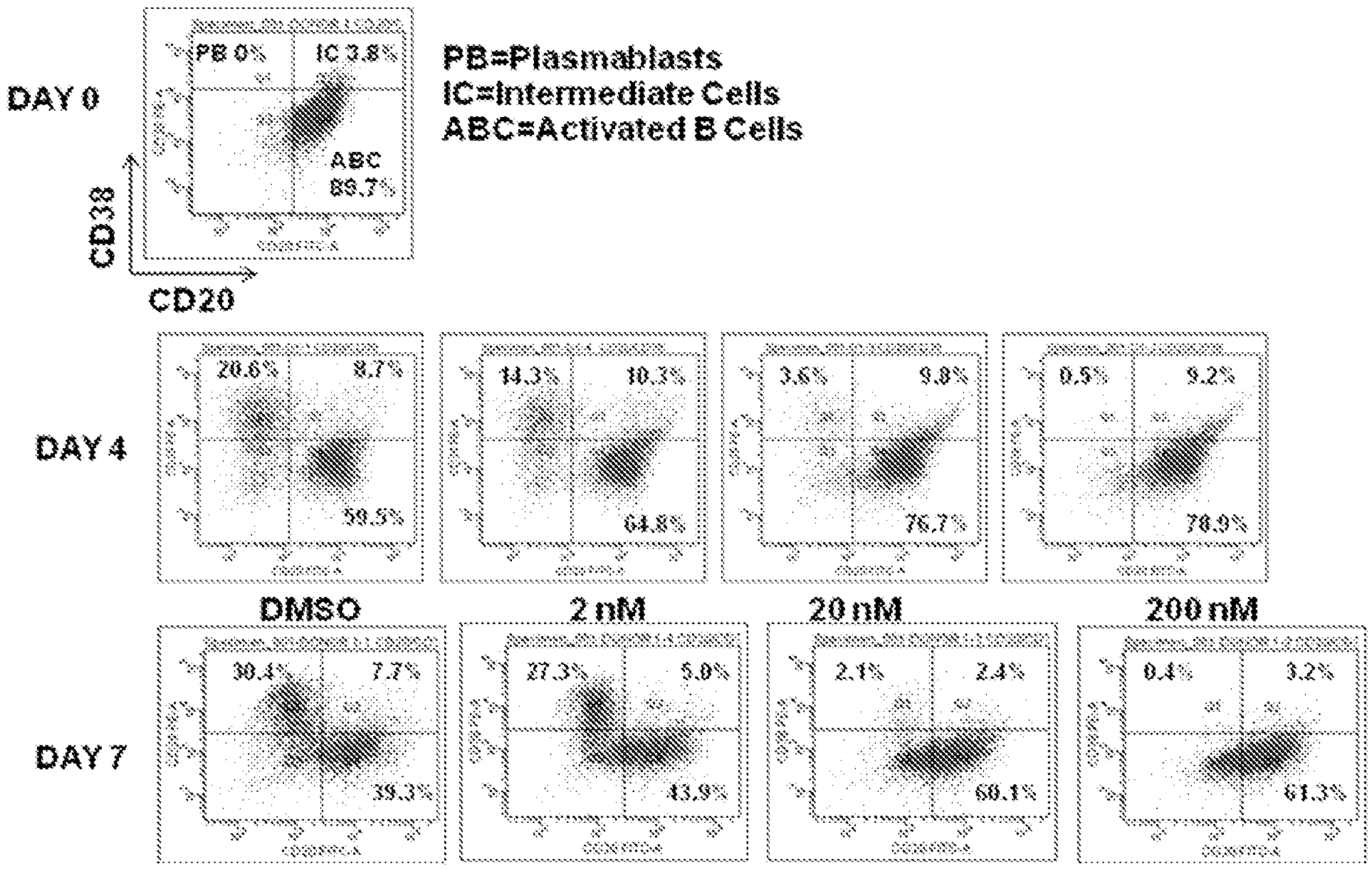
FIG. 1


DAY 0
PB 0%
IC 3.8%
ABC 89.7%
CD38
CD20
PB=Plasmablasts
IC=Intermediate Cells
ABC=Activated B Cells
DAY 4
20.6%
8.7%
59.5%
14.3%
10.3%
64.8%
3.6%
9.8%
76.7%
0.5%
9.2%
78.9%
DAY 7
DMSO
30.4%
7.7%
39.3%
2 nM
27.3%
5.0%
43.9%
20 nM
2.1%
2.4%
60.1%
200 nM
0.4%
3.2%
61.3%

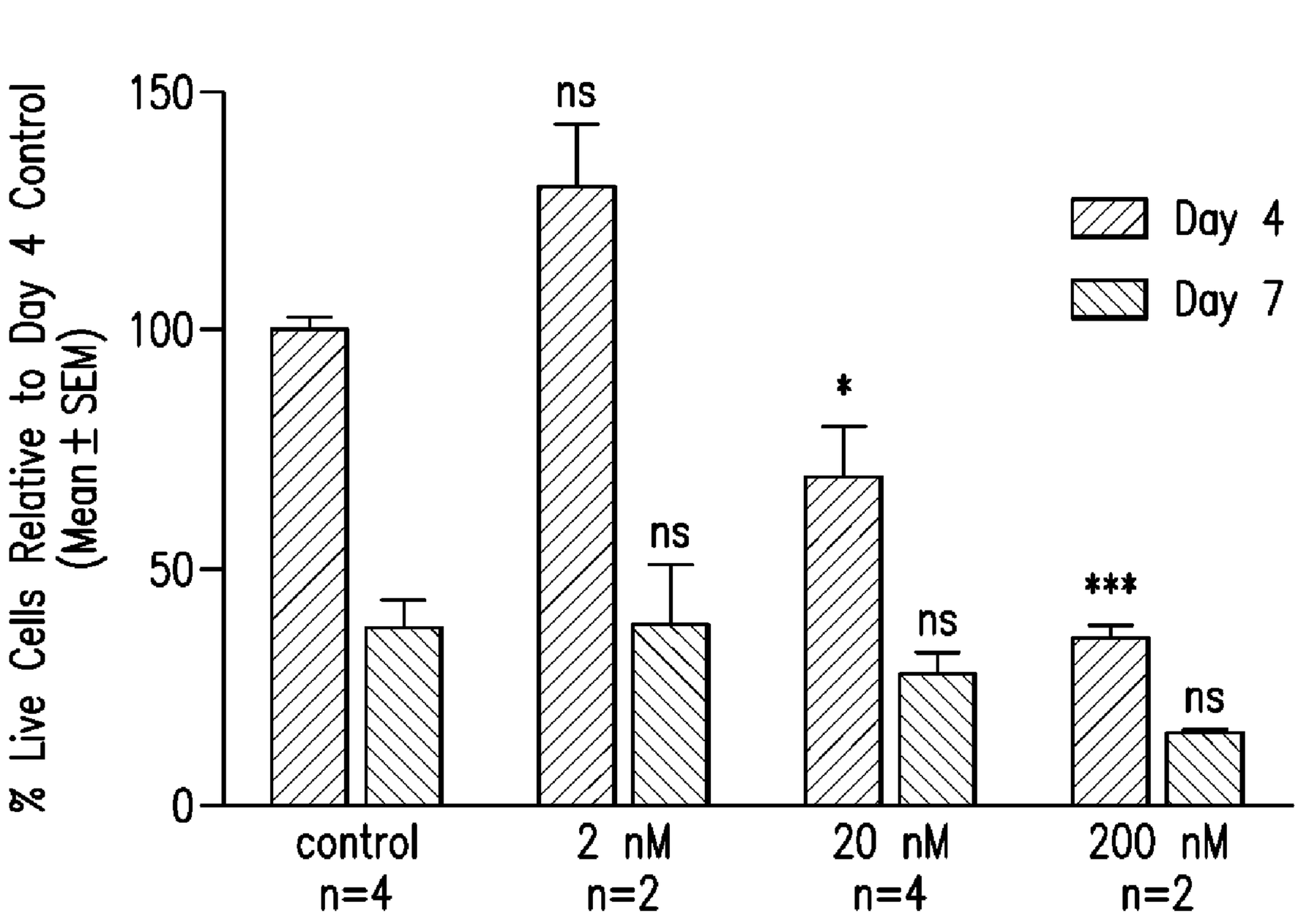

% Live Cells Relative to Day 4 Control
(Mean ± SEM)
150
100
50
0
ns
ns
*
ns
***
ns
Day 4
Day 7
control
n=4
2 nM
n=2
20 nM
n=4
200 nM
n=2
Test Compound

FIG. 2

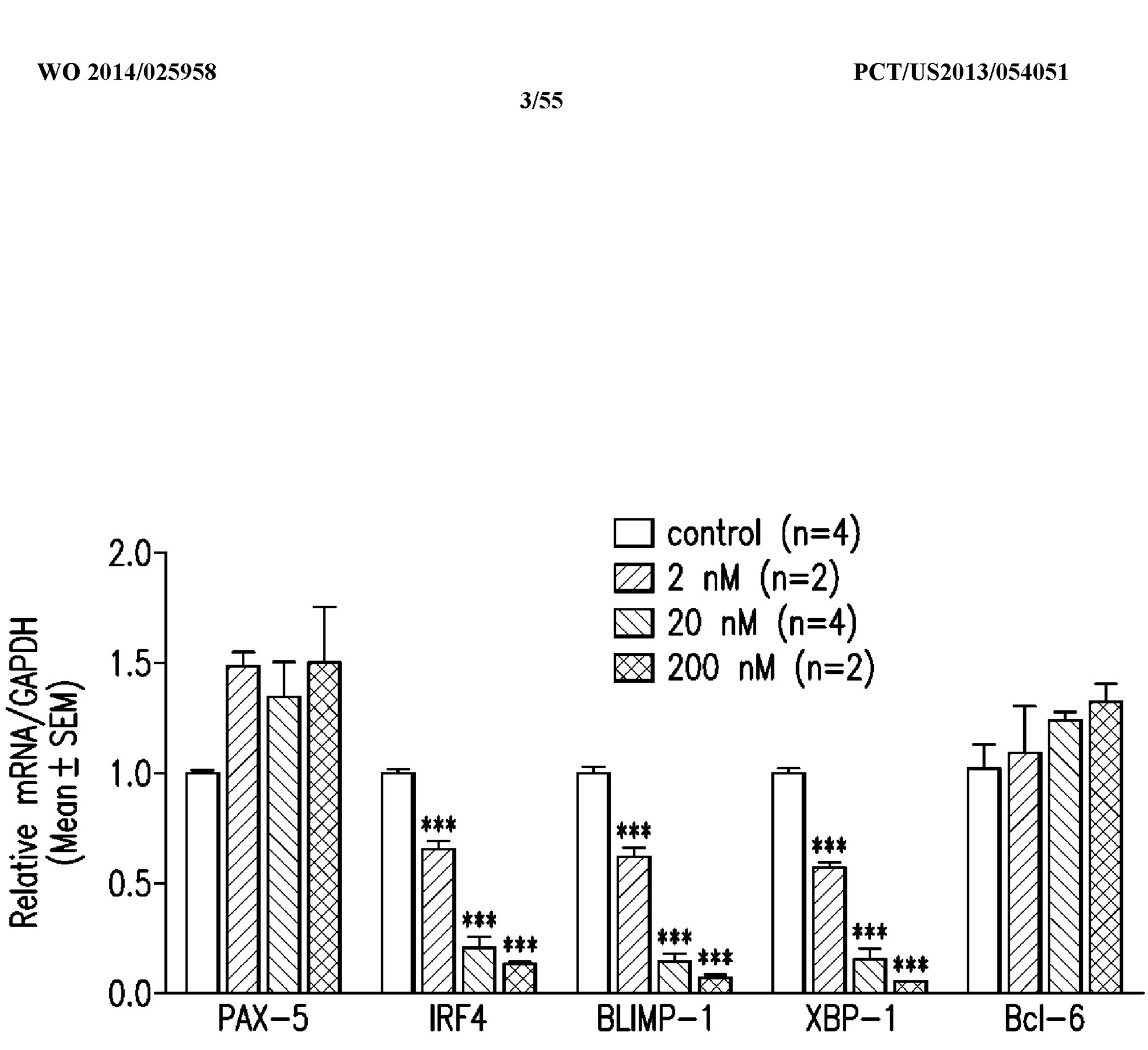

control (n=4)
2 nM (n=2)
20 nM (n=4)
200 nM (n=2)
Relative mRNA/GAPDH
(Mean ± SEM)
2.0
1.5
1.0
0.5
0.0
***
PAX-5
IRF4
BLIMP-1
XBP-1
Bcl-6
gene

FIG. 3

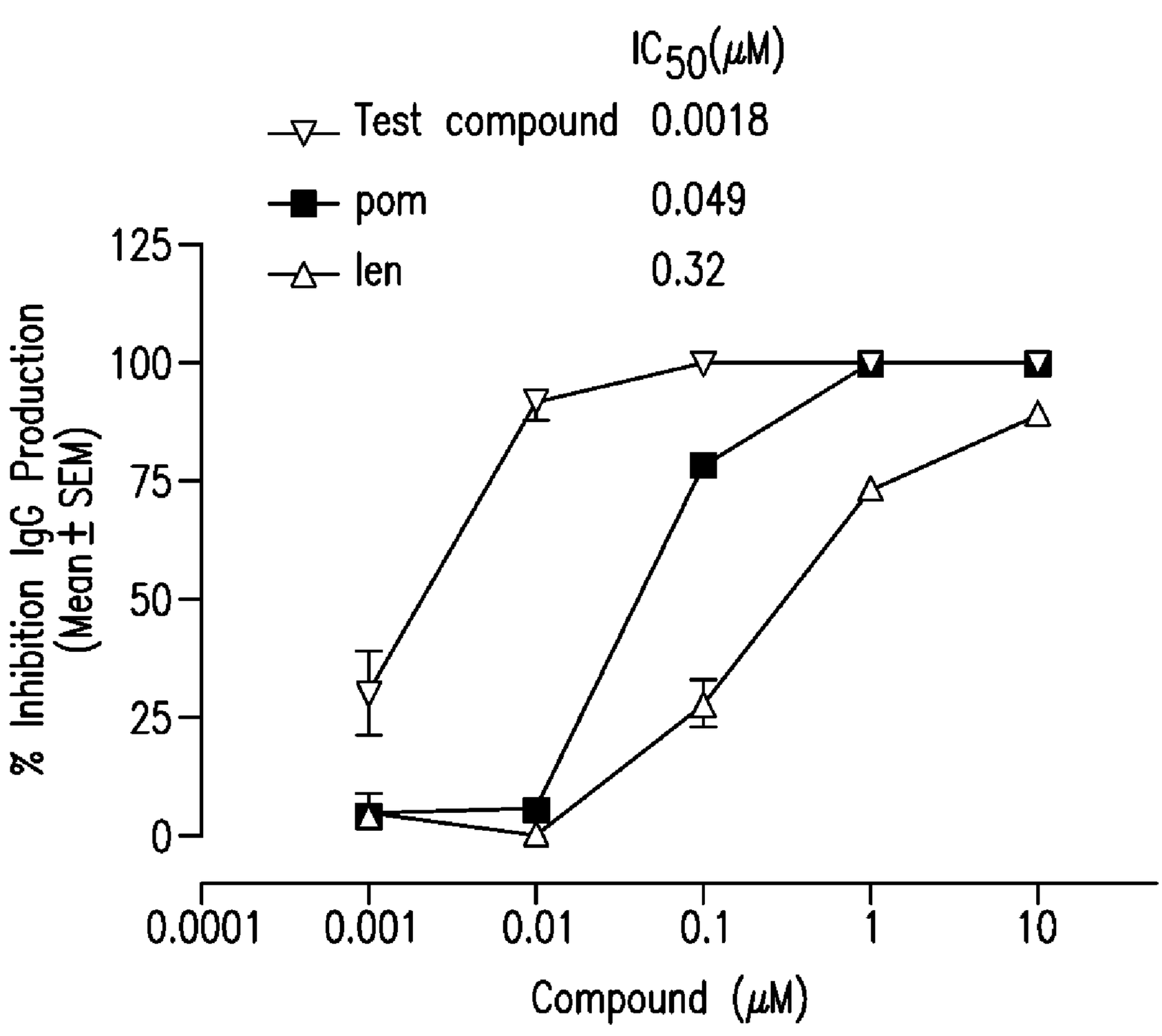

IC50(μM)
Test compound 0.0018
pom 0.049
len 0.32
% Inhibition IgG Production (Mean ± SEM)
125
100
75
50
25
0
0.0001
0.001
0.01
0.1
1
10
Compound (μM)

FIG. 4

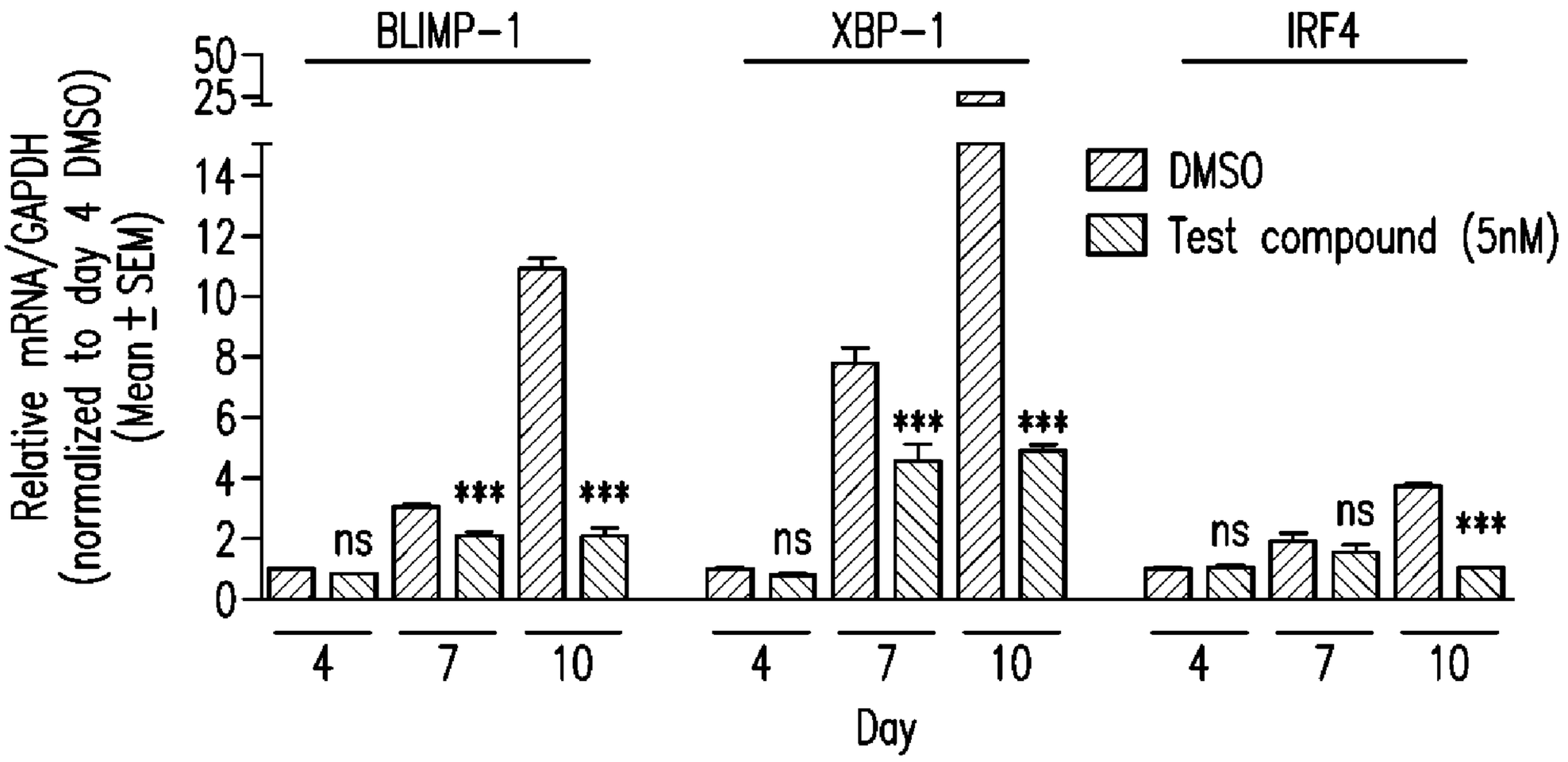

BLIMP-1
XBP-1
IRF4
Relative mRNA/GAPDH
(normalized to day 4 DMSO)
(Mean ± SEM)
50
25
14
12
10
8
6
4
2
0
DMSO
Test compound (5nM)
ns
***
4
7
10
Day

FIG. 5A

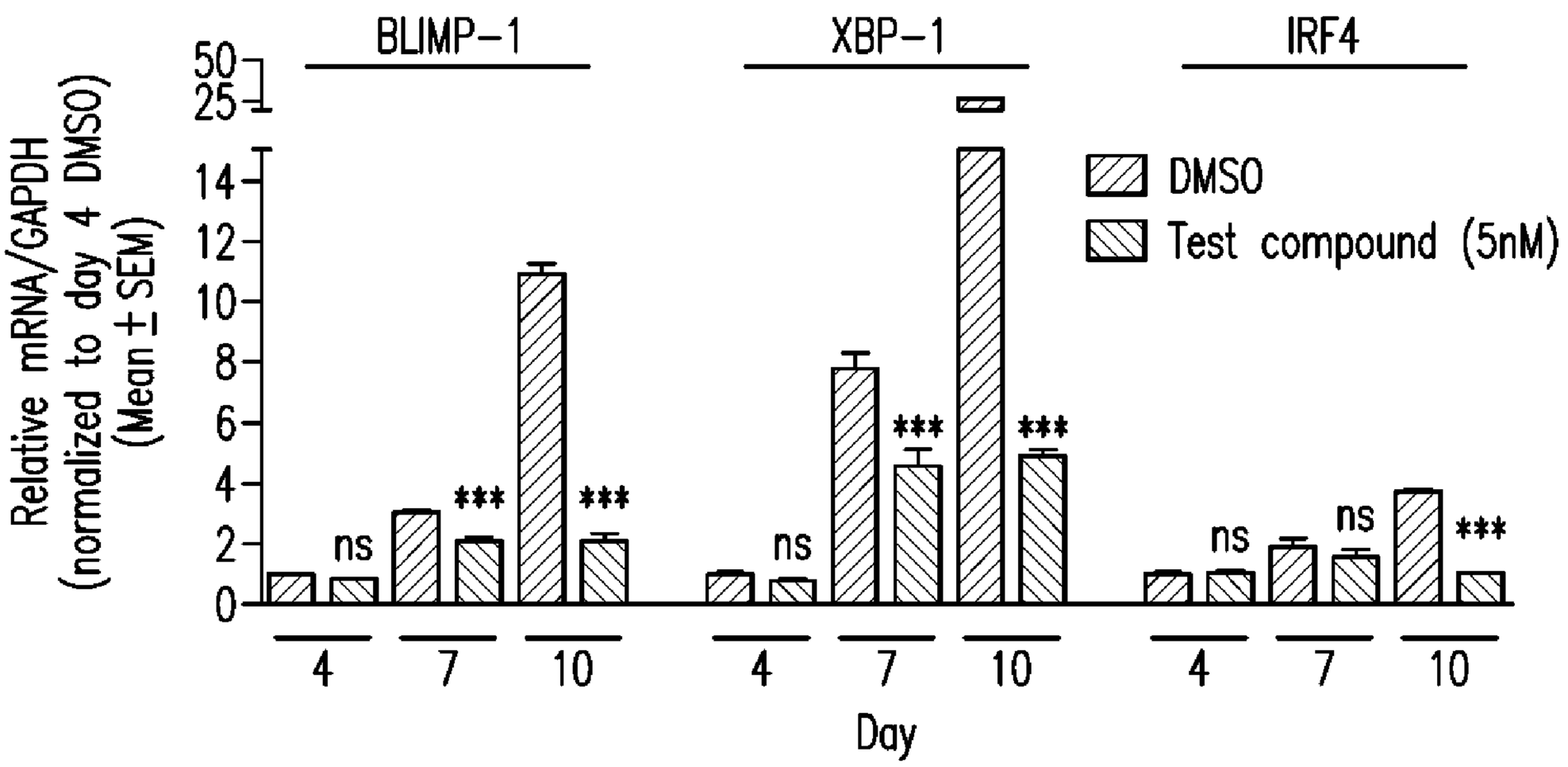

BLIMP-1
XBP-1
IRF4
Relative mRNA/GAPDH
(normalized to day 4 DMSO)
(Mean ± SEM)
50
25
14
12
10
8
6
4
2
0
DMSO
Test compound (5nM)
ns
***
4
7
10
Day

FIG. 5B

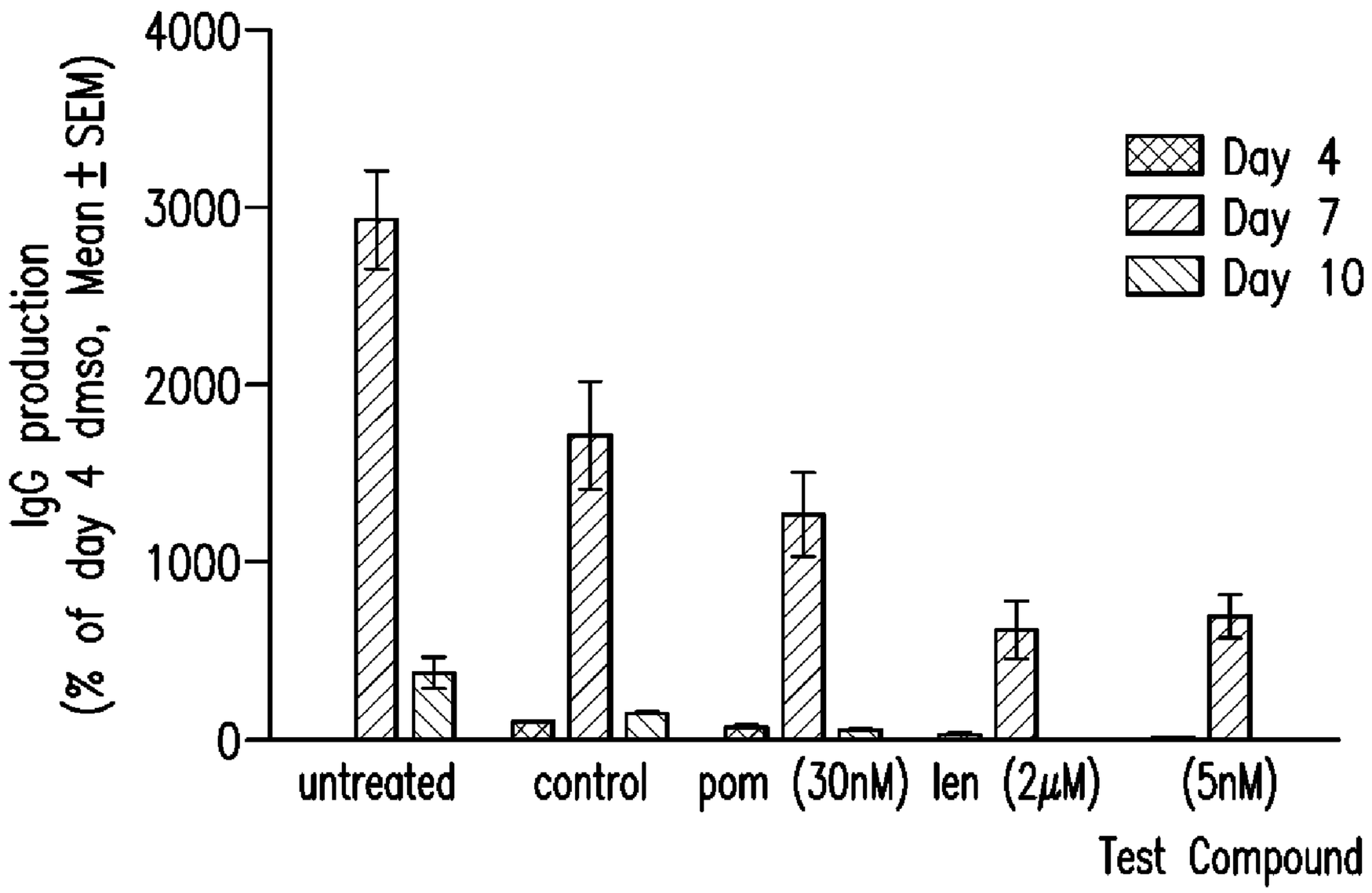

IgG production
(% of day 4 dmso, Mean ± SEM)
4000
3000
2000
1000
0
Day 4
Day 7
Day 10
untreated
control
pom (30nM)
len (2μM)
(5nM)
Test Compound

