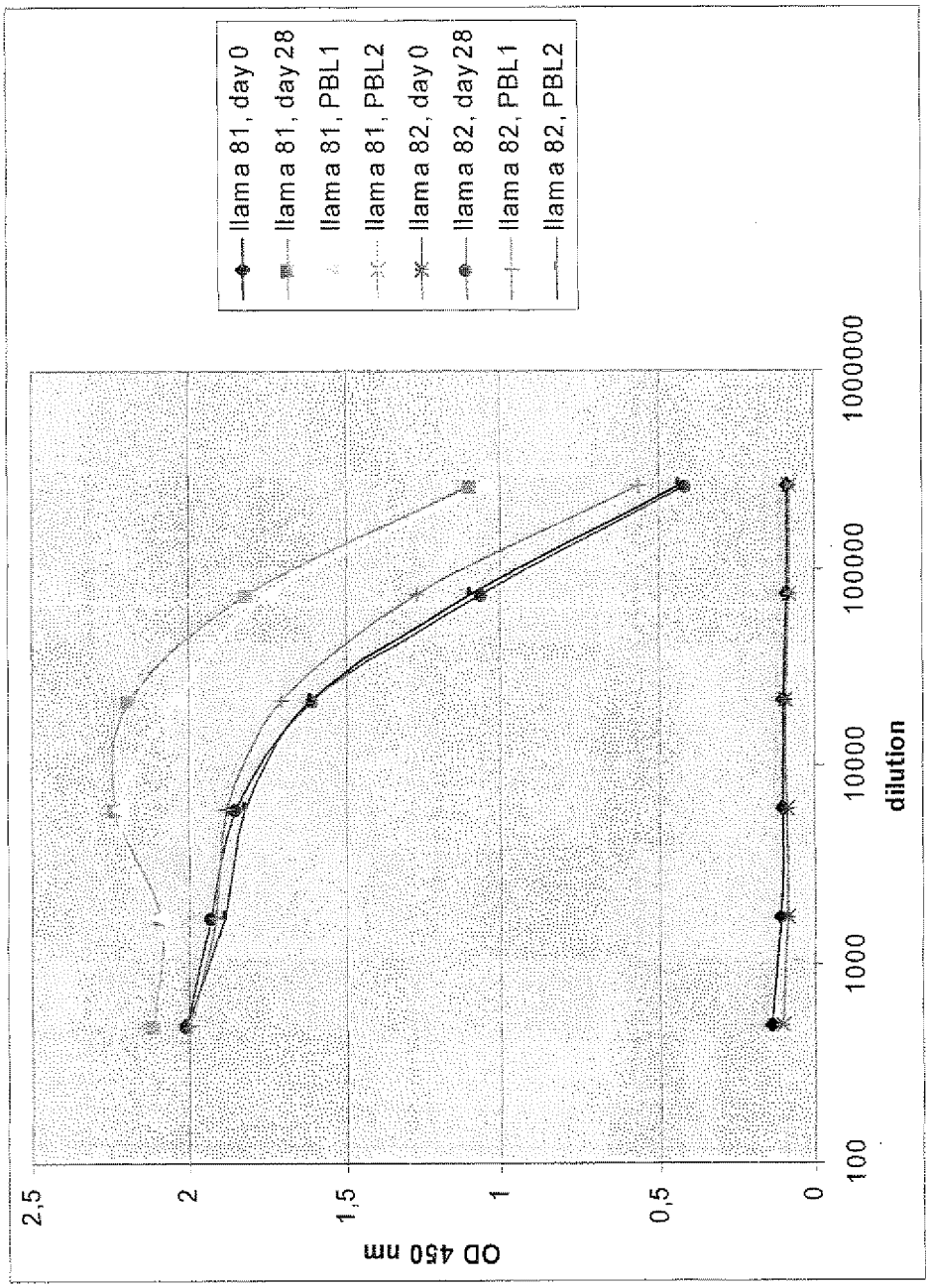

llama 81, day 0
llama 81, day 28
llama 81, PBL1
llama 81, PBL2
llama 82, day 0
llama 82, day 28
llama 82, PBL1
llama 82, PBL2
OD 450 nm
2,5
2
1,5
1
0,5
0
100
1000
10000
100000
1000000
dilution

Figure 1

Figure 2

U266B1

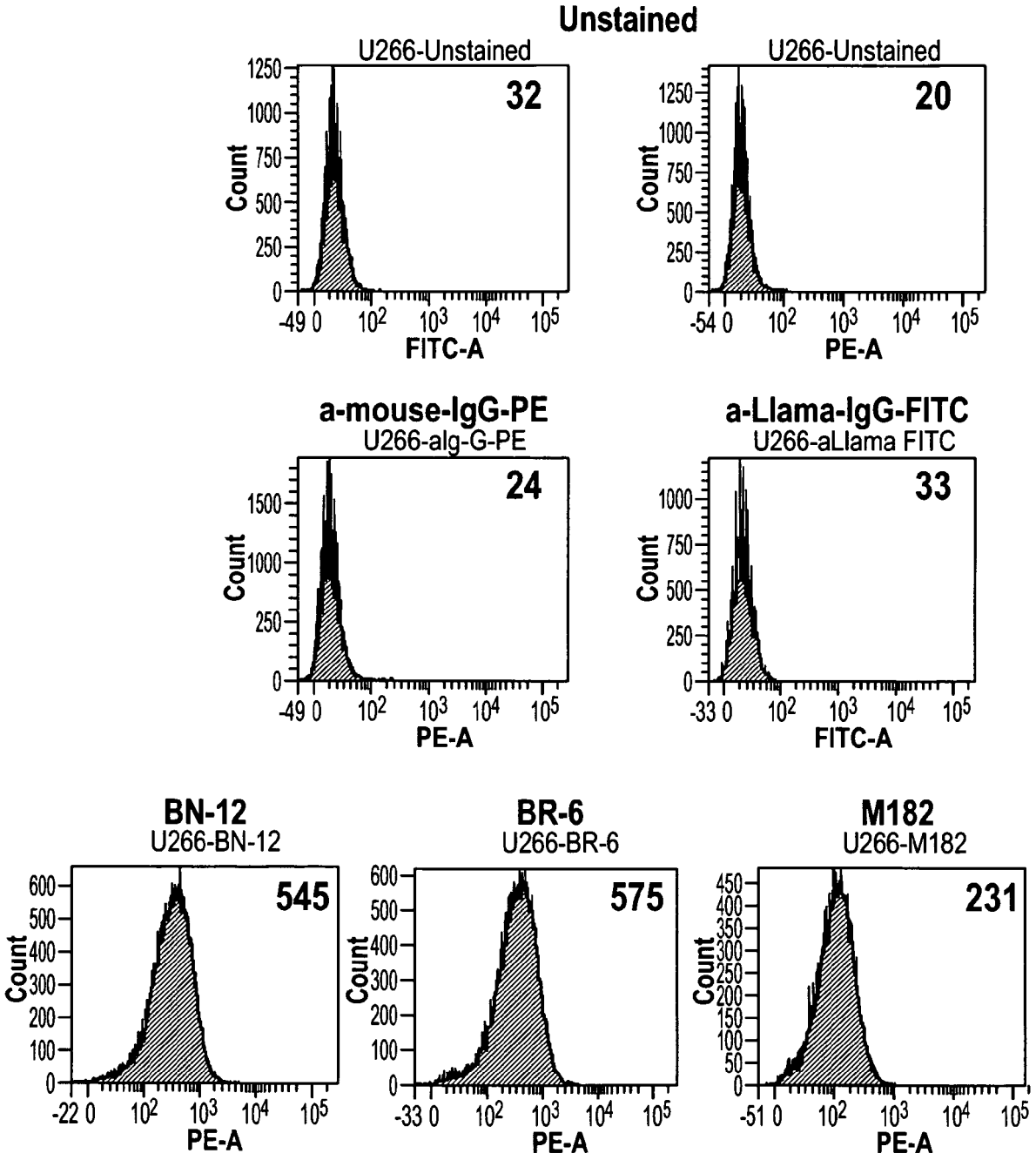
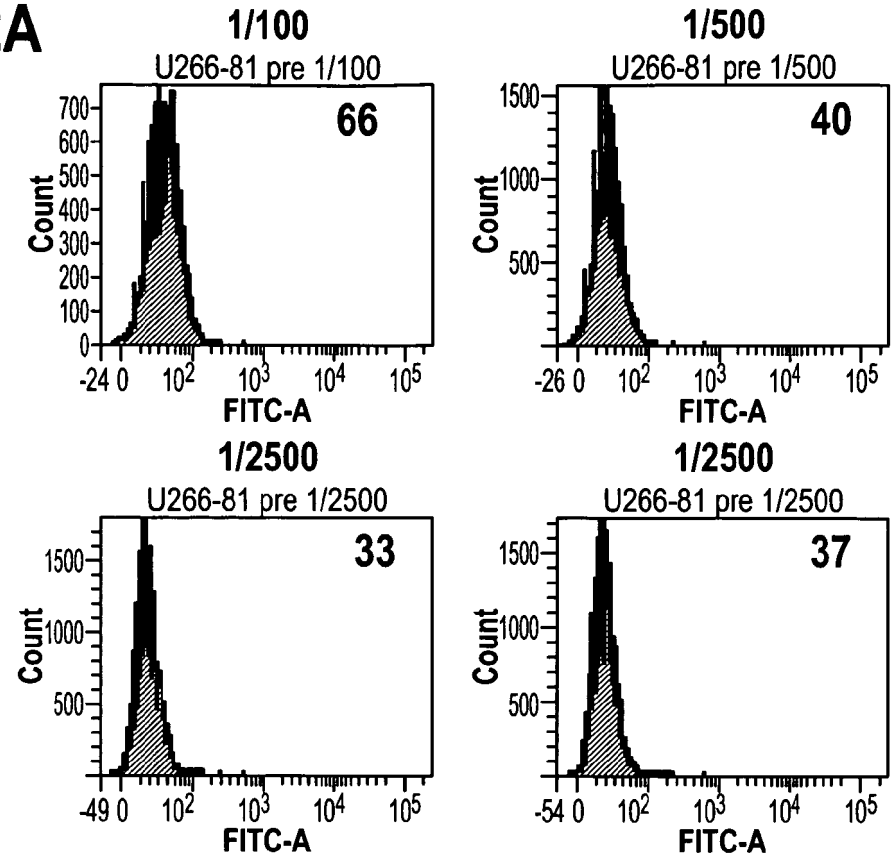


Figure 2A

LI81 pre



LI81 PBL1

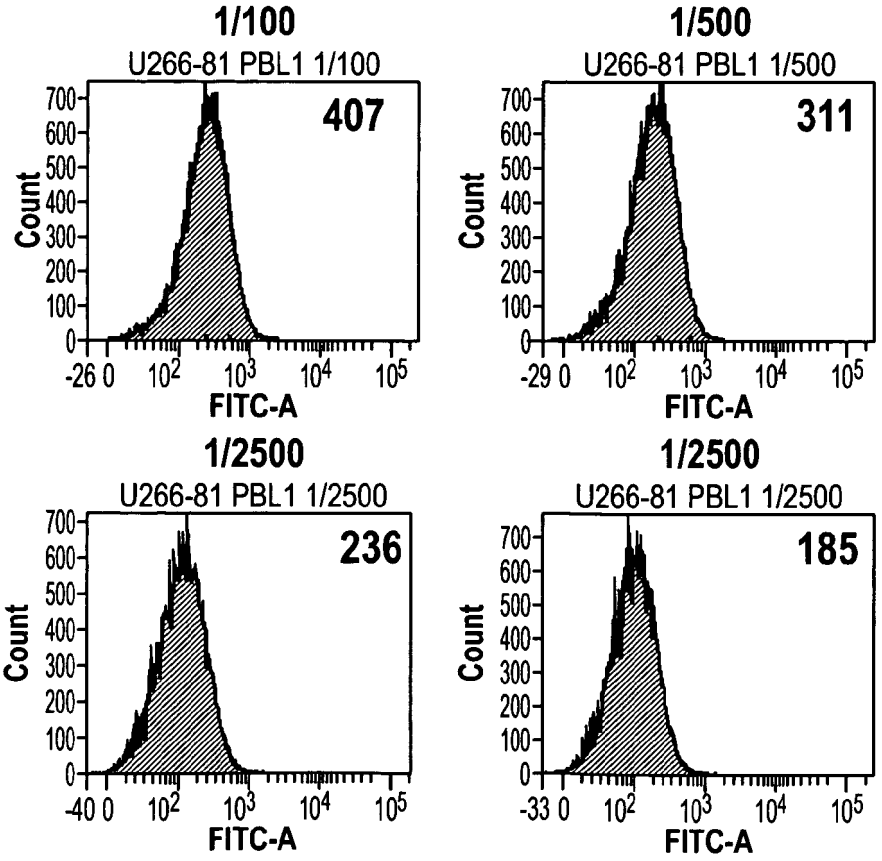
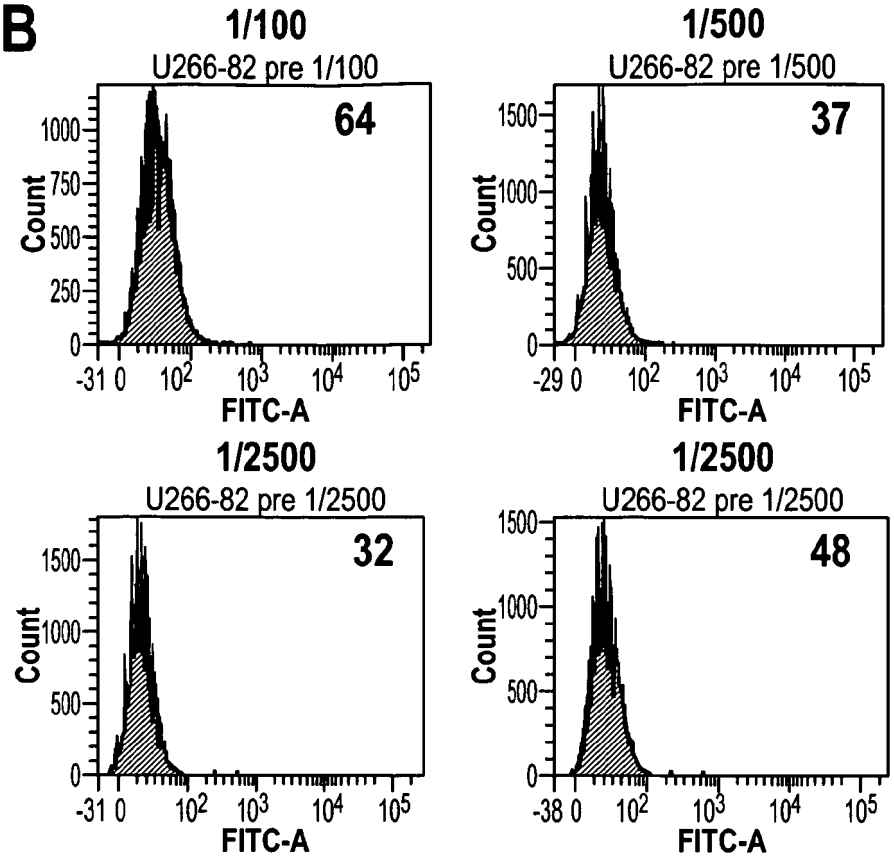
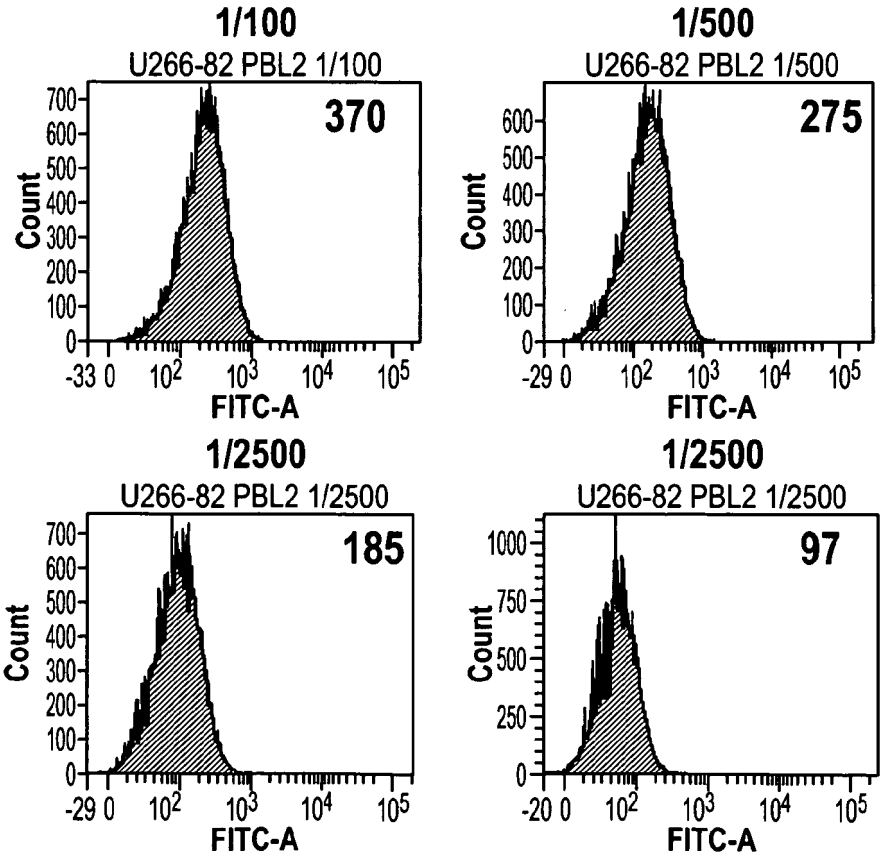


Figure 2B

LI82 pre



LI82 PBL2



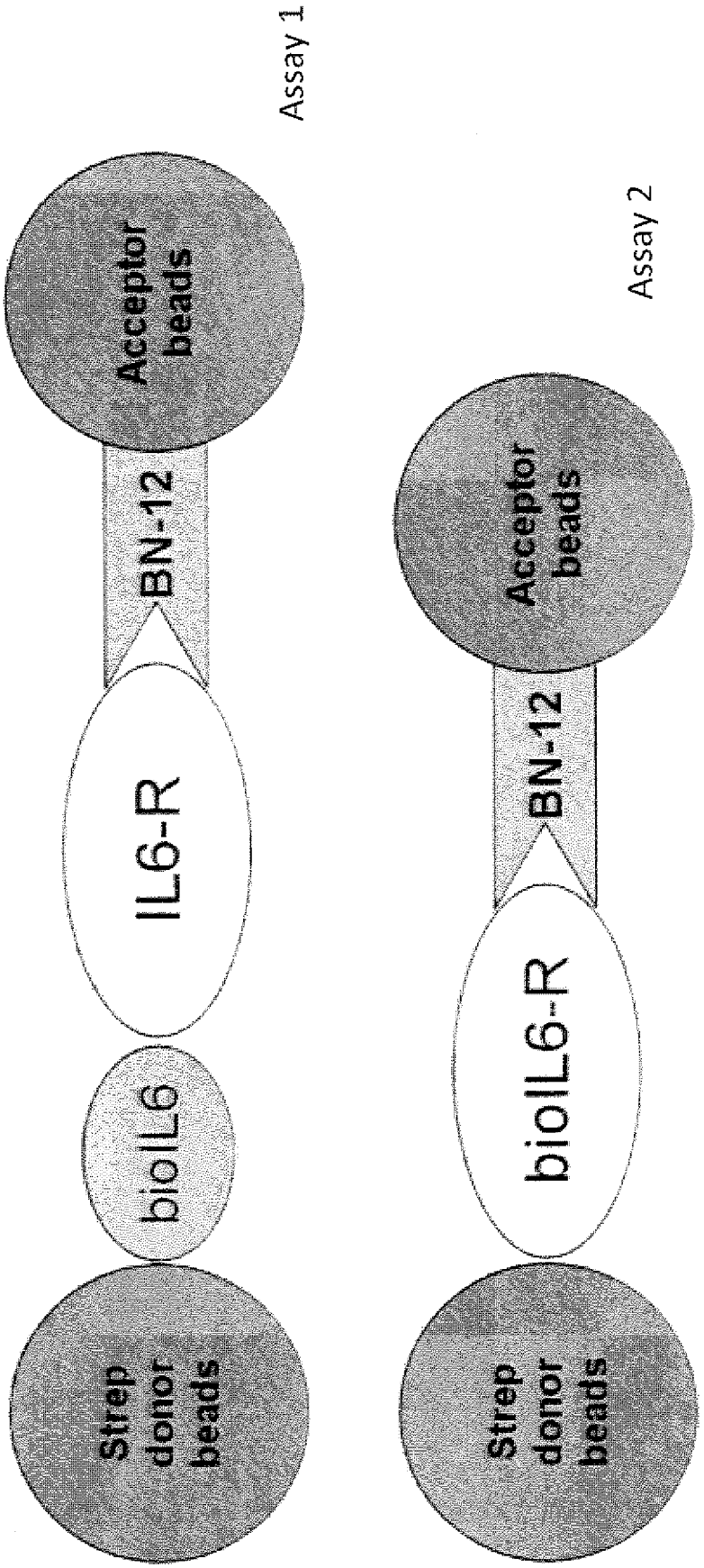

Assay 1
Acceptor beads
BN-12
IL6-R
bioIL6
Strep donor beads
Assay 2
Acceptor beads
BN-12
bioIL6-R
Strep donor beads

Figure 3

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
Inhibitors							
PMP40H5	EVQLVESGGGLVQPGGSLRLSCAASGFSLD YYAIG		WFRQAPGKEREGVS	CMDSSSGTTSTYYSDSVKG	RFTISRDDAKNTVYLQMNSLKPEDTAVYYCAA	DGHLNWGQRVYPCSQISWRGWNDY	WGQGTQVTVSS
PMP35E11	EVQLVESGGGLVQAGGSLRLSCAASGFTFD DYAIG		WFRQAPGKEHEGVS	CISSSDGSTYYADSVKG	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA	ERDVPARSLCGSYYWYDY	RGQGTQVTVSS
PMP32C9	EVQLVESGGGLVQAGGSLRLSCAASGFTFD DYDIG		WFRQAPGKEREGVS	GISSSDGNTYYADSVKG	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA	EPPDSSWYLDGSPEFFKY	WGQGTQVTVSS
PMP35H4	EVQLVESGGGLVQPGGSLRLSCAASGFTFD DYGMS		WVRQAPGRATEWVS	AISWNGNNTYYTESMKG	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCVK	GSTAIVGVPPTYPDEYDY	WGQGTQVTVSS
PMP32E10	EVQLVESGGGLVQPGGSLRLSCAASGFTFG SYDMS		WVRQAPGKGPEWVS	AINSGGGSTYYADSVKG	RFTISRDNAKNTLYLQMNSLKPEDTAVYYCAT	DWRYSDYDLPLPPPGDY	WGQGTQVTVSS
PMP30C11	EVQLVESGGGLVQAGGSLRLSCAASGRTFS SYDMG		WYRQAPGKEREFVA	VISRSGSSTYYADSVKG	RFTISRDNAKNTVYLQMNSLKPEDTAIYYCKA	EVVAGDYDY	WGQGTQVTVSS
PMP35C10	EVQLVESGGGLVQAGGSLRLSCAASGRTFS SYDMG		WYRQAPGKEREFVA	VIHWSSGSTYYADPVKG	RFTISRDNAKNTVYLQMNSLKPEDTAIYYCNA	FLPGPEGFHDY	WGQGTQVTVSS
PMP34G9	EVQLVESGGGLVQAGGSLRLSCAASGRTSS SYDMT		WYRQVPGKEREFVA	VISWSGGSTYYADSVKG	RFTISRDNAKNTVYLQMNSLKPEDTAIYYCNA	YTGGGDDY	WGQGTQVTVSS
PMP31A4	EVQLVESGGGLVQAGGSLRLSCAASGSIFK VNAMG		WYRQAPGKQRELVA	GIISGGSTNYADSVKG	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	EVQLVESGGGLVQPGGSLRLSCAASGFPLD YYAIG		WFRQAPGKEREGVS	CISSSDGSTYYADSVKG	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAL	VHTTAQATGVPQREYEYEW	WGQGTQVTVSS
PMP35F4	EVQLVESGGGLVQAGGSLRLSCAASGRTFS SYDMG		WYRQAPGKEREFVA	IITWNSSTYYADSVKG	RFTISRDNAKNTVYLQMNSLKPEDTAIYYCNA	QYGLGYAEDY	WGQGTQVTVSS

Figure 4

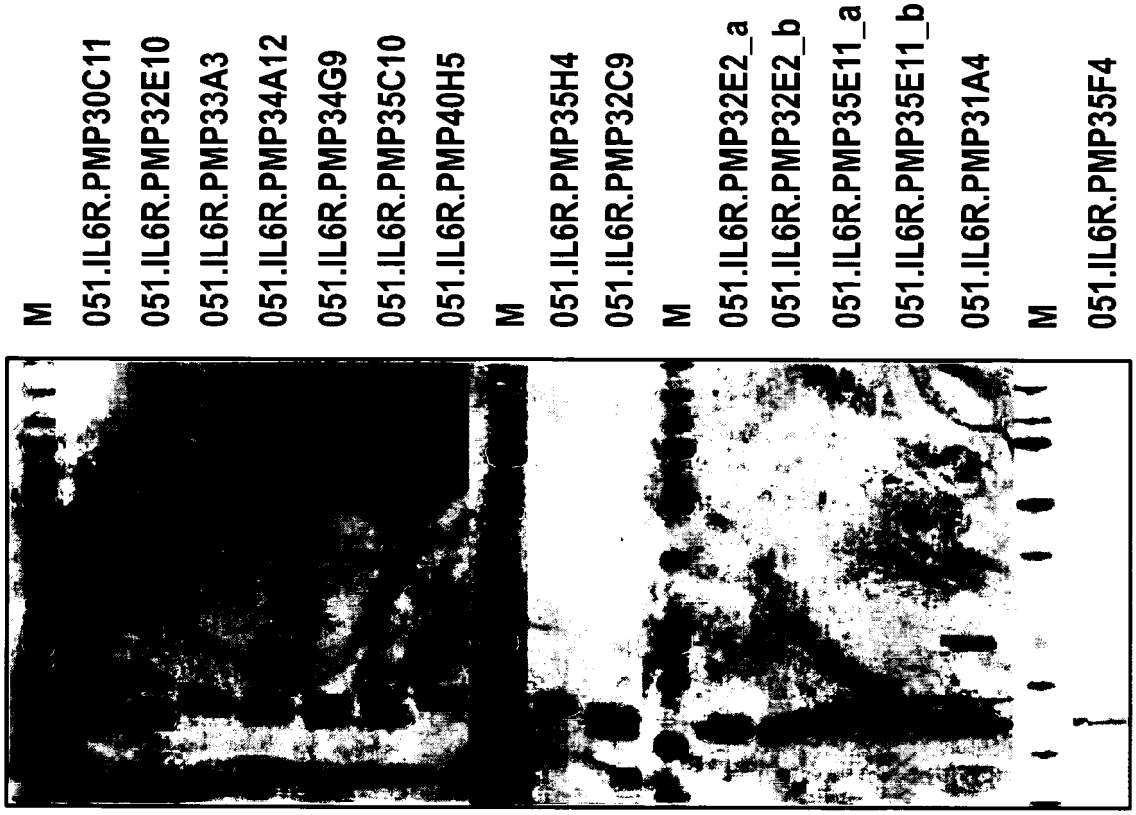

M
051.IL6R.PMP30C11
051.IL6R.PMP32E10
051.IL6R.PMP33A3
051.IL6R.PMP34A12
051.IL6R.PMP34G9
051.IL6R.PMP35C10
051.IL6R.PMP40H5
M
051.IL6R.PMP35H4
051.IL6R.PMP32C9
M
051.IL6R.PMP32E2_a
051.IL6R.PMP32E2_b
051.IL6R.PMP35E11_a
051.IL6R.PMP35E11_b
051.IL6R.PMP31A4
M
051.IL6R.PMP35F4

Figure 5

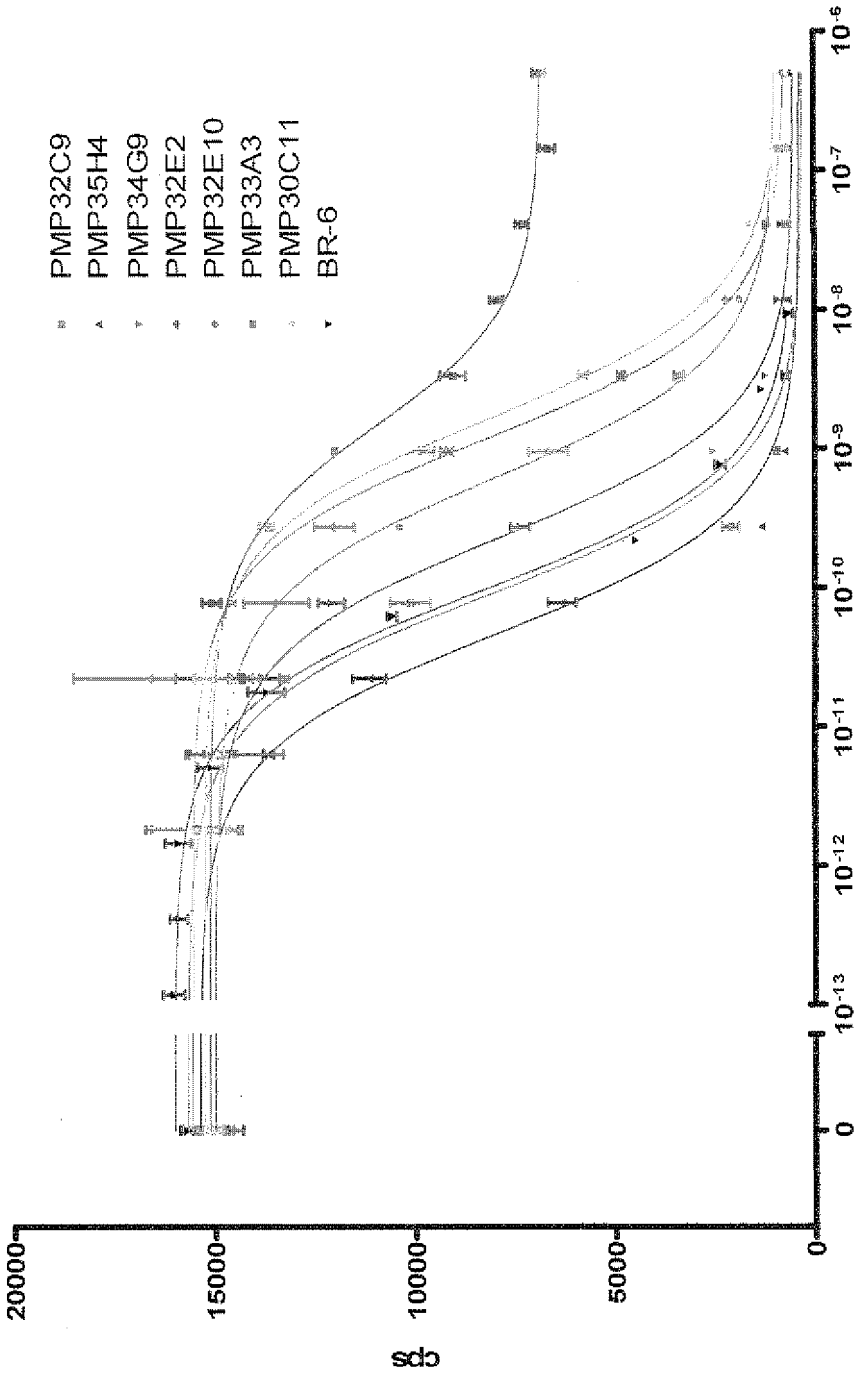

PMP32C9
PMP35H4
PMP34G9
PMP32E2
PMP32E10
PMP33A3
PMP30C11
BR-6
cps
20000
15000
10000
5000
0
0
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[competitor],M

Figure 6A

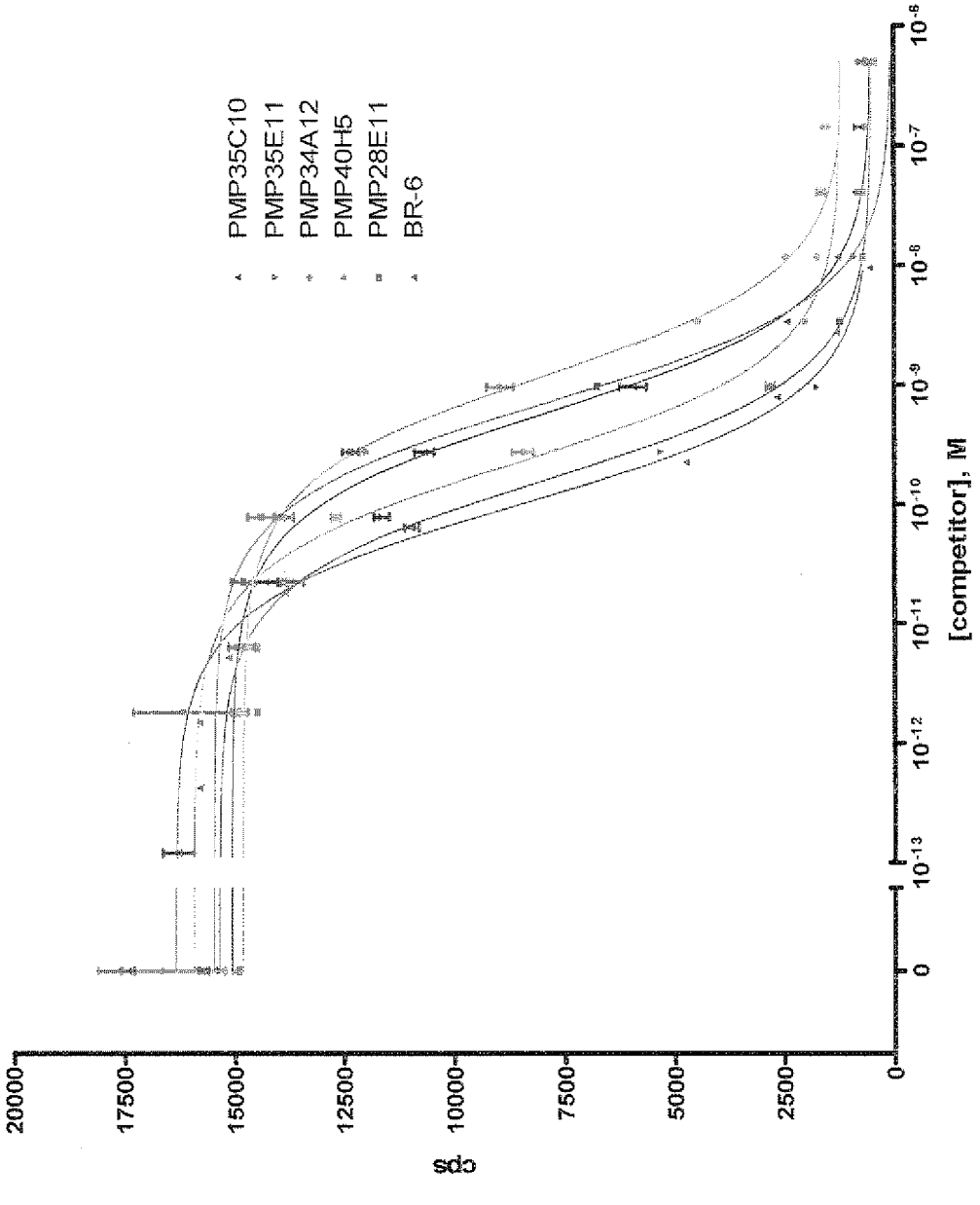

PMP35C10
PMP35E11
PMP34A12
PMP40H5
PMP28E11
BR-6
cps
[competitor], M
20000
17500
15000
12500
10000
7500
5000
2500
0
0
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6

