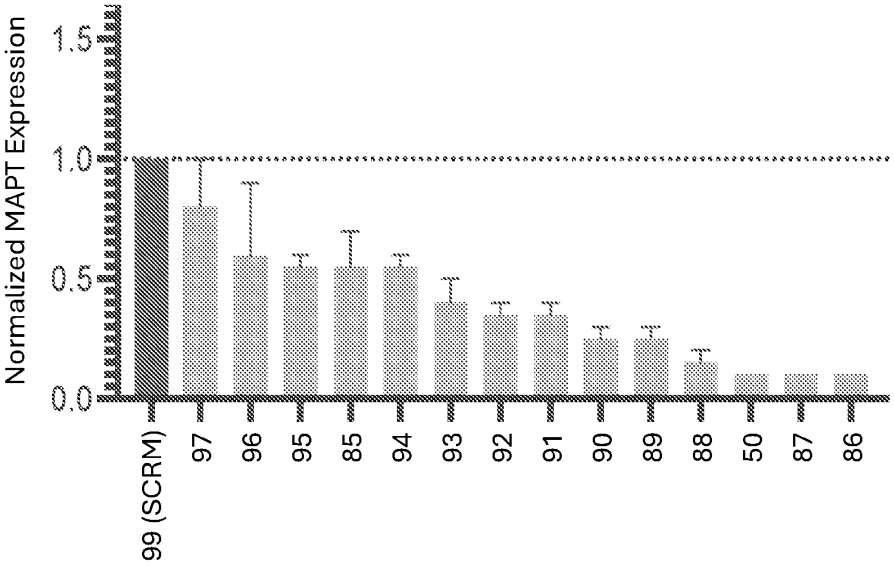

Normalized MAPT Expression
1.5
1.0
0.5
0.0
99 (SCRM)
97
96
95
85
94
93
92
91
90
89
88
50
87
86

FIG. 1

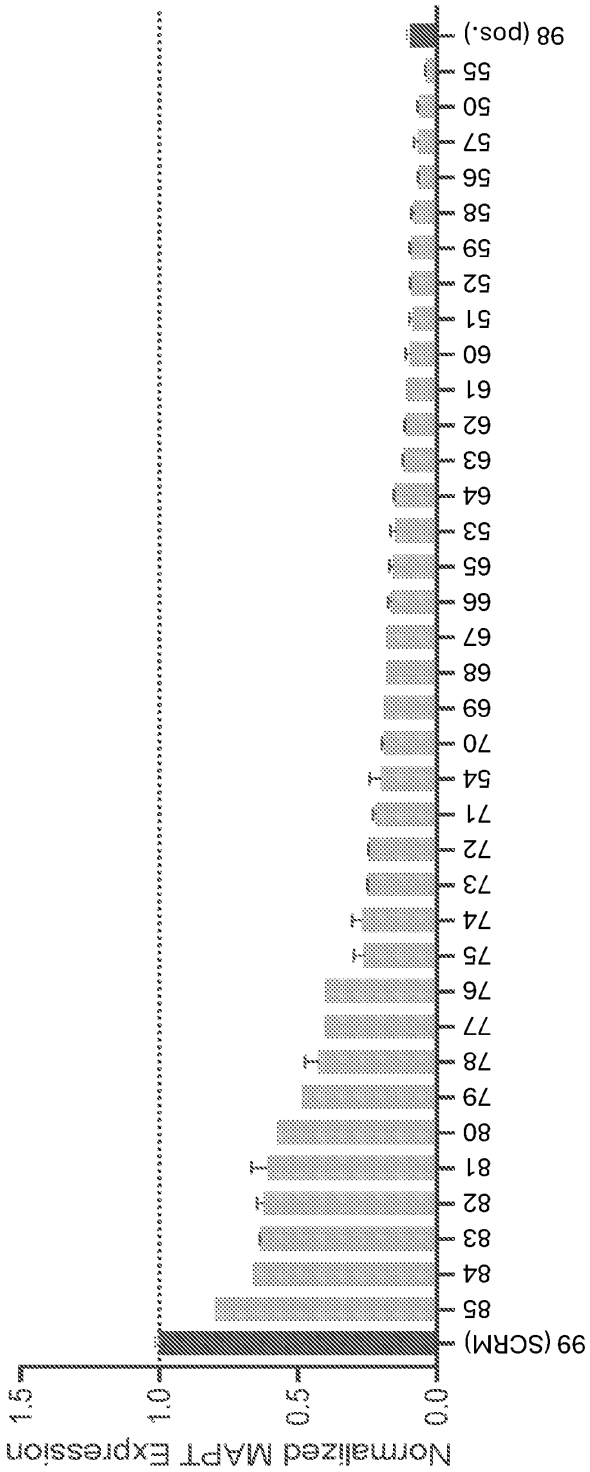

Normalized MAPT Expression
0.0
0.5
1.0
1.5
99 (SCRM)
85
84
83
82
81
80
79
78
77
76
75
74
73
72
71
54
70
69
68
67
66
65
53
64
63
62
61
60
51
52
59
58
56
57
50
55
98 (pos.)

