PRODUCT CANDIDATE PROFILES
MOLECULAR PHARMACOLOGY AND TOXICOLOGY
• 25 TO 100 GENES
• MULTIPLE CELLS / ORGANS
BETTER PRODUCT CANDIDATES
CLINICAL SURROGATE MARKER PROFILES
CLINICAL TESTING
• 5 TO 15 GENES
• SMALL BLOOD SAMPLES
ACCURATE CLINICAL DEVELOPMENT
HEALTH PROFILES
INDIVIDUALIZED MEDICINE
• 100 TO 500 GENES
• SMALL BLOOD SAMPES
BETTER HEALTH CARE MANAGEMENT

FIG. 1

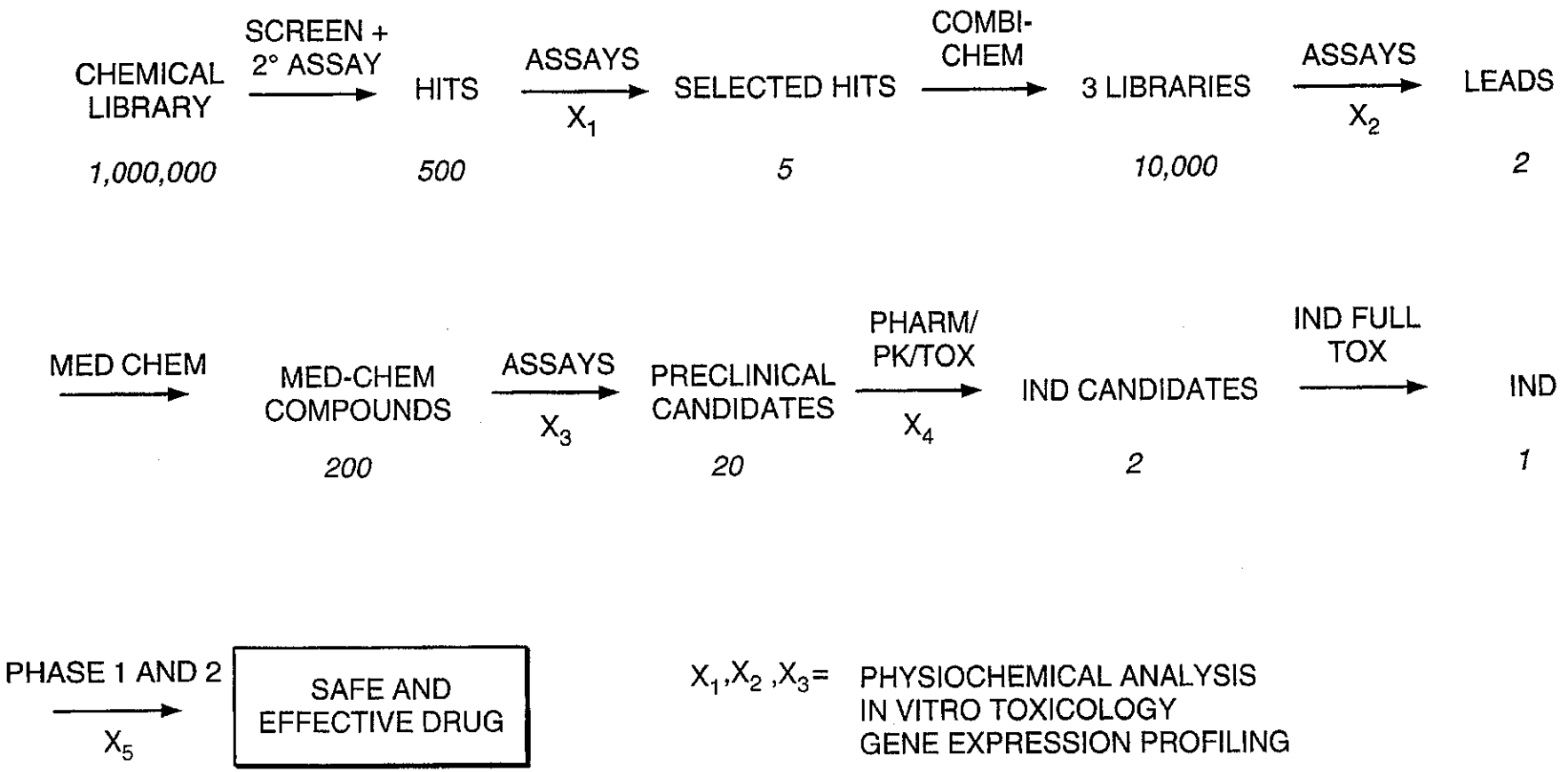

CHEMICAL LIBRARY
1,000,000
SCREEN + 2° ASSAY
HITS
500
ASSAYS
X1
SELECTED HITS
5
COMBI-CHEM
3 LIBRARIES
10,000
ASSAYS
X2
LEADS
2
MED CHEM
MED-CHEM COMPOUNDS
200
ASSAYS
X3
PRECLINICAL CANDIDATES
20
PHARM/ PK/TOX
X4
IND CANDIDATES
2
IND FULL TOX
IND
1
PHASE 1 AND 2
X5
SAFE AND EFFECTIVE DRUG
X1,X2 ,X3= PHYSIOCHEMICAL ANALYSIS
IN VITRO TOXICOLOGY
GENE EXPRESSION PROFILING
X4 = IN VIVO GENE PROFILING
X5 = SURROGATE MARKER

FIG. 2

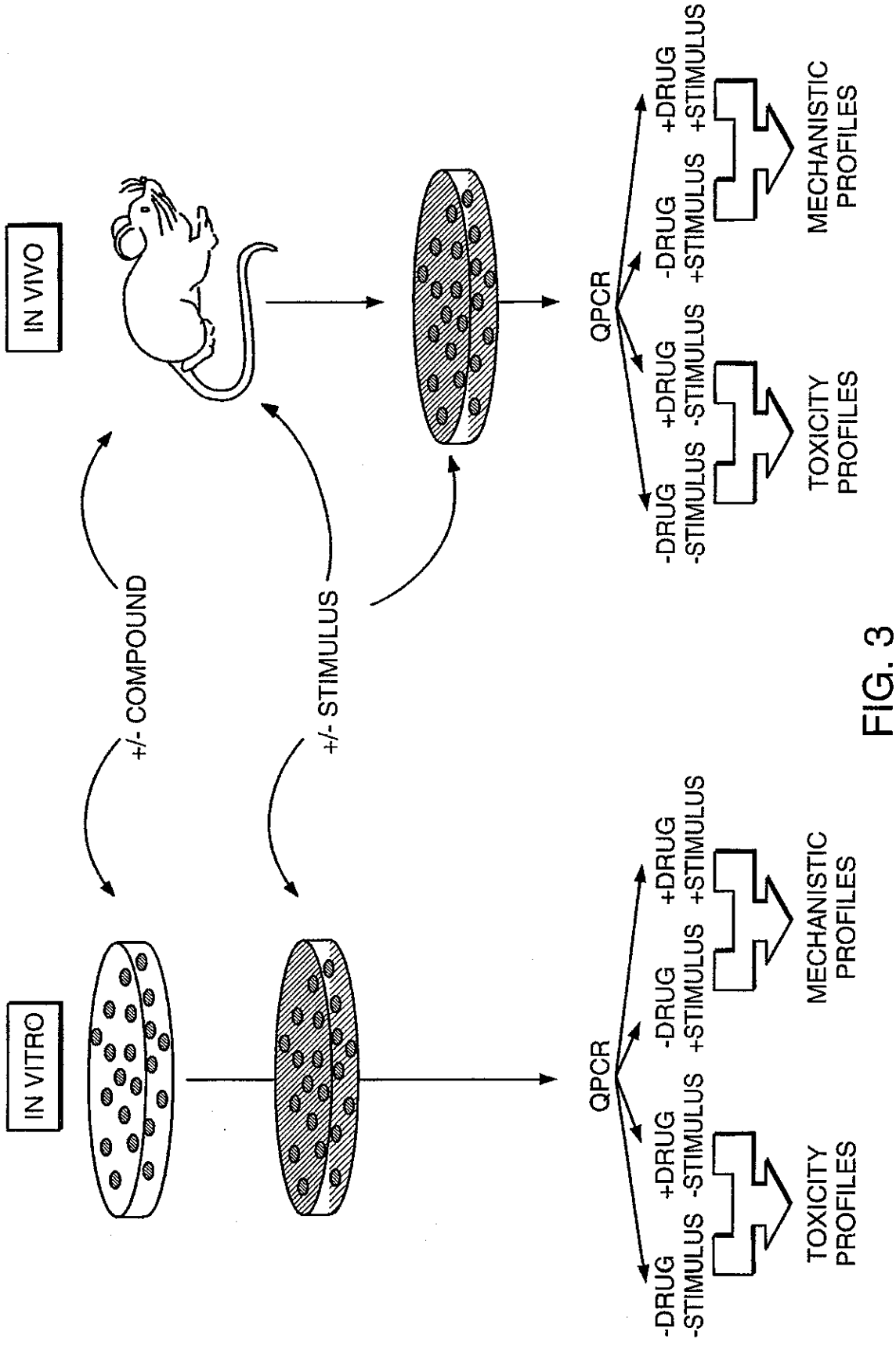

IN VIVO
IN VITRO
+/- COMPOUND
+/- STIMULUS
QPCR
-DRUG -STIMULUS
+DRUG -STIMULUS
-DRUG +STIMULUS
+DRUG +STIMULUS
TOXICITY PROFILES
MECHANISTIC PROFILES

FIG. 3

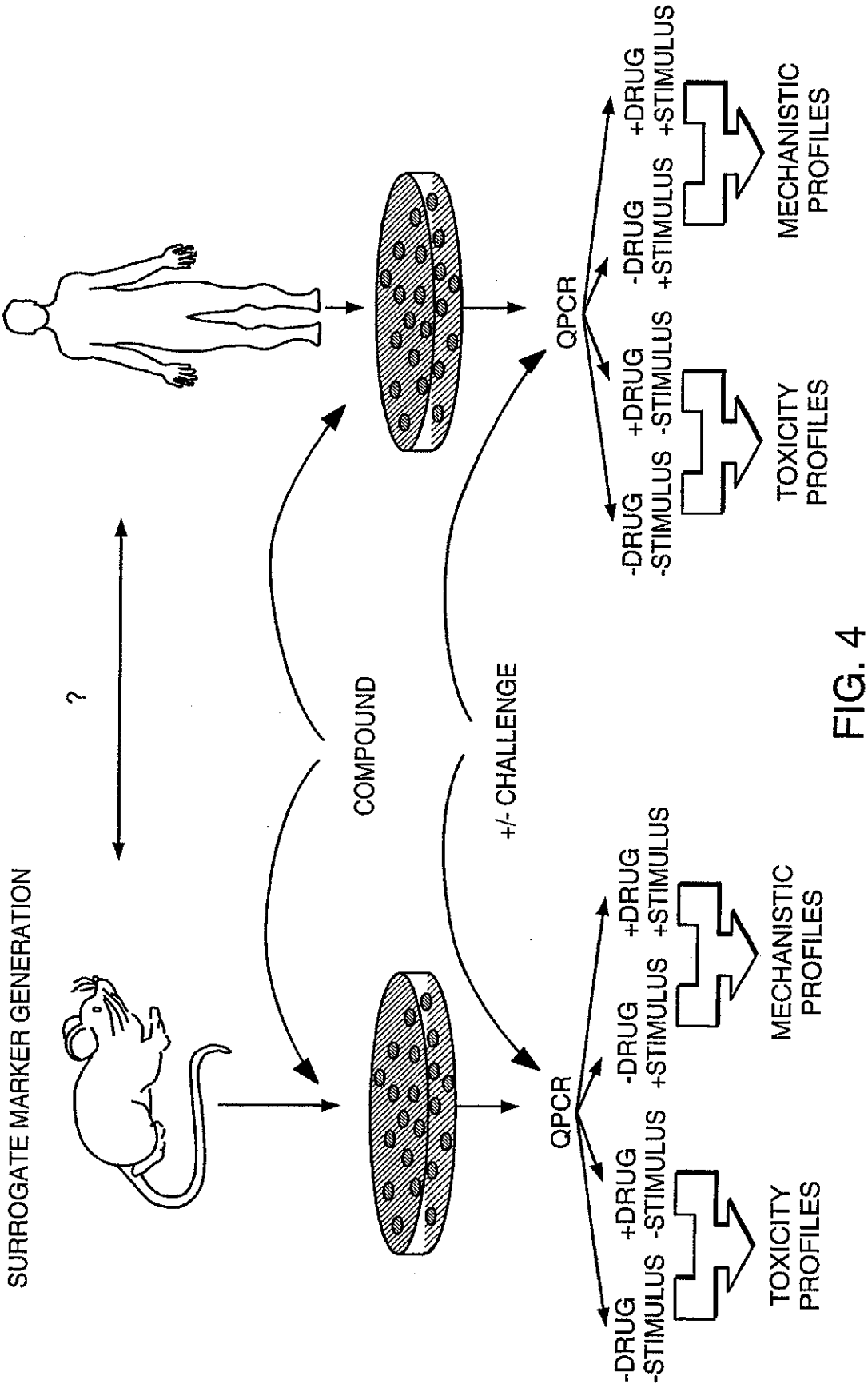

SURROGATE MARKER GENERATION
?
COMPOUND
+/- CHALLENGE
QPCR
-DRUG -STIMULUS
+DRUG -STIMULUS
-DRUG +STIMULUS
+DRUG +STIMULUS
TOXICITY PROFILES
MECHANISTIC PROFILES

FIG. 4

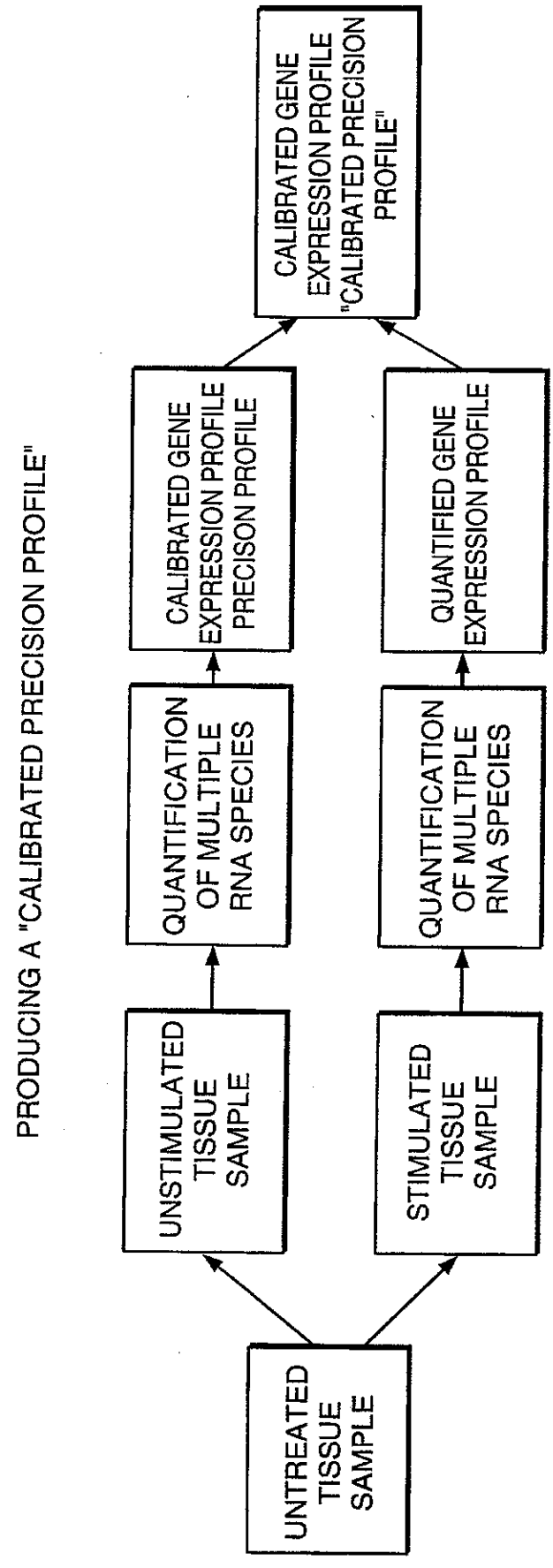

PRODUCING A "CALIBRATED PRECISION PROFILE"
UNTREATED TISSUE SAMPLE
UNSTIMULATED TISSUE SAMPLE
STIMULATED TISSUE SAMPLE
QUANTIFICATION OF MULTIPLE RNA SPECIES
QUANTIFICATION OF MULTIPLE RNA SPECIES
CALIBRATED GENE EXPRESSION PROFILE PRECISON PROFILE
QUANTIFIED GENE EXPRESSION PROFILE
CALIBRATED GENE EXPRESSION PROFILE "CALIBRATED PRECISION PROFILE"
SOURCE PRECISION MEDICINE

