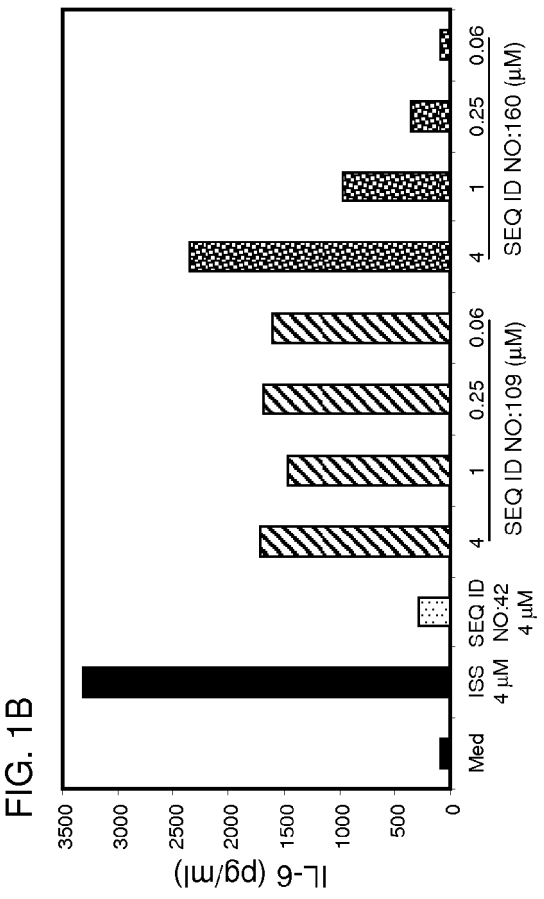
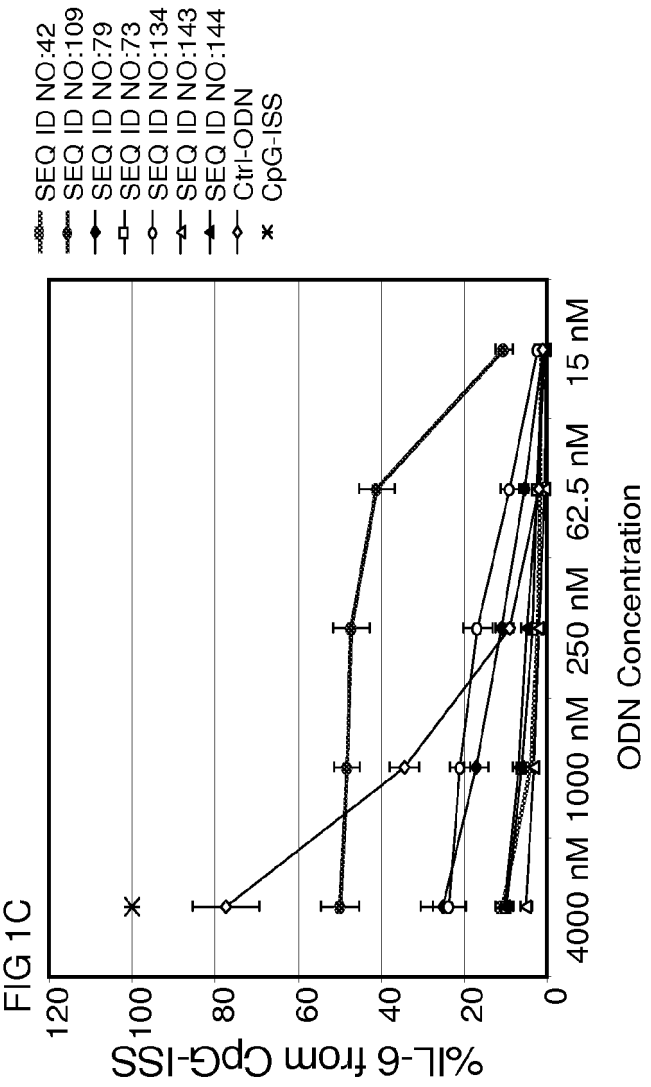
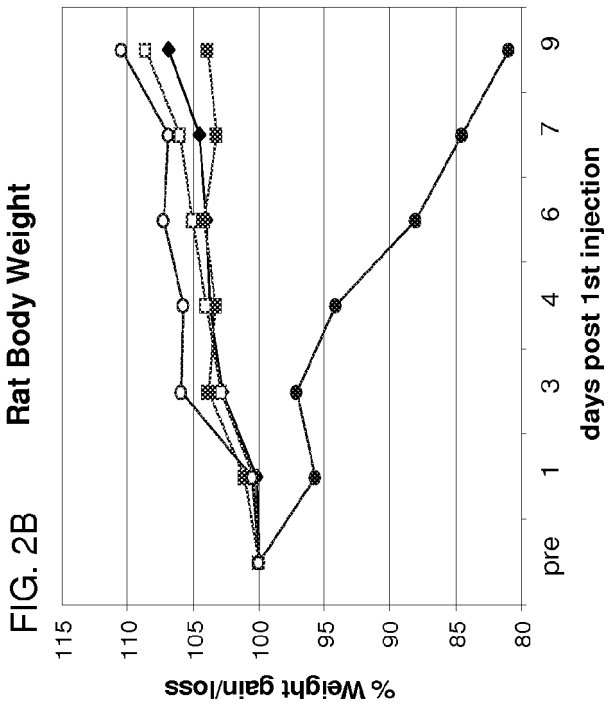
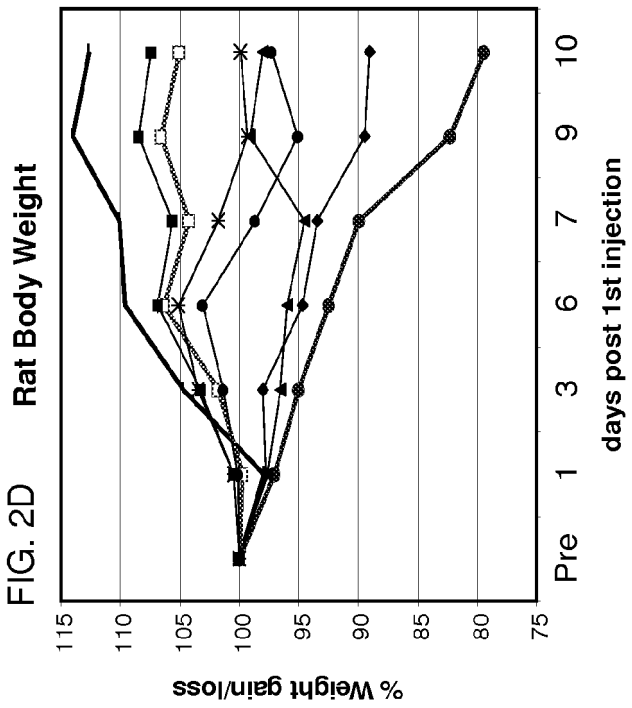
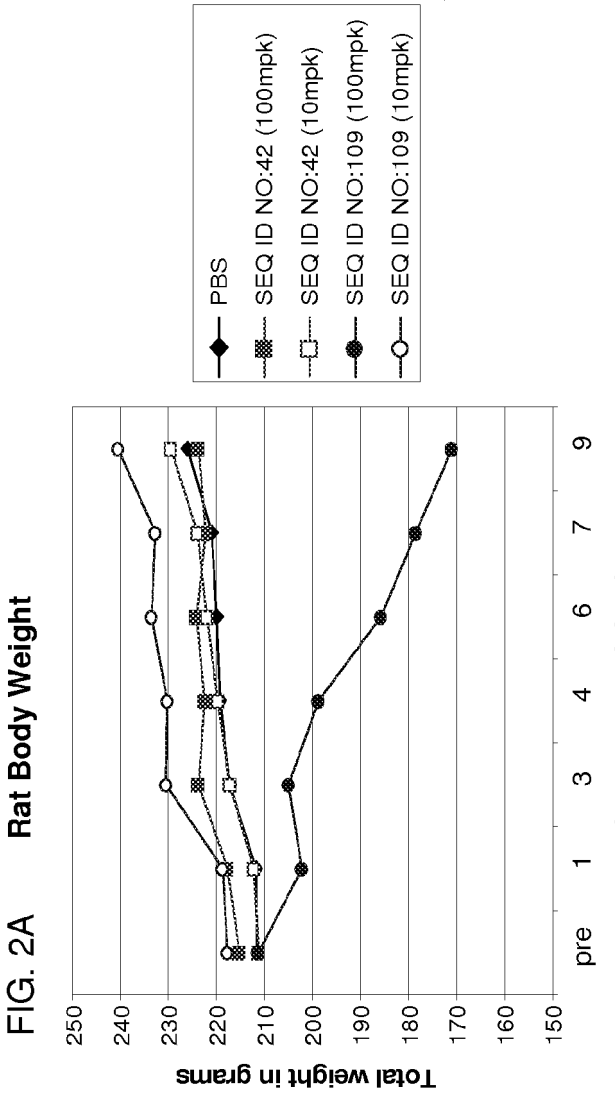

FIG. 1A
IL-6 (pg/ml)
0
500
1000
1500
2000
2500
3000
Med
ISS 2 µM
SEQ ID NO:160 2 µM
SEQ ID NO:159 2 µM
SEQ ID NO:109 2 µM
SEQ ID NO:42 2 µM

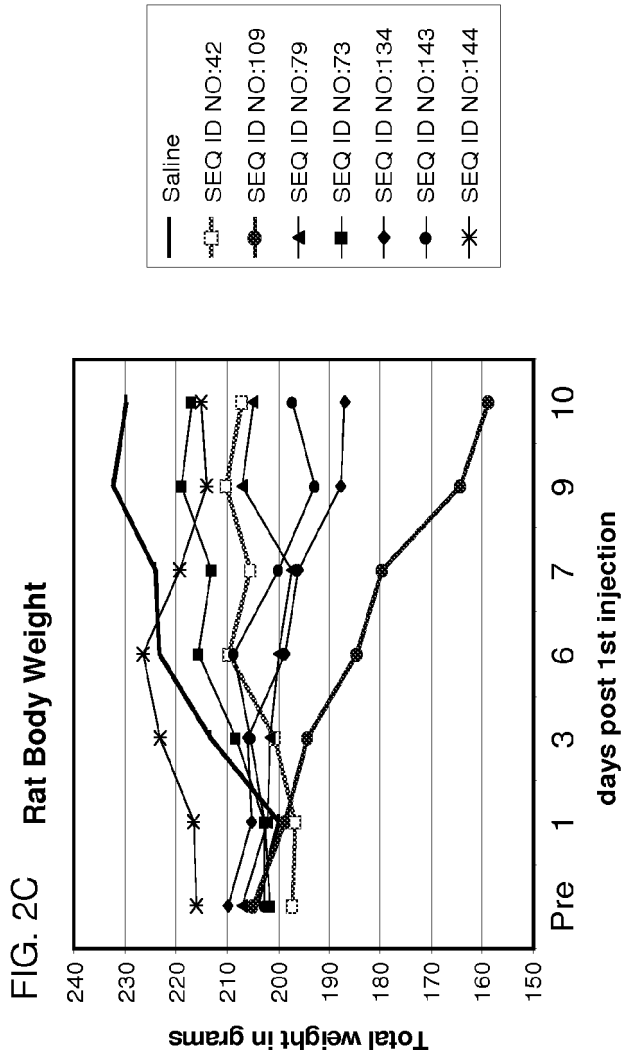
FIG. 1B
IL-6 (pg/ml)
0
500
1000
1500
2000
2500
3000
3500
Med
ISS 4 µM
SEQ ID NO:42 4 µM
SEQ ID NO:109 (µM)
4
1
0.25
0.06
SEQ ID NO:160 (µM)
4
1
0.25
0.06


FIG 1C
%IL-6 from CpG-ISS
0
20
40
60
80
100
120
4000 nM
1000 nM
250 nM
62.5 nM
15 nM
ODN Concentration
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
Ctrl-ODN
CpG-ISS


FIG. 2B Rat Body Weight
% Weight gain/loss
days post 1st injection
pre 1 3 4 6 7 9
115 110 105 100 95 90 85 80


FIG. 2D Rat Body Weight
% Weight gain/loss
days post 1st injection
Pre 1 3 6 7 9 10
115 110 105 100 95 90 85 80 75


FIG. 2A Rat Body Weight
Total weight in grams
days post 1st injection
pre 1 3 4 6 7 9
250 240 230 220 210 200 190 180 170 160 150
PBS
SEQ ID NO:42 (100mpk)
SEQ ID NO:42 (10mpk)
SEQ ID NO:109 (100mpk)
SEQ ID NO:109 (10mpk)


FIG. 2C Rat Body Weight
Total weight in grams
days post 1st injection
Pre 1 3 6 7 9 10
240 230 220 210 200 190 180 170 160 150
Saline
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144

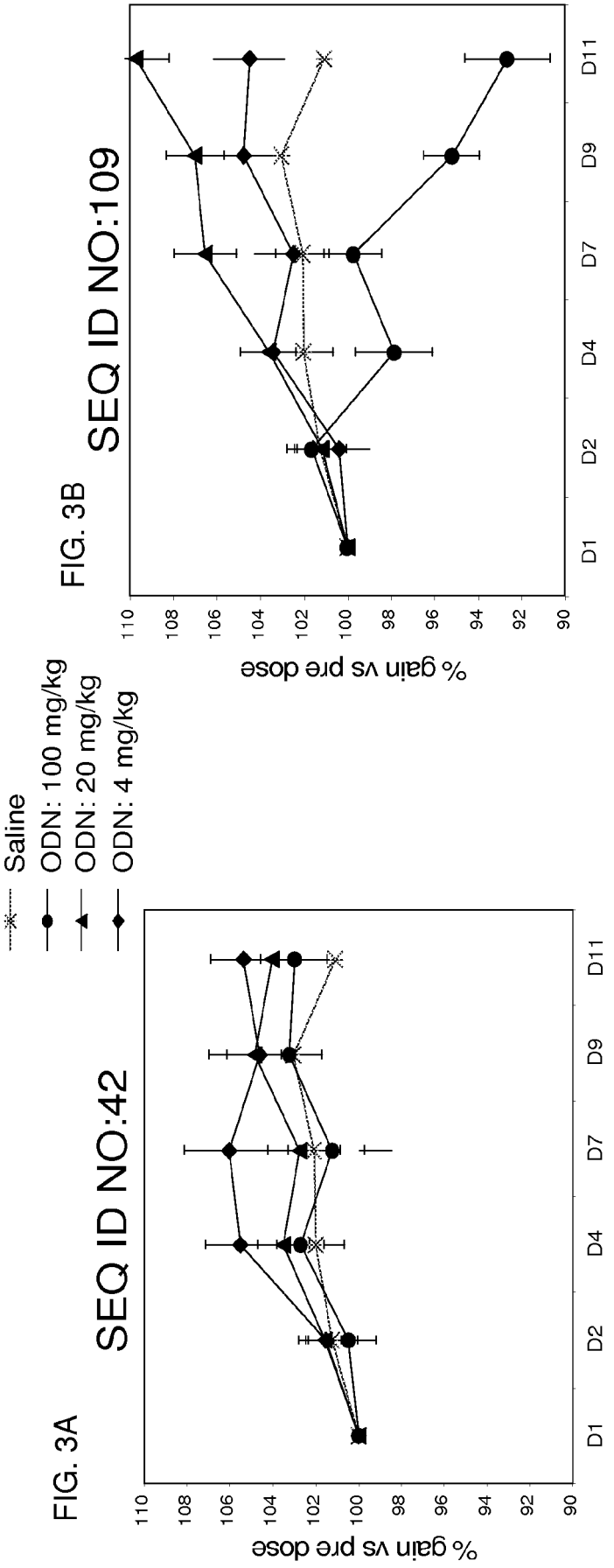

FIG. 3A
SEQ ID NO:42
Saline
ODN: 100 mg/kg
ODN: 20 mg/kg
ODN: 4 mg/kg
% gain vs pre dose
110
108
106
104
102
100
98
96
94
92
90
D1
D2
D4
D7
D9
D11

FIG. 3B
SEQ ID NO:109
% gain vs pre dose
110
108
106
104
102
100
98
96
94
92
90
D1
D2
D4
D7
D9
D11

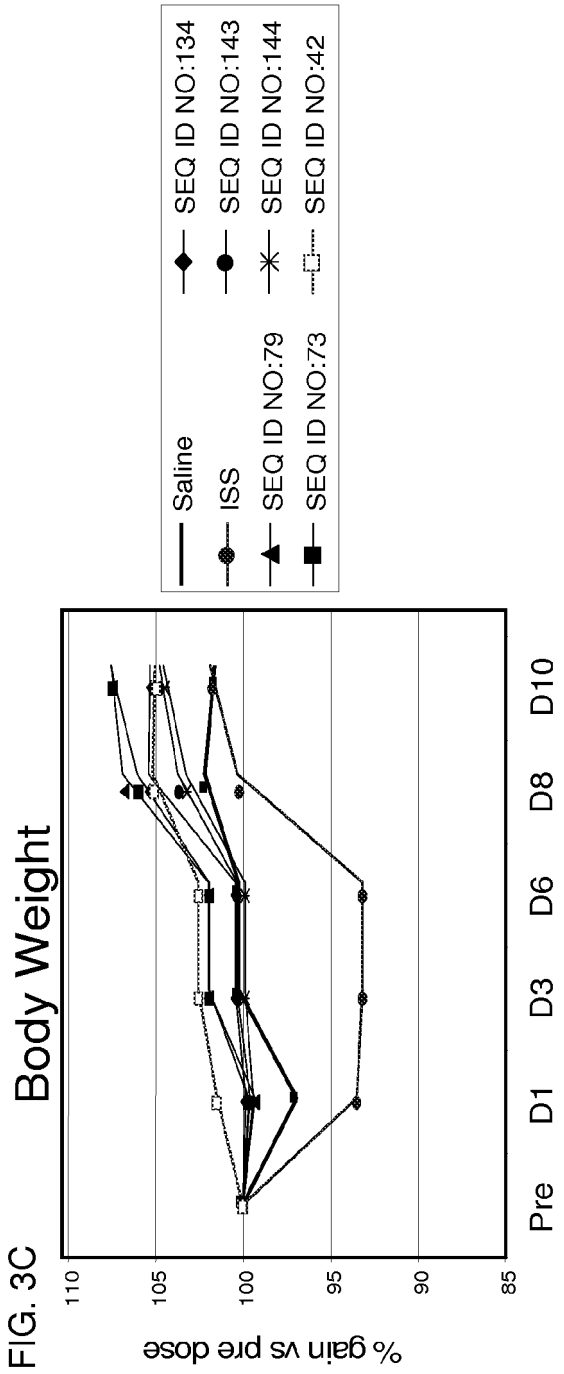

FIG. 3C
Body Weight
Saline
ISS
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
SEQ ID NO:42
% gain vs pre dose
110
105
100
95
90
85
Pre
D1
D3
D6
D8
D10