FIG. 6

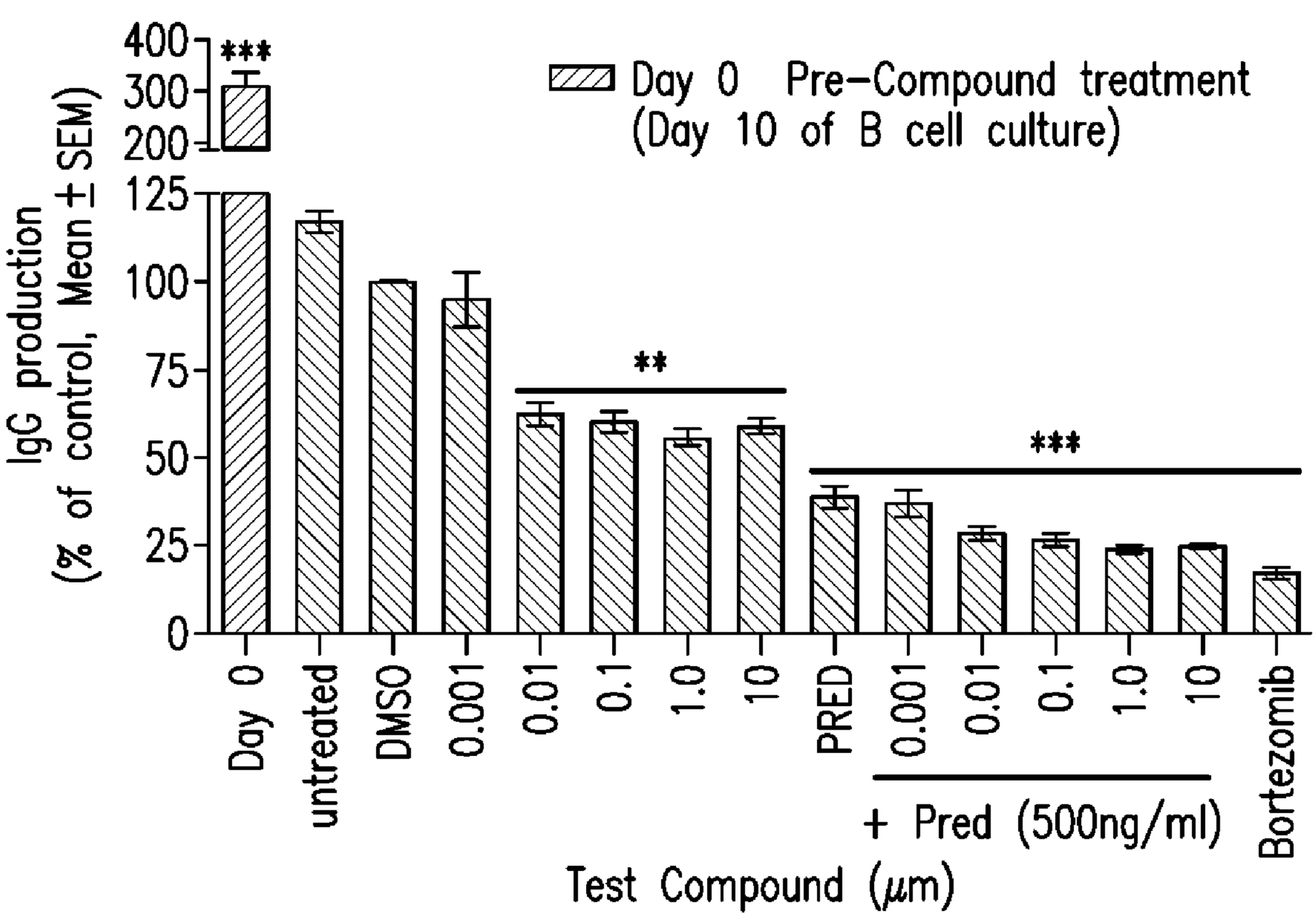
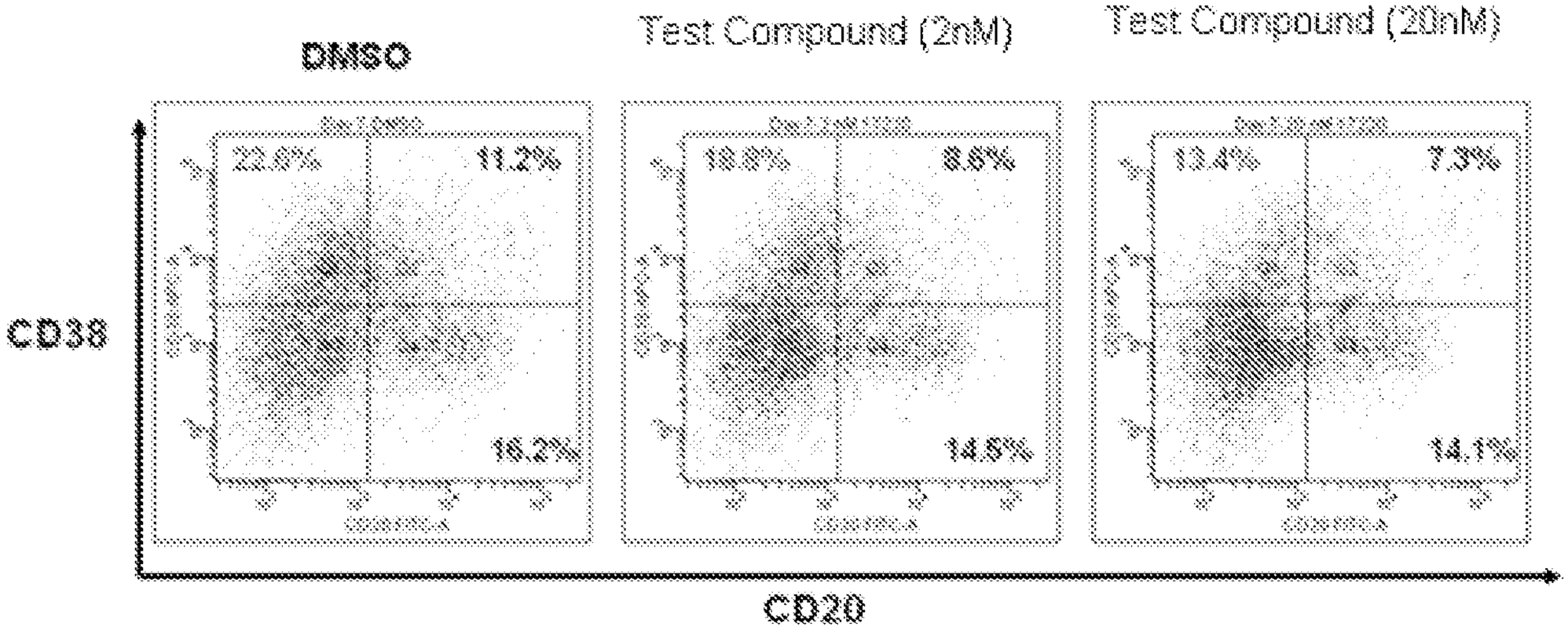

Day 0 Pre-Compound treatment
(Day 10 of B cell culture)
IgG production
(% of control, Mean ± SEM)
400
300
200
125
100
75
50
25
0
***
**
***
Day 0
untreated
DMSO
0.001
0.01
0.1
1.0
10
PRED
0.001
0.01
0.1
1.0
10
Bortezomib
+ Pred (500ng/ml)
Test Compound (μm)

FIG. 7

FIG. 8


DMSO
Test Compound (2nM)
Test Compound (20nM)
CD38
CD20
22.8%
11.2%
16.2%
18.8%
8.6%
14.8%
13.4%
7.3%
14.1%

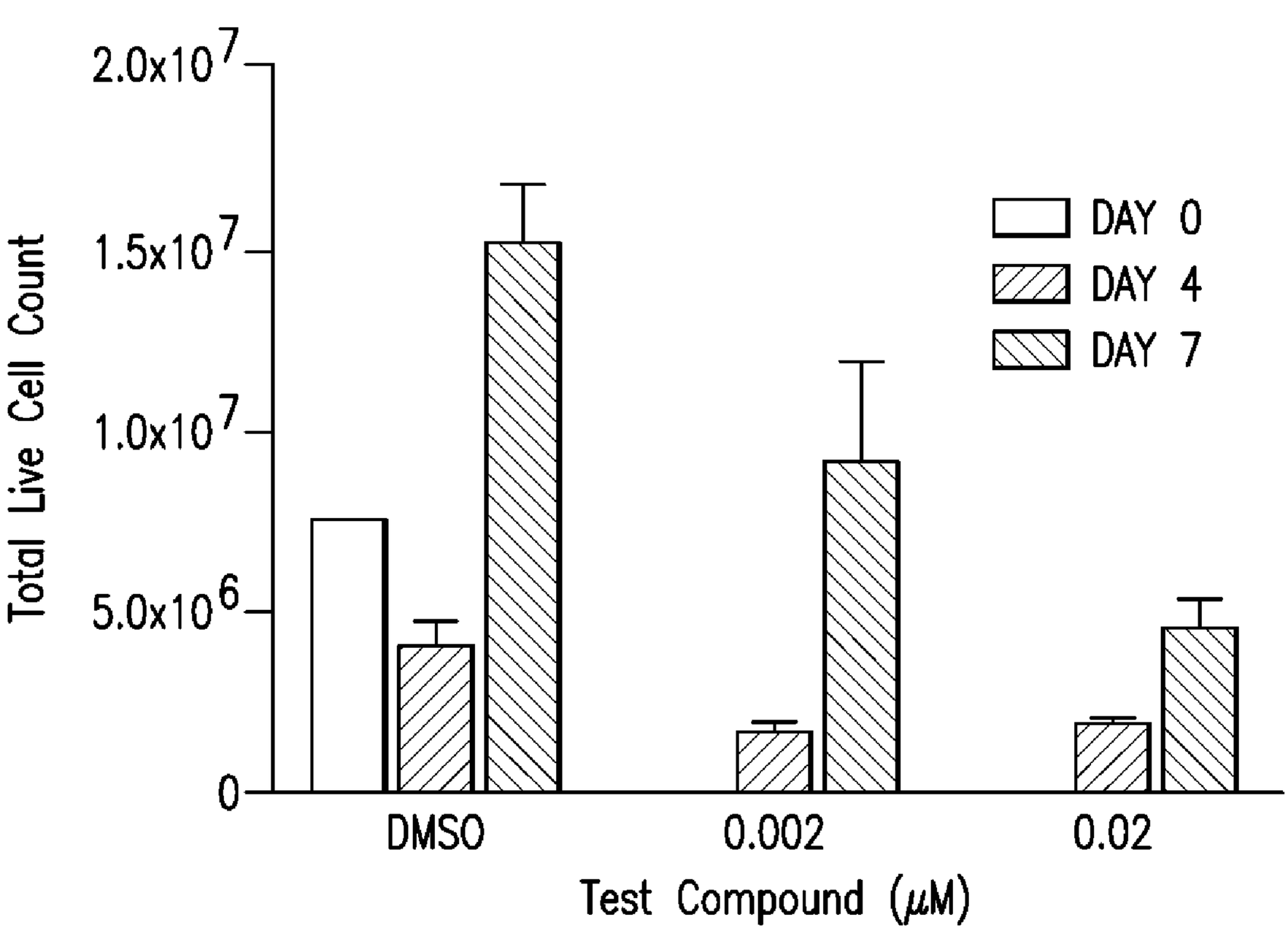

2.0x10^7
1.5x10^7
1.0x10^7
5.0x10^6
0
Total Live Cell Count
DAY 0
DAY 4
DAY 7
DMSO
0.002
0.02
Test Compound (μM)

FIG. 9

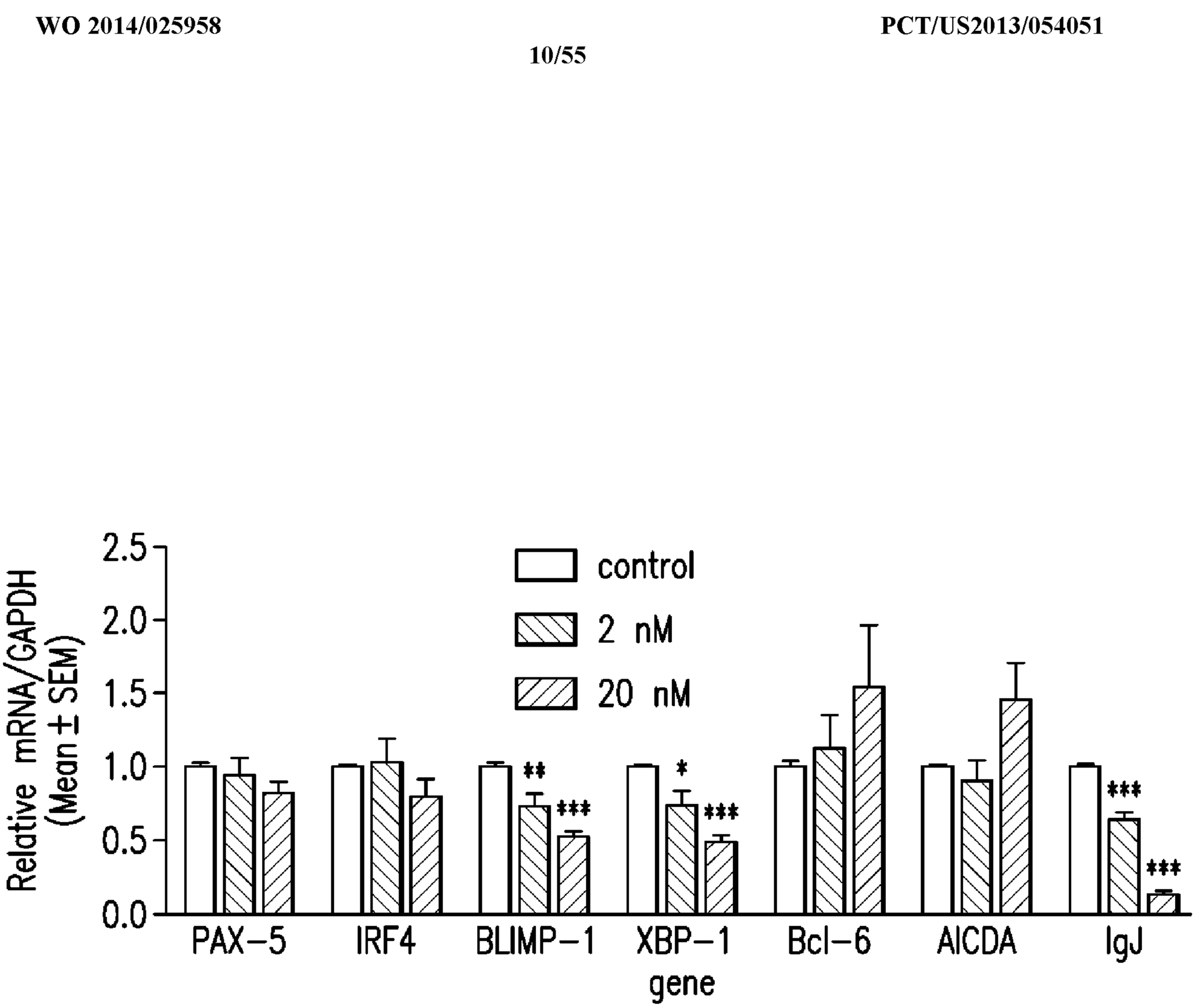

Relative mRNA/GAPDH
(Mean ± SEM)
2.5
2.0
1.5
1.0
0.5
0.0
control
2 nM
20 nM
**
***
*
***
***
***
PAX–5
IRF4
BLIMP–1
XBP–1
Bcl–6
AICDA
IgJ
gene