Figure 6B

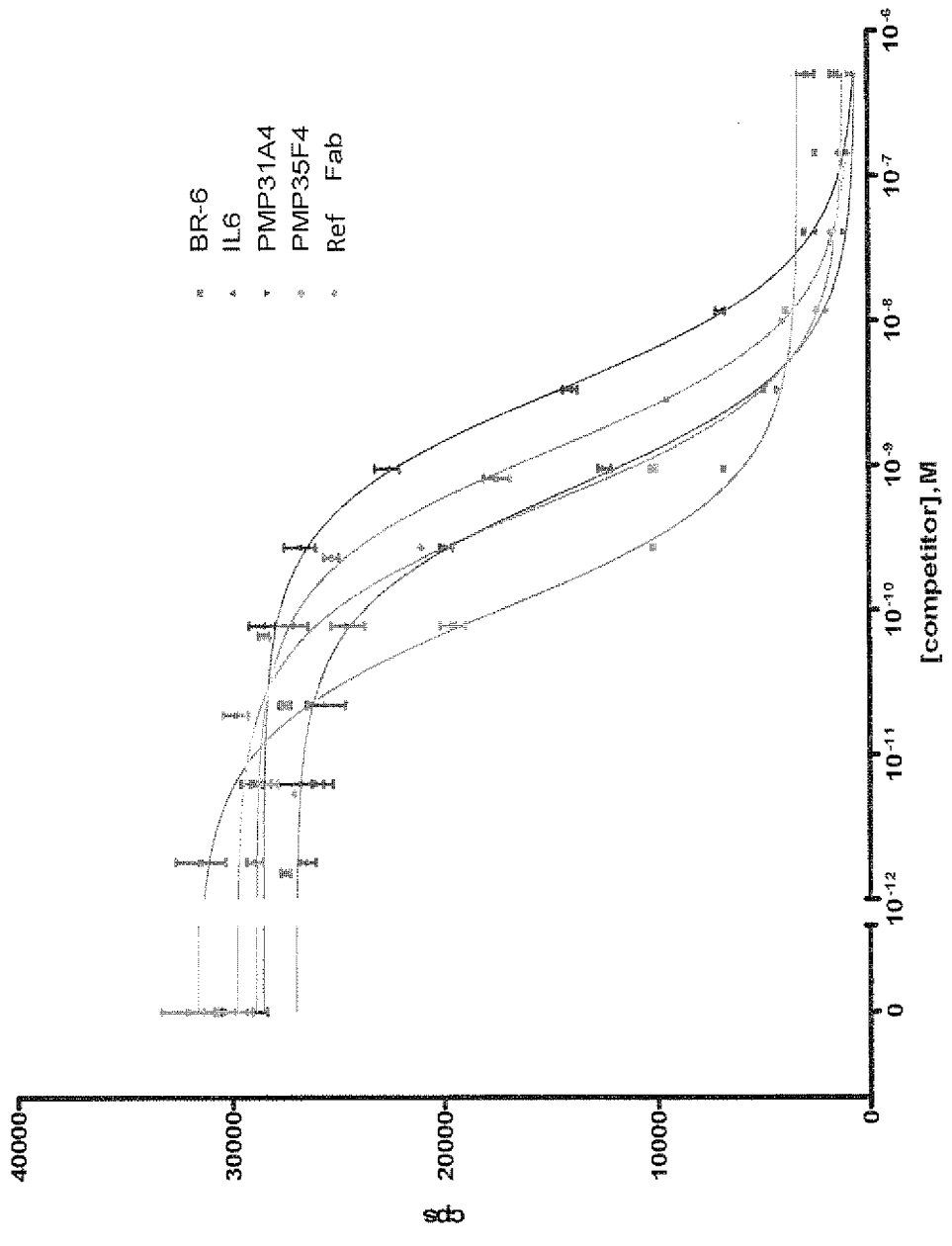

BR-6
IL6
PMP31A4
PMP35F4
Ref Fab
cps
40000
30000
20000
10000
0
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[competitor], M

Figure 6C

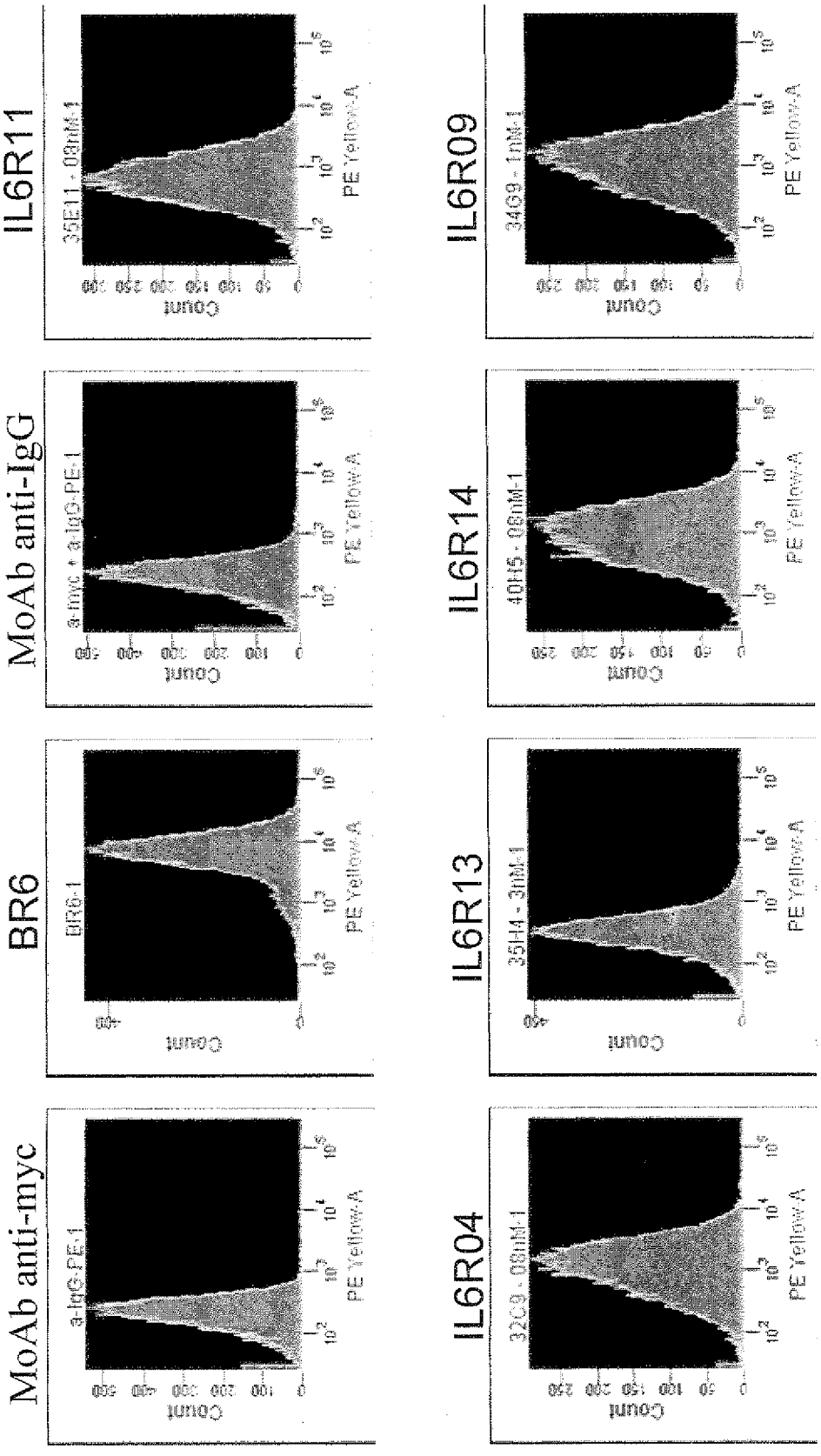

MoAb anti-myc
BR6
MoAb anti-IgG
IL6R11
IL6R04
IL6R13
IL6R14
IL6R09
Count
PE Yellow-A

Figure 7

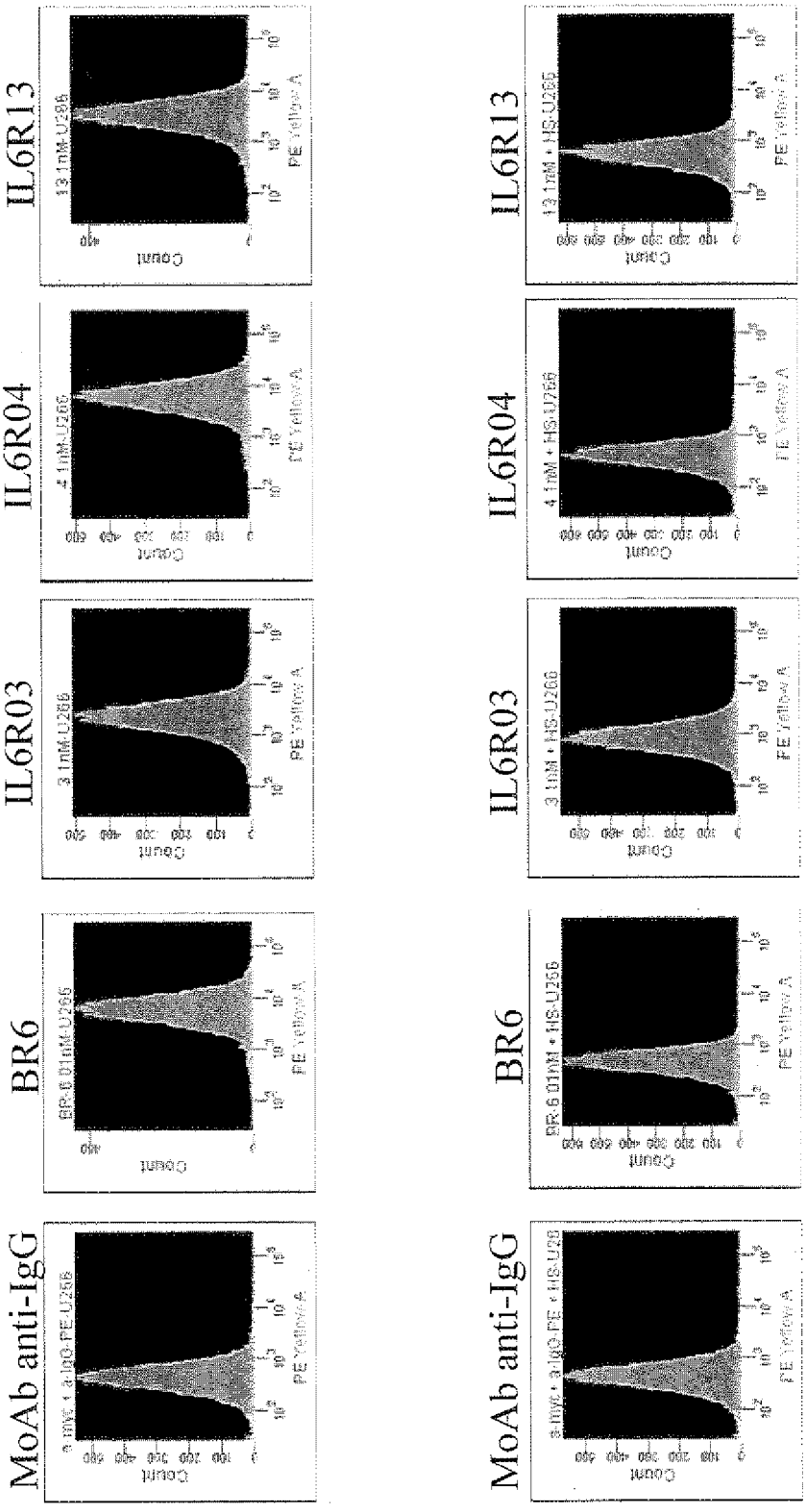


Figure 8

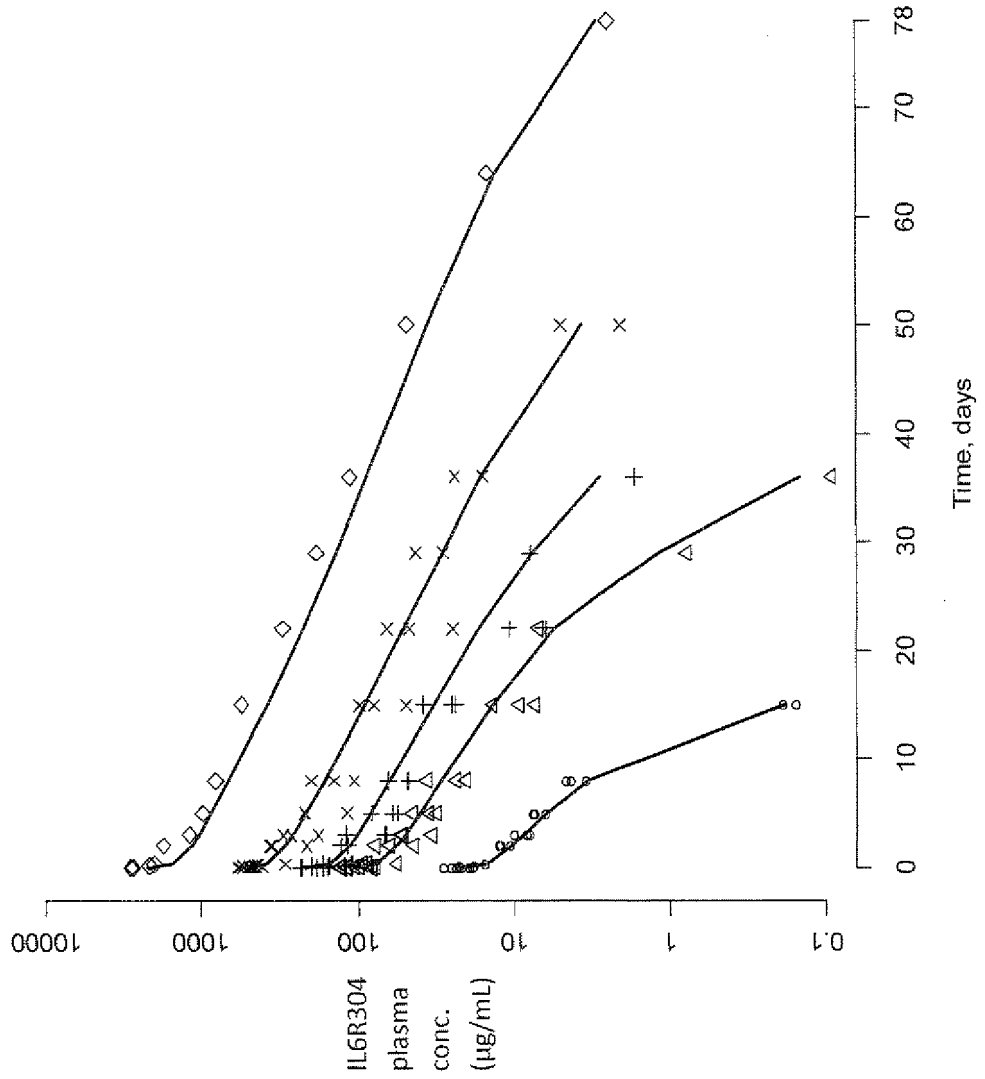

IL6R304 plasma conc. (µg/mL)
10000
1000
100
10
1
0.1
Time, days
0
10
20
30
40
50
60
70
78

Figure 9

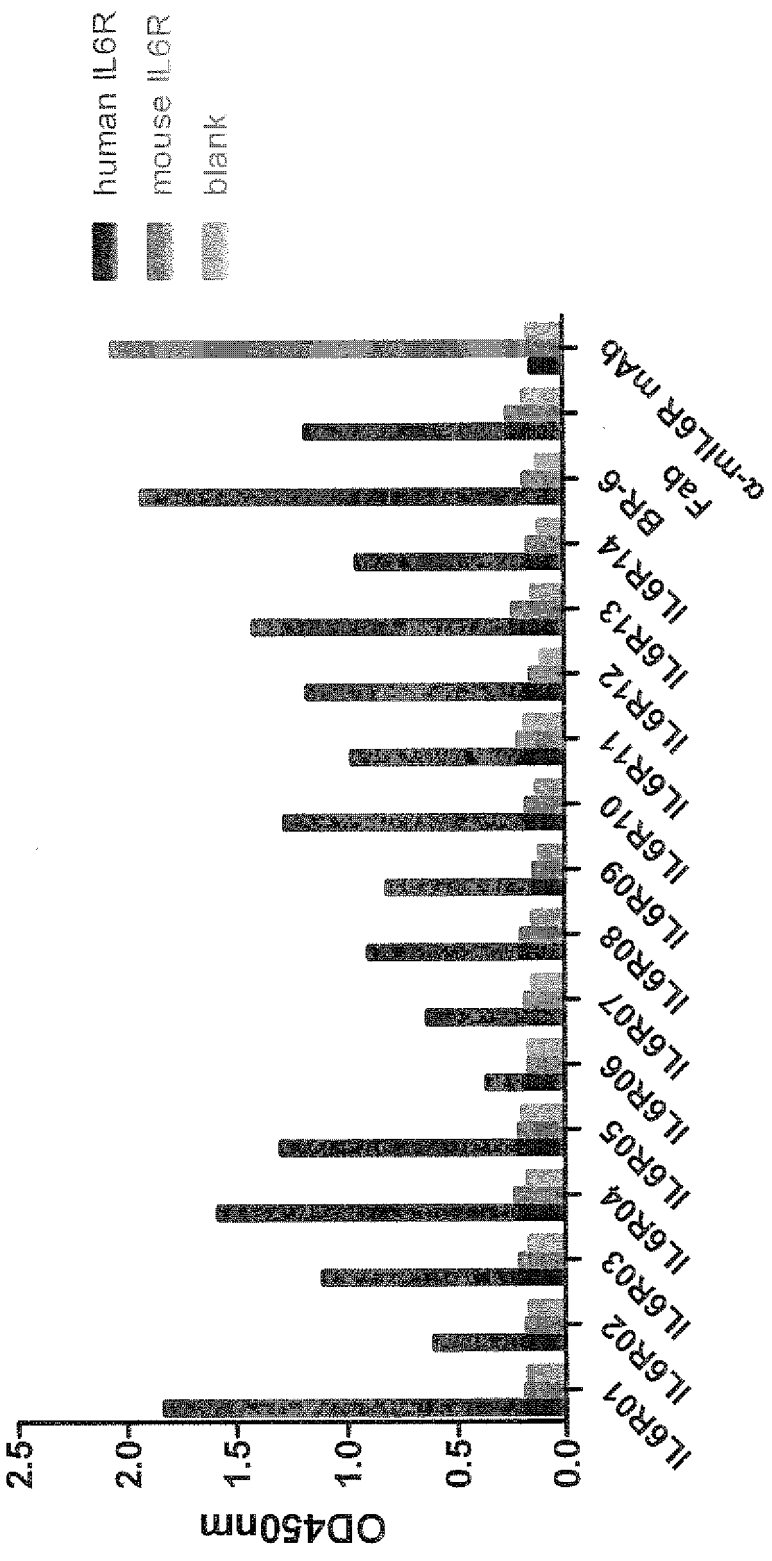

human IL6R
mouse IL6R
blank
OD450nm
2.5
2.0
1.5
1.0
0.5
0.0
IL6R01
IL6R02
IL6R03
IL6R04
IL6R05
IL6R06
IL6R07
IL6R08
IL6R09
IL6R10
IL6R11
IL6R12
IL6R13
IL6R14
BR-6
Fab
α-mIL6R mAb

Figure 10

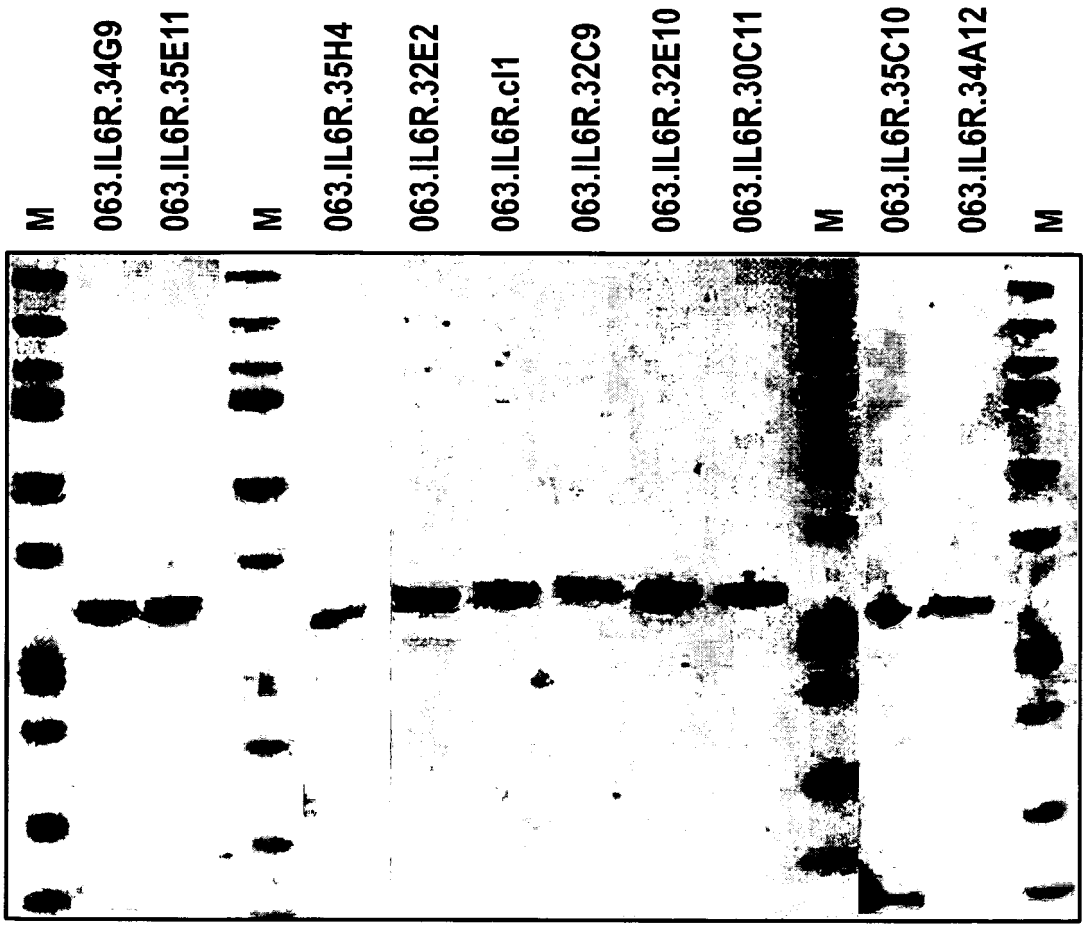

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063.IL6R.35E11
M
063.IL6R.35H4
063.IL6R.32E2
063.IL6R.cl1
063.IL6R.32C9
063.IL6R.32E10
063.IL6R.30C11
M
063.IL6R.35C10
063.IL6R.34A12
M

Figure 11

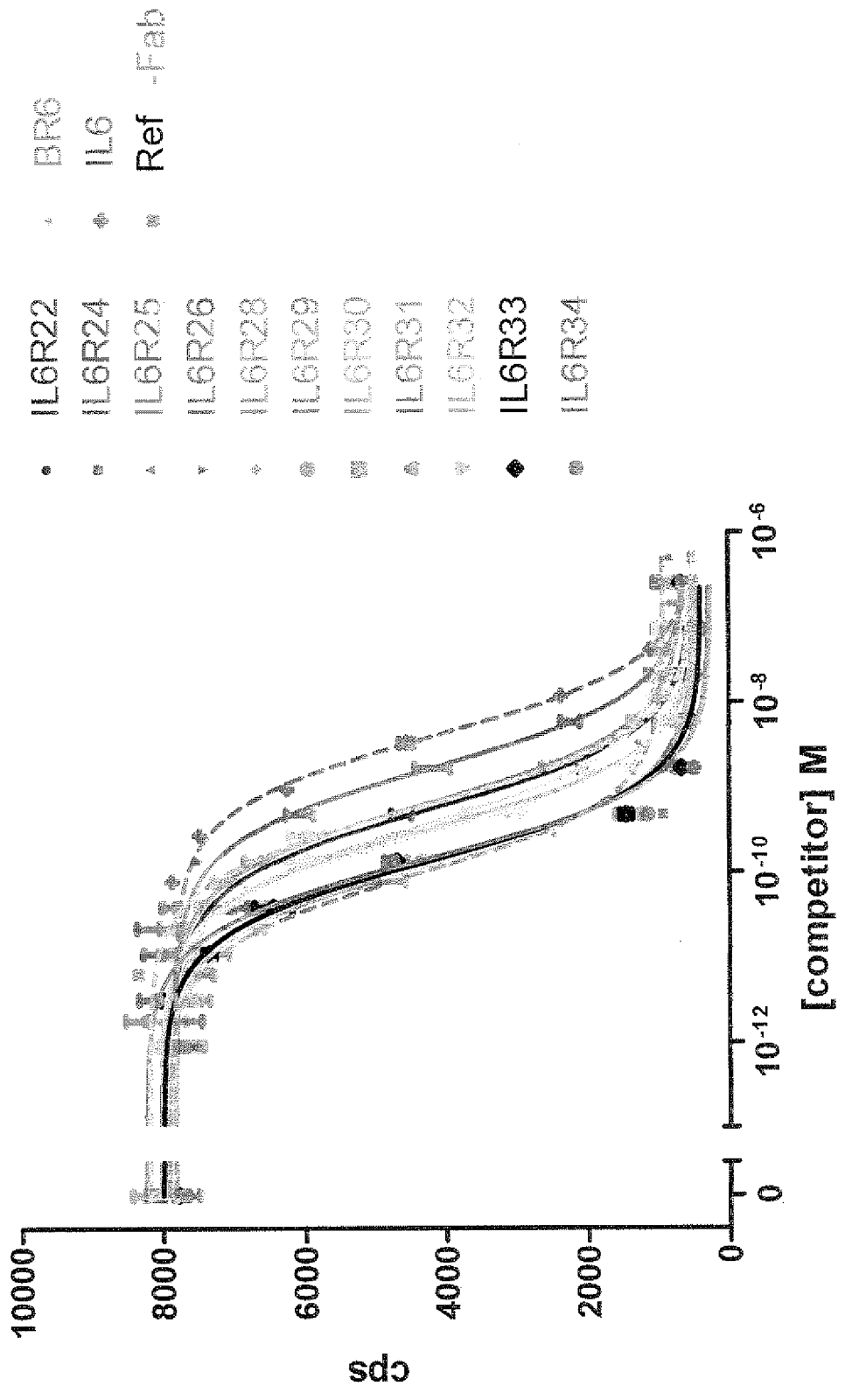

BR6
IL6
Ref -Fab
IL6R22
IL6R24
IL6R25
IL6R26
IL6R28
IL6R29
IL6R30
IL6R31
IL6R32
IL6R33
IL6R34
cps
10000
8000
6000
4000
2000
0
0
10-12
10-10
10-8
10-6
[competitor] M

Figure 12

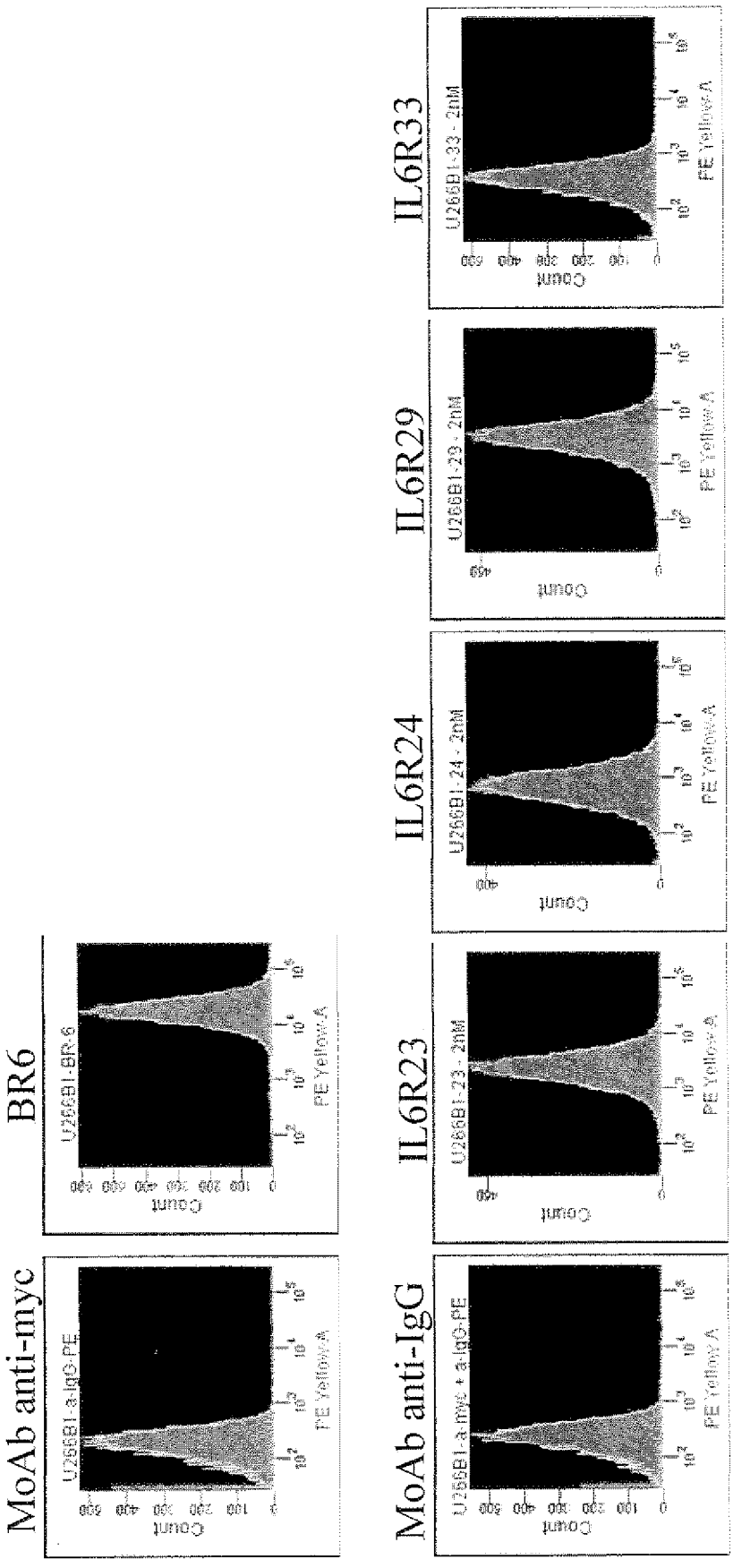

MoAb anti-myc
BR6
IL6R23
IL6R24
IL6R29
IL6R33
MoAb anti-IgG
Count
PE Yellow-A

Figure 13

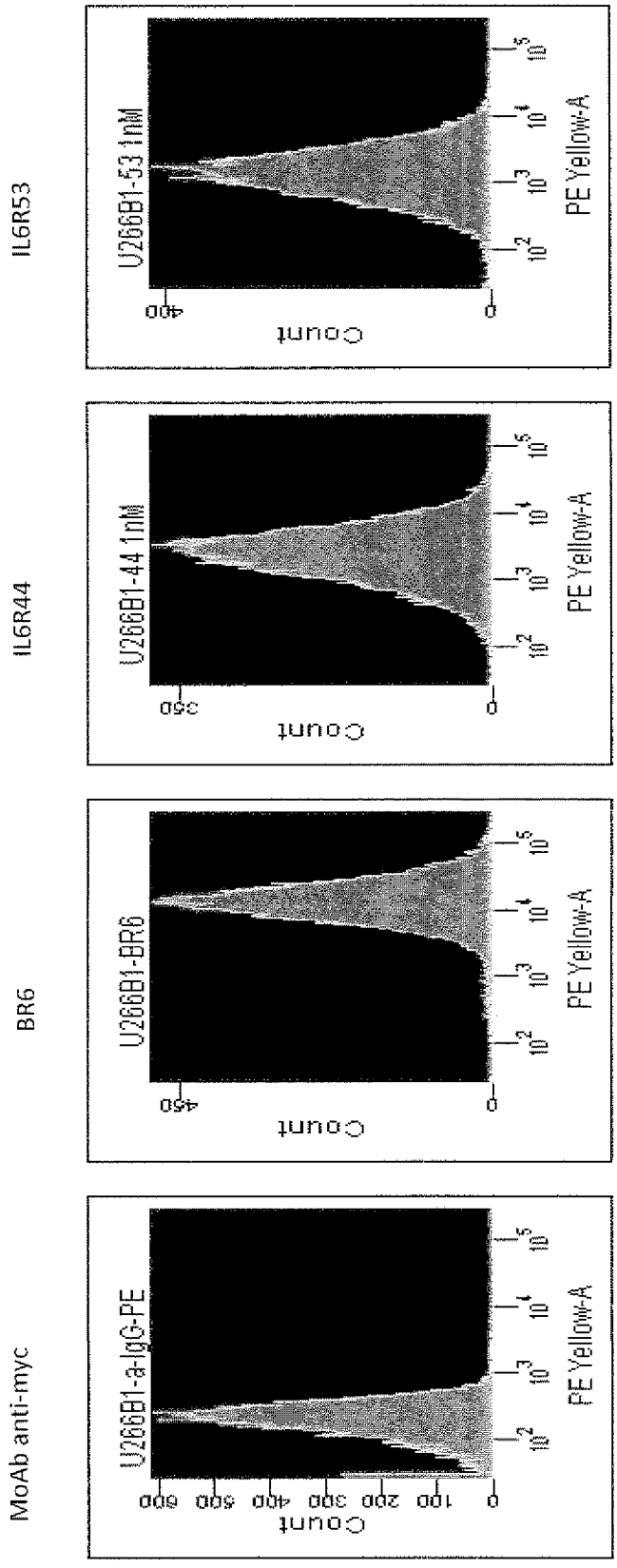

MoAb anti-myc
BR6
IL6R44
IL6R53
U266B1-a-IgG-PE
U266B1-BR6
U266B1-44 1nM
U266B1-53 1nM
Count
PE Yellow-A

Figure 14

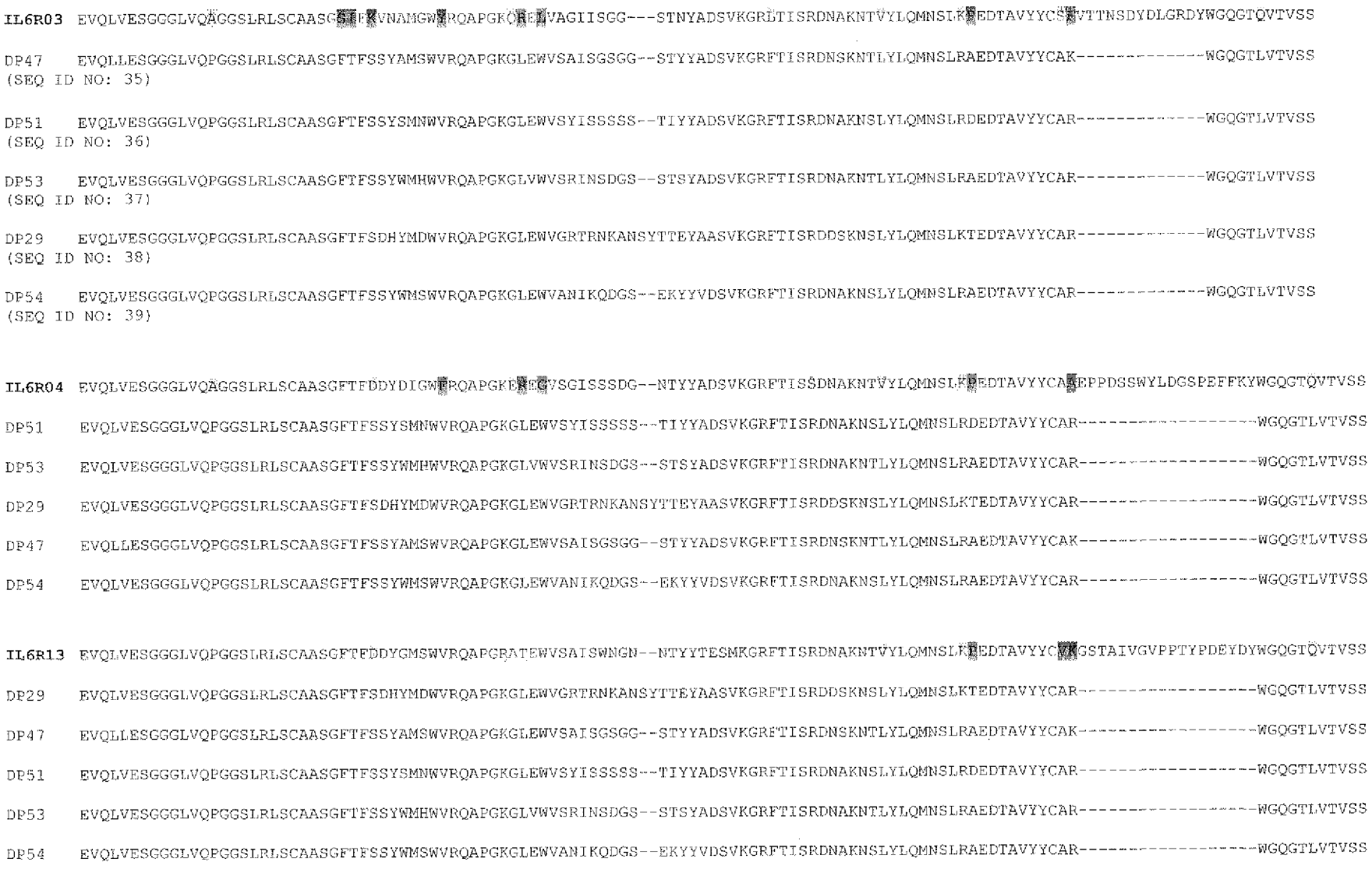

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DP47 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG--STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK----------WGQGTLVTVSS
(SEQ ID NO: 35)
DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSS--TIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR----------WGQGTLVTVSS
(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 EVQLVESGGGLVQAGGSLRLSCAASGFTFDDYDIGWFRQAPGKEREGVSGISSSDG--NTYYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAREPPDSSWYLDGSPEFFKYWGQGTQVTVSS
DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSS--TIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR----------WGQGTLVTVSS
DP53 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGS--STSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS
DP29 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGRTRNKANSYTTEYAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCAR----------WGQGTLVTVSS
DP47 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG--STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK----------WGQGTLVTVSS
DP54 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGS--EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS
IL6R13 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGN--NTYYTESMKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTQVTVSS
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DP47 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG--STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK----------WGQGTLVTVSS
DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSS--TIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR----------WGQGTLVTVSS
DP53 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGS--STSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS
DP54 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGS--EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR----------WGQGTLVTVSS