FIG. 4A

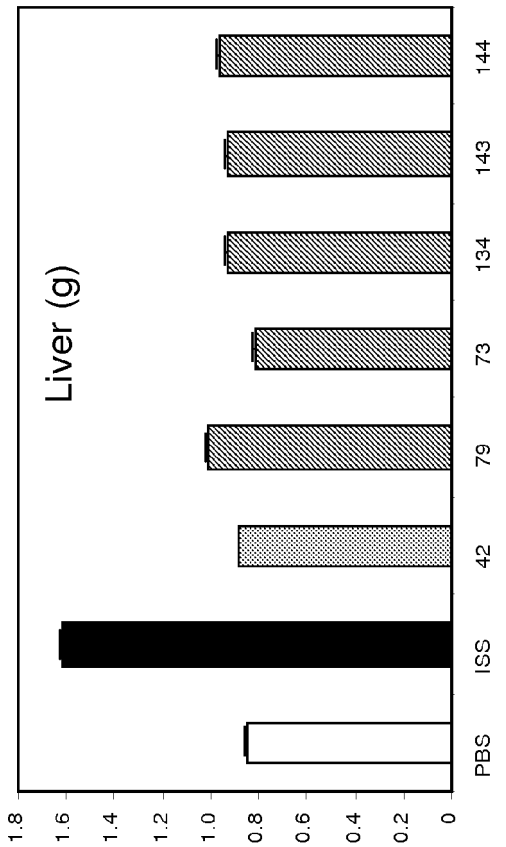


FIG. 4B

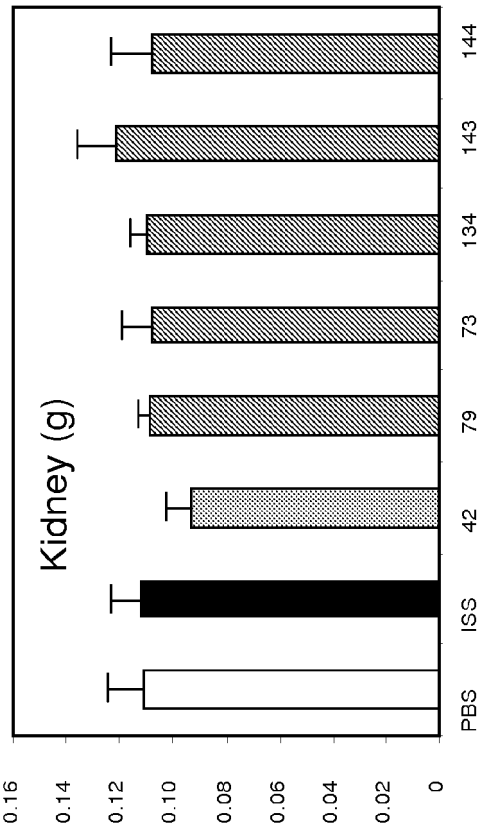


FIG. 4C

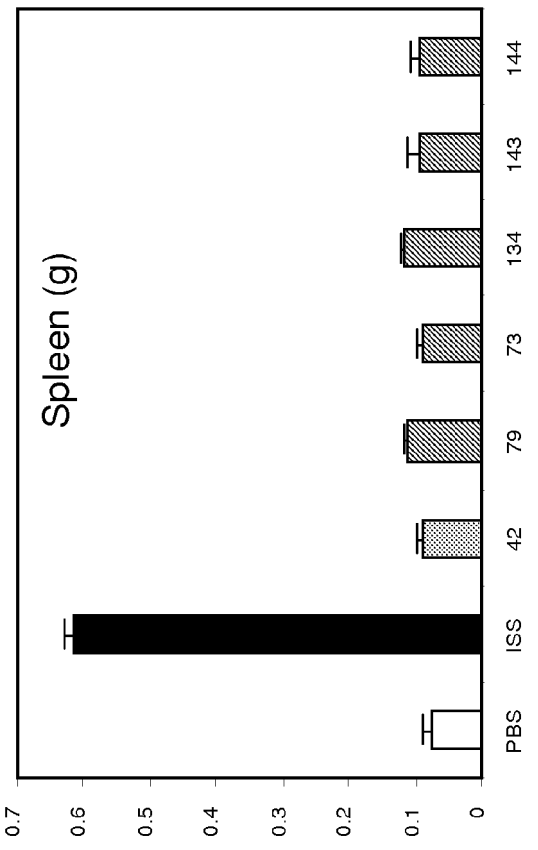
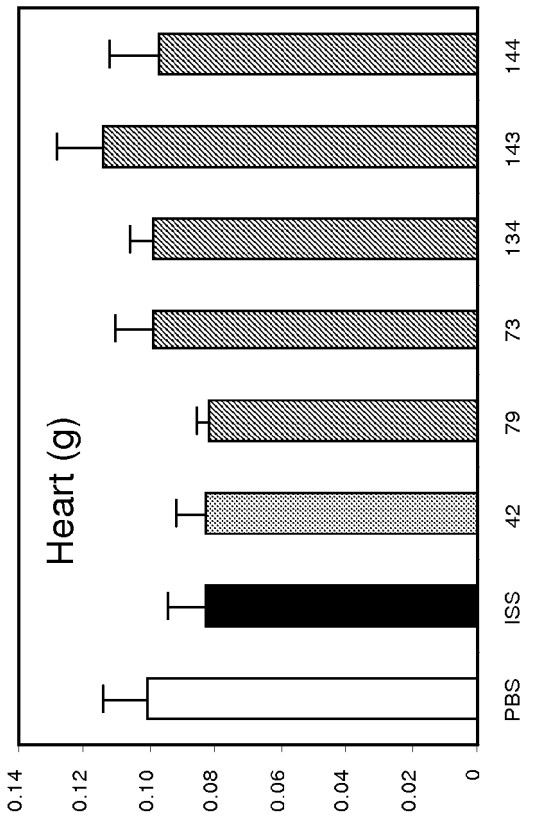
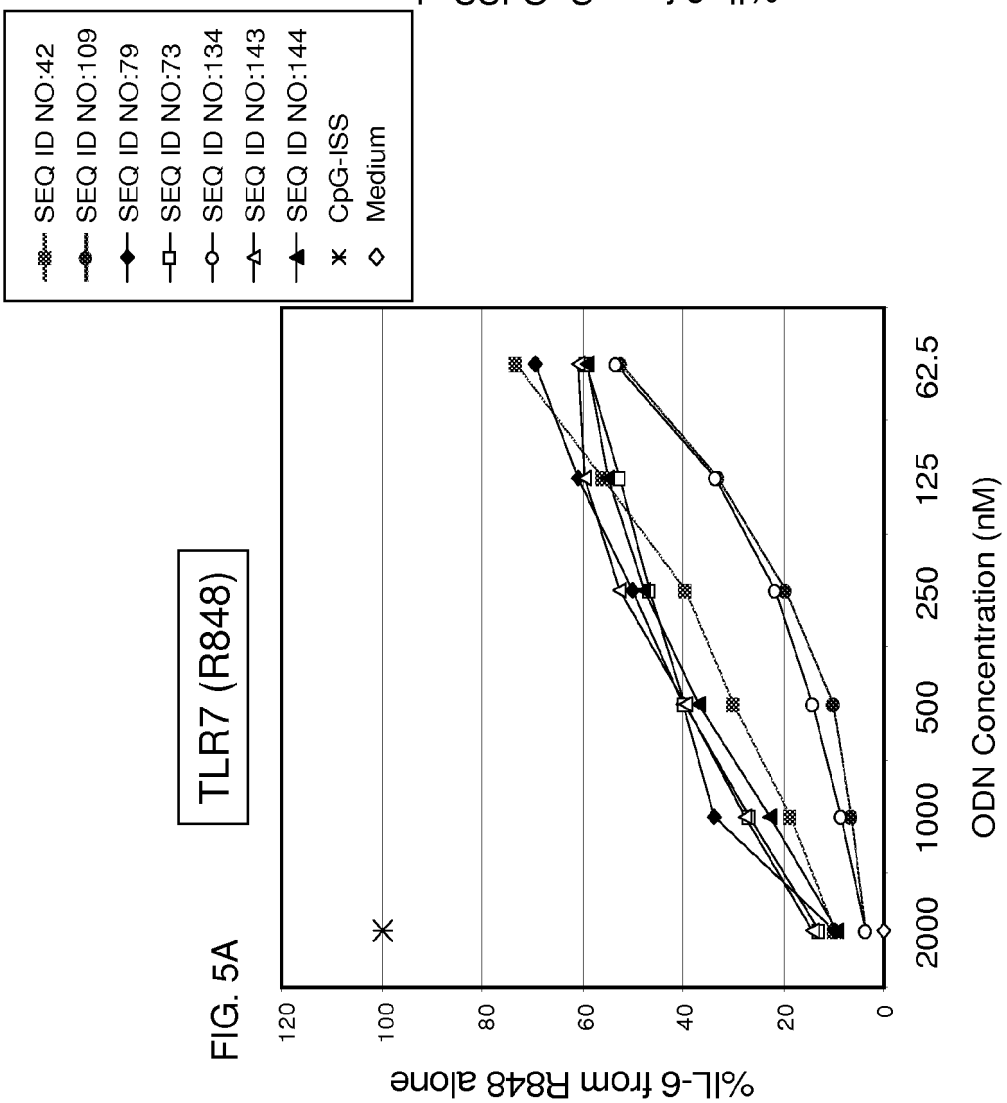
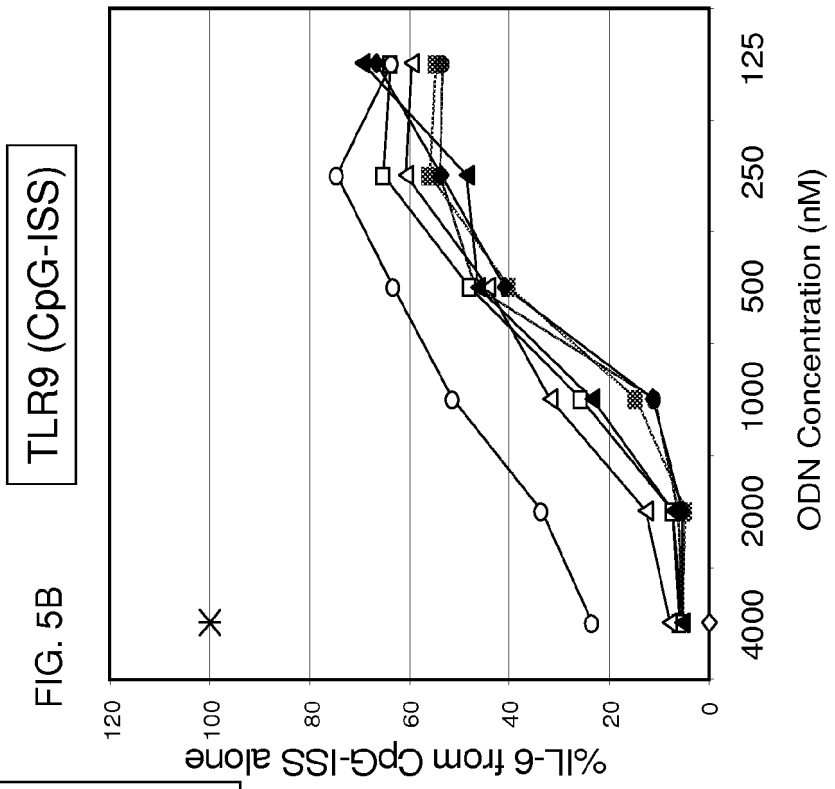
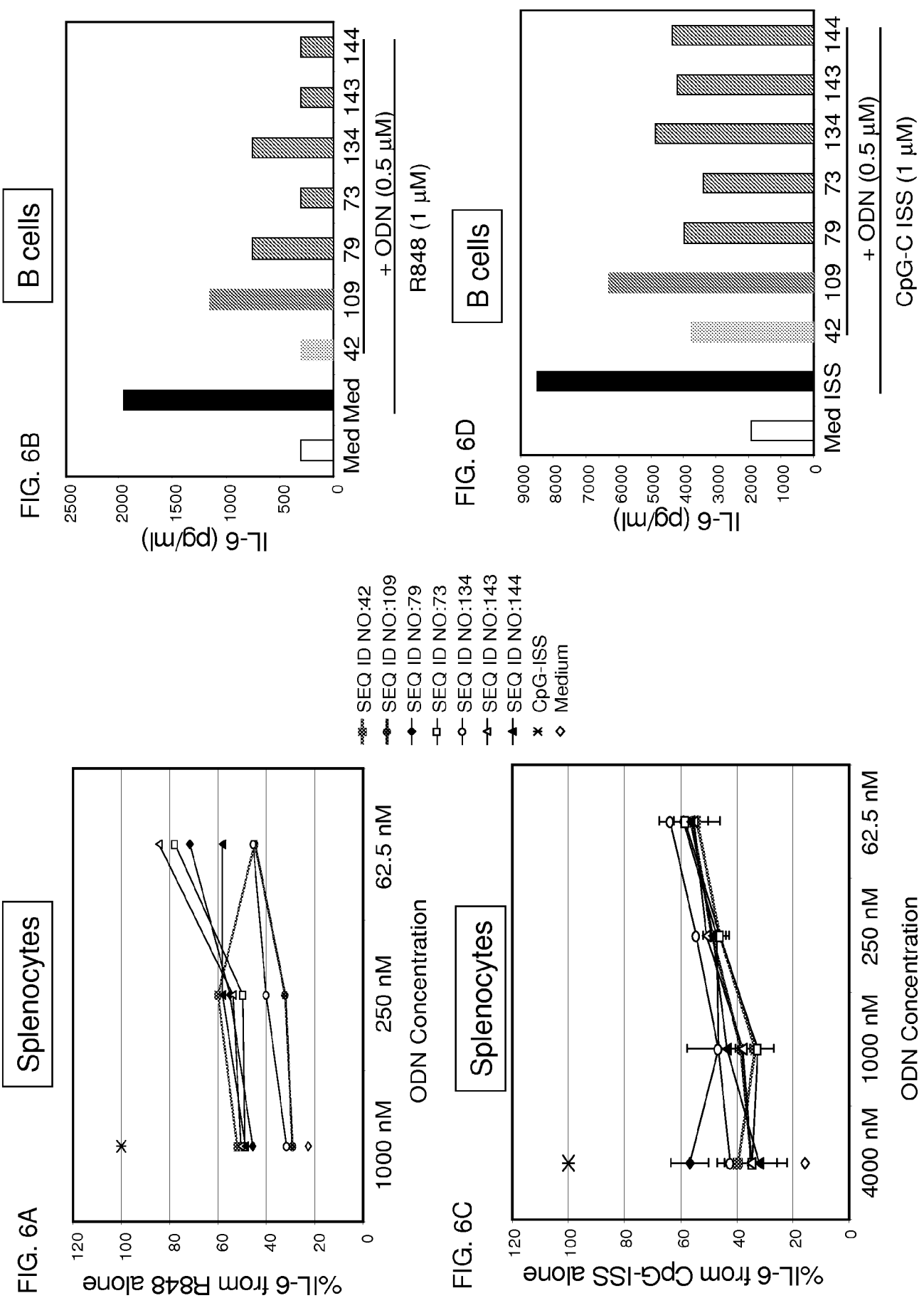


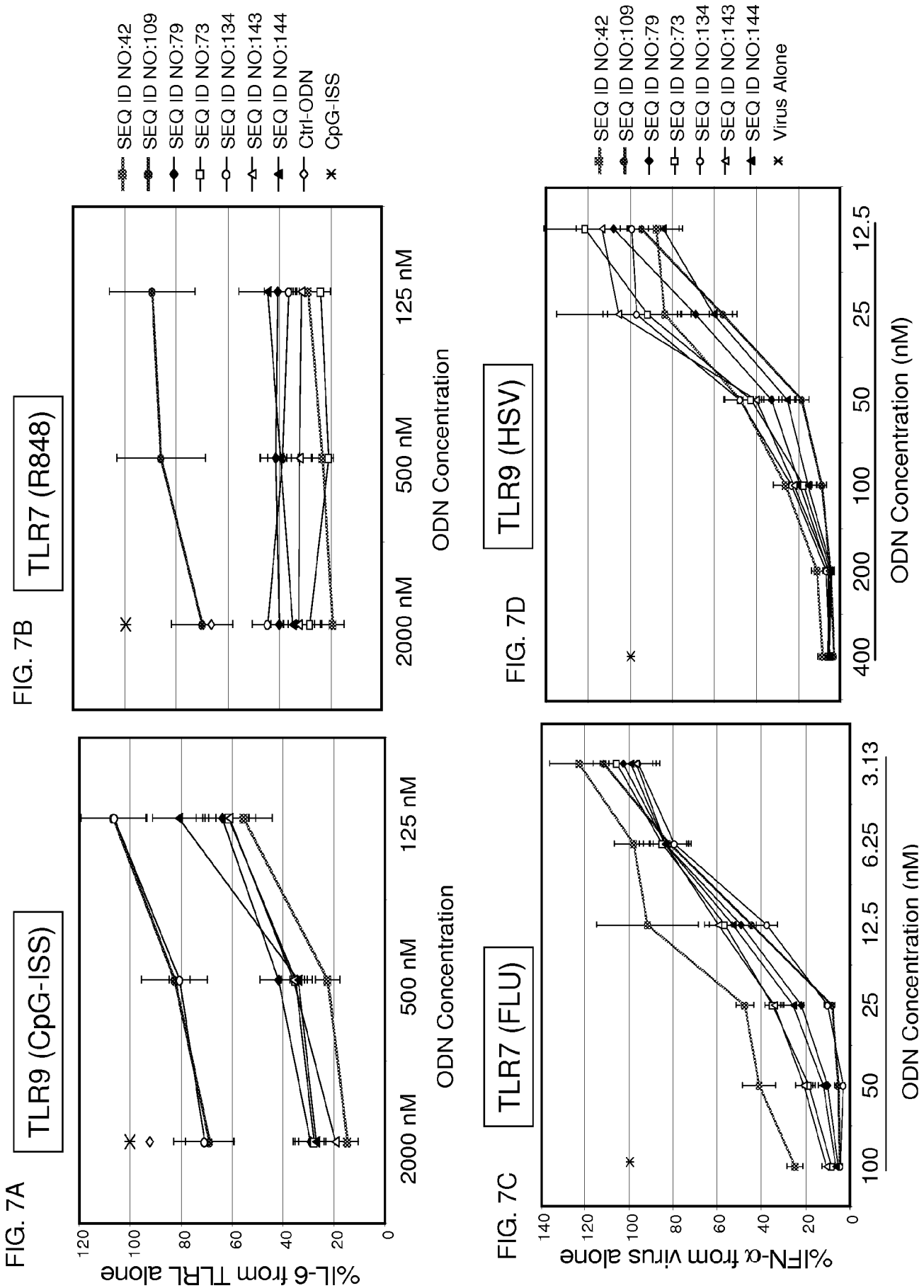
FIG. 4D

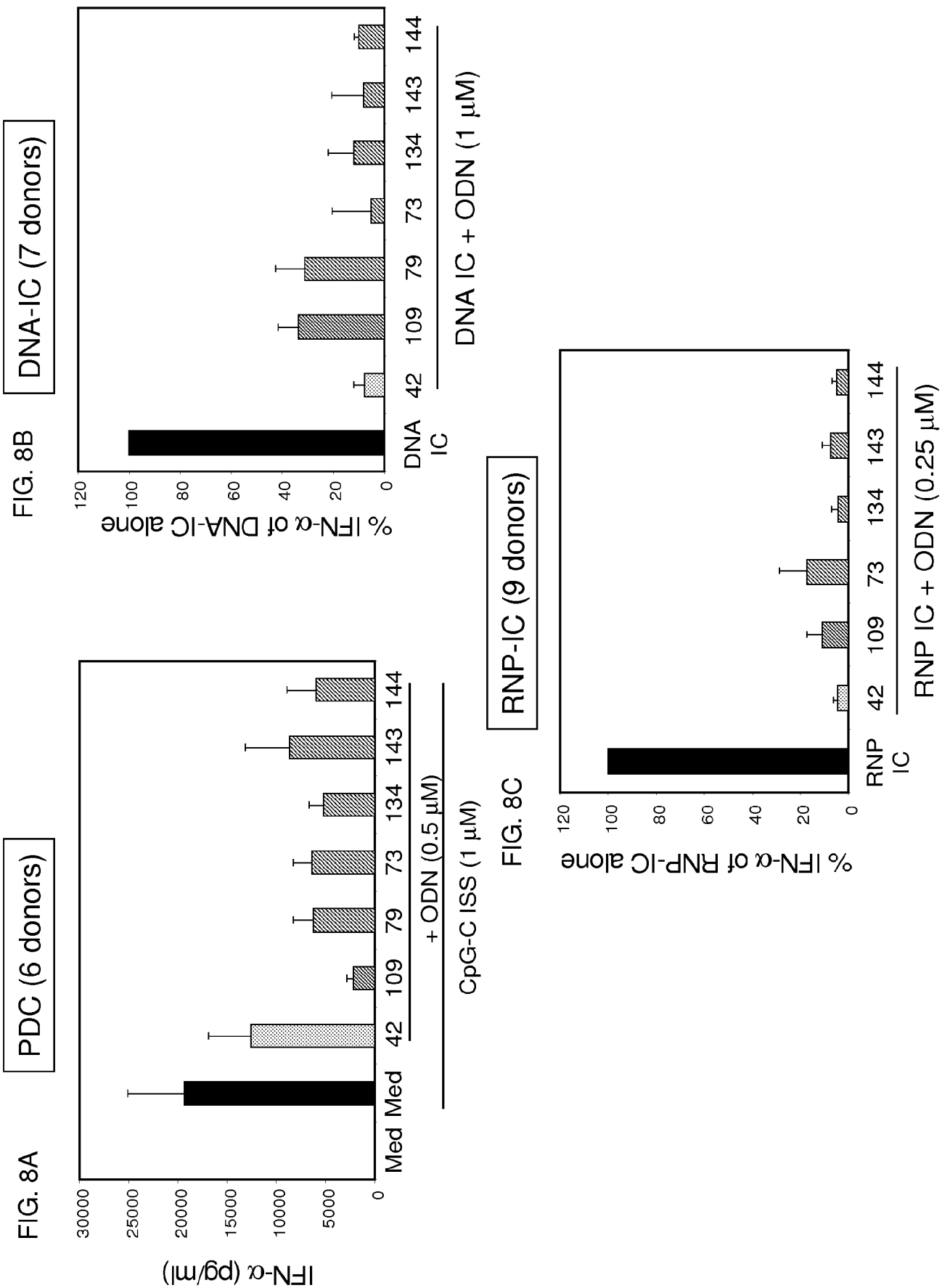


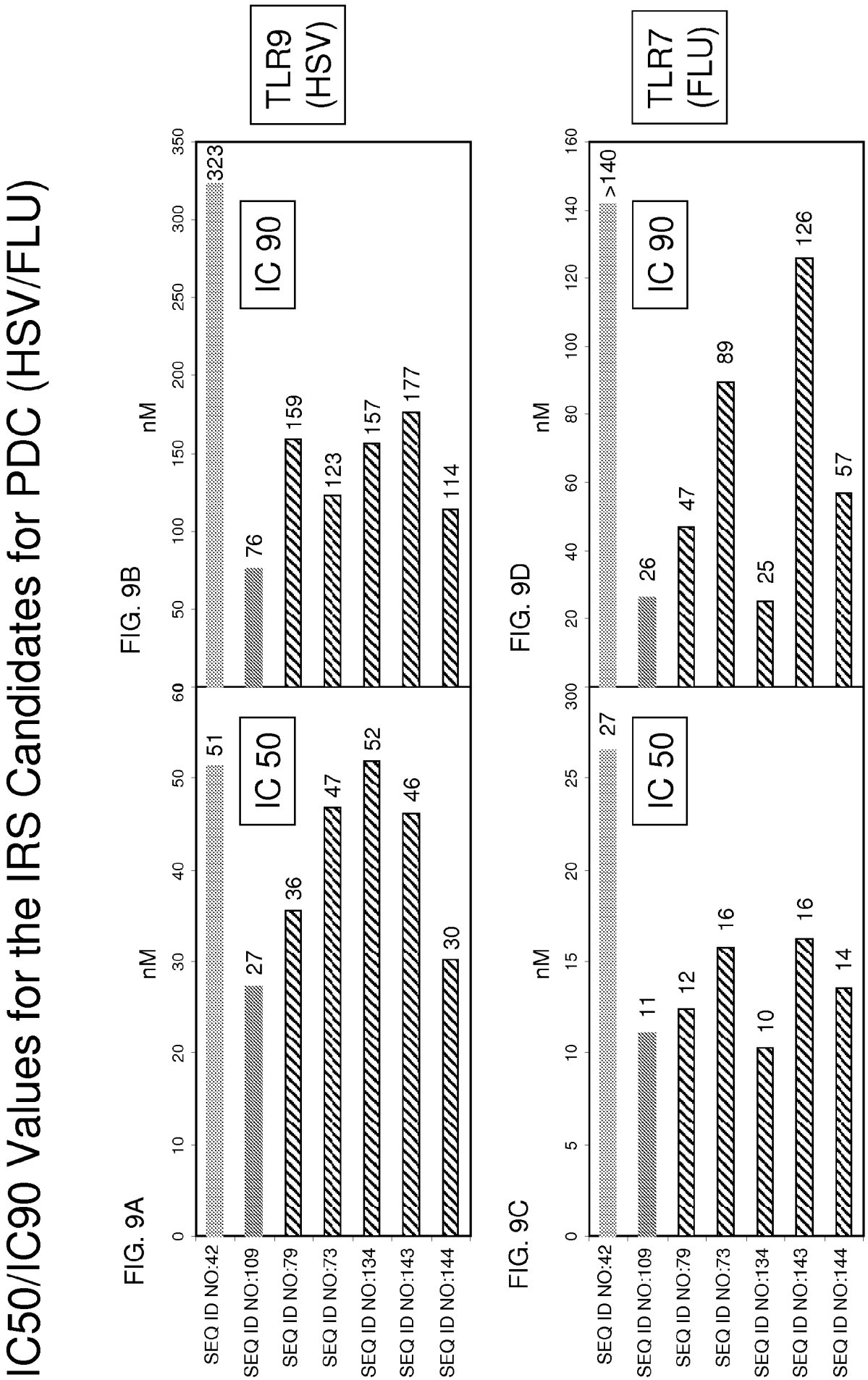

FIG. 5A
TLR7 (R848)
%IL-6 from R848 alone
ODN Concentration (nM)
0
20
40
60
80
100
120
2000
1000
500
250
125
62.5
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
CpG-ISS
Medium


FIG. 5B
TLR9 (CpG-ISS)
%IL-6 from CpG-ISS alone
ODN Concentration (nM)
0
20
40
60
80
100
120
4000
2000
1000
500
250
125


FIG. 6A
Splenocytes
%IL-6 from R848 alone
ODN Concentration
1000 nM
250 nM
62.5 nM
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
CpG-ISS
Medium
FIG. 6B
B cells
IL-6 (pg/ml)
Med Med 42 109 79 73 134 143 144
+ ODN (0.5 µM)
R848 (1 µM)
FIG. 6C
Splenocytes
%IL-6 from CpG-ISS alone
ODN Concentration
4000 nM
1000 nM
250 nM
62.5 nM
FIG. 6D
B cells
IL-6 (pg/ml)
Med ISS 42 109 79 73 134 143 144
+ ODN (0.5 µM)
CpG-C ISS (1 µM)


FIG. 7A
TLR9 (CpG-ISS)
%IL-6 from TLRL alone
120
100
80
60
40
20
0
2000 nM
500 nM
125 nM
ODN Concentration
FIG. 7B
TLR7 (R848)
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
Ctrl-ODN
CpG-ISS
2000 nM
500 nM
125 nM
ODN Concentration
FIG. 7C
TLR7 (FLU)
%IFN-α from virus alone
140
120
100
80
60
40
20
0
100
50
25
12.5
6.25
3.13
ODN Concentration (nM)
FIG. 7D
TLR9 (HSV)
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
Virus Alone
400
200
100
50
25
12.5
ODN Concentration (nM)


FIG. 8A
PDC (6 donors)
IFN-α (pg/ml)
30000
25000
20000
15000
10000
5000
0
Med Med 42 109 79 73 134 143 144
+ ODN (0.5 μM)
CpG-C ISS (1 μM)
FIG. 8B
DNA-IC (7 donors)
% IFN-α of DNA-IC alone
120
100
80
60
40
20
0
DNA 42 109 79 73 134 143 144
IC
DNA IC + ODN (1 μM)
FIG. 8C
RNP-IC (9 donors)
% IFN-α of RNP-IC alone
120
100
80
60
40
20
0
RNP 42 109 73 134 143 144
IC
RNP IC + ODN (0.25 μM)


IC50/IC90 Values for the IRS Candidates for PDC (HSV/FLU)
FIG. 9A
nM
IC 50
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
51
27
36
47
52
46
30
FIG. 9B
nM
IC 90
TLR9 (HSV)
323
76
159
123
157
177
114
FIG. 9C
nM
IC 50
27
11
12
16
10
16
14
FIG. 9D
nM
IC 90
TLR7 (FLU)
>140
26
47
89
25
126
57

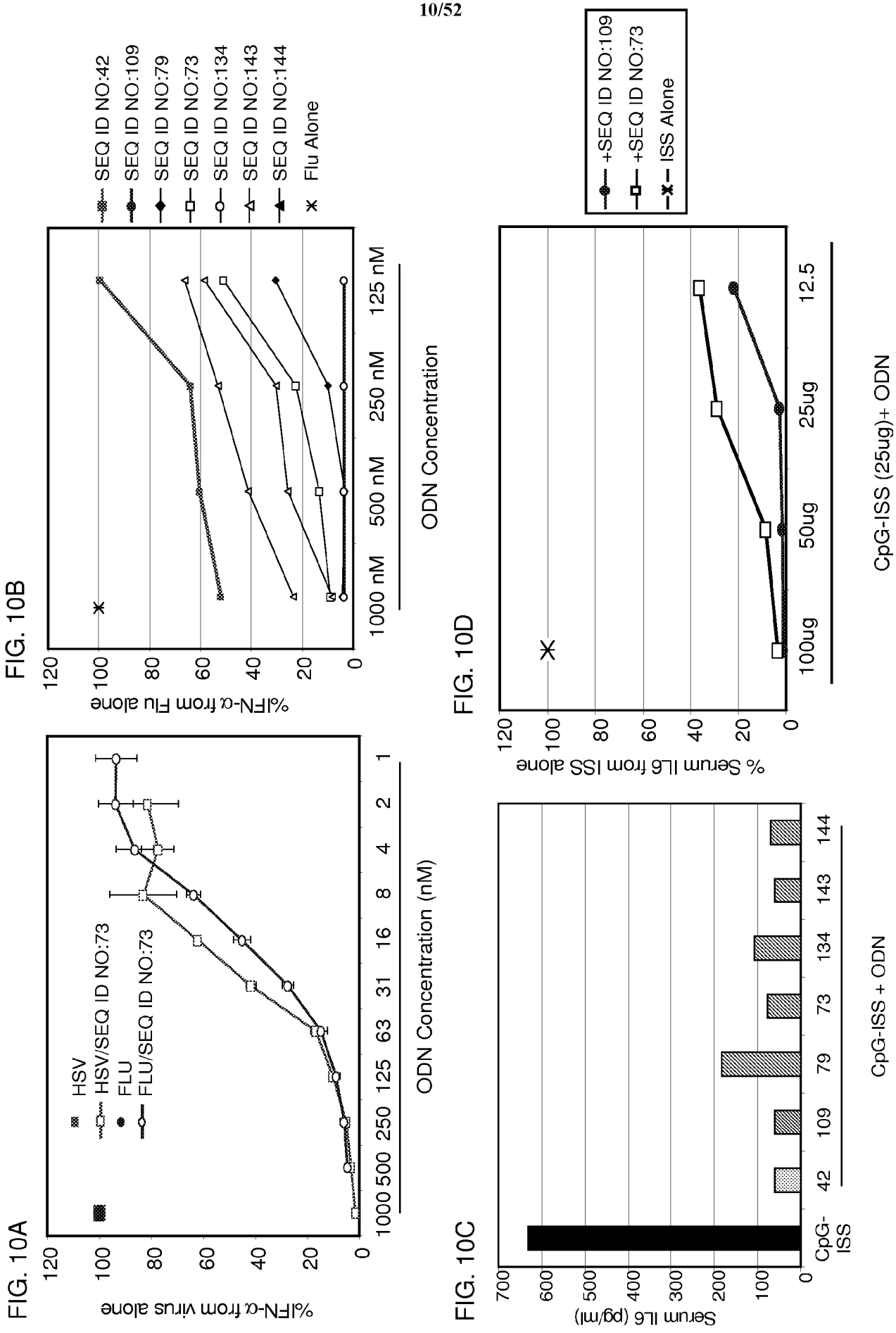

FIG. 10A
%IFN-α from virus alone
120
100
80
60
40
20
0
HSV
HSV/SEQ ID NO:73
FLU
FLU/SEQ ID NO:73
1000 500 250 125 63 31 16 8 4 2 1
ODN Concentration (nM)
FIG. 10B
%IFN-α from Flu alone
120
100
80
60
40
20
0
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
Flu Alone
1000 nM 500 nM 250 nM 125 nM
ODN Concentration
FIG. 10C
Serum IL6 (pg/ml)
700
600
500
400
300
200
100
0
CpG-ISS
42 109 79 73 134 143 144
CpG-ISS + ODN
FIG. 10D
% Serum IL6 from ISS alone
120
100
80
60
40
20
0
+SEQ ID NO:109
+SEQ ID NO:73
ISS Alone
100ug 50ug 25ug 12.5
CpG-ISS (25ug)+ ODN