FIG. 2

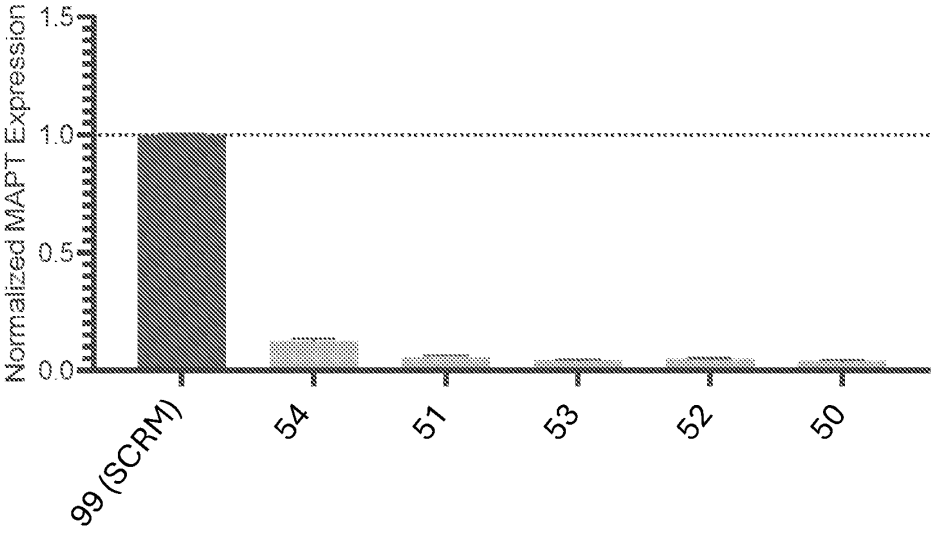
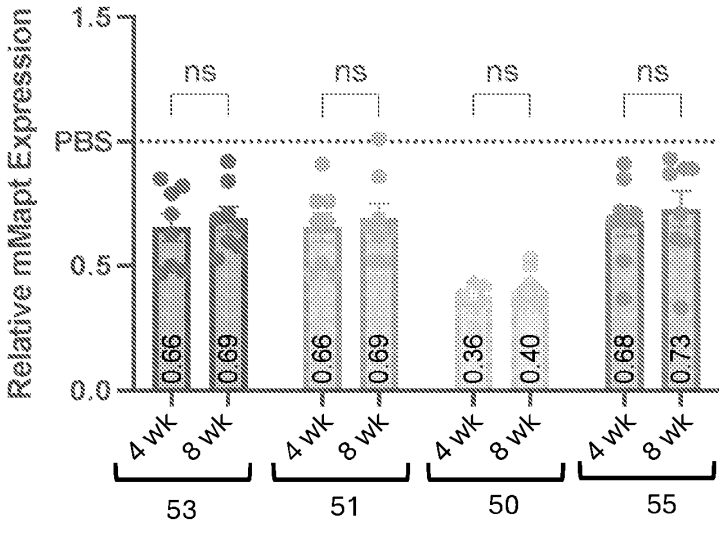