FIG. 10

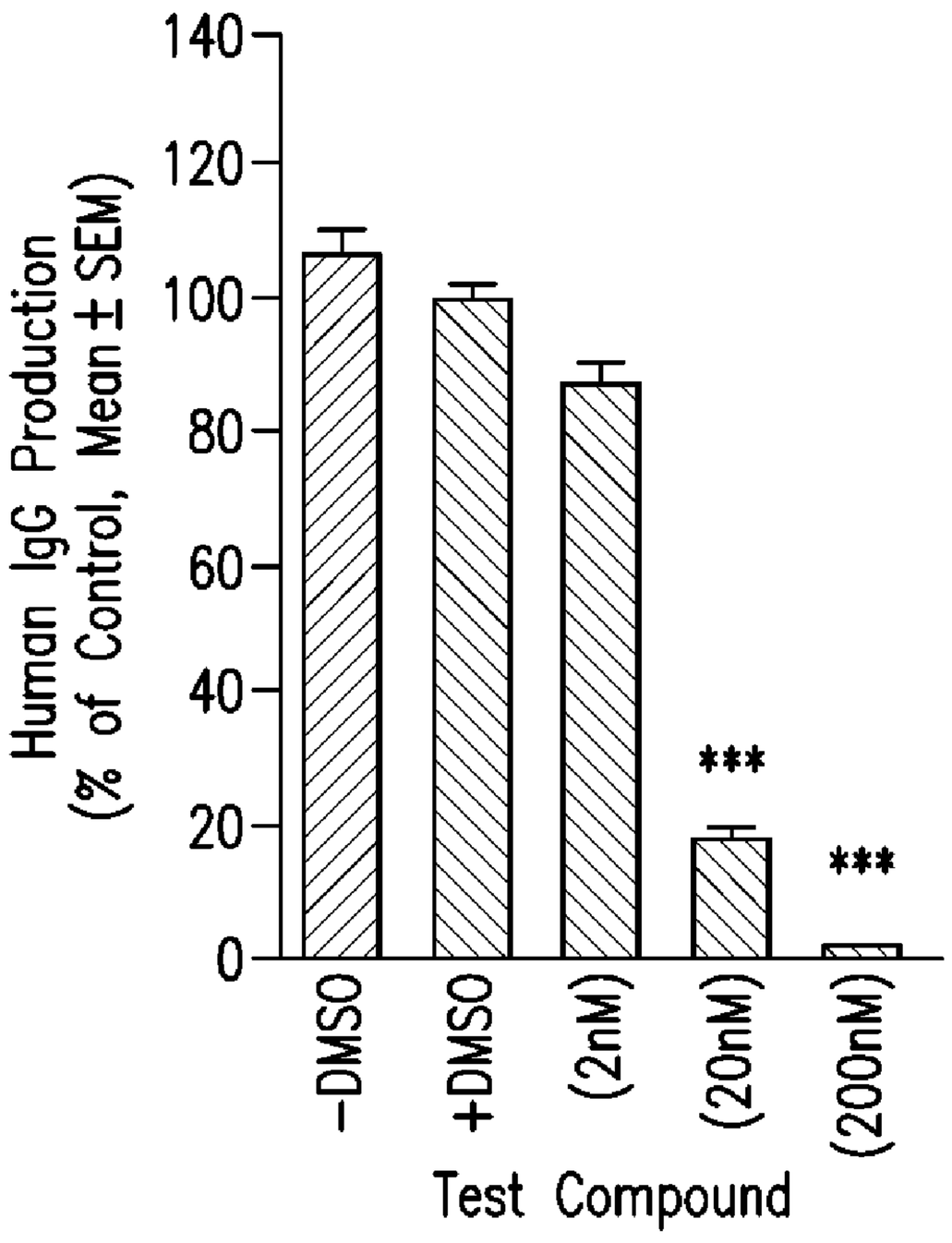


FIG. 11A

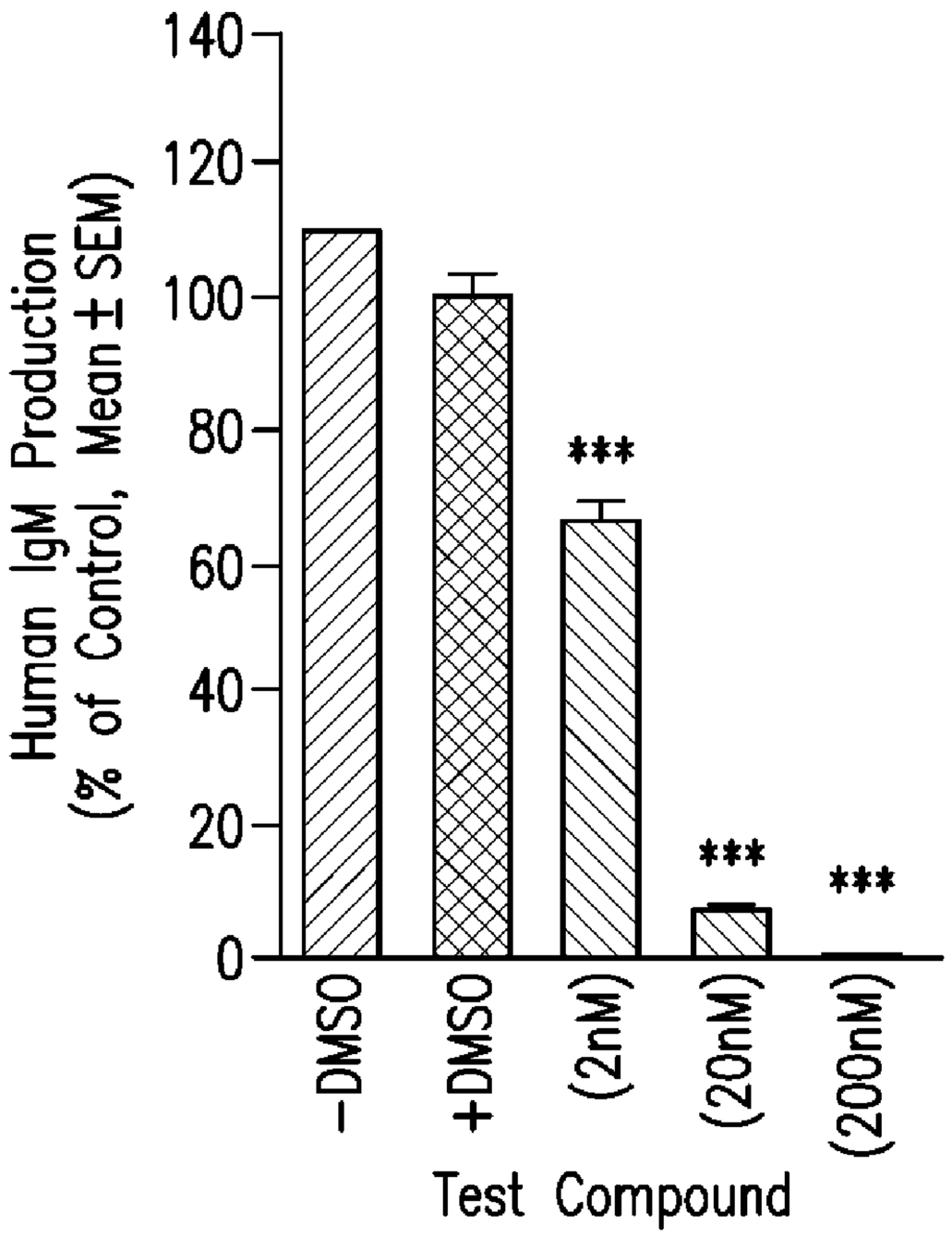


FIG. 11B

FIG. 12A

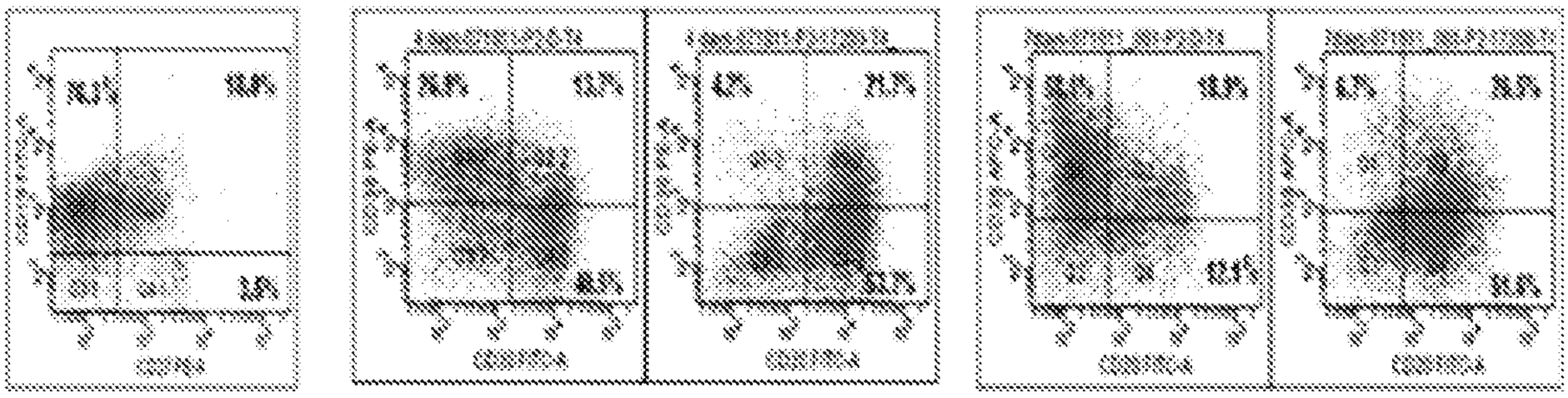


FIG. 12B

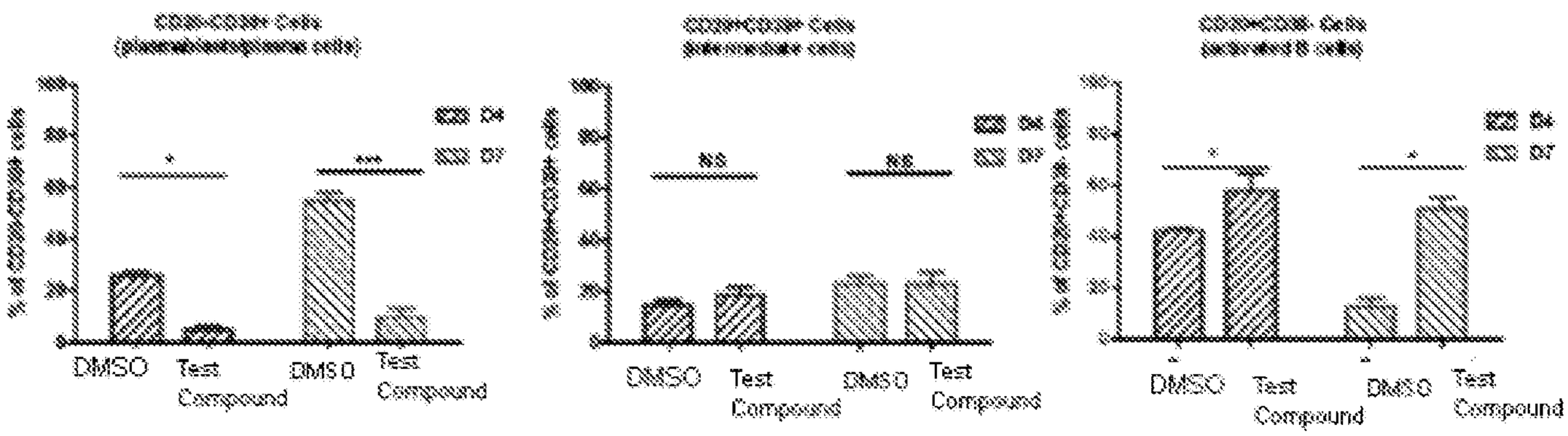


FIG. 13

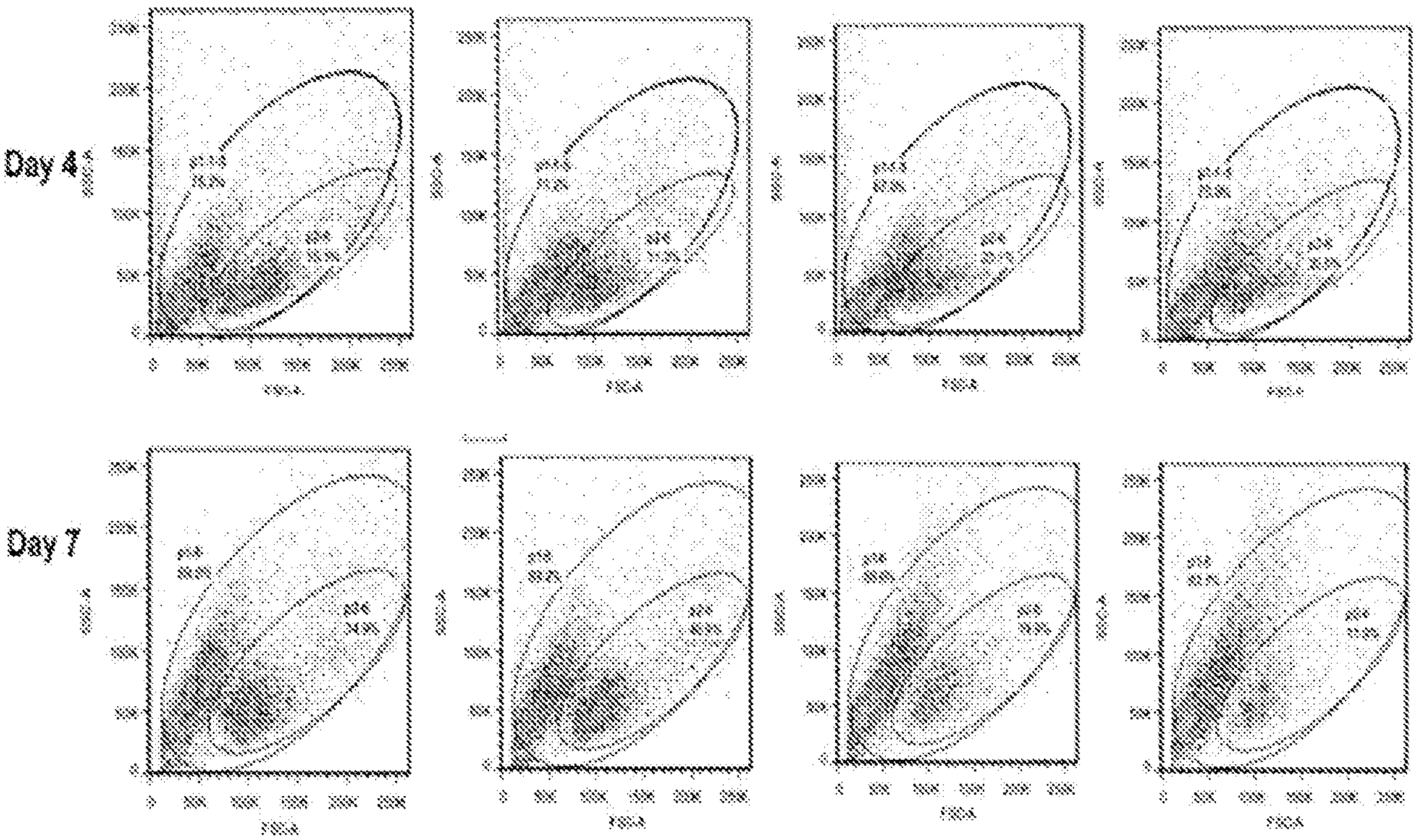
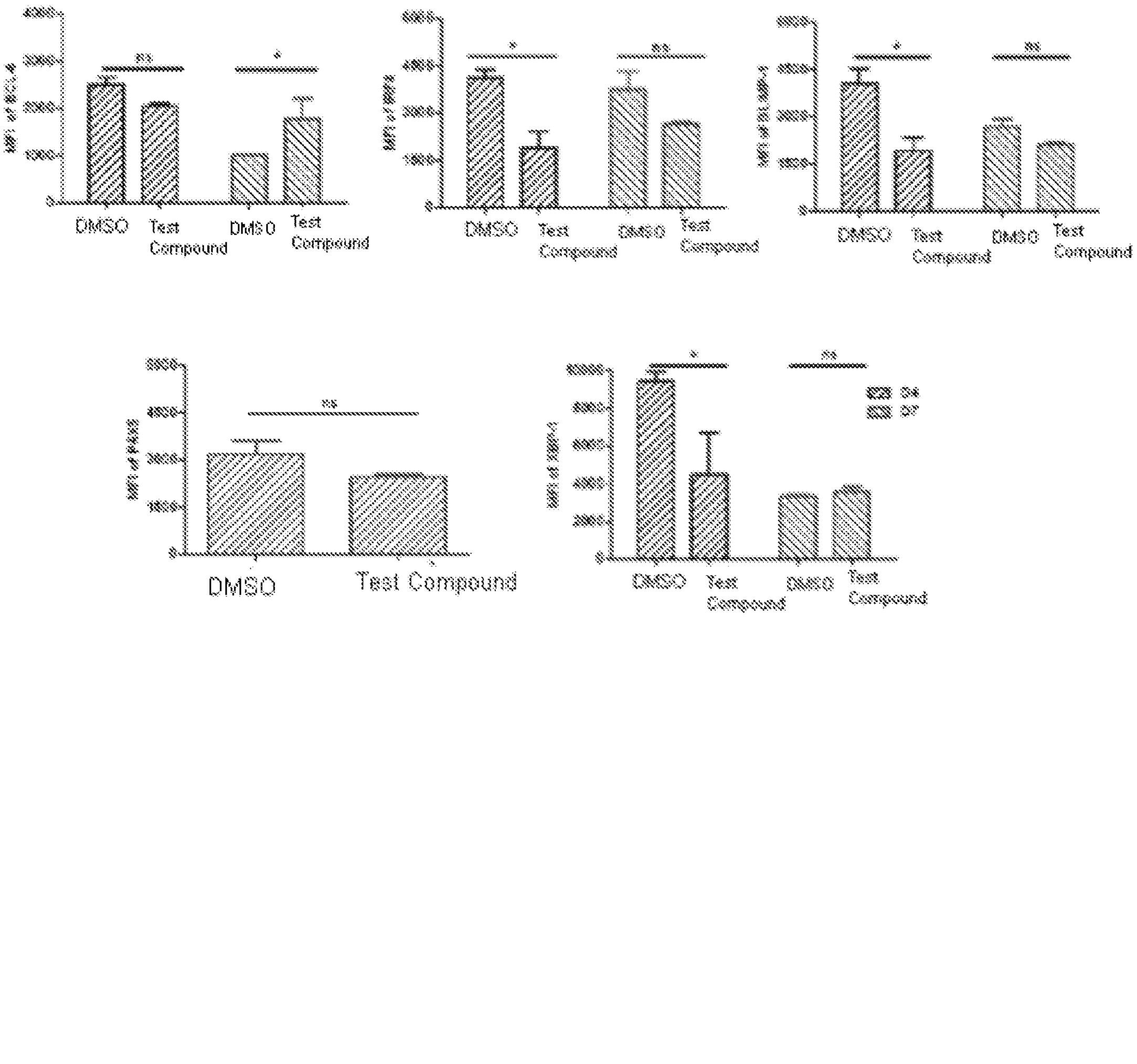
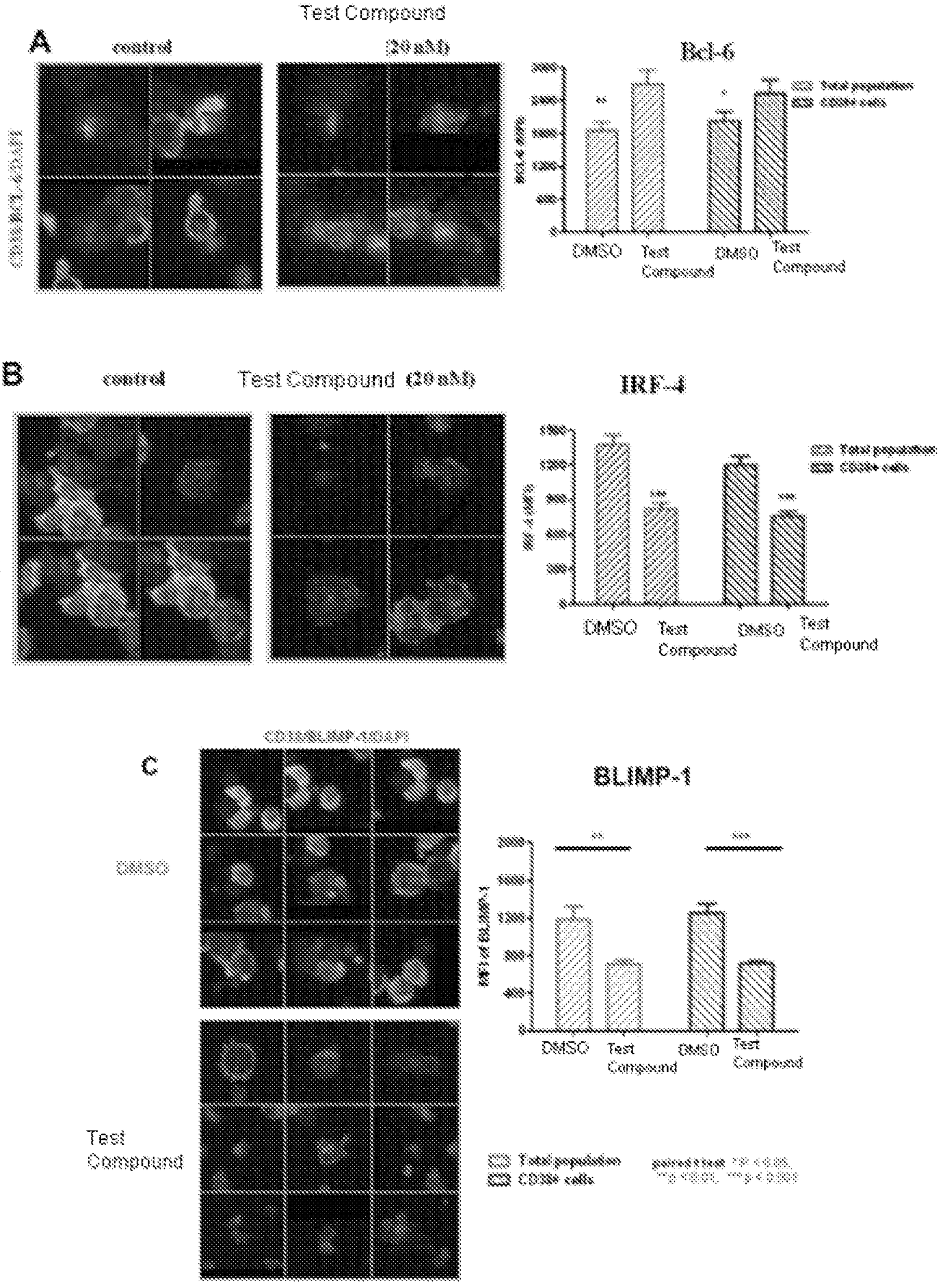


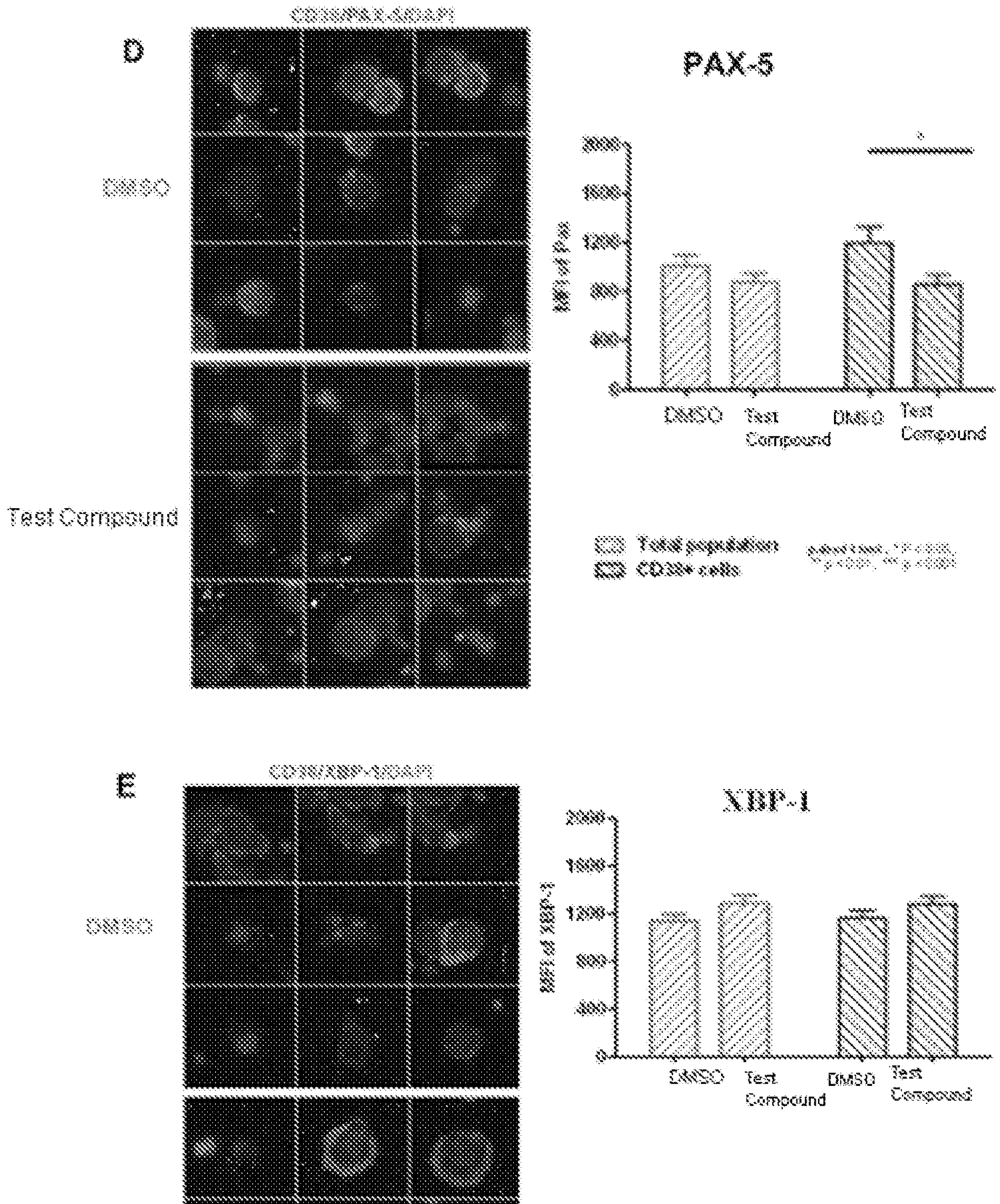
FIG. 14


DMSO
Test Compound
DMSO
Test Compound
DMSO
Test Compound
DMSO
Test Compound
DMSO
Test Compound
DMSO
Test Compound
DMSO
Test Compound
DMSO
Test Compound

FIGs. 15A, 15B and 15C



FIGs. 15D and 15E



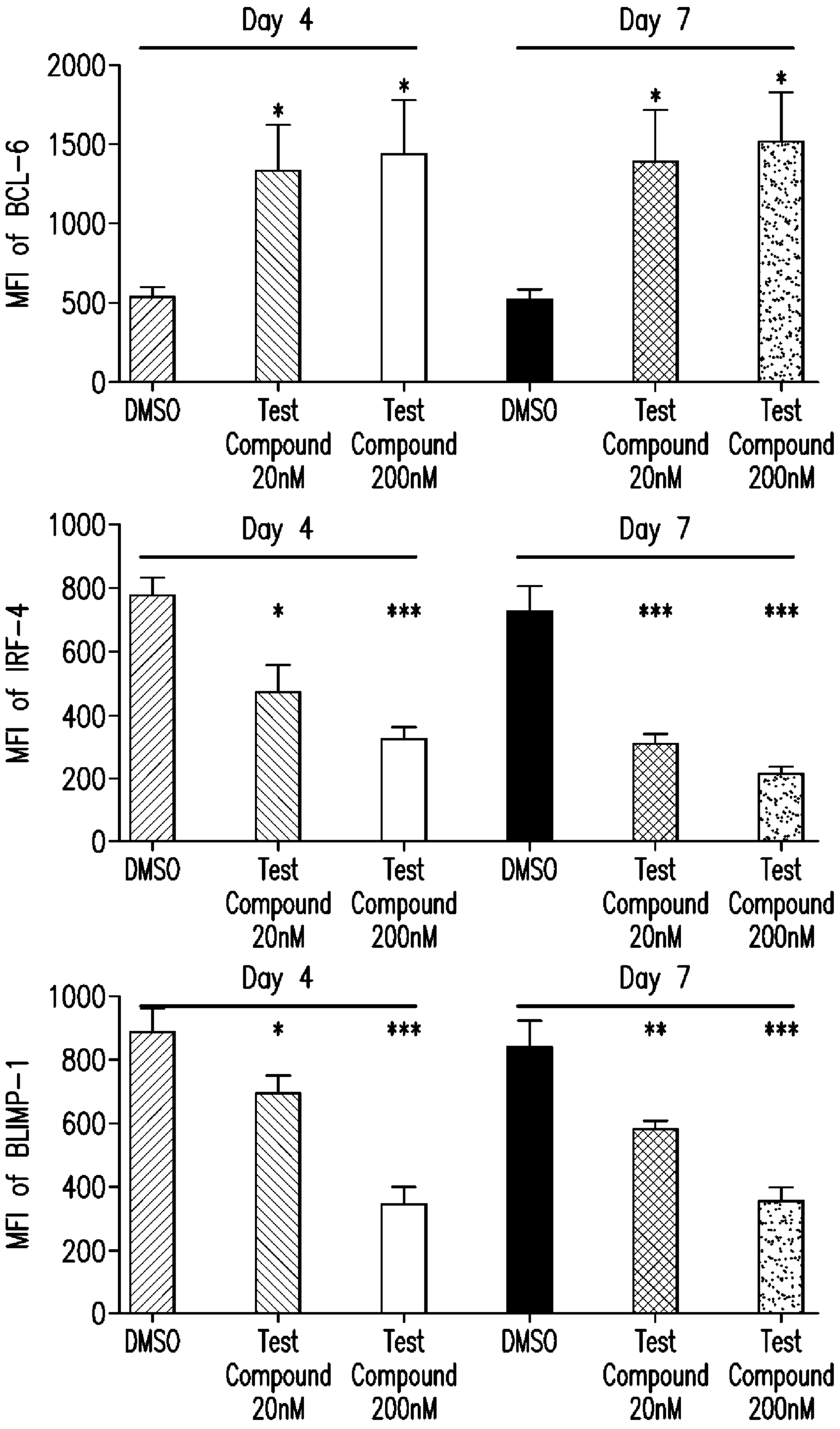

Day 4
Day 7
MFI of BCL-6
2000
1500
1000
500
0
*
DMSO
Test Compound 20nM
Test Compound 200nM
MFI of IRF-4
1000
800
600
400
200
0
*
***
MFI of BLIMP-1
1000
800
600
400
200
0
*
**
***

FIG. 16

FIG. 17

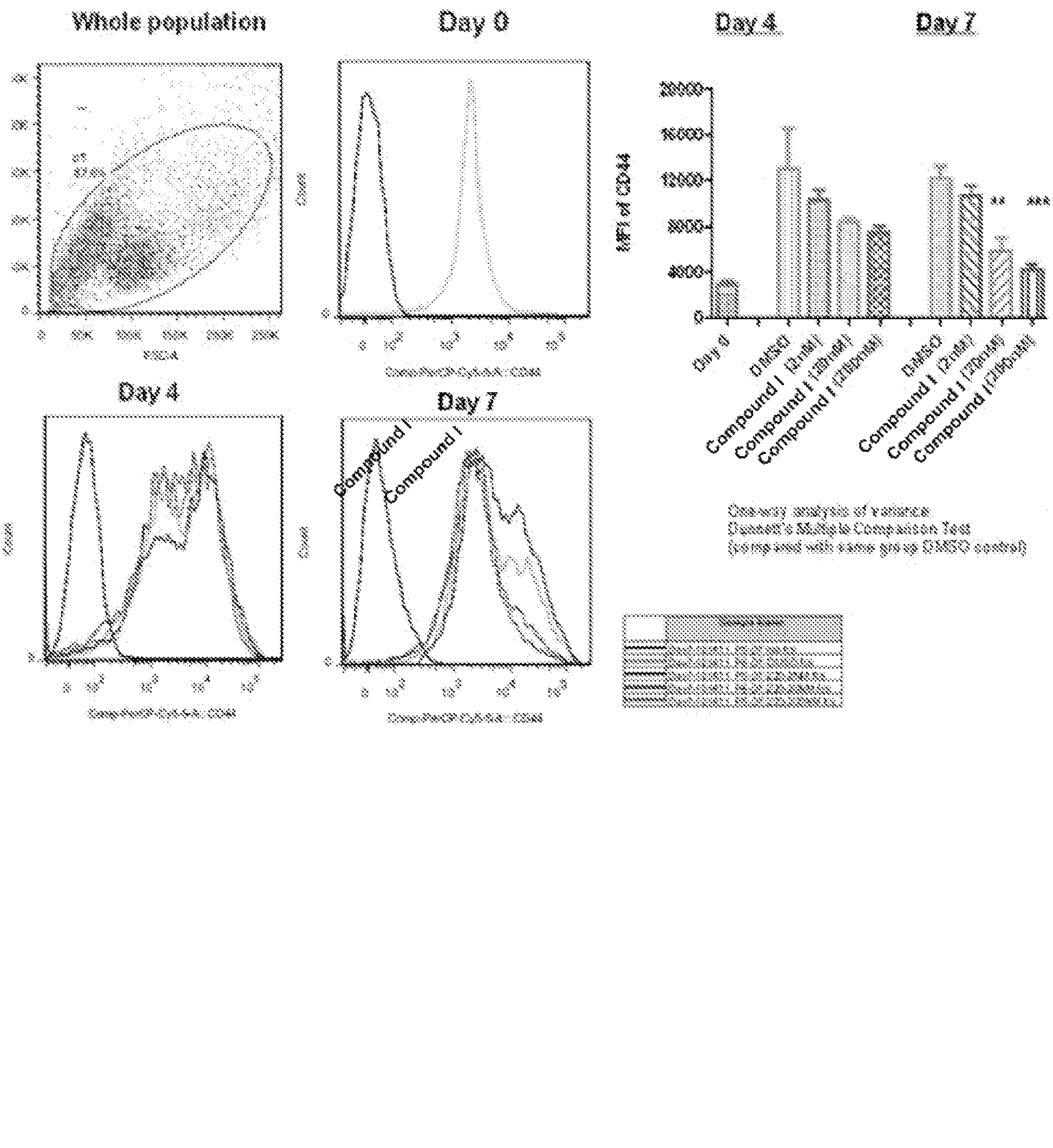

Whole population
Day 0
Day 4
Day 7
Day 4
Day 7
Compound I
Compound I
MFI of CD44
Day 0
DMSO
Compound I (2nM)
Compound I (10nM)
Compound I (50nM)
DMSO
Compound I (2nM)
Compound I (10nM)
Compound I (50nM)
**
***
One-way analysis of variance
Dunnett's Multiple Comparison Test
(compared with same group DMSO control)

FIG. 18

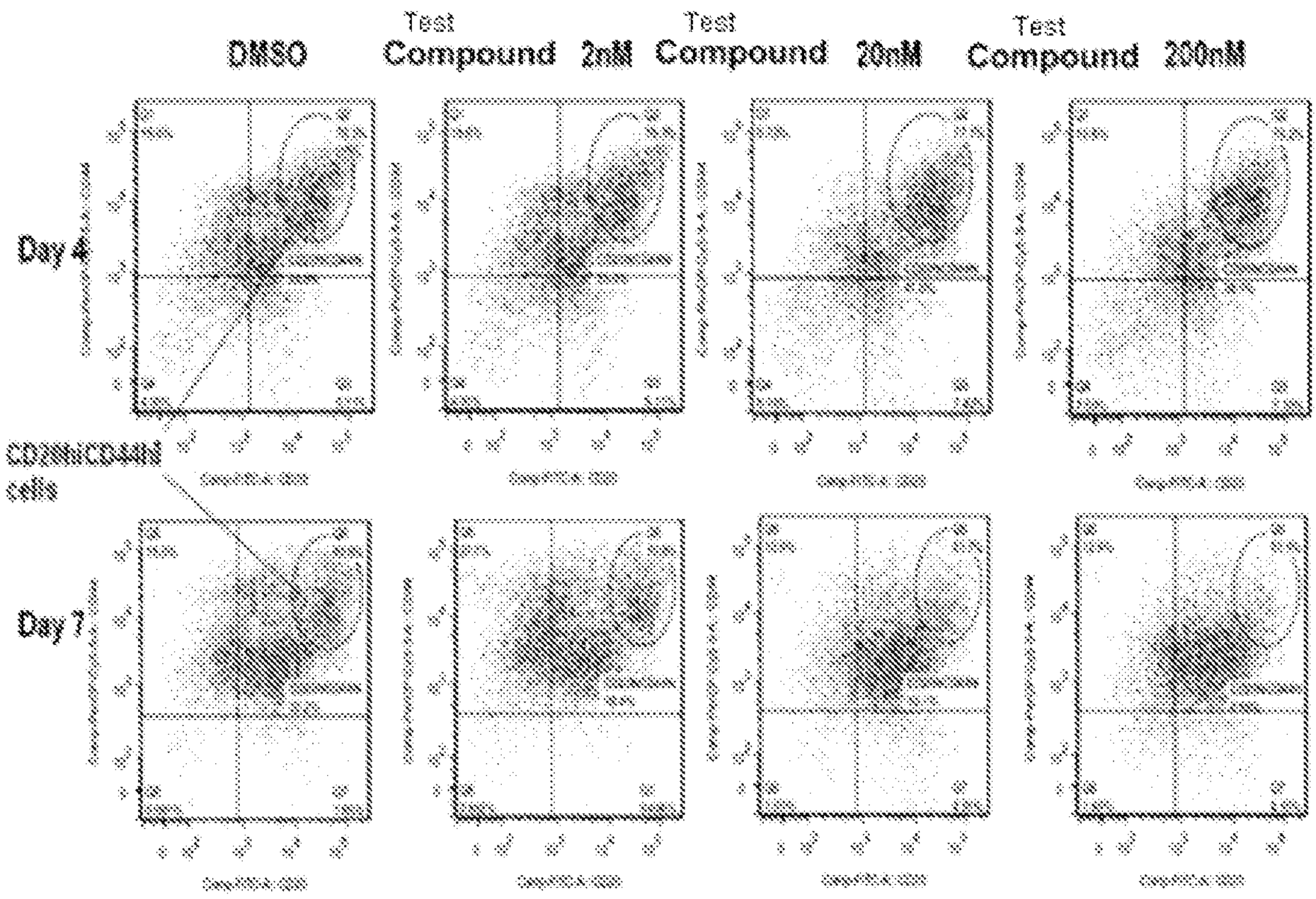

DMSO
Test Compound 2nM
Test Compound 20nM
Test Compound 200nM
Day 4
CD2intCD44hi cells
Day 7

