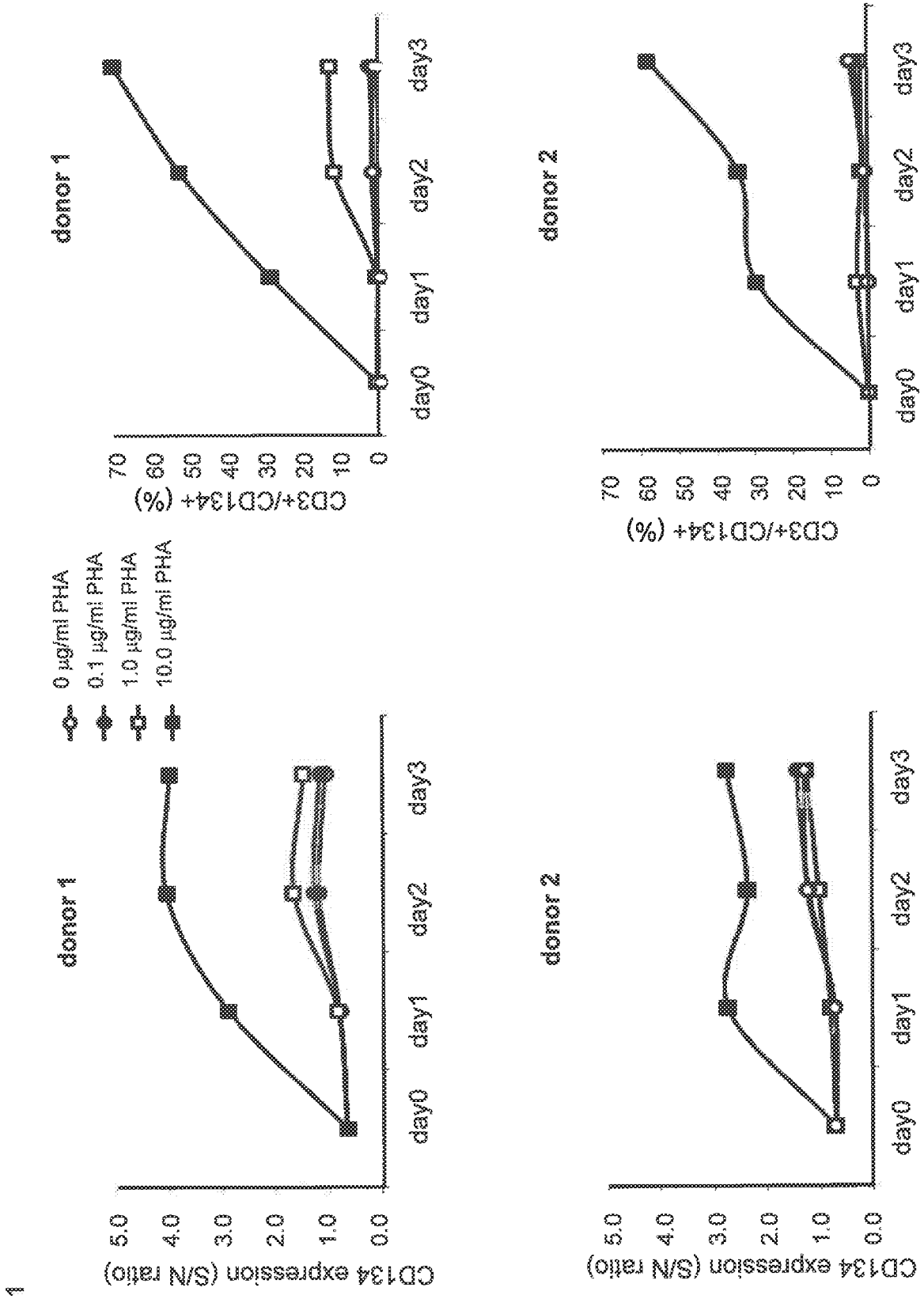

donor 1
donor 2
CD3+/CD134+ (%)
CD134 expression (S/N ratio)
day0
day1
day2
day3
0 µg/ml PHA
0.1 µg/ml PHA
1.0 µg/ml PHA
10.0 µg/ml PHA

Figure 1

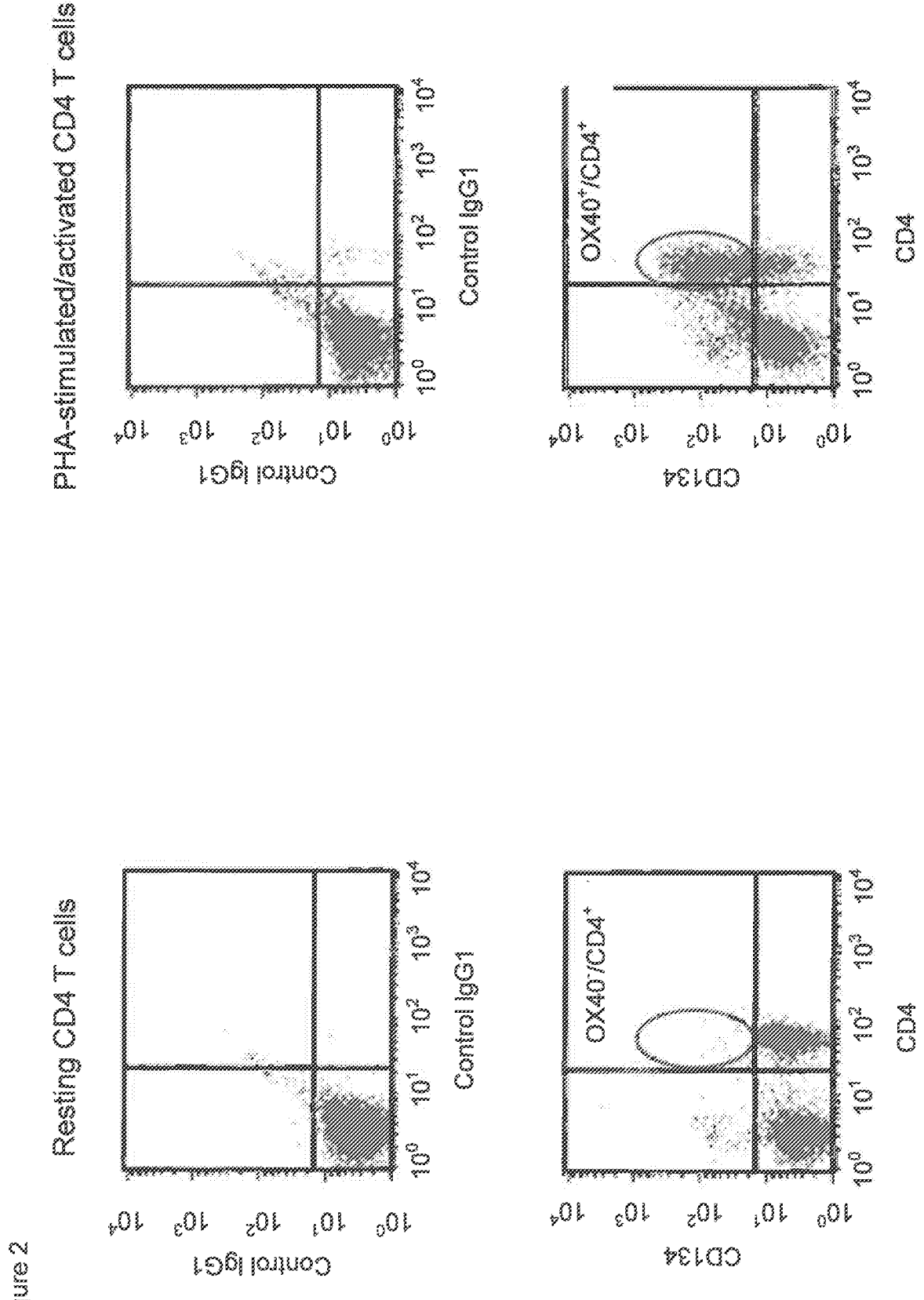

Resting CD4 T cells
PHA-stimulated/activated CD4 T cells
Control IgG1
Control IgG1
OX40+/CD4+
CD134
CD4
10^0 10^1 10^2 10^3 10^4

Figure 2

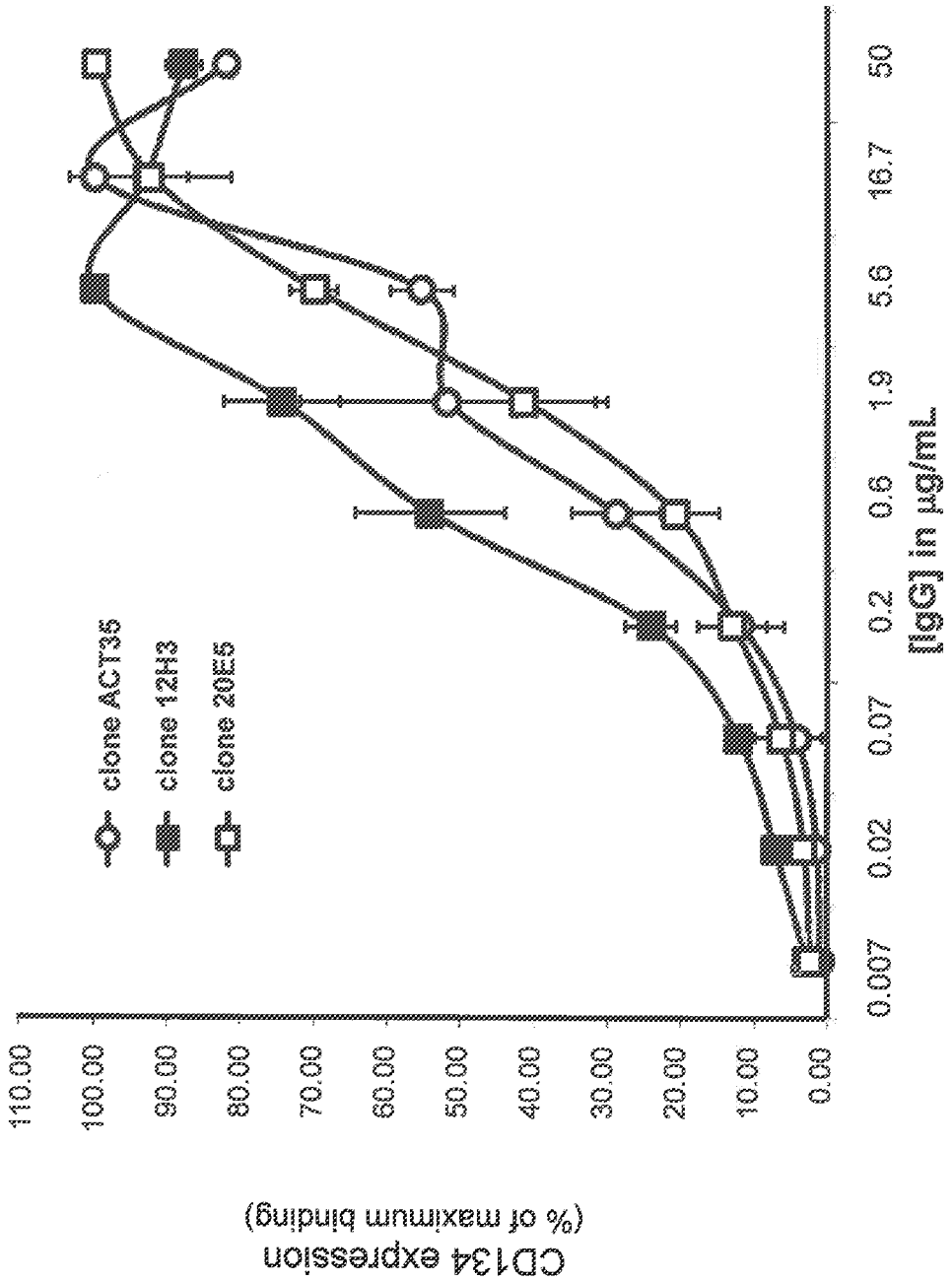

CD134 expression
(% of maximum binding)
110.00
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
clone ACT35
clone 12H3
clone 20E5
0.007
0.02
0.07
0.2
0.6
1.9
5.6
16.7
50
[IgG] in µg/mL

Figure 3

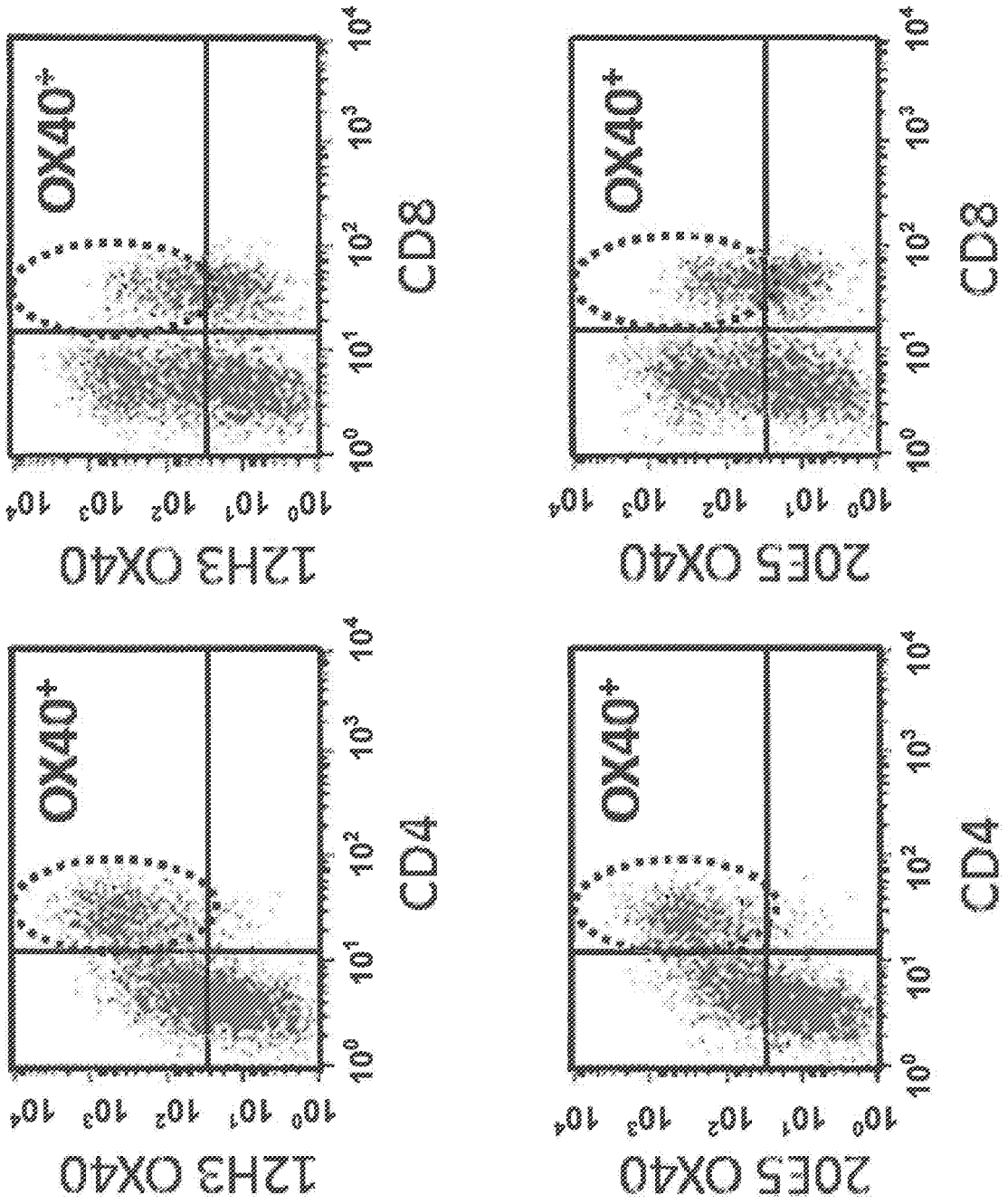

12H3 OX40
CD8
OX40+
20E5 OX40
CD8
OX40+
12H3 OX40
CD4
OX40+
20E5 OX40
CD4
OX40+

Figure 4

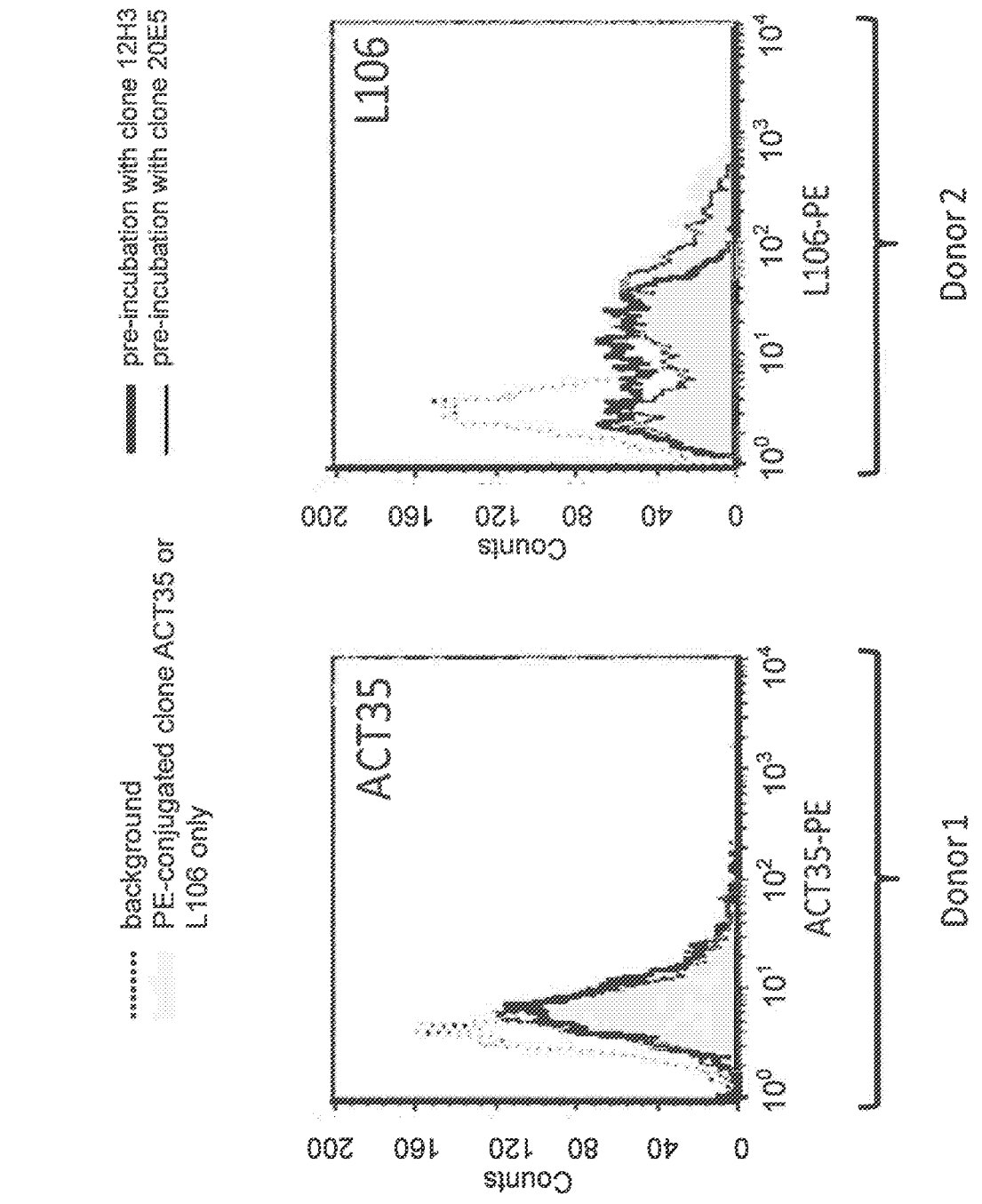

pre-incubation with clone 12H3
pre-incubation with clone 20E5
background
PE-conjugated clone ACT35 or L106 only
L106
ACT35
Counts
0
40
80
120
160
200
10^0
10^1
10^2
10^3
10^4
L106-PE
ACT35-PE
Donor 2
Donor 1

Figure 5

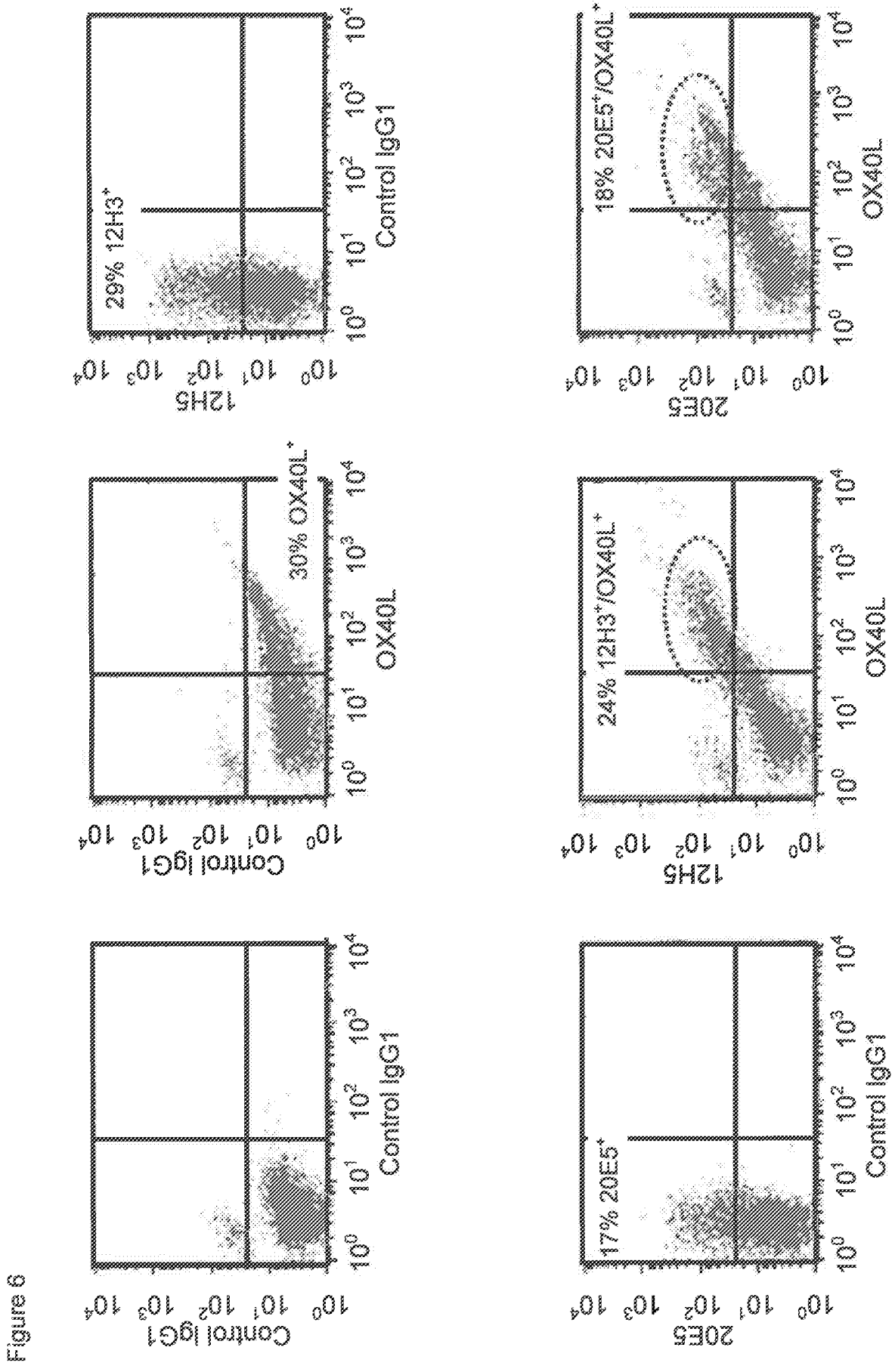

29% 12H3+
Control IgG1
12H5
18% 20E5+/OX40L+
OX40L
20E5
30% OX40L+
Control IgG1
OX40L
24% 12H3+/OX40L+
12H5
17% 20E5+
Control IgG1
20E5
10^0 10^1 10^2 10^3 10^4

