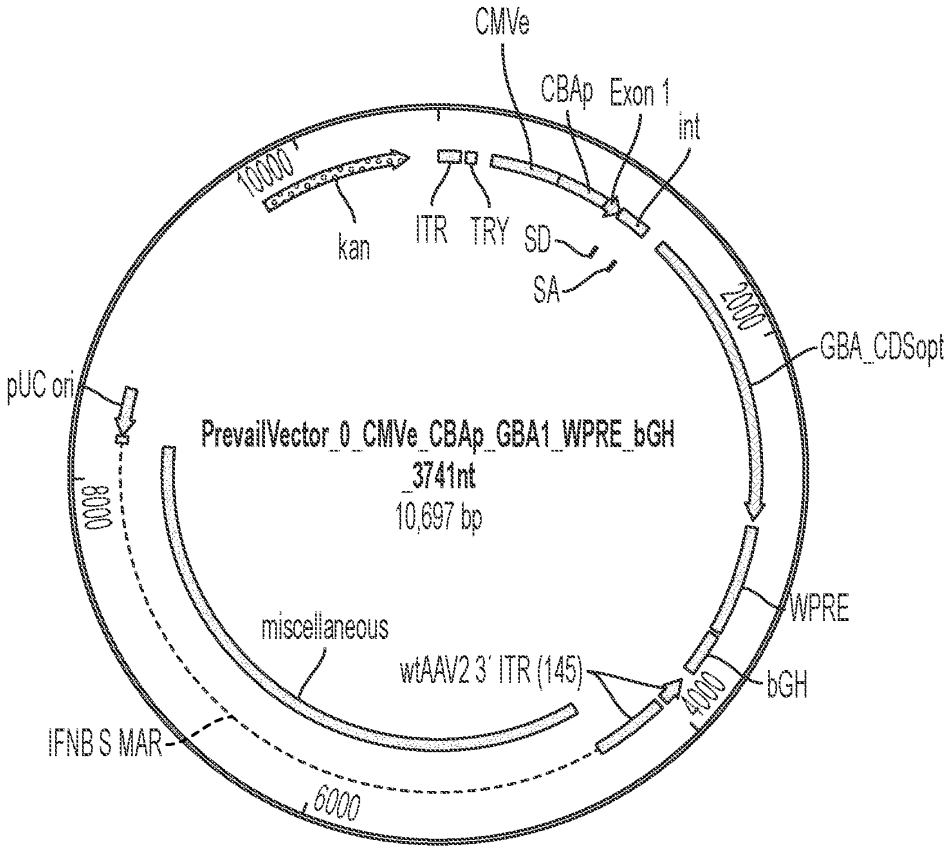

CMVe
CBAp
Exon 1
int
1000
kan
ITR
TRY
SD
SA
2000
GBA_CDSopt
pUC ori
PrevailVector_0_CMVe_CBAp_GBA1_WPRE_bGH
_3741nt
10,697 bp
8000
WPRE
miscellaneous
wtAAV2 3' ITR (145)
bGH
4000
IFNB S MAR
6000

FIG. 1

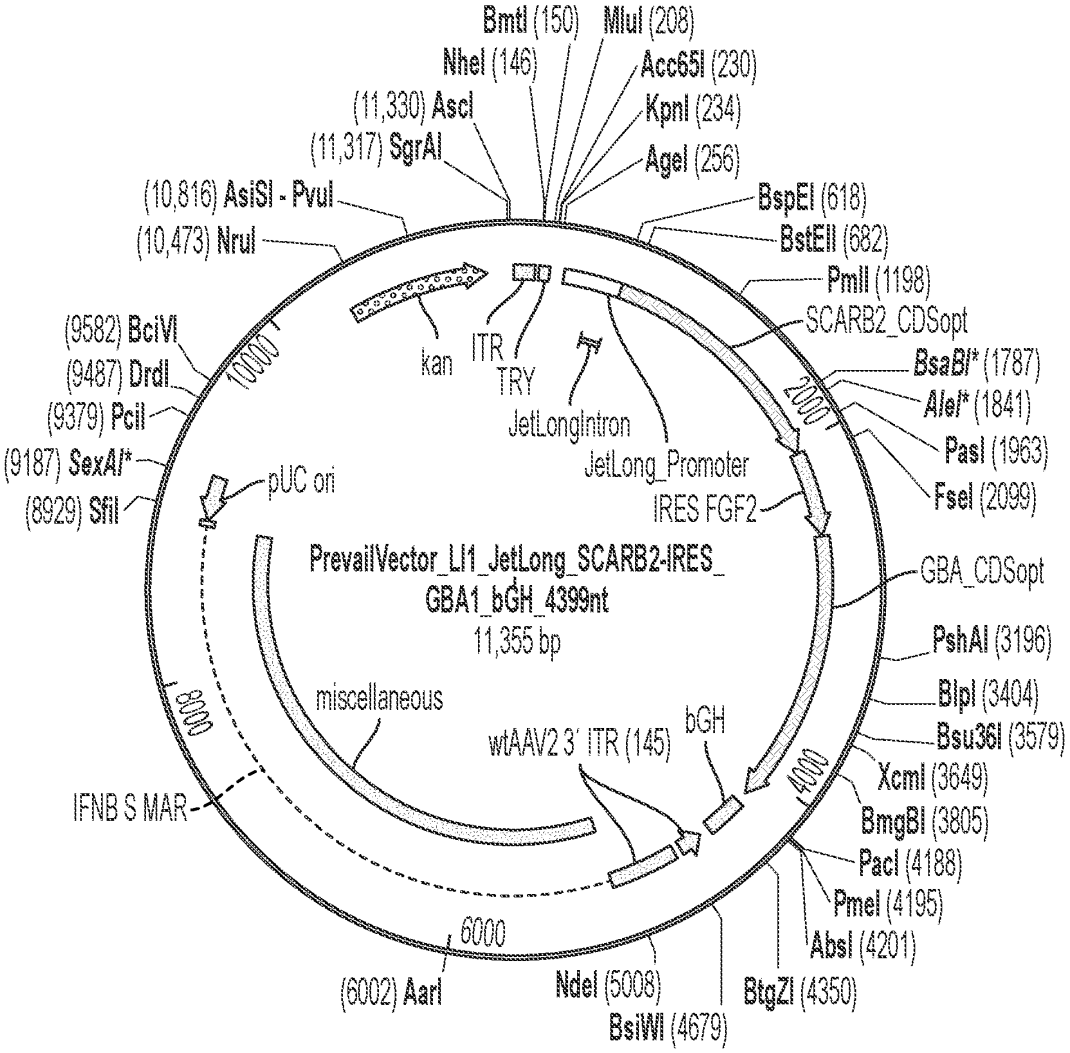
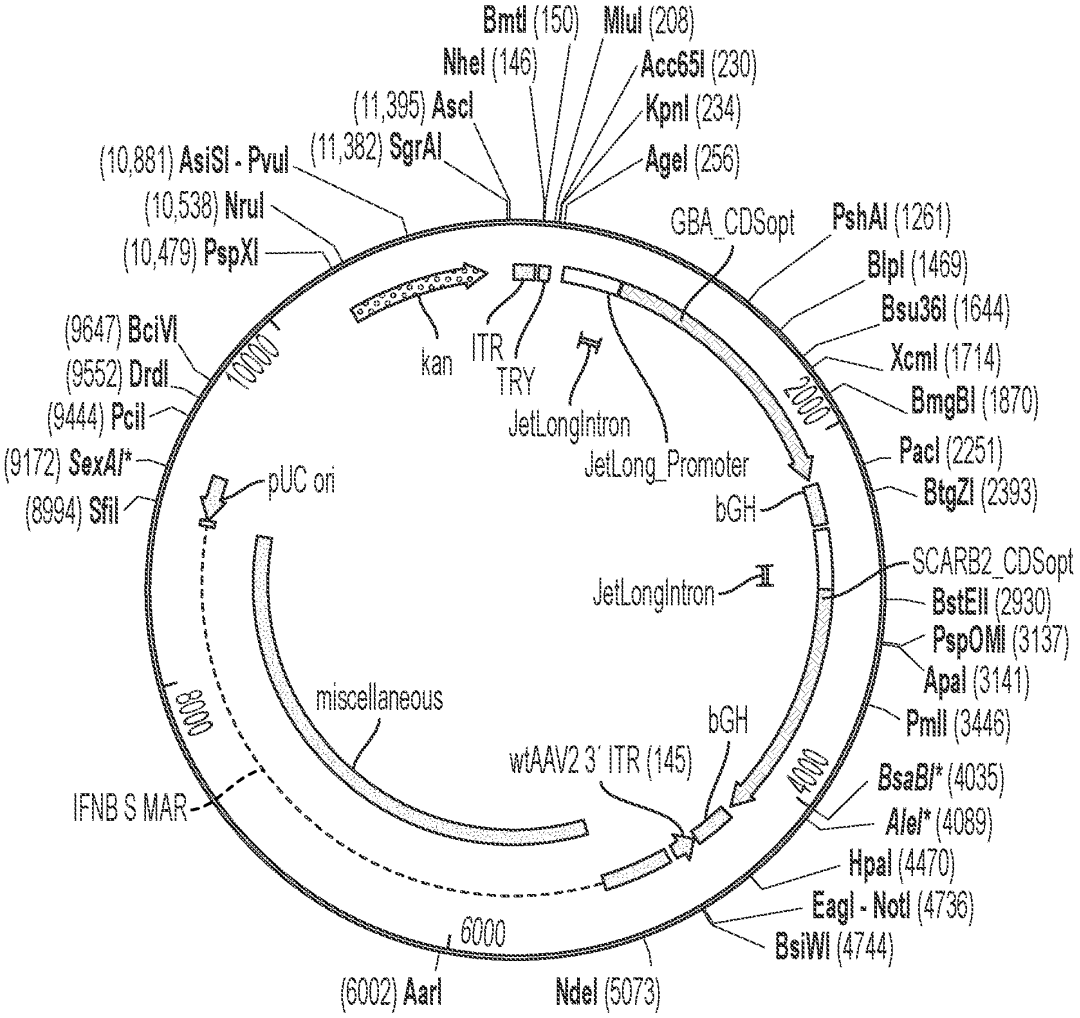

BmtI (150)
MluI (208)
NheI (146)
Acc65I (230)
(11,330) AscI
KpnI (234)
(11,317) SgrAI
AgeI (256)
(10,816) AsiSI - PvuI
BspEI (618)
(10,473) NruI
BstEII (682)
PmlI (1198)
SCARB2_CDSopt
(9582) BciVI
(9487) DrdI
(9379) PciI
(9187) SexAI*
(8929) SfiI
10000
kan
ITR
TRY
JetLongIntron
JetLong_Promoter
2000
BsaBI* (1787)
AleI* (1841)
PasI (1963)
FseI (2099)
pUC ori
IRES FGF2
PrevailVector_LI1_JetLong_SCARB2-IRES_
GBA1_bGH_4399nt
11,355 bp
GBA_CDSopt
PshAI (3196)
BlpI (3404)
miscellaneous
bGH
wtAAV2 3' ITR (145)
Bsu36I (3579)
8000
4000
XcmI (3649)
BmgBI (3805)
IFNB S MAR
PacI (4188)
PmeI (4195)
AbsI (4201)
6000
(6002) AarI
NdeI (5008)
BtgZI (4350)
BsiWI (4679)

FIG. 2



PrevailVector_FP1_JetLong_GBA1_bGH_JetLong_SCARB2_SV40L_4464nt
11,420 bp

FIG. 3

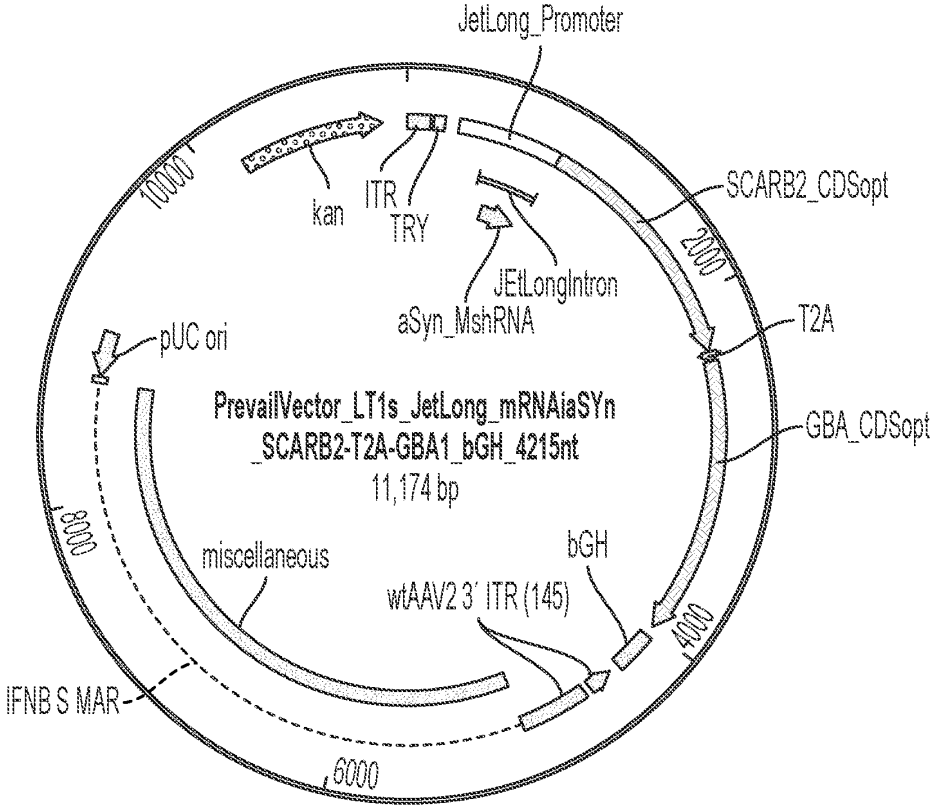

JetLong_Promoter
SCARB2_CDSopt
T2A
GBA_CDSopt
bGH
wtAAV2 3' ITR (145)
miscellaneous
IFNB S MAR
pUC ori
aSyn_MshRNA
JEtLongIntron
ITR
TRY
kan
PrevailVector_LT1s_JetLong_mRNAiaSYn
_SCARB2-T2A-GBA1_bGH_4215nt
11,174 bp
2000
4000
6000
8000
10000

FIG. 4

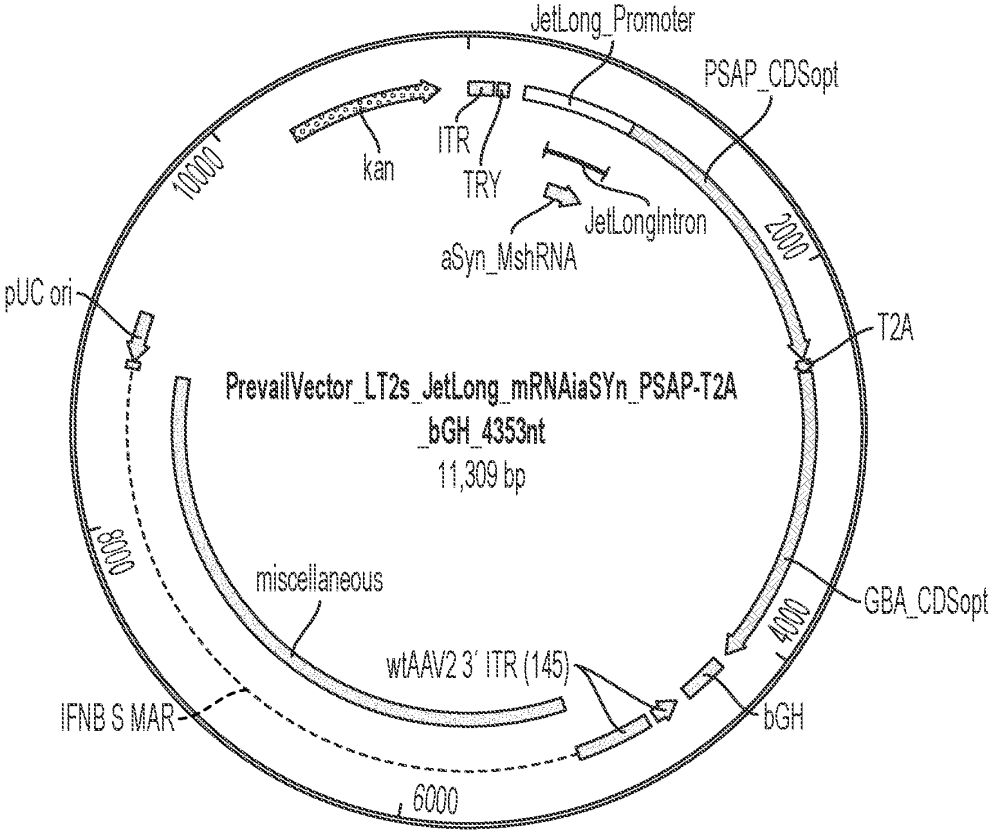

JetLong_Promoter
PSAP_CDSopt
kan
ITR
TRY
JetLongIntron
aSyn_MshRNA
pUC ori
T2A
PrevailVector_LT2s_JetLong_mRNAiaSYn_PSAP-T2A
_bGH_4353nt
11,309 bp
miscellaneous
GBA_CDSopt
wtAAV2 3' ITR (145)
bGH
IFNB S MAR
2000
4000
6000
8000
10000

FIG. 5

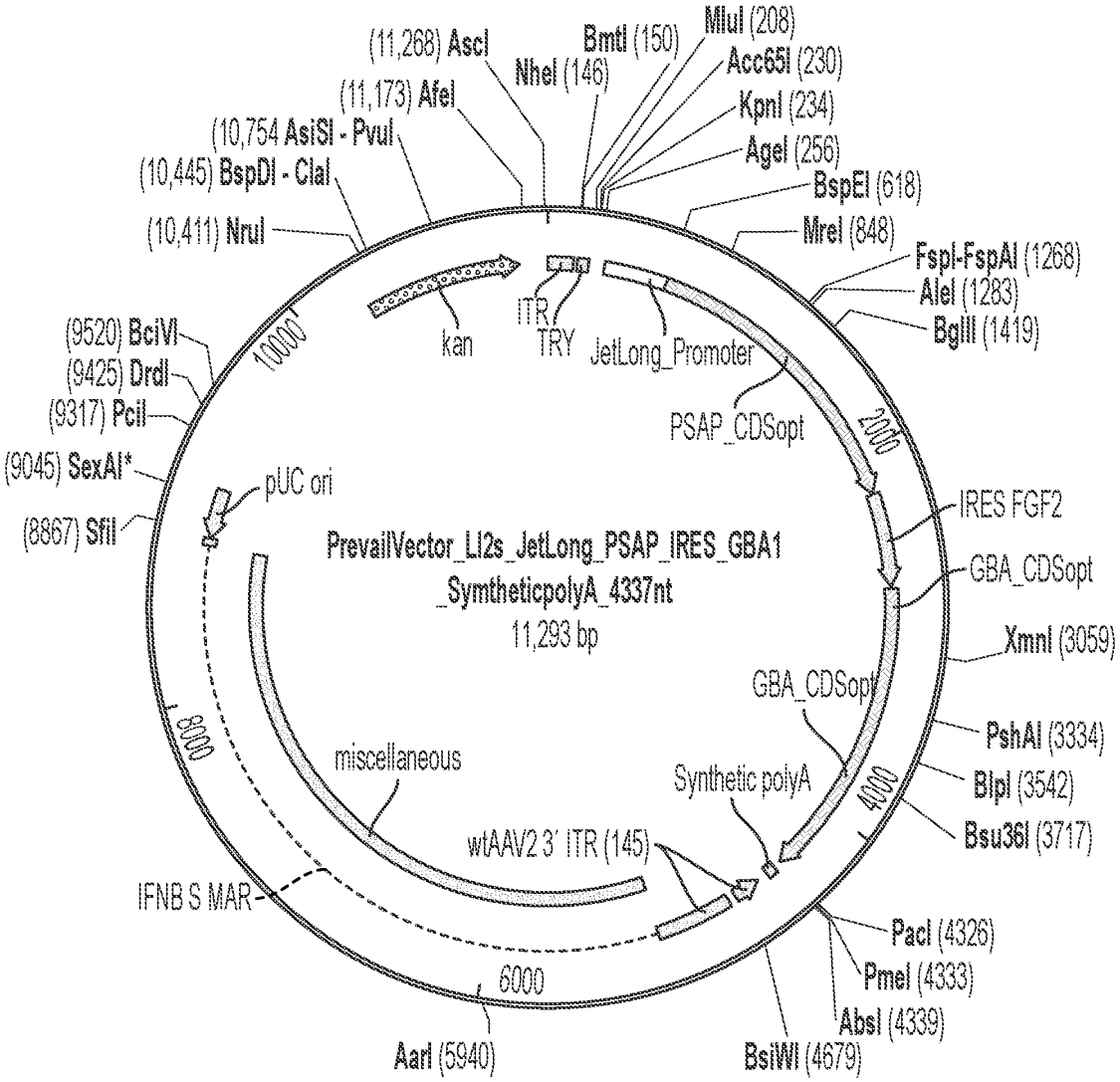

(11,268) AscI
BmtI (150)
MluI (208)
NheI (146)
Acc65I (230)
(11,173) AfeI
KpnI (234)
(10,754 AsiSI - PvuI
AgeI (256)
(10,445) BspDI - ClaI
BspEI (618)
(10,411) NruI
MreI (848)
FspI-FspAI (1268)
AleI (1283)
BglII (1419)
ITR
kan
TRY
JetLong_Promoter
(9520) BciVI
(9425) DrdI
(9317) PciI
PSAP_CDSopt
(9045) SexAI*
pUC ori
IRES FGF2
(8867) SfiI
PrevailVector_LI2s_JetLong_PSAP_IRES_GBA1
_SyntheticpolyA_4337nt
11,293 bp
GBA_CDSopt
XmnI (3059)
GBA_CDSopt
PshAI (3334)
miscellaneous
Synthetic polyA
BlpI (3542)
wtAAV2 3' ITR (145)
Bsu36I (3717)
IFNB S MAR
PacI (4326)
PmeI (4333)
AbsI (4339)
AarI (5940)
BsiWI (4679)

FIG. 6

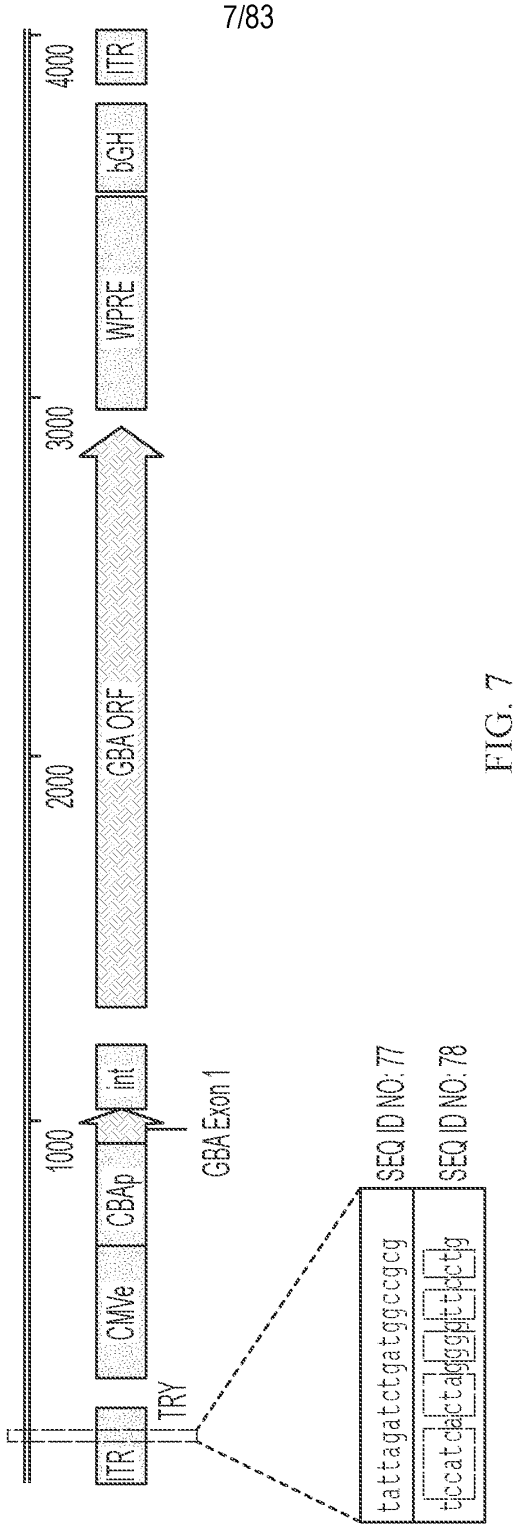

1000
2000
3000
4000
ITR
CMVe
CBAp
int.
TRY
GBA Exon 1
GBA ORF
WPRE
bGH
ITR
SEQ ID NO: 77
tattagatctgatggccgcg
SEQ ID NO: 78

FIG. 7

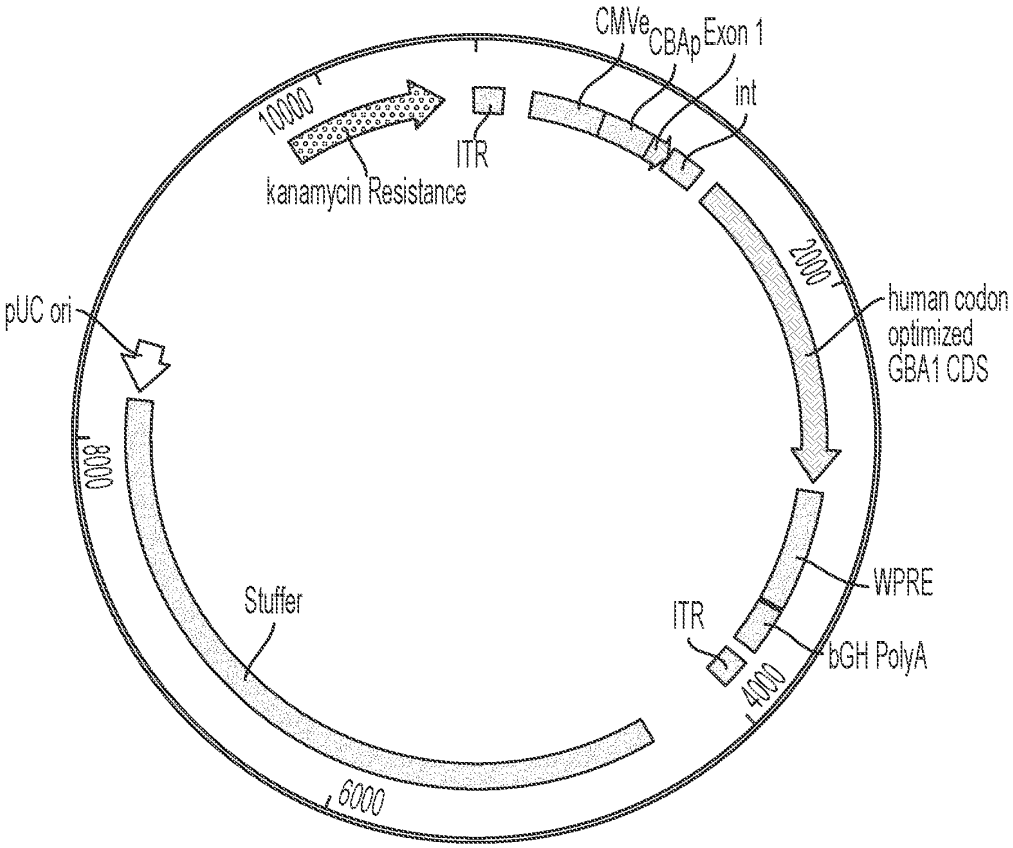

CMVe
CBAp
Exon 1
int
10000
ITR
kanamycin Resistance
2000
human codon optimized GBA1 CDS
pUC ori
8000
Stuffer
WPRE
ITR
bGH PolyA
4000
6000

FIG. 8

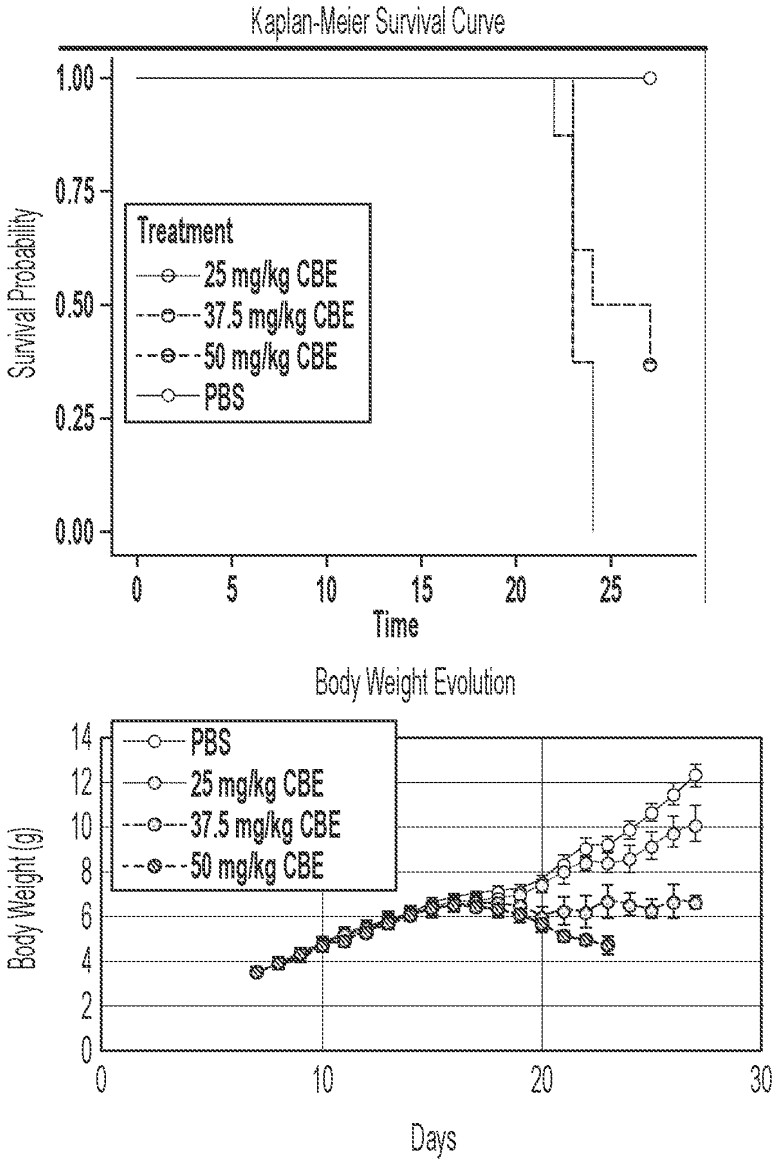

Kaplan-Meier Survival Curve
Survival Probability
1.00
0.75
0.50
0.25
0.00
Treatment
25 mg/kg CBE
37.5 mg/kg CBE
50 mg/kg CBE
PBS
0
5
10
15
20
25
Time
Body Weight Evolution
Body Weight (g)
14
12
10
8
6
4
2
0
PBS
25 mg/kg CBE
37.5 mg/kg CBE
50 mg/kg CBE
0
10
20
30
Days

