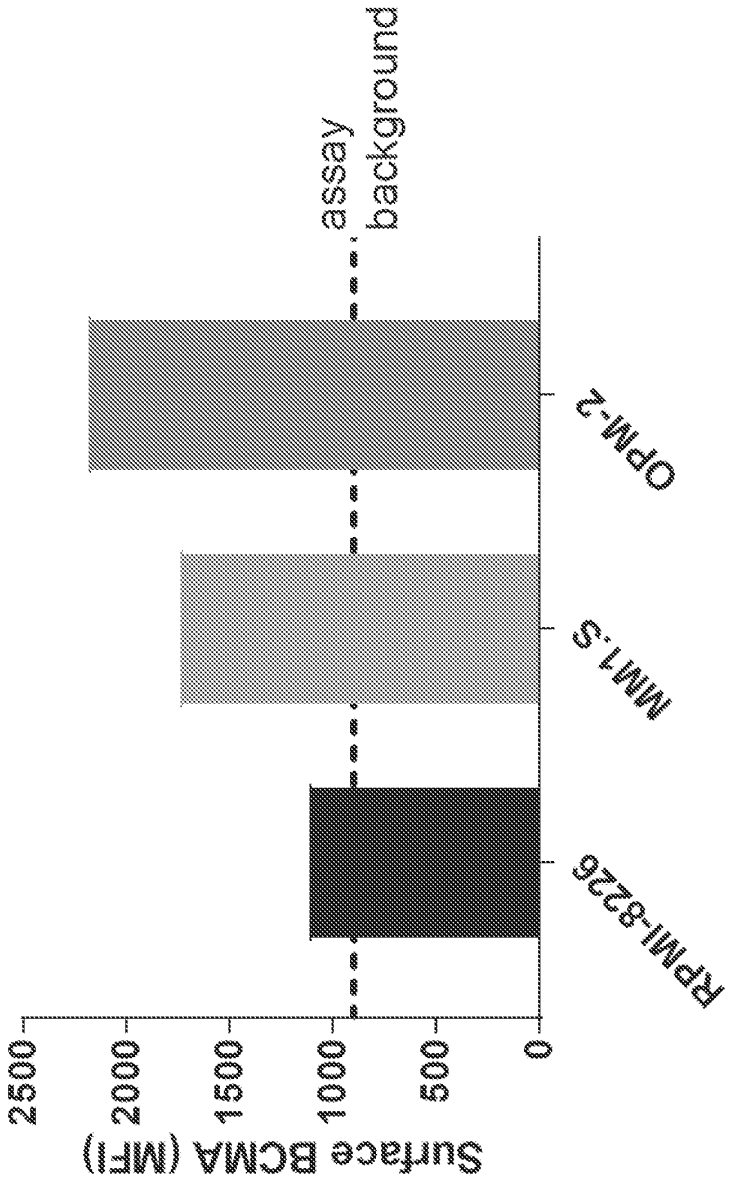

assay background
OPM-2
MM1.S
RPMI-8226
2500
2000
1500
1000
500
0
Surface BCMA (MFI)

FIG. 1A

FIG. 1B

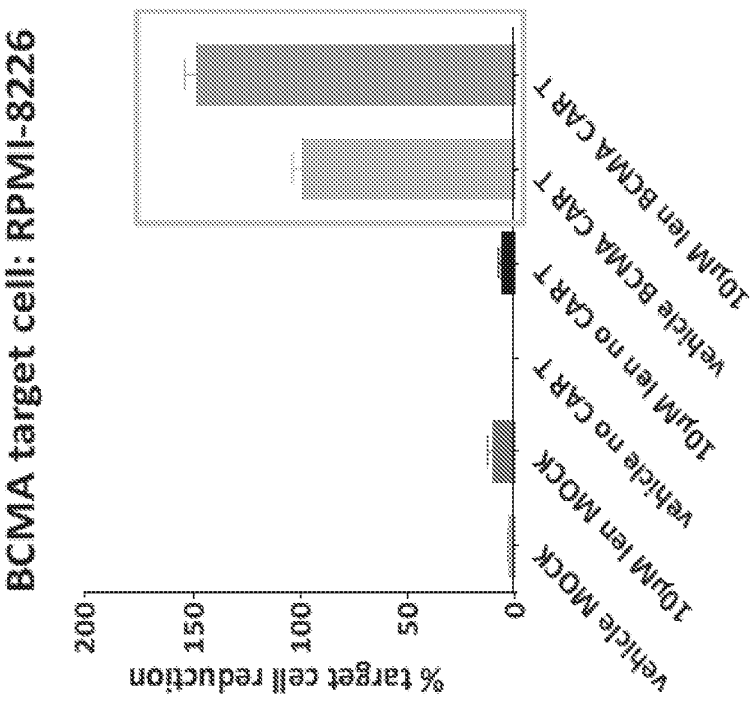
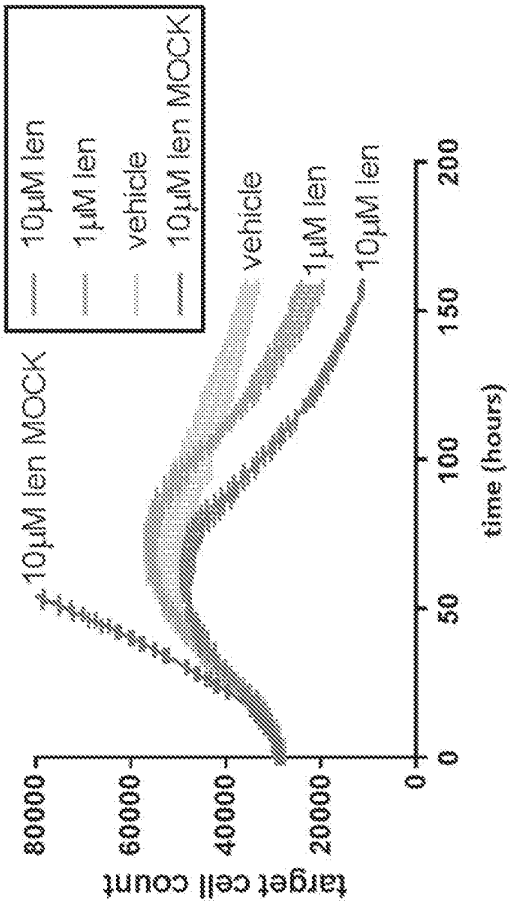

BCMA target cell: RPMI-8226
% target cell reduction
200
150
100
50
0
vehicle MOCK
10μM len MOCK
vehicle no CAR T
10μM len no CAR T
vehicle BCMA CAR T
10μM len BCMA CAR T

FIG. 1C


RPMI-8226
target cell count
80000
60000
40000
20000
0
0
50
100
150
200
time (hours)
10μM len MOCK
vehicle
1μM len
10μM len
10μM len MOCK
1μM len
vehicle

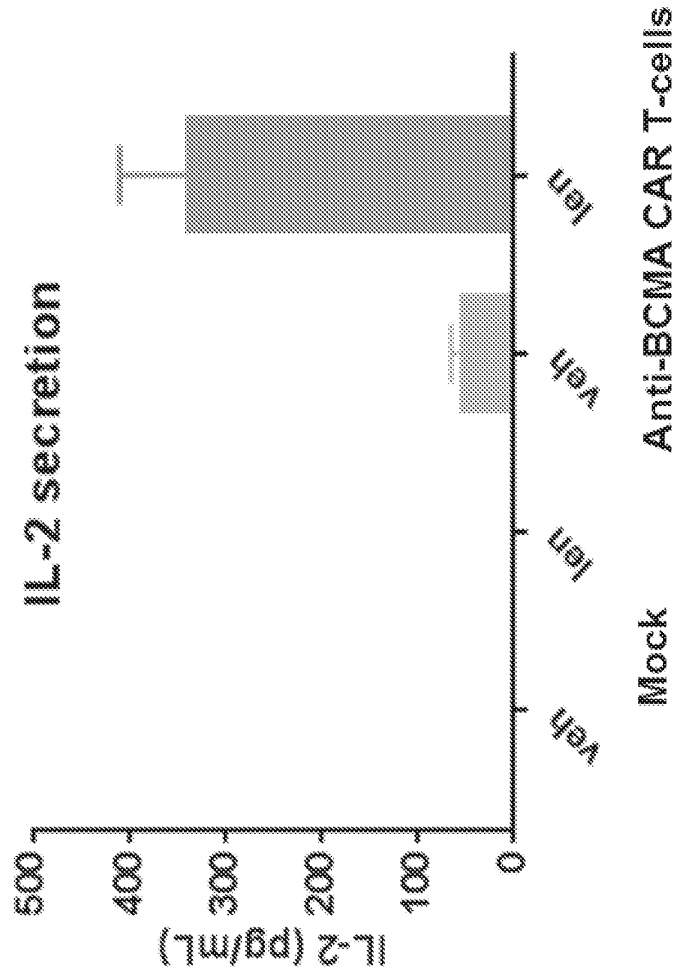

IL-2 secretion
IL-2 (pg/mL)
500
400
300
200
100
0
Mock
Anti-BCMA CAR T-cells
donor 1
donor 2
donor 3
donor 4

FIG. 2A

FIG. 2B

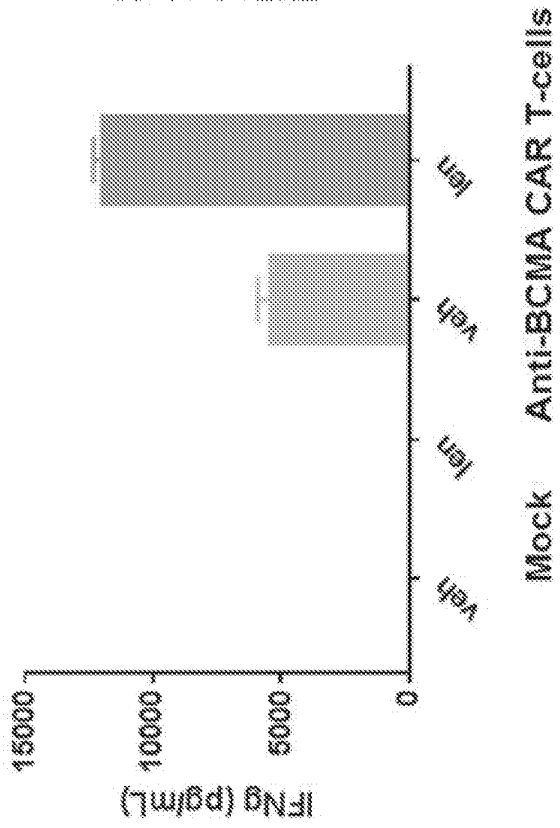

IFNg secretion
IFNg (pg/mL)
15000
10000
5000
0
Vβ1
Vβ3
Vβ1
Vβ3
Mock
Anti-BCMA CAR T-cells

FIG. 2C

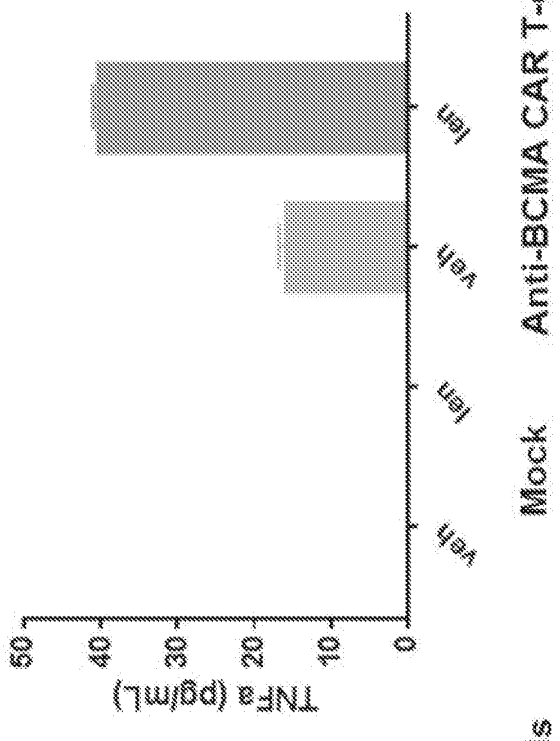

TNFa secretion
TNFa (pg/mL)
60
40
30
20
10
0
Vβ1
Vβ3
Vβ1
Vβ3
Mock
Anti-BCMA CAR T-cells

FIG. 3A

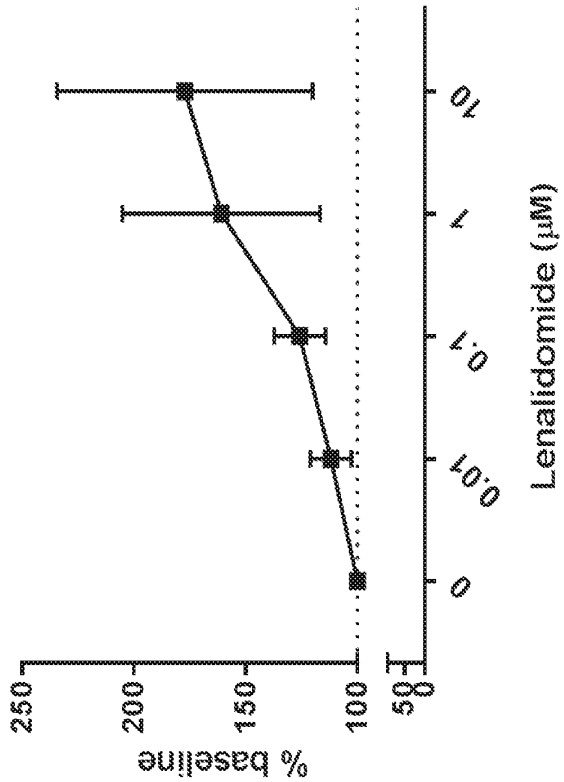

OPM2 % Killing
% baseline
250
200
150
100
50
0
10.0
1.0
0.1
0.01
0
Lenalidomide (μM)

FIG. 3B

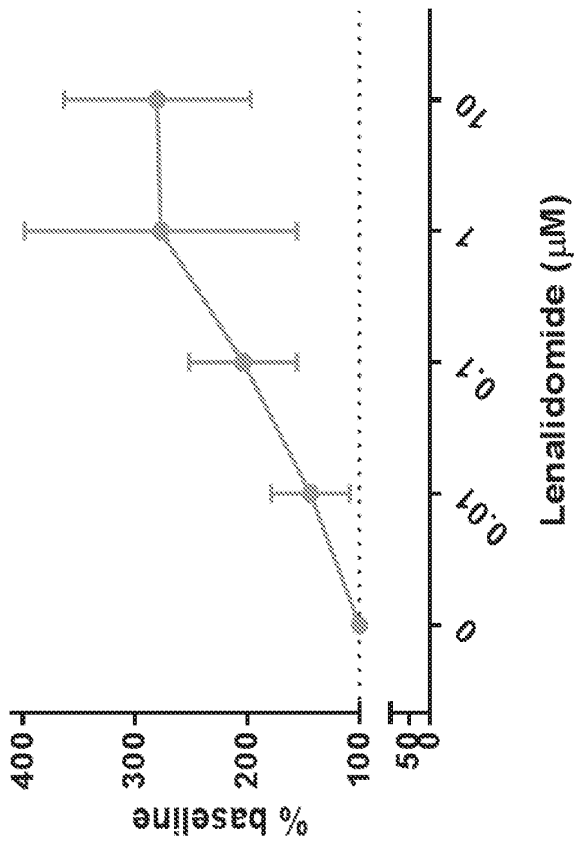

IFN-γ
% baseline
400
300
200
100
50
0
10.0
1.0
0.1
0.01
0
Lenalidomide (μM)

FIG. 3C

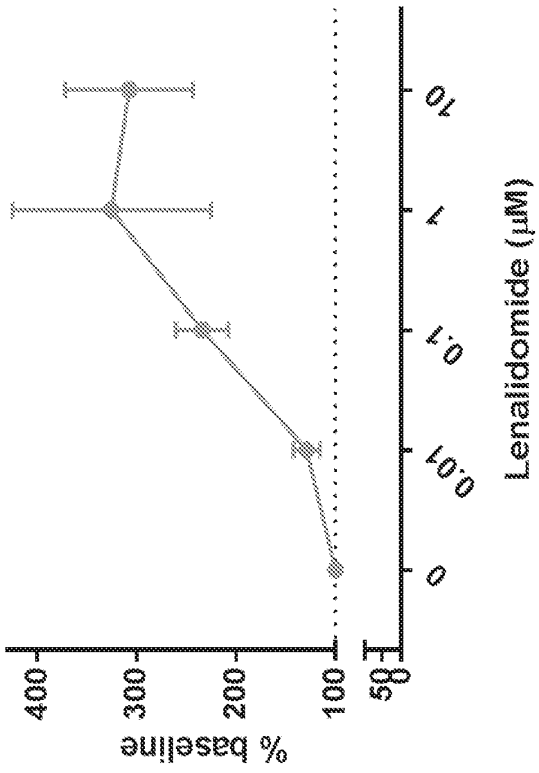

IL-2
% baseline
400
300
200
100
50
0
0.01
0.1
1
10
Lenalidomide (μM)

FIG. 3D

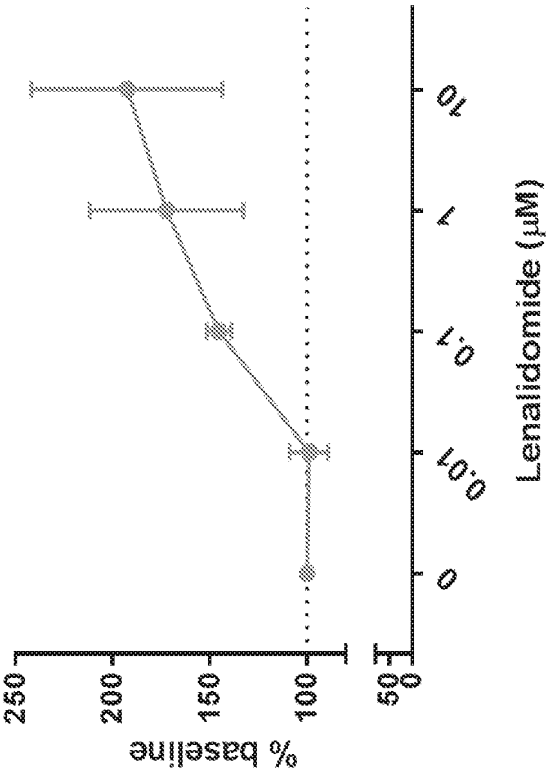
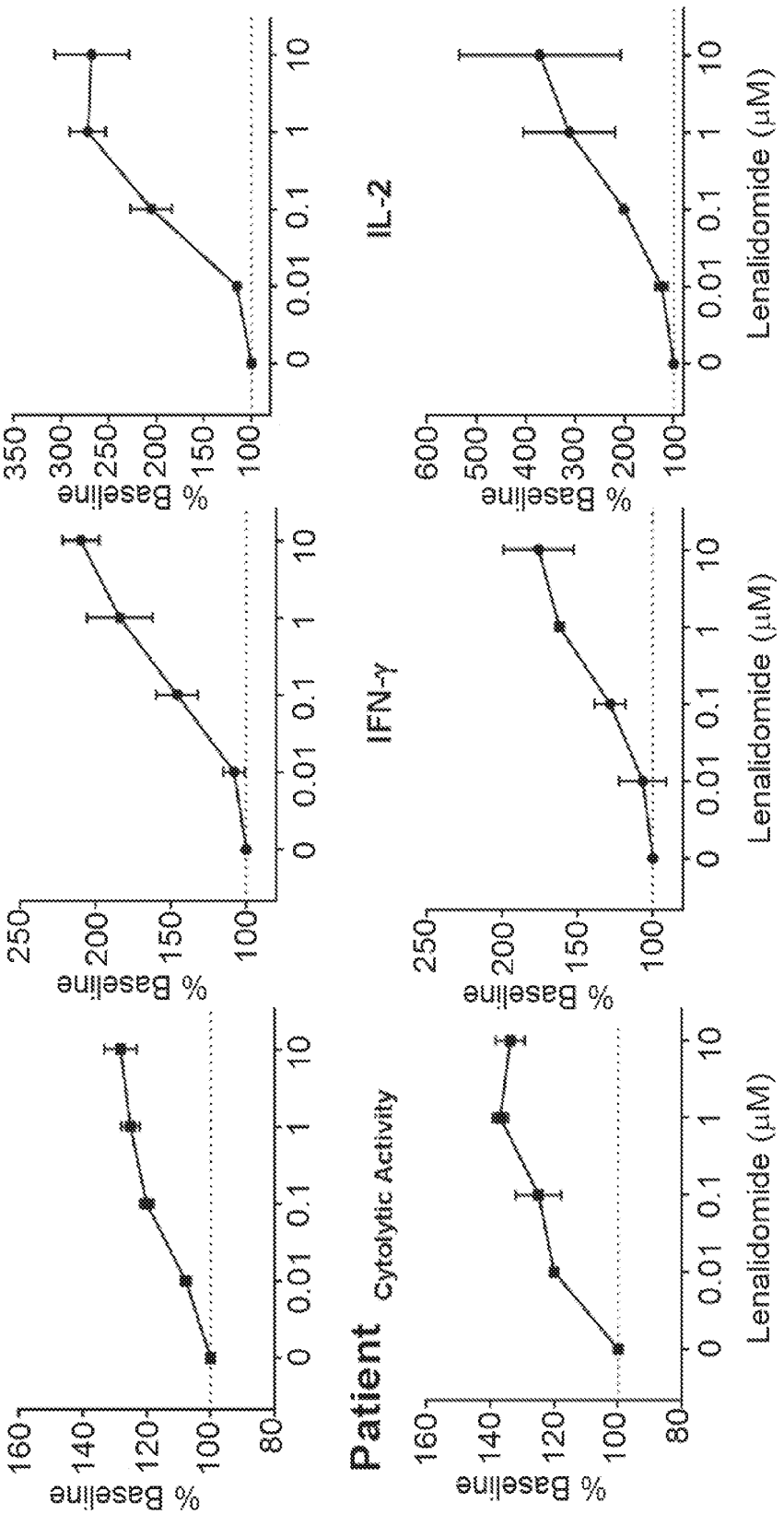

TNF-α
% baseline
250
200
150
100
50
0
0.01
0.1
1
10
Lenalidomide (μM)

FIG. 3E


Healthy
Patient
Cytolytic Activity
IFN-γ
IL-2
% Baseline
Lenalidomide (μM)
0
0.01
0.1
1
10
80
100
120
140
160
100
150
200
250
100
200
300
350
100
200
300
400
500
600

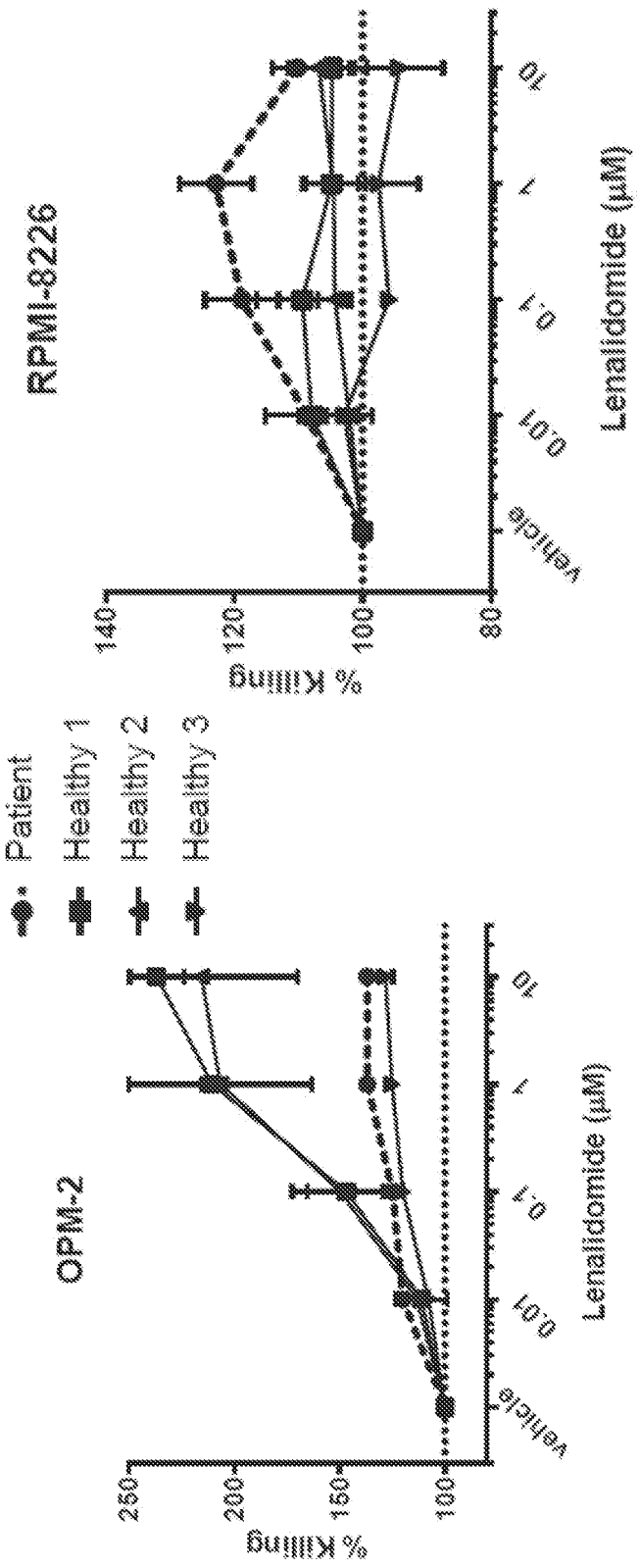

RPMI-8226
% Killing
140
120
100
80
Vehicle
0.01
0.1
1
10
Lenalidomide (μM)
Patient
Healthy 1
Healthy 2
Healthy 3
OPM-2
% Killing
250
200
150
100
Vehicle
0.01
0.1
1
10
Lenalidomide (μM)

FIG. 3F

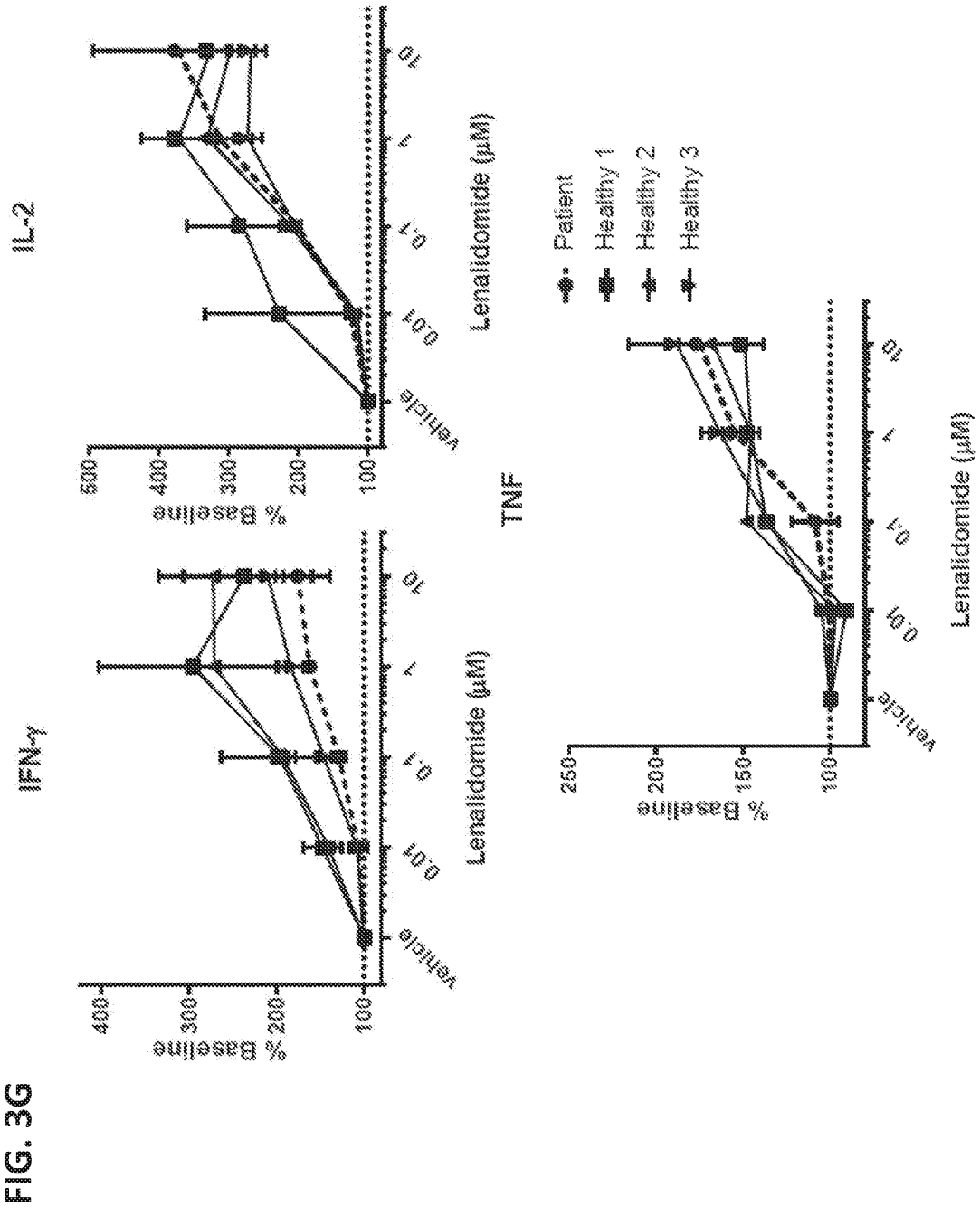

IL-2
% Baseline
Lenalidomide (μM)
vehicle
0.01
0.1
1
10
IFN-γ
TNF
Patient
Healthy 1
Healthy 2
Healthy 3

FIG. 3G

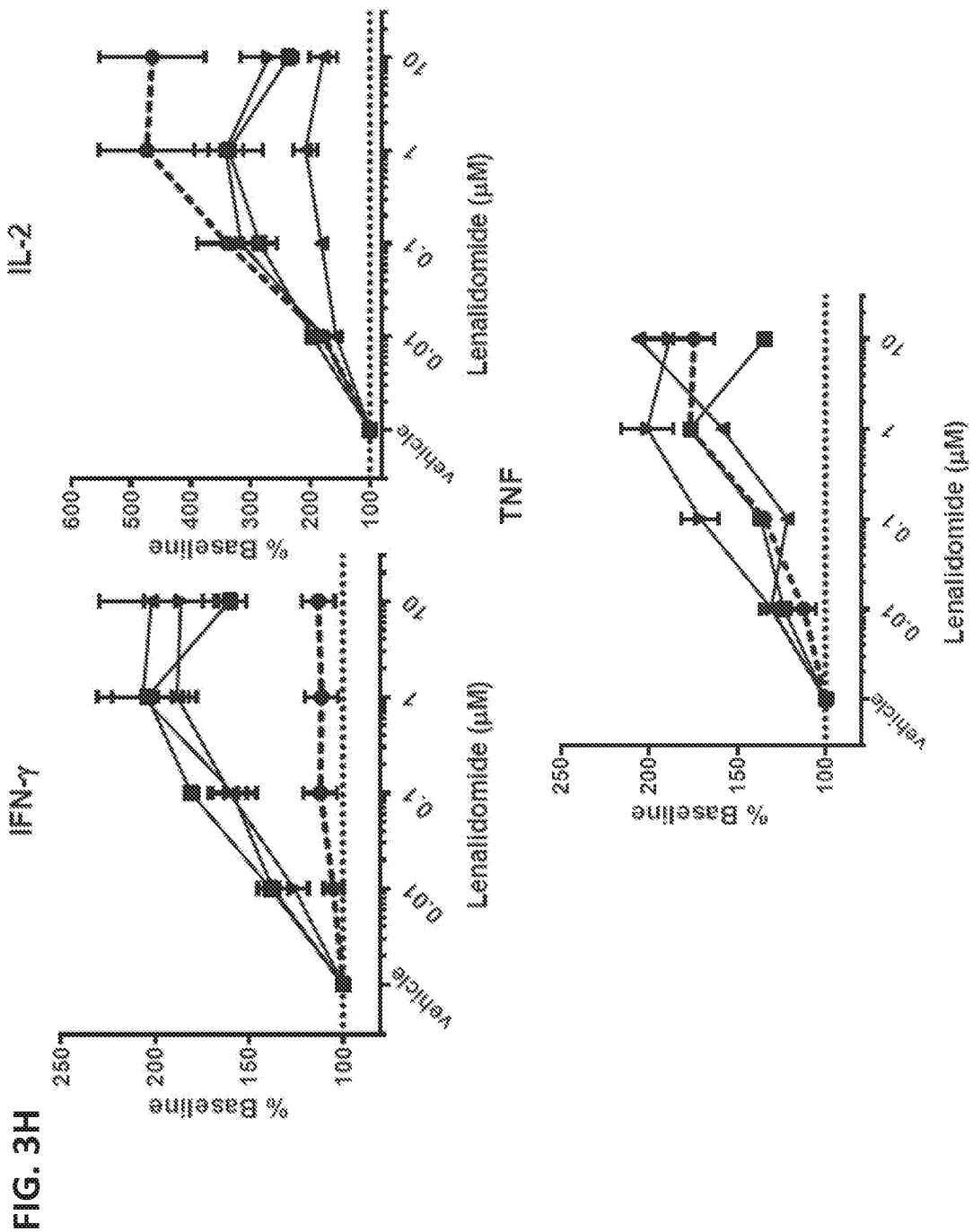

IL-2
IFN-γ
TNF
% Baseline
Lenalidomide (μM)
vehicle
0.01
0.1
1
10
100
150
200
250
300
400
500
600

FIG. 3H

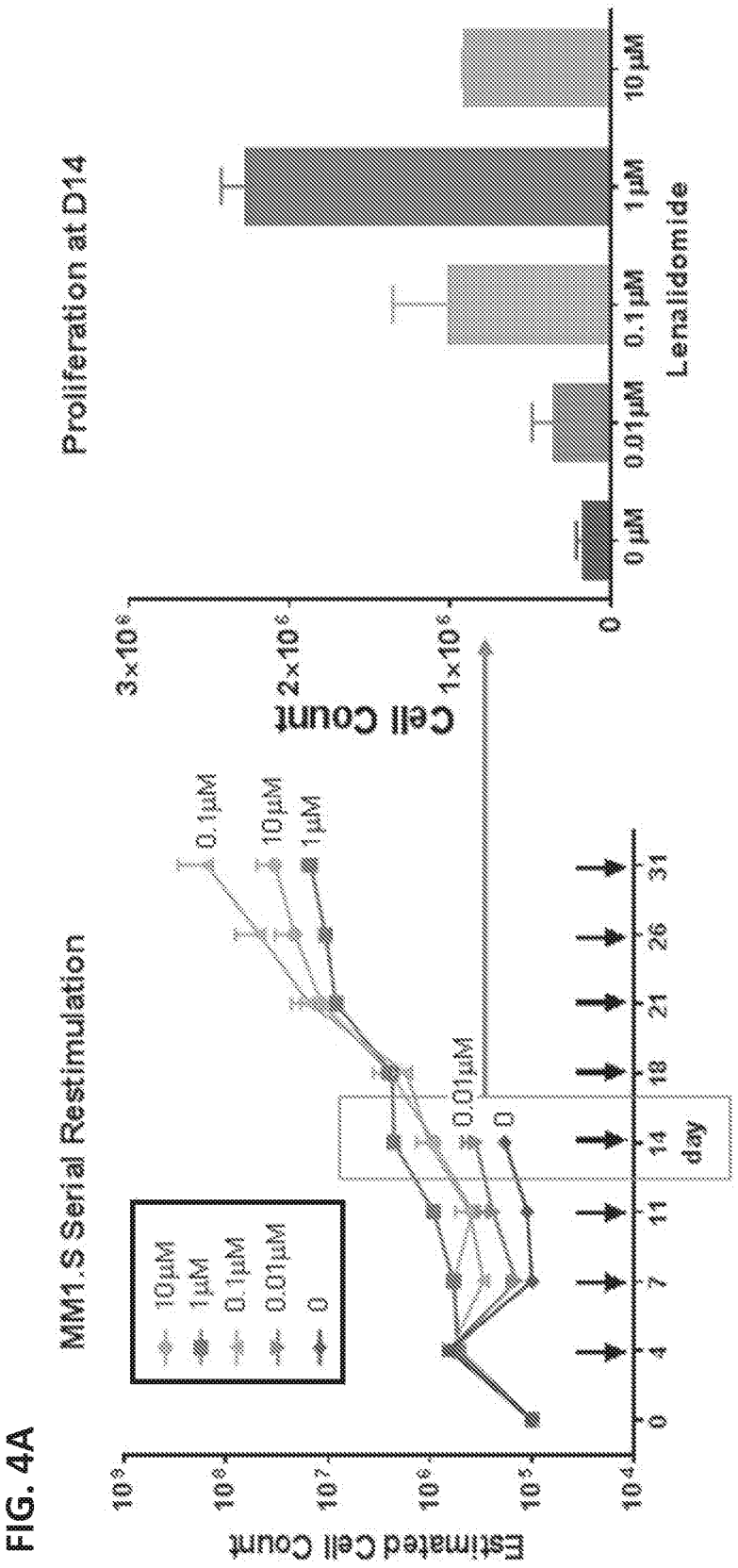

Proliferation at D14
Lenalidomide
0 μM
0.01μM
0.1μM
1μM
10μM
Cell Count
MM1.S Serial Restimulation
Estimated Cell Count
day
0
4
7
11
14
18
21
26
31

FIG. 4A

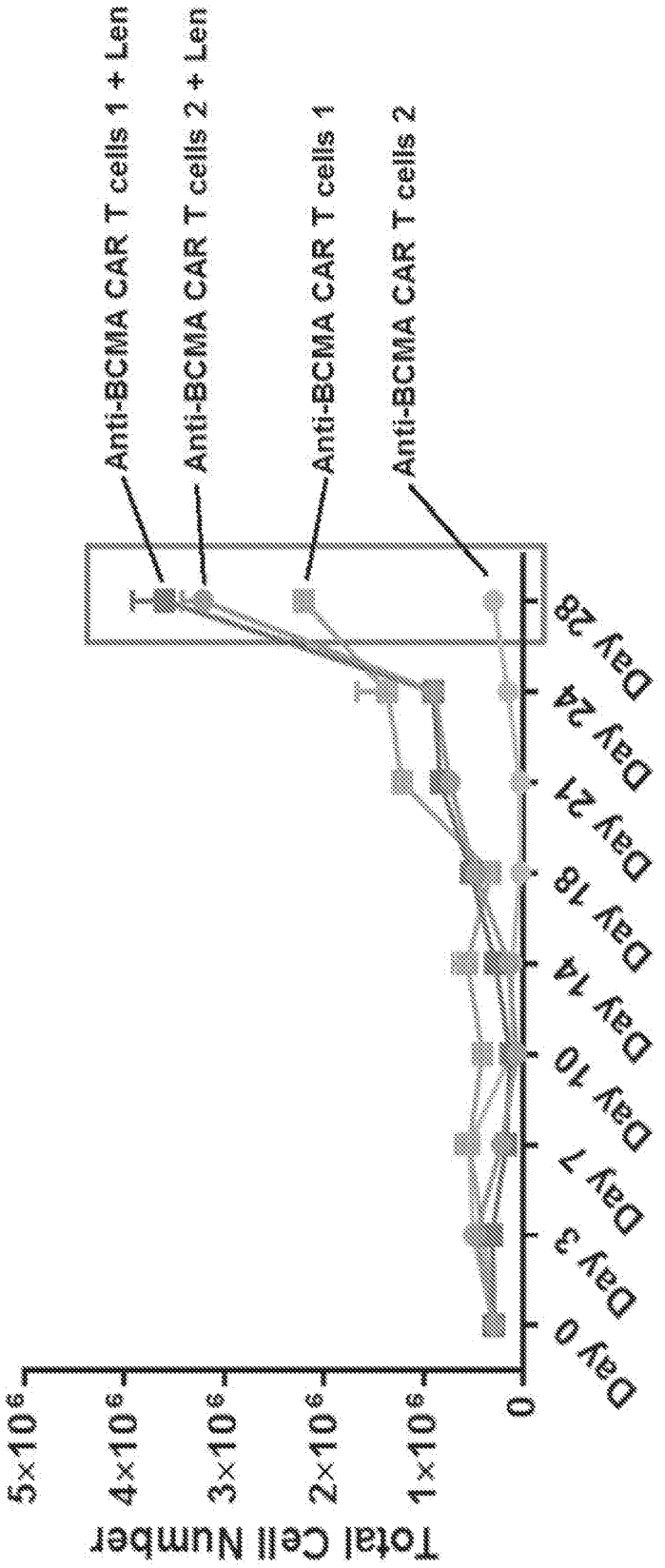
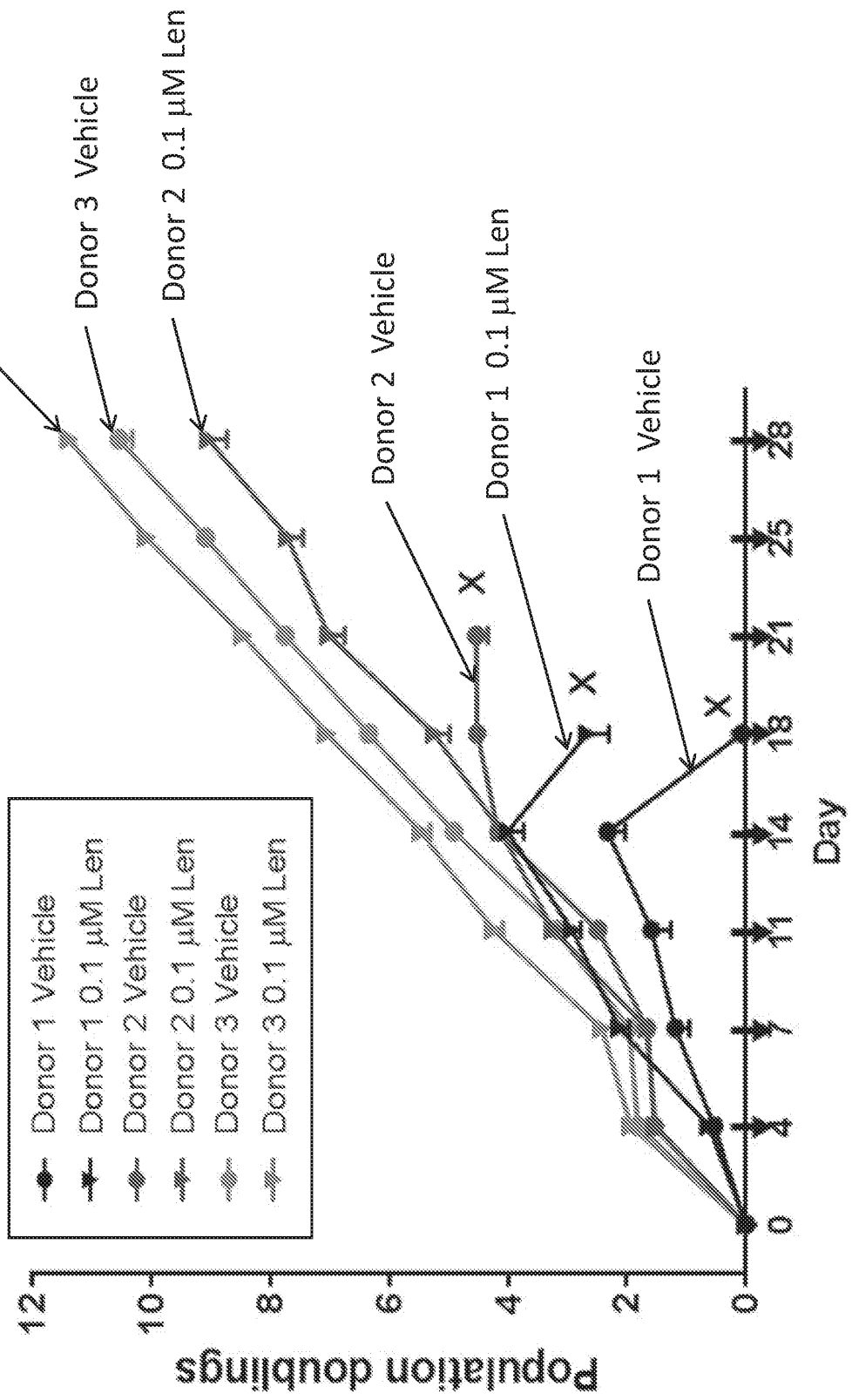

Anti-BCMA CAR T cells 1 + Len
Anti-BCMA CAR T cells 2 + Len
Anti-BCMA CAR T cells 1
Anti-BCMA CAR T cells 2
Total Cell Number
5×10⁶
4×10⁶
3×10⁶
2×10⁶
1×10⁶
0
Day 0
Day 3
Day 7
Day 10
Day 14
Day 18
Day 21
Day 24
Day 28

FIG. 4B

FIG. 5A


Serial stimulation - cell counts
Population doublings
Day
Donor 1 Vehicle
Donor 1 0.1 µM Len
Donor 2 Vehicle
Donor 2 0.1 µM Len
Donor 3 Vehicle
Donor 3 0.1 µM Len
Donor 3 0.1 µM Len
Donor 3 Vehicle
Donor 2 0.1 µM Len
Donor 2 Vehicle
Donor 1 0.1 µM Len
Donor 1 Vehicle
0
2
4
6
8
10
12
0
4
7
11
14
18
21
25
28

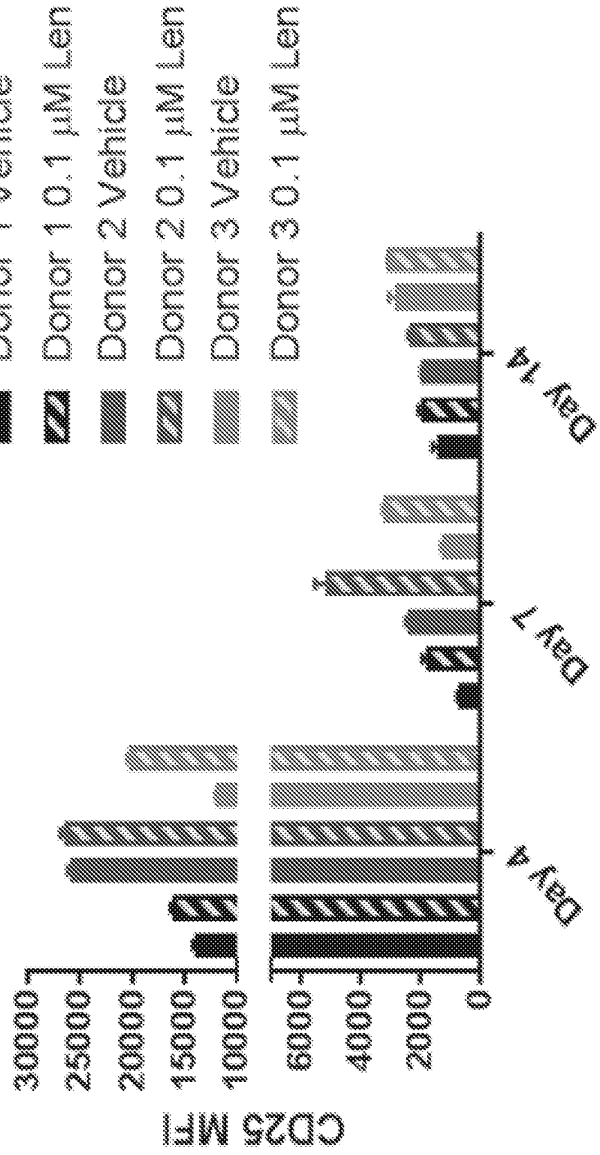

activation
Donor 1 Vehicle
Donor 1 0.1 μM Len
Donor 2 Vehicle
Donor 2 0.1 μM Len
Donor 3 Vehicle
Donor 3 0.1 μM Len
CD25 MFI
30000
25000
20000
15000
10000
6000
4000
2000
0
Day 4
Day 7
Day 14

FIG. 5B

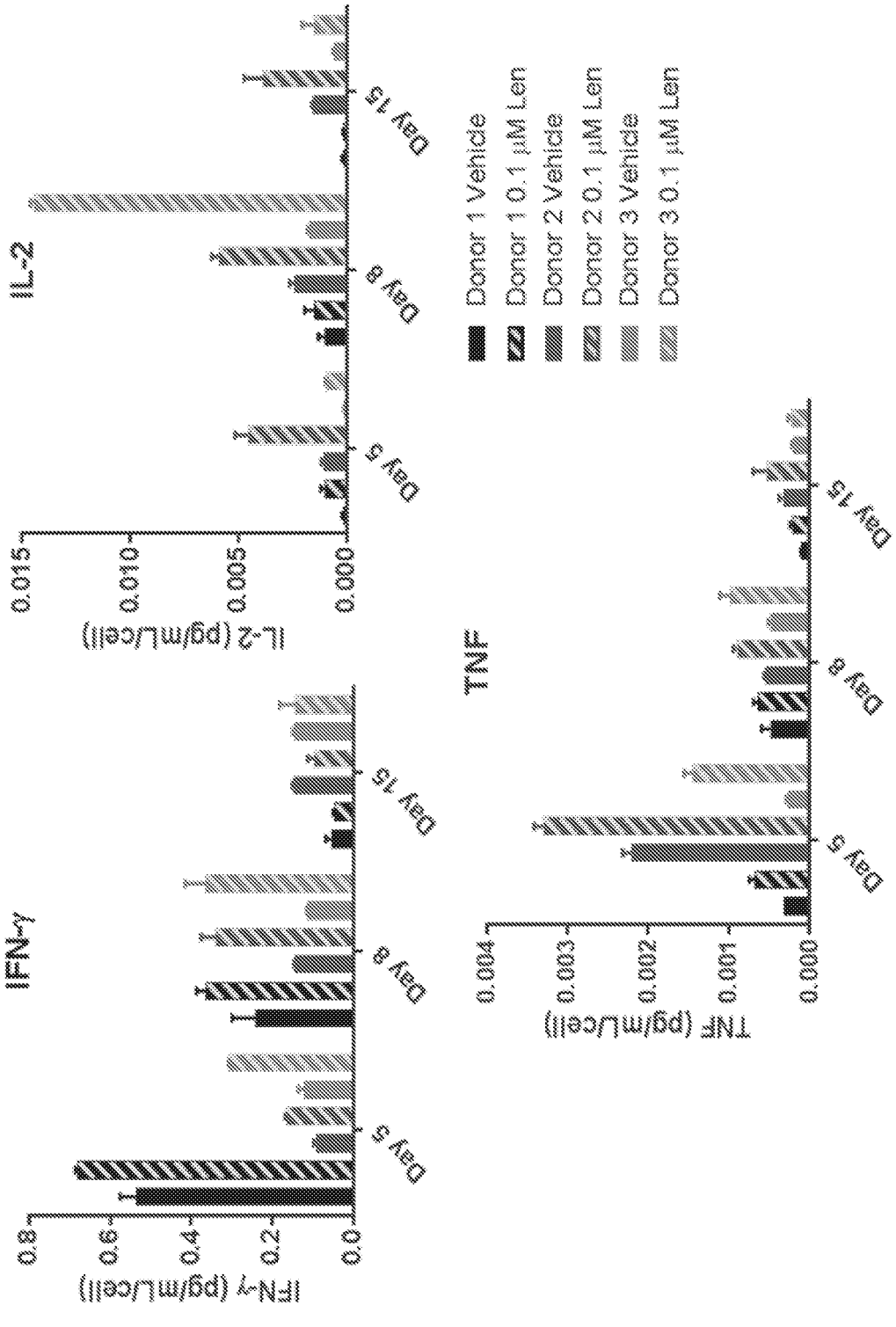

IL-2
IL-2 (pg/mL/cell)
0.015
0.010
0.005
0.000
Day 5
Day 8
Day 15
IFN-γ
IFN-γ (pg/mL/cell)
0.8
0.6
0.4
0.2
0.0
Day 5
Day 8
Day 15
TNF
TNF (pg/mL/cell)
0.004
0.003
0.002
0.001
0.000
Day 5
Day 8
Day 15
Donor 1 Vehicle
Donor 1 0.1 μM Len
Donor 2 Vehicle
Donor 2 0.1 μM Len
Donor 3 Vehicle
Donor 3 0.1 μM Len

