

FIG. 1

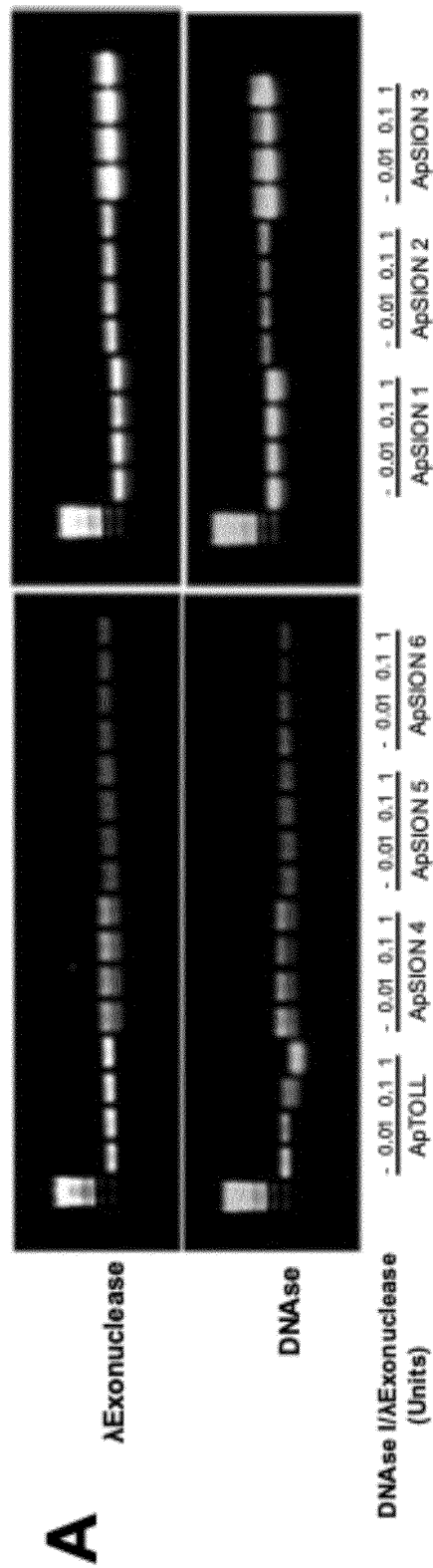


FIG. 1 (cont.)

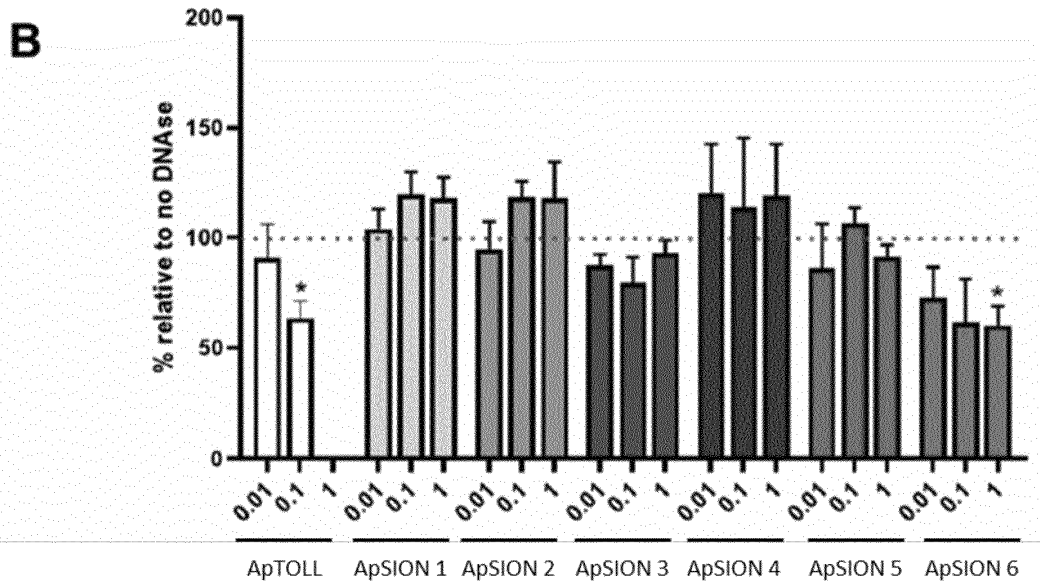


FIG. 2

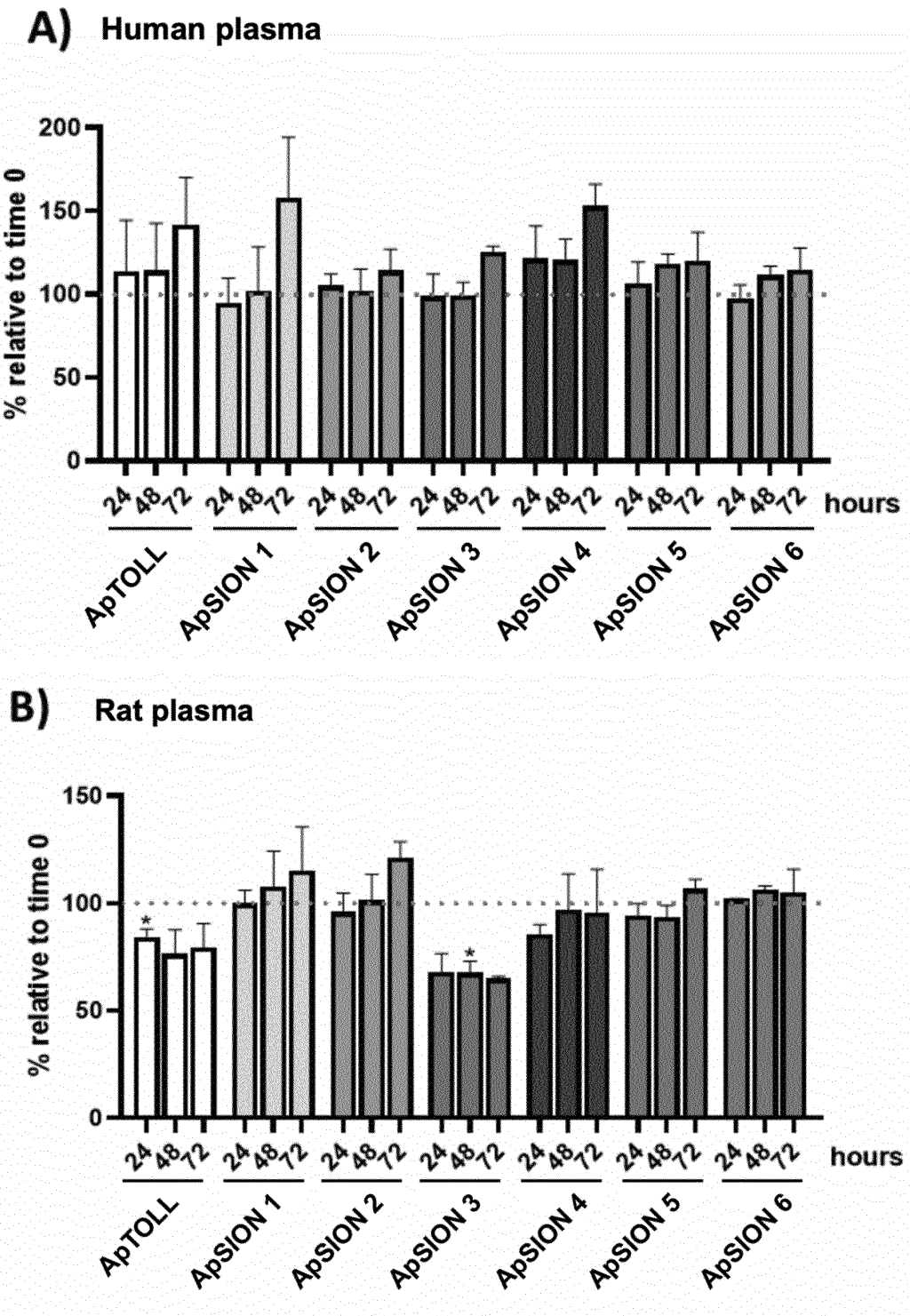


FIG. 2 (cont.)