FIG. 19

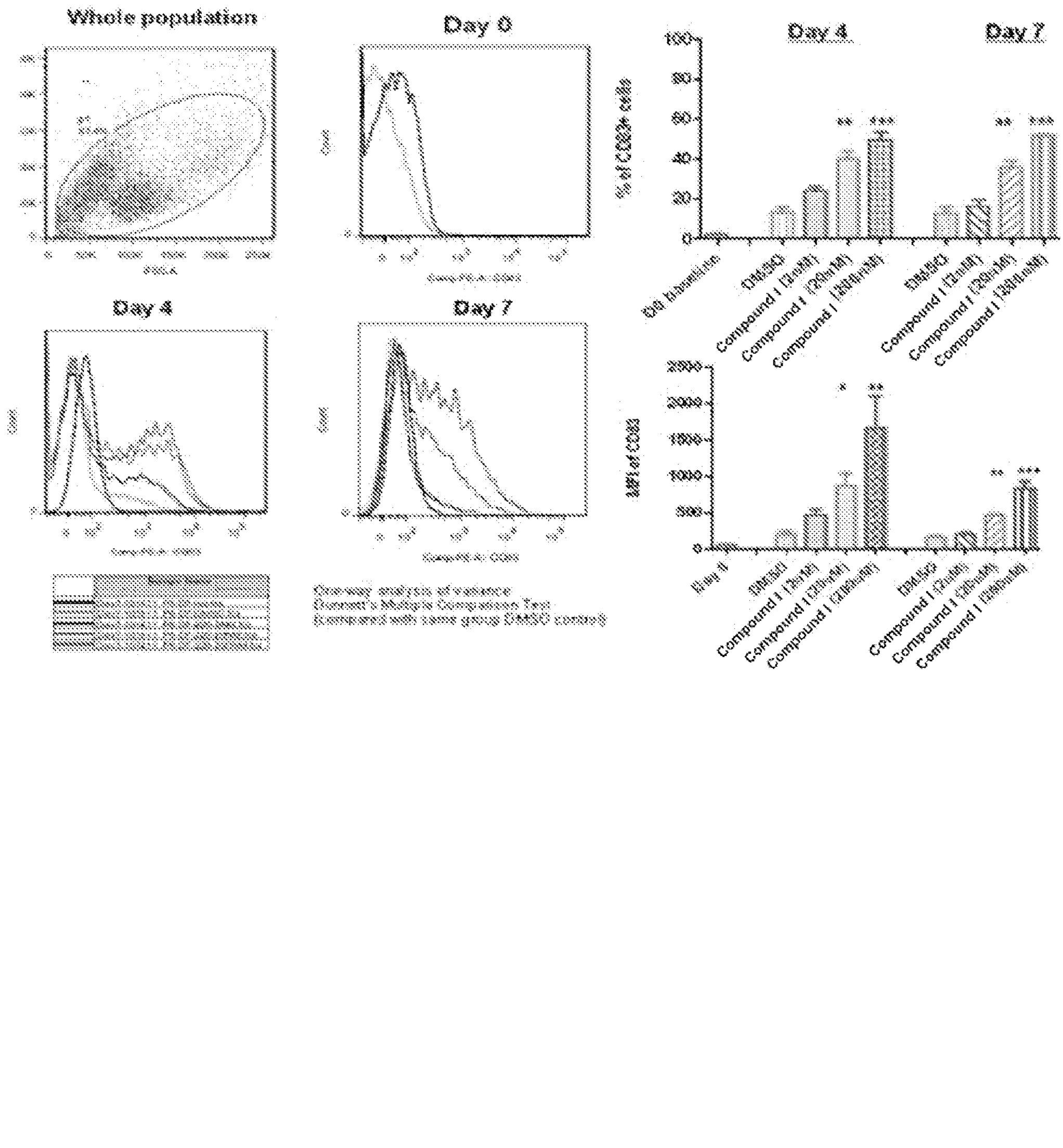
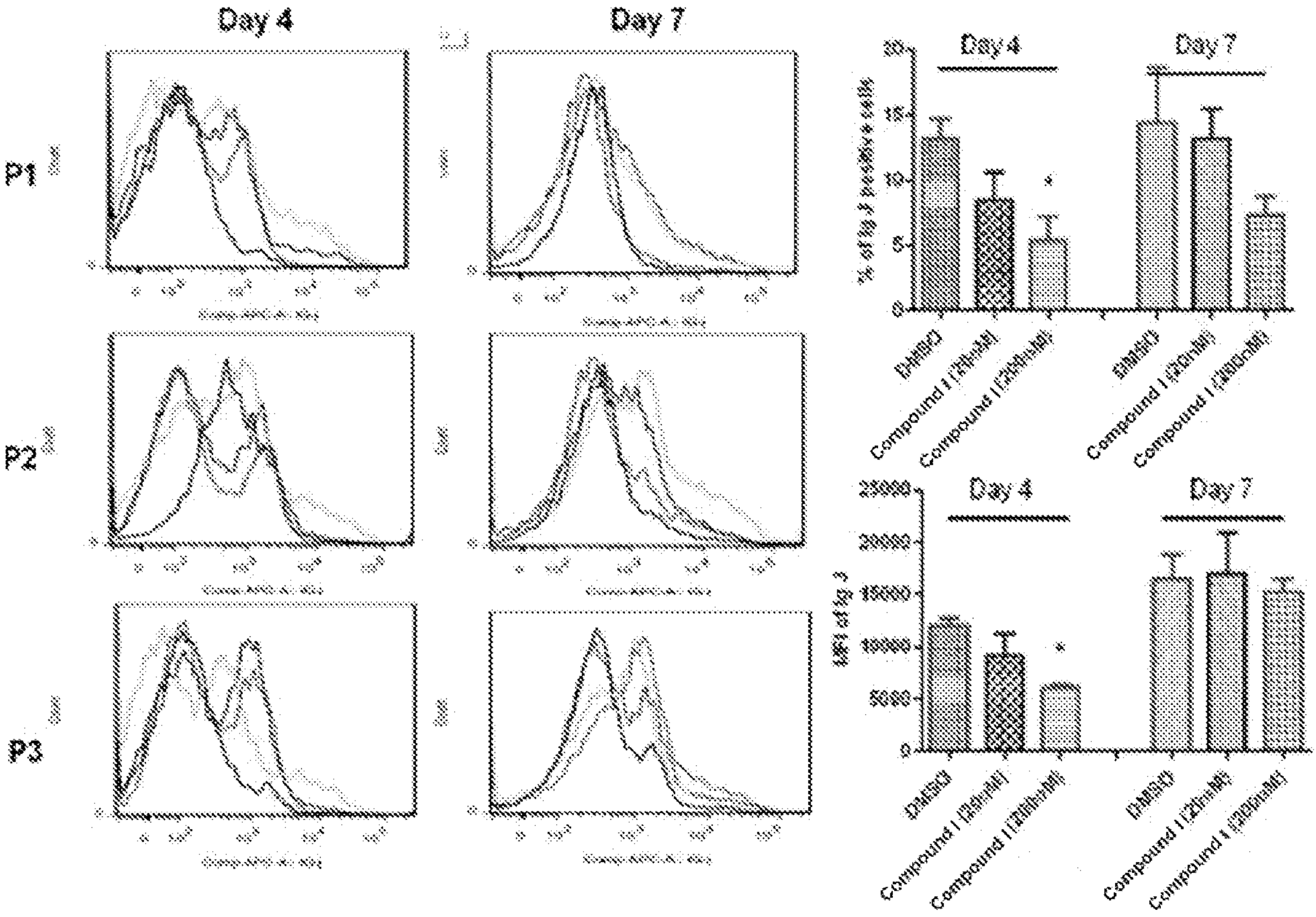

Whole population
Day 0
Day 4
Day 7
Day 4
Day 7
% of CD23+ cells
Compound 1 (3nM)
Compound 1 (30nM)
Compound 1 (300nM)
Compound 1 (3000nM)
MFI of CD23
One-way analysis of variance
Dunnett's Multiple Comparisons Test
Compared with same group DMSO control

FIG. 20



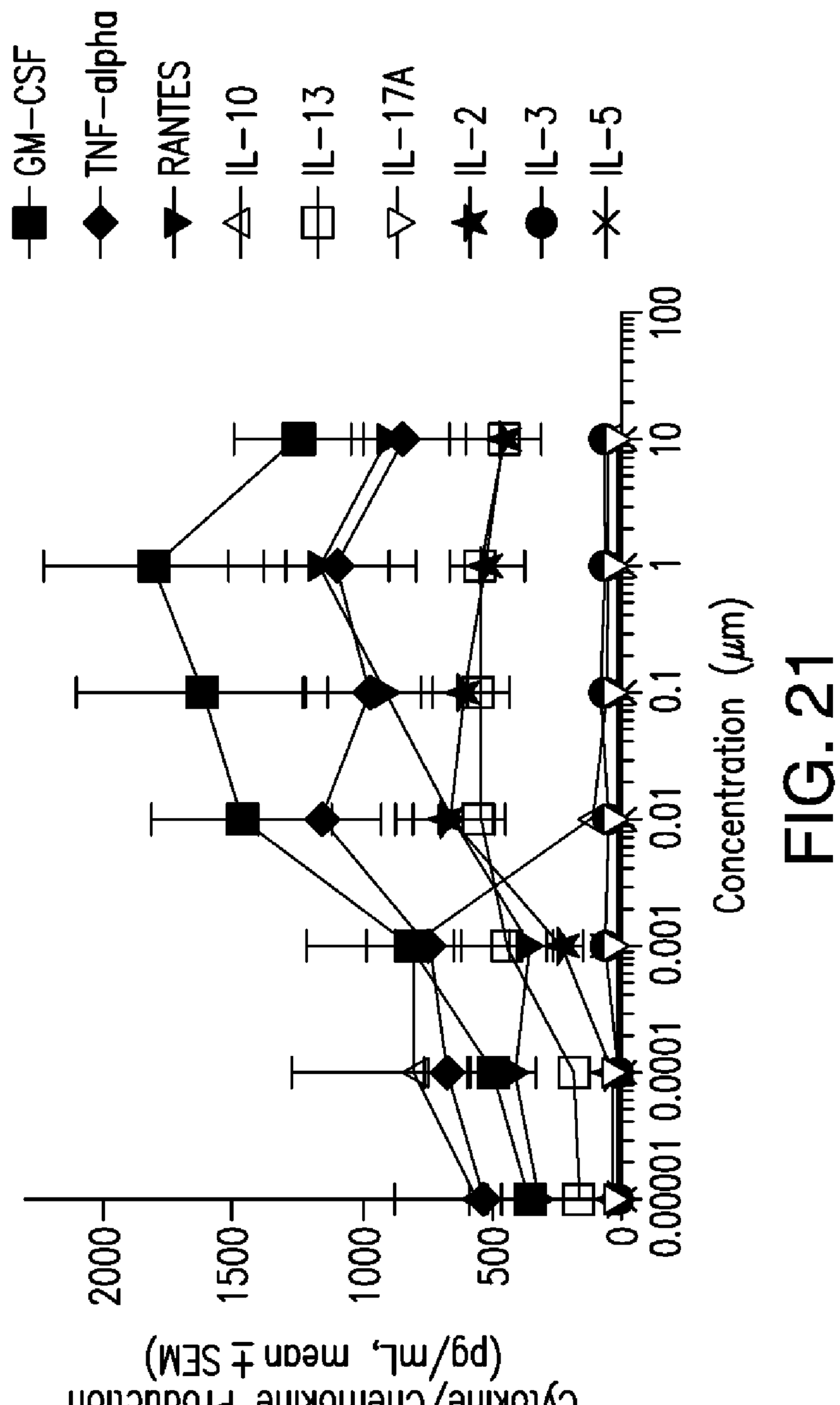

GM−CSF
TNF−alpha
RANTES
IL−10
IL−13
IL−17A
IL−2
IL−3
IL−5
0.00001
0.0001
0.001
0.01
0.1
1
10
100
Concentration (μm)
0
5
10
15
20
Cytokine/Chemokine Production
(pg/mL, mean ± SEM)

FIG. 21

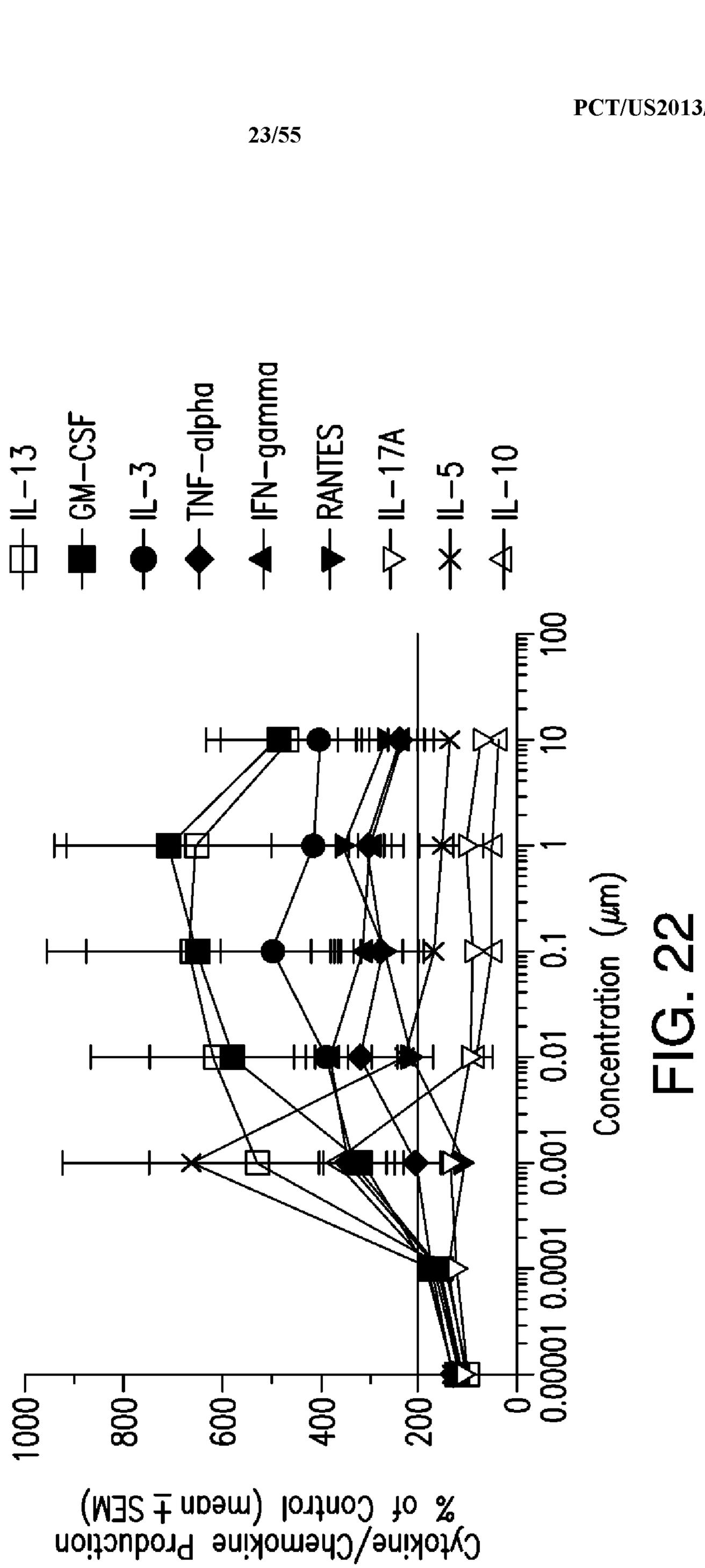

IL-13
GM-CSF
IL-3
TNF-alpha
IFN-gamma
RANTES
IL-17A
IL-5
IL-10
100
10
1
0.1
0.01
0.001
0.0001
0.00001
Concentration (μm)
0
200
400
600
800
1000
Cytokine/Chemokine Production
% of Control (mean ± SEM)

FIG. 22

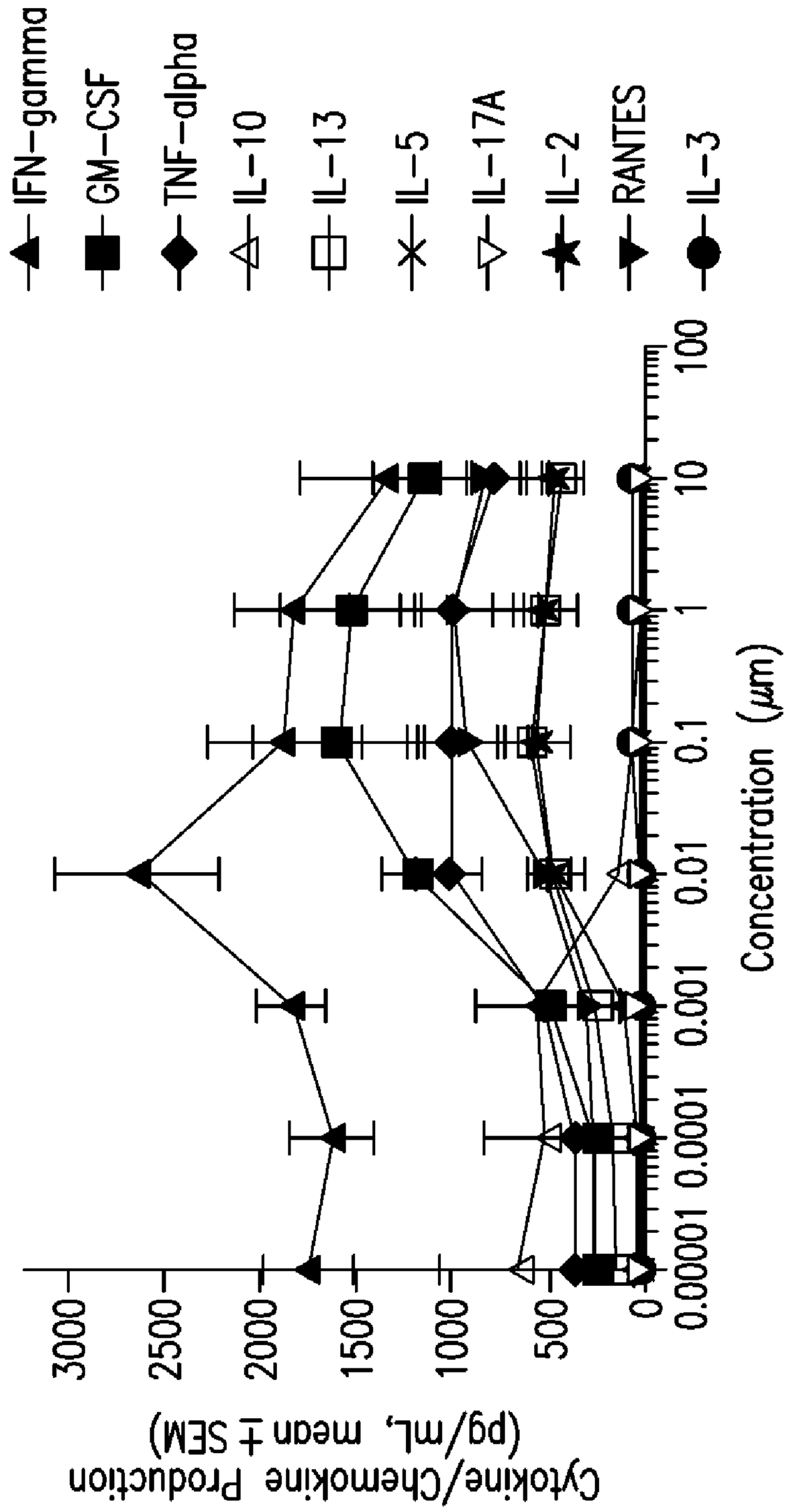

IFN-gamma
GM-CSF
TNF-alpha
IL-10
IL-13
IL-5
IL-17A
IL-2
RANTES
IL-3
100
10
1
0.1
0.01
0.001
0.0001
0.00001
Concentration (μm)
3 000
2 500
2 000
1 500
1 000
500
0
Cytokine/Chemokine Production
(pg/mL, mean ± SEM)

FIG. 23

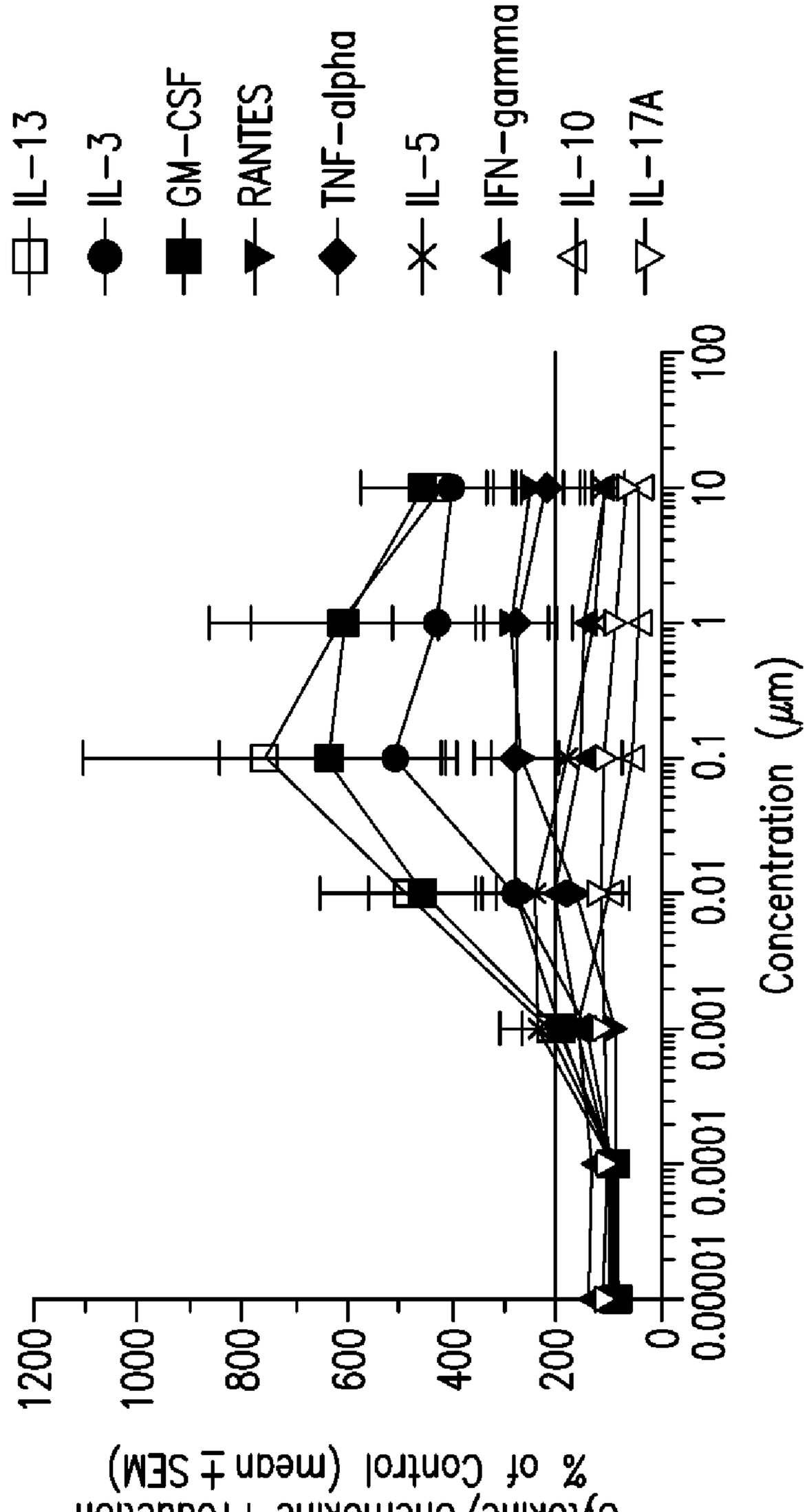

IL-13
IL-3
GM-CSF
RANTES
TNF-alpha
IL-5
IFN-gamma
IL-10
IL-17A
Concentration (μm)
0.00001
0.0001
0.001
0.01
0.1
1
10
100
0
200
400
600
800
1000
1200
Cytokine/Chemokine Production
% of Control (mean ± SEM)

FIG. 24

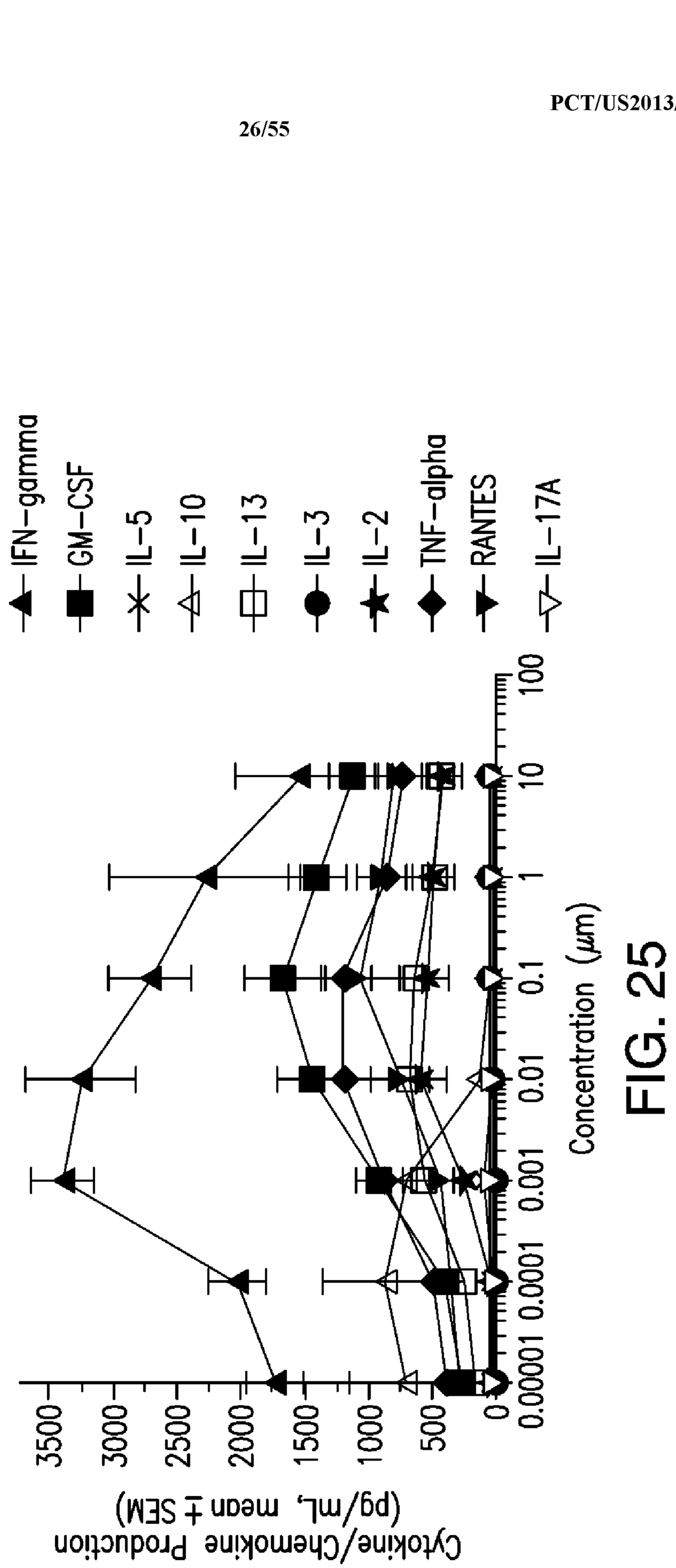

IFN-gamma
GM-CSF
IL-5
IL-10
IL-13
IL-3
IL-2
TNF-alpha
RANTES
IL-17A
Concentration (μm)
0.00001
0.0001
0.001
0.01
0.1
1
10
100
Cytokine/Chemokine Production
(pg/mL, mean ± SEM)
0
5
10
15
20
25
30
35

FIG. 25

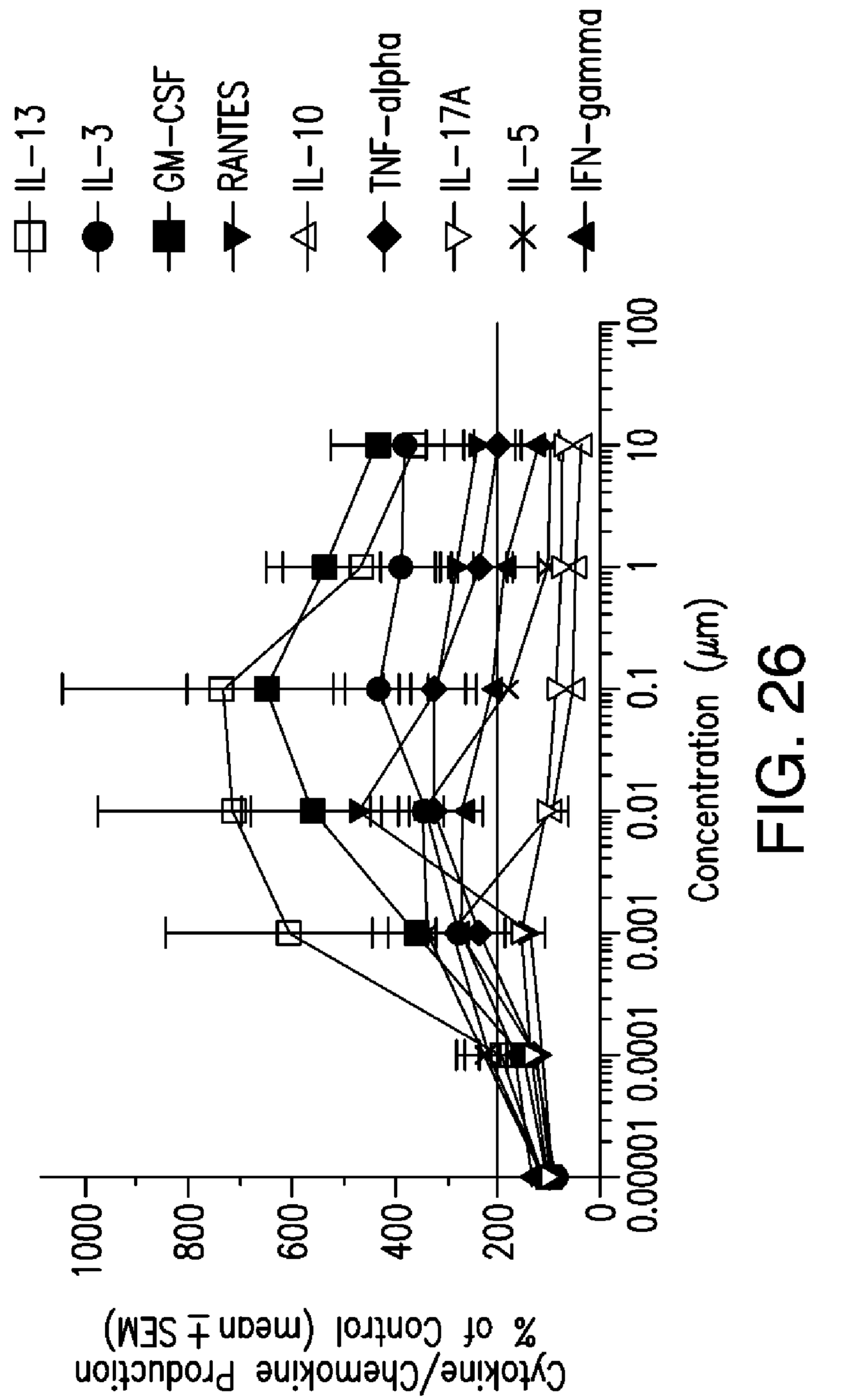

IL-13
IL-3
GM-CSF
RANTES
IL-10
TNF-alpha
IL-17A
IL-5
IFN-gamm
100
10
1
0.1
0.01
0.001
0.0001
0.00001
Concentration (μm)
0
200
400
600
800
000
Cytokine/Chemokine Production
% of Control (mean ± SEM)

