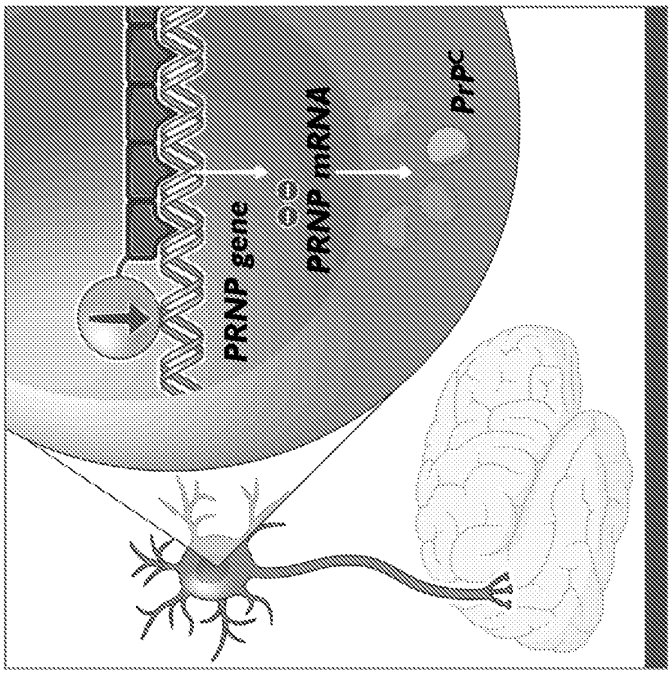

FIG. 1A

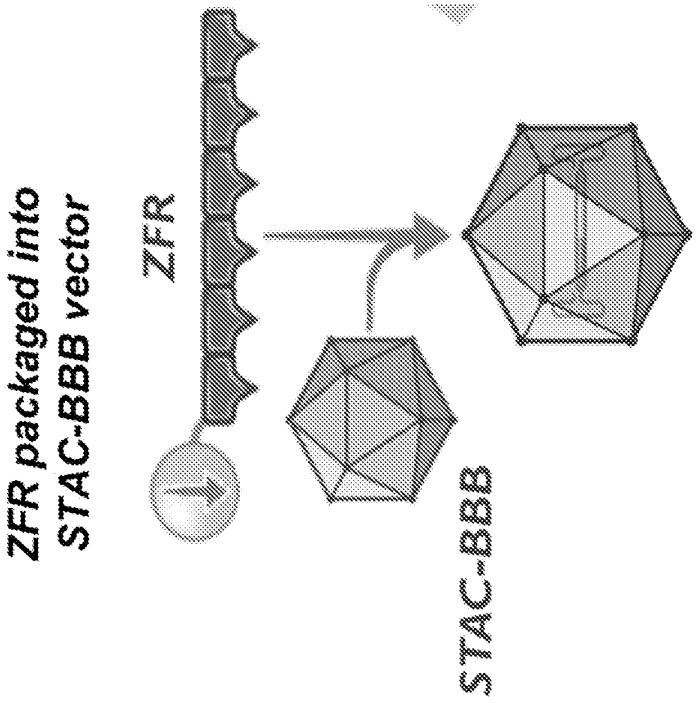

FIG. 1B

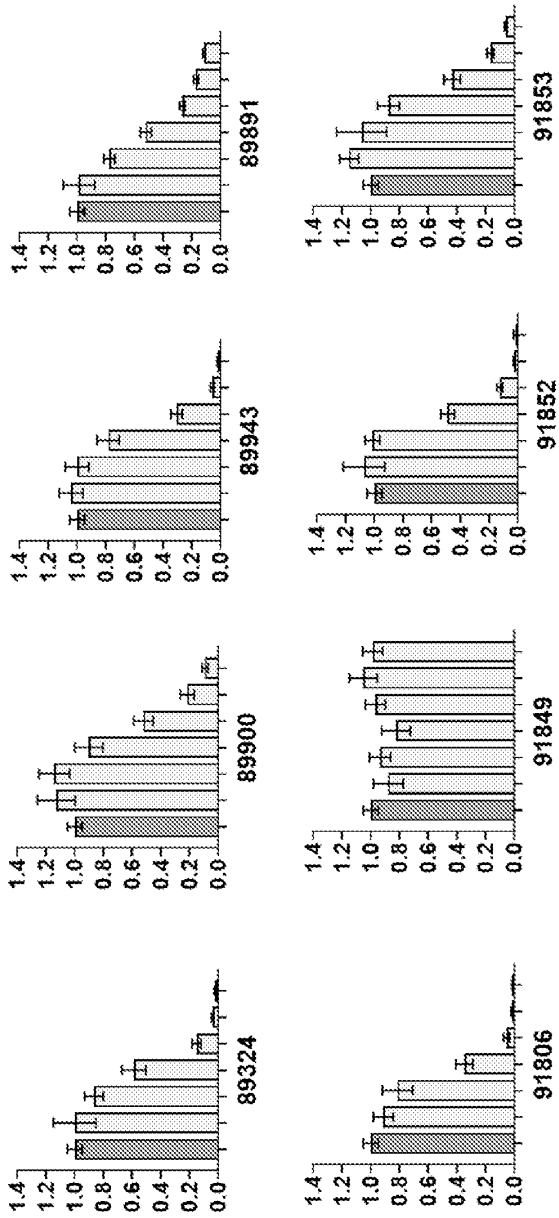
89324
89900
89943
89891
91806
91849
91852
91853
91870
91975
Control (ZFP 65976)
3
10
30
100
300
1000

