

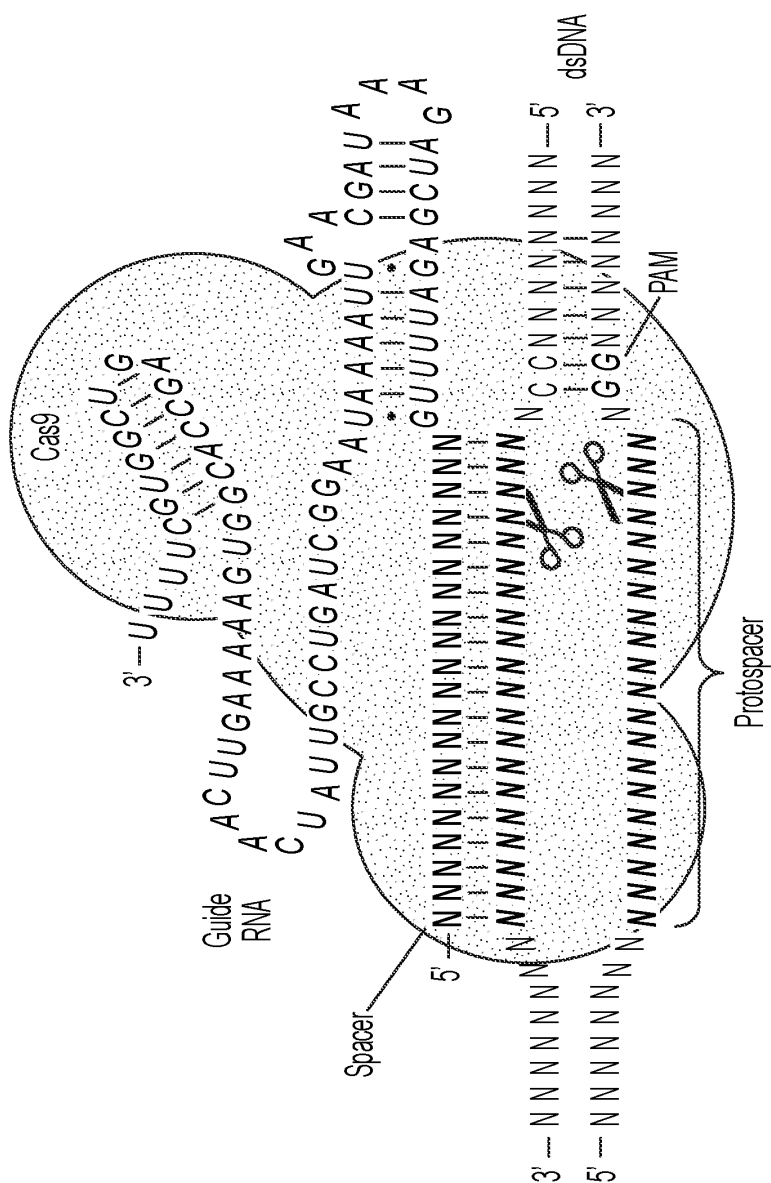


FIG. 1A

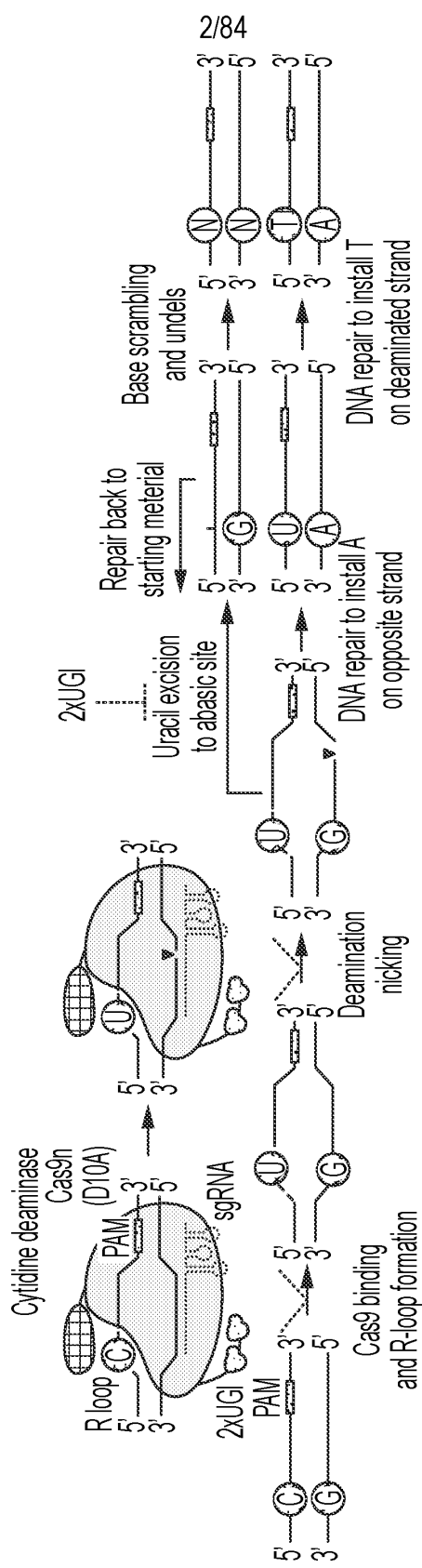


FIG. 1B

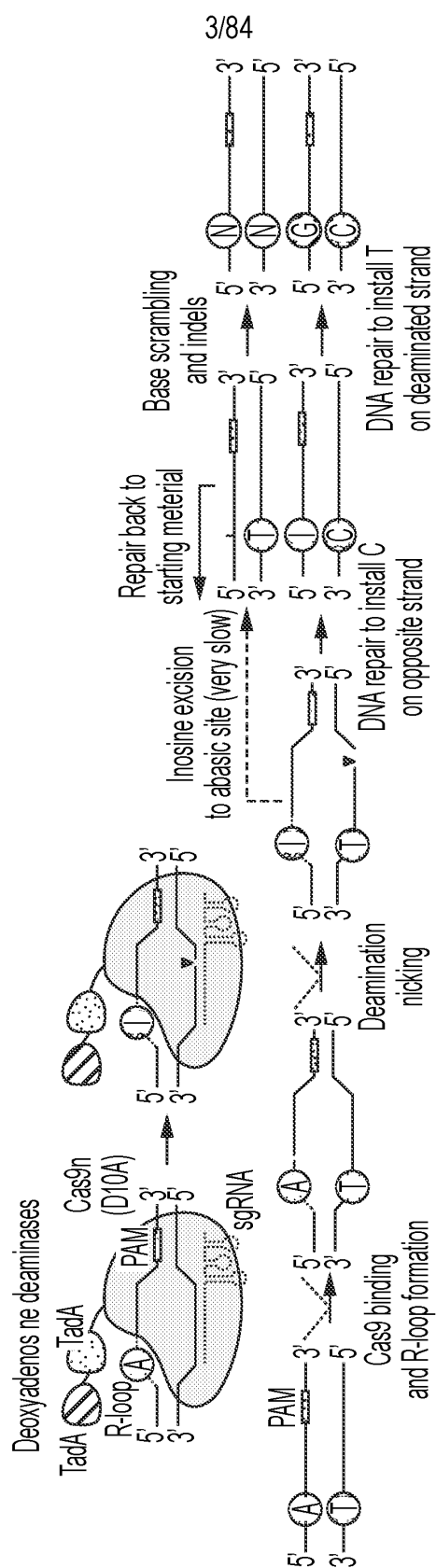


FIG. 1C

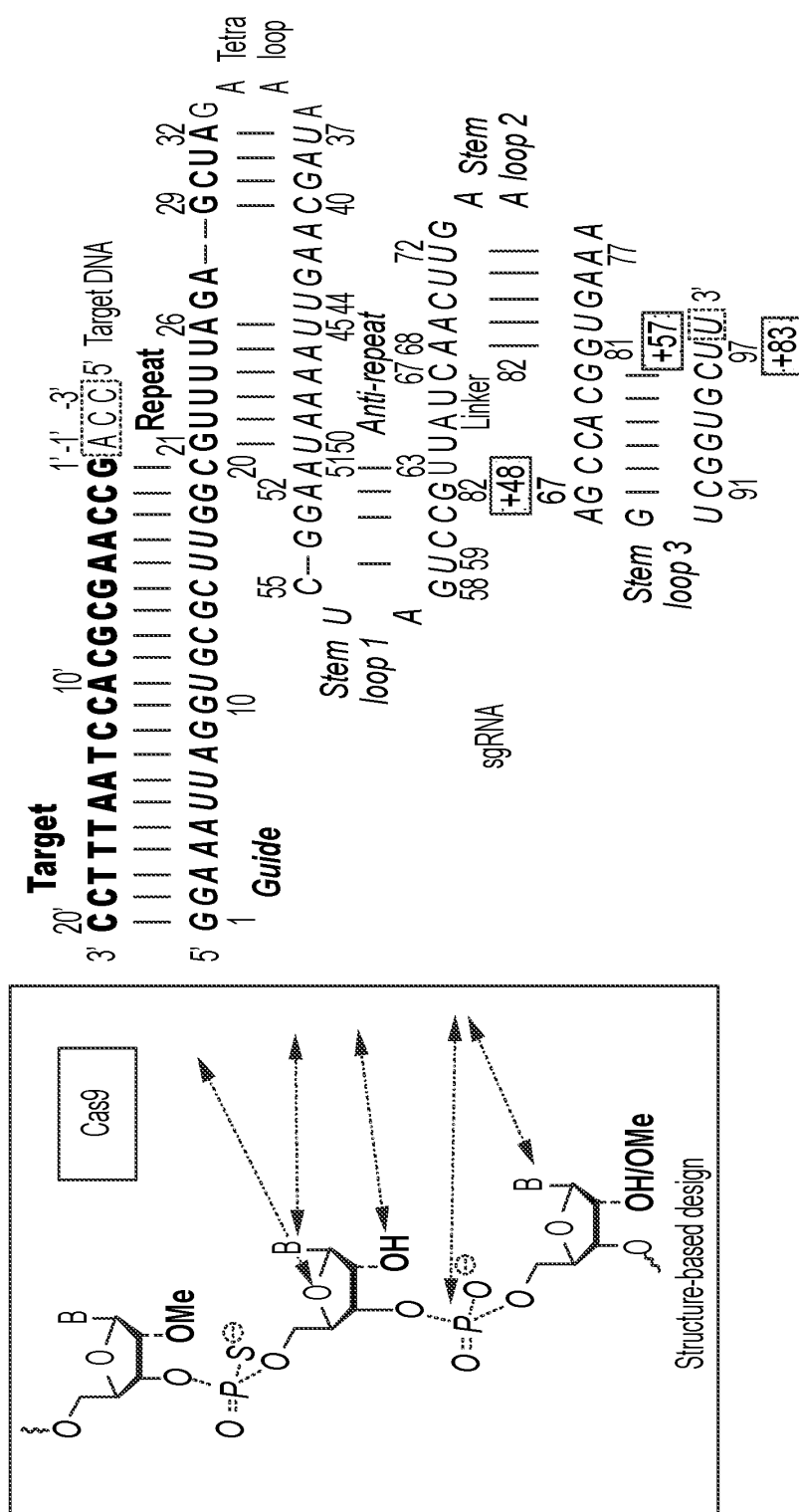


FIG. 1D

PDB ID	Components	State
4CMP	SpCas9 protein	Apo (pre-RNP formation)
4ZT0	SpCas9 protein + gRNA	RNP (forms in cytosol)
5F9R	SpCas9 protein + gRNA + target/non-target DNA	Pre-catalytic ternary complex
4UN3	SpCas9 protein + gRNA + target/non-target DNA	Post-catalytic ternary complex

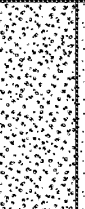
	4CMP	4ZT0	5F9R	4UN3
4CMP		15	20	20
4ZT0	15		4	3
5F9R	20	4		2
4UN3	20	3	2	

FIG. 2

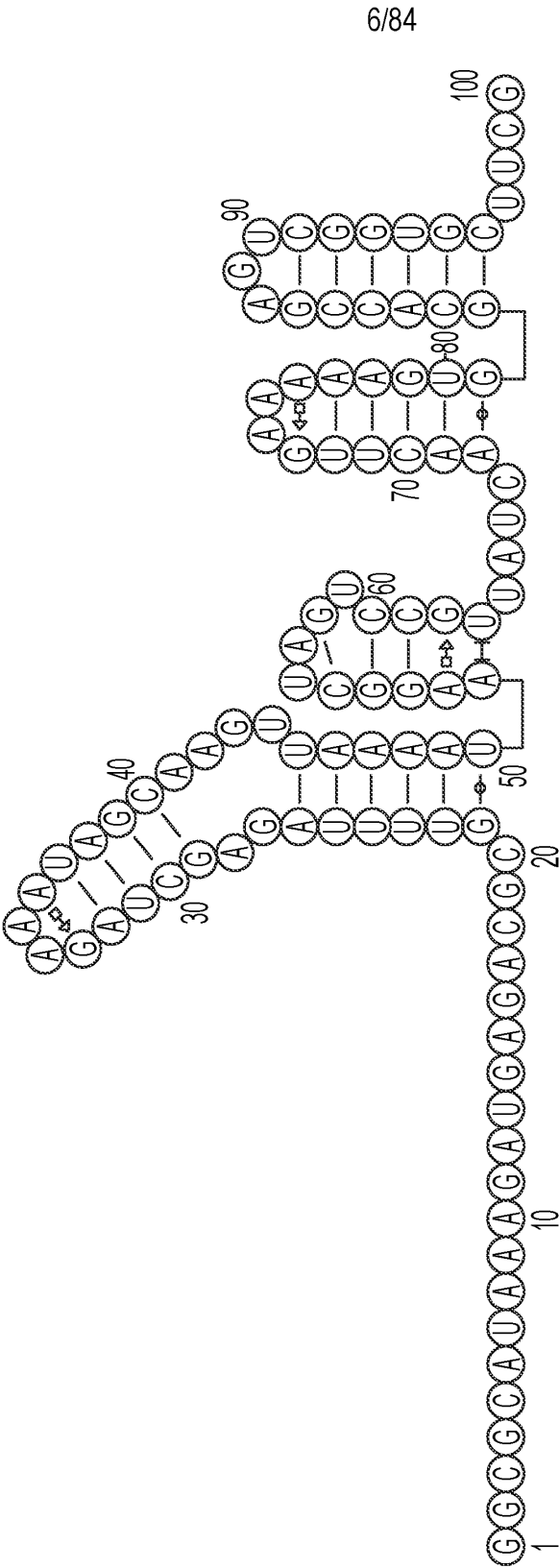


FIG. 3

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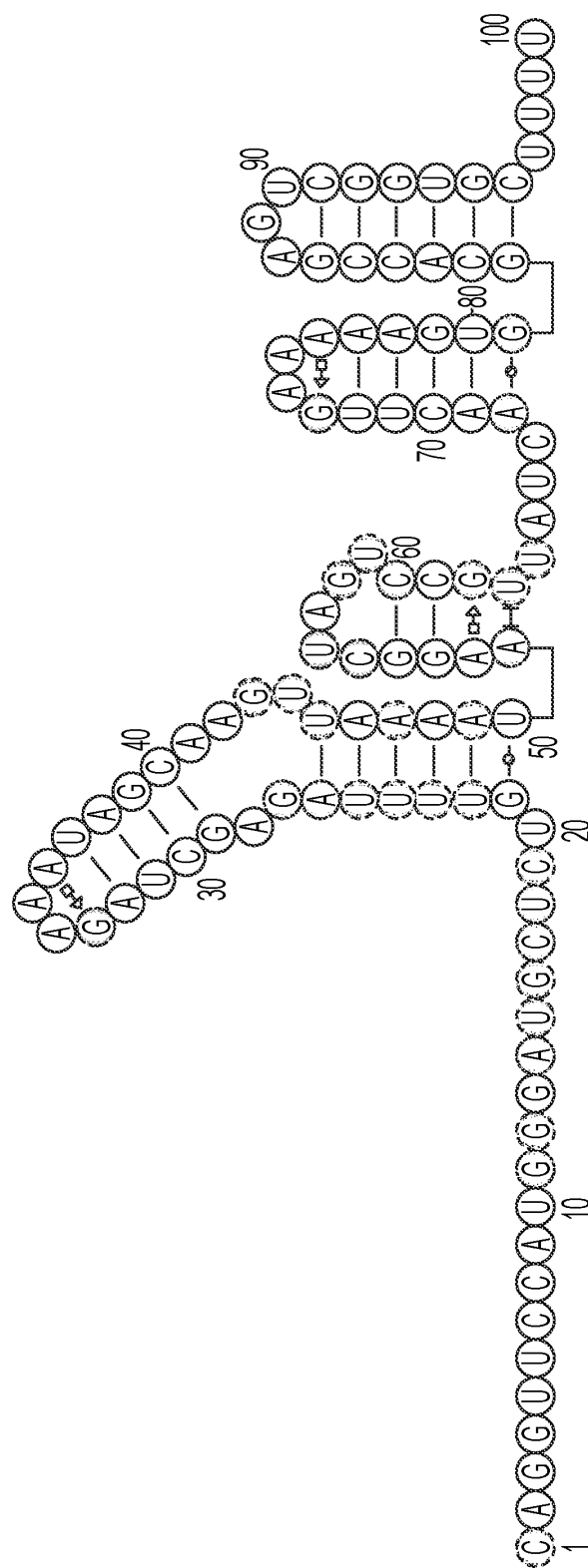