Figure 15

IL6R03	EVQLVESGGGLVQAGGSLRLSCAASGSIFKVNAMGWYRQAPGKQRELVAGIISGGSTNYADSVKGRLTISRDNAKNTVYLQMNSLKPEDTAVYYCSFVTTNSDYDLGRDYWGQGTQVTVSS
IL6R61	EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRLTISRDNAKNTVYLQMNSLRPEDTAVYYCSFVTTNSDYDLGRDYWGQGTLVTVSS
IL6R62	EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRFTISRDNAKNTVYLQMNSLRPEDTAVYYCSFVTTNSDYDLGRDYWGQGTLVTVSS
IL6R63	EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRLTISRDNAKNTLYLQMNSLRPEDTAVYYCSFVTTNSDYDLGRDYWGQGTLVTVSS
IL6R64	EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRLTISRDNAKNTVYLQMNSLRPEDTAVYYCAFVTTNSDYDLGRDYWGQGTLVTVSS
IL6R65	EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCAFVTTNSDYDLGRDYWGQGTLVTVSS

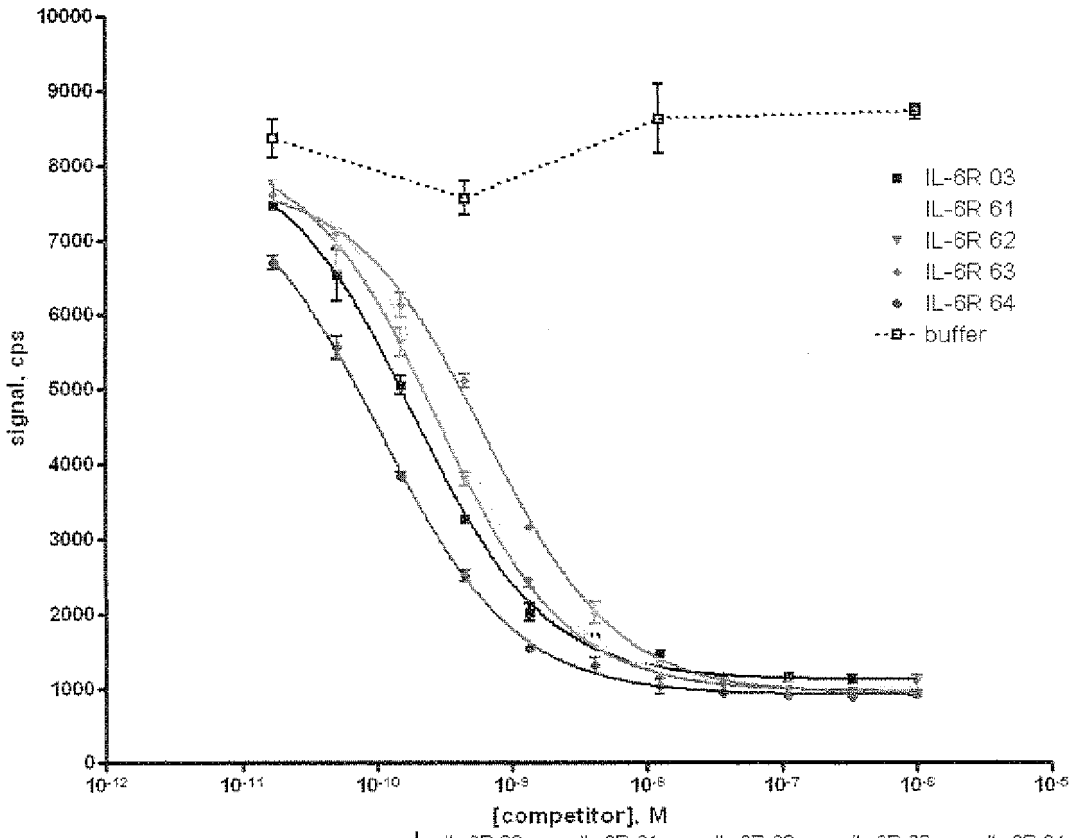
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IL6R71	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS
IL6R72	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS
IL6R73	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISRDNAKNTVYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS
IL6R74	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISSDNAKNTLYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS
IL6R75	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYDIGWFRQAPGKGREGVSGISSSDGNTYYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCAAEPPDSSWYLDGSPEFFKYWGQGTLVTVSS

Figure 16A

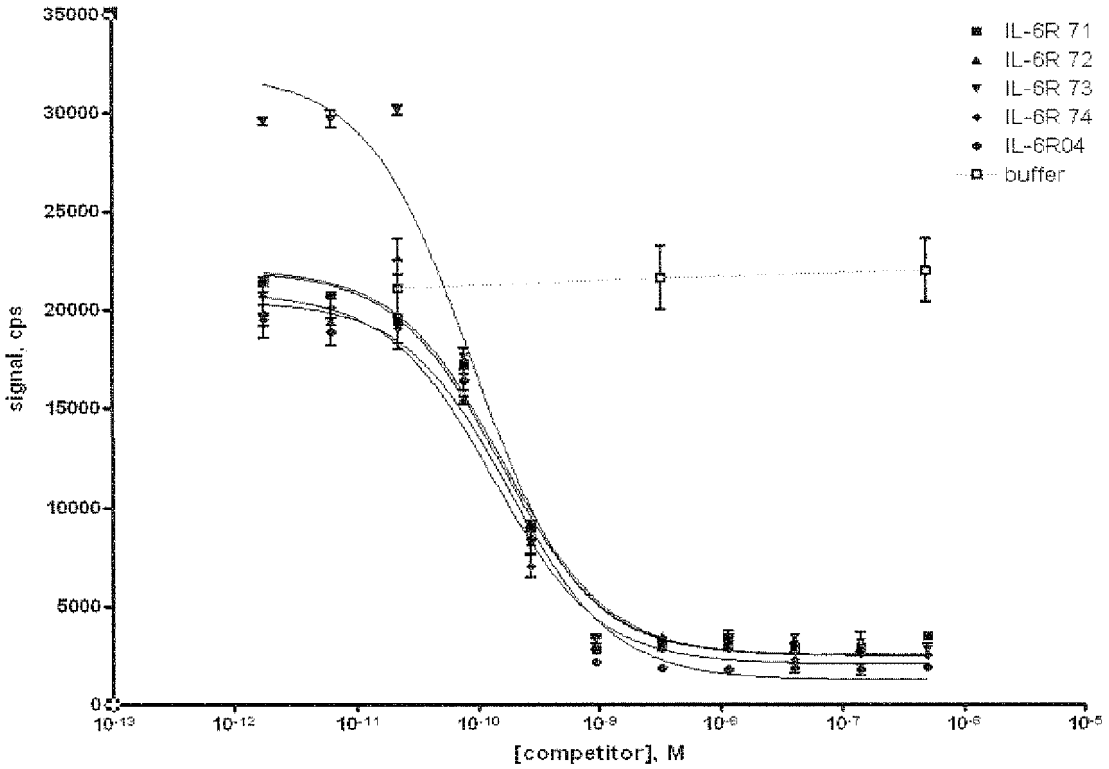
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IL6R81 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTVYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R82 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTVYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R83 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R84 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R85 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNARNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R86 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R87 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R88 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R89 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGRATEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTRYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS
IL6R90 EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKALEWVSAISWNGNNTYYTESMKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCVKGSTAIVGVPPTYPDEYDYWGQGTLVTVSS

Figure 16B



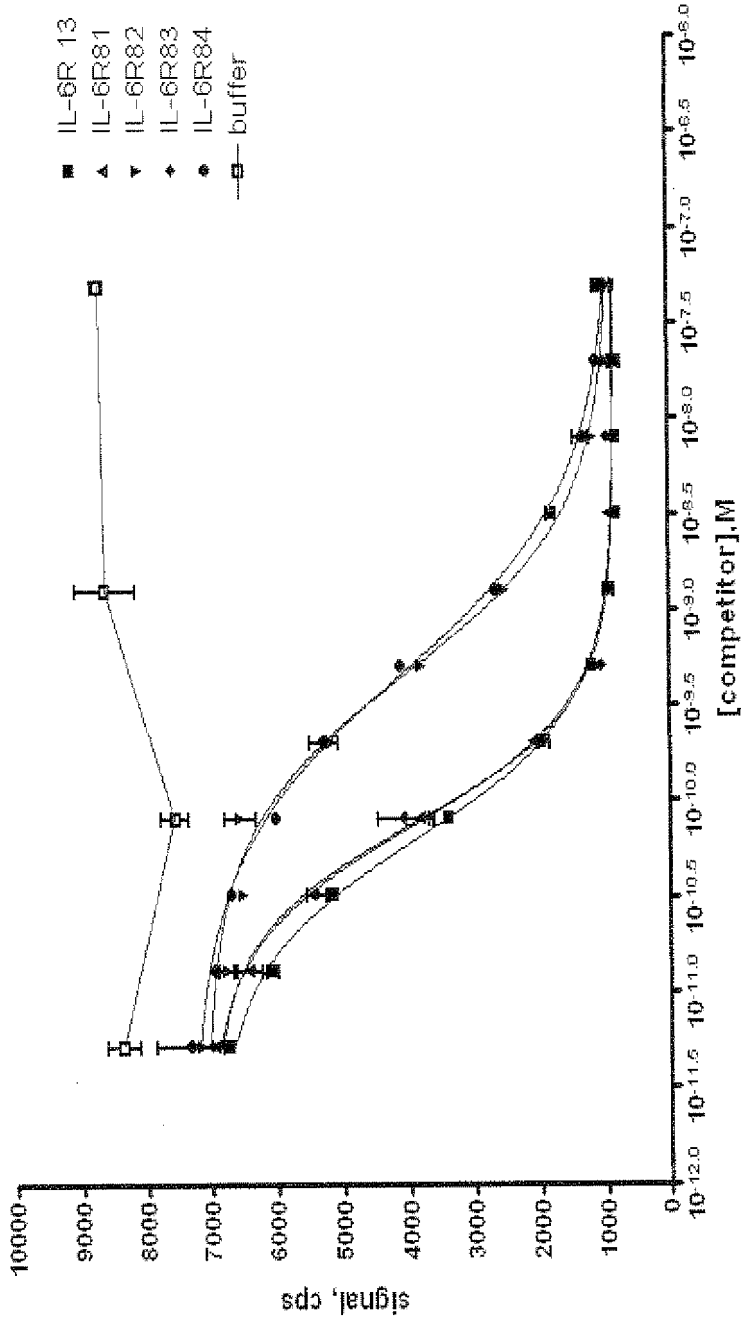
	IL-6R 03	IL-6R 61	IL-6R 62	IL-6R 63	IL-6R 64
Sigmoidal dose-response (variable slope)					
Best-fit values					
BOTTOM	1112	1011	957.9	926.5	908.6
TOP	8238	8206	8255	7788	7903
LOGEC50	-9.729	-9.473	-9.552	-9.187	-9.967
HILLSLOPE	-0.8898	-0.9841	-0.8962	-0.8886	-0.8624
EC50	1.867e-010	3.362e-010	2.804e-010	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	22034	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



Sigmoidal dose-response (variable slope)	IL-6R 13	IL-6R81	IL-6R82	IL-6R83	IL-6R84
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

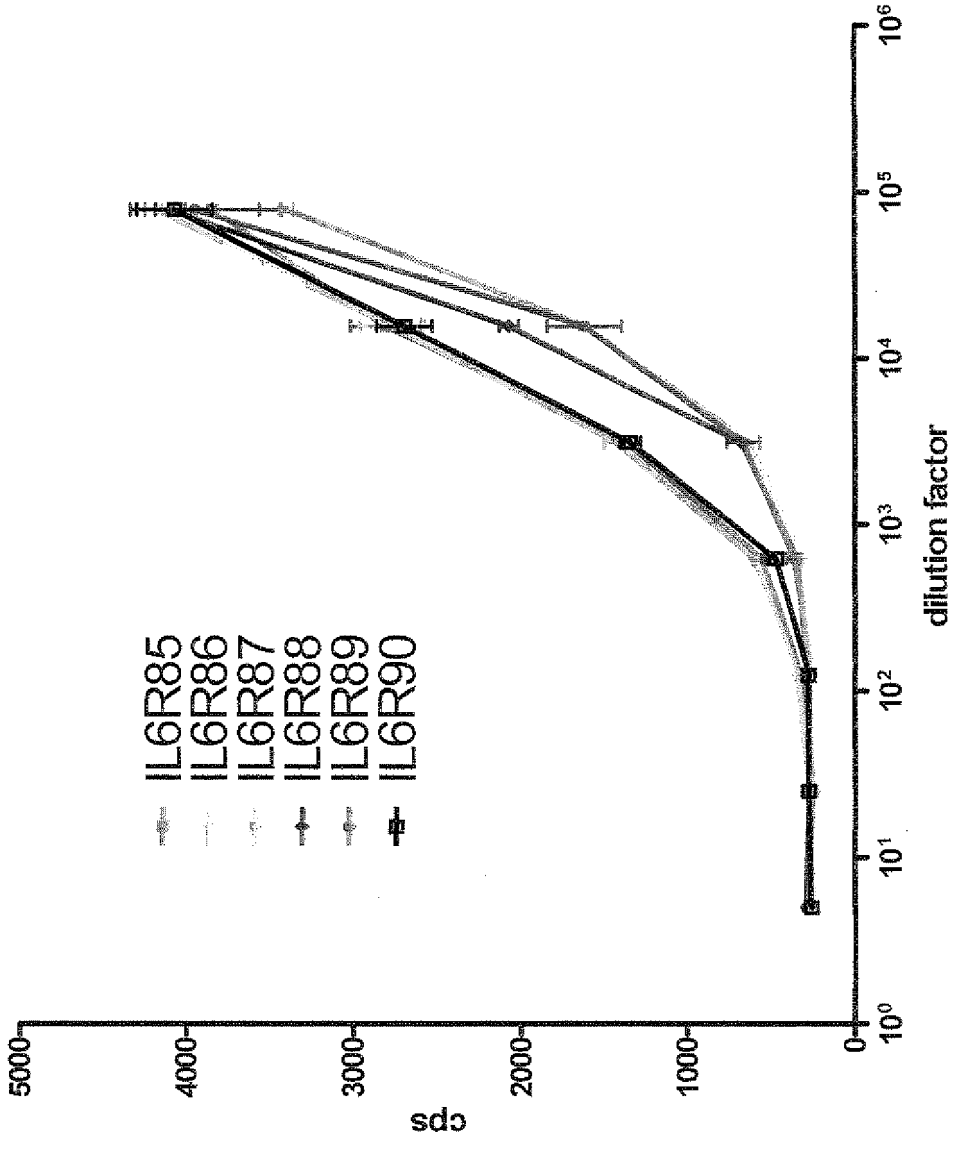

IL6R85
IL6R86
IL6R87
IL6R88
IL6R89
IL6R90
cps
5000
4000
3000
2000
1000
0
10^0
10^1
10^2
10^3
10^4
10^5
10^6
dilution factor

Figure 20

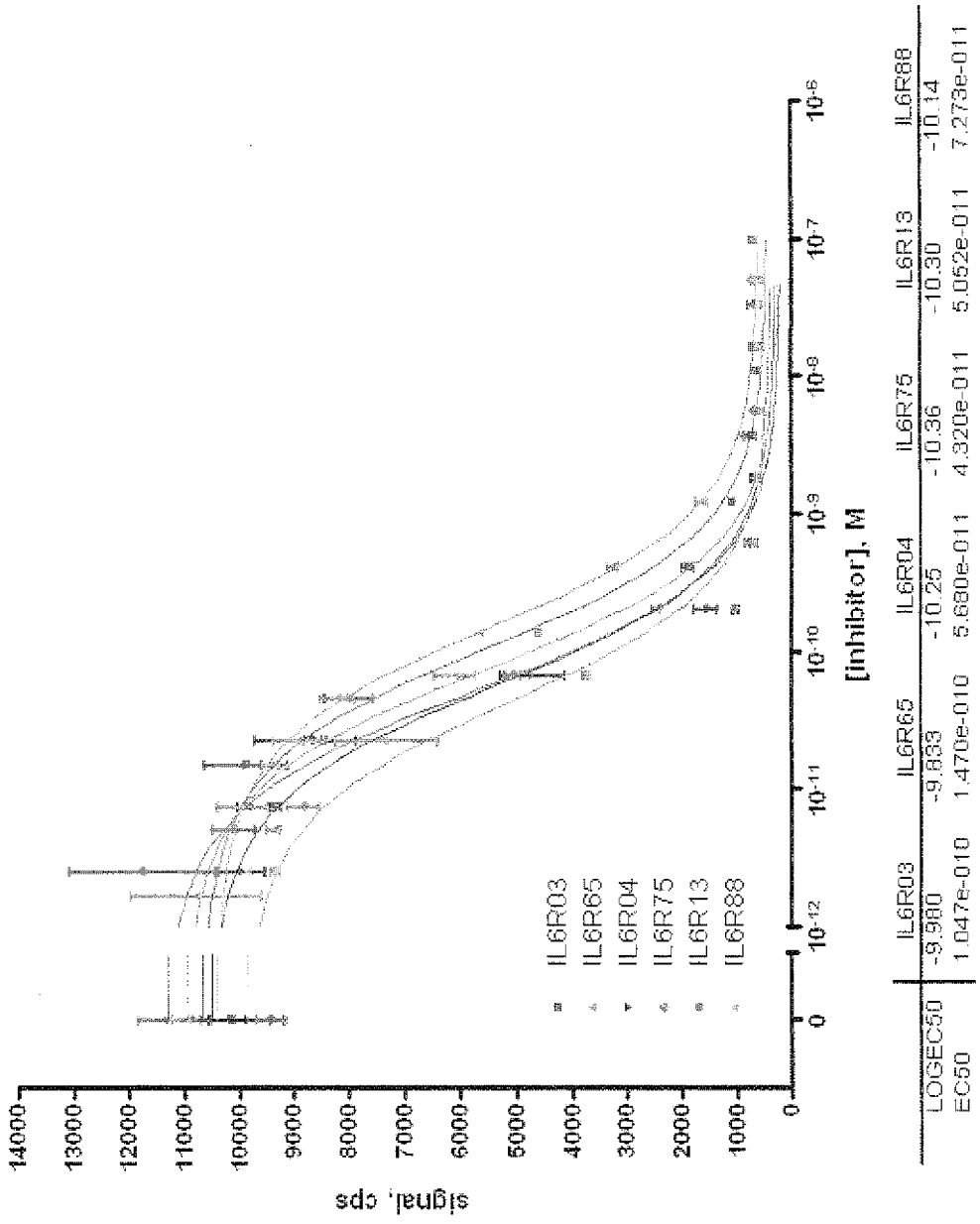

IL6R65-75-88
signal, cps
[inhibitor], M
IL6R03
IL6R65
IL6R04
IL6R75
IL6R13
IL6R88
LOGEC50 -9.980 -9.833 -10.25 -10.36 -10.30 -10.14
EC50 1.047e-010 1.470e-010 5.680e-011 4.320e-011 5.052e-011 7.273e-011

Figure 21

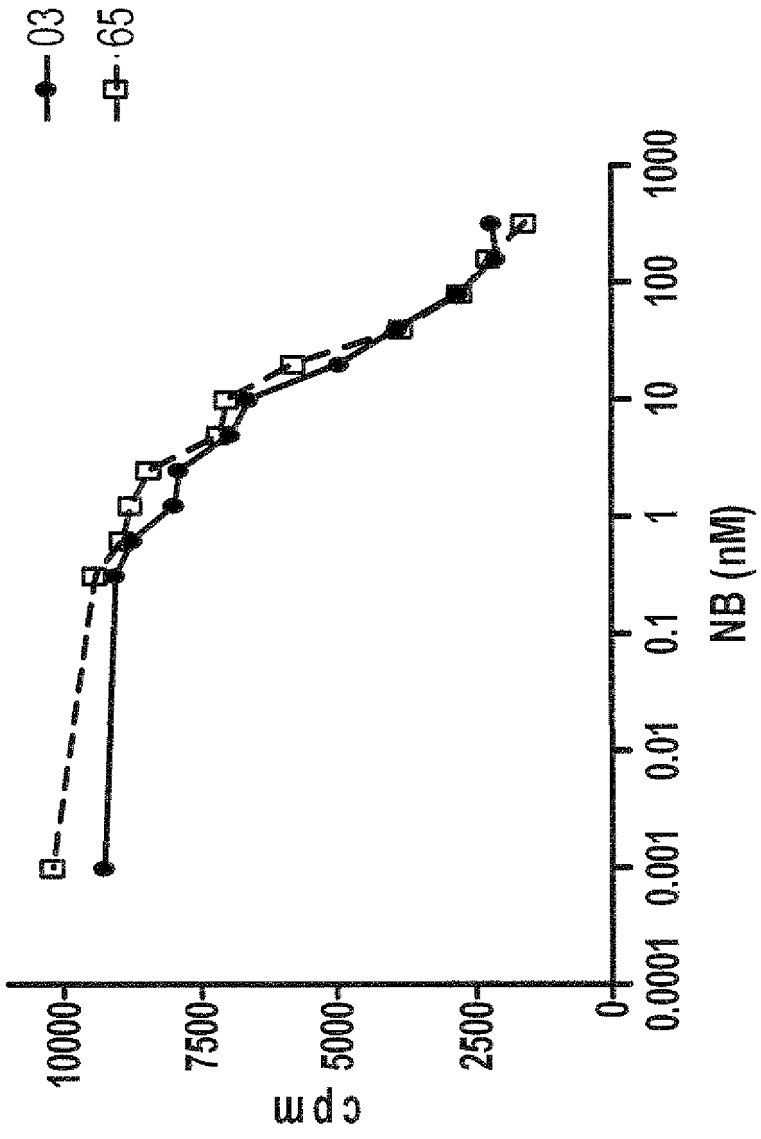

03
65
cpm
10000
7500
5000
2500
0
0.0001
0.001
0.01
0.1
1
10
100
1000
NB (nM)

Figure 22A

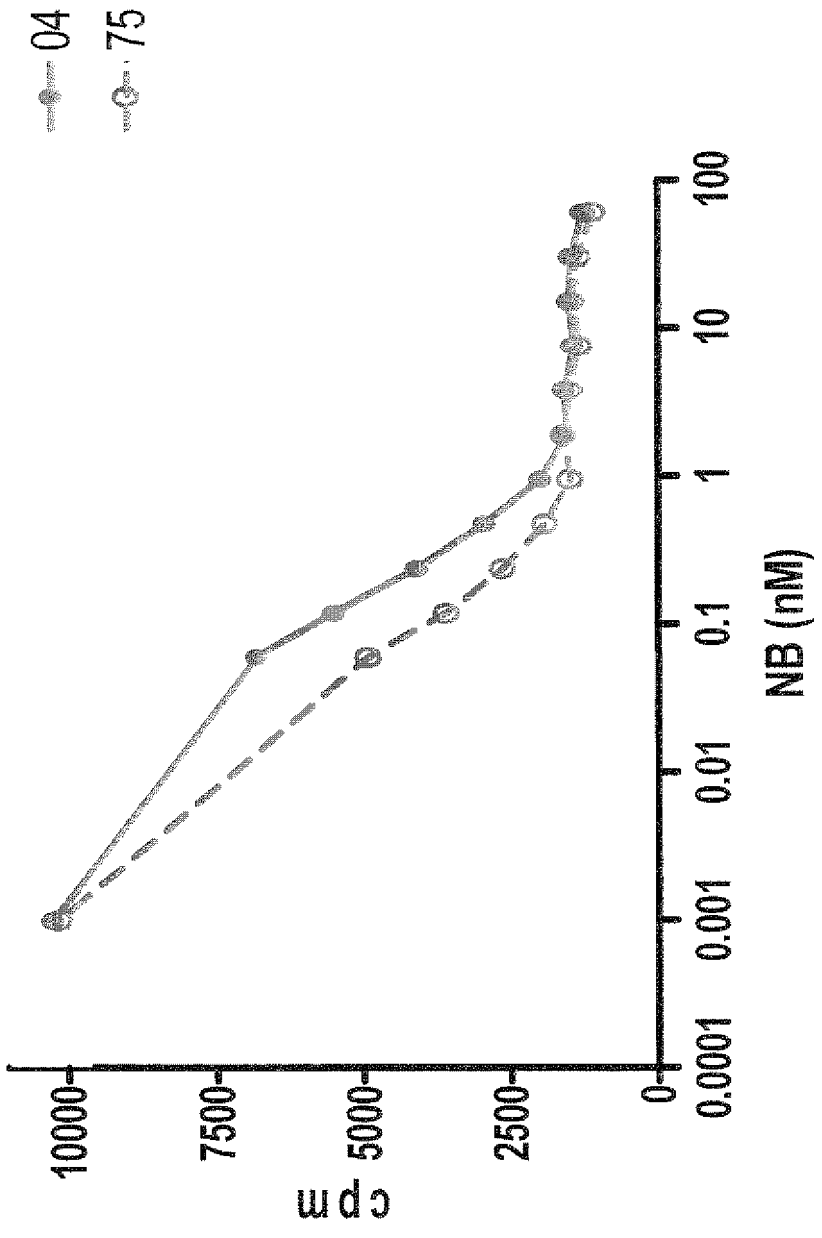


Figure 22B

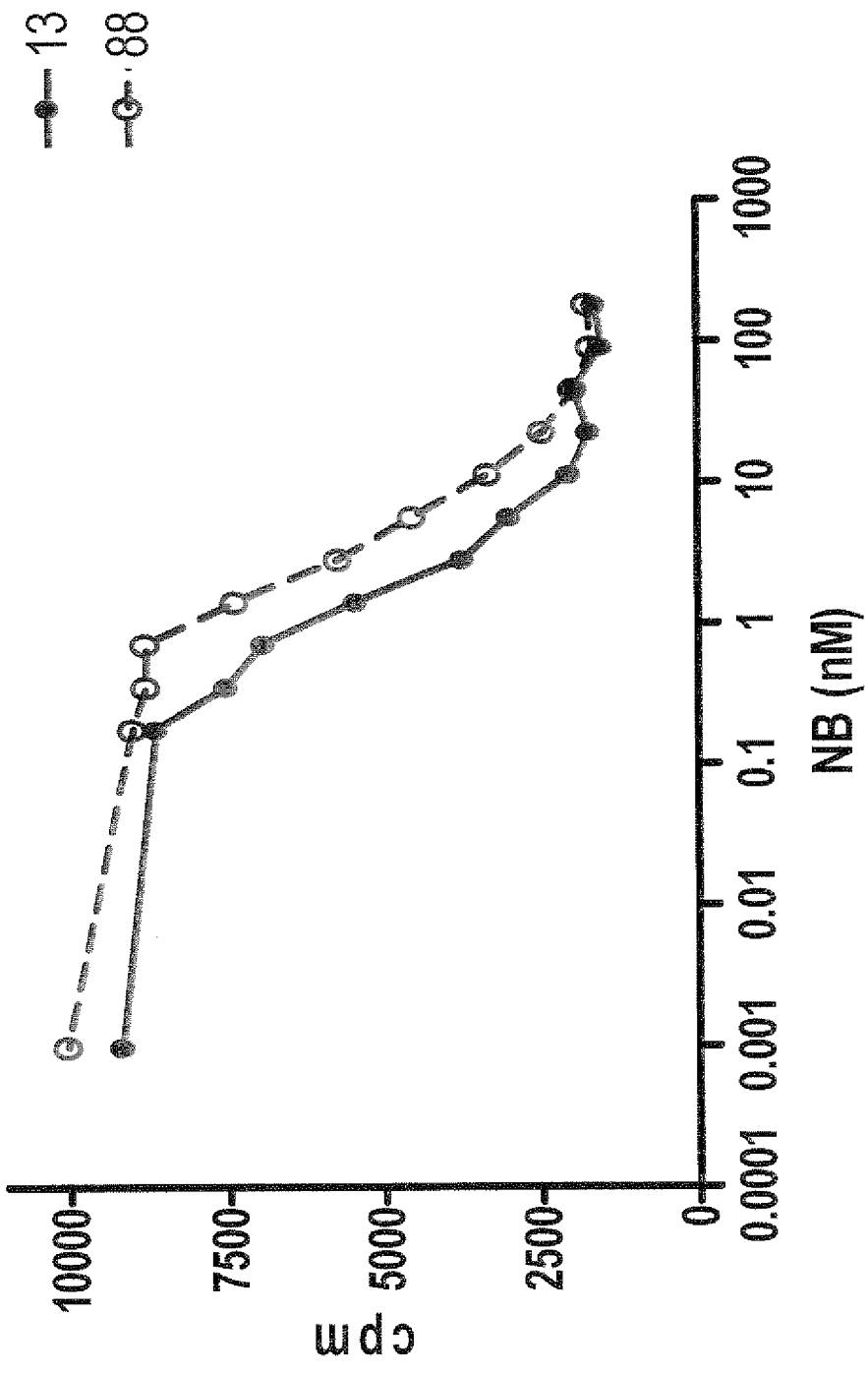

13
88
10000
7500
5000
2500
0
cpm
0.0001
0.001
0.01
0.1
1
10
100
1000
NB (nM)

Figure 22C

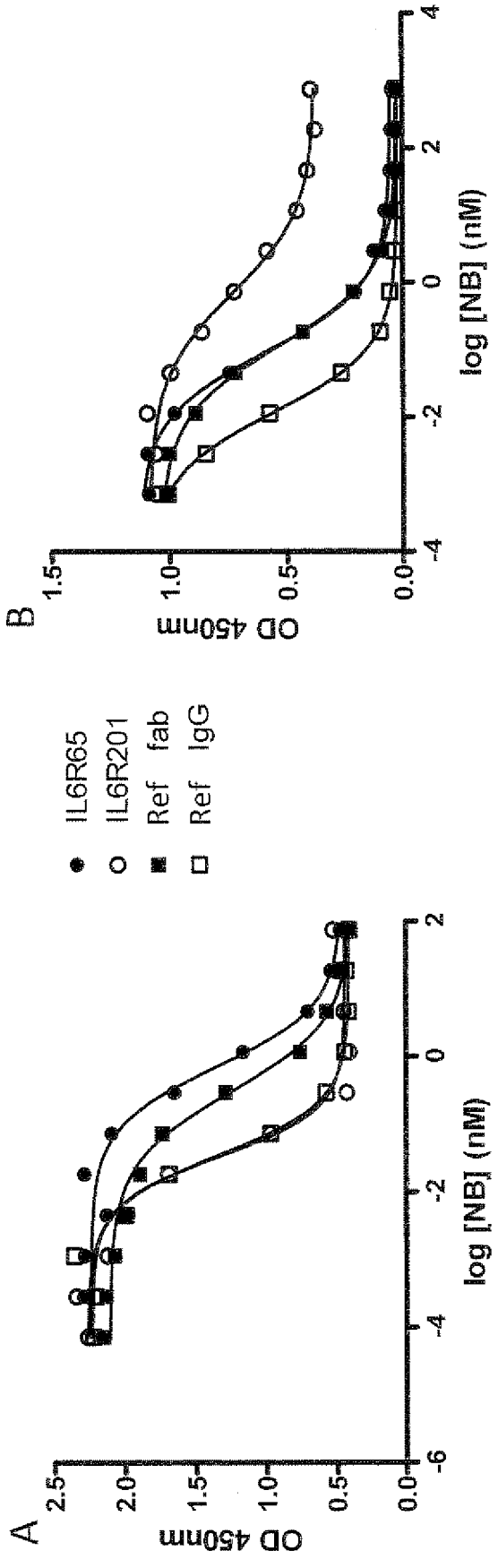

A
OD 450nm
2.5
2.0
1.5
1.0
0.5
0.0
-6
-4
-2
0
2
log [NB] (nM)
IL6R65
IL6R201
Ref fab
Ref IgG
B
OD 450nm
1.5
1.0
0.5
0.0
-4
-2
0
2
4
log [NB] (nM)

Figure 23

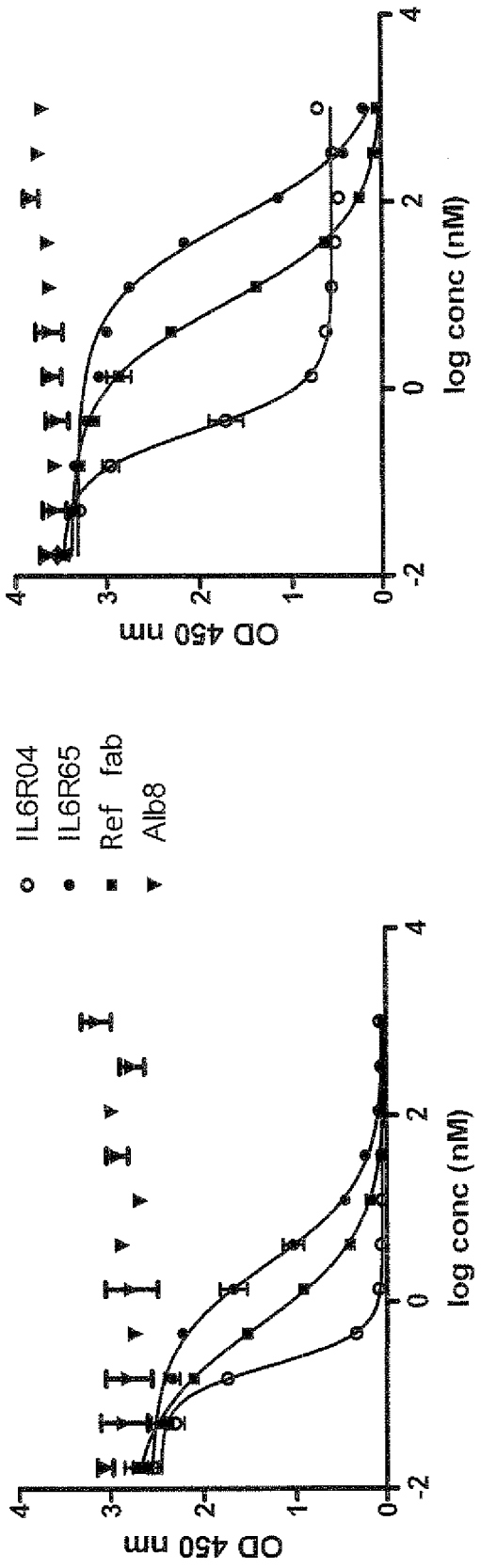


Figure 24

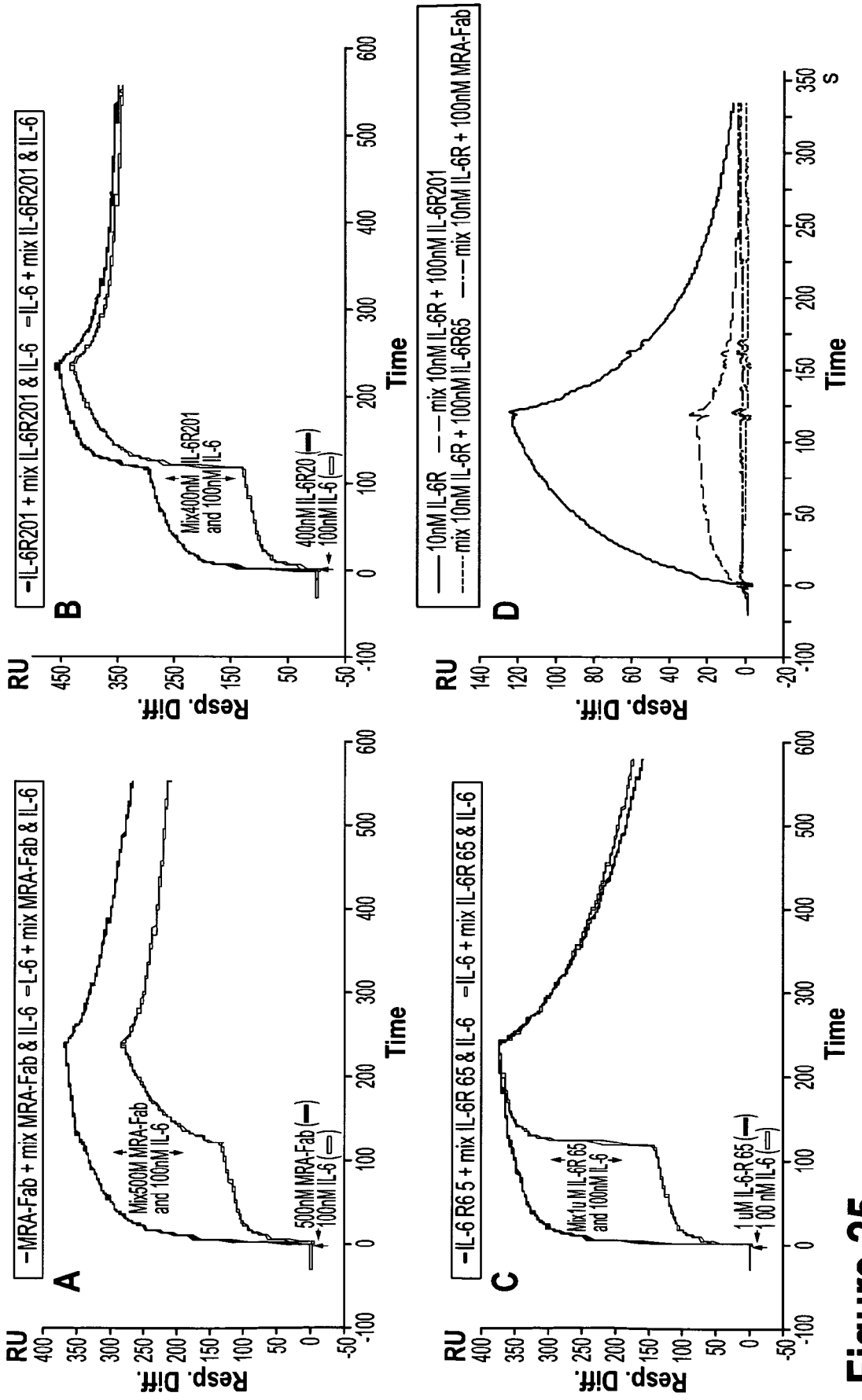

A
−MRA-Fab + mix MRA-Fab & IL-6 =IL-6 + mix MRA-Fab & IL-6
Mix500M MRA-Fab and 100nM IL-6
500nM MRA-Fab (—)
100nM IL-6 (═)
B
−IL-6R201 + mix IL-6R201 & IL-6 =IL-6 + mix IL-6R201 & IL-6
Mix400nM IL-6R201 and 100nM IL-6
400nM IL-6R20 (—)
100nM IL-6 (═)
C
−IL-6 R6 5 + mix IL-6R 65 & IL-6 =IL-6 + mix IL-6R 65 & IL-6
Mix1u M IL-6R 65 and 100nM IL-6
1 uM IL-6-R 65 (—)
1 00 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  EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYA
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

