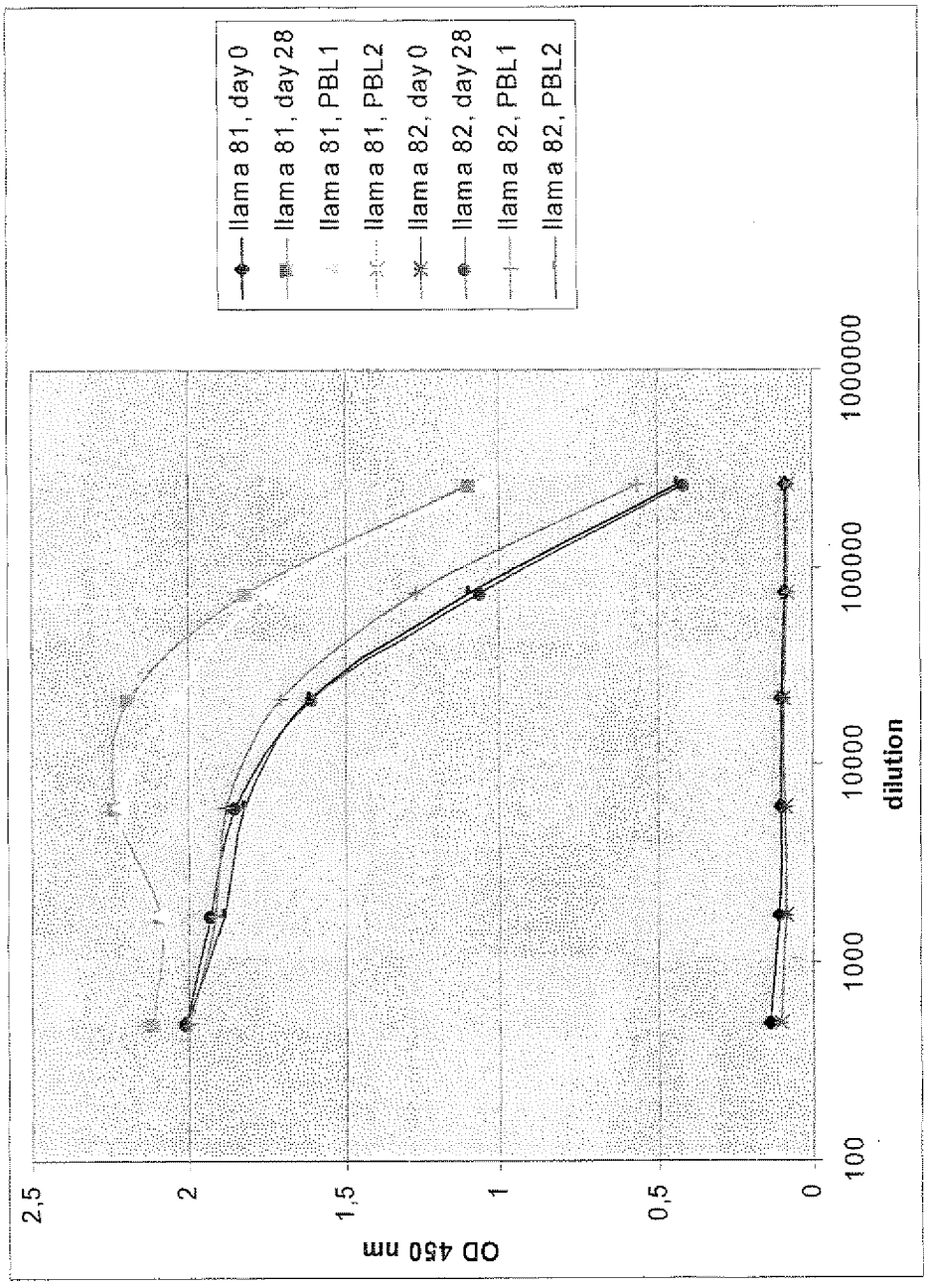

llama 81, day 0
llama 81, day 28
llama 81, PBL1
llama 81, PBL2
llama 82, day 0
llama 82, day 28
llama 82, PBL1
llama 82, PBL2
OD 450 nm
2,5
2
1,5
1
0,5
0
100
1000
10000
100000
1000000
dilution

Figure 1

Figure 2

U266B1

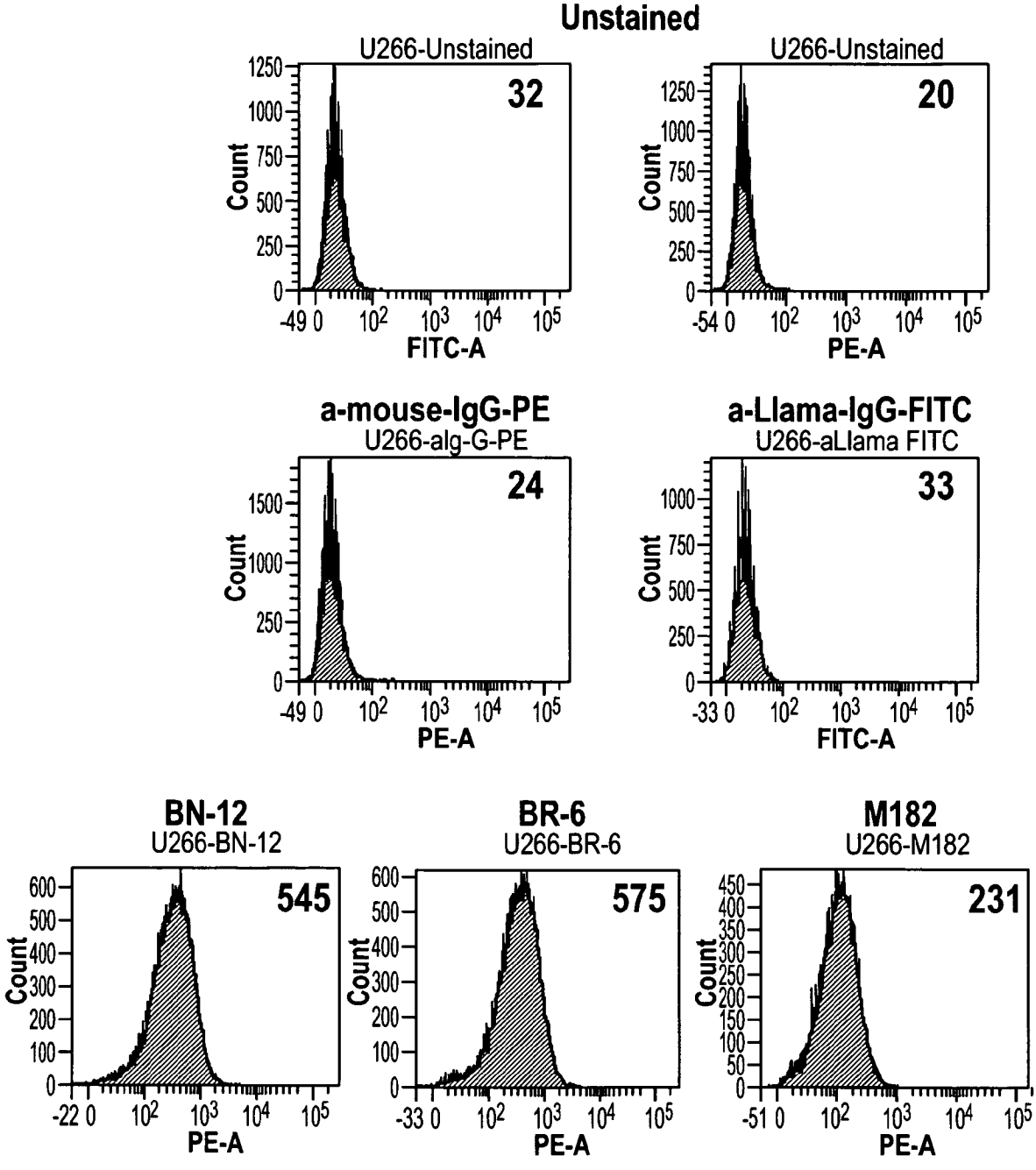
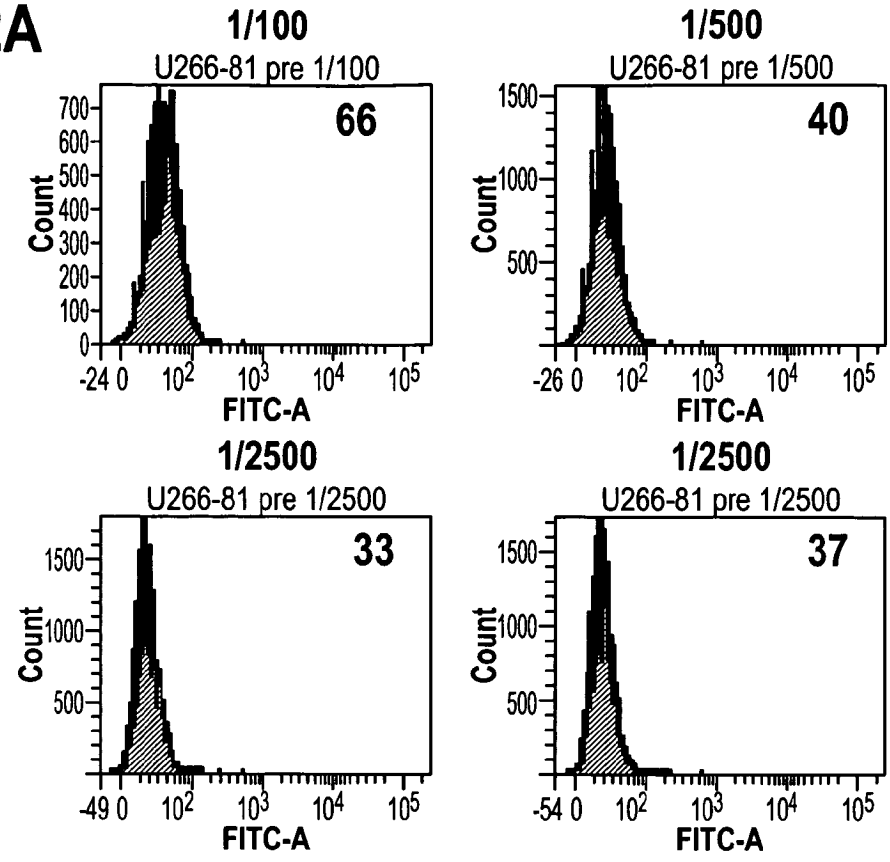


Figure 2A

LI81 pre



LI81 PBL1

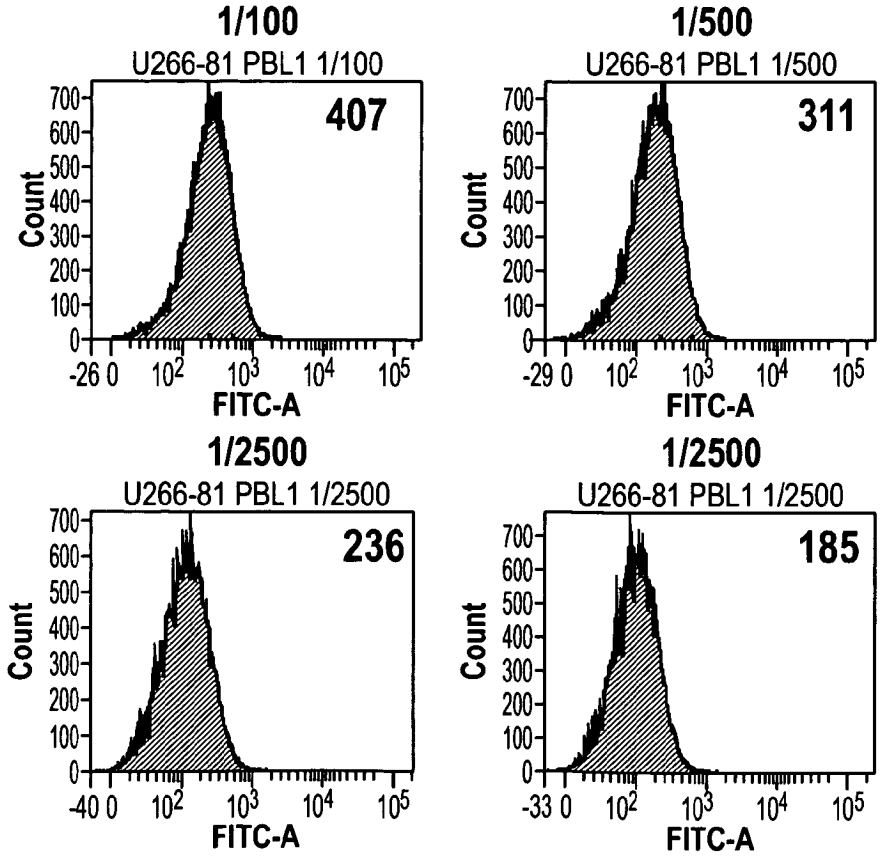
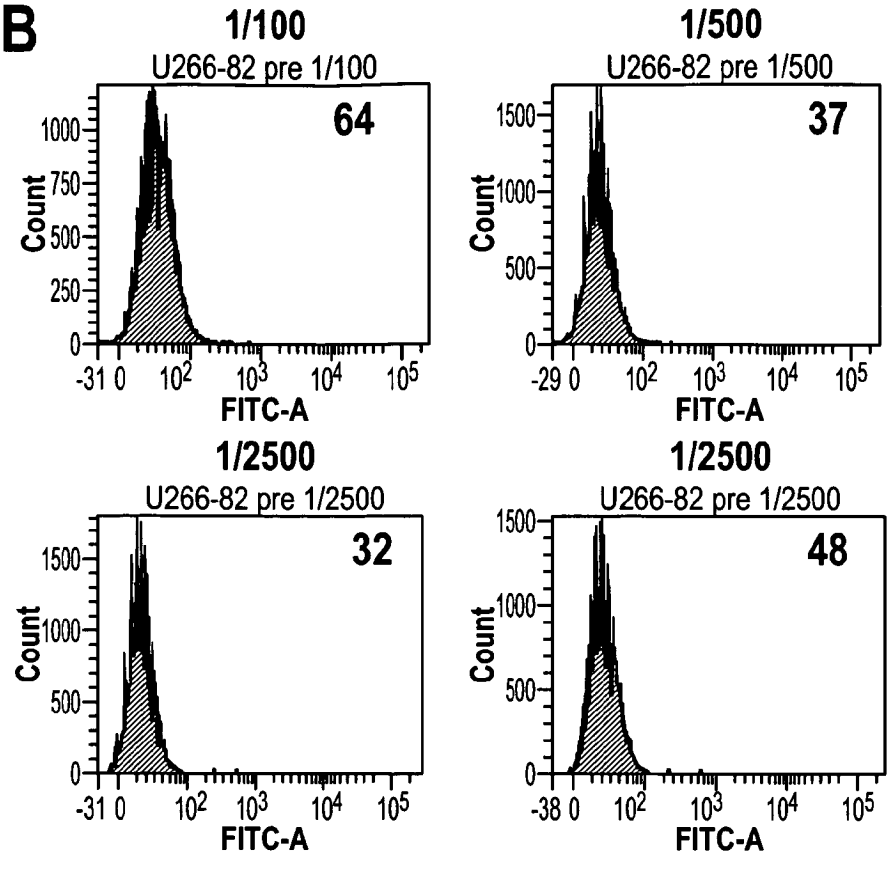
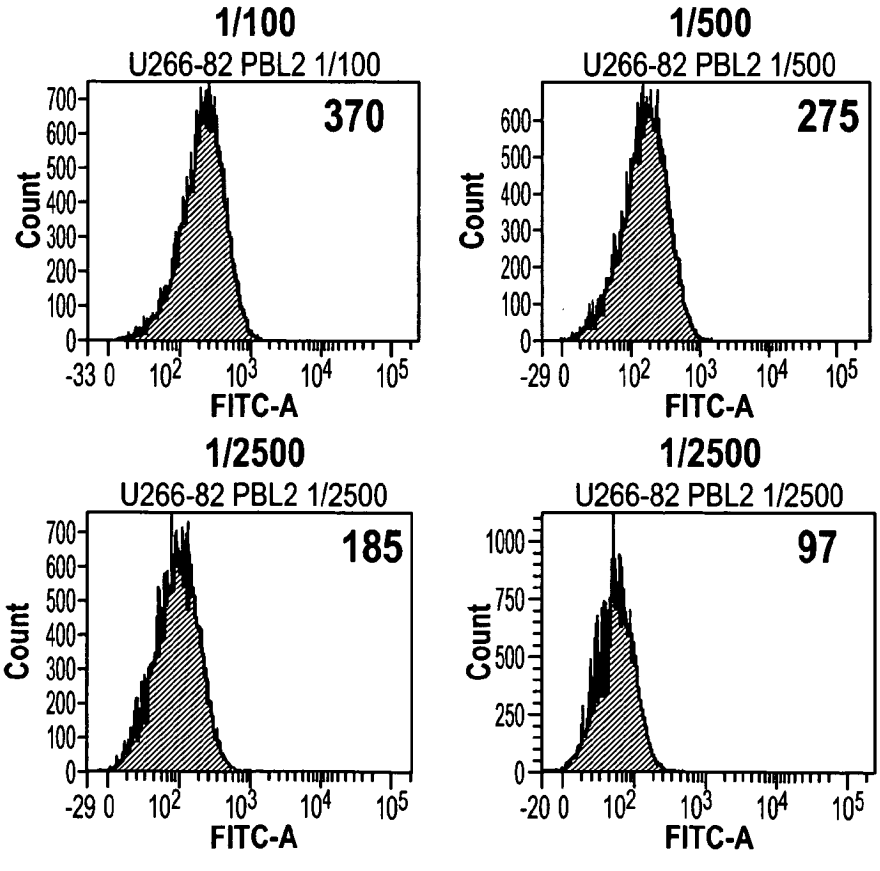


Figure 2B

LI82 pre



LI82 PBL2



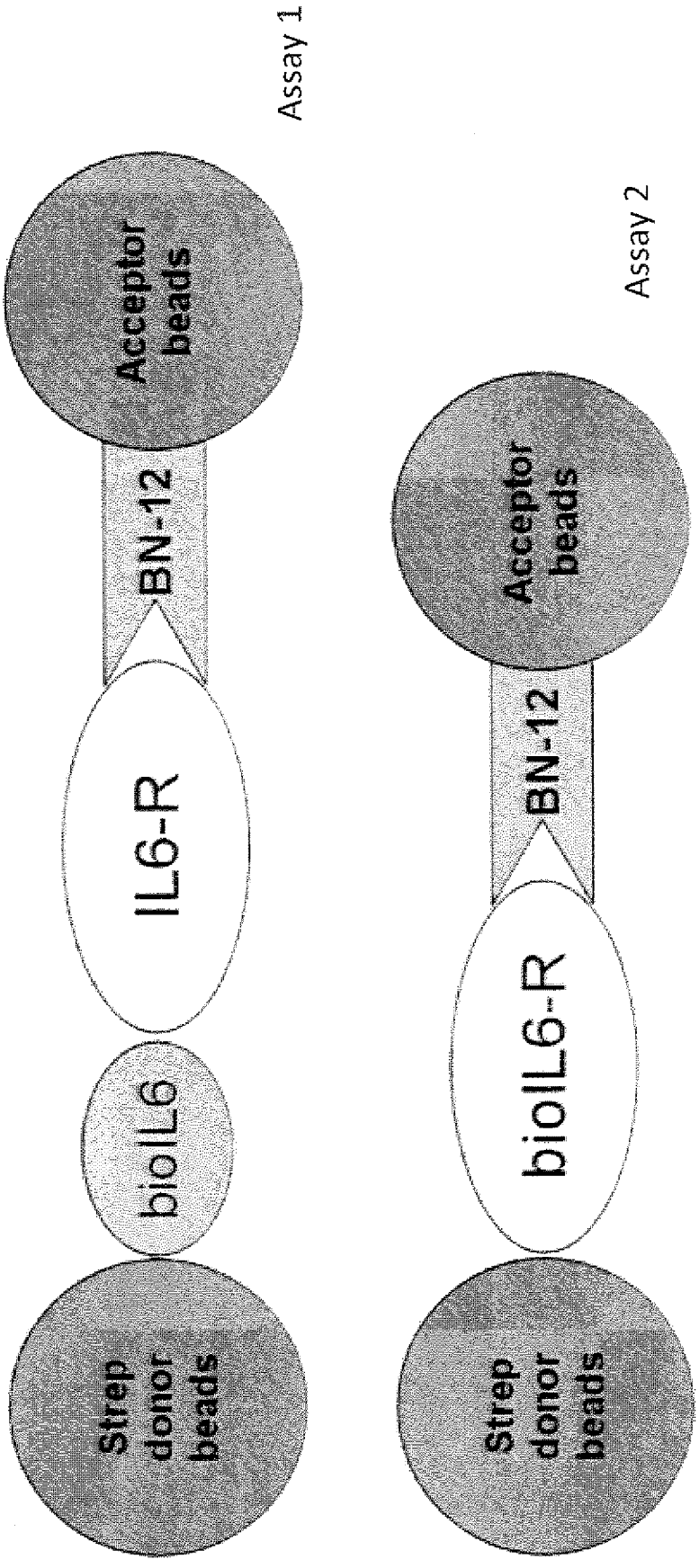

Assay 1
Acceptor beads
BN-12
IL6-R
bioIL6
Strep donor beads
Assay 2
Acceptor beads
BN-12
bioIL6-R
Strep donor beads