FIG. 5

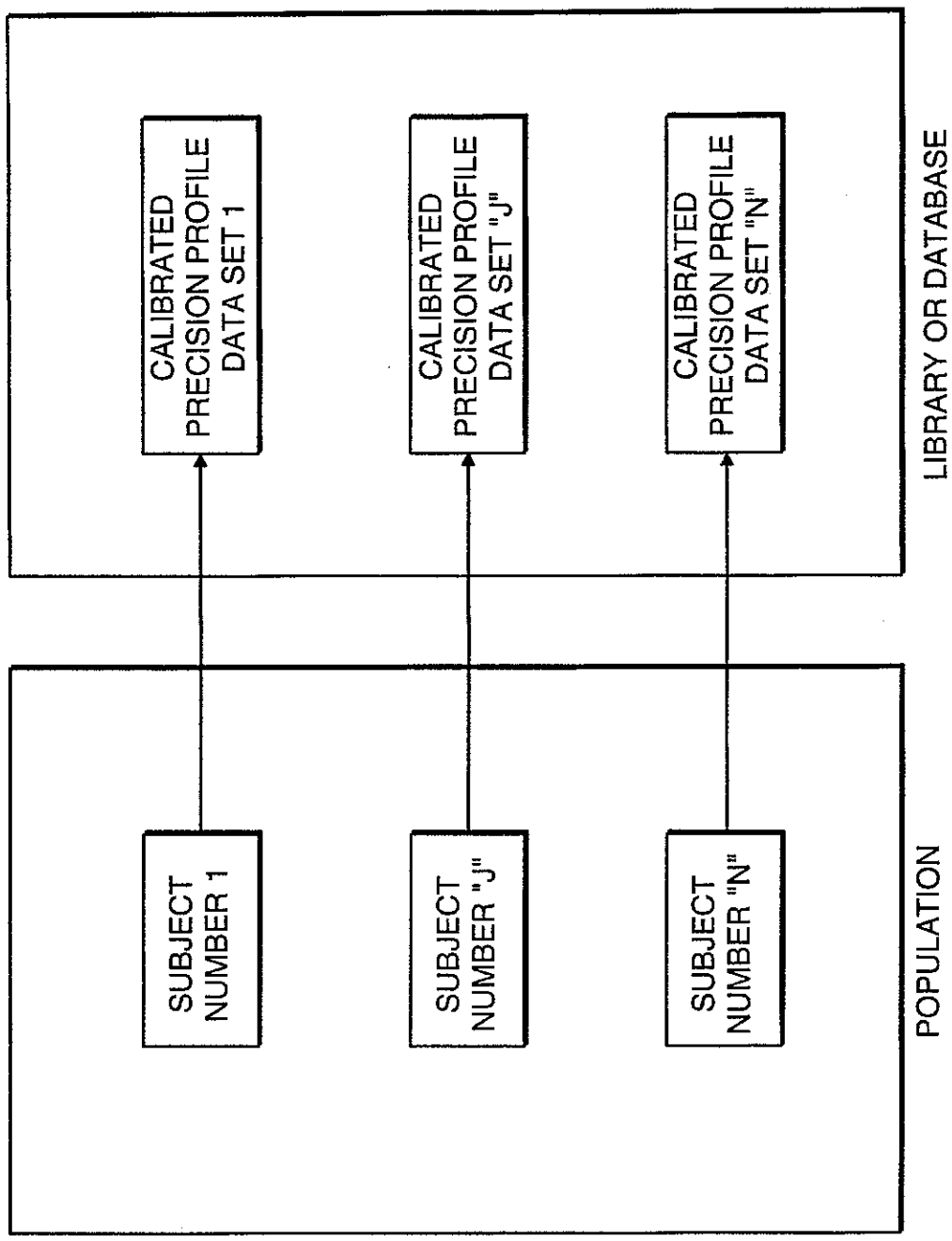

CALIBRATED PRECISION PROFILE DATA SET 1
CALIBRATED PRECISION PROFILE DATA SET "J"
CALIBRATED PRECISION PROFILE DATA SET "N"
LIBRARY OR DATABASE
SUBJECT NUMBER 1
SUBJECT NUMBER "J"
SUBJECT NUMBER "N"
POPULATION

FIG. 6

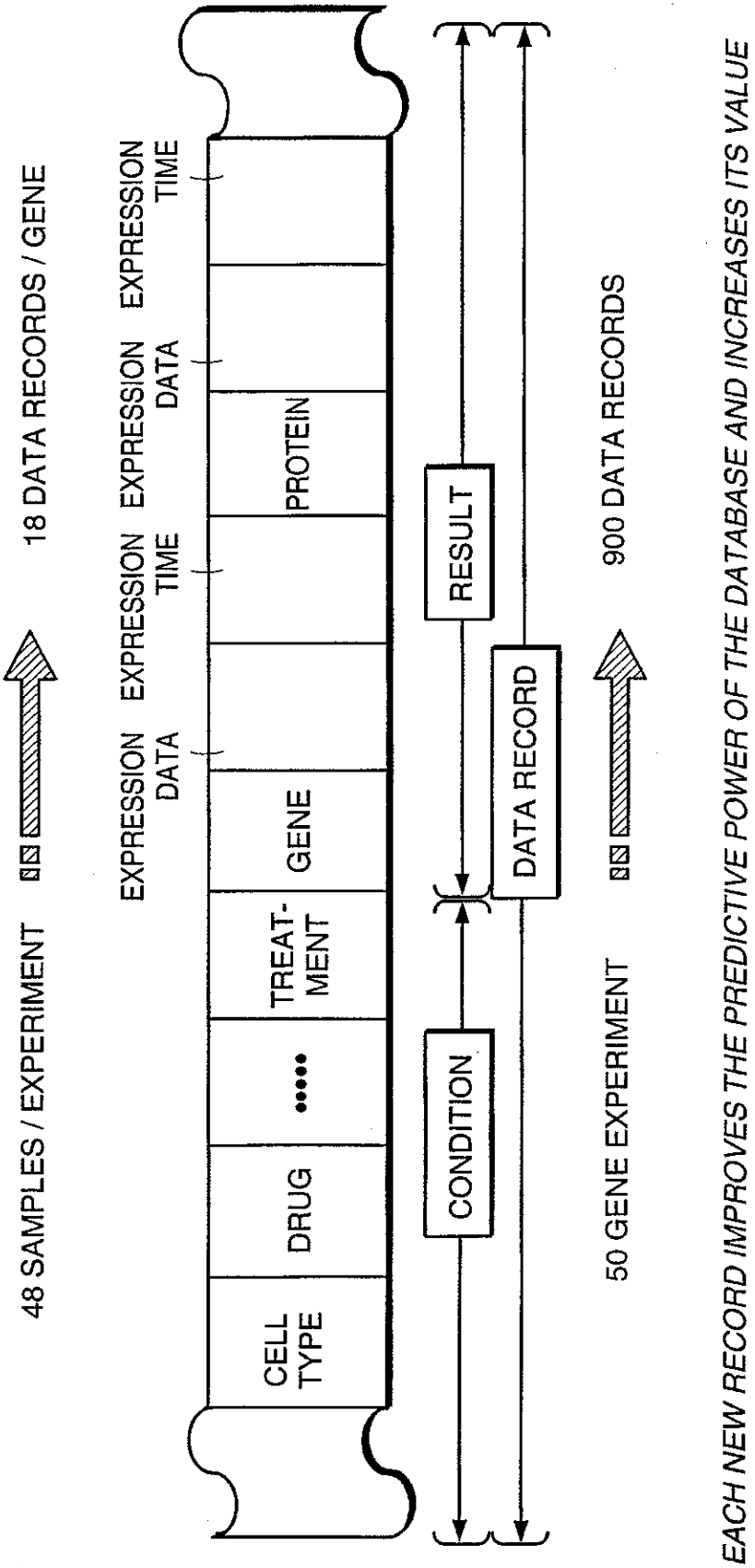


FIG. 7

EACH NEW RECORD IMPROVES THE PREDICTIVE POWER OF THE DATABASE AND INCREASES ITS VALUE

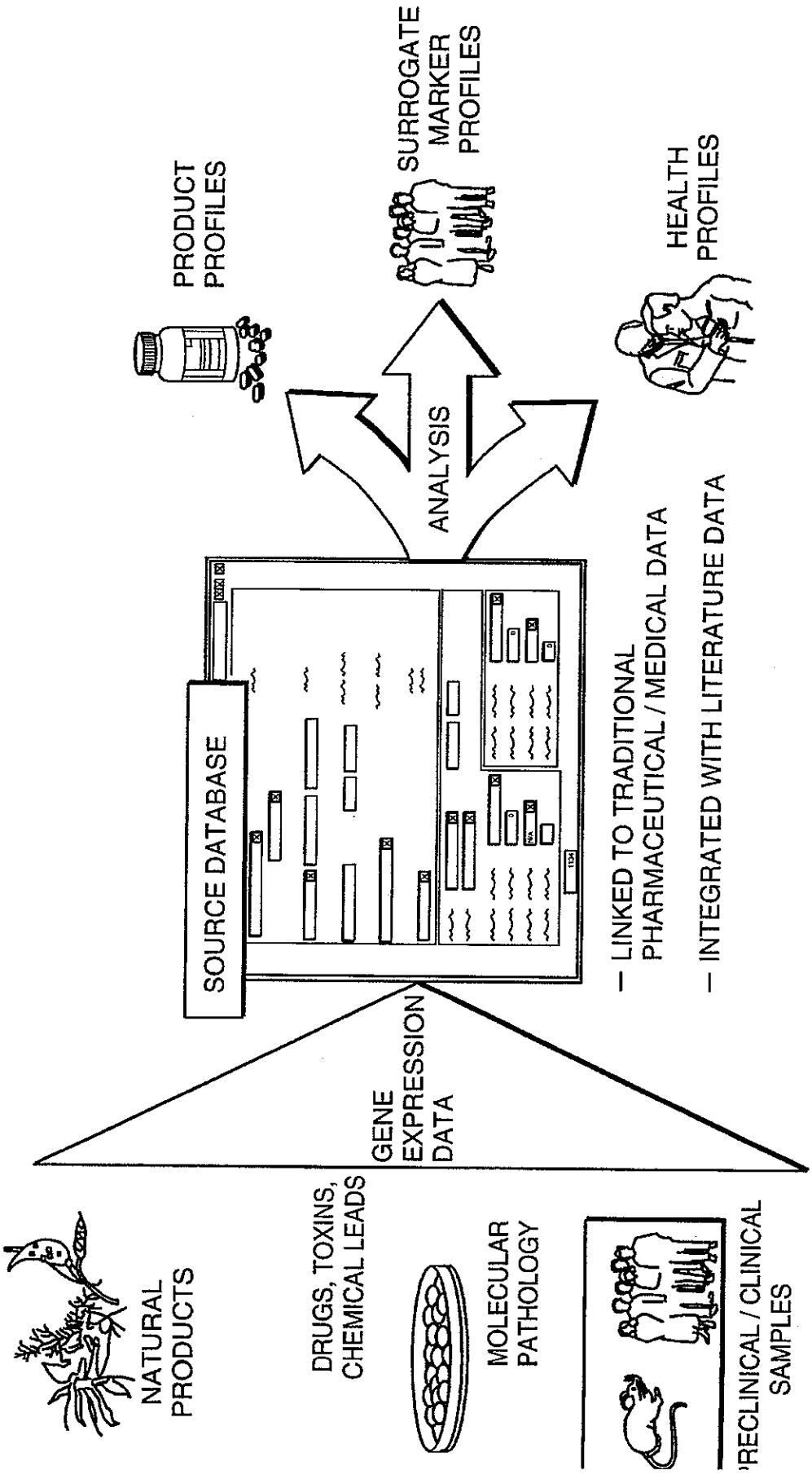

NATURAL PRODUCTS
DRUGS, TOXINS, CHEMICAL LEADS
MOLECULAR PATHOLOGY
PRECLINICAL / CLINICAL SAMPLES
GENE EXPRESSION DATA
SOURCE DATABASE
ANALYSIS
– LINKED TO TRADITIONAL PHARMACEUTICAL / MEDICAL DATA
– INTEGRATED WITH LITERATURE DATA
PRODUCT PROFILES
SURROGATE MARKER PROFILES
HEALTH PROFILES

FIG. 8

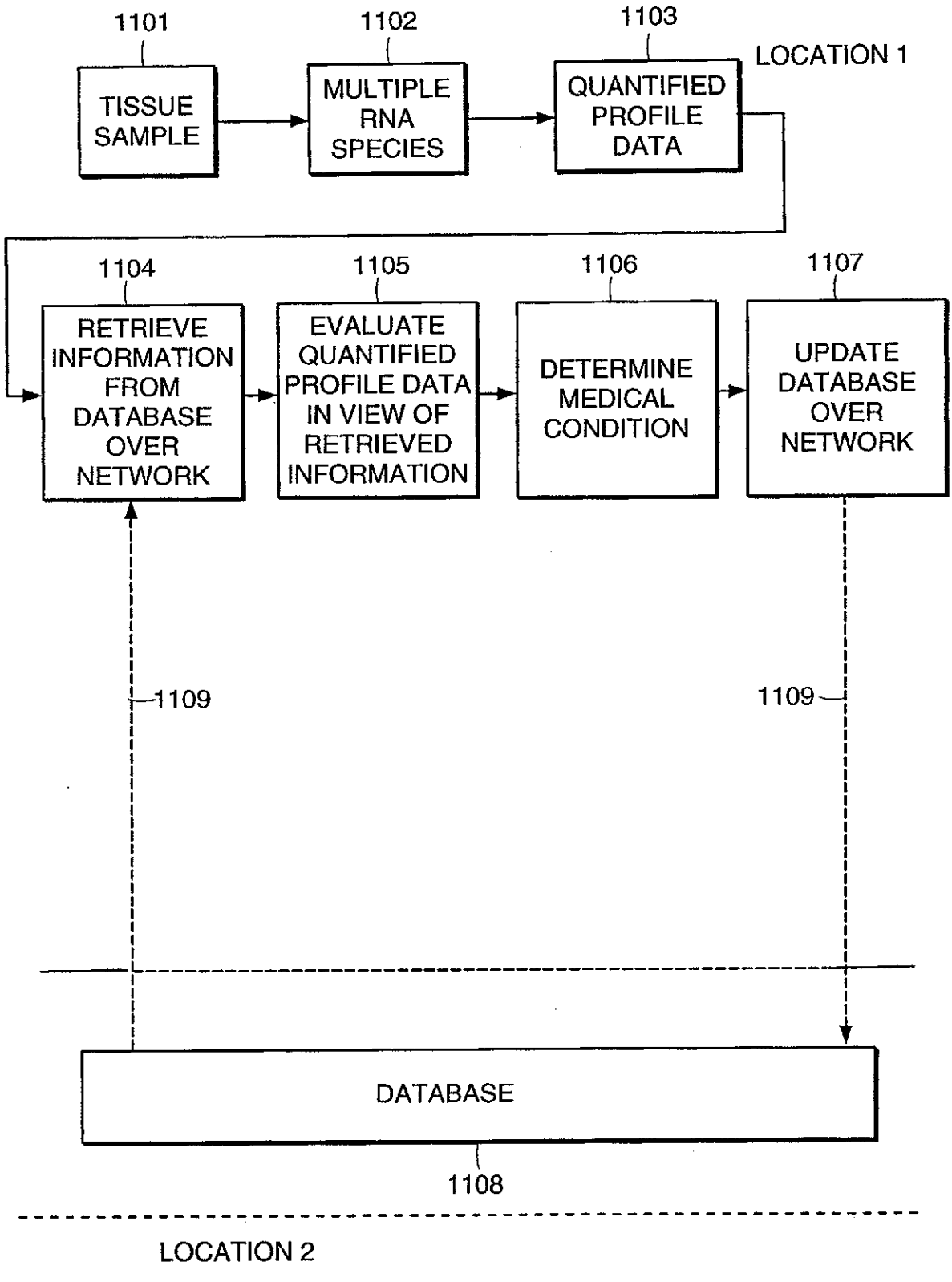
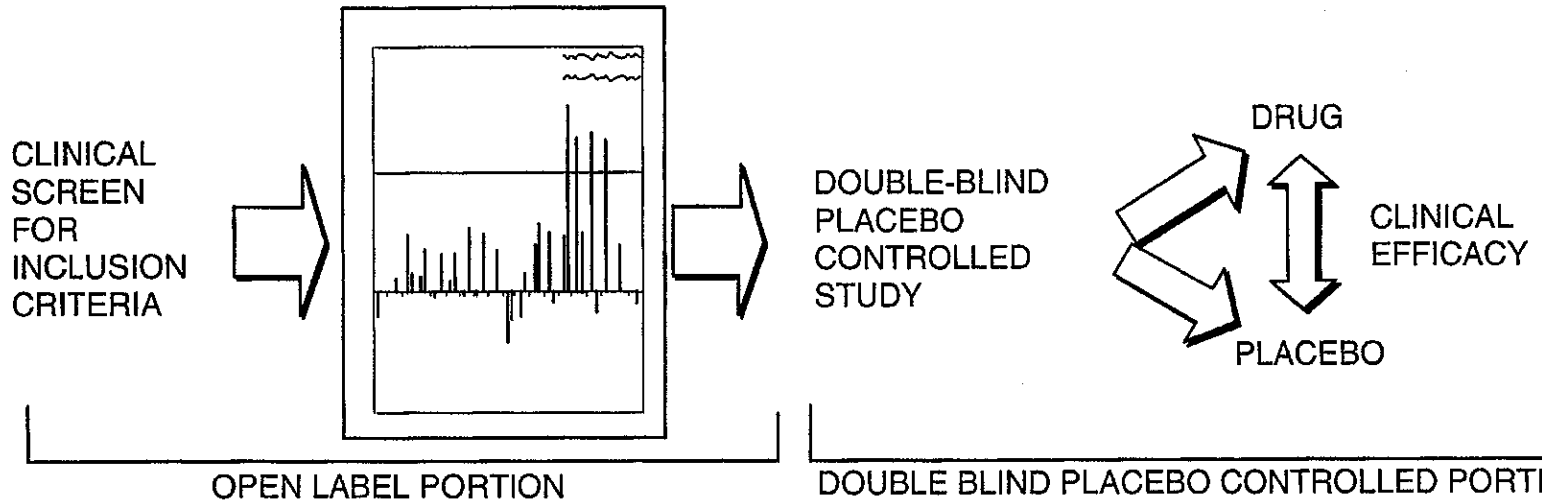

1101
TISSUE SAMPLE
1102
MULTIPLE RNA SPECIES
1103
QUANTIFIED PROFILE DATA
LOCATION 1
1104
RETRIEVE INFORMATION FROM DATABASE OVER NETWORK
1105
EVALUATE QUANTIFIED PROFILE DATA IN VIEW OF RETRIEVED INFORMATION
1106
DETERMINE MEDICAL CONDITION
1107
UPDATE DATABASE OVER NETWORK
1109
1109
DATABASE
1108
LOCATION 2

FIG. 9

PHASE TWO CLINICAL TRIAL DESIGN USING PRECISION PROFILING



- THE TARGET CLINICAL POPULATION CAN BE EVALUATED FOR RESPONSIVENESS TO THERAPY BY FOCUSING ON DRUG RESPONSE GENE PROFILING

- "SIGNAL TO NOISE" CAN BE ENHANCED BY REMOVING NON-RESPONDERS FROM THE SECOND PORTION OF THE STUDY

- DOSE CAN BE OPTIMIZED ON AN INDIVIDUAL BASIS TO MAXIMIZE THE IMPACT ON THERAPEUTIC OUTCOME

FIG. 10a

- CLINICAL RESPONSE/NON-RESPONSE CAN BE CORRELATED WITH DISEASE RESPONSE GENE PROFILING

- CLINICAL EFFICACY CAN BE MEASURED WITH GREATER PRECISION

- FUTURE STUDIES CAN BE PLANNED WITH GREATER CERTAINTY AND STATISTICAL POWER

- COMPARISION WITH CLINICAL DATABASES CAN PROVIDE IMPORTANT INFORMATION REGARDING COMPETITIVE POSITIONING RELATIVE TO EXISTING THERAPIES