FIG. 2

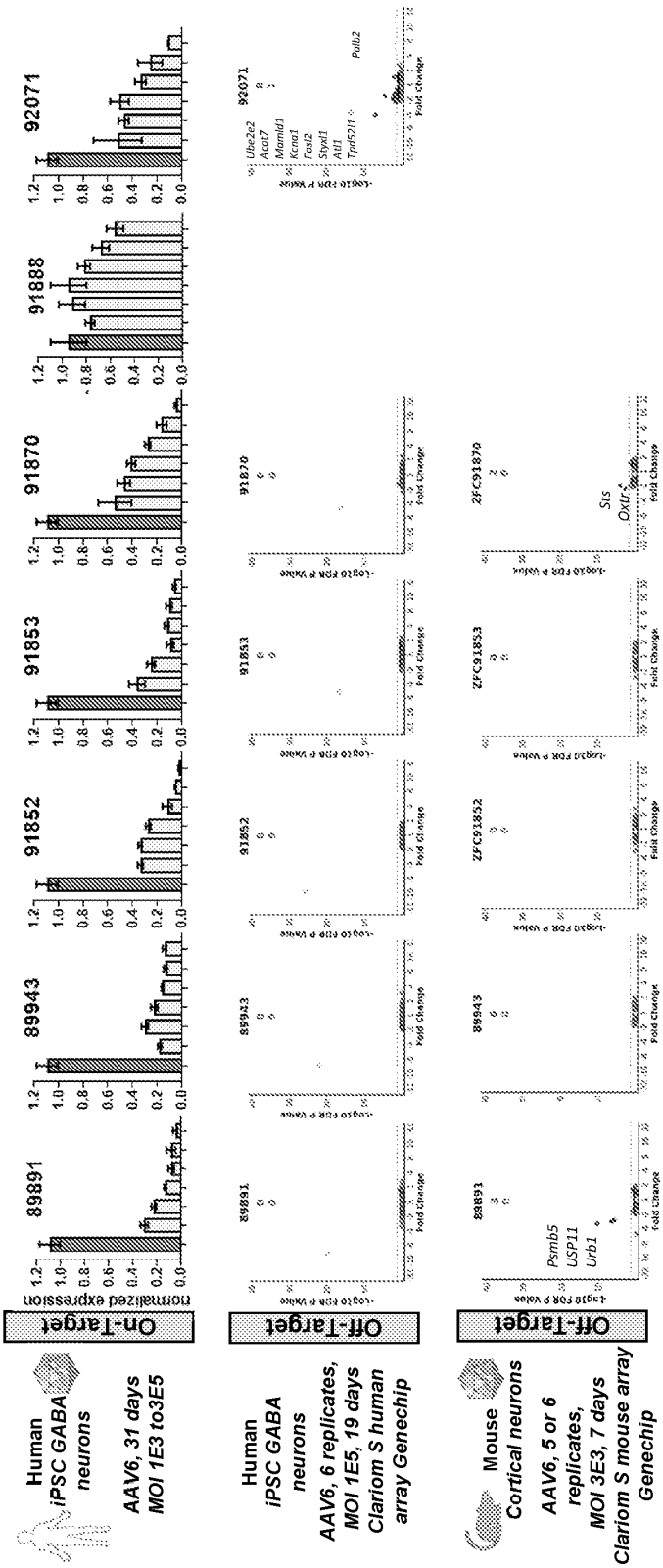
On-Target
Off-Target
Off-Target
Human iPSC GABA neurons
AAV6, 31 days
MOI 1E3 to3E5
Human iPSC GABA neurons
AAV6, 6 replicates, MOI 1E5, 19 days
Clariom S human array Genechip
Mouse Cortical neurons
AAV6, 5 or 6 replicates, MOI 3E3, 7 days
Clariom S mouse array Genechip
normalized expression
89891
89943
91852
91853
91870
91888
92071
Psmb5
USP11
Urb1
Sts
Oxtr
Ube2e2
Acot7
Mamld1
Kcna1
Fasl2
Styxl1
Atl1
Tpd52l1
Palb2
Prion
FDR p-val < 0.05; Downregulated
FDR p-val < 0.05; Upregulated
Untreated control
1e3
3e3
1e4
3e4
1e5
3e5
ZFP-R MOI per reaction

