

Fig. 1**Human IL-12 subunit alpha (IL-12 p35) precursor sequence** (SEQ ID NO: 1)

MCPARSLLLVATLVLLDHLNLPVATPDPMFCLHHSQNLRAVSNMLQKARQTLEFYPTCTSEEIDHEDITKD
KTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIIYEDLKMYQVEFKTMNAKLMDPKRQIF
LDQNMLAVIDELMQALNFNSETVFPQSSLEEDFYKTIKLCILLHAFRIRAVTIDRVMSYLNAS

Human IL-12 subunit alpha (IL-12 p35) signal sequence (SEQ ID NO: 91)

MCPARSLLLVATLVLLDHLNLPVATPDPMFCLHHSQNLRAVSNMLQKARQTLEFYPTCTSEEIDHEDITKD

Human IL-12 subunit alpha (IL-12 p35) mature form sequence (SEQ ID NO: 2)

RNLPVATPDPMFCLHHSQNLRAVSNMLQKARQTLEFYPTCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
RETSFITNGSCLASRKTSFMMALCLSSIIYEDLKMYQVEFKTMNAKLMDPKRQIFLDQNMLAVIDELMQALNFNSET
VFPQSSLEEDFYKTIKLCILLHAFRIRAVTIDRVMSYLNAS

Human IL-12 subunit beta (IL-12 p40) precursor sequence (SEQ ID NO: 3)

MCHQQLVISWFSVLFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTI
QVKEFGDAGQYTCHKGGEVLSHSLLLLLHKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWLLTTISTDLTF
SVKSSRGSSDPQGVTCGAATLSAERVVRGDNKEYEYSVECEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRD
I IKPDPKPNLQLKPLKNSRQVEVSWEYPTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISV
RAQDRYSSSWSEWASVPCS

Human IL-12 subunit beta (IL-12 p40) signal sequence (SEQ ID NO: 92)

MCHQQLVISWFSVLFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTI

Human IL-12 subunit beta (IL-12 p40) mature form sequence (SEQ ID NO: 4)

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSH
SLLLLLHKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWLLTTISTDLTFSVKSSRGSSDPQGVTCGAATLS
AERVVRGDNKEYEYSVECEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIIKPDPPKNLQLKPLKNSRQVE
VSWEYPTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYSSSWSEWASVPCS

Fig. 2

Human IL-12 receptor beta 1 sequence (SEQ ID NO: 5)

MEPLVTWVPLLFLLSRQGAACRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYECWSWQYEGPTAGVSHFL
RCCLSSGRCCYFAAGSATRLQFSDQAGVSVLYTVTLWVESWARNQTEKSPEVTLQLYNSVKYEPPLGDIKVSCLAGQ
LRMEWETPDNQVGAEVQFRHRTFSSPWKLGDGCPQDDDTESCLCLEMNVAQEFQLRRRQLGSQGSWSKWSPPVCV
PPENPPQPQVRFVSVEQLGQDGRRLTLKEQPTQLELEPGCQGLAPGTEVTYRLQLHMLSCPCAKATRTLHLGKMPY
LSGAAYNAVAVISSNQFGPGLNQTHIPADTHTEPVALNISVGTNGTTMYWPARAQSMTYCIEWQPVGQDGGIATCSL
TAPQDQDPAGMATYSWSRESGAMGQEKCYITIIFASAHPEKLTWSTVLSTYHFGGNASAAAGTPHHVSVKNHSLDSV
SVDWAPSLSTCPGVLKEYVVRCDDESKQVSEHPVQPTETQVTLSSGLRAGVAYTVQVRADTAWLRGVWSQPQRFSI
EVQVSDWLIFASLGSFLSILLVGVGLGYLGLNRAARHLCPPLTPCASSAIEFPGGKETWQWINPVDFQEEASLQEA
LVMEMWDKGERTEPLEKTELEPEGAPELALDTELSLEDGDRCKAKM

Human IL-12 receptor beta 1 extracellular domain (SEQ ID NO: 6)

CRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYECWSWQYEGPTAGVSHFLRCCLSSGRCCYFAAGSATRLQFS
DQAGVSVLYTVTLWVESWARNQTEKSPEVTLQLYNSVKYEPPLGDIKVSCLAGQLRMEWETPDNQVGAEVQFRHRTF
SSPWKLGDGCPQDDDTESCLCLEMNVAQEFQLRRRQLGSQGSWSKWSPPVCVPPENPPQPQVRFVSVEQLGQDGR
RLTLKEQPTQLELEPGCQGLAPGTEVTYRLQLHMLSCPCAKATRTLHLGKMPYLSGAAYNAVAVISSNQFGPGLNQTH
IPADTHTEPVALNISVGTNGTTMYWPARAQSMTYCIEWQPVGQDGGIATCSLTAPQDQDPAGMATYSWSRESGAM
GQEKCYITIIFASAHPEKLTWSTVLSTYHFGGNASAAAGTPHHVSVKNHSLDSVSDWAPSLSTCPGVLKEYVVRCD
DESKQVSEHPVQPTETQVTLSSGLRAGVAYTVQVRADTAWLRGVWSQPQRFSIEVQVSD

Human IL-12 receptor beta 2 sequence (SEQ ID NO: 7)

MAHTFRGCSLAFMFIITWLLIKAKIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFFHYSRRNKLILYKFDRRI
NFHHGHSLSNSQVTGLPLGTTLFVCKLACINSDEIQICGAEIFVGVAPQPNLSCIQKGEQGTACTWGERGRDTHLY
TEYTLQLSGPKNLTWQKQCKDIYCDYLDGFINLTPESPESNFTAKVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIR
IKFQKASVSRTLYWRDEGLVLLNRLRYRPSNSRLWNMVNVTAKGRHDLLDLKPFTEYEFQISSKLHLYKGSWSDW
SESLRAQTPEEEPTGMLDVWYMKRHIDYSRQQISLFWKNLSVSEARGKILHYQVTLQELTGKKAMTQNTGHTSWTT
VIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAGLLAPRQVSANSEGMDNILVTWQPPRKDPSAVQEYVVEWRELH
PGGDTQVPLNWLRSRPNVNSALISENIKSYICYEIRVYALSGDQGGCSSILGNSKHKAPLSGPHINAITEEKGSILI
SWNSIPVQEQMGCLLHYRIYWKERDSNSQPQLCEIPYRVSNHPINSLQPRVTYVLWMTALTAAGESSHGNREFC
LQKGANWMAFVAPISICIAIMVGIFSTHYFQQKFVLLAALRPQWCSREIPDPANSTCAKKYPIAEKTLPLDRLL
IDWPTPEDPEPLVISEVLHQVTPVFRHPPCSNWPQREKGIQGHQASEKDMMSASSPPPPRALQAESRQLVDLYKVL
ESRGSDPKPENPACPWTVLPAGDLPTHGDLPSNIDDLPSHEAPLADSLLEELEPQHISLSVFPSSSLHPLTFSCGDK
LTLDQLKMRCDLSML

Human IL-12 receptor beta 2 extracellular domain (SEQ ID NO: 8)

KIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFFHYSRRNKLILYKFDRRINFHHGHSLSNSQVTGLPLGTTLFV
CKLACINSDEIQICGAEIFVGVAPQPNLSCIQKGEQGTACTWGERGRDTHLYTEYTLQLSGPKNLTWQKQCKDIY
CDYLDGFINLTPESPESNFTAKVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIRIKFQKASVSRTLYWRDEGLVLL
NRLRYRPSNSRLWNMVNVTAKGRHDLLDLKPFTEYEFQISSKLHLYKGSWSDWSESLRAQTPEEEPTGMLDVWYMK
RHIDYSRQQISLFWKNLSVSEARGKILHYQVTLQELTGKKAMTQNTGHTSWTTVIPRTGNWAVAVSAANSKGSSLP
TRINIMNLCEAGLLAPRQVSANSEGMDNILVTWQPPRKDPSAVQEYVVEWRELHPGGDTQVPLNWLRSRPNVNSALI
SENIKSYICYEIRVYALSGDQGGCSSILGNSKHKAPLSGPHINAITEEKGSILISWNSIPVQEQMGCLLHYRIYWKE
RDSNSQPQLCEIPYRVSNHPINSLQPRVTYVLWMTALTAAGESSHGNREFCLQKAN

Fig. 3

Mouse IL-12 subunit alpha (IL-12 p35) precursor sequence (SEQ ID NO: 9)

MCQSRYLFLATLALLNHLSLARVIPVSGPARCLSQSRNLLKTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTST
LKTCLPLELHKNESCLATRETSSTTRGSCLPQKTSIMMTLCIGSIYEDLKMYQTEFQAINAALQNNHQQII LDKG
MLVAIDELMQSLNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSA

Mouse IL-12 subunit alpha (IL-12 p35) mature form sequence (SEQ ID NO: 10)

RVIPVSGPARCLSQSRNLLKTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETS
STTRGSCLPQKTSIMMTLCIGSIYEDLKMYQTEFQAINAALQNNHQQII LDKGMLVAIDELMQSLNHNGETLRQK
PPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSA

Mouse IL-12 subunit beta (IL-12 p40) precursor sequence (SEQ ID NO: 11)

MCPQKLTISWFAIVLLVSPLMAMWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQDRHGVIGSGKTLTI
TVKEFLDAGQYTCHKGETLSHSHLLLHKKENGWSTEILKNFKNKTFKCEAPNYSGRFTCSWLQVRNMDLKFNK
SSSSPDSRAVTCGMASLSAEKVTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQONKYENYSTSFIRDII
KPDPPKNLQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLEKTSTEVQCKGG
NVCVQAQDRYNNSSCSKWACVPCRVRS

Mouse IL-12 subunit beta (IL-12 p40) mature form sequence (SEQ ID NO: 12)

MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQDRHGVIGSGKTLTITVKEFLDAGQYTCHKGETLSH
SHLLLHKKENGWSTEILKNFKNKTFKCEAPNYSGRFTCSWLQVRNMDLKFNKSSSSPDSRAVTCGMASLSAEK
VTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQONKYENYSTSFIRDIIKPDPPKNLQMKPLKNSQVEVSW
EYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLEKTSTEVQCKGGNVCVQAQDRYNNSSCSKWACV
PCRVRS

Fig. 4

Mouse IL-12 receptor beta 1 sequence (SEQ ID NO: 13)

MDMMGLAGTSKHITFLLLCQLGASGPGDGCCVEKTSFPEGASGSPLGPRNLS CYRVSKTDYECSWQYDGPEDNVSHV
 LWCCFVPPNHTHTGQERCRYFSSGPDRTVQFWEQDGI PVLSKVNFWVESRLGNRTMKSQKISQYLYNWTKTTPPLGH
 IKVSQSHRQLRMDWNVSEEGA EVQFRRRMPTTNWTLGDCGPQVNSGSGVLGDIRGSMSESCLCPSENMAQEIQIRR
 RRLSSGAPGGPWSDWSMPVCPPEVLPAKIKFLVEPLNQGGRRRLTMQGQSPQLAVPEGCRGRPGAQVKKHLVLV
 RMLSCRCQAQTSKTVPLGKKLNLSGATYDLNVLAKTRFGRSTIQKWHLPAQELTETRALNVSVGGNMTSMQWAAQAP
 GTTYCLEWQPPWFQHRNHTHTCLIVPEEEDPAKMVTHSWSSKPTLEQEECYRITVFASKNPKNPMLWATVLSSYYFGG
 NASRAGTPRHVSVRNQTGDSVSVEWTASQLSTCPGVLTQYVVRCEAEDGAWESEWLVPPTKTQVTL DGLRSRVMYKV
 QVRADTARLPGAWSHPQRFSEFVQISRLSII FASLGSFASVLLVGS LGY IGLNRAAWHLCPPLPTPCGSTAVEFP GS
 QGKQAWQWCNPEDFPEVLYPRDALVVEMPGDRGDGTES PQAAPECALDTRRPLETQRQRQVQALSEARRRLGLAREDC
 PRGDLAHVTLP LLLGGVLTQ GASVLDLWRTHKTAEPGPPTLGQEA

Mouse IL-12 receptor beta 1 extracellular domain (SEQ ID NO: 14)

QLGASGPGDGCCVEKTSFPEGASGSPLGPRNLS CYRVSKTDYECSWQYDGPEDNVSHV LWCCFVPPNHTHTGQERCR
 YFSSGPDRTVQFWEQDGI PVLSKVNFWVESRLGNRTMKSQKISQYLYNWTKTTPPLGH IKVSQSHRQLRMDWNVSEE
 AGAEVQFRRRMPTTNWTLGDCGPQVNSGSGVLGDIRGSMSESCLCPSENMAQEIQIRRRRLSSGAPGGPWSDWSMP
 VCPPEVLPAKIKFLVEPLNQGGRRRLTMQGQSPQLAVPEGCRGRPGAQVKKHLVLV RMLSCRCQAQTSKTVPLGK
 KLNLSGATYDLNVLAKTRFGRSTIQKWHLPAQELTETRALNVSVGGNMTSMQWAAQAPGT TYCLEWQPPWFQHRNHTH
 CTLIVPEEEDPAKMVTHSWSSKPTLEQEECYRITVFASKNPKNPMLWATVLSSYYFGGNASRAGTPRHVSVRNQTGD
 SVSVEWTASQLSTCPGVLTQYVVRCEAEDGAWESEWLVPPTKTQVTL DGLRSRVMYKVQVRADTARLPGAWSHPQRF
 SFEVQIS

Mouse IL-12 receptor beta 2 sequence (SEQ ID NO: 15)

MAQTVRECSLALLFLFMWLLIKANIDVCKLGTVTVPAPVPIPLGSAANISCSLNPQGC SHYPSSNELILLKFVNDV
 LVENLHGKKVHDHTGHSSTFQVTNLSLGMTLFVCKLNCNSNSQKKPPVPVCGVEISVGVAPEPPQNISCVQEGENGTV
 ACSWNSGKVTYLKTNYTLQLSGPNNLT CQKQCFSDNRQNCNRLDLGINLSPDLAESRFIVRVTAINDLGNSSSLPHT
 FTFLDIVIPLPPWDIRINFLNASGSRGTLQWEDEGQVVLNQLRYQPLNSTSWNMVNATNAKGKYDLRDLRPFT EYEF
 QISSKLHLSGGSWSNWSESLRTRTPEEEPVGILDIWYMKQDIDYDRQQISLFWKSLNPSEARGKILHYQVTLQEVTK
 KTTLQNTTRHTSWTRV IPRTGAWTASVSAANSKGASAPTHINIVDL CGTGLLAPHQVSAKSENMDNILVTWQPPKKA
 DSAVREYIVEWRALQPGSITKFPPHWRIPPDNMSALISENIKPYICYEIRVHALSESQGGCSSIRGDSKHKAPVSG
 PHITAITTEKKERLFI SWTHIPFPEQRGCILHYRIYWKERDSTAQPELCEIQYRRSQNSHPISSLQPRVTYVLWMTAV
 TAAGESPQGNEREFCPQGGKANWKA FVISSICIAIITVGTFSIRYFRQKAFTLLSTLKPQWYSRTIPDPANSTWVKKY
 PILEEKIQLPTDNLMAWPTPEEPEPLIHEVLYHMI PVVRQPYF FKRQGFQGYSTSKQDAMYIANPQATGTLTAE
 TRQLVNLKYVLES RDPDSKLANLTSPLTVTPVNYLPSHEGYLPSNIEDLSPHEADPTDSFDLEHQHISLSIFASSSL
 RPLIFGGERLTLDRLKMGYDSLMSNEA

Mouse IL-12 receptor beta 2 extracellular domain (SEQ ID NO: 16)

NIDVCKLGTVTVPAPVPIPLGSAANISCSLNPQGC SHYPSSNELILLKFVNDV LVENLHGKKVHDHTGHSSTFQVT
 NLSLGMTLFVCKLNCNSNSQKKPPVPVCGVEISVGVAPEPPQNISCVQEGENGTVACSWNSGKVTYLKTNYTLQLSGP
 NNLTCQKQCFSDNRQNCNRLDLGINLSPDLAESRFIVRVTAINDLGNSSSLPHTFTFLDIVIPLPPWDIRINFLNAS
 GSRGTLQWEDEGQVVLNQLRYQPLNSTSWNMVNATNAKGKYDLRDLRPFT EYEFQISSKLHLSGGSWSNWSESLRTR
 TPEEEPVGILDIWYMKQDIDYDRQQISLFWKSLNPSEARGKILHYQVTLQEVTKKTTLQNTTRHTSWTRV IPRTGAW
 TASVSAANSKGASAPTHINIVDL CGTGLLAPHQVSAKSENMDNILVTWQPPKADS AVREYIVEWRALQPGSITKF
 PHWLRIPPDNMSALISENIKPYICYEIRVHALSESQGGCSSIRGDSKHKAPVSGPHITAITTEKKERLFI SWTHIPFP
 EQRGCILHYRIYWKERDSTAQPELCEIQYRRSQNSHPISSLQPRVTYVLWMTAVTAAGESPQGNEREFCPQGGKAN

Fig. 5**Human IL-12 subunit alpha (IL-12 p35) mature form sequence with Y40P/K168A mutations**

RNLPVATPDPGMFCLHHSQNLLRAVSNMLQKARQTLEFPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
RETSFITNGSCLASRKTSFMMALCLSSYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSET
VPQKSSLEEPDFYATKIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 17)

Human IL-12 subunit alpha (IL-12 p35) mature form sequence with Y40P/K170A mutations

RNLPVATPDPGMFCLHHSQNLLRAVSNMLQKARQTLEFPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
RETSFITNGSCLASRKTSFMMALCLSSYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSET
VPQKSSLEEPDFYKTAIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 18)

Human IL-12 subunit alpha (IL-12 p35) mature form sequence with Y40S/K170T mutations

RNLPVATPDPGMFCLHHSQNLLRAVSNMLQKARQTLEFSPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
RETSFITNGSCLASRKTSFMMALCLSSYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSET
VPQKSSLEEPDFYKTTIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 19)

Human IL-12 subunit alpha (IL-12 p35) mature form sequence with Y40S/K170A mutations

RNLPVATPDPGMFCLHHSQNLLRAVSNMLQKARQTLEFSPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
RETSFITNGSCLASRKTSFMMALCLSSYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSET
VPQKSSLEEPDFYKTAIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 20)

Human IL-12 subunit alpha (IL-12 p35) mature form sequence with Y40E/K170A mutations

RNLPVATPDPGMFCLHHSQNLLRAVSNMLQKARQTLEFEPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
RETSFITNGSCLASRKTSFMMALCLSSYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSET
VPQKSSLEEPDFYKTAIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 21)

Mouse IL-12 subunit alpha (IL-12 p35) mature form sequence with Y36E mutation

RVIPVSGPARCLSQSRNLLKTDDMVKTAREKLKHESCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETS
STTRGSCLPPQKTSLMMTLCLGSIYEDLKMYQTEFQAINAALQNNHQIILDKGMLVAIDELMQSLNHNGETLRQK
PPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSA (SEQ ID NO: 22)

Fig. 6**Human IL-12 subunit beta (IL-12 p40) mature form sequence with C177S mutation** (SEQ ID NO: 23)

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSH
SLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLS
AERVGRDNKEYEYSVEQCQEDSASPAAEESLPIEVMVDAVHKLYENYTSSFFIRDI IKPDPPKNLQLKPLKNSRQVE
VSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCS

Human IL-12 subunit beta (IL-12 p40) mature form sequence with C252S mutation (SEQ ID NO: 24)

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSH
SLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLS
AERVGRDNKEYEYSVEQCQEDSACPAAEESLPIEVMVDAVHKLYENYTSSFFIRDI IKPDPPKNLQLKPLKNSRQVE
VSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCS

Human IL-12 subunit beta (IL-12 p40) mature form sequence with C177S/C252S mutations (SEQ ID NO: 25)

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSH
SLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLS
AERVGRDNKEYEYSVEQCQEDSASPAAEESLPIEVMVDAVHKLYENYTSSFFIRDI IKPDPPKNLQLKPLKNSRQVE
VSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCS

Fig. 7

Human IgG1 Fc - G1m allotype sequence (SEQ ID NO: 26)

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

Human IgG1 Fc - knob with FES mutant sequence (SEQ ID NO: 27)

EPKSCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG

Human IgG1 Fc - hole with FES mutant sequence (SEQ ID NO: 28)

EPKSCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG

Human IgG1 Fc - knob with C220S and FES mutant sequence (SEQ ID NO: 29)

EPKSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG

Human IgG1 Fc - hole with C220S and FES mutant sequence (SEQ ID NO: 30)

EPKSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG

Fig. 8

Domain Linkers

Name	SEQ ID NO:	Sequence
(G4S)	31	GGGGS
(G4S)2	32	GGGGSGGGGS
(G4S)3	33	GGGGSGGGGSGGGGS
TR(G4S)3	34	TRGGGGSGGGGSGGGGS
(G4S)4	35	GGGGSGGGGSGGGGSGGGGS
(G4S)5	36	GGGGSGGGGSGGGGSGGGGSGGGGS
(G4S)6	37	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
(G4S)7	38	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
(G4S)8	39	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
Whitlow	40	GSTSGSGKPGSGEGSTKG

Fig. 9**A. Anti-hen egg-white lysozyme clone HYHEL10 (human IgG1 format)****A1. VH Domain**

DVQLQESGPSLVKPSQTLSLTCSVTGDSITSDYWSWIRKFPGNRLEYMGYVSYSGSTYYNPSLKSRIISITRDTSKNQ
YYLDLNSVTTEDTATYYCANWDGDYWGQGLTVTVSA (SEQ ID NO: 41)

A2. VL Domain

DIVLTQSPATLSVTPGNSVSLSCRASQSIGNNLHWYQQKSHESPRLLIKYASQSIGIPSRFSGSGSGTDFTLSINS
VETEDFGMYFCQQNSWPYTFGGGTKLEIK (SEQ ID NO: 42)

A3. Heavy chain (human IgG1 format with Knob and FES mutations)

MKWVTFISLLFLFSSAYSADVQLQESGPSLVKPSQTLSLTCSVTGDSITSDYWSWIRKFPGNRLEYMGYVSYSGSTYY
NPSLKSRIISITRDTSKNQYYLDLNSVTTEDTATYYCANWDGDYWGQGLTVTVSAASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKHTCPCPPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPG
(SEQ ID NO: 43)

A4. Light Chain

MGILPSPGMPALLSLVSLLSVLLMGCVAEDIVLTQSPATLSVTPGNSVSLSCRASQSIGNNLHWYQQKSHESPRLLI
KYASQSIGIPSRFSGSGSGTDFTLSINSVETEDFGMYFCQQNSWPYTFGGGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLS
SPVTKSFNRGEC (SEQ ID NO: 44)

B. Anti-hen egg-white lysozyme clone HYHEL10 (mouse IgG1 format)**B1. VH Domain**

DVQLQESGPSLVKPSQTLSLTCSVTGDSITSDYWSWIRKFPGNRLEYMGYVSYSGSTYYNPSLKSRIISITRDTSKNQ
YYLDLNSVTTEDTATYYCANWDGDYWGQGLTVTVSA (SEQ ID NO: 41)

B2. VL Domain

DIVLTQSPATLSVTPGNSVSLSCRASQSIGNNLHWYQQKSHESPRLLIKYASQSIGIPSRFSGSGSGTDFTLSINS
VETEDFGMYFCQQNSWPYTFGGGTKLEIK (SEQ ID NO: 42)

B3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MGILPSPGMPALLSLVSLLSVLLMGCVAEDVQLQESGPSLVKPSQTLSLTCSVTGDSITSDYWSWIRKFPGNRLEYM
GYVSYSGSTYYNPSLKSRIISITRDTSKNQYYLDLNSVTTEDTATYYCANWDGDYWGQGLTVTVSAAKTPPSVYPLA
PGSAAQTNSMVTGLCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPPSPRPSETVTCNVAPAS
STKVDKKIVPRDCGCKPCICTVPEVSSVFI FPPKPKDVLITITLTPKVTCTVVAISKDDPEVQFSWFVDDVEVHTAQT
QPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTI PPPKEQMAKDKVSLT
CMITDFFPEDITVEWQWNGQPAENYKNTQPIMNTNGSYFVYSKLVQKSNWEAGNTFTCSVLHEGLHNNHTEKSLSH
SPGK (SEQ ID NO: 45)

B4. Light Chain

MKWVTFISLLFLFSSAYSDIVLTQSPATLSVTPGNSVSLSCRASQSIGNNLHWYQQKSHESPRLLIKYASQSIGIP
SRFSGSGSGTDFTLSINSVETEDFGMYFCQQNSWPYTFGGGTKLEIKRADAAPTVSI FPPSSEQLTSGGASVVCFL
NNFYPKDINVKKIDGSRQNGVLNSWTDQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLS
C (SEQ ID NO: 46)

Fig. 10 – Fig. 10A**A. hiL12(WT)-hlgG1(Hole/FES)**

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKE
FGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDLKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKS
SRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIKIP
DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQD
RYYSSSWSEWASVPCSGGGGSGGGGSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLLHHSQNLRAVSNMLQKARQT
LEFYPTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ
VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRV
MSYLNASGGGGSGGGGSEPSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYDGVVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG (**SEQ ID NO: 47**)

B. hiL12(Y40P/K168A)-hlgG1(Hole/FES)

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKE
FGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDLKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKS
SRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIKIP
DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQD
RYYSSSWSEWASVPCSGGGGSGGGGSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLLHHSQNLRAVSNMLQKARQT
LEFPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ
VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYATKIKLCILLHAFRIRAVTIDRV
MSYLNASGGGGSGGGGSEPSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYDGVVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG (**SEQ ID NO: 48**)

C. hiL12(Y40S/K170A)-hlgG1(Hole/FES)

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKE
FGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDLKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKS
SRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIKIP
DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQD
RYYSSSWSEWASVPCSGGGGSGGGGSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLLHHSQNLRAVSNMLQKARQT
LEFSPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ
VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTAIKLCILLHAFRIRAVTIDRV
MSYLNASGGGGSGGGGSEPSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYDGVVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG (**SEQ ID NO: 49**)

Fig. 10 – Fig. 10B**D. hIL12(Y40S/K170T)-hlgG1(Hole/FES)**

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKE
FGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDLKDQKEPKNKTFLRCEAKNYSGRFTCWLLTTISTDLTFSVKS
SRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIKIP
DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQD
RYYSSSWSEWASVPCSGGGGSGGGGSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLLHHSQNLLRAVSNMLQKARQT
LEFSPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ
VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTTIKLCILLHAFRIRAVTIDRV
MSYLNASGGGGSGGGGSEPSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYDGVVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG (**SEQ ID NO: 50**)

E. hIL12(Y40P/K170A)-hlgG1(Hole/FES)

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKE
FGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDLKDQKEPKNKTFLRCEAKNYSGRFTCWLLTTISTDLTFSVKS
SRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIKIP
DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQD
RYYSSSWSEWASVPCSGGGGSGGGGSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLLHHSQNLLRAVSNMLQKARQT
LEFPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ
VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTAIKLCILLHAFRIRAVTIDRV
MSYLNASGGGGSGGGGSEPSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYDGVVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG (**SEQ ID NO: 51**)

F. hIL12(Y40E/K170A)-hlgG1(Hole/FES)

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKE
FGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDLKDQKEPKNKTFLRCEAKNYSGRFTCWLLTTISTDLTFSVKS
SRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSFFIRDIKIP
DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQD
RYYSSSWSEWASVPCSGGGGSGGGGSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLLHHSQNLLRAVSNMLQKARQT
LEFEPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ
VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTAIKLCILLHAFRIRAVTIDRV
MSYLNASGGGGSGGGGSEPSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYDGVVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG (**SEQ ID NO: 52**)

Fig. 10 – Fig. 10C**G. mIL12(Y36E)-mIgG1 (DE and D265A mutations)**

MKWVTFISLLFLFSSAYSMSWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQDRHGVI GSGKTLTITVKE
 FLDAGQYTCHKGGETLSHSHLLLHKKENGWSTELKKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLKFNKSSSS
 SPDSRAVTCGMASLSAEKVTLQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQNKYENYSTSFFIRDIIKPDP
 PKNLQMKPLKNSQVEVSWEY PDSWSTPHSYFSLKFFVRIQRKKEKMKETE EGCNQKGAF LVEKTS TEVQCKGGNVCV
 QAQDRYNNSSCSKWACVPCRVRSGGGSGGGSGGGSGGGSGGGSGGGSRVIPVSGPARCLSQSRNLLKTTDDMVKTA
 REKLKHESCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSSSTRGSCLPPQKTSLMMTLCLGSIYEDLK
 MYQTEFQAINAALQNNHQQI ILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTI
 NRVMGYLLSAGGGSGGGSGGGSVPRDSGCKPCICTVPEVSSVFI FPPKPKDVLTTITLTPKVT CVVVAISKDDPEVQFSW
 FVDDVEVHTAQTPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTI PPP
 KKQMAKDQVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMKTDGSYFVYSKLNQKSNWEAGNTFTCSVLHEG
 LHNHHTKSLSHSPGK (SEQ ID NO: 53)

H. Human IL-12 Fc containing Y40P/K168A mutations (IL-12 Fc mut9)**H1. IL12p35 (Y40P/K168A)-human IgG1 Fc (Hole and FES mutations)**

RNLPVATPDPMFPCLLHHSQNLRAVS NMLQKARQTLEFPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS
 RETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLVAIDELMQALNFNSET
 VPQKSLEEDPDFYATKIKLCILLHAFRIRAVTIDRVMSYLNASGGGGSGGGGSEPKSSDKTHTCPPCPAPEFEGGPS
 VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
 KEYKCKVSNKALPASIETISKAKGQPREPQVCTLPSPRDELTKNQVSLSCAVKGFPYPSDIAVEWESNGQPENNYKT
 TTPVLDSDGSFFLVSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPG (SEQ ID NO: 89)

H2. IL-12p40 (C252S)-human IgG1 Fc (Knob and FES mutations)

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLQDSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSH
 SLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLS
 AERVGRDNKEYEYSVECEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVE
 VSWEY PDTWSTPHSYFSLTFSVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYSSSWSEWASVPCSGG
 GGGSGGGSEPKSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
 HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTI SKAKGQPREPQVYTLPPCRDELTKN
 QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQ
 KSLSLSPG (SEQ ID NO: 90)

Fig. 10 – Fig. 10D**I. Mouse IL-12 Fc containing Y36E mutation (IL-12 Fc Y36E)****I1. Mouse IL12p35 (Y36E)-mouse IgG1 Fc (DE and D265A mutations)**

MKWVTFISLLFLFSSAYSRIIPVSGPARCLSQSRNLLKTTDDMVKTAREKCLKHESCTAEDIDHEDITRDQTSTLKTC
LPLELHKNESCLATRETSSTTRGSCLPQKTSMMTLCLGSIYEDLKMYQTEFQAINAALQNNHQQIILDKGMLVA
IDELMQSLNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSAGGGGSGGGGSPRDSGCKPC
ICTVPEVSSVFIFFPKPKDVLTTITLTPKVTCTVVAISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELP
IMHQDWLNGKEFKCRVNAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWN
GQPAENYKNTQPIMDTDGSYFVYSDLVQKSNWEAGNTFTCSVLHEGLHNHHTEESLSHSPGK (SEQ ID NO:
135)

I2. Mouse IL12p40-mouse IgG1 Fc (KK and D265A mutations)

MKWVTFISLLFLFSSAYSMWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQDRHGVIGSGKTLTITVKE
FLDAGQYTCHKGETLSHSHLLHKKENGIWSTEILKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLKFNKSSSS
SPDSRAVTCGMASLSAEKVTLDQRDYEKYSVSCQEDVTCPTAETLPIELALEARQQNKYENYSTSFFIRDIKPD
PKNLQMKPLKNSQVEVSWEYPDWSWTPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTEVQCKGGNVCV
QAQDRYNNSSCSKWACVPCRVRSAGGGGSGGGGSPRDSGCKPCICTVPEVSSVFIFFPKPKDVLTTITLTPKVTCTV
AISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNAAFPAPIEKTISKTKG
RPAQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMKTDGSYFVYSKLVQKSNWE
AGNTFTCSVLHEGLHNHHTEESLSHSPGK (SEQ ID NO: 136)

Fig. 11 – Fig. 11A**A. Anti-human PD-1 clone 10 from WO2019166946****A1. VH Domain**

QVQLVQSGAEVKKPGSSVKVSKASGYTFTSYWINWVRQAPGQGLEWMGNIYPGSSITNYAQKFQGRVTITADESTS
TAYMELSSLRSED TAVYYCARLTGTGTFAYWGQGLTVTVSS (SEQ ID NO: 54)

A2. VL Domain

DIQMTQSPSSLSASVGDRVTITCKSSQSLWDSGNQKNFLTQYQQKPGKAPKLLIYWTSYRESGVPSRFSGSGSGTDFTLTISSLPEDFATYYCQNDYFYPLTFGGGTKVEIK (SEQ ID NO: 55)

A3. Heavy chain (human IgG1 format with Knob and FES mutations)

MKWVTFISLLFLFSSAYSQVQLVQSGAEVKKPGSSVKVSKASGYTFTSYWINWVRQAPGQGLEWMGNIYPGSSITN
YAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARLTGTGTFAYWGQGLTVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
RVEPKSCDKTHTCTPPCPAPEFEGGSPVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVSVLTVHLQDNLNGKEYKKVSNKALPASIEKTIKAKGQPREPQVYTLPPCRDELTKNQVSLWC
LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLS
PG (SEQ ID NO: 56)

A4. Light Chain

MGILPSPGMPALLSLVSLLSVLLMGCVAEDIQMTQSPSSLSASVGDRVTITCKSSQSLWDSGNQKNFLTQYQQKPGK
APKLLIYWTSYRESGVPSRFSGSGSGTDFTLTISSLPEDFATYYCQNDYFYPLTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC (SEQ ID NO: 57)

B. Anti-mouse PD-1 clone F12/3 from WO2019166946**B1. VH Domain**

EVQLVESGGGLVQPGGSLLESCAASGFTFSSYWMSWVRQAPKGLEWVAISPSGGSTYYADSVKGRFTISRDAKN
TLFLQMTSLRSED TAMYCAKESWGAYYDLWGQGTITVTVSS (SEQ ID NO: 58)

B2. VL Domain

DIVMTQSPSSLSVSAGDKVTMSCRASQGISSWLAWYQQKQWPPKLLIYKASTLESQVDRFTGSGSGTDFTLTISS
VQAEDLAVYYCQQSYSTPWTFGGGTKLEIK (SEQ ID NO: 59)

B3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MKWVTFISLLFLFSSAYSEVQLVESGGGLVQPGGSLLESCAASGFTFSSYWMSWVRQAPKGLEWVAISPSGGSTY
YADSVKGRFTISRDAKNKTLFLQMTSLRSED TAMYCAKESWGAYYDLWGQGTITVTVSSAKTTPPSVYPLAPGSAAQ
TNSMVTLGCLVKGYFPEPVTVWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSPPRSETVTCNVAPASSTKVDK
KIVPRDCGCKPCICTVPEVSSVFI FPPKPKDVLTIITLTPKVTQVVAISKDDPEVQFSWFVDDVEVHTAQTQPREEQ
FNSTFRSVSELPIMHQDWLNGKEFKCRVNSAFAPIEKTISKTKGRPKAPQVYTI PPPKEQMAKDKVSLTCMITDF
FPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSDLVNQKSNWEAGNTFTCSVLHEGLHNHTEESLSHSPGK
(SEQ ID NO: 60)

B4. Light Chain

MKWVTFISLLFLFSSAYS DIVMTQSPSSLSVSAGDKVTMSCRASQGISSWLAWYQQKQWPPKLLIYKASTLESQV
DRFTGSGSGTDFTLTISSVQAEDLAVYYCQQSYSTPWTFGGGTKLEIKRADAPT VSI FPPSSEQLTSGGASVVCFL
NNFYPKDINVWKIDGSRQNGVLNSWTDQDSKDSSTYSMSSTLTITKDEYERHNSYTCEATHKTSSTSPIVKSFNRNE
C (SEQ ID NO: 61)

Fig. 11 – Fig. 11B**C. Anti-human PD-1 Nivolumab****C1. VH Domain**

QVQLVESGGGVVQPGSRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWDGSKRIYADSVKGRFTISRDN SKN
TLFLQMNSLRAEDTAVYYCATNDDYWGQGT LVT VSS (SEQ ID NO: 93)

C2. VL Domain

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN RATGI PARFSGSGSGTDFTLT ISS
LEPEDFAVYYCQQSSNWPRTFGQGTKVEIK (SEQ ID NO: 94)

D. Anti-human PD-1 Pembrolizumab**D1. VH Domain**

QVQLVQSGVEVKKPGASVKVSKASGYTFNTNYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTDSSTT
TAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGT T VTVSS (SEQ ID NO: 95)

D2. VL Domain

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLA SYLESGV PARFSGSGSGTDFTL
TISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK (SEQ ID NO: 96)

E. Anti-human PD-1 Zeluvalimab**E1. VH Domain**

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVSLISGGGSQTYIAESVKGRFTISRDN SKN
TLYLQMNSLRAEDTAVYFCASPSGHYFYAMDVWGQGT T VTVSS (SEQ ID NO: 97)

E2. VL Domain

DIQMTQSPSSVSASVGDRVITITCRASQGISNWLAWYQQKPGKAPKLLIFAASSLQSGVPSRFSGSGSGTDFTLT ISS
LQPEDFATYYCQQAESFPHTFGGGTKVEIK (SEQ ID NO: 98)

F. Anti-human PD-1 Toripalimab**F1. VH Domain**

QQQLVQSGAEVKKPGASVKVSKASGYTFTDYEMHWVRQAPIHGLEWIGVIESETGGTAYNQKFGRVTITADKSTS
TAYMELSSLRSED TAVYYCAREGITTVATYYWYFDVWGQGT T VTVSS (SEQ ID NO: 99)

F2. VL Domain

DVVMTQSPPLSLPVTLGQPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFT
LKISRVEAEDVGYVCFQGSHPVPLTFGQGTKLEIK (SEQ ID NO: 100)

G. Anti-human PD-1 clone TPP-77658**G1. VH Domain**

EVQLVESGGGLVQPGGSLRLSCAASGFSFGDFDMRWFRQAPGKGLEWVGTIKSRAYLEATEFAASVEGRFTISRDDA
KNSAYLQMNSLRAEDTAVYYCTRDAYSSGLLDYWGQGT LVT VSS (SEQ ID NO: 101)

G2. VL Domain

DIQMTQSPSSLSASVGDRVITITCRASQGISNYLAWFQQKPGKAPKRLIYAAQIPGSGVPSRFSGSGSGTDFTLT ISS
LQPEDFATYYCLQHYSYPLTFGGGTKVEIK (SEQ ID NO: 102)

Fig. 12 – Fig. 12A**A. Anti-mouse/human LAG3 clone ADI31853 from EP18893532NW****A1. VH Domain**

QLQLQESGPGLVKPKSETLSLTCTVSGGSIYSESYWGWIROPKPGKLEWIGSIVYSGYTYNPSLKSRTISVDTSK
NQFSLKLSSVTAADTAVYYCARVRTWDAAFDIWGQGTMTVSS (SEQ ID NO: 62)

A2. VL Domain

DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSTRFSGSGSGTDFTFTISS
LQPEDATYYCQQVLELPPWTFGGGTKVEIK (SEQ ID NO: 63)

A3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MKWVTFISLLFLFSSAYSQQLQESGPGLVKPKSETLSLTCTVSGGSIYSESYWGWIROPKPGKLEWIGSIVYSGYT
YYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARVRTWDAAFDIWGQGTMTVSSAKTTPPSVYPLAPGSA
AQTNMVTGLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSPPRPSETVTCNVAPASSTKV
DKKIVPRDCGCKPCICTVPEVSSVFIAPPKPKDVLITLTPKVTCTVVAISKDDPEVQFSWFVDDVEVHTAQTQPRE
EQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAPPAPIEKTISKTKGRPKAPQVYTIAPPKEQMAKDKVSLTCMIT
DFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFYVSDLNQKSNWEAGNTFTCSVLHEGLHNHHTESLSHSPGK
(SEQ ID NO: 64)

A4. Light Chain

MKWVTFISLLFLFSSAYSQQLQESGPGLVKPKSETLSLTCTVSGGSIYSESYWGWIROPKPGKAPKLLIYDASNLETGVP
SRFSGSGSGTDFTFTISSLQPEDATYYCQQVLELPPWTFGGGTKVEIKRADAAPTVSIFPPSSEQLTSGGASVVCF
LNNFYPKDINVKKIDGSEKQNGVLNSWTDQDSKSDSTYSMSSTLTTLTKDEYERHNSYTCEATHKSTSPIVKSFNRN
EC (SEQ ID NO: 65)

B. Anti-human LAG3 clone BMS986016 (Relatlimab)**B1. VH Domain**

QVQLQWGWGAGLLKPKSETLSLTCAVYGGSFSDYYWNWIRQPPGKLEWIGEINHRGSTNSNPSLKSRTLSLDTSKNQ
FSLKLRSVTAADTAVYYCAFGYSDYEYNWFDPWGQGTTLTVSS (SEQ ID NO: 103)