FIG. 4

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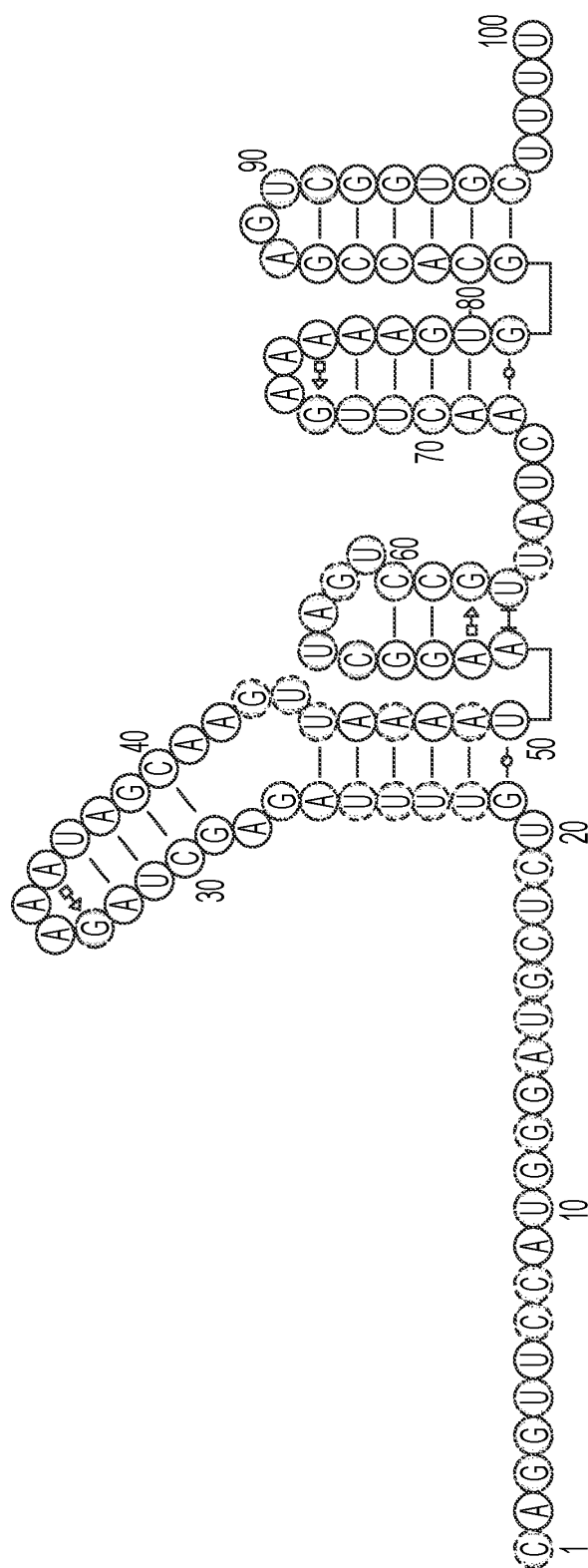


FIG. 5

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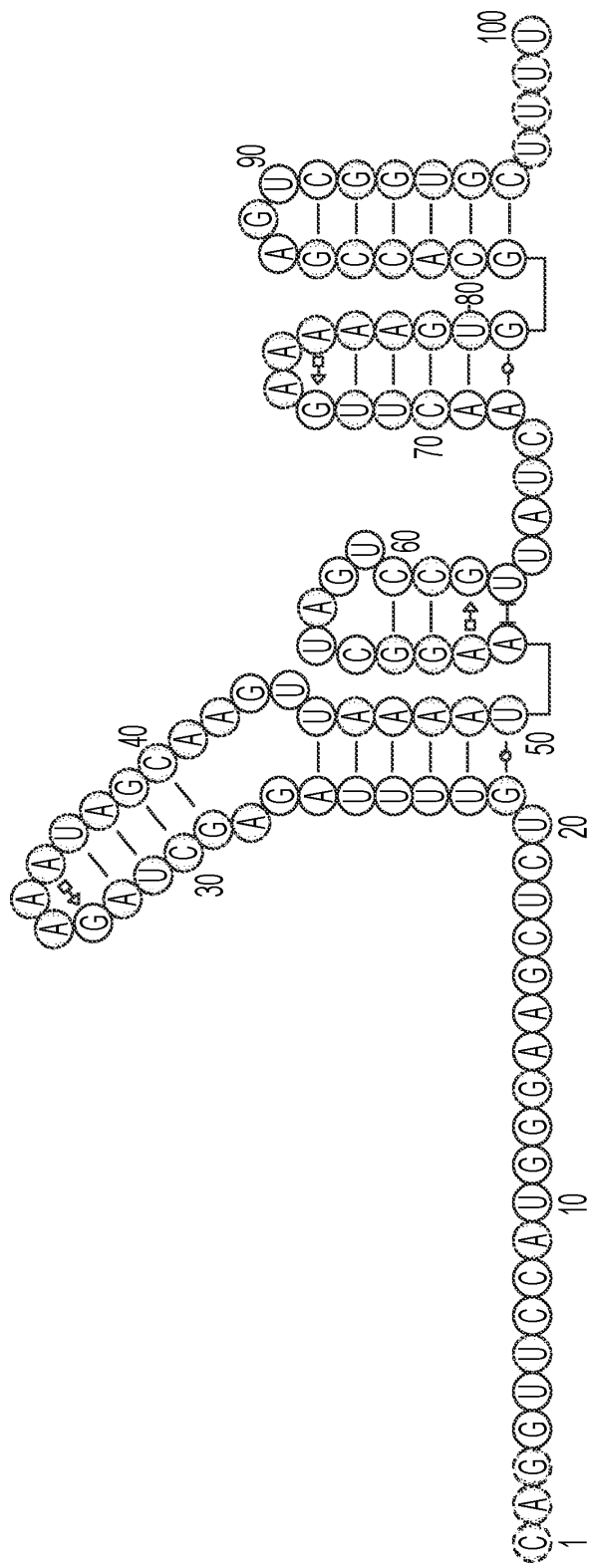


FIG. 6

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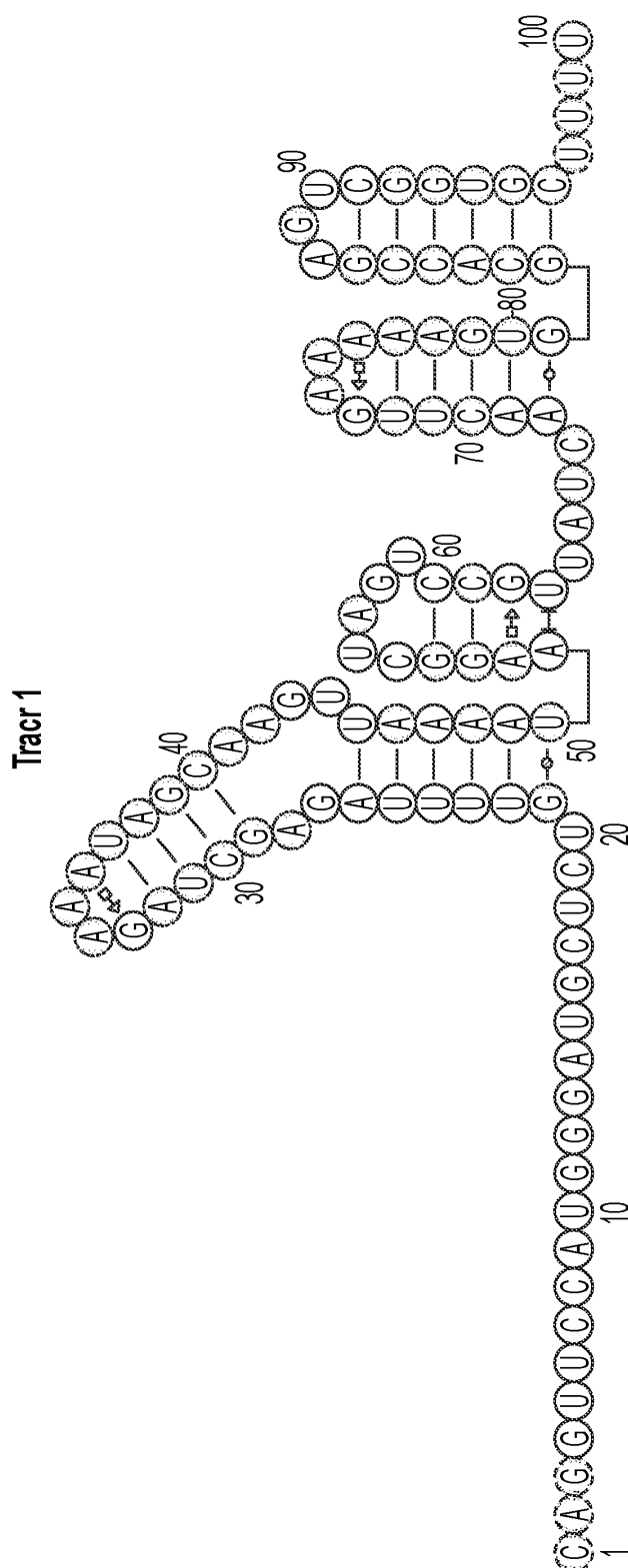


FIG. 7A

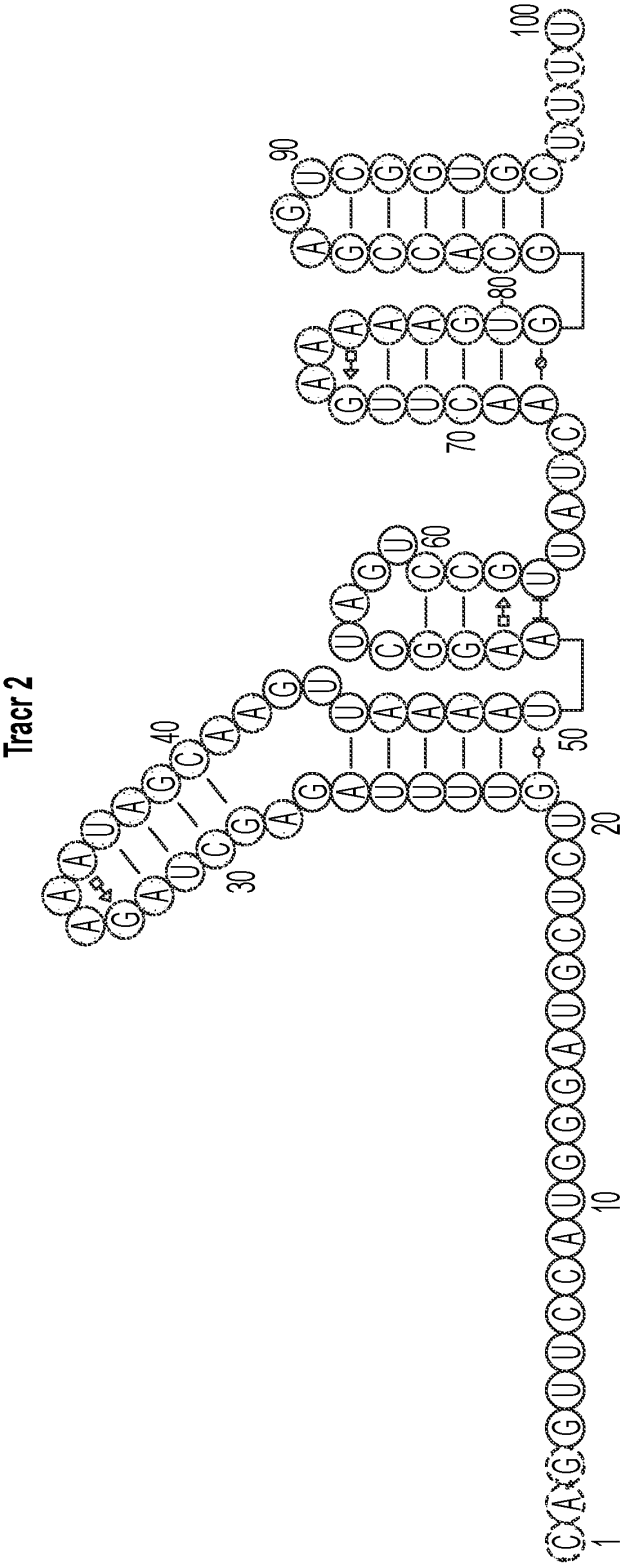


FIG. 7A
(Continued)

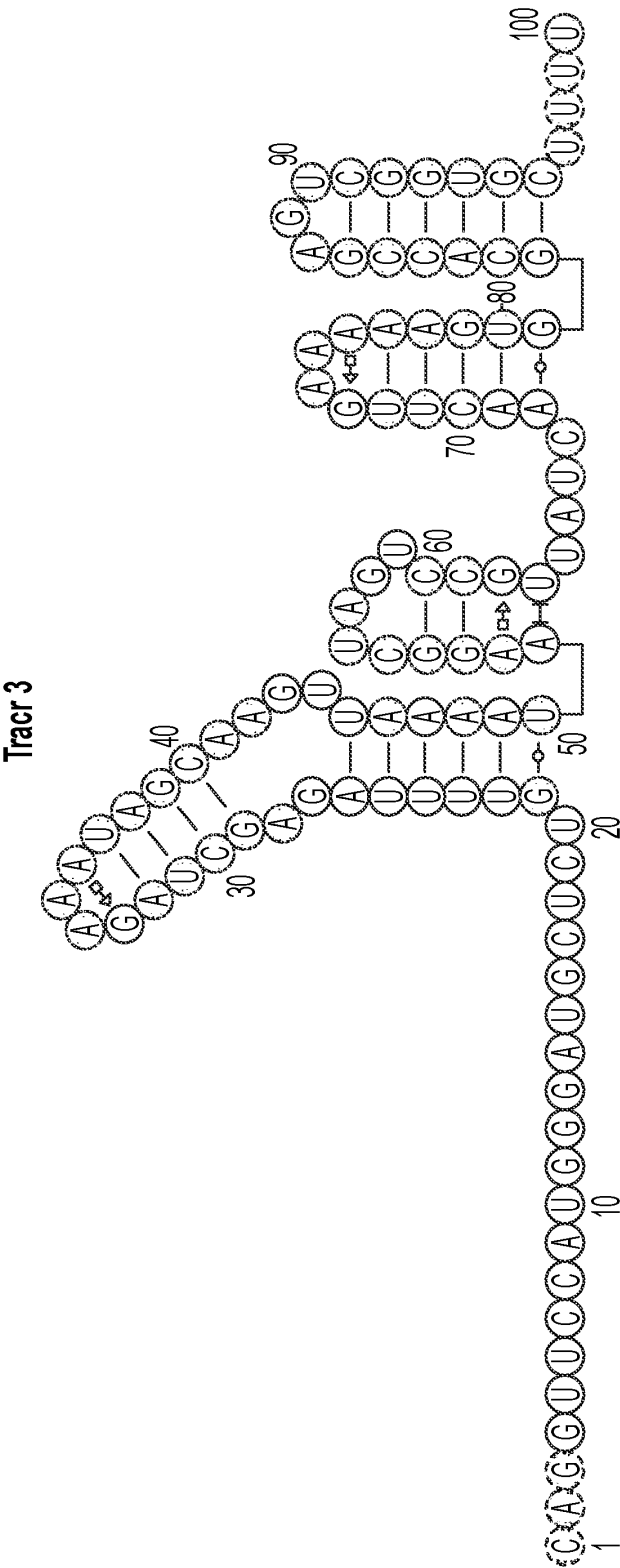


FIG. 7A
(Continued)

	10	20	30	40	50	60	70	80
SEQ ID NO: 61	123456789X	123456789X	123456789X	123456789X	123456789X	123456789X	123456789X	123456789X
Lit Tracr	GUUUUAGAGC	UAGAAUAGC	AGUUAAAAU	AAGGUAGUC	CGUUAUCAAC	UUGAAAAAGU	GGCACCAGU	CGGUGCUUUU
Tracr1	GUUUUAGAgc	uagaaauagc	AGUUAAAAU	AAGGUAGUC	CGUUAUCAAc	uugaaaaaagu	ggcaccgagu	cggugcucususu
Tracr2	gUUUUAGAgc	uaGaaauagc	aaGUUaAaAu	AaggCUaGUC	cGUUAucAAc	uuGaaaaaagu	GgcaccgAgU	Cggugcucususu
Tracr3	gUUUUAGAgc	uagaaaauagc	aaGUUaAaAu	AaggcuagUc	cGUUAucAAc	uugaaaaaagu	gGcaccgagu	cggugcucususu
	GUUUUAGAgc	uaGaaauagc	aaGUUaAaAu	AaggcuagUc	cGUUAucAAc	uuGaaaaaagu	gGcaccgagu	cggugcucususu