FIG. 11A Liver

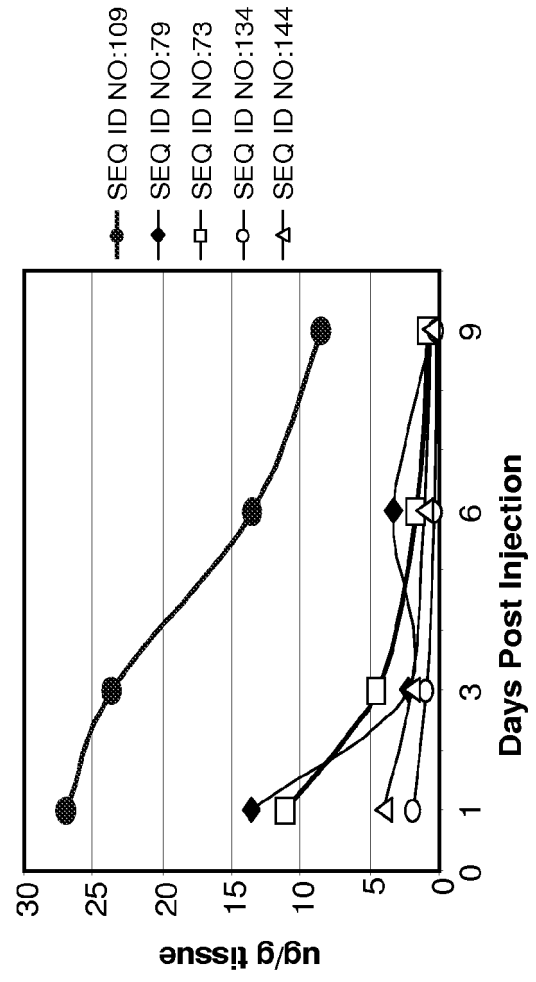


FIG. 11B Kidney

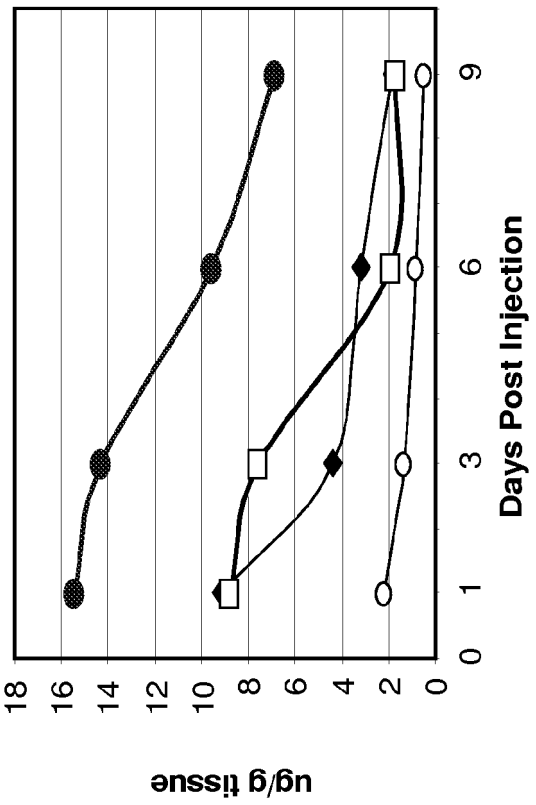


FIG. 11C SEQ ID NO:73

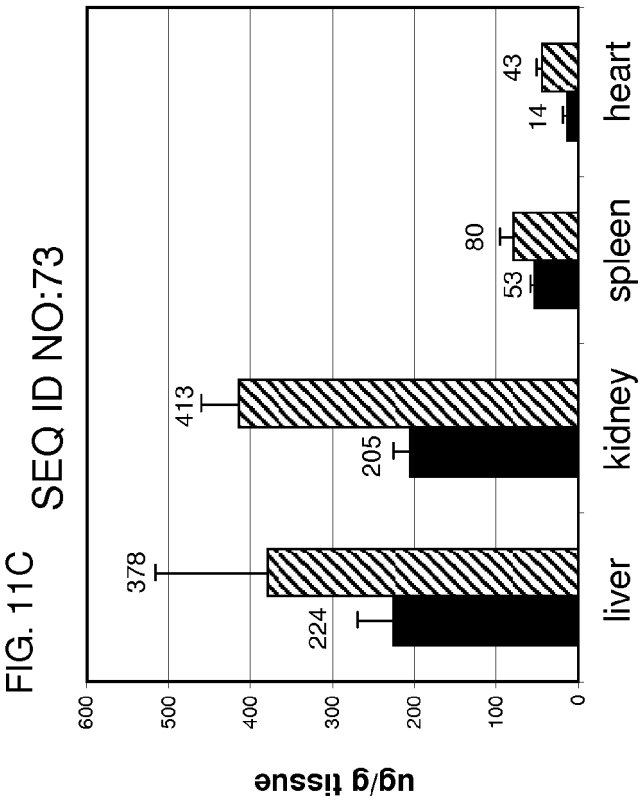
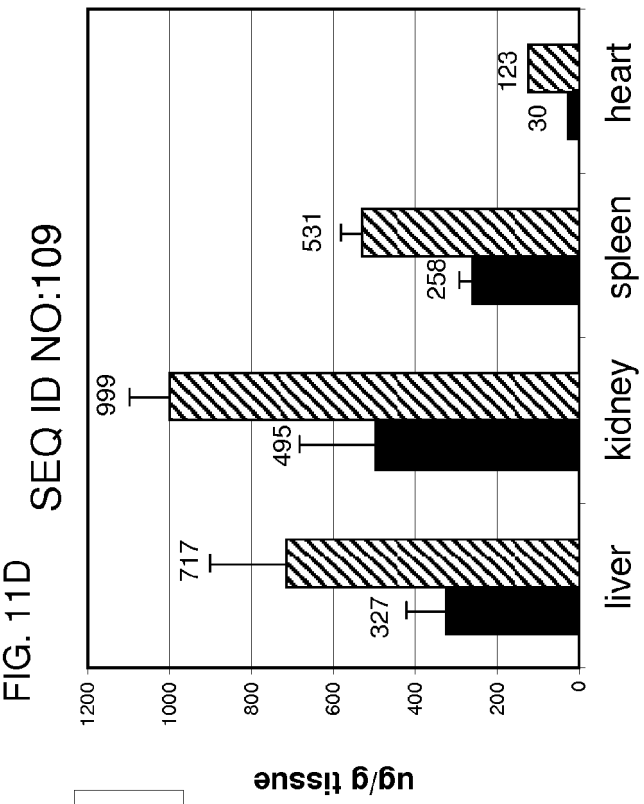


FIG. 11D SEQ ID NO:109



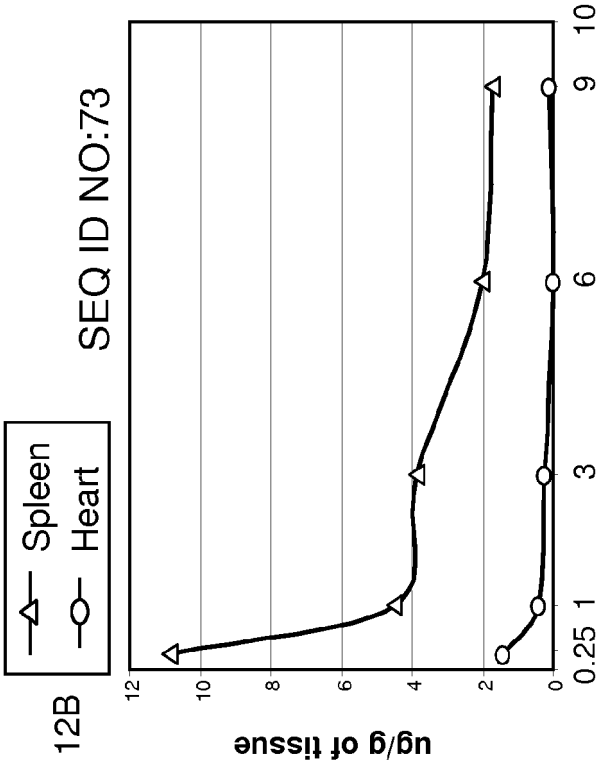


FIG. 12B

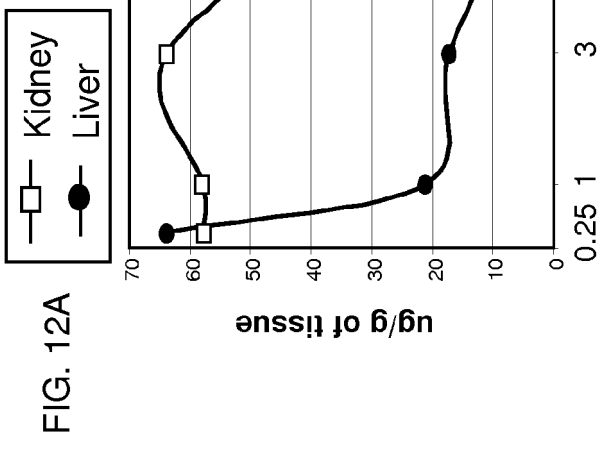


FIG. 12A

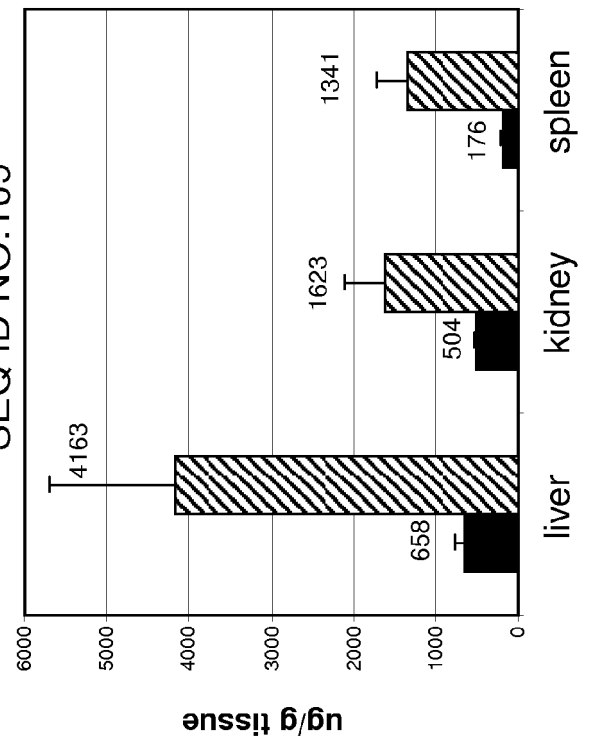


FIG. 12D

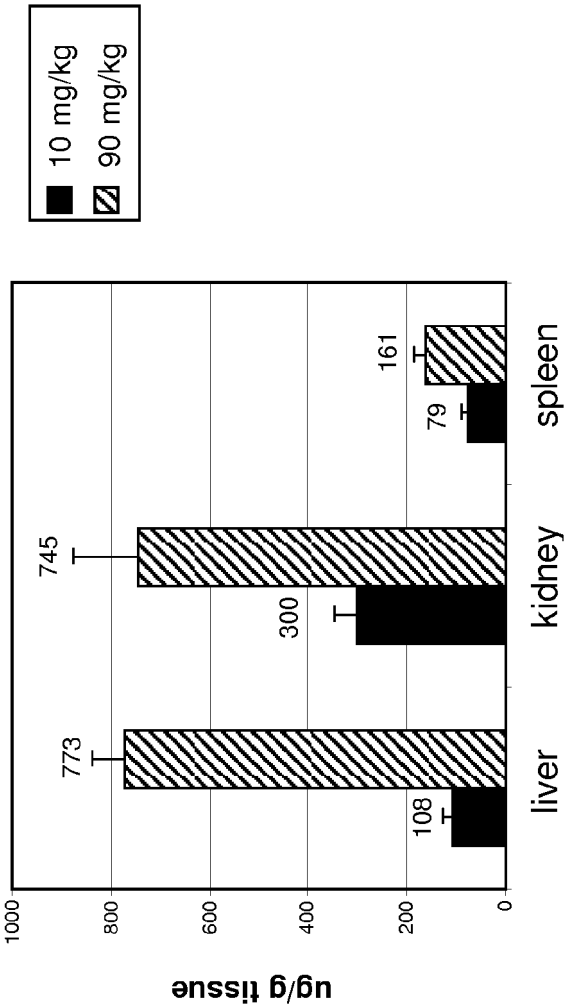
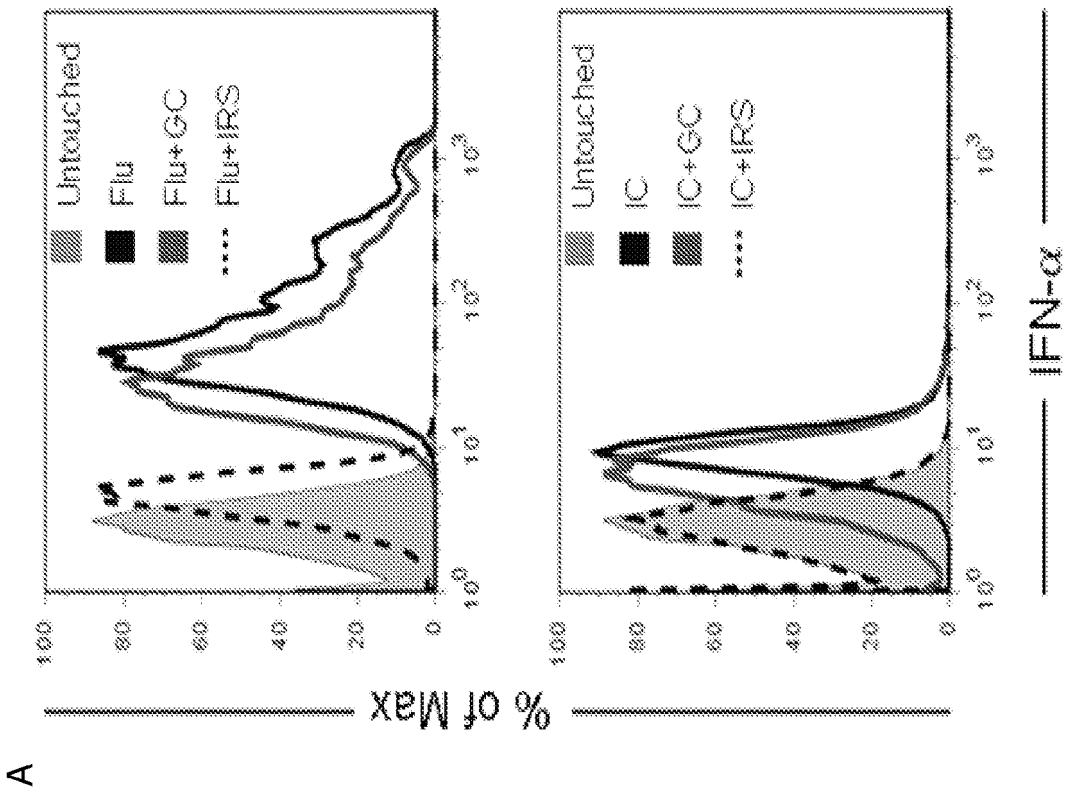


FIG. 12C

FIG. 13


A
% of Max
Untouched
Flu
Flu+GC
Flu+IRS
IC
IC+GC
IC+IRS
IFN-α
B
Fold change of IFN Module
Number of circulating PDC/ml
Number of circulating CD14/ml
P=0.0002
ns
ns
p=0.0022
p=0.01
p=0.007
ns
p=0.02
ns
Un-treated
Oral GC 5-10 mg
Oral GC 20-30 mg
IV Pulse

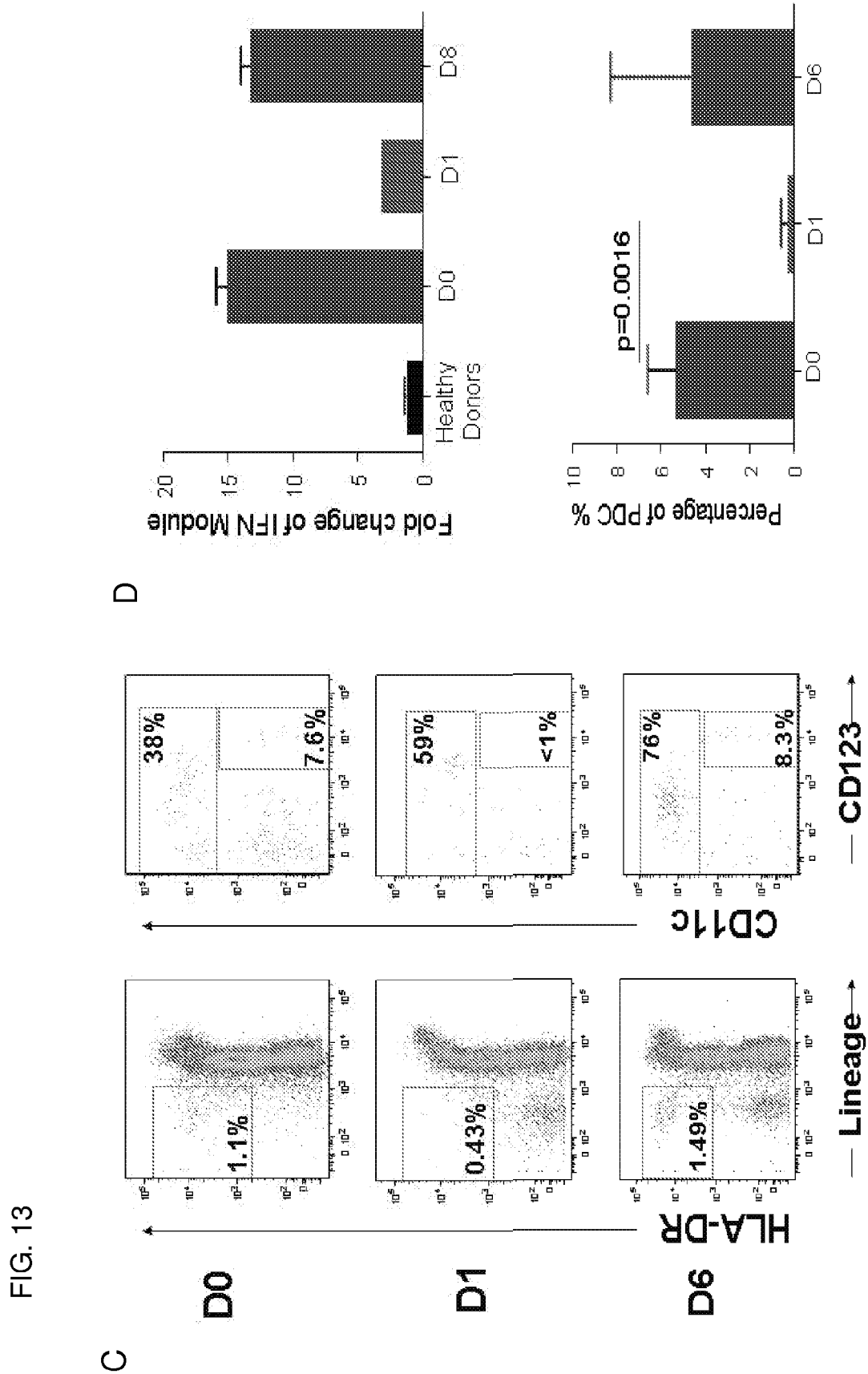

C
D0
D1
D6
HLA-DR
CD11c
Lineage
CD123
1.1%
7.6%
38%
0.43%
59%
<1%
1.49%
76%
8.3%
D
Fold change of IFN Module
Healthy Donors
D0
D1
D8
Percentage of PDC %
p=0.0016
D0
D1
D6

FIG. 13

FIG. 14

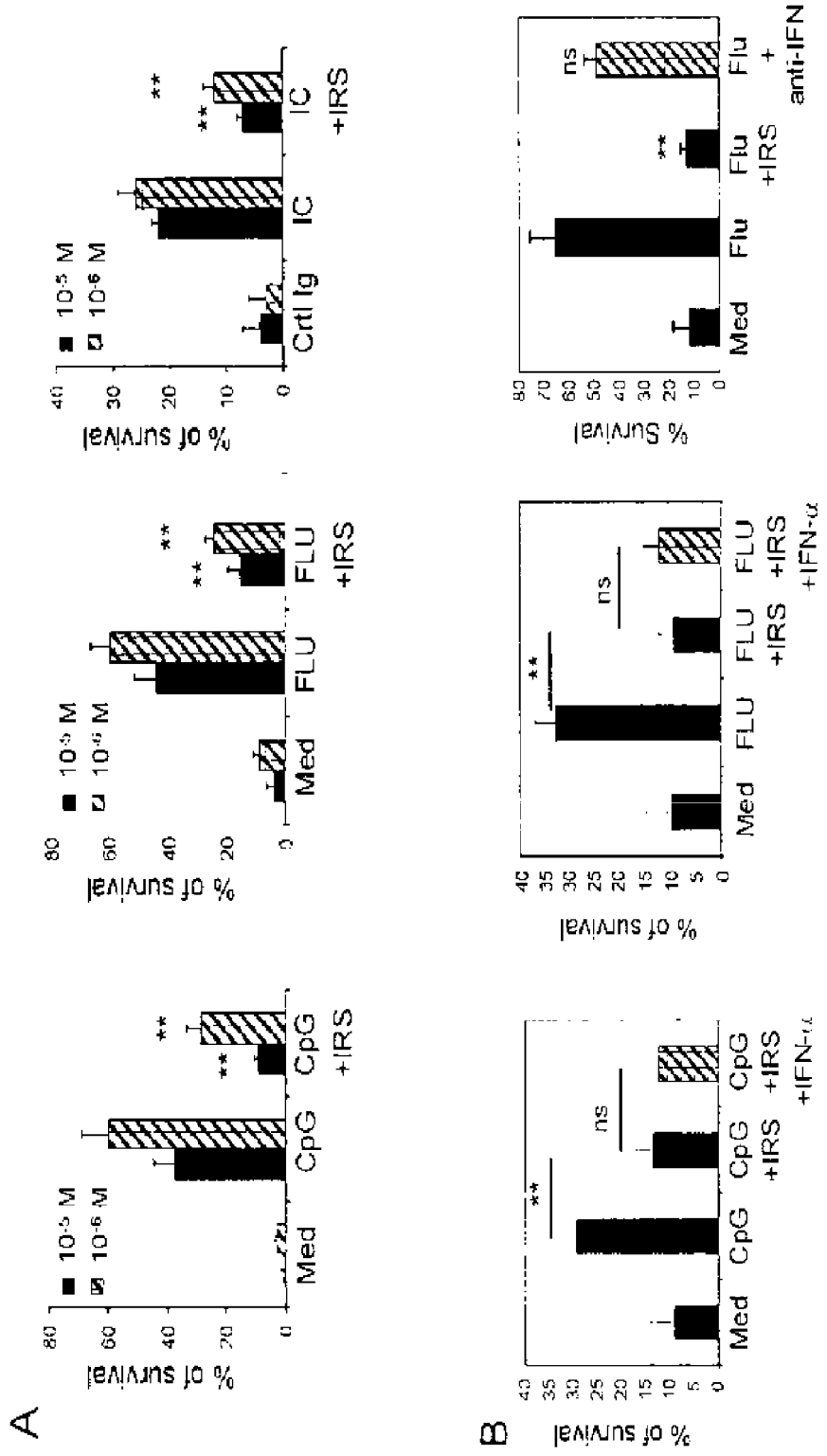

A
B
% of survival
10-5 M
10-6 M
Med
CpG
FLU
IC
Ctrl Ig
Flu
anti-IFN
+IRS
+IFN-α
ns
**

FIG. 14

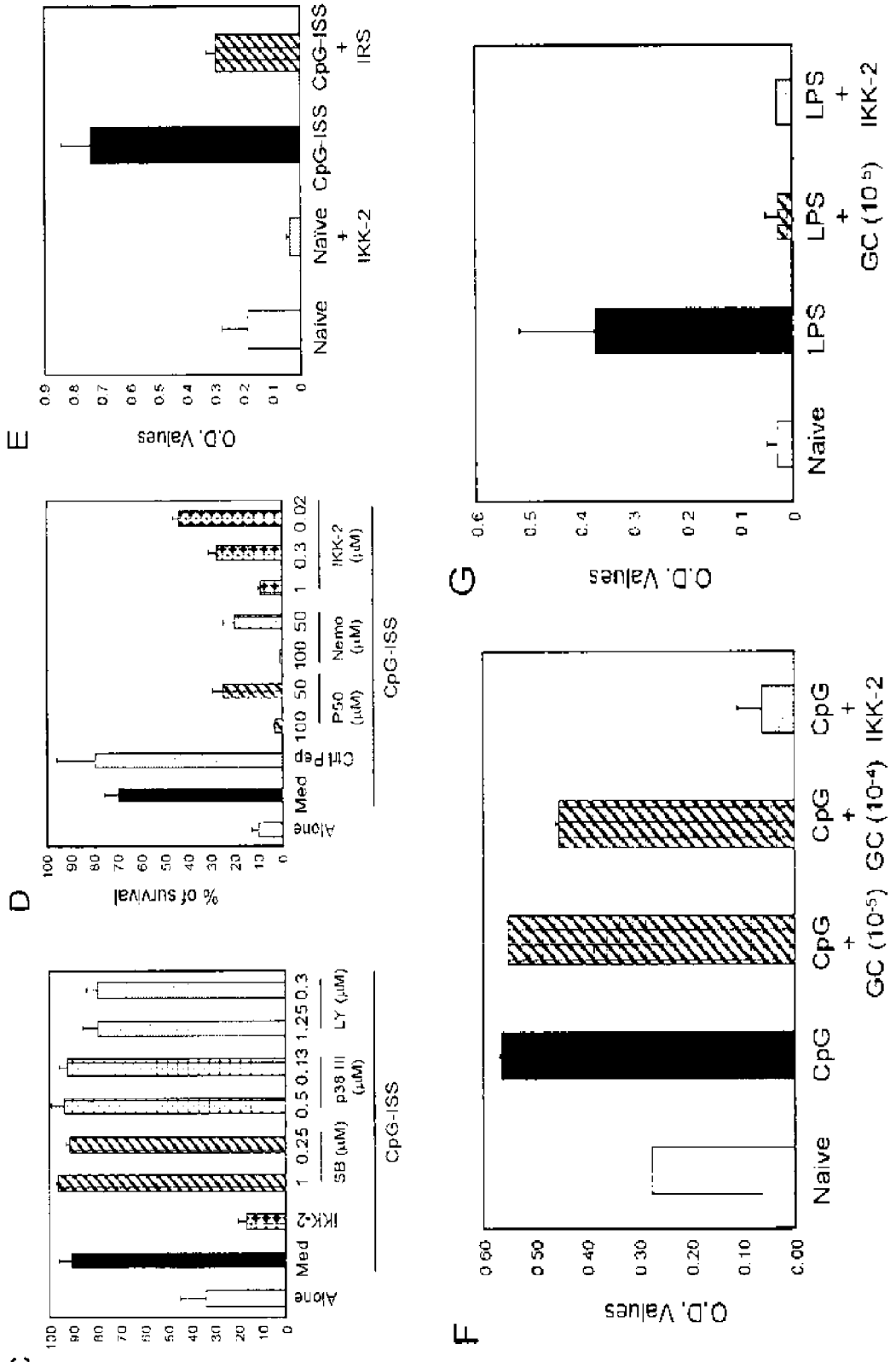

C
% of survival
Alone
Med
IKK-2
SB (μM)
p38 III (μM)
LY (μM)
CpG-ISS
D
% of survival
Alone
Med
Ctrl Pep
P50 (μM)
Nemo (μM)
IKK-2 (μM)
CpG-ISS
E
O.D. Values
Naive
Naive + IKK-2
CpG-ISS
CpG-ISS + IRS
F
O.D. Values
Naive
CpG
CpG + GC (10-5)
CpG + GC (10-4)
CpG + GC (10-5) IKK-2
G
O.D. Values
Naive
LPS
LPS + GC (10-5)
LPS + IKK-2

