FIG. 1A

Heavy Chain IgG1 Constant Region

```
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg    60
ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg   120
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca   180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc   240
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc   300
aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga   360
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct   420
gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg   480
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac   540
agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag   600
gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc   660
aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggatgag   720
ctgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc   780
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg   840
ctggactccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg   900
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg   960
cagaagagcc tctccctgtc tccgggtaaa                                    990
```

FIG. 1B

```
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS    60
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG   120
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN   180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE   240
LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW   300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                                    330
```

FIG. 2A

Kappa Chain Constant Region

```
cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct    60
ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag   120
tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac   180
agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag   240
aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag   300
agcttcaaca ggggagagtg t                                             321
```

FIG. 2B

```
RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD    60
SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC                 107
```

FIG. 3A

Heavy Chain IgG2 Constant Region

```
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag    60
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg   120
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca   180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc   240
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc   300
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc   360
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc   420
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc   480
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt   540
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc   600
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg   660
cagccccgag aaccacaggt gtacaccctg ccccatcccc gggaggagat gaccaagaac   720
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg   780
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac   840
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   900
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   960
tccctgtctc cgggtaaa                                                978
```

FIG. 3B

```
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS    60
GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF   120
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR   180
VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL PPSREEMTKN   240
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD GSFFLYSKLT VDKSRWQQGN   300
VFSCSVMHEA LHNHYTQKSL SLSPGK                                        326
```

FIG. 4A

Heavy Chain IgG4 Constant Region

```
gccagcacca aggggccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag    60
agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg   120
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca   180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc   240
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc   300
aaatatggtc ccccatgccc atcatgccca gcacctgagt tcctgggggg accatcagtc   360
ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg   420
tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat   480
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac   540
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag   600
tgcaaggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa   660
gggcagcccc gagagccaca ggtgtacacc ctgccccccat cccaggagga gatgaccaag   720
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag   780
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   840
gacggctcct tcttcctcta cagcaggcta accgtgraca agagcaggtg gcaggagggg   900
aatgtcttct catgctccgt gakgcatgag gctctgcaca accactacac acagaagagc   960
ctctccctgt ctctgggtaa a                                             981
```

FIG. 4B

```
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS    60
GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPSCP APEFEGGPSV   120
FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY   180
RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK   240
NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG   300
NVFSCSVMHE ALHNHYTQKS LSLSLGK                                       327
```

FIG. 5A

26F5 Heavy Chain

```
atggagtttg ggctgagctg ggtcttcctc gttgctcttt taagaggtgt ccagtgtcag    60
gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc   120
tgtgcagcgt ctggattcac cttcagcaac tatggcatgc actgggtccg ccaggctcca   180
ggcaaggggc tggagtgggt ggcaggcatt tggaatgatg gaattaataa ataccatgca   240
cactccgtga ggggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg   300
caaatgaaca gcccgagagc cgaggacacg gctgtgtatt actgtgcgag agcacggtct   360
ttcgactggc tattatttga gttctggggc cagggaaccc tggtcaccgt ctctagt      417
```

FIG. 5B

```
MEFGLSWVFL VALLRGVQCQ VQLVESGGGV VQPGRSLRLS CAASGFTFSN YGMHWVRQAP    60
GKGLEWVAGI WNDGINKYHA HSVRGRFTIS RDNSKNTLYL QMNSPRAEDT AVYYCARARS   120
FDWLLFEFWG QGTLVTVSS                                                139
```

FIG. 6A

26F5 Kappa Chain

```
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga    60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc   120
ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct   180
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc   240
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct   300
gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctccgct cactttcggc   360
ggagggacca aggtggagat caaa                                          384
```

FIG. 6B

```
MEAPAQLLFL LLLWLPDTTG EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP    60
GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPLTFG   120
GGTKVEIK                                                            128
```

FIG. 7A

27F2 Heavy Chain

```
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag    60
gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc   120
tgtgcagtgt ctggattcac cttcagtaac tatggcatgc actgggtccg ccaggctcca   180
ggcaaggggc tggagtgggt ggcagctata tggaatgatg gagaaaataa acaccatgca   240
ggctccgtga ggggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg   300
caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag aggacgatat   360
tttgactggt tattatttga gtattggggc cagggaaccc tggtcaccgt ctctagt      417
```

FIG. 7B

```
MEFGLSWVFL VALLRGVQCQ VQLVESGGGV VQPGRSLRLS CAVSGFTFSN YGMHWVRQAP    60
GKGLEWVAAI WNDGENKHHA GSVRGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARGRY   120
FDWLLFEYWG QGTLVTVSS                                                139
```

FIG. 8A

15C4 Heavy Chain

```
atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgag    60
gtgcagctga tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc   120
tgtaagggtt ctggatacag cttttccttc cactggatcg cctgggtgcg ccagatgccc   180
gggaaaggcc tggagtggat ggggatcatc atcctggtg cctctgatac cagatacagc    240
ccgtccttcc aaggccaggt caccatctca gccgacaact ccaacagcgc cacctacctg   300
cagtggagca gcctgaaggc ctcggacacc gccatgtatt tctgtgcgag acaaagggaa   360
ctcgactact ttgactactg gggccaggga accctggtca ccgtctctag t            411
```

FIG. 8B

```
MGSTAILALL LAVLQGVCAE VQLMQSGAEV KKPGESLKIS CKGSGYSFSF HWIAWVRQMP    60
GKGLEWMGII HPGASDTRYS PSFQGQVTIS ADNSNSATYL QWSSLKASDT AMYFCARQRE   120
LDYFDYWGQG TLVTVSS                                                  137
```

FIG. 9A

15C4 Kappa Chain

```
atgtcgccat cacaactcat tgggtttctg ctgctctggg ttccagcctc caggggtgaa    60
attgtgctga ctcagtctcc agactttcag tctgtgactc caaaggagaa agtcaccatc   120
acctgccggg ccagtcagag cattggtagt agcttacact ggtaccagca gaaaccagat   180
cagtctccaa agctcctcat caagtatgct tcccagtcct tctcaggggt cccctcgagg   240
ttcagtggca gtggatctgg gacagatttc accctcacca tcaatagcct ggaagctgaa   300
gatgctgcag cgtattactg tcatcagagt agtagtttac ctctcacttt cggcggaggg   360
accaaggtgg agatcaaa                                                 378
```

FIG. 9B

```
MSPSQLIGFL LLWVPASRGE IVLTQSPDFQ SVTPKEKVTI TCRASQSIGS SLHWYQQKPD    60
QSPKLLIKYA SQSFSGVPSR FSGSGSGTDF TLTINSLEAE DAAAYYCHQS SSLPLTFGGG   120
TKVEIK                                                              126
```

