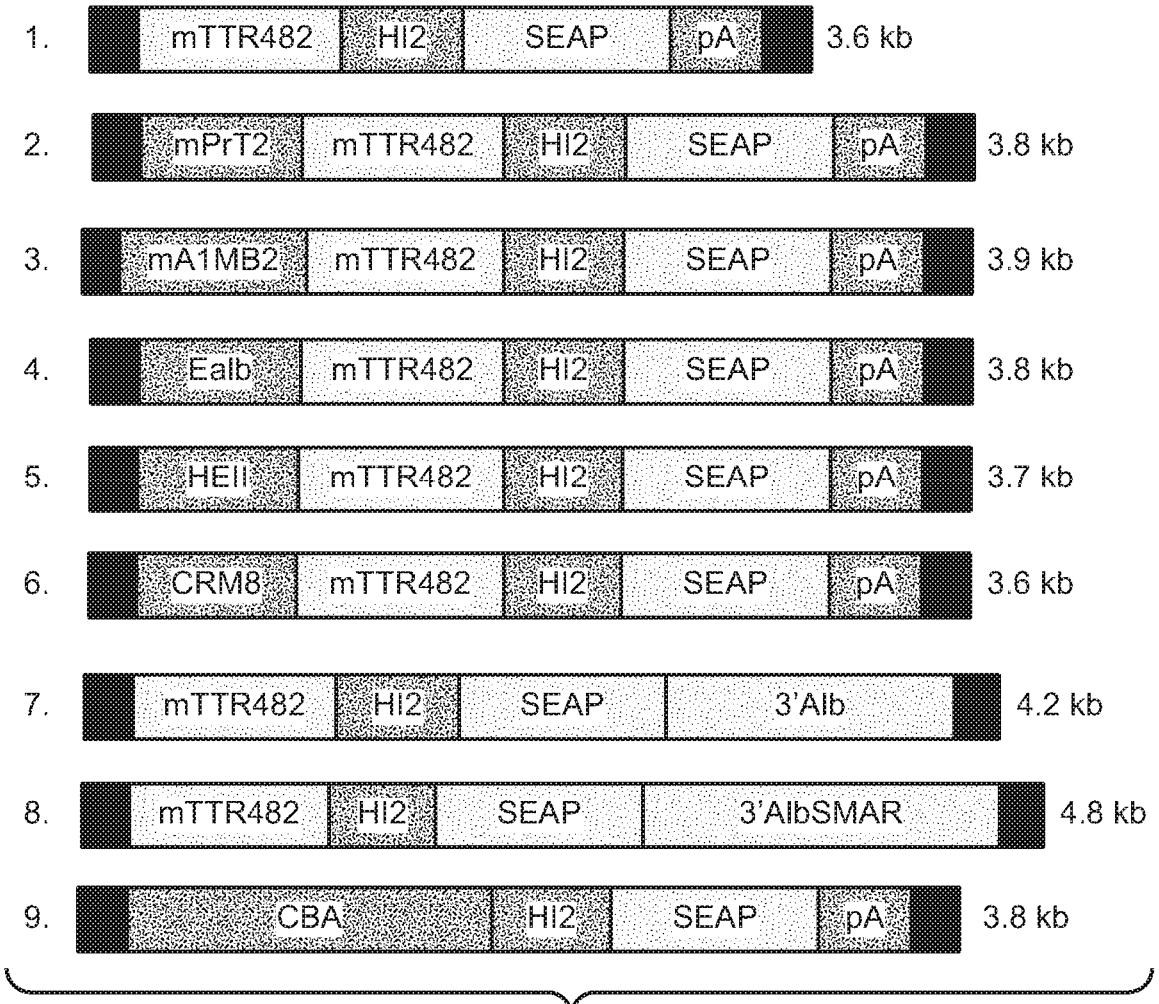

1.
mTTR482
HI2
SEAP
pA
3.6 kb
2.
mPrT2
mTTR482
HI2
SEAP
pA
3.8 kb
3.
mA1MB2
mTTR482
HI2
SEAP
pA
3.9 kb
4.
Ealb
mTTR482
HI2
SEAP
pA
3.8 kb
5.
HEII
mTTR482
HI2
SEAP
pA
3.7 kb
6.
CRM8
mTTR482
HI2
SEAP
pA
3.6 kb
7.
mTTR482
HI2
SEAP
3'Alb
4.2 kb
8.
mTTR482
HI2
SEAP
3'AlbSMAR
4.8 kb
9.
CBA
HI2
SEAP
pA
3.8 kb

FIG. 1A

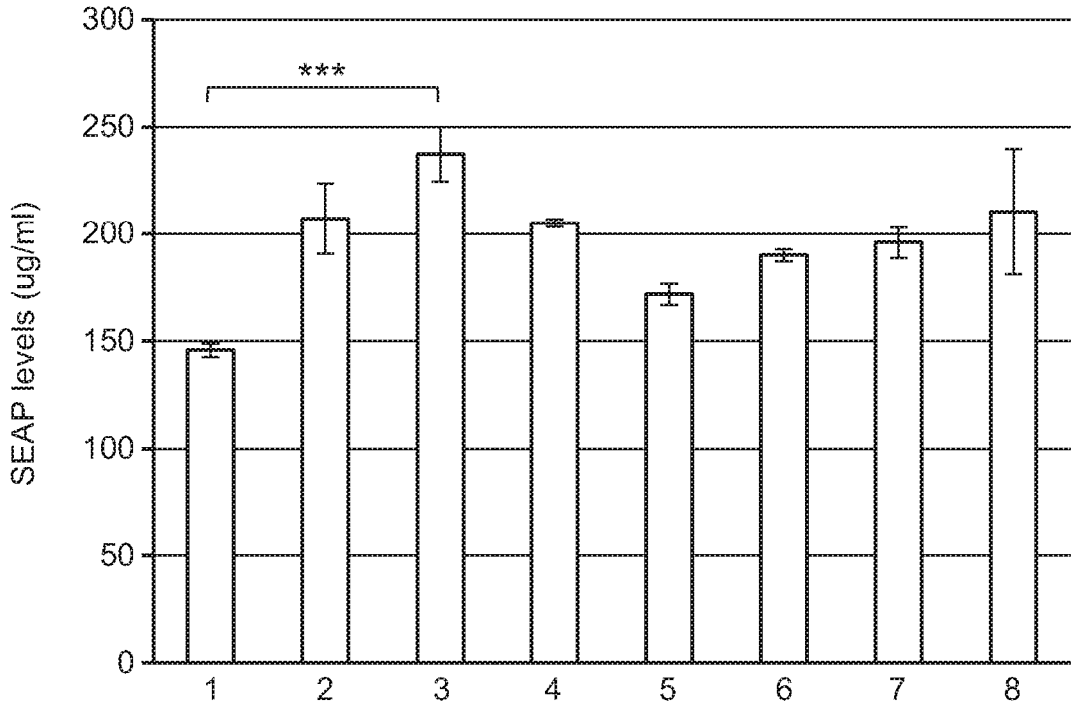

300
250
200
150
100
50
0
SEAP levels (ug/ml)
***
1
2
3
4
5
6
7
8

FIG. 1B

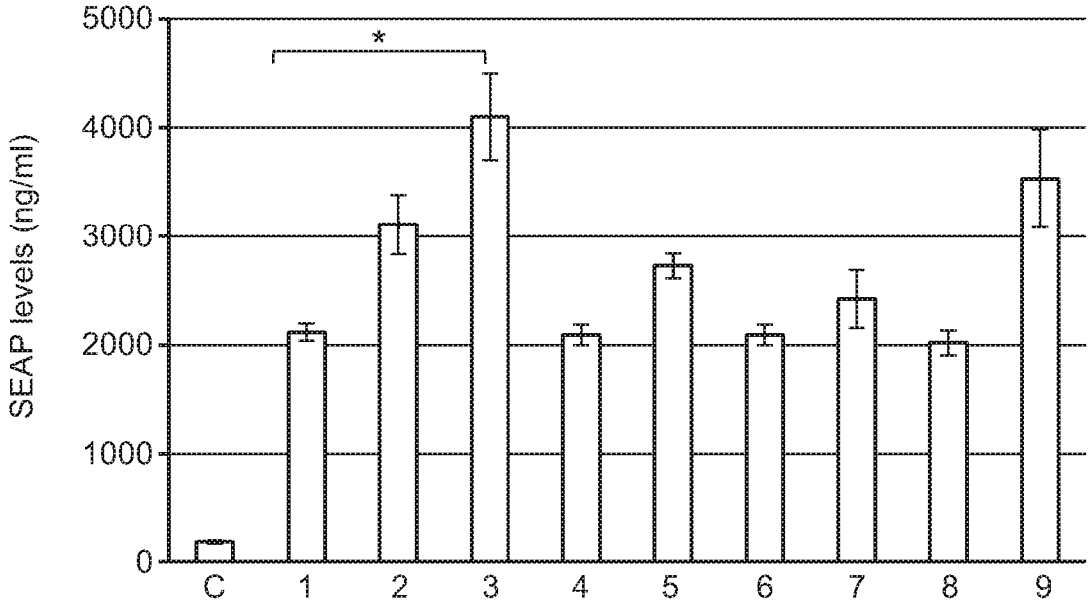

5000
4000
3000
2000
1000
0
SEAP levels (ng/ml)
*
C
1
2
3
4
5
6
7
8
9

FIG. 1C

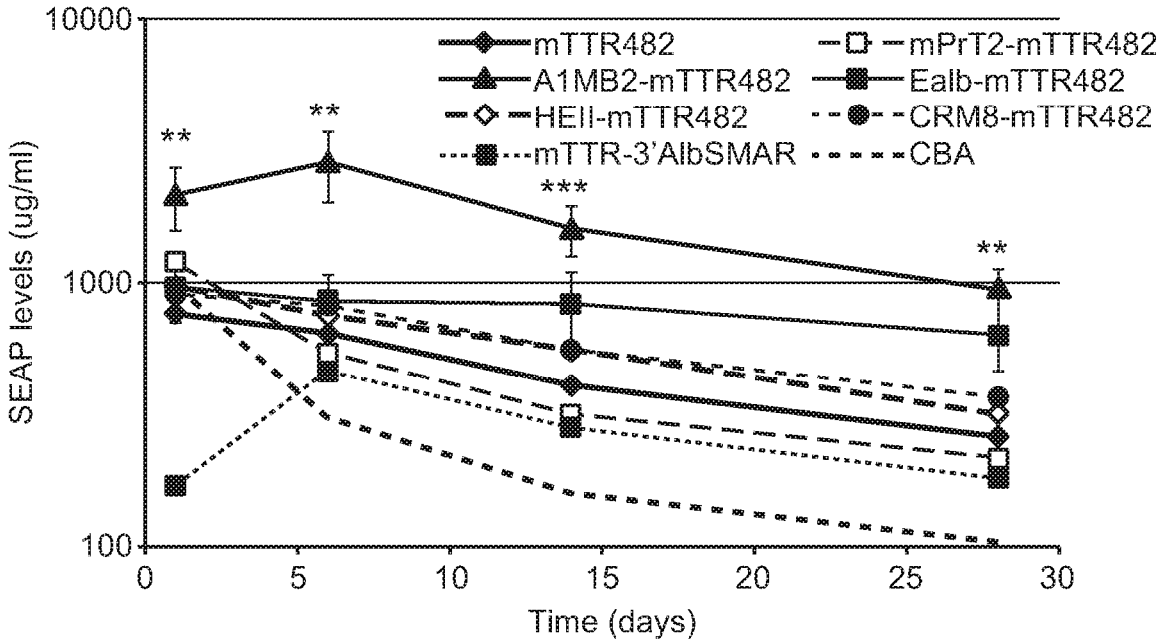

10000
1000
100
SEAP levels (ug/ml)
0
5
10
15
20
25
30
Time (days)
mTTR482
mPrT2-mTTR482
A1MB2-mTTR482
Ealb-mTTR482
HEII-mTTR482
CRM8-mTTR482
mTTR-3'AlbSMAR
CBA
**
**
***
**

FIG. 2A

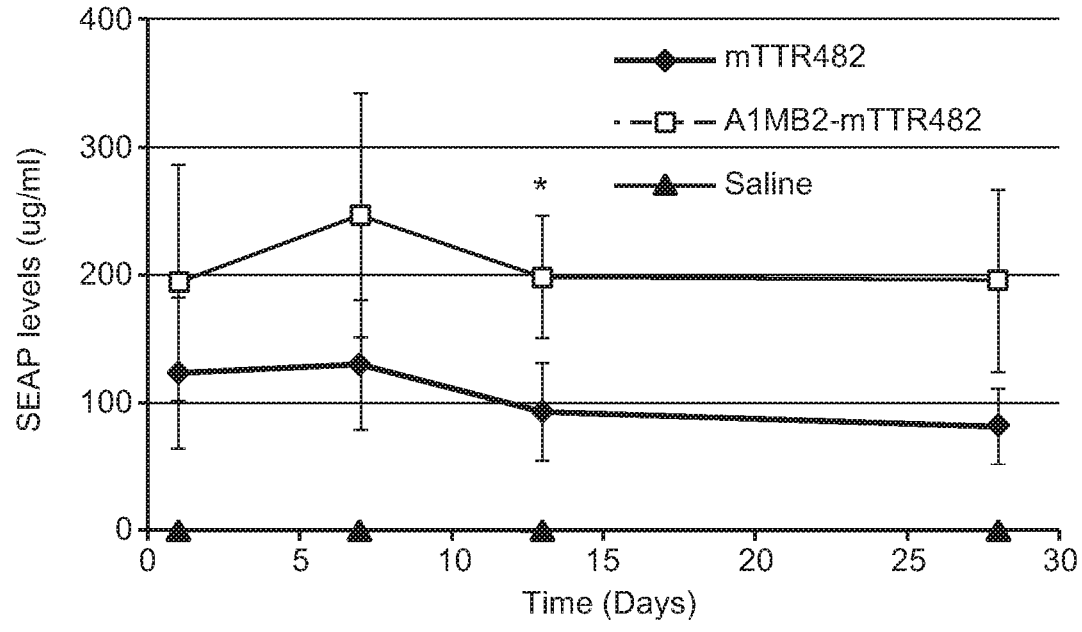

400
300
200
100
0
SEAP levels (ug/ml)
0
5
10
15
20
25
30
Time (Days)
mTTR482
A1MB2-mTTR482
Saline
*