B2. VL Domain

EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS
LEPEDFAVYYCQQRNWLPLTFGQGTNLEIK (SEQ ID NO: 104)

C. Anti-human LAG3 clone BI-754111 (Miptenalimab)**C1. VH Domain**

QVTLVESGGGVVQPGRLRLSCAFSGFSLSTSDMGVGVIRQAPGKLEWVAHIWDDVKRYNPALKSRFTISRDNK
NTLYLQMNSLRADTAVYFCARIEDYGVSYFFDYWGQGTITVTVSS (SEQ ID NO: 105)

C2. VL Domain

DIQMTQSPSFLSASVGDRVSITCKASQDVSTAVAWYQQKPGKAPKLLIYASRYRTGVPDRFSGSGSGTDFTLTISS
LQPEDFATYYCQHHYSIPLTFGQGTKLEIK (SEQ ID NO: 106)

Fig. 12 – Fig. 12B**D. Anti-human LAG3 clone LAG-525 (Ieramilimab)****D1. VH Domain**

QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVFSLDTSVS
TAYLQISSLKAEDTAVYYCARNPPYYGTNNAEAMDYWGQGT^TTVTVSS (SEQ ID NO: 107)

D2. VL Domain

DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSPQLLIYYTSTLHLGVPSRFSGSGSGTEFTLTSS
LQPD^DFATYYCQQY^NLPWT^FFGG^TTKVEIK (SEQ ID NO: 108)

E. Anti-human LAG3 clone REGN3767 (Fianlimab)**E1. VH Domain**

QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAIIWYDGSNKYYADSVKGRFTISRDNKN
TQYLQMNSLR^AEDTAVYYC^ASVATSGDFDY^GMDVWGQGT^TTVTVSS (SEQ ID NO: 109)

E2. VL Domain

EIVLTQSPATLSLSPGER^TTLS^CCRASQ^RISTYLAWYQQKPGQAPRLLIYD^ASKRATGIPARFSGSGSGTGFTLTSS
LEPEDFAVYYCQQR^SNWPL^TFGG^TTKVEIK (SEQ ID NO: 110)

F. Anti-human LAG3 clone MK-4280 (Favezelimab)**F1. VH Domain**

QMQLVQSGPEVKKPGTSVKVSCKASGYTFTDYNVDWVRQARGQRLEWIGDINPNDGGTIYAQKFQERV^TITVDKSTS
TAYMELSSLR^SEDTAVYYCARNYRWF^GAMDH^WGQGT^TTVTVSS (SEQ ID NO: 111)

F2. VL Domain

DIVMTQTPLSLSVTPGQPASISCKASQSLDYEGSDMNWYLQKPGQPPQLLIYGASNLES^GVPDRFSGSGSGTDFTL
KISRVEAEDVG^VY^CQQSTEDPRT^FGGG^TTKVEIK (SEQ ID NO: 112)

Fig. 13**A. Anti-mouse OX40 clone OX86 from US9738723****A1. VH Domain**

QVQLKESGPGGLVQPSQTLSTCTVSGFSLTGYNLHWVRQPPGKGLEWMGRMRYDGDITYNSVLKSRLSISRDTSKNQ
VFLKMNSLQTDITAIYYCTRDGRGDSFDYWGGVMVTVSS (SEQ ID NO: 66)

A2. VL Domain

DIVMTQGALPNPVPSPGESASITCRSSQSLVYKDGQTYLNWFLQRPQGSPQLLTYWMSTRASGVSDRFSGSGSGTYFT
LKISRVRAEDAGVYYCQQVREYPFTFGSGTKLEIK (SEQ ID NO: 67)

A3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MKWVTFISLLFLFSSAYSQVQLKESGPGGLVQPSQTLSTCTVSGFSLTGYNLHWVRQPPGKGLEWMGRMRYDGDITY
NSVLKSRLSISRDTSKNQVFLKMNSLQTDITAIYYCTRDGRGDSFDYWGGVMVTVSSAKTTPPSVYPLAPGSAAQT
NSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTPSSPRPSETVTCNVHPASSTKVDDK
IVPRDCGCKPCICTVPEVSSVFI FPPKPKDVLITITLPKVT CVVVAISKDDPEVQFSWFVDDVEVHTAQTQPREEQF
NSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTI PPPKEQMAKD KVS L TCMITDFF
PEDITVEWQWNGQPAENYKNTQ PIMDTDGSYFVYSD LNVQKSNWEAGNTFTCSVLHEGLHNHHTESLSHSPGK
(SEQ ID NO: 68)

A4. Light Chain

MKWVTFISLLFLFSSAYS DIVMTQGALPNPVPSPGESASITCRSSQSLVYKDGQTYLNWFLQRPQGSPQLLTYWMSTR
ASGVSDRFSGSGSGTYFTLKISRVRAEDAGVYYCQQVREYPFTFGSGTKLEIKRADAAPTVSI FPPSSEQLTSGGAS
VVCFLNNFY PKDINVKWKIDG SERQNGVLNSWTDQDSK DSTYSMSSTLT LTKDEYERHNSYTCEATHKTSTSPIVKS
FNRNEC (SEQ ID NO: 69)

B. Anti-human OX40 clone ADI-20057**B1. VH Domain**

QVQLVQSGAEVKKPGASVKVSCKASGYFTFTSYIMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTTRDTSTS
TVYME LSSLRSED TAVYYCARD HASSSWYTHLDLWGRGTLTVSS (SEQ ID NO: 130)

B2. VL Domain

DIQMTQSPSSLSASVGDRVITITCQASQDISNYLNWYQQKPKGAPKLLIY DASNLETGVPSRFSGSGSGTDFTFTISS
LQPED IATYYC QQSANYPYTFGGG TKVEIK (SEQ ID NO: 131)

C. Anti-human OX40 clone 445-3**C1. VH Domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTSYIIHWVRQAPGQGLEWMGYINPYNEGTRYNQKFQGRVTLTADKSTS
TAYME LSSLRSED TAVYYC ARGYYGSSYAMDYWGQGT TTVTVSS (SEQ ID NO: 132)

C2. VL Domain

DIQMTQSPSSLSASVGDRVITITCRASQGISNYLNWYQQKPDGAIKLLIY DASTLYSGVPSRFSGSGSGTDFTLTISS
LQPED FATYYC QQYSKLPYTFGGG TKVEIK (SEQ ID NO: 133)

Fig. 14 – Fig. 14A**A. Anti-mouse/human 41BB clone TABBY107 from WO2017205745****A1. VH Domain**

QVKLVQSGAALVKPGASVKMSCKASDYTFNDYWVSWVKQRHGESLEWIGEIYPNSGATNFNGKFRGKATLTVDNPTS
TAYMELSRLTSEDSAIYYCTREYTRDWFAYWGQGLTVTVSS (SEQ ID NO: 70)

A2. VL Domain

DVVLVTQTPSILSATIGQSVSISCRSSQSLDSDGNTYLYWFLQRPQGSPQRLLIYLVSNLGSVGNRFSGSGSGTDFT
LKISGVEAEDLGIYYCMQPTHAPYTFGAGTKLELK (SEQ ID NO: 71)

A3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MKWVTFISLLFLFSSAYSQVKLVQSGAALVKPGASVKMSCKASDYTFNDYWVSWVKQRHGESLEWIGEIYPNSGATN
FNGKFRGKATLTVDNPTSTAYMELSRLTSEDSAIYYCTREYTRDWFAYWGQGLTVTVSSAKTTPPSVYPLAPGSAAQ
TNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSRPSETVTCNVHPASSTKVDK
KIVPRDCGCKPCICTVPEVSSVFI FPPKPKDVLITLTPKVTCTVVAISKDDPEVQFSWFVDDVEVHTAQTQPREEQ
FNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTI PPPKEQMAKDKVSLTCMITDF
FPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSDLVNQKSNWEAGNTFTCSVLHEGLHNHHTESLSHSPGK
(SEQ ID NO: 72)

A4. Light Chain

MKWVTFISLLFLFSSAYSQVVLVTQTPSILSATIGQSVSISCRSSQSLDSDGNTYLYWFLQRPQGSPQRLLIYLVSNL
GSVGNRFSGSGSGTDFTLKISGVEAEDLGIYYCMQPTHAPYTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGAS
VVCFLNNFYPKDINVKKIDGSRQNGVLNSWTDQDSKDYSTYSMSSTLTLTKEDEYERHNSYTCEATHKTSTSPIVKS
FNRNEC (SEQ ID NO: 73)

B. Anti-human 41BB clone 20H4.9 (Urelumab)**B1. VH Domain**

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWVIRQSPEKGLEWIGELNHGGYVTYNPSLESRVTISVDTSKNQ
FSLKLSSTAAADTAVYYCARDYGPNGYDWYFDLWGRGTLTVTS (SEQ ID NO: 123)

B2. VL Domain

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTIS
LEPEDFAVYYCQQRSNWPPALTFGGGTKVEIK (SEQ ID NO: 124)

Fig. 14 – Fig. 14B**C. Anti-human 41BB clone Fab 1618 (Aptevo)****C1. VH Domain**

EVQLLESGGGLVQPGGSLRLSCAASGFTFSYGSMYWVRQAPGKGLEWVSSISSGSGSTYYADSVKGRFRTISRDNSKN
TLYLQMNSLRAEDTAVYYCARSSYYGSYYSIDYWGQGTLVTVS (SEQ ID NO: 125)

C2. VL Domain

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQYDNLPTFGQGTKLEIK (SEQ ID NO: 126)

D. Anti-human 41BB clone 38-27-A11 sc02**D1. VH Domain**

EVQLVESGGGLVQPGGSLRLSCAASGFSFSANYYPCWVRQAPGKLEWIGCIYGGSSDITYDANWTKGRFRTISRDNS
KNTVYLQMNSLRAEDTAVYYCARSAWYSGWGGDLWGQGTLVTVSS (SEQ ID NO: 127)

D2. VL Domain

DIQMTQSPSSLSASVGDRVTITCQASQSISNRLAWYQQKPGKAPKLLIYSASTLASGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQSTYYGNDGNAFGTGTKVTVL (SEQ ID NO: 128)

E. Anti-human 41BB clone HZ-L-Yr-16**E1. VHH Domain**

QVQLVESGGGVVQPGRSLRLSCAASGSTFSIVAMGWYRQAPGKQRELVASIITGDGDTNYADSVKGRFRTISRDNSKN
TMYLQMNSLKPEDTAVYYCYARTGYGSSWLMGHEYDYWGQGTQVTVSSL (SEQ ID NO: 129)

Fig. 15 – Fig. 15A**A. Anti-mouse/human ICOS clone KY1044 from US9957323****A1. VH Domain**

EVQLVESGGGVVRPGGSLRLSCVASGVTFDYDYGMSWVRQAPGKGLEWVSGINWNGGDTDYSDSVKGRFTISRDAKN
SLYLQMNSLRRAEDTALYYCARDIFYGSGSYHVPFDYWGQILVTVSS (SEQ ID NO: 74)

A2. VL Domain

EIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPRLLIYGASSRATGIPDRFSGDGS GTDFTLSIS
RLEPEDFAVYYCHQYDMSPTFTGPGTKVDIK (SEQ ID NO: 75)

A3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MKWVTFISLLFLFSSAYSEVQLVESGGGVVRPGGSLRLSCVASGVTFDYDYGMSWVRQAPGKGLEWVSGINWNGGDTD
YSDSVKGRFTISRDAKNKNSLYLQMNSLRRAEDTALYYCARDIFYGSGSYHVPFDYWGQILVTVSSAKTTPPSVYPLA
PGSAAQTNSMVTGLCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTPSSPRPSETVTCNVAHPAS
STKVDKKIVPRDCGCKPCICTVPEVSSVFI FPPKPKDVLITITLTPKVT CVVAISKDDPEVQFSWFVDDVEVHTAQT
QPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTI PPPKEQMAKD KVS LT
CMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSDLVNQKSNWEAGNTFTCSVLHEGLHNHHTESLSH
SPGK (SEQ ID NO: 76)

A4. Light Chain

MKWVTFISLLFLFSSAYSEIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPRLLIYGASSRATGI
PDRFSGDGS GTDFTLSISRLEPEDFAVYYCHQYDMSPTFTGPGTKVDIKRADAAPT VSI FPPSSEQLTSGGASVVC F
LNNFYPKDINVKWKIDGSE RQNGVLNSWTDQDSKDYSTYSMSSTLT LTKDEYERHNSYTCEATHKTSTSPIVKSFNRN
EC (SEQ ID NO: 77)

B. Anti-human ICOS clone 3E8**B1. VH Domain**

QVQLVESGGGVVQPGMSRLRLSCAASGFTFTSTYGMQWVRQAPGKGLEWVTVIWHDGSHKDYADSVKGRFTISRDN SKN
TMYLQMNSLRRAEDTAVYYCARDROTGE GYFDFWGQGLTVTVSS (SEQ ID NO: 117)

B2. VL Domain

DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFRSGSGSGTDFLT TISS
LQPEDFATYYCQQYNSYPYTFGQGTKLEIK (SEQ ID NO: 118)

Fig. 15 – Fig. 15B**C. Anti-human ICOS clone JTX-2011****C1. VH Domain**

EVQLVESGGGLVQPGGSLRLSCAASGFTFS¹SDYWMDWVRQAPGKGLVWVSN²IDEDGSITEYSPFVKGRFTISRDNAKN
TLYLQMNSLRAEDTAVYYCTRWGRFGFDS³WGQGLTVTVSS (SEQ ID NO: 119)

C2. VL Domain

DIVMTQSPDSLAVSLGERATINCKSSQ¹SLLSGSFNYLTWYQQKPGQPPKLLIFYASTRHTGVPDRFSGSGSGTDFTL
TISSLQAEDVAVYYCHHHYNAPPTFGPGTKVDIK (SEQ ID NO: 120)

D. Anti-human ICOS clone GSK-3359609**D1. VH Domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYAMHWVRQAPGQGLEWMGLISIYSDHTNYNQKFQGRVTITADKSTS
TAYMELSSLRSEDTAVYYCGRN¹NYGNYGWYFDVWGQGT²TVTVSS (SEQ ID NO: 121)

D2. VL Domain

EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDYTLTISSL
EPEDFAVYYCFQSGGYPYTFGQGTKLEIK (SEQ ID NO: 122)

Fig. 16**A. Anti-human CCR7 clone 674J13 from WO2018142322****A1. VH Domain**

DVQLQESGPGLVKPSQTLSTCTVSGYSITSGYSWHWIRQHPGKGLEWMAHIHSSGSTNYPNPSLKSRLTISRDTSKN
QFSLKLSSVTAADTAVYYCARGGVQAFAYWGQGLTVTVSS (SEQ ID NO: 78)

A2. VL Domain

EIVLTQSPATLSASPGERVMTSCSASSSVIYMHWYQQKPGQAPRRWIYDTSKLGVPARFSGSGSGTDYTLTISSM
EPEDAAYYCQQWSSNPLTFGQGTKLEIK (SEQ ID NO: 79)

A3. Heavy chain (human IgG1 format with Knob and FES mutations)

MKWVTFISLLFLFSSAYSQVQLQESGPGLVKPSQTLSTCTVSGYSITSGYSWHWIRQHPGKGLEWMAHIHSSGSTN
YPNPSLKSRLTISRDTSKNQFSLKLSSVTAADTAVYYCARGGVQAFAYWGQGLTVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKHTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWC
LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLS
PG (SEQ ID NO: 80)

A4. Light Chain

MGILPSPGMPALLSLVSLLSVLLMGCVAEEIVLTQSPATLSASPGERVMTSCSASSSVIYMHWYQQKPGQAPRRWIY
DTSKLGVPARFSGSGSGTDYTLTISSMEPEDAAYYCQQWSSNPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
PVTCSFNRGEC (SEQ ID NO: 81)

Fig. 17 – Fig. 17A**A. Anti-human CCR8 clone 4A19 from WO2021194942****A1. VH Domain**

QVQLVQSGAEVKKPGASVKVSKASGYTFTDSEMHWRQATGQGLEWMGAIQPETGGTAYNQKFKARVTMTRDTSIS
TAYMELSSLRSEDVAVYYCARRRRNFDYWGQGLTVTVSS (SEQ ID NO: 82)

A2. VL Domain

DIVMTQTPLSLSVTPGQPASISCRSSQSLFHSSGNTYLHWYLVKPGQPPQLLIYKVSNRFSGVPDRFSGSGSGTDFT
LKISRVEAEDVGVYYCSQSTHVPFTFGQGTKLEIK (SEQ ID NO: 83)

A3. Heavy chain (human IgG1 format with Knob and FES mutations)

MKWVTFISLLFLFSSAYSQVQLVQSGAEVKKPGASVKVSKASGYTFTDSEMHWRQATGQGLEWMGAIQPETGGTA
YNQKFKARVTMTRDTSISTAYMELSSLRSEDVAVYYCARRRRNFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSG
GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVYTLPPCRDELTKNQVSLWCL
VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 84)

A4. Light Chain

MGILPSPGMPALLSLVSLLSVLLMGCVAEDIVMTQTPLSLSVTPGQPASISCRSSQSLFHSSGNTYLHWYLVKPGQP
PQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPFTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVT
HQGLSSPVTKSFNRGEC (SEQ ID NO: 85)

B. Anti-human/mouse CCR8 clone VHH120 from WO2022136650**B1. Nanobody**

DVQLVESGGGLVQPGGSLRLSCTVSGSIFSLRTVGWYRQAPGKQRELVATISAGGATDYADSVKGRFTISRDNKNT
VYLQMNSLRPEDTAVYYCYAQDSYKIYKSRYTQDYWGQGLTVTVSS (SEQ ID NO: 86)

B2. Heavy chain in human IgG1 format with Knob and FES mutations

MKWVTFISLLFLFSSAYSQVQLVESGGGLVQPGGSLRLSCTVSGSIFSLRTVGWYRQAPGKQRELVATISAGGATDY
ADSVKGRFTISRDNKNTVYLQMNSLRPEDTAVYYCYAQDSYKIYKSRYTQDYWGQGLTVTVSSGGGGSGGGGSEPK
SSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTIKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGF
YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 87)

B3. Heavy chain (mouse IgG1 format with DE (heterodimer) and D265A (silencing) mutants)

MKWVTFISLLFLFSSAYSQVQLVESGGGLVQPGGSLRLSCTVSGSIFSLRTVGWYRQAPGKQRELVATISAGGATDY
ADSVKGRFTISRDNKNTVYLQMNSLRPEDTAVYYCYAQDSYKIYKSRYTQDYWGQGLTVTVSSGGGGSGGGGSPR
DSGCKPCICTVPEVSSVFIFFPKPKDVLITLTPKVTCTVVAISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTF
RSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDI
TVEWQWNGQPAENYKNTQPIMDTDGSYFVYSDLVNQQSNWEAGNTFTCSVLHEGLHNHHTTEESLSHSPGK (SEQ
ID NO: 134)

Fig. 17 – Fig. 17B**C. Anti-human CCR8 clone Ab5-H13L1****C1. VH Domain**

EVQLLESGGGLVQPGGSLRLSCAASGIDLSTYAMGWVRQAPGKGLEWVGLIHRSGRTYYATWAKGRFTISKDSSKNT
LYLQMNSLRAEDTAVYYCTRSYPDYSATASIWGQGTTVTVSS (SEQ ID NO: 113)

C2. VL Domain

DIQVTQSPSSLSASVGDRVTITCQASENIANALAWYQOKPGKPKFLIYGASNLASGVPSRFSGSGSGTDFTFTISS
LQPEDIATYYCQQAYYGNSFVEGTFGGGTKVEIK (SEQ ID NO: 114)

D. Anti-human CCR8 clone Ab4-H12L3**D1. VH Domain**

EVQLLESGGGLVQPGGSLRLSCAASGFSLSNYAMIWVRQAPGKGLEWVTISLGGYTYANWAKGRFTISRDSKTT
VYLQMNSLRAEDTAVYFCARARWSDSAITYAFDPWGPGLTVTVSS (SEQ ID NO: 115)

D2. VL Domain

DYQMTQSPSSLSASVGDRVTITCQASQSISSYLSWYQOKPGKAPKLLIYKASTLASGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQGYTSSNIDNIFGGGTKVEIK (SEQ ID NO: 116)

Fig. 18

Fig. 18A

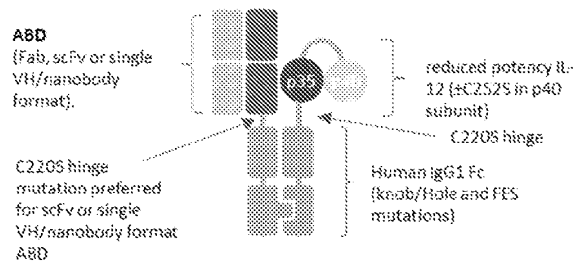


Fig. 18B

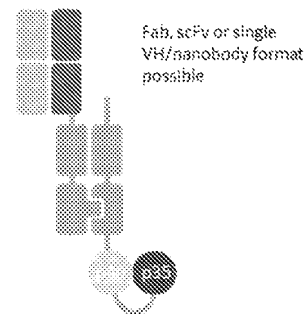


Fig. 18C

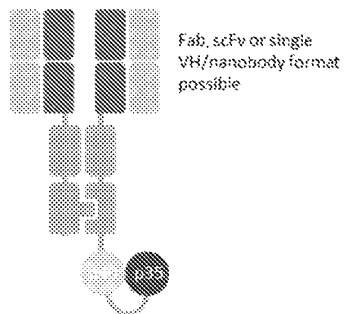


Fig. 18D

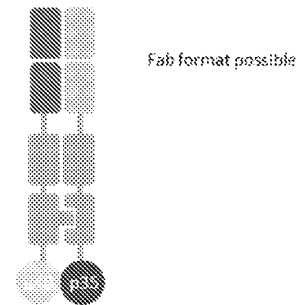


Fig. 18 (Continued)

Fig. 18E

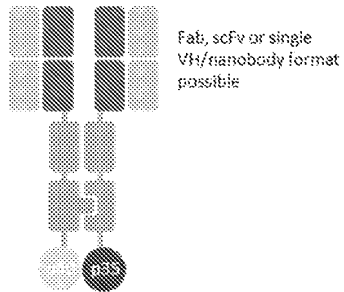


Fig. 18F

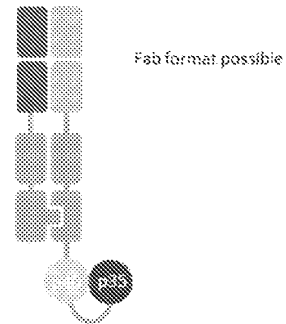


Fig. 18G

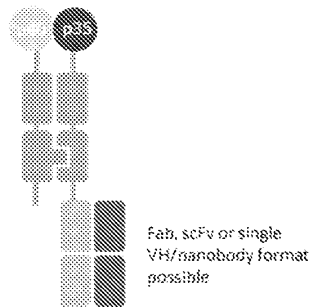


Fig. 18H

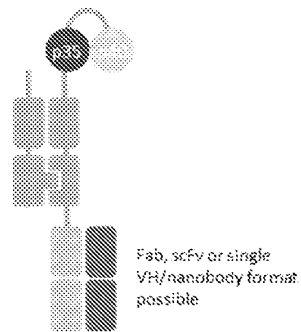


Fig. 19

Name	Human IL-12 p35 mutation	ABD specificity	Chain A seqID	Chain B seqID	Chain C seqID
mono-WT-C10	-	Human PD1	47	56	57
mono-mut9-C10	Y40P/K168A	Human PD1	48	56	57
mono-mut23-C10	Y40S/K170A	Human PD1	49	56	57
mono-mut24-C10	Y40S/K170T	Human PD1	50	56	57
mono-mut51-C10	Y40P/K170A	Human PD1	51	56	57
mono-mut52-C10	Y40E/K170A	Human PD1	52	56	57
mono-WT-Hyhel10	-	Hen egg-white lysozyme	47	43	44
mono-mut9-Hyhel10	Y40P/K168A	Hen egg-white lysozyme	48	43	44
mono-mut23-Hyhel10	Y40S/K170A	Hen egg-white lysozyme	49	43	44
mono-mut24-Hyhel10	Y40S/K170T	Hen egg-white lysozyme	50	43	44
mono-mut51-Hyhel10	Y40P/K170A	Hen egg-white lysozyme	51	43	44
mono-mut52-Hyhel10	Y40E/K170A	Hen egg-white lysozyme	52	43	44
mono-mut9-4A19	Y40P/K168A	Human CCR8	48	84	85
mono-mut9-VHH120	Y40P/K168A	Human and mouse CCR8	48	87	-
mono-mut9-674J13	Y40P/K168A	Human CCR7	48	80	81
IL-12 Fc mut9	Y40P/K168A	-	89	90	-

Fig. 20 – Fig. 20A

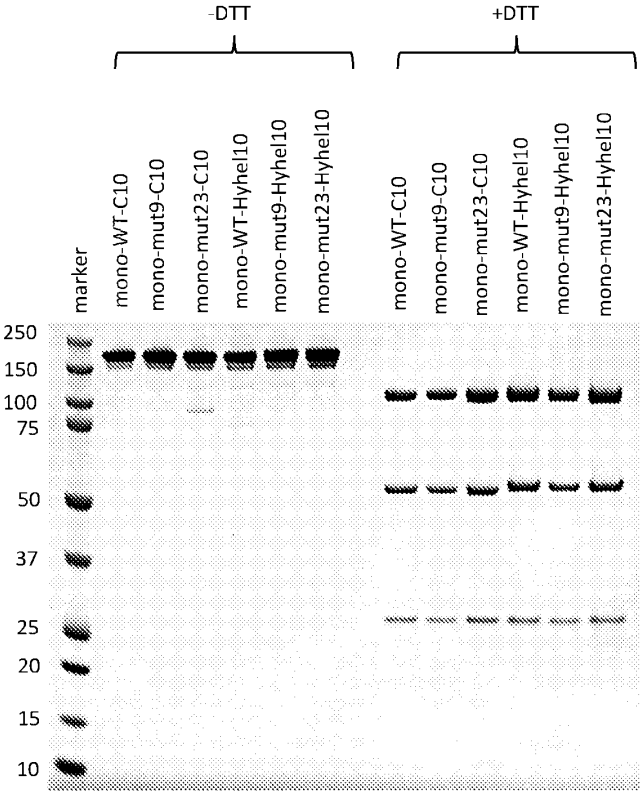


Fig. 20 – Fig. 20B

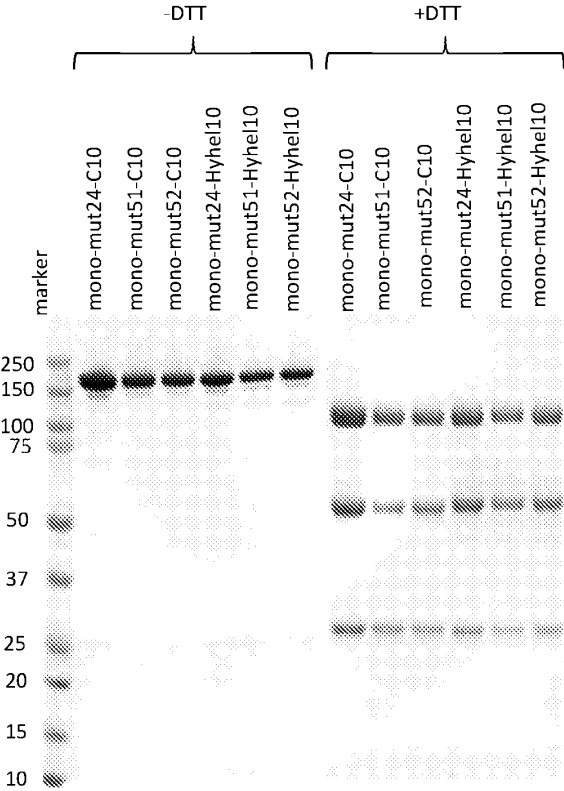


Fig. 21

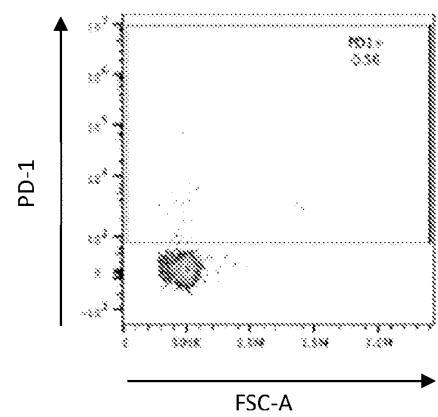


Fig. 22 – Fig. 22A

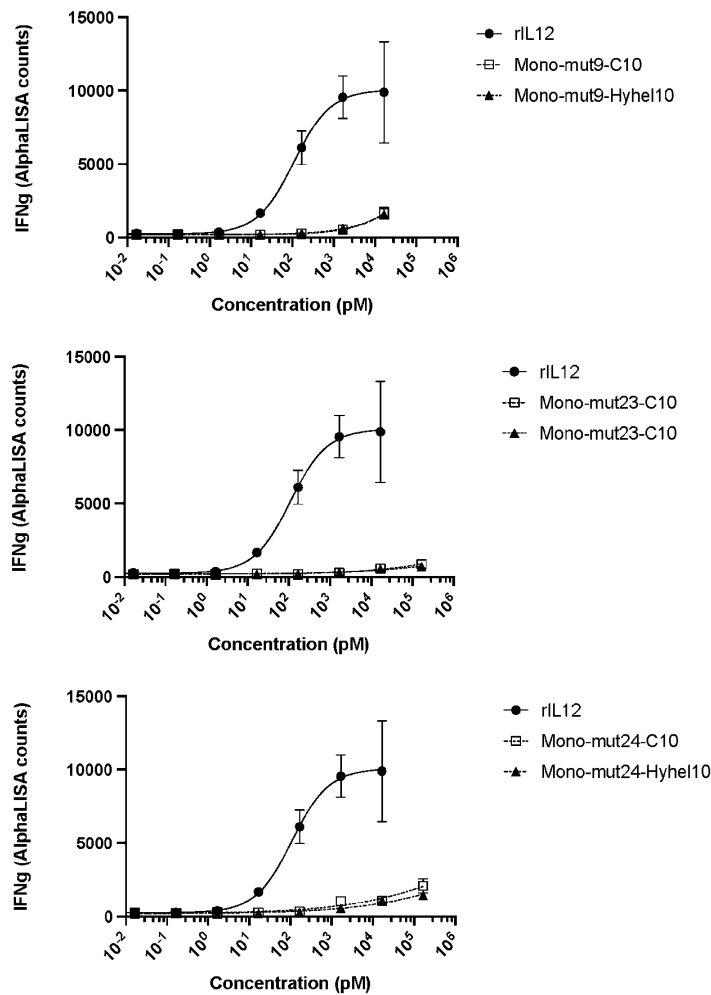


Fig. 22 – Fig. 22B

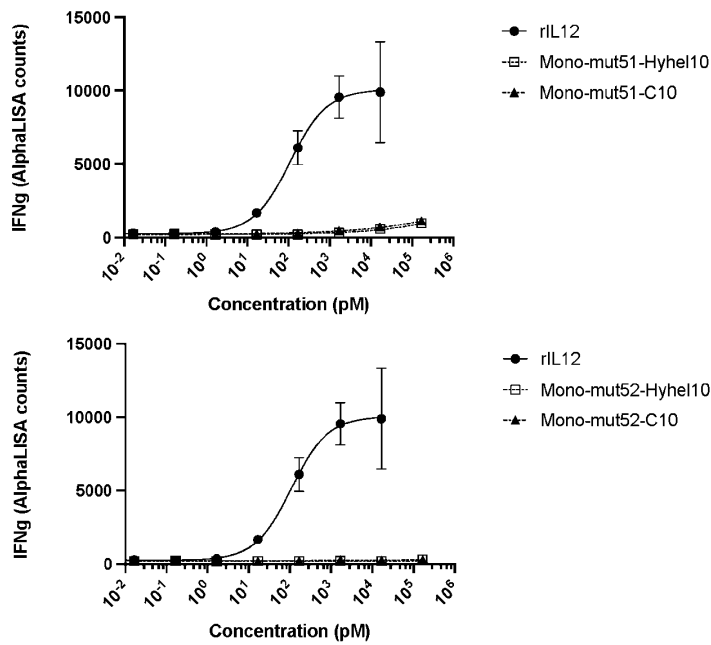


Fig. 23

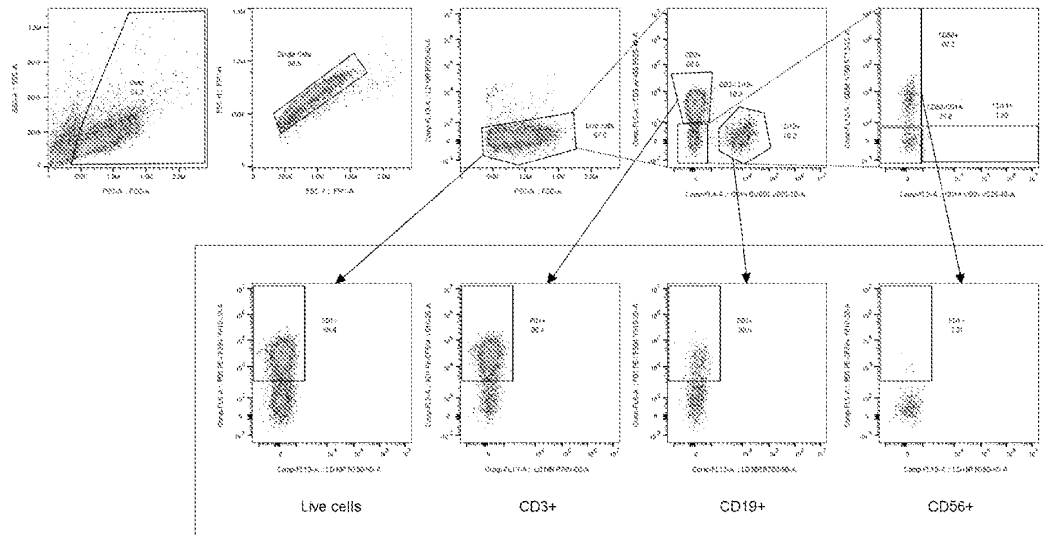


Fig. 24 – Fig. 24A

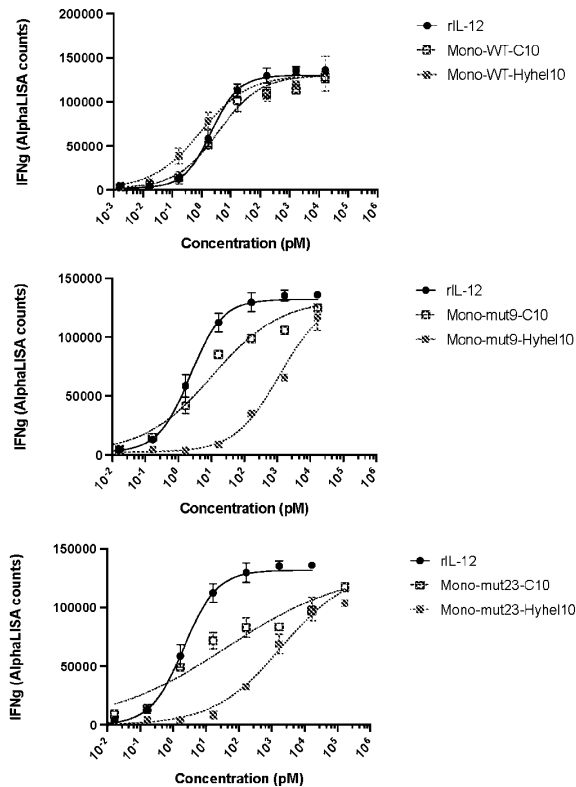


Fig. 24 – Fig. 24B

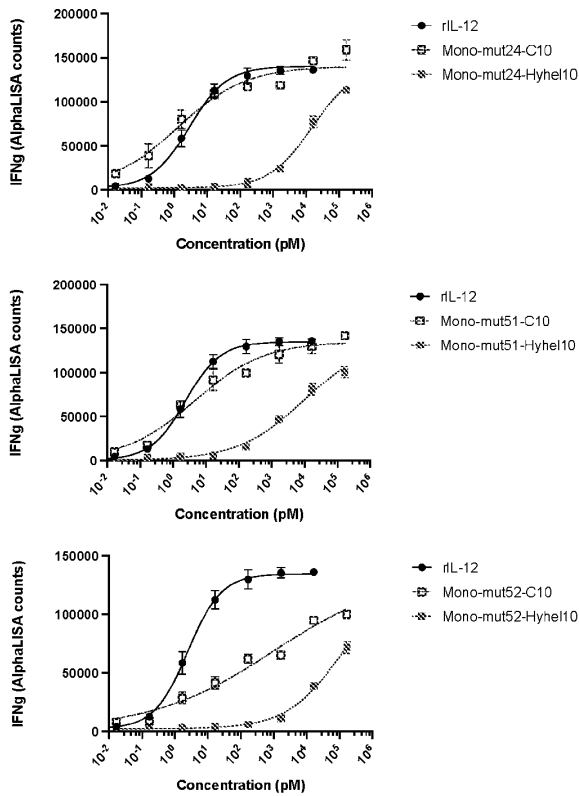


Fig. 25

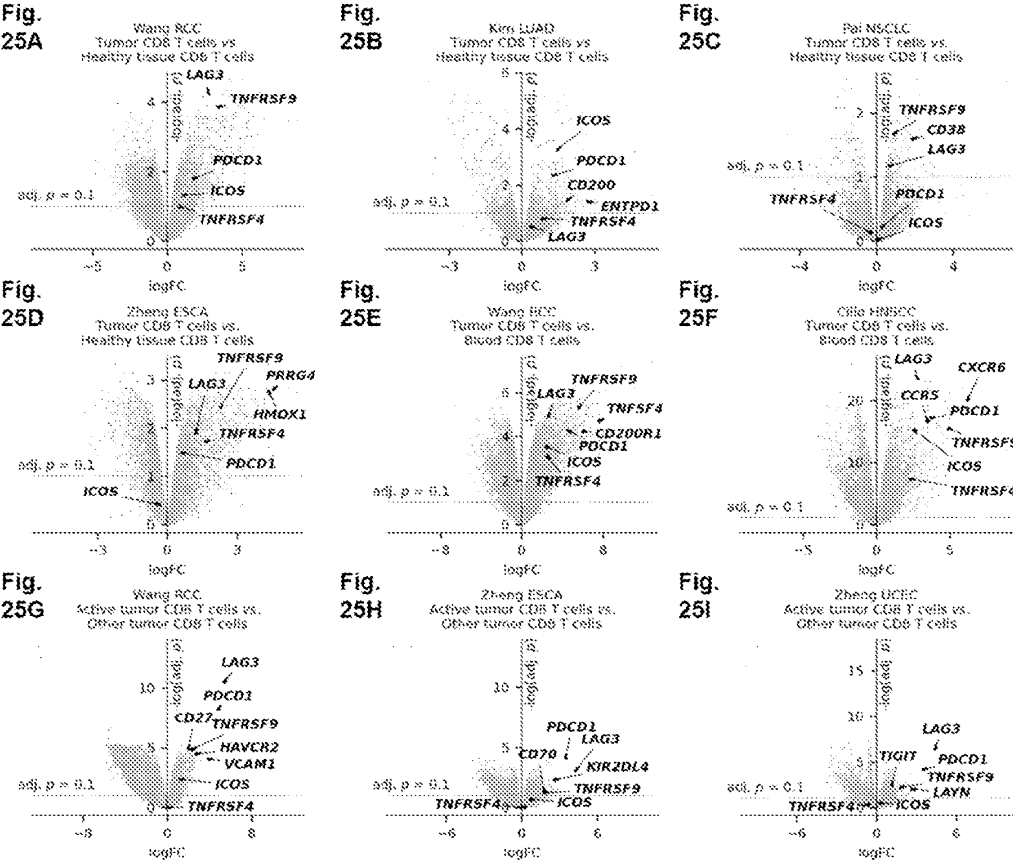


Fig.
25J

25J

Tumor vs Healthy Tissue					Tumor vs Blood				Tumor infiltrating: Active vs 'Other'						Ranked by product of ranks
Wang	Kim	Pai	Zheng		Wang	Cillo			Wang	Kim	Zheng	Zheng			
RCC	LUAD	NSCLC	ESCA		RCC	HNSCC			RCC	LUAD	ESCA	THCA	UCEC		
LAGE3	196	1314	328	587		586	118			1	1	1	1	1	
PDCD1	429	161	1698	1338		137	47			2	2	2	2	2	
VCAM1	19	324	76	287		38	19			3	60	35	6	3	
EXTFO1	20	16	18	50		104	14			708	27	4	149	25	
TNFRSF4	87	15	125	21		9	31			47	452	54	31	28	
H4VCR2	70	1237	85	196		49	26			7	16	14	22	26	
LAYN	39	14	43	85		64	15			53	206	9	4503	4	
CXCR6	9288	113	248	7087		87	2			121	7	7	5	11	
HMOX1	62	860	19	7		53	349			4	4058	10	251	30	
TNFRSF9	119	1886	197	200		66	12			23	65	32	79	24	
PRRG4	34	202	94	5		33	1263			8	5996	108	11507	72	
CD38	259	315	36	70		355	124			39	1854	237	138	86	
CD70	556	115	3535	388		552	137			1150	61	30	10	114	
CCR5	627	108	1107	1114		149	59			129	123	739	36	192	
TRIF	1655	794	317	680		775	164			151	13	105	117	96	
KR2DL4	252	883	51	676		470	17			6514	1780	5	4143	8	
CD200	76	57	166	137		77	323			98	3751	1042	3080	107	
CD27	211	127	360	955		405	904			52	1592	1121	576	1163	
CD208A1	343	401	755	750		47	100			74	7928	5580	2509	740	
KO5	847	108	5274	8533		656	151			237	1556	704	110	1844	
TNFRSF4	1270	415	11513	399		606	183			5629	8894	3677	8332	8498	