Figure 3

```
                ----------FR1---------- -CDR1-- -----FR2------ -------CDR2-------- ----------FR3---------- ---------CDR3--------- ----FR4---
Inhibitors
PMP40H5         EVQLVESGGGLVQPGGSLRLSCAASGFSLD YYAIG WFRQAPGKEREGVS CMDSSSGTTSTYYSDSVKG RFTISRDDAKNTVYLQMNSLKPEDTAVYYCAA DGHLWWGQRVYPCSQISWRGWNDY WGQGTQVTVSS
PMP35E11        EVQLVESGGGLVQAGGSLRLSCAASGFTFD DYAIG WFRQAPGKEHEGVS CISSSDGSTYYADSVKG RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA ERDVPARSLCGSYYWYDY RGQGTQVTVSS
PMP32C9        EVQLVESGGGLVQAGGSLRLSCAASGFTFD DYDIG WFRQAPGKEREGVS GISSSDGNTYYADSVKG RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA EPPDSSWYLDGSPEFFKY WGQGTQVTVSS
PMP35H4        EVQLVESGGGLVQPGGSLRLSCAASGFTFD DYGMS WVRQAPGRAPEWVS AISWNGNNTYYTESMKG RFTISRDNAKNTVYLQMNSLKPEDTAVYYCVK GSTAIVGVPPTYPDEYDY WGQGTQVTVSS
PMP32E10       EVQLVESGGGLVQPGGSLRLSCAASGFTFG SYDMS WVRQAPGKGPEWVS AINSGGGSTYYADSVKG RFTISRDNAKNTLYLQMNSLKPEDTAVYYCAT DWRYSDYDLPLPPPGDY WGQGTQVTVSS
PMP30C11       EVQLVESGGGLVQAGGSLRLSCAASGRTFS SYDMG WYRQAPGKEREFVA VISRSGSSTYYADSVKG RFTISRDNAKNTVYLQMNSLKPEDTAIYYCKA EVVAGDYDY WGQGTQVTVSS
PMP35C10       EVQLVESGGGLVQAGGSLRLSCAASGRTFS SYDMG WYRQAPGKEREFVA VIHWSGSTYYADPVKG RFTISRDNAKNTVYLQMNSLKPEDTAIYYCNA FLPGPEGFHDY WGQGTQVTVSS
PMP34G9        EVQLVESGGGLVQAGGSLRLSCAASGRTSS SYDMT WYRQVPGKEREFVA VISWSGGSTYYADSVKG RFTISRDNAKNTVYLQMNSLKPEDTAIYYCNA YTGGGDDY WGQGTQVTVSS
PMP31A4        EVQLVESGGGLVQAGGSLRLSCAASGSIFK VNAMG WYRQAPGKQRELVA GITSGGSTNYADSVKG RLTISRDNAKNTVYLQMNSLKPEDTAVYYCSF VTTNSDYDLGRDY WGQGTQVTVSS
PMP32E2        EVQLVESGGGLVQAGGSLRLSCAASGNIFD DNTMGWT WNRQPPGKQRELVA IIATDGSTNYADSVKG RFTISRDNAKNTVYLQMNSLKPEDTAVYYCNL FSLRLGRDY WGQGTQVTVSS
PMP33A3        EVQLVESGGGLVQPGGSLRLSCAASGFTLD YGAIG WFRQAPGKEREGVS CISSSTGSTYYADSVKG RFTISRDNGKNTVYLQMNSLKPEDTAVYYCAA DKMWSPCLVAANEEALFEYDY WGQGTQVTVSS
PMP34A12       EVQLVESGGGLVQPGGSLRLSCVASGFSLD YYVIG WFRQAPGKEREGVS CISSSDGSTYYADSVKG RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA DLLRTPEFCVDSAPYDY WGQGTQVTVSS
PMP28E11       EVQLVESGGGLVQPGGSLRLSCAASGFTLD YYAIG WFRQAPGKEREGVS CISSSDGSTYYADSVKG RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAL VHTTAQATGVFQREYEYEW WGQGTQVTVSS
PMP35F4        EVQLVESGGGLVQAGGSLRLSCAASGRTFS SYDMG WYRQAPGKEREFVA IITWNSSTYYADSVKG RFTISRDNAKNTVYLQMNSLKPEDTAIYYCNA QYGLGYAEDY WGQGTQVTVSS
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Figure 4

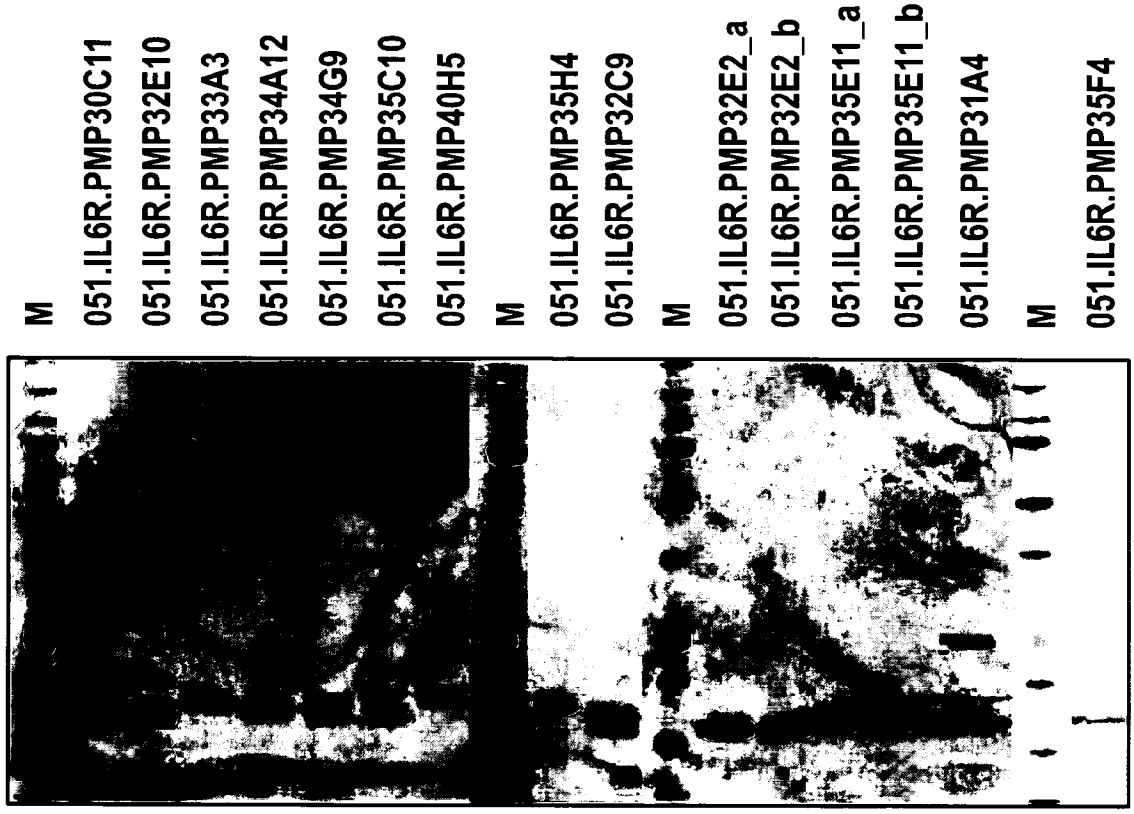

M
051.IL6R.PMP30C11
051.IL6R.PMP32E10
051.IL6R.PMP33A3
051.IL6R.PMP34A12
051.IL6R.PMP34G9
051.IL6R.PMP35C10
051.IL6R.PMP40H5
M
051.IL6R.PMP35H4
051.IL6R.PMP32C9
M
051.IL6R.PMP32E2_a
051.IL6R.PMP32E2_b
051.IL6R.PMP35E11_a
051.IL6R.PMP35E11_b
051.IL6R.PMP31A4
M
051.IL6R.PMP35F4

Figure 5

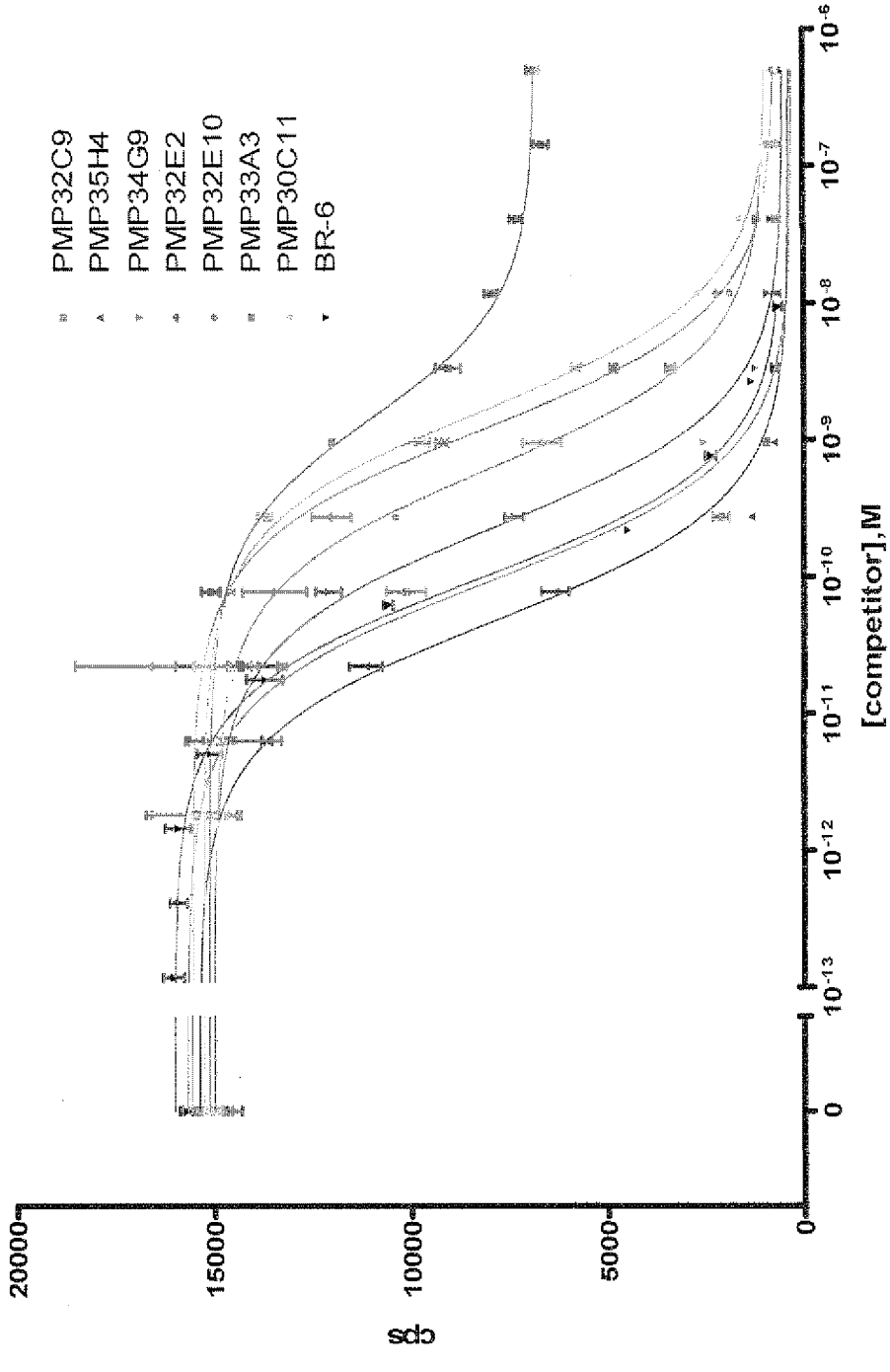

PMP32C9
PMP35H4
PMP34G9
PMP32E2
PMP32E10
PMP33A3
PMP30C11
BR-6
cps
20000
15000
10000
5000
0
0
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[competitor],M

Figure 6A

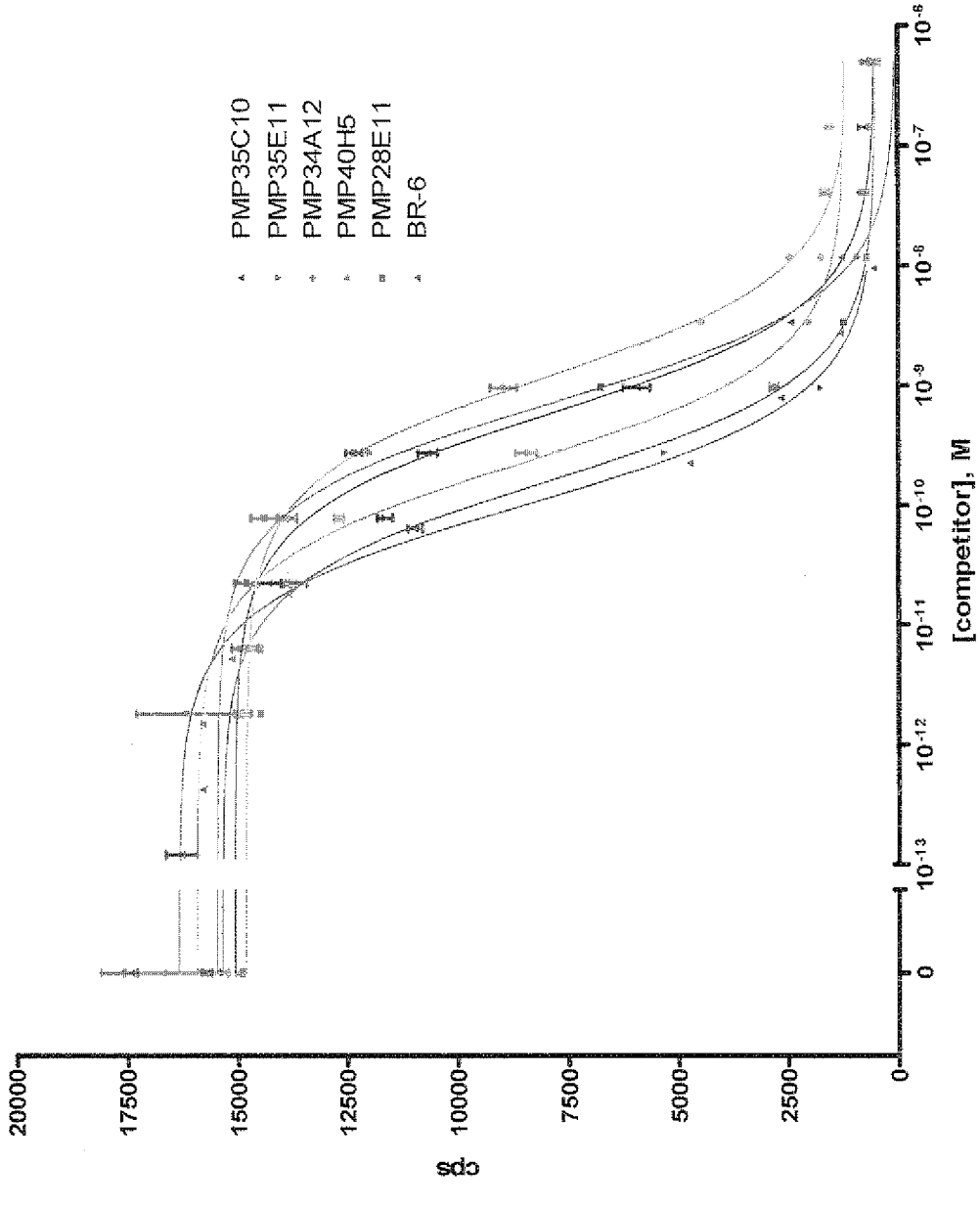

PMP35C10
PMP35E11
PMP34A12
PMP40H5
PMP28E11
BR-6
cps
20000
17500
15000
12500
10000
7500
5000
2500
0
0
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[competitor], M

Figure 6B

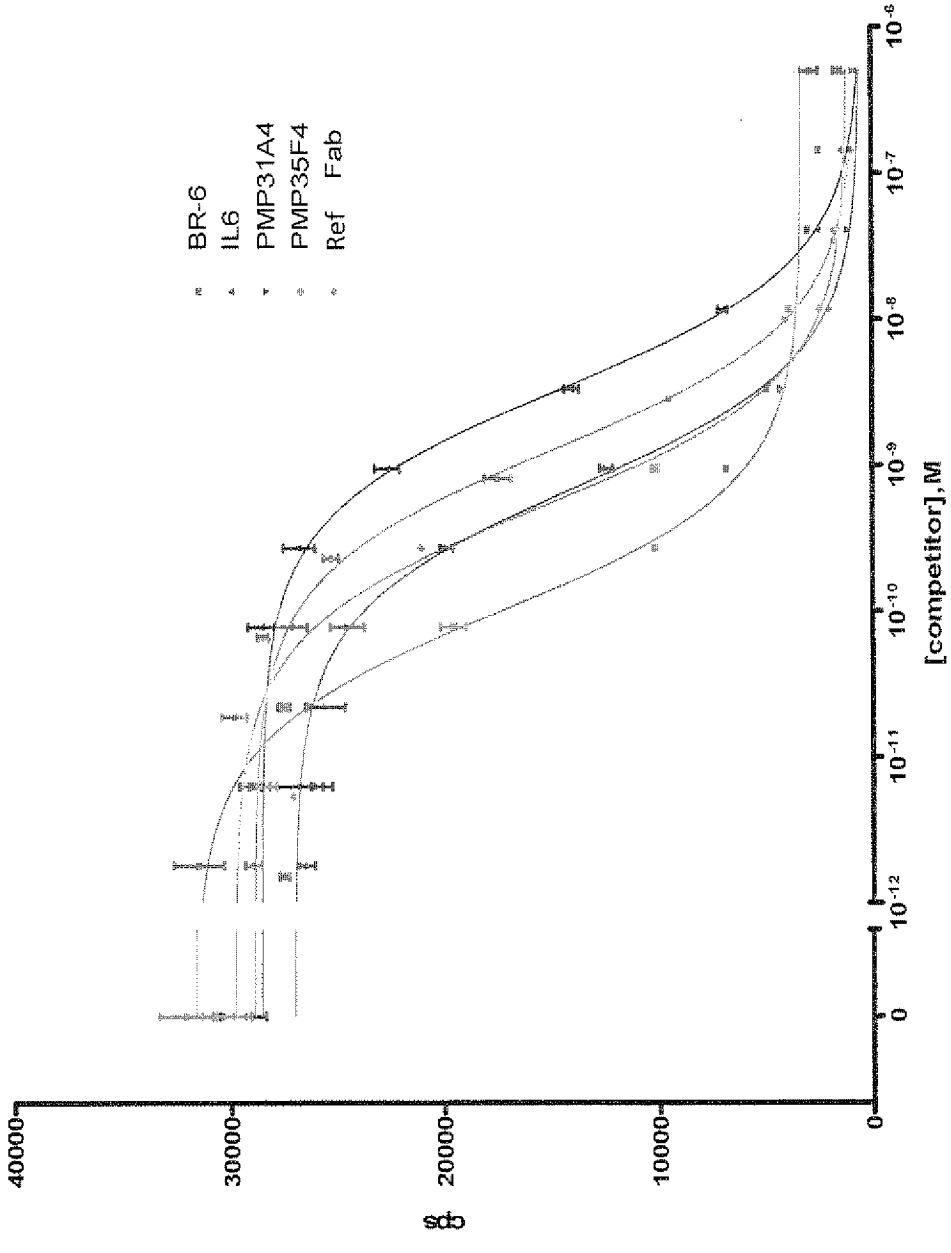

BR-6
IL6
PMP31A4
PMP35F4
Ref Fab
cps
40000
30000
20000
10000
0
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[competitor], M

Figure 6C

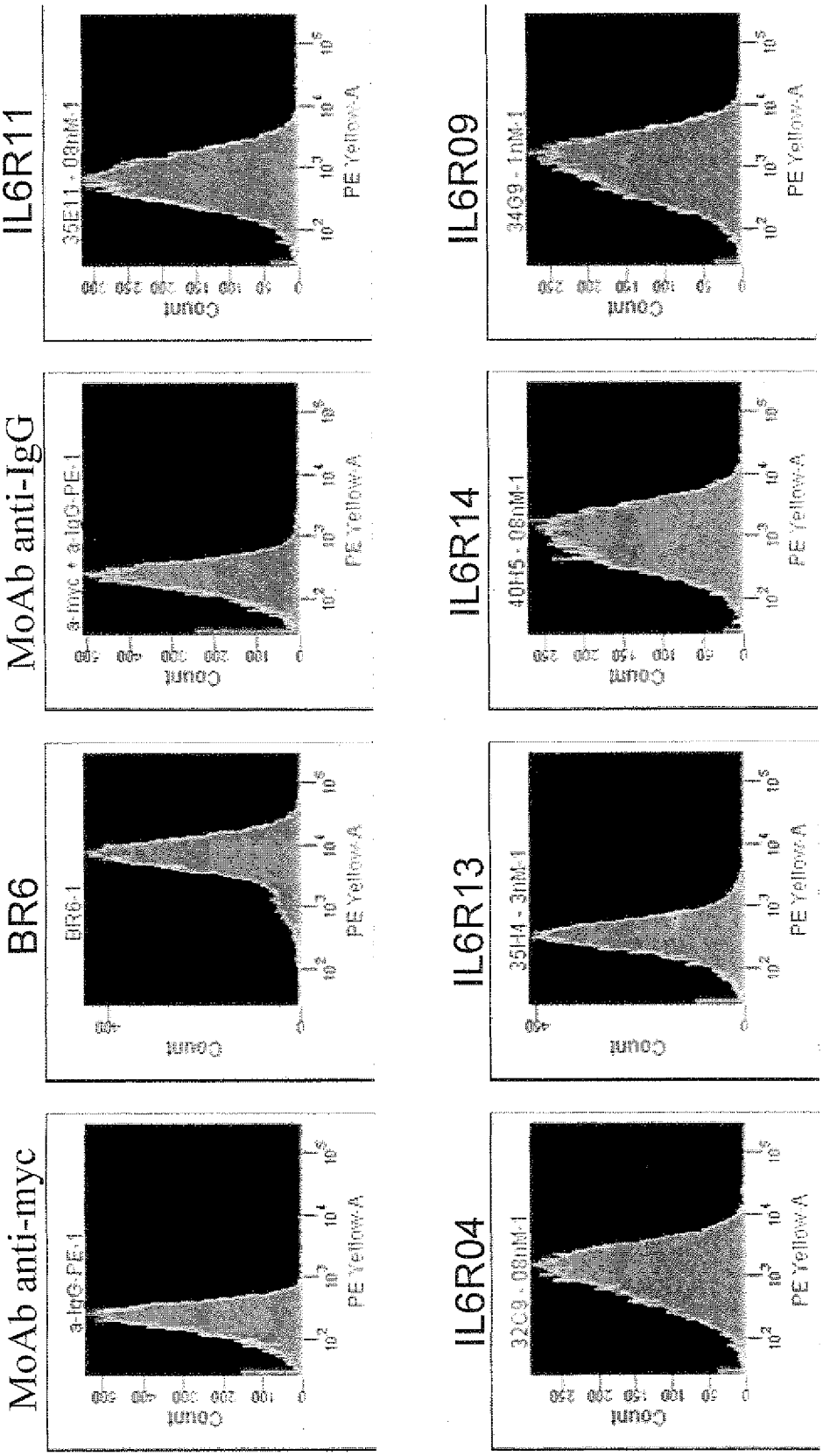

MoAb anti-myc
BR6
MoAb anti-IgG
IL6R11
IL6R04
IL6R13
IL6R14
IL6R09
Count
PE Yellow-A

Figure 7

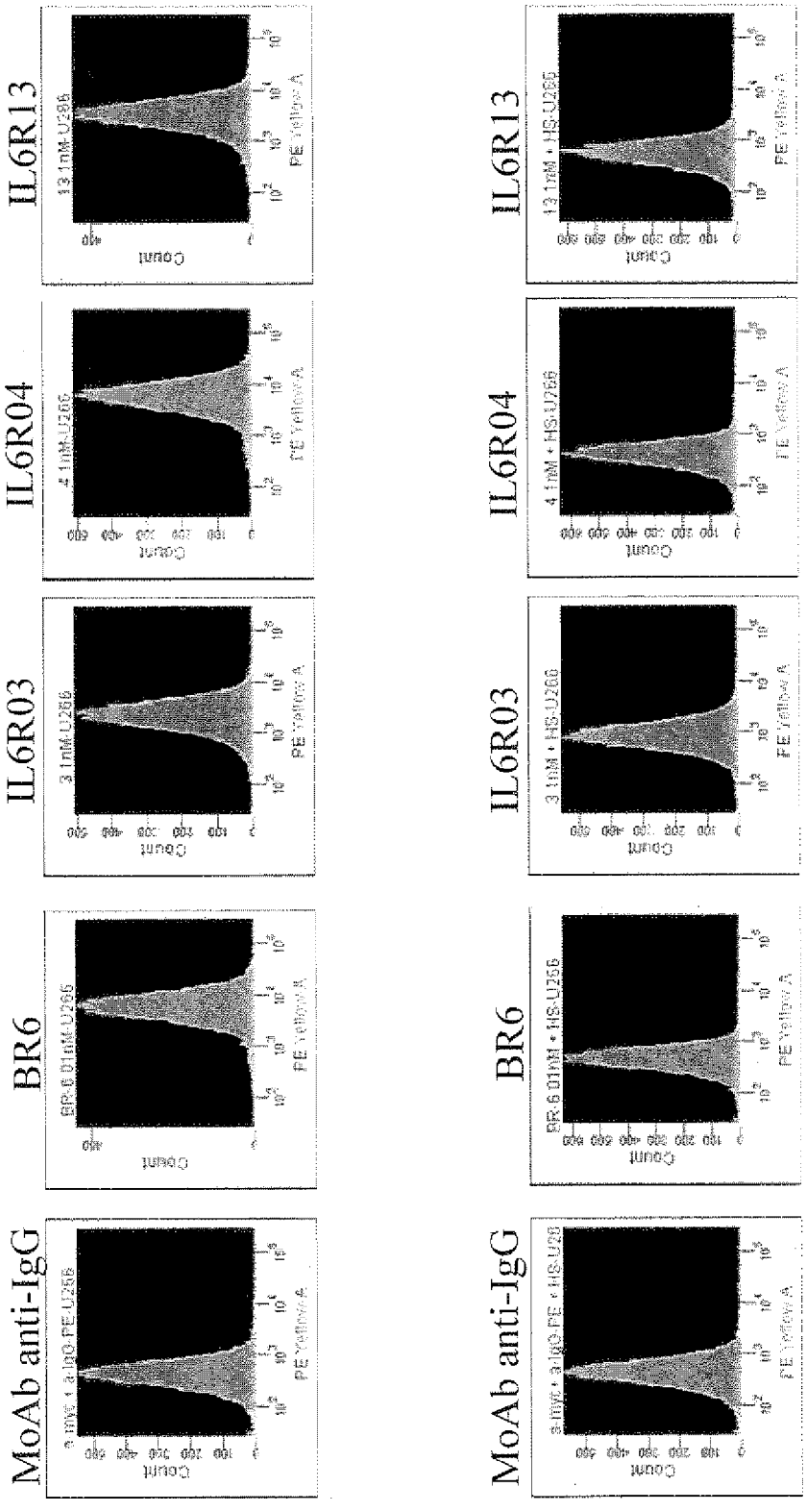

MoAb anti-IgG
BR6
IL6R03
IL6R04
IL6R13
MoAb anti-IgG
BR6
IL6R03
IL6R04
IL6R13

Figure 8

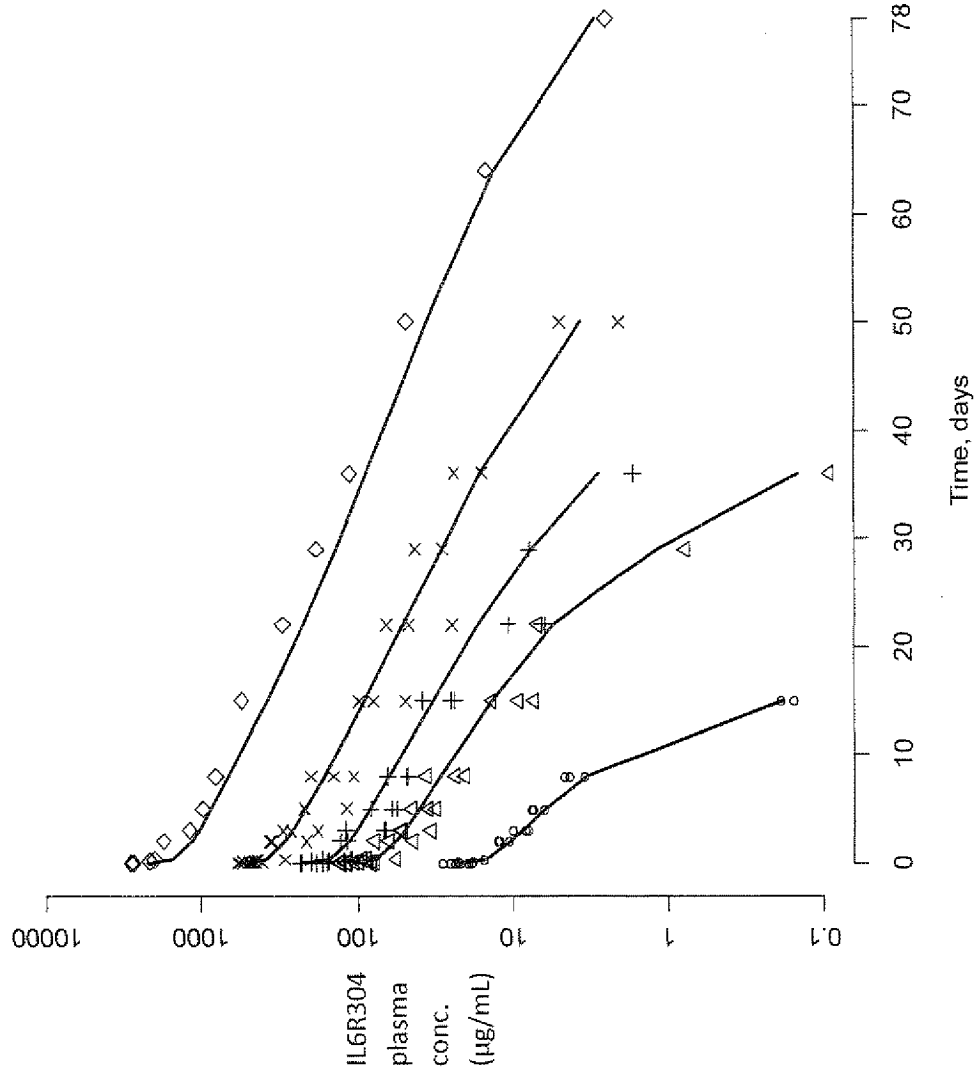

IL6R304 plasma conc. (µg/mL)
10000
1000
100
10
1
0.1
Time, days
0
10
20
30
40
50
60
70
78

Figure 9

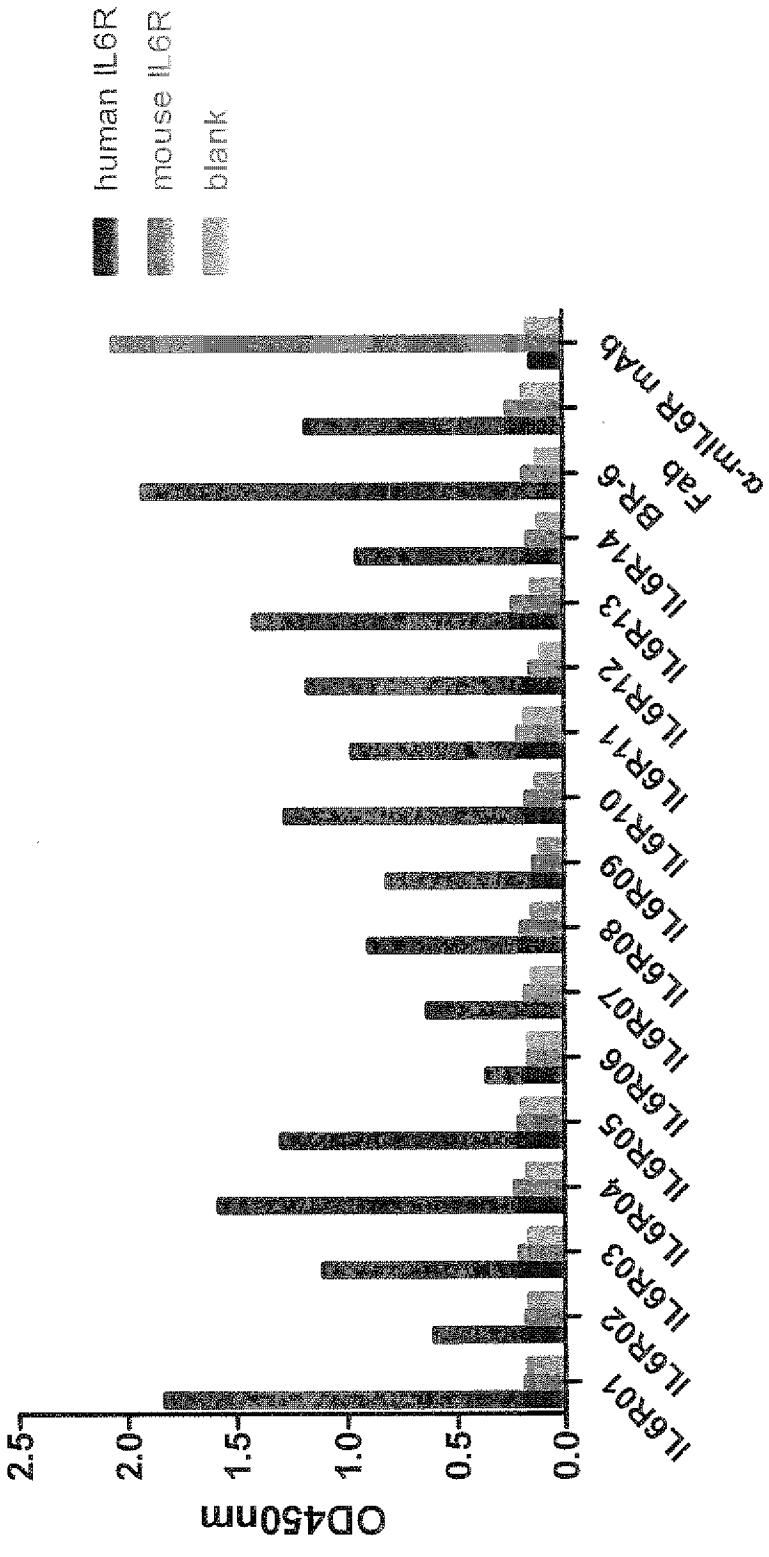

human IL6R
mouse IL6R
blank
OD450nm
2.5
2.0
1.5
1.0
0.5
0.0
IL6R01
IL6R02
IL6R03
IL6R04
IL6R05
IL6R06
IL6R07
IL6R08
IL6R09
IL6R10
IL6R11
IL6R12
IL6R13
IL6R14
BR-6
Fab
α-mIL6R mAb

Figure 10

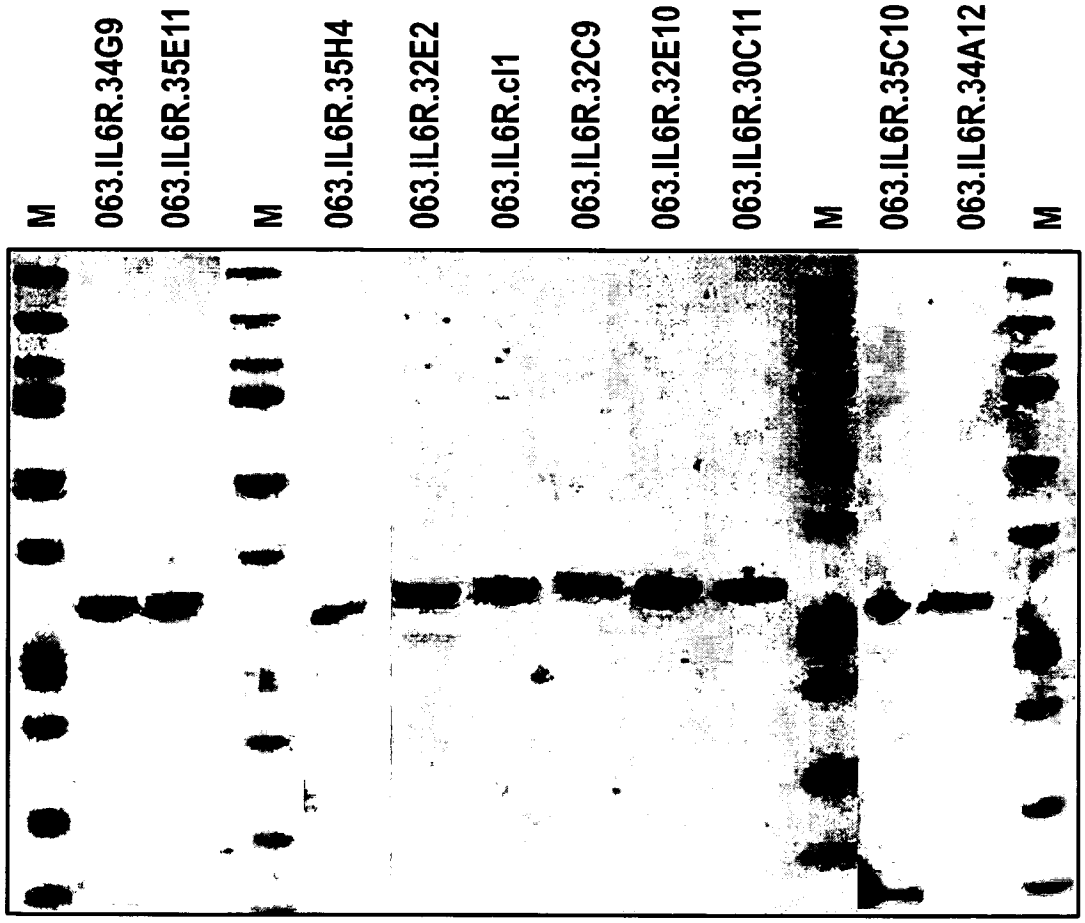

M
063.IL6R.34G9
063.IL6R.35E11
M
063.IL6R.35H4
063.IL6R.32E2
063.IL6R.cl1
063.IL6R.32C9
063.IL6R.32E10
063.IL6R.30C11
M
063.IL6R.35C10
063.IL6R.34A12
M

Figure 11

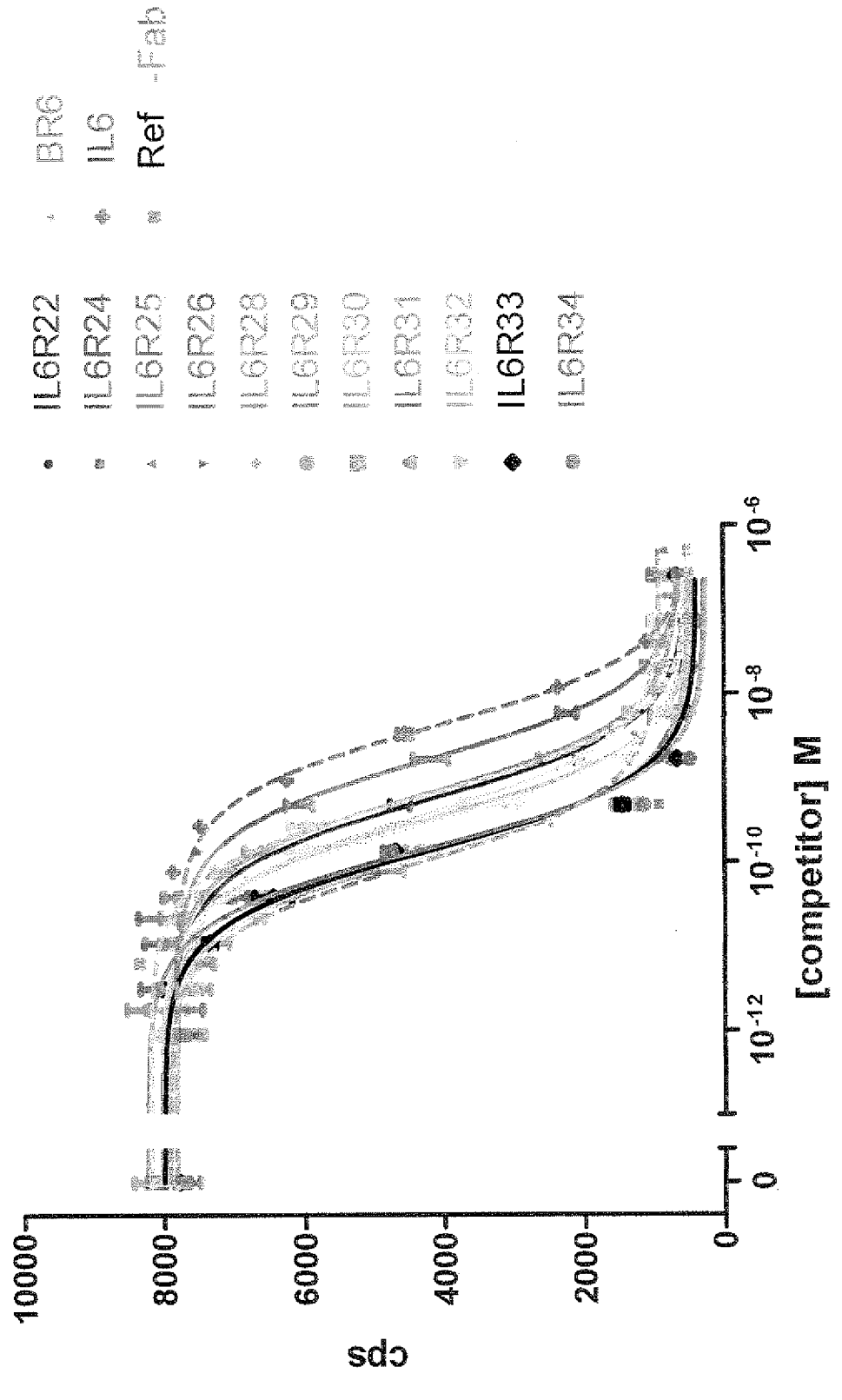

BR6
IL6
Ref -Fab
IL6R22
IL6R24
IL6R25
IL6R26
IL6R28
IL6R29
IL6R30
IL6R31
IL6R32
IL6R33
IL6R34
cps
10000
8000
6000
4000
2000
0
0
10-12
10-10
10-8
10-6
[competitor] M

Figure 12

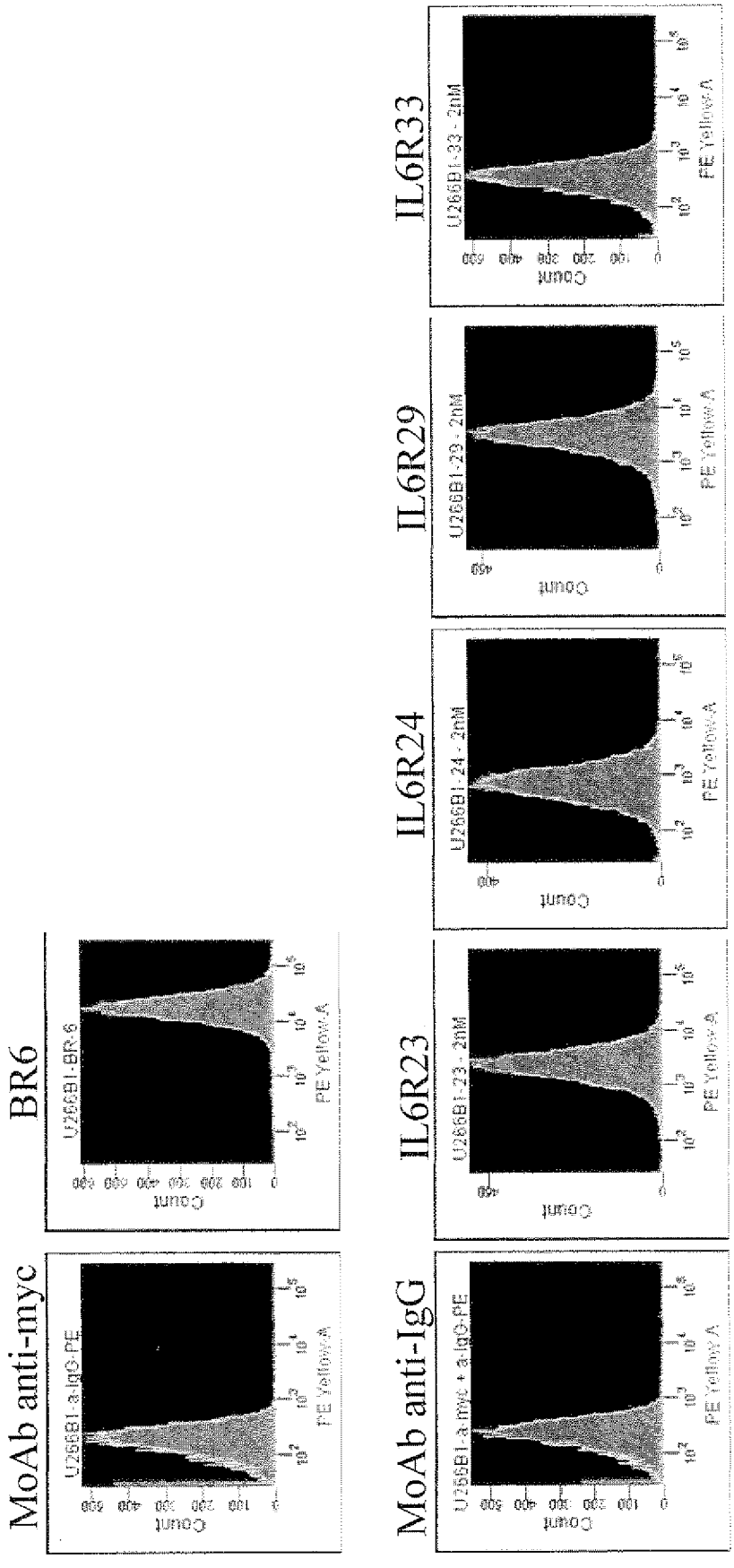

MoAb anti-myc
BR6
IL6R23
IL6R24
IL6R29
IL6R33
MoAb anti-IgG
U266B1-a-IgG-PE
U266B1-BR-6
U266B1-23 - 2nM
U266B1-24 - 2nM
U266B1-29 - 2nM
U266B1-33 - 2nM
U266B1-a-myc + a-IgG-PE
Count
PE Yellow-A

Figure 13

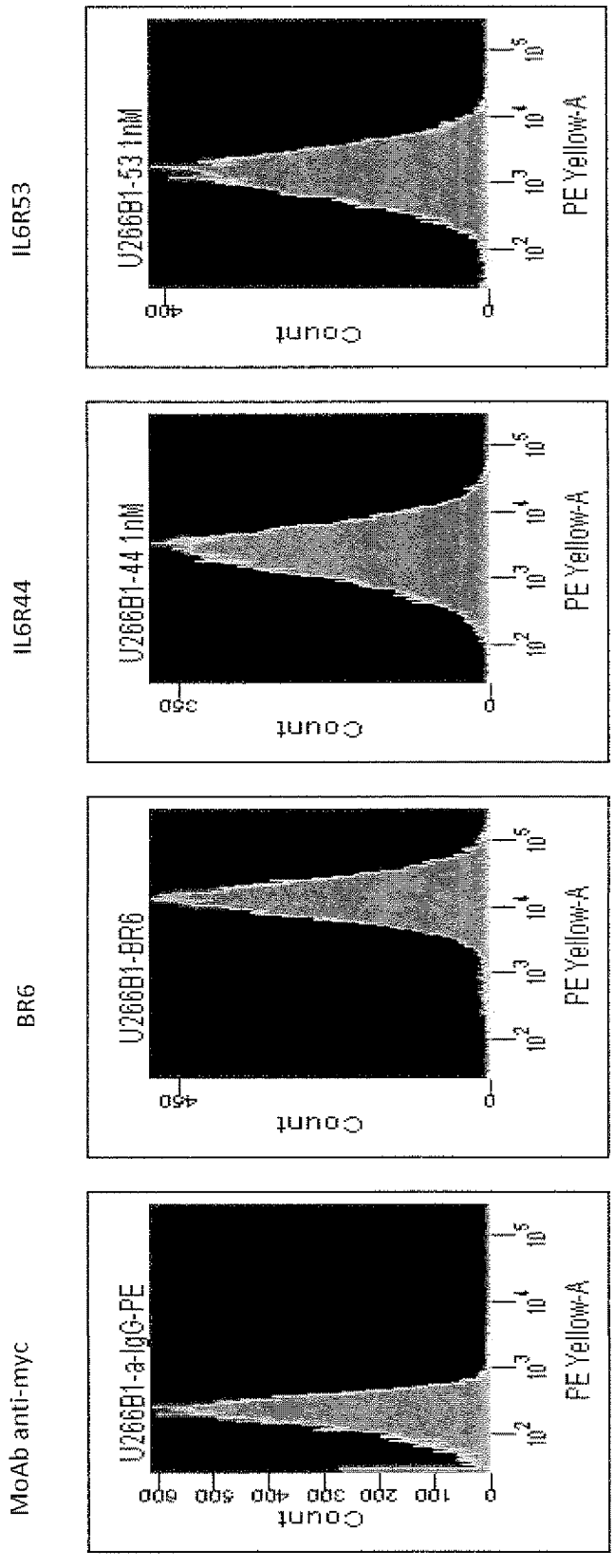

MoAb anti-myc
BR6
IL6R44
IL6R53
U266B1-a-IgG-PE
U266B1-BR6
U266B1-44 1nM
U266B1-53 1nM
Count
PE Yellow-A
0
100
200
300
400
500
600
450
350
400

Figure 14

IL6R03 EVQLVESGGGLVQ[illegible]GGSLRLSCAAS[illegible]VNAMGW[illegible]RQAPGK[illegible]VAGIISGG---STNYADSVKGRFTISRDNAKNTVYLQMNSLK[illegible]EDTAVYYC[illegible]TTNSDYDLGRDYWGQGTQVTVSS

DP47 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG--STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK----------WGQGTLVTVSS
(SEQ ID NO: 35)

DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSS--TIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR----------WGQGTLVTVSS
(SEQ ID NO: 36)

DP53 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGS--STSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS
(SEQ ID NO: 37)

DP29 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGRTRNKANSYTTEYAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCAR----------WGQGTLVTVSS
(SEQ ID NO: 38)

DP54 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGS--EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS
(SEQ ID NO: 39)

IL6R04 EVQLVESGGGLVQ[illegible]GGSLRLSCAASGFTF[illegible]DYDLGM[illegible]RQAPGK[illegible]GV[illegible]SGISSSDG--NTYYADSVKGRFTIS[illegible]DNAKNTVYLQMNSL[illegible]EDTAVYYCA[illegible]GPPDSSWYLDGSPEFFKYWGQGTQVTVSS

DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSS--TIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR----------WGQGTLVTVSS

DP53 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGS--STSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS

DP29 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGRTRNKANSYTTEYAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCAR----------WGQGTLVTVSS

DP47 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG--STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK----------WGQGTLVTVSS

DP54 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGS--EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS

IL6R13 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGN--NTYYTESMKGRFTISRDNAKNTVYLQMNSLK[illegible]EDTAVYYC[illegible]GSTAIVGVPFTYPDEYDYWGQGTQVTVSS

DP29 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGRTRNKANSYTTEYAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCAR----------WGQGTLVTVSS

DP47 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG--STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK----------WGQGTLVTVSS

DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSS--TIYYADSVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCAR----------WGQGTLVTVSS

DP53 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGS--STSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS

DP54 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGS--EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS

Figure 15

```
IL6R03  EVQLVESGGGLVQAGGSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAIISGGSTNYADSVKGRLTISRDNAKNTVYLQMNSLKPEDTAVYYCSTVTTNSDYDLGRDYWGQGTQVTVSS

IL6R61  EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKQRELVAGIISGGSTNYADSVKGRLTISRDNAKNTVYLQMNSLKPEDTAVYYCSFVTTNSDYDLGRDYWGQGTLVTVSS

IL6R62  EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRTTISRDNAKNTVYLQMNSLRPEDTAVYYCSFVTTNSDYDLGRDYWGQGTRVTVSS

IL6R63  EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRLTISRDNAKNTIYLQMNSLRPEDTAVYYCSFVTTNSDYDLGRDYWGQGTLVTVSS

IL6R64  EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRLTISRDNAKNTVYLQMNSLRPEDTAVYYCQFVTTNSDYDLGRDYWGQGTLVTVSS

IL6R65  EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRRTISRDNAKNTILQMNSLRPEDTAVYYCAFVTTNSDYDLGRDYWGQGTLVTVSS

********************************************************************************************************************************

IL6R04  EVQLVESGGGLVQAGGSLRLSCAASGFTFDDYDIGWFRQAPGKEREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTQVTVSS

IL6R71  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS

IL6R72  EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS

IL6R73  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTTSRDNAKNTVYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS

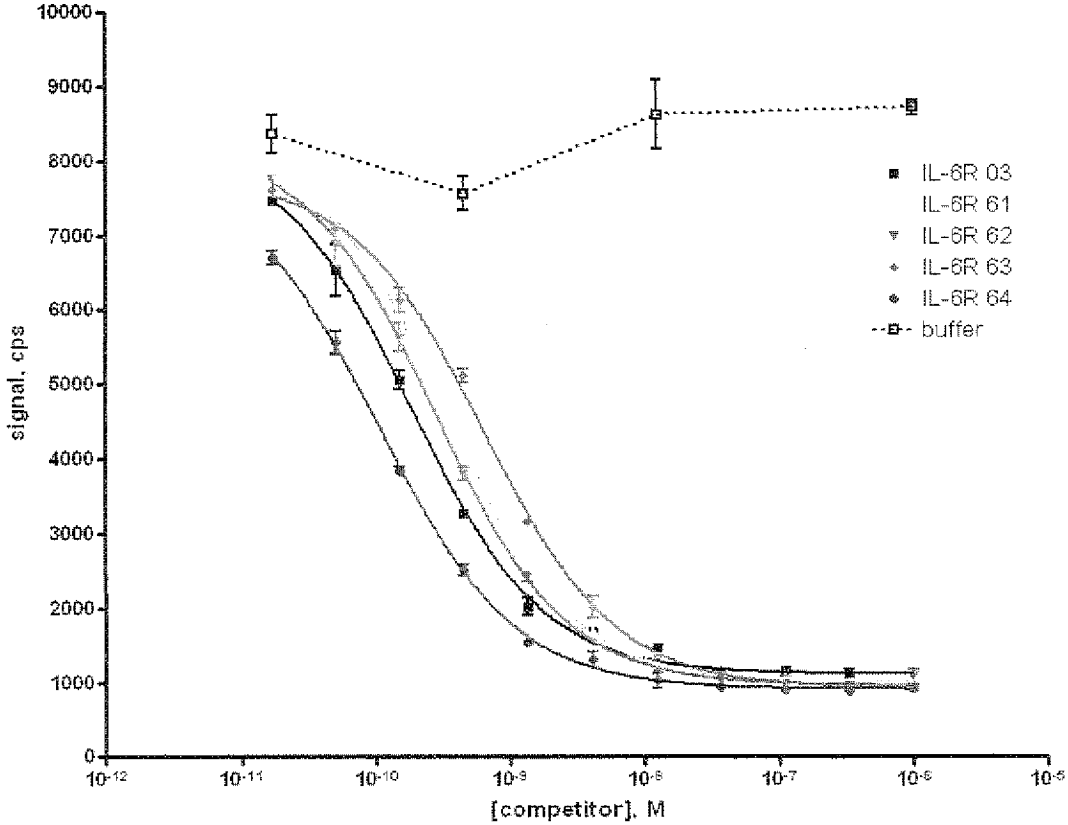
IL6R74  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTLYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS

IL6R75  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISRDNAKNTKYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS
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Figure 16A

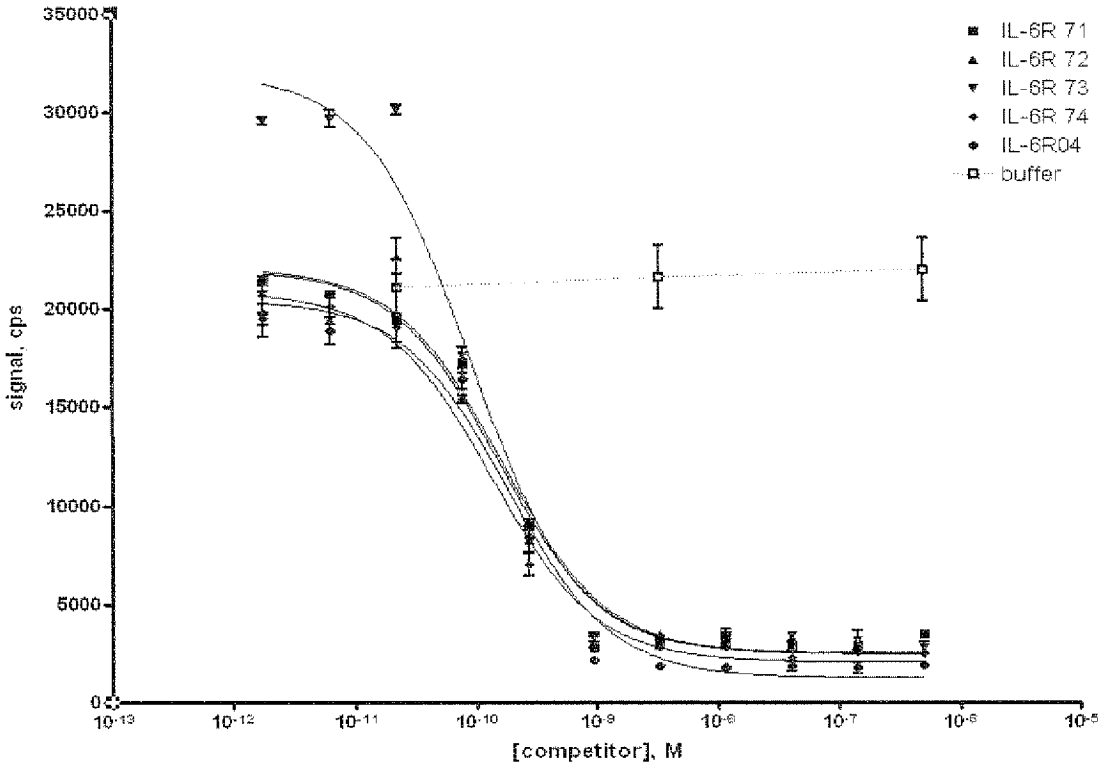
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IL6R13  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTQVTVSS
IL6R81  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTVYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R82  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTVYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R83  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R84  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R85  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGPGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R86  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R87  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R88  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R89  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R90  EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
```

Figure 16B



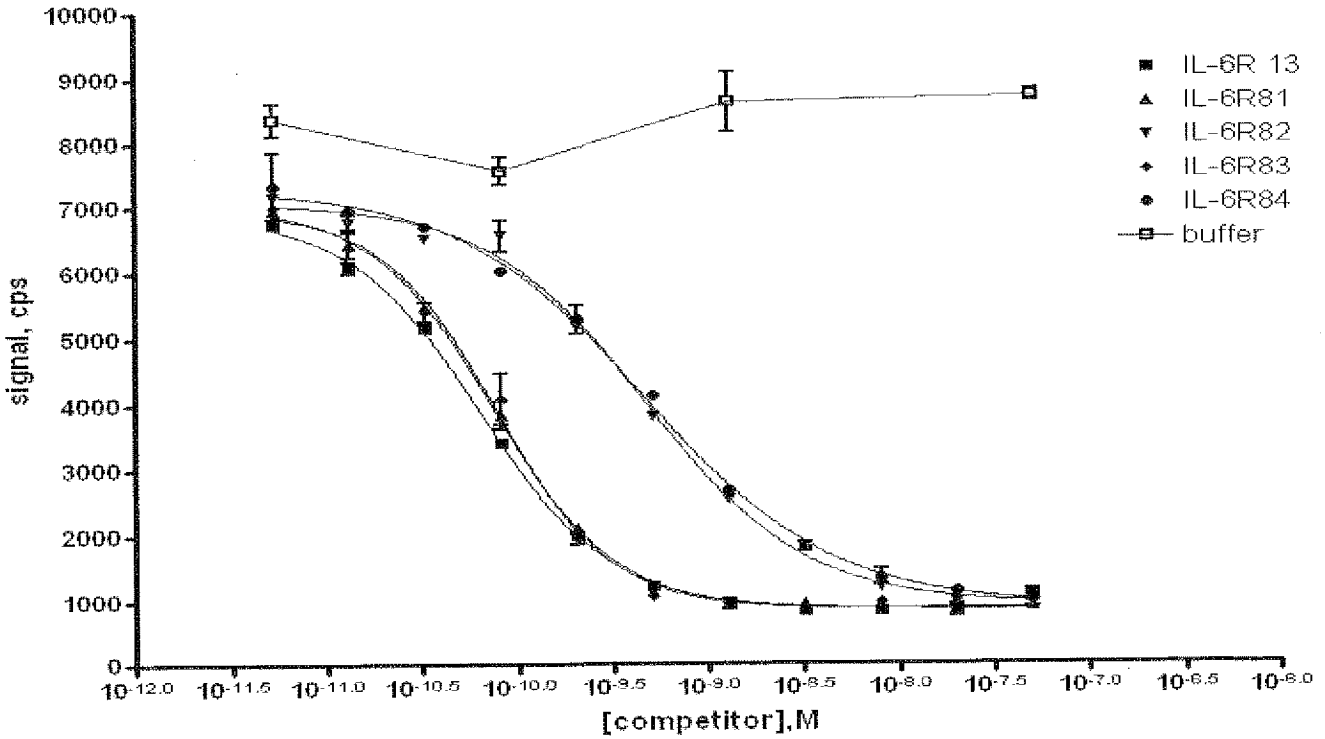
	IL-6R 03	IL-6R 61	IL-6R 62	IL-6R 63	IL-6R 64
Sigmoidal dose-response (variable slope)					
Best-fit values					
BOTTOM	1112	1011	957.9	926.6	908.6
TOP	8238	8206	8255	7788	7903
LOGEC50	-9.729	-9.473	-9.552	-9.187	-9.967
HILLSLOPE	-0.8898	-0.9341	-0.8962	-0.8886	-0.8624
EC50	1.867e-010	3.362e-010	2.804e-010	6.496e-010	1.080e-010

Figure 17



	IL-6R 71	IL-6R 72	IL-6R 73	IL-6R 74	IL-6R04
Sigmoidal dose-response					
Best-fit values					
BOTTOM	2437	2456	2476	2030	1216
TOP	22084	22123	32092	20905	20499
LOGEC50	-9.816	-9.795	-10.04	-9.878	-9.744
EC50	1.527e-010	1.605e-010	9.165e-011	1.325e-010	1.802e-010

Figure 18



	IL-6R 13	IL-6R81	IL-6R82	IL-6R83	IL-6R84
Sigmoidal dose-response (variable slope)					
Best-fit values					
BOTTOM	859.7	865.8	925.7	860.9	901.0
TOP	6888	7027	7080	6955	7303
LOGEC50	-10.19	-10.13	-9.322	-10.11	-9.332
HILLSLOPE	-1.270	-1.369	-1.039	-1.442	-0.8822
EC50	6.437e-011	7.466e-011	4.764e-010	7.789e-011	4.654e-010

Figure 19

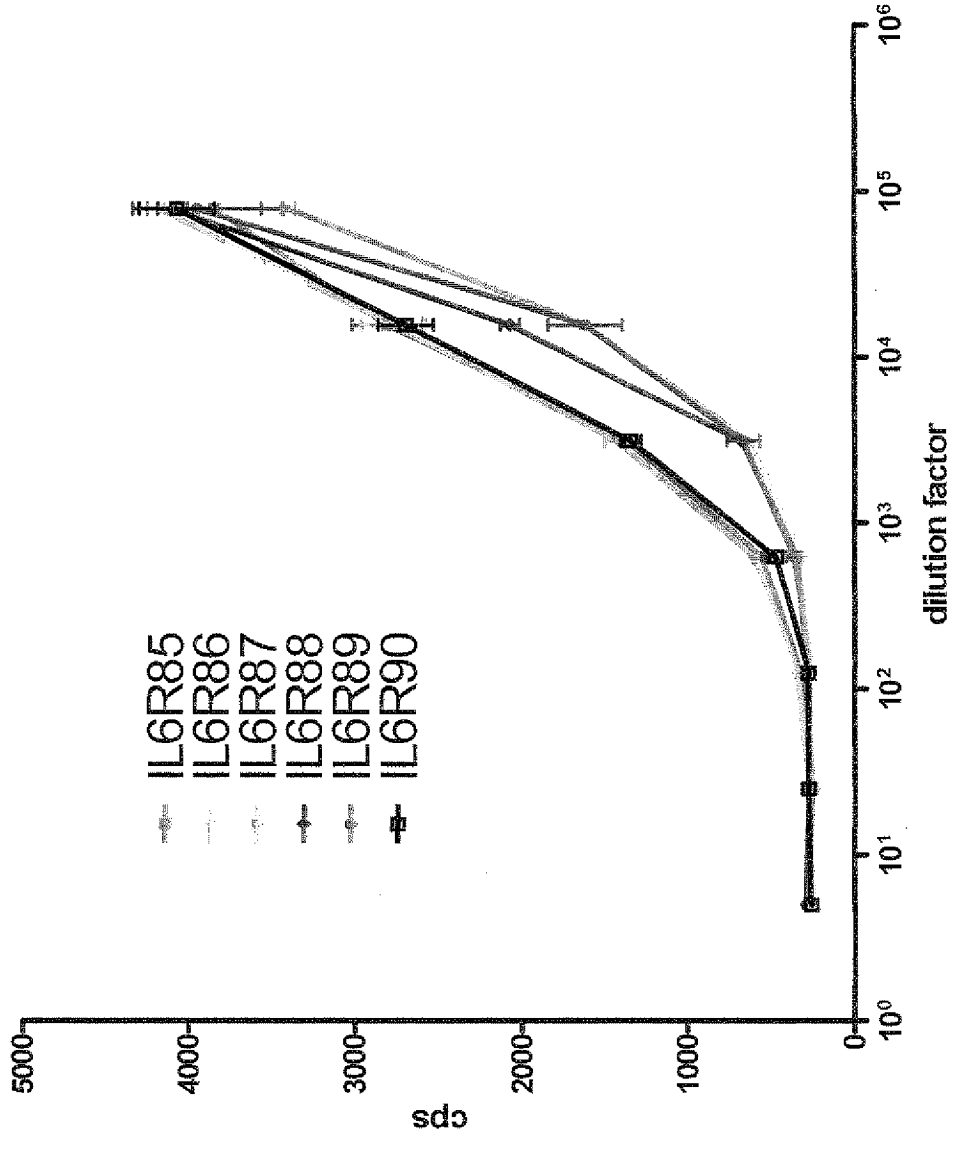

IL6R85
IL6R86
IL6R87
IL6R88
IL6R89
IL6R90
cps
5000
4000
3000
2000
1000
0
10^0
10^1
10^2
10^3
10^4
10^5
10^6
dilution factor

Figure 20

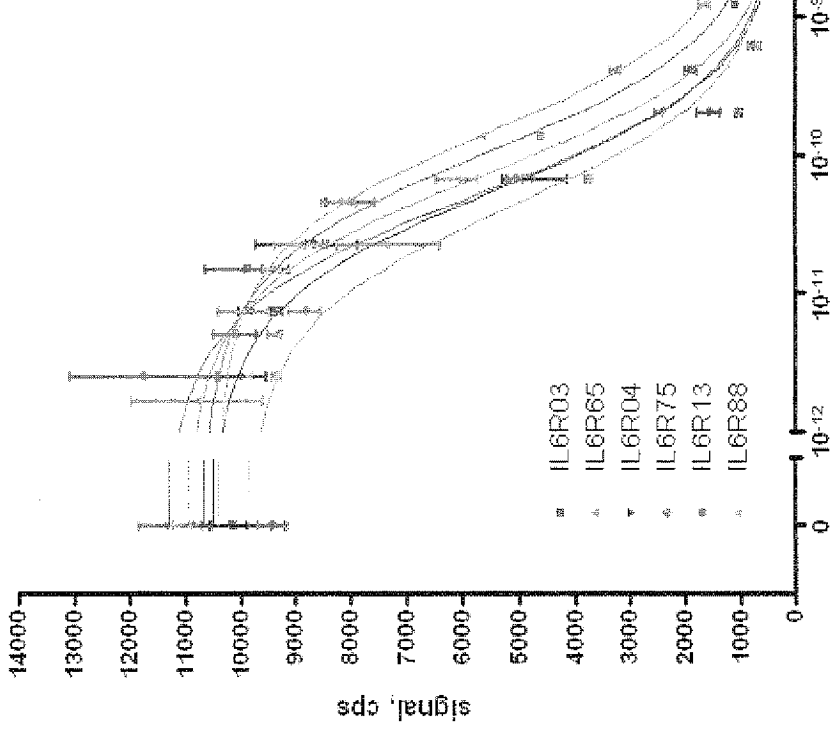

IL6R65-75-88
signal, cps
[inhibitor], M
IL6R03
IL6R65
IL6R04
IL6R75
IL6R13
IL6R88
LOGEC50 -9.980 -9.833 -10.25 -10.36 -10.30 -10.14
EC50 1.047e-010 1.470e-010 5.680e-011 4.320e-011 5.052e-011 7.273e-011

Figure 21

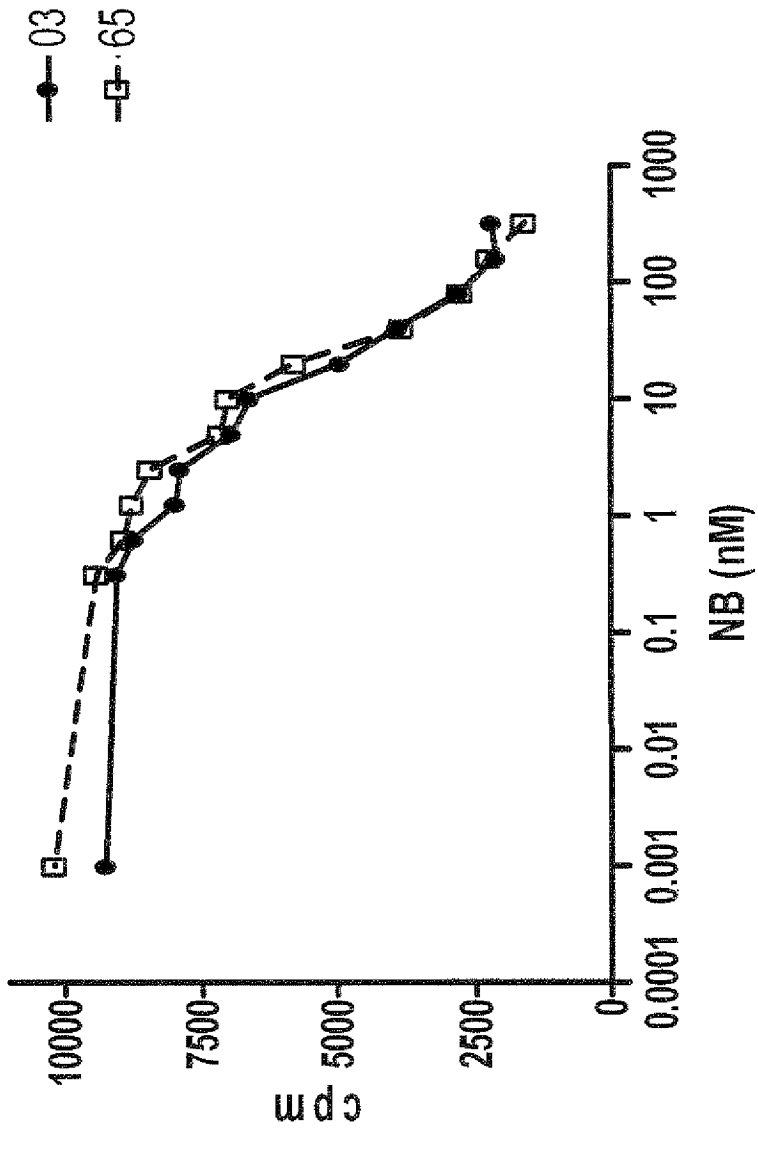

03
65
cpm
10000
7500
5000
2500
0
0.0001
0.001
0.01
0.1
1
10
100
1000
NB (nM)

Figure 22A

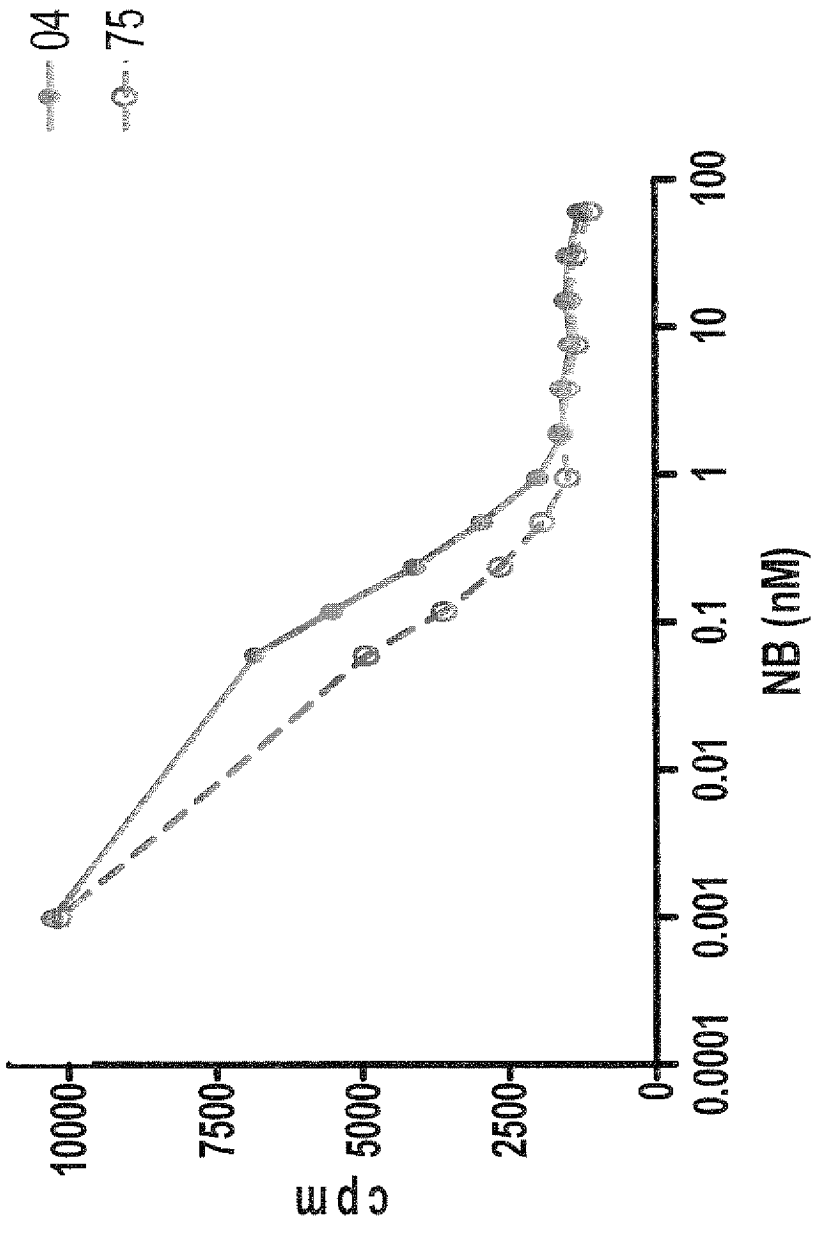


Figure 22B

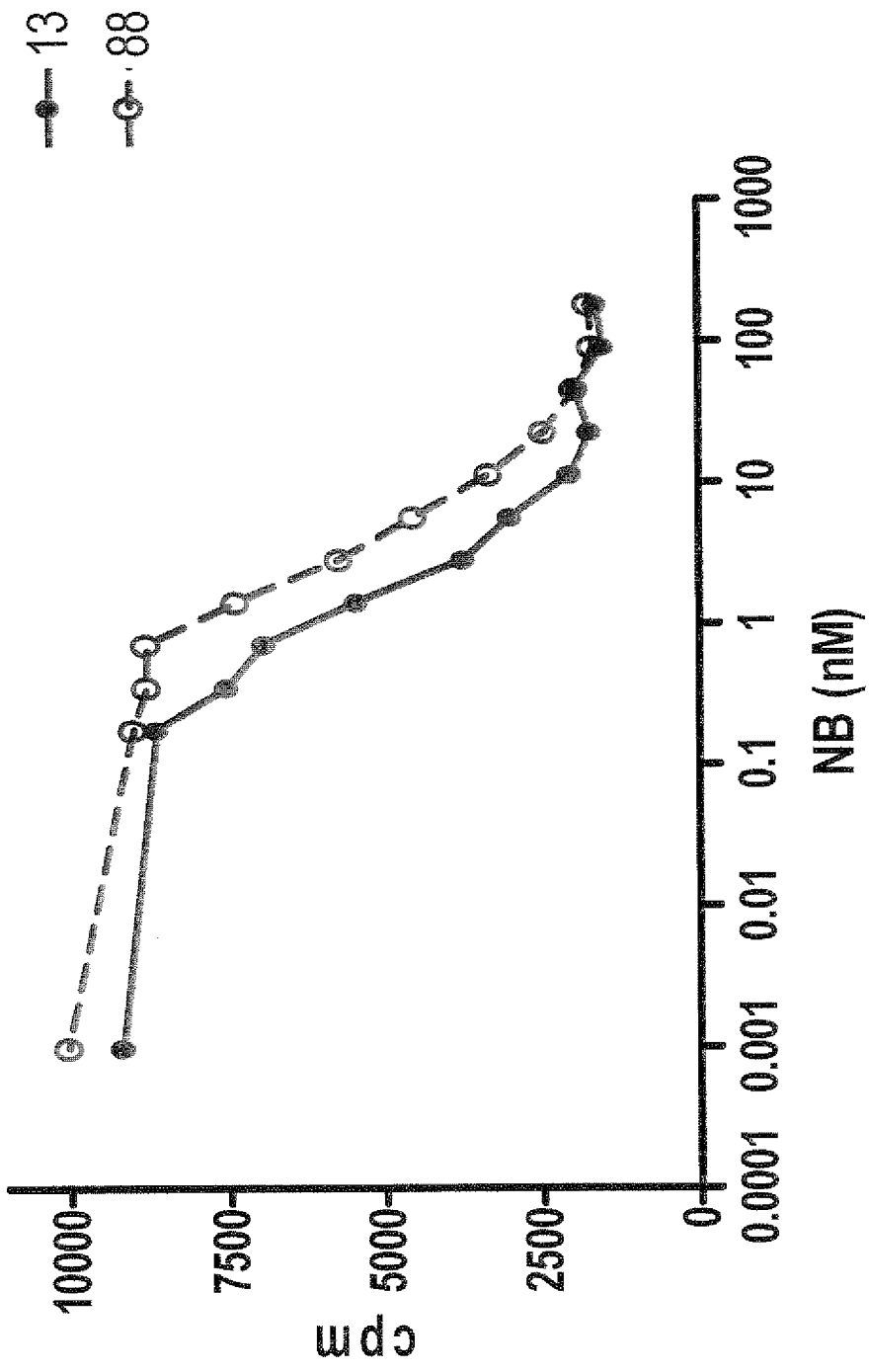

13
88
cpm
10000
7500
5000
2500
0
0.0001
0.001
0.01
0.1
1
10
100
1000
NB (nM)

Figure 22C

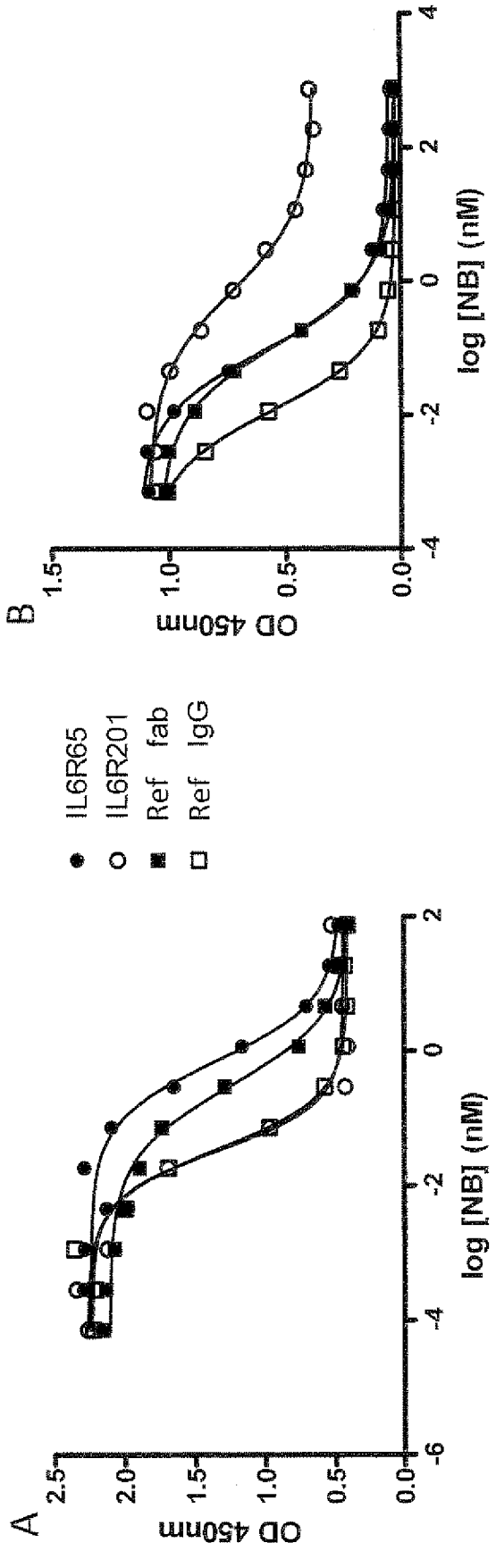


Figure 23

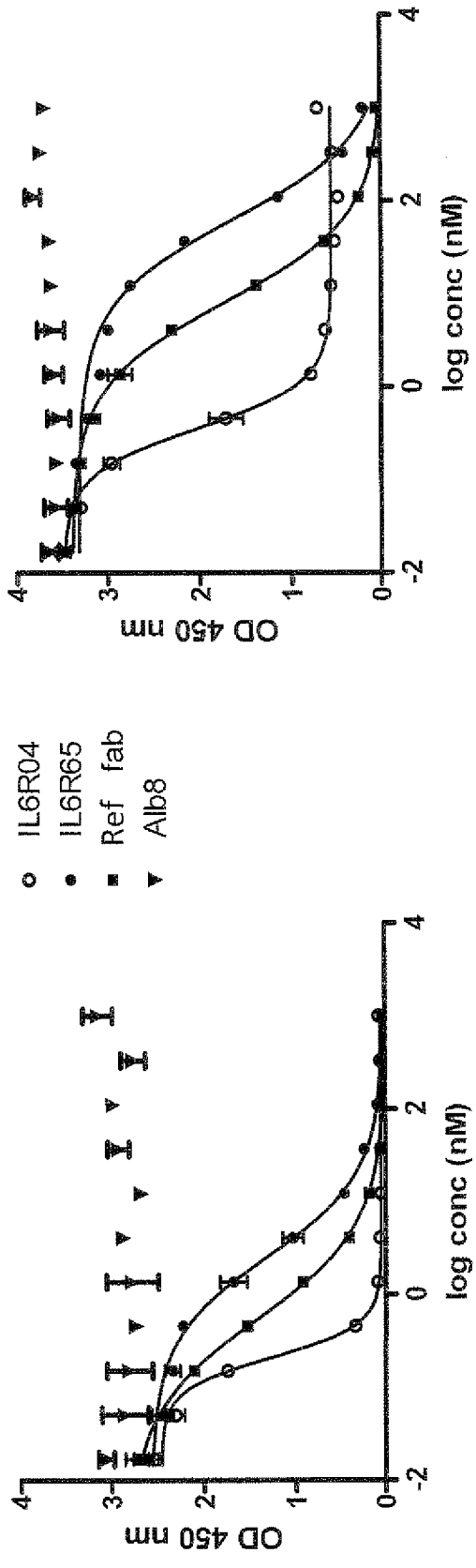


Figure 24

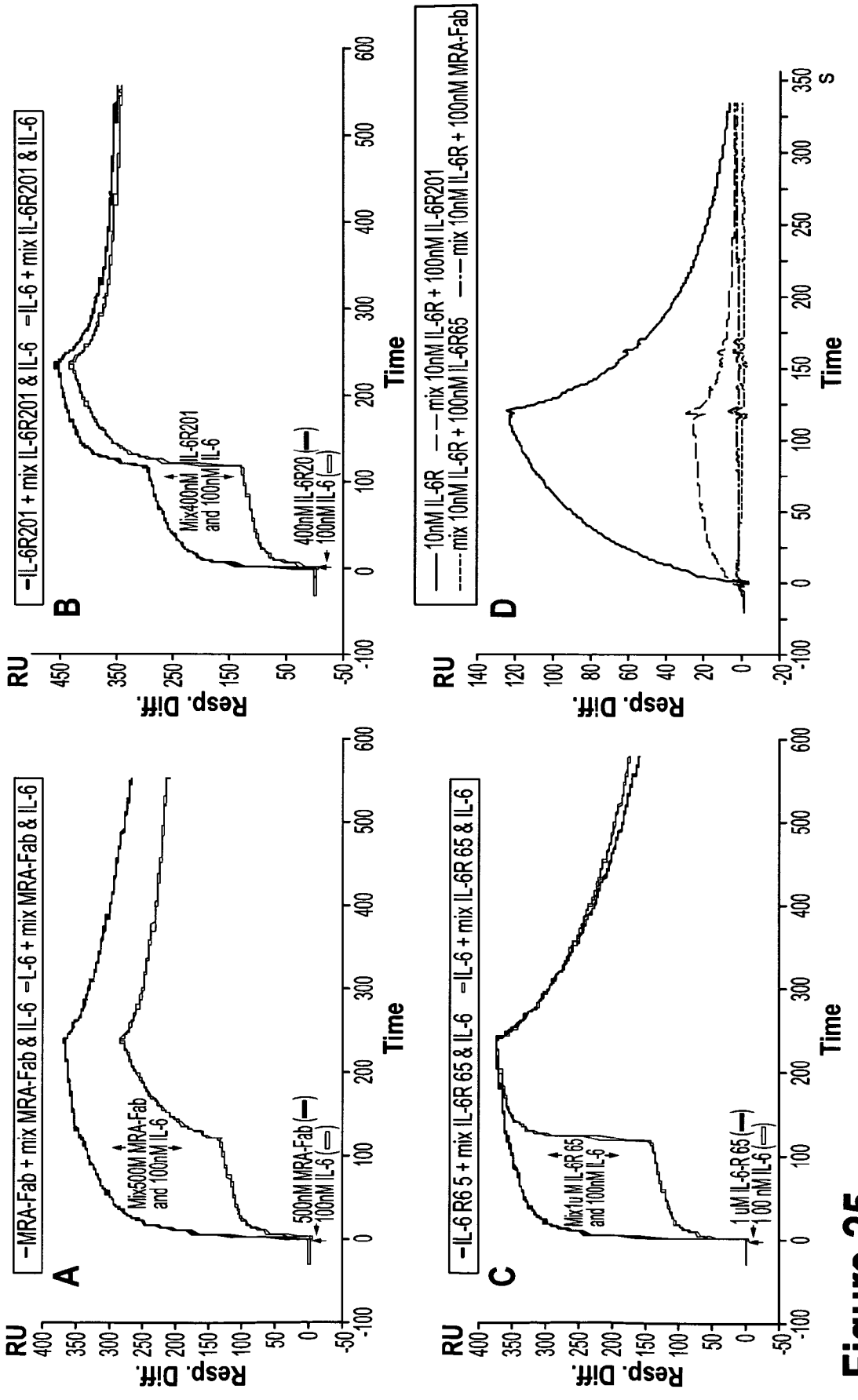

A
−MRA-Fab + mix MRA-Fab & IL-6 =L-6 + mix MRA-Fab & IL-6
Mix500M MRA-Fab and 100nM IL-6
500nM MRA-Fab (—)
100nM IL-6 (—)
B
−IL-6R201 + mix IL-6R201 & IL-6 =IL-6 + mix IL-6R201 & IL-6
Mix400nM IL-6R201 and 100nM IL-6
400nM IL-6R20 (—)
100nM IL-6 (—)
C
−IL-6 R6 5 + mix IL-6R 65 & IL-6 =IL-6 + mix IL-6R 65 & IL-6
Mix1u M IL-6R 65 and 100nM IL-6
1 uM IL-6-R 65 (—)
100 nM IL-6 (—)
D
10nM IL-6R
mix 10nM IL-6R + 100nM IL-6R201
mix 10nM IL-6R + 100nM IL-6R65
mix 10nM IL-6R + 100nM MRA-Fab
RU
Resp. Diff.
Time
s

Figure 25

```
                10        20        30        40        50        60
     ----:----|----:----|----:----|----:----|----:----|----:----|
IL6R65 EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGITSGGSTNYA
PMP7F4 ..........................TT....V.A.....................N....T..
PMP7C4 ..........................TT.RI.V.A.....................TN...S..
PMP7D6 ..........................R..V.A.....................AV.N..T.T..
PMP7G7 ..........................TT..I.I.A.....................V.T..N.T..
PMP7G8 ..........................T.RI.V.A.....................V.ND...T..