FIG. 2B

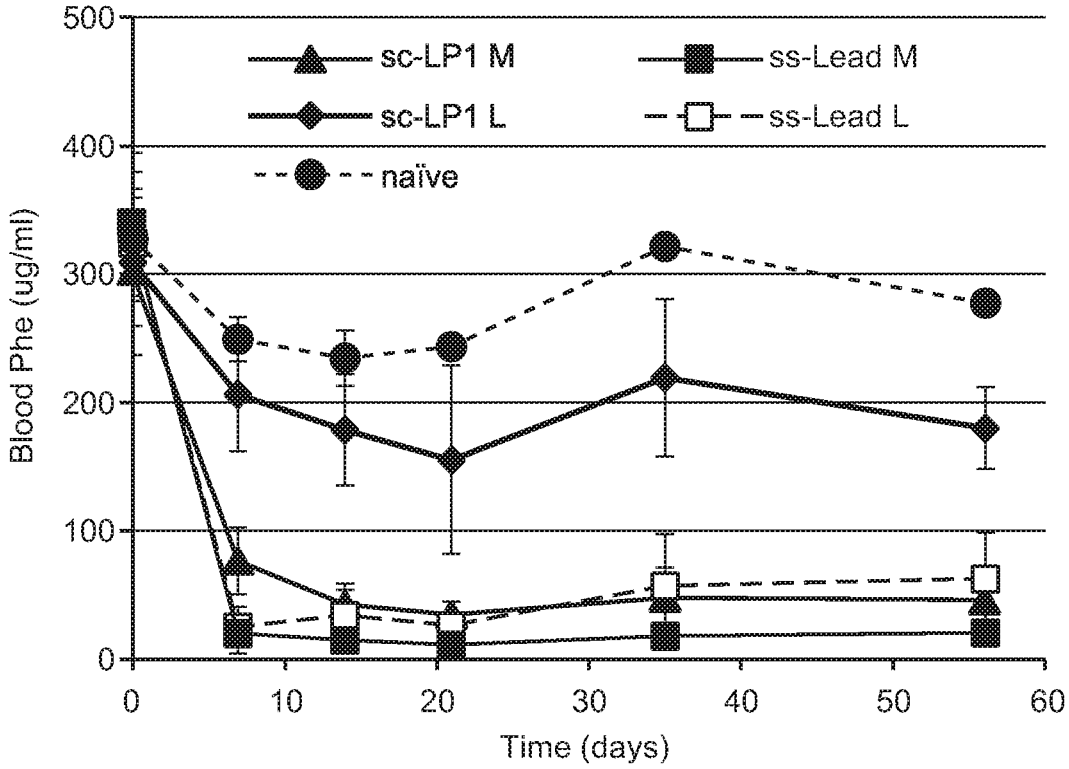

500
400
300
200
100
0
Blood Phe (ug/ml)
sc-LP1 M
ss-Lead M
sc-LP1 L
ss-Lead L
naïve
0
10
20
30
40
50
60
Time (days)

FIG. 3A

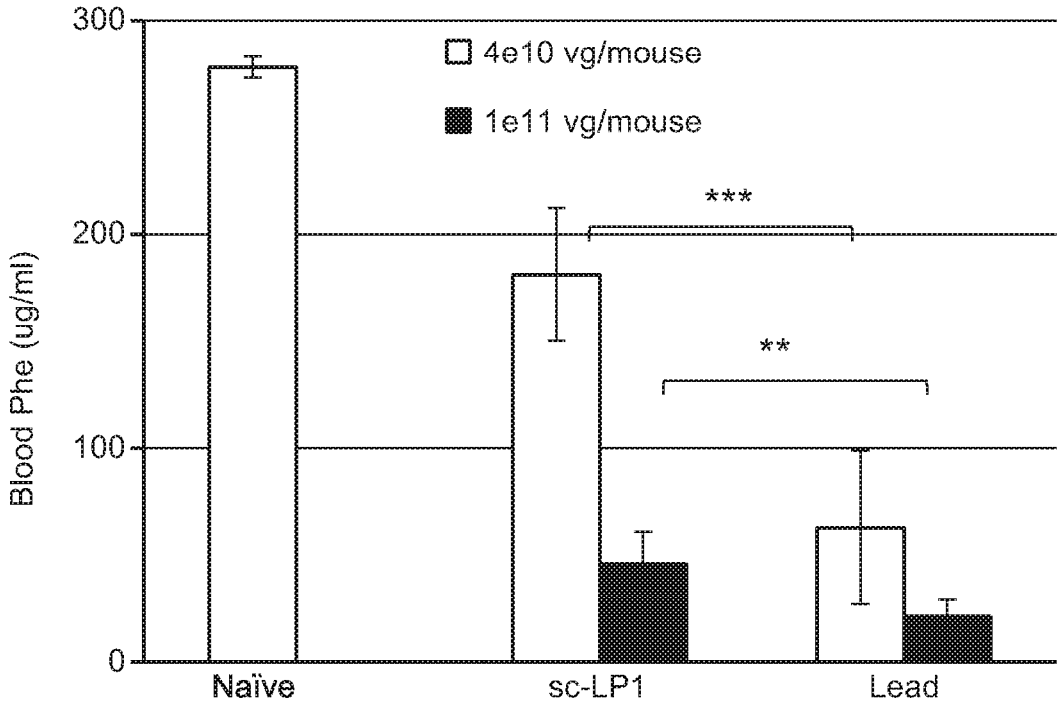

300
200
100
0
Blood Phe (ug/ml)
4e10 vg/mouse
1e11 vg/mouse
***
**
Naïve
sc-LP1
Lead

FIG. 3B

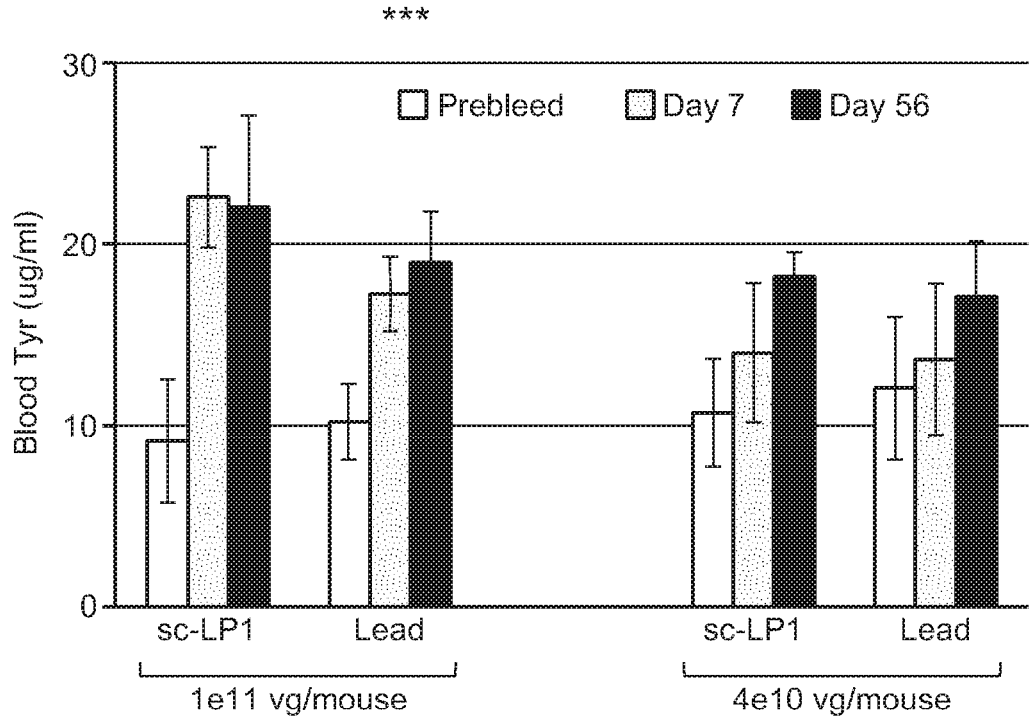

***
30
20
10
0
Blood Tyr (ug/ml)
Prebleed
Day 7
Day 56
sc-LP1
Lead
sc-LP1
Lead
1e11 vg/mouse
4e10 vg/mouse

FIG. 3C

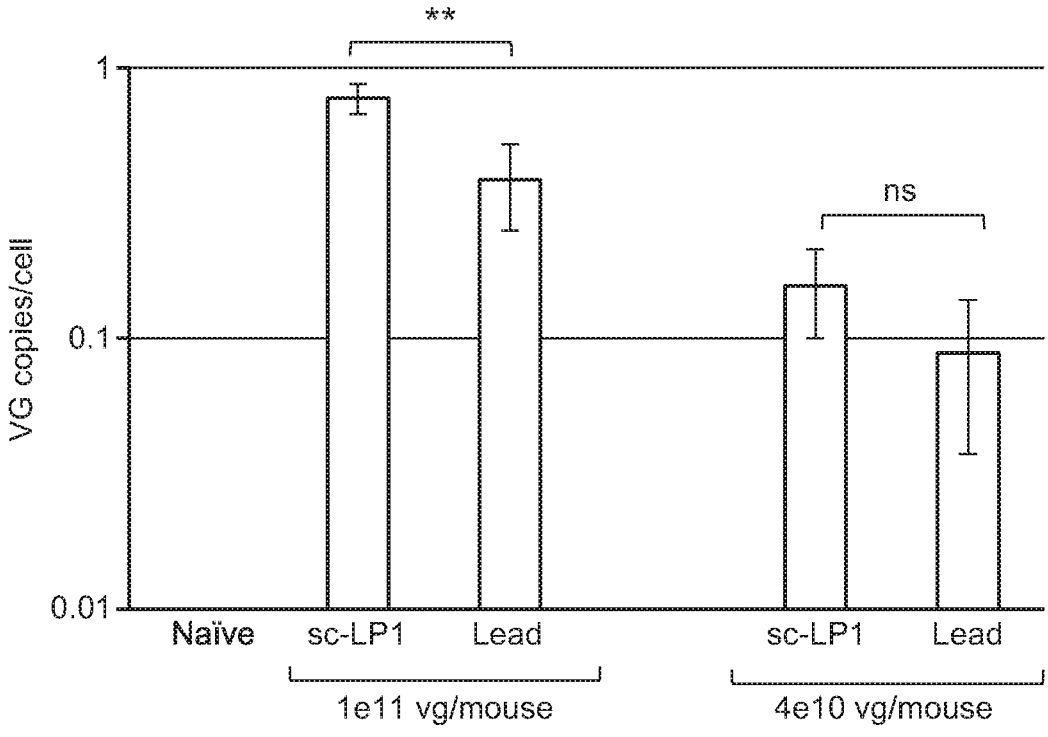

**
ns
1
0.1
0.01
VG copies/cell
Naïve
sc-LP1
Lead
sc-LP1
Lead
1e11 vg/mouse
4e10 vg/mouse

FIG. 3D

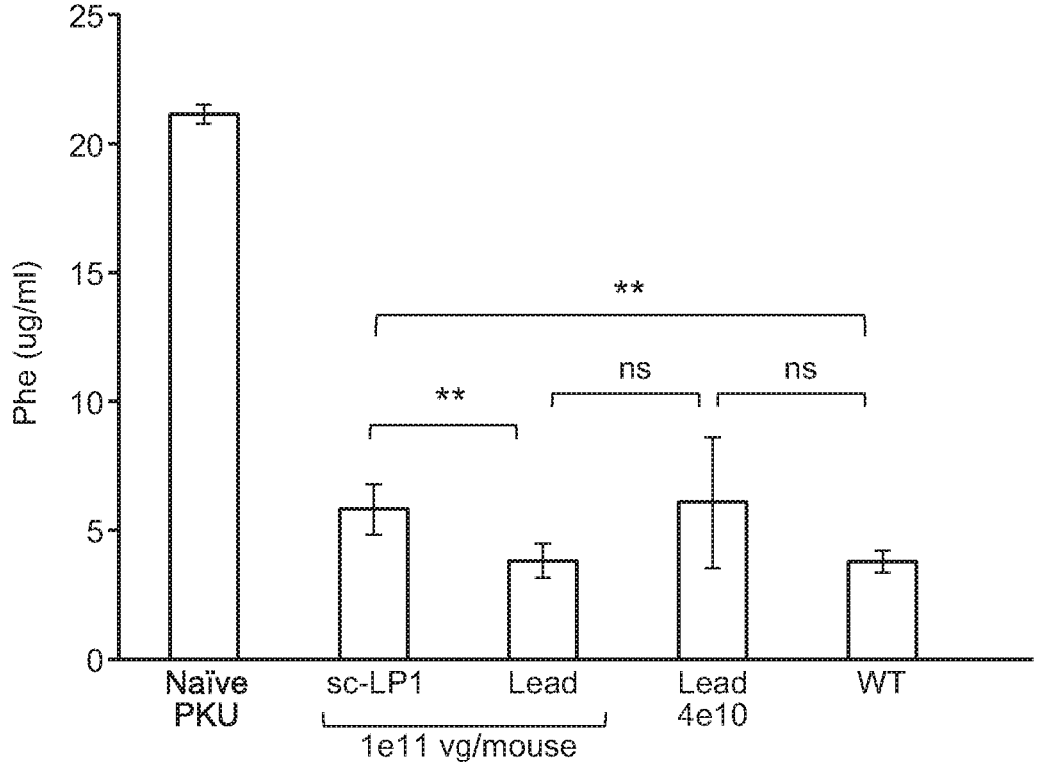

25
20
15
10
5
0
Phe (ug/ml)
**
**
ns
ns
Naïve PKU
sc-LP1
Lead
Lead 4e10
WT
1e11 vg/mouse

FIG. 4A

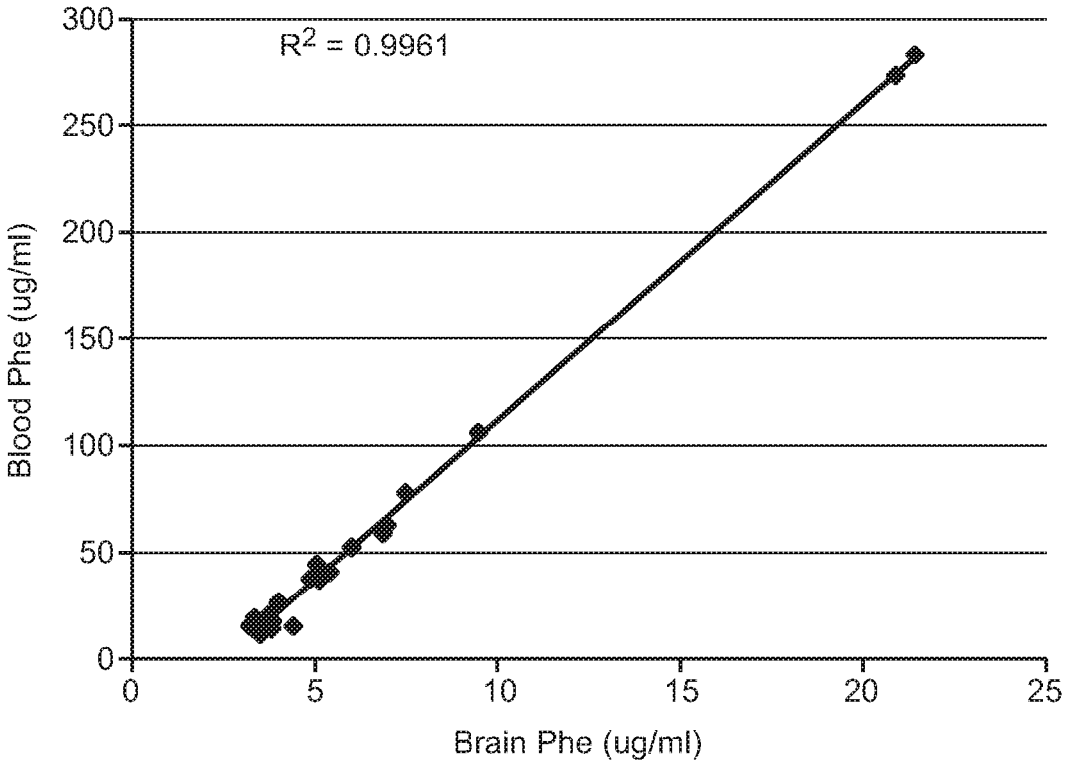

300
250
200
150
100
50
0
Blood Phe (ug/ml)
R2 = 0.9961
0
5
10
15
20
25
Brain Phe (ug/ml)

