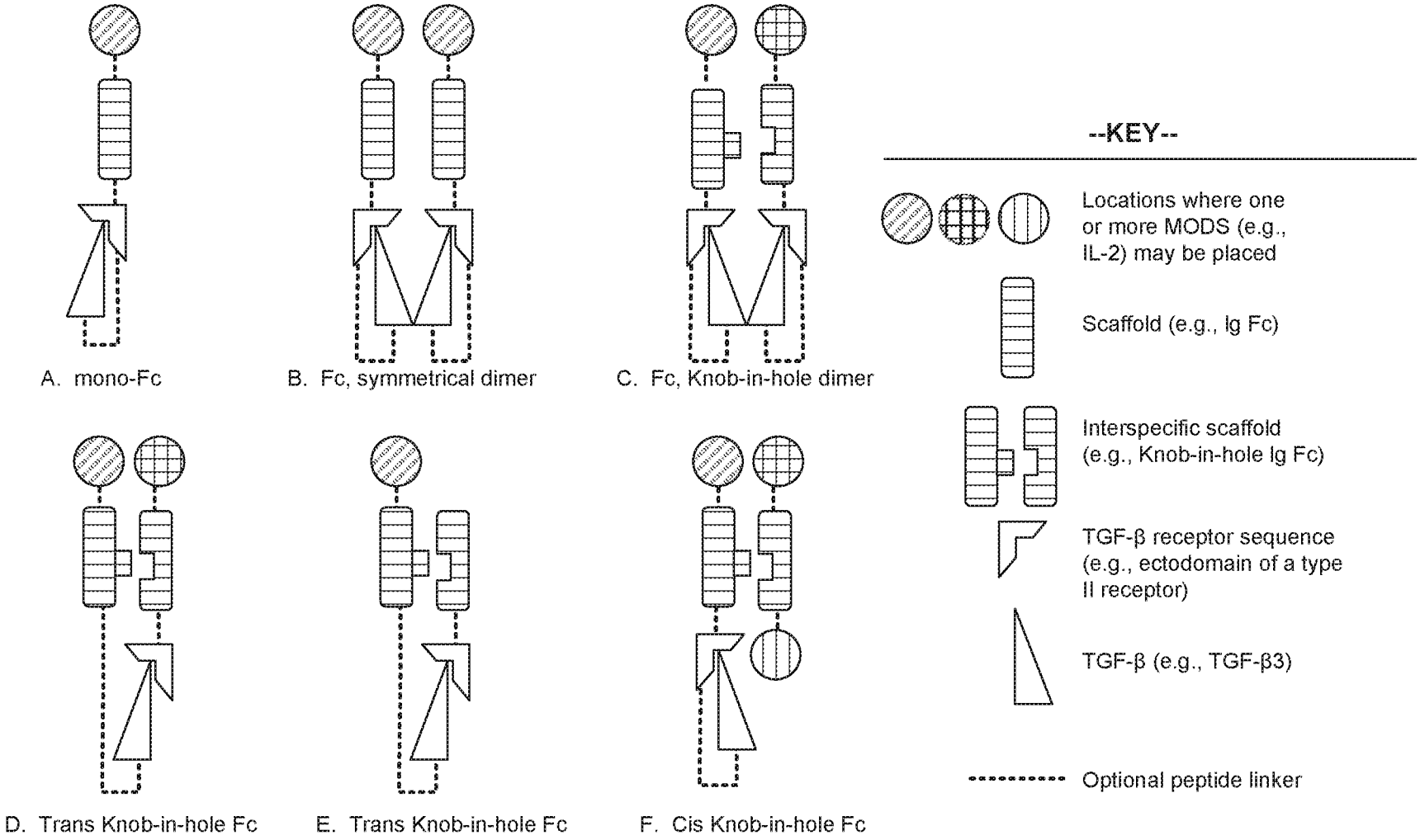
FIG. 1


A. mono-Fc
B. Fc, symmetrical dimer
C. Fc, Knob-in-hole dimer
D. Trans Knob-in-hole Fc
E. Trans Knob-in-hole Fc
F. Cis Knob-in-hole Fc
--KEY--
Locations where one or more MODS (e.g., IL-2) may be placed
Scaffold (e.g., Ig Fc)
Interspecific scaffold (e.g., Knob-in-hole Ig Fc)
TGF-β receptor sequence (e.g., ectodomain of a type II receptor)
TGF-β (e.g., TGF-β3)
Optional peptide linker

VII. Fig 2

FIG. 2A

***Homo sapiens* IgA Fc GenBank P01876 (amino acids 120-353) (SEQ ID NO:68) 234 aa**

```
1   ASPTSPKVFP LSLCSTQPDG NVVIACLVQG FFPQEPLSVT WSESGQGVTA RNFPPSQDAS
61  GDLYTTSSQL TLPATQCLAG KSVTCHVKHY TNPSQDVTVP CPVPSTPPTP SPSTPPTPSP
121 SCCHPRLSLH RPALEDLLLG SEANLTCTLT GLRDASGVTF TWTPSSGKSA VQGPPERDLC
181 GCYSVSSVLP GCAEPWNHGK TFTCTAAYPE SKTPLTATLS KSGNTFRPEV HLLPPPSEEL
241 ALNELVTLTC LARGFSPKDV LVRWLQGSQE LPREKYLTWA SRQEPSQGTT TFAVTSILRV
301 AAEDWKKGDT FSCMVGHEAL PLAFTQKTID RLAGKPTHVN VSVVMAEVDG TCY
```

FIG. 2B

***Homo sapiens* IgD Fc GenBank AAA52770 (amino acids 162-383) (SEQ ID NO:69) 222 aa**

```
1   PTKAPDVFPI ISGCRHPKDN SPVVLACLIT GYHPTSVTVT WYMGTQSQPQ RTFPEIQRRD
61  SYYMTSSQLS TPLQQWRQGE YKCVVQHTAS KSKKEIFRWP ESPKAQASSV PTAQPQAEGS
121 LAKATTAPAT TRNTGRGGEE KKKEKEKEEQ EERETKTPEC PSHTQPLGVY LLTPAVQDLW
181 LRDKATFTCF VVGSDLKDAH LTWEVAGKVP TGGVEEGLLE RHSNGSQSQH SRLTLPRSLW
241 NAGTSVTCTL NHPSLPPQRL MALREPAAQA PVKLSLNLLA SSDPPEAASW LLCEVSGFSP
301 PNILLMWLED QREVNTSGFA PARPPPQPRS TTFWAWSVLR VPAPPSPQPA TYTCVVSHED
361 SRTLLNASRS LEVSYVTDHG PMK
```

FIG. 2C

***Homo sapiens* IgE Fc GenBank 1F6A_B (amino acids 6-222) (SEQ ID NO:70) 212 aa**

```
1   ADPCDSNPRG VSAYLSRPSP FDLFIRKSPT ITCLVVDLAP SKGTVNLTWS RASGKPVNHS
61  TRKEEKQRNG TLTVTSTLPV GTRDWIEGET YQCRVTHPHL PRALMRSTTK TSGPRAAPEV
121 YAFATPEWPG SRDKRTLACL IQNFMPEDIS VQWLHNEVQL PDARHSTTQP RKTKGSGFFV
181 FSRLEVTRAE WEQKDEFICR AVHEAASPSQ TVQRAVSVNP GK
```

FIG. 2D

WT *Homo sapiens* IgG1 Fc Sequence (SEQ ID NO:71) 227 aa

```
1   DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
61  GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
121 GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
181 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
```

***Homo sapiens* IgG1 Fc GenBank 3S7G_A (SEQ ID NO:72) 227 aa**

```
1   DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
61  GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
121 GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
181 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
```

***Homo sapiens* IgG1 Fc Mutant: L234F/L235E/P331S (Triple Mutant "TM") (SEQ ID NO:73)**

```
DKTHTCPPCP APE***FE***GGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA **S**IEKTISKAK
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
```

***Homo sapiens* IgG1 Fc Mutant: N297A (SEQ ID NO:74)**

```
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
GVEVHNAKTK PREEQY**A**STY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
```

FIG. 2D (continued)

***Homo sapiens* IgG1 Fc Mutant: L234A/L235A ("LALA") (SEQ ID NO:75)**

DKTHTCPPCP APE**AA**GGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK

***Homo sapiens* IgG1 Fc Mutant: (N-terminal Δ10) L234A/L235A ("LALA") L351K, T366S, P395V, F405R, Y407A, and K409Y (SEQ ID NO:76)**

APE**AA**GGPS VFLFPPKPK DTLMISRTP EVTCVVVDV SHEDPEVKF NWYVDGVEV HNAKTKPRE
EQYNSTYRV VSVLTVLHQ DWLNGKEYK CKVSNKALP APIEKTISK AKGQPREPQ VYT**K**PPSRE
EMTKNQVSL **S**CLVKGFYP SDIAVEWES NGQPENNYK TT**V**PVLDSD GSF**R**L**A**S**Y**L TVDKSRWQQ
GNVFSCSVM HEALHNHYT QKSLSLSP

***Homo sapiens* IgG1 Fc Mutant: L234A/L235A ("LALA") and T366W Knob-in-Hole "Knob"(SEQ ID NO:77)**

DKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSL**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSP

***Homo sapiens* IgG1 Fc Mutant: L234A/L235A ("LALA") and T366S and L368A Knob-in-Hole "Hole" (SEQ ID NO:78)**

DKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*V*SKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP

Residue numbered according to EU index (Kabat Numbering)

FIG. 2E

***Homo sapiens* IgG2 Fc GenBank AAN76044 (amino acids 99-325) (SEQ ID NO:79) 227 aa**

1 STKGPSVFPL APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG
61 LYSLSSVVTV PSSNFGTQTY TCNVDHKPSN TKVDKTVERK CCVECPPCPA PPVAGPSVFL
121 FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV
181 VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSREEMTKNQ
241 VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV
301 FSCSVMHEAL HNHYTQKSLS LSPGK

FIG. 2F

***Homo sapiens* IgG3 Fc GenBank AAW65947(amino acids 19-246) (SEQ ID NO:80) 238 aa**

1 HKPSNTKVDK RVELKTPLGD TTHTCPPCPA PELLGGPSVF LFPPKPKDTL MISRTPEVTC
61 VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC
121 KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW
181 ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL
241 SLSPGK

FIG. 2G

***Homo sapiens* IgG4 Fc GenBank P01861 (amino acids 100-327) (SEQ ID NO:81) 228 aa**

```
1   ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPSCP APEFLGGPSV
121 FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY
181 RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK
241 NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG
301 NVFSCSVMHE ALHNHYTQKS LSLSLGK
```

***Homo sapiens* IgG4 Fc Segment (SEQ ID NO:82) 223 aa**

```
1   PPCPSCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE
61  VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP
121 REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS
181 FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SPG
```

FIG. 2H

***Homo sapiens* IgM Fc GenBank 0308221A (SEQ ID NO:83) 276 aa**

```
1   VTSTLTIKZS DWLGESMFTC RVDHRGLTFQ QNASSMCVPD QDTAIRVFAI PPSFASIFLT
61  KSTKLTCLVT DLTTYBSVTI SWTREENGAV KTHTNISESH PNATFSAVGE ASICEDBDWS
121 GERFTCTVTH TDLPSPLKQT ISRPKGVALH RPBVYLLPPA RZZLNLRESA TITCLVTGFS
181 PADVFVEWMQ RGEPLSPQKY VTSAPMPEPQ APGRYFAHSI LTVSEEEWNT GGTYTCVVAH
241 EALPNRVTER TVDKSTGKPT LYNVSLVMSD TAGTCY
```

FIG. 2I

***Homo sapiens* J-Chain NCBI Reference Sequence: NP_653247.1 SEQ ID NO:84)**

```
MKNHLLFWGV LAVFIKAVHV KAQEDERIVL VDNKCKCARI TSRIIRSSED PNEDIVERNI
RIIVPLNNRE NISDPTSPLR TRFVYHLSDL CKKCDPTEVE LDNQIVTATQ SNICDEDSAT
ETCYTYDRNK CYTAVVPLVY GGETKMVETA LTPDACYPD
```

Amino acids 1-22 (underlined) are the signal peptide.

FIG. 2J

***Homo sapiens* Ig CH1 domain (SEQ ID NO:85)**

```
 1 FTVRETASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP
61 AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KT
```

FIG. 2K

***Homo sapiens* Ig κ chain constant region (SEQ ID NO:86)**

```
1  TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS
61 KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

***Homo sapiens* Ig λ chain constant region(SEQ ID NO:87)**

```
1 GQPKANPTVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADGSPVK AGVETTKPSK
61 QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS
```

FIG. 3

***Homo sapiens* TGF-β -1 preproprotein NCBI Ref. Seq. NP_000651.3 (SEQ ID NO:106)**

```
1   MPPSGLRLLP LLLPLLWLLV LTPGRPAAGL STCKTIDMEL VKRKRIEAIR GQILSKLRLA
61  SPPSQGEVPP GPLPEAVLAL YNSTRDRVAG ESAEPEPEPE ADYYAKEVTR VLMVETHNEI
121 YDKFKQSTHS IYMFFNTSEL REAVPEPVLL SRAELRLLRL KLKVEQHVEL YQKYSNNSWR
181 YLSNRLLAPS DSPEWLSFDV TGVVRQWLSR GGEIEGFRLS AHCSCDSRDN TLQVDINGFT
241 TGRRGDLATI HGMNRPFLLL MATPLERAQH LQSSRHRRAL DTNYCFSSTE KNCCVRQLYI
301 DFRKDLGWKW IHEPKGYHAN FCLGPCPYIW SLDTQYSKVL ALYNQHNPGA SAAPCCVPQA
361 LEPLPIVYYV GRKPKVEQLS NMIVRSCKCS
```

1..29 Signal Peptide
29..261 TGF-β propeptide
244..246 Cell attachment site
279..390 mature peptide
See also UniProtKB - P01137 having a P10L substitution in the signal sequence (SEQ ID NO:190)

***Homo sapiens* TGF-β-2 preproprotein GenBank: AAA50405.1 (SEQ ID NO:109)**

```
1   MHYCVLSAFL ILHLVTVALS LSTCSTLDMD QFMRKRIEAI RGQILSKLKL TSPPEDYPEP
61  EEVPPEVISI YNSTRDLLQE KASRRAAACE RERSDEEYYA KEVYKIDMPP FFPSEAIPPT
121 FYRPYFRIVR FDVSAMEKNA SNLVKAEFRV FRLQNPKARV PEQRIELYQI LKSKDLTSPT
181 QRYIDSKVVK TRAEGEWLSF DVTDAVHEWL HHKDRNLGFK ISLHCPCCTF VPSNNYIIPN
241 KSEELEARFA GIDGTSTYTS GDQKTIKSTR KKNSGKTPHL LLMLLPSYRL ESQQTNRRKK
301 RALDAAYCFR NVQDNCCLRP LYIDFKRDLG WKWIHEPKGY NANFCAGACP YLWSSDTQHS
361 RVLSLYNTIN PEASASPCCV SQDLEPLTIL YYIGKTPKIE QLSNMIVKSC KCS
```

1..20 Signal Peptide
21..227 TGF-β propeptide
302..413 mature peptide
Lys 25, Ile 92, and Lys 94 of the mature peptide are emphasized by bolding, italicization, and underline

***Homo sapiens* TGF-β-3 preproprotein isoform 1 NCBI Ref. Seq. NP_001316868.1 UniProt Ref.: P10600.1 (SEQ ID NO:112)**