                70        80        90        100       110       120
     ----:----|----:----|----:----|----:----|----:----|----:----|-
IL6R65 DSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCAFVTTNSDYDLGRDYWGQGTLVTVSS
PMP7F4 ..........................................................
PMP7C4 ..........................................................
PMP7D6 ..........................................................
PMP7G7 ..........................................................
PMP7G8 ..........................................................
```

Figure 26

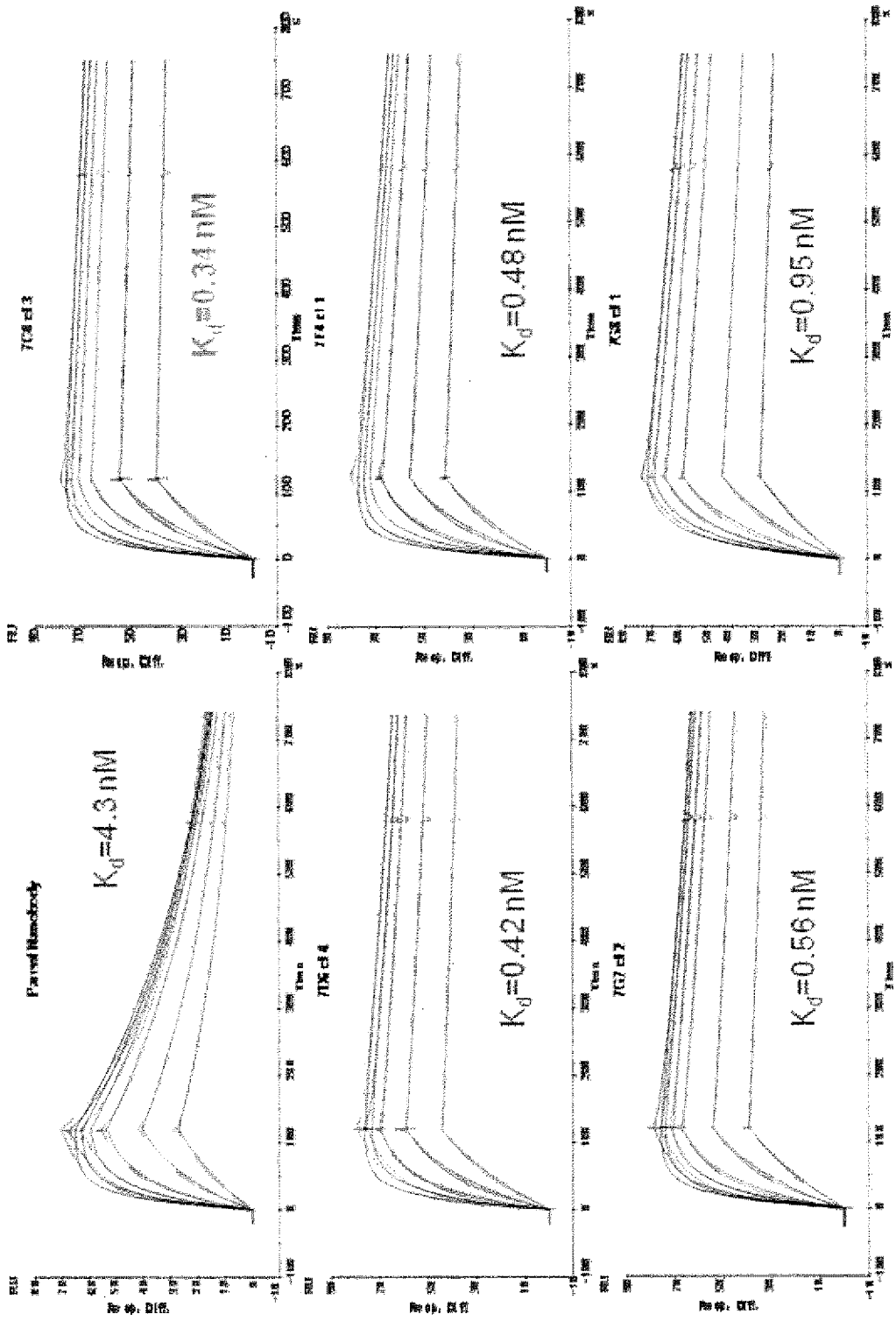

Parent Monoclonal
K_d=4.3 nM
K_d=0.34 nM
K_d=0.48 nM
K_d=0.42 nM
K_d=0.95 nM
K_d=0.56 nM

Figure 27

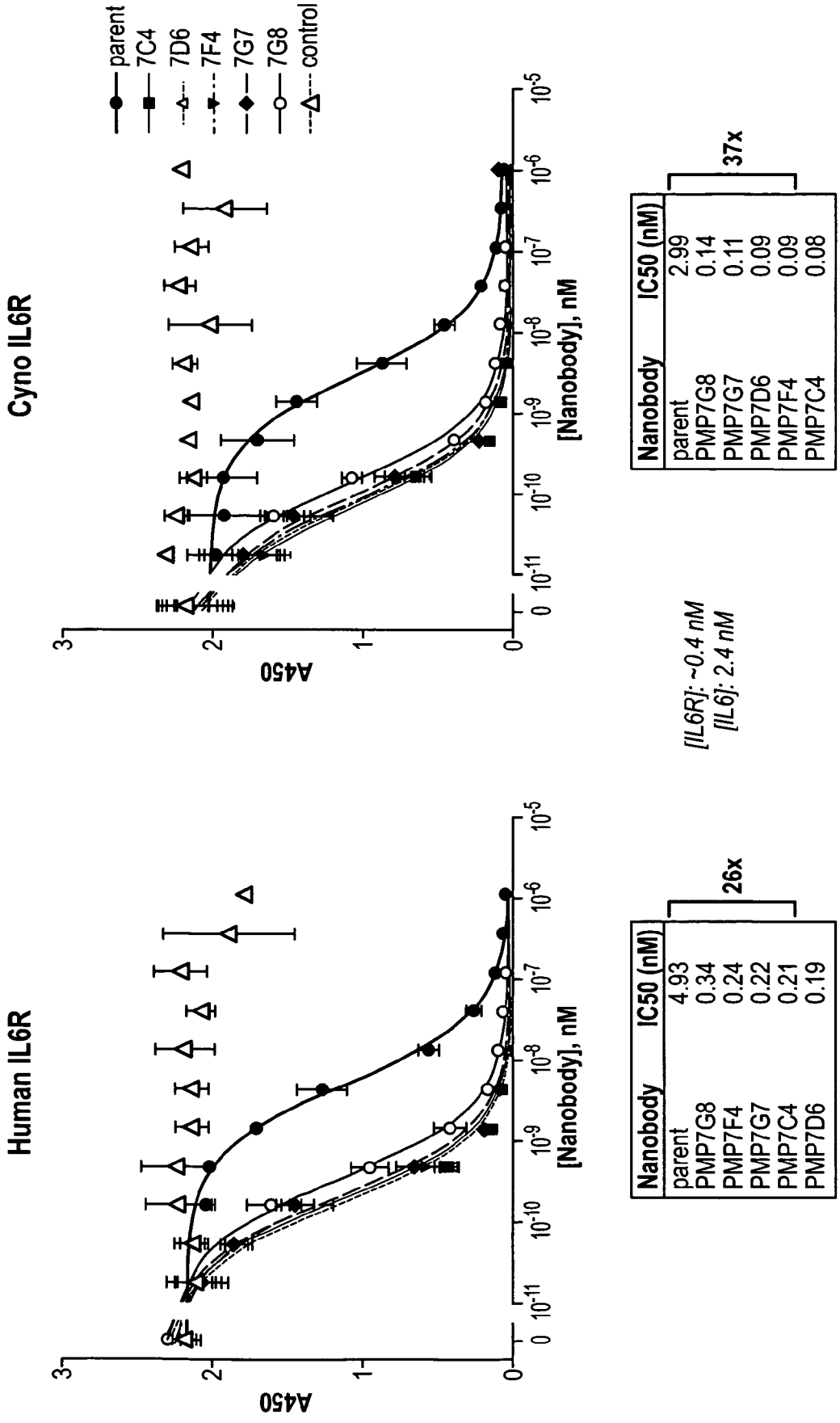
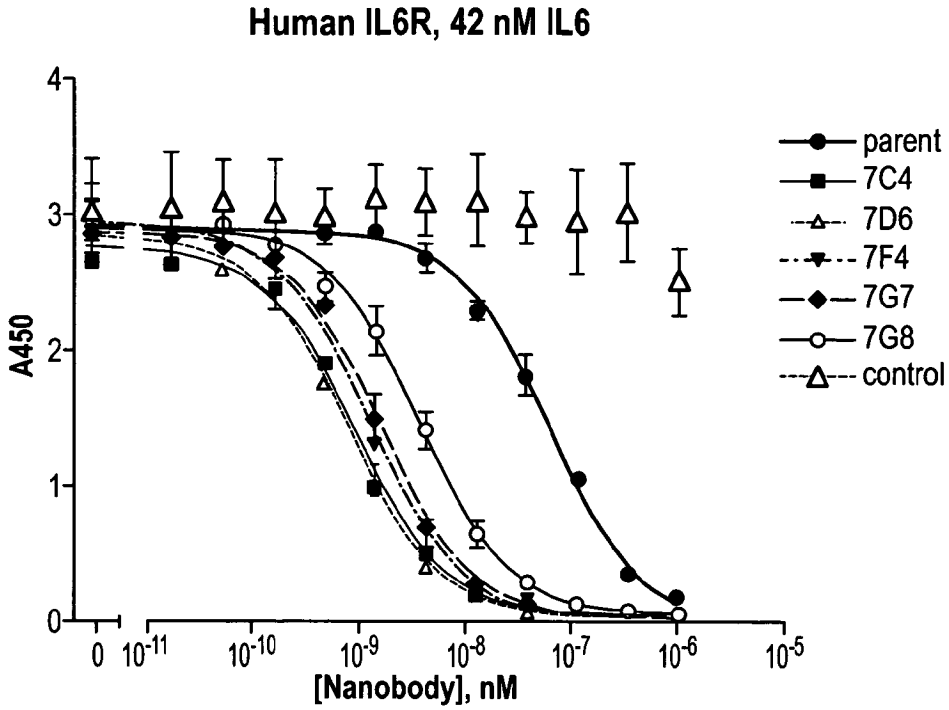

Cyno IL6R
parent
7C4
7D6
7F4
7G7
7G8
control
A450
[Nanobody], nM
Nanobody IC50 (nM)
parent 2.99
PMP7G8 0.14
PMP7G7 0.11
PMP7D6 0.09
PMP7F4 0.09
PMP7C4 0.08
37x
[IL6R]: ~0.4 nM
[IL6]: 2.4 nM
Human IL6R
A450
[Nanobody], nM
Nanobody IC50 (nM)
parent 4.93
PMP7G8 0.34
PMP7F4 0.24
PMP7G7 0.22
PMP7C4 0.21
PMP7D6 0.19
26x

Figure 28A



Nanobody	IC50 (nM)	
parent	61.5	
PMP7G8	3.5	
PMP7G7	1.5	77x
PMP7D6	0.8	
PMP7F4	1.2	
PMP7C4	0.9	

Figure 28B

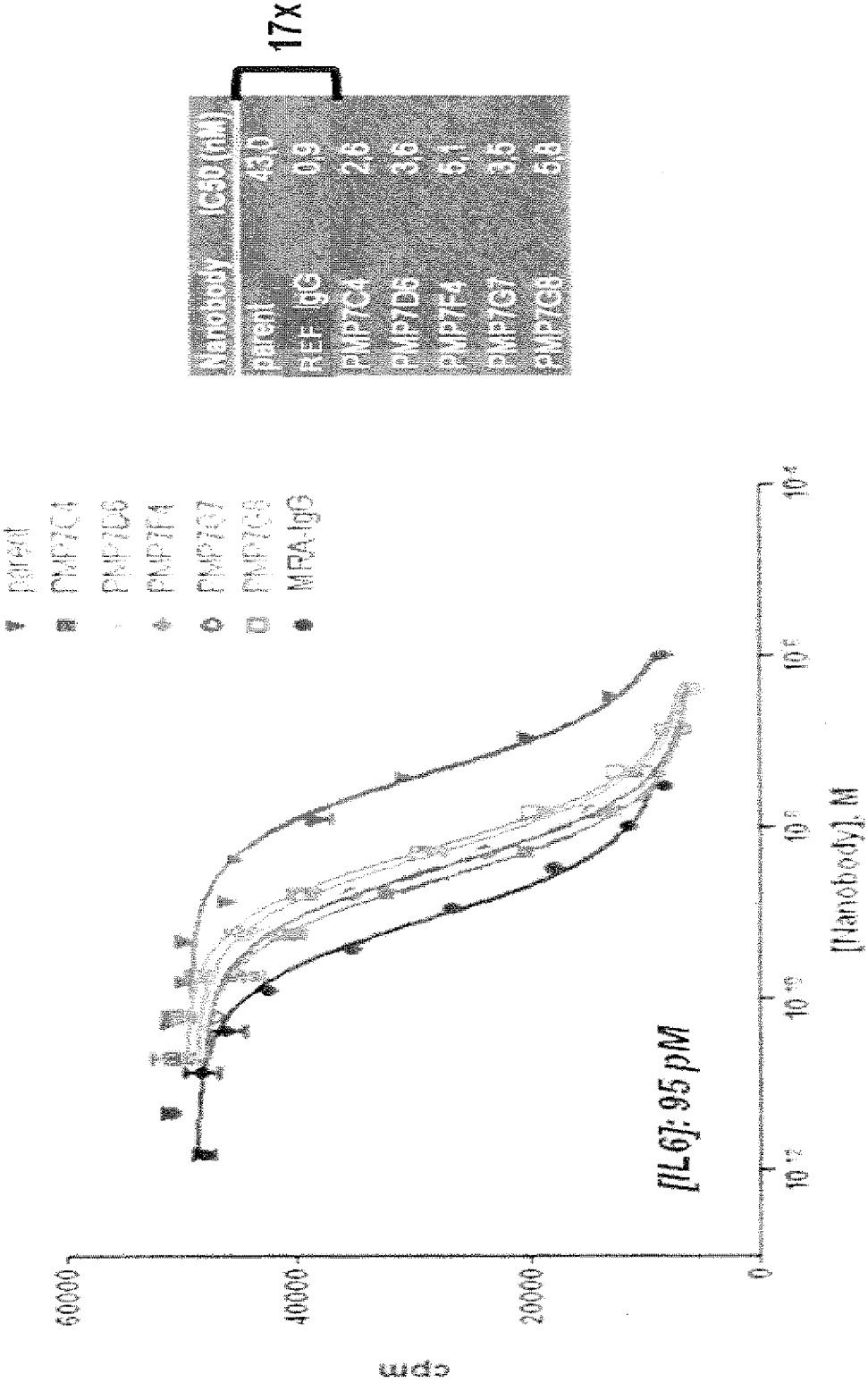

17x
Nanobody (CSP) (nM)
Parent 4.80
hEF-dp6 6.9
pNP7C4 2.5
pNP7D6 3.6
pNP7F4 6.4
pNP7G7 5.5
pNP7G8 5.8
parent
pNP7C4
pNP7D6
pNP7F4
pNP7G7
pNP7G8
MPA-IgG
cpm
60000
40000
20000
0
10⁻¹²
10⁻⁹
10⁻⁶
10⁻³
10⁰
[Nanobody], M
IL6: 95 pM

Figure 29

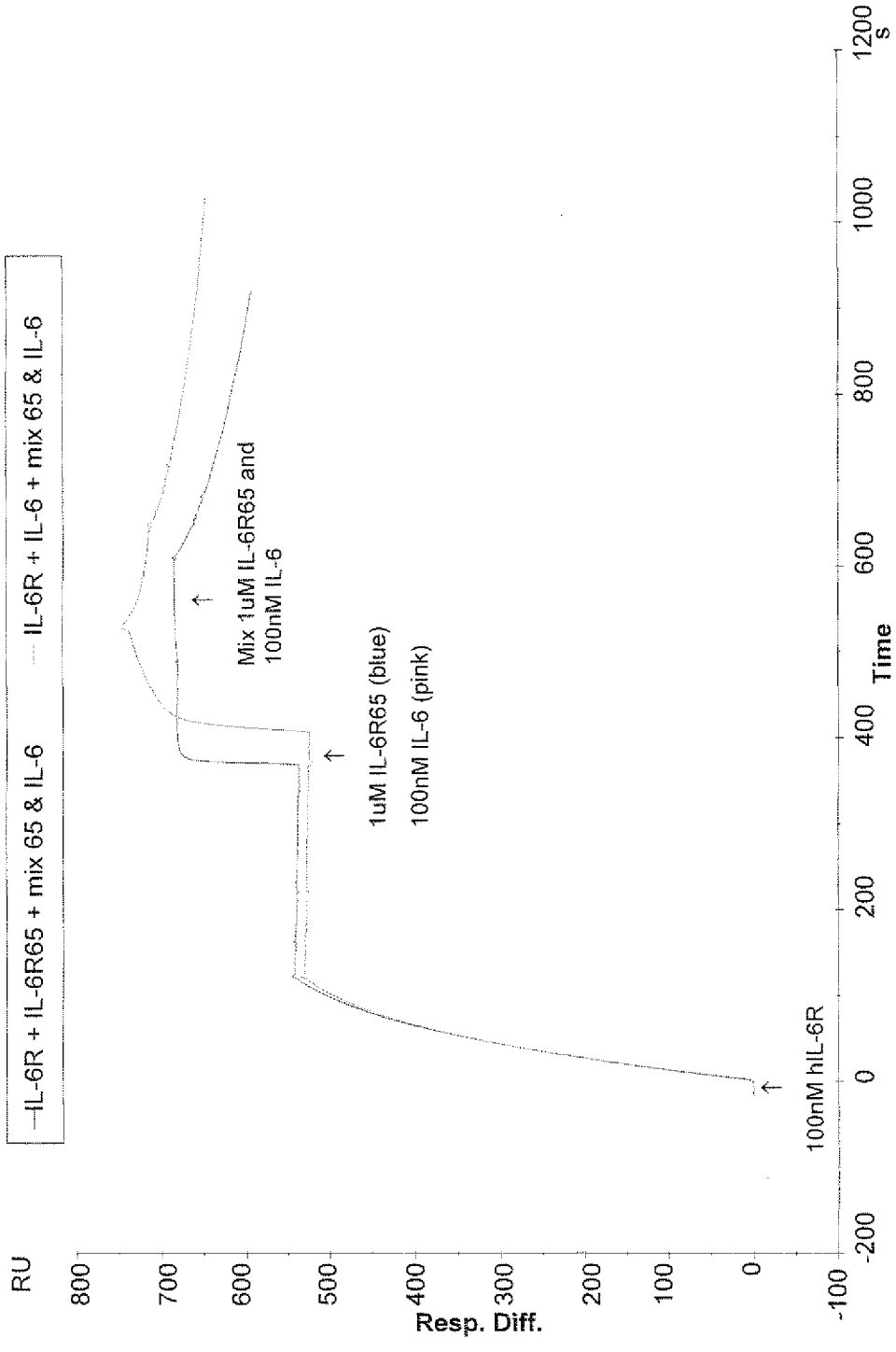

RU
800
700
600
500
400
300
200
100
0
-100
Resp. Diff.
-200
0
200
400
600
800
1000
1200
s
Time
IL-6R + IL-6R65 + mix 65 & IL-6
IL-6R + IL-6 + mix 65 & IL-6
100nM hIL-6R
1uM IL-6R65 (blue)
100nM IL-6 (pink)
Mix 1uM IL-6R65 and
100nM IL-6

Figure 30A

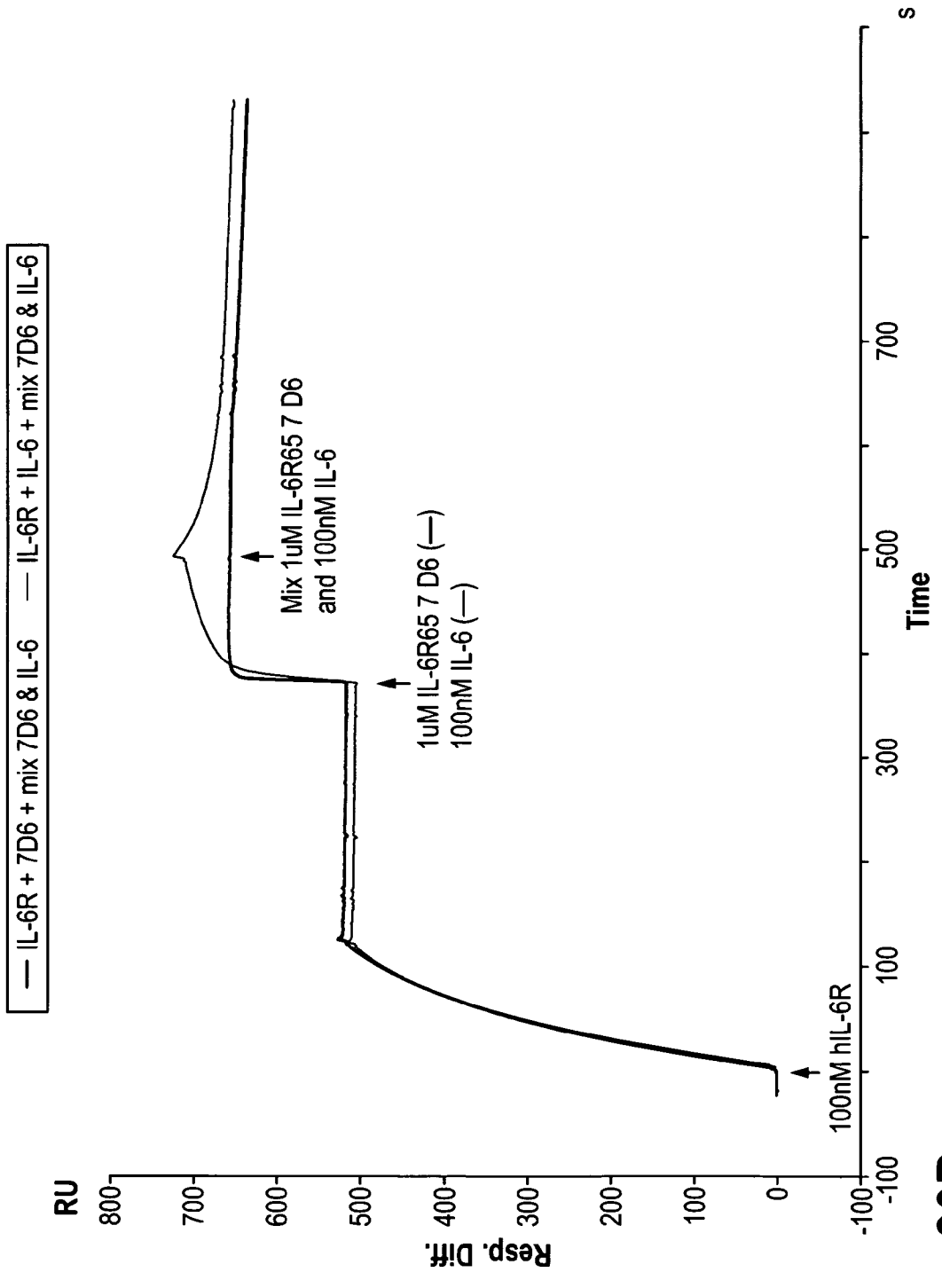

— IL-6R + 7D6 + mix 7D6 & IL-6
— IL-6R + IL-6 + mix 7D6 & IL-6
Mix 1uM IL-6R65 7 D6
and 100nM IL-6
1uM IL-6R65 7 D6 (—)
100nM IL-6 (—)
100nM hIL-6R
RU
Resp. Diff.
Time
s
800
700
600
500
400
300
200
100
0
-100
-100
100
300
500
700

Figure 30B

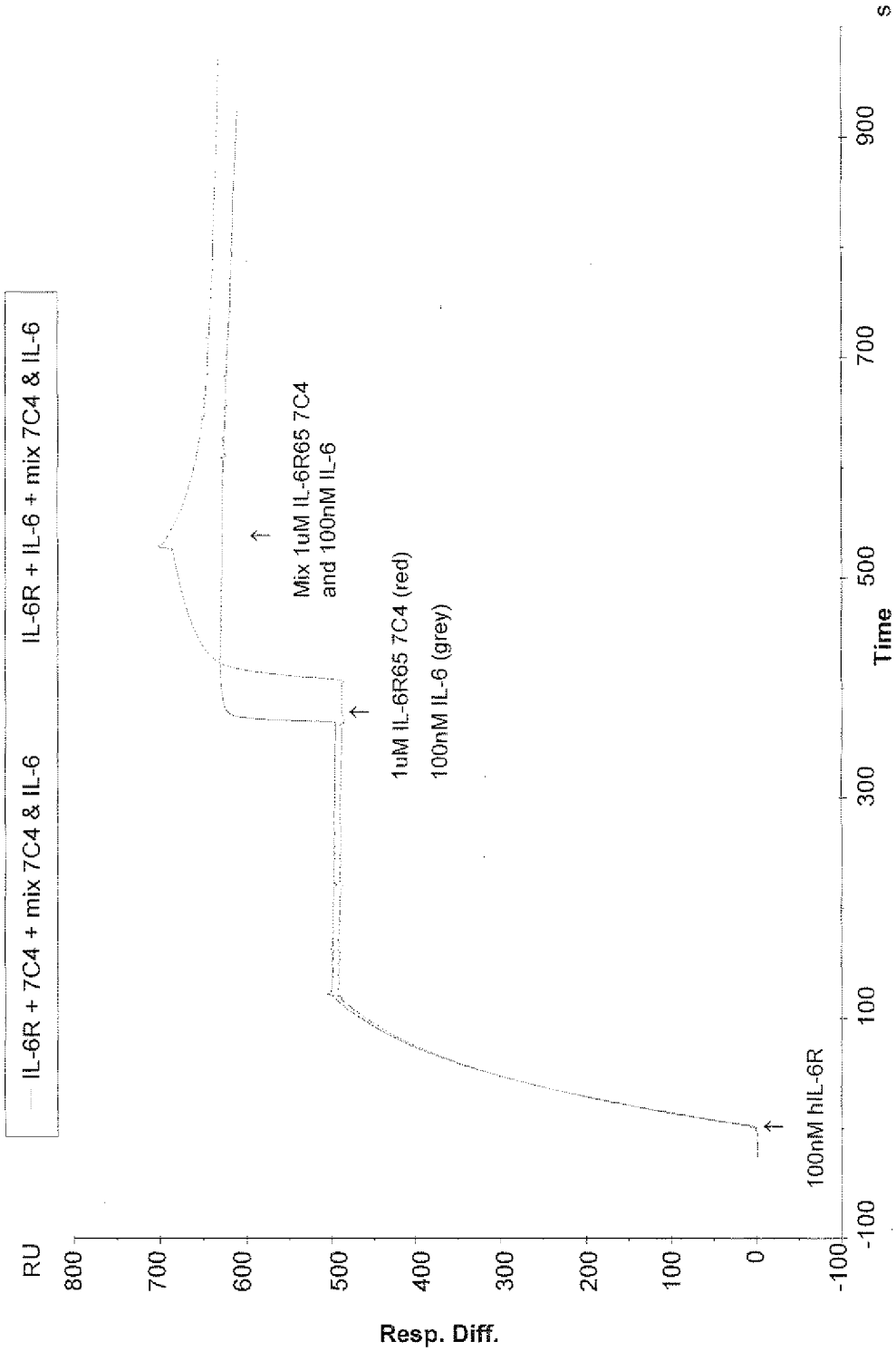

IL-6R + 7C4 + mix 7C4 & IL-6
IL-6R + IL-6 + mix 7C4 & IL-6
RU
800
700
600
500
400
300
200
100
0
-100
Resp. Diff.
100nM hIL-6R
1uM IL-6R65 7C4 (red)
100nM IL-6 (grey)
Mix 1uM IL-6R65 7C4
and 100nM IL-6
-100
100
300
500
700
900
Time
s

Figure 30C

```
IL6R65    EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGITSGGSTNYADSVKG

PMP20F6   ..............................V..I.V.A.....................V.....S.....

PMP20A11  ..............................V..I.V.A.....................S.....

PMP20E10  ..............................V..I.V.A.....................V.....S.....

PMP21A10  ..............................I.V.A.....................VT....S.....

PMP21D11  ..............................V..I.V.A.....................VT....S.....


IL6R65    RFTISRDNAKNTLYLQMNSLRPEDTAVYYCAFVTTNSDYDLGRDYWGQGTLVTVSS

PMP20F6   ..............................I.....................R.....

PMP20A11  ..............................I..E.....................R.....

PMP20E10  ..............................I..E.....................R.....

PMP21A10  ..............................I..E.....................R.....