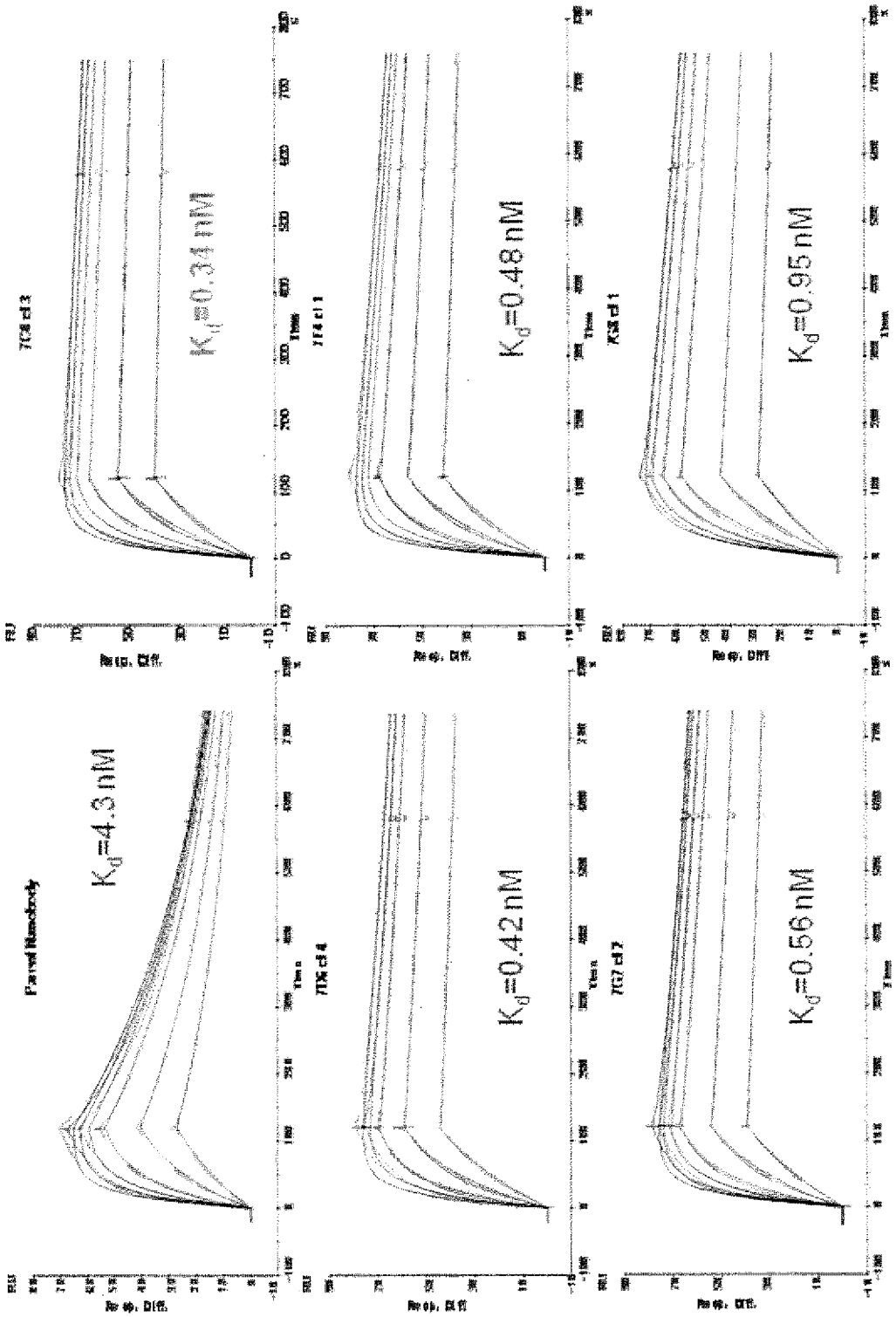
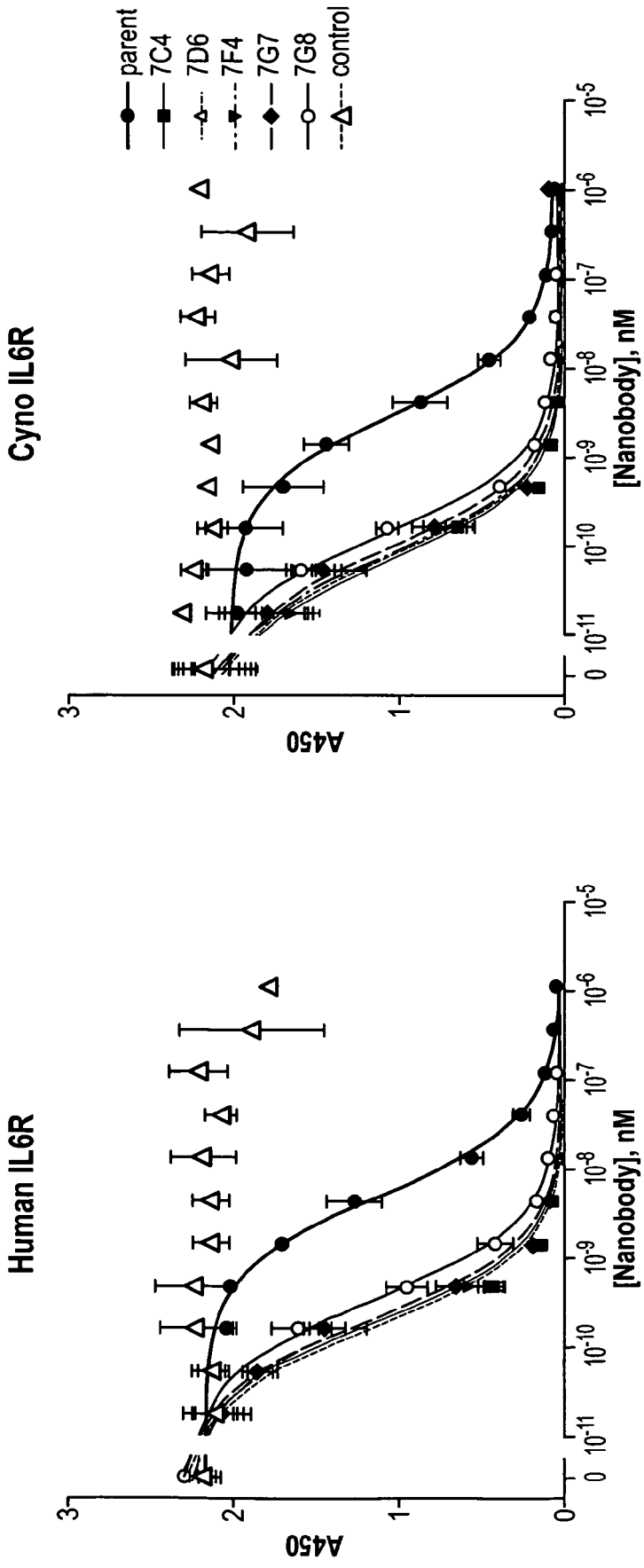

Parent Monoclonal
K_d=4.3 nM
K_d=0.34 nM
K_d=0.48 nM
K_d=0.95 nM
K_d=0.42 nM
K_d=0.56 nM

Figure 27



Nanobody	IC50 (nM)
parent	2.99
PMP7G8	0.14
PMP7G7	0.11
PMP7D6	0.09
PMP7F4	0.09
PMP7C4	0.08

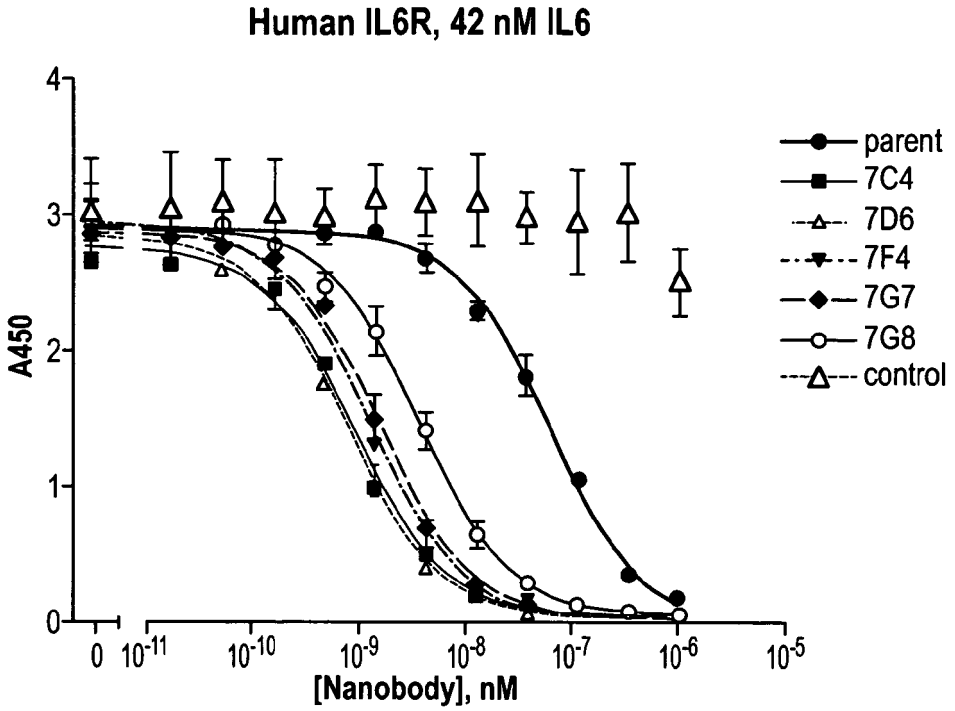
37x

[IL6R]: ~0.4 nM
[IL6]: 2.4 nM

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

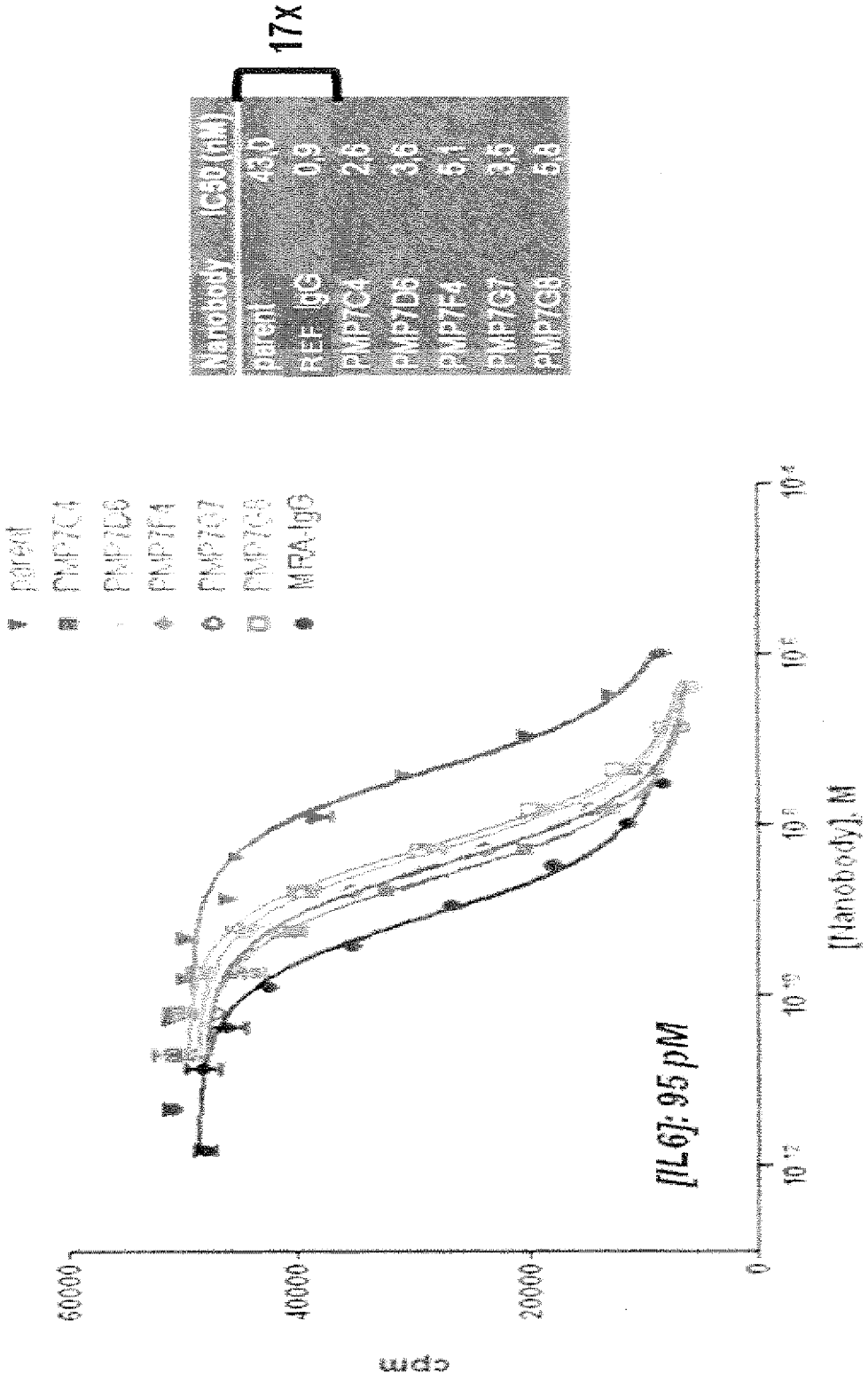

17x
Nanobody (GC)(nM)
Parent 4.80
EGFR 0.8
pMP7C4 2.6
pMP7B5 3.6
pMP7F1 6.4
pMP7C7 3.6
pMP7C8 6.8
pMP7C4
pMP7B5
pMP7F1
pMP7C7
pMP7C8
MPA-IgG
[IL6]: 95 pM
cpm
60000
40000
20000
0
[Nanobody] M

Figure 29

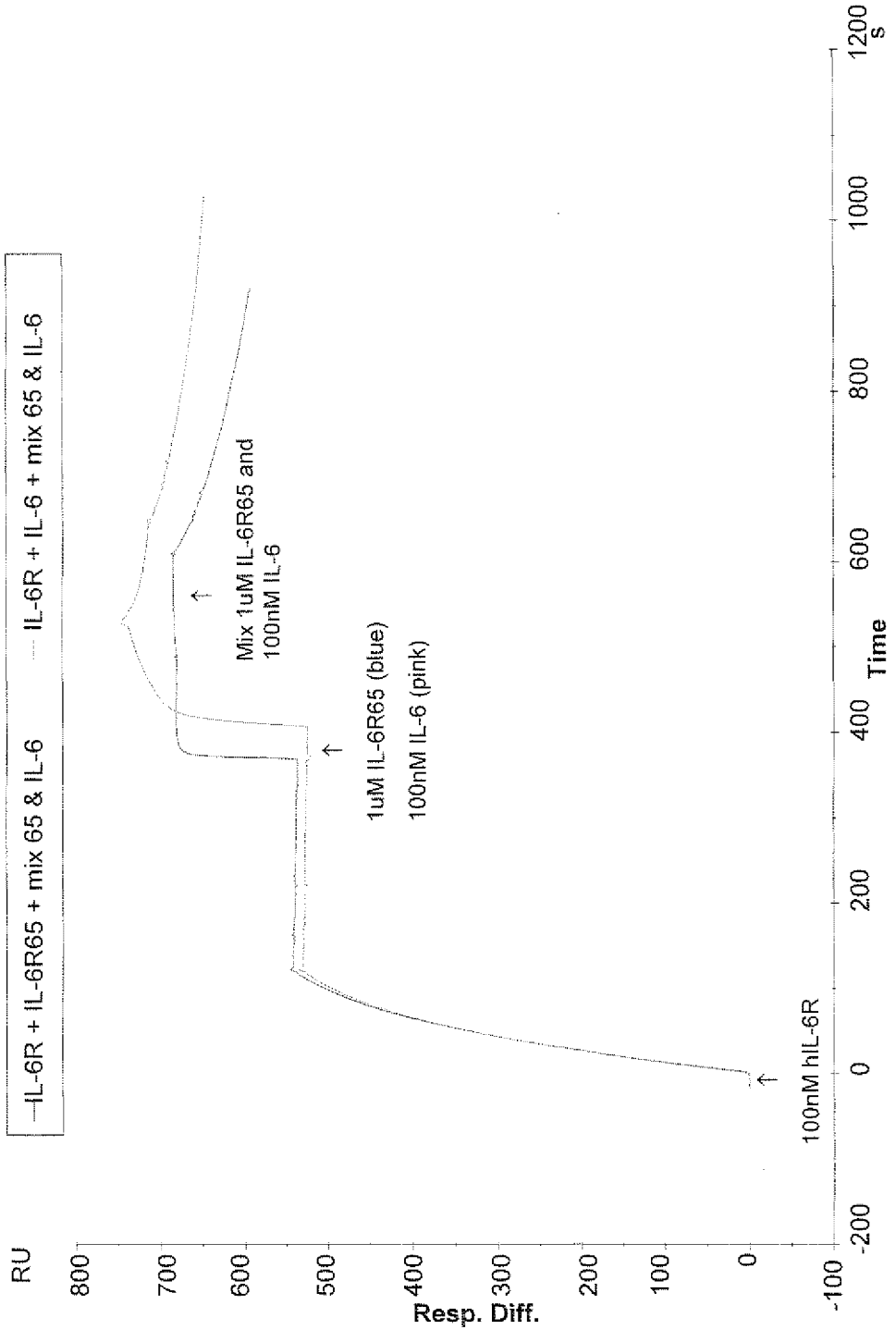

RU
800
700
600
500
400
300
200
100
0
-100
Resp. Diff.
-200
0
200
400
600
800
1000
1200
s
Time
—IL-6R + IL-6R65 + mix 65 & IL-6
--- IL-6R + IL-6 + mix 65 & IL-6
100nM hIL-6R
1uM IL-6R65 (blue)
100nM IL-6 (pink)
Mix 1uM IL-6R65 and
100nM IL-6

Figure 30A

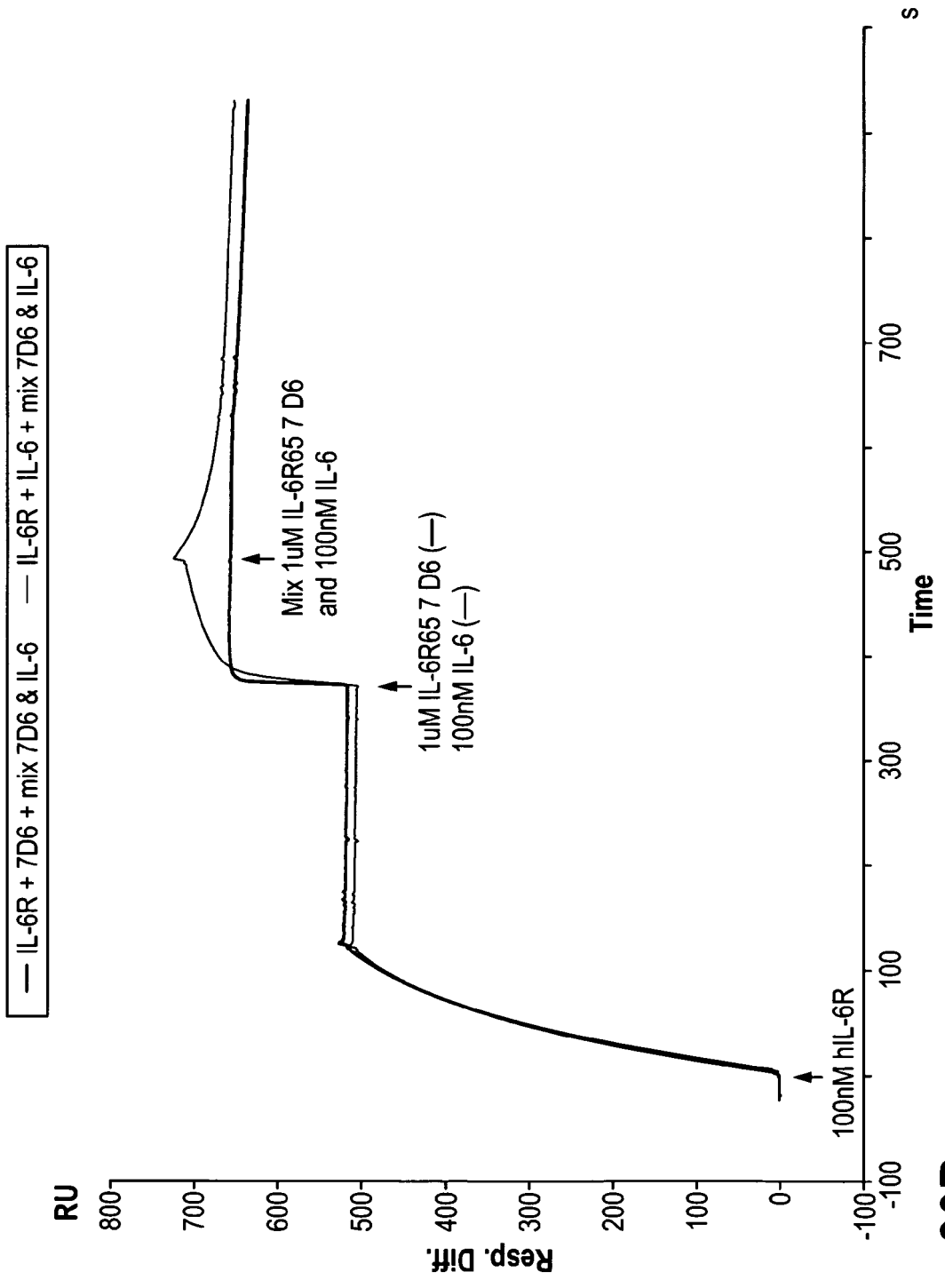

— IL-6R + 7D6 + mix 7D6 & IL-6
— IL-6R + IL-6 + mix 7D6 & IL-6
Mix 1uM IL-6R65 7 D6
and 100nM IL-6
1uM IL-6R65 7 D6 (—)
100nM IL-6 (—)
100nM hIL-6R
RU
Resp. Diff.
Time
s
800
700
600
500
400
300
200
100
0
-100
-100
100
300
500
700

Figure 30B

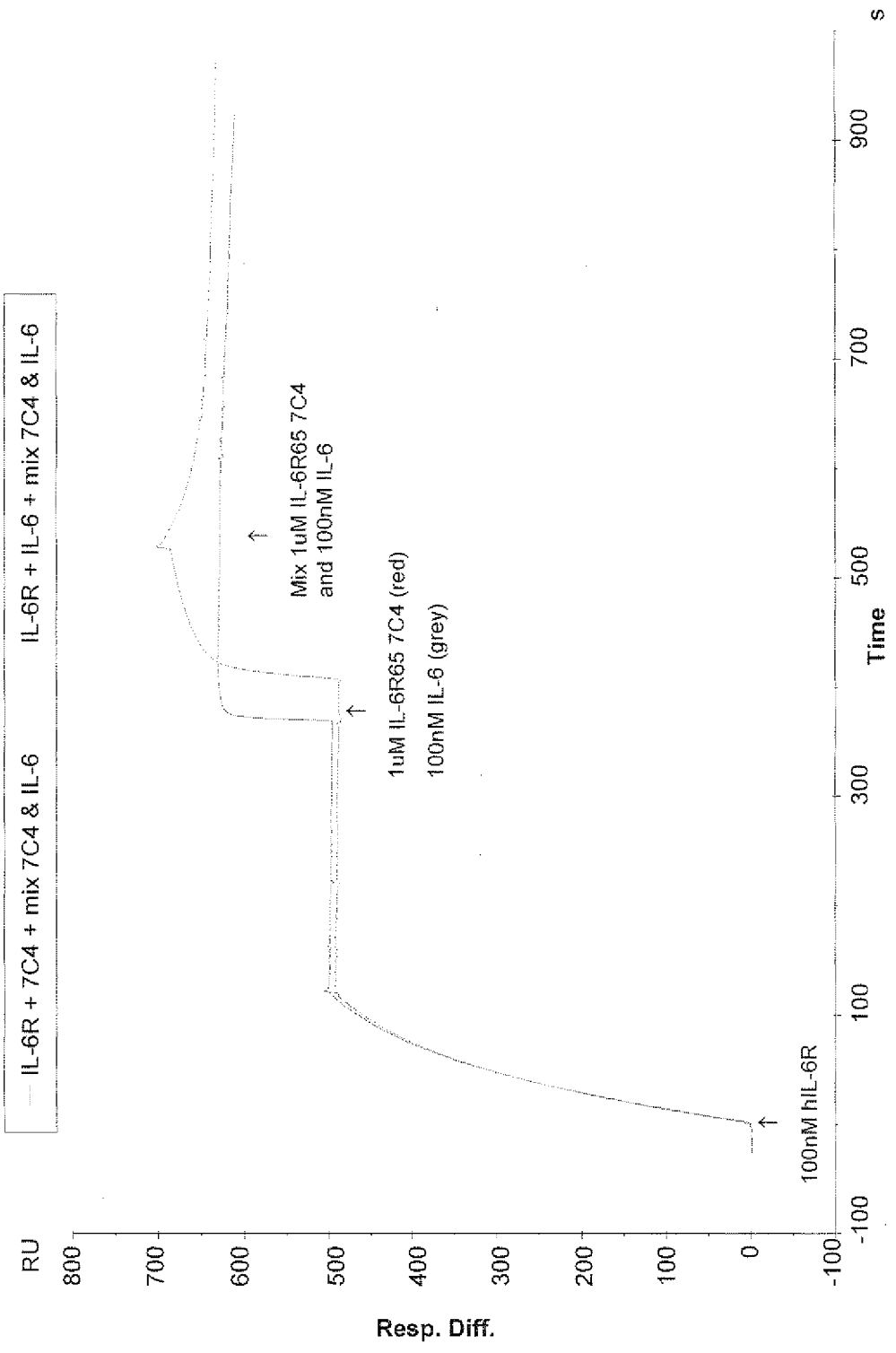

IL-6R + 7C4 + mix 7C4 & IL-6
IL-6R + IL-6 + mix 7C4 & IL-6
Mix 1uM IL-6R65 7C4
and 100nM IL-6
1uM IL-6R65 7C4 (red)
100nM IL-6 (grey)
100nM hIL-6R
RU
800
700
600
500
400
300
200
100
0
-100
-100
100
300
500
700
900
s
Time
Resp. Diff.

Figure 30C

```
IL6R65   EVQLVESGGGLVQPGGSLRLSCAASGSIFKVNAMGWYRQAPGKGRELVAGIISGGSTNYADSVKG
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 ............................I..E......R...........
```

Figure 31

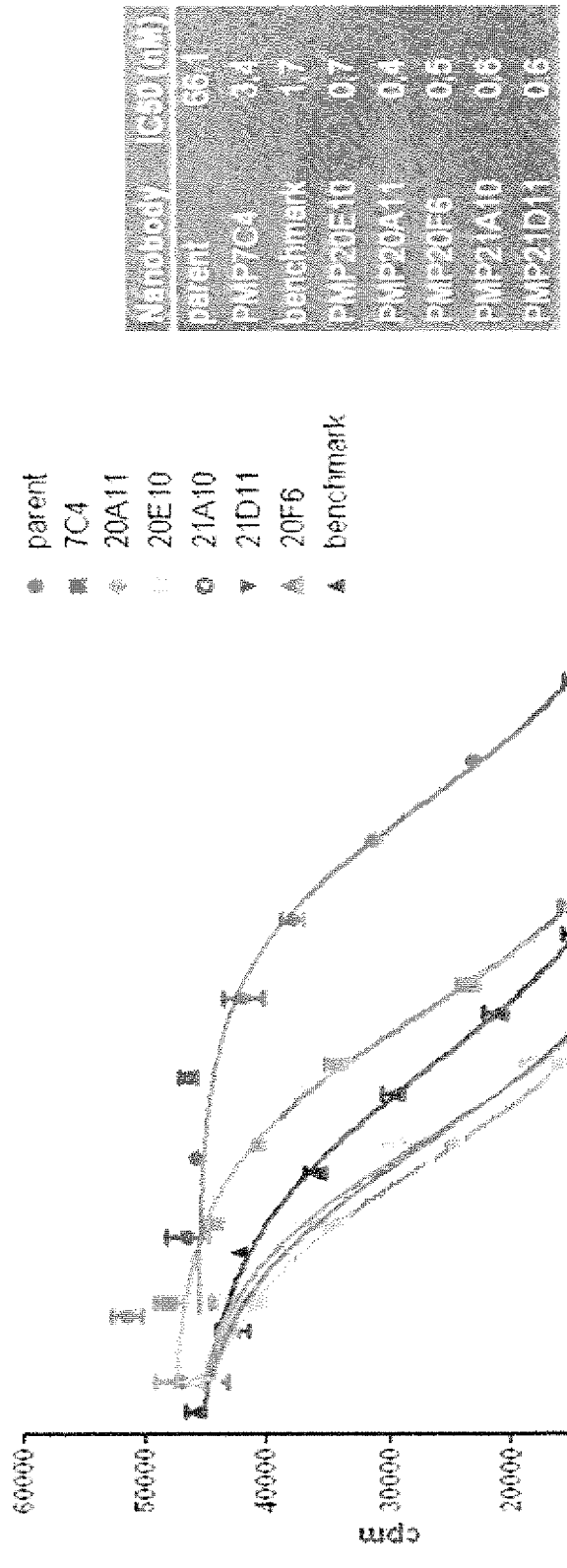

Antibody IC50 (nM)
parent 68.1
RMP7C4 3.4
benchmark 1.7
RMP24E10 0.7
RMP20A11 0.4
RMP20F6 0.5
RMP21A10 0.6
RMP21D11 0.8
parent
7C4
20A11
20E10
21A10
21D11
20F6
benchmark
[ligand]: 95 pM
cpm
[Nanobody], nM

Figure 32

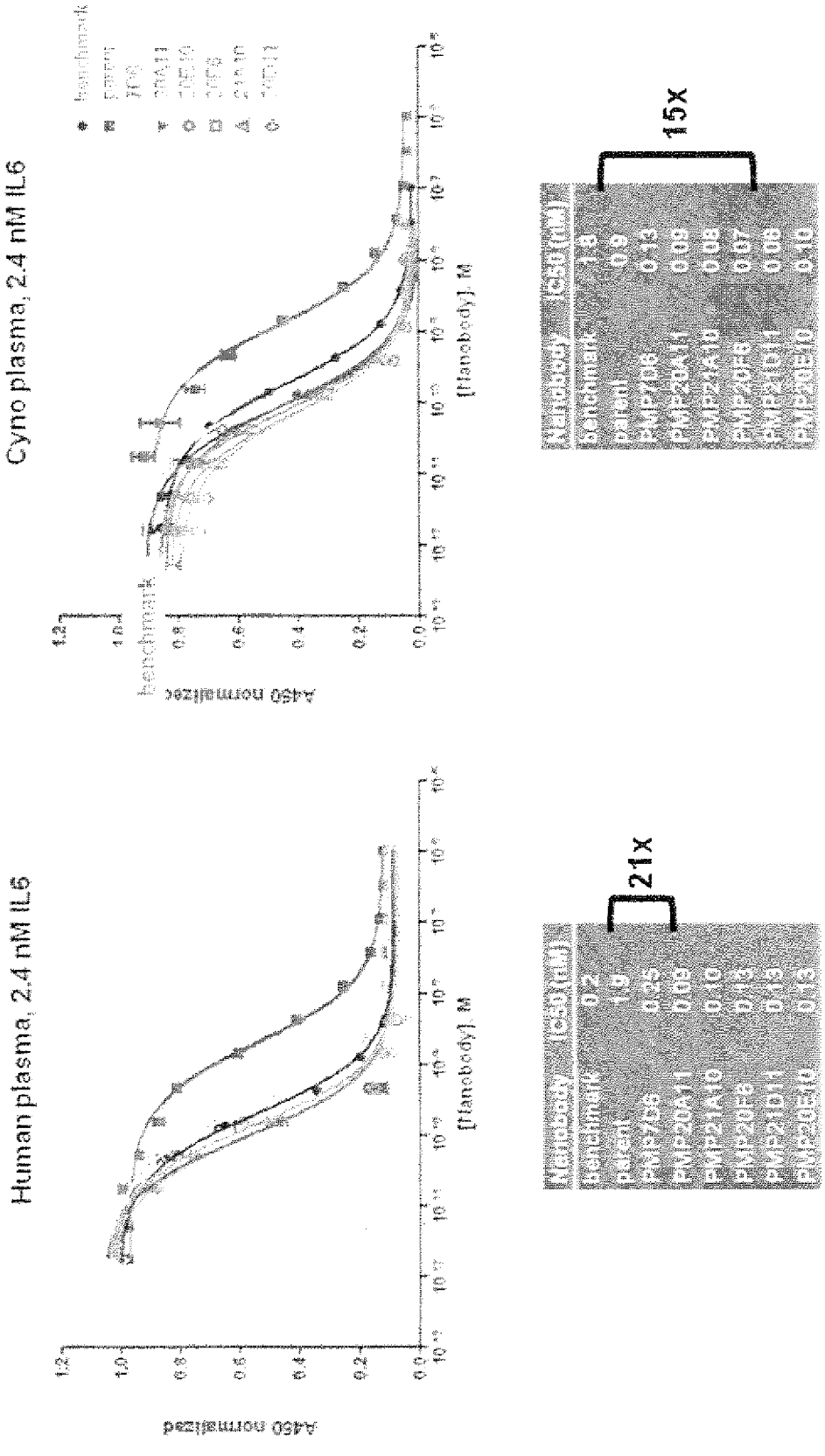
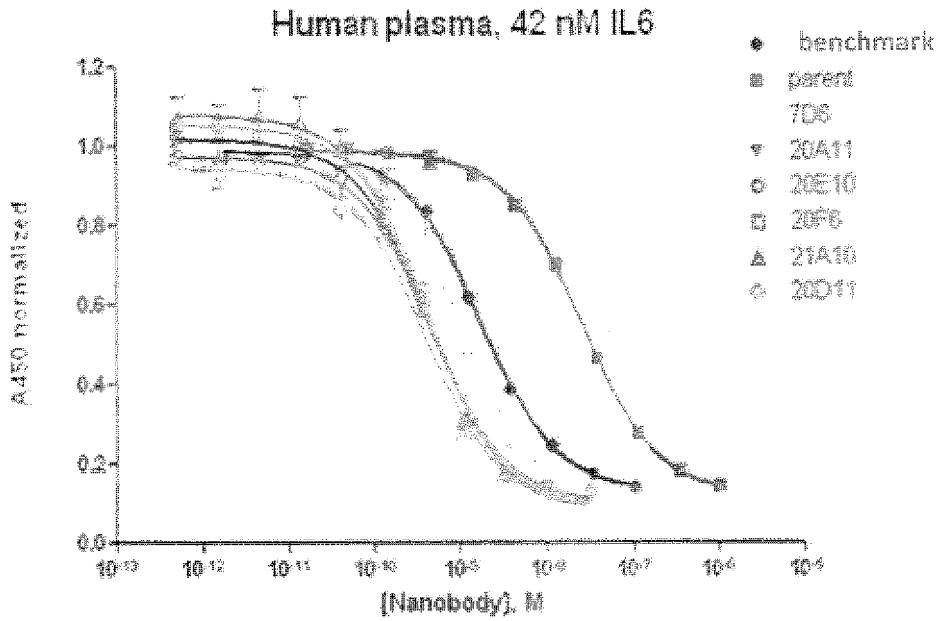

Human plasma, 2.4 nM IL5
A450 normalized
[Nanobody], M
Cyno plasma, 2.4 nM IL6
A450 normalized
[Nanobody], M
21x
15x