FIG. 9

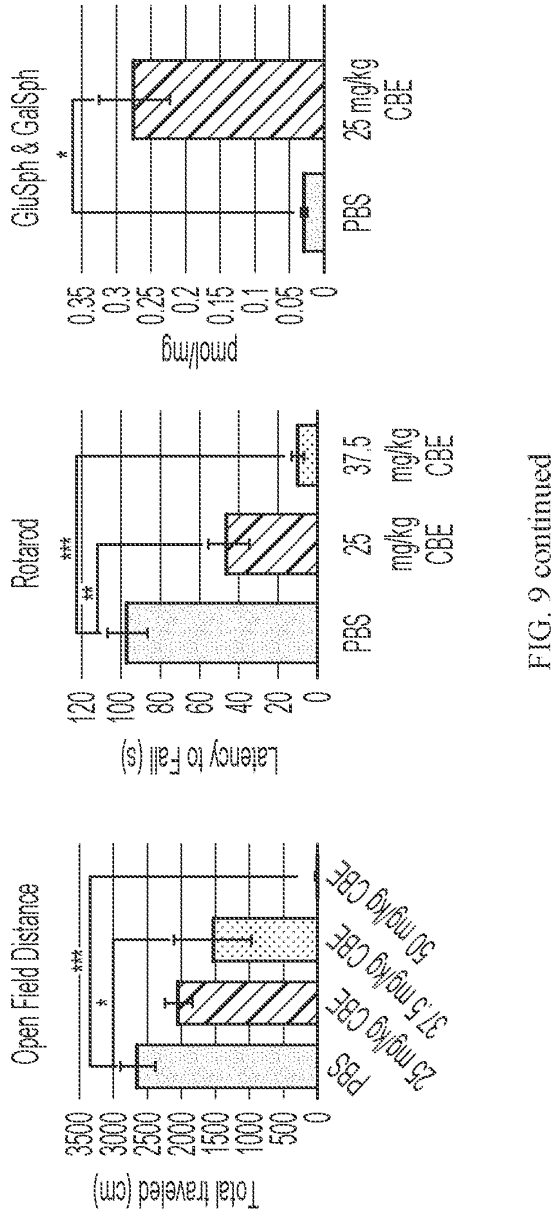
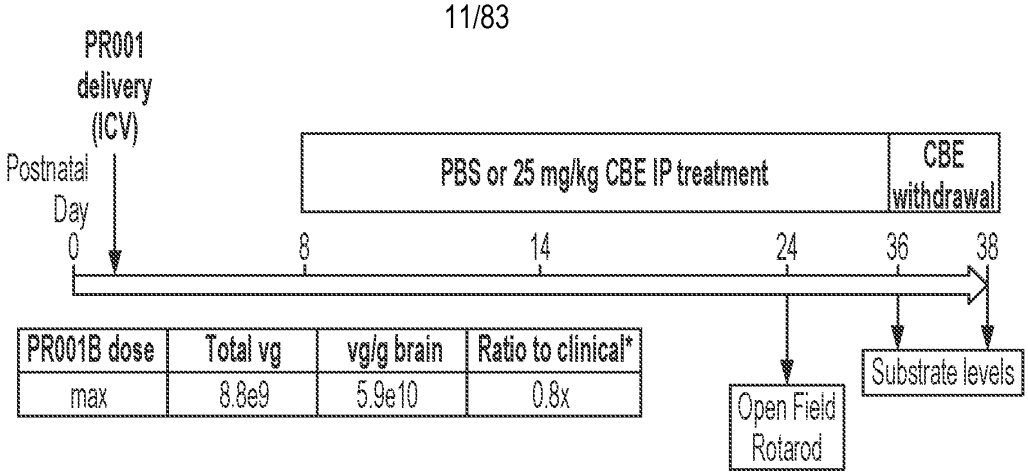


FIG. 9 continued



PR001B dose	Total vg	vg/g brain	Ratio to clinical*
max	8.8e9	5.9e10	0.8x

FIG. 10

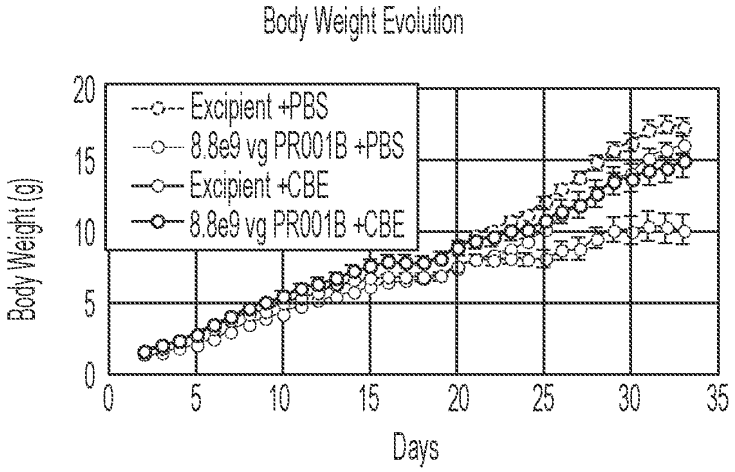


FIG. 11

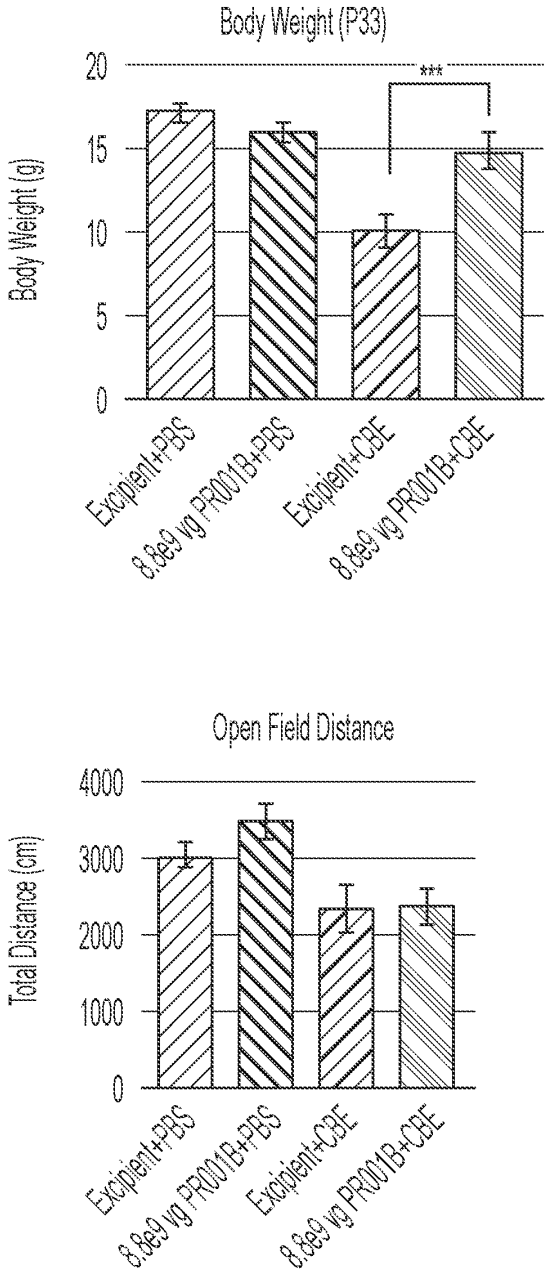


FIG. 11 continued

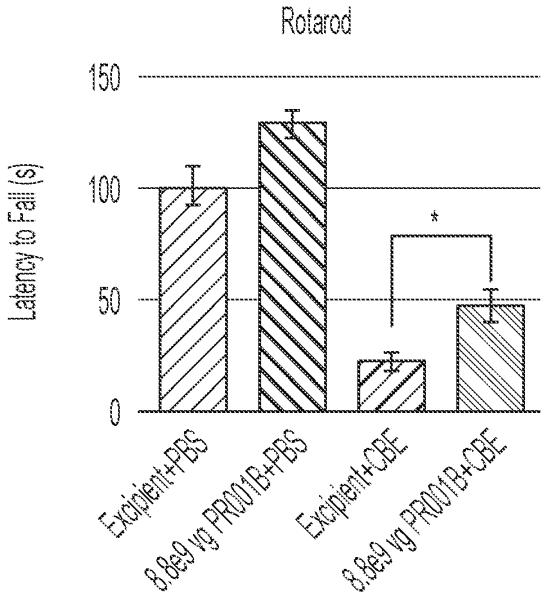


FIG. 11 continued

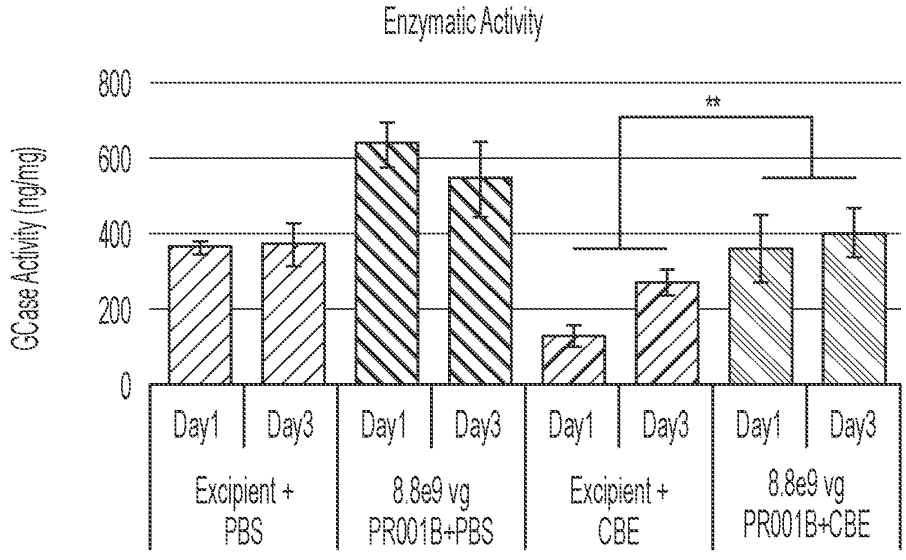


FIG. 12

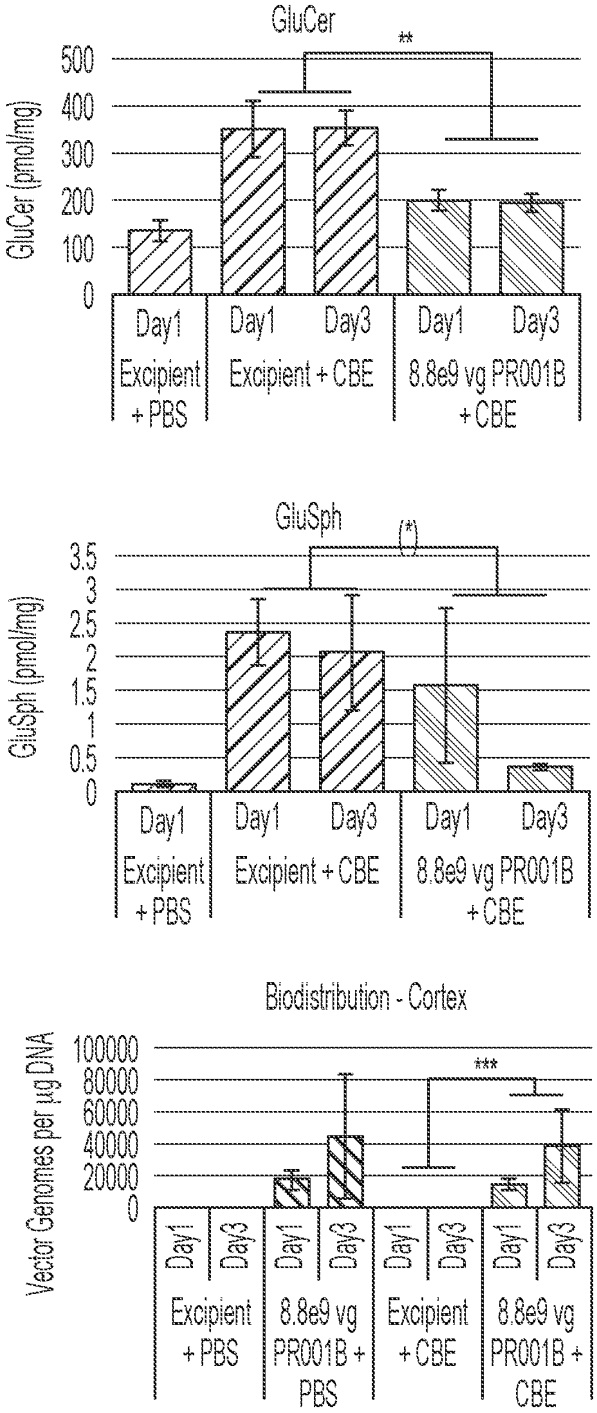


FIG. 12 continued

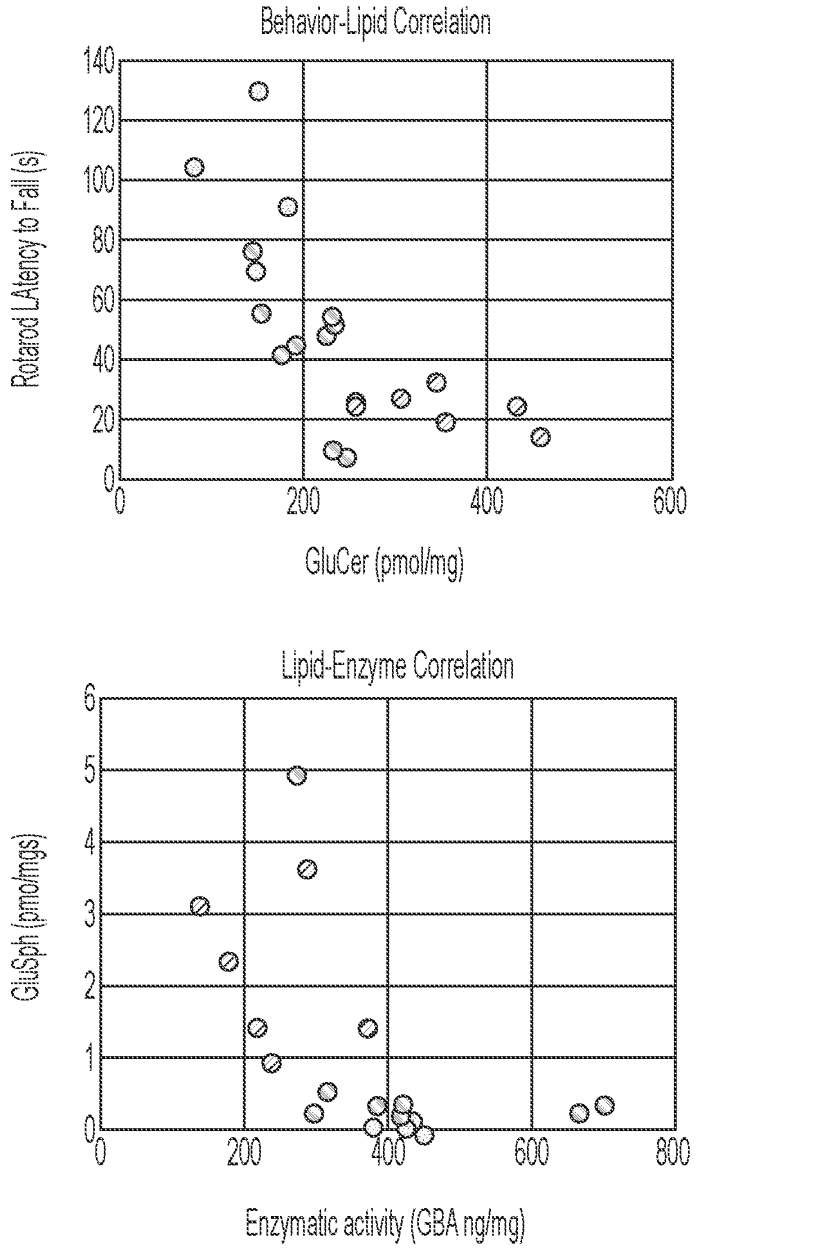

Behavior-Lipid Correlation
Rotarod LAtency to Fall (s)
140
120
100
80
60
40
20
0
0
200
400
600
GluCer (pmol/mg)
Lipid-Enzyme Correlation
GluSph (pmo/mgs)
6
5
4
3
2
1
0
0
200
400
600
800
Enzymatic activity (GBA ng/mg)
Excipient + PBS
Excipient + CBE
8.8e9 vg PR001B + CBE

FIG. 13

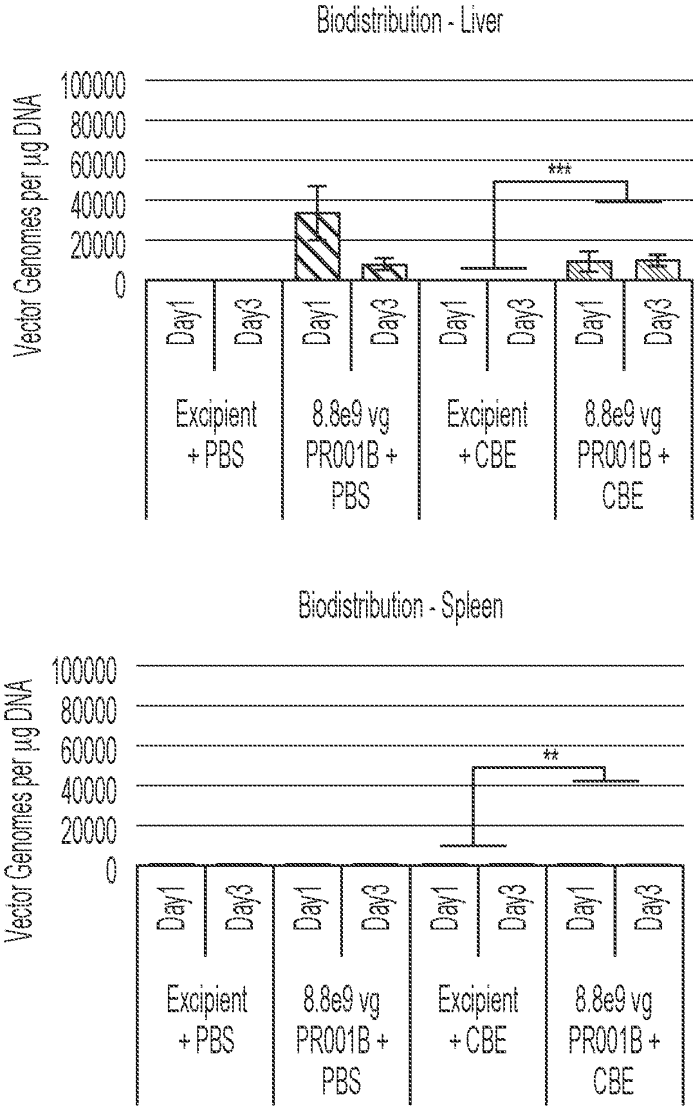

Biodistribution - Liver
Vector Genomes per µg DNA
100000
80000
60000
40000
20000
0
***
Day1
Day3
Excipient + PBS
8.8e9 vg PR001B + PBS
Excipient + CBE
8.8e9 vg PR001B + CBE
Biodistribution - Spleen
Vector Genomes per µg DNA
100000
80000
60000
40000
20000
0
**
Day1
Day3
Excipient + PBS
8.8e9 vg PR001B + PBS
Excipient + CBE
8.8e9 vg PR001B + CBE

FIG. 14

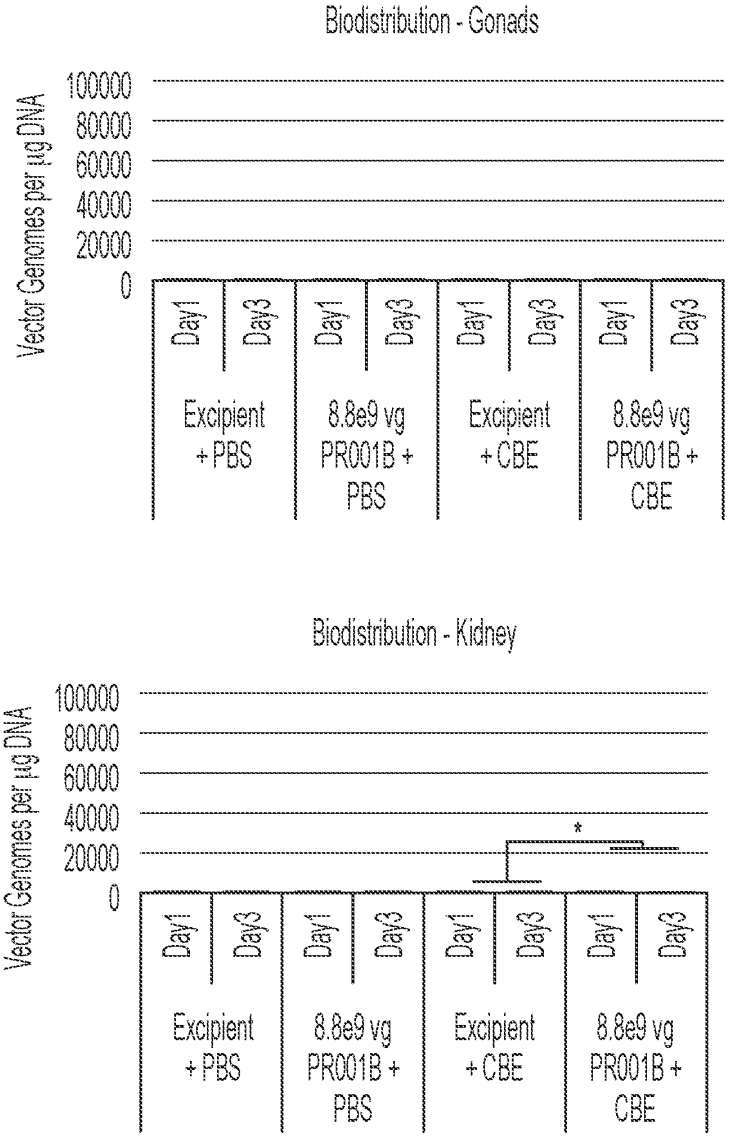


FIG. 14 continued

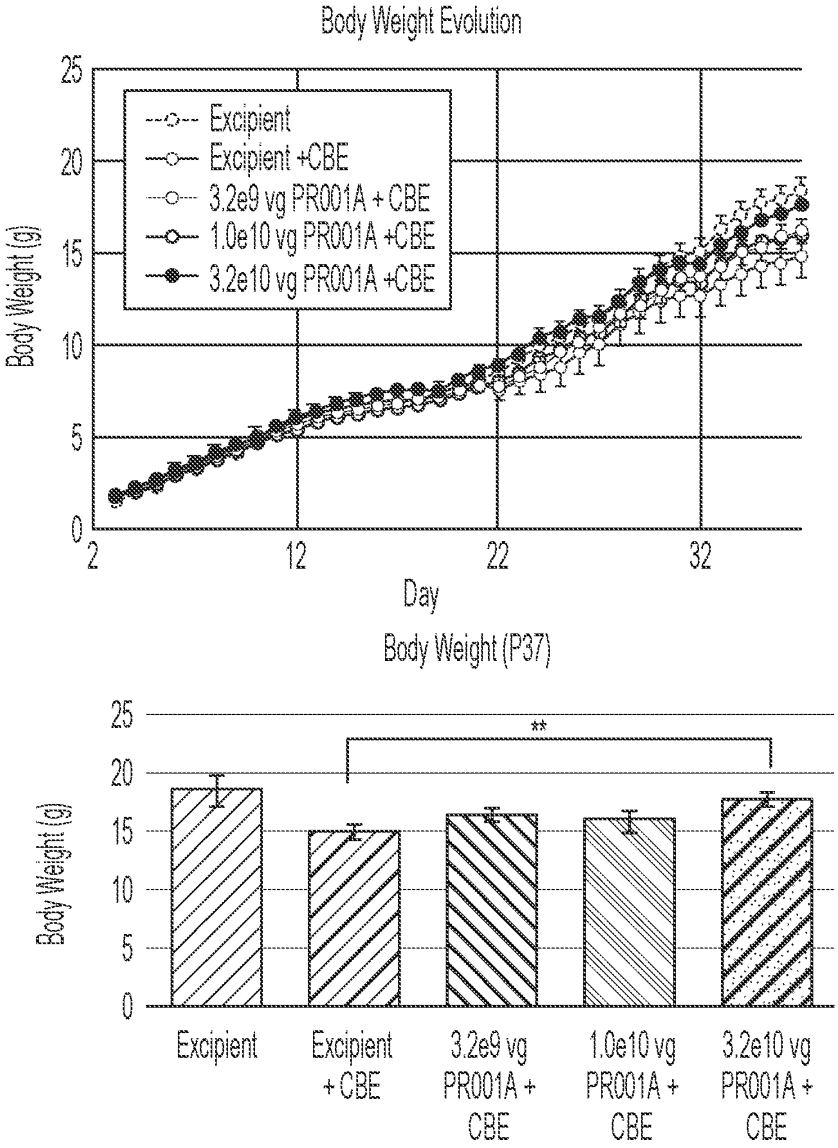

Body Weight Evolution
Body Weight (g)
25
20
15
10
5
0
2
12
22
32
Day
Excipient
Excipient +CBE
3.2e9 vg PR001A + CBE
1.0e10 vg PR001A +CBE
3.2e10 vg PR001A +CBE
Body Weight (P37)
Body Weight (g)
25
20
15
10
5
0
**
Excipient
Excipient + CBE
3.2e9 vg PR001A + CBE
1.0e10 vg PR001A + CBE
3.2e10 vg PR001A + CBE

FIG. 15

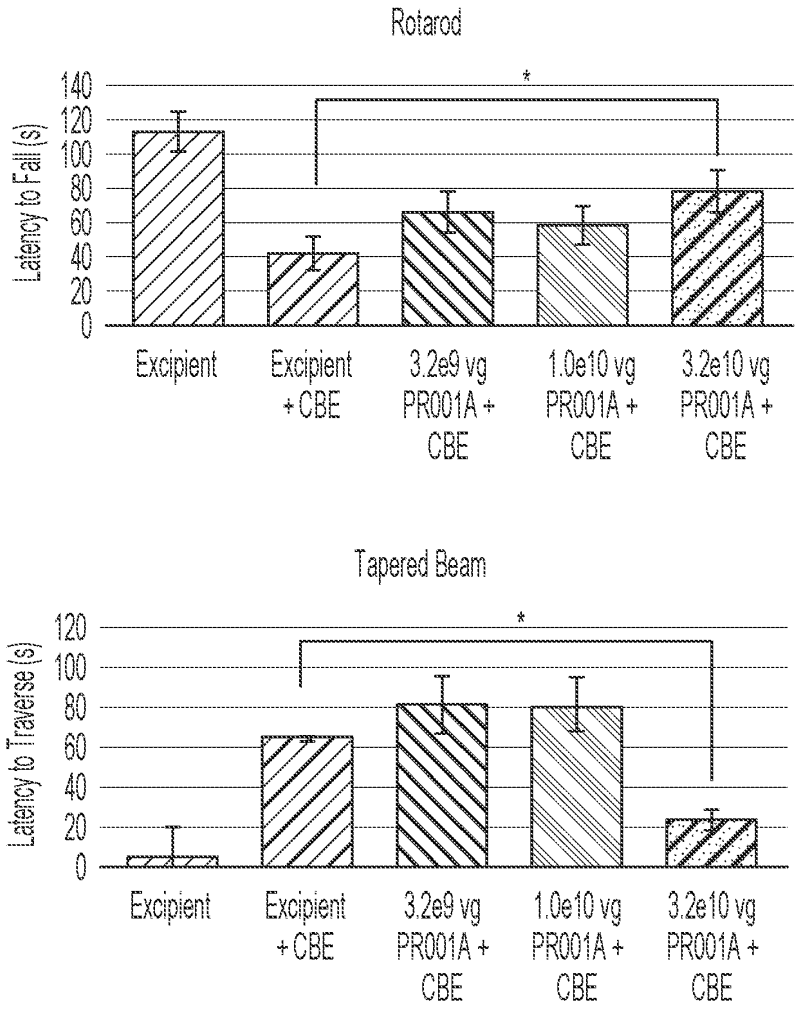


FIG. 15 continued

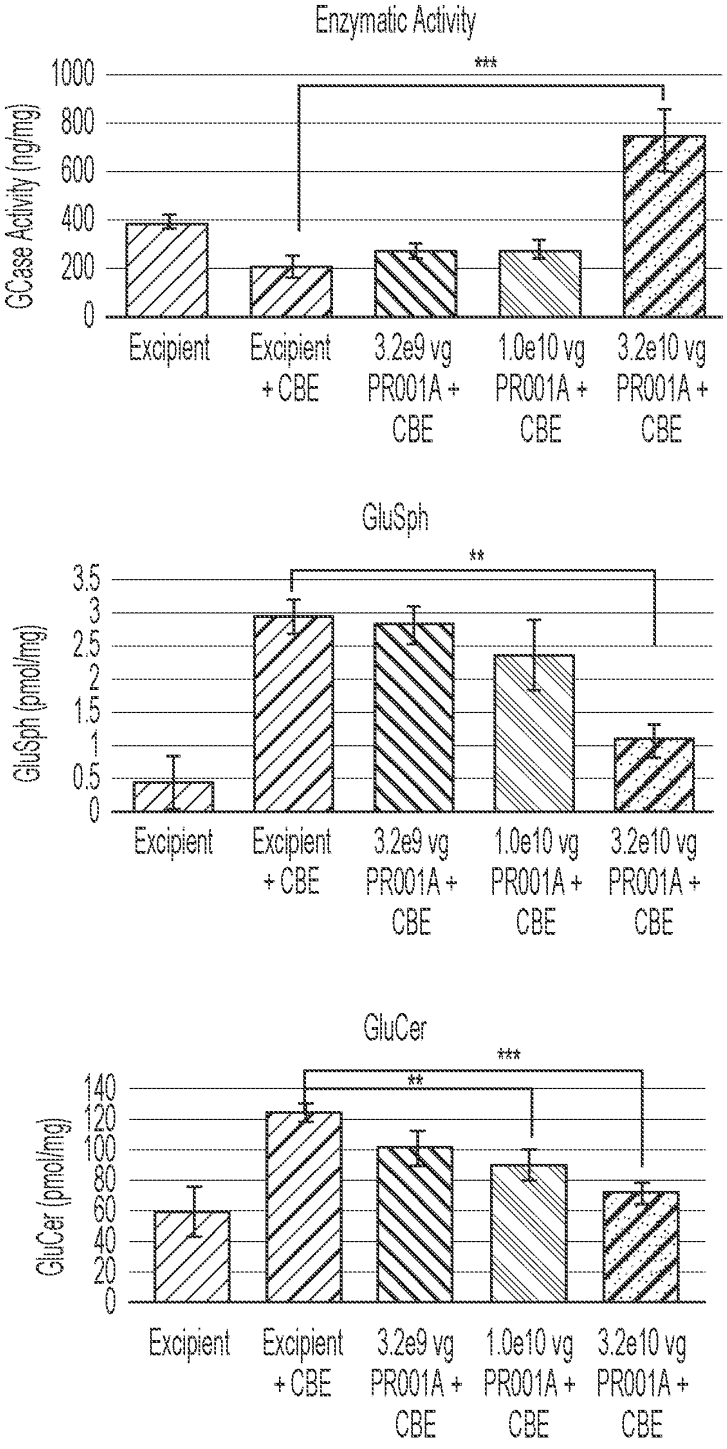

Enzymatic Activity
GCase Activity (ng/mg)
1000
800
600
400
200
0
***
Excipient
Excipient + CBE
3.2e9 vg PR001A + CBE
1.0e10 vg PR001A + CBE
3.2e10 vg PR001A + CBE
GluSph
GluSph (pmol/mg)
3.5
3
2.5
2
1.5
1
0.5
0
**
Excipient
Excipient + CBE
3.2e9 vg PR001A + CBE
1.0e10 vg PR001A + CBE
3.2e10 vg PR001A + CBE
GluCer
GluCer (pmol/mg)
140
120
100
80
60
40
20
0
***
**
Excipient
Excipient + CBE
3.2e9 vg PR001A + CBE
1.0e10 vg PR001A + CBE
3.2e10 vg PR001A + CBE