Fig. 26

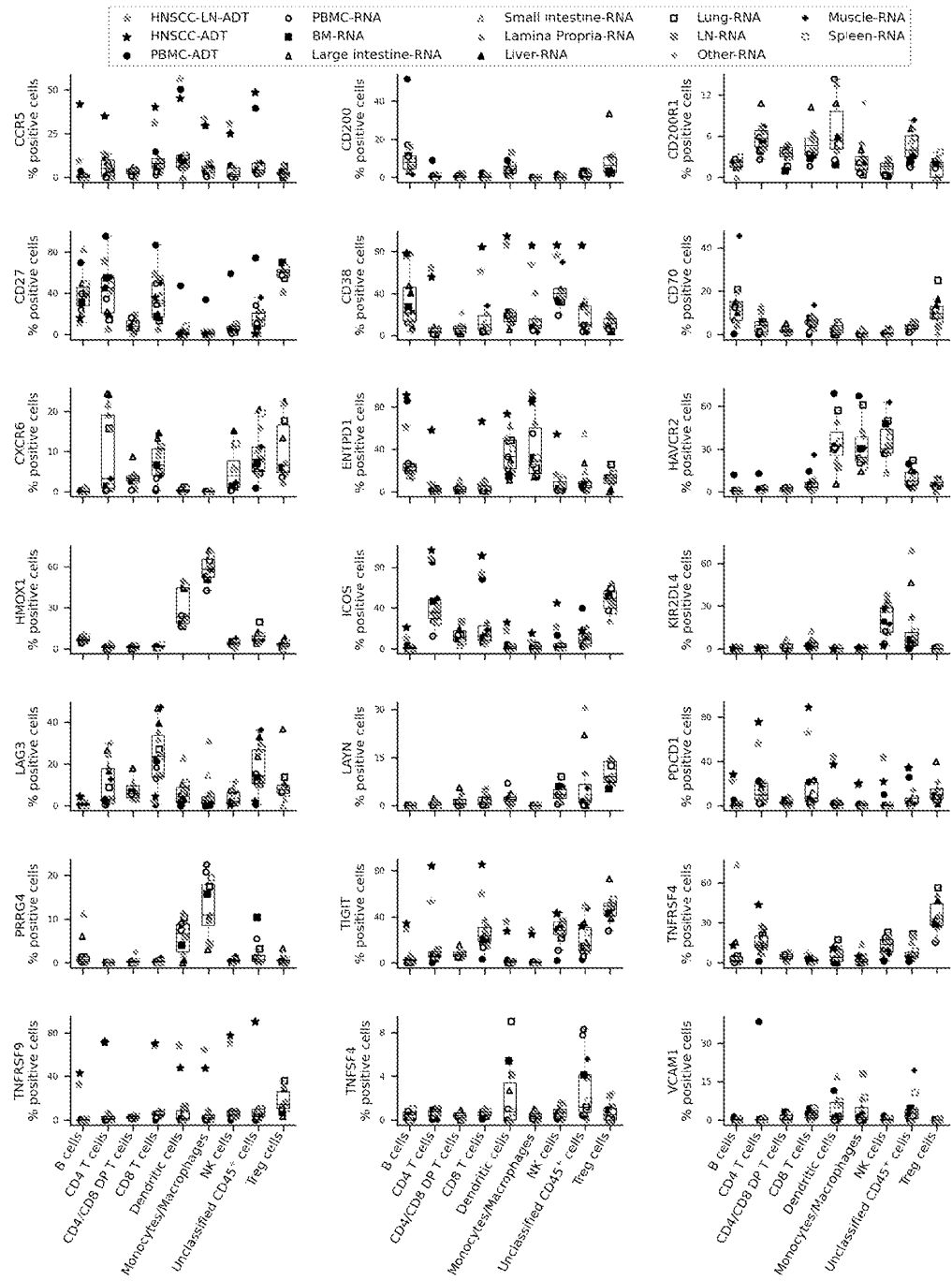


Fig. 27

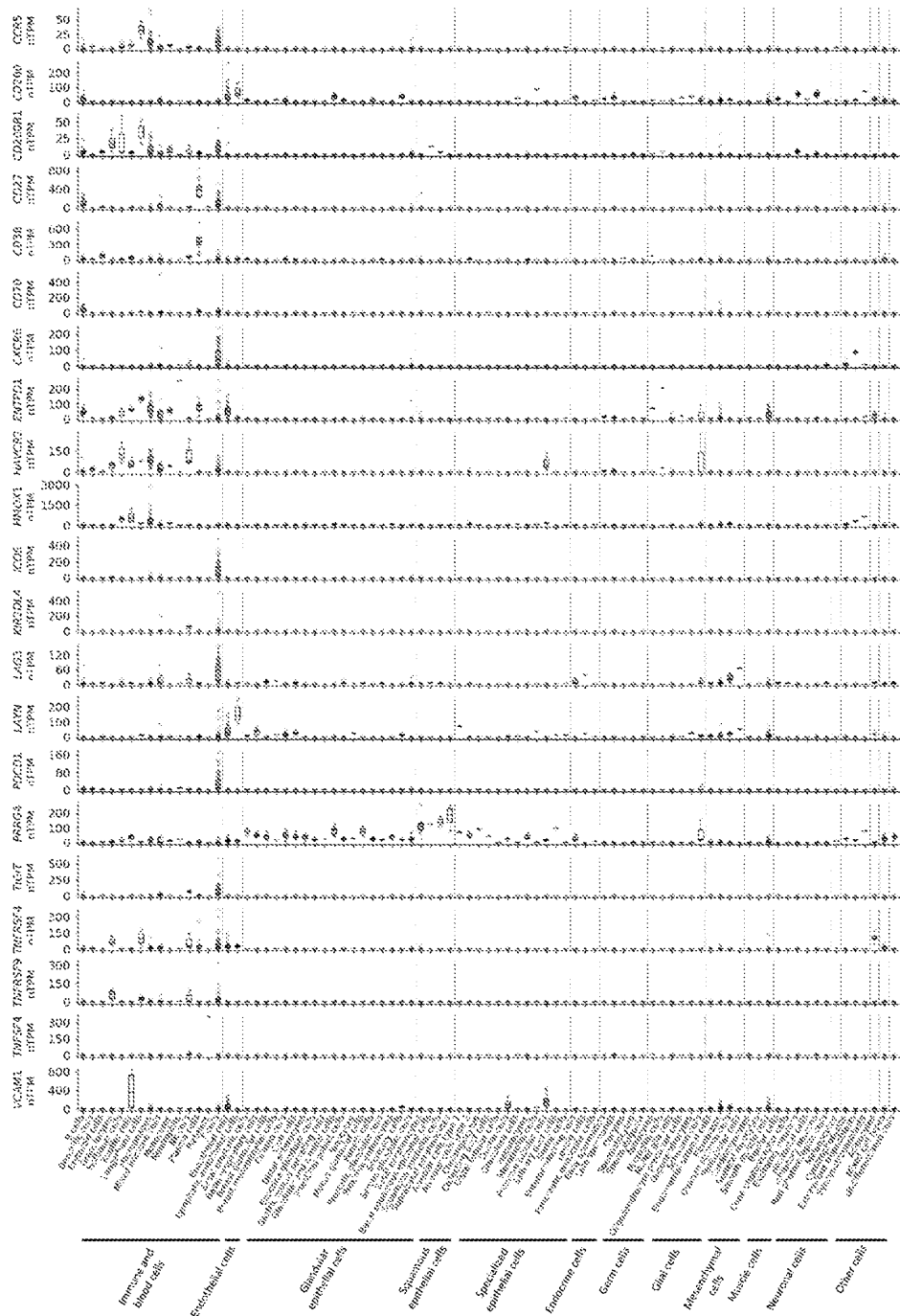


Fig. 28

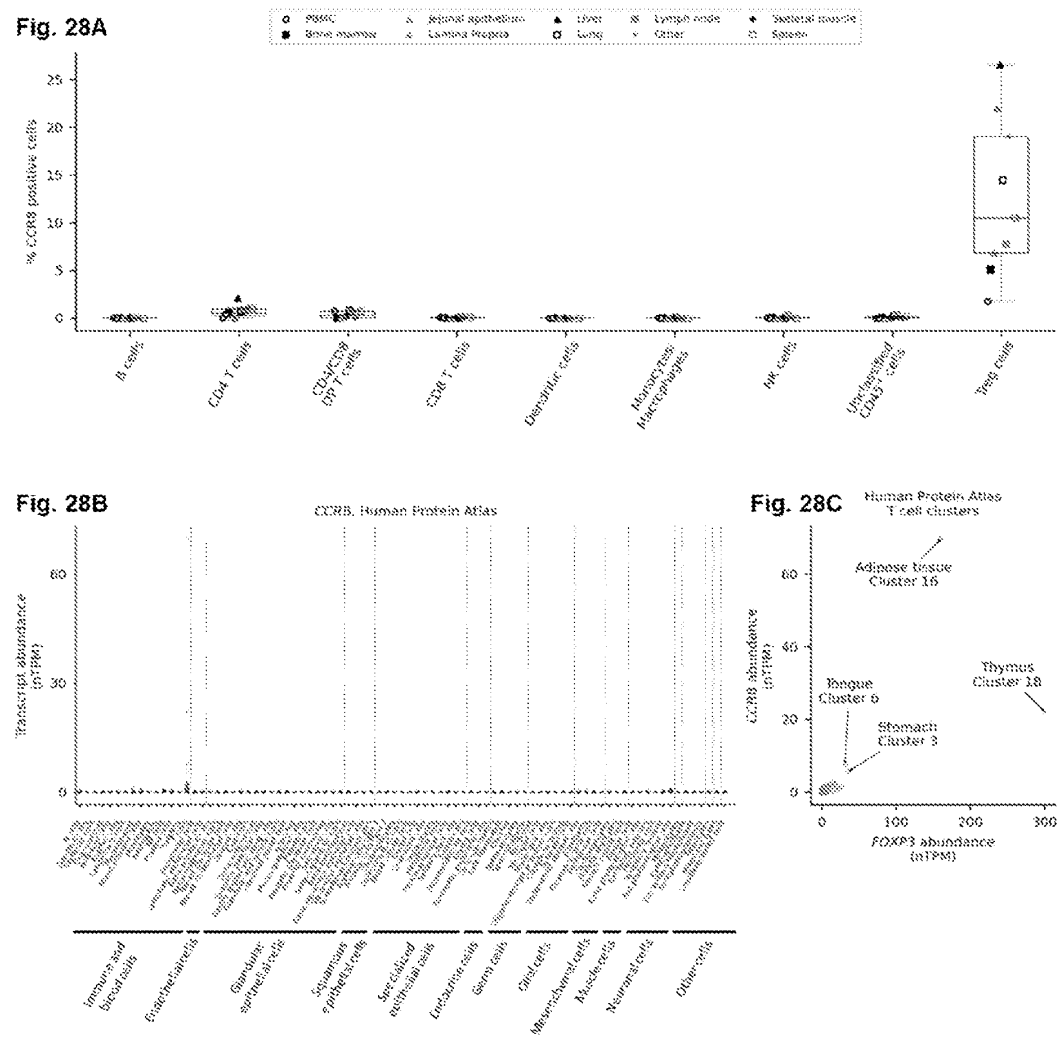


Fig. 29

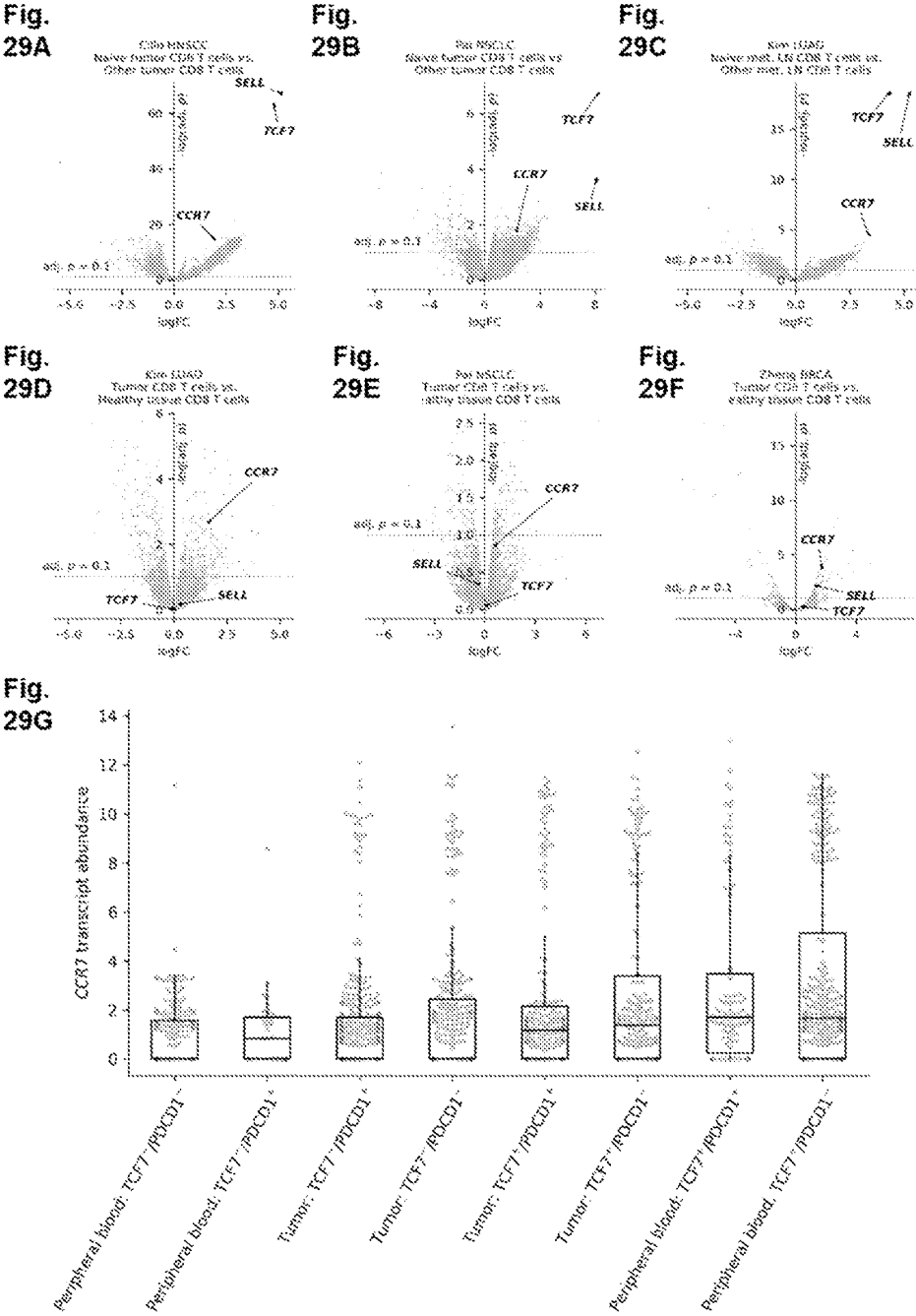


Fig. 30 – Fig. 30A

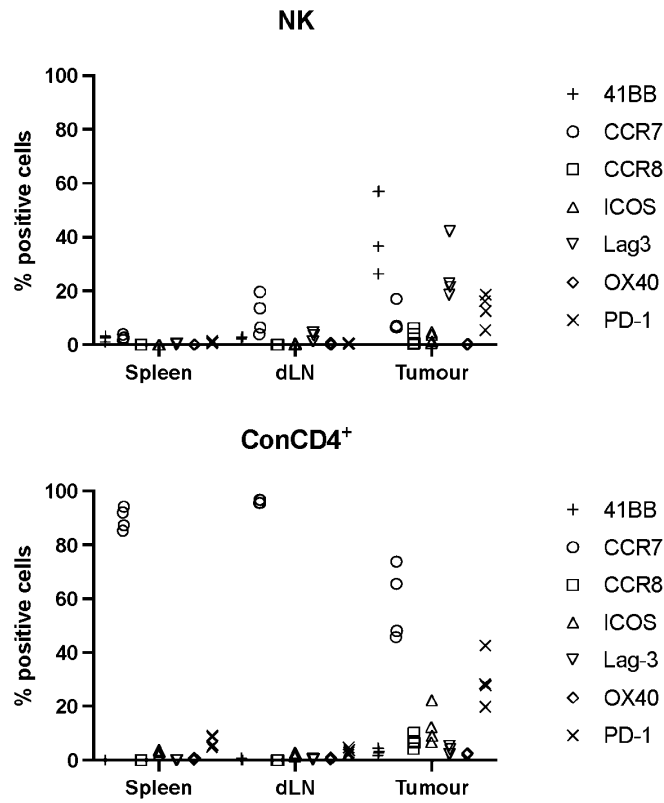


Fig. 30 – Fig. 30B

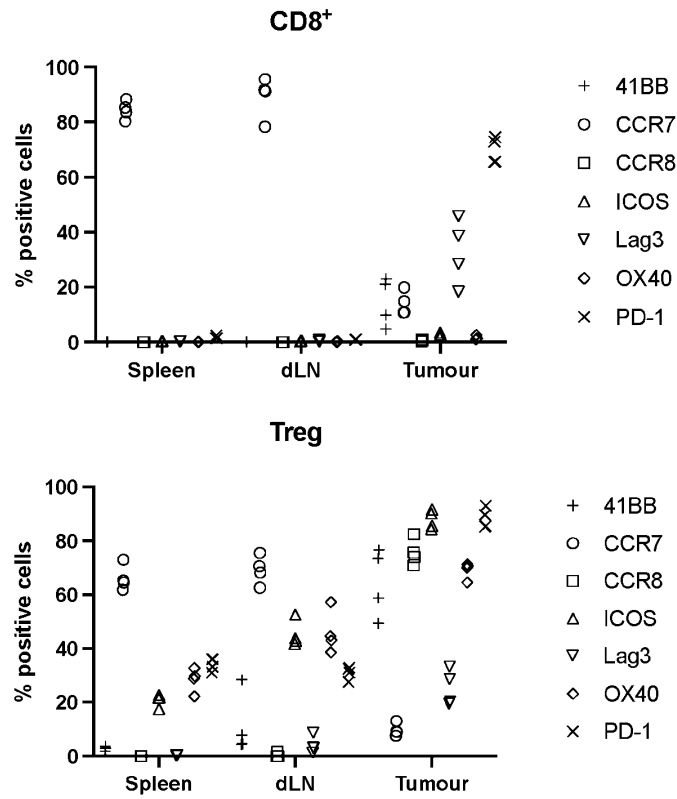


Fig. 31

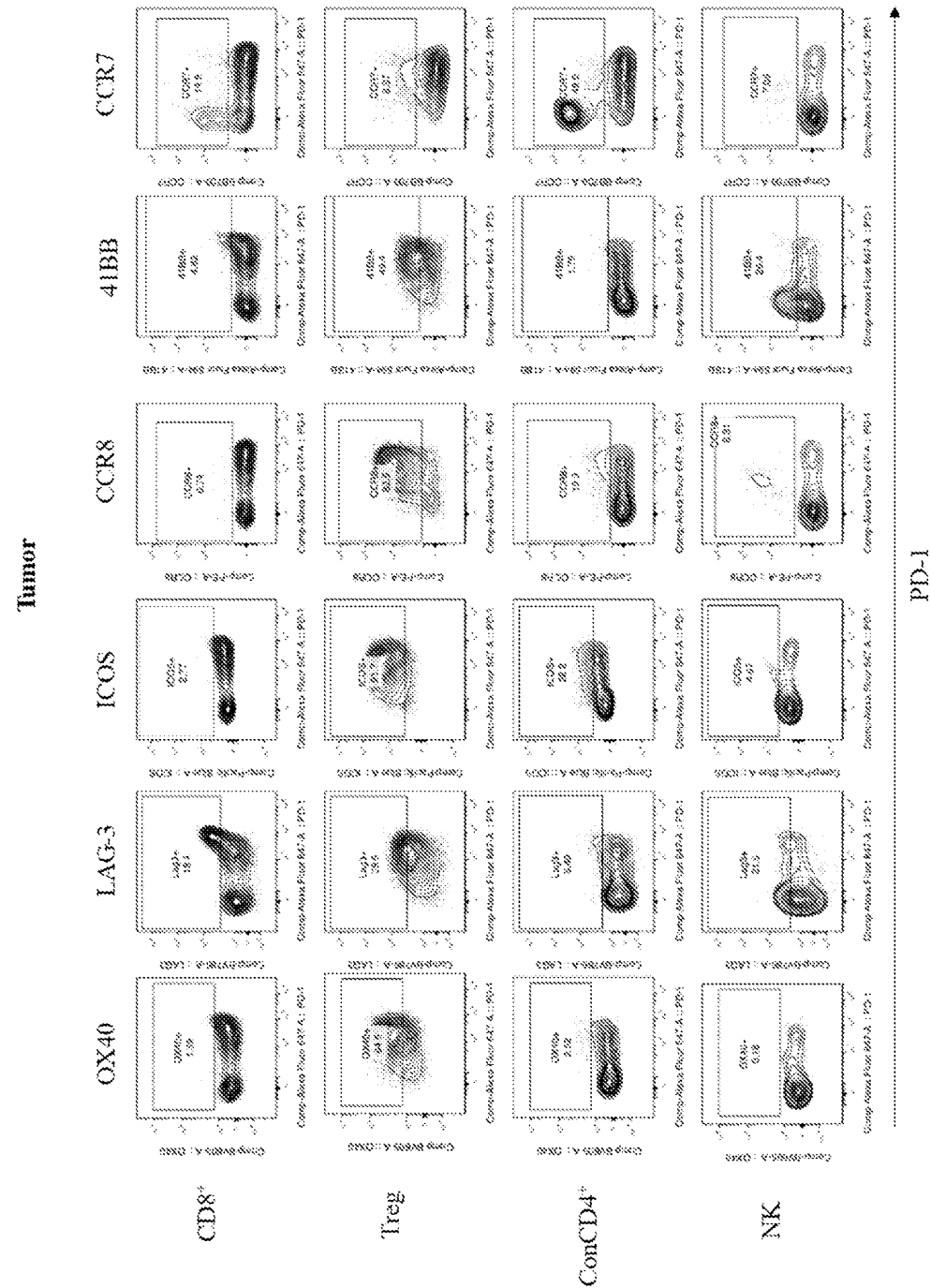


Fig. 32

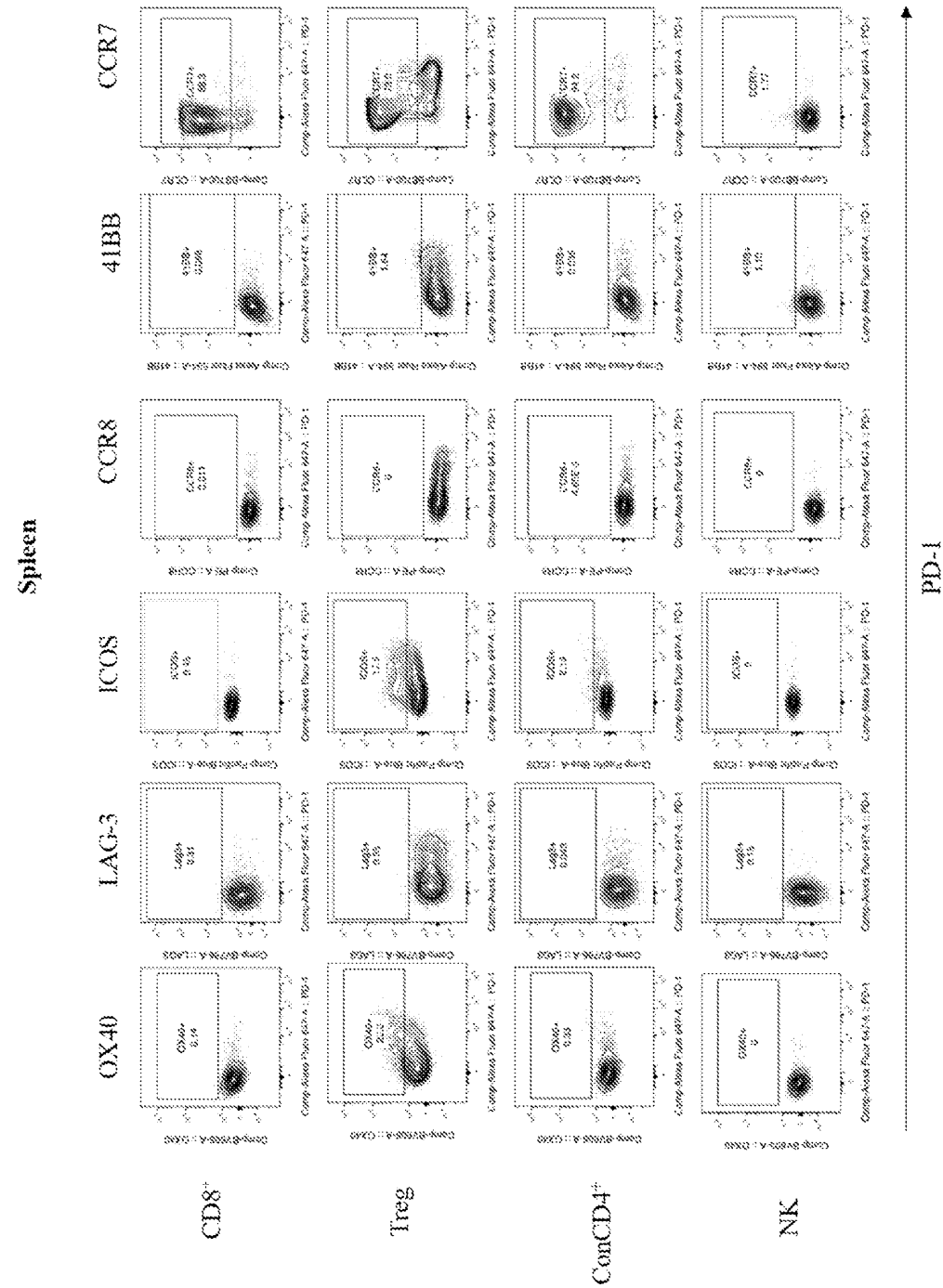


Fig. 33

Name	Mouse IL-12 p35 mutation	ABD specificity	Chain A seqID	Chain B seqID	Chain C seqID
mono-Y36E- Hyhel10	Y36E	Hen egg-white lysozyme	53	45	46
mono-Y36E-F12/3	Y36E	Mouse PD1	53	60	61
mono-Y36E- ADI31853	Y36E	Mouse and human LAG3	53	64	65
mono-Y36E-OX86	Y36E	Mouse OX40	53	68	69
mono-Y36E- TABBY107	Y36E	Mouse and human 41BB	53	72	73
mono-Y36E- KY1044	Y36E	Mouse and human ICOS	53	76	77
Mono-Y36E- VHH120	Y36E	Mouse and human CCR8	53	134	-
IL-12 Fc Y36E	Y36E	-	135	136	-

Fig. 34

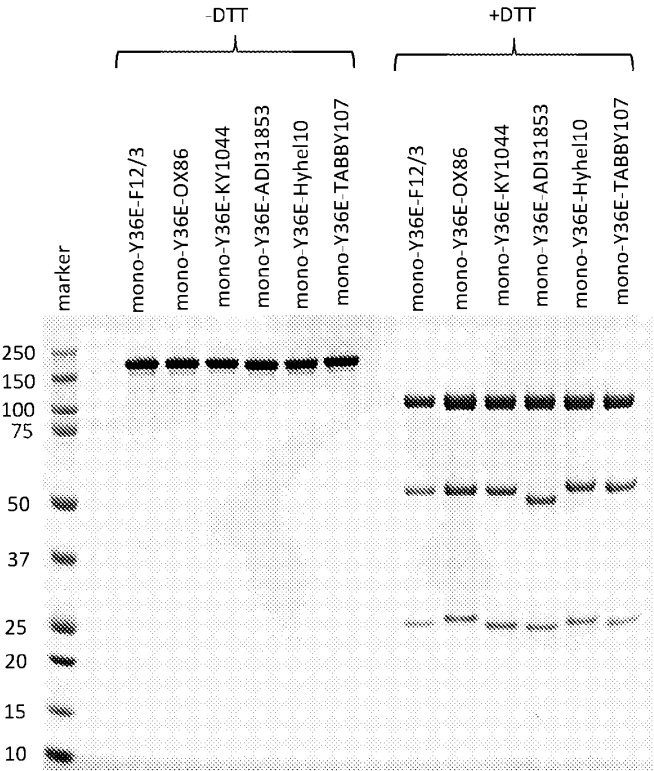


Fig. 36 – Fig. 36A

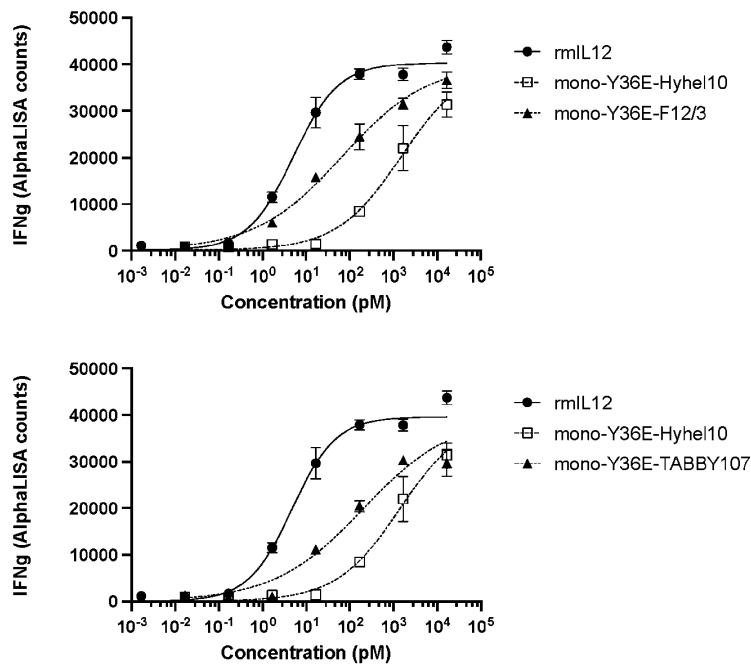


Fig. 36 – Fig. 36B

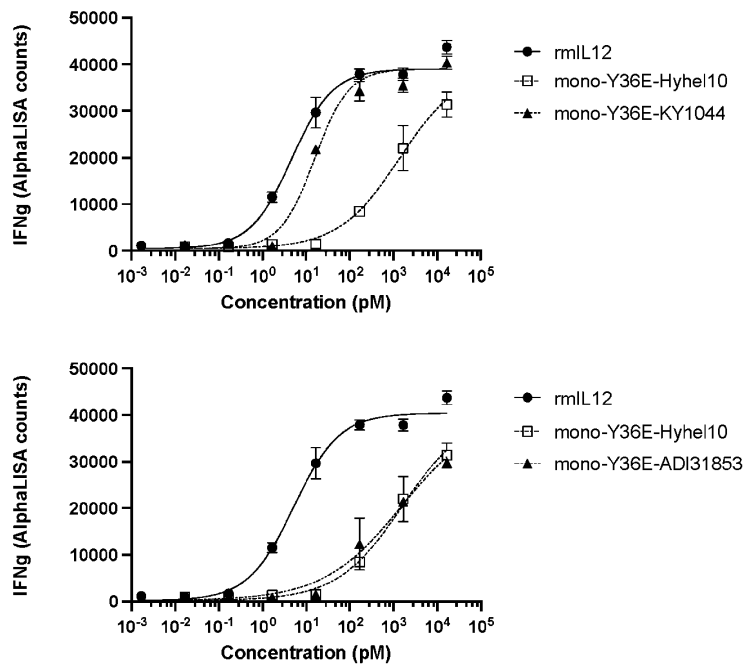


Fig. 37

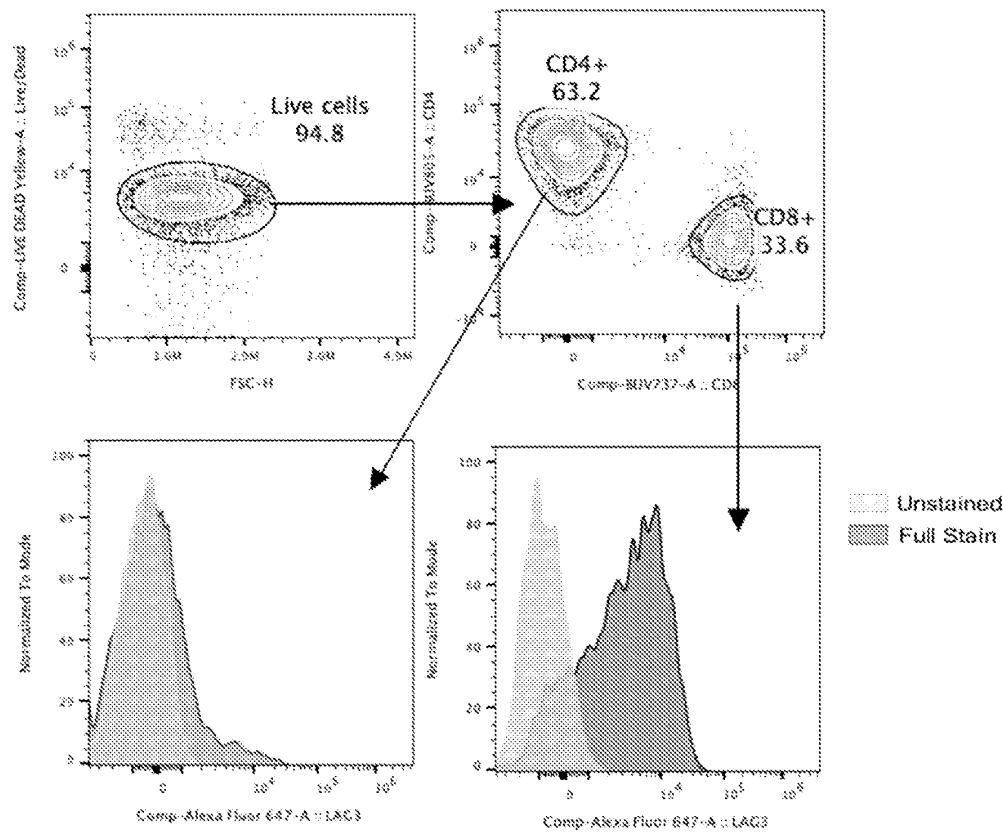


Fig. 38

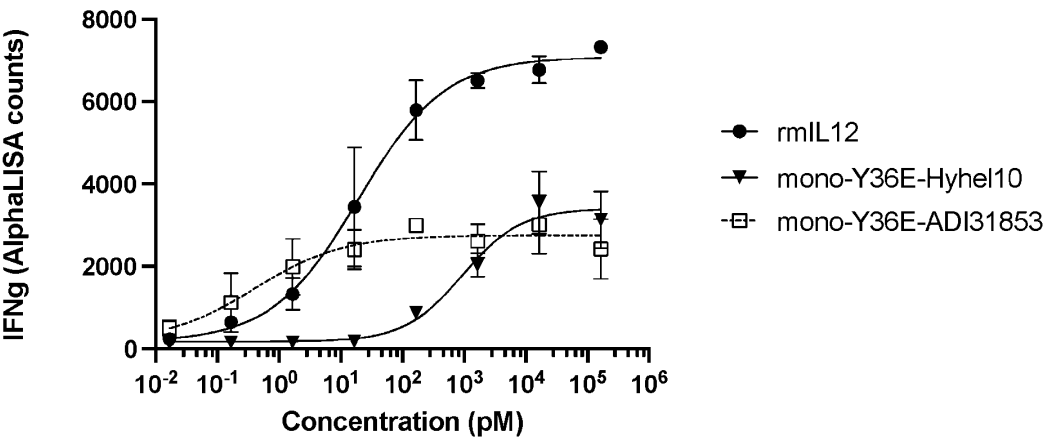


Fig. 39

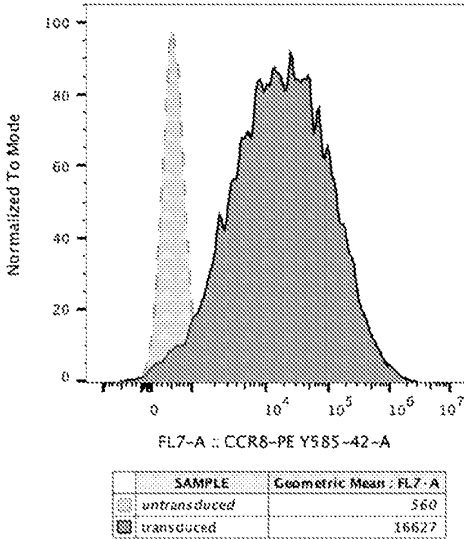


Fig. 40

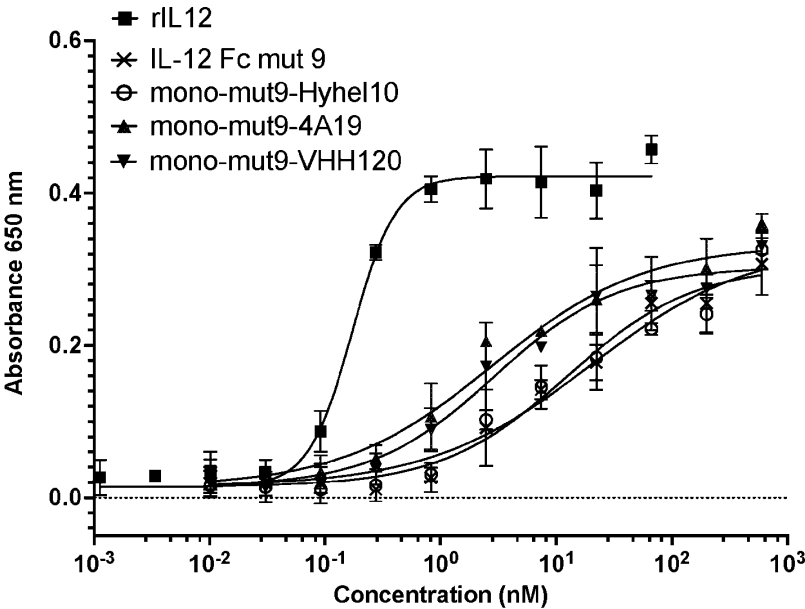


Fig. 41

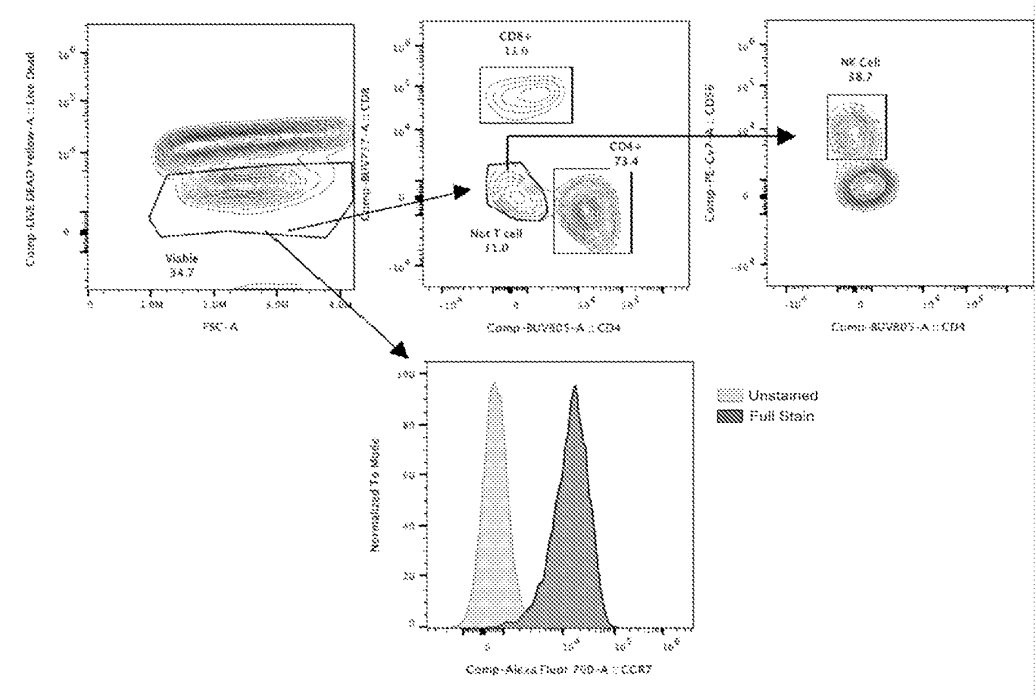


Fig. 42

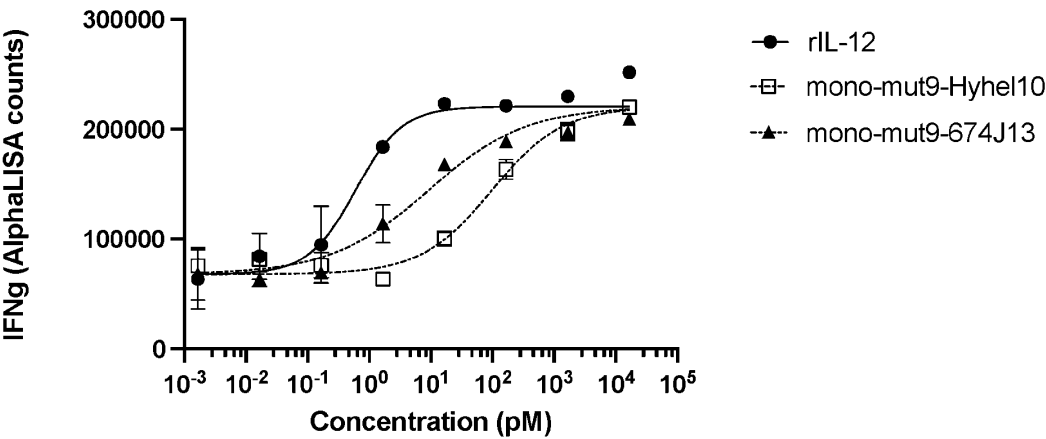


Fig. 43

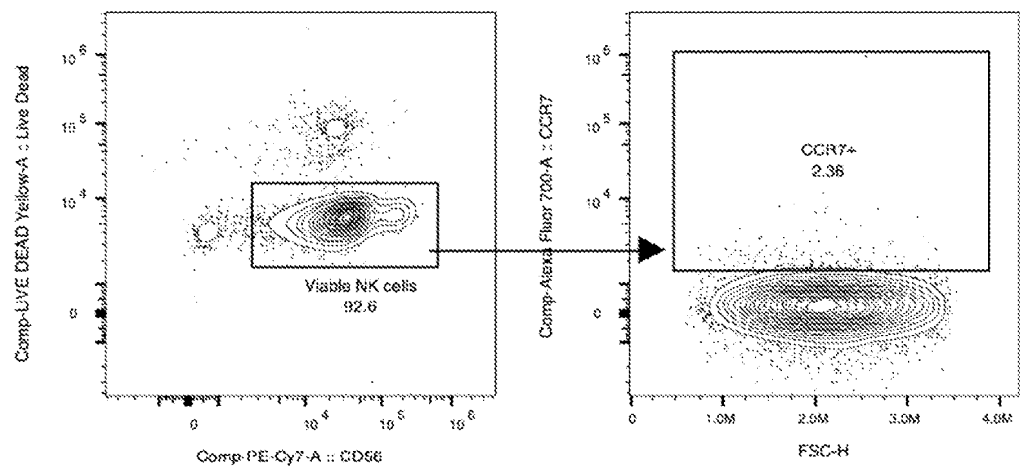


Fig. 44

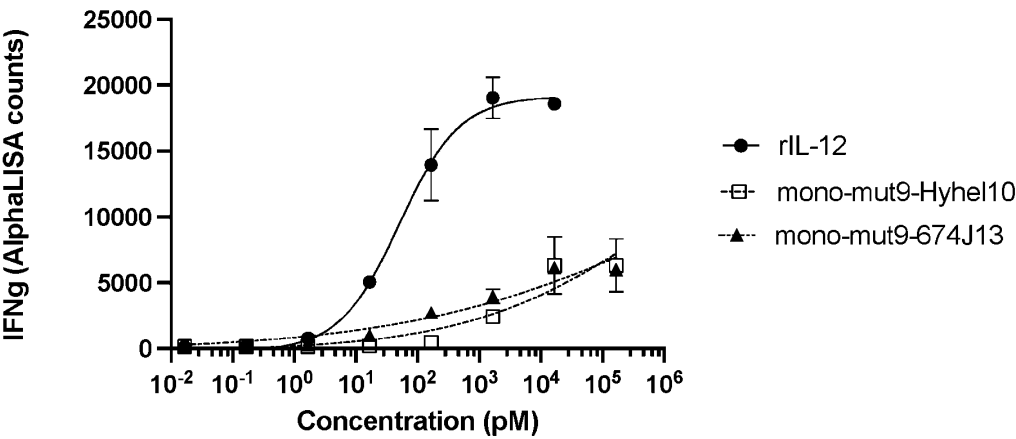


Fig. 45**A. Full length human CCR8 protein**

MDYTLDLSTTVTDYYYPDIFSSPCDAELIQTN GKLLLAVFYCLLFVFSLLGNSLVILVLVVCKKLRSITDVYLLNL
ALSDLLFVFSFPFQTYLLDQWVFGTVMCKVVSGFYIIGFYSSMFFITLMSVDRYLAVVHAVYALKVRTIRMGTTLCL
LAVWLTAIMATIPLLVFYQVASEDGVLCYSFYNNQTLKWKIFTNFKMNLGLLIPFTIFMFCYIKILHQLKRCQNH
NKTKAIRLVLIIVIASLLFWVPFNVVLFSLHSMHILDGCSISQQLTYATHVTEIISFTHCCVNPVIYAFVGEKFK
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Fig. 46