FIG. 26

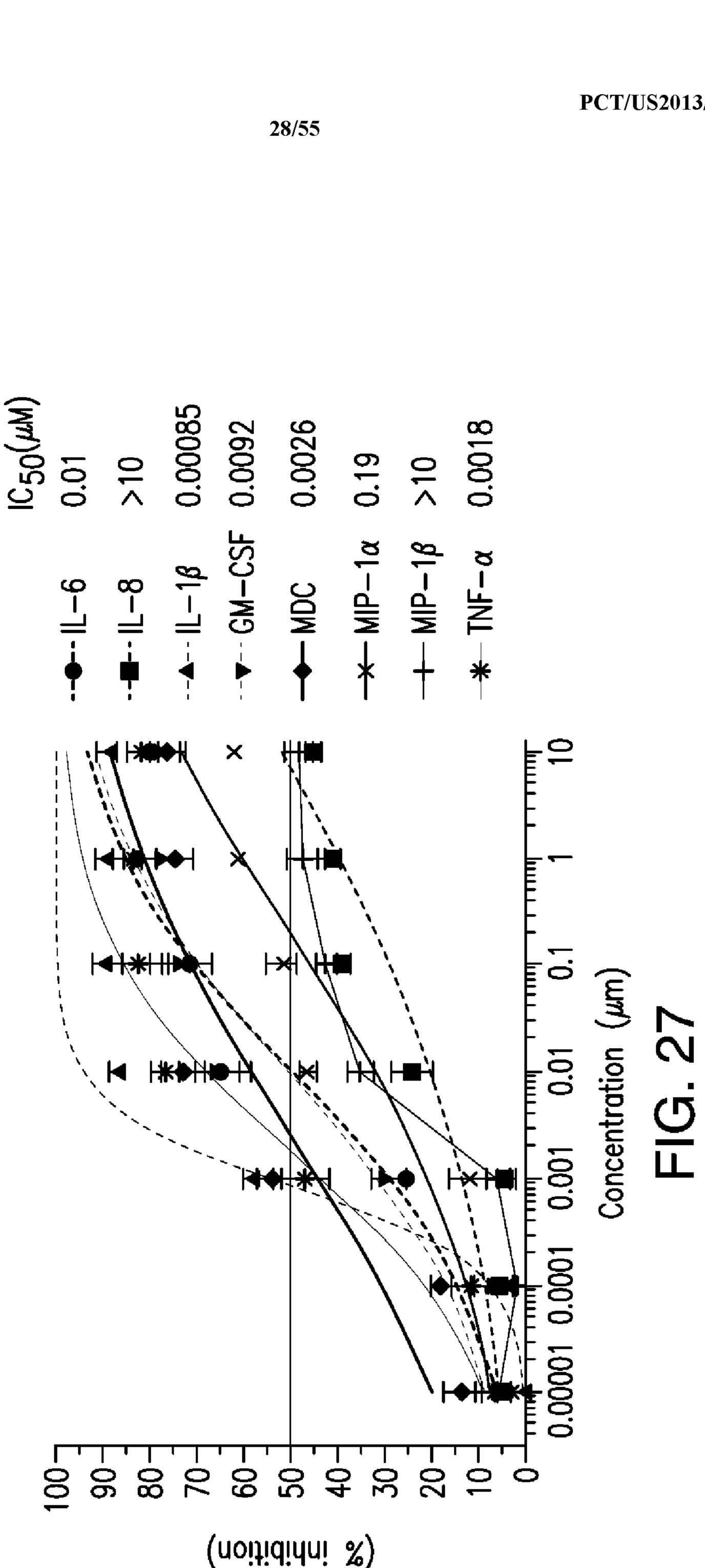

IC50(μM)
0.01
>10
0.00085
0.0092
0.0026
19
>10
0.0018
IL-6
IL-8
IL-1β
GM-CSF
MDC
MIP-1α
MIP-1β
TNF-α
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration (μm)
100
90
80
70
60
50
40
30
20
10
0
Cytokine Production
(% inhibition)

FIG. 27

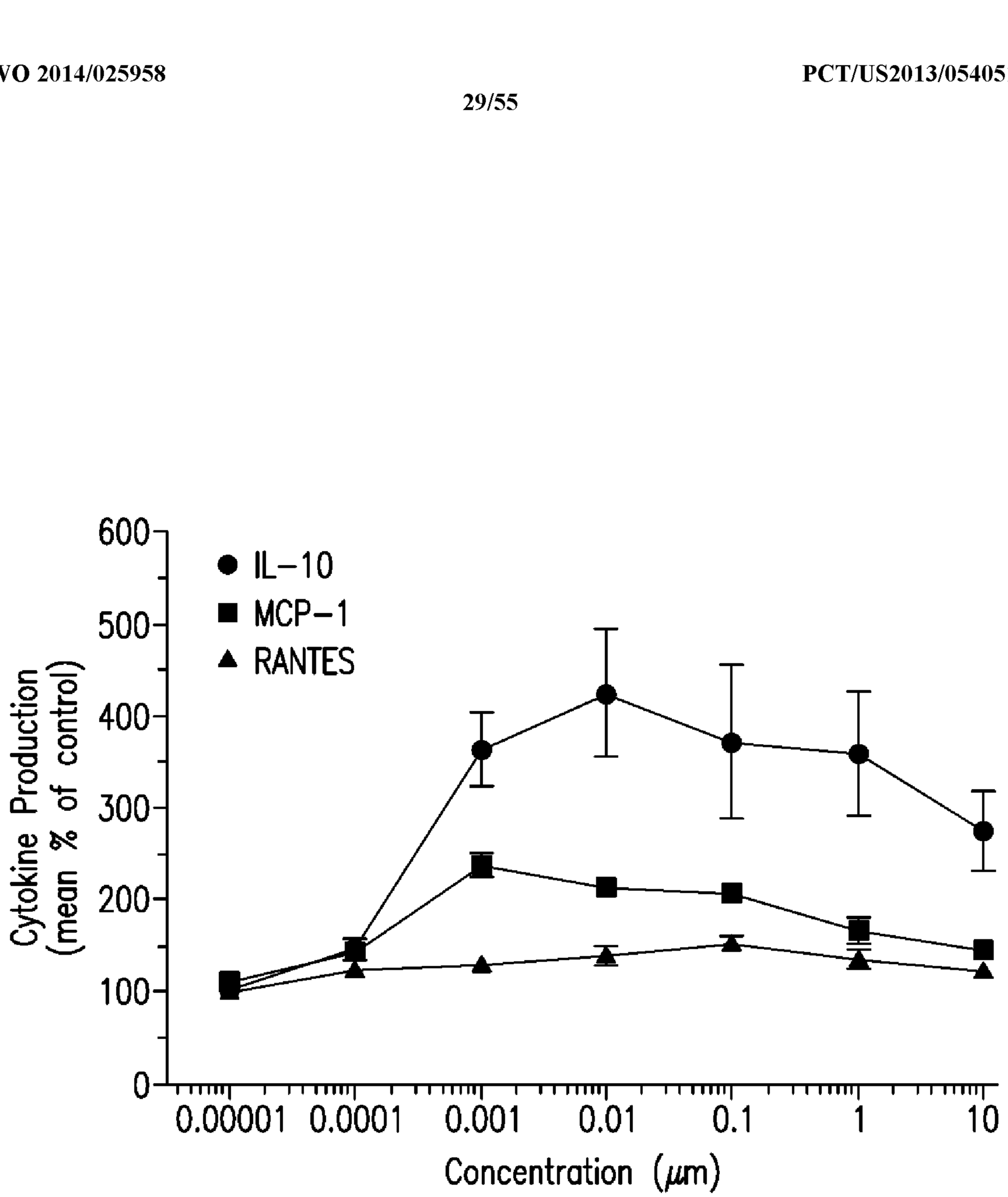

600
500
400
300
200
100
0
IL-10
MCP-1
RANTES
Cytokine Production
(mean % of control)
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration (μm)

FIG. 28

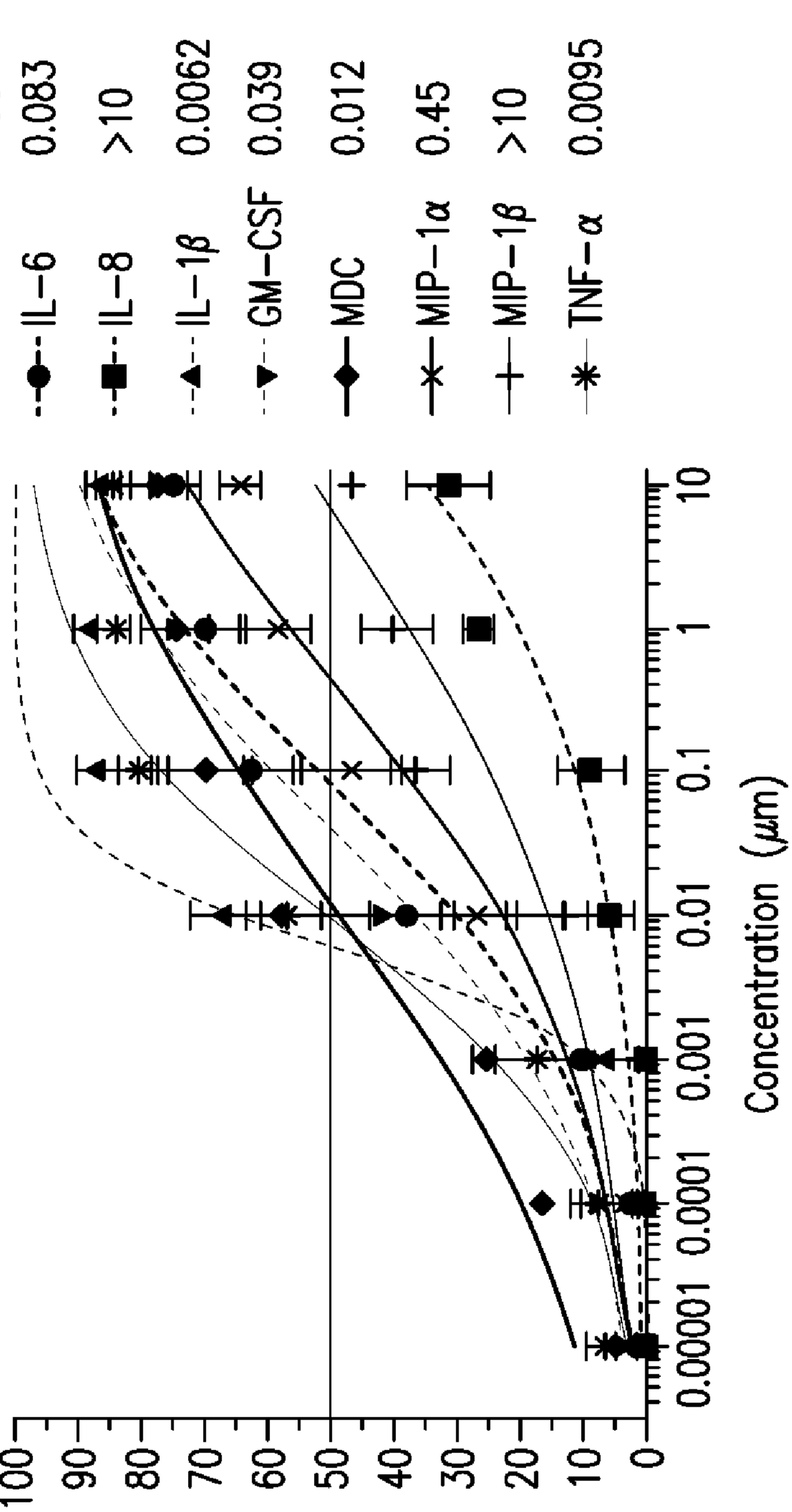

IC50(μM)
0.083
> 10
0.0062
0.039
0.012
0.45
> 10
0.0095
IL-6
IL-8
IL-1β
GM-CSF
MDC
MIP-1α
MIP-1β
TNF-α
100
90
80
70
60
50
40
30
20
10
0
Cytokine Production
(% inhibition)
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration (μm)

FIG. 29

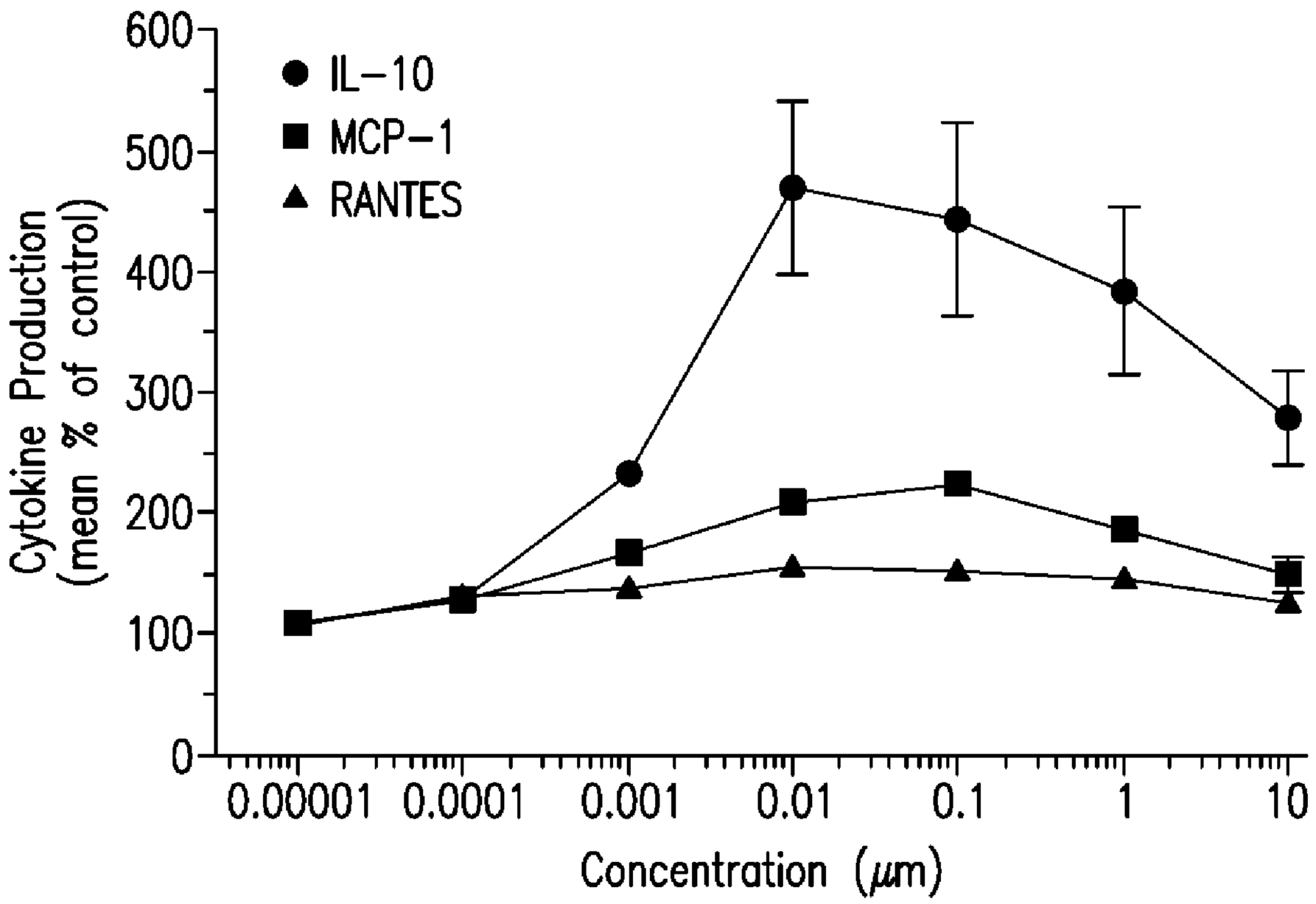

600
500
400
300
200
100
0
IL-10
MCP-1
RANTES
Cytokine Production
(mean % of control)
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration (μm)

FIG. 30

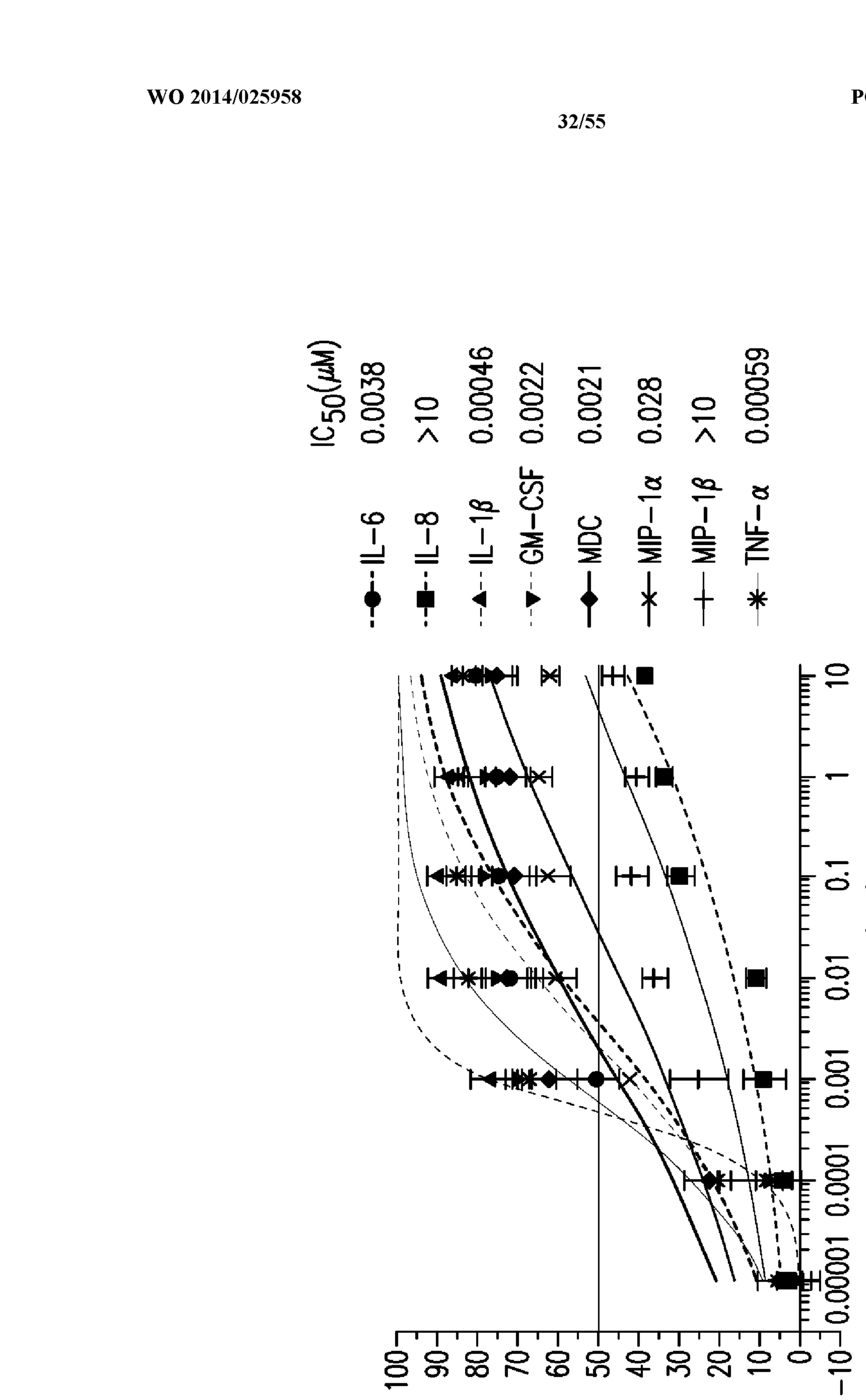

IC50(μM)
0.0038
>10
0.00046
0.0022
0.0021
0.028
>10
0.00059
IL-6
IL-8
IL-1β
GM-CSF
MDC
MIP-1α
MIP-1β
TNF-α
100
90
80
70
60
50
40
30
20
10
0
-10
Cytokine Production
(% inhibition)
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration (μm)

FIG. 31

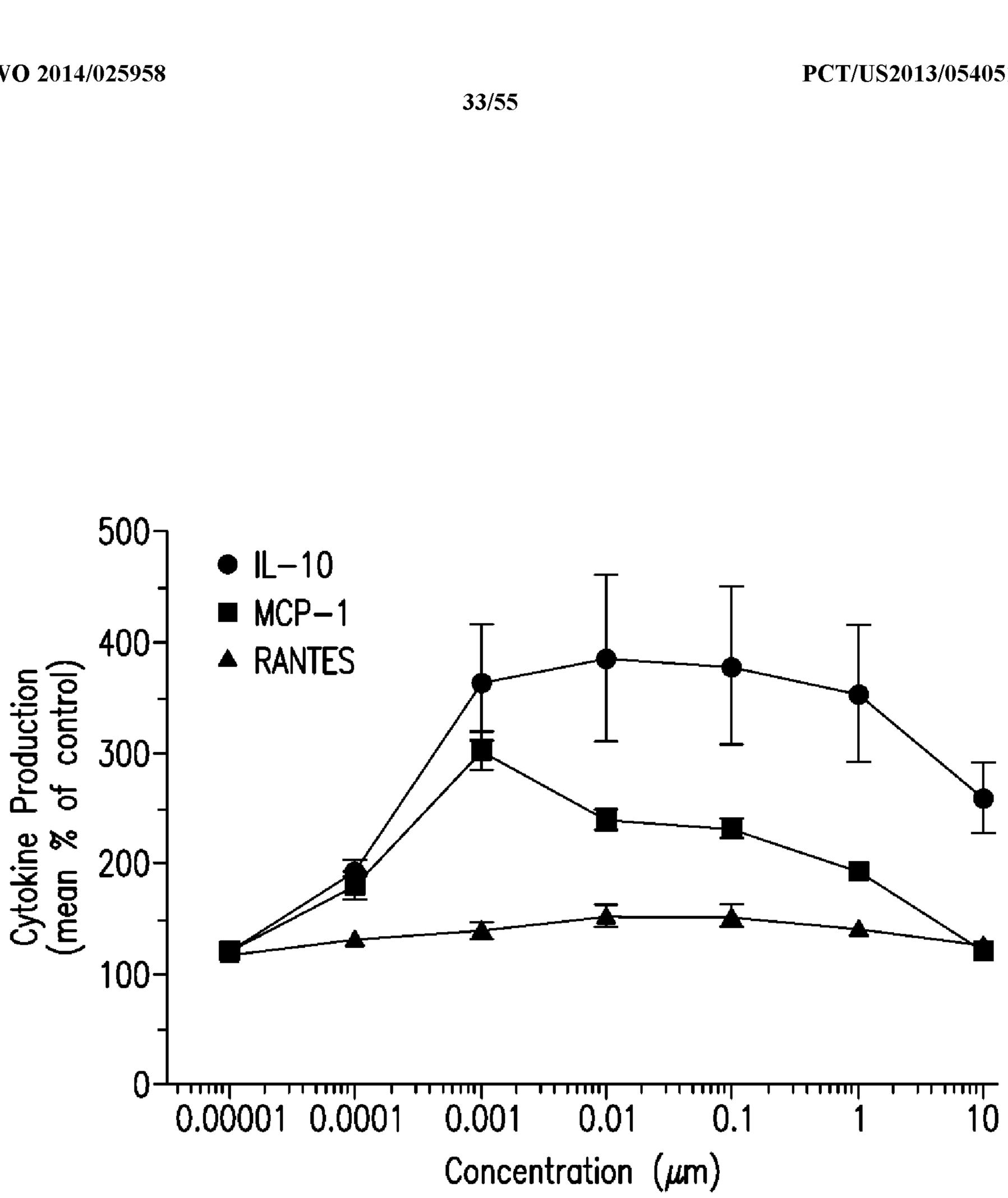

500
400
300
200
100
0
IL-10
MCP-1
RANTES
Cytokine Production
(mean % of control)
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration (μm)

FIG. 32

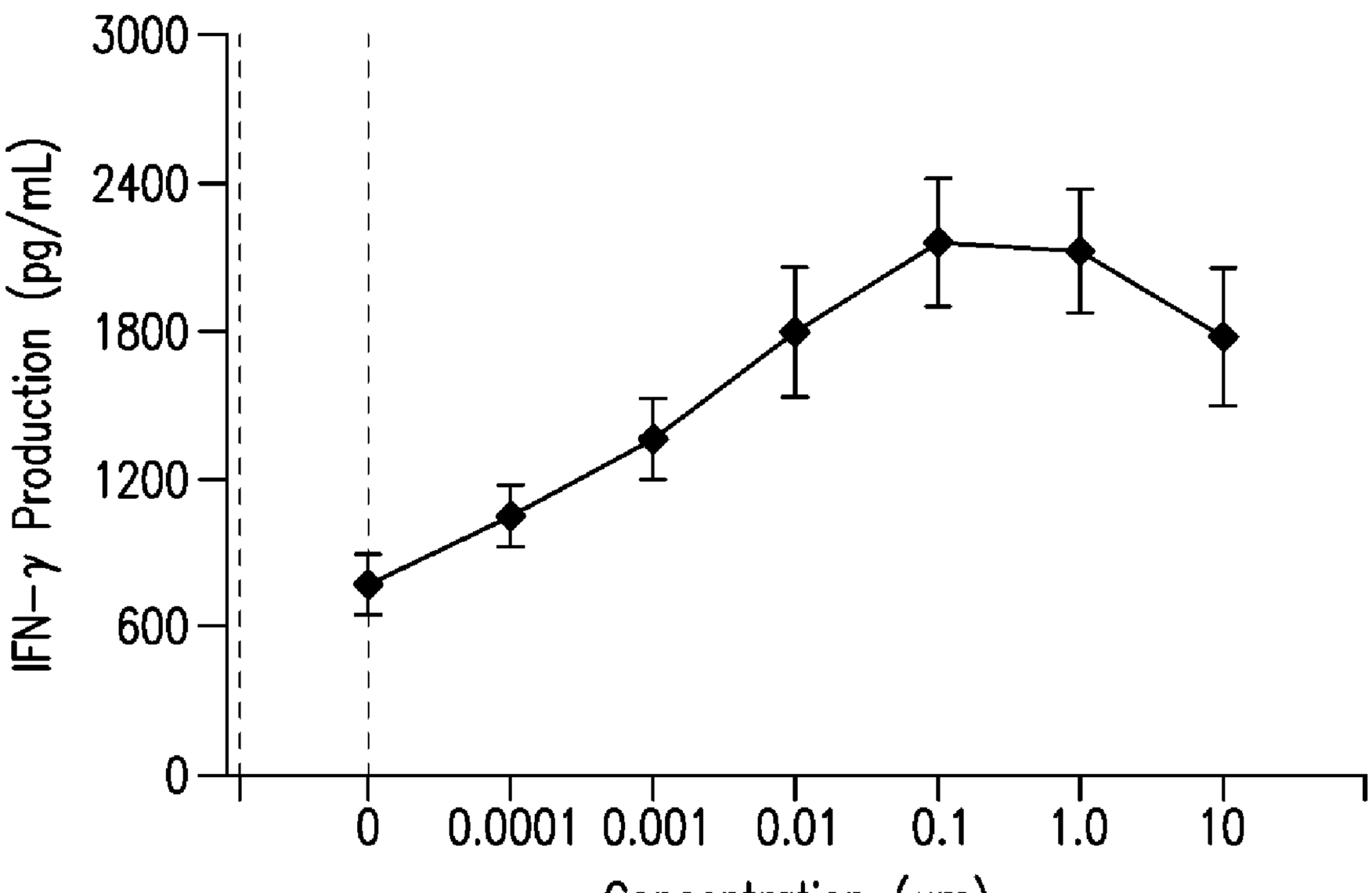

3000
2400
1800
1200
600
0
IFN-γ Production (pg/mL)
0
0.0001
0.001
0.01
0.1
1.0
10
Concentration (μm)