FIG. 10b

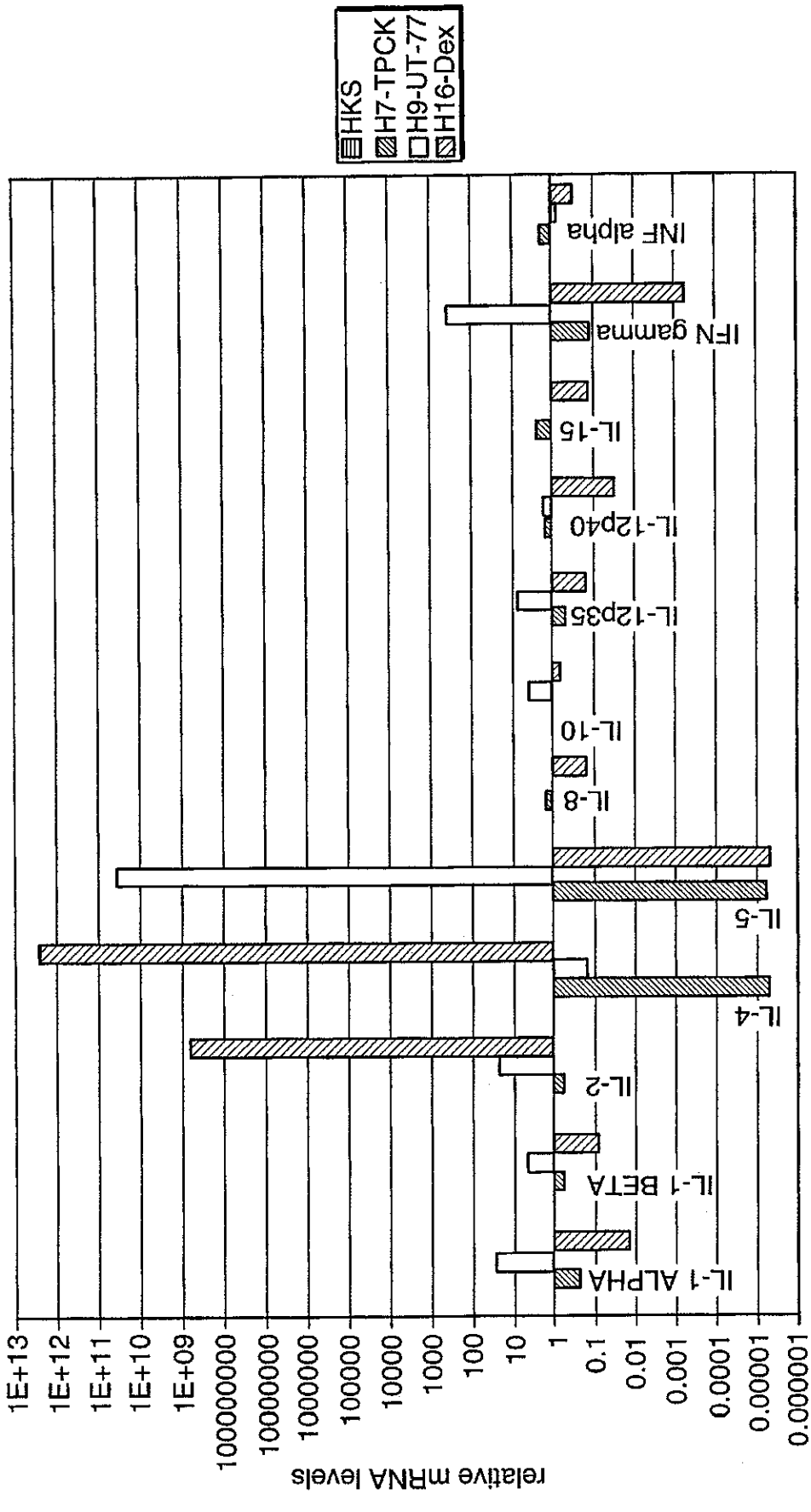

HKS
H7-TPCK
H9-UT-77
H16-Dex
relative mRNA levels
1E+13
1E+12
1E+11
1E+10
1E+09
100000000
10000000
1000000
100000
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
IL-1 ALPHA
IL-1 BETA
IL-2
IL-4
IL-5
IL-8
IL-10
IL-12p35
IL-12p40
IL-15
IFN gamma
INF alpha

FIG. 11a

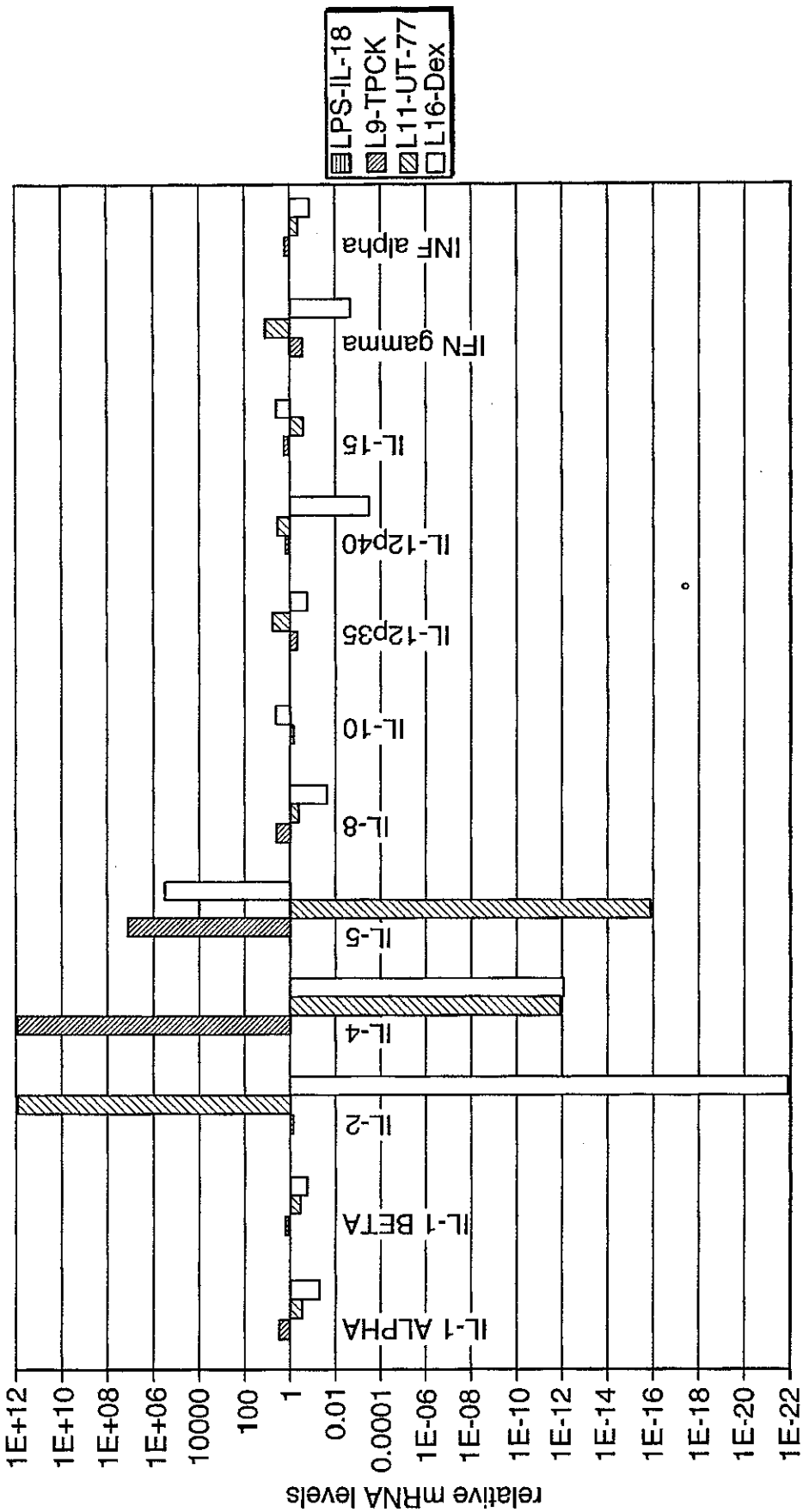

LPS-IL-18
L9-TPCK
L11-UT-77
L16-Dex
IL-1 ALPHA
IL-1 BETA
IL-2
IL-4
IL-5
IL-8
IL-10
IL-12p35
IL-12p40
IL-15
IFN gamma
INF alpha
relative mRNA levels
1E+12
1E+10
1E+08
1E+06
10000
100
1
0.01
0.0001
1E-06
1E-08
1E-10
1E-12
1E-14
1E-16
1E-18
1E-20
1E-22

FIG. 11b

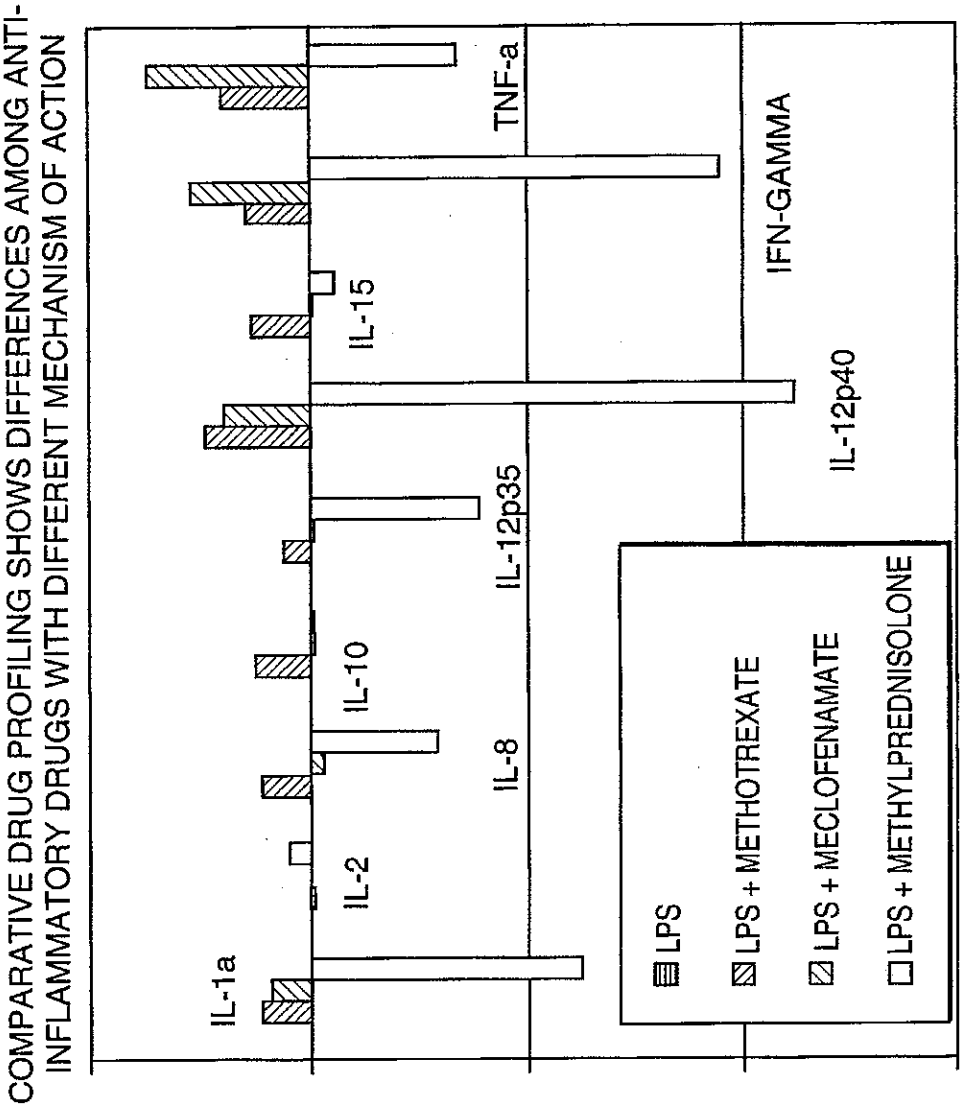

COMPARATIVE DRUG PROFILING SHOWS DIFFERENCES AMONG ANTI-INFLAMMATORY DRUGS WITH DIFFERENT MECHANISM OF ACTION
IL-1a
IL-2
IL-10
IL-8
IL-12p35
IL-15
TNF-a
IFN-GAMMA
IL-12p40
LPS
LPS + METHOTREXATE
LPS + MECLOFENAMATE
LPS + METHYLPREDNISOLONE

FIG. 12a

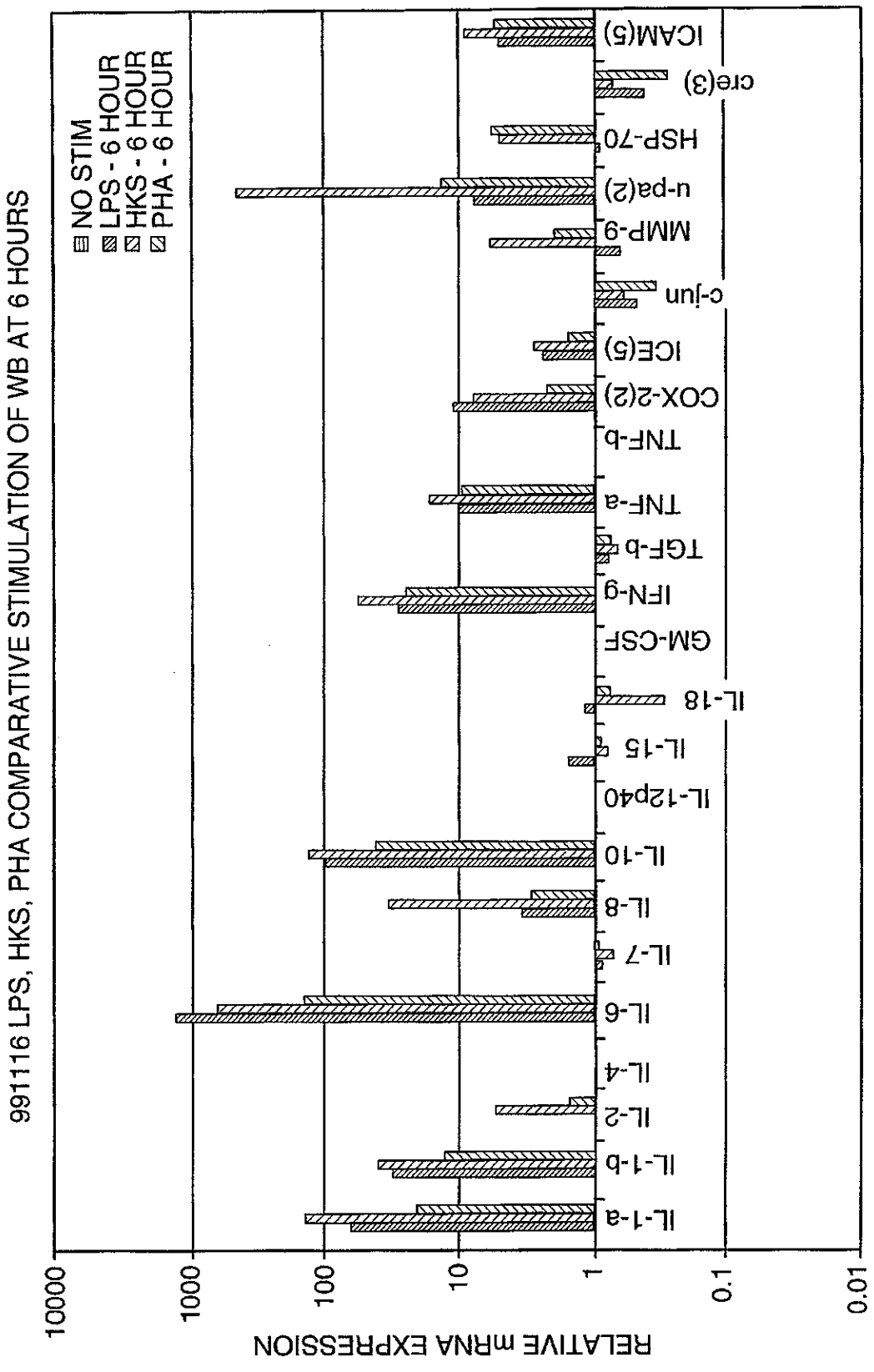

991116 LPS, HKS, PHA COMPARATIVE STIMULATION OF WB AT 6 HOURS
NO STIM
LPS - 6 HOUR
HKS - 6 HOUR
PHA - 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TNF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MMP-9
u-pa(2)
HSP-70
cre(3)
ICAM(5)

FIG. 13a

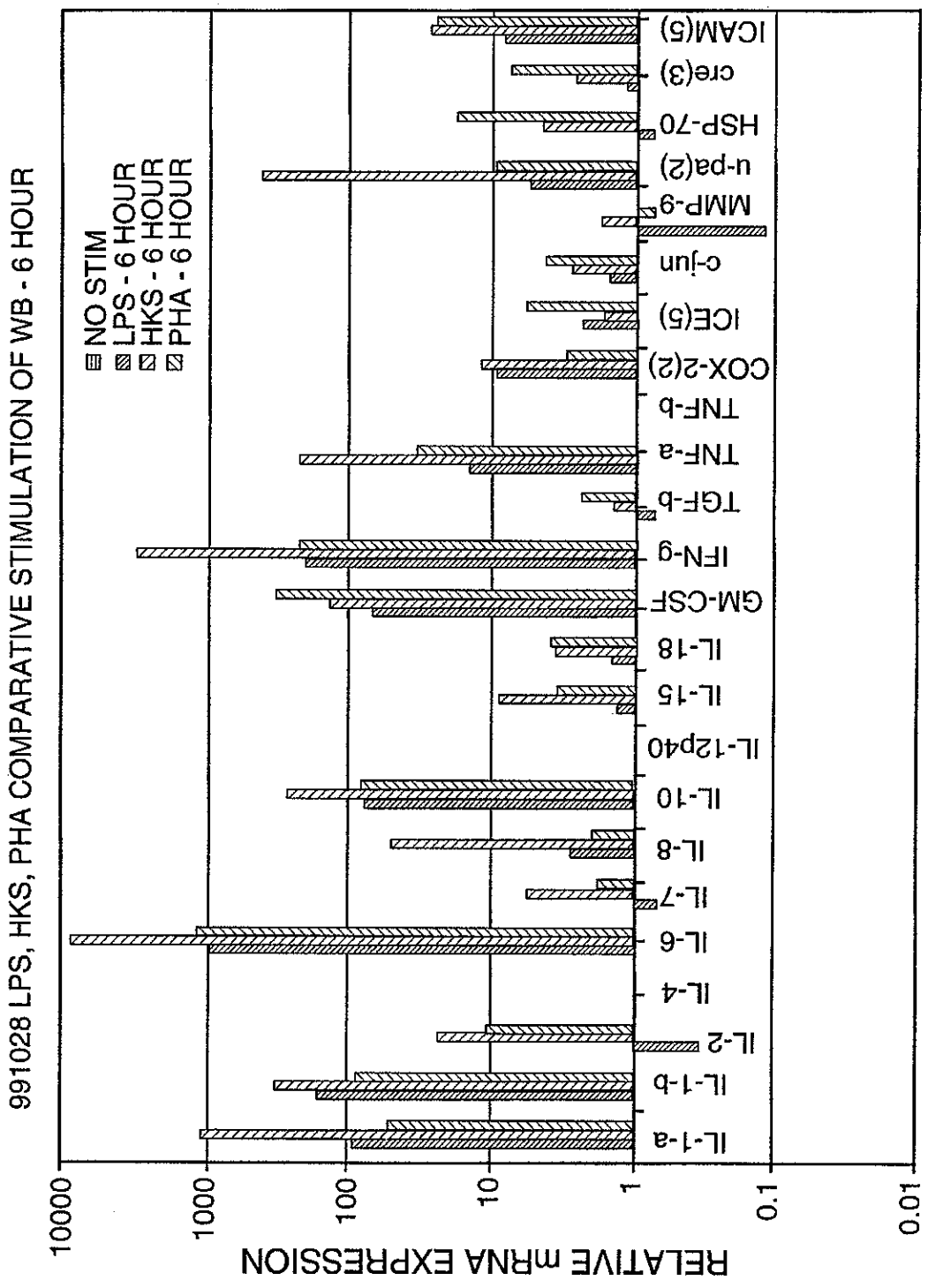

991028 LPS, HKS, PHA COMPARATIVE STIMULATION OF WB - 6 HOUR
NO STIM
LPS - 6 HOUR
HKS - 6 HOUR
PHA - 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TNF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MMP-9
u-pa(2)
HSP-70
cre(3)
ICAM(5)