Figure 6

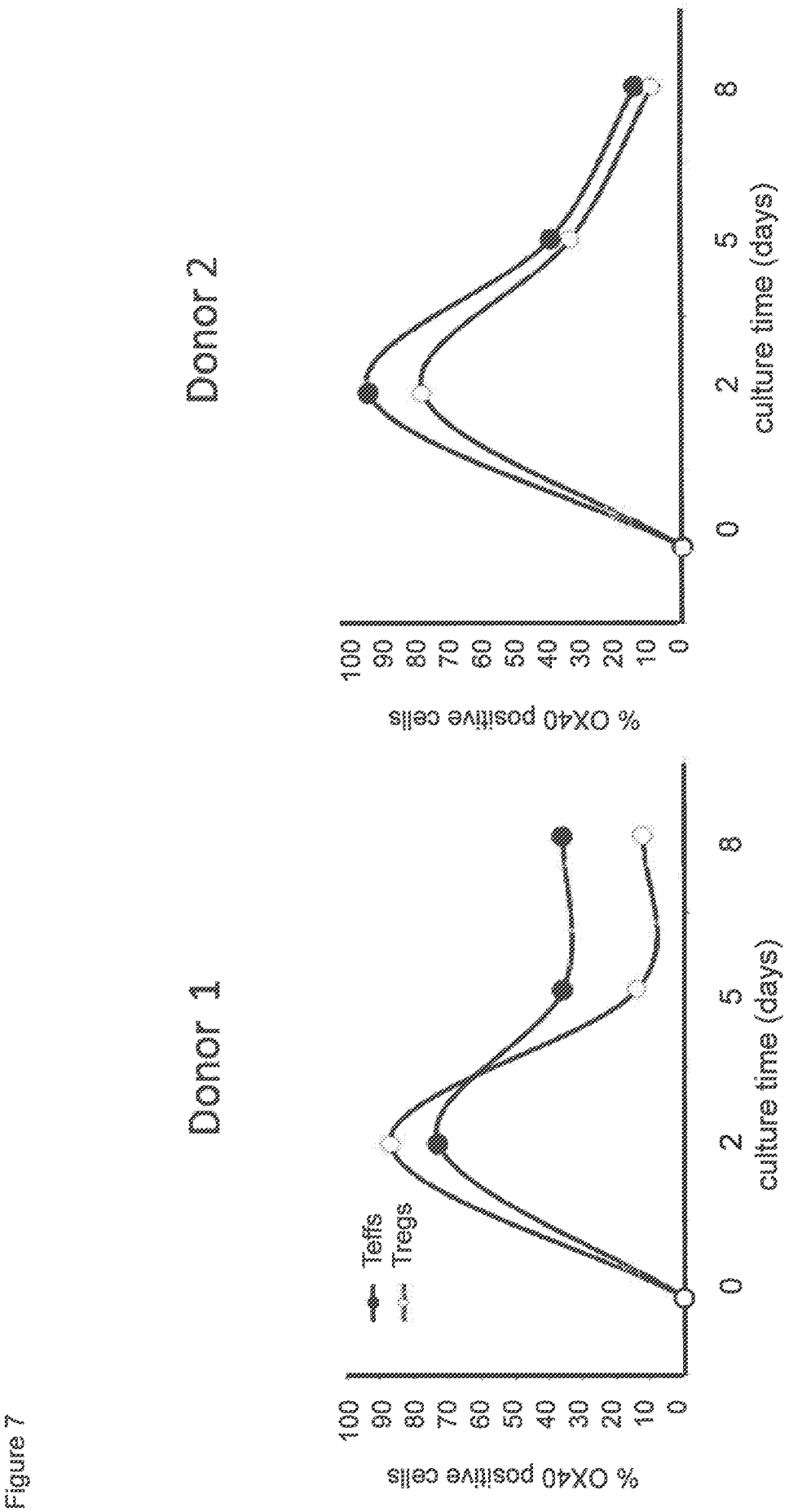

Donor 1
Donor 2
Teffs
Tregs
% OX40 positive cells
culture time (days)
0
10
20
30
40
50
60
70
80
90
100
2
5
8

Figure 7

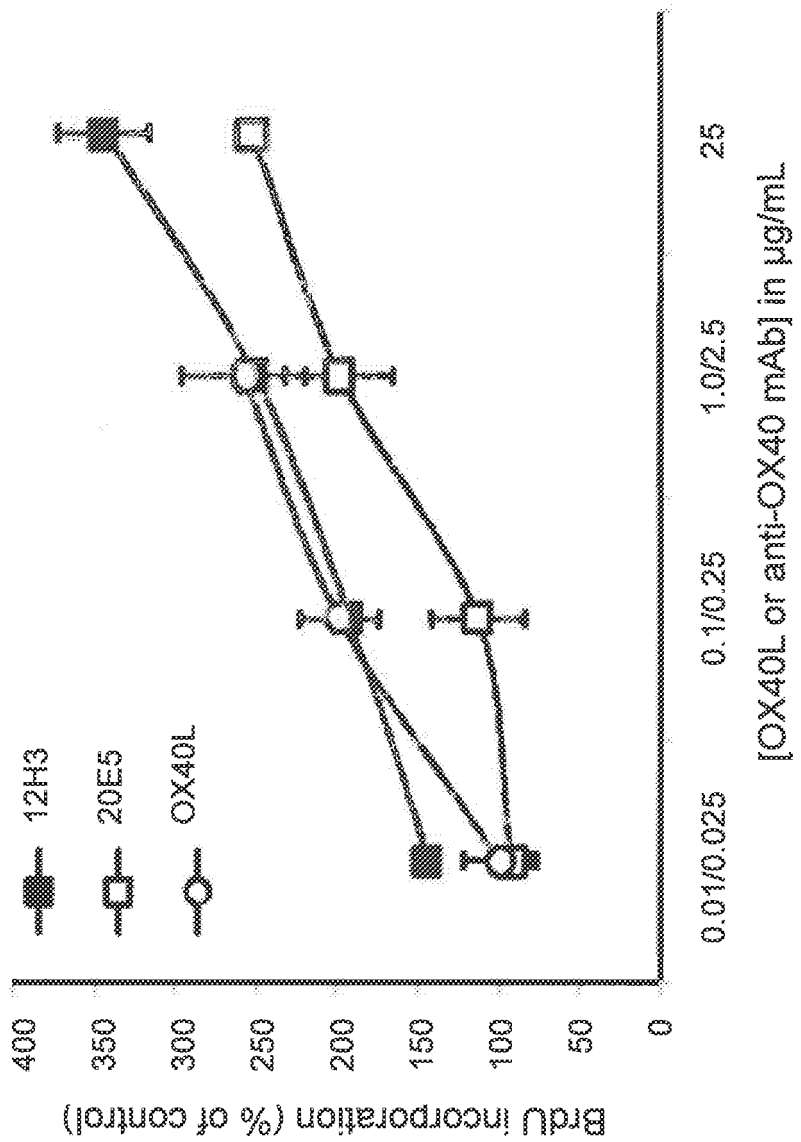

BrdU incorporation (% of control)
400
350
300
250
200
150
100
50
0
12H3
20E5
OX40L
0.01/0.025
0.1/0.25
1.0/2.5
25
[OX40L or anti-OX40 mAb] in µg/mL

Figure 8

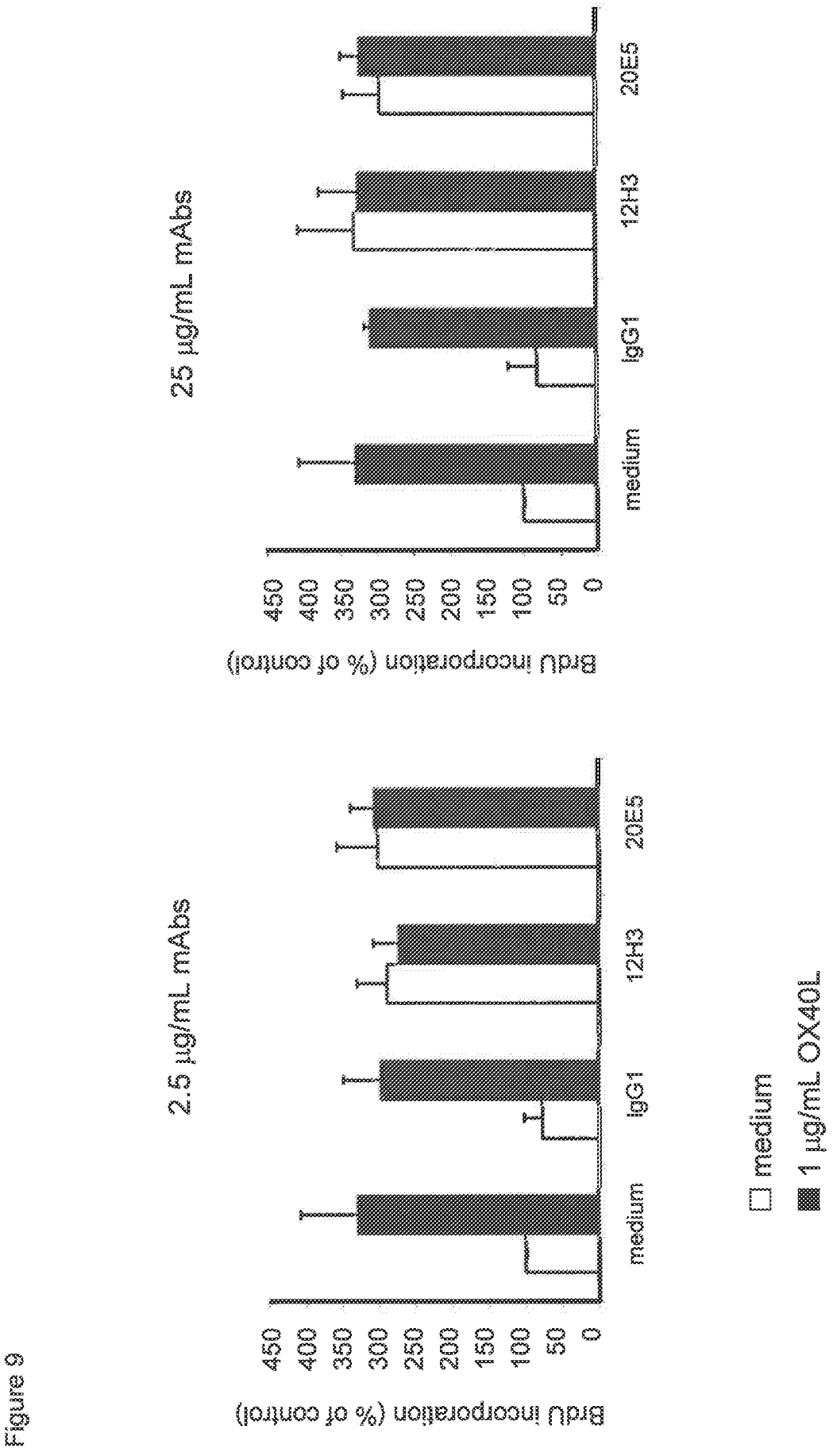

2.5 µg/mL mAbs
25 µg/mL mAbs
BrdU incorporation (% of control)
0
50
100
150
200
250
300
350
400
450
medium
IgG1
12H3
20E5
medium
1 µg/mL OX40L

Figure 9

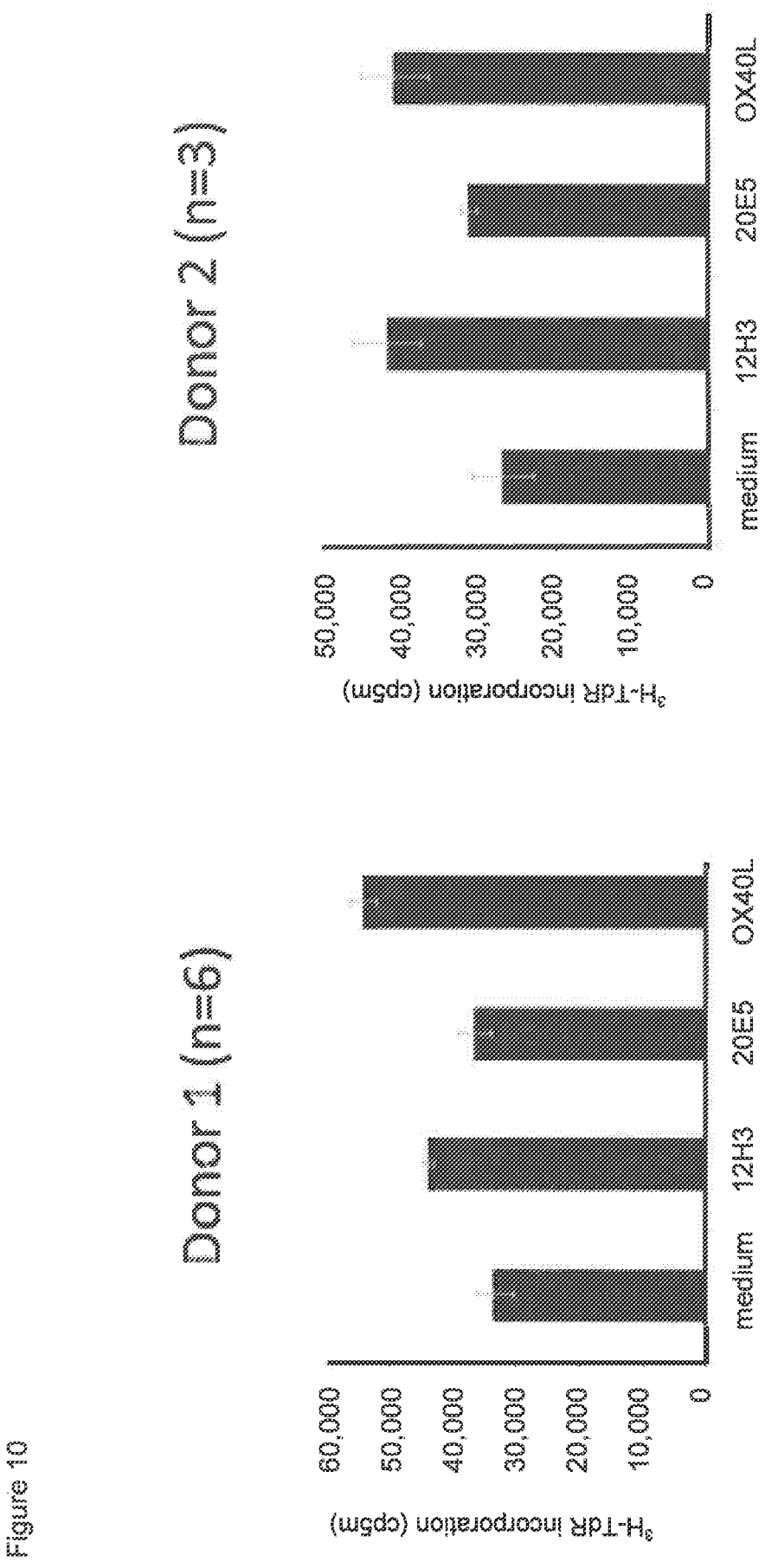

Donor 1 (n=6)
^{3}H-TdR incorporation (cpδm)
60,000
50,000
40,000
30,000
20,000
10,000
0
medium
12H3
20E5
OX40L
Donor 2 (n=3)
^{3}H-TdR incorporation (cpδm)
50,000
40,000
30,000
20,000
10,000
0
medium
12H3
20E5
OX40L

Figure 10

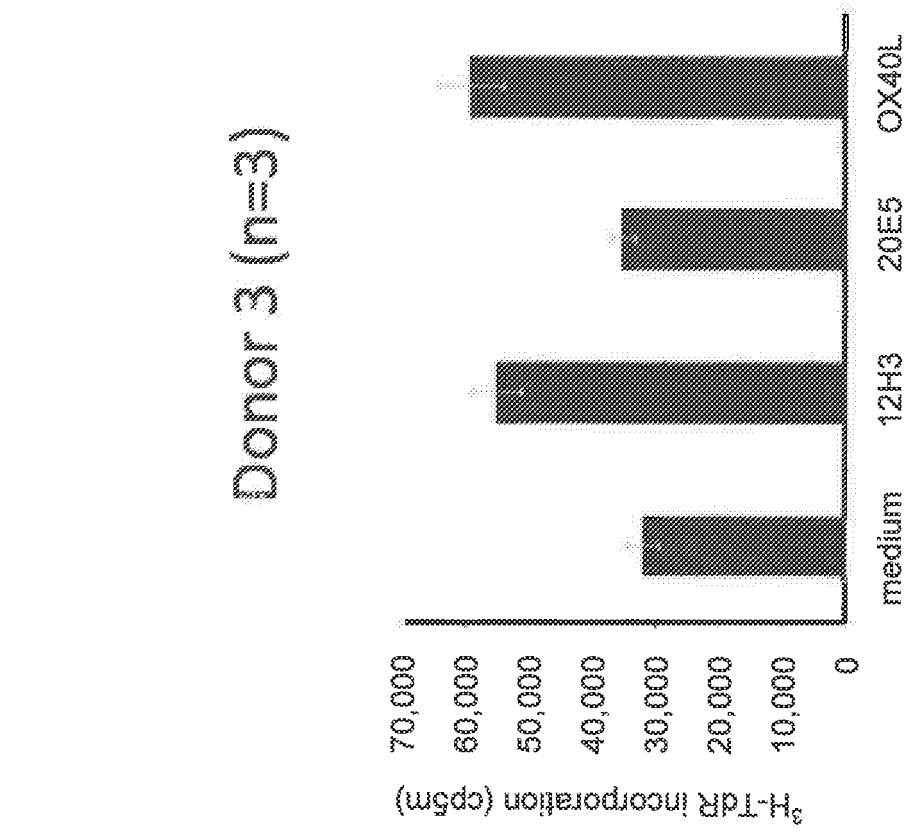


Figure 10 (cont.)

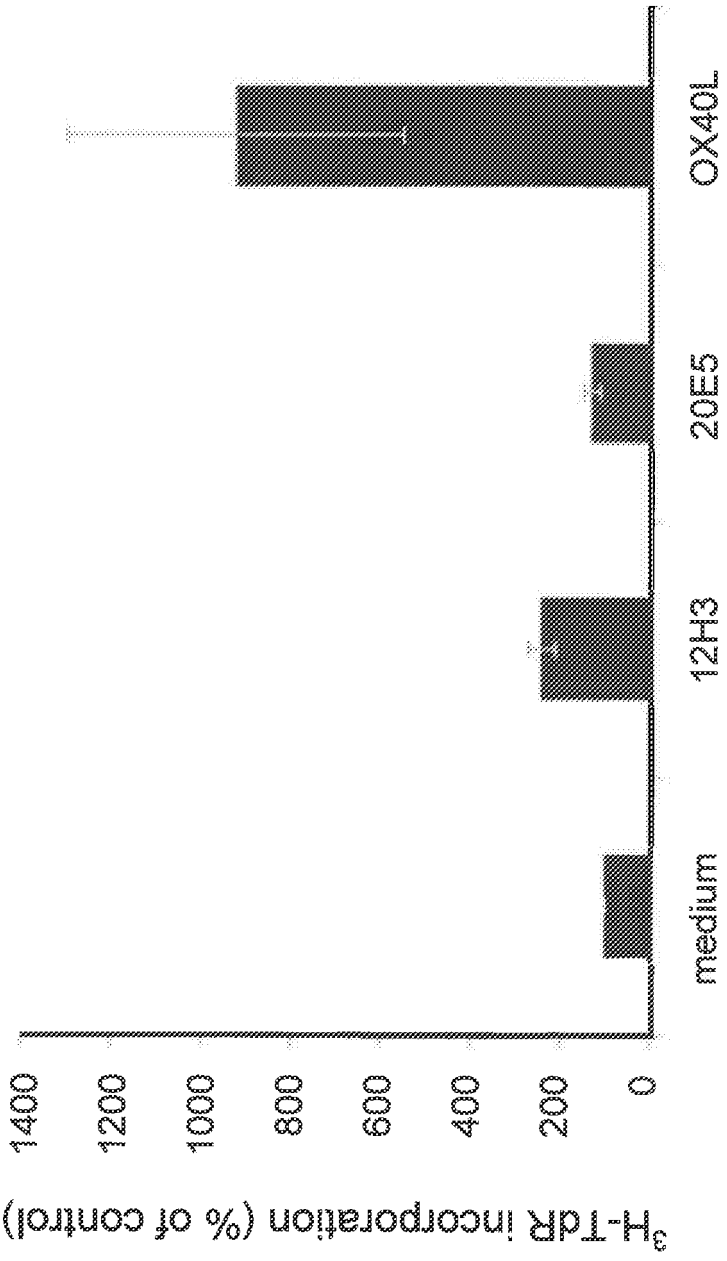

^{3}H-TdR incorporation (% of control)
1400
1200
1000
800
600
400
200
0
medium
12H3
20E5
OX40L