FIG. 16

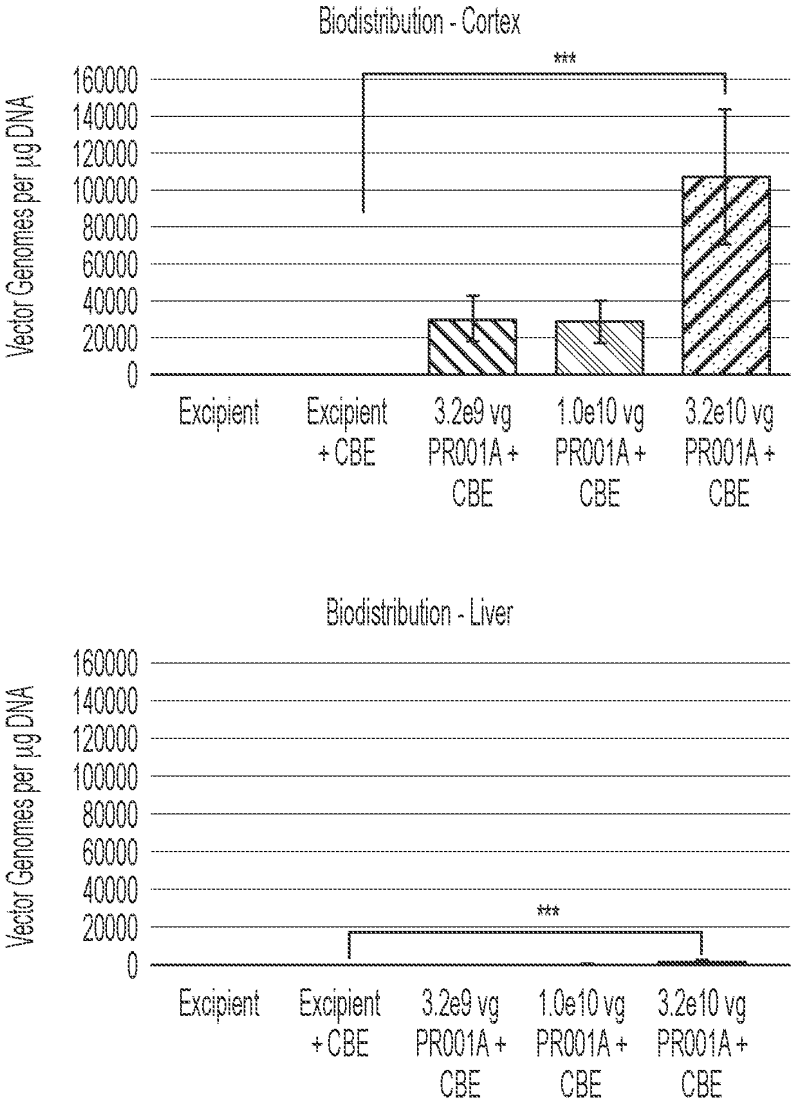


FIG. 16 continued

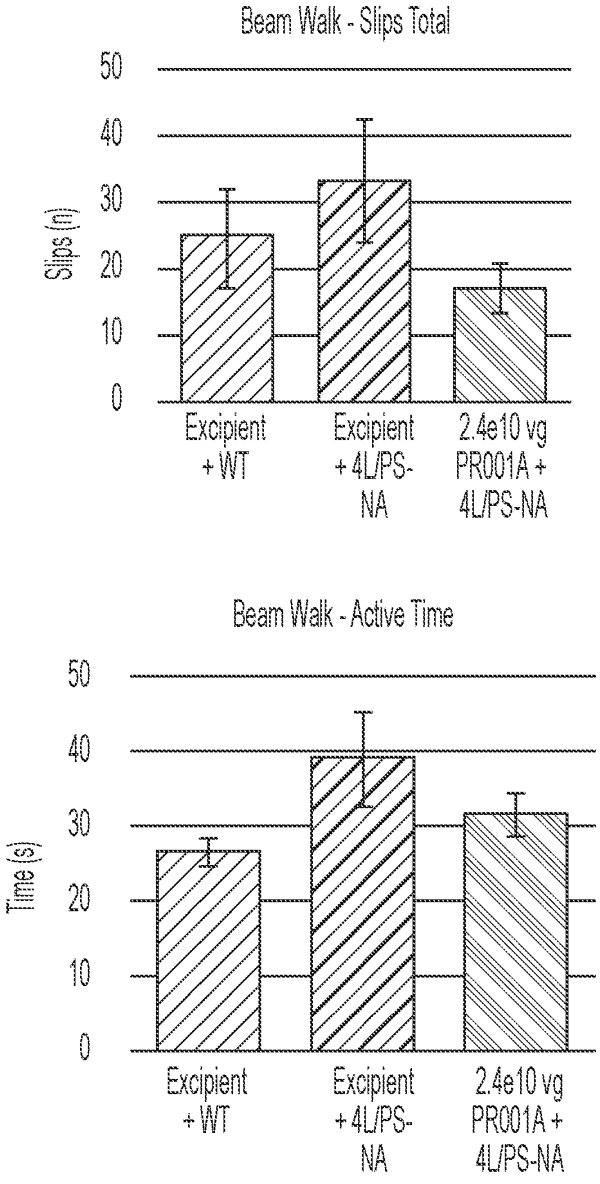

Beam Walk - Slips Total
Slips (n)
50
40
30
20
10
0
Excipient + WT
Excipient + 4L/PS-NA
2.4e10 vg PR001A + 4L/PS-NA
Beam Walk - Active Time
Time (s)
50
40
30
20
10
0
Excipient + WT
Excipient + 4L/PS-NA
2.4e10 vg PR001A + 4L/PS-NA

FIG. 17

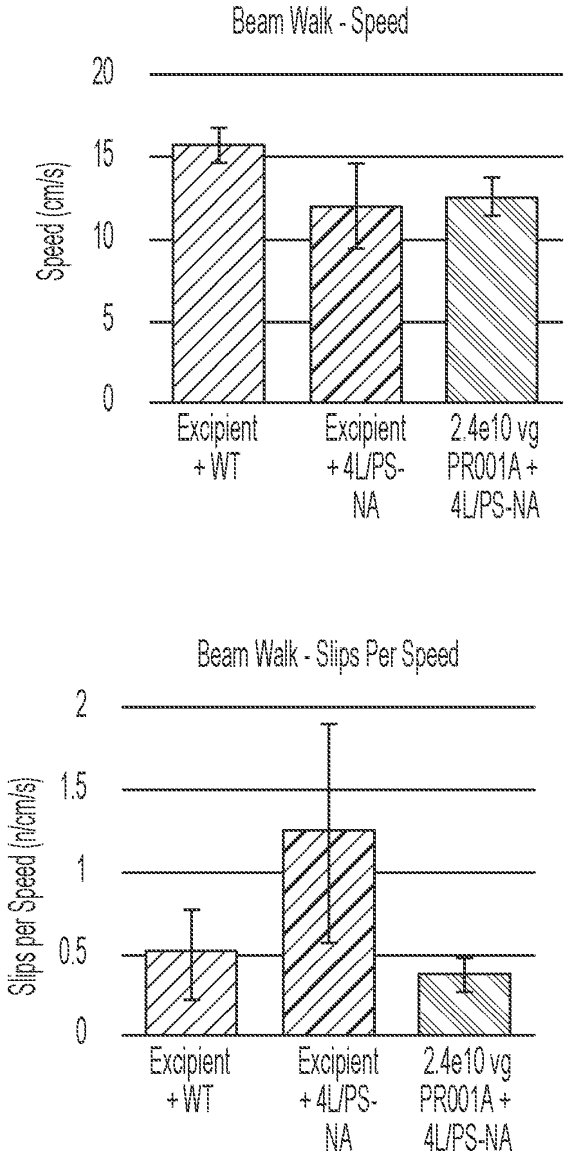

Beam Walk - Speed
Speed (cm/s)
20
15
10
5
0
Excipient + WT
Excipient + 4L/PS-NA
2.4e10 vg PR001A + 4L/PS-NA
Beam Walk - Slips Per Speed
Slips per Speed (n/cm/s)
2
1.5
1
0.5
0
Excipient + WT
Excipient + 4L/PS-NA
2.4e10 vg PR001A + 4L/PS-NA

FIG. 17 cont.

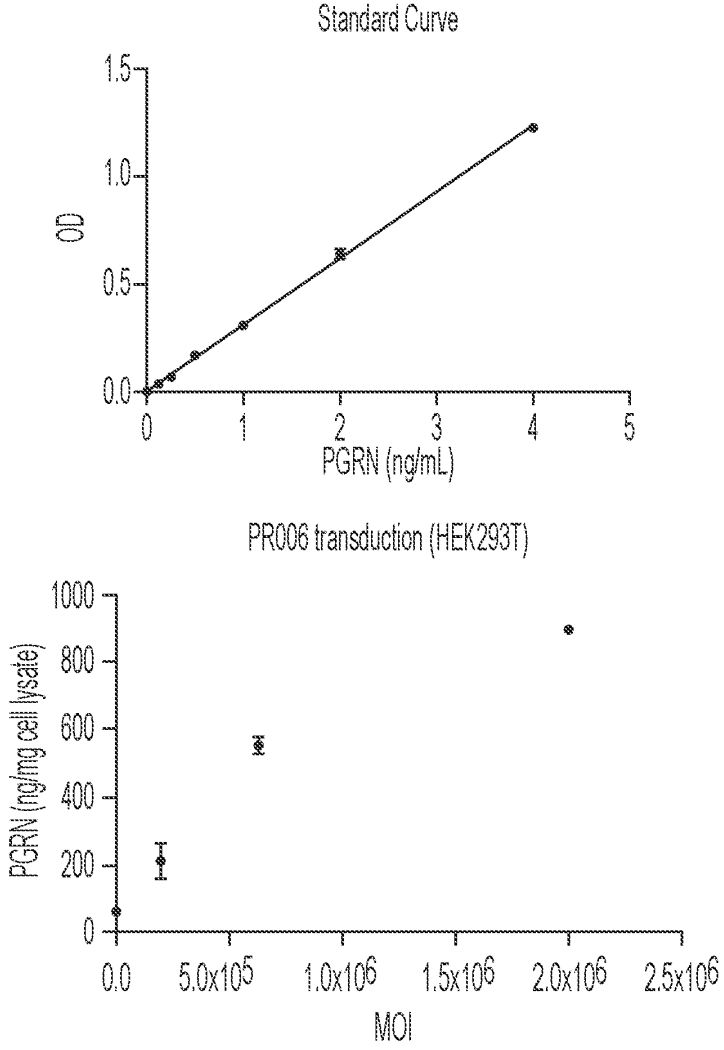

Standard Curve
OD
1.5
1.0
0.5
0.0
0
1
2
3
4
5
PGRN (ng/mL)
PR006 transduction (HEK293T)
PGRN (ng/mg cell lysate)
1000
800
600
400
200
0
0.0
5.0x10^5
1.0x10^6
1.5x10^6
2.0x10^6
2.5x10^6
MOI

FIG. 18

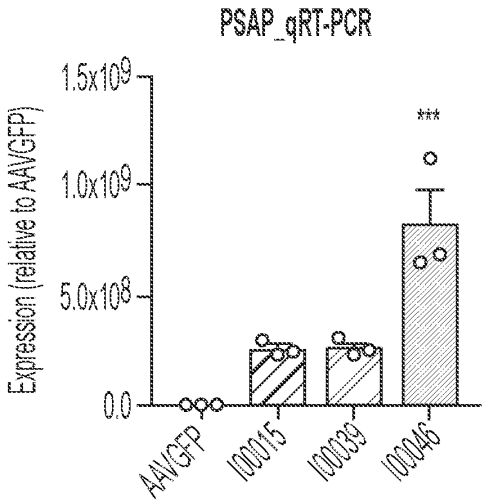

PSAP_qRT-PCR
Expression (relative to AAVGFP)
1.5x10^9
1.0x10^9
5.0x10^8
0.0
***
AAVGFP
I00015
I00039
I00046

FIG. 19

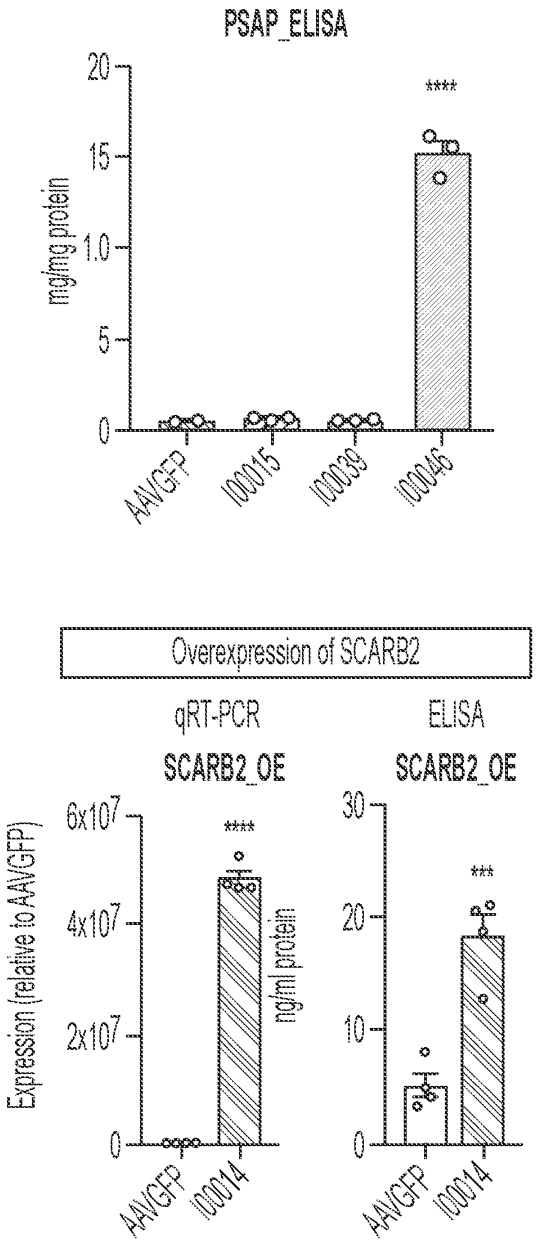


FIG. 19 continued

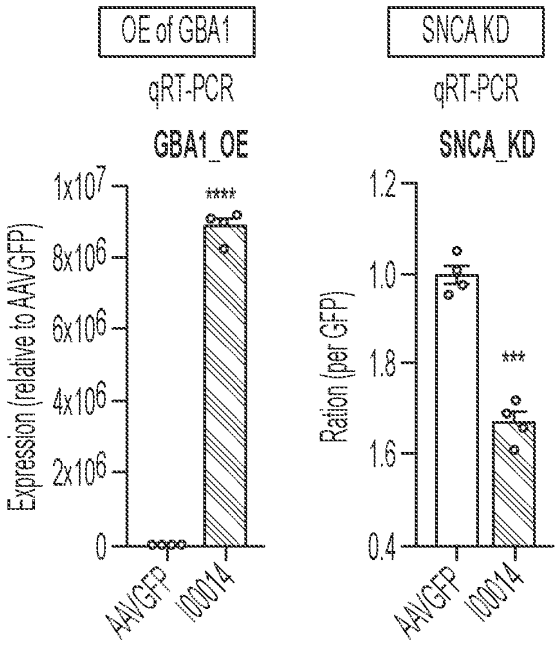


FIG. 19 continued

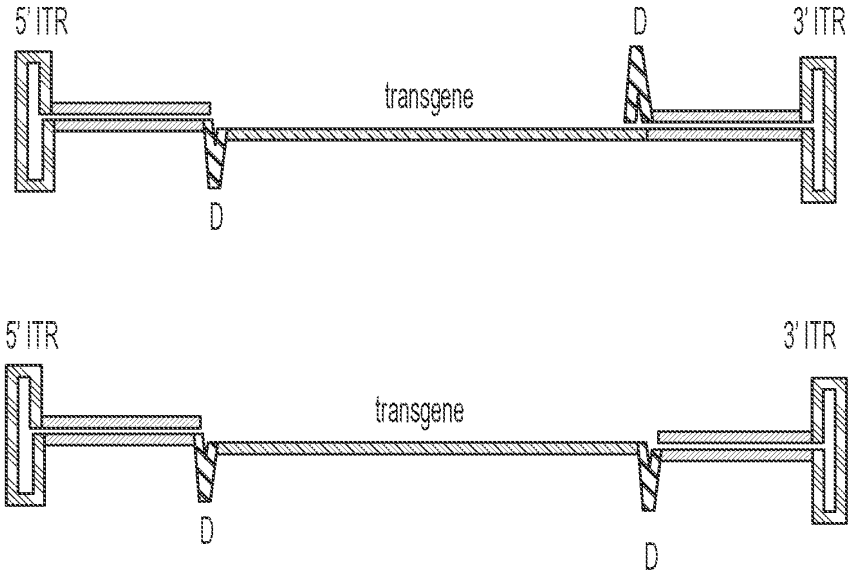


FIG. 20

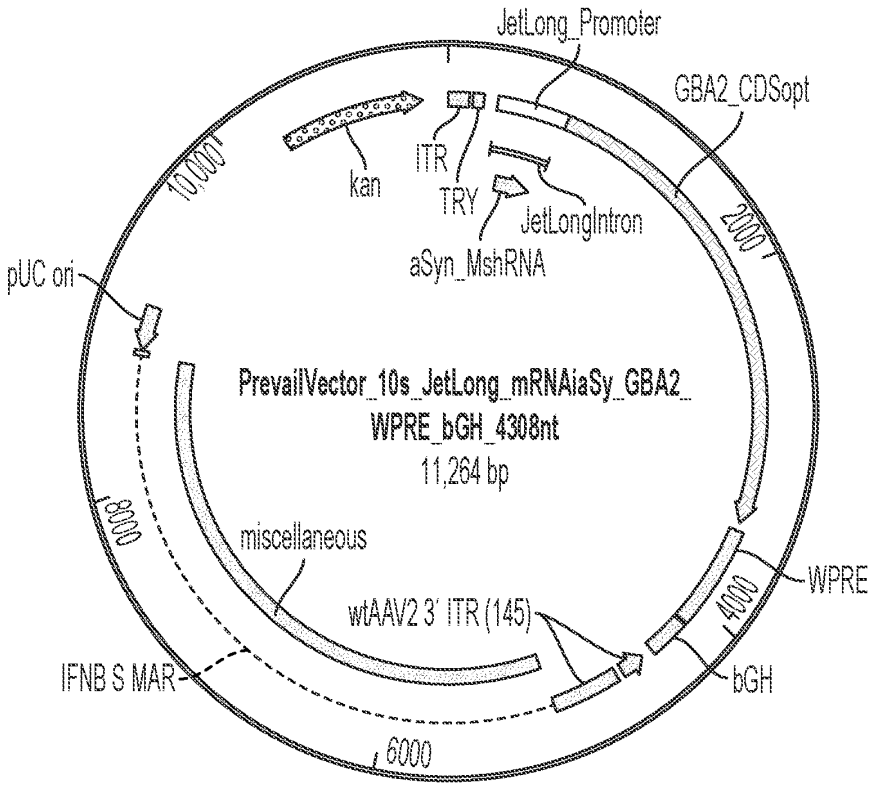

JetLong_Promoter
GBA2_CDSopt
ITR
kan
TRY
JetLongIntron
aSyn_MshRNA
pUC ori
PrevailVector_10s_JetLong_mRNAiaSy_GBA2_
WPRE_bGH_4308nt
11,264 bp
miscellaneous
wtAAV2 3' ITR (145)
WPRE
bGH
IFNB S MAR
10,000
2000
4000
6000
8000

FIG. 21

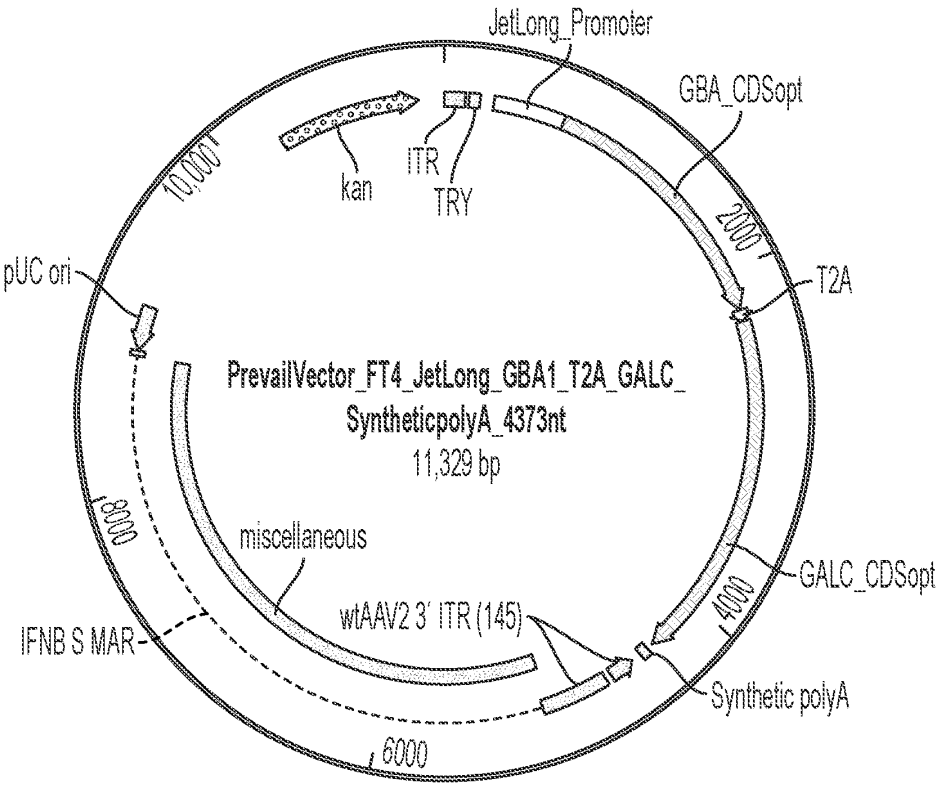

JetLong_Promoter
GBA_CDSopt
kan
ITR
TRY
10,000
2000
T2A
pUC ori
PrevailVector_FT4_JetLong_GBA1_T2A_GALC_
SyntheticpolyA_4373nt
11,329 bp
8000
miscellaneous
GALC_CDSopt
4000
wtAAV2 3' ITR (145)
IFNB S MAR
Synthetic polyA
6000

FIG. 22

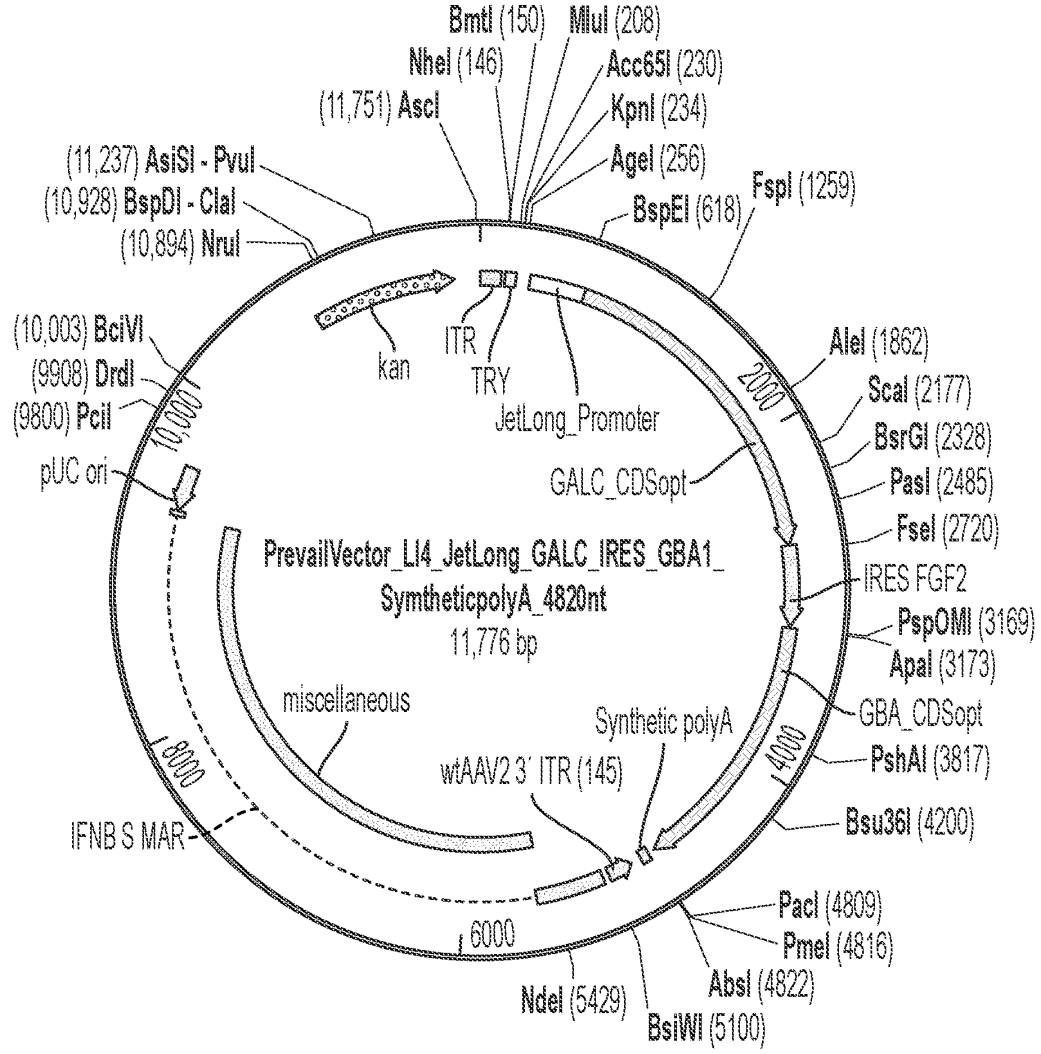
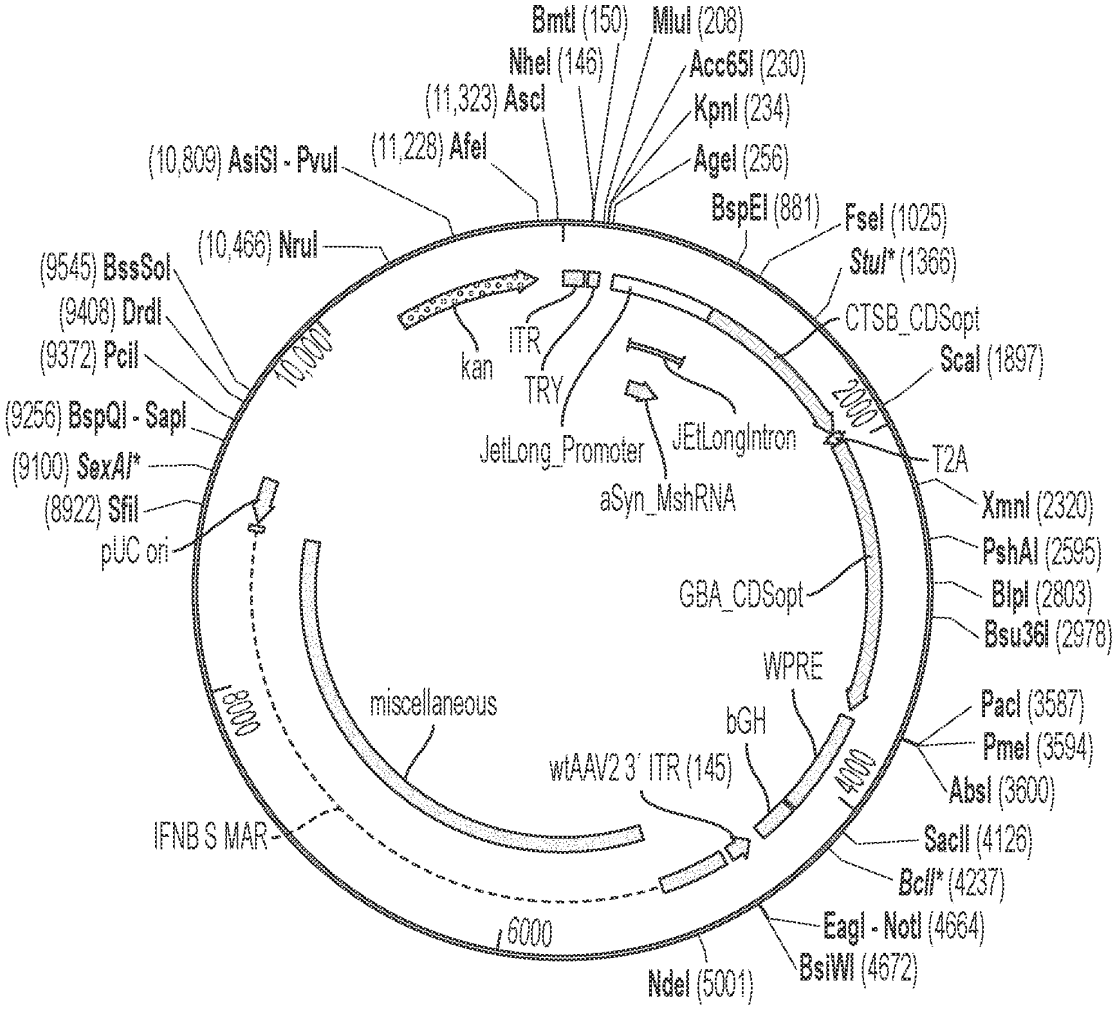

BmtI (150)
MluI (208)
NheI (146)
Acc65I (230)
(11,751) AscI
KpnI (234)
(11,237) AsiSI - PvuI
AgeI (256)
(10,928) BspDI - ClaI
BspEI (618)
FspI (1259)
(10,894) NruI
(10,003) BciVI
AleI (1862)
(9908) DrdI
ScaI (2177)
(9800) PciI
BsrGI (2328)
pUC ori
PasI (2485)
GALC_CDSopt
FseI (2720)
PrevailVector_LI4_JetLong_GALC_IRES_GBA1_
SyntheticpolyA_4820nt
IRES FGF2
11,776 bp
PspOMI (3169)
ApaI (3173)
miscellaneous
GBA_CDSopt
Synthetic polyA
wtAAV2 3' ITR (145)
PshAI (3817)
Bsu36I (4200)
IFNB S MAR
PacI (4809)
PmeI (4816)
AbsI (4822)
NdeI (5429)
BsiWI (5100)
kan
ITR
TRY
JetLong_Promoter
2000
4000
6000
8000
10,000

FIG. 23



PrevailVector_LTSs_JetLong_mRNAiaSyn_CTSB-T2A-GBA1_WPRE_bGH_4392nt

11,348 bp

FIG. 24

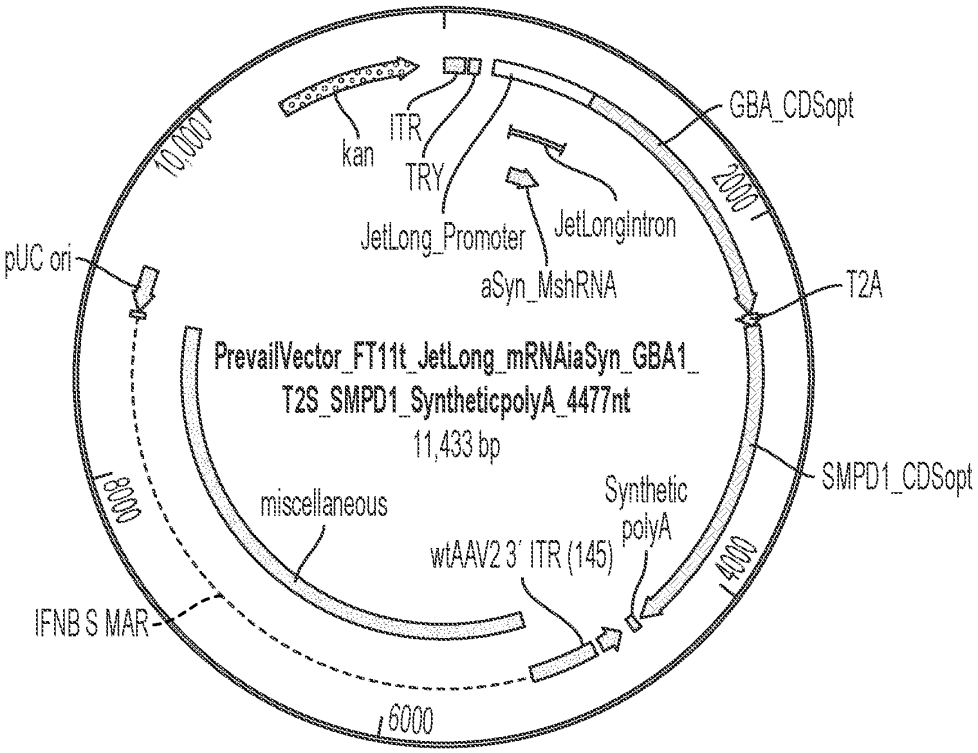

10,000
kan
ITR
TRY
JetLong_Promoter
JetLongintron
aSyn_MshRNA
GBA_CDSopt
2000
T2A
pUC ori
PrevailVector_FT11t_JetLong_mRNAiaSyn_GBA1_
T2S_SMPD1_SyntheticpolyA_4477nt
11,433 bp
SMPD1_CDSopt
8000
miscellaneous
Synthetic
polyA
wtAAV2 3' ITR (145)
4000
IFNB S MAR
6000