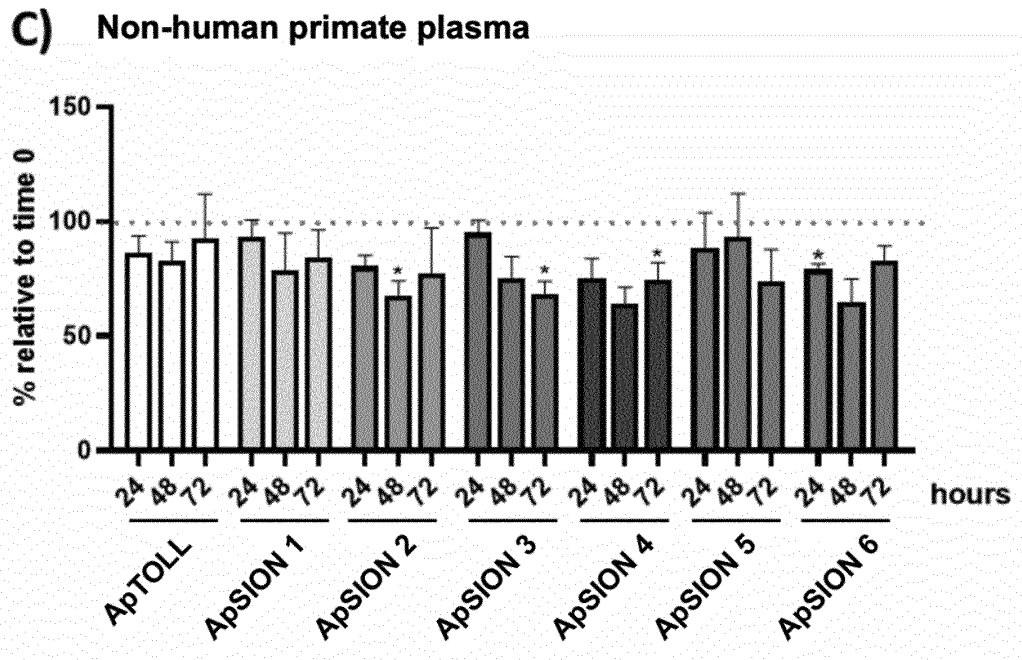


FIG. 3

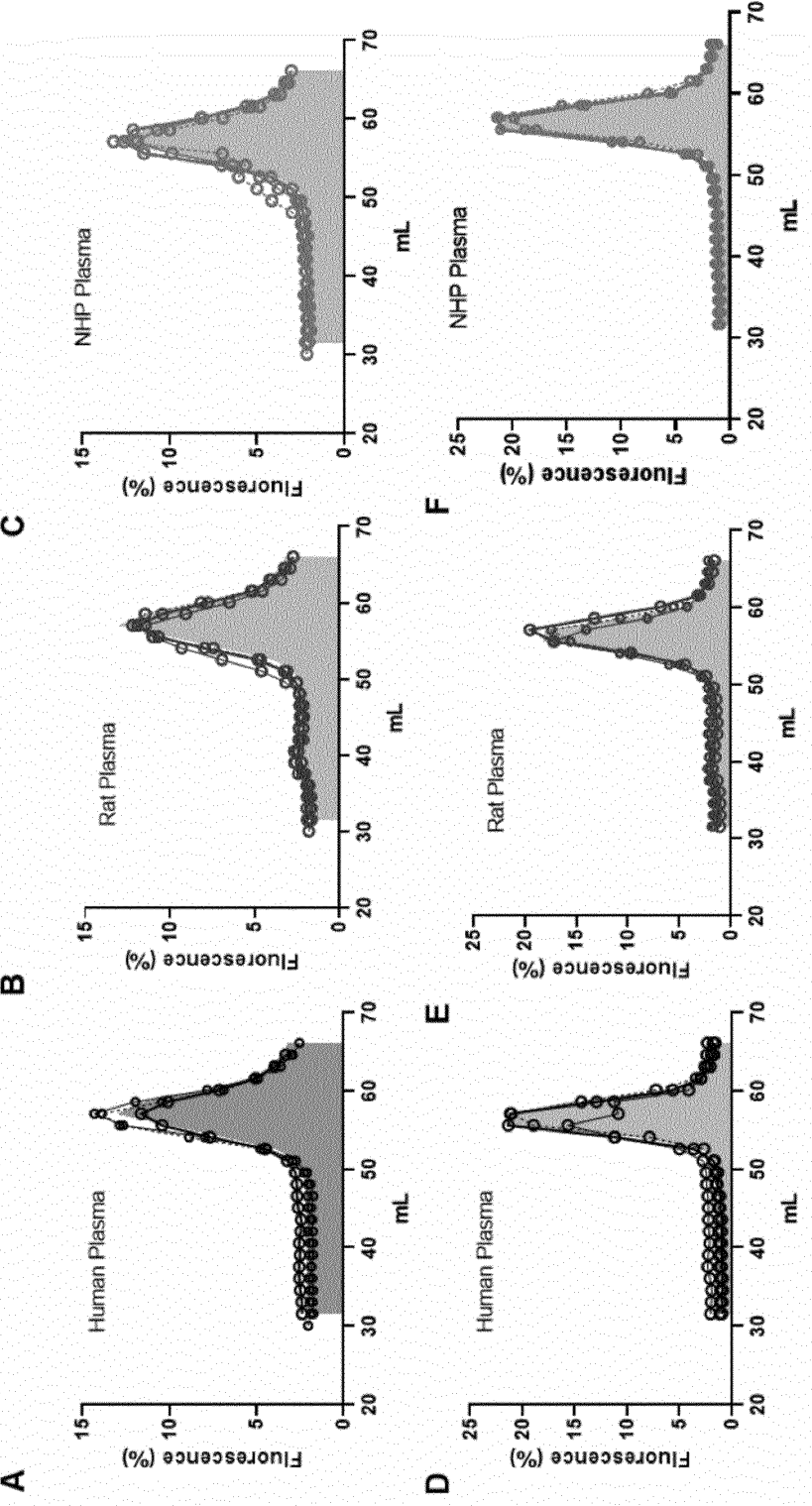


FIG. 4

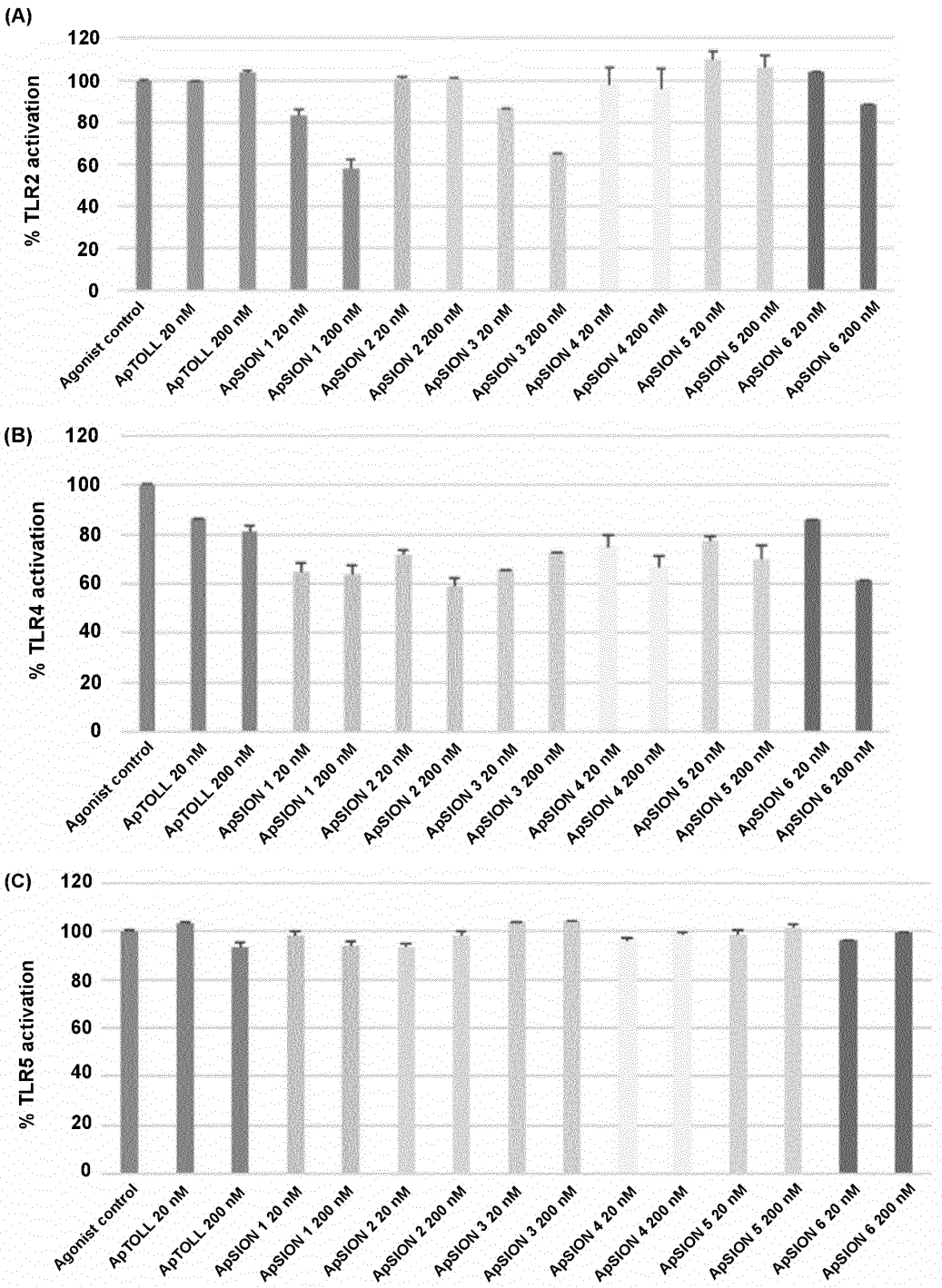


FIG. 5

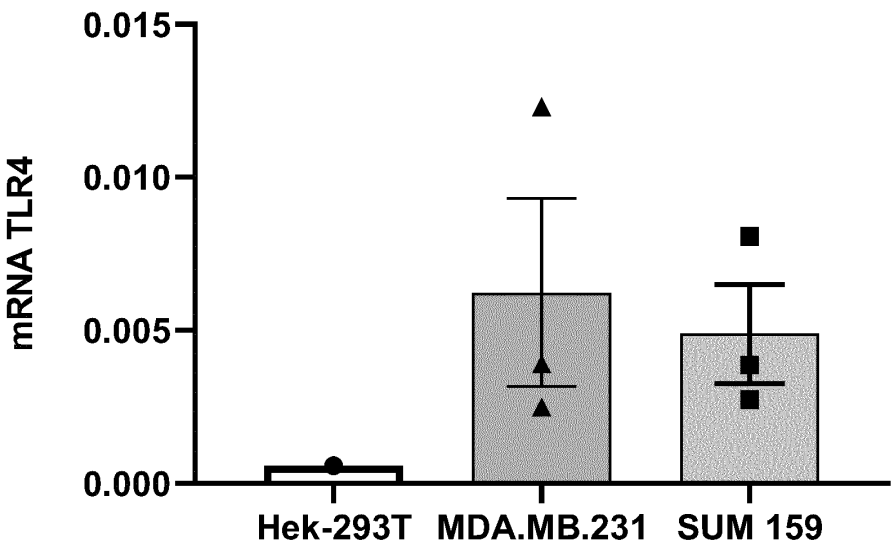


FIG. 6

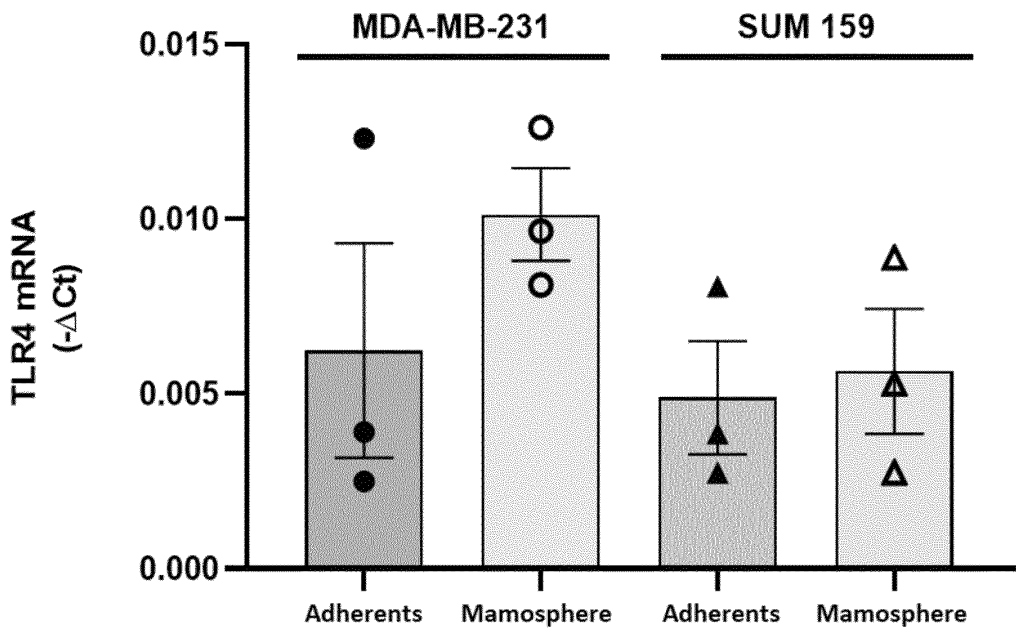


FIG. 7

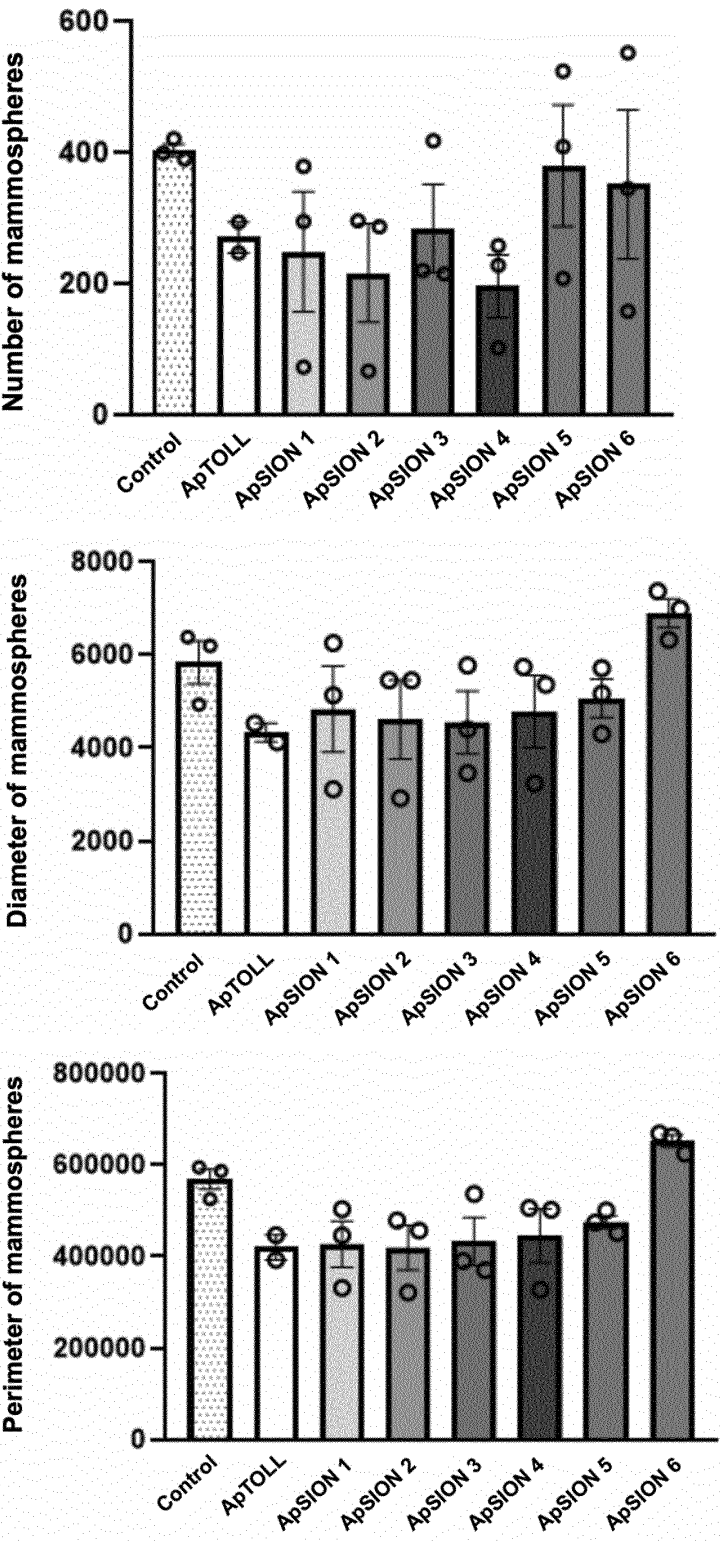


FIG. 8

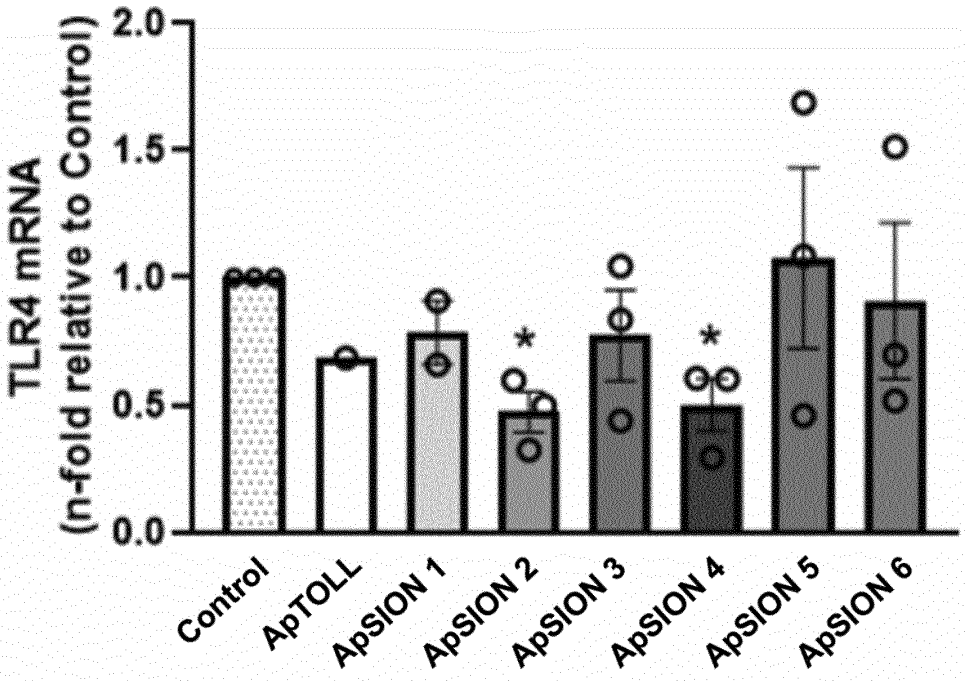


FIG. 9