Figure 11

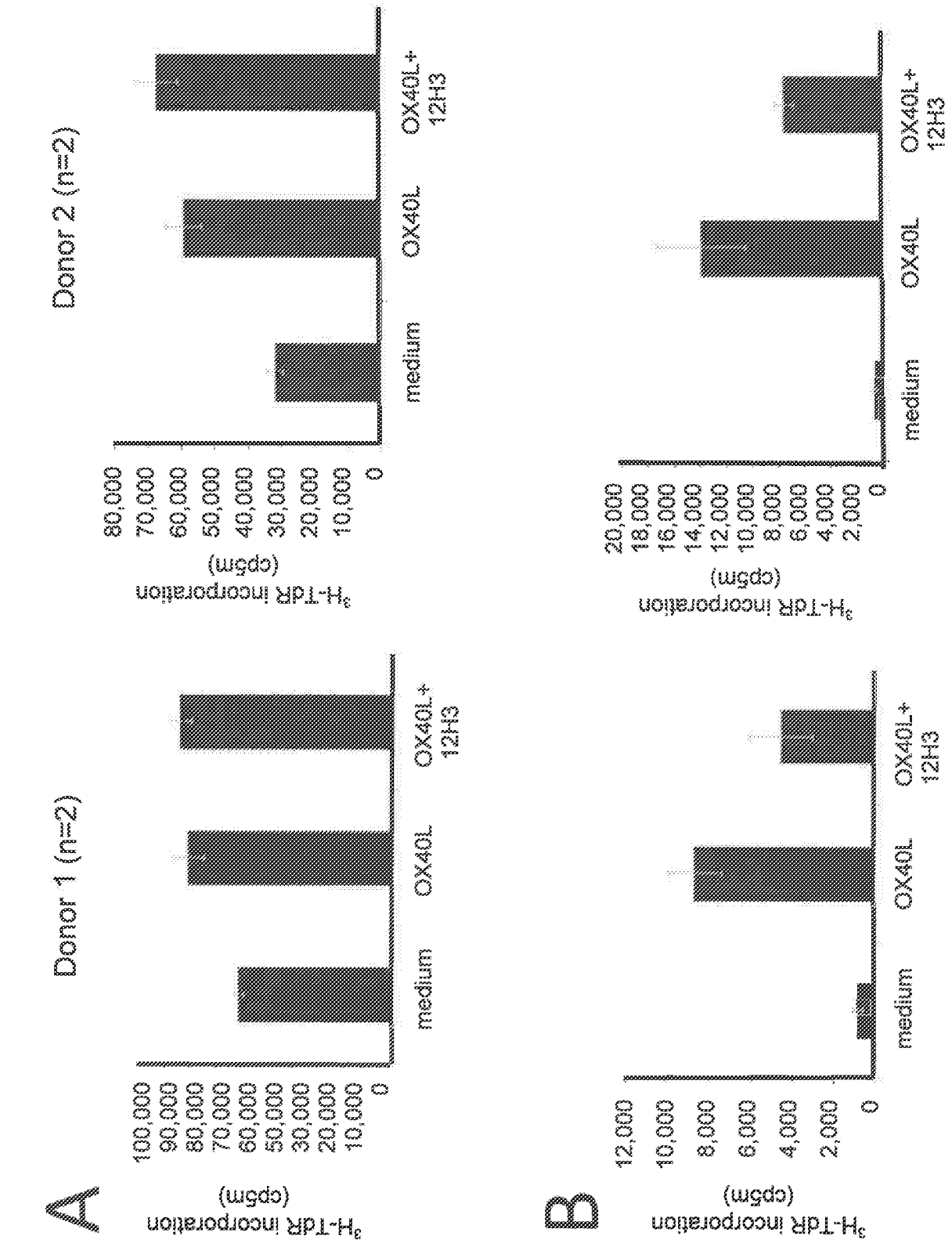

A
Donor 1 (n=2)
^{3}H-TdR incorporation (cpδm)
100,000
90,000
80,000
70,000
60,000
50,000
30,000
20,000
10,000
0
medium
OX40L
OX40L+ 12H3
Donor 2 (n=2)
^{3}H-TdR incorporation (cpδm)
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
medium
OX40L
OX40L+ 12H3
B
^{3}H-TdR incorporation (cpδm)
12,000
10,000
8,000
6,000
4,000
2,000
0
medium
OX40L
OX40L+ 12H3
^{3}H-TdR incorporation (cpδm)
20,000
18,000
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
medium
OX40L
OX40L+ 12H3

Figure 12

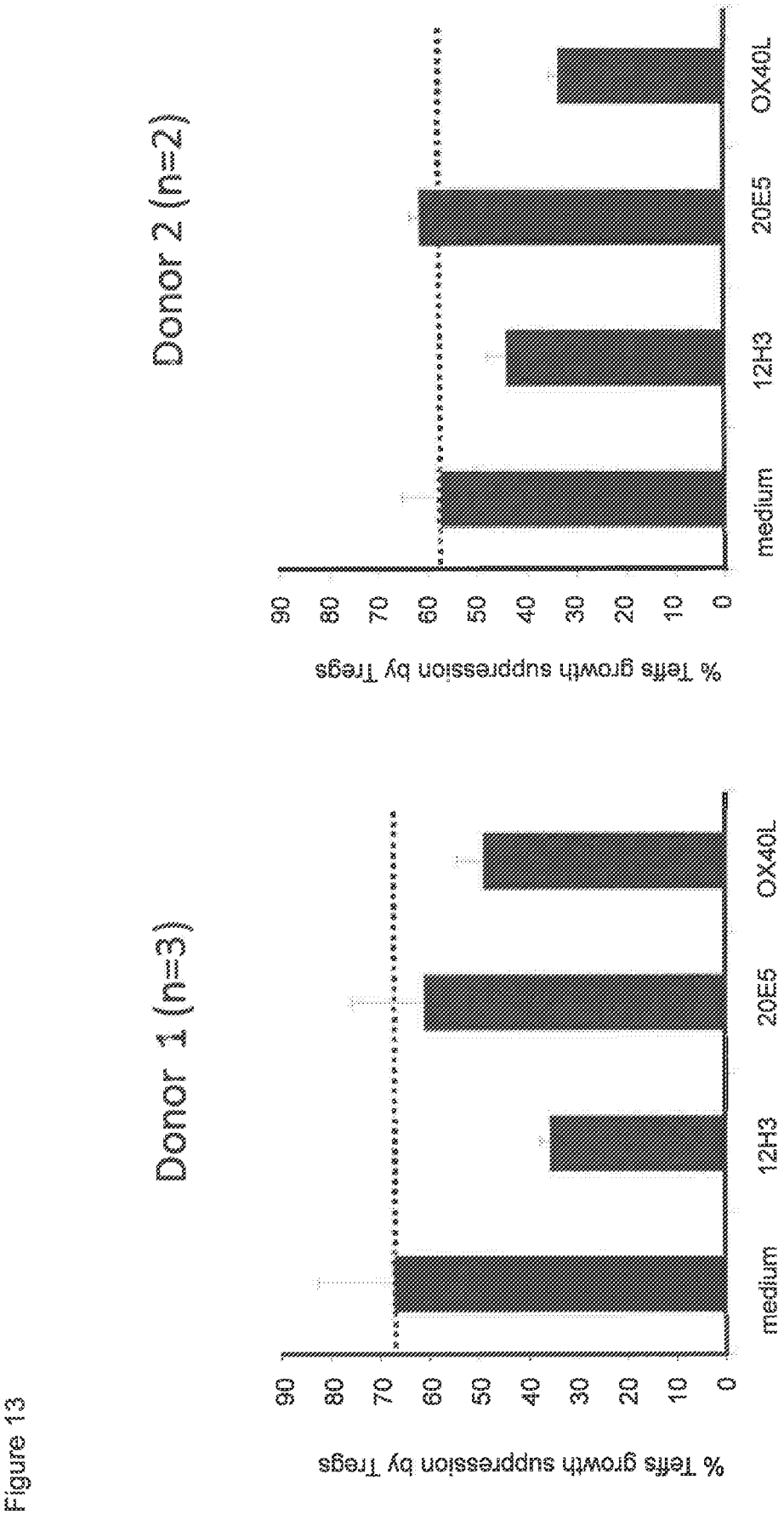

Donor 1 (n=3)
% Teffs growth suppression by Tregs
0
10
20
30
40
50
60
70
80
90
medium
12H3
20E5
OX40L
Donor 2 (n=2)
% Teffs growth suppression by Tregs
0
10
20
30
40
50
60
70
80
90
medium
12H3
20E5
OX40L

Figure 13

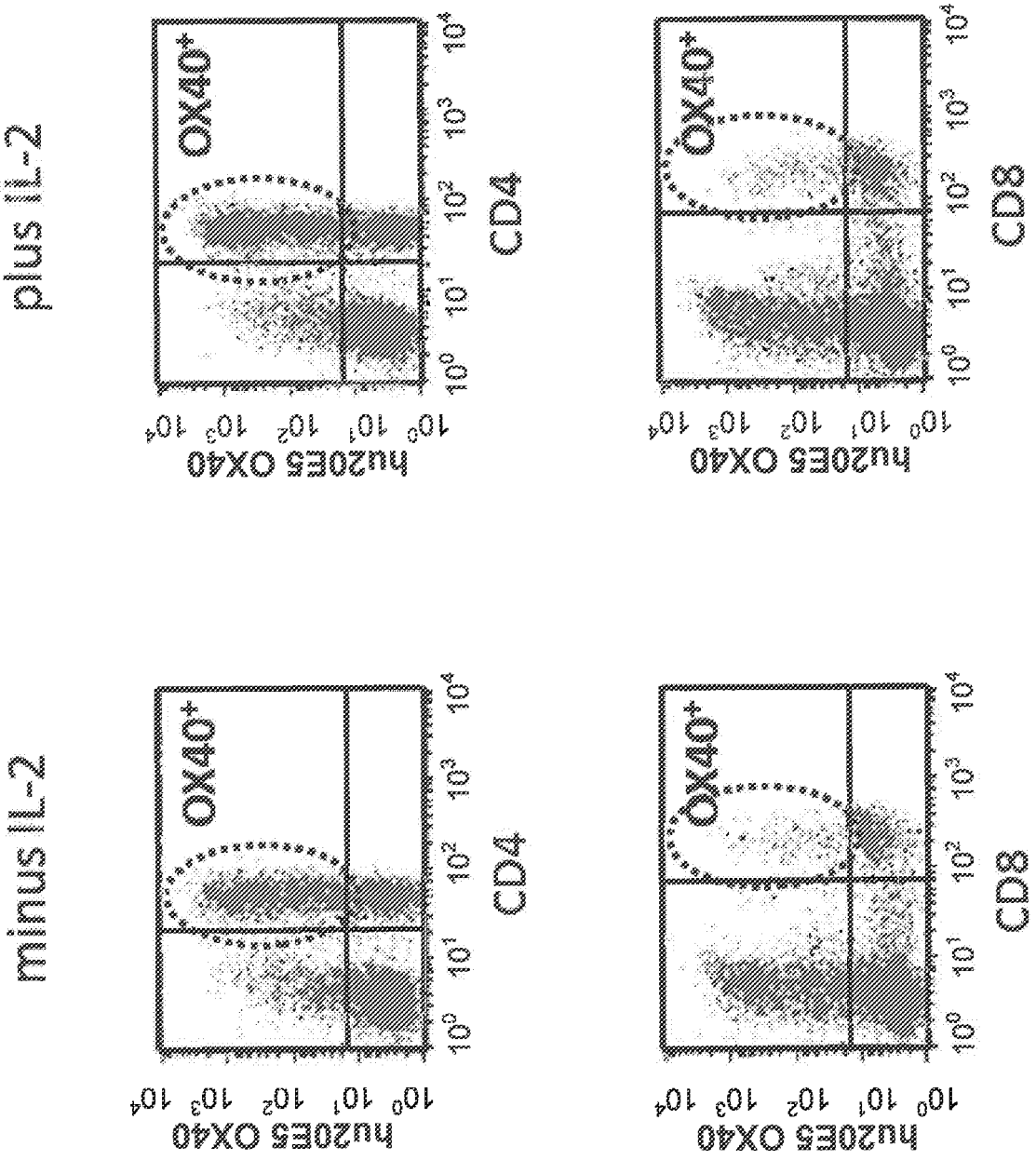

plus IL-2
minus IL-2
CD4
CD8
OX40+
hu20E5 OX40
10^0 10^1 10^2 10^3 10^4

Figure 14

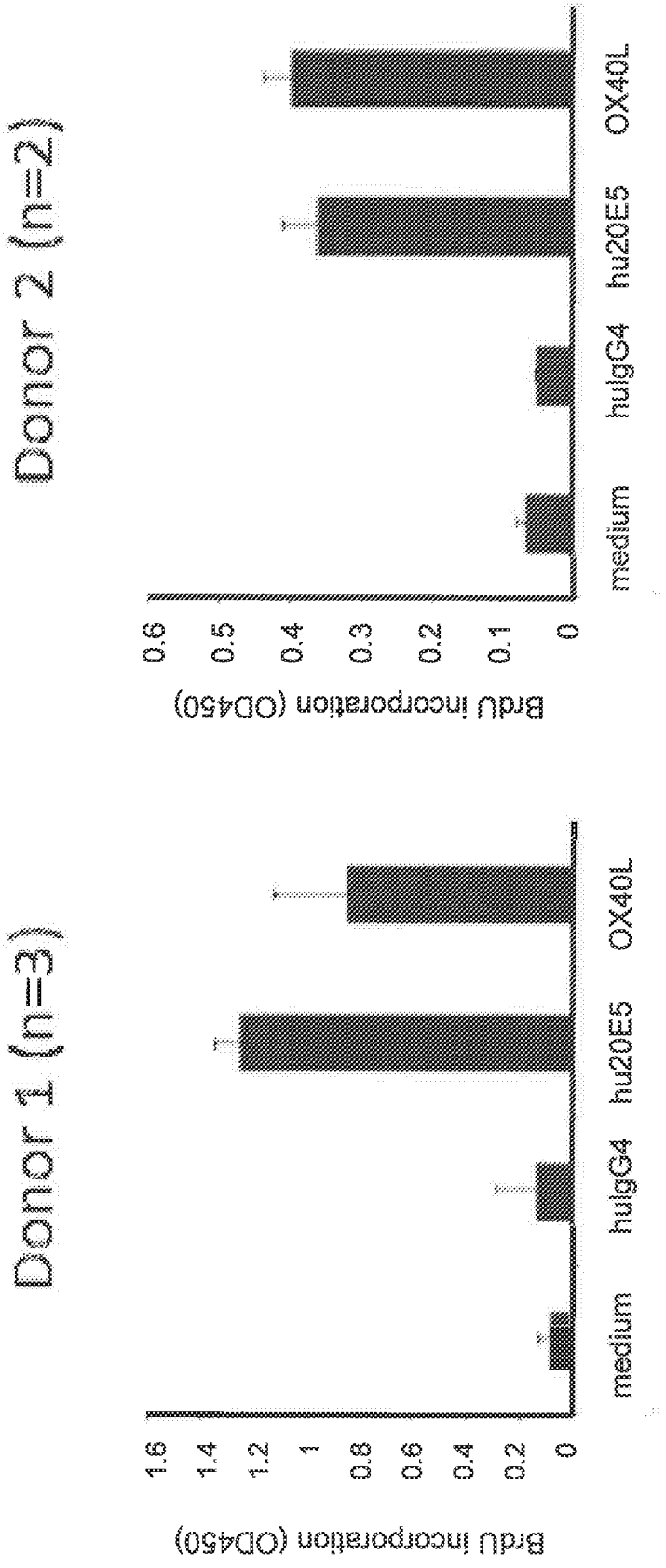
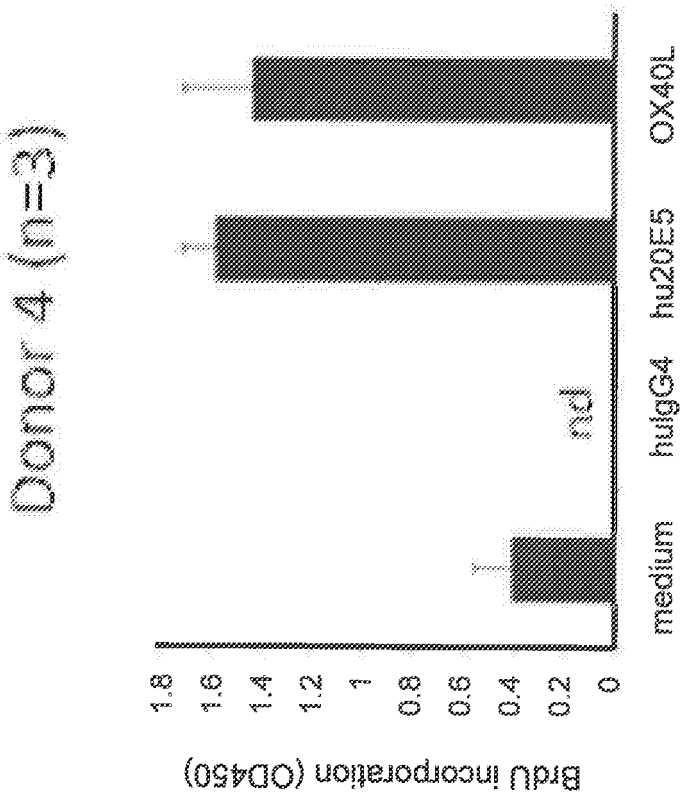

Donor 1 (n=3)
BrdU incorporation (OD450)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
medium
huIgG4
hu20E5
OX40L
Donor 2 (n=2)
BrdU incorporation (OD450)
0.6
0.5
0.4
0.3
0.2
0.1
0
medium
huIgG4
hu20E5
OX40L

Figure 15



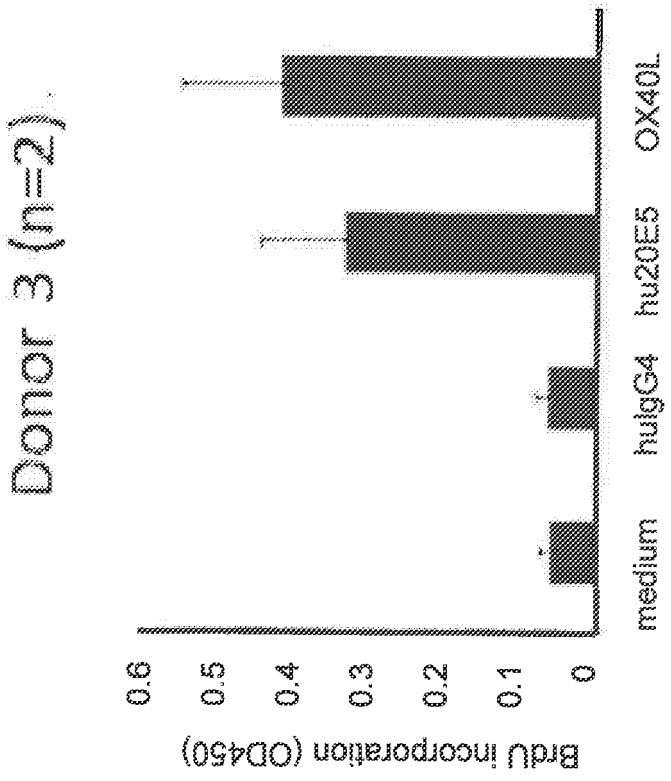


Figure 15 (cont.)

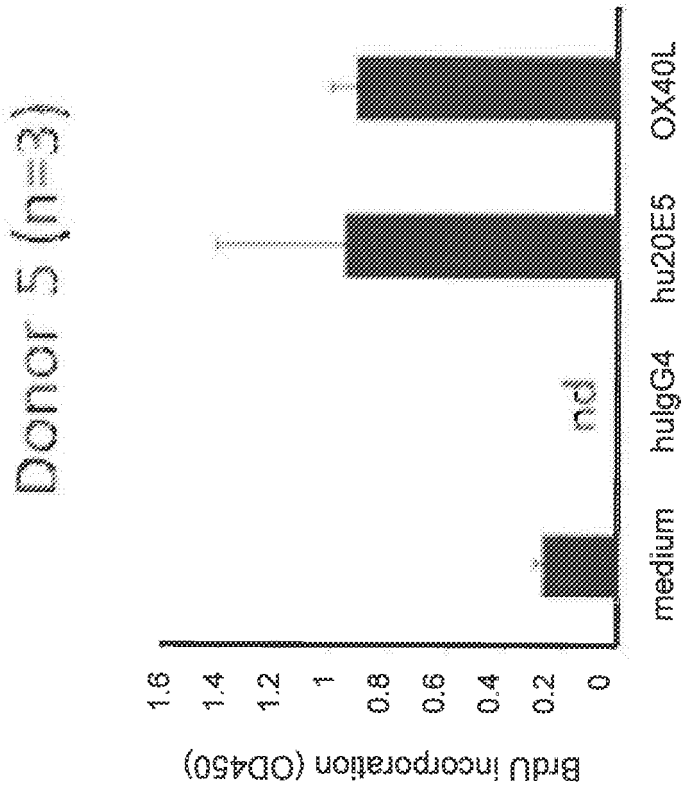


Figure 15 (cont.)

