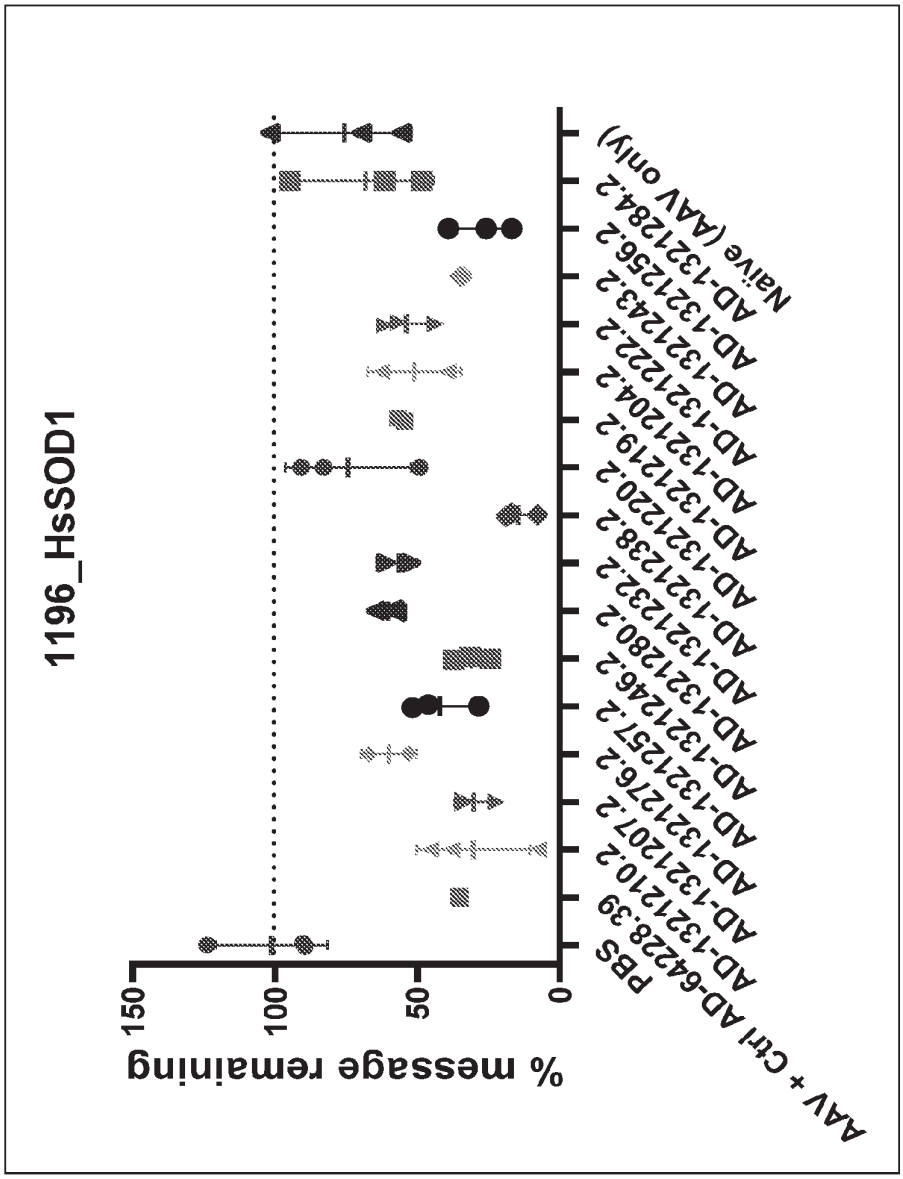

1196_HsSOD1
% message remaining
150
100
50
0
AAV + Ctrl
PBS
AD-64228.39
AD-132120.2
AD-132107.2
AD-132176.2
AD-132157.2
AD-132146.2
AD-132180.2
AD-132132.2
AD-132138.2
AD-132120.2
AD-132119.2
AD-132104.2
AD-132122.2
AD-132143.2
AD-132156.2
AD-132128.2
Naïve (AAV only)

FIG. 1

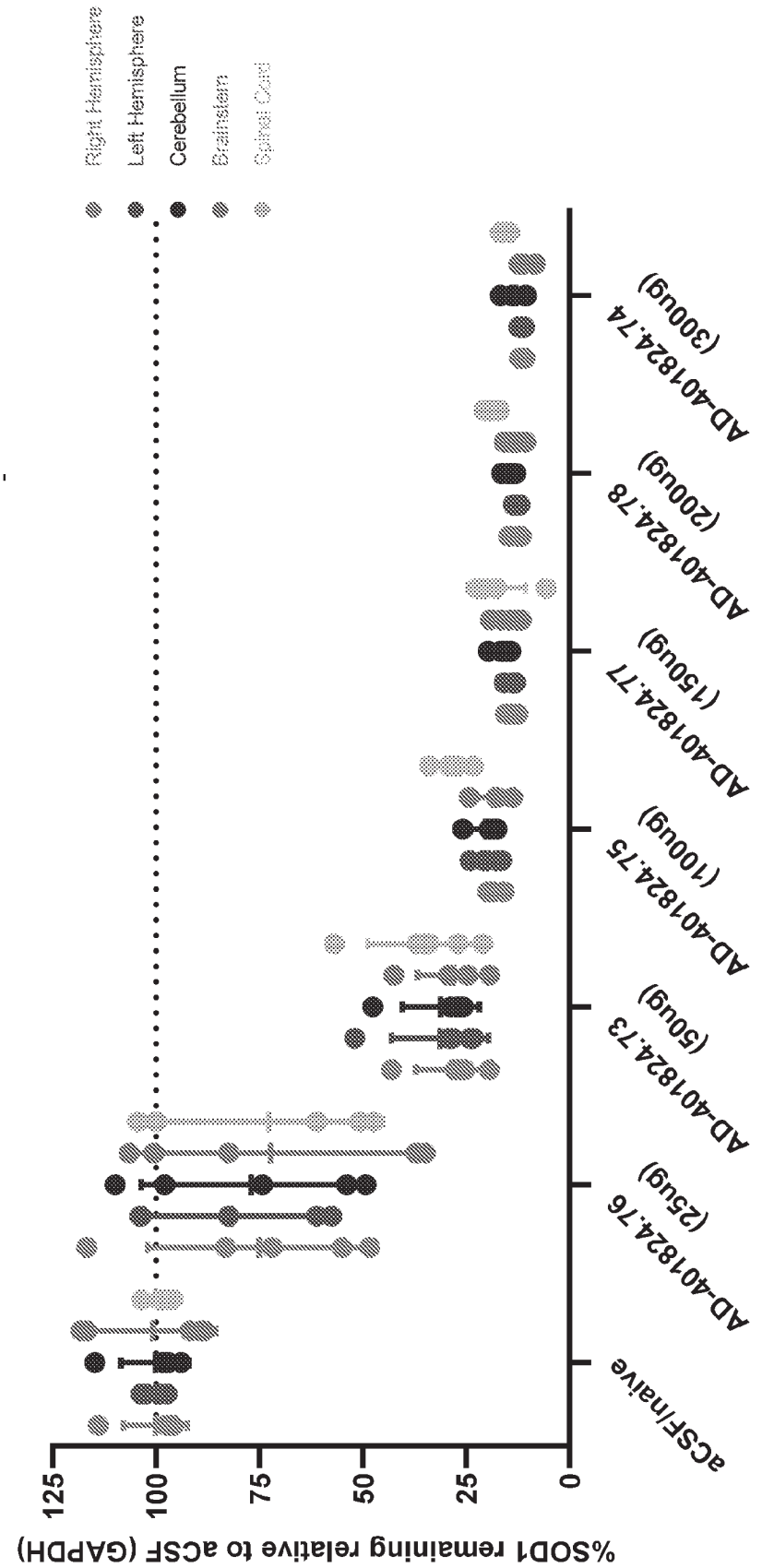

Right Hemisphere
Left Hemisphere
Cerebellum
Brainstem
Spinal Cord
%SOD1 remaining relative to aCSF (GAPDH)
125
100
75
50
25
0
aCSF/naive
AD-401824.76 (25ug)
AD-401824.73 (50ug)
AD-401824.75 (100ug)
AD-401824.77 (150ug)
AD-401824.78 (200ug)
AD-401824.74 (300ug)