FIG. 7B

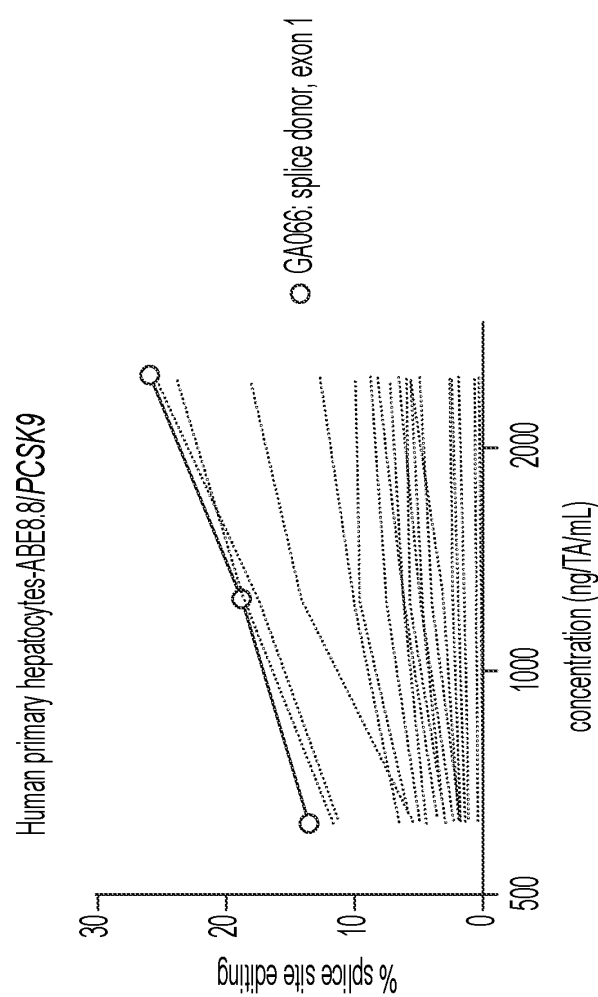


FIG. 8

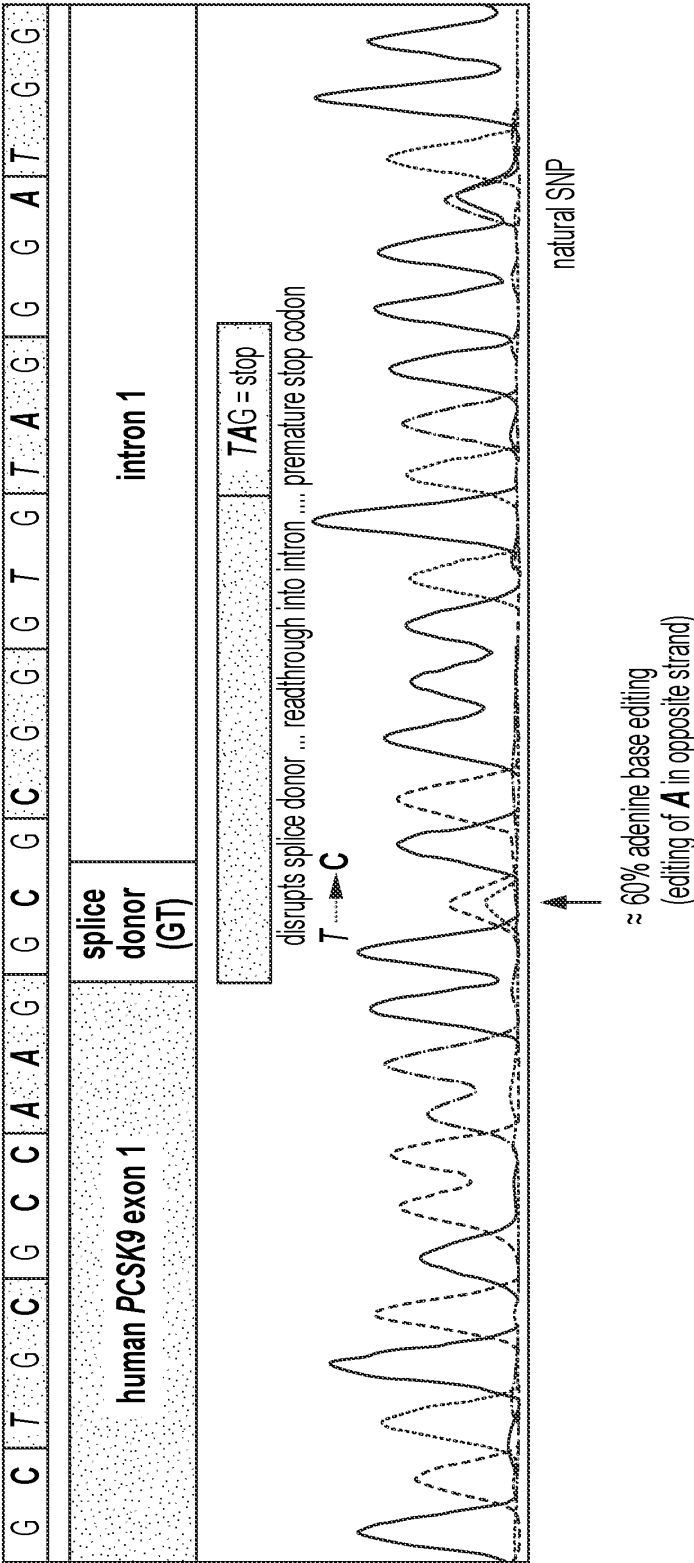


FIG. 9

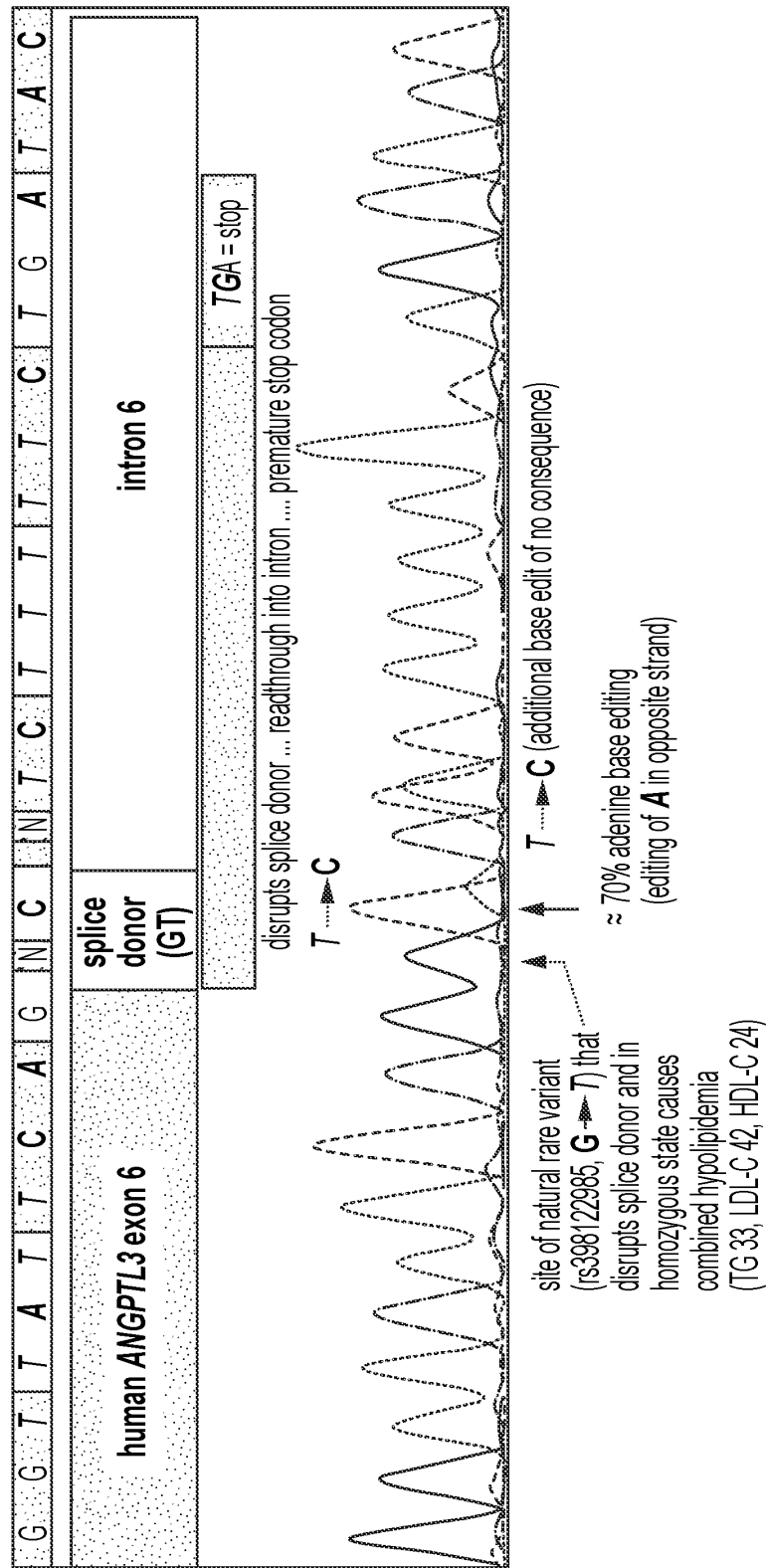
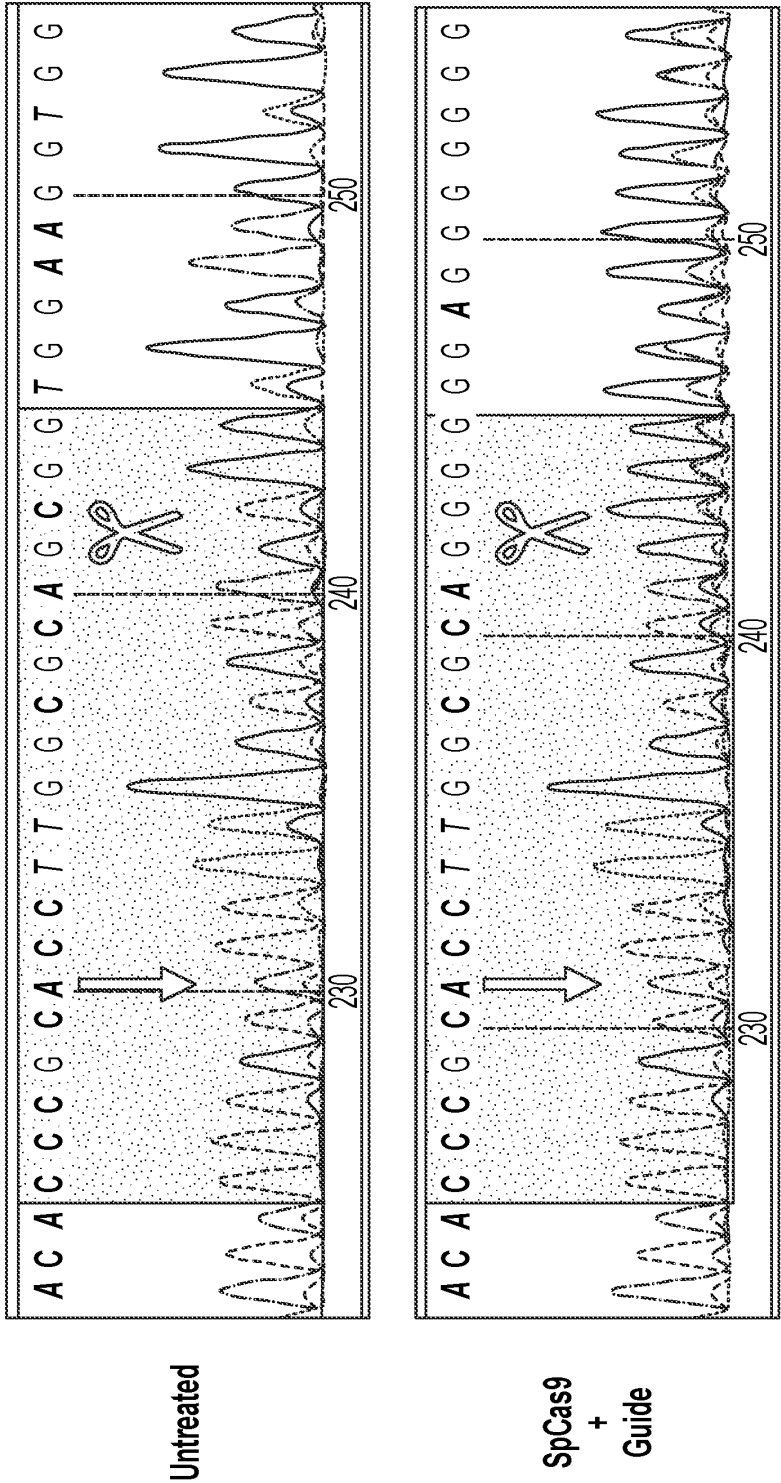
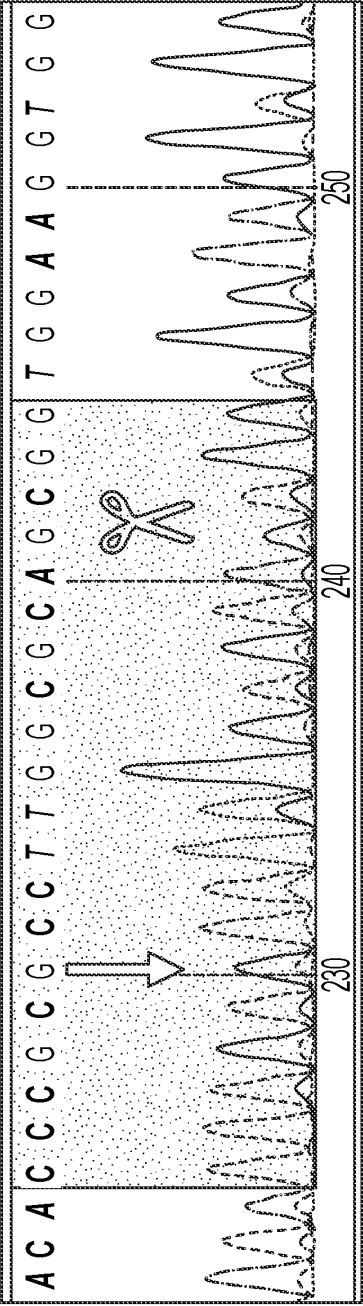


FIG. 10



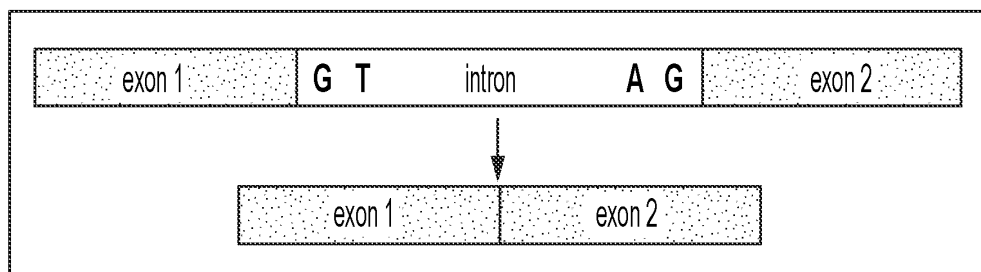


ABE
+
Guide

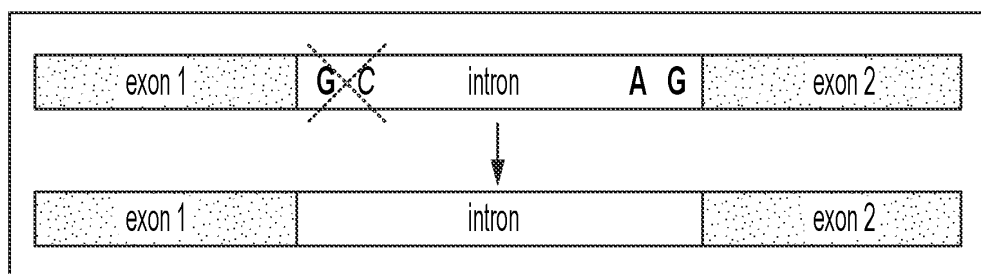
FIG. 11 CONT.

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Normal splice sites



Disrupted splice donor



Disrupted splice acceptor

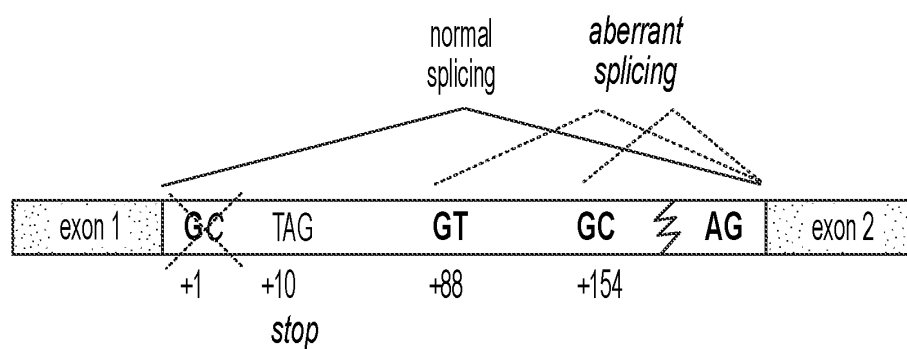
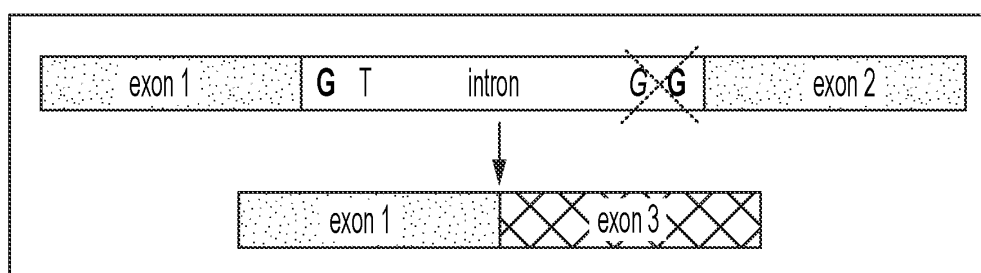