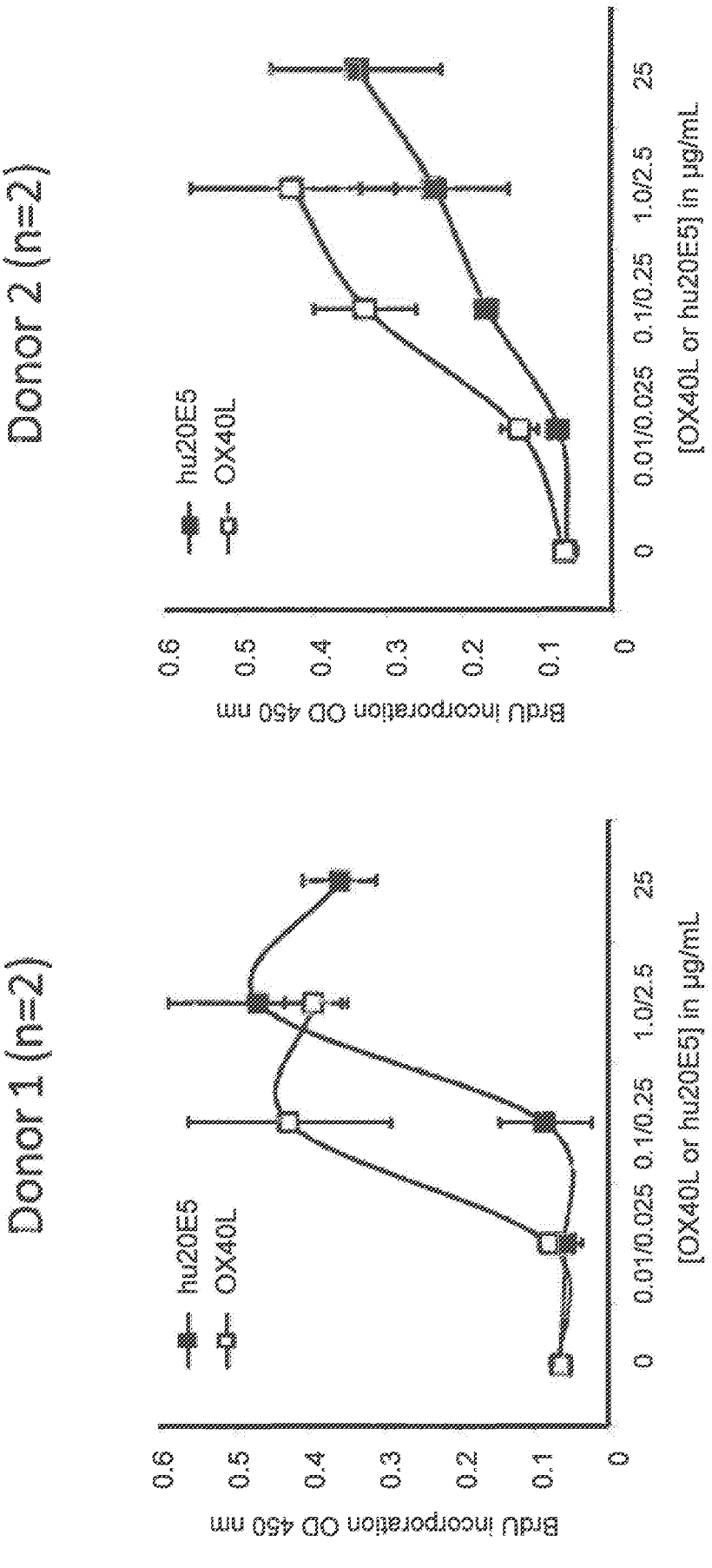

Donor 1 (n=2)
Donor 2 (n=2)
hu20E5
OX40L
BrdU incorporation OD 450 nm
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.01/0.025
0.1/0.25
1.0/2.5
25
[OX40L or hu20E5] in µg/mL

Figure 16

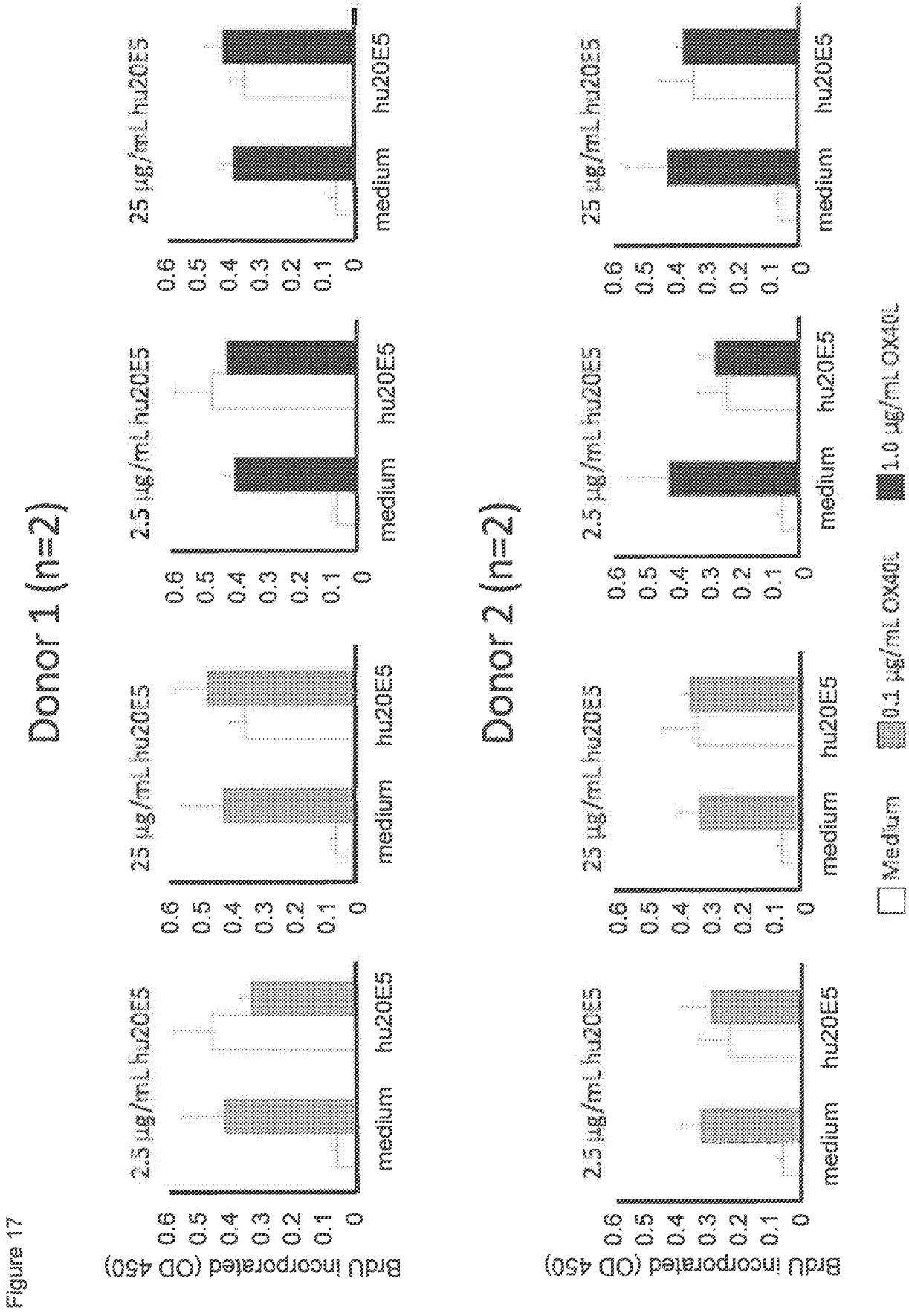

Donor 1 (n=2)
Donor 2 (n=2)
BrdU incorporated (OD 450)
2.5 µg/mL hu20E5
25 µg/mL hu20E5
medium
hu20E5
0
0.1
0.2
0.3
0.4
0.5
0.6
Medium
0.1 µg/mL OX40L
1.0 µg/mL OX40L

Figure 17

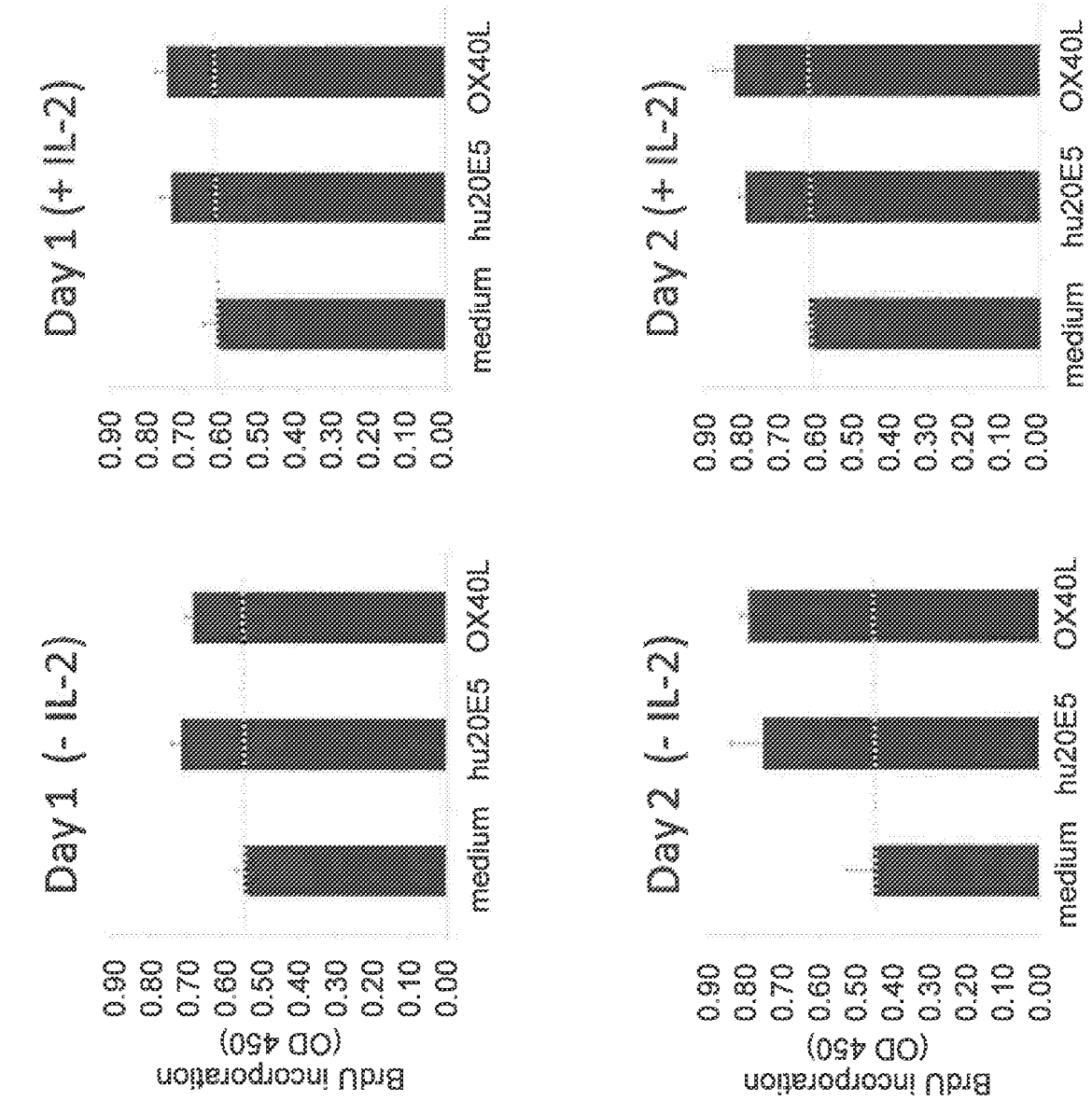

Day1 (- IL-2)
Day1 (+ IL-2)
Day2 (- IL-2)
Day2 (+ IL-2)
BrdU incorporation (OD 450)
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
medium
hu20E5
OX40L

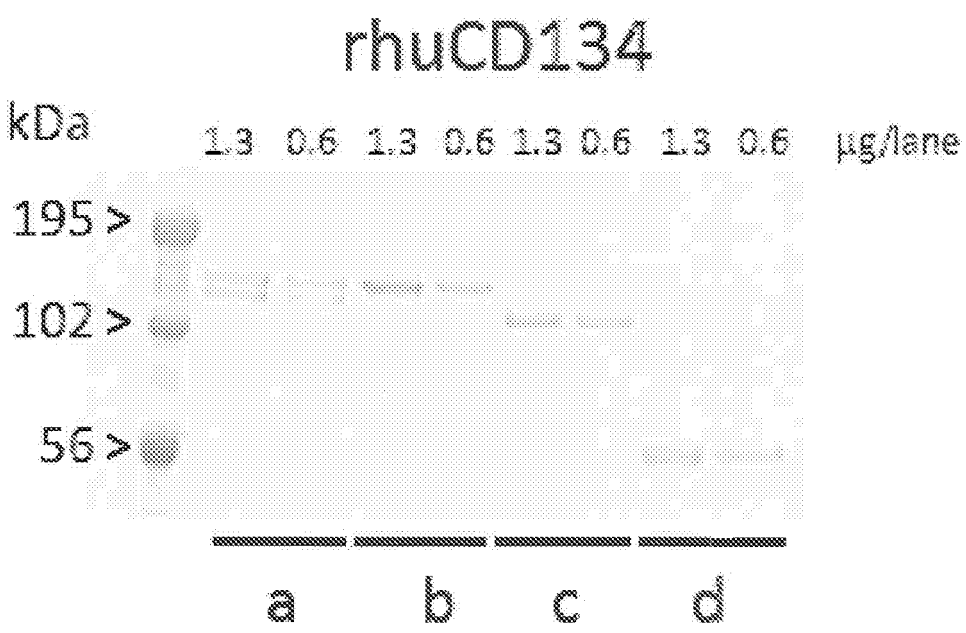
Figure 18

Figure 19

A

	reduction	70 °C heating
a	-	-
b	-	+
c	+	-
d	+	+

B



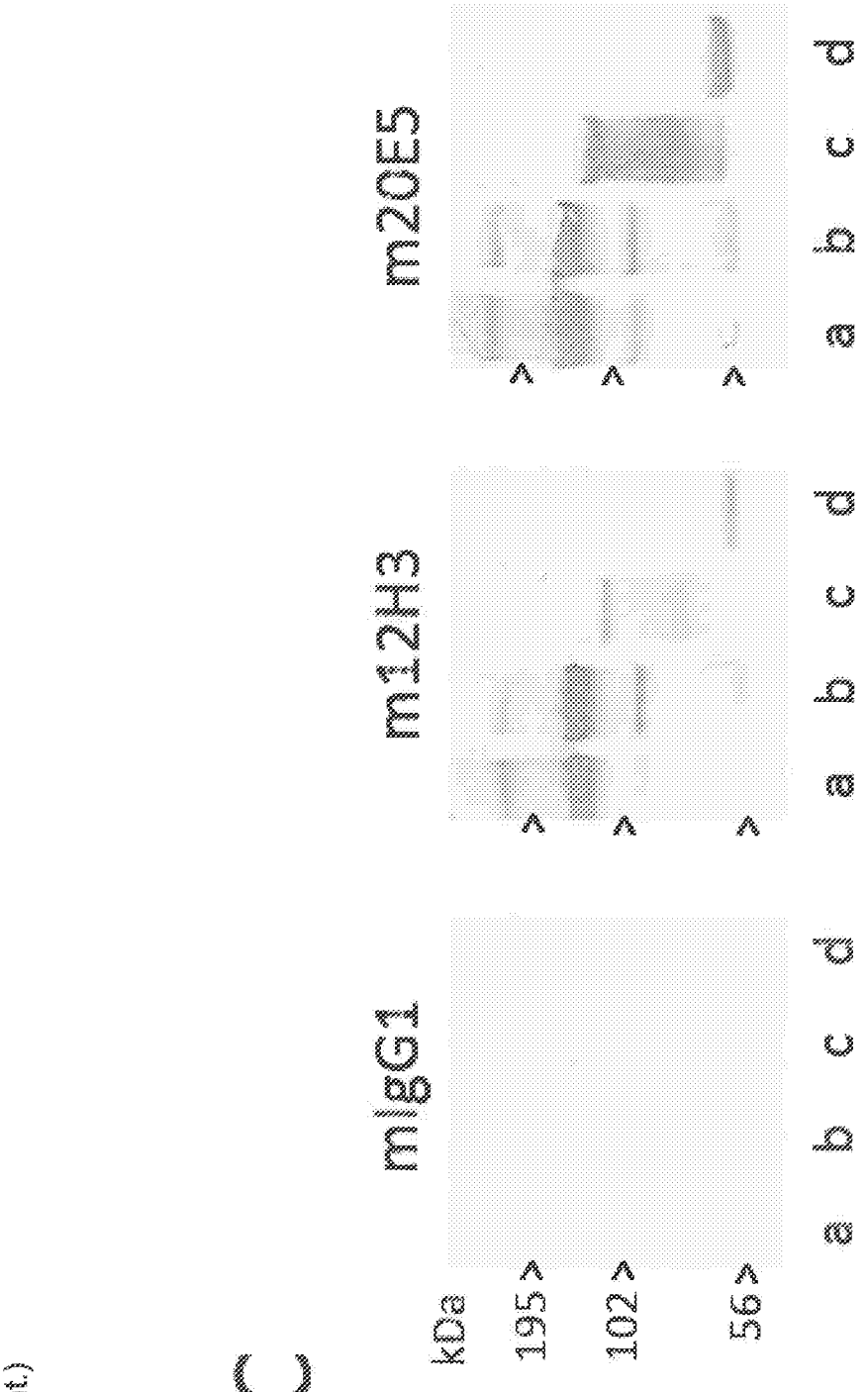


Figure 19 (cont.)

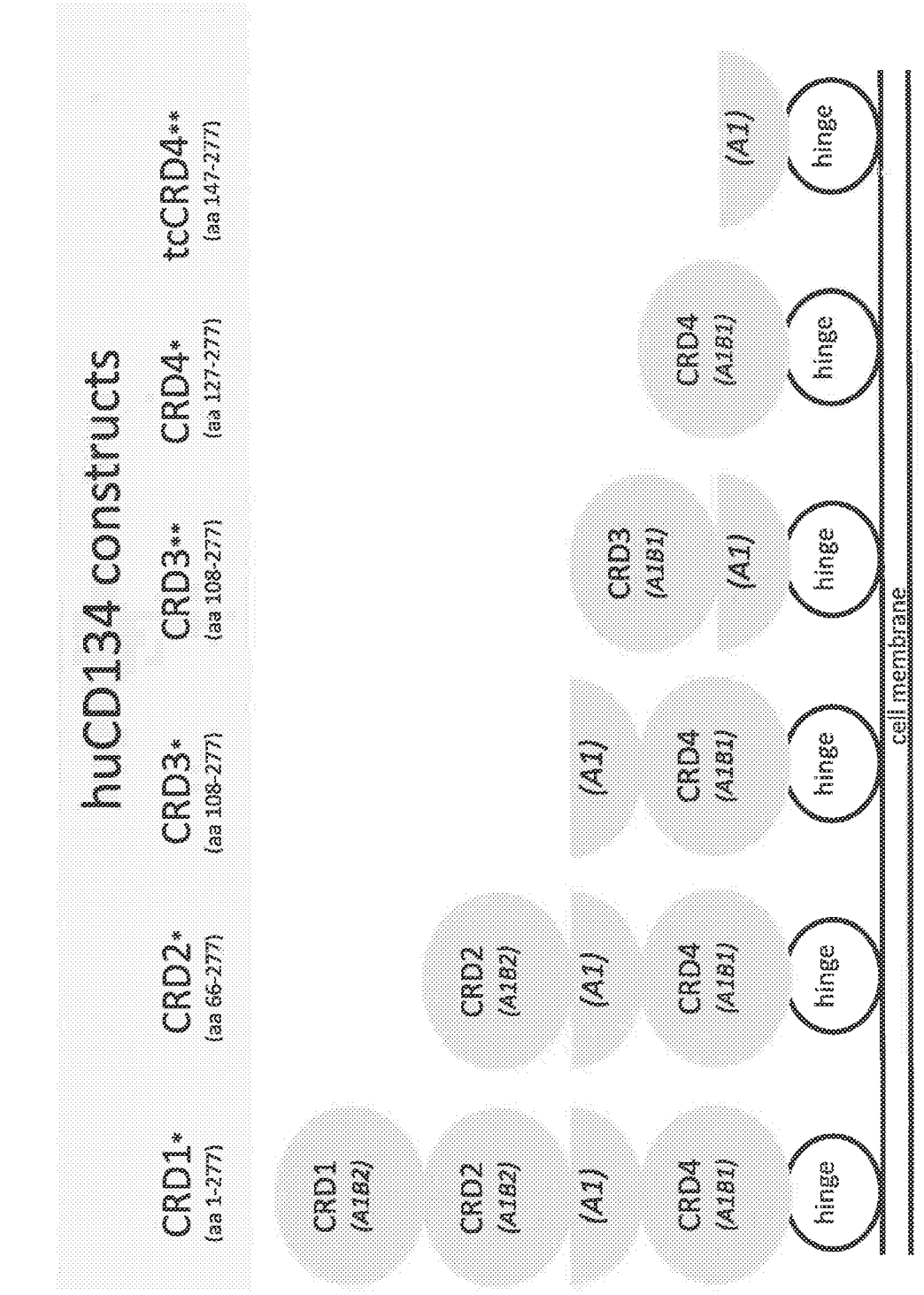

huCD134 constructs
CRD1* (aa 1-277)
CRD2* (aa 66-277)
CRD3* (aa 108-277)
CRD3** (aa 108-277)
CRD4* (aa 127-277)
tcCRD4** (aa 147-277)
CRD1 (A182)
CRD2 (A182)
(A1)
CRD4 (A181)
CRD2 (A182)
(A1)
CRD4 (A181)
(A1)
CRD4 (A181)
CRD3 (A181)
(A1)
CRD4 (A181)
(A1)
hinge
hinge
hinge
hinge
hinge
hinge
cell membrane
Extracellular cystein-rich domains
* According to Latza et al. Eur J Immunol 1994
** According to Compaan et al. Structure 2006

Figure 20

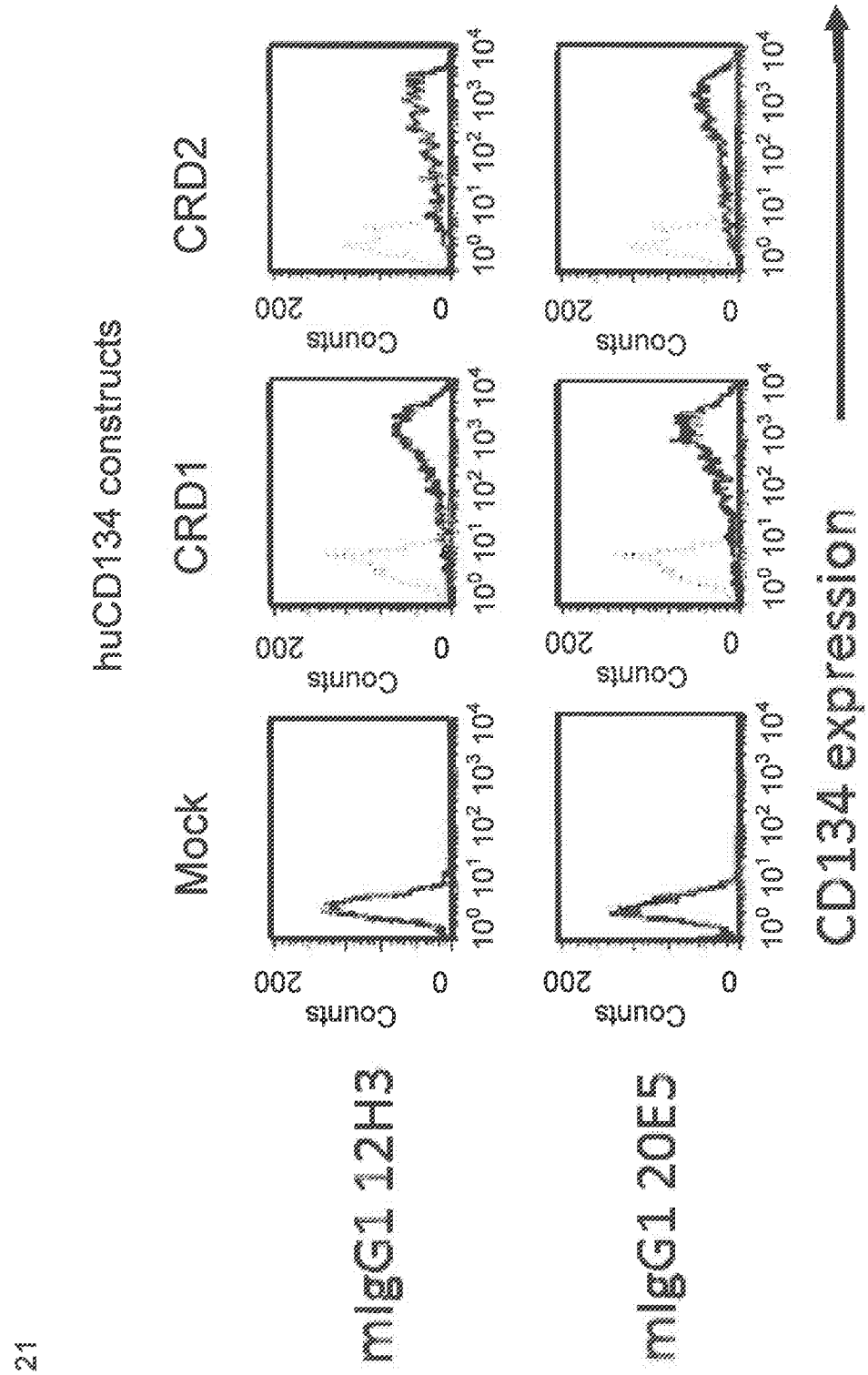

huCD134 constructs
Mock
CRD1
CRD2
mIgG1 12H3
mIgG1 20E5
Counts
200
0
10^0 10^1 10^2 10^3 10^4
CD134 expression
Background
Mouse IgG1 clone 12H3 or 20E5