FIG. 2

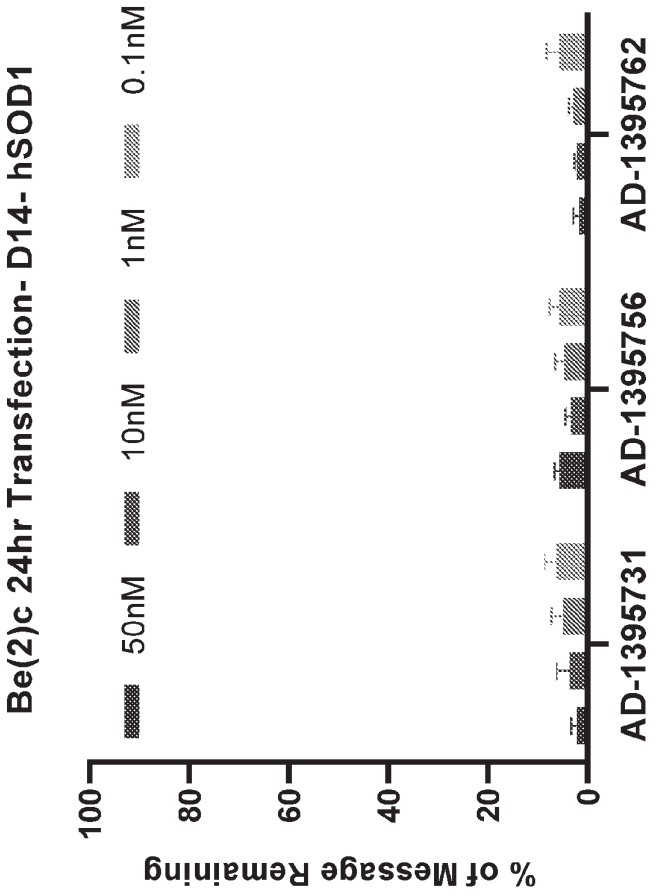

Be(2)c 24hr Transfection- D14- hSOD1
50nM
10nM
1nM
0.1nM
% of Message Remaining
100
80
60
40
20
0
AD-1395731
AD-1395756
AD-1395762

FIG. 3A

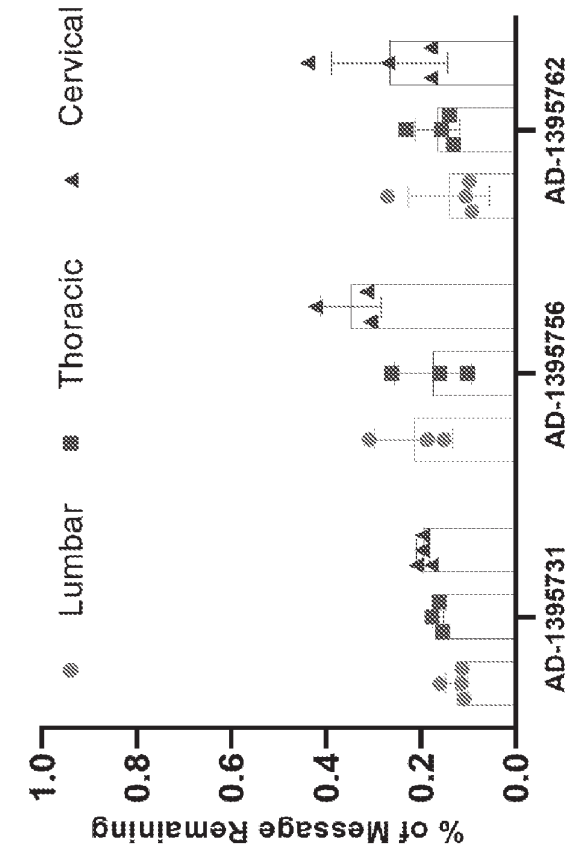

Single IT 0.9mg D14 hSOD1 G93A rat
Lumbar
Thoracic
Cervical
% of Message Remaining
1.0
0.8
0.6
0.4
0.2
0.0
AD-1395731
AD-1395756
AD-1395762

FIG. 3B

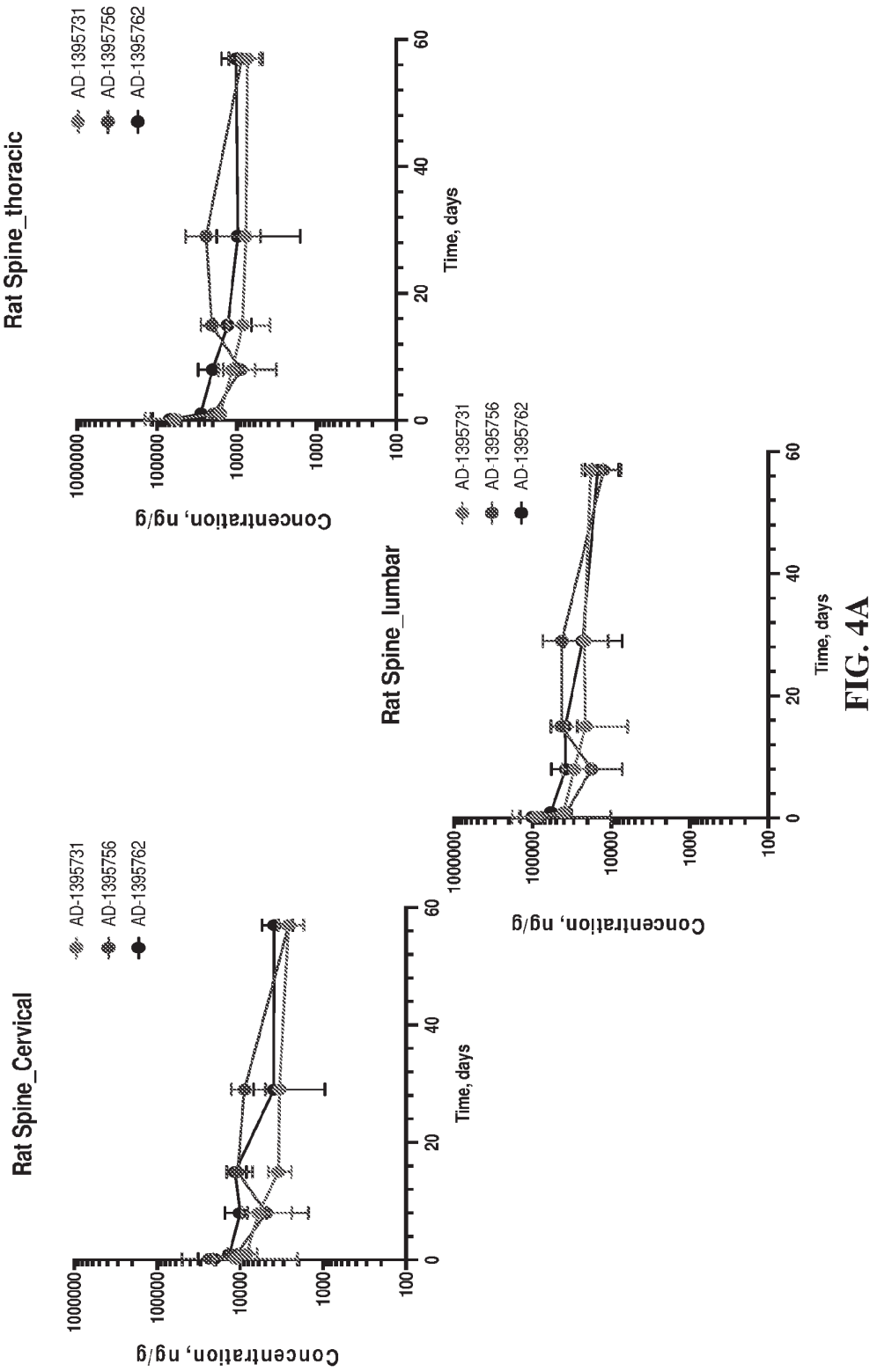

Rat Spine_thoracic
AD-1395731
AD-1395756
AD-1395762
Concentration, ng/g
1000000
100000
10000
1000
100
0
20
40
60
Time, days
Rat Spine_lumbar
AD-1395731
AD-1395756
AD-1395762
Concentration, ng/g
1000000
100000
10000
1000
100
0
20
40
60
Time, days
Rat Spine_Cervical
AD-1395731
AD-1395756
AD-1395762
Concentration, ng/g
1000000
100000
10000
1000
100
0
20
40
60
Time, days