FIG. 5C

FIG. 6A

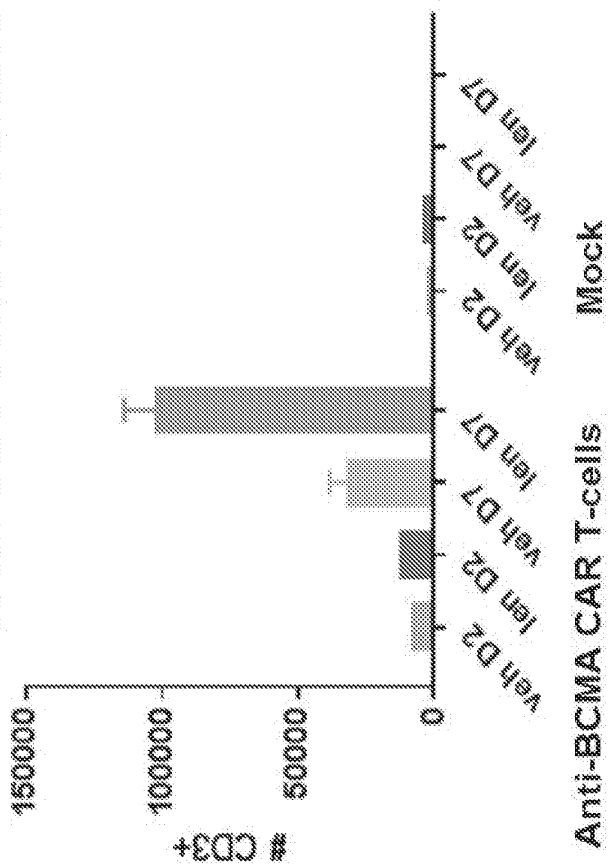

Total CD3 cells in culture
CD3+
150000
100000
50000
0
Veh D2
Ven D2
Veh D7
Ven D7
Veh D2
Ven D2
Veh D7
Ven D7
Anti-BCMA CAR T-cells
Mock

FIG. 6B

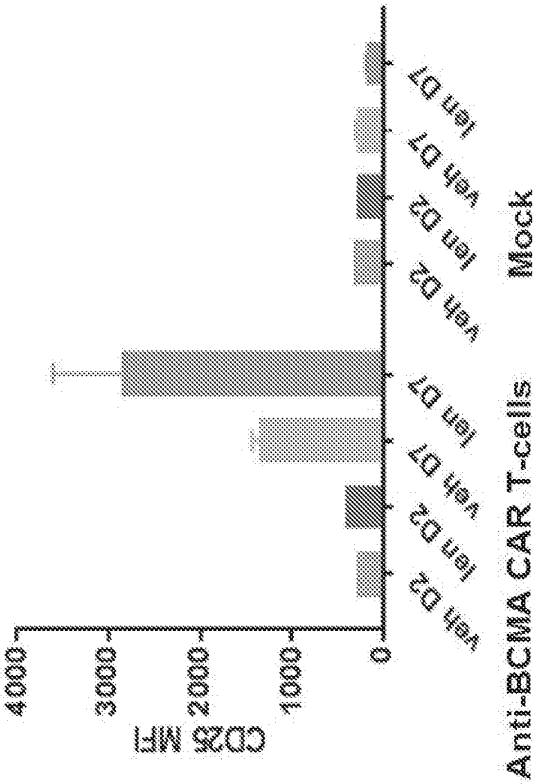

CD4
CD25 MFI
4000
3000
2000
1000
0
Veh D2
Len D2
Veh D7
Len D7
Mock
Anti-BCMA CAR T-cells

FIG. 6C

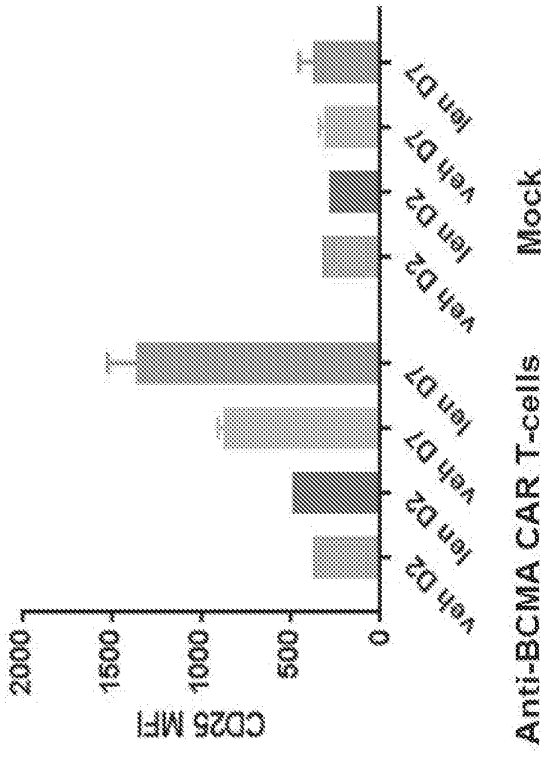

CD8
CD25 MFI
2000
1500
1000
500
0
Veh D2
Len D2
Veh D7
Len D7
Mock
Anti-BCMA CAR T-cells

FIG. 7A

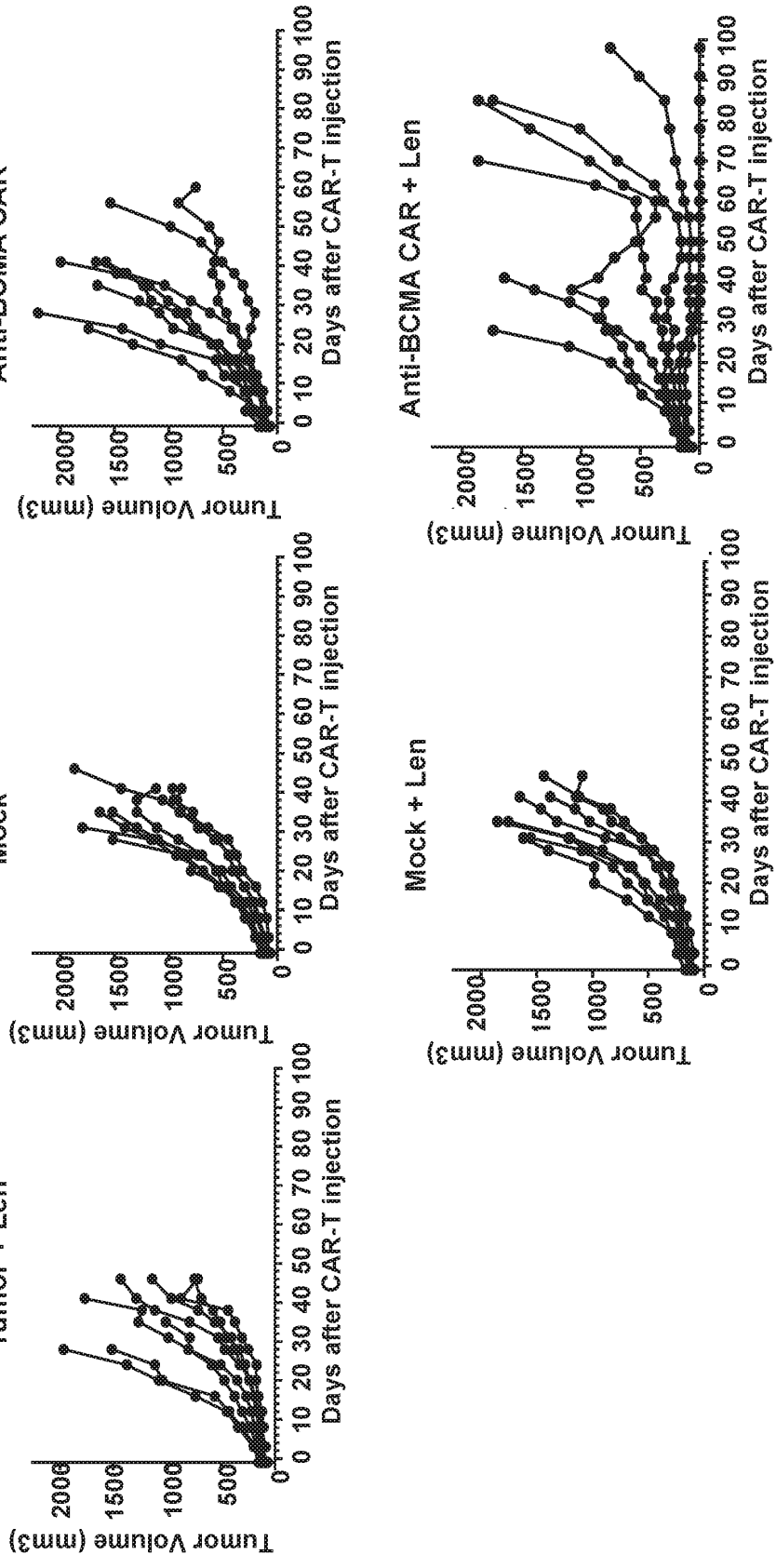
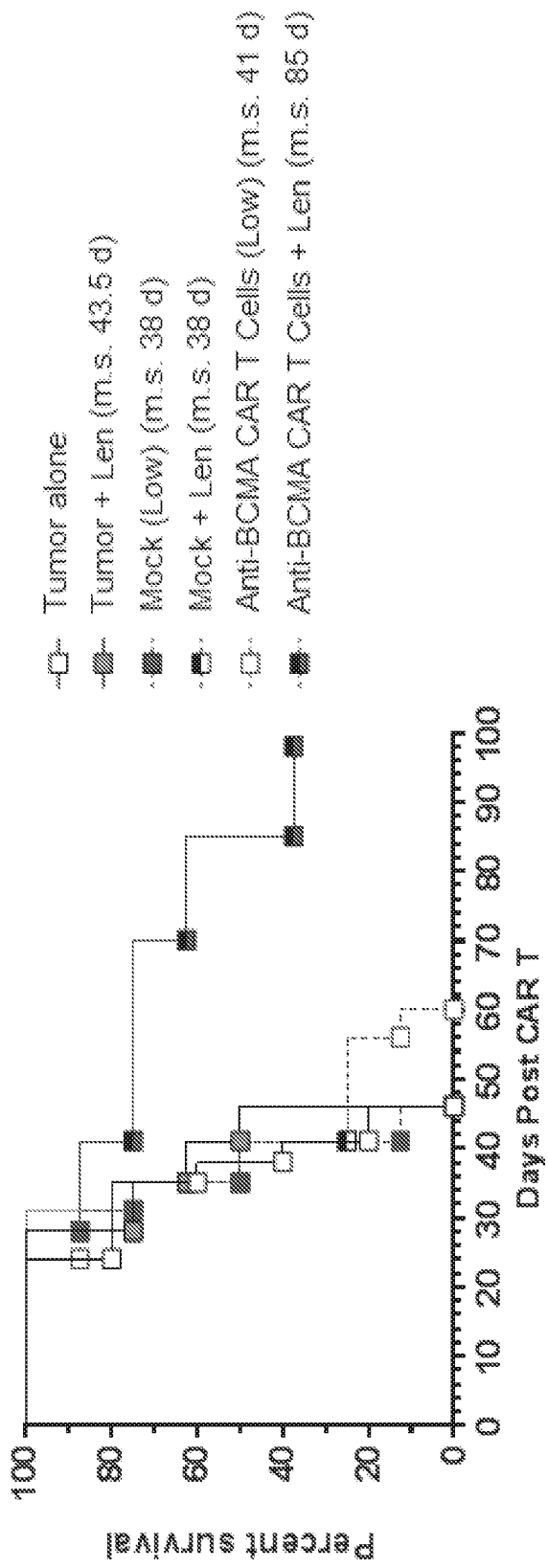

Tumor + Len
Mock
Anti-BCMA CAR
Mock + Len
Anti-BCMA CAR + Len
Tumor Volume (mm3)
0
500
1000
1500
2000
0 10 20 30 40 50 60 70 80 90 100
Days after CAR-T injection

FIG. 7B


Tumor alone
Tumor + Len (m.s. 43.5 d)
Mock (Low) (m.s. 38 d)
Mock + Len (m.s. 38 d)
Anti-BCMA CAR T Cells (Low) (m.s. 41 d)
Anti-BCMA CAR T Cells + Len (m.s. 85 d)
Percent survival
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T

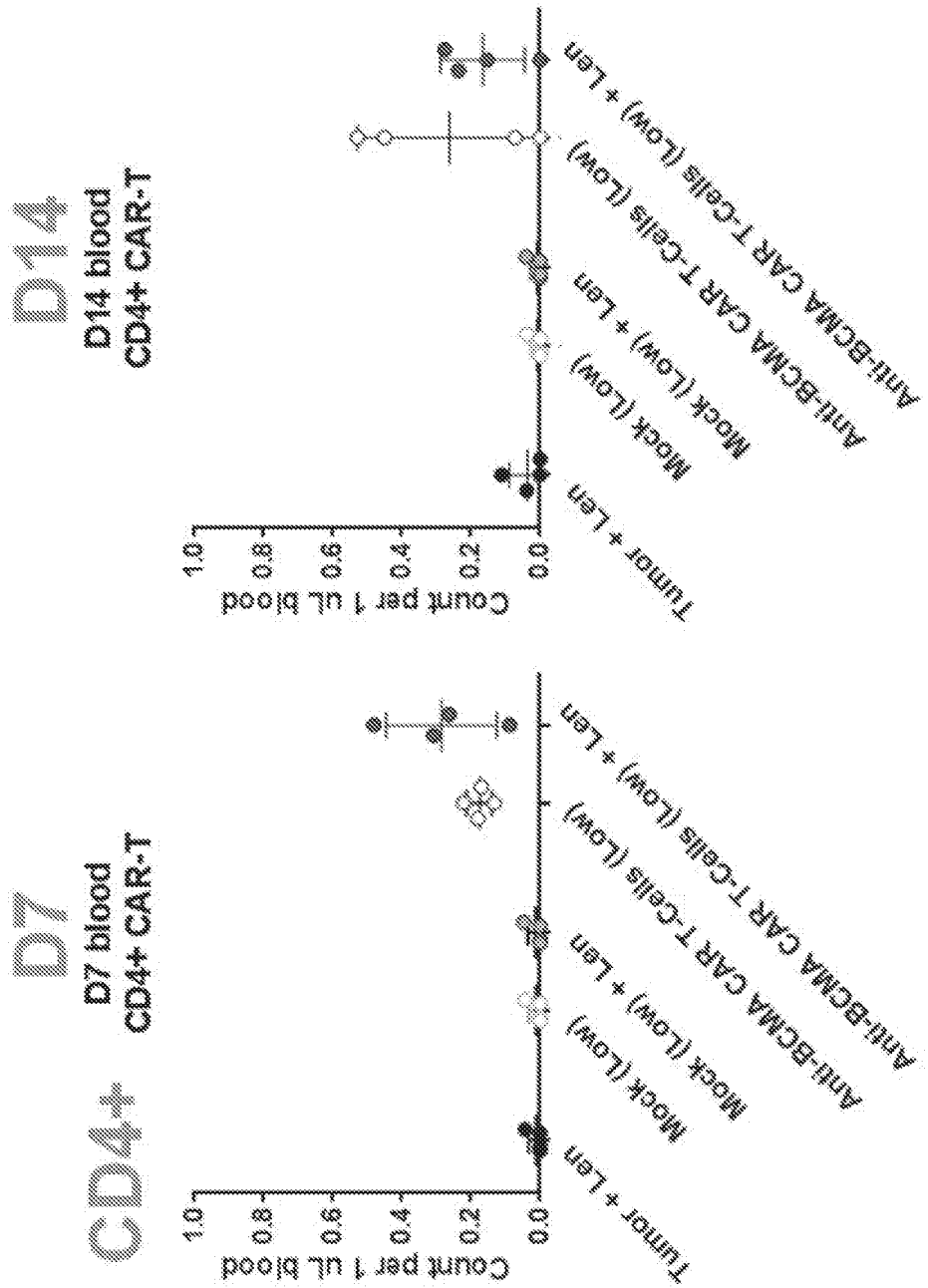

D14
D14 blood
CD4+ CAR-T
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len
D7
D7 blood
CD4+ CAR-T
CD4+
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8A

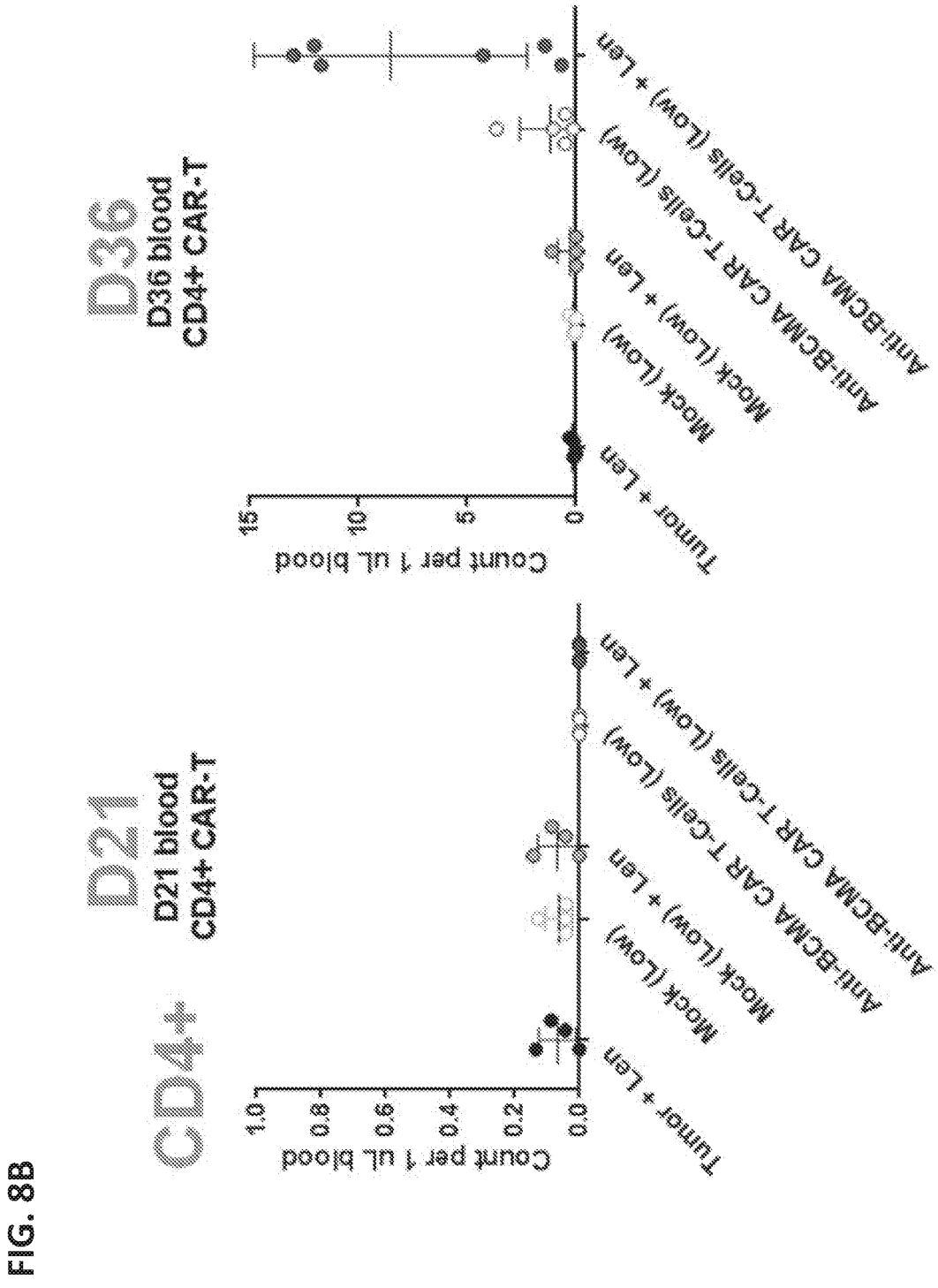

D21
D21 blood
CD4+ CAR-T
CD4+
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len
D36
D36 blood
CD4+ CAR-T
Count per 1 uL blood
15
10
5
0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8B

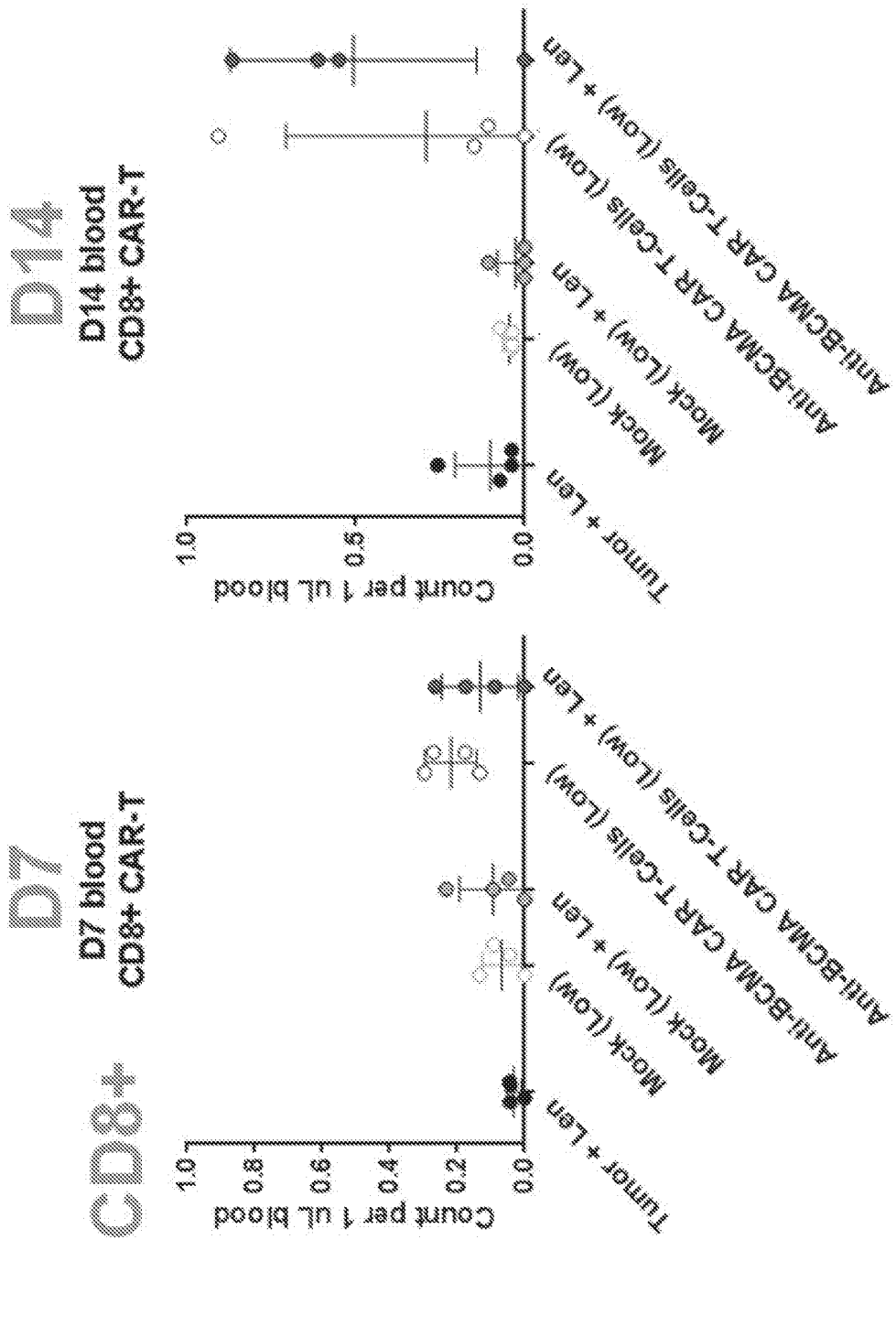

D14
D14 blood
CD8+ CAR-T
Count per 1 uL blood
1.0
0.5
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len
D7
D7 blood
CD8+ CAR-T
CD8+
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8C

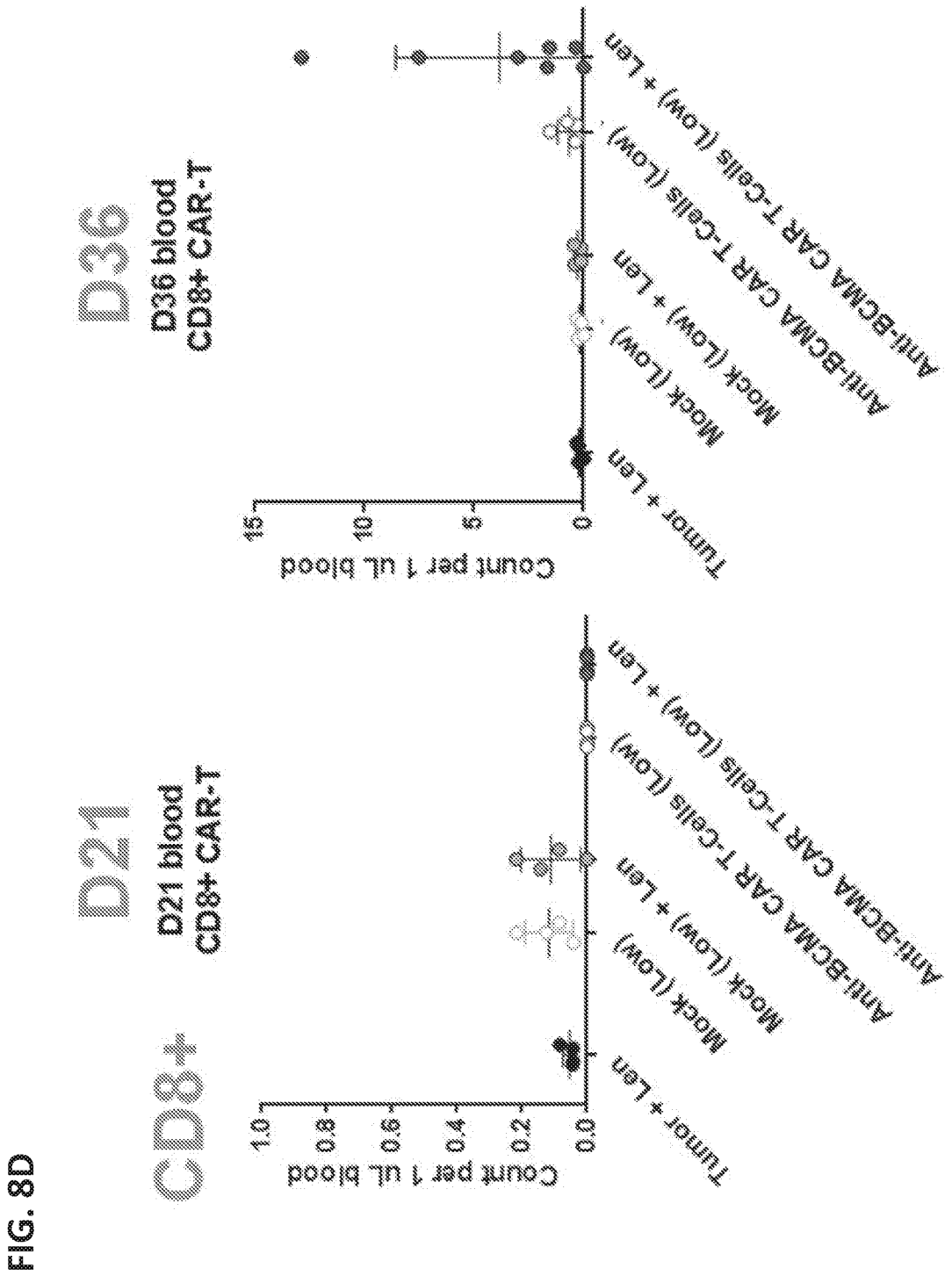

CD8+
D21
D21 blood
CD8+ CAR-T
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len
D36
D36 blood
CD8+ CAR-T
Count per 1 uL blood
15
10
5
0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8D

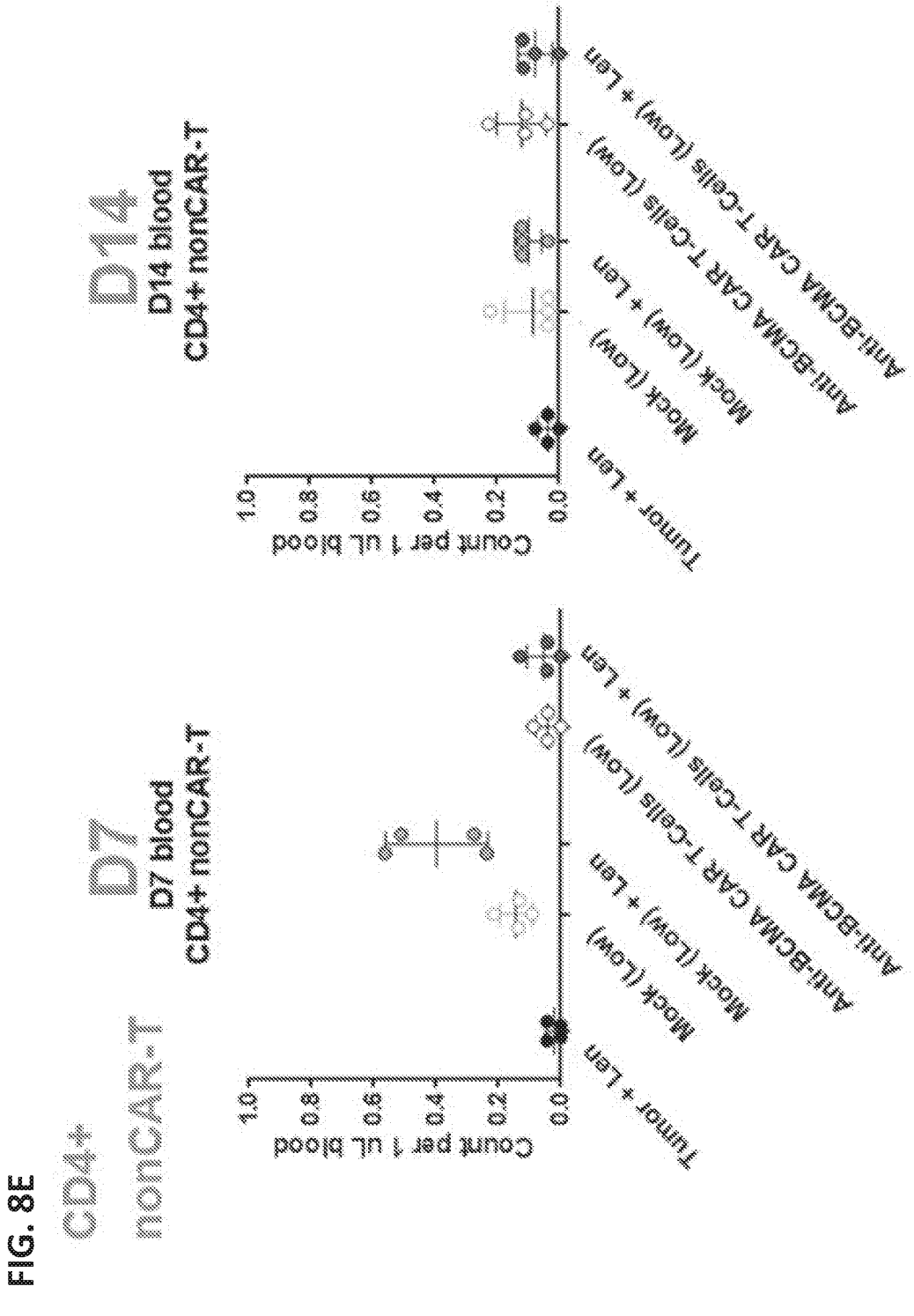

CD4+
nonCAR-T
D7
D7 blood
CD4+ nonCAR-T
D14
D14 blood
CD4+ nonCAR-T
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8E

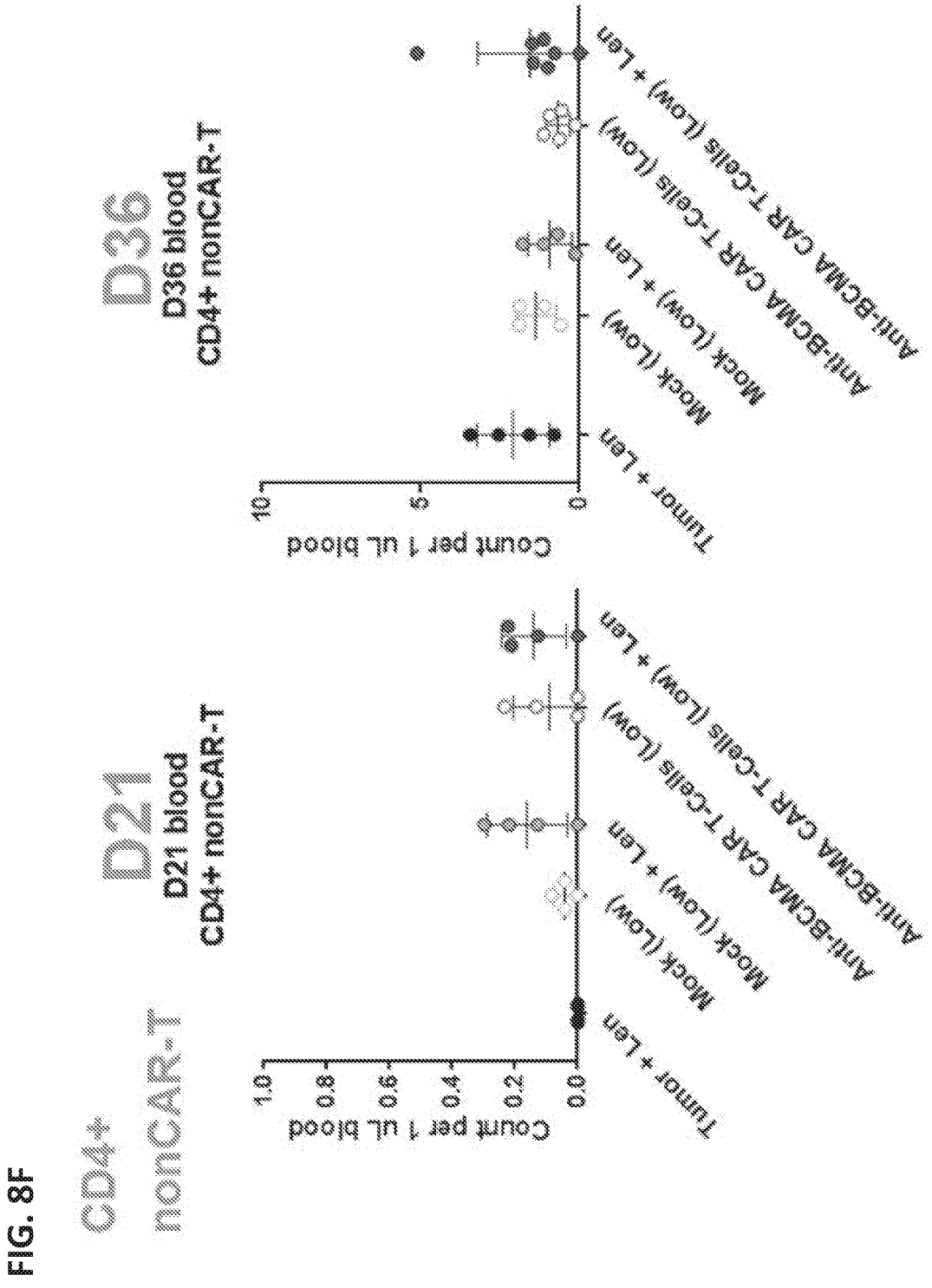

D21
D21 blood
CD4+ nonCAR-T
D36
D36 blood
CD4+ nonCAR-T
CD4+
nonCAR-T
Count per 1 uL blood
1.0
0.8
0.6
0.4
0.2
0.0
10
5
0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8F

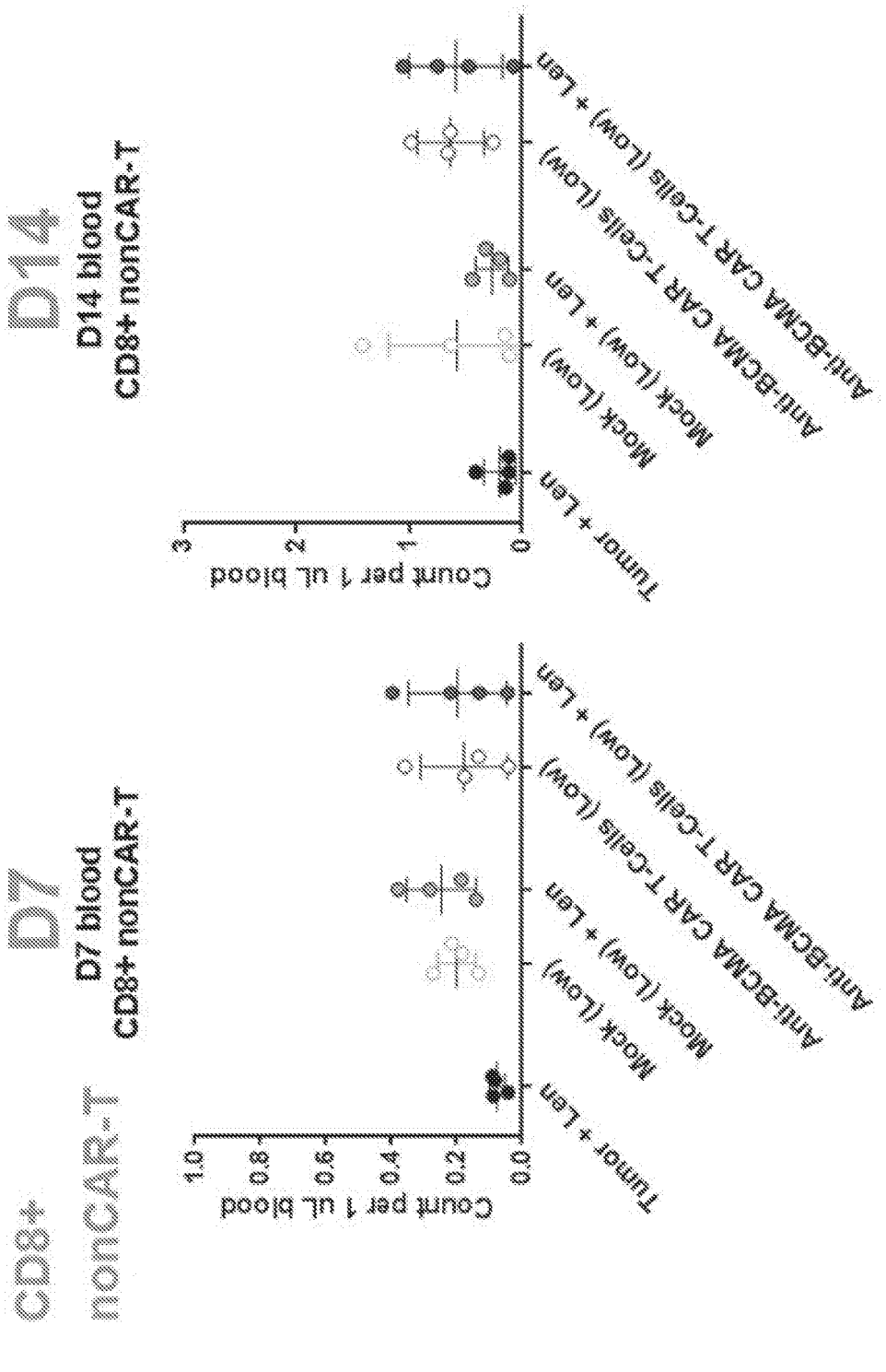

D14
D14 blood
CD8+ nonCAR-T
Count per 1 uL blood
0
1
2
3
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len
D7
D7 blood
CD8+ nonCAR-T
Count per 1 uL blood
0.0
0.2
0.4
0.6
0.8
1.0
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8G

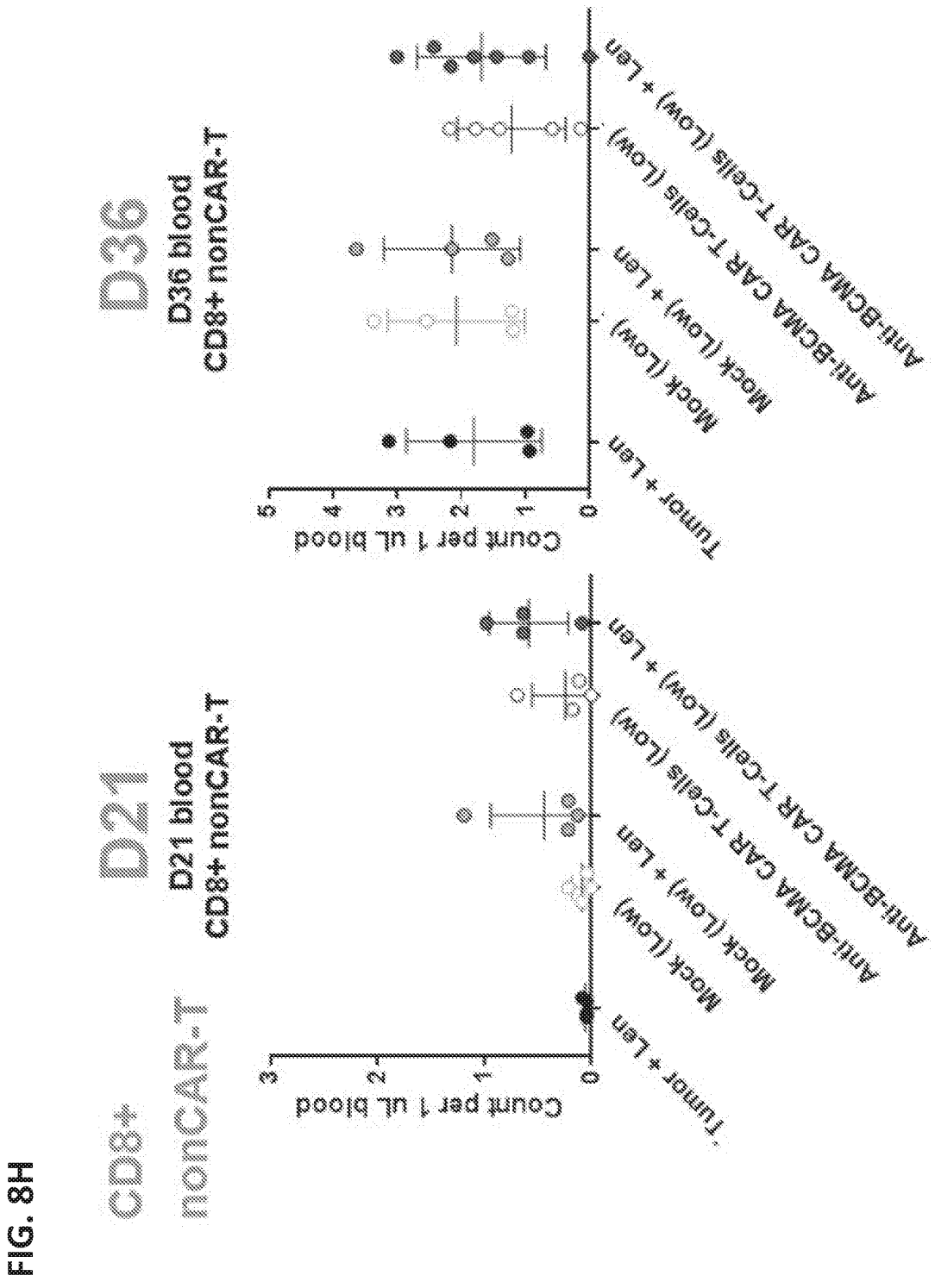

CD8+
nonCAR-T
D21
D21 blood
CD8+ nonCAR-T
Count per 1 uL blood
0
1
2
3
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len
D36
D36 blood
CD8+ nonCAR-T
Count per 1 uL blood
0
1
2
3
4
5
Tumor + Len
Mock (Low)
Mock (Low) + Len
Anti-BCMA CAR T-Cells (Low)
Anti-BCMA CAR T-Cells (Low) + Len

FIG. 8H

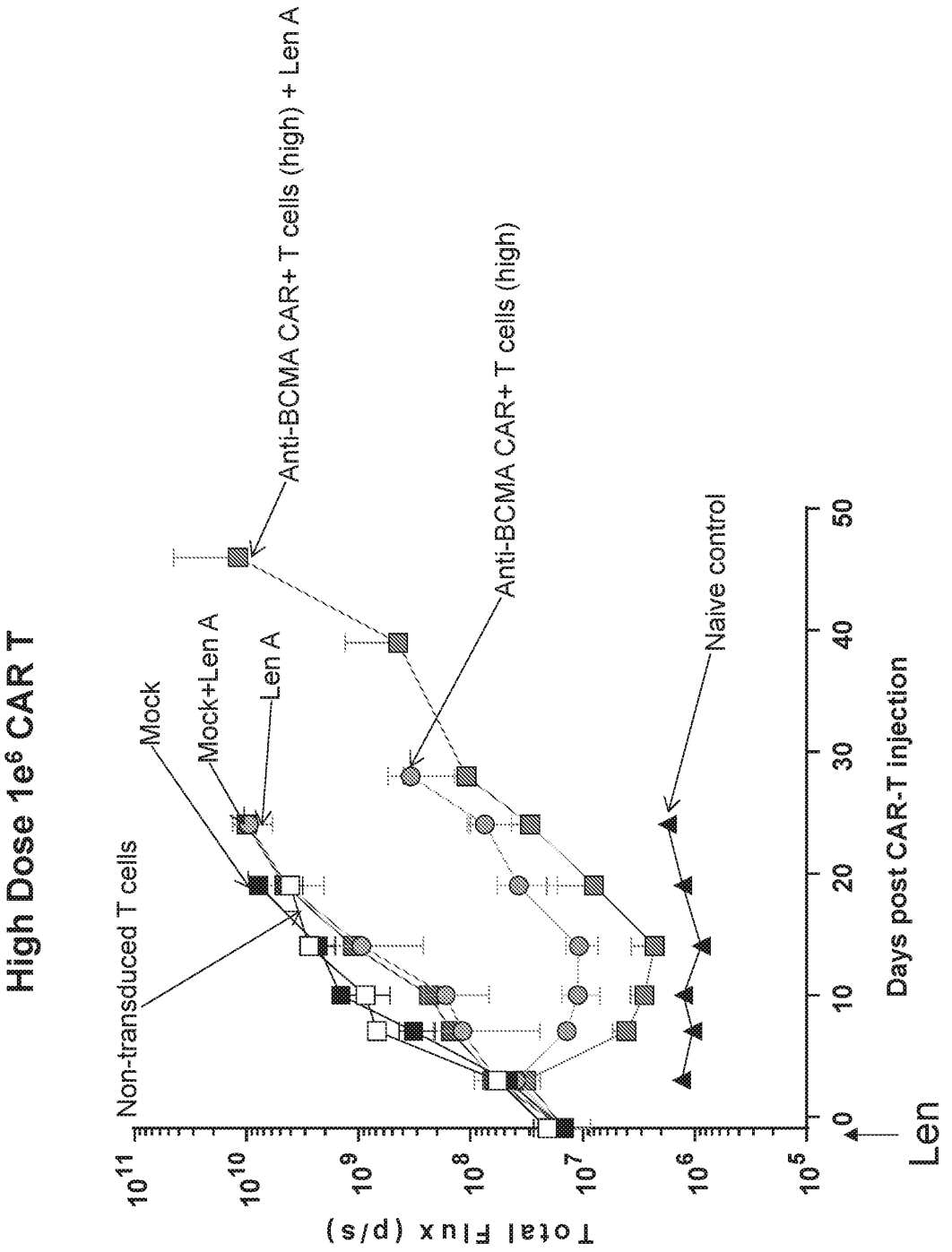

High Dose 1e6 CAR T
Anti-BCMA CAR+ T cells (high) + Len A
Anti-BCMA CAR+ T cells (high)
Naive control
Non-transduced T cells
Mock
Mock+Len A
Len A
Total Flux (p/s)
Days post CAR-T injection
Len