FIG. 33

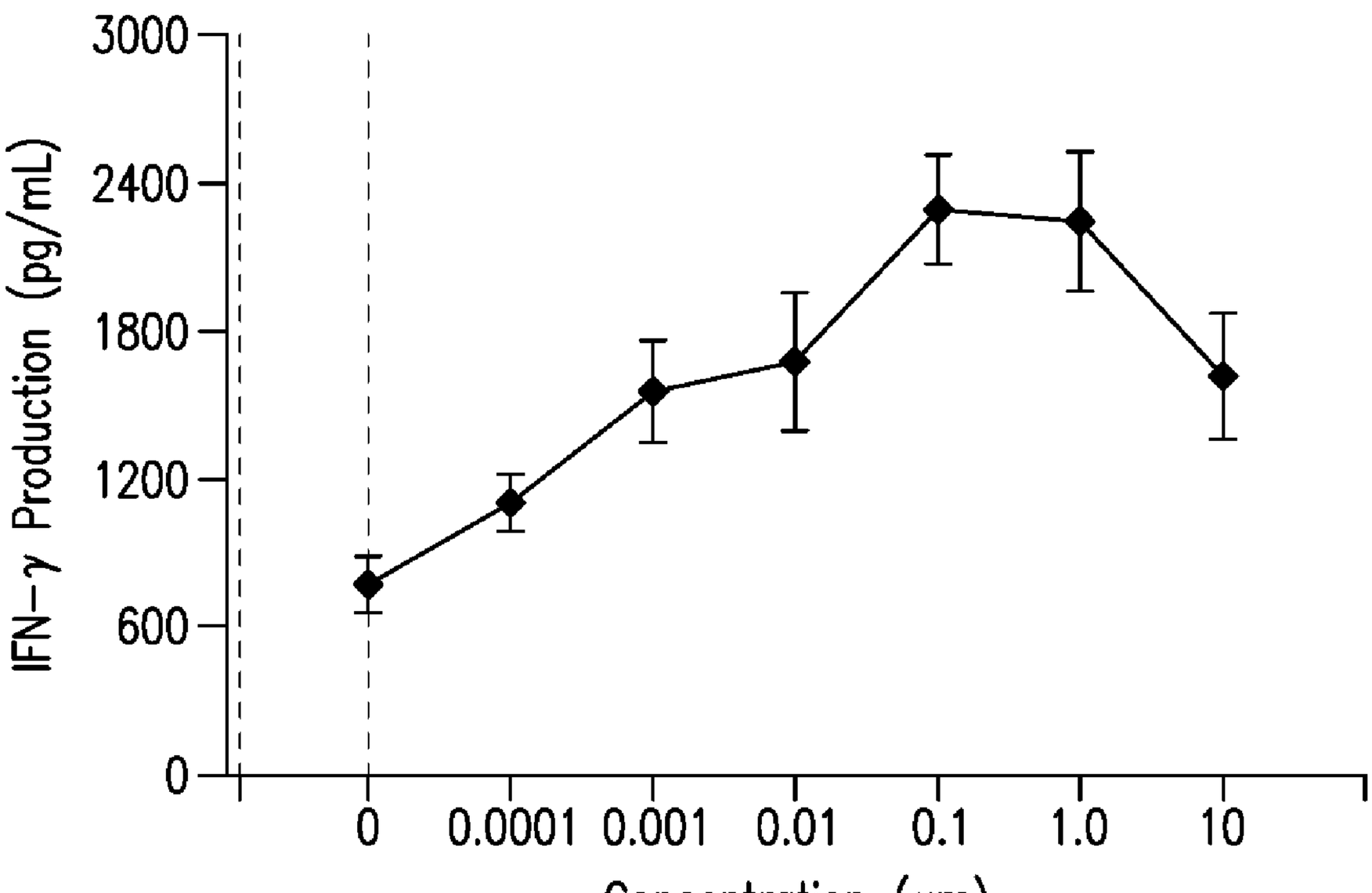

3000
2400
1800
1200
600
0
IFN-γ Production (pg/mL)
0
0.0001
0.001
0.01
0.1
1.0
10
Concentration (μm)

FIG. 34

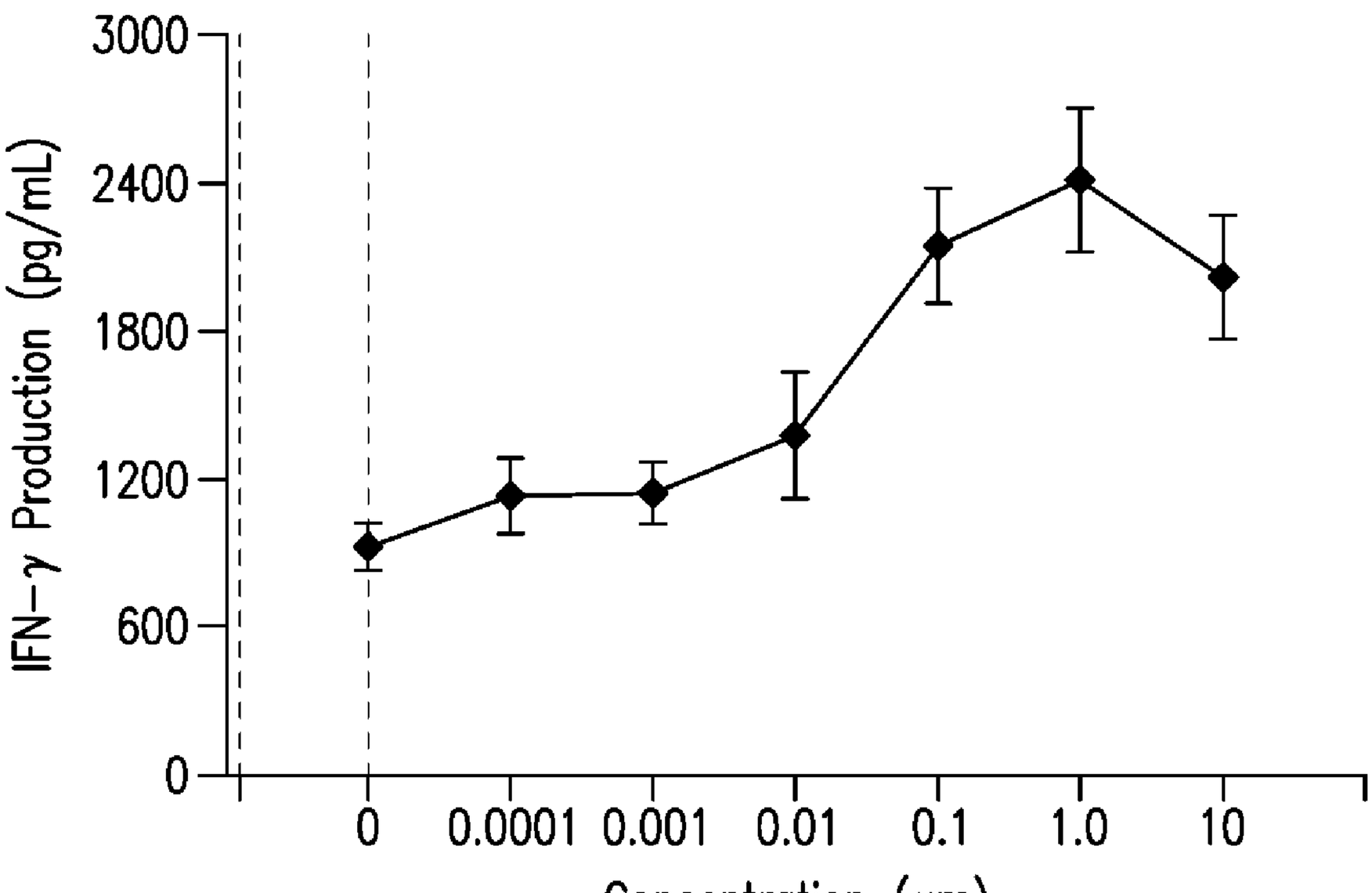

3000
2400
1800
1200
600
0
IFN-γ Production (pg/mL)
0
0.0001
0.001
0.01
0.1
1.0
10
Concentration (μm)

FIG. 35

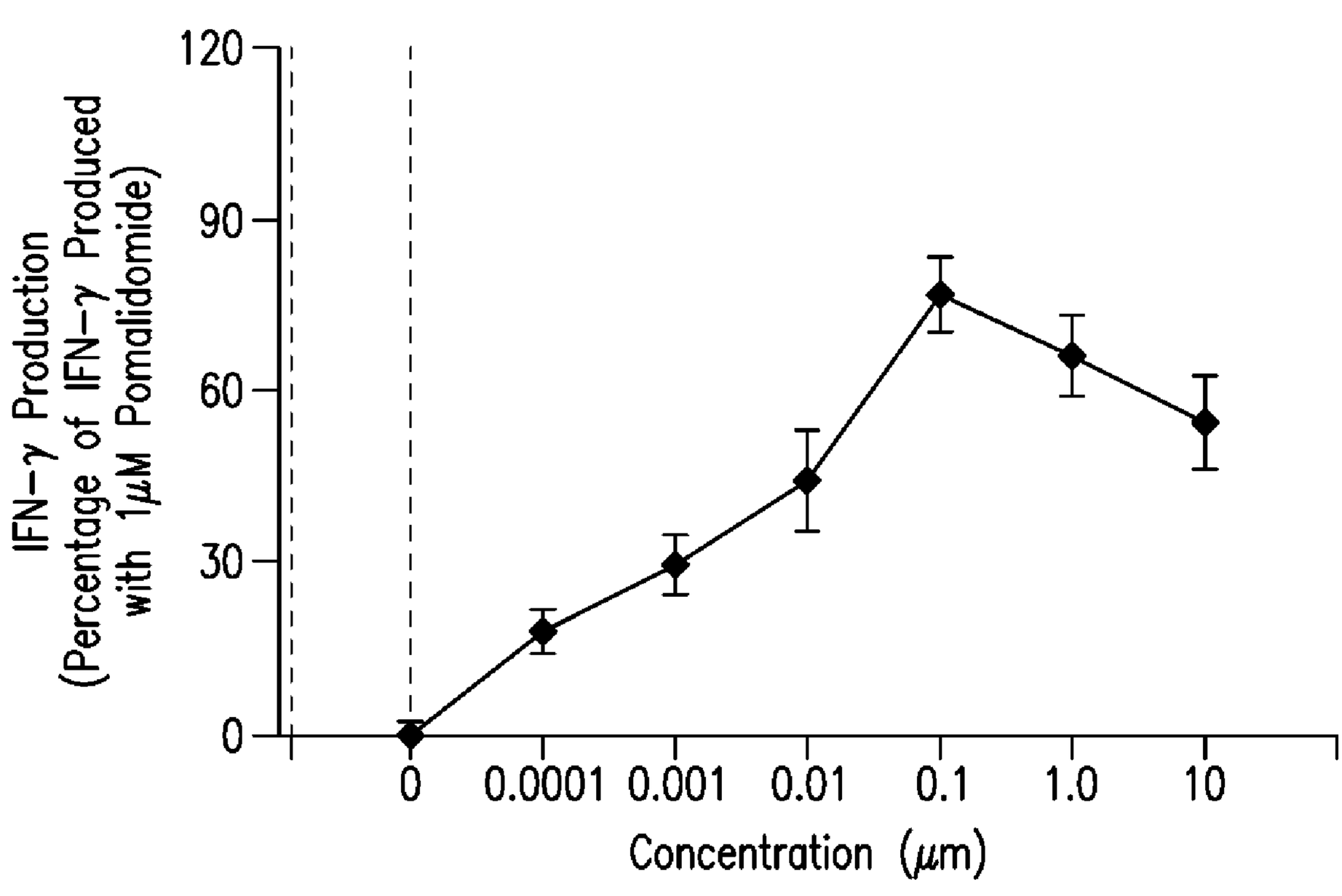

IFN-γ Production
(Percentage of IFN-γ Produced
with 1μM Pomalidomide)
120
90
60
30
0
0
0.0001
0.001
0.01
0.1
1.0
10
Concentration (μm)

FIG. 36

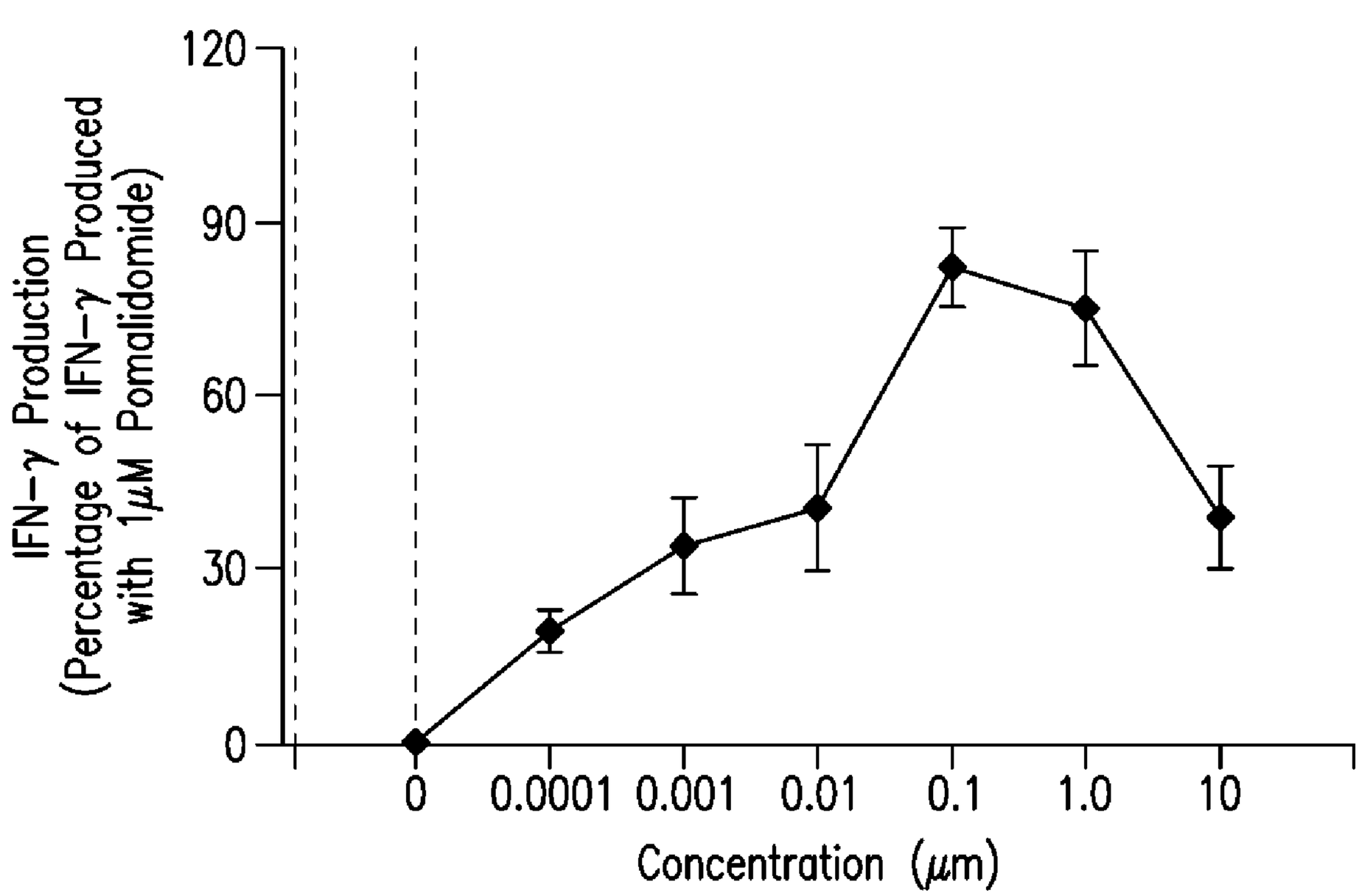

IFN-γ Production
(Percentage of IFN-γ Produced
with 1μM Pomalidomide)
120
90
60
30
0
0
0.0001
0.001
0.01
0.1
1.0
10
Concentration (μm)

FIG. 37

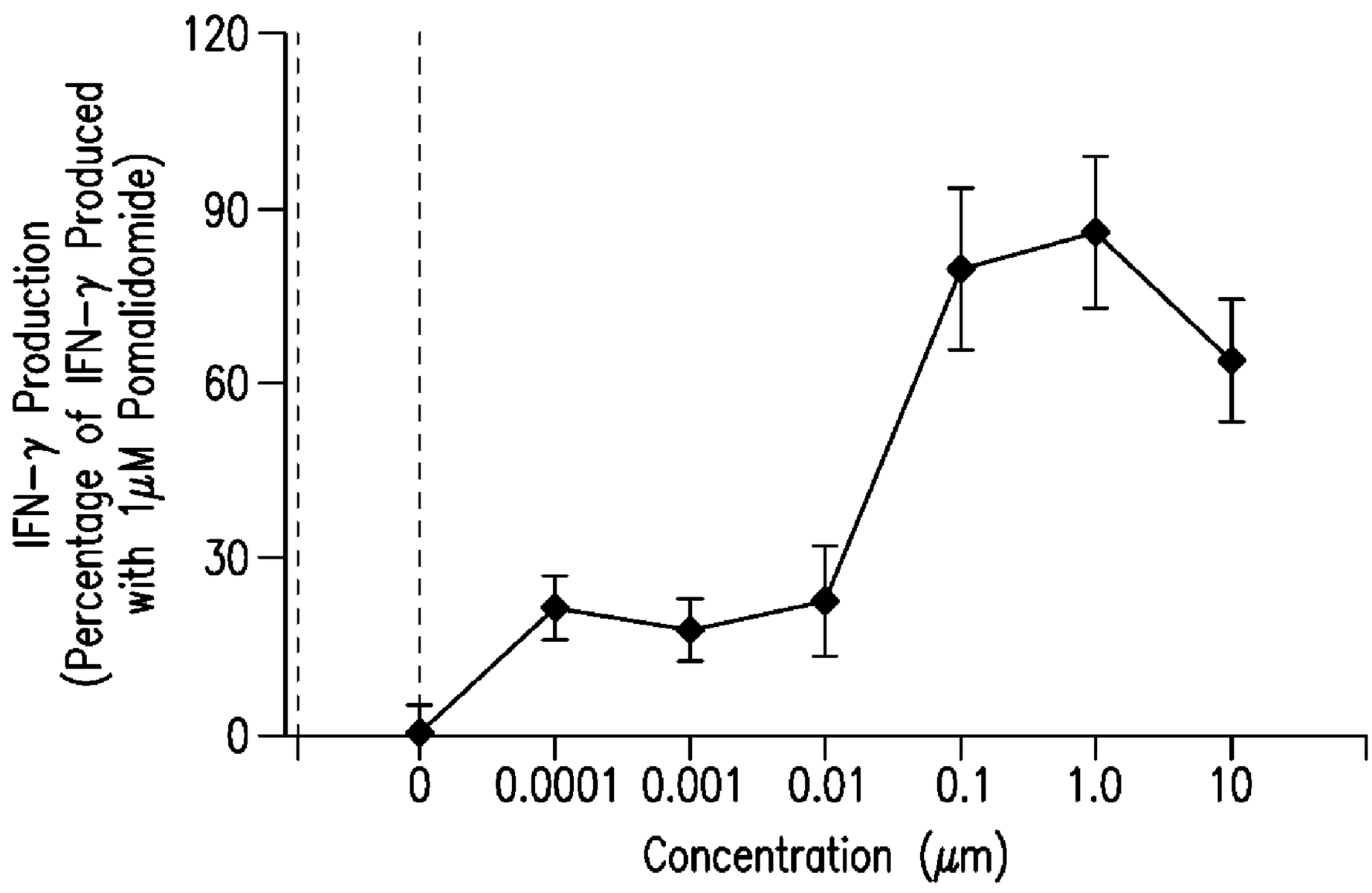

IFN-γ Production
(Percentage of IFN-γ Produced
with 1μM Pomalidomide)
120
90
60
30
0
0
0.0001
0.001
0.01
0.1
1.0
10
Concentration (μm)

FIG. 38

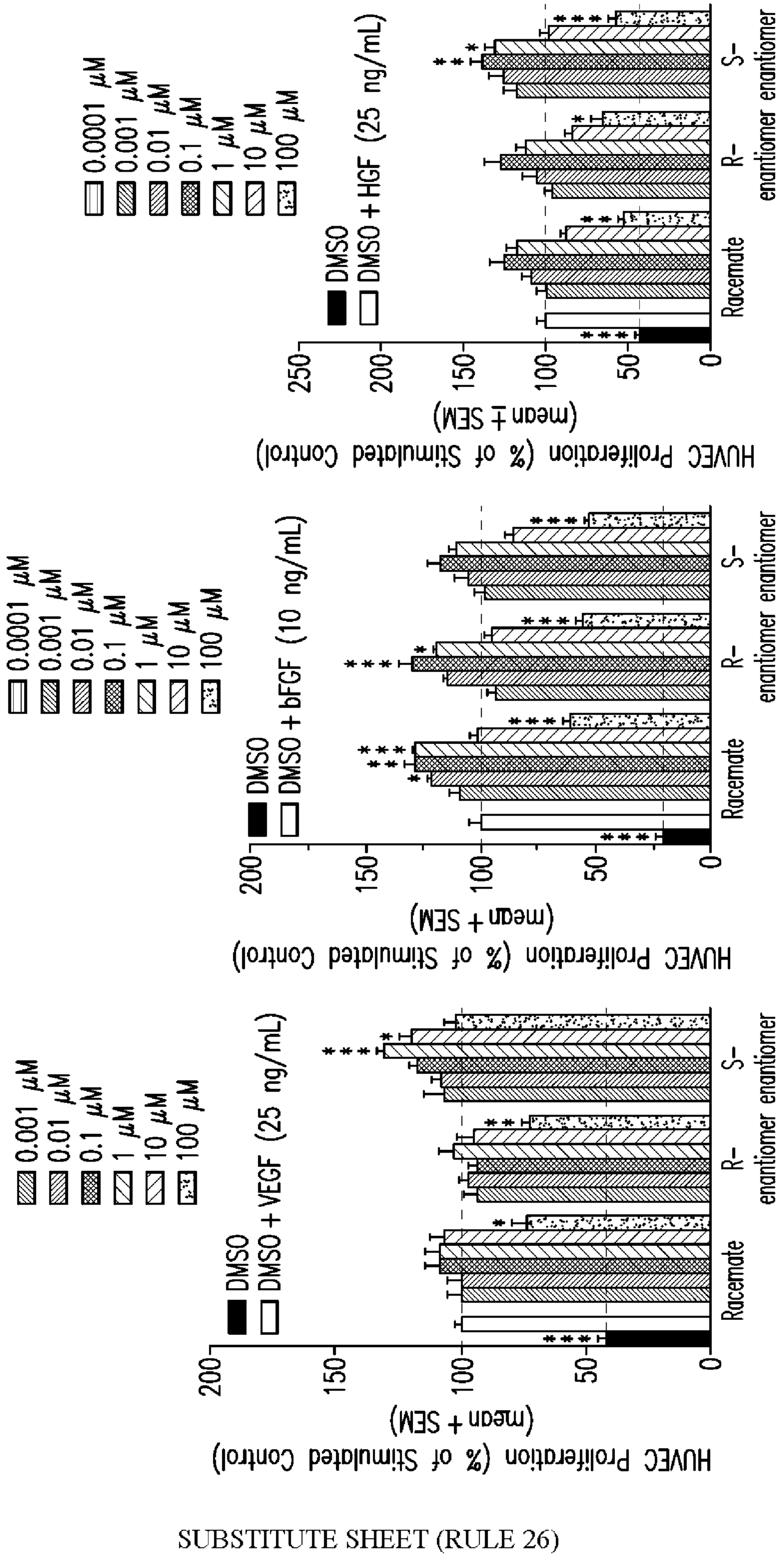

HUVEC Proliferation (% of Stimulated Control)
(mean ± SEM)
250
200
150
100
50
0
DMSO
DMSO + HGF (25 ng/mL)
0.0001 μM
0.001 μM
0.01 μM
0.1 μM
1 μM
10 μM
100 μM
S– enantiomer
R– enantiomer
Racemate
DMSO
DMSO + bFGF (10 ng/mL)
0.0001 μM
0.001 μM
0.01 μM
0.1 μM
1 μM
10 μM
100 μM
S– enantiomer
R– enantiomer
Racemate
DMSO
DMSO + VEGF (25 ng/mL)
0.001 μM
0.01 μM
0.1 μM
1 μM
10 μM
100 μM
S– enantiomer
R– enantiomer
Racemate

FIG. 39

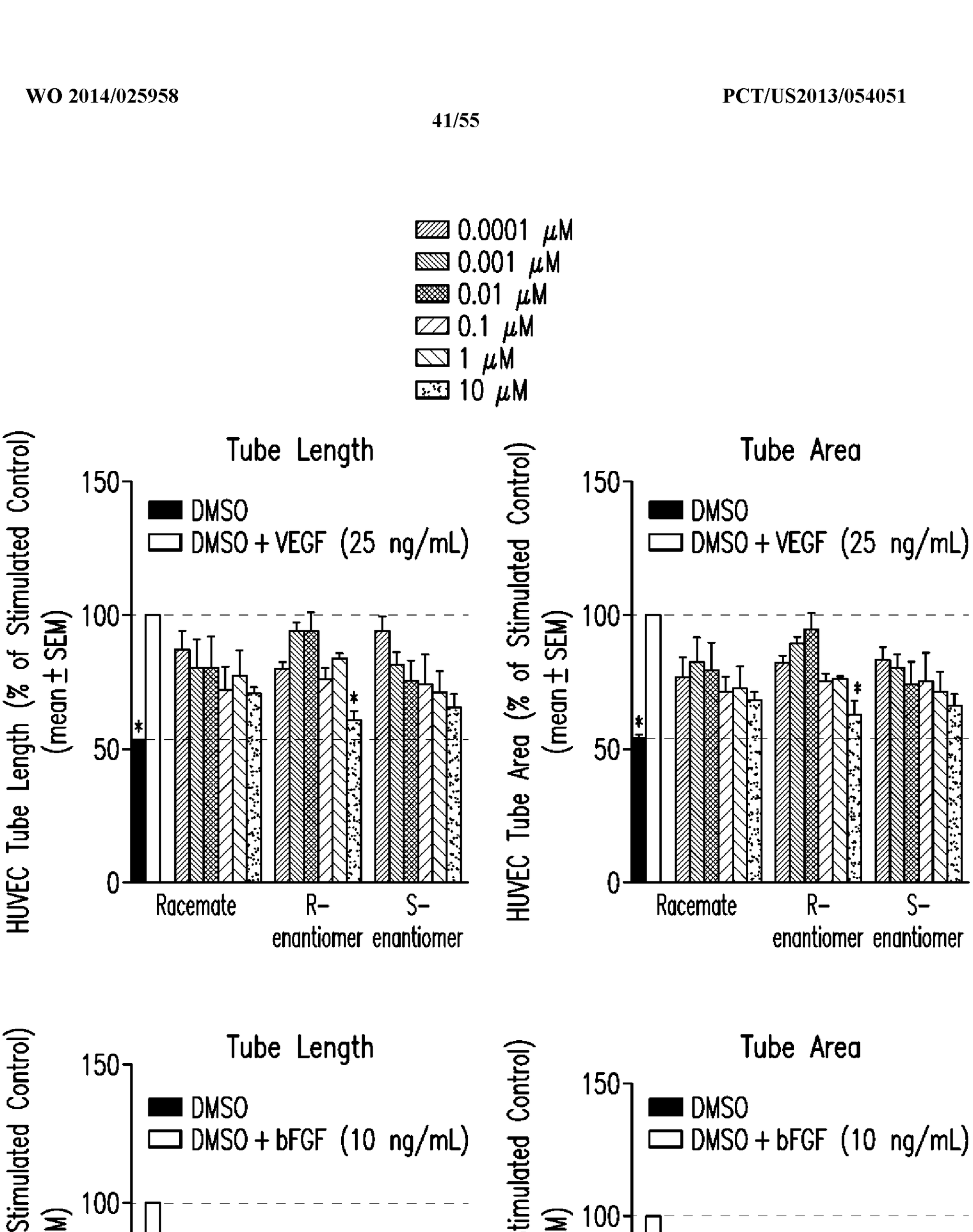

0.0001 μM
0.001 μM
0.01 μM
0.1 μM
1 μM
10 μM
Tube Length
Tube Area
DMSO
DMSO + VEGF (25 ng/mL)
DMSO + bFGF (10 ng/mL)
HUVEC Tube Length (% of Stimulated Control) (mean ± SEM)
HUVEC Tube Area (% of Stimulated Control) (mean ± SEM)
150
100
50
0
*
**
Racemate
R- enantiomer
S- enantiomer

