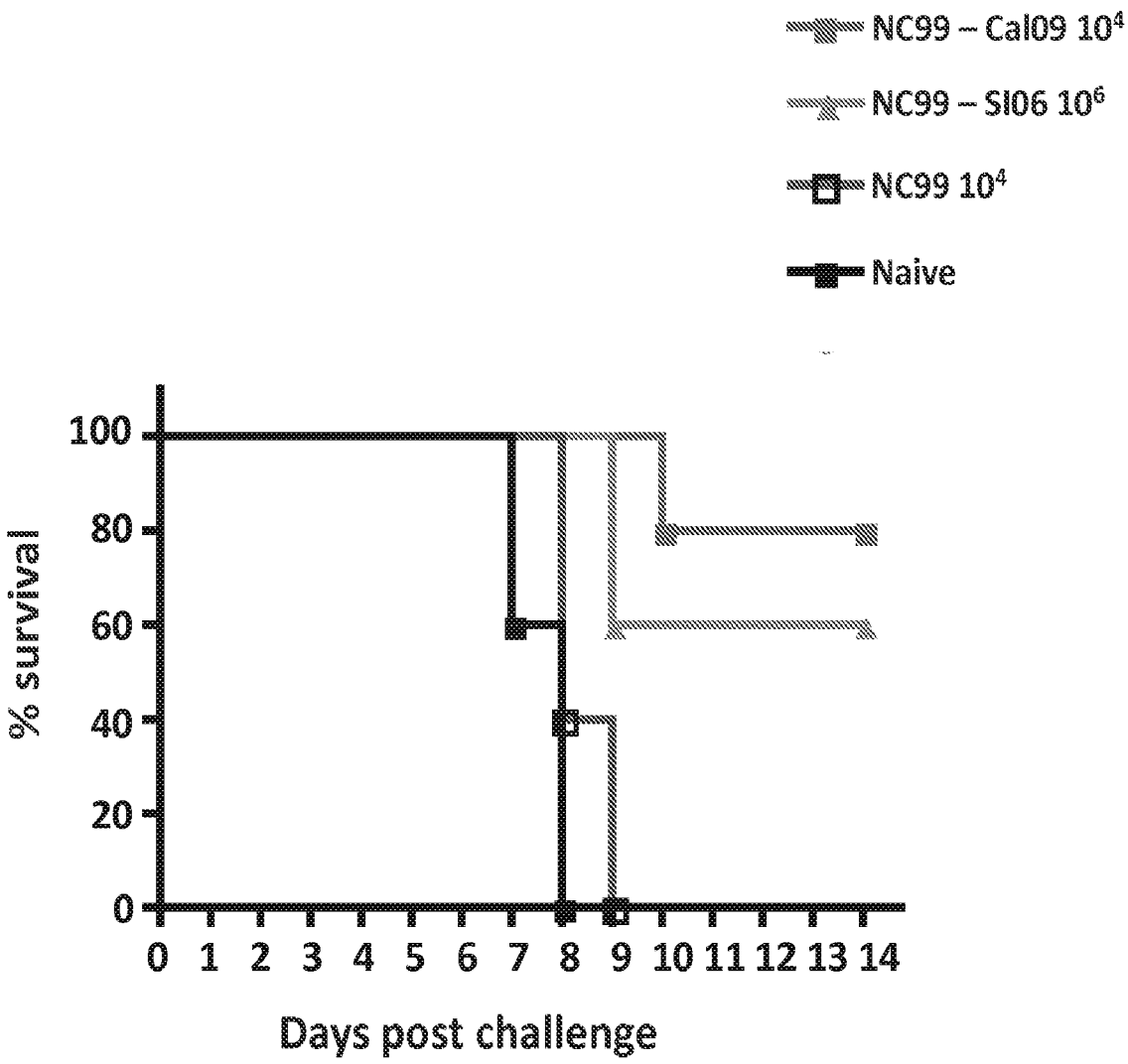
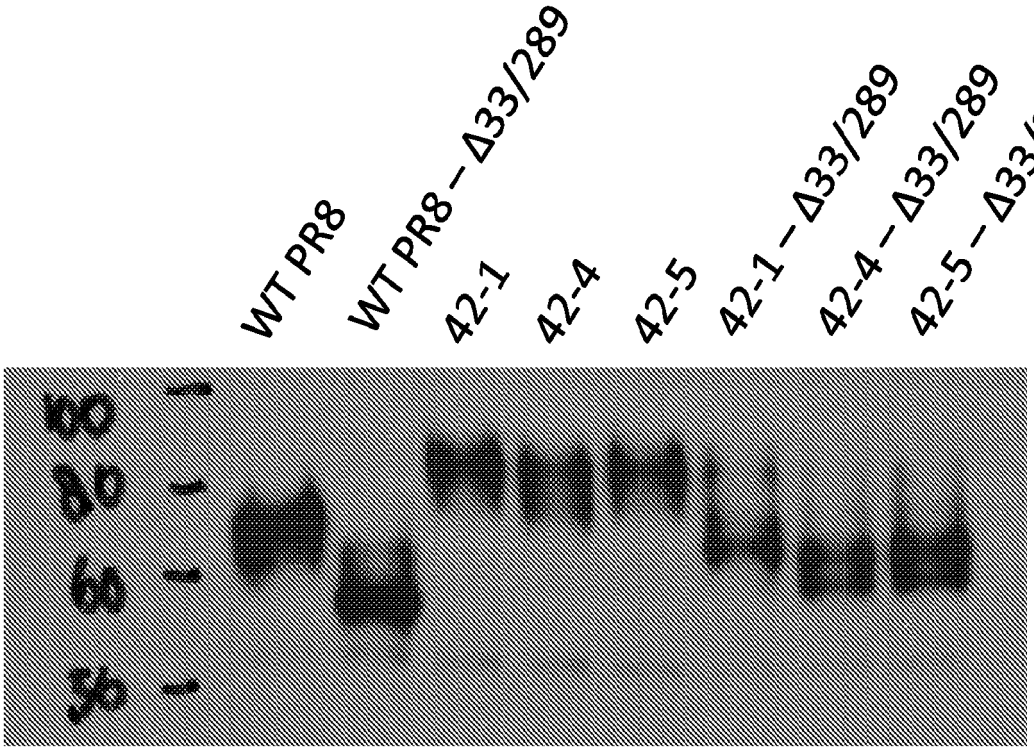

NC99 – Cal09 10^4
NC99 – SI06 10^6
NC99 10^4
Naive
% survival
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days post challenge

