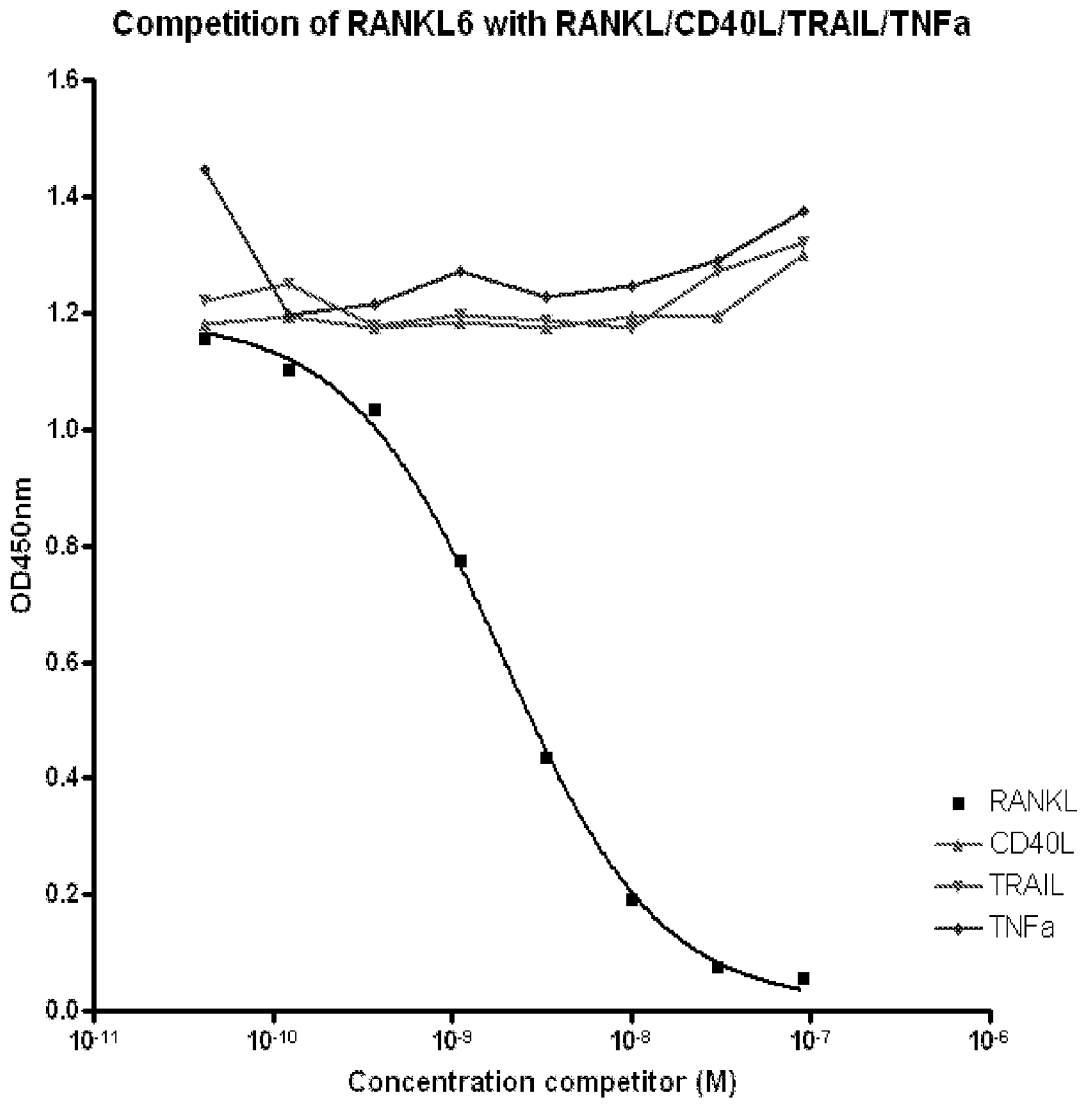

Competition of RANKL6 with RANKL/CD40L/TRAIL/TNFa
OD450nm
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
10-11
10-10
10-9
10-8
10-7
10-6
Concentration competitor (M)
RANKL
CD40L
TRAIL
TNFa

Figure 1-A

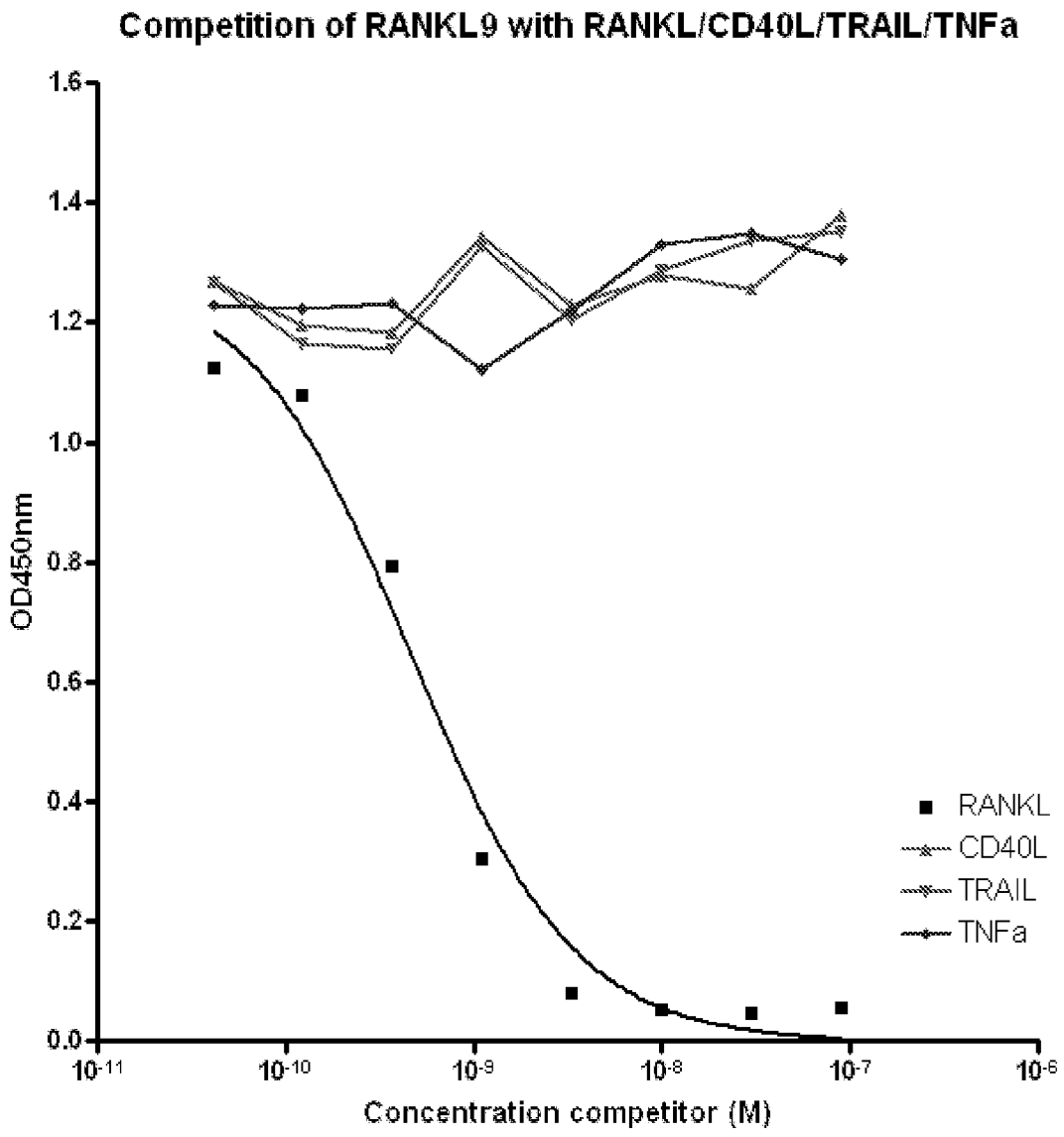

Competition of RANKL9 with RANKL/CD40L/TRAIL/TNFa
OD450nm
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
10-11
10-10
10-9
10-8
10-7
10-6
Concentration competitor (M)
RANKL
CD40L
TRAIL
TNFa

Figure 1-B

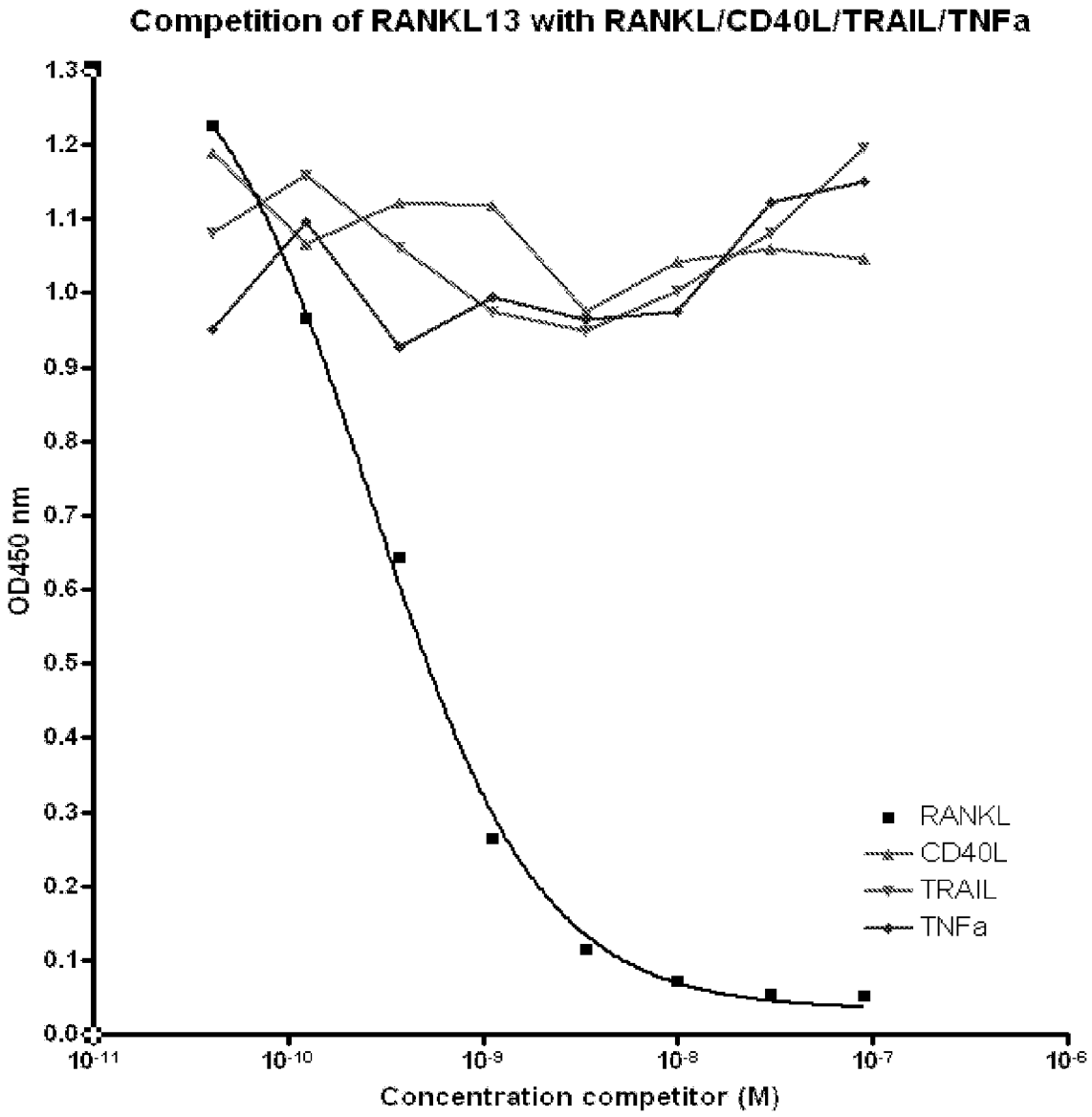

Competition of RANKL13 with RANKL/CD40L/TRAIL/TNFa
OD450 nm
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
10-11
10-10
10-9
10-8
10-7
10-6
Concentration competitor (M)
RANKL
CD40L
TRAIL
TNFa