PMP21D11  ..............................T..E.....................R.....
```

Figure 31

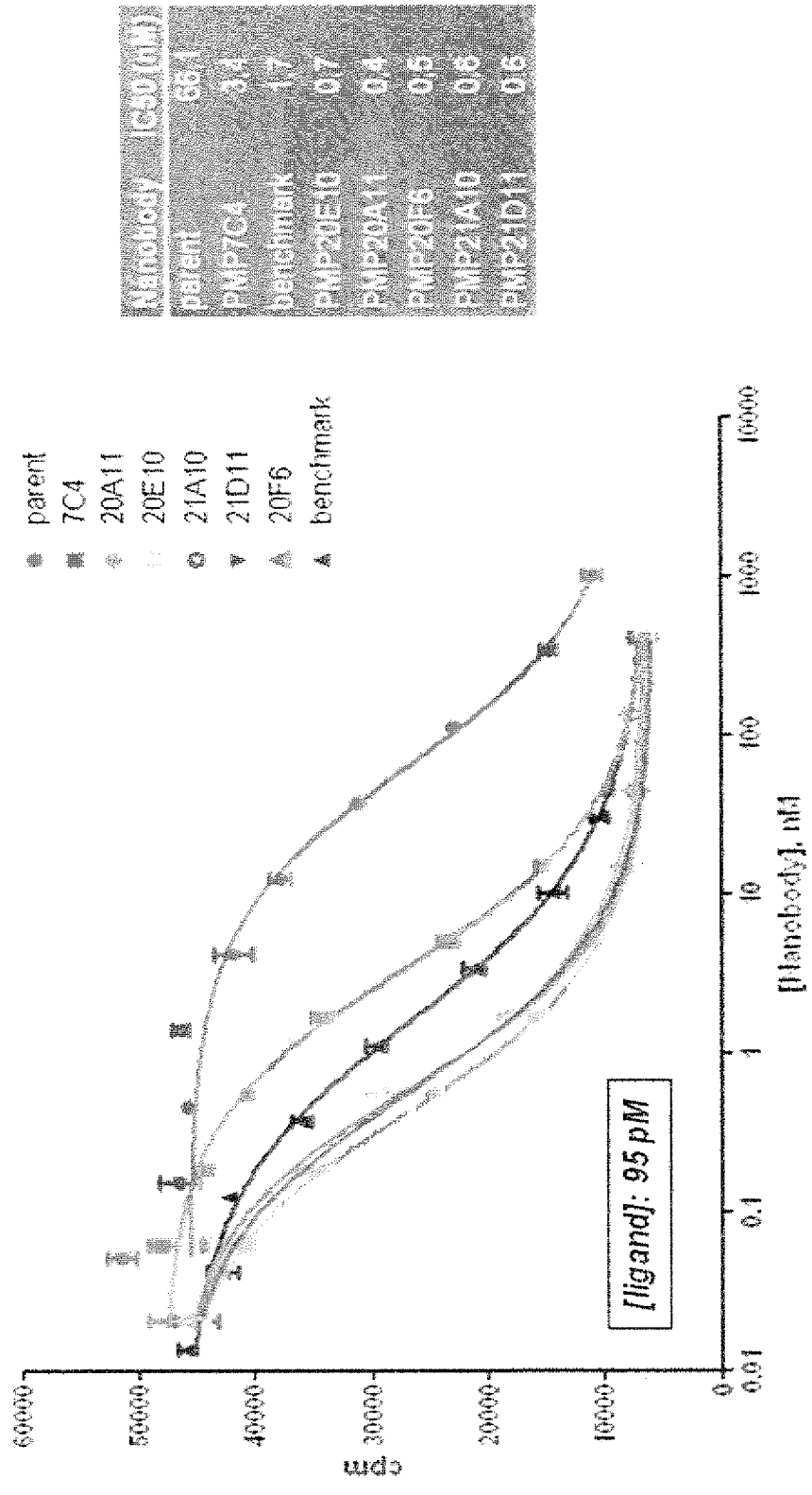

Antibody IC50 (nM)
parent 68.1
RMP7C4 3.4
benchmark 1.7
RMP20E10 0.7
RMP20A11 0.4
RMP20F6 0.5
RMP21A10 0.8
RMP21D11 0.6
parent
7C4
20A11
20E10
21A10
21D11
20F6
benchmark
[ligand]: 95 pM
cpm
[Hanobody], nM

Figure 32

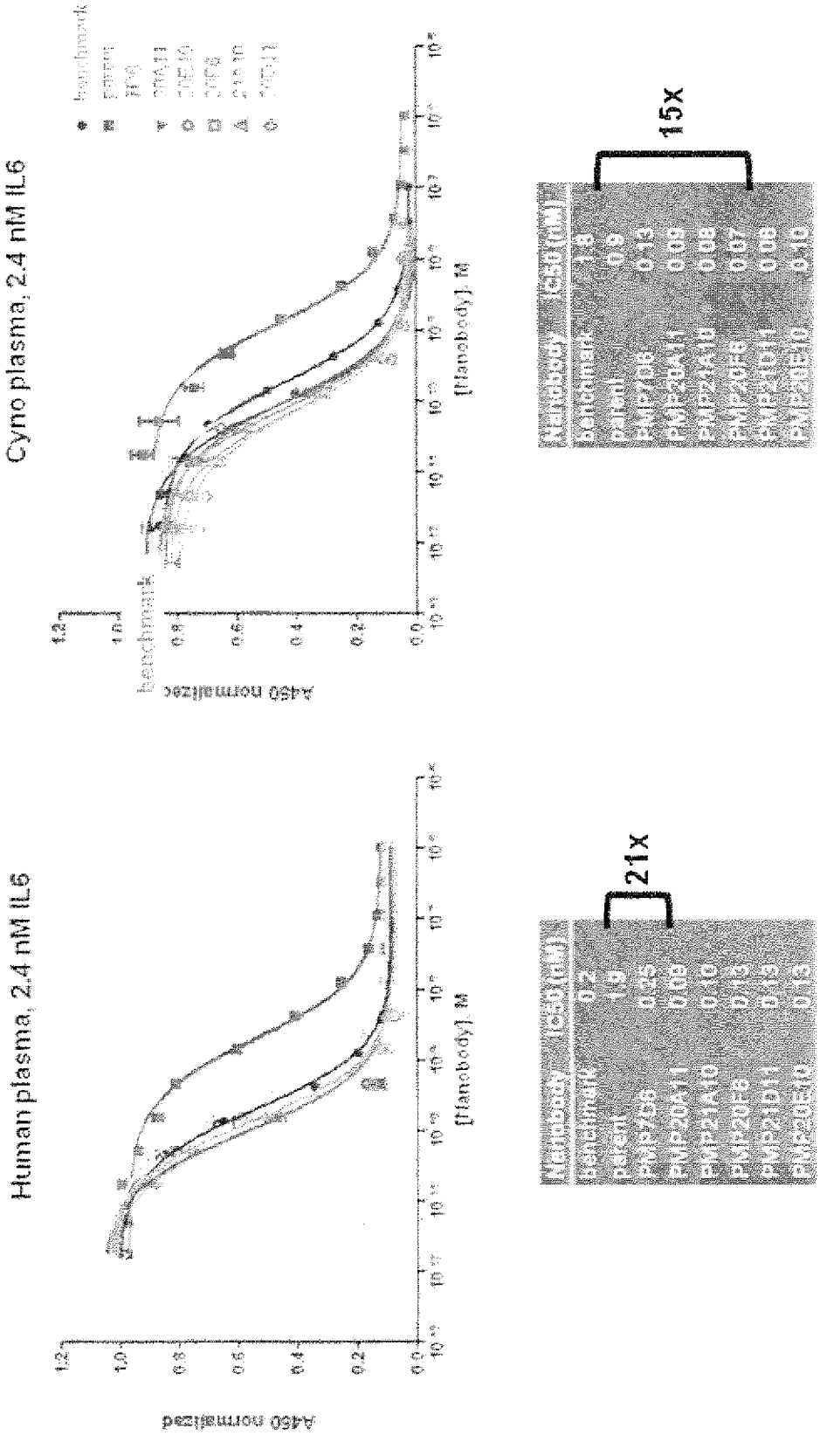
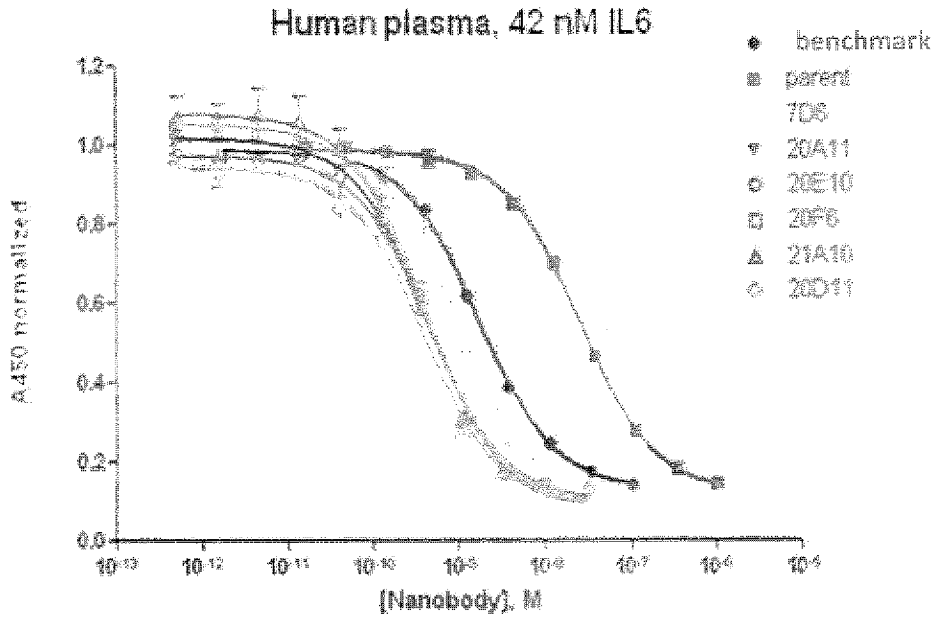

Cyno plasma, 2.4 nM IL6
Human plasma, 2.4 nM IL5
benchmark
[Nanobody] M
A450 normalized
15x
21x

Figure 33A



Nanobody	IC50 (nM)
benchmark	1.7
parent	24.3
PMP7D5	0.95
PMP20A11	0.44
PMP21A10	0.40
PMP20F6	0.44
PMP21D11	0.39
PMP20E10	0.47

62x

Figure 33B

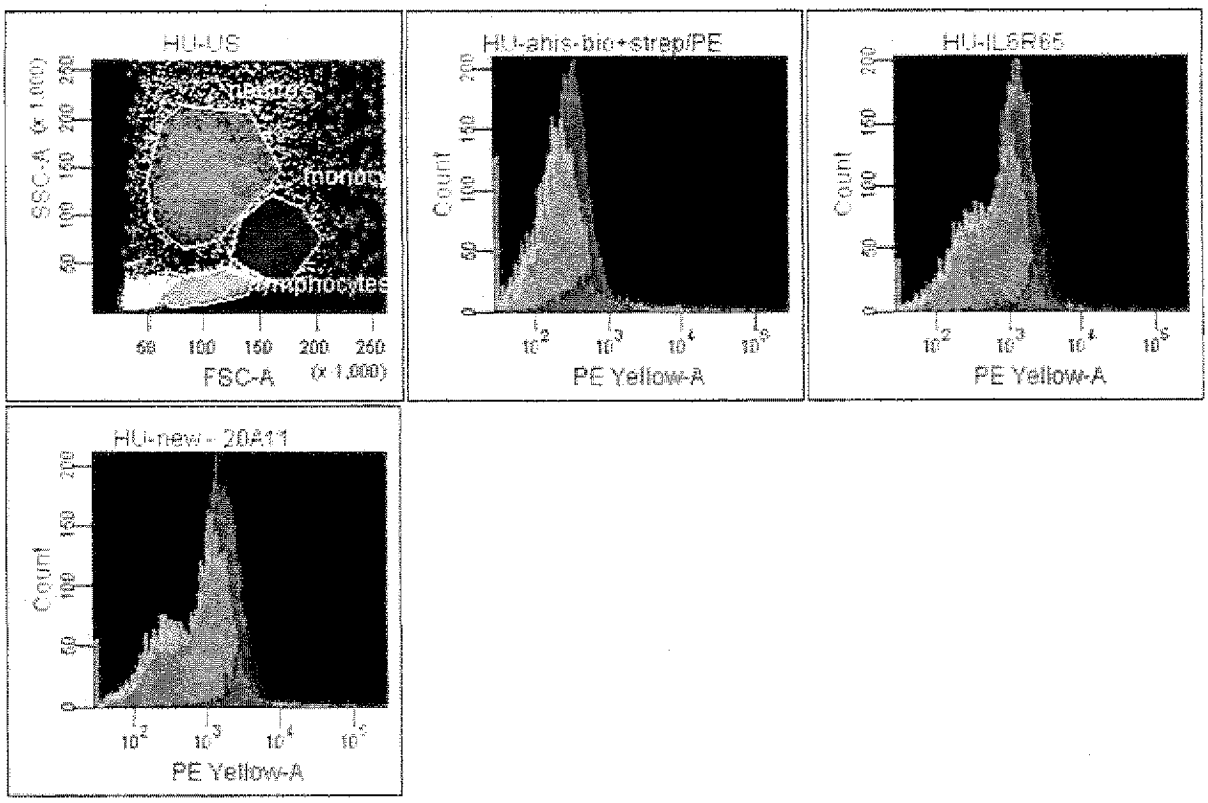

HU-US
SSC-A (x 1,000)
FSC-A (x 1,000)
neutrophils
monocytes
lymphocytes
HU-anti-bio+strep/PE
HU-ILSR65
HU-new - 20A11
Count
PE Yellow-A

Figure 34

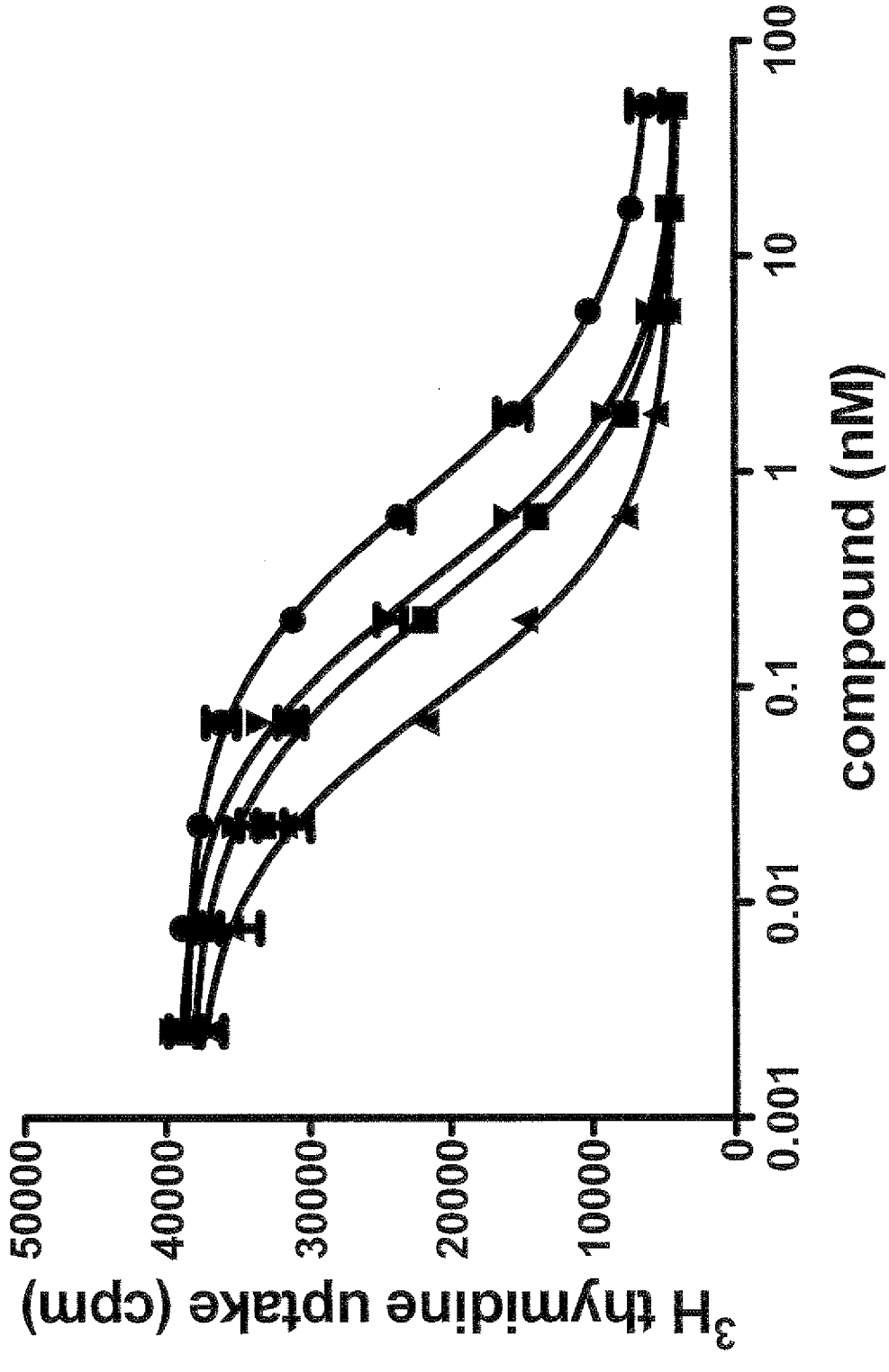

^{3}H thymidine uptake (cpm)
50000
40000
30000
20000
10000
0
0.001
0.01
0.1
1
10
100
compound (nM)

Figure 35

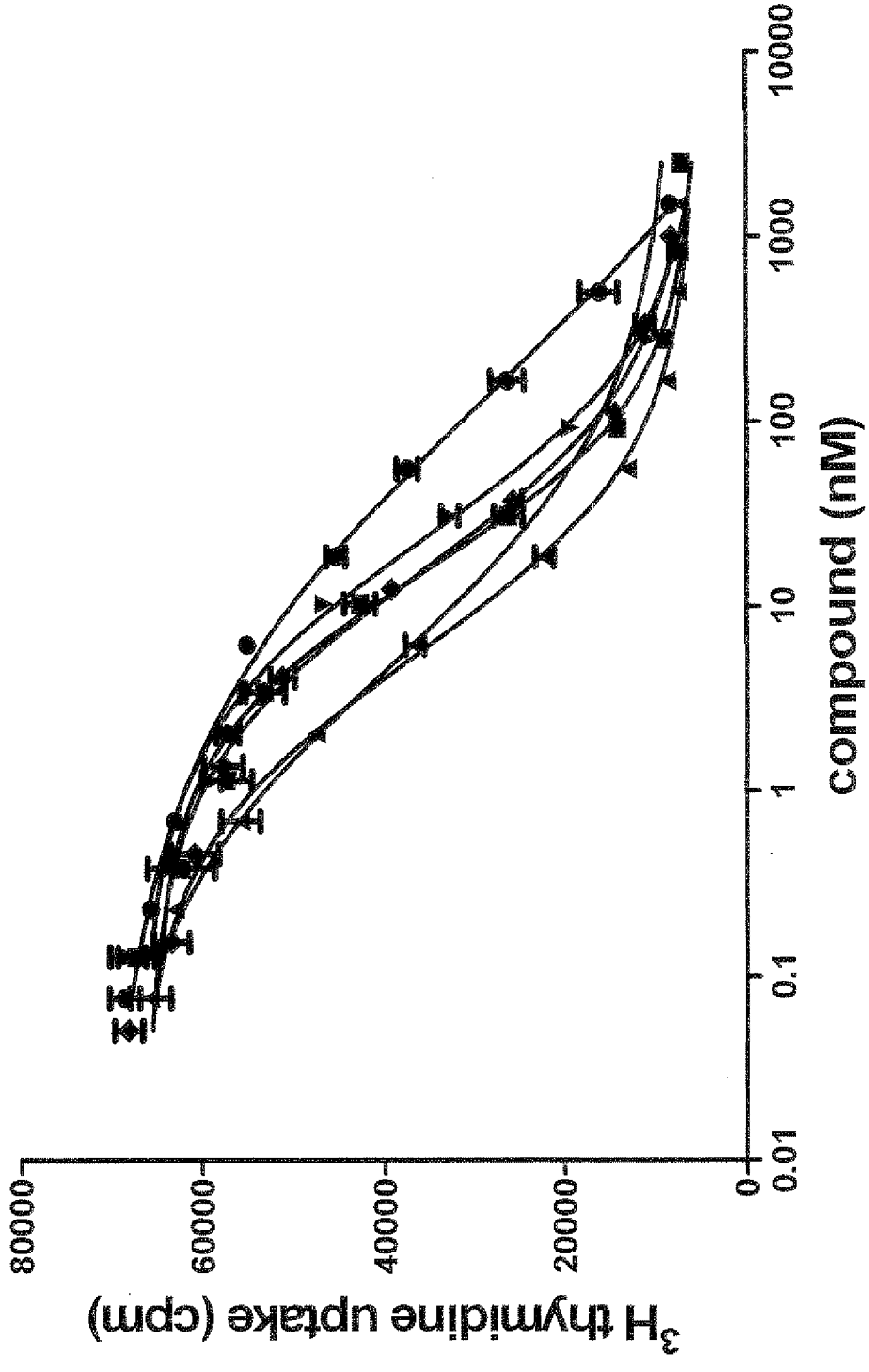

80000
60000
40000
20000
0
^{3}H thymidine uptake (cpm)
0.01
0.1
1
10
100
1000
10000
compound (nM)

Figure 36

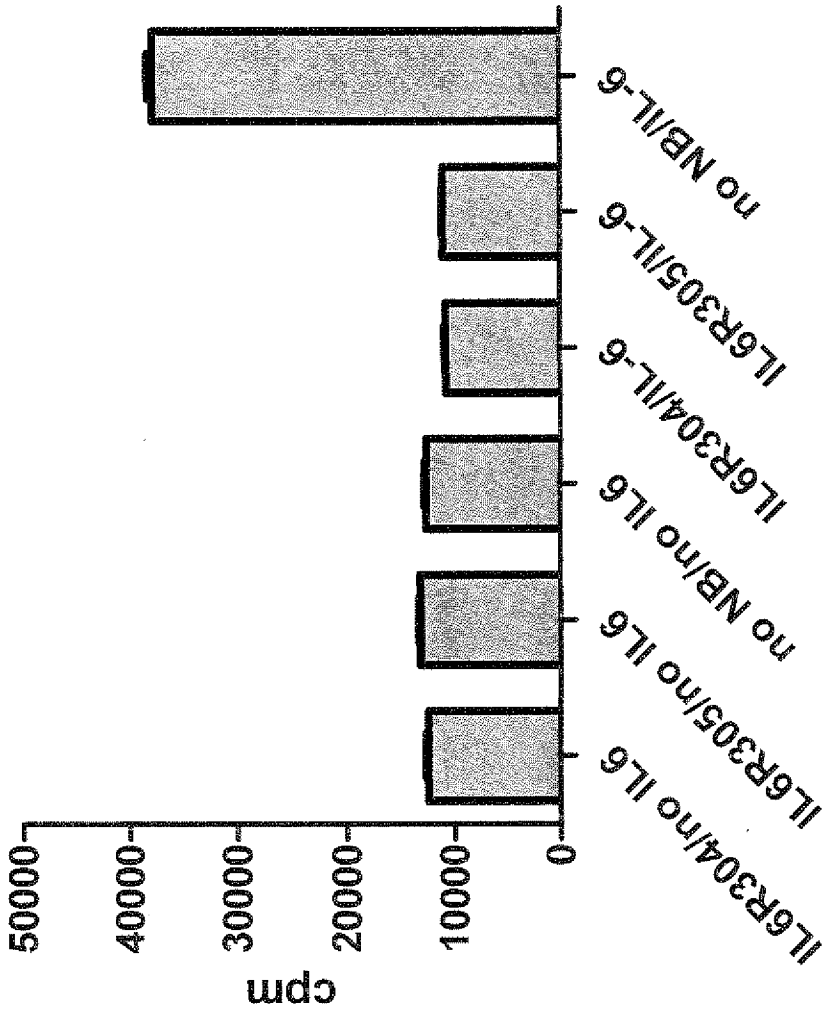

cpm
50000
40000
30000
20000
10000
0
IL6R304/no IL6
IL6R305/no IL6
no NB/no IL6
IL6R304/IL-6
IL6R305/IL-6
no NB/IL-6

Figure 37

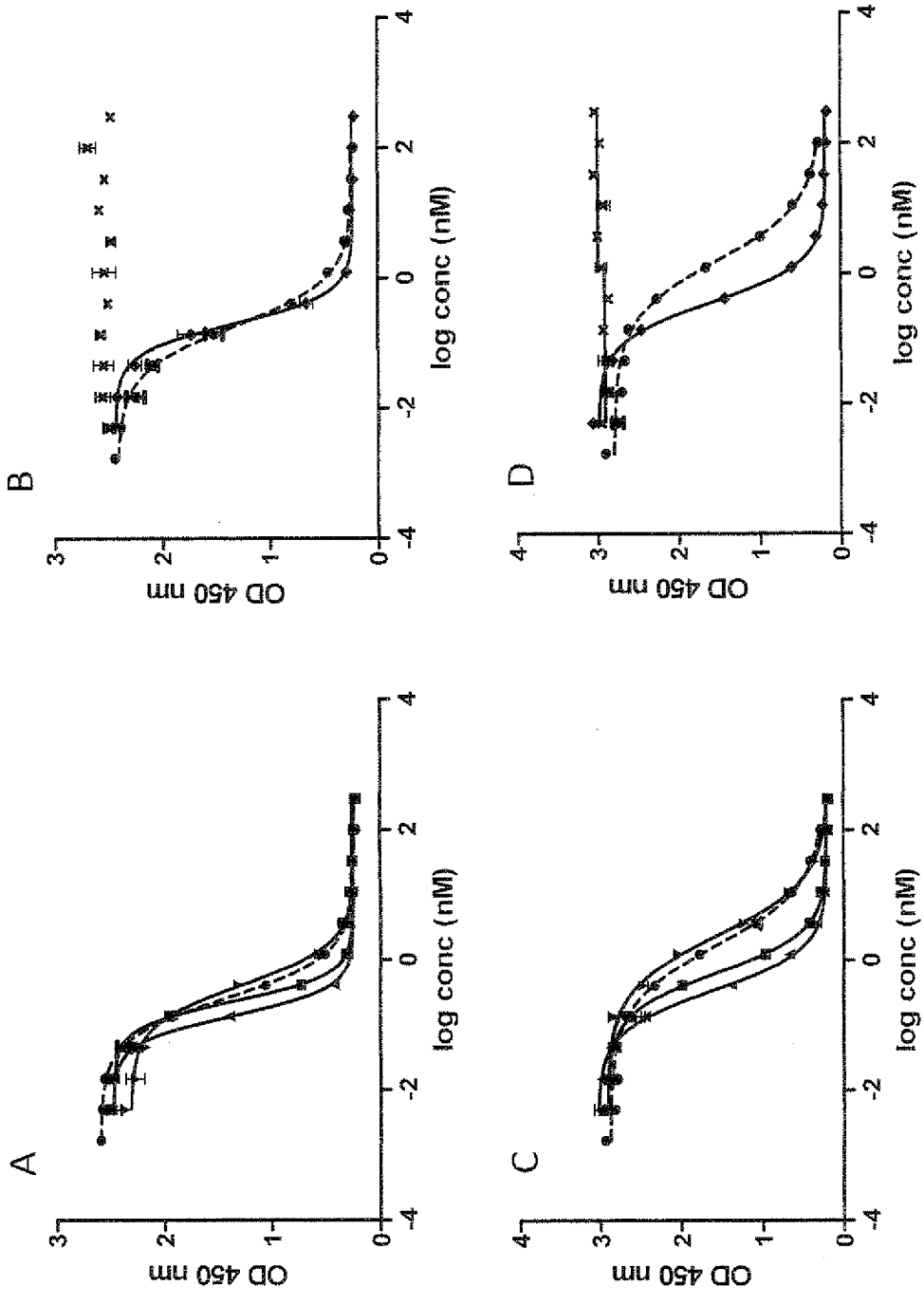
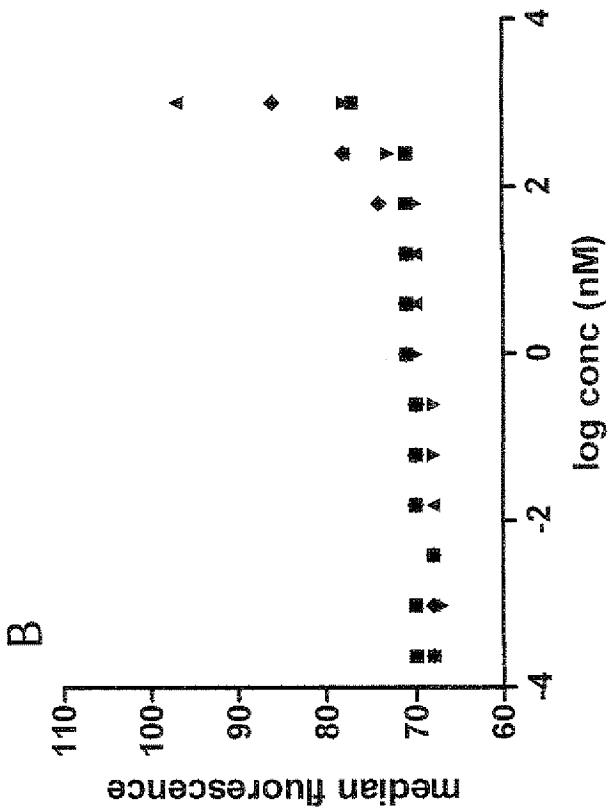


Figure 38


B
median fluorescence
110
100
90
80
70
60
-4
-2
0
2
4
log conc (nM)

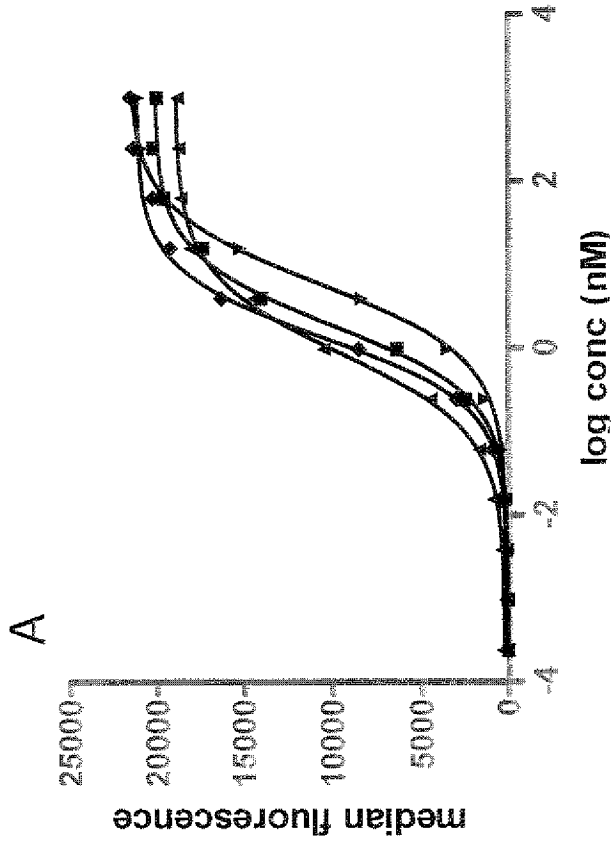

A
median fluorescence
25000
20000
15000
10000
5000
0
-4
-2
0
2
4
log conc (nM)

Figure 39

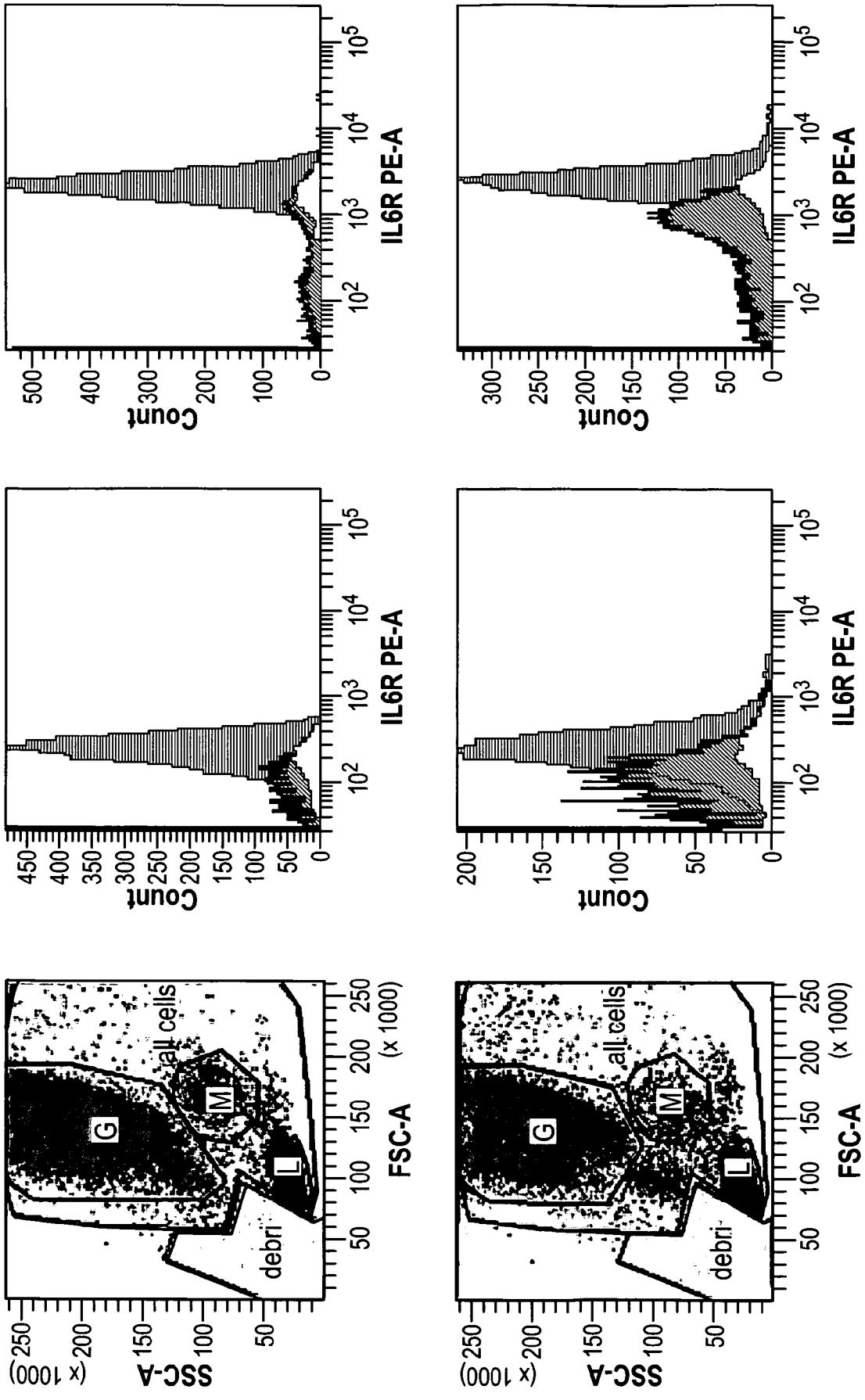


Figure 40

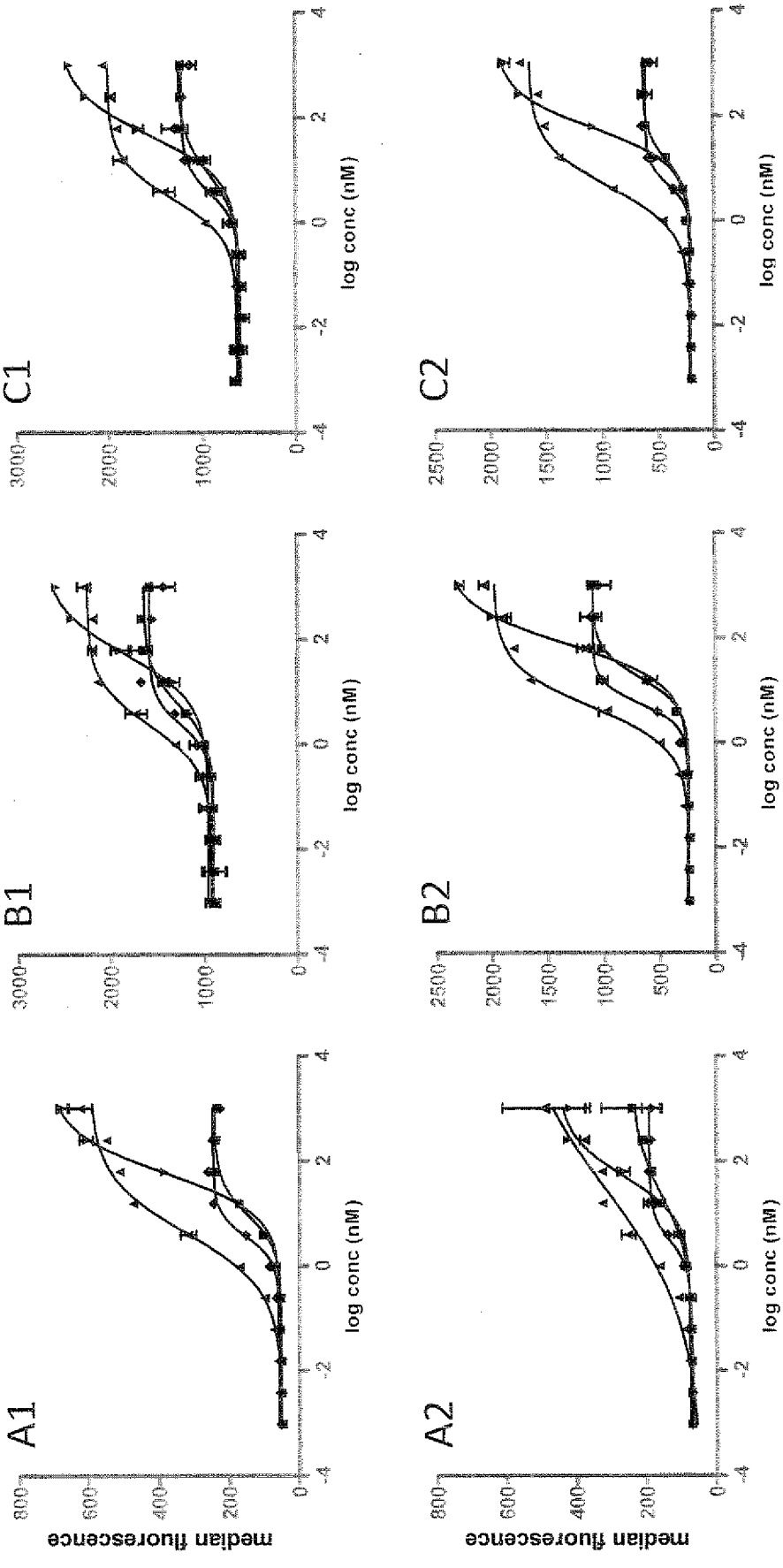


Figure 41

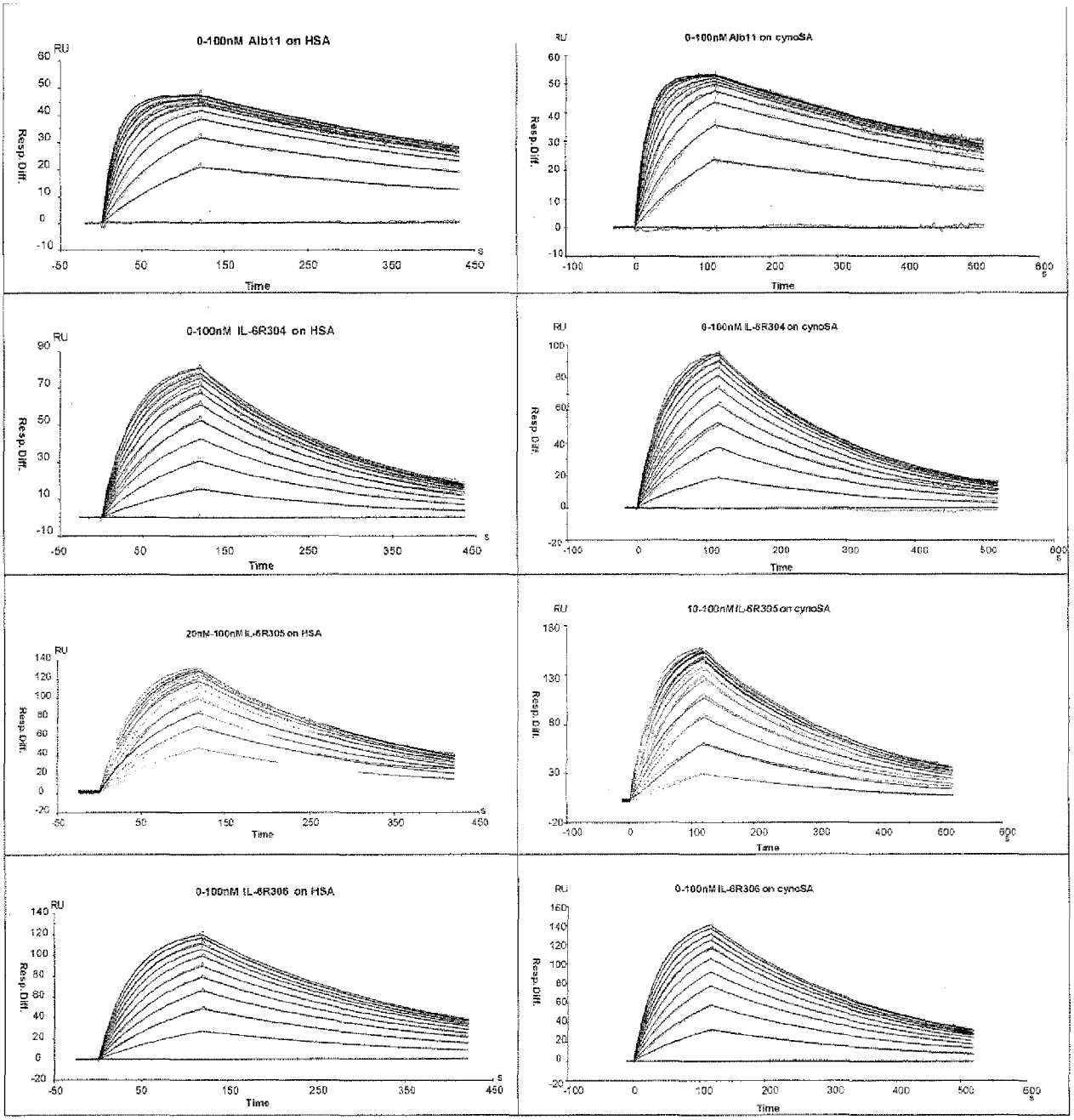

0-100nM Alb11 on HSA
0-100nM Alb11 on cynoSA
0-100nM IL-6R304 on HSA
0-100nM IL-6R304 on cynoSA
20nM-100nM IL-6R305 on HSA
10-100nM IL-6R305 on cynoSA
0-100nM IL-6R306 on HSA
0-100nM IL-6R306 on cynoSA
RU
Resp. Diff.
Time
s

Figure 42

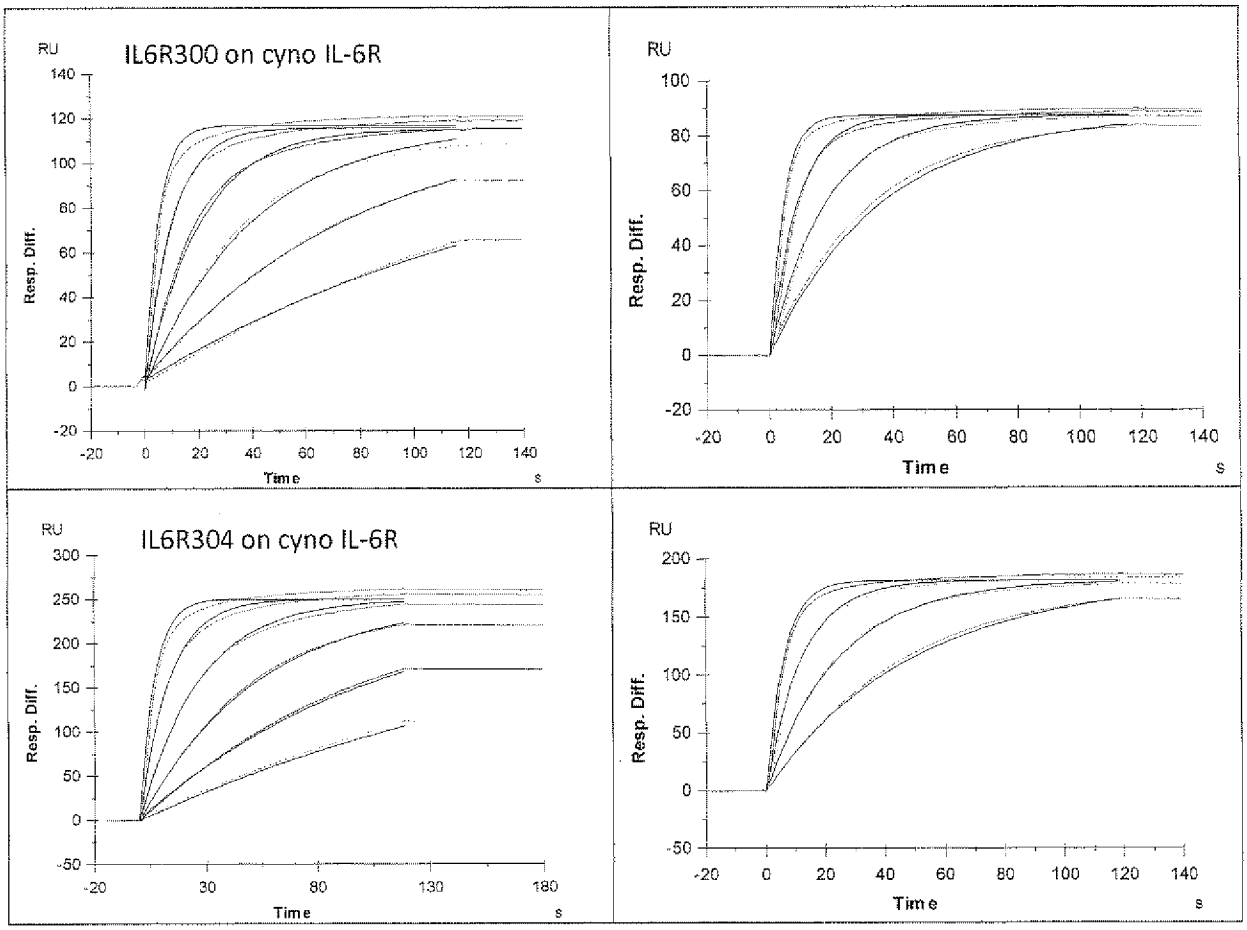

IL6R300 on cyno IL-6R
RU
Resp. Diff.
Time
s
IL6R304 on cyno IL-6R
RU
Resp. Diff.
Time
s

Figure 43

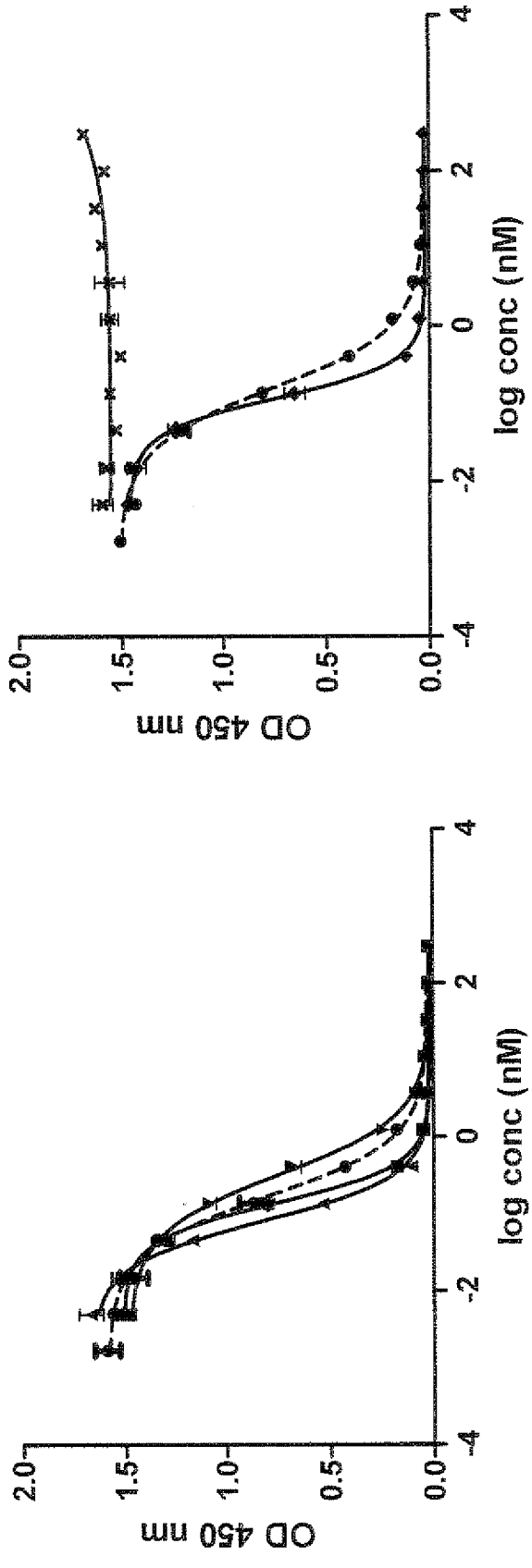

OD 450 nm
2.0
1.5
1.0
0.5
0.0
-4
-2
0
2
4
log conc (nM)
OD 450 nm
2.0
1.5
1.0
0.5
0.0
-4
-2
0
2
4
log conc (nM)

Figure 44

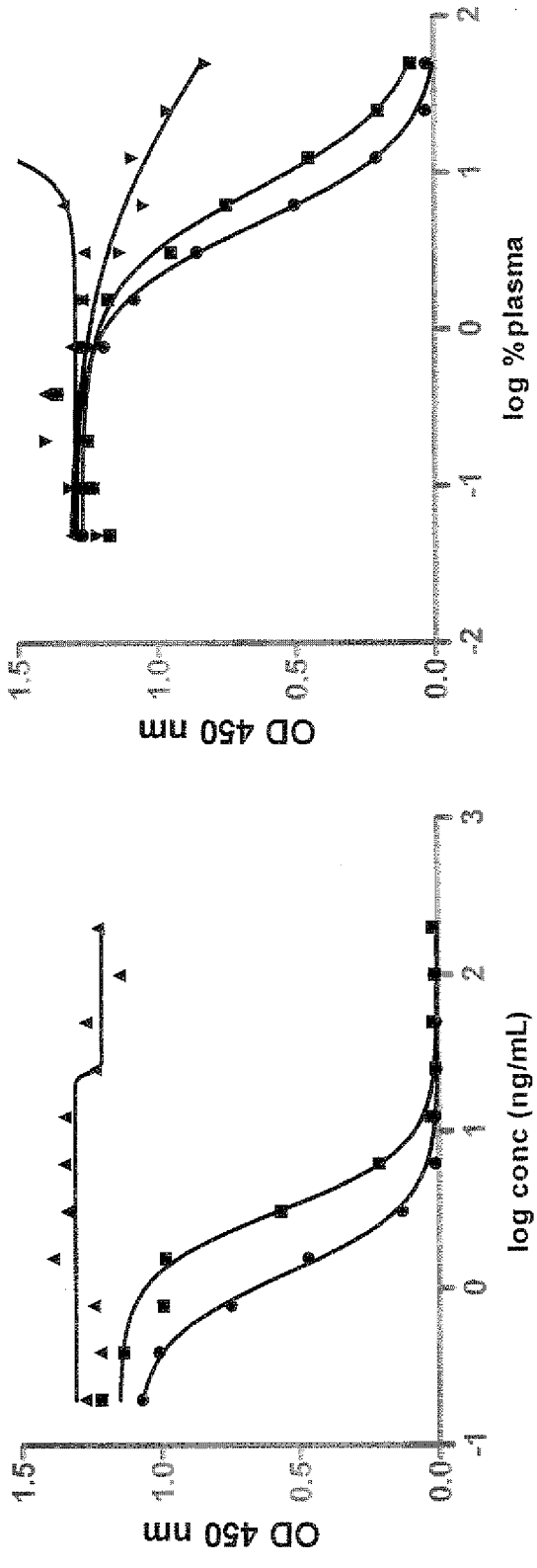

OD 450 nm
1.5
1.0
0.5
0.0
-2
-1
0
1
2
log % plasma
OD 450 nm
1.5
1.0
0.5
0.0
-1
0
1
2
3
log conc (ng/mL)

Figure 45

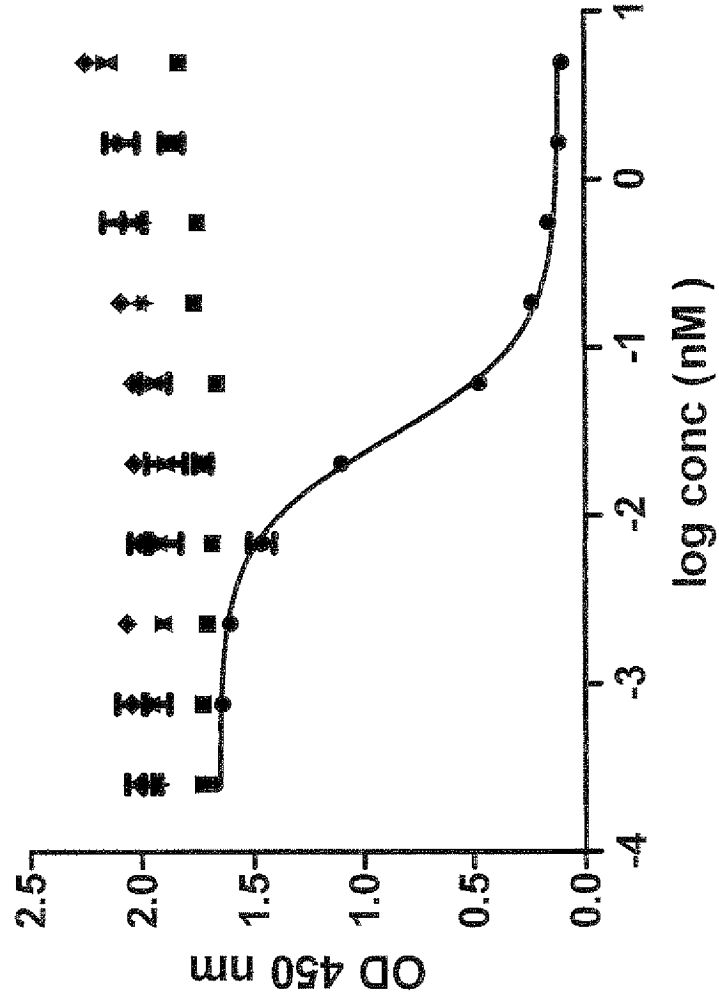


Figure 46

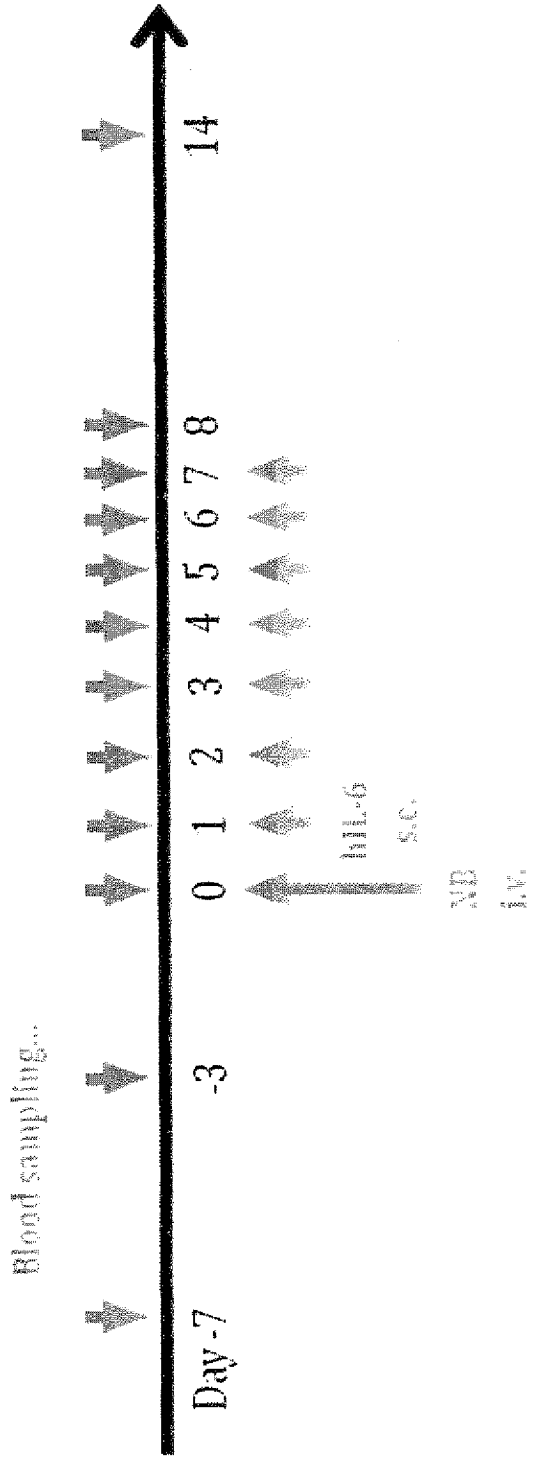
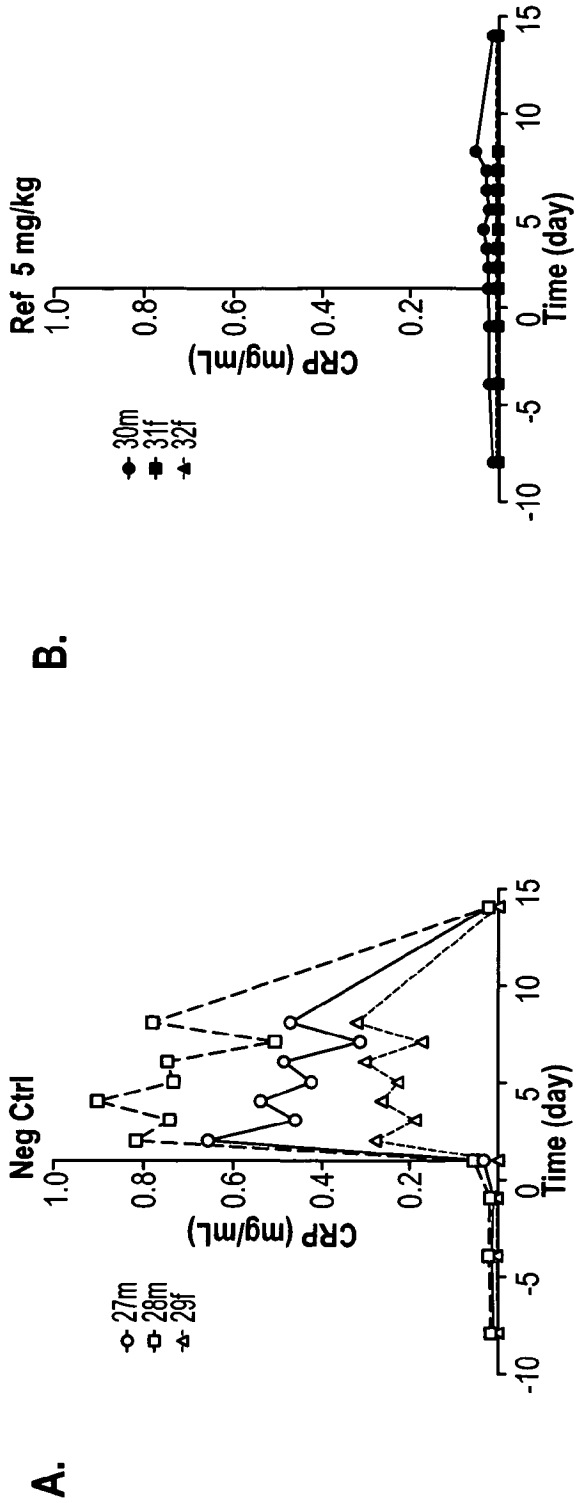