FIG. 3

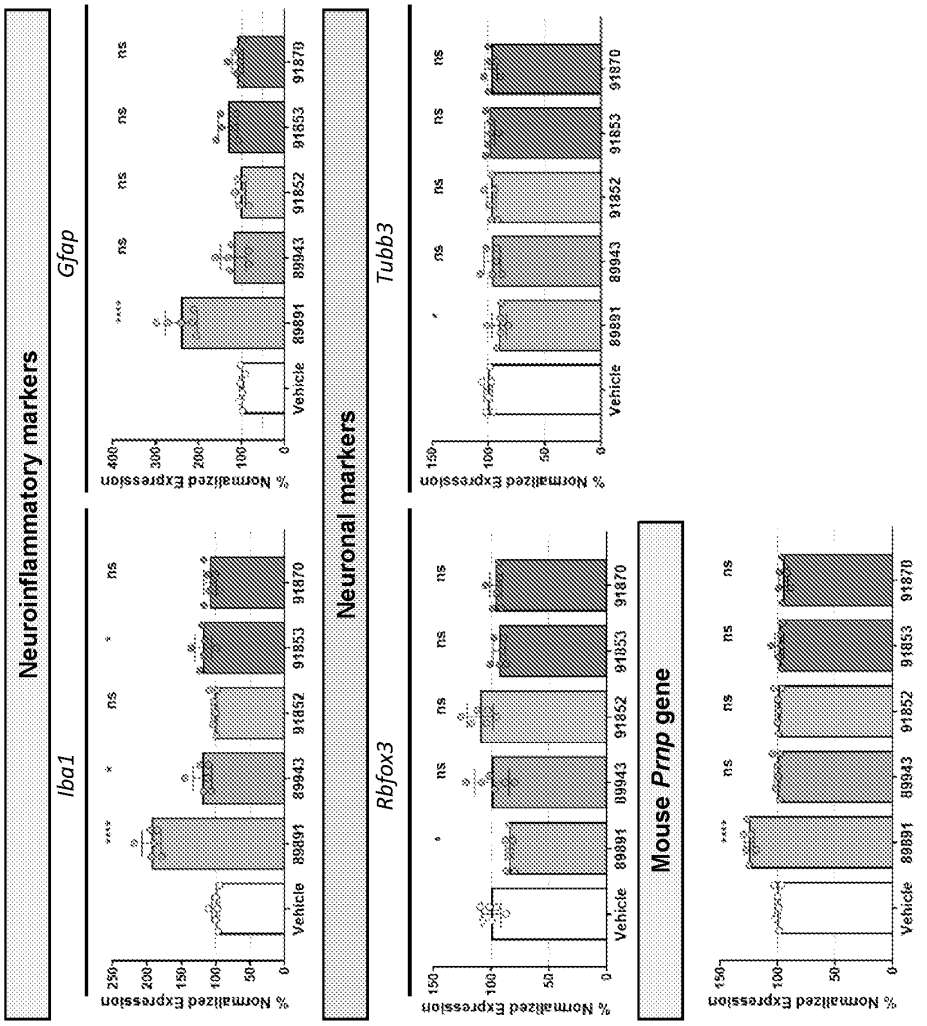
Neuroinflammatory markers
Iba1
Gfap
Neuronal markers
Rbfox3
Tubb3
Mouse Prnp gene
% Normalized Expression
Vehicle
89891
89943
91852
91853
91870
ns

FIG. 4A

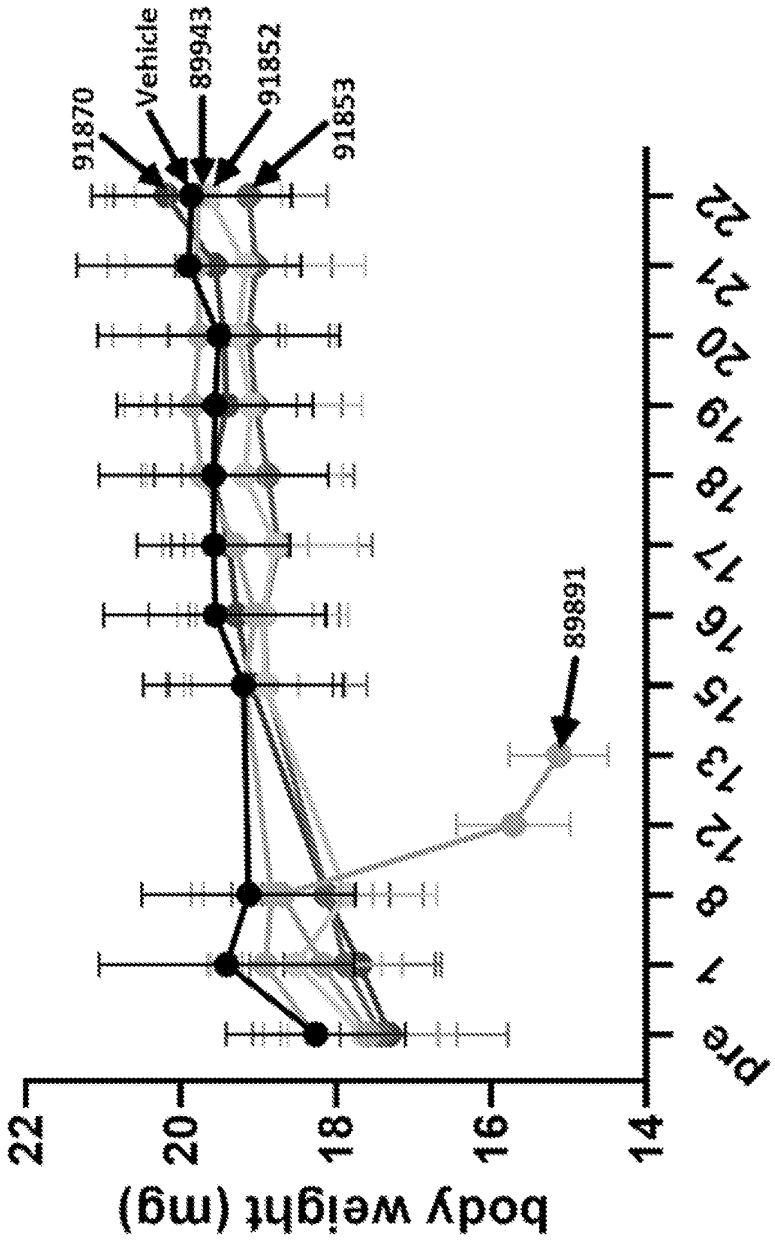
91870
Vehicle
89943
91852
91853
89891
body weight (mg)
22
20
18
16
14
pre
1
8
12
13
15
16
17
18
19
20
21
22
study days