Figure 1-C

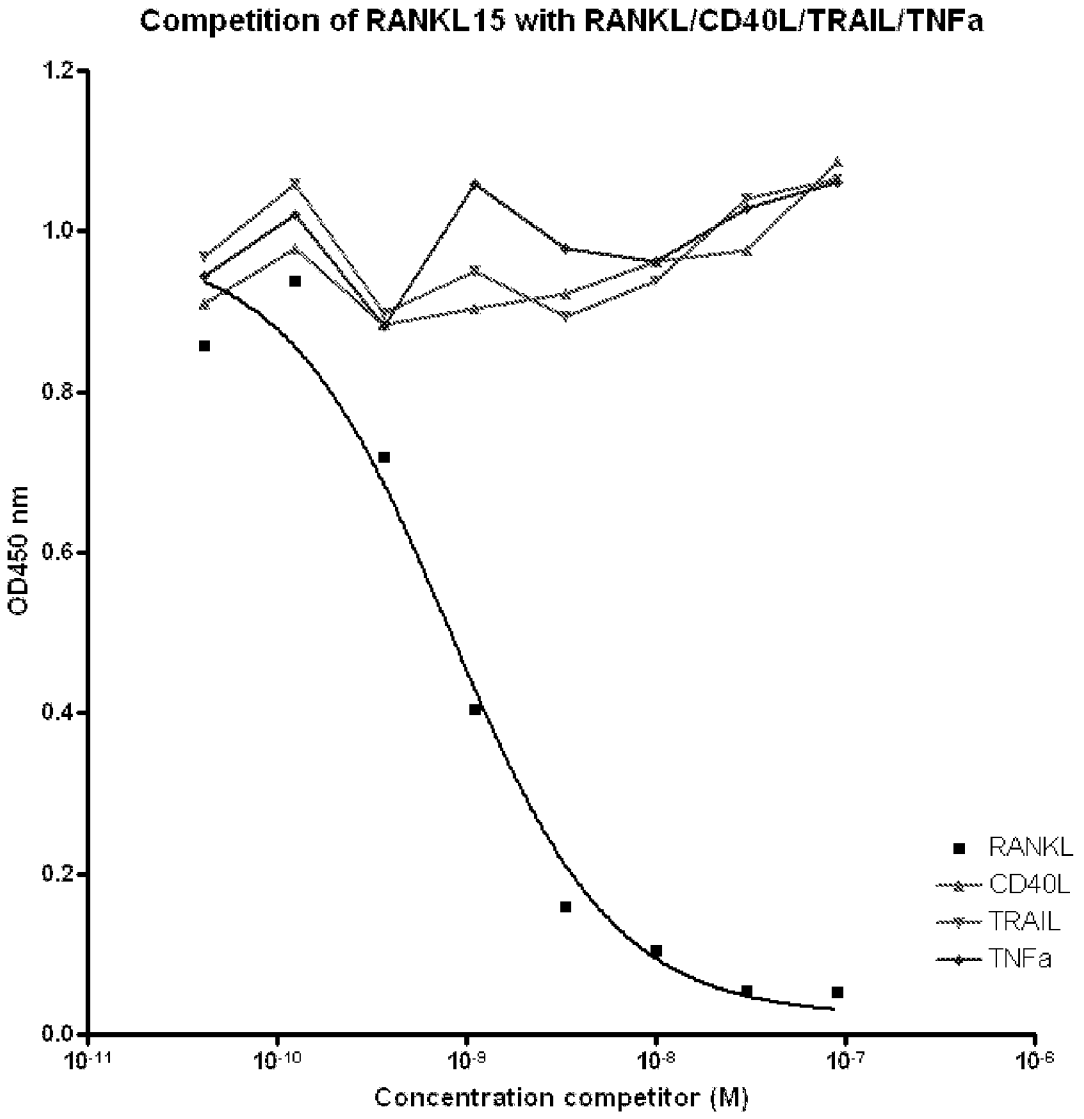

Competition of RANKL15 with RANKL/CD40L/TRAIL/TNFa
OD450 nm
1.2
1.0
0.8
0.6
0.4
0.2
0.0
10-11
10-10
10-9
10-8
10-7
10-6
Concentration competitor (M)
RANKL
CD40L
TRAIL
TNFa

Figure 1-D

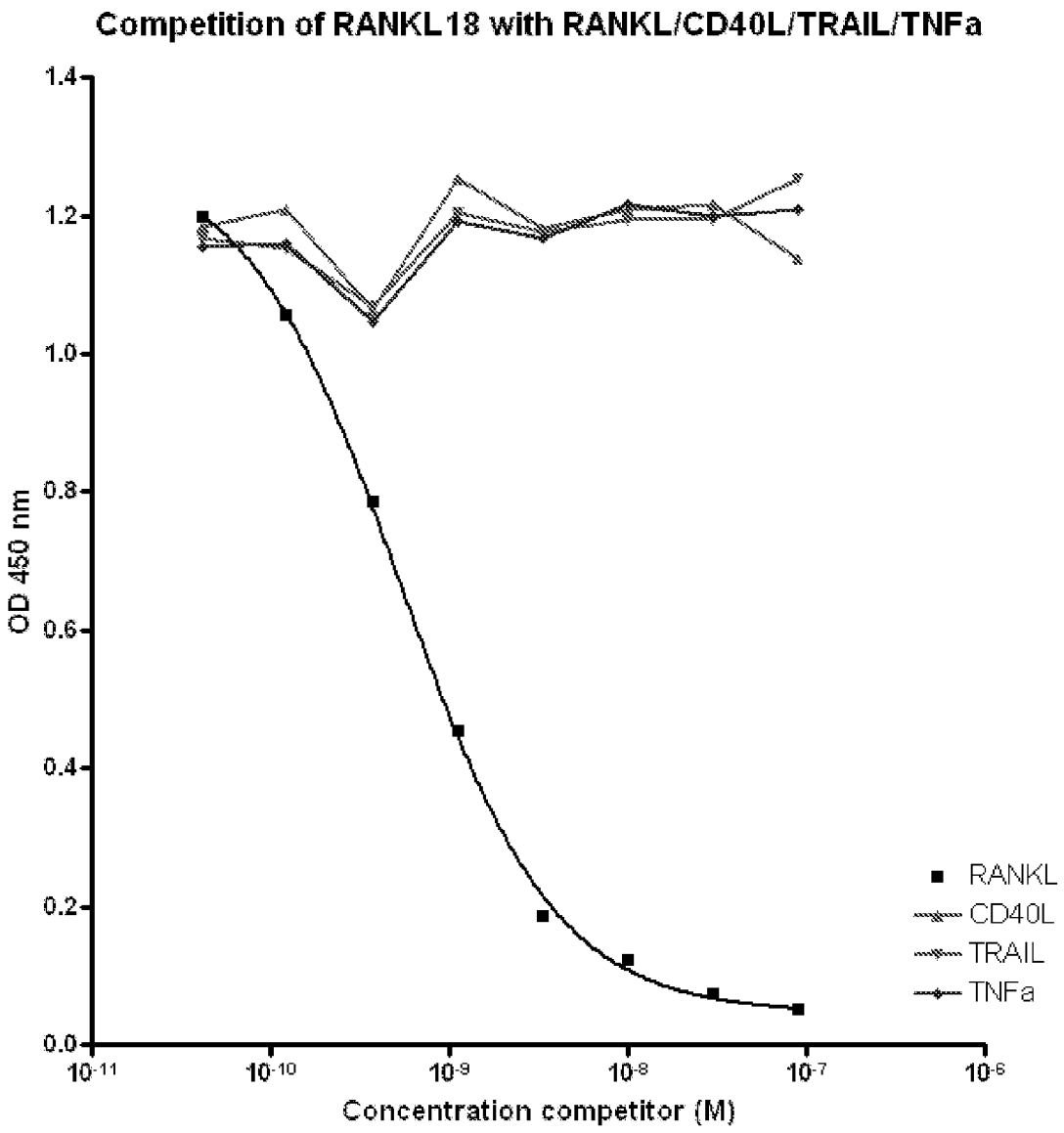

Competition of RANKL18 with RANKL/CD40L/TRAIL/TNFa
OD 450 nm
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
10-11
10-10
10-9
10-8
10-7
10-6
Concentration competitor (M)
RANKL
CD40L
TRAIL
TNFa

Figure 1-E

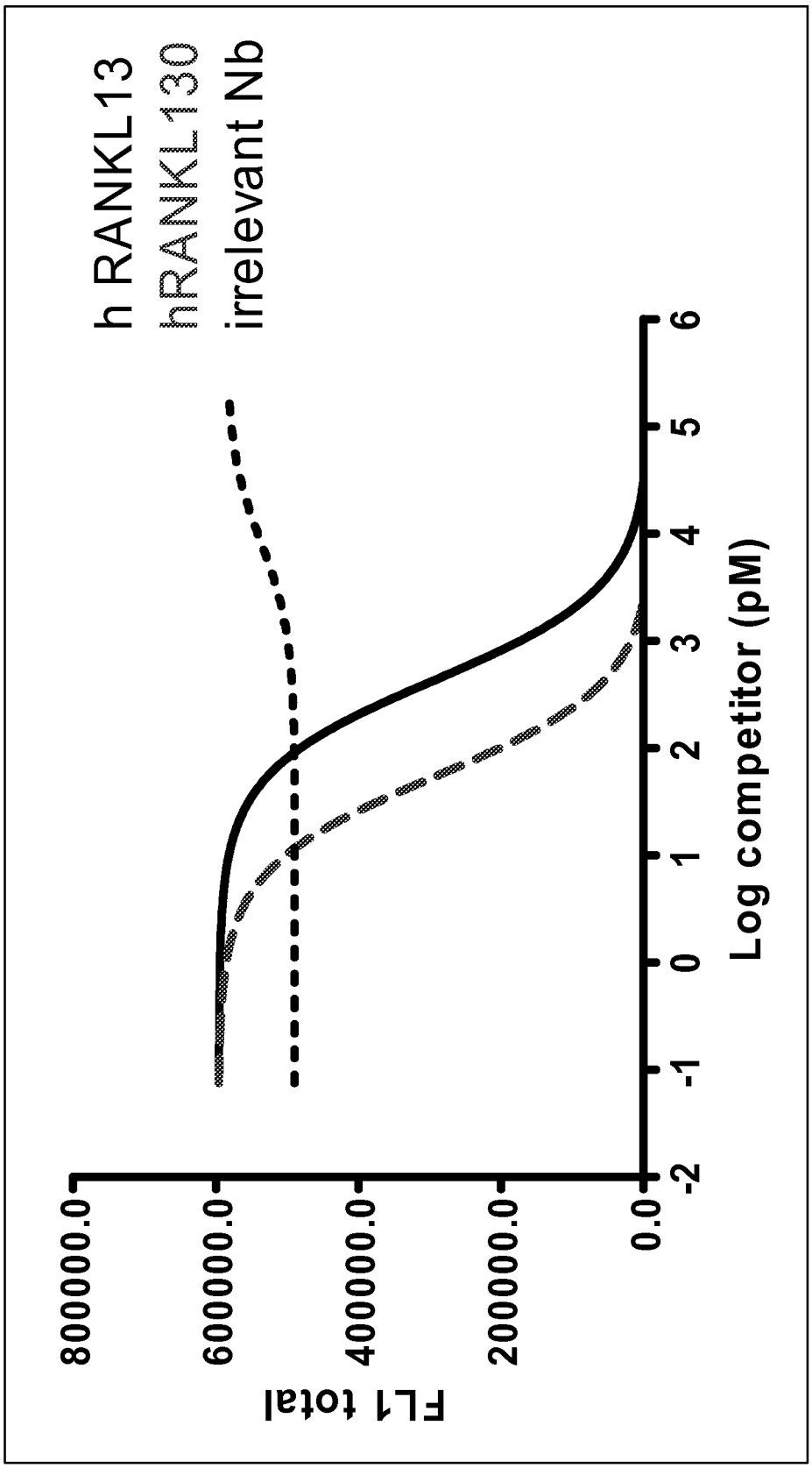

h RANKL13
hRANKL130
irrelevant Nb
FL1 total
800000.0
600000.0
400000.0
200000.0
0.0
-2
-1
0
1
2
3
4
5
6
Log competitor (pM)

Figure 2-A

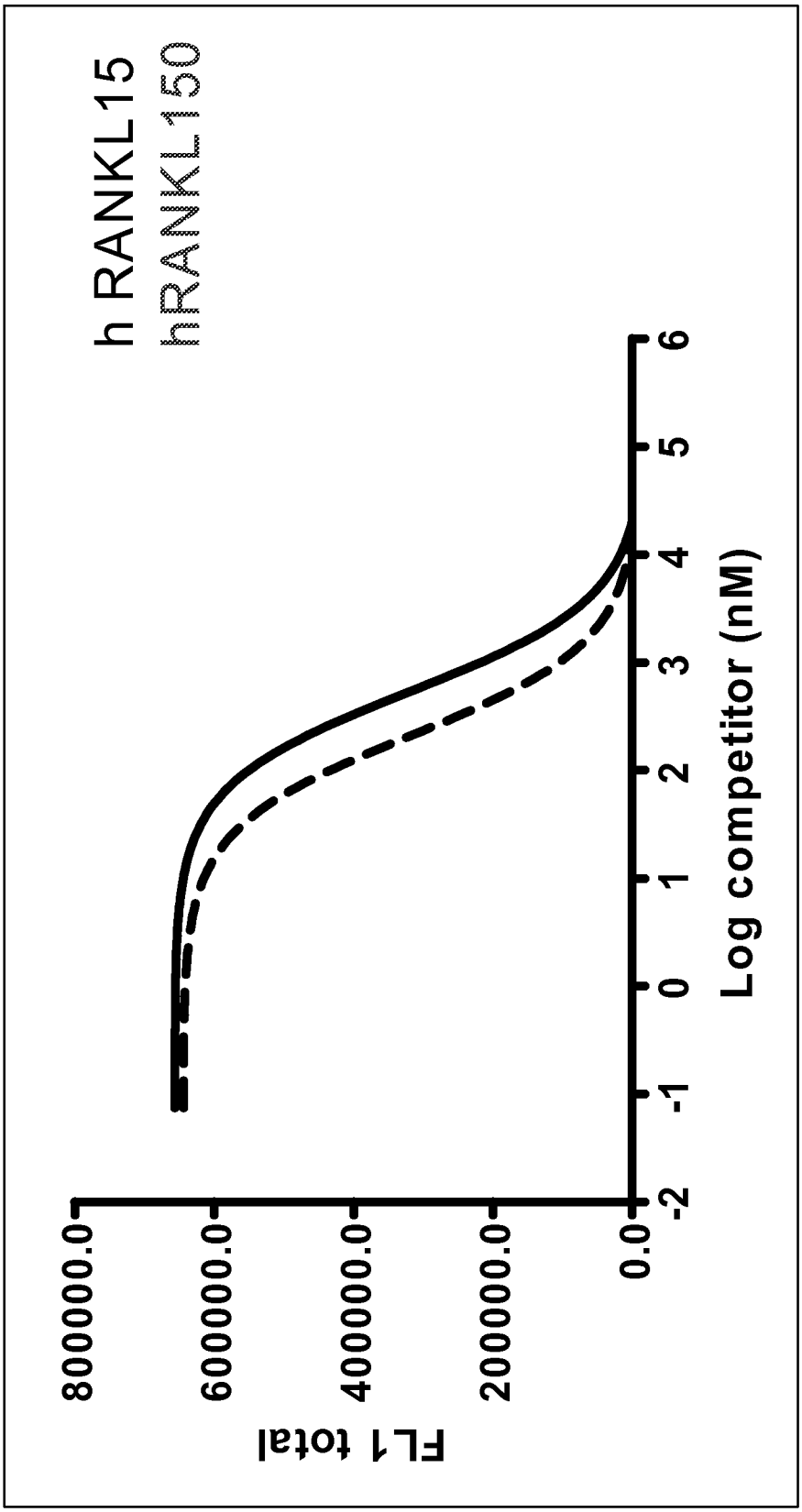

h RANKL15
hRANKL150
FL1 total
800000.0
600000.0
400000.0
200000.0
0.0
-2
-1
0
1
2
3
4
5
6
Log competitor (nM)

