FIG. 1A

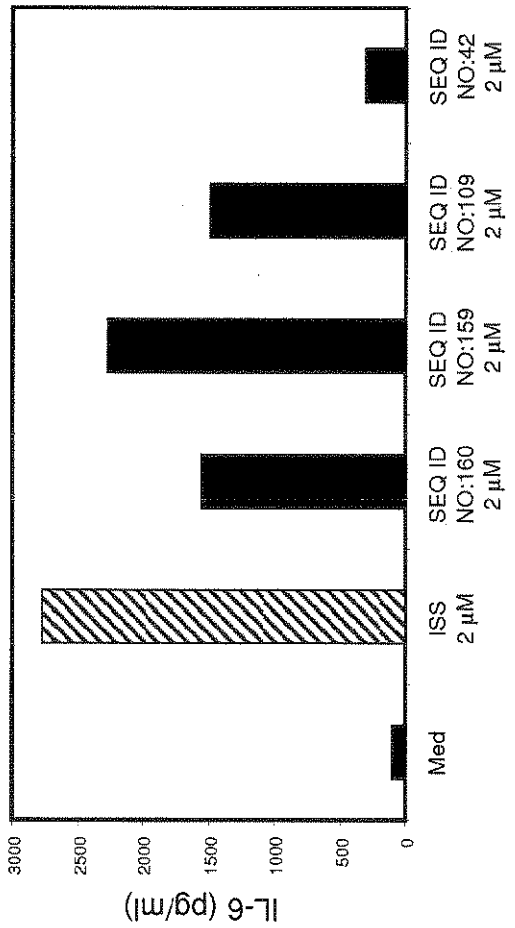


FIG. 1B

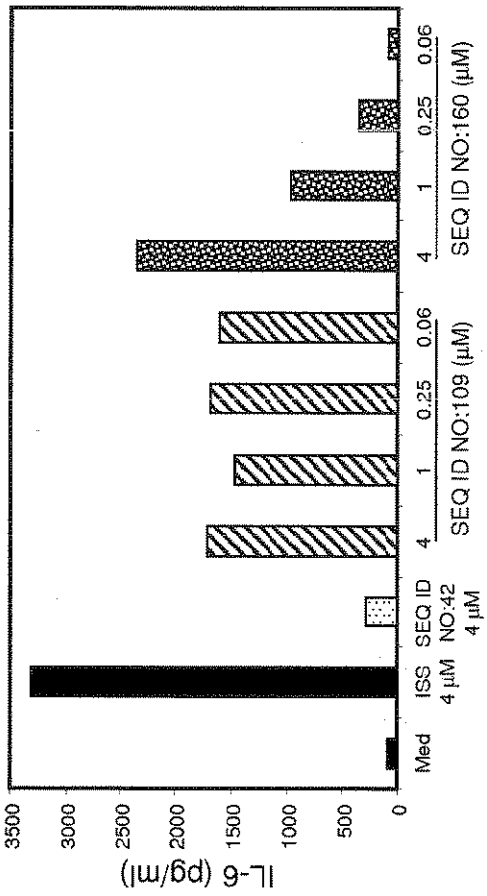
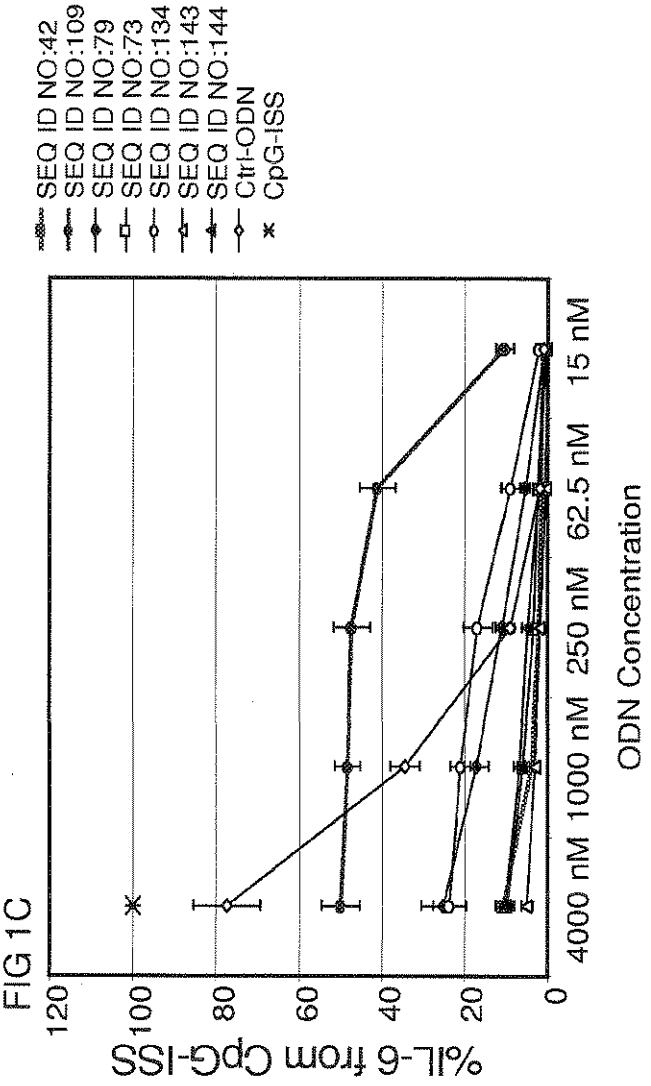
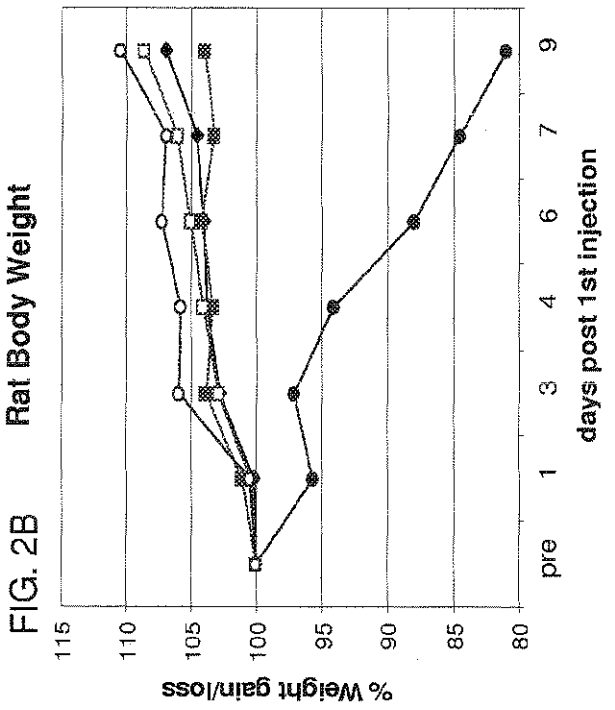
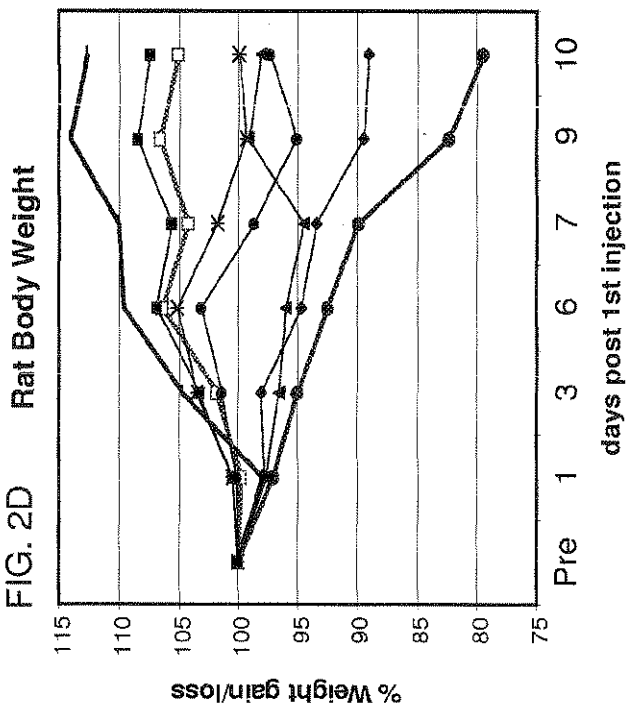
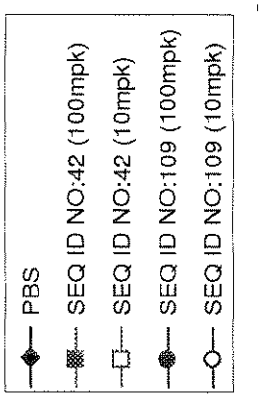


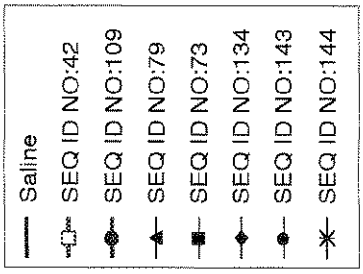
FIG 1C

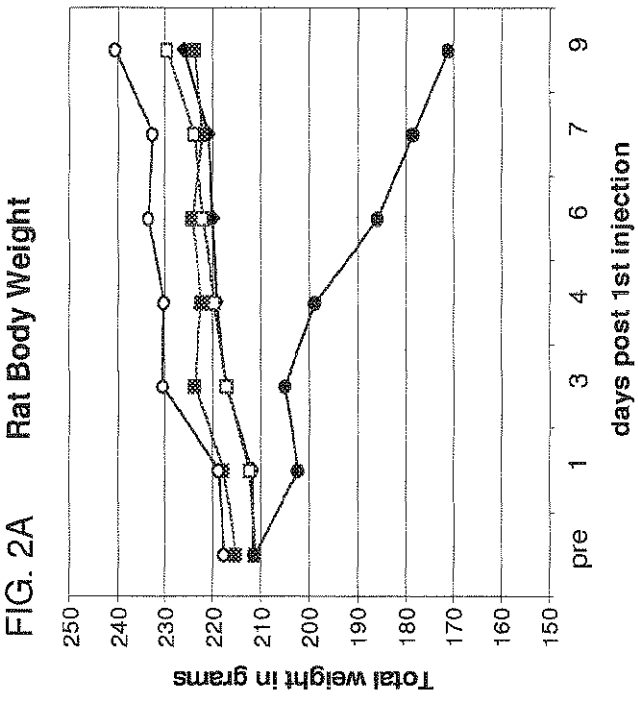


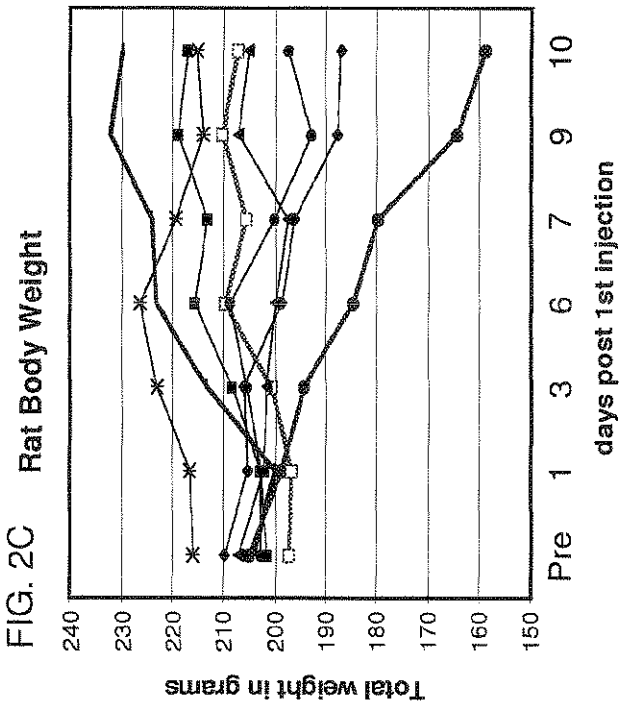

FIG. 2B Rat Body Weight
% Weight gain/loss
days post 1st injection
pre 1 3 4 6 7 9
115 110 105 100 95 90 85 80


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


PBS
SEQ ID NO:42 (100mpk)
SEQ ID NO:42 (10mpk)
SEQ ID NO:109 (100mpk)
SEQ ID NO:109 (10mpk)


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. 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


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

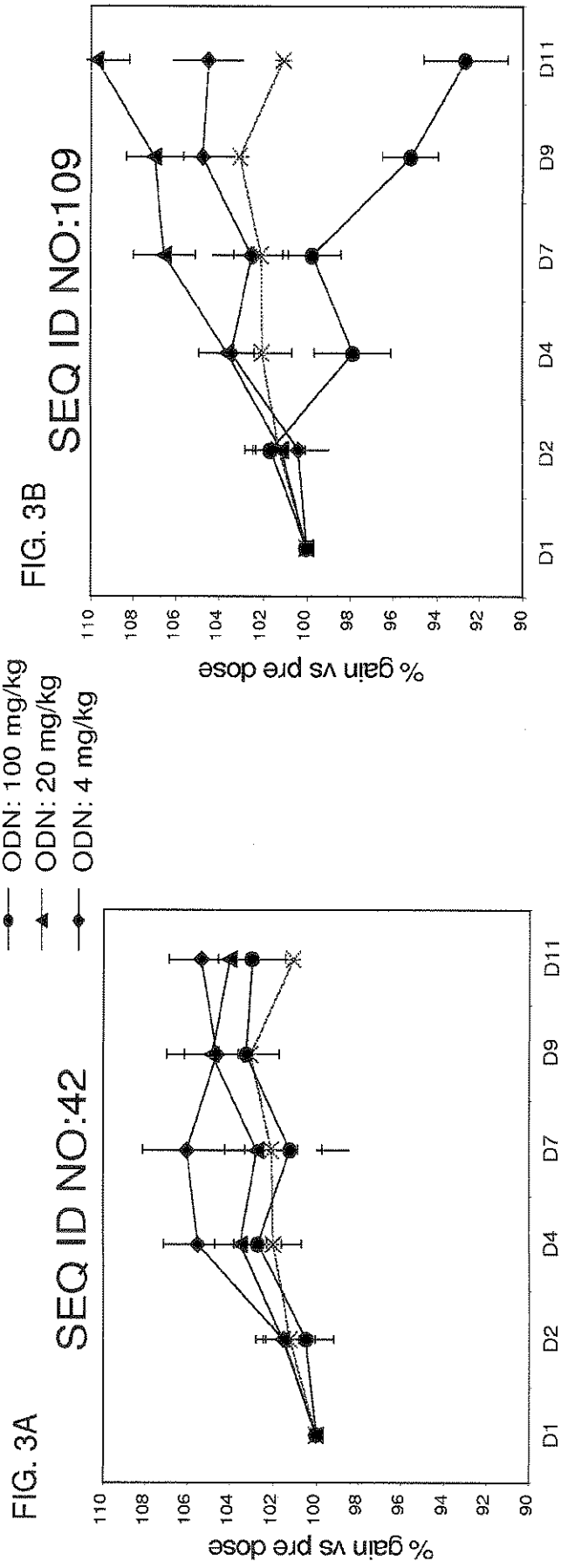

FIG. 3A
SEQ ID NO:42
% gain vs pre dose
110
108
106
104
102
100
98
96
94
92
90
D1
D2
D4
D7
D9
D11
Saline
ODN: 100 mg/kg
ODN: 20 mg/kg
ODN: 4 mg/kg

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

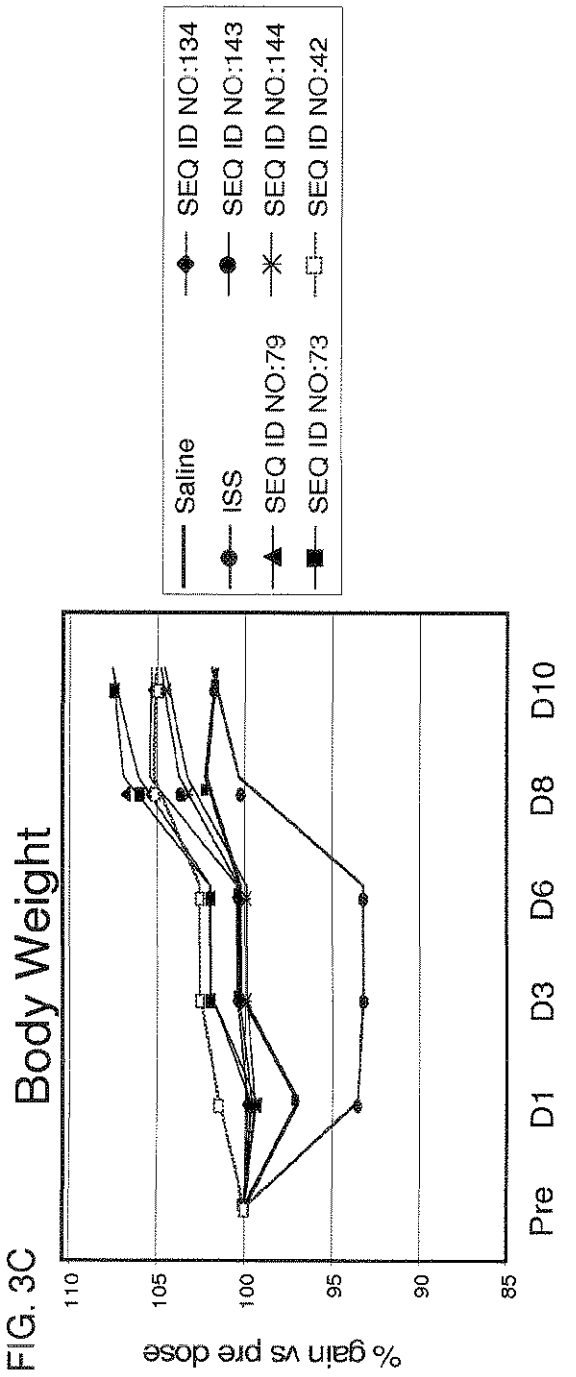

FIG. 3C
Body Weight
% gain vs pre dose
110
105
100
95
90
85
Pre
D1
D3
D6
D8
D10
Saline
ISS
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
SEQ ID NO:42