FIG. 15

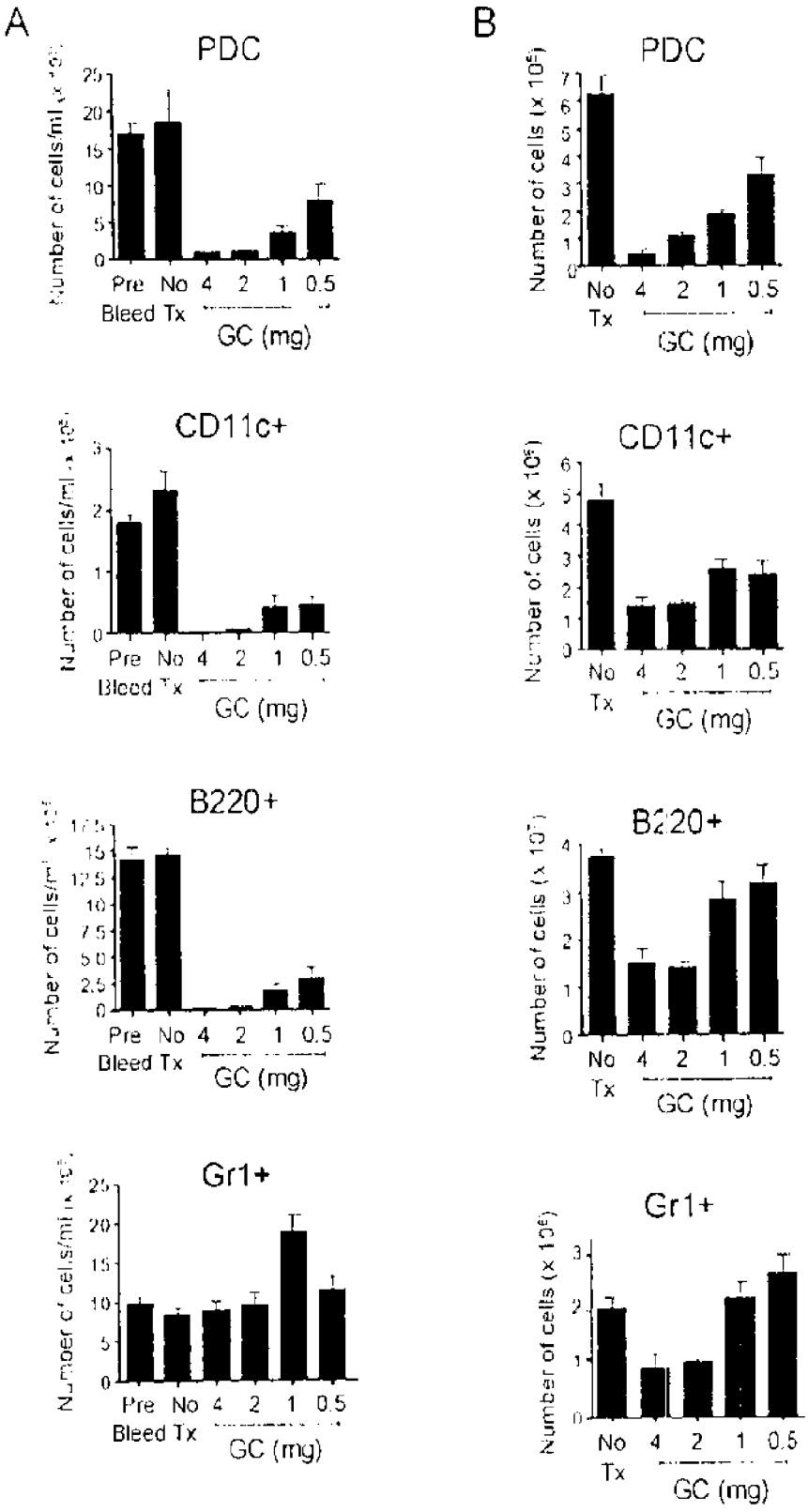

A
PDC
Pre No 4 2 1 0.5
Bleed Tx
GC (mg)
CD11c+
B220+
Gr1+
B
PDC
Number of cells (x 10⁵)
No 4 2 1 0.5
Tx
GC (mg)
CD11c+
B220+
Gr1+

FIG. 15

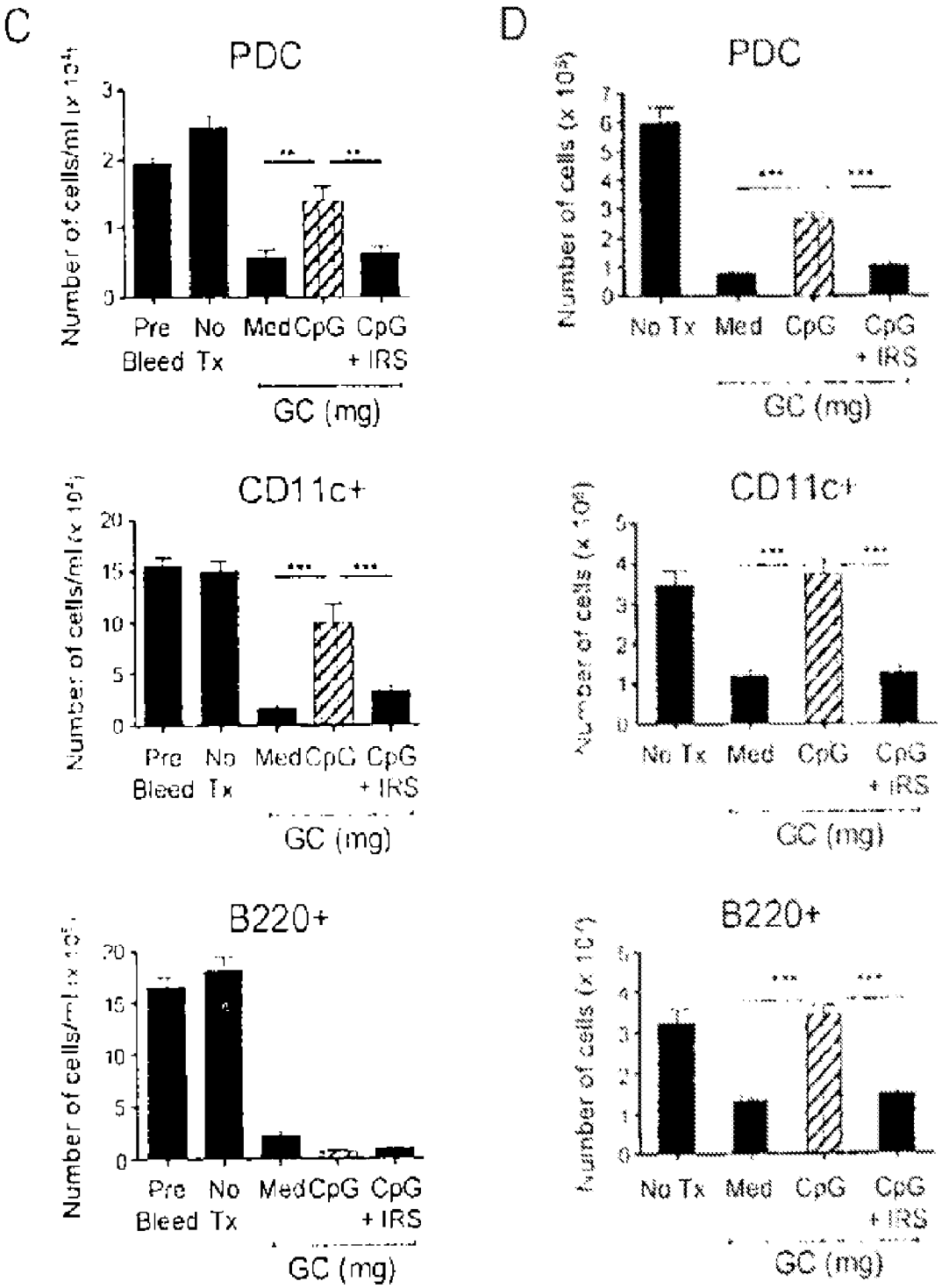

C
PDC
Number of cells/ml (x 10⁴)
Pre Bleed
No Tx
Med
CpG
CpG + IRS
GC (mg)
CD11c+
B220+
D
PDC
Number of cells (x 10⁴)
No Tx
Med
CpG
CpG + IRS
GC (mg)
CD11c+
B220+

FIG. 16

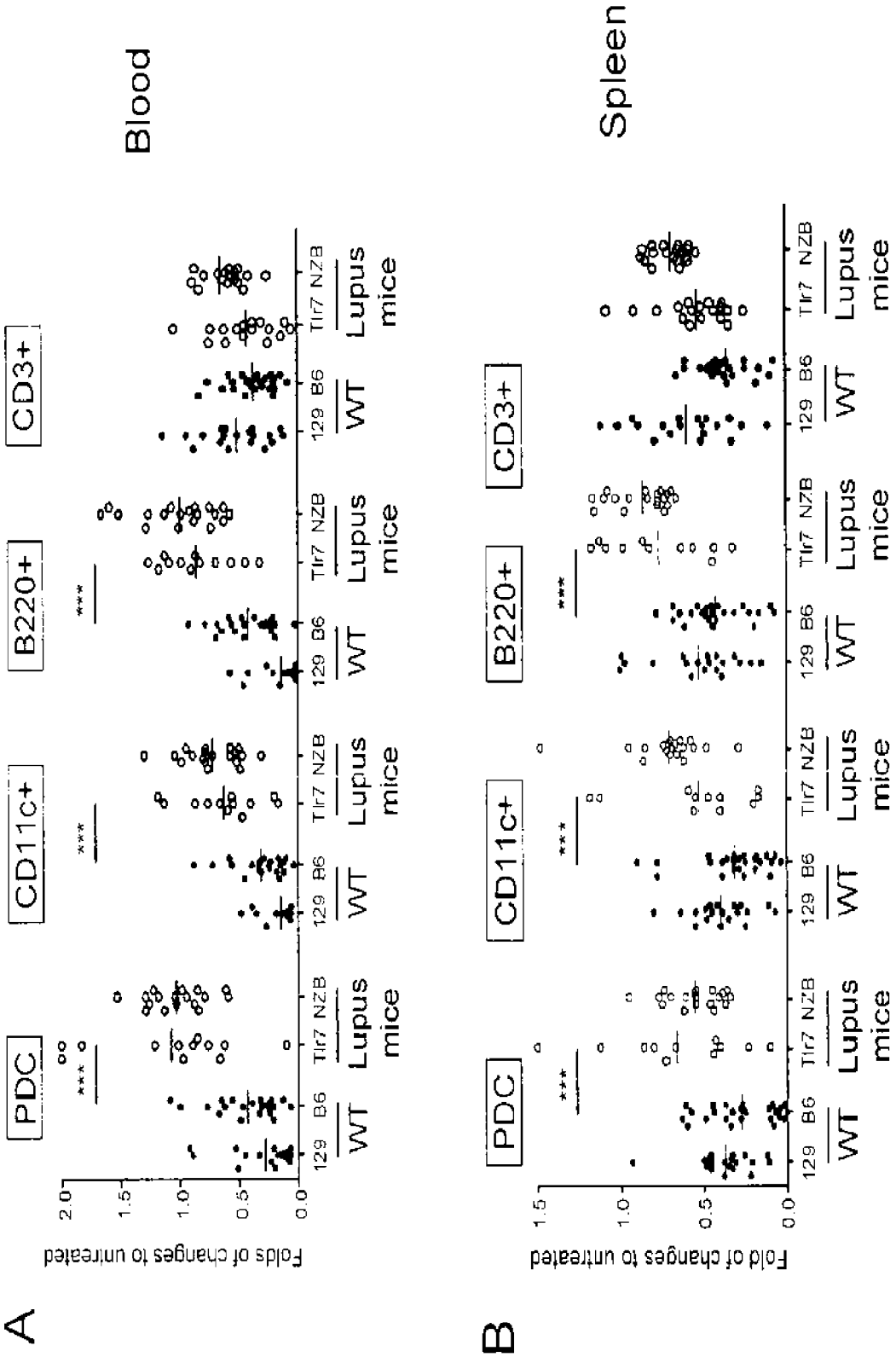
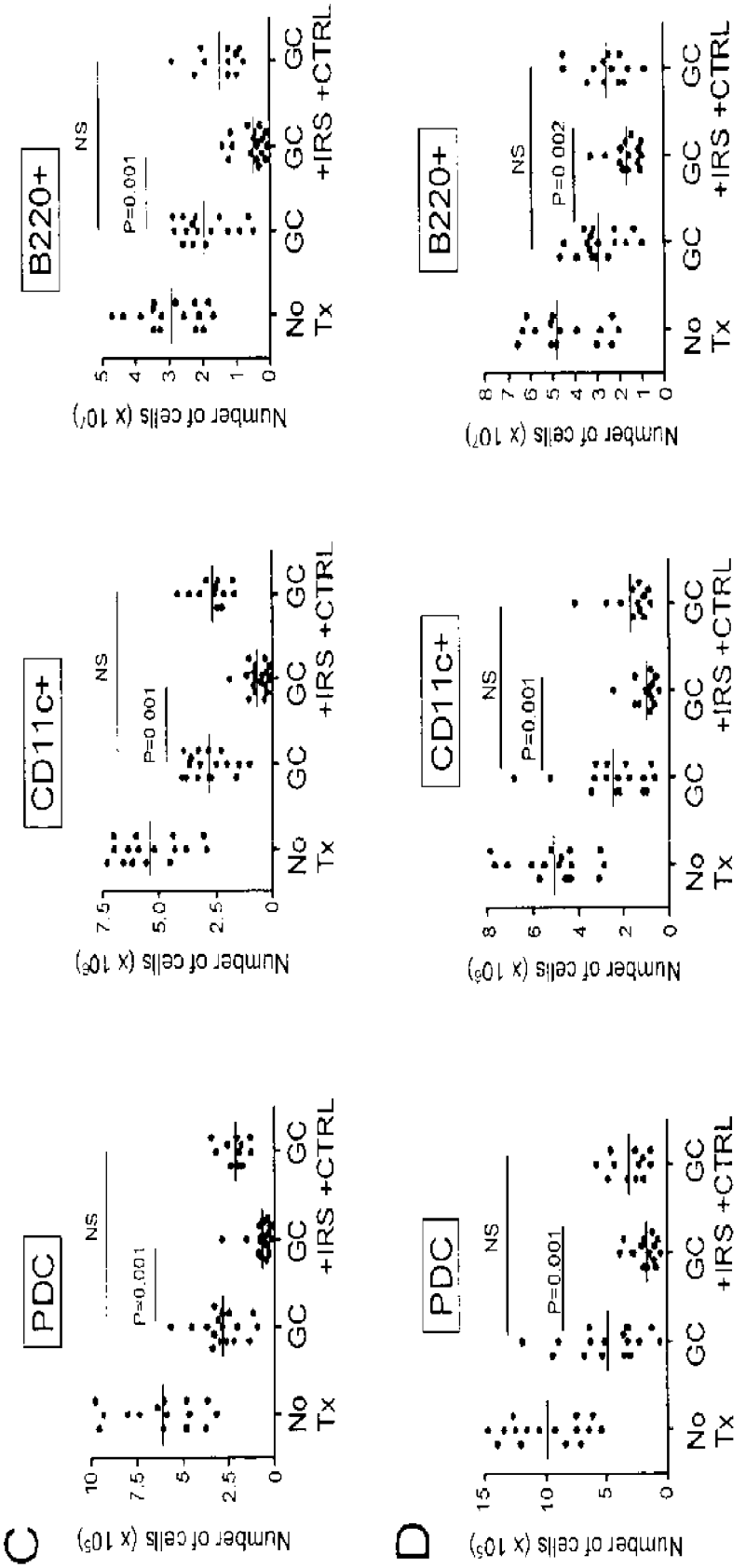

A
Blood
PDC
CD11c+
B220+
CD3+
Folds of changes to untreated
2.0
1.5
1.0
0.5
0.0
***
129 B6 Tlr7 NZB
WT Lupus mice
B
Spleen
Fold of changes to untreated

FIG. 16


C
PDC
Number of cells (x 10⁵)
P=0.001
NS
No Tx
GC +IRS
GC +CTRL
CD11c+
Number of cells (x 10⁶)
P=0.001
NS
B220+
Number of cells (x 10⁷)
P=0.001
NS
D
PDC
Number of cells (x 10⁵)
P=0.001
NS
CD11c+
Number of cells (x 10⁵)
P=0.001
NS
B220+
Number of cells (x 10⁷)
P=0.002
NS

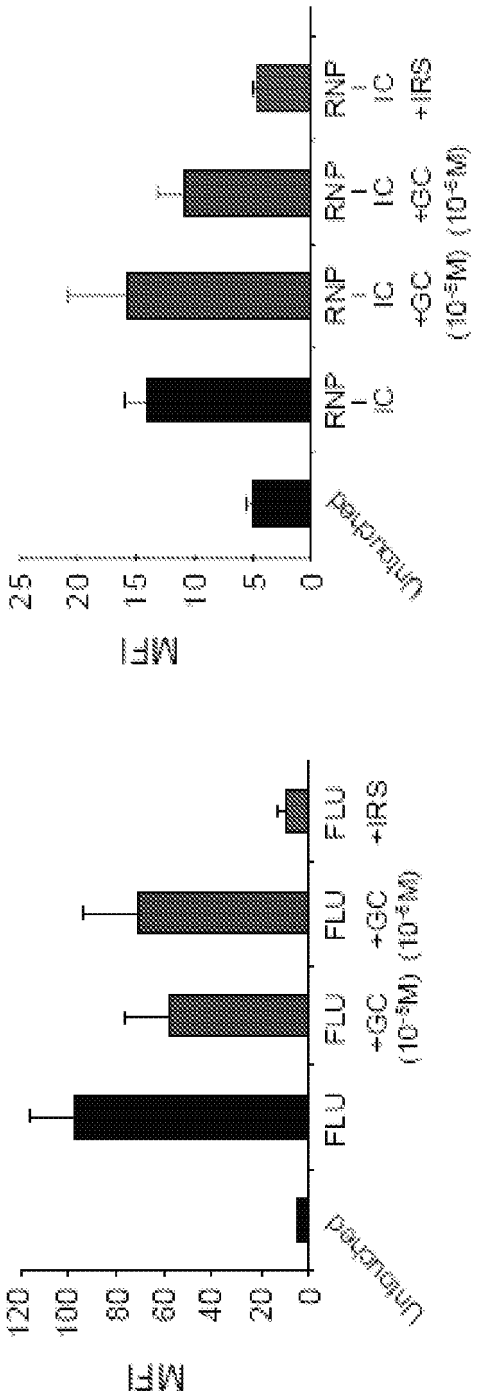
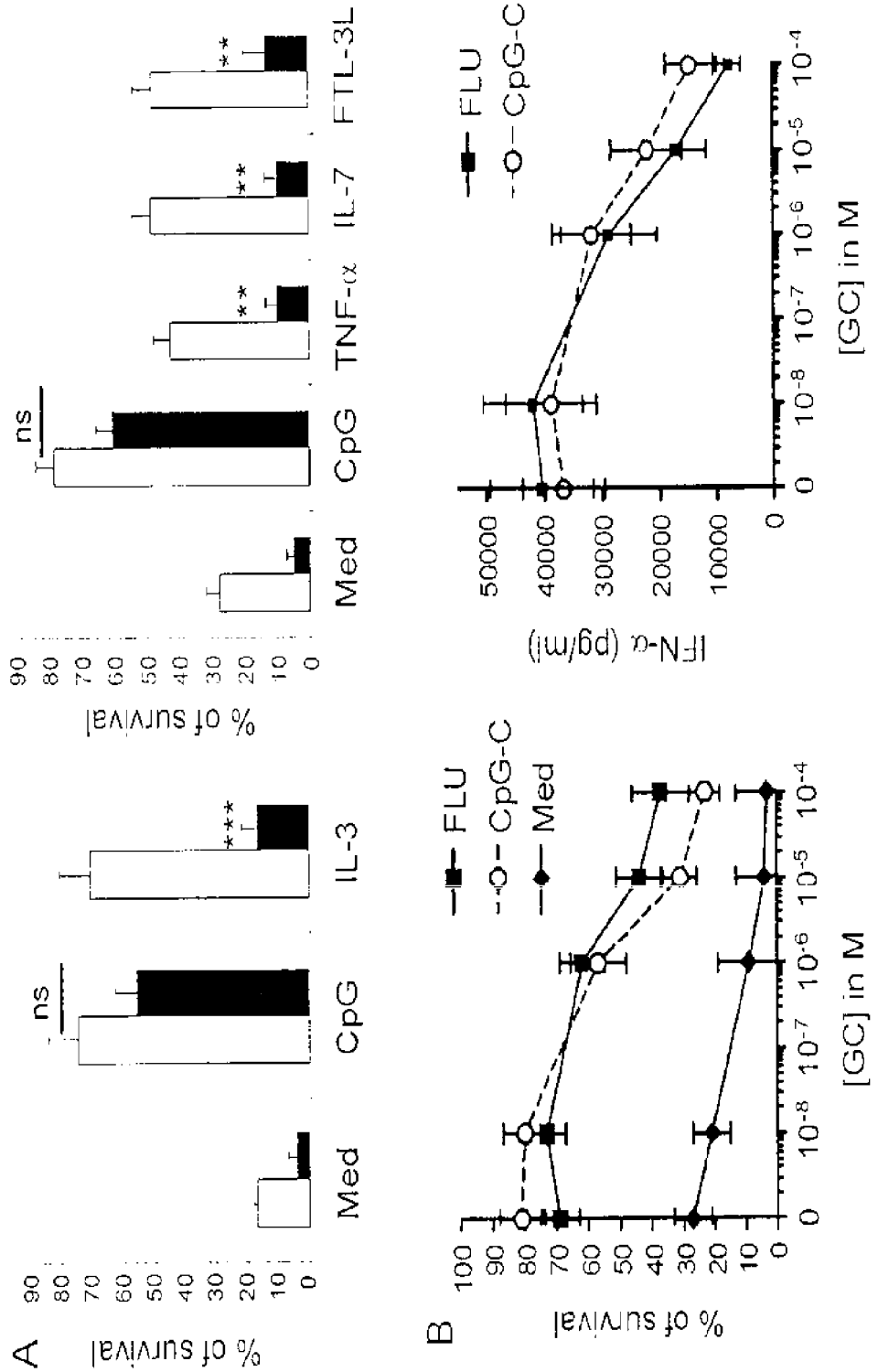

MFI
0
5
10
15
20
25
Uninfected
RNP
RNP + IC
RNP + IC +GC (10⁻⁵M)
RNP + IC +GC (10⁻⁴M)
RNP + IC +IRS
MFI
0
20
40
60
80
100
120
Uninfected
FLU
FLU +GC (10⁻⁵M)
FLU +GC (10⁻⁴M)
FLU +IRS

FIG. 17

FIG. 18


A
% of survival
Med
CpG
IL-3
ns
***
IL-7
TNF-α
FTL-3L
**
B
FLU
CpG-C
Med
[GC] in M
IFN-α (pg/ml)