FIG. 13b

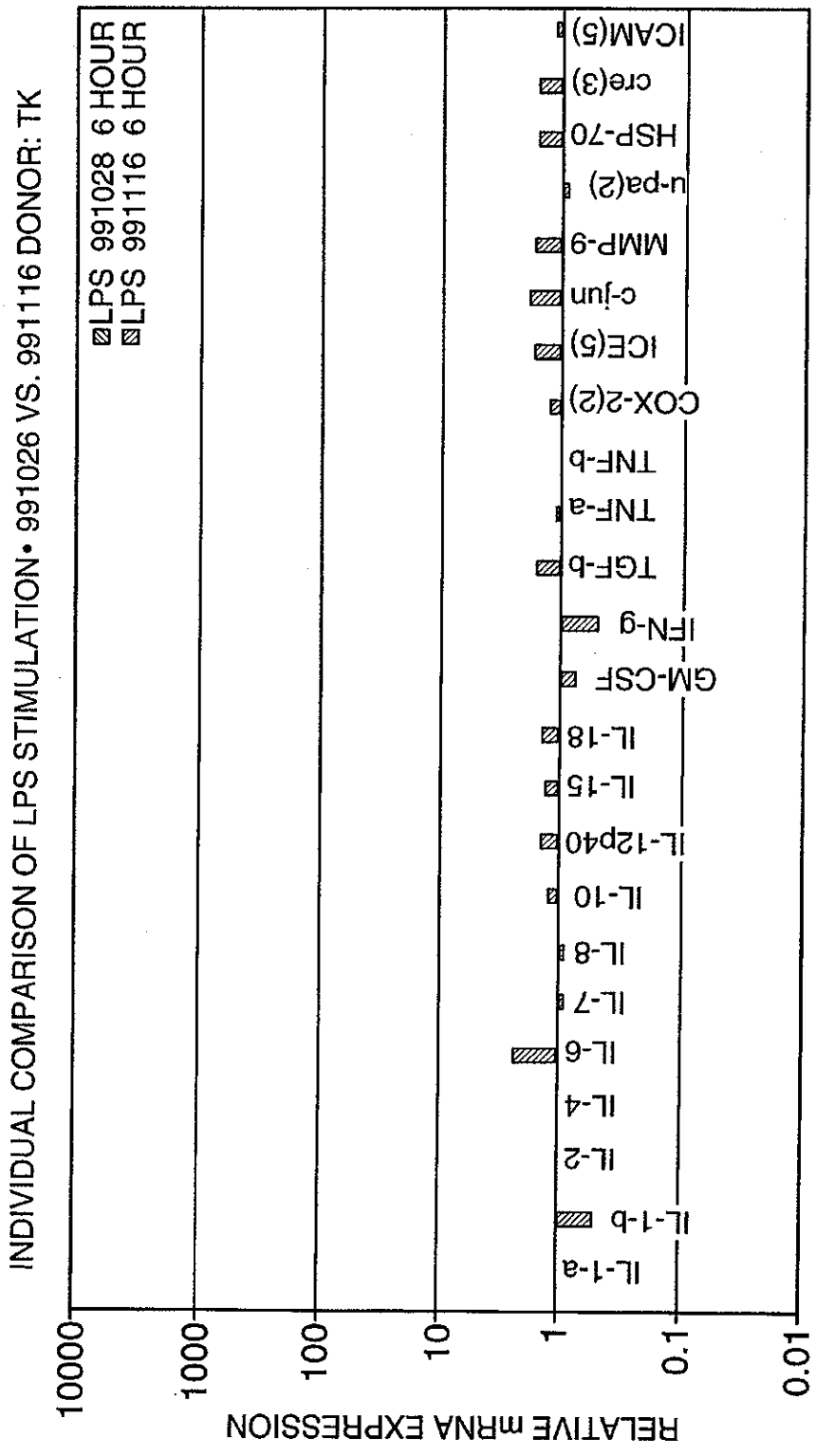

INDIVIDUAL COMPARISON OF LPS STIMULATION• 991026 VS. 991116 DONOR: TK
LPS 991028 6 HOUR
LPS 991116 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TNF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MMP-9
u-pa(2)
HSP-70
cre(3)
ICAM(5)

FIG. 13c

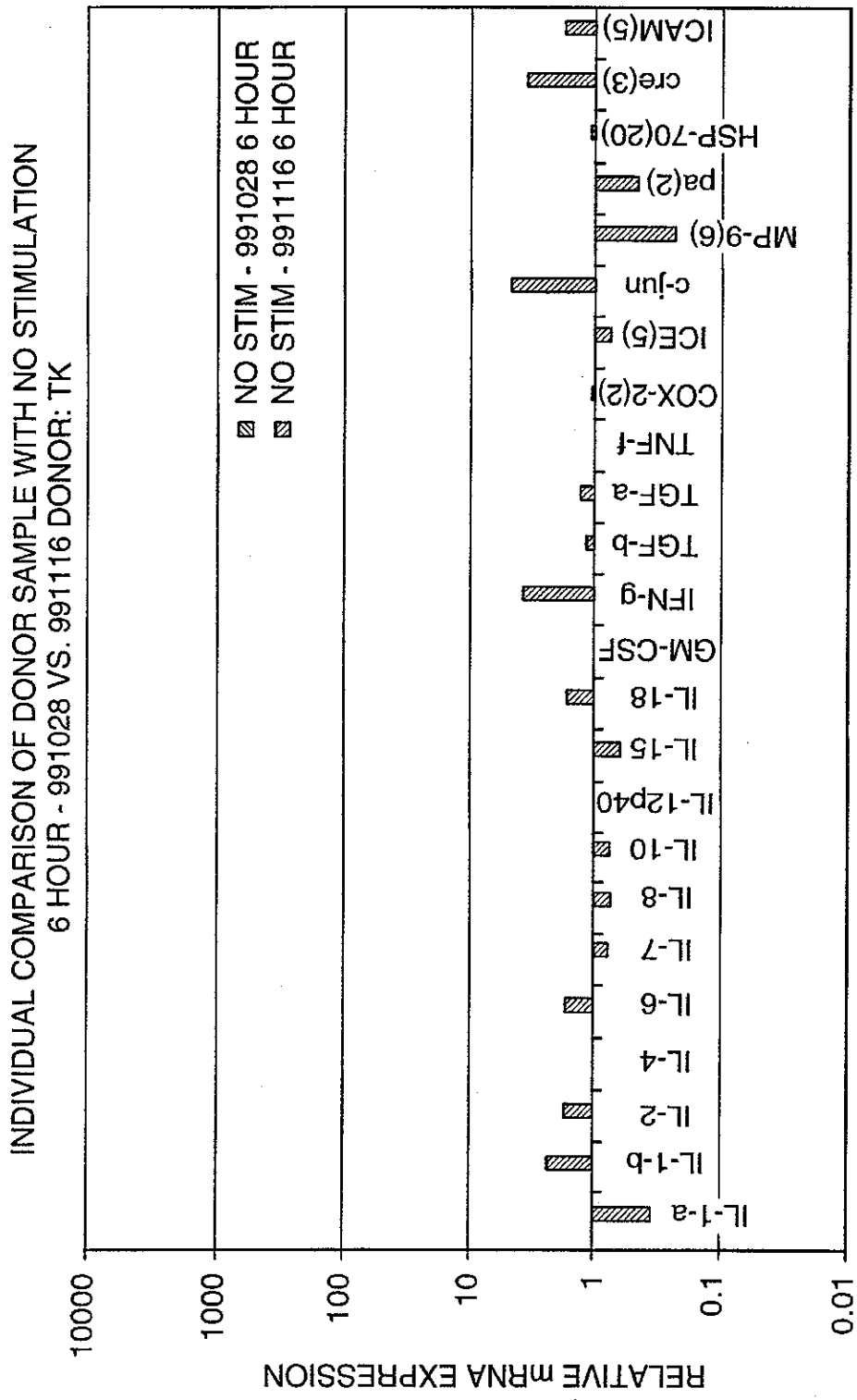

INDIVIDUAL COMPARISON OF DONOR SAMPLE WITH NO STIMULATION
6 HOUR - 991028 VS. 991116 DONOR: TK
NO STIM - 991028 6 HOUR
NO STIM - 991116 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TGF-a
TNF-f
COX-2(2)
ICE(5)
c-jun
MP-9(6)
pa(2)
HSP-70(20)
cre(3)
ICAM(5)

FIG. 13d

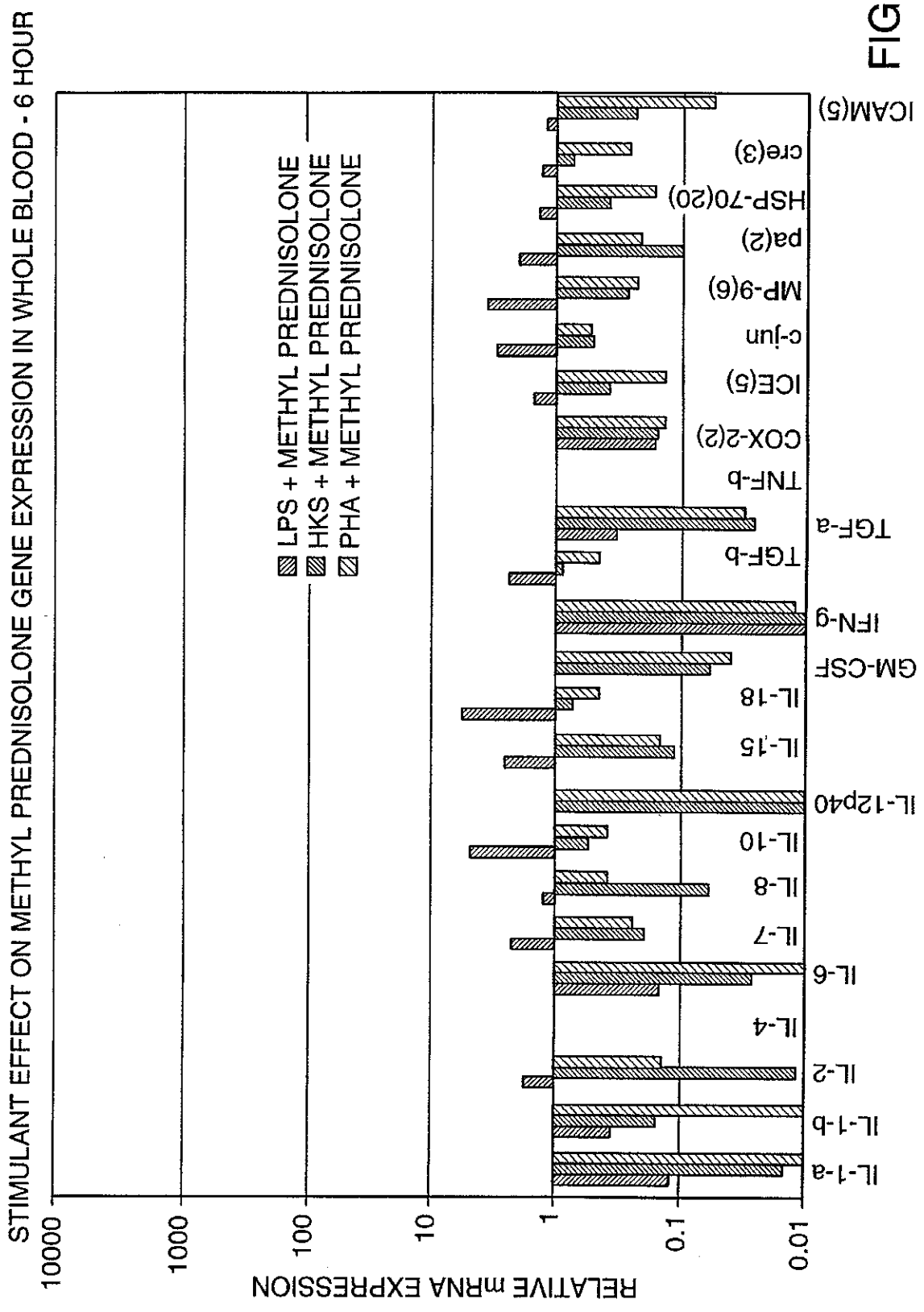

STIMULANT EFFECT ON METHYL PREDNISOLONE GENE EXPRESSION IN WHOLE BLOOD - 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
LPS + METHYL PREDNISOLONE
HKS + METHYL PREDNISOLONE
PHA + METHYL PREDNISOLONE
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TGF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MP-9(6)
pa(2)
HSP-70(20)
cre(3)
ICAM(5)

FIG. 14

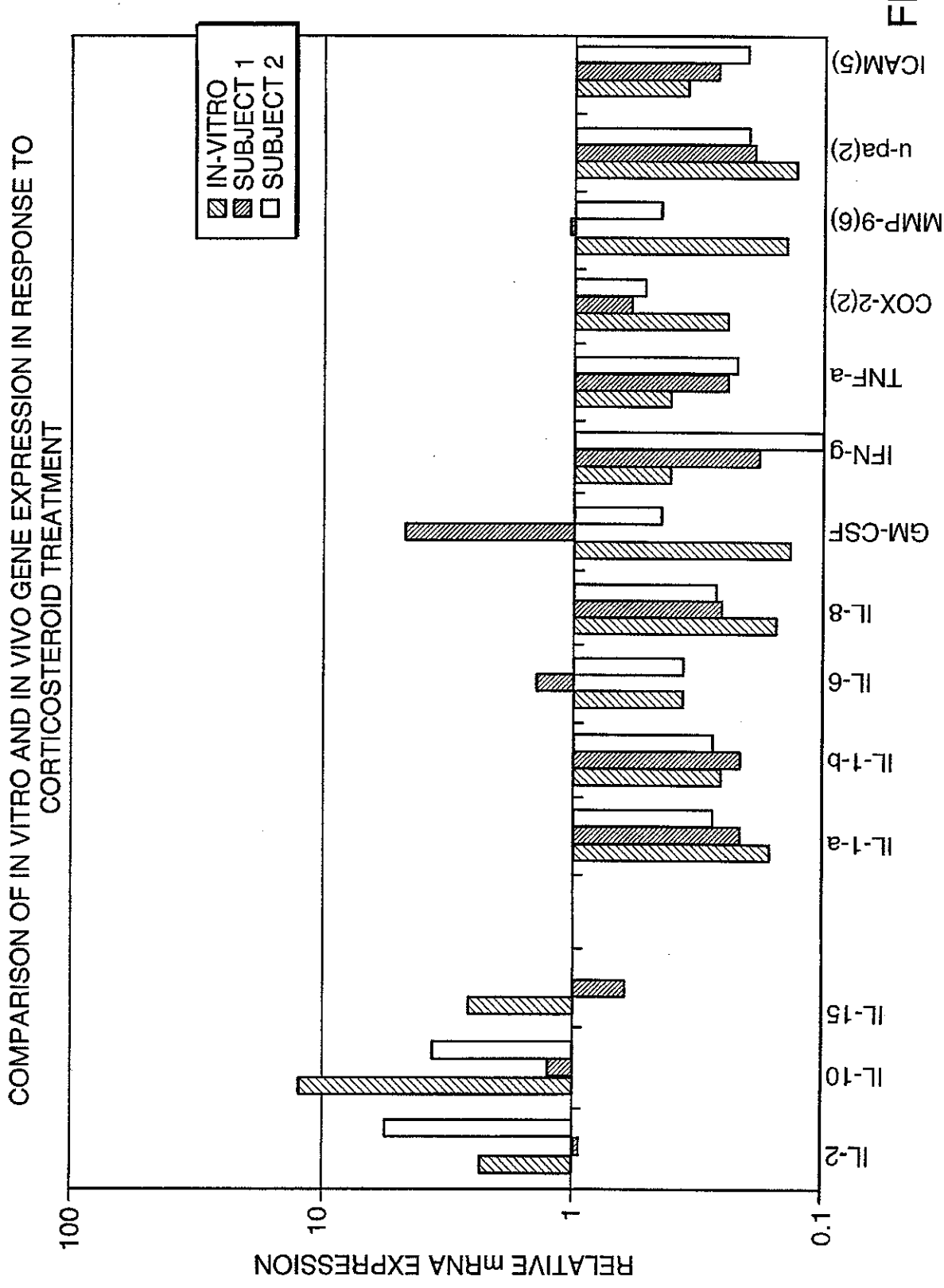

COMPARISON OF IN VITRO AND IN VIVO GENE EXPRESSION IN RESPONSE TO CORTICOSTEROID TREATMENT
IN-VITRO
SUBJECT 1
SUBJECT 2
RELATIVE mRNA EXPRESSION
100
10
1
0.1
IL-2
IL-10
IL-15
IL-1-a
IL-1-b
IL-6
IL-8
GM-CSF
IFN-g
TNF-a
COX-2(2)
MMP-9(6)
u-pa(2)
ICAM(5)