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

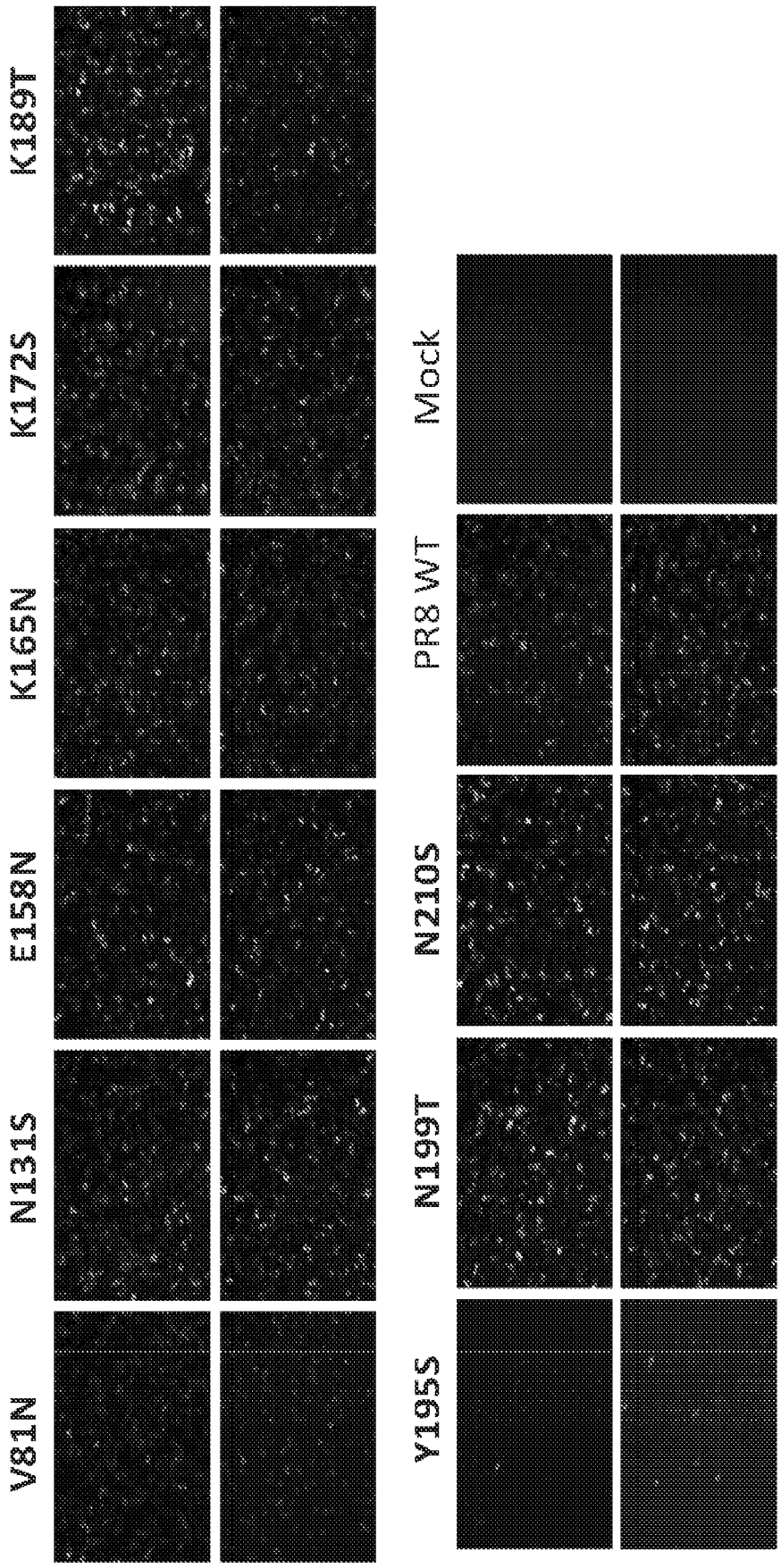

V81N
N131S
E158N
K165N
K172S
K189T
Y195S
N199T
N210S
PR8 WT
Mock
Serum
6F12
Stalk
Serum
6F12
Stalk