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

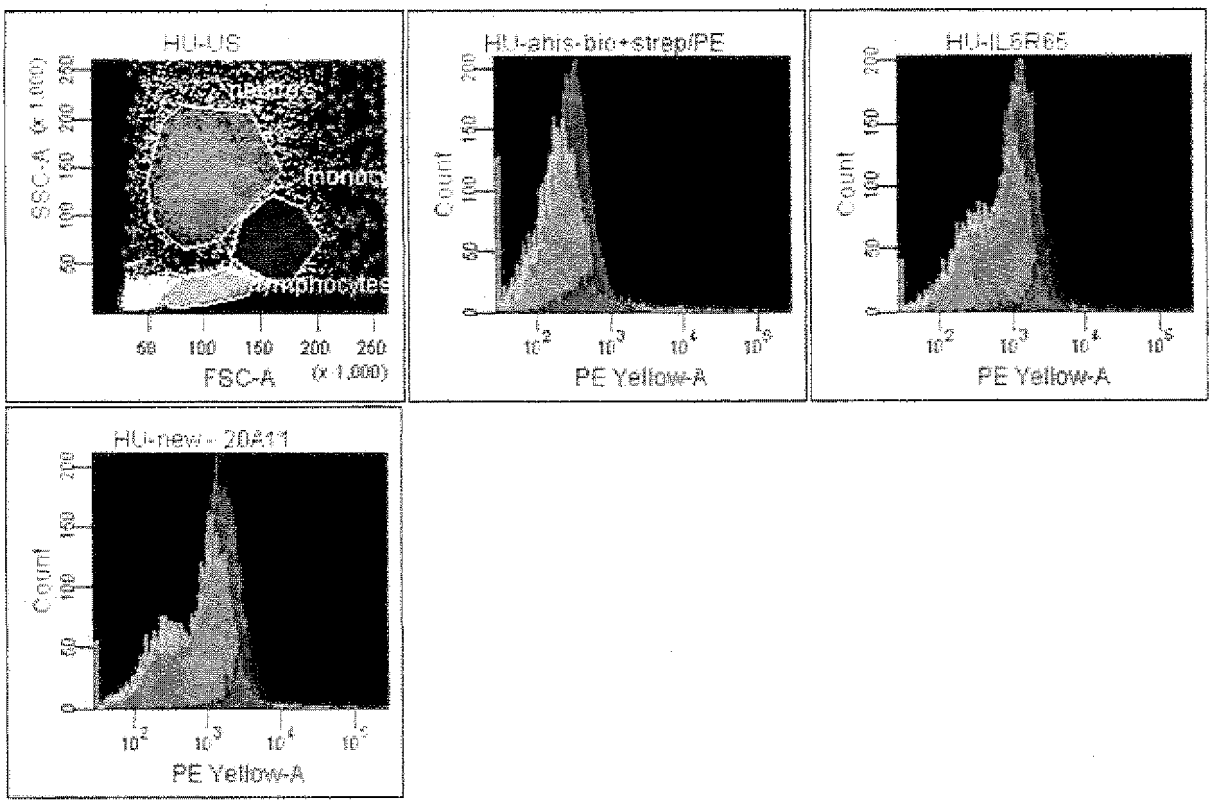

HU-US
SSC-A (x 1.000)
FSC-A (x 1.000)
monocytes
lymphocytes
HU-ehrs-bio+strep/PE
Count
PE Yellow-A
HU-ILSR65
Count
PE Yellow-A
HU-new - 20A11
Count
PE Yellow-A

Figure 34

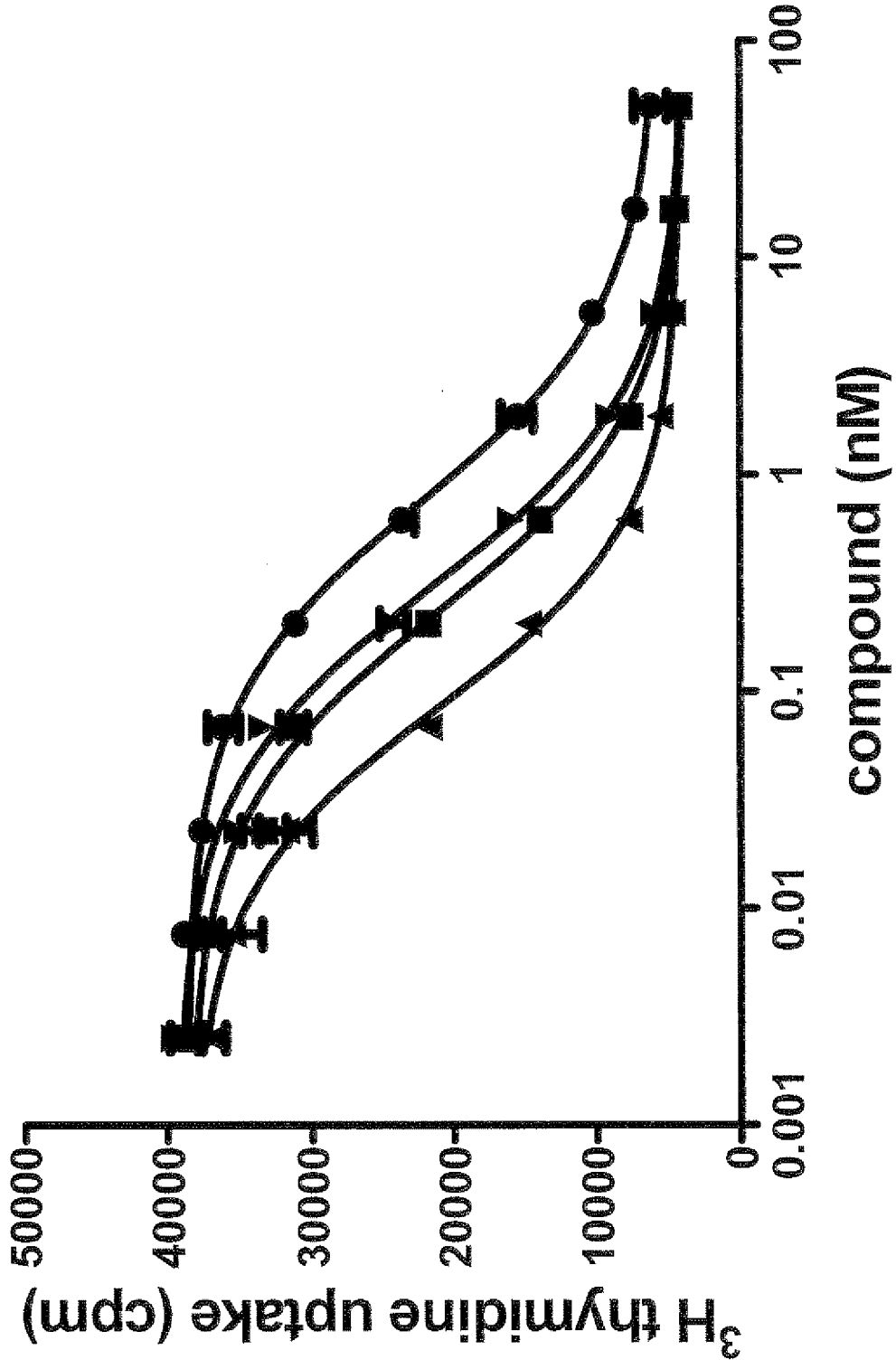

^{3}H thymidine uptake (cpm)
50000
40000
30000
20000
10000
0
0.001
0.01
0.1
1
10
100
compound (nM)

Figure 35

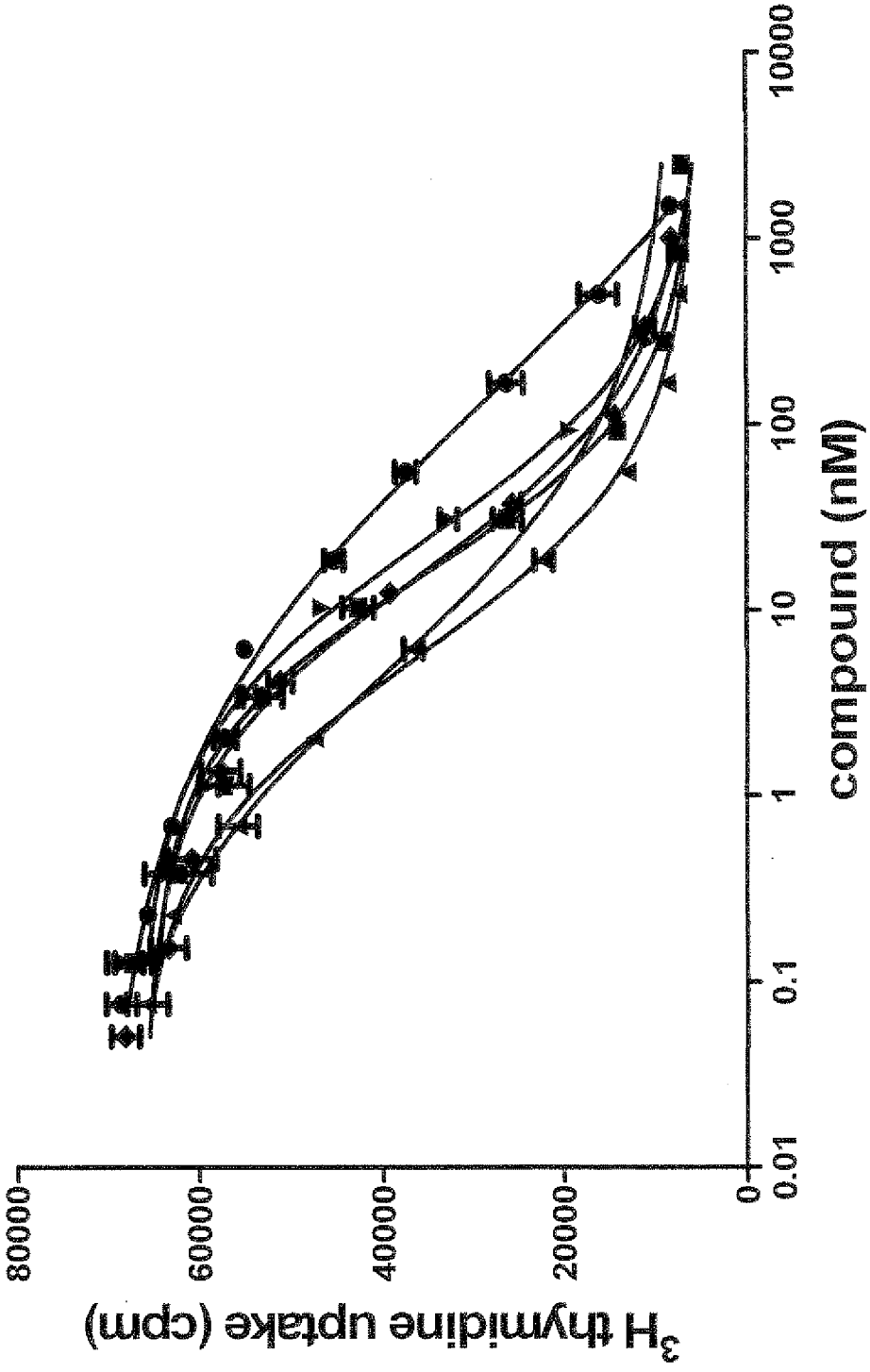

^{3}H thymidine uptake (cpm)
80000
60000
40000
20000
0
0.01
0.1
1
10
100
1000
10000
compound (nM)

Figure 36

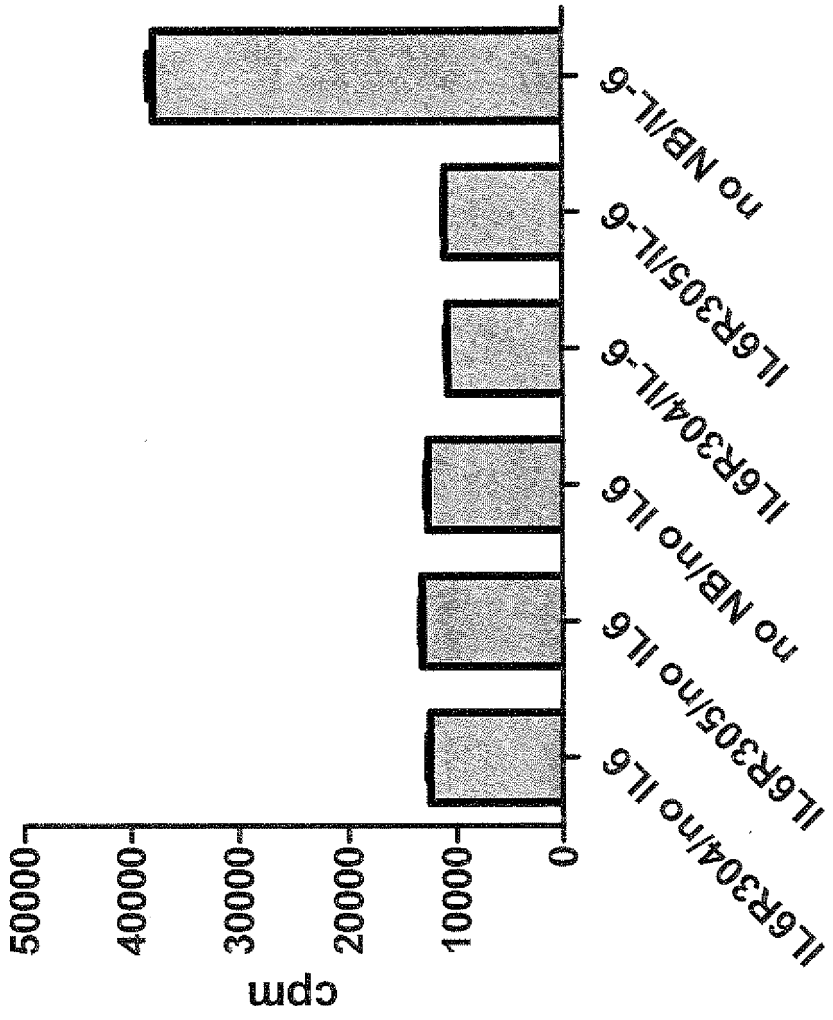

cpm
50000
40000
30000
20000
10000
0
IL6R304/no IL6
IL6R305/no IL6
no NB/no IL6
IL6R304/IL-6
IL6R305/IL-6
no NB/IL-6

Figure 37

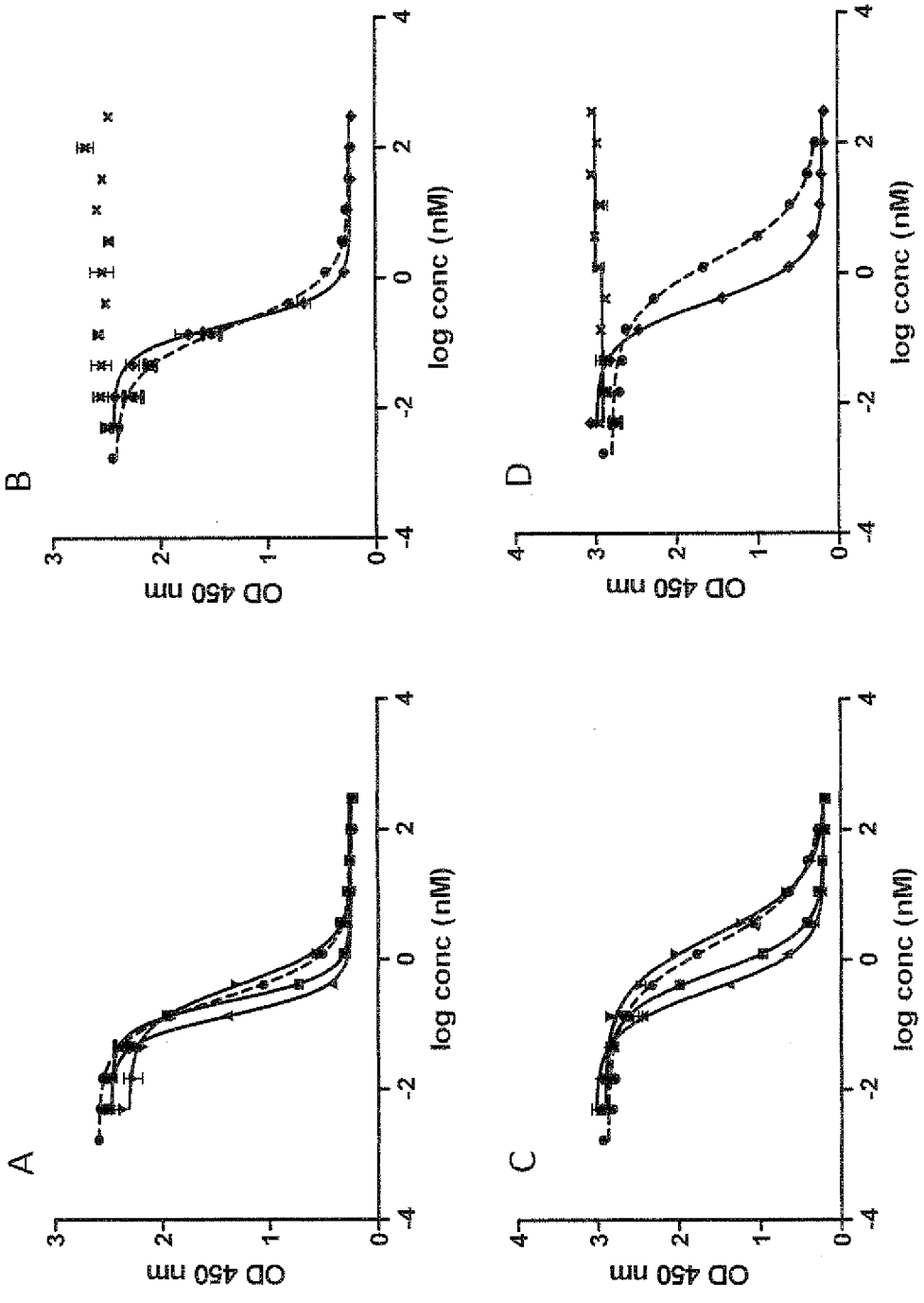
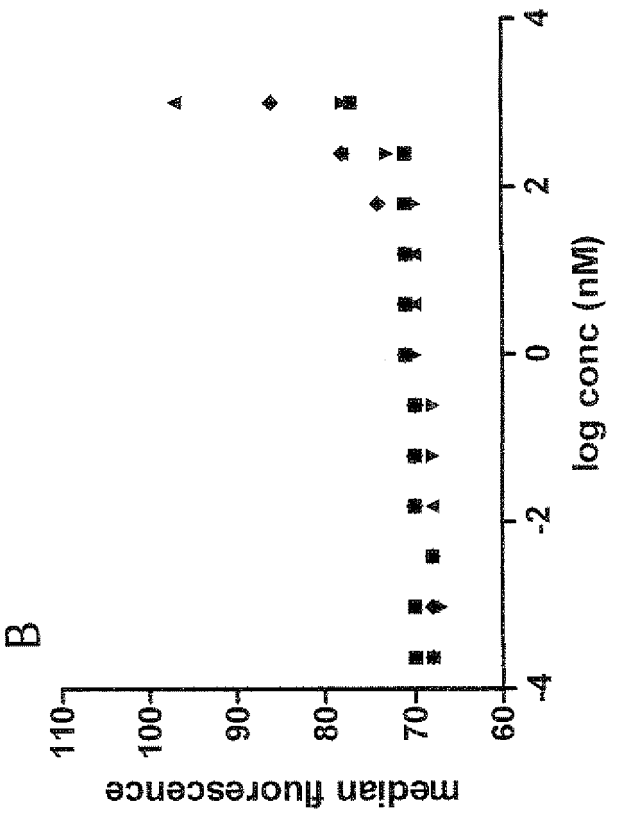


Figure 38


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

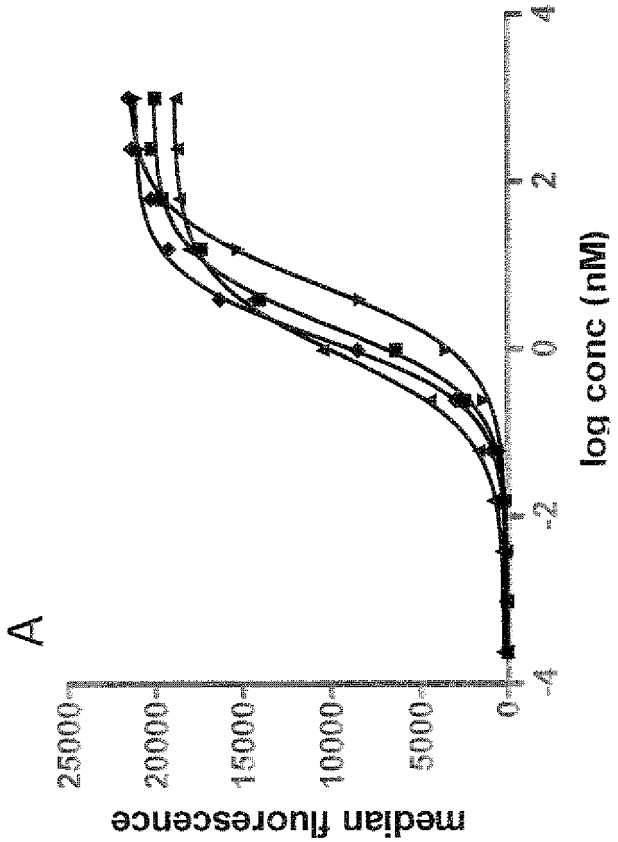

A
median fluorescence
25000
20000
15000
10000
5000
0
-4
-2
0
2
4
log conc (nM)

Figure 39

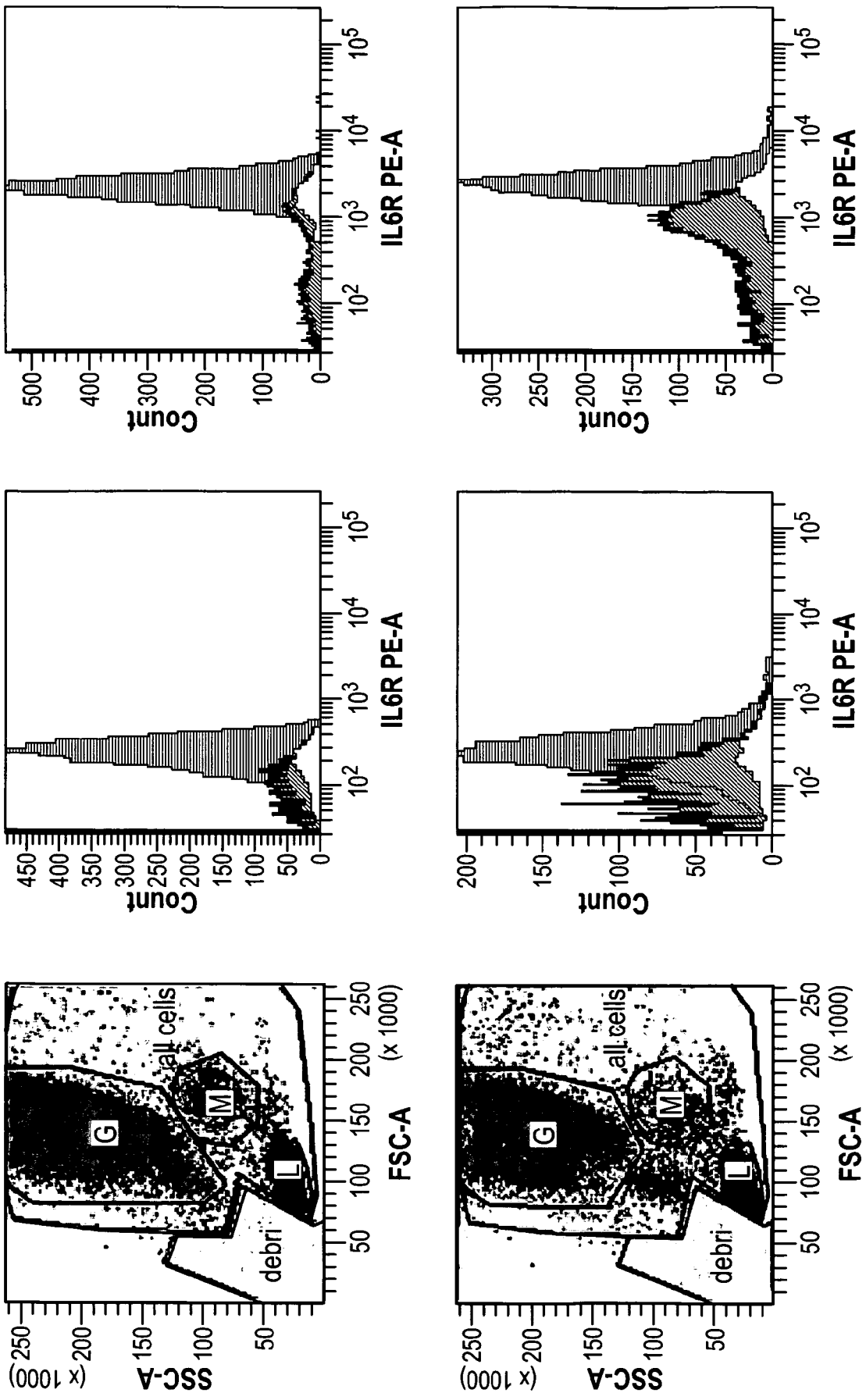


Figure 40

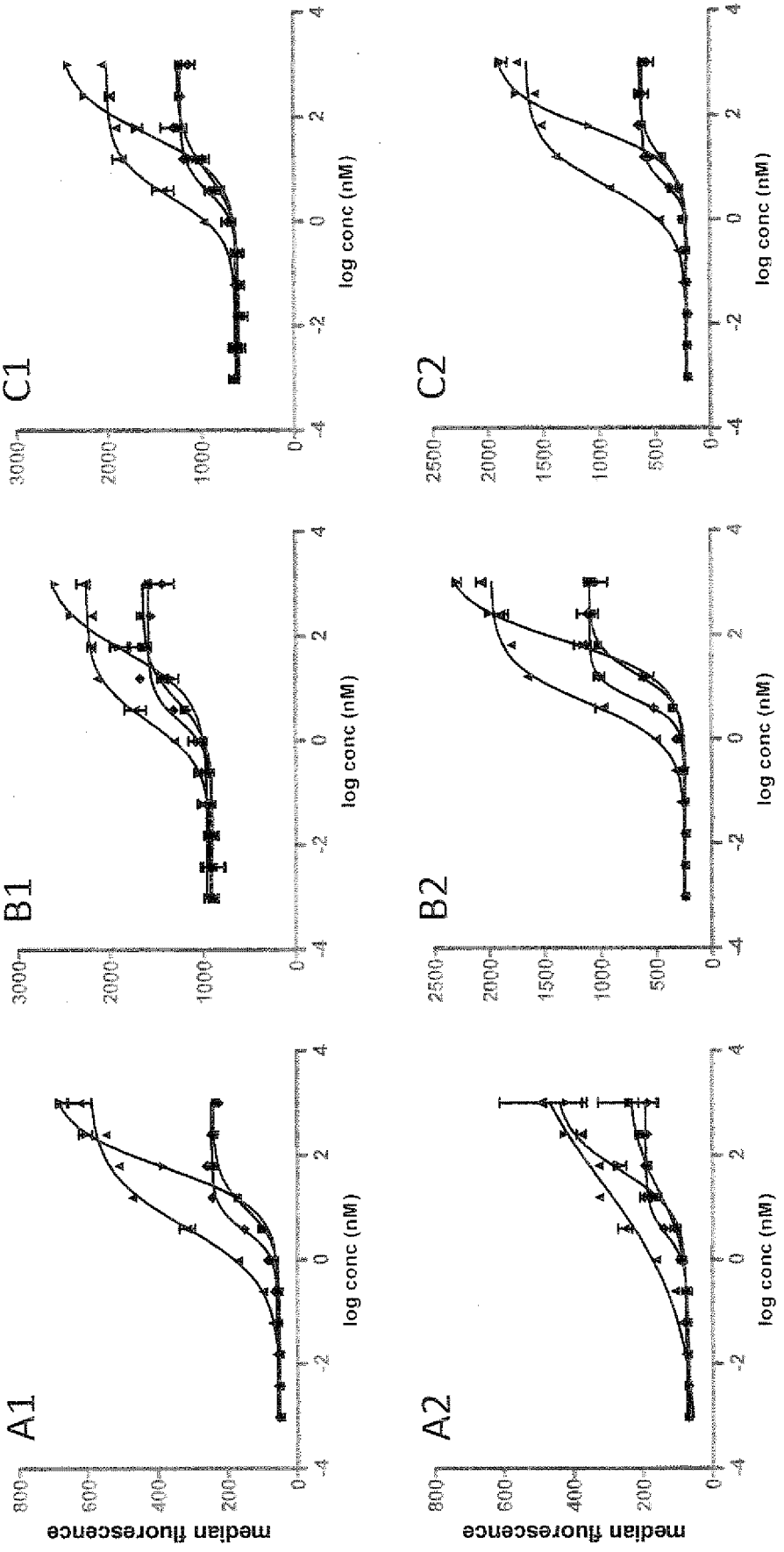


Figure 41

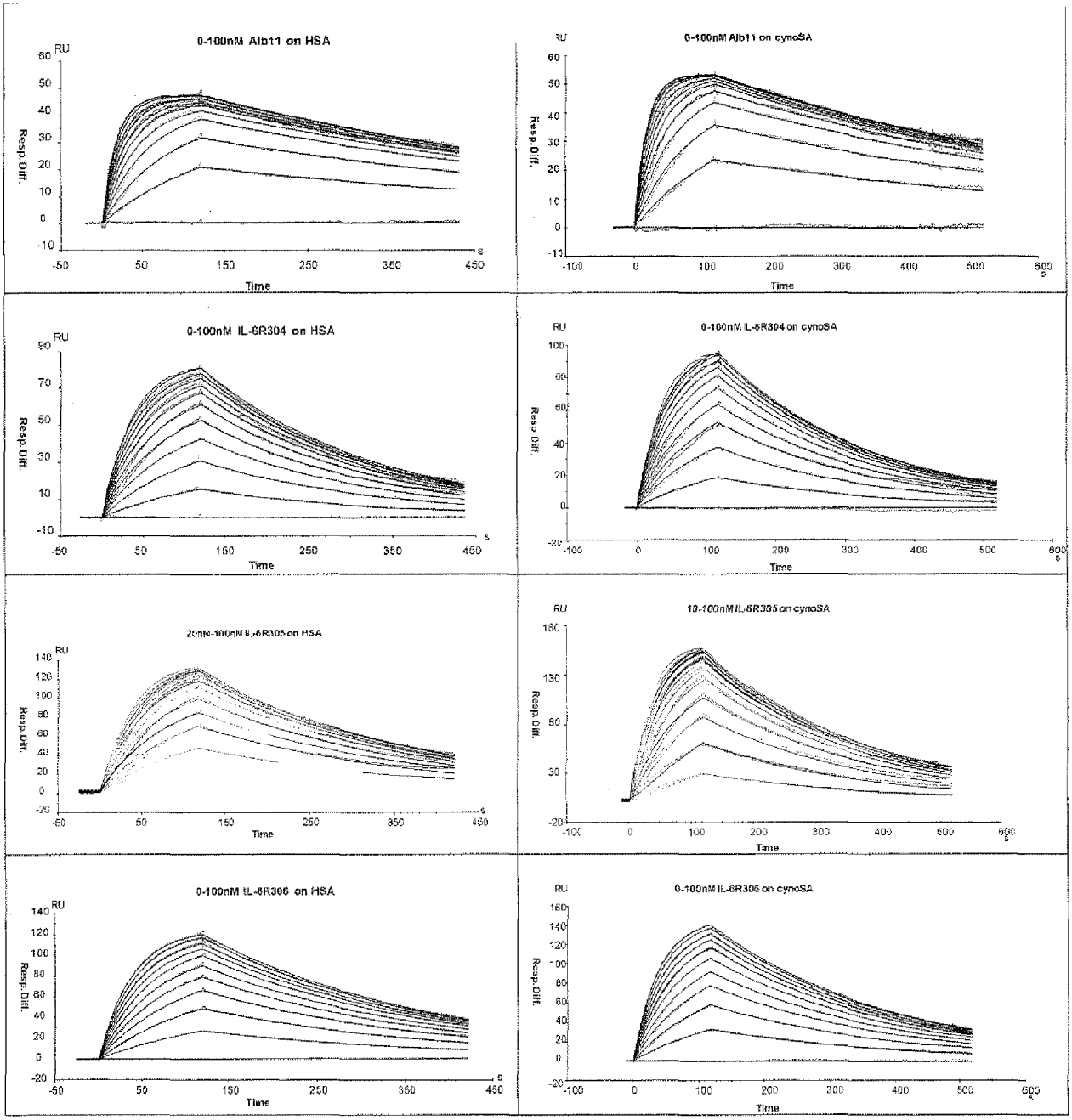

0-100nM Alb11 on HSA
0-100nM Alb11 on cynoSA
0-100nM IL-6R304 on HSA
0-100nM IL-6R304 on cynoSA
20nM-100nM IL-6R305 on HSA
10-100nM IL-6R305 on cynoSA
0-100nM IL-6R306 on HSA
0-100nM IL-6R306 on cynoSA
RU
Resp. Diff.
Time
s

Figure 42

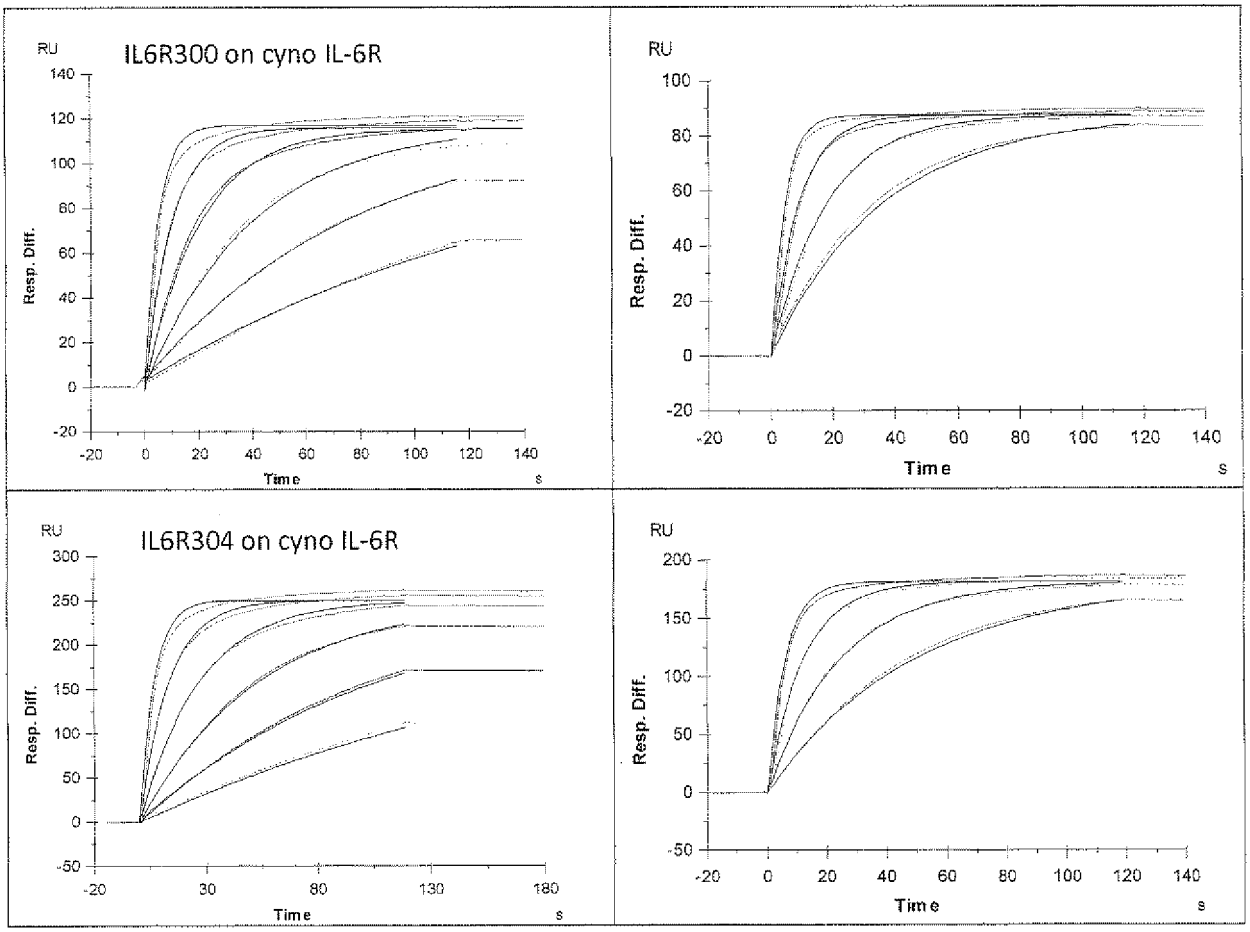
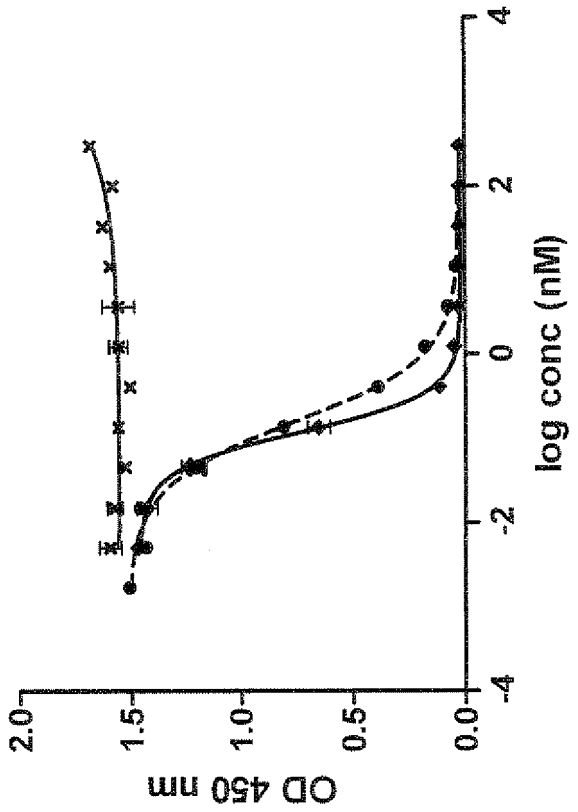

IL6R300 on cyno IL-6R
RU
Resp. Diff.
Time
s
IL6R304 on cyno IL-6R
RU
Resp. Diff.
Time
s