FIG. 4A

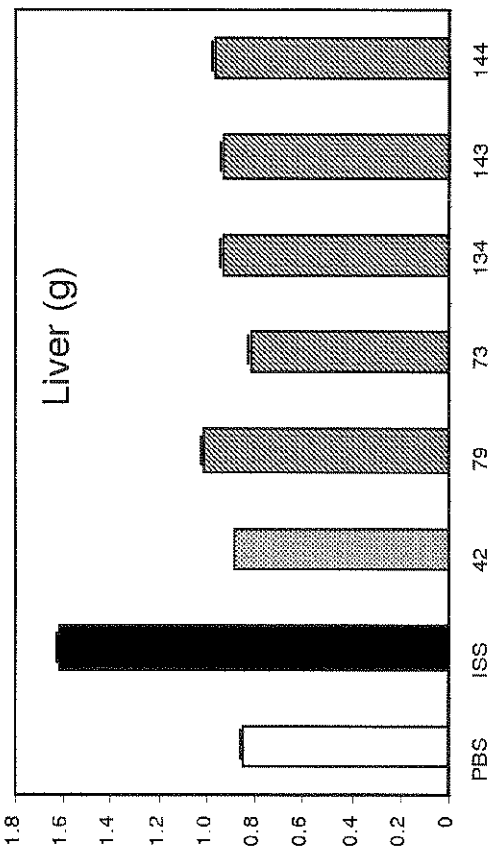


FIG. 4B

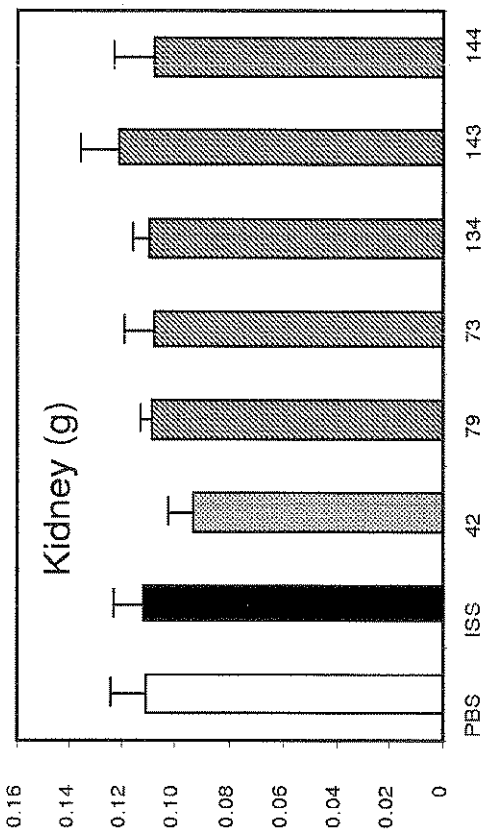


FIG. 4C

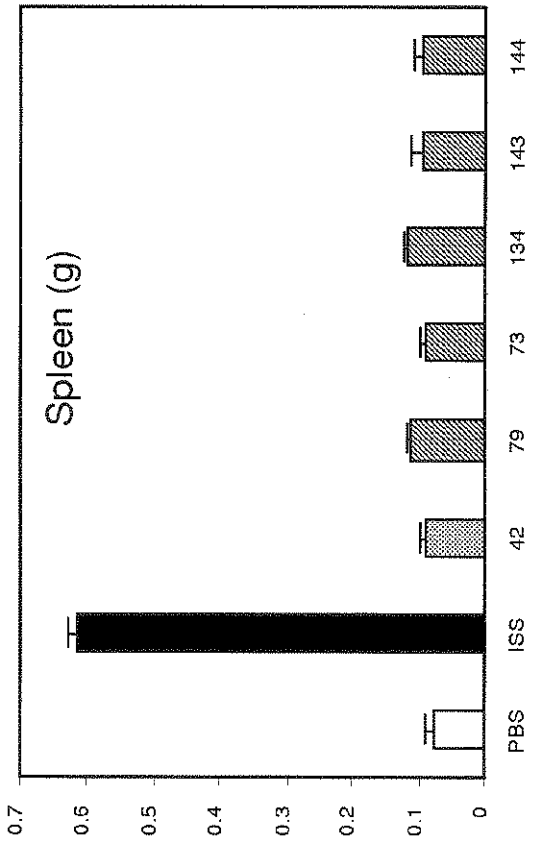
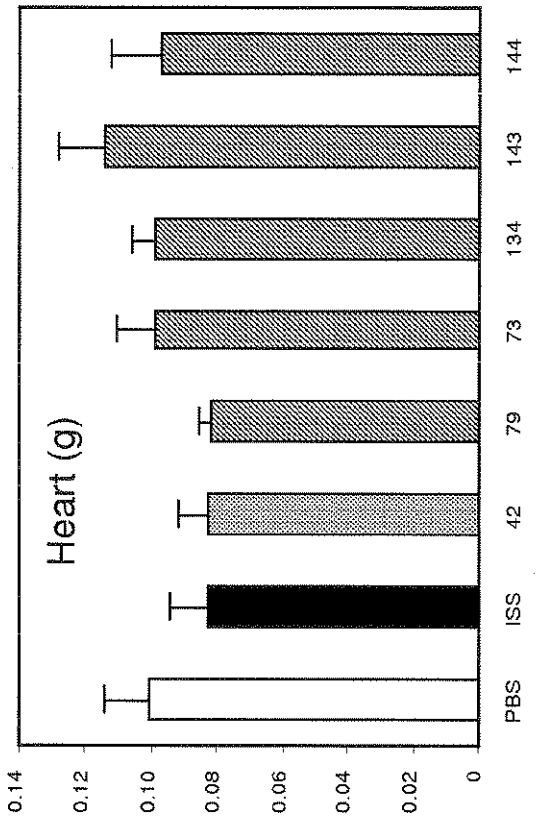
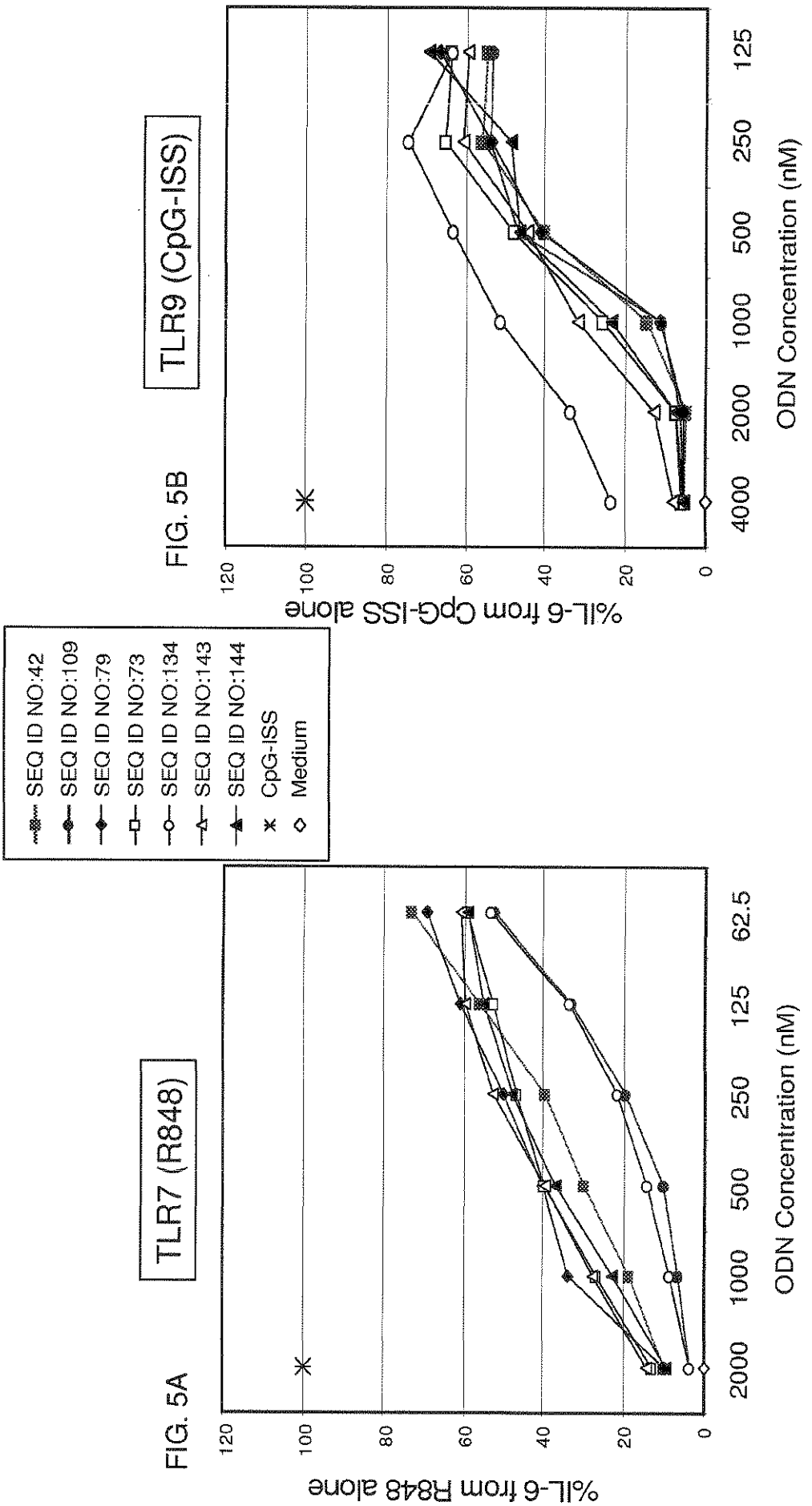
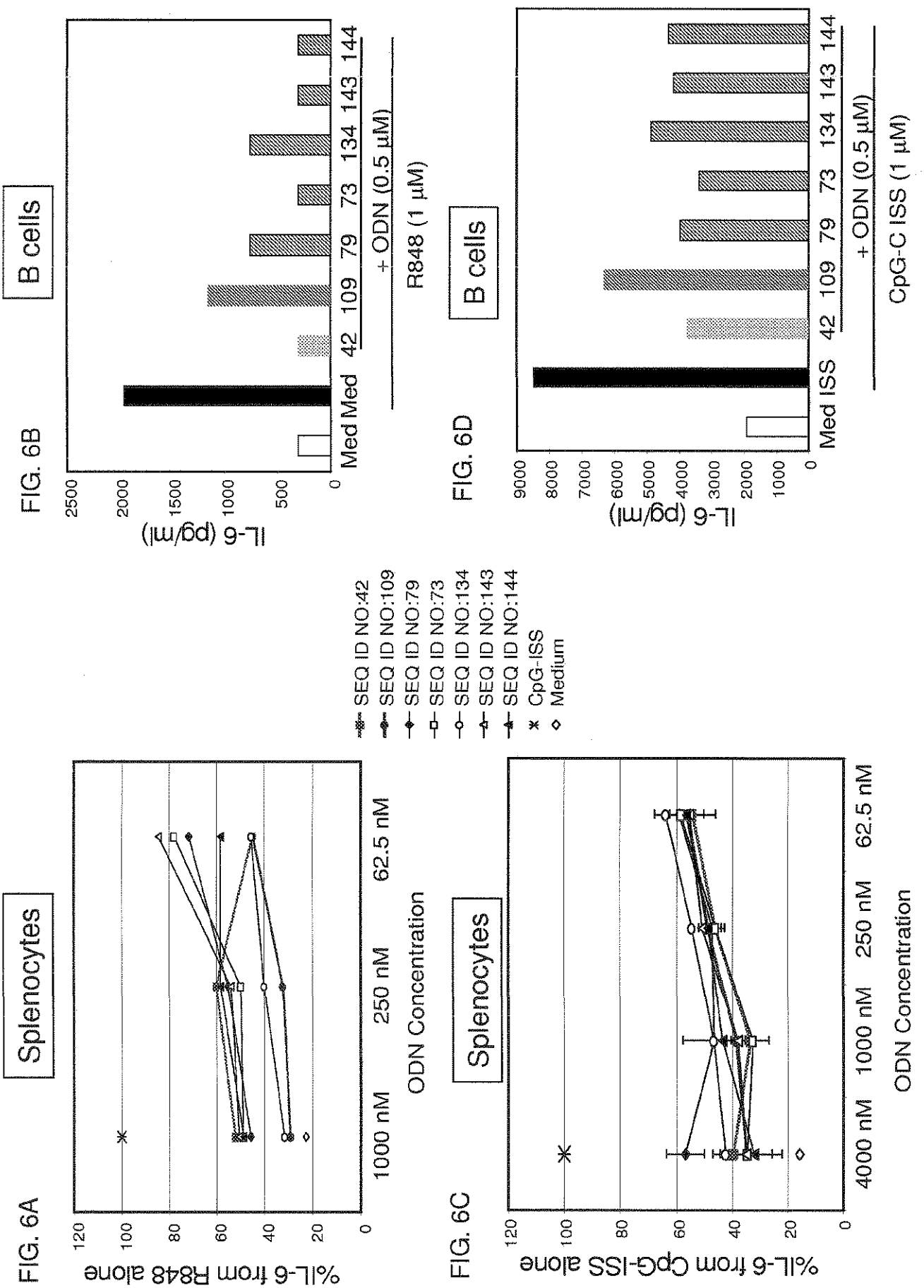
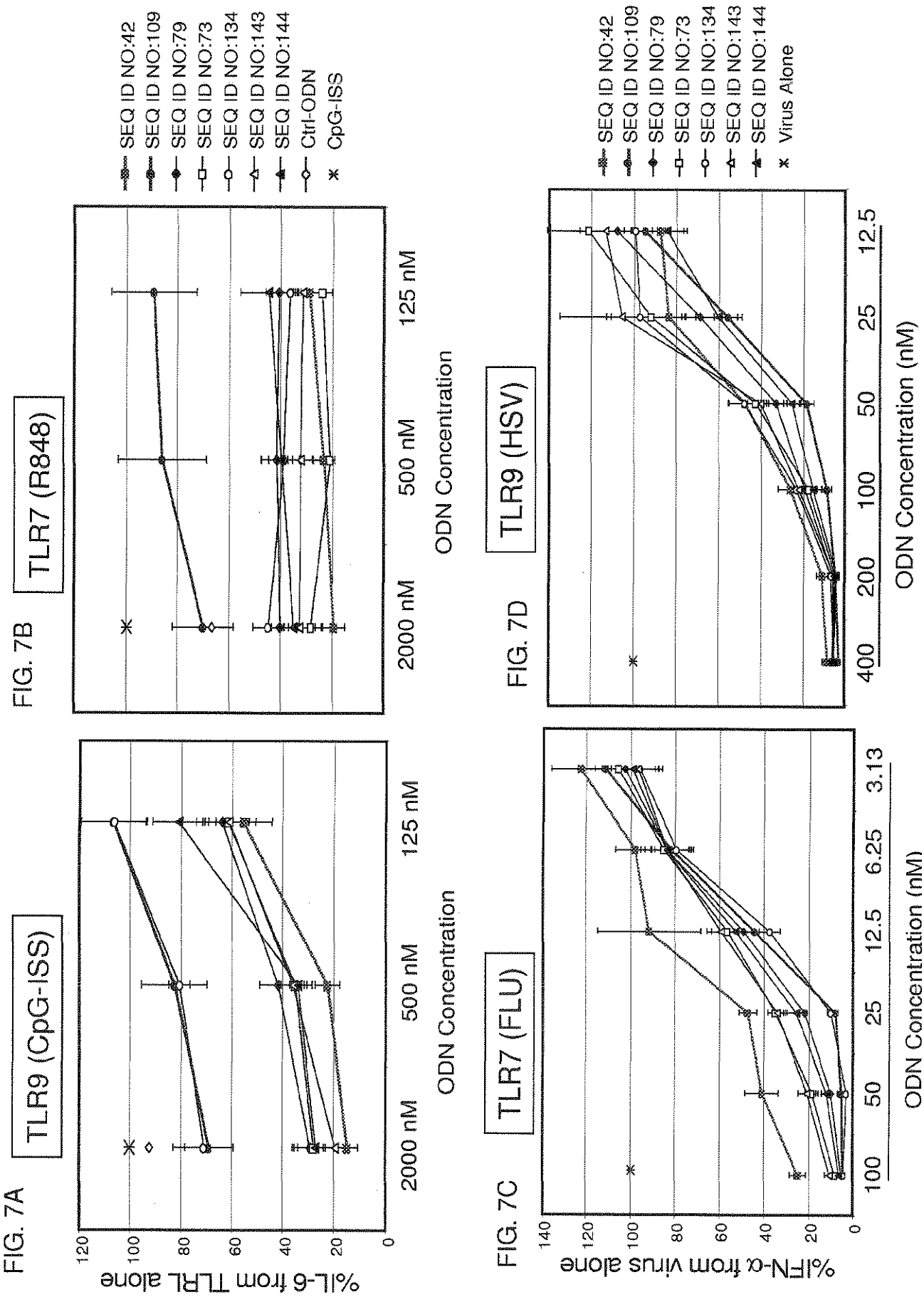


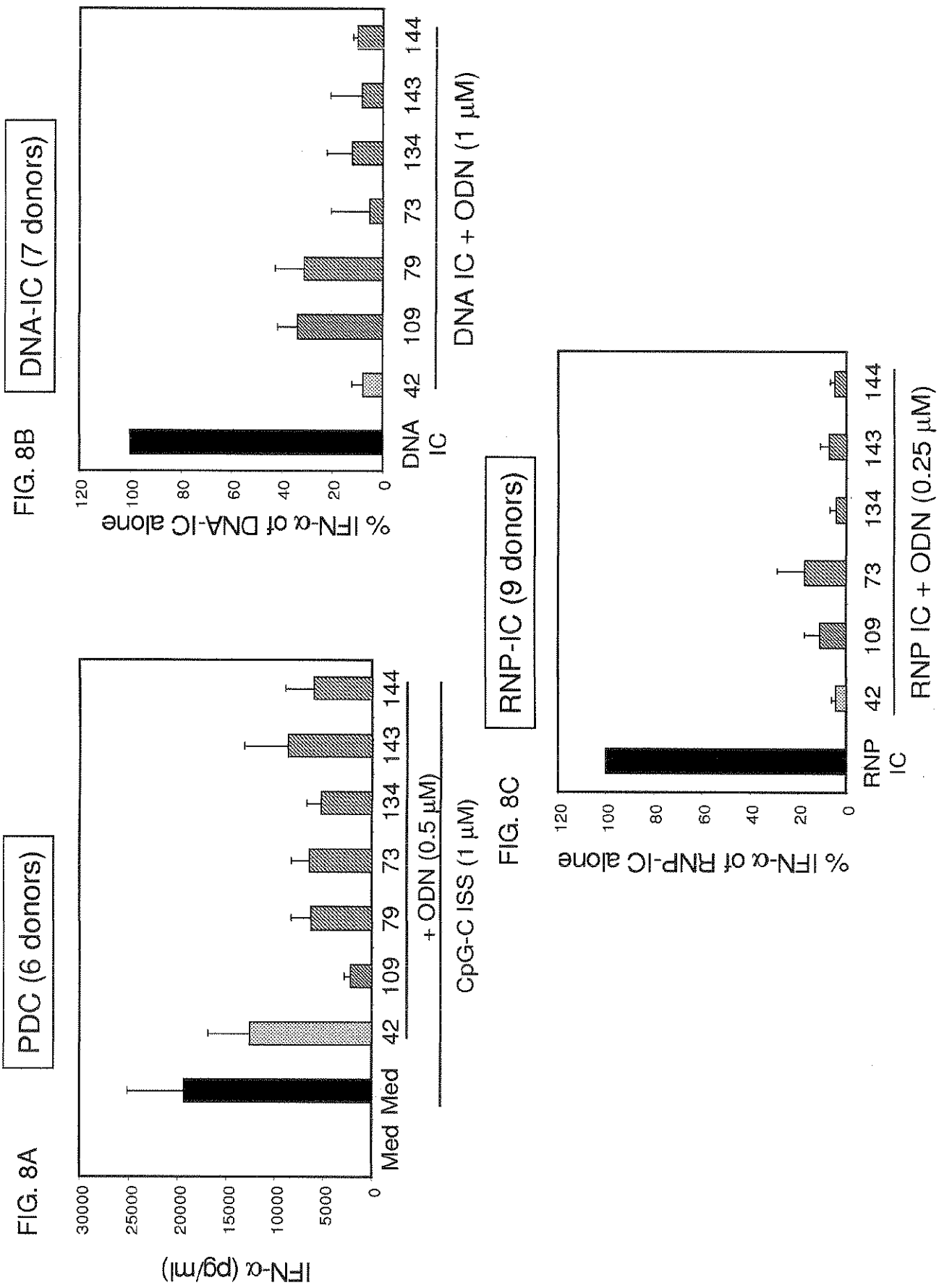
FIG. 4D

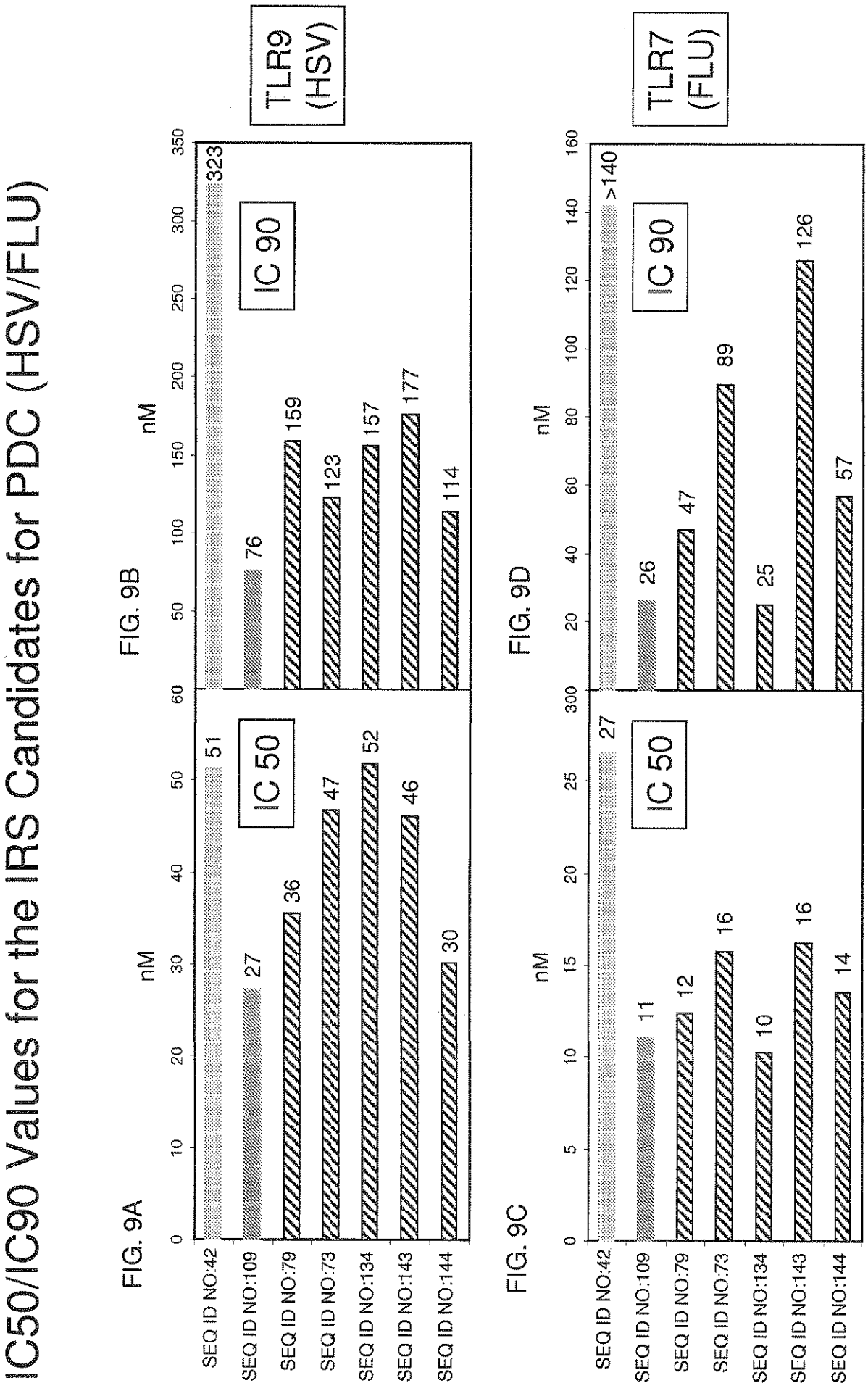



FIG. 5A
TLR7 (R848)
%IL-6 from R848 alone
ODN Concentration (nM)
2000
1000
500
250
125
62.5
0
20
40
60
80
100
120
SEQ ID NO:42
SEQ ID NO:109
SEQ ID NO:79
SEQ ID NO:73
SEQ ID NO:134
SEQ ID NO:143
SEQ ID NO:144
CpG-ISS
Medium
FIG. 5B
TLR9 (CpG-ISS)
%IL-6 from CpG-ISS alone
ODN Concentration (nM)
4000
2000
1000
500
250
125
0
20
40
60
80
100
120


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
FIG. 9B
FIG. 9C
FIG. 9D
nM
IC 50
IC 90
TLR9 (HSV)
TLR7 (FLU)
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
323
76
159
123
157
177
114
27
11
12
16
10
16
14
>140
26
47
89
25
126
57