FIG. 12

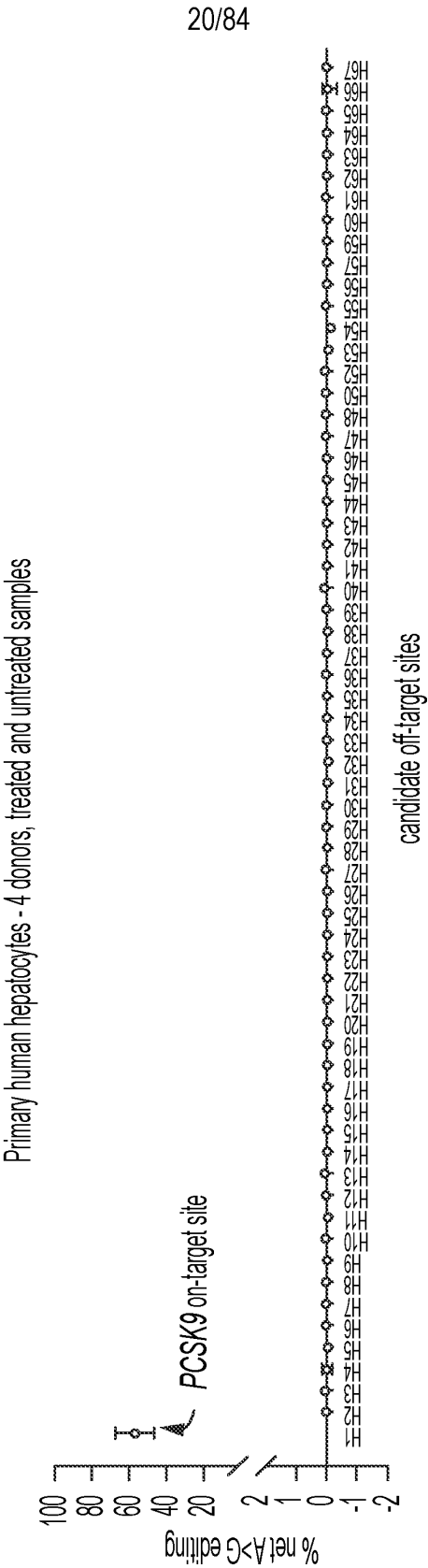


FIG. 13

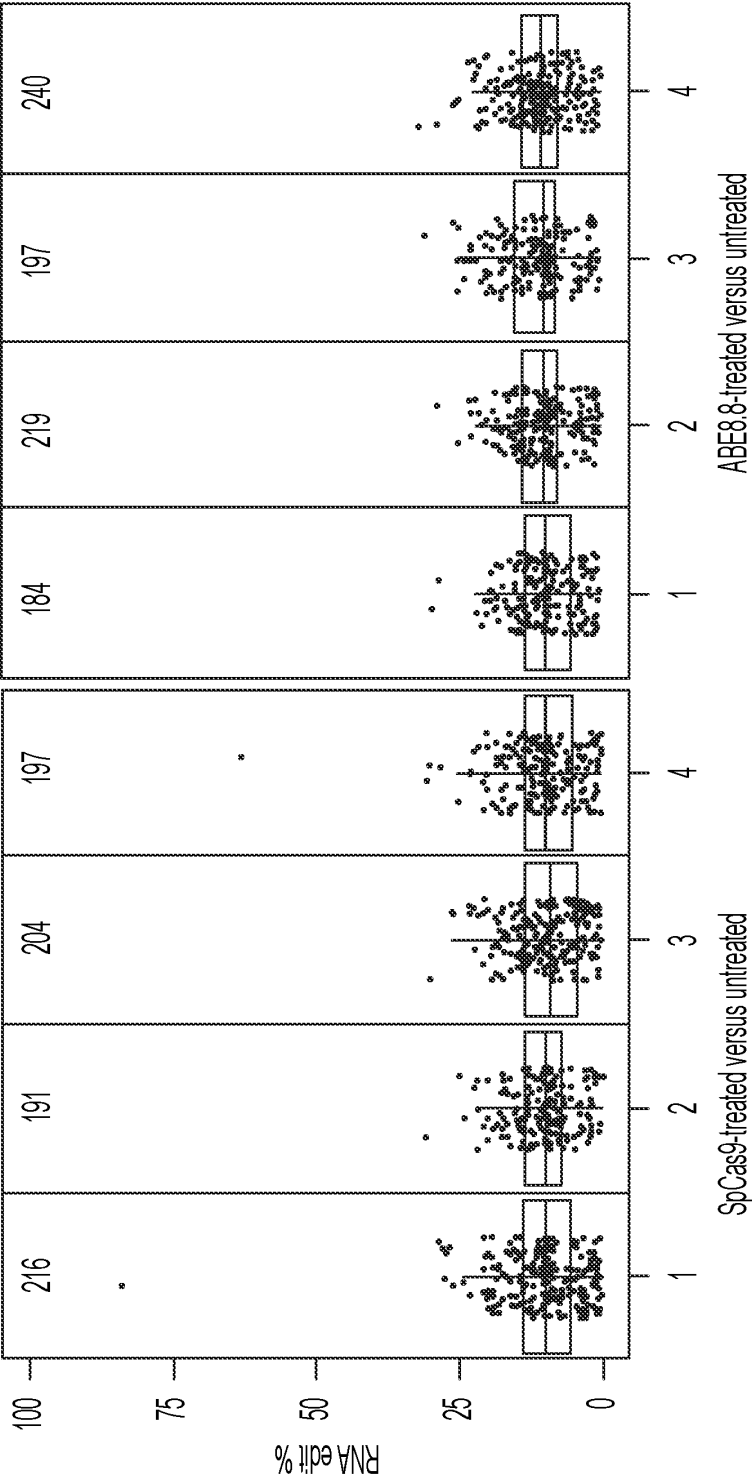


FIG. 14

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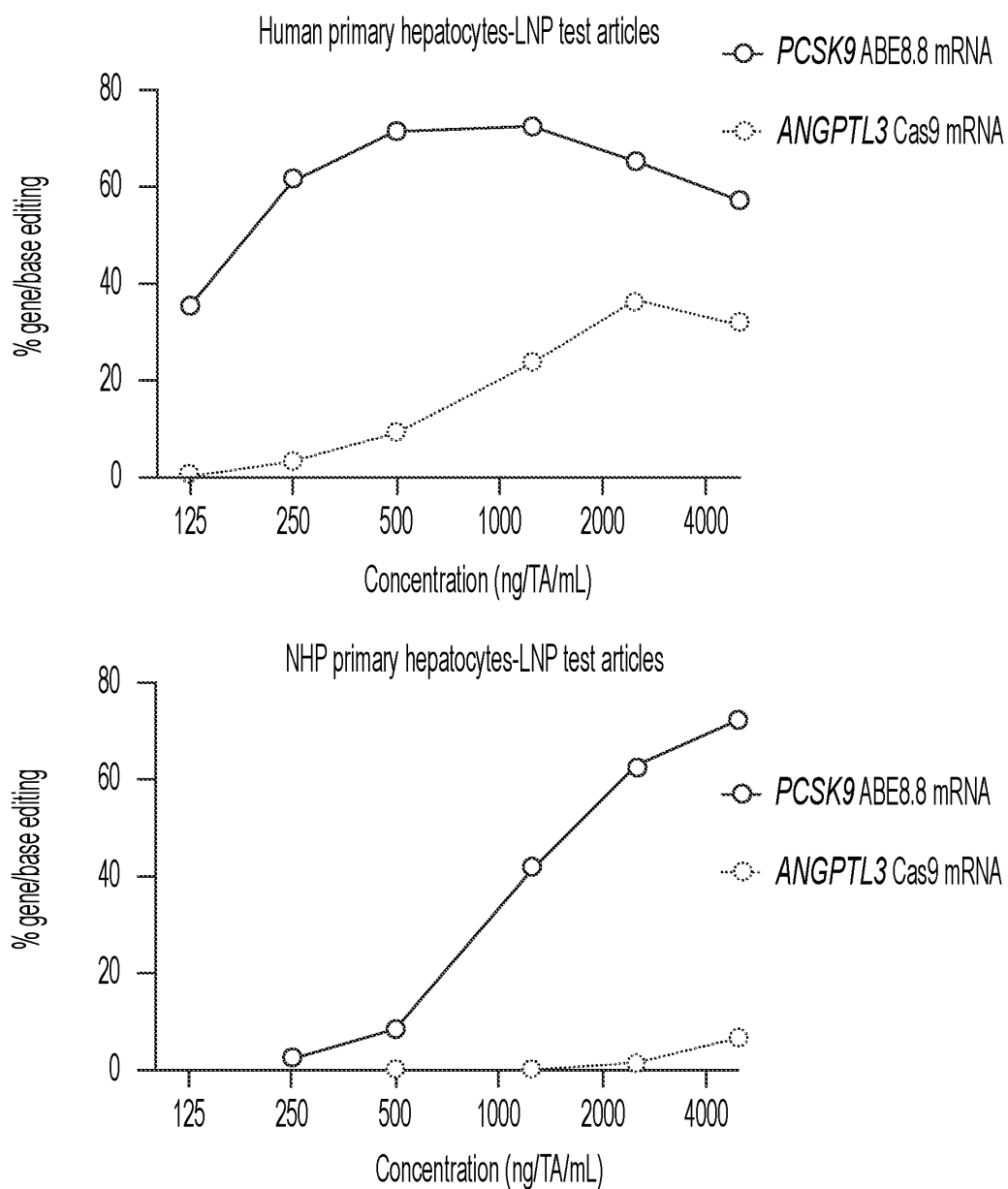


FIG. 15

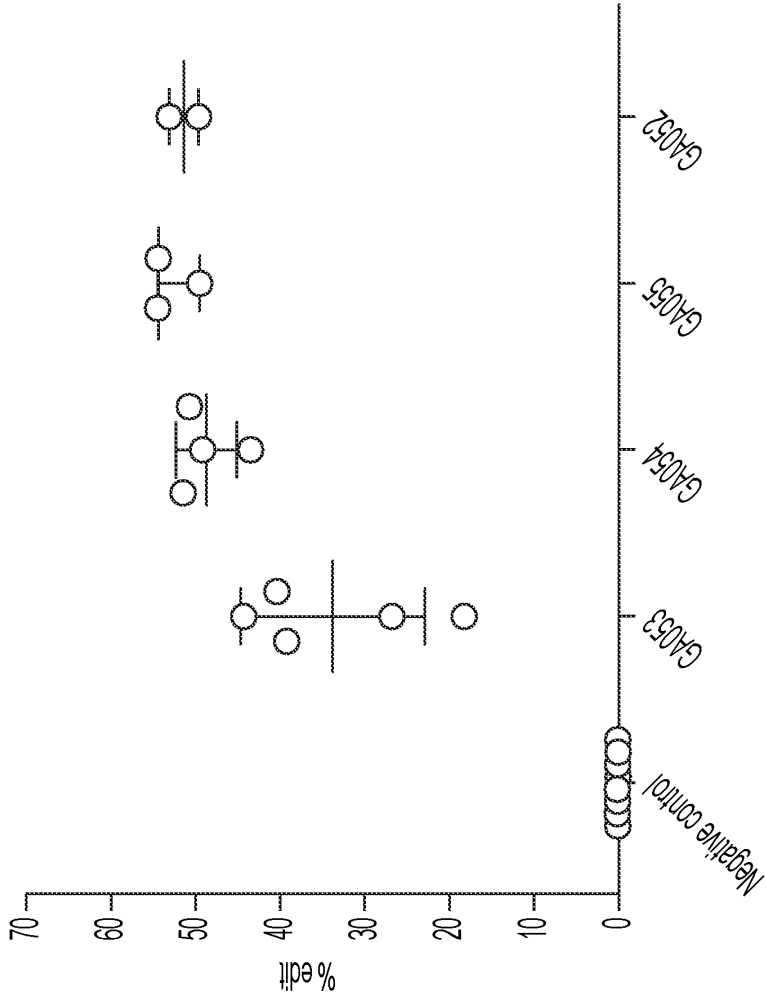


FIG. 16

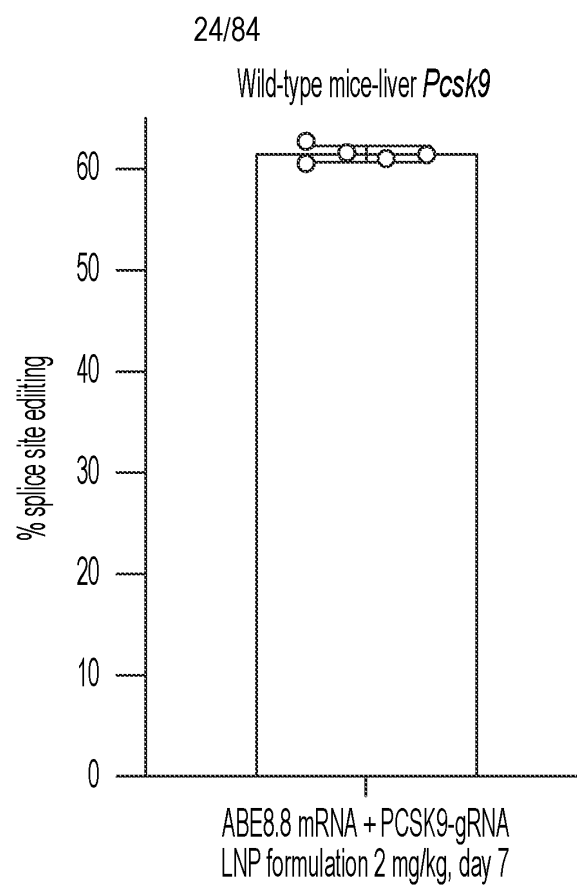


FIG. 17

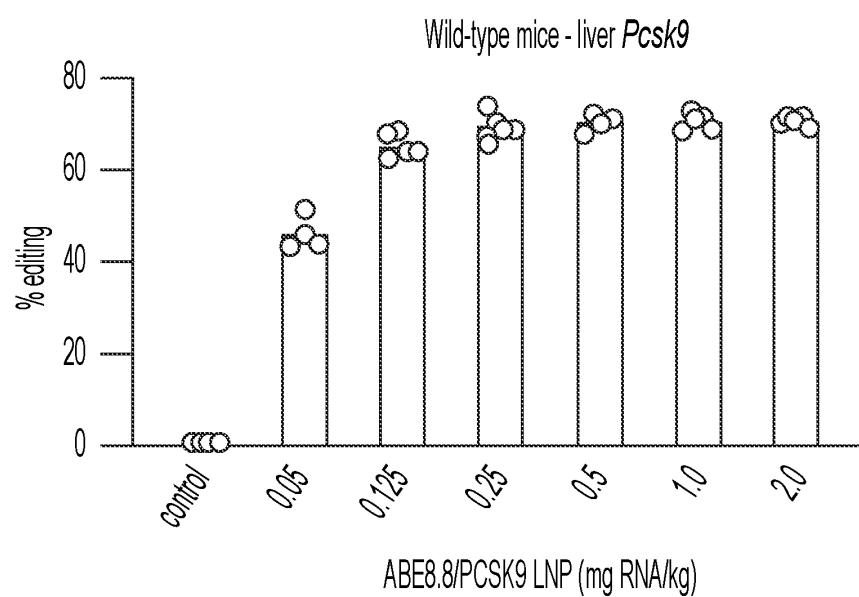
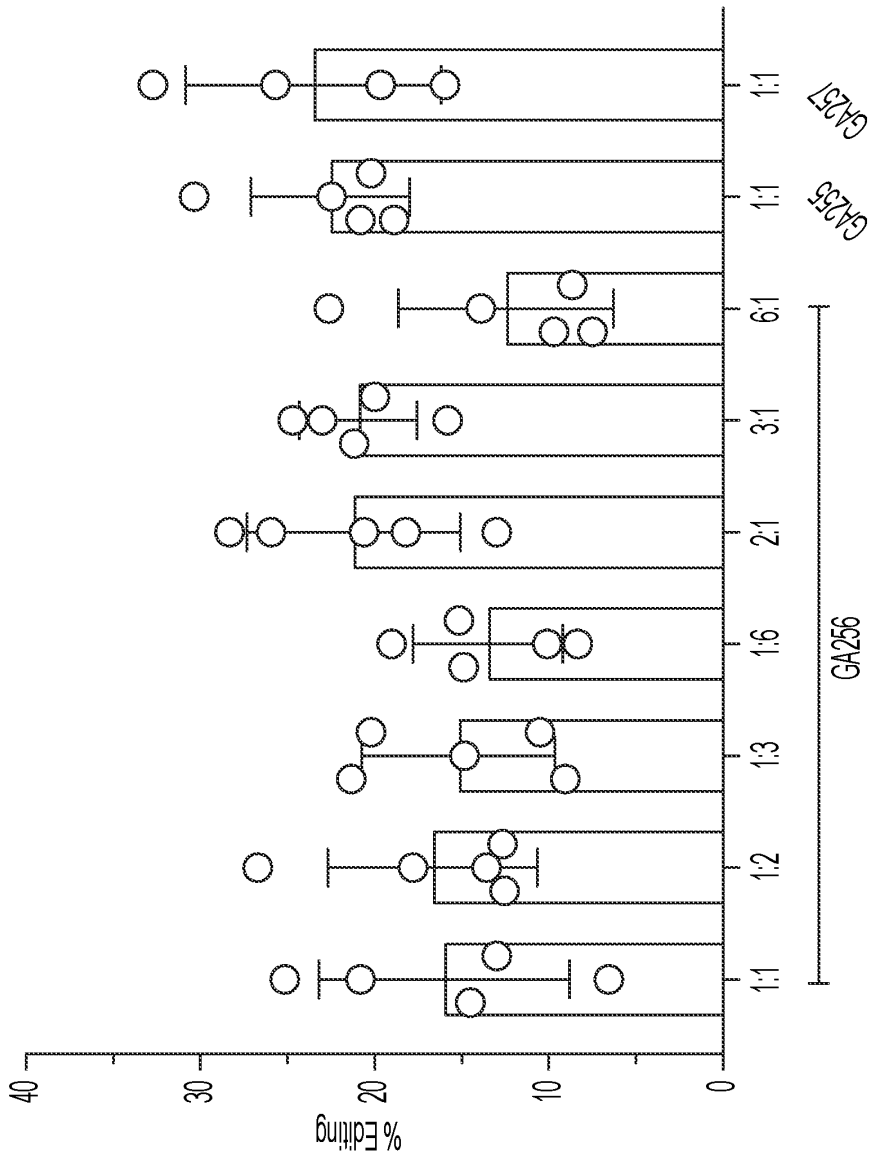


FIG. 18



Ratio of gRNA:mRNA
FIG. 19

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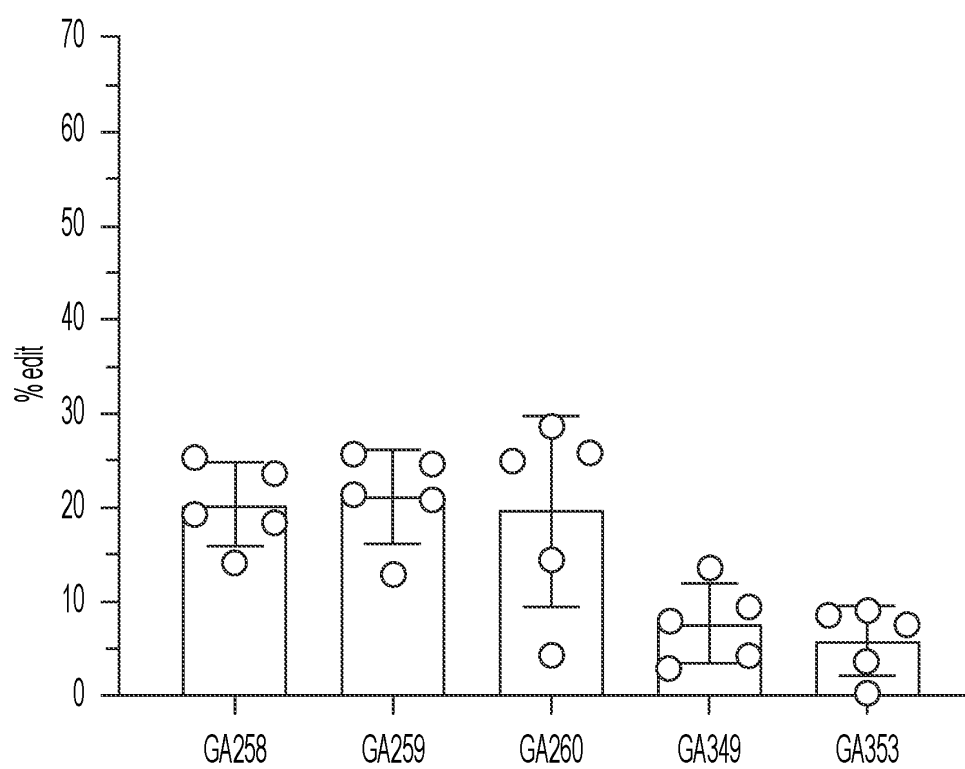