FIG. 3

Hippocampus



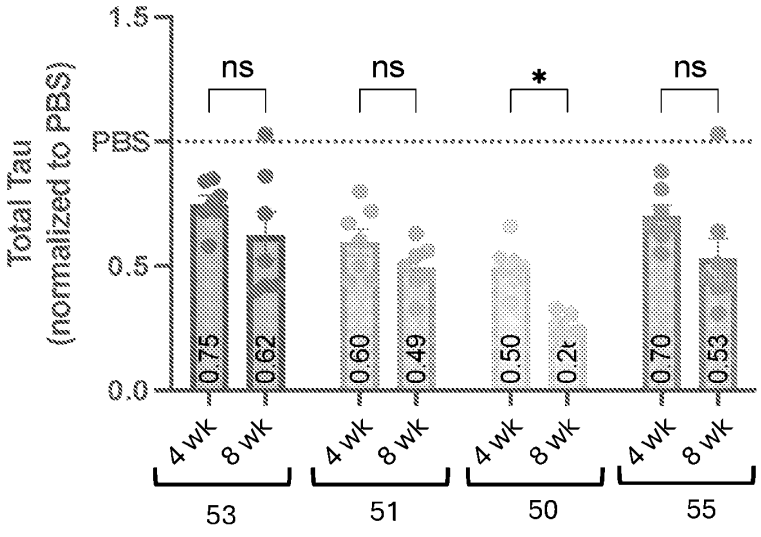


FIG. 4A

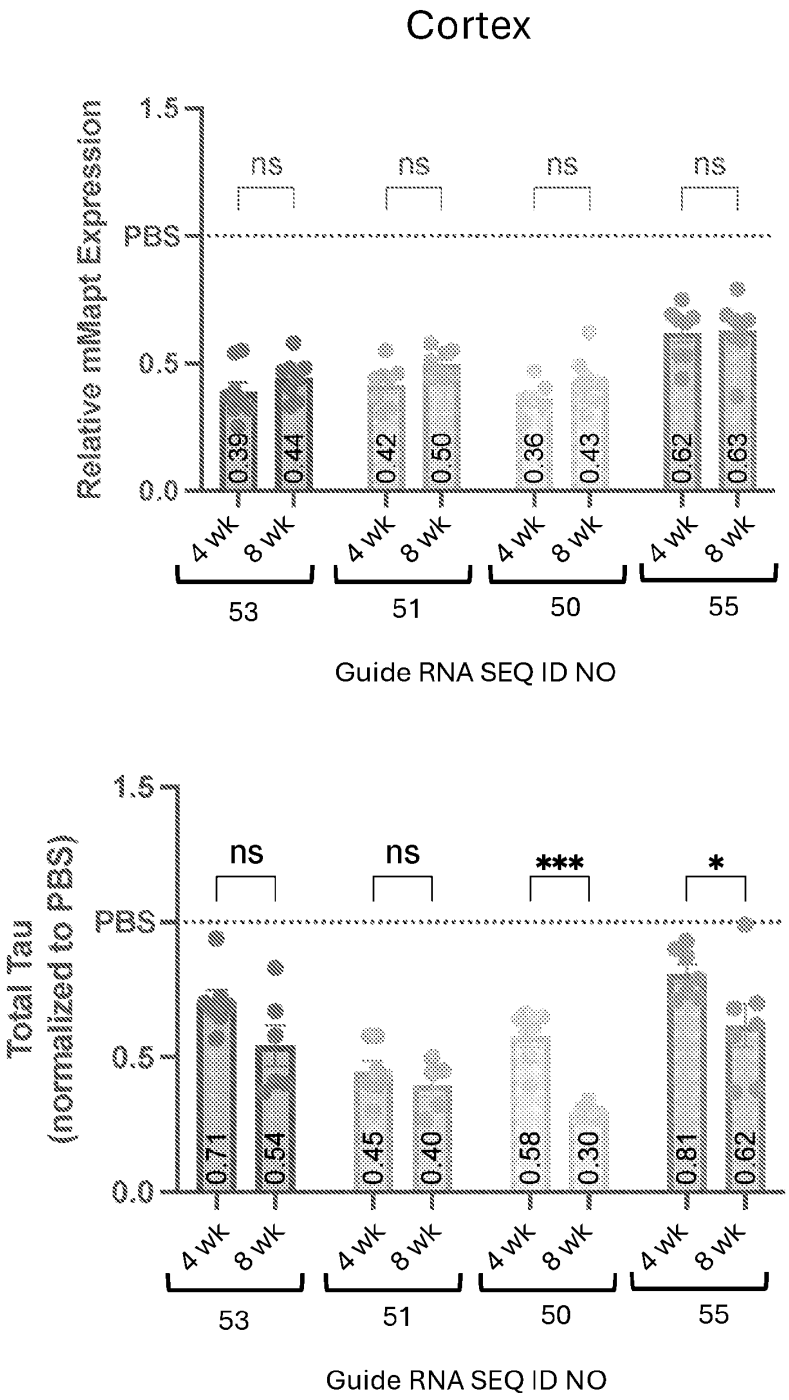

Cortex
Relative mMapt Expression
1.5
0.5
0.0
PBS
ns
ns
ns
ns
0.39
0.44
0.42
0.50
0.36
0.43
0.62
0.63
4 wk
8 wk
53
51
50
55
Guide RNA SEQ ID NO
Total Tau
(normalized to PBS)
1.5
0.5
0.0
PBS
ns
ns
***
*
0.71
0.54
0.45
0.40
0.58
0.30
0.81
0.62
4 wk
8 wk
53
51
50
55
Guide RNA SEQ ID NO

FIG. 4B

Low Dose (1E4)

Guide RNA SEQ ID NO	miR-E	miR-100	miR-132	miR-190a	miR-451	miR-130a
53	8.50	21.00	24.00	13.50	2.00	13.50
51	29.00	30.00	35.50	31.50	11.50	28.00
50	15.00	14.00	36.00	26.50	9.50	28.00

Scaffold

High Dose (1E6)

Guide RNA SEQ ID NO	miR-E	miR-100	miR-132	miR-190a	miR-451	miR-130a
53	67.33	95.33	95.33	69.67	17.00	92.00
51	88.33	92.33	91.33	89.33	74.67	91.67
50	88.00	86.67	95.33	95.00	24.33	95.33
55	91.51	97.04	97.04	96.03	ND	96.77