FIG. 15

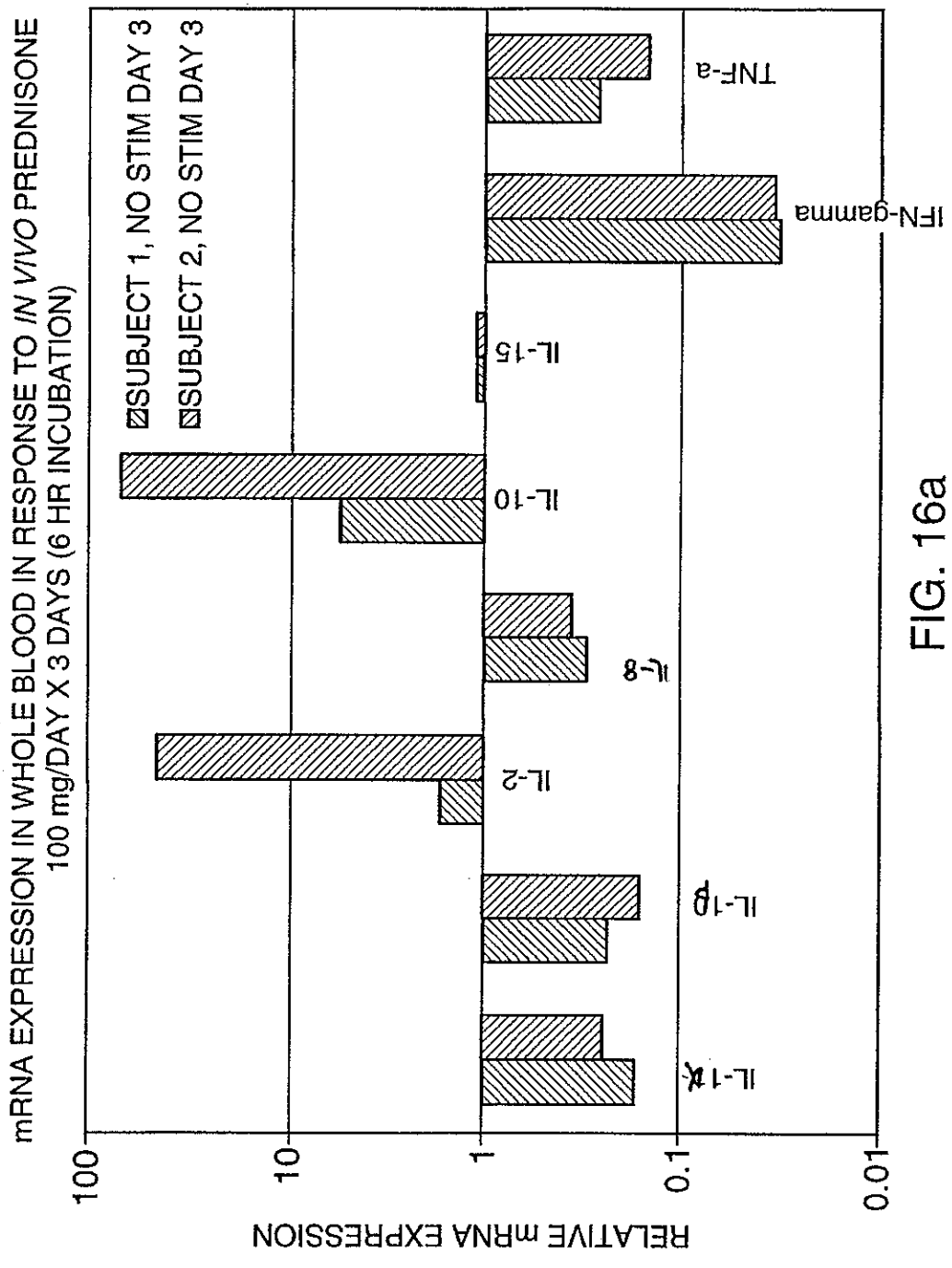

mRNA EXPRESSION IN WHOLE BLOOD IN RESPONSE TO IN VIVO PREDNISONE
100 mg/DAY X 3 DAYS (6 HR INCUBATION)
SUBJECT 1, NO STIM DAY 3
SUBJECT 2, NO STIM DAY 3
RELATIVE mRNA EXPRESSION
100
10
1
0.1
0.01
IL-1α
IL-1β
IL-2
IL-8
IL-10
IL-15
IFN-gamma
TNF-a

FIG. 16a

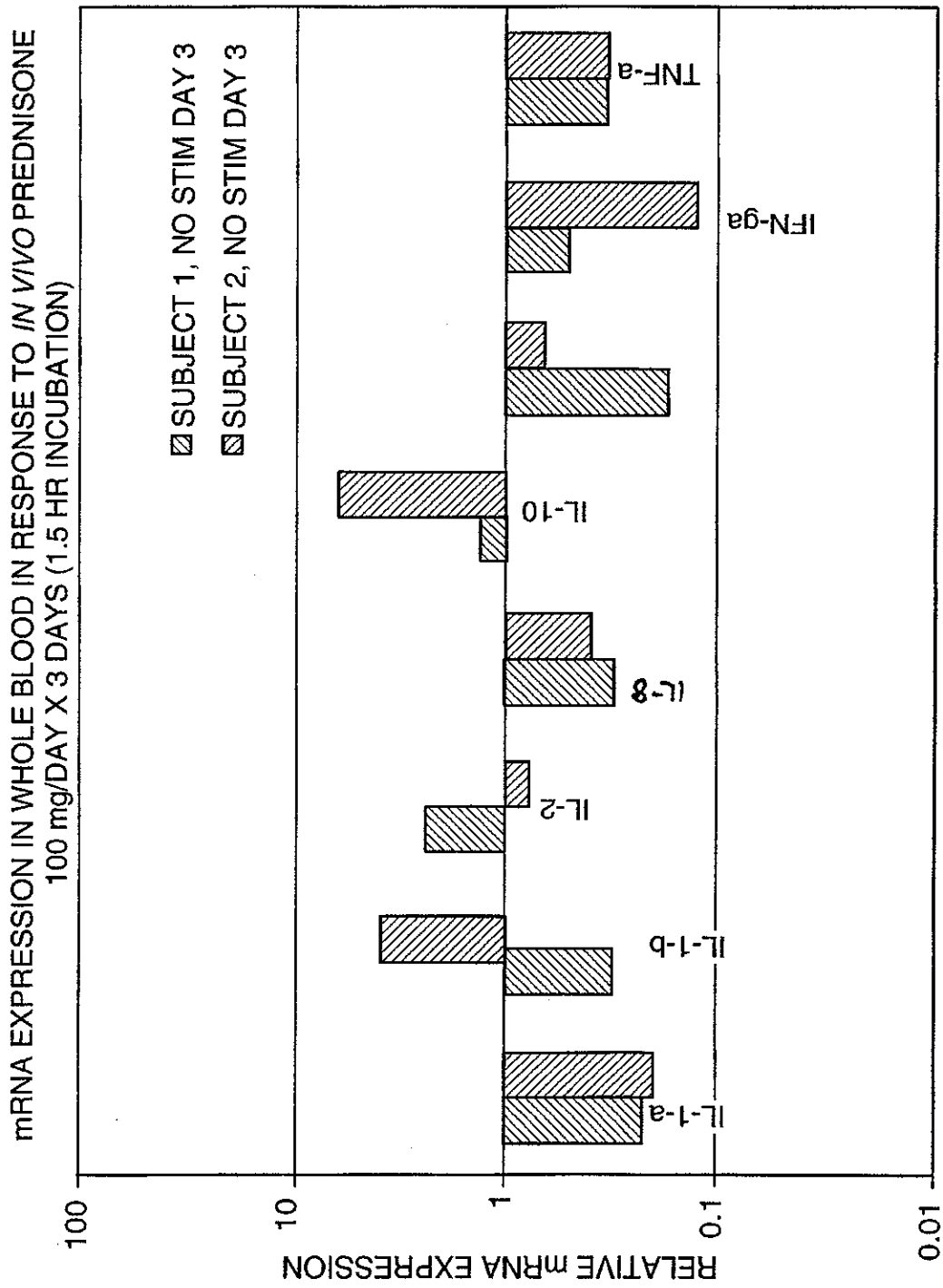

mRNA EXPRESSION IN WHOLE BLOOD IN RESPONSE TO IN VIVO PREDNISONE
100 mg/DAY X 3 DAYS (1.5 HR INCUBATION)
SUBJECT 1, NO STIM DAY 3
SUBJECT 2, NO STIM DAY 3
RELATIVE mRNA EXPRESSION
100
10
1
0.1
0.01
TNF-a
IFN-ga
IL-10
IL-8
IL-2
IL-1-b
IL-1-a

FIG. 16b

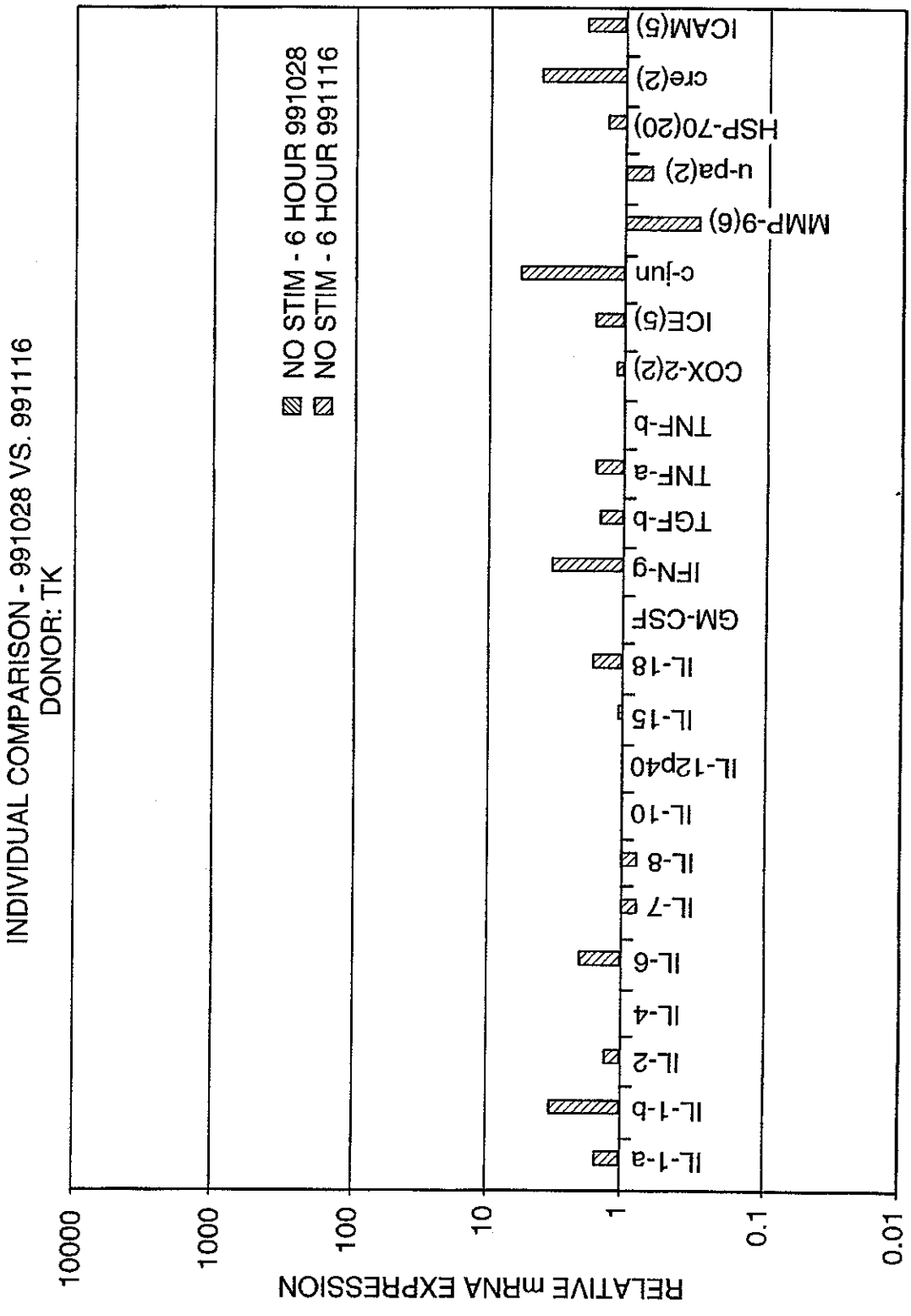

INDIVIDUAL COMPARISON - 991028 VS. 991116
DONOR: TK
NO STIM - 6 HOUR 991028
NO STIM - 6 HOUR 991116
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TNF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MMP-9(6)
u-pa(2)
HSP-70(20)
cre(2)
ICAM(5)

FIG. 17

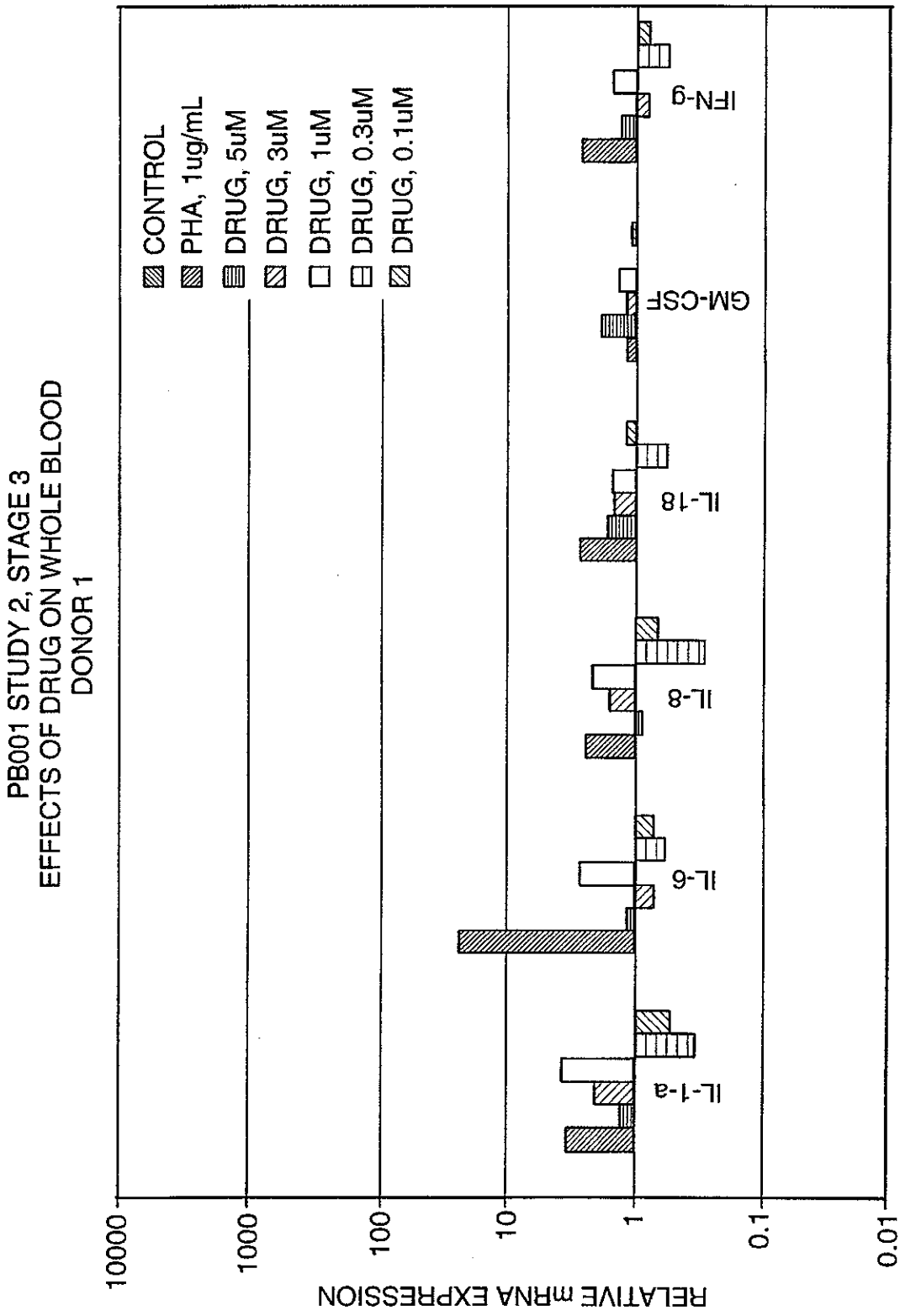

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 1
CONTROL
PHA, 1ug/mL
DRUG, 5uM
DRUG, 3uM
DRUG, 1uM
DRUG, 0.3uM
DRUG, 0.1uM
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-6
IL-8
IL-18
GM-CSF
IFN-g

FIG. 18a

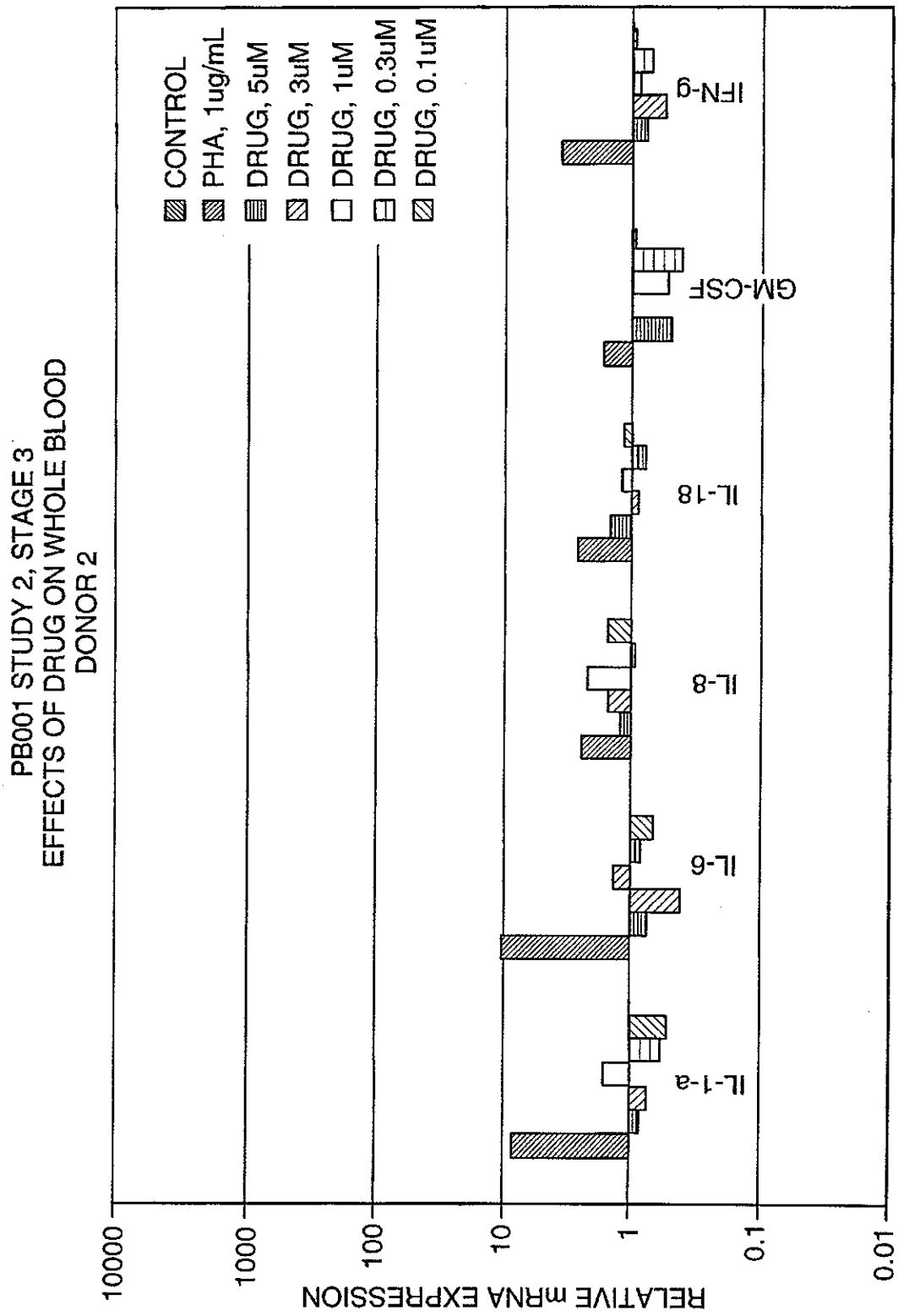

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 2
CONTROL
PHA, 1ug/mL
DRUG, 5uM
DRUG, 3uM
DRUG, 1uM
DRUG, 0.3uM
DRUG, 0.1uM
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-6
IL-8
IL-18
GM-CSF
IFN-g