FIG. 4A

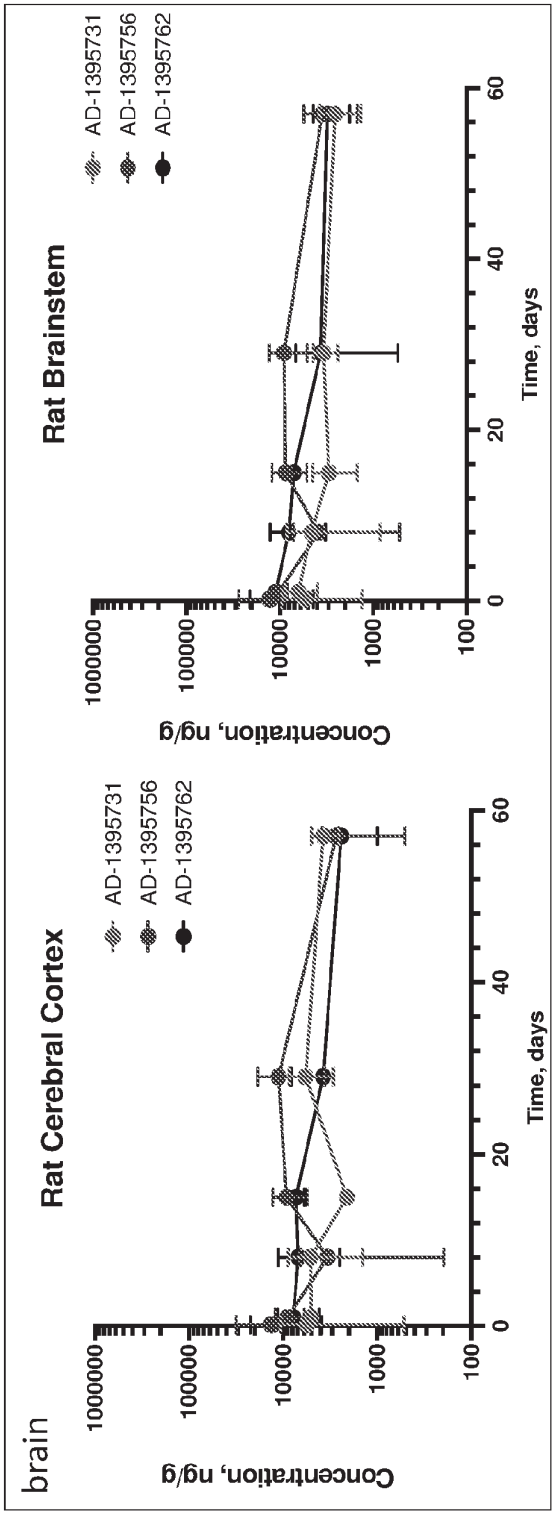


FIG. 4B

Tissues	AD-1395731	AD-1395756	AD-1395762
	AUC_{last} (day*µg/g)	AUC_{last} (day*µg/g)	AUC_{last} (day*µg/g)
Cerebral Cortex	255	438	276
Brain stem	197	406	299
Spine (cervical)	225	431	392
Spine (Thoracic)	528	1020	771
Spine (lumbar)	1300	1830	1640

FIG. 4C

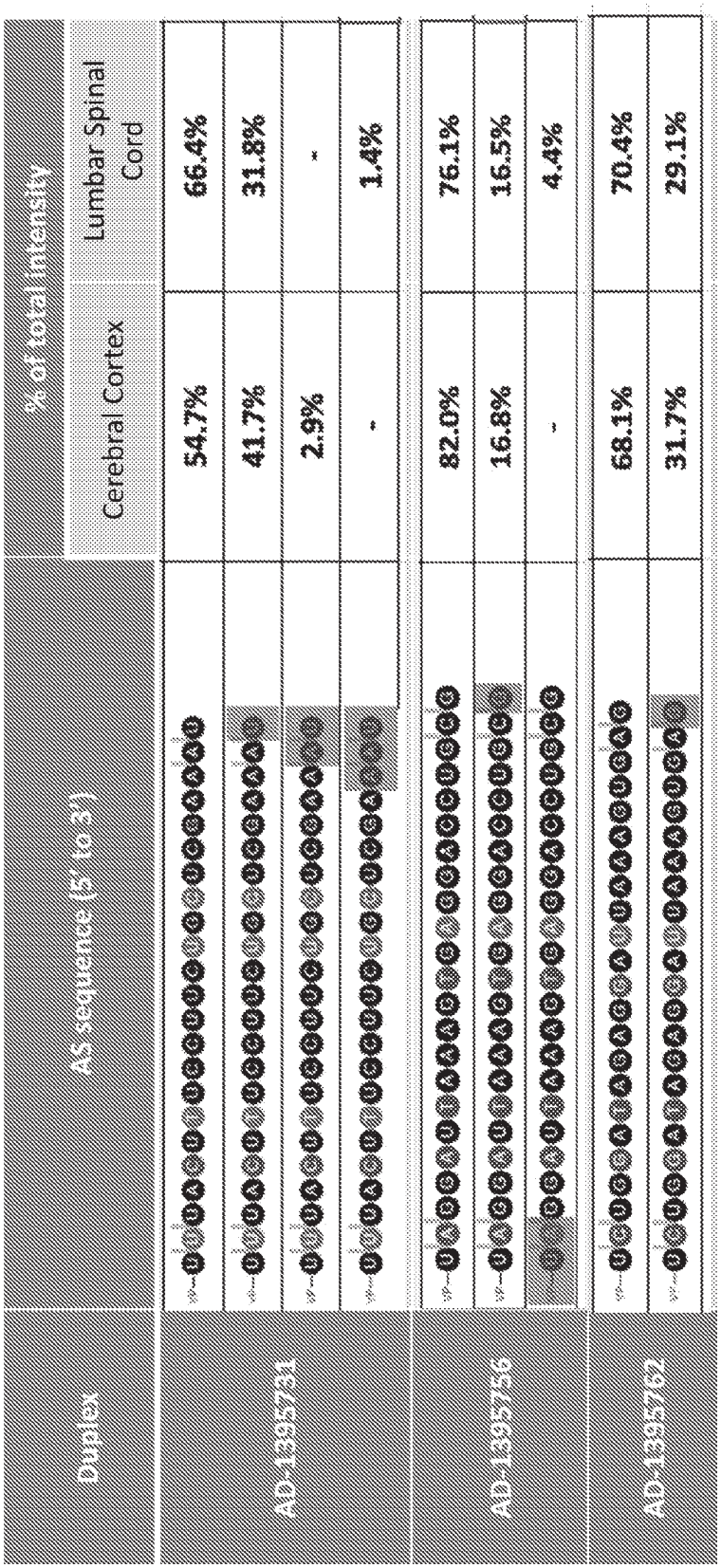

Duplex
AS sequence (5' to 3')
% of total intensity
Cerebral Cortex
Lumbar Spinal Cord
AD-1395731
54.7%
66.4%
41.7%
31.8%
2.9%
-
-
1.4%
AD-1395756
82.0%
76.1%
16.8%
16.5%
-
4.4%
AD-1395762
68.1%
70.4%
31.7%
29.1%

FIG. 5

siRNA	Rat PK[a]					Mo4D	
	Tissue exposure (AUC_{last} (day*µg/g))					Antisense	
	Cerebral Cortex	Brain-stem	Spine (cervical)	Spine (thoracic)	Spine (lumbar)	(4-1344 hr pool)[b]	
AD-1395731	255	197	225	528	1300	3' N-1 (37%)	
AD-1395756	438	406	431	1020	1830	3' N-1 (17%)	
AD-1395762	276	299	392	771	1640	3' N-1 (30%)	

[a] Parents and active metabolites are combined
[b] mean of cerebral cortex and lumbar spinal cord

FIG. 6

Group No.	Test Material	Dose Level (mg/dose)	Dose Volume (mL/dose)	Dose Concentration (mg/mL)	Number of Main Study Males		
					Necropsy Day 31	Necropsy Day 85	Necropsy Day 169
1	aCSF	0	2	0	2	2	-
2	AD-1395731	70	2	35	4	4	1
3	AD-1395756	70	2	35	4	4	1
4	AD-1395762	70	2	35	4	4	1
5	aCSF	0	2	0	2	2	-
6	AD-1395731	120	2	60	4	4	-

FIG. 7

	AD-1395731	AD-1395756	AD-1395762
Bad (<1k ng/mL)	5 / 9	3 / 9	1 / 9
Partial (1k-3k ng/mL)	1 / 9	1 / 9	1 / 9
Good (>3k ng/mL)	3 / 9	5 / 9	8 / 9