Fig. 50A

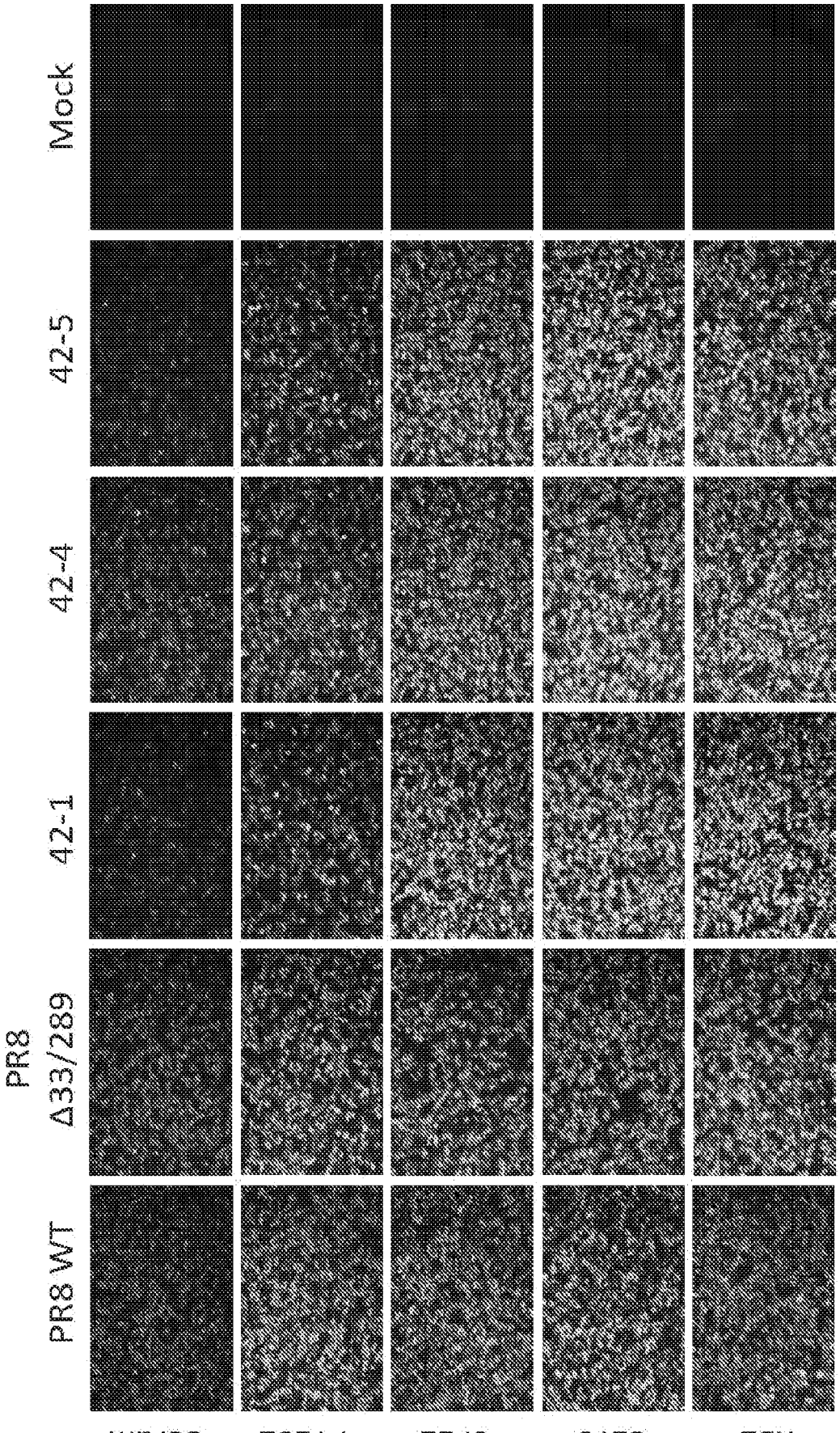

Mock
42-5
42-4
42-1
PR8 Δ33/289
PR8 WT
131/158/165/ 189/172/210
81/131/158/ 189/172/210
81/131/158/165/ 189/172/210
Serum
PY102
6F12
C179
KB2
Head
Stalk

Fig. 50B

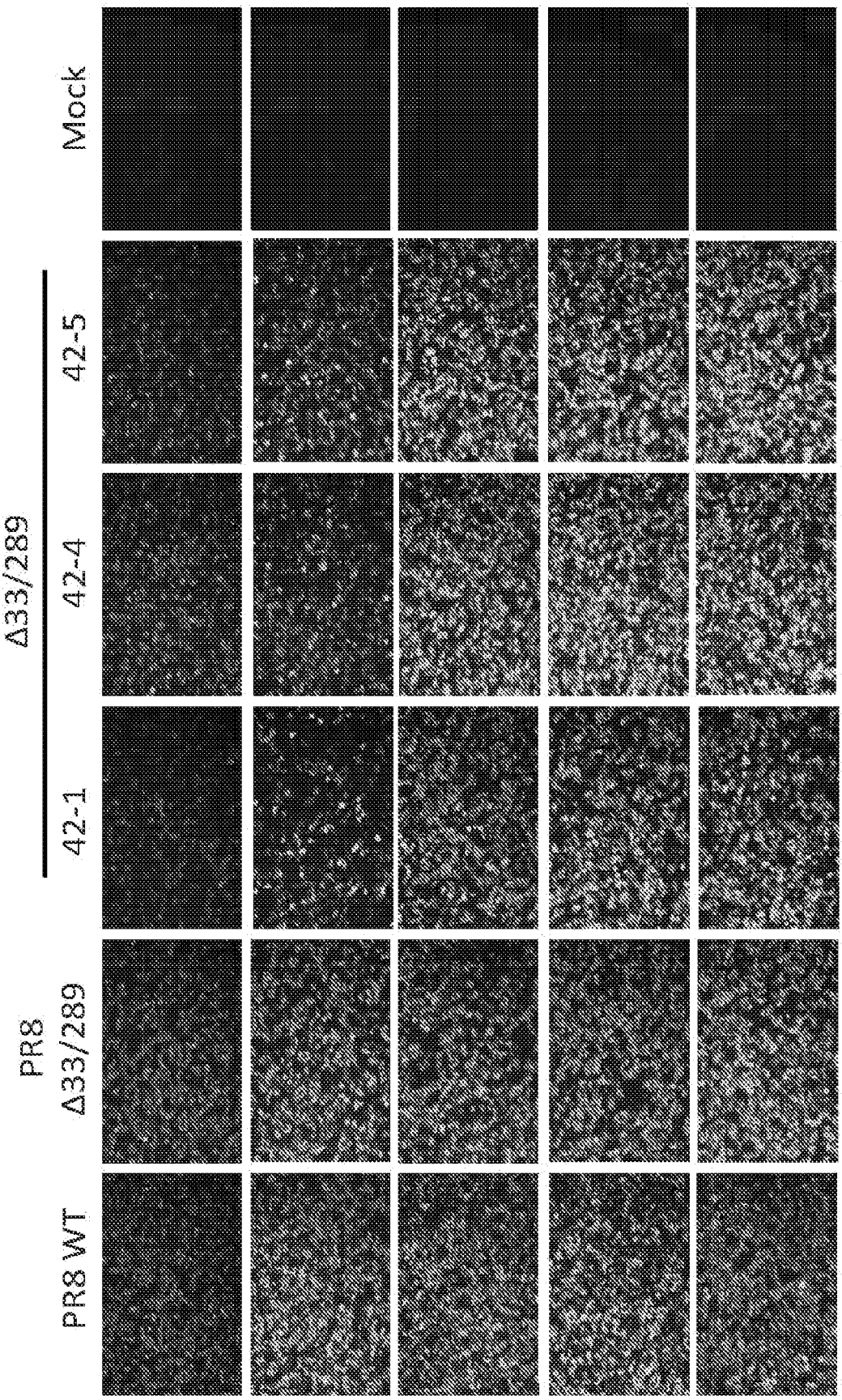

Mock
Δ33/289
42-5
42-4
42-1
PR8
Δ33/289
PR8 WT
131/158/165/
189/172/210
81/131/158/
189/172/210
81/131/158/165/
189/172/210
Serum
PY102
6F12
C179
KB2
Head
Stalk