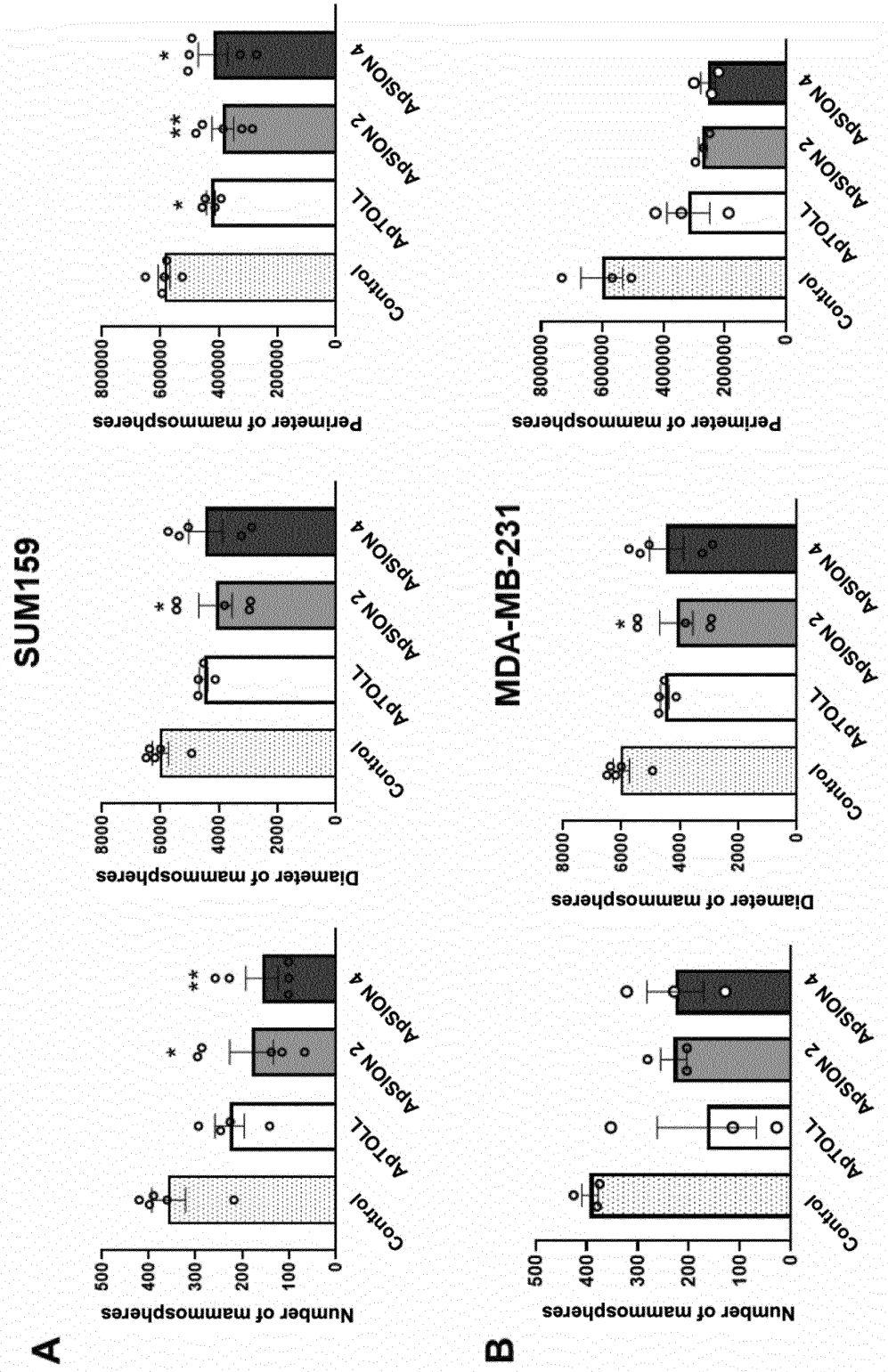


FIG. 10

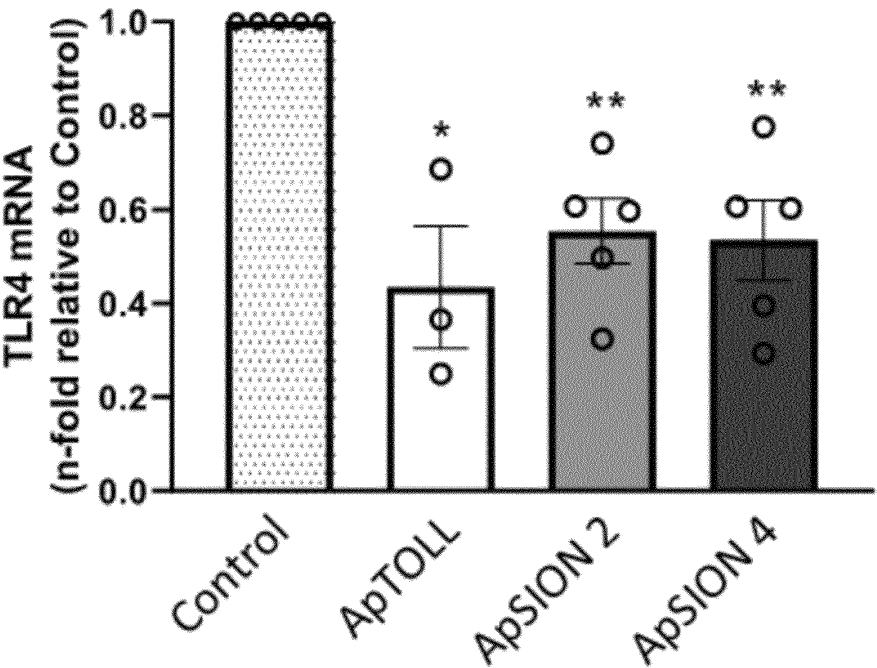


FIG. 11

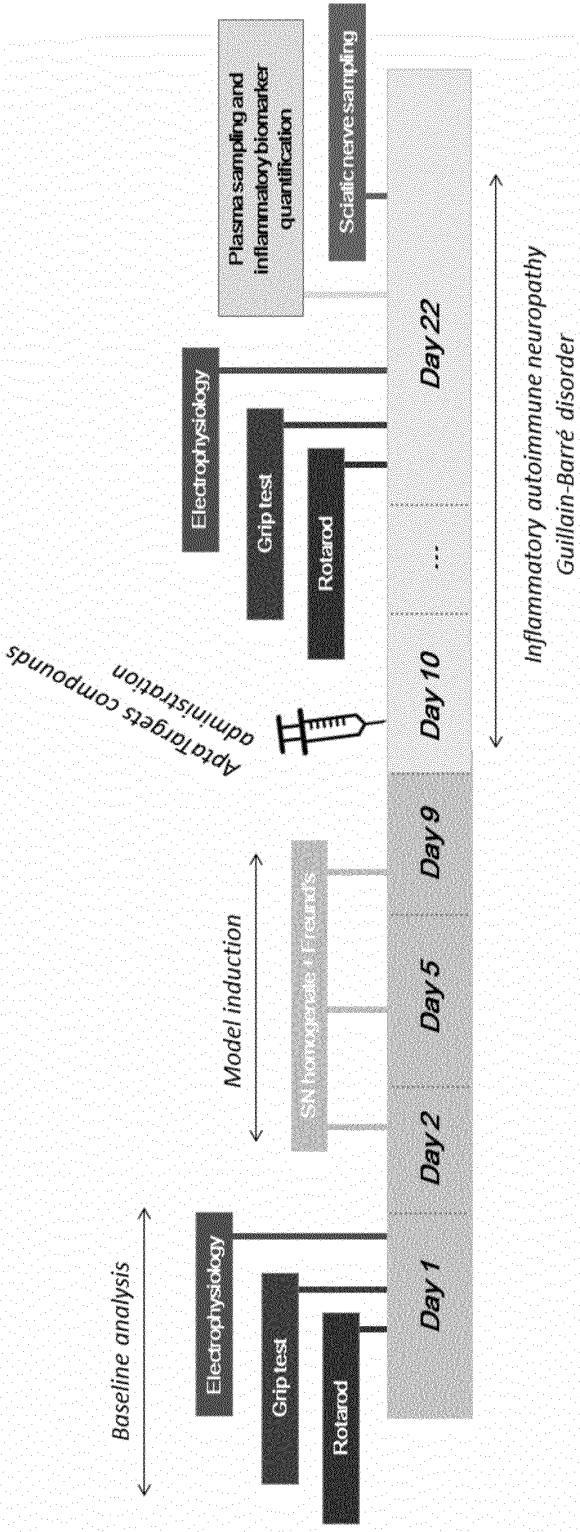


FIG. 12

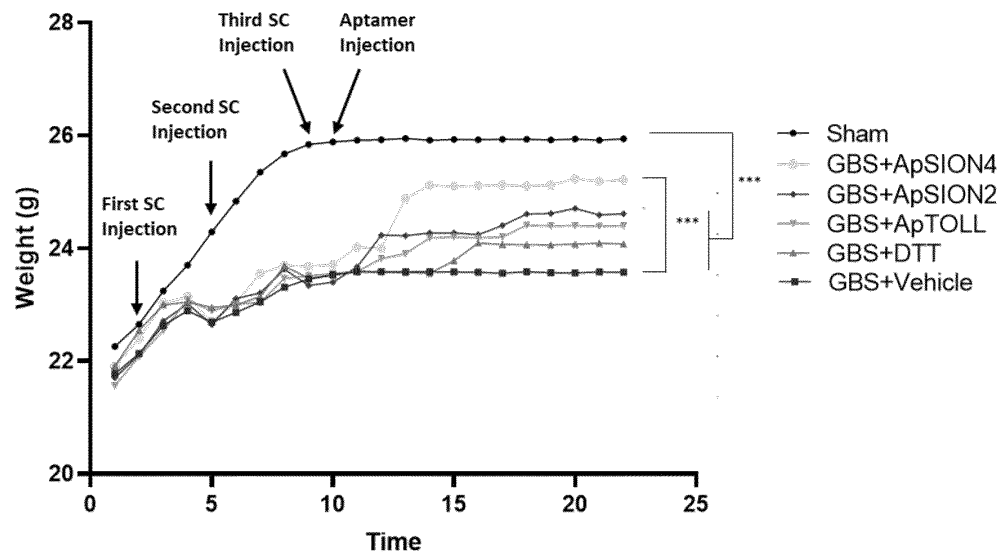


FIG. 13

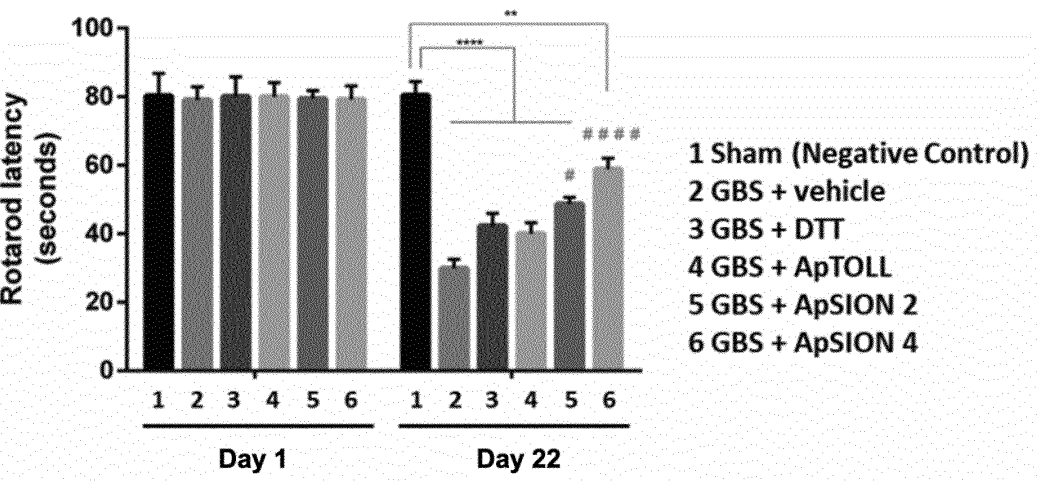


FIG. 14

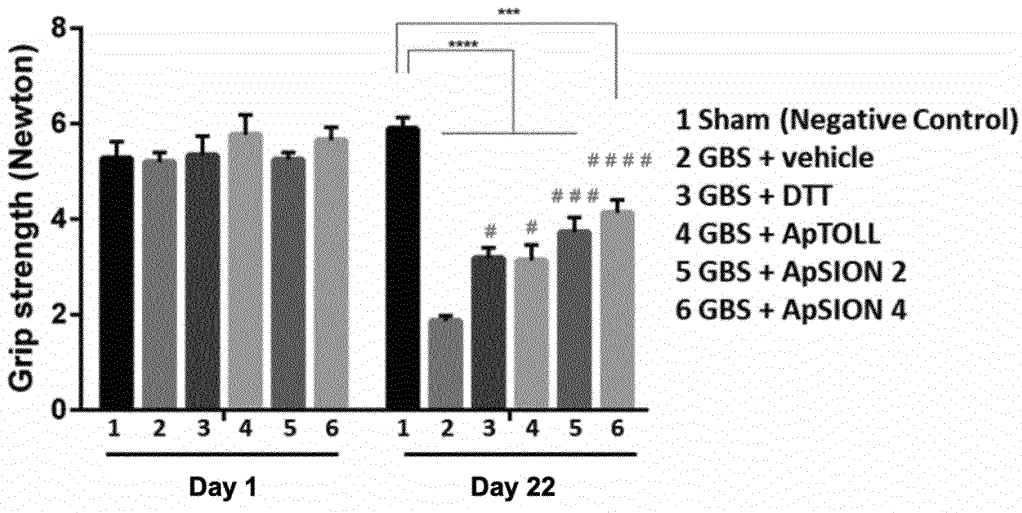


FIG. 15

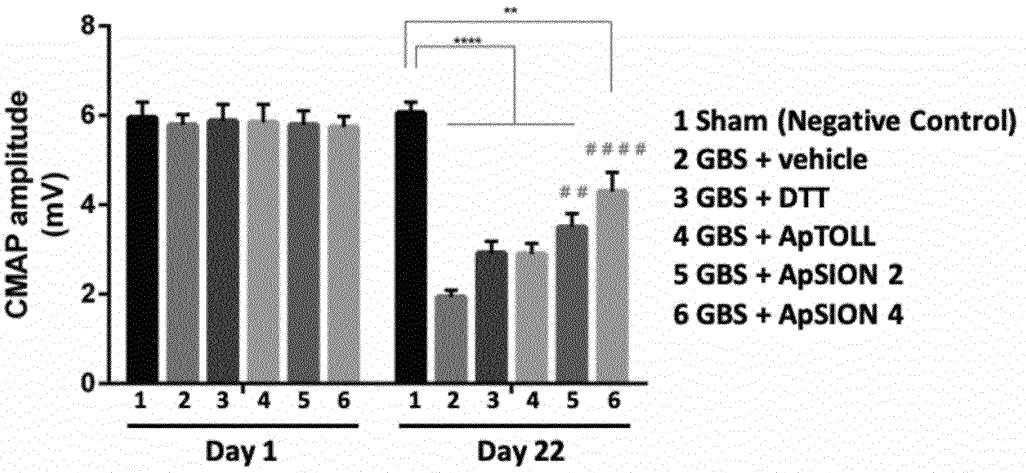