FIG. 8A

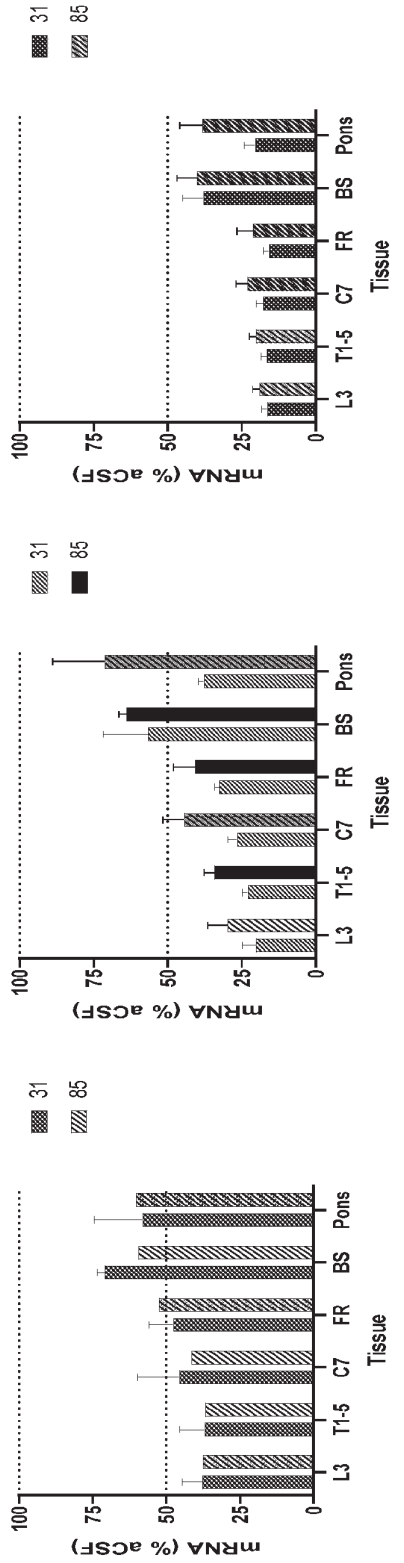
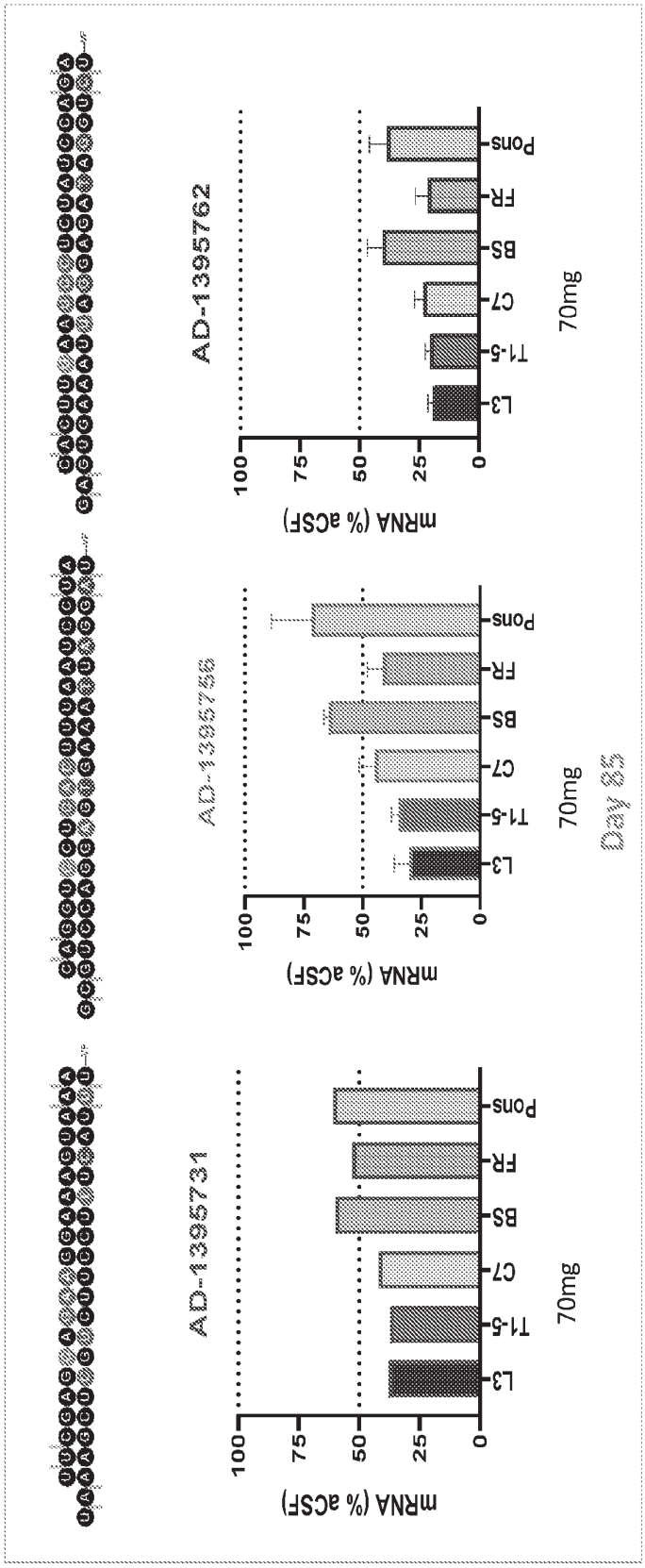


FIG. 8B



*Samples removed from graphs if drug exposure levels at 24hrs in CSF were lower than 1500 ng/ml, these are considered suboptimal doses

FIG. 8C

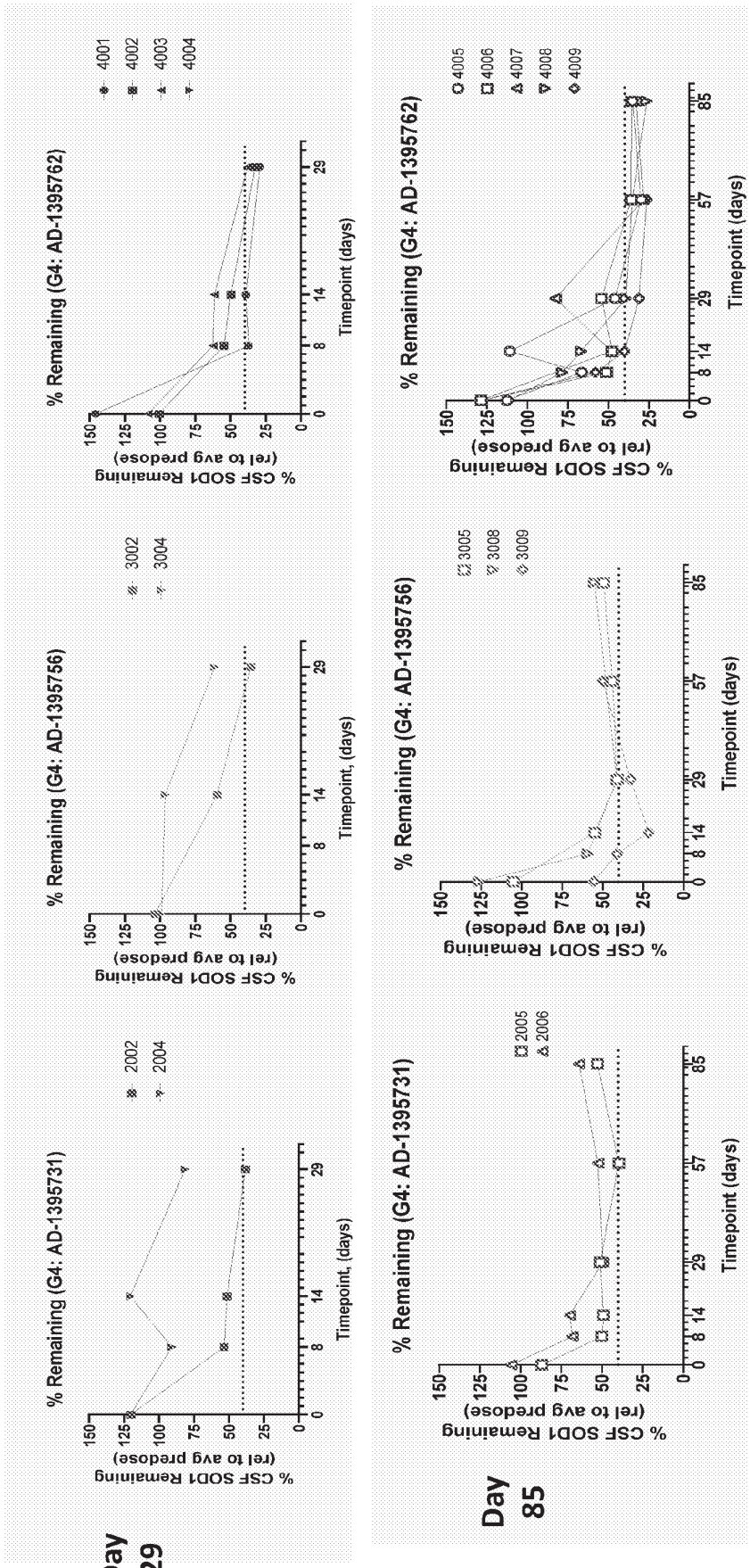

Day 29
Day 85
% Remaining (G4: AD-1395731)
% Remaining (G4: AD-1395756)
% Remaining (G4: AD-1395762)
% CSF SOD1 Remaining (rel to avg predose)
Timepoint, (days)
Timepoint (days)
2002
2004
2005
2006
3002
3004
3005
3008
3009
4001
4002
4003
4004
4005
4006
4007
4008
4009