Figure 21

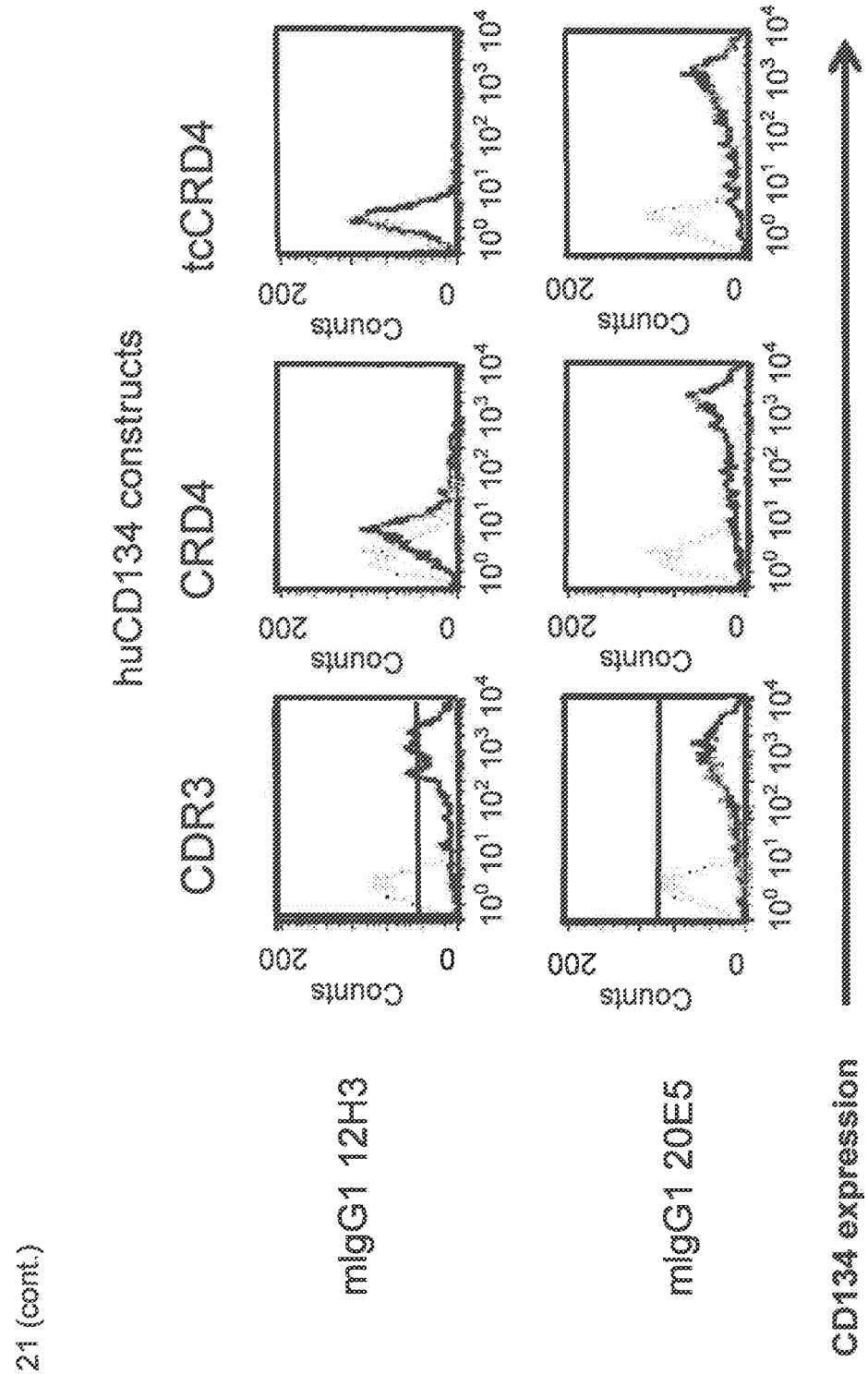


Figure 21 (cont.)

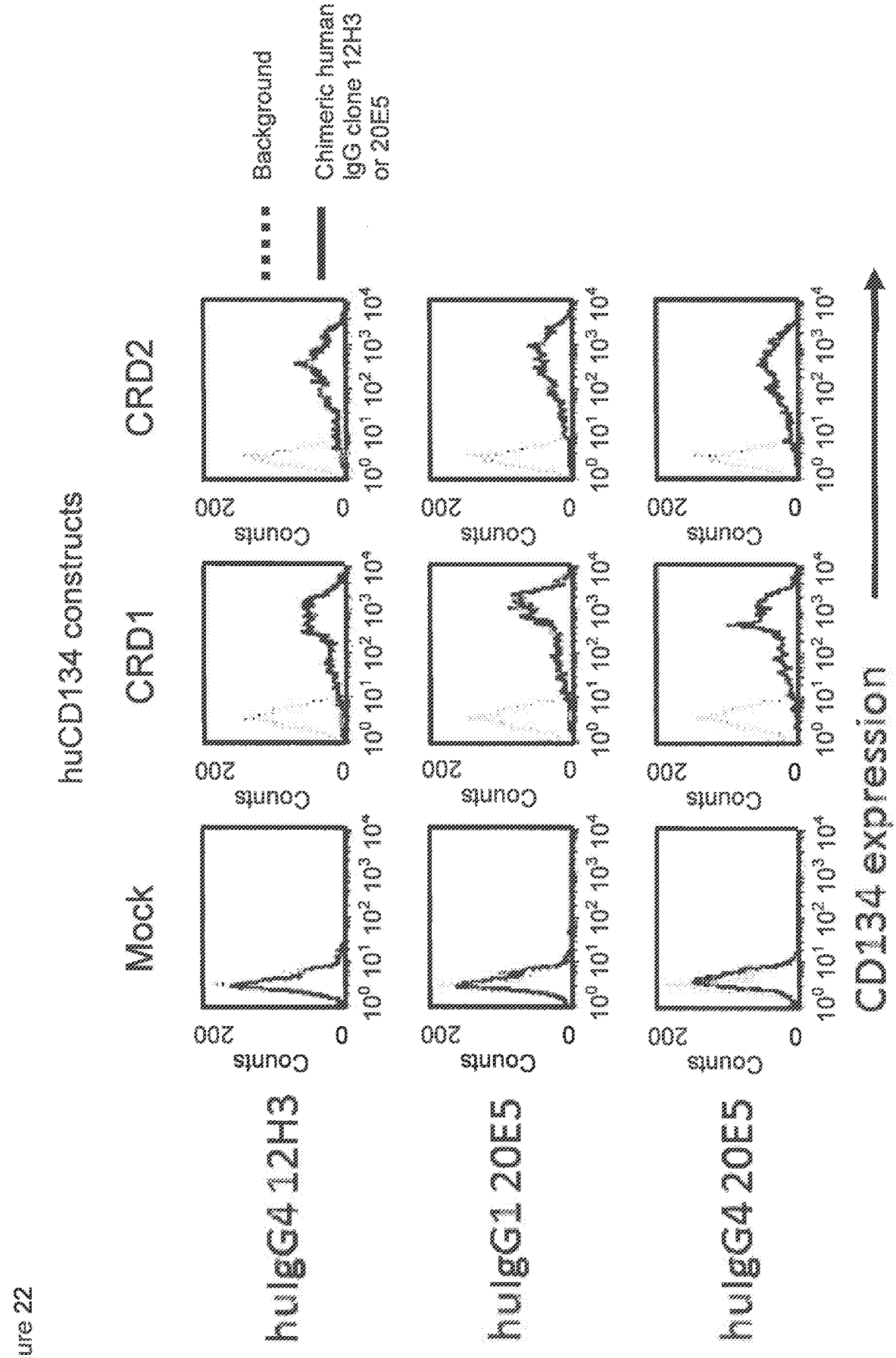

huCD134 constructs
Mock
CRD1
CRD2
Background
Chimeric human IgG clone 12H3 or 20E5
huIgG4 12H3
huIgG1 20E5
huIgG4 20E5
Counts
0
200
10^0 10^1 10^2 10^3 10^4
CD134 expression

Figure 22

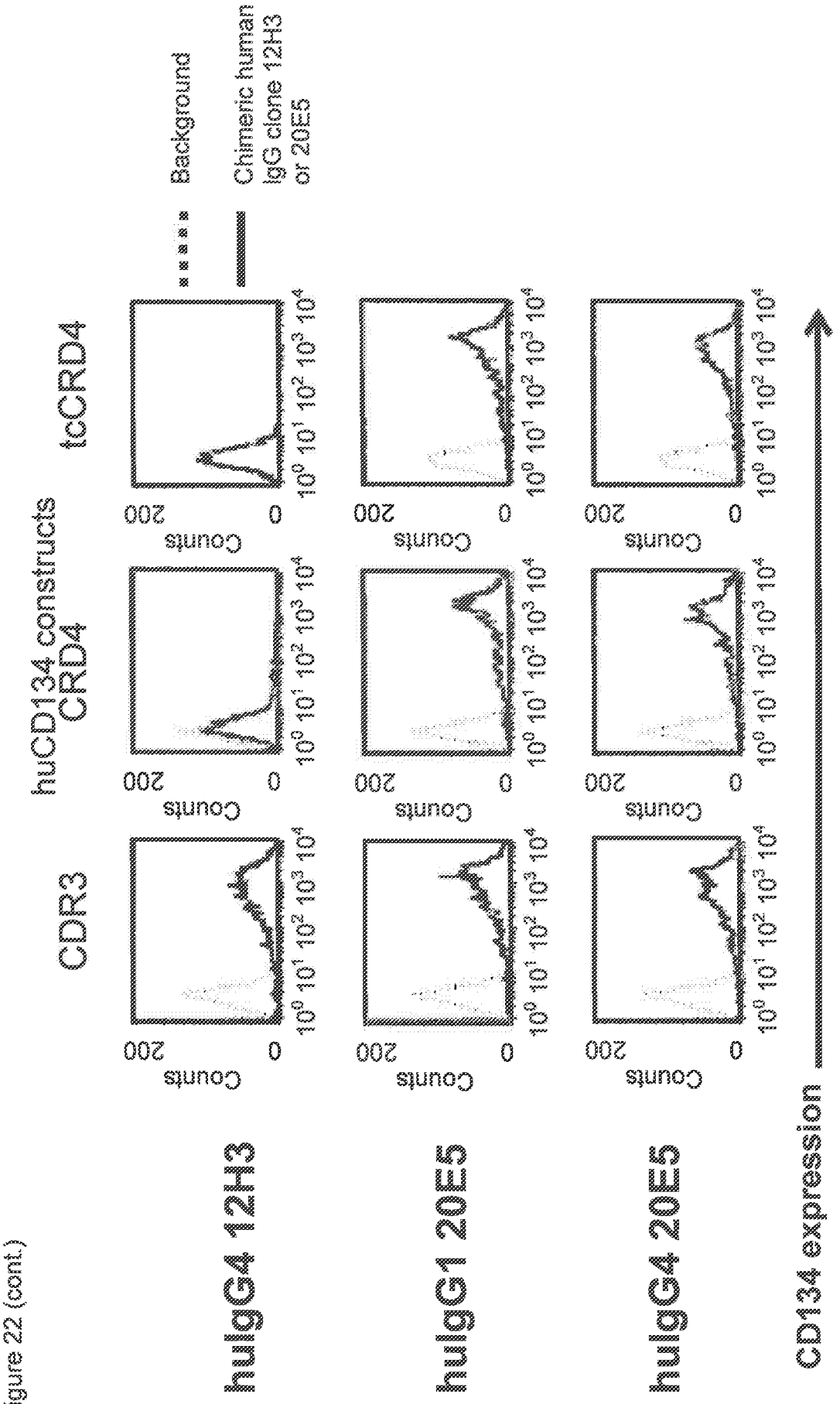


Figure 22 (cont.)

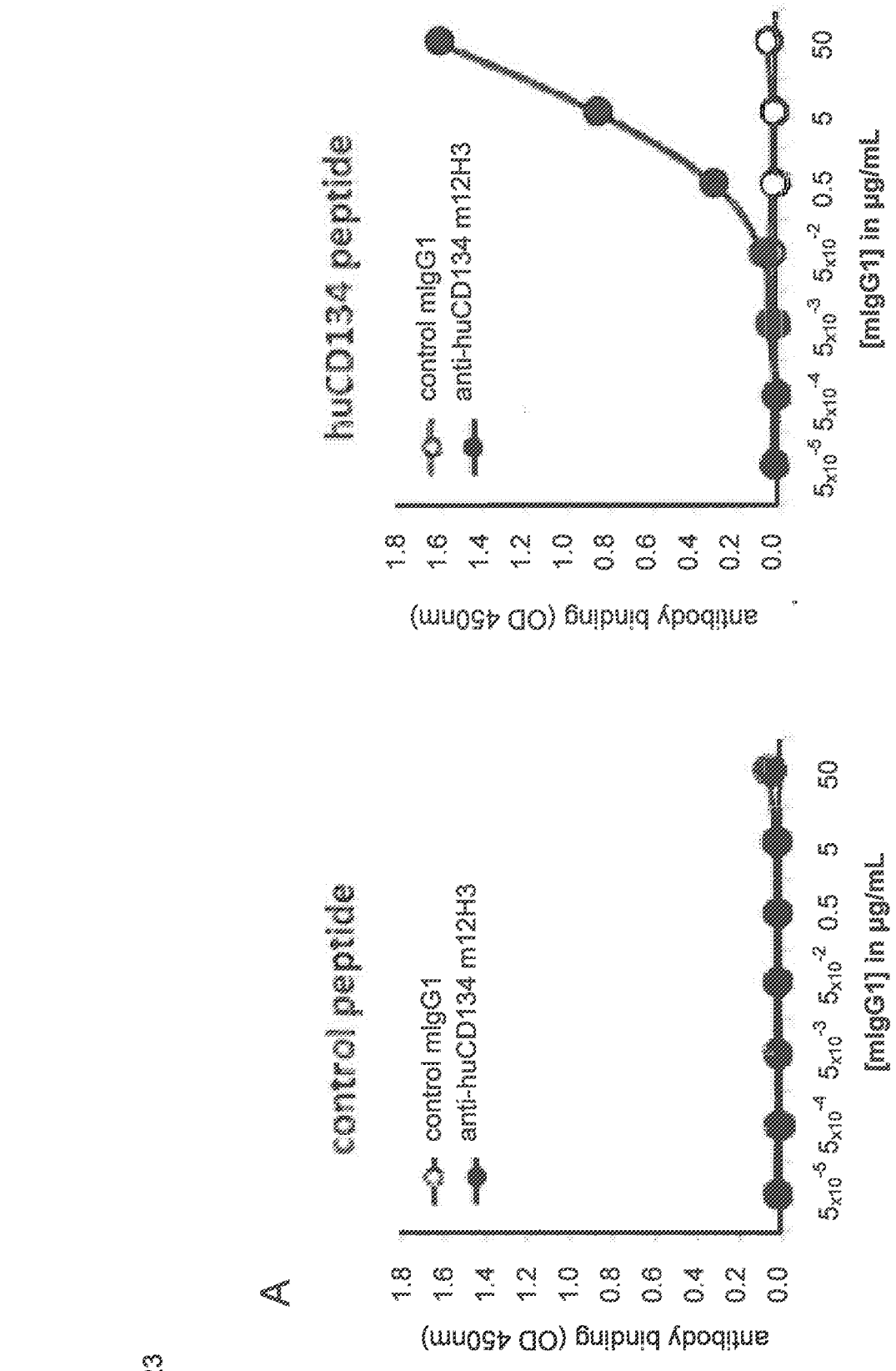

A
control peptide
huCD134 peptide
control mIgG1
anti-huCD134 m12H3
antibody binding (OD 450nm)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
5x10-5 5x10-4 5x10-3 5x10-2 0.5 5 50
[mIgG1] in µg/mL

Figure 23

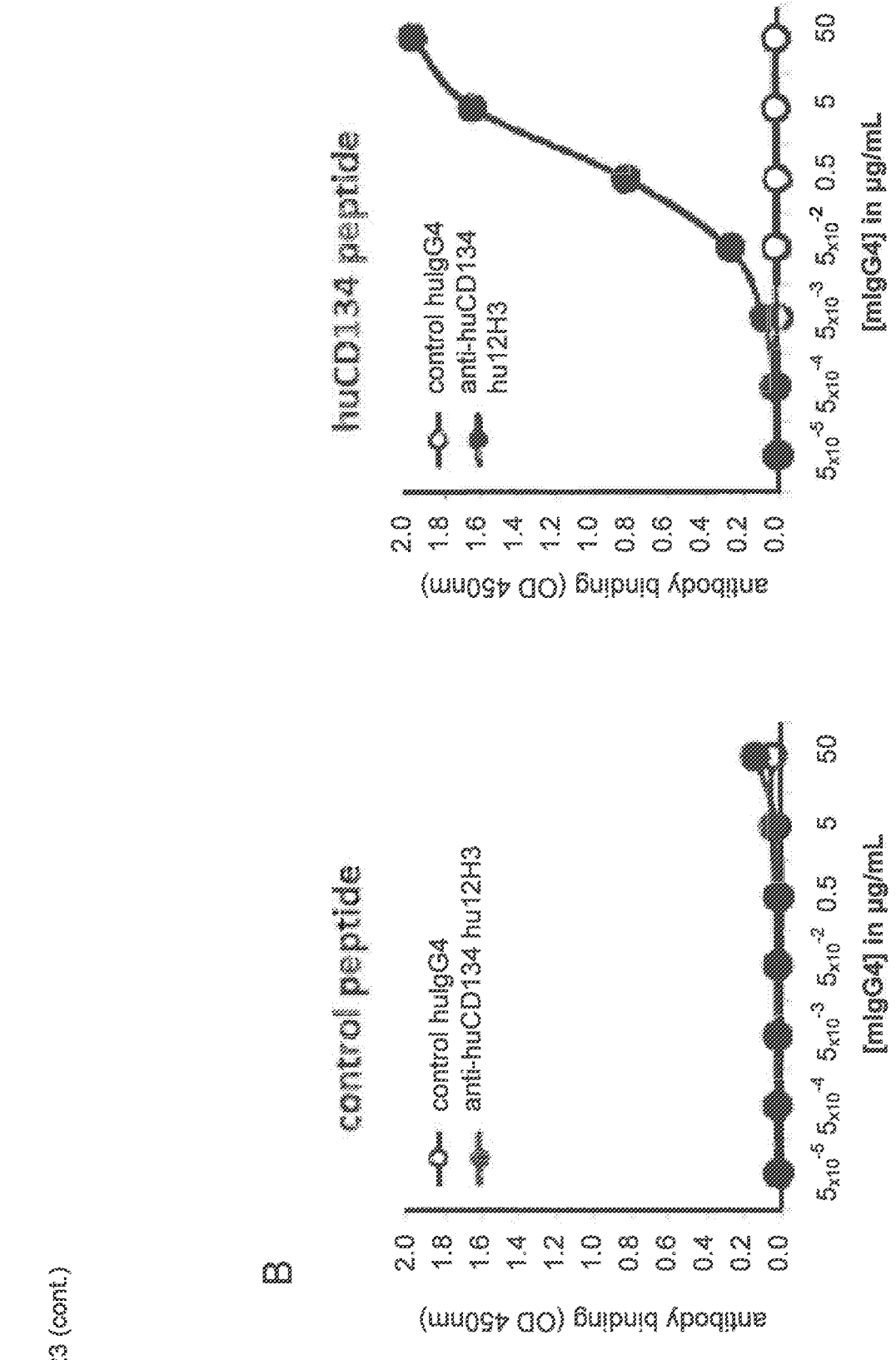


Figure 23 (cont.)

Figure 24

m20E5VH
hu20E5_h1
hu20H3_h2
hu20H3_h3
m20E5VH
hu20E5_h1
hu20H3_h2
hu20H3_h3
mu20E5VL
hu20E5_l1
hu20E5_l2
mu20E5VL
hu20E5_l1
hu20E5_l2
Hu 20E5_l1 = SEQ 62
Hu 20E5_l2 = SEQ 63
Hu 20E5_h1 = SEQ 64
Hu 20E5_h2 = SEQ 65
Hu 20E5_h3 = SEQ 66

Figure 25

mu12H3VH
hu12H3_h1
hu12H3_h2
hu12H3_h3
mu12H3VH
hu12H3_h1
hu12H3_h2
hu12H3_h3
mu12H3VL
hu12H3_l1
hu12H3_l2
mu12H3VL
hu12H3_l1
hu12H3_l2
Hu 12H3_l1 = SEQ 67
Hu 12H3_l2 = SEQ 68
Hu 12H3_h1 = SEQ 69
Hu 12H3_h2 = SEQ 70
Hu 12H3_h3 = SEQ 71

Figure 26

Humanized 20E5 antibody variable heavy chain (SEQ ID NO: 97)

QVQLV QSGAE VKKPG ASVKV SCKAS GYTFT SYVMH WVRQA PGQRL EWX$_1$GY INPYN DGTKY NEKFK GRX$_2$TX$_3$ TSDX$_4$S ASTAY MELSS LRSED TAVYY CANYY GSSLS MDYWG QGTLV TVSS;

wherein X_1 = I or M,
X_2 = A or V,
X_3 = L OR I, and
X_4 = K or T.

Humanized 20E5 antibody variable light chain (SEQ ID NO: 98)

DIQMT QSPSS LSASV GDRVT ITCRA SQDIS NYLNW YQQKP GKAX$_5$K LLIYY TSRLH SGVPS RFSGS GSGTD YTLTI SSLQP EDFAT YX$_6$CQQ GNTLP WTFGQ GTKVE IKR

wherein X_5 = V or P, and
X_6 = F or Y.

Figure 27

Humanized 12H3 antibody variable heavy chain (SEQ ID NO: 99)

QVQLV QSGAE VKKPG SSVKV SCKAS GYTFK DYTMH WVRQA PGQGL EWX$_7$GG IYPNN GGSTY NQNFK DRX$_8$TX$_9$ TX$_{10}$DKS TSTAY MELSS LRSED TAVYY CARMG YHGPH LDFDV WGQGT TVTVS S;

wherein X$_7$ = I or M,
X$_8$ = A or V,
X$_9$ = L OR I, and
X$_{10}$ = V or A.

Humanized 12H3 antibody variable light chain (SEQ ID NO: 100)

DIQMT QSPSS LSASV GDRVT ITCKA SQDVG AAVAW YQQKP GKAPK LLIYW ASTRH TGVPX$_{11}$ RFSGX$_{12}$ GSGTD FTLTI SSLQP EDFAT YYCQQ YINYP LTFGG GTKVE IKR

wherein X$_{11}$ = D or S, and
X$_{12}$ = G or S.