FIG. 20

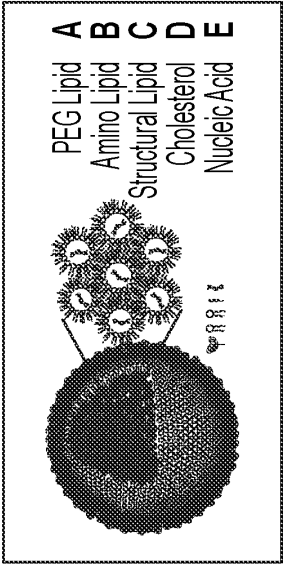
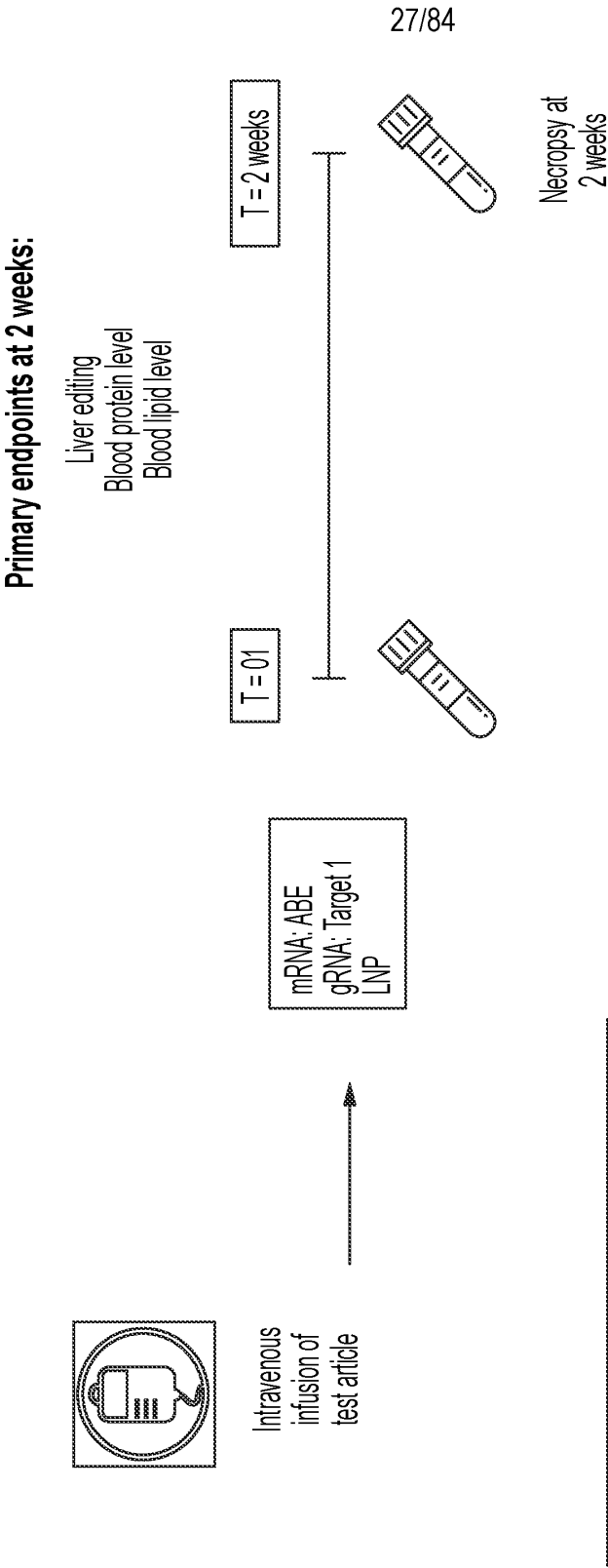


FIG. 21

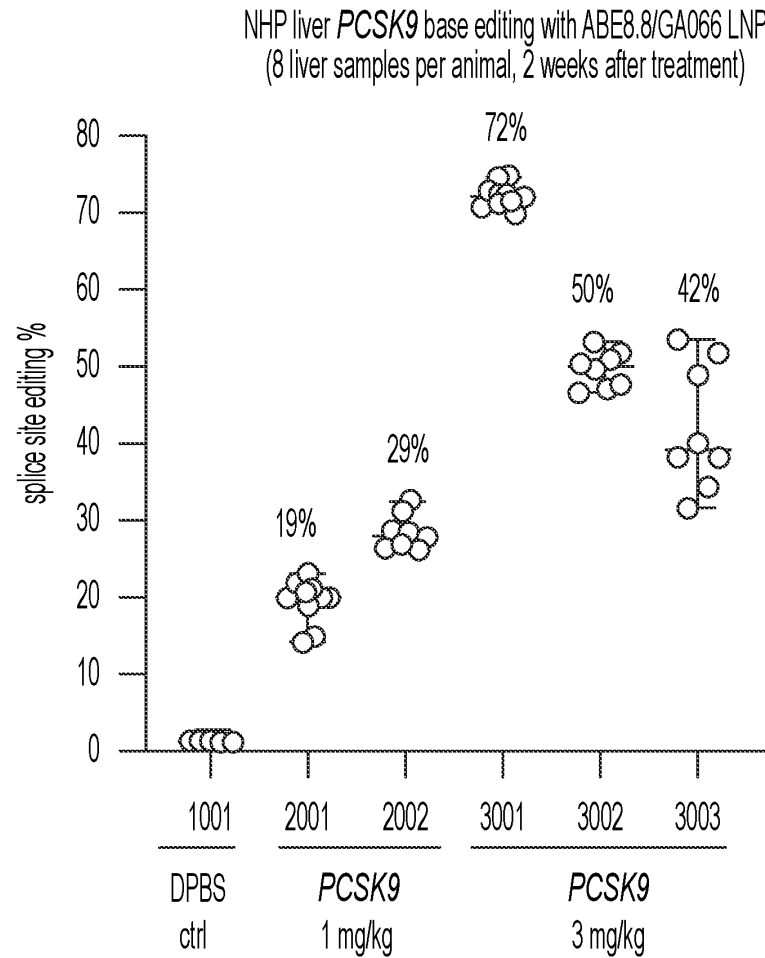


FIG. 22

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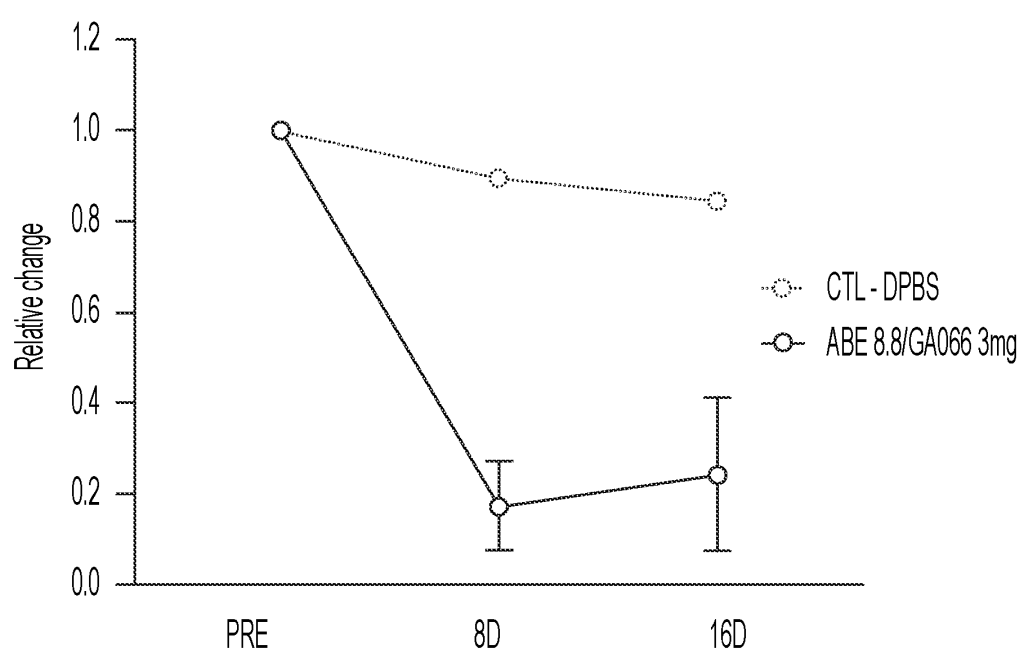


FIG. 23

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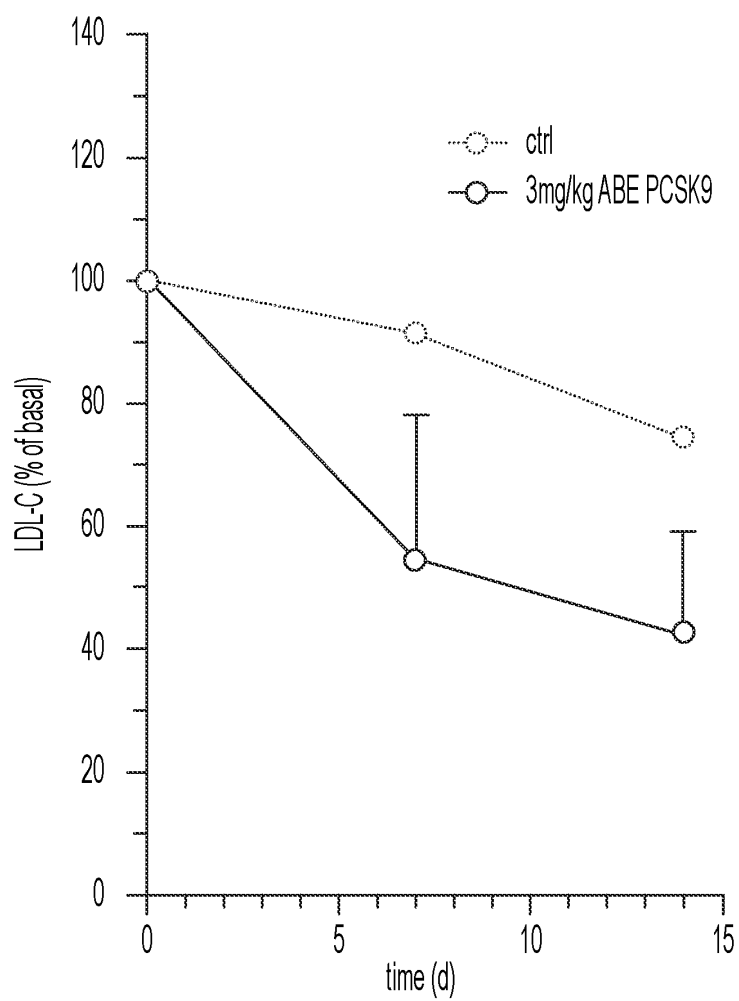


FIG. 24

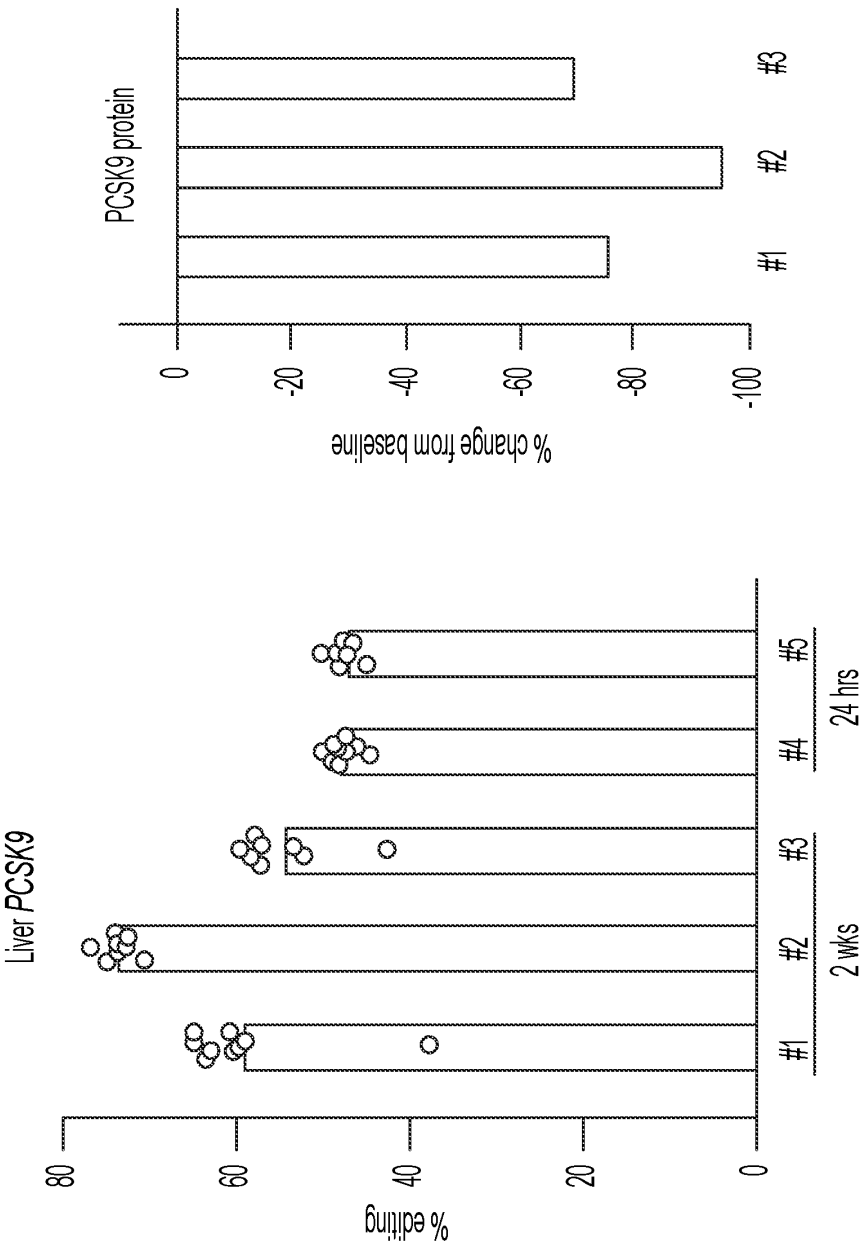


FIG. 25B

FIG. 25A

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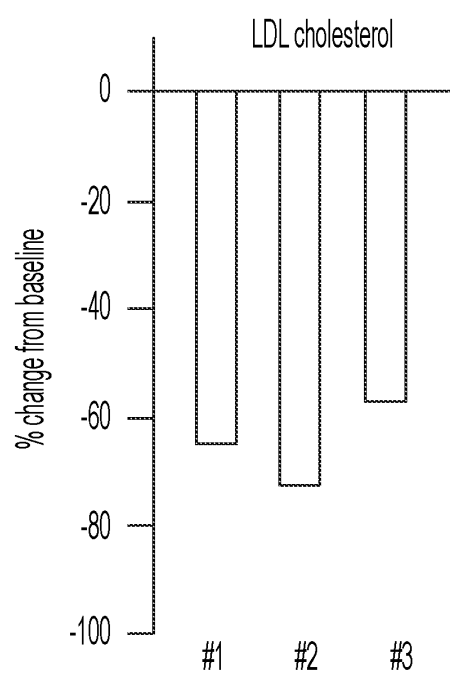