FIG. 9A

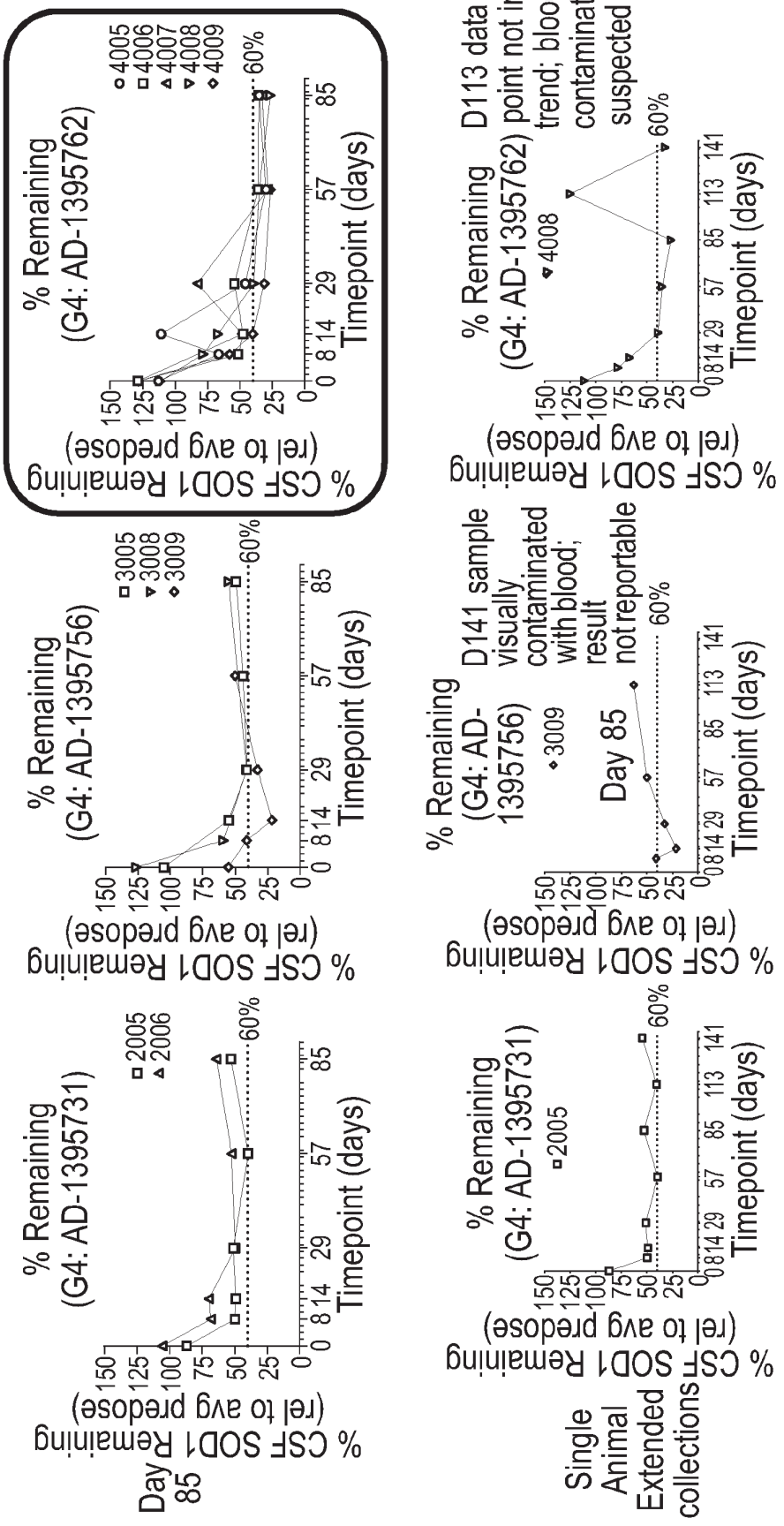

Single Animal Extended collections
Day 85
% CSF SOD1 Remaining (rel to avg predose)
% Remaining (G4: AD-1395731)
2005
2006
% Remaining (G4: AD-1395756)
3005
3008
3009
% Remaining (G4: AD-1395762)
4005
4006
4007
4008
4009
D141 sample visually contaminated with blood; result not reportable
D113 data point not in trend; blood contamination suspected
Timepoint (days)
60%

FIG. 9B

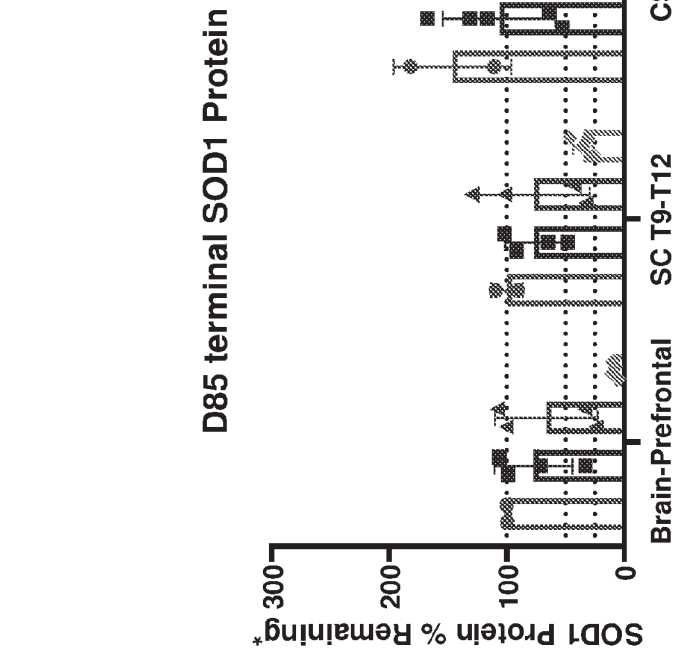
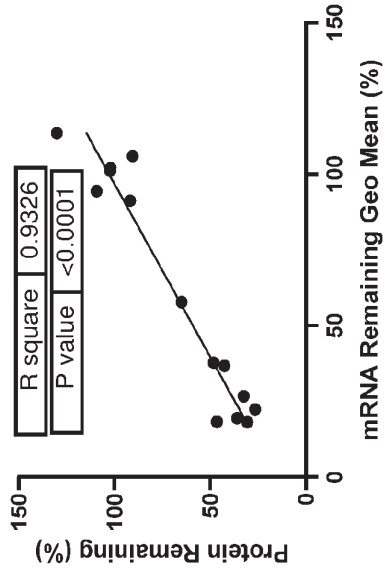

D85 terminal SOD1 Protein
SOD1 Protein % Remaining*
300
200
100
0
aCSF
AD-1395731
AD-1395756
AD-1395762
Brain-Prefrontal
SC T9-T12
CSF

FIG. 9C


SC T9-T12 mRNA v Protein
R square 0.9326
P value <0.0001
Protein Remaining (%)
mRNA Remaining Geo Mean (%)
150
100
50
0
0
50
100
150

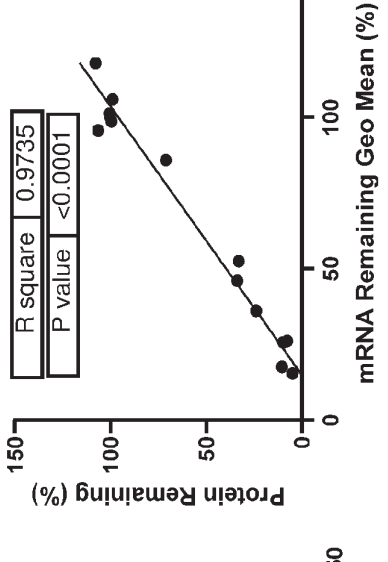

Prefrontal mRNA v Protein
R square 0.9735
P value <0.0001
Protein Remaining (%)
mRNA Remaining Geo Mean (%)
150
100
50
0
0
50
100
150