Figure 2-B

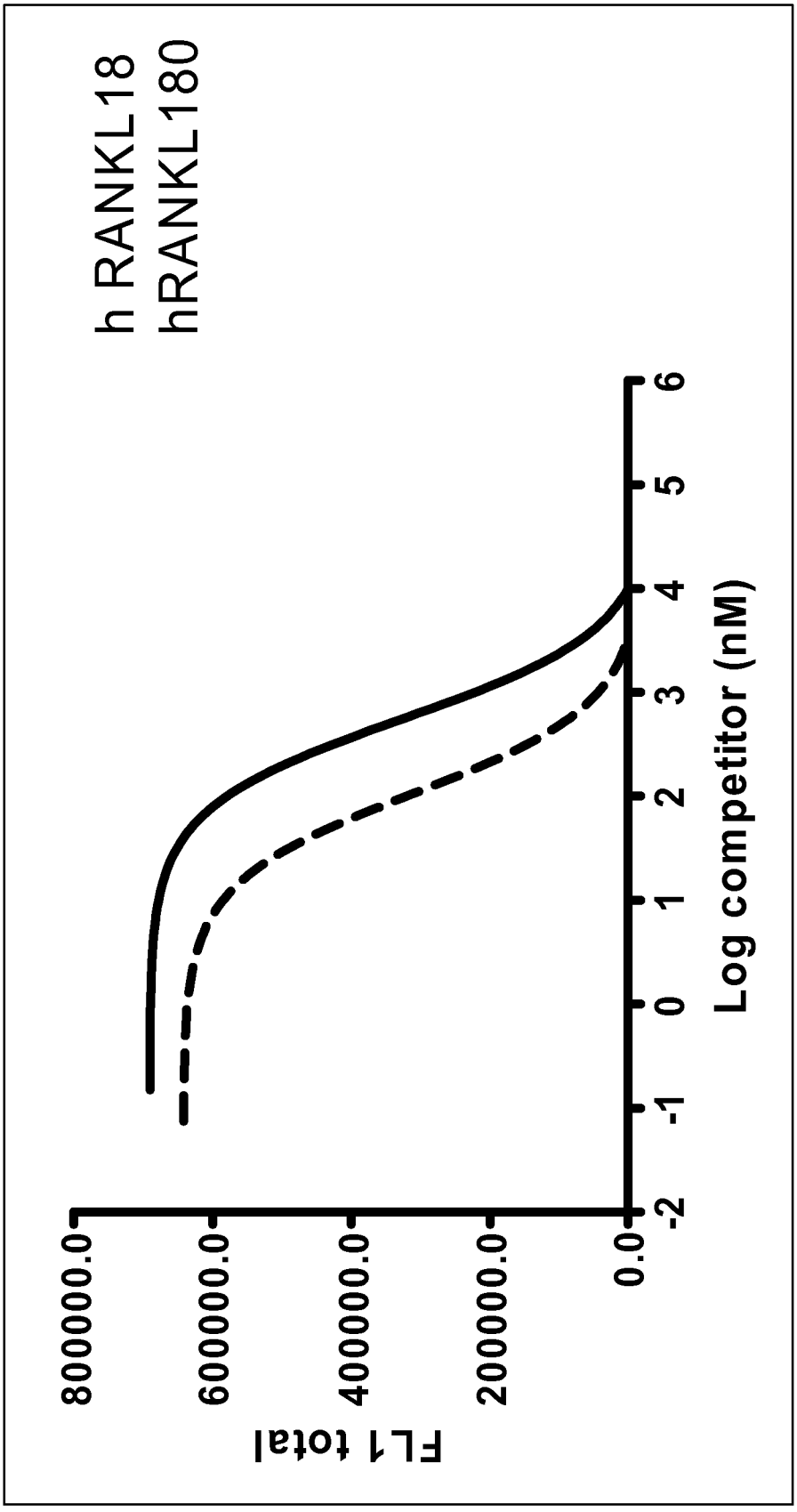

h RANKL18
hRANKL180
FL1 total
800000.0
600000.0
400000.0
200000.0
0.0
-2
-1
0
1
2
3
4
5
6
Log competitor (nM)

Figure 2-C

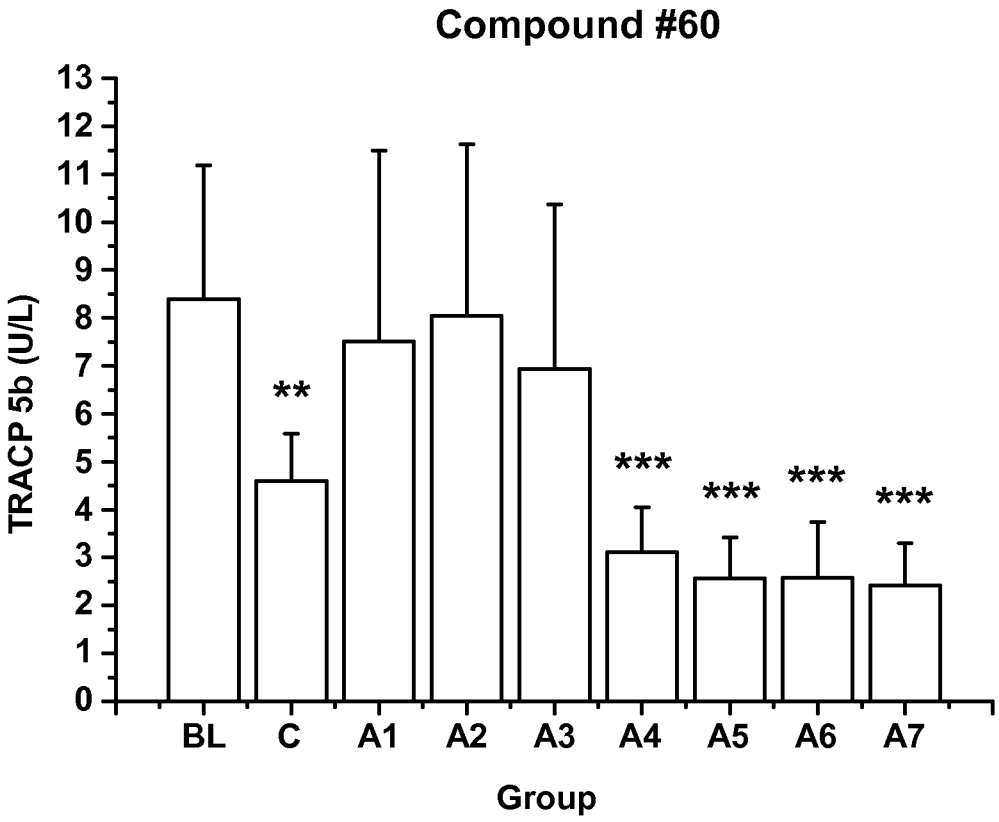

Compound #60
TRACP 5b (U/L)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
**
***
***
***
***
BL
C
A1
A2
A3
A4
A5
A6
A7
Group

Figure 3-A

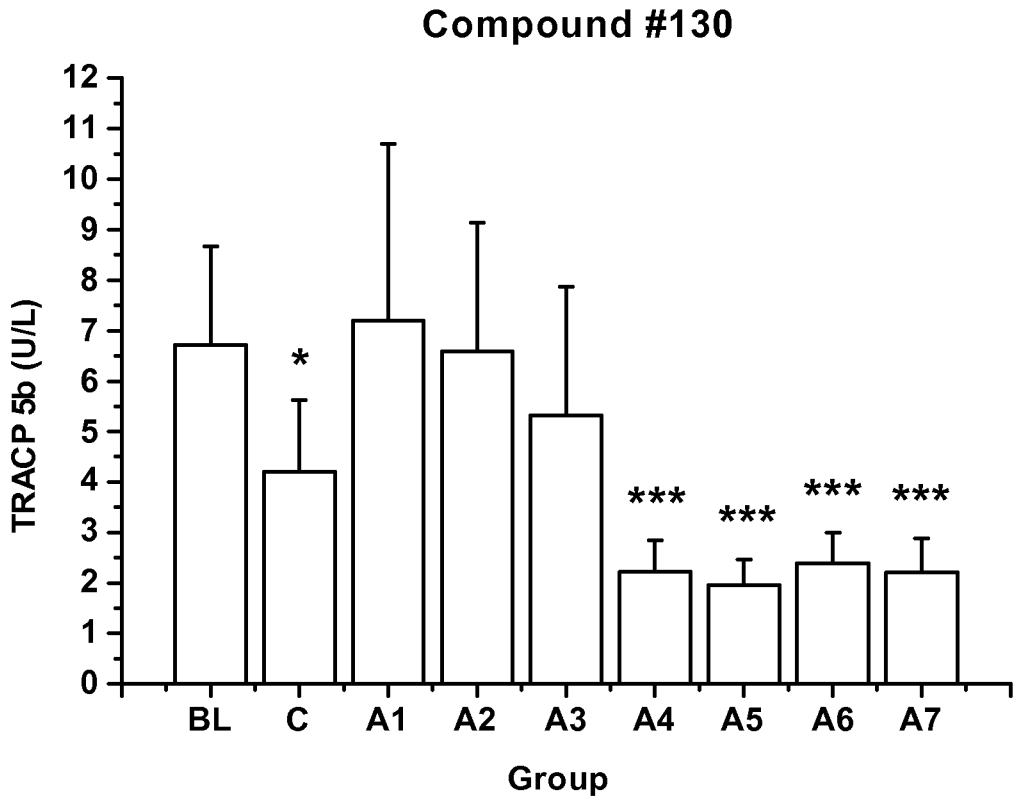

Compound #130
TRACP 5b (U/L)
0
1
2
3
4
5
6
7
8
9
10
11
12
*
***
***
***
***
BL
C
A1
A2
A3
A4
A5
A6
A7
Group

Figure 3-B

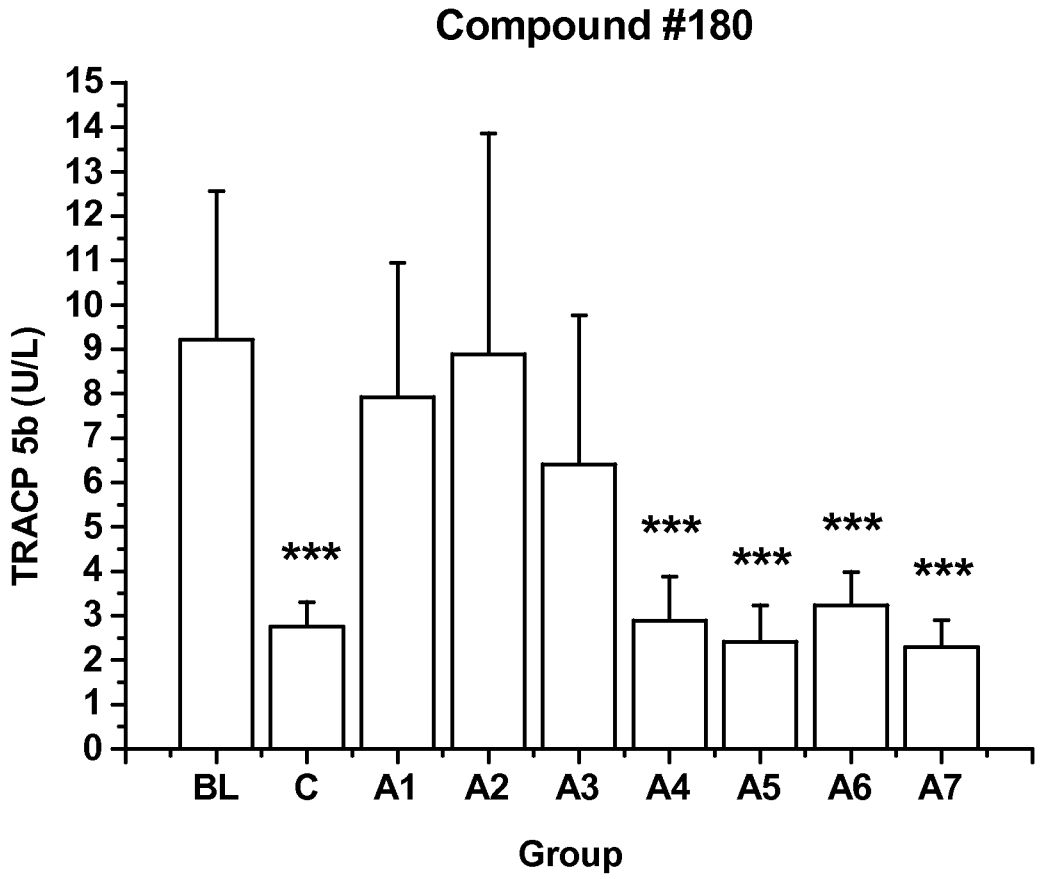

Compound #180
TRACP 5b (U/L)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
***
***
***
***
BL
C
A1
A2
A3
A4
A5
A6
A7
Group