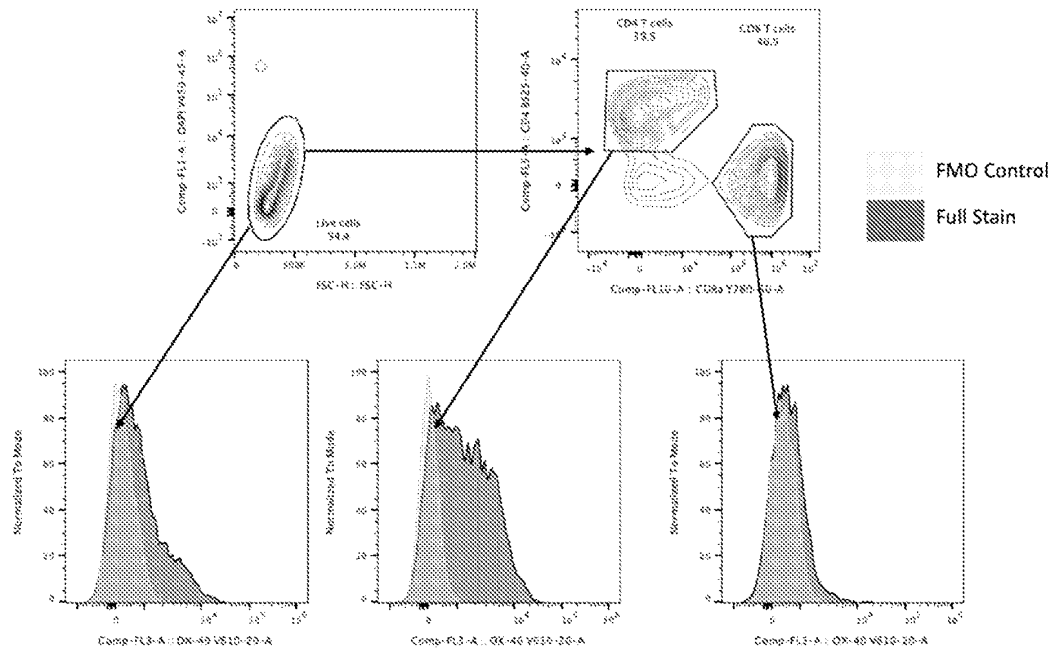


Fig. 47

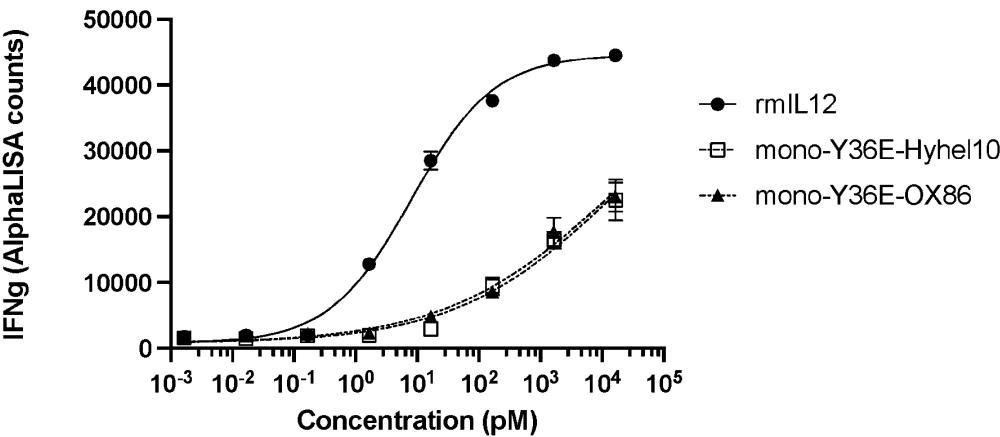


Fig. 48

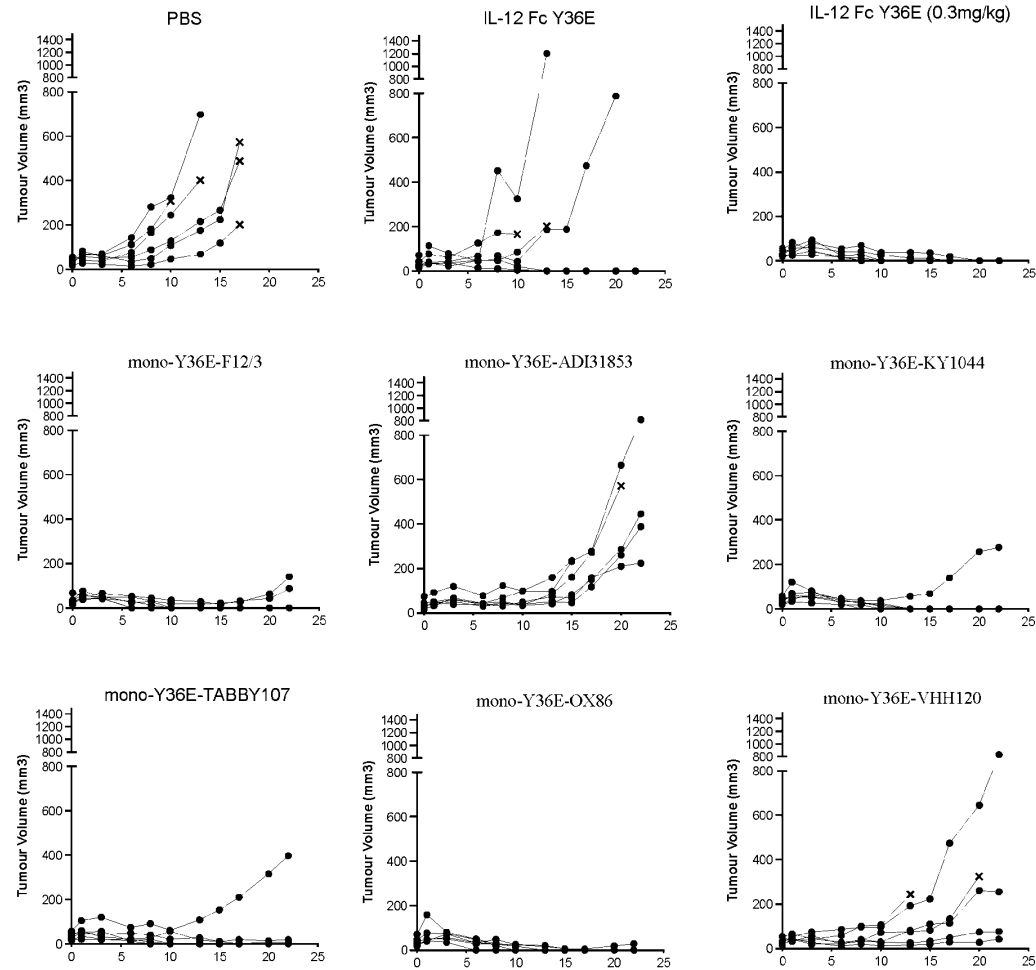


Fig. 49 – Fig. 49A

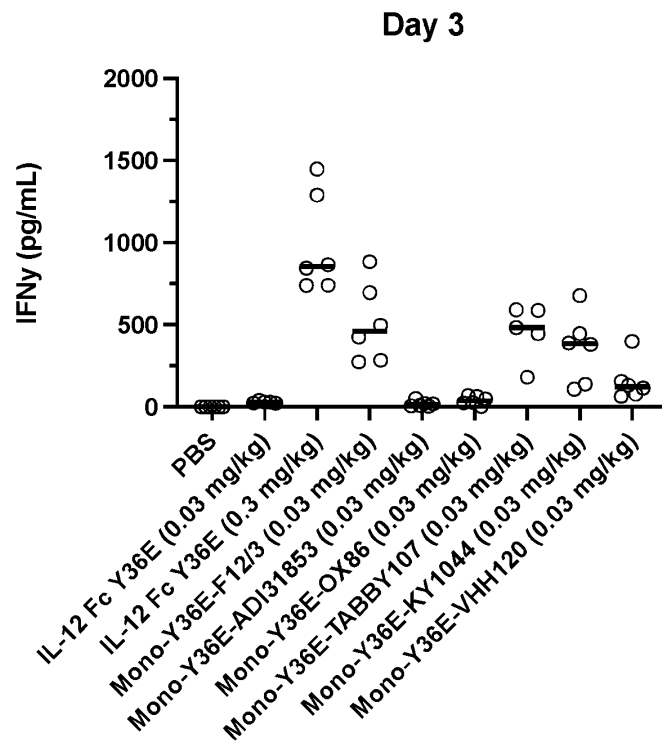


Fig. 50 – Fig. 50A

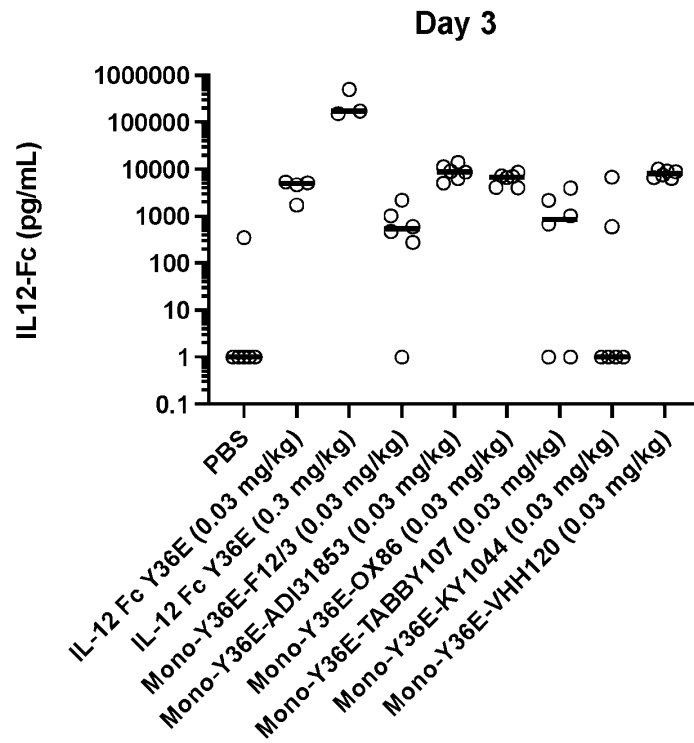


Fig. 50 – Fig. 50B

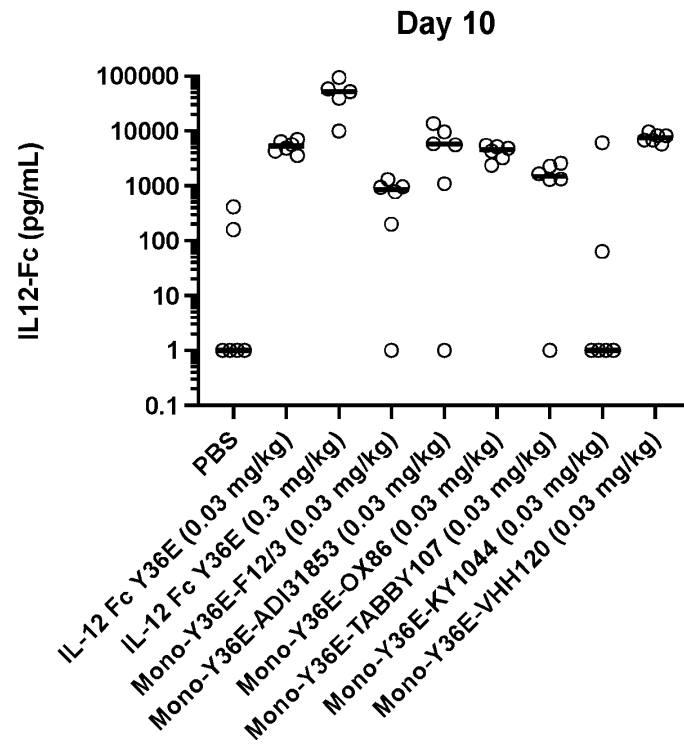


Fig. 50 – Fig. 50C

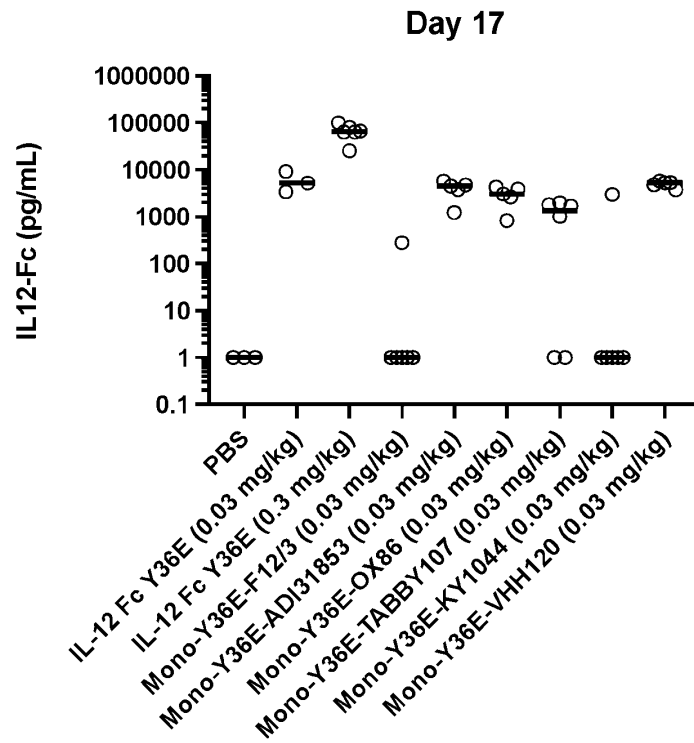


Fig. 51

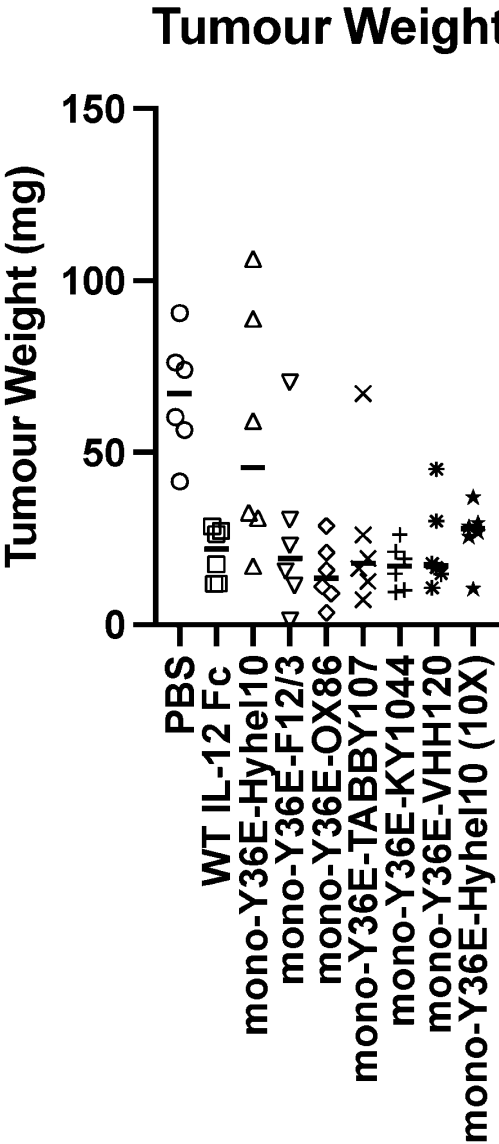
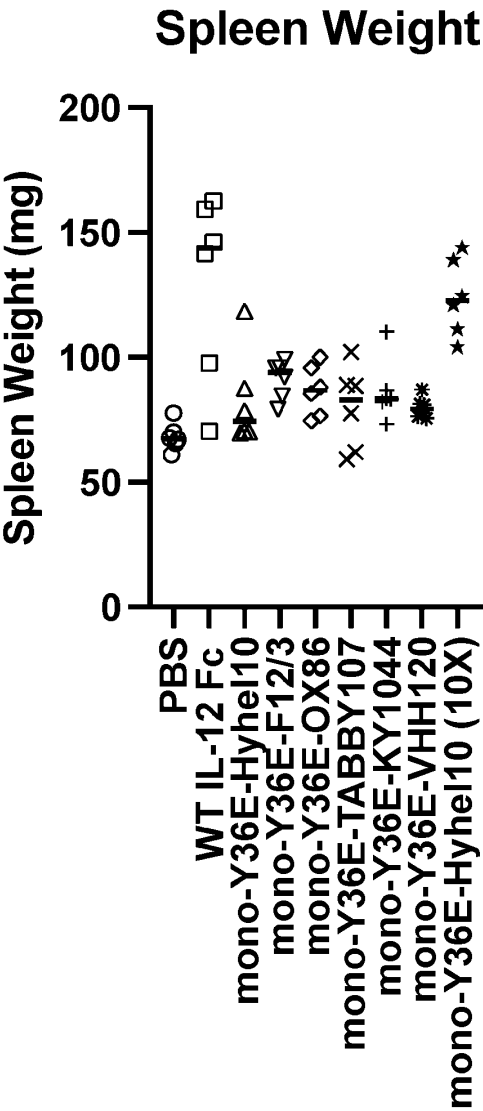


Fig. 52



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Fig. 53

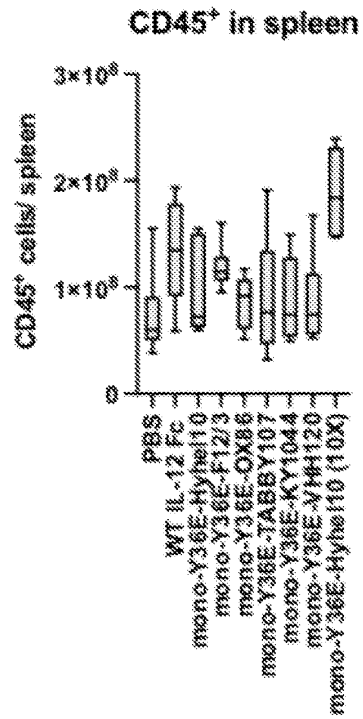


Fig. 54

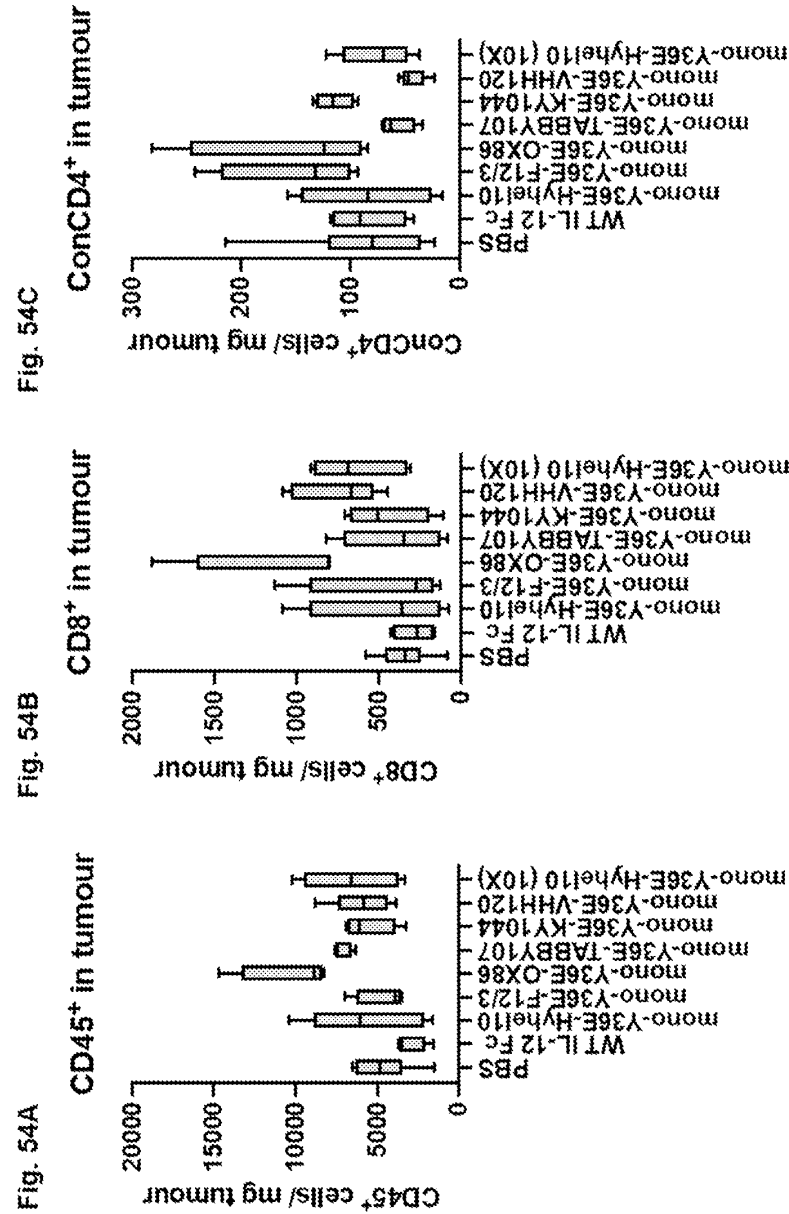


Fig. 54 (Continued)

Fig. 54D

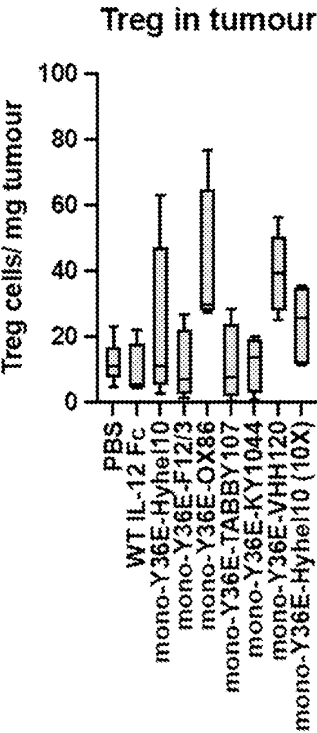


Fig. 54E

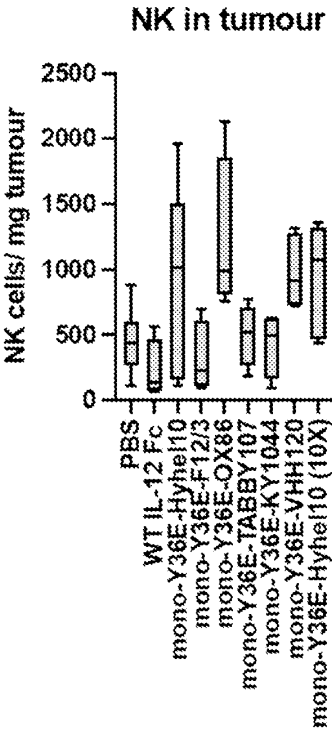


Fig. 55

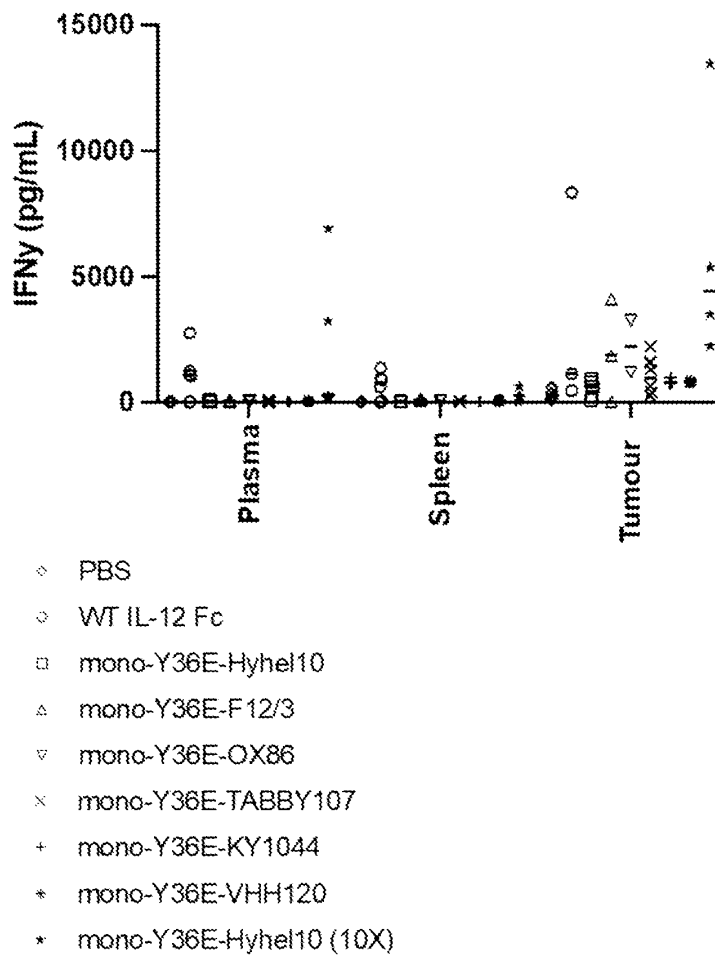


Fig. 56

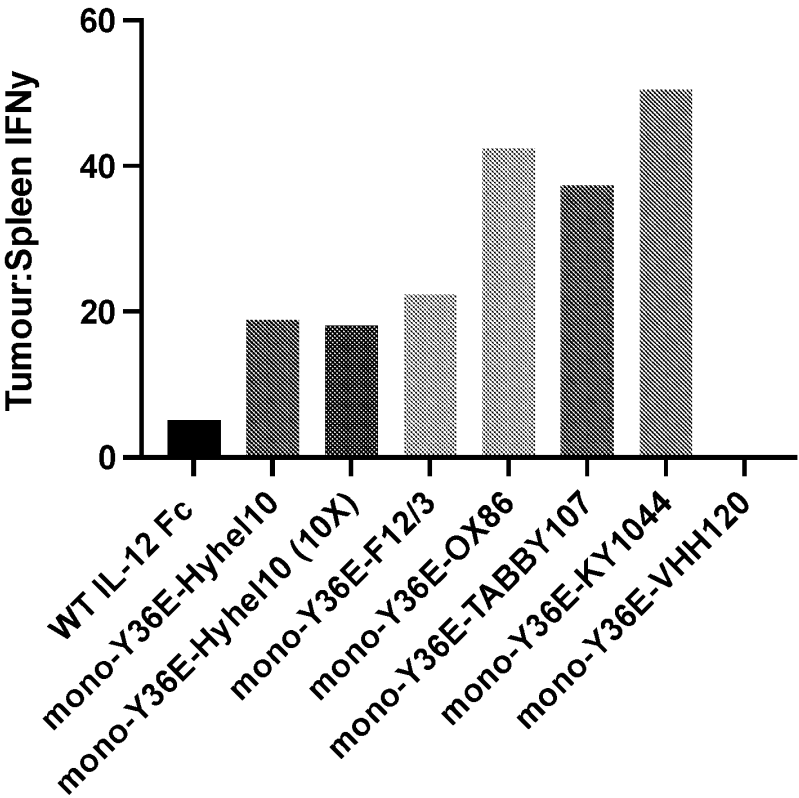


Fig. 57

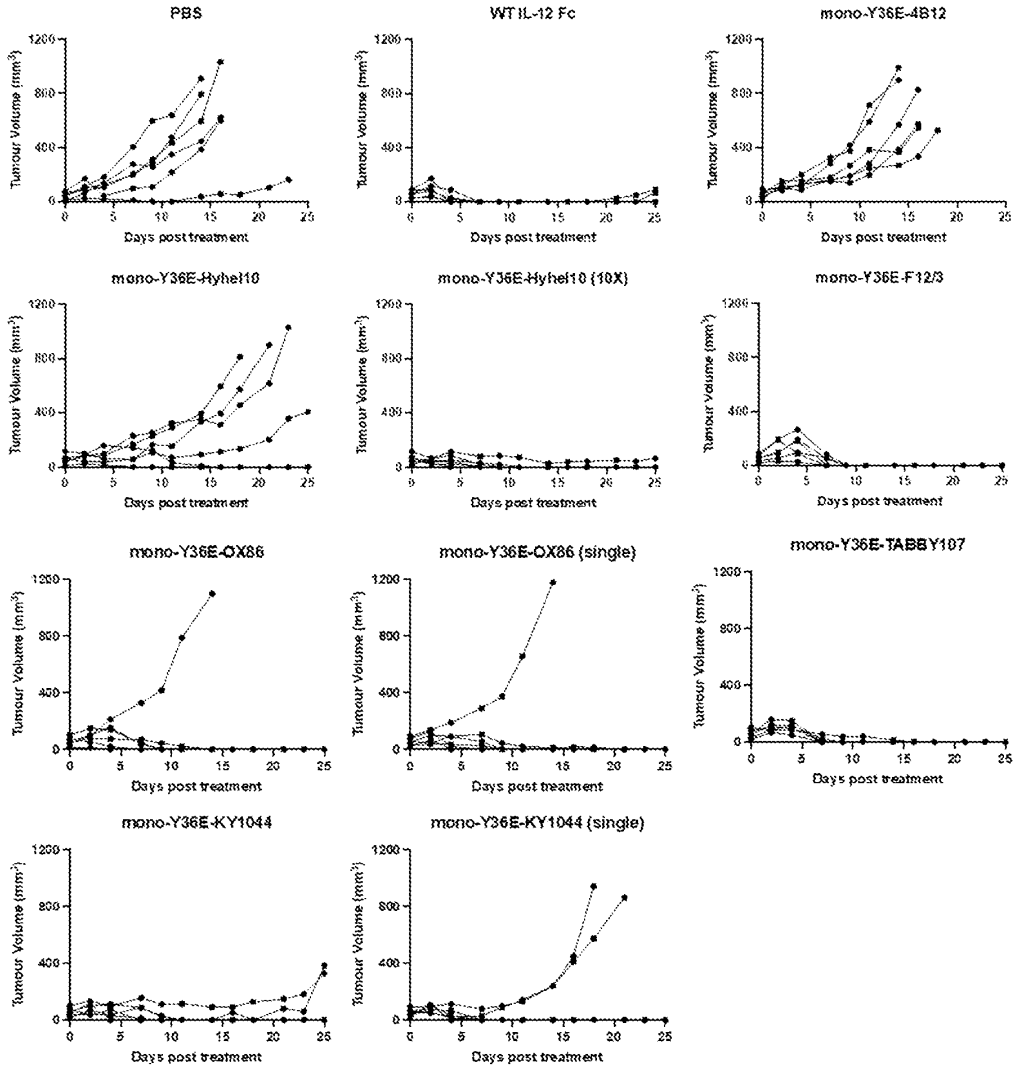


Fig. 58 – Fig. 58A

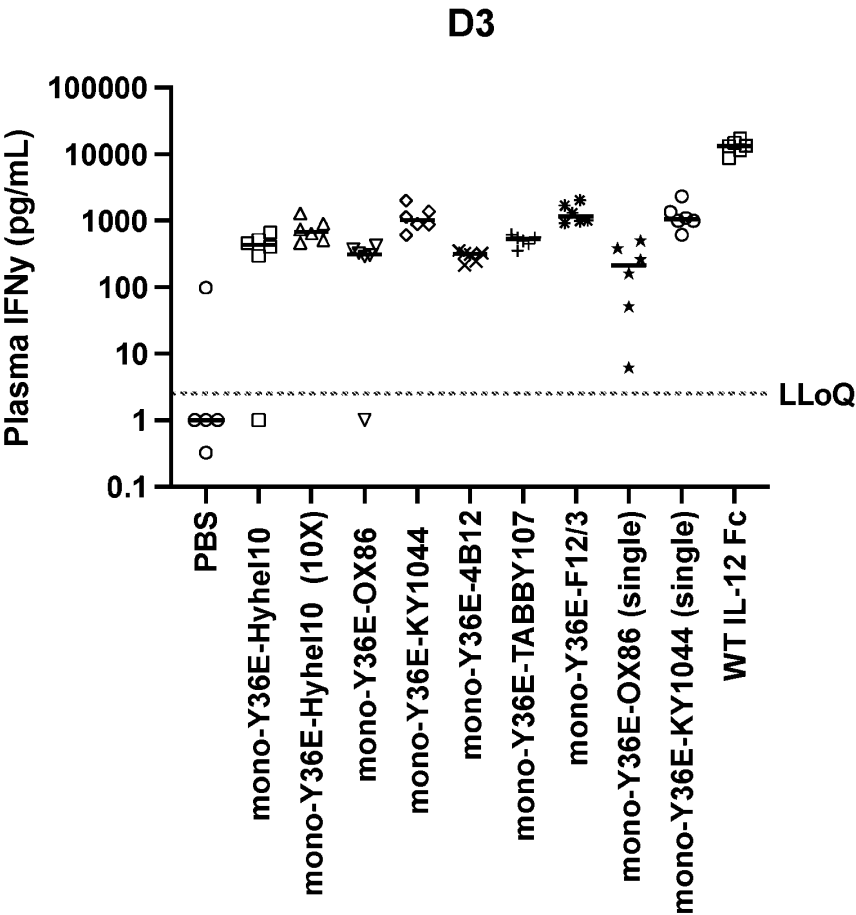


Fig. 58 – Fig. 58B

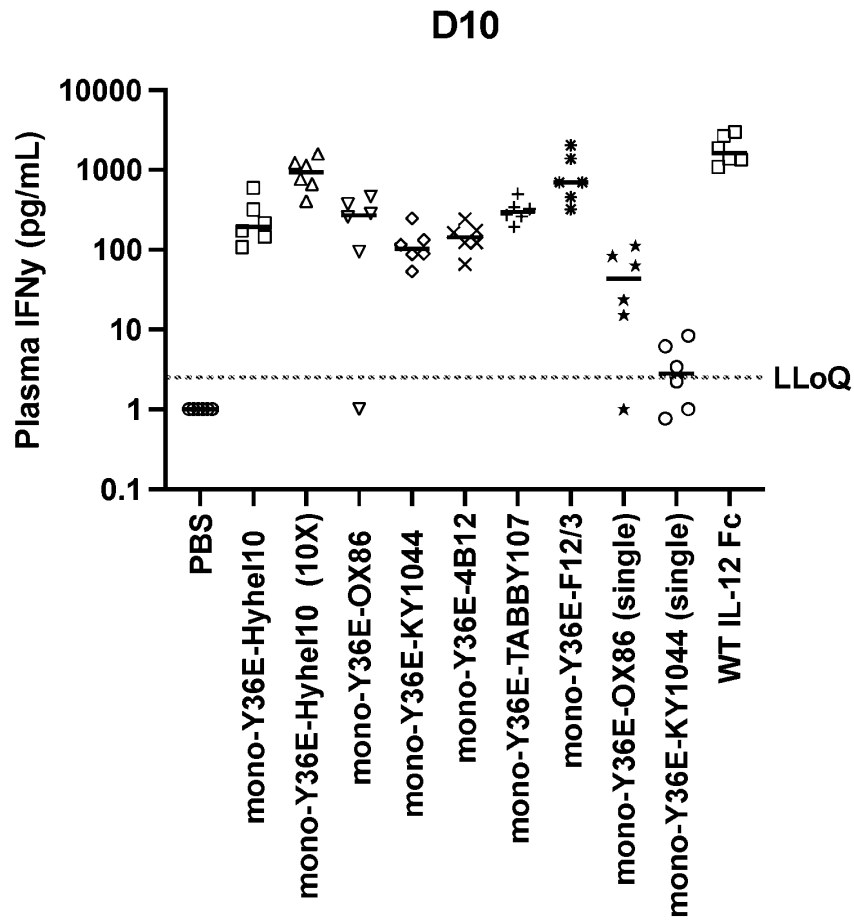


Fig. 58 – Fig. 58C

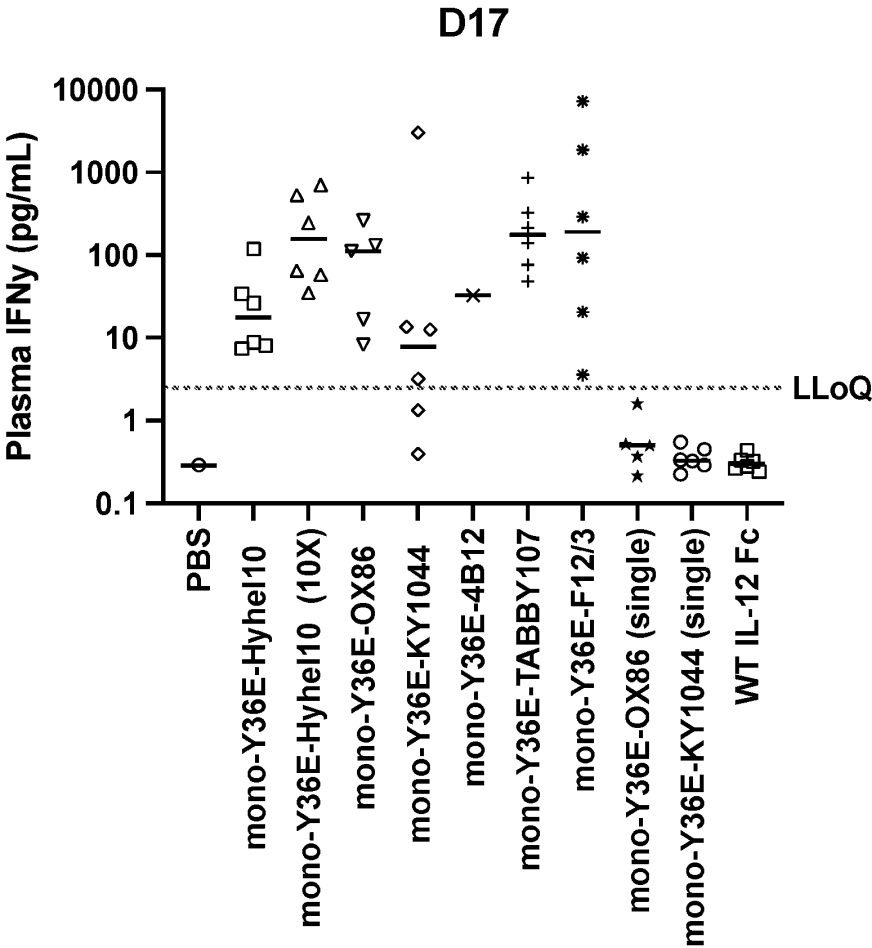


Fig. 59

Wellness:

- Cumulative Score 0-3: No concerns
- Cumulative Score 4-5 or individual criteria score of 2: Daily monitoring. Provide Much Stinging and Jelly.
- Cumulative Score 6-7 or individual criteria score of 3: Twice daily monitoring. Provide Much Stinging, Jelly, and heat mat.
- Cumulative Score 8 or individual criteria score of 4: Euthanasia.