FIG. 4B

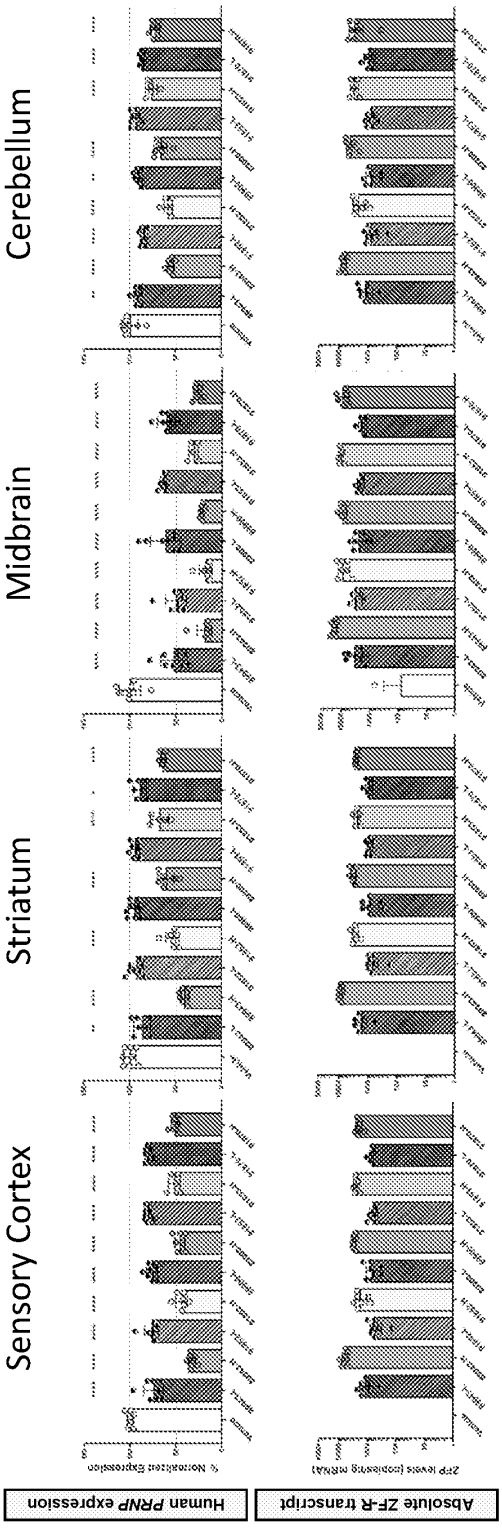
Sensory Cortex
Striatum
Midbrain
Cerebellum
Human PRNP expression
Absolute ZF-R transcript