Figure 3-C

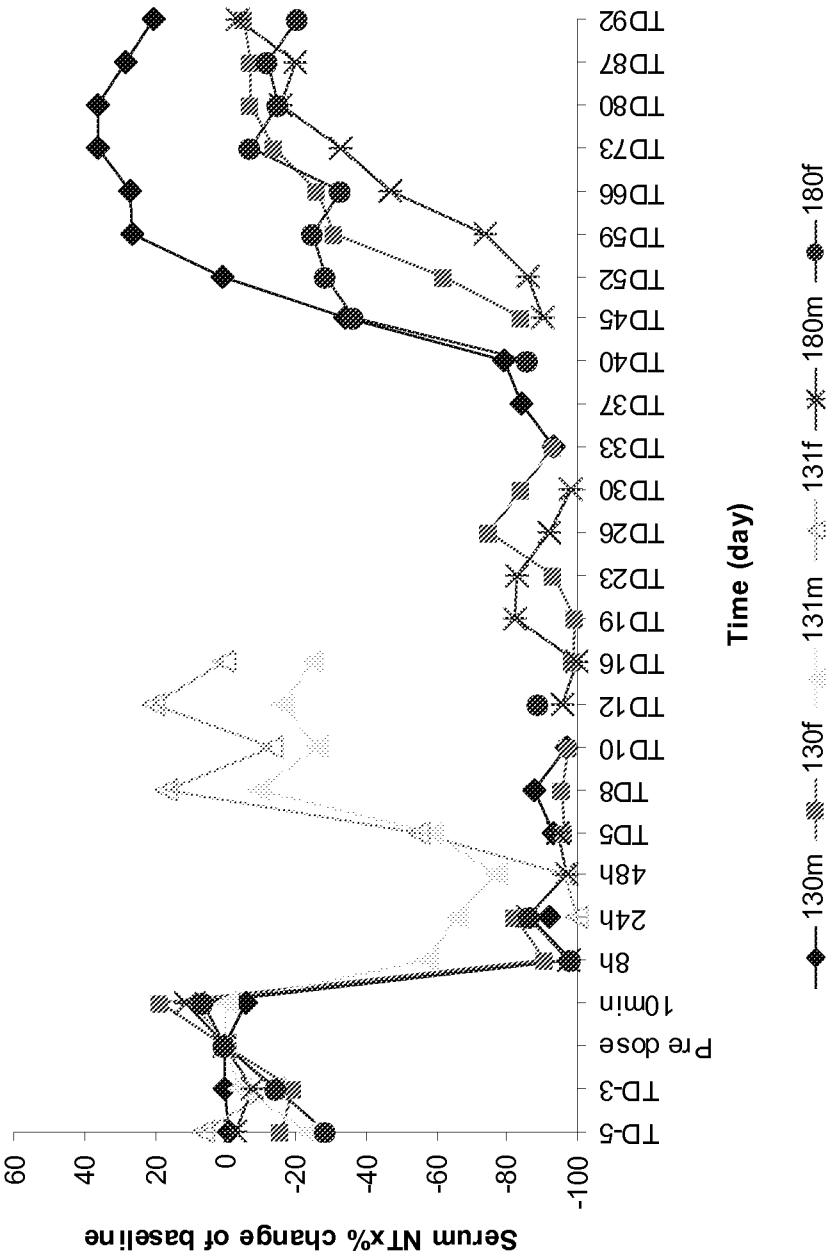

Serum NTx% change of baseline
60
40
20
0
-20
-40
-60
-80
-100
TD-5
TD-3
Pre dose
10min
8h
24h
48h
TD5
TD8
TD10
TD12
TD16
TD19
TD23
TD26
TD30
TD33
TD37
TD40
TD45
TD52
TD59
TD66
TD73
TD80
TD87
TD92
Time (day)
130m
130f
131m
131f
180m
180f

Figure 4-A

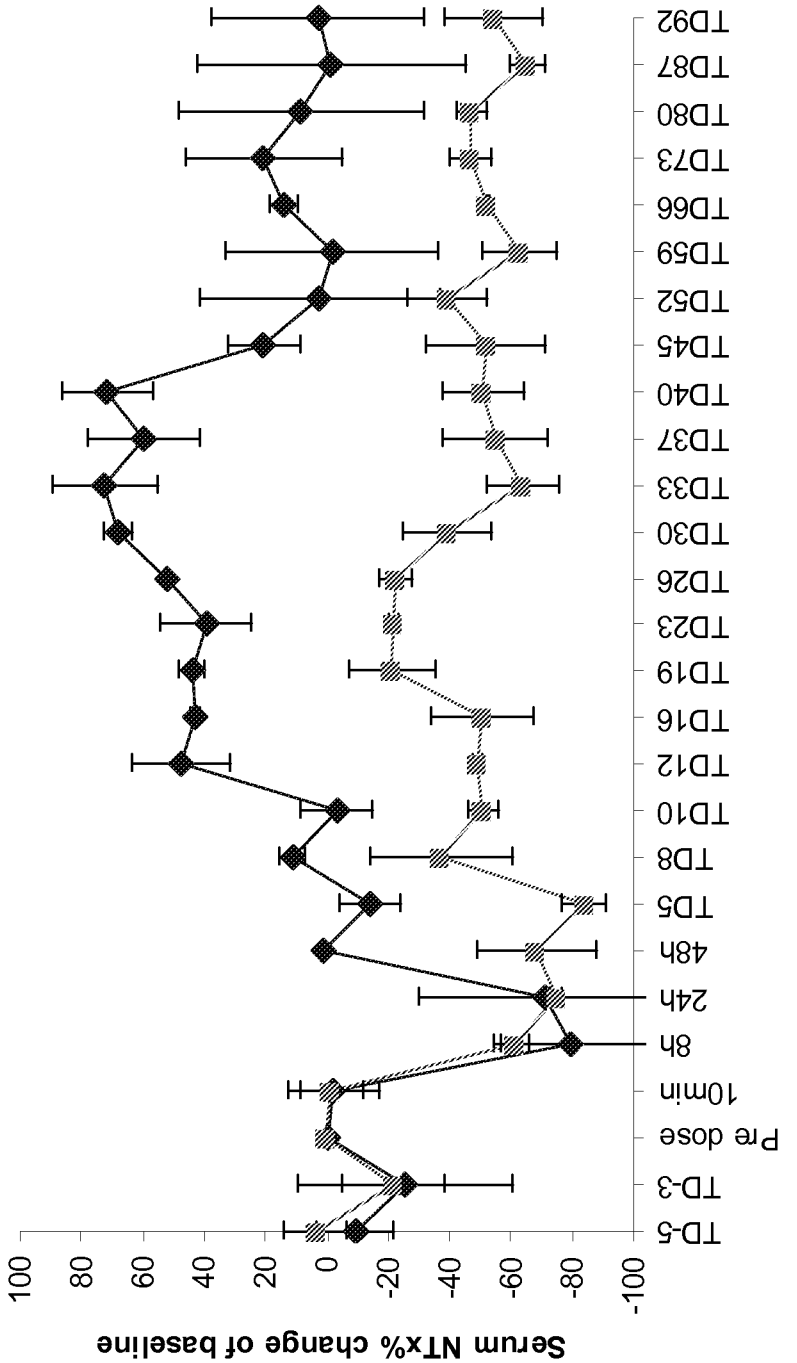

Serum NTx% change of baseline
100
80
60
40
20
0
-20
-40
-60
-80
-100
TD-5
TD-3
Pre dose
10min
8h
24h
48h
TD5
TD8
TD10
TD12
TD16
TD19
TD23
TD26
TD30
TD33
TD37
TD40
TD45
TD52
TD59
TD66
TD73
TD80
TD87
TD92
Time (day)
ALB-1
IBN

Figure 4-B

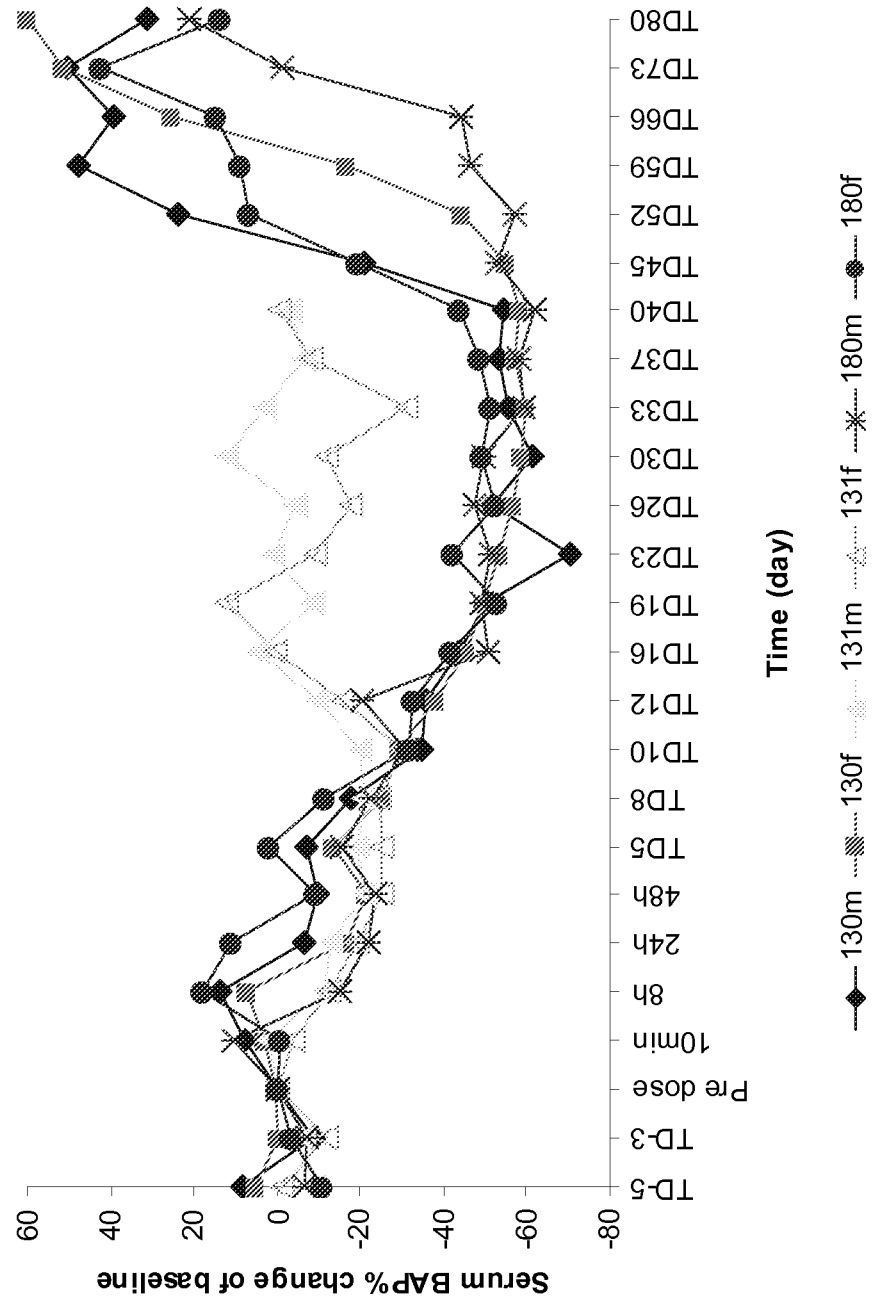

Serum BAP% change of baseline
60
40
20
0
-20
-40
-60
-80
TD-5
TD-3
Pre dose
10min
8h
24h
48h
TD5
TD8
TD10
TD12
TD16
TD19
TD23
TD26
TD30
TD33
TD37
TD40
TD45
TD52
TD59
TD66
TD73
TD80
Time (day)
130m
130f
131m
131f
180m
180f

Figure 5

```
RANKL13WT          EVQLVESGGGLVQAGGSLRLSCAASGRTFRSYPMGWFRQAPGKEREFVASITGSGGSTYYADSVKG
RANKL13hum5        EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYPMGWFRQAPGKGREFVSSITGSGGSTYYADSVKG
                   EVQL+ESGGGLVQPGGSLRLSCAASGFTFSSY M W RQAPGKG E+V+ I+GSGGSTYYADSVKG
VH3-23 (DP47)      EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKG

RANKL13WT          RFTISRDNAKNTVYLQMNSLRPEDTAVYSCAAYIRPDTYLSRDYRKYDYWGQGTQVTVSS (SEQ ID NO: 572)
RANKL13hum5        RFTISRDNAKNTLYLQMNSLRPEDTAVYYCAAYIRPDTYLSRDYRKYDYWGQGTLVTVSS (SEQ ID NO: 755)
                   RFTISRDN+KNTLYLQMNSLR EDTAVYYCA
VH3-23 (DP47)      RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR.................WGQGTLVTVSS (SEQ ID NO: 763-4)
```

Figure 6

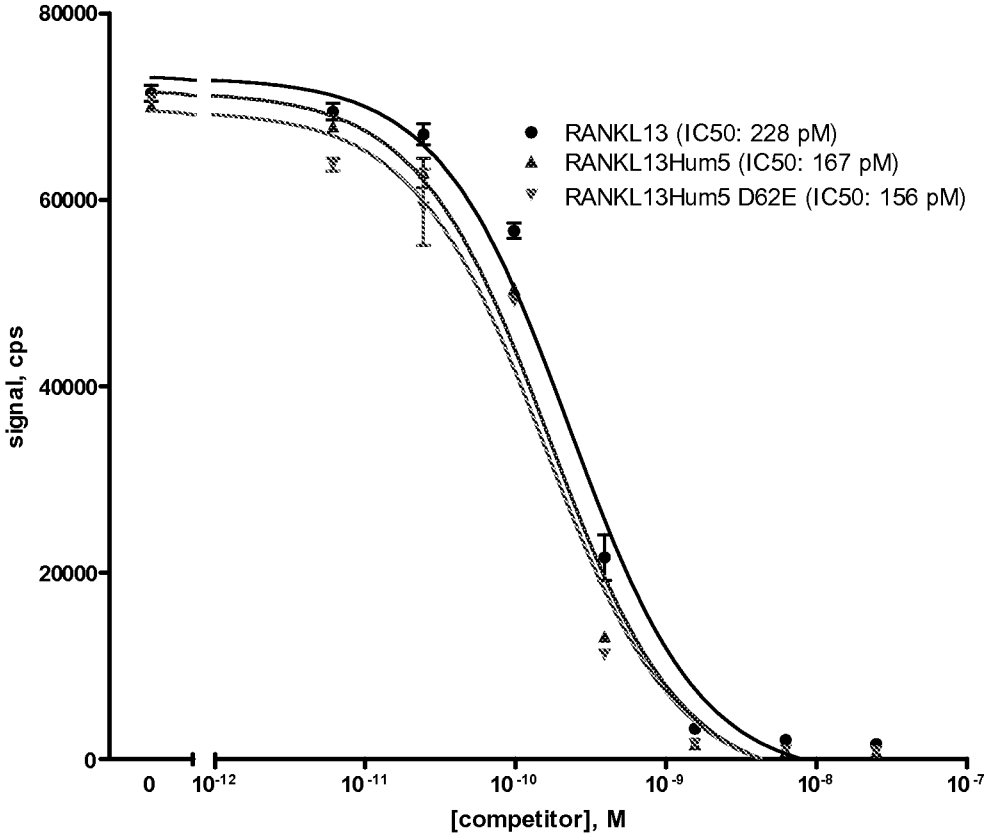

80000
60000
40000
20000
0
signal, cps
0
10-12
10-11
10-10
10-9
10-8
10-7
[competitor], M
RANKL13 (IC50: 228 pM)
RANKL13Hum5 (IC50: 167 pM)
RANKL13Hum5 D62E (IC50: 156 pM)