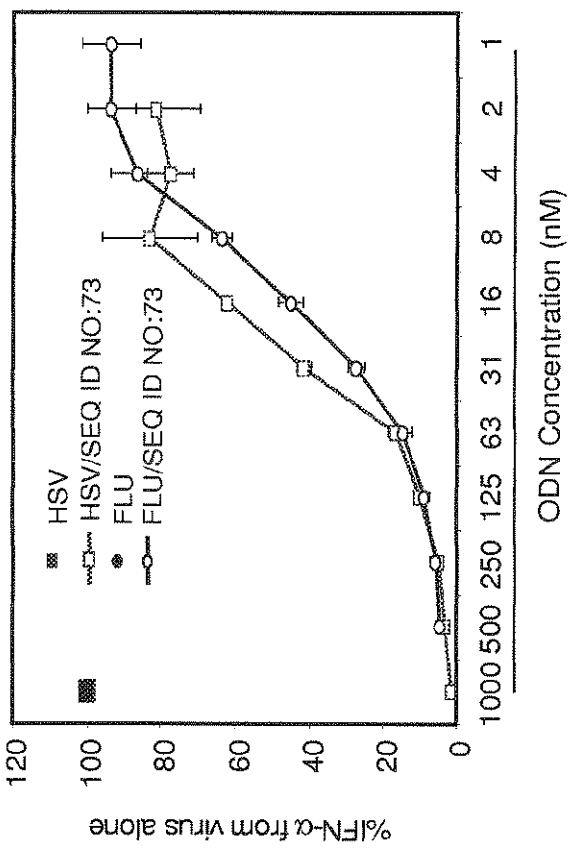


FIG. 10A

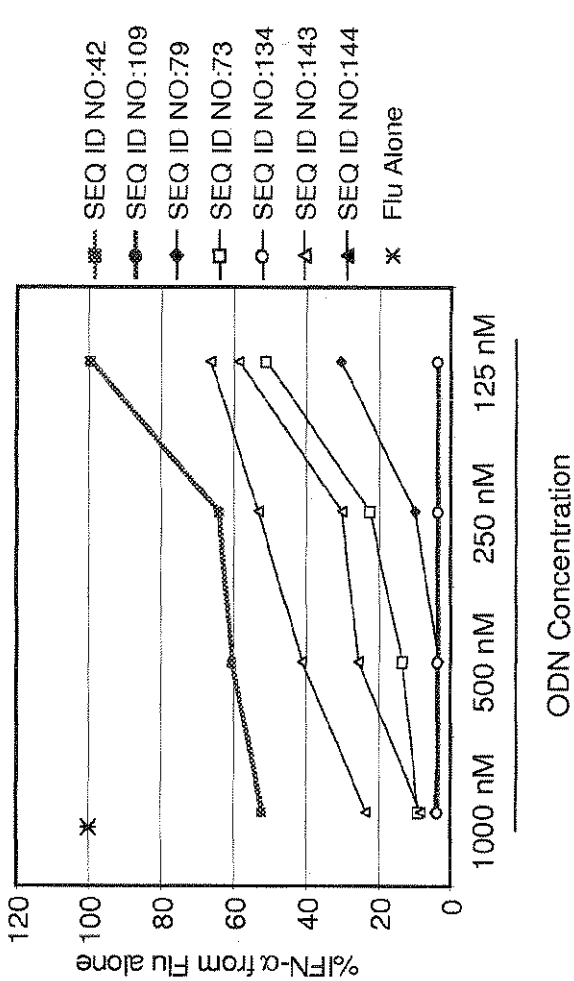


FIG. 10B



FIG. 10C

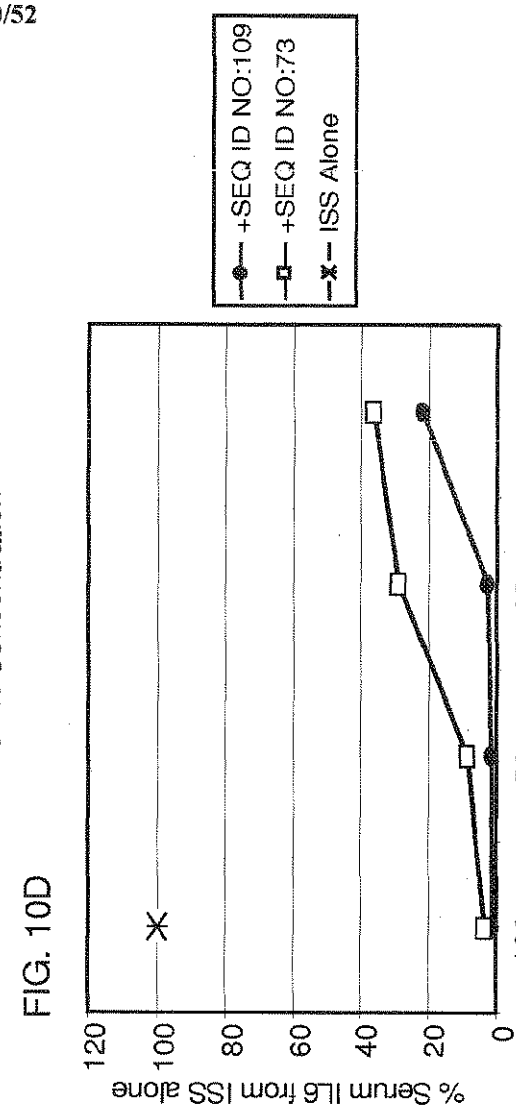


FIG. 10D

FIG. 11A Liver

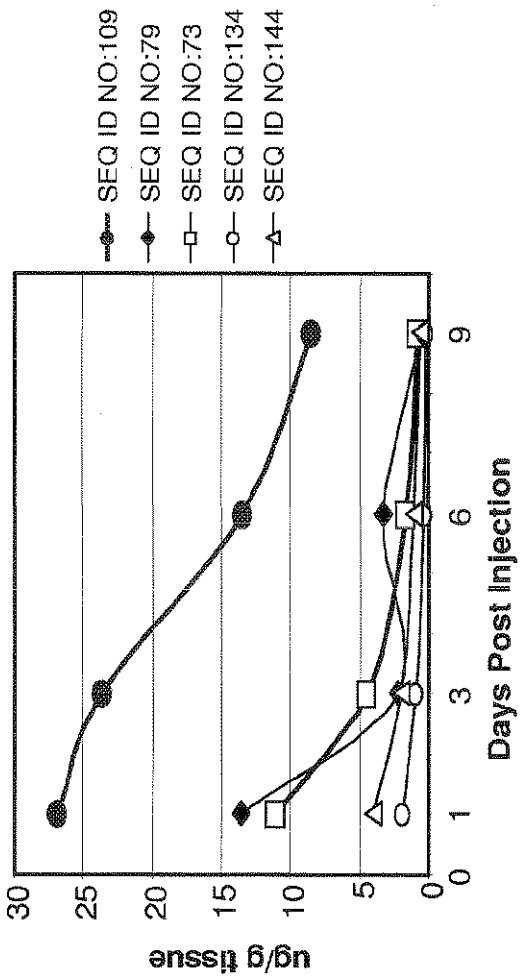


FIG. 11B Kidney

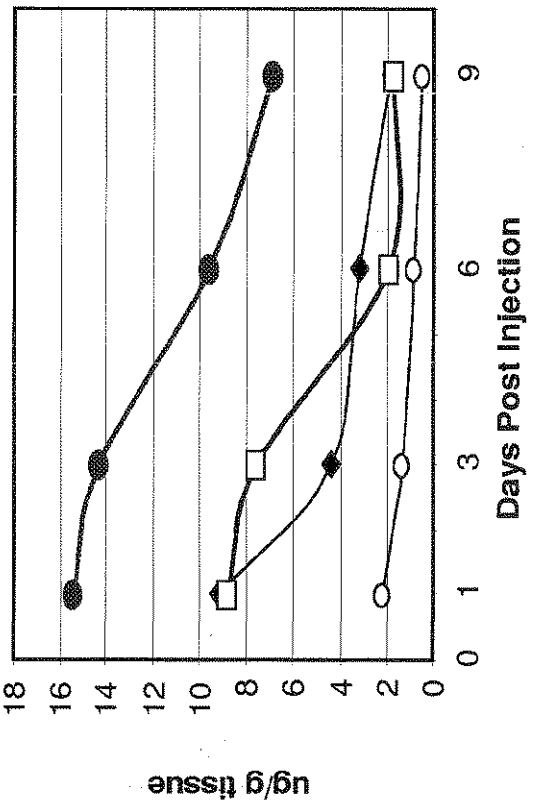


FIG. 11C SEQ ID NO:73

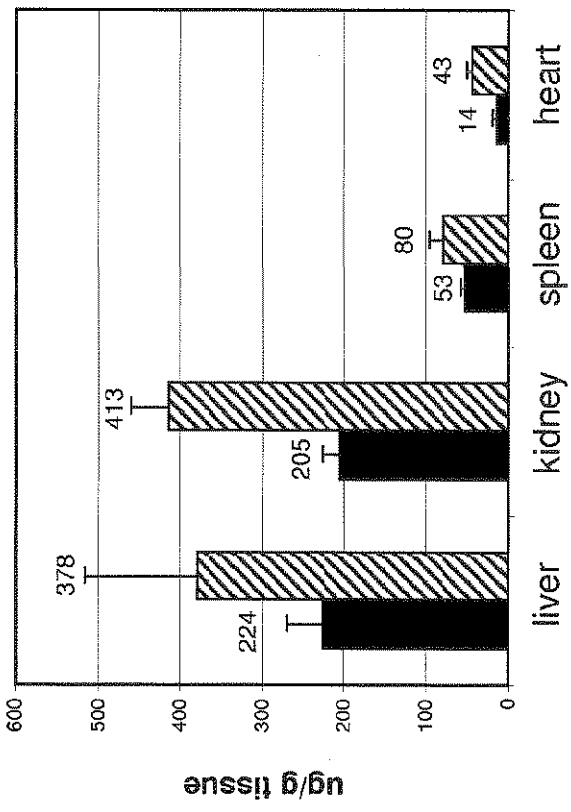
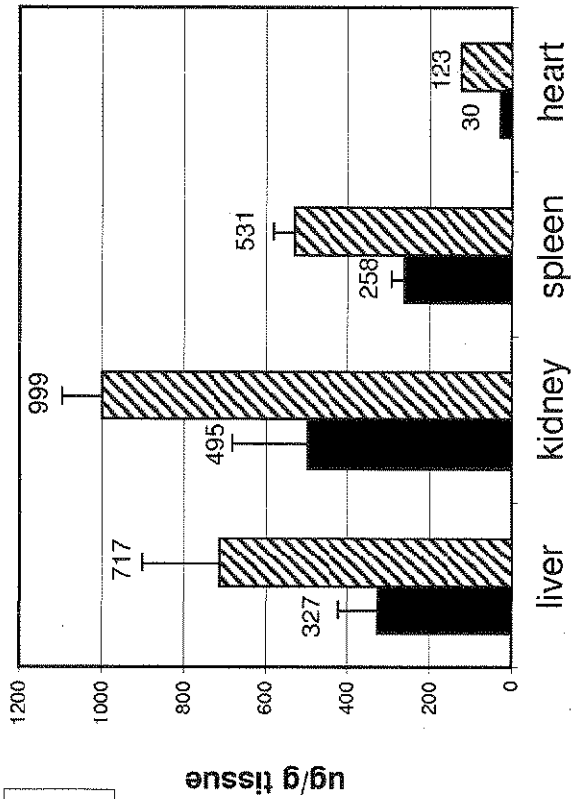


FIG. 11D SEQ ID NO:109



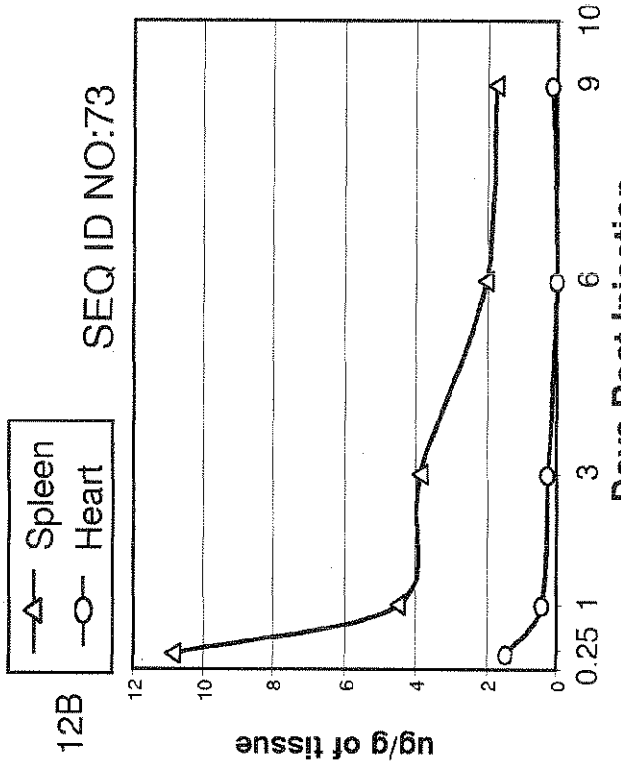


FIG. 12A

FIG. 12B

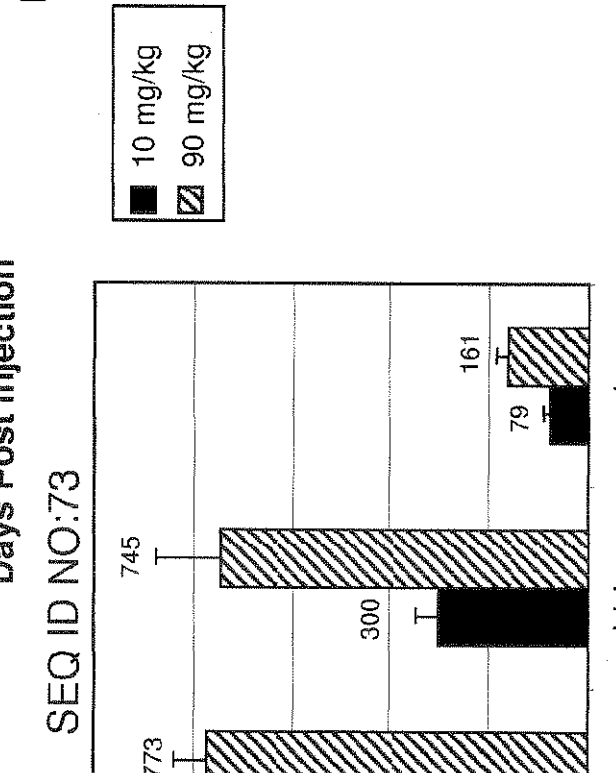


FIG. 12C

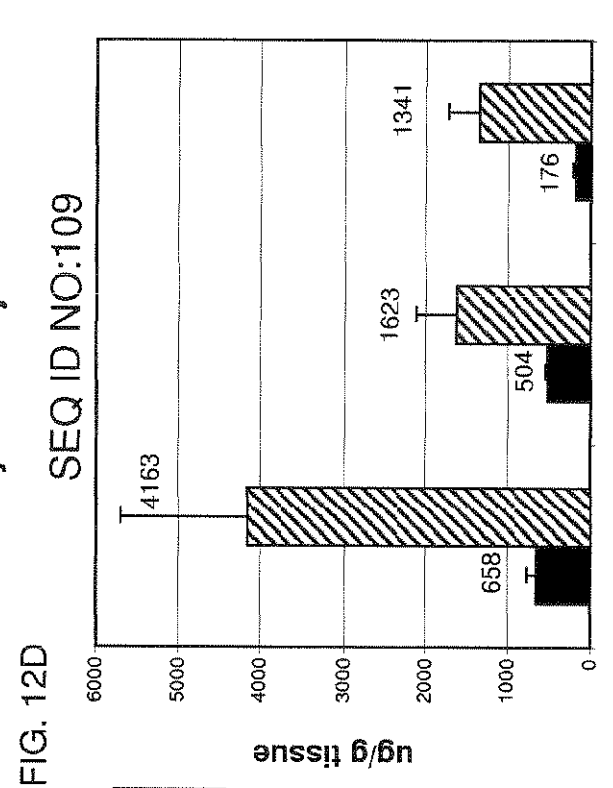
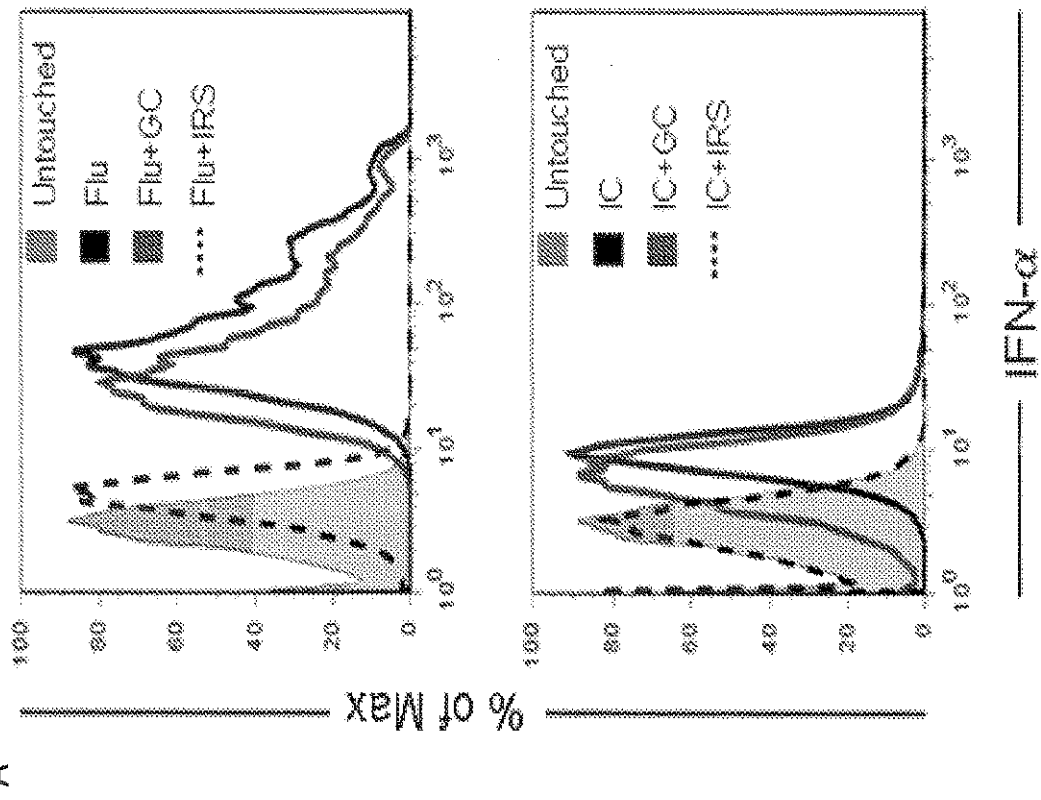


FIG. 12D

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

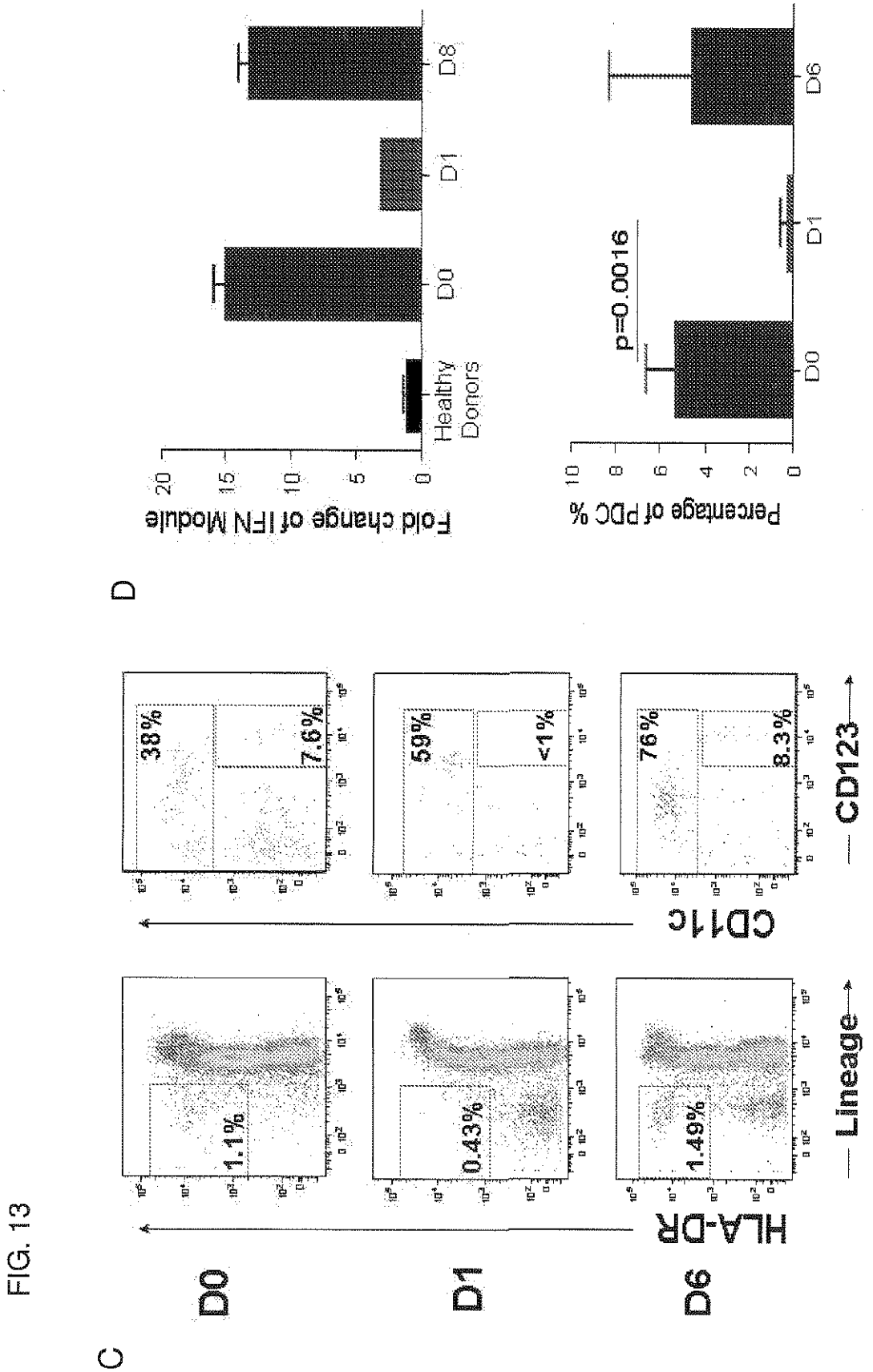

C
D0
D1
D6
HLA-DR
Lineage
CD1c
CD123
1.1%
0.43%
1.49%
38%
7.6%
59%
<1%
76%
8.3%
D
Fold change of IFN Module
Healthy Donors
D0
D1
D8
Percentage of pDC %
p=0.0016
D0
D1
D6

FIG. 13

FIG. 14

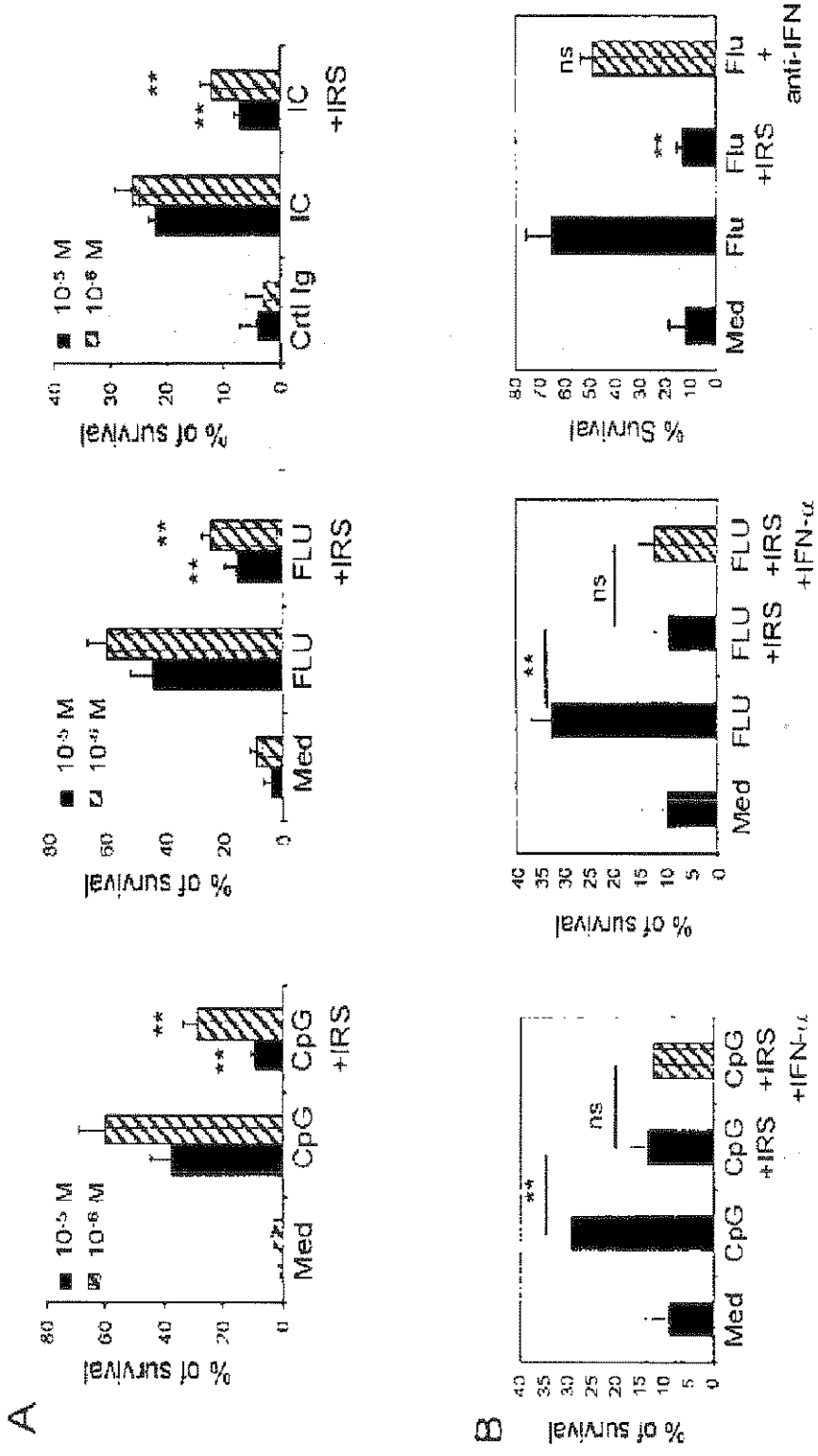

A
B
% of survival
10-5 M
10-6 M
Med
CpG
CpG +IRS
Ctrl Ig
IC
IC +IRS
FLU
FLU +IRS
Flu
Flu +IRS
Flu + anti-IFN
+IFN-α
ns
**

FIG. 14

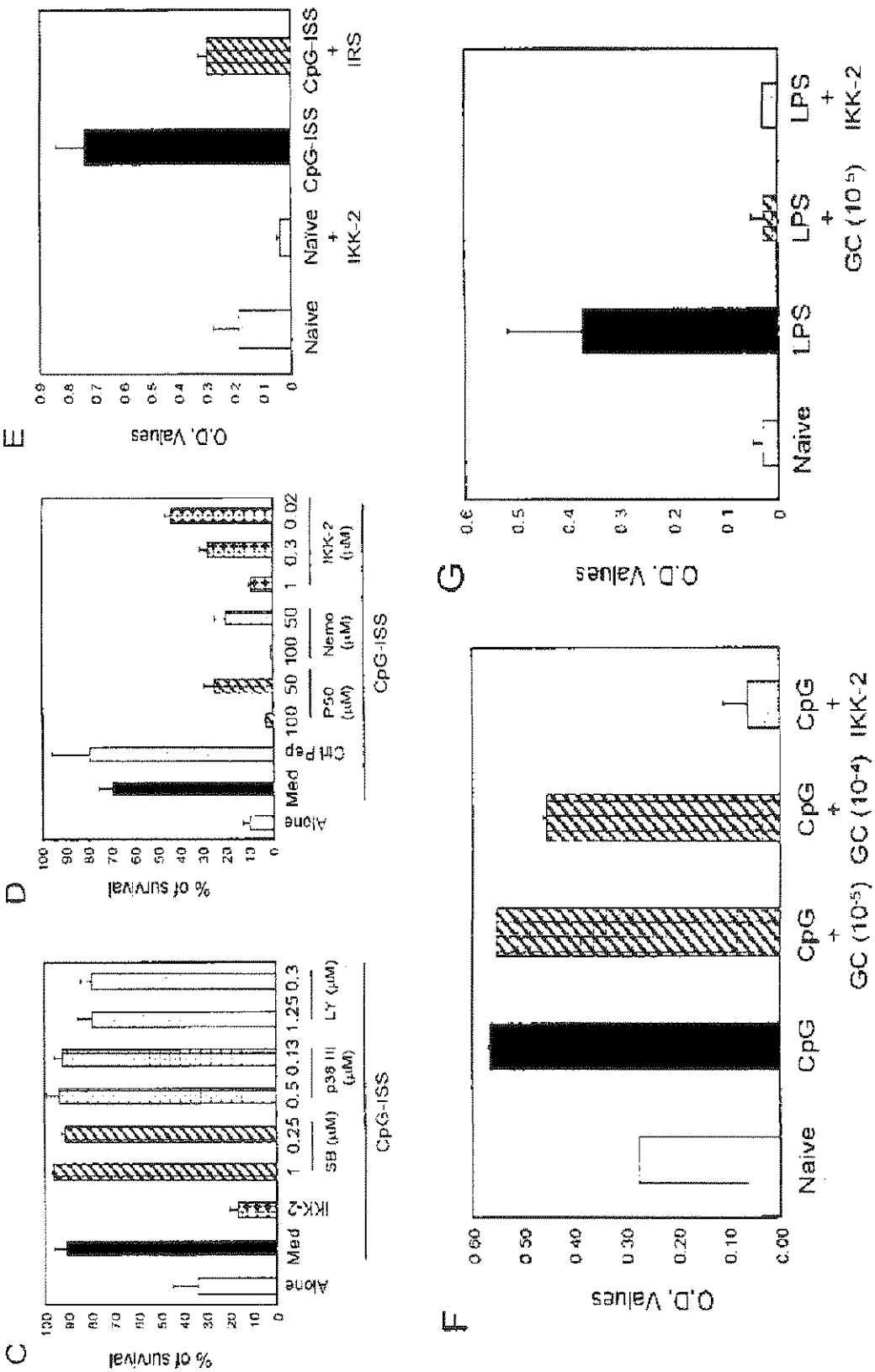

C
% of survival
Alone
Med
IKK-2
SB (μM)
p38 III (μM)
LY (μM)
CpG-ISS
D
% of survival
Alone
Med
Cell Pep
P50 (μM)
Nemo (μM)
IKK-2 (μM)
CpG-ISS
E
O.D. Values
Naive
Naive + IKK-2
CpG-ISS
CpG-ISS + IRS
F
O.D. Values
Naive
CpG
CpG + GC (10-5)
CpG + GC (10-4)
CpG + IKK-2
G
O.D. Values
Naive
LPS
LPS + GC (10-5)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