Fig. 50C

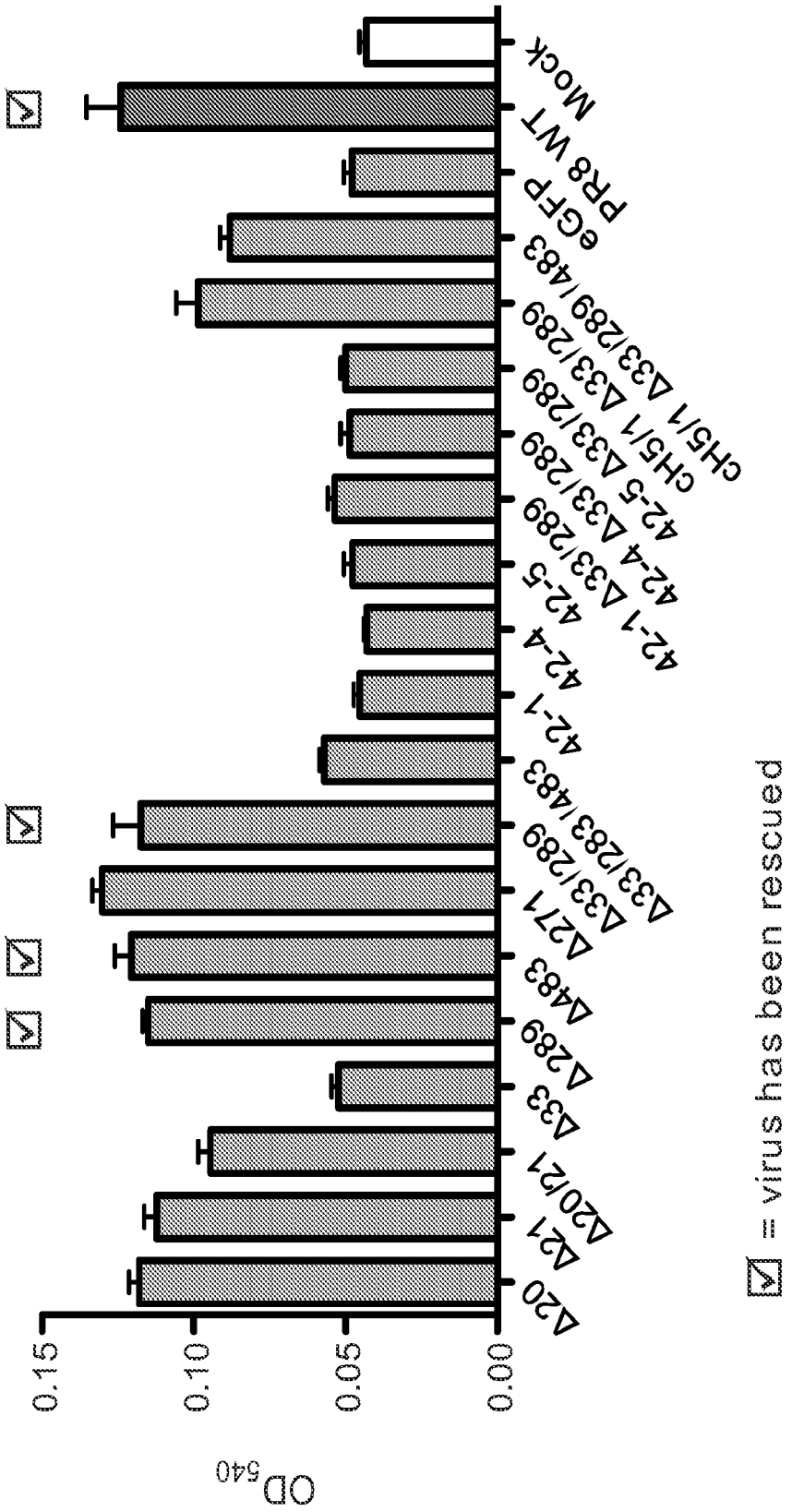

OD540
0.15
0.10
0.05
0.00
Δ20
Δ21
Δ20/21
Δ33
Δ289
Δ483
Δ271
Δ33/289
Δ33/283/483
42-1
42-4
42-5
42-1 Δ33/289
42-4 Δ33/289
42-5 Δ33/289
CH5/1 Δ33/289
CH5/1 Δ33/289/483
eGFP
PR8 WT
Mock
= virus has been rescued

Fig. 51

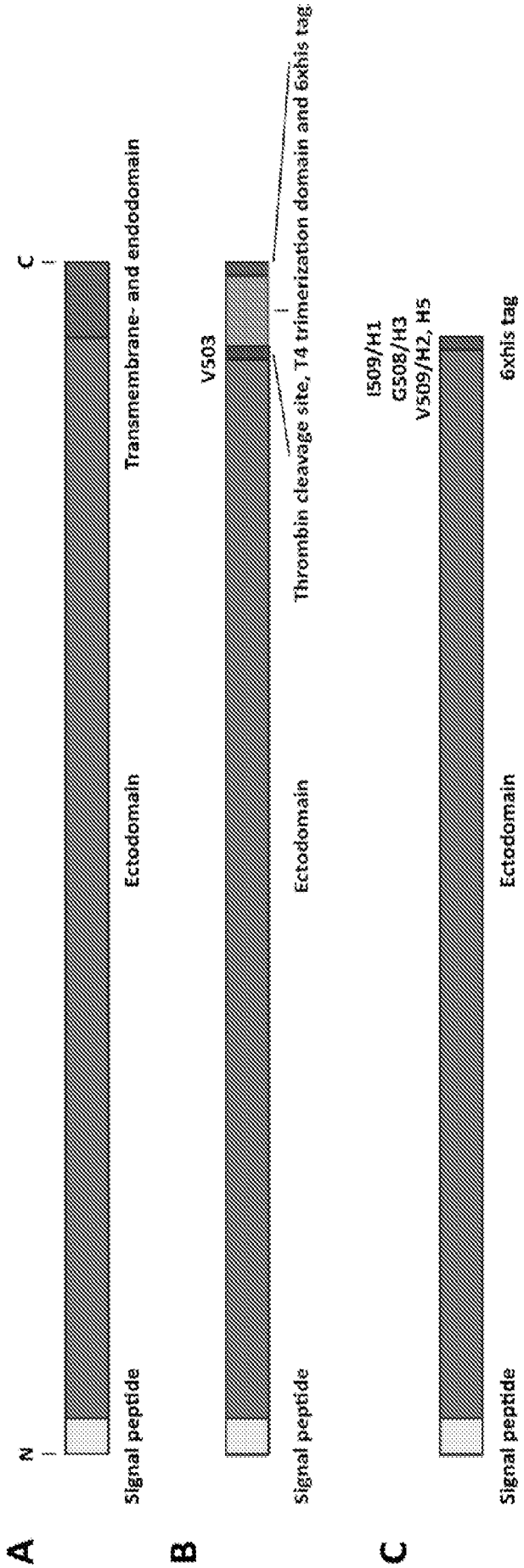

A
N
C
Signal peptide
Ectodomain
Transmembrane- and endodomain
B
V503
Signal peptide
Ectodomain
Thrombin cleavage site, T4 trimerization domain and 6xhis tag
C
I509/H1
G508/H3
V509/H2, H5
Signal peptide
Ectodomain
6xhis tag