FIG. 25C

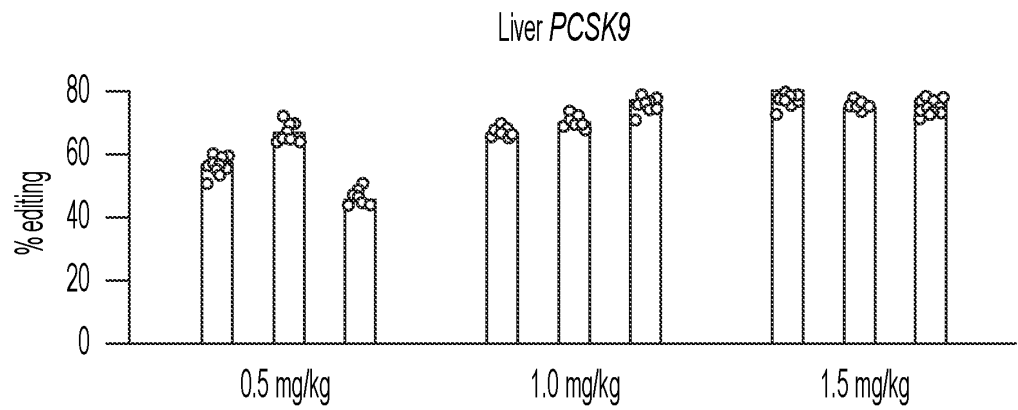


FIG. 26A

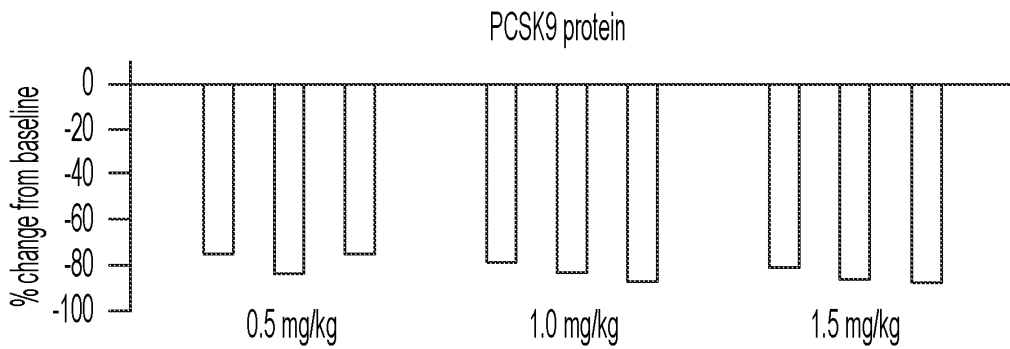


FIG. 26B

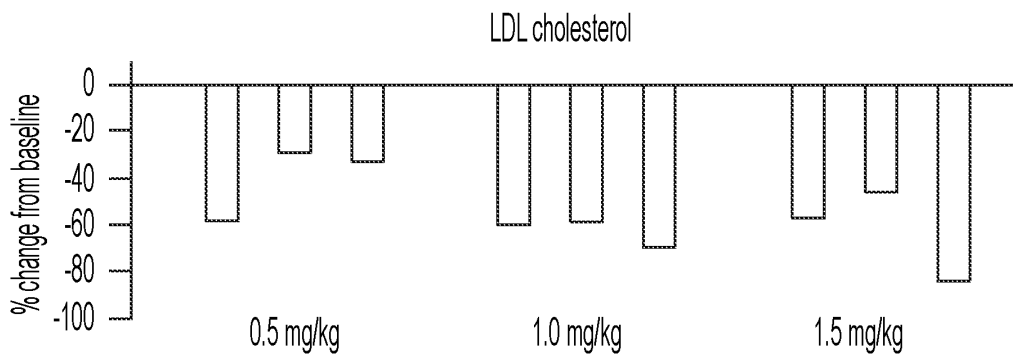


FIG. 26C

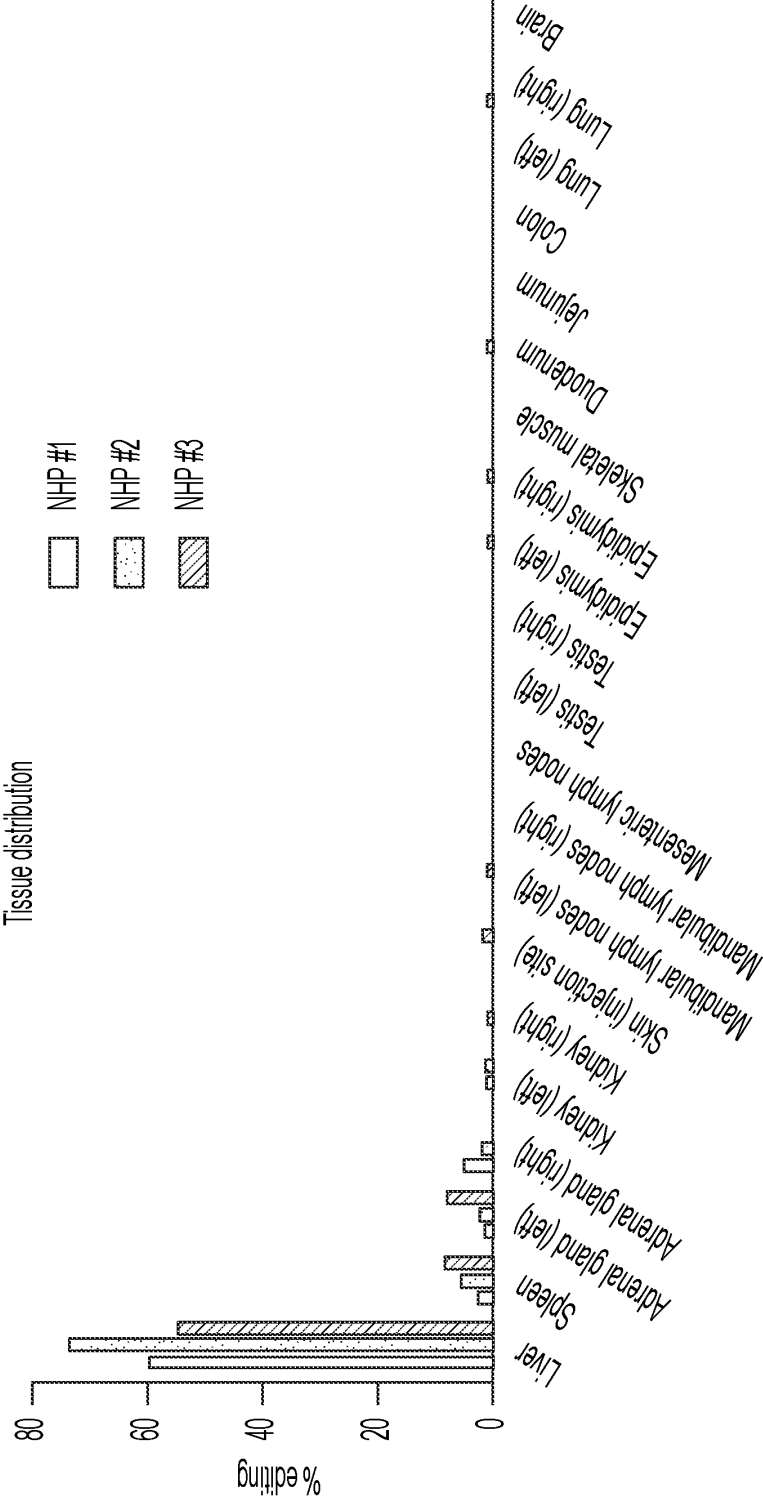


FIG. 27

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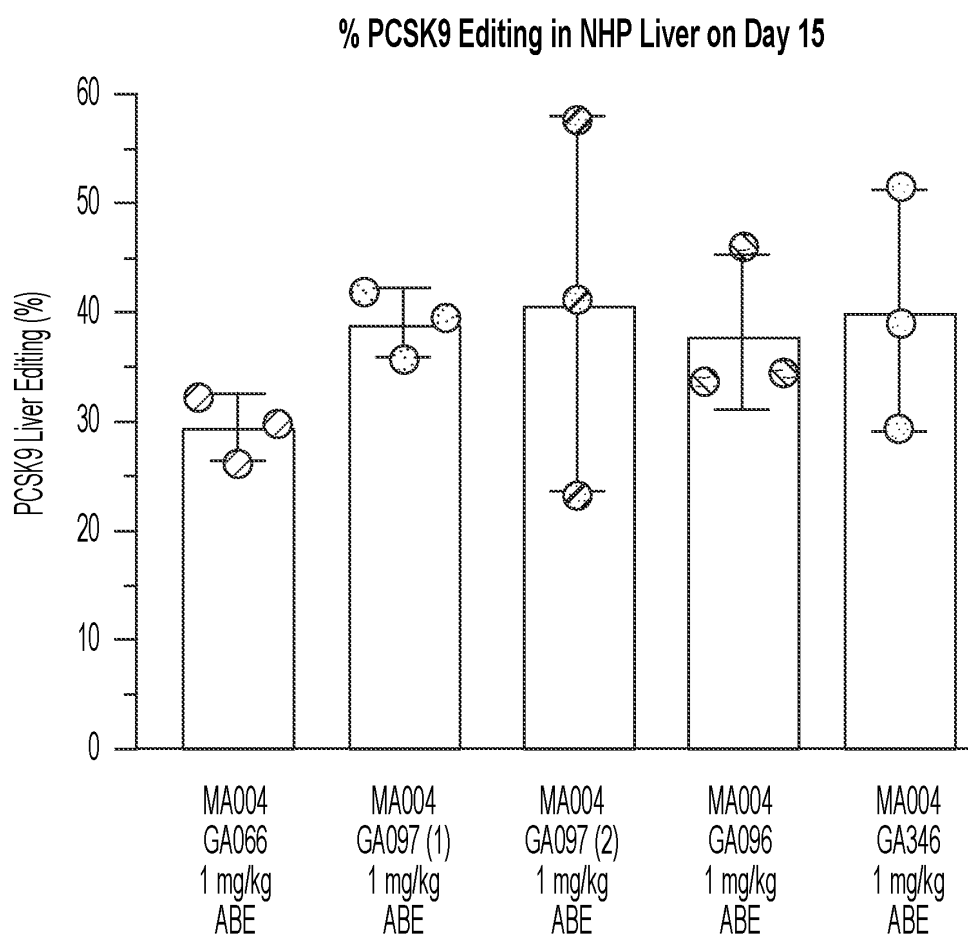


FIG. 28

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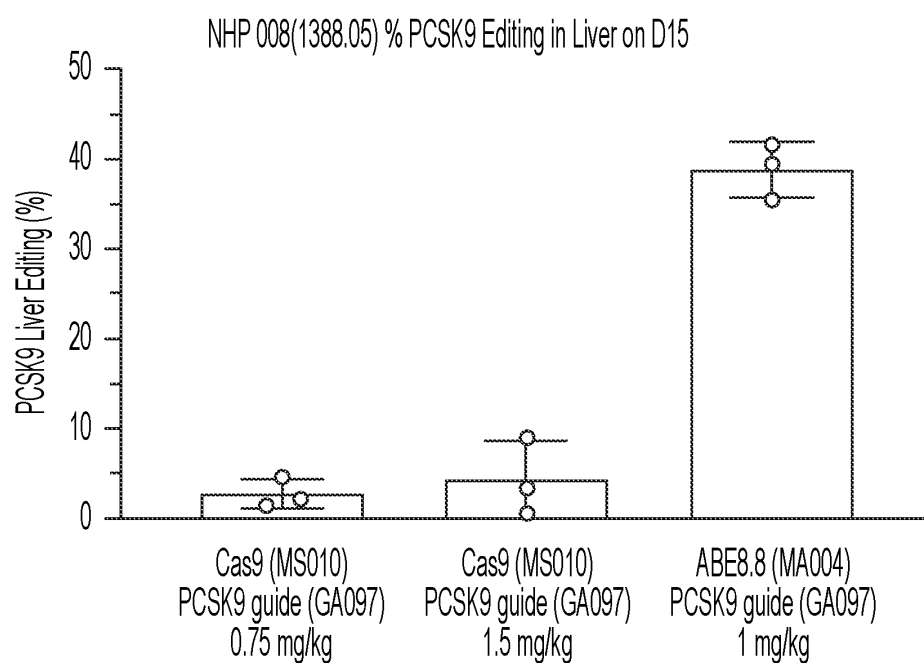