FIG. 4B

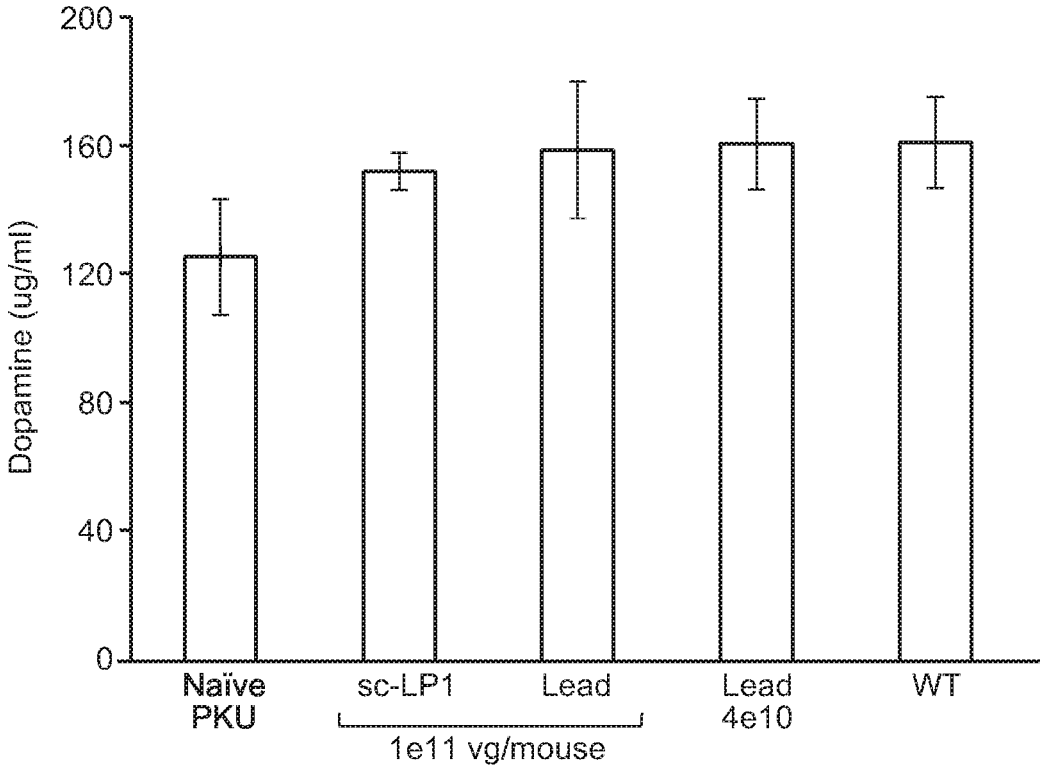

200
160
120
80
40
0
Dopamine (ug/ml)
Naïve PKU
sc-LP1
Lead
Lead 4e10
WT
1e11 vg/mouse