FIG. 10

```
                                                CDR1                                CDR2
26F5  QVQLVESGGG VVQPGRSLRL SCAASGFTFS NYGMHWVRQA PGKGLEWVAG IWNDGINKYH
27F2  QVQLVESGGG VVQPGRSLRL SCAVSGFTFS NYGMHWVRQA PGKGLEWVAA IWNDGENKHH
15C4  EVQLMQSGAE VKKPGESLKI SCKGSGYSFS FHWIAWVRQM PGKGLEWMGI IHPGASDTRY

                                                    CDR3
26F5  AHSVRGRFTI SRDNSKNTLY LQMNSPRAED TAVYYCARAR SFDWLLFEFW GQGTLVTVSS
27F2  AGSVRGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGR YFDWLLFEYW GQGTLVTVSS
15C4  SPSFQGQVTI SADNSNSATY LQWSSLKASD TAMYFCARQR ELDYFDYWGQ GTLVTVSS
```

FIG. 11

```
                                        CDR1
26F5/27F2   EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD
15C4        EIVLTQSPDF QSVTPKEKVT ITCRASQSIG SSLHWYQQKP DQSPKLLIKY

            CDR2                                            CDR3
26F5/27F2   ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPLTFG
15C4        ASQSFSGVPS RFSGSGSGTD FTLTINSLEA EDAAAYYCHQ SSSLPLTFGG


26F5/27F2   GGTKVEIK
15C4        GTKVEIK
```

FIG. 12

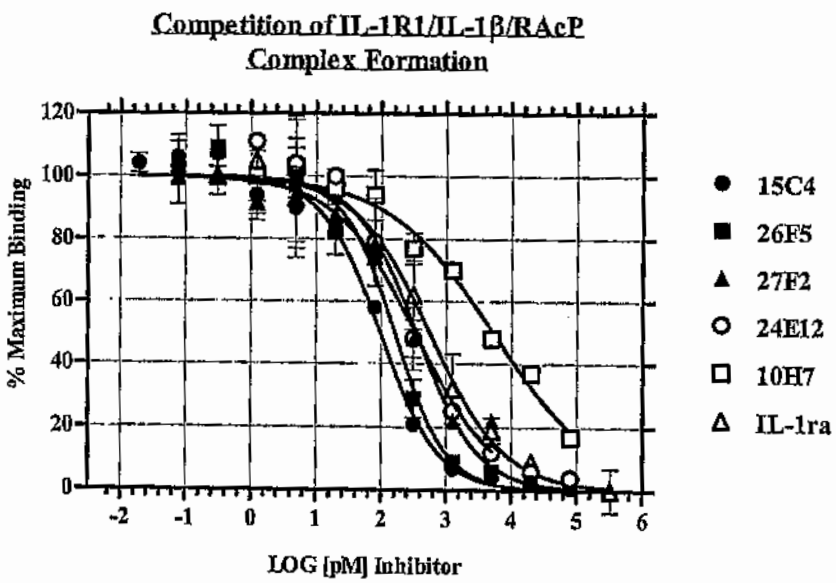

Competition of IL-1R1/IL-1β/RAcP
Complex Formation
% Maximum Binding
120
100
80
60
40
20
0
-2
-1
0
1
2
3
4
5
6
LOG [pM] Inhibitor
15C4
26F5
27F2
24E12
10H7
IL-1ra

FIG. 13

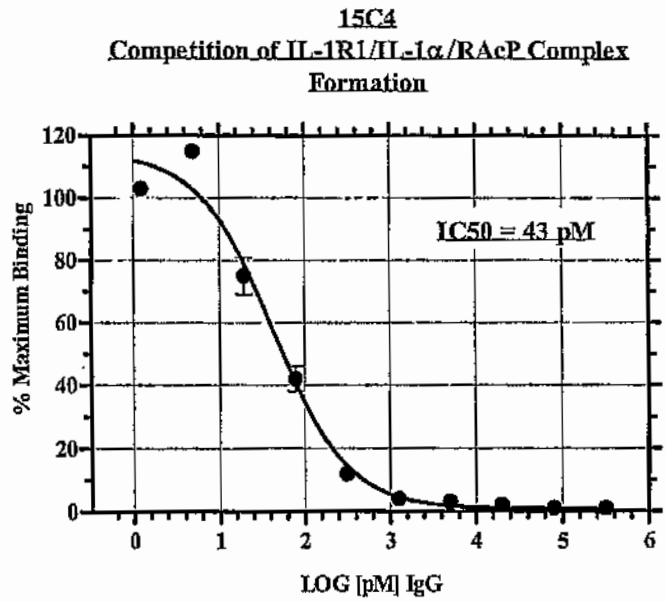

15C4
Competition of IL-1R1/IL-1α/RAcP Complex Formation
% Maximum Binding
120
100
80
60
40
20
0
IC50 = 43 pM
0
1
2
3
4
5
6
LOG [pM] IgG

FIG. 14

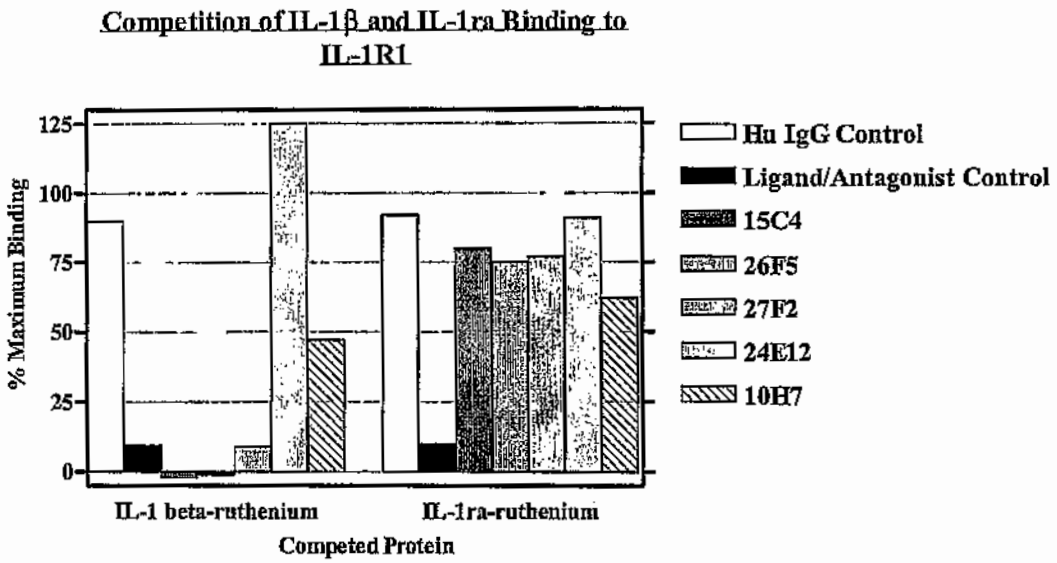

Competition of IL-1β and IL-1ra Binding to IL-1R1
% Maximum Binding
125
100
75
50
25
0
IL-1 beta-ruthenium
IL-1ra-ruthenium
Competed Protein
Hu IgG Control
Ligand/Antagonist Control
15C4
26F5
27F2
24E12
10H7