```
1   MKMHLQRALV VLALLNFATV SLSLSTCTTL DFGHIKKKRV EAIRGQILSK LRLTSPPEPT
61  VMTHVPYQVL ALYNSTRELL EEMHGEREEG CTQENTESEY YAKEIHKFDM IQGLAEHNEL
121 AVCPKGITSK VFRFNVSSVE KNRTNLFRAE FRVLRVPNPS SKRNEQRIEL FQILRPDEHI
181 AKQRYIGGKN LPTRGTAEWL SFDVTDTVRE WLLRRESNLG LEISIHCPCH TFQPNGDILE
241 NIHEVMEIKF KGVDNEDDHG RGDLGRLKKQ KDHHNPHLIL MMIPPHRLDN PGQGGQRKKR
301 ALDTNYCFRN LEENCCVRPL YIDFRQDLGW KWVHEPKGYY ANFCSGPCPY LRSADTTHST
361 VLGLYNTLNP EASASPCCVP QDLEPLTILY YVGRTPKVEQ LSNMVVKSCK CS
```

1..23 Signal Peptide
24..300 mature latency associated peptide
24..230 TGF-β propeptide`
261..263 Cell attachment site
301..412 mature peptide

FIG. 3 (continued)

***Homo sapiens* Mature TGF-β-3 isoform 1 NCBI Ref. Seq. NP_001316868.1 UniProt Ref.: P10600.1, SEQ ID NO:111 (aas 301-412 of SEQ ID NO:112)**

```
1  ALDTNYCFRN LEENCCVRPL YIDFRQDLGW KWVHEPKGYY ANFCSGPCPY LRSADTTHST
61 VLGLYNTLNP EASASPCCVP QDLEPLTILY YVGRTPKVEQ LSNMVVKSCK CS
```

***Homo sapiens* Mature TGF-β-3 isoform 1 Mutant: C77S NCBI Ref. Seq. NP_001316868.1 UniProt Ref.: P10600.1, SEQ ID NO:113 (aas 301-412 of SEQ ID NO:112 with a C77S substitution)**

```
1  ALDTNYCFRN LEENCCVRPL YIDFRQDLGW KWVHEPKGYY ANFCSGPCPY LRSADTTHST
61 VLGLYNTLNP EASASP***S***CVP QDLEPLTILY YVGRTPKVEQ LSNMVVKSCK CS
```

C77S substitution bolded, underlined, and italicized.

FIG. 4

Alignment of *Homo sapiens* TGF-β sequences

```
NP_000651.3     MPPSGLRLLPLLLPLLWLLVLTPGRPAAGLSTCKTIDMELVKRKRIEAIRGQILSKLRLA 60
P01137          MPPSGLRLLLLLLPLLWLLVLTPGRPAAGLSTCKTIDMELVKRKRIEAIRGQILSKLRLA 60
AAA50405.1      --------MHY-CVLSAFLILHLVTVALSLSTCSTLDMDQFMRKRIEAIRGQILSKLKLT 51
NP_001316868.1  ------MKMHLQRALVVLALLNFATVSLSLSTCTTLDFGHIKKKRVEAIRGQILSKLRLT 54
                        :     *  : :*     : .****.*:*:  . :**:************:*:

NP_000651.3     SPPSQGEVPPGPLPEAVLALYNSTRDRVAGESAE-----PEPEPEADYYAKEVTRVLMVE 115
P01137          SPPSQGEVPPGPLPEAVLALYNSTRDRVAGESAE-----PEPEPEADYYAKEVTRVLMVE 115
AAA50405.1      SPPEDY-PEPEEVPPEVISIYNSTRDLLQEKASRRAAACERERSDEEYYAKEVYKIDMPP 110
NP_001316868.1  SPPEPT-V-MTHVPYQVLALYNSTRELLEEMHGEREEGCTQENTESEYYAKEIHKFDMIQ 112
                ***.        :*  *:::*****: :    ..      . . : :*****: :. *

NP_000651.3     TH---NEIYDKFKQSTHSIYMFFNTSELREAVPEPVLLSRAELRLLRLKL----KVEQHV 168
P01137          TH---NEIYDKFKQSTHSIYMFFNTSELREAVPEPVLLSRAELRLLRLKL----KVEQHV 168
AAA50405.1      FFPSEAI-PPTFYRPYFRIVR-FDVSAME---KNASNLVKAEFRVFRLQNPKARVPEQRI 165
NP_001316868.1  GLAEHNELAVCPKGITSKVFR-FNVSSVE---KNRTNLFRAEFRVLRVPNPSSKRNEQRI 168
                             :   *:.* :.    :   * :**:*::*:        **::

NP_000651.3     ELYQKYSN-----NSWRYLSNRLLAPSDSPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHC 223
P01137          ELYQKYSN-----NSWRYLSNRLLAPSDSPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHC 223
AAA50405.1      ELYQILKSKDLTSPTQRYIDSKVVKTRAEGEWLSFDVTDAVHEWLHHKDRNLGFKISLHC 225
NP_001316868.1  ELFQILRPDEH-IAKQRYIGGKNLPTRGTAEWLSFDVTDTVREWLLRRESNLGLEISIHC 227
                **:*          . **:..: :      ********..*::** :     *:.:* **

NP_000651.3     SCDSRDNTLQ-----------V---DINGFTTGRRGDLATIH------GMNRPFLLLMAT 263
P01137          SCDSRDNTLQ-----------V---DINGFTTGRRGDLATIH------GMNRPFLLLMAT 263
AAA50405.1      PCCTFVPSNNYIIPNKSEELEARFAGIDGTSTYTSGDQKTIKSTRKKNSGKTPHLLLMLL 285
NP_001316868.1  PCHTFQPNGD-ILENIHEVMEIKFKGVDNEDDHGRGDLGRLK---KQKDHHNPHLILMMI 283
                 * :   . :               .::.      **   ::      . : *.*:**

NP_000651.3     PLERAQH--LQSSRHRR<b>ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANF</b> 321
P01137          PLERAQH--LQSSRHRR<b>ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANF</b> 321
AAA50405.1      PSYRLESQ-QTNRRKKR<b>ALDAAYCFRNVQDNCCLRPLYIDFKRDLGWKWIHEPKGYNANF</b> 344
NP_001316868.1  PPHRLDNPGQGGQRKKR<b>ALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANF</b> 343
                *  * :     . *::****: *** . :.***:* *****::******:****** ***
```

FIG. 4 (continued)

```
NP_000651.3     CLGPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSN 381
P01137          CLGPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSN 381
AAA50405.1      CAGACPYLWSSDTQHSRVLSLYNTINPEASASPCCVSQDLEPLTILYYIGKTPKIEQLSN 404
NP_001316868.1 CSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCCVPQDLEPLTILYYVGRTPKVEQLSN 403
                * * ***: * ** :* **.***  ** ***:**** * **** *:**:*:.**:*****

NP_000651.3     MIVRSCKCS 390
P01137          MIVRSCKCS 390
AAA50405.1      MIVKSCKCS 413
NP_001316868.1 MVVKSCKCS 412
                *:*:*****
```

Amino acid positions 25, 77, 92 and 94 of the mature **TGF-β sequences** are underlinded, and italicized, but not bolded.

FIG. 5A

***Homo sapiens* TGF-β receptor type-1 isoform 1 precursor, NCBI Ref. Seq. NP_004603.1 and UniProtKB/Swiss-Prot: P36897.1 (SEQ ID NO:114)**

```
1   MEAAVAAPRP RLLLLVLAAA AAAAAALLPG ATALQCFCHL CTKDNFTCVT DGLCFVSVTE
61  TTDKVIHNSM CIAEIDLIPR DRPFVCAPSS KTGSVTTTYC CNQDHCNKIE LPTTVKSSPG
121 LGPVELAAVI AGPVCFVCIS LMLMVYICHN RTVIHHRVPN EEDPSLDRPF ISEGTTLKDL
181 IYDMTTSGSG SGLPLLVQRT IARTIVLQES IGKGRFGEVW RGKWRGEEVA VKIFSSREER
241 SWFREAEIYQ TVMLRHENIL GFIAADNKDN GTWTQLWLVS DYHEHGSLFD YLNRYTVTVE
301 GMIKLALSTA SGLAHLHMEI VGTQGKPAIA HRDLKSKNIL VKKNGTCCIA DLGLAVRHDS
361 ATDTIDIAPN HRVGTKRYMA PEVLDDSINM KHFESFKRAD IYAMGLVFWE IARRCSIGGI
421 HEDYQLPYYD LVPSDPSVEE MRKVVCEQKL RPNIPNRWQS CEALRVMAKI MRECWYANGA
481 ARLTALRIKK TLSQLSQQEG IKM
```

1..33	signal peptide
34-126	extracellular region (ectodomain)
127-147	transmembrane region
176..203	Transforming growth factor beta type I GS-motif
205..492	Protein tyrosine kinase
209..496	Catalytic domain of the Serine/Threonine Kinases,

***Homo sapiens* TGF-β receptor type-1 isoform 1 ectodomain (SEQ ID NO:115)**

```
34   LQCFCHL CTKDNFTCVT DGLCFVSVTE TTDKVIHNSM CIAEIDLIPR DRPFVCAPSS

91   KTGSVTTTYC CNQDHCNKIE LPTTVKSSPG LGPVEL
```

FIG. 5B

***Homo sapiens* TGF-β receptor type-2 (TβRII) isoform A precursor NCBI Ref. Seq. NP_001020018.1 (SEQ ID NO:116)**

```
1   MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND
61  MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
121 TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT
181 SNPDLLLVIF QVTGISLLPP LGVAISVIII FYCYRVNRQQ KLSSTWETGK TRKLMEFSEH
241 CAIILEDDRS DISSTCANNI NHNTELLPIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA
301 VKIFPYEEYA SWKTEKDIFS DINLKHENIL QFLTAEERKT ELGKQYWLIT AFHAKGNLQE
361 YLTRHVISWE DLRKLGSSLA RGIAHLHSDH TPCGRPKMPI VHRDLKSSNI LVKNDLTCCL
421 CDFGLSLRLD PTLSVDDLAN SGQVGTARYM APEVLESRMN LENVESFKQT DVYSMALVLW
481 EMTSRCNAVG EVKDYEPPFG SKVREHPCVE SMKDNVLRDR GRPEIPSFWL NHQGIQMVCE
541 TLTECWDHDP EARLTAQCVA ERFSELEHLD RLSGRSCSEE KIPEDGSLNT TK
```

1..23	signal peptide
24..592	mature peptide
24..177	extracellular region (ectodomain)

***Homo sapiens* TGF-β receptor type-2 (TβRII) isoform A ectodomain(SEQ ID NO:117)**

```
24 IPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND MIVTDNNGAV KFPQLCKFCD
80         VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI TLETVCHDPK
130        LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEE
```

***Homo sapiens* TGF-β receptor type-2 (TβRII) isoform B precursor, UniProtKB Ref. P37173, NCBI Ref. Seq. NP_003233.4 (SEQ ID NO:118)**

```
1   MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
61  CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
121 CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQVTGI SLLPPLGVAI
181 SVIIIFYCYR VNRQQKLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNTE
241 LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
301 HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
361 LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSGQVG
421 TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
481 HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARLT AQCVAERFSE
541 LEHLDRLSGR SCSEEKIPED GSLNTTK
```

1..23	Signal peptide (As noted below, NCBI records report the signal sequence to be aas 1-22.)
24..567	Mature peptide
24..166	Transforming growth factor beta receptor 2 ectodomain

***Homo sapiens* TGF-β receptor type-2 (TβRII) isoform B, ectodomain sequence (SEQ ID NO:119)**

```
                                    30 32                    52  55
                                     |  |                     |  |
1   IPPHVQKSVN NDMIVTDNNG AVKFPQLCKF CDVRFSTCDN QKSCMSNCSI TSICEKPQEV

                                                              118
                                                               |
61  CVAVWRKNDE NITLETVCHD PKLPYHDFIL EDAASPKCIM KEKKKPGETF FMCSCSSDEC

121 NDNIIFSEEY NTSNPDLLLV IFQ
```

FIG. 5B (Continued)

Homo sapiens **TGF-β receptor type-2 (TβRII) isoform B, ectodomain fragment sequence (SEQ ID NO:120)**

```
                                    30 32                    52  55
                                    |  |                     |  |
1   IPPHVQKSVN NDMIVTDNNG AVKFPQLCKF CDVRFSTCDN QKSCMSNCSI TSICEKPQEV

                                                                118
                                                                 |
61 CVAVWRKNDE NITLETVCHD PKLPYHDFIL EDAASPKCIM KEKKKPGETF FMCSCSSDEC

121 NDNIIFSEE
```

Homo sapiens **TGF-β receptor type-2 isoform B, ectodomain fragment Δ14 (N-terminus) D118A (SEQ ID NO:121)**

```
                   30 32                    52  55
                   |  |                     |  |
15  TDNNG AVKFPQLCKF CDVRFSTCDN QKSCMSNCSI TSICEKPQEV CVAVWRKNDE
NITLETVCHD

                                            118
                                             |
80  PKLPYHDFIL EDAASPKCIM KEKKKPGETF FMCSCSSAEC NDNIIFSEE
```

Homo sapiens **TGF-β receptor type-2 (TβRII) isoform B, ectodomain fragment Δ25 (N-terminus) D118A (SEQ ID NO:122)**

```
        30 32                    52  55
        |  |                     |  |
26  QLCKF CDVRFSTCDN QKSCMSNCSI TSICEKPQEV CVAVWRKNDE NITLETVCHD

                                                  118
                                                   |
80        PKLPYHDFIL EDAASPKCIM KEKKKPGETF FMCSCSSAEC NDNIIFSEE
```

Homo sapiens **TGF-β receptor type-2 (TβRII) isoform B, ectodomain fragment Δ25 (N-terminus), D118A ectodomain sequence (SEQ ID NO:123)**

```
26  QLCKF CDVRFSTCDN QKSCMSNCSI TSICEKPQEV CVAVWRKNDE NITLETVCH

80        DPKLPYHDFI LEDAASPKCI MKEKKKPGET FFMCSCSSAE CNDNIIFSE EYNTSNPD
```

Based upon NCBI Ref. Seq. NP_003233.4, and UniProtKB Ref. P37173; with the sequence corresponding to aas 49 to 159 of those sequences. The substitution at aspartic acid "D119" of the mature protein with an alanine "***A***" (bolded, italicized, and underlined) is marked as a "D118A" substitution for consistency with the literature describing that substitution. Note that aa D119 numbering is based on the mature protein, and accordingly it is D 141 of the precursor protein when the 22 aa signal sequence is included. The location of D32, sometimes substituted with asparagine (D32N), is also shown bolded, italicized, and underlined. D32 in corresponds to D55 in the precursor protein.

FIG. 5C

***Homo sapiens* TGF-β receptor type 3 isoform A precursor, (BETA Glycan), NCBI Ref. Seq. NP_003234.2 and UniProtKB/Swiss-Prot: Q03167.3 (SEQ ID NO:124)**