FIG. 4C

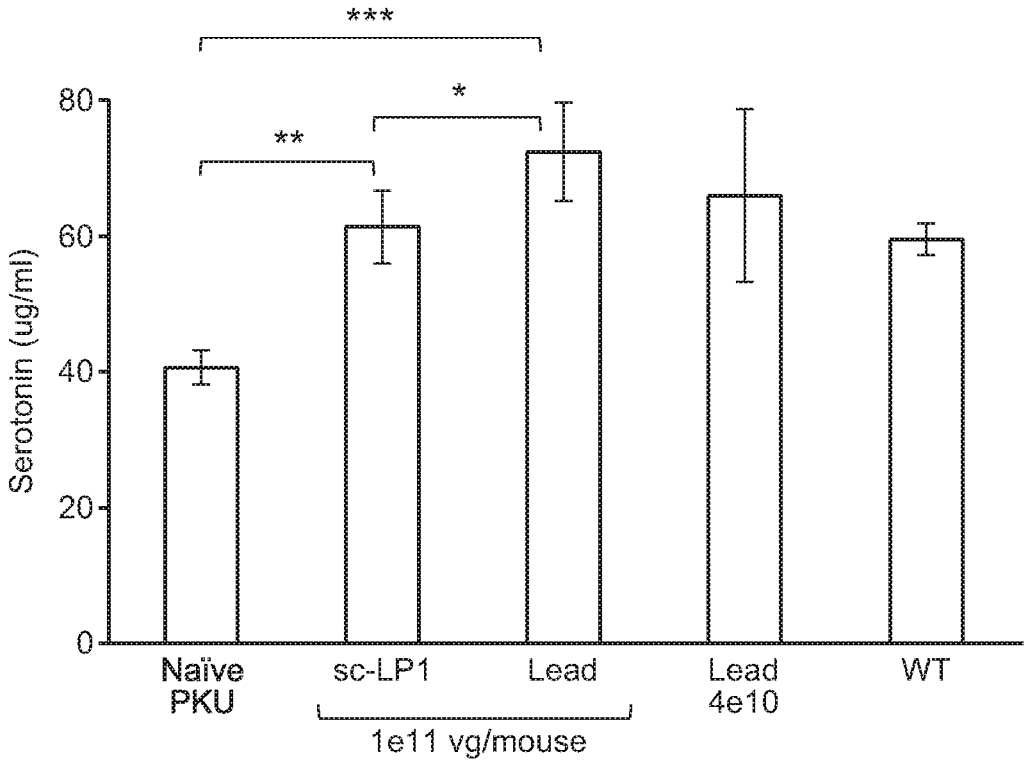

***
**
*
80
60
40
20
0
Serotonin (ug/ml)
Naïve PKU
sc-LP1
Lead
Lead 4e10
WT
1e11 vg/mouse

FIG. 4D

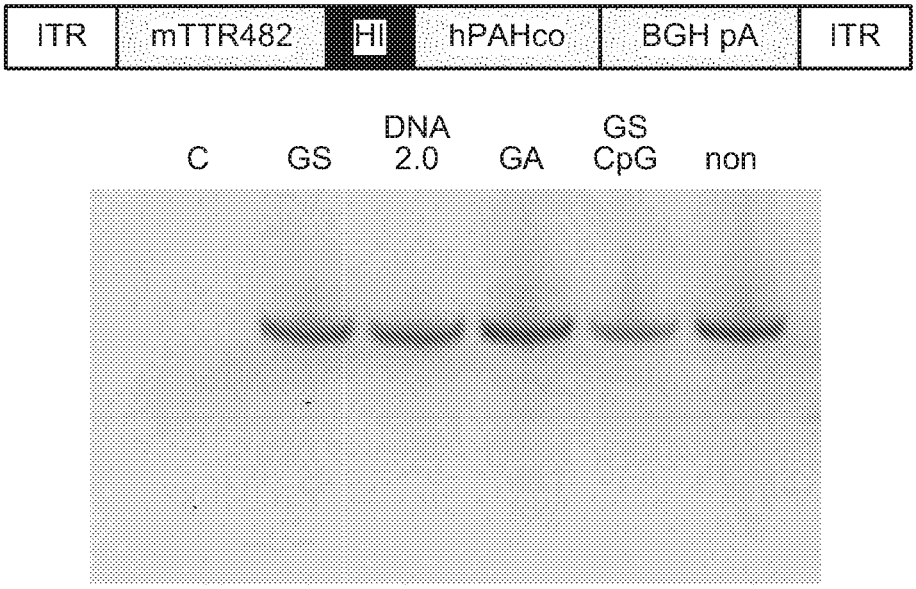

ITR
mTTR482
HI
hPAHco
BGH pA
ITR
C
GS
DNA 2.0
GA
GS CpG
non

FIG. 5A

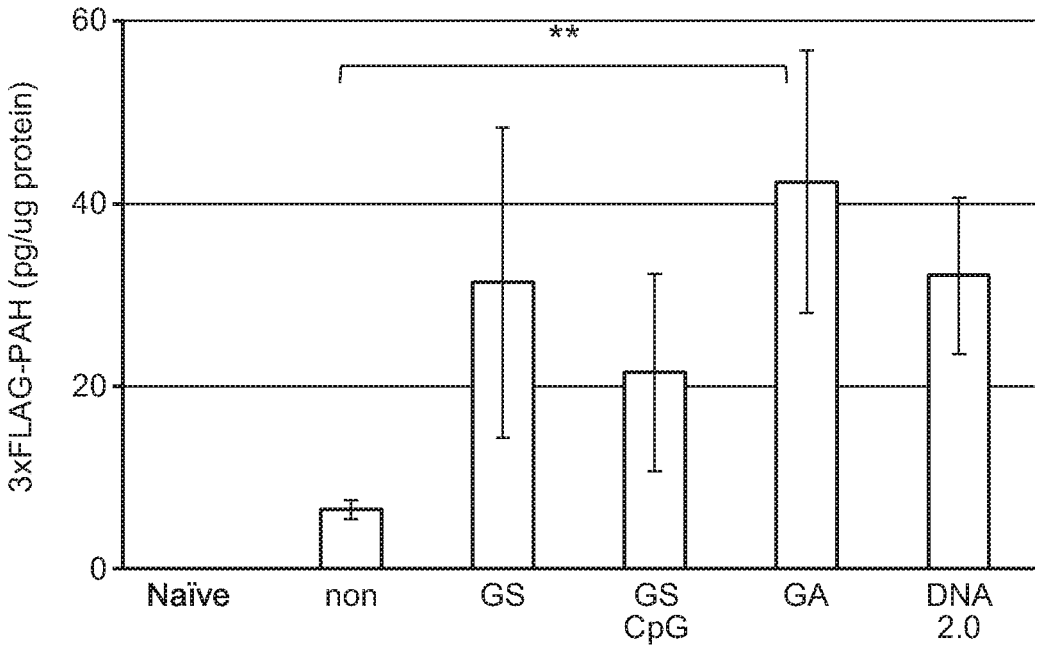

60
40
20
0
3xFLAG-PAH (pg/ug protein)
**
Naïve
non
GS
GS CpG
GA
DNA 2.0

FIG. 5B

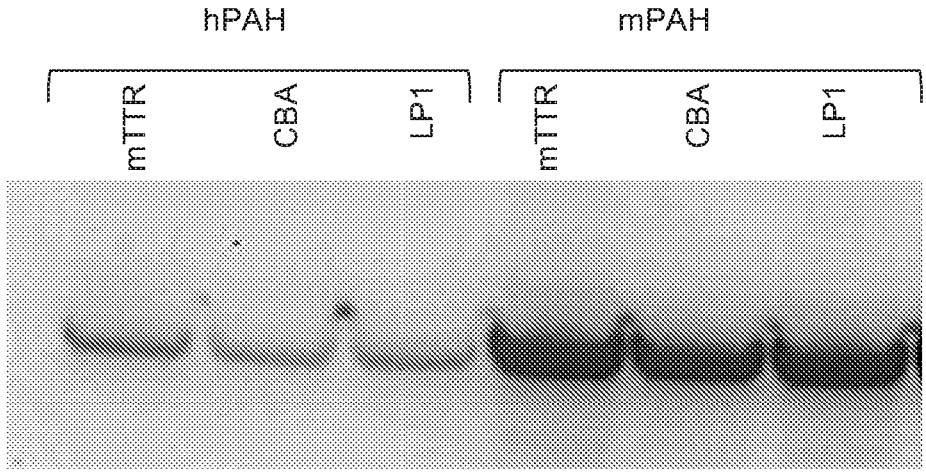

hPAH
mPAH
mTTR
CBA
LP1
mTTR
CBA
LP1

FIG. 6A

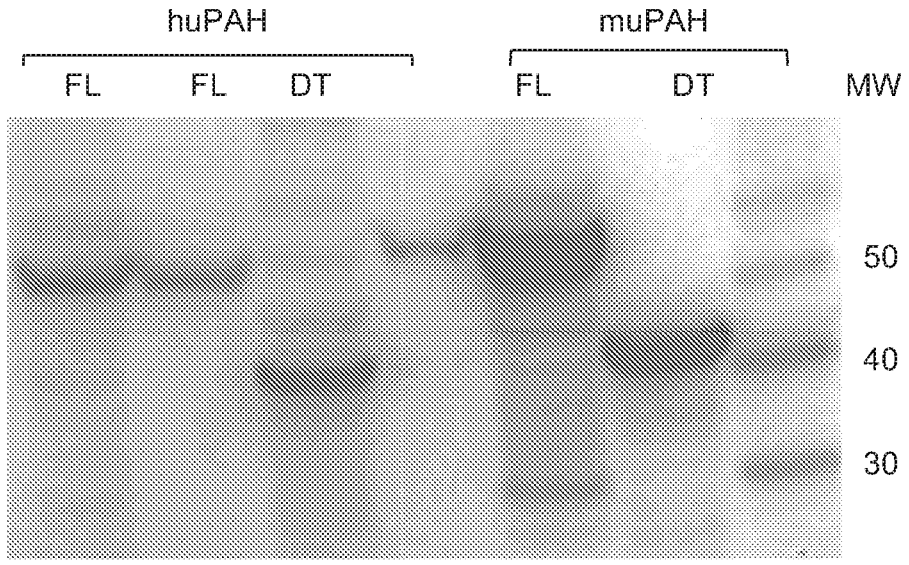

huPAH
muPAH
FL
FL
DT
FL
DT
MW
50
40
30

FIG. 6B

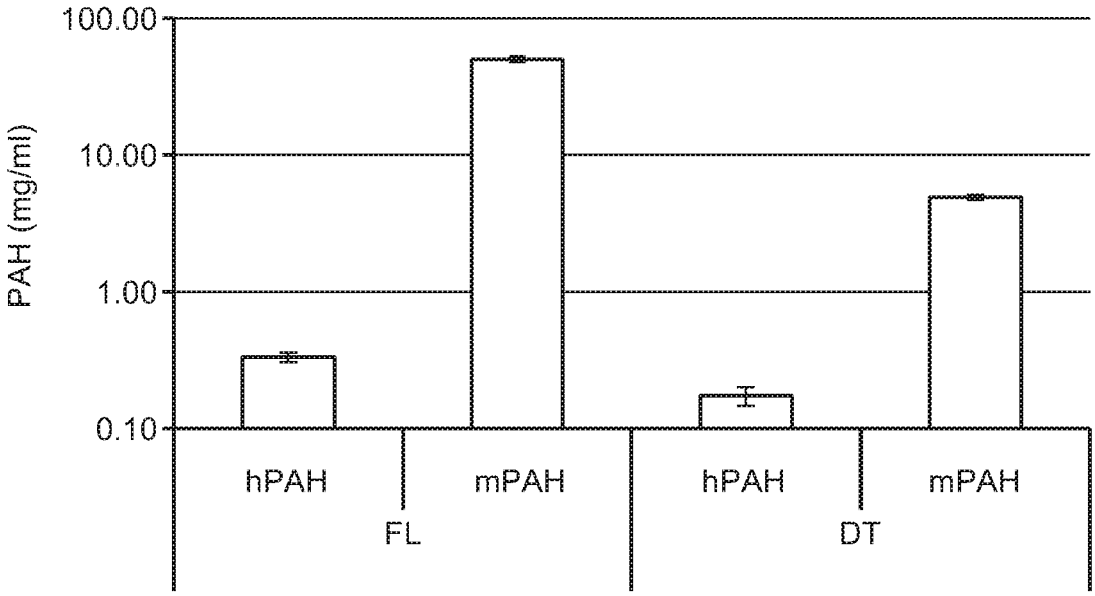

100.00
10.00
1.00
0.10
PAH (mg/ml)
hPAH
mPAH
hPAH
mPAH
FL
DT

FIG. 6C

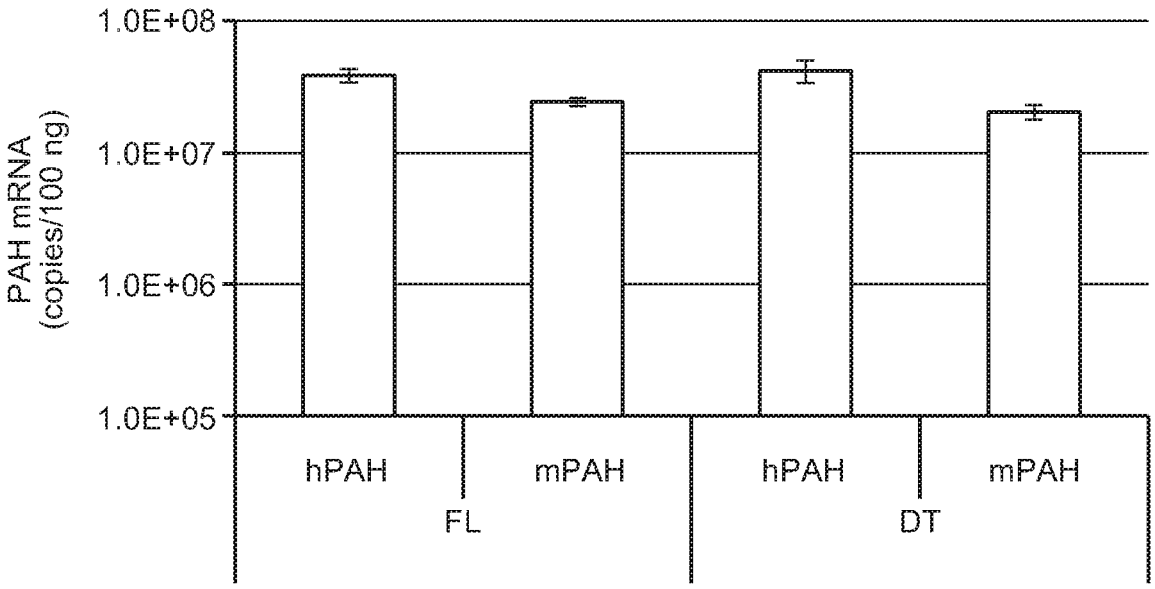

1.0E+08
1.0E+07
1.0E+06
1.0E+05
PAH mRNA
(copies/100 ng)
hPAH
mPAH
hPAH
mPAH
FL
DT

FIG. 6D

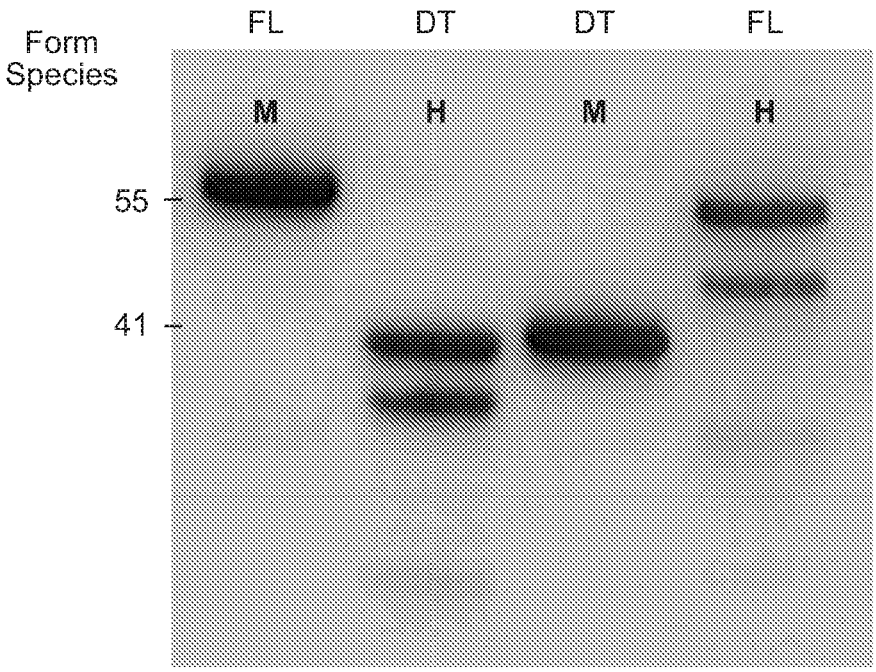

Form
Species
FL
DT
DT
FL
M
H
M
H
55
41

FIG. 6E

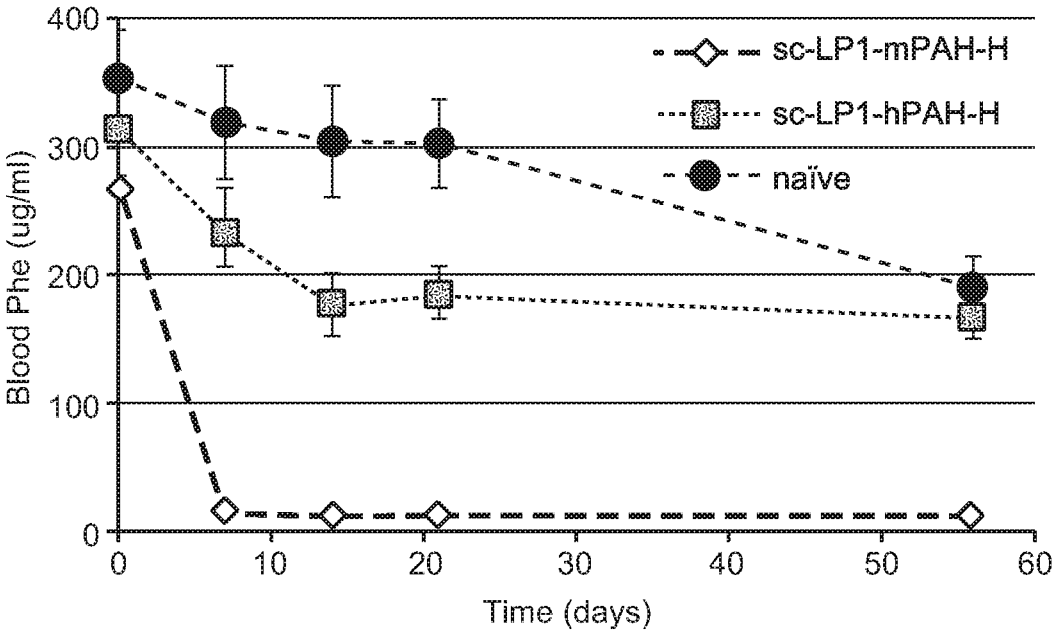

400
300
200
100
0
Blood Phe (ug/ml)
0
10
20
30
40
50
60
Time (days)
sc-LP1-mPAH-H
sc-LP1-hPAH-H
naïve

FIG. 6F

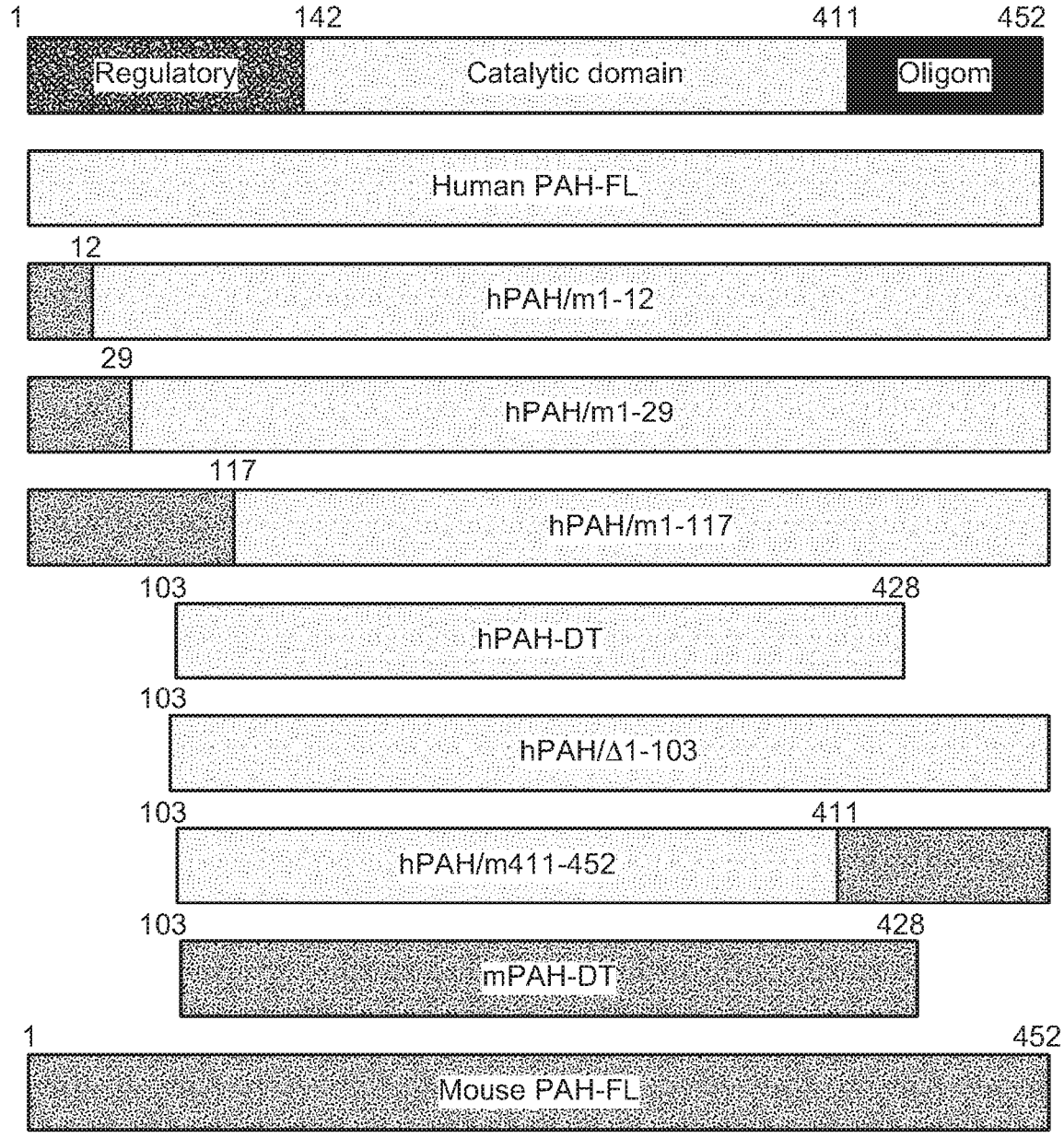

1
142
411
452
Regulatory
Catalytic domain
Oligom
Human PAH-FL
12
hPAH/m1-12
29
hPAH/m1-29
117
hPAH/m1-117
103
428
hPAH-DT
103
hPAH/Δ1-103
103
411
hPAH/m411-452
103
428
mPAH-DT
1
452
Mouse PAH-FL

FIG. 7A

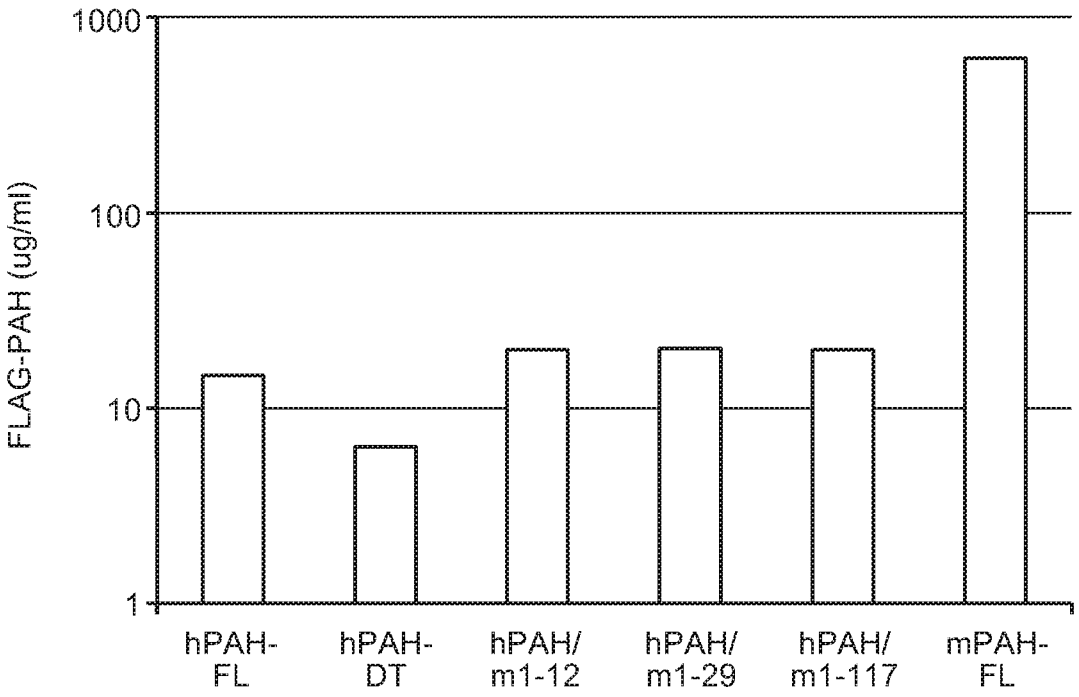

1000
100
10
1
FLAG-PAH (ug/ml)
hPAH-FL
hPAH-DT
hPAH/m1-12
hPAH/m1-29
hPAH/m1-117
mPAH-FL