FIG. 5

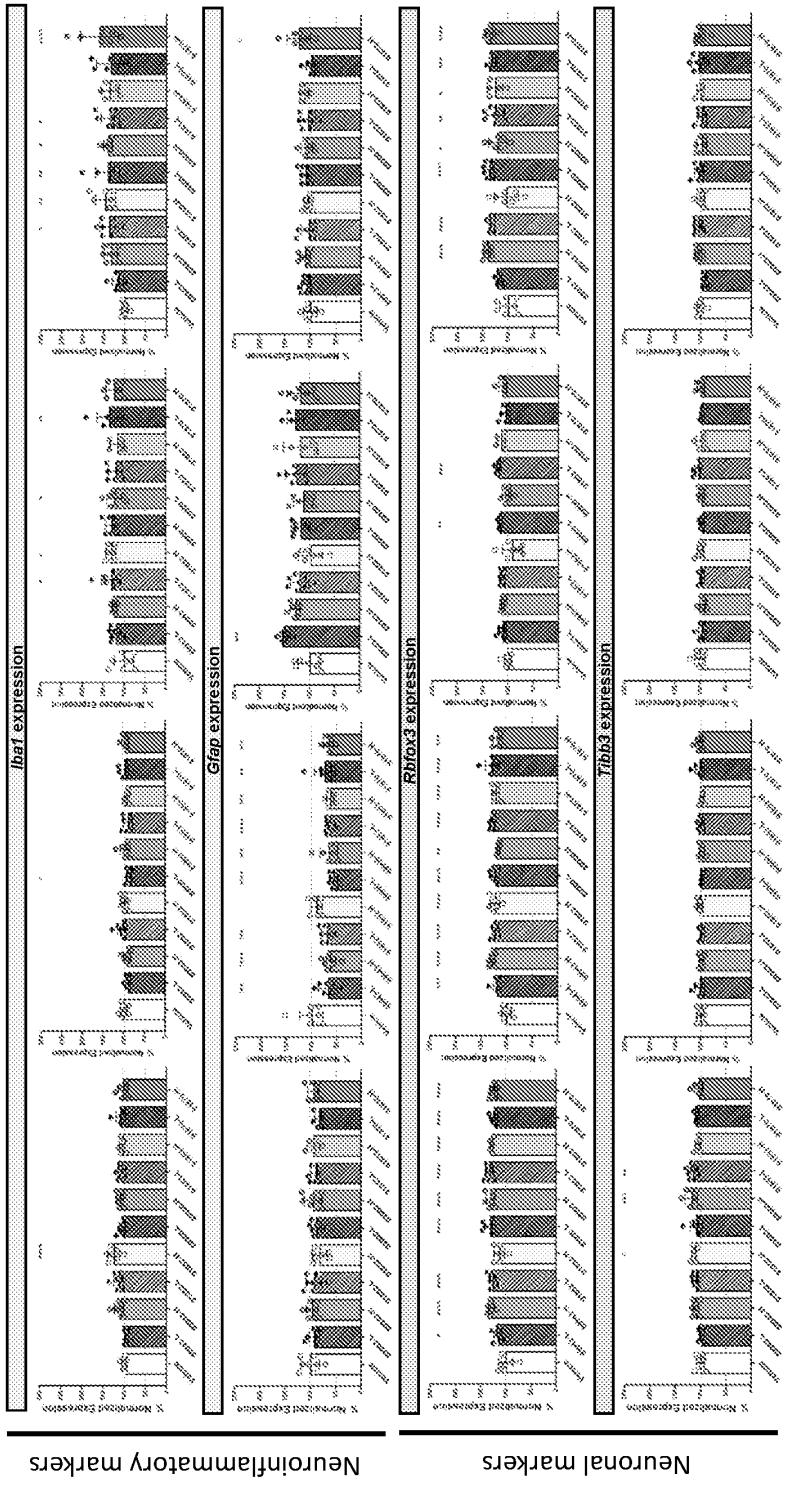
Sensory Cortex
Striatum
Midbrain
Cerebellum
Iba1 expression
Gfap expression
Rbfox3 expression
Tubb3 expression
Neuroinflammatory markers
Neuronal markers

FIG. 6

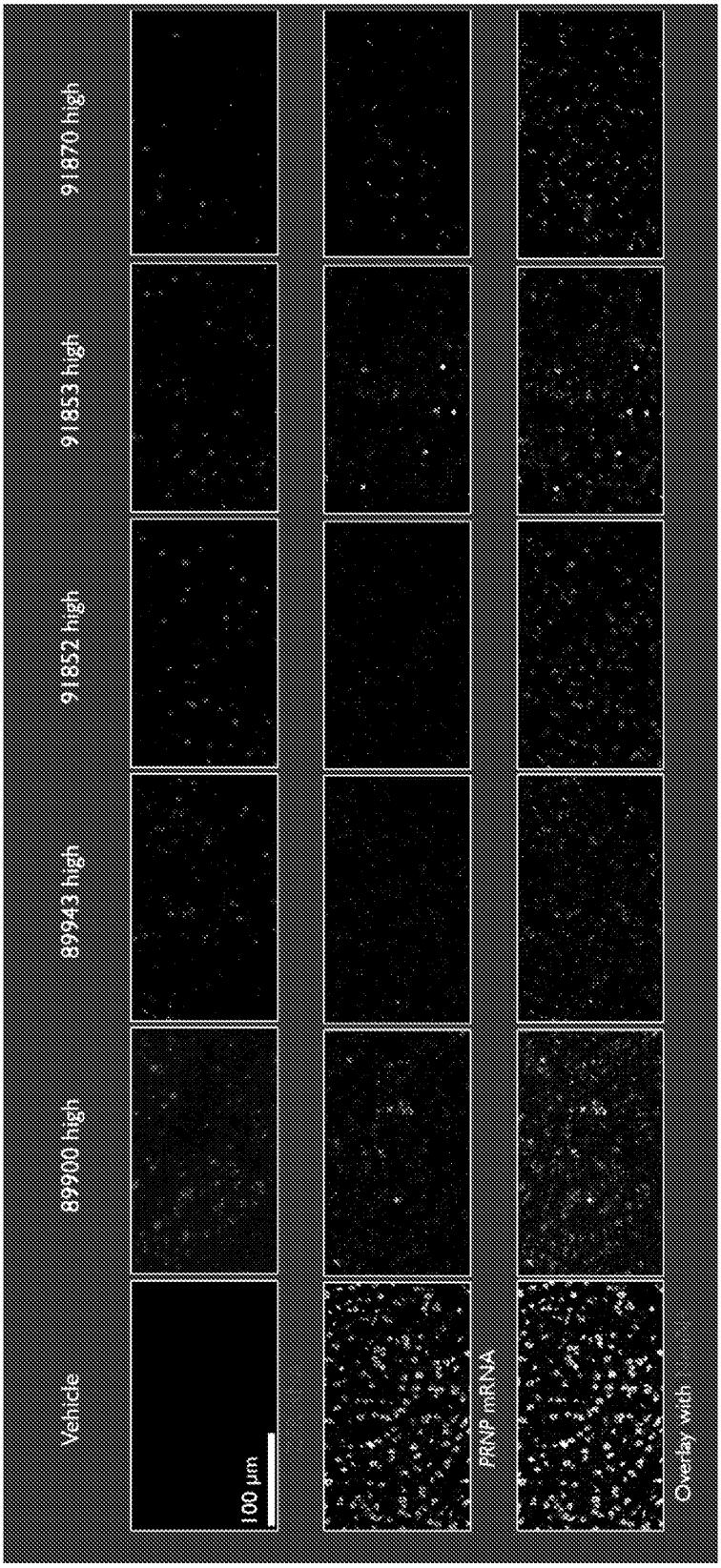
Vehicle
89900 high
89943 high
91852 high
91853 high
91870 high
100 µm
PRNP mRNA
Overlay with