```
1   MTSHYVIAIF ALMSSCLATA GPEPGALCEL SPVSASHPVQ ALMESFTVLS GCASRGTTGL
61  PQEVHVLNLR TAGQGPGQLQ REVTLHLNPI SSVHIHHKSV VFLLNSPHPL VWHLKTERLA
121 TGVSRLFLVS EGSVVQFSSA NFSLTAETEE RNFPHGNEHL LNWARKEYGA VTSFTELKIA
181 RNIYIKVGED QVFPPKCNIG KNFLSLNYLA EYLQPKAAEG CVMSSQPQNE EVHIIELITP
241 NSNPYSAFQV DITIDIRPSQ EDLEVVKNLI LILKCKKSVN WVIKSFDVKG SLKIIAPNSI
301 GFGKESERSM TMTKSIRDDI PSTQGNLVKW ALDNGYSPIT SYTMAPVANR FHLRLENNAE
361 EMGDEEVHTI PPELRILLDP GALPALQNPP IRGGEGQNGG LPFPFPDISR RVWNEEGEDG
421 LPRPKDPVIP SIQLFPGLRE PEEVQGSVDI ALSVKCDNEK MIVAVEKDSF QASGYSGMDV
481 TLLDPTCKAK MNGTHFVLES PLNGCGTRPR WSALDGVVYY NSIVIQVPAL GDSSGWPDGY
541 EDLESGDNGF PGDMDEGDAS LFTRPEIVVF NCSLQQVRNP SSFQEQPHGN ITFNMELYNT
601 DLFLVPSQGV FSVPENGHVY VEVSVTKAEQ ELGFAIQTCF ISPYSNPDRM SHYTIIENIC
661 PKDESVKFYS PKRVHFPIPQ ADMDKKRFSF VFKPVFNTSL LFLQCELTLC TKMEKHPQKL
721 PKCVPPDEAC TSLDASIIWA MMQNKKTFTK PLAVIHHEAE SKEKGPSMKE PNPISPPIFH
781 GLDTLTVMGI AFAAFVIGAL LTGALWYIYS HTGETAGRQQ VPTSPPASEN SSAAHSIGST
841 QSTPCSSSST A
```

1..18	Signal peptide
27..787	Extracellular domain (ectodomain)
788-809	Transmembrane domain
567..724	Zona pellucida-like domain
737..751	Interaction with TGF-beta ligand
788..809	site_type="transmembrane region"

***Homo sapiens* TGF-β receptor type 3 isoform B precursor, (BETA Glycan) NCBI Ref. Seq. NP_001182612.1 and (SEQ ID NO:125)**