FIG. 15

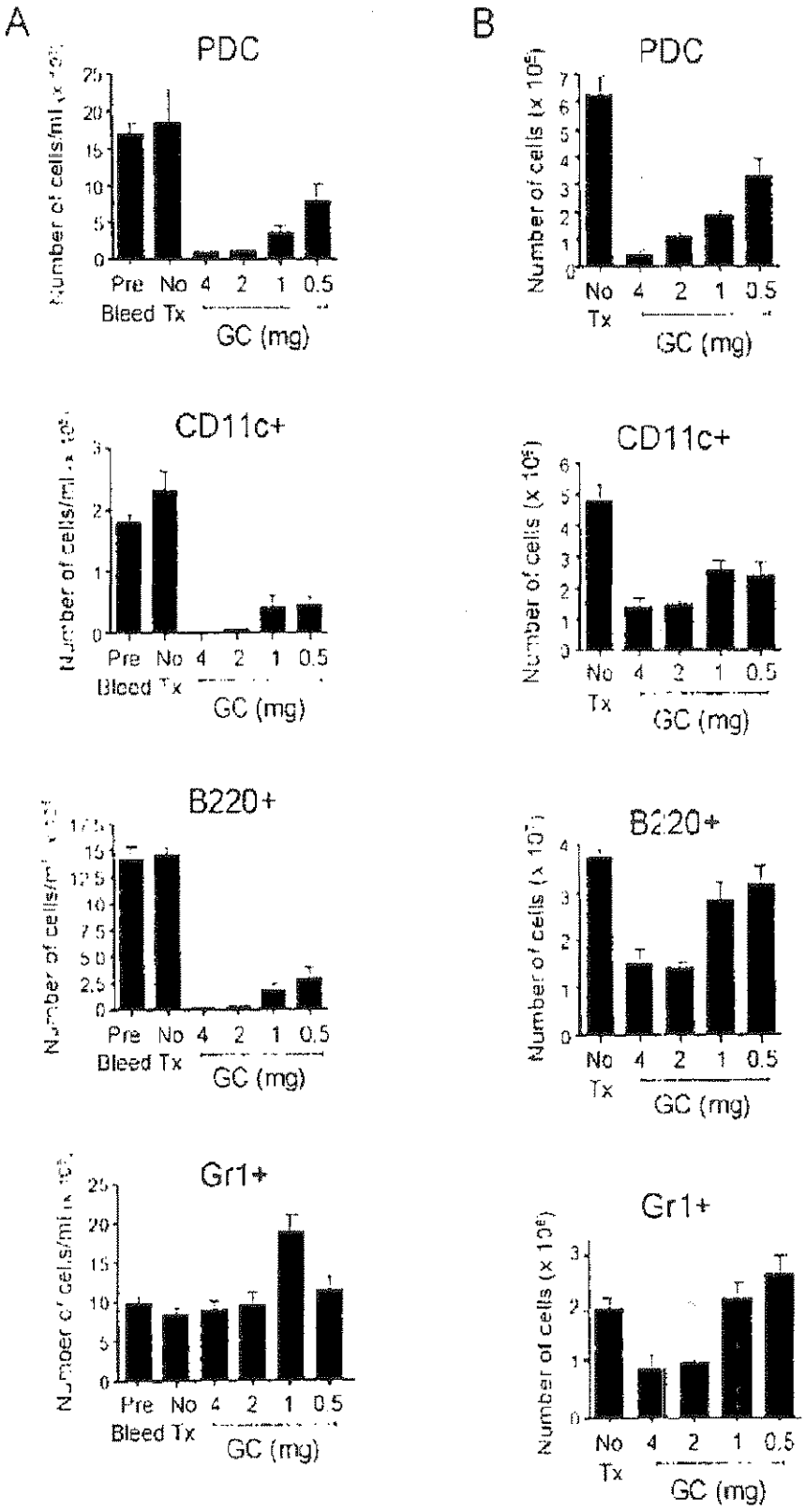

A
PDC
Number of cells/ml
Pre No 4 2 1 0.5
Bleed Tx
GC (mg)
CD11c+
B220+
Gr1+
B
PDC
Number of cells (x 10⁶)
No 4 2 1 0.5
Tx
GC (mg)
CD11c+
B220+
Gr1+

FIG. 15

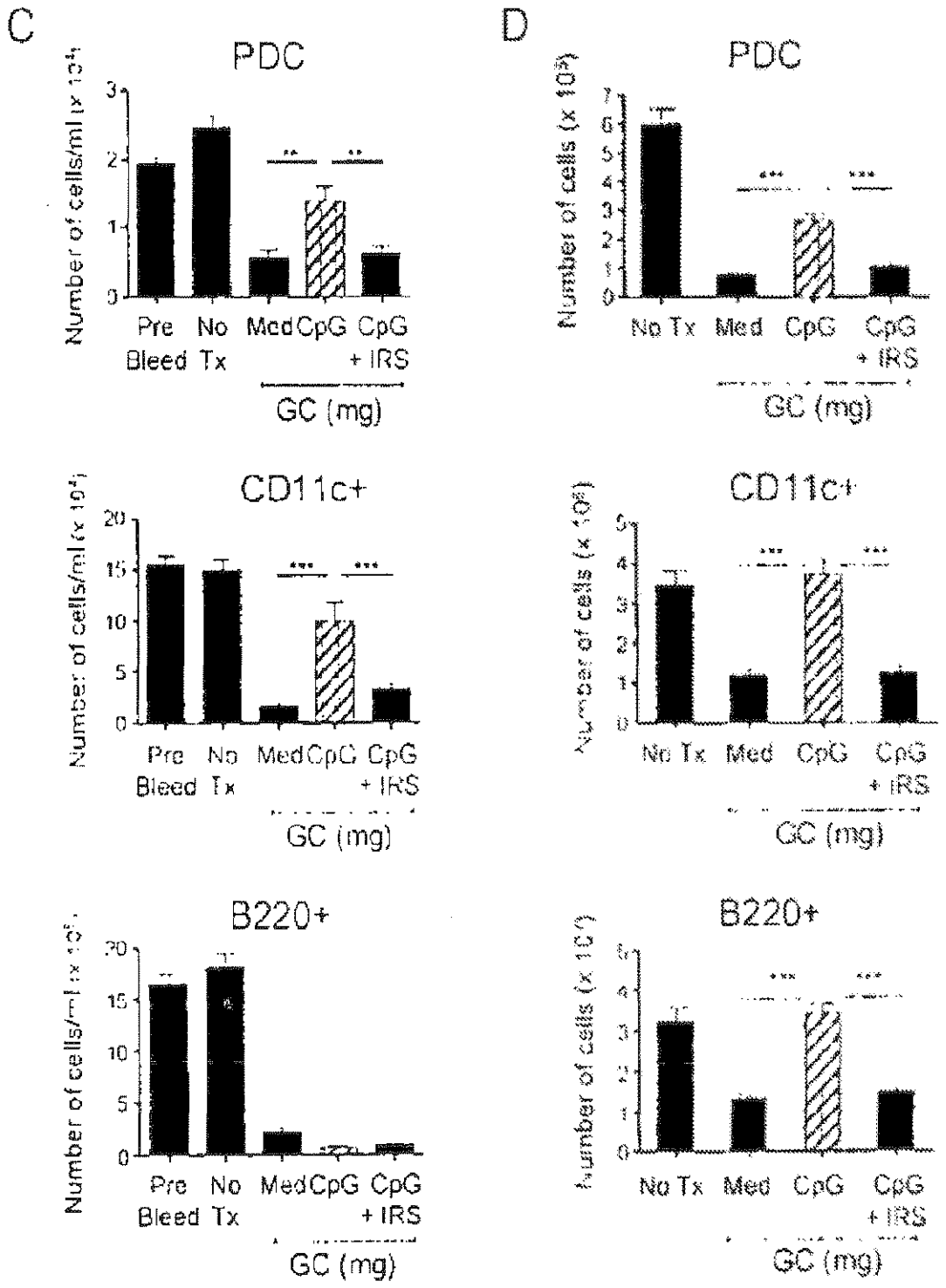

C
PDC
Number of cells/ml (x 10⁴)
Pre Bleed
No Tx
Med
CpG
CpG + IRS
GC (mg)
CD11c+
B220+
D
PDC
Number of cells (x 10⁵)
No Tx
Med
CpG
CpG + IRS
GC (mg)
CD11c+
B220+

FIG. 16

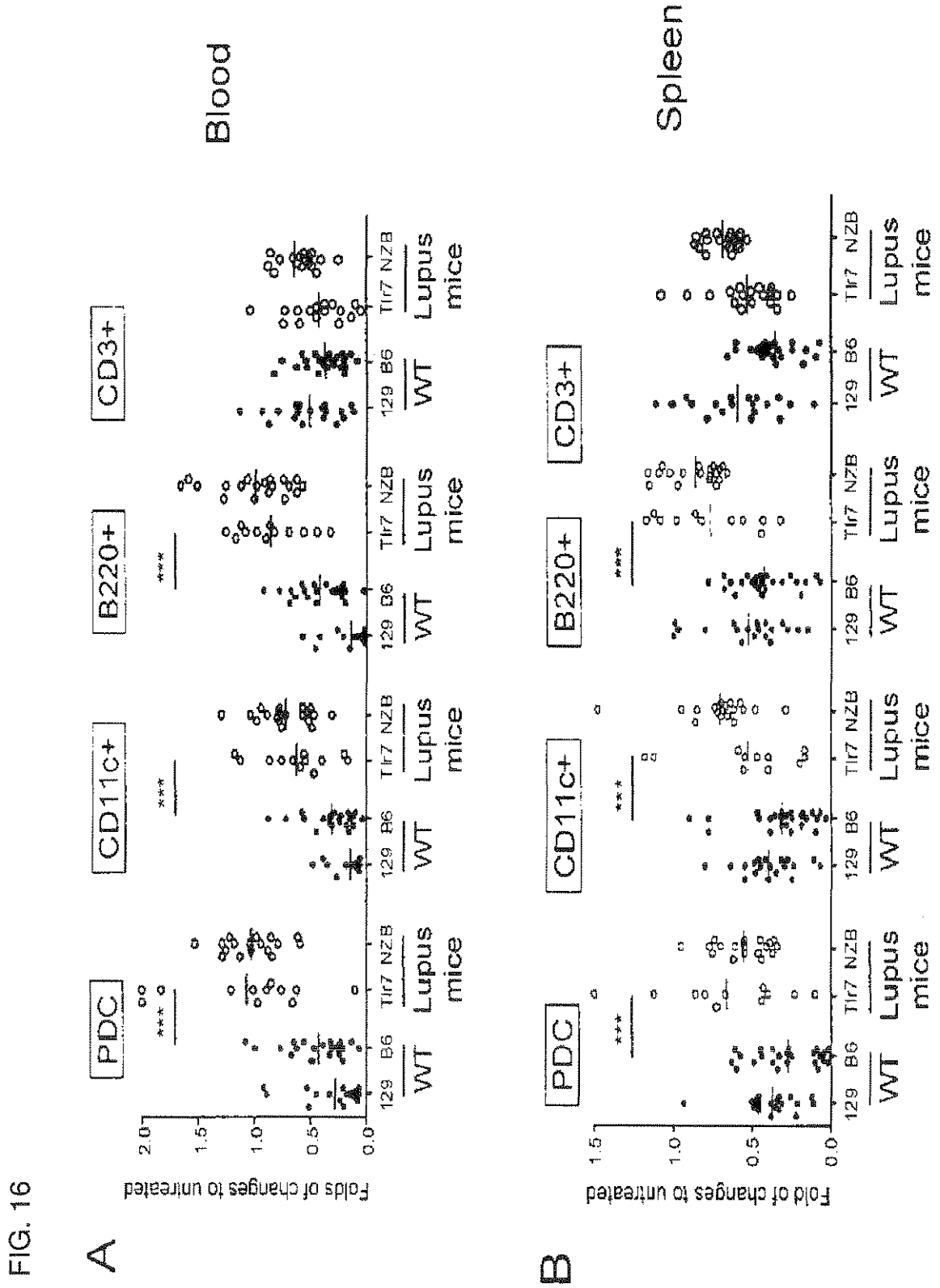
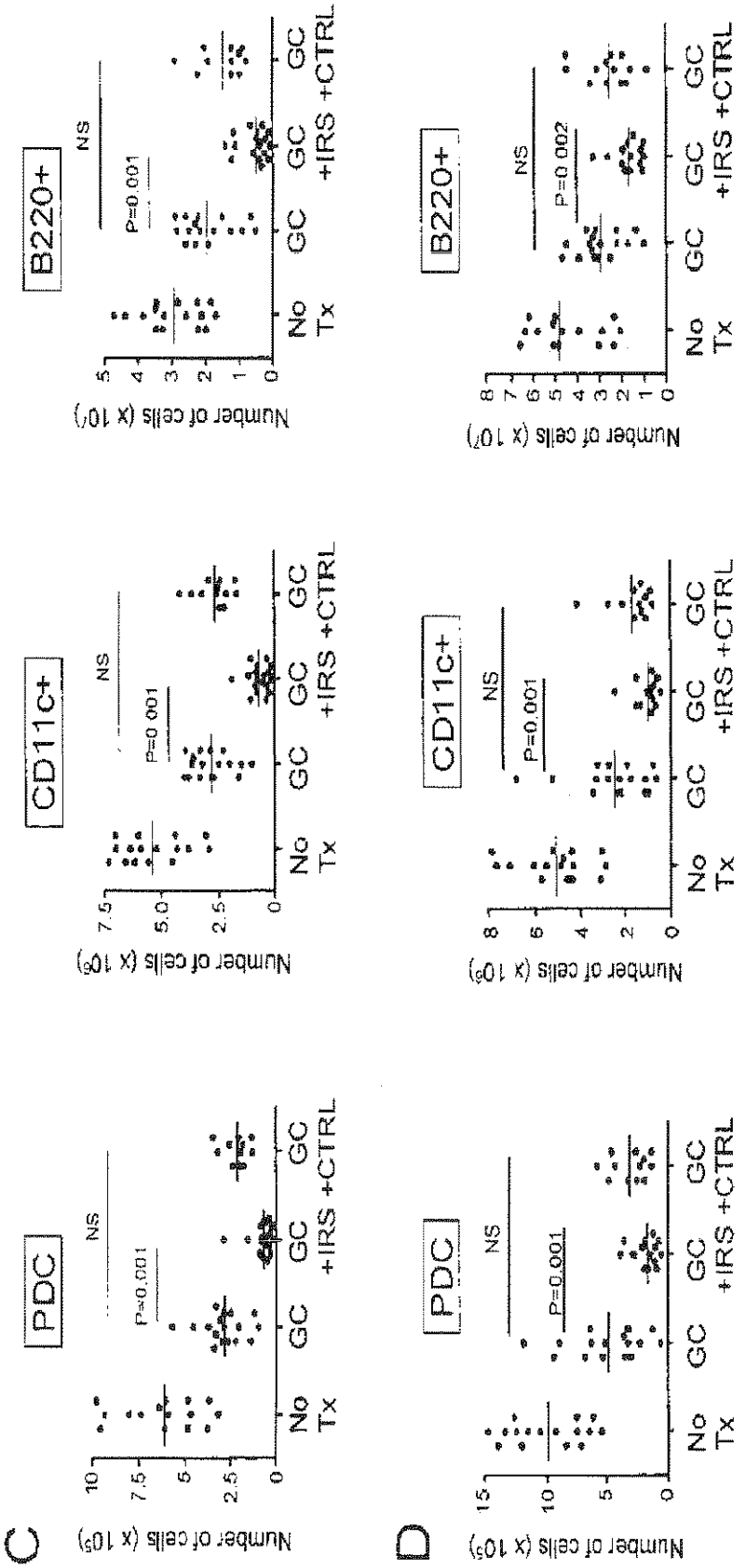
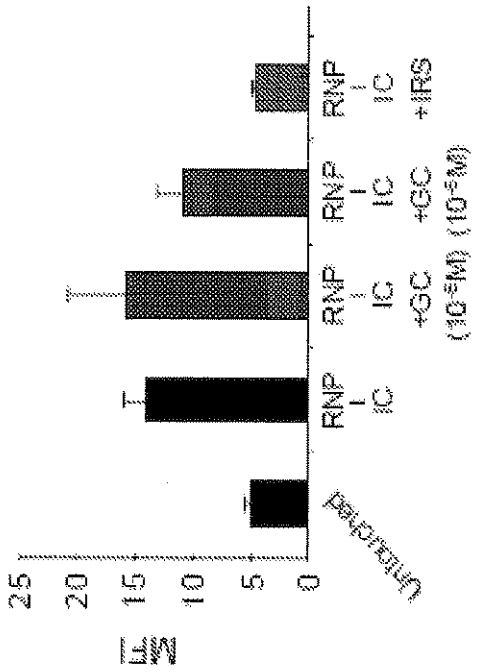

A
Blood
PDC
CD11c+
B220+
CD3+
Folds of changes to untreated
***
129 B6 Tlr7 NZB
WT Lupus mice
B
Spleen
Fold of changes to untreated

FIG. 16


C
PDC
CD11c+
B220+
D
PDC
CD11c+
B220+
Number of cells (x 10^5)
Number of cells (x 10^6)
Number of cells (x 10^7)
NS
P=0.001
P=0.002
No Tx
GC
GC
GC
+IRS +CTRL


MFI
25
20
15
10
5
0
Uninfected
RNP
IC
RNP
IC
+GC
(10⁻⁵M)
RNP
IC
+GC
(10⁻⁴M)
RNP
IC
+IRS

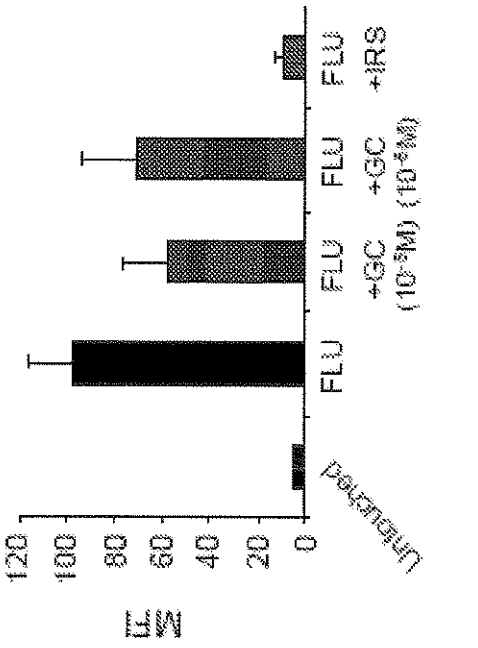
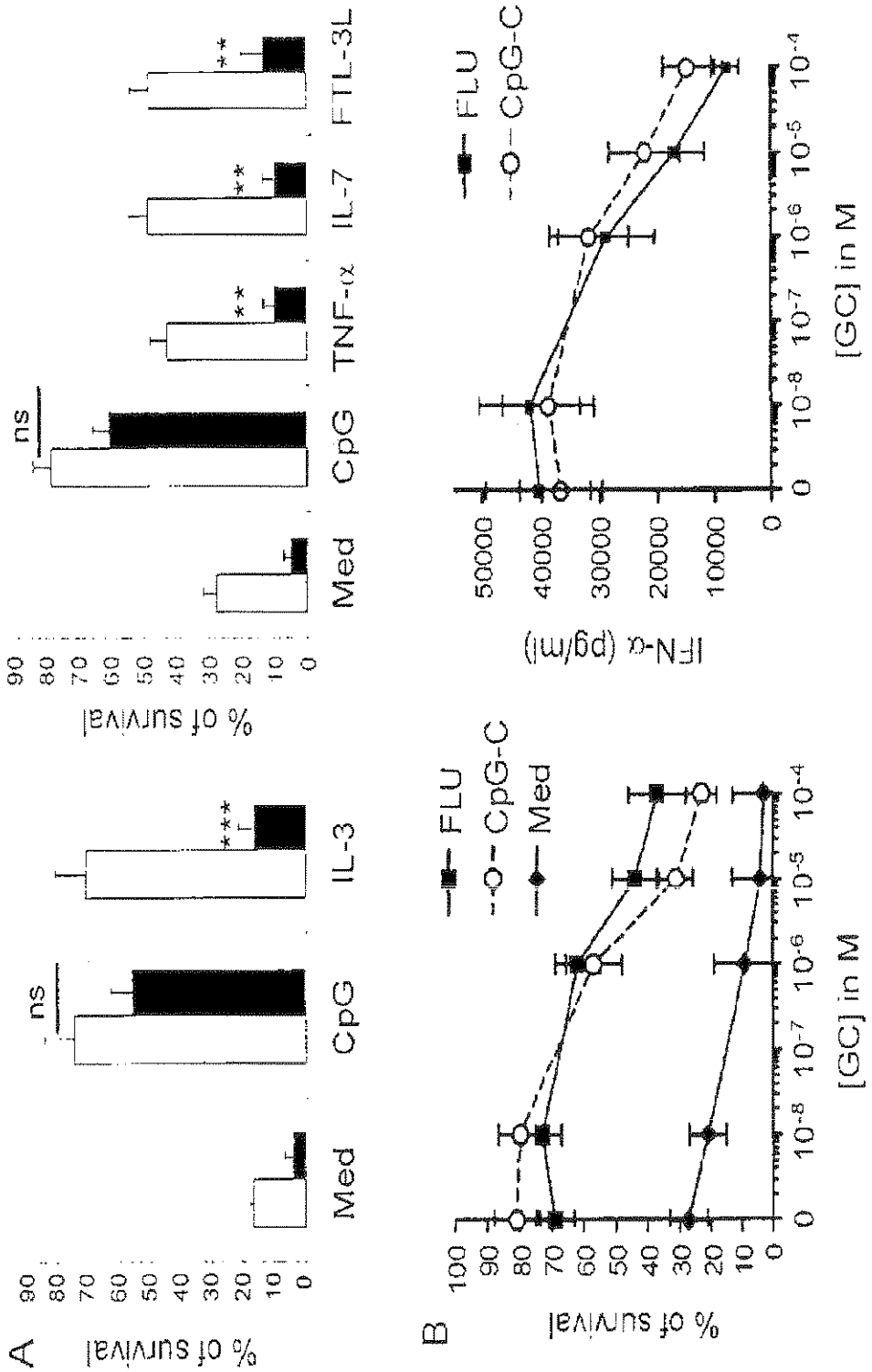

MFI
120
100
80
60
40
20
0
Uninfected
FLU
FLU
+GC
(10⁻⁵M)
FLU
+GC
(10⁻⁴M)
FLU
+IRS

FIG. 17

FIG. 18


A
% of survival
Med
CpG
IL-3
IL-7
TNF-α
FTL-3L
ns
***
**
B
% of survival
FLU
CpG-C
Med
[GC] in M
IFN-α (pg/ml)
50000
40000
30000
20000
10000
0
10^-8
10^-7
10^-6
10^-5
10^-4

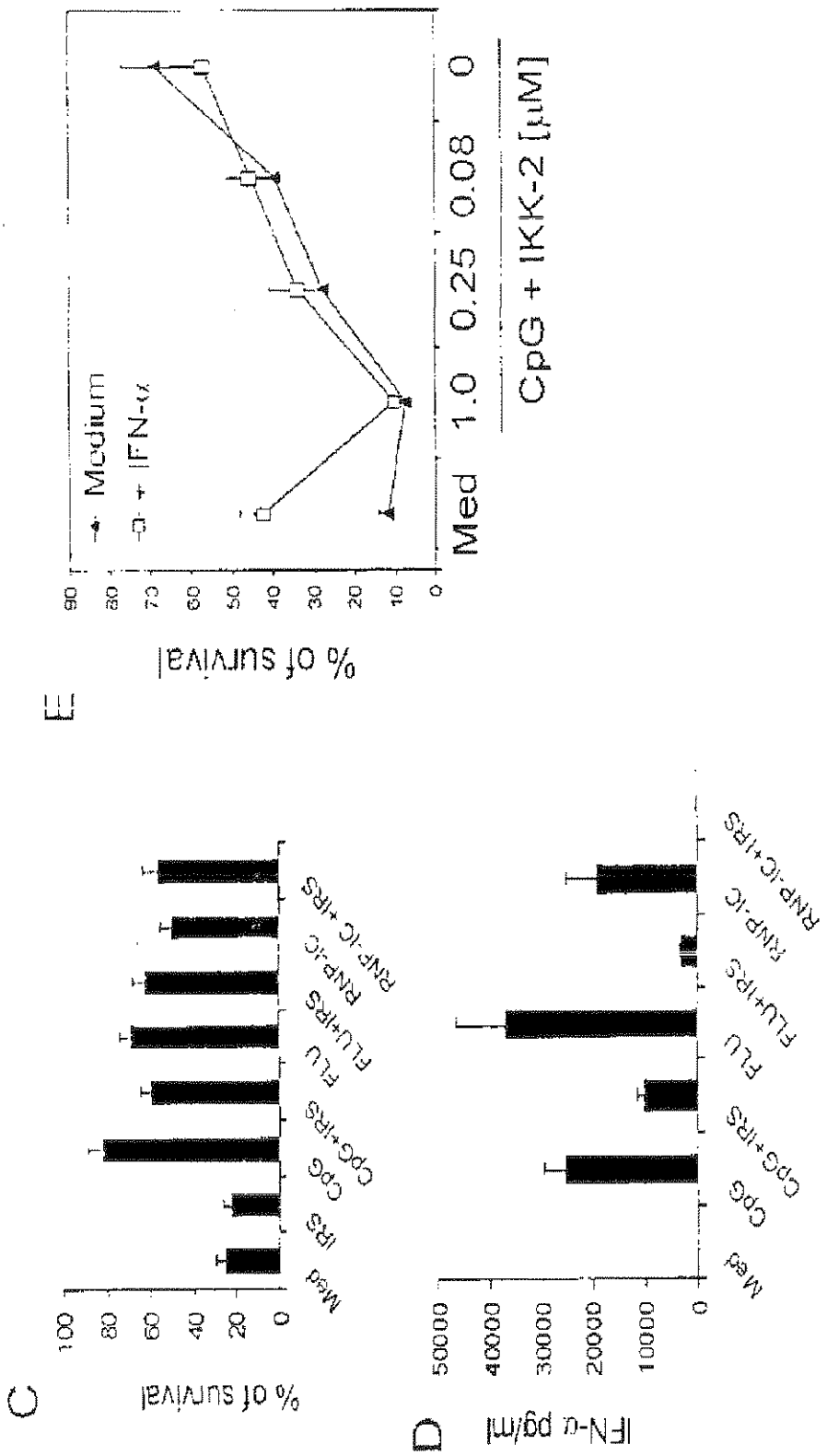

E
% of survival
Medium
+ IFN-α
Med 1.0 0.25 0.08 0
CpG + IKK-2 [μM]
C
% of survival
Med
IRS
CpG
CpG+IRS
FLU
FLU+IRS
RNP-IC
RNP-IC +IRS
D
IFN-α pg/ml
Med
CpG
CpG+IRS
FLU
FLU+IRS
RNP-IC
RNP-IC+IRS