FIG. 7A

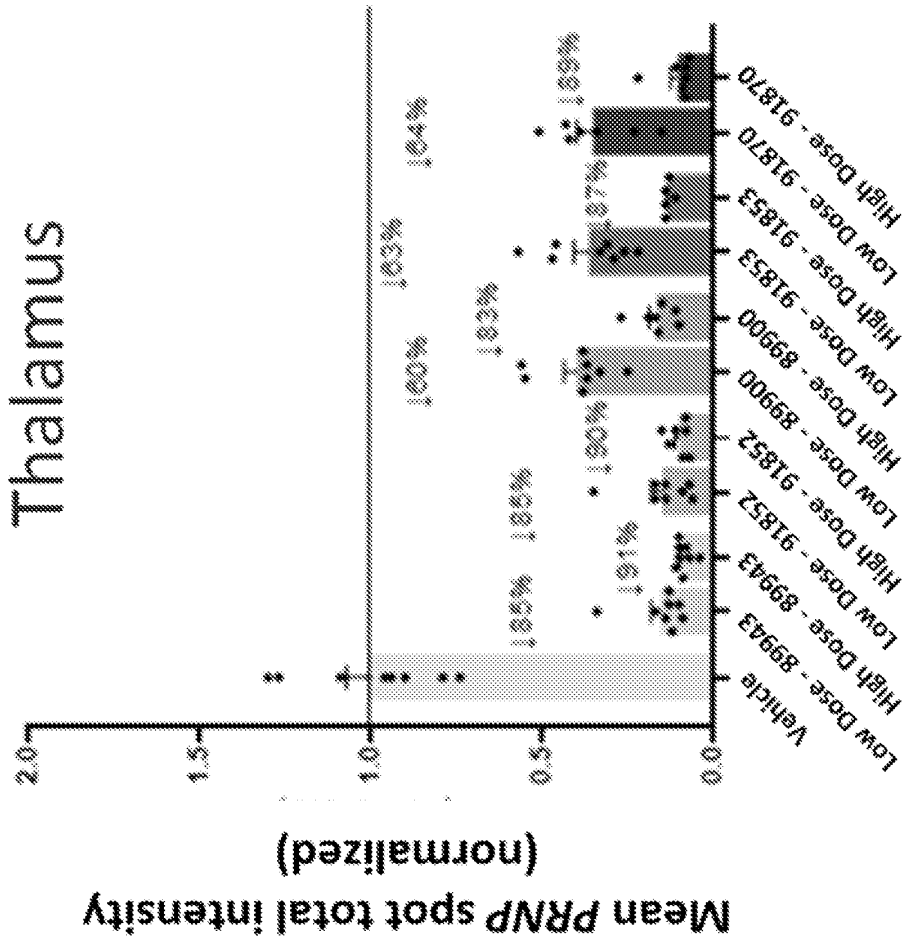
Thalamus
Mean PRNP spot total intensity (normalized)
2.0
1.5
1.0
0.5
0.0
Vehicle
Low Dose - 89943
High Dose - 89943
Low Dose - 91852
High Dose - 91852
Low Dose - 89900
High Dose - 89900
Low Dose - 91853
High Dose - 91853
Low Dose - 91870
High Dose - 91870
185%
185%
191%
190%
160%
183%
163%
187%
164%
189%