FIG. 10

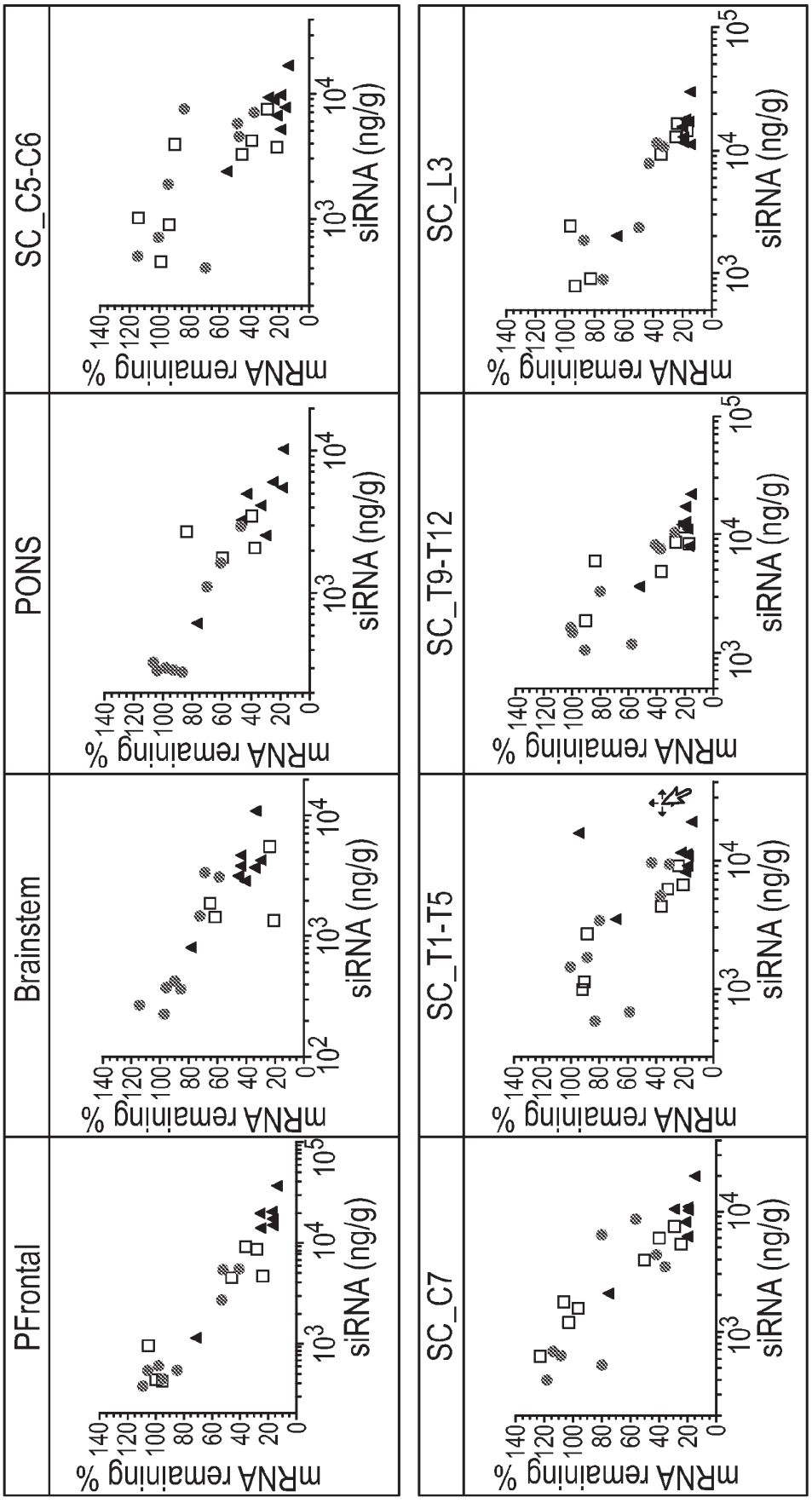
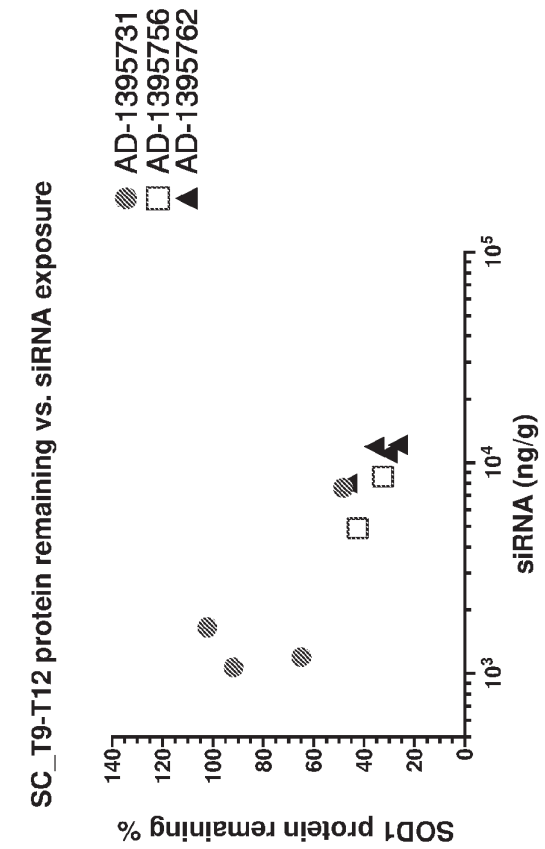

PFrontal
Brainstem
PONS
SC_C5-C6
SC_C7
SC_T1-T5
SC_T9-T12
SC_L3
mRNA remaining %
siRNA (ng/g)
AD-1395731
AD-1395756
AD-1395762

FIG. 11A


SC_T9-T12 protein remaining vs. siRNA exposure
AD-1395731
AD-1395756
AD-1395762
SOD1 protein remaining %
siRNA (ng/g)
0
20
40
60
80
100
120
140
10^3
10^4
10^5

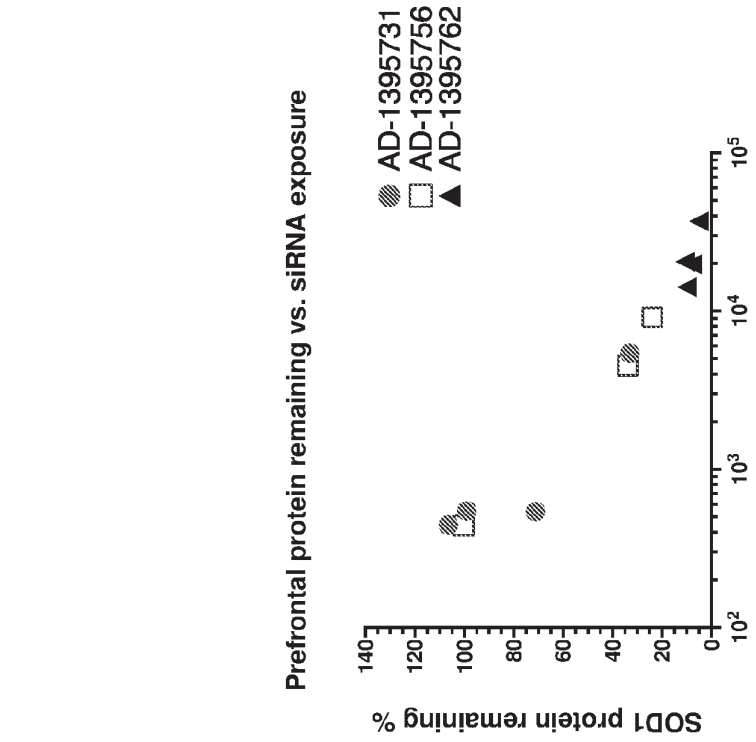

Prefrontal protein remaining vs. siRNA exposure
AD-1395731
AD-1395756
AD-1395762
SOD1 protein remaining %
siRNA (ng/g)
0
20
40
60
80
100
120
140
10^2
10^3
10^4
10^5