FIG. 52A-C

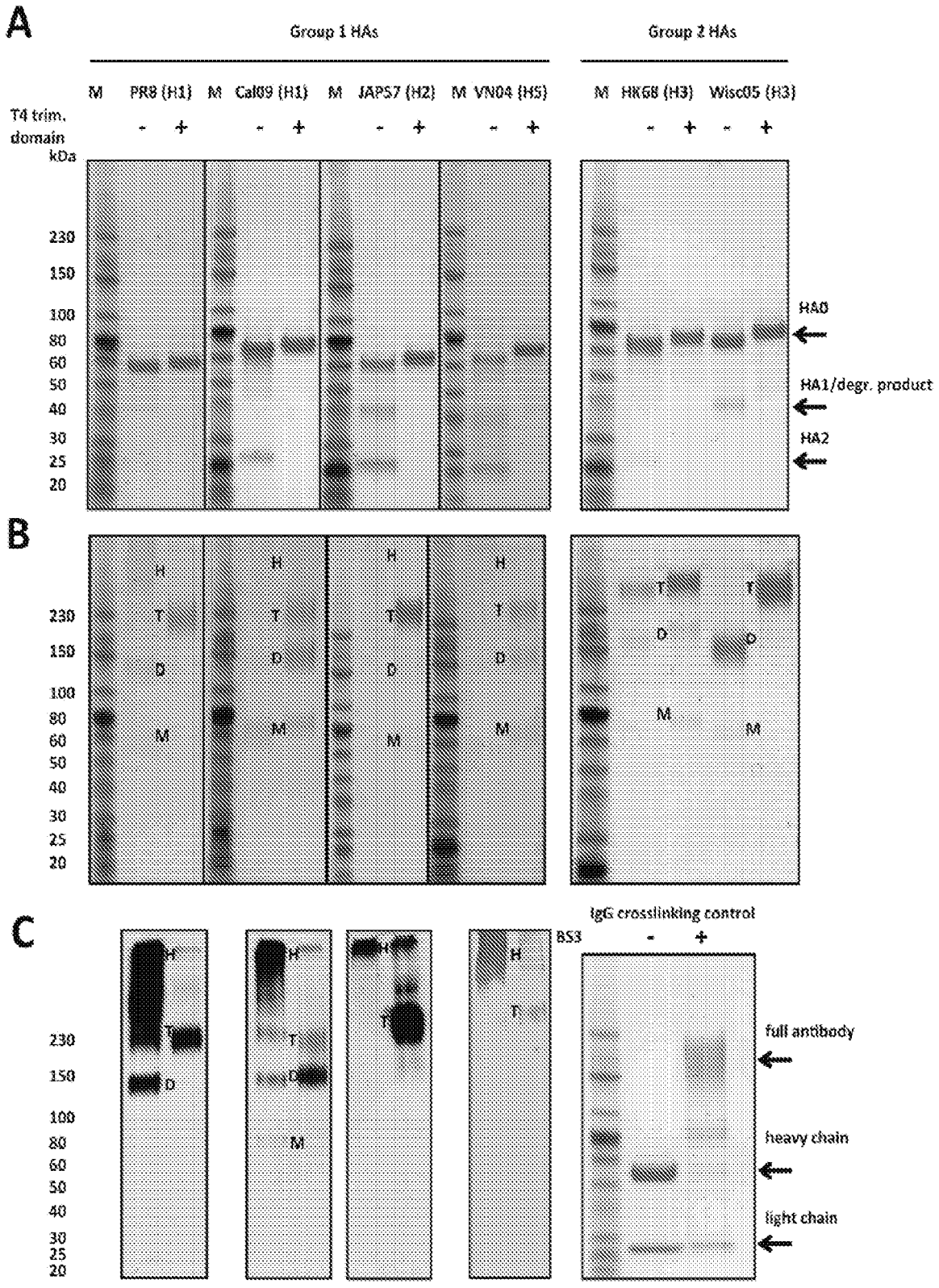

A
Group 1 HAs
Group 2 HAs
M PR8 (H1) M Cal09 (H1) M JAPS7 (H2) M VN04 (H5) M HK68 (H3) Wisc05 (H3)
T4 trim. domain
- + - + - + - + - + - +
kDa
230
150
100
80
60
50
40
30
25
20
HA0
HA1/degr. product
HA2
B
H
T
D
M
C
IgG crosslinking control
BS3 - +
full antibody
heavy chain
light chain