```
1   MTSHYVIAIF ALMSSCLATA GPEPGALCEL SPVSASHPVQ ALMESFTVLS GCASRGTTGL
61  PQEVHVLNLR TAGQGPGQLQ REVTLHLNPI SSVHIHHKSV VFLLNSPHPL VWHLKTERLA
121 TGVSRLFLVS EGSVVQFSSA NFSLTAETEE RNFPHGNEHL LNWARKEYGA VTSFTELKIA
181 RNIYIKVGED QVFPPKCNIG KNFLSLNYLA EYLQPKAAEG CVMSSQPQNE EVHIIELITP
241 NSNPYSAFQV DITIDIRPSQ EDLEVVKNLI LILKCKKSVN WVIKSFDVKG SLKIIAPNSI
301 GFGKESERSM TMTKSIRDDI PSTQGNLVKW ALDNGYSPIT SYTMAPVANR FHLRLENNEE
361 MGDEEVHTIP PELRILLDPG ALPALQNPPI RGGEGQNGGL PFPFPDISRR VWNEEGEDGL
421 PRPKDPVIPS IQLFPGLREP EEVQGSVDIA LSVKCDNEKM IVAVEKDSFQ ASGYSGMDVT
481 LLDPTCKAKM NGTHFVLESP LNGCGTRPRW SALDGVVYYN SIVIQVPALG DSSGWPDGYE
541 DLESGDNGFP GDMDEGDASL FTRPEIVVFN CSLQQVRNPS SFQEQPHGNI TFNMELYNTD
601 LFLVPSQGVF SVPENGHVYV EVSVTKAEQE LGFAIQTCFI SPYSNPDRMS HYTIIENICP
661 KDESVKFYSP KRVHFPIPQA DMDKKRFSFV FKPVFNTSLL FLQCELTLCT KMEKHPQKLP
721 KCVPPDEACT SLDASIIWAM MQNKKTFTKP LAVIHHEAES KEKGPSMKEP NPISPPIFHG
781 LDTLTVMGIA FAAFVIGALL TGALWYIYSH TGETAGRQQV PTSPPASENS SAAHSIGSTQ
841 STPCSSSSTA
```

1..18	Signal peptide
27..786	Extracellular domain (ectodomain)
566..723	Zona pellucida-like domain
736..750	Interaction with TGF-beta ligand
787..808	site_type="transmembrane region"

FIG. 6A

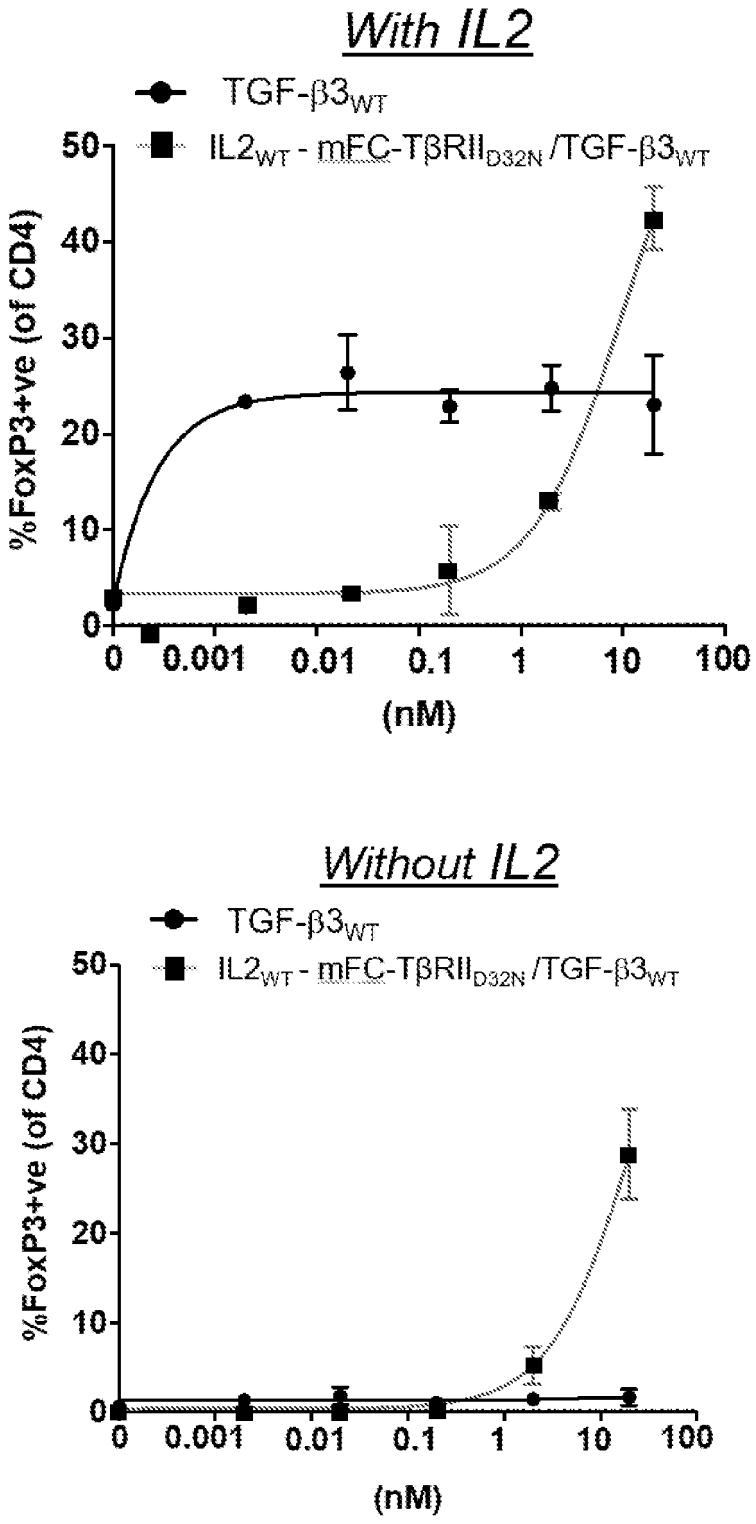

With IL2
TGF-β3WT
IL2WT - mFC-TβRIID32N /TGF-β3WT
%FoxP3+ve (of CD4)
50
40
30
20
10
0
0
0.001
0.01
0.1
1
10
100
(nM)
Without IL2
TGF-β3WT
IL2WT - mFC-TβRIID32N /TGF-β3WT
%FoxP3+ve (of CD4)
50
40
30
20
10
0
0
0.001
0.01
0.1
1
10
100
(nM)

FIG. 6B

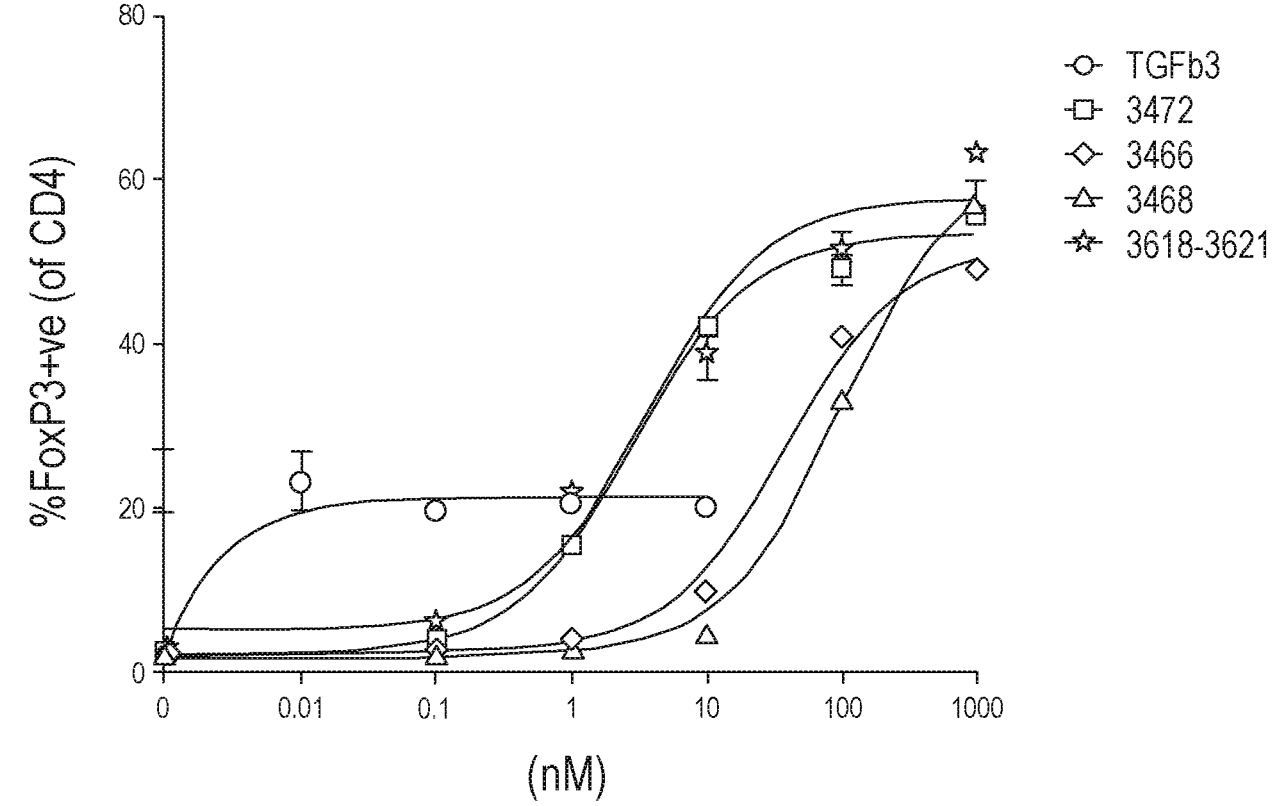

80
60
40
20
0
%FoxP3+ve (of CD4)
0
0.01
0.1
1
10
100
1000
(nM)
TGFb3
3472
3466
3468
3618-3621

FIG. 6C

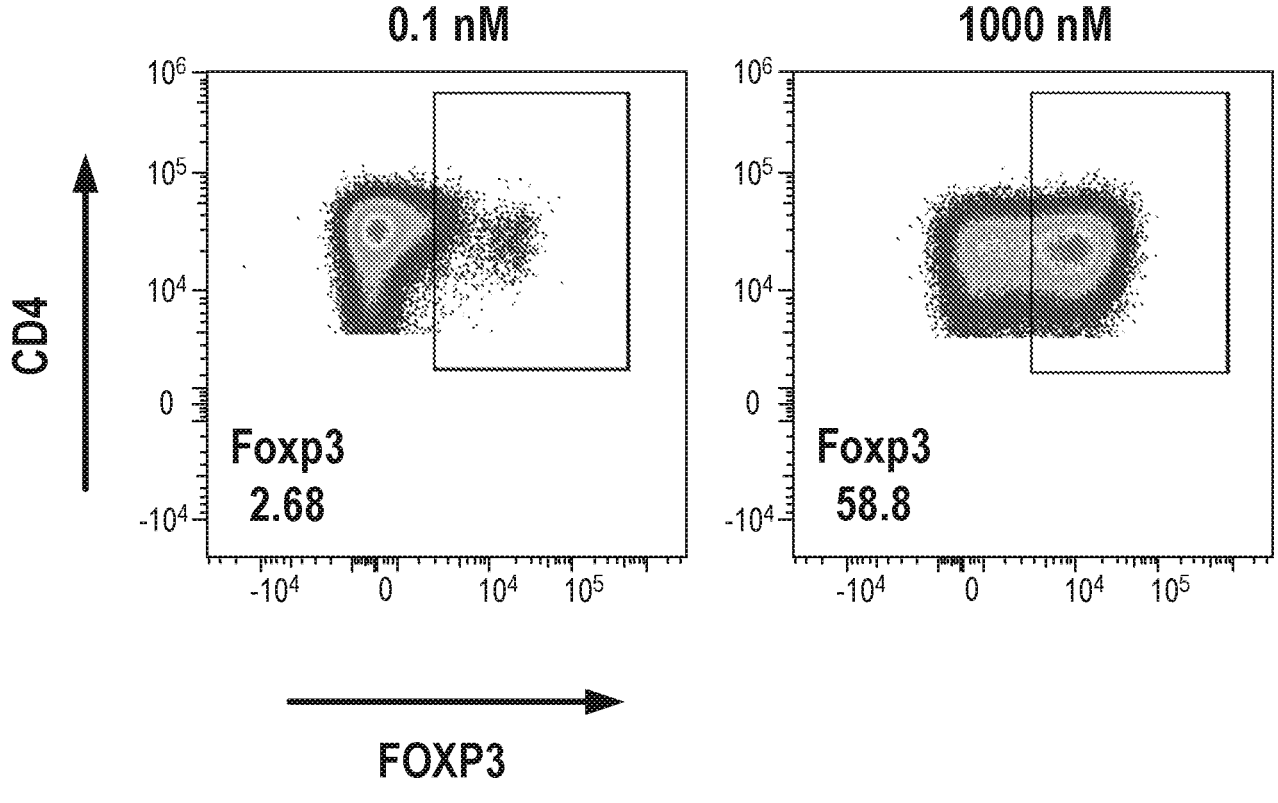

0.1 nM
1000 nM
CD4
FOXP3
Foxp3
2.68
Foxp3
58.8
10^6
10^5
10^4
0
-10^4

FIG. 7A