FIG. 11B

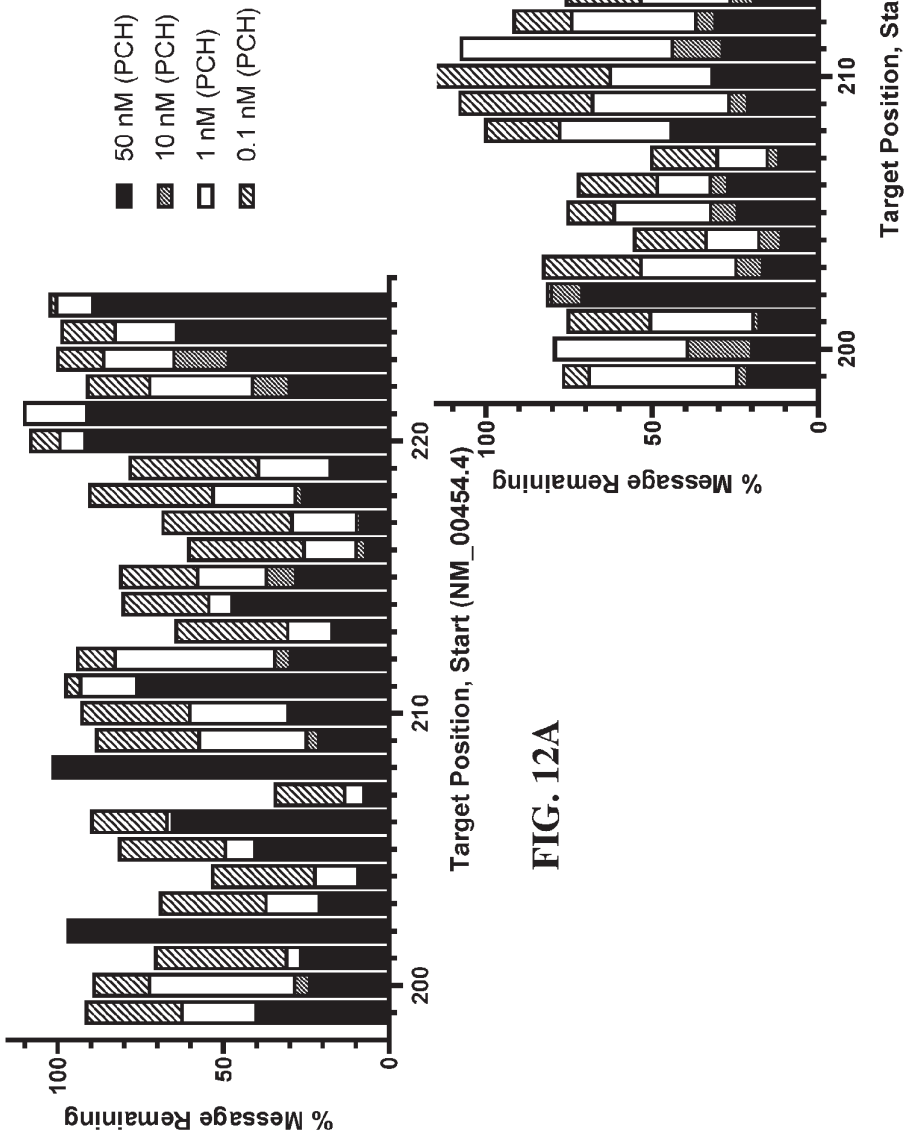


FIG. 12A

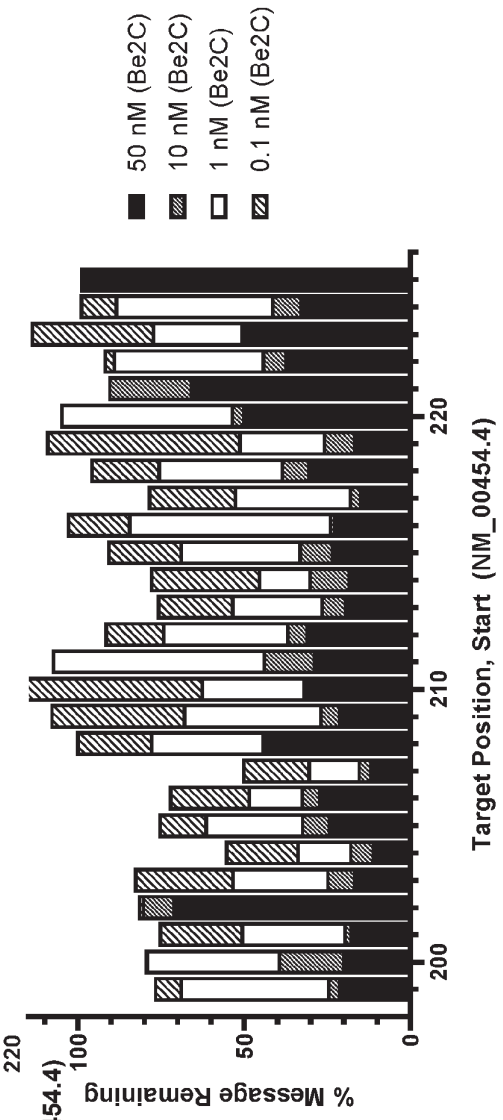


FIG. 12B

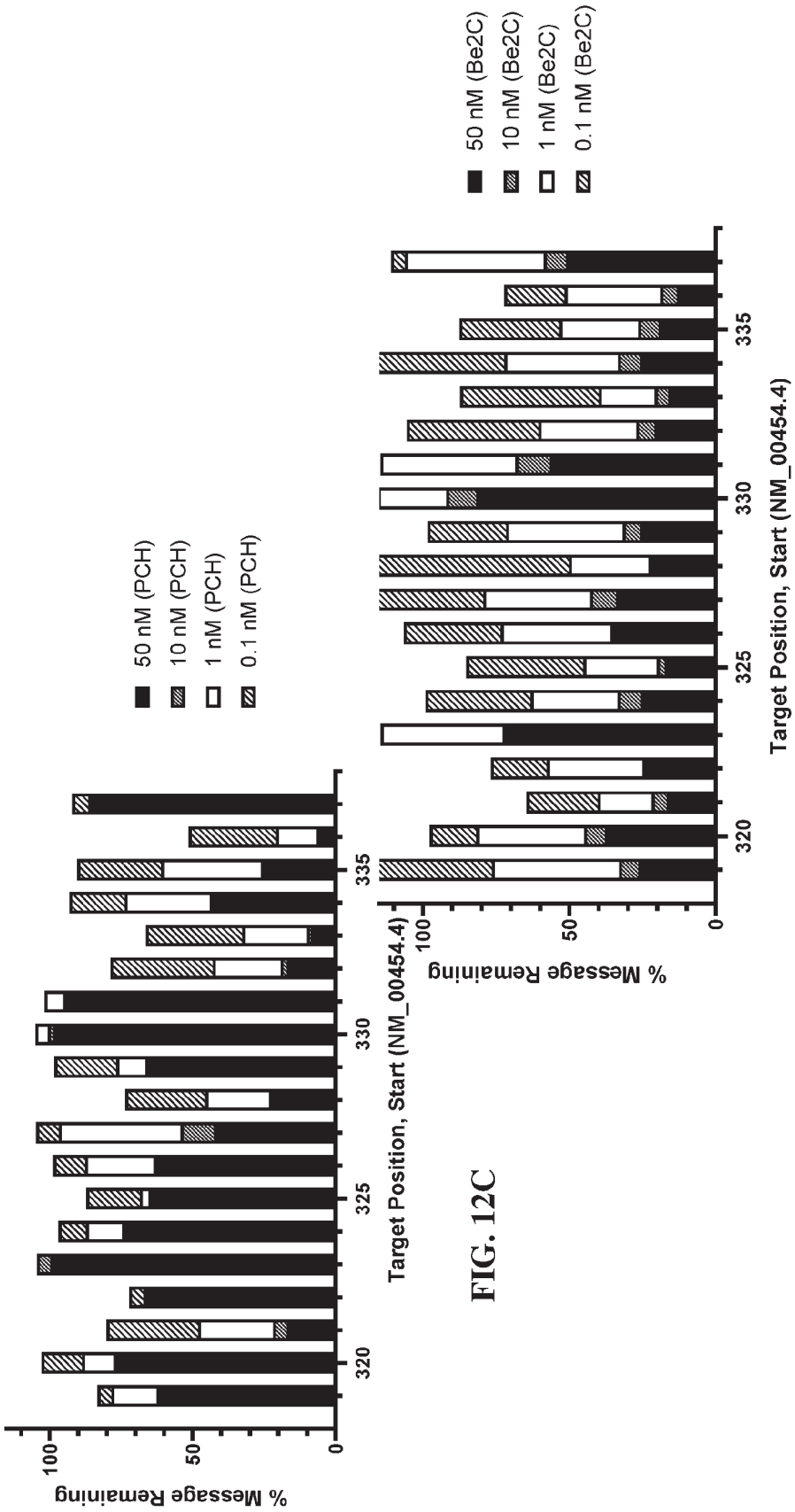


FIG. 12C

FIG. 12D

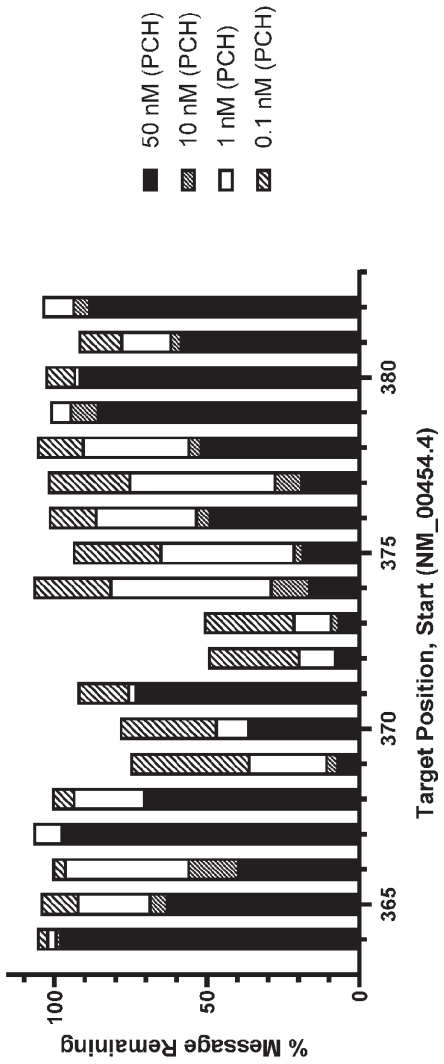


FIG. 12E

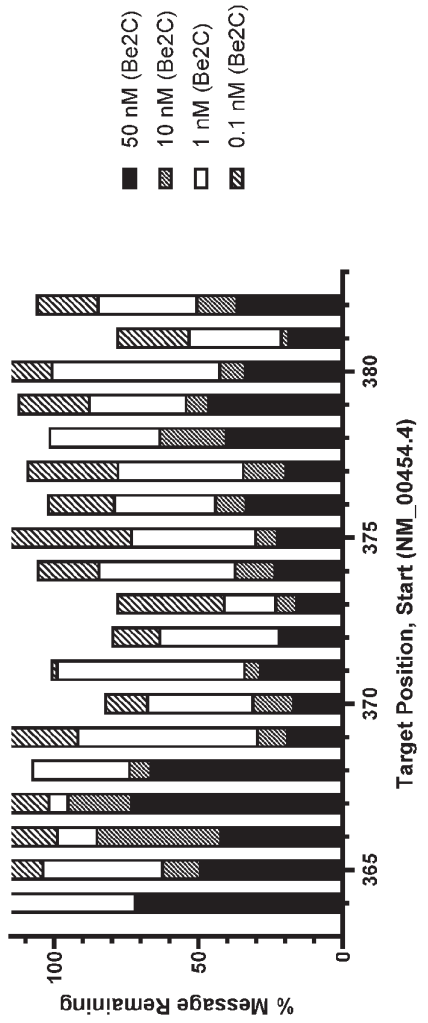


FIG. 12F