Figure 7

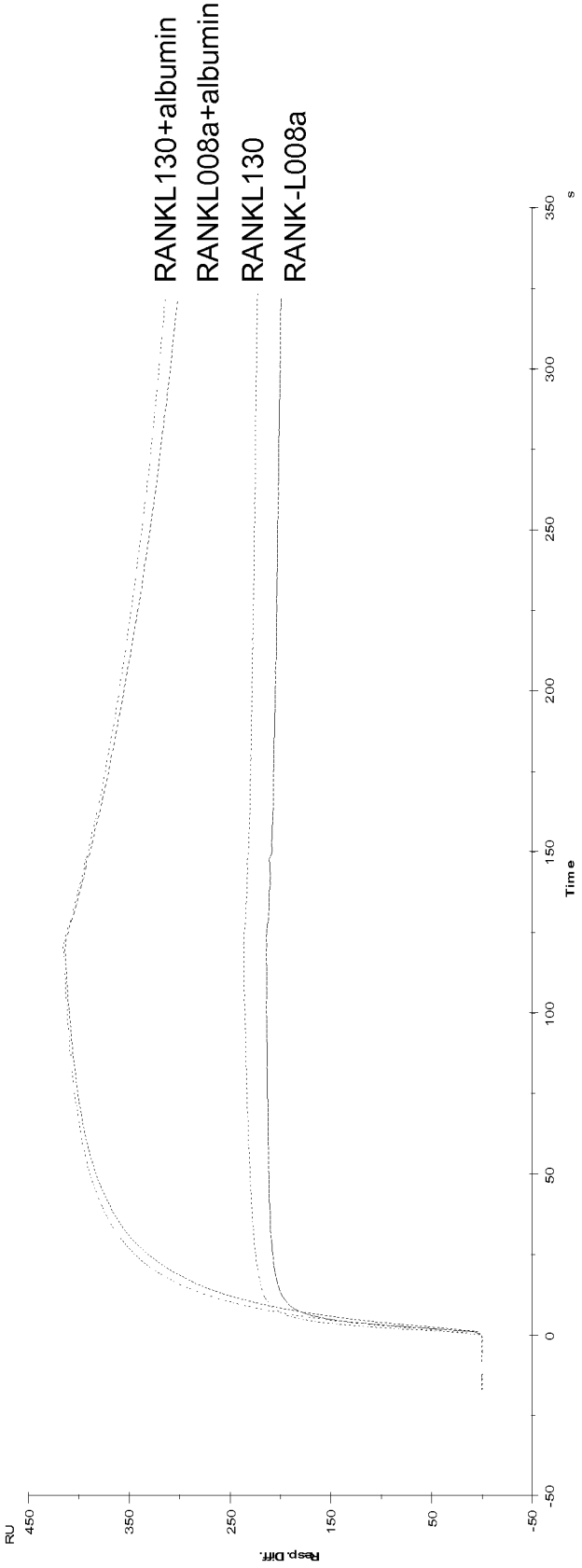

RANKL130+albumin
RANKL008a+albumin
RANKL130
RANK-L008a
RU
Resp. Diff.
Time
s
450
350
250
150
50
-50
-50
0
50
100
150
200
250
300
350

Figure 8

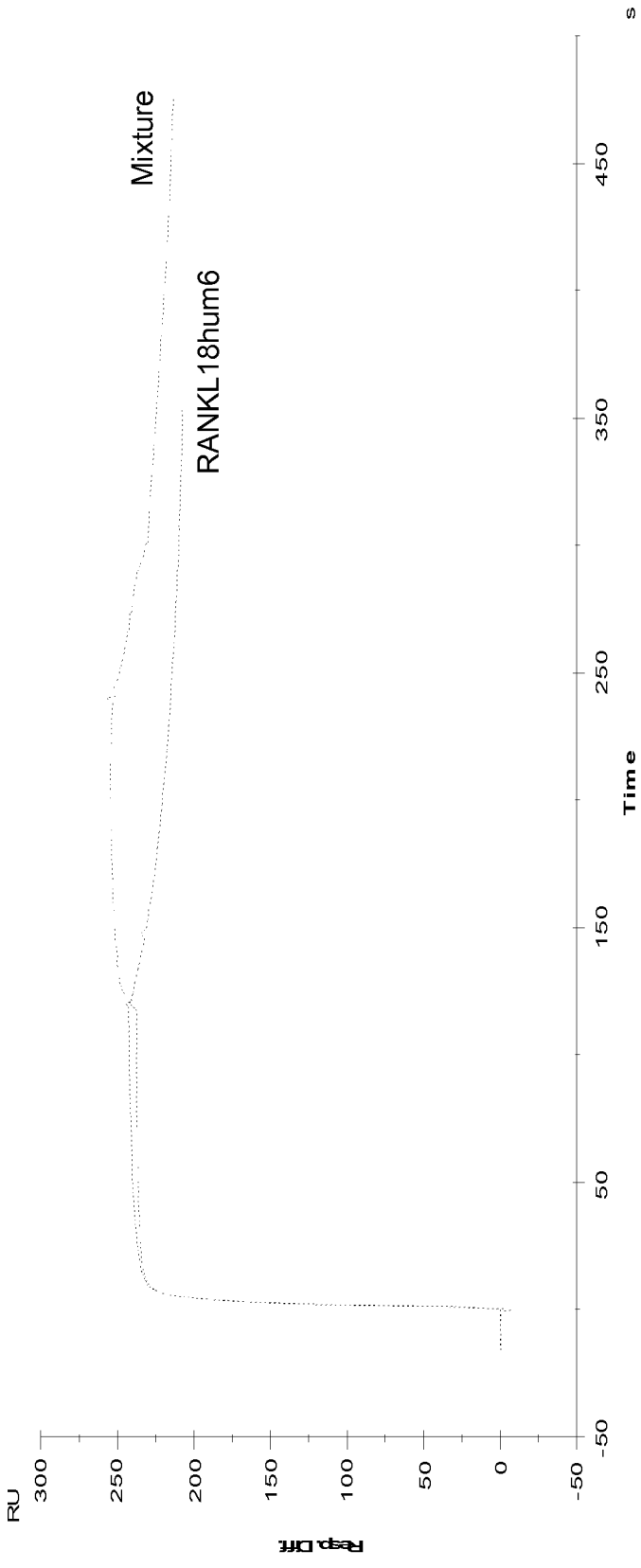

Mixture
RANKL18hum6
RU
300
250
200
150
100
50
0
-50
Resp Diff
-50
50
150
250
350
450
Time
s

Figure 9

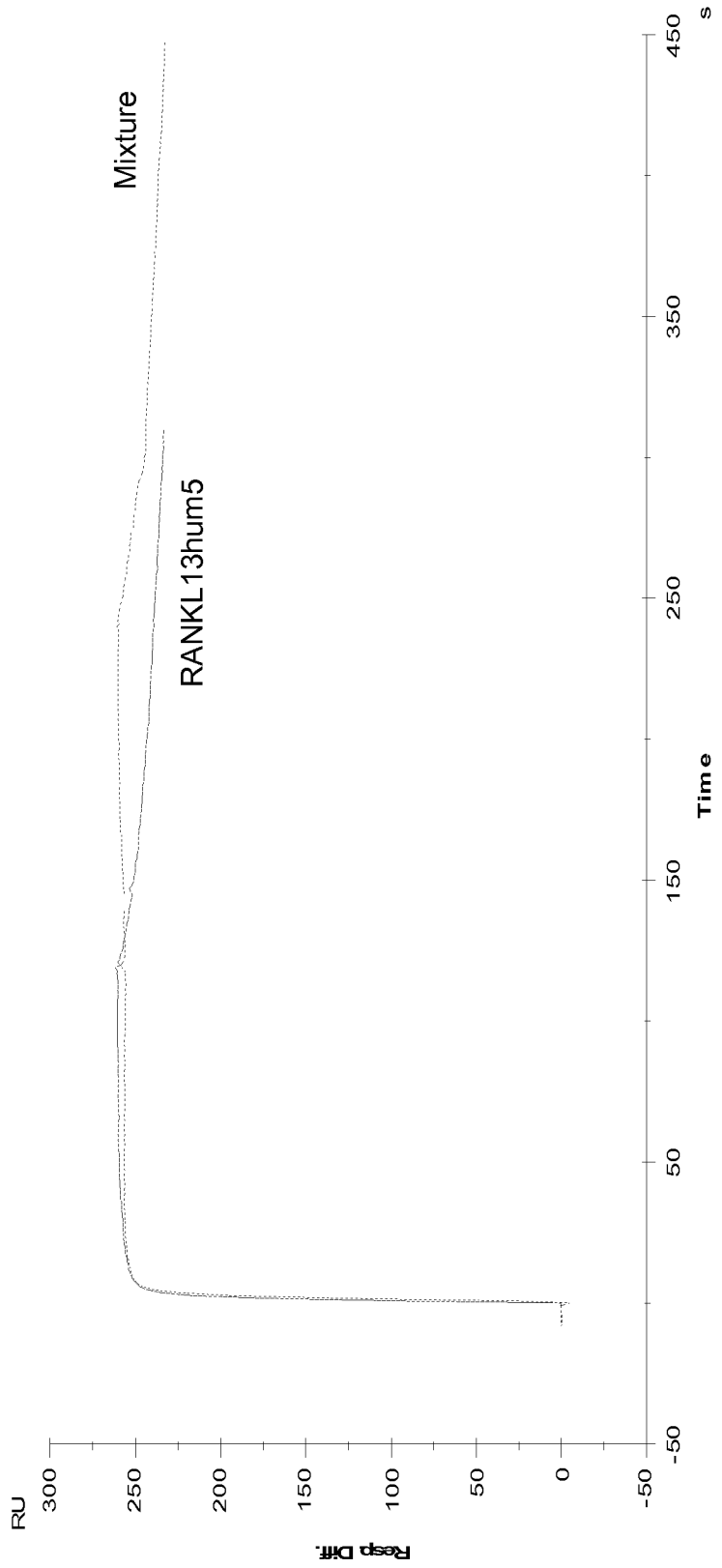

Mixture
RANKL13hum5
RU
300
250
200
150
100
50
0
-50
Resp Diff.
-50
50
150
250
350
450
s
Time

Figure 10

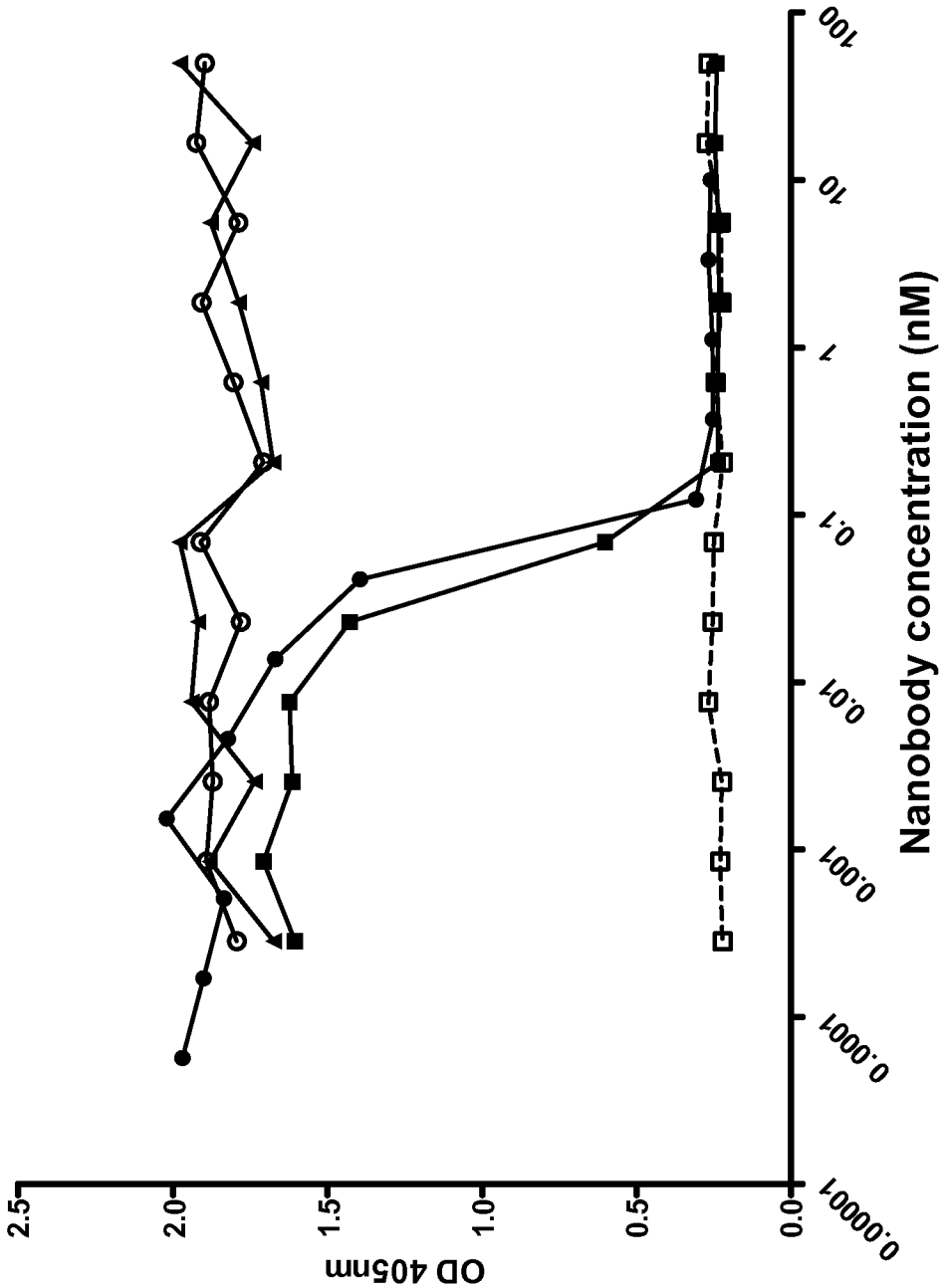

OD 405nm
2.5
2.0
1.5
1.0
0.5
0.0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
Nanobody concentration (nM)