FIG. 16

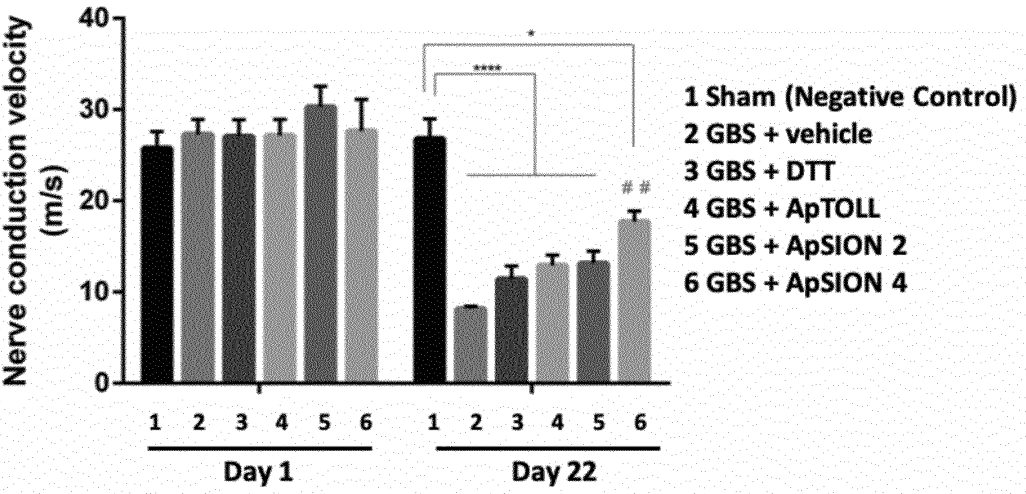


FIG. 17

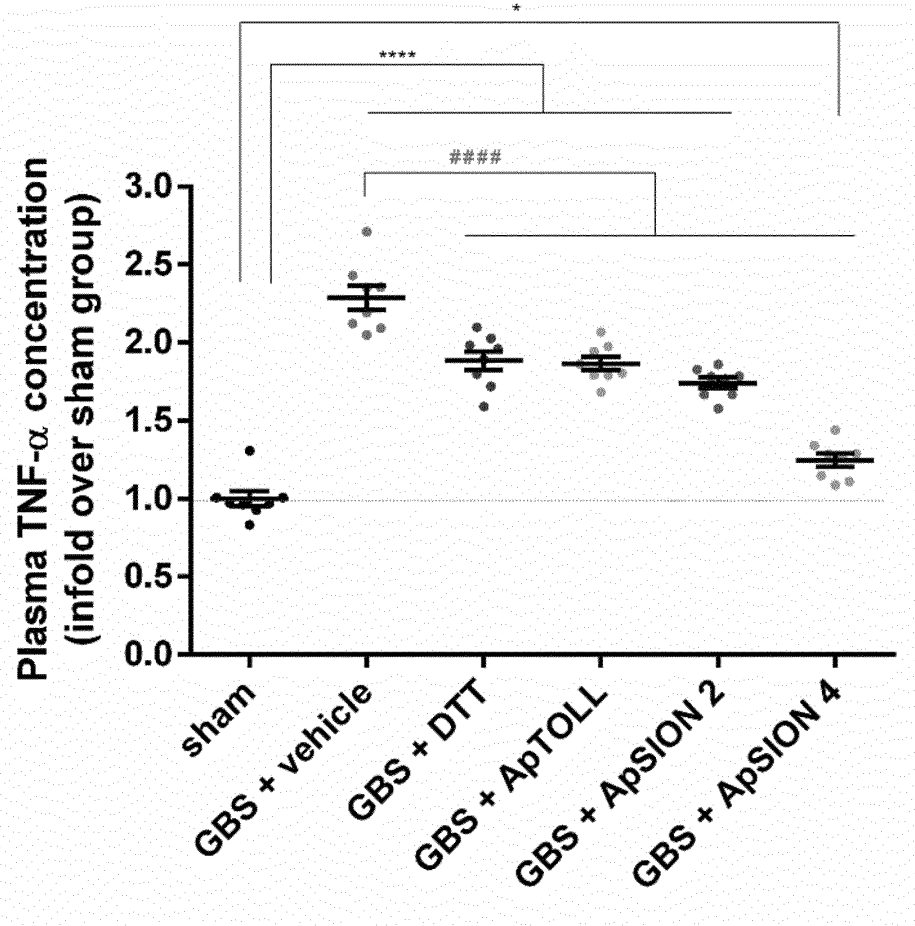


FIG. 18

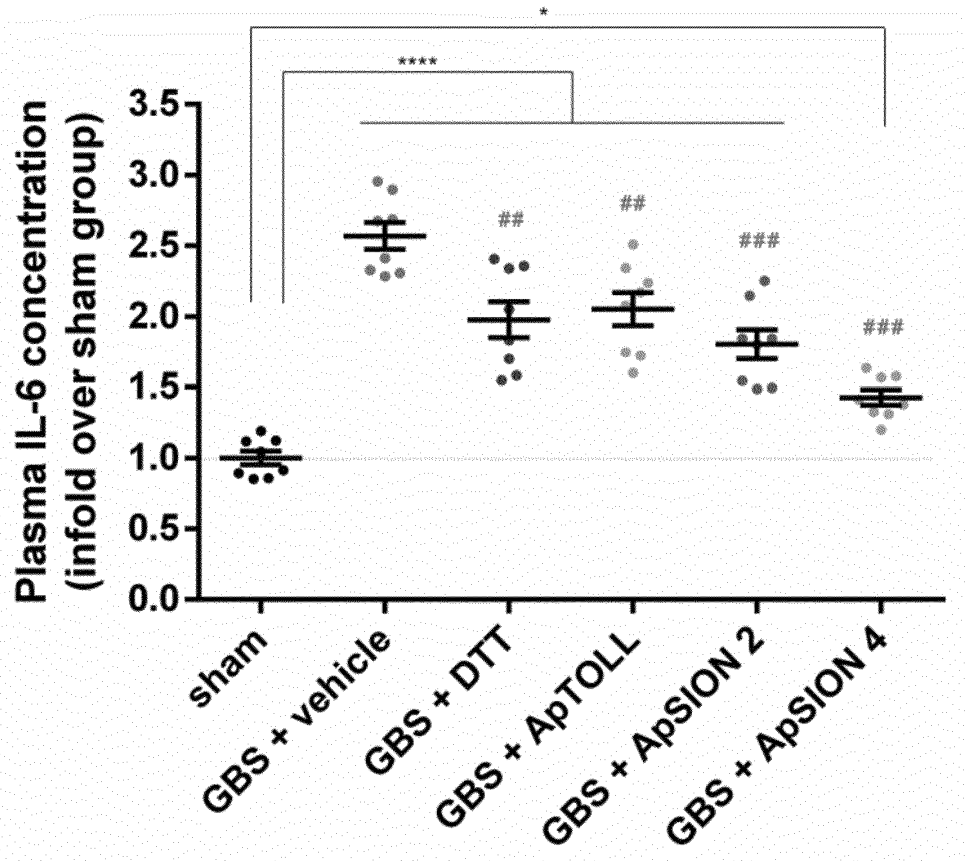


FIG. 19

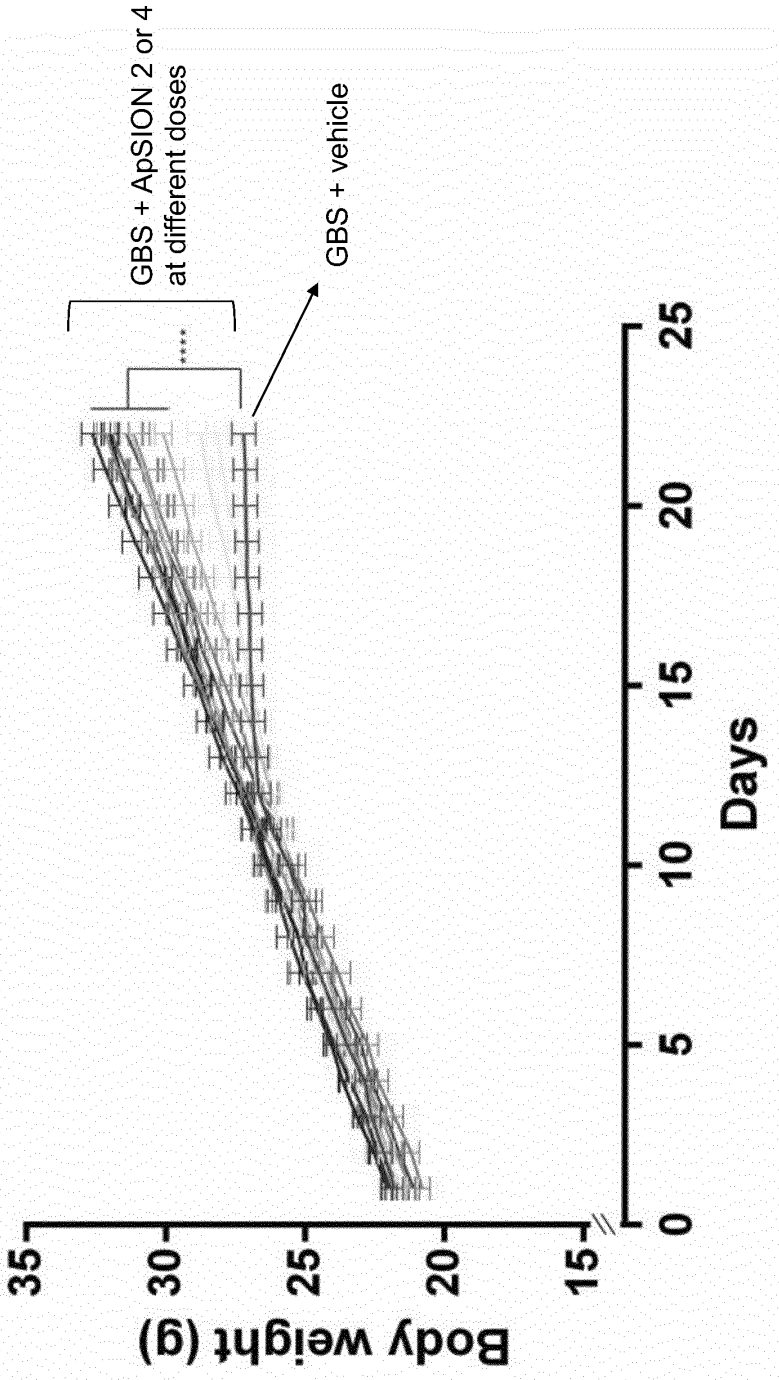


FIG. 21

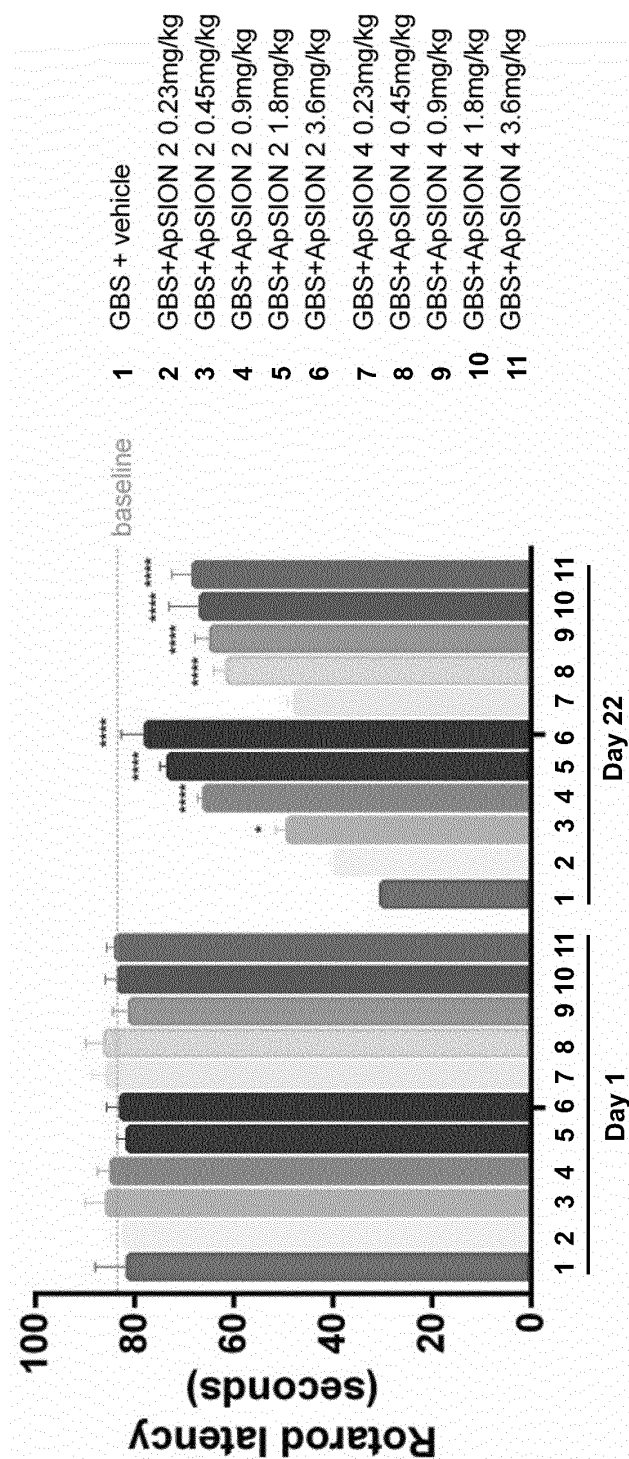


FIG. 22

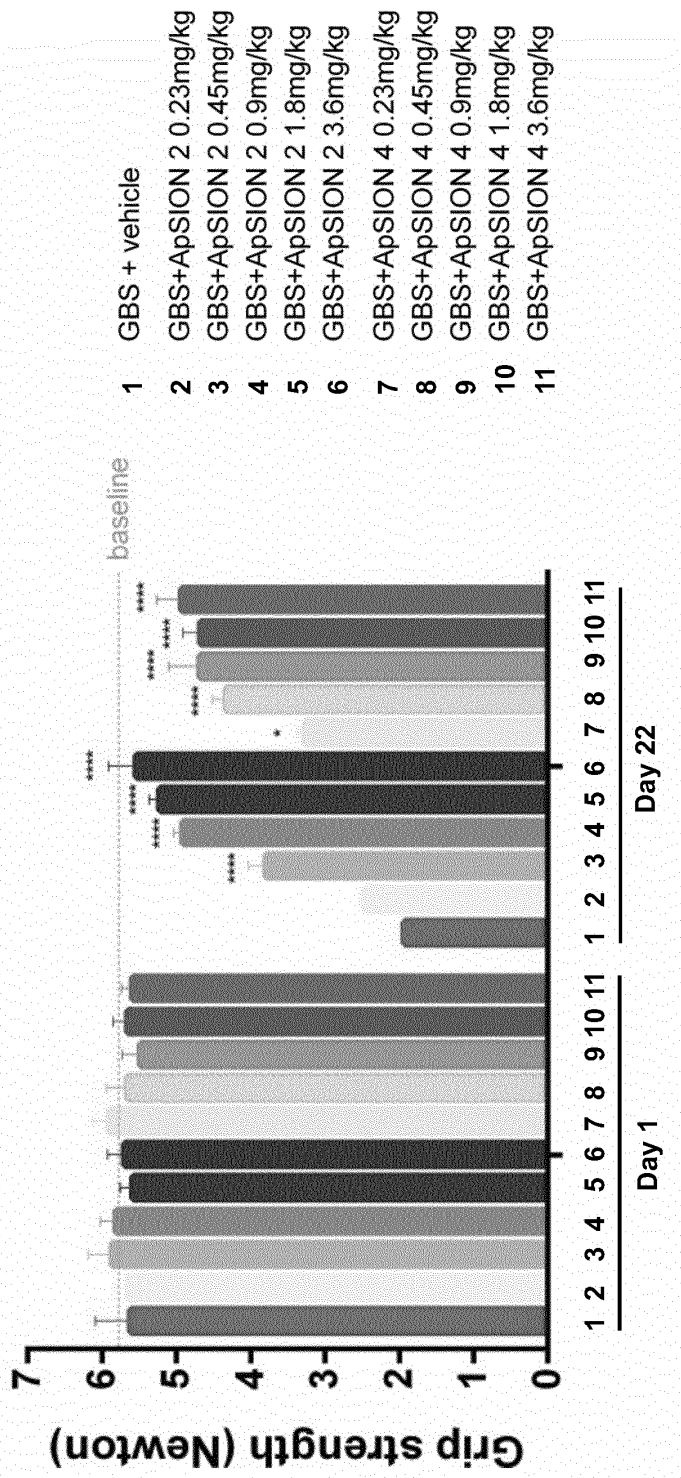


FIG. 23

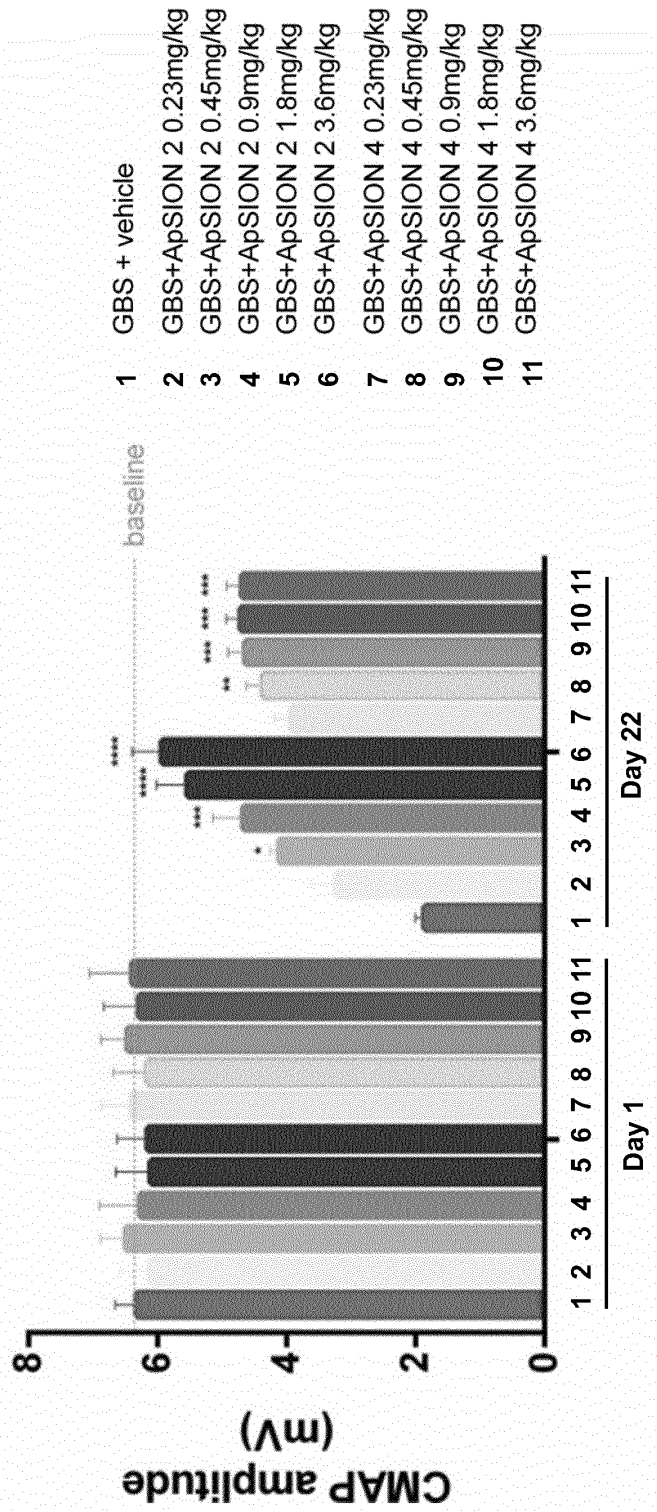