FIG. 53A-C

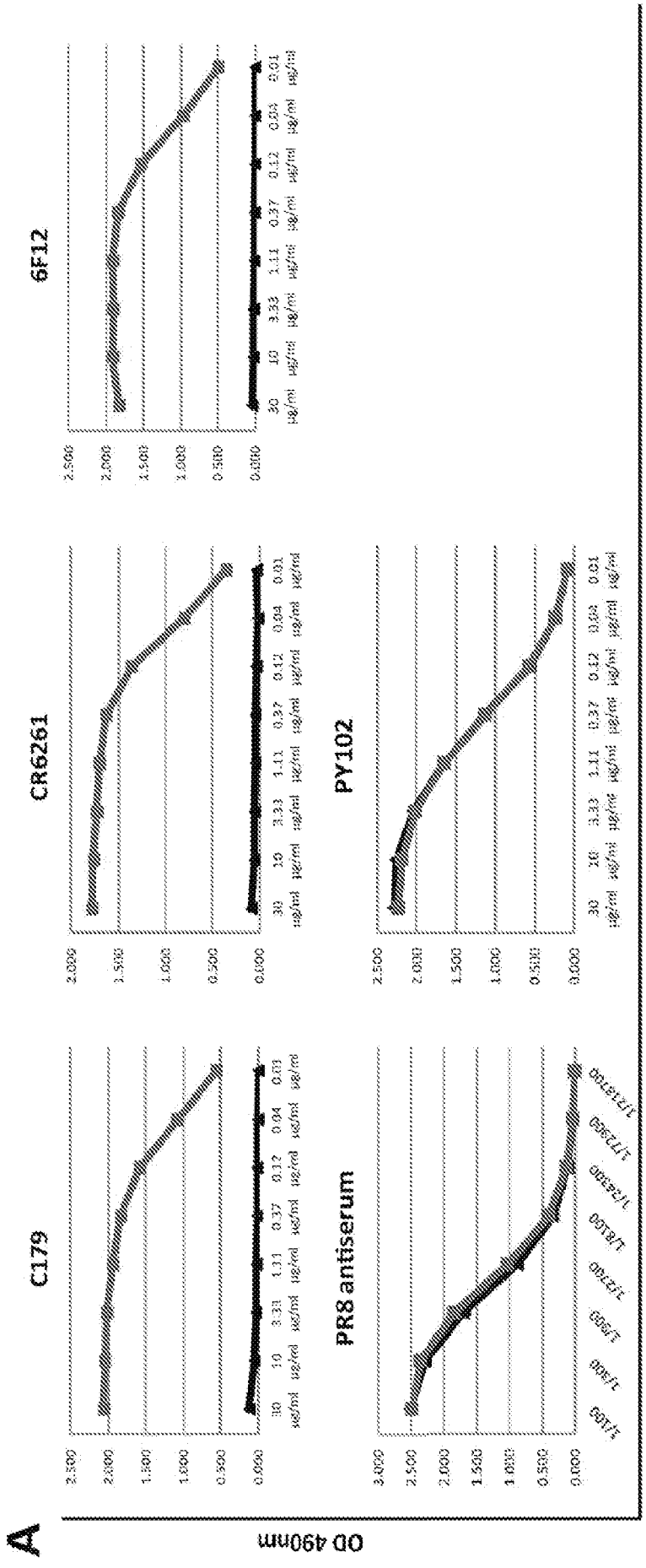

A
OD 490nm
C179
CR6261
6F12
PR8 antiserum
PY102
30 10 3.33 1.11 0.37 0.12 0.04 0.01 μg/ml
1/100
1/300
1/900
1/2700
1/8100
1/24300
1/72900
1/218700

FIG. 54A

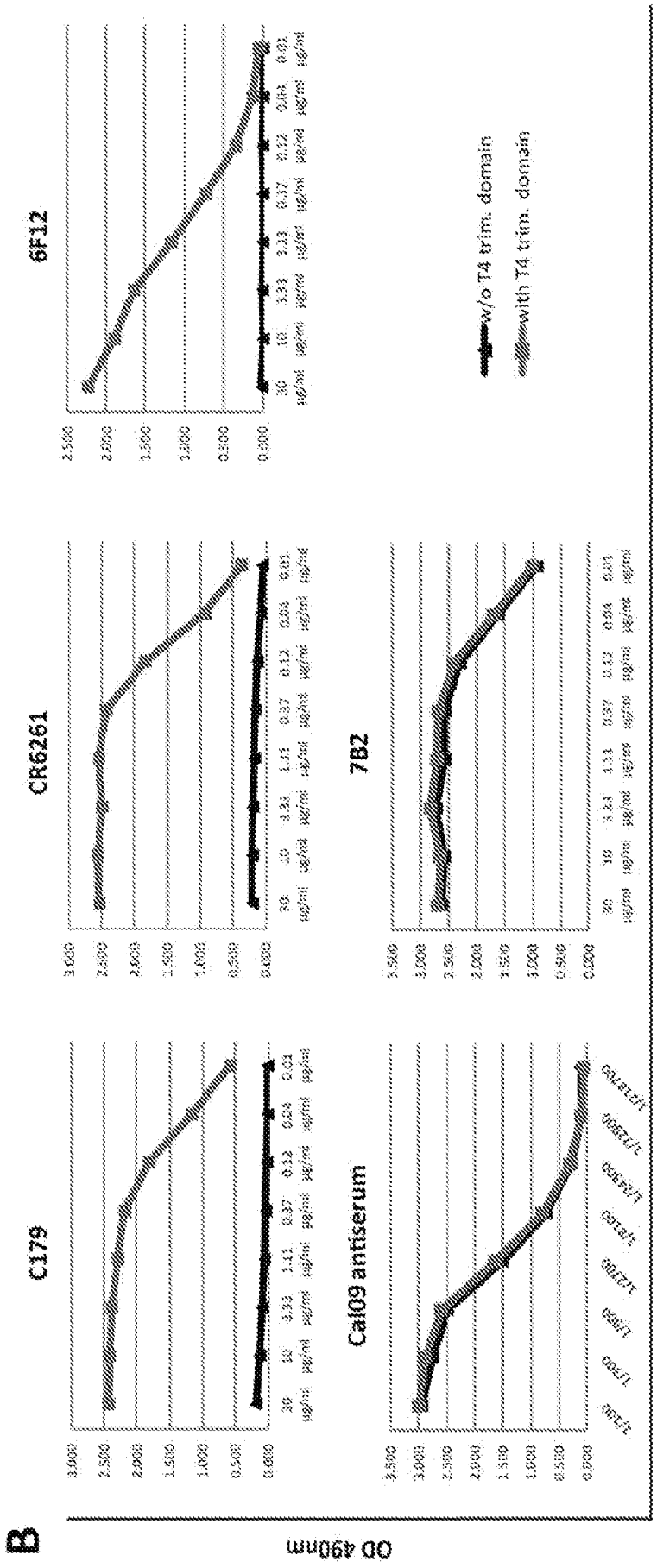

B
OD 490nm
C179
CR6261
6F12
Ca109 antiserum
7B2
w/o T4 trim. domain
with T4 trim. domain
Dilution