Figure 43


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

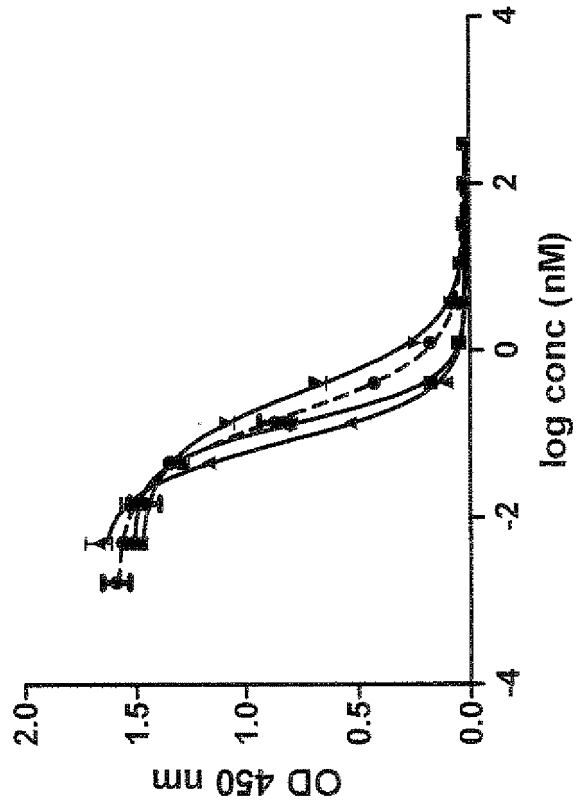

OD 450 nm
2.0
1.5
1.0
0.5
0.0
-4
-2
0
2
4
log conc (nM)

Figure 44

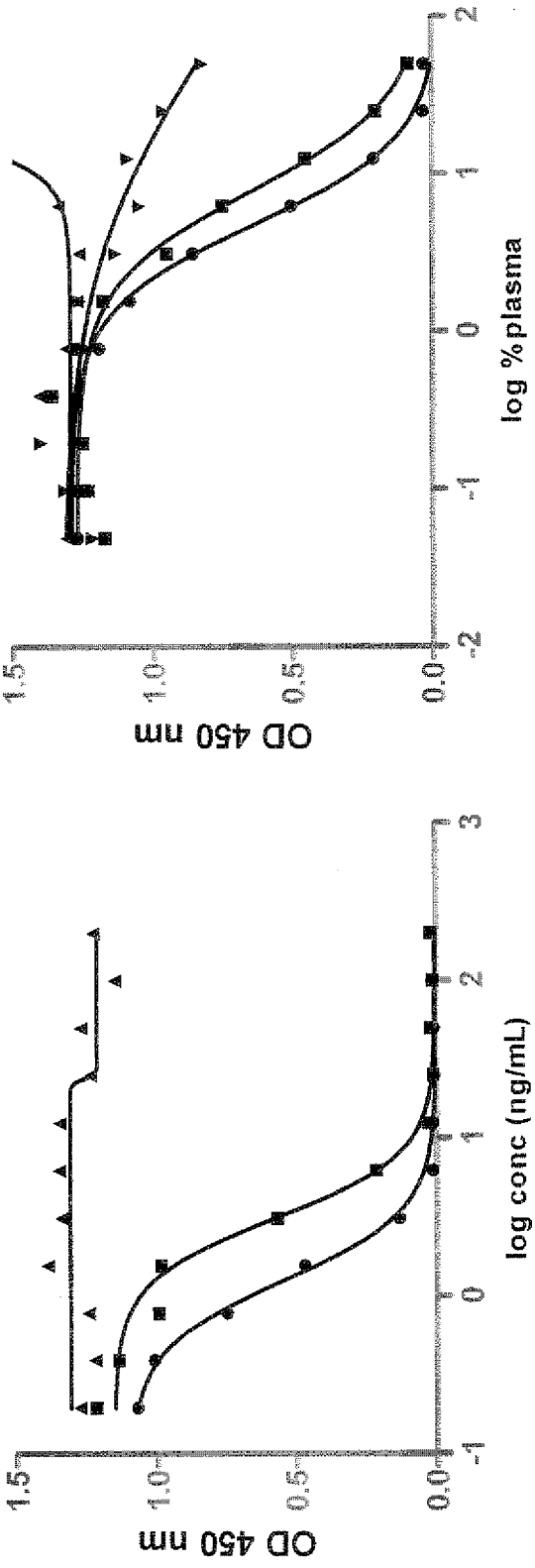

OD 450 nm
1.5
1.0
0.5
0.0
-2
-1
0
1
2
log % plasma
OD 450 nm
1.5
1.0
0.5
0.0
-1
0
1
2
3
log conc (ng/mL)

Figure 45

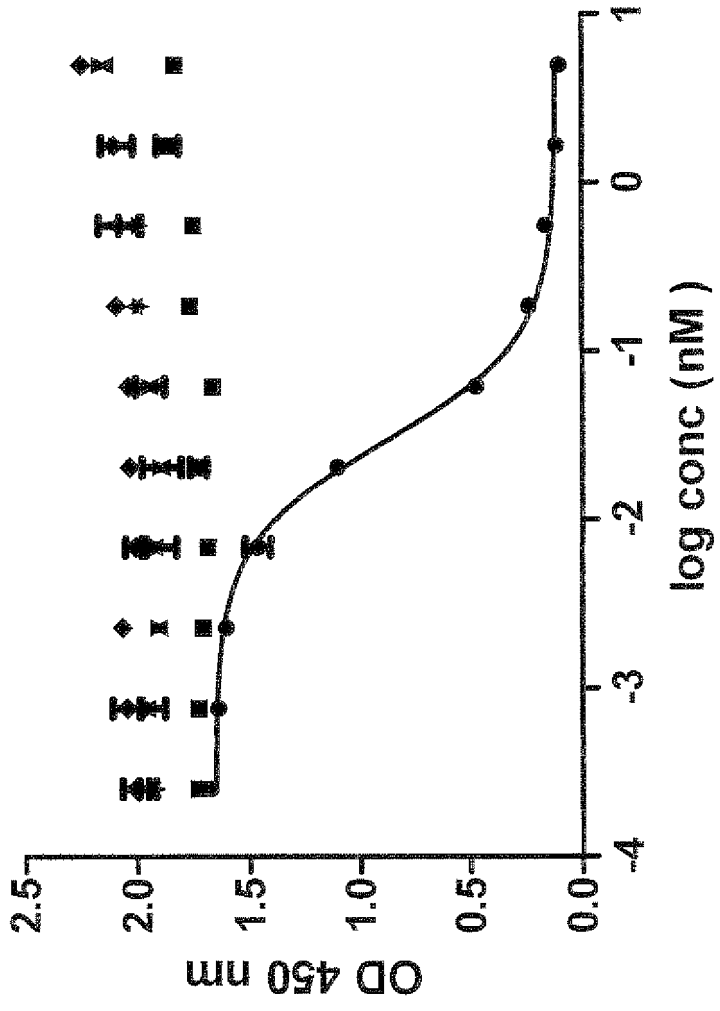


Figure 46

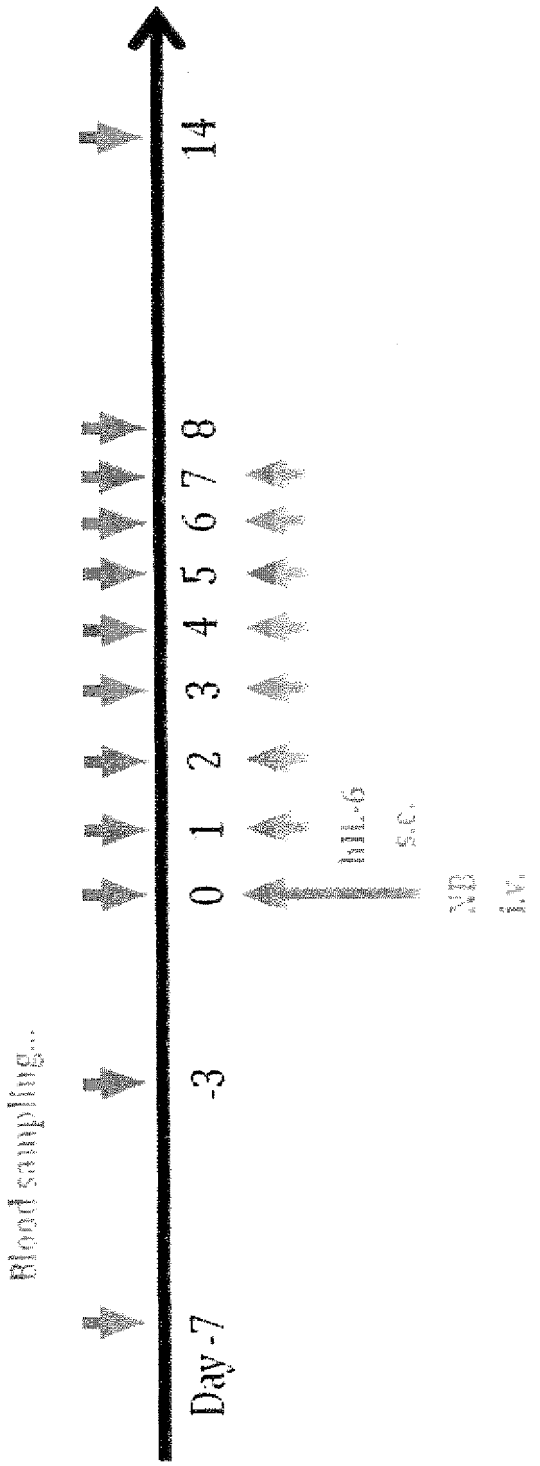
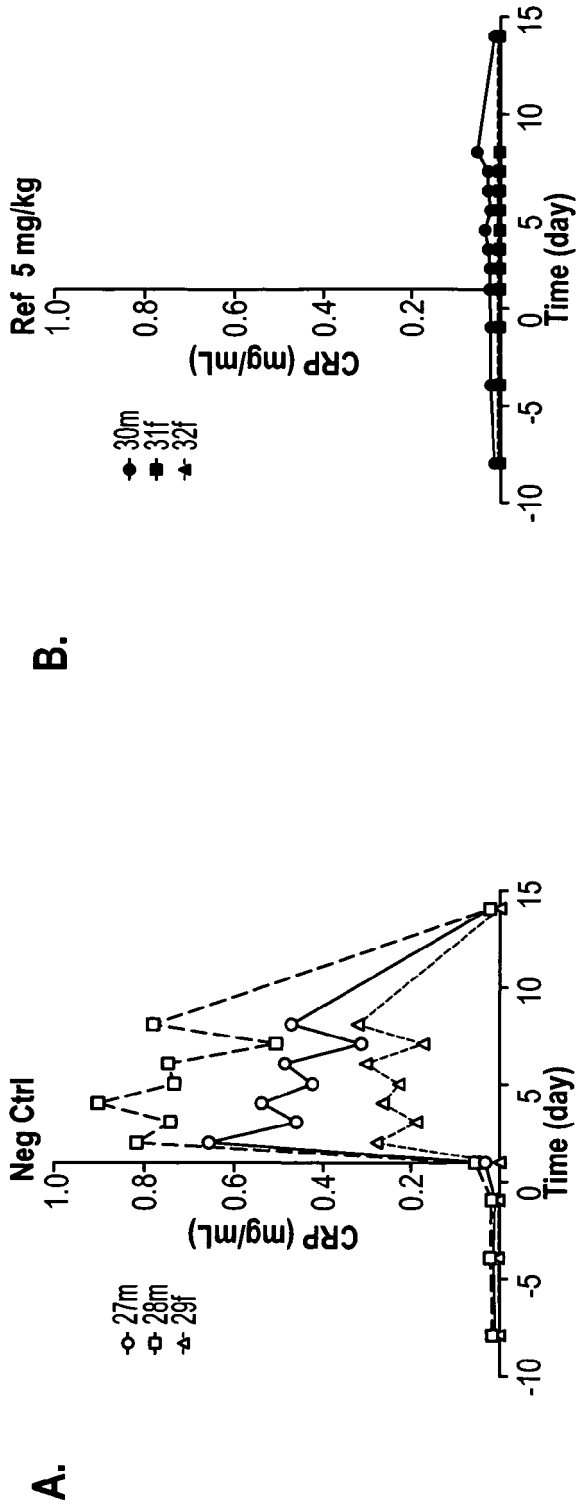


Figure 47

Figure 48


A.
Neg Ctrl
CRP (mg/mL)
1.0
0.8
0.6
0.4
0.2
Time (day)
-10
-5
0
5
10
15
27m
28m
29f
B.
Ref 5 mg/kg
CRP (mg/mL)
1.0
0.8
0.6
0.4
0.2
Time (day)
-10
-5
0
5
10
15
30m
31f
32f

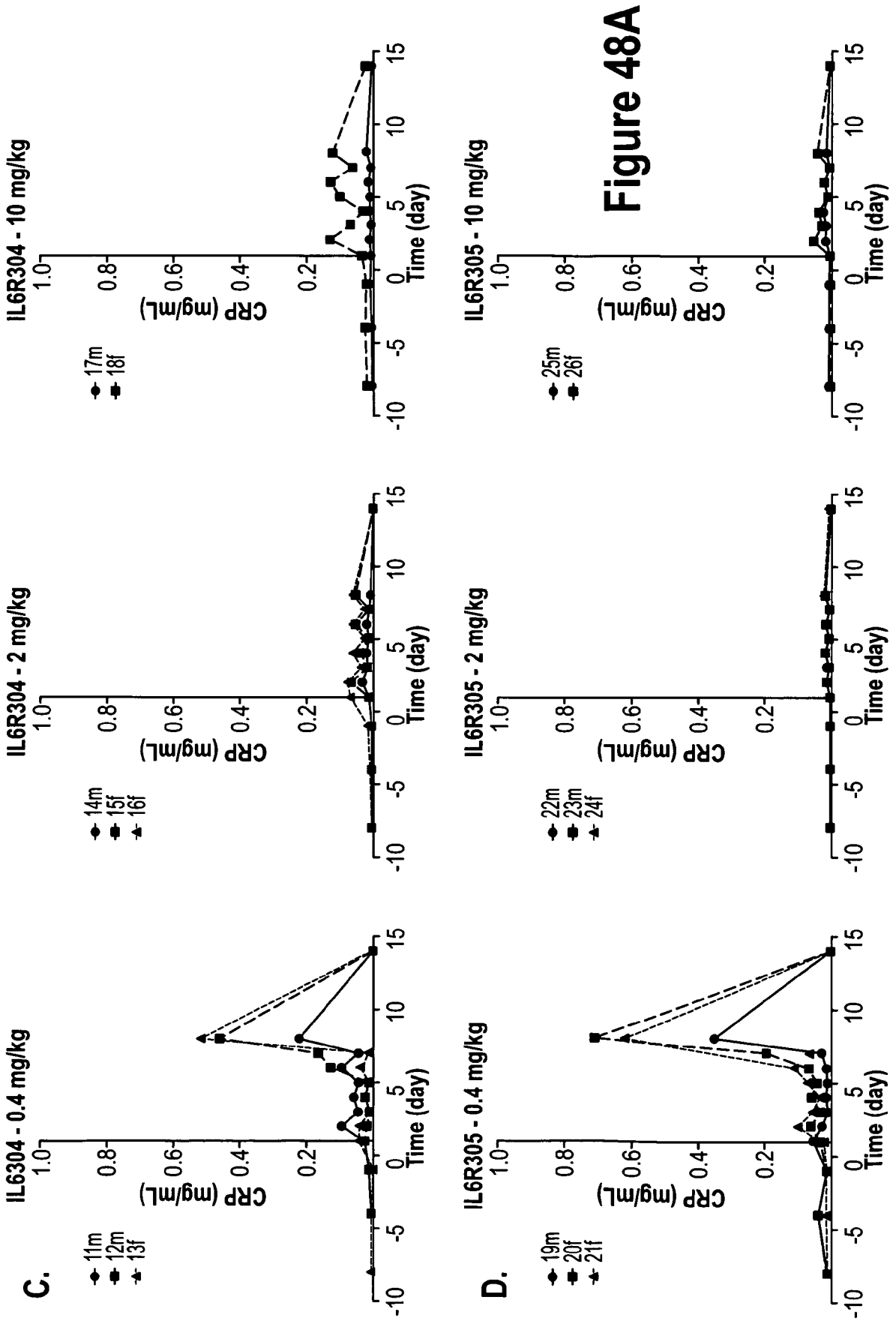

IL6R304 - 10 mg/kg
17m
18f
IL6R304 - 2 mg/kg
14m
15f
16f
IL6R305 - 10 mg/kg
25m
26f
IL6R305 - 2 mg/kg
22m
23m
24f
C.
IL6304 - 0.4 mg/kg
11m
12m
13f
D.
IL6R305 - 0.4 mg/kg
19m
20f
21f
CRP (mg/mL)
Time (day)

Figure 48A

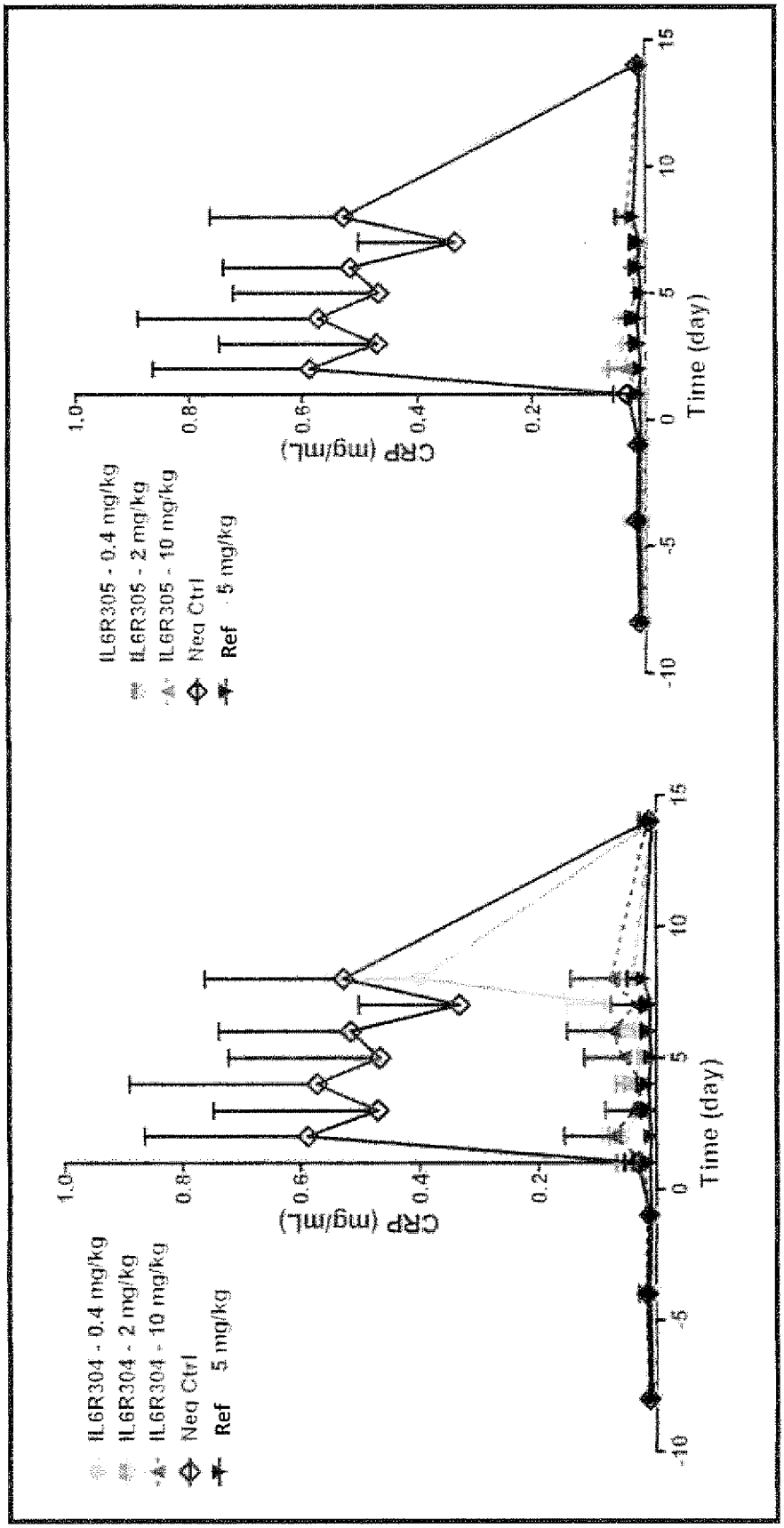

IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
Neg Ctrl
Ref 5 mg/kg
CRP (mg/mL)
Time (day)
IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
Neg Ctrl
Ref 5 mg/kg
CRP (mg/mL)
Time (day)

Figure 49

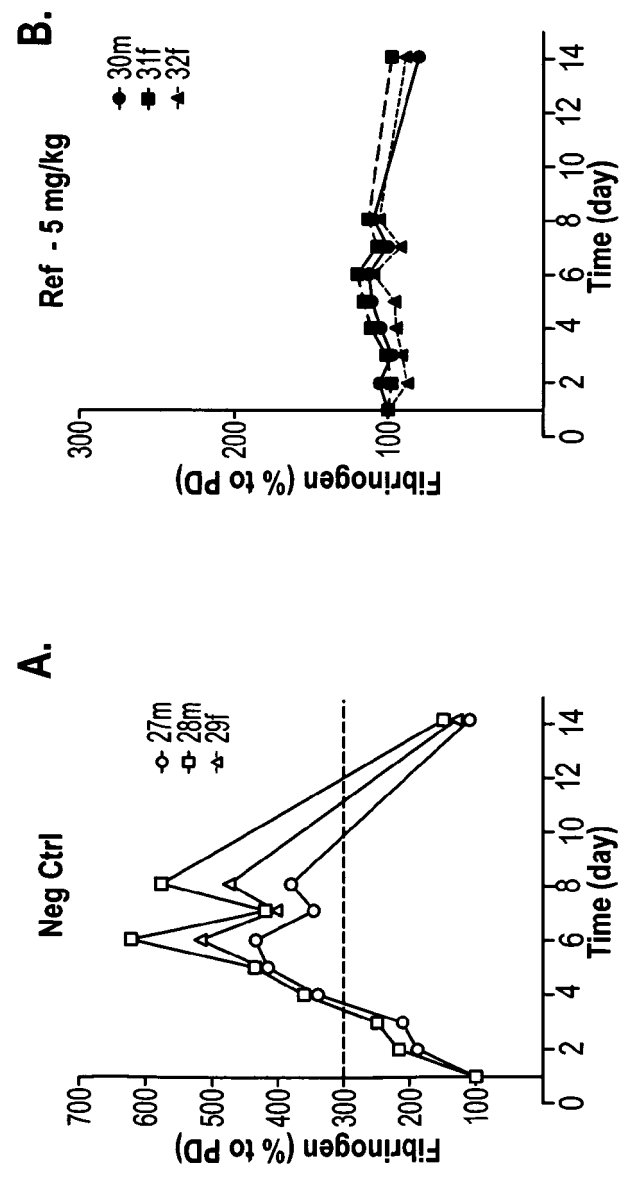

A.
Neg Ctrl
27m
28m
29f
Fibrinogen (% to PD)
700
600
500
400
300
200
100
0
2
4
6
8
10
12
14
Time (day)
B.
Ref - 5 mg/kg
30m
31f
32f
Fibrinogen (% to PD)
300
200
100
0
2
4
6
8
10
12
14
Time (day)

Figure 50

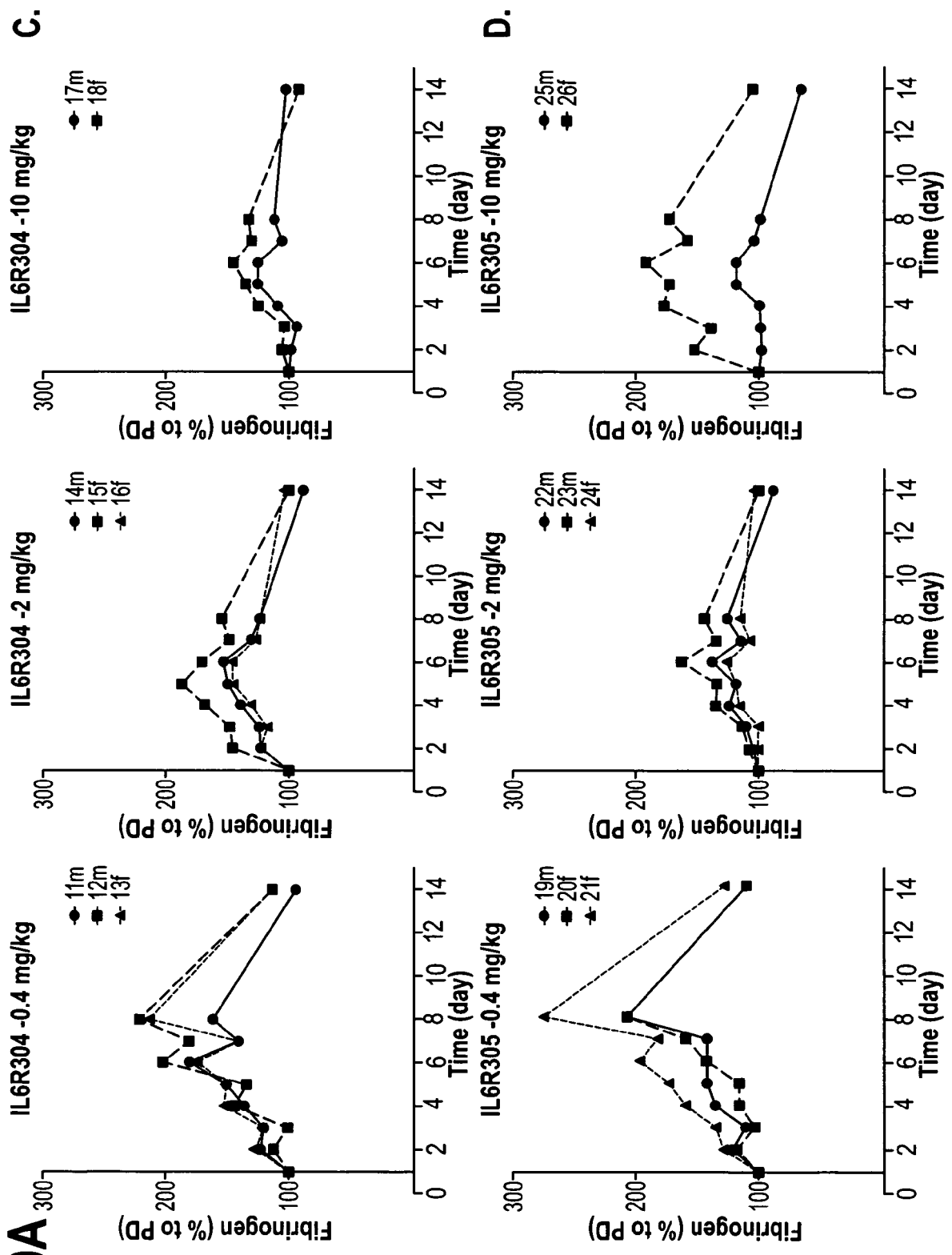

C.
D.
IL6R304 -10 mg/kg
IL6R305 -10 mg/kg
IL6R304 -2 mg/kg
IL6R305 -2 mg/kg
IL6R304 -0.4 mg/kg
IL6R305 -0.4 mg/kg
17m
18f
25m
26f
14m
15f
16f
22m
23m
24f
11m
12m
13f
19m
20f
21f
Fibrinogen (% to PD)
Time (day)
0
2
4
6
8
10
12
14
100
200
300

Figure 50A

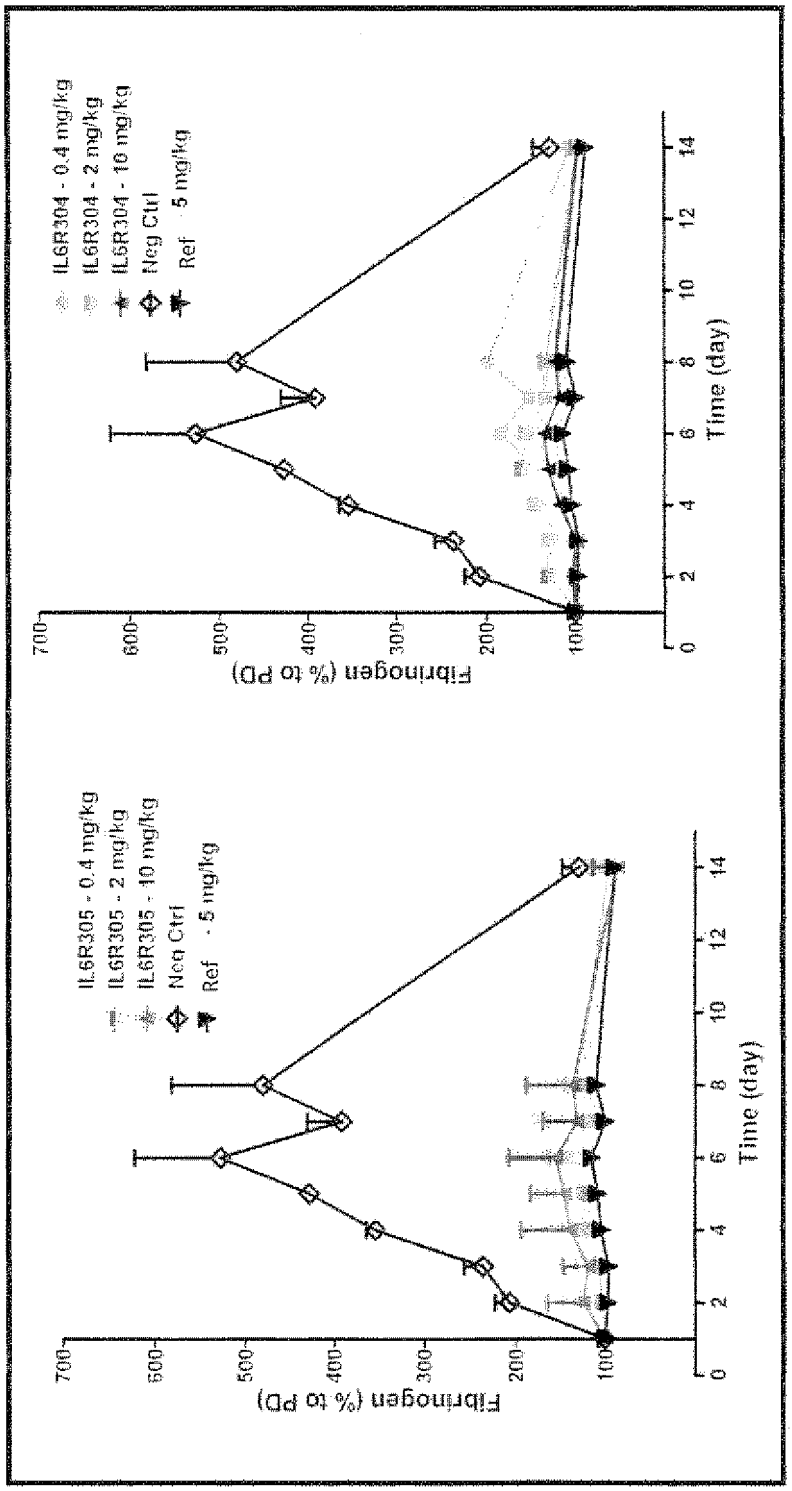
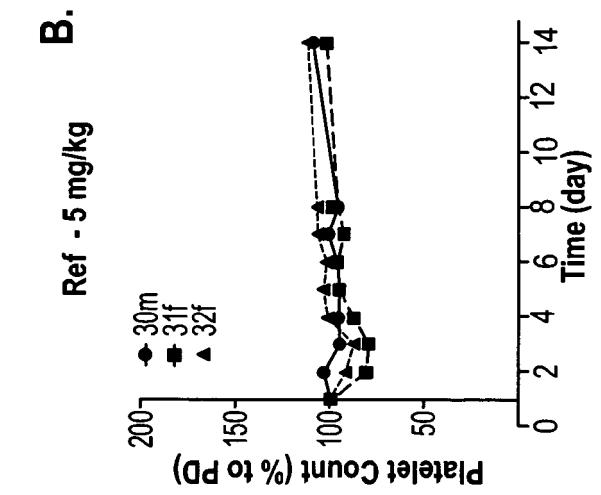

IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Fibrinogen (% to PD)
Time (day)
IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Fibrinogen (% to PD)
Time (day)

Figure 51


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)

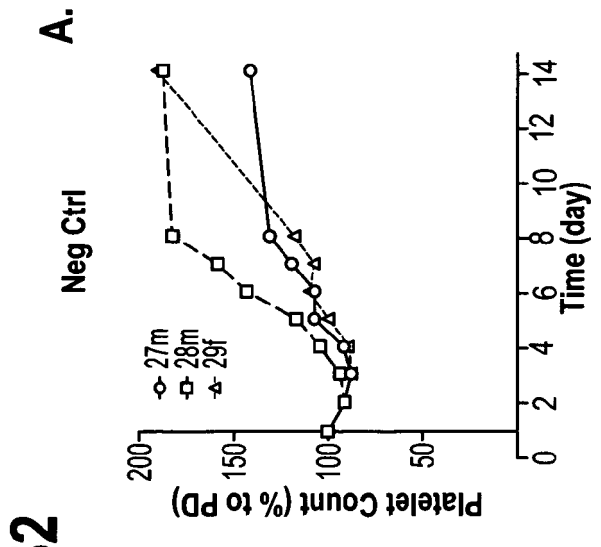
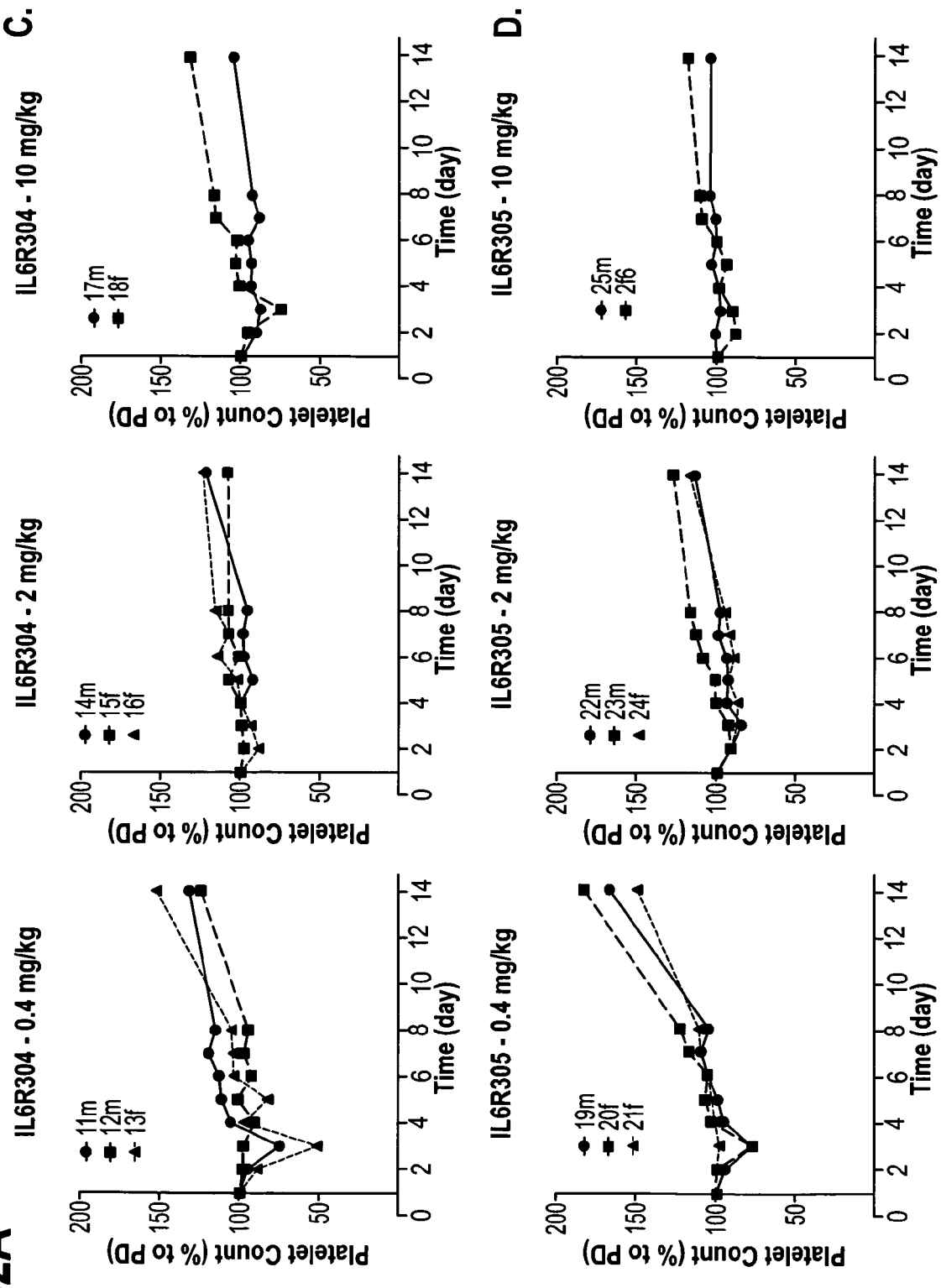

A.
Neg Ctrl
27m
28m
29f
Platelet Count (% to PD)
200
150
100
50
0
2
4
6
8
10
12
14
Time (day)

Figure 52

Figure 52A


IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
C.
D.
11m
12m
13f
14m
15f
16f
17m
18f
19m
20f
21f
22m
23m
24f
25m
2f6
Platelet Count (% to PD)
Time (day)
0
2
4
6
8
10
12
14
50
100
150
200