FIG. 18b

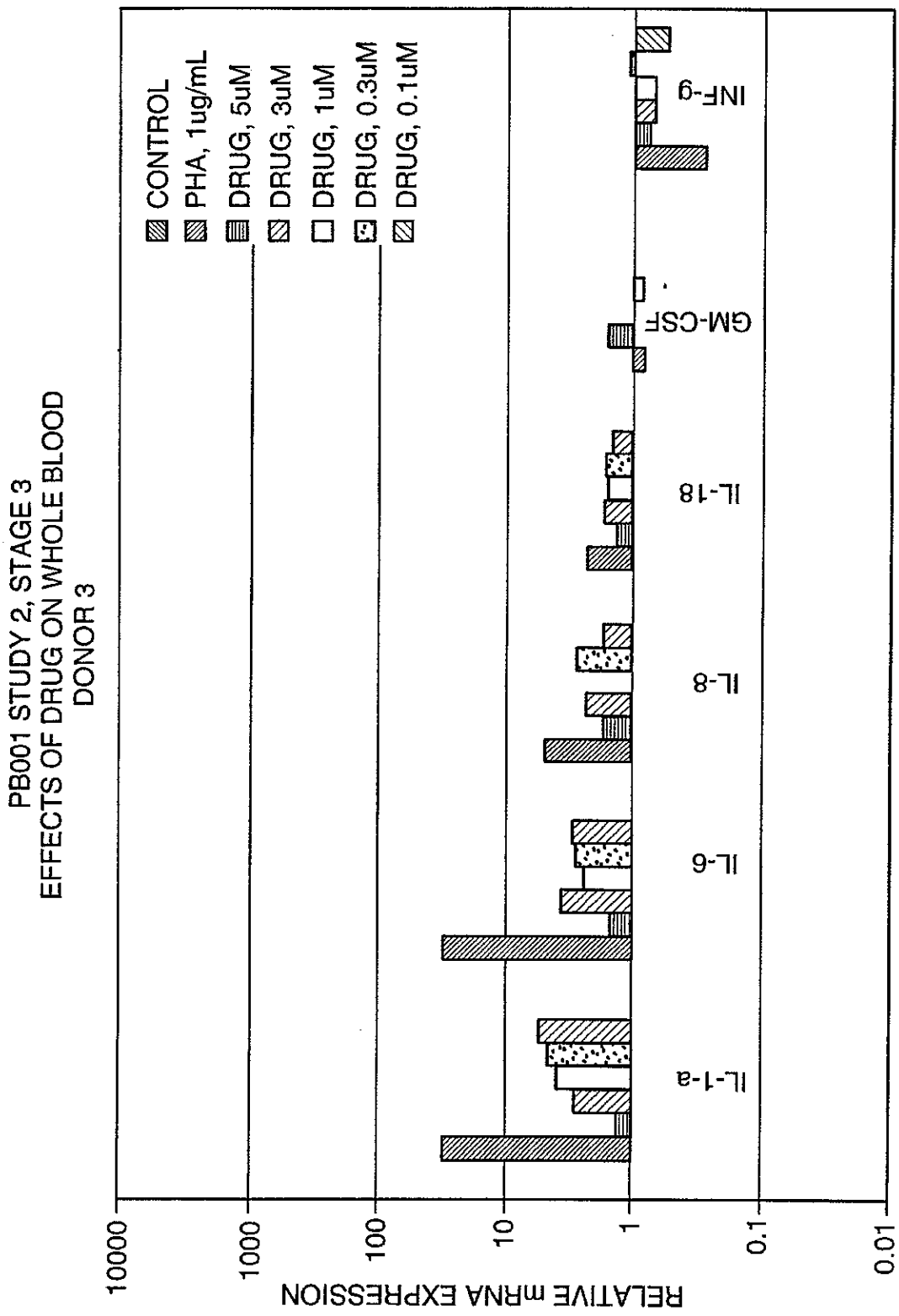

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 3
CONTROL
PHA, 1ug/mL
DRUG, 5uM
DRUG, 3uM
DRUG, 1uM
DRUG, 0.3uM
DRUG, 0.1uM
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-6
IL-8
IL-18
GM-CSF
INF-g

FIG. 18c

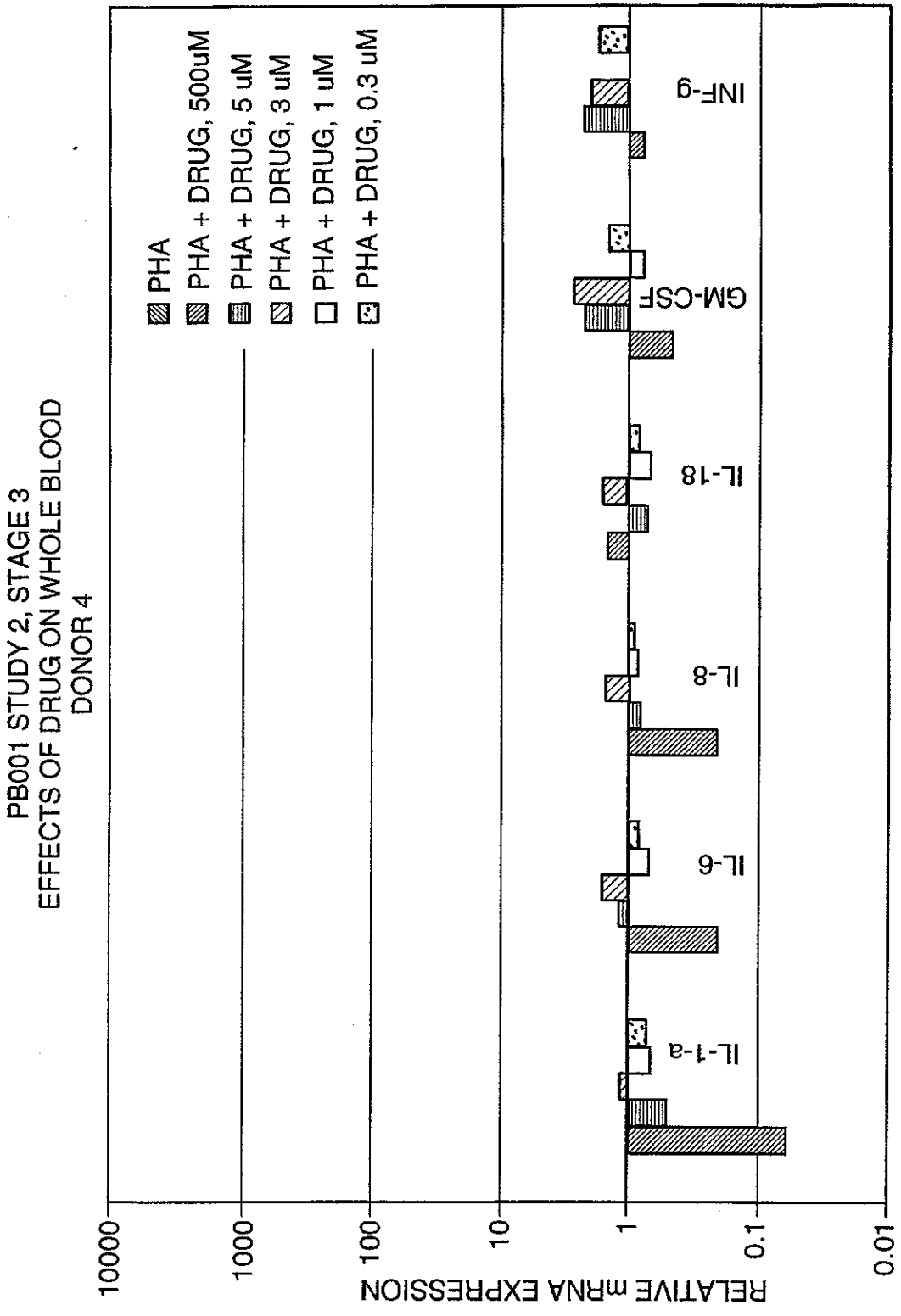

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 4
PHA
PHA + DRUG, 500uM
PHA + DRUG, 5 uM
PHA + DRUG, 3 uM
PHA + DRUG, 1 uM
PHA + DRUG, 0.3 uM
INF-g
GM-CSF
IL-18
IL-8
IL-6
IL-1-a
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01

FIG. 18d

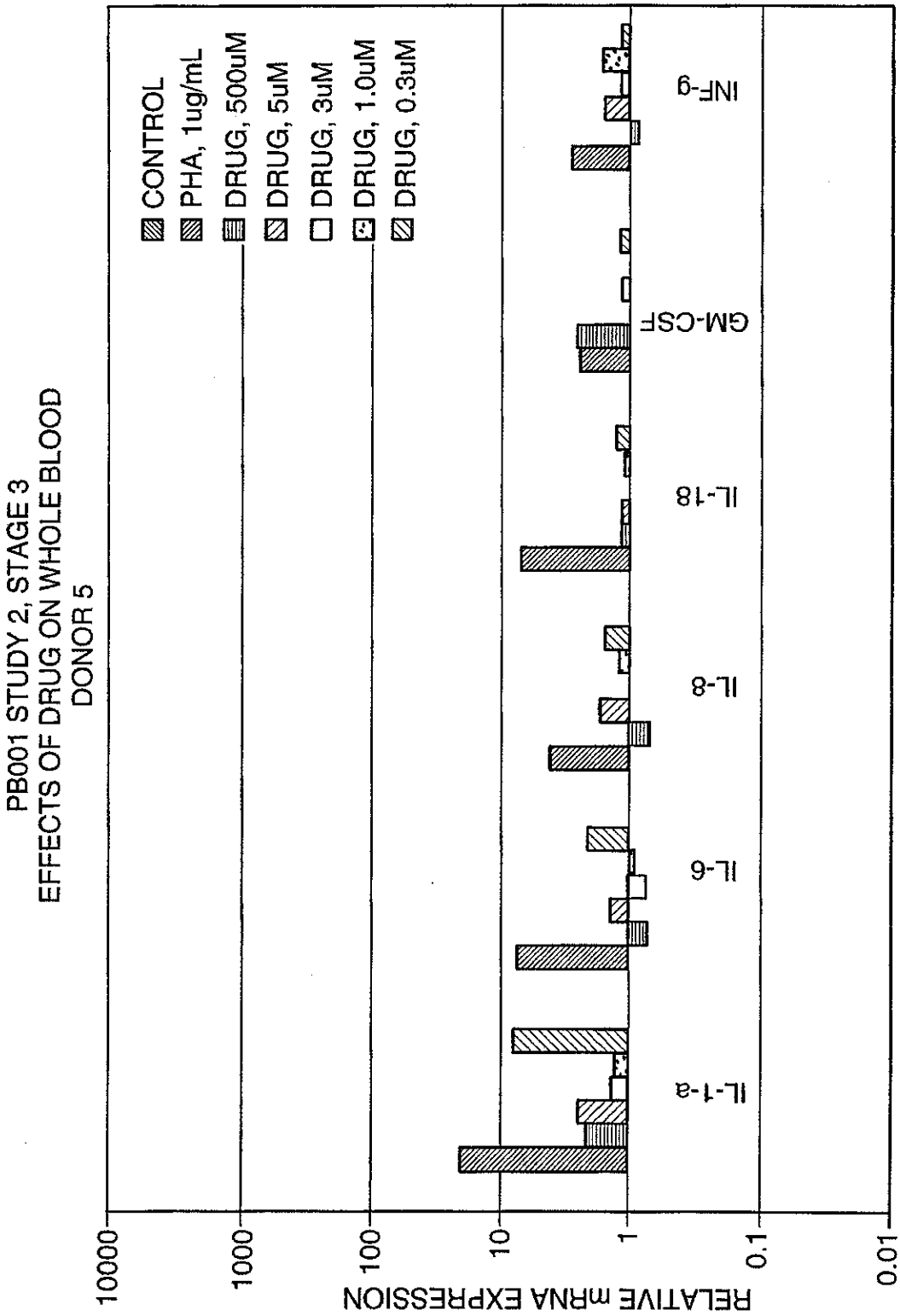

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 5
CONTROL
PHA, 1ug/mL
DRUG, 500uM
DRUG, 5uM
DRUG, 3uM
DRUG, 1.0uM
DRUG, 0.3uM
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
IL-1-a
IL-6
IL-8
IL-18
GM-CSF
INF-g

FIG. 18e

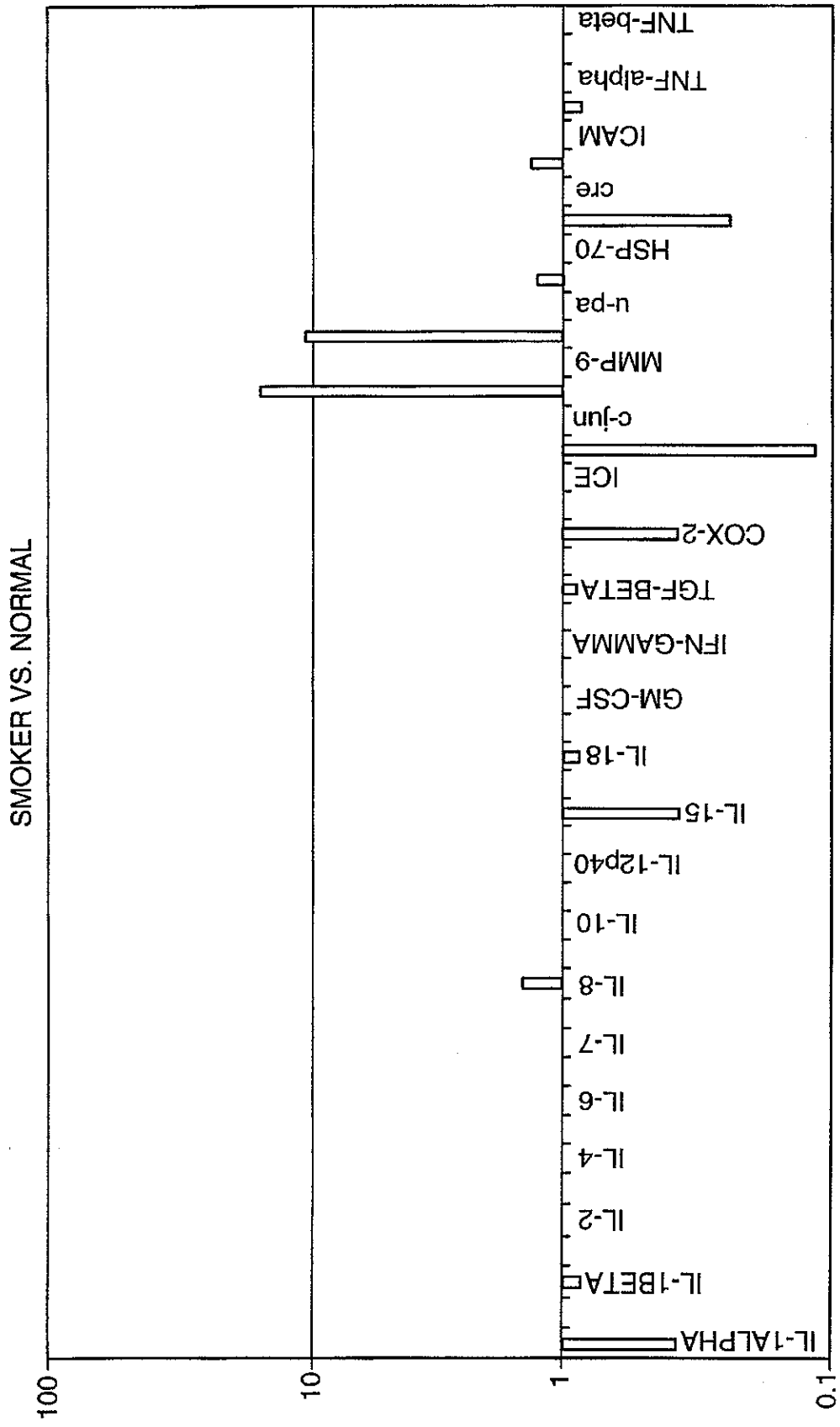

SMOKER VS. NORMAL
100
10
1
0.1
IL-1ALPHA
IL-1BETA
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-GAMMA
TGF-BETA
COX-2
ICE
c-jun
MMP-9
u-pa
HSP-70
cre
ICAM
TNF-alpha
TNF-beta