FIG. 18

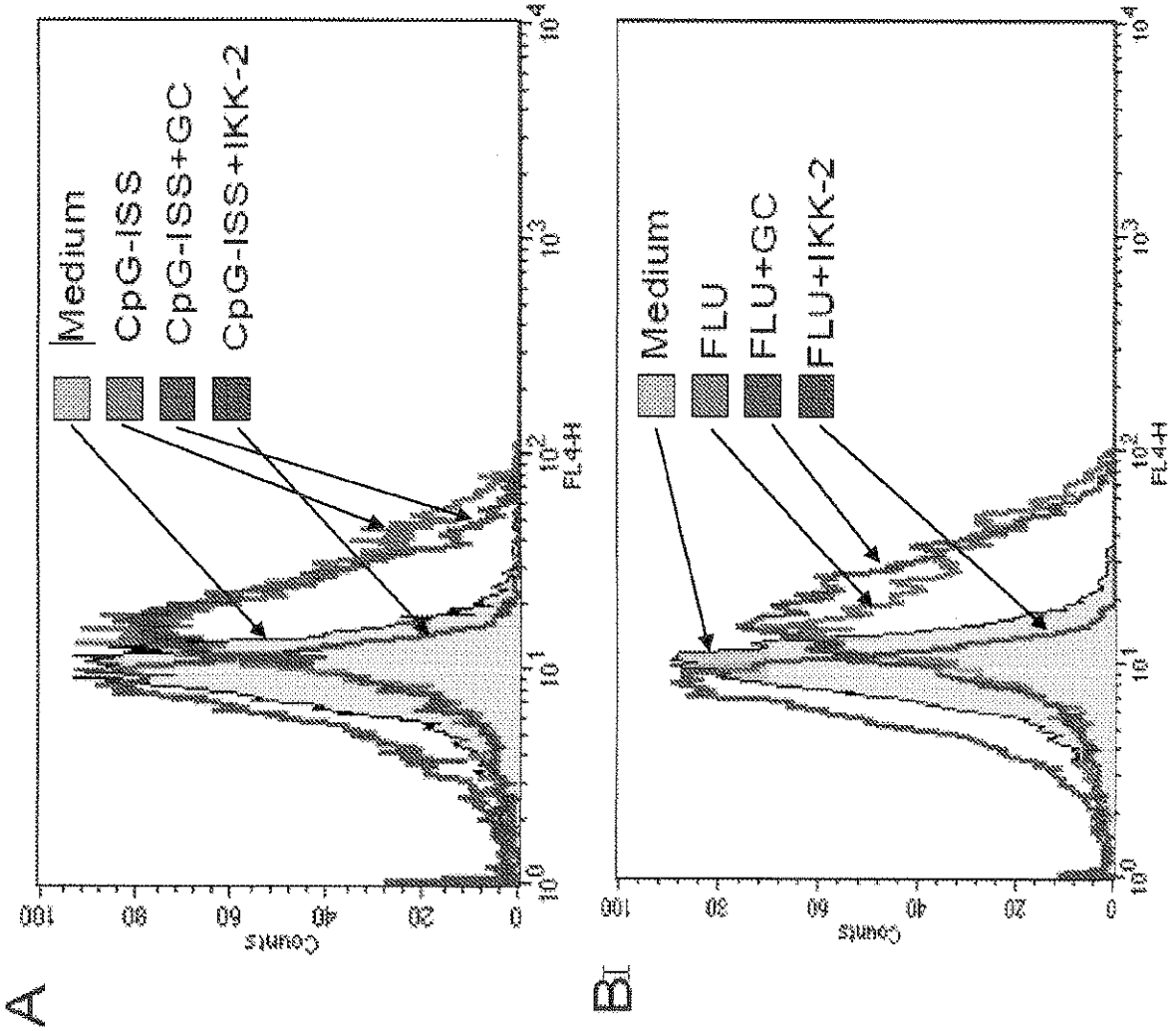
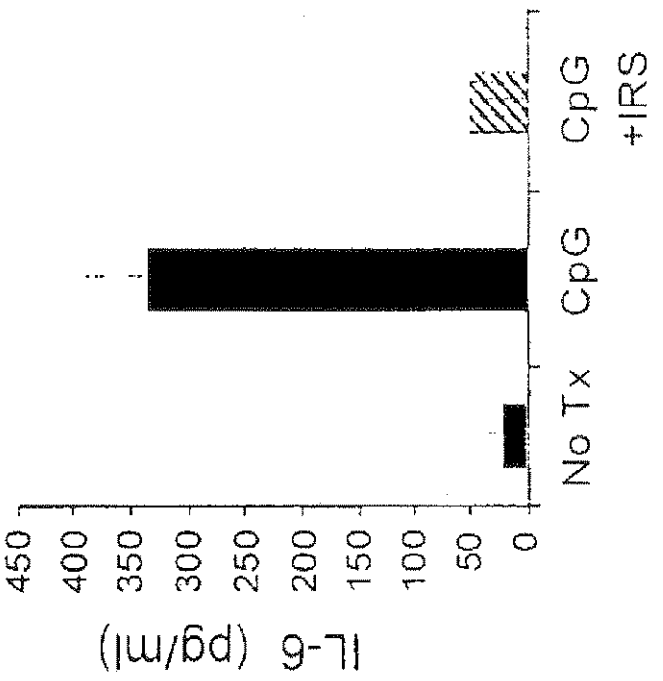

A
Medium
CpG-ISS
CpG-ISS+GC
CpG-ISS+IKK-2
Counts
FL4-H
Bi
Medium
FLU
FLU+GC
FLU+IKK-2
Counts
FL4-H

FIG. 19


IL-6 (pg/ml)
450
400
350
300
250
200
150
100
50
0
No Tx
CpG
CpG +IRS

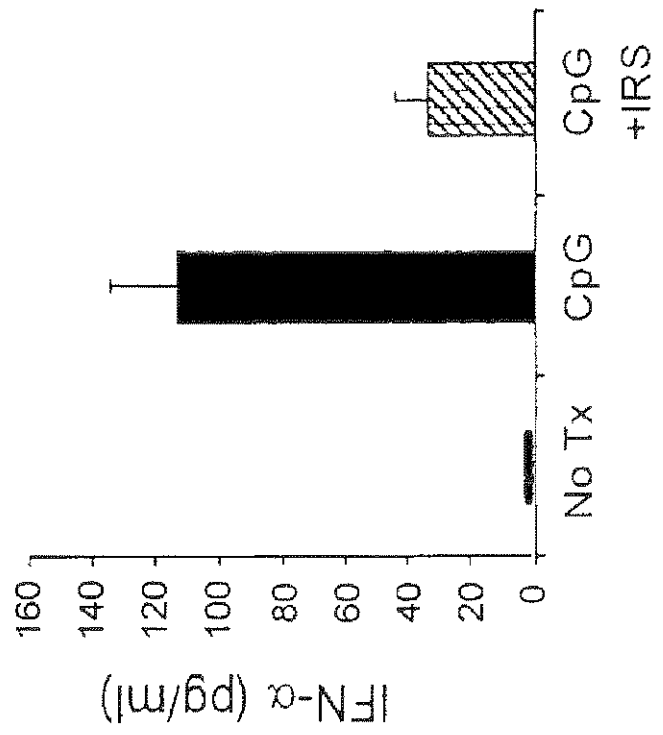

IFN-α (pg/ml)
160
140
120
100
80
60
40
20
0
No Tx
CpG
CpG +IRS

FIG. 20

FIG. 21

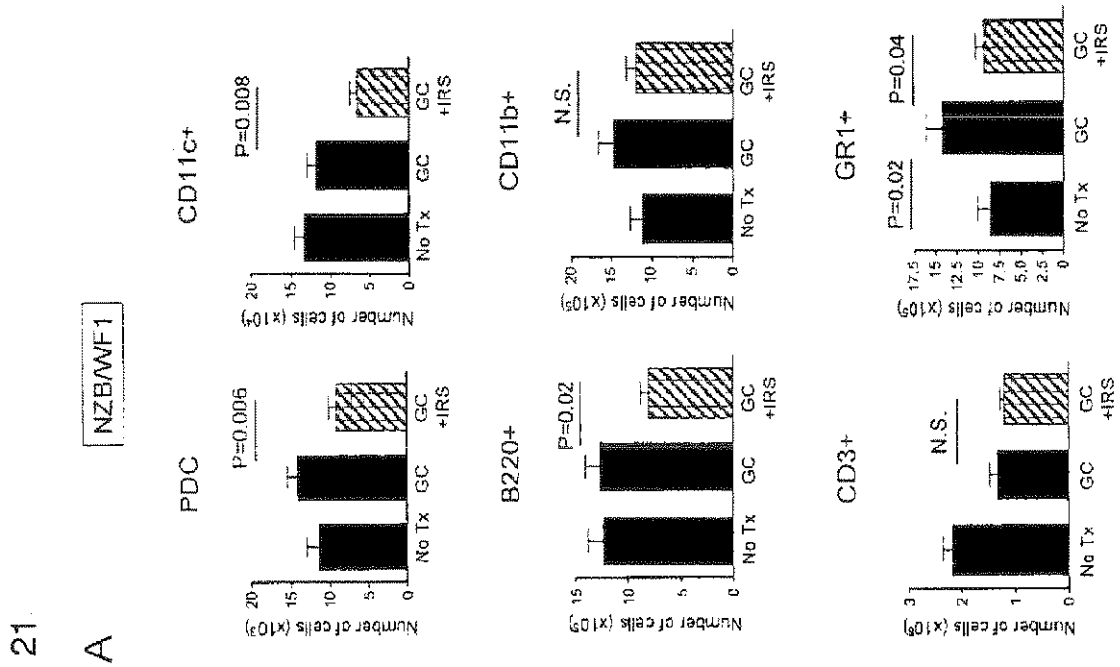
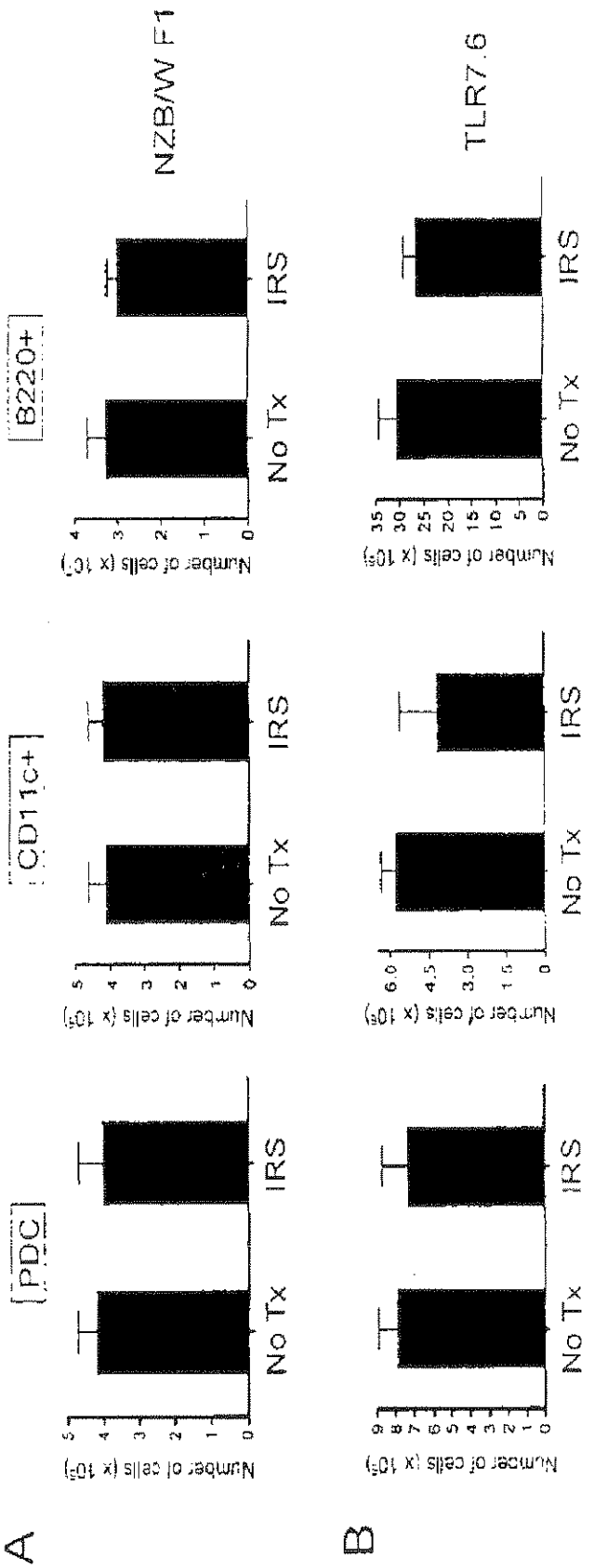

A
NZB/WF1
PDC
CD11c+
CD11b+
B220+
CD3+
GR1+
P=0.006
P=0.008
N.S.
P=0.02
P=0.02
P=0.04
No Tx
GC
GC +IRS
Number of cells (x10³)
Number of cells (x10⁵)
B
TLR7.Tg.6
PDC
CD11c+
CD11b+
B220+
CD3
GR1
P=0.0002
P=0.02
N.S.
P=0.002
N.S.
N.S.
N.S.
No Tx
GC
GC +IRS
Number of cells (x10⁵)

FIG. 22



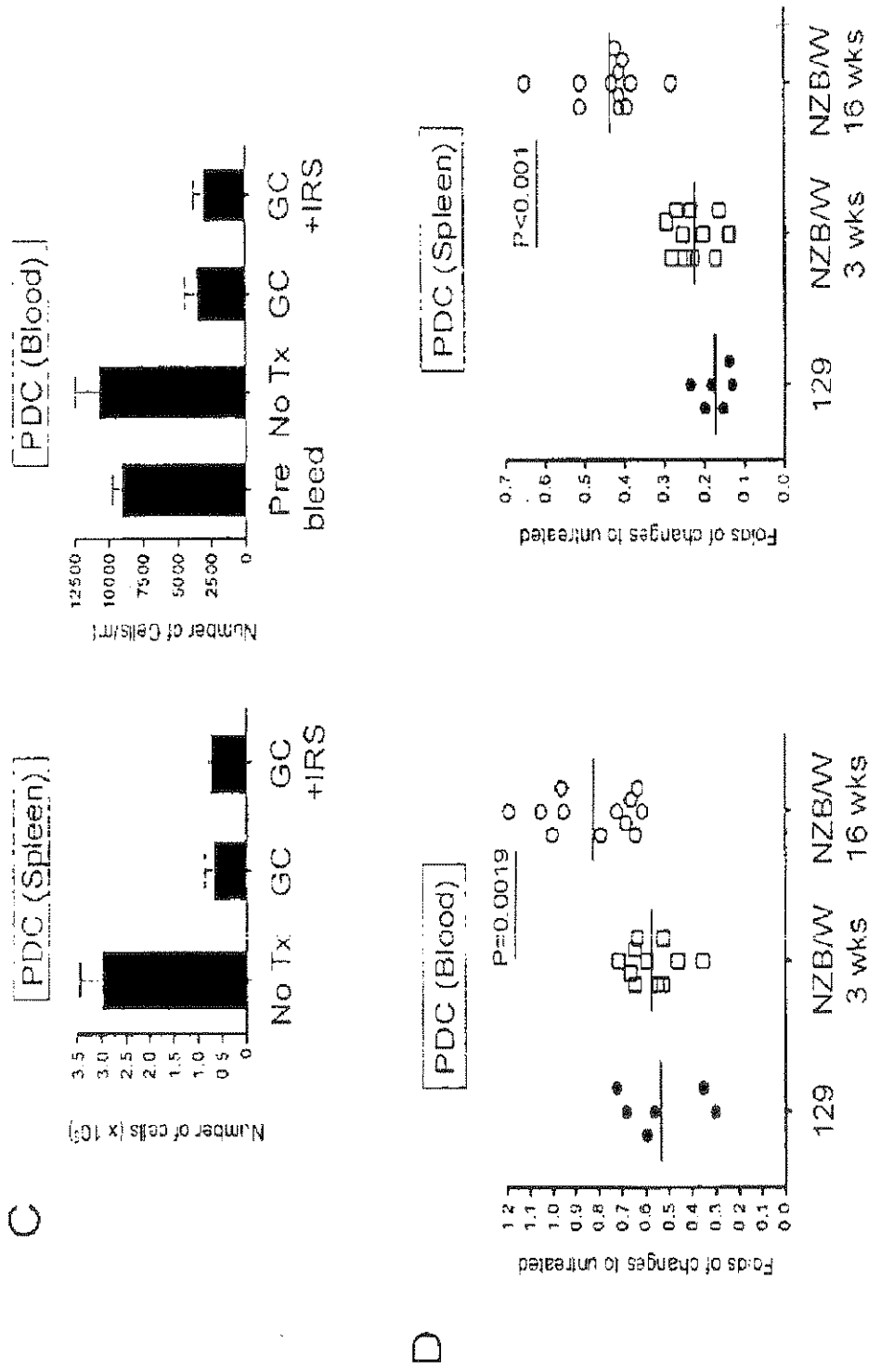

C
PDC (Spleen)
Number of cells (x 10^6)
No Tx
GC
GC +IRS
PDC (Blood)
Number of Cells/mL
Pre bleed
No Tx
GC
GC +IRS
D
PDC (Blood)
P=0.0019
Folds of changes to untreated
129
NZB/W 3 wks
NZB/W 16 wks
PDC (Spleen)
P<0.001
Folds of changes to untreated
129
NZB/W 3 wks
NZB/W 16 wks

FIG. 22

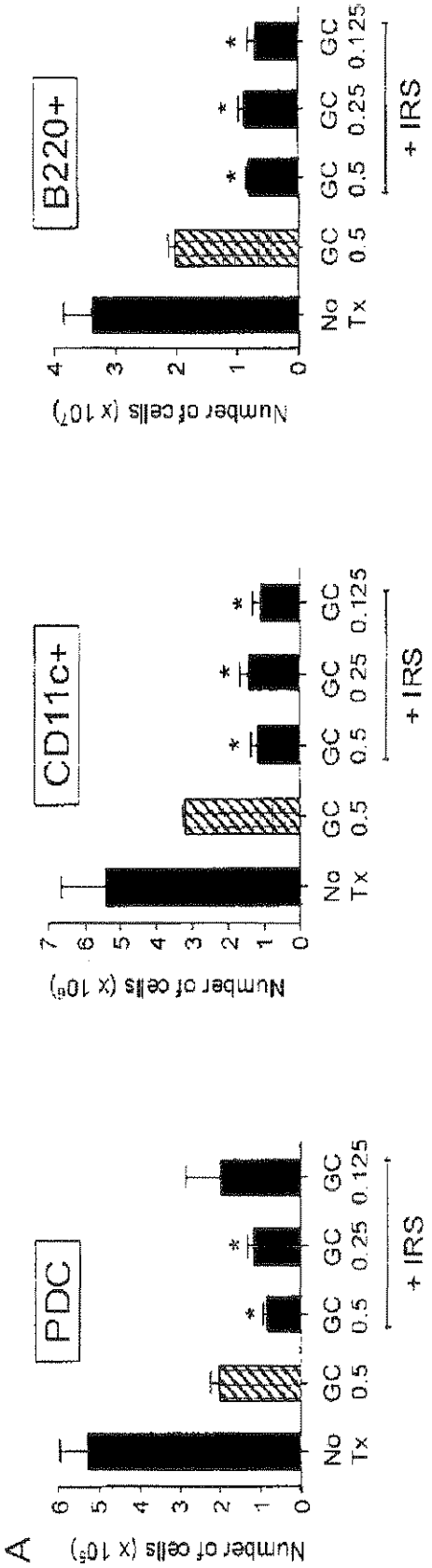

A
PDC
CD11c+
B220+
Number of cells (x 10^5)
Number of cells (x 10^6)
Number of cells (x 10^7)
No Tx
GC 0.5
GC 0.5
GC 0.25
GC 0.125
+ IRS
*

FIG. 23

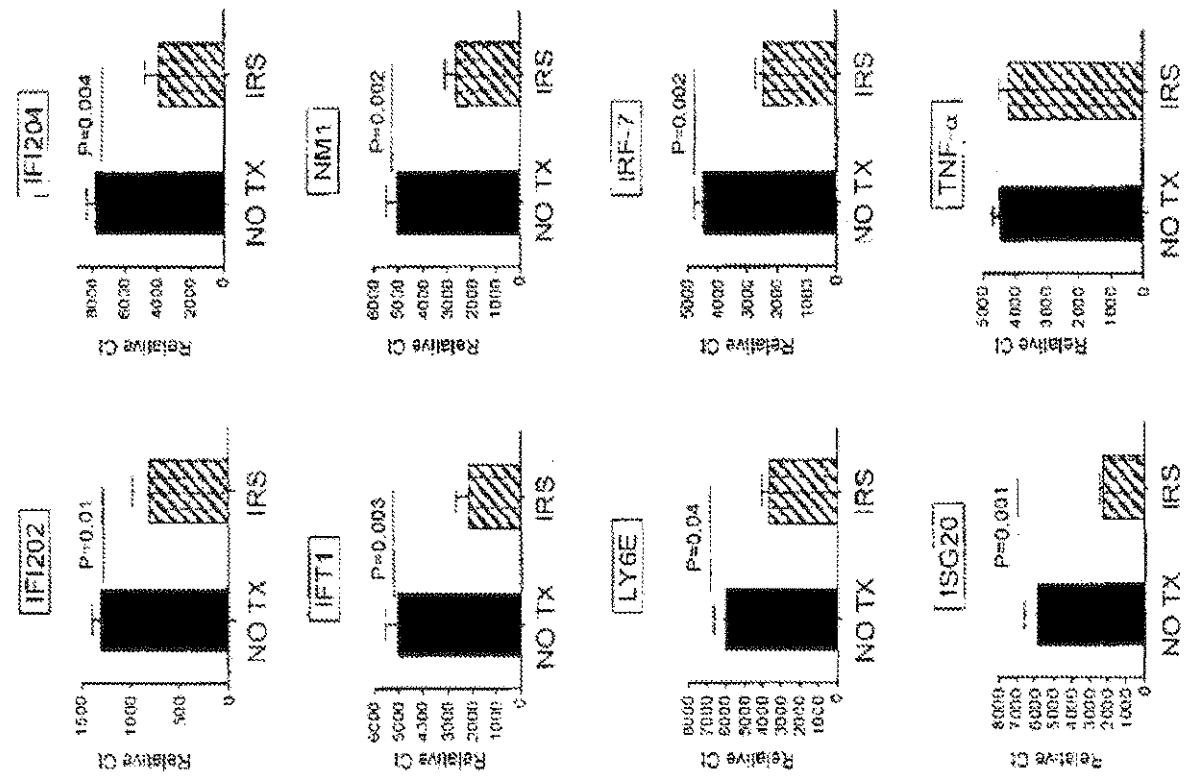

B
IFI202
P=0.01
IFI204
P=0.004
IFT1
P=0.003
NM1
P=0.002
LY6E
P=0.04
IRF-7
P=0.002
ISG20
P=0.001
TNF-α
Relative CI
NO TX
IRS