FIG. 9A

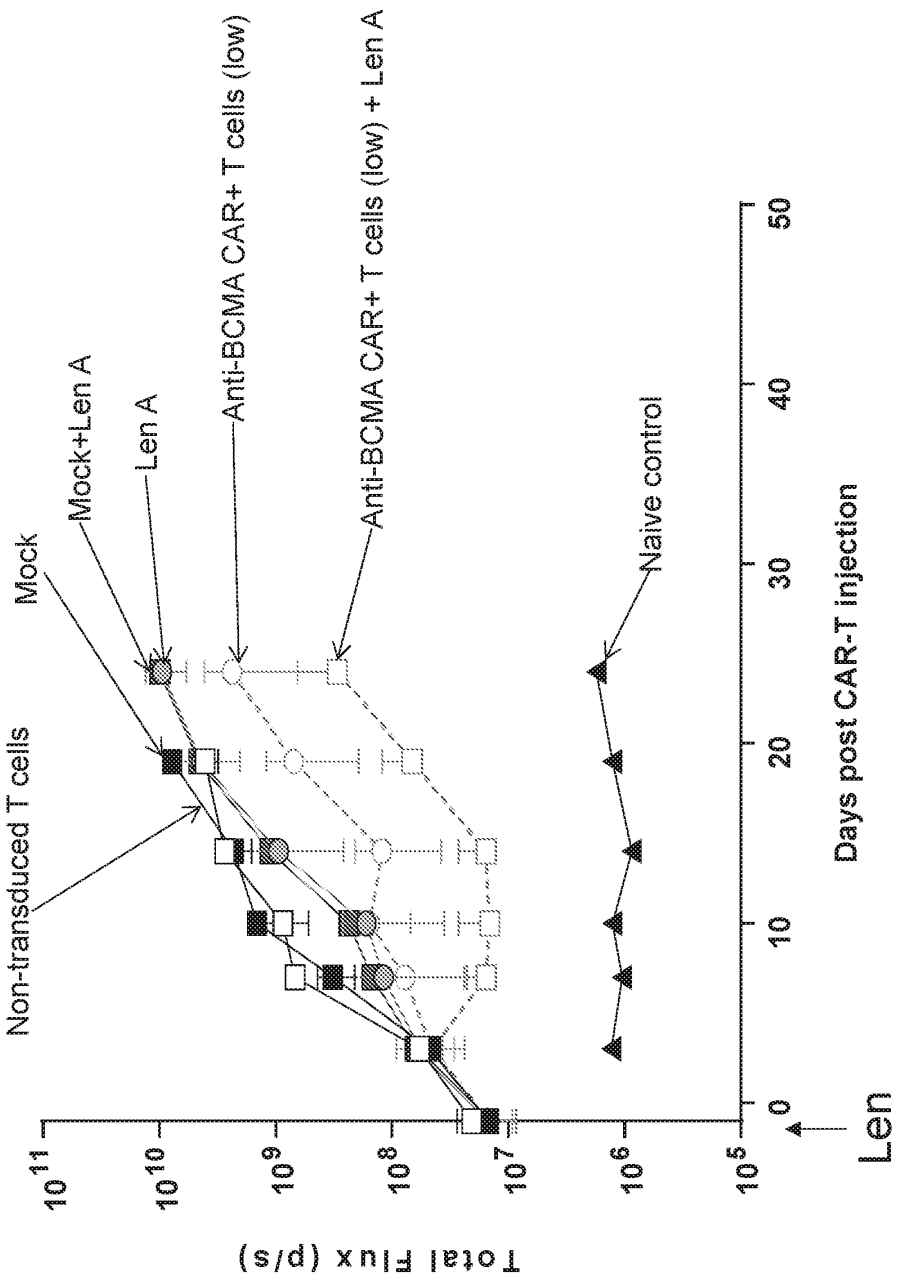
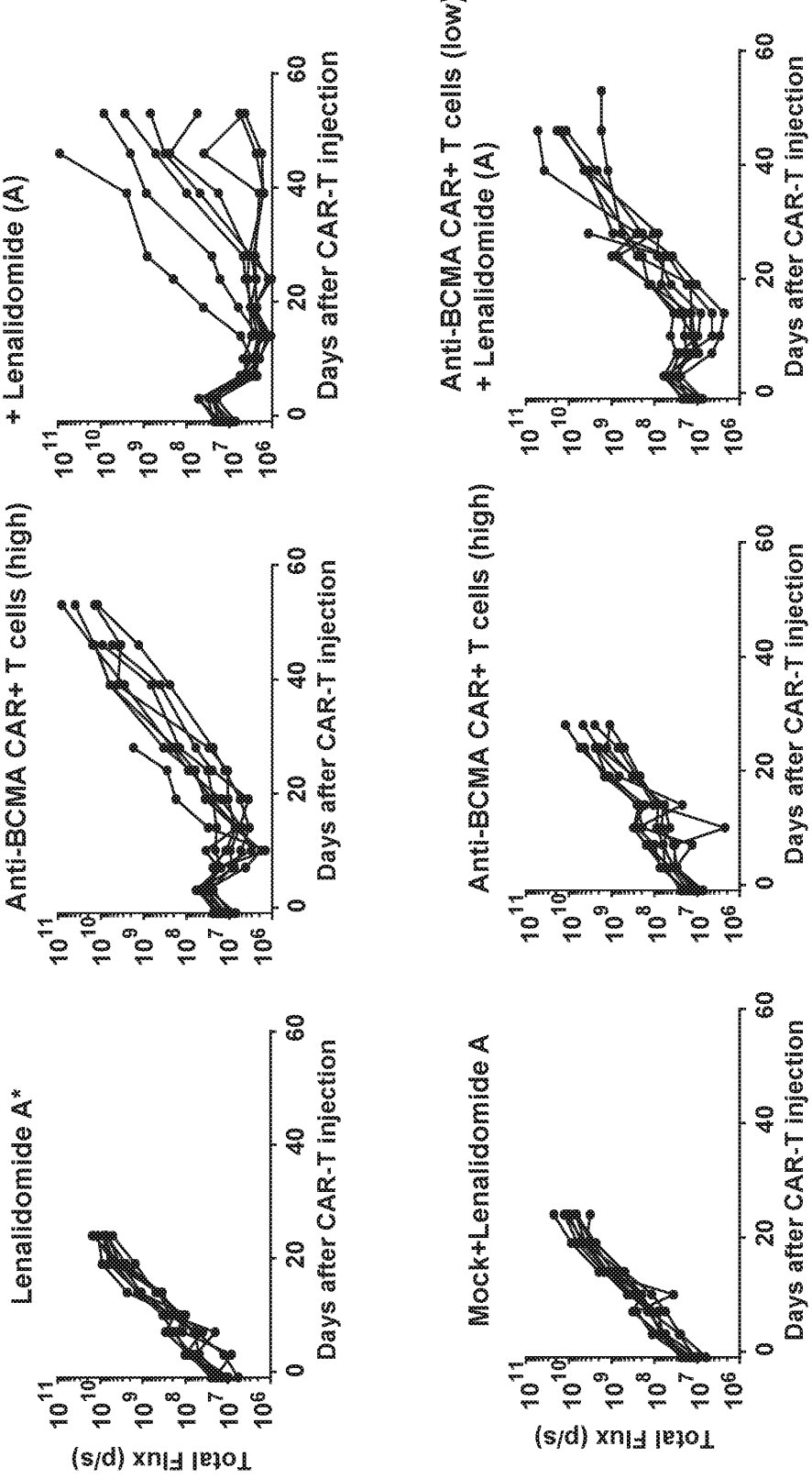

Low Dose 5e5 CAR T cells
Non-transduced T cells
Mock
Mock+Len A
Len A
Anti-BCMA CAR+ T cells (low)
Anti-BCMA CAR+ T cells (low) + Len A
Naive control
Total Flux (p/s)
Days post CAR-T injection
Len

FIG. 9B

FIG. 9C


Lenalidomide A*
Anti-BCMA CAR+ T cells (high)
Anti-BCMA CAR+ T cells (high) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (A)
Mock+Lenalidomide A
Anti-BCMA CAR+ T cells (high)
Total Flux (p/s)
Days after CAR-T injection

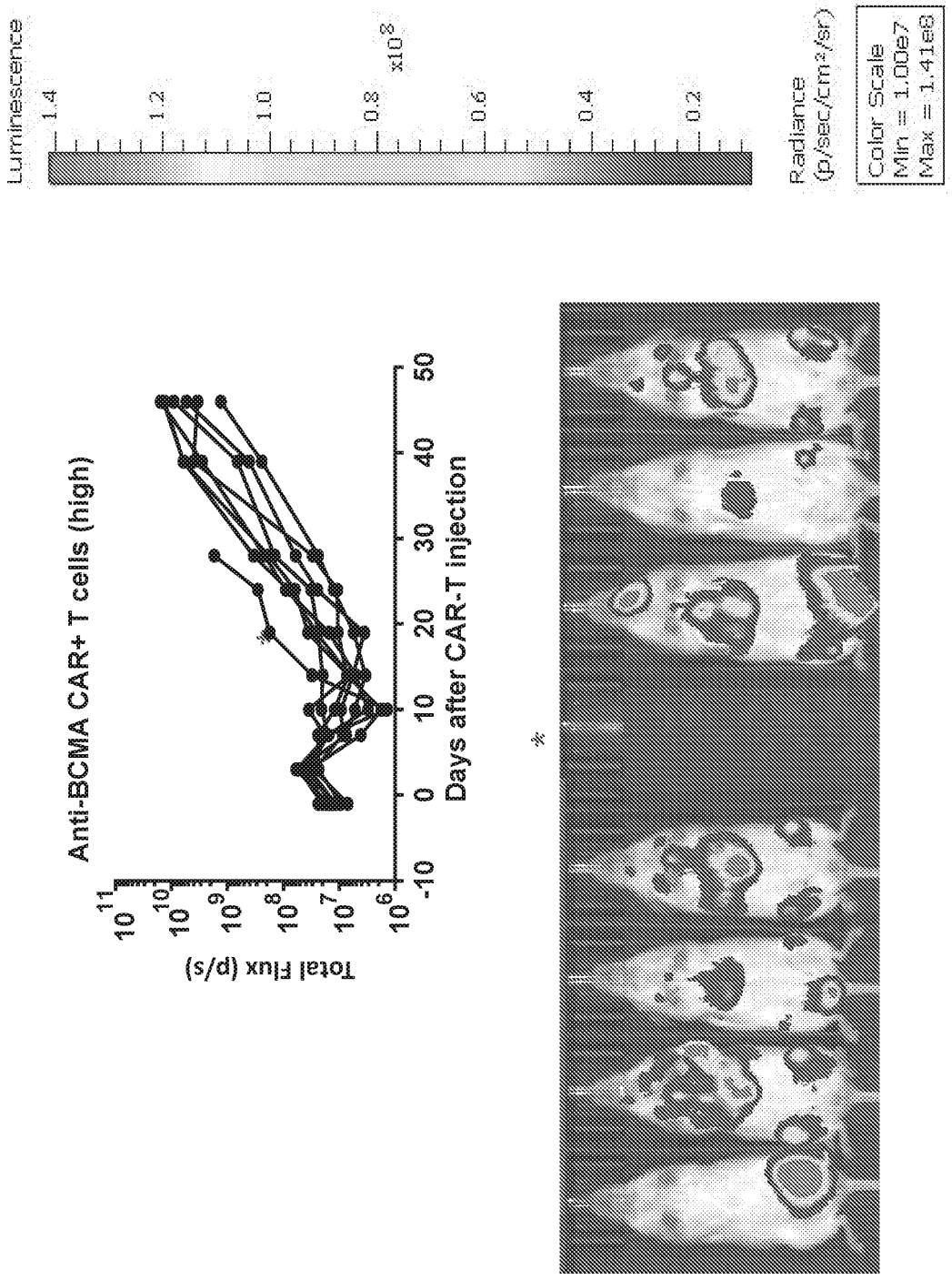
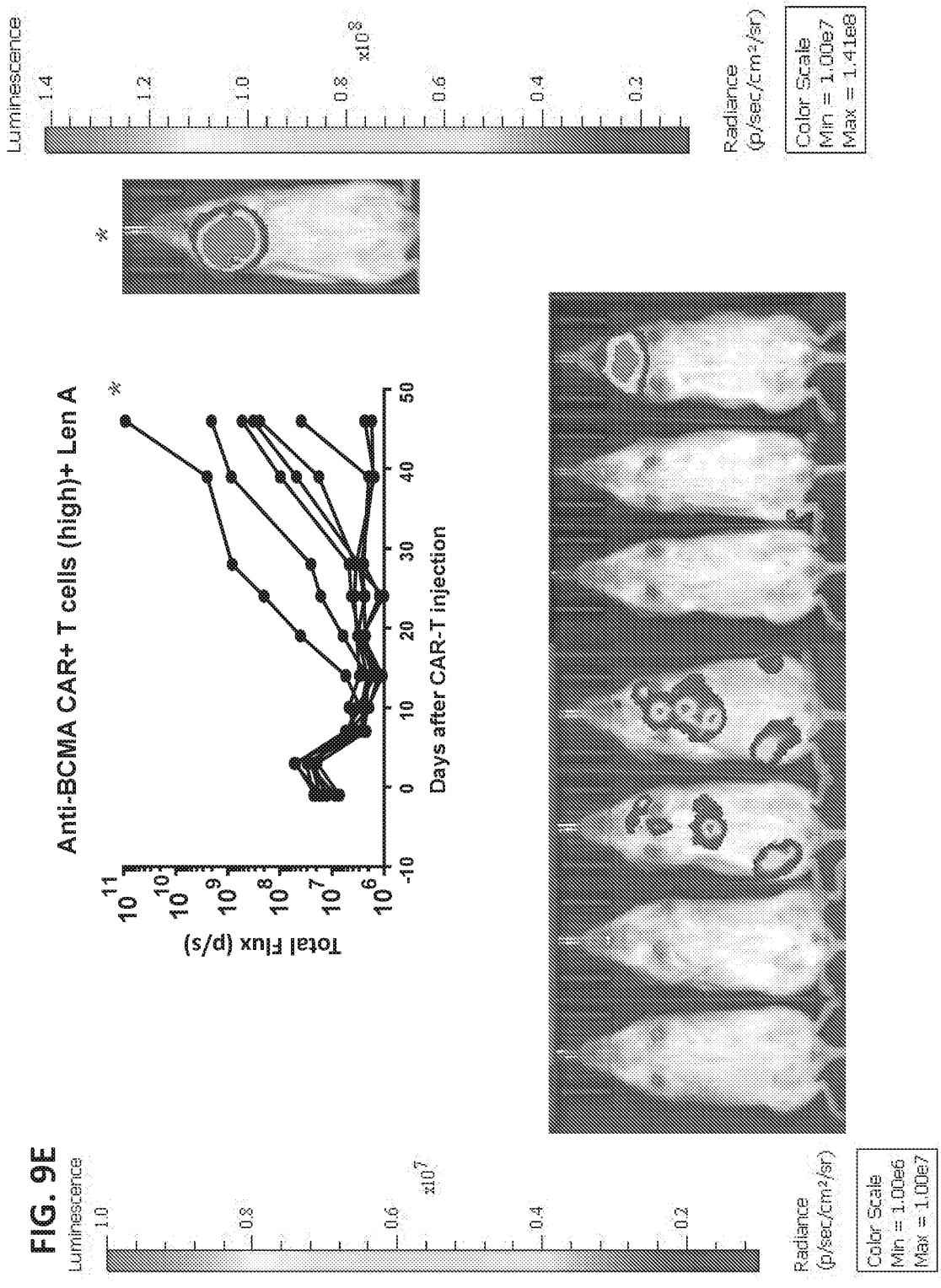

Luminescence
1.4
1.2
1.0
0.8
x10^3
0.6
0.4
0.2
Radiance (p/sec/cm²/sr)
Color Scale
Min = 1.00e7
Max = 1.41e8
Anti-BCMA CAR+ T cells (high)
Total Flux (p/s)
10^11
10^10
10^9
10^8
10^7
10^6
-10
0
10
20
30
40
50
Days after CAR-T injection

FIG. 9D

FIG. 9E


Luminescence
1.0
0.8
0.6
0.4
0.2
x10^7
Radiance (p/sec/cm²/sr)
Color Scale
Min = 1.00e6
Max = 1.00e7
Anti-BCMA CAR+ T cells (high)+ Len A
Total Flux (p/s)
Days after CAR-T injection
Luminescence
1.4
1.2
1.0
0.8
0.6
0.4
0.2
x10^8
Radiance (p/sec/cm²/sr)
Color Scale
Min = 1.00e7
Max = 1.41e8

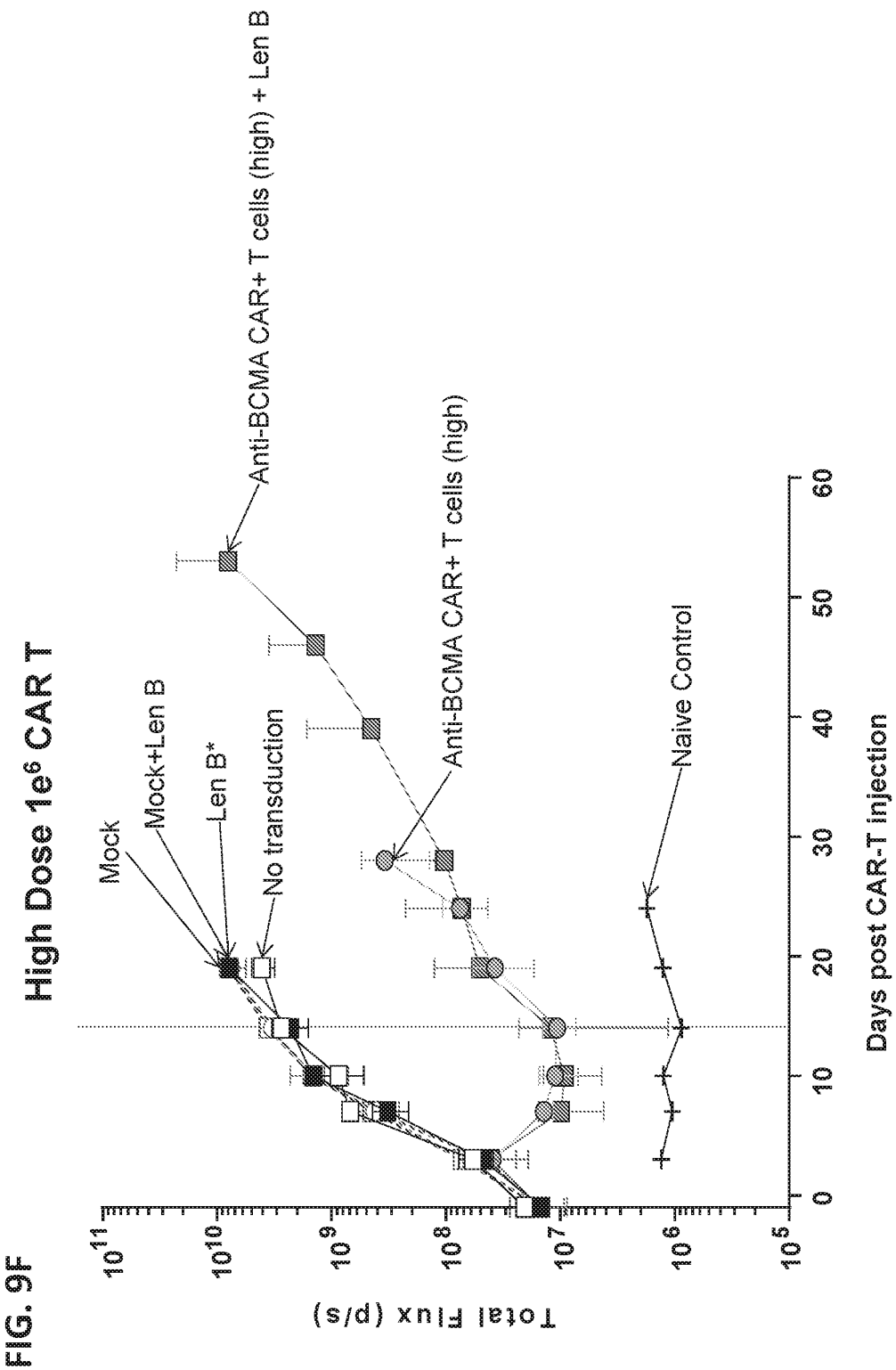

High Dose 1e6 CAR T
Mock
Mock+Len B
Len B*
No transduction
Anti-BCMA CAR+ T cells (high) + Len B
Anti-BCMA CAR+ T cells (high)
Naive Control
Total Flux (p/s)
Days post CAR-T injection

FIG. 9F

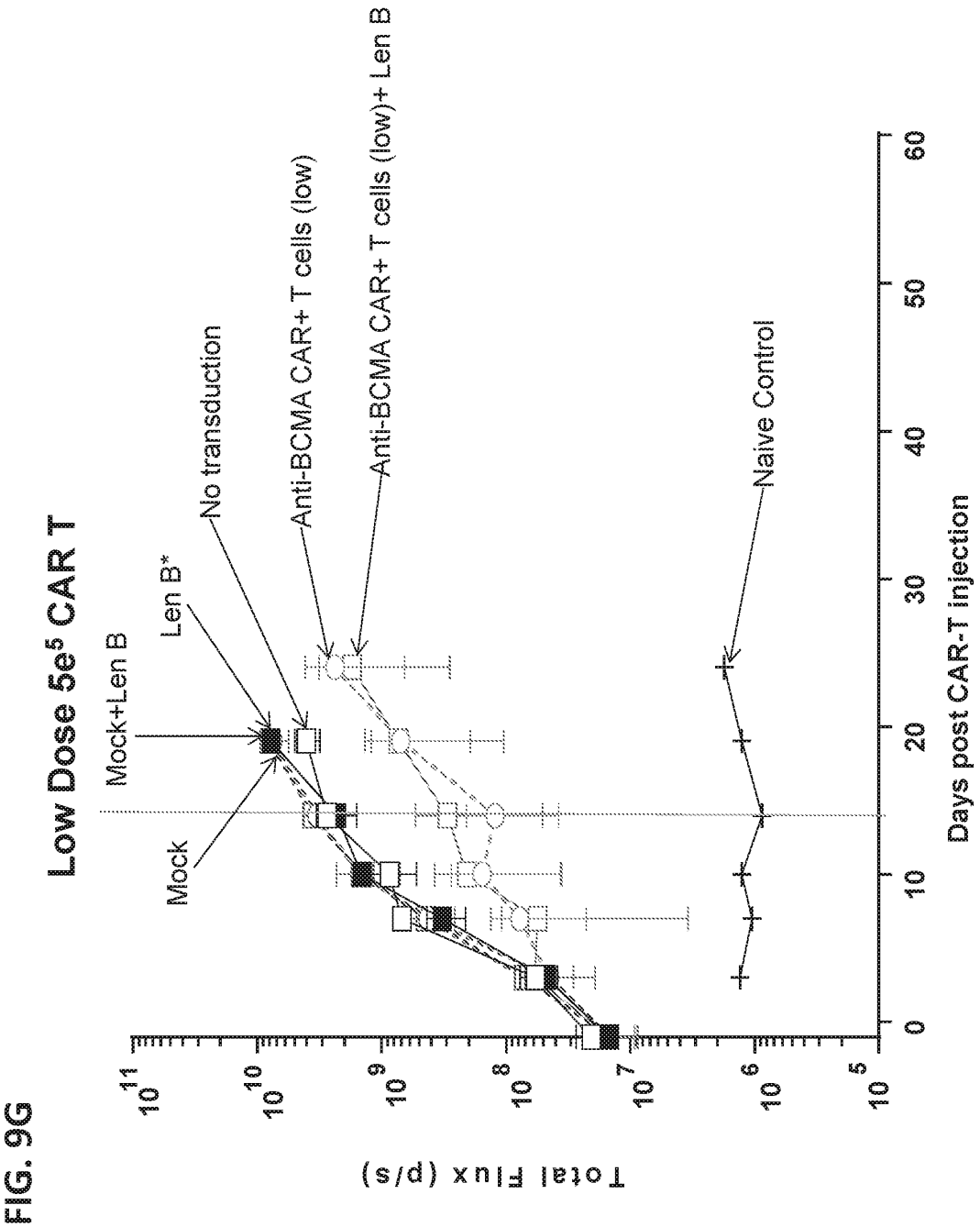
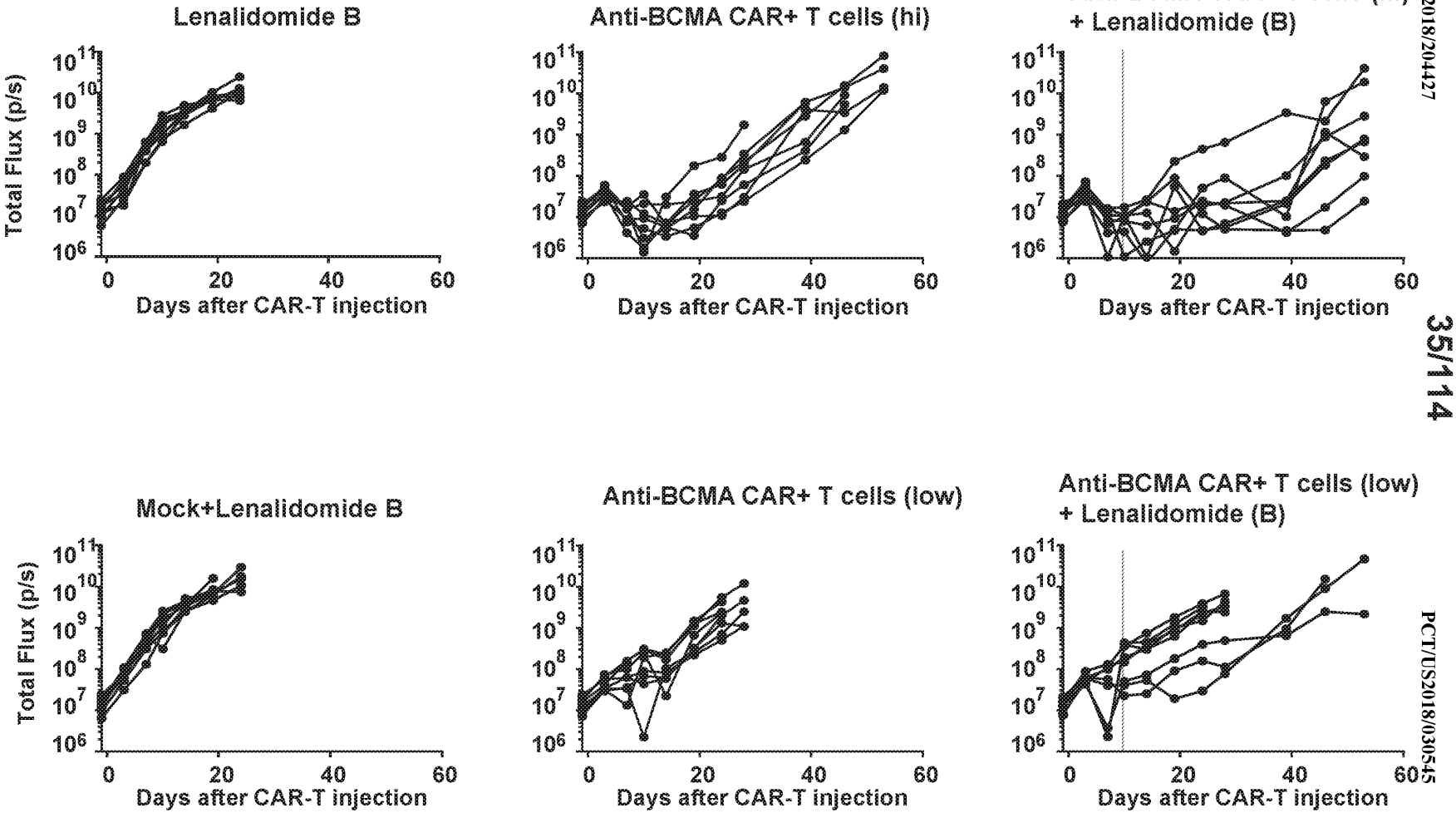

Low Dose 5e5 CAR T
Mock+Len B
Len B*
Mock
No transduction
Anti-BCMA CAR+ T cells (low)
Anti-BCMA CAR+ T cells (low)+ Len B
Naive Control
Total Flux (p/s)
Days post CAR-T injection
10^11
10^10
10^9
10^8
10^7
10^6
10^5
0
10
20
30
40
50
60

FIG. 9G

FIG. 9H


Lenalidomide B
Anti-BCMA CAR+ T cells (hi)
Anti-BCMA CAR+ T cells (hi) + Lenalidomide (B)
Mock+Lenalidomide B
Anti-BCMA CAR+ T cells (low)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (B)
Total Flux (p/s)
Days after CAR-T injection

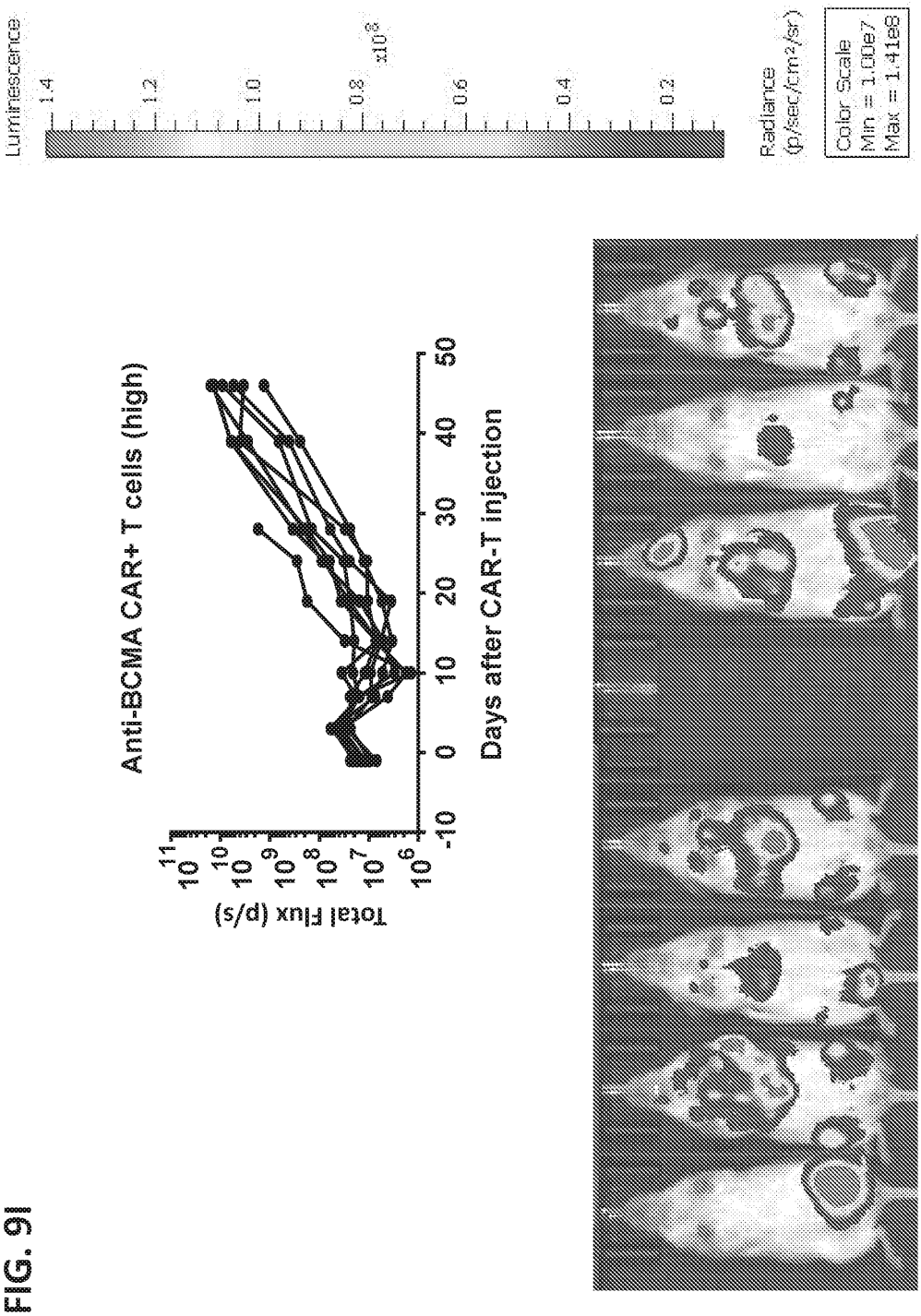

Luminescence
1.4
1.2
1.0
0.8
x10^3
0.6
0.4
0.2
Radiance (p/sec/cm²/sr)
Color Scale
Min = 1.00e7
Max = 1.41e8
Anti-BCMA CAR+ T cells (high)
Total Flux (p/s)
10^11
10^10
10^9
10^8
10^7
10^6
-10
0
10
20
30
40
50
Days after CAR-T injection

FIG. 9I

FIG. 9J

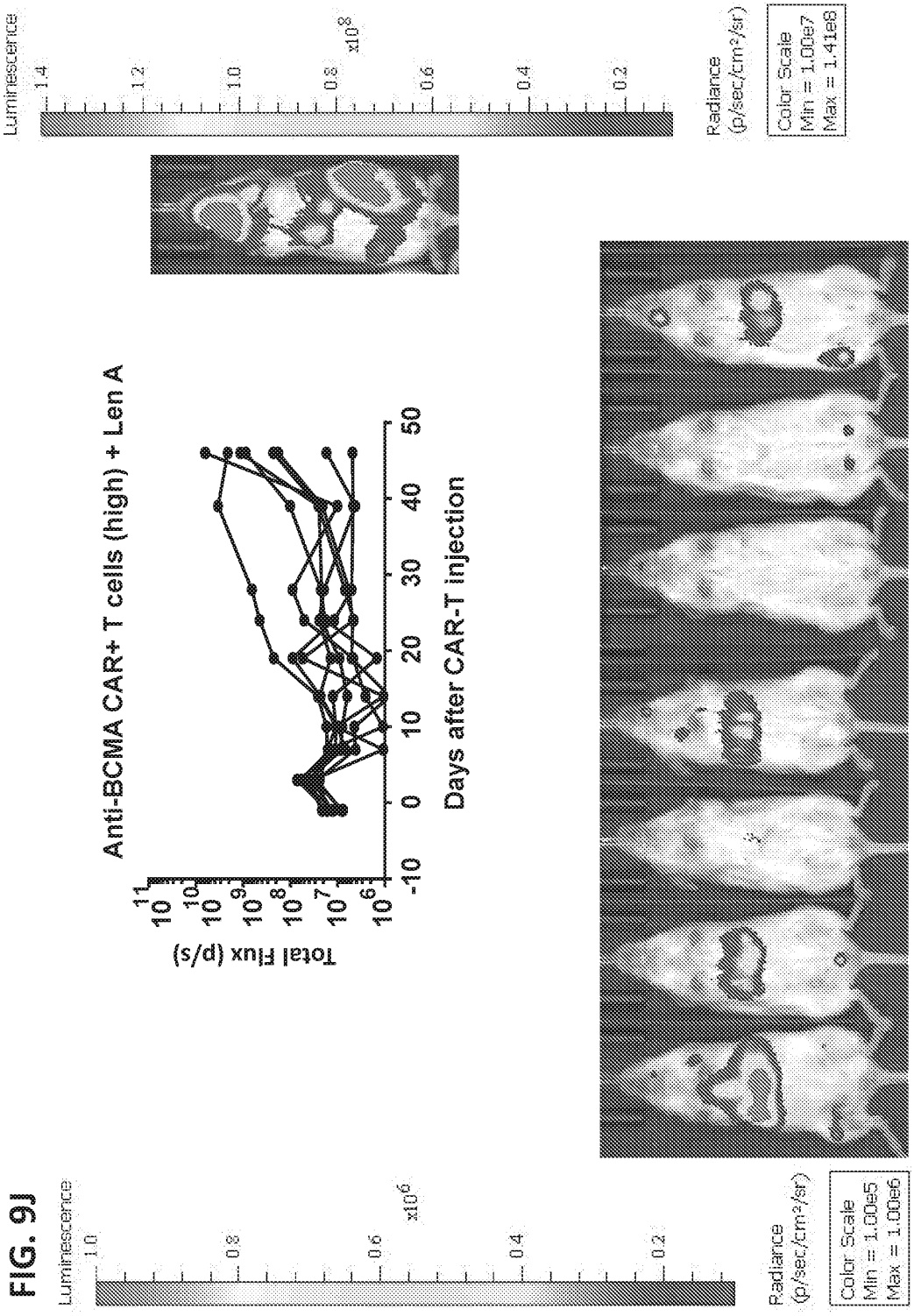

Luminescence
1.4
1.2
1.0
0.8
x10^8
0.6
0.4
0.2
Radiance (p/sec/cm²/sr)
Color Scale
Min = 1.00e7
Max = 1.41e8
Anti-BCMA CAR+ T cells (high) + Len A
Total Flux (p/s)
10^11
10^10
10^9
10^8
10^7
10^6
-10
0
10
20
30
40
50
Days after CAR-T injection
Luminescence
1.0
0.8
0.6
x10^6
0.4
0.2
Radiance (p/sec/cm²/sr)
Color Scale
Min = 1.00e5
Max = 1.00e6

FIG. 10A

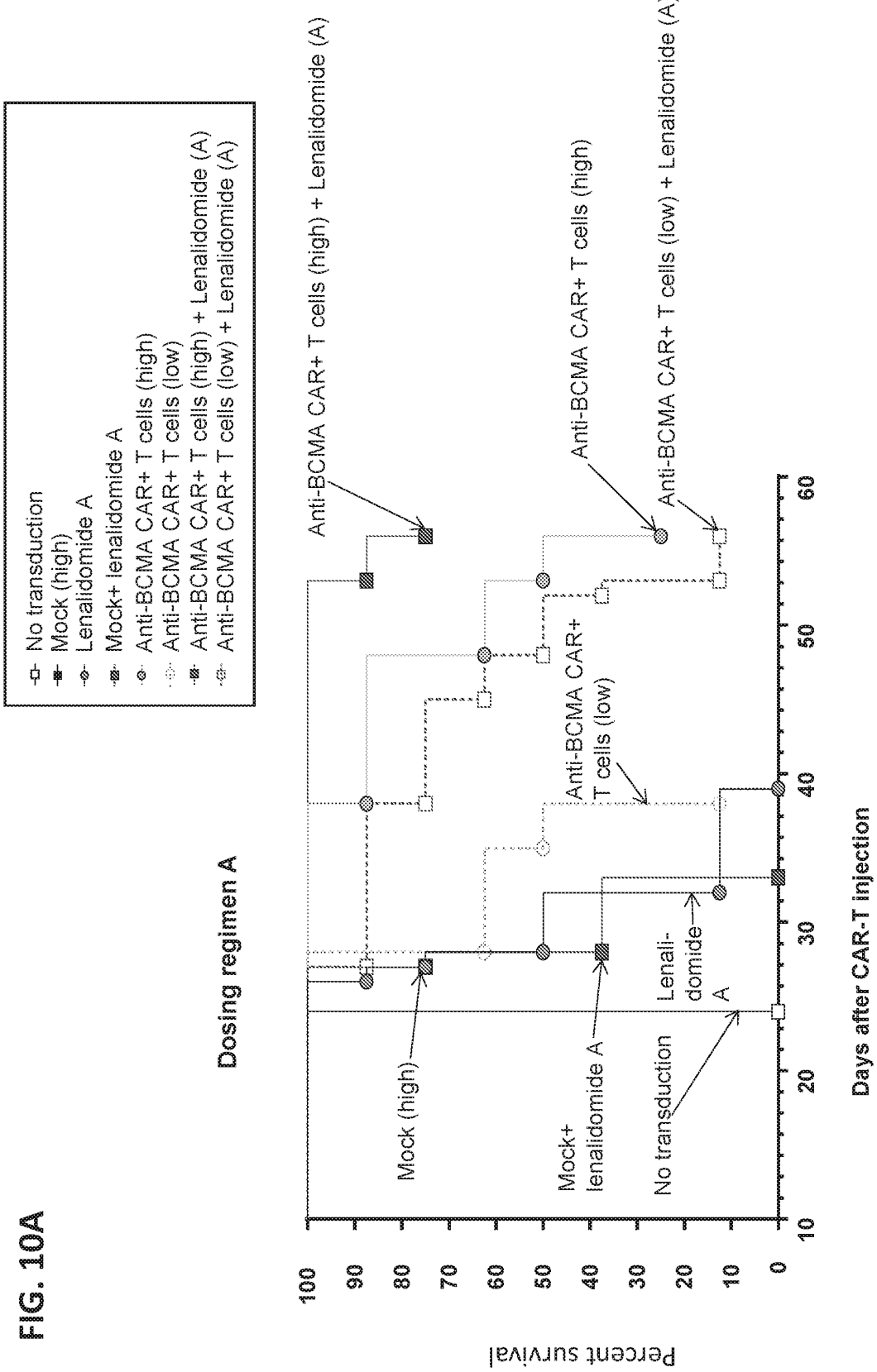

No transduction
Mock (high)
Lenalidomide A
Mock+ lenalidomide A
Anti-BCMA CAR+ T cells (high)
Anti-BCMA CAR+ T cells (low)
Anti-BCMA CAR+ T cells (high) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (A)
Dosing regimen A
Percent survival
Days after CAR-T injection
Anti-BCMA CAR+ T cells (high) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (high)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (low)
Mock (high)
Mock+ lenalidomide A
No transduction
Lenali-domide A

FIG. 10B

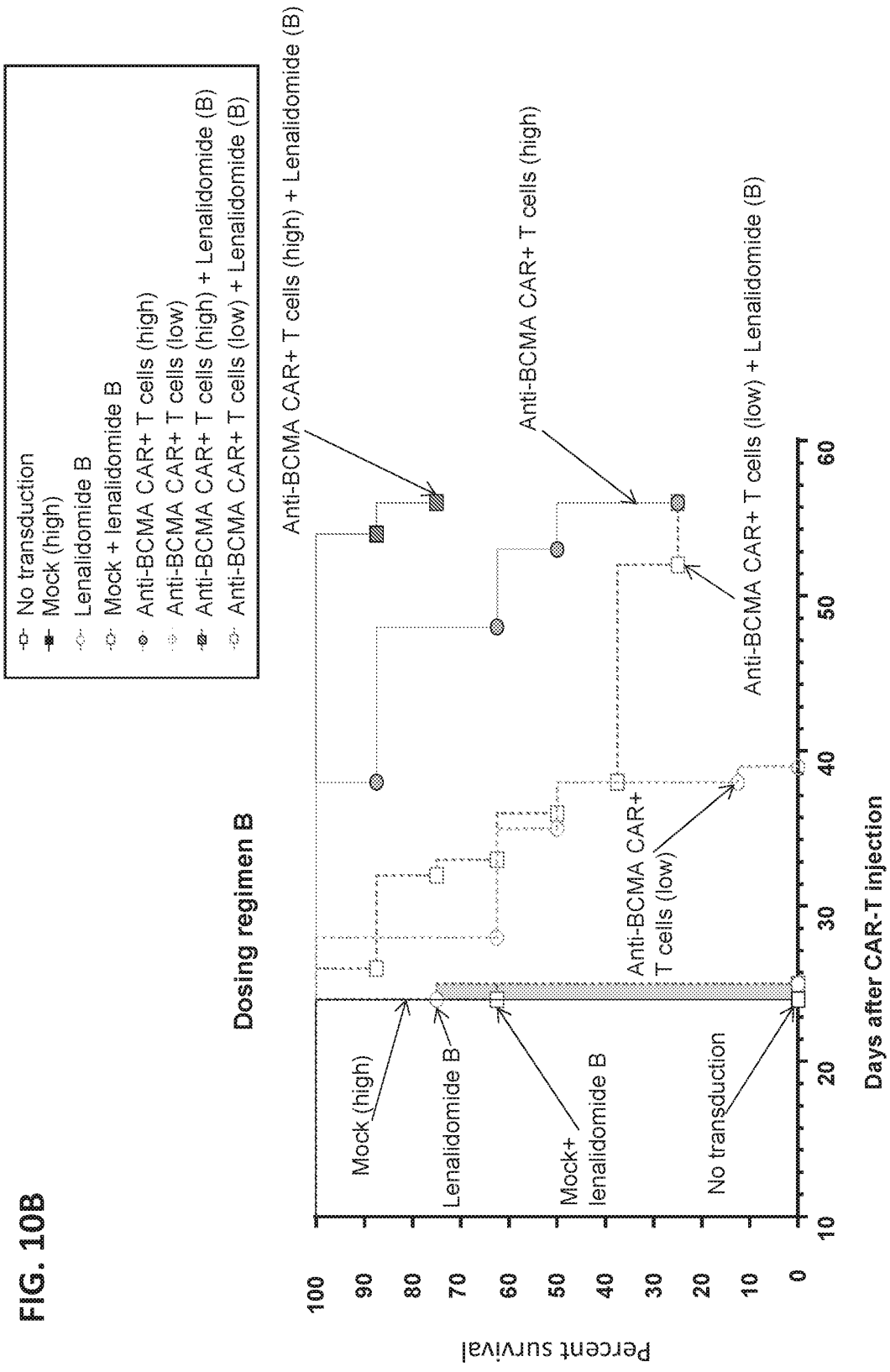

No transduction
Mock (high)
Lenalidomide B
Mock + lenalidomide B
Anti-BCMA CAR+ T cells (high)
Anti-BCMA CAR+ T cells (low)
Anti-BCMA CAR+ T cells (high) + Lenalidomide (B)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (B)
Dosing regimen B
Anti-BCMA CAR+ T cells (high) + Lenalidomide (B)
Anti-BCMA CAR+ T cells (high)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (B)
Mock (high)
Lenalidomide B
Mock+ lenalidomide B
Anti-BCMA CAR+ T cells (low)
No transduction
Percent survival
Days after CAR-T injection
0
10
20
30
40
50
60
70
80
90
100

FIG. 10C

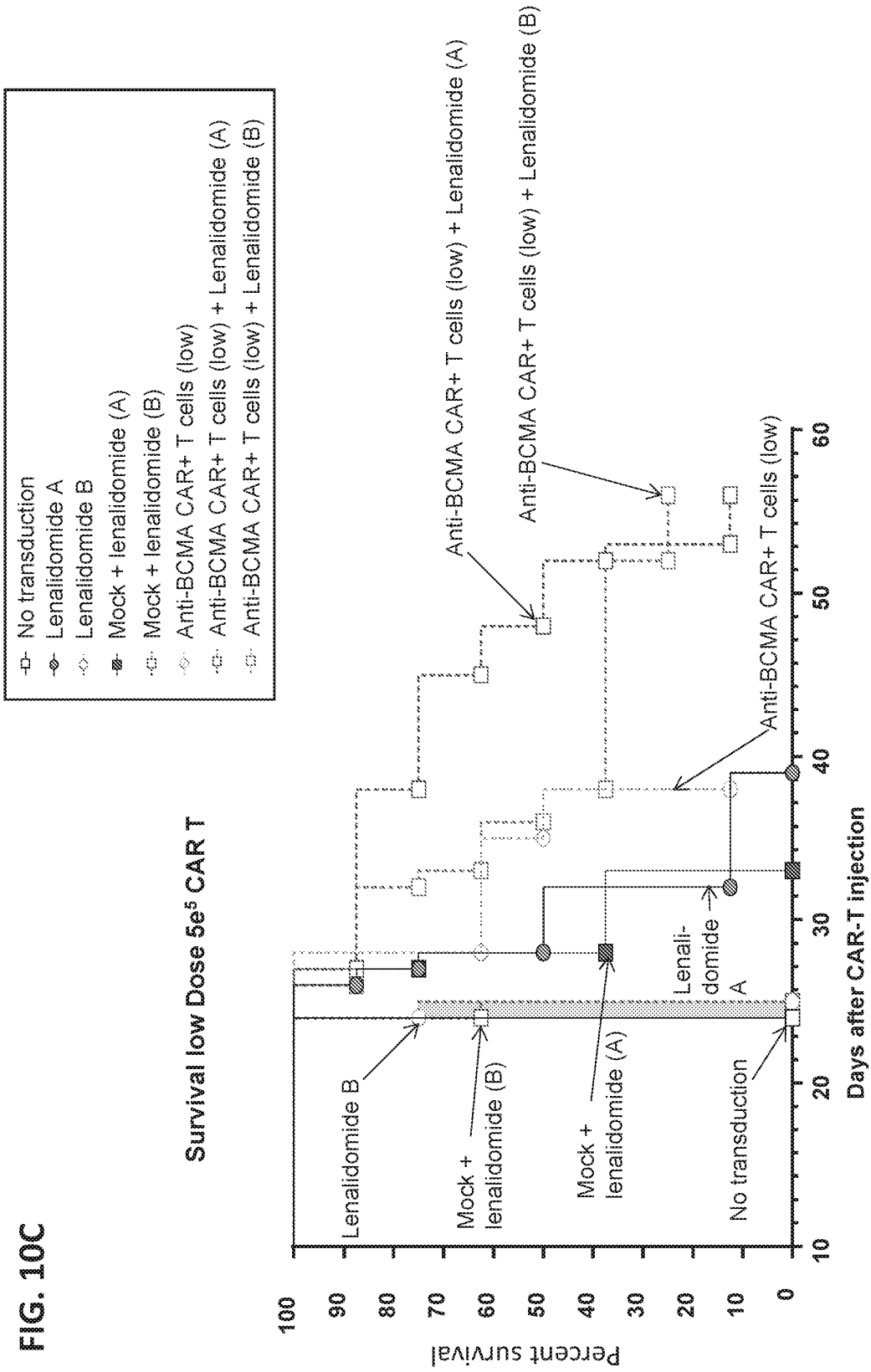

Survival low Dose 5e5 CAR T
No transduction
Lenalidomide A
Lenalidomide B
Mock + lenalidomide (A)
Mock + lenalidomide (B)
Anti-BCMA CAR+ T cells (low)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (B)
Percent survival
Days after CAR-T injection
Lenalidomide B
Mock + lenalidomide (B)
Mock + lenalidomide (A)
No transduction
Lenali-domide A
Anti-BCMA CAR+ T cells (low) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (low) + Lenalidomide (B)
Anti-BCMA CAR+ T cells (low)

FIG. 10D

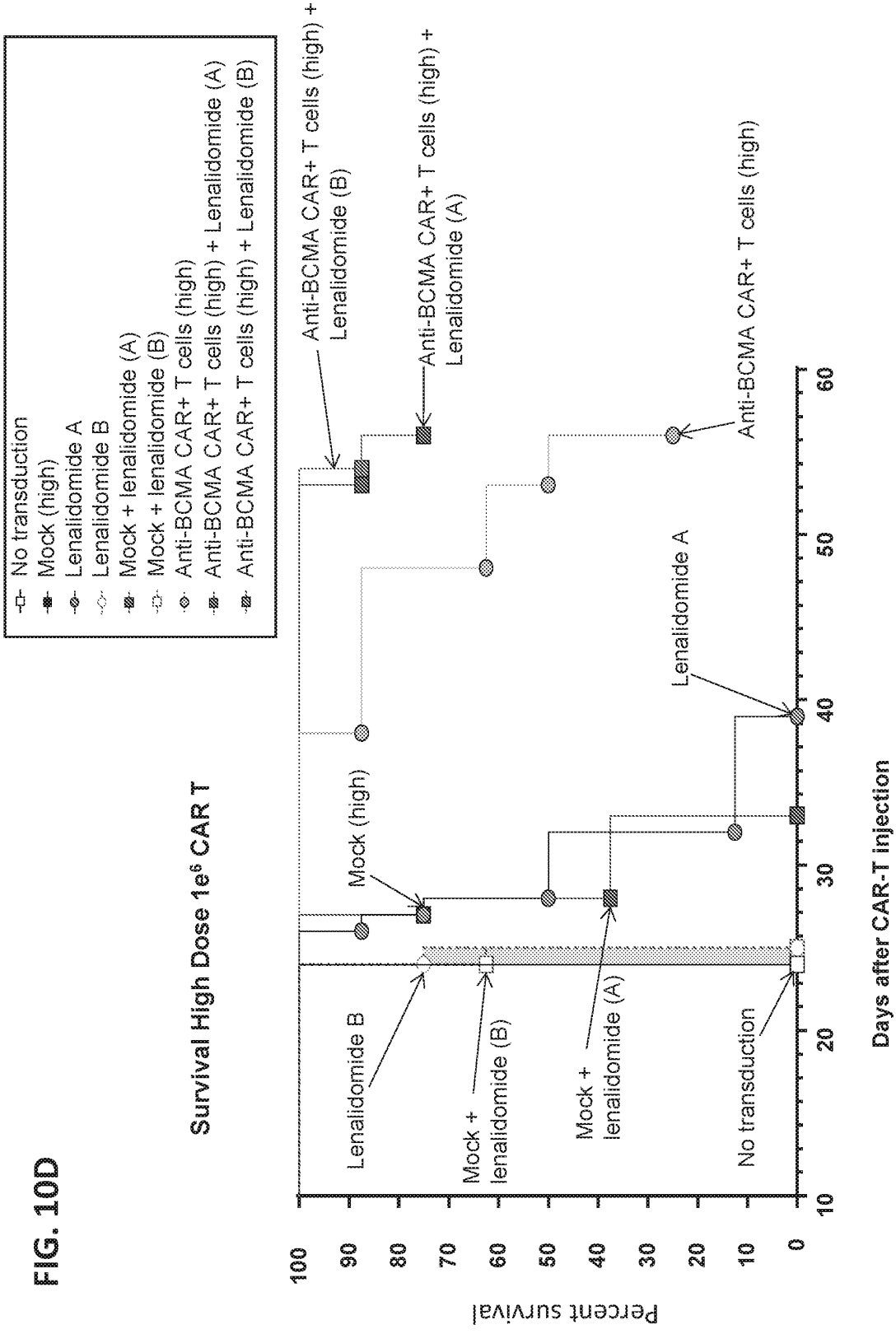
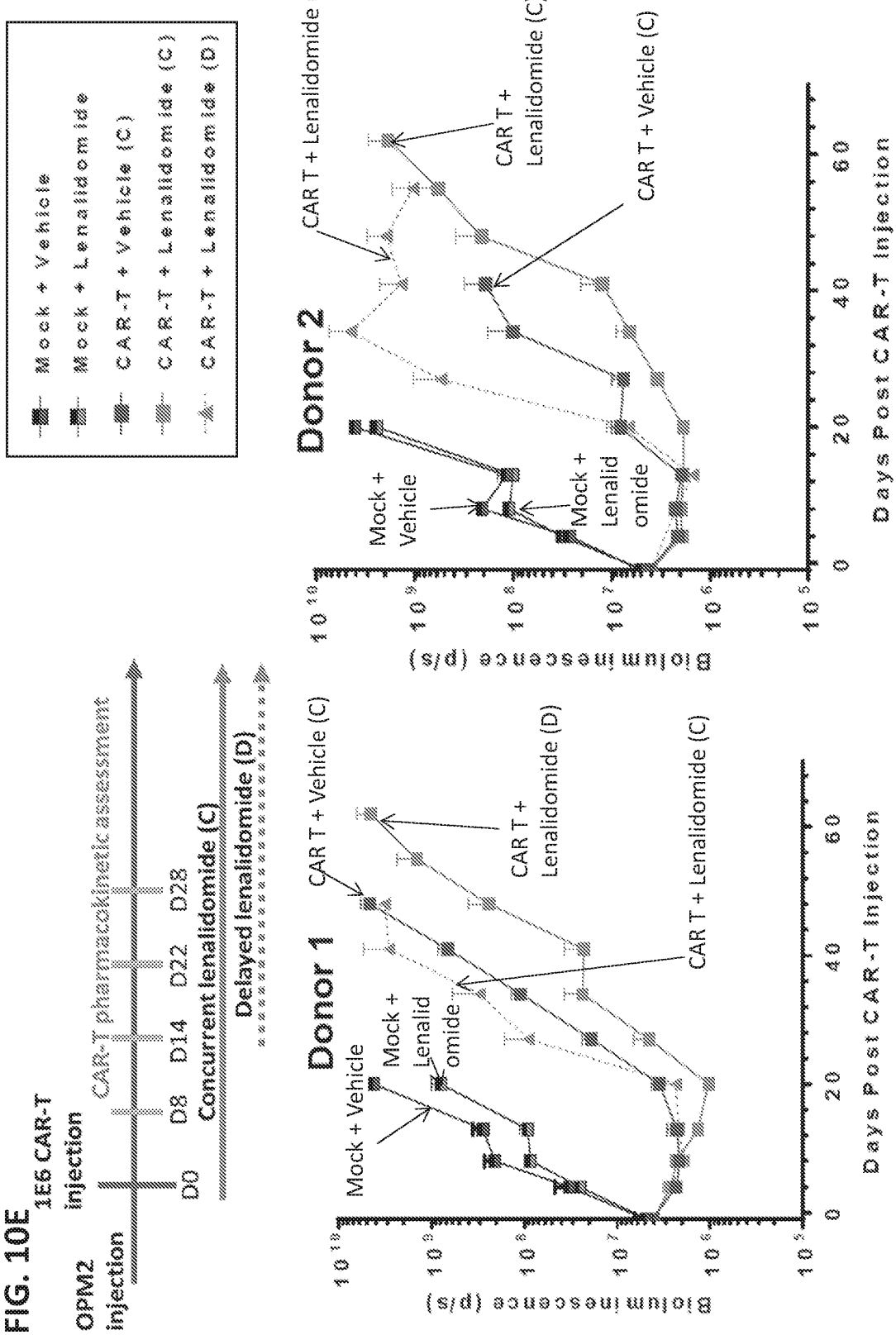