Scaffold

FIG. 5

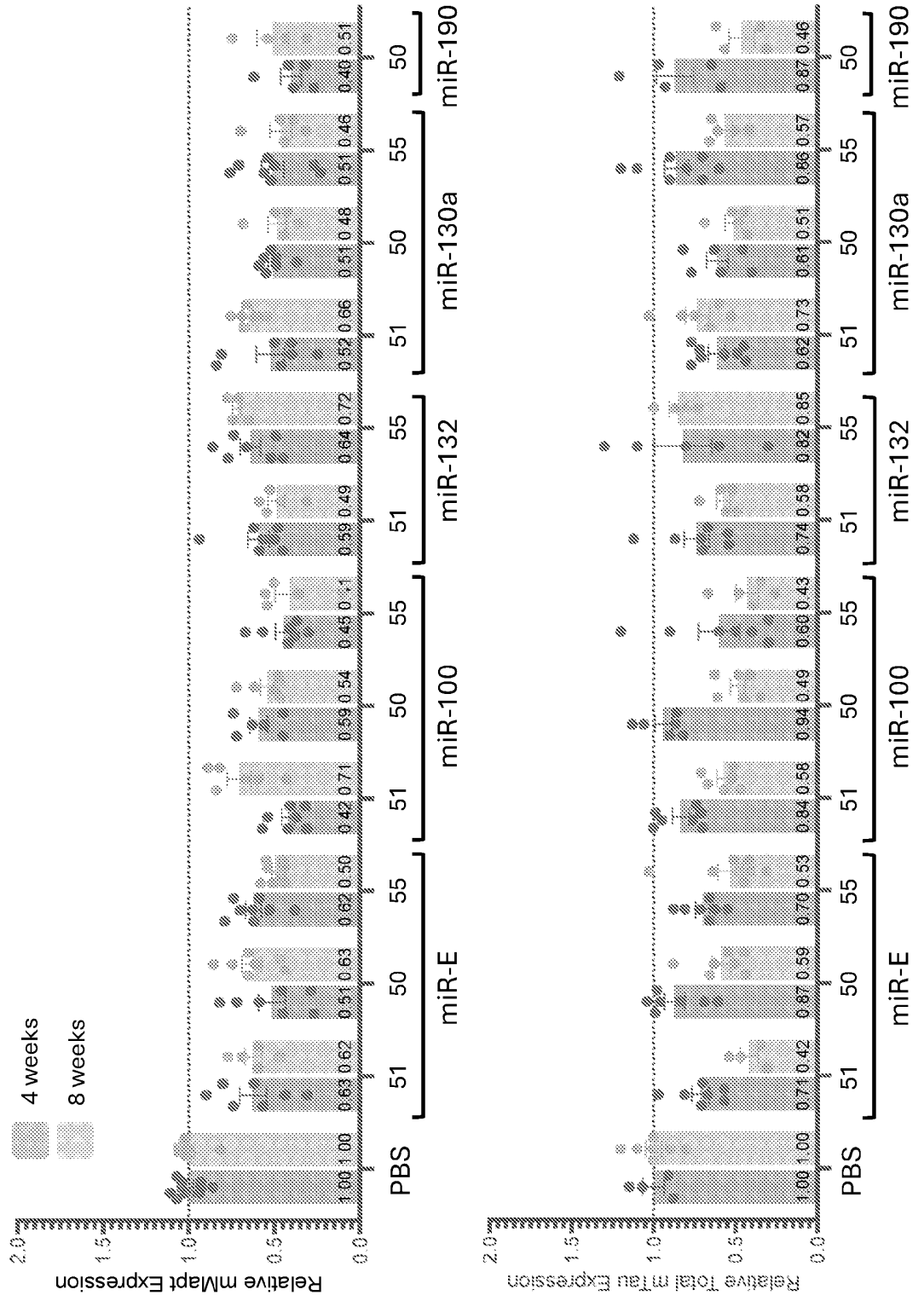
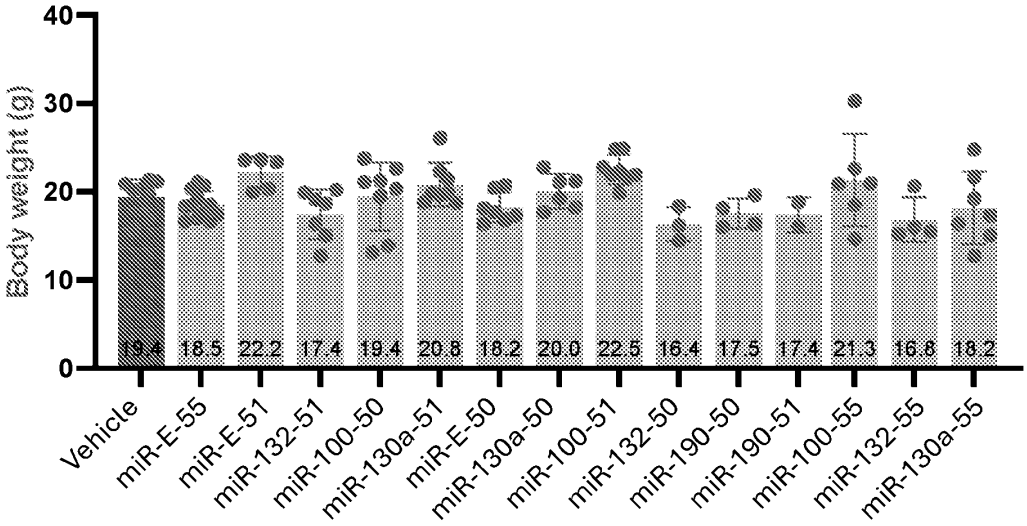

4 weeks
8 weeks
Relative mMapt Expression
Relative Total mTau Expression
PBS
miR-E
miR-100
miR-132
miR-130a
miR-190
51
50
55

FIG. 6


Body weight (g)
40
30
20
10
0
19.4
18.5
22.2
17.4
19.4
20.8
18.2
20.0
22.5
16.4
17.5
17.4
21.3
16.8
18.2
Vehicle
miR-E-55
miR-E-51
miR-132-51
miR-100-50
miR-130a-51
miR-E-50
miR-130a-50
miR-100-51
miR-132-50
miR-190-50
miR-190-51
miR-100-55
miR-132-55
miR-130a-55