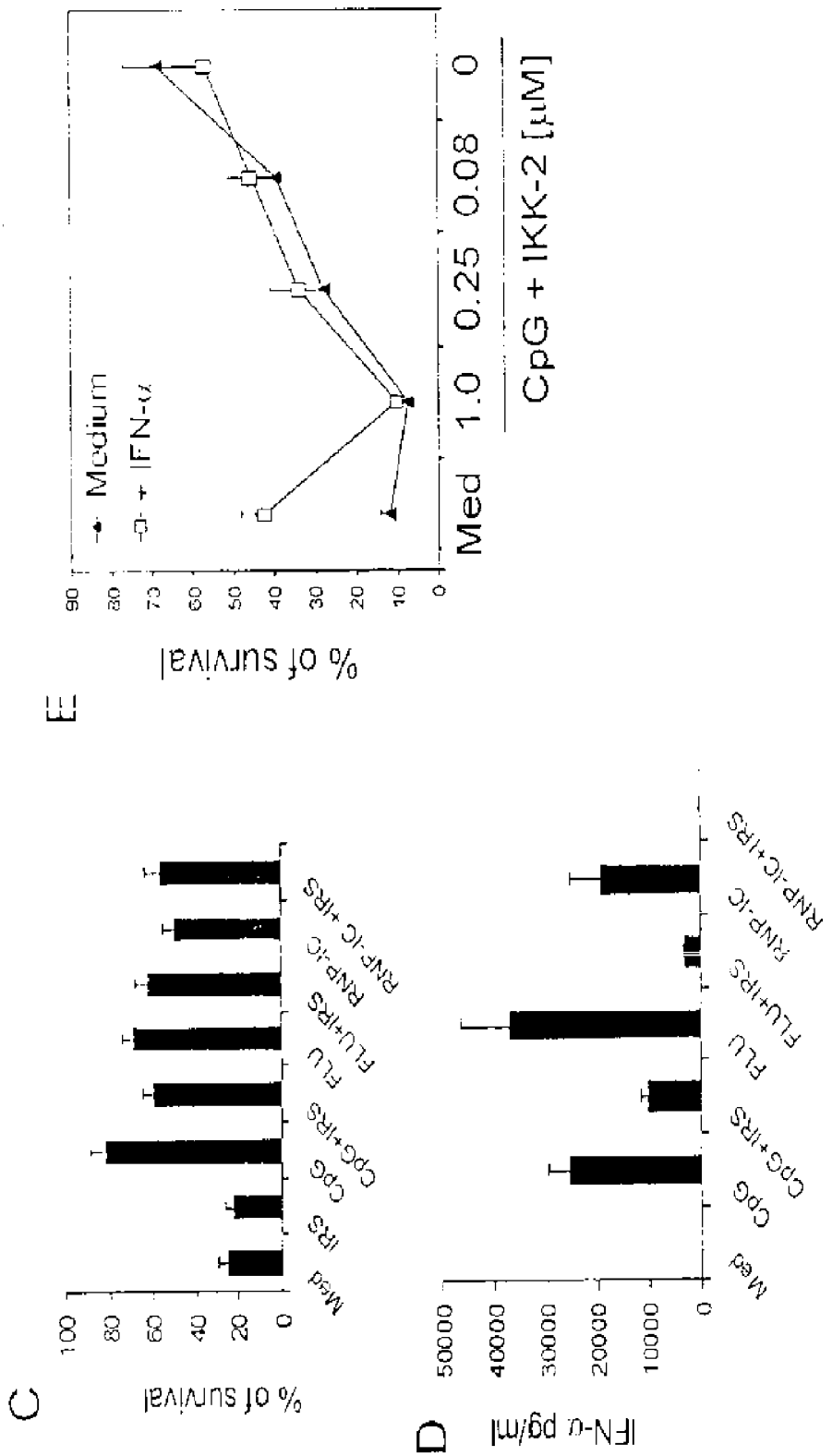

E
% of survival
Medium
+ IFN-α
Med 1.0 0.25 0.08 0
CpG + IKK-2 [μM]
C
% of survival
Med
IRS
CpG
CpG+IRS
FLU
FLU+IRS
RNP-IC
RNP-IC+IRS
D
IFN-α pg/ml
Med
CpG
CpG+IRS
FLU
FLU+IRS
RNP-IC
RNP-IC+IRS

FIG. 18

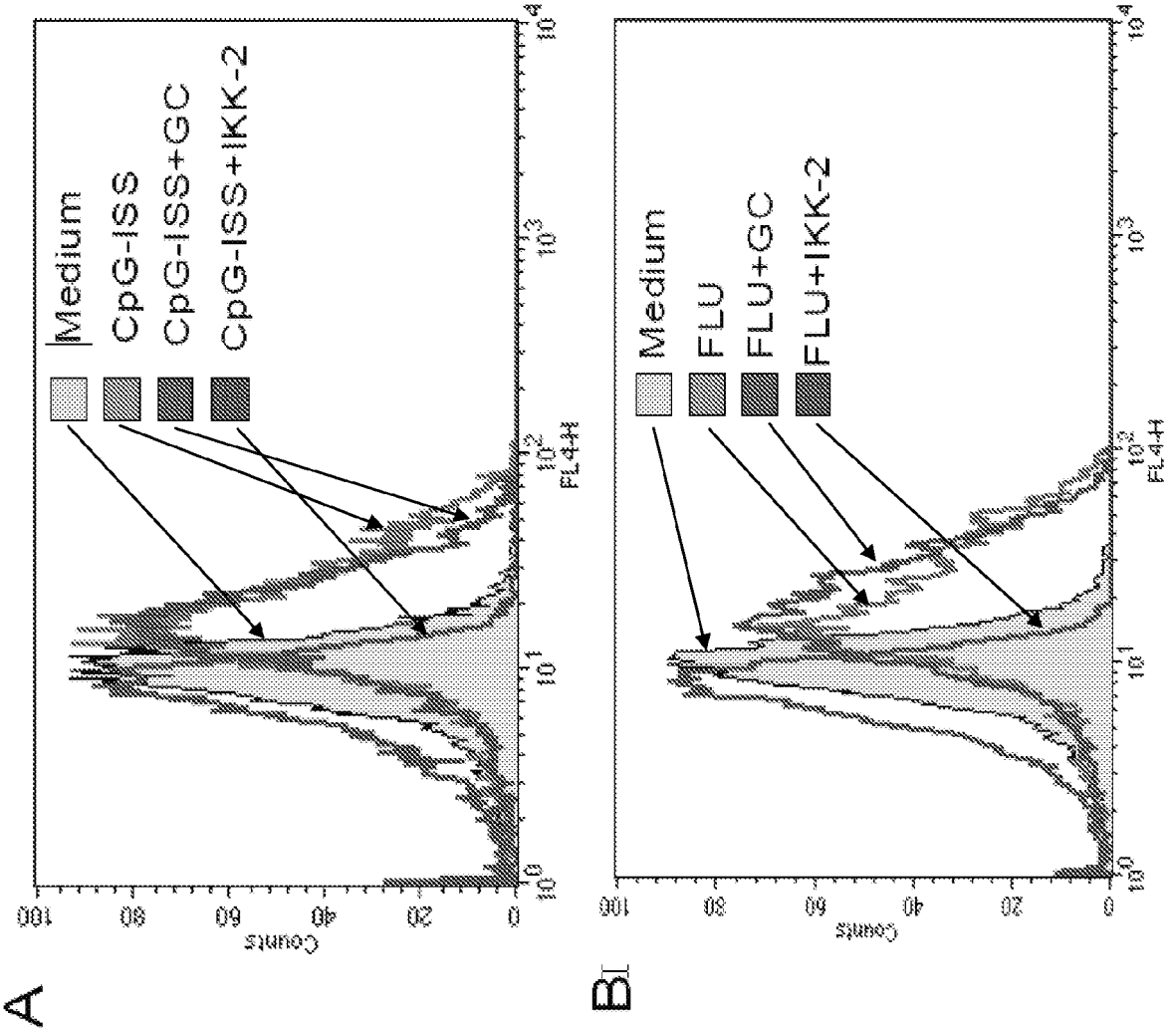

A
Medium
CpG-ISS
CpG-ISS+GC
CpG-ISS+IKK-2
Counts
FL4-H
B
Medium
FLU
FLU+GC
FLU+IKK-2
Counts
FL4-H

FIG. 19

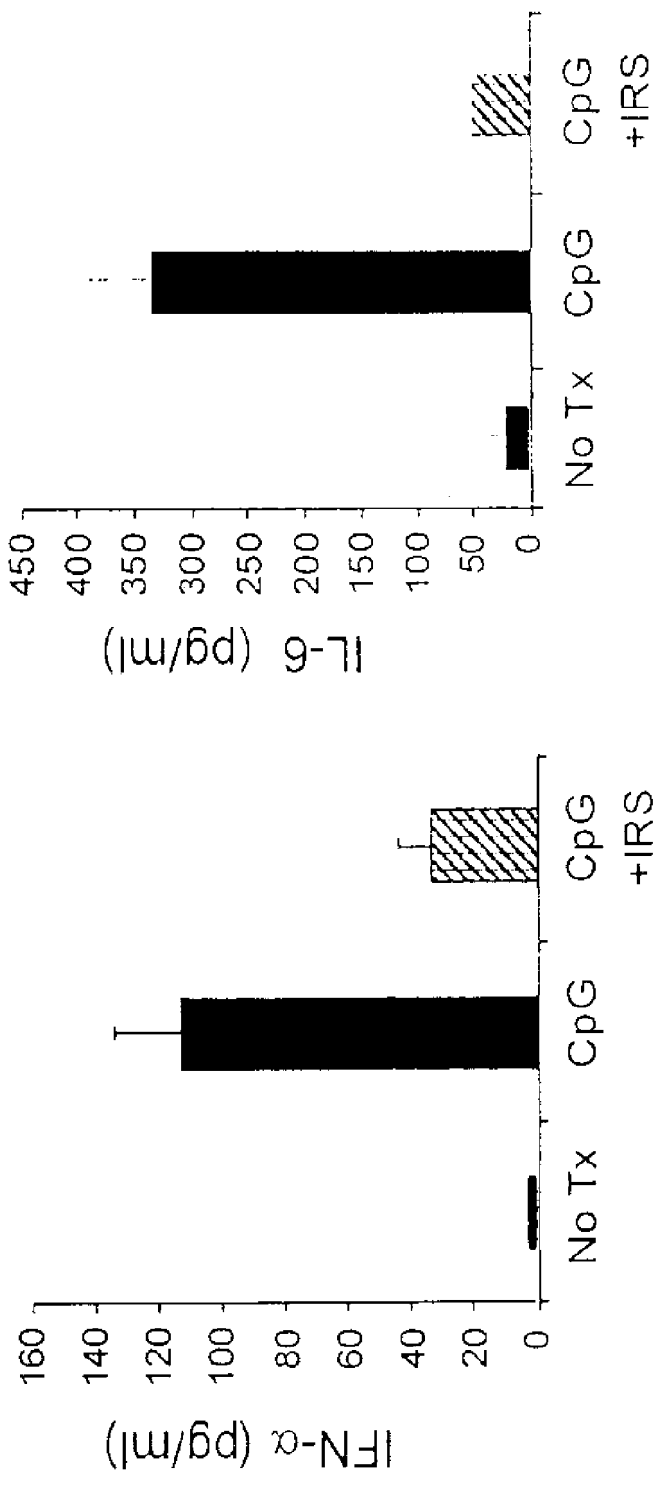

IFN-α (pg/ml)
160
140
120
100
80
60
40
20
0
No Tx
CpG
CpG +IRS
IL-6 (pg/ml)
450
400
350
300
250
200
150
100
50
0
No Tx
CpG
CpG +IRS

FIG. 20

FIG. 21

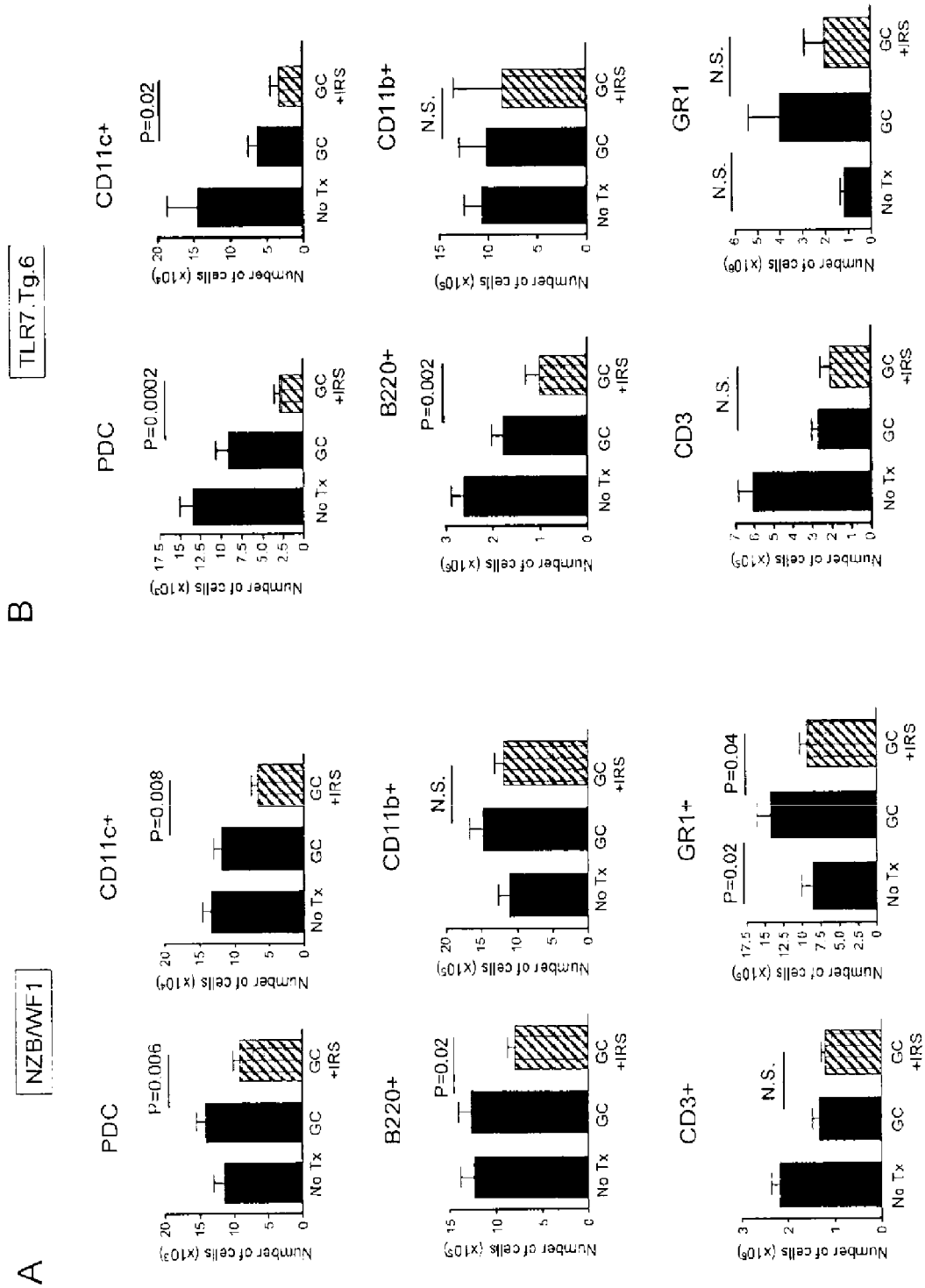
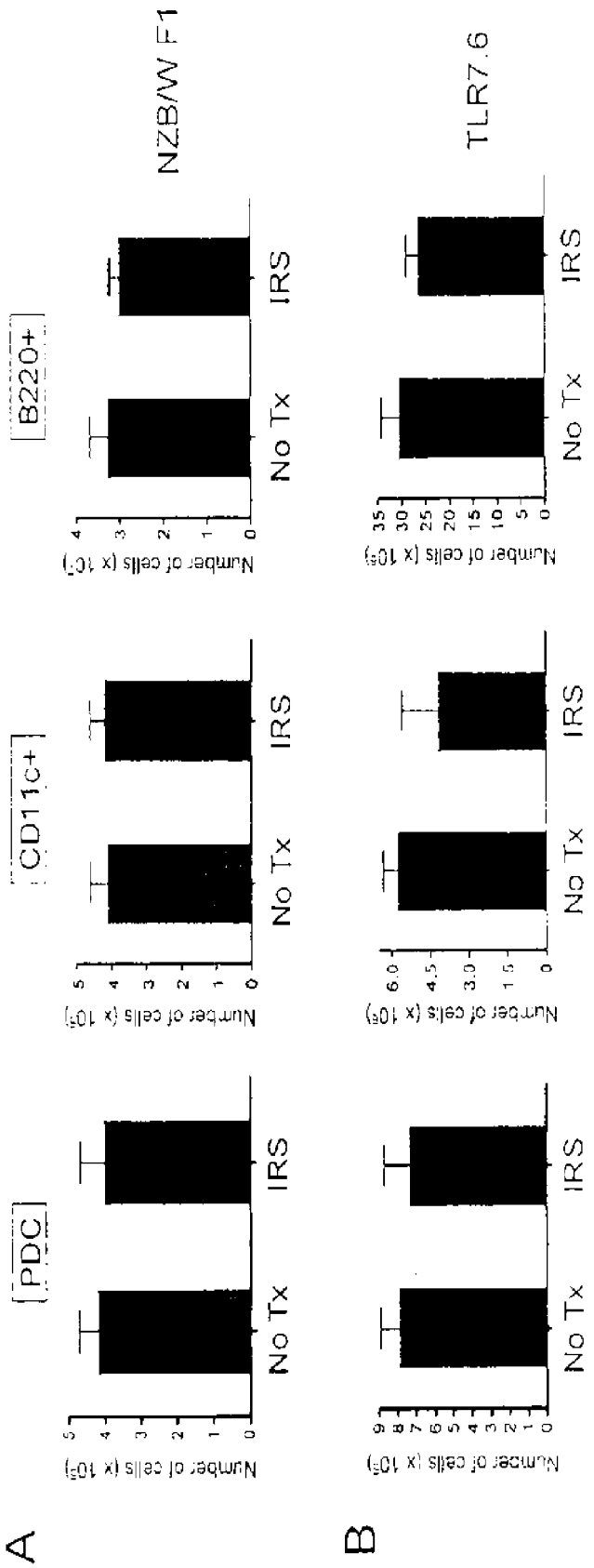

A
NZB/WF1
PDC
CD11c+
CD11b+
B220+
GR1+
CD3+
B
TLR7.Tg.6
PDC
CD11c+
B220+
CD11b+
CD3
GR1
No Tx
GC
GC +IRS
N.S.
P=0.006
P=0.008
P=0.02
P=0.04
P=0.0002
P=0.002

FIG. 22


A
B
PDC
CD11c+
B220+
NZB/W F1
TLR7.6
No Tx
IRS
Number of cells (x 10^5)
Number of cells (x 10^6)

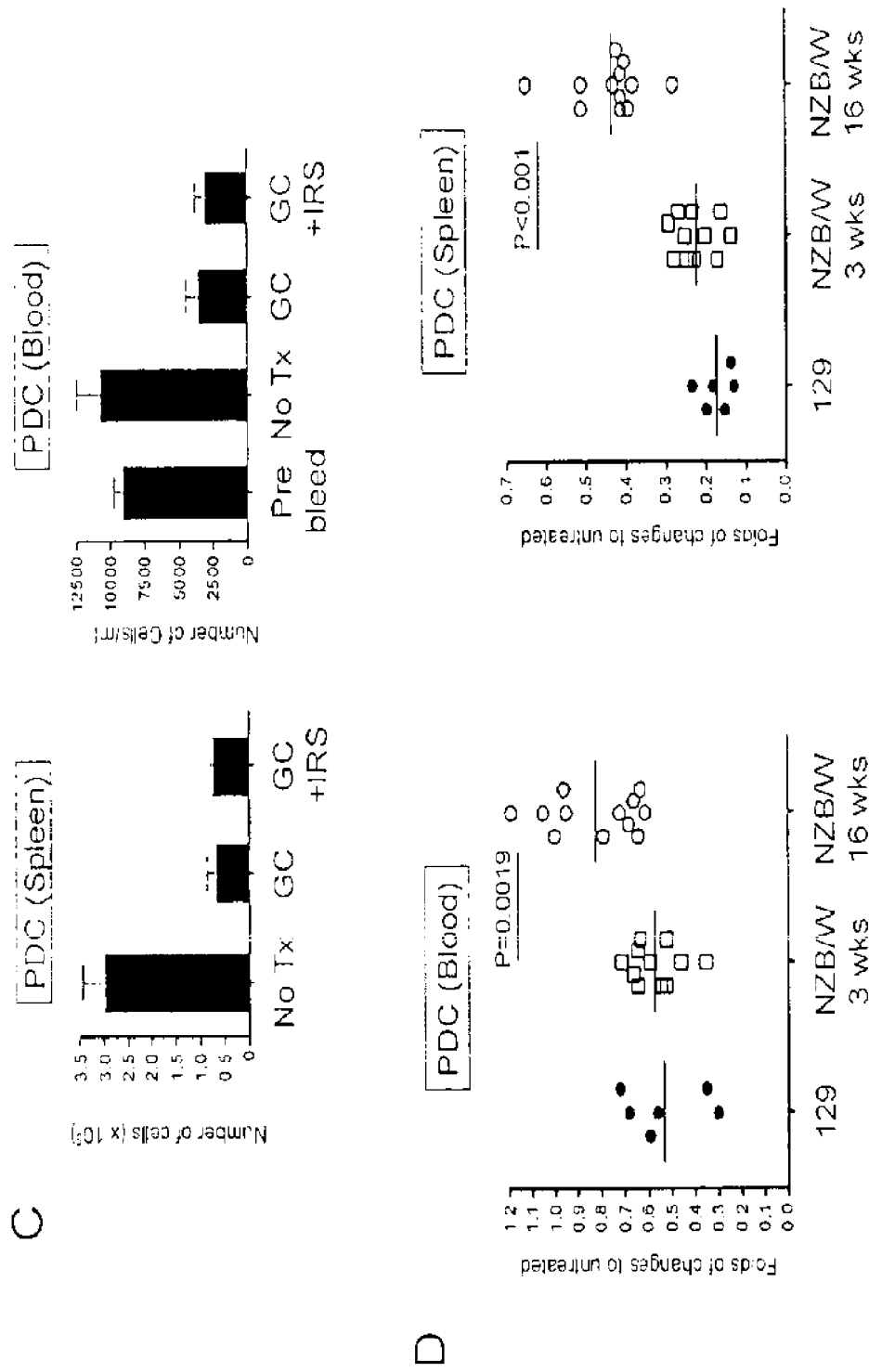

C
PDC (Spleen)
Number of cells (x 10⁵)
No Tx GC GC +IRS
PDC (Blood)
Number of Cells/ml
Pre bleed No Tx GC GC +IRS
D
PDC (Blood)
P=0.0019
Folds of changes to untreated
129 NZB/W 3 wks NZB/W 16 wks
PDC (Spleen)
P<0.001
Folds of changes to untreated
129 NZB/W 3 wks NZB/W 16 wks

FIG. 22

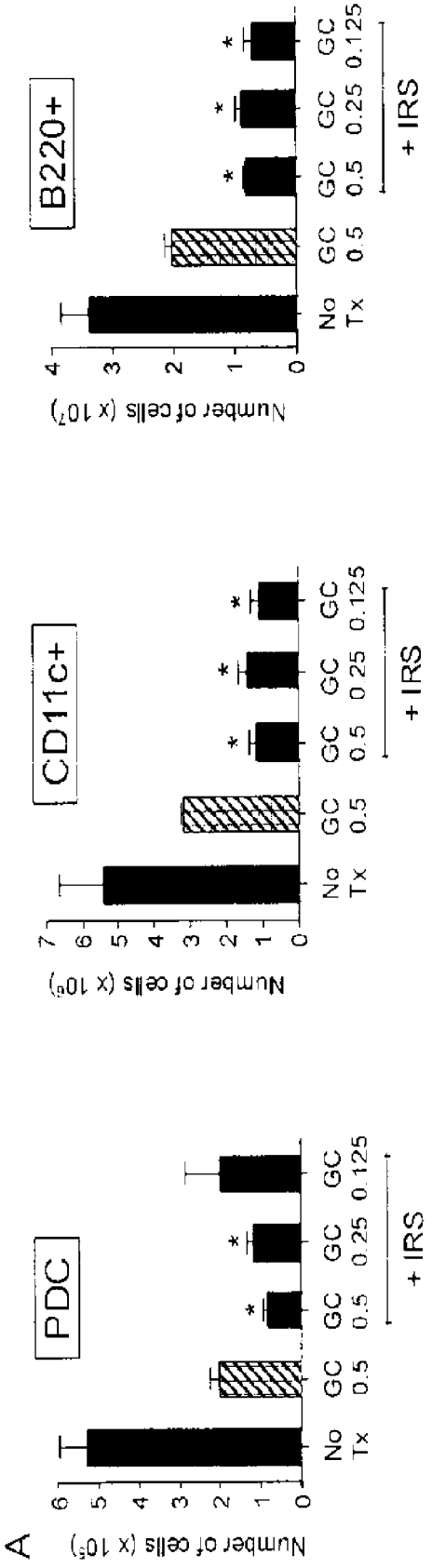

A
PDC
CD11c+
B220+
Number of cells (x 10^5)
Number of cells (x 10^6)
Number of cells (x 10^7)
No Tx
GC 0.5
GC 0.5
GC 0.25
GC 0.125
+ IRS
*

FIG. 23

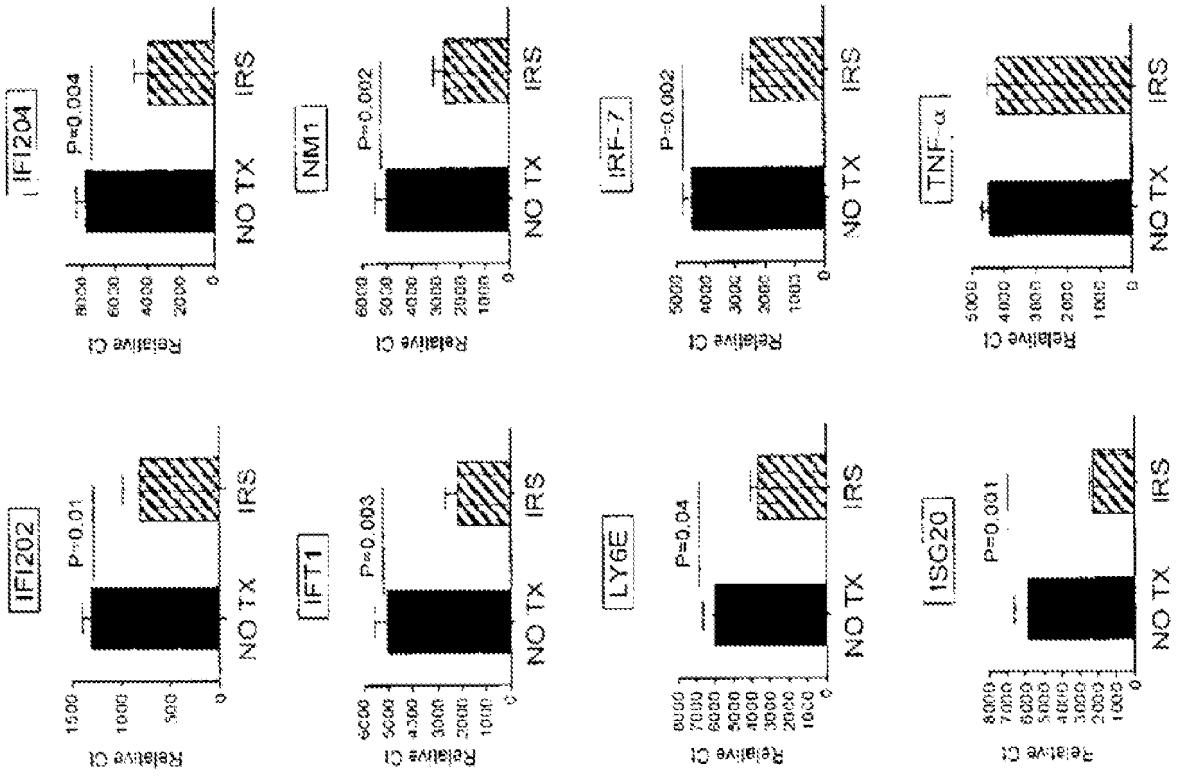

B
IFI202
P=0.01
IFI204
P=0.004
IFT1
P=0.003
NM1
P=0.002
LY6E
P=0.04
IRF-7
P=0.002
ISG20
P=0.001
TNF-α
NO TX
IRS
Relative CI