FIG. 19a

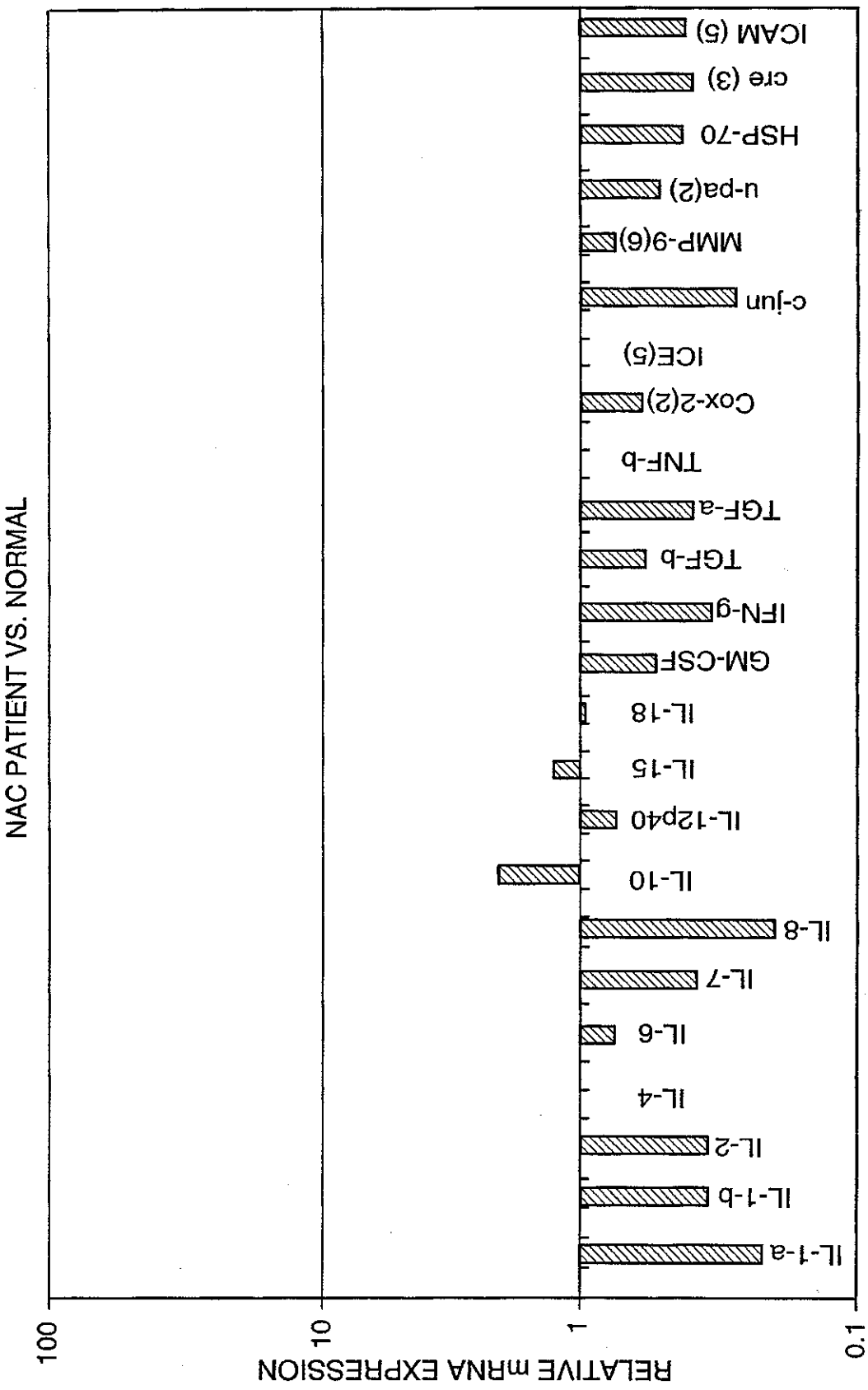

NAC PATIENT VS. NORMAL
RELATIVE mRNA EXPRESSION
100
10
1
0.1
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TGF-a
TNF-b
Cox-2(2)
ICE(5)
c-jun
MMP-9(6)
u-pa(2)
HSP-70
cre (3)
ICAM (5)

FIG. 19b

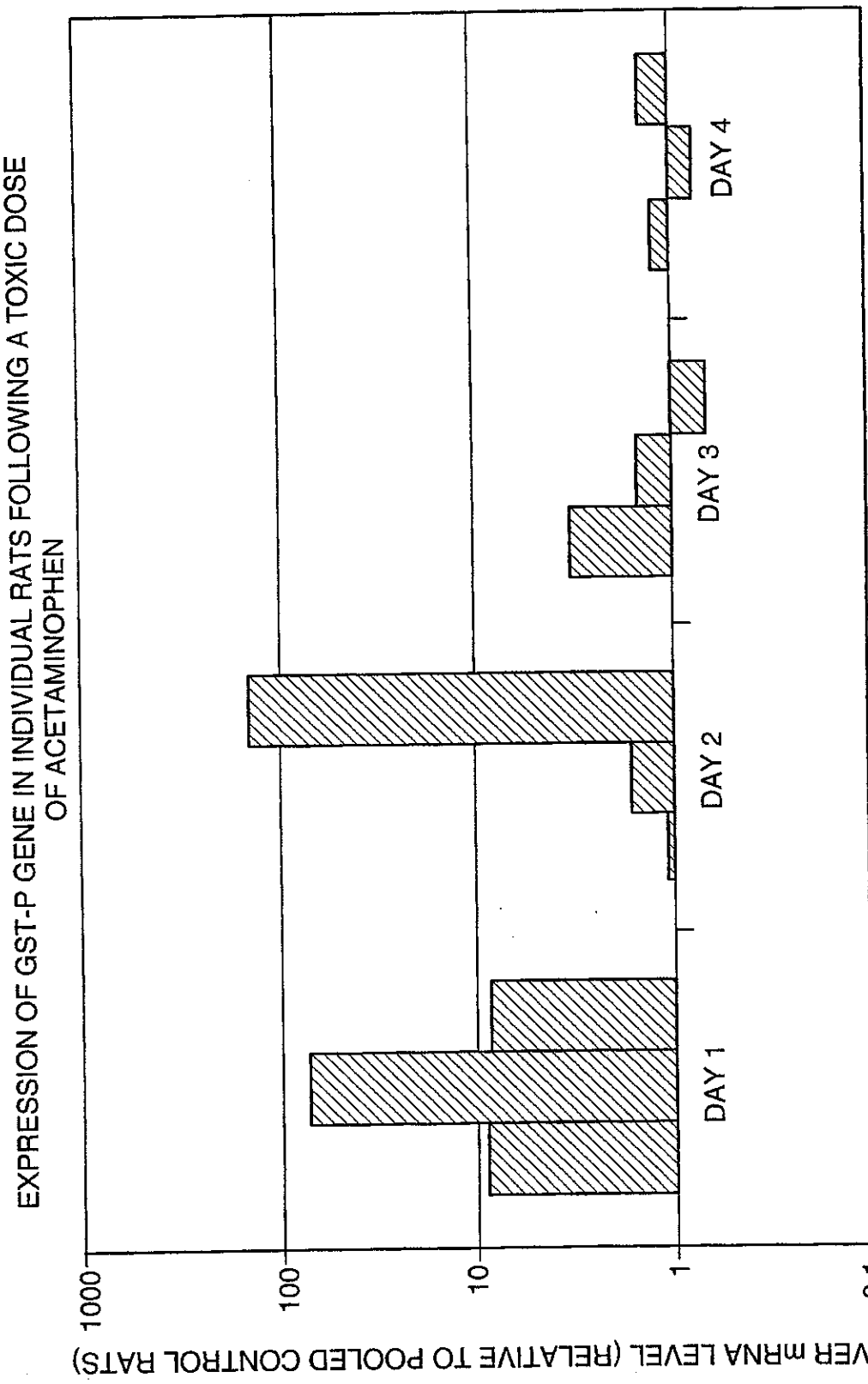

EXPRESSION OF GST-P GENE IN INDIVIDUAL RATS FOLLOWING A TOXIC DOSE OF ACETAMINOPHEN
LIVER mRNA LEVEL (RELATIVE TO POOLED CONTROL RATS)
1000
100
10
1
0.1
DAY 1
DAY 2
DAY 3
DAY 4

FIG. 20

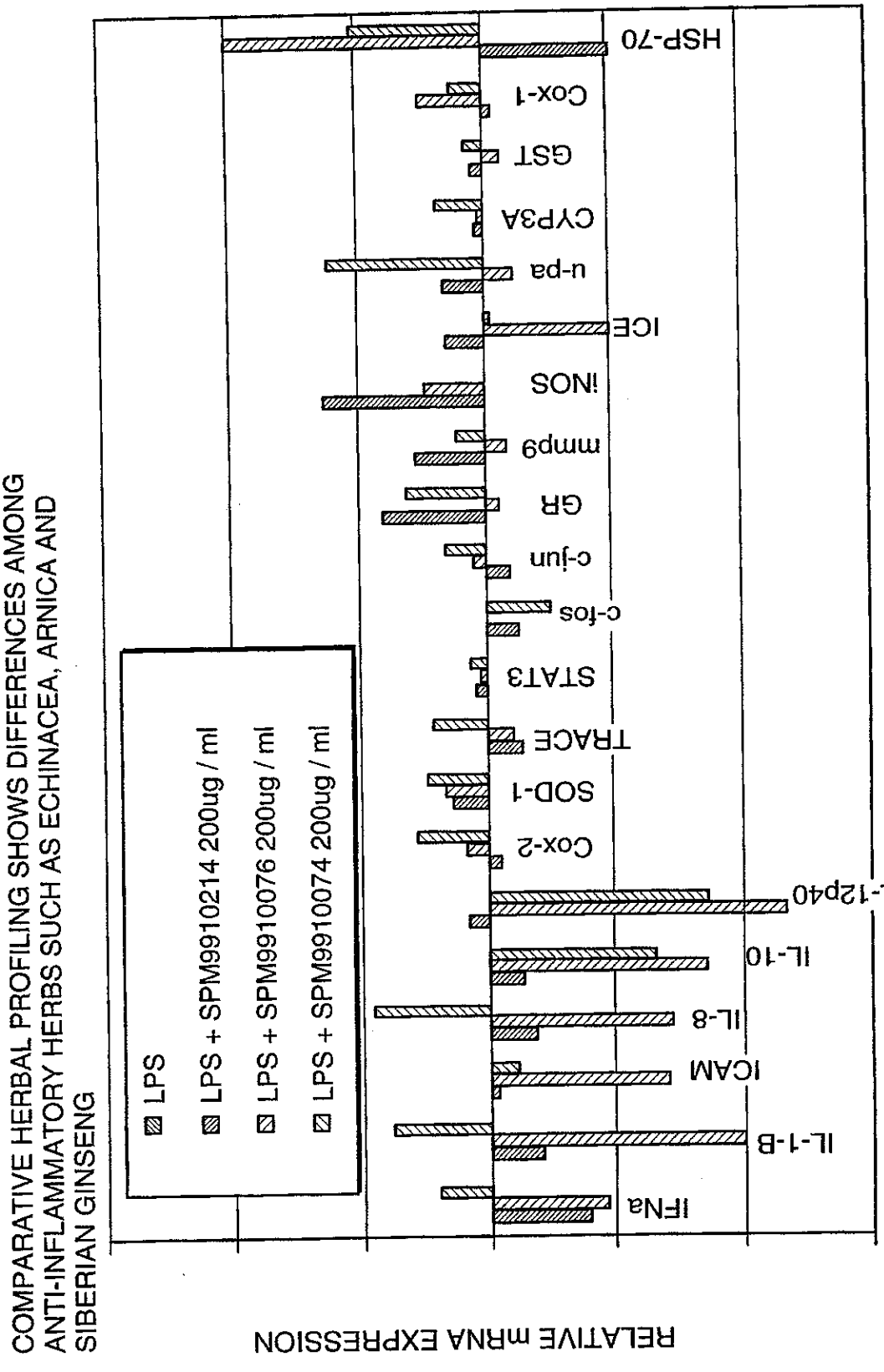

COMPARATIVE HERBAL PROFILING SHOWS DIFFERENCES AMONG ANTI-INFLAMMATORY HERBS SUCH AS ECHINACEA, ARNICA AND SIBERIAN GINSENG
RELATIVE mRNA EXPRESSION
LPS
LPS + SPM9910214 200ug / ml
LPS + SPM9910076 200ug / ml
LPS + SPM9910074 200ug / ml
IFNa
IL-1-B
ICAM
IL-8
IL-10
IL-12p40
Cox-2
SOD-1
TRACE
STAT3
c-fos
c-jun
GR
mmp9
iNOS
ICE
u-pa
CYP3A
GST
Cox-1
HSP-70

FIG. 21

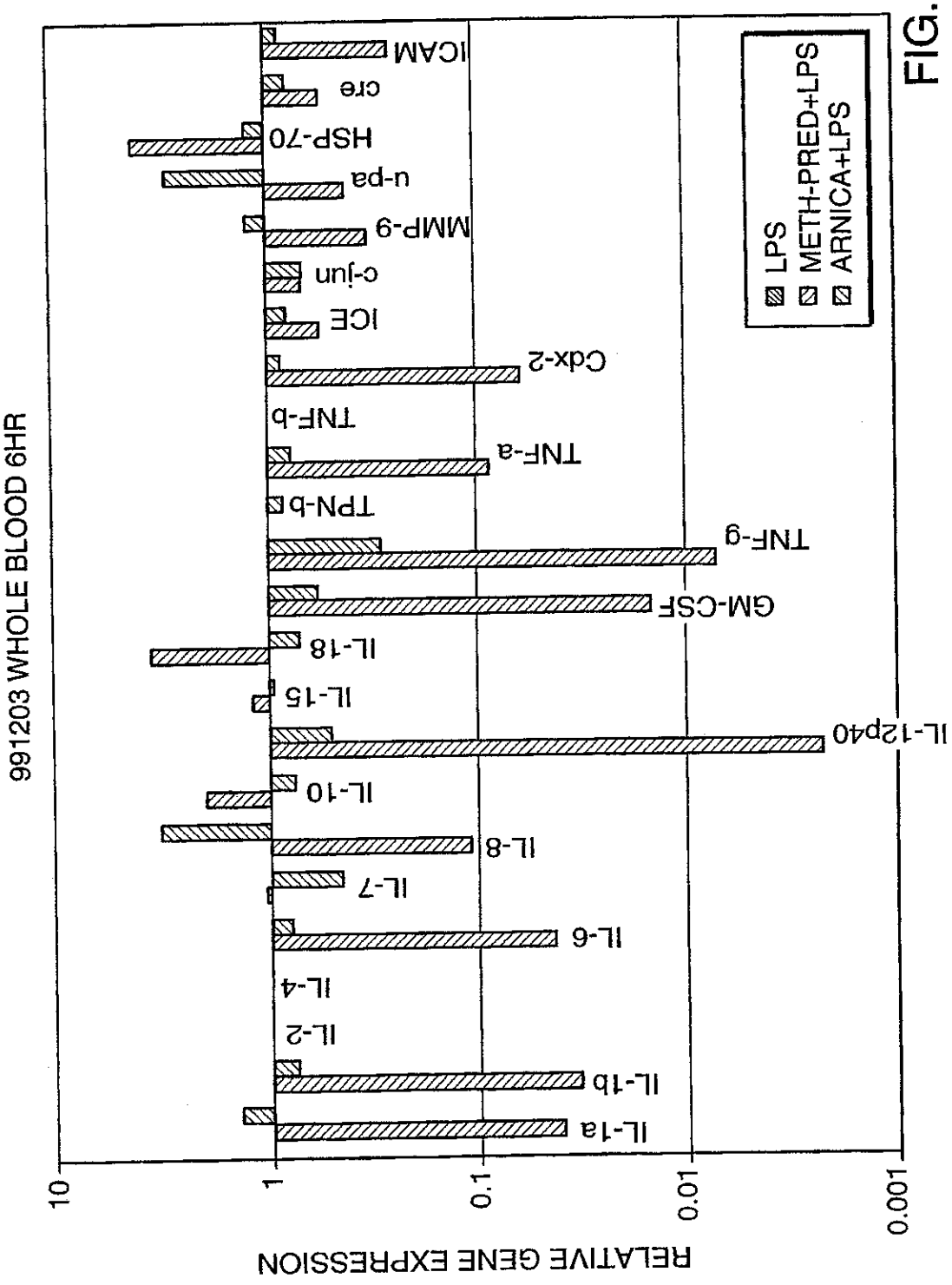

991203 WHOLE BLOOD 6HR
RELATIVE GENE EXPRESSION
10
1
0.1
0.01
0.001
LPS
METH-PRED+LPS
ARNICA+LPS
IL-1a
IL-1b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
TNF-g
TPN-b
TNF-a
TNF-b
Cdx-2
ICE
c-jun
MMP-9
u-pa
HSP-70
cre
ICAM

FIG. 22

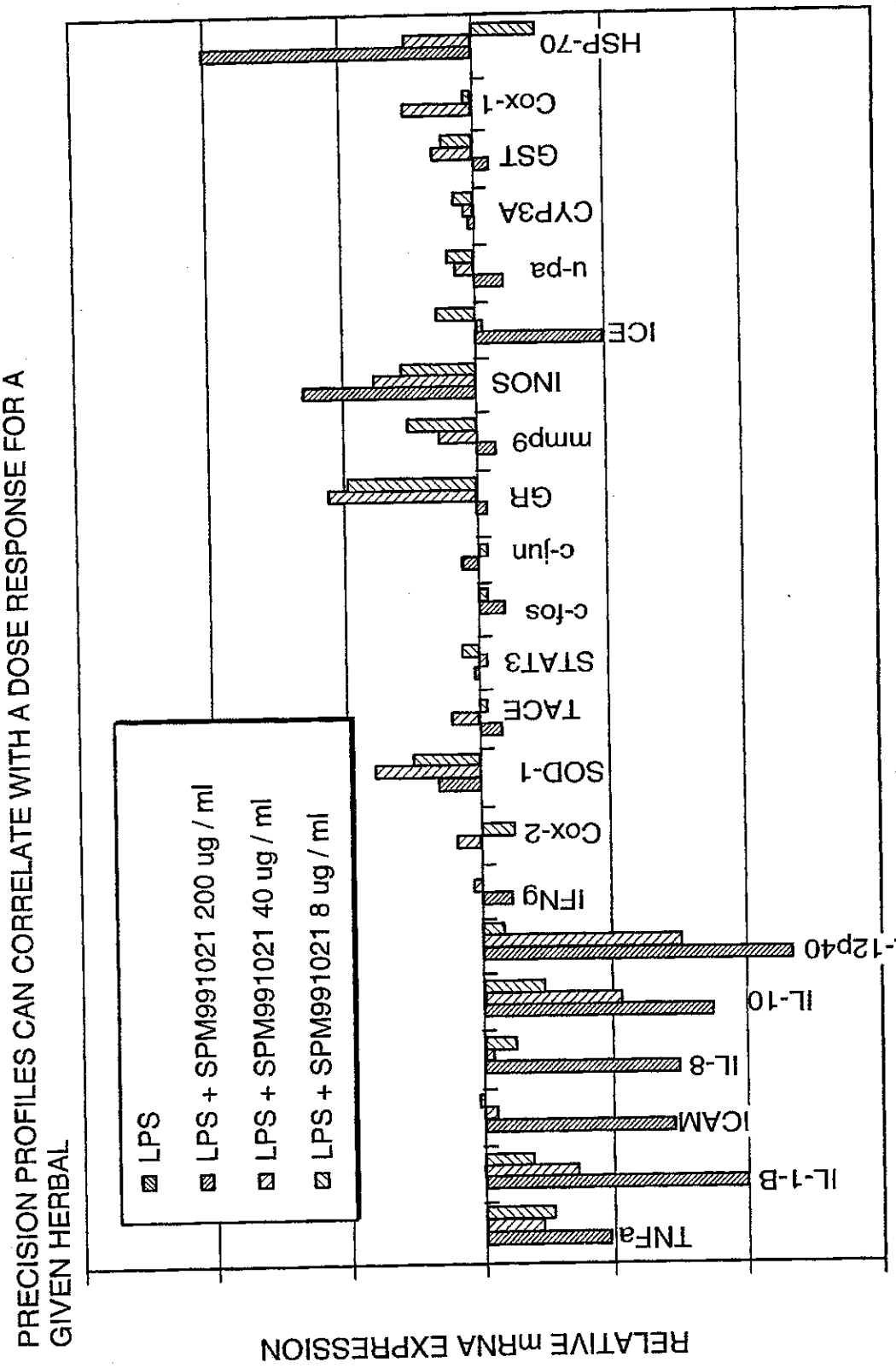

PRECISION PROFILES CAN CORRELATE WITH A DOSE RESPONSE FOR A GIVEN HERBAL
RELATIVE mRNA EXPRESSION
LPS
LPS + SPM991021 200 ug / ml
LPS + SPM991021 40 ug / ml
LPS + SPM991021 8 ug / ml
TNFa
IL-1-B
ICAM
IL-8
IL-10
IL-12p40
IFNg
Cox-2
SOD-1
TACE
STAT3
c-fos
c-jun
GR
mmp9
iNOS
ICE
u-pa
CYP3A
GST
Cox-1
HSP-70