FIG. 24

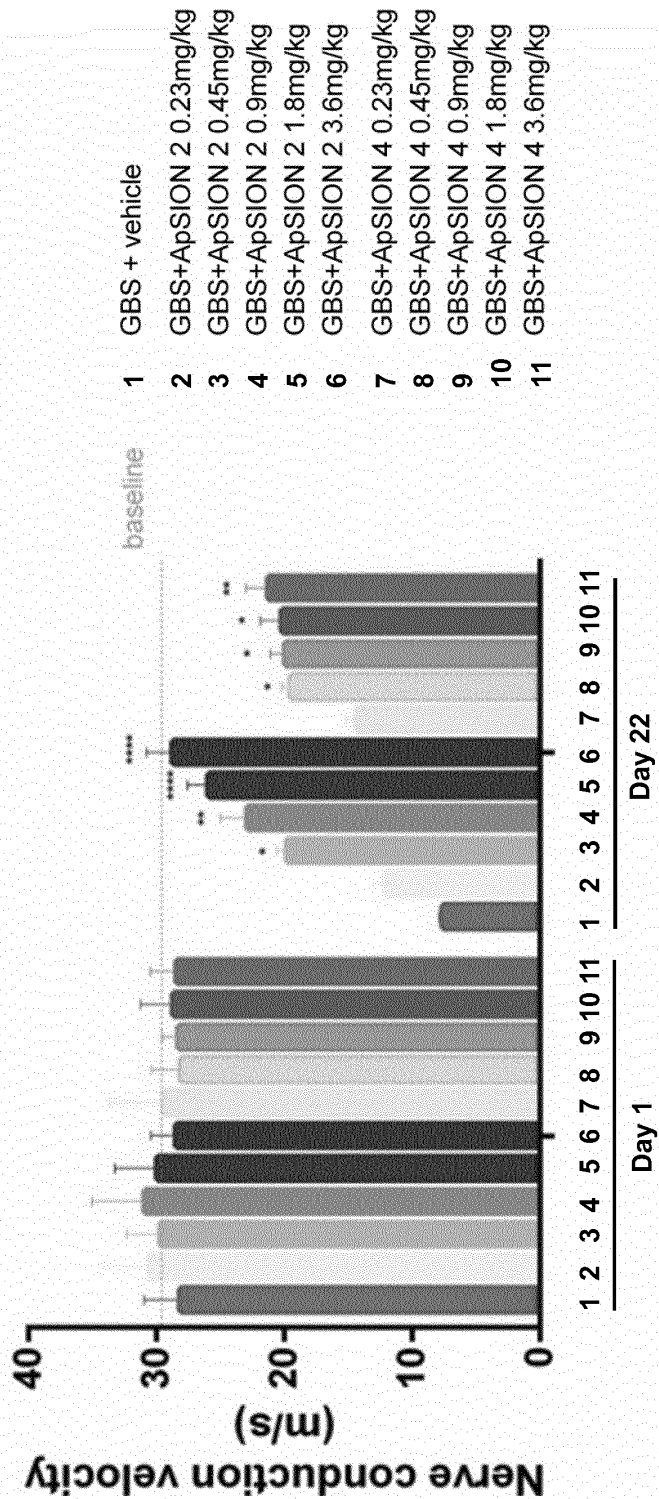


FIG. 25

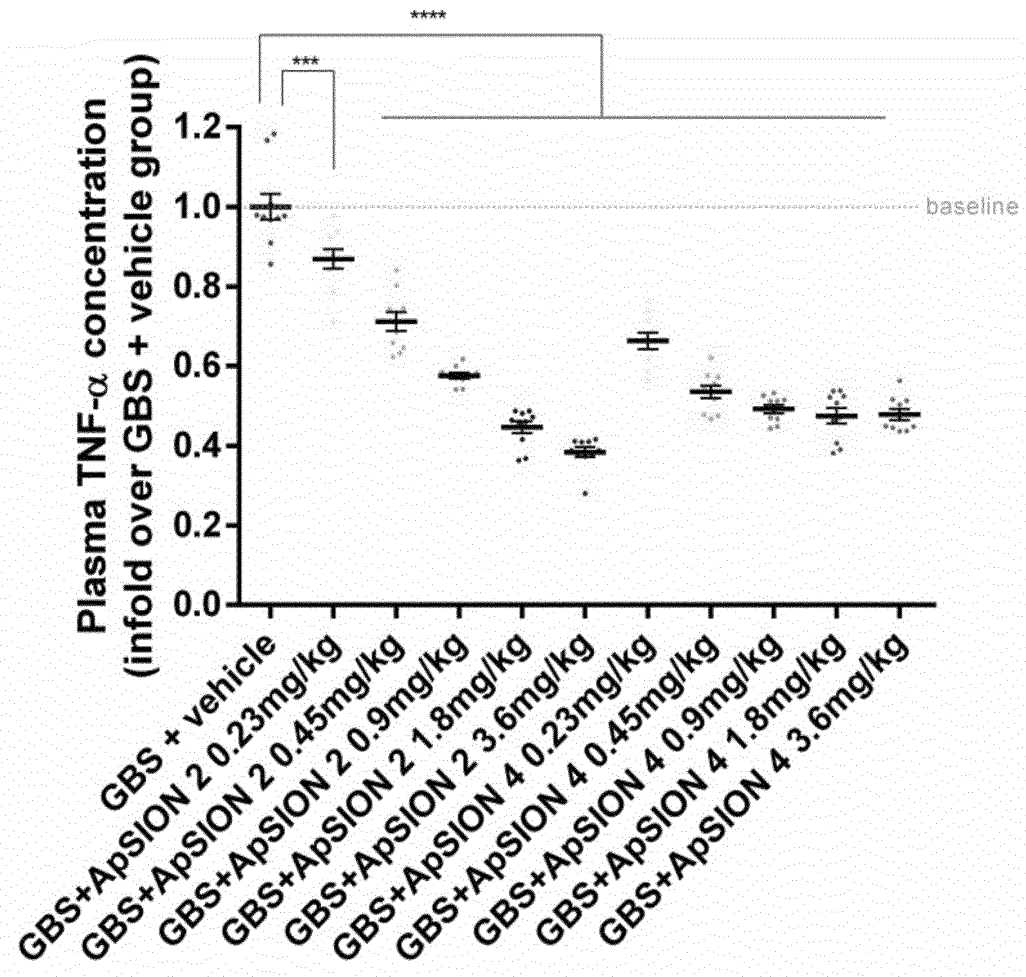


FIG. 26

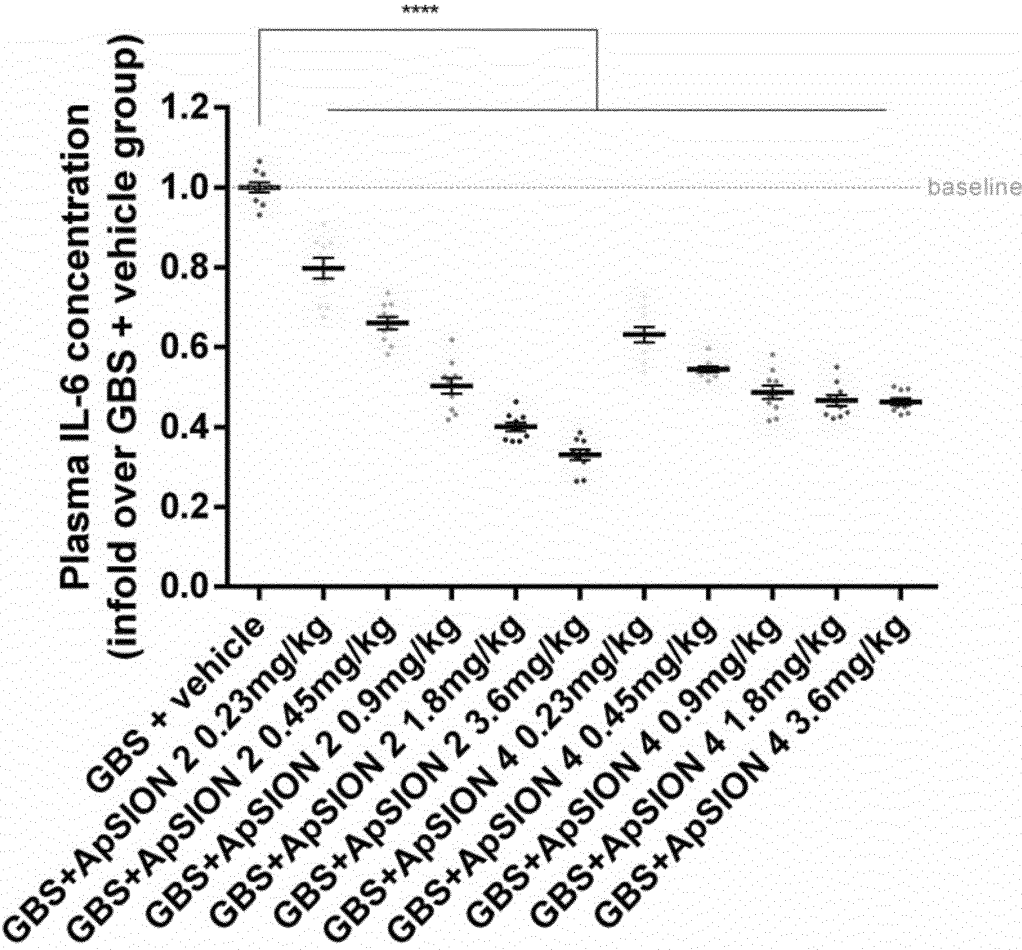


FIG. 27

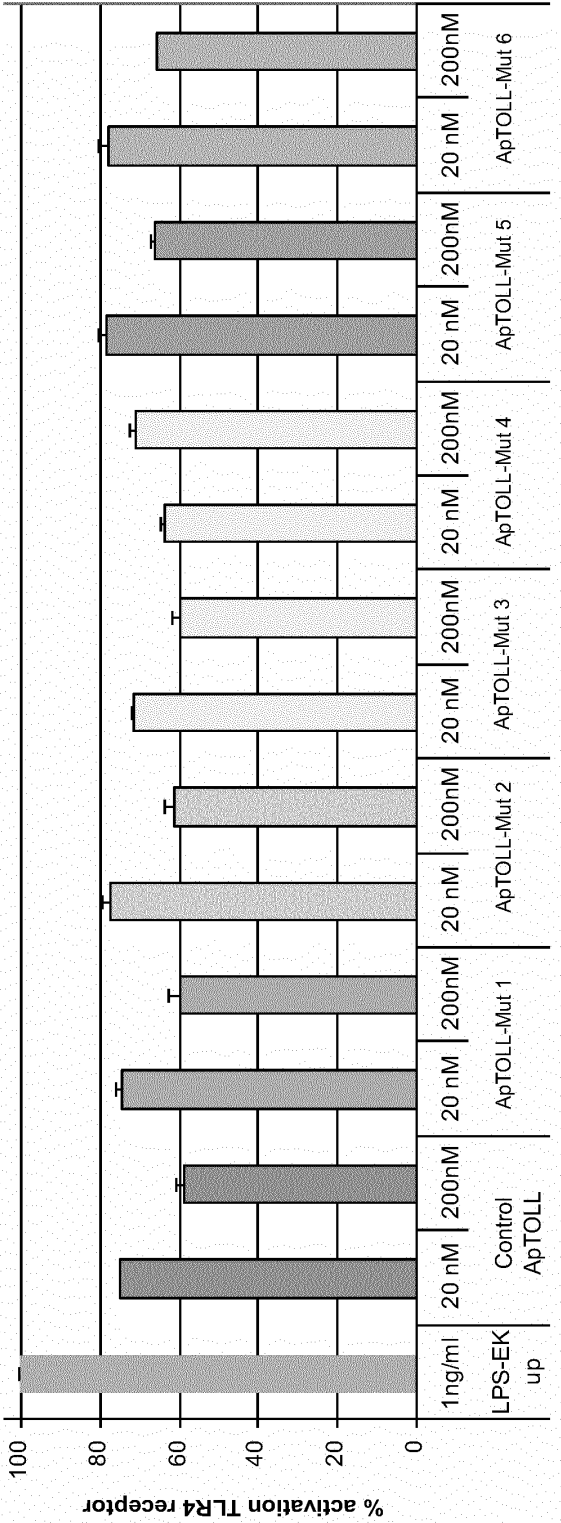


FIG. 28

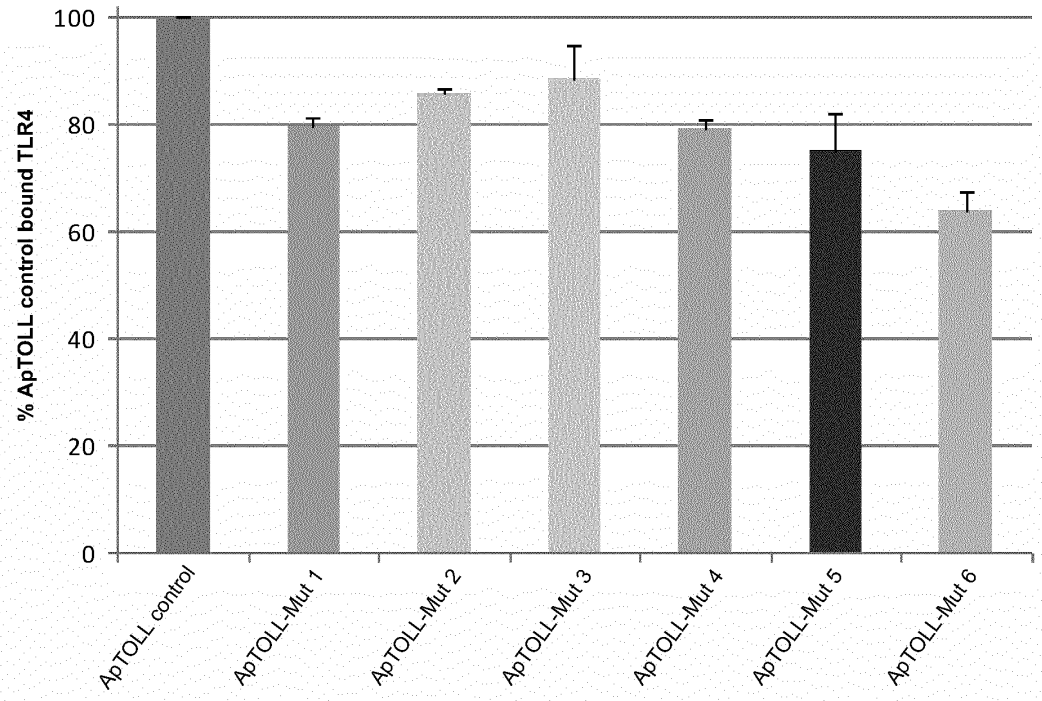
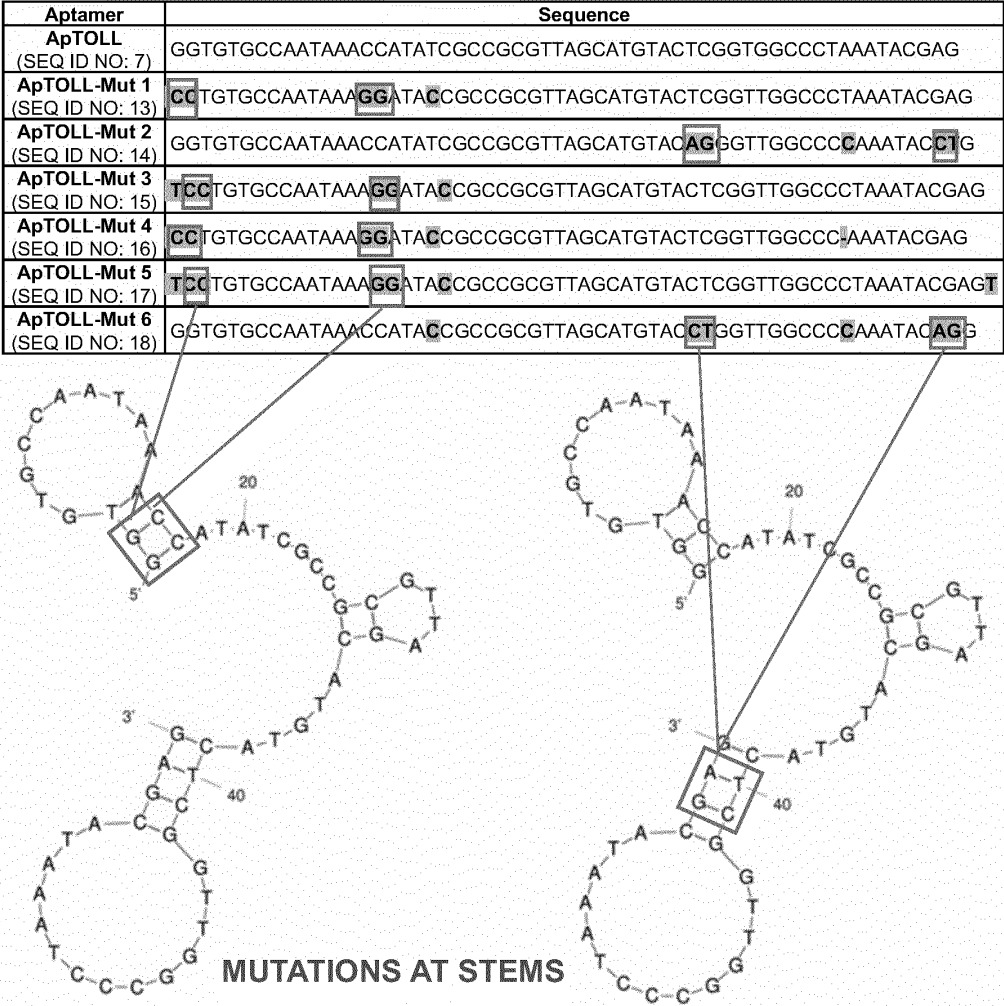


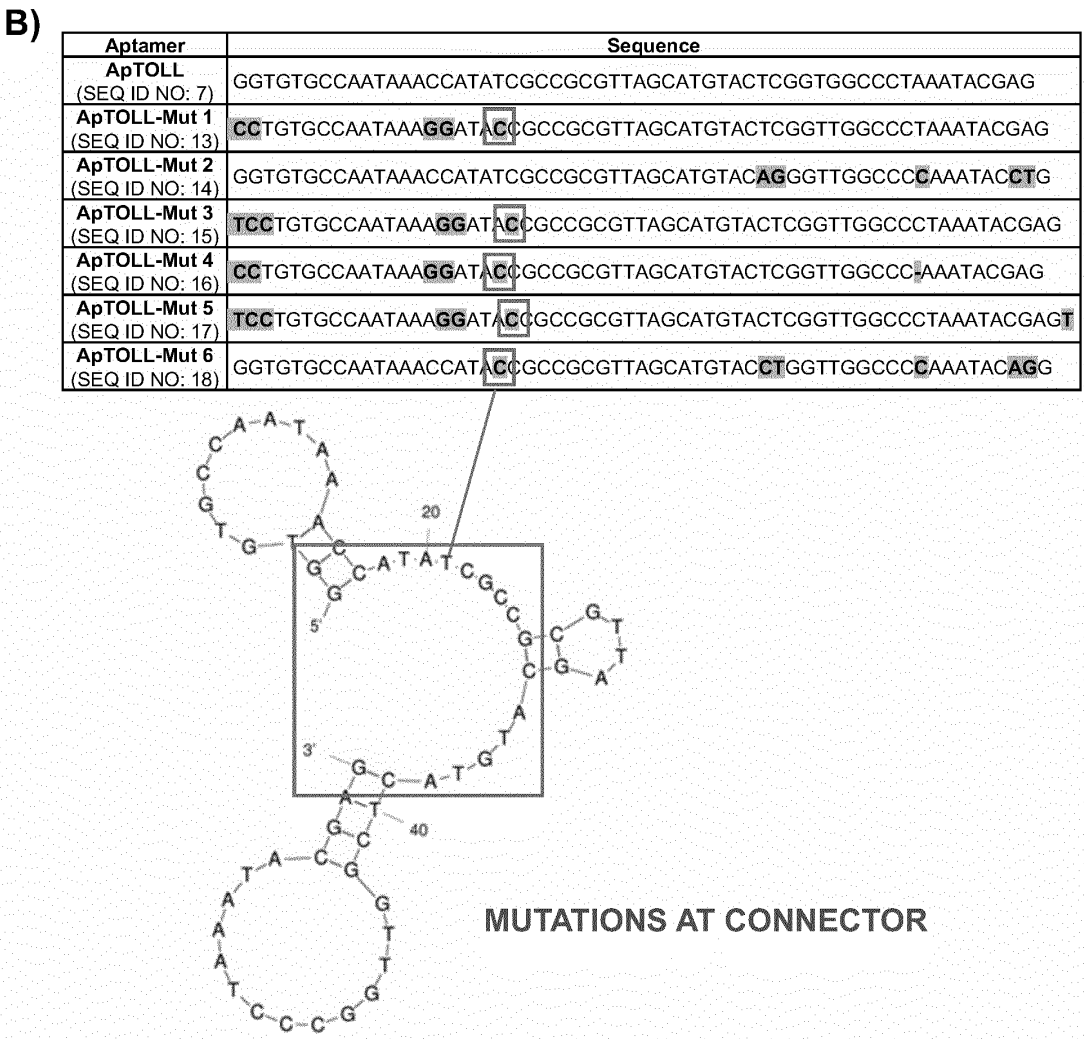
FIG. 29

A)