FIG. 7B

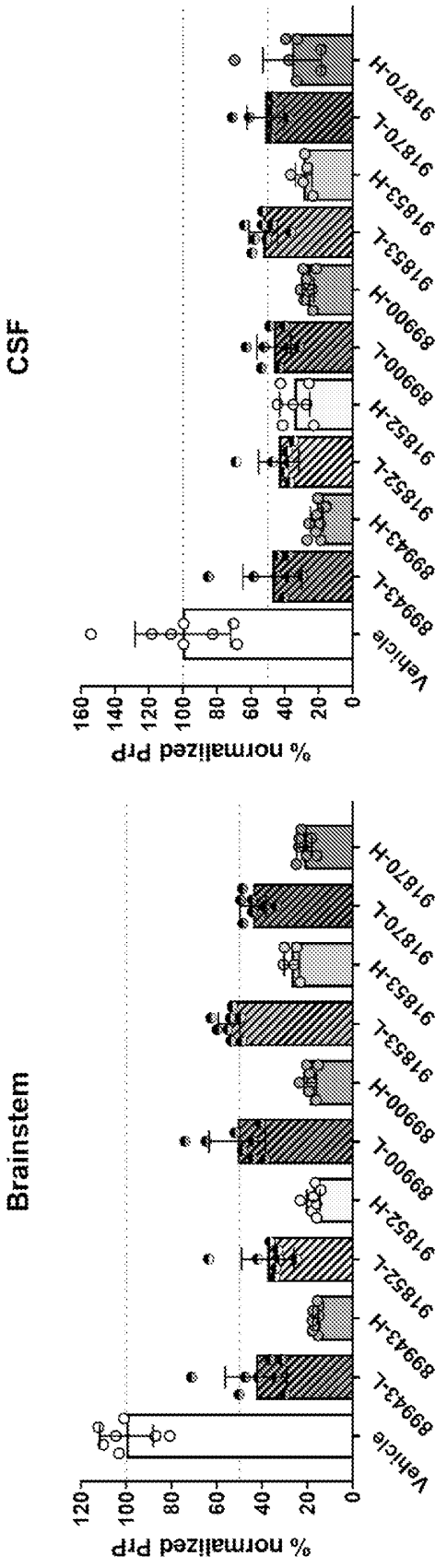
Brainstem
% normalized PrP
0
20
40
60
80
100
120
Vehicle
89943-L
89943-H
91852-L
91852-H
89900-L
89900-H
91853-L
91853-H
91870-L
91870-H
CSF
% normalized PrP
0
20
40
60
80
100
120
140
160
Vehicle
89943-L
89943-H
91852-L
91852-H
89900-L
89900-H
91853-L
91853-H
91870-L
91870-H

FIG. 8

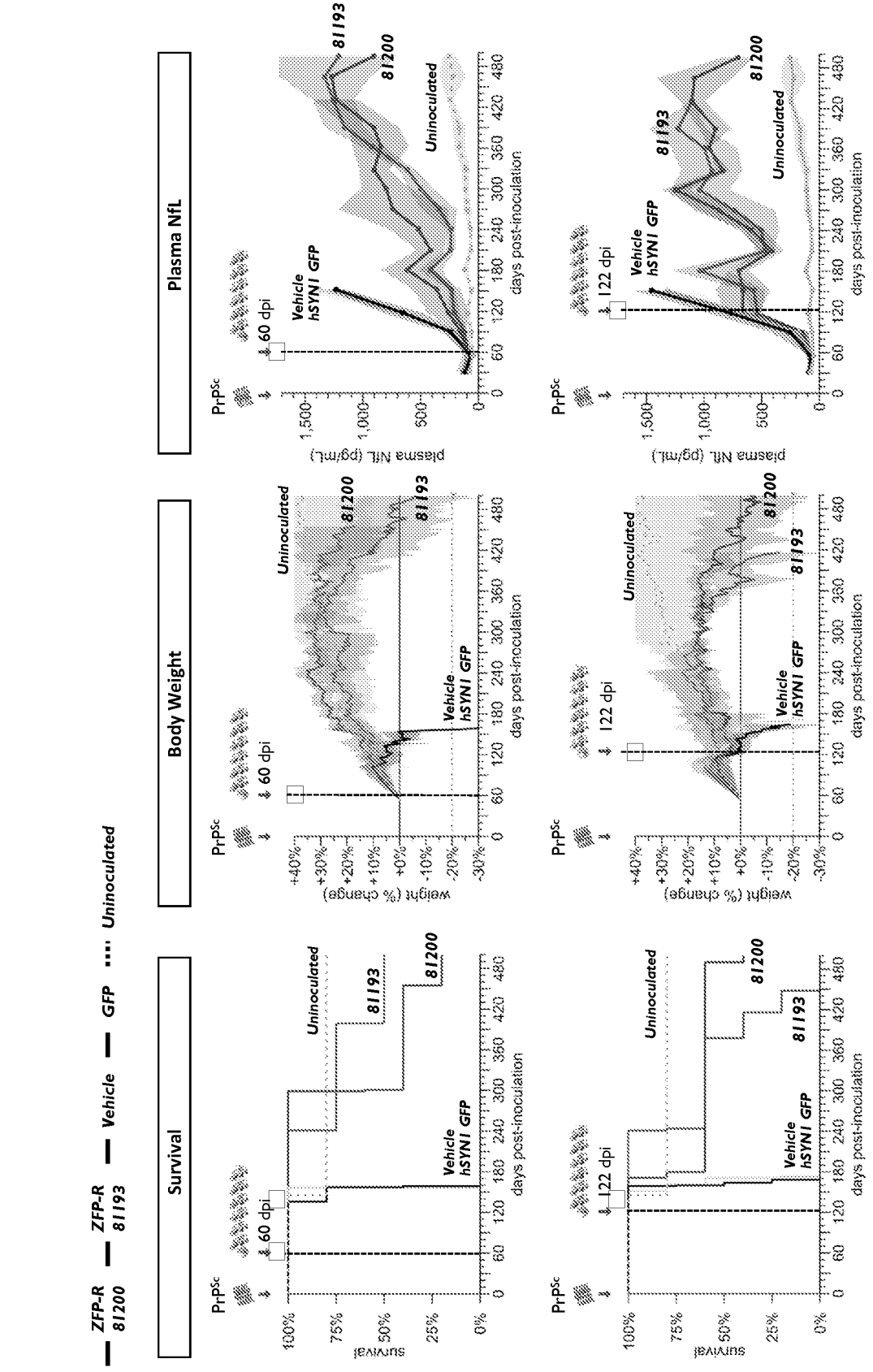
ZFP-R 81200
ZFP-R 81193
Vehicle
GFP
Uninoculated
Survival
Body Weight
Plasma NfL
PrPSc
60 dpi
122 dpi
survival
weight (% change)
plasma NfL (pg/mL)
days post-inoculation
Uninoculated
81200
81193
Vehicle hSYN1 GFP