Figure 47

Figure 48


A.
Neg Ctrl
CRP (mg/mL)
Time (day)
27m
28m
29f
B.
Ref 5 mg/kg
CRP (mg/mL)
Time (day)
30m
31f
32f

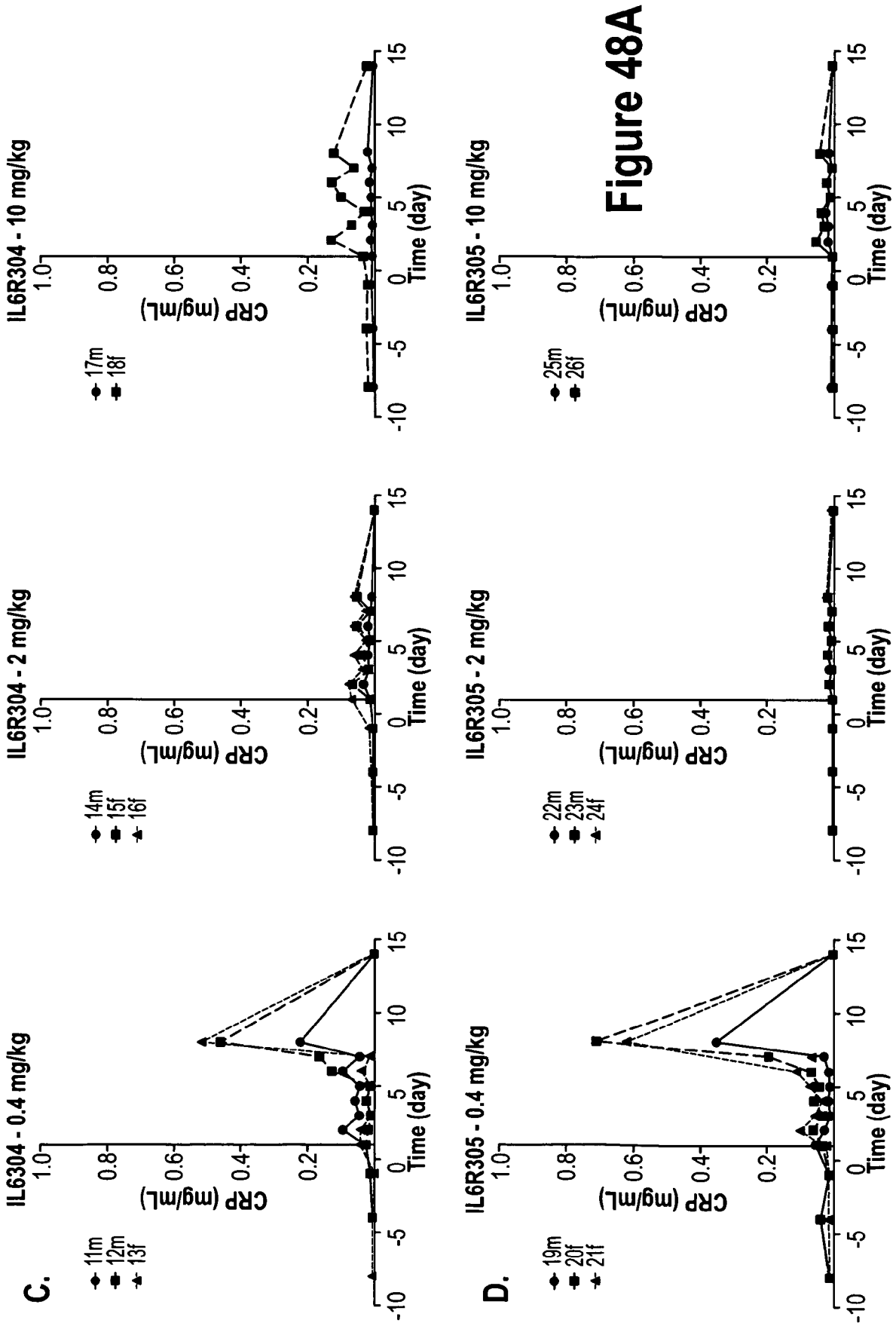

C.
IL6304 - 0.4 mg/kg
11m
12m
13f
IL6R304 - 2 mg/kg
14m
15f
16f
IL6R304 - 10 mg/kg
17m
18f
D.
IL6R305 - 0.4 mg/kg
19m
20f
21f
IL6R305 - 2 mg/kg
22m
23m
24f
IL6R305 - 10 mg/kg
25m
26f
CRP (mg/mL)
Time (day)

Figure 48A

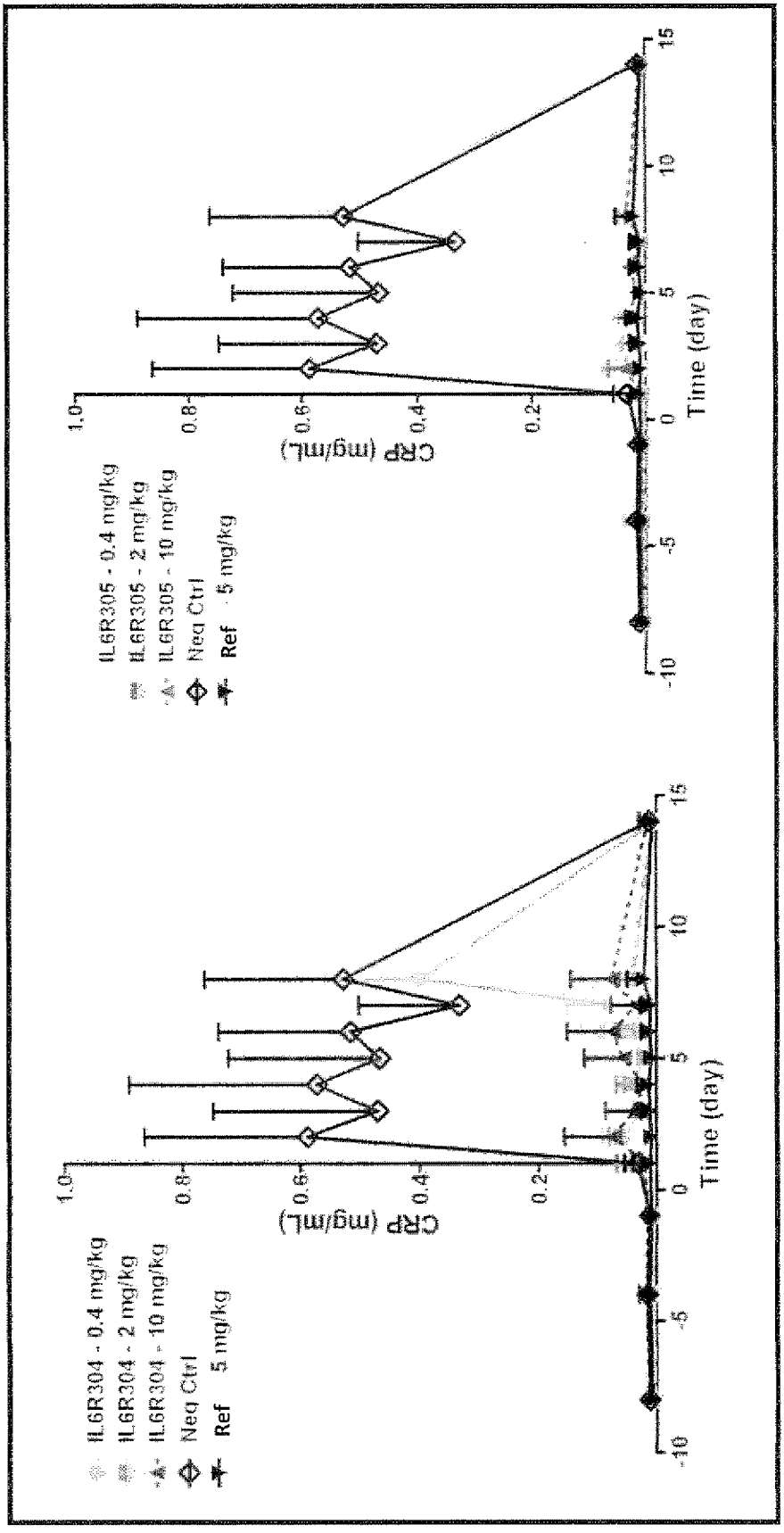

IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
Neg Ctrl
Ref 5 mg/kg
CRP (mg/mL)
Time (day)
IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
Neg Ctrl
Ref 5 mg/kg
CRP (mg/mL)
Time (day)

Figure 49

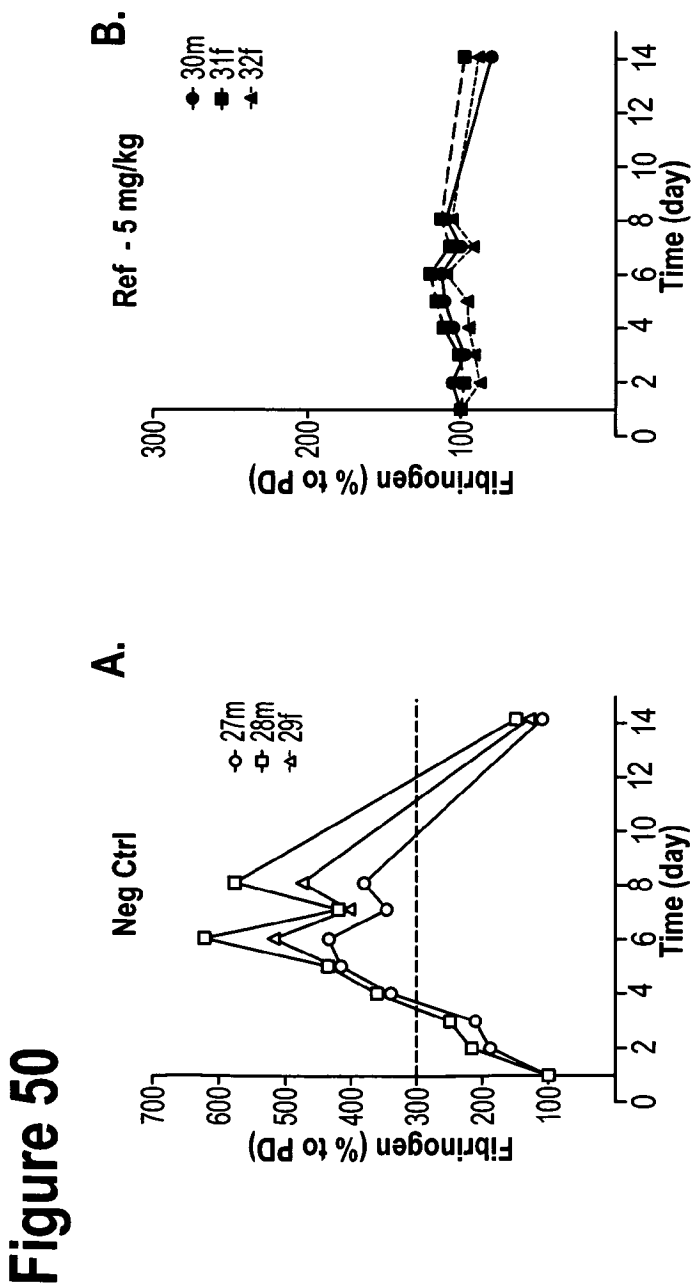

A.
Neg Ctrl
27m
28m
29f
Fibrinogen (% to PD)
700
600
500
400
300
200
100
0
2
4
6
8
10
12
14
Time (day)
B.
Ref - 5 mg/kg
30m
31f
32f
Fibrinogen (% to PD)
300
200
100
0
2
4
6
8
10
12
14
Time (day)

Figure 50

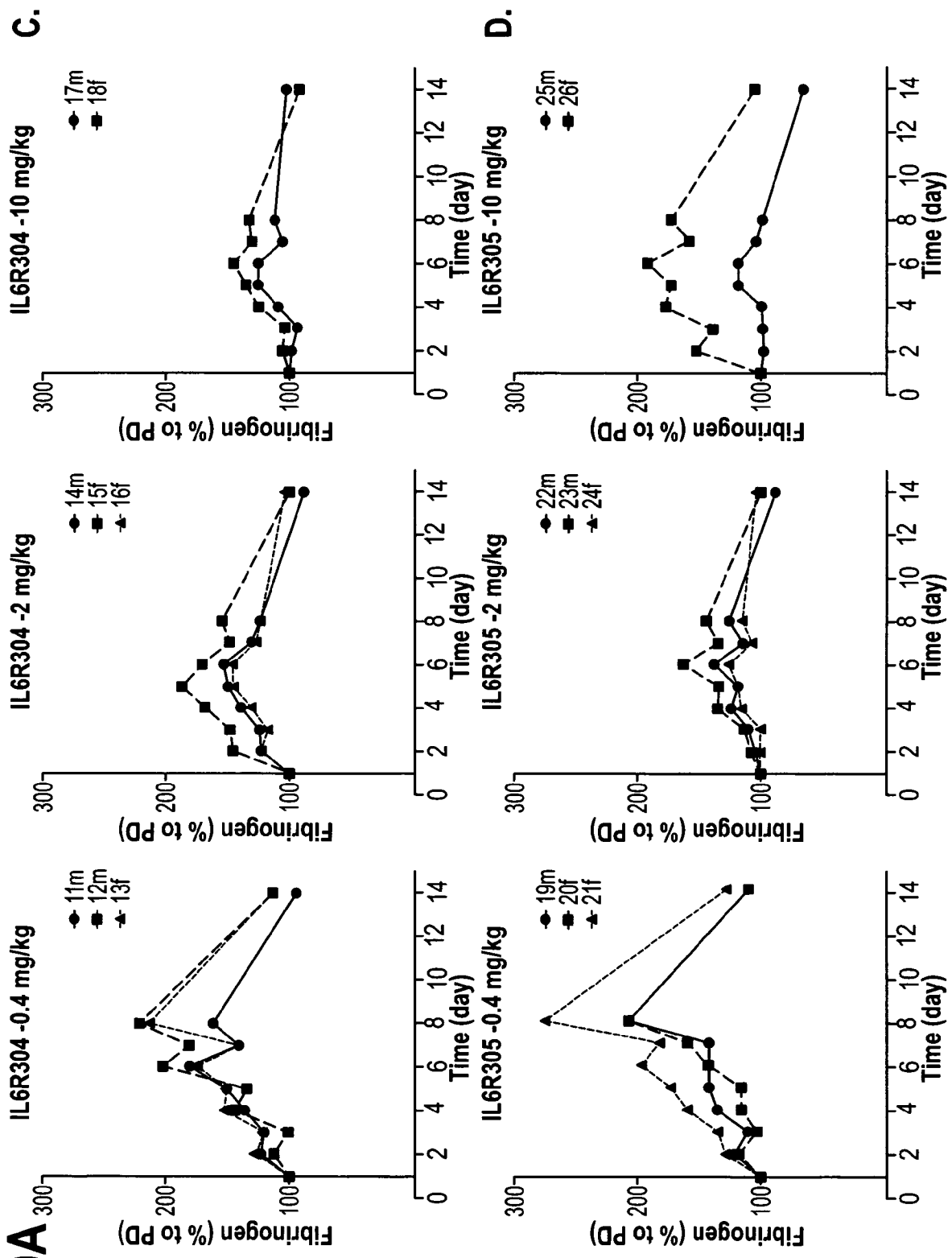

C.
D.
IL6R304 -10 mg/kg
17m
18f
IL6R305 -10 mg/kg
25m
26f
IL6R304 -2 mg/kg
14m
15f
16f
IL6R305 -2 mg/kg
22m
23m
24f
IL6R304 -0.4 mg/kg
11m
12m
13f
IL6R305 -0.4 mg/kg
19m
20f
21f
Fibrinogen (% to PD)
Time (day)
0
2
4
6
8
10
12
14
100
200
300

Figure 50A

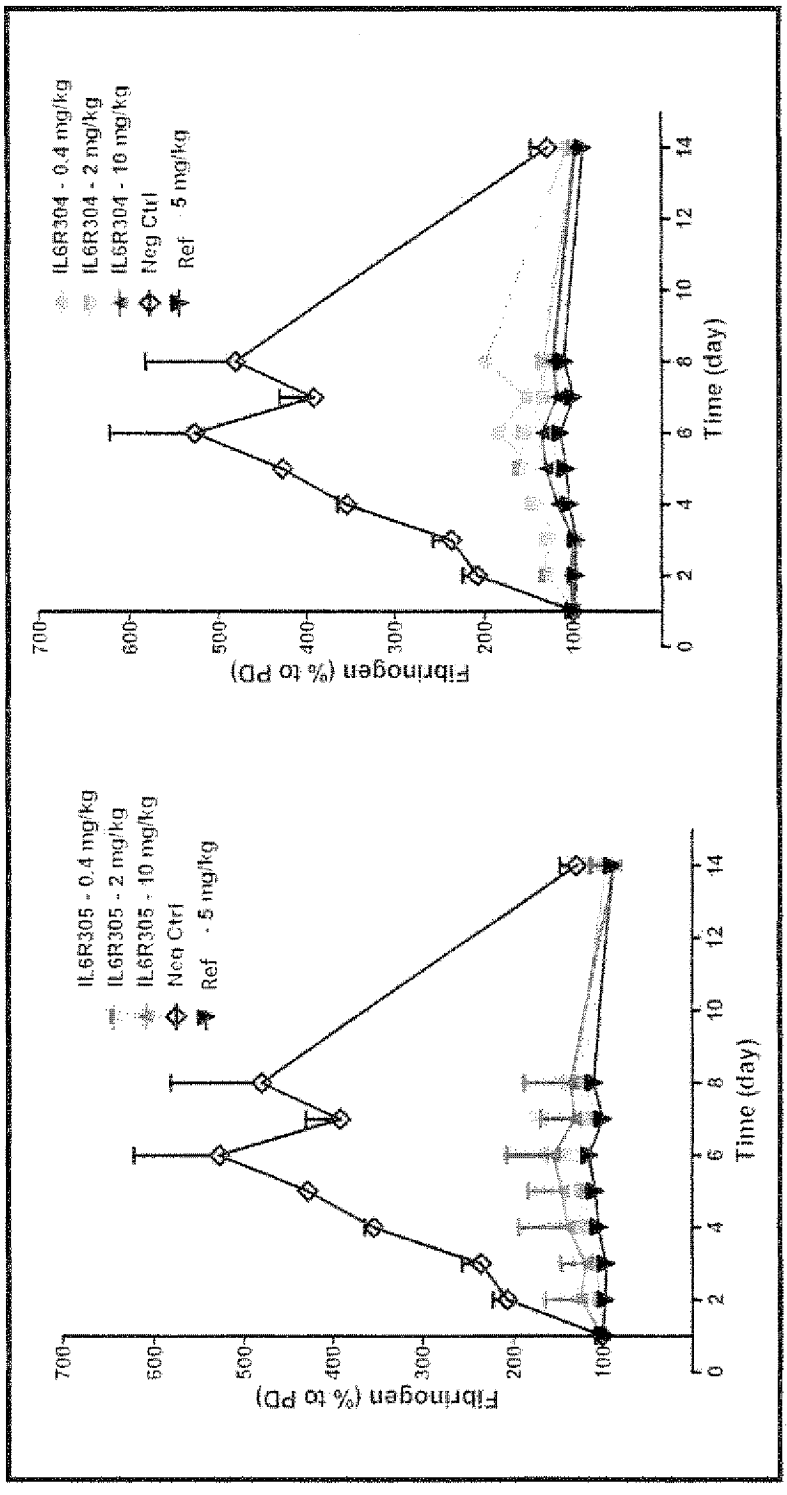

IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Fibrinogen (% to PD)
Time (day)
IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Fibrinogen (% to PD)
Time (day)

Figure 51

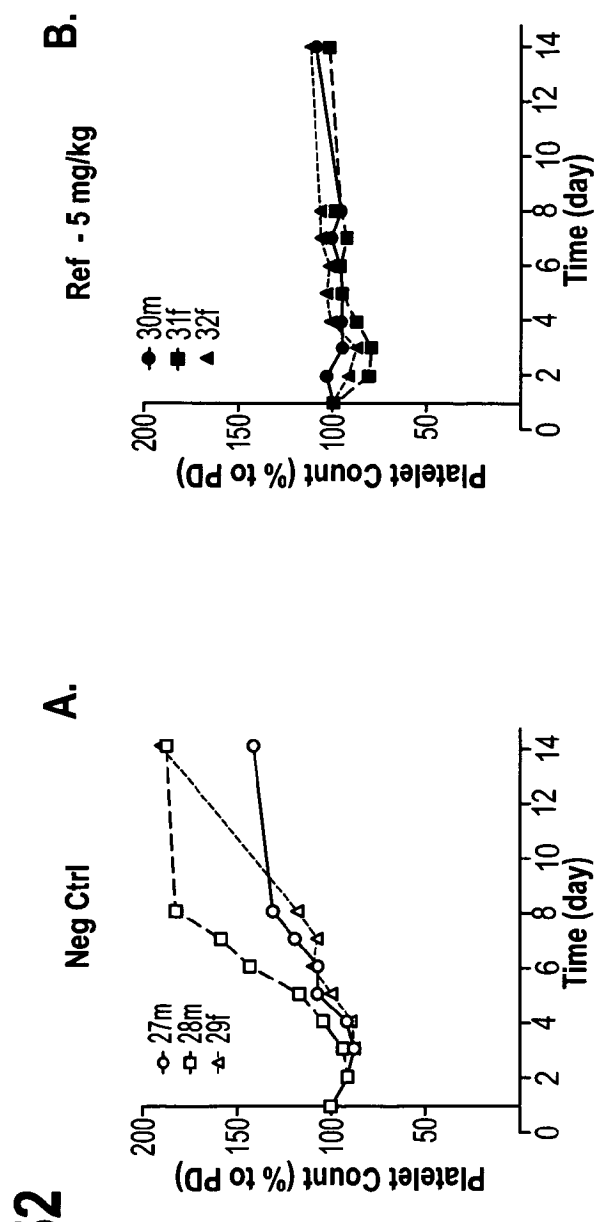
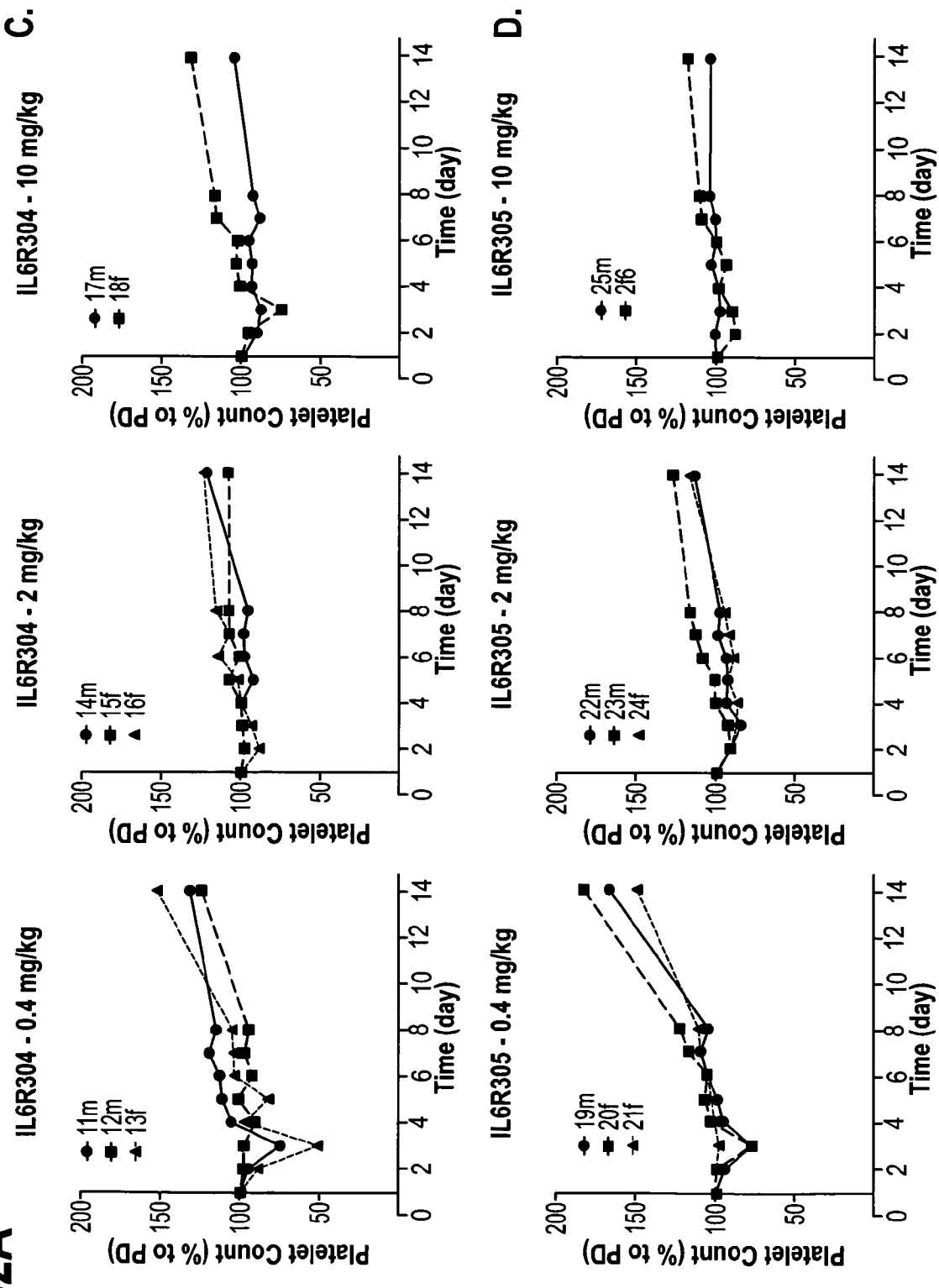

A.
Neg Ctrl
27m
28m
29f
Platelet Count (% to PD)
200
150
100
50
0
2
4
6
8
10
12
14
Time (day)
B.
Ref - 5 mg/kg
30m
31f
32f
Platelet Count (% to PD)
200
150
100
50
0
2
4
6
8
10
12
14
Time (day)

Figure 52

Figure 52A


A.
IL6R304 - 0.4 mg/kg
11m
12m
13f
B.
IL6R304 - 2 mg/kg
14m
15f
16f
C.
IL6R304 - 10 mg/kg
17m
18f
D.
IL6R305 - 0.4 mg/kg
19m
20f
21f
IL6R305 - 2 mg/kg
22m
23m
24f
IL6R305 - 10 mg/kg
25m
26f
Platelet Count (% to PD)
Time (day)
0
2
4
6
8
10
12
14
50
100
150
200

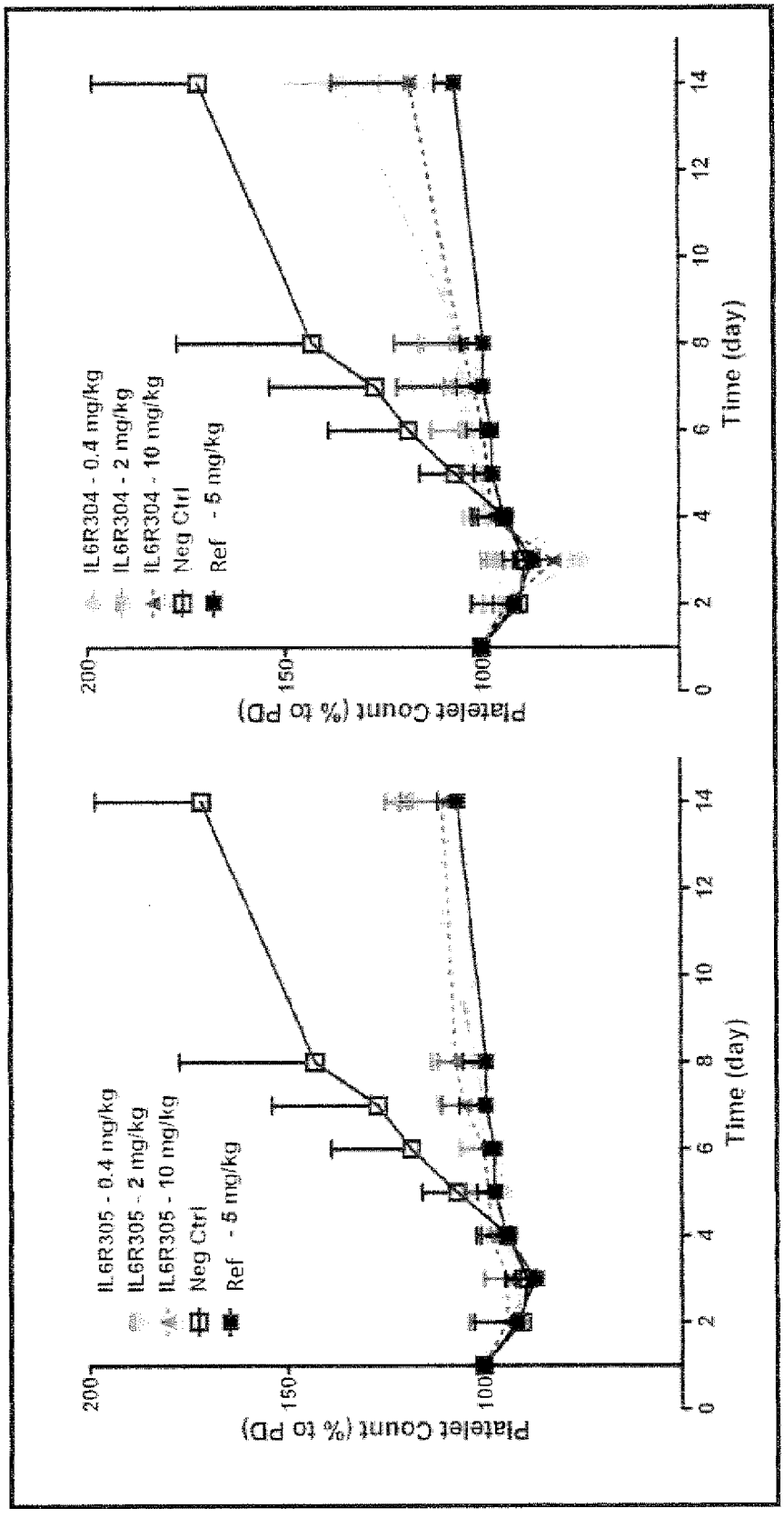

IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Platelet Count (% to PD)
Time (day)
IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Platelet Count (% to PD)
Time (day)

Figure 53

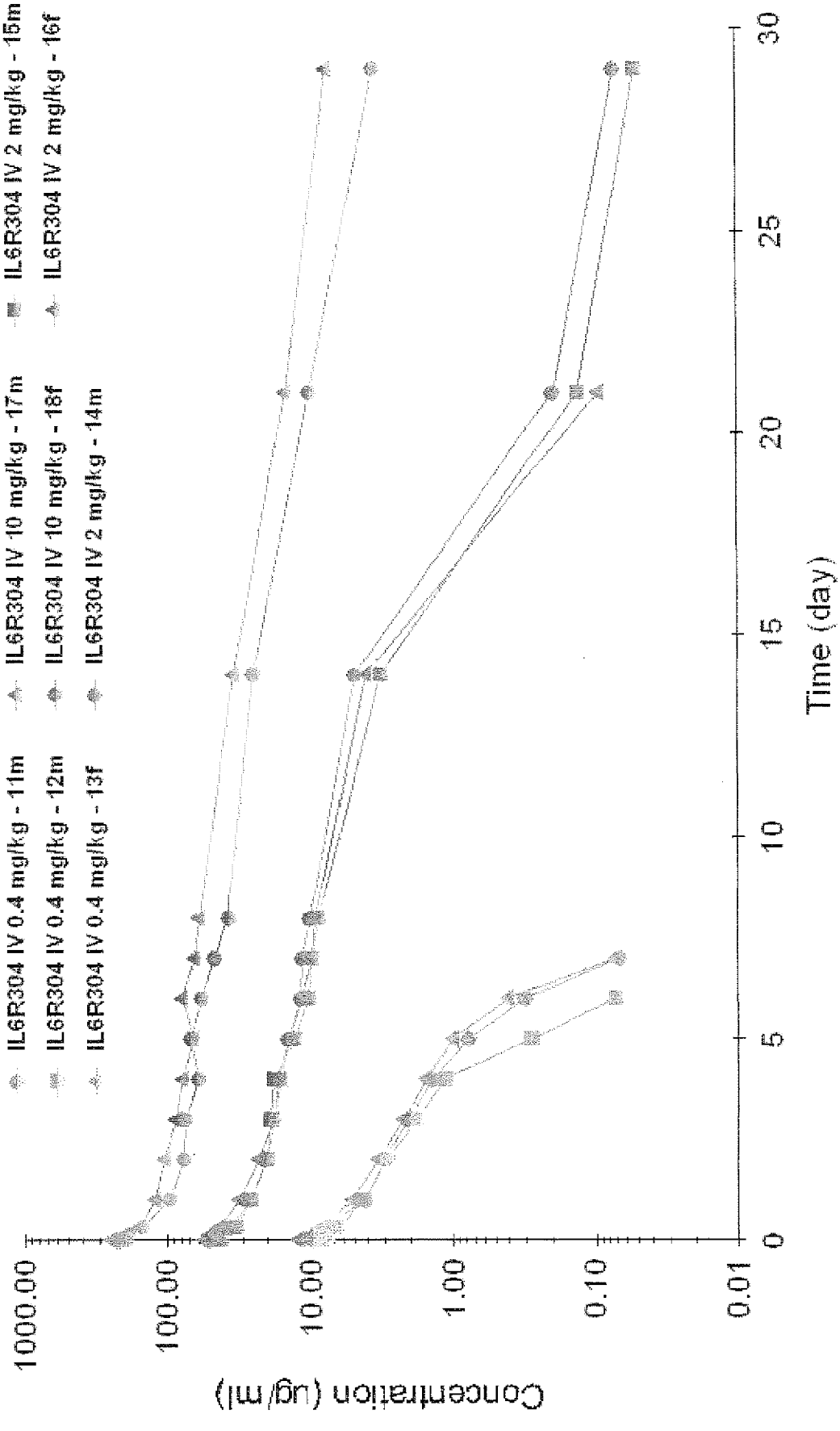

IL6R304 IV 0.4 mg/kg - 11m
IL6R304 IV 0.4 mg/kg - 12m
IL6R304 IV 0.4 mg/kg - 13f
IL6R304 IV 10 mg/kg - 17m
IL6R304 IV 10 mg/kg - 18f
IL6R304 IV 2 mg/kg - 14m
IL6R304 IV 2 mg/kg - 15m
IL6R304 IV 2 mg/kg - 16f
1000.00
100.00
10.00
1.00
0.10
0.01
Concentration (ug/ml)
0
5
10
15
20
25
30
Time (day)

Figure 54

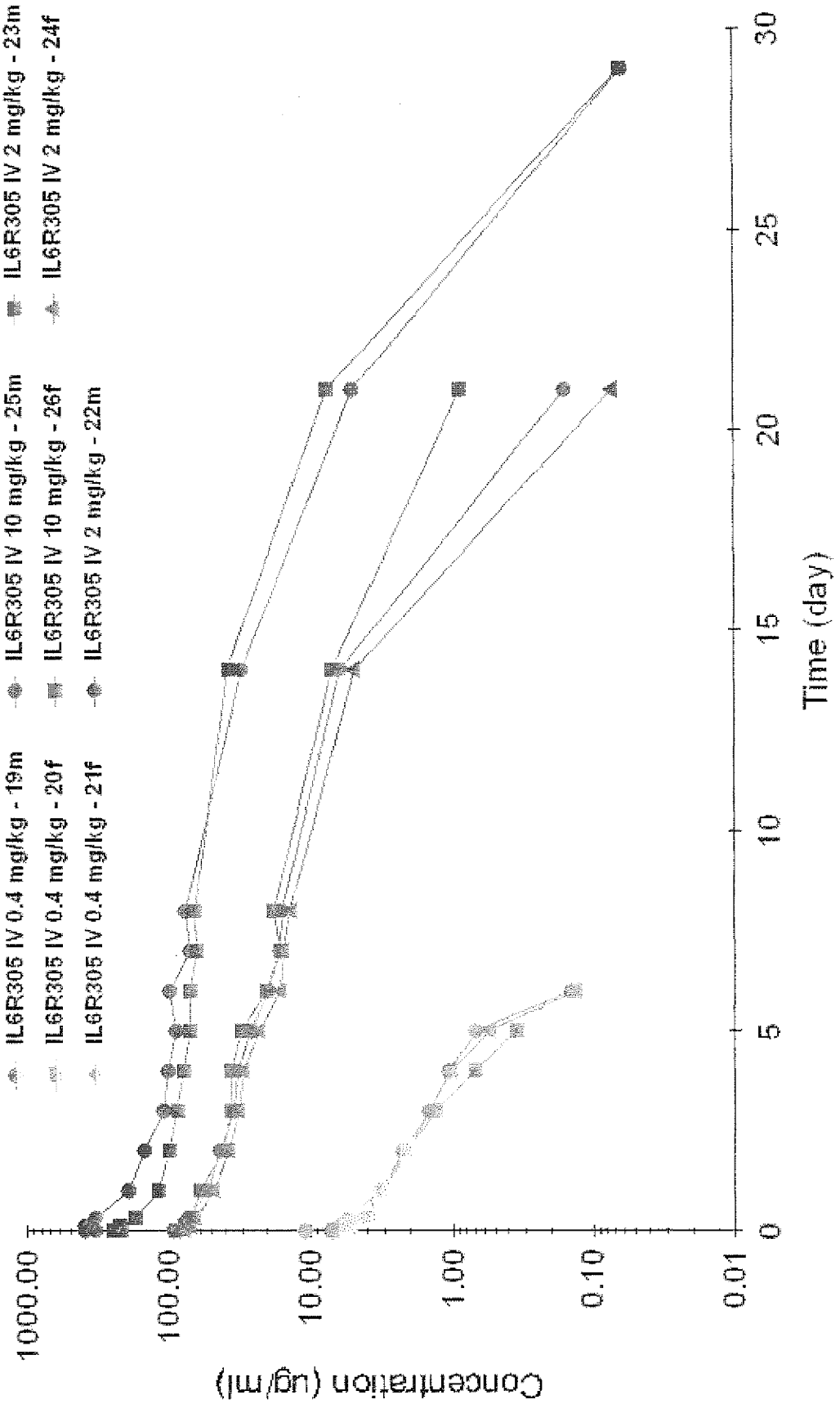

IL6R305 IV 0.4 mg/kg - 19m