FIG. 23

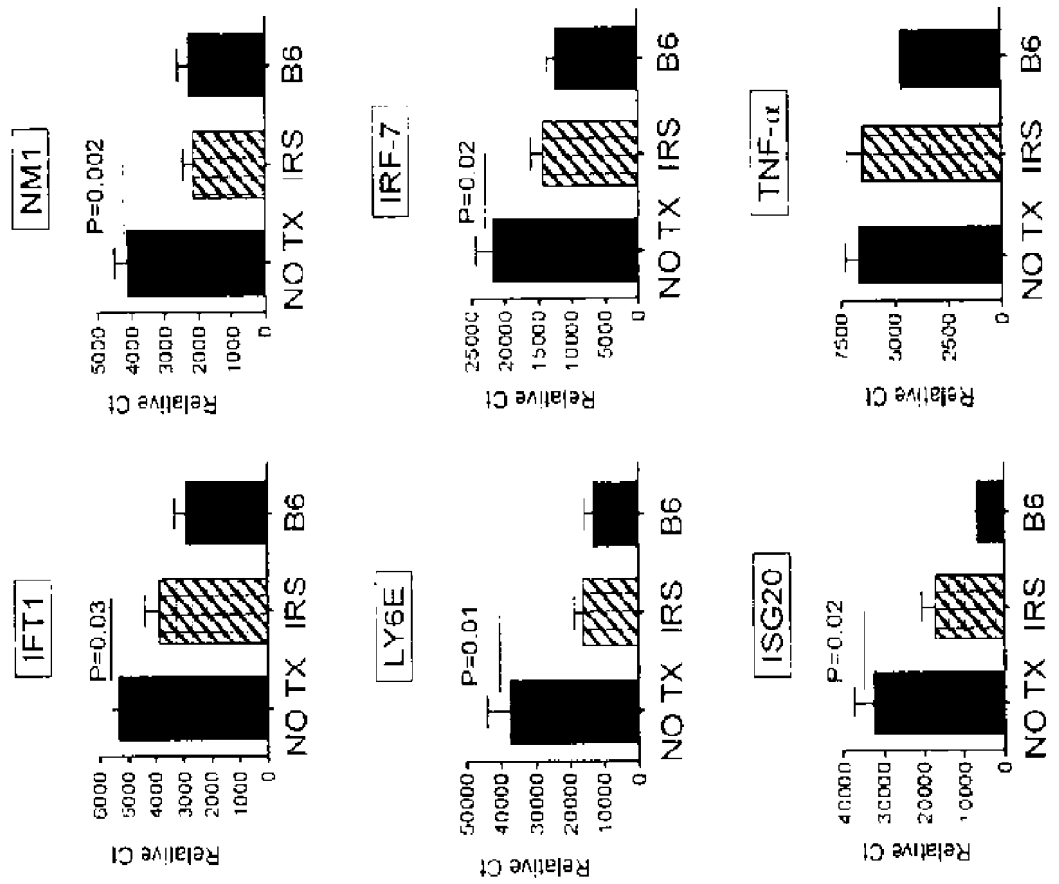

C
IFT1
P=0.03
Relative Ct
6000
5000
4000
3000
2000
1000
0
NO TX
IRS
B6
NM1
P=0.002
Relative Ct
5000
4000
3000
2000
1000
0
NO TX
IRS
B6
LY6E
P=0.01
Relative Ct
50000
40000
30000
20000
10000
0
NO TX
IRS
B6
IRF-7
P=0.02
Relative Ct
25000
20000
15000
10000
5000
0
NO TX
IRS
B6
ISG20
P=0.02
Relative Ct
40000
30000
20000
10000
0
NO TX
IRS
B6
TNF-α
Relative Ct
7500
5000
2500
0
NO TX
IRS
B6

FIG. 23

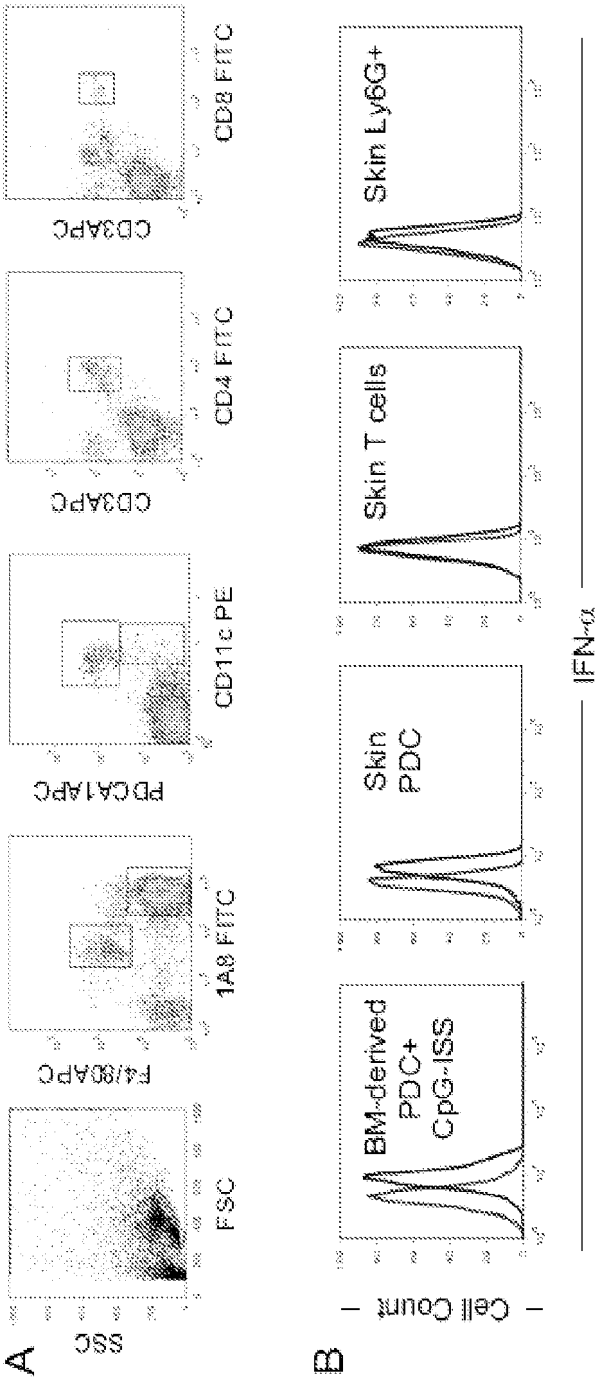

A
SSC
FSC
F4/80APC
1A8 FITC
PDCA1APC
CD11c PE
CD3APC
CD4 FITC
CD3APC
CD8 FITC
B
Cell Count
BM-derived PDC+ CpG-ISS
Skin PDC
Skin T cells
Skin Ly6G+
IFN-α

FIG. 24

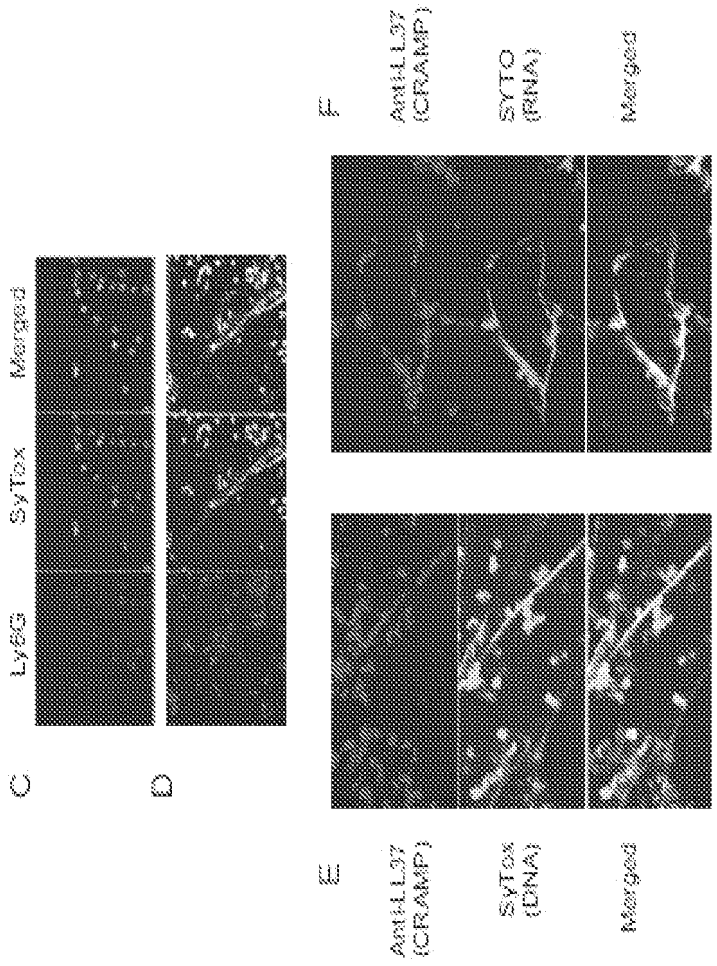

C
Ly6G
SyTox
Merged
D
E
Anti-LL37 (CRAMP)
SyTox (DNA)
Merged
F
Anti-LL37 (CRAMP)
SYTO (RNA)
Merged

FIG. 24

FIG. 25

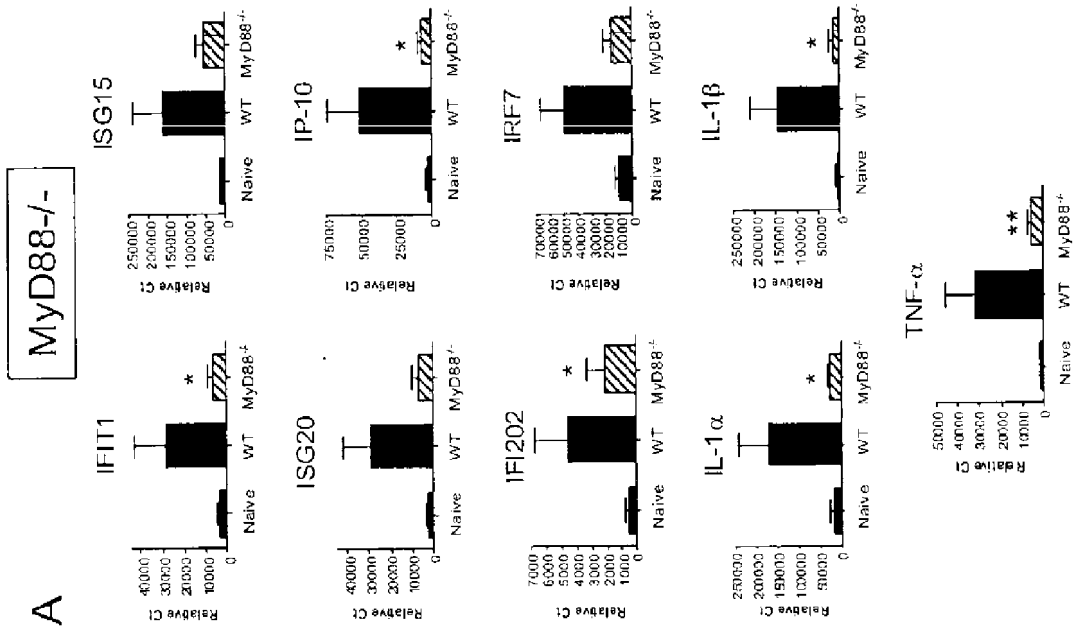
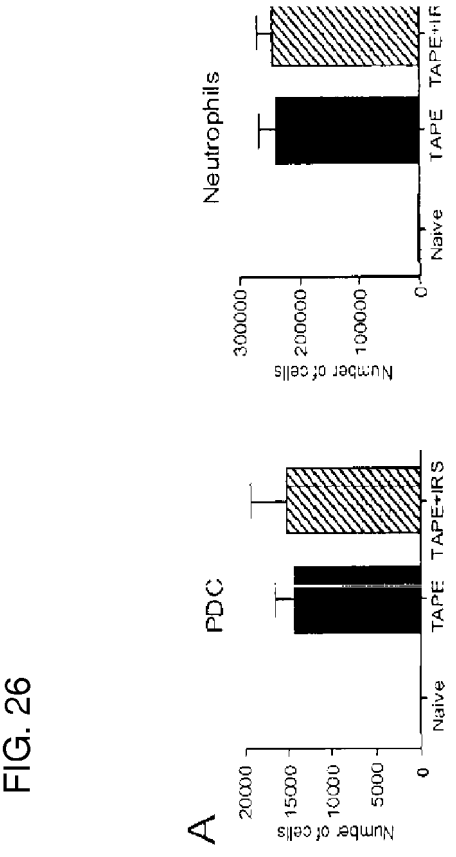

A
MyD88-/-
IFIT1
ISG15
ISG20
IP-10
IFI202
IRF7
IL-1α
IL-1β
TNF-α
Relative CI
Naive
WT
MyD88-/-
B
IFNAR-/-
IFIT1
ISG15
ISG20
IP-10
IFI202
IRF7
IL-1α
IL-1β
TNF-α
Relative CI
Naive
WT
IFNAR-/-

FIG. 26


A
PDC
Number of cells
20000
15000
10000
5000
0
Naive
TAPE
TAPE+IRS
Neutrophils
Number of cells
300000
200000
100000
0
Naive
TAPE
TAPE+IR

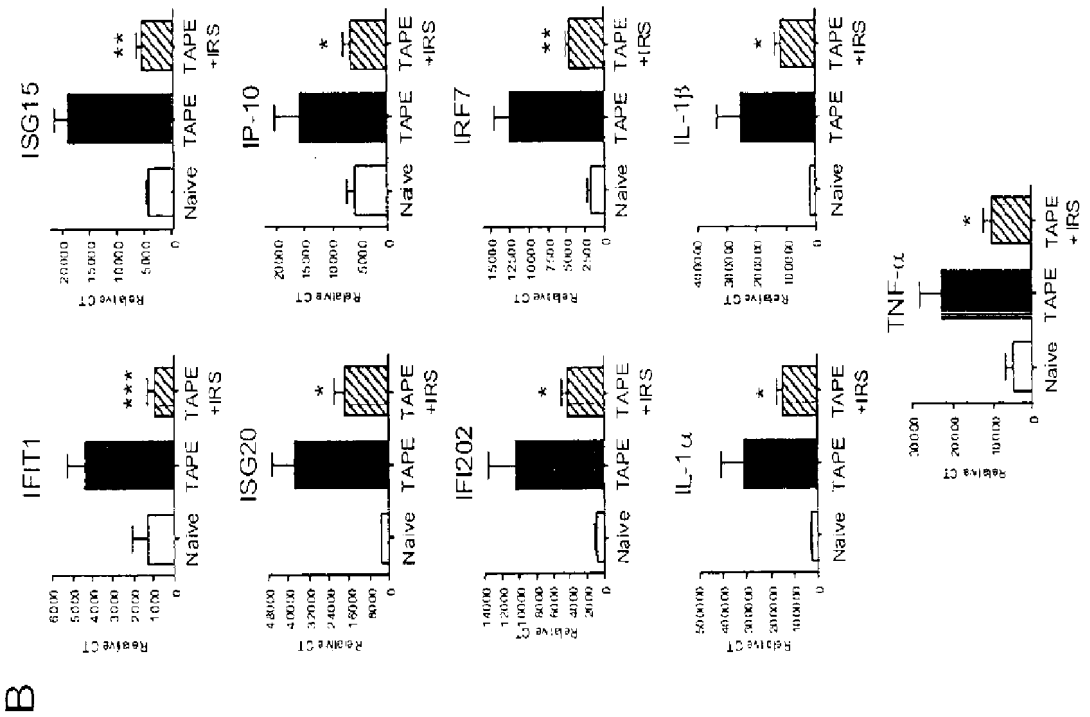

B
ISG15
IP-10
IRF7
IL-1β
IFIT1
ISG20
IFI202
IL-1α
TNF-α
Naive
TAPE
TAPE +IRS

FIG. 27

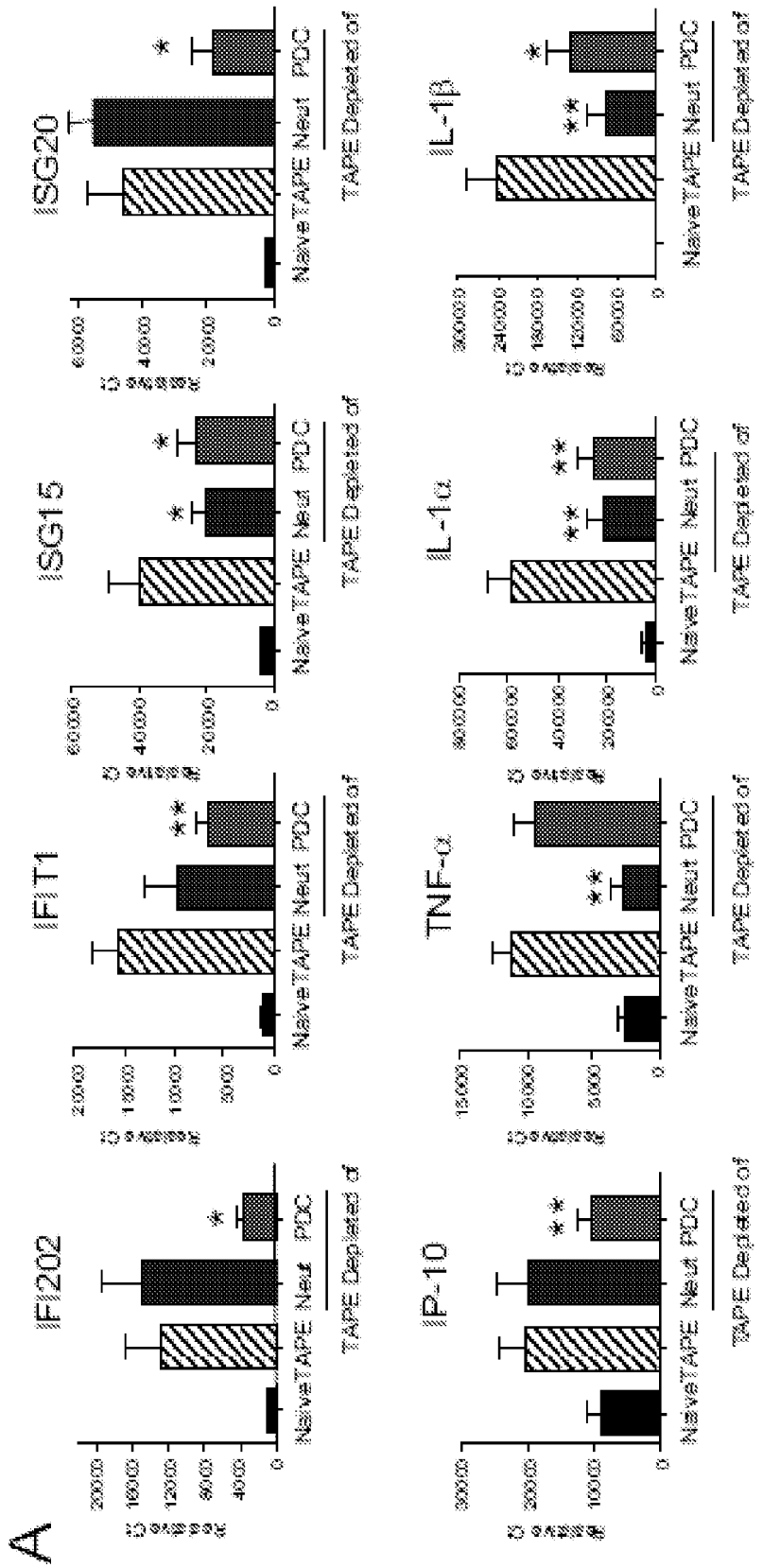

A
IFI202
IFIT1
ISG15
ISG20
IP-10
TNF-α
IL-1α
IL-1β
Naive
TAPE Neut
PDC
TAPE Depleted of

FIG. 27
continued

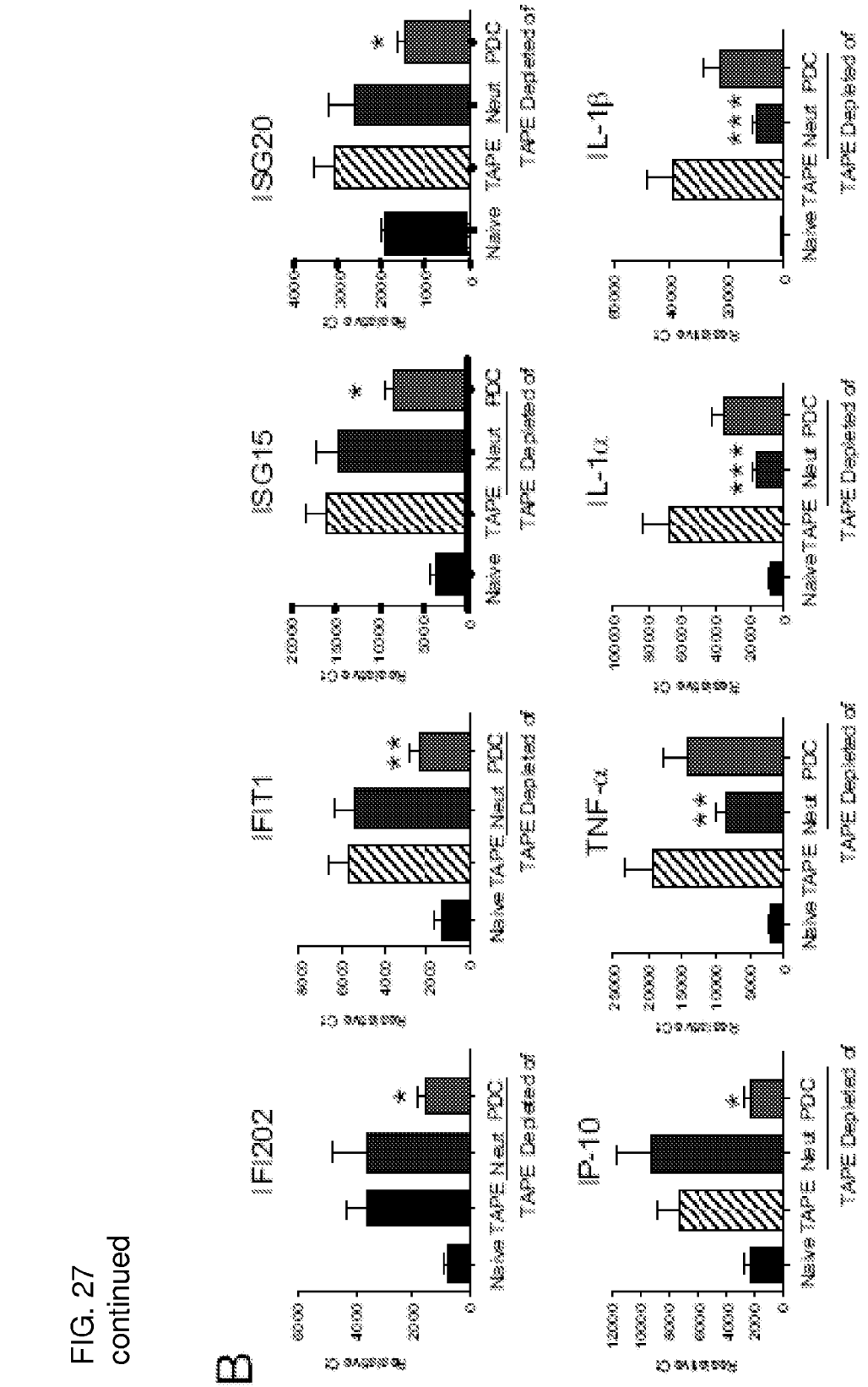
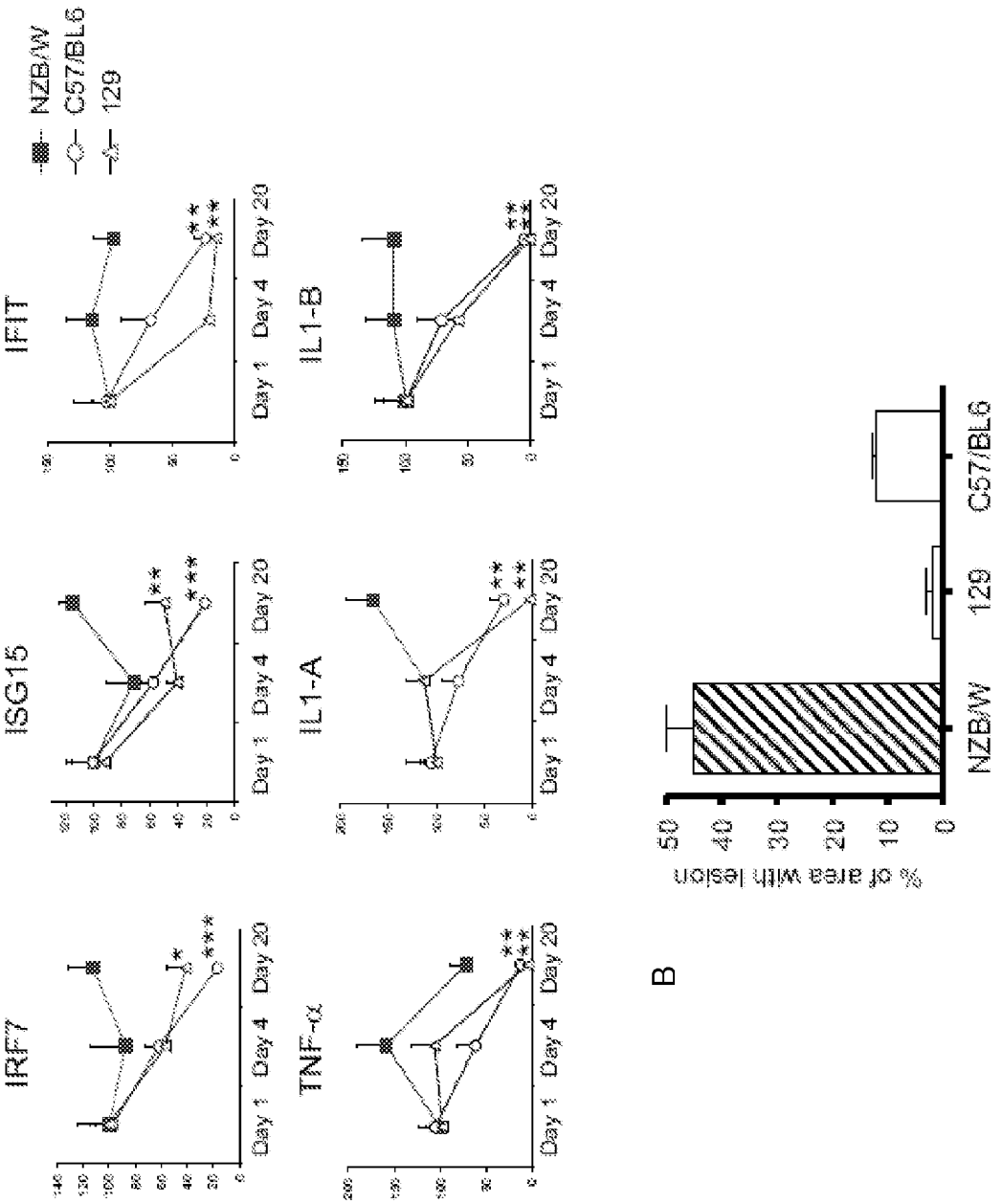