Behavior	Score 1	Score 2	Score 3	Score 4	Score 5
Posture score	Normal: Mouse moves freely and exhibits a contained, smooth gait without any signs of lameness or abnormalities.	Slight impairment: Mouse occasionally exhibits a slight hunched posture but spends most of the time in a normal position.	Moderate hunching: Mouse spends a significant portion of the time in a hunched posture.	Severe hunching: Mouse maintains a hunched posture, showing signs of discomfort and may stop walking around on their own.	Extreme hunching: Mouse is consistently hunched over, unable to maintain a normal posture, and displays signs of severe distress.
Movement Unit score	Normal: Mouse moves freely and exhibits a contained, smooth gait without any signs of lameness or abnormalities.	Slight impairment: Mouse displays occasional slight abnormalities in gait but can still move around freely.	Mild impairment: Mouse exhibits consistent noticeable abnormalities in movement and gait, including slower movements or stiffness, may start walking on their own.	Severe impairment: Mouse exhibits severely impaired gait, including reduced movements, reduced ability to bear weight on one or more limbs, limping, walking.	Complete inability to move: Mouse is completely immobile or unable to move due to paralysis, severe injury, or other incapacitating conditions.
Anxiety Score	Normal: Mouse displays typical exploratory behavior, grooming, and engagement with environmental stimuli and cage mates.	Slightly reduced activity: Mouse shows slightly decreased activity compared to normal behavior with occasionally less frequent interaction with the environment.	Moderately reduced activity: Mouse exhibits a significant reduction in activity compared to normal behavior with minimal movement and limited interaction with the environment.	Very low activity: Mouse displays few activities, spending most of the time in one space. May show signs of lethargy and little to no interest in environmental stimuli.	Complete inactivity: Mouse is completely immobile and unresponsive to stimuli, showing no signs of activity or engagement with the environment.
Coat condition score	Normal: Excellent coat condition. Mouse has a shiny, smooth, and well-groomed coat.	Minimal abnormalities: Mouse's coat appears mostly healthy but may be slightly duller.	Moderate abnormalities: Mouse's coat displays abnormalities, such as dullness, maintains a rough/shedding appearance.	Severe deterioration: Mouse's coat is in poor condition and will appear dark, maintains a rough/shedding appearance and exhibits photophobia.	Critical condition: Mouse's coat is in poor condition and will appear dull, maintains a rough/shedding appearance and exhibits photophobia, is completely fluffed up and hair is clumped together.
Breathing score	Normal: Mouse exhibits normal, quiet breathing with no signs of labored breathing or respiratory distress.	Slight abnormalities: Mouse displays occasional irregularities in breathing but returns to normal.	Moderate respiratory distress: Mouse exhibits moderate respiratory distress with pronounced increases in respiratory rate and labored breathing at rest.		Critical respiratory distress: Mouse is in critical respiratory distress which may include symptoms of extreme difficulty breathing, shallow breaths, gasping for air, and audible wheezing or rattling.

Fig. 60

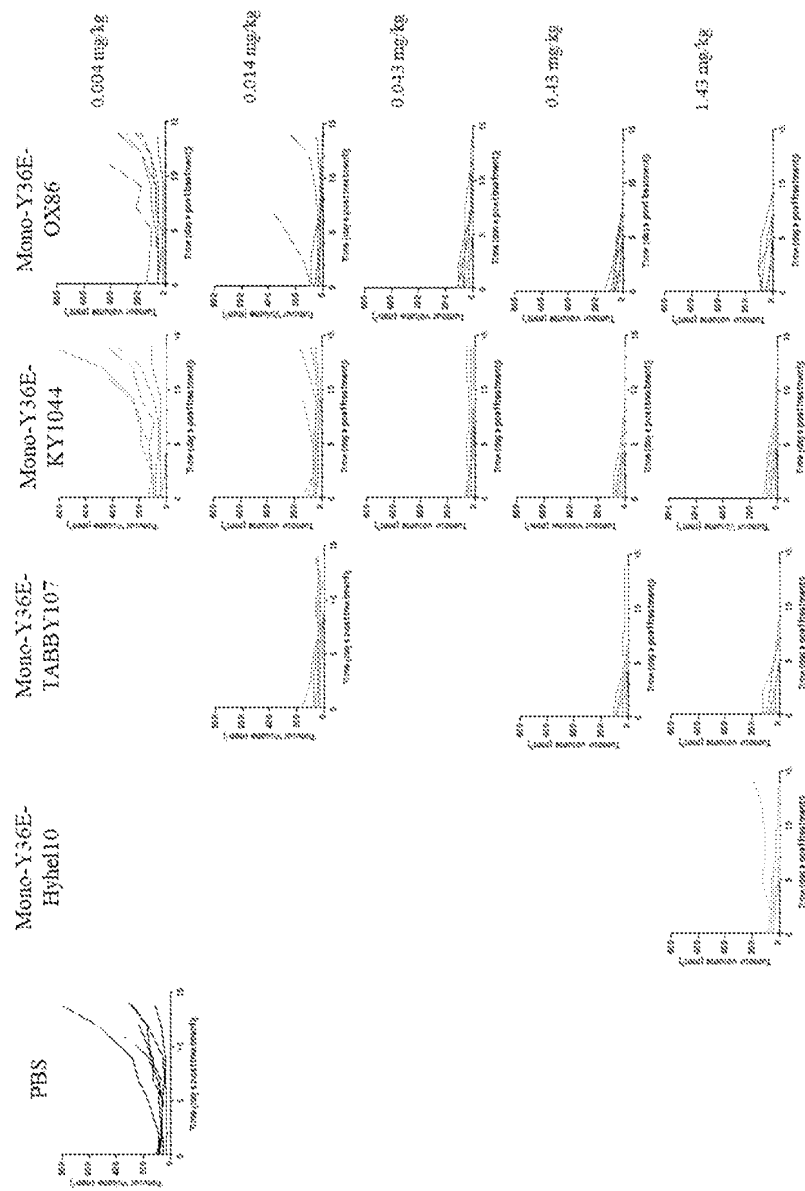


Fig. 61 – Fig. 61A

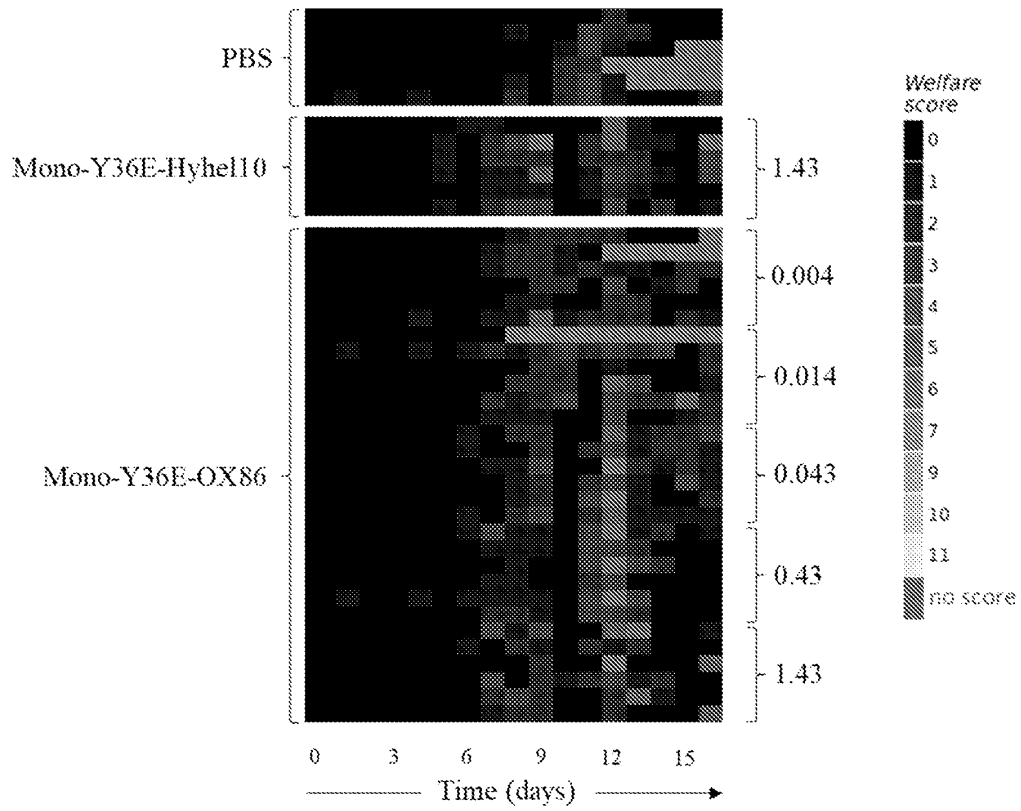


Fig. 61 – Fig. 61B

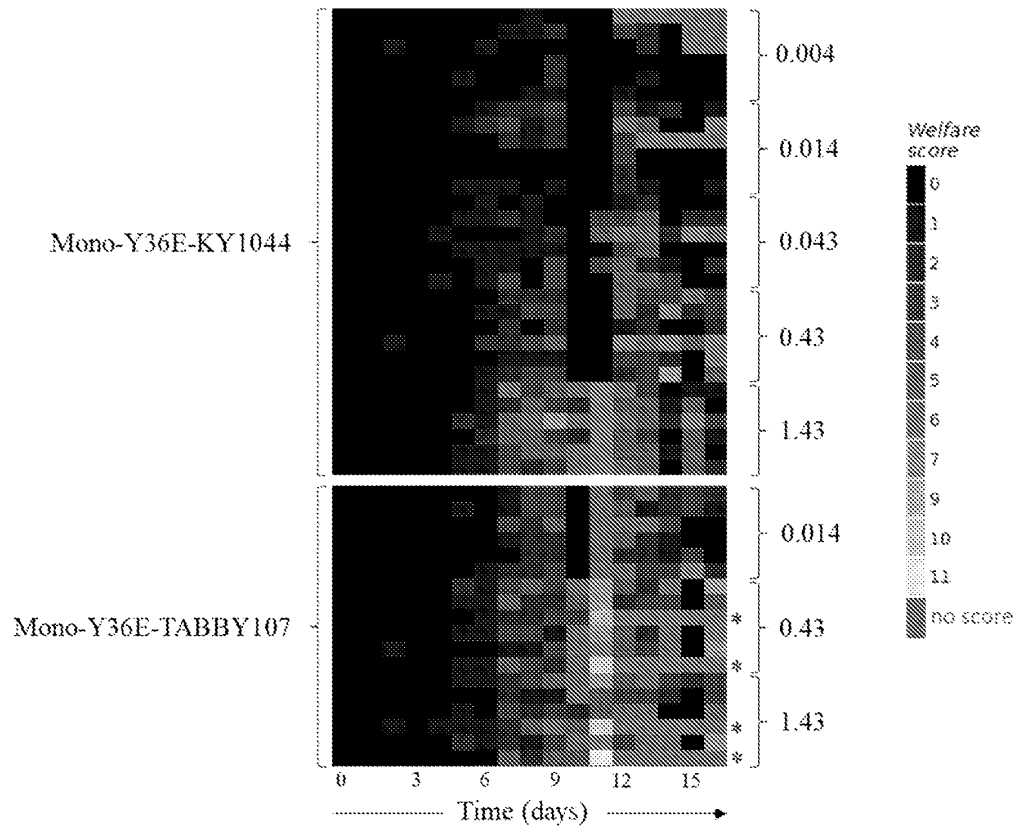


Fig. 62

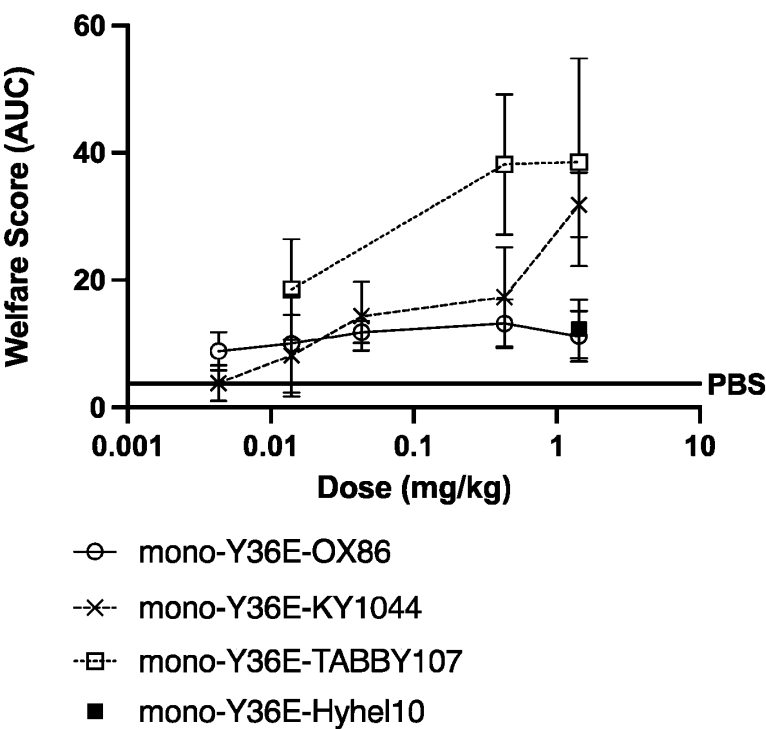


Fig. 63 – Fig. 63A

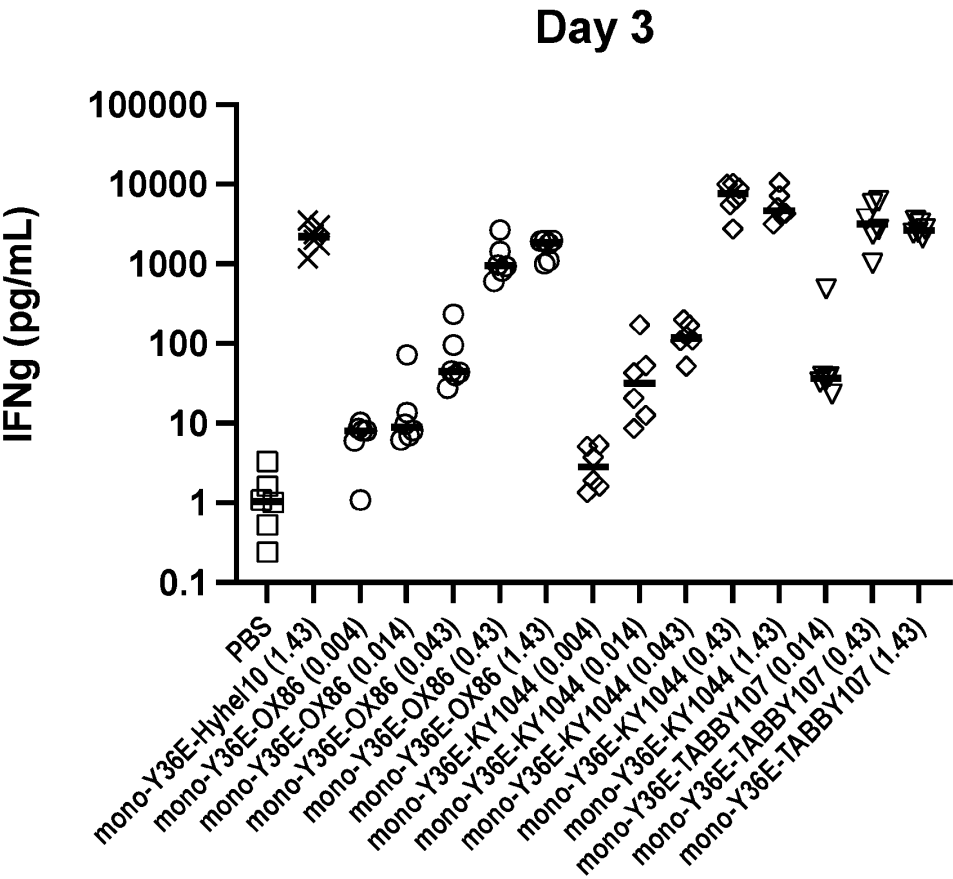


Fig. 63 – Fig. 63B

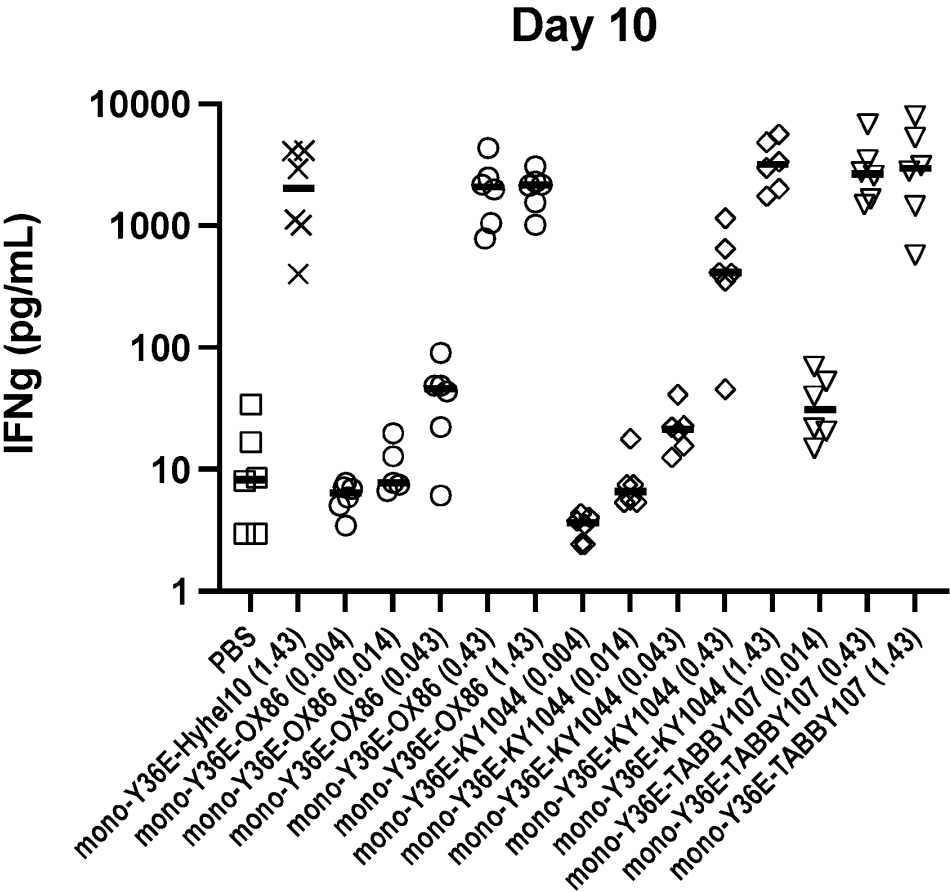


Fig. 63 – Fig. 63C

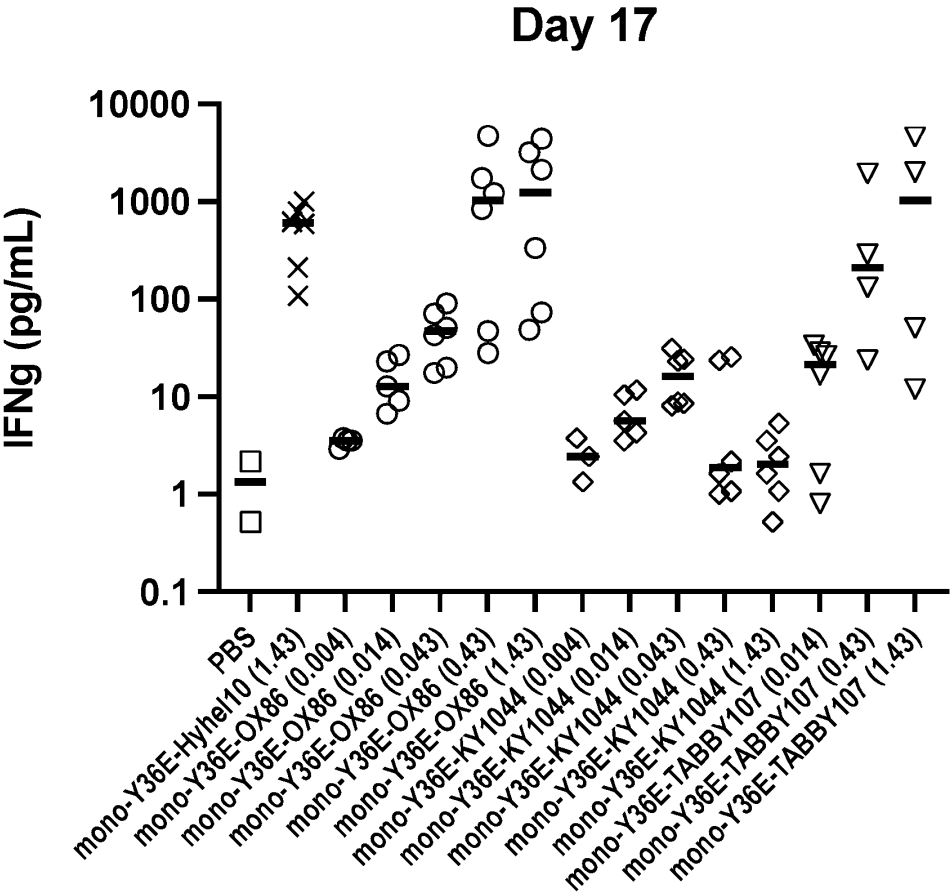


Fig. 64

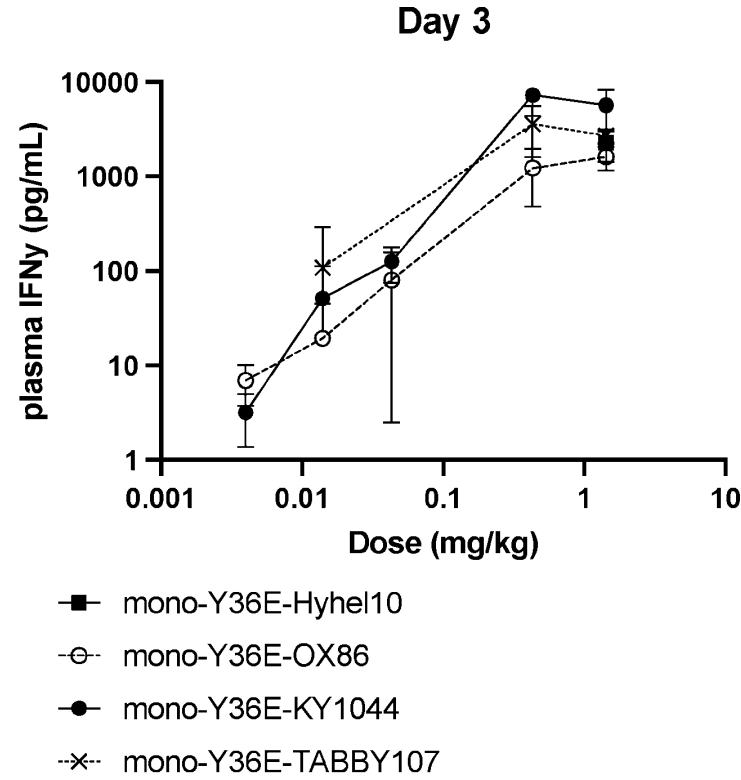


Fig. 65 – Fig. 65A

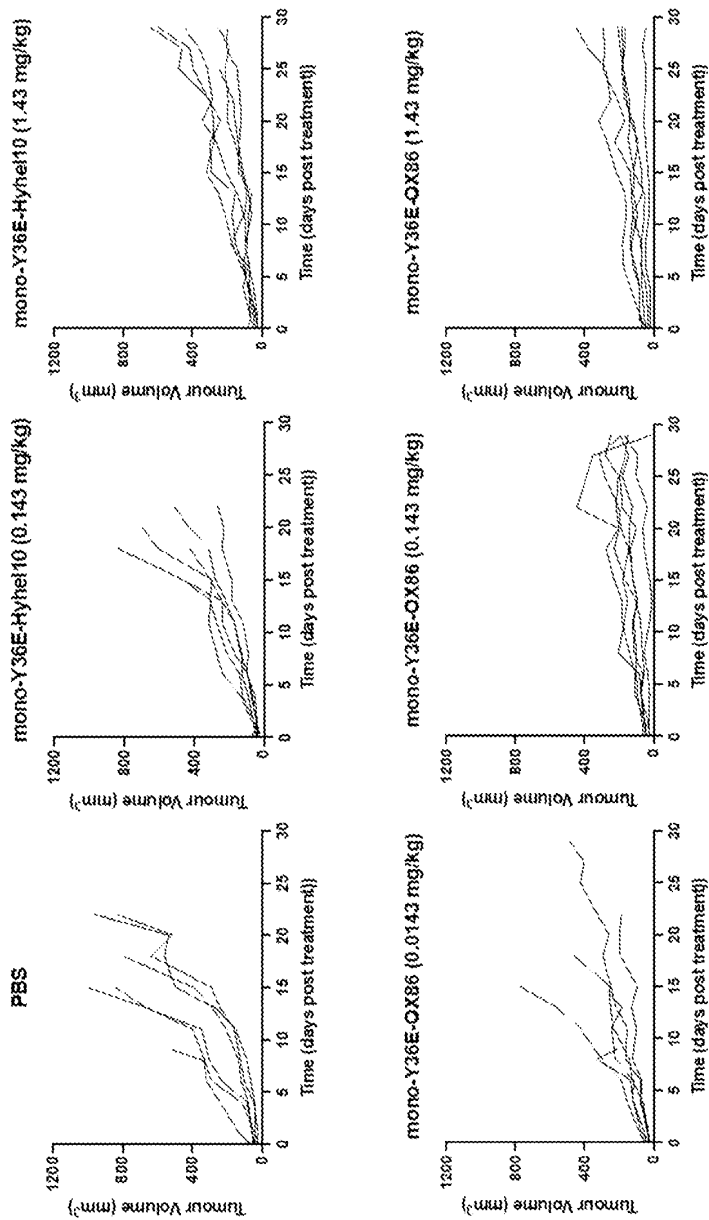


Fig. 65 – Fig. 65B

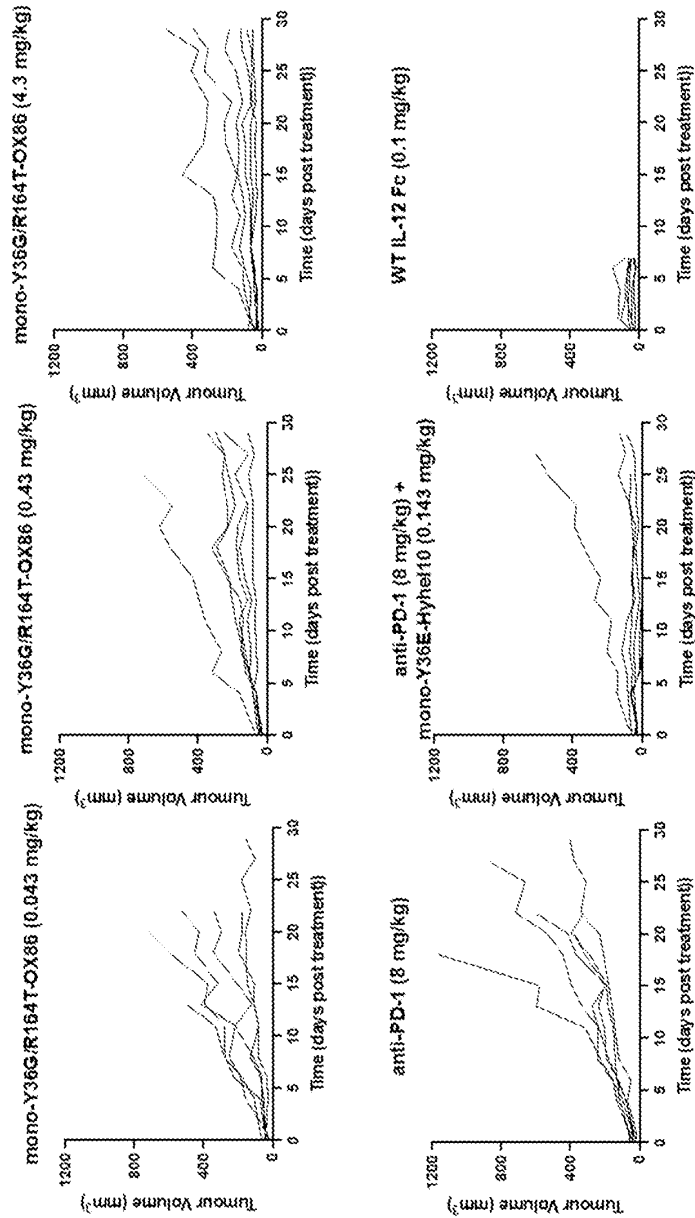


Fig. 66 – Fig. 66A

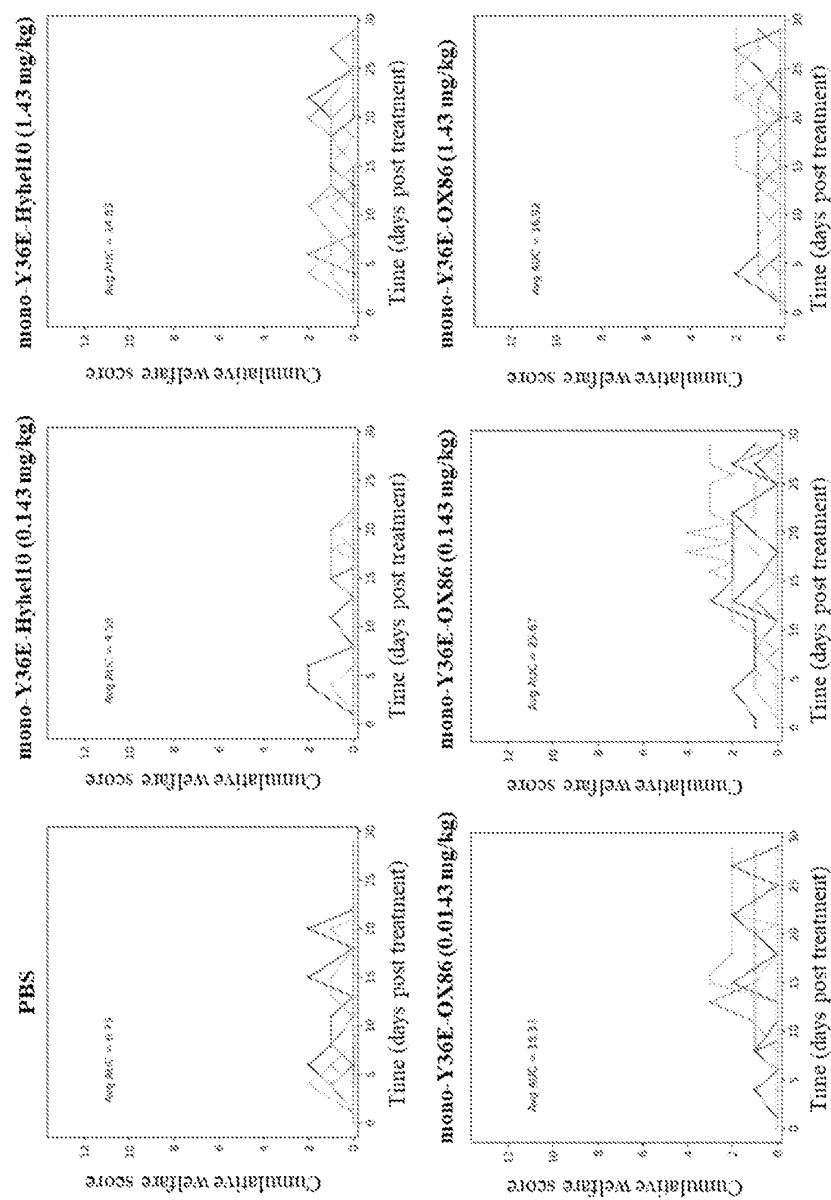


Fig. 66 – Fig. 66B

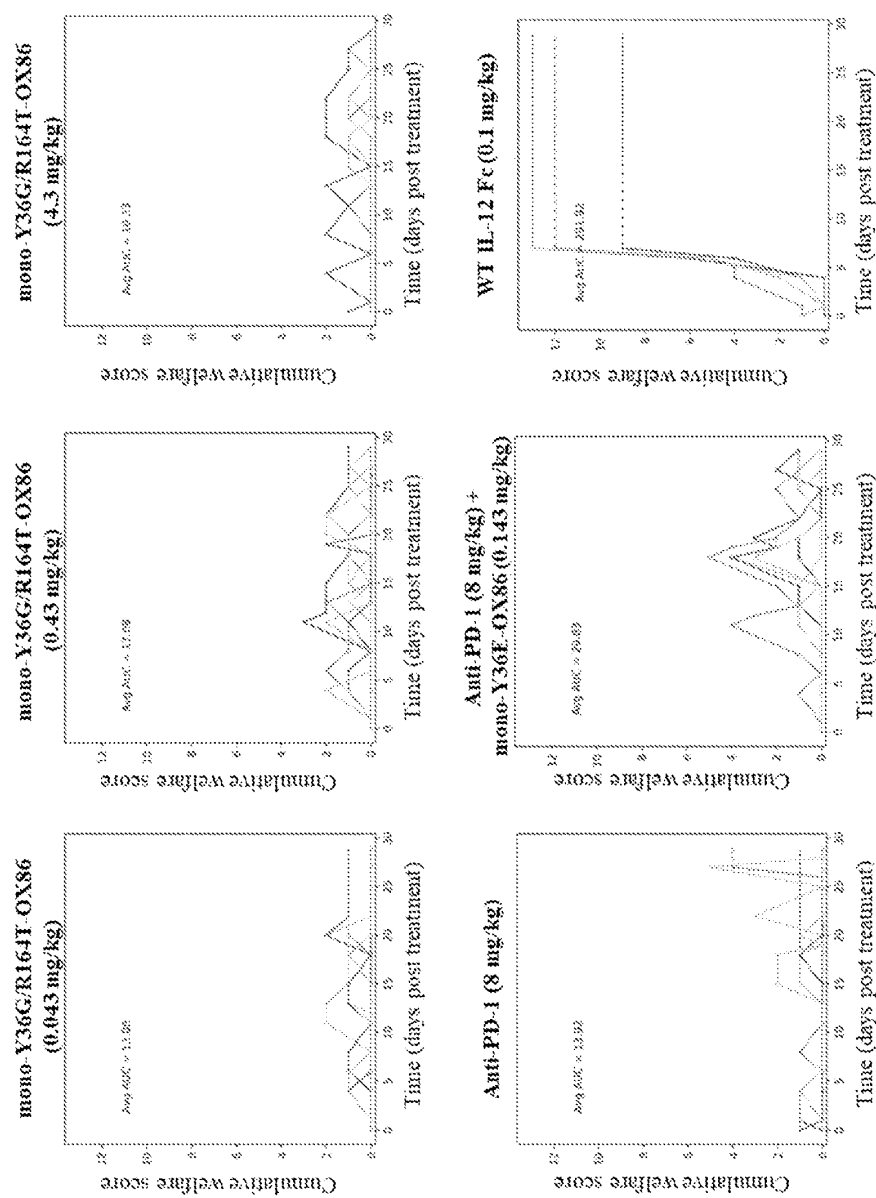
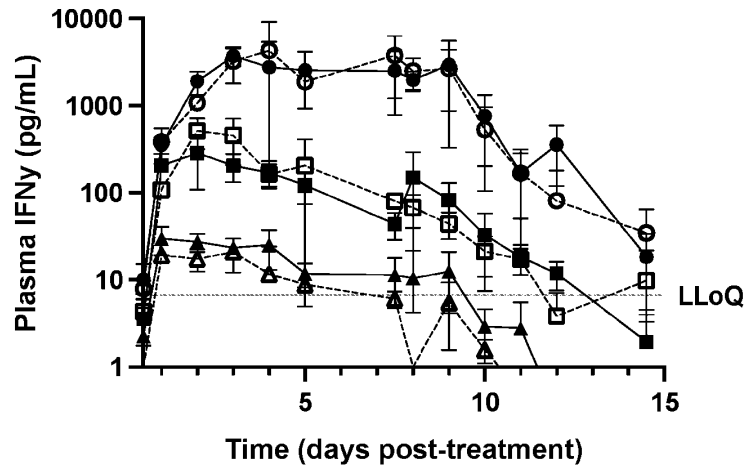
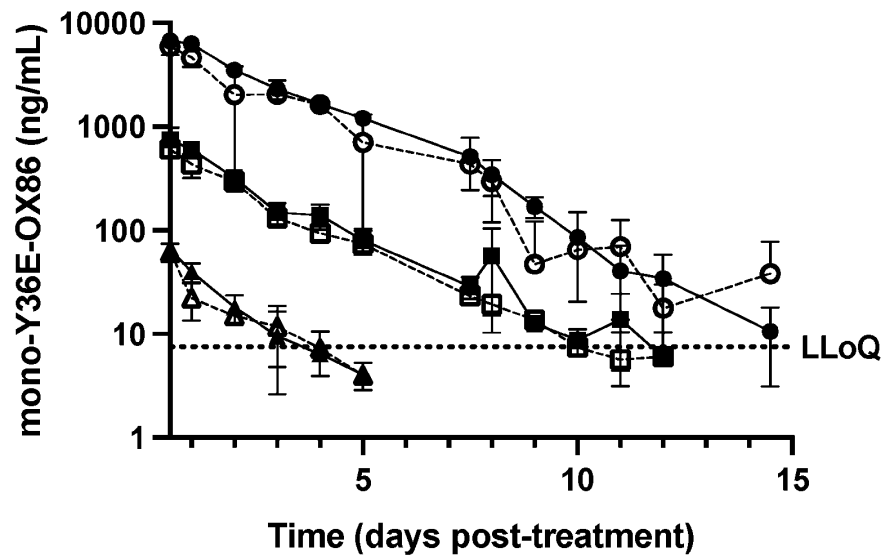


Fig. 68



- Tumour 1.43 mg/kg
- Tumour 0.143 mg/kg
- ▲ Tumour 0.0143 mg/kg
- No Tumour 1.43 mg/kg
- No Tumour 0.143 mg/kg
- △ No Tumour 0.0143 mg/kg

Fig. 69



- Tumour 1.43 mg/kg
- Tumour 0.143 mg/kg
- ▲ Tumour 0.0143 mg/kg
- No Tumour 1.43 mg/kg
- No Tumour 0.143 mg/kg
- △ No Tumour 0.0143 mg/kg