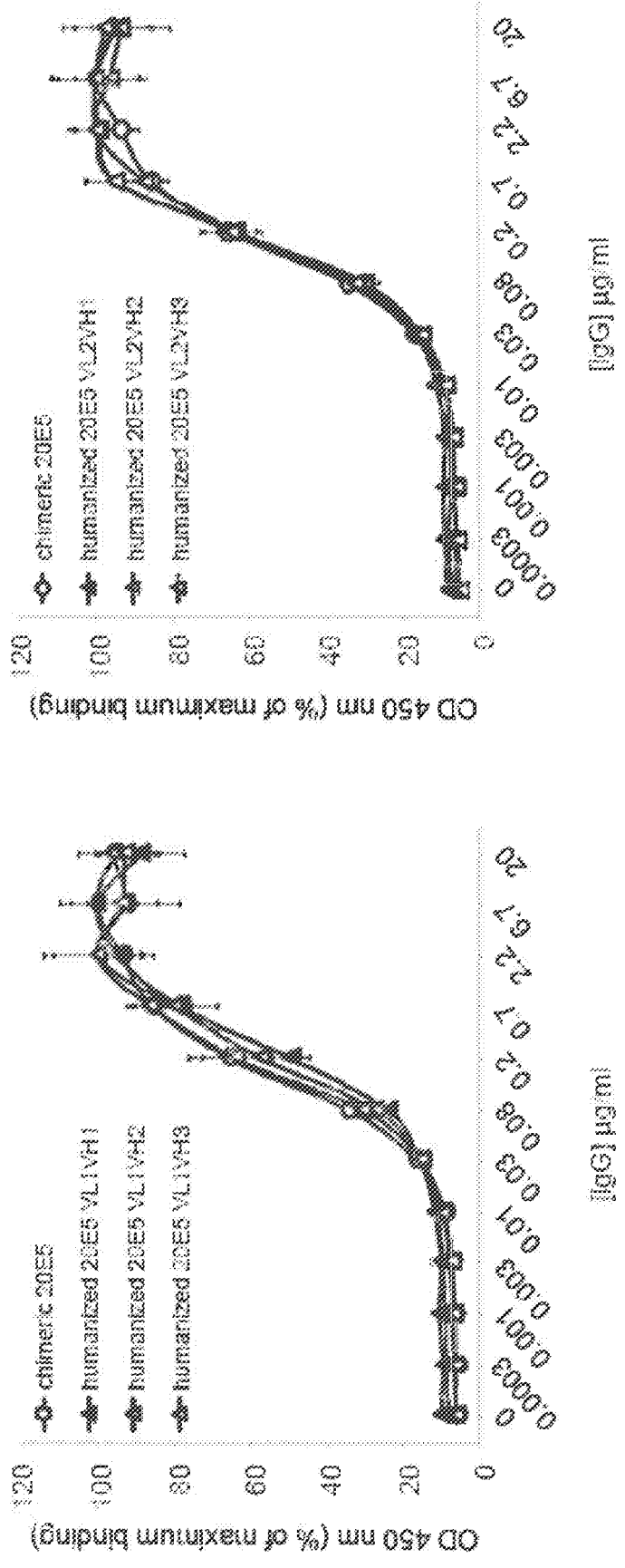

A
B
chimeric 20E5
humanized 20E5 VL1VH1
humanized 20E5 VL1VH2
humanized 20E5 VL1VH3
humanized 20E5 VL2VH1
humanized 20E5 VL2VH2
humanized 20E5 VL2VH3
OD 450 nm (% of maximum binding)
[IgG] µg/ml
0
20
40
60
80
100
120
0,0003
0,001
0,003
0,01
0,03
0,08
0,2
0,7
2,2
6,7
20

Figure 28

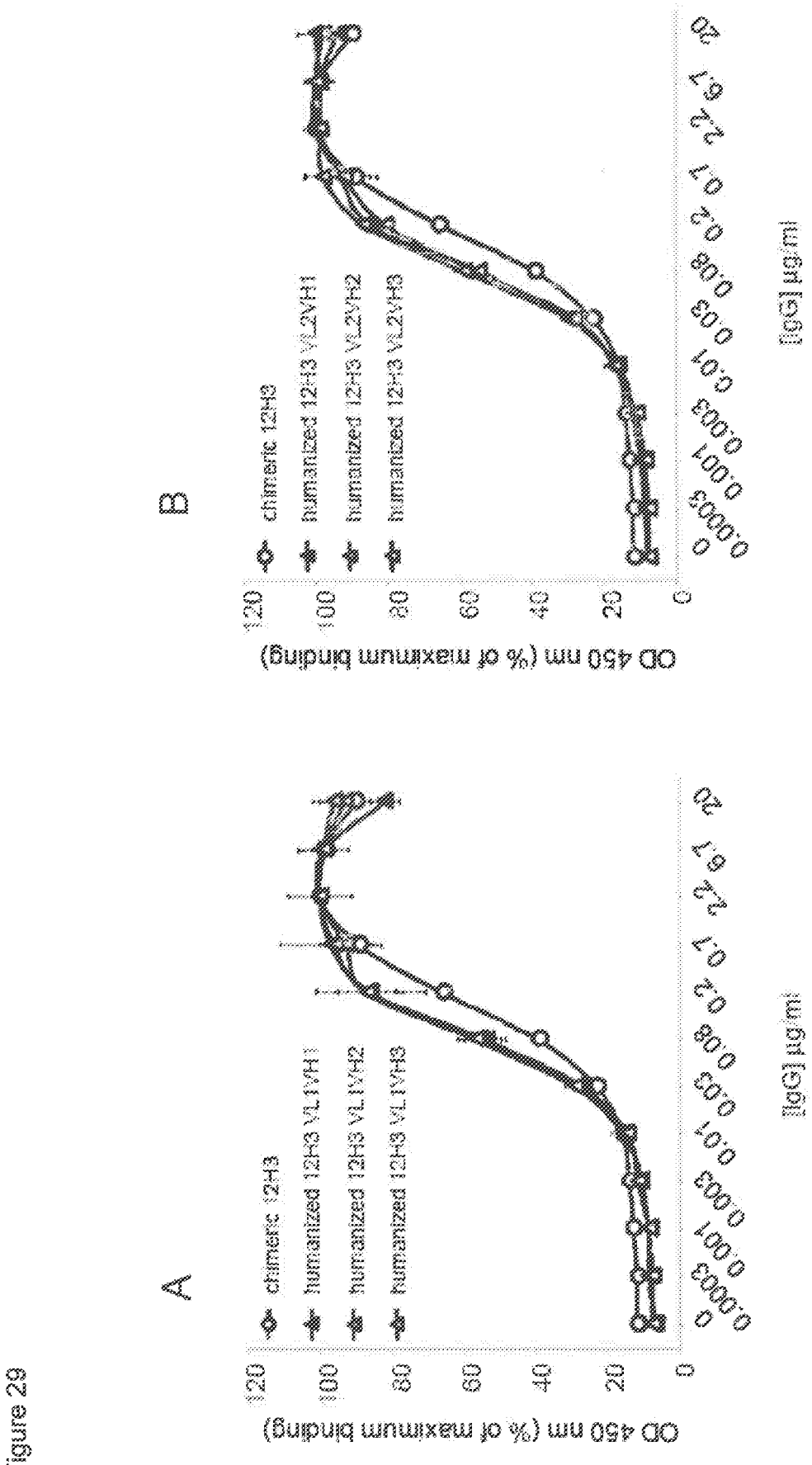

A
B
chimeric 12H3
humanized 12H3 VL1VH1
humanized 12H3 VL1VH2
humanized 12H3 VL1VH3
humanized 12H3 VL2VH1
humanized 12H3 VL2VH2
humanized 12H3 VL2VH3
OD 450 nm (% of maximum binding)
[IgG] µg/ml
0
0.0003
0.001
0.003
0.01
0.03
0.08
0.2
0.7
2.2
6.7
20
120
100
80
60
40
20
0

Figure 29

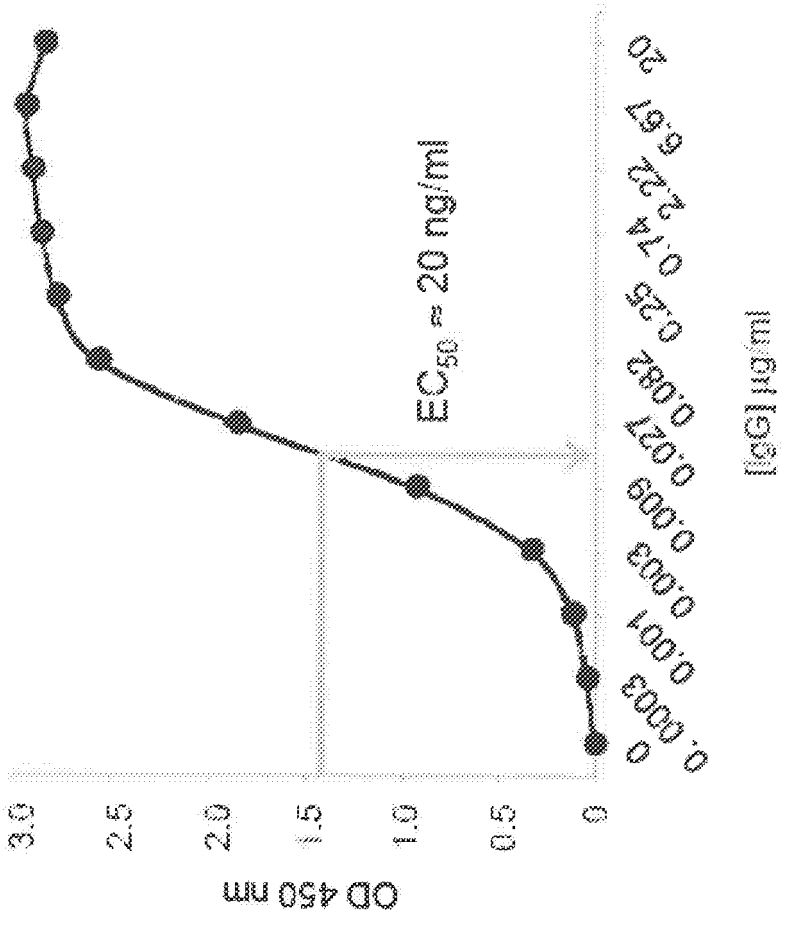
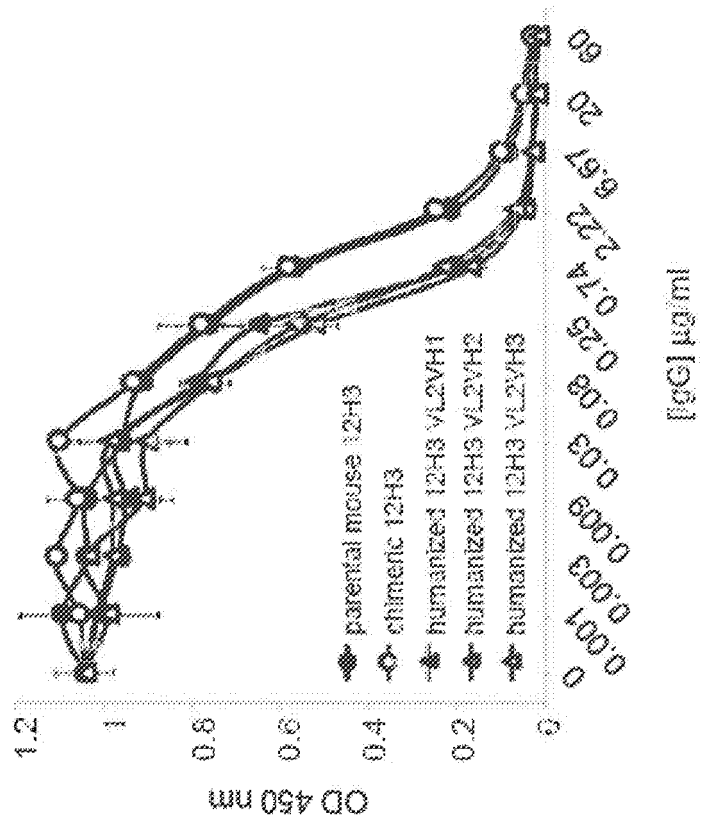

OD 450 nm
3.0
2.5
2.0
1.5
1.0
0.5
0
EC_{50} ≈ 20 ng/ml
0
0.0003
0.001
0.003
0.009
0.027
0.082
0.25
0.74
2.22
6.67
20
[IgG] µg/ml

Figure 30


B
OD 450 nm
1.2
1
0.8
0.6
0.4
0.2
0
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL2VH1
humanized 12H3 VL2VH3
humanized 12H3 VL2VH3
0
0.001
0.003
0.006
0.03
0.08
0.25
0.74
2.22
6.67
20
60
[IgG] µg/ml

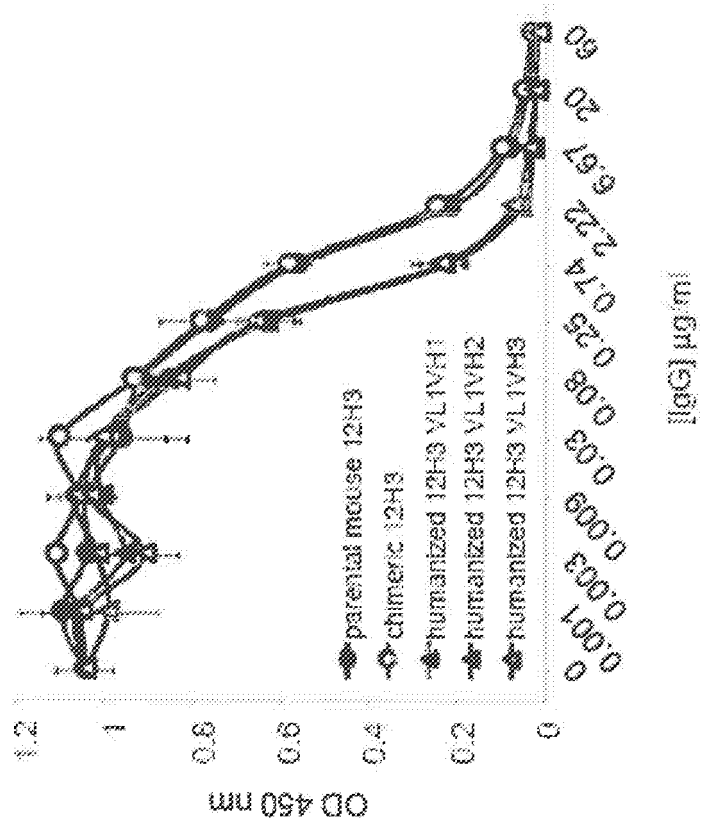

A
OD 450 nm
1.2
1
0.8
0.6
0.4
0.2
0
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL1VH1
humanized 12H3 VL1VH2
humanized 12H3 VL1VH3
0
0.001
0.003
0.006
0.03
0.08
0.25
0.74
2.22
6.67
20
60
[IgG] µg/ml

Figure 31

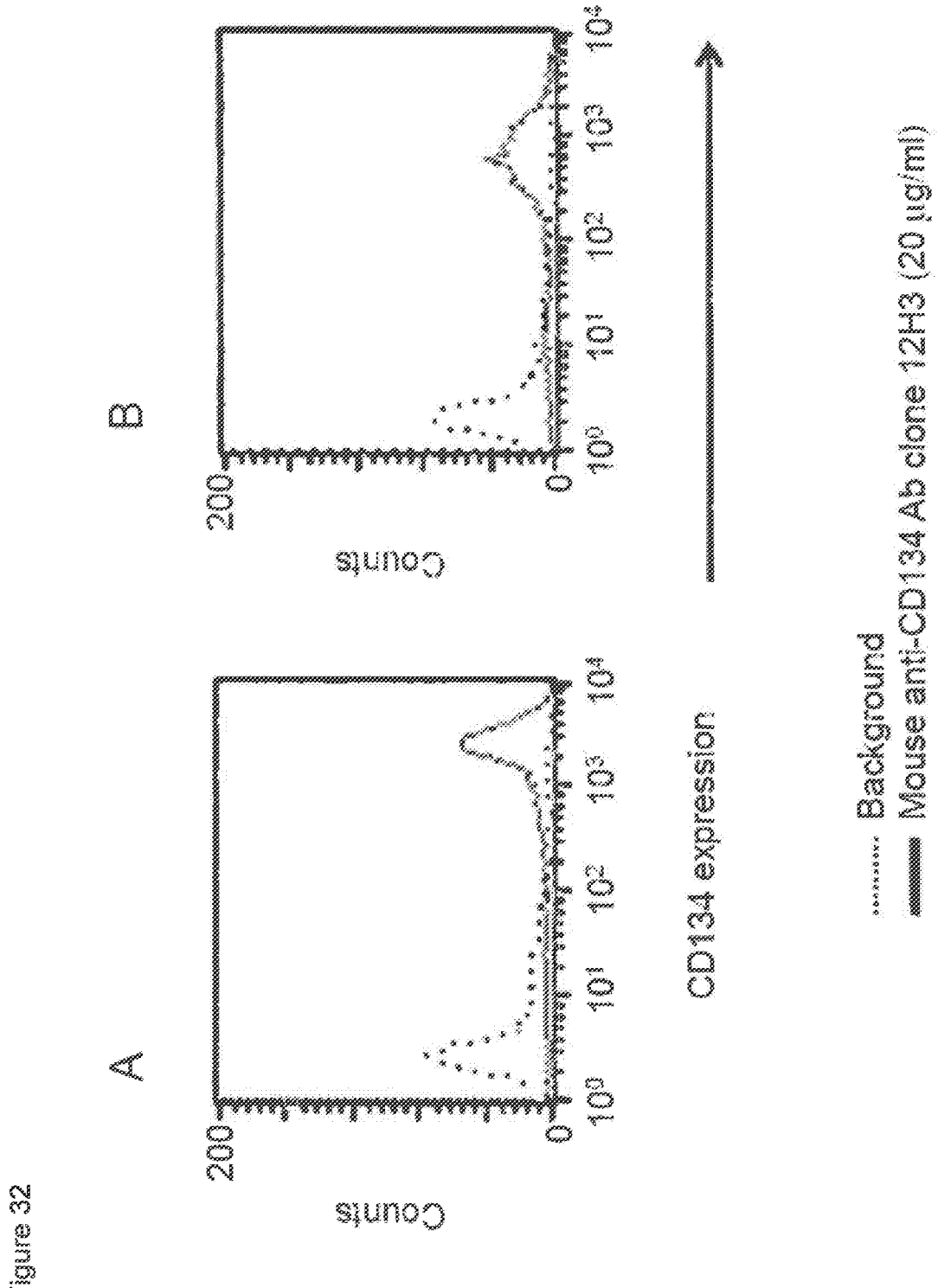

A
B
Counts
200
0
10^0
10^1
10^2
10^3
10^4
CD134 expression
Background
Mouse anti-CD134 Ab clone 12H3 (20 µg/ml)

Figure 32

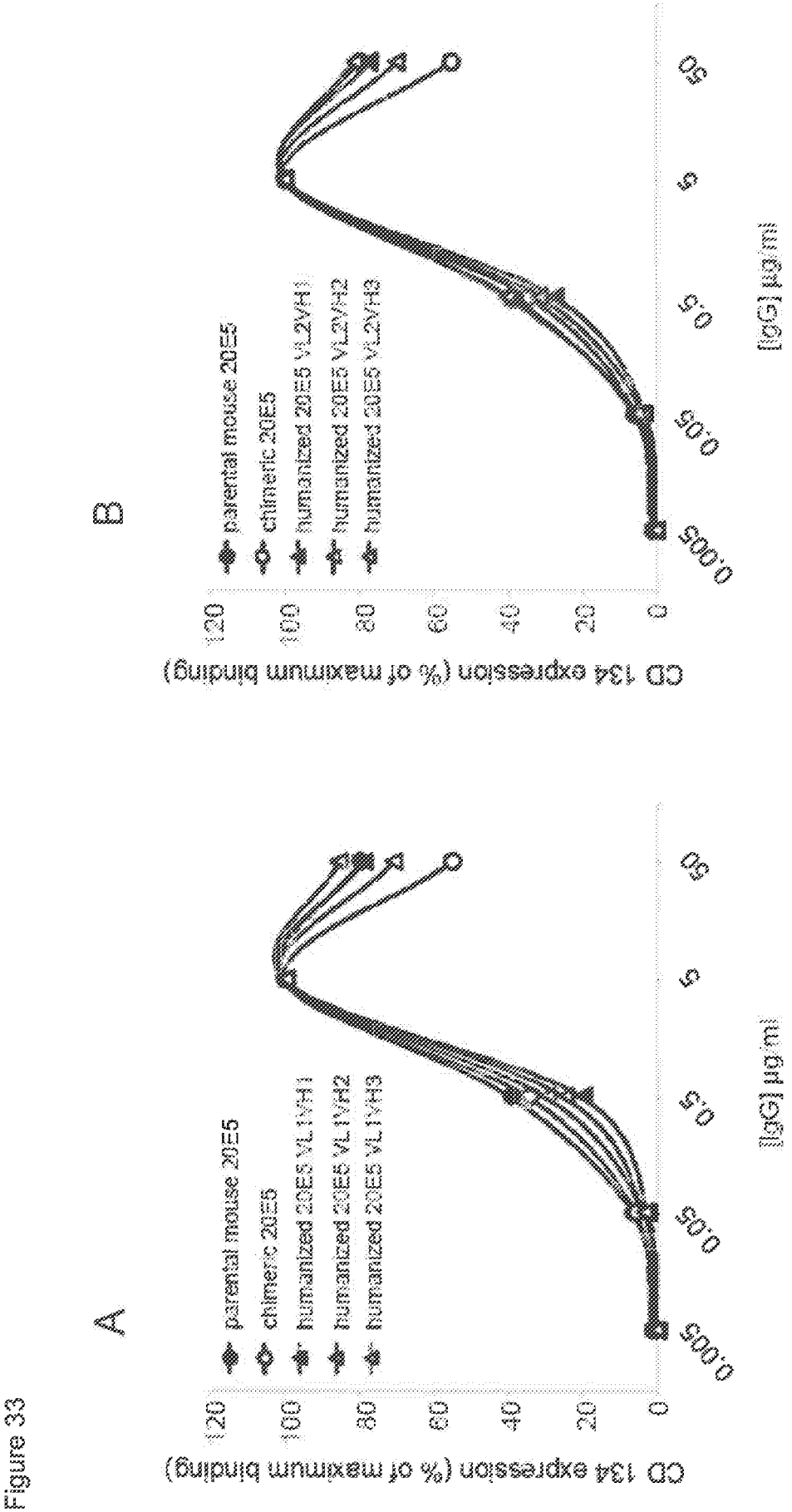

A
B
parental mouse 20E5
chimeric 20E5
humanized 20E5 VL1VH1
humanized 20E5 VL1VH2
humanized 20E5 VL1VH3
humanized 20E5 VL2VH1
humanized 20E5 VL2VH2
humanized 20E5 VL2VH3
CD 134 expression (% of maximum binding)
[IgG] µg/ml
0
20
40
60
80
100
120
0.005
0.05
0.5
5
50