Figure 11

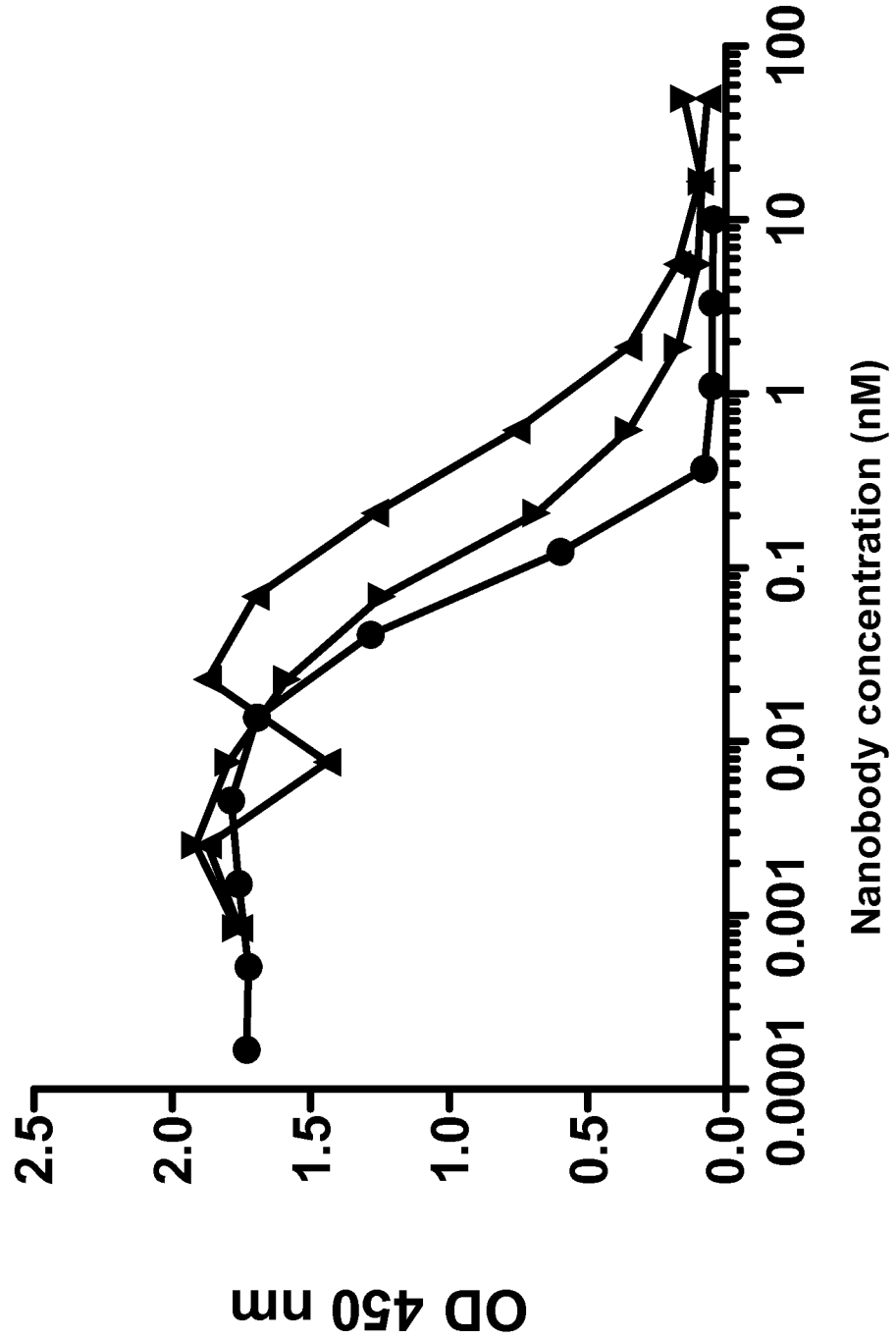

OD 450 nm
2.5
2.0
1.5
1.0
0.5
0.0
0.0001
0.001
0.01
0.1
1
10
100
Nanobody concentration (nM)

Figure 12

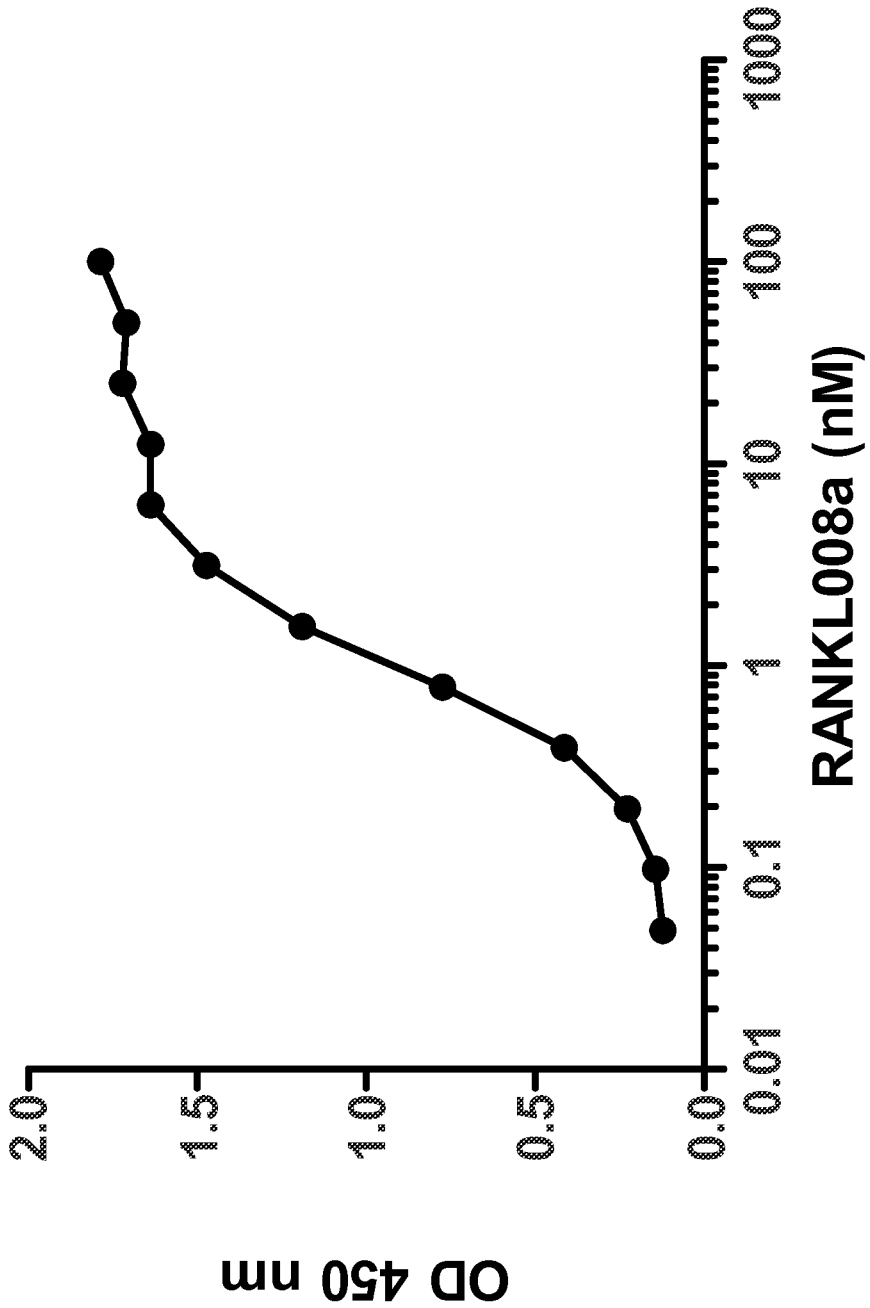


Figure 13

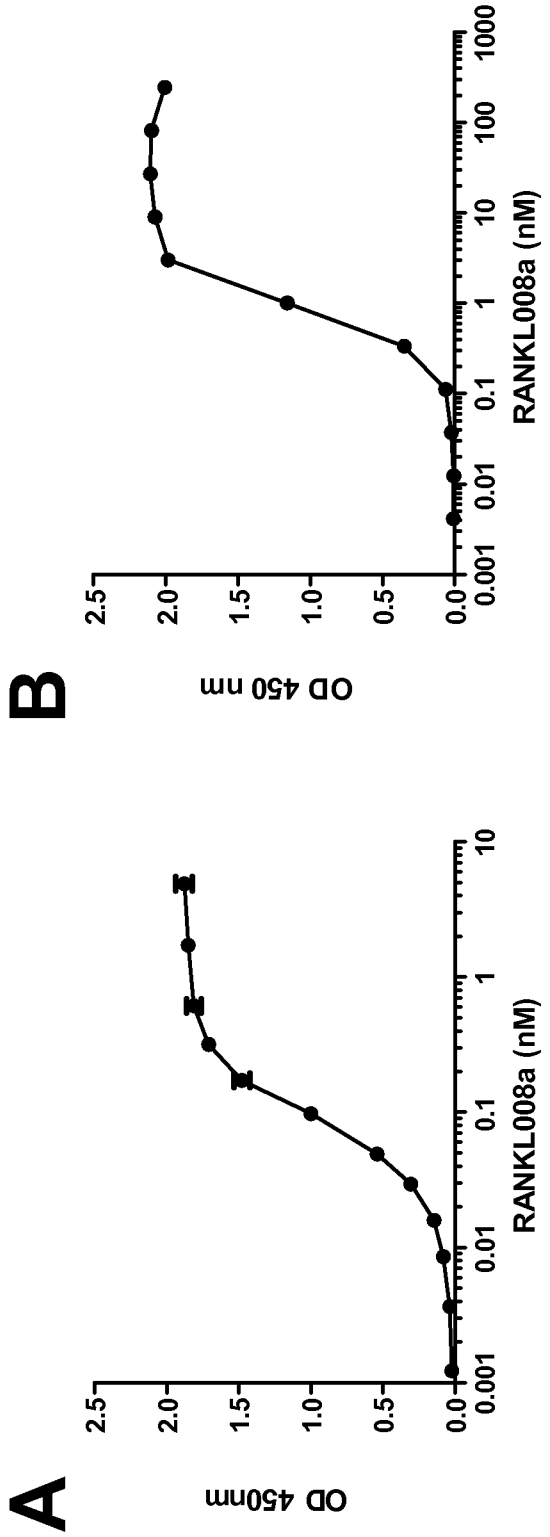

A
OD 450nm
2.5
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
RANKL008a (nM)
B
OD 450 nm
2.5
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
100
1000
RANKL008a (nM)

Figure 14

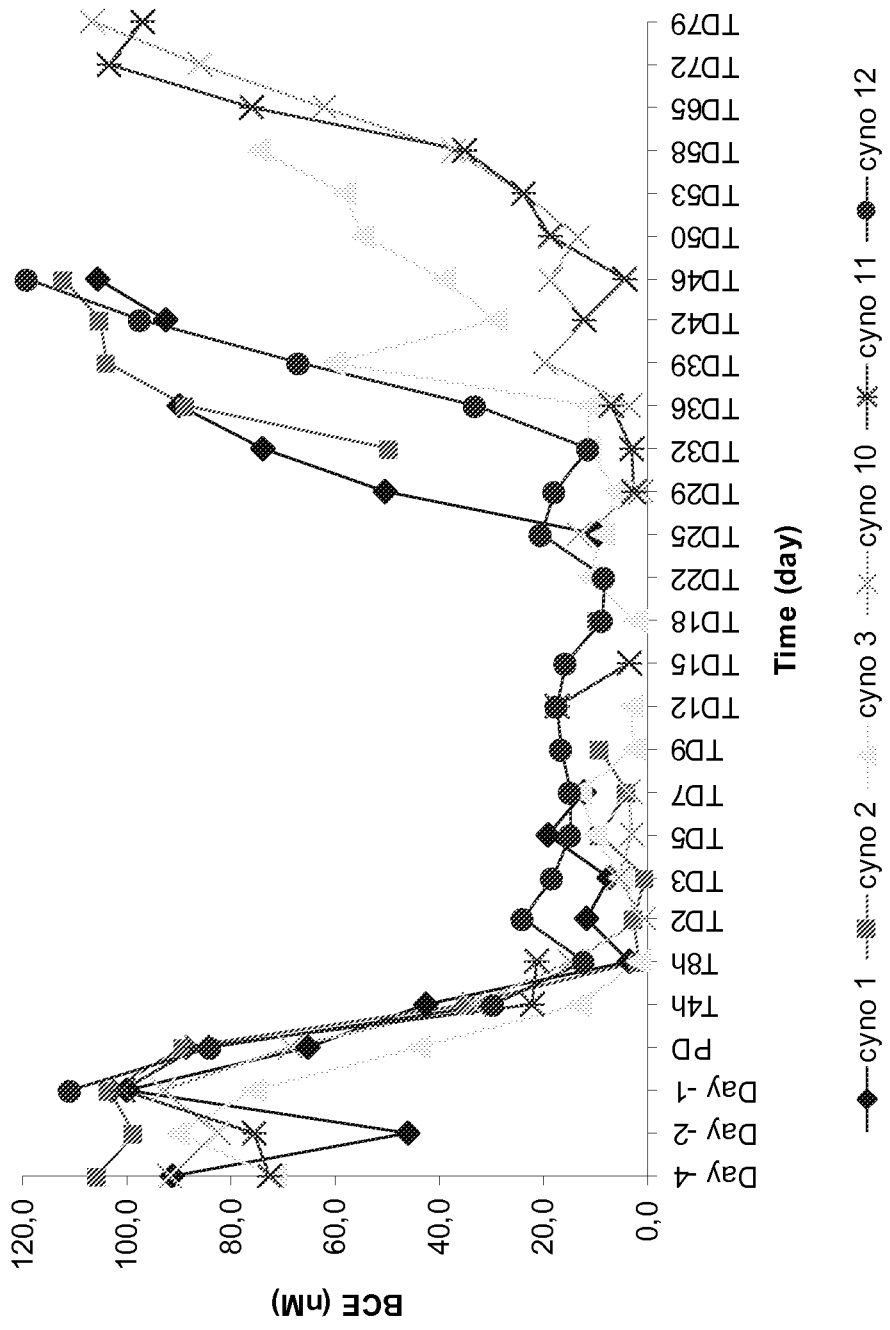

BCE (nM)
120,0
100,0
80,0
60,0
40,0
20,0
0,0
Day -4
Day -2
Day -1
PD
T4h
T8h
TD2
TD3
TD5
TD7
TD9
TD12
TD15
TD18
TD22
TD25
TD29
TD32
TD36
TD39
TD42
TD46
TD50
TD53
TD58
TD65
TD72
TD79
Time (day)
cyno 1
cyno 2
cyno 3
cyno 10
cyno 11
cyno 12