Fig. 70

Parameter	+Tumour		
Dose (mg/kg)	1.43	0.143	0.0143
Cmax (ug/mL)	6.884	0.749	0.098
AUC ₀₋₄ (days x ug/mL)	20.643	1.785	0.135
CL 1 (L/kg/Day/F)	6.927e-2	8.013e-2	0.130
CL 2 (L/kg/Day/F)	6.573e-2	3.291e-2	3.981e-2
Vss (L/kg/F)*	0.184	0.184	0.220
T1/2 Alpha	0.373	0.560	0.540
T1/2 Beta	2.385	2.263	2.468

Fig. 71

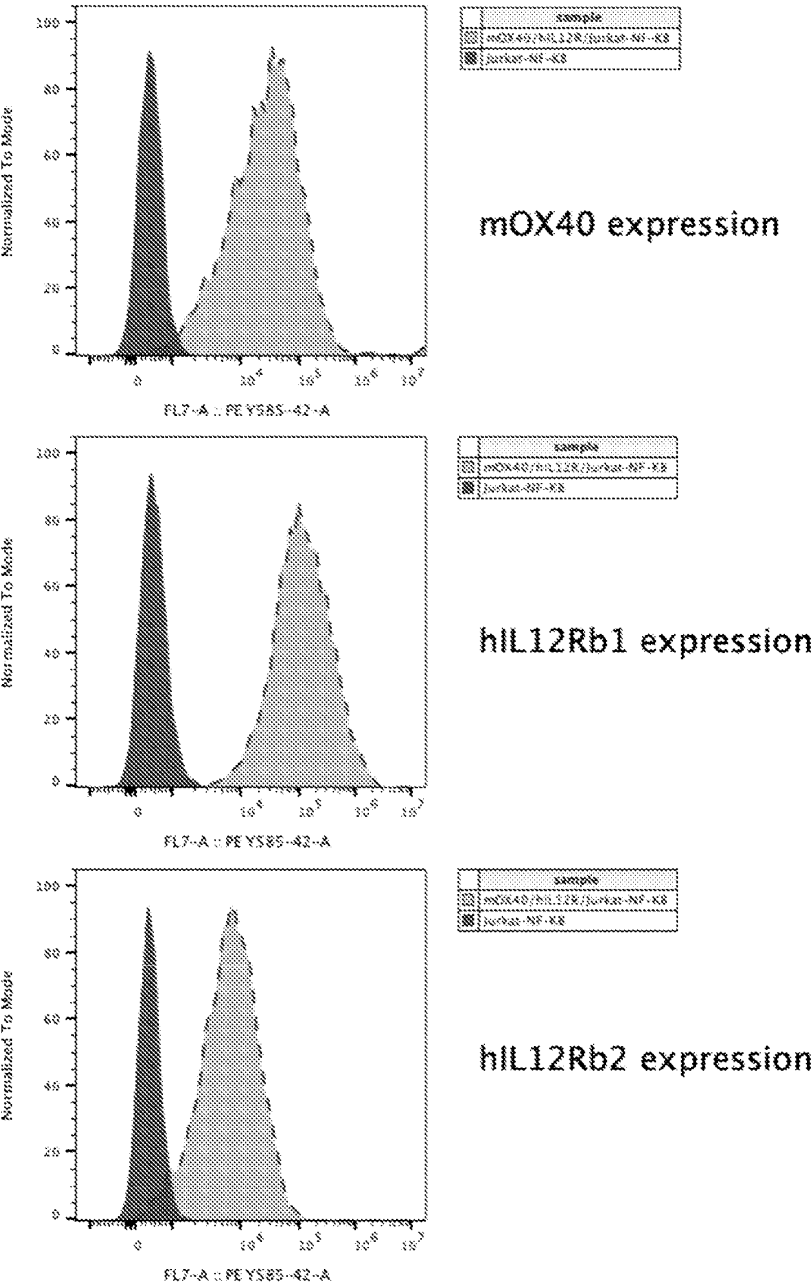


Fig. 72

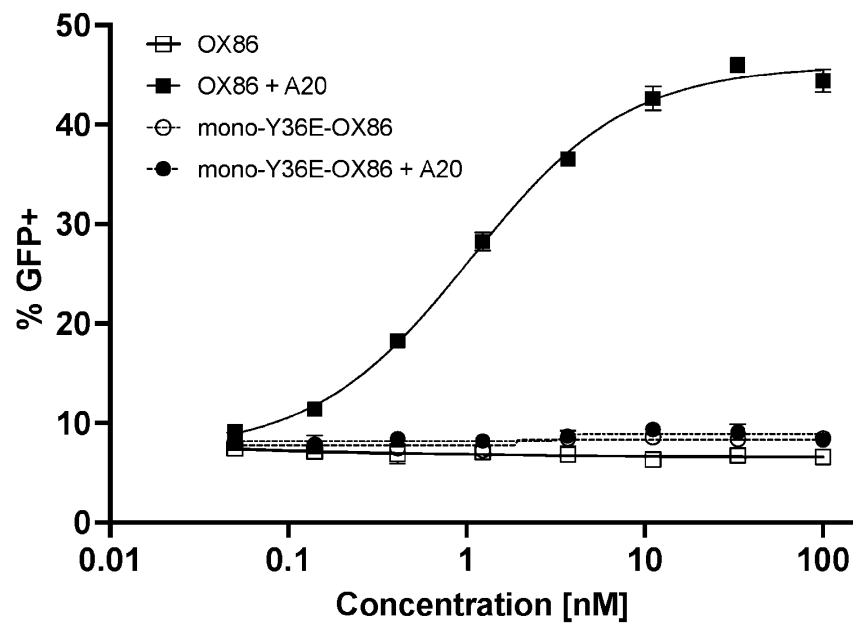


Fig. 73

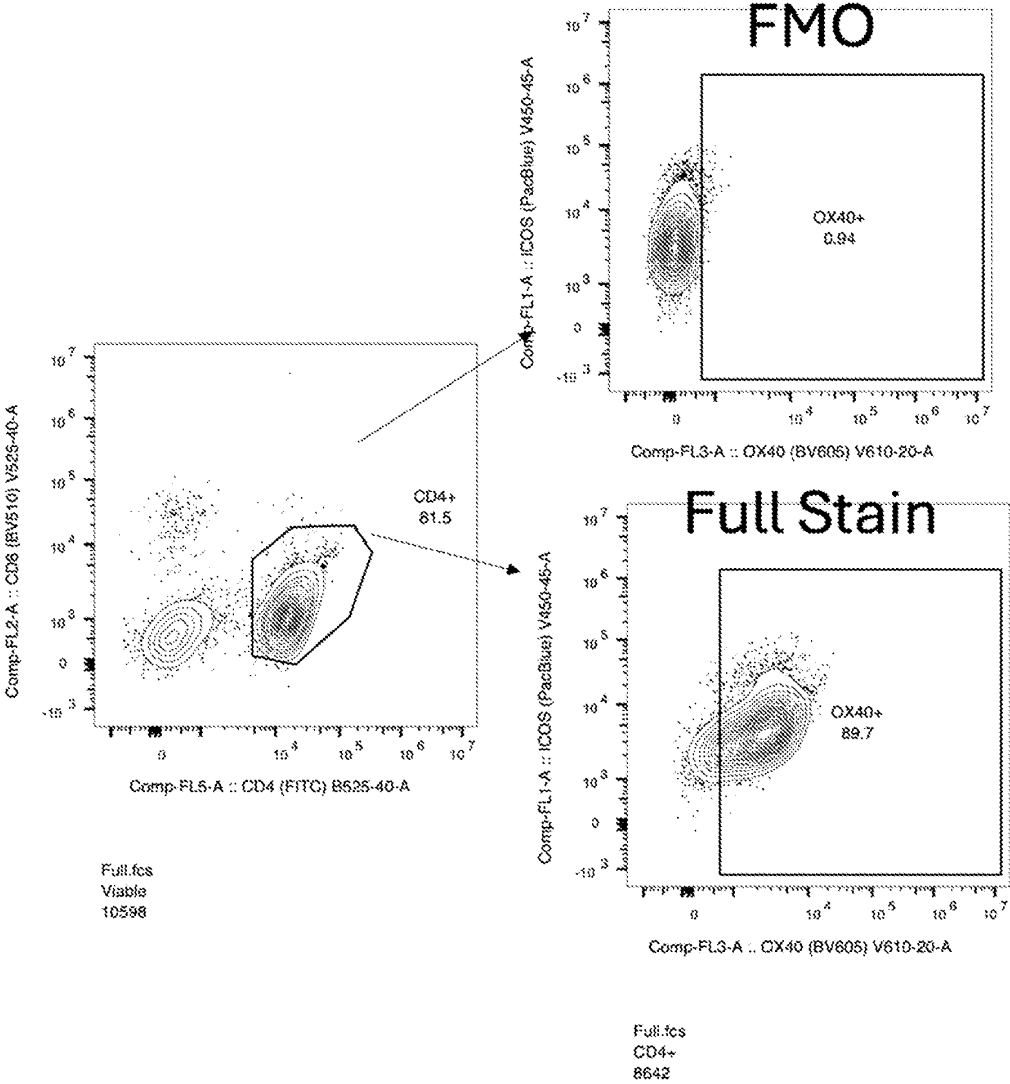


Fig. 74

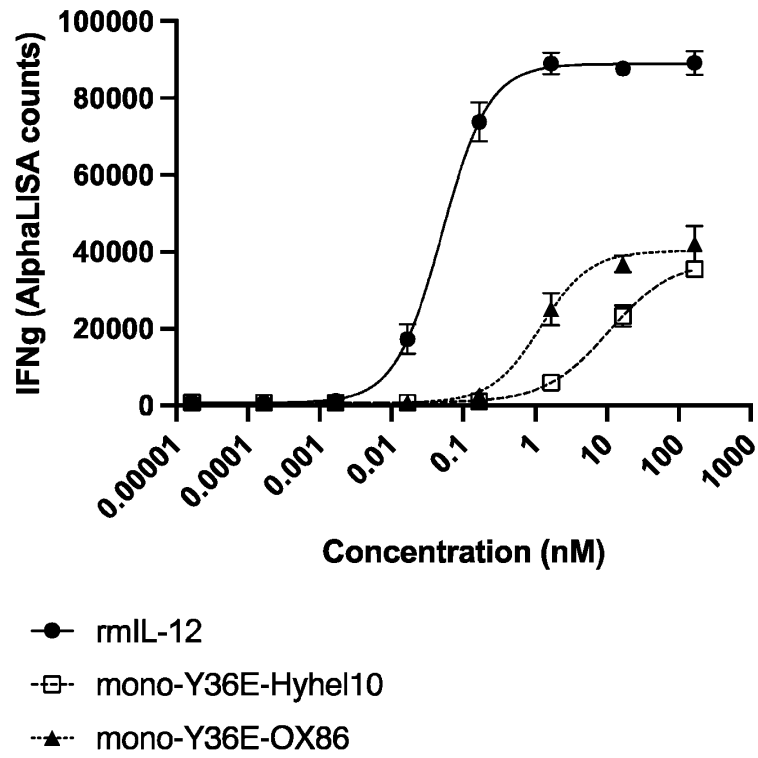


Fig. 75 – Fig. 75A**A. Anti-human OX40 clone BGB-A445 from WO2019223733****A1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTSYIIHWVRQAPGQGLEWMGYINPYNEGTRYNQKFQGRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARGYYGSSYAMDYWGQGT~~TVTVSS (SEQ ID NO: 137)

A2. VL domain

DIQMTQSPSSLSASVGDRVITTCRASQGISNYLNWYQQKPDGAIKLLIYDASTLYSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQYSKLPYTFGGGTKVEIK (SEQ ID NO: 138)

A3. Heavy chain (human IgG1 format)

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTSYIIHWVRQAPGQGLEWMGYINPYNEGTRYNQKFQGRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARGYYGSSYAMDYWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKXTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
139), wherein "X" can be "T" or "A".

A4. Light chain

DIQMTQSPSSLSASVGDRVITTCRASQGISNYLNWYQQKPDGAIKLLIYDASTLYSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQYSKLPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNAL
QSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 140)

A5. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTSYIIHWVRQAPGQGLEWMGYINPYNEGTRYNQKFQGRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARGYYGSSYAMDYWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP
CPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWE
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
141)

Fig. 75 – Fig. 75B**B. Anti-human OX40 clone 20E5 from WO2014148895****B1. VH domain**

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSS (SEQ ID NO: 142)

B2. VL domain

DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAVKLLIYYTSRLHSGVPSRFSGSGSGTDYTLTISS
LQPEDFATYFCQQGNTLPWTFGQGTKVEIK (SEQ ID NO: 143)

B3. Heavy chain (human IgG1 format)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKXTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
144), wherein "X" can be "T" or "A".

B4. Light chain

DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAVKLLIYYTSRLHSGVPSRFSGSGSGTDYTLTISS
LQPEDFATYFCQQGNTLPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNAL
QSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 145)

B5. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC
PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWES
NGQPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
146)

Fig. 75 – Fig. 75C**C. Anti-human OX40 clone 12H3 from WO2014148895****C1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARMGYHGPHLDFDVWGQGT~~TVTVSS (SEQ ID NO: 147)

C2. VL domain

DIQMTQSPSSLSASVGDRVTITCKASQDVGA~~AAVAWYQQKPGKAPKLLIYWASTRHTGVPSR~~FSGSGSGTDFTLTSS
LQPEDFATYYCQ~~QYIN~~YPLT~~FGGGTKVEIK~~ (SEQ ID NO: 148)

C3. Heavy chain (human IgG1 format)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARMGYHGPHLDFDVWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKXTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC~~SCVMHEALHNHYTQKSLSLSPGK~~ (SEQ ID
NO: 149), wherein "X" can be "T" or "A".

C4. Light chain

DIQMTQSPSSLSASVGDRVTITCKASQDVGA~~AAVAWYQQKPGKAPKLLIYWASTRHTGVPSR~~FSGSGSGTDFTLTSS
LQPEDFATYYCQ~~QYIN~~YPLT~~FGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV~~VCLLN~~FYPREAKVQWKVDNAL~~
QSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 150)

C5. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARMGYHGPHLDFDVWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW
ESNGQPENNYKTT~~PPVLDSDGSFFLYSKLTVDKSRWQQGNVFC~~SCVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
151)

Fig. 76

Name	ABD specificity	Heavy chain seqID	Light chain seqID
hG1-BGB-A445	Human OX40	139	140
hG1-20E5	Human OX40	144	145
hG1-12H3	Human OX40	149	150

Fig. 77

Name	Human IL-12 p35 mutation	ABD specificity	Chain A seqID	Chain B seqID	Chain C seqID
mono-mut23-BGB-A445	Y40S/K170A	Human OX40	49	141	140
mono-mut23-20E5	Y40S/K170A	Human OX40	49	146	145
mono-mut23-12H3	Y40S/K170A	Human OX40	49	151	150
mono-mut52-BGB-A445	Y40E/K170A	Human OX40	52	141	140

Fig. 78

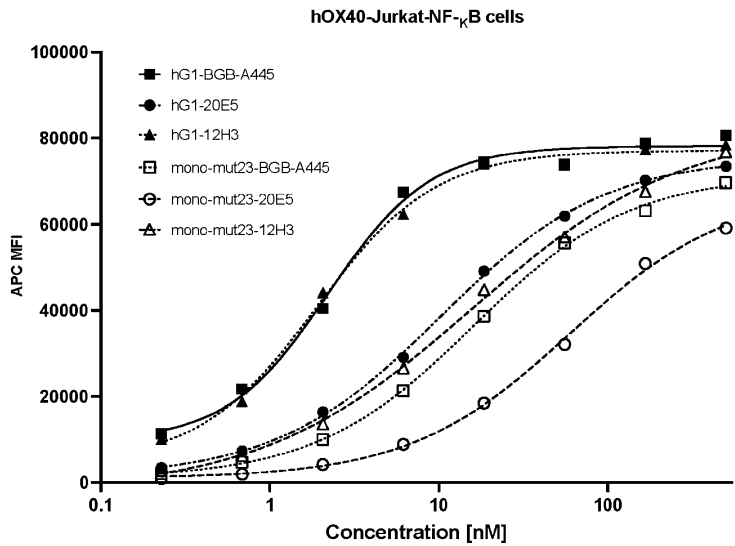


Fig. 79

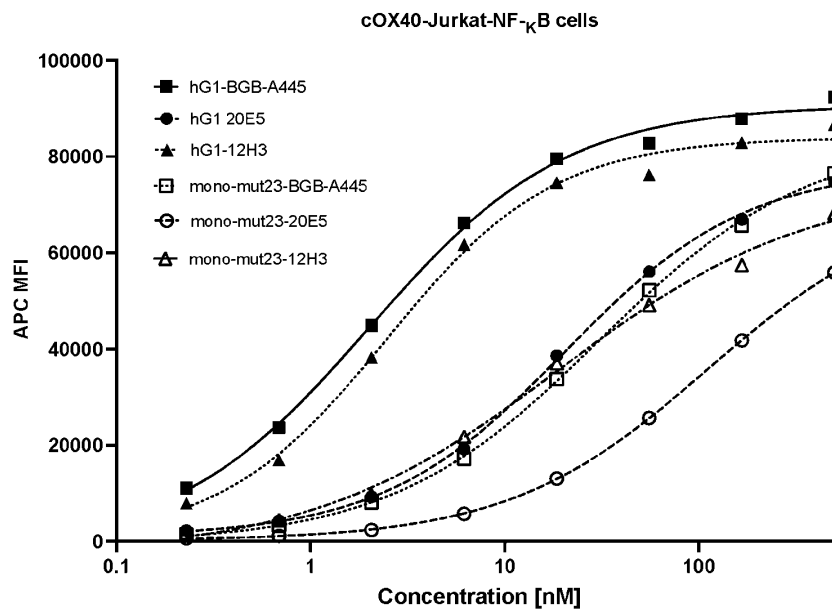


Fig. 80

Sample	Cell type	EC50 (nM)
hG1-BGB-A445	hOX40-Jurkat-NF- κ B	2.2
hG1-BGB-A445	cOX40-Jurkat-NF- κ B	2.0
hG1-20E5	hOX40-Jurkat-NF- κ B	10.2
hG1-20E5	cOX40-Jurkat-NF- κ B	20.3
hG1-12H3	hOX40-Jurkat-NF- κ B	1.9
hG1-12H3	cOX40-Jurkat-NF- κ B	2.5
mono-mut23-BGB-A445	hOX40-Jurkat-NF- κ B	15.9
mono-mut23-BGB-A445	cOX40-Jurkat-NF- κ B	30.6
mono-mut23-20E5	hOX40-Jurkat-NF- κ B	59.2
mono-mut23-20E5	cOX40-Jurkat-NF- κ B	111.1
mono-mut23-12H3	hOX40-Jurkat-NF- κ B	15.6
mono-mut23-12H3	cOX40-Jurkat-NF- κ B	19.2

Fig. 81 – Fig. 81A**A. Sequence optimized anti-human OX40 clone 20E5 V4****A1. VH domain**

QVQLVQSGAEVKKPGASVKVSCKASGYTFSTSYVMHWVRQAPGQRLEWIGYINPYNEGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSS (SEQ ID NO: 152)

A2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGASVKVSCKASGYTFSTSYVMHWVRQAPGQRLEWIGYINPYNEGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC
PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPASIIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
153)

B. Sequence optimized anti-human OX40 clone 20E5 V5**B1. VH domain**

QVQLVQSGAEVKKPGASVKVSCKASGYTFSTSYVMHWVRQAPGQRLEWIGYINPYNAGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSS (SEQ ID NO: 154)

B2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGASVKVSCKASGYTFSTSYVMHWVRQAPGQRLEWIGYINPYNAGTYNEKFKGRATLTSDKSAS
TAYMELSSLRSED~~TAVYYCANYYGSSLSMDYWGQGT~~LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC
PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPASIIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
155)

Fig. 81 – Fig. 81B**C. Sequence optimized anti-human OX40 clone 20E5 V6****C1. VH domain**

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDATKYNEKFGRATLTSDKSAS
TAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO: 156)

C2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDATKYNEKFGRATLTSDKSAS
TAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC
PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
157)

Fig. 82

Name	Human IL-12 p35 mutation	ABD specificity	Chain A seqID	Chain B seqID	Chain C seqID
mono-mut23-20E5_V4	Y40S/K170A	Human OX40	49	153	145
mono-mut23-20E5_V5	Y40S/K170A	Human OX40	49	155	145
mono-mut23-20E5_V6	Y40S/K170A	Human OX40	49	157	145

Fig. 83

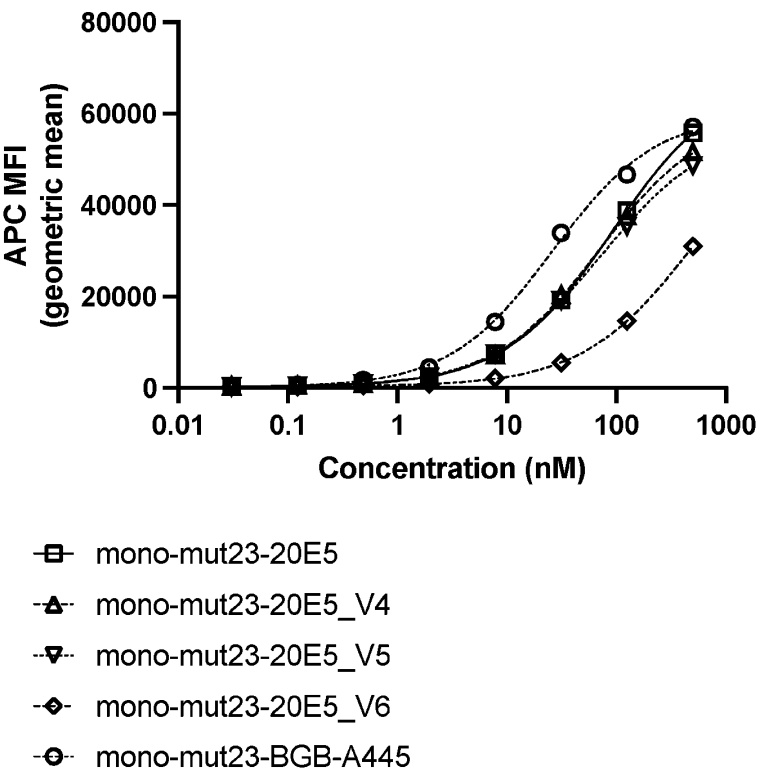


Fig. 84

Sample	Cell type	EC50 (nM)
mono-mut23-BGB-A445	hOX40-Jurkat-NF- κ B	26.3
mono-mut23-20E5	hOX40-Jurkat-NF- κ B	92.6
mono-mut23-20E5_V4	hOX40-Jurkat-NF- κ B	69.2
mono-mut23-20E5_V5	hOX40-Jurkat-NF- κ B	73.0
mono-mut23-20E5_V6	hOX40-Jurkat-NF- κ B	537.5

Fig. 85 – Fig. 85A**A. Sequence optimized anti-human OX40 clone 12H3 V3****A1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNQGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED¹⁵⁸TAVYYCARMGYHGPHLDFDVWGQGT¹⁵⁹TVTVSS (SEQ ID NO: 158)

A2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNQGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED¹⁵⁹TAVYYCARMGYHGPHLDFDVWGQGT¹⁶⁰TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVT¹⁶¹SWNSGALTSGVHTFPAVLQSSGLYSLSSVTV¹⁶²PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPEFEGG¹⁶³PSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLT¹⁶⁴VLHQDWLNGKEYKCKVSNKALPASI¹⁶⁵EKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV¹⁶⁶FSCSV¹⁶⁷MHEALHNHYTQKSLSLSPG (SEQ ID NO: 159)

B. Sequence optimized anti-human OX40 clone 12H3 V4**B1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNAGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED¹⁶⁰TAVYYCARMGYHGPHLDFDVWGQGT¹⁶¹TVTVSS (SEQ ID NO: 160)

B2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNAGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED¹⁶¹TAVYYCARMGYHGPHLDFDVWGQGT¹⁶²TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVT¹⁶³SWNSGALTSGVHTFPAVLQSSGLYSLSSVTV¹⁶⁴PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPEFEGG¹⁶⁵PSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLT¹⁶⁶VLHQDWLNGKEYKCKVSNKALPASI¹⁶⁷EKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV¹⁶⁸FSCSV¹⁶⁹MHEALHNHYTQKSLSLSPG (SEQ ID NO: 161)

Fig. 85 – Fig. 85B**C. Sequence optimized anti-human OX40 clone 12H3 V5****C1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNAGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARMGYHGPHLDFDVWGQGT~~TVTVSS (SEQ ID NO: 162)

C2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNAGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARMGYHGPHLDFDVWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVT~~SWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TVPS~~SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP~~
PCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLT~~VLHQDWLNGKEYKCKVSNKALPASI~~EKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW
ESNGQPENNYKTT~~PPVLDSDGSFFLYSKLTVDKSRWQQGNV~~FSCSVMEALHNHYTQKSLSLSPG (SEQ ID NO:
163)

D. Sequence optimized anti-human OX40 clone 12H3 V6**D1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARLGYHGPHLDFDVWGQGT~~TVTVSS (SEQ ID NO: 164)

D2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARLGYHGPHLDFDVWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVT~~SWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TVPS~~SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP~~
PCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLT~~VLHQDWLNGKEYKCKVSNKALPASI~~EKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW
ESNGQPENNYKTT~~PPVLDSDGSFFLYSKLTVDKSRWQQGNV~~FSCSVMEALHNHYTQKSLSLSPG (SEQ ID NO:
165)

Fig. 85 – Fig. 85C**E. Sequence optimized anti-human OX40 clone 12H3 V7****E1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARIGYHGPHLDFDVWGQGT~~TVTVSS (SEQ ID NO: 166)

E2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTYNQNFKDRVTLTADKSTS
TAYMELSSLRSED~~TAVYYCARIGYHGPHLDFDVWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVT~~SV~~WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS~~SSL~~GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPEFEGG~~PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS~~
VLT~~VL~~HQD~~W~~LN~~G~~KEYKCKVSNKALPASI~~EKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW~~
ESNGQPENNYK~~TT~~PPVLDSDGSFFLYSKLTVDKSRWQQGNV~~FSCSV~~MHEALHNHYTQKSLSLSPG (SEQ ID NO:
167)

F. Sequence optimized anti-human OX40 clone 12H3 V8**F1. VH domain**

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNQGGS~~TYNQNFKDRVTLTADKSTS~~
TAYMELSSLRSED~~TAVYYCARIGYHGPHLDFDVWGQGT~~TVTVSS (SEQ ID NO: 168)

F2. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNQGGS~~TYNQNFKDRVTLTADKSTS~~
TAYMELSSLRSED~~TAVYYCARIGYHGPHLDFDVWGQGT~~TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVT~~SV~~WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS~~SSL~~GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPEFEGG~~PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS~~
VLT~~VL~~HQD~~W~~LN~~G~~KEYKCKVSNKALPASI~~EKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEW~~
ESNGQPENNYK~~TT~~PPVLDSDGSFFLYSKLTVDKSRWQQGNV~~FSCSV~~MHEALHNHYTQKSLSLSPG (SEQ ID NO:
169)

Fig. 86

Name	Human IL-12 p35 mutation	ABD specificity	Chain A seqID	Chain B seqID	Chain C seqID
mono-mut23-12H3_V3	Y40S/K170A	Human OX40	49	159	150
mono-mut23-12H3_V4	Y40S/K170A	Human OX40	49	161	150
mono-mut23-12H3_V5	Y40S/K170A	Human OX40	49	163	150
mono-mut23-12H3_V6	Y40S/K170A	Human OX40	49	165	150
mono-mut23-12H3_V7	Y40S/K170A	Human OX40	49	167	150
mono-mut23-12H3_V8	Y40S/K170A	Human OX40	49	169	150

Fig. 87

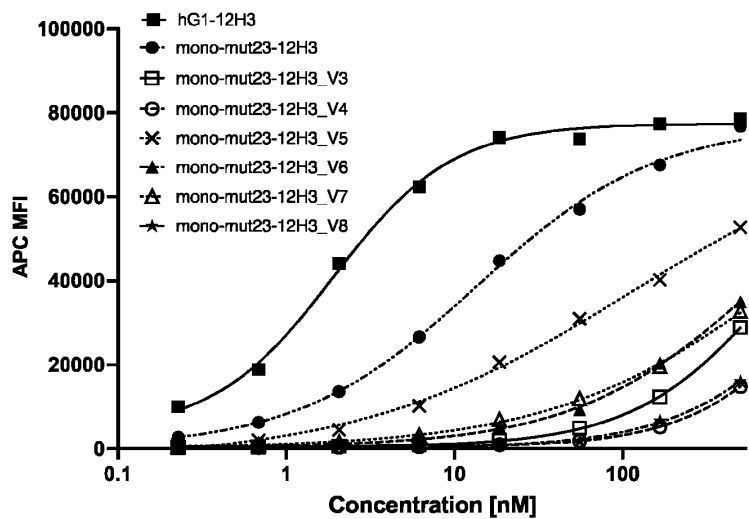


Fig. 88

Sample	Cell type	EC50 (nM)
hG1-12H3	hOX40-Jurkat-NF- κ B	1.9
mono-mut23-12H3	hOX40-Jurkat-NF- κ B	13.6
mono-mut23-12H3_V3	hOX40-Jurkat-NF- κ B	839.1
mono-mut23-12H3_V4	hOX40-Jurkat-NF- κ B	1875
mono-mut23-12H3_V5	hOX40-Jurkat-NF- κ B	112.6
mono-mut23-12H3_V6	hOX40-Jurkat-NF- κ B	645.1
mono-mut23-12H3_V7	hOX40-Jurkat-NF- κ B	841.2
mono-mut23-12H3_V8	hOX40-Jurkat-NF- κ B	1911