FIG. 7B

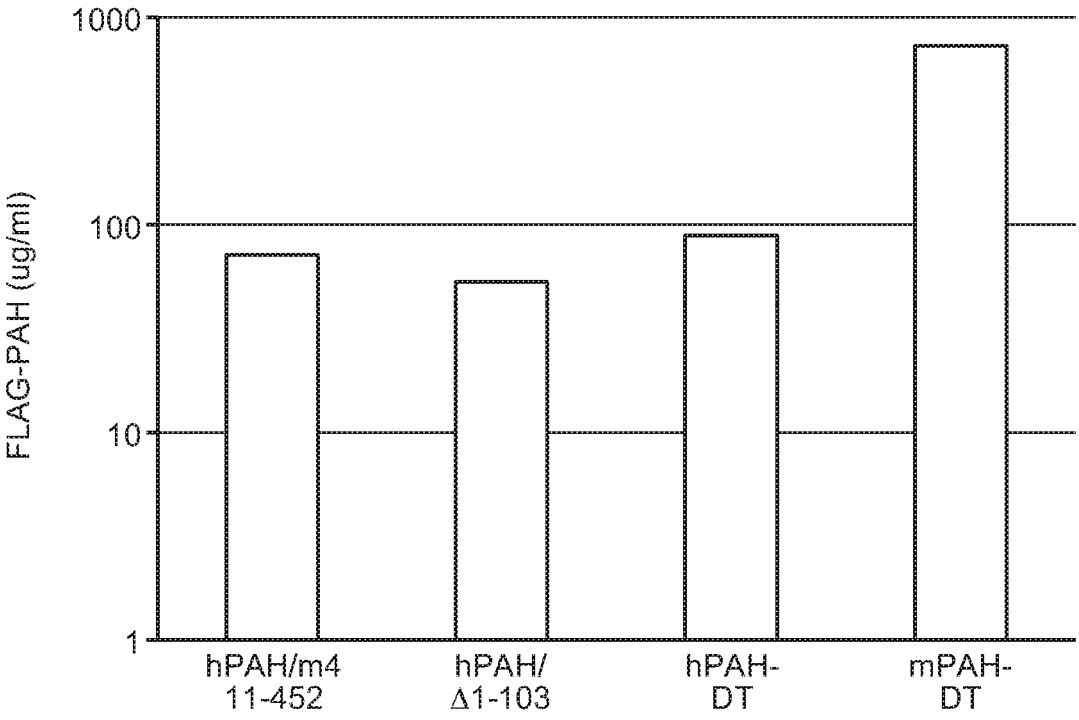

1000
100
10
1
FLAG-PAH (ug/ml)
hPAH/m4 11-452
hPAH/ Δ1-103
hPAH-DT
mPAH-DT

FIG. 7C

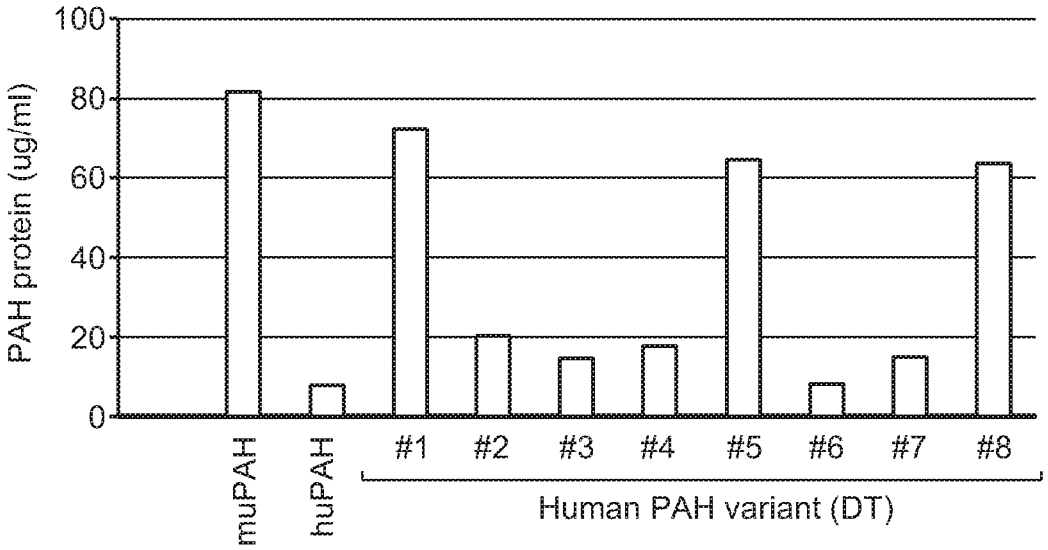

100
80
60
40
20
0
PAH protein (ug/ml)
muPAH
huPAH
#1
#2
#3
#4
#5
#6
#7
#8
Human PAH variant (DT)

FIG. 8A

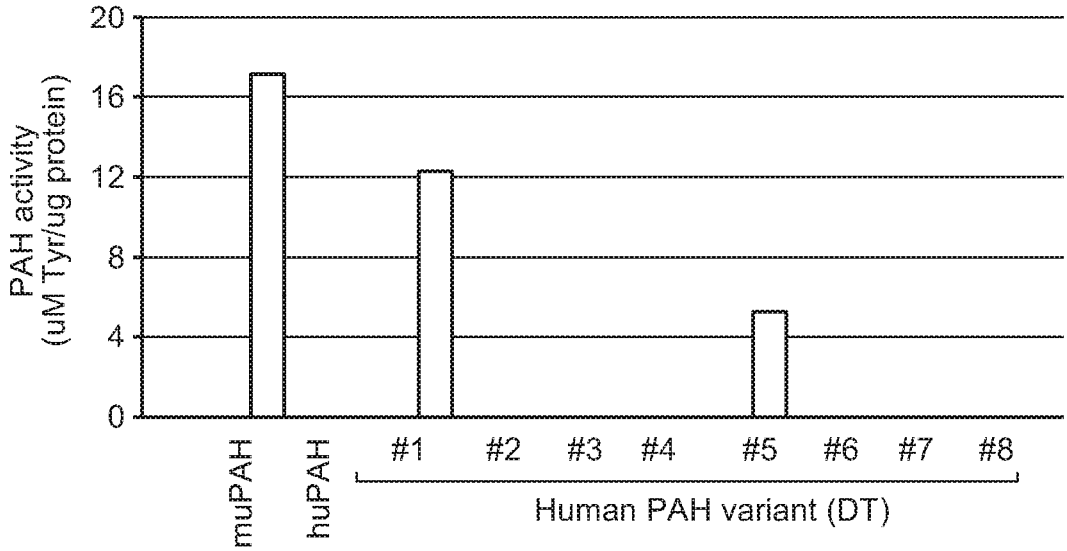

20
16
12
8
4
0
PAH activity
(uM Tyr/ug protein)
muPAH
huPAH
#1
#2
#3
#4
#5
#6
#7
#8
Human PAH variant (DT)