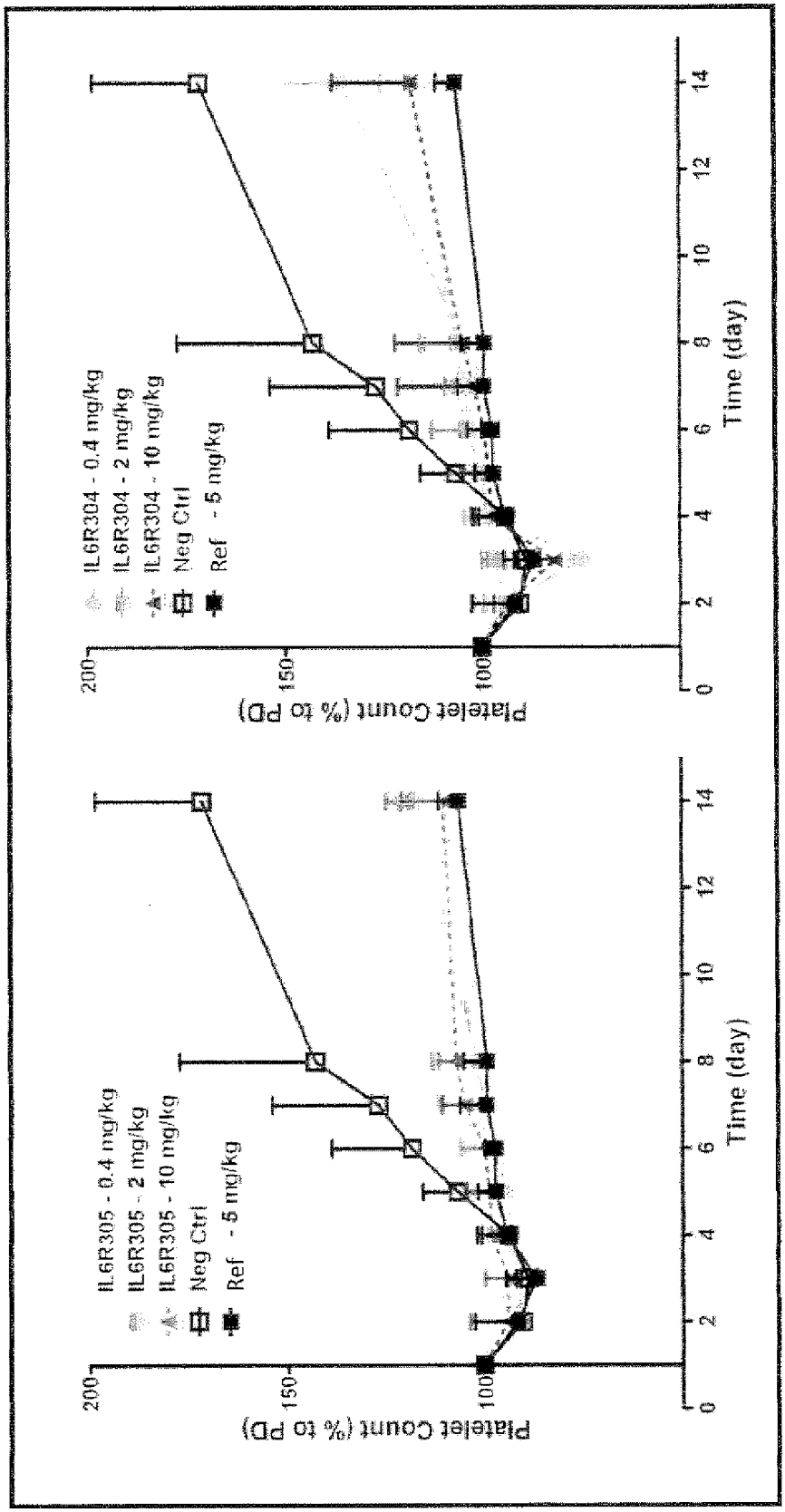

IL6R304 - 0.4 mg/kg
IL6R304 - 2 mg/kg
IL6R304 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Platelet Count (% to PD)
Time (day)
IL6R305 - 0.4 mg/kg
IL6R305 - 2 mg/kg
IL6R305 - 10 mg/kg
Neg Ctrl
Ref - 5 mg/kg
Platelet Count (% to PD)
Time (day)

Figure 53

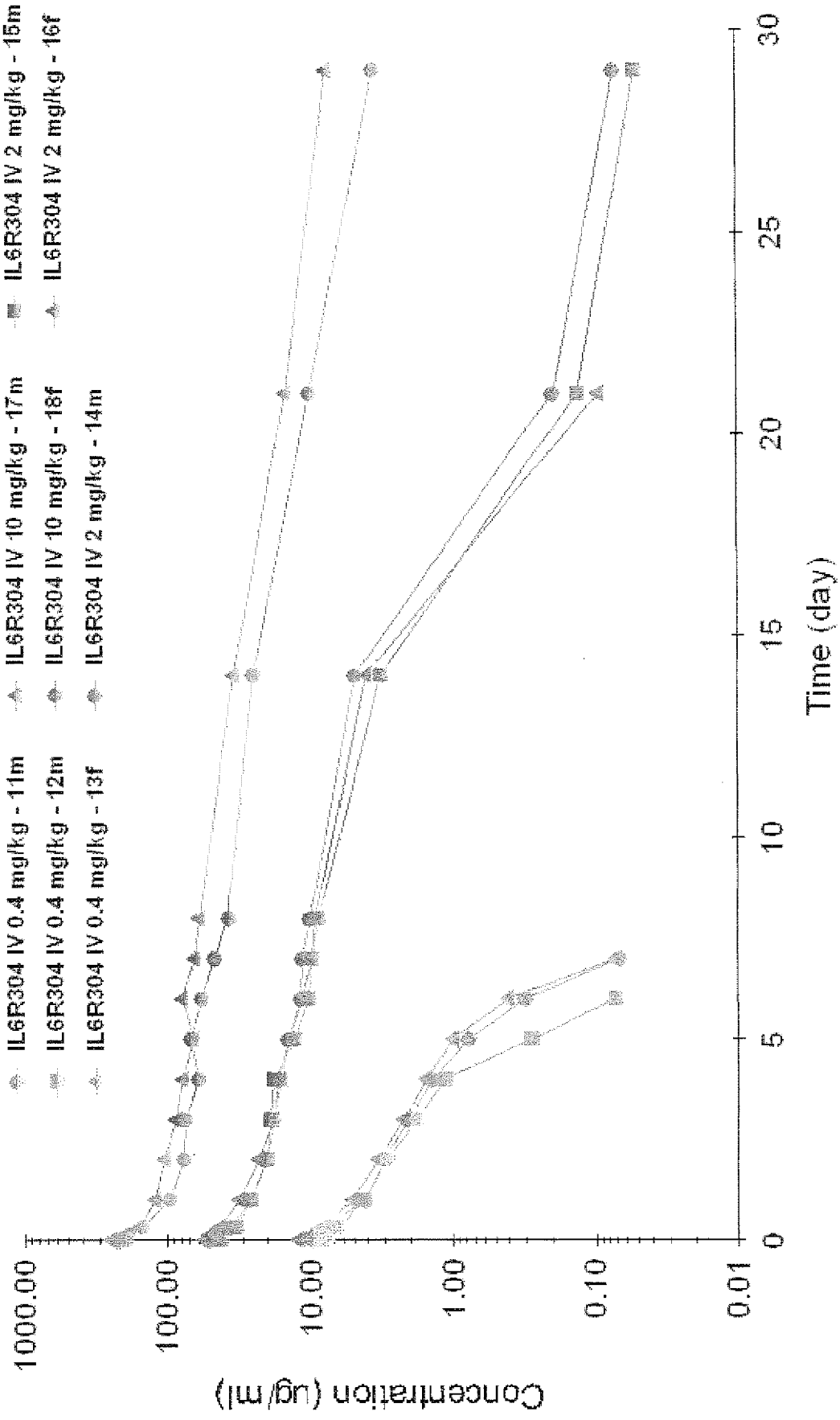

IL6R304 IV 0.4 mg/kg - 11m
IL6R304 IV 0.4 mg/kg - 12m
IL6R304 IV 0.4 mg/kg - 13f
IL6R304 IV 10 mg/kg - 17m
IL6R304 IV 10 mg/kg - 18f
IL6R304 IV 2 mg/kg - 14m
IL6R304 IV 2 mg/kg - 15m
IL6R304 IV 2 mg/kg - 16f
1000.00
100.00
10.00
1.00
0.10
0.01
Concentration (ug/ml)
0
5
10
15
20
25
30
Time (day)

Figure 54

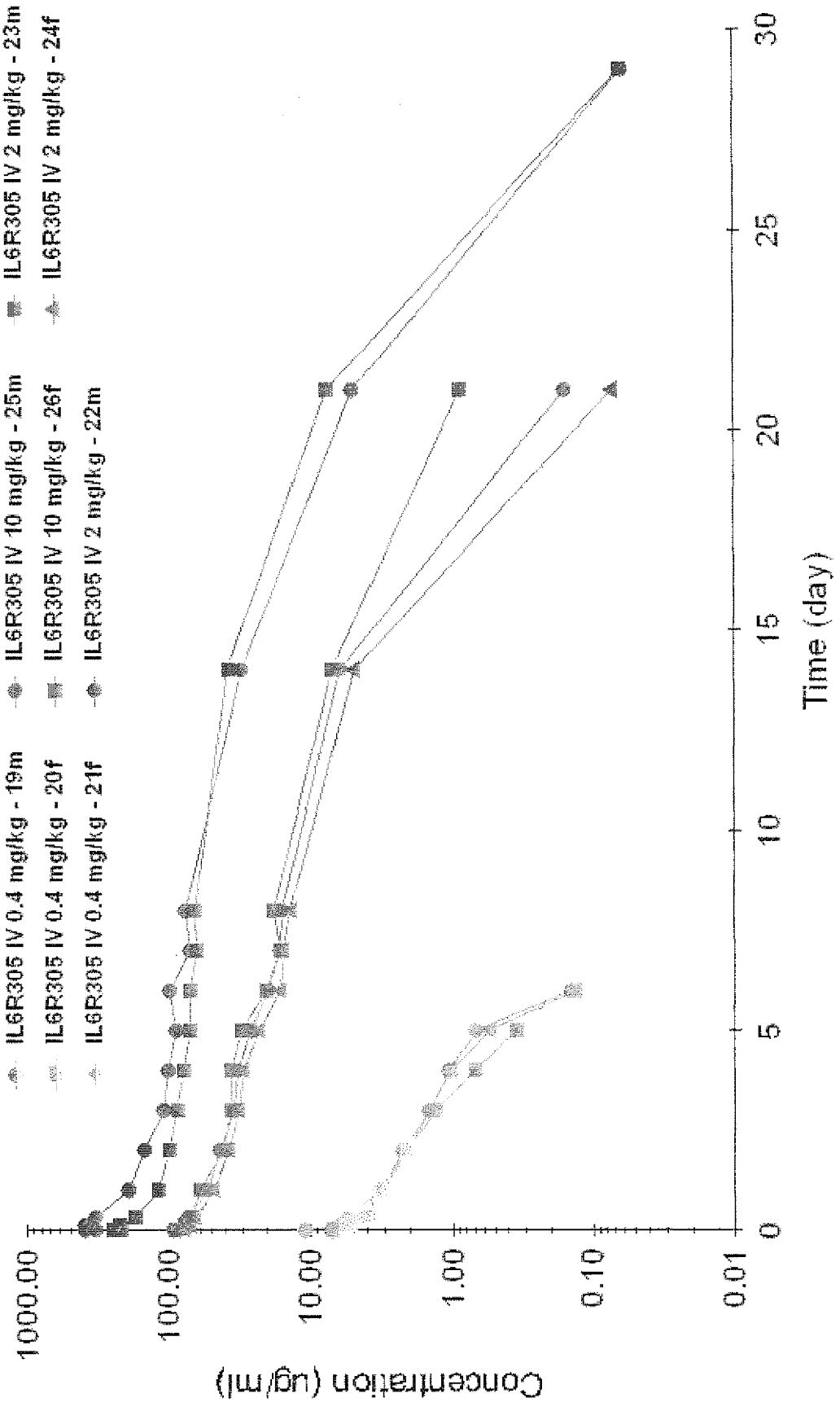

IL6R305 IV 0.4 mg/kg - 19m
IL6R305 IV 0.4 mg/kg - 20f
IL6R305 IV 0.4 mg/kg - 21f
IL6R305 IV 10 mg/kg - 25m
IL6R305 IV 10 mg/kg - 26f
IL6R305 IV 2 mg/kg - 22m
IL6R305 IV 2 mg/kg - 23m
IL6R305 IV 2 mg/kg - 24f
Concentration (ug/ml)
1000.00
100.00
10.00
1.00
0.10
0.01
0
5
10
15
20
25
30
Time (day)

Figure 55

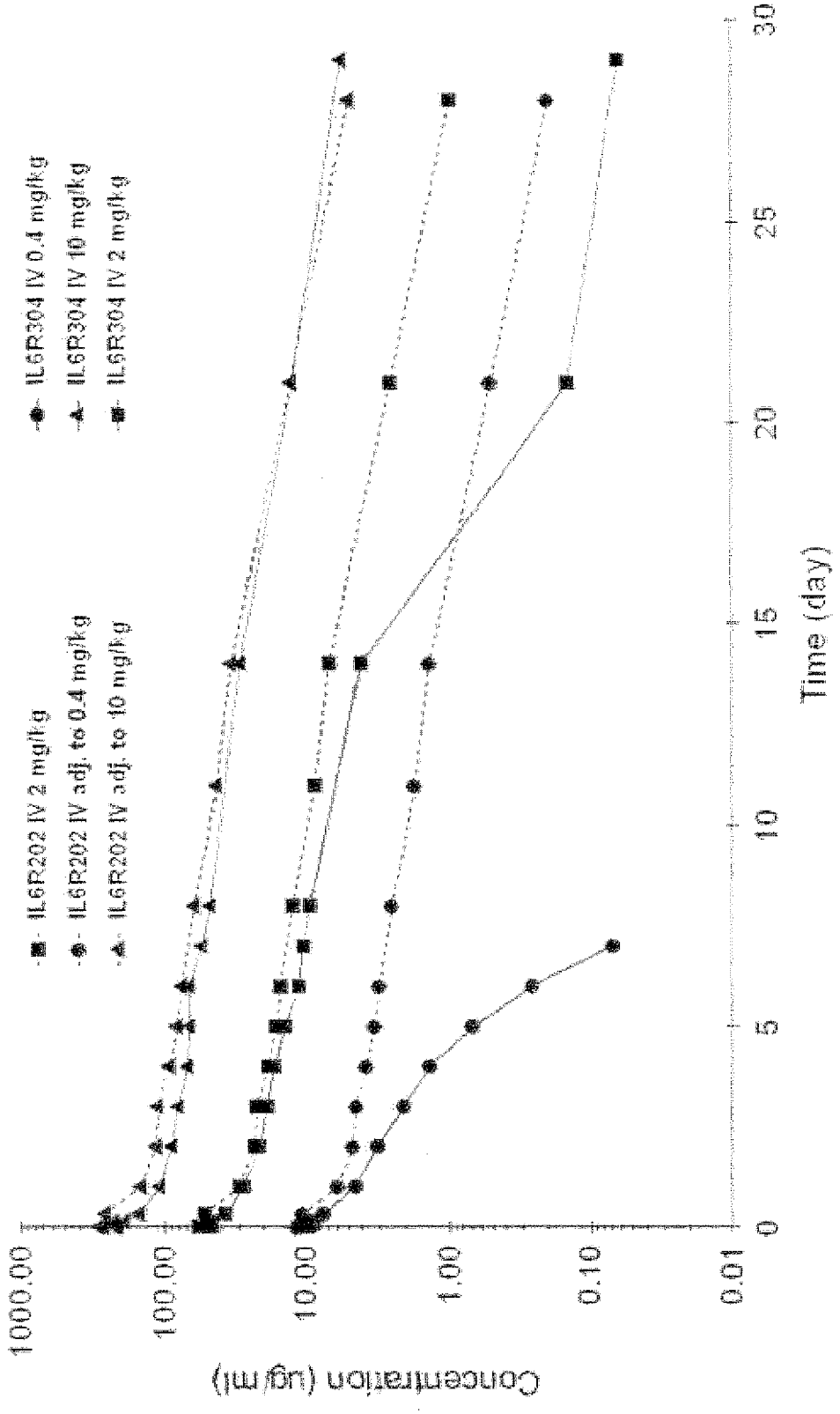
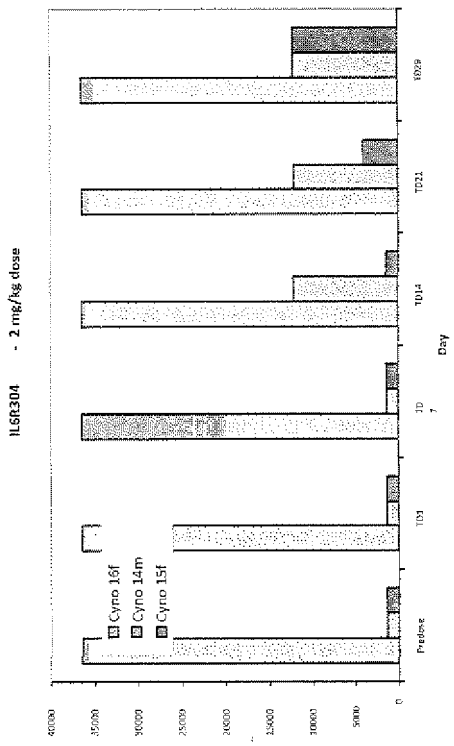
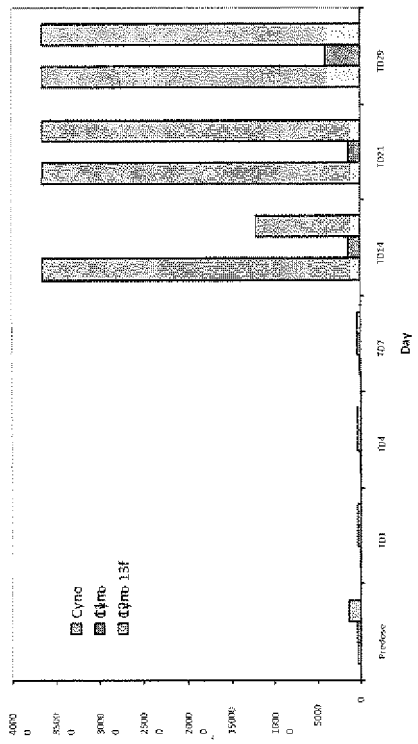

IL6R202 IV 2 mg/kg
IL6R202 IV adj. to 0.4 mg/kg
IL6R202 IV adj. to 10 mg/kg
IL6R304 IV 0.4 mg/kg
IL6R304 IV 10 mg/kg
IL6R304 IV 2 mg/kg
1000.00
100.00
10.00
1.00
0.10
0.01
Concentration (ug/ml)
0
5
10
15
20
25
30
Time (day)

Figure 56


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


IL6R304 - 0.4 mg/kg dose
Cyno
Predose
Day

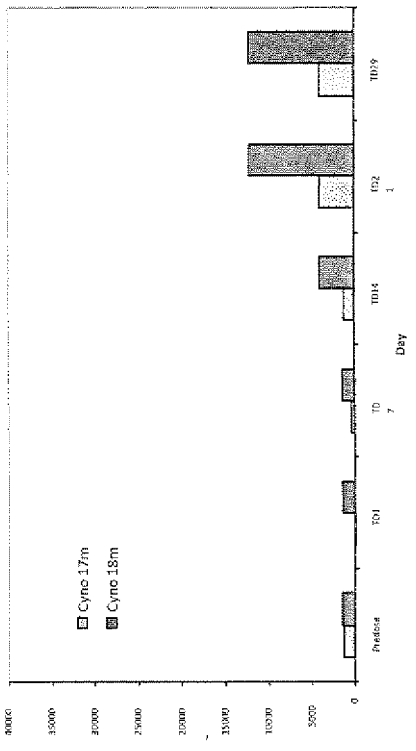
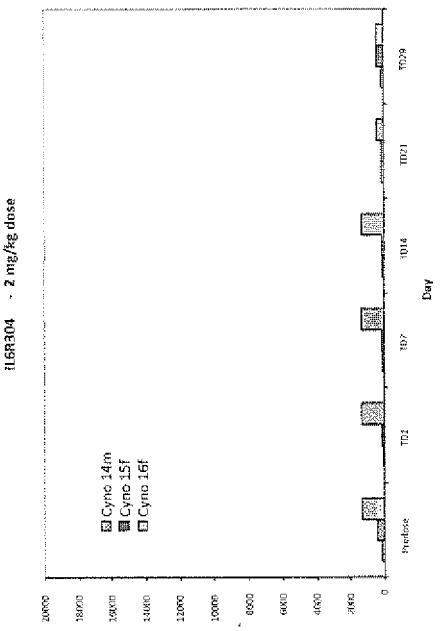
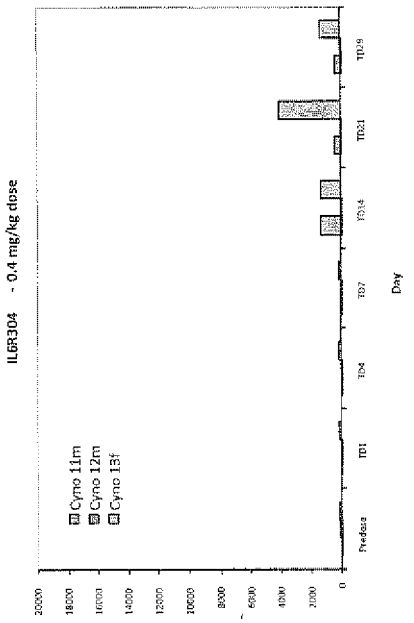

IL6R304 - 10 mg/kg dose
Cyno 17m
Cyno 18m
Predose
Day

Figure 57


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


IL6R304 - 0.4 mg/kg dose
Cyno 11m
Cyno 12m
Cyno 13f
Day

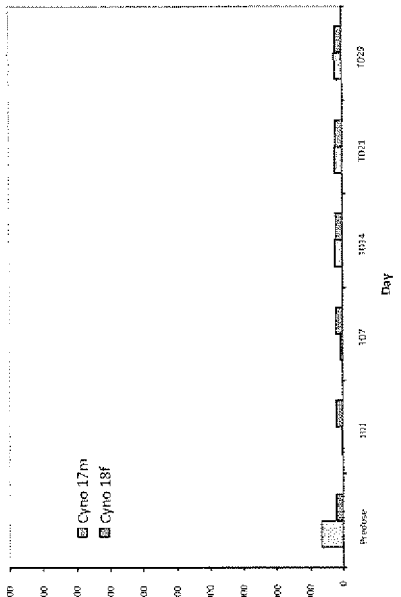

IL6R304 - 10 mg/kg dose
Cyno 17m
Cyno 18f
Day

Figure 58

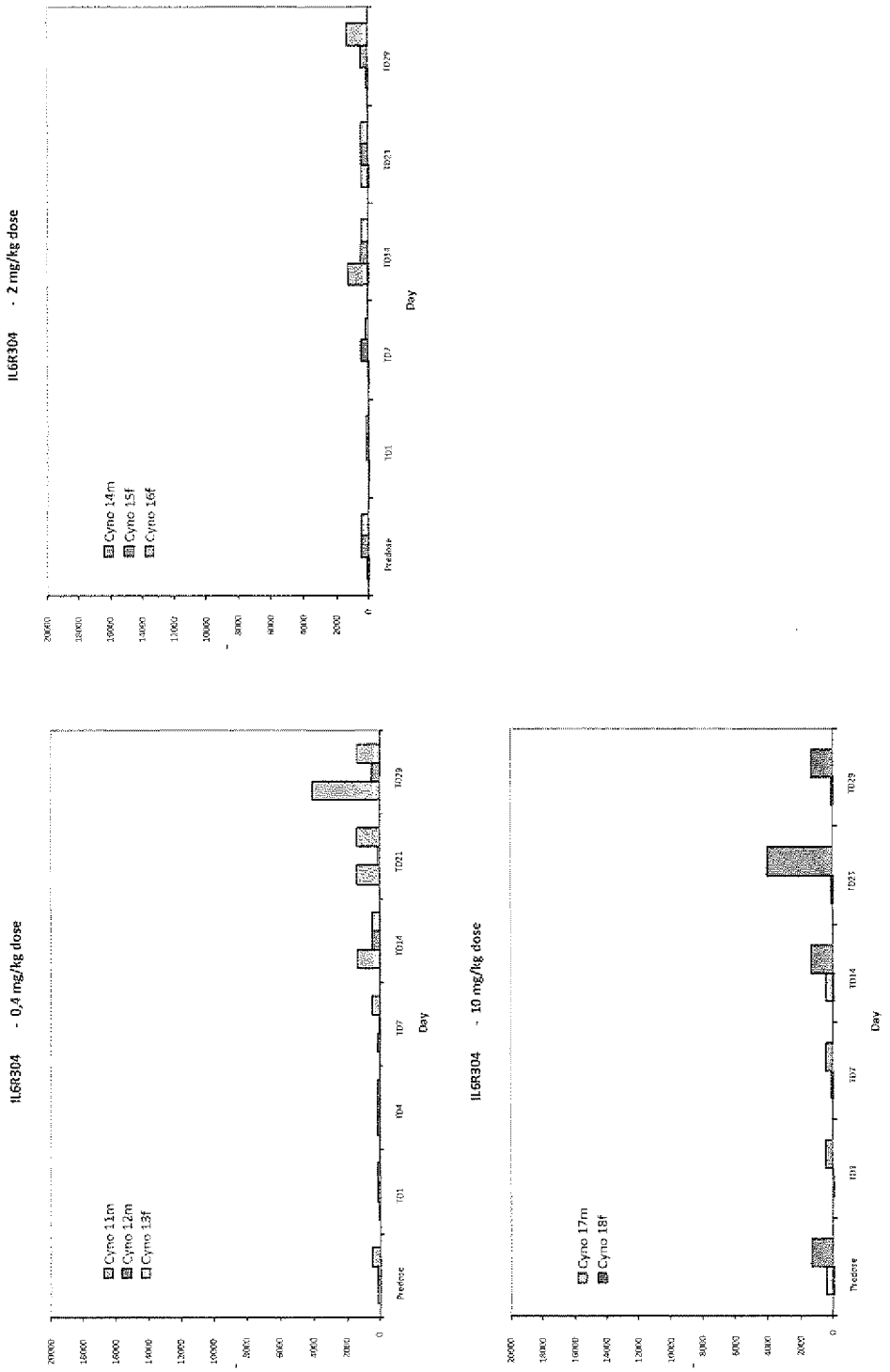

IL6R304 - 0,4 mg/kg dose
Cyno 11m
Cyno 12m
Cyno 13f
Predose
Day
IL6R304 - 2 mg/kg dose
Cyno 14m
Cyno 15f
Cyno 16f
IL6R304 - 10 mg/kg dose
Cyno 17m
Cyno 18f

Figure 59

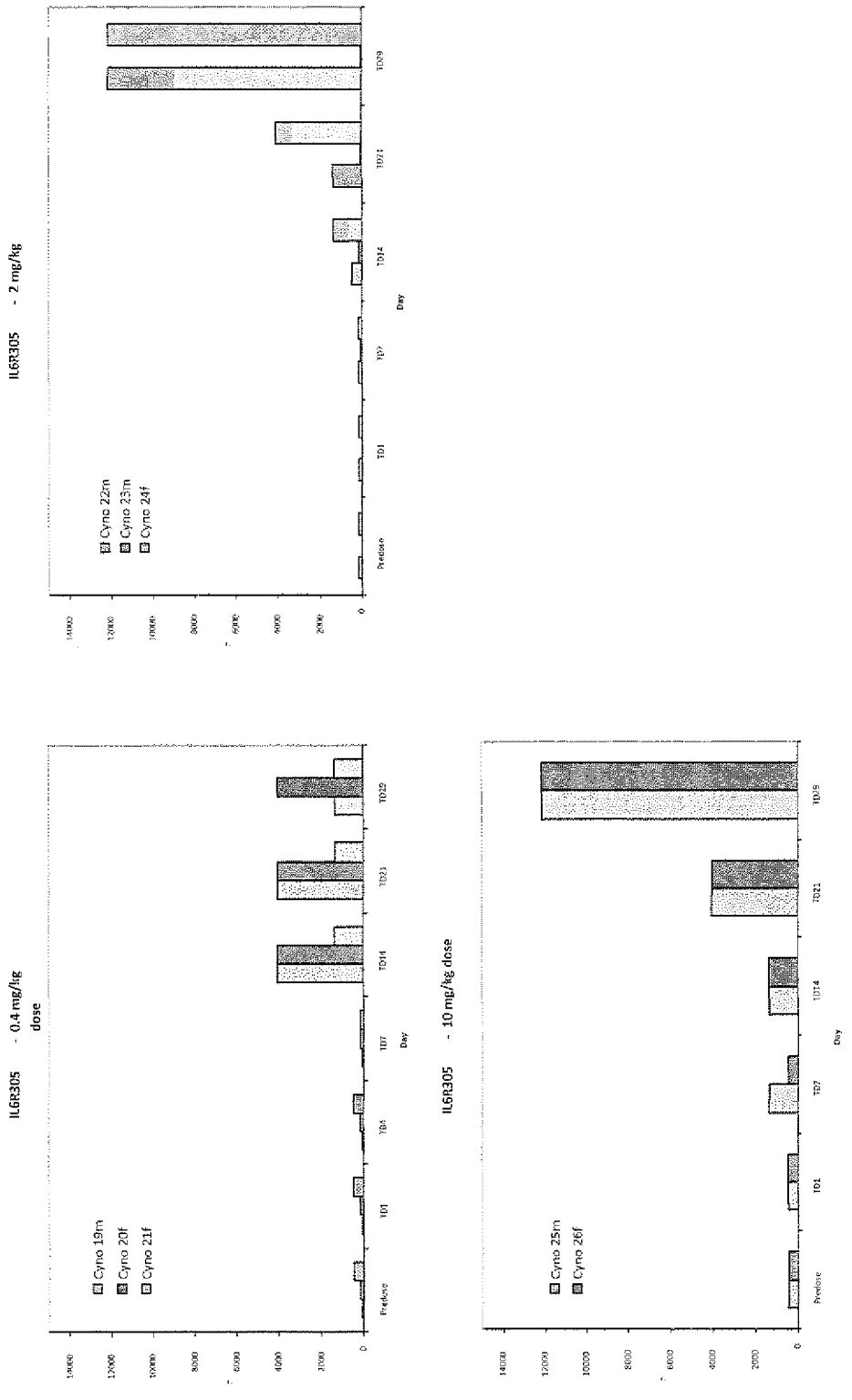
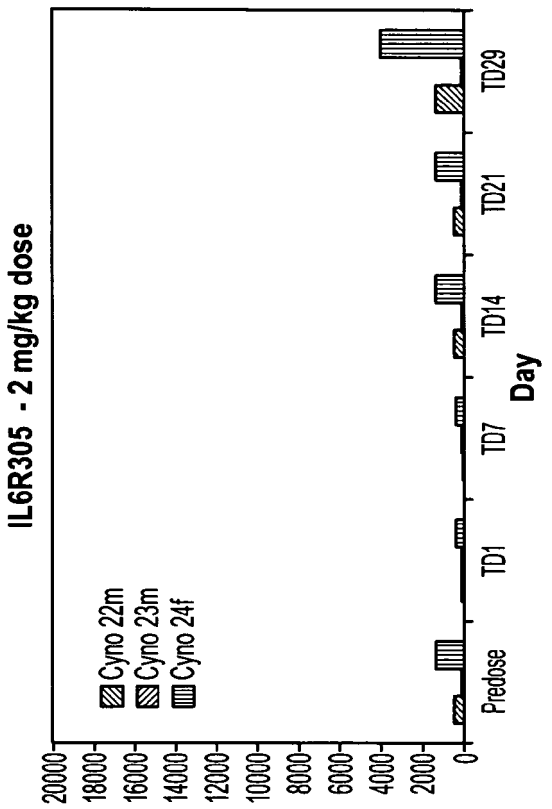
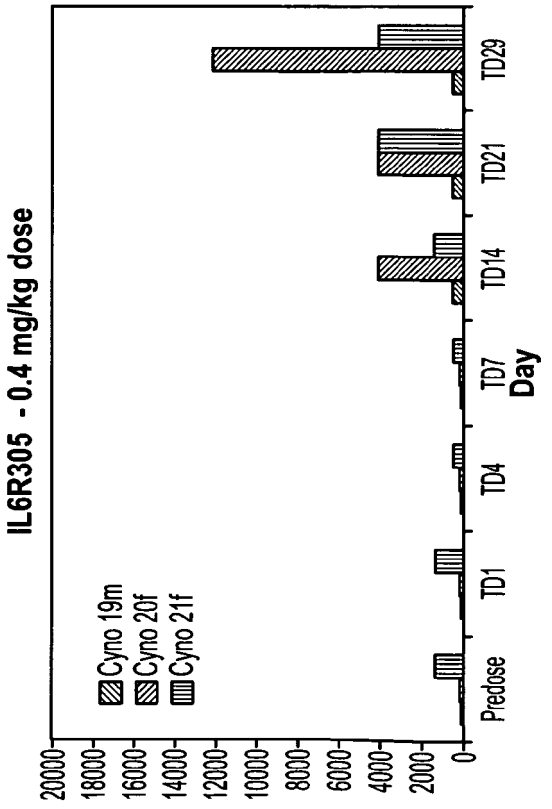

IL6R305 - 2 mg/kg
Cyno 22m
Cyno 23m
Cyno 24f
Predose
TD1
TD7
TD14
TD21
TD29
Day
IL6R305 - 0.4 mg/kg dose
Cyno 19m
Cyno 20f
Cyno 21f
IL6R305 - 10 mg/kg dose
Cyno 25m
Cyno 26f

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

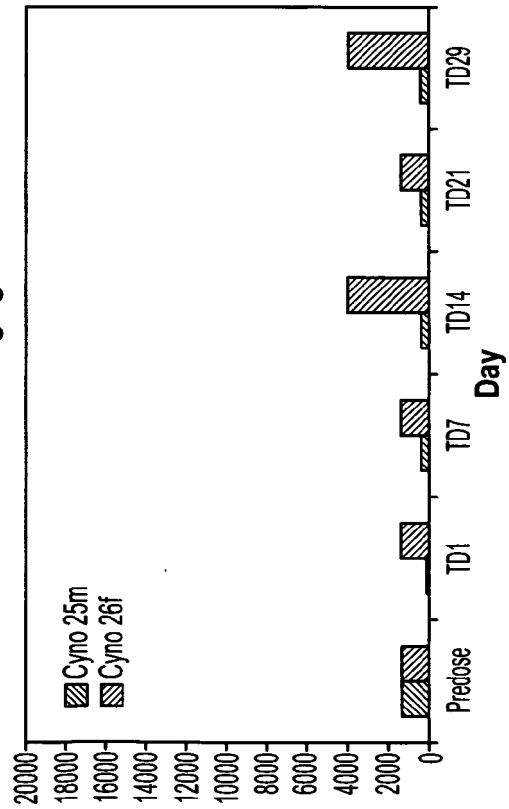

IL6R305 -10 mg/kg dose
Cyno 25m
Cyno 26f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD7
TD14
TD21
TD29
Day

Figure 61

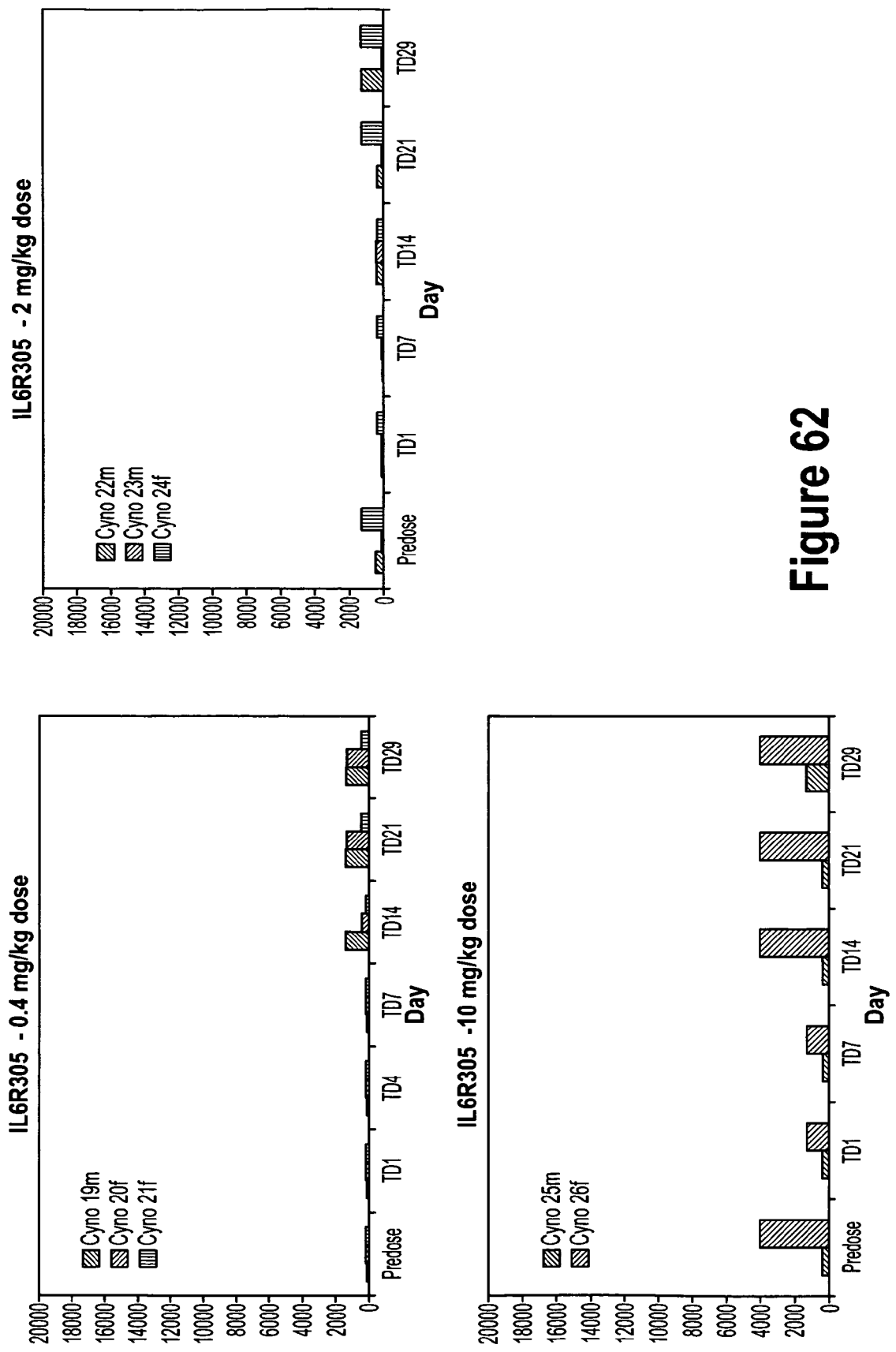

IL6R305 - 2 mg/kg dose
Cyno 22m
Cyno 23m
Cyno 24f
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Predose
TD1
TD7
TD14
TD21
TD29
Day
IL6R305 - 0.4 mg/kg dose
Cyno 19m
Cyno 20f
Cyno 21f
Predose
TD1
TD4
TD7
TD14
TD21
TD29
Day
IL6R305 -10 mg/kg dose
Cyno 25m
Cyno 26f
Predose
TD1
TD7
TD14
TD21
TD29
Day