121/158

Fig. 89

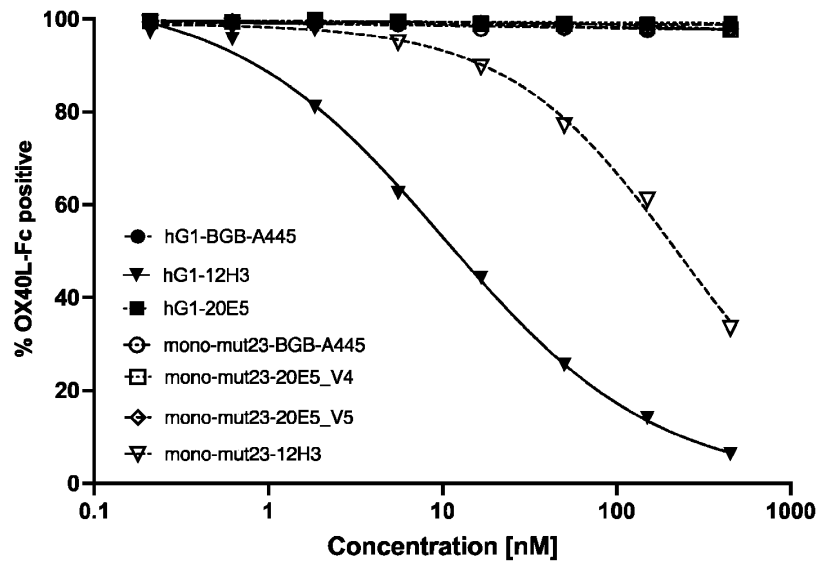


Fig. 90 – Fig. 90A

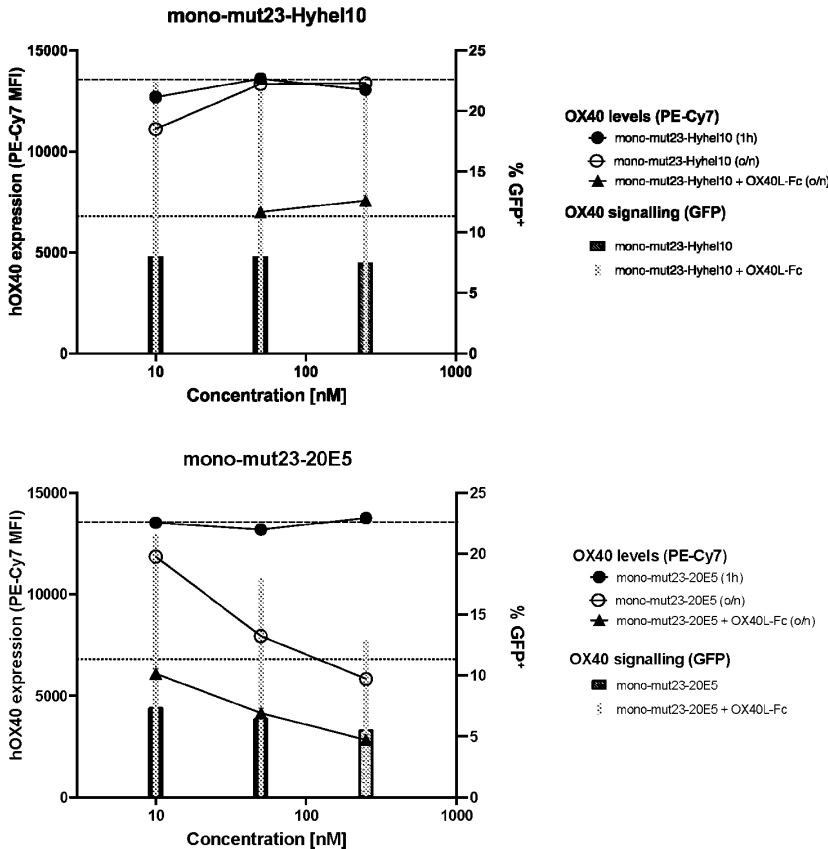


Fig. 90 – Fig. 90B

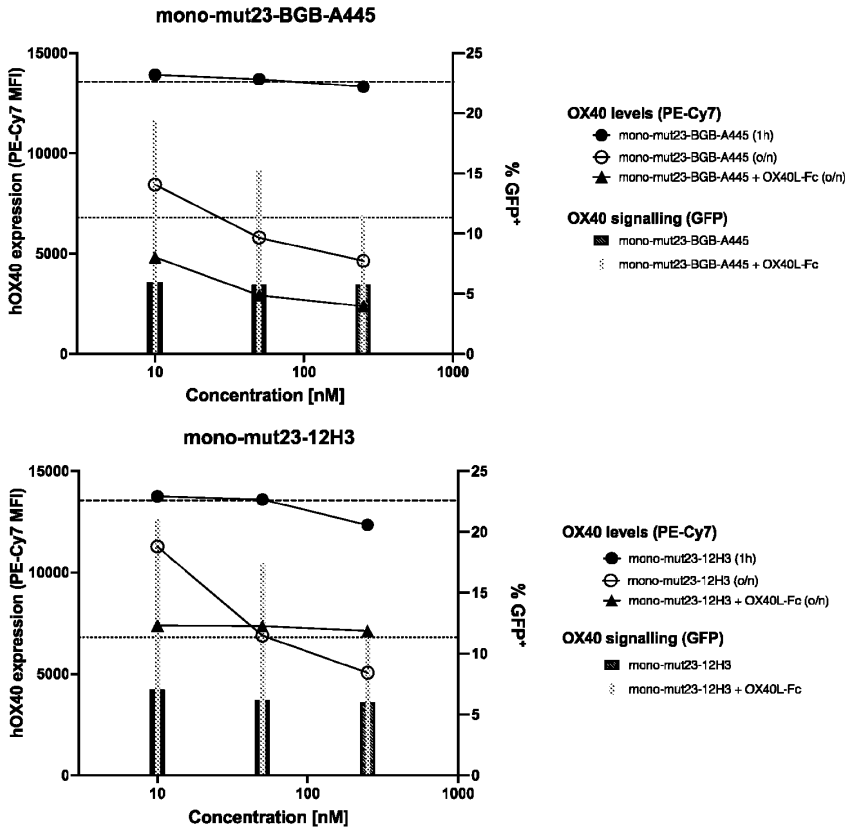


Fig. 91 – Fig. 91A

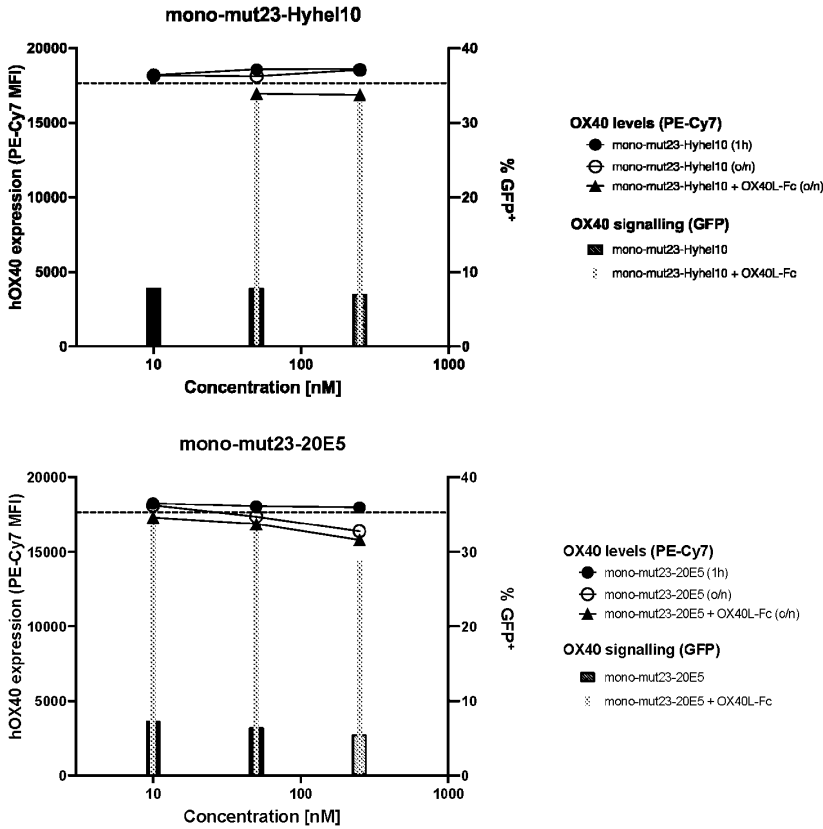


Fig. 91 – Fig. 91B

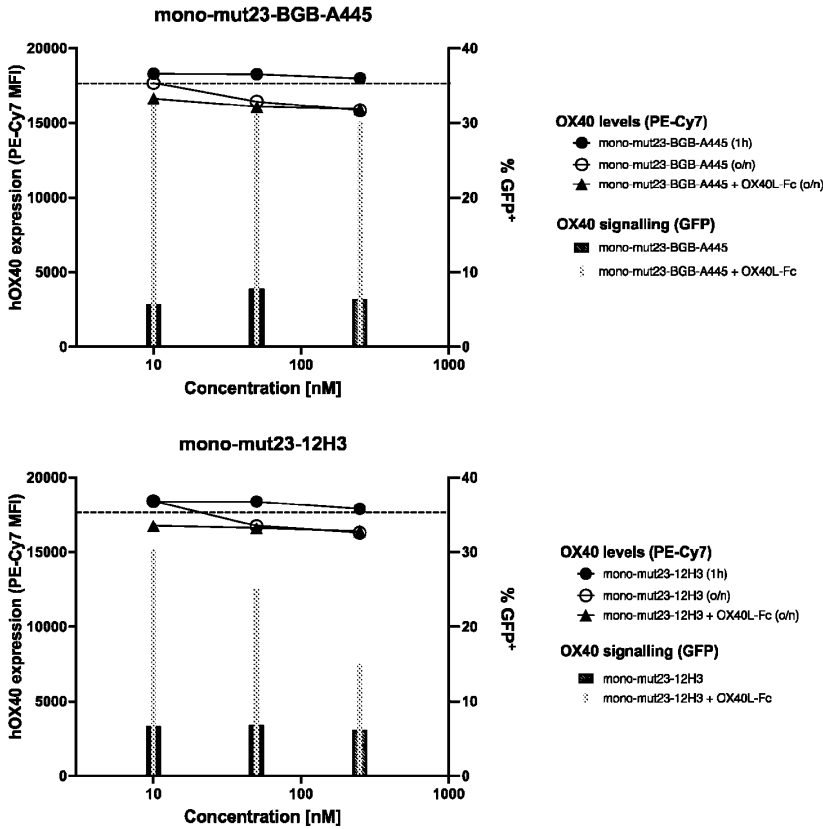


Fig. 92 – Fig. 92A

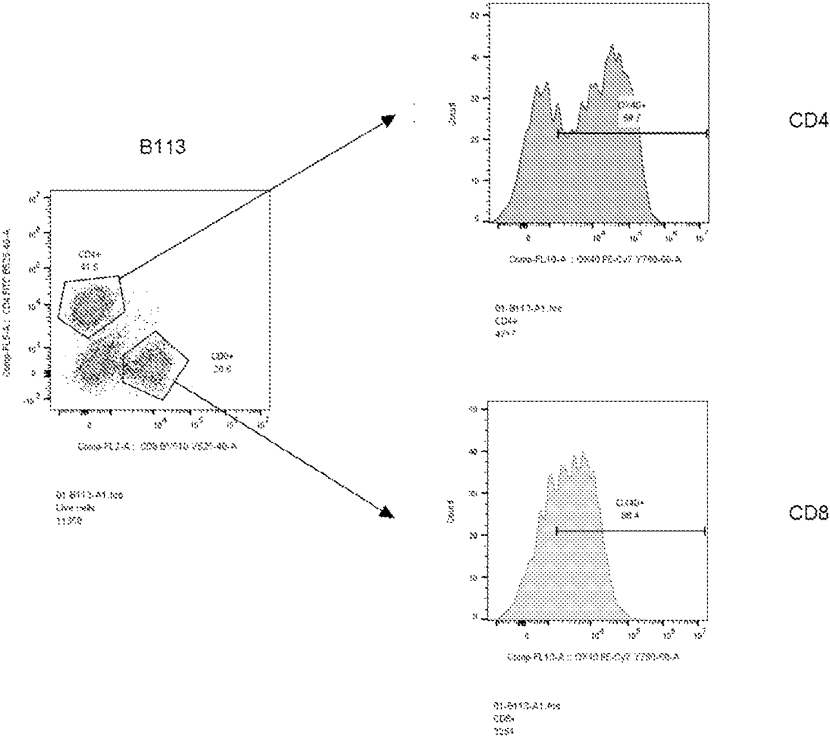


Fig. 92 – Fig. 92B

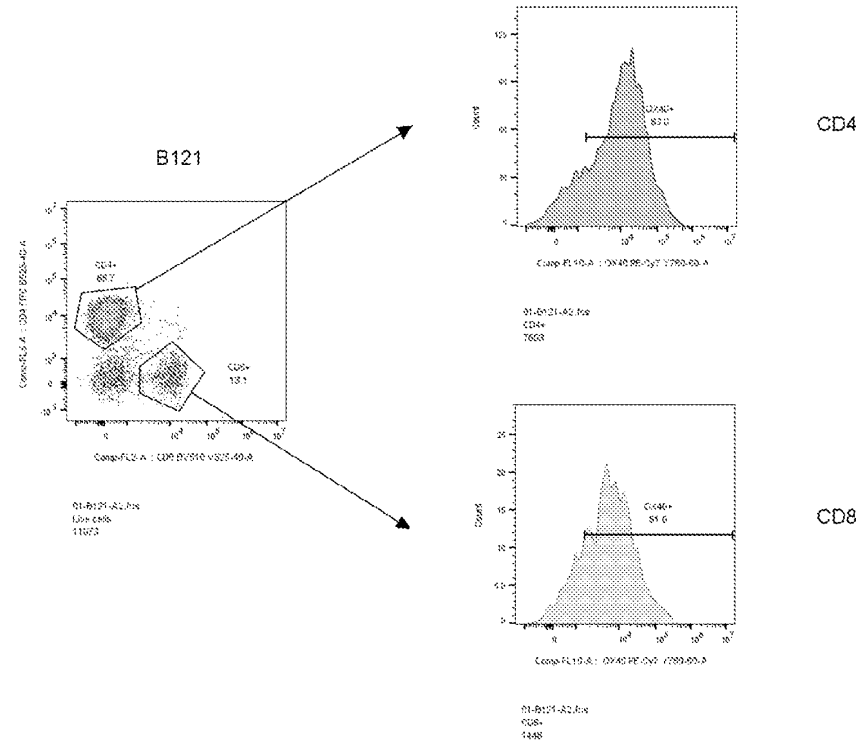


Fig. 93

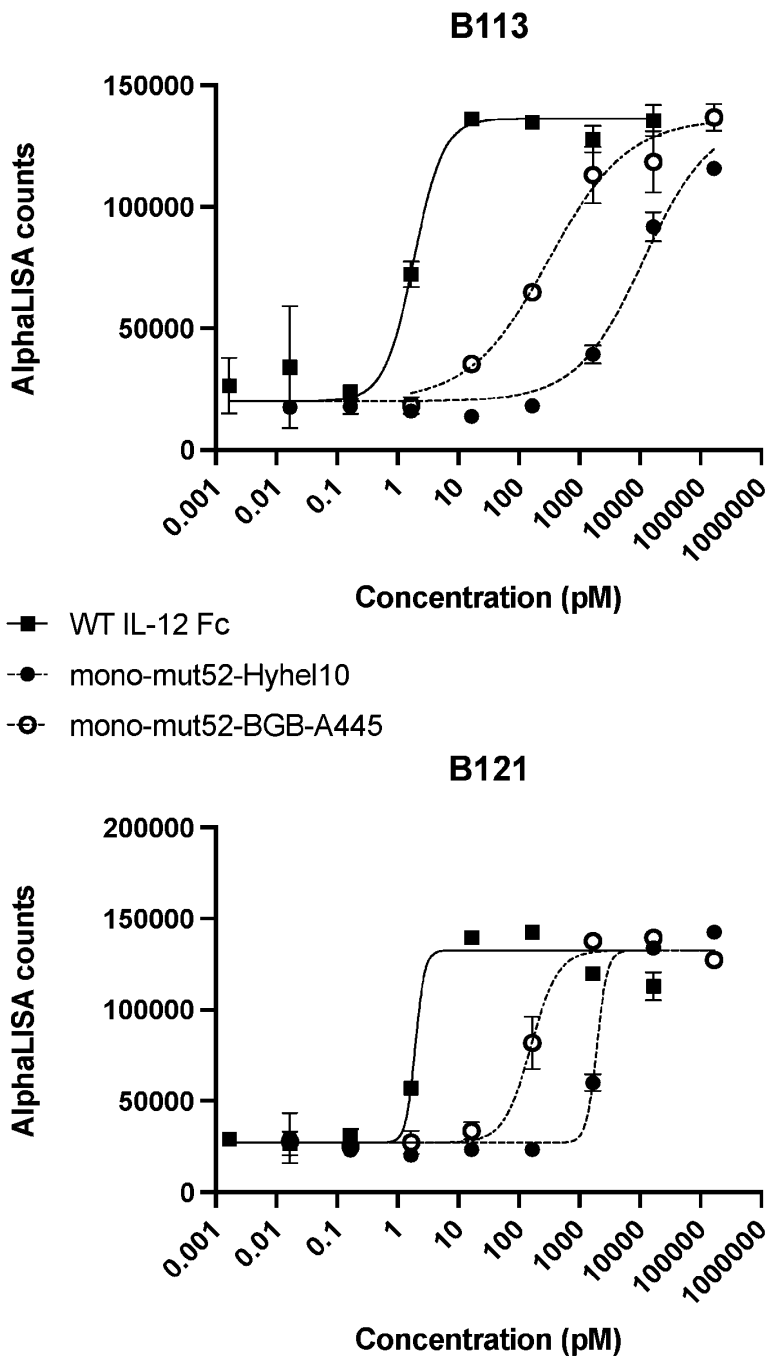


Fig. 94

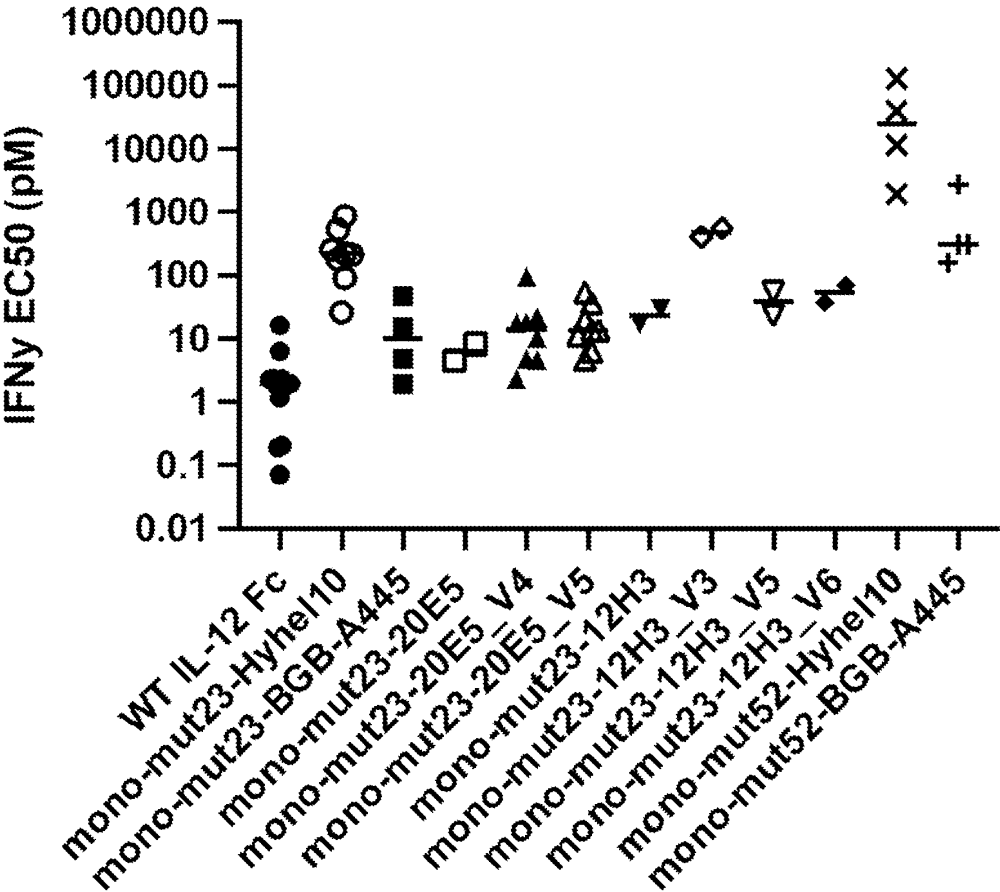


Fig. 95

Sample	EC50 (pM) (mean $\pm$ s.d.)	Number of measurements
WT IL-12 Fc	3.1 $\pm$ 4.4	12
mono-mut23-Hyhel10	296.1 $\pm$ 272.3	8
mono-mut23-BGB-A445	17.4 $\pm$ 20.8	4
mono-mut23-20E5	6.4 $\pm$ 2.7	2
mono-mut23-20E5_V4	21.8 $\pm$ 30.4	8
mono-mut23-20E5_V5	20.0 $\pm$ 17.0	8
mono-mut23-12H3	23.0 $\pm$ 8.5	2
mono-mut23-12H3_V3	479.5 $\pm$ 110.6	2
mono-mut23-12H3_V5	38.9 $\pm$ 21.8	2
mono-mut23-12H3_V6	52.7 $\pm$ 22.0	2
mono-mut52-Hyhel10	45,604 $\pm$ 58,201	4
mono-mut52-BGB-A445	885.2 $\pm$ 1253.3	4

Fig. 96 – Fig. 96A

Donor B130

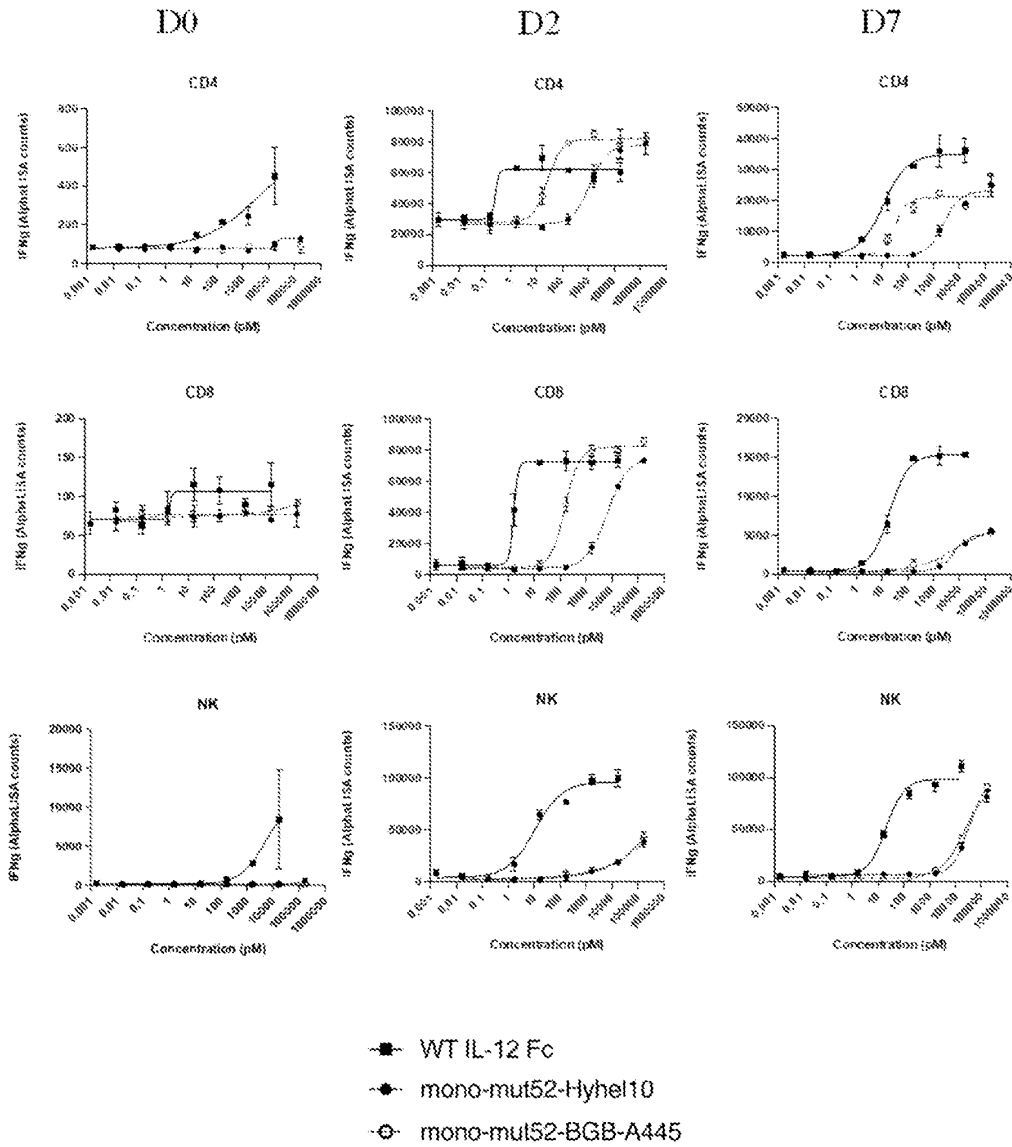


Fig. 96 – Fig. 96B

Donor B134

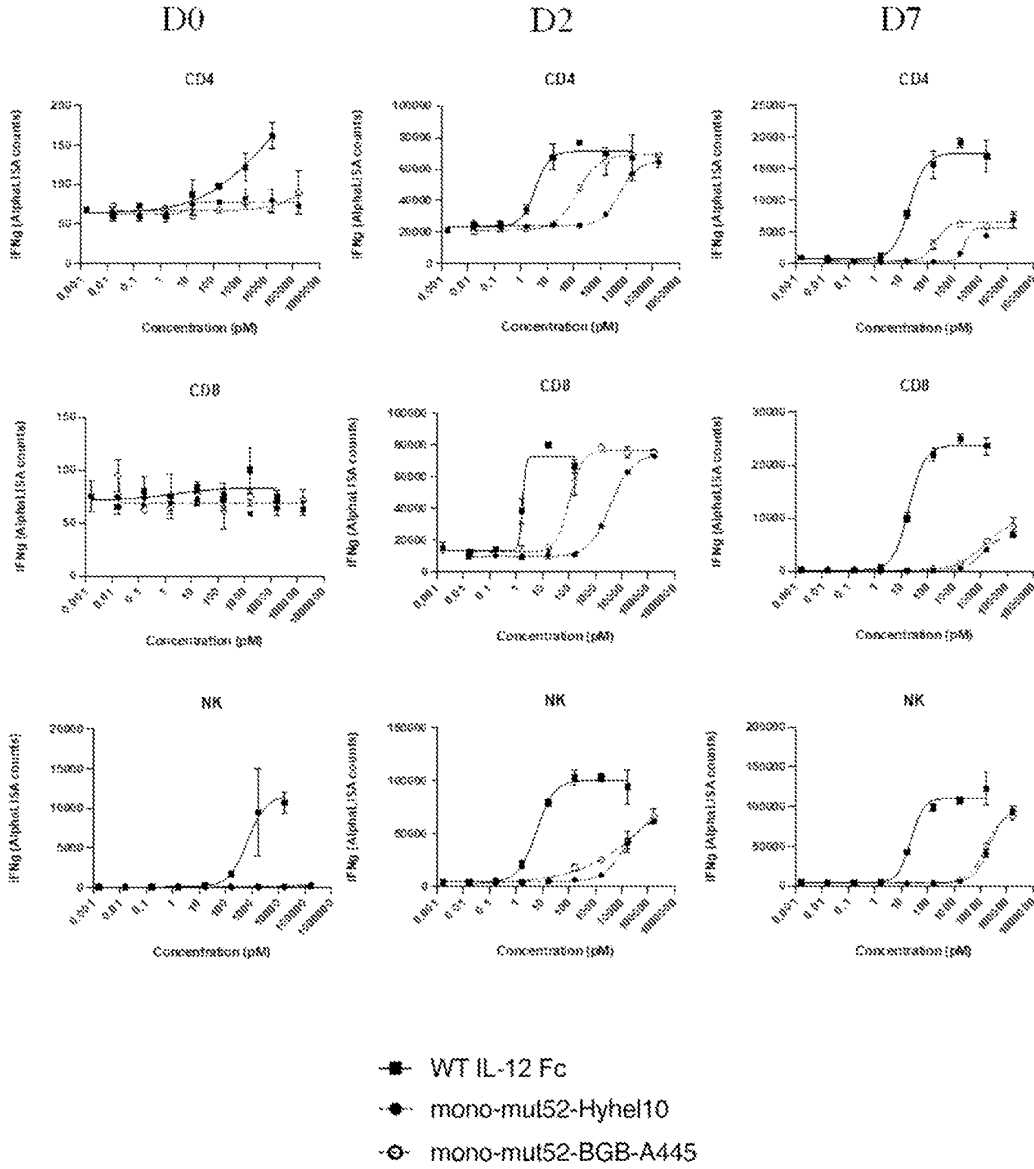


Fig. 96 – Fig. 96C

Donor B177

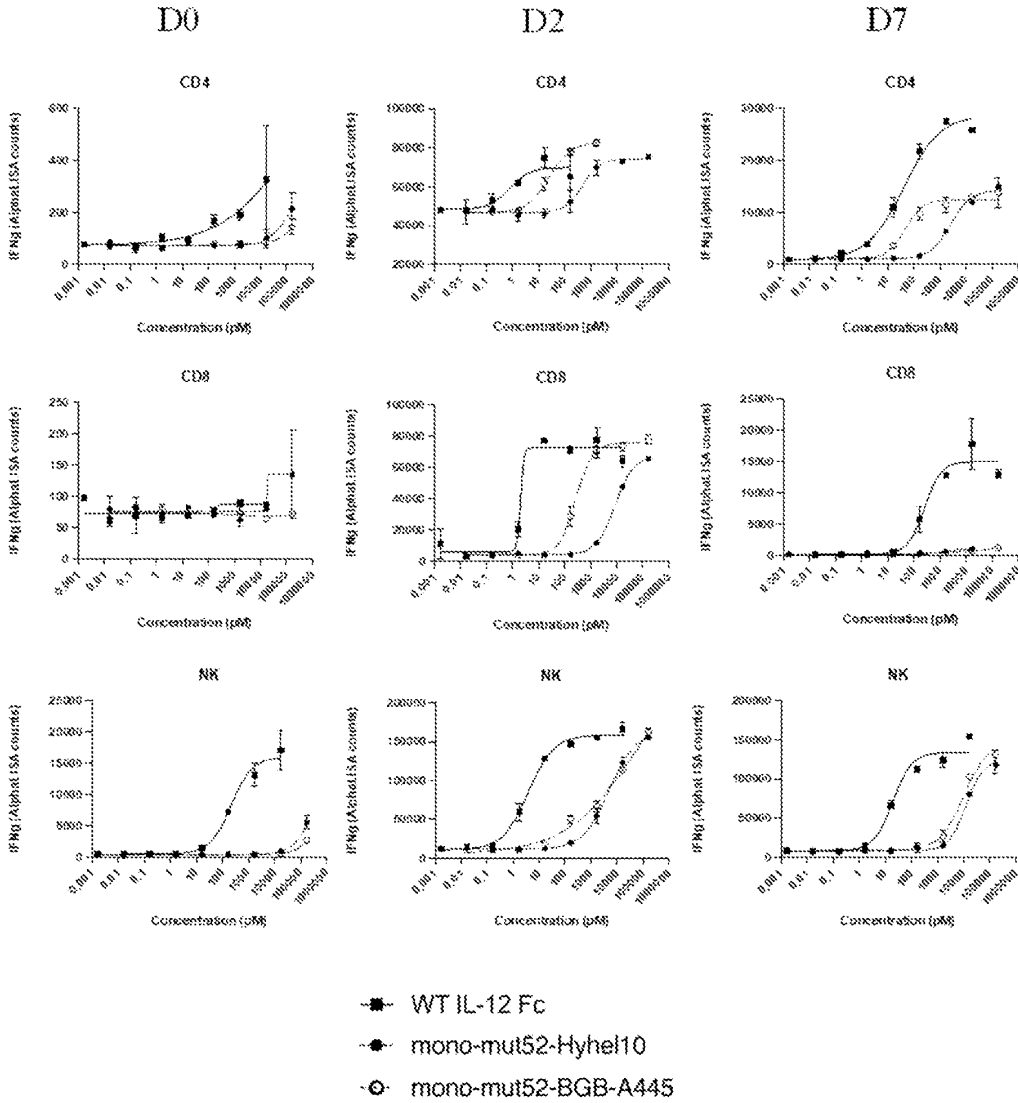


Fig. 97



Fig. 98 – Fig. 98A

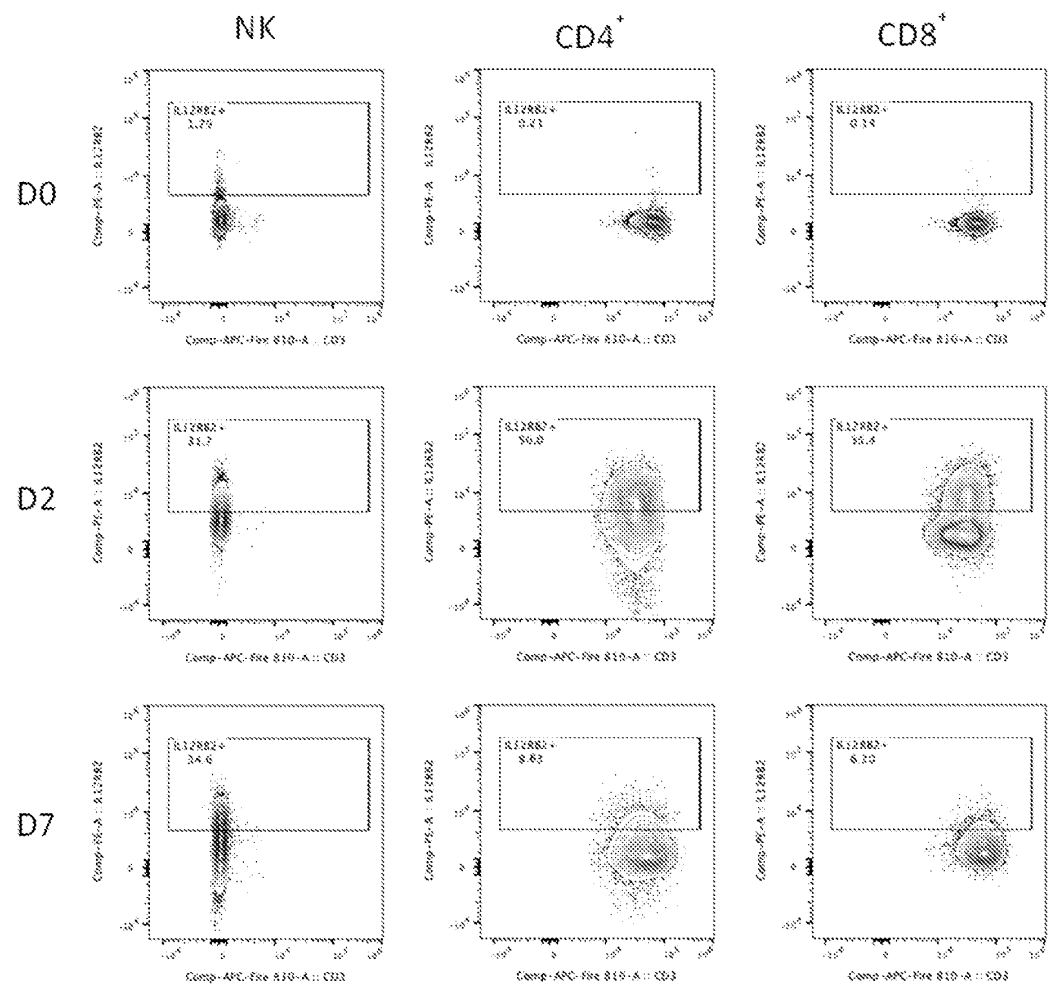


Fig. 98 – Fig. 98B

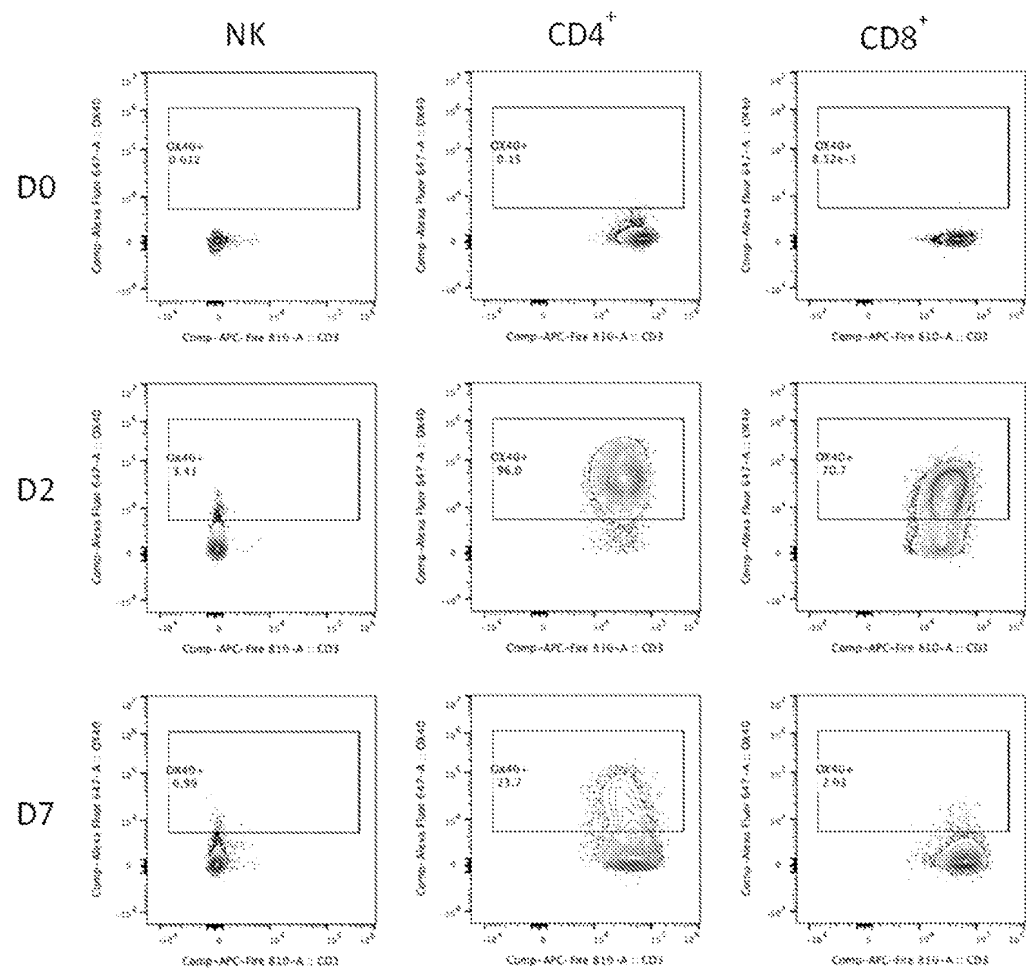


Fig. 99

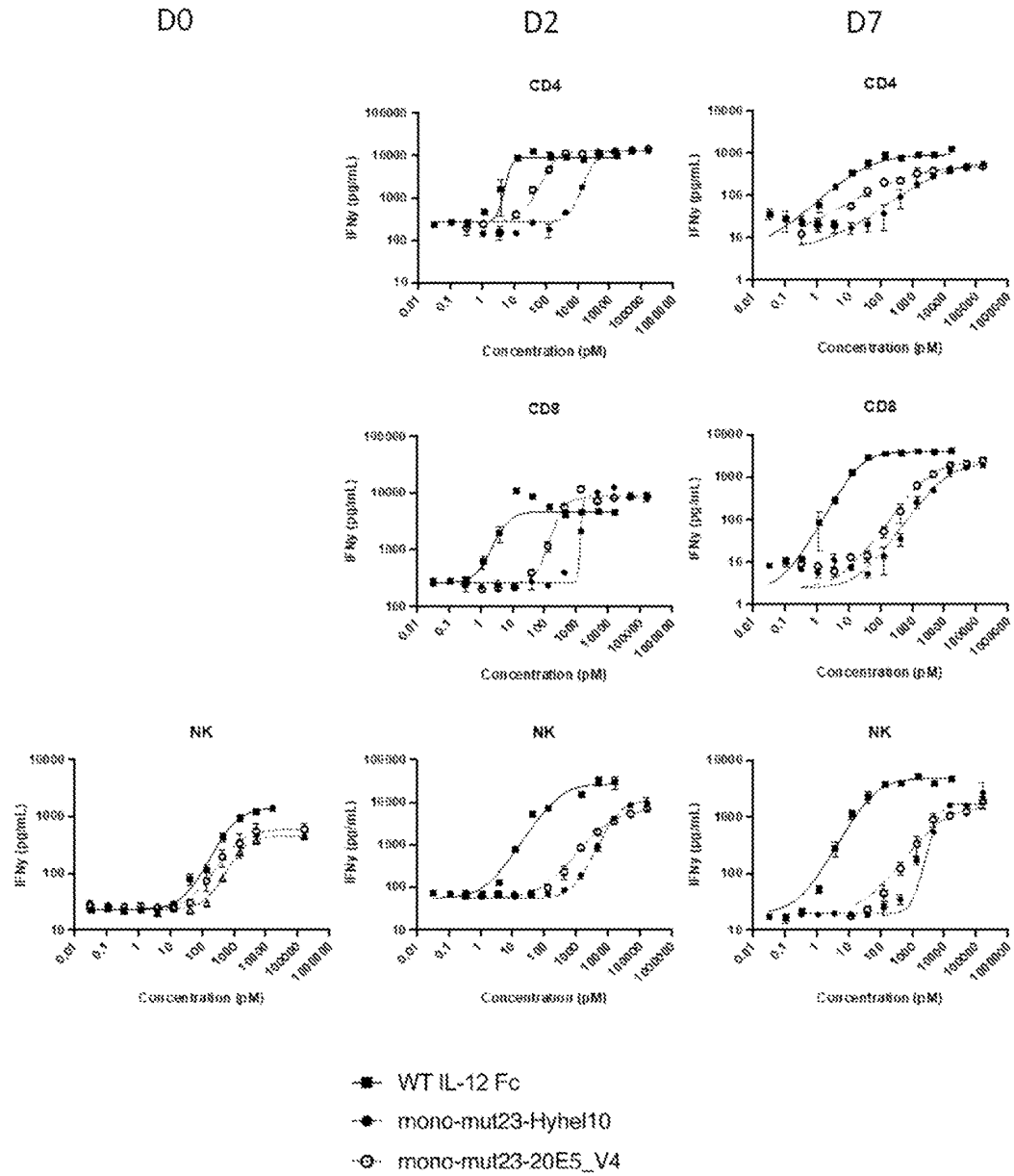


Fig. 100

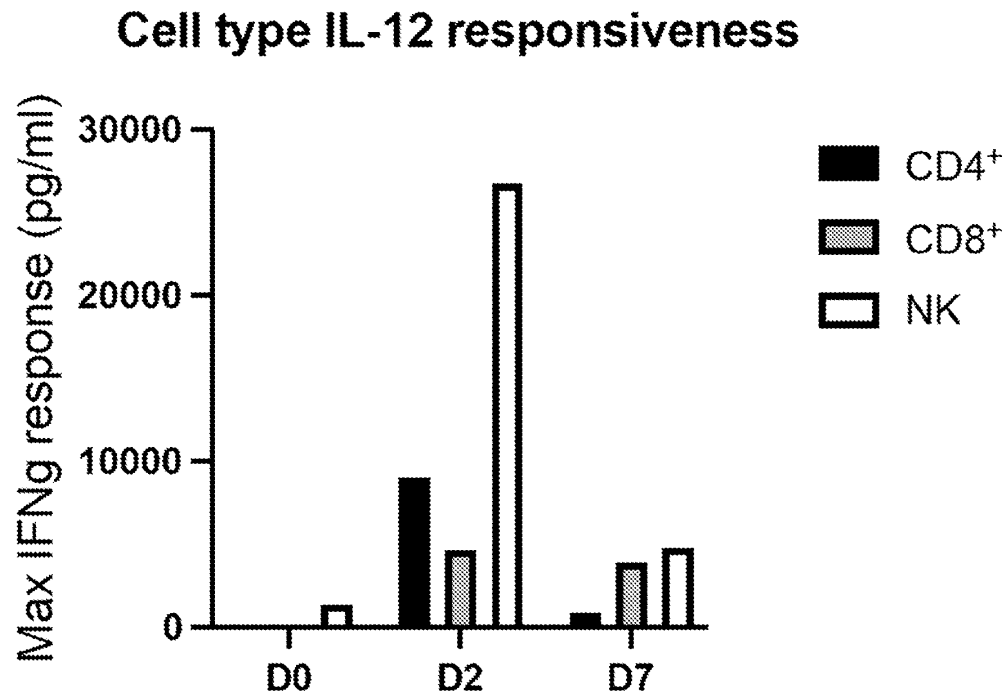


Fig. 101

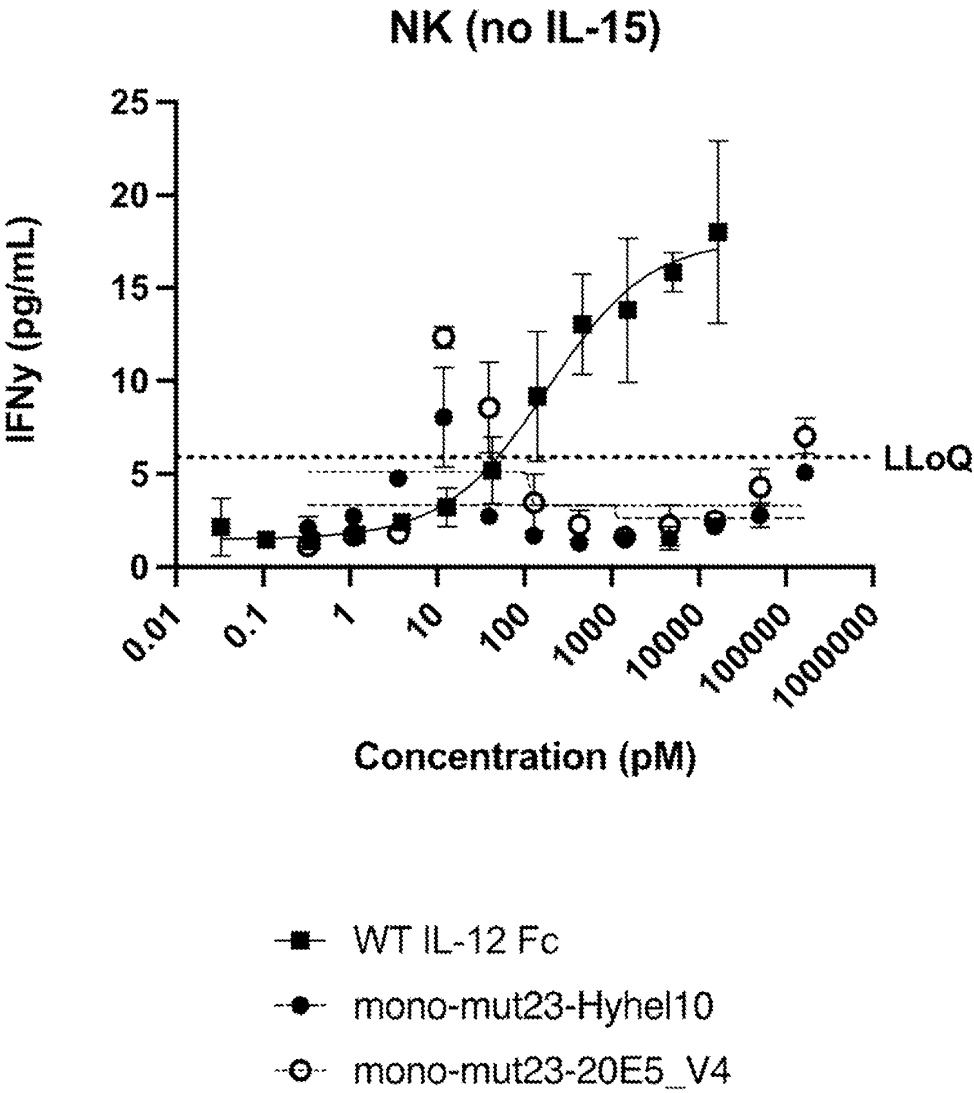


Fig. 102

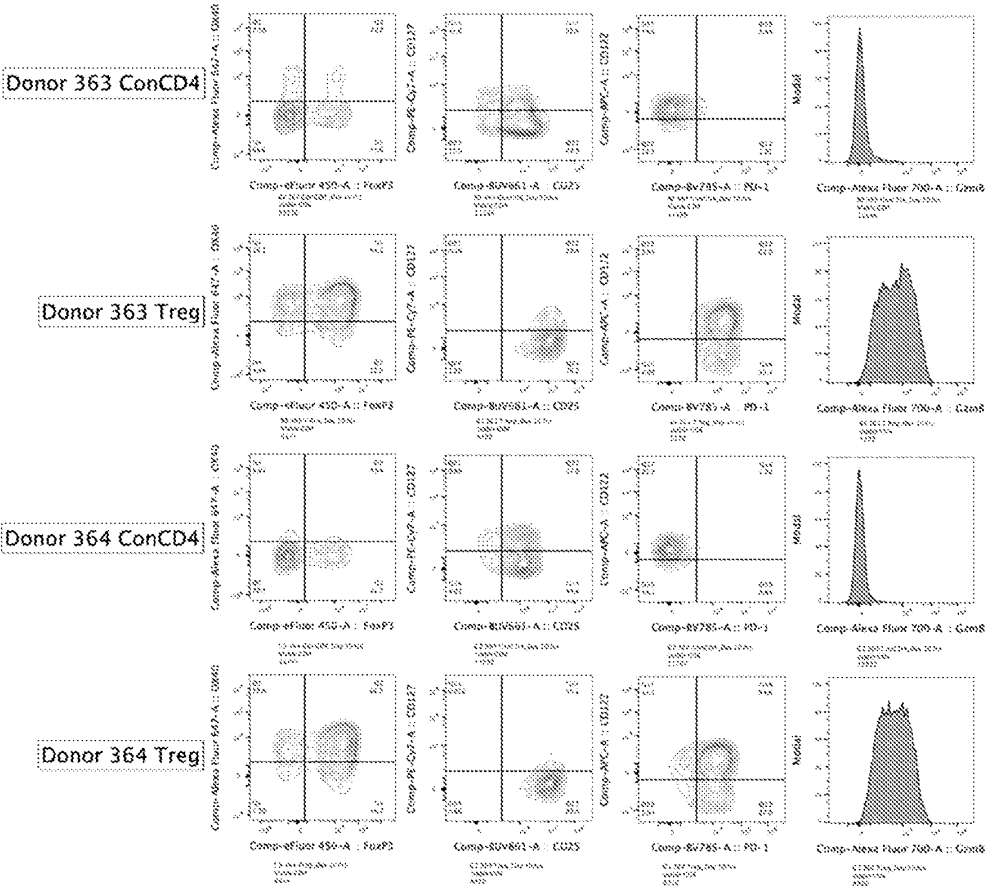


Fig. 103

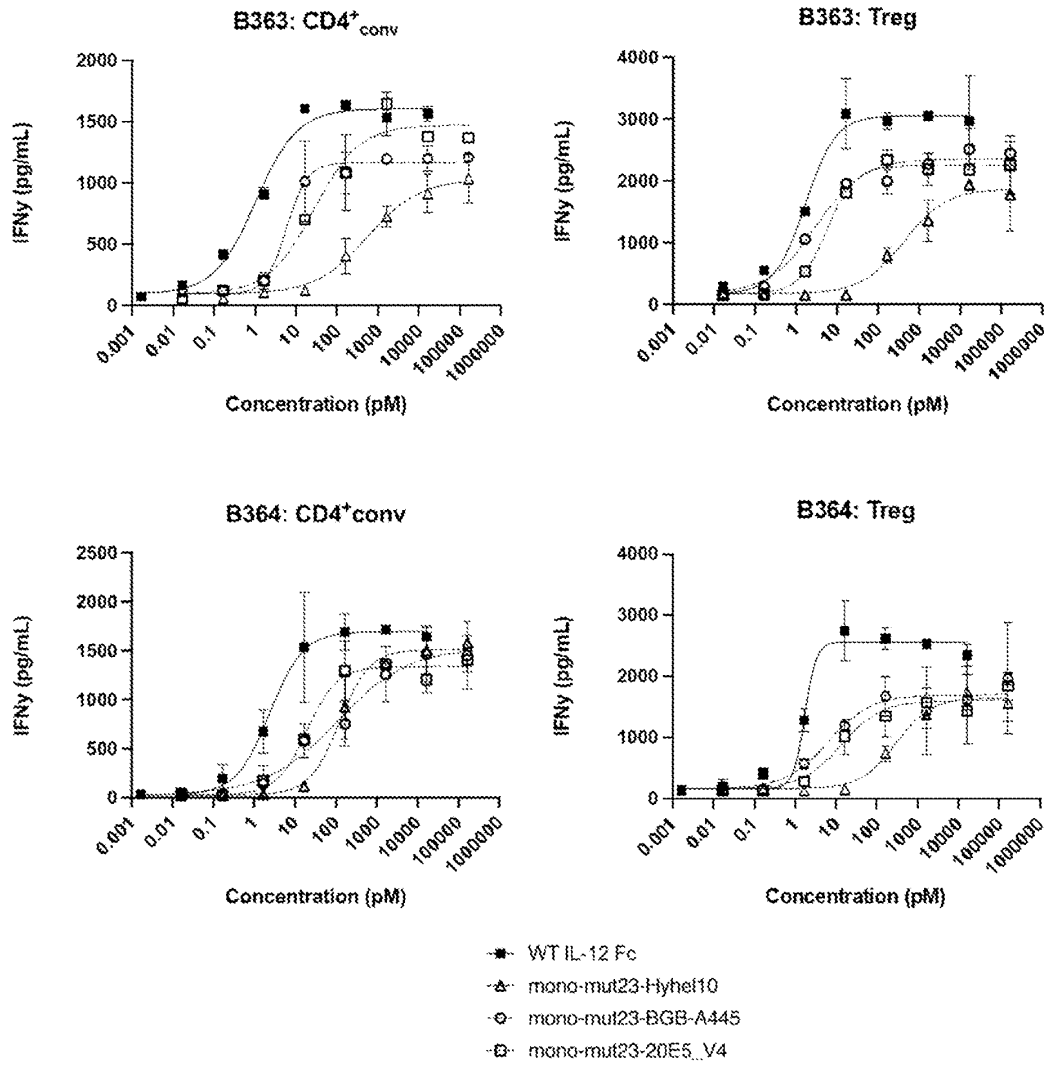


Fig. 104

Sample	Donor B363				Donor B364			
	Treg		CD4 ⁺ _{conv}		Treg		CD4 ⁺ _{conv}	
	EC50 (pM)	Fold change	EC50 (pM)	Fold change	EC50 (pM)	Fold change	EC50 (pM)	Fold change
WT IL-12 Fc	1.7	1	1.1	1	1.7	1	2.4	1
mono-mut23-Hybel10	435.7	258.4	577.7	550.5	295.6	169.9	123.4	51.3
mono-mut23-BGB-A445	3.1	1.8	5.9	5.6	6.5	3.7	108.9	45.2
Mono-mut23-20ES_V4	5.7	3.4	27.7	26.4	13.8	7.9	19.5	8.1