FIG. 8B

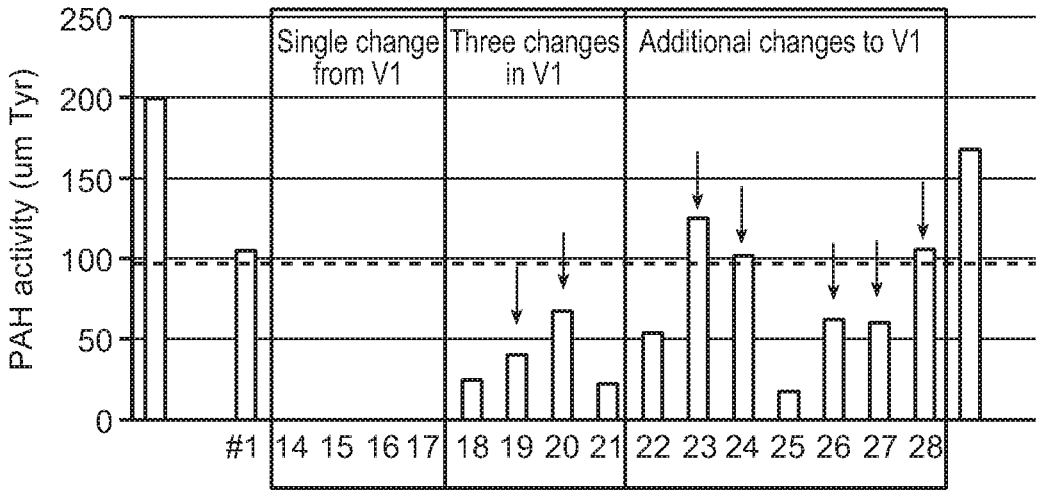


FIG. 9A

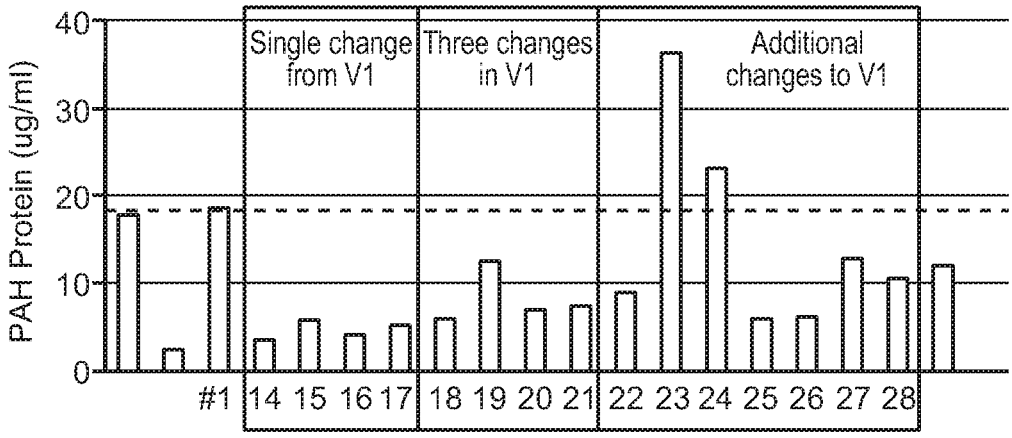


FIG. 9B

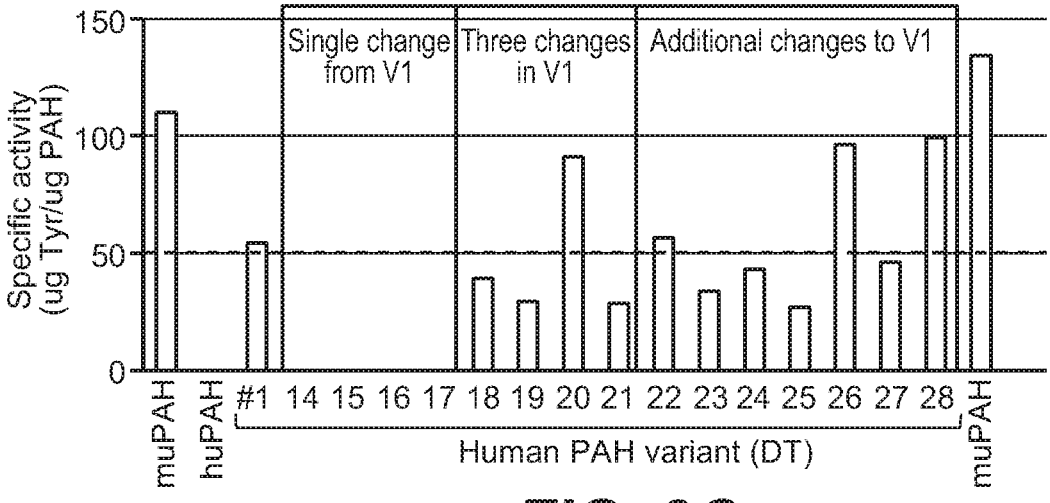


FIG. 9C

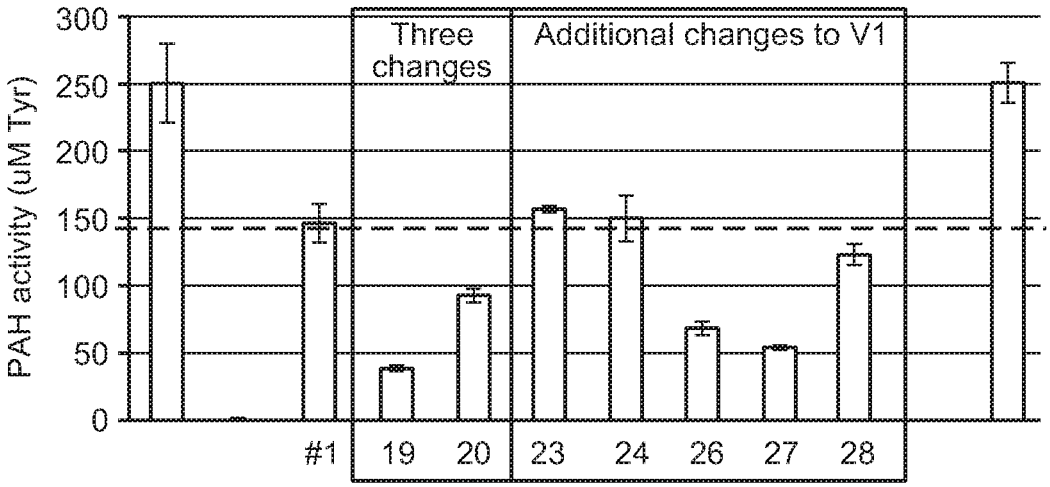


FIG. 10A

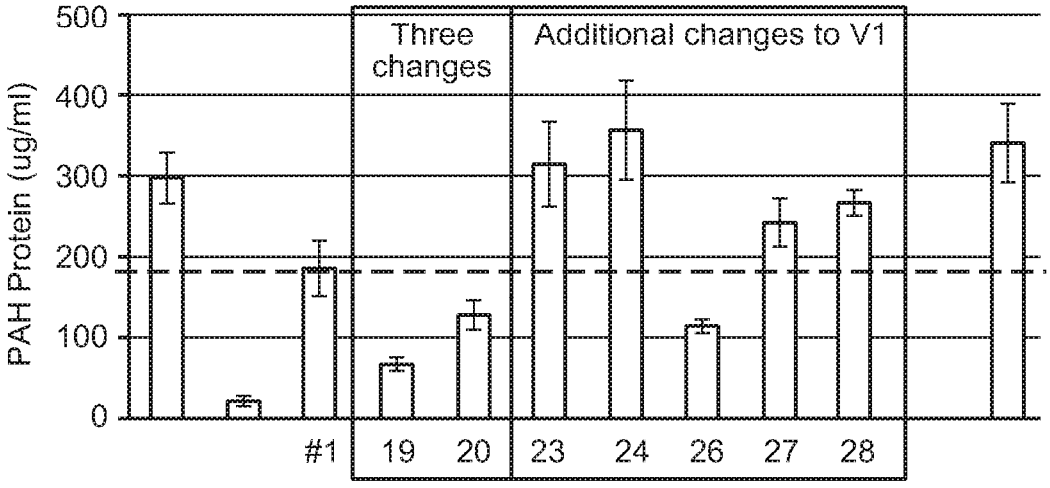


FIG. 10B

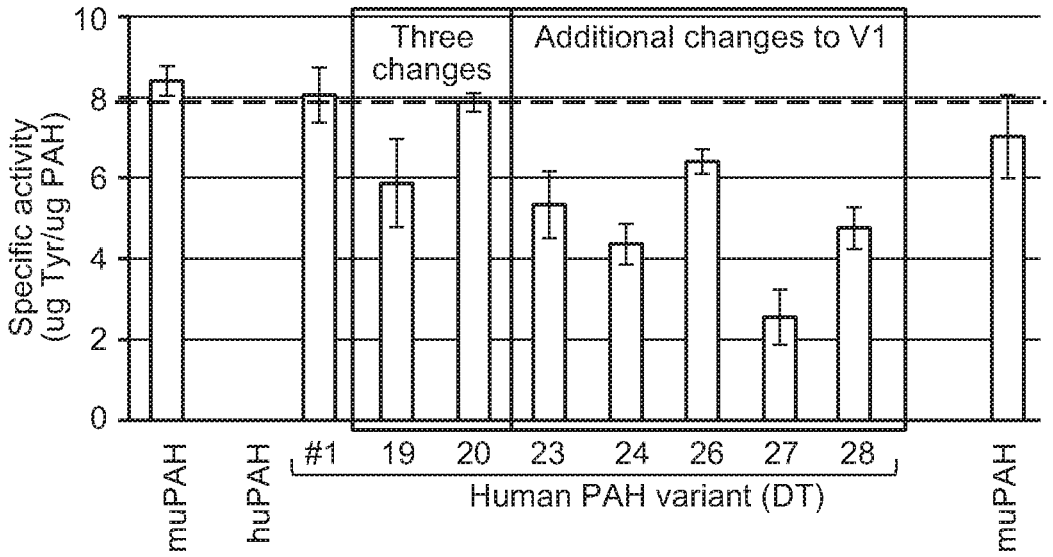


FIG. 10C

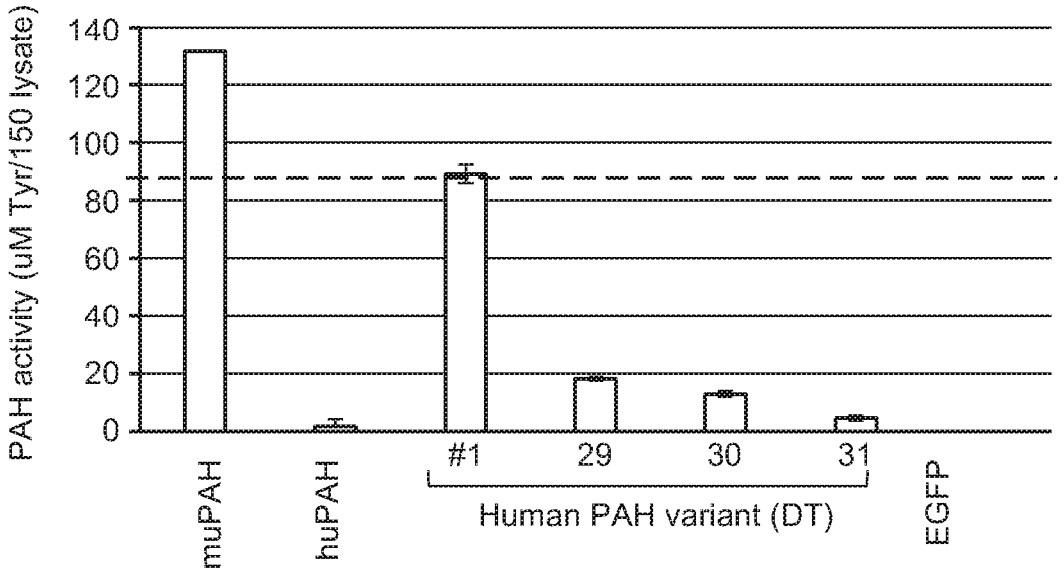


FIG. 10D

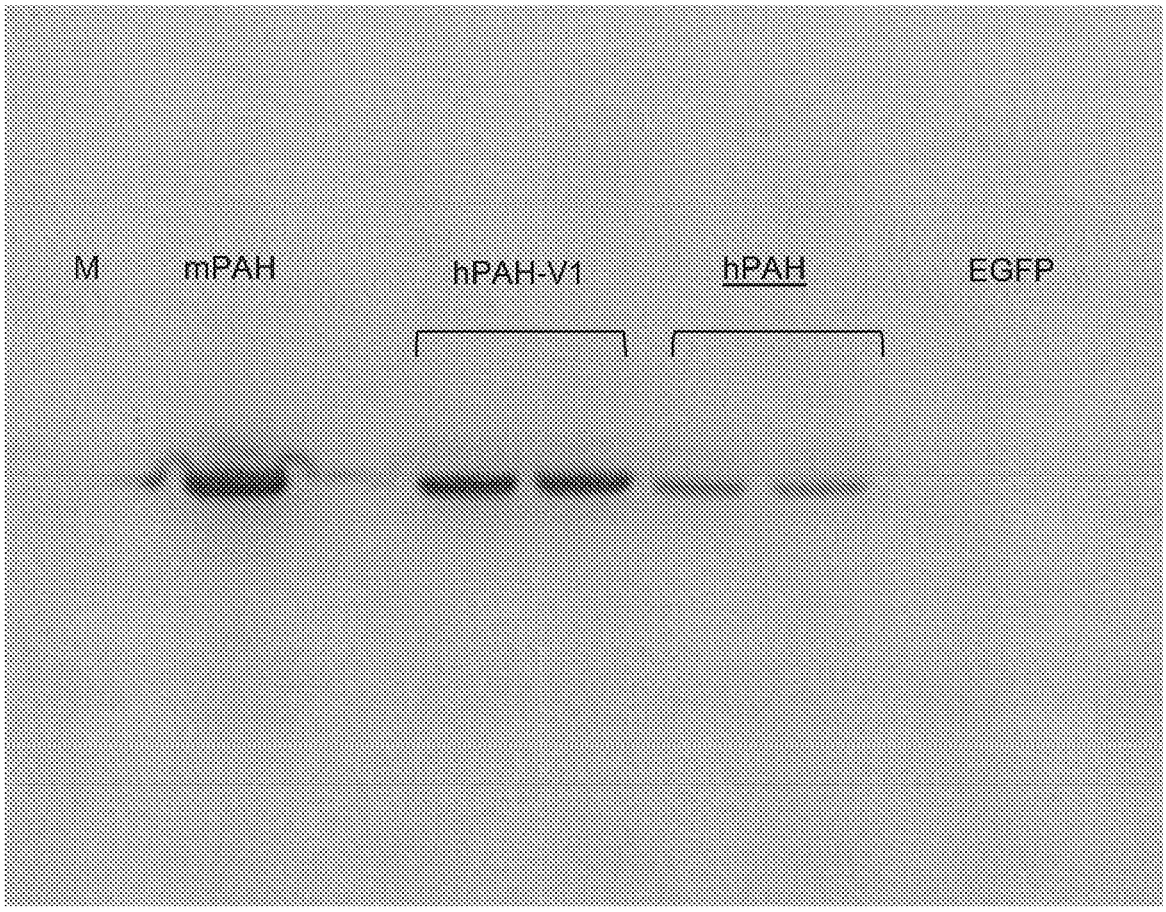