FIG. 23

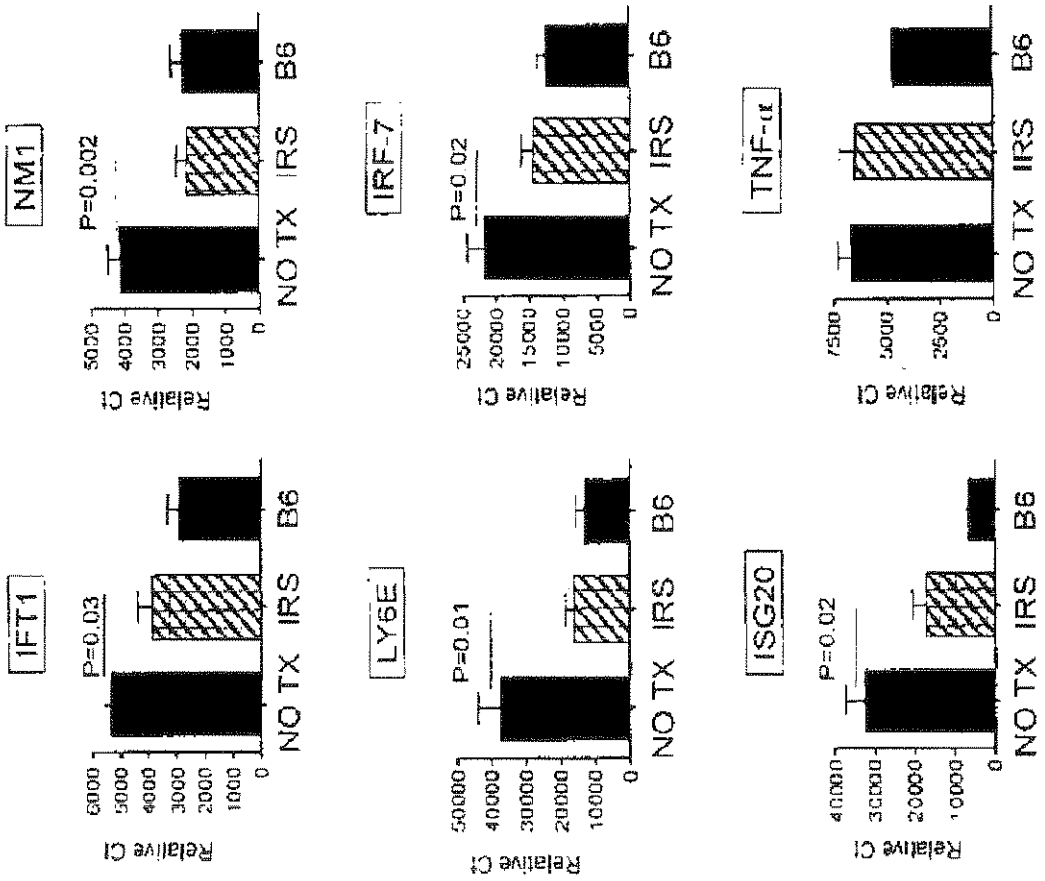

C
IFT1
P=0.03
Relative CI
NO TX
IRS
B6
NM1
P=0.002
IRF-7
P=0.02
LY6E
P=0.01
ISG20
P=0.02
TNF-α

FIG. 23

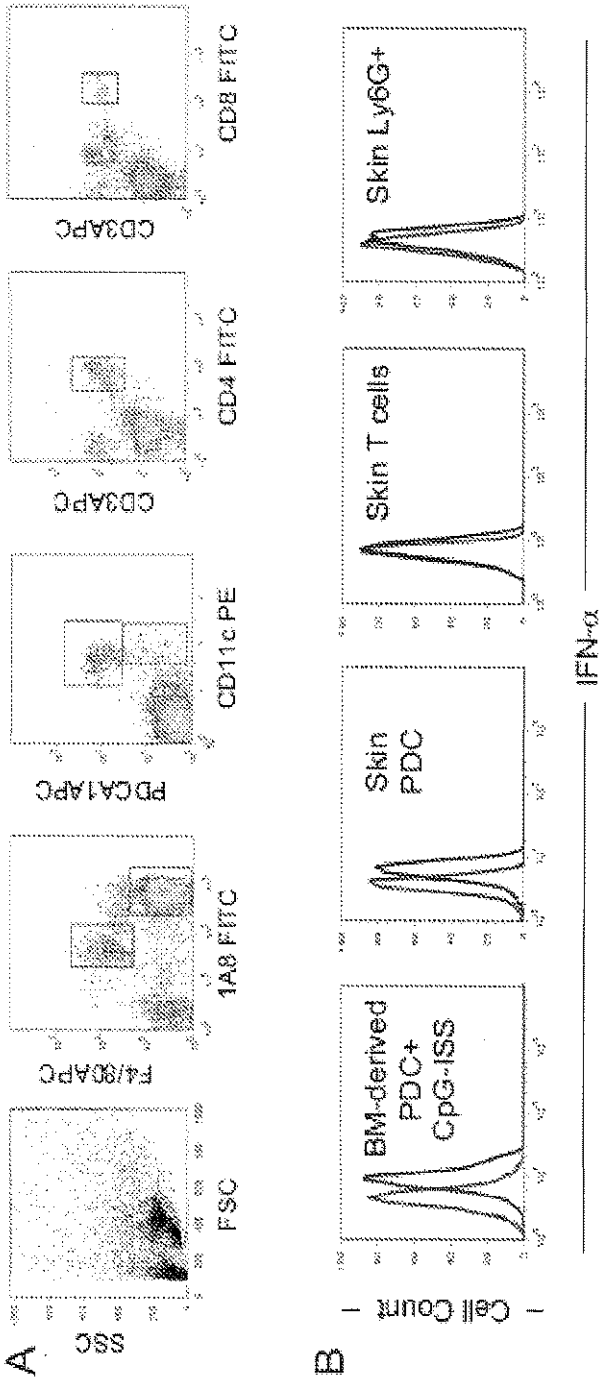

A
SSC
FSC
F4/80APC
1A8 FITC
PDCA1APC
CD11c PE
CD3APC
CD4 FITC
CD3APC
CD8 FITC
B
Cell Count
BM-derived PDC+ CpG-ISS
Skin PDC
Skin T cells
Skin Ly6G+
IFN-α

FIG. 24

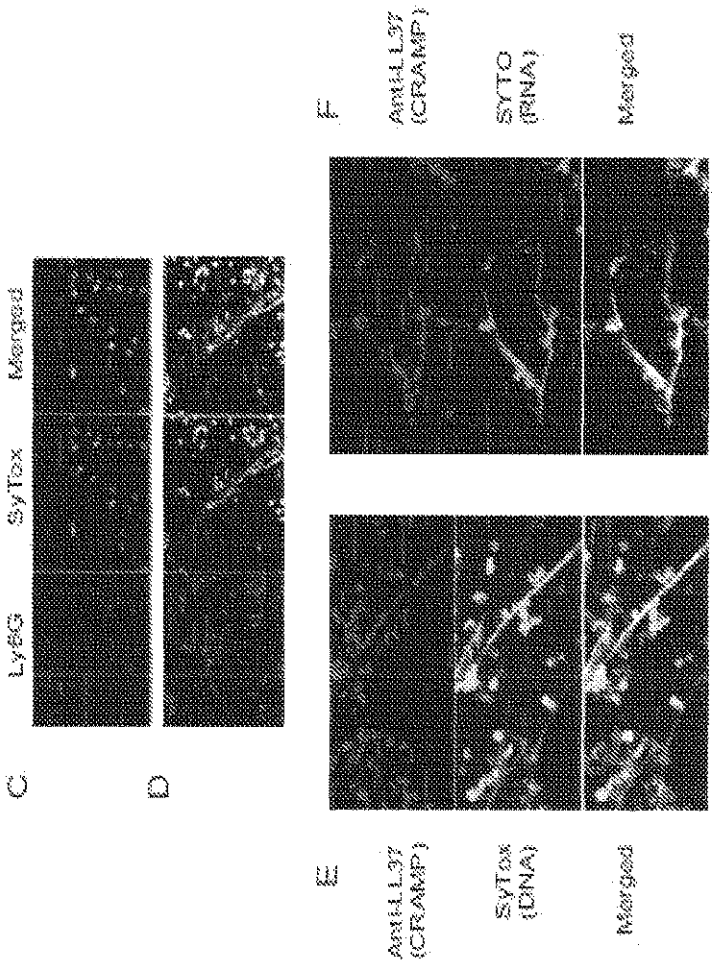

C
Ly6G
SyTox
Merged
D
E
Anti-LL37 (CRAMP)
SyTox (DNA)
Merged
F
Anti-LL37 (CRAMP)
SYTO (RNA)
Merged

FIG. 24

FIG. 25

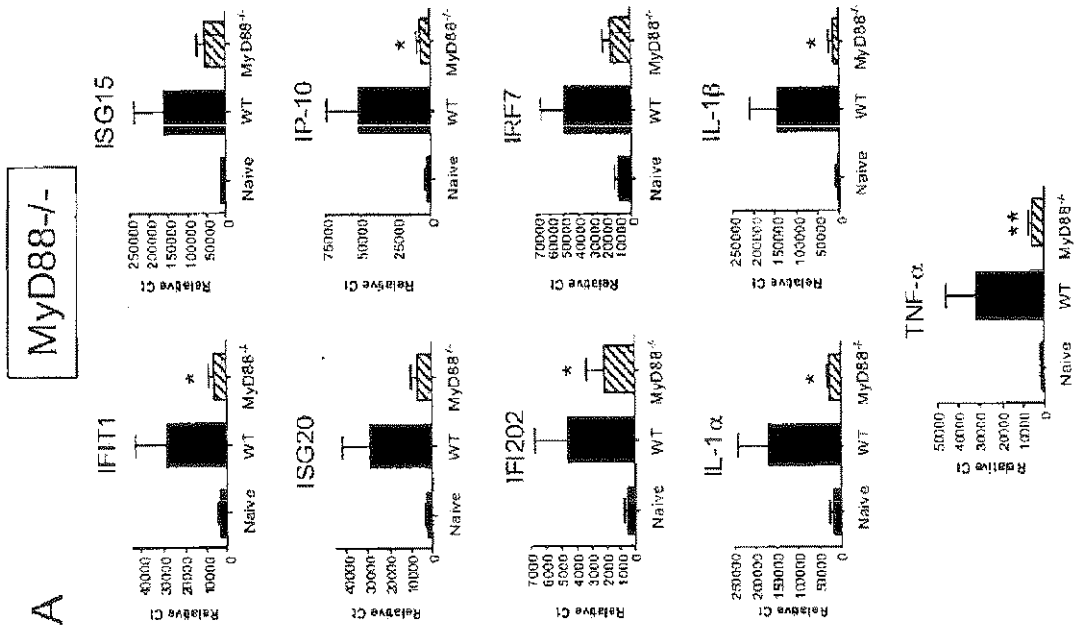

A
MyD88-/-
IFIT1
ISG15
ISG20
IP-10
IFI202
IRF7
IL-1α
IL-1β
TNF-α
Relative CI
Naive
WT
MyD88-/-
B
IFNAR-/-
IFIT1
ISG15
ISG20
IP-10
IFI202
IRF7
IL-1α
IL-1β
TNF-α
Relative CI
Naive
WT
IFNAR-/-

FIG. 26

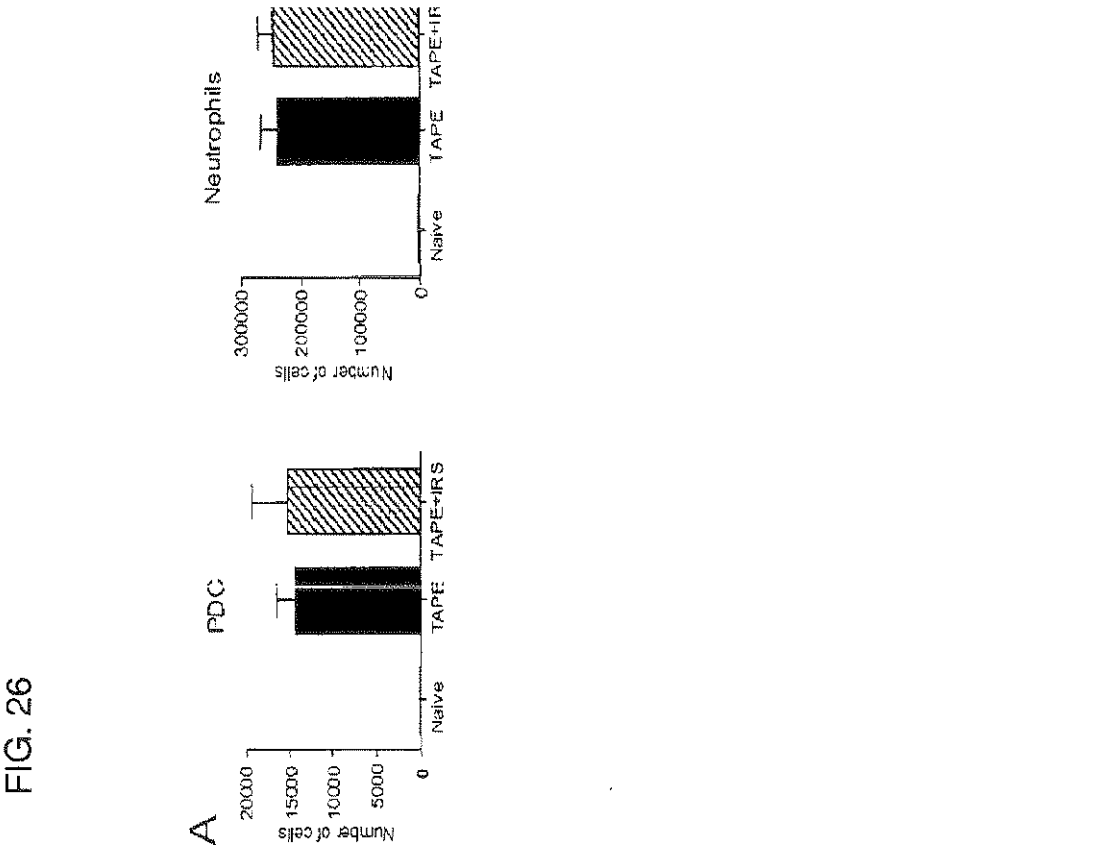

A
PDC
Number of cells
20000
15000
10000
5000
0
Naive
TAPE
TAPE+IRS
Neutrophils
Number of cells
300000
200000
100000
0
Naive
TAPE
TAPE+IR
B
ISG15
IP-10
IRF7
IL-1β
IFIT1
ISG20
IFI202
IL-1α
TNF-α
Relative CT
Naive
TAPE
TAPE +IRS
*
**
***

FIG. 27

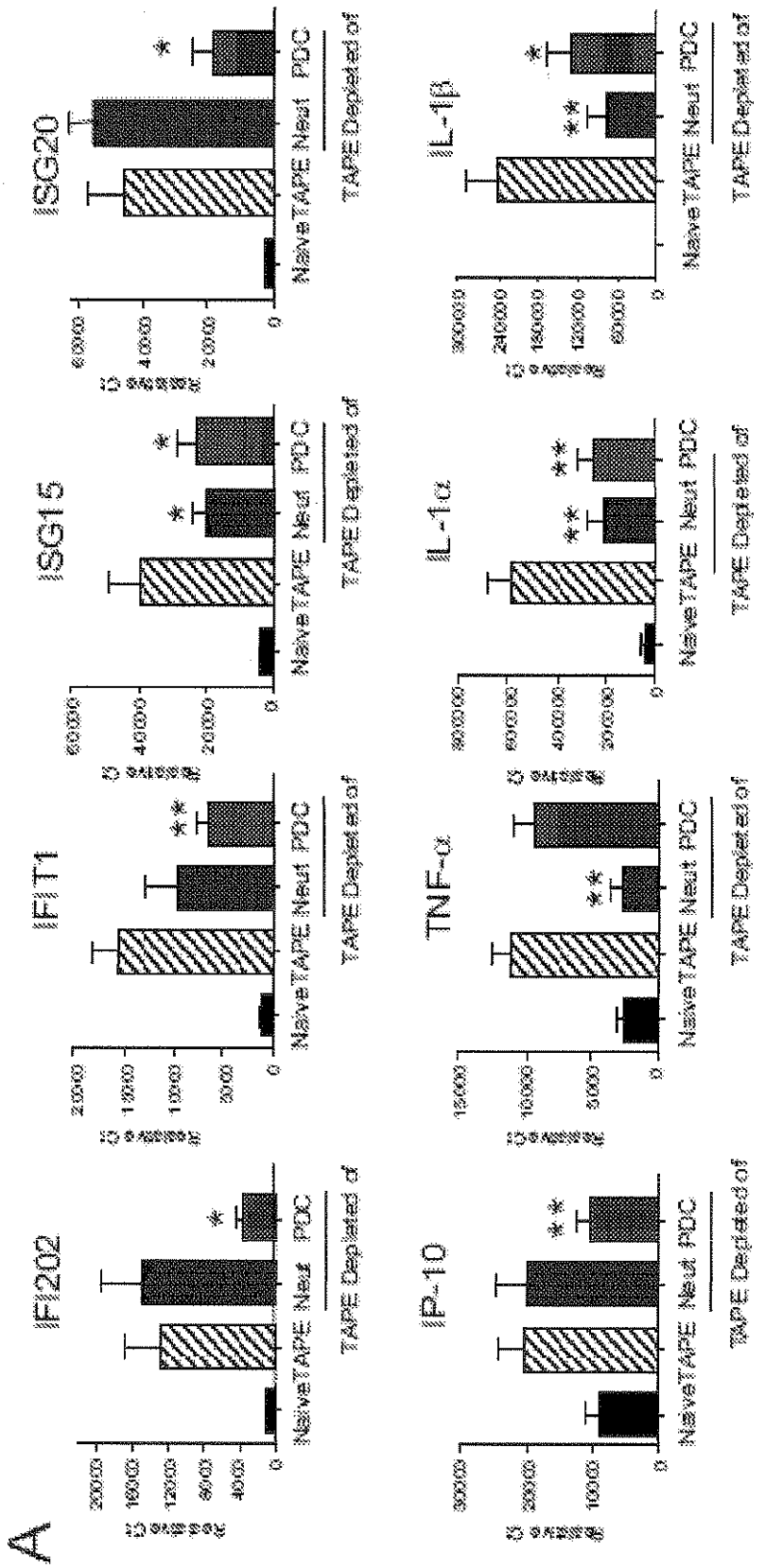

A
IFI202
IFIT1
ISG15
ISG20
IP-10
TNF-α
IL-1α
IL-1β
Naive TAPE Neut PDC
TAPE Depleted of