FIG. 29

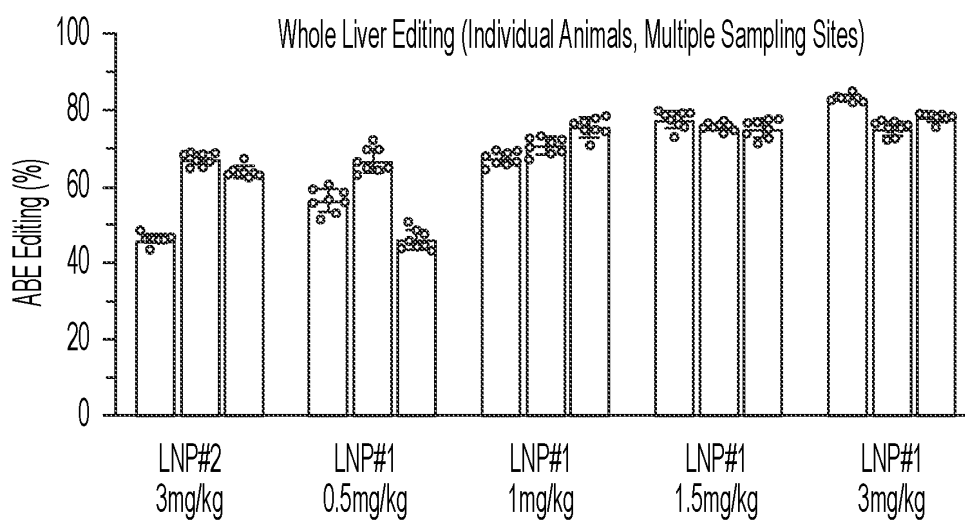


FIG. 30

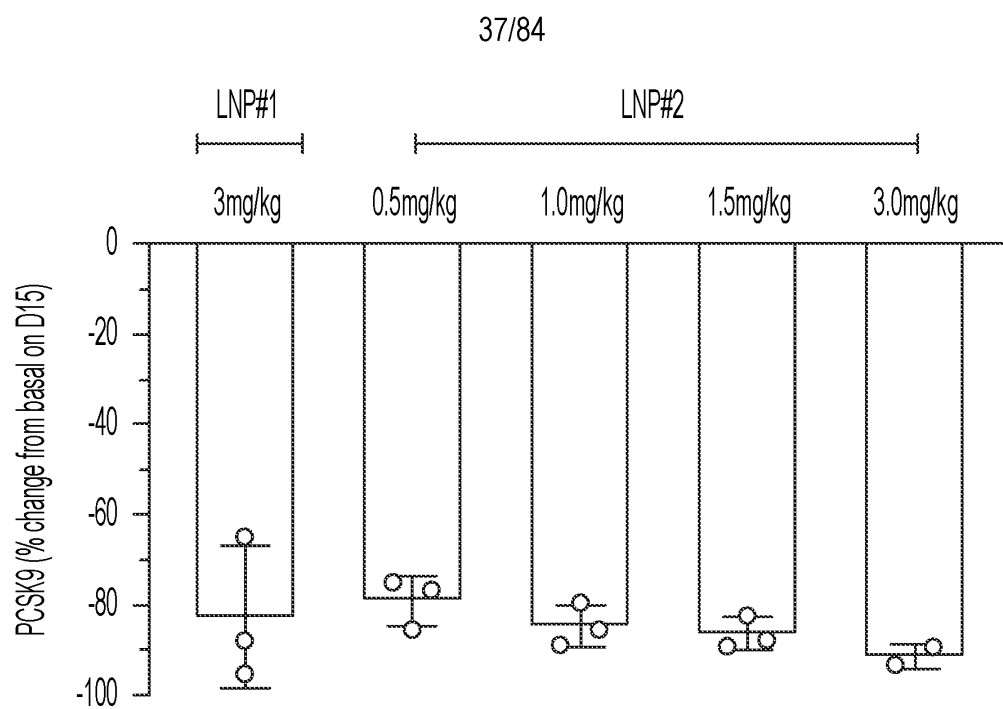


FIG. 31

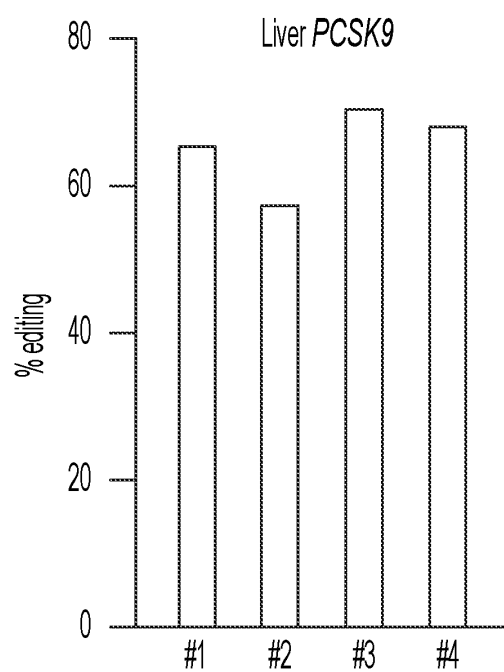


FIG. 32

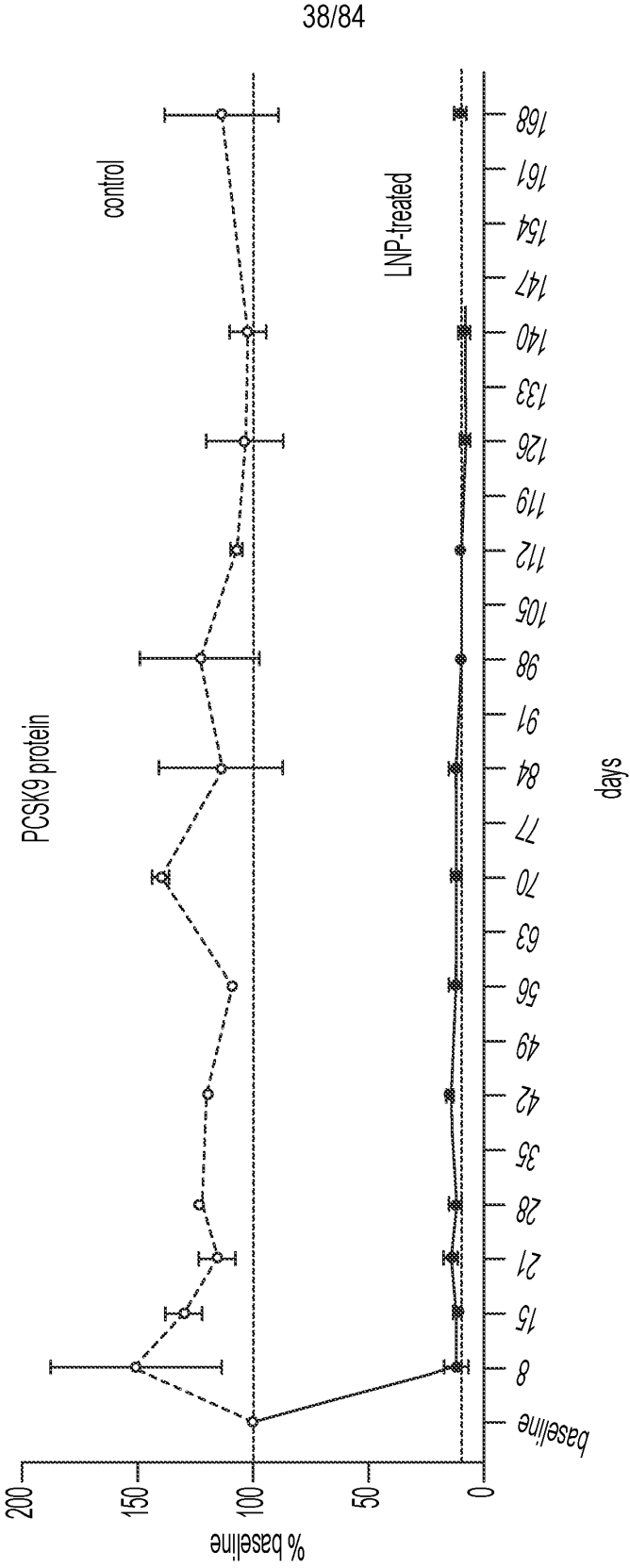


FIG. 33

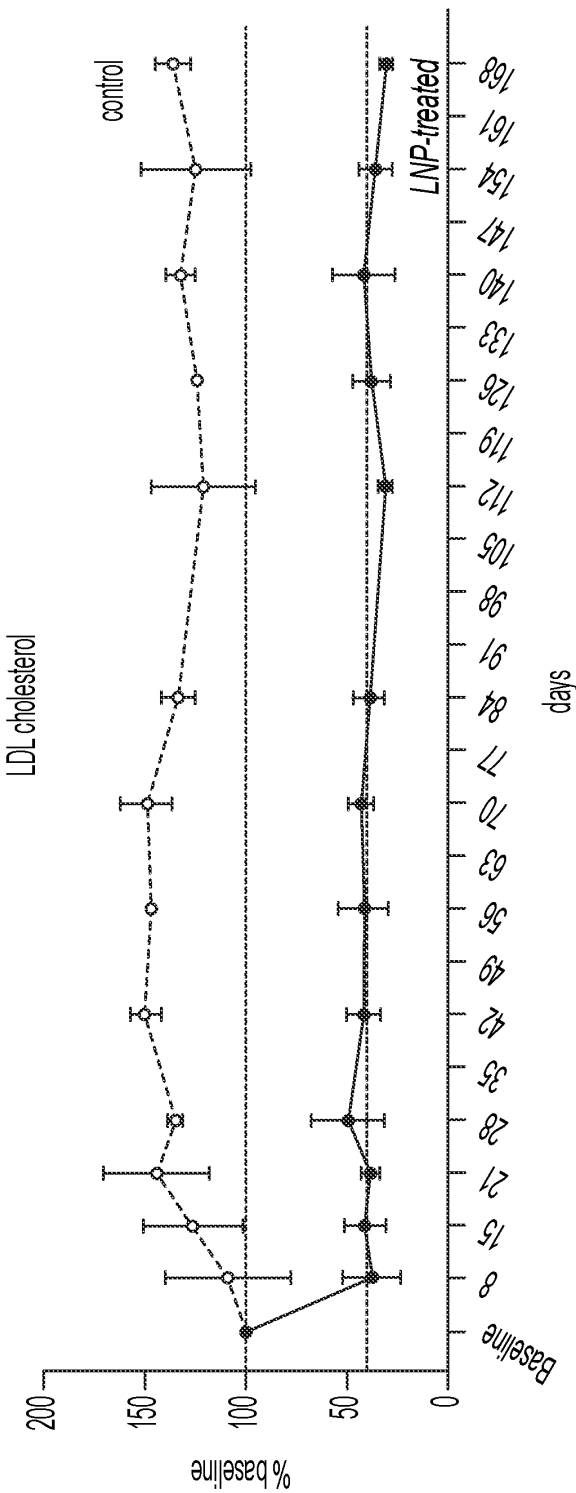


FIG. 34

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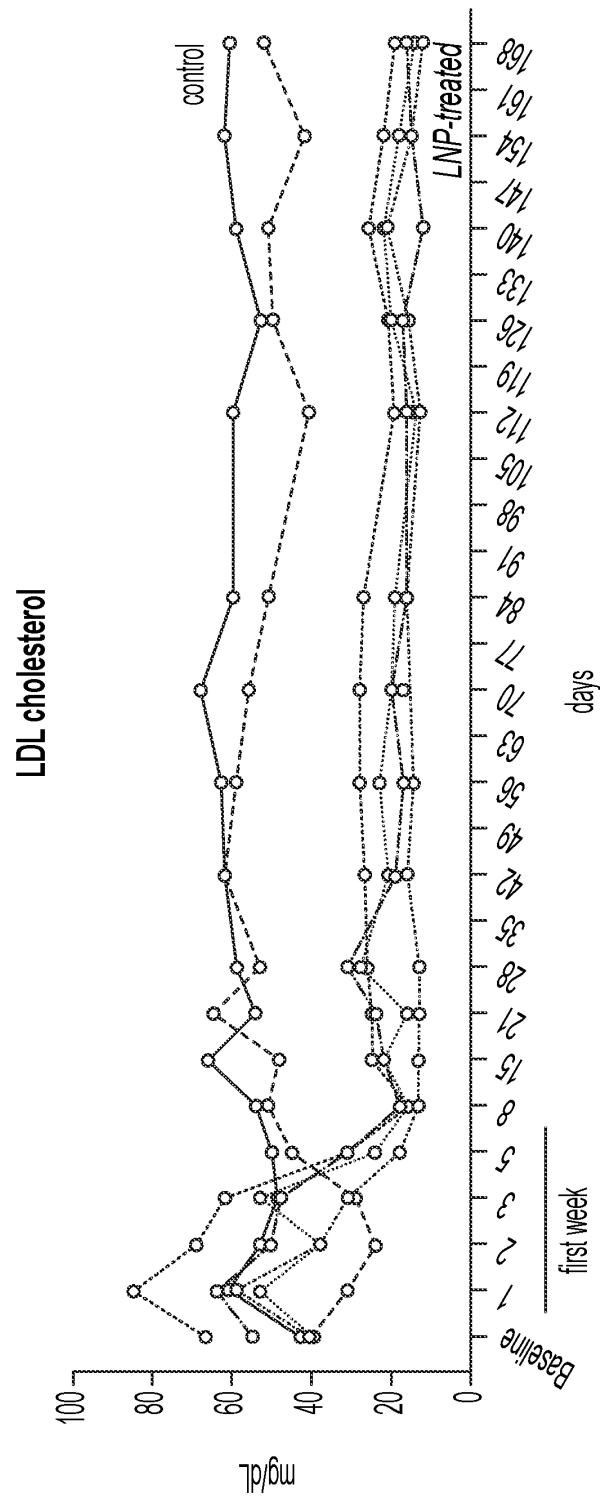


FIG. 34
(Continued)

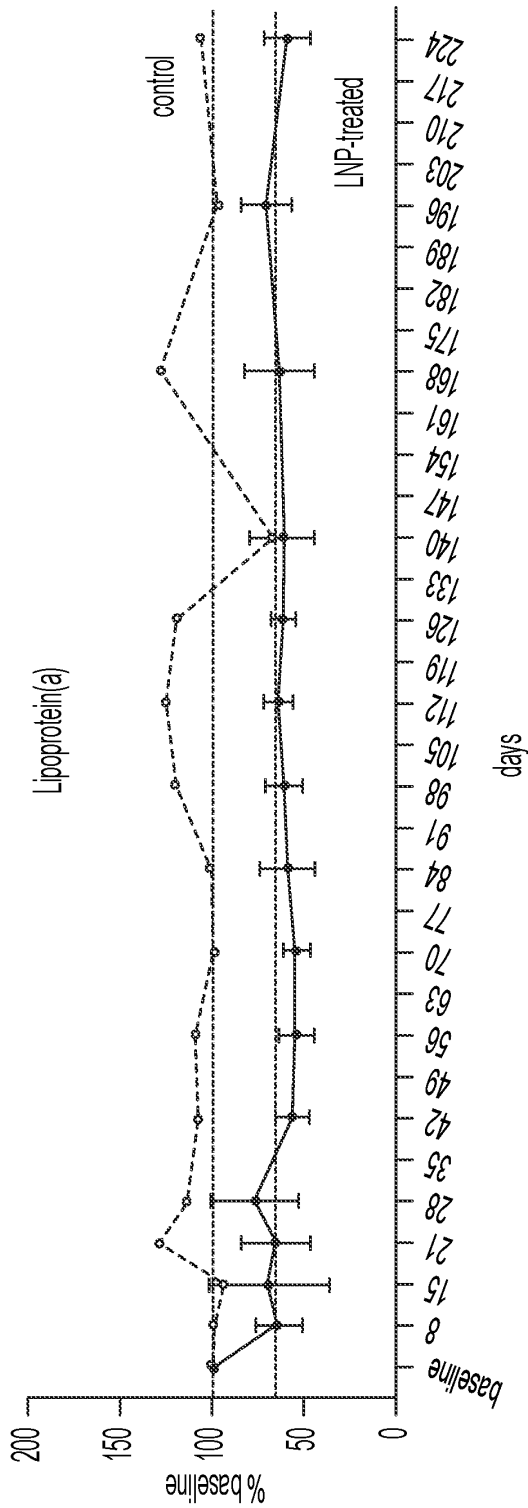


FIG. 35

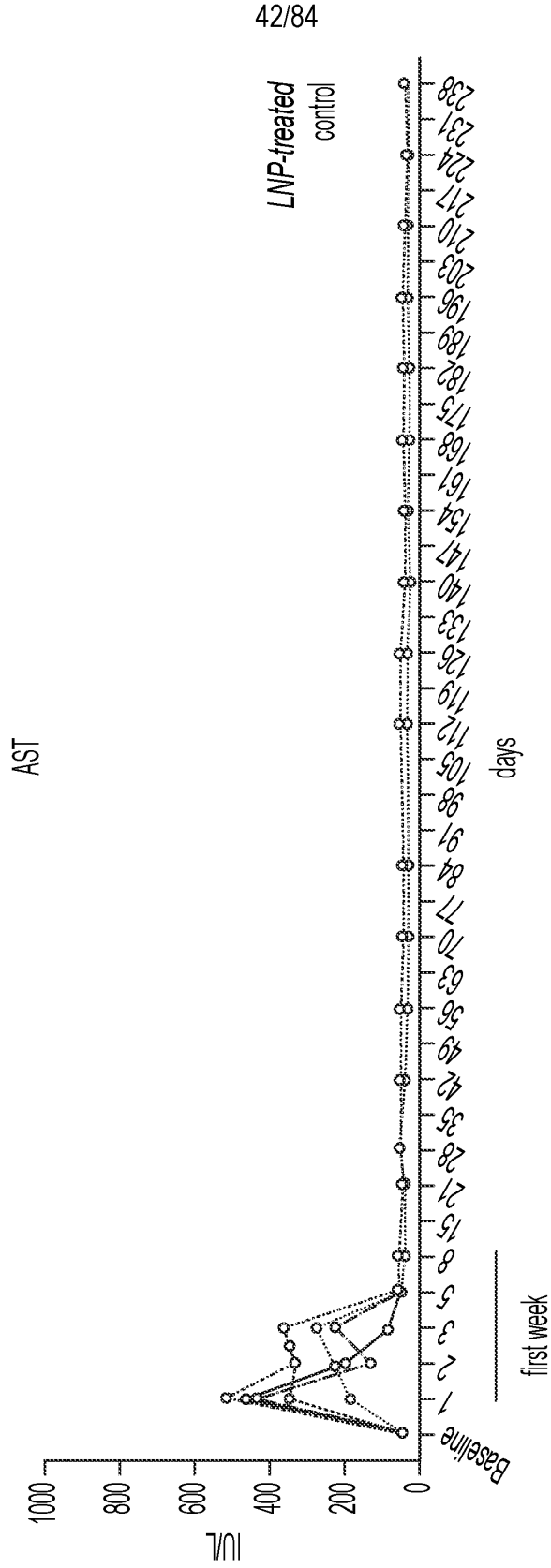


FIG. 36

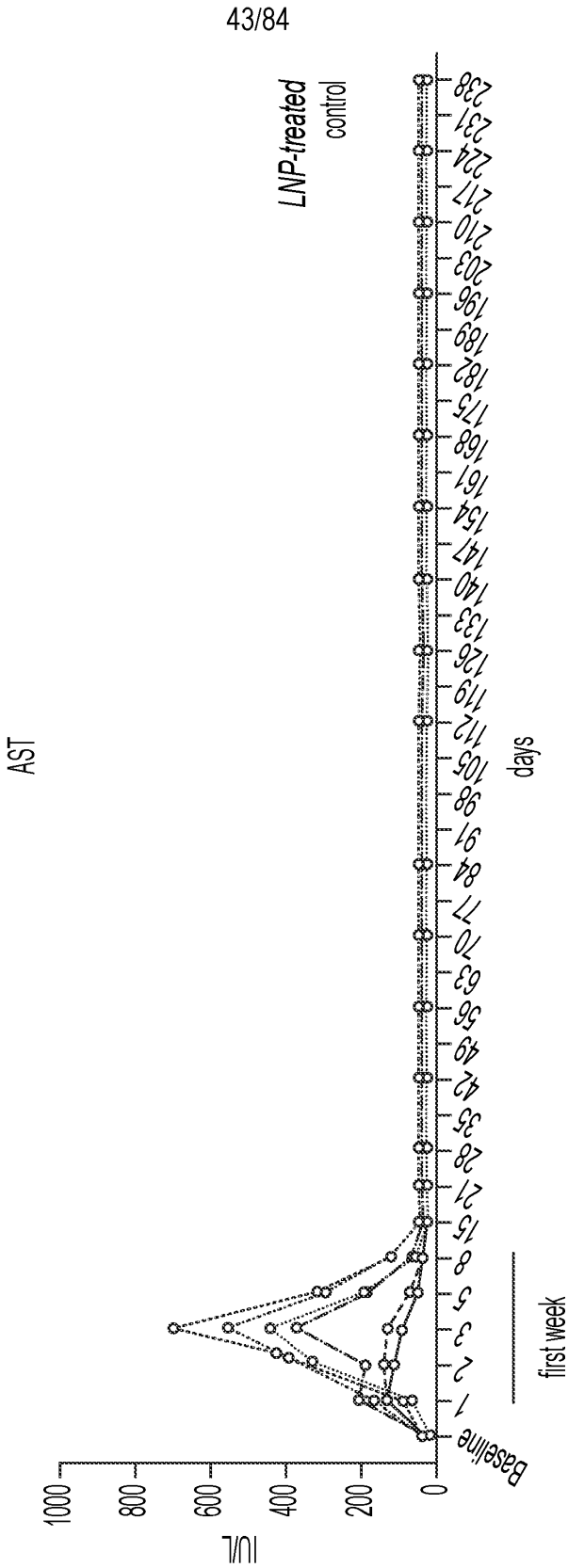


FIG. 36
(Continued)

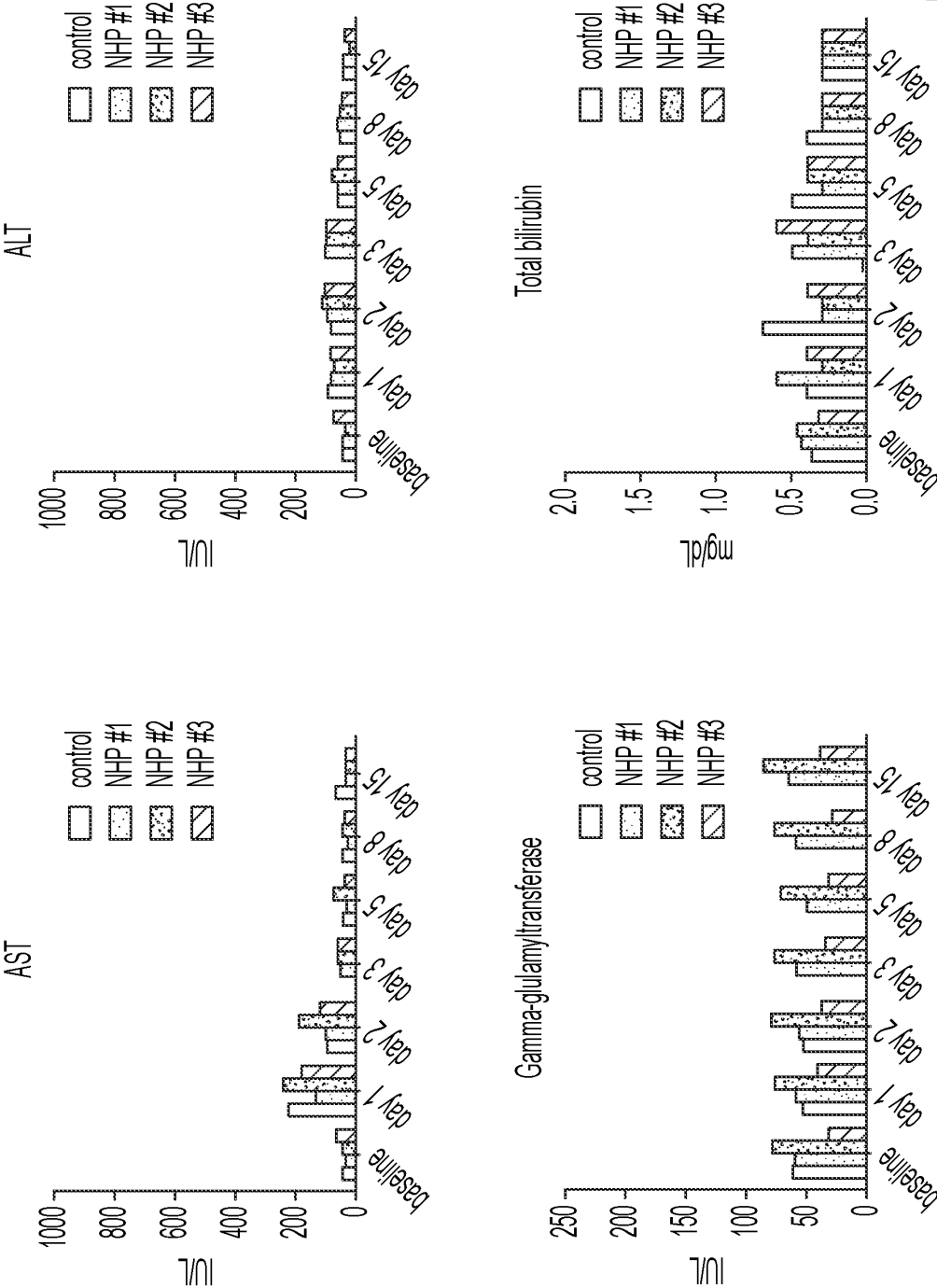


FIG. 37A

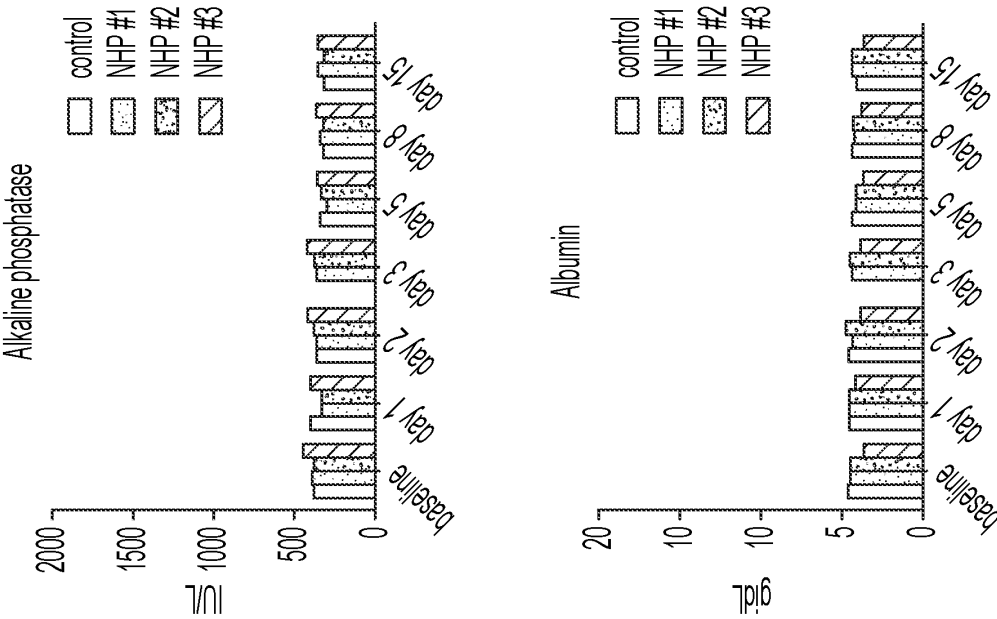


FIG. 37A
(Continued)