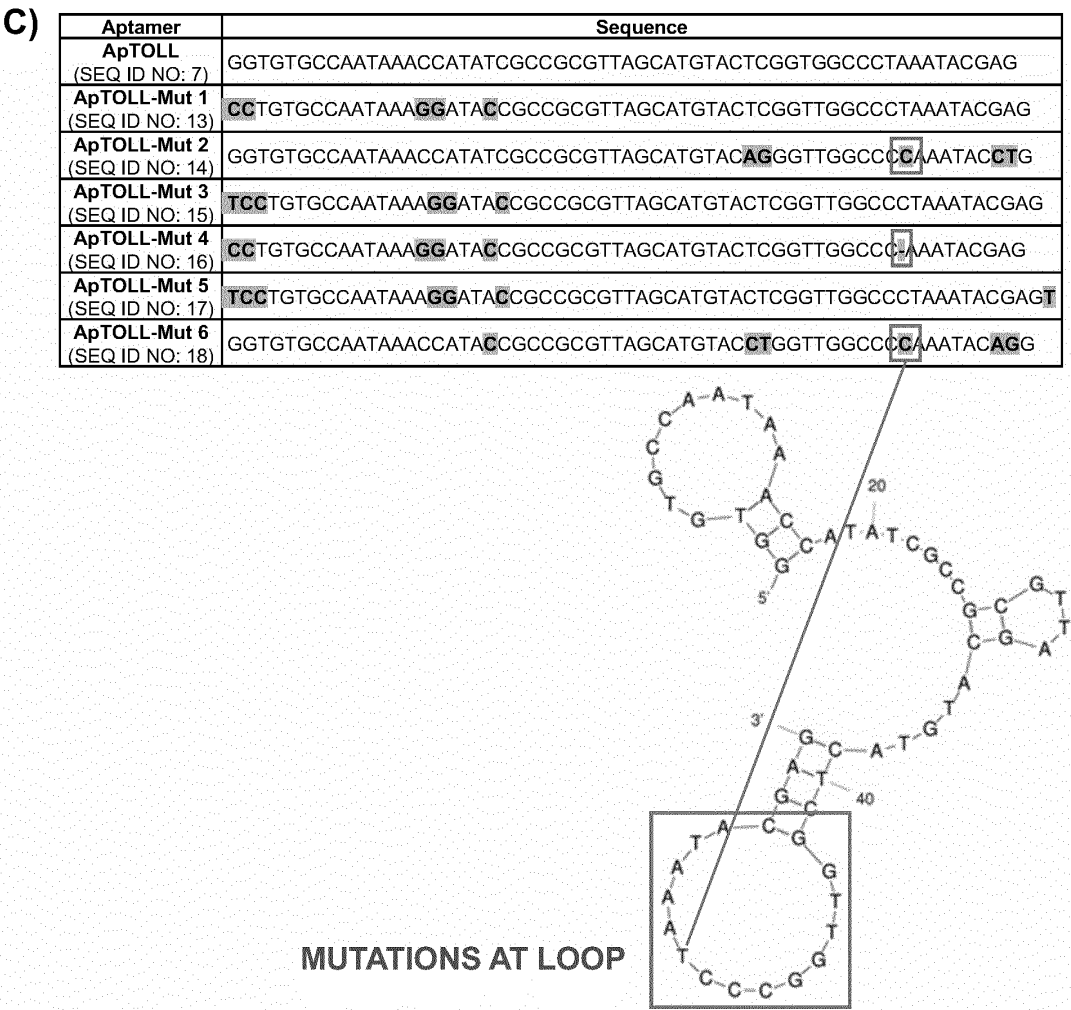
Aptamer	% identity to SEQ ID NO: 7	Nucleotides number
ApTOLL (SEQ ID NO: 7)	100.00	59
ApTOLL-Mut 1 (SEQ ID NO: 13)	91.53	59
ApTOLL-Mut 2 (SEQ ID NO: 14)	91.53	59
ApTOLL-Mut 3 (SEQ ID NO: 15)	90.76	60
ApTOLL-Mut 4 (SEQ ID NO: 16)	90.60	58
ApTOLL-Mut 5 (SEQ ID NO: 17)	90.00	61
ApTOLL-Mut 6 (SEQ ID NO: 18)	89.83	59

FIG. 29 (cont.)



Aptamer	% identity to SEQ ID NO: 7	Nucleotides number
ApTOLL (SEQ ID NO: 7)	100.00	59
ApTOLL-Mut 1 (SEQ ID NO: 13)	91.53	59
ApTOLL-Mut 2 (SEQ ID NO: 14)	91.53	59
ApTOLL-Mut 3 (SEQ ID NO: 15)	90.76	60
ApTOLL-Mut 4 (SEQ ID NO: 16)	90.60	58
ApTOLL-Mut 5 (SEQ ID NO: 17)	90.00	61
ApTOLL-Mut 6 (SEQ ID NO: 18)	89.83	59

FIG. 29 (cont.)



Aptamer	% identity to SEQ ID NO: 7	Nucleotides number
ApTOLL (SEQ ID NO: 7)	100.00	59
ApTOLL-Mut 1 (SEQ ID NO: 13)	91.53	59
ApTOLL-Mut 2 (SEQ ID NO: 14)	91.53	59
ApTOLL-Mut 3 (SEQ ID NO: 15)	90.76	60
ApTOLL-Mut 4 (SEQ ID NO: 16)	90.60	58
ApTOLL-Mut 5 (SEQ ID NO: 17)	90.00	61
ApTOLL-Mut 6 (SEQ ID NO: 18)	89.83	59

FIG. 30

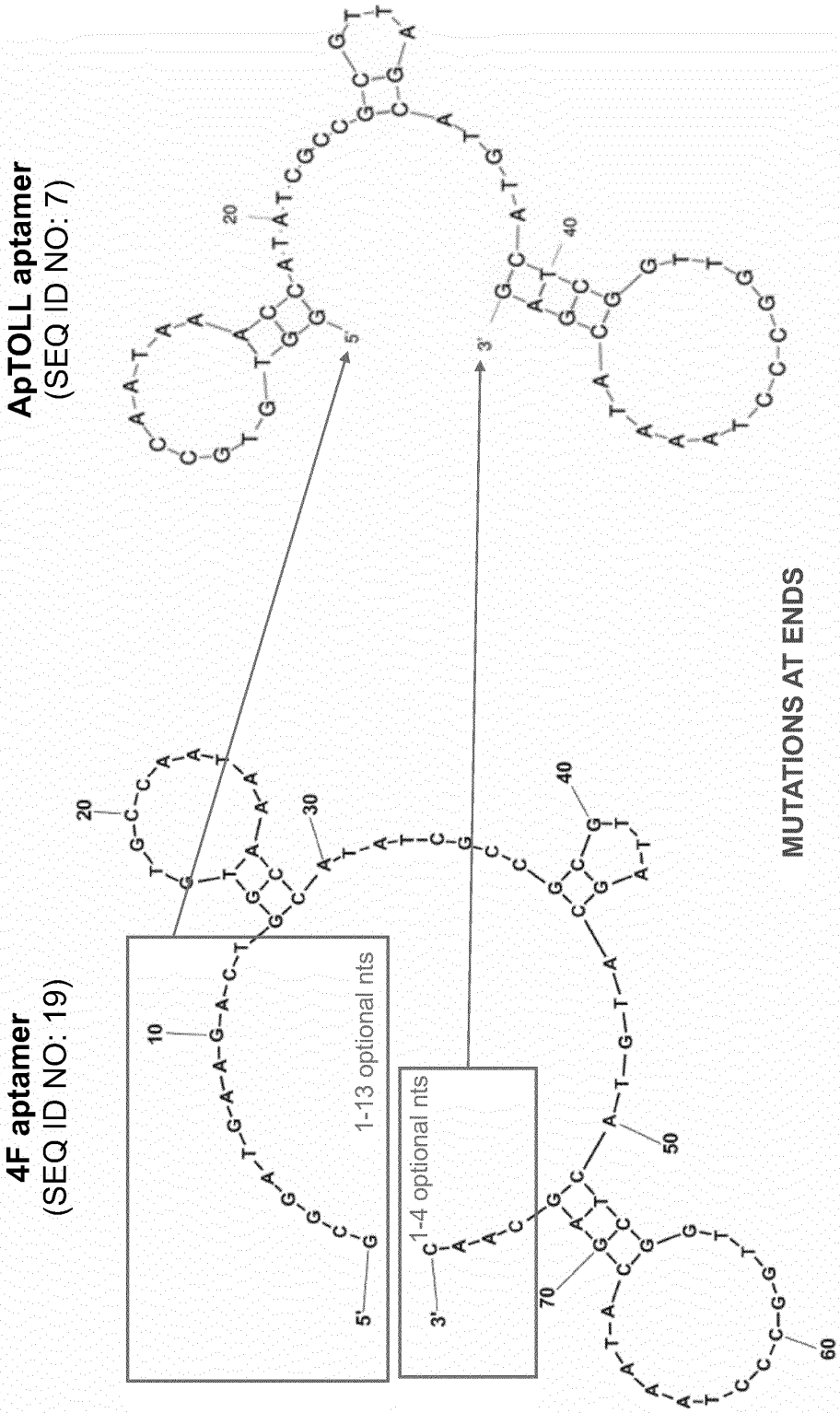


FIG. 31

(A)

Name	ApSION 2	Manufacturing date	Oct-2022			
Batch	17102022	Manufacturer	Sylentis			
Method	Description	Specification	T0		T1	
IEX-HPLC (Sylentis)	Purity	≥70% (% UV-area)	82.0		80.8	
	Impurity profile	Report RRT and % area for peaks ≥0,10% UV- area	RRT	% UV-area	RRT	% UV-area
			0.898	0.16	0.876	0.12
			0.910	0.14	0.908	0.17
			0.927	0.73	0.926	0.80
			0.948	1.2	0.947	1.3
			0.958	0.64	0.958	0.59
			0.962	0.76	0.961	0.84
			0.979	3.9	0.979	3.9
			1.045	5.7	1.049	6.2
			1.056	2.0	1.062	2.2
			1.068	2.7	1.078	3.0
	Total impurity	<30% (% UV-area)	18.0		19.2	
	Single highest imp	Report (% UV-area)	5.7		6.2	
Biological activity (Aptus)	20 nM	Report (% SEAP activity)	77.0		75,0	
	200 nM		71.0		64,0	

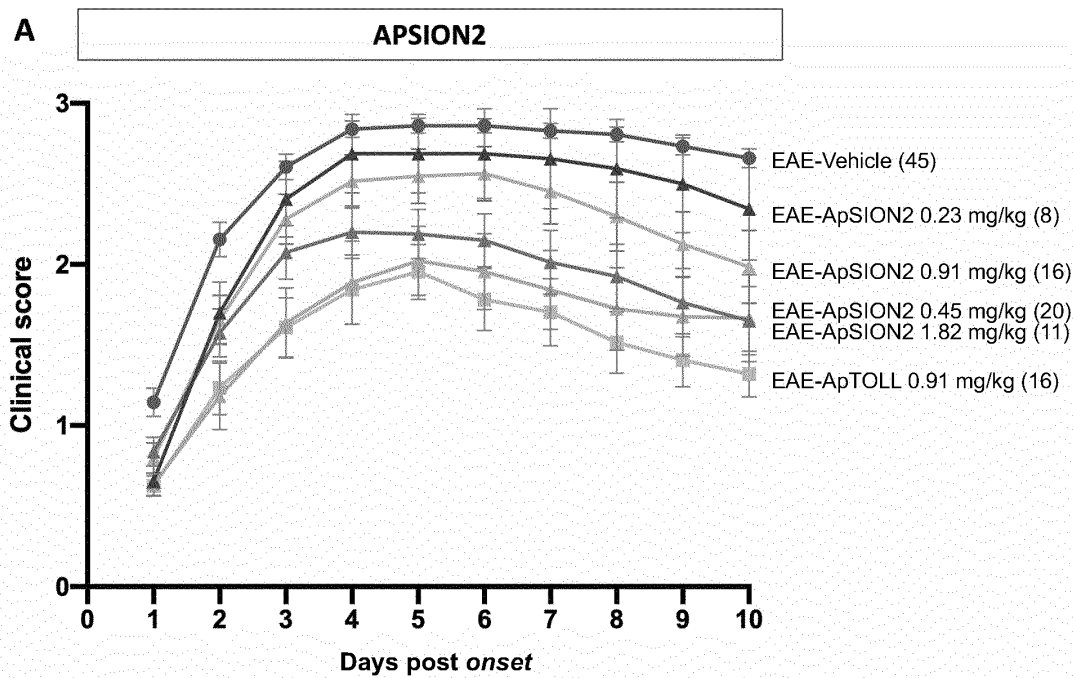
T3		T6		T9		T12	
80.7		80.4		80.4		80.4	
RRT	% UV-area	RRT	% UV-area	RRT	% UV-area	RRT	% UV-area
0.876	0.11	0.876	0.10	0.882	0.11	0.879	0.11
0.895	0.15	0.893	0.22	0.899	0.17	0.896	0.16
0.912	0.15	0.908	0.17	0.911	0.18	0.909	0.17
0.927	0.77	0.927	0.78	0.927	0.78	0.926	0.79
0.954	1.3	0.944	0.73	0.948	1.40	0.953	1.5
0.959	0.55	0.952	0.93	0.958	0.50	0.959	0.98
0.960	0.4	0.958	1.1	0.963	0.77	0.966	0.49
0.983	4.6	0.979	4.1	0.979	4.00	0.978	4.1
1.048	6.3	1.043	6.5	1.044	6.1	1.041	6.0
1.069	2.4	1.056	2.0	1.057	2.0	1.052	2.0
1.092	2.5	1.071	3.0	1.070	3.7	1.065	3.3
19.3		19.6		19.6		19.6	
6.3		6.5		6.1		6.0	
75		73.2		54.2		77.9	
65		58.9		44.0		62.8	

FIG. 31 (cont.)
(B)

Name	ApSion 4	Manufacturing date	Jul-2023
Batch	1107023	Manufacturer	Sylentis
Method	Description	Specification	T0
IEX-HPLC (Sylentis)	Purity	≥70% (% UV-area)	73.8
	Impurity profile	Report RRT and % area for peaks ≥0.10% UV- area	RRT
			0.908
			0.920
			0.939
			0.950
			0.955
			0.966
			0.972
			0.976
			0.980
			1.034
			1.042
			1.046
			1.053
			1.060
			1.064
			1.074
			1.083
			26.1
	Total impurity	<30% (% UV-area)	26.1
Biological activity (Aptus)	Single highest imp	Report (% UV-area)	4.2
	20 nM	Report (% SEAP activity)	57.1
	200 nM		45.3