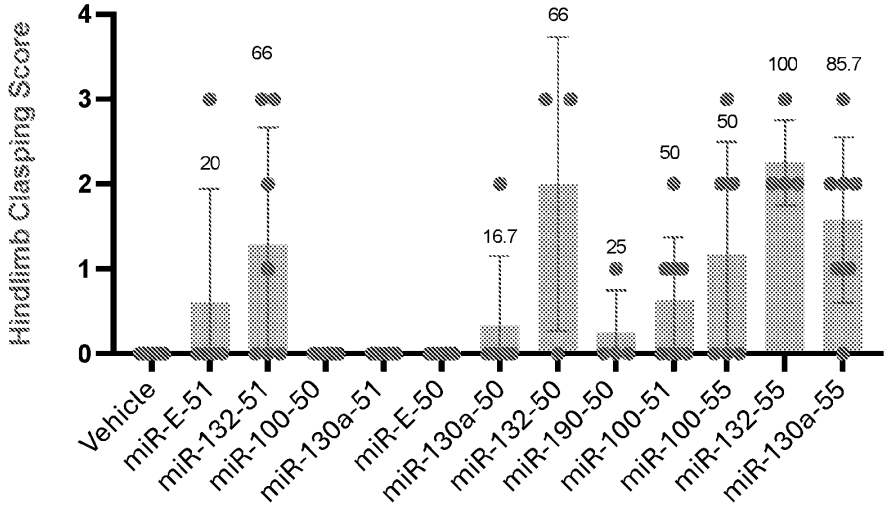

Hindlimb Clasping Score
4
3
2
1
0
20
66
16.7
66
25
50
50
100
85.7
Vehicle
miR-E-51
miR-132-51
miR-100-50
miR-130a-51
miR-E-50
miR-130a-50
miR-132-50
miR-190-50
miR-100-51
miR-100-55
miR-132-55
miR-130a-55

FIG. 7

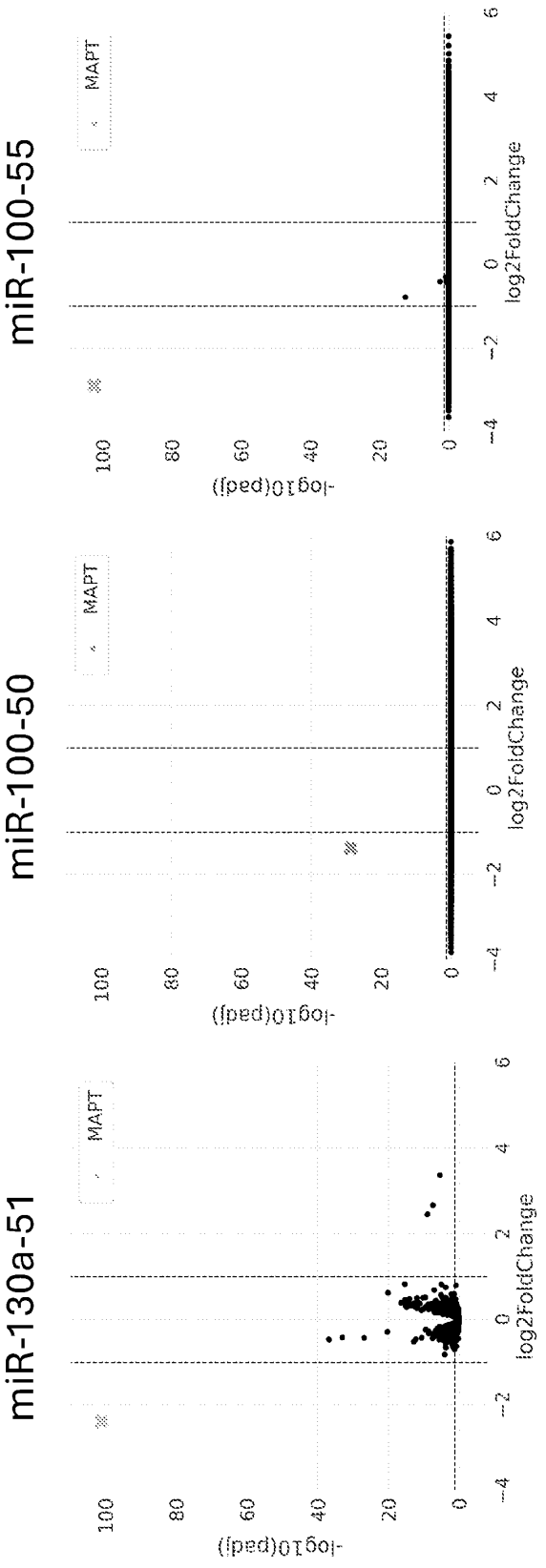

miR-130a-51
miR-100-50
miR-100-55
MAPT
log2FoldChange
-log10(padj)