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*GGGGSGGGGSGGGGS*APE*AA*GGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYT*K*PPSREEMTKNQVSL*S*CLVKGFYPSDIAVEWESNGQPENNYKTT*I*PVLDSDGSF*R*L*A*S*Y*LTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSP*GGGGGSGGGGSGGGGS*QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKND
ENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPD*GGGGSGGGGSGGGGSGGGG*
*SGGGGS*ALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASP*S*C
VPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

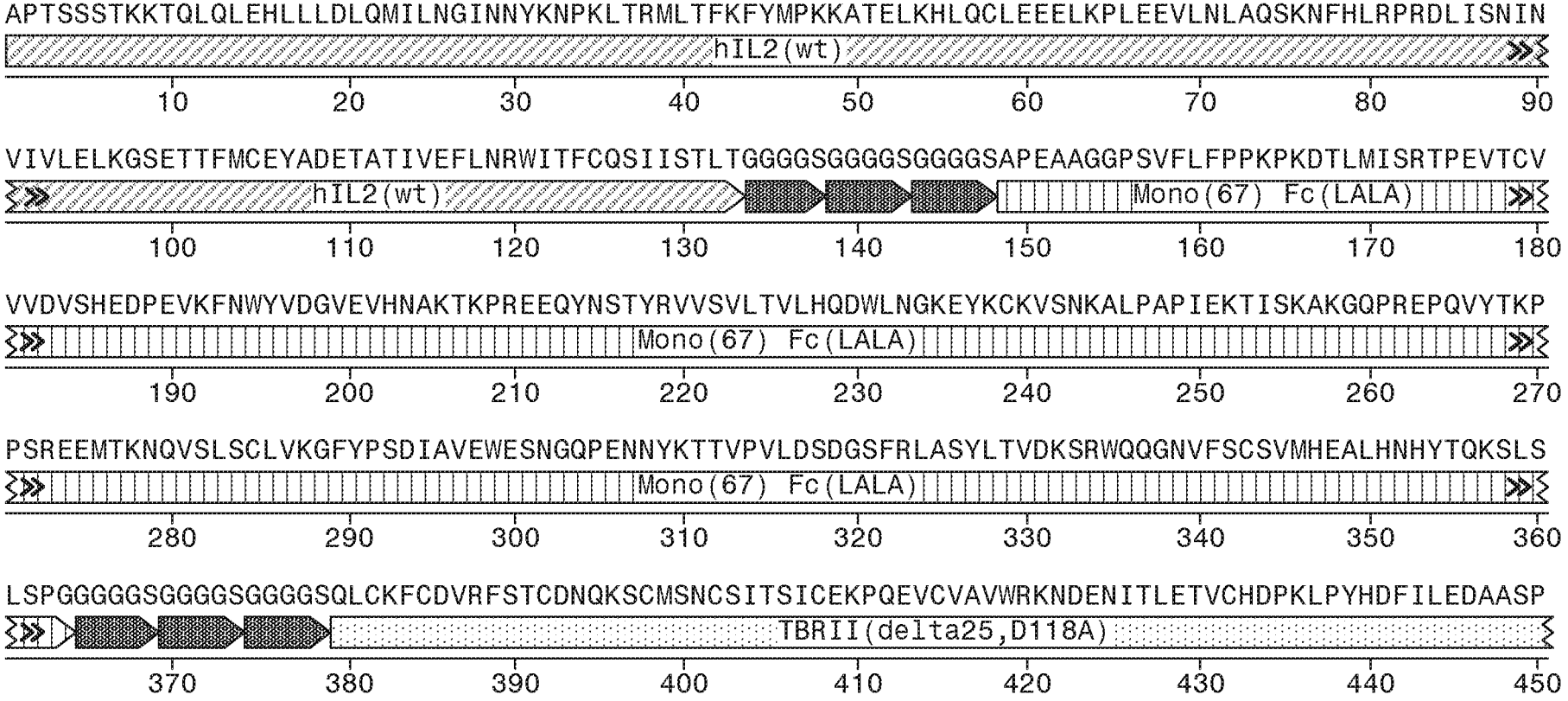


FIG. 7A (continued)

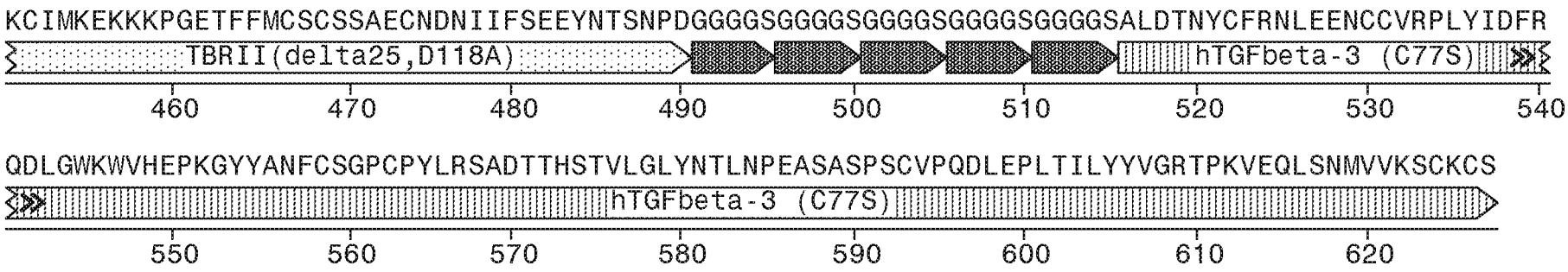


FIG. 7B

APTSSSTKKTQLQLETLLLDLQMILNGINNYKNPKLTRMLTAKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT***GGGGSGGGGSGGGGS***DKTHTCPPCPAPE***AA***GGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP***GGGGGSGGGGSGGGGS***QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQE
VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPD***GGGGSGGG***
GSGGGGSGGGGSGGGGSALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLY
NTLNPEASASPCCVPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

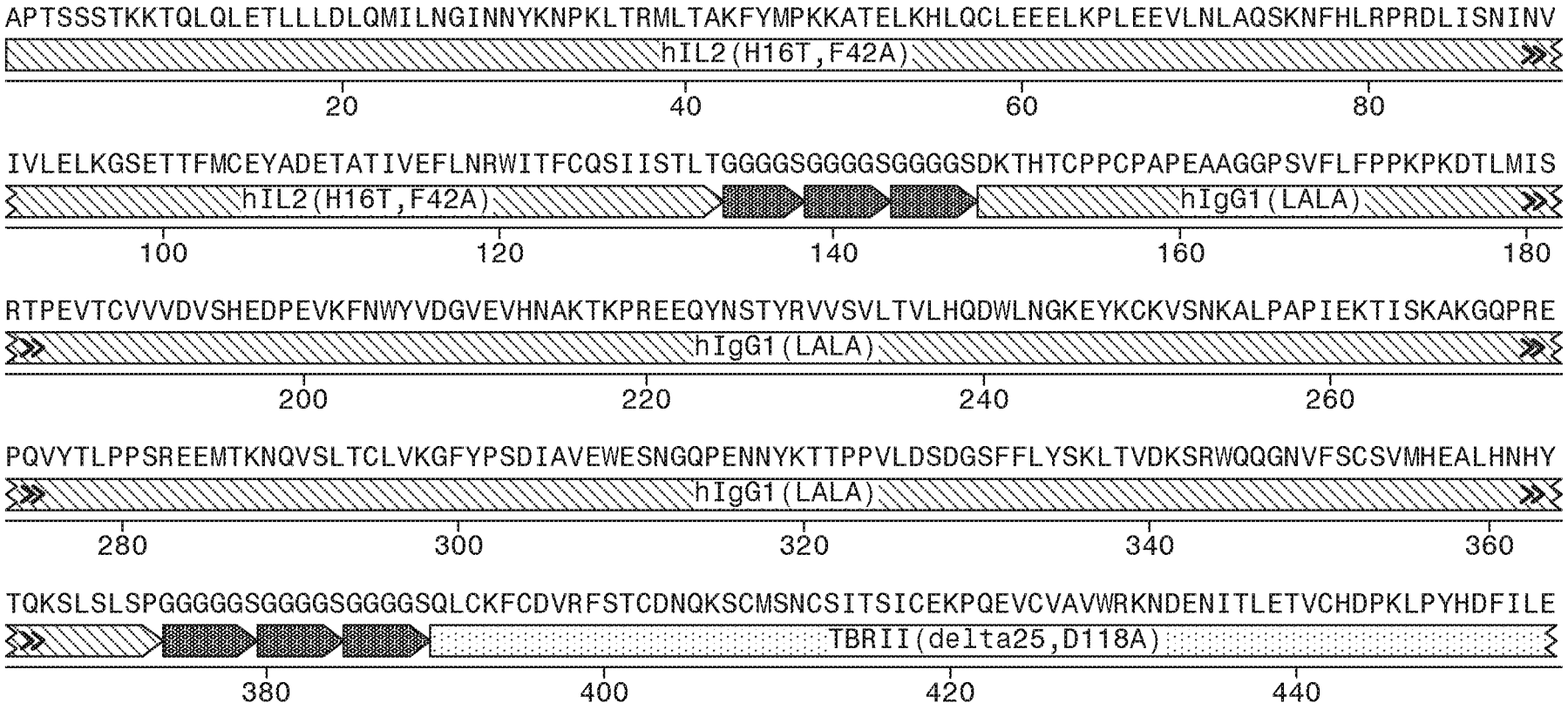


FIG. 7B (continued)

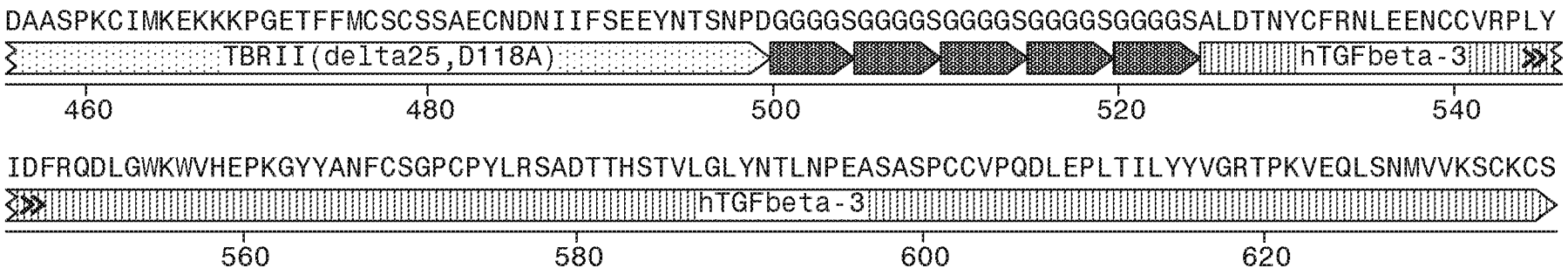


FIG. 7C

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*GGGGSGGGGSGGGGS*DKTHTCPPCPAPE*AA*GGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP*GGGGSGGGGSGGGGSGGGGSGGGGS*ALDTNYCFRNLEENCCVRPLYI
DFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASP*S*CVPQDLEPLTILYYVGRTPKVEQLSNMV
VKSCKCS

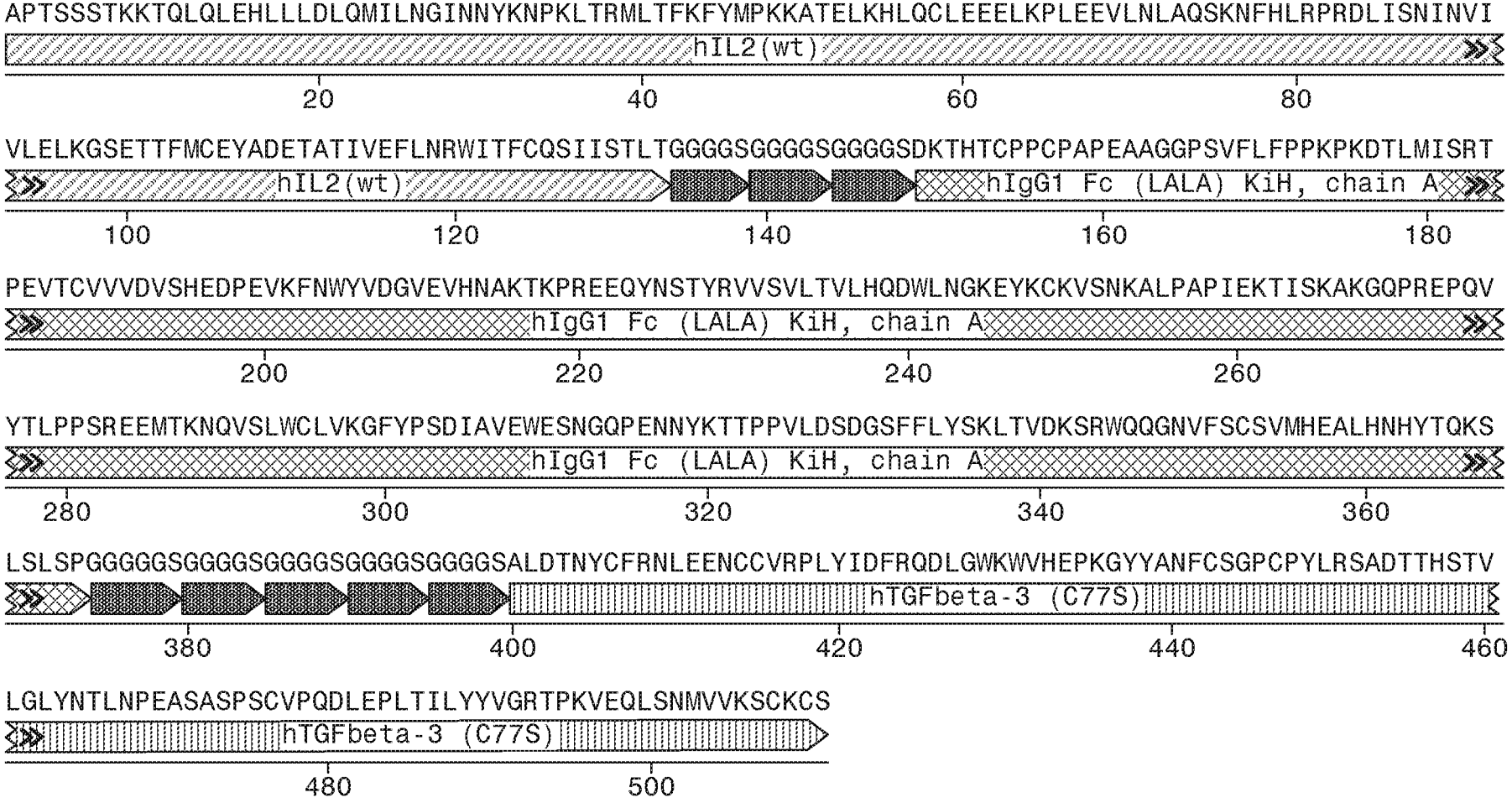


FIG. 7C (continued)

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*GGGGSGGGGSGGGGS*DKTHTCPPCPAPE*AA*GGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP*GGGGSGGGGSGGGGS*QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQE
VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPD

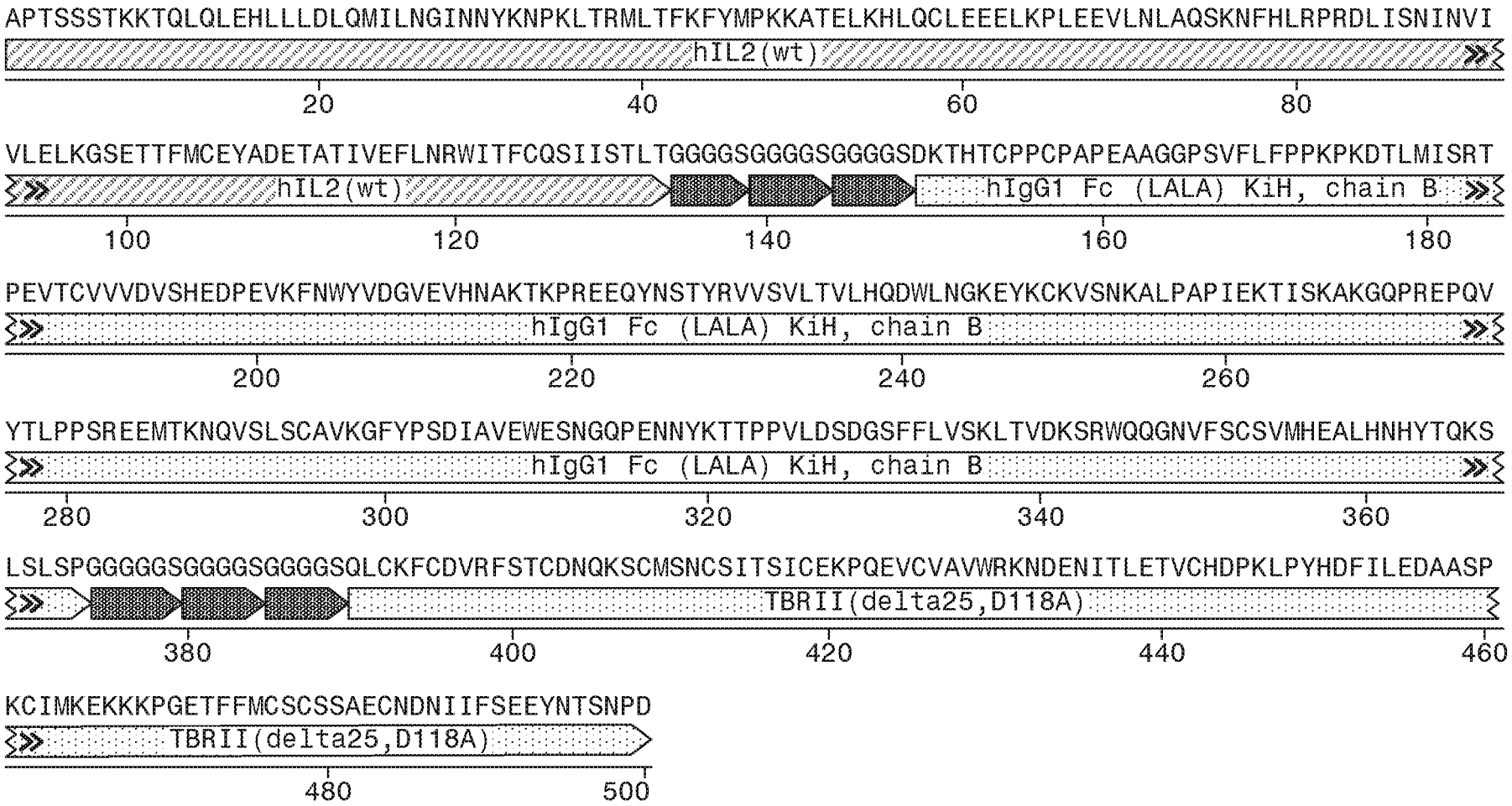