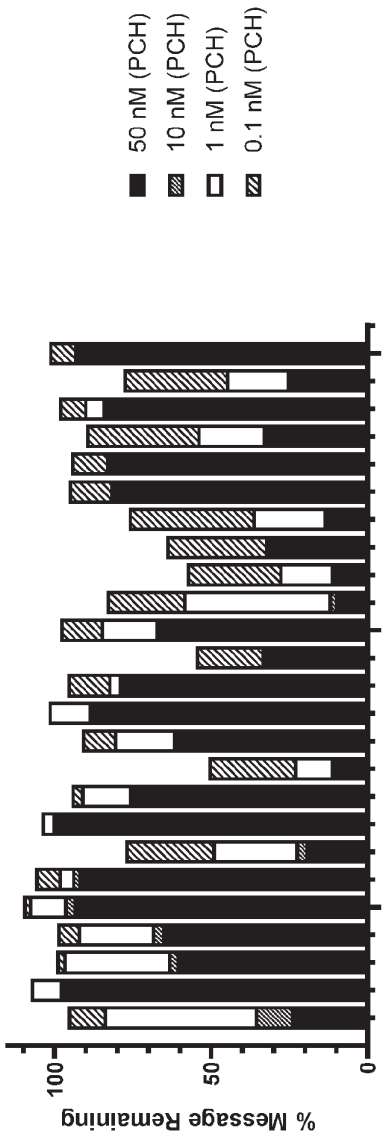


FIG. 12G

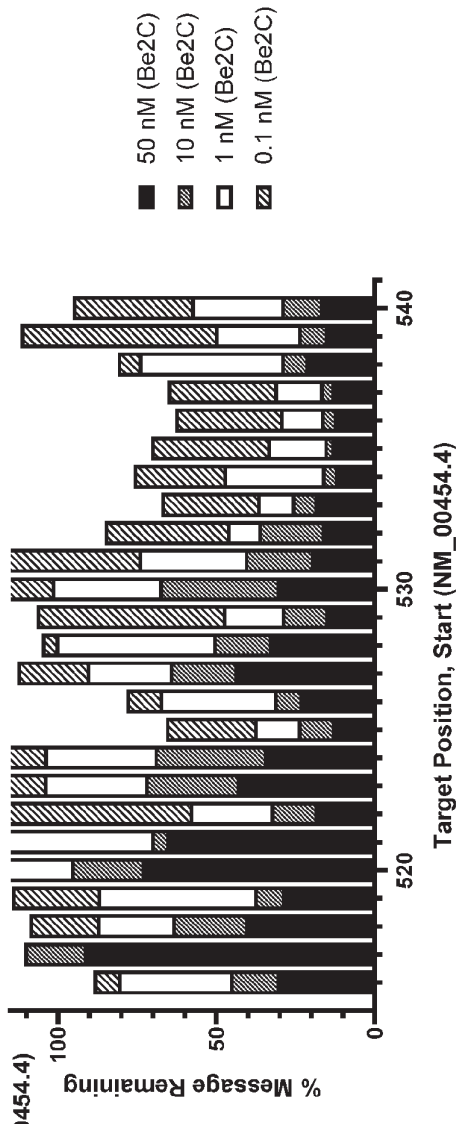


FIG. 12H

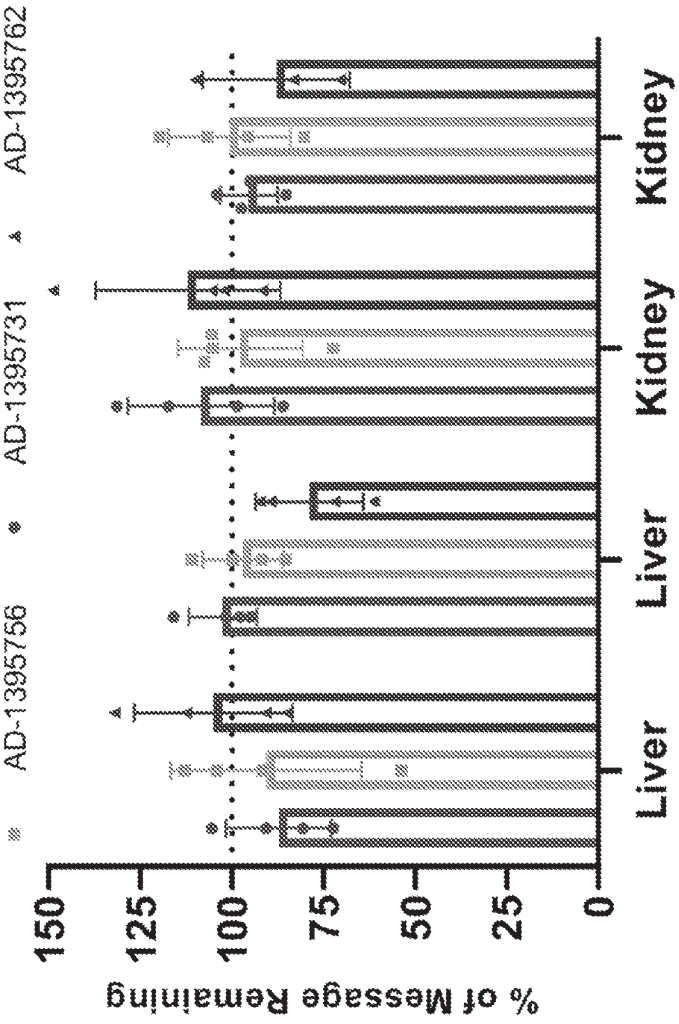

AD-1395756
AD-1395731
AD-1395762
% of Message Remaining
150
125
100
75
50
25
0
Liver
Liver
Kidney
Kidney
D31
D85
D31
D85

FIG. 13