Figure 15-A

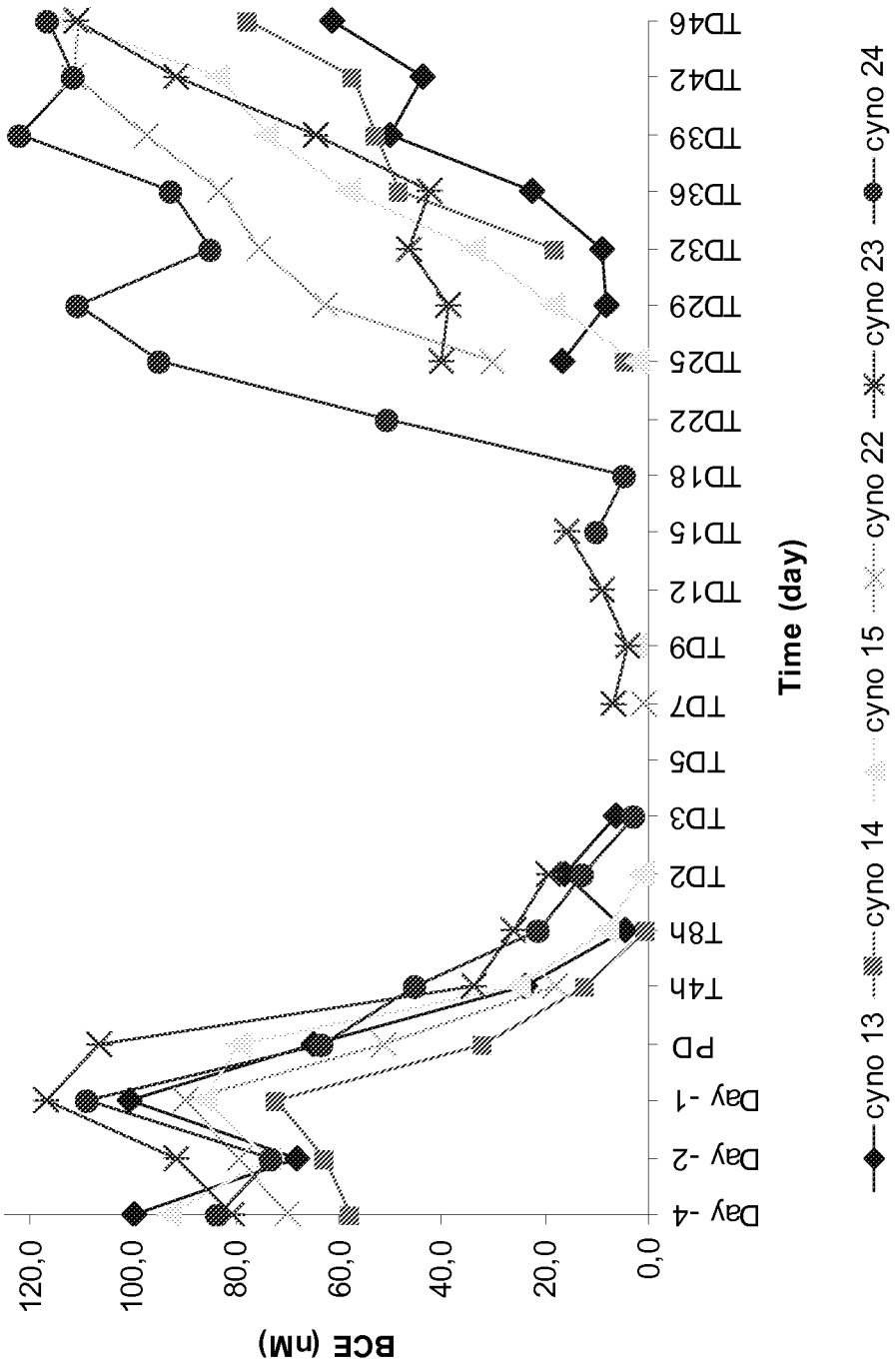

BCE (nM)
120,0
100,0
80,0
60,0
40,0
20,0
0,0
Day -4
Day -2
Day -1
PD
T4h
T8h
TD2
TD3
TD5
TD7
TD9
TD12
TD15
TD18
TD22
TD25
TD29
TD32
TD36
TD39
TD42
TD46
Time (day)
cyno 13
cyno 14
cyno 15
cyno 22
cyno 23
cyno 24

Figure 15-B

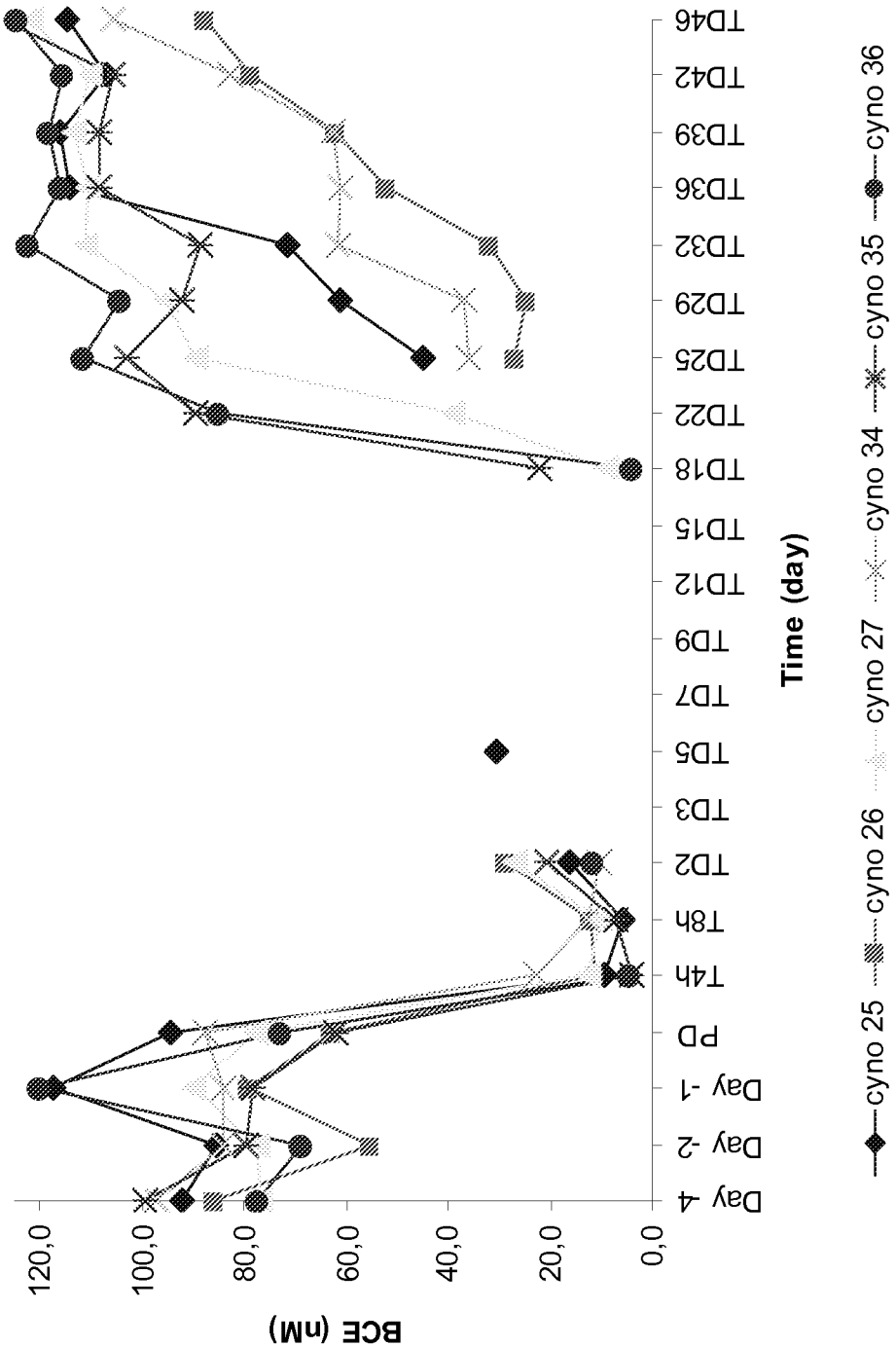

BCE (nM)
120,0
100,0
80,0
60,0
40,0
20,0
0,0
Day -4
Day -2
Day -1
PD
T4h
T8h
TD2
TD3
TD5
TD7
TD9
TD12
TD15
TD18
TD22
TD25
TD29
TD32
TD36
TD39
TD42
TD46
Time (day)
cyno 25
cyno 26
cyno 27
cyno 34
cyno 35
cyno 36

Figure 15-C

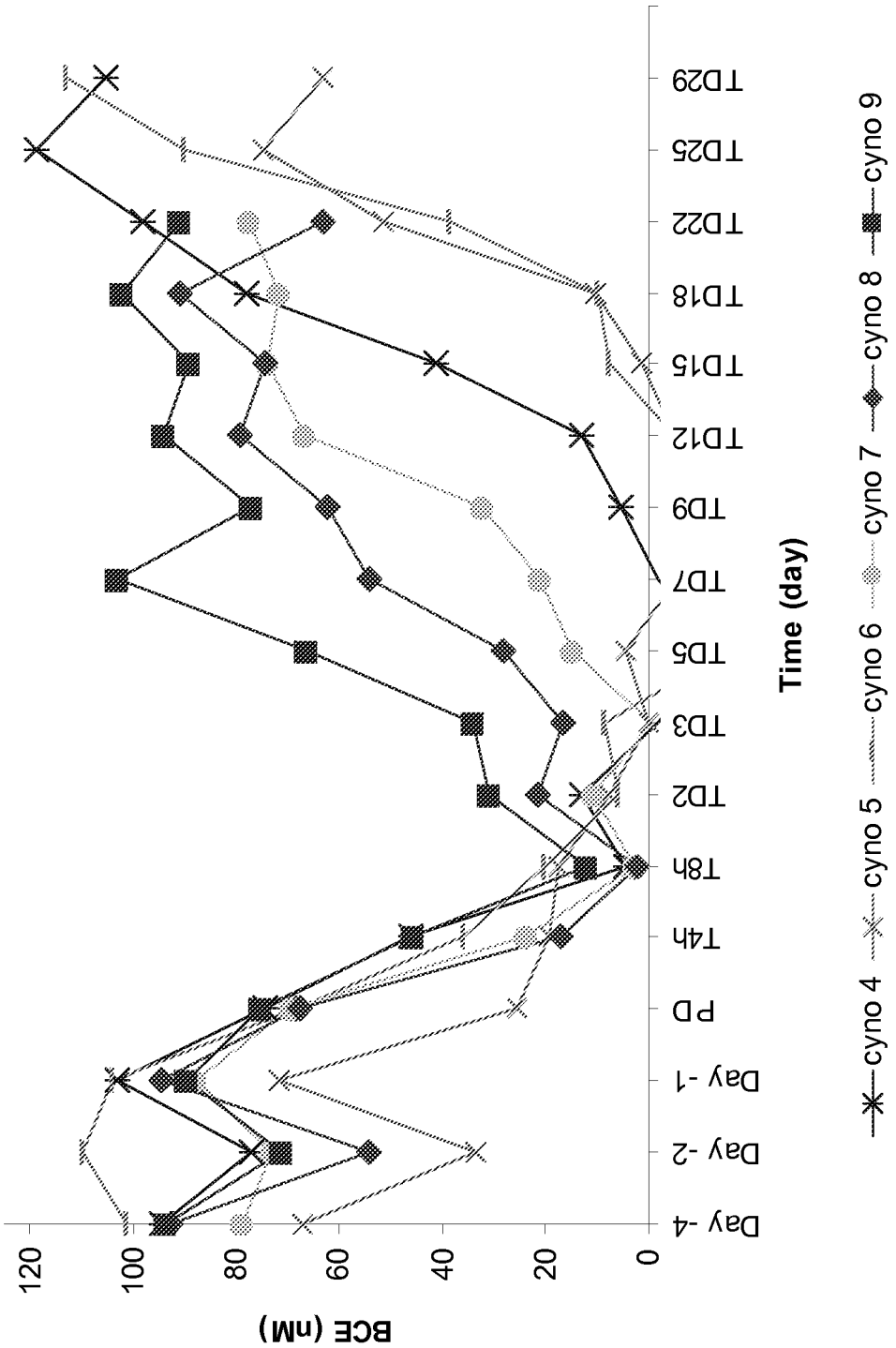

BCE (nM)
120
100
80
60
40
20
0
Day -4
Day -2
Day -1
PD
T4h
T8h
TD2
TD3
TD5
TD7
TD9
TD12
TD15
TD18
TD22
TD25
TD29
Time (day)
cyno 4
cyno 5
cyno 6
cyno 7
cyno 8
cyno 9