FIG. 54B

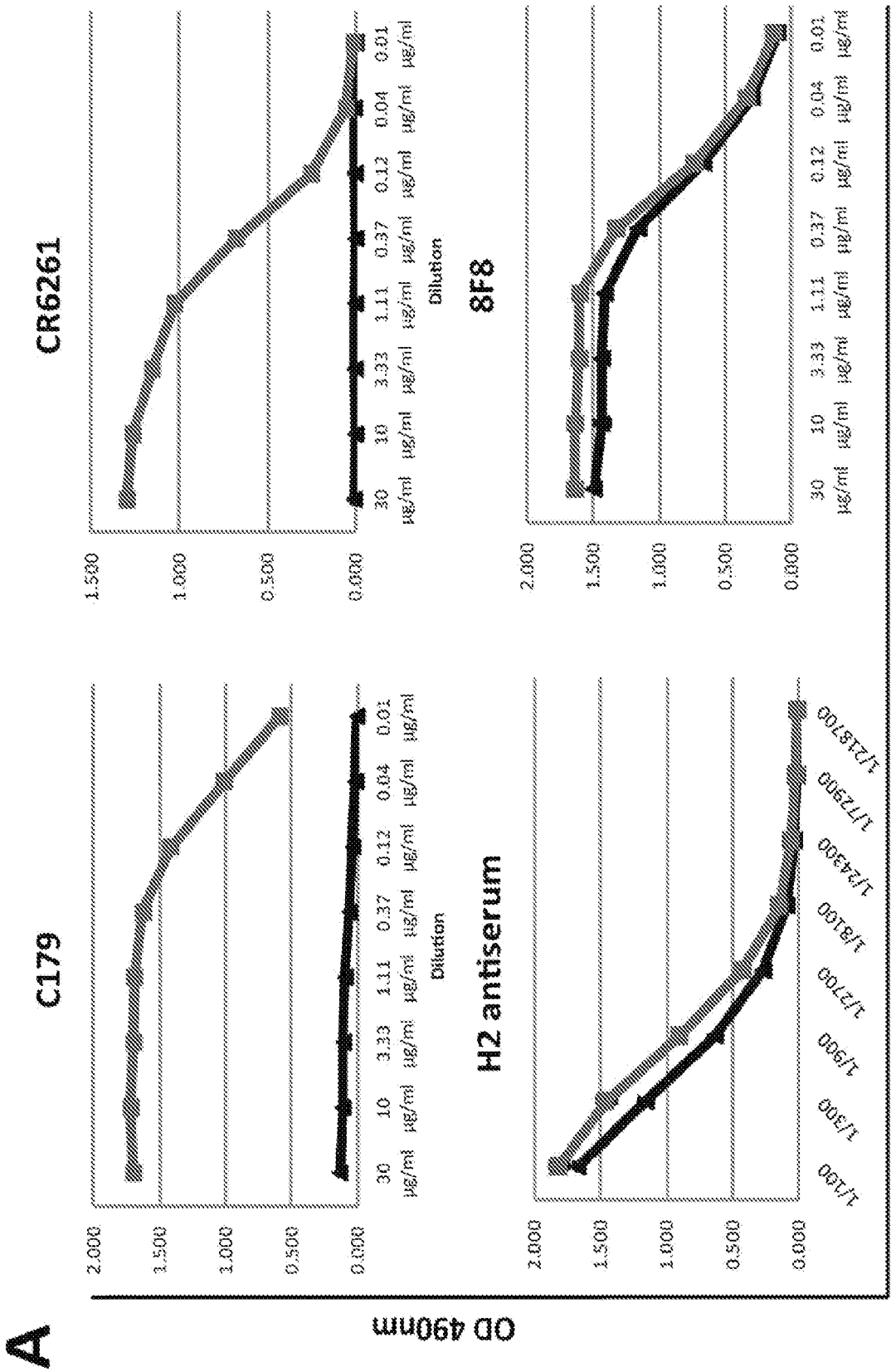

A
OD 490nm
C179
CR6261
H2 antiserum
8F8
2.000
1.500
1.000
0.500
0.000
30 µg/ml
10 µg/ml
3.33 µg/ml
1.11 µg/ml
0.37 µg/ml
0.12 µg/ml
0.04 µg/ml
0.01 µg/ml
Dilution
1/100
1/300
1/900
1/2700
1/8100
1/24300
1/72900
1/218700
Dilution

FIG. 55A

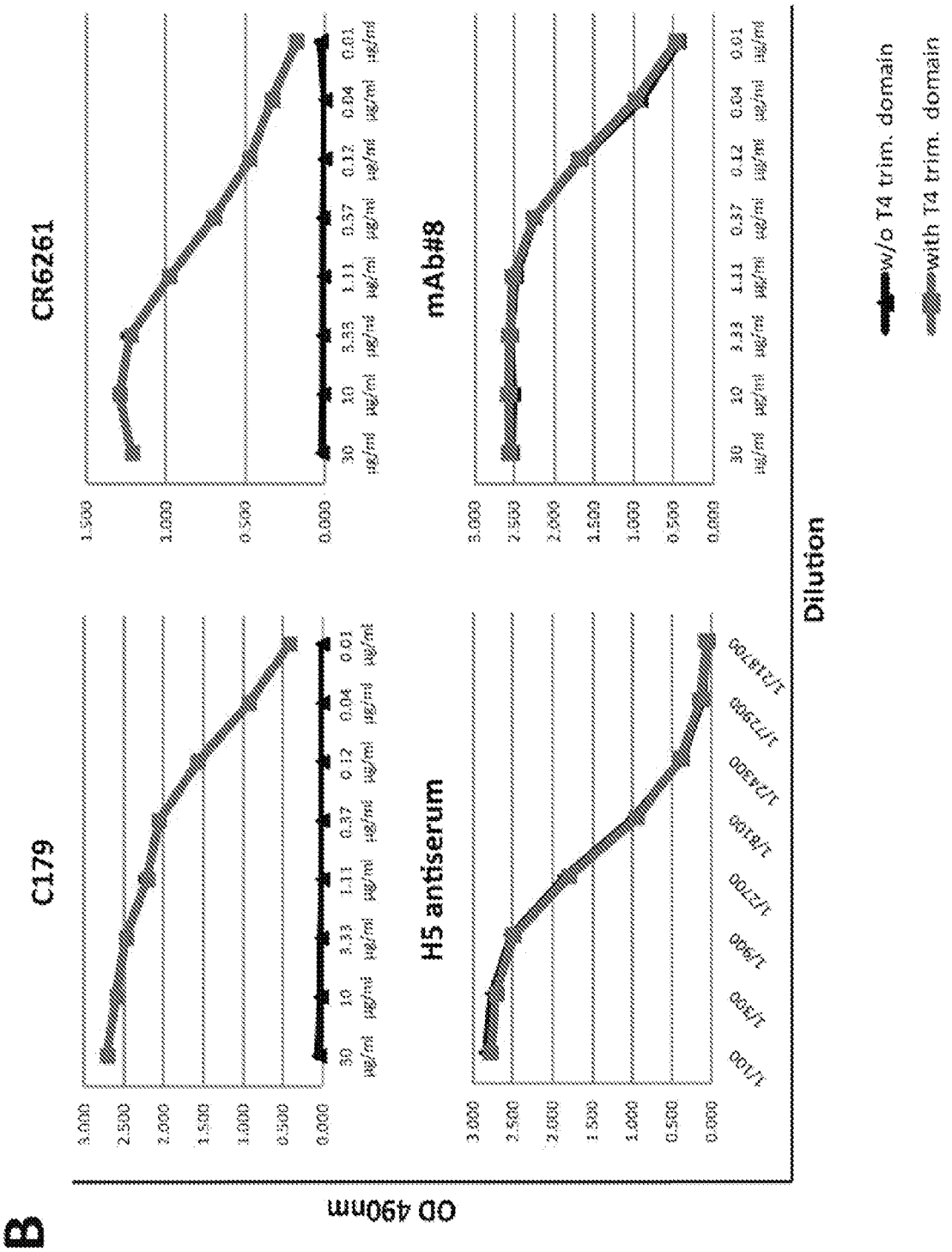

B
C179
CR6261
H5 antiserum
mAb#8
OD 490nm
Dilution
w/o T4 trim. domain
with T4 trim. domain