FIG. 8

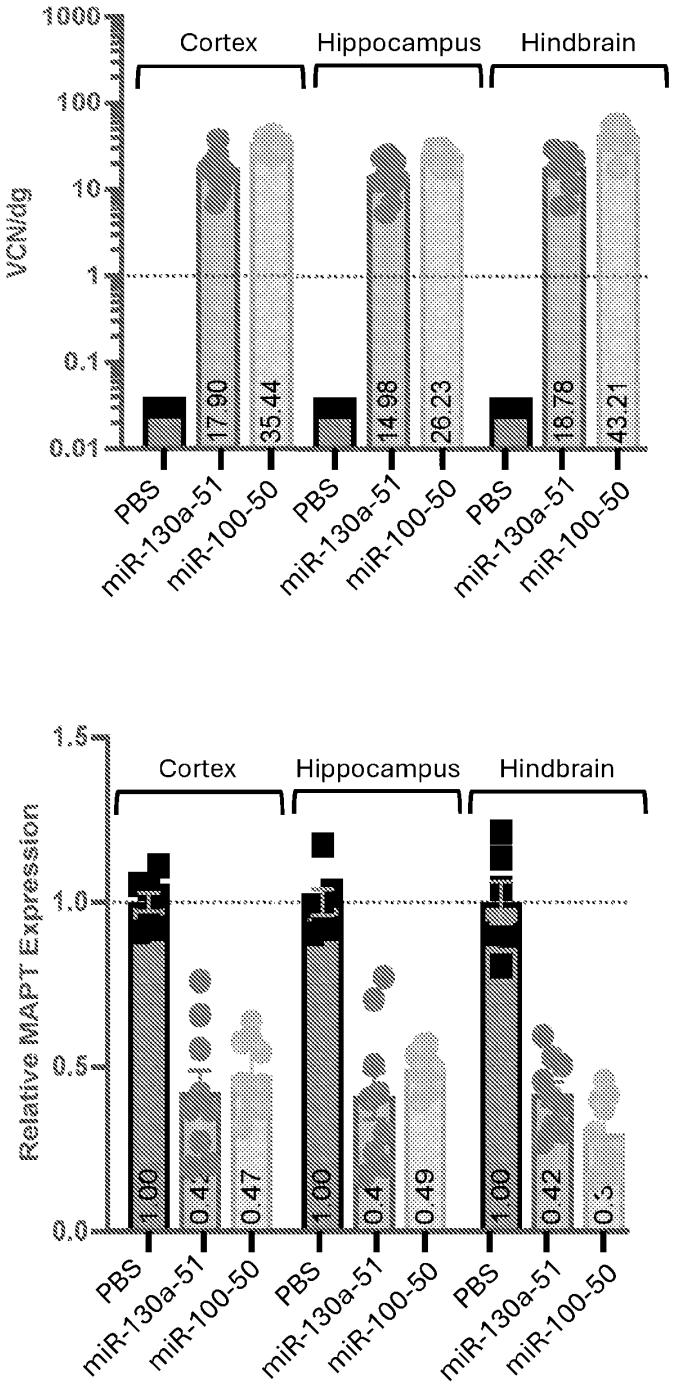

VCN/dg
1000
100
10
1
0.1
0.01
Cortex
Hippocampus
Hindbrain
17.90
35.44
14.98
26.23
18.78
43.21
PBS
miR-130a-51
miR-100-50
Relative MAPT Expression
1.5
1.0
0.5
0.0
1.00
0.41
0.47
1.00
0.4
0.49
1.00
0.42
0.3

FIG. 9

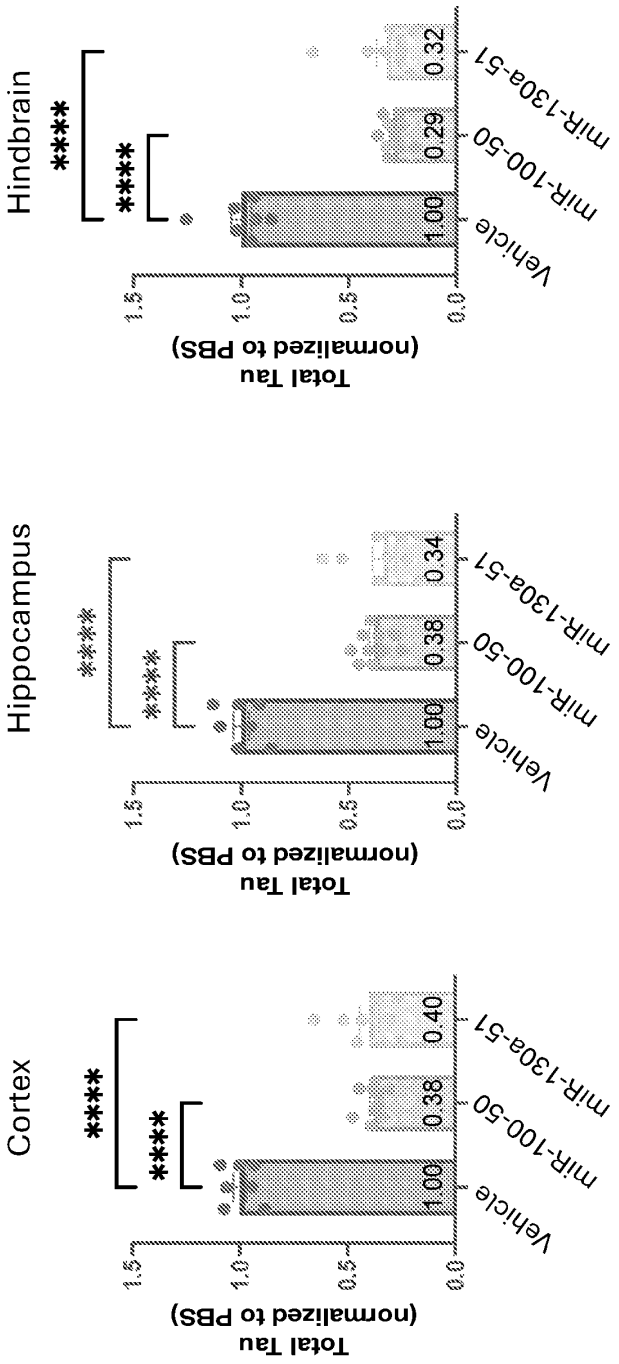

Cortex
Hippocampus
Hindbrain
Total Tau
(normalized to PBS)
1.5
1.0
0.5
0.0
****
****
1.00
0.38
0.40
0.29
0.34
0.32
Vehicle
miR-100-50
miR-130a-51