Survival High Dose 1e6 CAR T
No transduction
Mock (high)
Lenalidomide A
Lenalidomide B
Mock + lenalidomide (A)
Mock + lenalidomide (B)
Anti-BCMA CAR+ T cells (high)
Anti-BCMA CAR+ T cells (high) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (high) + Lenalidomide (B)
Percent survival
Days after CAR-T injection
Anti-BCMA CAR+ T cells (high) + Lenalidomide (B)
Anti-BCMA CAR+ T cells (high) + Lenalidomide (A)
Anti-BCMA CAR+ T cells (high)
Mock (high)
Lenalidomide A
Lenalidomide B
Mock + lenalidomide (B)
Mock + lenalidomide (A)
No transduction

FIG. 10E


Mock + Vehicle
Mock + Lenalidomide
CAR-T + Vehicle (C)
CAR-T + Lenalidomide (C)
CAR-T + Lenalidomide (D)
1E6 CAR-T injection
OPM2 injection
CAR-T pharmacokinetic assessment
D0
D8
D14
D22
D28
Concurrent lenalidomide (C)
Delayed lenalidomide (D)
Donor 1
Donor 2
Mock + Vehicle
Mock + Lenalidomide
CAR T + Vehicle (C)
CAR T + Lenalidomide (D)
CAR T + Lenalidomide (C)
Bolum inescence (p/s)
Days Post CAR-T Injection

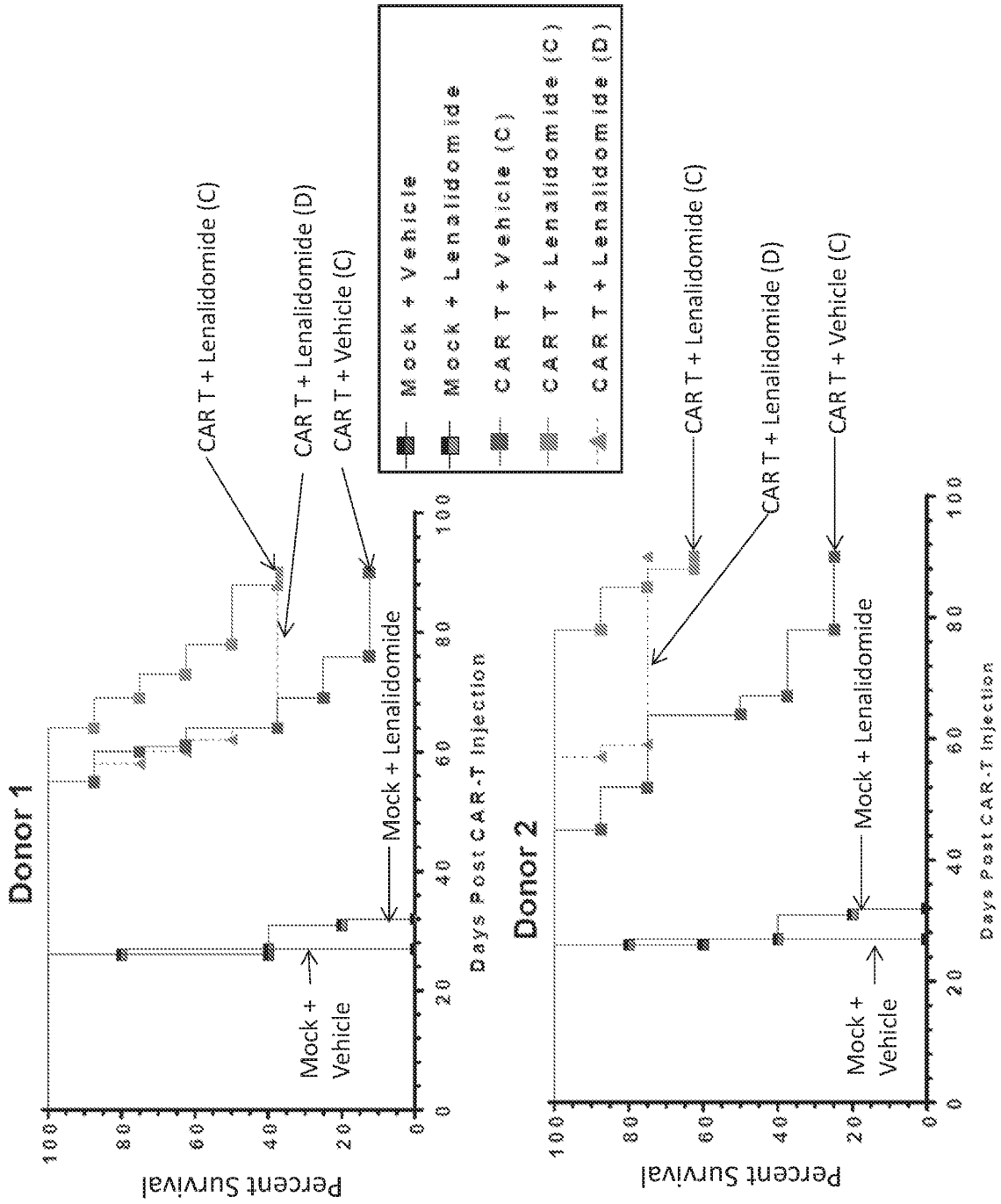

Donor 1
Donor 2
Percent Survival
Days Post CAR-T Injection
Mock + Vehicle
Mock + Lenalidomide
CAR T + Vehicle (C)
CAR T + Lenalidomide (C)
CAR T + Lenalidomide (D)
Mock + Vehicle
Mock + Lenalidomide
CAR T + Vehicle (C)
CAR T + Lenalidomide (C)
CAR T + Lenalidomide (D)

FIG. 10F

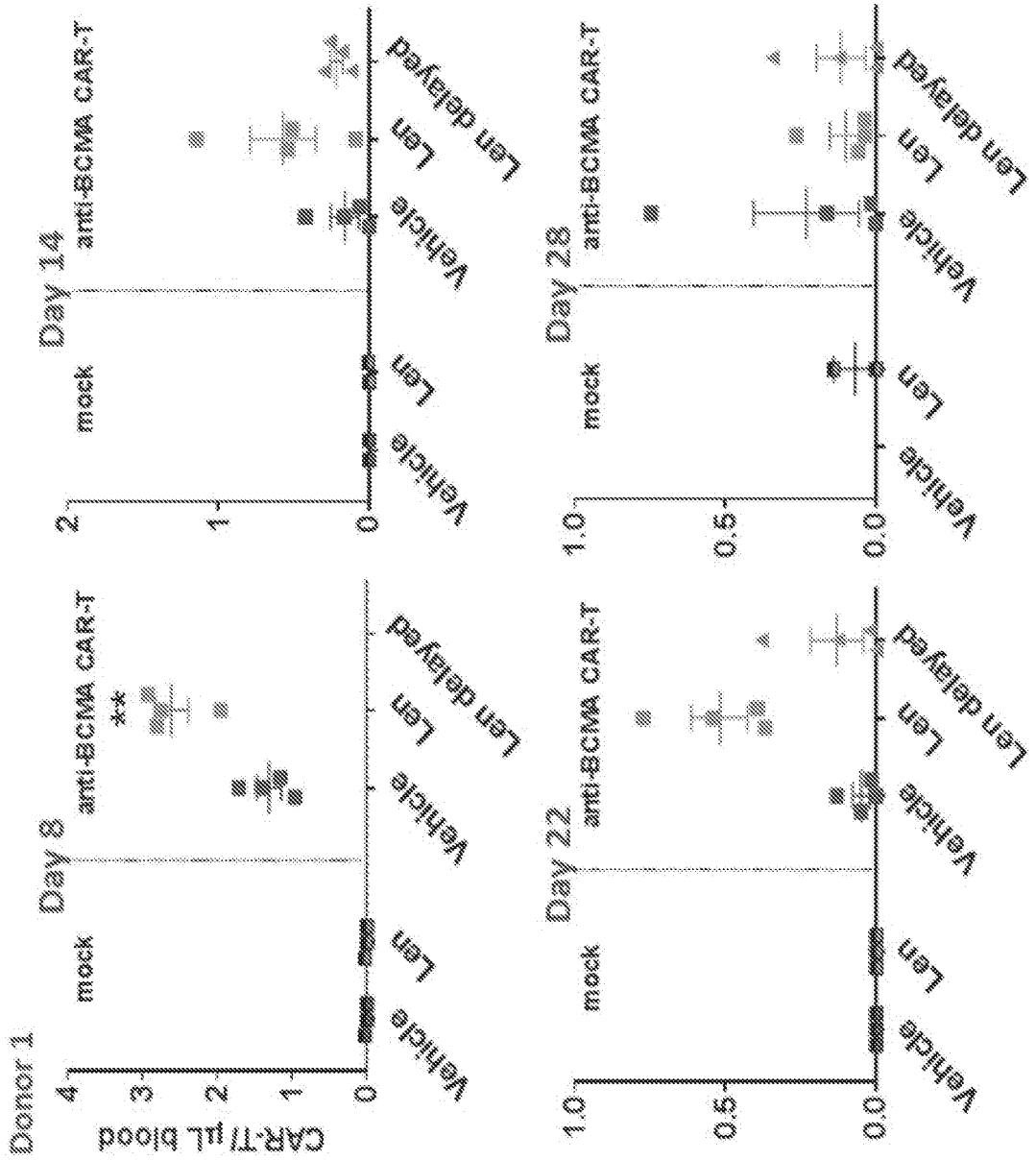

Donor 1
CAR-T/ µL blood
Day 8
Day 14
Day 22
Day 28
mock
anti-BCMA CAR-T
Vehicle
Len
Len delayed
**

FIG. 10G

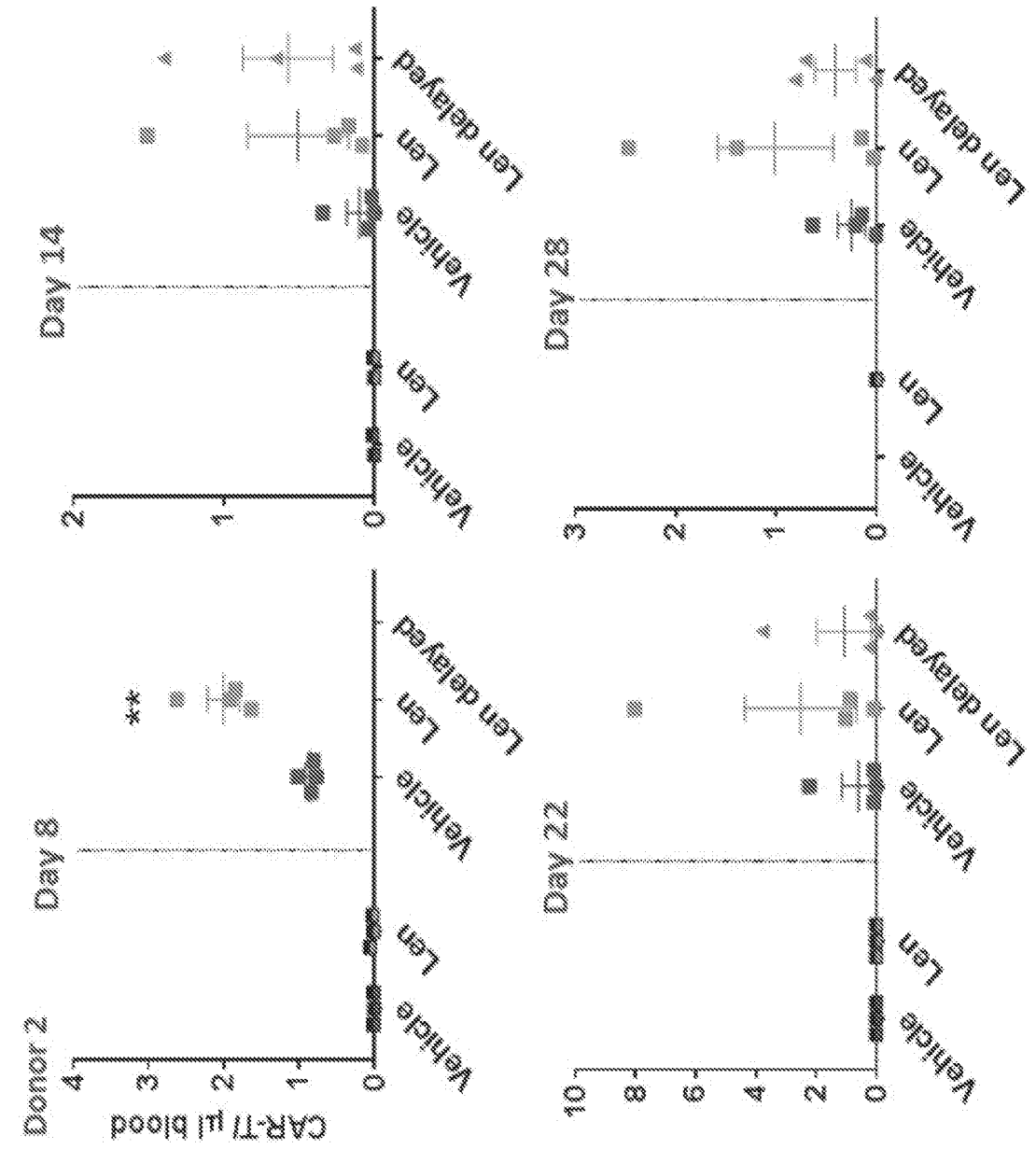

Donor 2
CAR-T/ µl blood
Day 8
Day 14
Day 22
Day 28
Vehicle
Len
Len delayed
**

FIG. 10H

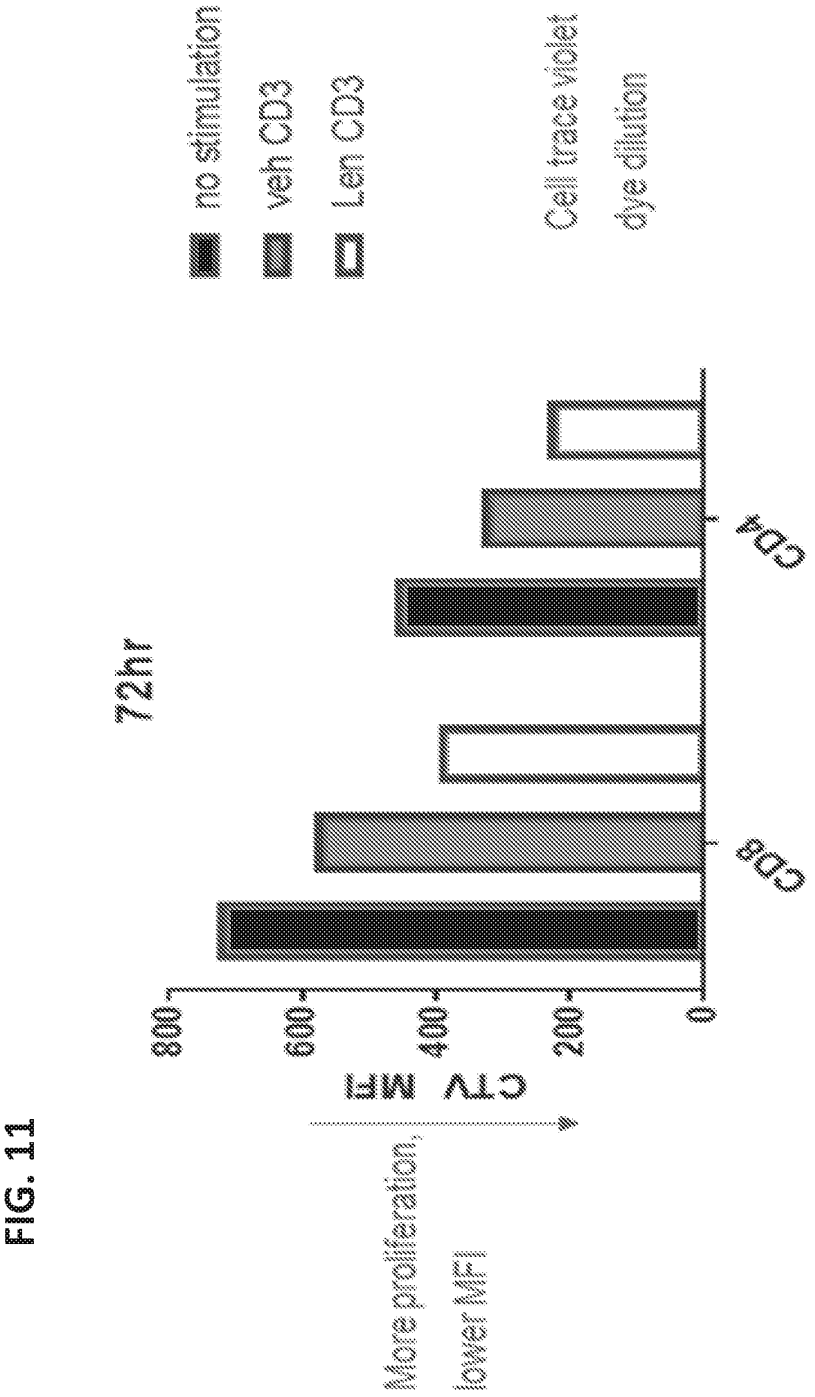

no stimulation
veh CD3
Len CD3
Cell trace violet
dye dilution
72hr
CD4
CD8
0
200
400
600
800
CTV MFI
More proliferation,
lower MFI

FIG. 11

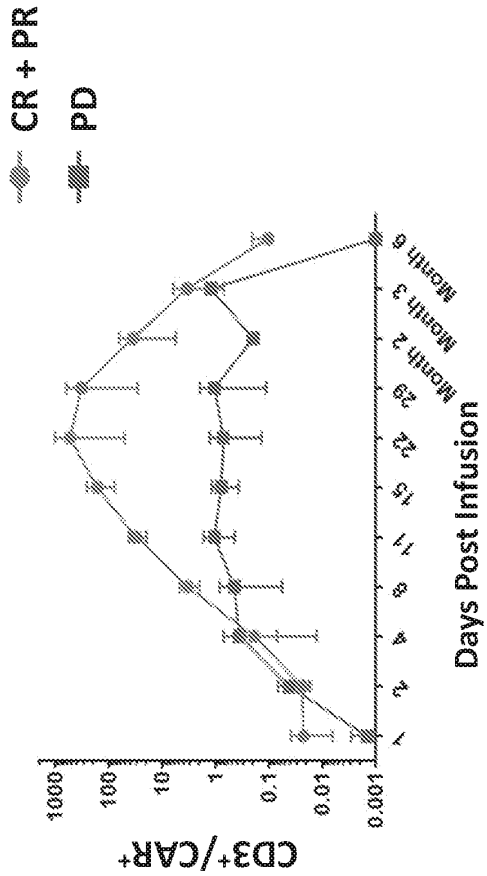


FIG. 12A

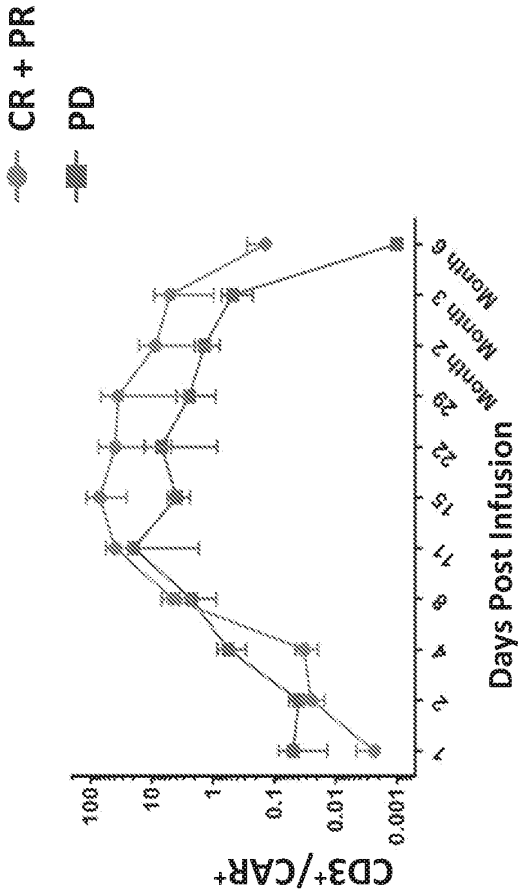


FIG. 12B

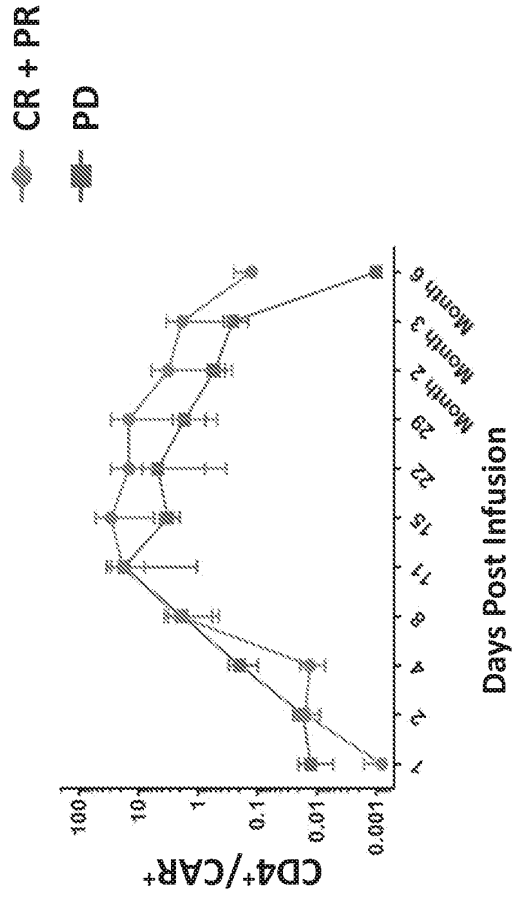


FIG. 12C

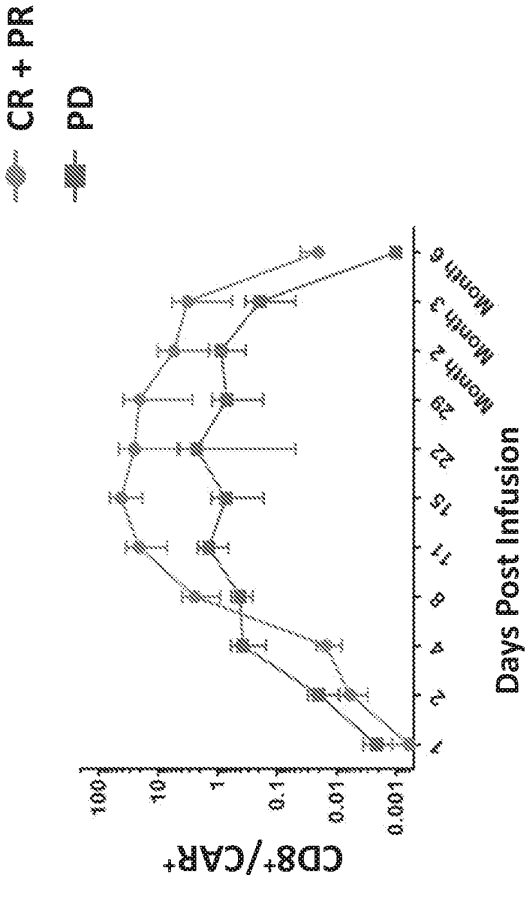


FIG. 12D

FIG. 13A

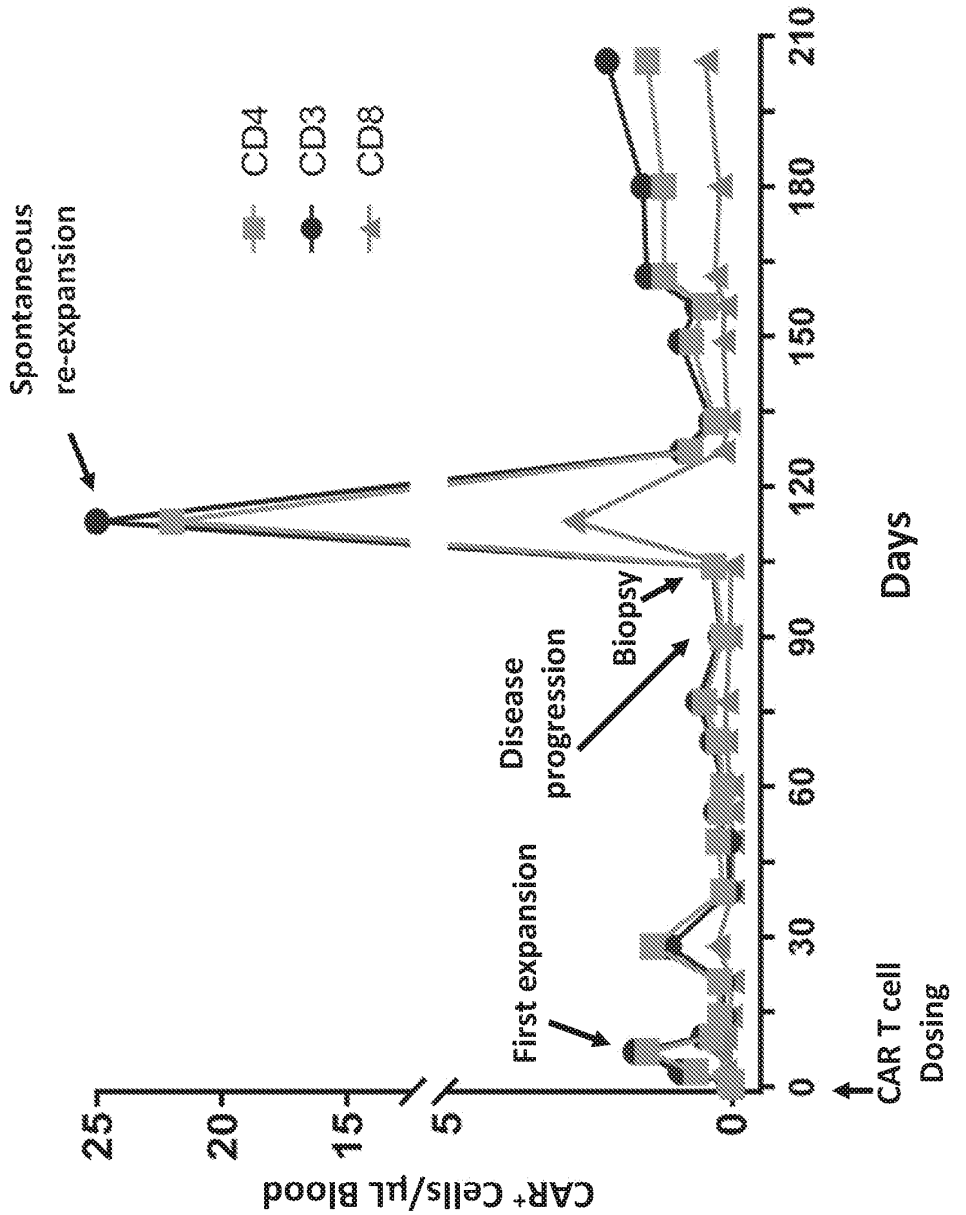

CD4
CD3
CD8
Spontaneous re-expansion
First expansion
Disease progression
Biopsy
CAR T cell Dosing
Days
CAR+ Cells/μL Blood
0
5
15
20
25
0
30
60
90
120
150
180
210

FIG. 13D



FIG. 13G

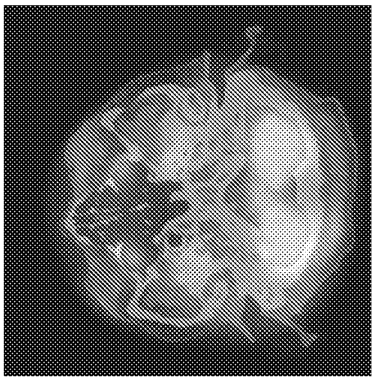


FIG. 13C

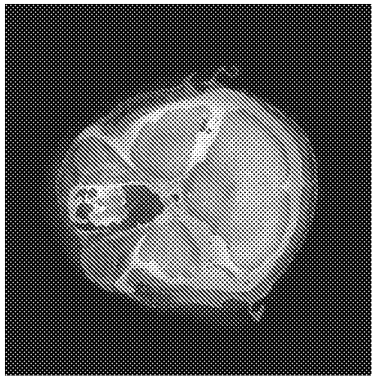


FIG. 13F

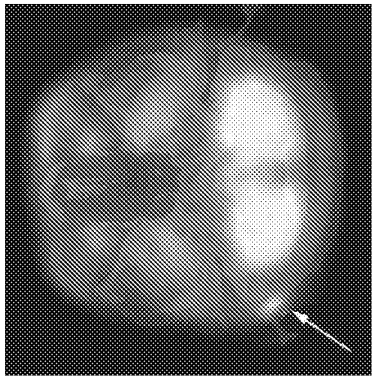


FIG. 13B

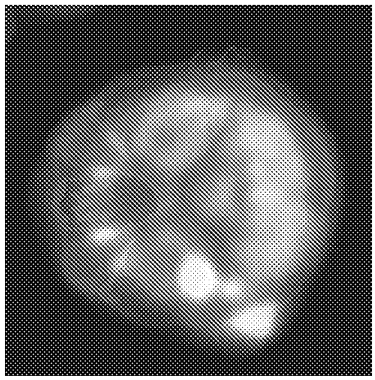


FIG. 13E

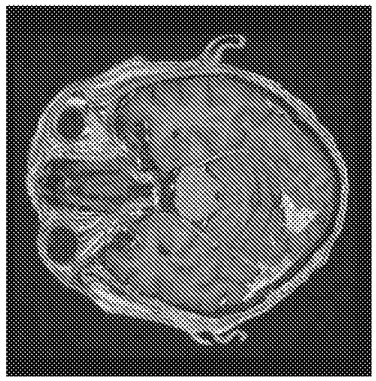
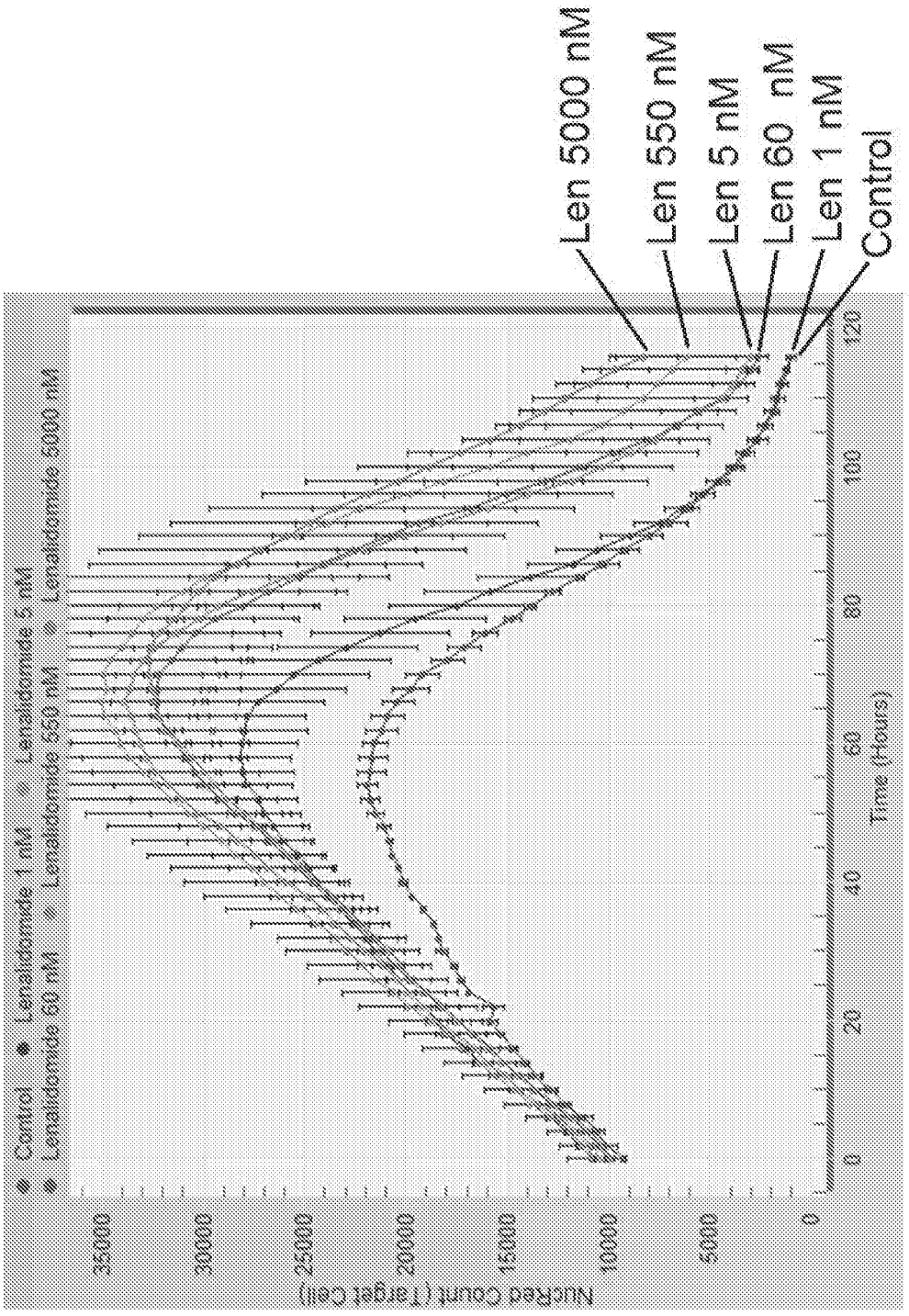


FIG. 14


Len 5000 nM
Len 550 nM
Len 5 nM
Len 60 nM
Len 1 nM
Control
Control
Lenalidomide 1 nM
Lenalidomide 5 nM
Lenalidomide 60 nM
Lenalidomide 550 nM
Lenalidomide 5000 nM
NucRed Count (Target Cell)
Time (Hours)
0
5000
10000
15000
20000
25000
30000
35000
0
20
40
60
80
100
120

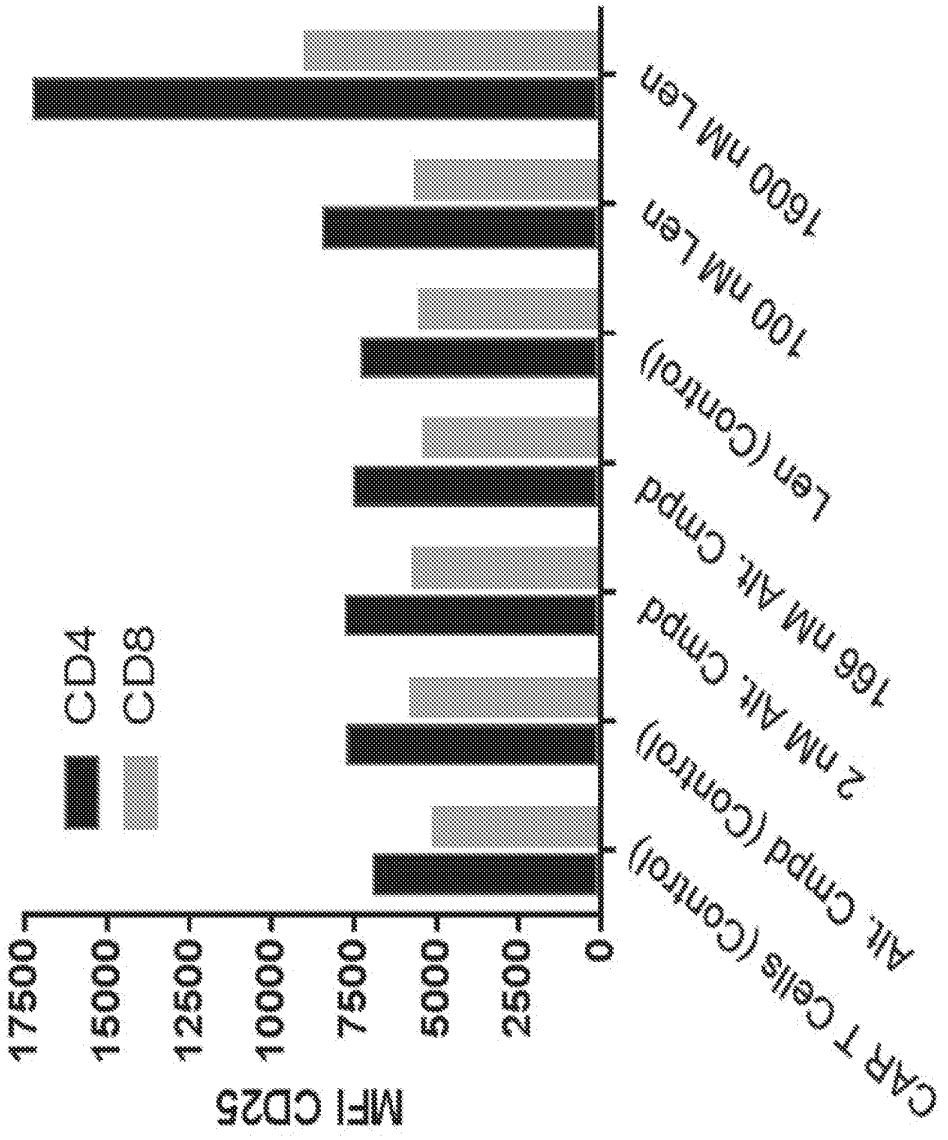

CD4
CD8
MFI CD25
17500
15000
12500
10000
7500
5000
2500
0
CAR T Cells (Control)
Alt. Cmpd (Control)
2 nM Alt. Cmpd
166 nM Alt. Cmpd
Len (Control)
100 nM Len
1600 nM Len

FIG. 15A

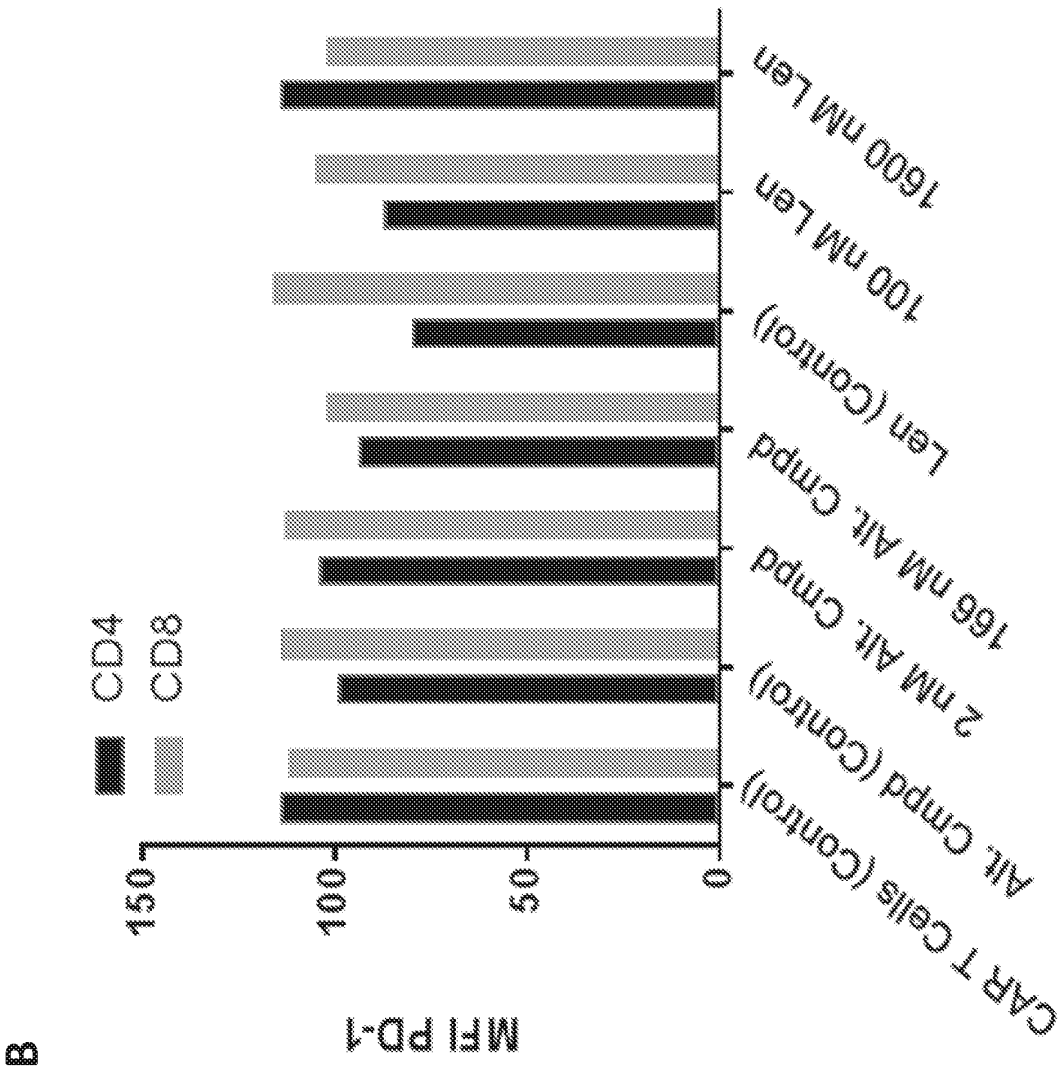

CD4
CD8
MFI PD-1
150
100
50
0
CAR T Cells (Control)
Alt Cmpd (Control)
2 nM Alt. Cmpd
166 nM Alt. Cmpd
Len (Control)
100 nM Len
1600 nM Len

FIG. 15B

FIG. 16

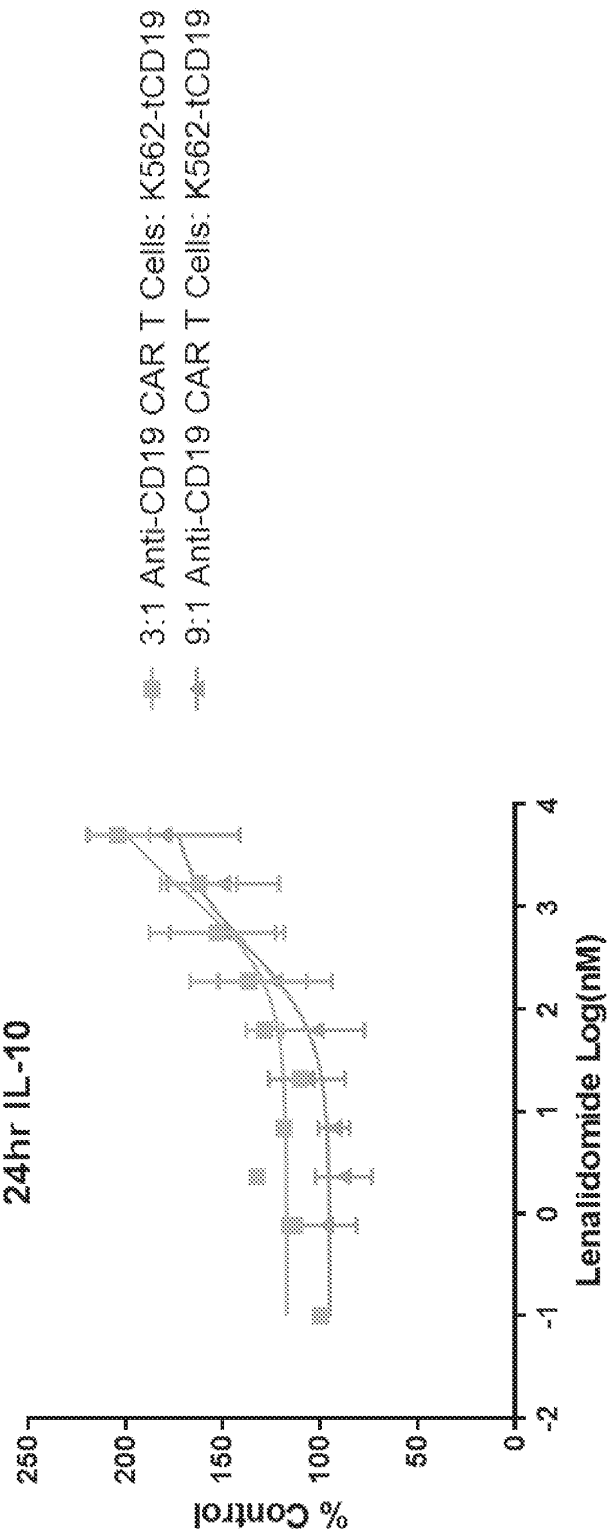
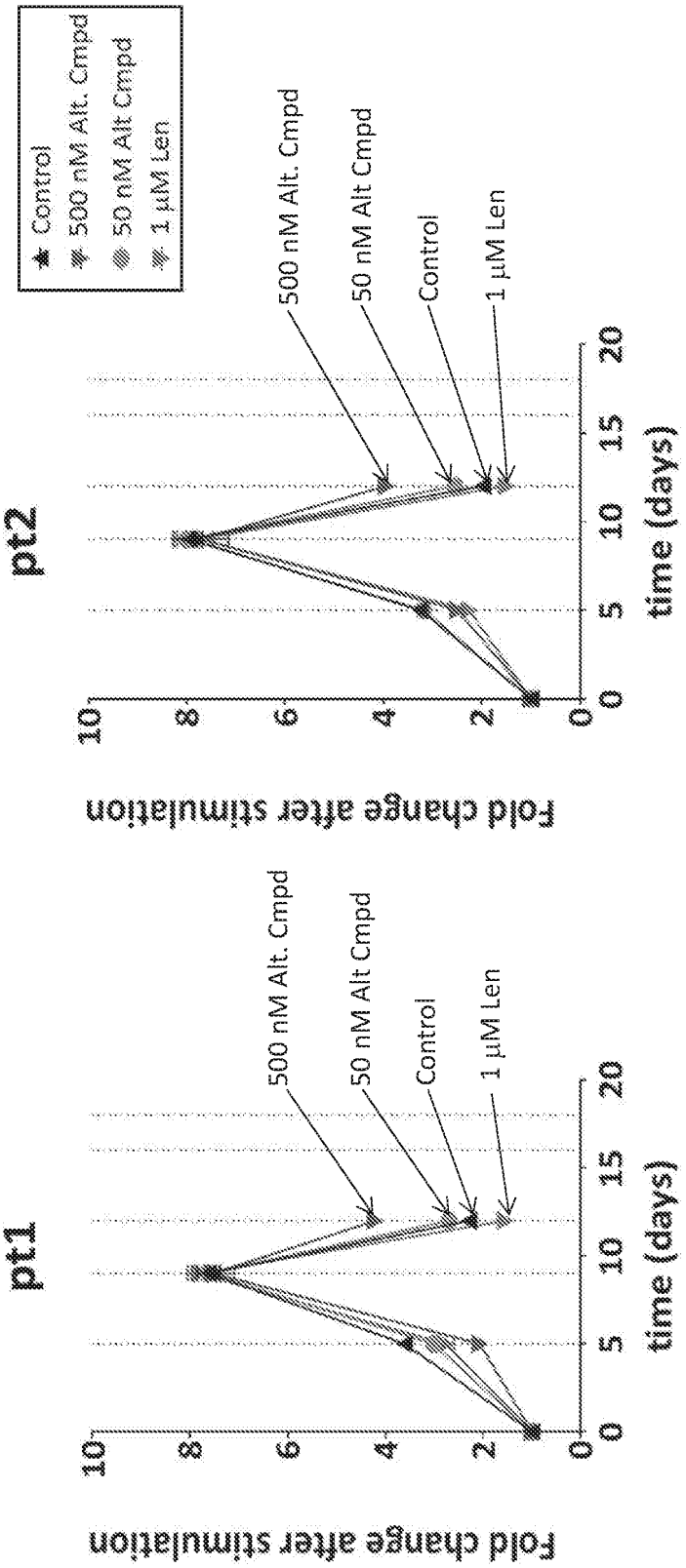
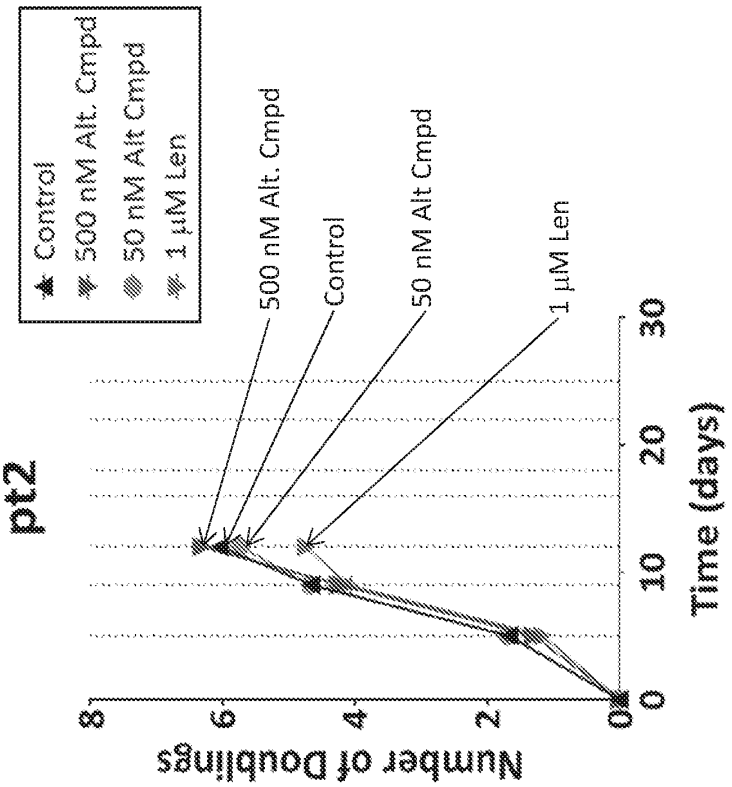

3:1 Anti-CD19 CAR T Cells: K562-tCD19
9:1 Anti-CD19 CAR T Cells: K562-tCD19
24hr IL-10
% Control
250
200
150
100
50
0
-2
-1
0
1
2
3
4
Lenalidomide Log(nM)