IL6R305 IV 0.4 mg/kg - 20f
IL6R305 IV 0.4 mg/kg - 21f
IL6R305 IV 10 mg/kg - 25m
IL6R305 IV 10 mg/kg - 26f
IL6R305 IV 2 mg/kg - 22m
IL6R305 IV 2 mg/kg - 23m
IL6R305 IV 2 mg/kg - 24f
1000.00
100.00
10.00
1.00
0.10
0.01
Concentration (ug/ml)
0
5
10
15
20
25
30
Time (day)

Figure 55

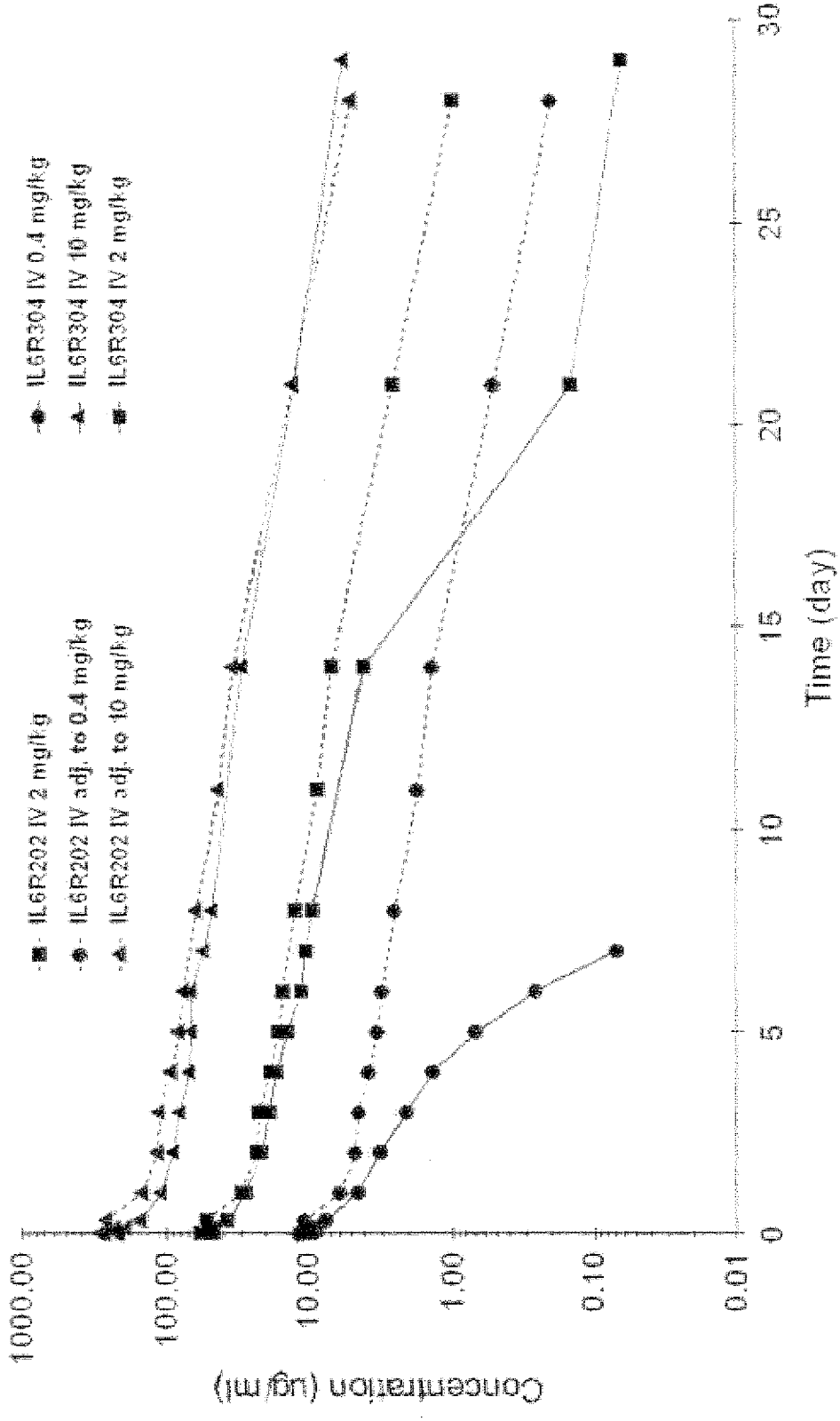
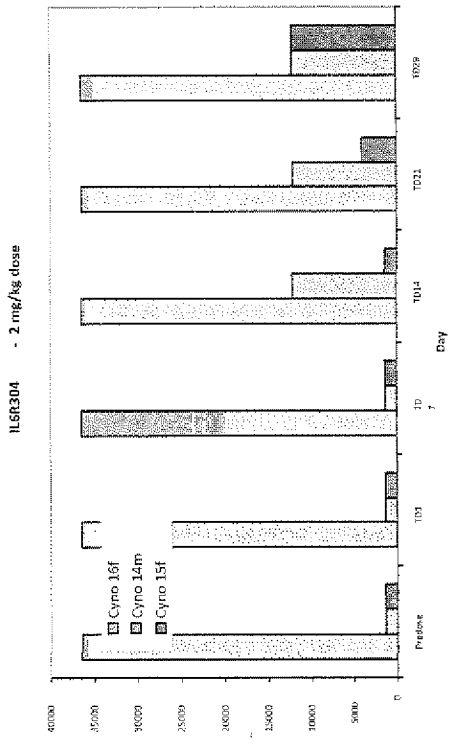
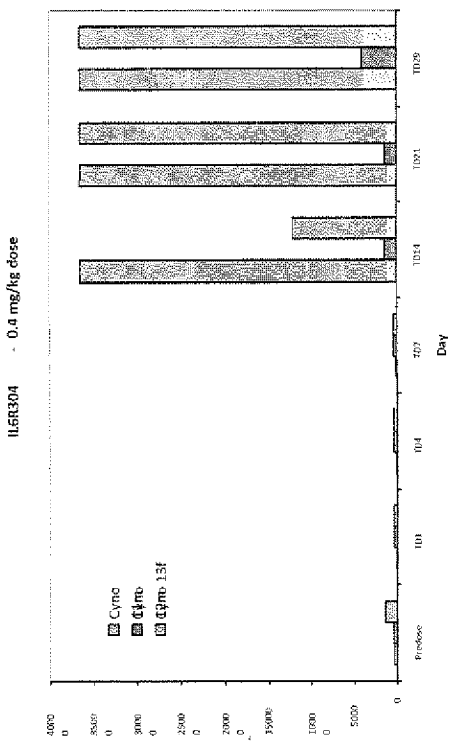

IL6R304 IV 0.4 mg/kg
IL6R304 IV 10 mg/kg
IL6R304 IV 2 mg/kg
IL6R202 IV 2 mg/kg
IL6R202 IV adj. to 0.4 mg/kg
IL6R202 IV adj. to 10 mg/kg
1000,00
100,00
10,00
1,00
0,10
0,01
Concentration (µg/ml)
0
5
10
15
20
25
30
Time (day)

Figure 56


IL6R304 - 2 mg/kg dose
Cyno 16f
Cyno 14m
Cyno 15f
Predose
Day


IL6R304 - 0.4 mg/kg dose
Cyno
Predose
Day

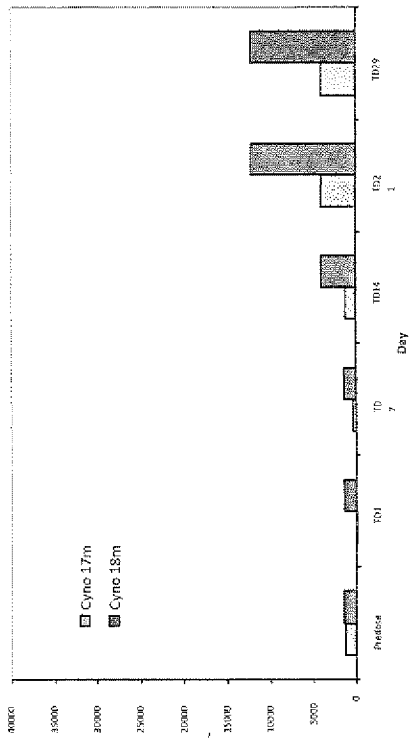
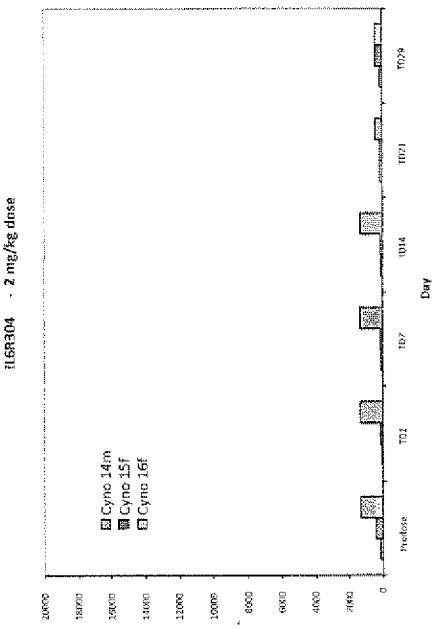
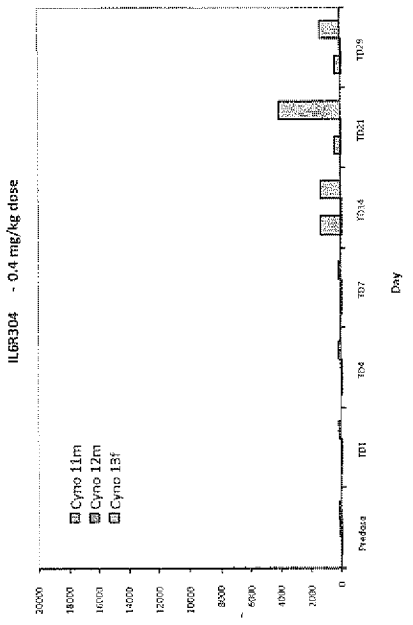

IL6R304 - 10 mg/kg dose
Cyno 17m
Cyno 18m
Predose
Day

Figure 57


IL6R304 - 2 mg/kg dose
Cyno 14m
Cyno 15f
Cyno 16f
Predose
TD2
TD7
TD14
TD21
TD29
Day


IL6R304 - 0.4 mg/kg dose
Cyno 11m
Cyno 12m
Cyno 13f
Predose
TD1
TD4
TD7
TD14
TD21
TD29
Day

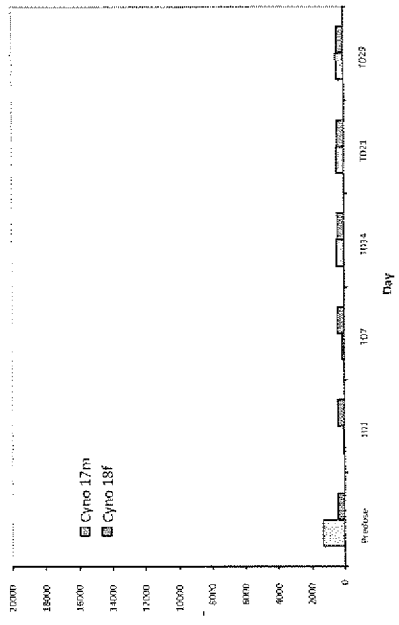

IL6R304 - 10 mg/kg dose
Cyno 17m
Cyno 18f
Predose
TD1
TD7
TD14
TD21
TD29
Day

Figure 58

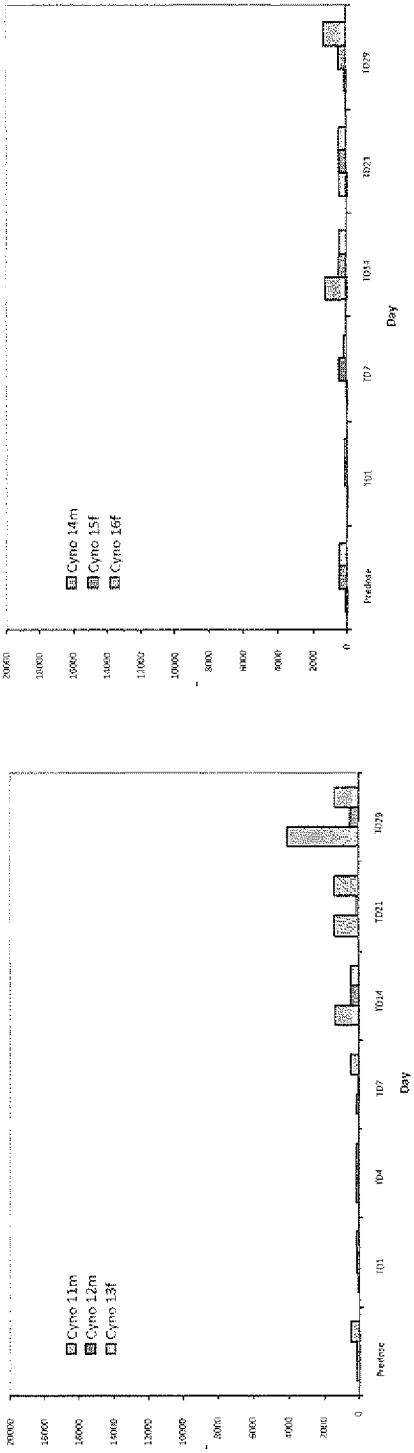
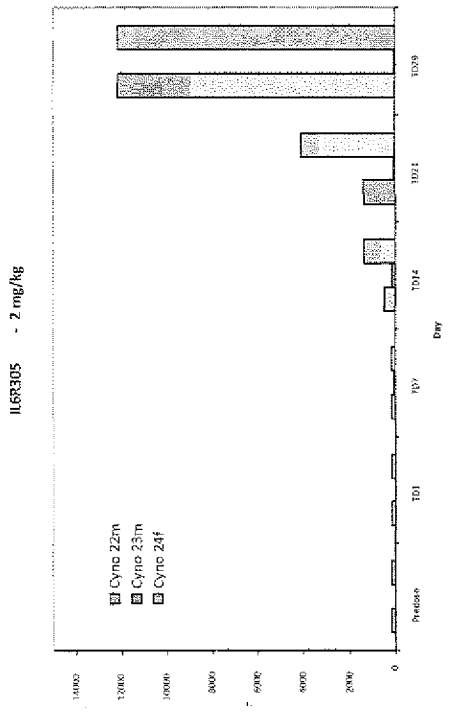
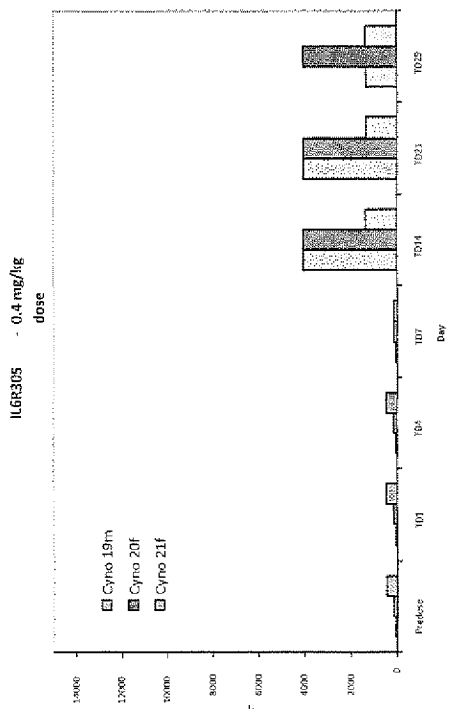

IL6R304 - 0,4 mg/kg dose
Cyno 11m
Cyno 12m
Cyno 13f
Predose
D1
D4
D7
D14
D21
D29
Day
IL6R304 - 2 mg/kg dose
Cyno 14m
Cyno 15f
Cyno 16f
Predose
D1
D7
D14
D21
D29
Day
IL6R304 - 10 mg/kg dose
Cyno 17m
Cyno 18f
Predose
D1
D7
D14
D21
D29
Day

Figure 59


IL6R305 - 2 mg/kg
Cyno 22m
Cyno 23m
Cyno 24f
Predose
D1
D7
D14
D21
D28
Day


IL6R305 - 0.4 mg/kg dose
Cyno 19m
Cyno 20f
Cyno 21f
Predose
D1
D7
D14
D21
D28
Day

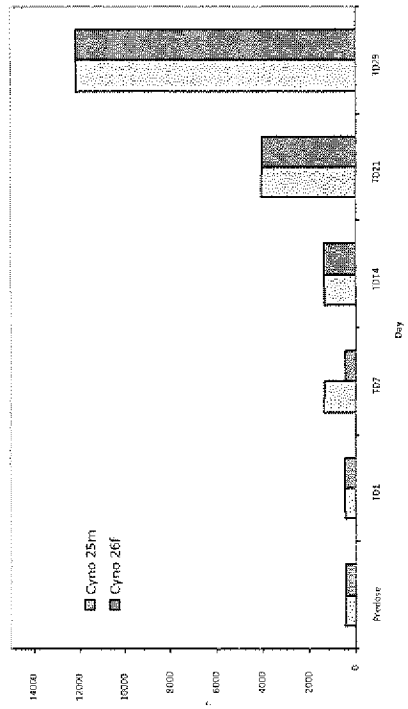
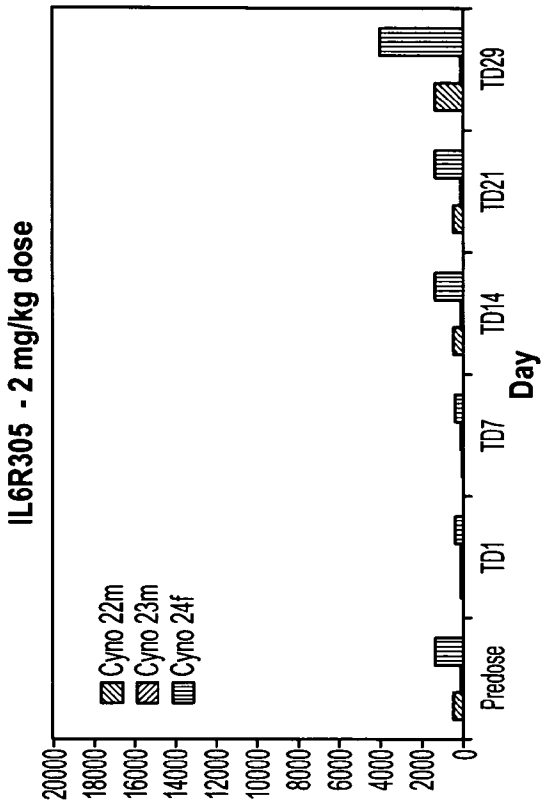
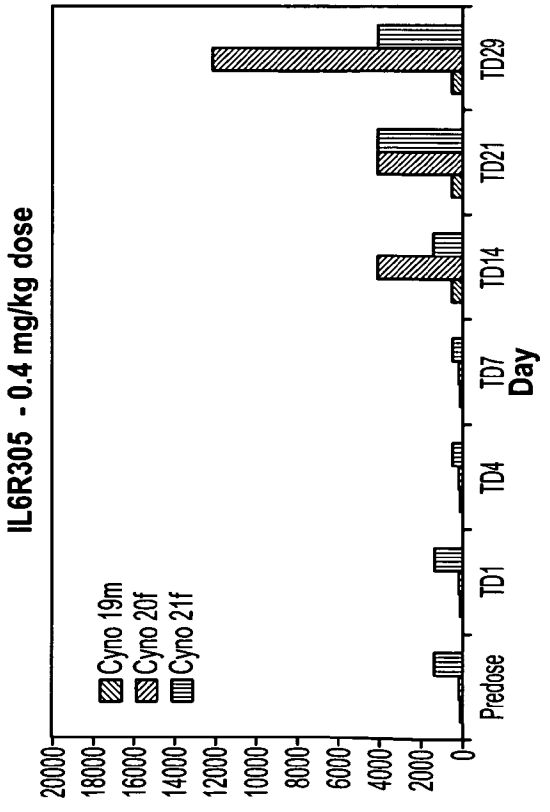

IL6R305 - 10 mg/kg dose
Cyno 25m
Cyno 26f
Predose
D1
D7
D14
D21
D28
Day

Figure 60


IL6R305 - 2 mg/kg dose
Cyno 22m
Cyno 23m
Cyno 24f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD7
TD14
TD21
TD29
Day


IL6R305 - 0.4 mg/kg dose
Cyno 19m
Cyno 20f
Cyno 21f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD4
TD7
TD14
TD21
TD29
Day

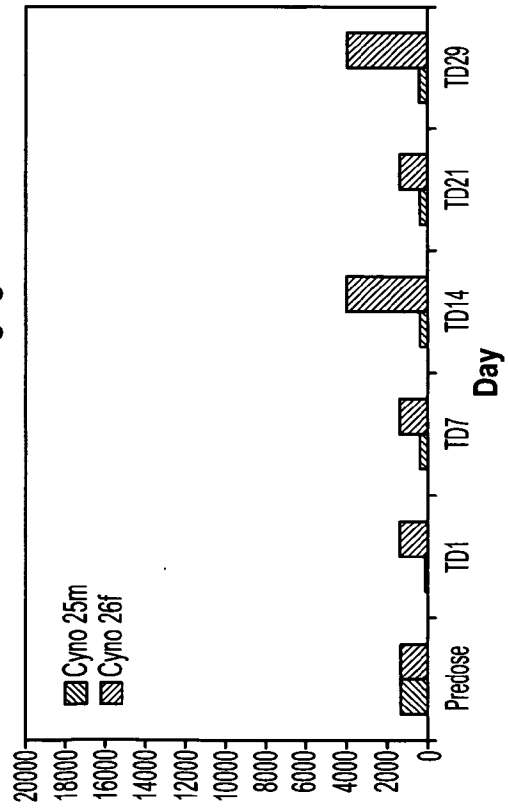
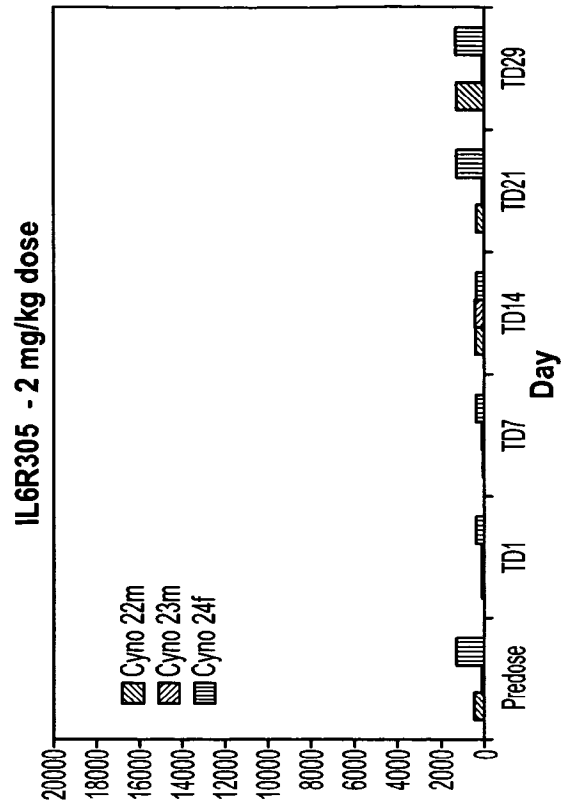
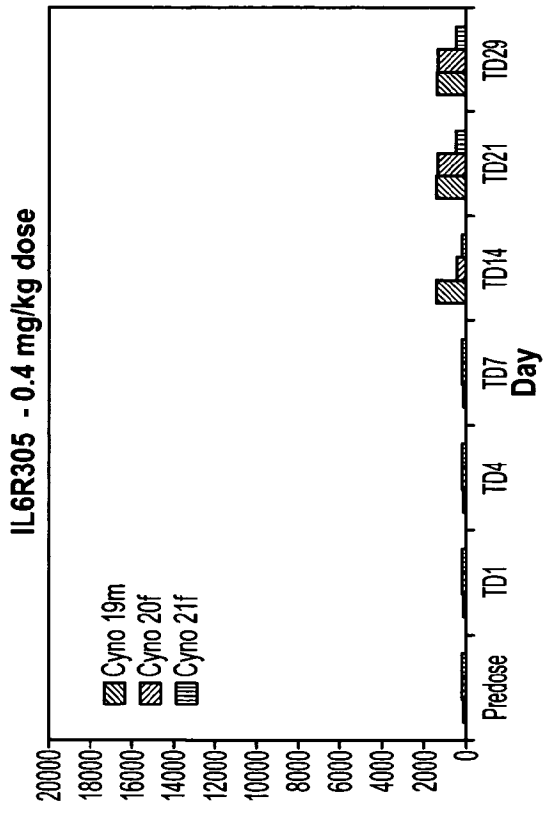

IL6R305 -10 mg/kg dose
Cyno 25m
Cyno 26f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD7
TD14
TD21
TD29
Day

Figure 61


IL6R305 - 2 mg/kg dose
Cyno 22m
Cyno 23m
Cyno 24f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD7
TD14
TD21