FIG. 28


A
IRF7
ISG15
IFIT
TNF-α
IL1-A
IL1-B
NZB/W
C57/BL6
129
Day 1
Day 4
Day 20
B
% of area with lesion
NZB/W
129
C57/BL6

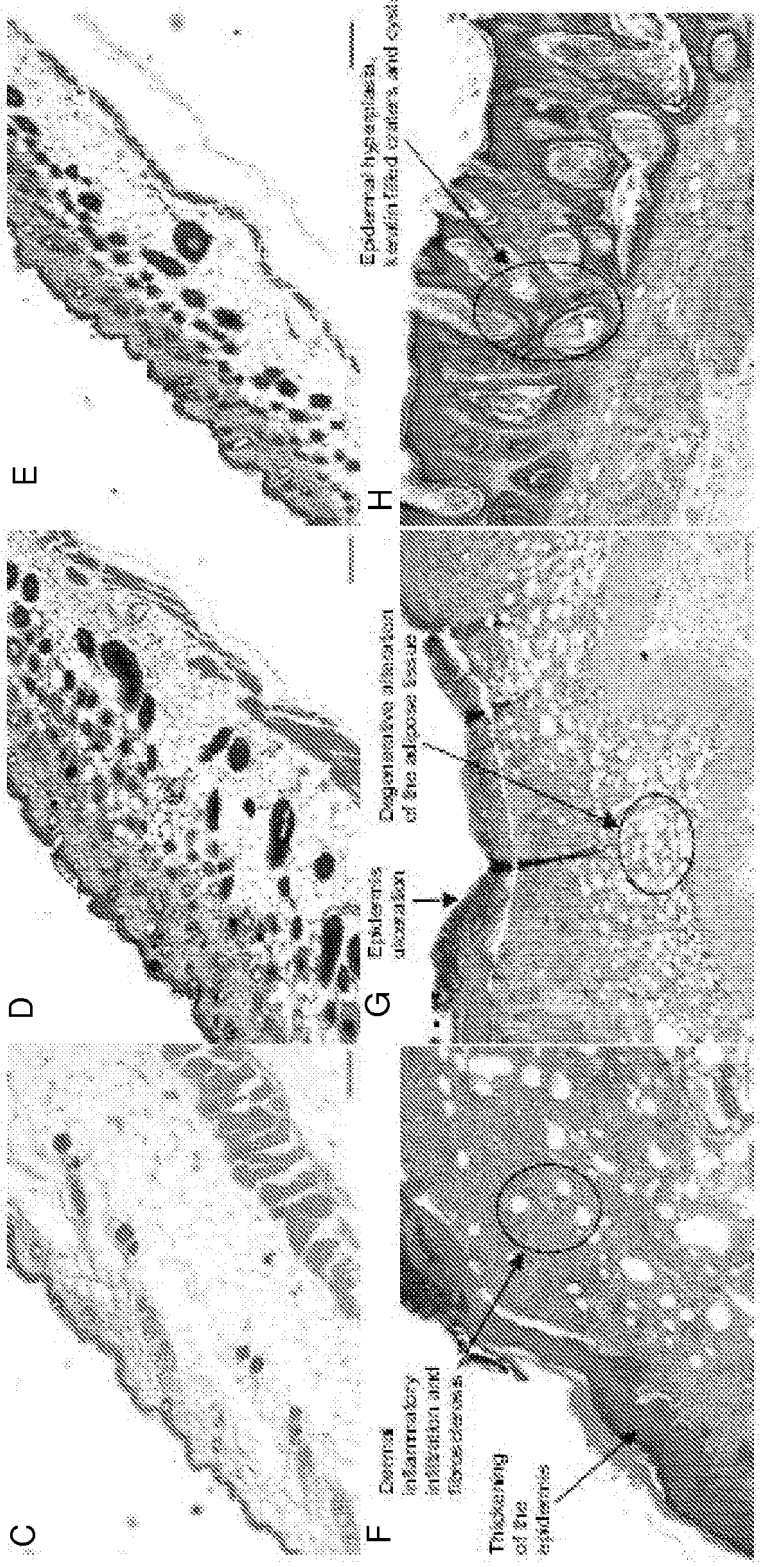

C
D
E
F
G
H
Dermal inflammatory infiltration and fibroplasia
Thickening of the epidermis
Epidermis degradation
Degenerative alteration of the adipose tissue
Epidermal hyperplasia, keratin filled craters and cysts

FIG. 28

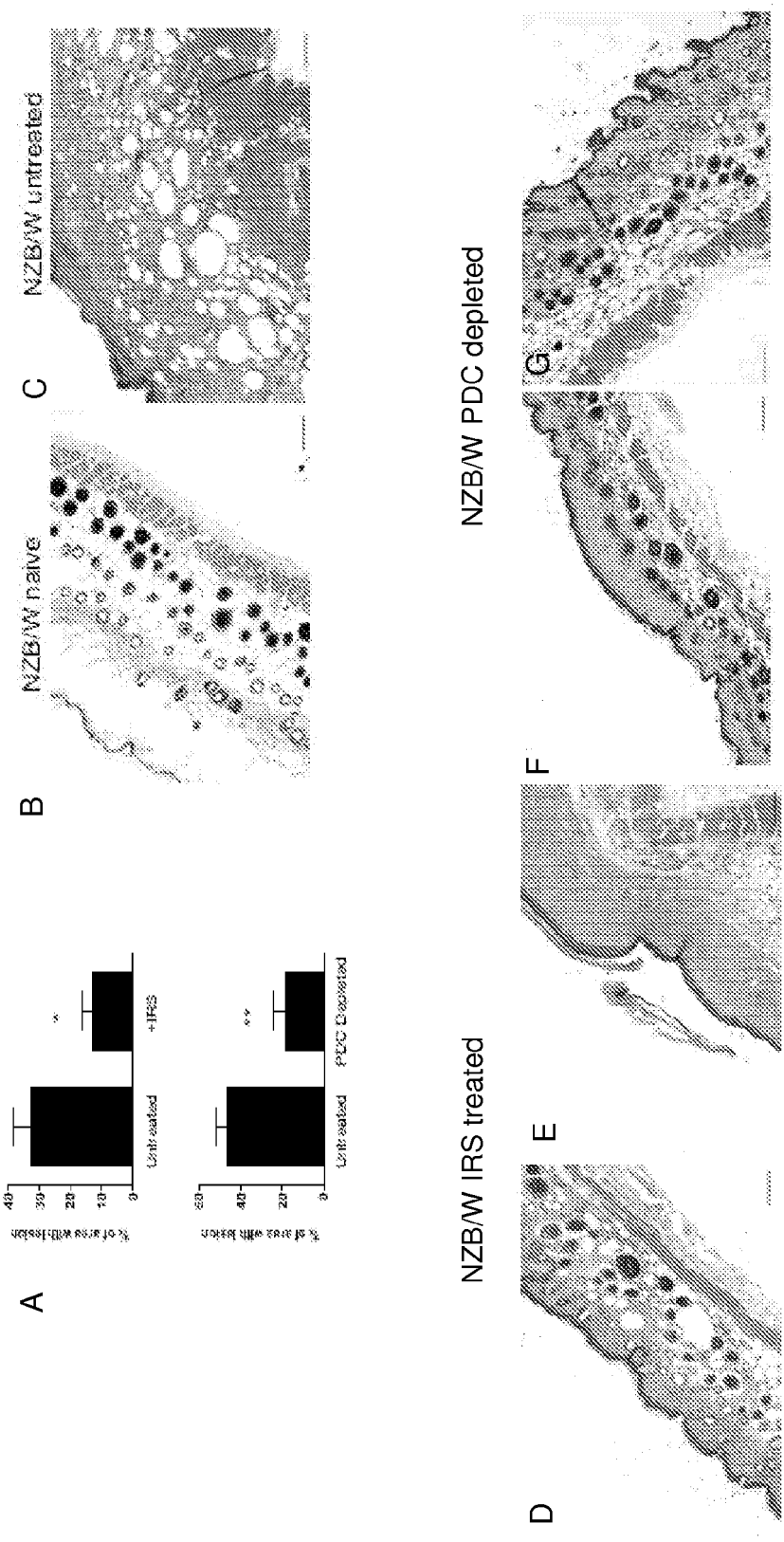

A
B
C
D
E
F
G
NZB/W naive
NZB/W untreated
NZB/W IRS treated
NZB/W PDC depleted
Untreated
+IRS
PDC Depleted

FIG. 29

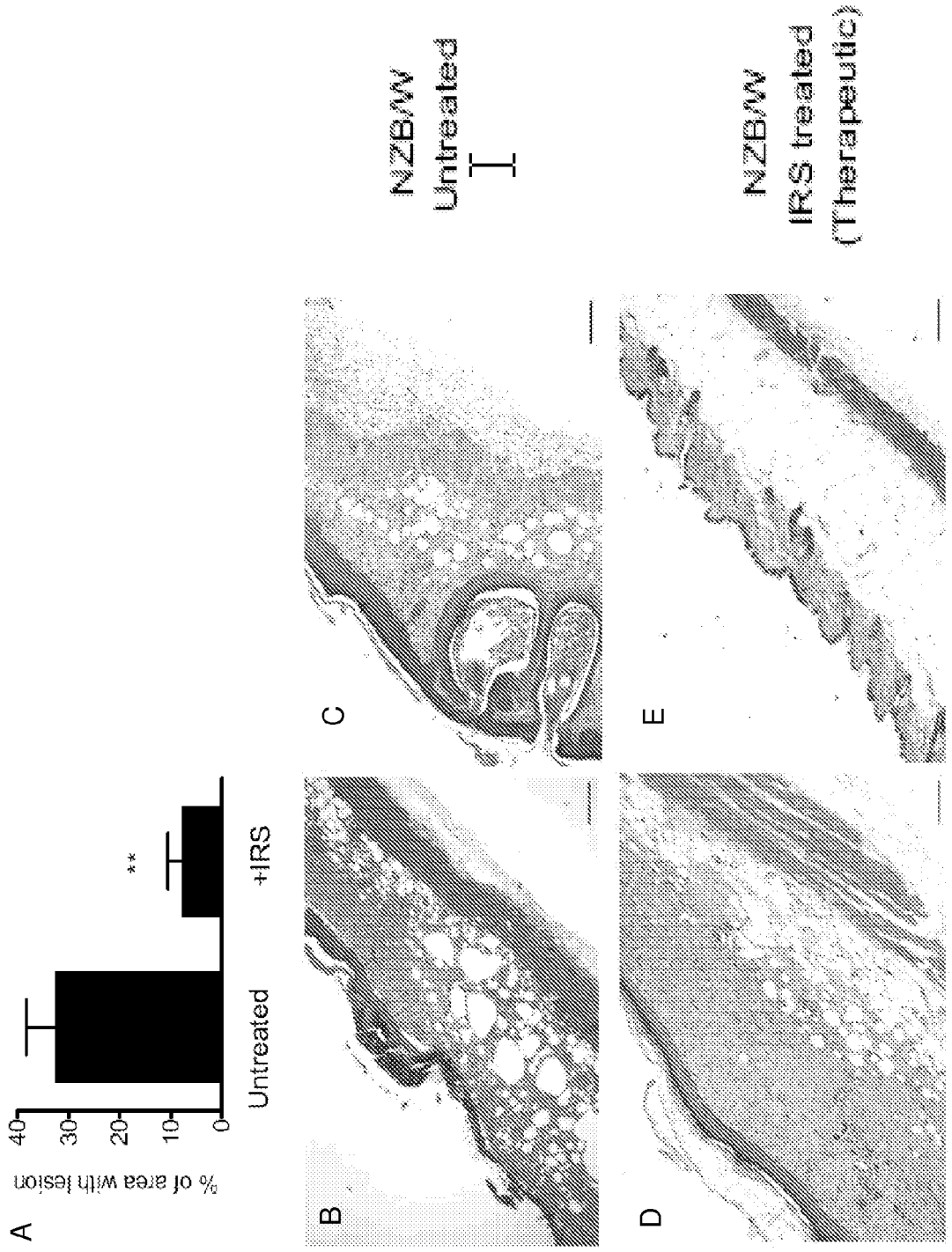
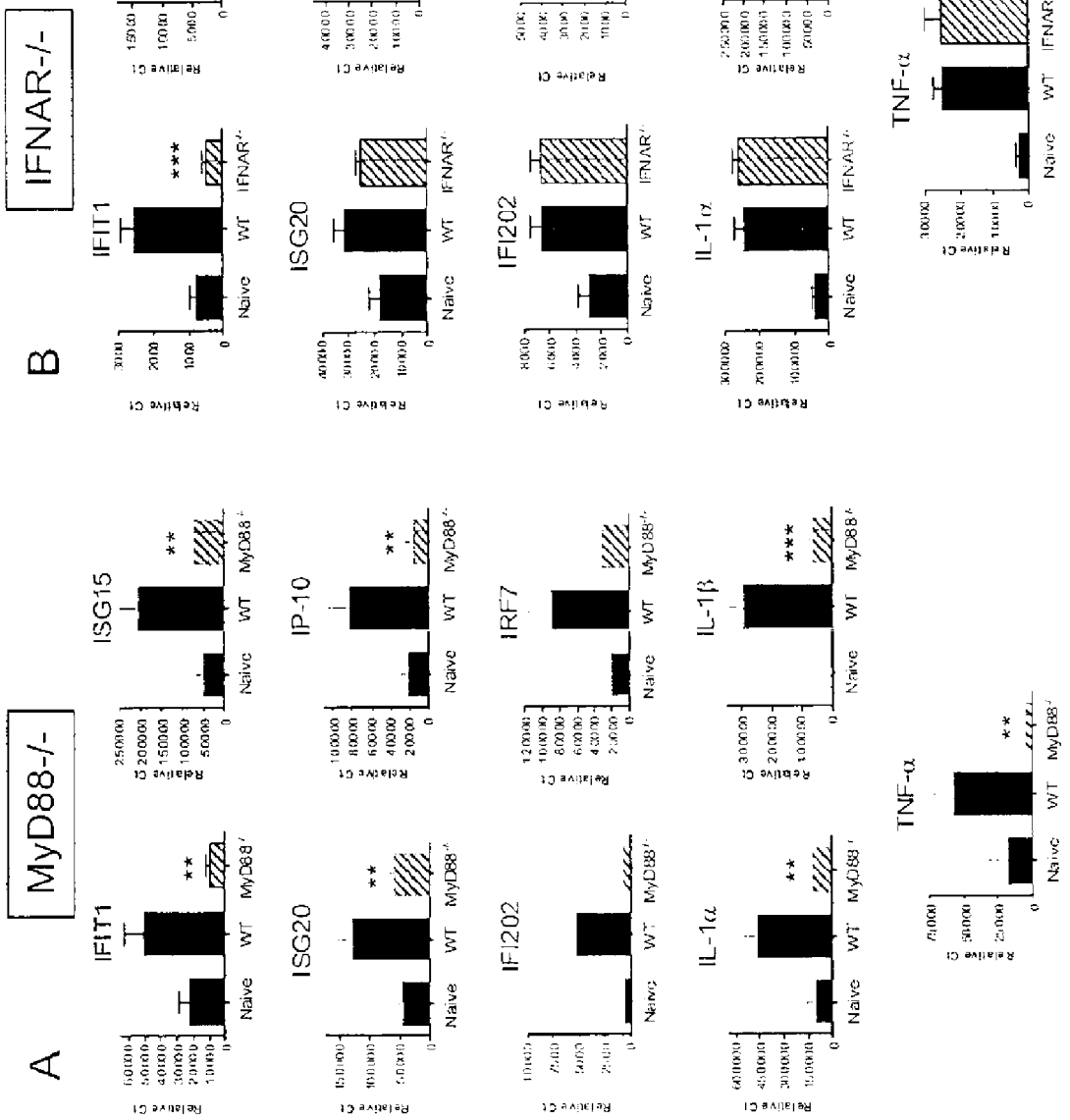

A
% of area with lesion
40
30
20
10
0
**
Untreated
+IRS
B
C
NZB/W
Untreated
D
E
NZB/W
IRS treated
(Therapeutic)

FIG. 30

FIG. 31


A
MyD88-/-
IFIT1
ISG15
ISG20
IP-10
IRF7
IFI202
IL-1α
IL-1β
TNF-α
Relative CI
Naive
WT
MyD88-/-
B
IFNAR-/-
IFIT1
ISG15
ISG20
IP-10
IRF7
IFI202
IL-1α
IL-1β
TNF-α
Relative CI
Naive
WT
IFNAR-/-

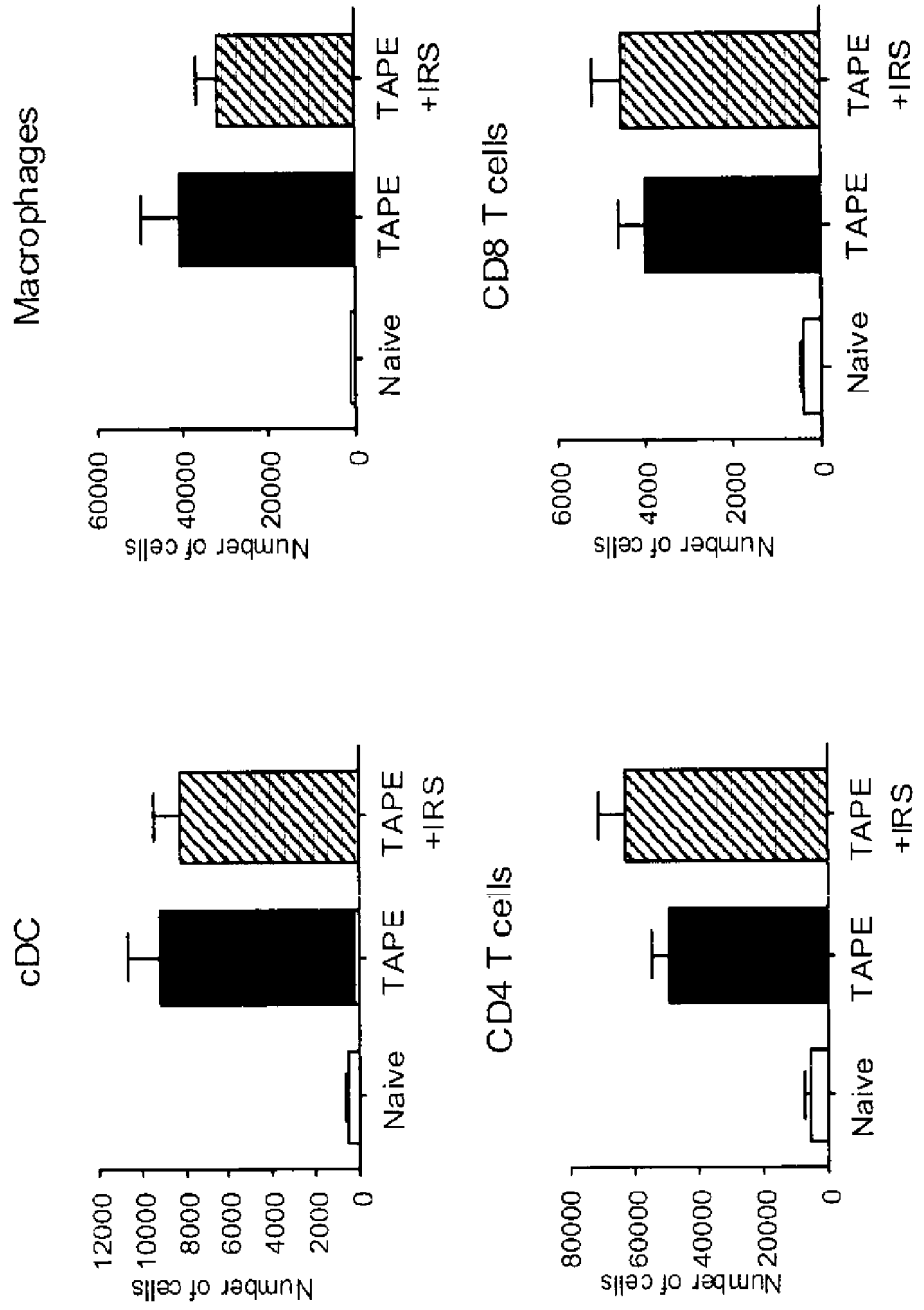
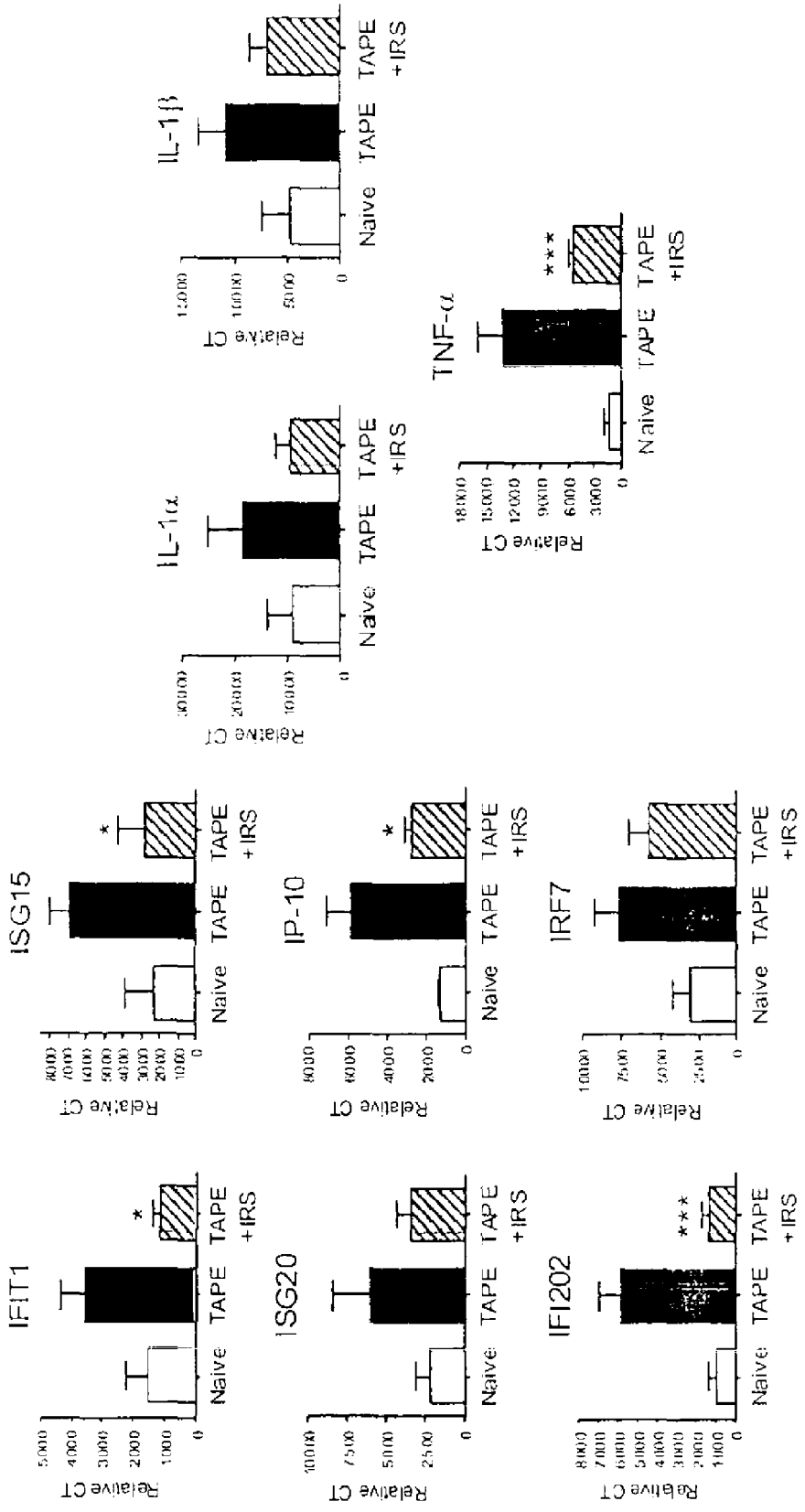