Figure 62

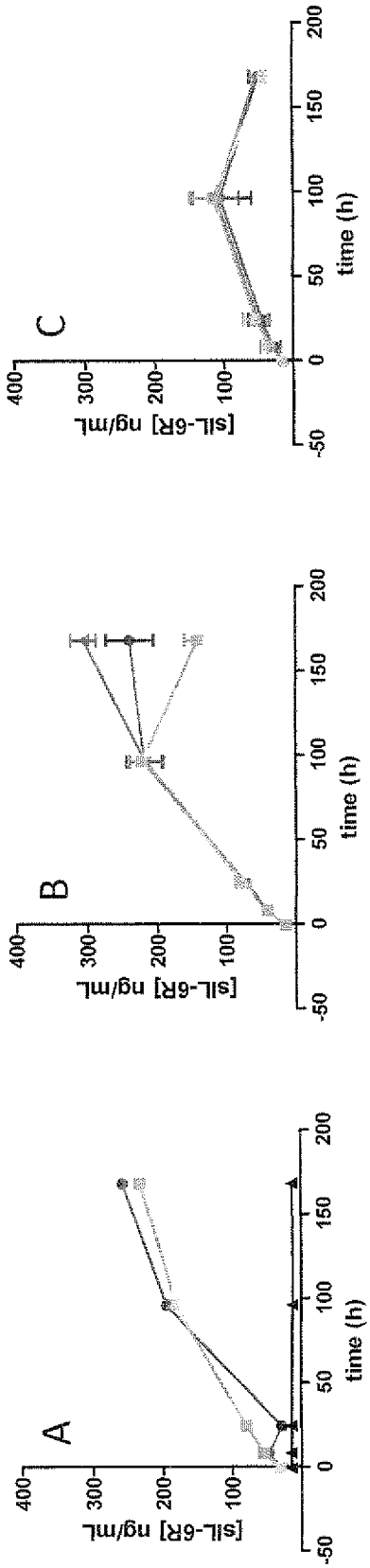


Figure 63

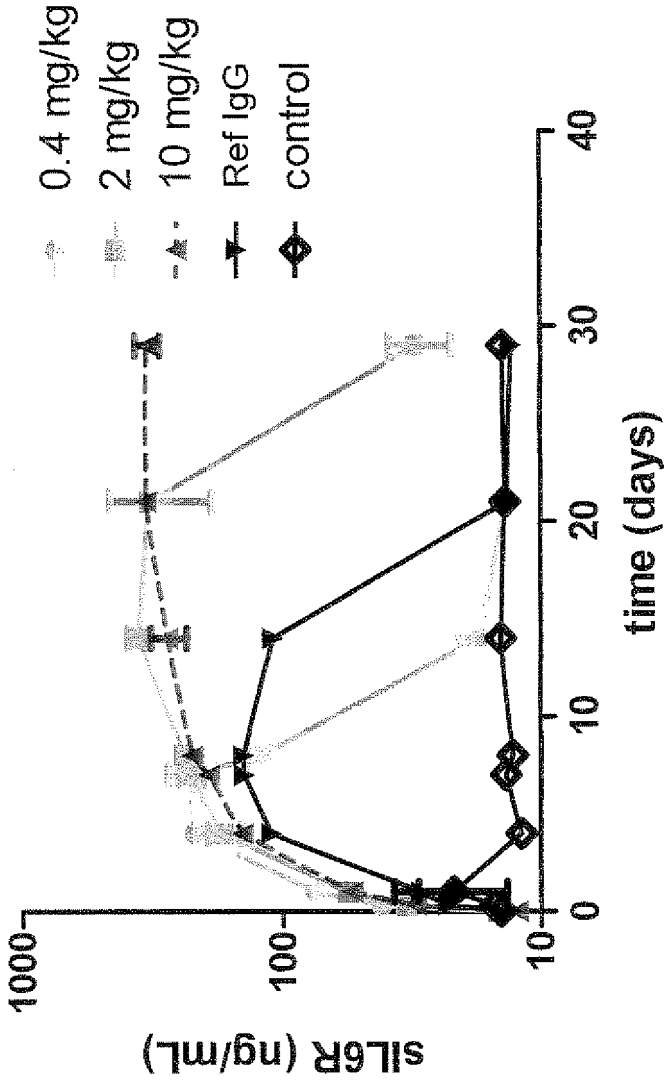

0.4 mg/kg
2 mg/kg
10 mg/kg
Ref IgG
control
1000
100
10
sIL6R (ng/mL)
0
10
20
30
40
time (days)

Figure 64A

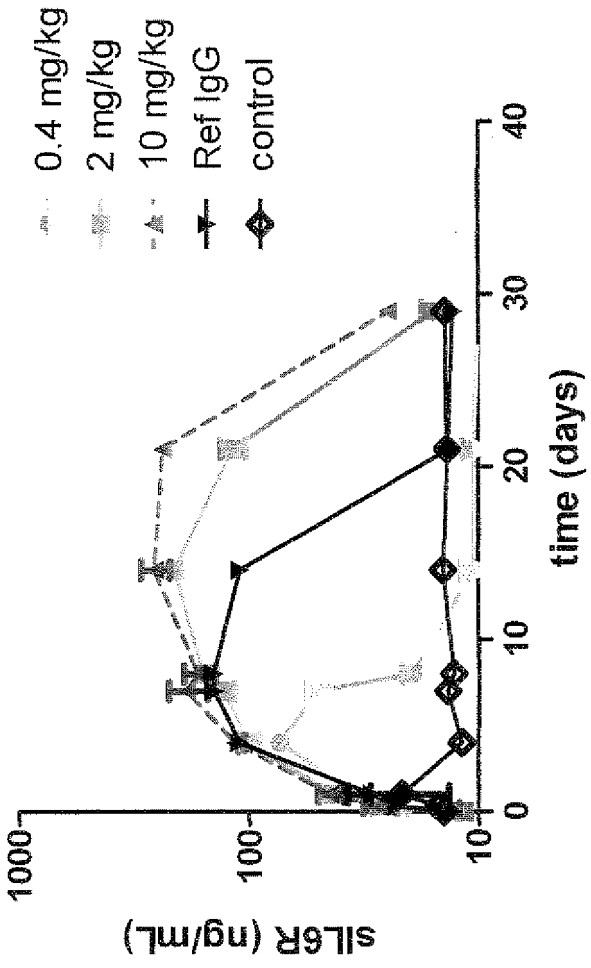

0.4 mg/kg
2 mg/kg
10 mg/kg
Ref IgG
control
1000
100
10
sIL6R (ng/mL)
0
10
20
30
40
time (days)

Figure 64B

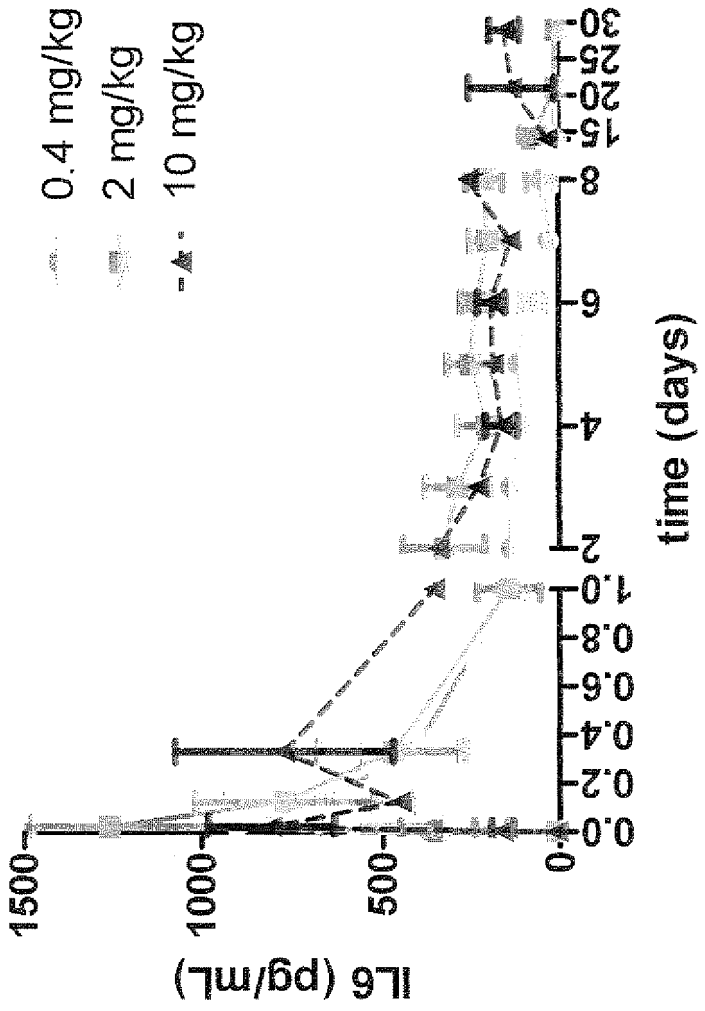

0.4 mg/kg
2 mg/kg
10 mg/kg
IL6 (pg/mL)
1500
1000
500
0
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
15
20
25
30
time (days)

Figure 65A

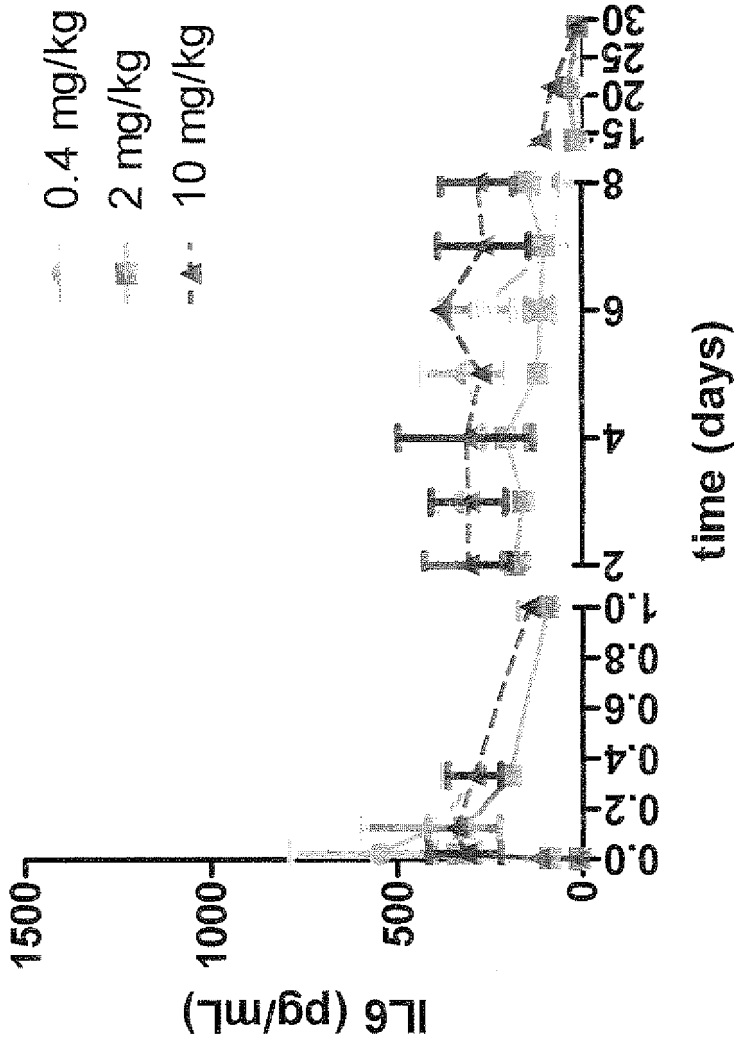

0.4 mg/kg
2 mg/kg
10 mg/kg
IL6 (pg/mL)
1500
1000
500
0
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
15
20
25
30
time (days)

Figure 65B

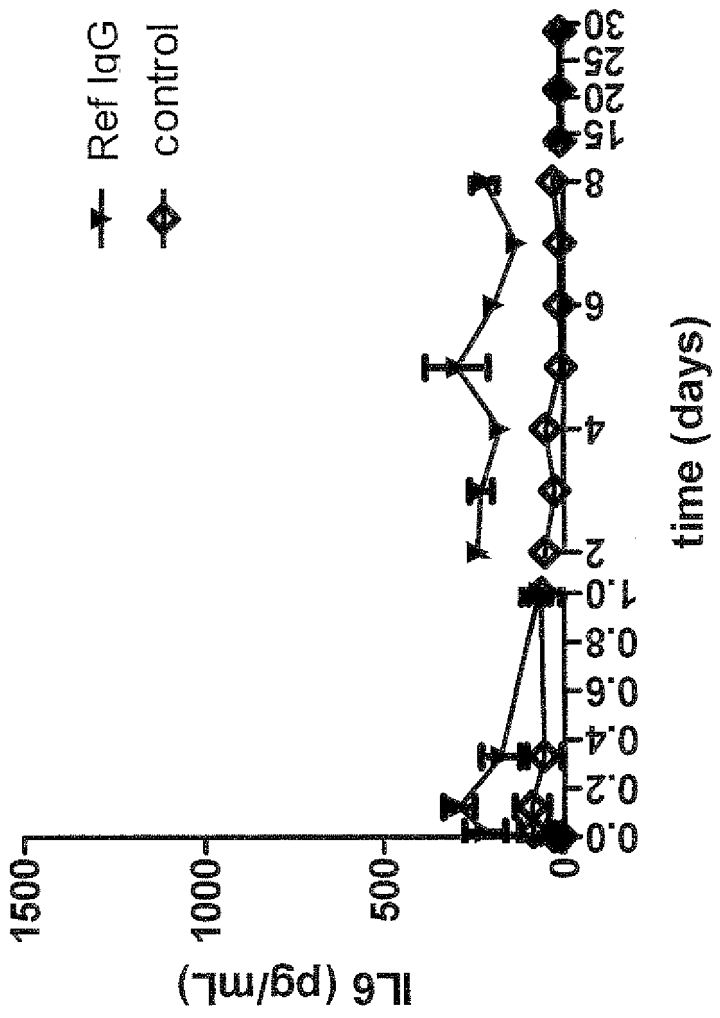

Ref IgG
control
IL6 (pg/mL)
1500
1000
500
0
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
15
20
25
30
time (days)

Figure 65C

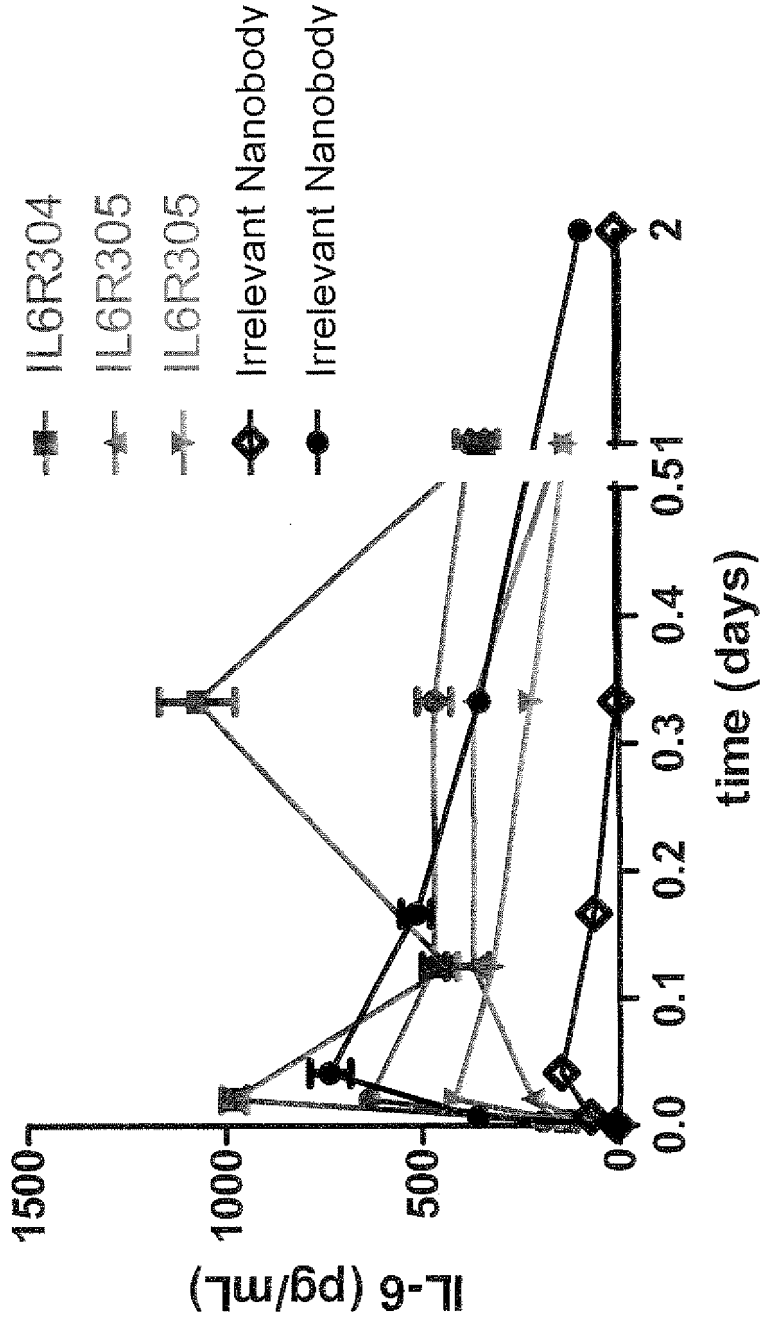

IL6R304
IL6R304
IL6R305
IL6R305
Irrelevant Nanobody
Irrelevant Nanobody
IL-6 (pg/mL)
1500
1000
500
0
0.0
0.1
0.2
0.3
0.4
0.5
1
2
time (days)

Figure 65D

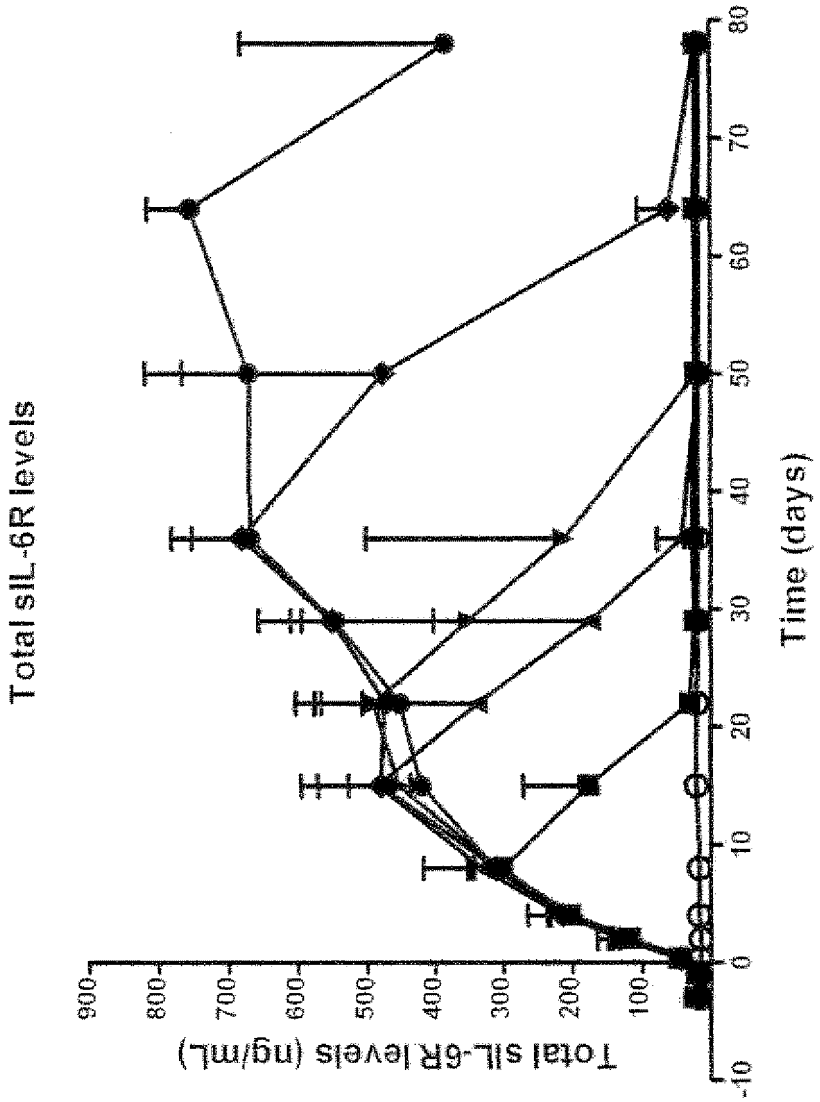

Total sIL-6R levels
Total sIL-6R levels (ng/mL)
900
800
700
600
500
400
300
200
100
-10
0
10
20
30
40
50
60
70
80
Time (days)

Figure 66A

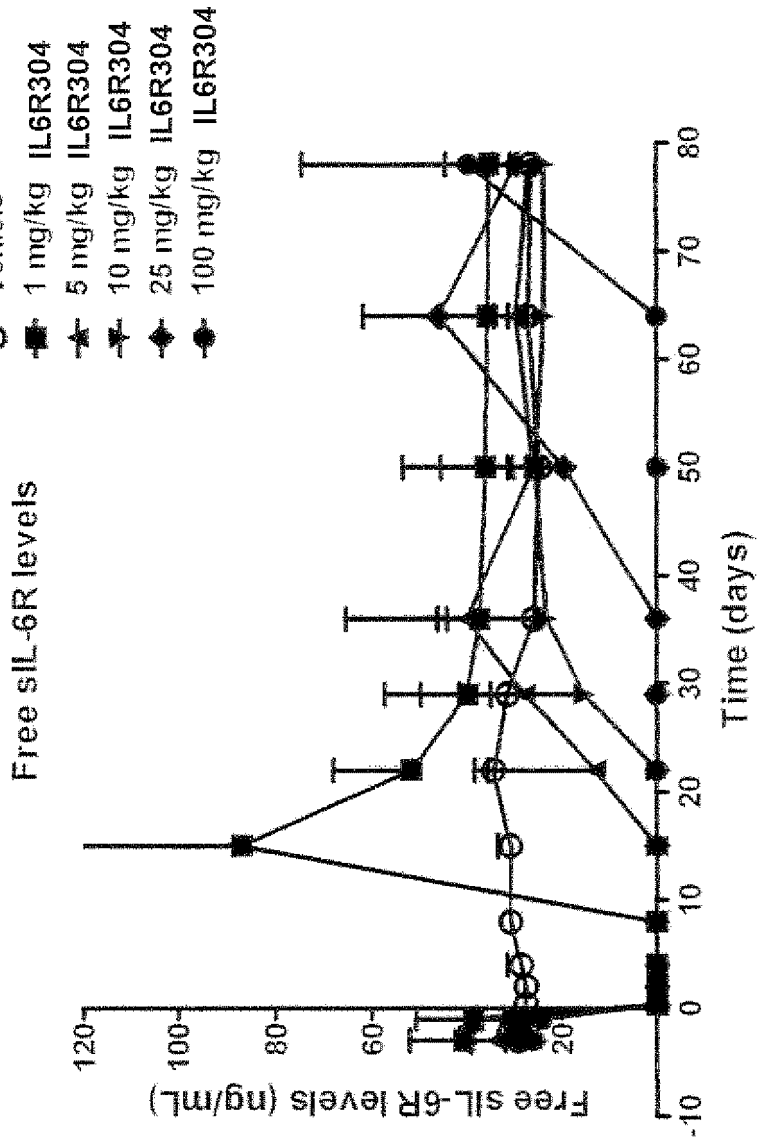

Free sIL-6R levels
Vehicle
1 mg/kg IL6R304
5 mg/kg IL6R304
10 mg/kg IL6R304
25 mg/kg IL6R304
100 mg/kg IL6R304
Free sIL-6R levels (ng/mL)
120
100
80
60
20
-10
0
10
20
30
40
50
60
70
80
Time (days)

Figure 66B

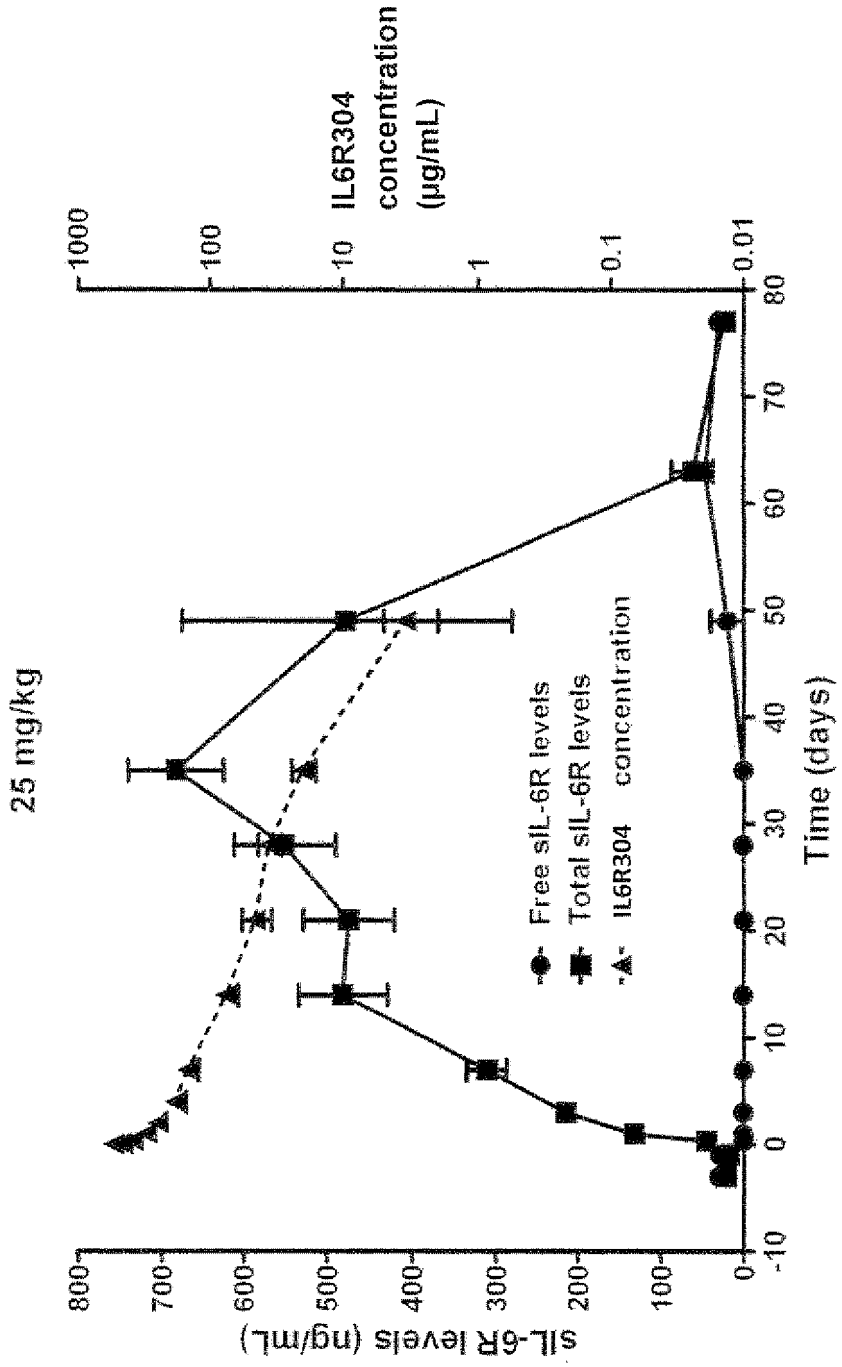

25 mg/kg
sIL-6R levels (ng/mL)
IL6R304 concentration (µg/mL)
Time (days)
Free sIL-6R levels
Total sIL-6R levels
IL6R304 concentration
800
700
600
500
400
300
200
100
0
-10
1000
100
10
1
0.1
0.01
0
10
20
30
40
50
60
70
80

Figure 67

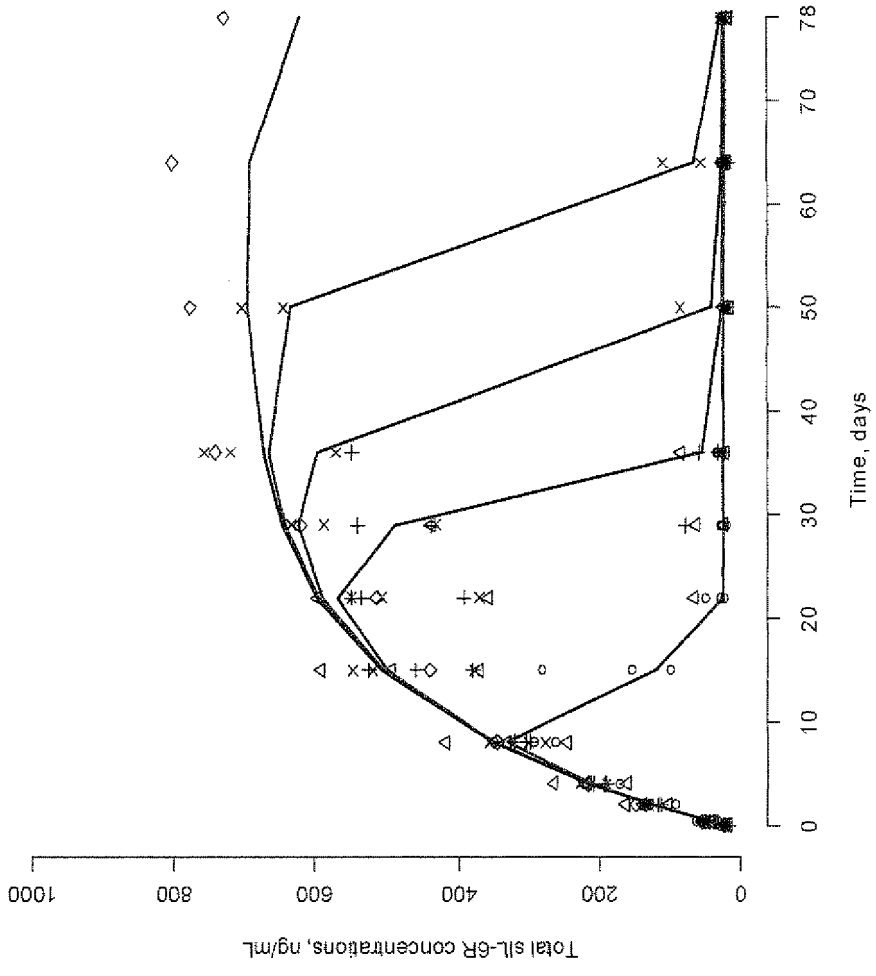

Total sIL-6R concentrations, ng/mL
0
200
400
600
800
1000
Time, days
0
10
20
30
40
50
60
70
78

Figure 68

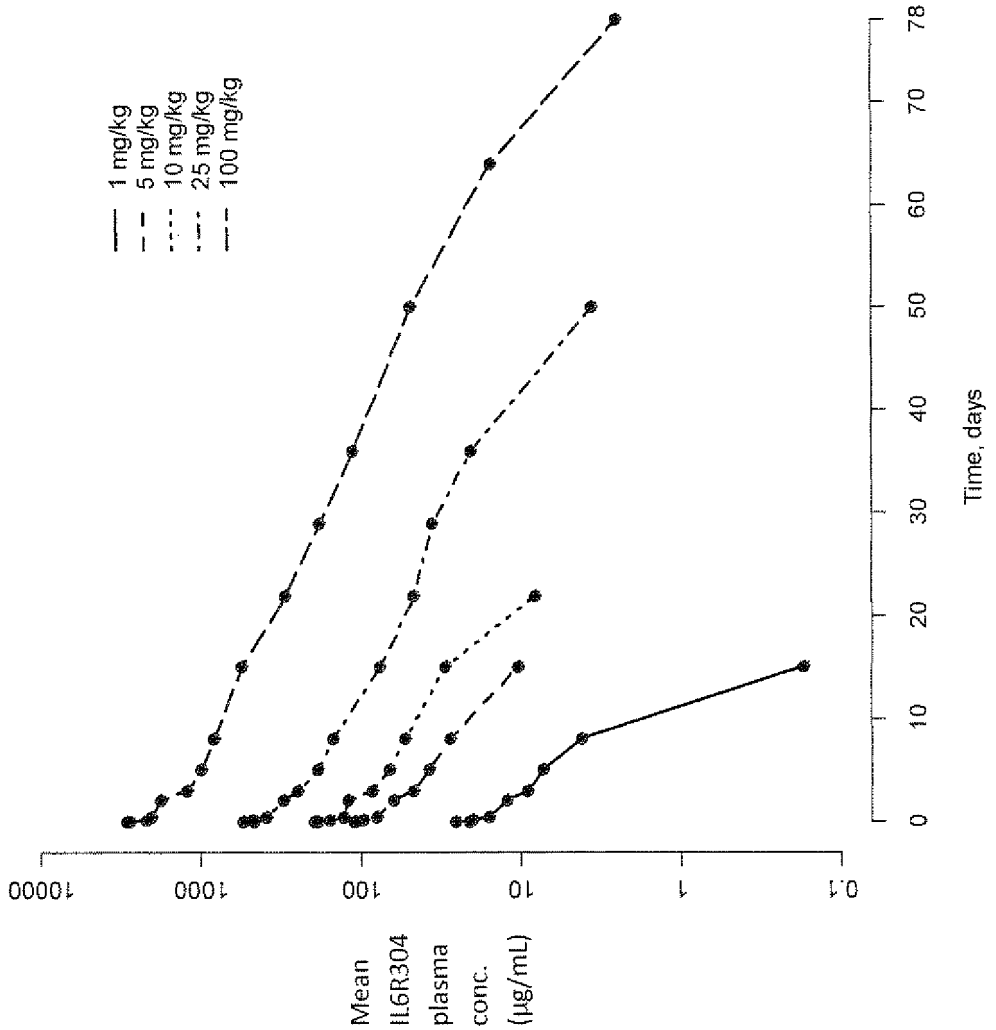

1 mg/kg
5 mg/kg
10 mg/kg
25 mg/kg
100 mg/kg
Mean IL6R304 plasma conc. (µg/mL)
10000
1000
100
10
1
0.1
0
10
20
30
40
50
60
70
78
Time, days

Figure 69

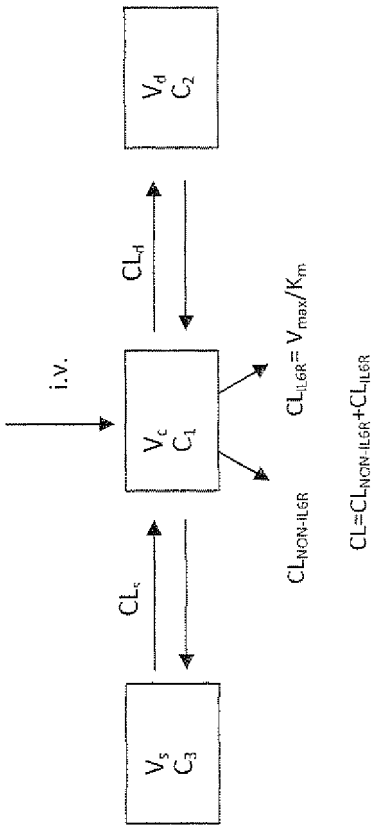

i.v.
V_c C_1
V_d C_2
V_s C_3
CL_d
CL_s
CL_{IL6R}= V_{max}/K_m
$CL_{NON-IL6R}$
$CL=CL_{NON-IL6R}+CL_{IL6R}$

Figure 70