TD29
Day


IL6R305 - 0.4 mg/kg dose
Cyno 19m
Cyno 20f
Cyno 21f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD4
TD7
TD14
TD21
TD29
Day

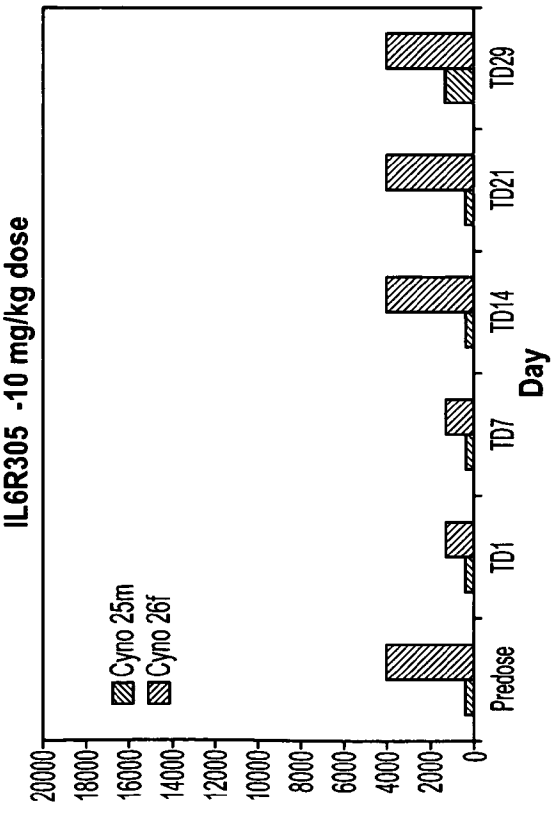

IL6R305 -10 mg/kg dose
Cyno 25m
Cyno 26f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD7
TD14
TD21
TD29
Day

Figure 62

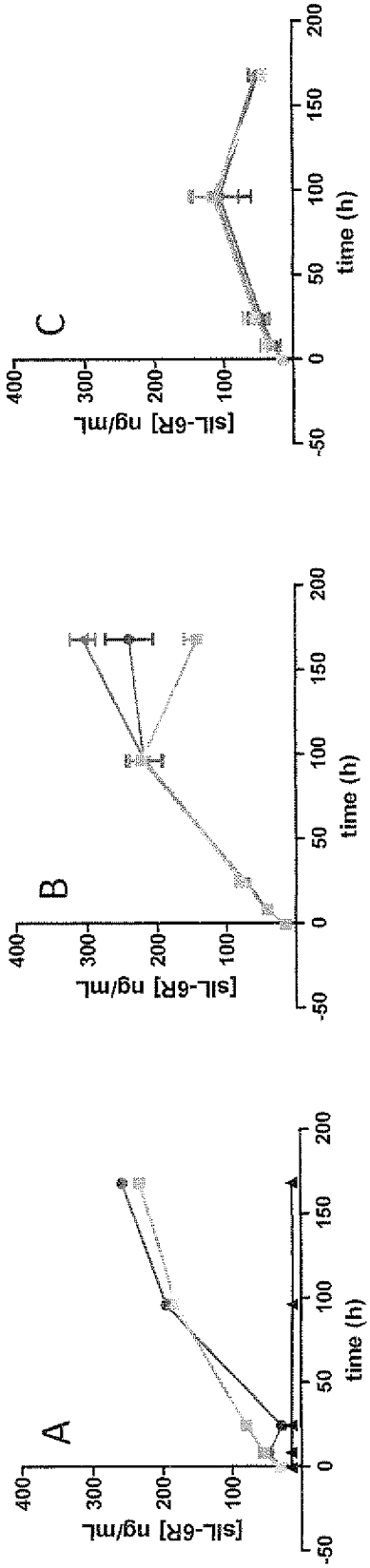


Figure 63

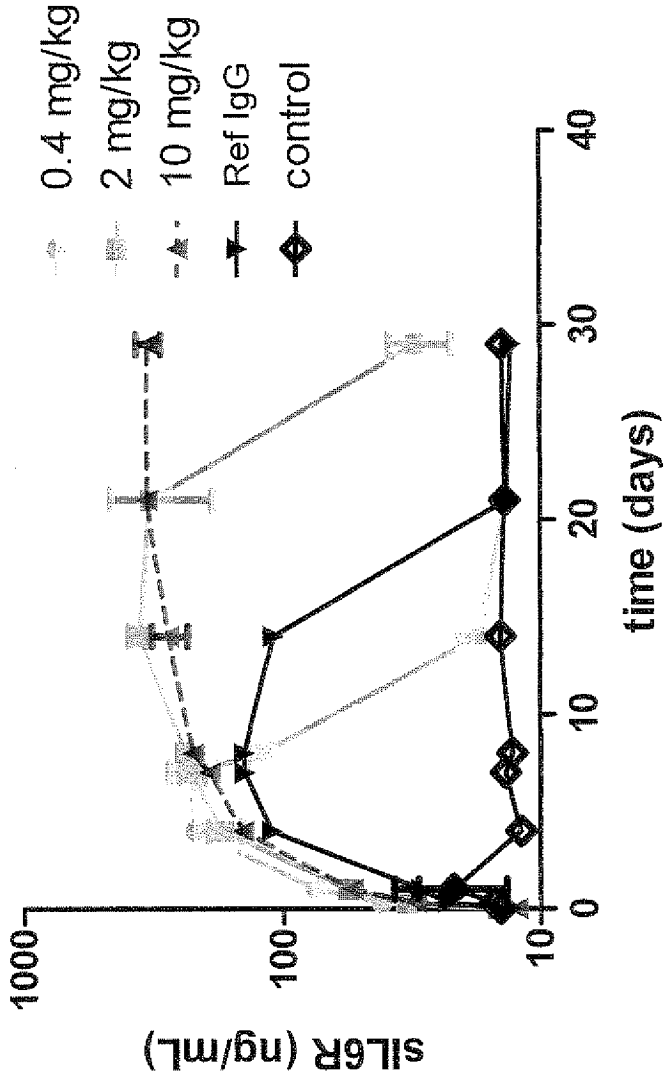

0.4 mg/kg
2 mg/kg
10 mg/kg
Ref IgG
control
1000
100
10
sIL6R (ng/mL)
0
10
20
30
40
time (days)

Figure 64A

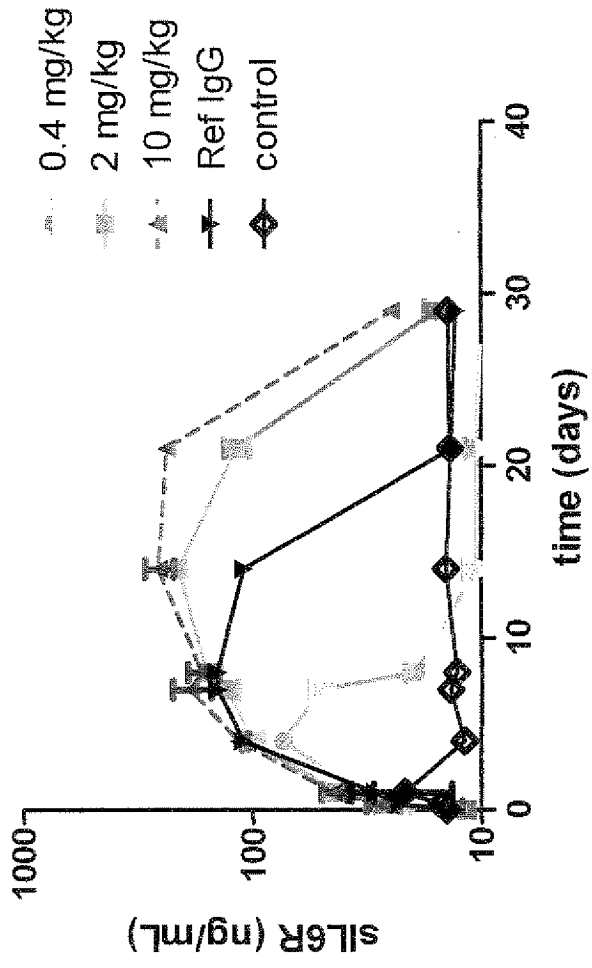

0.4 mg/kg
2 mg/kg
10 mg/kg
Ref IgG
control
1000
100
10
sIL6R (ng/mL)
0
10
20
30
40
time (days)

Figure 64B

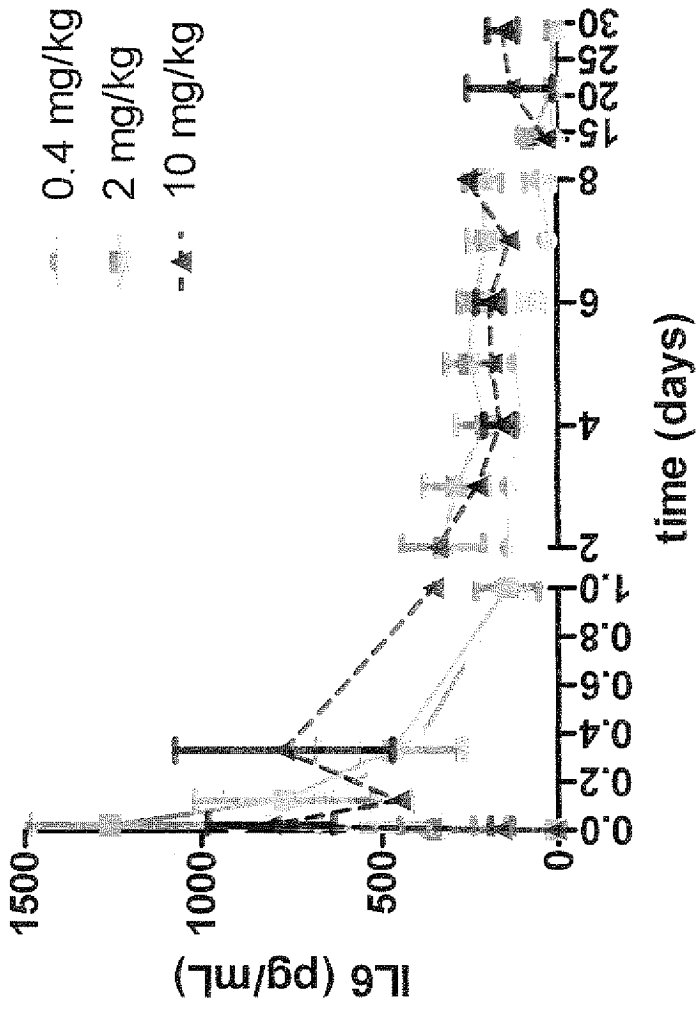

0.4 mg/kg
2 mg/kg
10 mg/kg
IL6 (pg/mL)
1500
1000
500
0
time (days)
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
15
20
25
30

Figure 65A

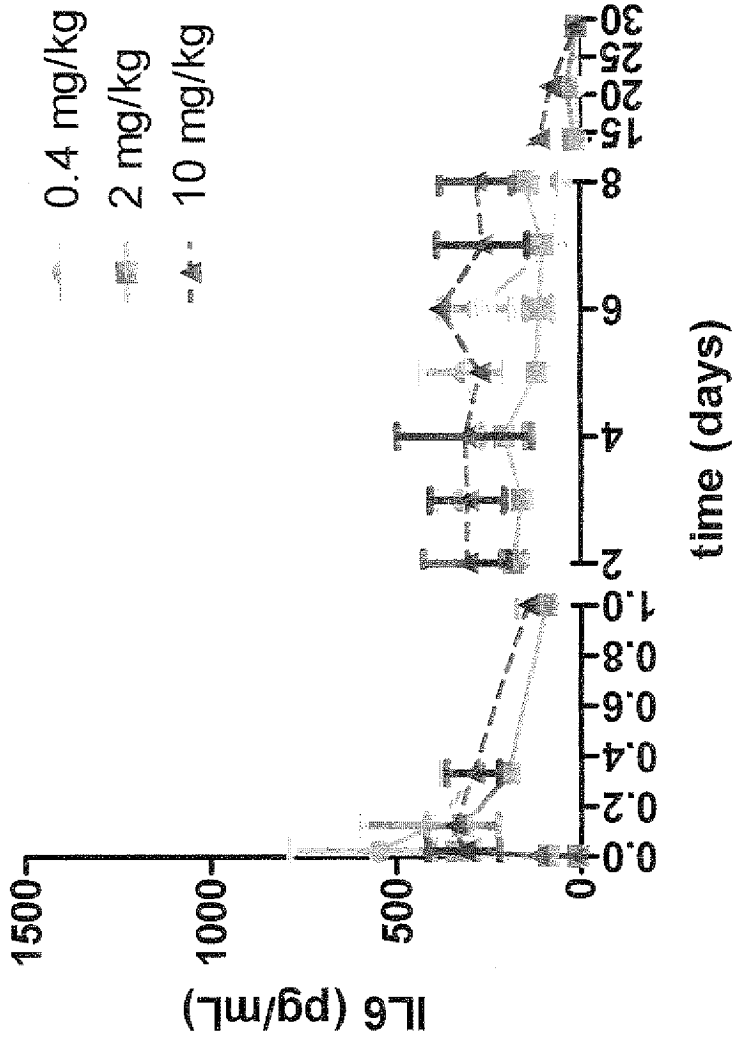

0.4 mg/kg
2 mg/kg
10 mg/kg
IL6 (pg/mL)
1500
1000
500
0
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
15
20
25
30
time (days)

Figure 65B

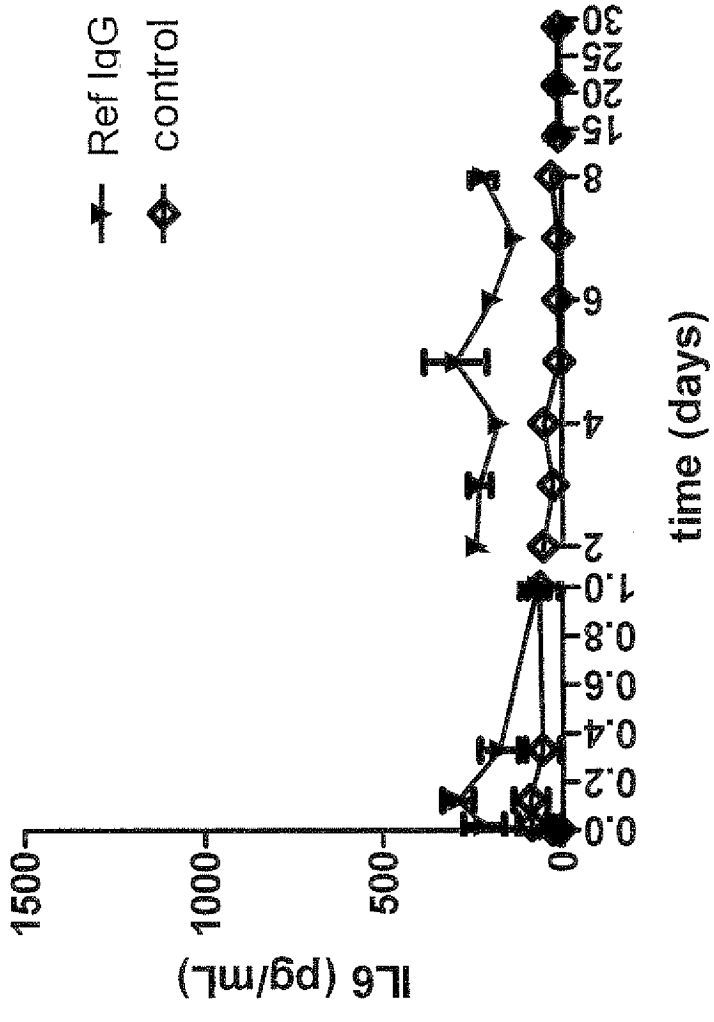

Ref IgG
control
IL6 (pg/mL)
1500
1000
500
0
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
15
20
25
30
time (days)

Figure 65C

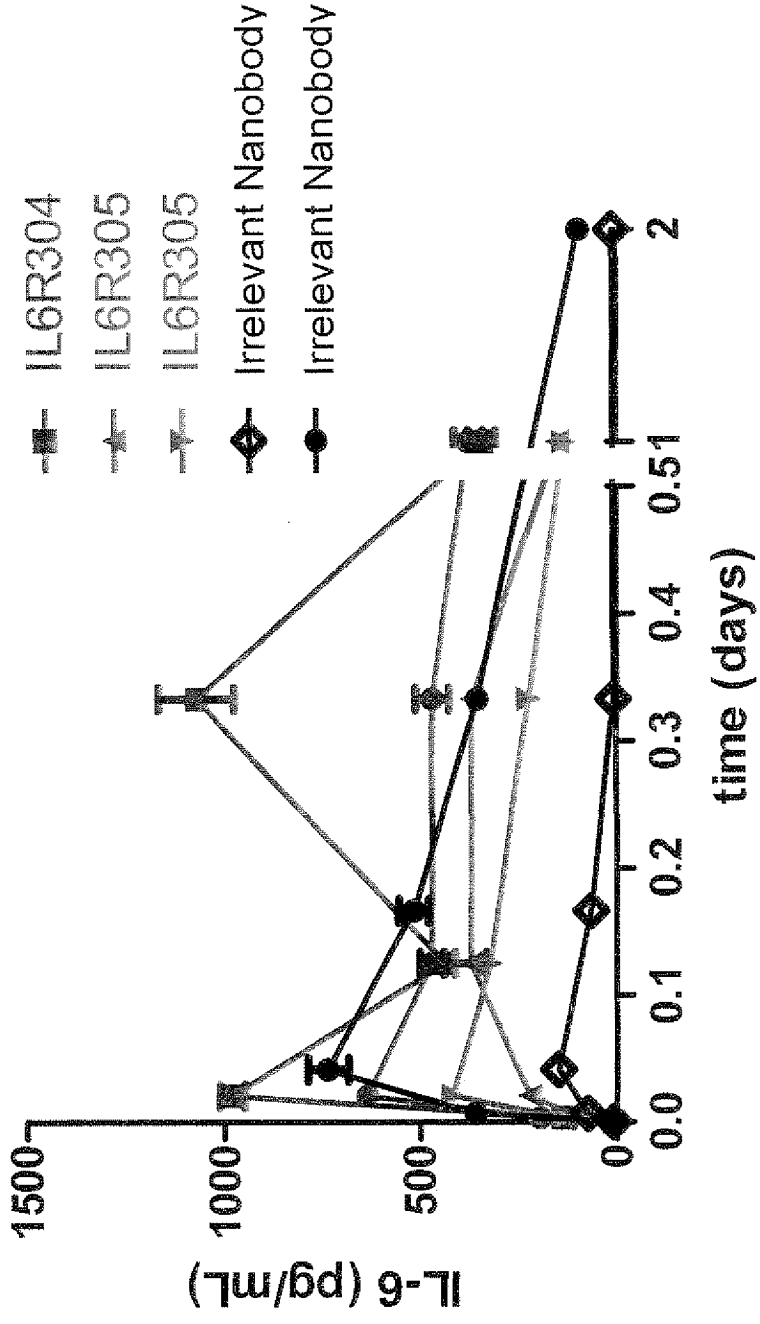

IL6R304
IL6R304
IL6R305
IL6R305
Irrelevant Nanobody
Irrelevant Nanobody
IL-6 (pg/mL)
1500
1000
500
0
0.0
0.1
0.2
0.3
0.4
0.5
1
2
time (days)

Figure 65D

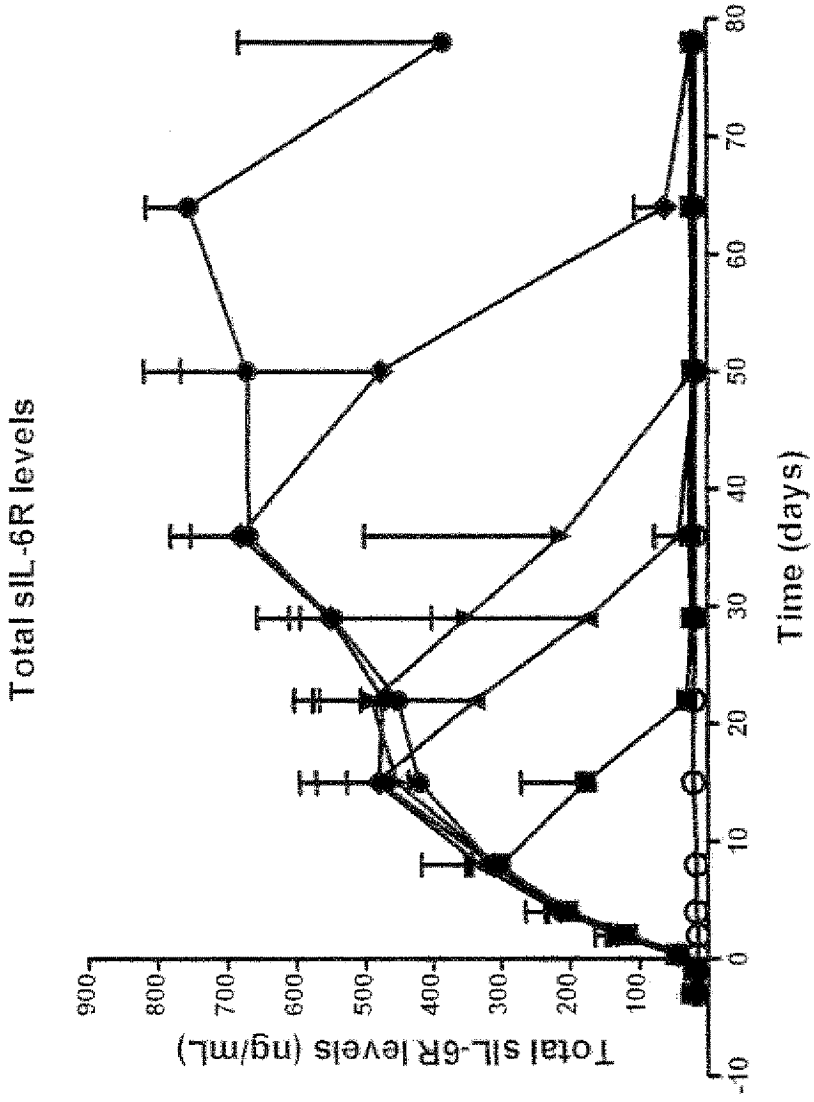

Total sIL-6R levels
Total sIL-6R levels (ng/mL)
900
800
700
600
500
400
300
200
100
-10
0
10
20
30
40
50
60
70
80
Time (days)

Figure 66A

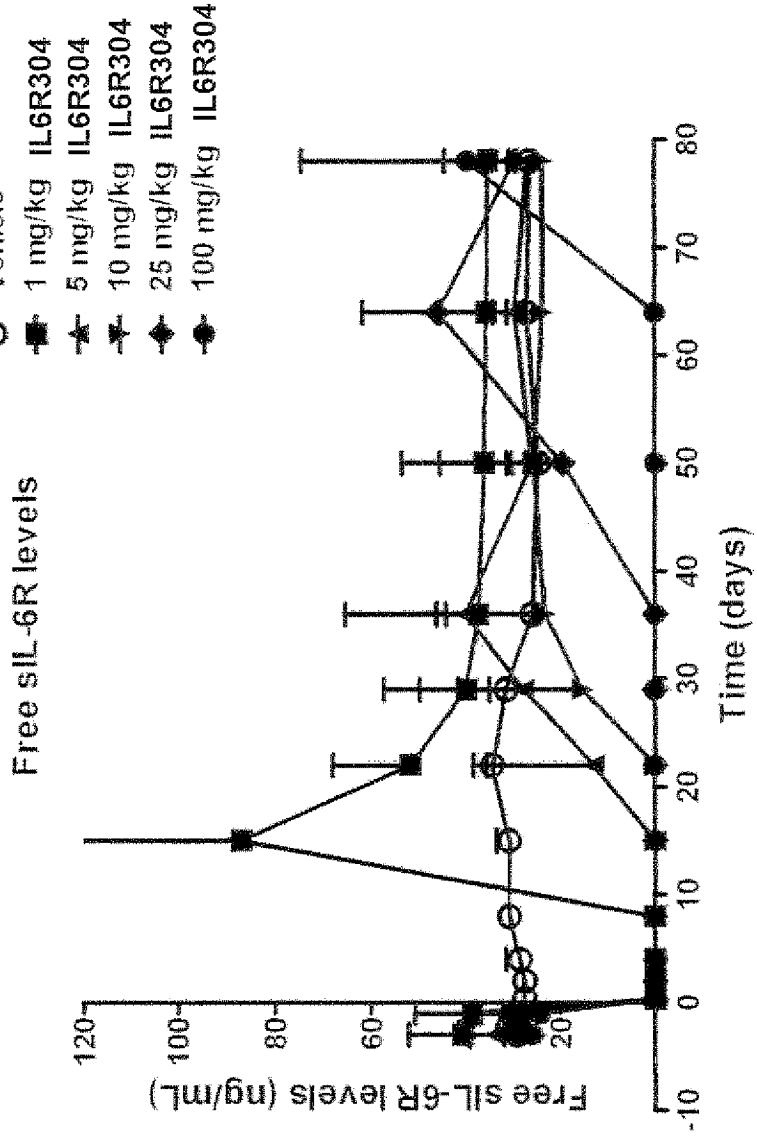

Free sIL-6R levels
Vehicle
1 mg/kg IL6R304
5 mg/kg IL6R304
10 mg/kg IL6R304
25 mg/kg IL6R304
100 mg/kg IL6R304
Free sIL-6R levels (ng/mL)
120
100
80
60
20
-10
0
10
20
30
40
50
60
70
80
Time (days)

Figure 66B

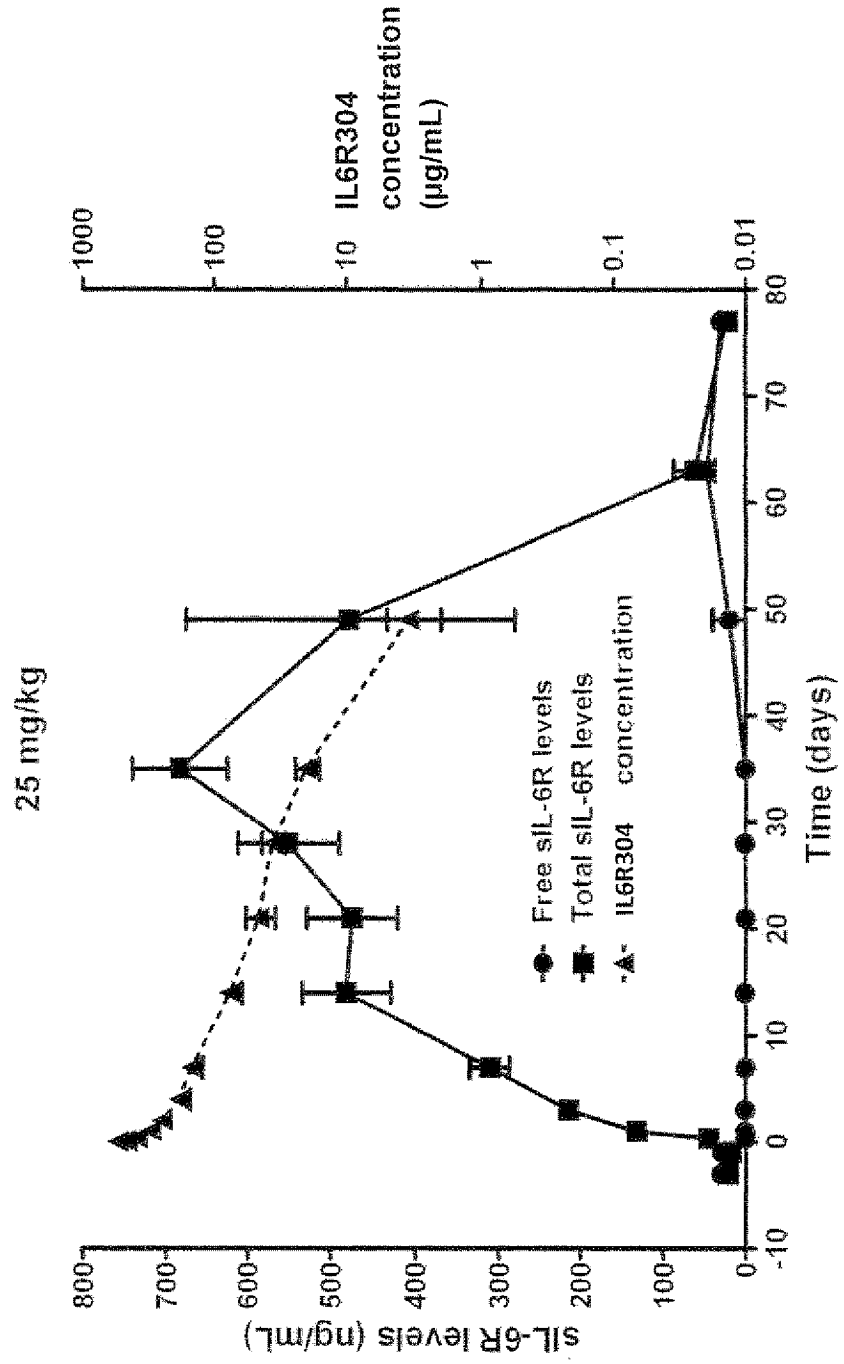

25 mg/kg
sIL-6R levels (ng/mL)
IL6R304 concentration (µg/mL)
Time (days)
Free sIL-6R levels
Total sIL-6R levels
IL6R304 concentration
800
700
600
500
400
300
200
100
0
1000
100
10
1
0.1
0.01
-10
0
10
20
30
40
50
60
70
80

Figure 67

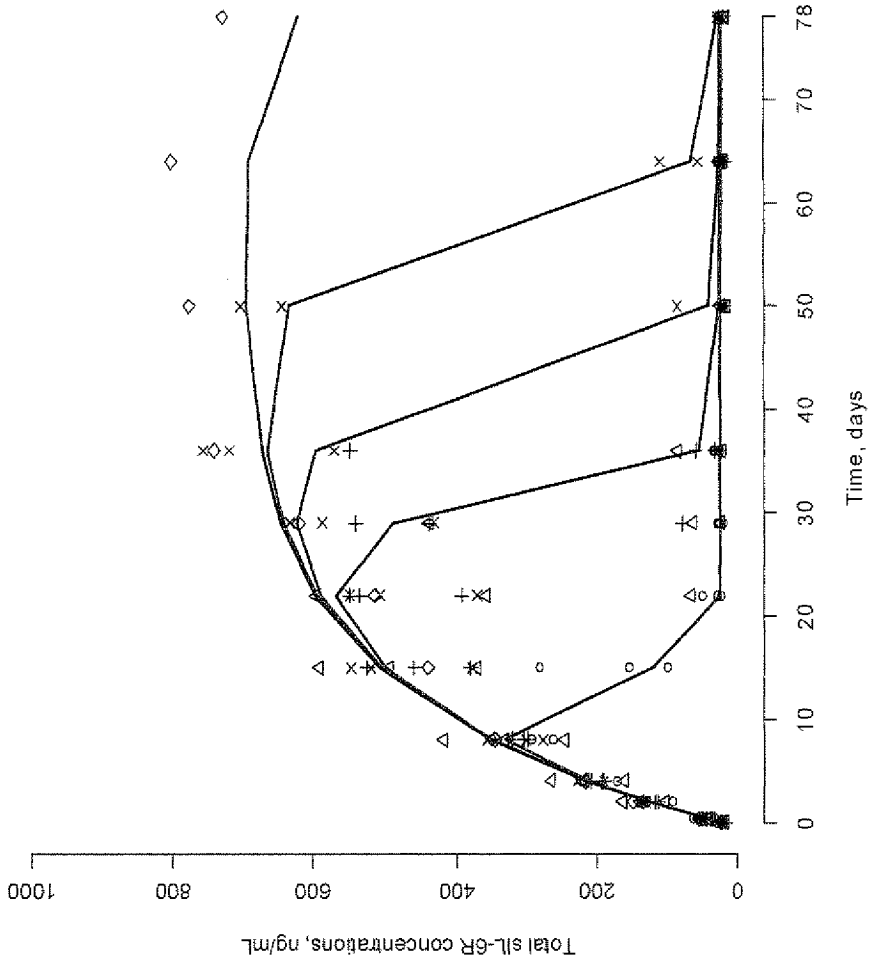

Total sIL-6R concentrations, ng/mL
0
200
400
600
800
1000
Time, days
0
10
20
30
40
50
60
70
78

Figure 68

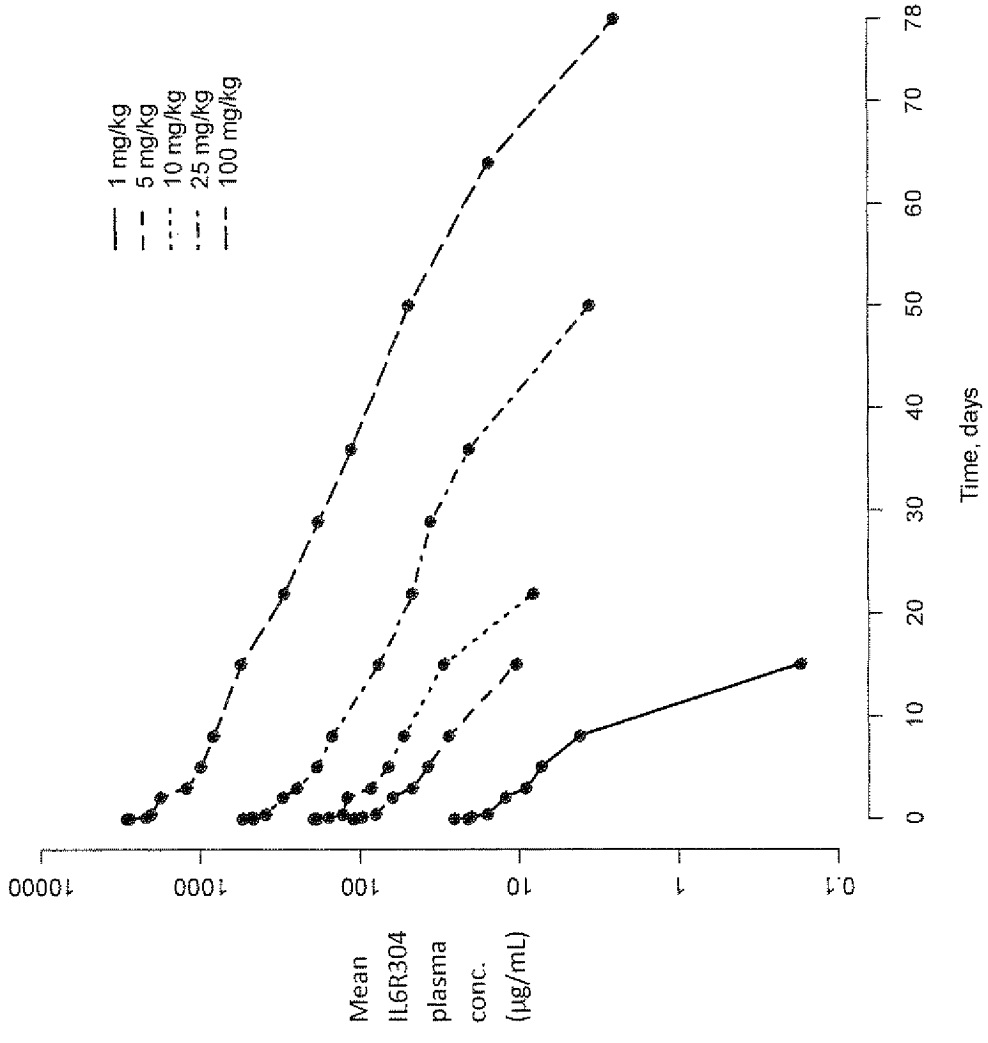

1 mg/kg
5 mg/kg
10 mg/kg
25 mg/kg
100 mg/kg
Mean IL6R304 plasma conc. (µg/mL)
10000
1000
100
10
1
0.1
0
10
20
30
40
50
60
70
78
Time, days

Figure 69

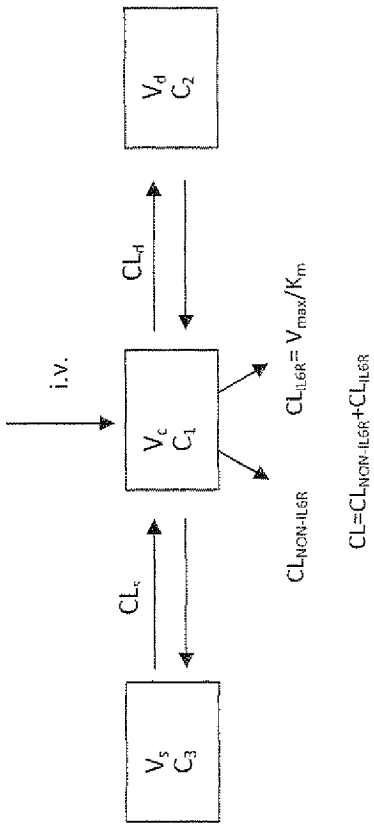

i.v.
V_c C_1
V_d C_2
V_s C_3
CL_d
CL_s
$CL_{IL6R} = V_{max}/K_m$
$CL_{NON-IL6R}$
$CL=CL_{NON-IL6R}+CL_{IL6R}$

Figure 70