FIG. 7D

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*GGGGSGGGGSGGGGS*DKTHTCPPCPAPE*AA*GGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP*GGGGGSGGGGSGGGGSGGGGSGGGGS*ALDTNYCFRNLEENCCVRPLYI
DFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASP*S*CVPQDLEPLTILYYVGRTPKVEQLSNMV
VKSCKCS

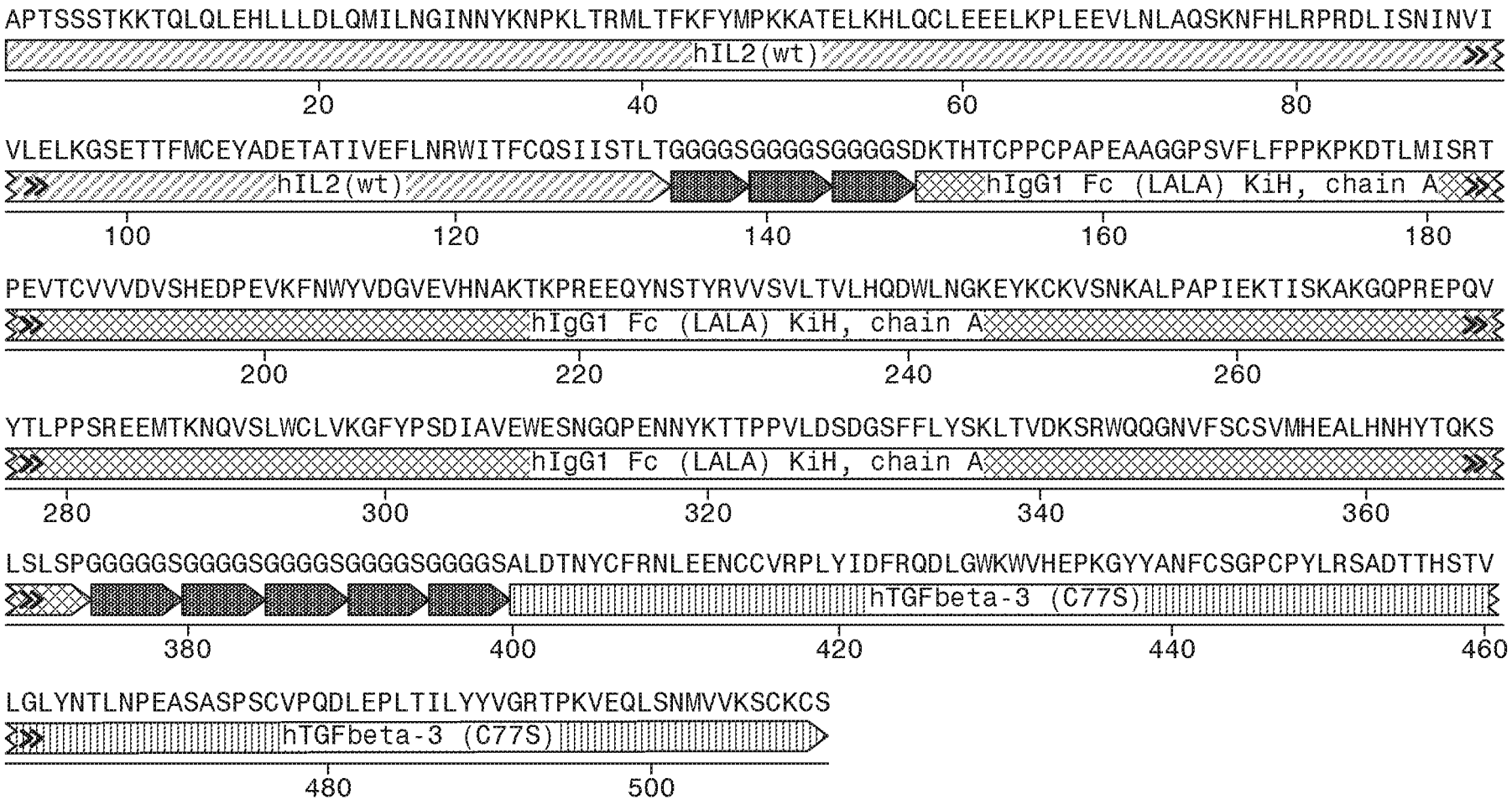


FIG. 7D (continued)

and 3855

DKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP*GGGGGSGGGGSGGGG*SQLCKFCDVRF
STCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAEC
NDNIIFSEEYNTSNPD

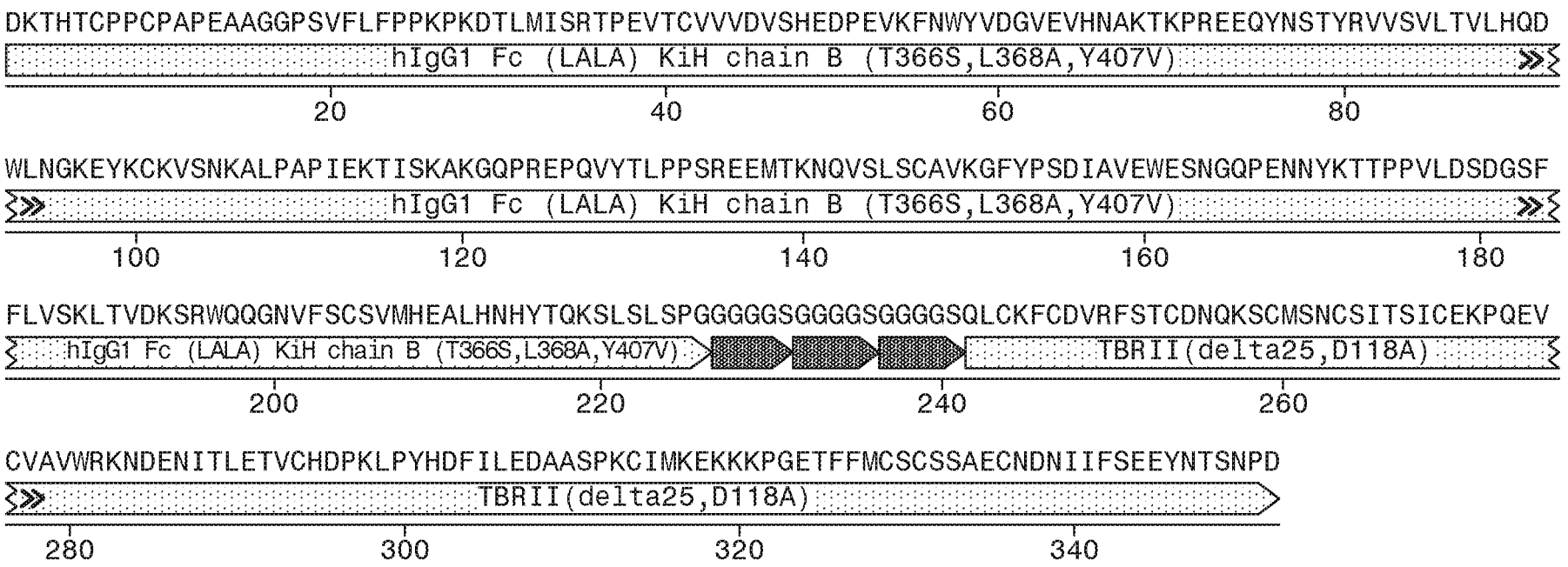


FIG. 7E

APTSSSTKKTQLQLETLLLDLQMILNGINNYKNPKLTRMLTAKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*GGGGSGGGGSGGGGS*DKTHTCPPCPAPE*AA*GGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP*GGGGSGGGGSGGGGS*QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQ
EVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPD*GGGGSGG*
*GGSGGGGSGGGGSGGGGS*ALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGL
YNTLNPEASASP*S*CVPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

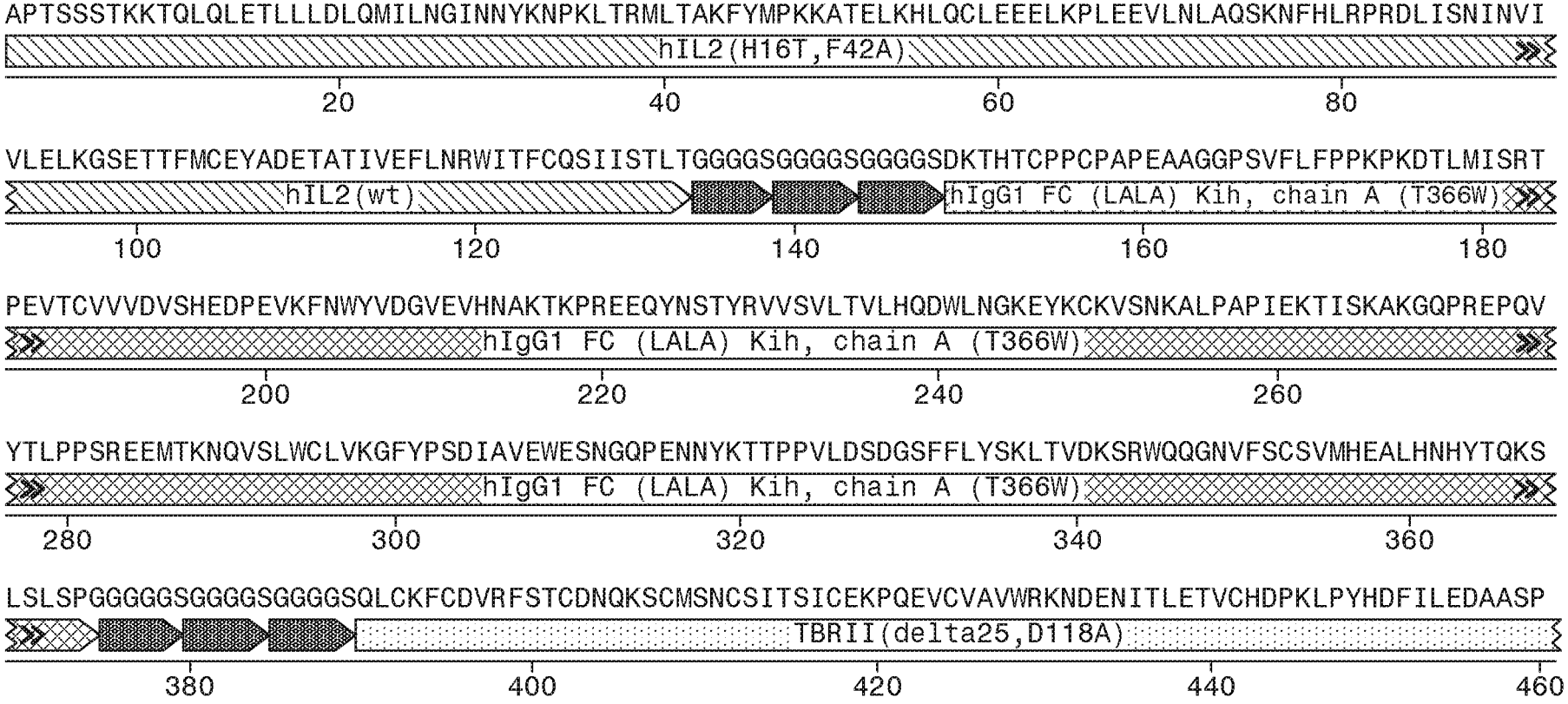


FIG. 7E (continued)

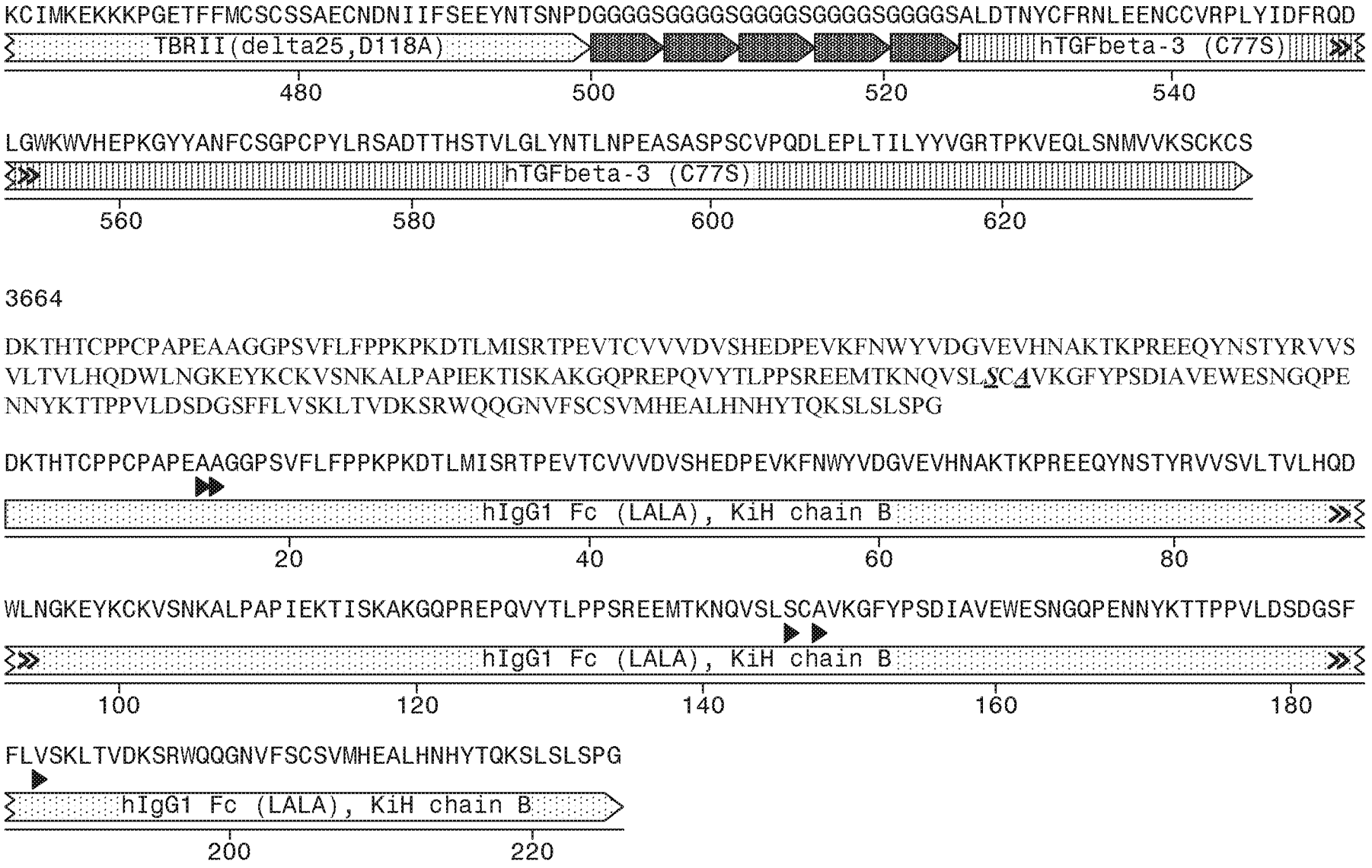


FIG. 7F

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSQLCKFCNVRF
STCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAEC
NDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSGGGGSGGGGSALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYAN
FCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPSCVPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

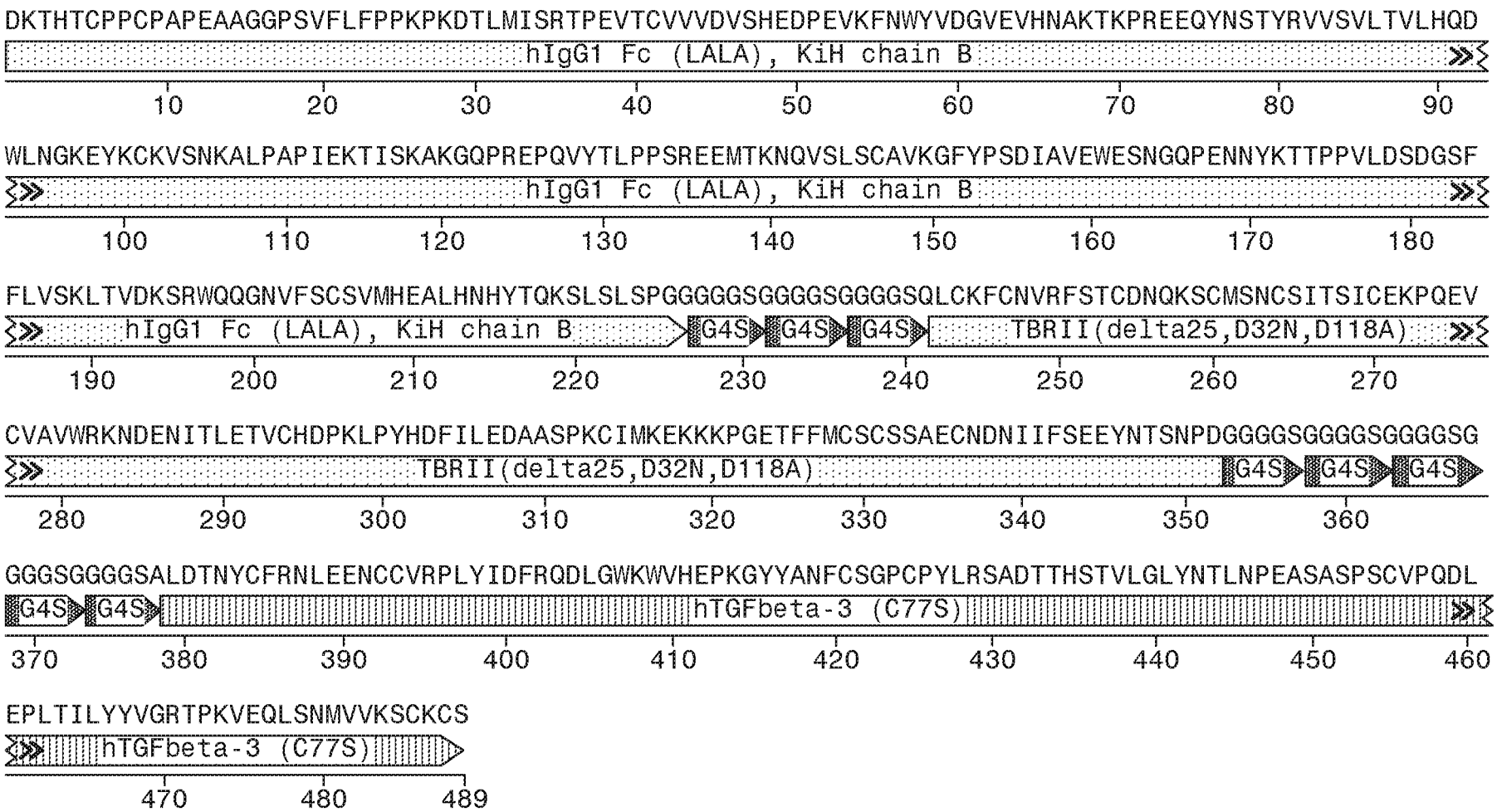


FIG. 7F (continued)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSAPTSSSTKKT
QLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL
KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

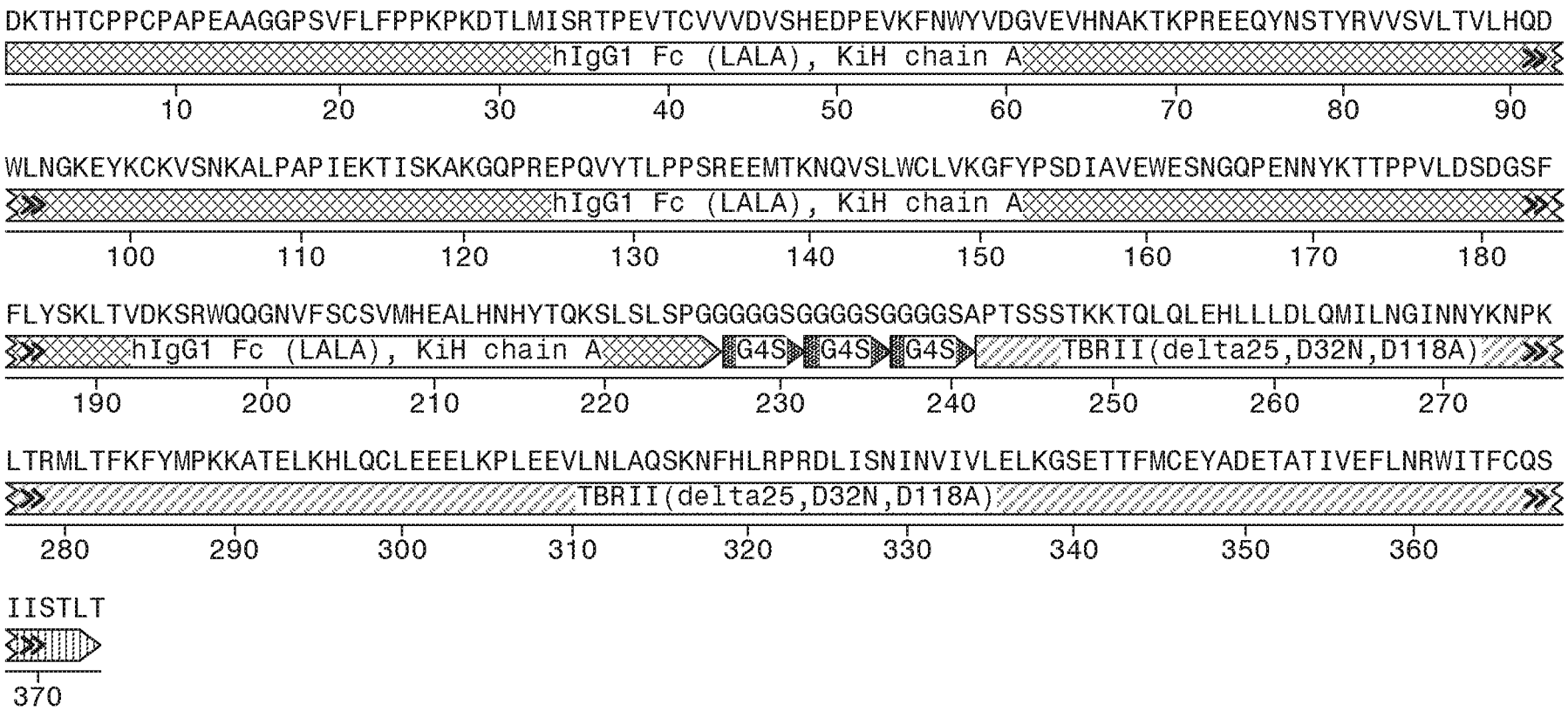


FIG. 7G