FIG. 15A

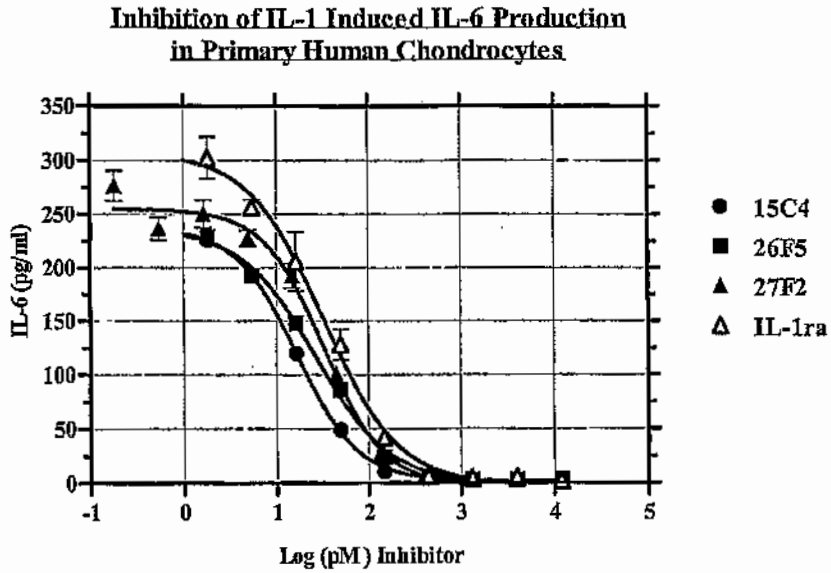


FIG. 15B

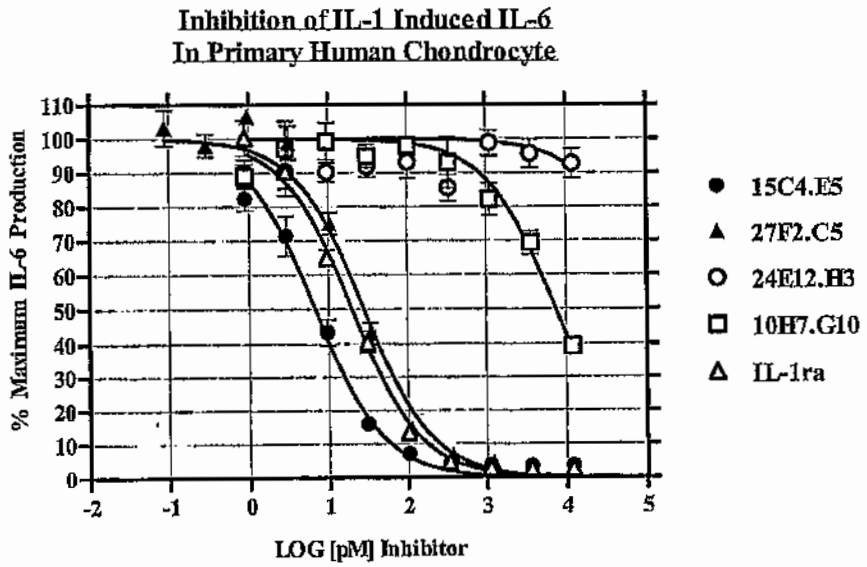


FIG. 16

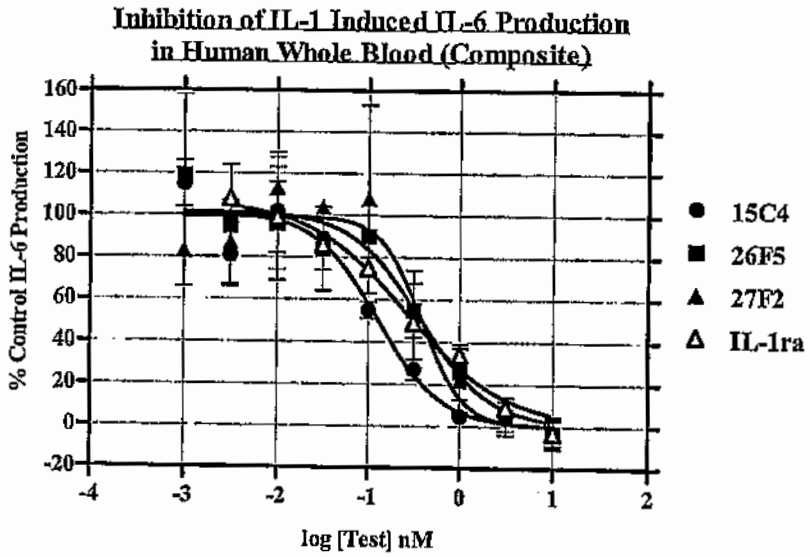

Inhibition of IL-1 Induced IL-6 Production
in Human Whole Blood (Composite)
% Control IL-6 Production
160
140
120
100
80
60
40
20
0
-20
-4
-3
-2
-1
0
1
2
log [Test] nM
15C4
26F5
27F2
IL-1ra