FIG.10

Relative MAPT mRNA Levels

		Candidate		
Region	**Braak Stage**	**miR-100-50**	**miR-130a-51**	**miR-100-55**
Entorhinal Cortex	I-II	0.82	0.76*	0.95
Hippocampus	III	0.76	0.68*	0.82
Amygdala	III	0.74*	0.94	0.91*
Thalamus	III-IV	0.84	0.73	0.99
Cingulate Cortex	IV	0.73*	0.79	0.84
Inferior Temporal Cortex	IV	0.84	0.71*	0.91
Inferior Parietal Cortex	V_1	0.75**	0.66*	0.80*
Lateral Occipital Cortex	V_1	0.68	0.67	0.79
Frontal Cortex	V_2	0.82	0.72*	0.88

FIG. 11A

Relative Tau Protein Levels

		Candidate		
Region	**Braak Stage**	**miR-100-50**	**miR-130a-51**	**miR-100-55**
Entorhinal Cortex	I-II	1.33	0.89	1.24
Hippocampus	III	0.76	0.81	0.69
Amygdala	III	1.03	1.19	0.86
Thalamus	III-IV	0.71	0.81	0.76
Cingulate Cortex	IV	0.88	0.99	0.95
Inferior Temporal Cortex	IV	0.84	0.99	0.94
Inferior Parietal Cortex	V_1	1.15	1.00	0.95
Lateral Occipital Cortex	V_1	0.76	0.92	0.90
Frontal Cortex	V_2	0.81	0.89	1.07
Average Cortex	NA	0.97	0.95	1.01
All Regions	NA	0.92	0.94	0.95

FIG. 11B

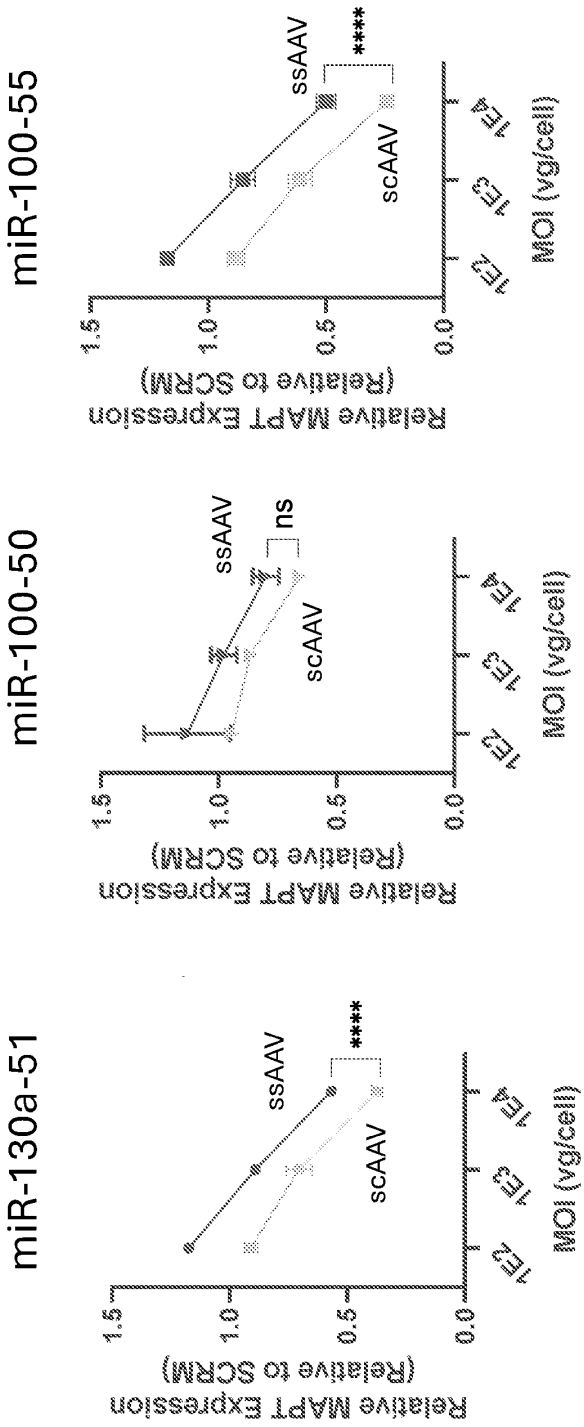

miR-130a-51
miR-100-50
miR-100-55
Relative MAPT Expression
(Relative to SCRM)
1.5
1.0
0.5
0.0
ssAAV
scAAV
****
ns
1E2
1E3
1E4
MOI (vg/cell)