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTGGGGSGGGGSGGGGSAPEAAGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTKPPSREEMTKNQVSLSCLVKGFYPSDIAVEWESNGQPENNYKTTVPVLDSDGSFRLASYLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSQLCKFCNVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKN
DENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSGGG
GSGGGGSALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPS
CVPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

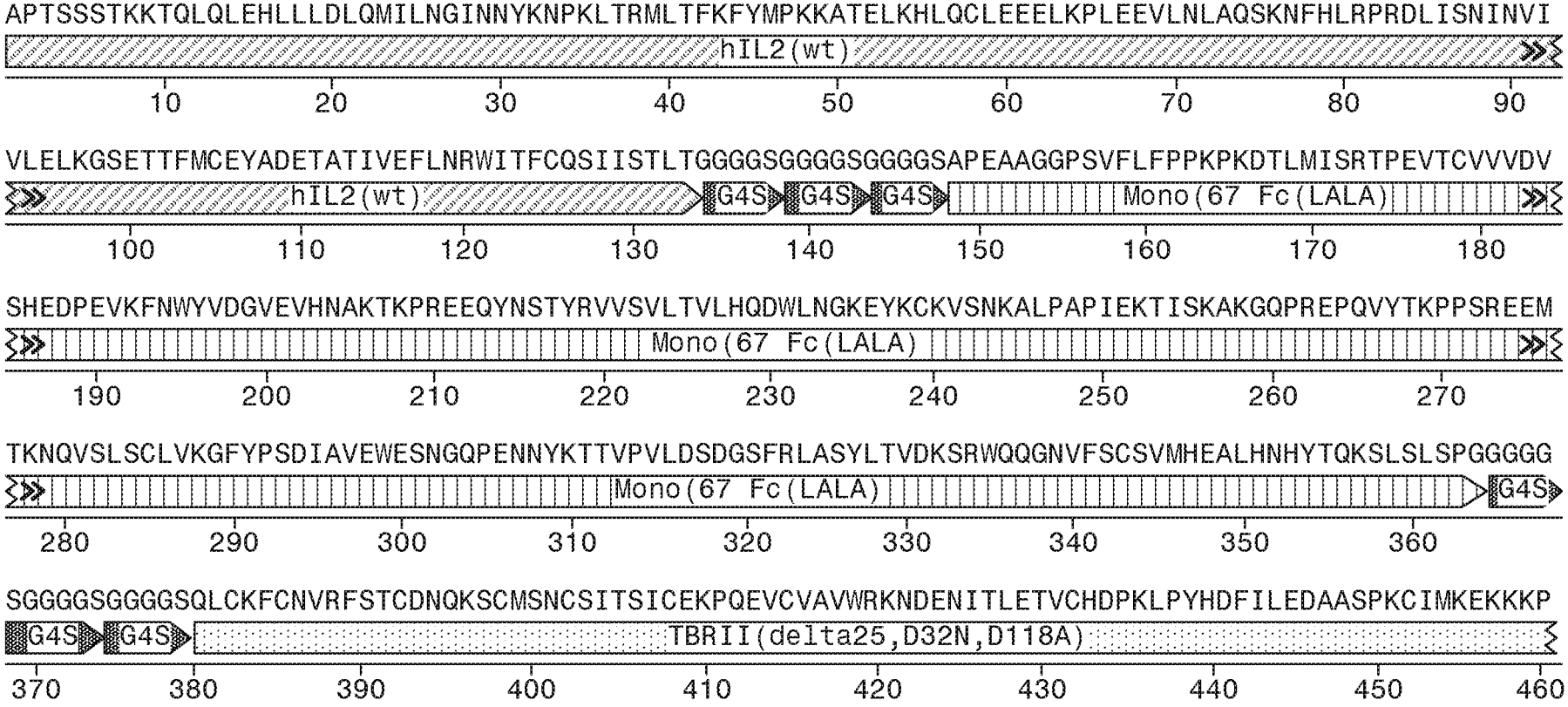


FIG. 7G (continued)



FIG. 7H

APTSSSTKKTQLQLETLLLDLQMILNGINNYKNPKLTRMLTAKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTGGGGSGGGGSGGGGSAPEAAGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTKPPSREEMTKNQVSLSCLVKGFYPSDIAVEWESNGQPENNYKTTVPVLDSDGSFRLASYLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKN
DENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSGGG
GSGGGGSALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPS
CVPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

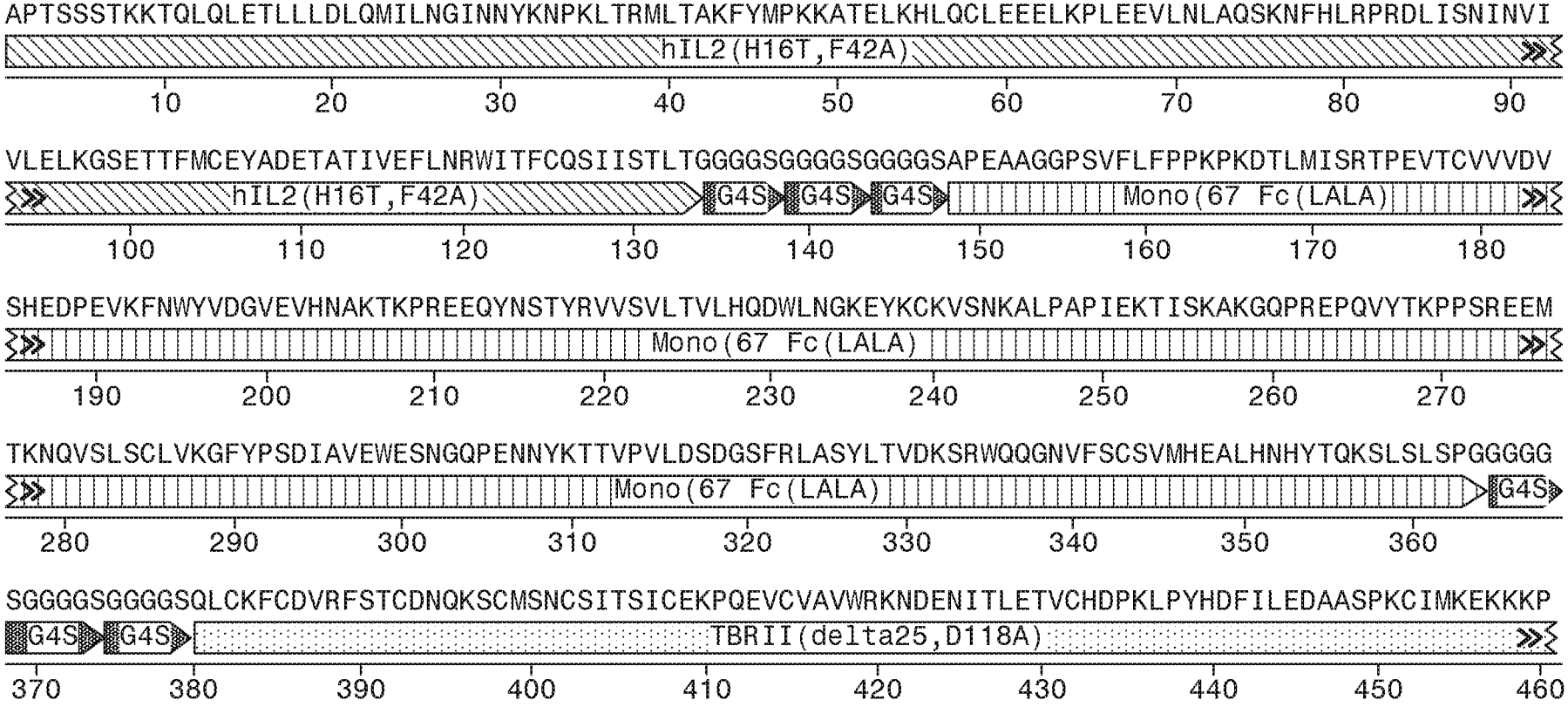


FIG. 7H (continued)



FIG. 7I

APTSSSTKKTQLQLETLLLDLQMILNGINNYKNPKLTRMLTAKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTGGGGSGGGGSGGGGSAPEAAGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTKPPSREEMTKNQVSLSCLVKGFYPSDIAVEWESNGQPENNYKTTVPVLDSDGSFRLASYLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSQLCKFCNVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKN
DENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSGGG
GSGGGGSALDTNYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPS
CVPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS

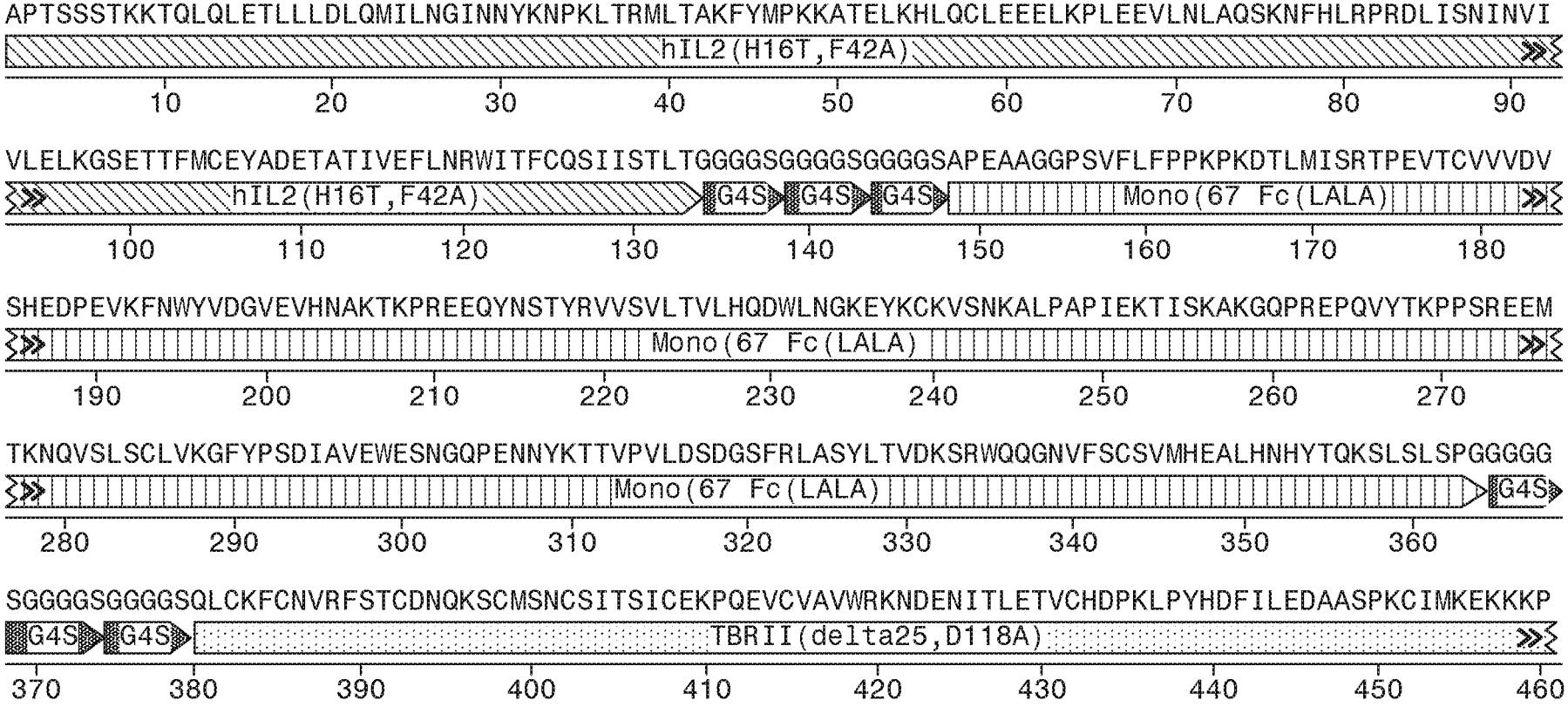


FIG. 7I (continued)



FIG. 7J

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL
ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTGGGGSGGGGSGGGGSDKTHTCPPCPAPEAAGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSQLCKFCNVRFSTCDNQKSCMSNCSITSICEKPQE
VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPD

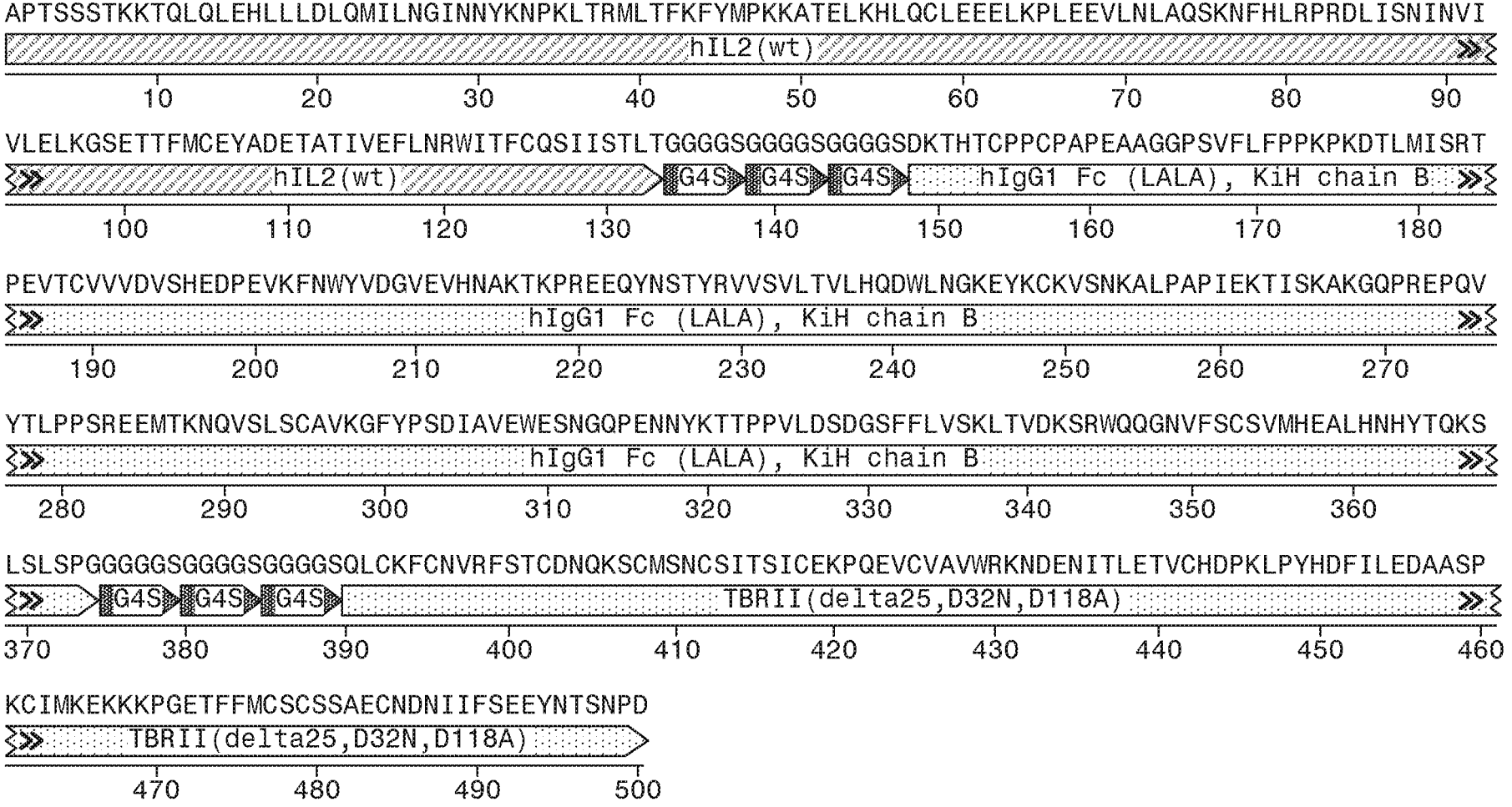


FIG. 8

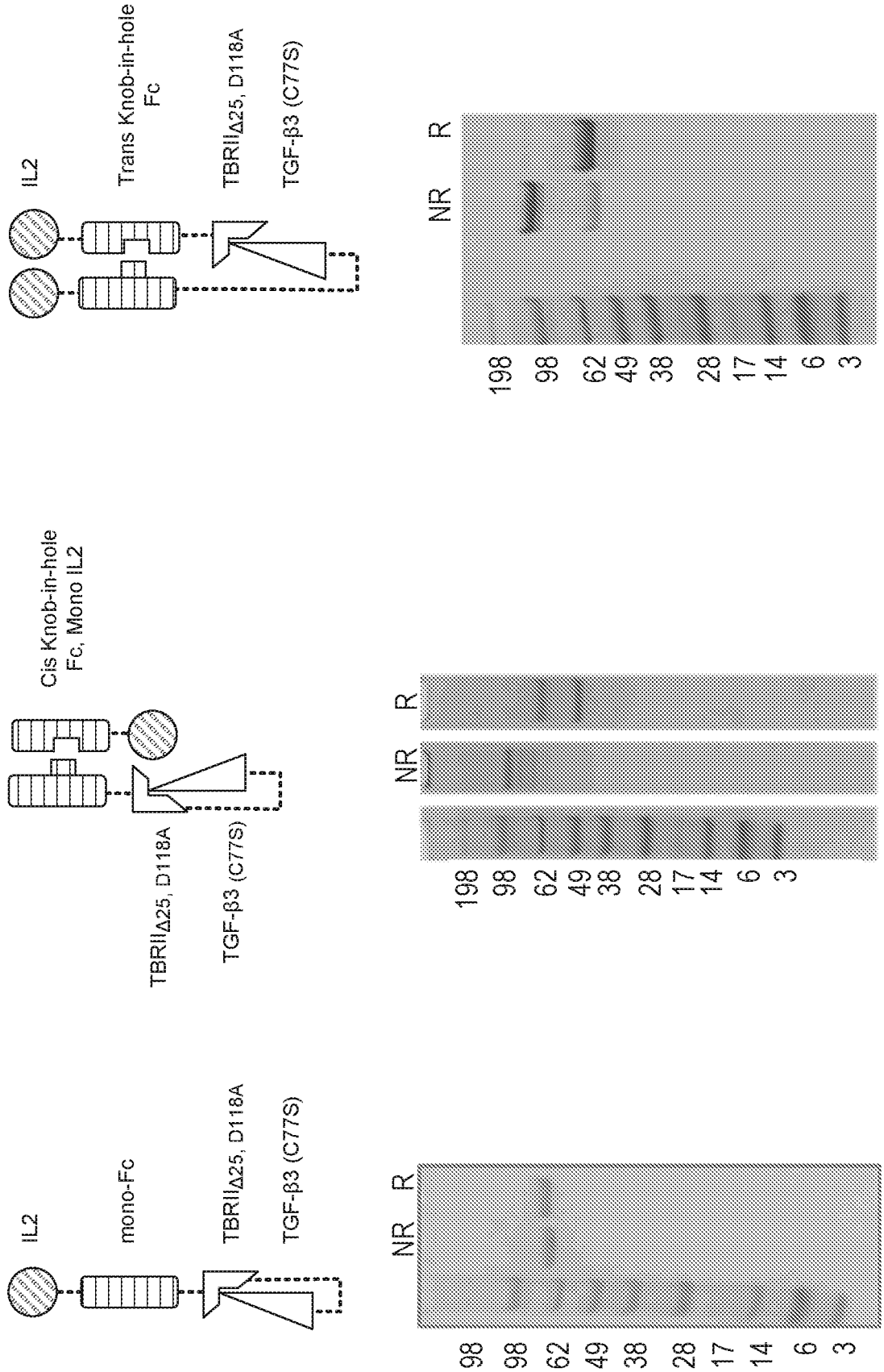

IL2
mono-Fc
TBRII$_{\Delta 25, D118A}$
TGF-β3 (C77S)
Cis Knob-in-hole Fc, Mono IL2
TBRII$_{\Delta 25, D118A}$
TGF-β3 (C77S)
IL2
Trans Knob-in-hole Fc
TBRII$_{\Delta 25, D118A}$
TGF-β3 (C77S)
NR R
198
98
62
49
38
28
17
14
6
3

FIG. 9

Mutation	Kd (μM) TGF-β1	Kd (μM) TGF-β3
Δ14	0.32	0.68
L27A	7.97	14.8
F30A	44.0	104
D32A	3.52	8.87
D32N	5.90	19.9
S49A	0.79	1.18
I50A	7.96	16.7
T51A	2.97	8.75
S52A	0.60	0.98
S52L	154	620
I53A	2.49	6.87
E55A	2.99	5.30
V77A	0.69	1.37
D118A	1.51	2.69
E119A	3.35	8.47
E119Q	5.95	10.6

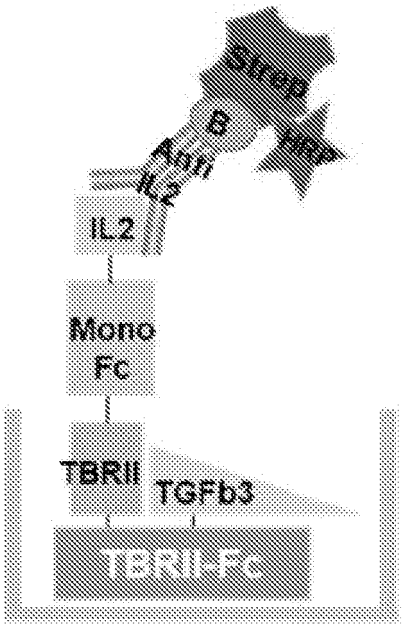


FIG. 10A

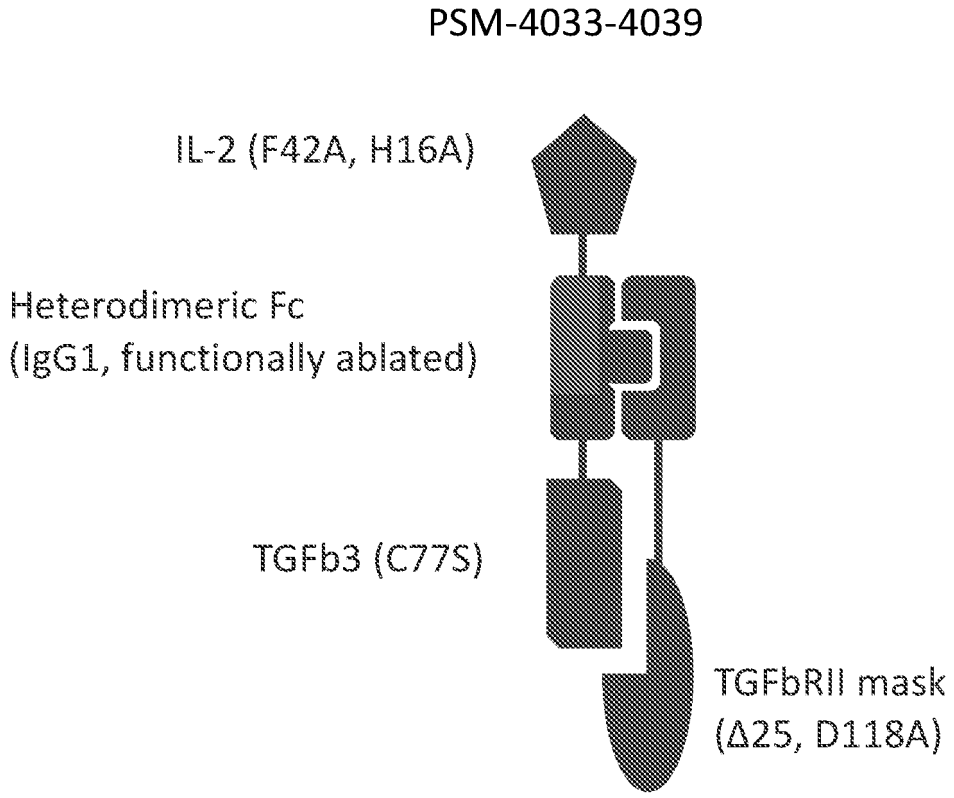


FIG. 10B

Construct 4033 (SEQ ID NO:191)

APTSSSTKKTQLQLEALLLDLQMILNGINNYKNPKLTRMLTAKFYMPKKATELKHLQCLE
EELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT
FCQSIISTLTGGGGSGGGGSGGGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLWCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGGGGGSGGGGSGGGGSGGGGSGGGGSALDTNYCFRNLEENCCVRPLYIDFR
QDLGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPSCVPQDLEP
LTILYYVGRTPKVEQLSNMVVKSCKCS

FIG. 10C

Construct 4039 (SEQ ID NO:192)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGS
QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYH
DFILEDAASPKCIMKEKKKPGETFFMCSCSSAECNDNIIFSEEYNTSNPD

FIG. 11

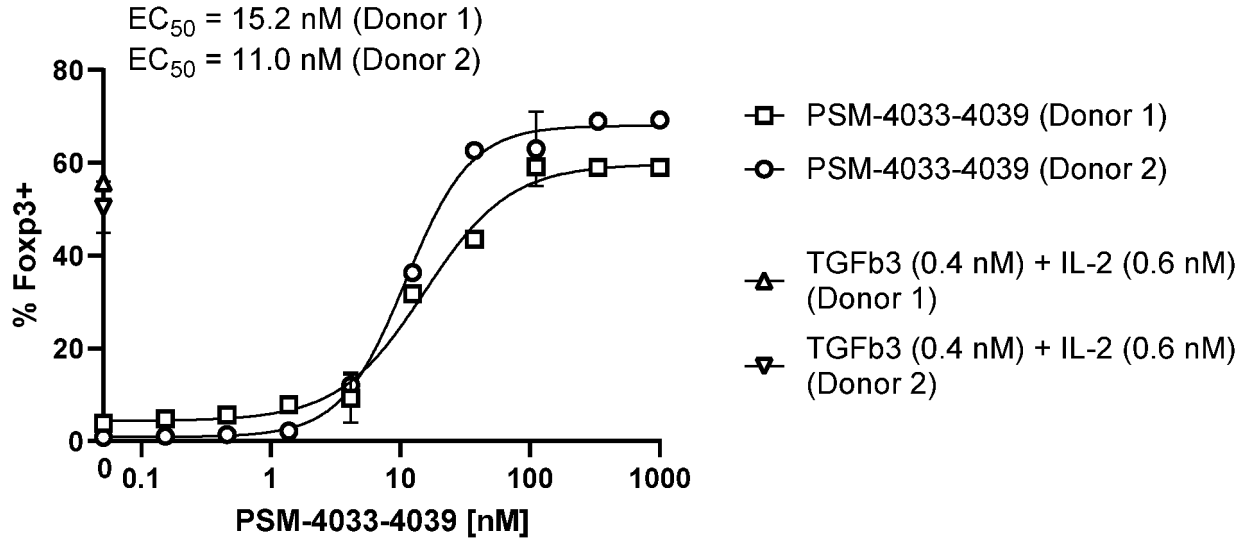


FIG. 12

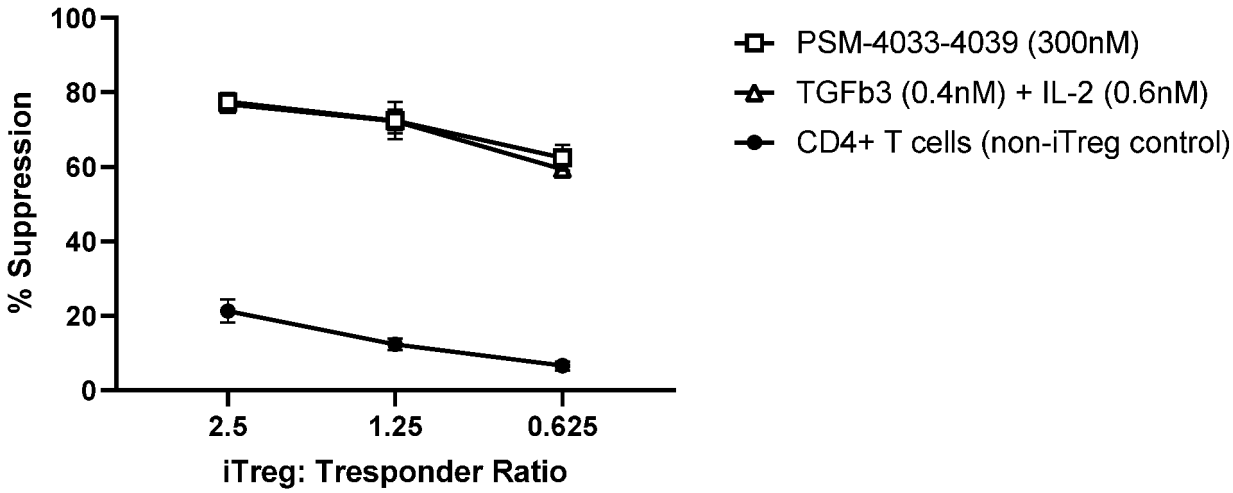


FIG. 13A

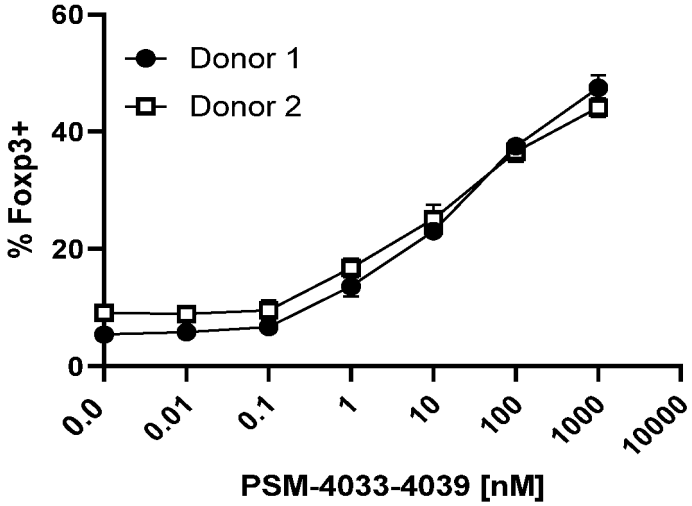


FIG. 13B

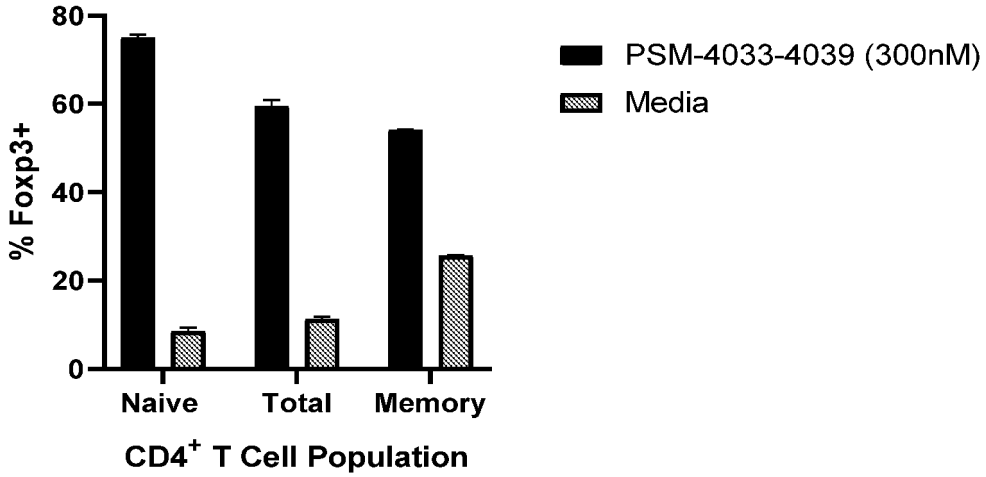


FIG. 14A

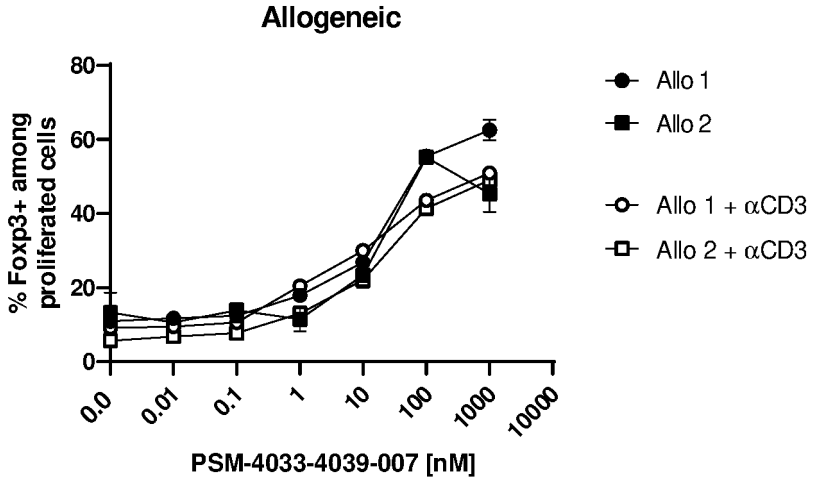


FIG. 14B

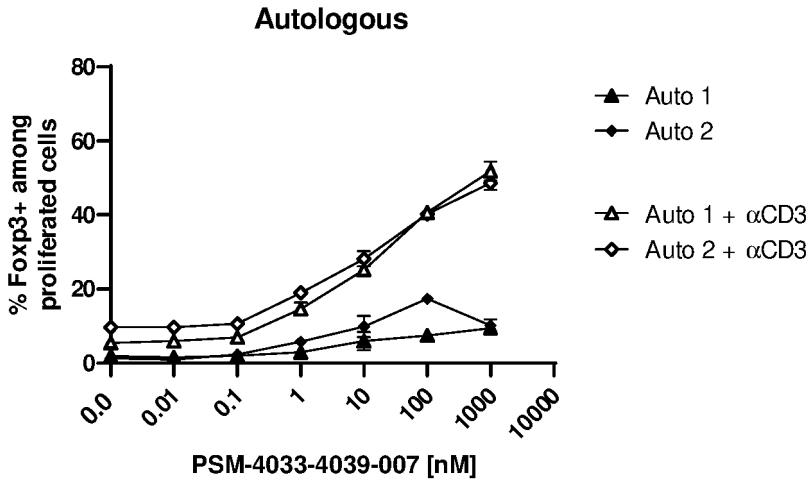


FIG. 15