FIG. 40

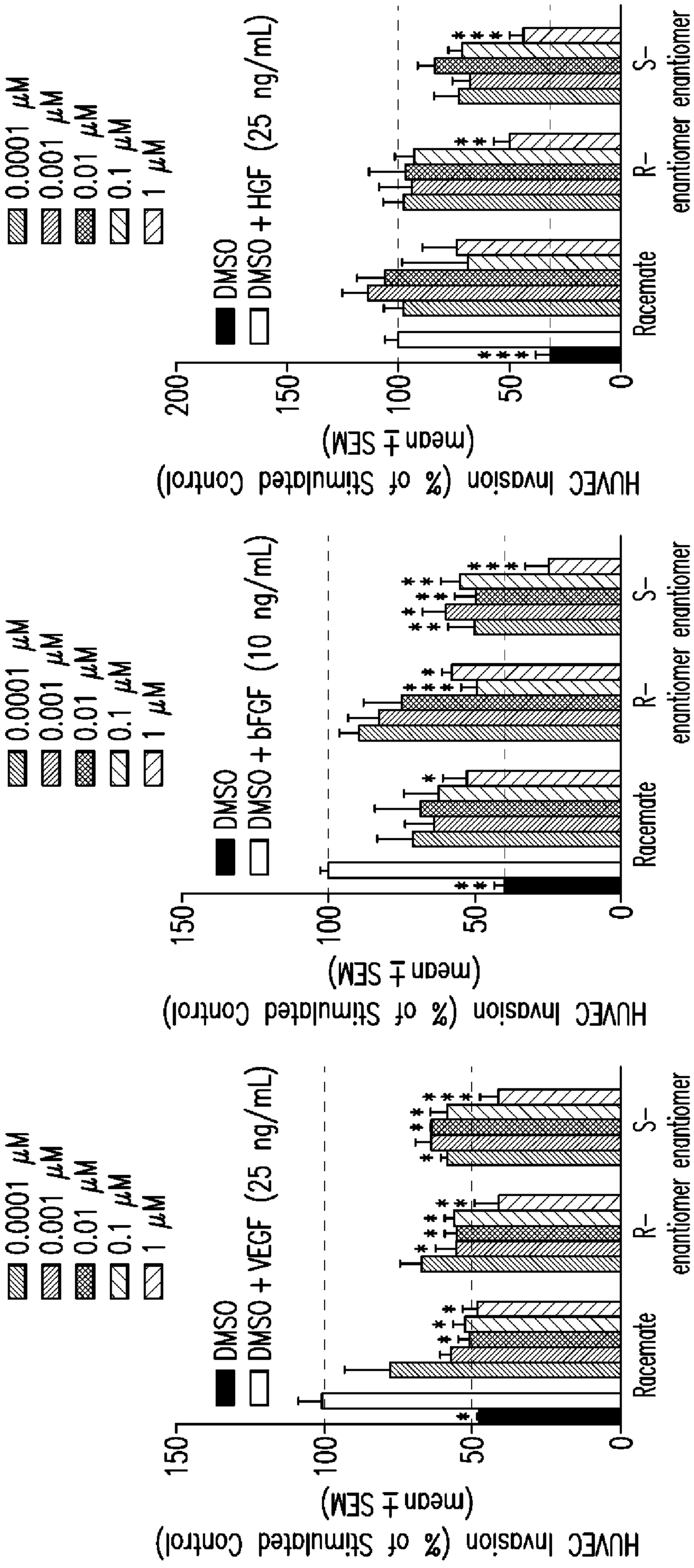

0.0001 μM
0.001 μM
0.01 μM
0.1 μM
1 μM
DMSO
DMSO + HGF (25 ng/mL)
DMSO + bFGF (10 ng/mL)
DMSO + VEGF (25 ng/mL)
HUVEC Invasion (% of Stimulated Control)
(mean ± SEM)
200
150
100
50
0
Racemate
R– enantiomer
S– enantiomer

FIG. 41

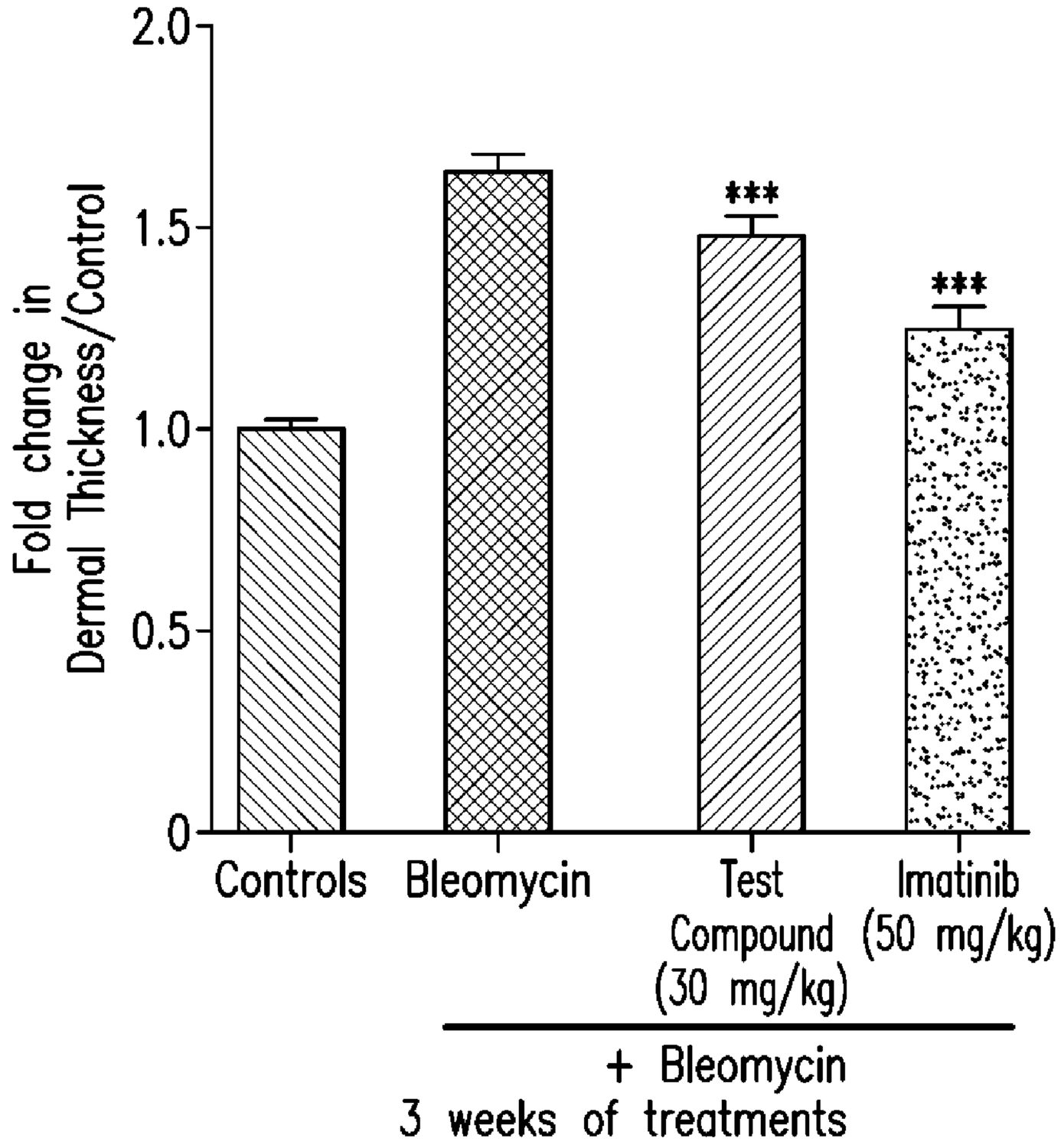
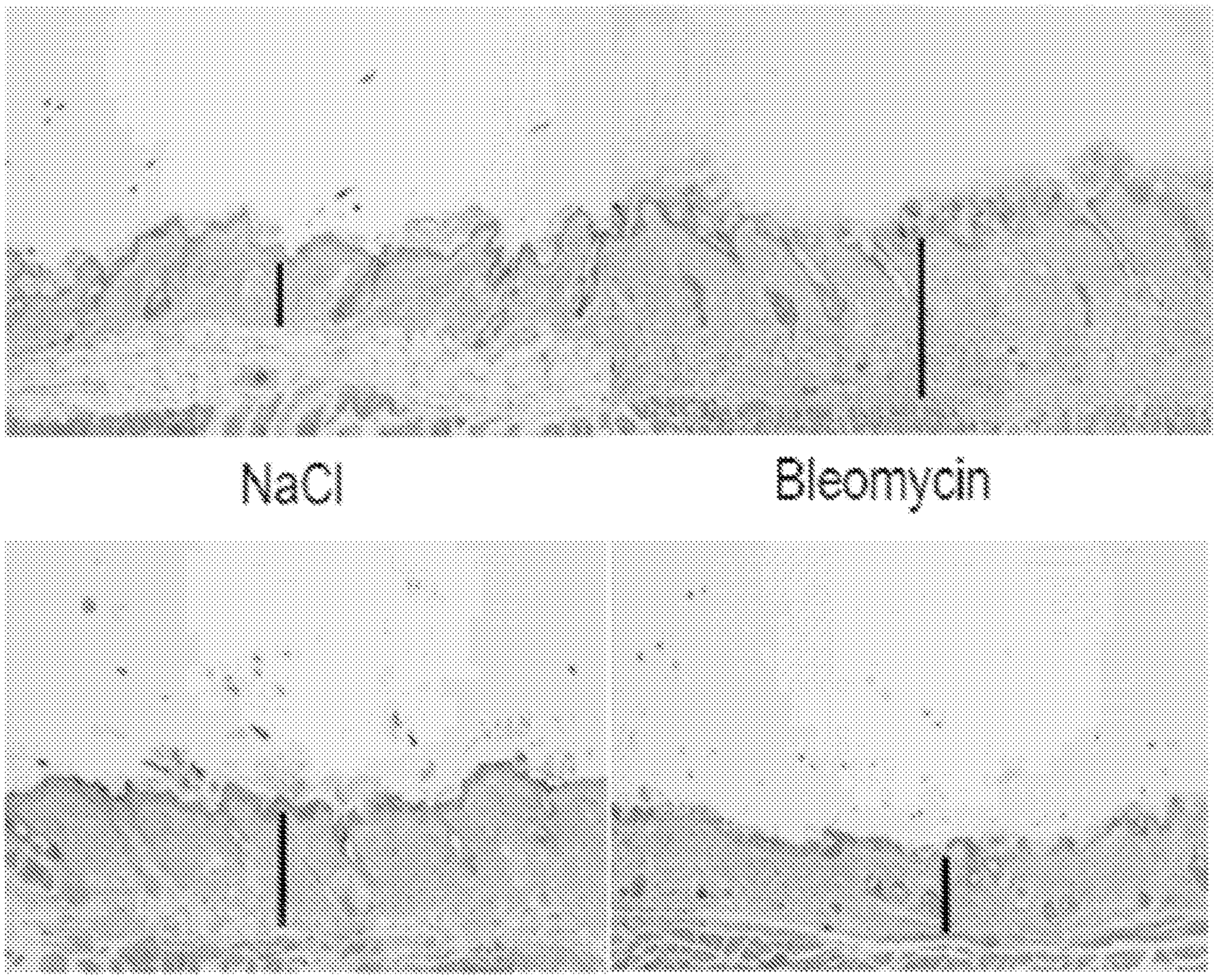

Fold change in Dermal Thickness/Control
2.0
1.5
1.0
0.5
0
***
***
Controls
Bleomycin
Test Compound (30 mg/kg)
Imatinib (50 mg/kg)
+ Bleomycin
3 weeks of treatments

FIG. 42

FIG. 43



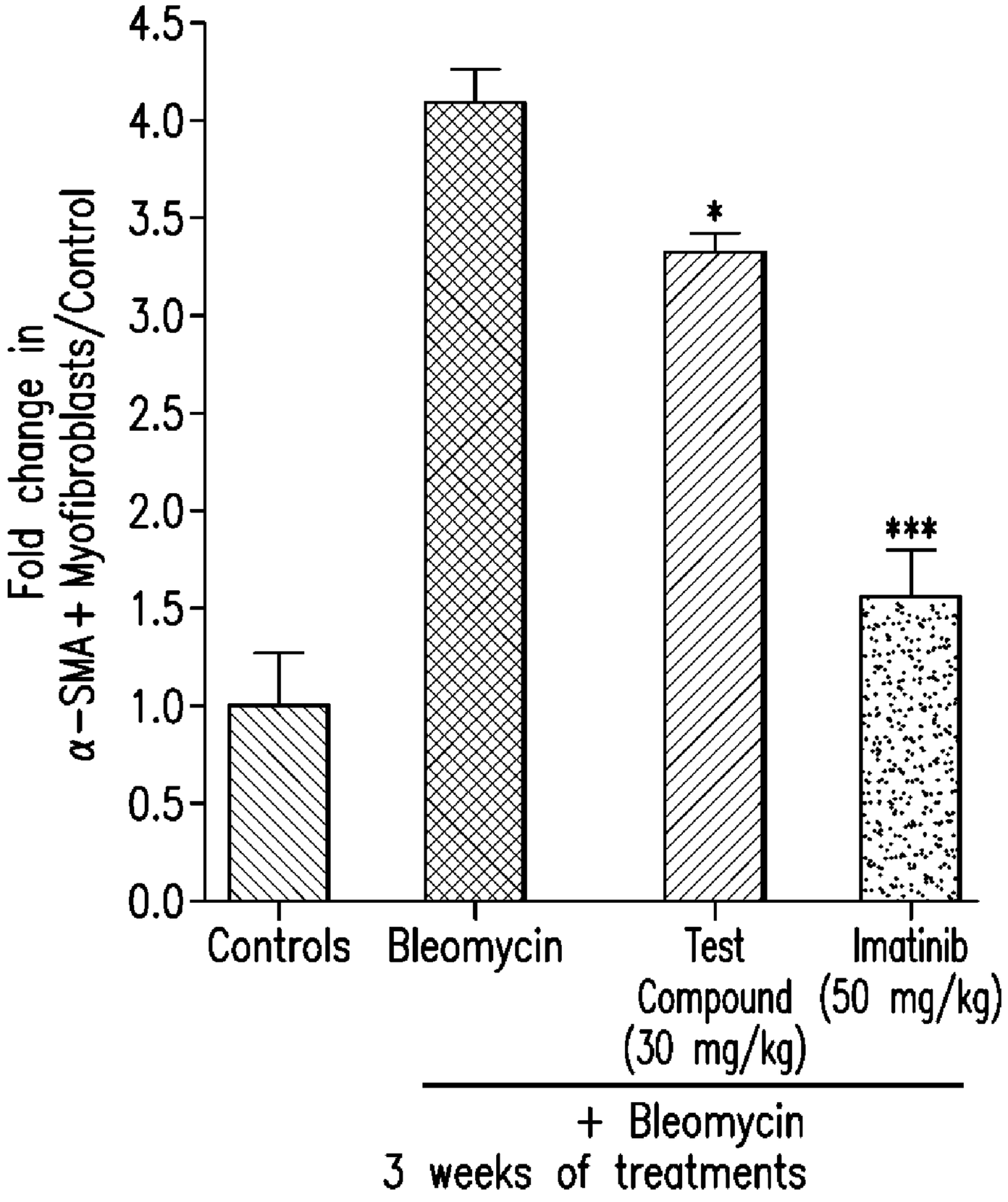

Fold change in
α−SMA + Myofibroblasts/Control
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
***
Controls
Bleomycin
Test Compound (30 mg/kg)
Imatinib (50 mg/kg)
+ Bleomycin
3 weeks of treatments

FIG. 44

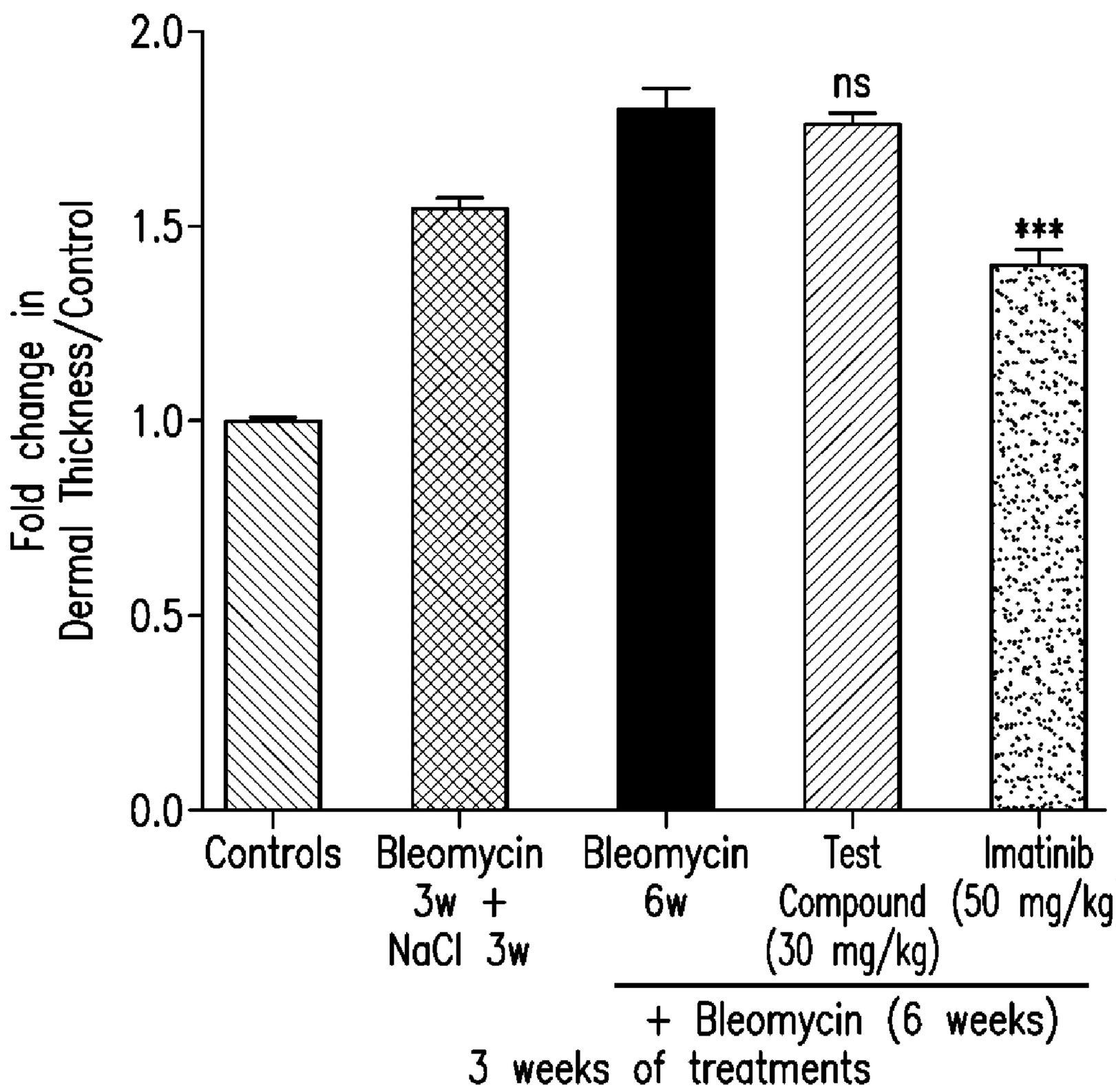
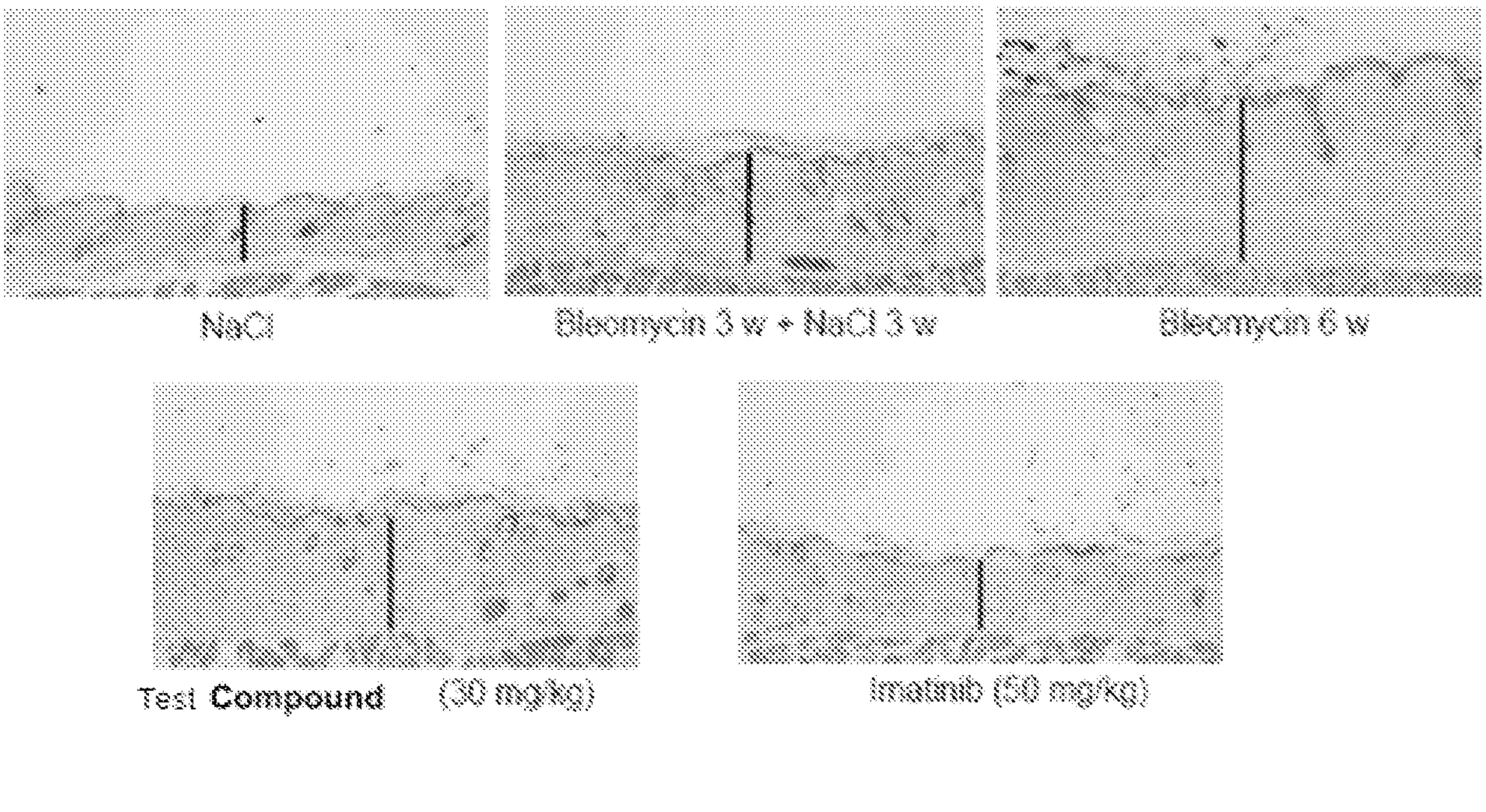

2.0
1.5
1.0
0.5
0.0
Fold change in Dermal Thickness/Control
ns
***
Controls
Bleomycin 3w + NaCl 3w
Bleomycin 6w
Test Compound (30 mg/kg)
Imatinib (50 mg/kg)
+ Bleomycin (6 weeks)
3 weeks of treatments

FIG. 45

FIG. 46


NaCl
Bleomycin 3 w + NaCl 3 w
Bleomycin 6 w
Test Compound (30 mg/kg)
Imatinib (50 mg/kg)

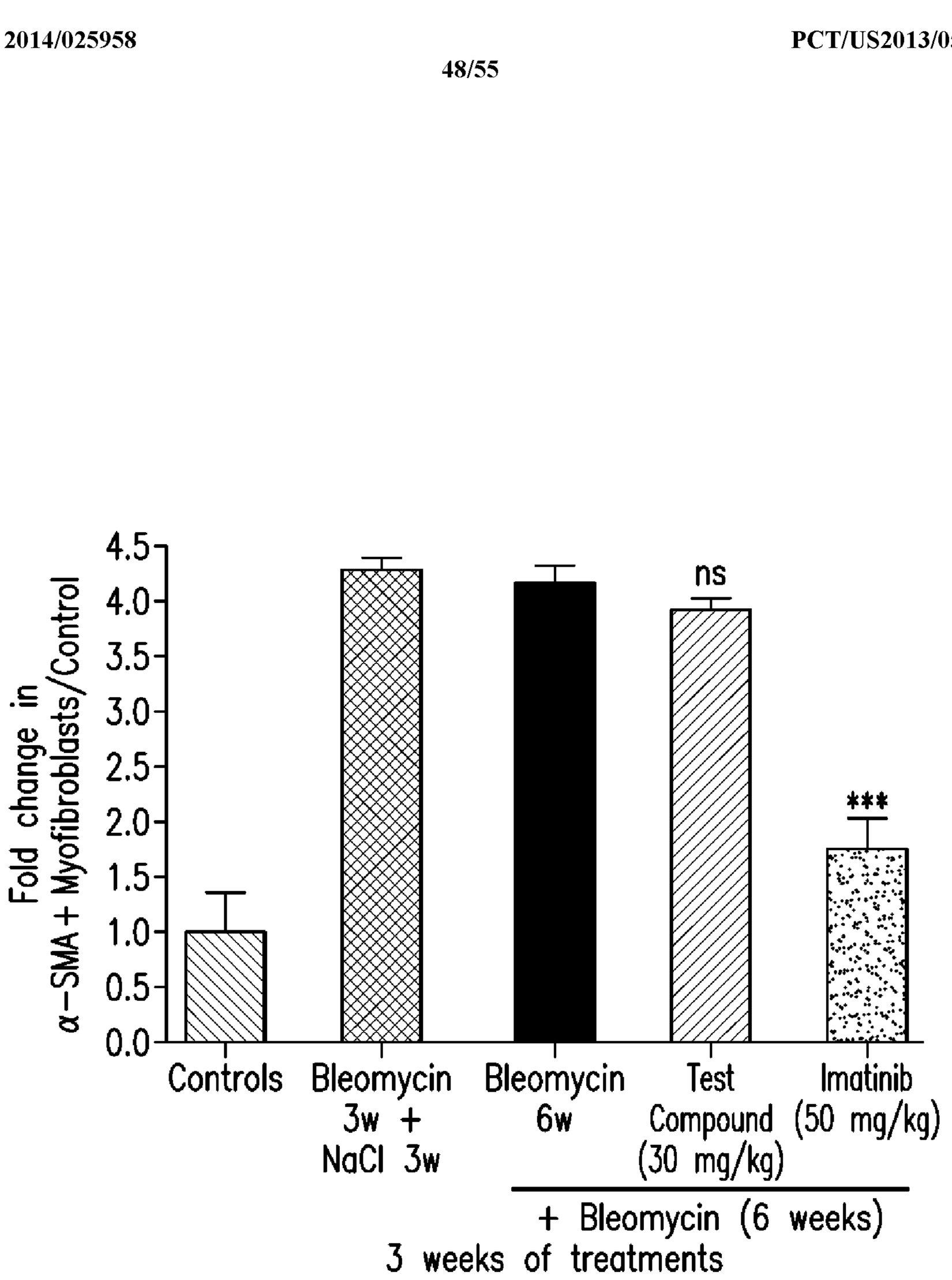

Fold change in
α−SMA+ Myofibroblasts/Control
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ns
***
Controls
Bleomycin 3w + NaCl 3w
Bleomycin 6w
Test Compound (30 mg/kg)
Imatinib (50 mg/kg)
+ Bleomycin (6 weeks)
3 weeks of treatments