FIG. 11A

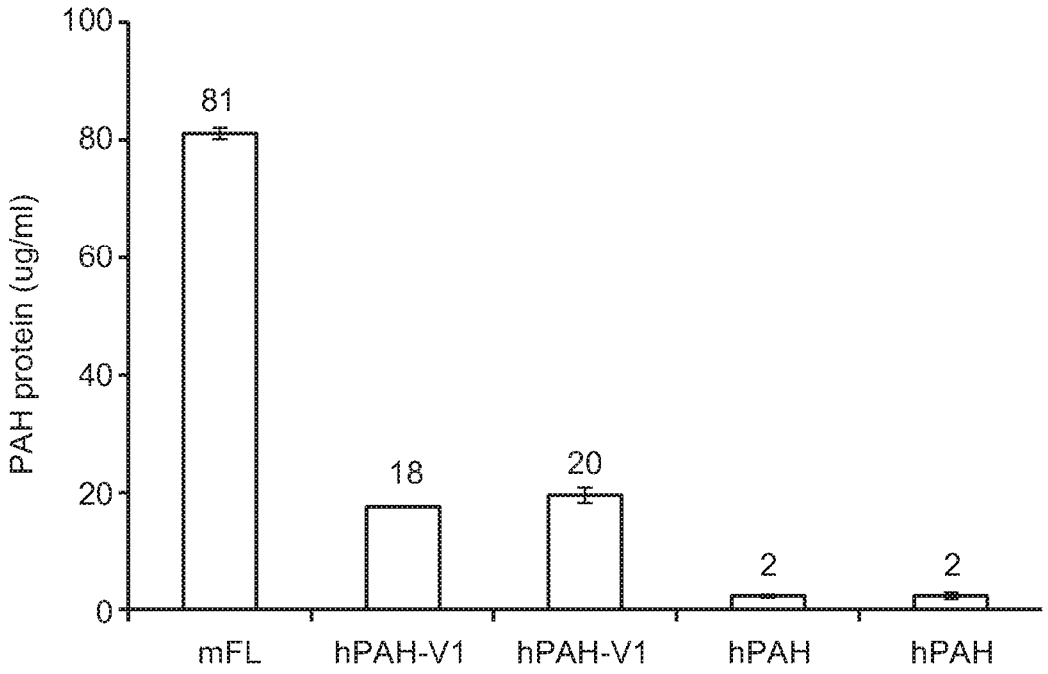


FIG. 11B

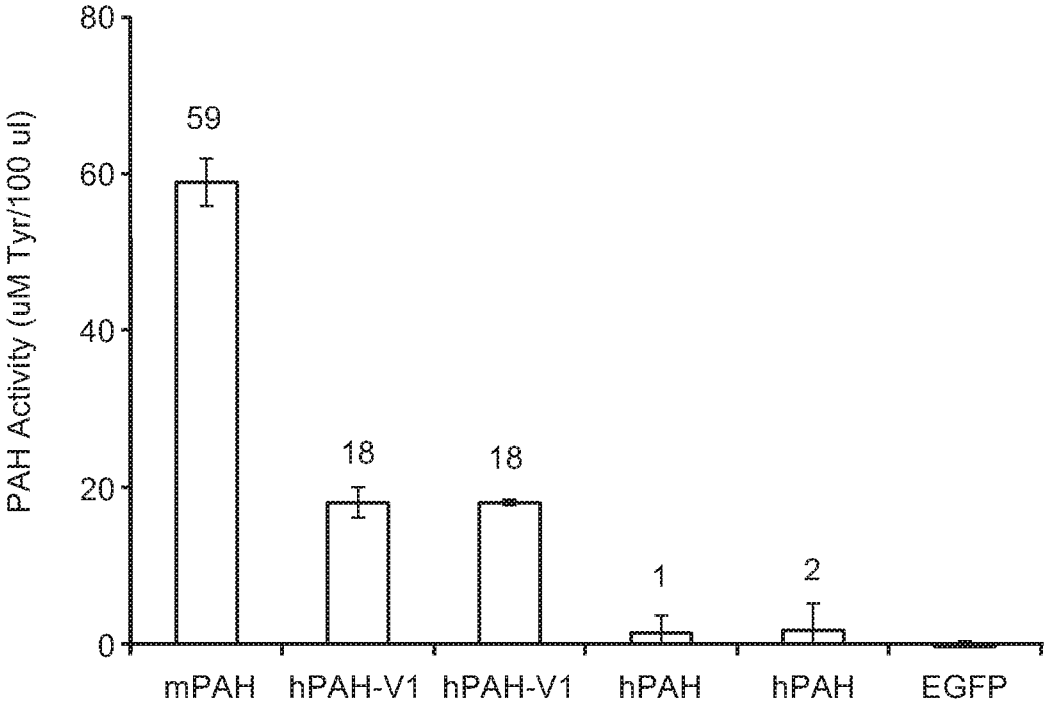


FIG. 11C

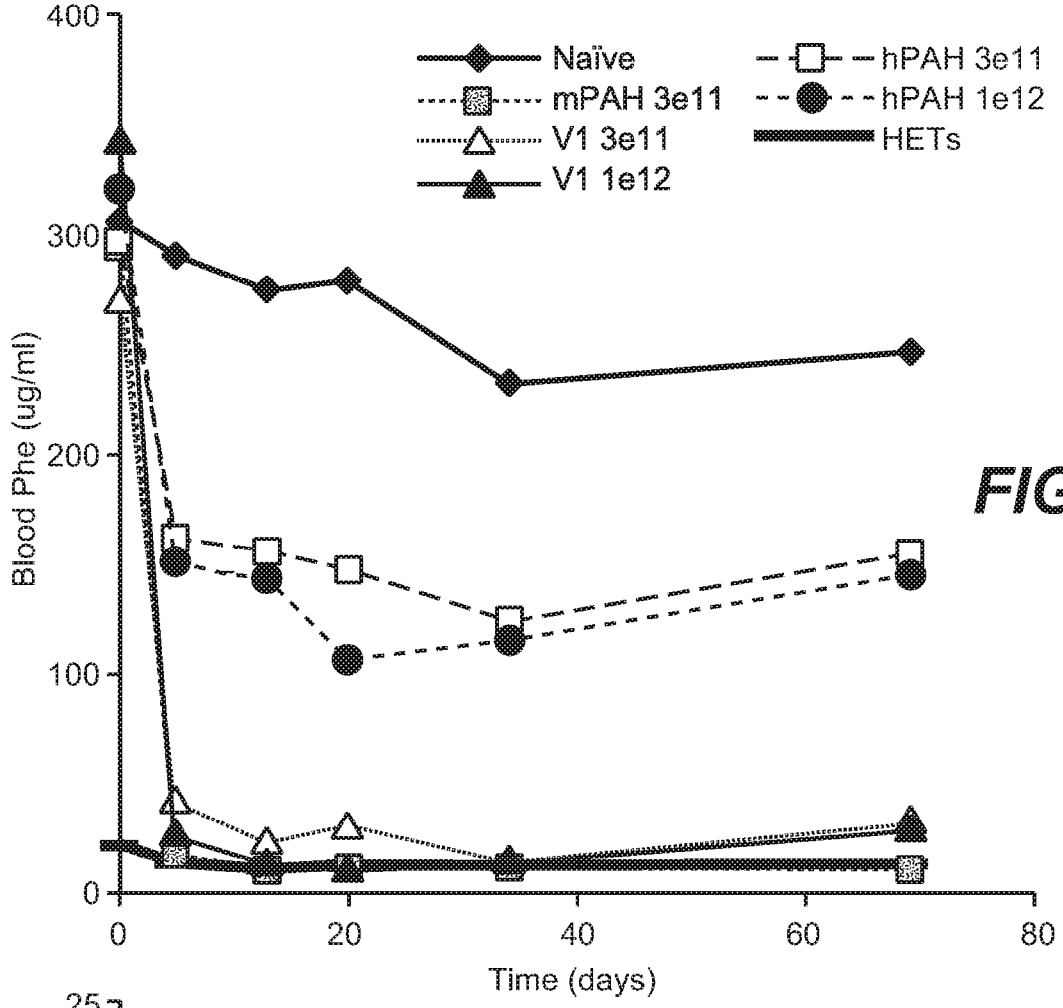


FIG. 12A

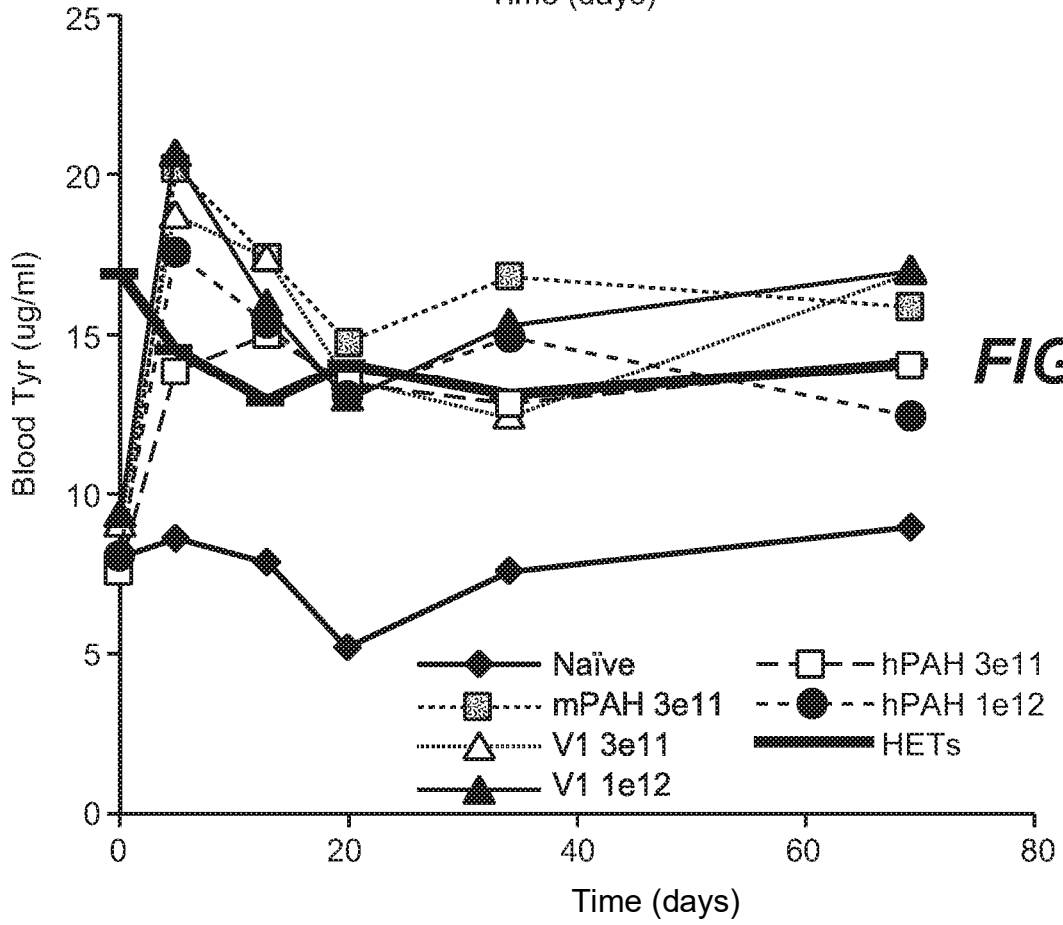


FIG. 12B

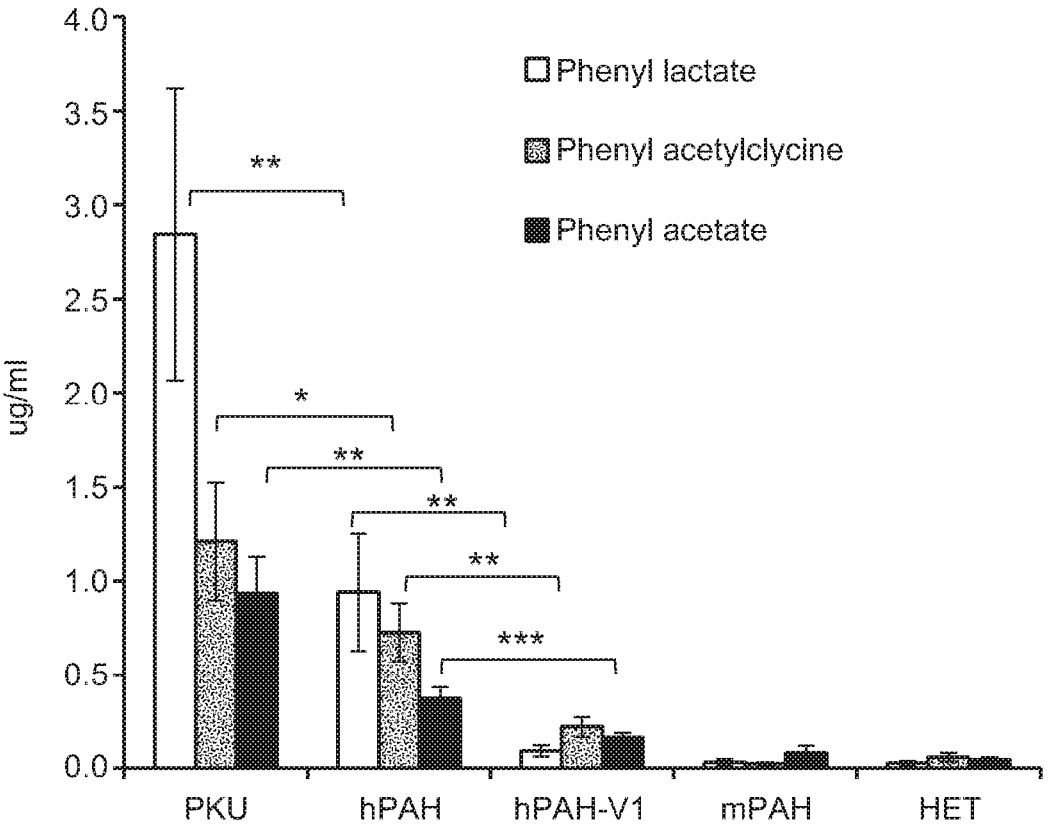

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ug/ml
Phenyl lactate
Phenyl acetylclycine
Phenyl acetate
**
*
**
**
**
***
PKU
hPAH
hPAH-V1
mPAH
HET