FIG. 17A


pt1
fold change after stimulation
time (days)
0
5
10
15
20
2
4
6
8
10
500 nM Alt. Cmpd
50 nM Alt Cmpd
Control
1 µM Len
pt2
fold change after stimulation
time (days)
Control
500 nM Alt. Cmpd
50 nM Alt Cmpd
1 µM Len


pt2
Control
500 nM Alt. Cmpd
50 nM Alt Cmpd
1 µM Len
Number of Doublings
Time (days)
0
2
4
6
8
0
10
20
30

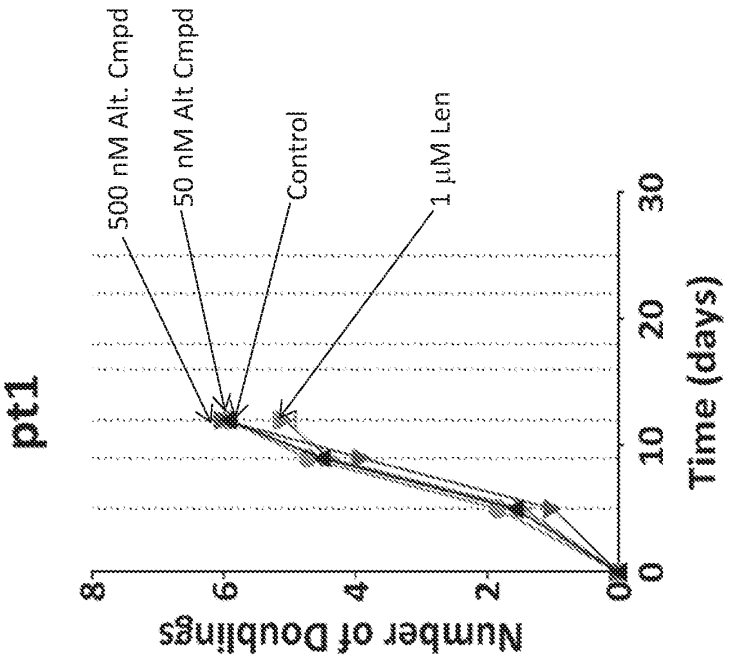
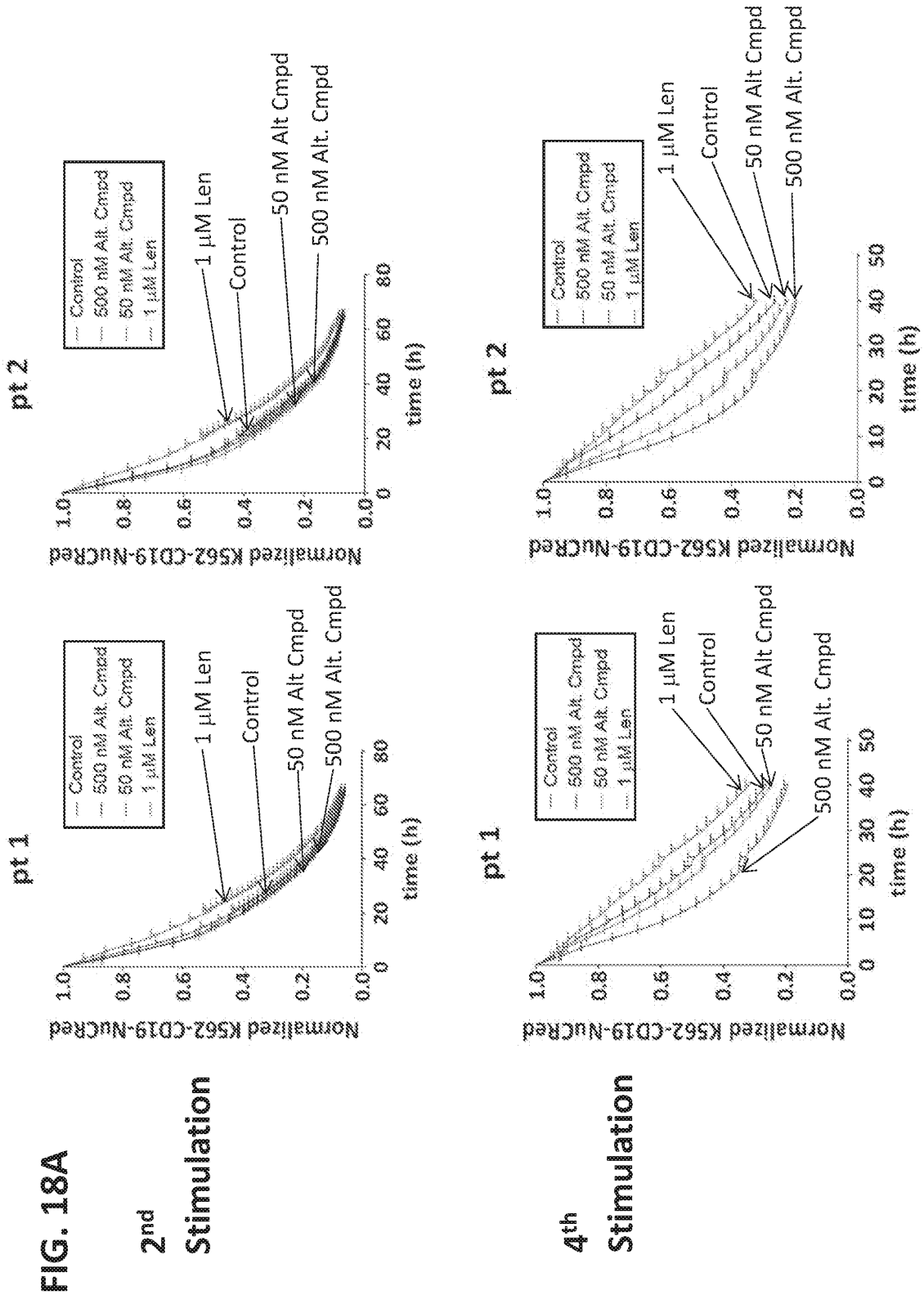
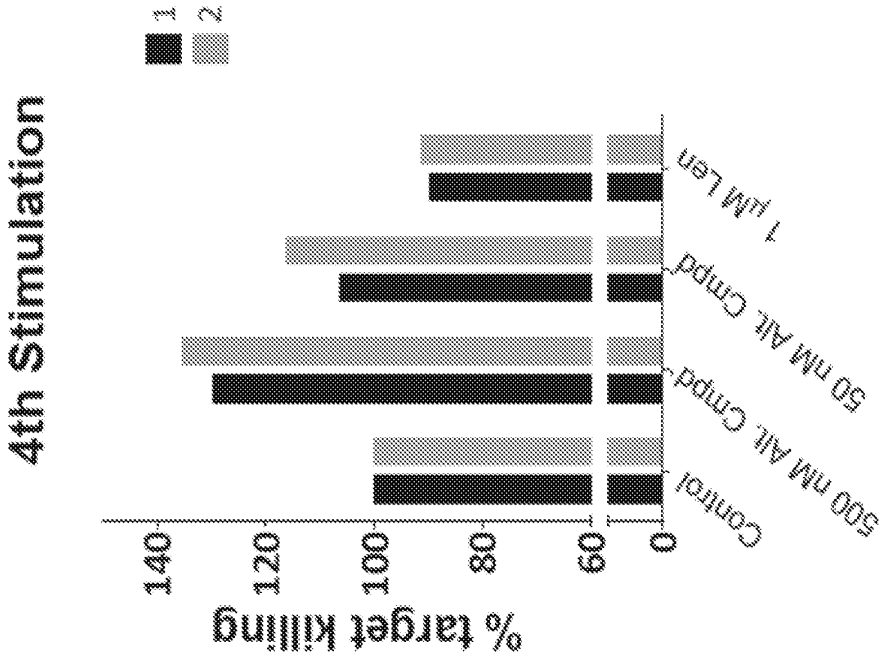

pt1
500 nM Alt. Cmpd
50 nM Alt Cmpd
Control
1 µM Len
Number of Doublings
Time (days)
0
2
4
6
8
0
10
20
30

FIG. 17B

FIG. 18A


2nd Stimulation
pt 1
pt 2
4th Stimulation
Normalized K562-CD19-NucRed
time (h)
Control
500 nM Alt. Cmpd
50 nM Alt. Cmpd
1 µM Len
1 µM Len
Control
50 nM Alt Cmpd
500 nM Alt. Cmpd


4th Stimulation
1
2
% target killing
140
120
100
80
60
0
Control
500 nM Ali_Cmpd
50 nM Ali_Cmpd
1 μM Len

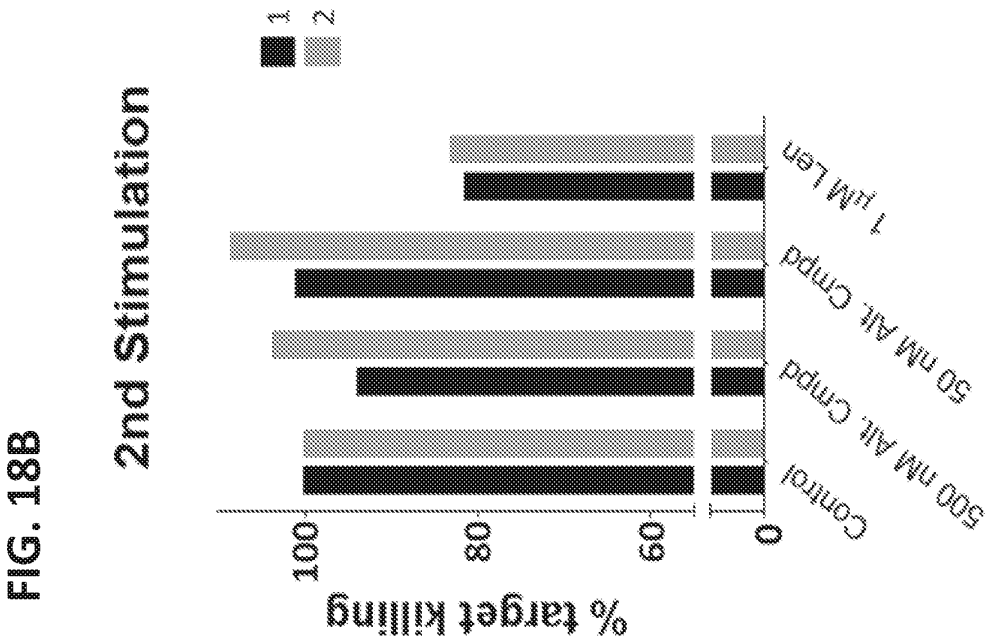

2nd Stimulation
1
2
% target killing
100
80
60
0
Control
500 nM Ali_Cmpd
50 nM Ali_Cmpd
1 μM Len

FIG. 18B

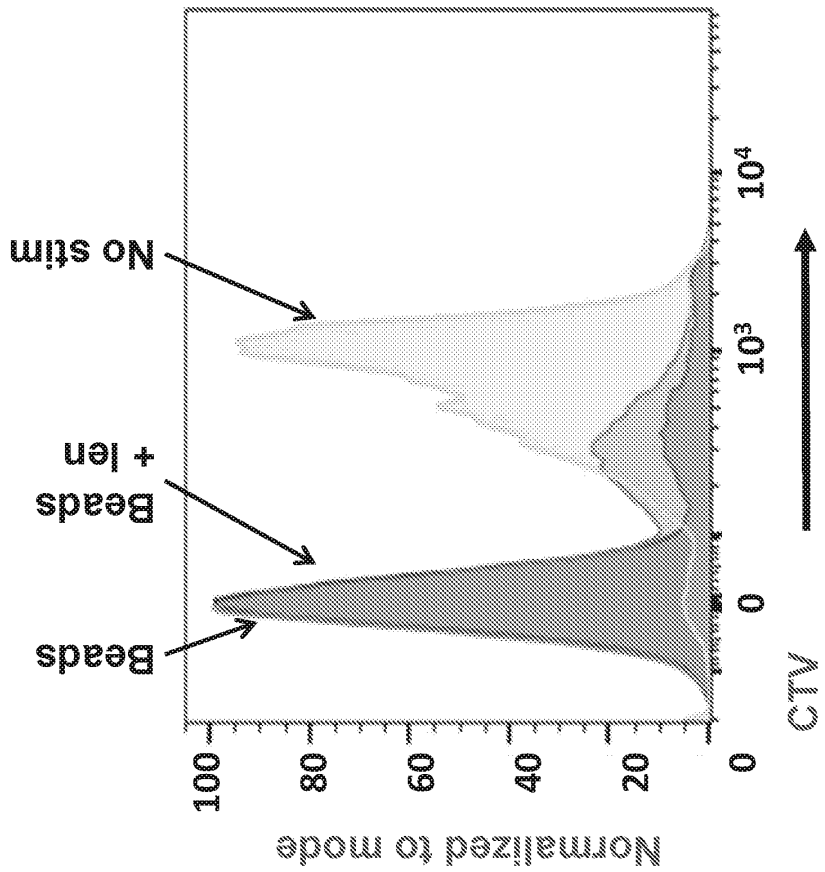
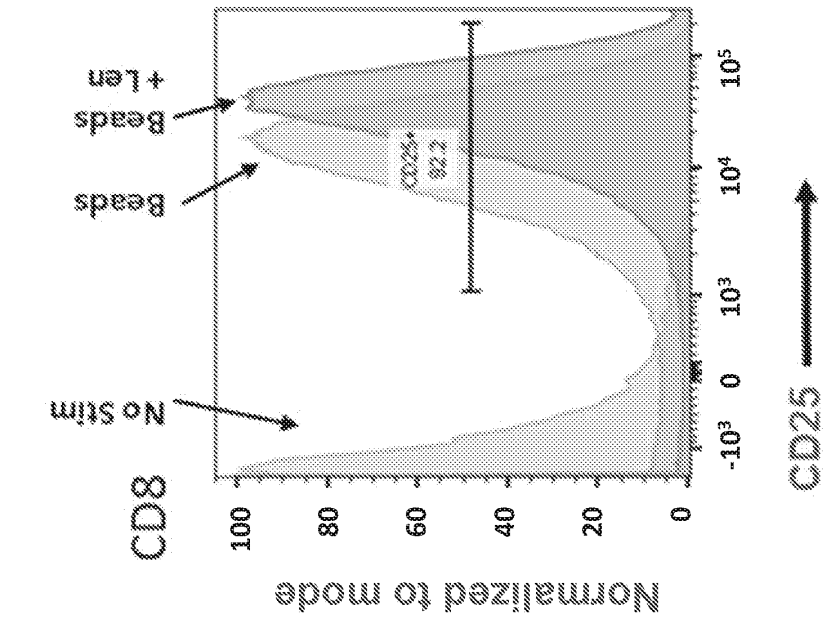

Normalized to mode
100
80
60
40
20
0
0
10^3
10^4
CTV
Beads
Beads + len
No stim

FIG. 19A


CD8
Normalized to mode
100
80
60
40
20
0
-10³
0
10³
10⁴
10⁵
CD25
No Stim
Beads
Beads +Len
CD25+ 92.2

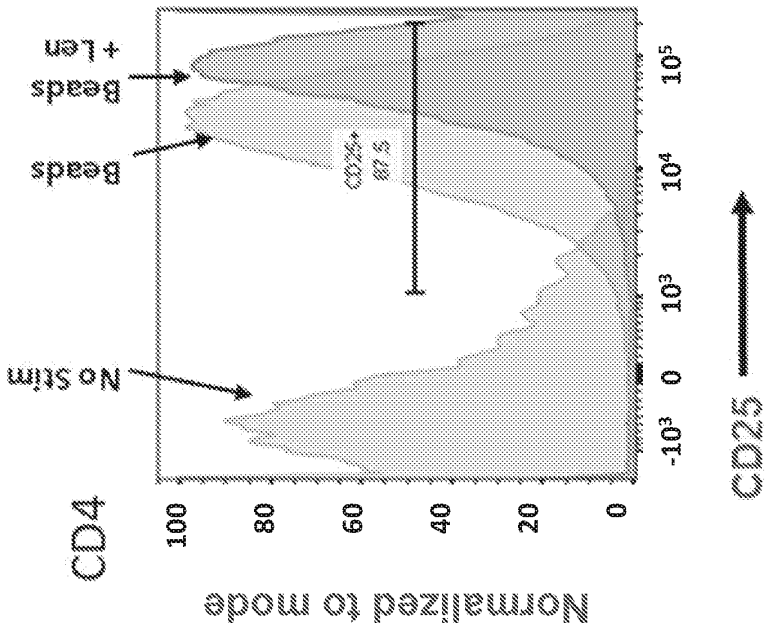

CD4
Normalized to mode
100
80
60
40
20
0
-10³
0
10³
10⁴
10⁵
CD25
No Stim
Beads
Beads +Len
CD25+ 87.5

FIG. 19B

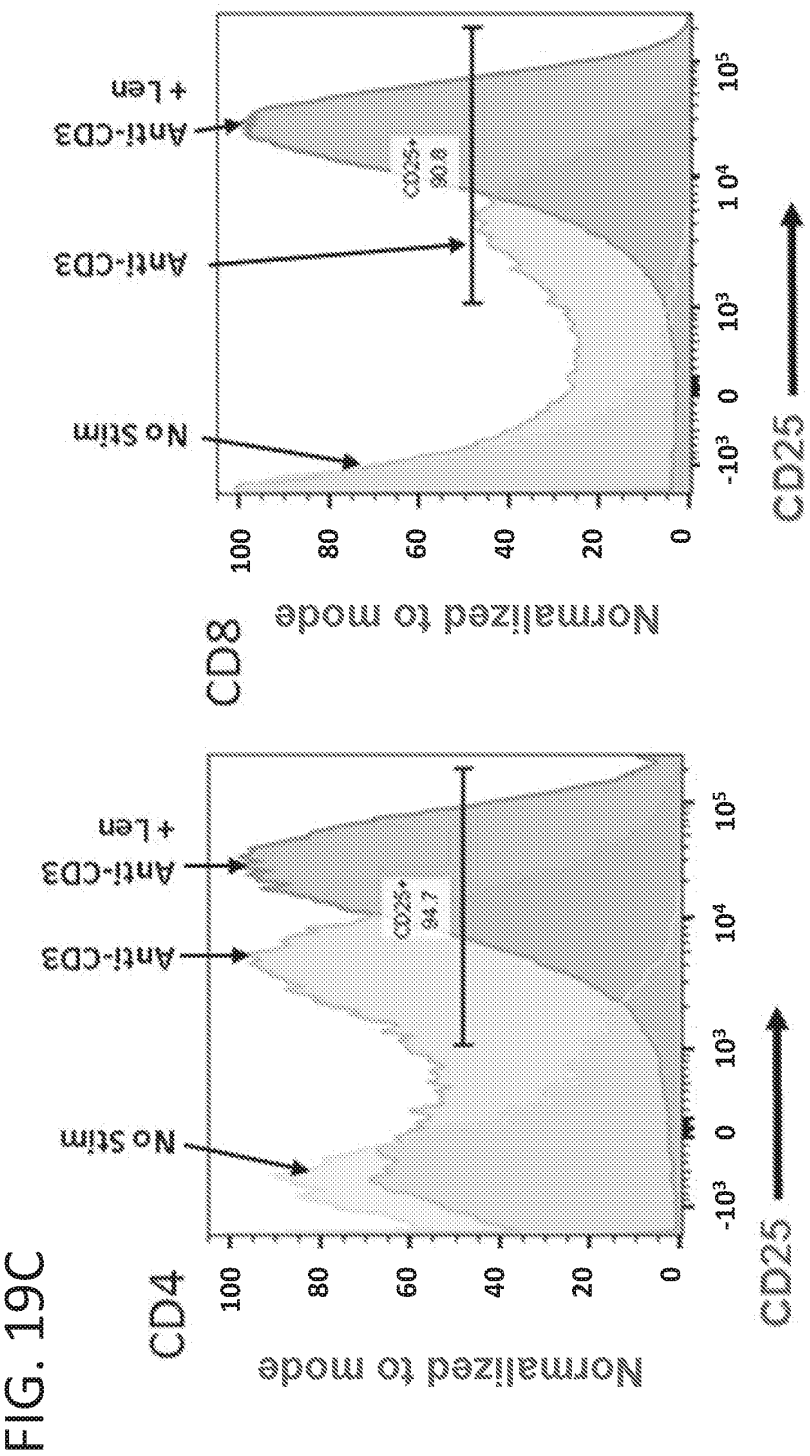

CD8
Normalized to mode
100
80
60
40
20
0
No Stim
Anti-CD3
Anti-CD3 + Len
CD25+ 90.8
-10³
0
10³
10⁴
10⁵
CD25
CD4
Normalized to mode
100
80
60
40
20
0
No Stim
Anti-CD3
Anti-CD3 + Len
CD25+ 94.7
-10³
0
10³
10⁴
10⁵
CD25

FIG. 19C

FIG. 20A

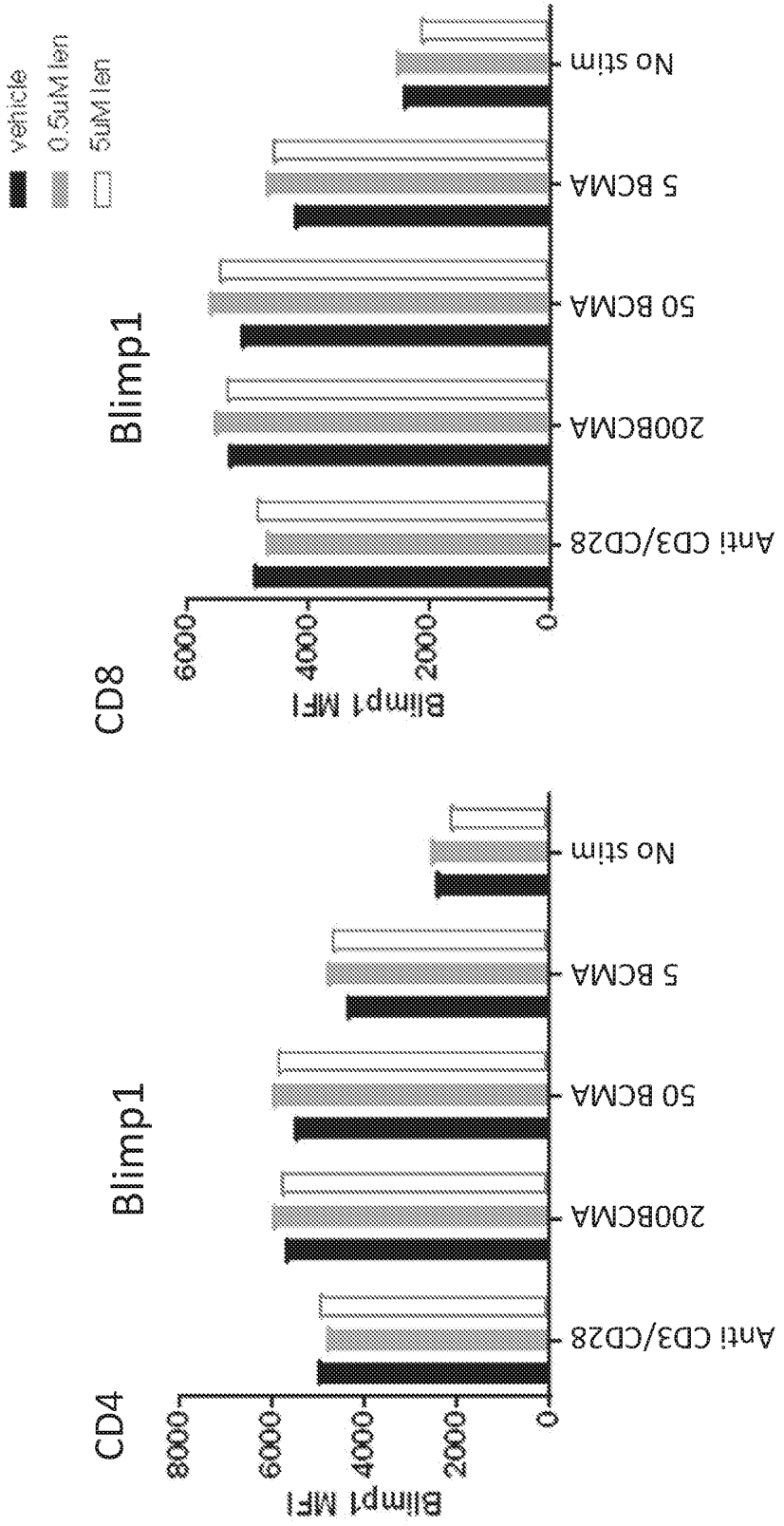

CD4
Blimp1
Blimp1 MFI
8000
6000
4000
2000
0
Anti CD3/CD28
200BCMA
50 BCMA
5 BCMA
No stim
CD8
Blimp1
Blimp1 MFI
6000
4000
2000
0
Anti CD3/CD28
200BCMA
50 BCMA
5 BCMA
No stim
vehicle
0.5uM len
5uM len

FIG. 20B

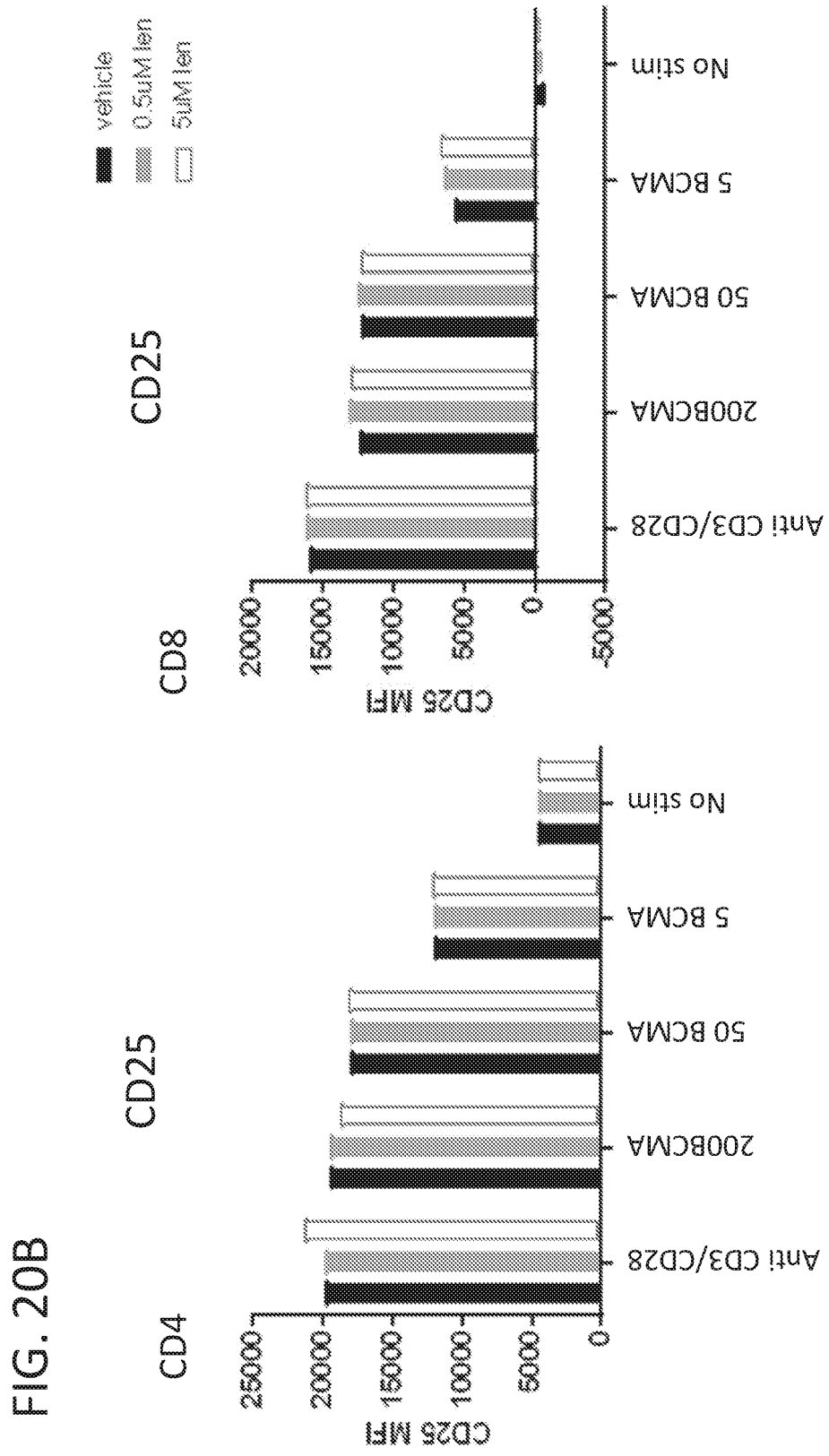
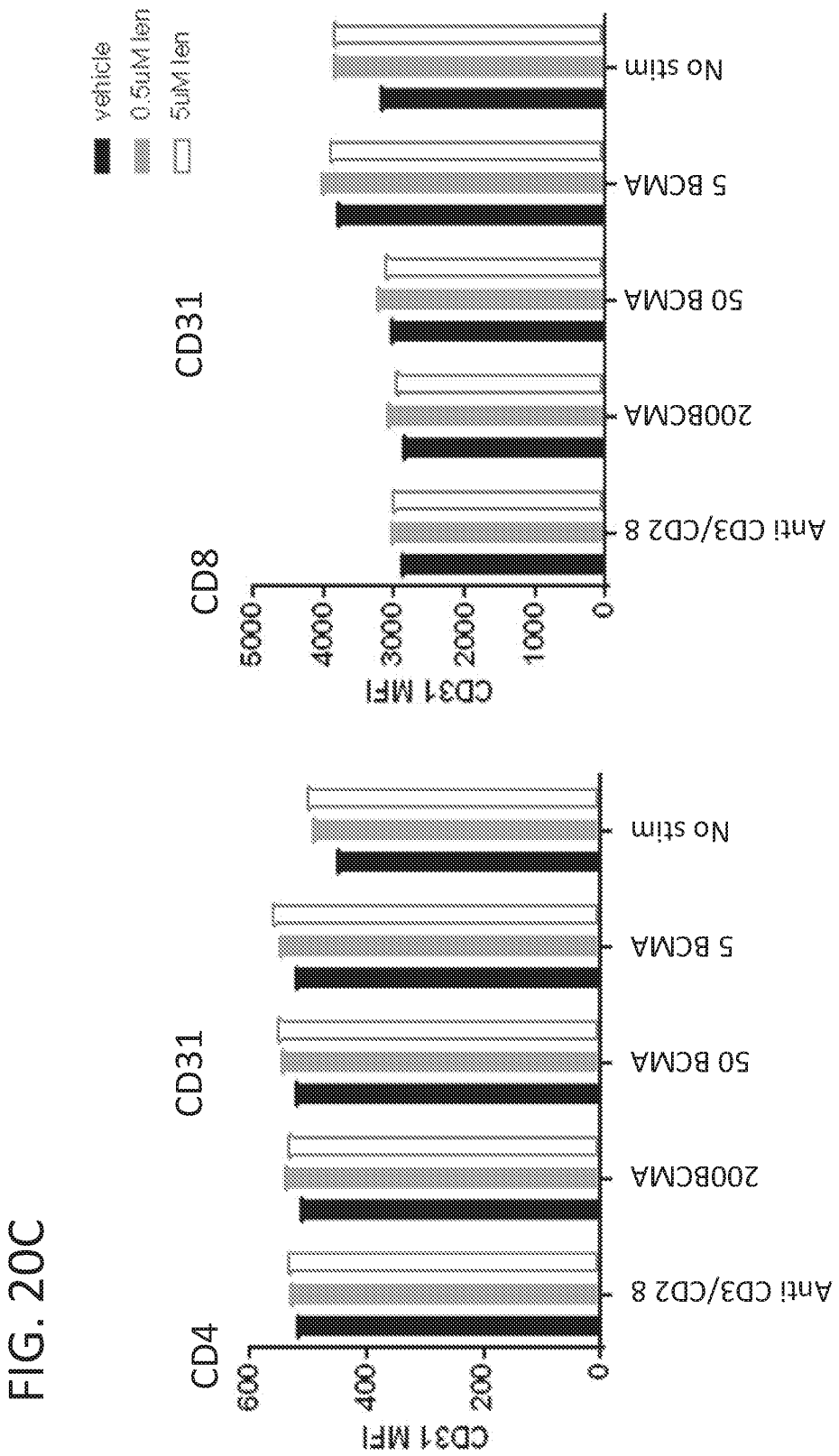

CD4
CD25
CD25 MFI
25000
20000
15000
10000
5000
0
Anti CD3/CD28
200BCMA
50 BCMA
5 BCMA
No stim
CD8
CD25
CD25 MFI
20000
15000
10000
5000
0
-5000
Anti CD3/CD28
200BCMA
50 BCMA
5 BCMA
No stim
vehicle
0.5uM Ien
5uM Ien

FIG. 20C


CD4
CD31
CD31 MFI
600
400
200
0
Anti CD3/CD2 8
200BCMA
50 BCMA
5 BCMA
No stim
CD8
CD31
CD31 MFI
5000
4000
3000
2000
1000
0
Anti CD3/CD2 8
200BCMA
50 BCMA
5 BCMA
No stim
vehicle
0.5uM Ien
5uM Ien

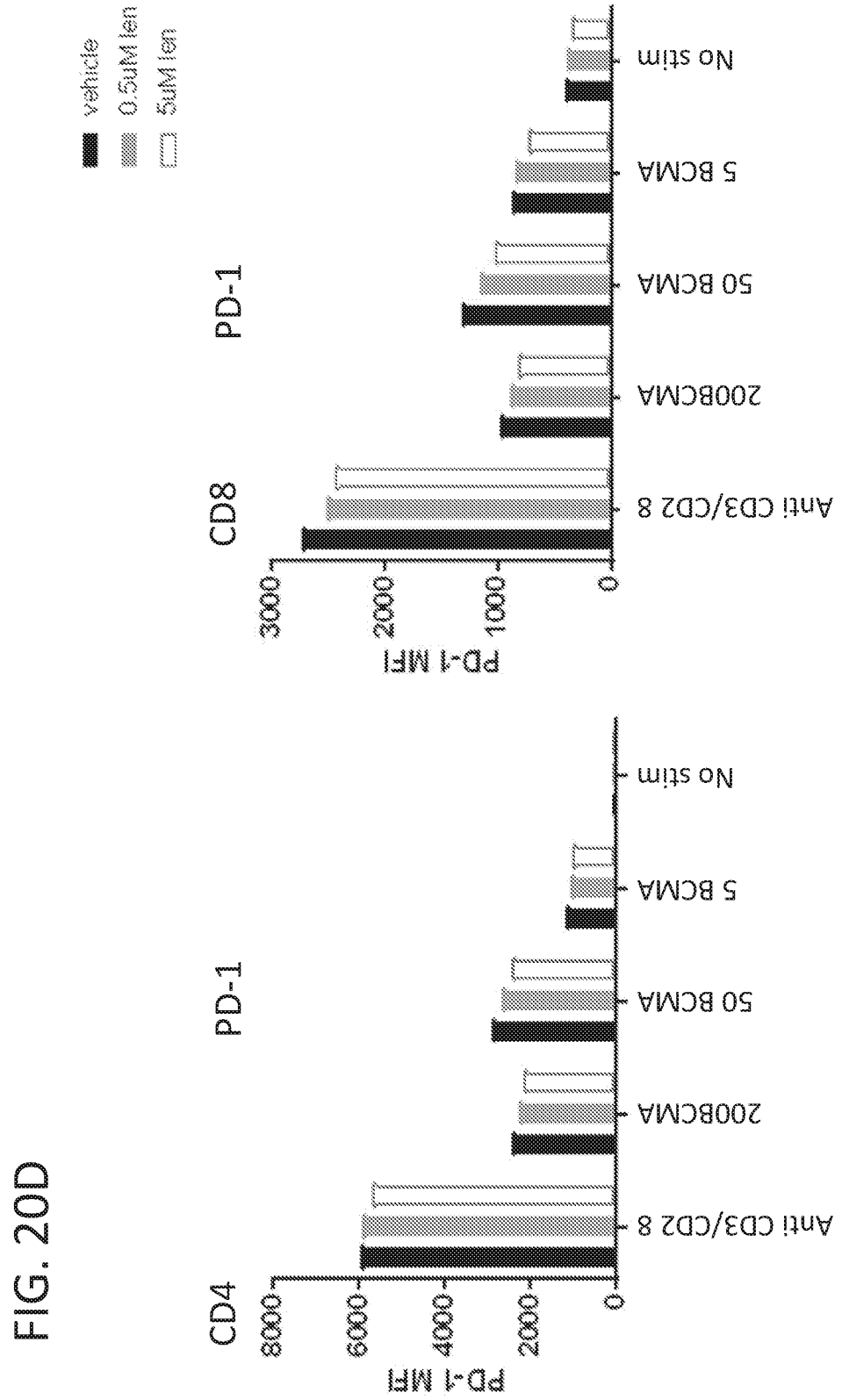

vehicle
0.5uM Ien
5uM Ien
CD8
PD-1
PD-1 MFI
3000
2000
1000
0
Anti CD3/CD2 8
200BCMA
50 BCMA
5 BCMA
No stim
CD4
PD-1
PD-1 MFI
8000
6000
4000
2000
0
Anti CD3/CD2 8
200BCMA
50 BCMA
5 BCMA
No stim

FIG. 20D

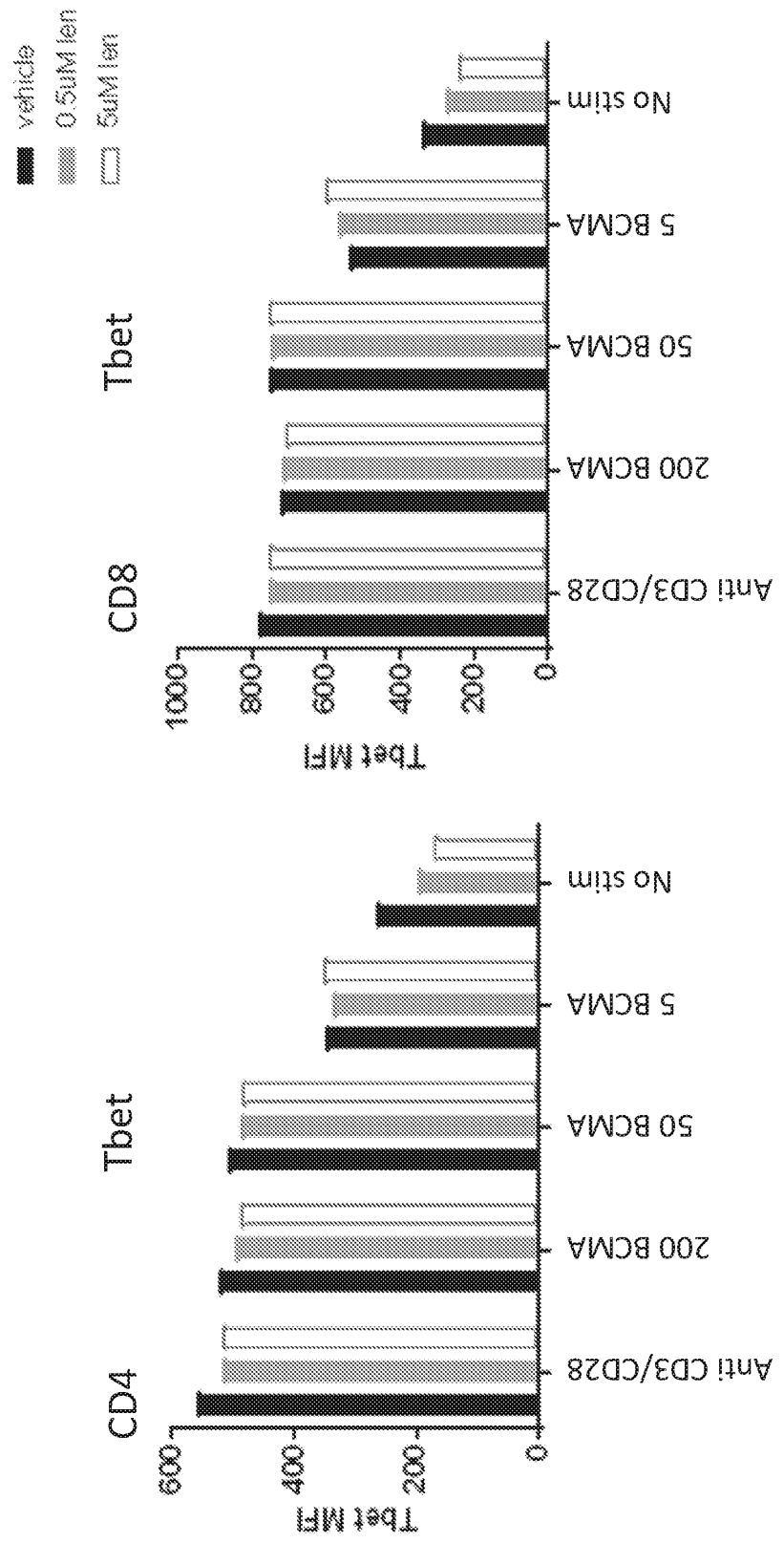

vehicle
0.5uM len
5uM len
CD8
Tbet
Tbet MFI
1000
800
600
400
200
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim
CD4
Tbet
Tbet MFI
600
400
200
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim

FIG. 20E

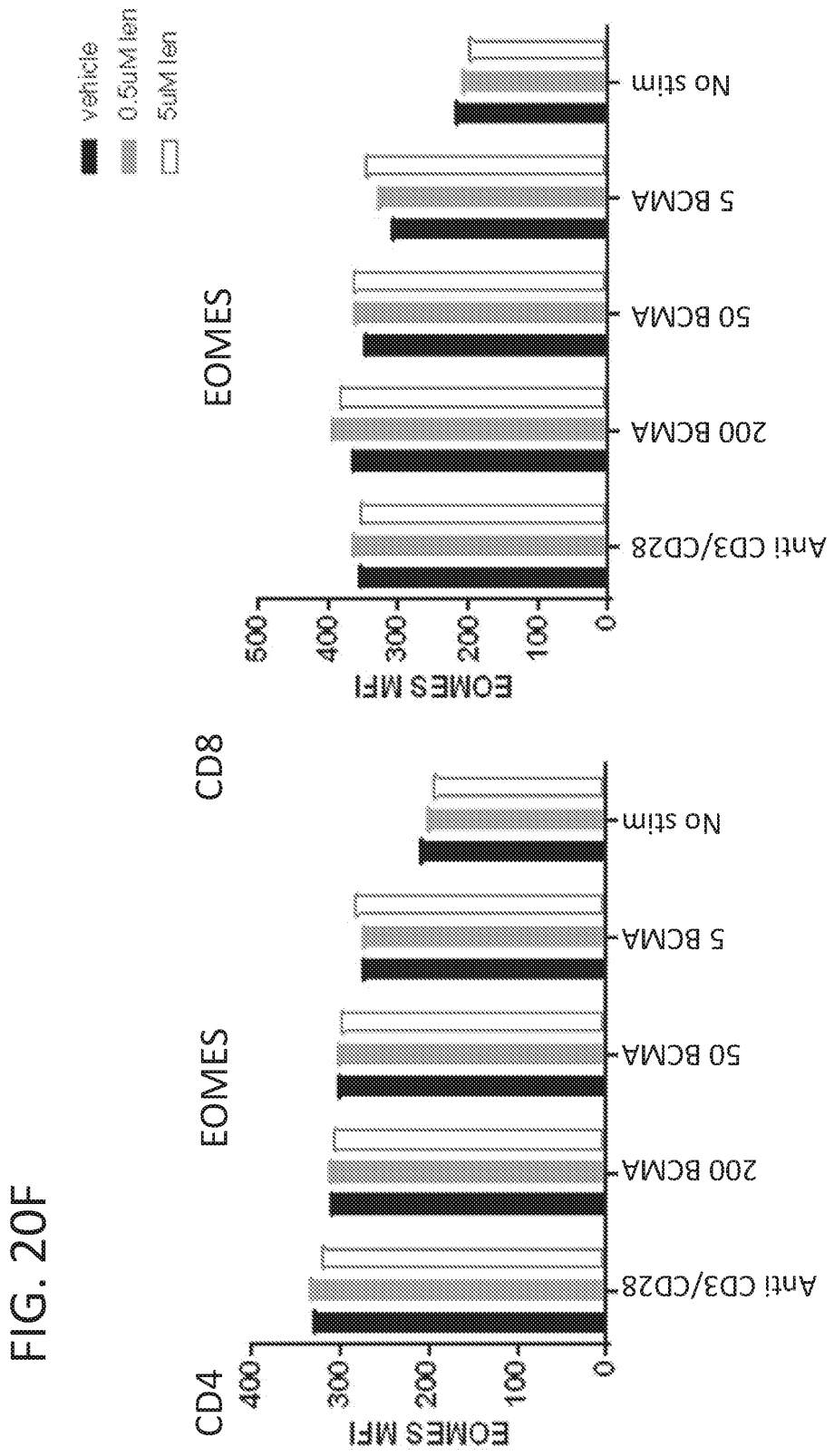
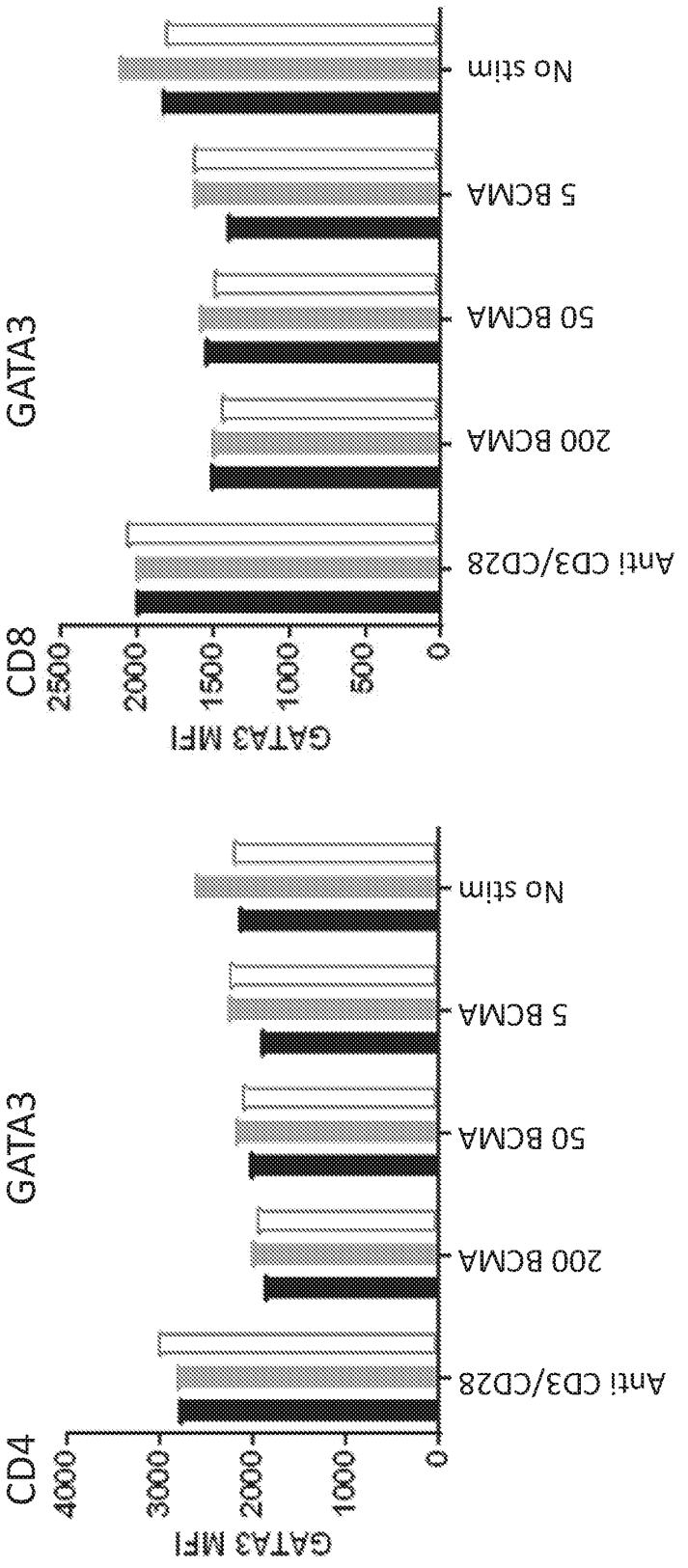
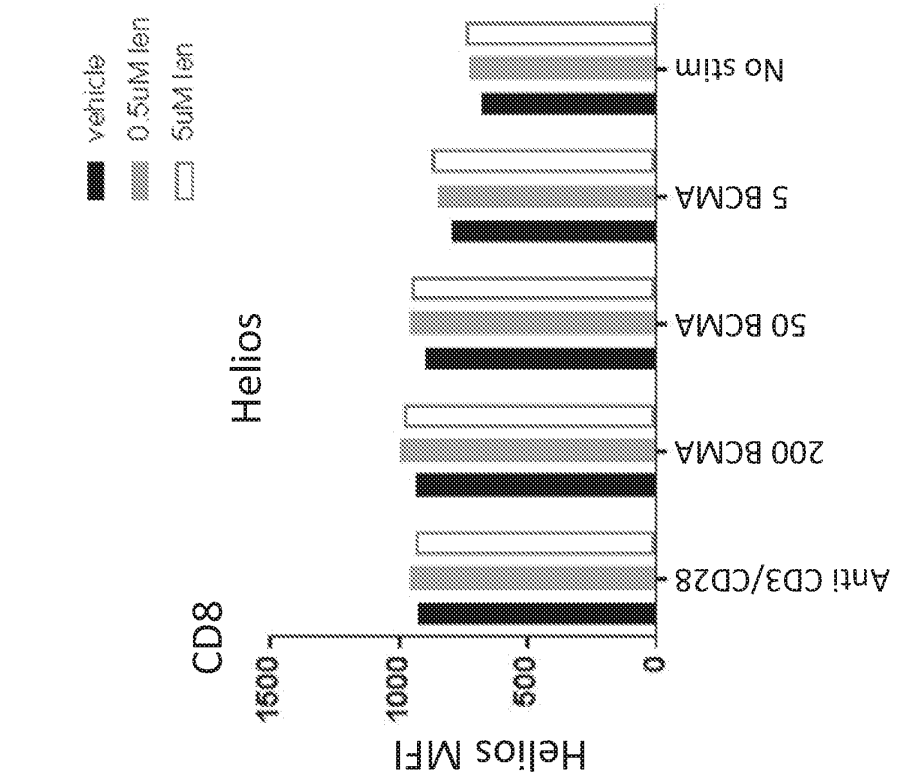

vehicle
0.5uM Ien
5uM Ien
CD8
EOMES
EOMES MFI
500
400
300
200
100
0
No stim
5 BCMA
50 BCMA
200 BCMA
Anti CD3/CD28
CD4
EOMES
EOMES MFI
400
300
200
100
0
No stim
5 BCMA
50 BCMA
200 BCMA
Anti CD3/CD28

FIG. 20F

FIG. 20G


vehicle
0.5uM Ien
5uM Ien
CD8
GATA3
GATA3 MFI
2500
2000
1500
1000
500
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim
CD4
GATA3
GATA3 MFI
4000
3000
2000
1000
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim


vehicle
0.5uM len
5uM len
CD8
Helios
Helios MFI
1500
1000
500
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim

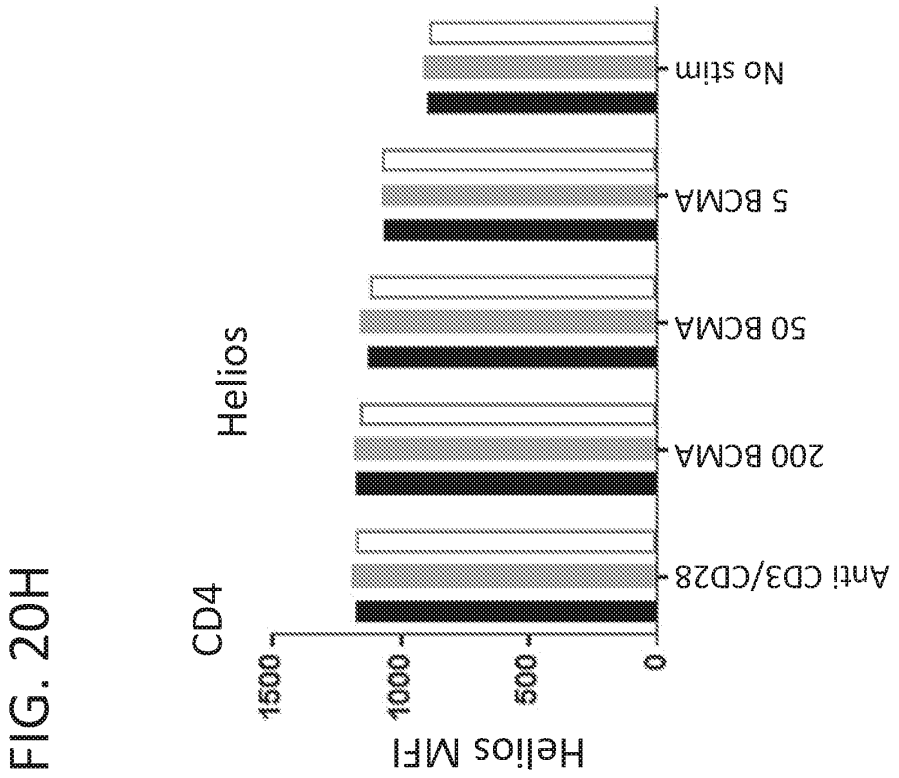

CD4
Helios
Helios MFI
1500
1000
500
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim

FIG. 20H

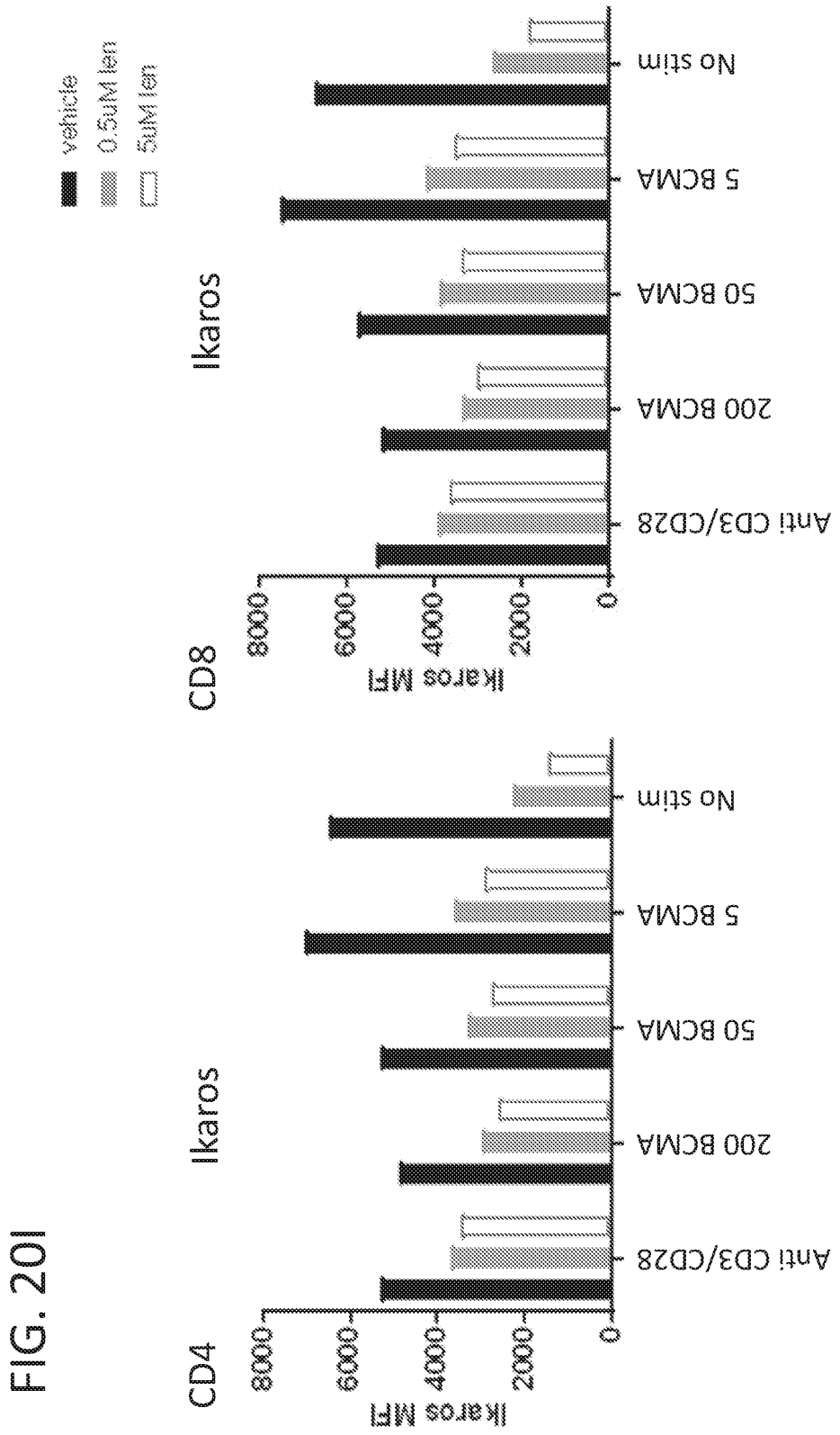

vehicle
0.5uM len
5uM len
CD8
Ikaros
Ikaros MFI
8000
6000
4000
2000
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim
CD4
Ikaros
Ikaros MFI
8000
6000
4000
2000
0
Anti CD3/CD28
200 BCMA
50 BCMA
5 BCMA
No stim

FIG. 20I

FIG. 21A

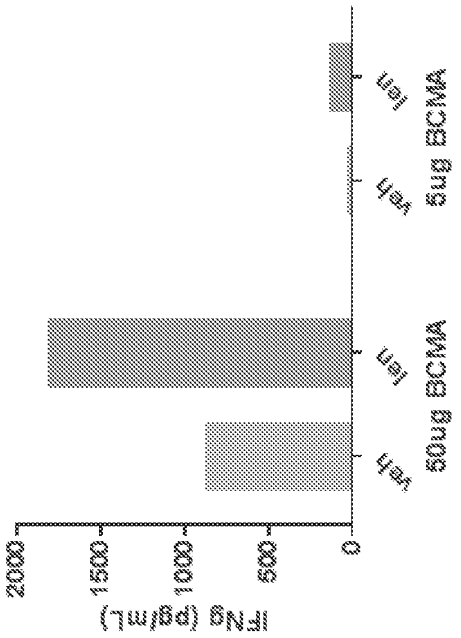
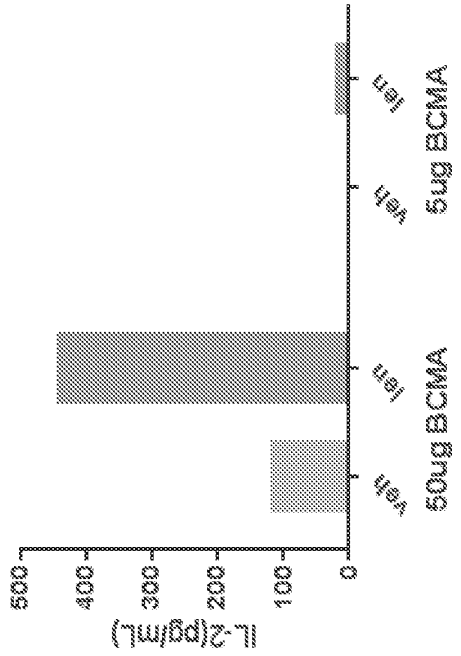


FIG. 21B



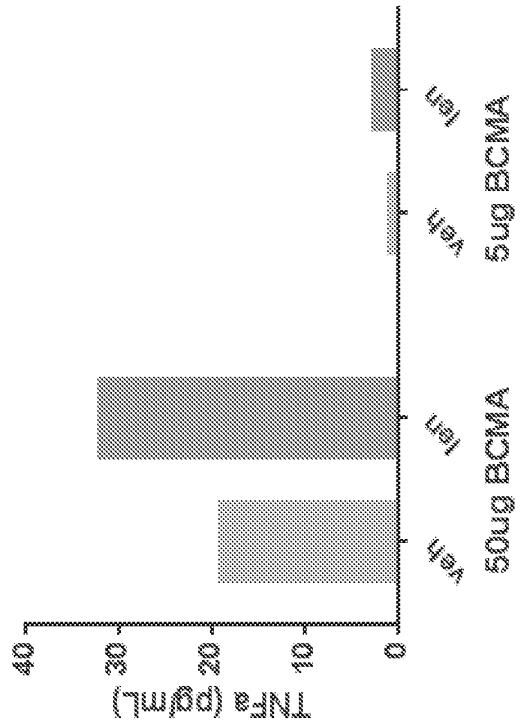
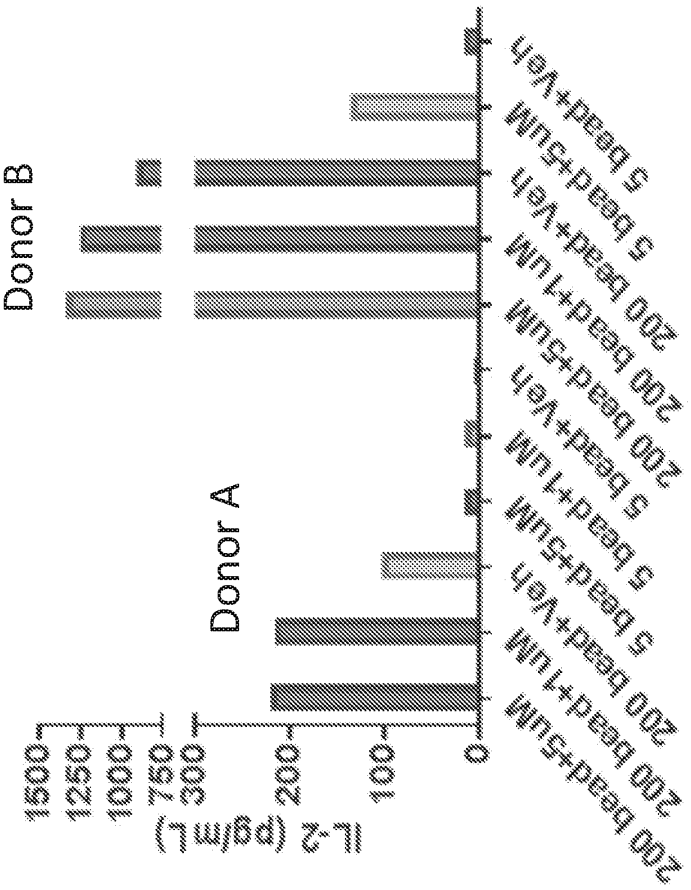

TNFa secretion
TNFa (pg/mL)
40
30
20
10
0
Ven
Ten
Ven
Ten
50ug BCMA
5ug BCMA

FIG. 21C

FIG. 21D


Donor B
Donor A
IL-2 (pg/mL)
1500
1250
1000
750
500
200
100
0
5 bead+Veh
5 bead+5uM
200 bead+1uM
200 bead+5uM
5 bead+Veh
5 bead+1uM
5 bead+5uM
200 bead+Veh
200 bead+1uM
200 bead+5uM

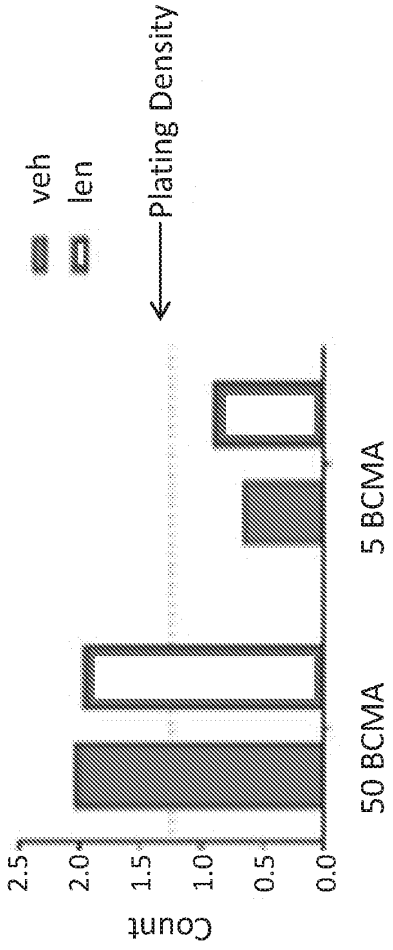


FIG. 21E

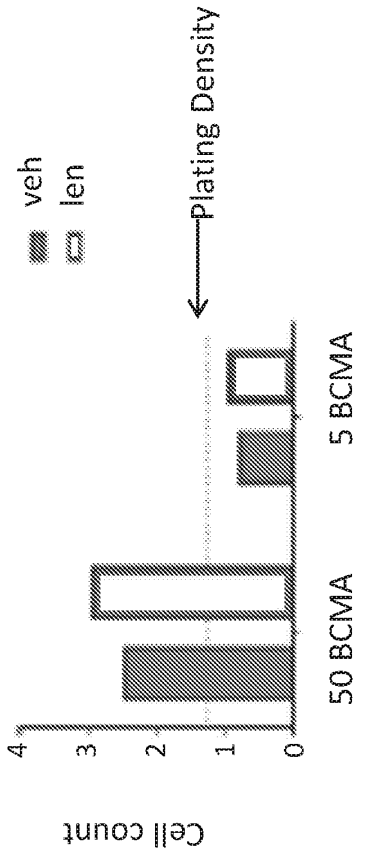
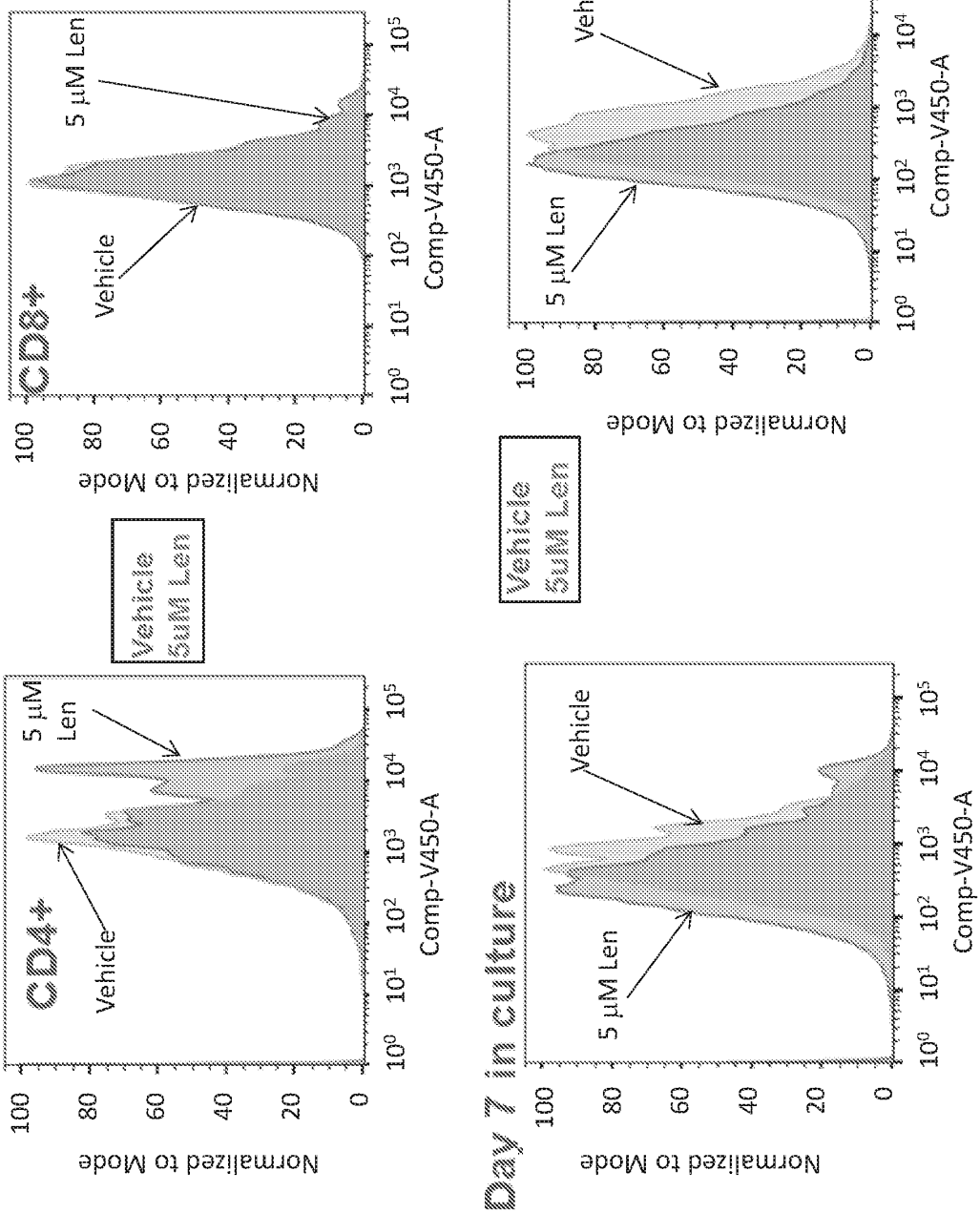


FIG. 21F

FIG. 21G


Day 4 in culture Cell trace violet dye dilution assay
CD4+
Vehicle
5 µM Len
CD8+
Vehicle
5 µM Len
Vehicle Sum Len
Day 7 in culture
Vehicle
5 µM Len
Vehicle
5 µM Len
Vehicle Sum Len
Normalized to Mode
Comp-V450-A

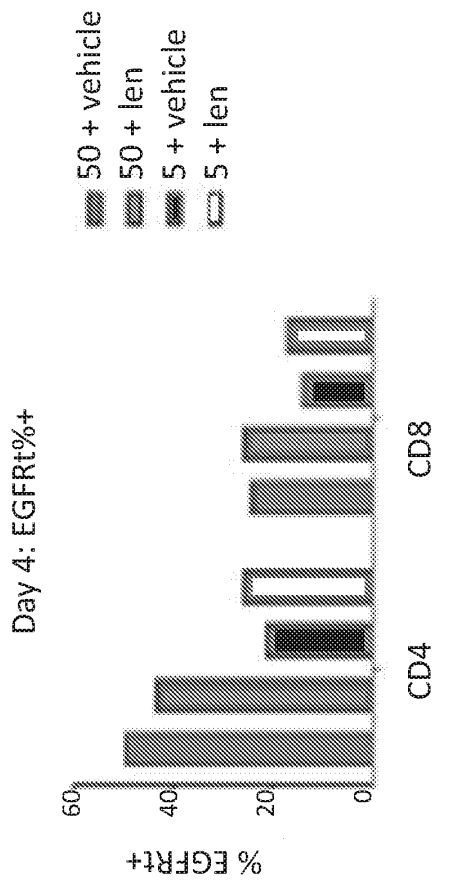


FIG. 21H

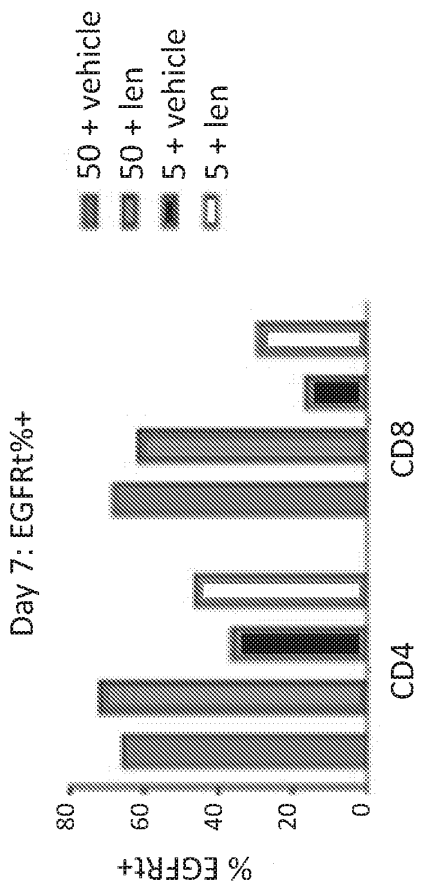


FIG. 21I

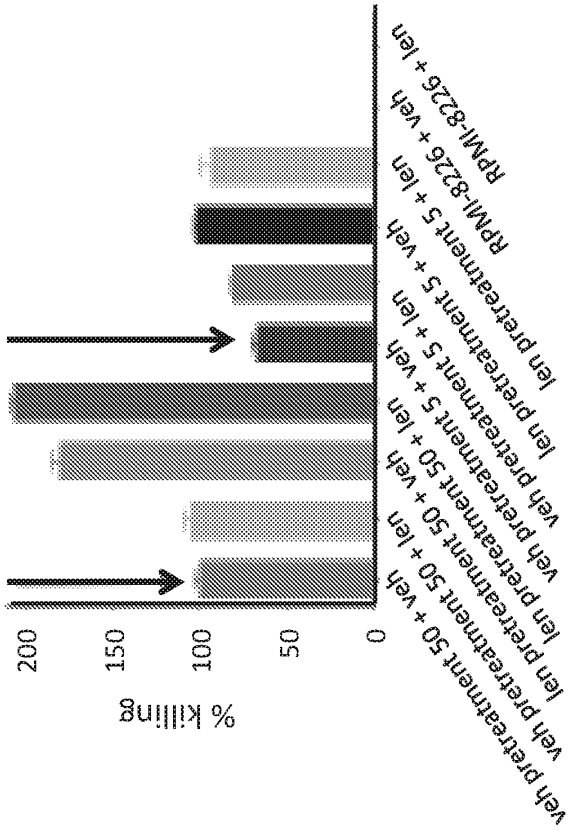

% killing
200
150
100
50
0
Veh pretreatment 50 + veh
Veh pretreatment 50 + len
len pretreatment 50 + veh
len pretreatment 50 + len
Veh pretreatment 5 + veh
Veh pretreatment 5 + len
len pretreatment 5 + veh
len pretreatment 5 + len
RPMI-8226 + veh
RPMI-8226 + len

FIG. 21J

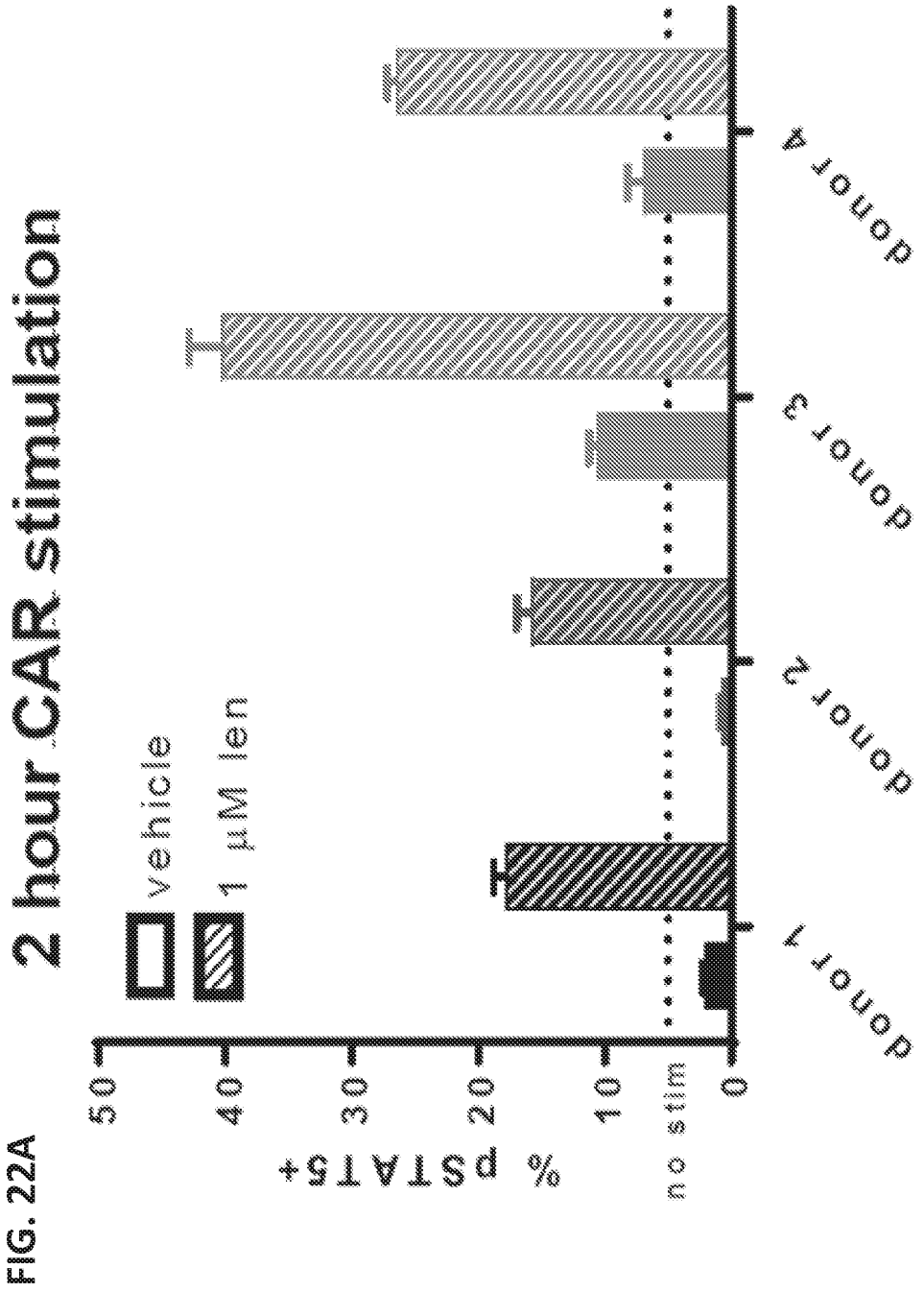

2 hour CAR stimulation
vehicle
1 μM len
% pSTAT5+
50
40
30
20
10
0
no stim
donor 1
donor 2
donor 3
donor 4

FIG. 22A

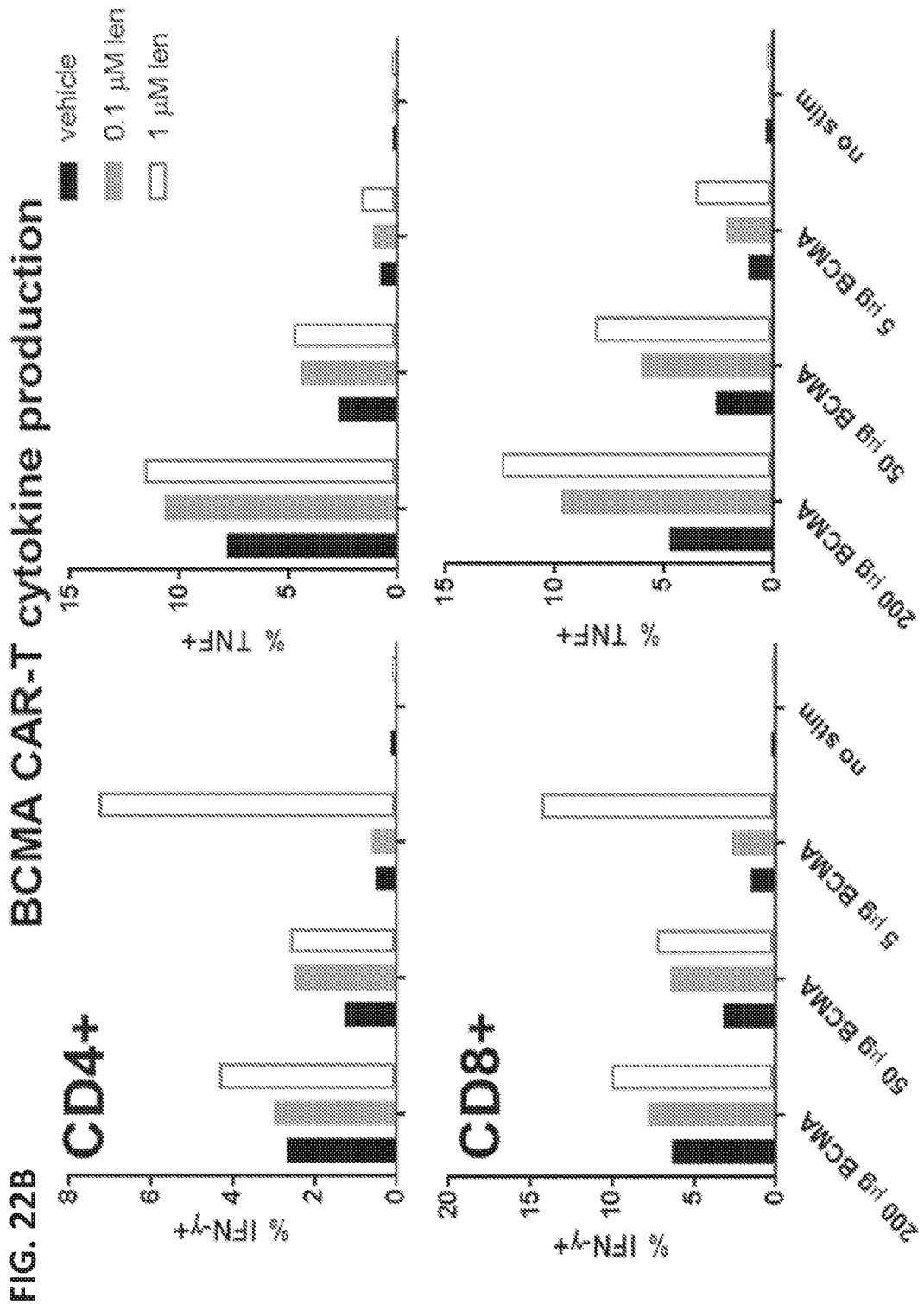

BCMA CAR-T cytokine production
vehicle
0.1 µM len
1 µM len
CD4+
CD8+
% IFN-γ+
% TNF+
0
2
4
6
8
0
5
10
15
20
0
5
10
15
no stim
5 µg BCMA
50 µg BCMA
200 µg BCMA

FIG. 22B

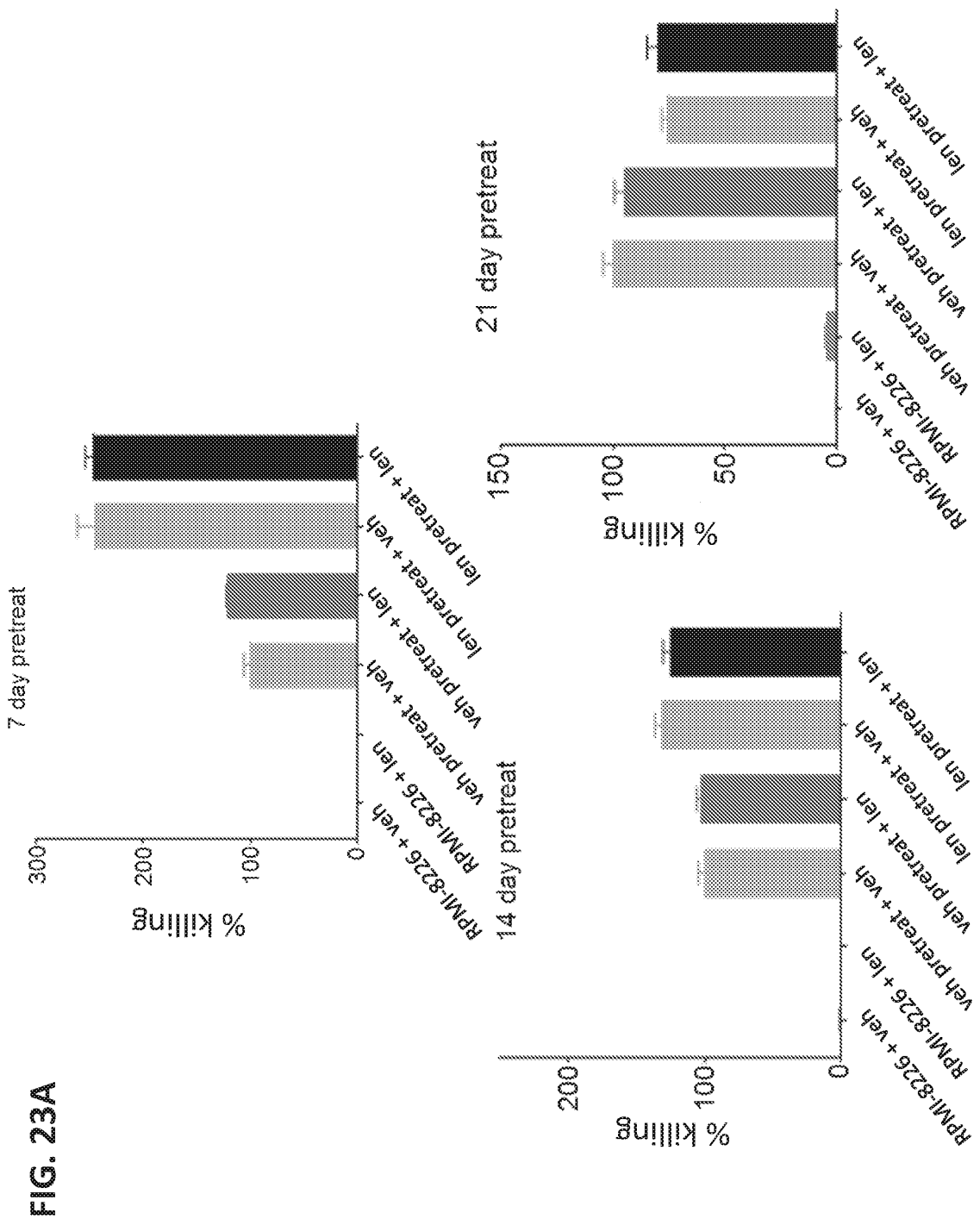

7 day pretreat
% killing
300
200
100
0
RPMI-8226 + veh
RPMI-8226 + len
veh pretreat + veh
veh pretreat + len
len pretreat + veh
len pretreat + len
14 day pretreat
% killing
200
100
0
21 day pretreat
% killing
150
100
50
0

FIG. 23A

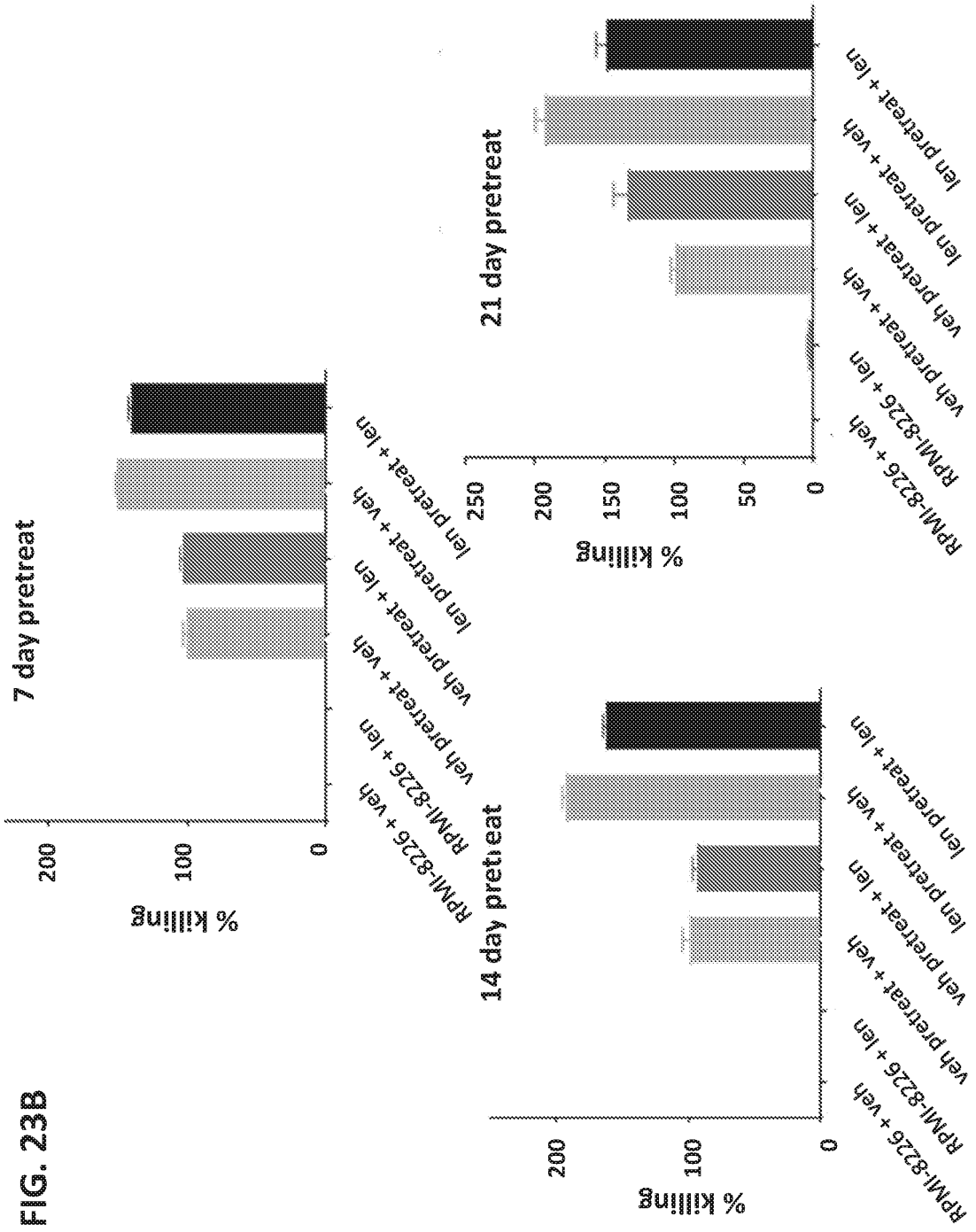

7 day pretreat
% killing
200
100
0
RPMI-8226 + veh
veh pretreat + len
veh pretreat + veh
len pretreat + len
len pretreat + veh
14 day pretreat
% killing
200
100
0
RPMI-8226 + veh
RPMI-8226 + len
veh pretreat + veh
veh pretreat + len
len pretreat + veh
len pretreat + len
21 day pretreat
% killing
250
200
150
100
50
0
RPMI-8226 + veh
RPMI-8226 + len
veh pretreat + veh
veh pretreat + len
len pretreat + veh
len pretreat + len

FIG. 23B

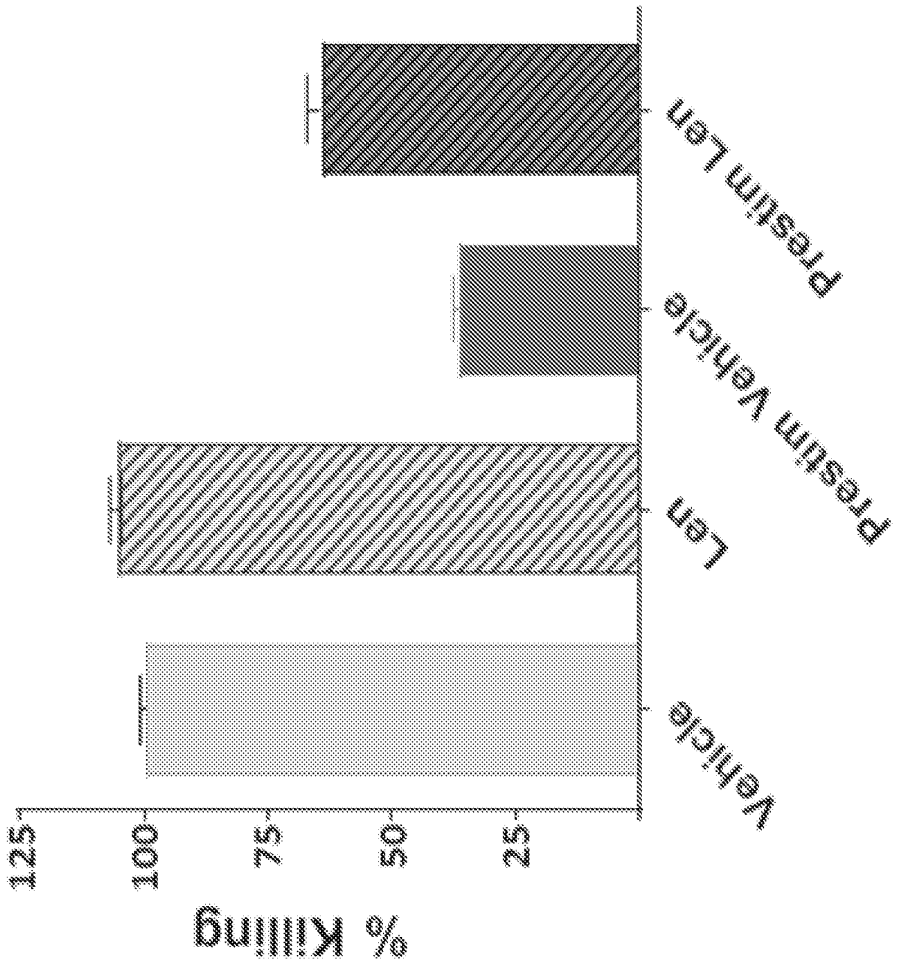

% Killing
125
100
75
50
25
Vehicle
Len
Presto Vehicle
Presto Len

FIG. 24A

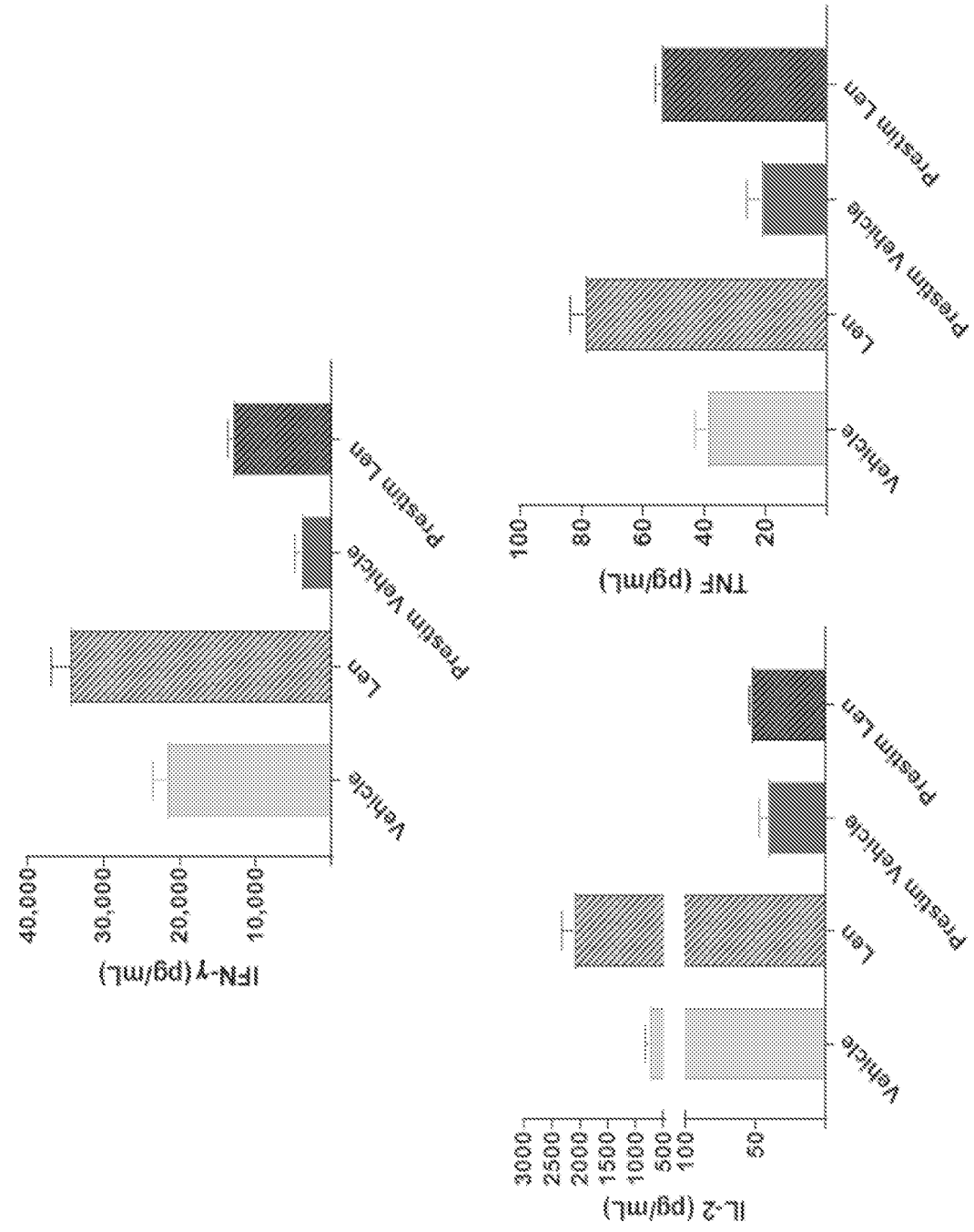

IFN-γ (pg/mL)
40,000
30,000
20,000
10,000
Vehicle
Len
Presun Vehicle
Presun Len
TNF (pg/mL)
100
80
60
40
20
Vehicle
Len
Presun Vehicle
Presun Len
IL-2 (pg/mL)
3000
2500
2000
1500
1000
500
100
50
Vehicle
Len
Presun Vehicle
Presun Len

FIG. 24B


Percent Vehicle
200
150
100
50
Healthy 1
Healthy 2
Healthy 3
Viability
Count
166
120
113
122
103
80

FIG. 24C

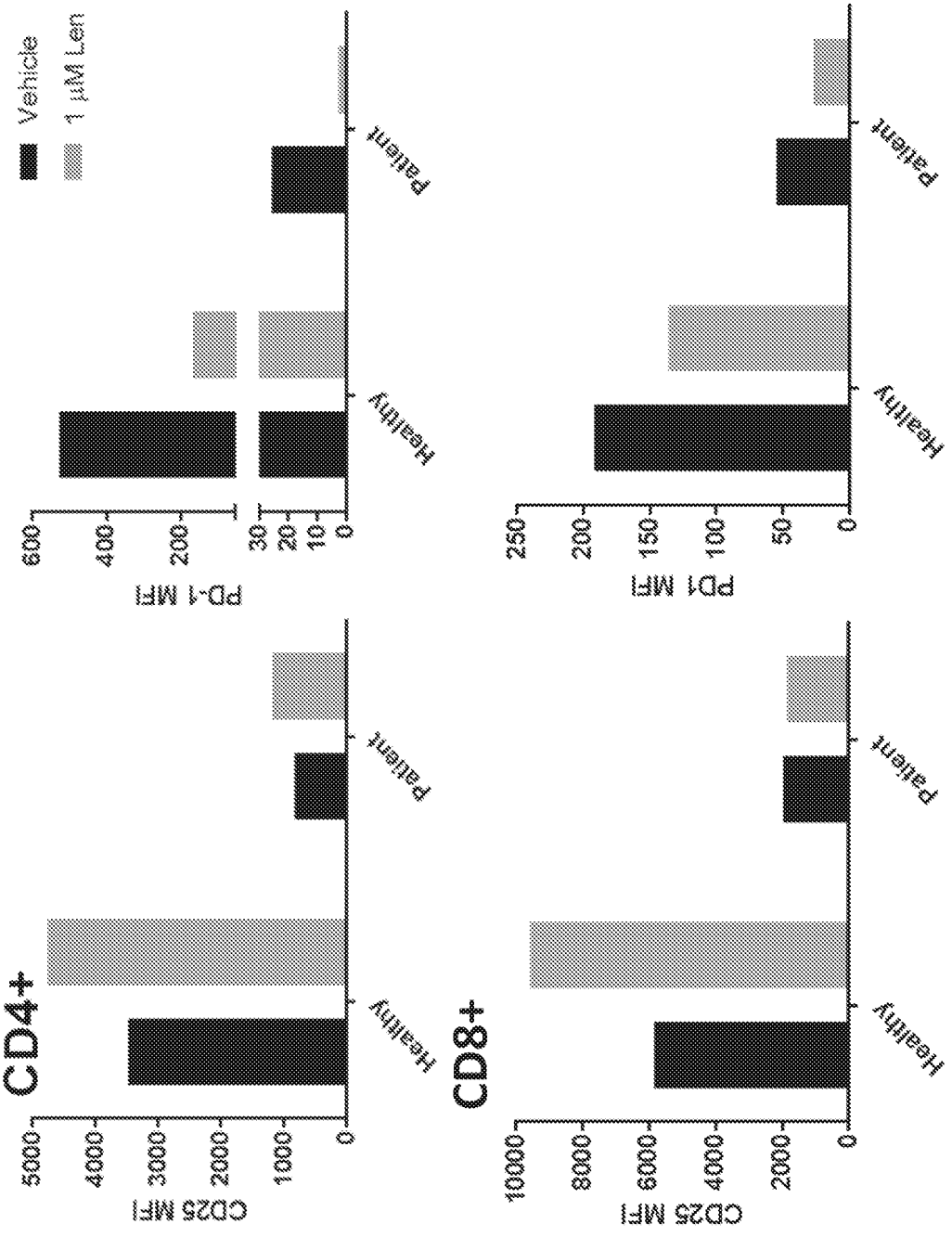
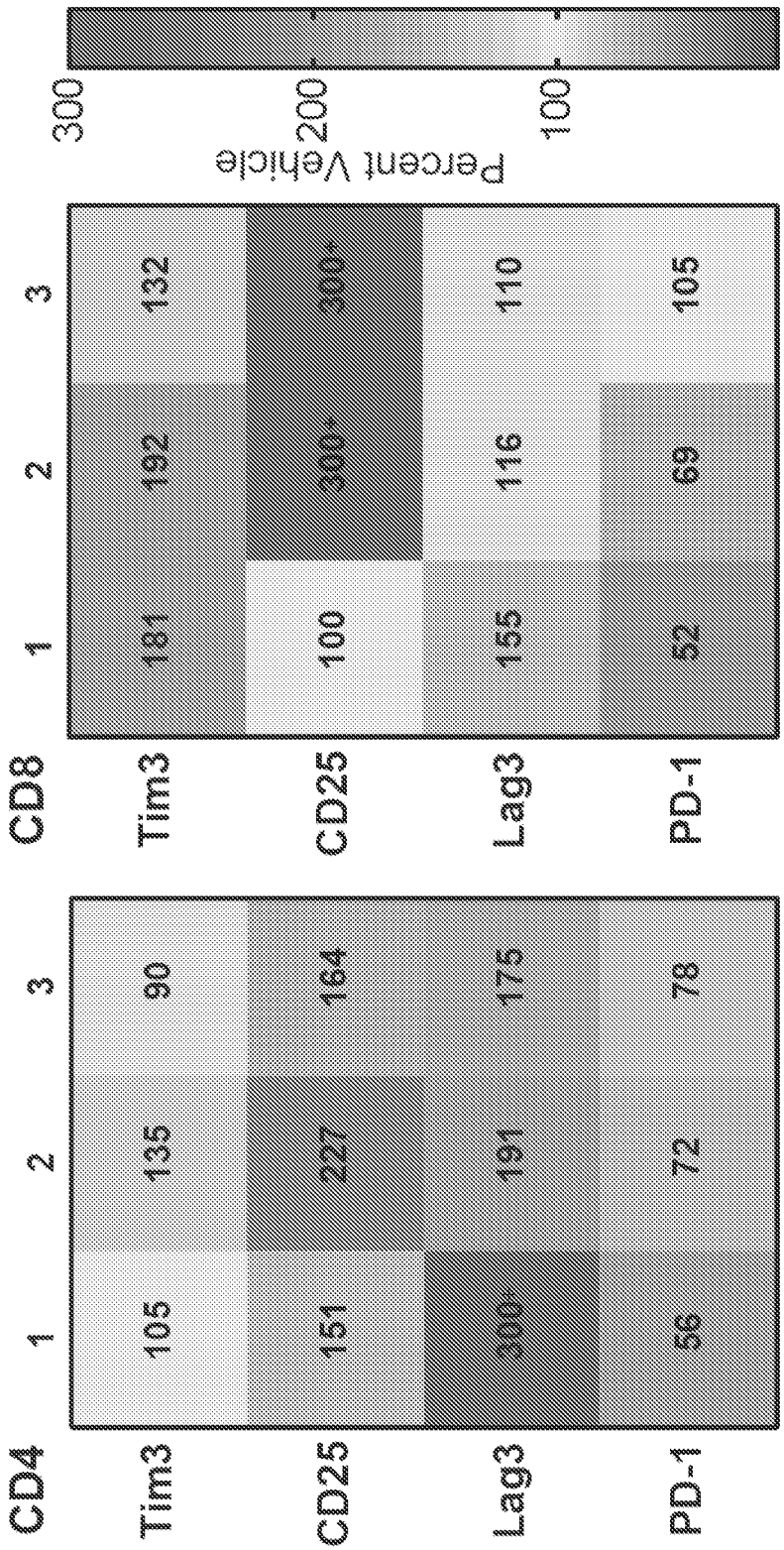