Fig. 105

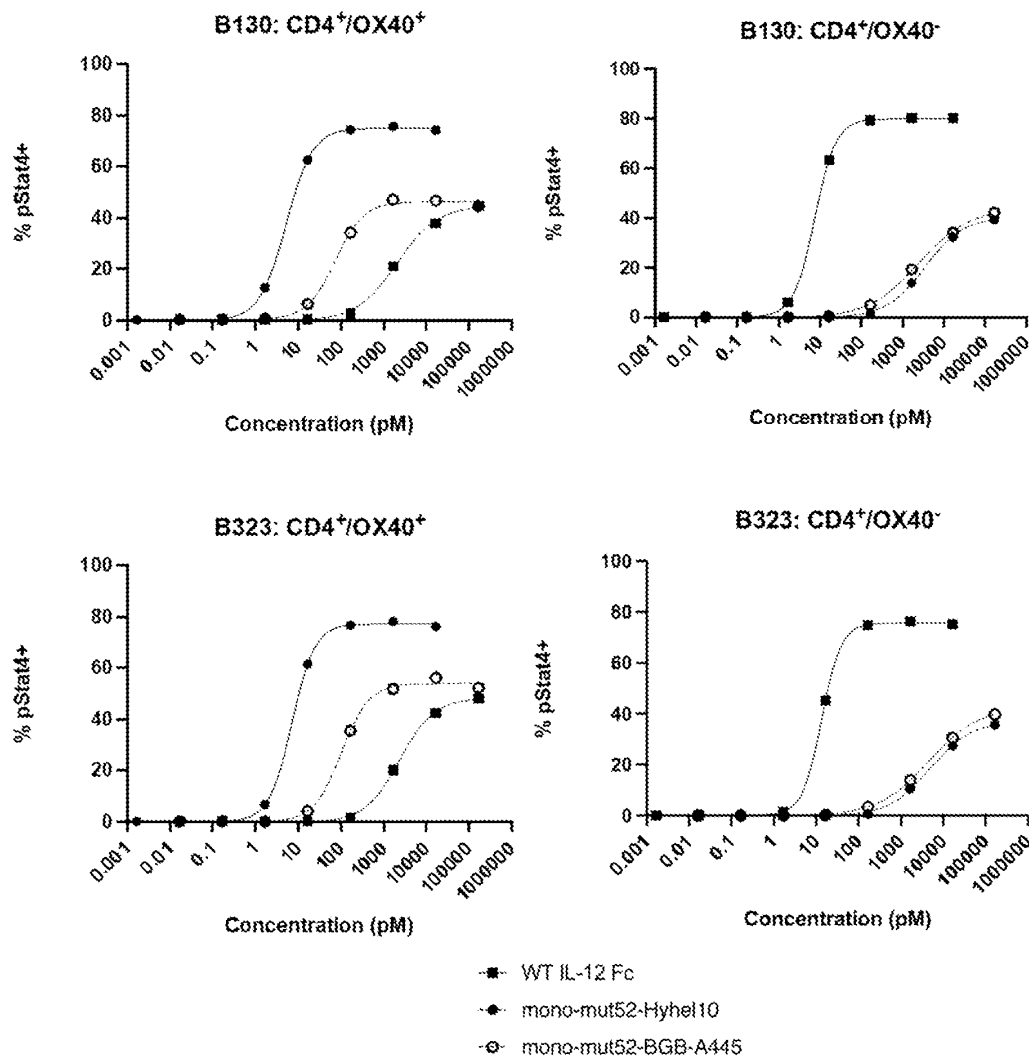


Fig. 106

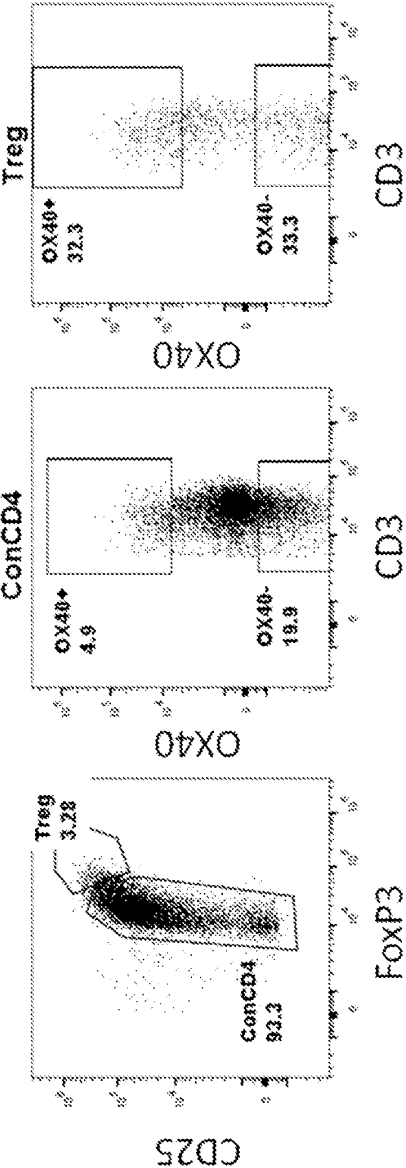


Fig. 107

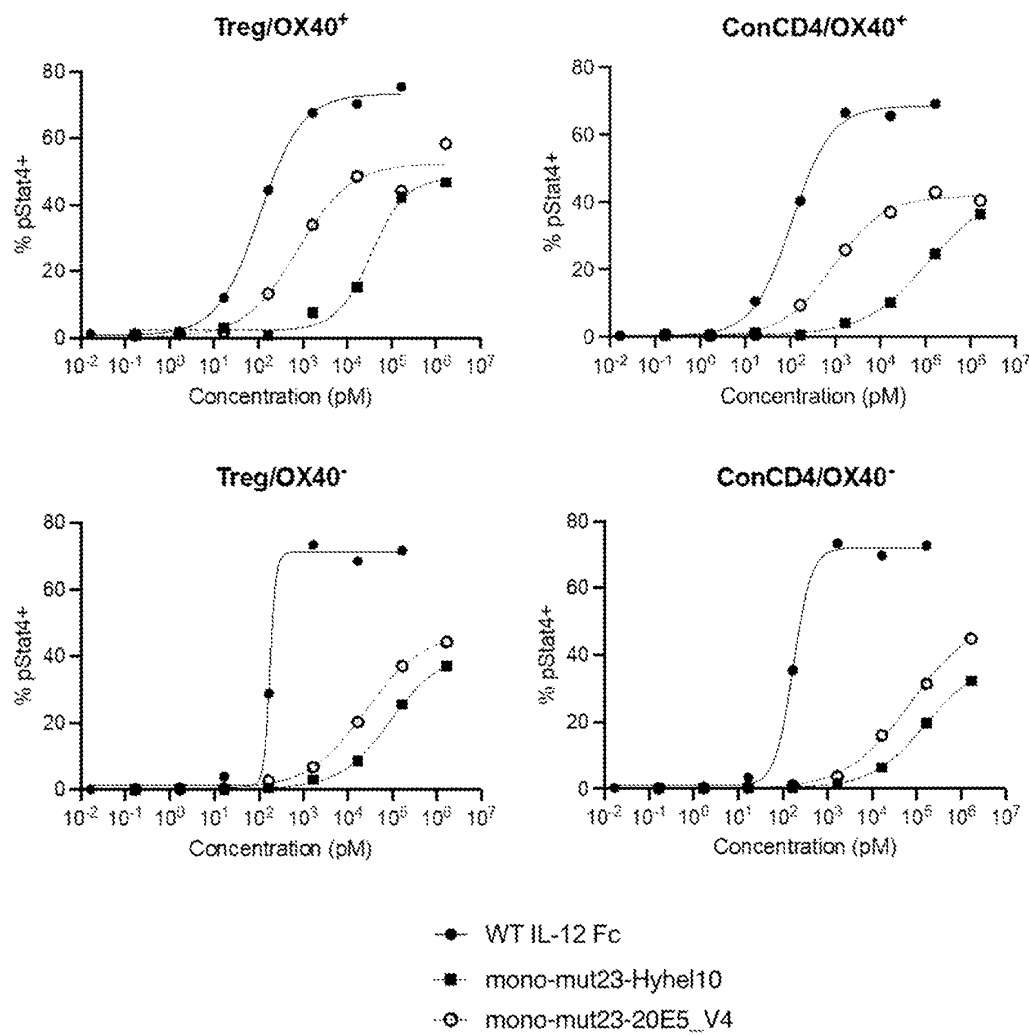


Fig. 108

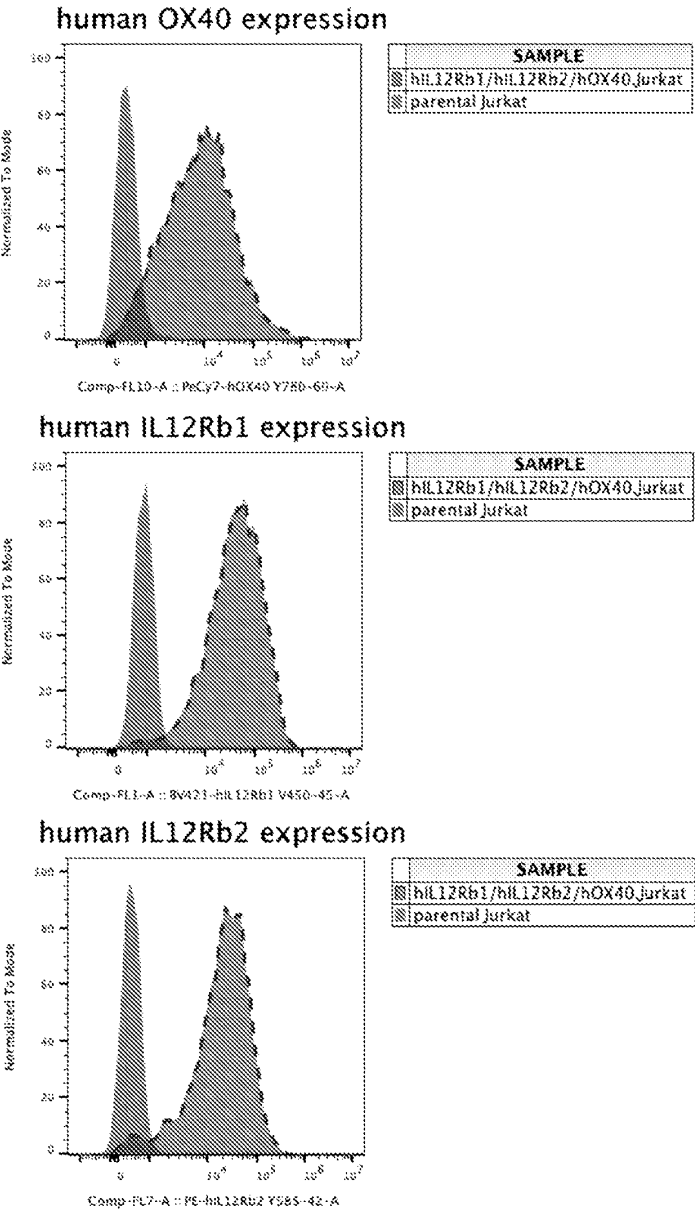


Fig. 109 – Fig. 109A

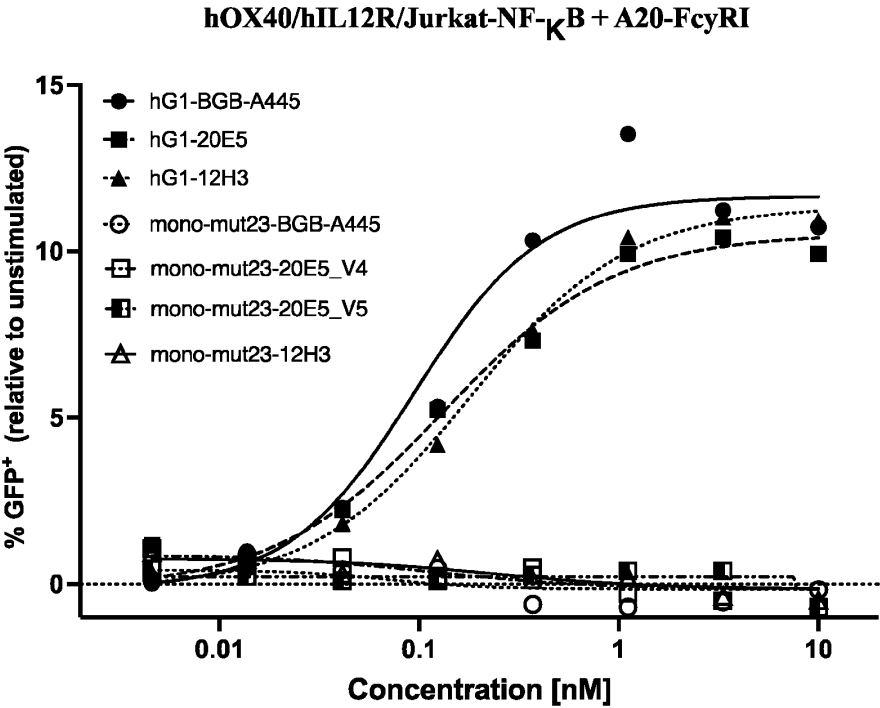


Fig. 109 – Fig. 109B

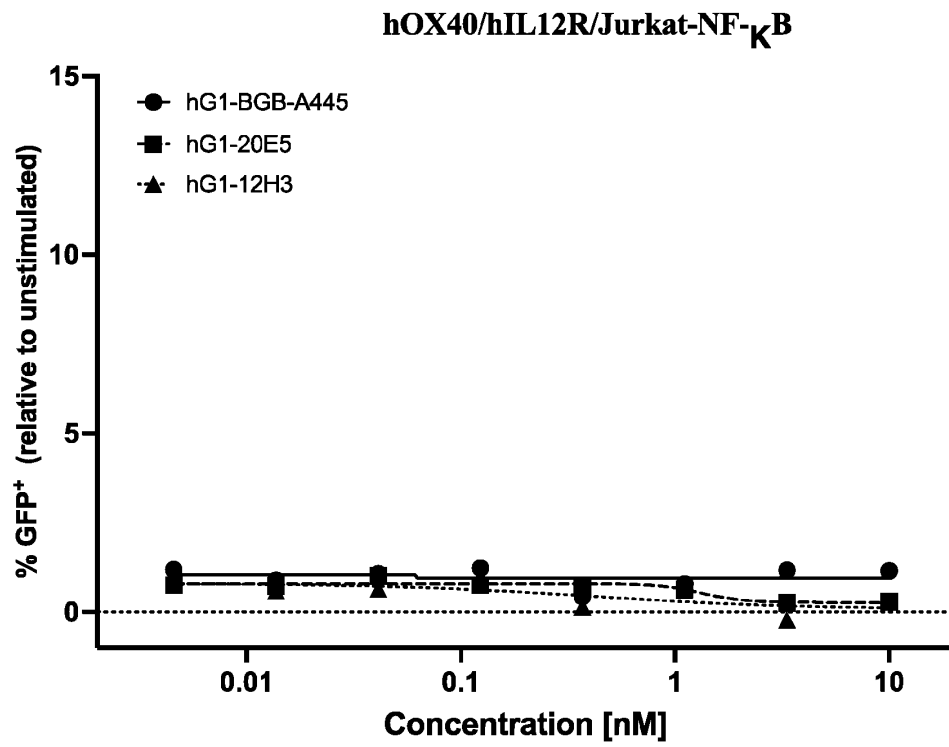


Fig. 110

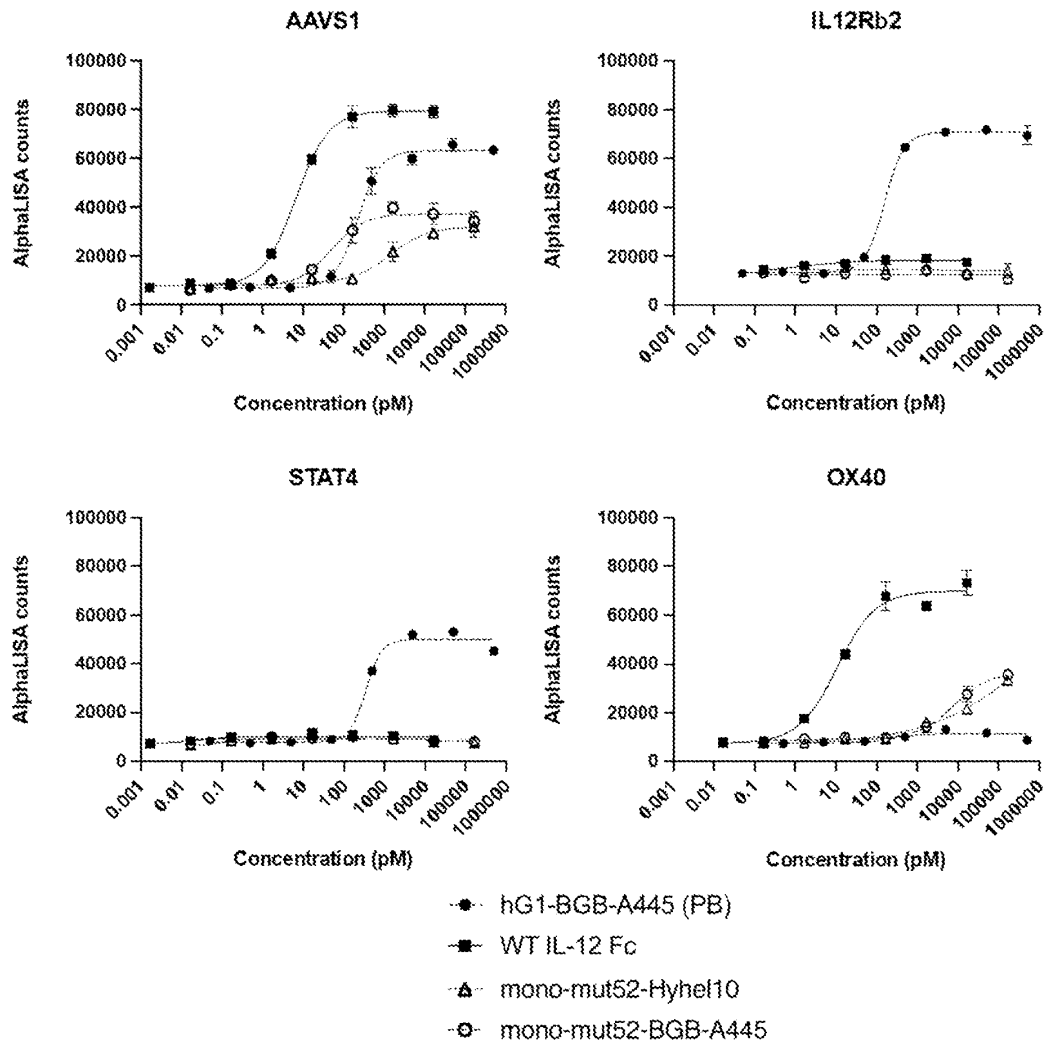


Fig. 111

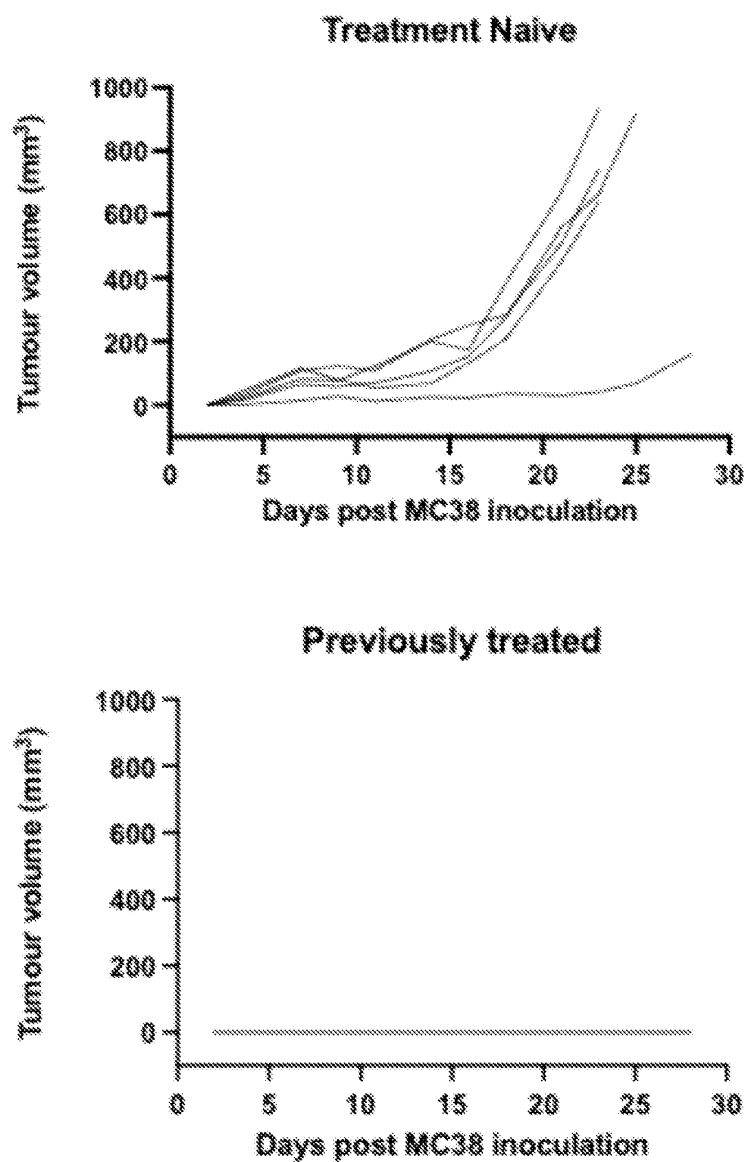


Fig. 112**A. Anti-human OX40 clone 41****A1. VH domain**

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYG¹MHWVRQAPGKGLEWVALIS²YDGSN³KIYTDSVKGRFTISRDN⁴SKN⁵
TLYLQMNSLRPEDTAVYYCAKGREIVATYFDYWGQGT⁶LVTVSS (SEQ ID NO: 170)

A2. VL domain

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQNPGQP¹PKLLIYWASTRESGV²PDRFSGSGSGTDF³
TLTISSLQAEDVSVYYCQ⁴QYYRTPYTFGQGT⁵KVEIK (SEQ ID NO: 171)

A3. Heavy chain (human IgG1 format)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYG¹MHWVRQAPGKGLEWVALIS²YDGSN³KIYTDSVKGRFTISRDN⁴SKN⁵
TLYLQMNSLRPEDTAVYYCAKGREIVATYFDYWGQGT⁶LVTVSSASTKGPSVF⁷FLAPSSKSTSGGTAALGCLVKDYF⁸P⁹
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV¹⁰PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP¹¹
CPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV¹²
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE¹³
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV¹⁴MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 172)

A4. Light chain

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQNPGQP¹PKLLIYWASTRESGV²PDRFSGSGSGTDF³
TLTISSLQAEDVSVYYCQ⁴QYYRTPYTFGQGT⁵KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC⁶CLNNFYPREAKVQW⁷
KVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADY⁸EKKHVKYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 173)

A5. Heavy chain (human IgG1 format with Knob and FES mutations)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYG¹MHWVRQAPGKGLEWVALIS²YDGSN³KIYTDSVKGRFTISRDN⁴SKN⁵
TLYLQMNSLRPEDTAVYYCAKGREIVATYFDYWGQGT⁶LVTVSSASTKGPSVF⁷FLAPSSKSTSGGTAALGCLVKDYF⁸P⁹
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV¹⁰PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP¹¹
CPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV¹²
LTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWE¹³
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV¹⁴MHEALHNHYTQKSLSLSPG (SEQ ID NO: 174)

Fig. 113

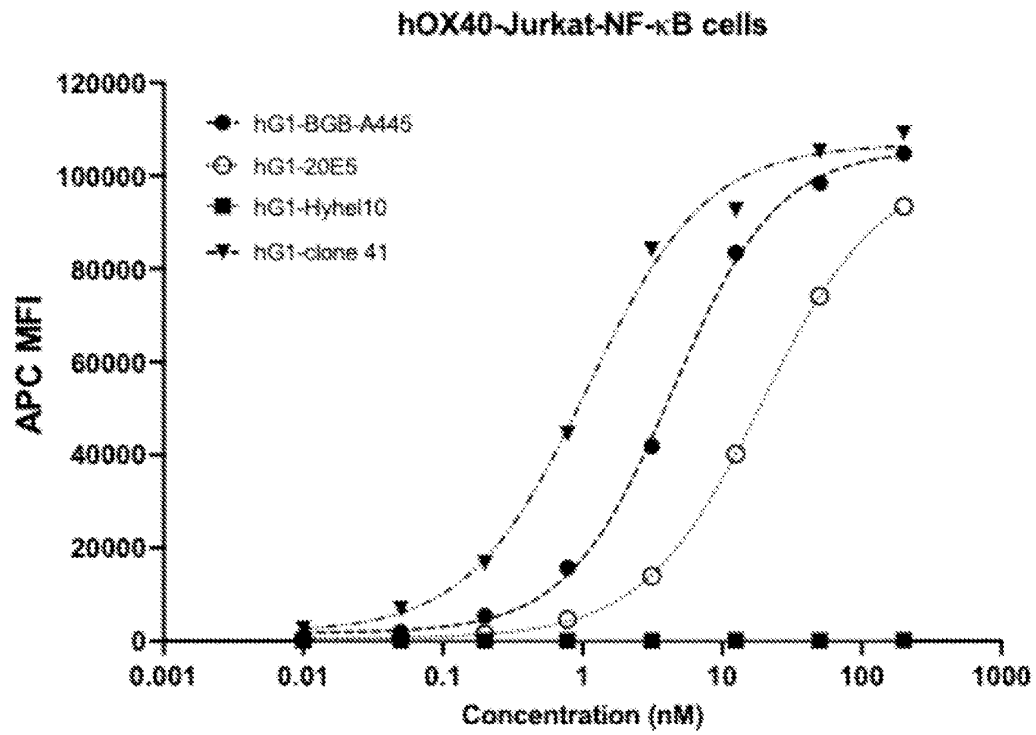


Fig. 114

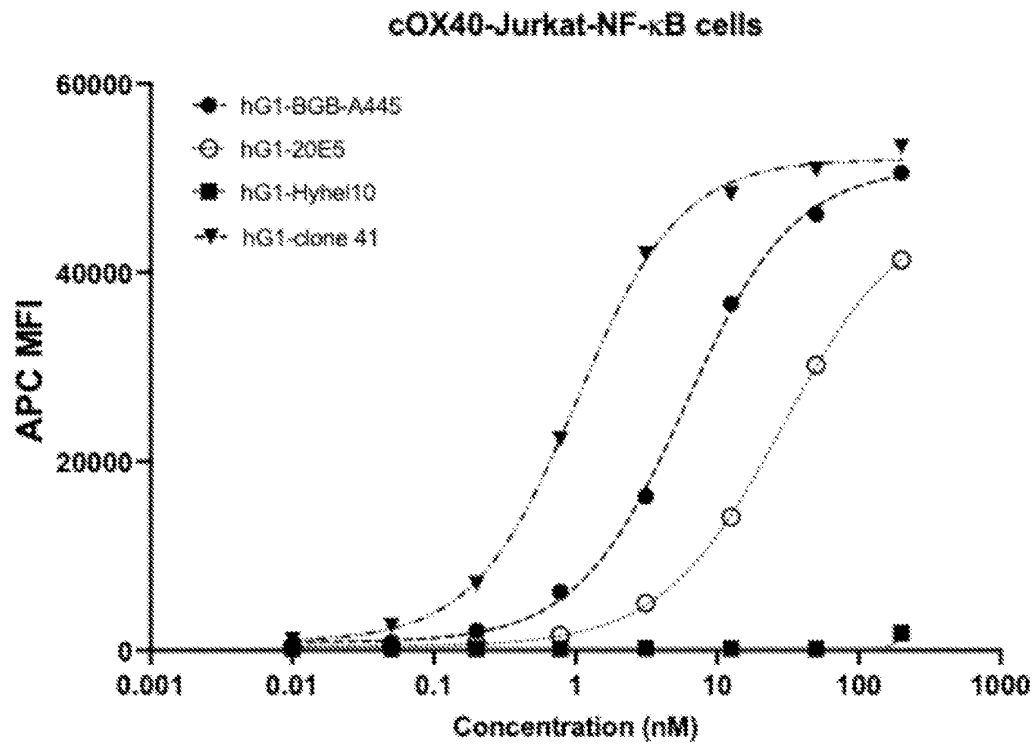


Fig. 115

Sample	Cell type	EC50 (nM)
hG1-BGB-A445	hOX40-Jurkat-NF-κB	4.4
hG1-BGB-A445	cOX40-Jurkat-NF-κB	6.0
hG1-20E5	hOX40-Jurkat-NF-κB	19.3
hG1-20E5	cOX40-Jurkat-NF-κB	29.0
hG1-Hyhel10	hOX40-Jurkat-NF-κB	ND
hG1-Hyhel10	cOX40-Jurkat-NF-κB	ND
hG1-clone 41	hOX40-Jurkat-NF-κB	1.1
hG1-clone 41	cOX40-Jurkat-NF-κB	1.0

Fig. 116

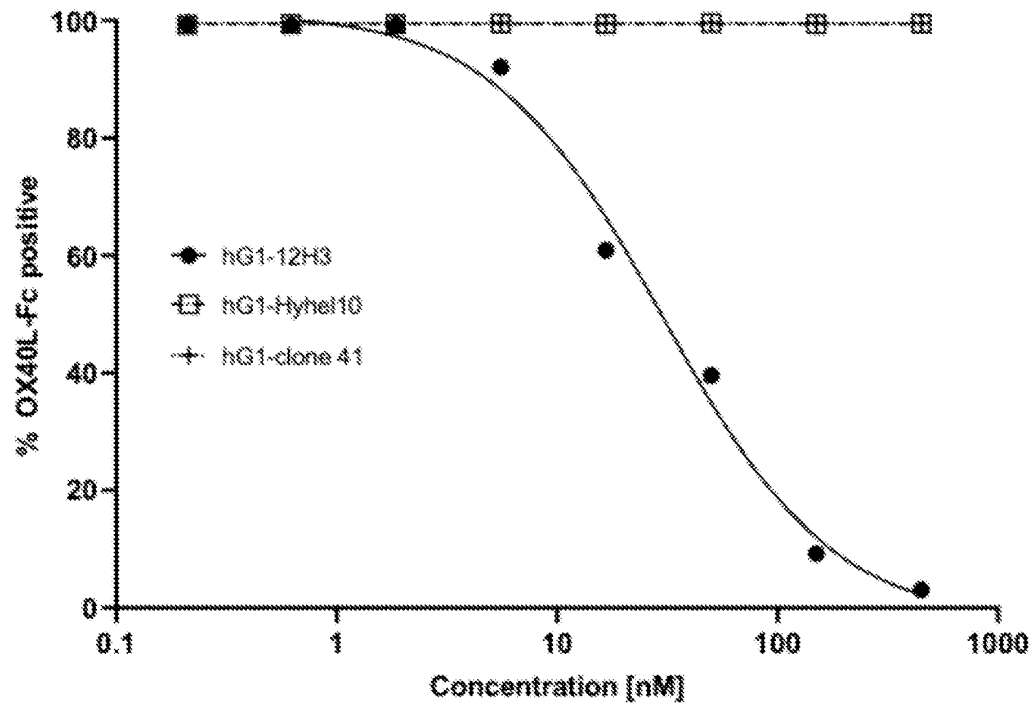


Fig. 117

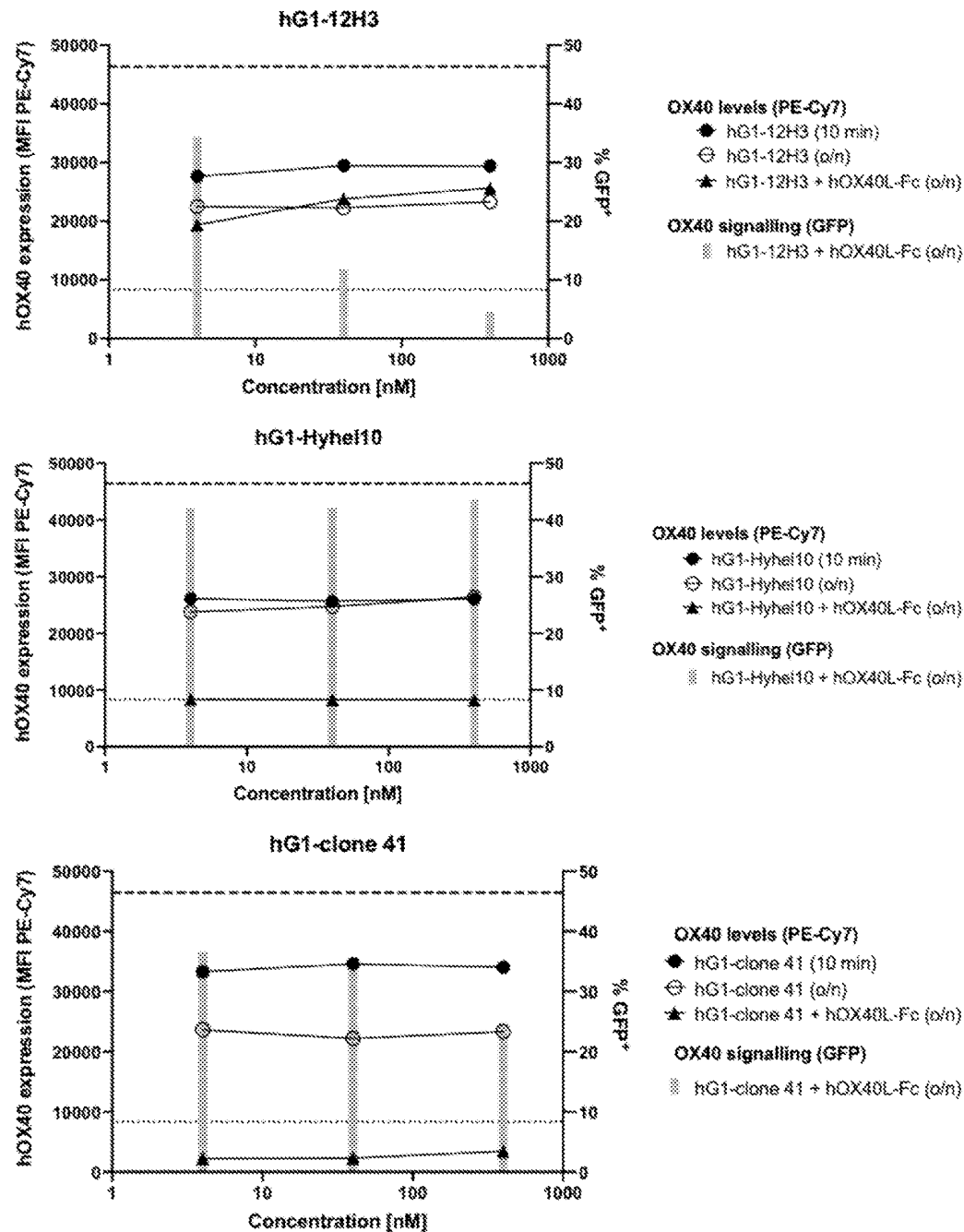


Fig. 118 – Fig. 118A

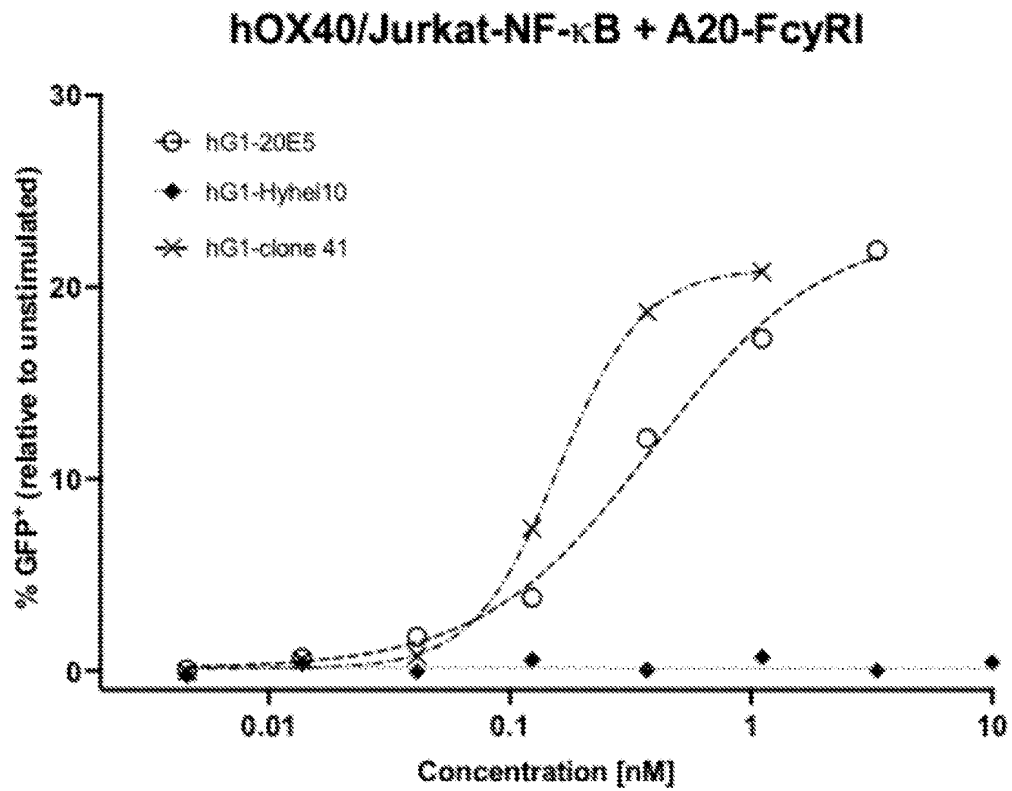


Fig. 118 – Fig. 118B