FIG. 17

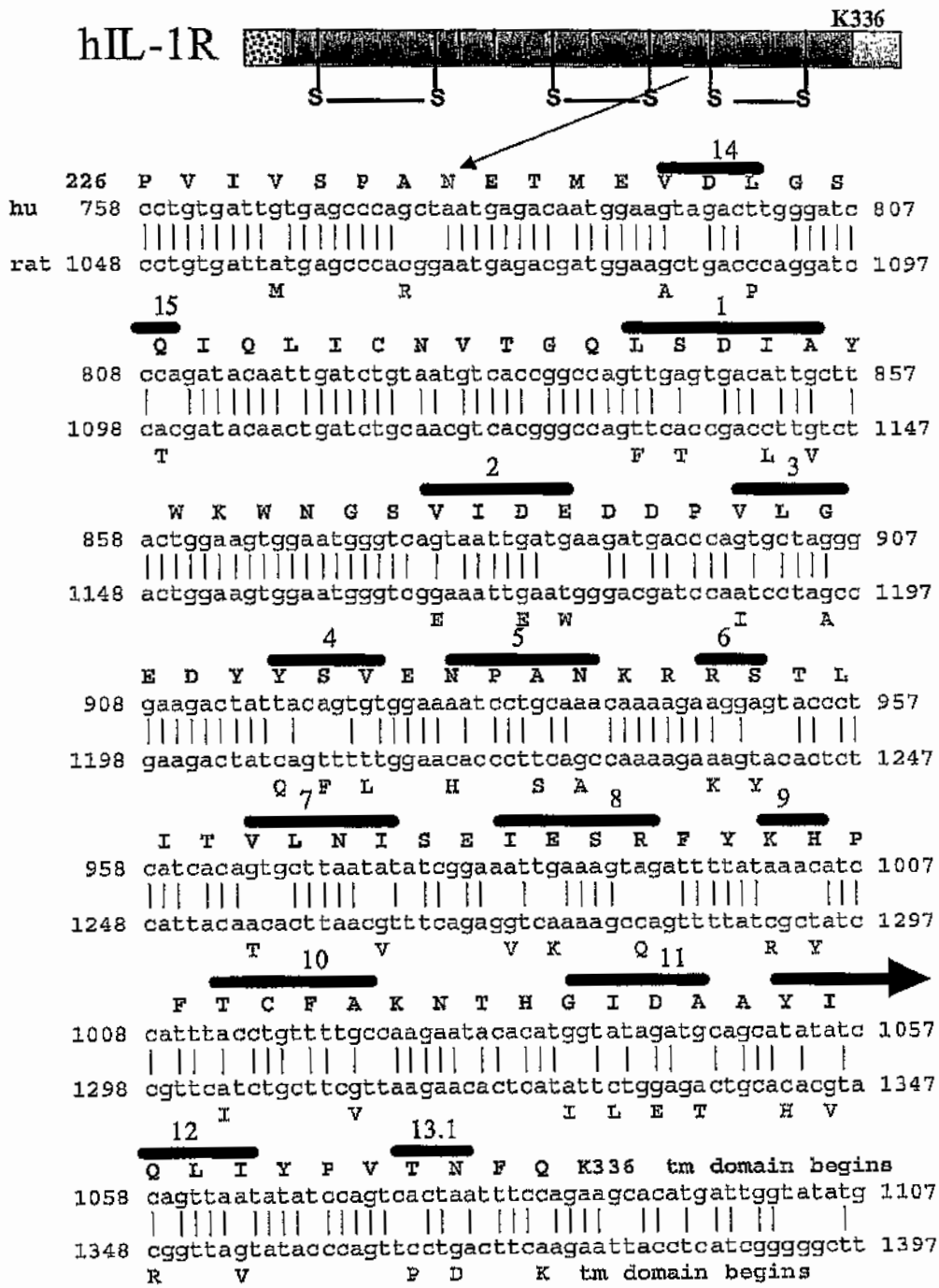

hIL-1R
K336
S S S S S S
14
226 P V I V S P A N E T M E V D L G S
hu 758 cctgtgattgtgagcccagctaatgagacaatggaagtagacttgggatc 807
rat 1048 cctgtgattatgagcccacggaatgagacgatggaagctgacccaggatc 1097
M R A P
15
1
Q I Q L I C N V T G Q L S D I A Y
808 ccagatacaattgatctgtaatgtcaccggccagttgagtgacattgctt 857
1098 cacgatacaactgatctgcaacgtcacgggccagttcaccgaccttgtct 1147
T F T L V
2
3
W K W N G S V I D E D D P V L G
858 actggaagtggaatgggtcagtaattgatgaagatgacccagtgctaggg 907
1148 actggaagtggaatgggtcggaaattgaatgggacgatccaatcctagcc 1197
E E W I A
4
5
6
E D Y Y S V E N P A N K R R S T L
908 gaagactattacagtgtggaaaatcctgcaaacaaaagaaggagtaccct 957
1198 gaagactatcagtttttggaacaccttcagccaaaagaaagtacactct 1247
Q F L H S A K Y
7
8
9
I T V L N I S E I E S R F Y K H P
958 catcacagtgcttaatatatcggaaattgaaagtagatttttataaacatc 1007
1248 cattacaacacttaacgtttcagaggtcaaaagccagttttatcgctatc 1297
T V V K Q R Y
10
11
F T C F A K N T H G I D A A Y I
1008 catttacctgttttgccaagaatacacatggtatagatgcagcatatatc 1057
1298 cgttcatctgcttcgttaagaacactcatattctggagactgcacacgta 1347
I V I L E T H V
12
13.1
Q L I Y P V T N F Q K336 tm domain begins
1058 cagttaatatatccagtcactaatttccagaagcacatgattggtatatg 1107
1348 cggttagtatacccagttcctgacttcaagaattacctcatcgggggctt 1397
R V P D K tm domain begins

FIG. 18

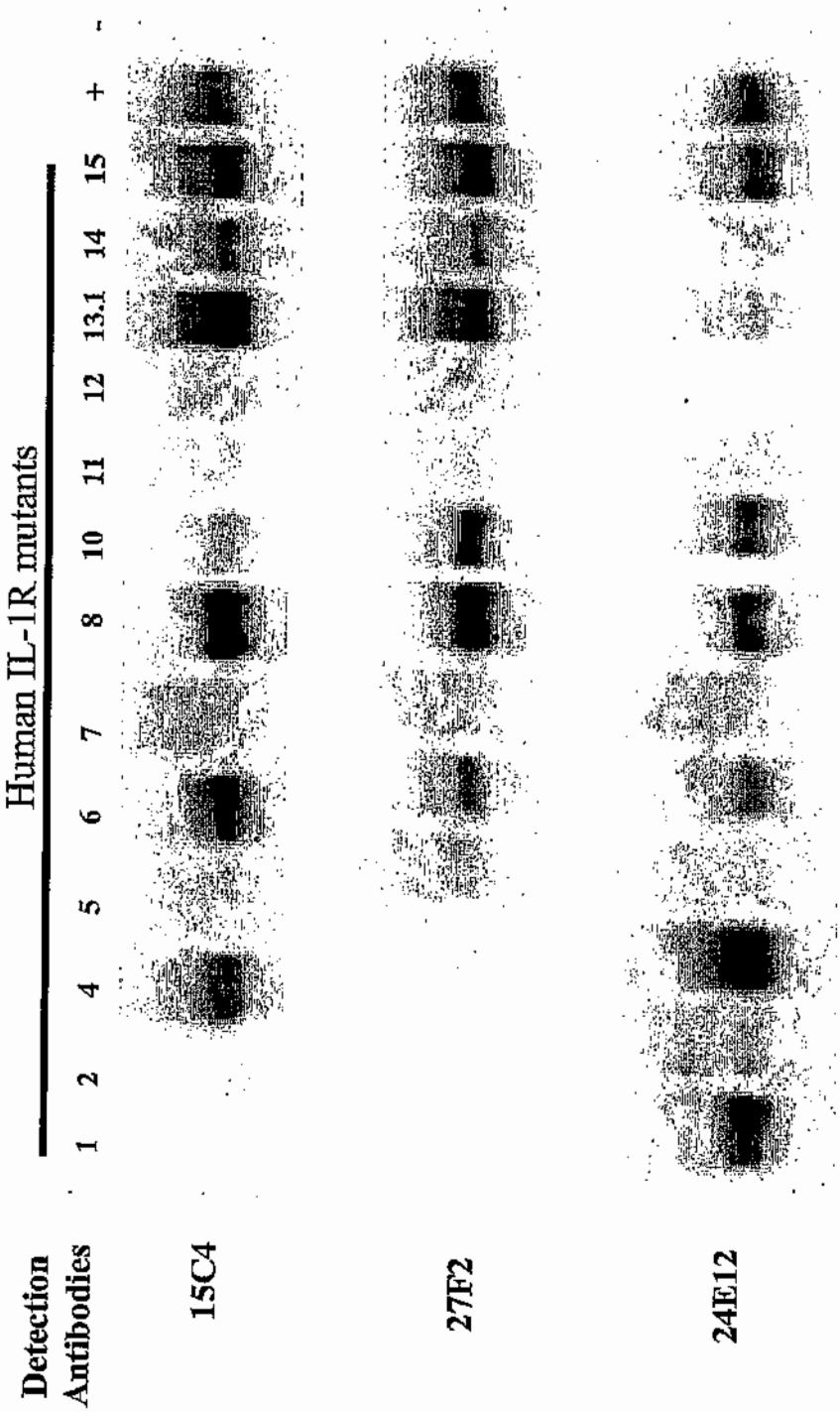

Human IL-1R mutants
1
2
4
5
6
7
8
10
11
12
13.1
14
15
+
-
Detection Antibodies
15C4
27F2
24E12