FIG. 9

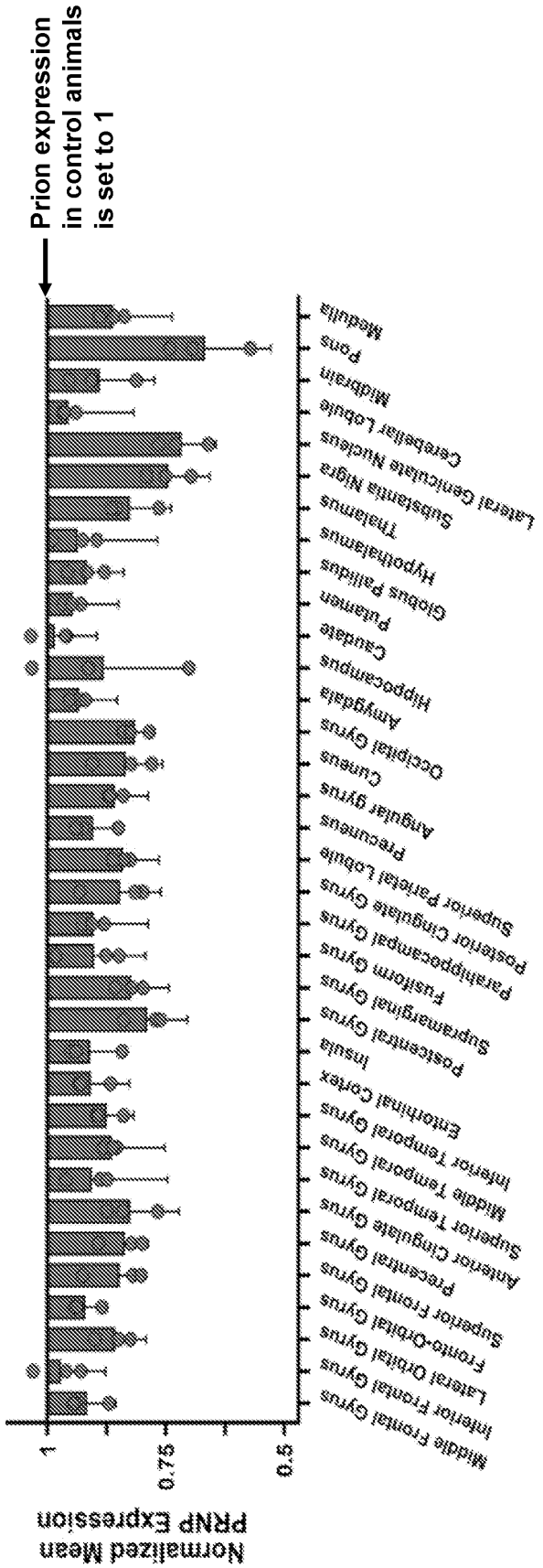
Prion expression
in control animals
is set to 1
Normalized Mean
PRNP Expression
1
0.75
0.5
Middle Frontal Gyrus
Inferior Frontal Gyrus
Lateral Orbital Gyrus
Fronto-Orbital Gyrus
Superior Frontal Gyrus
Precentral Gyrus
Anterior Cingulate Gyrus
Superior Temporal Gyrus
Middle Temporal Gyrus
Inferior Temporal Gyrus
Entorhinal Cortex
Insula
Postcentral Gyrus
Supramarginal Gyrus
Fusiform Gyrus
Parahippocampal Gyrus
Posterior Cingulate Gyrus
Superior Parietal Lobule
Precuneus
Angular Gyrus
Cuneus
Occipital Gyrus
Amygdala
Hippocampus
Caudate
Putamen
Globus Pallidus
Hypothalamus
Thalamus
Substantia Nigra
Lateral Geniculate Nucleus
Cerebellar Lobule
Midbrain
Pons
Medulla

FIG. 10