FIG. 12C

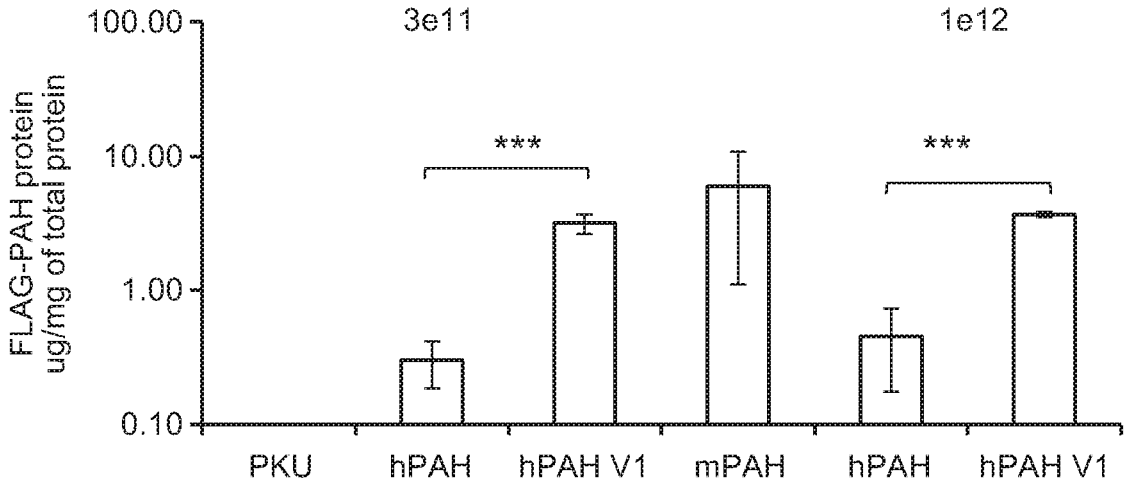


FIG. 13A

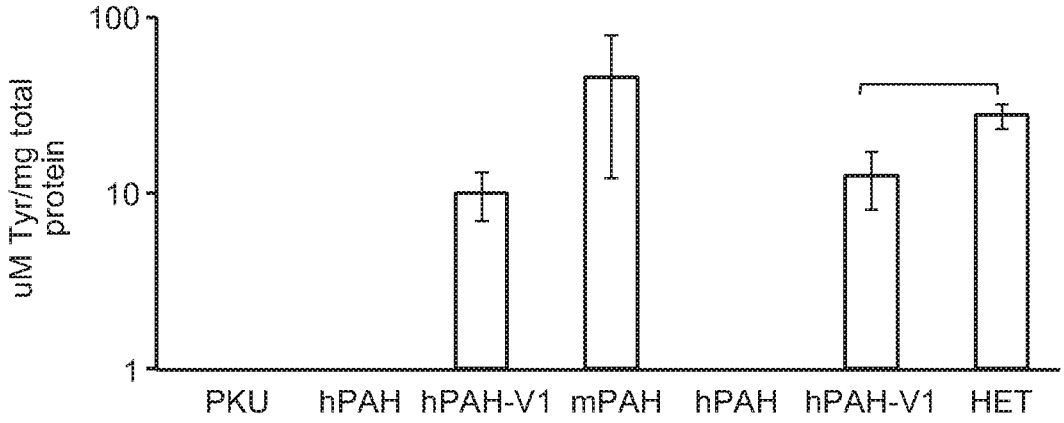


FIG. 13B

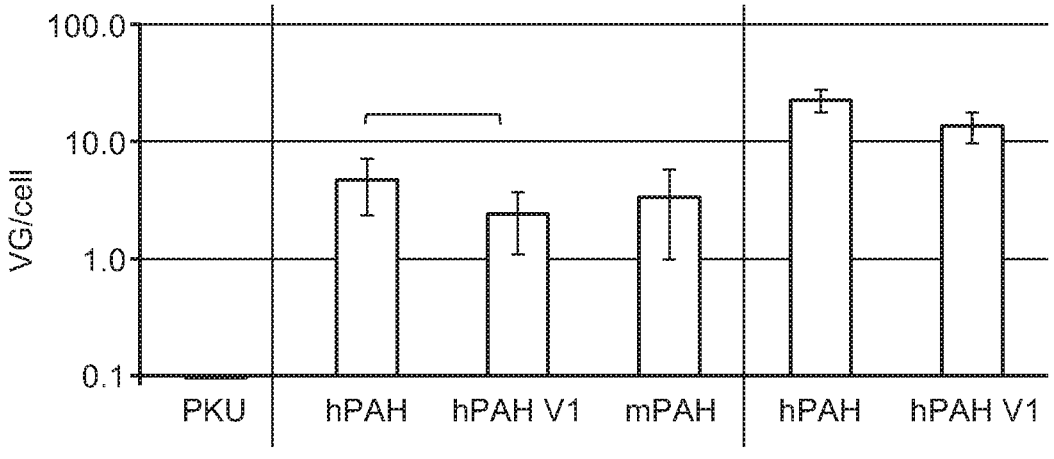


FIG. 13C

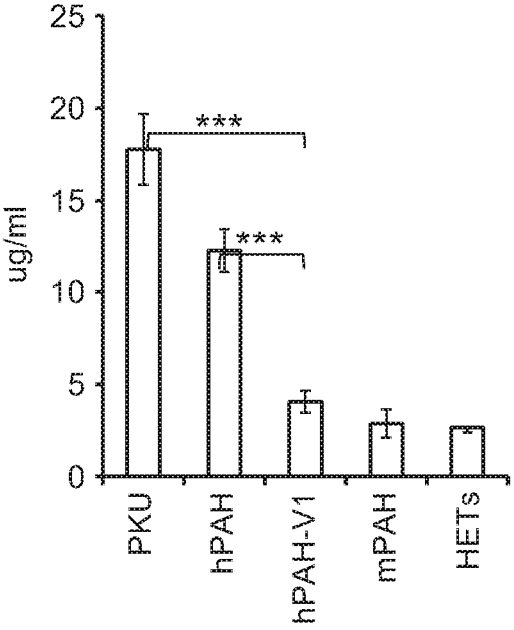


FIG. 14A

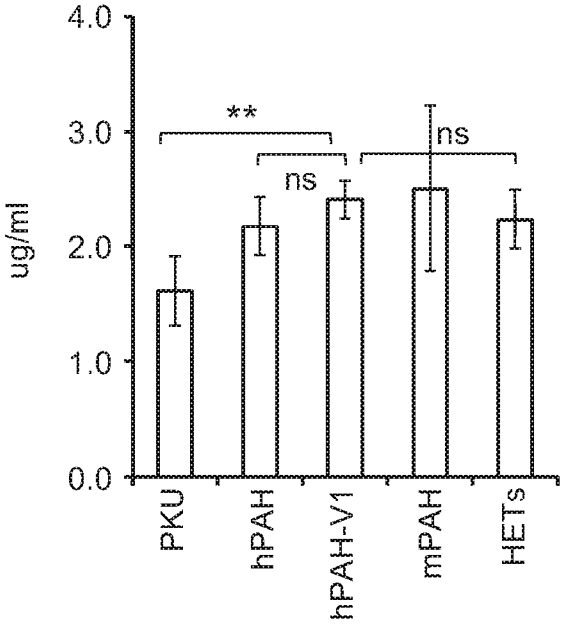


FIG. 14B

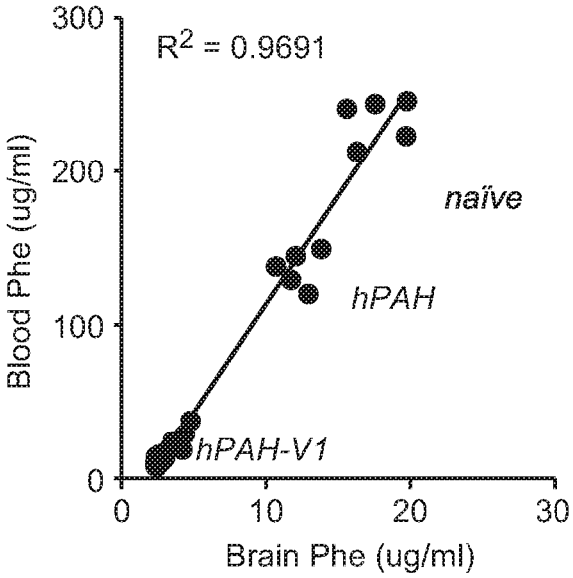


FIG. 14C

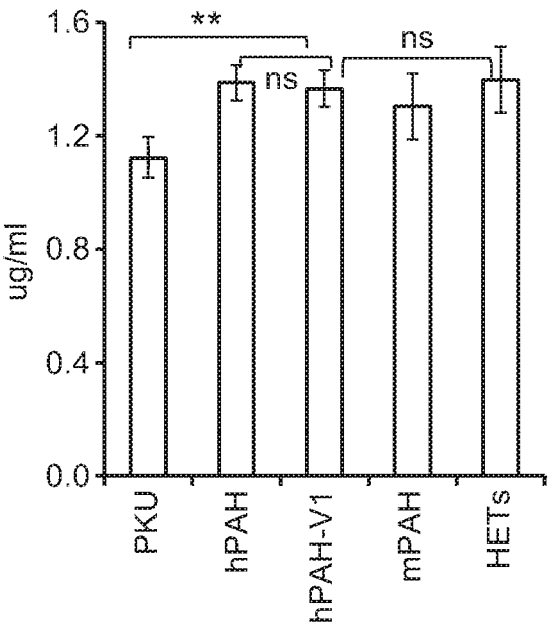


FIG. 14D

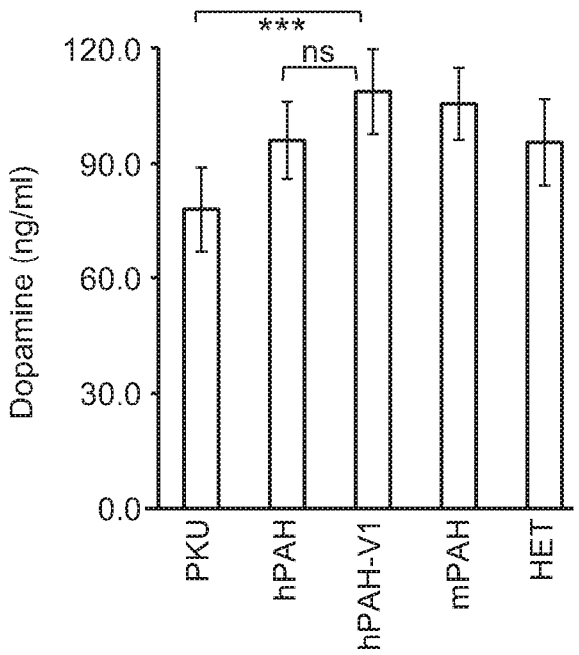


FIG. 15A

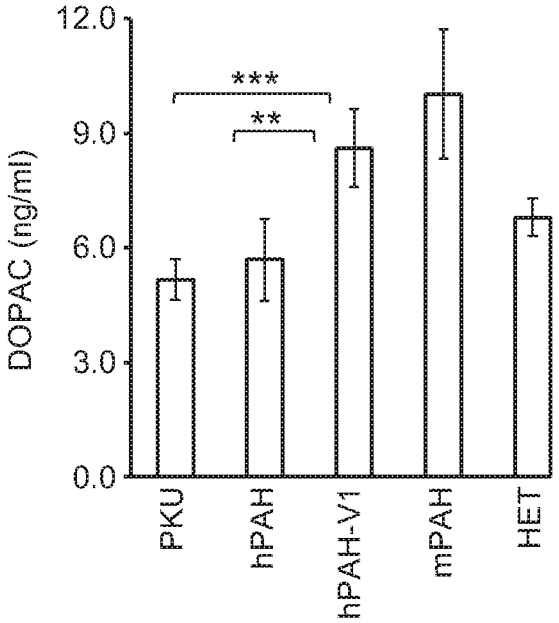


FIG. 15B

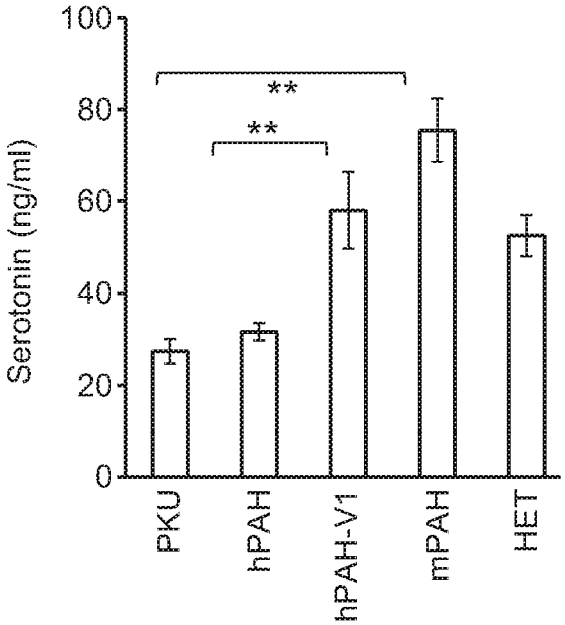


FIG. 15C

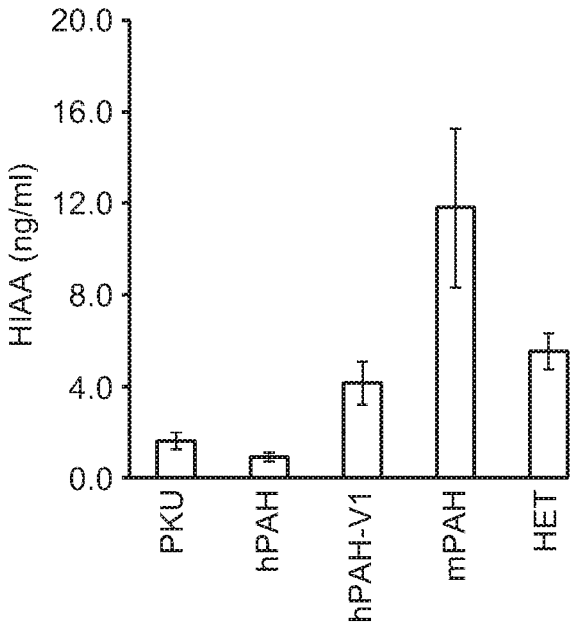


FIG. 15D

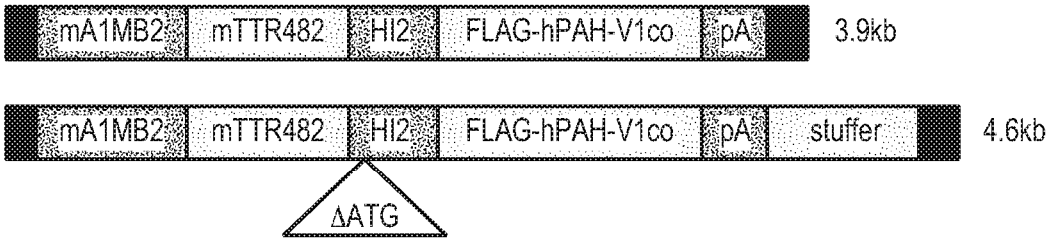


FIG. 16A

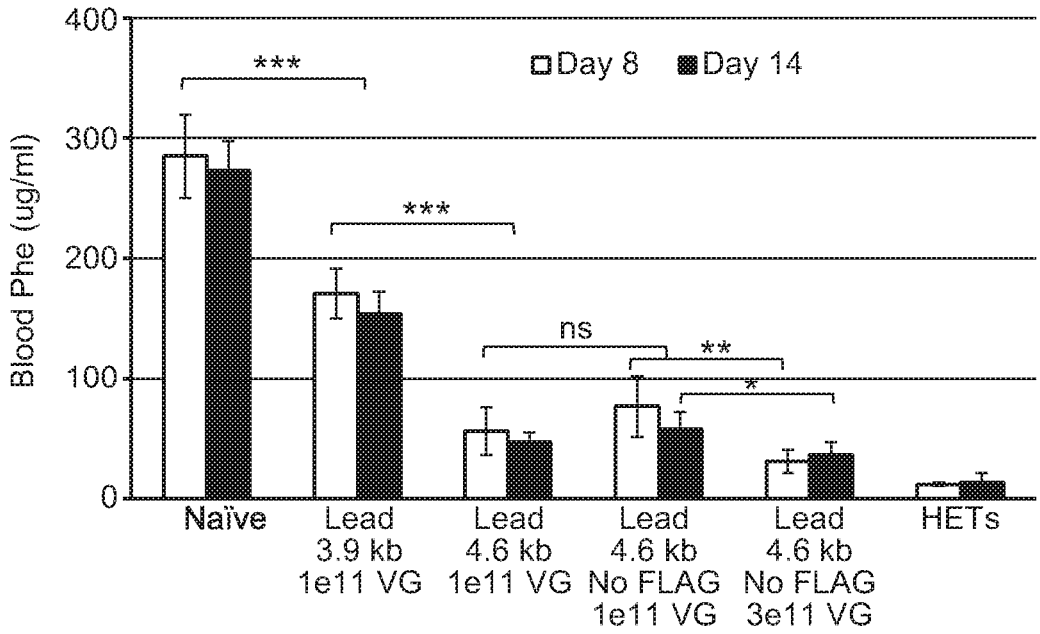


FIG. 16B

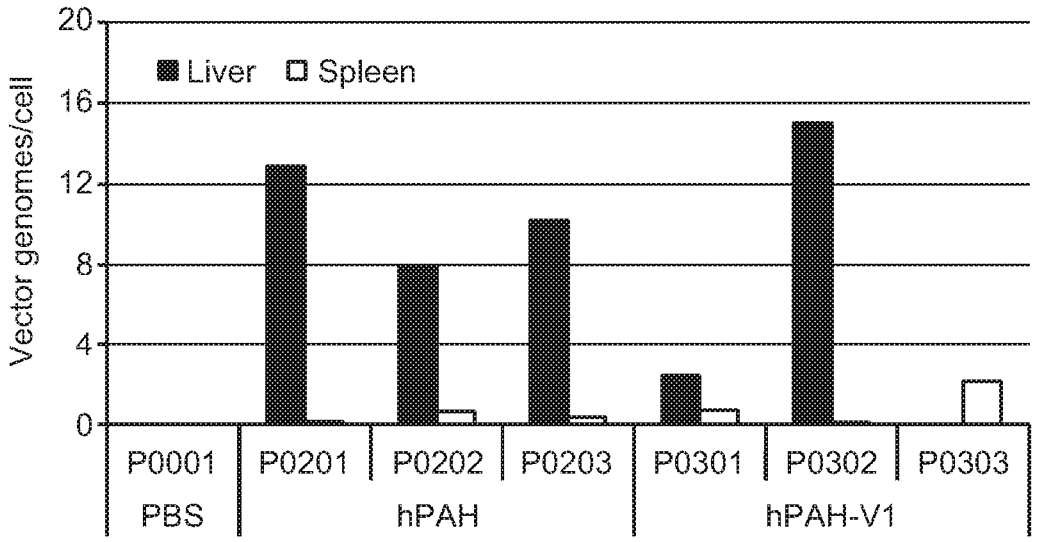


FIG. 17A

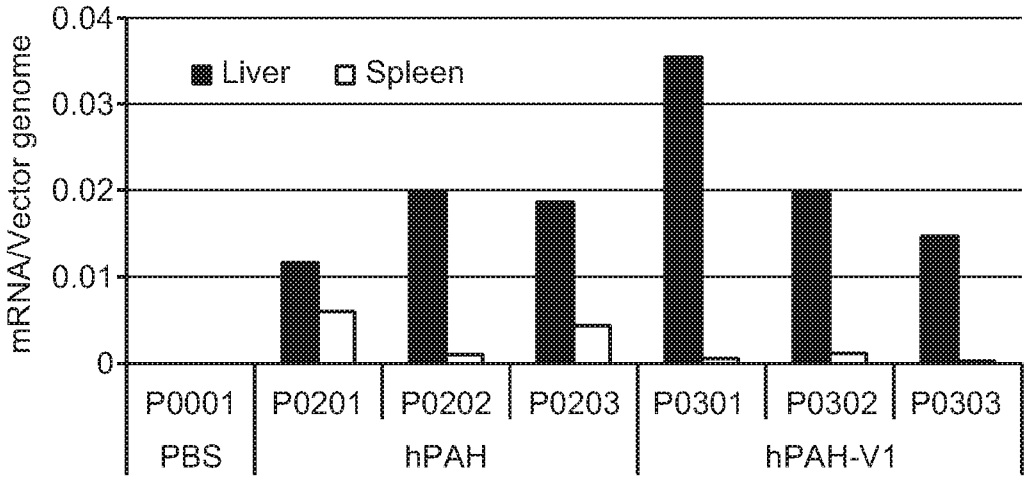


FIG. 17B

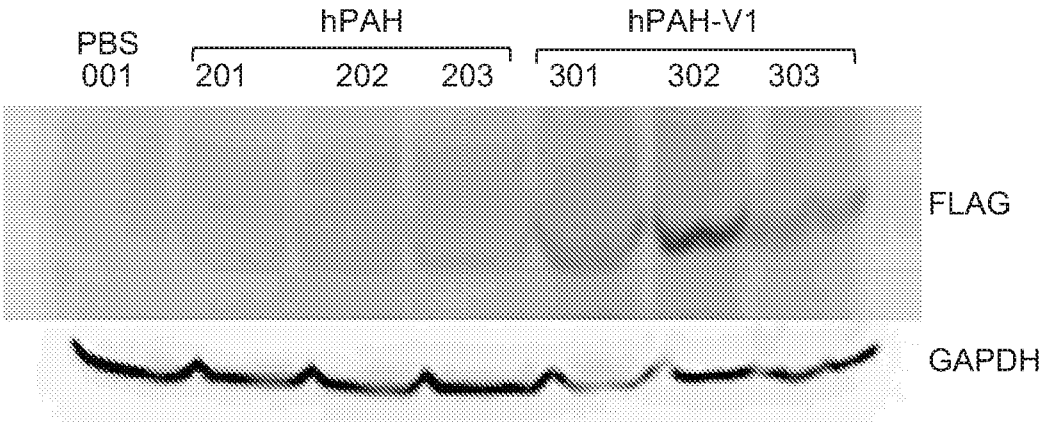


FIG. 17C