FIG. 19

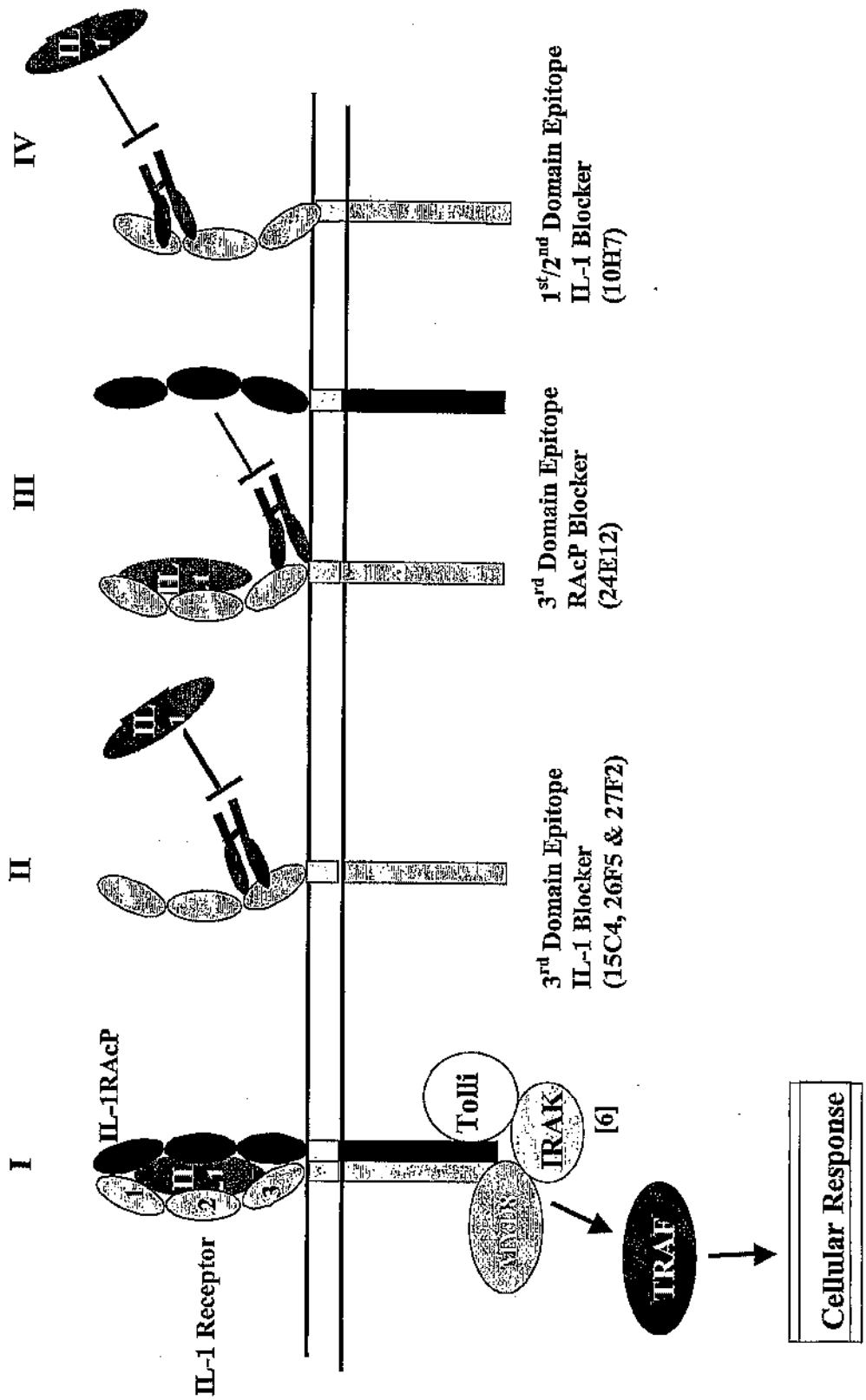

I
II
III
IV
IL-1RAcP
IL-1 Receptor
Tolli
IRAK
MYD88
[6]
TRAF
Cellular Response
3rd Domain Epitope
IL-1 Blocker
(15C4, 26F5 & 27F2)
3rd Domain Epitope
RAcP Blocker
(24E12)
1st/2nd Domain Epitope
IL-1 Blocker
(10H7)