Macrophages
Number of cells
60000
40000
20000
0
Naive
TAPE
TAPE +IRS
CD8 T cells
Number of cells
6000
4000
2000
0
Naive
TAPE
TAPE +IRS
cDC
Number of cells
12000
10000
8000
6000
4000
2000
0
Naive
TAPE
TAPE +IRS
CD4 T cells
Number of cells
80000
60000
40000
20000
0
Naive
TAPE
TAPE +IRS

FIG. 32

FIG. 33


IL-1β
IL-1α
TNF-α
ISG15
IP-10
IRF7
IFIT1
ISG20
IFI202
Relative CT
Naive
TAPE
TAPE +IRS
*
***

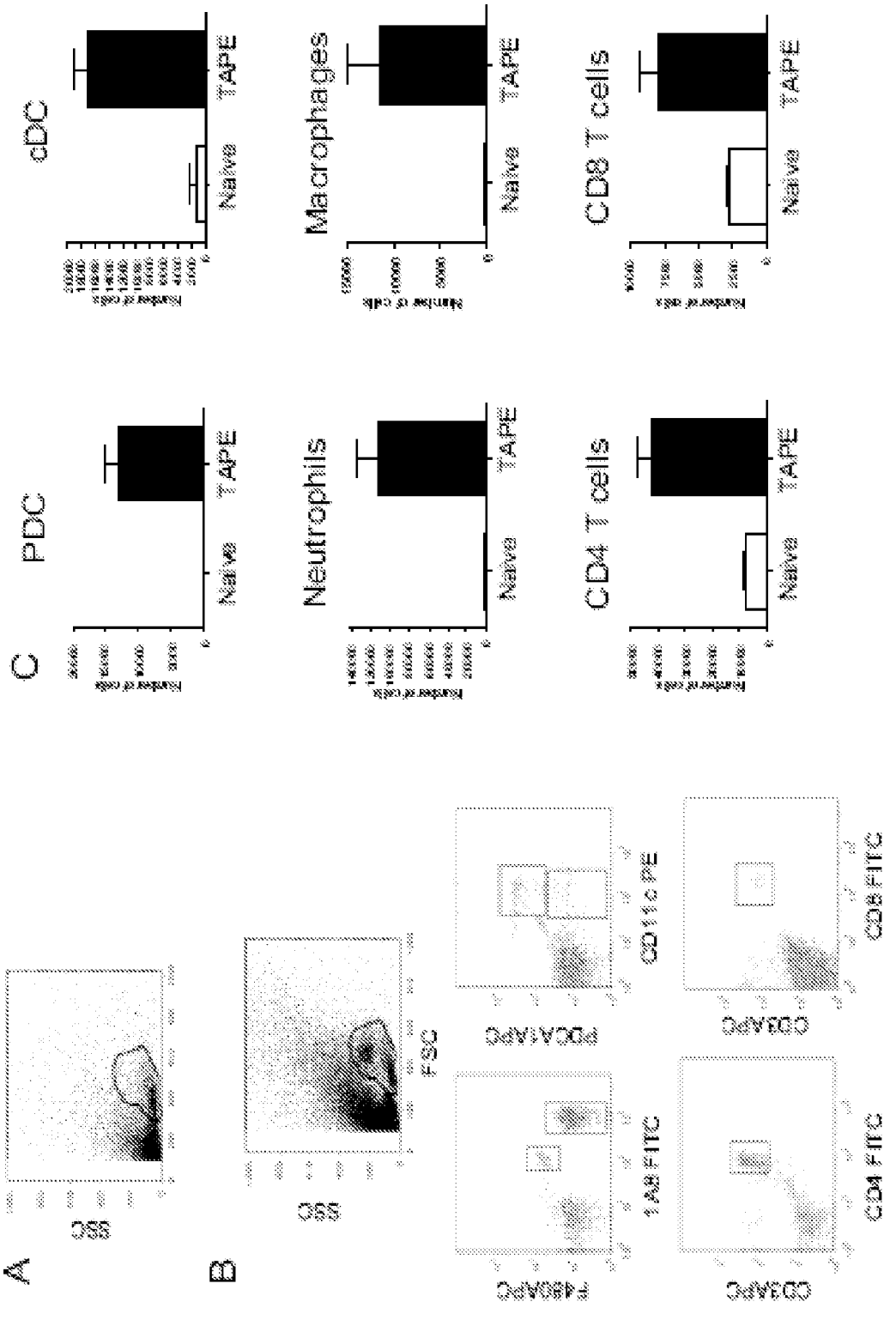
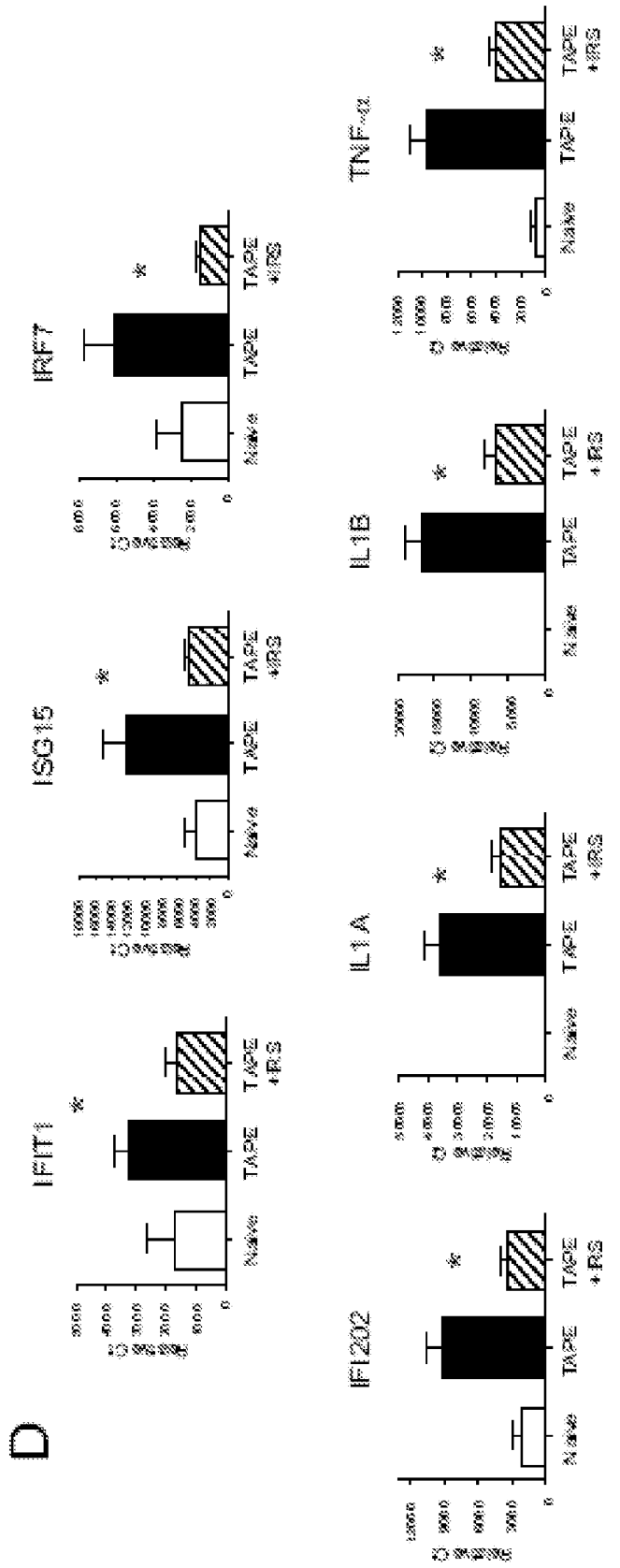

A
SSC
B
SSC
FSC
F480APC
1A8 FITC
PDCA1APC
CD11c PE
CD3APC
CD4 FITC
CD3APC
CD8 FITC
C
PDC
Naive
TAPE
Neutrophils
Naive
TAPE
CD4 T cells
Naive
TAPE
cDC
Naive
TAPE
Macrophages
Naive
TAPE
CD8 T cells
Naive
TAPE

FIG. 34

FIG. 34



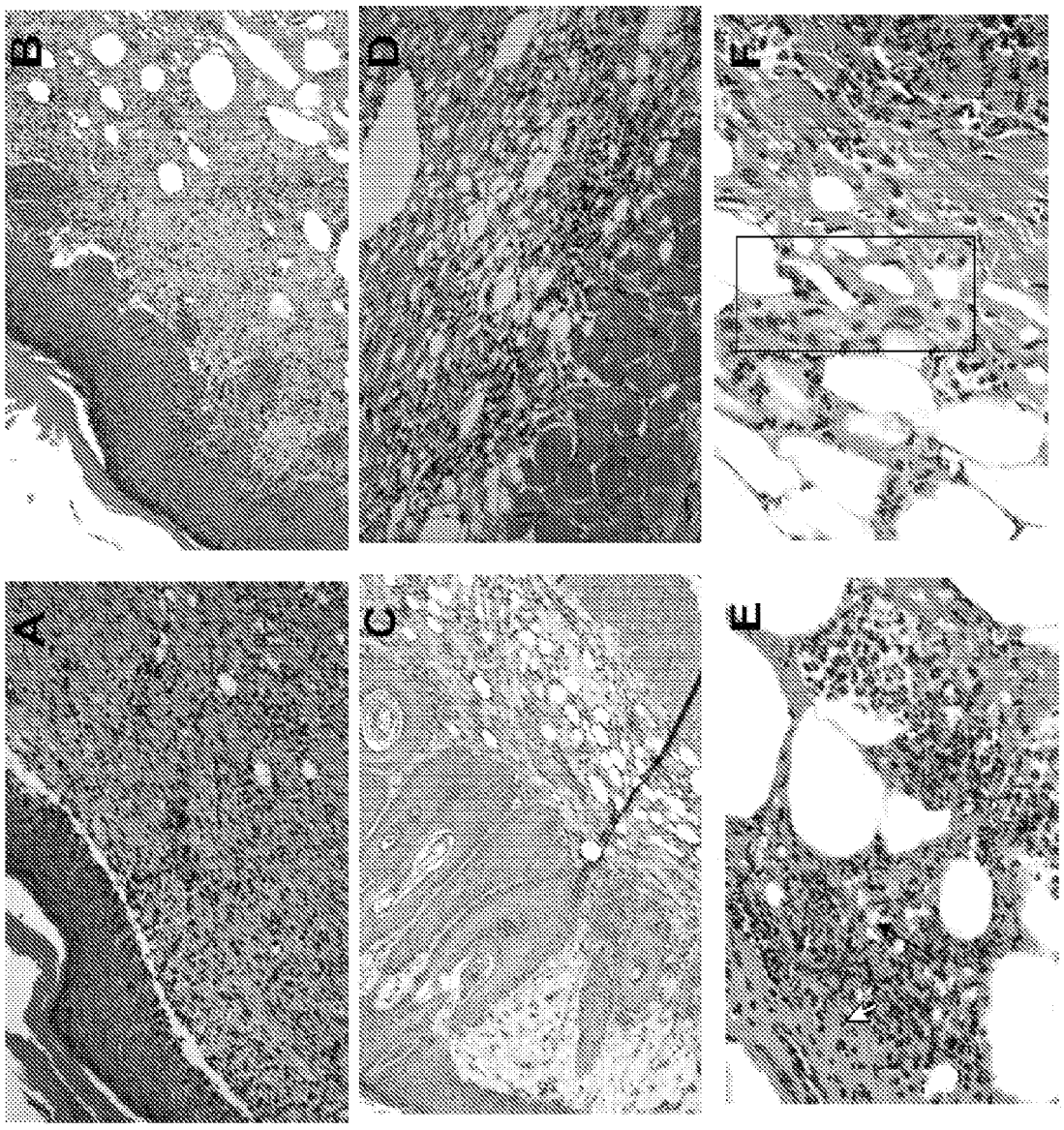


FIG. 35

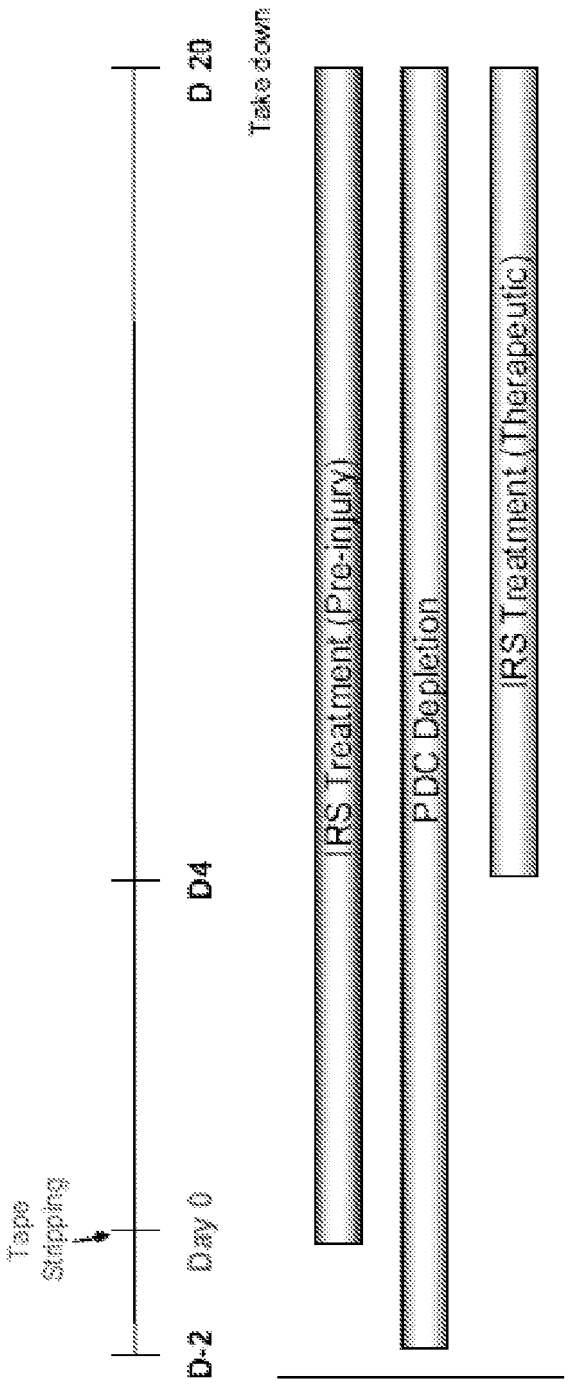

D-2
Day 0
D4
D 20
Take down
Tape Stripping
IRS Treatment (Pre-injury)
PDC Depletion
IRS Treatment (Therapeutic)
Fig. 29A, D, E
Fig. 29A, F, G
Fig. 30A, D, E

FIG. 36

FIG. 37

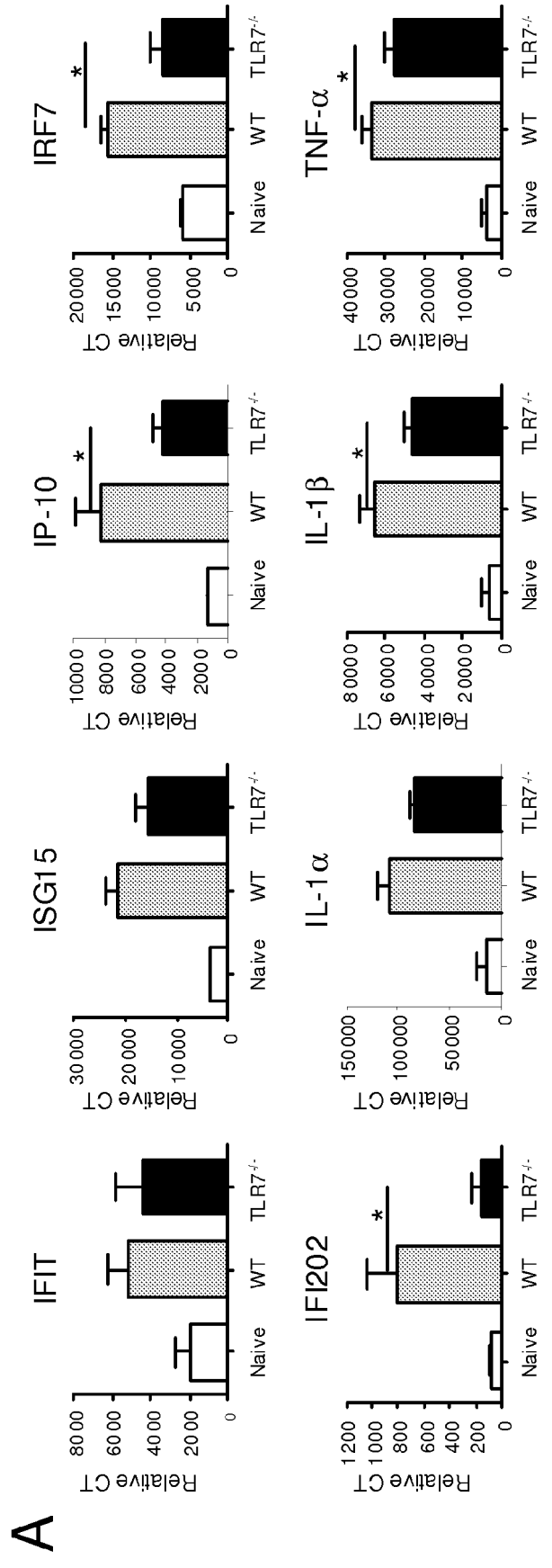

A
IFIT
ISG15
IP-10
IRF7
IFI202
IL-1α
IL-1β
TNF-α
Relative CT
Naive
WT
TLR7-/-
*

FIG. 37

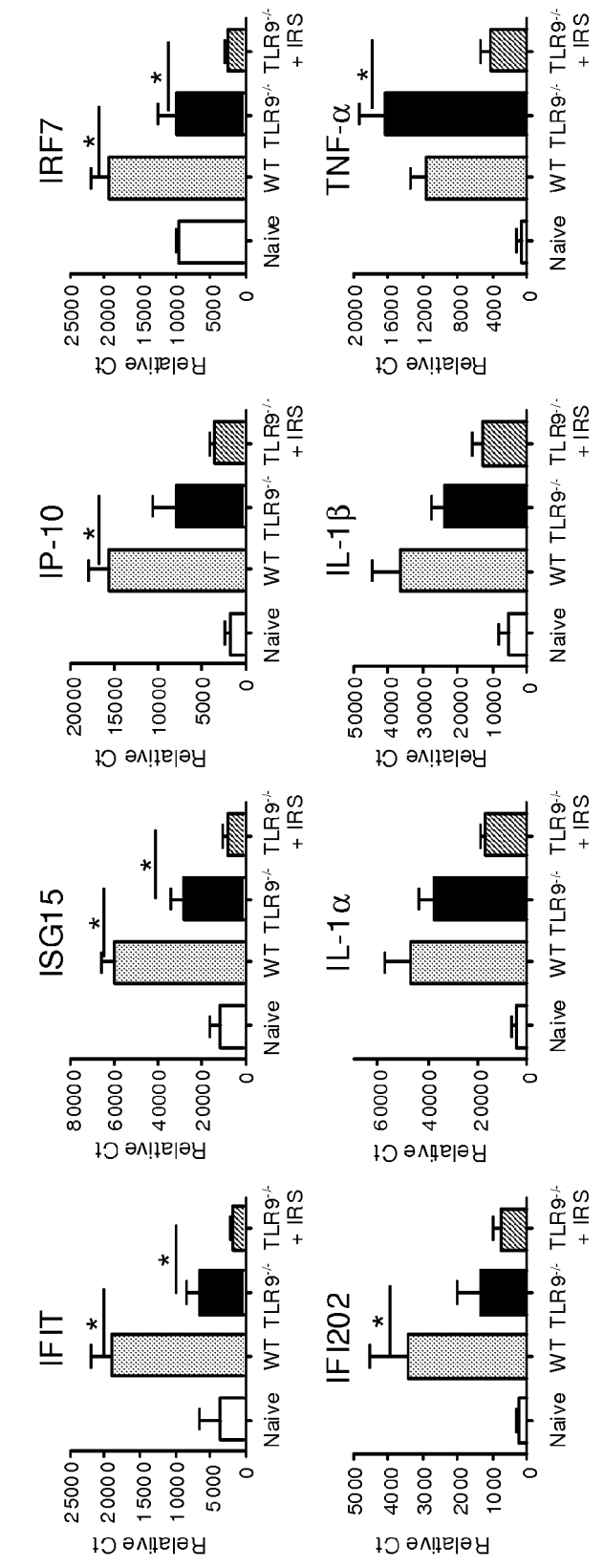
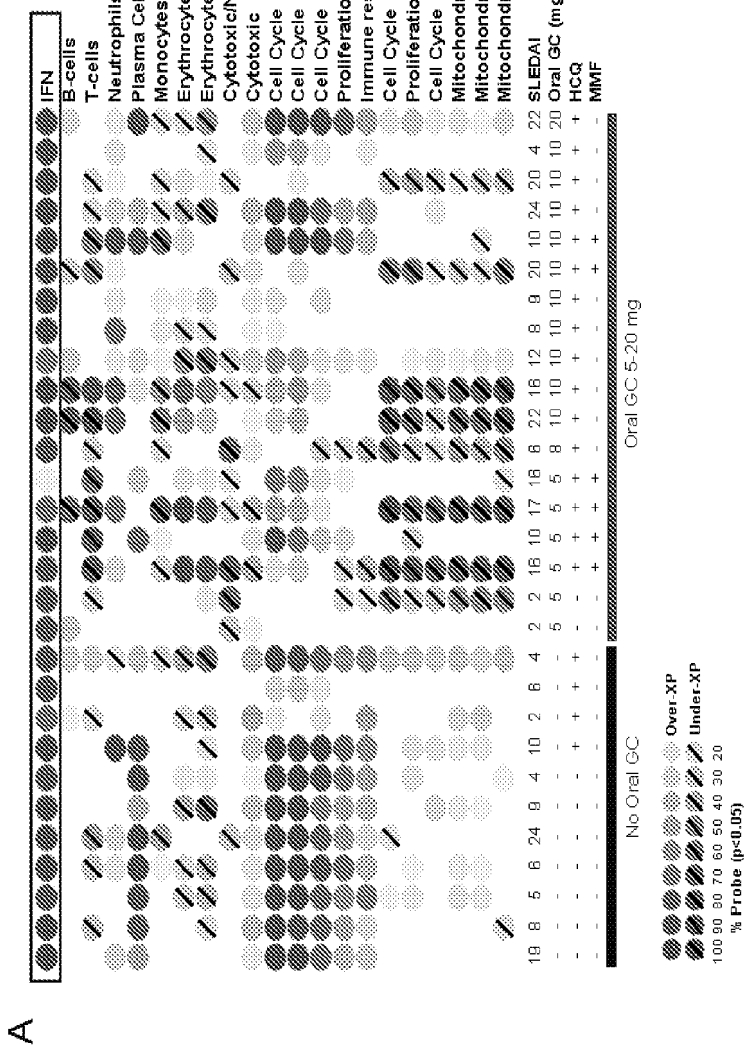

B
IFIT
ISG15
IP-10
IRF7
IFI202
IL-1α
IL-1β
TNF-α
Relative Ct
Naive
WT
TLR9-/-
TLR9-/- + IRS
*

FIG. 38


A
IFN
B-cells
T-cells
Neutrophils
Plasma Cells
Monocytes
Erythrocytes
Erythrocytes
Cytotoxic/NK
Cytotoxic
Cell Cycle
Cell Cycle
Cell Cycle
Proliferation
Immune responses
Cell Cycle
Proliferation
Cell Cycle
Mitochondrial Respiration
Mitochondrial Respiration
Mitochondrial Stress
SLEDAI
Oral GC (mg)
HCQ
MMF
No Oral GC
Oral GC 5-20 mg
Over-XP
Under-XP
% Probe (p<0.05)

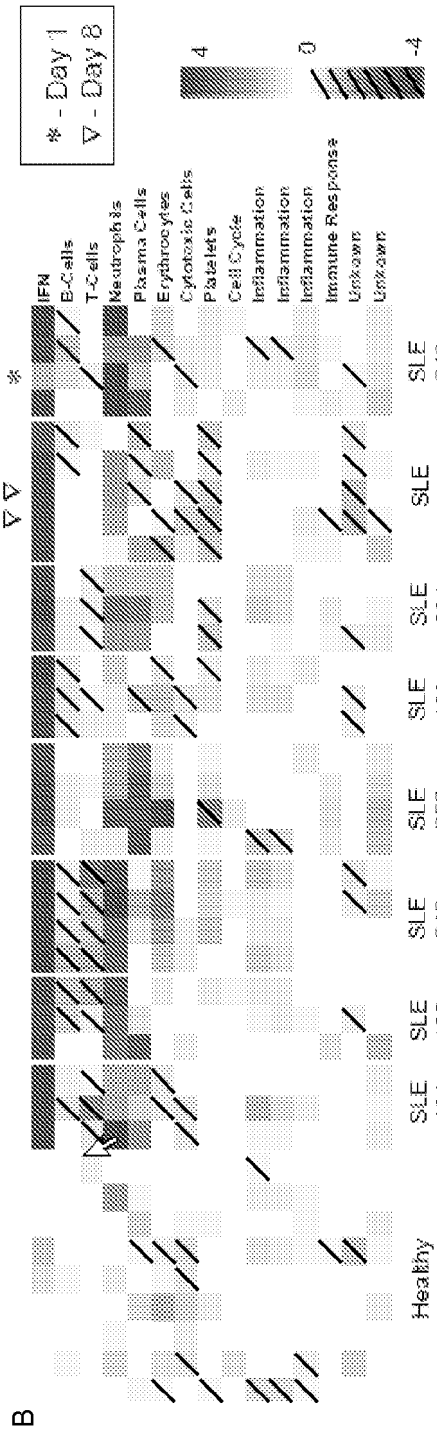

B
Healthy Controls
SLE 164
SLE 190
SLE 212
SLE 252
SLE 133
SLE 231
SLE 242
SLE 249
IFN
B-Cells
T-Cells
Neutrophils
Plasma Cells
Erythrocytes
Cytotoxic Cells
Platelets
Cell Cycle
Inflammation
Inflammation
Inflammation
Immune Response
Unknown
Unknown
* - Day 1
∇ - Day 8
4
0
-4

FIG. 38