Figure 33

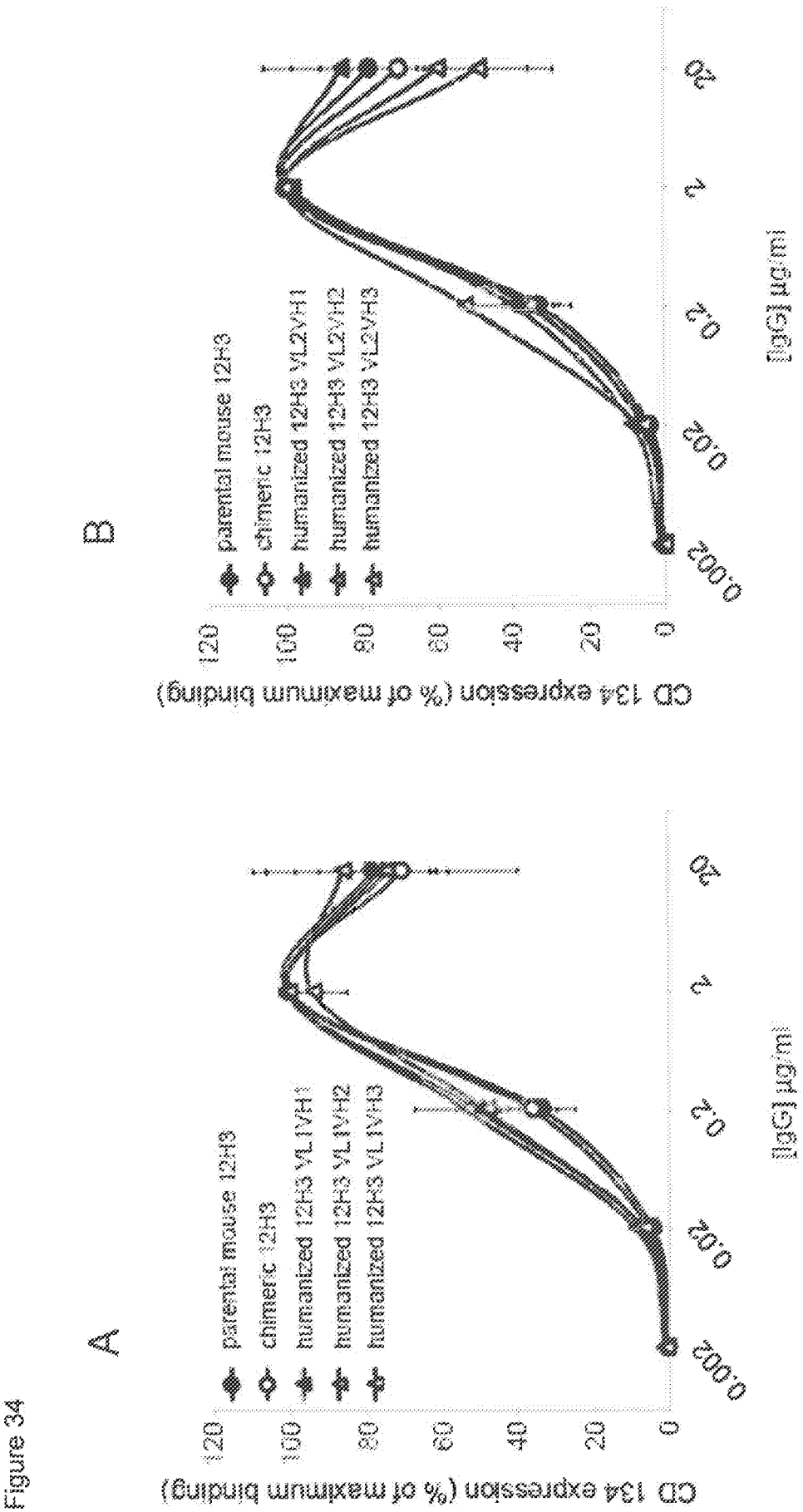
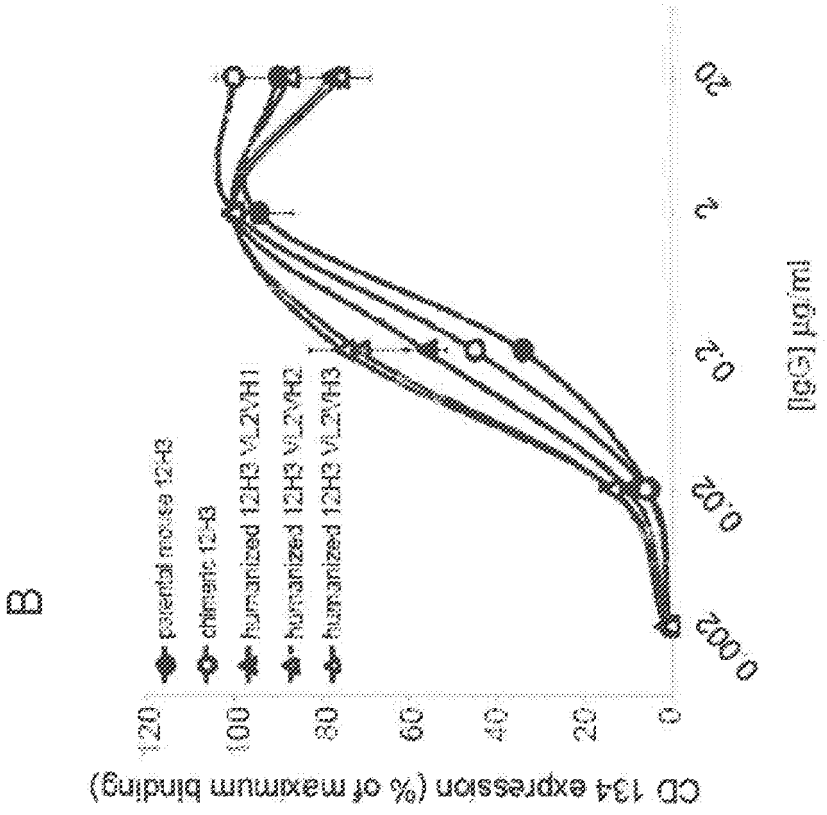

A
B
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL1VH1
humanized 12H3 VL1VH2
humanized 12H3 VL1VH3
humanized 12H3 VL2VH1
humanized 12H3 VL2VH2
humanized 12H3 VL2VH3
CD 134 expression (% of maximum binding)
[IgG] µg/ml
0
20
40
60
80
100
120
0,02
0,2
2
20
200

Figure 34


B
CD 134 expression (% of maximum binding)
120
100
80
60
40
20
0
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL2VH1
humanized 12H3 VL2VH2
humanized 12H3 VL2VH3
0,002
0,02
0,2
2
20
[IgG] µg/ml

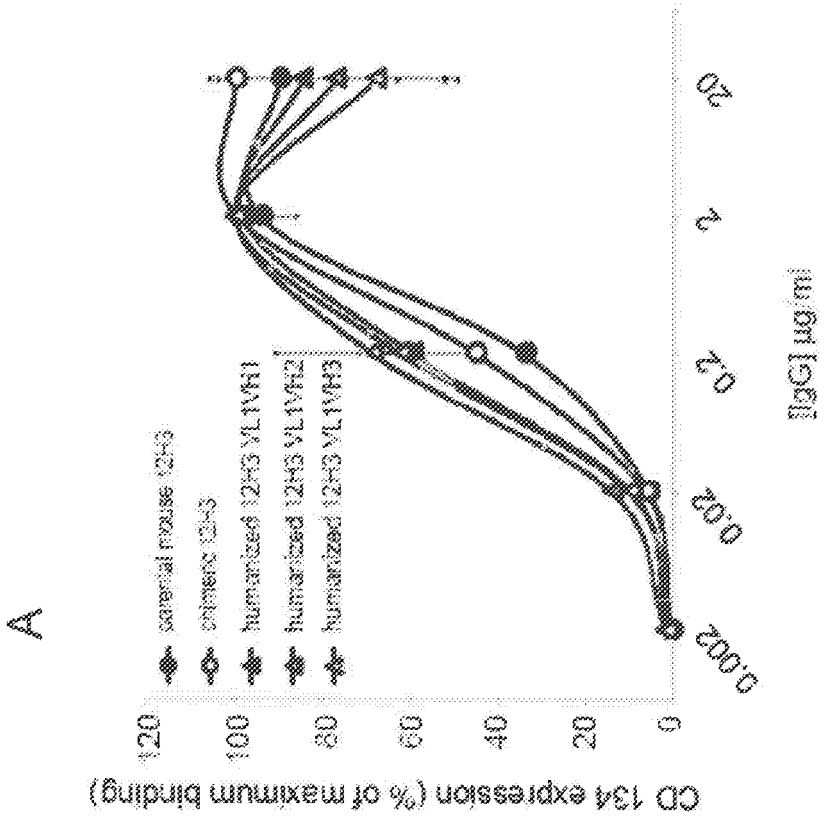

A
CD 134 expression (% of maximum binding)
120
100
80
60
40
20
0
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL1VH1
humanized 12H3 VL1VH2
humanized 12H3 VL1VH3
0,002
0,02
0,2
2
20
[IgG] µg/ml

Figure 35

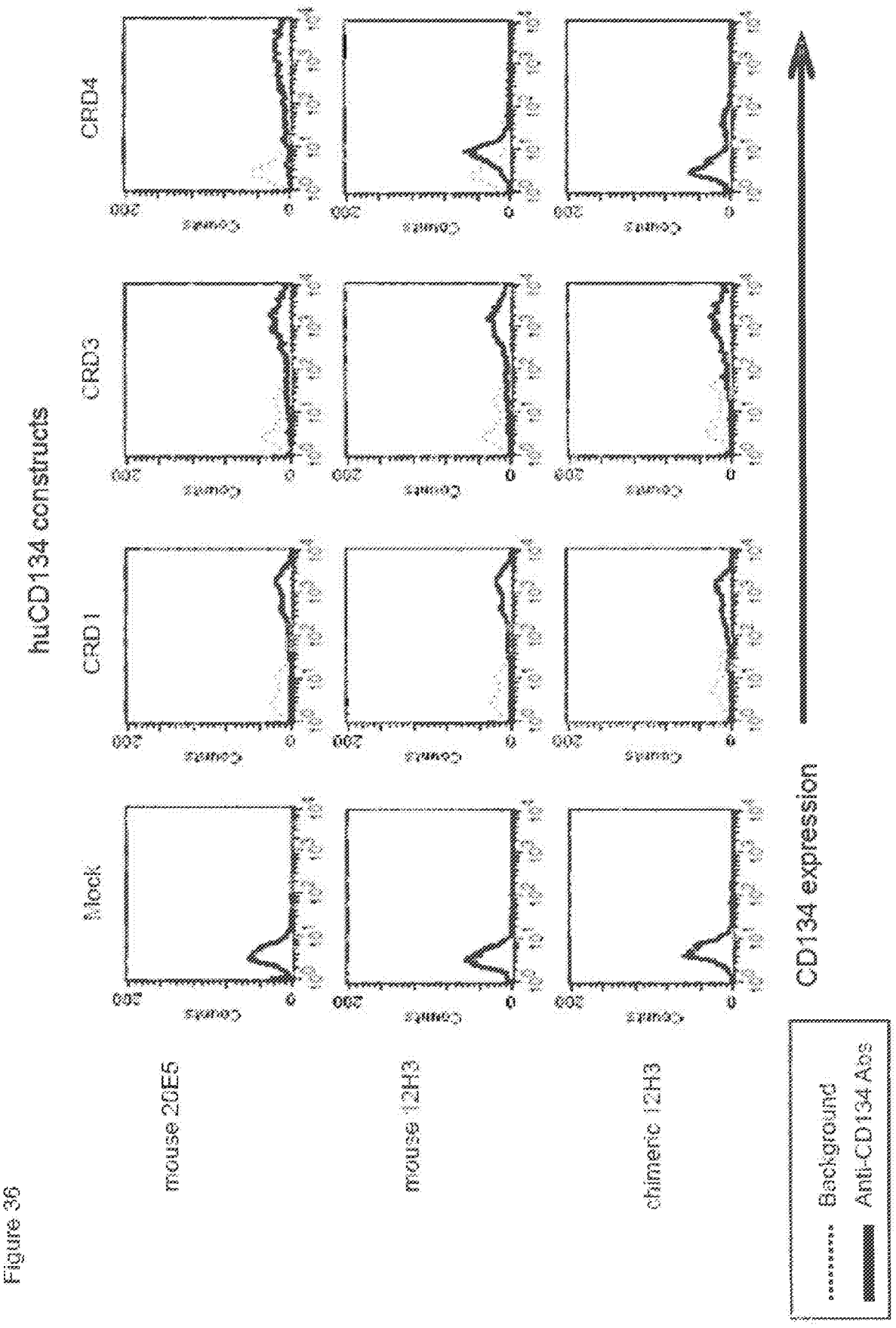

huCD134 constructs
Mock
CRD1
CRD3
CRD4
mouse 20E5
mouse 12H3
chimeric 12H3
Counts
CD134 expression
Background
Anti-CD134 Abs

Figure 36

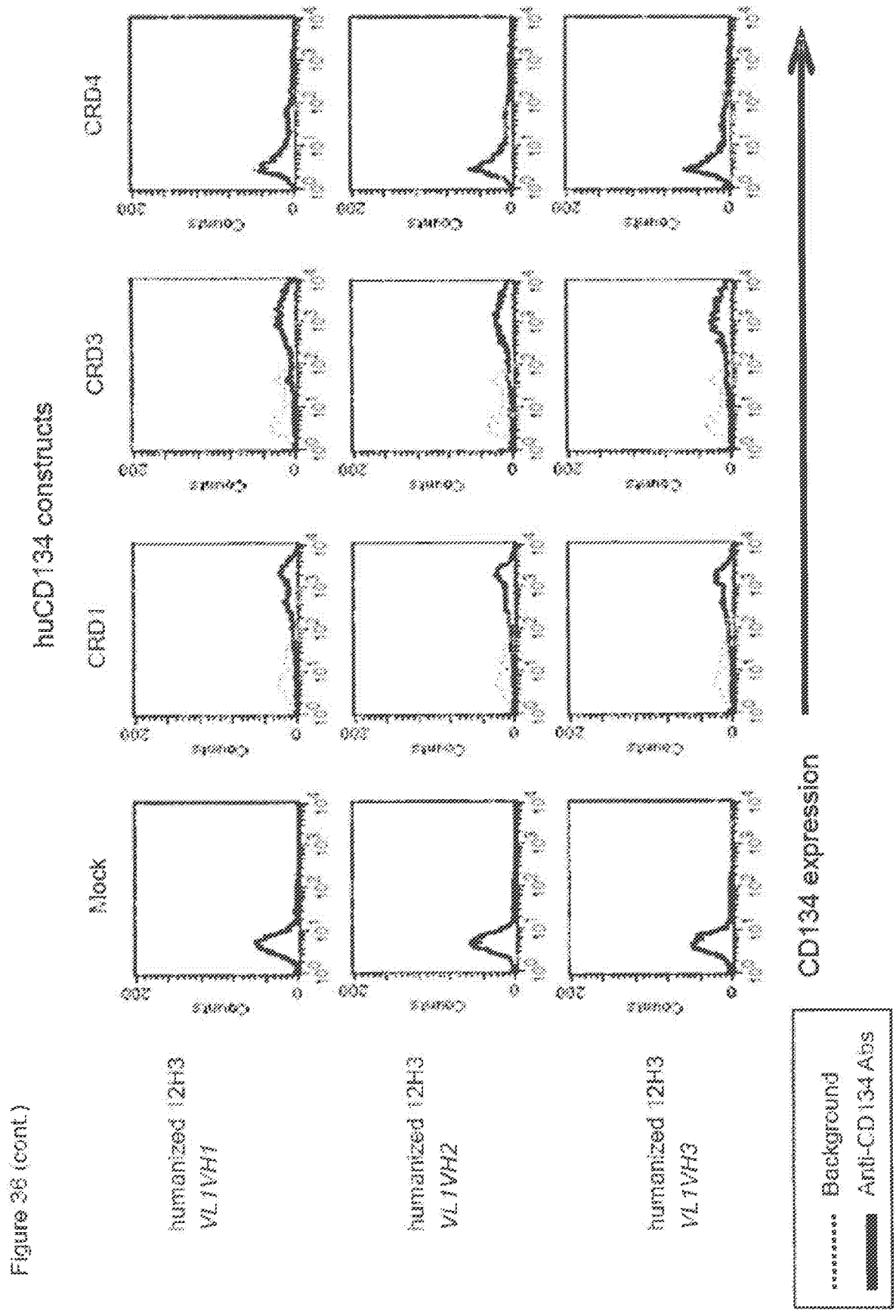


Figure 38 (cont.)

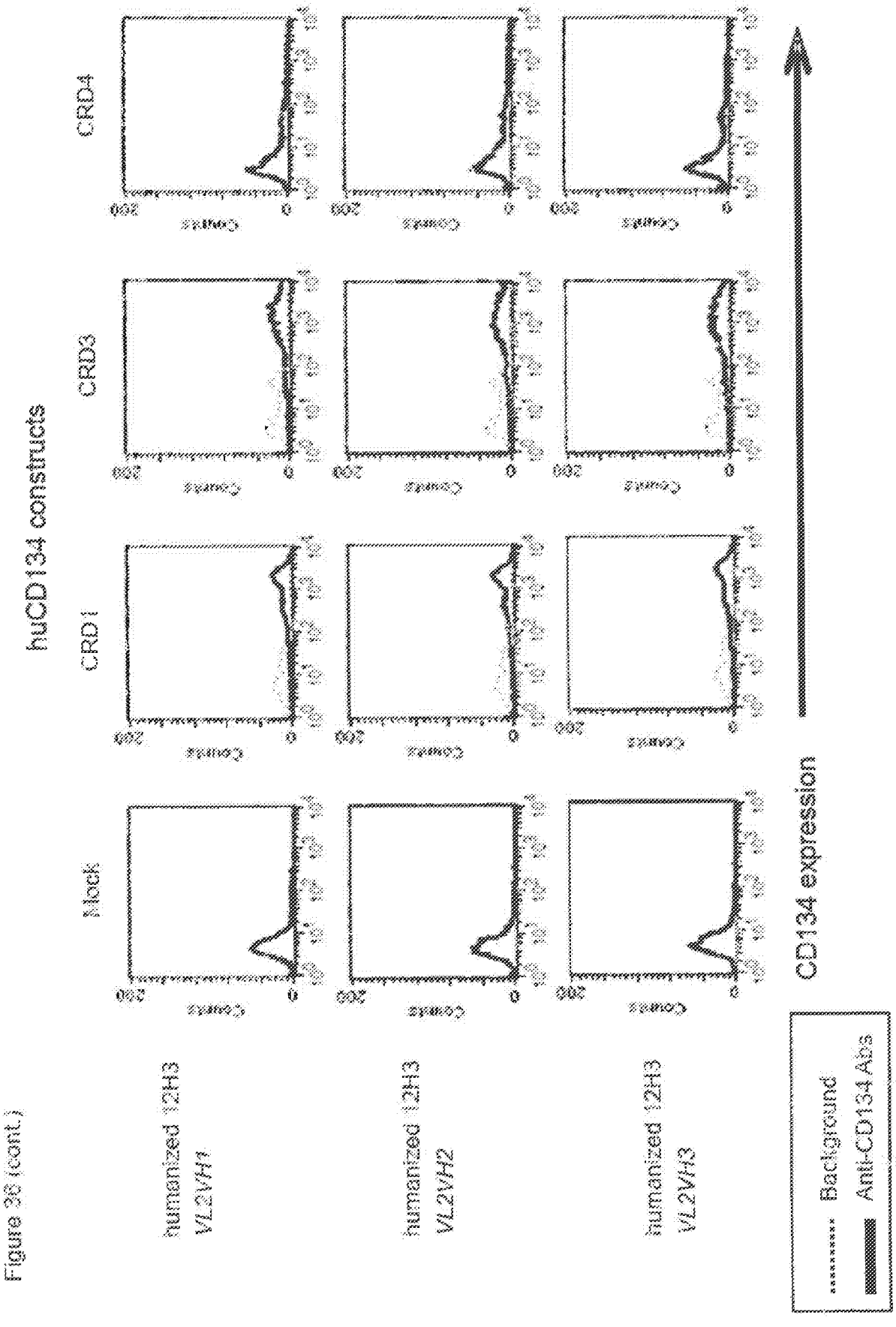


Figure 36 (cont.)