FIG. 27
continued

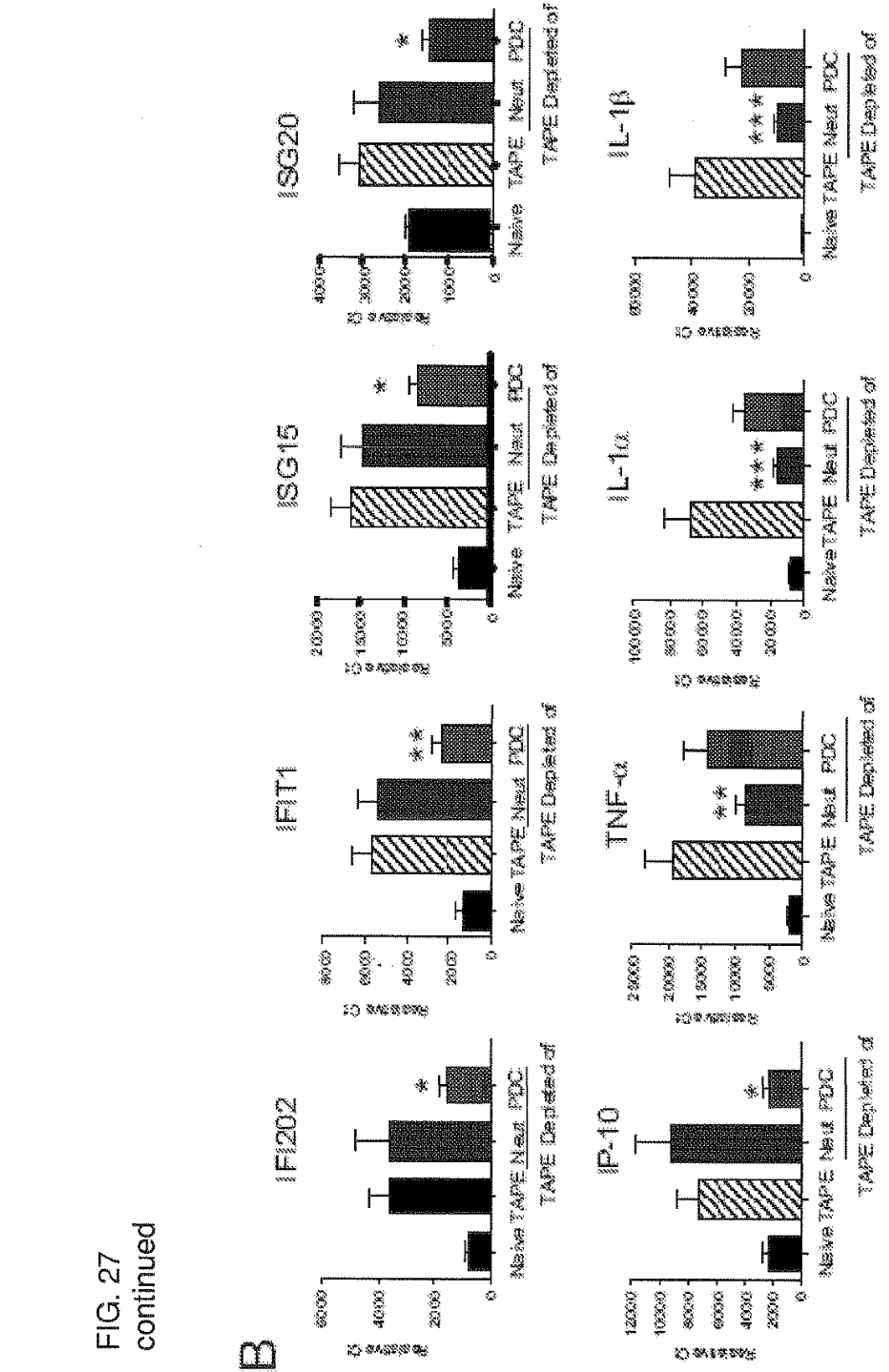


FIG. 28

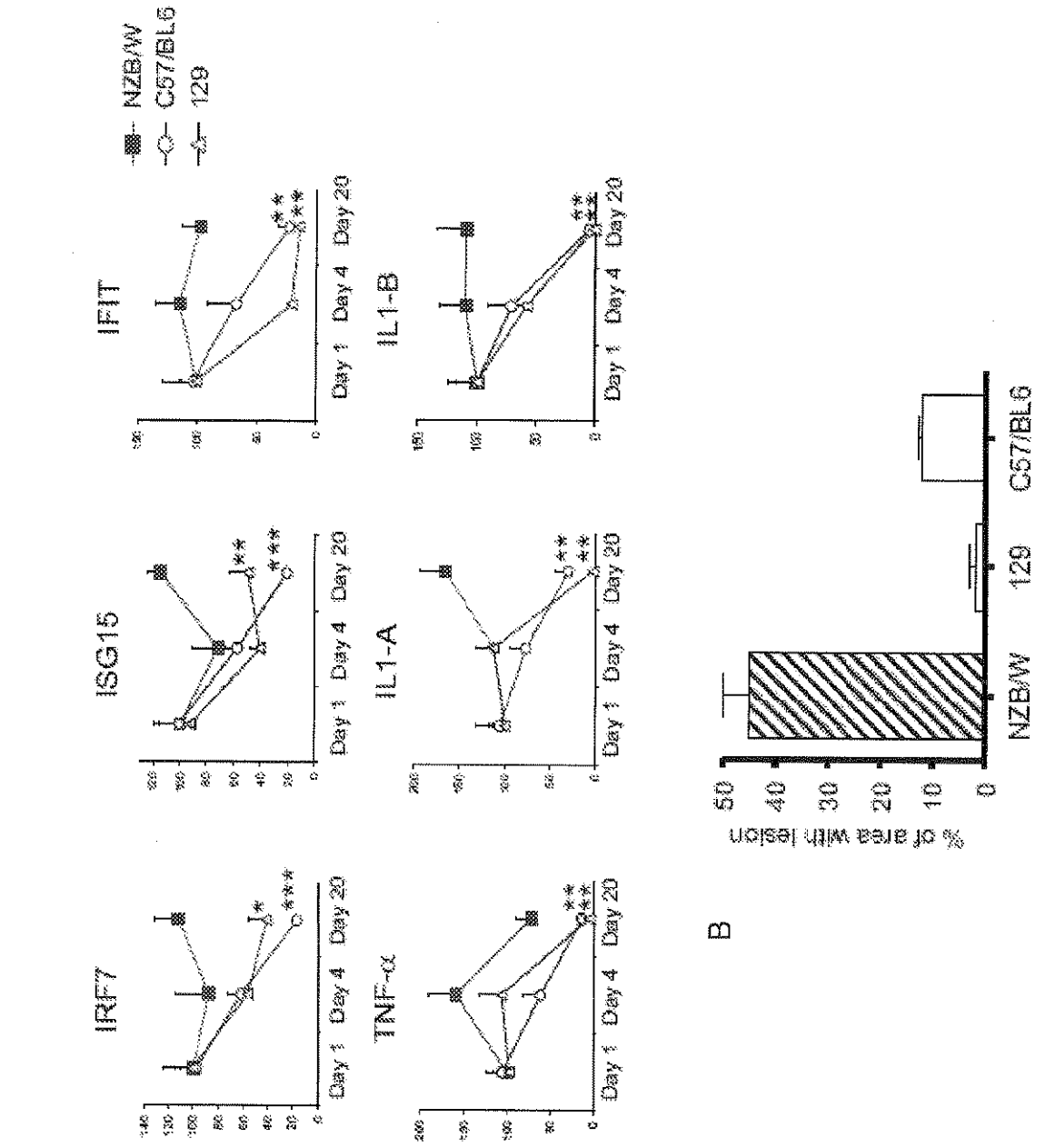
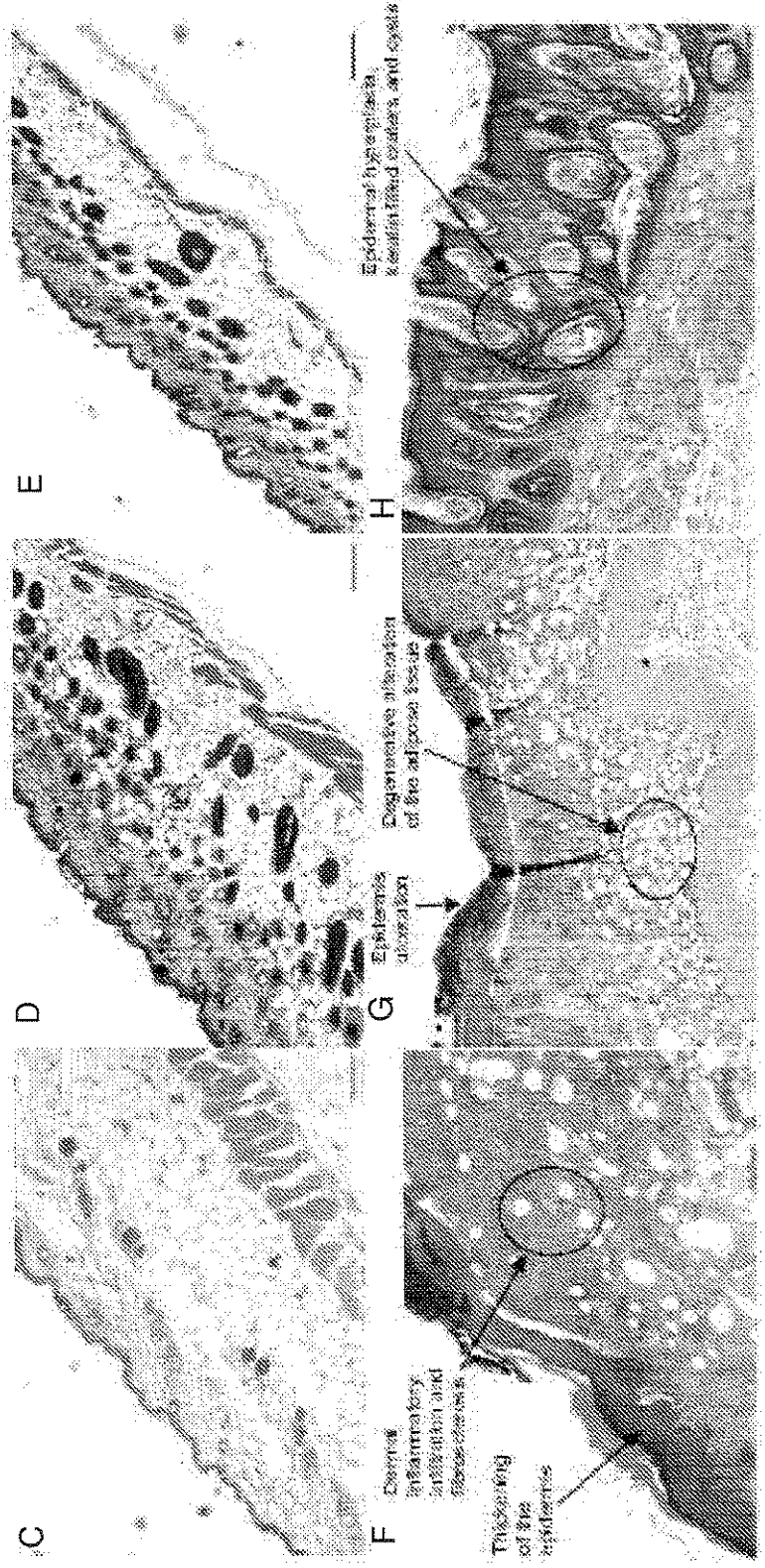

A
IRF7
ISG15
IFIT
TNF-α
IL1-A
IL1-B
NZB/W
C57/BL6
129
Day 1
Day 4
Day 20
B
% of area with lesion
NZB/W
129
C57/BL6

FIG. 28


C
D
E
F
G
H
Epidermal hyperplasia, keratinized cysts, pustules
Dermal inflammatory infiltrate (HE)
Trichofolliculitis and perifolliculitis
Epidermal ulceration
Epidermal ulceration of the adjacent tissue

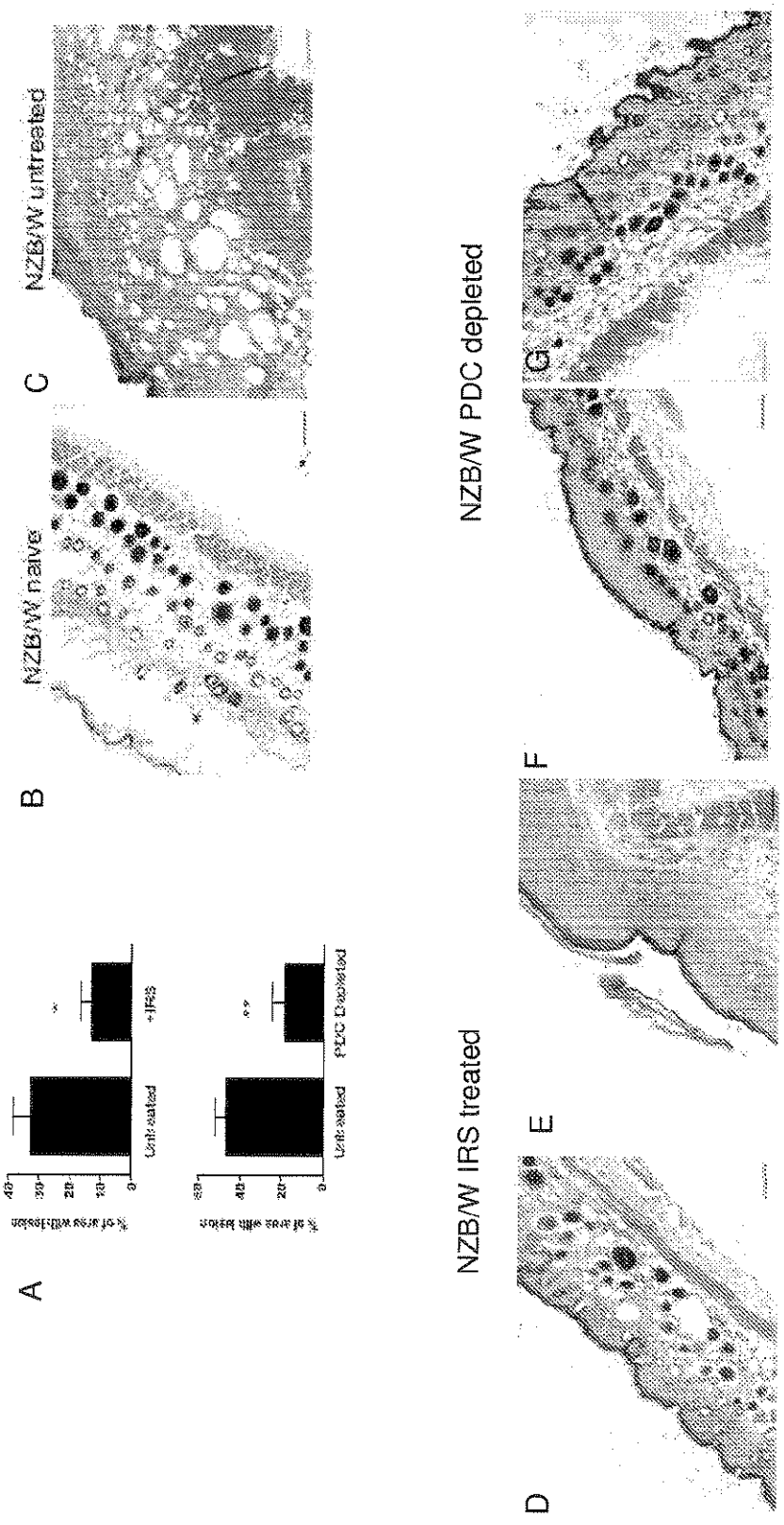

A
B
C
D
E
F
G
NZB/W naive
NZB/W untreated
NZB/W IRS treated
NZB/W PDC depleted
Untreated
+IRS
PDC Depleted

FIG. 29

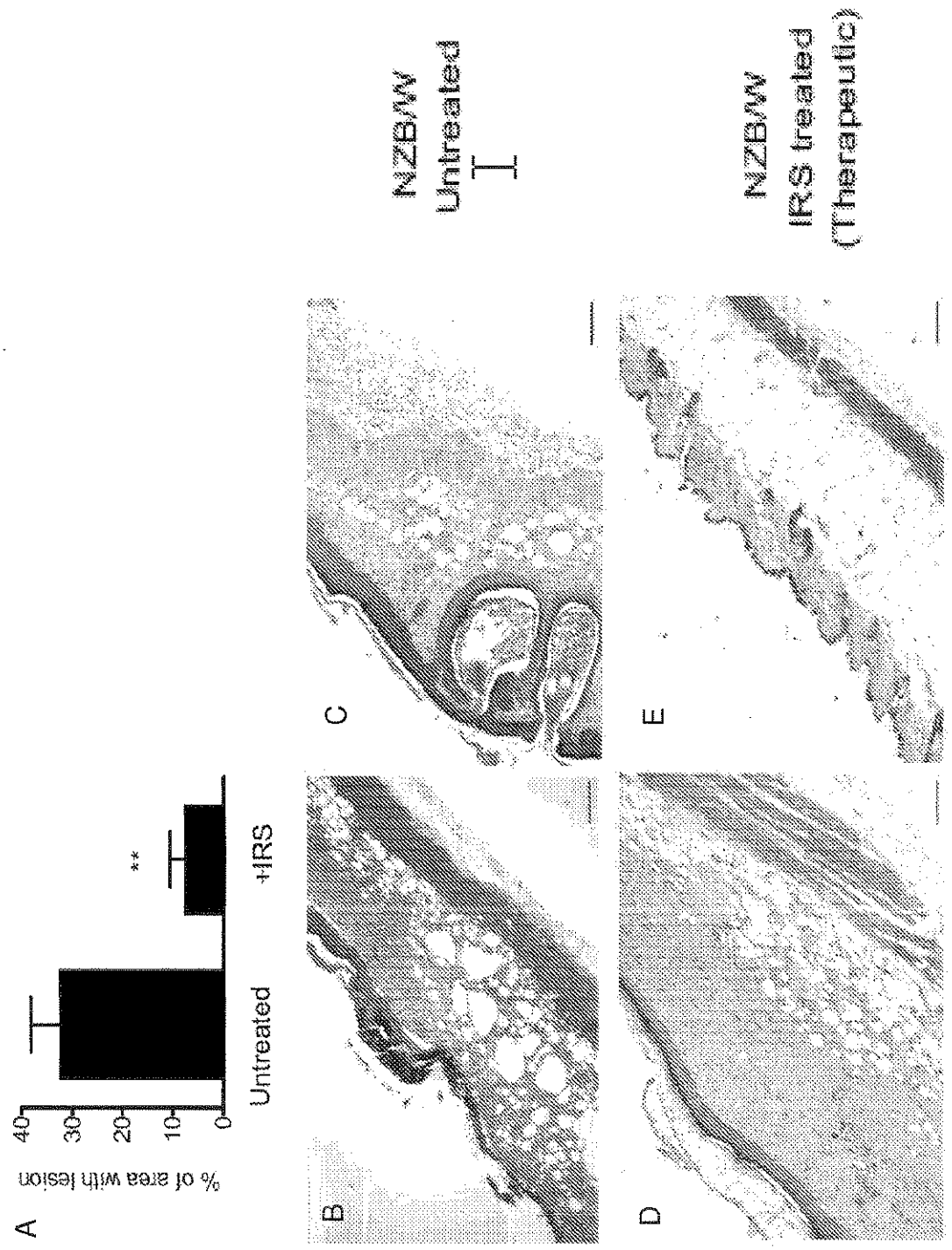
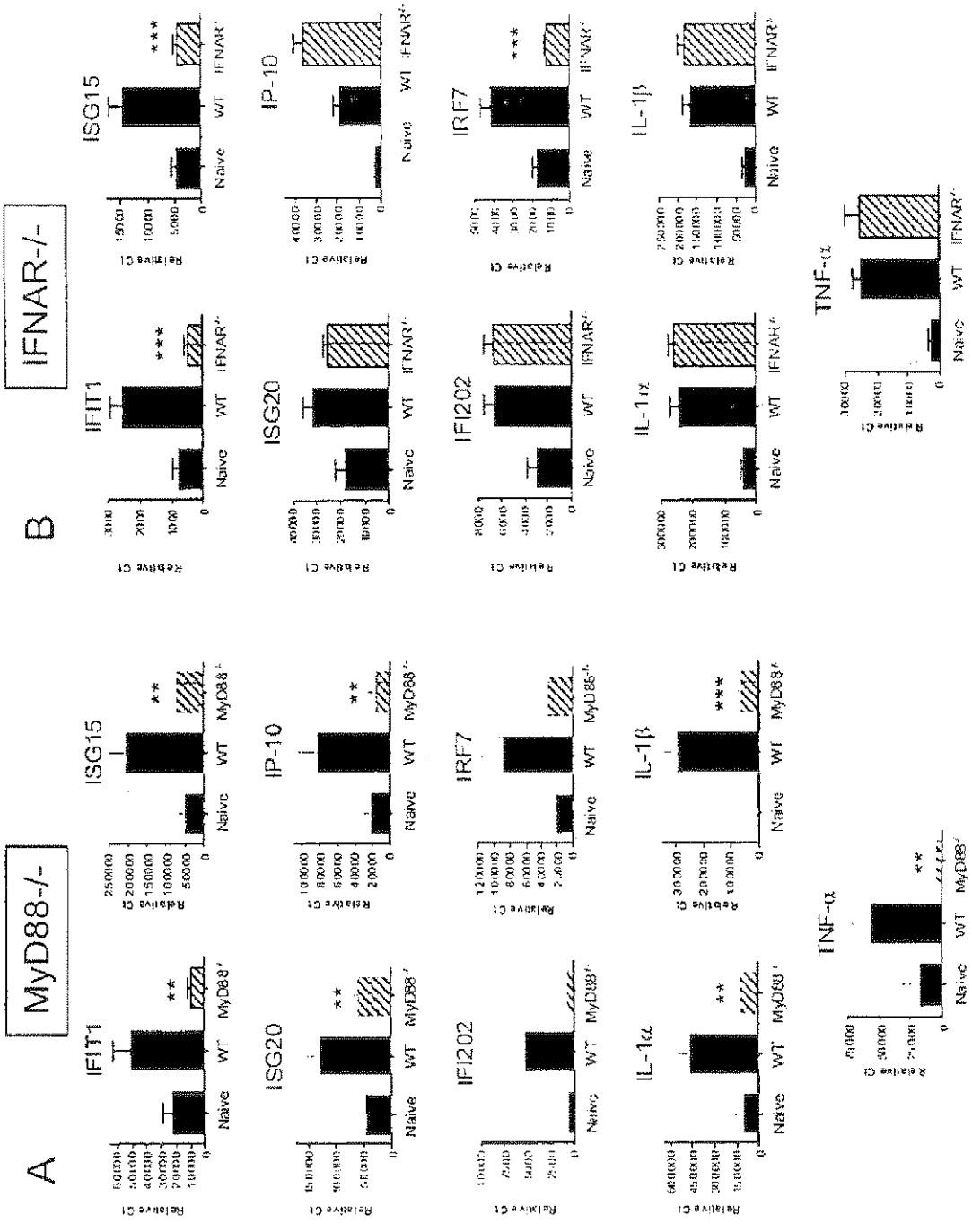

A
% of area with lesion
40
30
20
10
0
**
Untreated
+IRS
B
C
NZB/W
Untreated
D
E
NZB/W
IRS treated
(Therapeutic)

FIG. 30

FIG. 31


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

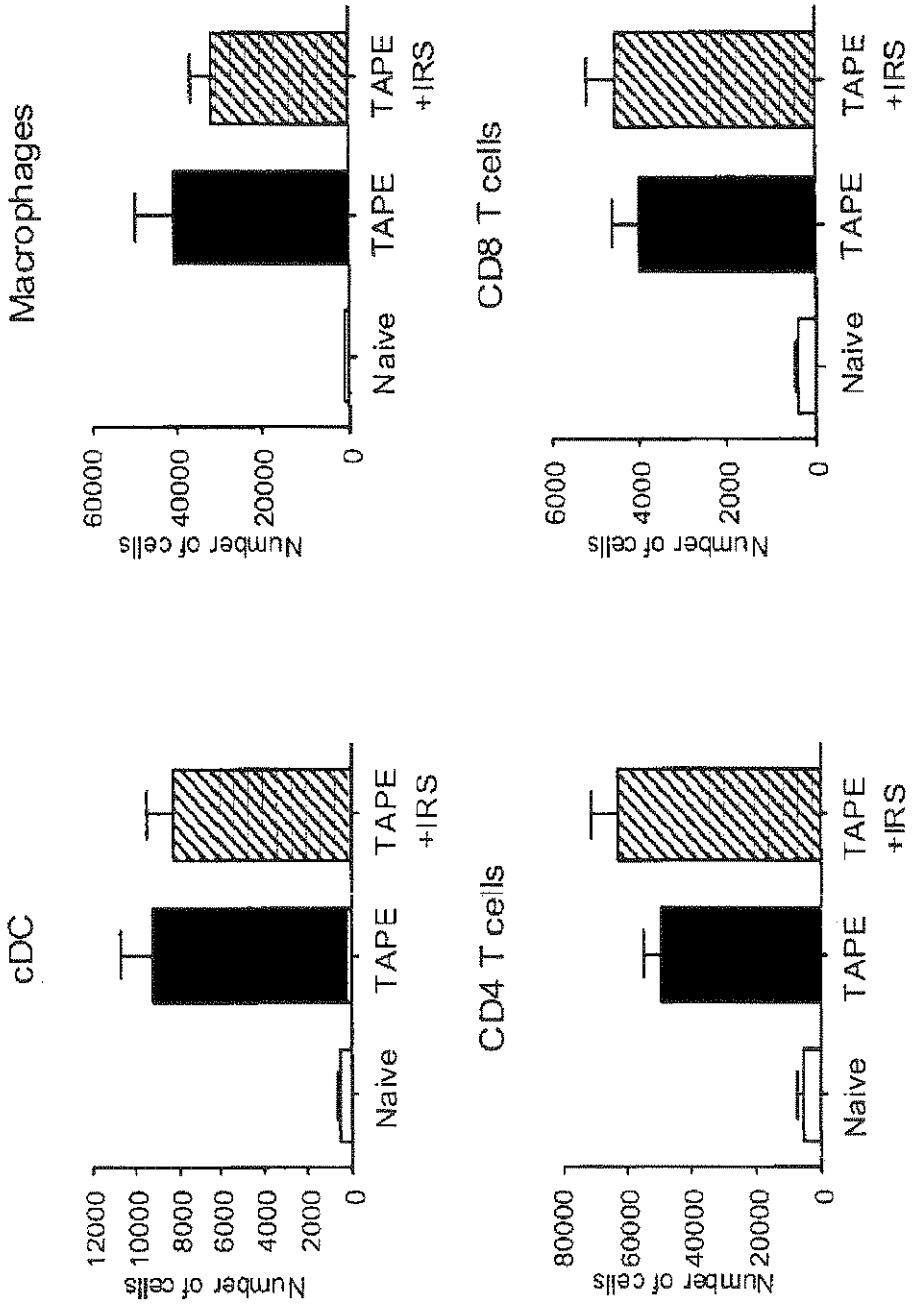

Macrophages
Number of cells
60000
40000
20000
0
Naive
TAPE
TAPE +IRS
CD8 T cells
Number of cells
6000
4000
2000
0
Naive
TAPE
TAPE +IRS
cDC
Number of cells
12000
10000
8000
6000
4000
2000
0
Naive
TAPE
TAPE +IRS
CD4 T cells
Number of cells
80000
60000
40000
20000
0
Naive
TAPE
TAPE +IRS

FIG. 32

FIG. 33

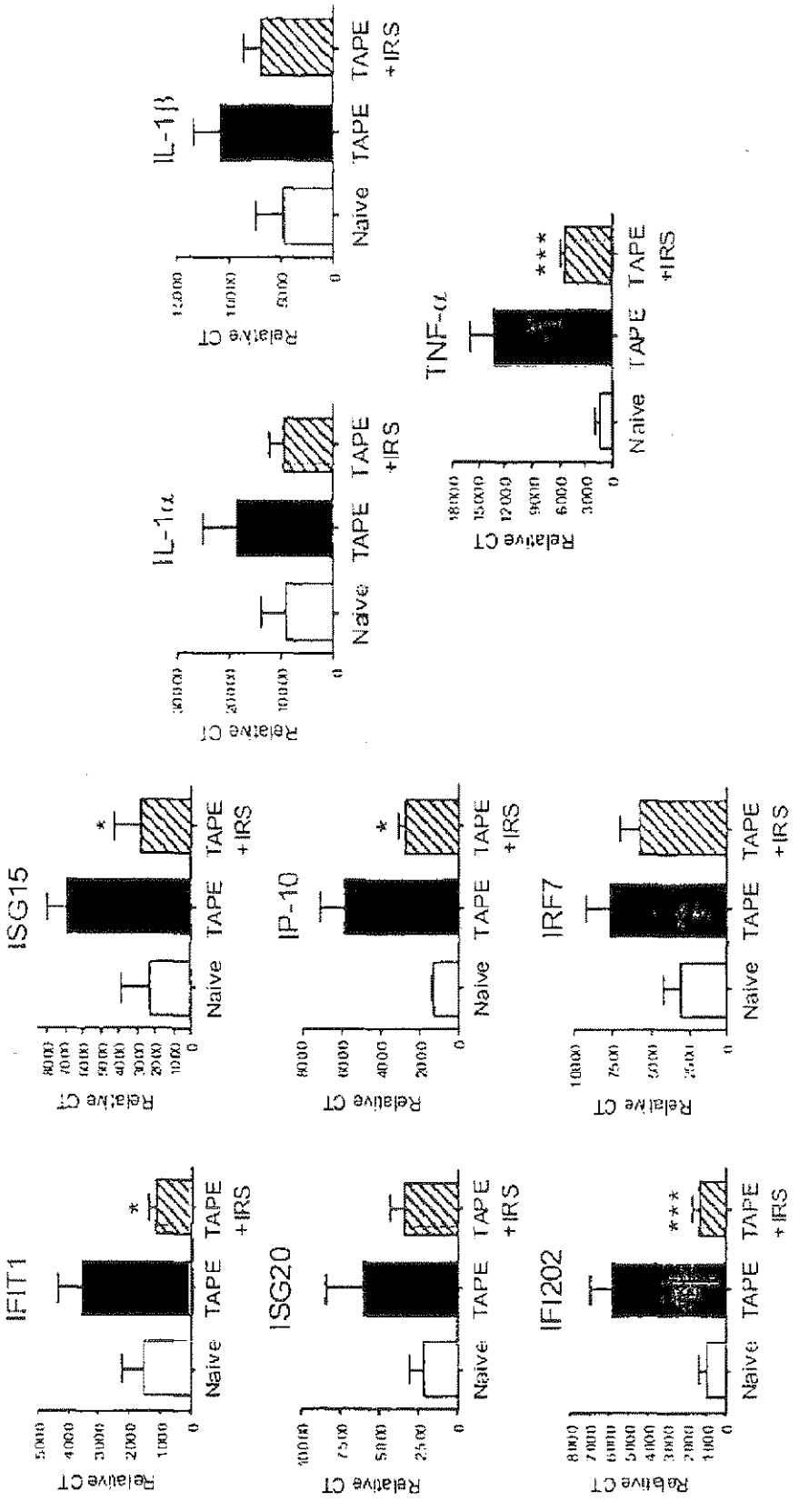

IL-1β
IL-1α
TNF-α
ISG15
IP-10
IRF7
IFIT1
ISG20
IFI202
Relative CT
Naive
TAPE
TAPE +IRS
*
***