FIG. 20



FIG. 21

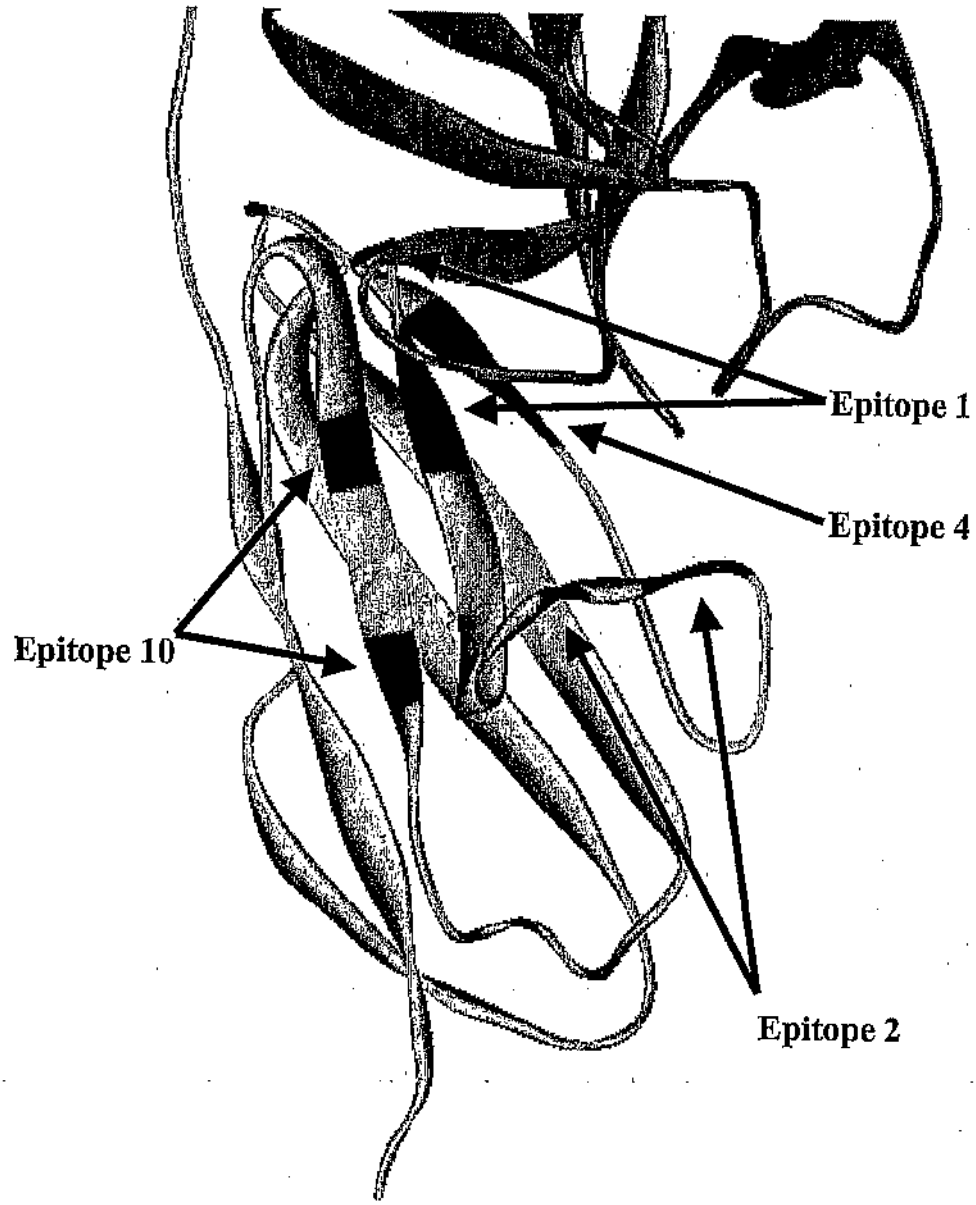


FIG. 22

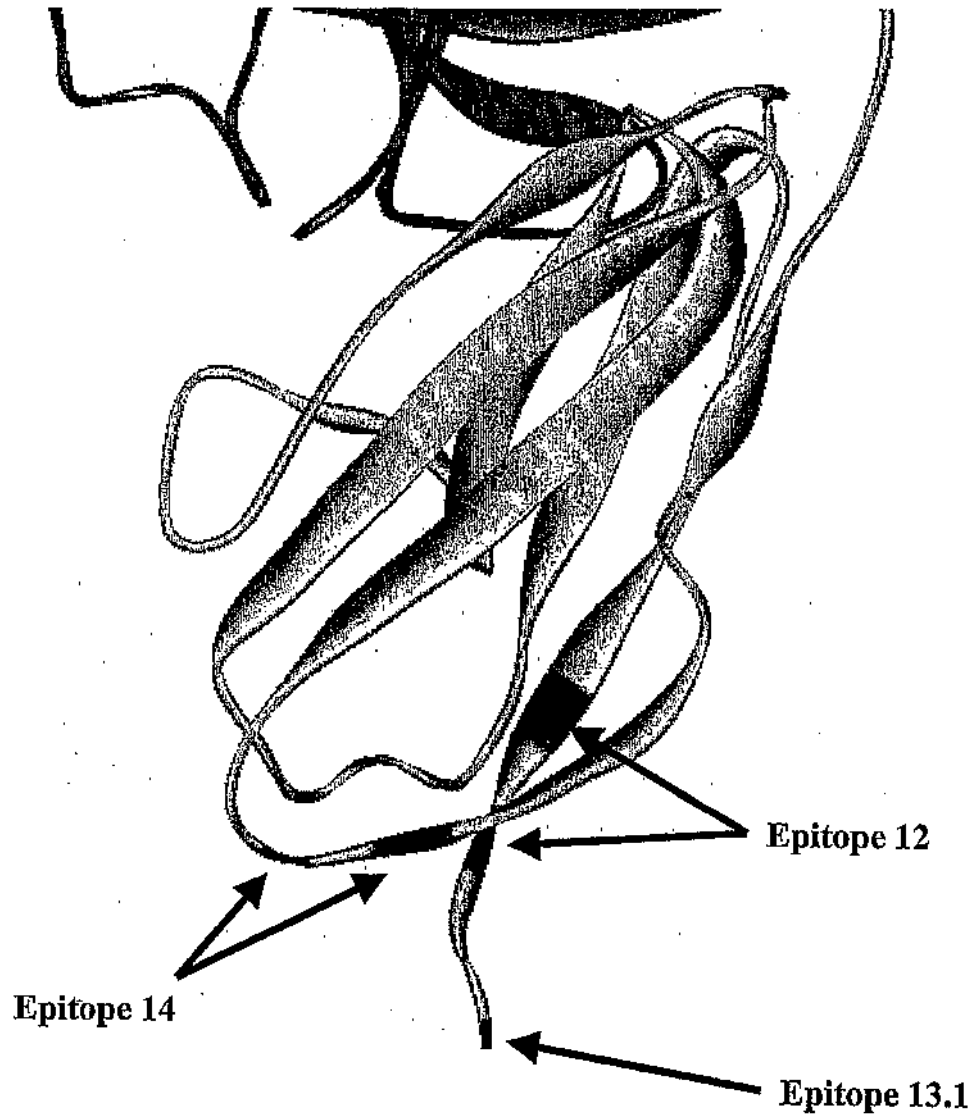


FIG. 23

```
MVHATSPLLL LLLLSLALVA PGLSARKCSL TGKWTNDLGS NMTIGAVNSK GEFTGTYTTA      60
VTATSNEIKE SPLHGTQNTI NKRTQPTFGF TVNWKFSEST TVFTGQCFID RNGKEVLKTM     120
WLLRSSVNDI GDDWKATRVG INIFTRLRTQ KEQLLASLLE ADKCKEREEK IILVSSANEI     180
DVRPCPLNPN EHKGTITWYK DDSKTPVSTE QASRIHQHKE KLWFVPAMVE DSGHYYCVVR     240
NSSYCLRIKI SAKFVENEPN LCYNAQAIFK QKLPVAGDGG LVCPYMEFFK NENNELPKLQ     300
WYKDCKPLLL DNIHFSGVKD RLIVMNVAEK HRGNYTCHAS YTYLGKQYPI TRVIEFITLE     360
ENKPTRPVIV SPANETMEVD LGSQIQLICN VTGQLSDIAY WKWNGSVIDE DDPVLGEDYY     420
SVENPANKRR STLITVLNIS EIESRFYKHP FTCFAKNTHG IDAAYIQLIY PVTNFQKDYK     480
DDDDK                                                                 485
```