T2		T3		T6		T9	
74.1		74.0		74.0		74.1	
RRT	% UV-area	RRT	% UV-area	RRT	% UV-area	RRT	% UV-area
0.903	0.2	0.902	0.19	0.909	0.22	0.899	0.21
0.916	0.23	0.915	0.23	0.920	0.25	0.913	0.23
0.937	0.92	0.937	0.93	0.938	0.89	0.936	0.96
0.948	0.79	0.944	0.50	0.950	0.84	0.943	0.50
0.953	2.8	0.952	2.85	0.956	3.20	0.952	2.80
0.963	1.8	0.961	1.96	0.965	1.60	0.960	1.90
0.969	2.5	0.969	2.80	0.971	2.00	0.969	2.90
0.976	4.2	0.977	4.10	0.974	3.70	0.978	3.80
0.978	2.8	0.980	2.60	0.979	3.70	0.980	2.80
1.029	3.4	1.033	3.30	1.027	3.70	1.036	3.30
1.036	1.4	1.043	1.60	1.031	1.40	1.046	1.60
1.038	1.9	1.050	0.90	1.035	1.40	1.052	1.10
1.046	1.1	1.055	1.00	1.060	1.10	1.060	1.10
1.053	0.84	1.061	0.90	1.042	0.97	1.068	0.83
1.058	0.78	1.073	0.90	1.047	0.77	1.083	0.71
1.067	0.28	1.078	0.70	1.050	0.56	1.091	0.82
1.074	0.13	1.088	0.30	1.056	0.34	1.108	0.39
25.9	25.9	26.0	26.0	26.0	26.0	25.9	25.9
4.2	4.2	4.10	4.10	3.70	3.70	3.80	3.80
57.1	64.1	77.0	77.0	75.2	75.2	60.5	60.5
45.3	53.1	59.4	59.4	58.6	58.6	55.8	55.8

FIG. 33



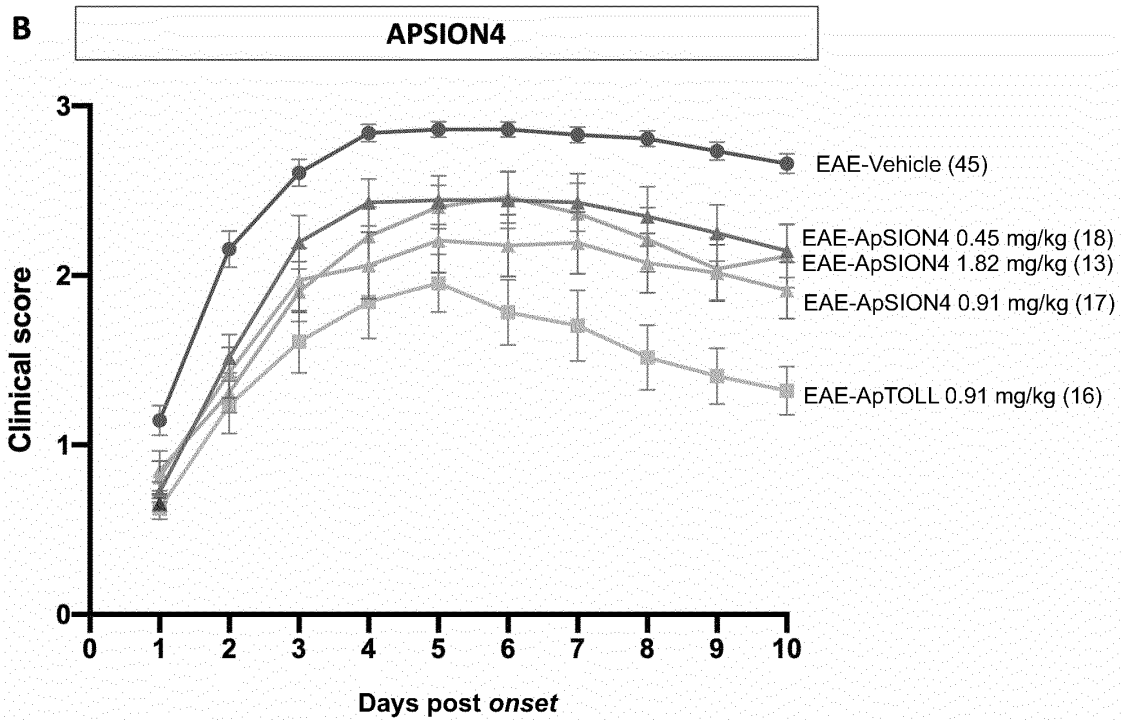
Days post-onset

	1	2	3	4	5
Veh vs. ApSION2 0.23 mg/Kg	*	n.s	n.s	n.s	n.s
ApTOLL vs. ApSION2 0.23 mg/Kg	n.s	n.s	#	#	#
Veh vs. ApSION2 0.45 mg/Kg	n.s	**	**	***	***
ApTOLL vs. ApSION2 0.45 mg/Kg	#	n.s	n.s	n.s	n.s
Veh vs. ApSION2 0.91 mg/Kg	*	*	n.s	*	*
ApTOLL vs. ApSION2 0.91 mg/Kg	n.s	n.s	##	#	#
Veh vs. ApSION2 1.82 mg/Kg	**	***	***	***	***
ApTOLL vs. ApSION2 1.82 mg/Kg	n.s	n.s	n.s	n.s	n.s
Veh vs. ApTOLL 0.91 mg/Kg	***	***	***	***	***

Days post-onset

	6	7	8	9	10
Veh vs. ApSION2 0.23 mg/Kg	n.s	n.s	n.s	n.s	n.s
ApTOLL vs. ApSION2 0.23 mg/Kg	##	##	##	##	##
Veh vs. ApSION2 0.45 mg/Kg	***	***	***	***	***
ApTOLL vs. ApSION2 0.45 mg/Kg	n.s	n.s	n.s	n.s	n.s
Veh vs. ApSION2 0.91 mg/Kg	n.s	n.s	**	***	**
ApTOLL vs. ApSION2 0.91 mg/Kg	##	##	#	##	#
Veh vs. ApSION2 1.82 mg/Kg	***	***	***	***	***
ApTOLL vs. ApSION2 1.82 mg/Kg	n.s	n.s	n.s	n.s	n.s
Veh vs. ApTOLL 0.91 mg/Kg	***	***	***	***	***

FIG. 33 (cont.)



	Days post-onset				
	1	2	3	4	5
Veh vs. ApSION4 0.45 mg/Kg	**	**	*	**	**
ApTOLL vs. ApSION4 0.45 mg/Kg	n.s	n.s	#	#	#
Veh vs. ApSION4 0.91 mg/Kg	*	***	**	***	***
ApTOLL vs. ApSION4 0.91 mg/Kg	n.s	n.s	n.s	n.s	n.s
Veh vs. ApSION4 1.82 mg/Kg	n.s	***	***	***	***
ApTOLL vs. ApSION4 1.82 mg/Kg	n.s	n.s	n.s	n.s	n.s
Veh vs. ApTOLL 0.91 mg/Kg	***	***	***	***	***

	Days post-onset				
	6	7	8	9	10
Veh vs. ApSION4 0.45 mg/Kg	**	*	**	**	**
ApTOLL vs. ApSION4 0.45 mg/Kg	#	##	##	##	###
Veh vs. ApSION4 0.91 mg/Kg	***	***	***	***	***
ApTOLL vs. ApSION4 0.91 mg/Kg	n.s	n.s	#	#	#
Veh vs. ApSION4 1.82 mg/Kg	**	**	***	***	**
ApTOLL vs. ApSION4 1.82 mg/Kg	#	#	#	#	##
Veh vs. ApTOLL 0.91 mg/Kg	***	***	***	***	***

FIG. 34

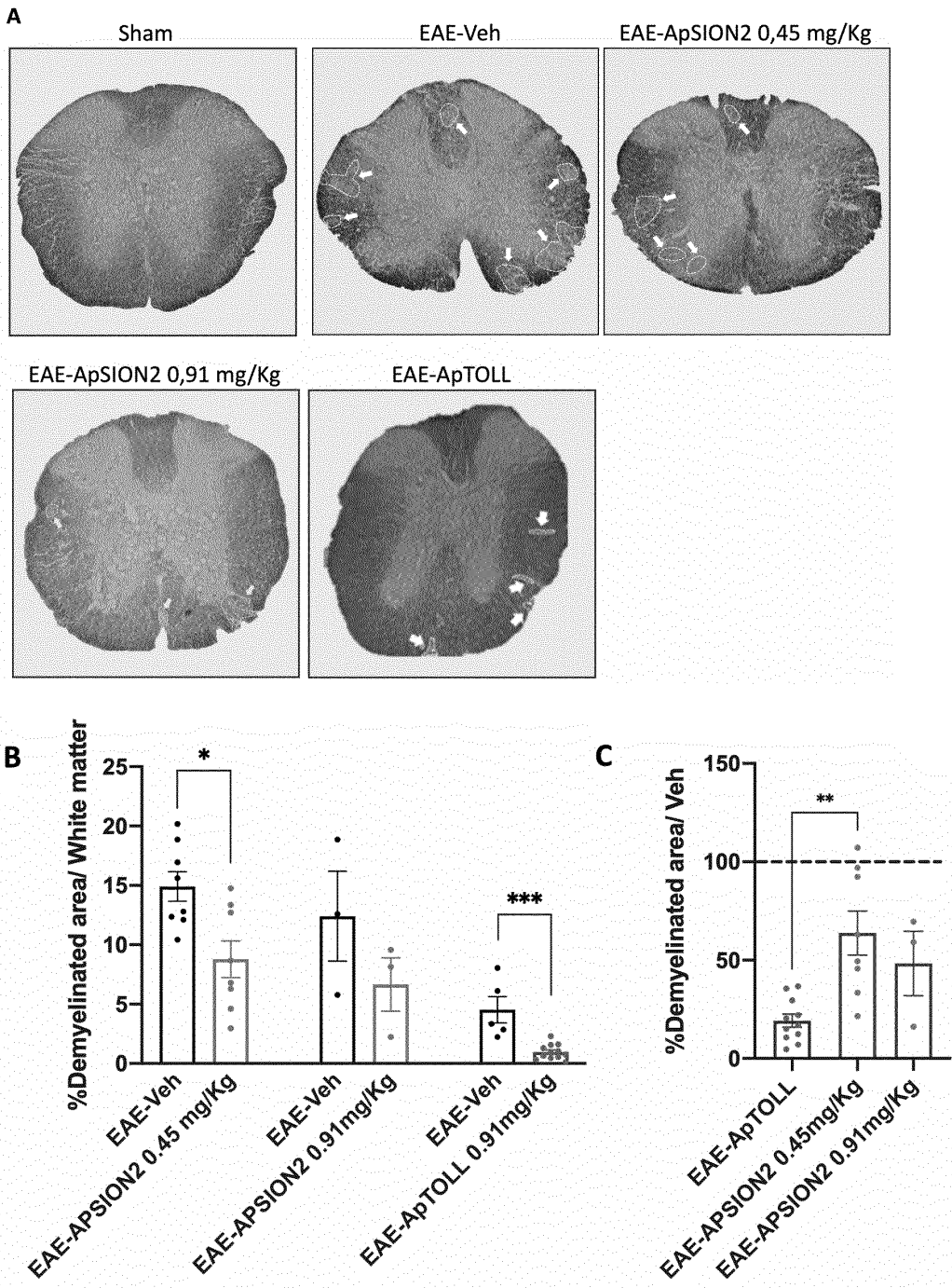


FIG. 35

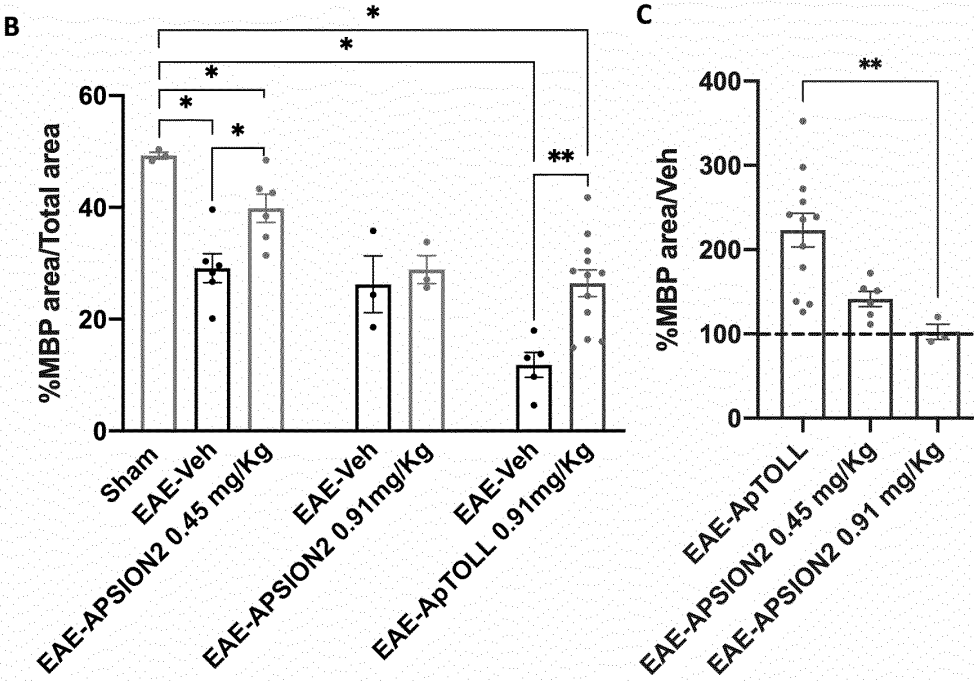
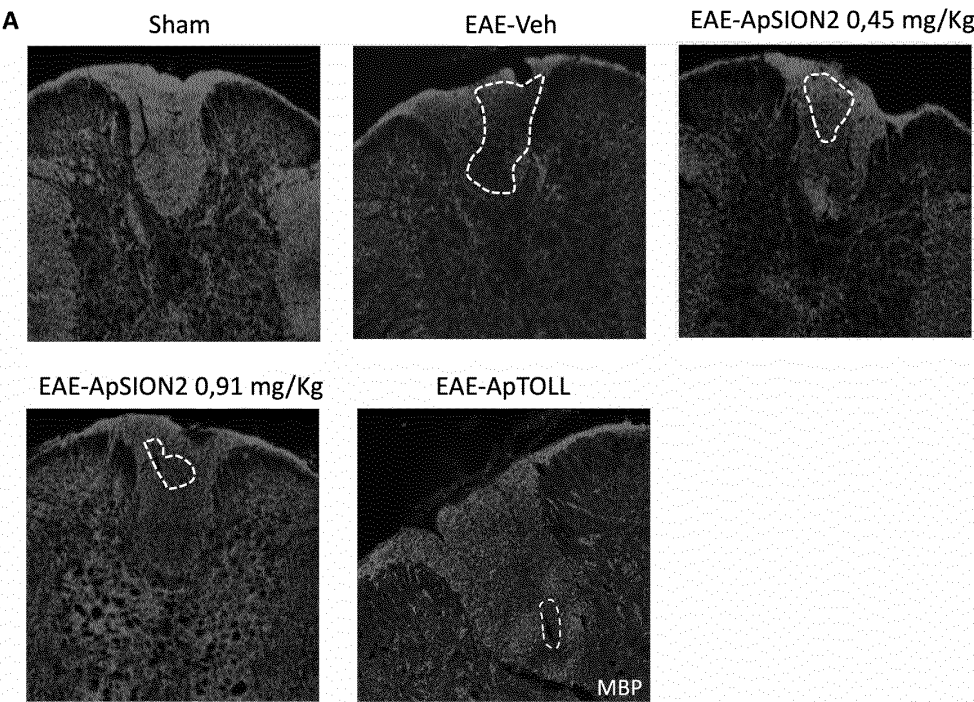