FIG. 12

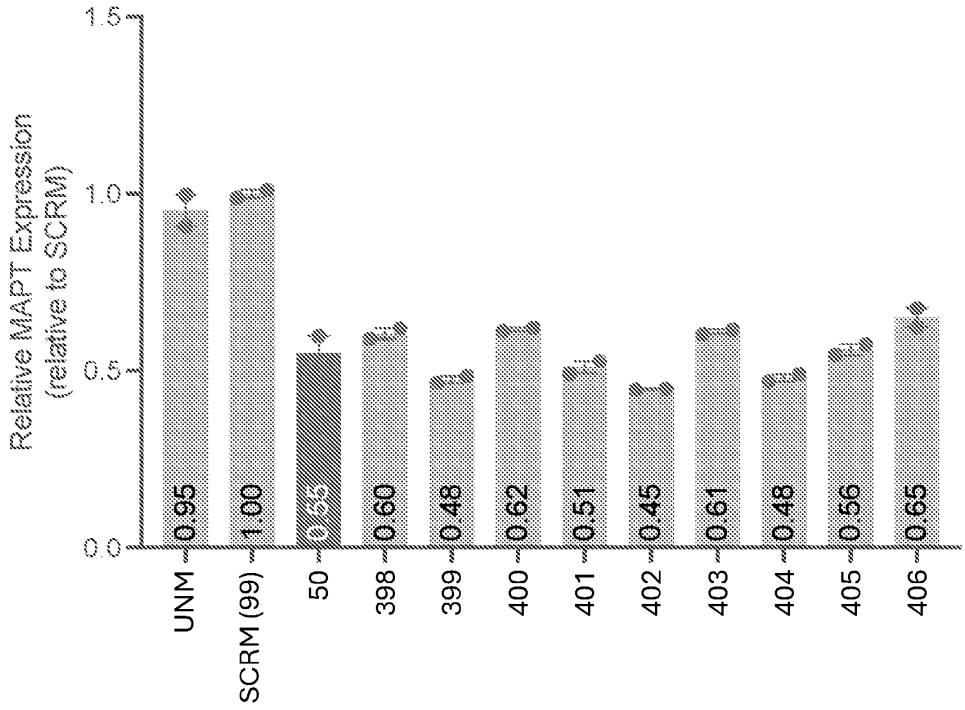

Relative MAPT Expression
(relative to SCRM)
1.5
1.0
0.5
0.0
0.95
1.00
0.55
0.60
0.48
0.62
0.51
0.45
0.61
0.48
0.56
0.65
UNM
SCRM (99)
50
398
399
400
401
402
403
404
405
406

FIG. 13

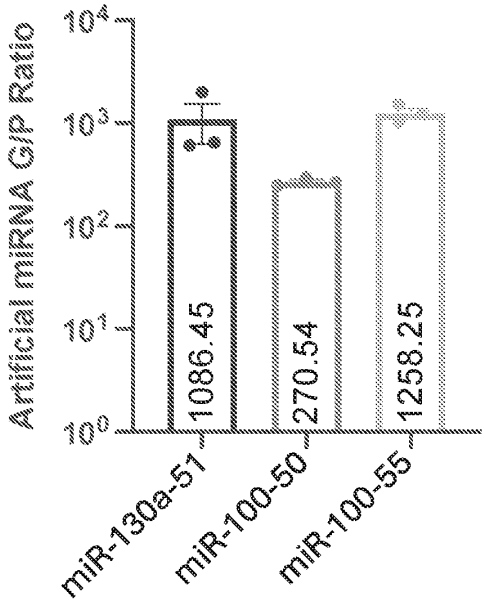
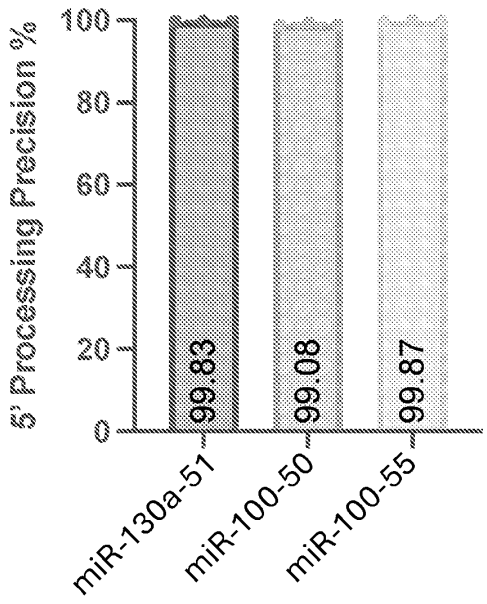

Artificial miRNA G/P Ratio
10^4
10^3
10^2
10^1
10^0
1086.45
270.54
1258.25
miR-130a-51
miR-100-50
miR-100-55

FIG. 14A



	18	19	20	21	22	23	24	25	26
miR-130a-51	(-)	(-)	(-)	(-)	0.98	0.01	(-)	(-)	(-)
miR-100-50	(-)	(-)	0.03	0.29	0.46	0.20	0.01	(-)	(-)
miR-100-55	(-)	0.01	0.13	0.1	0.58	0.13	0.04	(-)	(-)

Base pair length

FIG. 14B