FIG. 25

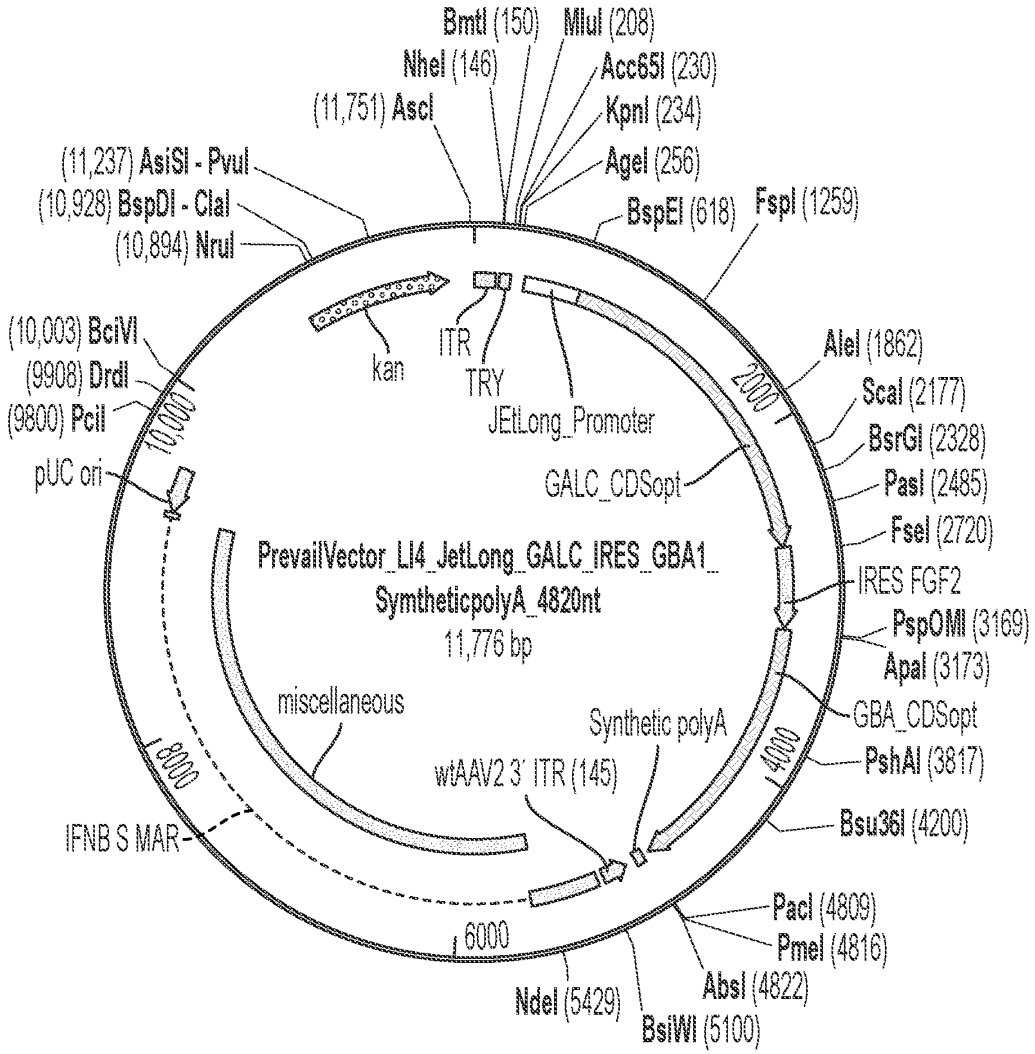
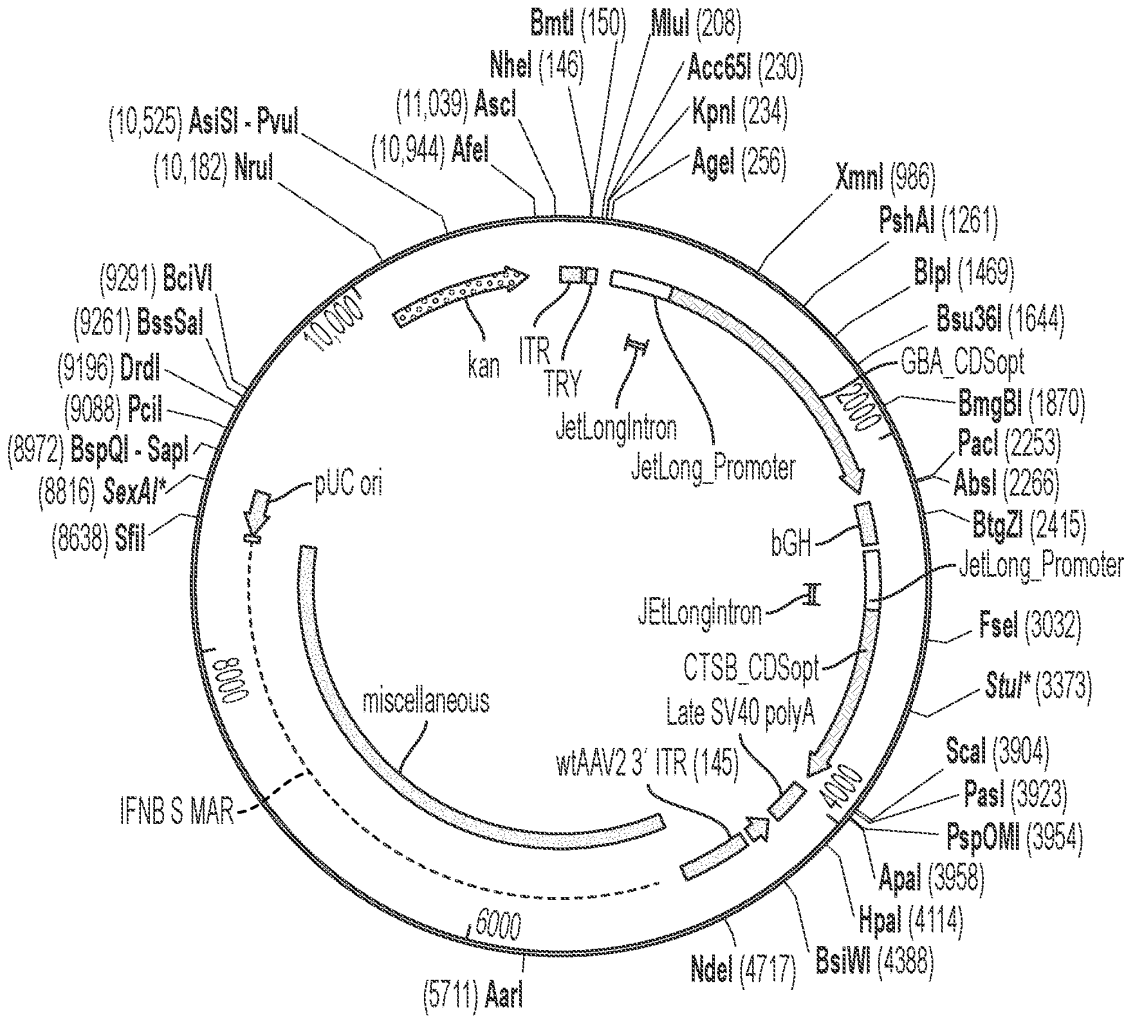

BmtI (150)
MluI (208)
NheI (146)
Acc65I (230)
(11,751) AscI
KpnI (234)
AgeI (256)
(11,237) AsiSI - PvuI
(10,928) BspDI - ClaI
(10,894) NruI
BspEI (618)
FspI (1259)
(10,003) BciVI
(9908) DrdI
(9800) PciI
pUC ori
kan
ITR
TRY
JEtLong_Promoter
AleI (1862)
ScaI (2177)
BsrGI (2328)
PasI (2485)
FseI (2720)
GALC_CDSopt
IRES FGF2
PspOMI (3169)
ApaI (3173)
PrevailVector_LI4_JetLong_GALC_IRES_GBA1_
SymtheticpolyA_4820nt
11,776 bp
GBA_CDSopt
PshAI (3817)
miscellaneous
Synthetic polyA
wtAAV2 3' ITR (145)
Bsu36I (4200)
IFNB S MAR
PacI (4809)
PmeI (4816)
AbsI (4822)
NdeI (5429)
BsiWI (5100)
2000
4000
6000
8000
10,000

FIG. 26



PrevailVector_FP5_JetLong_GBA1_bGH_JetLong_CTSB_SV40I_4108nt
11,064 bp

FIG. 27

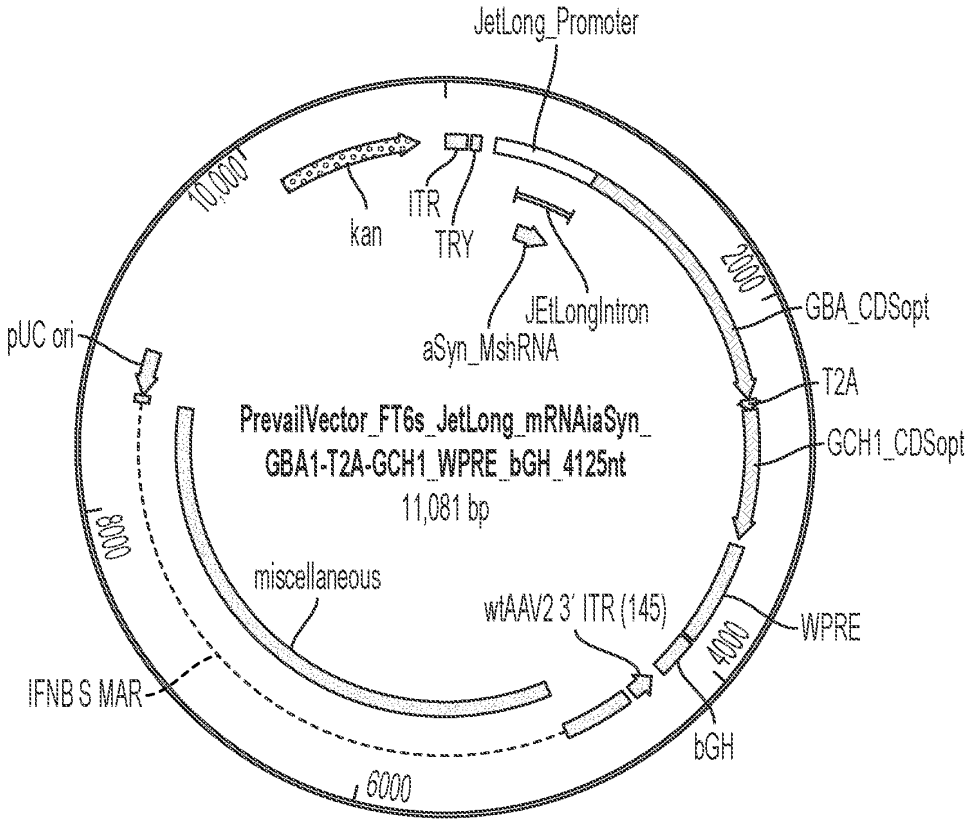
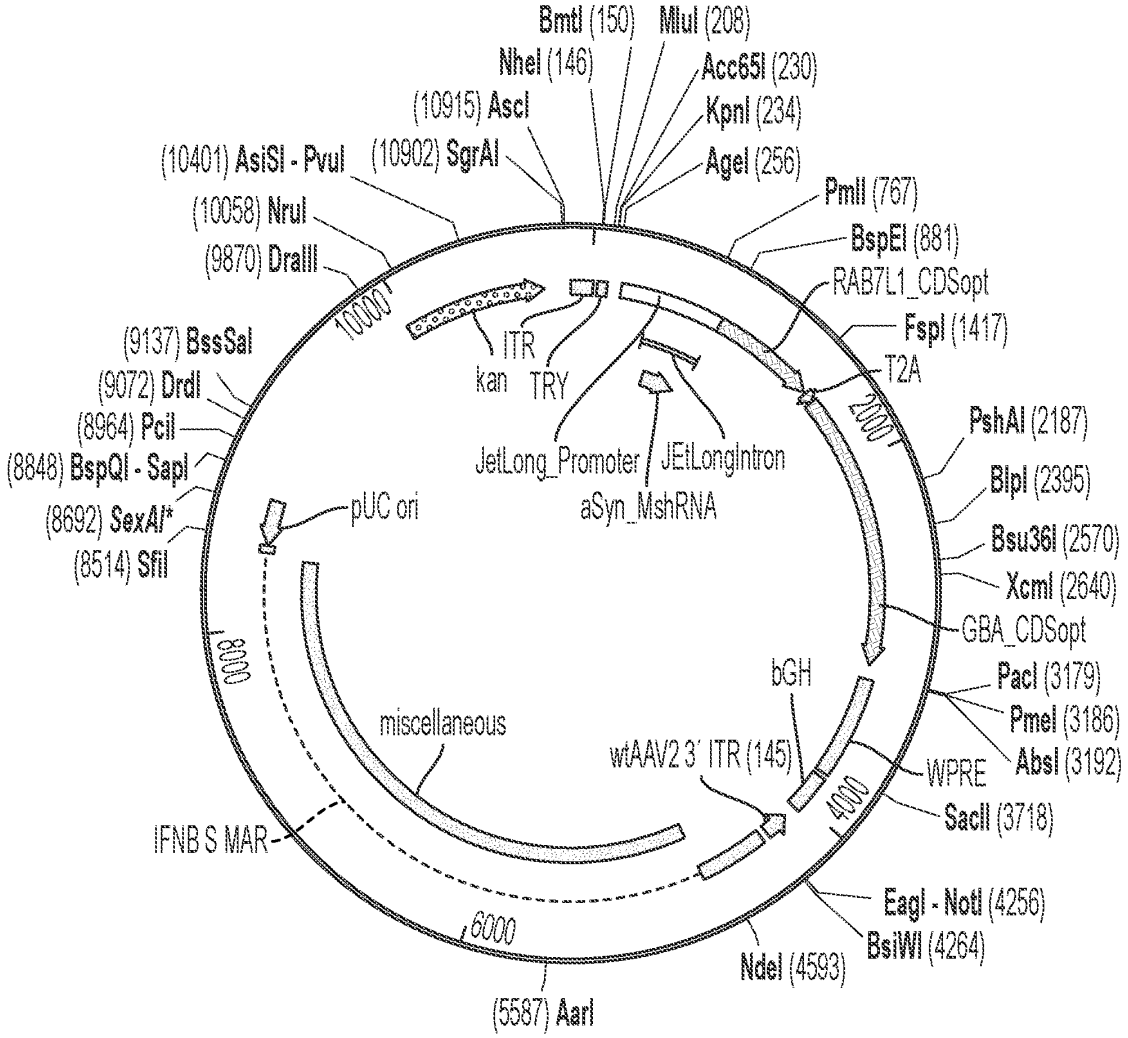

JetLong_Promoter
10,000
kan
ITR
TRY
JEtLongIntron
aSyn_MshRNA
2000
GBA_CDSopt
T2A
GCH1_CDSopt
pUC ori
PrevailVector_FT6s_JetLong_mRNAiaSyn_
GBA1-T2A-GCH1_WPRE_bGH_4125nt
11,081 bp
8000
miscellaneous
wtAAV2 3' ITR (145)
WPRE
4000
IFNB S MAR
bGH
6000

FIG. 28



PrevailVector_LT7s_JetLong_mRNAiaSyn_RAB7L1-T2A-GBA1_WPRE_bGH_3984nt

10940 bp

FIG. 29

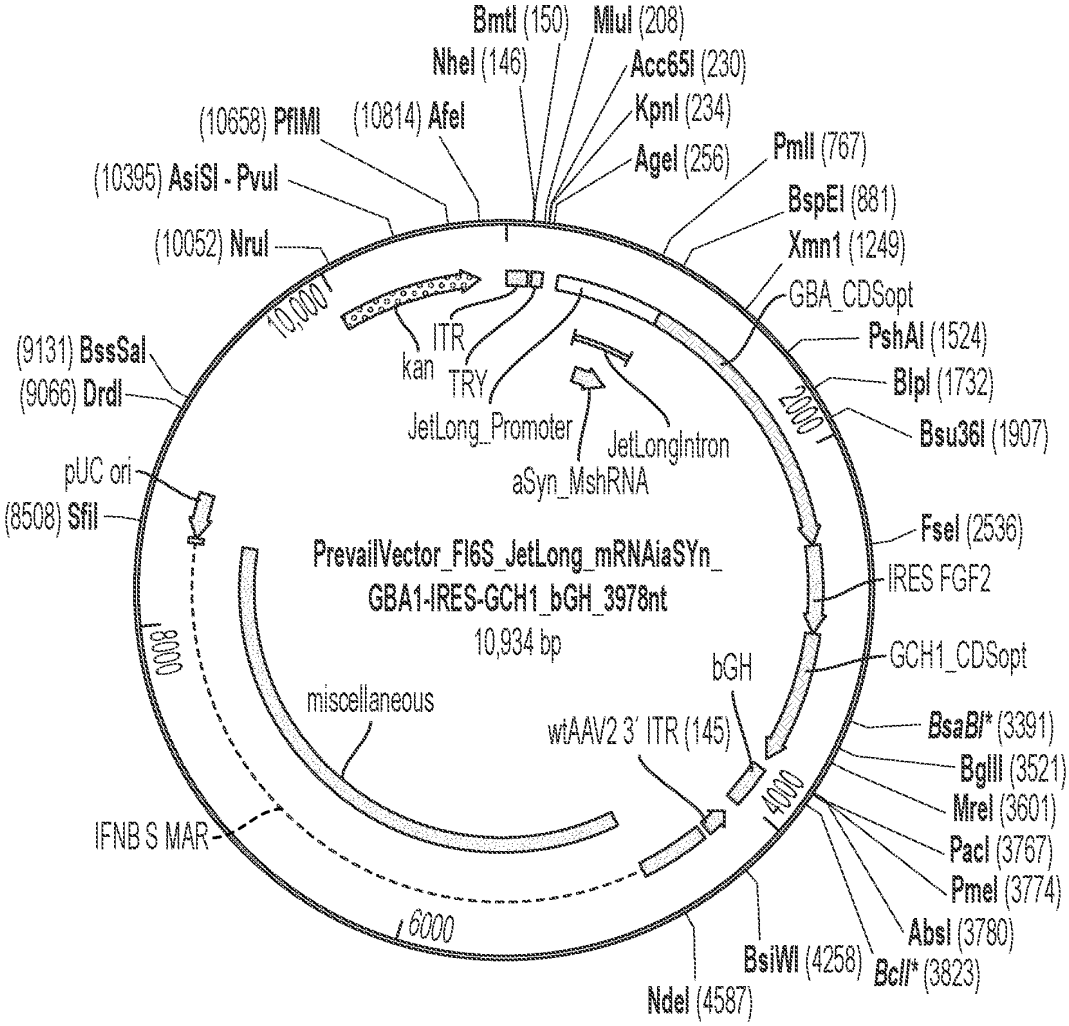

BmtI (150)
MluI (208)
NheI (146)
Acc65I (230)
KpnI (234)
(10658) PflMI
(10814) AfeI
AgeI (256)
PmlI (767)
(10395) AsiSI - PvuI
BspEI (881)
(10052) NruI
Xmn1 (1249)
GBA_CDSopt
10,000
ITR
kan
TRY
PshAI (1524)
(9131) BssSaI
(9066) DrdI
BlpI (1732)
JeiLong_Promoter
JetLongIntron
2000
Bsu36I (1907)
aSyn_MshRNA
pUC ori
(8508) SfiI
FseI (2536)
PrevailVector_FI6S_JetLong_mRNAiaSYn_
GBA1-IRES-GCH1_bGH_3978nt
IRES FGF2
10,934 bp
8000
bGH
GCH1_CDSopt
miscellaneous
wtAAV2 3' ITR (145)
BsaBI* (3391)
BglII (3521)
MreI (3601)
4000
PacI (3767)
PmeI (3774)
IFNB S MAR
AbsI (3780)
6000
BsiWI (4258)
BclI* (3823)
NdeI (4587)

FIG. 30

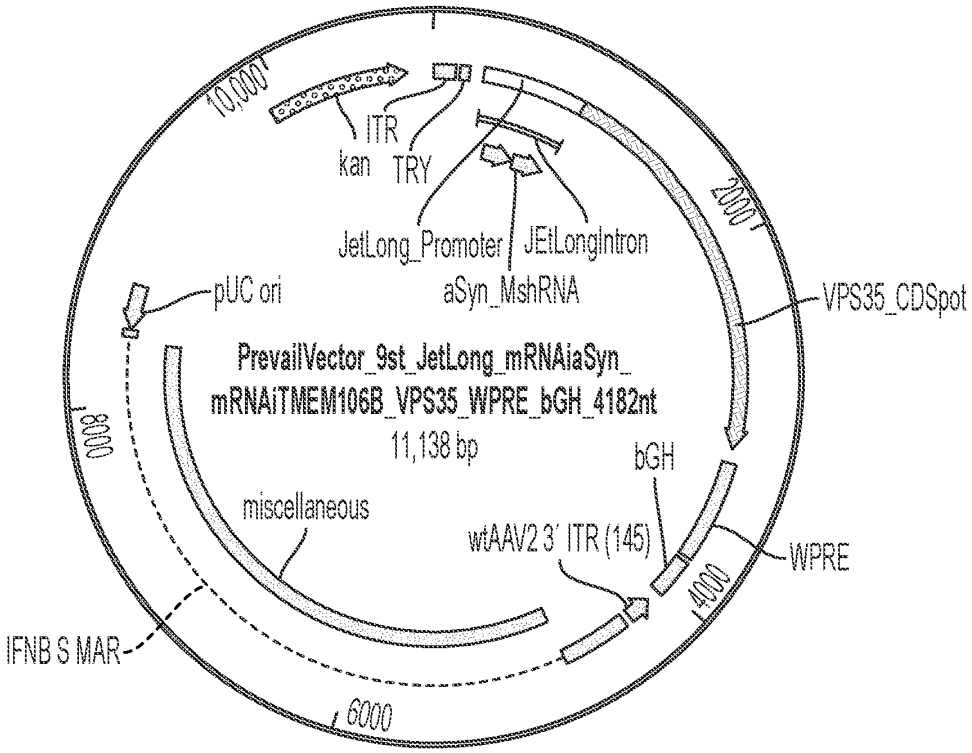

10,000
2000
4000
6000
8000
ITR
kan
TRY
JetLong_Promoter
JEtLongIntron
aSyn_MshRNA
pUC ori
VPS35_CDSpot
PrevailVector_9st_JetLong_mRNAiaSyn_
mRNAiTMEM106B_VPS35_WPRE_bGH_4182nt
11,138 bp
bGH
miscellaneous
wtAAV2 3' ITR (145)
WPRE
IFNB S MAR

FIG. 31

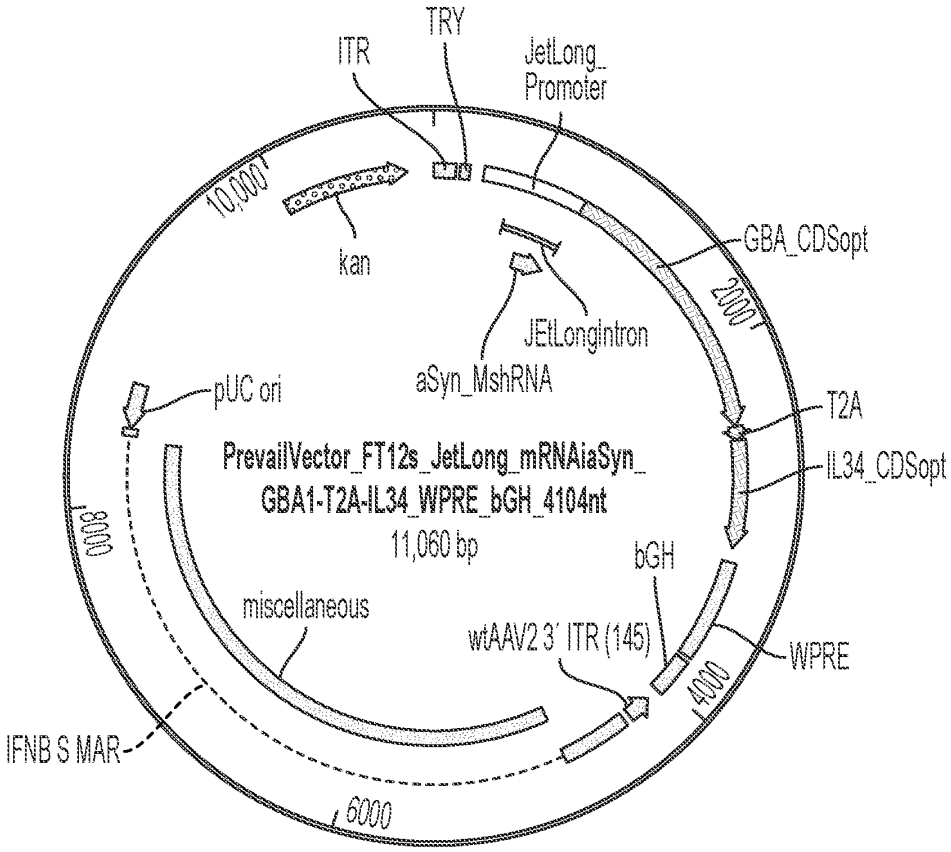
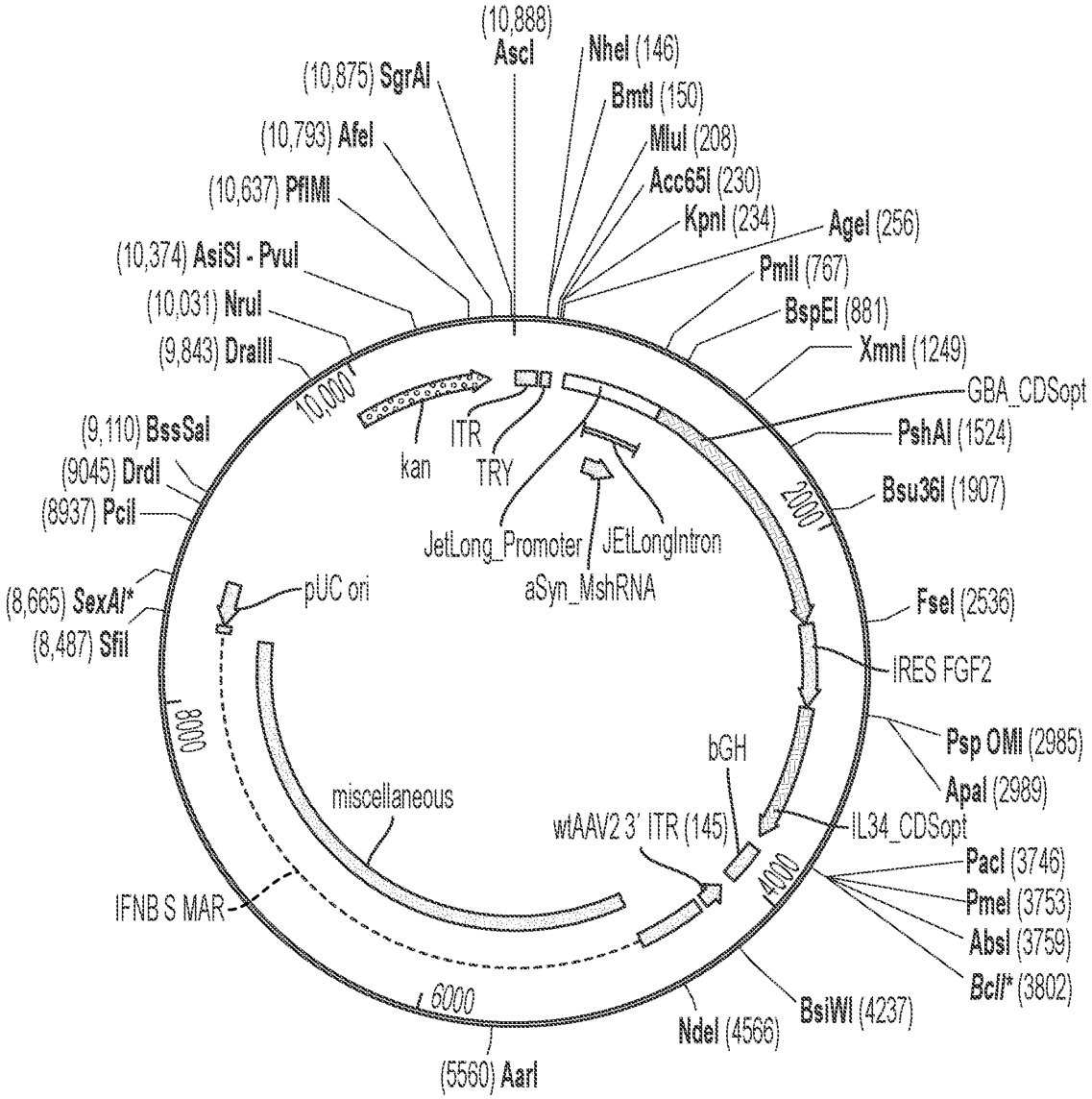

TRY
ITR
JetLong_
Promoter
10,000
kan
GBA_CDSopt
2000
JEtLongintron
aSyn_MshRNA
pUC ori
T2A
IL34_CDSopt
PrevailVector_FT12s_JetLong_mRNAiaSyn_
GBA1-T2A-IL34_WPRE_bGH_4104nt
11,060 bp
8000
bGH
miscellaneous
wtAAV2 3' ITR (145)
WPRE
4000
IFNB S MAR
6000

FIG. 32



PrevailVector_FI12s_JetLong_mRNAiaSYn_GBA1-IRES-IL34_bGH_3957nt
10,913 bp

FIG. 33

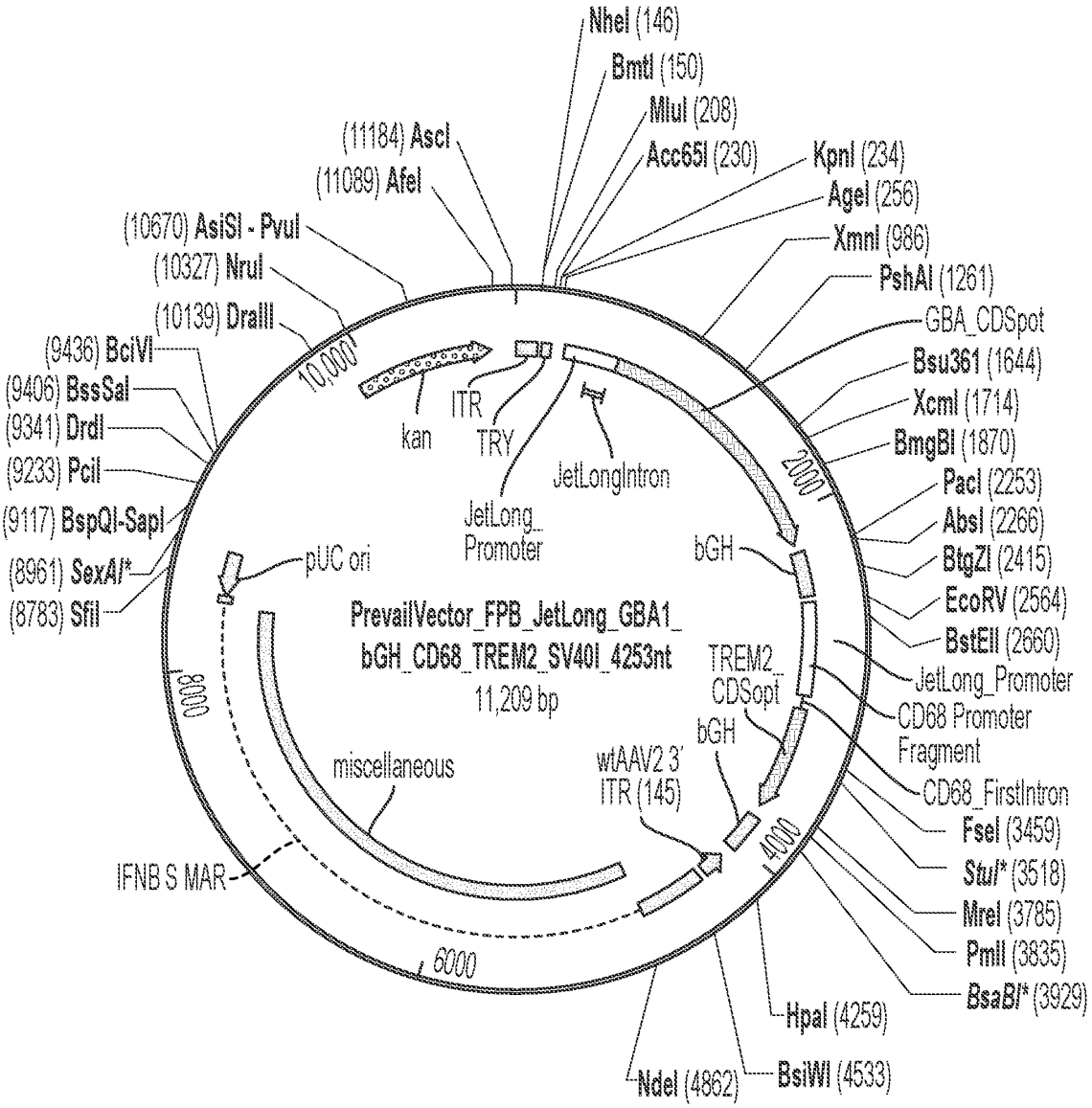
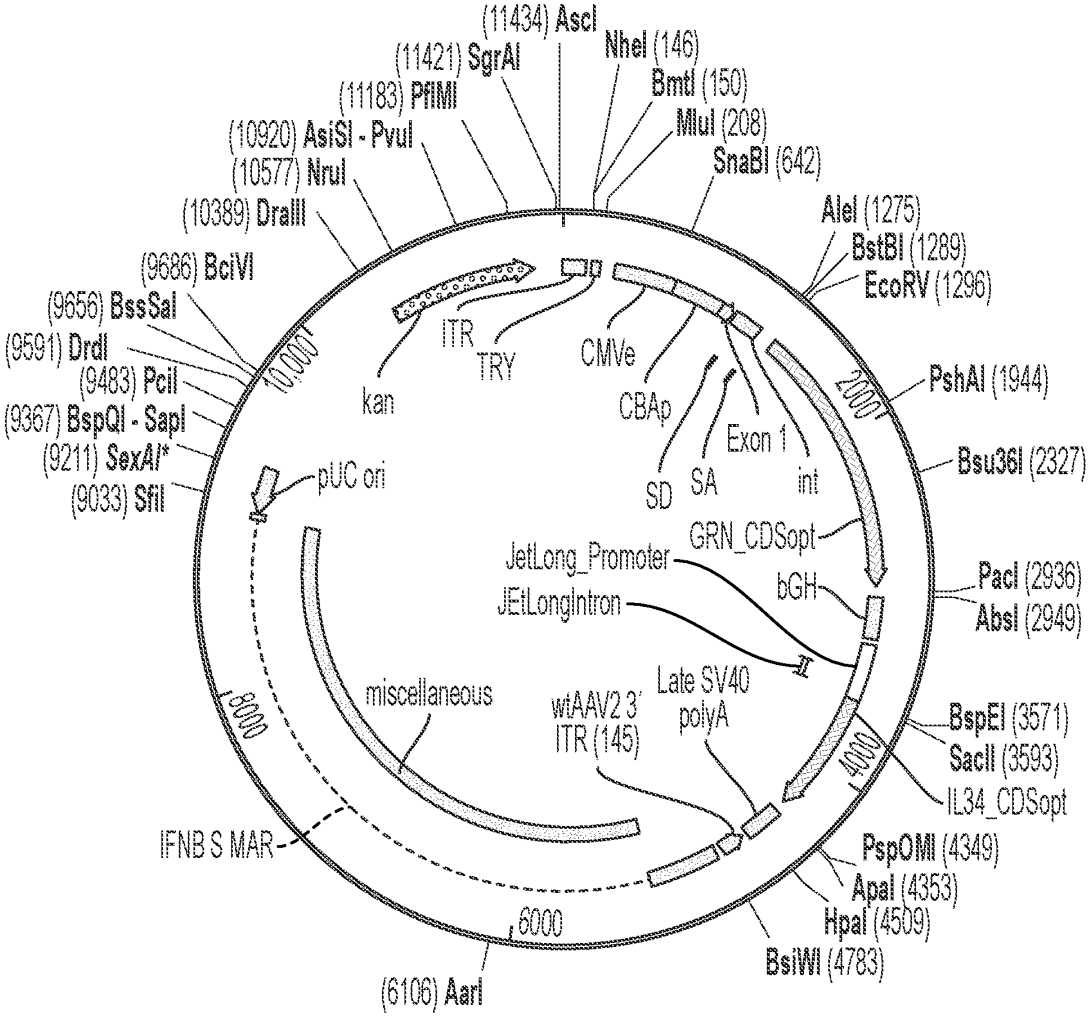