FIG. 36

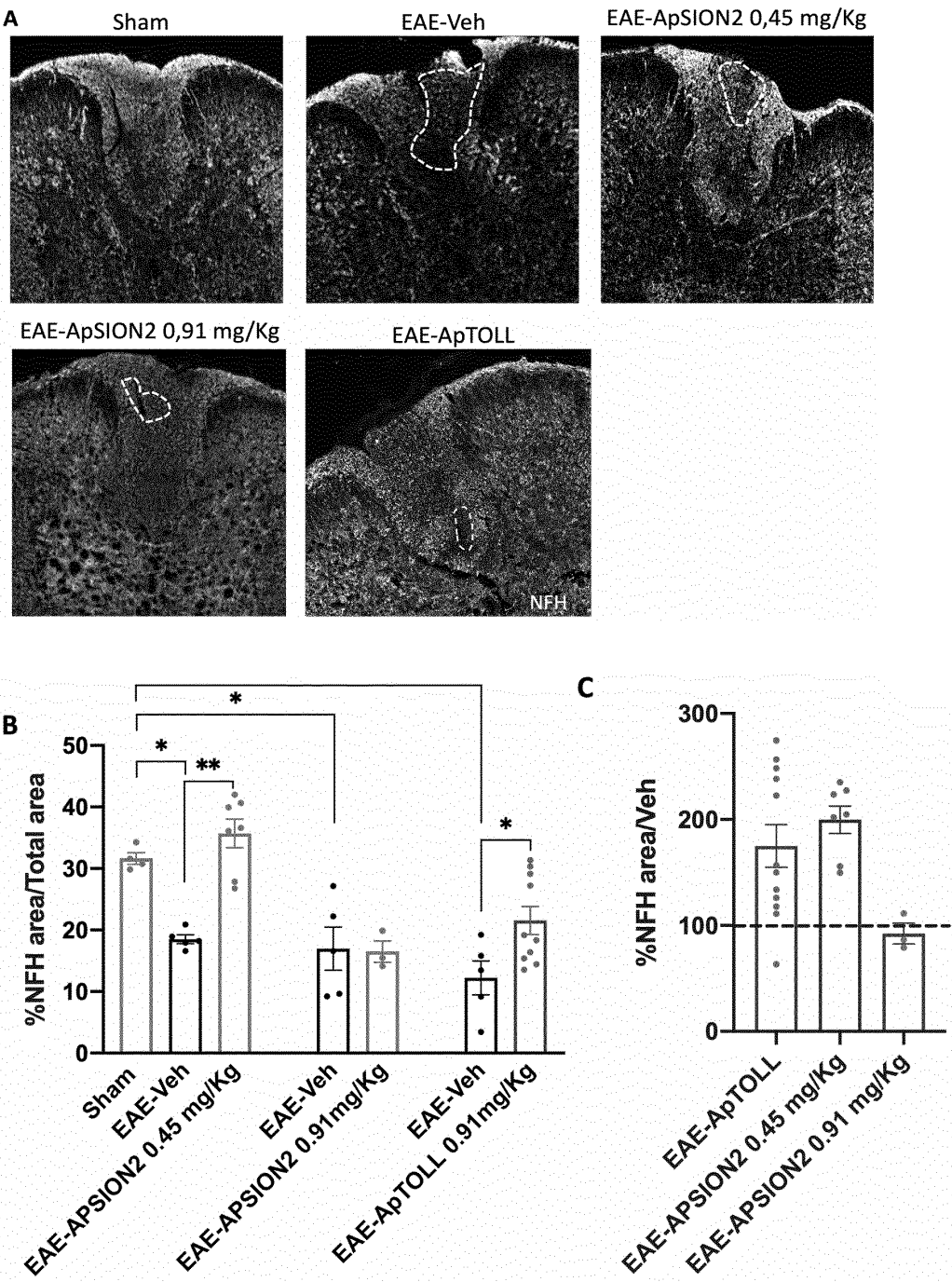


FIG. 37

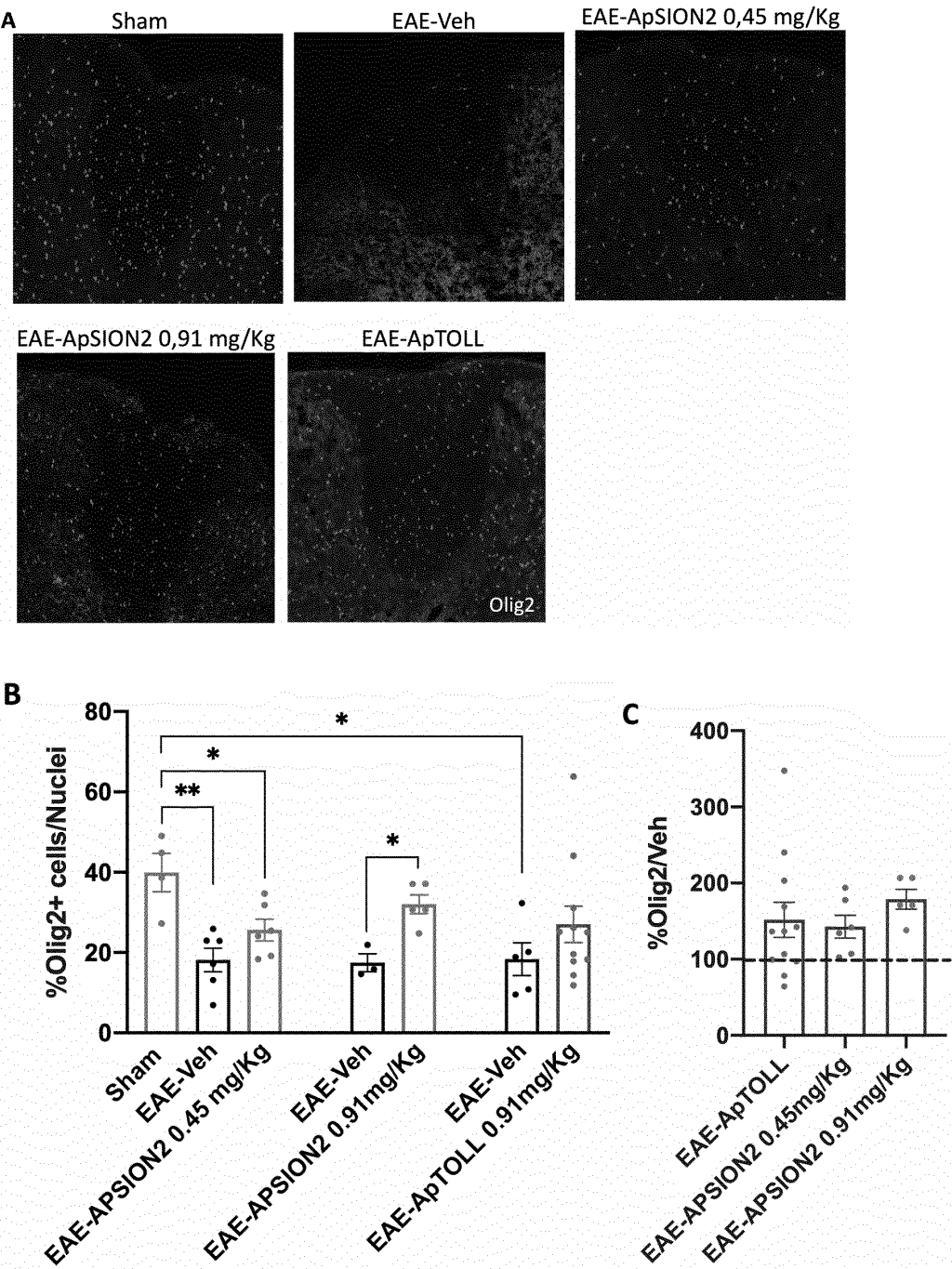


FIG. 38

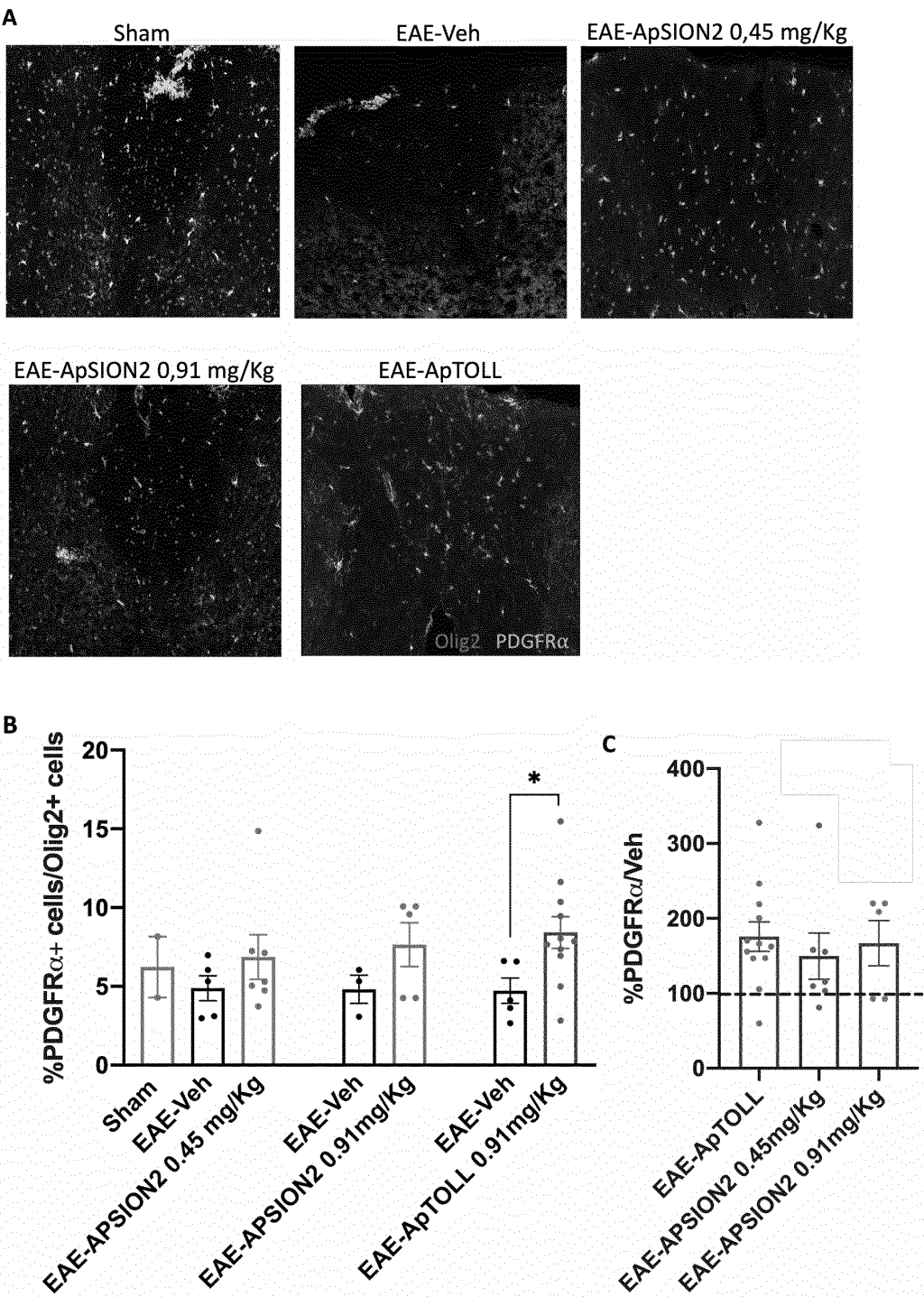


FIG. 39

A

Molecule	Sample		Molecule	Sample	
	Vehicle	ApTOLL		Vehicle	ApTOLL
BLC (CXCL13/BCA-1)	26,29 ± 3,31	27,77 ± 2,98	MIP-1β (CCL4)	3,38 ± 0,35	3,02 ± 0,25
C5/C5a	17,08 ± 2,93	17,89 ± 2,54	MIP-2 (CXCL2)	4,28 ± 0,23	4,25 ± 0,09
G-CSF	6,40 ± 0,57	7,29 ± 0,65	RANTES (CCL5)	6,25 ± 0,51	6,97 ± 0,45
GM-CSF	3,10 ± 0,49	2,70 ± 0,36	SDF-1 (CXCL12)	8,96 ± 1,61	9,68 ± 1,34
I-309 (CCL1/TCA-3)	4,20 ± 0,29	4,07 ± 0,11	IL-3	4,46 ± 0,48	4,04 ± 0,18
Eotaxin (CCL11)	3,32 ± 0,36	3,08 ± 0,24	IL-4	4,76 ± 0,49	4,46 ± 0,12
ICAM-1 (CD54)	54,43 ± 6,67	64,33 ± 4,56	IL-5	2,97 ± 0,52	2,58 ± 0,39
IFN-γ	6,77 ± 0,87	7,41 ± 0,81	IL-6	3,06 ± 0,51	2,91 ± 0,32
IL-1α (IL-1F1)	6,06 ± 0,37	6,01 ± 0,27	IL-7	4,93 ± 0,46	4,57 ± 0,18
IL-1β (IL-1F2)	4,52 ± 0,32	4,39 ± 0,10	IL-10	3,19 ± 0,39	2,88 ± 0,31
IL-1ra (IL-1F3)	6,46 ± 0,46	7,48 ± 0,64	IL-13	4,67 ± 0,26	4,48 ± 0,17
IL-2	3,65 ± 0,25	3,25 ± 0,20	IL-12 p70	3,01 ± 0,43	2,75 ± 0,35
IP-10 (CXCL10/CRG-2)	6,17 ± 0,50	5,97 ± 0,15	IL-16	12,02 ± 1,59	14,2 ± 1,30
I-TAC (CXCL11)	4,40 ± 0,43	4,09 ± 0,07	IL-17	5,37 ± 0,56	5,46 ± 0,30
KC (CXCL1)	5,37 ± 1,11	6,44 ± 0,88	IL-23	4,13 ± 0,25	3,69 ± 0,12
M-CSF	12,05 ± 1,70	13,57 ± 2,15	IL-27	5,32 ± 0,66	4,73 ± 0,31
JE (CCL2/MCP-1)	13,47 ± 2,06	16,49 ± 1,71	TARC (CCL17)	3,49 ± 0,64	2,92 ± 0,44
MCP-5 (CCL12)	4,02 ± 0,34	4,17 ± 0,13	TIMP-1	22,29 ± 3,49	31,65 ± 3,57
MIG (CXCL9)	6,95 ± 0,59	8,36 ± 0,80	TNF-α	6,04 ± 0,55	6,20 ± 0,28
MIP-1α (CCL3)	4,16 ± 0,23	4,05 ± 0,12	TREM-1	7,25 ± 0,64	8,93 ± 0,66

B

Molecule	Sample		Molecule	Sample	
	Vehicle	ApS10N2		Vehicle	ApS10N2
BLC (CXCL13/BCA-1)	24,46 ± 3,05	15,13 ± 0,98	MIP-1β (CCL4)	3,41 ± 0,14	3,47 ± 0,15
C5/C5a	13,05 ± 0,71	11,81 ± 0,66	MIP-2 (CXCL2)	3,68 ± 0,24	3,85 ± 0,12
G-CSF	6,26 ± 0,61	4,95 ± 0,08	RANTES (CCL5)	6,02 ± 0,31	4,94 ± 0,19
GM-CSF	3,43 ± 0,02	3,49 ± 0,15	SDF-1 (CXCL12)	6,13 ± 1,02	4,93 ± 0,16
I-309 (CCL1/TCA-3)	3,66 ± 0,20	3,56 ± 0,13	IL-3	4,10 ± 0,07	4,23 ± 0,19
Eotaxin (CCL11)	3,32 ± 0,06	3,47 ± 0,14	IL-4	4,17 ± 0,03	4,31 ± 0,17
ICAM-1 (CD54)	69,02 ± 2,19	60,13 ± 2,48	IL-5	3,24 ± 0,05	3,5 ± 0,15
IFN-γ	4,81 ± 0,41	4,18 ± 0,01	IL-6	3,4 ± 0,09	3,48 ± 0,15
IL-1α (IL-1F1)	5,10 ± 0,41	4,64 ± 0,07	IL-7	4,16 ± 0,24	3,88 ± 0,14
IL-1β (IL-1F2)	3,89 ± 0,20	3,80 ± 0,08	IL-10	3,42 ± 0,1	3,5 ± 0,16
IL-1ra (IL-1F3)	5,14 ± 0,51	6,65 ± 0,36	IL-13	4,07 ± 0,24	3,92 ± 0,09
IL-2	3,27 ± 0,15	3,43 ± 0,12	IL-12 p70	3,34 ± 0,08	3,47 ± 0,14
IP-10 (CXCL10/CRG-2)	5,81 ± 0,38	5,16 ± 0,11	IL-16	12,6 ± 2,67	7,98 ± 0,17
I-TAC (CXCL11)	4,06 ± 0,16	4,06 ± 0,13	IL-17	4,44 ± 0,33	4,01 ± 0,13
KC (CXCL1)	7,10 ± 0,34	7,38 ± 0,51	IL-23	3,65 ± 0,08	3,6 ± 0,09
M-CSF	11,38 ± 0,75	8,95 ± 0,07	IL-27	3,73 ± 0,23	3,7 ± 0,07
JE (CCL2/MCP-1)	13,39 ± 0,78	16,45 ± 1,05	TARC (CCL17)	3,82 ± 0,06	3,73 ± 0,03
MCP-5 (CCL12)	3,76 ± 0,11	3,75 ± 0,10	TIMP-1	25,02 ± 5,07	16,64 ± 0,23
MIG (CXCL9)	5,75 ± 0,74	5,14 ± 0,09	TNF-α	5,71 ± 0,33	5,31 ± 0,13
MIP-1α (CCL3)	3,67 ± 0,26	3,72 ± 0,05	TREM-1	7,12 ± 0,69	6,58 ± 0,10

FIG. 39 (cont.)