Vehicle
1 μM Len
CD4+
CD8+
CD25 MFI
PD-1 MFI
PD1 MFI
Healthy
Patient
0
1000
2000
3000
4000
5000
10
20
30
200
400
600
50
100
150
200
250
4000
6000
8000
10000

FIG. 24D

FIG. 24E


CD4
1
2
3
Tim3
105
135
90
CD25
151
227
164
Lag3
300+
191
175
PD-1
56
72
78
CD8
1
2
3
Tim3
181
192
132
CD25
100
300+
300+
Lag3
155
116
110
PD-1
52
69
105
Percent Vehicle
300
200
100

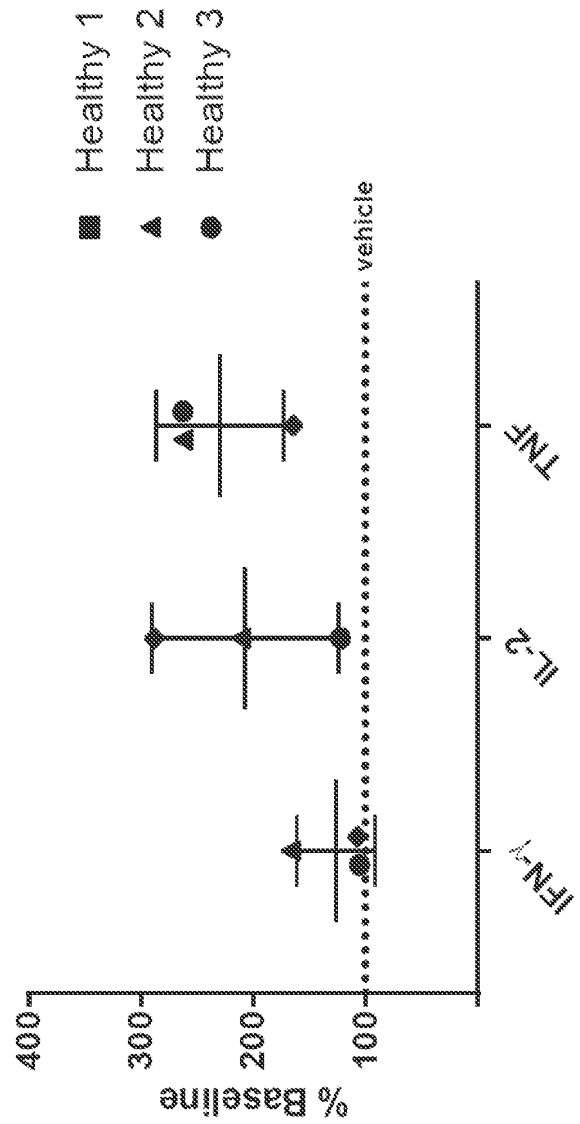

24-hour secreted cytokines
Healthy 1
Healthy 2
Healthy 3
vehicle
% Baseline
400
300
200
100
IFNγ
IL-2
TNF

FIG. 25A

FIG. 25B

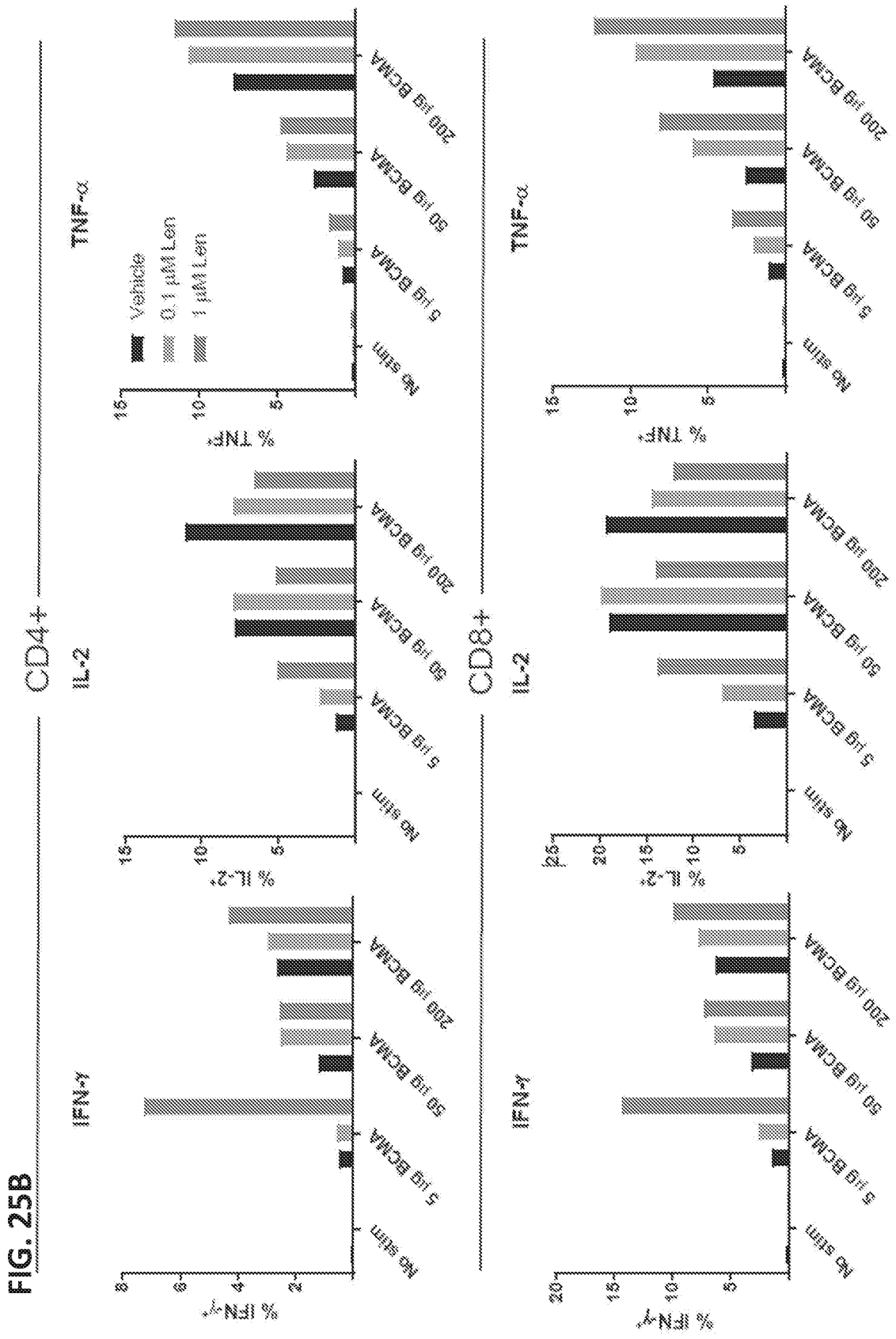

CD4+
CD8+
TNF-α
IL-2
IFN-γ
% TNF+
% IL-2+
% IFN-γ+
Vehicle
0.1 μM Len
1 μM Len
No stim
5 μg BCMA
50 μg BCMA
200 μg BCMA

FIG. 25C

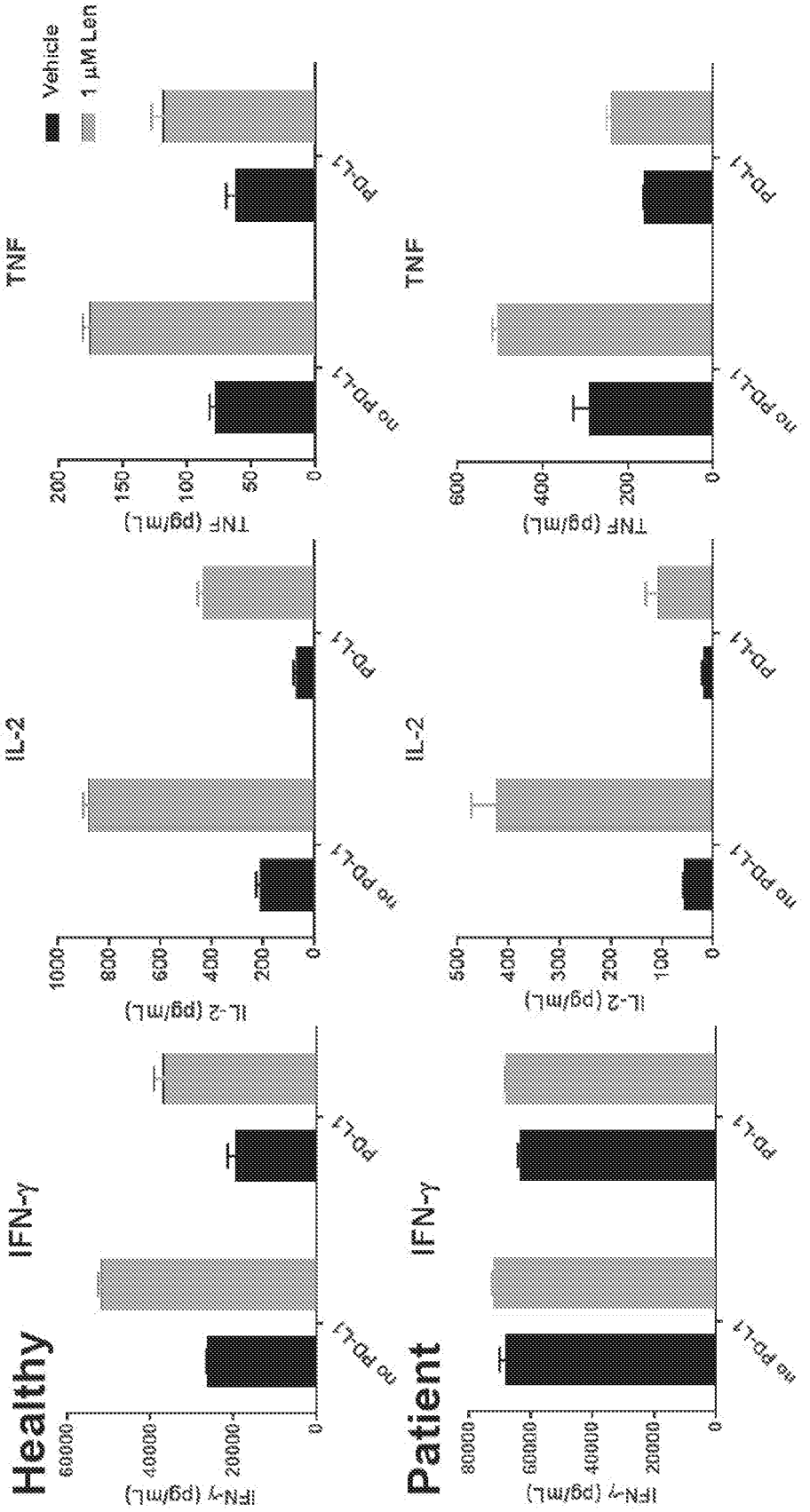
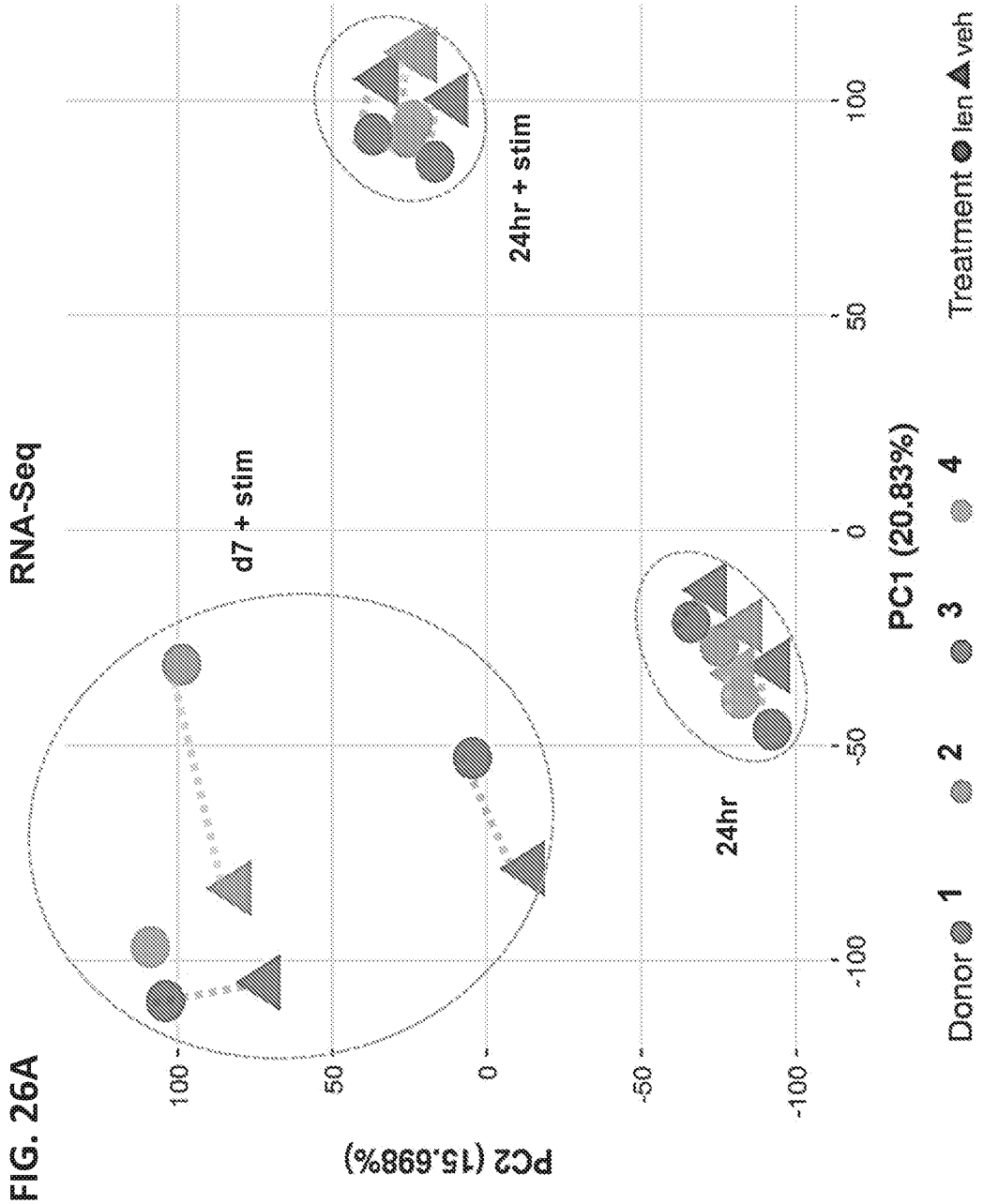

Healthy
Patient
IFN-γ
IL-2
TNF
Vehicle
1 μM Len
no PD-L1
PD-L1
IFN-γ (pg/mL)
IL-2 (pg/mL)
TNF (pg/mL)

FIG. 26A


RNA-Seq
d7 + stim
24hr + stim
24hr
PC2 (15.698%)
PC1 (20.83%)
100
50
0
-50
-100
Donor 1 2 3 4
Treatment len veh

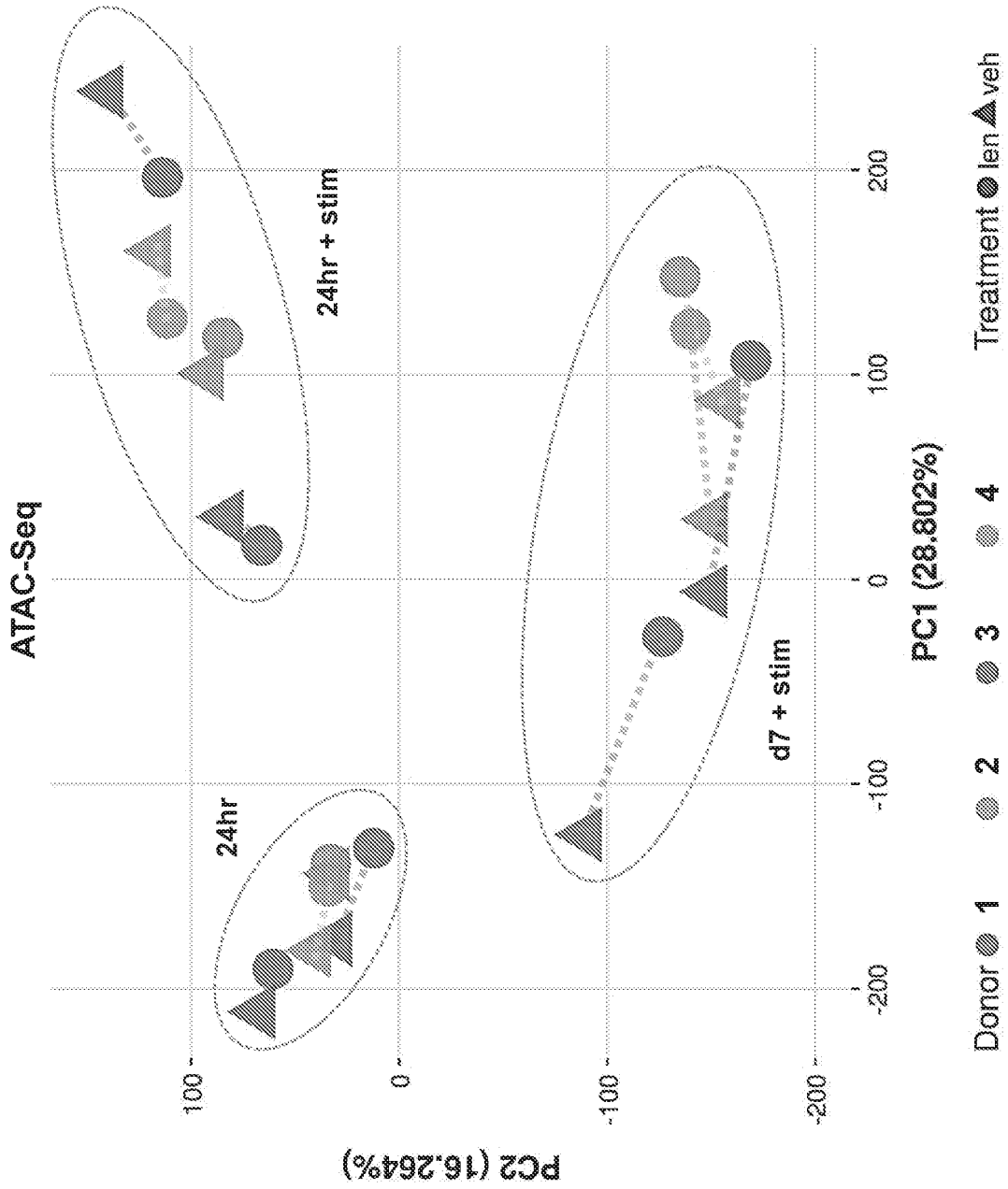
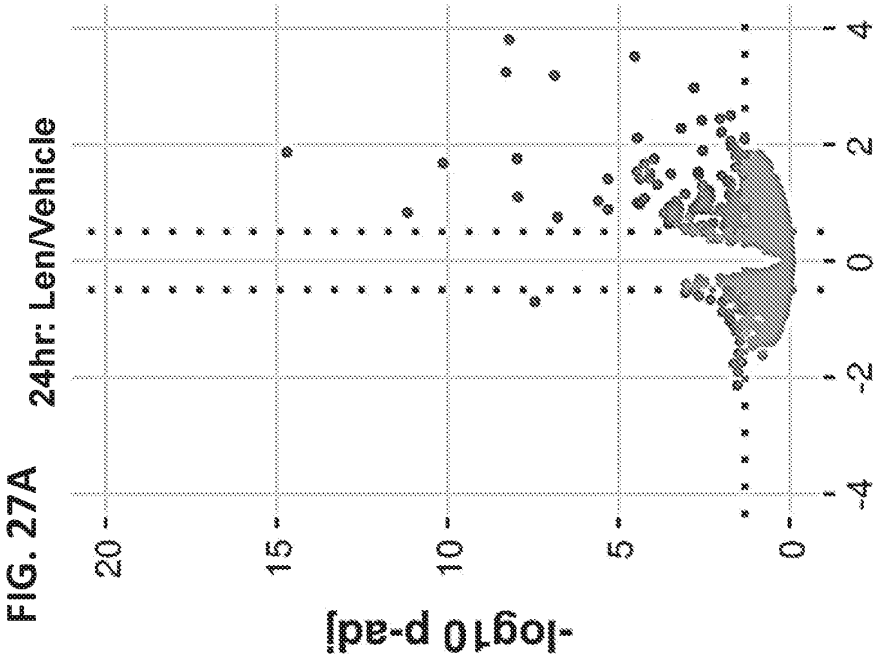

ATAC-Seq
24hr
24hr + stim
d7 + stim
PC2 (16.264%)
PC1 (28.802%)
100
0
-100
-200
200
100
0
-100
-200
Donor 1 2 3 4
Treatment len veh

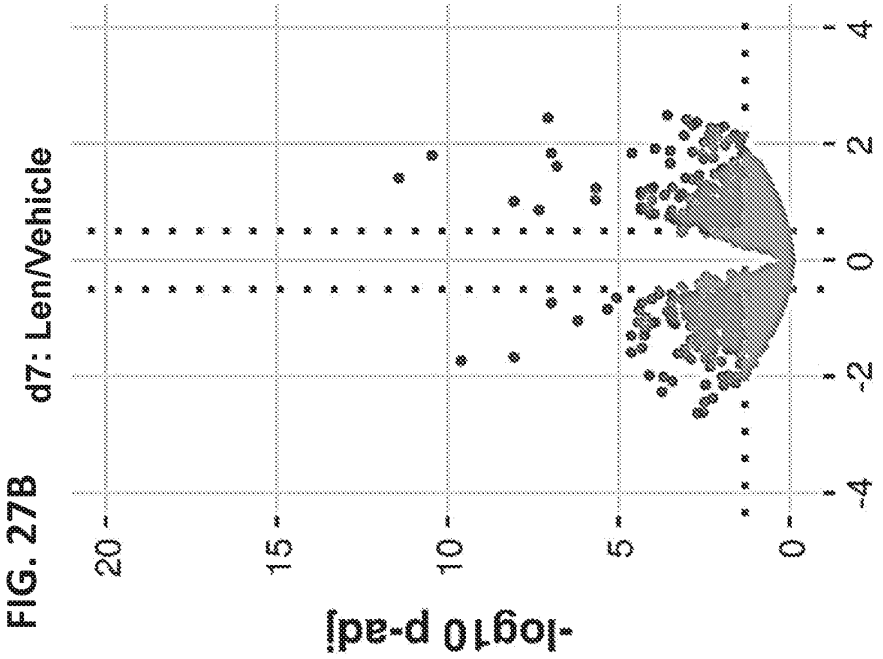
FIG. 26B

FIG. 27A



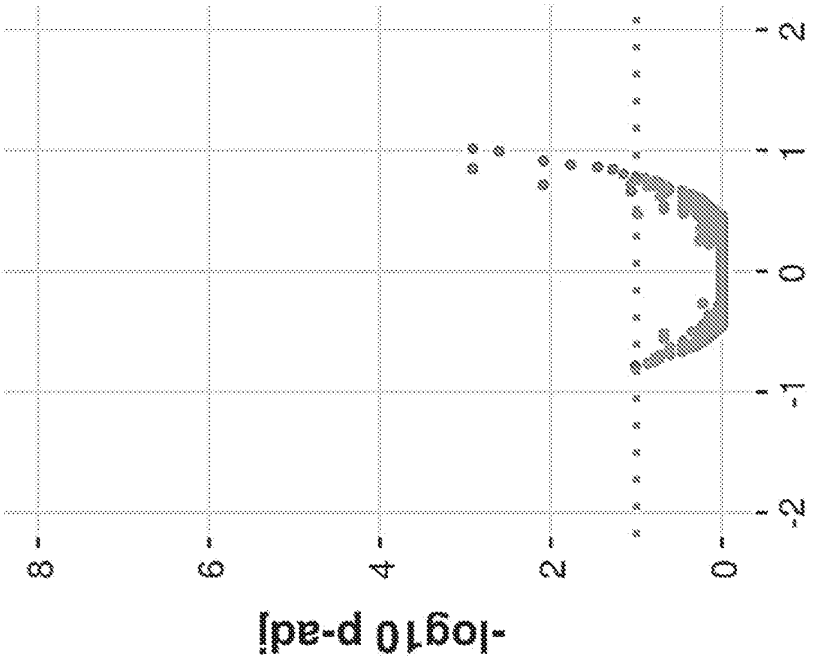
log2 fold change		
down	up	total
37	177	214

FIG. 27B



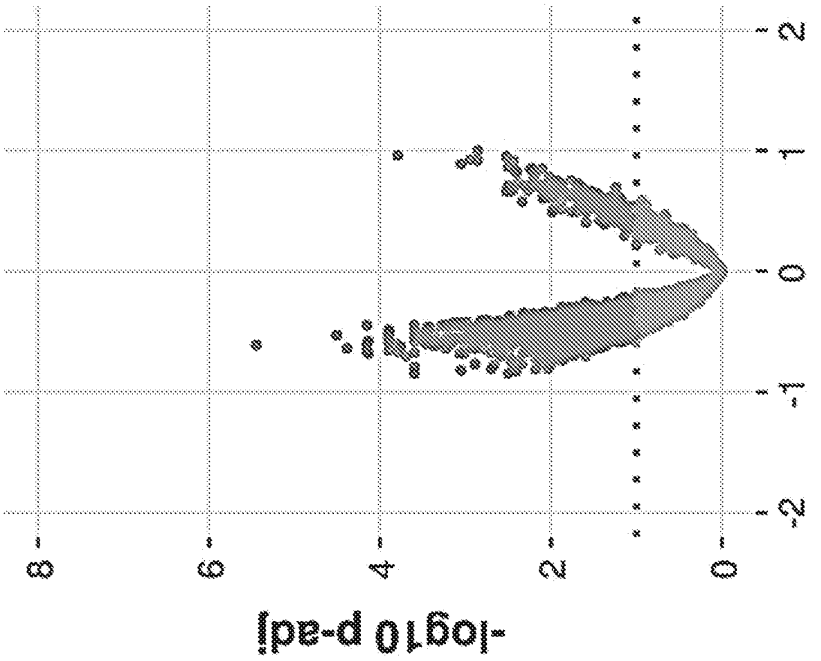
log2 fold change		
down	up	total
255	328	583

FIG. 27C



down	up	total
2	13	15

FIG. 27D



down	up	total
2510	294	2804

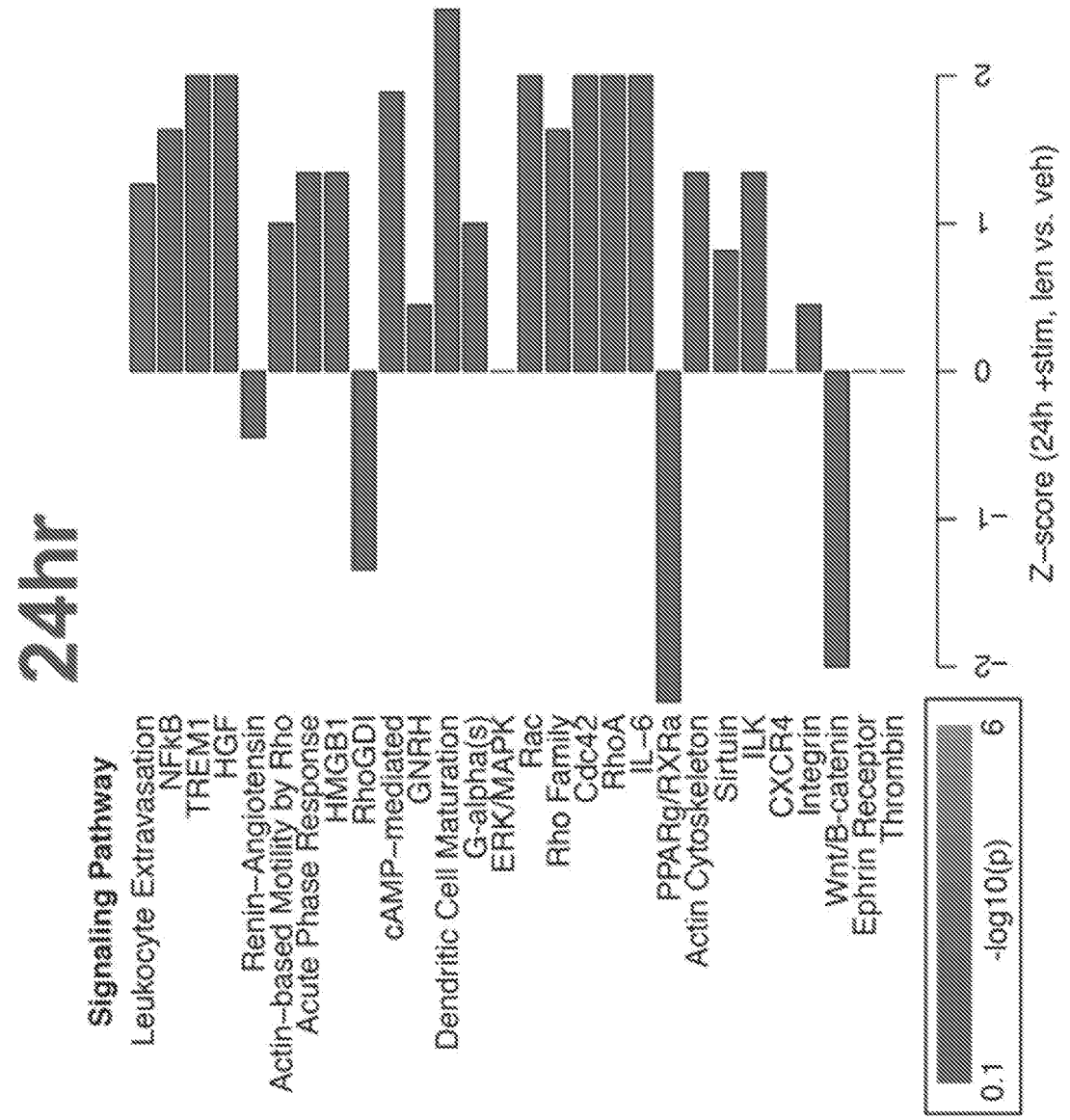
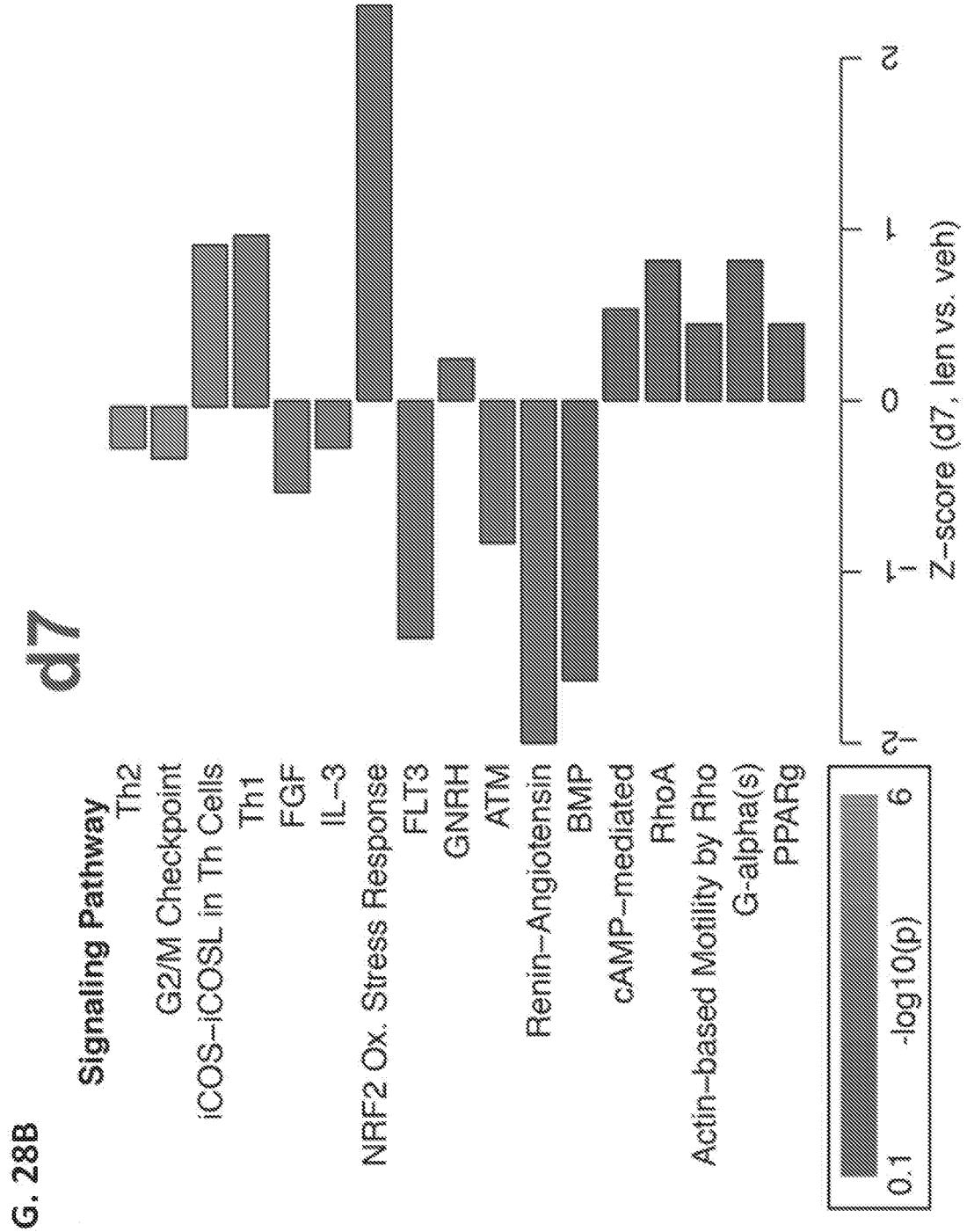

24hr
Signaling Pathway
Leukocyte Extravasation
NFkB
TREM1
HGF
Renin–Angiotensin
Actin–based Motility by Rho
Acute Phase Response
HMGB1
RhoGDI
cAMP–mediated
GNRH
Dendritic Cell Maturation
G-alpha(s)
ERK/MAPK
Rac
Rho Family
Cdc42
RhoA
IL–6
PPARg/RXRa
Actin Cytoskeleton
Sirtuin
ILK
CXCR4
Integrin
Wnt/B-catenin
Ephrin Receptor
Thrombin
0.1
-log10(p)
6
-2
-1
0
1
2
Z-score (24h +stim, len vs. veh)

FIG. 28A

FIG. 28B


d7
Signaling Pathway
Th2
G2/M Checkpoint
iCOS–iCOSL in Th Cells
Th1
FGF
IL–3
NRF2 Ox. Stress Response
FLT3
GNRH
ATM
Renin–Angiotensin
BMP
cAMP–mediated
RhoA
Actin–based Motility by Rho
G-alpha(s)
PPARg
0.1
-log10(p)
6
-2
-1
0
1
2
Z–score (d7, len vs. veh)

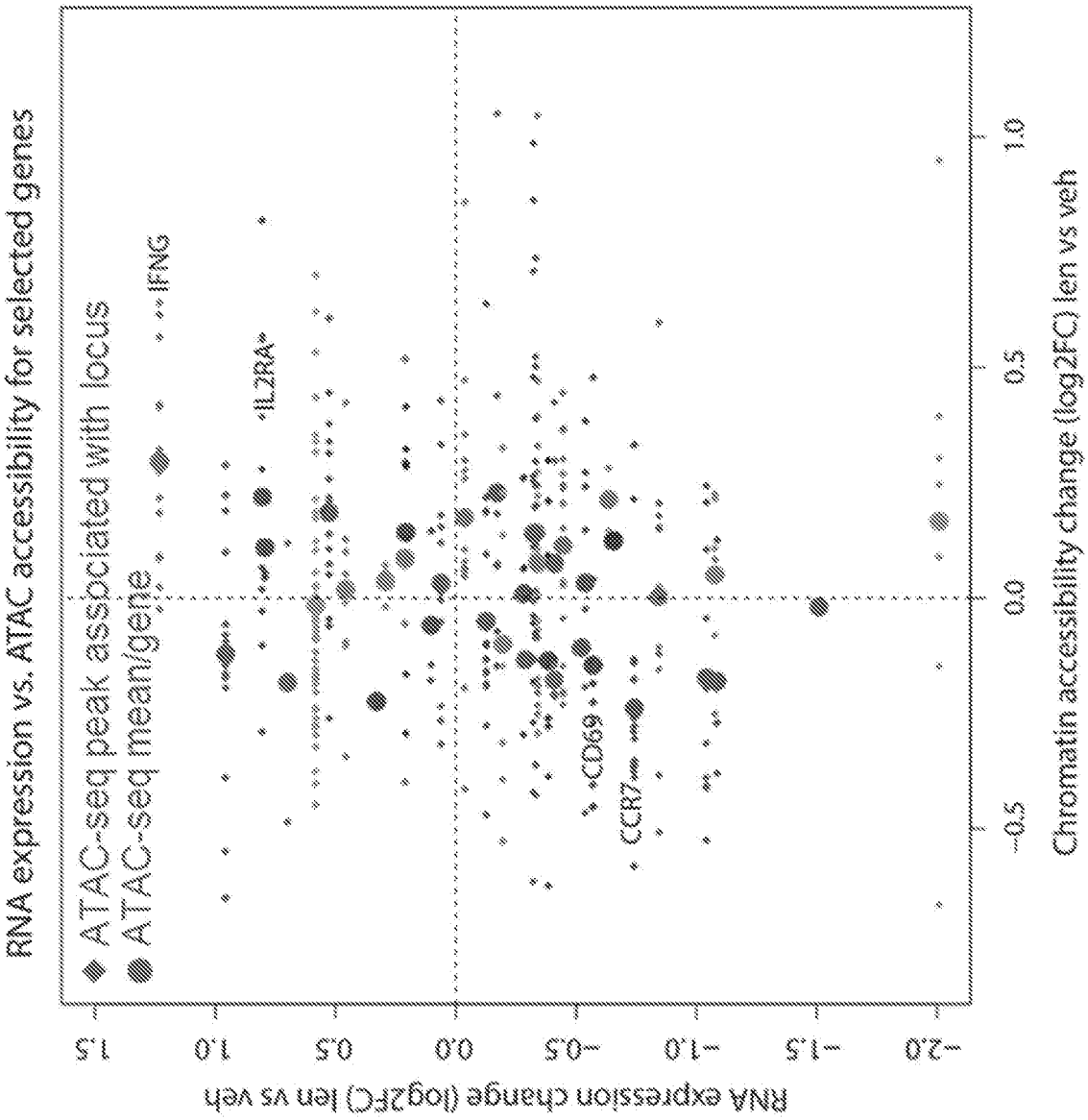

RNA expression vs. ATAC accessibility for selected genes
ATAC-seq peak associated with locus
ATAC-seq mean/gene
IFNG
IL2RA
CD69
CCR7
RNA expression change (log2FC) len vs veh
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
Chromatin accessibility change (log2FC) len vs veh
−0.5
0.0
0.5
1.0

FIG. 29

FIG. 30

Motif Name	Motif	Log P-value	% of Target Sequences with Motif
Atf3(bZIP)/GBM-ATF3		-7.66E+01	61.90%
BATF(bZIP)/Th17-BATF		-7.54E+01	61.56%
Fra1(bZIP)/BT549-Fra1		-7.39E+01	58.50%
AP-1(bZIP)/ThioMac-PU.1		-7.33E+01	62.24%
JunB(bZIP)/DendriticCells-Junb		-7.17E+01	58.16%
Fosl2(bZIP)/3T3L1-Fosl2		-6.18E+01	46.94%
Jun-AP1(bZIP)/K562-cJun		-5.14E+01	39.12%
Smad3(MAD)/NPC-Smad3		-4.50E+01	56.46%
NFkB-p65(RHD)/GM12787-p65		-4.41E+01	29.59%
RUNX1(Runt)/Jurkat-RUNX1		-4.04E+01	50.00%
RUNX(Runt)/HPC7-Runx1		-3.77E+01	41.16%
Bach2(bZIP)/OCILy7-Bach2		-3.62E+01	26.53%

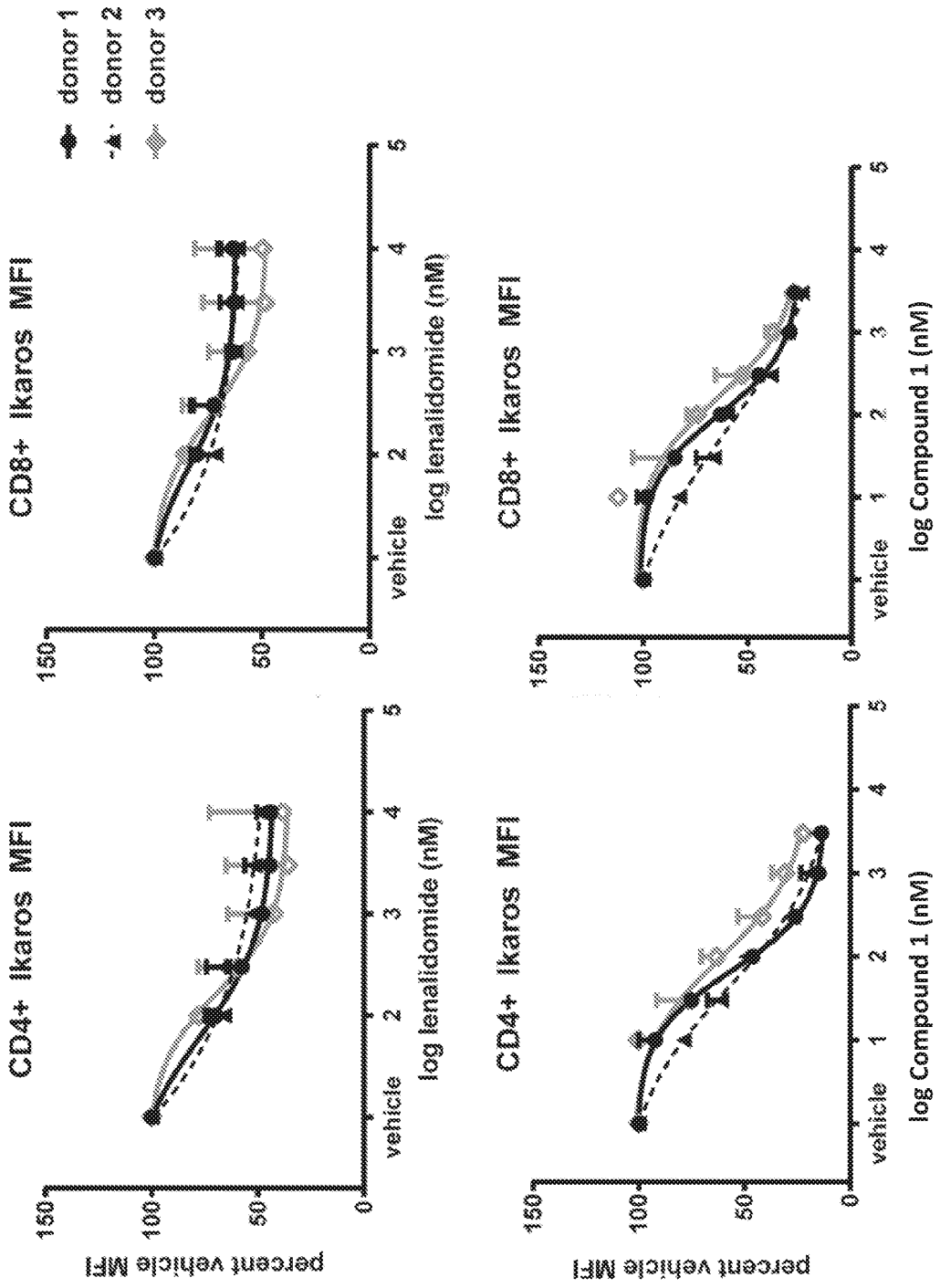

donor 1
donor 2
donor 3
CD8+ Ikaros MFI
CD4+ Ikaros MFI
percent vehicle MFI
150
100
50
0
vehicle
1
2
3
4
5
log lenalidomide (nM)
log Compound 1 (nM)

FIG. 31

FIG. 32A

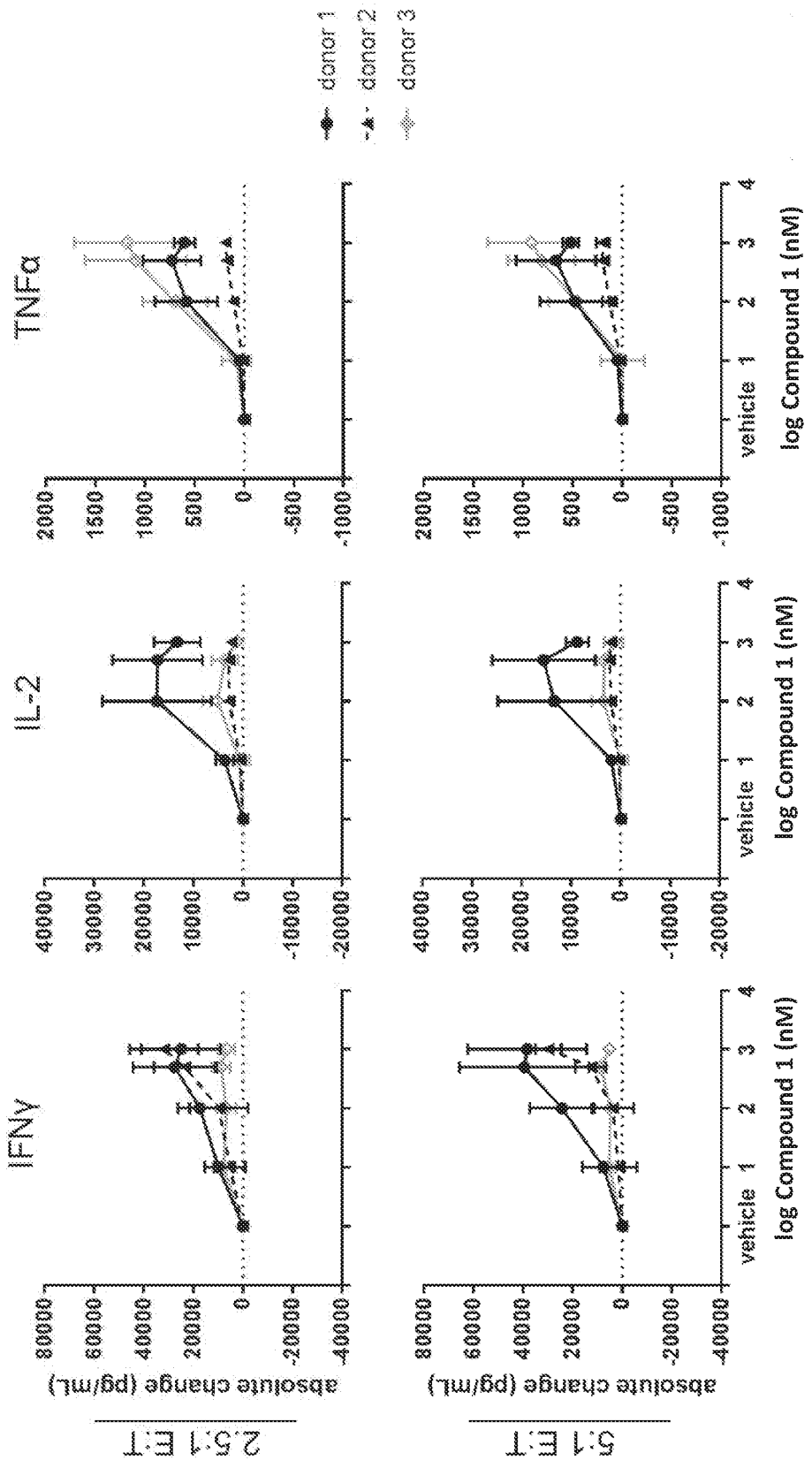
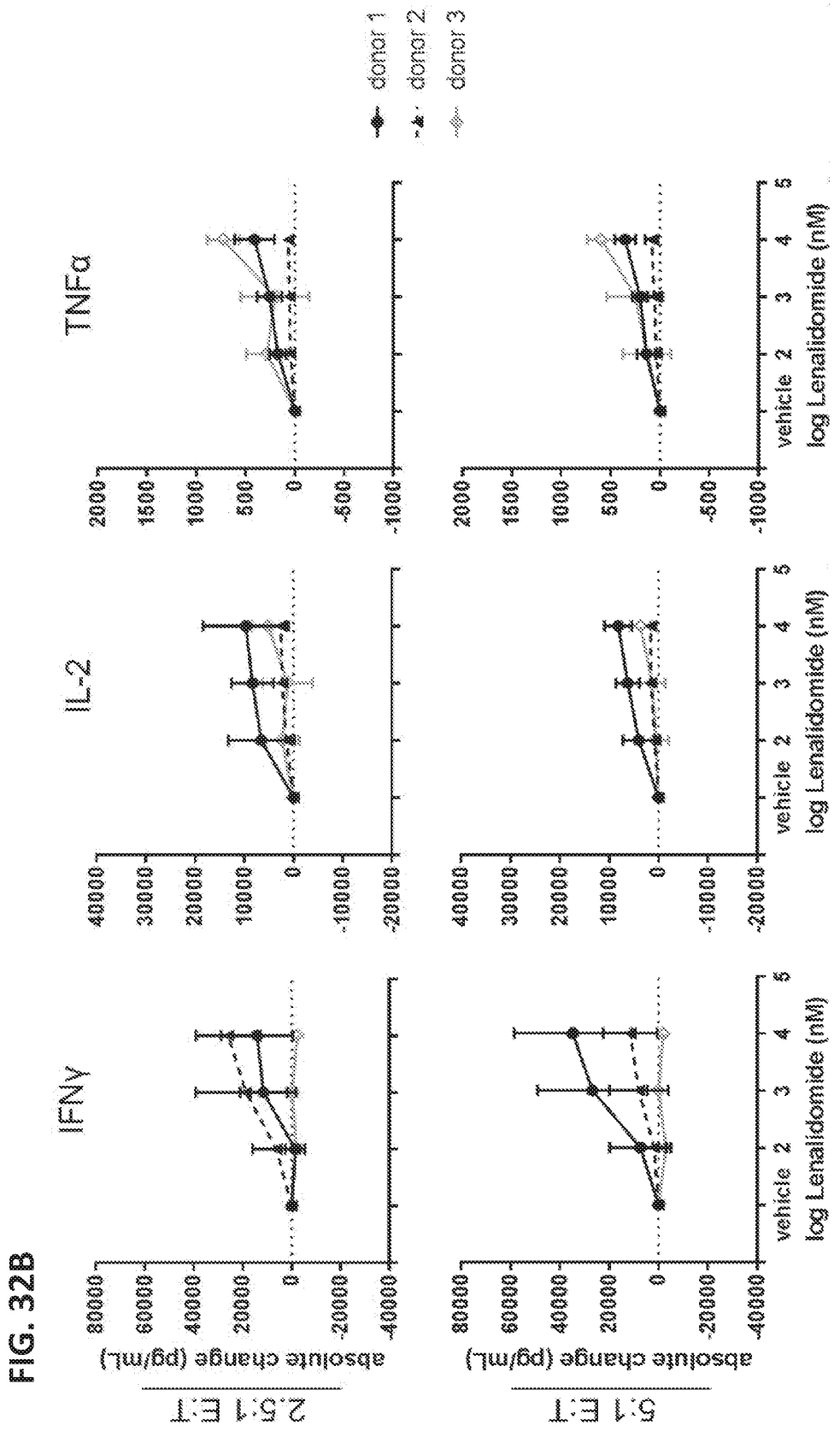

donor 1
donor 2
donor 3
IFNγ
IL-2
TNFα
2.5:1 E:T
5:1 E:T
absolute change (pg/mL)
log Compound 1 (nM)
vehicle 1
2
3
4
80000
60000
40000
20000
0
-20000
-40000
30000
10000
-10000
2000
1500
1000
500
-500
-1000