NheI (146)
BmtI (150)
MluI (208)
Acc65I (230)
KpnI (234)
AgeI (256)
XmnI (986)
PshAI (1261)
GBA_CDSpot
Bsu36I (1644)
XcmI (1714)
BmgBI (1870)
PacI (2253)
AbsI (2266)
BtgZI (2415)
EcoRV (2564)
BstEII (2660)
JetLong_Promoter
CD68 Promoter Fragment
CD68_FirstIntron
FseI (3459)
SturI* (3518)
MreI (3785)
PmlI (3835)
BsaBI* (3929)
HpaI (4259)
BsiWI (4533)
NdeI (4862)
(11184) AscI
(11089) AfeI
(10670) AsiSI - PvuI
(10327) NruI
(10139) DraIII
(9436) BciVI
(9406) BssSaI
(9341) DrdI
(9233) PciI
(9117) BspQI-SapI
(8961) SexAI*
(8783) SfiI
10,000
kan
ITR
TRY
JetLong_ Promoter
JetLongIntron
2000
bGH
TREM2_ CDSopt
bGH
wtAAV2 3' ITR (145)
4000
6000
IFNB S MAR
miscellaneous
PrevailVector_FPB_JetLong_GBA1_ bGH_CD68_TREM2_SV40I_4253nt
11,209 bp
pUC ori

FIG. 34



PrevailVector_FP12_CMVe_CBA_GBA1_bGH_JetLong_IL34_SV401_4503nt

11,459 bp

FIG. 35

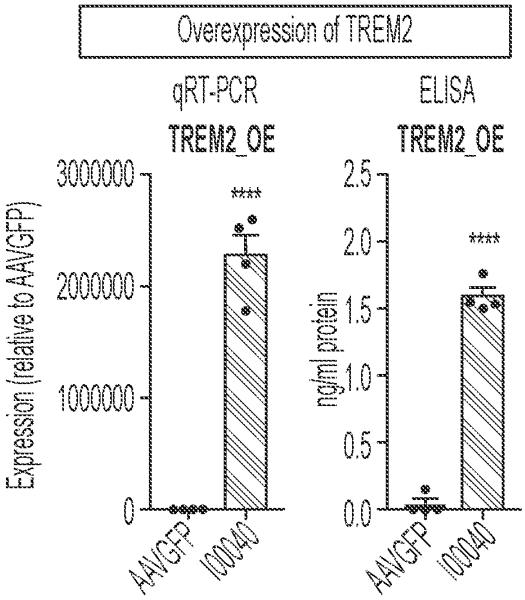


FIG. 36A

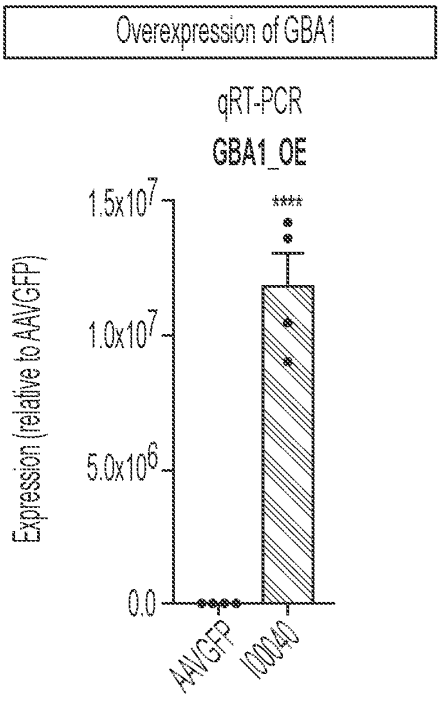


FIG. 36B

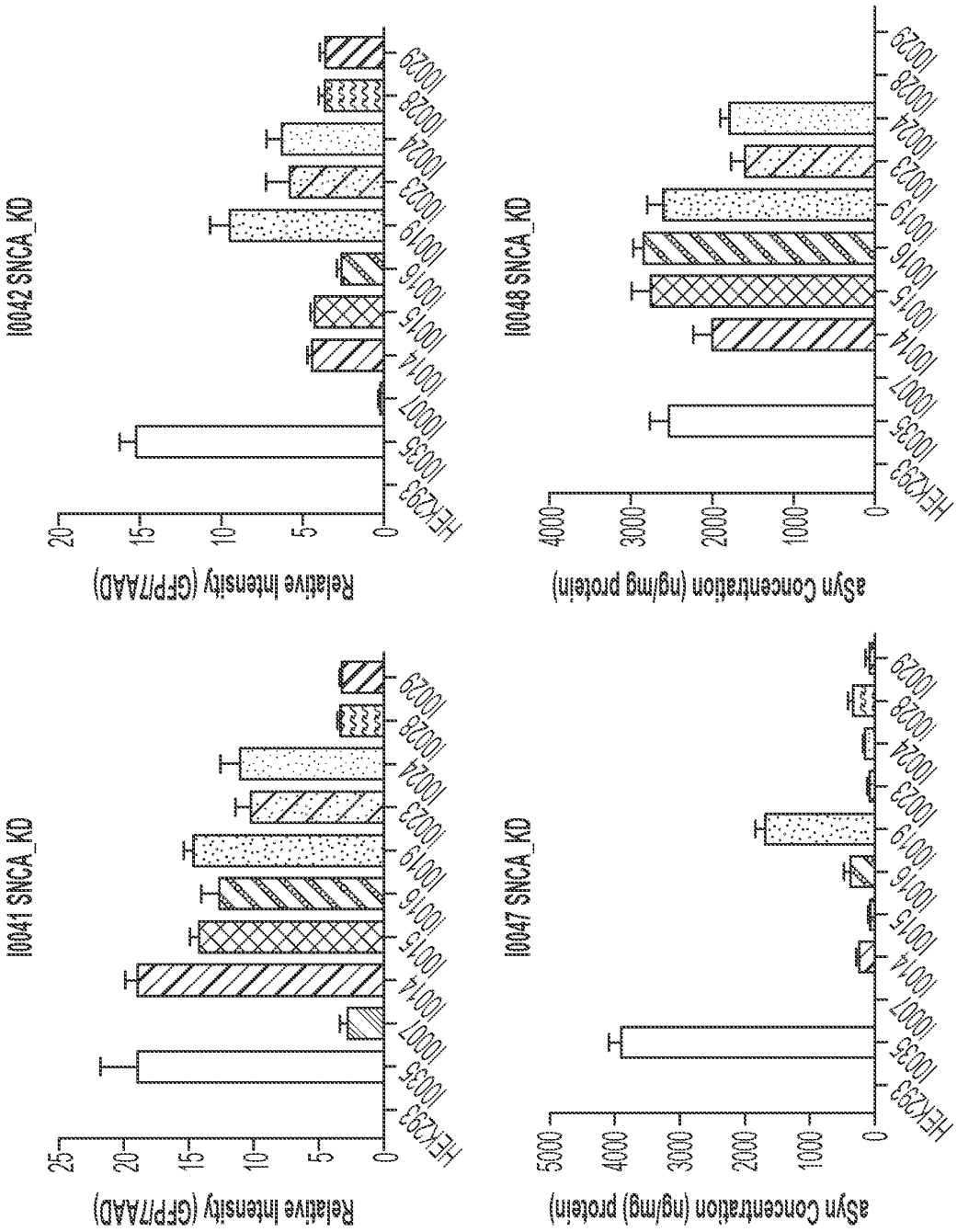

I0042 SNCA_KD
Relative Intensity (GFP7AAD)
20
15
10
5
0
HEK293
I0035
I0007
I0014
I0015
I0016
I0019
I0023
I0024
I0028
I0029
I0048 SNCA_KD
aSyn Concentration (ng/mg protein)
4000
3000
2000
1000
0
HEK293
I0035
I0007
I0014
I0015
I0016
I0019
I0023
I0024
I0028
I0029
I0041 SNCA_KD
Relative Intensity (GFP7AAD)
25
20
15
10
5
0
HEK293
I0035
I0007
I0014
I0015
I0016
I0019
I0023
I0024
I0028
I0029
I0047 SNCA_KD
aSyn Concentration (ng/mg) protein)
5000
4000
3000
2000
1000
0
HEK293
I0035
I0007
I0014
I0015
I0016
I0019
I0023
I0024
I0028
I0029

FIG. 37

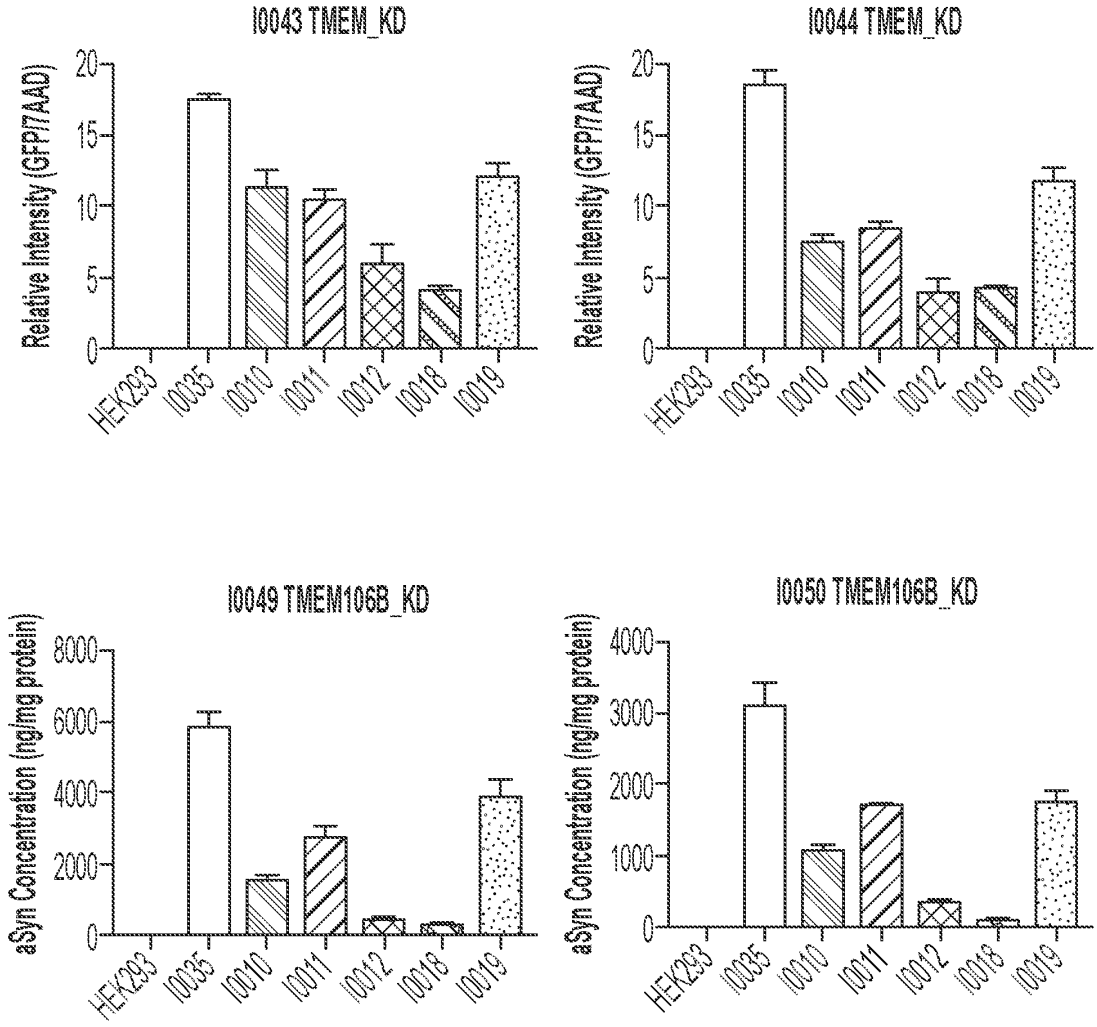

I0043 TMEM_KD
Relative Intensity (GFP/7AAD)
20
15
10
5
0
HEK293
I0035
I0010
I0011
I0012
I0018
I0019
I0044 TMEM_KD
Relative Intensity (GFP/7AAD)
20
15
10
5
0
HEK293
I0035
I0010
I0011
I0012
I0018
I0019
I0049 TMEM106B_KD
aSyn Concentration (ng/mg protein)
8000
6000
4000
2000
0
HEK293
I0035
I0010
I0011
I0012
I0018
I0019
I0050 TMEM106B_KD
aSyn Concentration (ng/mg protein)
4000
3000
2000
1000
0
HEK293
I0035
I0010
I0011
I0012
I0018
I0019

FIG. 38

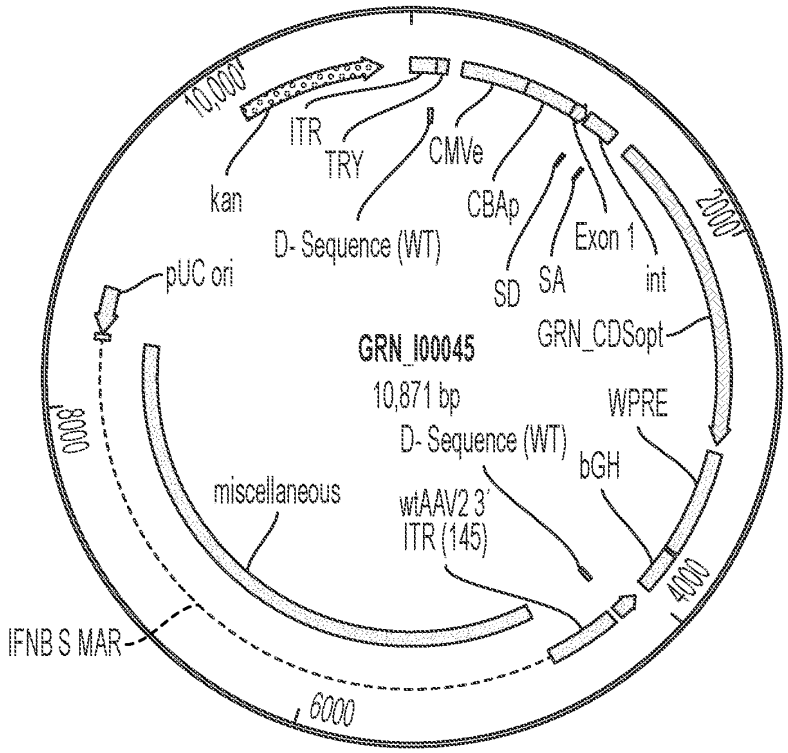

10,000
2000
4000
6000
8000
ITR
TRY
CMVe
CBAp
Exon 1
int
SA
SD
kan
D- Sequence (WT)
pUC ori
GRN_I00045
10,871 bp
GRN_CDSopt
WPRE
bGH
D- Sequence (WT)
wtAAV2 3'
ITR (145)
miscellaneous
IFNB S MAR

FIG. 39

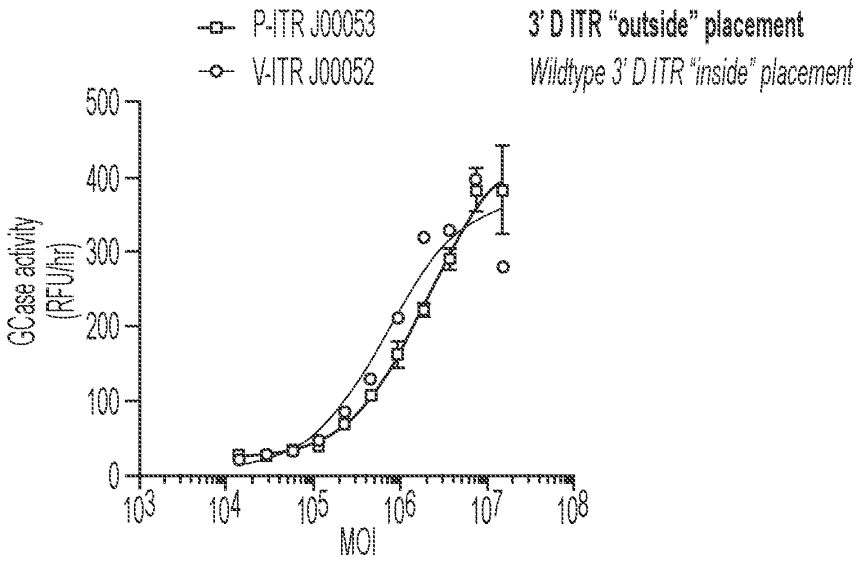

P-ITR J00053
V-ITR J00052
3' D ITR "outside" placement
Wildtype 3' D ITR "inside" placement
GCase activity (RFU/hr)
500
400
300
200
100
0
10^3
10^4
10^5
10^6
10^7
10^8
MOI

FIG. 40

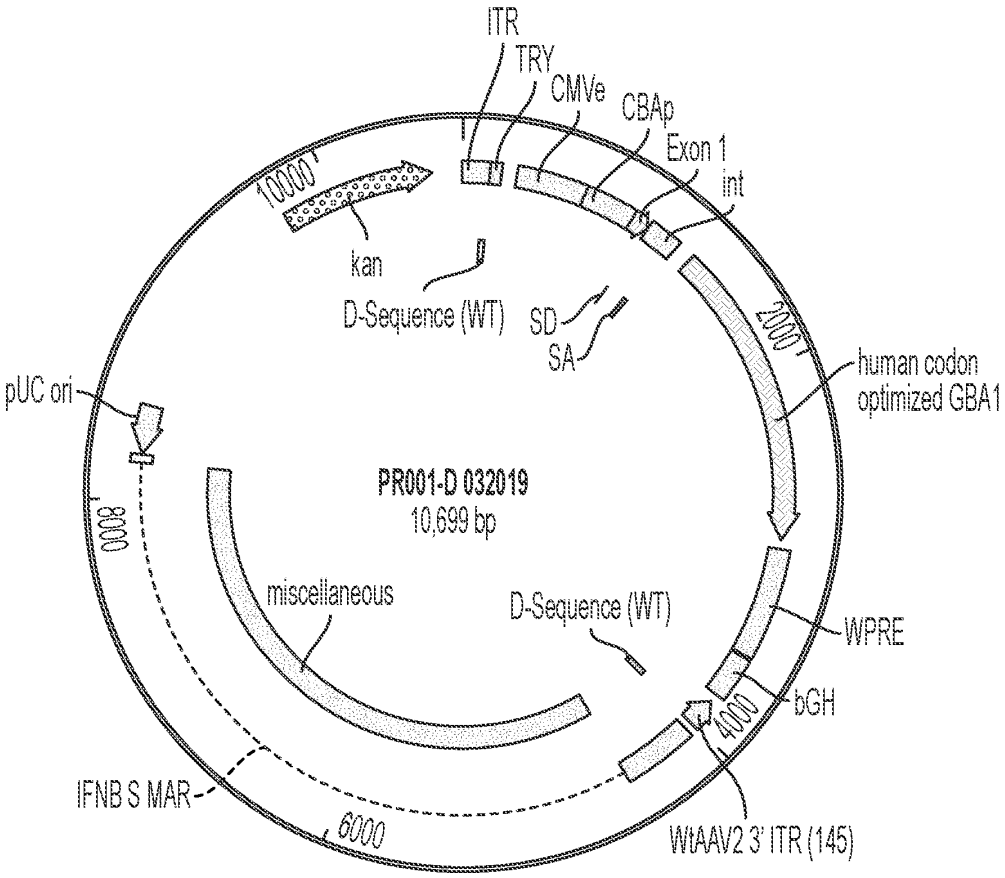

ITR
TRY
CMVe
CBAp
Exon 1
int
10000
kan
D-Sequence (WT)
SD
SA
2000
human codon optimized GBA1
pUC ori
PR001-D 032019
10,699 bp
8000
miscellaneous
D-Sequence (WT)
WPRE
bGH
4000
IFNB S MAR
6000
WtAAV2 3' ITR (145)

FIG. 41

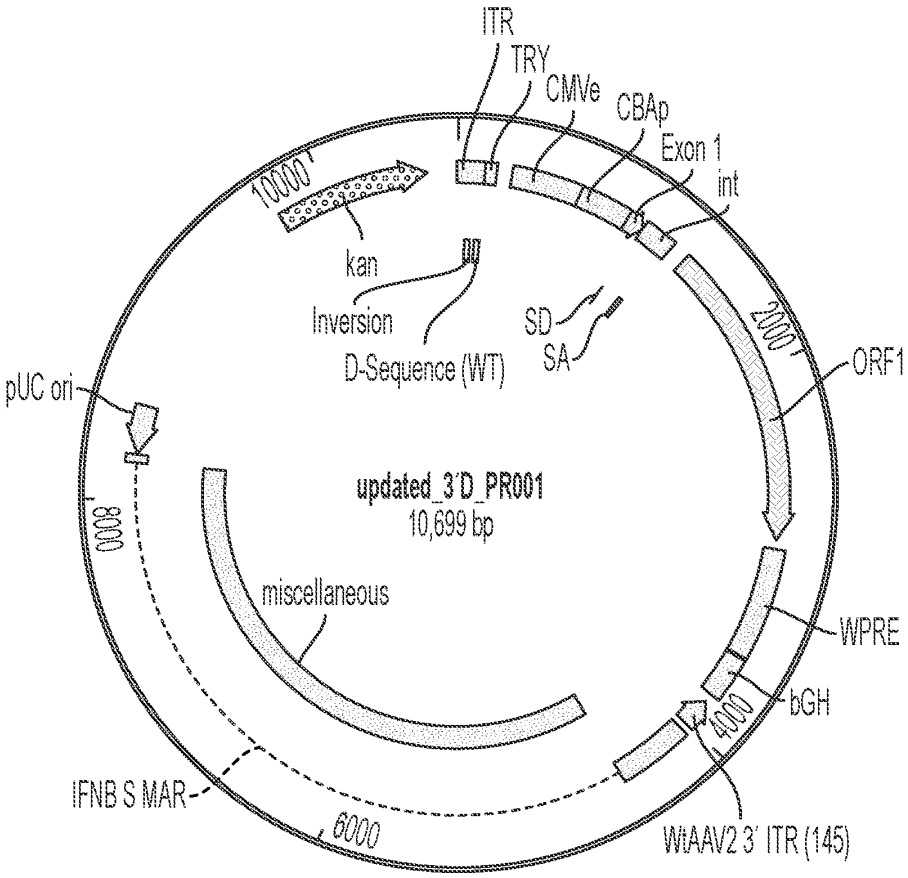

ITR
TRY
CMVe
CBAp
Exon 1
int
10000
kan
Inversion
D-Sequence (WT)
SD
SA
2000
ORF1
pUC ori
updated_3'D_PR001
10,699 bp
8000
miscellaneous
WPRE
bGH
4000
IFNB S MAR
6000
WtAAV2 3' ITR (145)

FIG. 42

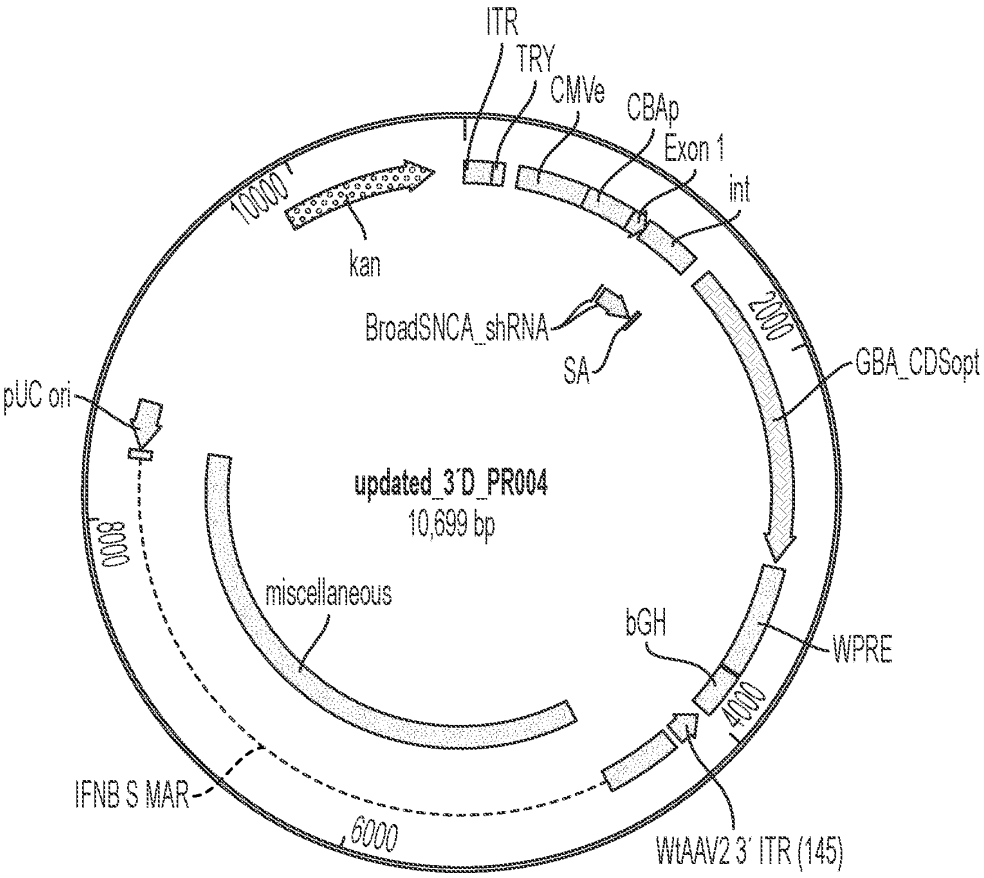

ITR
TRY
CMVe
CBAp
Exon 1
int
10000
kan
BroadSNCA_shRNA
SA
2000
GBA_CDSopt
pUC ori
updated_3'D_PR004
10,699 bp
8000
miscellaneous
bGH
WPRE
4000
IFNB S MAR
6000
WtAAV2 3' ITR (145)

FIG. 43

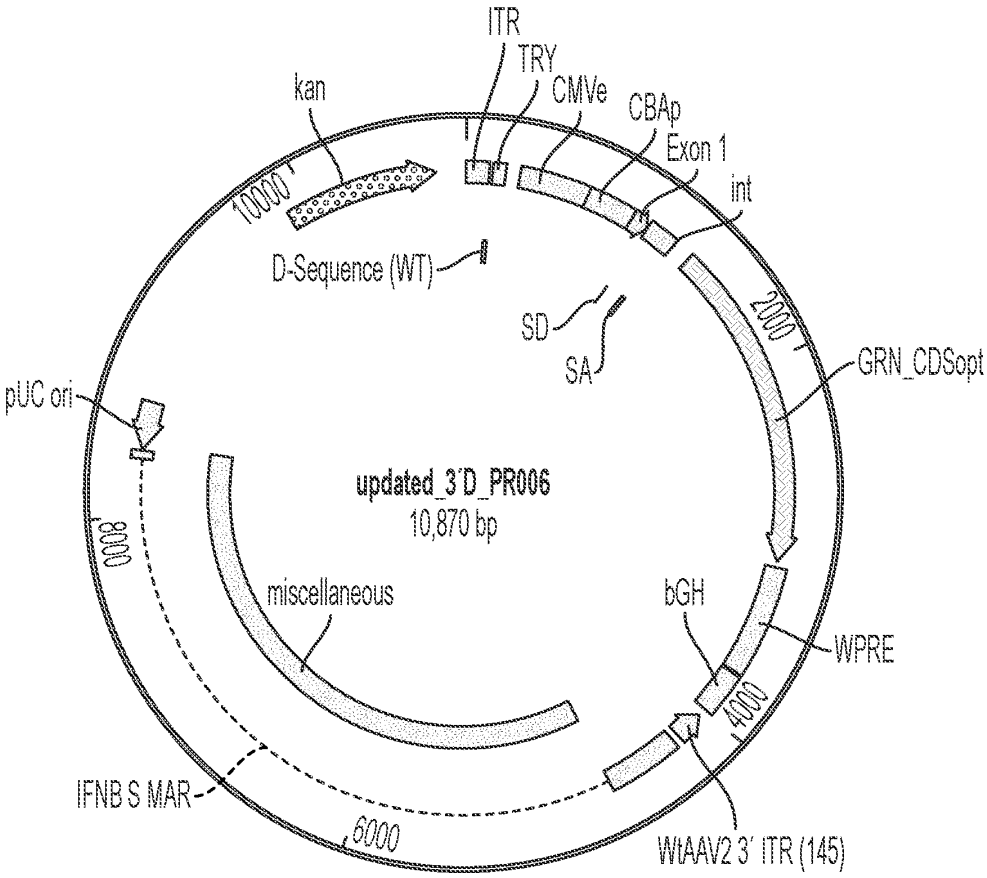
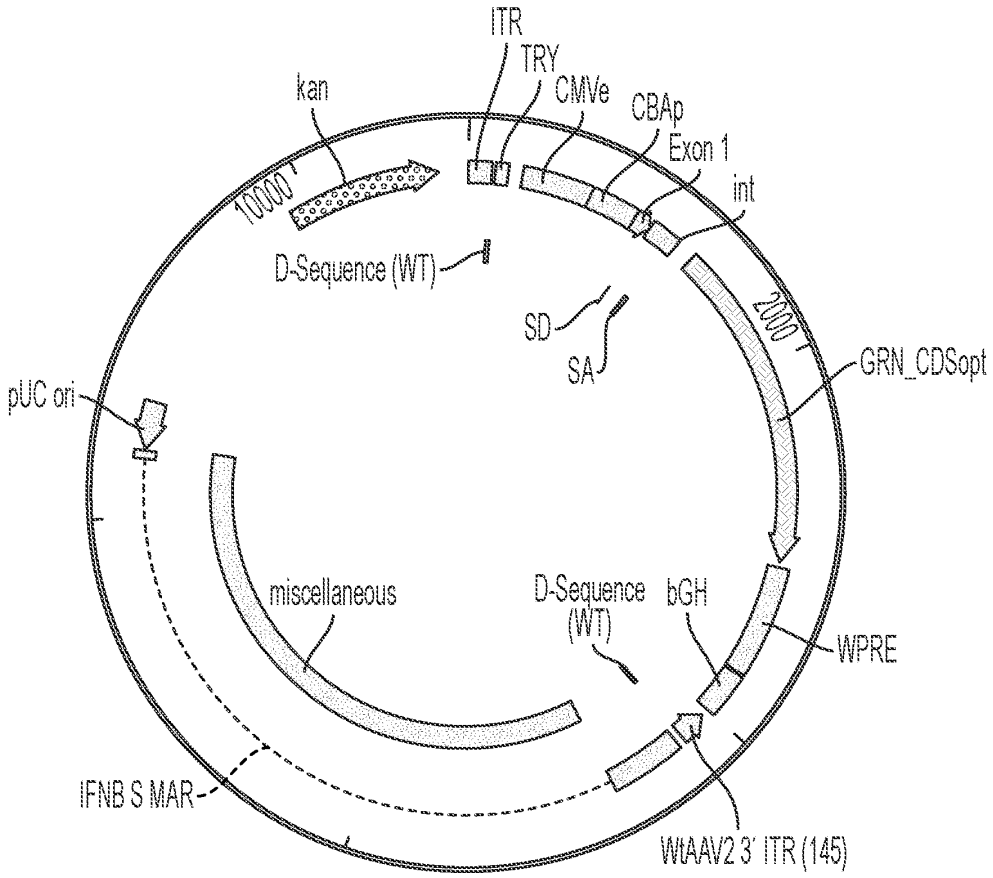