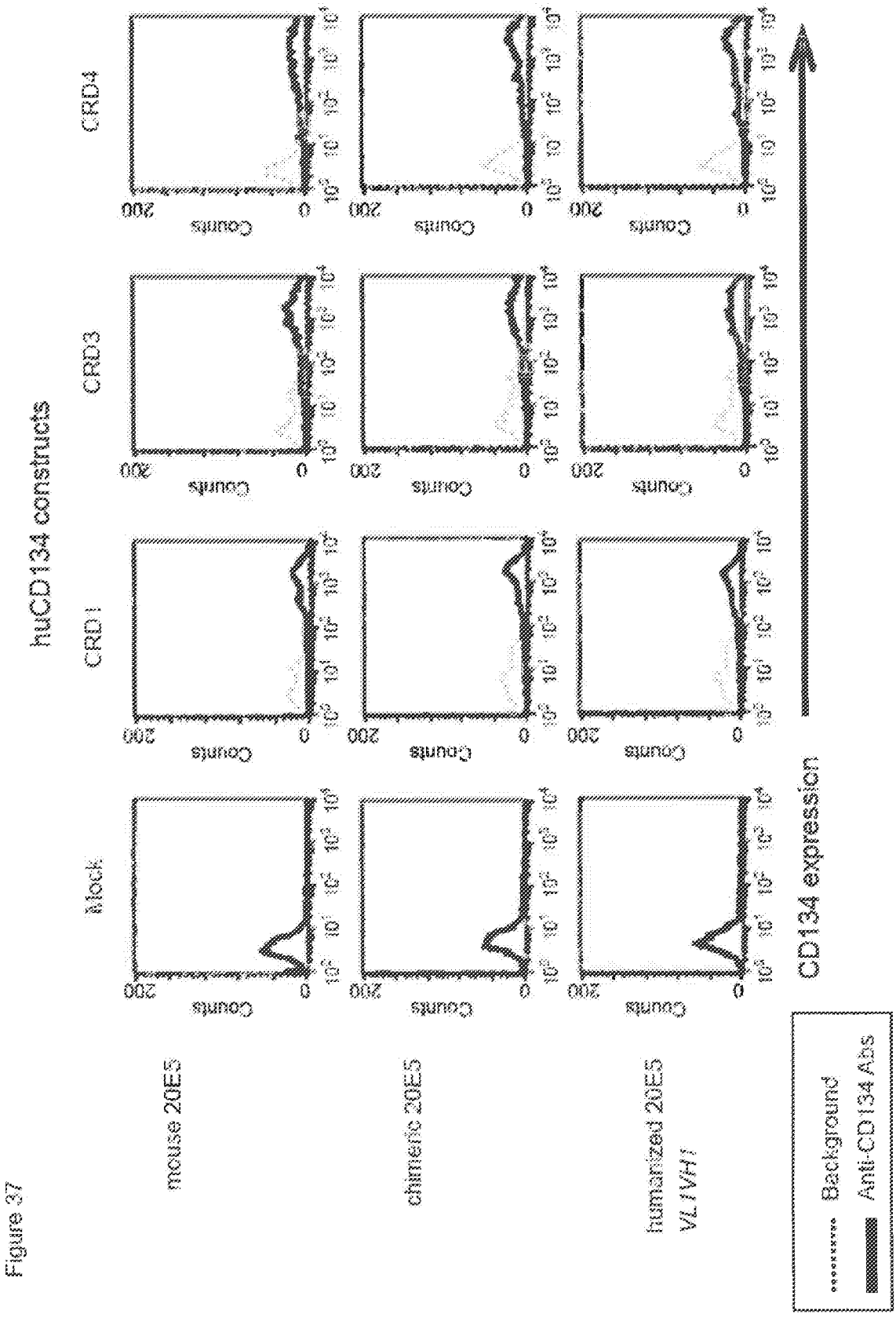

huCD134 constructs
Mock
CRD1
CRD3
CRD4
mouse 20E5
chimeric 20E5
humanized 20E5
VL1VH1
Counts
CD134 expression
Background
Anti-CD134 Abs

Figure 37

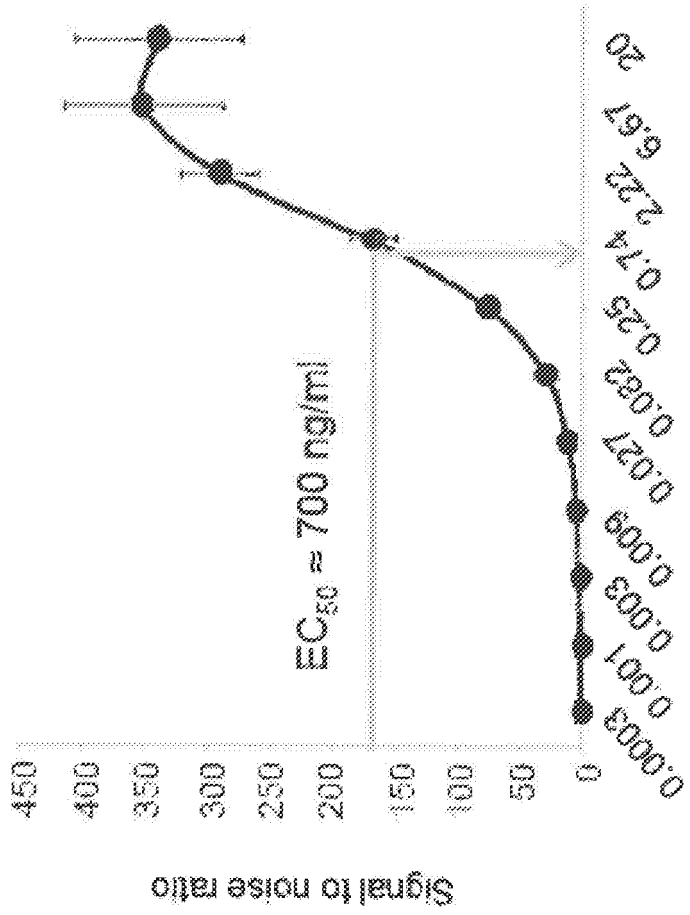
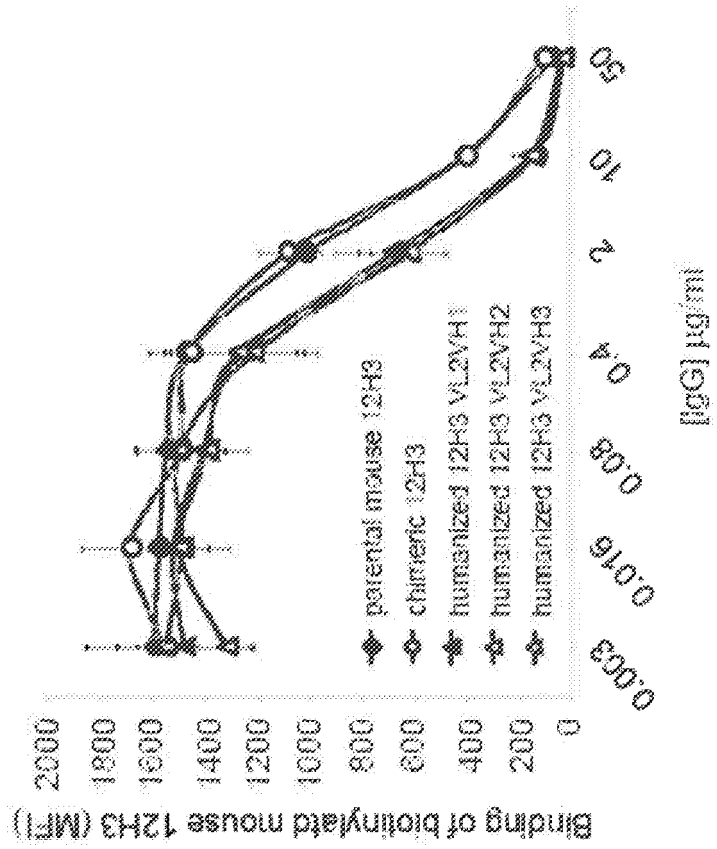

Signal to noise ratio
450
400
350
300
250
200
150
100
50
0
EC_{50} ≈ 700 ng/ml
0.0003
0.001
0.003
0.009
0.027
0.082
0.25
0.74
2.22
6.67
20
[IgG] µg/ml

Figure 38


B
Binding of biotinylated mouse 12H3 (MFI)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL2VH1
humanized 12H3 VL2VH2
humanized 12H3 VL2VH3
0,003
0,016
0,08
0,4
2
10
50
[IgG] µg/ml

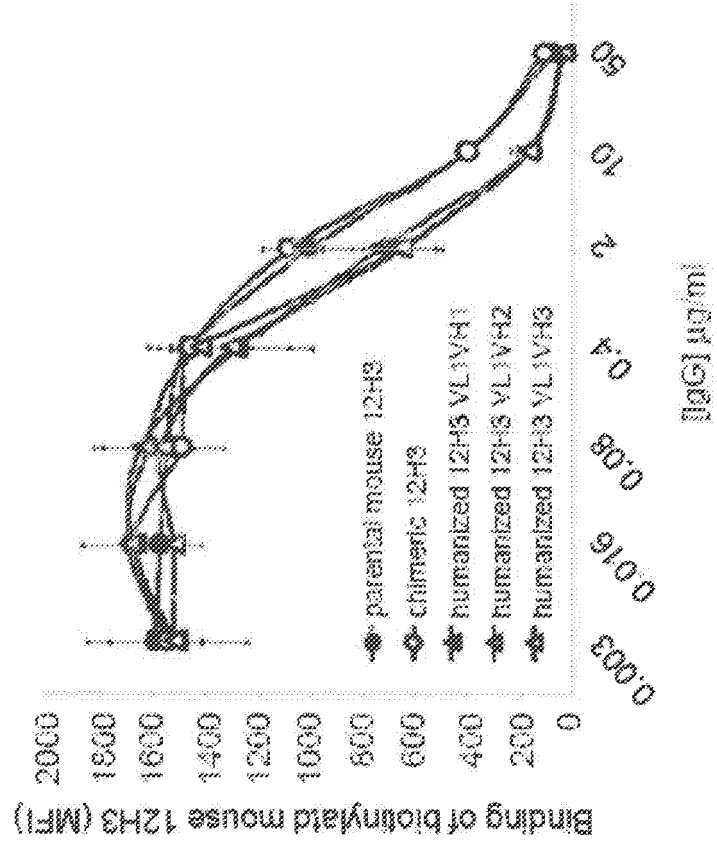

A
Binding of biotinylated mouse 12H3 (MFI)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
parental mouse 12H3
chimeric 12H3
humanized 12H3 VL1VH1
humanized 12H3 VL1VH2
humanized 12H3 VL1VH3
0,003
0,016
0,08
0,4
2
10
50
[IgG] µg/ml

Figure 39

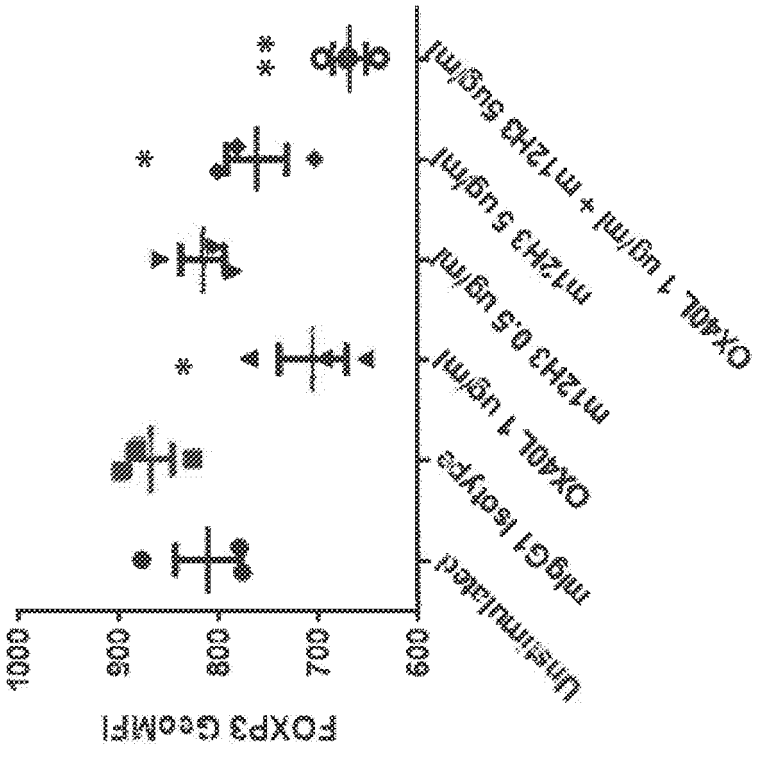

FOXP3
FOXP3 GeoMFI
1000
900
800
700
600
Unstimulated
mIgG1 isotype
OX40L 1 ug/ml
mI2H3 0.5 ug/ml
mI2H3 5 ug/ml
OX40L 1 ug/ml + mI2H3 5ug/ml
* p<0.05 compared to Isotype
** p<0.01 compared to Isotype

Figure 40

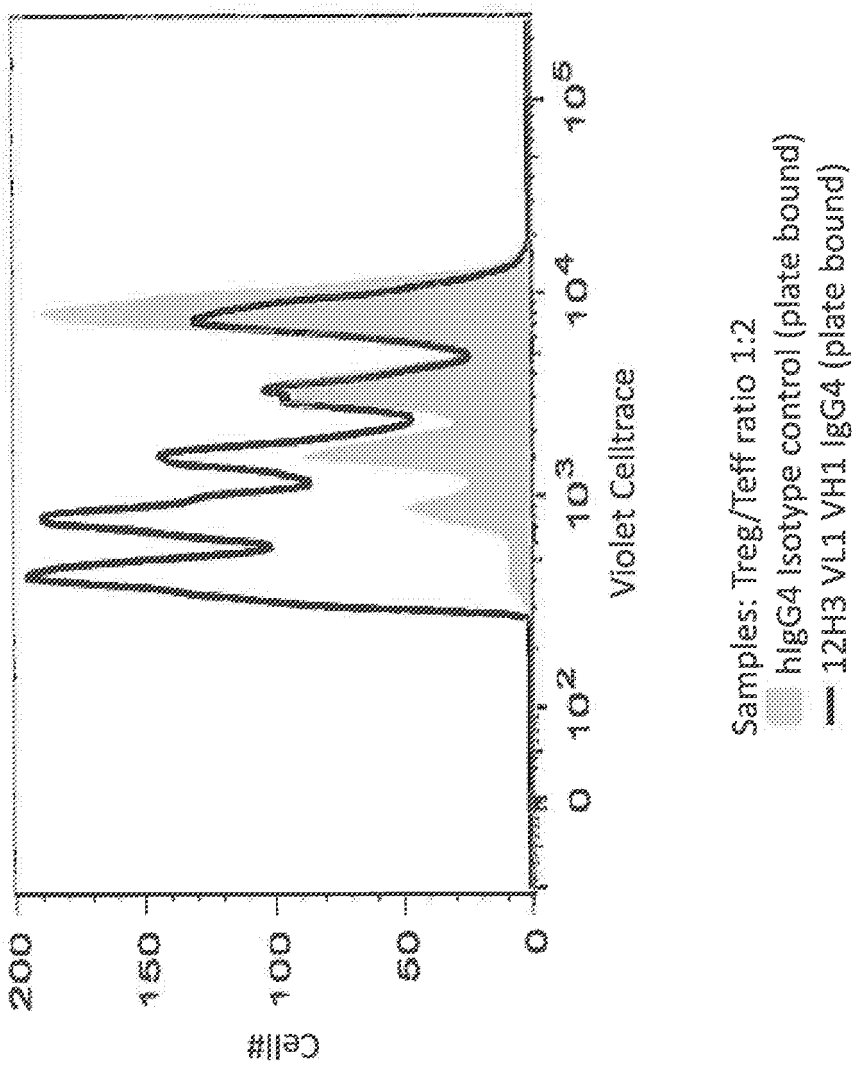

Cell#
200
150
100
50
0
0
10^2
10^3
10^4
10^5
Violet Celltrace
Samples: Treg/Teff ratio 1:2
hIgG4 Isotype control (plate bound)
12H3 VL1 VH1 IgG4 (plate bound)

Figure 41

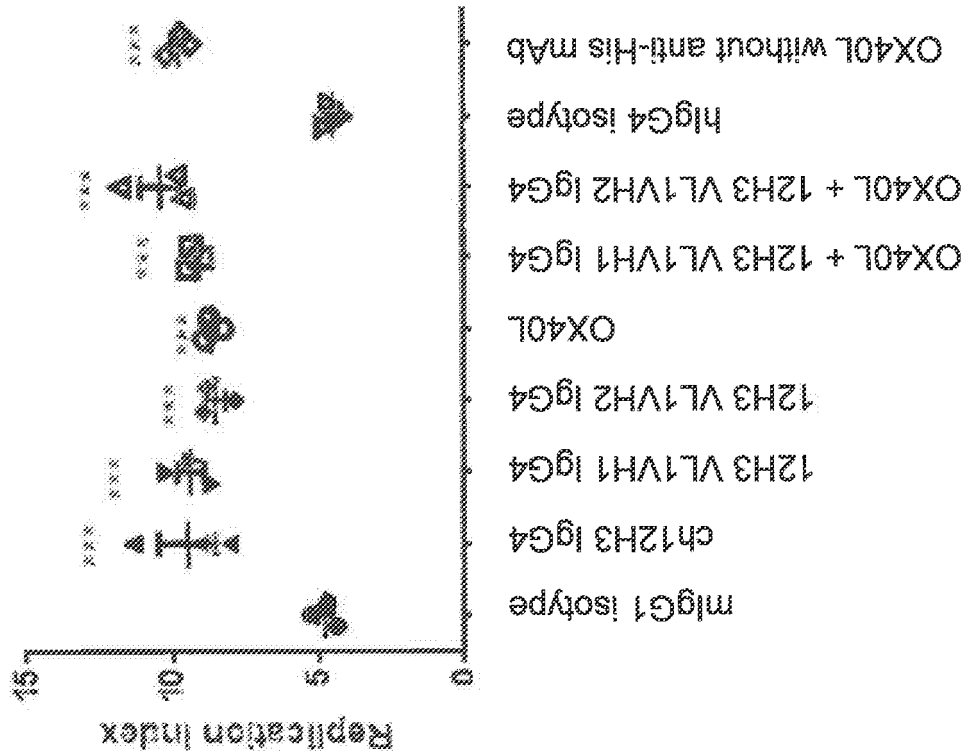

7015 0-1
Replication Index
0
5
10
15
mIgG1 isotype
ch12H3 IgG4
12H3 VL1VH1 IgG4
12H3 VL1VH2 IgG4
OX40L
OX40L + 12H3 VL1VH1 IgG4
OX40L + 12H3 VL1VH2 IgG4
hIgG4 isotype
OX40L without anti-His mAb

Figure 42A.

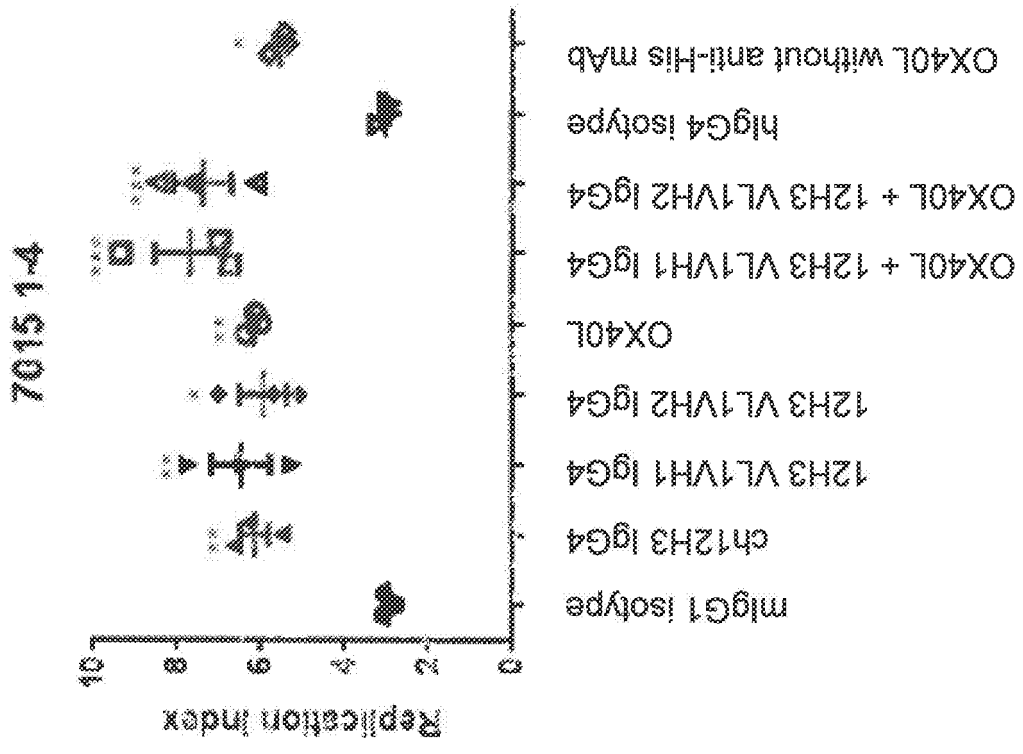

7015 14
Replication index
0
2
4
6
8
10
mIgG1 isotype
ch12H3 IgG4
12H3 VL1VH1 IgG4
12H3 VL1VH2 IgG4
OX40L
OX40L + 12H3 VL1VH1 IgG4
OX40L + 12H3 VL1VH2 IgG4
hIgG4 isotype
OX40L without anti-His mAb

Figure 42B.

Figure 43

```
20E5_VH1_64              QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNDGTKY
20E5_VH2_65              QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH3_66              QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH1_D56G_101        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNGGTKY
20E5_VH2_D56G_102        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNGGTKY
20E5_VH3_D56G_103        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNGGTKY
20E5_VH1_D56A_104        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNAGTKY
20E5_VH2_D56A_105        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNAGTKY
20E5_VH3_D56A_106        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNAGTKY
20E5_VH1_D56S_107        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNSGTKY
20E5_VH2_D56S_108        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNSGTKY
20E5_VH3_D56S_109        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNSGTKY
20E5_VH1_D56E_110        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNEGTKY
20E5_VH2_D56E_111        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNEGTKY
20E5_VH3_D56E_112        QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNEGTKY
20E5_VH1_M106L_113       QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNDGTKY
20E5_VH2_M106L_114       QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH3_M106L_115       QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH1_M106I_116       QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNDGTKY
20E5_VH2_M106I_117       QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH3_M106I_118       QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH1_V11L_149        QVQLVQSGAELKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNDGTKY
20E5_VH2_V11L_150        QVQLVQSGAELKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
20E5_VH3_V11L_151        QVQLVQSGAELKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY
                         **********:**************************************:******* ****
```

Figure 43 (cont.)

```
20E5_VH1_64              NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH2_65              NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH3_66              NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH1_D56G_101        NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH2_D56G_102        NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH3_D56G_103        NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH1_D56A_104        NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH2_D56A_105        NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH3_D56A_106        NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH1_D56S_107        NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH2_D56S_108        NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH3_D56S_109        NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH1_D56E_110        NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH2_D56E_111        NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH3_D56E_112        NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH1_M106L_113       NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSLDYWGQGTLVTVSS
20E5_VH2_M106L_114       NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSLDYWGQGTLVTVSS
20E5_VH3_M106L_115       NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSLDYWGQGTLVTVSS
20E5_VH1_M106I_116       NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSIDYWGQGTLVTVSS
20E5_VH2_M106I_117       NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSIDYWGQGTLVTVSS
20E5_VH3_M106I_118       NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSIDYWGQGTLVTVSS
20E5_VH1_V11L_149        NEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH2_V11L_150        NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
20E5_VH3_V11L_151        NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS
                         *******.*:***.********************************:**********
```

Figure 44.

```
12H3_VH1_69          QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNNGGSTY
12H3_VH2_70          QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH3_71          QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH1_N55Q_119    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNQGGSTY
12H3_VH2_N55Q_120    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNQGGSTY
12H3_VH3_N55Q_121    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNQGGSTY
12H3_VH1_N55A_122    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNAGGSTY
12H3_VH2_N55A_123    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNAGGSTY
12H3_VH3_N55A_124    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNAGGSTY
12H3_VH1_N55E_125    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNEGGSTY
12H3_VH2_N55E_126    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNEGGSTY
12H3_VH3_N55E_127    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNEGGSTY
12H3_VH1_M99L_128    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNNGGSTY
12H3_VH2_M99L_129    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH3_M99L_130    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH1_M99I_131    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNNGGSTY
12H3_VH2_M99I_132    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH3_M99I_133    QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH1_V11L_146    QVQLVQSGAELKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNNGGSTY
12H3_VH2_V11L_147    QVQLVQSGAELKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
12H3_VH3_V11L_148    QVQLVQSGAELKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY
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Figure 44 (Cont.)

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12H3_VH1_69          NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_70          NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_71          NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH1_N55Q_119    NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_N55Q_120    NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_N55Q_121    NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH1_N55A_122    NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_N55A_123    NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_N55A_124    NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH1_N55E_125    NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_N55E_126    NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_N55E_127    NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH1_M99L_128    NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARLGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_M99L_129    NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARLGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_M99L_130    NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARLGYHGPHLDFDVWGQGTTVTVSS
12H3_VH1_M99I_131    NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARIGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_M99I_132    NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARIGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_M99I_133    NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARIGYHGPHLDFDVWGQGTTVTVSS
12H3_VH1_V11L_146    NQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH2_V11L_147    NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
12H3_VH3_V11L_148    NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVSS
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