FIG. 55B

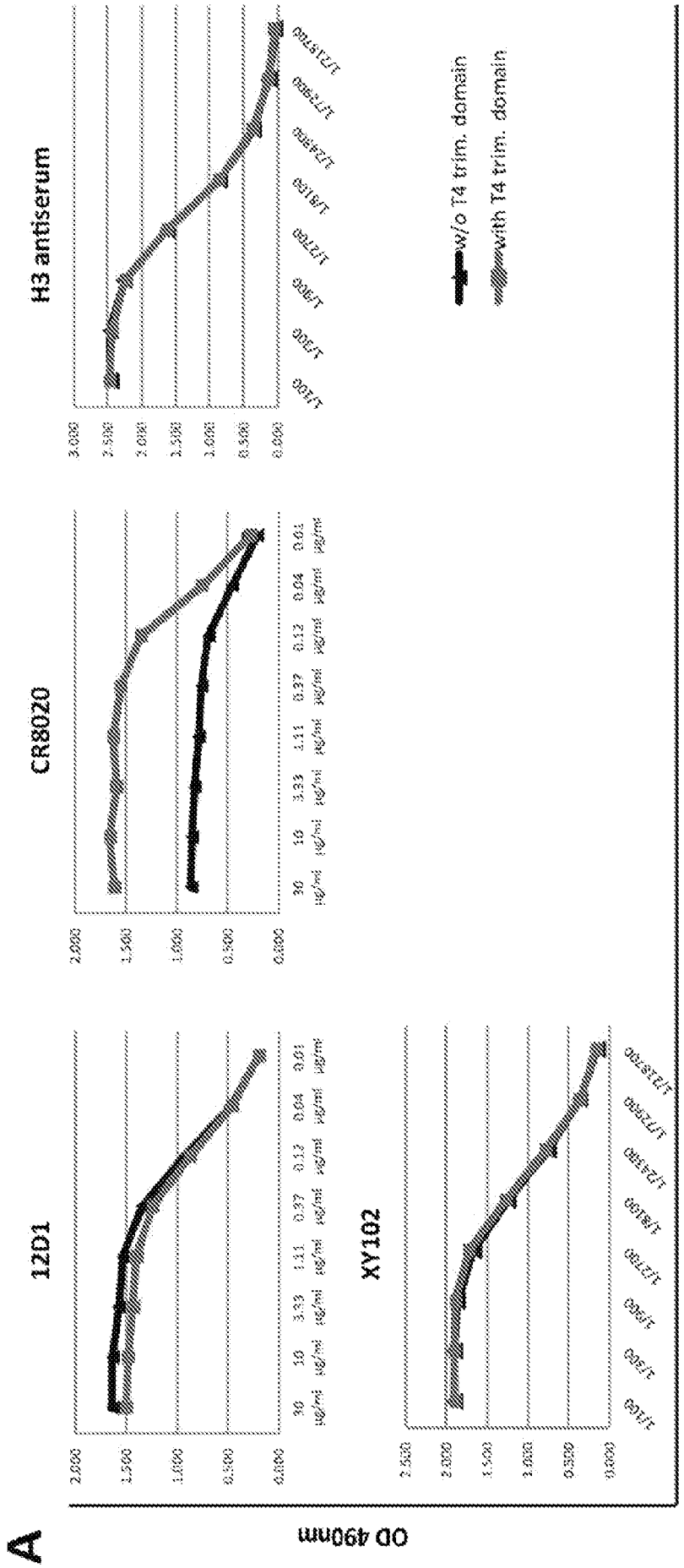

A
OD 490nm
12D1
CR8020
H3 antiserum
XY102
w/o T4 trim. domain
with T4 trim. domain
Dilution

FIG. 56A

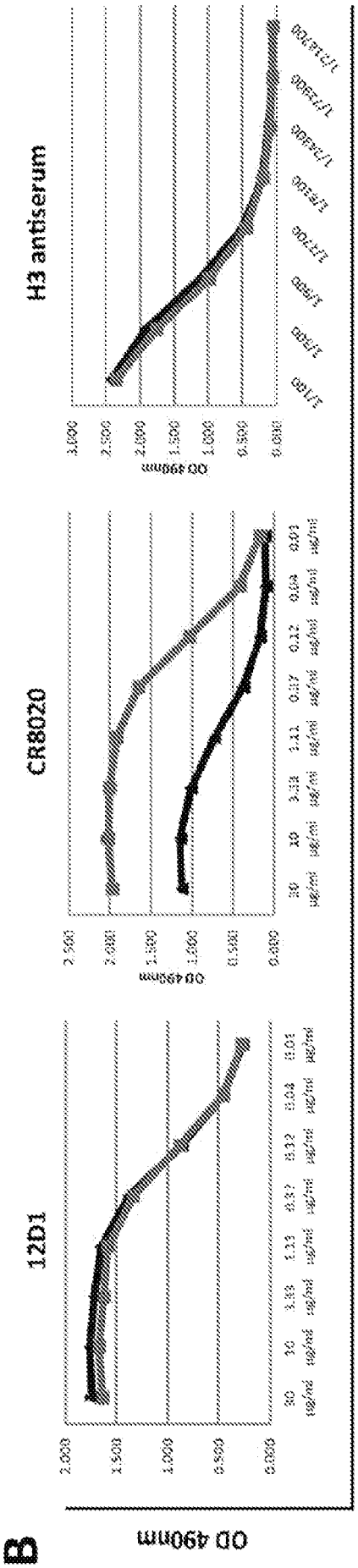


FIG. 56B