ITR
TRY
kan
CMVe
CBAp
Exon 1
int
10000
D-Sequence (WT)
SD
SA
2000
GRN_CDSopt
pUC ori
updated_3'D_PR006
10,870 bp
8000
miscellaneous
bGH
WPRE
4000
IFNB S MAR
6000
WtAAV2 3' ITR (145)

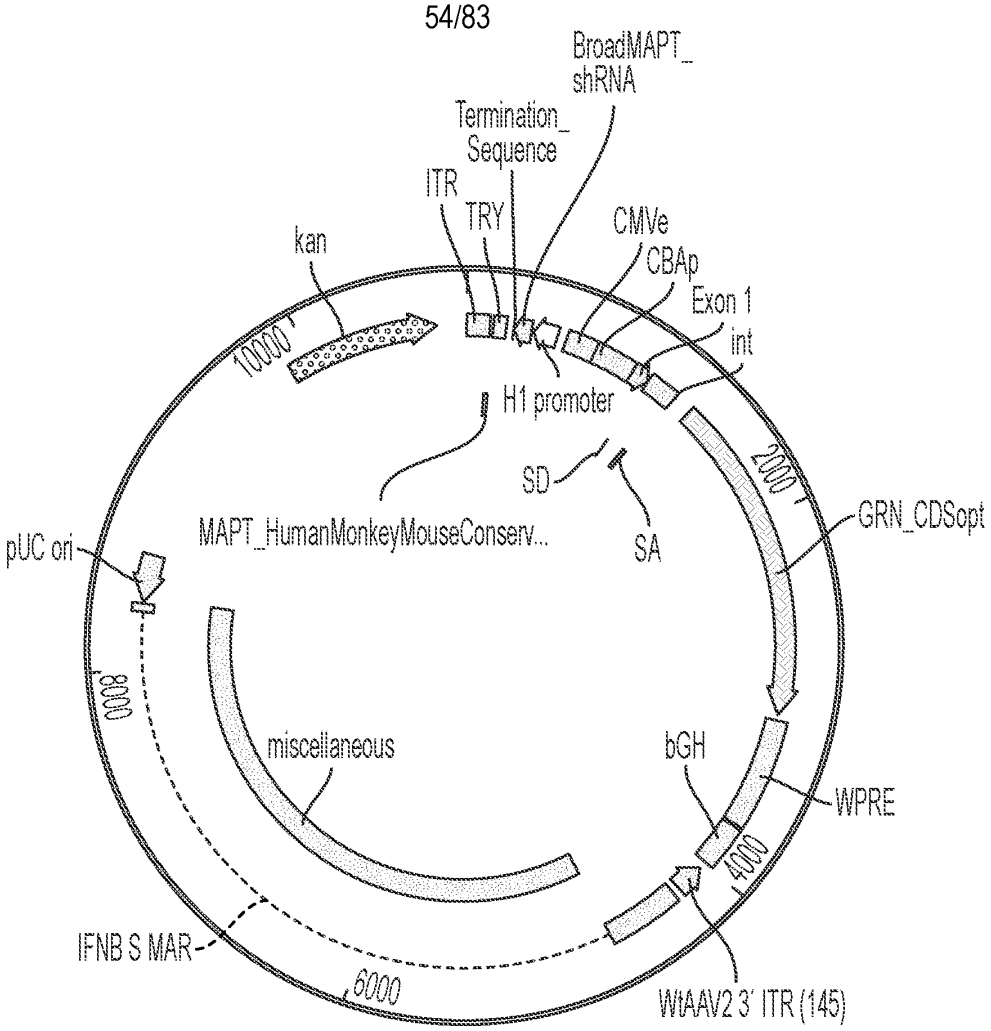
FIG. 44



updated_38.GRN_PW aligned both VM and P (1)

10,870 bp

FIG. 45



updated_H1_BroadConservedMAPTshRNA_GRN_alignment

11,264 bp

FIG. 46

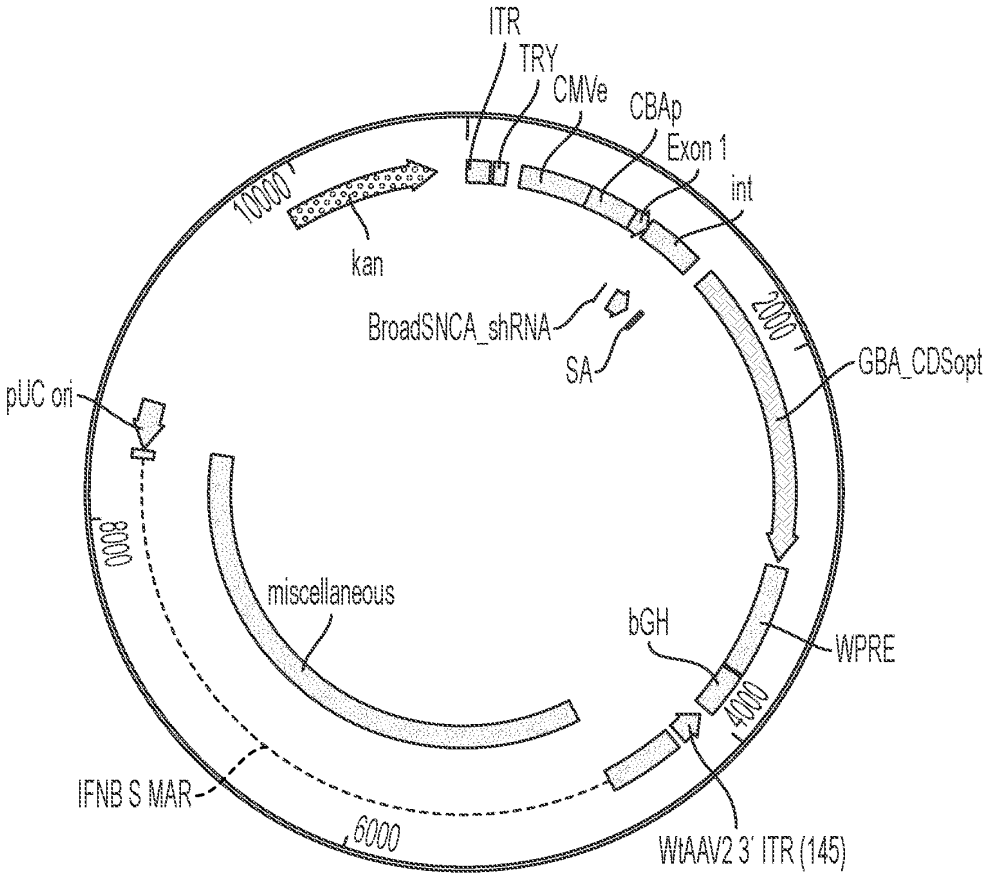

ITR
TRY
CMVe
CBAp
Exon 1
int
GBA_CDSopt
WPRE
bGH
WtAAV2 3' ITR (145)
IFNB S MAR
pUC ori
kan
BroadSNCA_shRNA
SA
miscellaneous
10000
2000
4000
6000
8000
updated_Intronic_SNCA_Broad_sh_GBA1_aligned
10,848 bp

FIG. 47

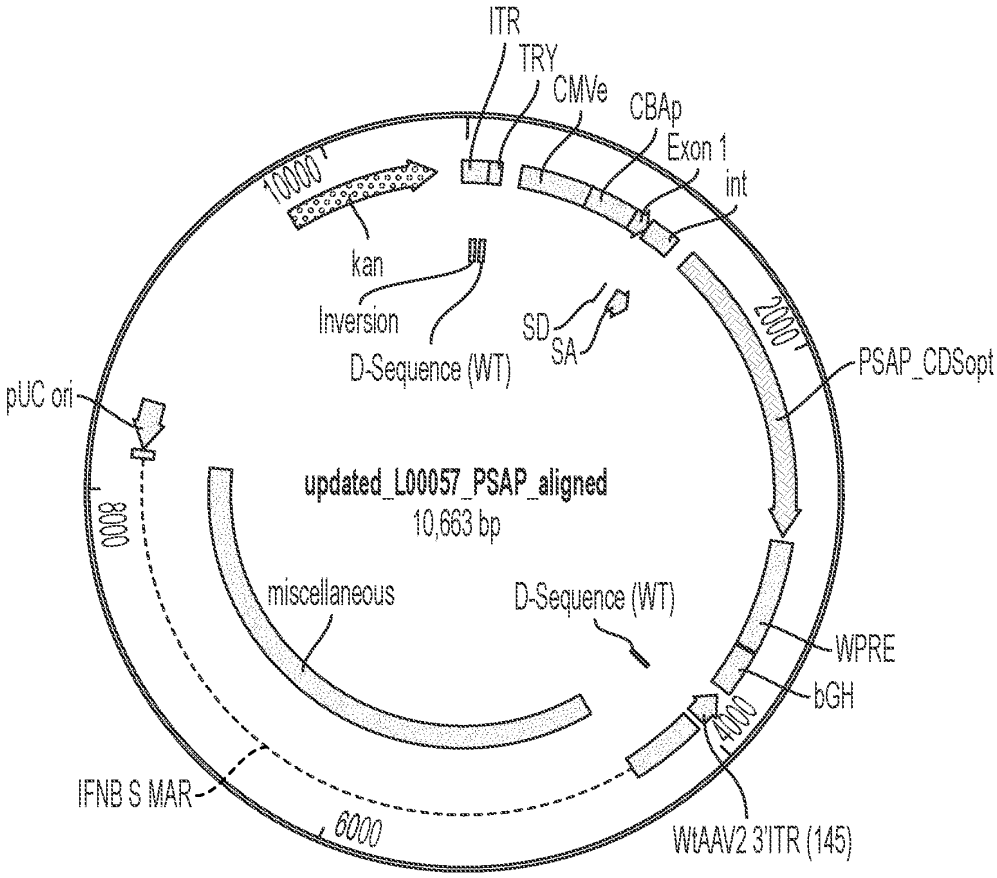

ITR
TRY
CMVe
CBAp
Exon 1
int
10000
kan
Inversion
D-Sequence (WT)
SD
SA
2000
PSAP_CDSopt
pUC ori
updated_L00057_PSAP_aligned
10,663 bp
8000
miscellaneous
D-Sequence (WT)
WPRE
bGH
4000
IFNB S MAR
6000
WtAAV2 3'ITR (145)

FIG. 48

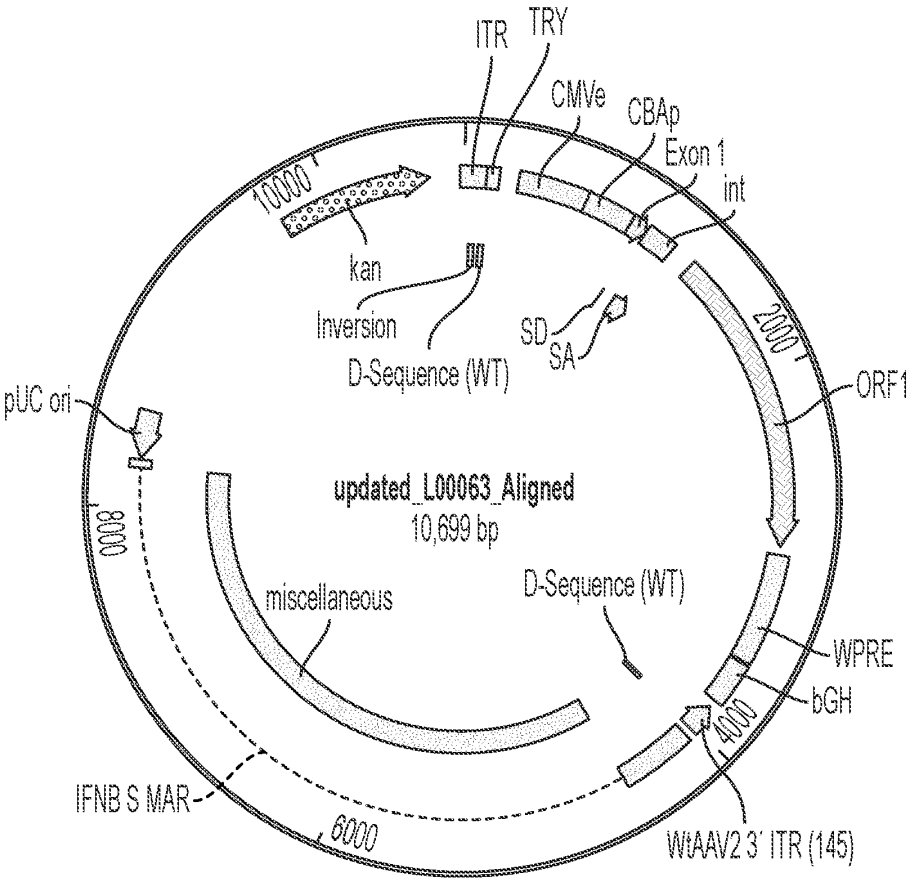

ITR
TRY
CMVe
CBAp
Exon 1
int
10000
kan
Inversion
D-Sequence (WT)
SD
SA
2000
ORF1
pUC ori
updated_L00063_Aligned
10,699 bp
8000
miscellaneous
D-Sequence (WT)
WPRE
bGH
4000
IFNB S MAR
6000
WtAAV2 3' ITR (145)

FIG. 49

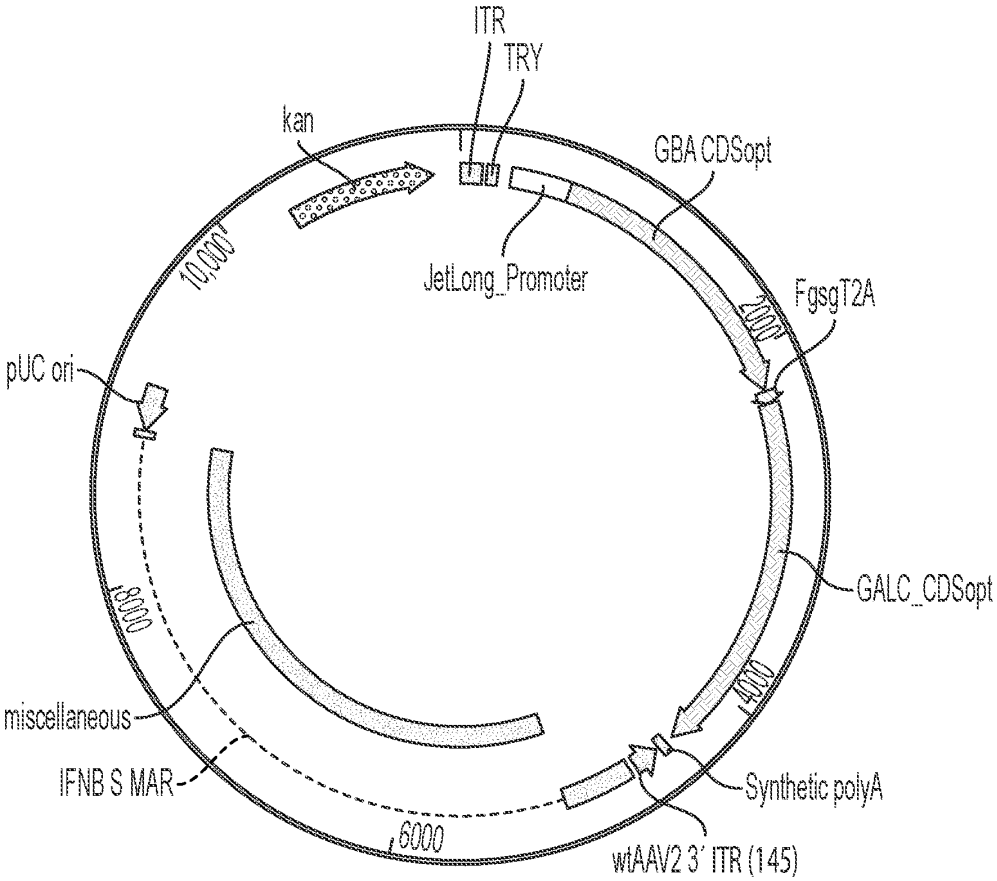

ITR
TRY
kan
GBA CDSopt
JetLong_Promoter
FgsgT2A
pUC ori
GALC_CDSopt
miscellaneous
IFNB S MAR
Synthetic polyA
wtAAV2 3' ITR (145)
10,000
2000
8000
4000
6000
updated_PrevailVector_FT4_JetLong_GBA1_FgsgT2A_GALC_SyntheticpolyA_4394nt_aligned
11,311 bp

FIG. 50

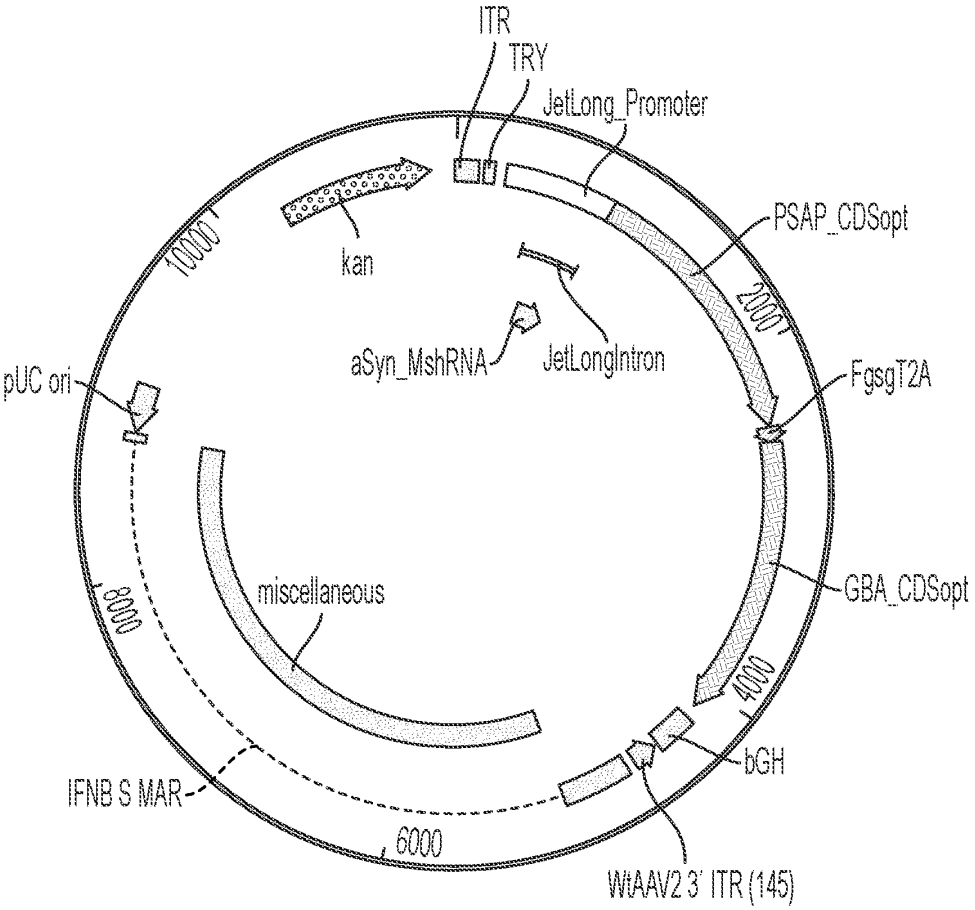

ITR
TRY
JetLong_Promoter
PSAP_CDSopt
kan
10000
2000
aSyn_MshRNA
JetLongIntron
pUC ori
FgsgT2A
miscellaneous
8000
GBA_CDSopt
4000
bGH
IFNB S MAR
6000
WtAAV2 3' ITR (145)
updated_PrevailVector_LT2s_JetLong_mRNAiaSYn_PSAP-FgsgT2A-GBA1_bGH_4374nt_aligned
11,292 bp

FIG. 51

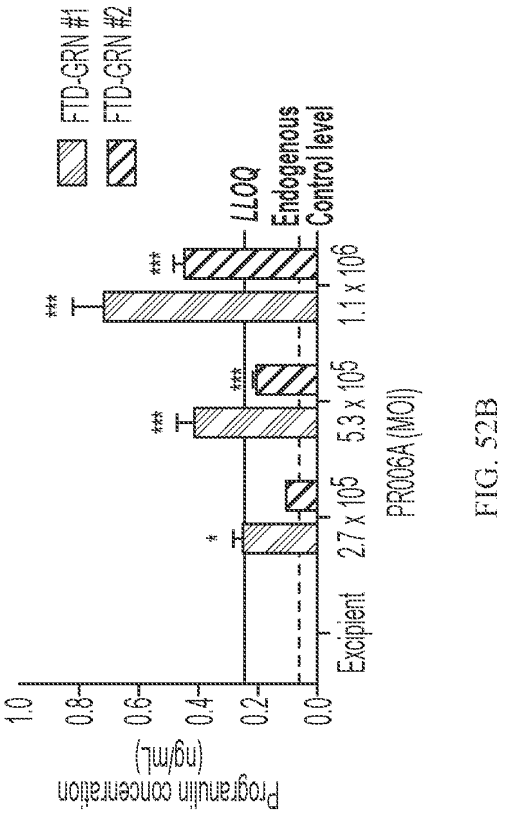


FIG. 52B

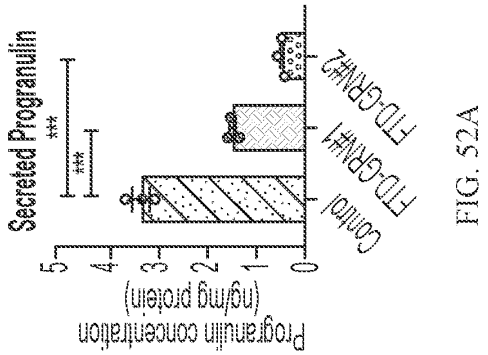


FIG. 52A

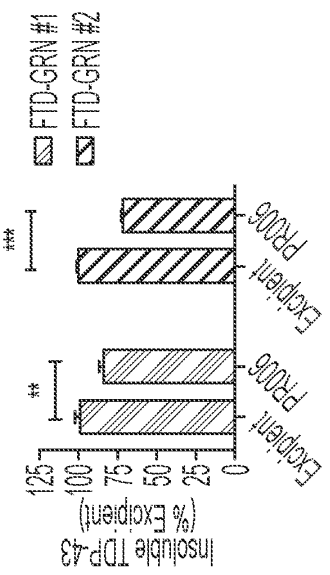


FIG. 52D

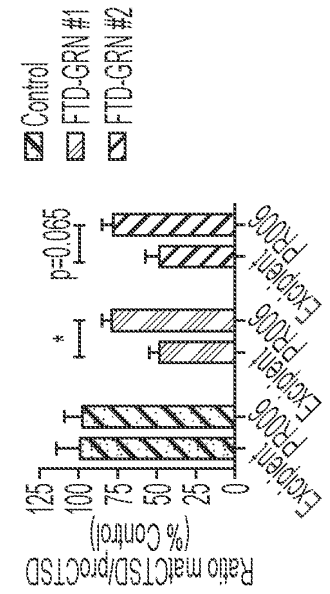


FIG. 52C

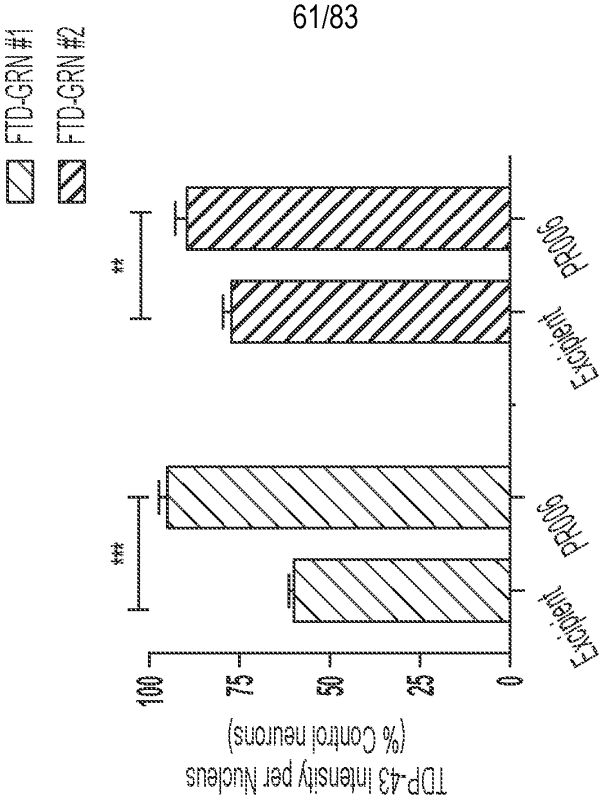


FIG. 52F

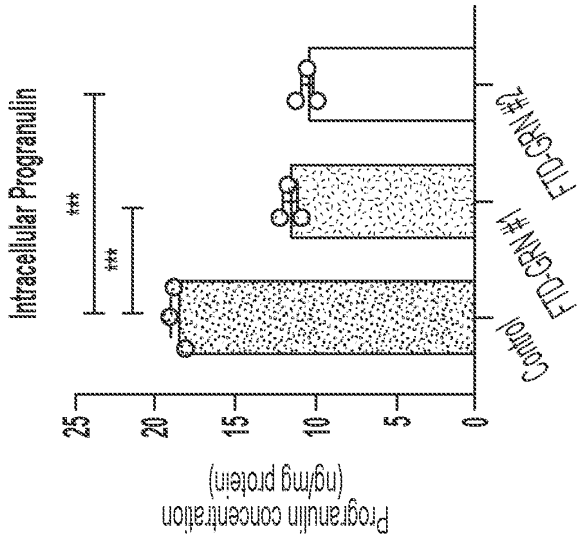


FIG. 52E

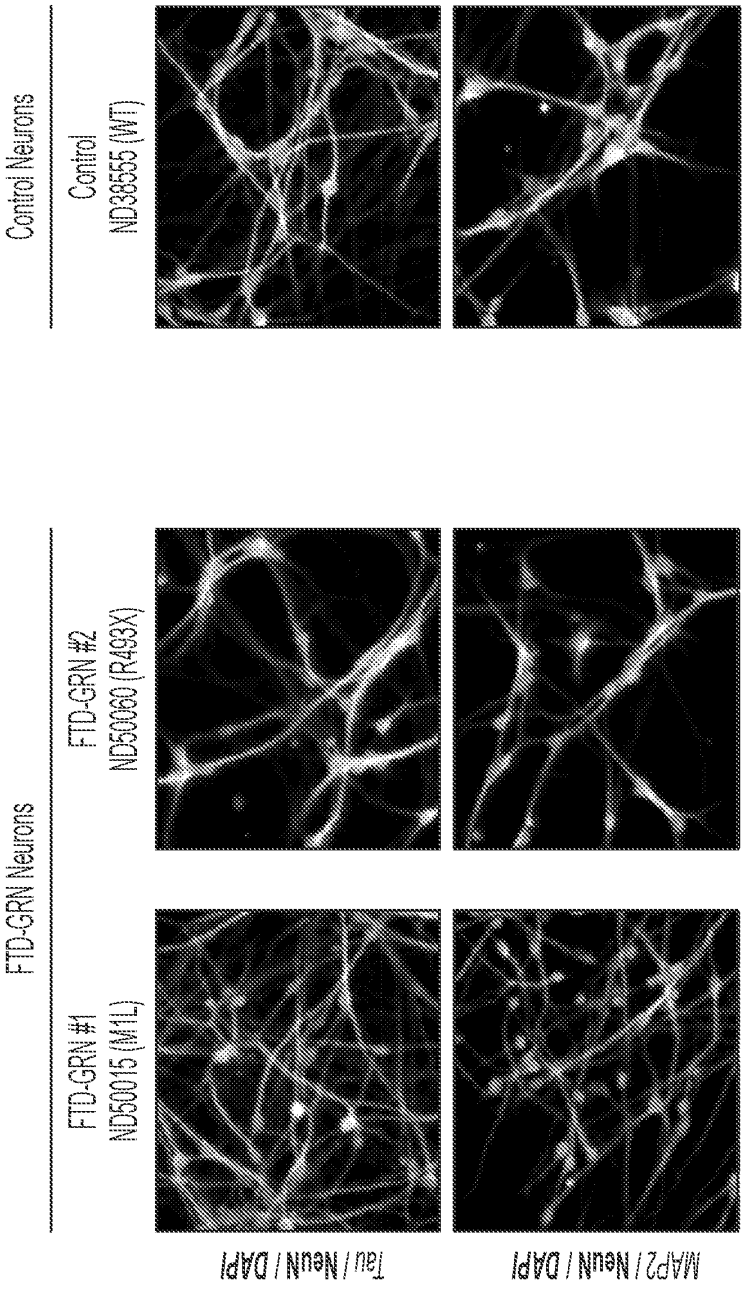

Control Neurons
Control
ND38555 (WT)
FTD-GRN Neurons
FTD-GRN #1
ND50015 (M1L)
FTD-GRN #2
ND50060 (R493X)
Tau / NeuN / DAPI
MAP2 / NeuN / DAPI