FIG. 24

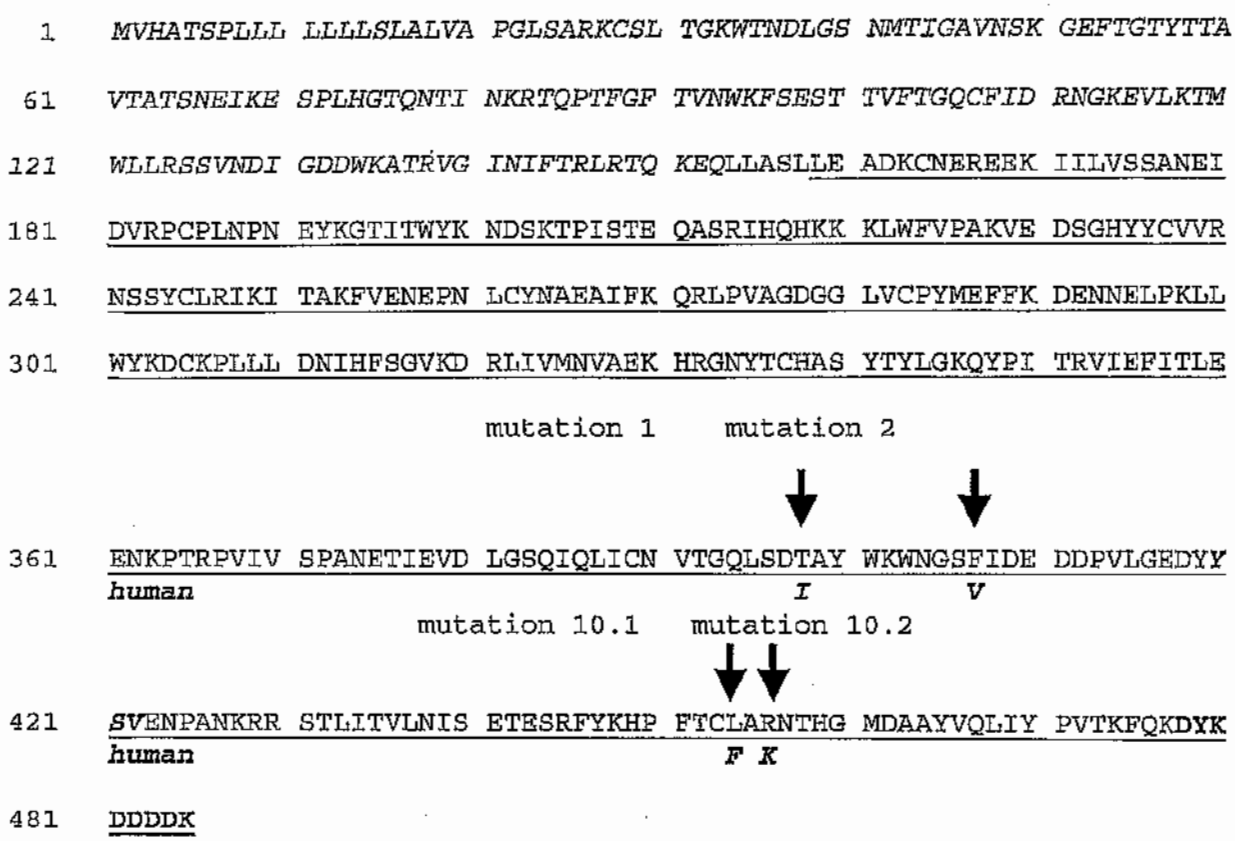

1 MVHATSPLLL LLLLSLALVA PGLSARKCSL TGKWTNDLGS NMTIGAVNSK GEFTGTYTTA
61 VTATSNEIKE SPLHGTQNTI NKRTQPTFGF TVNWKFSEST TVFTGQCFID RNGKEVLKTM
121 WLLRSSVNDI GDDWKATRVG INIFTRLRTQ KEQLLASLLE ADKCNEREEK IILVSSANEI
181 DVRPCPLNPN EYKGTITWYK NDSKTPISTE QASRIHQHKK KLWFVPAKVE DSGHYYCVVR
241 NSSYCLRIKI TAKFVENEPN LCYNAEAIFK QRLPVAGDGG LVCPYMEFFK DENNELPKLL
301 WYKDCKPLLL DNIHFSGVKD RLIVMNVAEK HRGNYTCHAS YTYLGKQYPI TRVIEFITLE
mutation 1
mutation 2
361 ENKPTRPVIV SPANETIEVD LGSQIQLICN VTGQLSDTAY WKWNGSFIDE DDPVLGEDYY
human
I
V
mutation 10.1
mutation 10.2
421 SVENPANKRR STLITVLNIS ETESRFYKHP FTCLARNTHG MDAAYVQLIY PVTKFQKDYK
human
F K
481 DDDDK

FIG. 25A

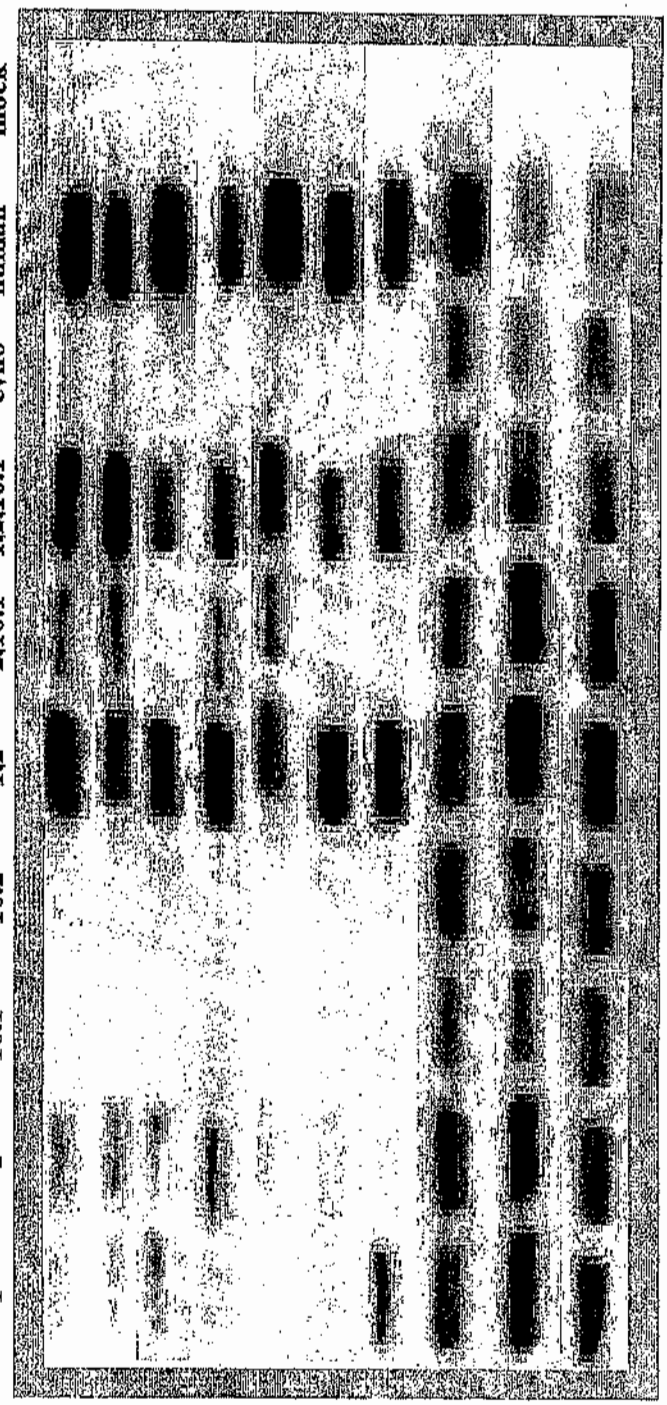
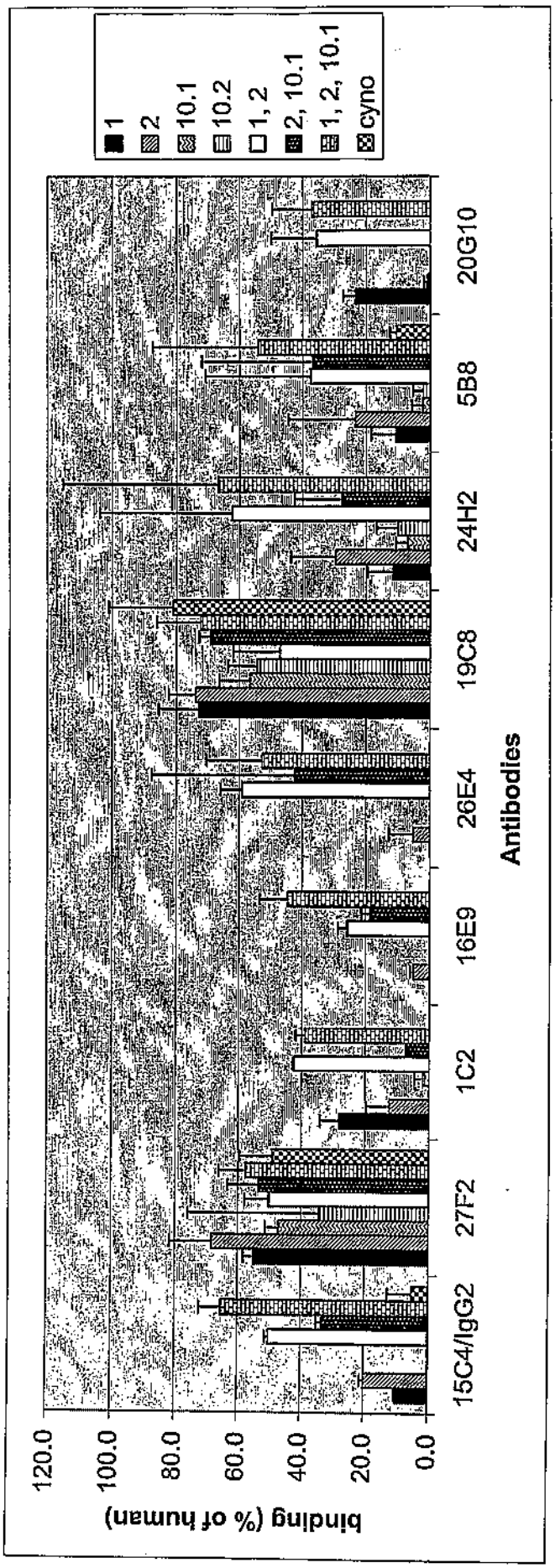