FIG. 32B


IFNγ
IL-2
TNFα
2.5:1 E:T
5:1 E:T
absolute change (pg/mL)
log Lenalidomide (nM)
vehicle
donor 1
donor 2
donor 3

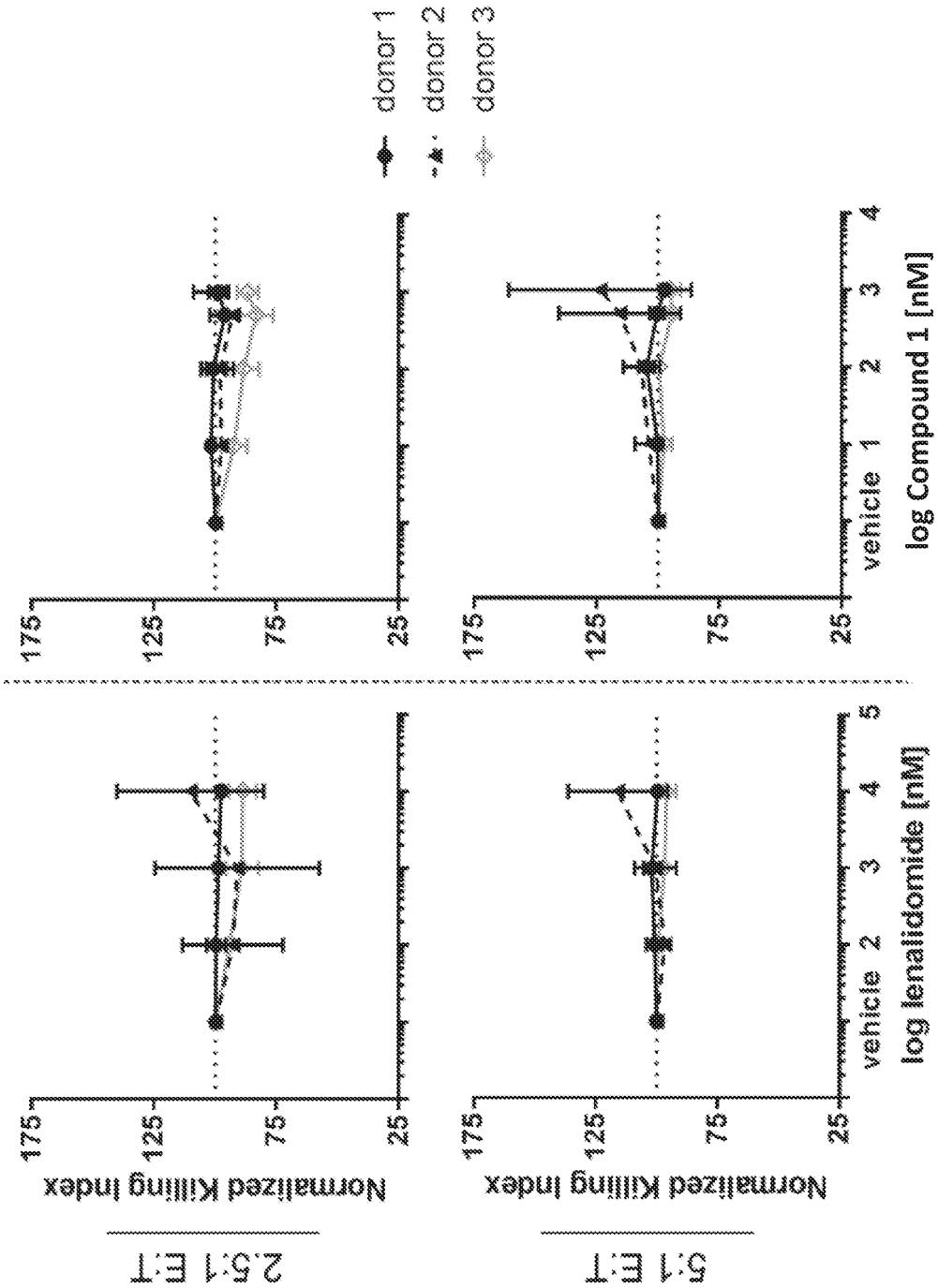

donor 1
donor 2
donor 3
2.5:1 E:T
5:1 E:T
Normalized Killing Index
175
125
75
25
vehicle
1
2
3
4
5
log Compound 1 [nM]
log lenalidomide [nM]

FIG. 33

FIG. 34A

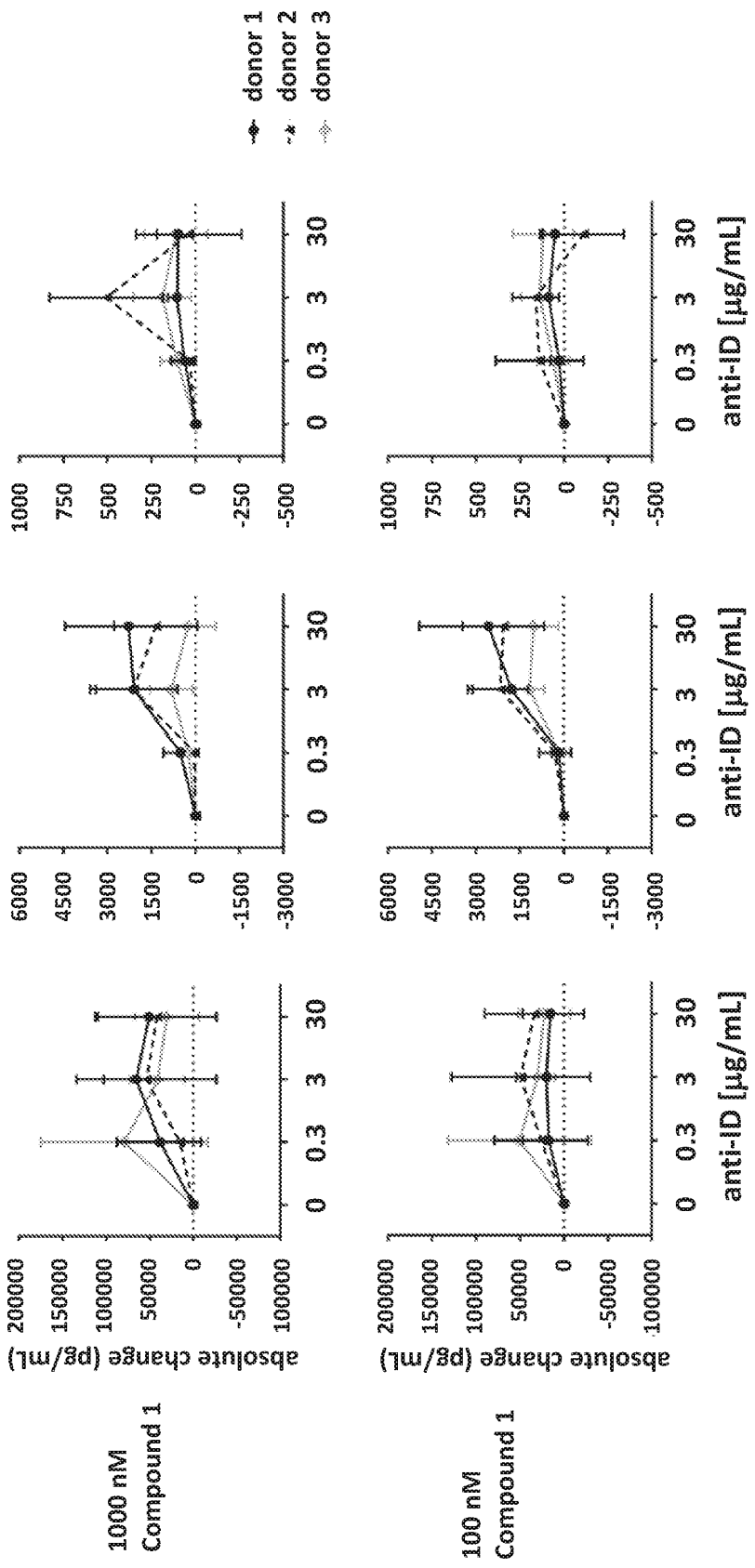

IFN-γ
IL-2
TNF-α
donor 1
donor 2
donor 3
1000 nM Compound 1
100 nM Compound 1
absolute change (pg/mL)
anti-ID [µg/mL]
200000
150000
100000
50000
0
-50000
100000
6000
4500
3000
1500
0
-1500
-3000
1000
750
500
250
0
-250
-500
0
0.3
3
30

FIG. 34B

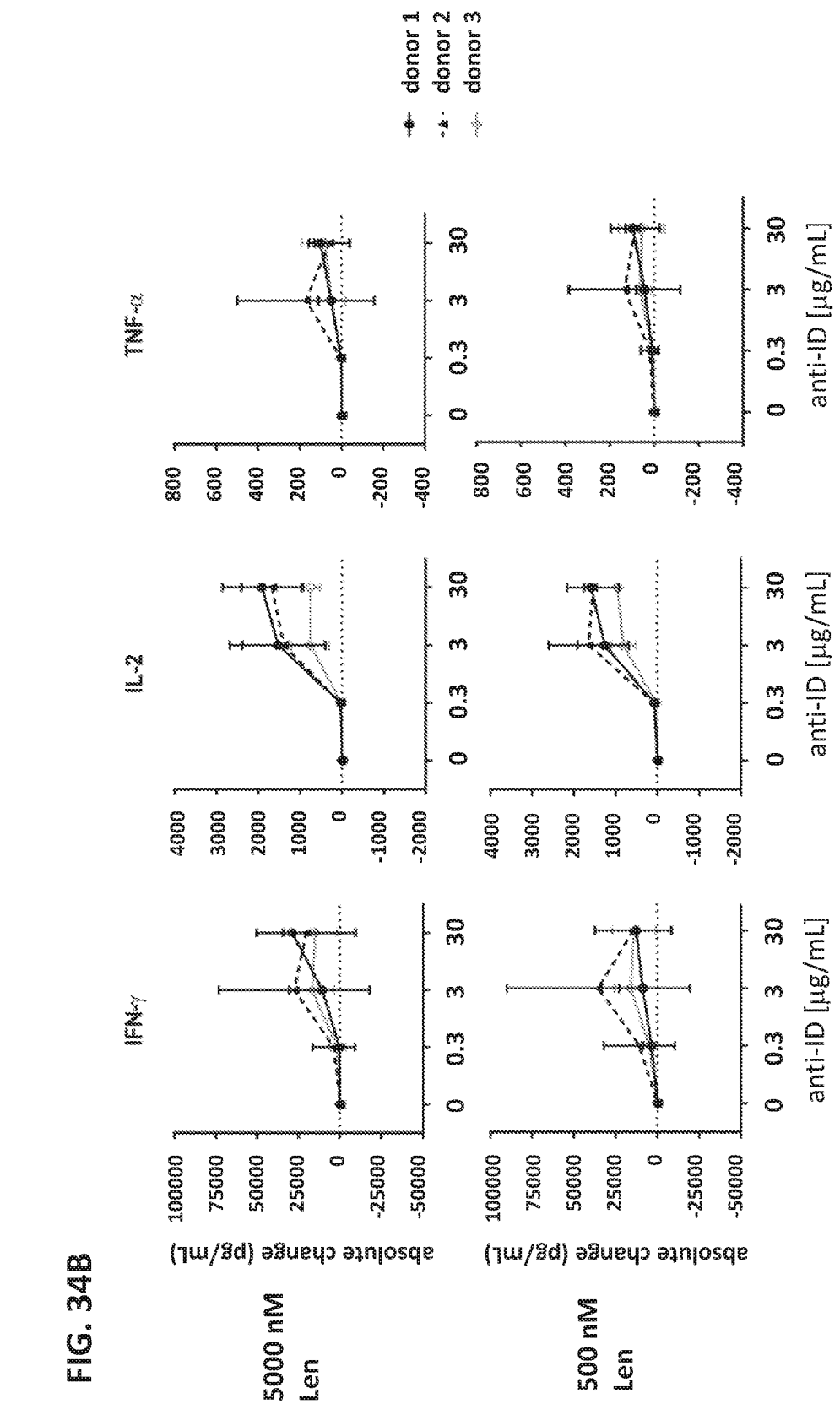

donor 1
donor 2
donor 3
IFN-γ
IL-2
TNF-α
5000 nM Len
500 nM Len
absolute change (pg/mL)
anti-ID [μg/mL]
0
0.3
3
30
100000
75000
50000
25000
0
-25000
-50000
4000
3000
2000
1000
-1000
-2000
800
600
400
200
-200
-400

FIG. 35A

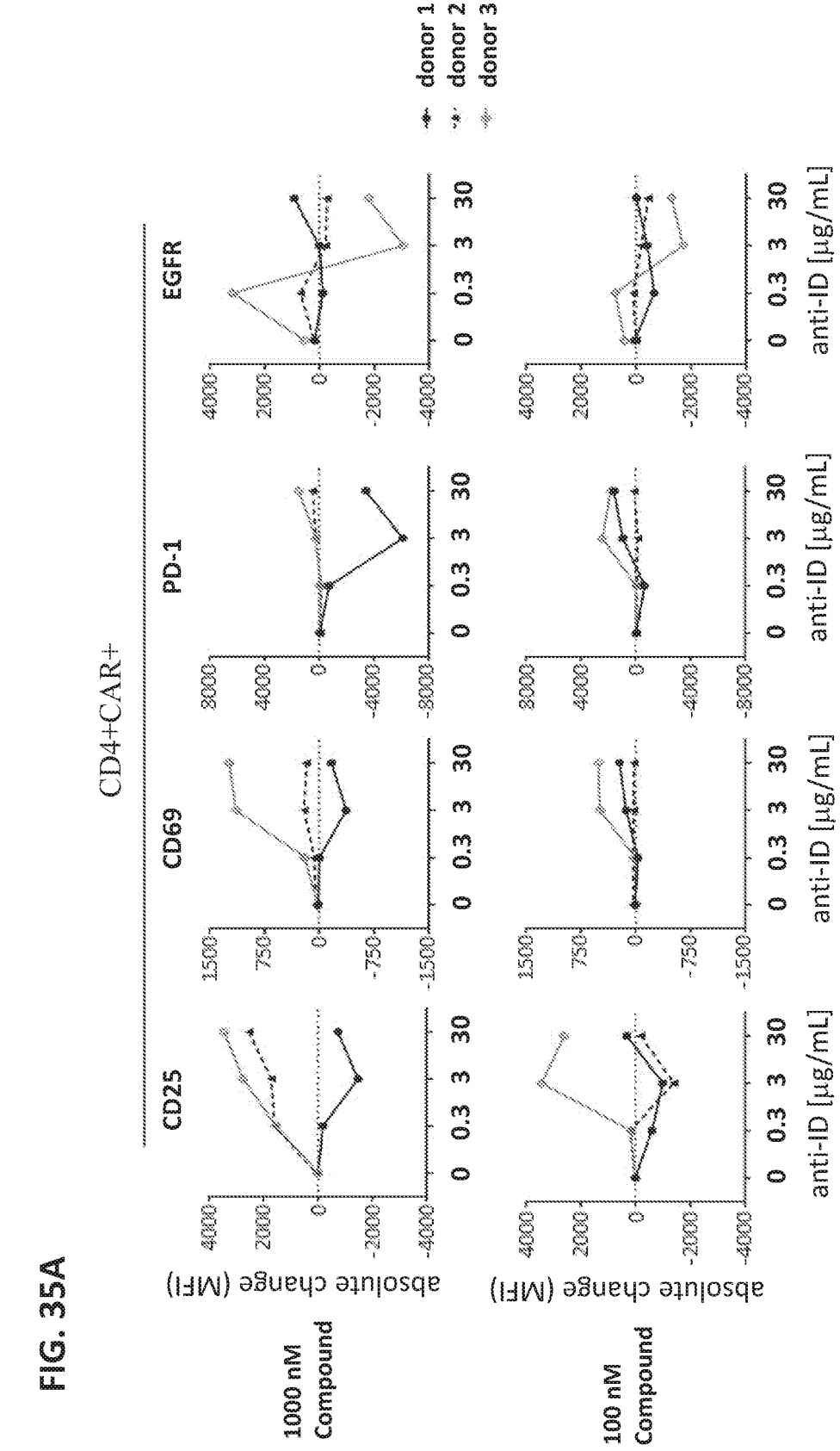

CD4+CAR+
CD25
CD69
PD-1
EGFR
donor 1
donor 2
donor 3
1000 nM Compound
100 nM Compound
absolute change (MFI)
anti-ID [µg/mL]
0 0.3 3 30

FIG. 35B

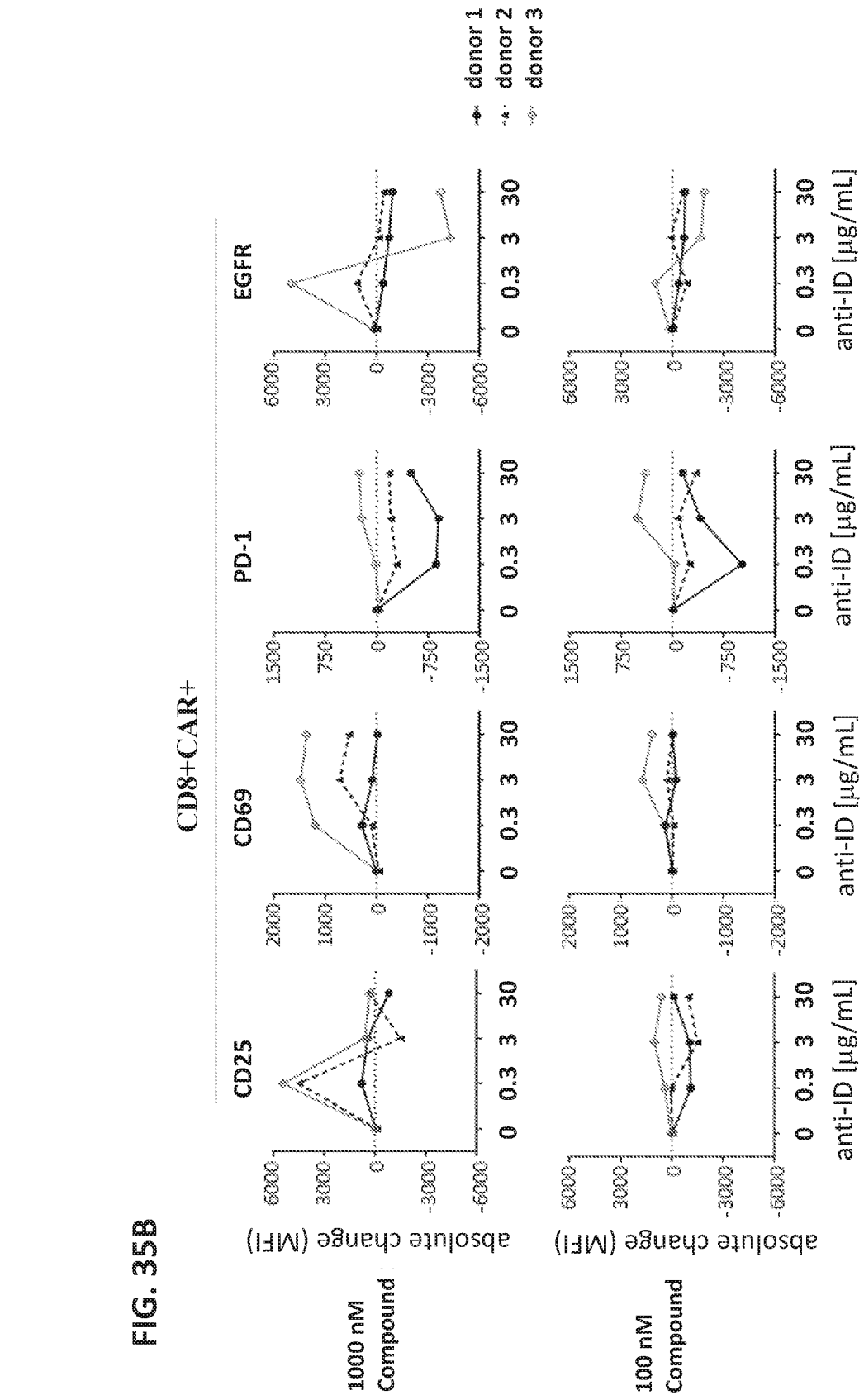

CD8+CAR+
CD25
CD69
PD-1
EGFR
donor 1
donor 2
donor 3
1000 nM Compound
100 nM Compound
absolute change (MFI)
anti-ID [µg/mL]
0 0.3 3 30
6000
3000
0
-3000
-6000
2000
1000
-1000
-2000
1500
750
-750
-1500

FIG. 36A

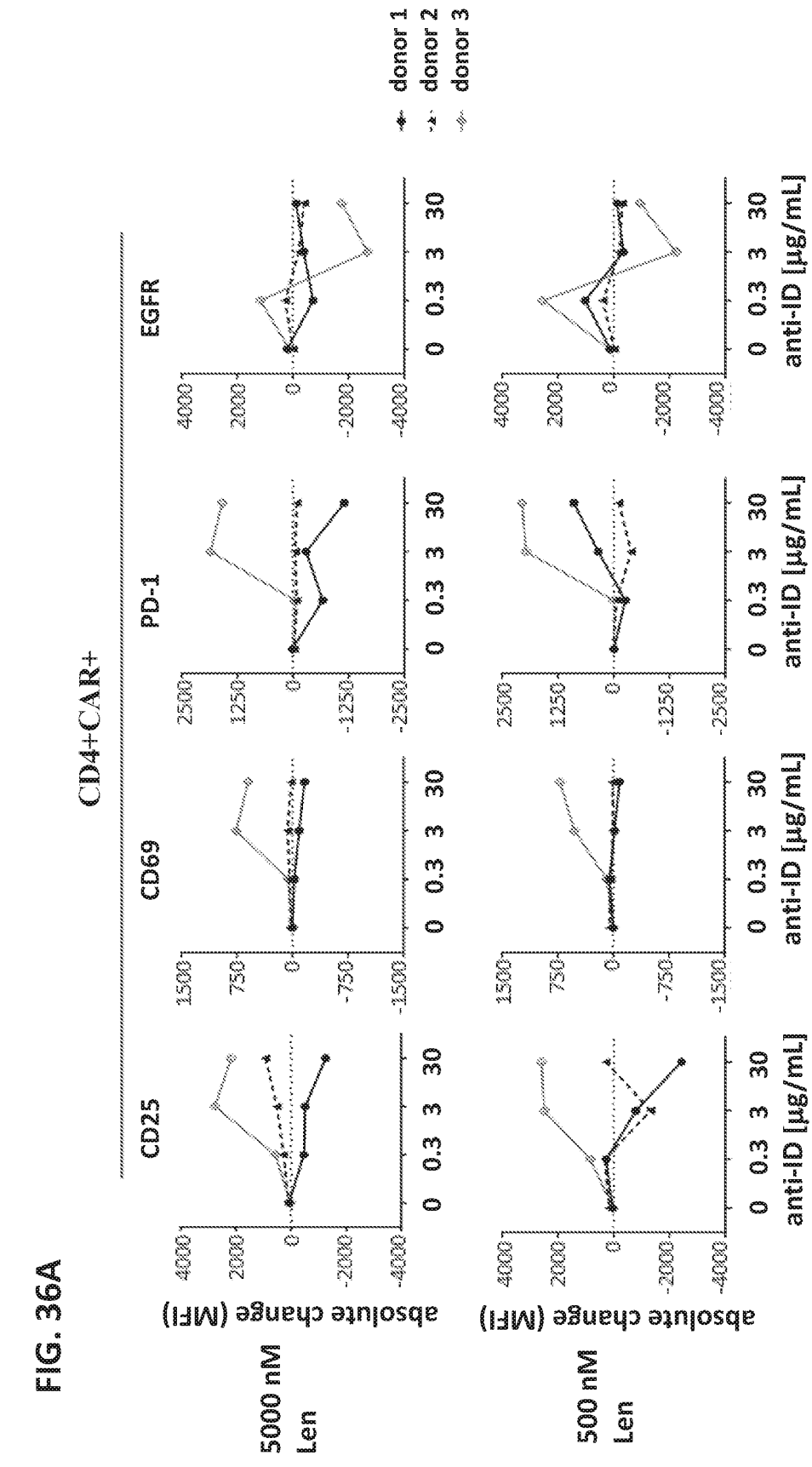
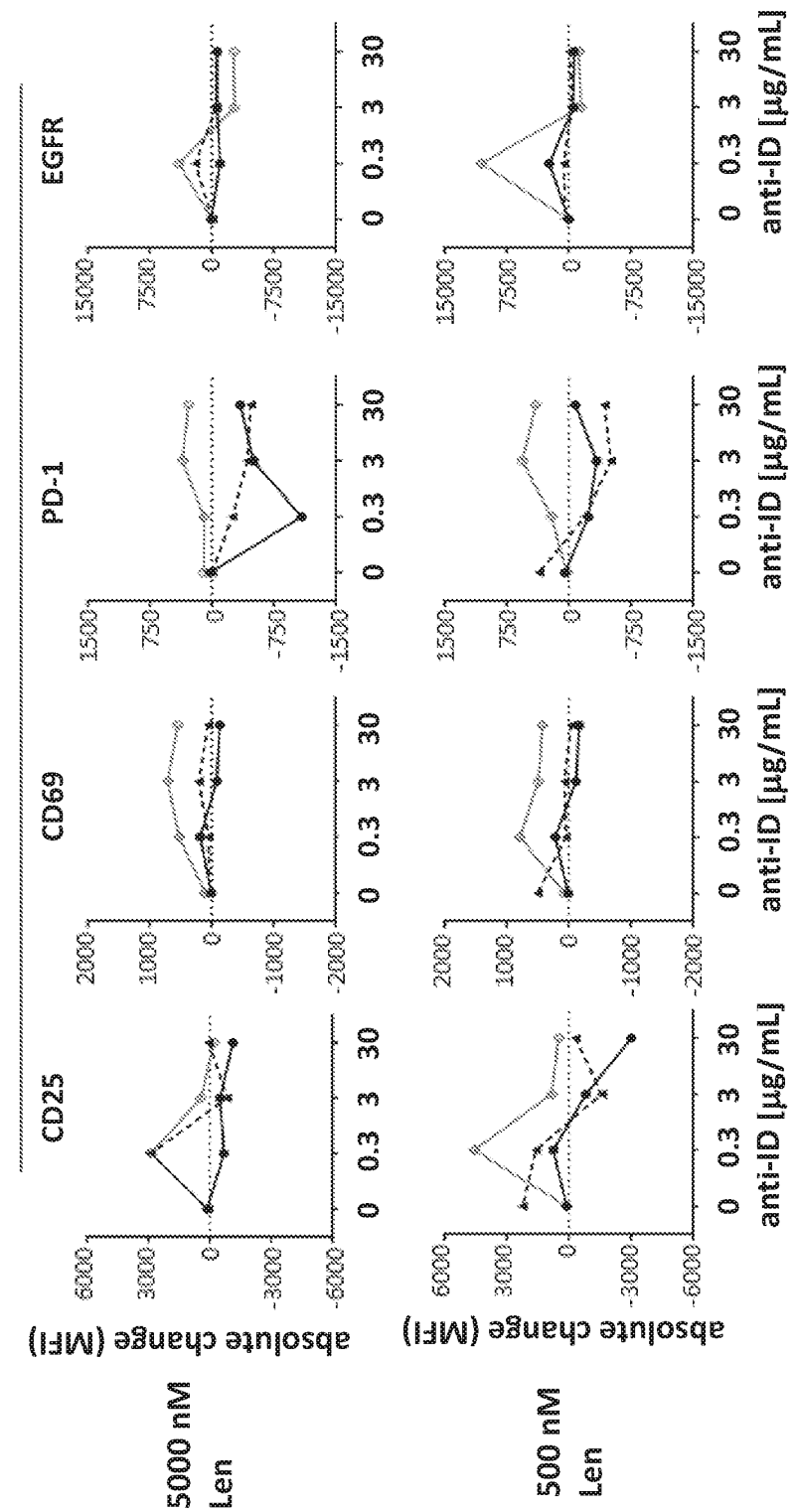

CD4+CAR+
donor 1
donor 2
donor 3
CD25
CD69
PD-1
EGFR
5000 nM Len
500 nM Len
absolute change (MFI)
anti-ID [µg/mL]
0 0.3 3 30
4000
2000
0
-2000
-4000
1500
750
-750
-1500
2500
1250
-1250
-2500

FIG. 36B


CD8+CAR+
CD25
CD69
PD-1
EGFR
donor 1
donor 2
donor 3
5000 nM Len
500 nM Len
absolute change (MFI)
anti-ID [µg/mL]
0 0.3 3 30
6000
3000
0
-3000
-6000
2000
1000
-1000
-2000
1500
750
-750
-1500
15000
7500
-7500
-15000

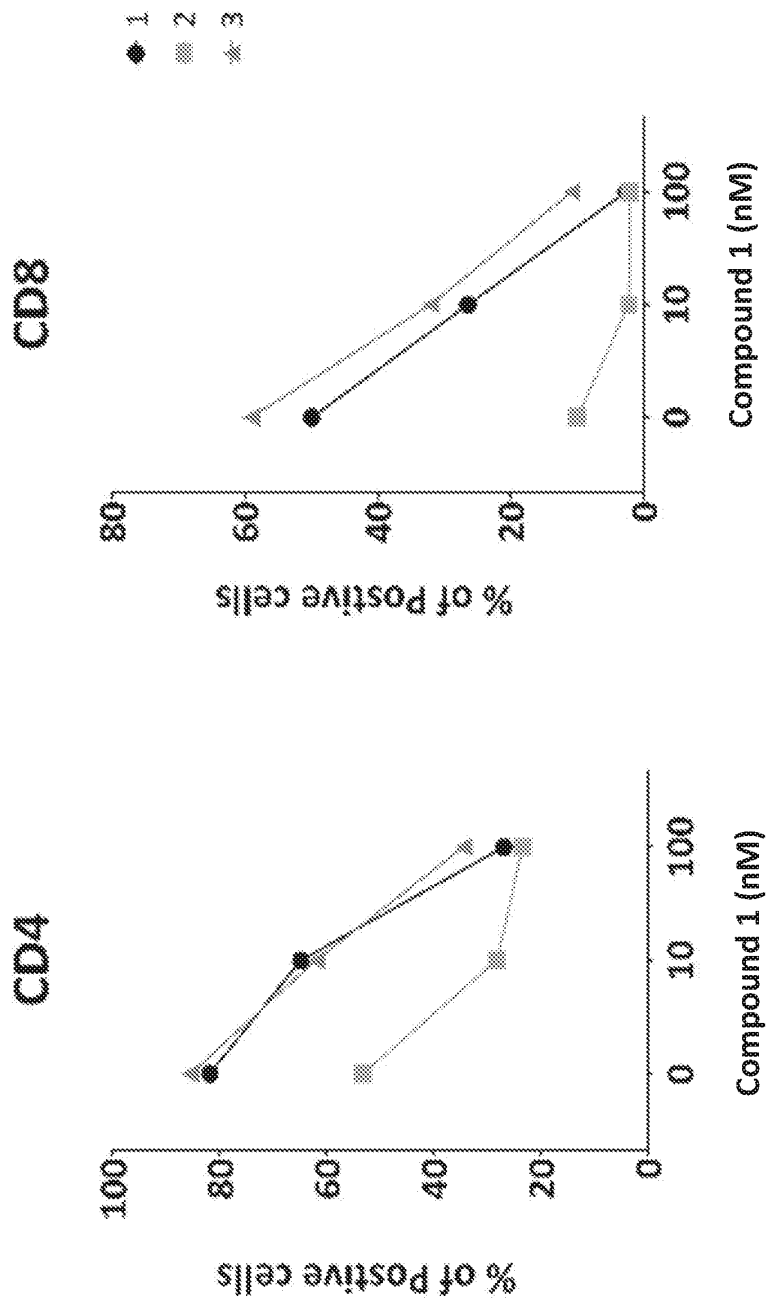

CD8
1
2
3
% of Positive cells
0
20
40
60
80
0
10
100
Compound 1 (nM)
CD4
% of Positive cells
0
20
40
60
80
100
0
10
100
Compound 1 (nM)

FIG. 37A

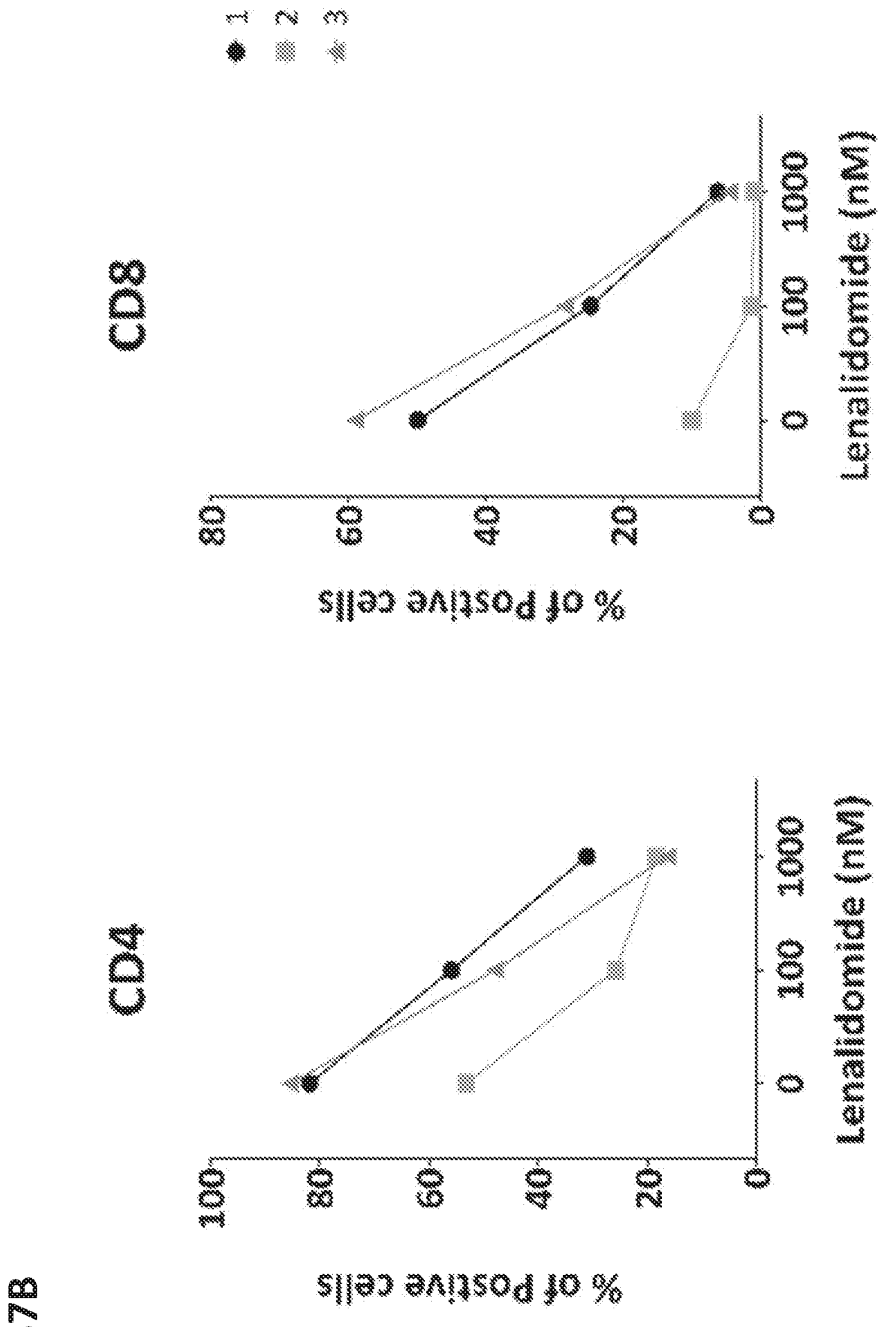

CD8
1
2
3
% of Positive cells
0
20
40
60
80
0
100
1000
Lenalidomide (nM)
CD4
% of Positive cells
0
20
40
60
80
100
0
100
1000
Lenalidomide (nM)

FIG. 37B

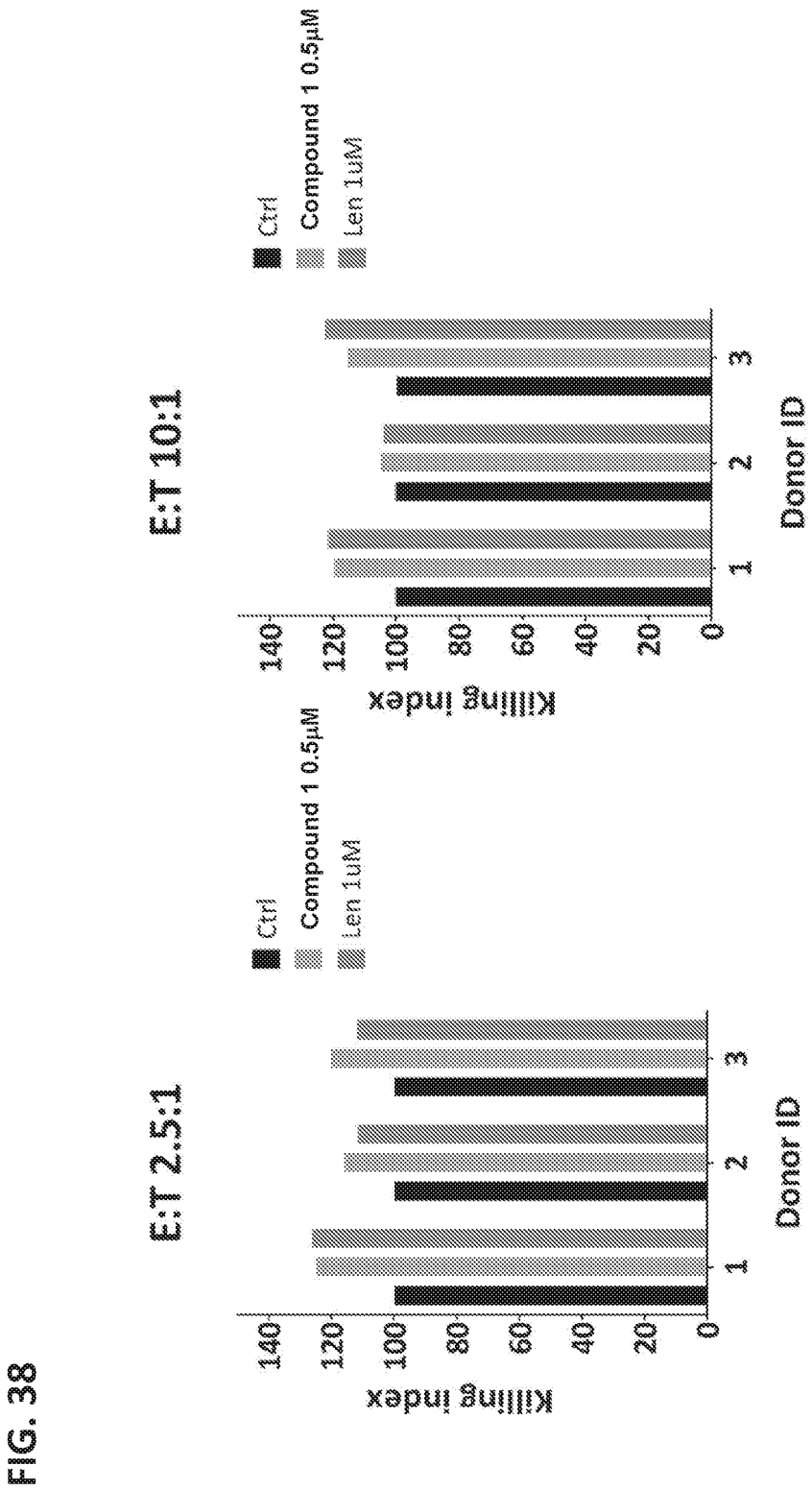
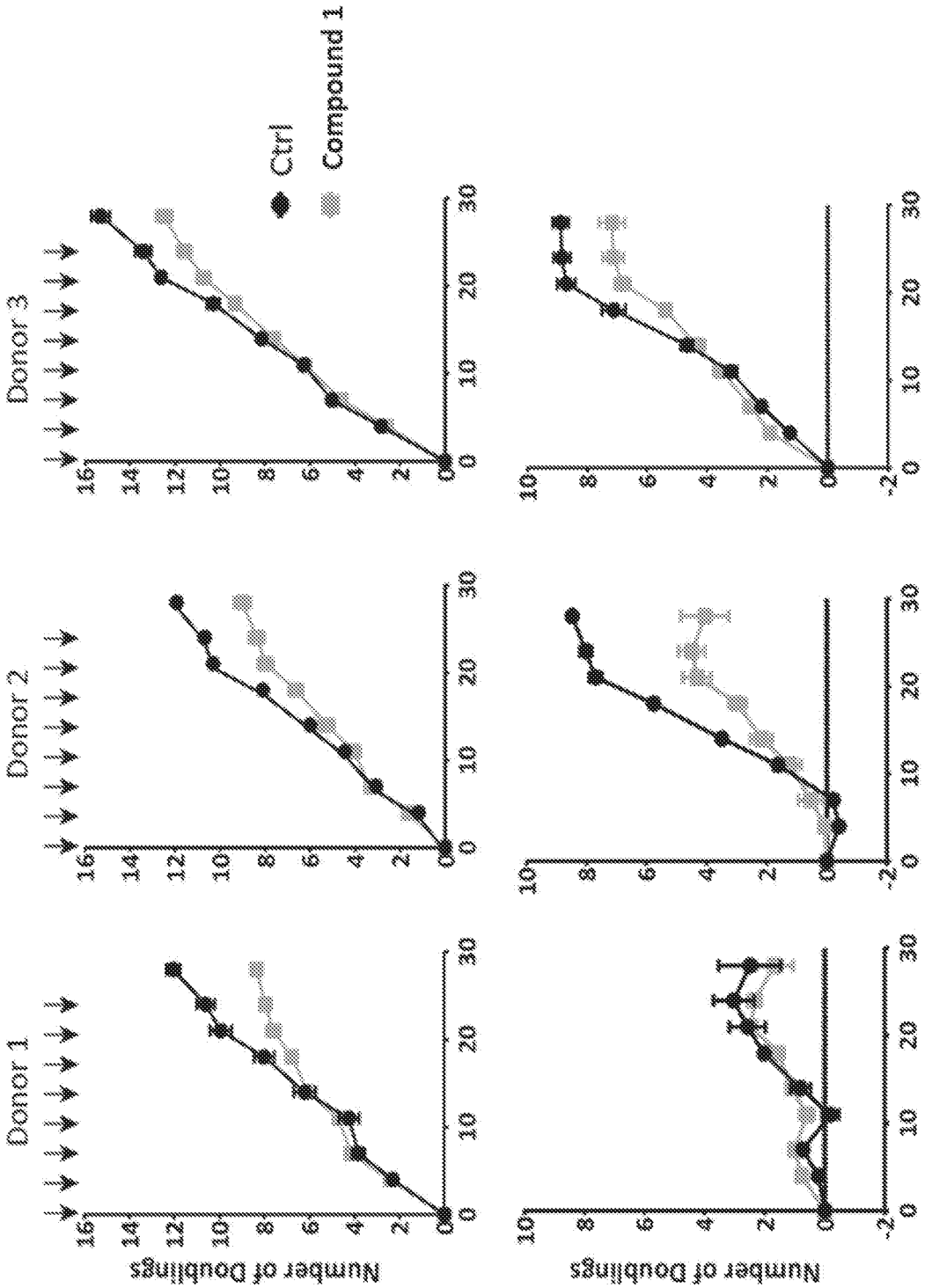

E:T 10:1
Ctrl
Compound 1 0.5μM
Len 1uM
Killing index
140
120
100
80
60
40
20
0
1
2
3
Donor ID
E:T 2.5:1
Ctrl
Compound 1 0.5μM
Len 1uM
Killing index
140
120
100
80
60
40
20
0
1
2
3
Donor ID

FIG. 38

FIG. 39A


Donor 1
Donor 2
Donor 3
Ctrl
Compound 1
Number of Doublings
E:T
2.5:1
10:1

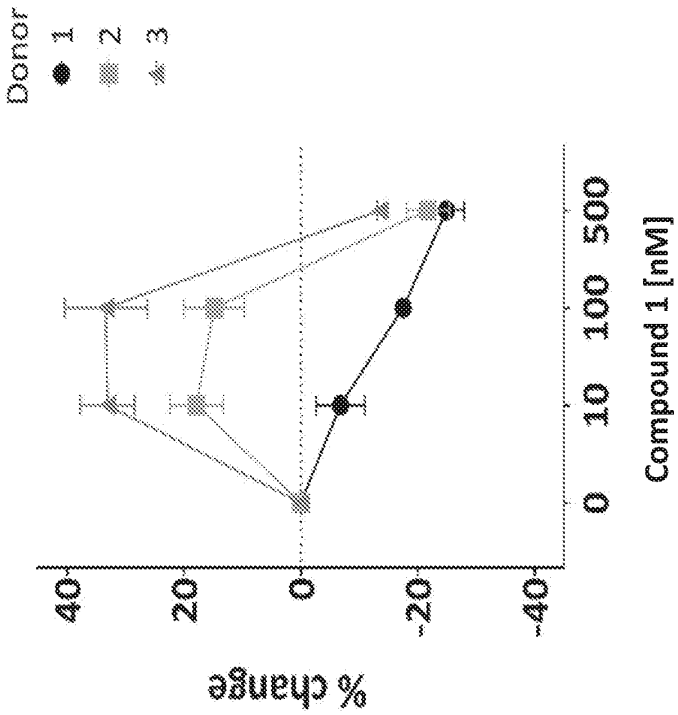


FIG. 39B

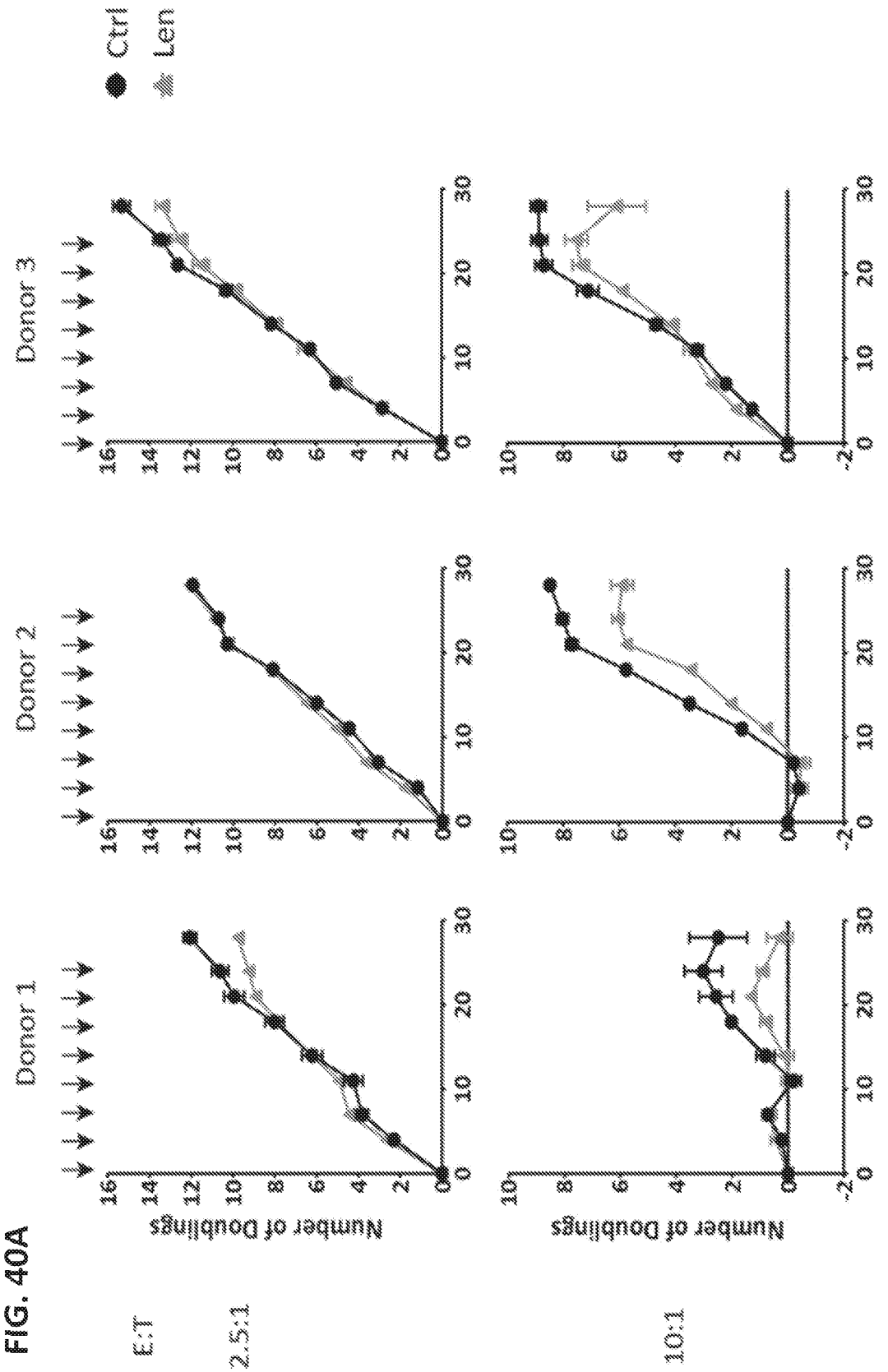

Ctrl
Len
Donor 1
Donor 2
Donor 3
E:T
2.5:1
10:1
Number of Doublings
0
2
4
6
8
10
12
14
16
-2
0
10
20
30

FIG. 40A

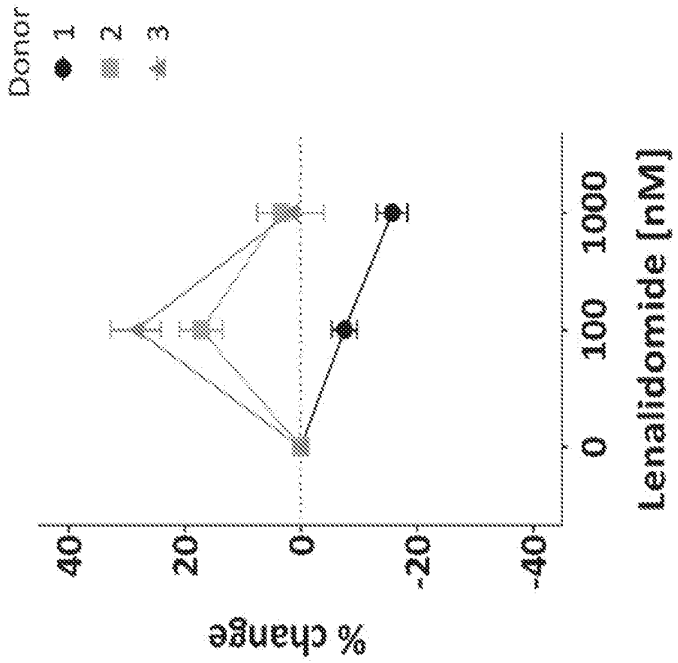


FIG. 40B