FIG. 52G

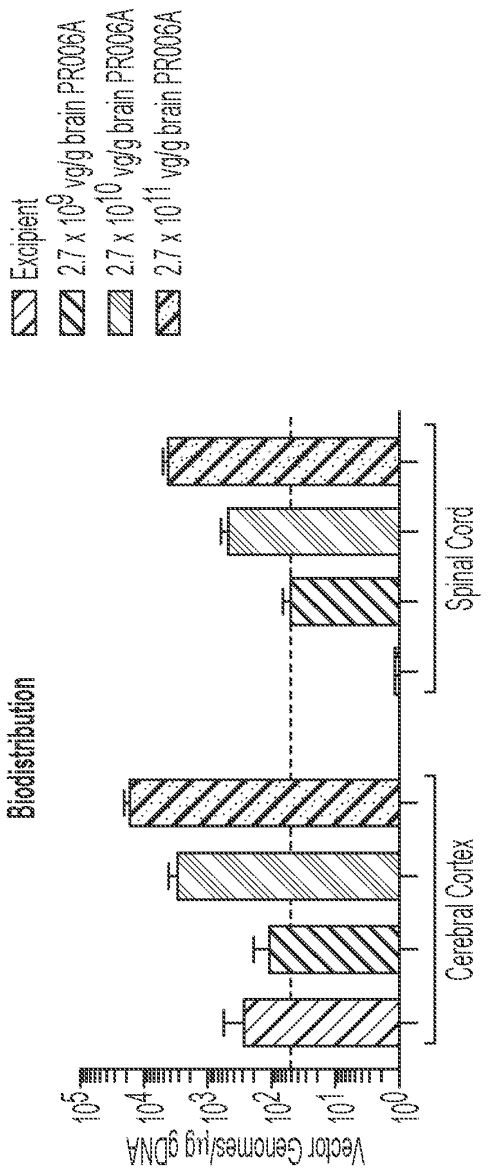


FIG. 53A

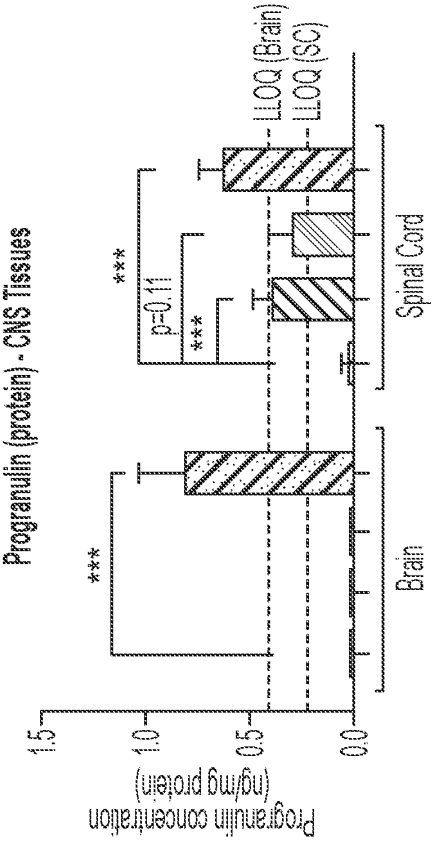


FIG. 53C

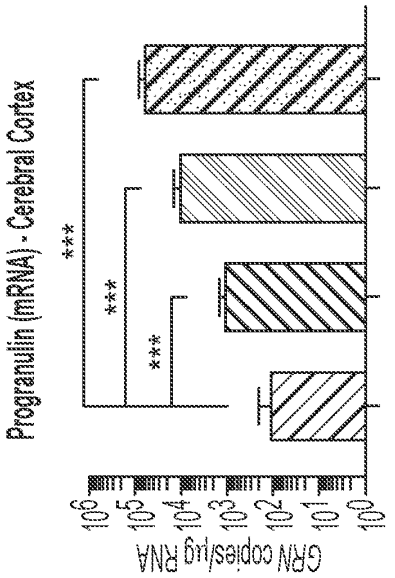


FIG. 53B

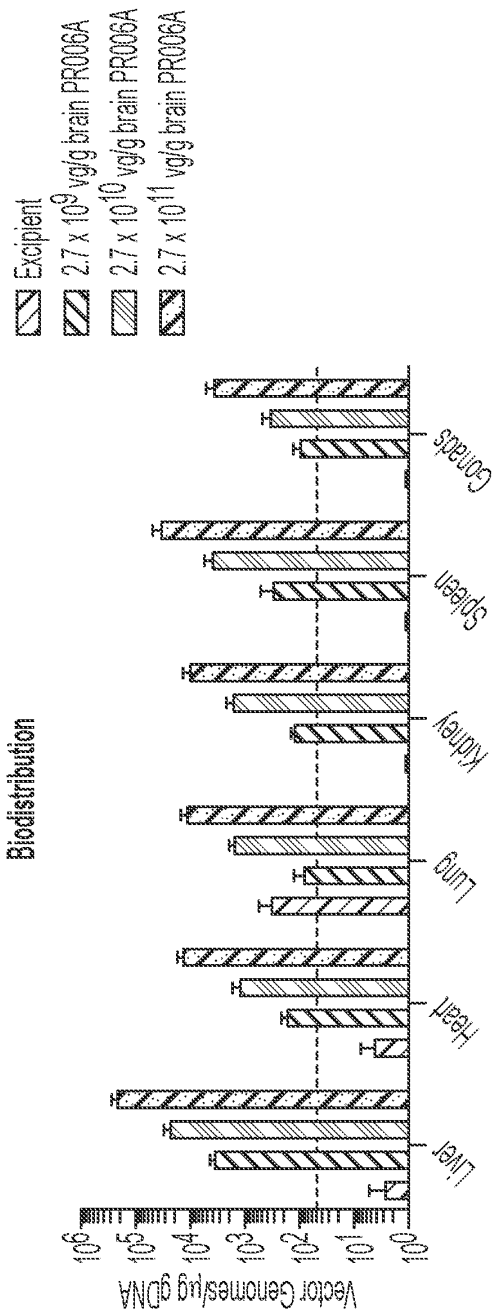


FIG. 53D

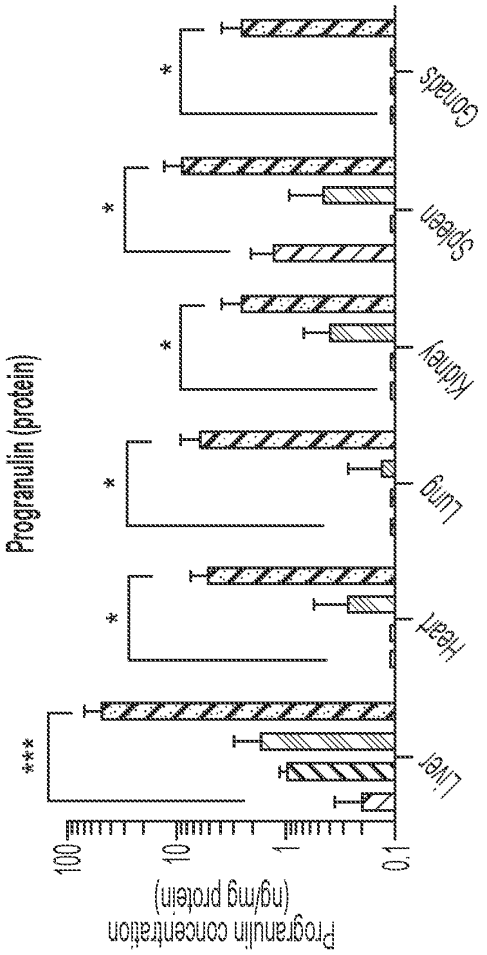


FIG. 53E

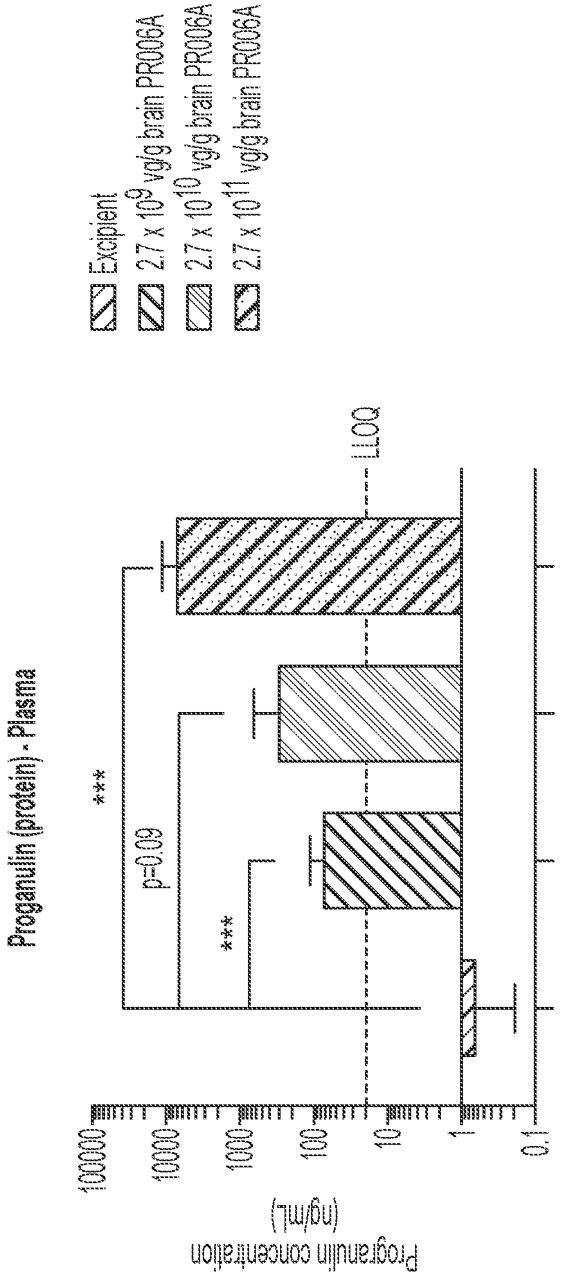

Excipient
2.7 x 10^9 vg/g brain PR006A
2.7 x 10^10 vg/g brain PR006A
2.7 x 10^11 vg/g brain PR006A
Progranulin (protein) - Plasma
***
p=0.09
***
LLOQ
100000
10000
1000
100
10
1
0.1
Progranulin concentration
(ng/mL)

FIG. 53F

FIG. 53G

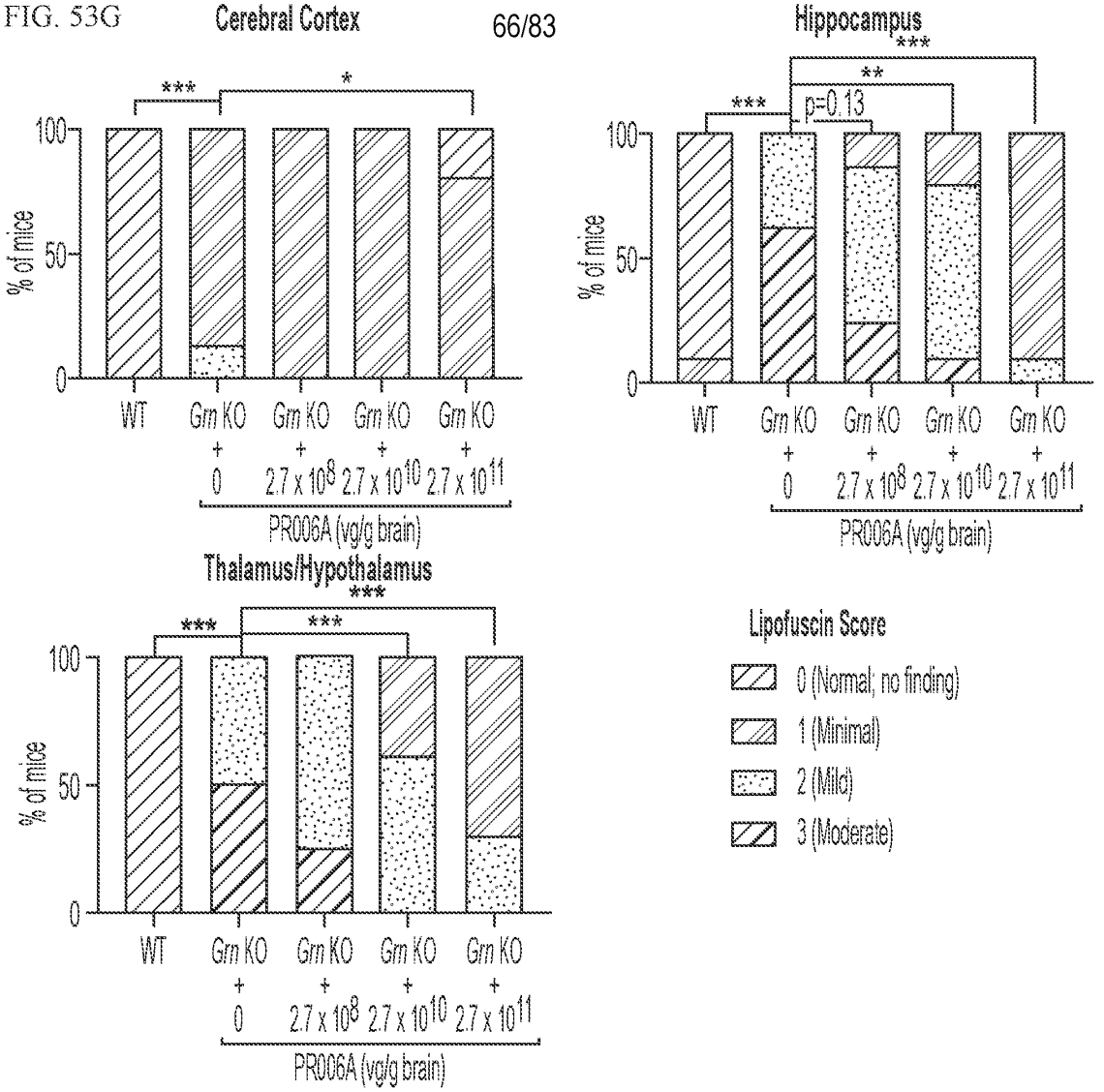
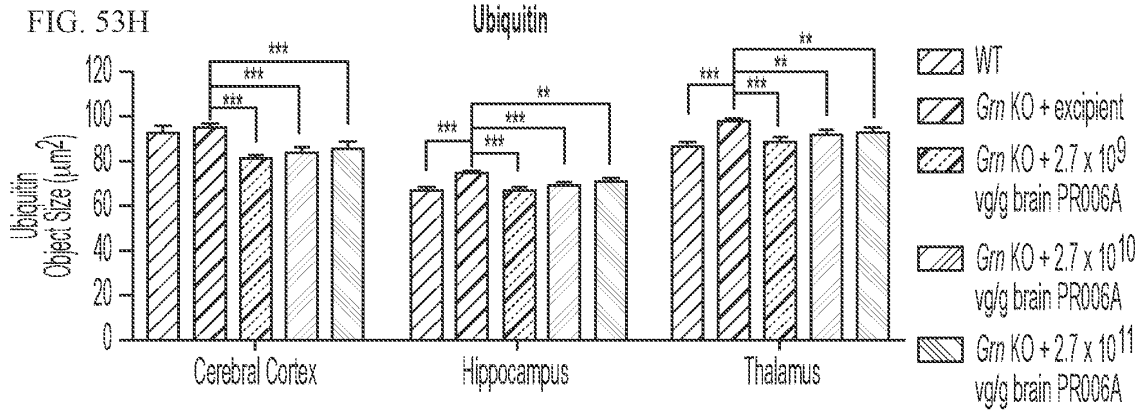


FIG. 53H



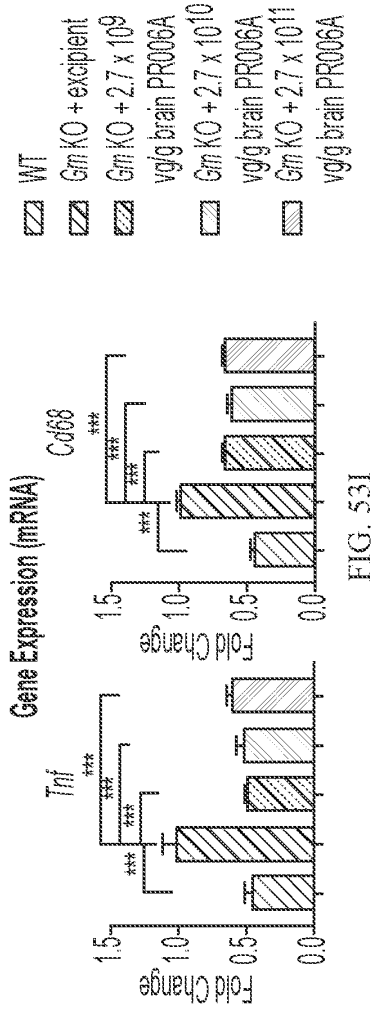


FIG. 53I

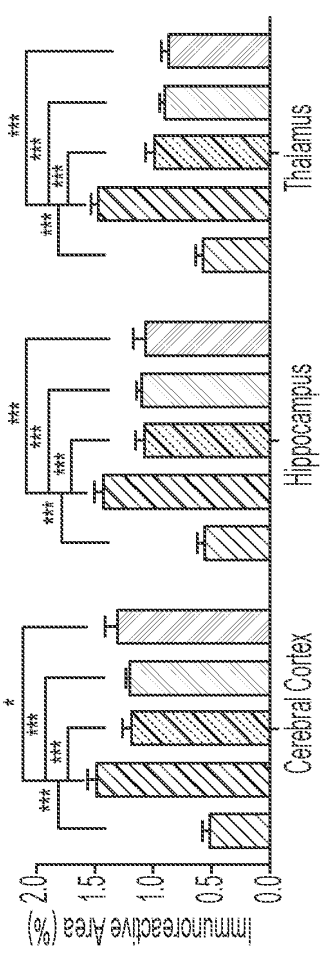


FIG. 53J

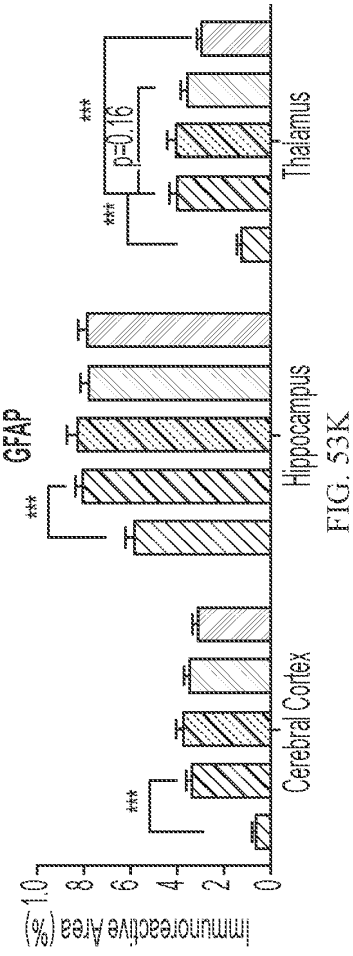


FIG. 53K

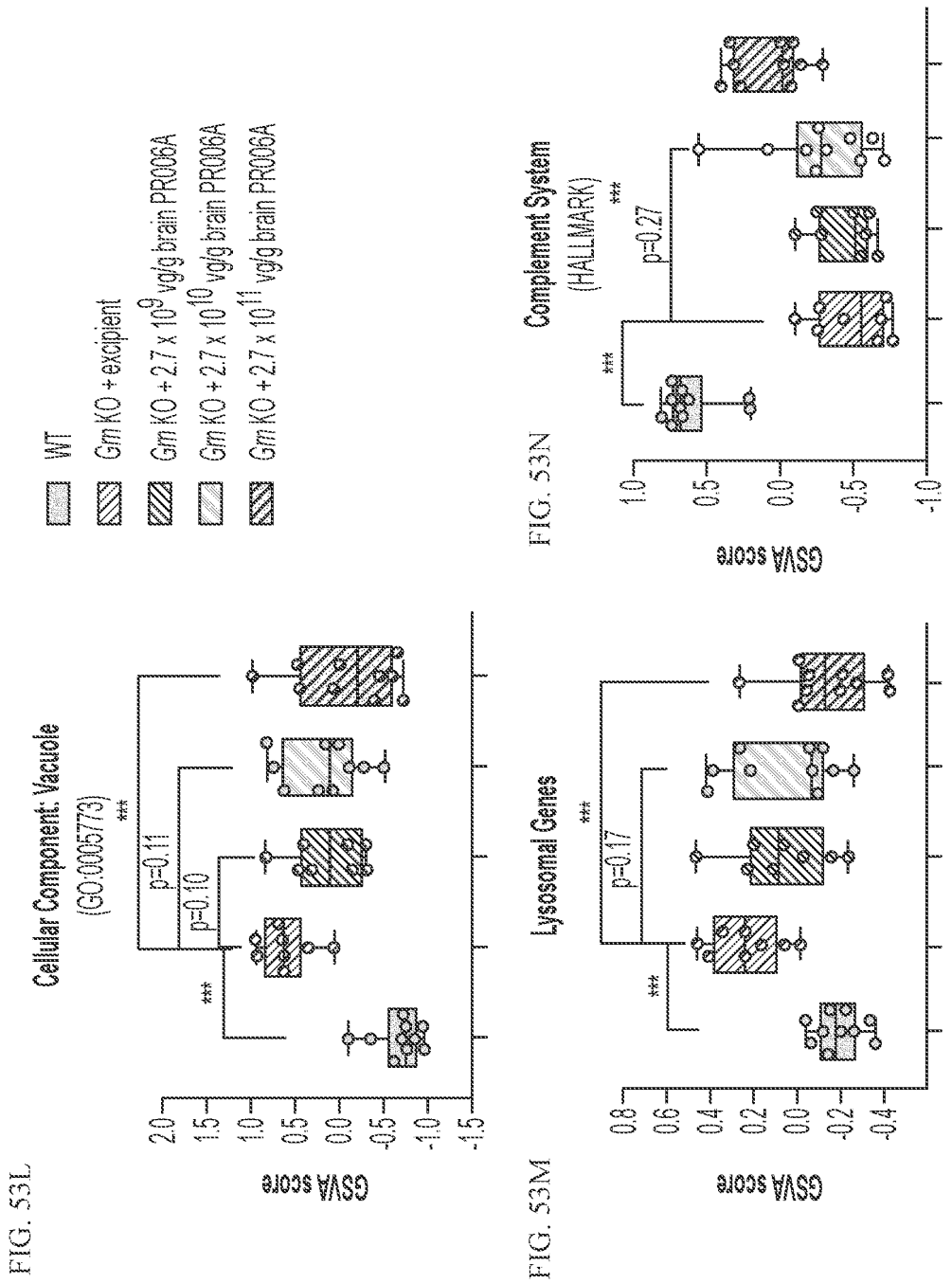


FIG. 53L

FIG. 53N

FIG. 53M

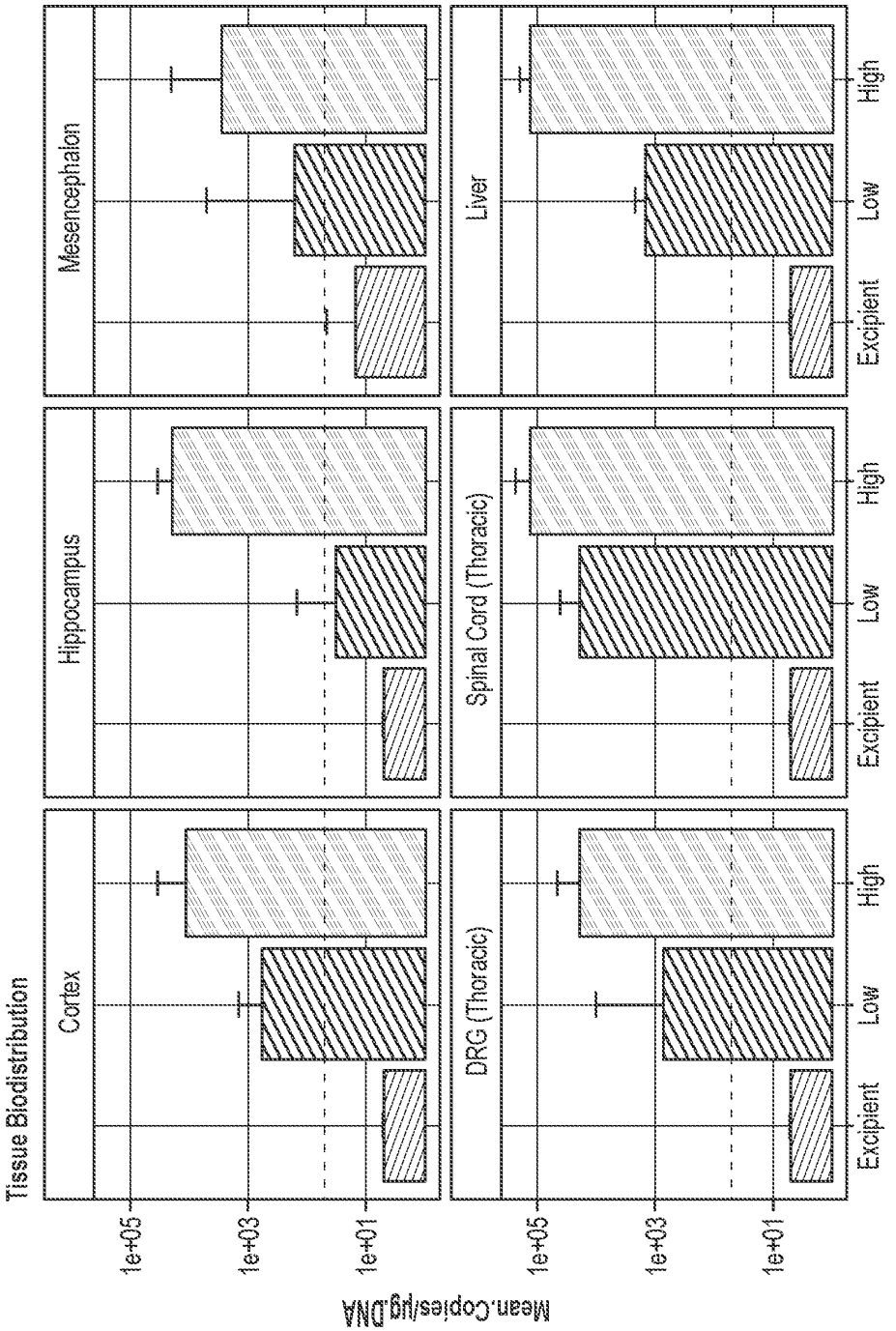

Tissue Biodistribution
Cortex
Hippocampus
Mesencephalon
DRG (Thoracic)
Spinal Cord (Thoracic)
Liver
Mean.Copies/µg.DNA
1e+05
1e+03
1e+01
Excipient
Low
High
Dose

FIG. 54A

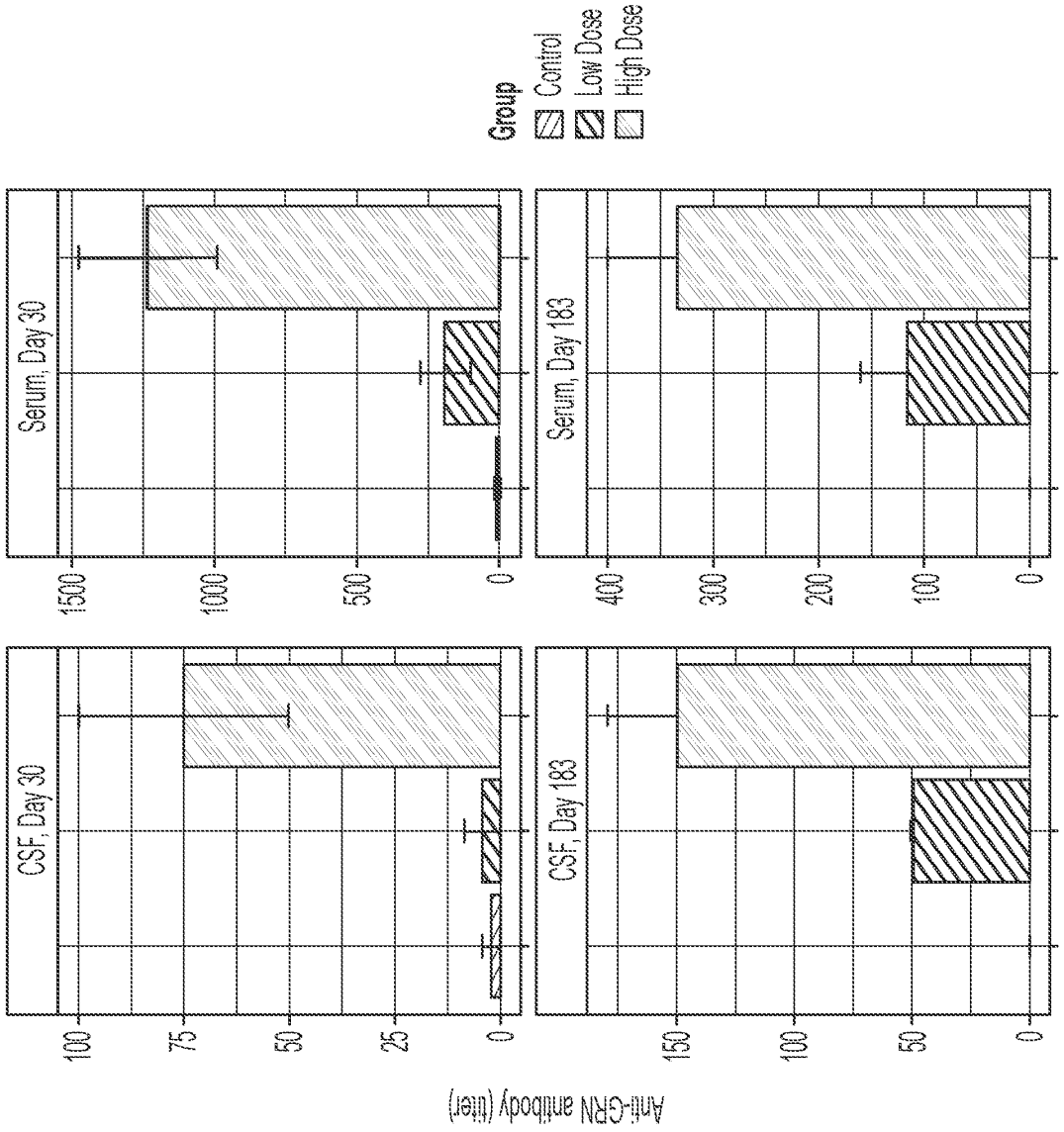

Group
Control
Low Dose
High Dose
Serum, Day 30
Serum, Day 183
CSF, Day 30
CSF, Day 183
Anti-GRN antibody (titer)
1500
1000
500
0
400
300
200
100
0
100
75
50
25
0
150
100
50
0

FIG. 54B

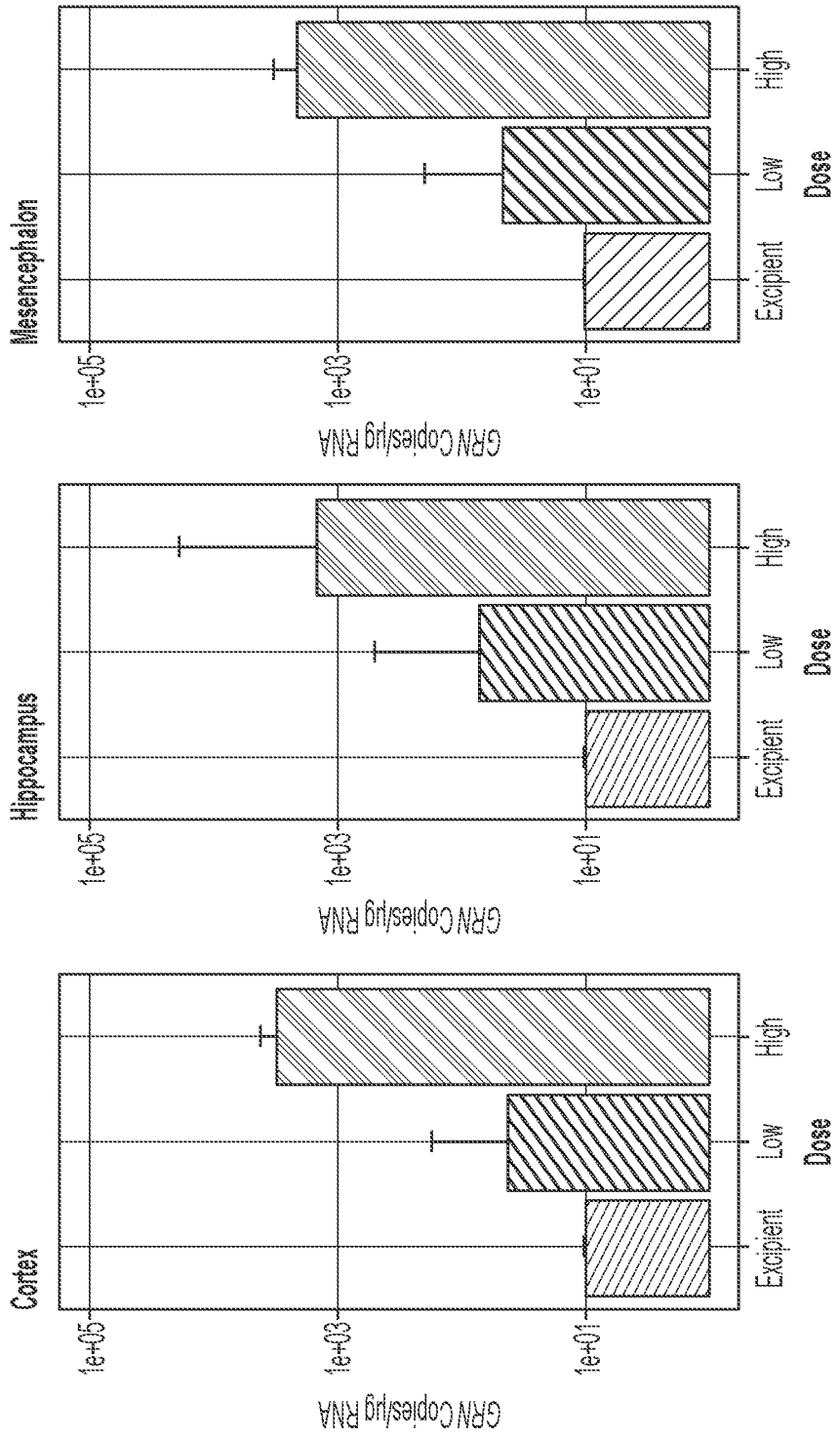

Mesencephalon
Hippocampus
Cortex
GRN Copies/µg RNA
1e+05
1e+03
1e+01
Excipient
Low
High
Dose