Figure 16-A

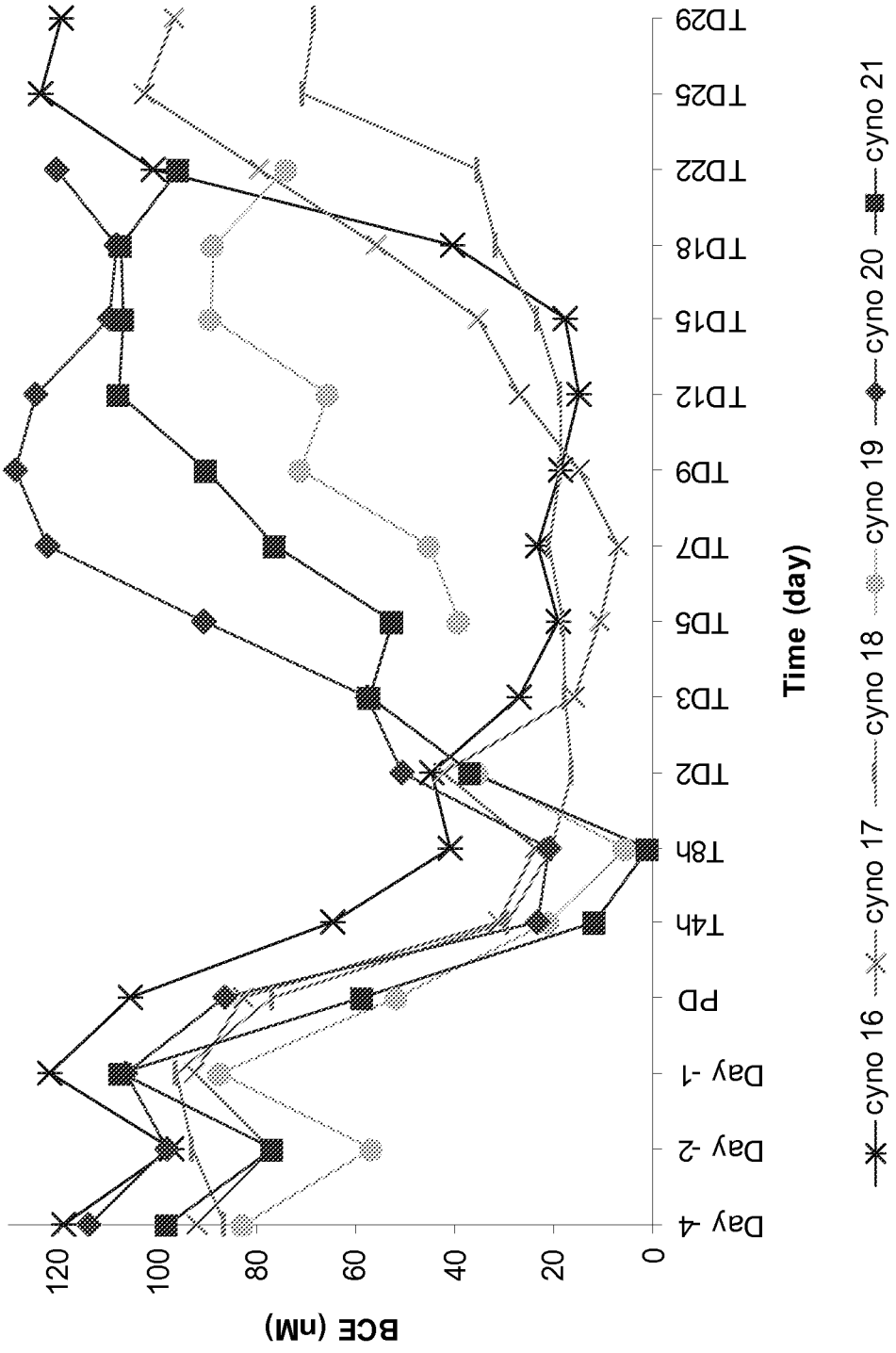

BCE (nM)
120
100
80
60
40
20
0
Day -4
Day -2
Day -1
PD
T4h
T8h
TD2
TD3
TD5
TD7
TD9
TD12
TD15
TD18
TD22
TD25
TD29
Time (day)
cyno 16
cyno 17
cyno 18
cyno 19
cyno 20
cyno 21

Figure 16-B

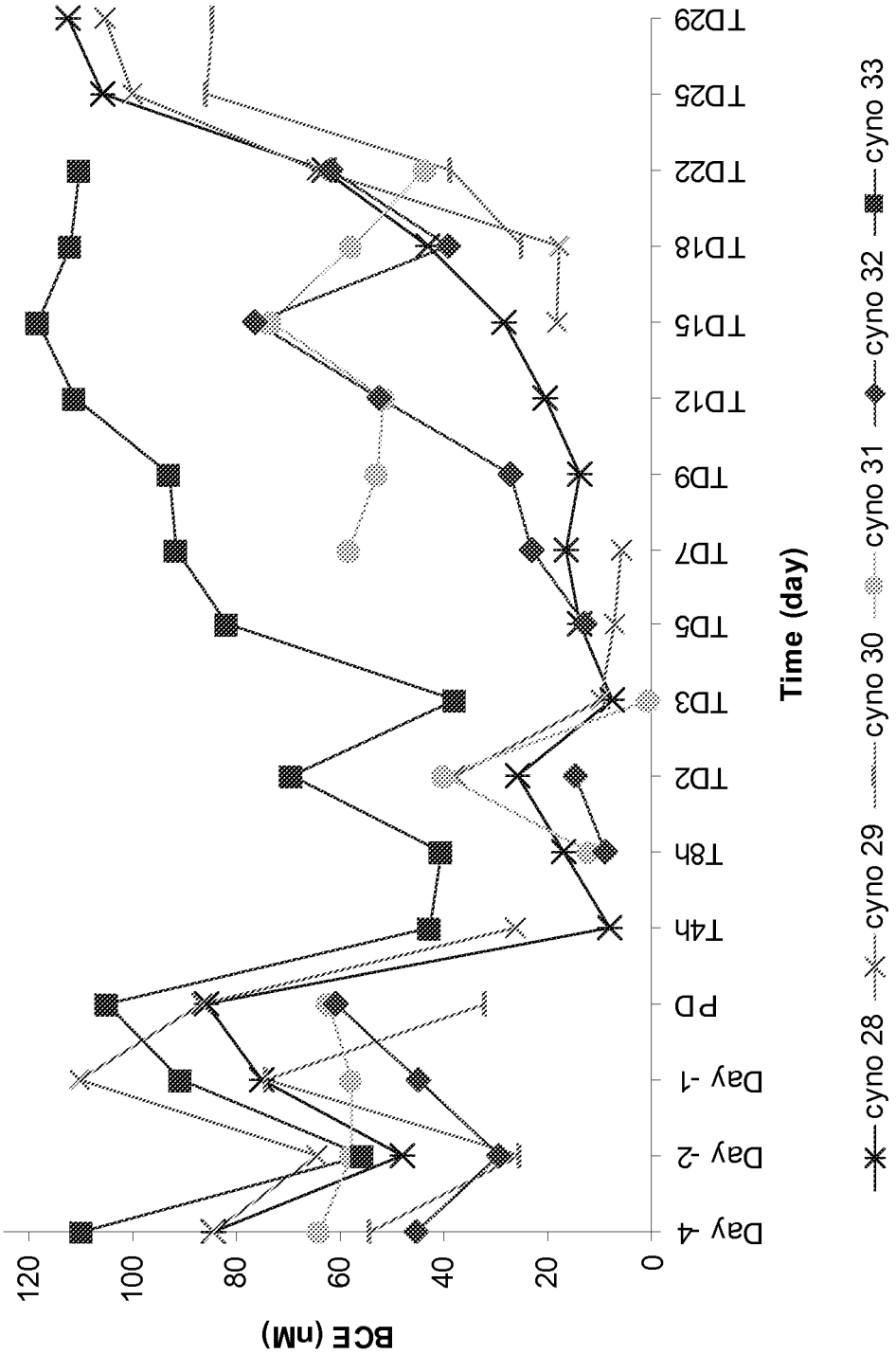

BCE (nM)
120
100
80
60
40
20
0
Day -4
Day -2
Day -1
PD
T4h
T8h
TD2
TD3
TD5
TD7
TD9
TD12
TD15
TD18
TD22
TD25
TD29
Time (day)
cyno 28
cyno 29
cyno 30
cyno 31
cyno 32
cyno 33

Figure 16-C

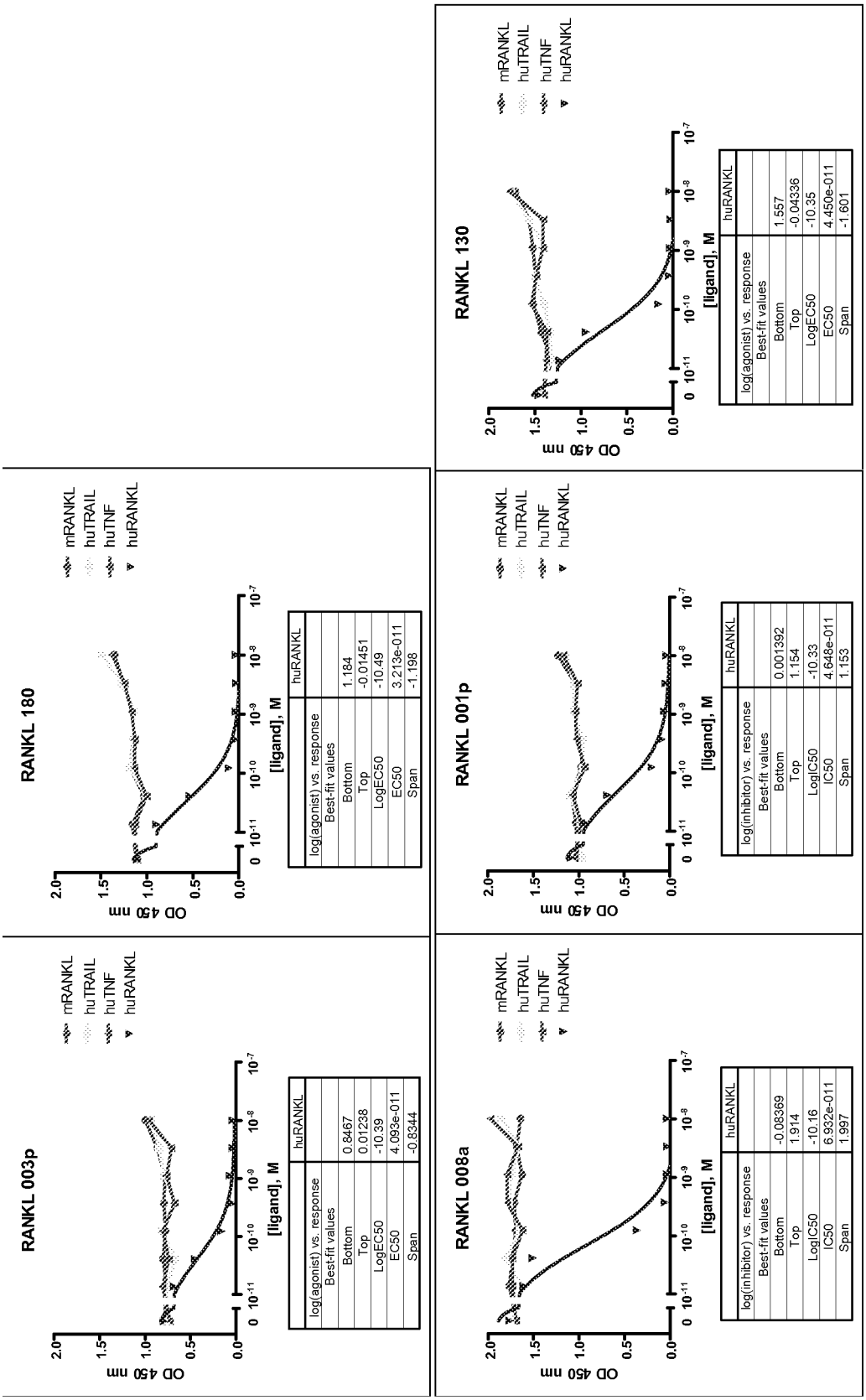

RANKL 003p
mRANKL
huTRAIL
huTNF
huRANKL
OD 450 nm
[ligand], M
log(agonist) vs. response
Best-fit values
Bottom 0.8467
Top 0.01238
LogEC50 -10.39
EC50 4.093e-011
Span -0.8344
RANKL 180
log(agonist) vs. response
Best-fit values
Bottom 1.184
Top -0.01451
LogEC50 -10.49
EC50 3.213e-011
Span -1.198
RANKL 008a
log(inhibitor) vs. response
Best-fit values
Bottom -0.08369
Top 1.914
LogIC50 -10.16
IC50 6.932e-011
Span 1.997
RANKL 001p
log(inhibitor) vs. response
Best-fit values
Bottom 0.001392
Top 1.154
LogIC50 -10.33
IC50 4.648e-011
Span 1.153
RANKL 130
log(agonist) vs. response
Best-fit values
Bottom 1.557
Top -0.04336
LogEC50 -10.35
EC50 4.450e-011
Span -1.601

Figure 17