FIG. 23

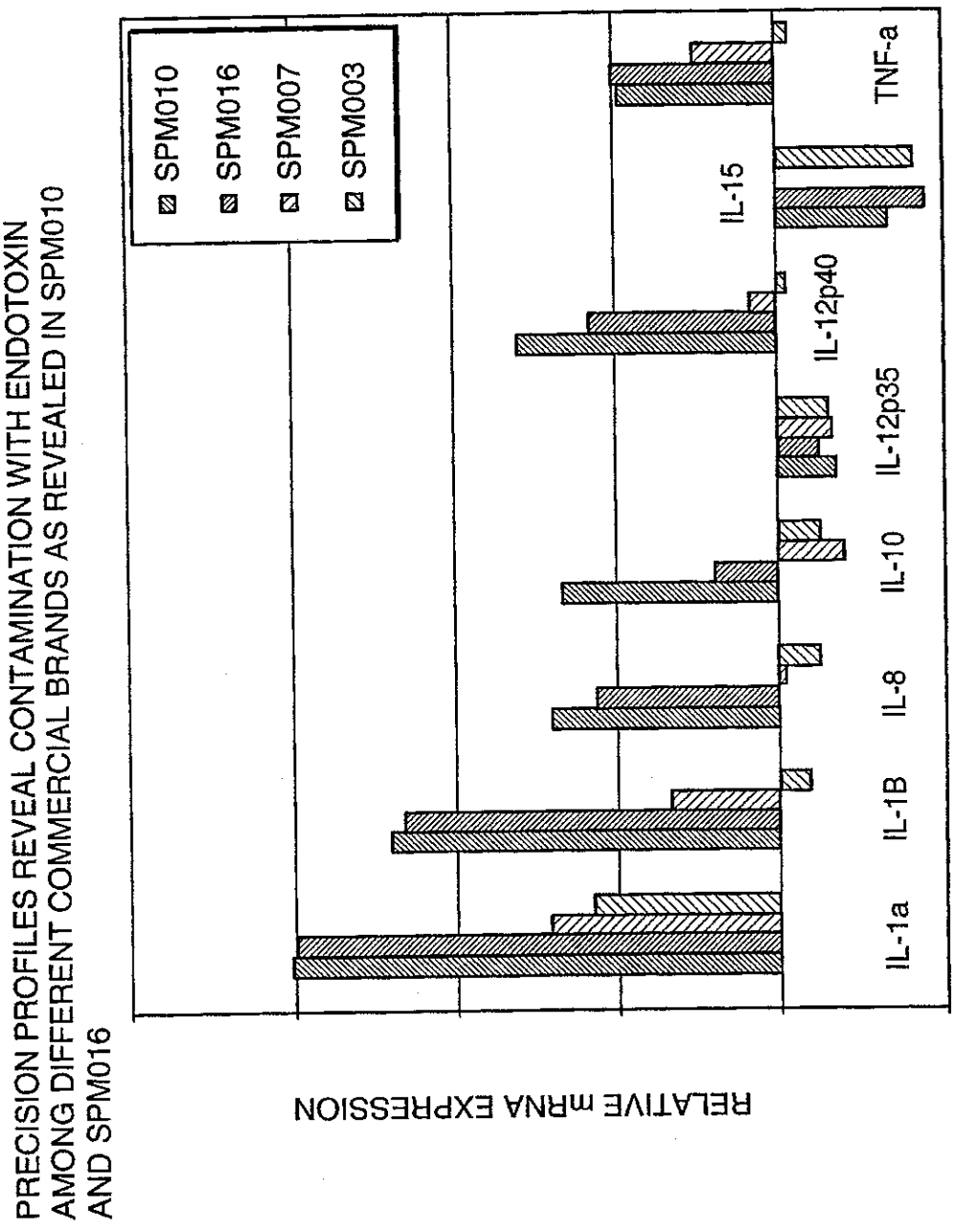

PRECISION PROFILES REVEAL CONTAMINATION WITH ENDOTOXIN
AMONG DIFFERENT COMMERCIAL BRANDS AS REVEALED IN SPM010
AND SPM016
SPM010
SPM016
SPM007
SPM003
RELATIVE mRNA EXPRESSION
IL-1a
IL-1B
IL-8
IL-10
IL-12p35
IL-12p40
IL-15
TNF-a

FIG. 24

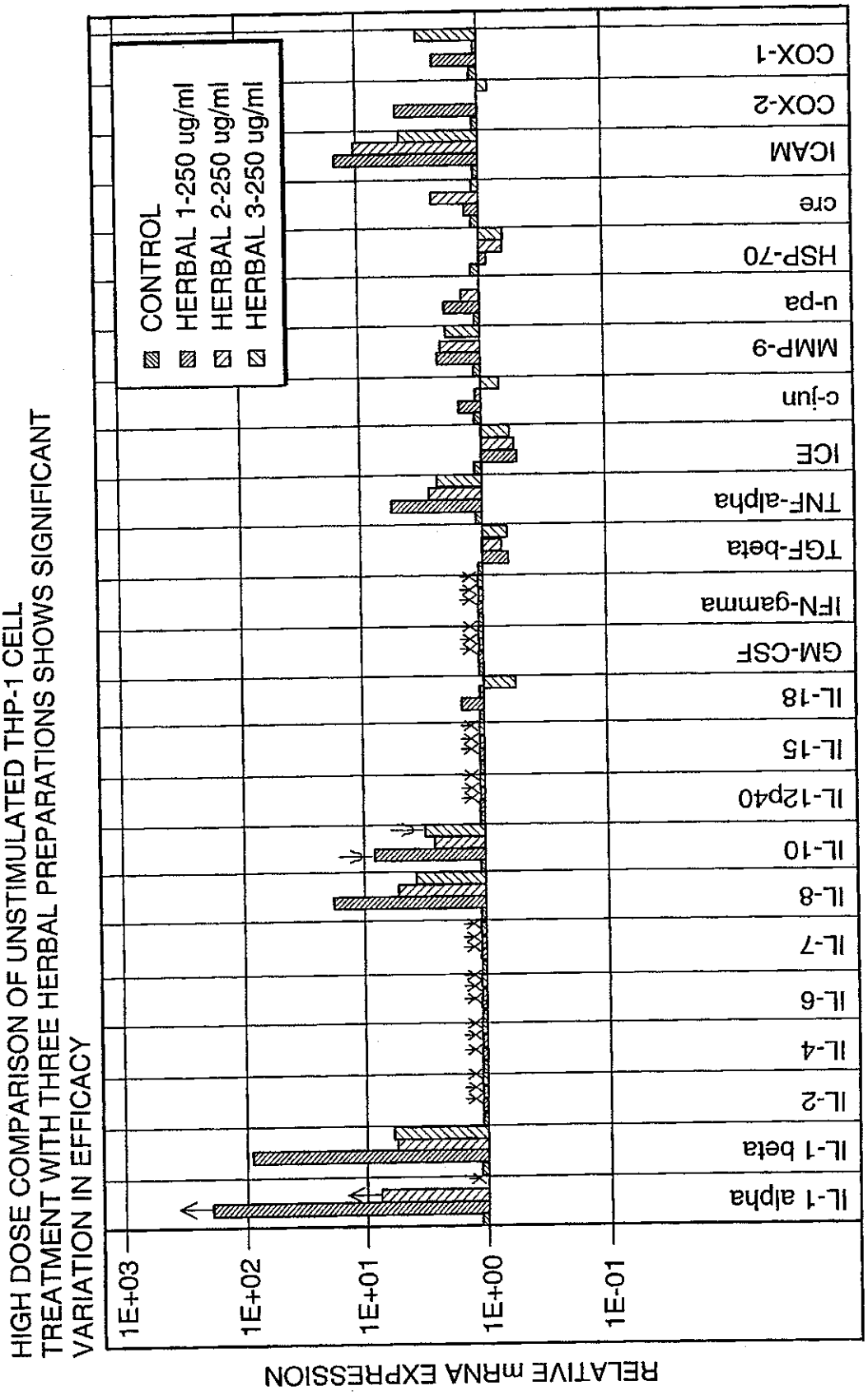

HIGH DOSE COMPARISON OF UNSTIMULATED THP-1 CELL
TREATMENT WITH THREE HERBAL PREPARATIONS SHOWS SIGNIFICANT
VARIATION IN EFFICACY
CONTROL
HERBAL 1-250 ug/ml
HERBAL 2-250 ug/ml
HERBAL 3-250 ug/ml
RELATIVE mRNA EXPRESSION
1E+03
1E+02
1E+01
1E+00
1E-01
IL-1 alpha
IL-1 beta
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-gamma
TGF-beta
TNF-alpha
ICE
c-jun
MMP-9
u-pa
HSP-70
cre
ICAM
COX-2
COX-1

FIG. 25a

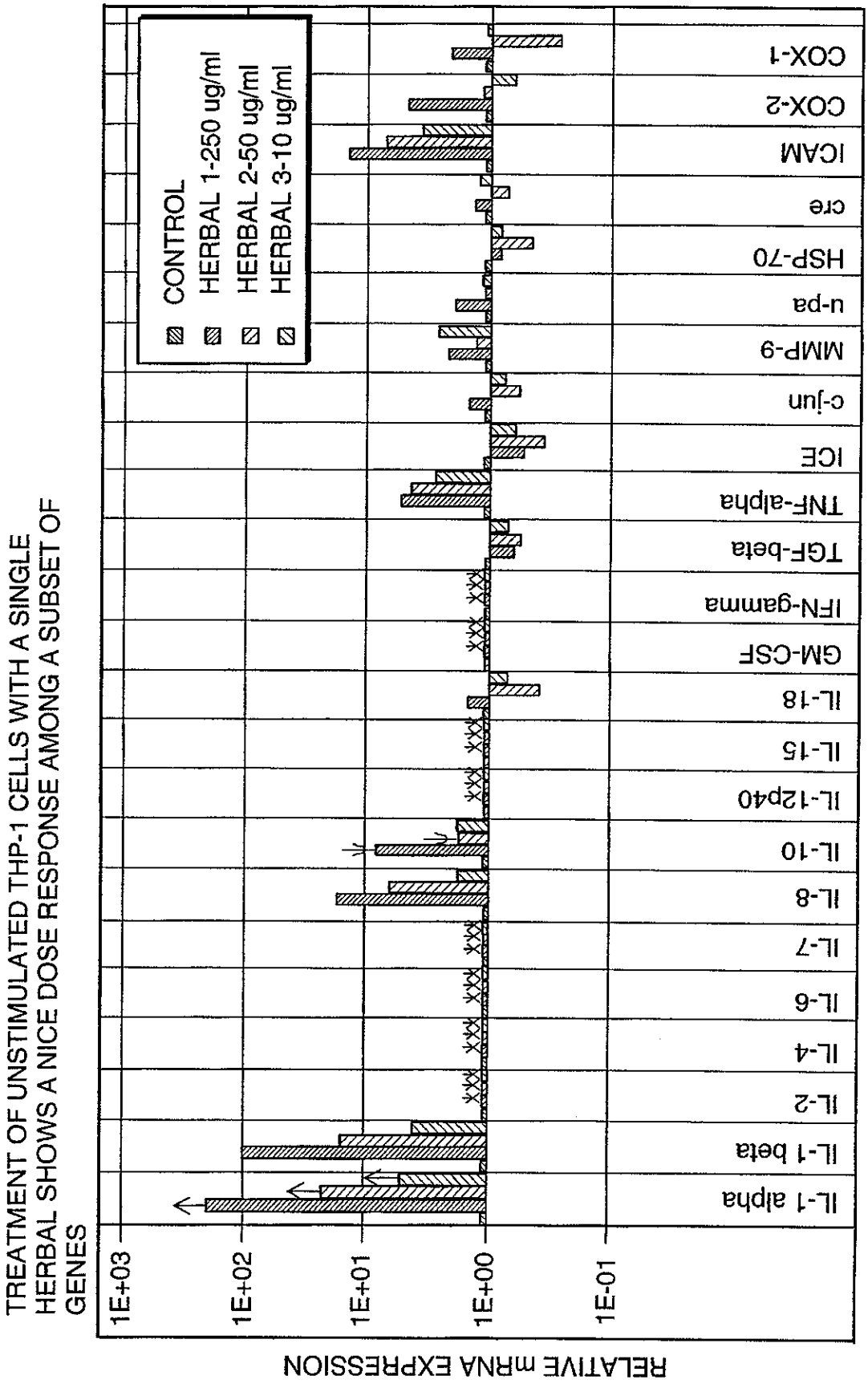

TREATMENT OF UNSTIMULATED THP-1 CELLS WITH A SINGLE HERBAL SHOWS A NICE DOSE RESPONSE AMONG A SUBSET OF GENES
CONTROL
HERBAL 1-250 ug/ml
HERBAL 2-50 ug/ml
HERBAL 3-10 ug/ml
RELATIVE mRNA EXPRESSION
1E+03
1E+02
1E+01
1E+00
1E-01
IL-1 alpha
IL-1 beta
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-gamma
TGF-beta
TNF-alpha
ICE
c-jun
MMP-9
u-pa
HSP-70
cre
ICAM
COX-2
COX-1

FIG. 25b

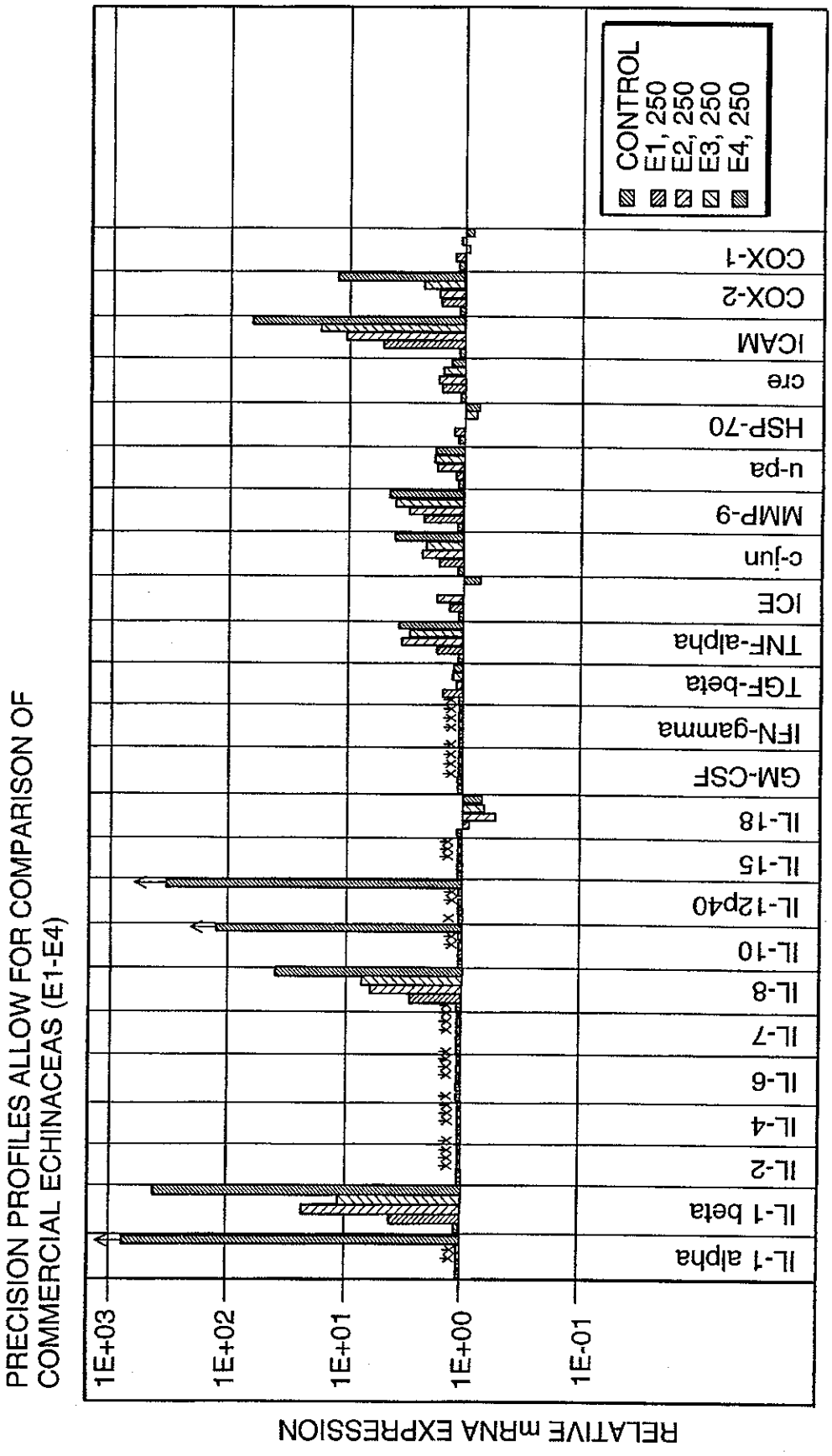

PRECISION PROFILES ALLOW FOR COMPARISON OF COMMERCIAL ECHINACEAS (E1-E4)
RELATIVE mRNA EXPRESSION
1E+03
1E+02
1E+01
1E+00
1E-01
CONTROL
E1, 250
E2, 250
E3, 250
E4, 250
IL-1 alpha
IL-1 beta
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-gamma
TGF-beta
TNF-alpha
ICE
c-jun
MMP-9
u-pa
HSP-70
cre
ICAM
COX-2
COX-1

FIG. 25c