Avidin-cynoIL-1RFLAG mutants
1
2
10.1
10.2
1.2
2.10.1
1.2.10.1
cyno
human
mock
AMG108
5B8*
1C2
4H7
16E9
26E4
20G10
27F2
19C8*
anti-FLAG

FIG. 25B


1
2
10.1
10.2
1, 2
2, 10.1
1, 2, 10.1
cyno
120.0
100.0
80.0
60.0
40.0
20.0
0.0
binding (% of human)
15C4/IgG2
27F2
1C2
16E9
26E4
19C8
24H2
5B8
20G10
Antibodies

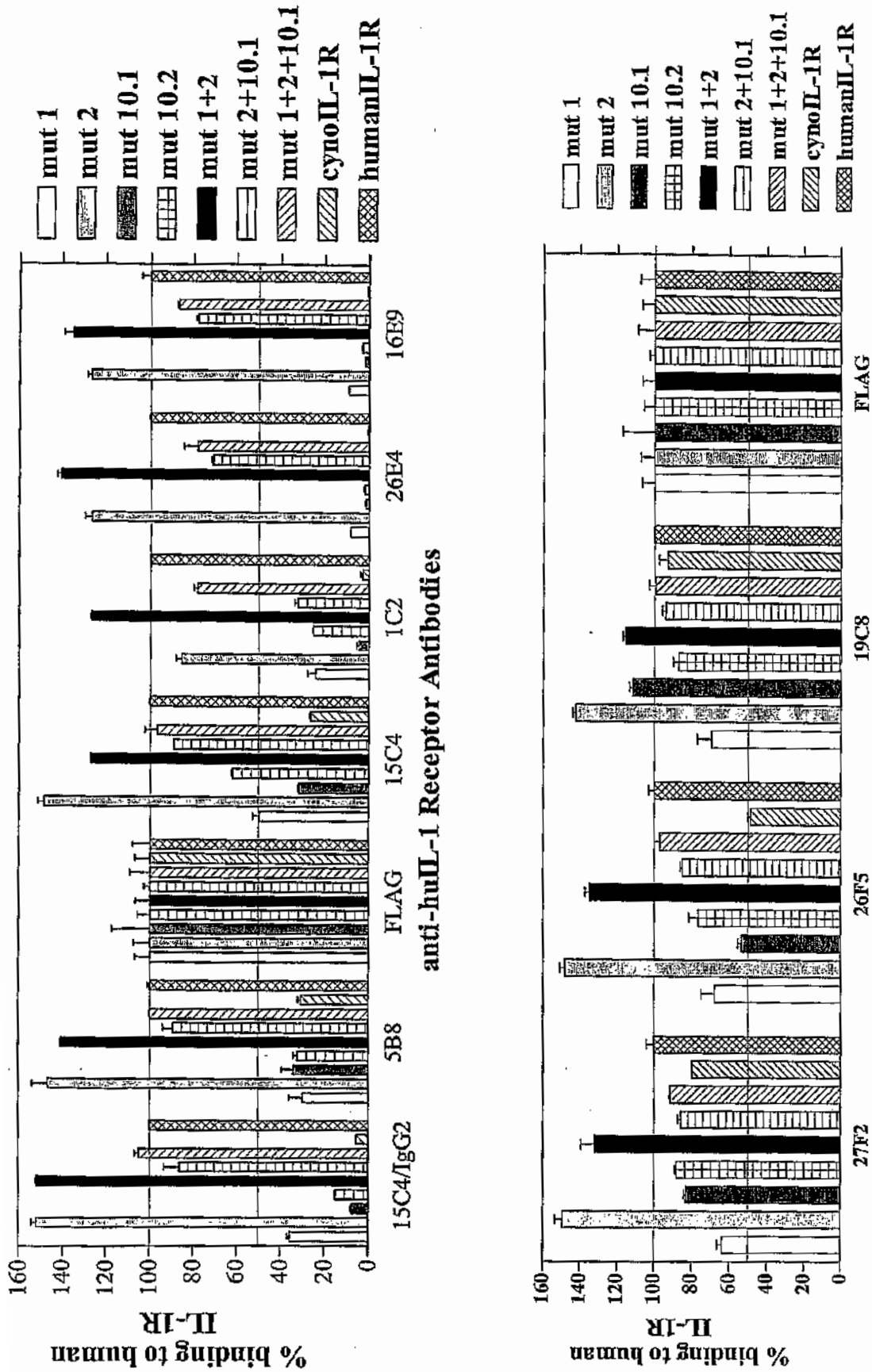

mut 1
mut 2
mut 10.1
mut 10.2
mut 1+2
mut 2+10.1
mut 1+2+10.1
cynoIL-1R
humanIL-1R
% binding to human IL-1R
anti-huIL-1 Receptor Antibodies
15C4/IgG2
5B8
FLAG
15C4
1C2
26E4
16E9
27F2
26F5
19C8
FLAG

FIG. 26