FIG. 47

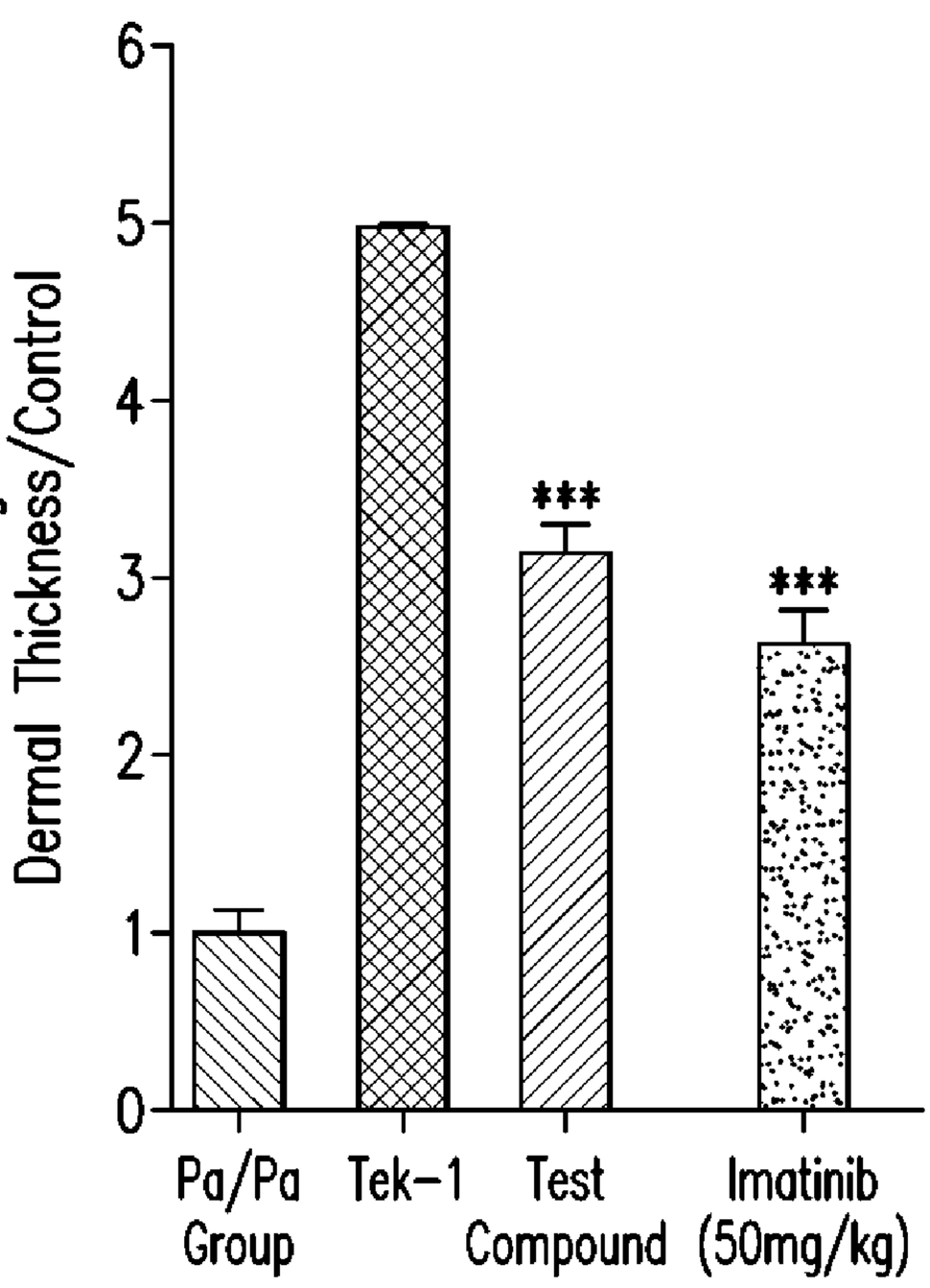


FIG. 48A

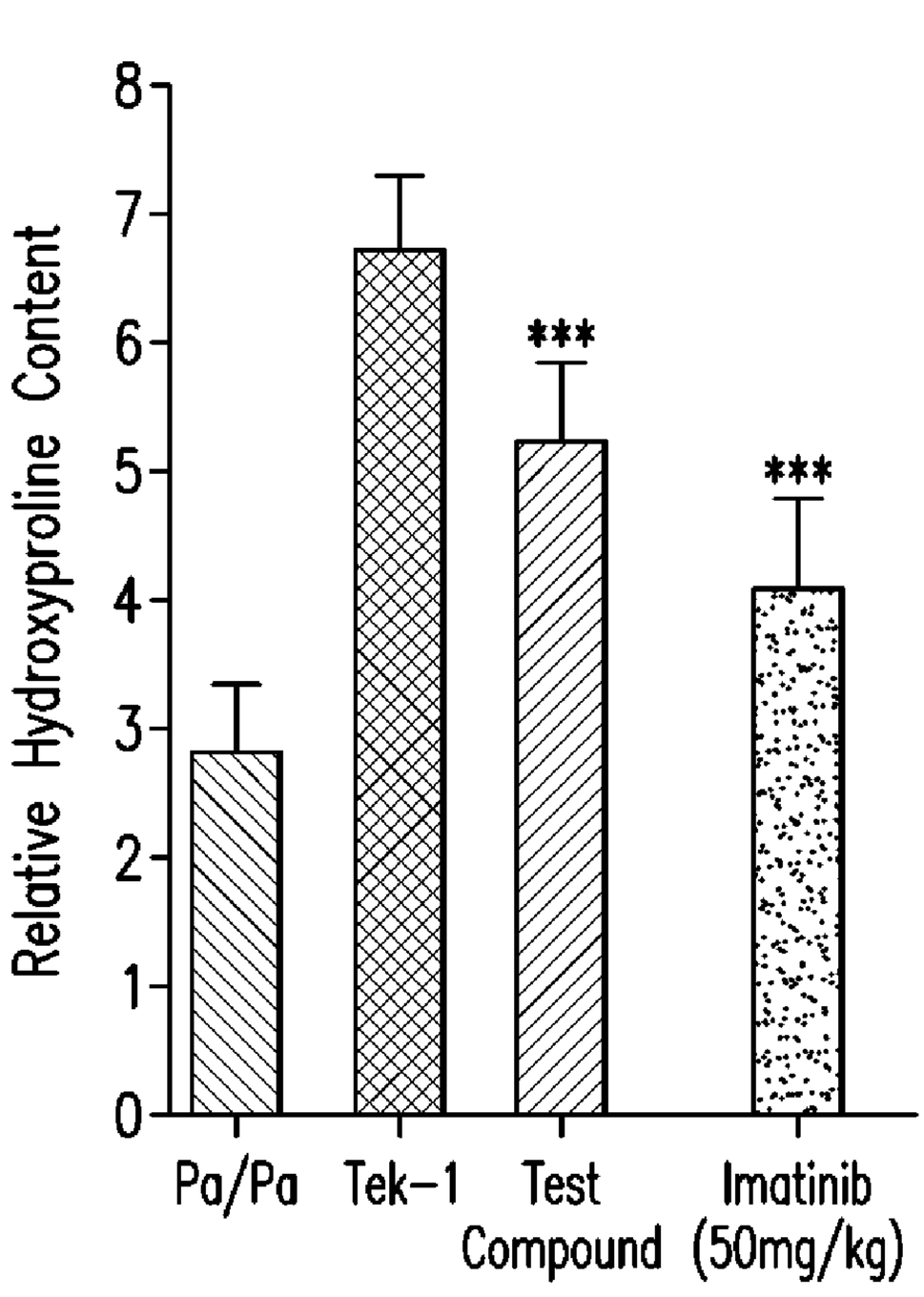
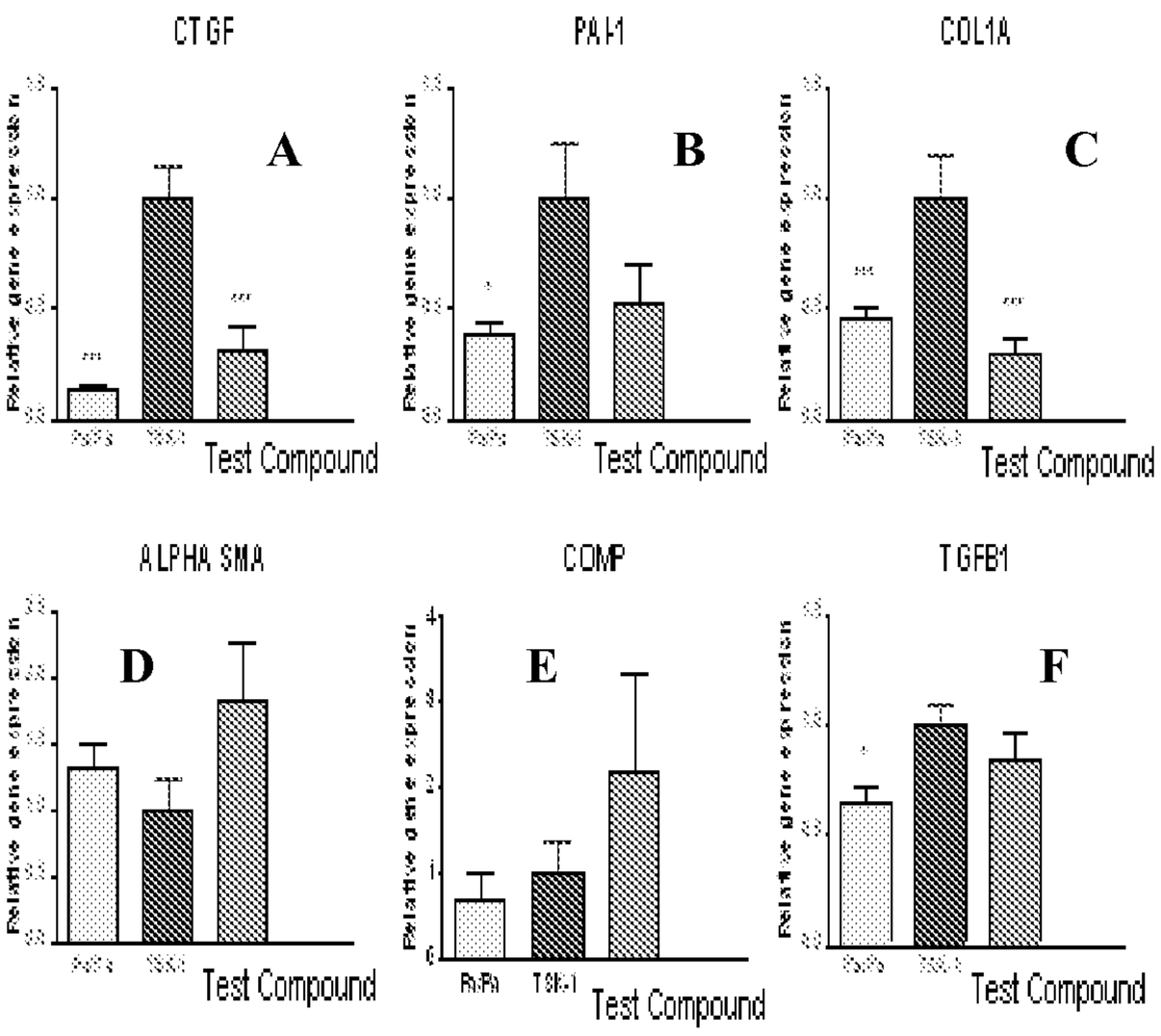


FIG. 48B

FIG. 49


CTGF
PAI-1
COL1A
A
B
C
Test Compound
Test Compound
Test Compound
ALPHA SMA
COMP
TGFB1
D
E
F
Test Compound
Test Compound
Test Compound

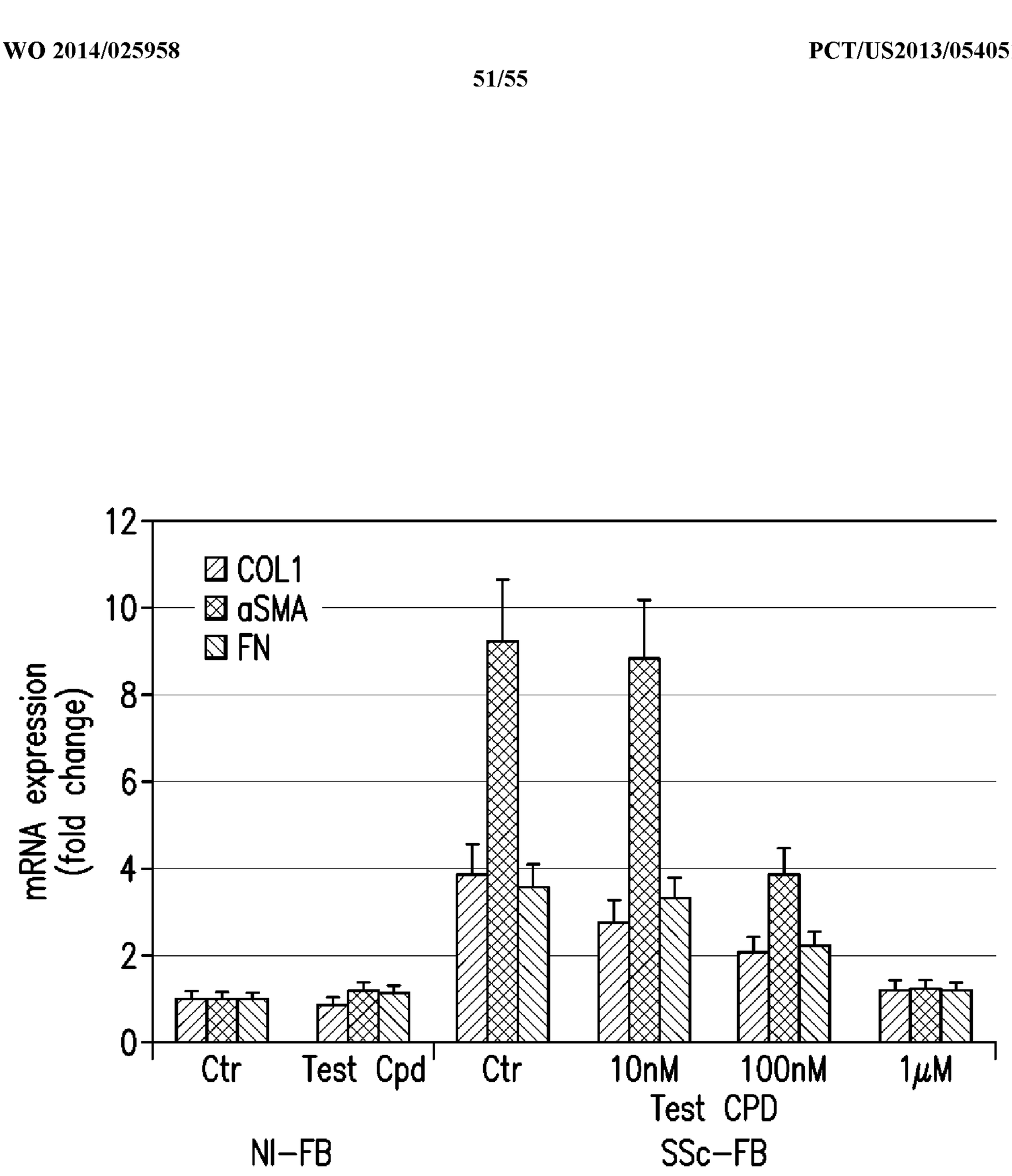

12
10
8
6
4
2
0
COL1
αSMA
FN
mRNA expression (fold change)
Ctr
Test Cpd
Ctr
10nM
100nM
1μM
Test CPD
NI-FB
SSc-FB

FIG. 50

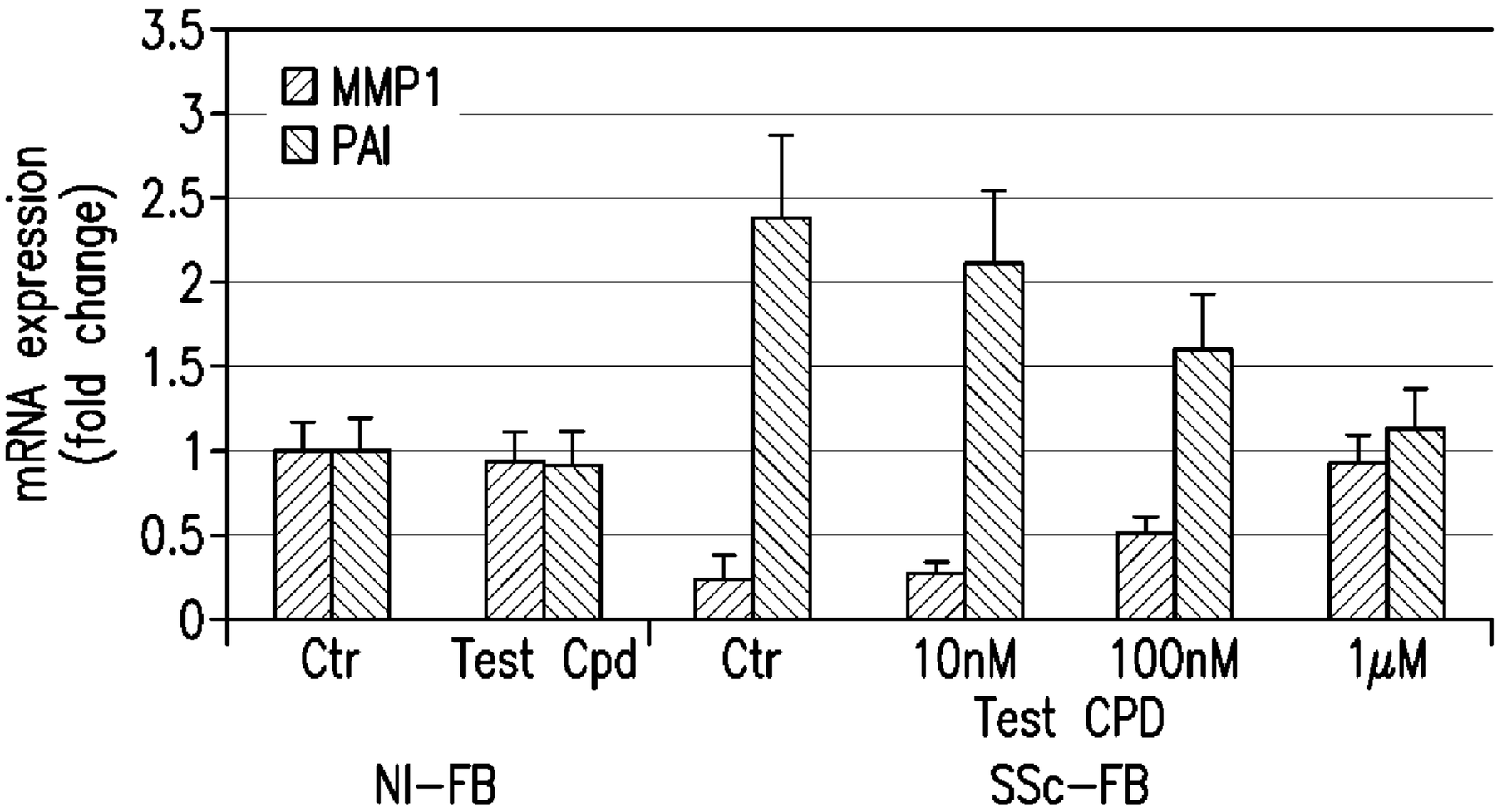

MMP1
PAI
mRNA expression (fold change)
3.5
3
2.5
2
1.5
1
0.5
0
Ctr
Test Cpd
Ctr
10nM
100nM
1μM
Test CPD
NI-FB
SSc-FB

FIG. 51

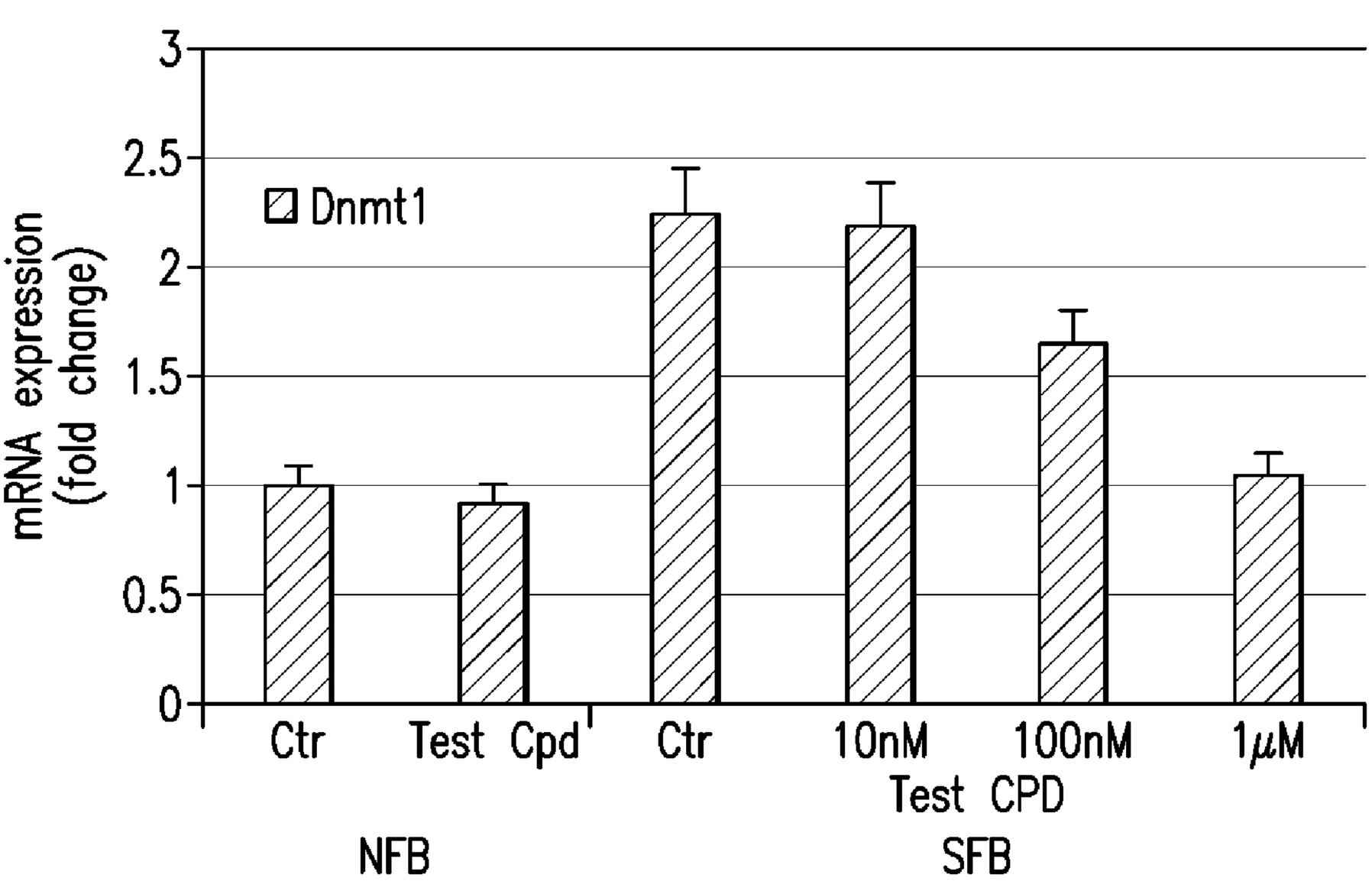

mRNA expression (fold change)
Dnmt1
3
2.5
2
1.5
1
0.5
0
Ctr
Test Cpd
Ctr
10nM
100nM
1μM
Test CPD
NFB
SFB

FIG. 52

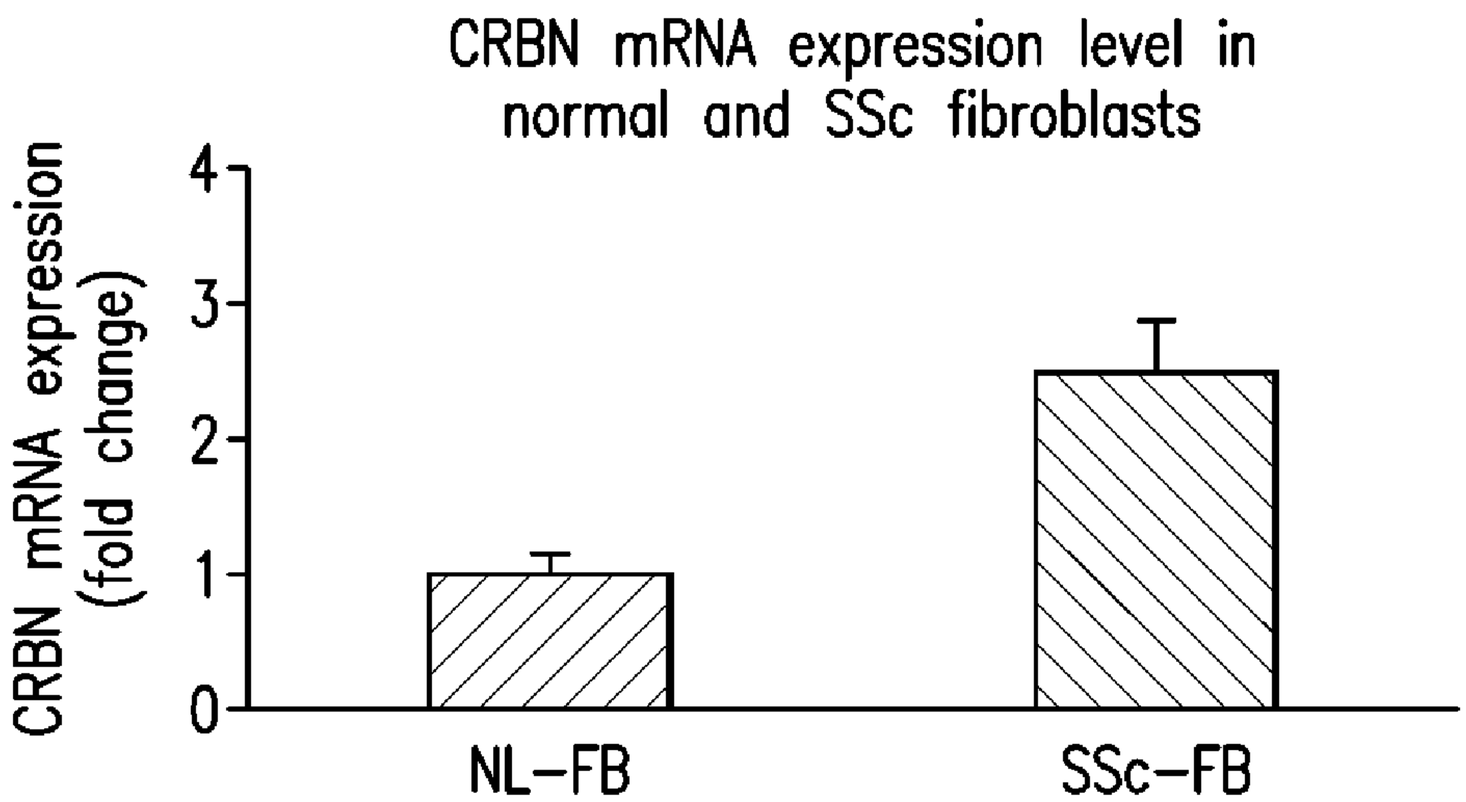

CRBN mRNA expression level in
normal and SSc fibroblasts
CRBN mRNA expression
(fold change)
4
3
2
1
0
NL-FB
SSc-FB

FIG. 53

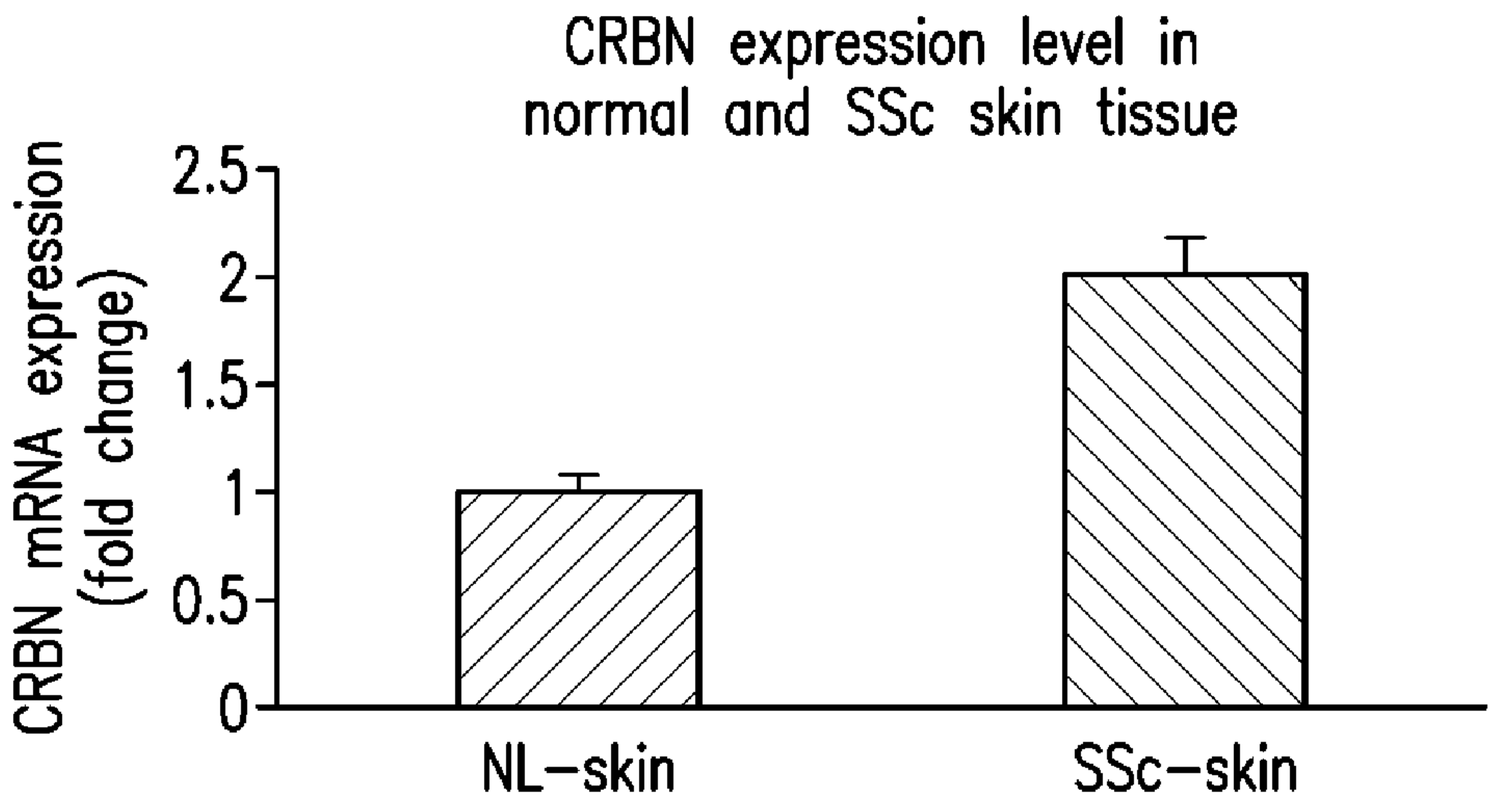

CRBN expression level in
normal and SSc skin tissue
CRBN mRNA expression
(fold change)
2.5
2
1.5
1
0.5
0
NL-skin
SSc-skin

FIG. 54