FIG. 54C

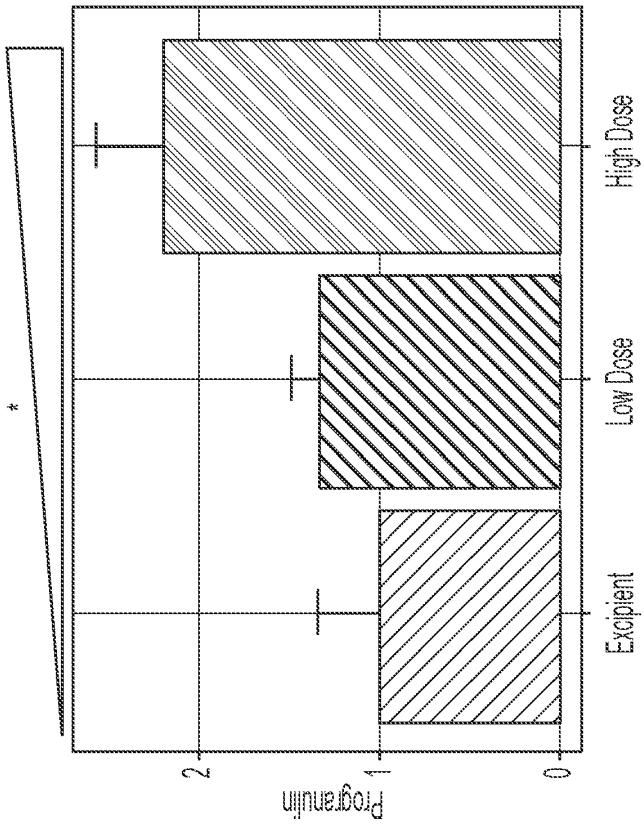


FIG. 54D

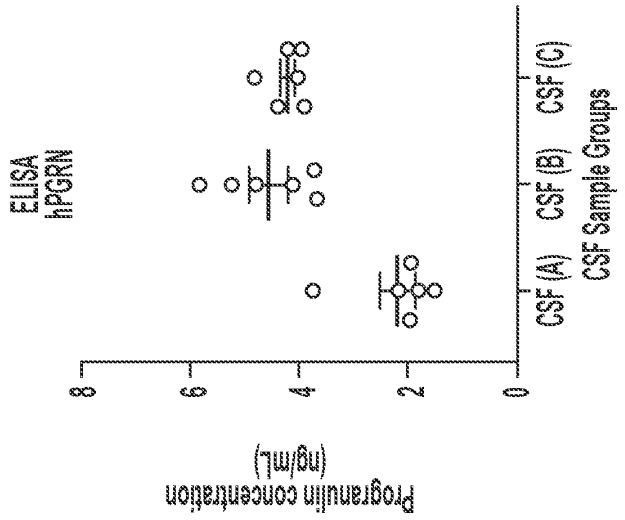

ELISA
hPGRN
Progranulin concentration
(ng/mL)
8
6
4
2
0
CSF (A)
CSF (B)
CSF (C)
CSF Sample Groups

FIG. 56

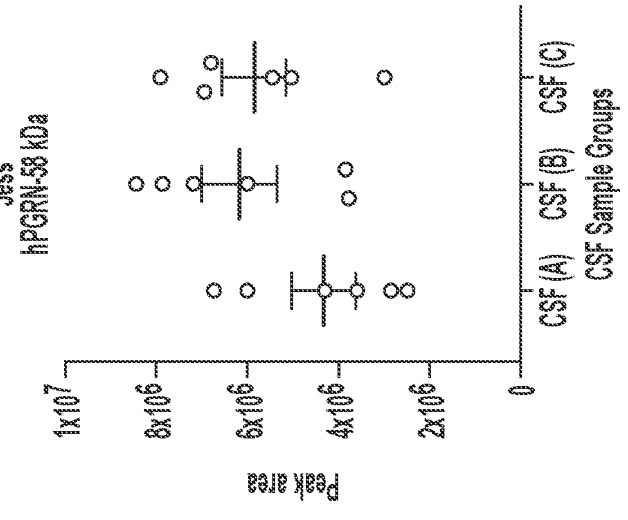

Jess
hPGRN-58 kDa
Peak area
1x10^7
8x10^6
6x10^6
4x10^6
2x10^6
0
CSF (A)
CSF (B)
CSF (C)
CSF Sample Groups

FIG. 55

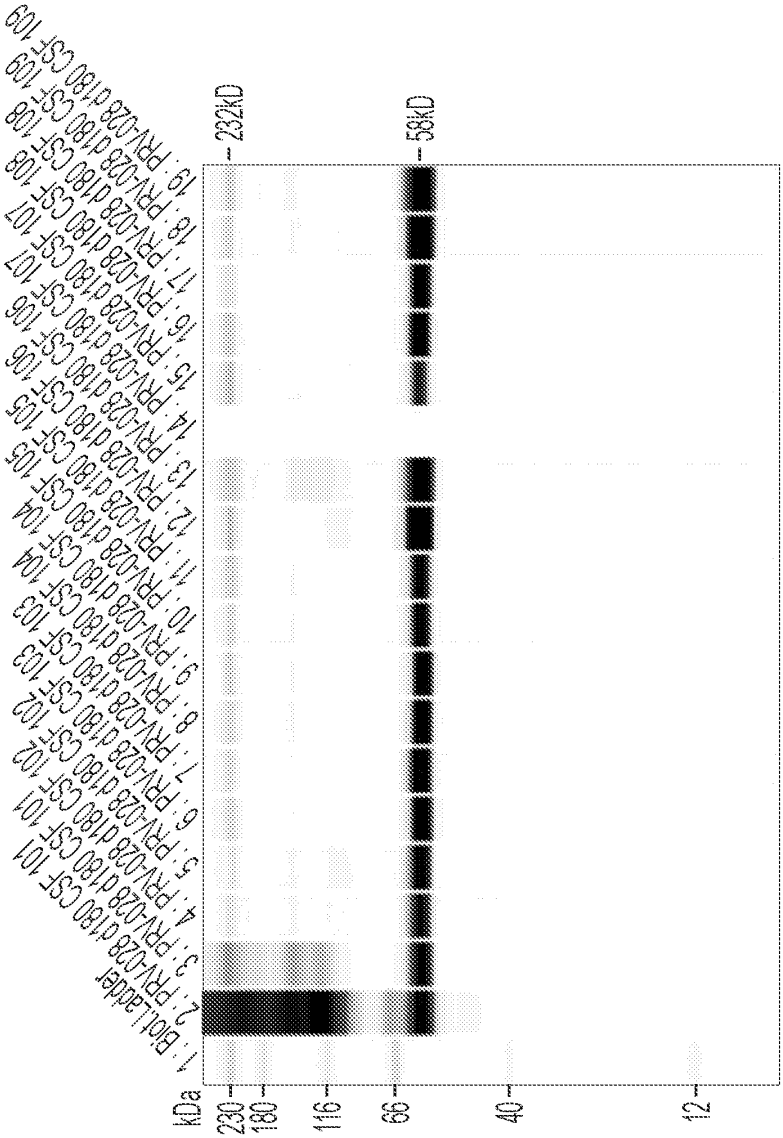

kDa
230
180
116
66
40
12
232kD
58kD
1. BioLadder
2. PRV-028 d180 CST 101
3. PRV-028 d180 CST 101
4. PRV-028 d180 CST 101
5. PRV-028 d180 CST 101
6. PRV-028 d180 CST 102
7. PRV-028 d180 CST 102
8. PRV-028 d180 CST 103
9. PRV-028 d180 CST 103
10. PRV-028 d180 CST 104
11. PRV-028 d180 CST 104
12. PRV-028 d180 CST 105
13. PRV-028 d180 CST 105
14. PRV-028 d180 CST 106
15. PRV-028 d180 CST 106
16. PRV-028 d180 CST 107
17. PRV-028 d180 CST 107
18. PRV-028 d180 CST 108
19. PRV-028 d180 CST 108
PRV-028 d180 CST 109
PRV-028 d180 CST 109

FIG. 57

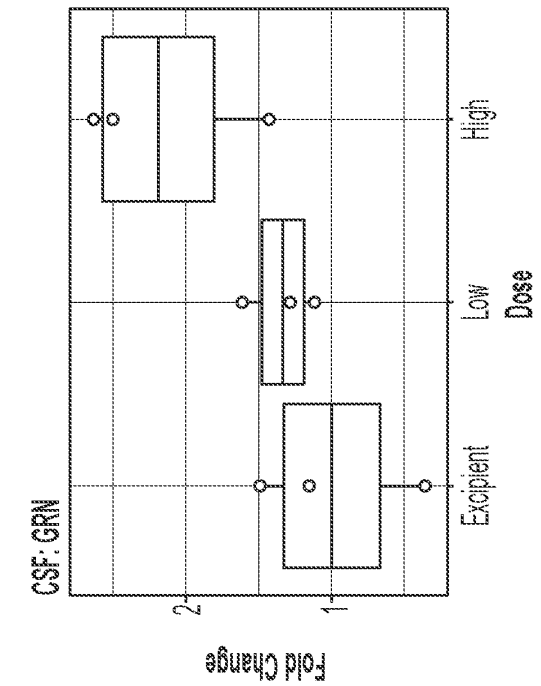


FIG. 58B

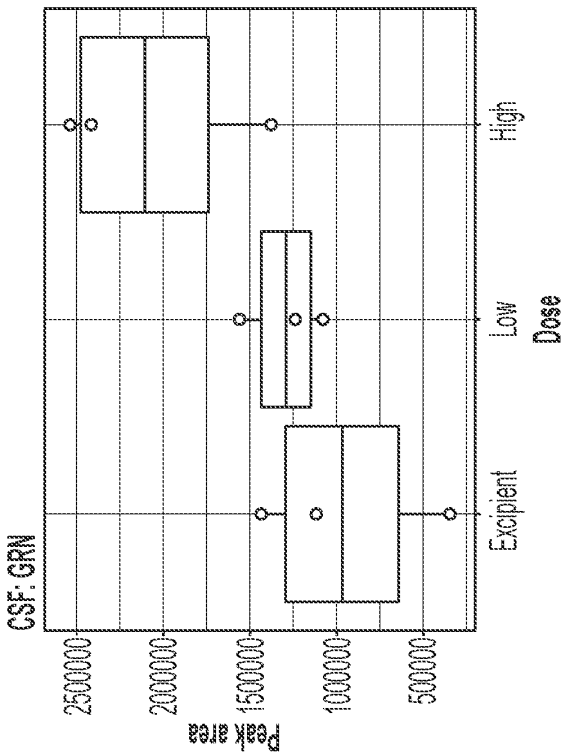


FIG. 58A

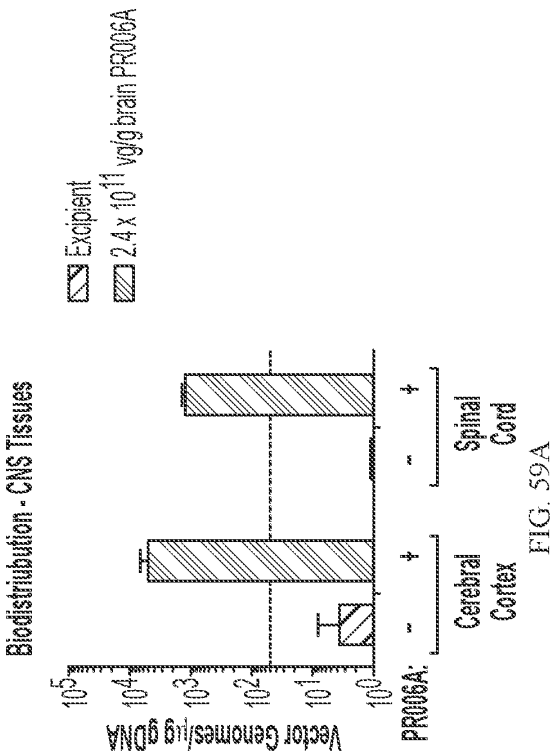


FIG. 59A

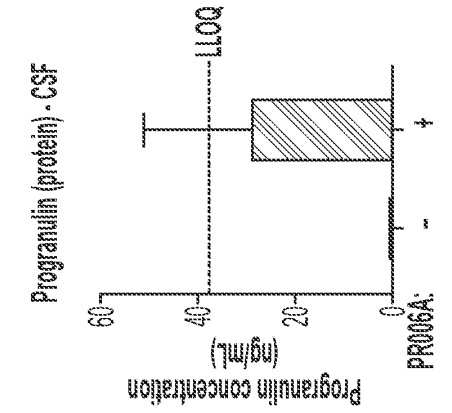


FIG. 59C

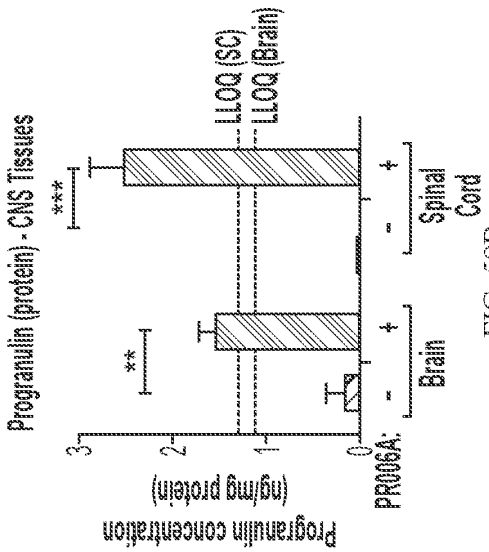


FIG. 59B

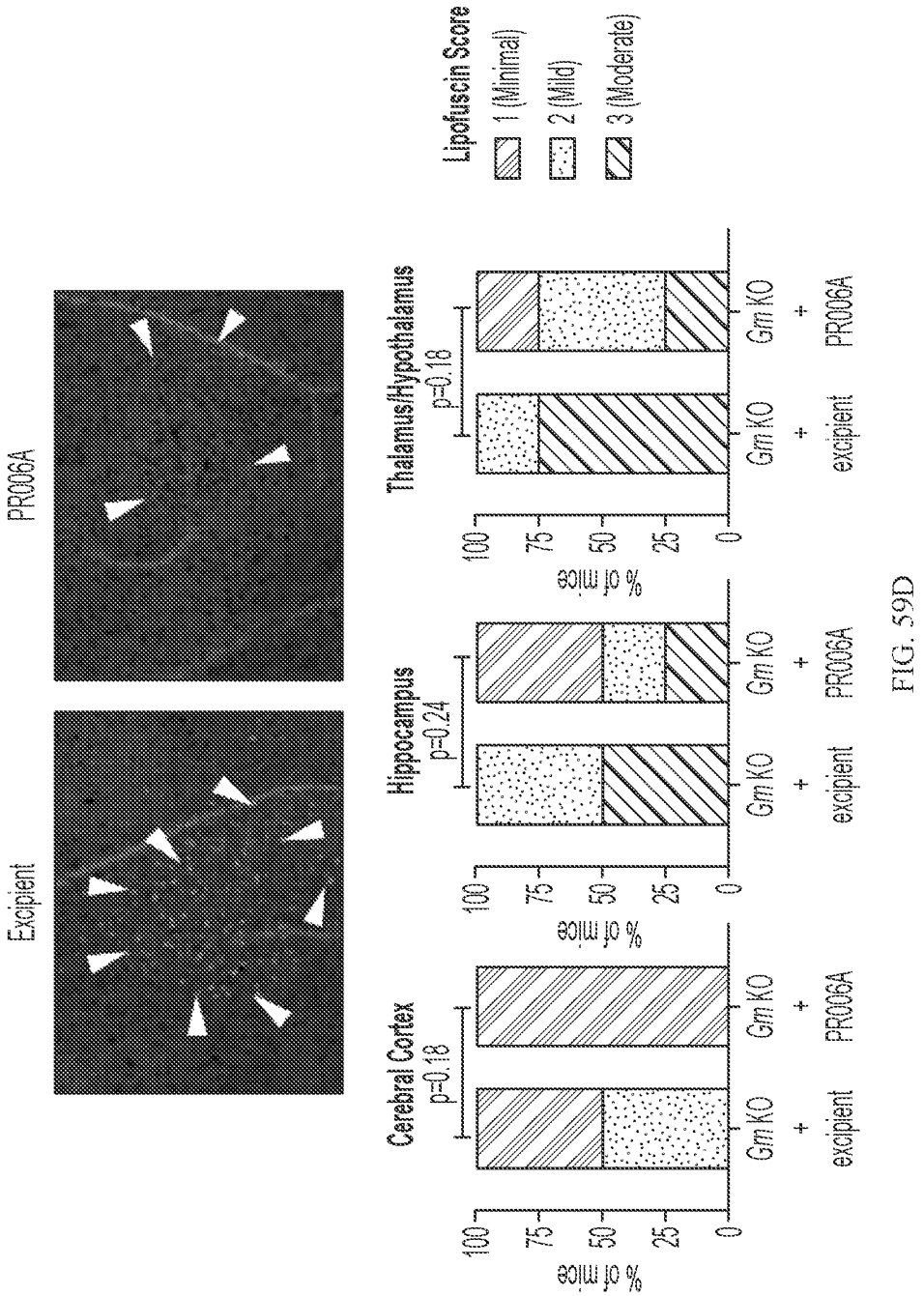

Excipient
PR006A
Lipofuscin Score
1 (Minimal)
2 (Mild)
3 (Moderate)
Thalamus/Hypothalamus
p=0.18
Hippocampus
p=0.24
Cerebral Cortex
p=0.18
% of mice
0
25
50
75
100
Gm KO
+
excipient
PR006A

FIG. 59D

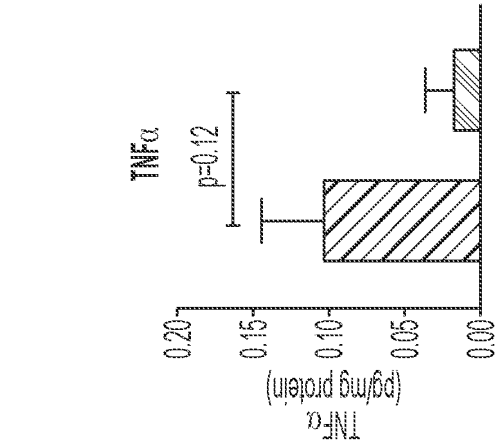


FIG. 59G

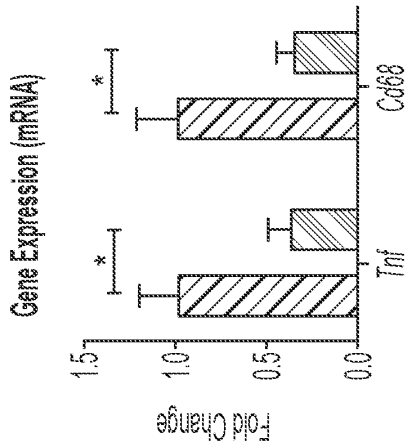


FIG. 59F

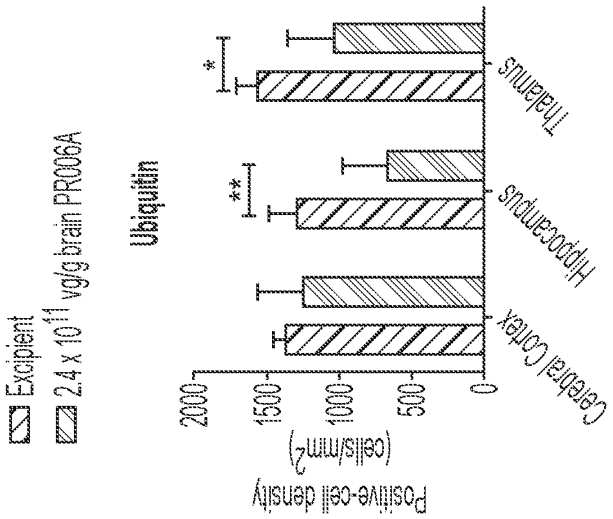


FIG. 59E

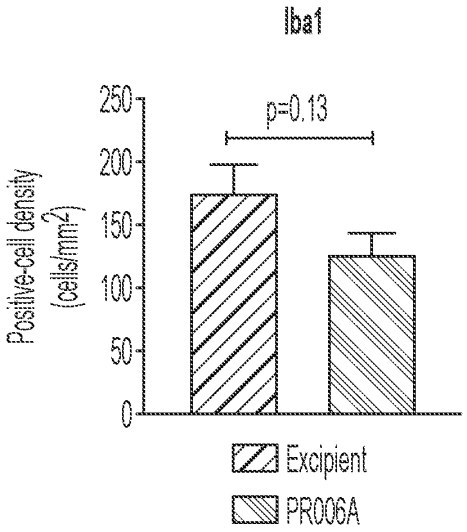


FIG. 59H

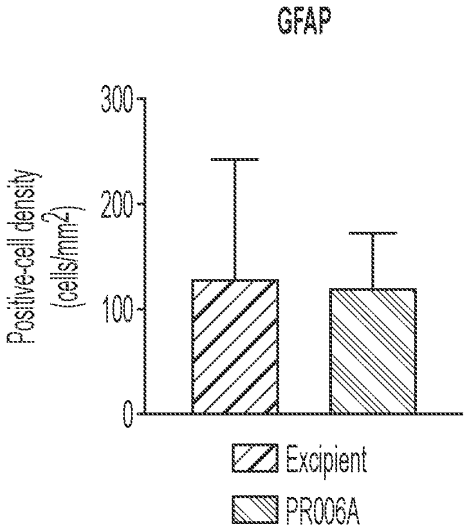


FIG. 59I

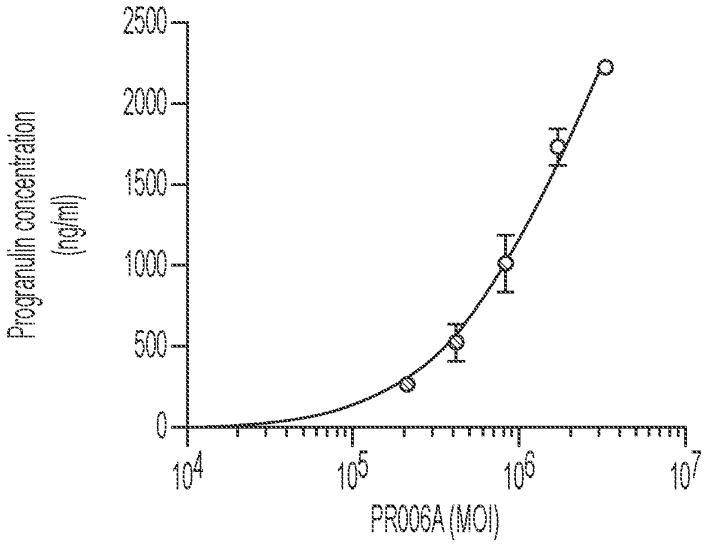
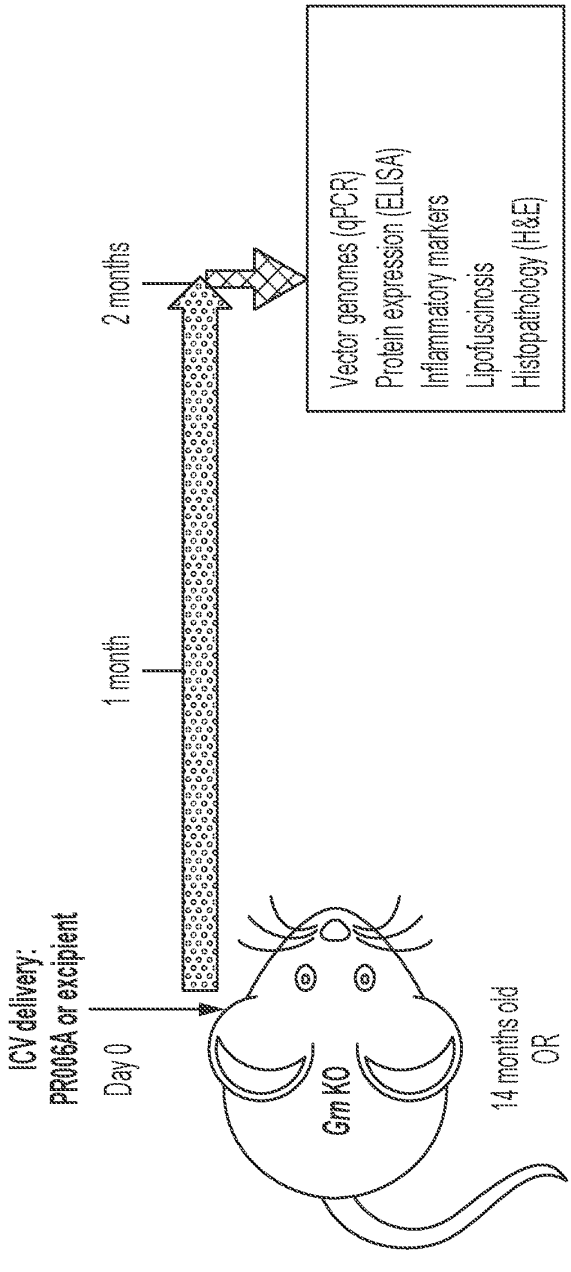


FIG. 60



PR006A dose	Total vg	vg / g brain
single	9.7×10^{10}	2.4×10^{11}

FIG. 61

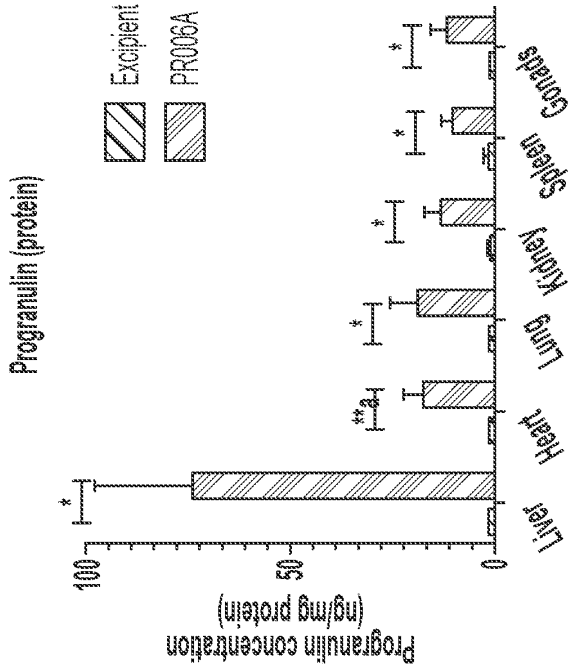


FIG. 62B

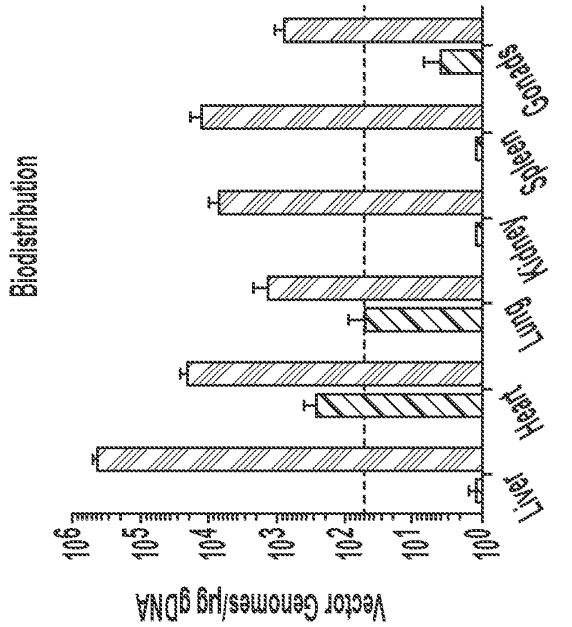
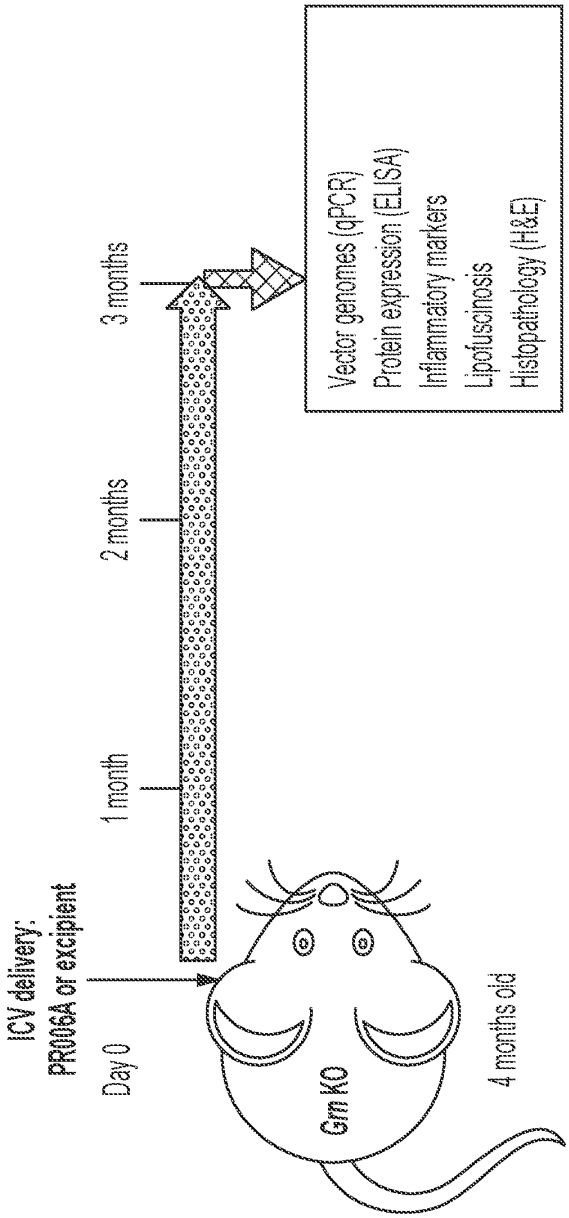


FIG. 62A



PR006A dose	Total vg	vg / g brain
Low	1.1×10^9	2.7×10^9
Medium	1.1×10^{10}	2.7×10^{10}
High	1.1×10^{11}	2.7×10^{11}

FIG. 63

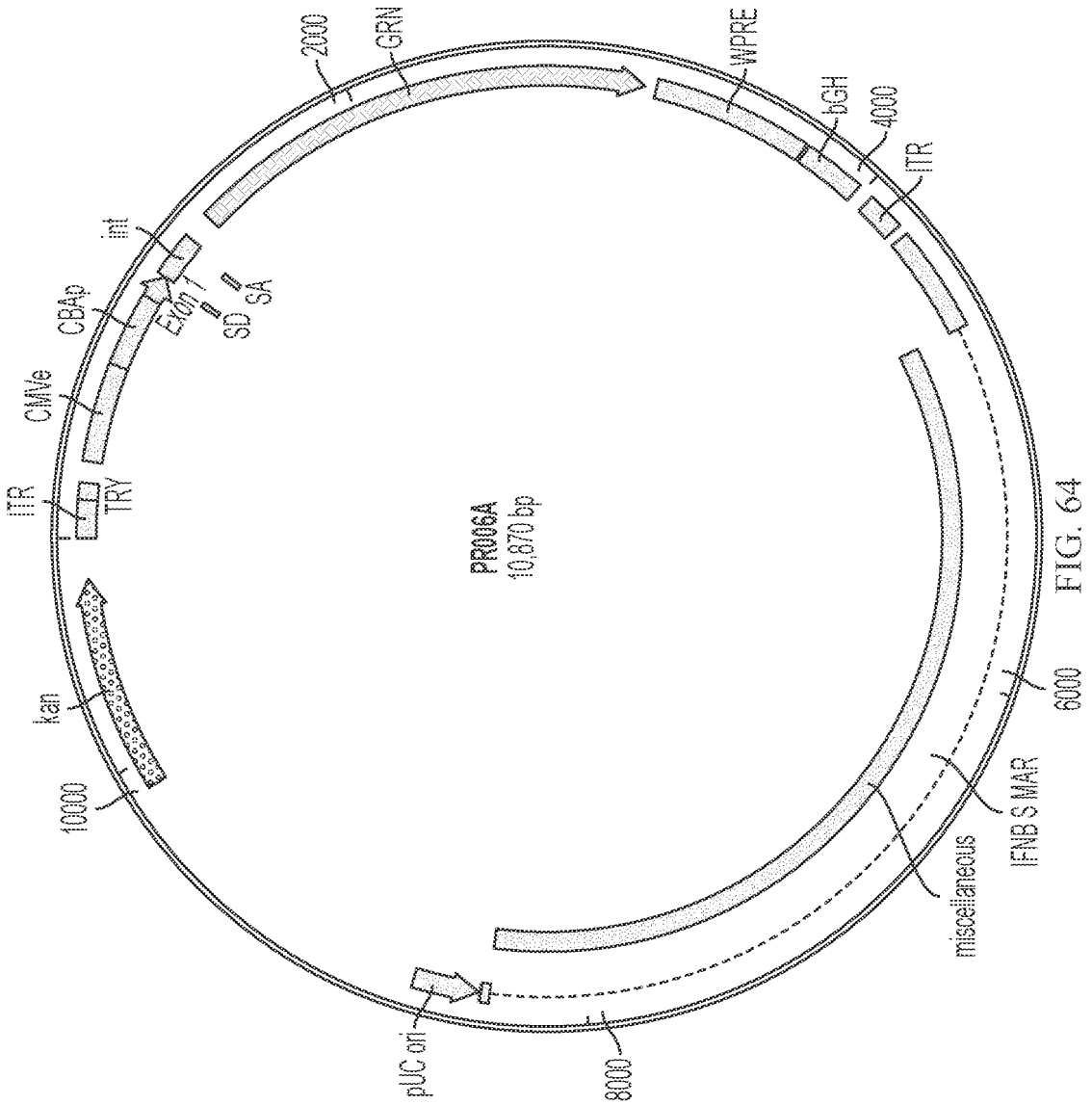

2000
GRN
WPRE
bGH
4000
ITR
int
CBAp
Exon 1
SD
SA
CMVe
ITR
TRY
PR006A
10,870 bp
kan
10000
pUC ori
8000
miscellaneous
IFNB S MAR
6000

FIG. 64