FIG. 34

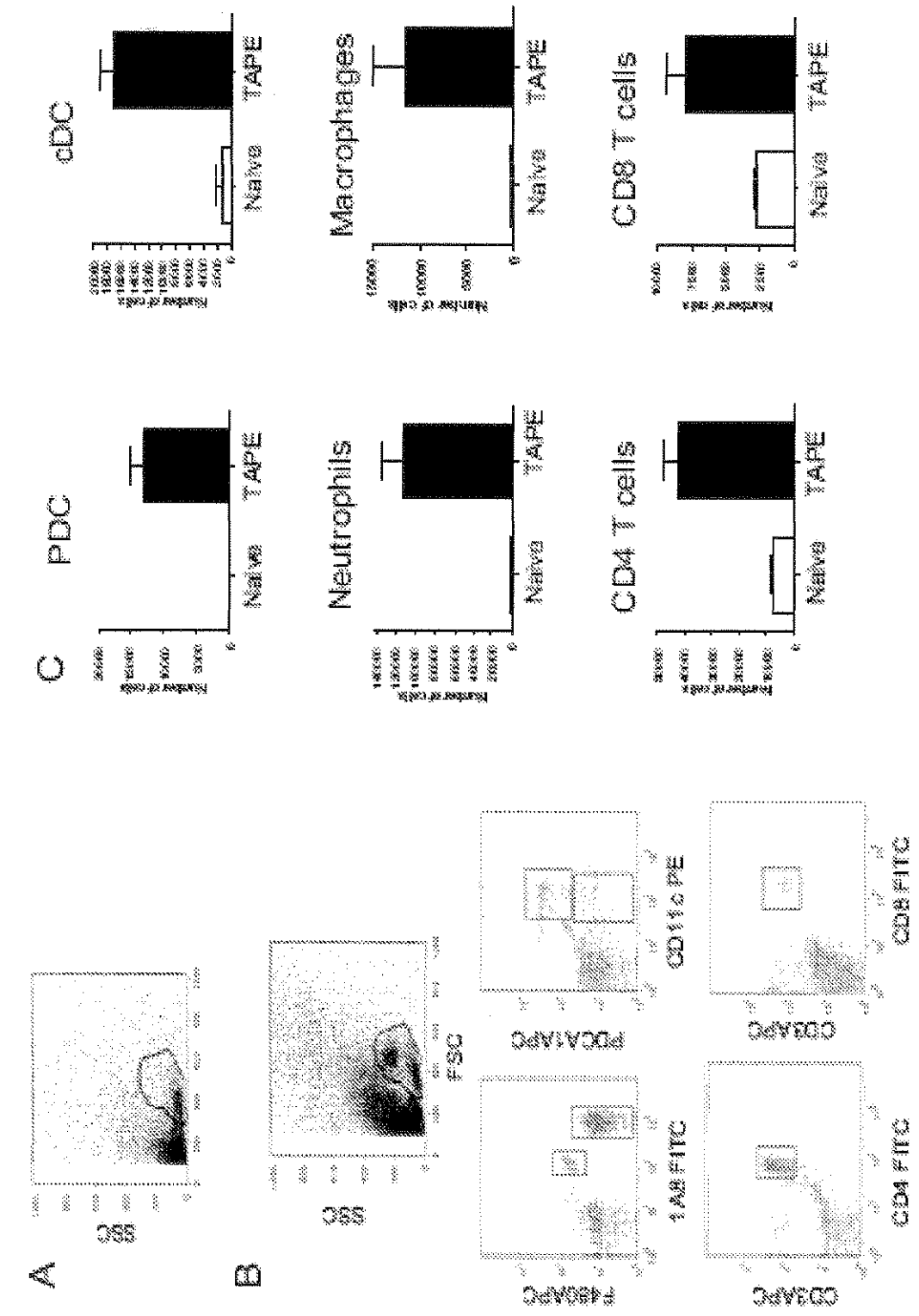
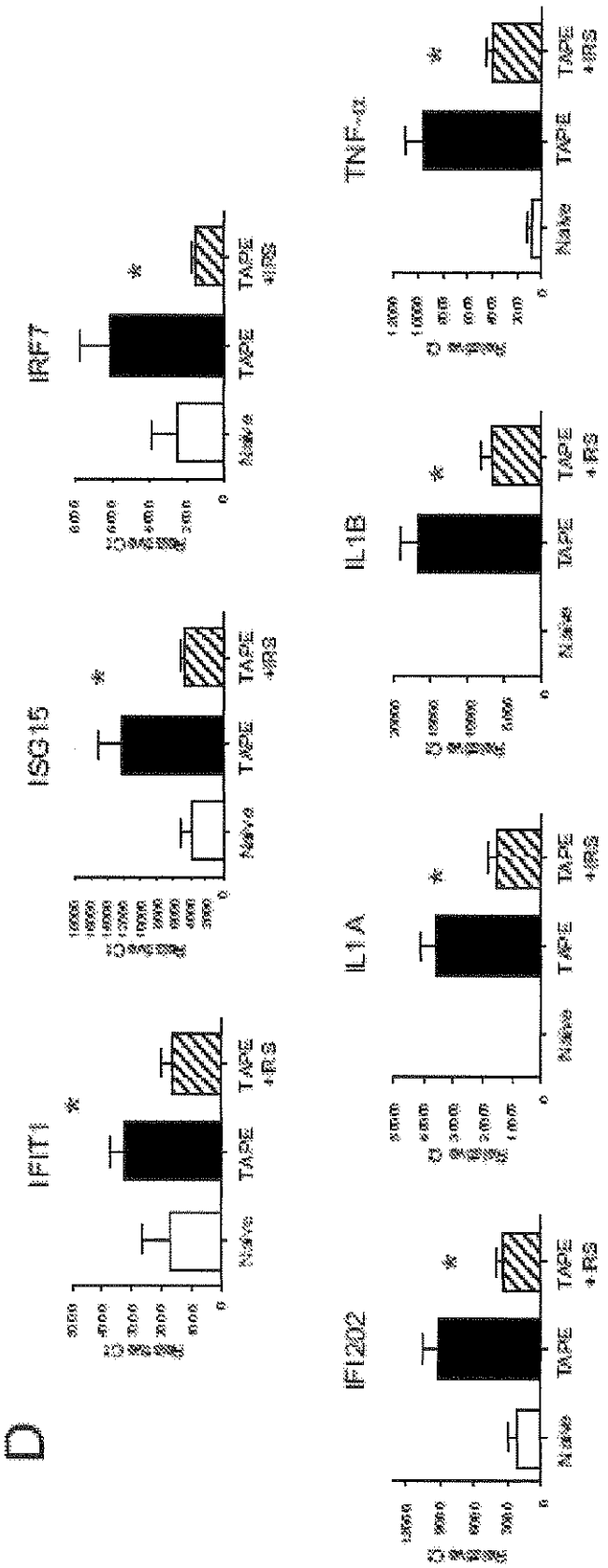

A
SSC
B
SSC
FSC
PDCA1APC
CD11cPE
CD3APC
CD8 FITC
T1A8APC
1A8 FITC
CD3APC
CD4 FITC
C
PDC
Native
TAPE
cDC
Native
TAPE
Neutrophils
Native
TAPE
Macrophages
Native
TAPE
CD4 T cells
Native
TAPE
CD8 T cells
Native
TAPE

FIG. 34



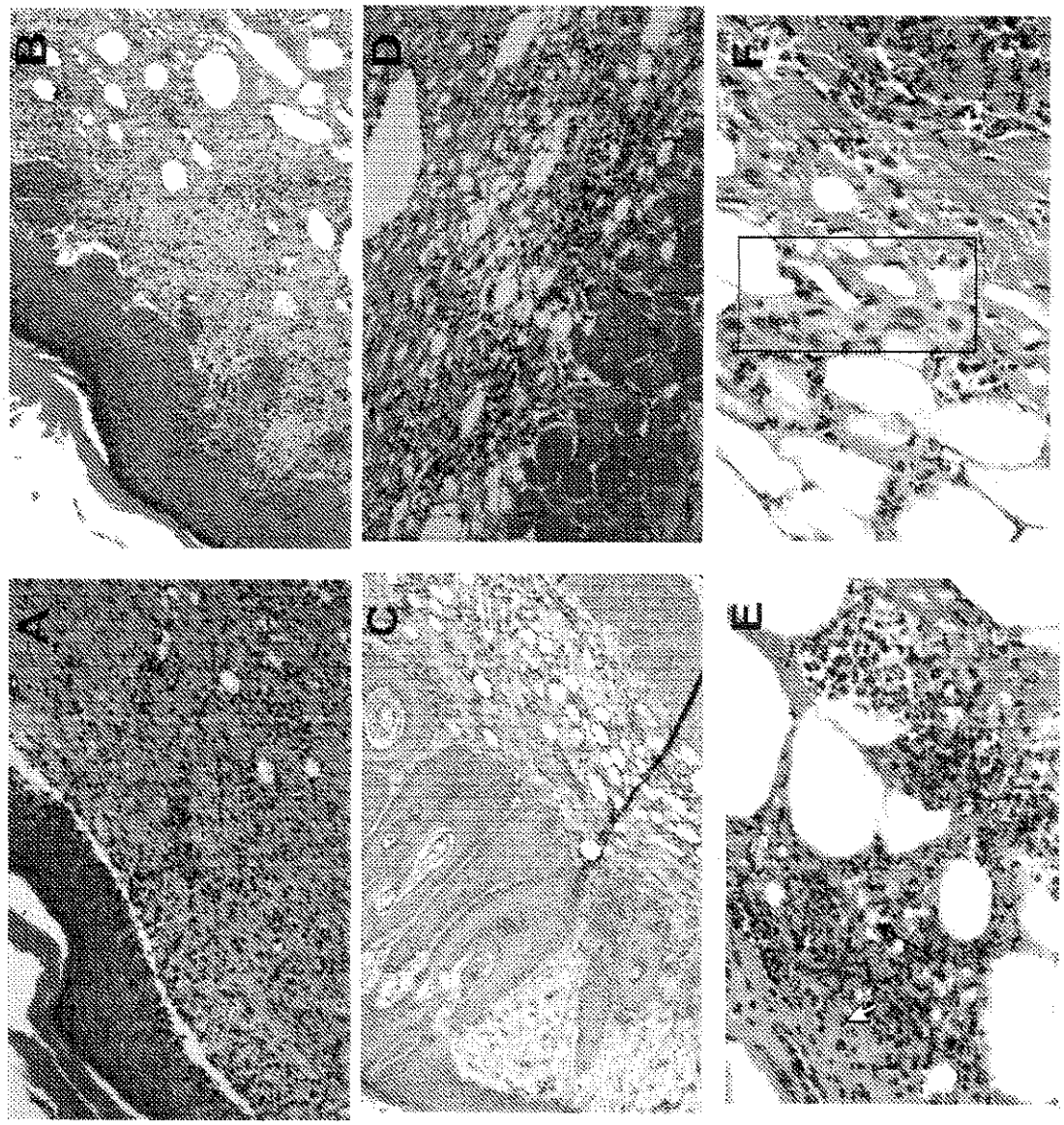


FIG. 35

FIG. 36

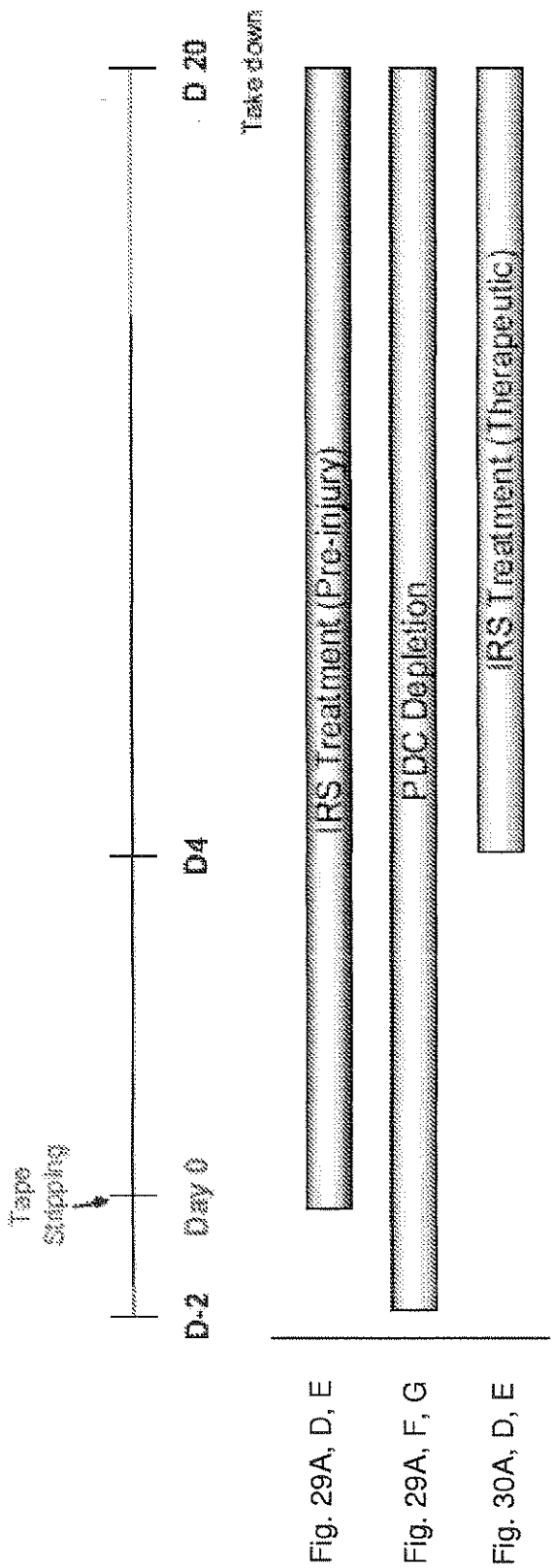

D-2
Day 0
Tape Stripping
D4
D 28
Take down
IRS Treatment (Pre-injury)
PDC Depletion
IRS Treatment (Therapeutic)
Fig. 29A, D, E
Fig. 29A, F, G
Fig. 30A, D, E

FIG. 37

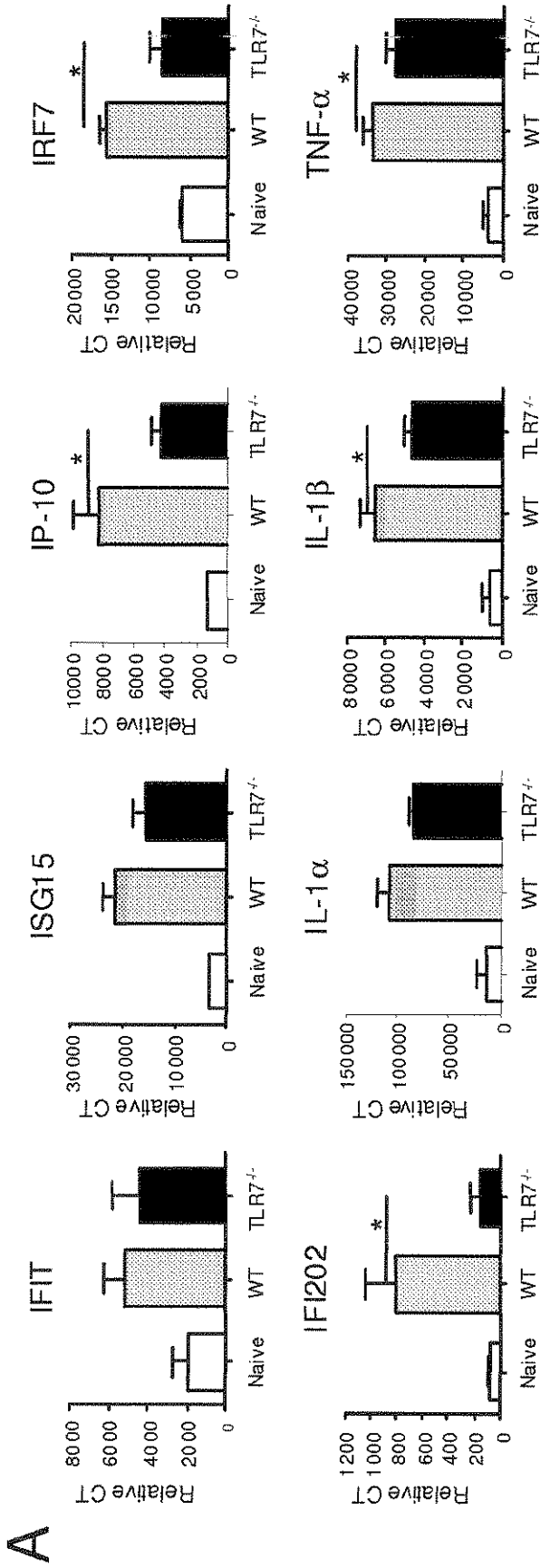

A
IFIT
ISG15
IP-10
IRF7
IF202
IL-1α
IL-1β
TNF-α
Relative CT
Naive
WT
TLR7-/-
*

FIG. 37

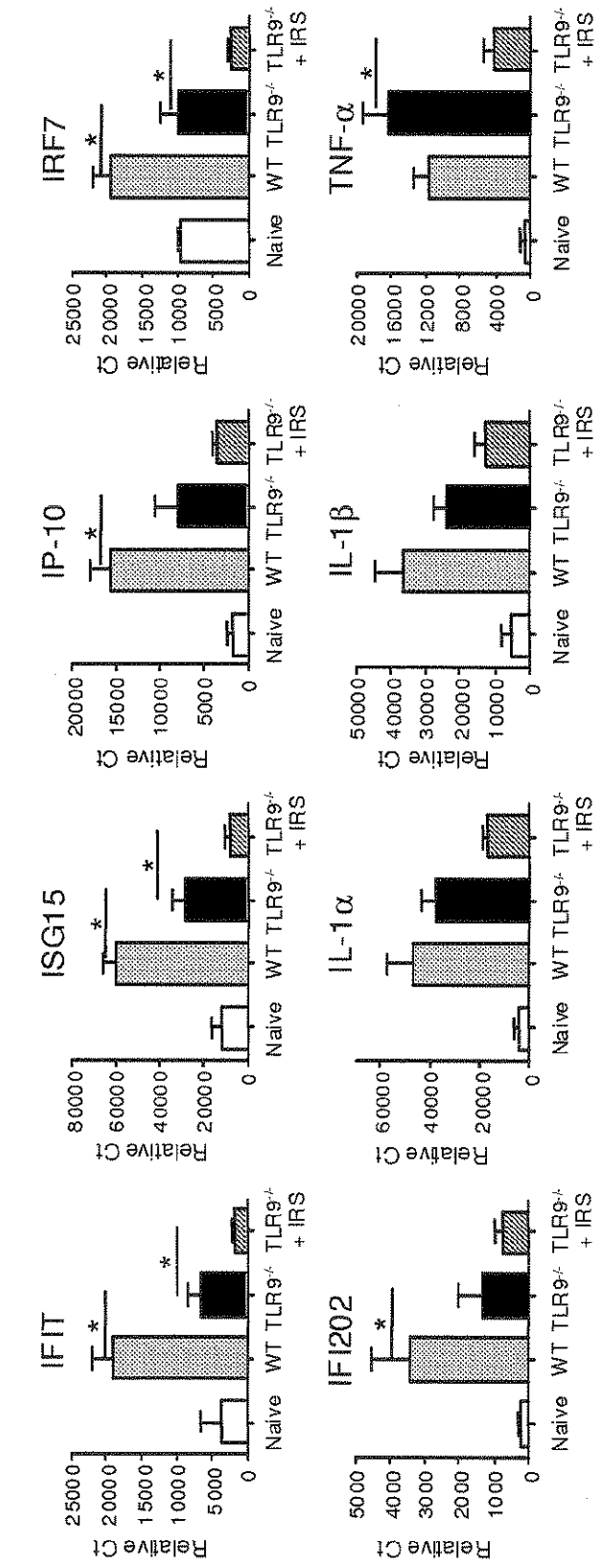
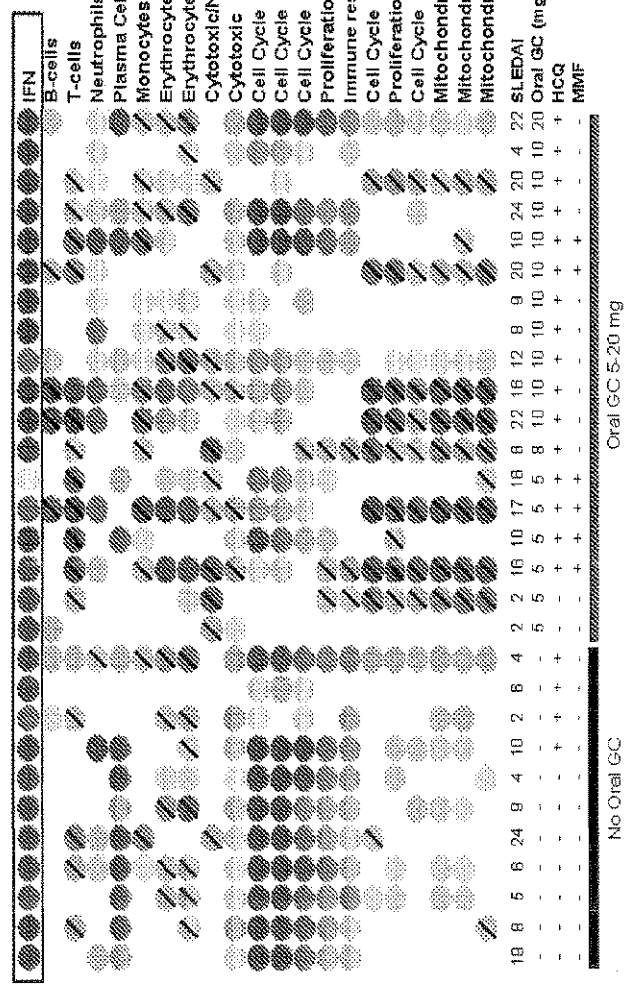

B
IFIT
ISG15
IP-10
IRF7
IFI202
IL-1α
IL-1β
TNF-α
Relative Ct
Naive
WT
TLR9-/-
TLR9-/- + IRS

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)

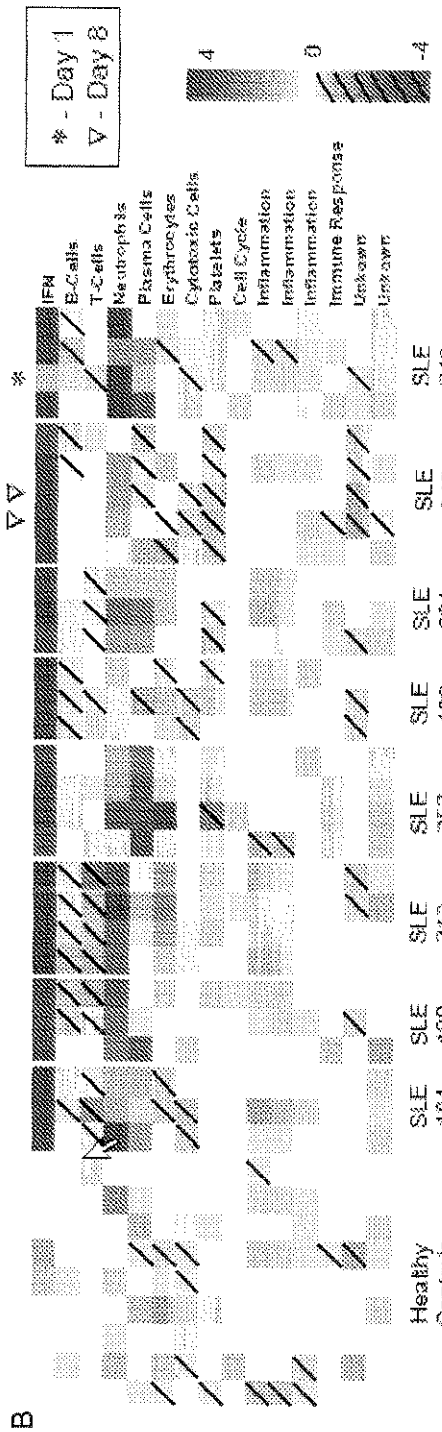

B
* - Day 1
∇ - Day 8
4
0
-4
IFN
B-Cells
T-Cells
Neutrophils
Plasma Cells
Erythrocytes
Cytotoxic Cells
Platelets
Cell Cycle
Inflammation
Inflammation
Inflammation
Immune Response
Unknown
Unknown
Healthy Controls
SLE 184
SLE 190
SLE 212
SLE 252
SLE 133
SLE 231
SLE 242
SLE 249

FIG. 38