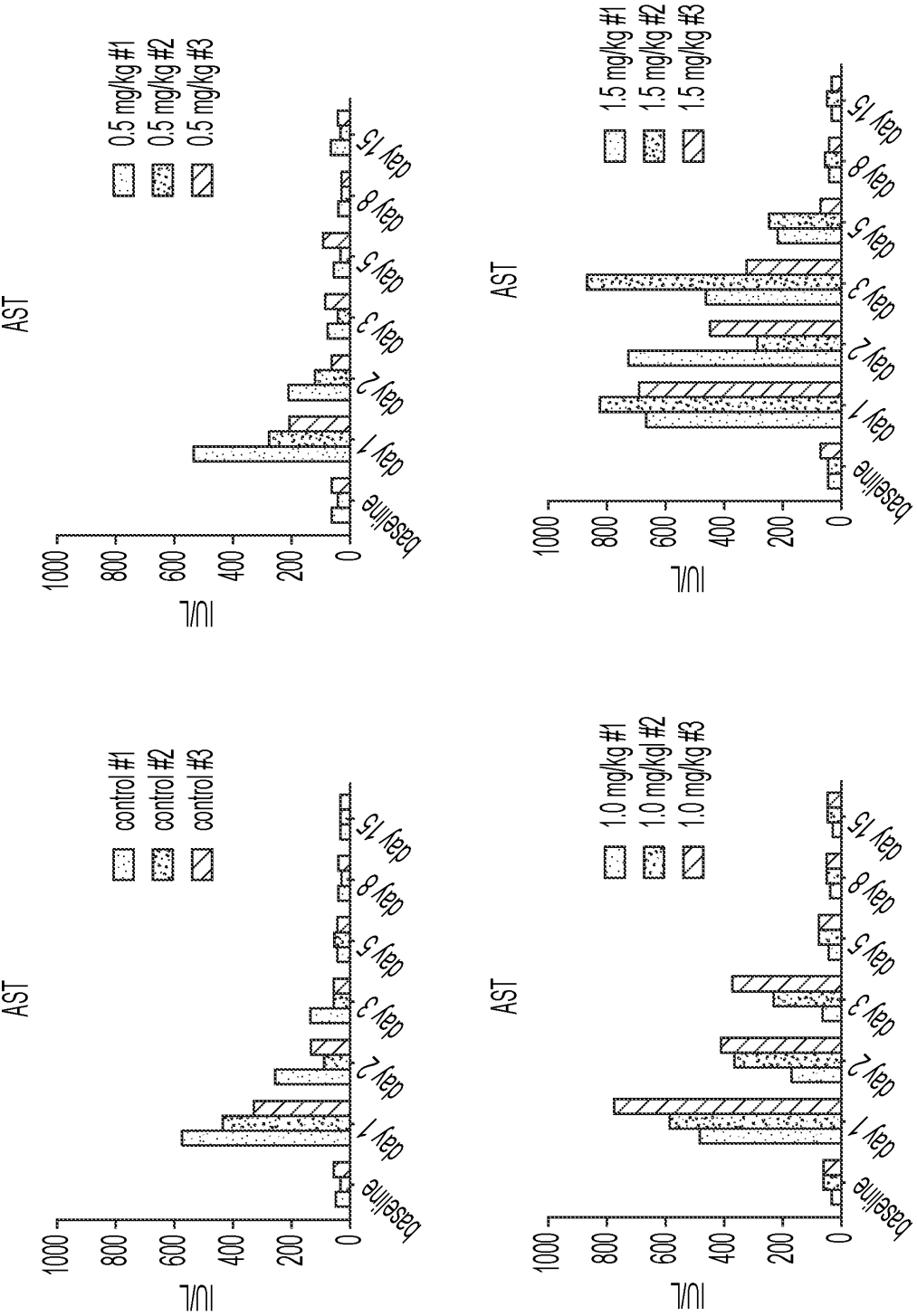


FIG. 37B

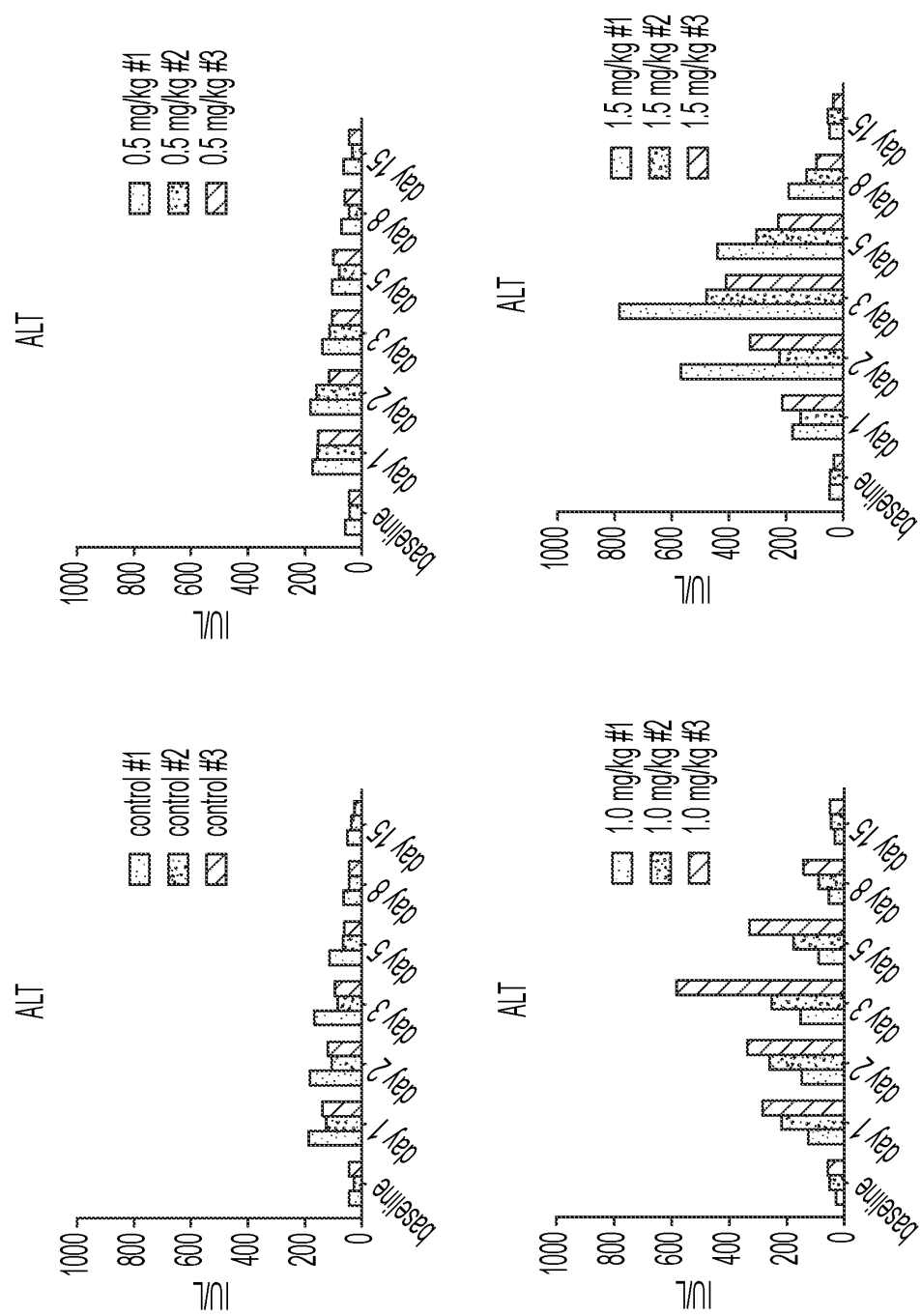


FIG. 37C

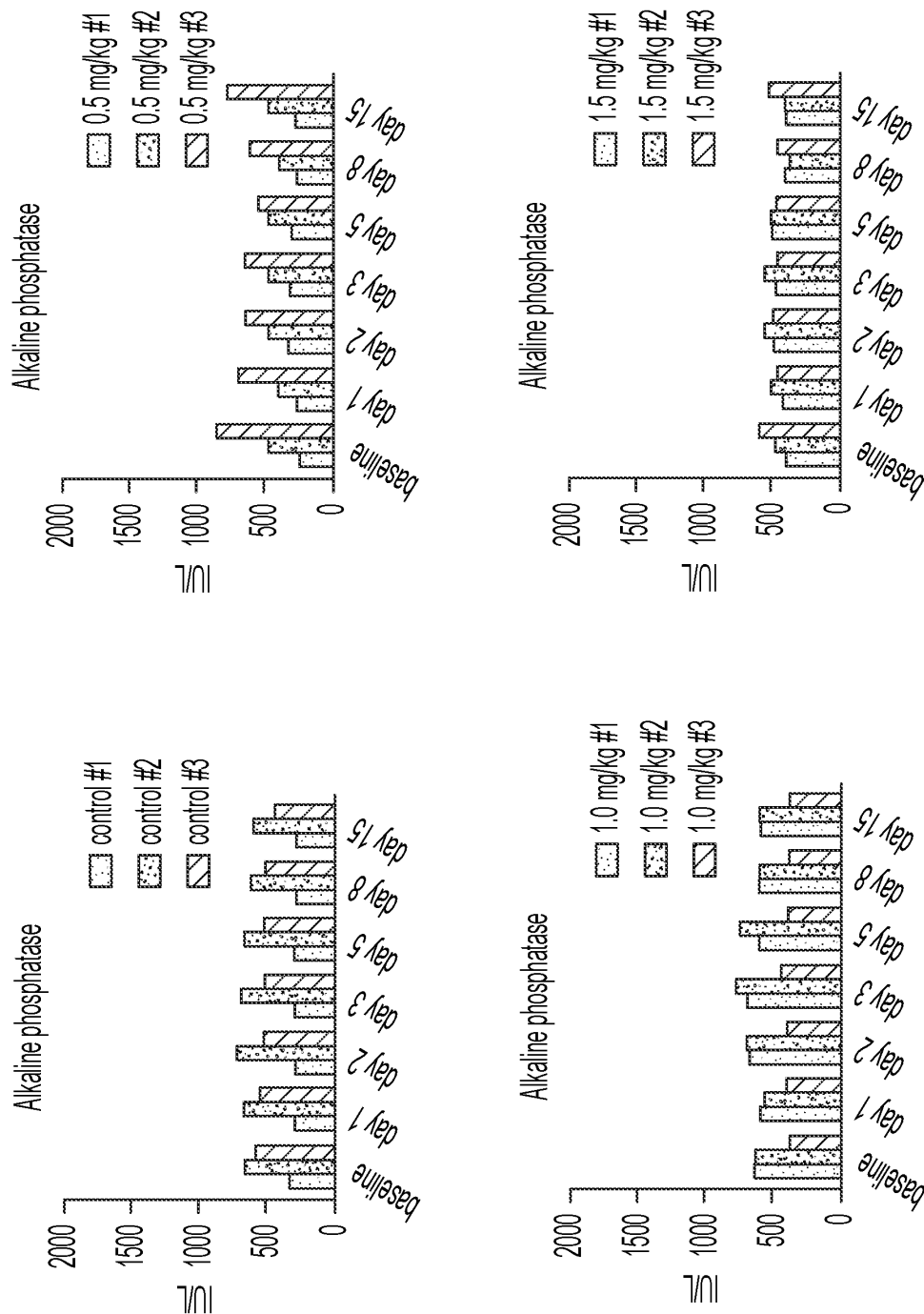


FIG. 37D

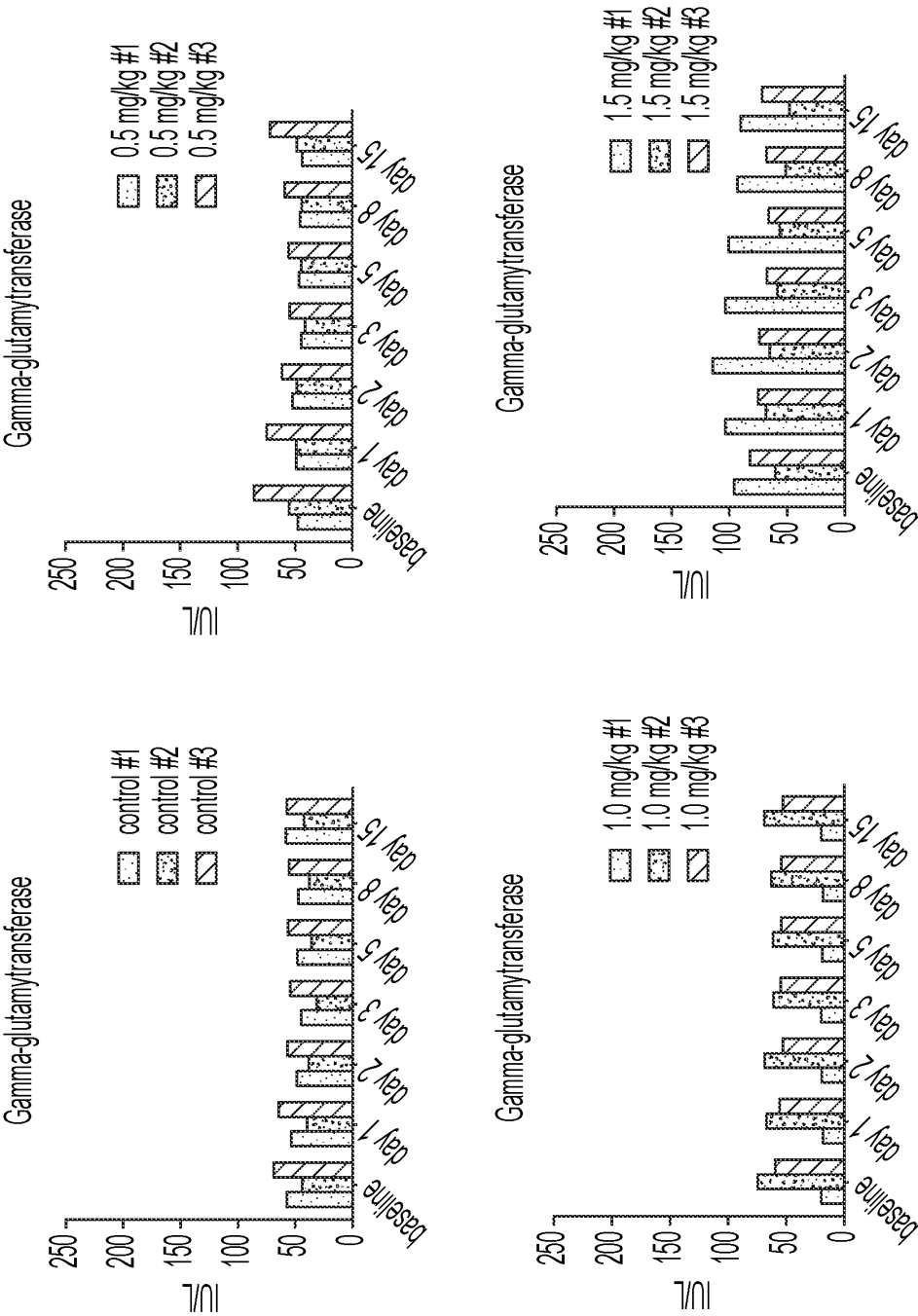


FIG. 37E

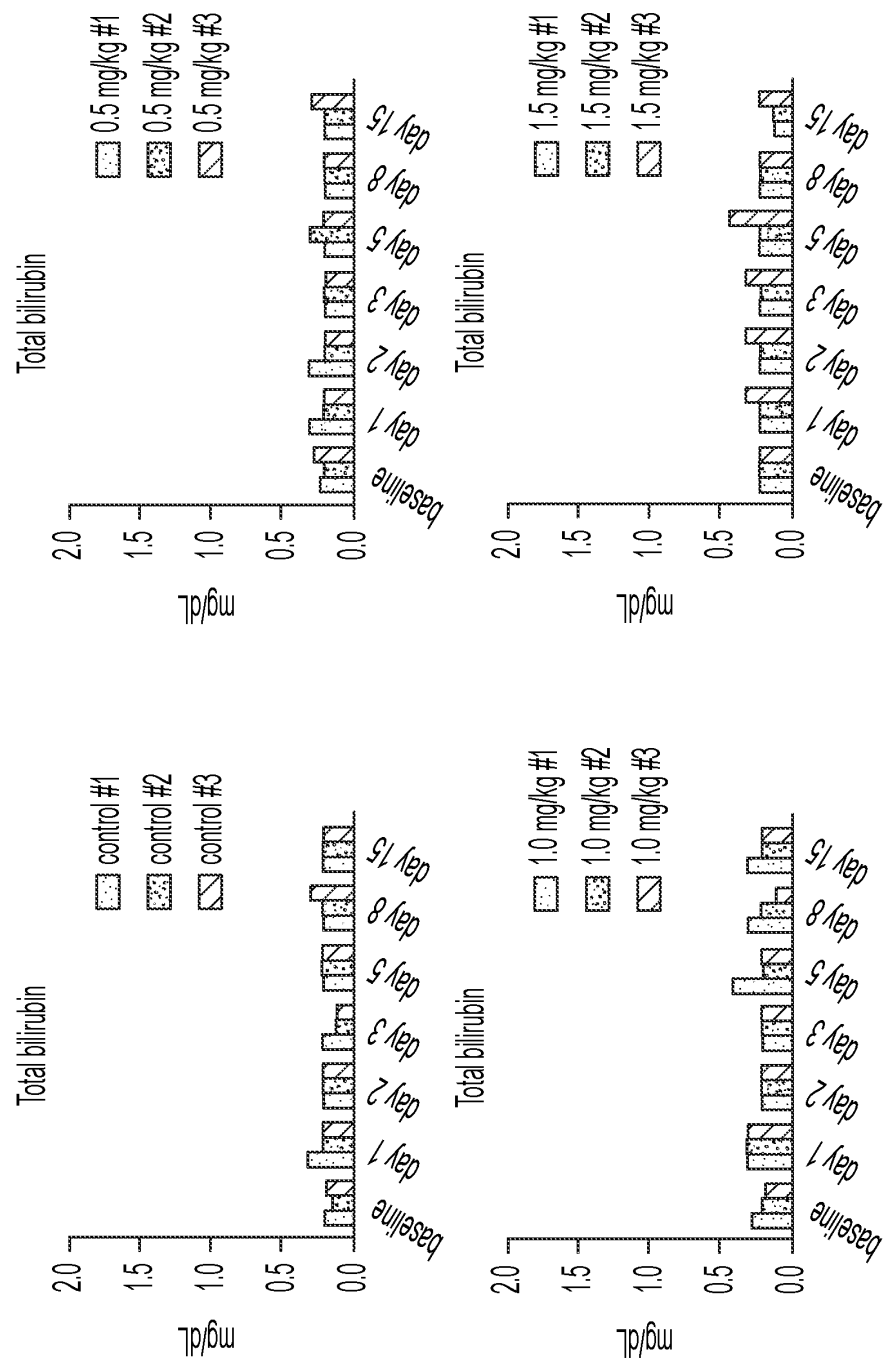


FIG. 37F

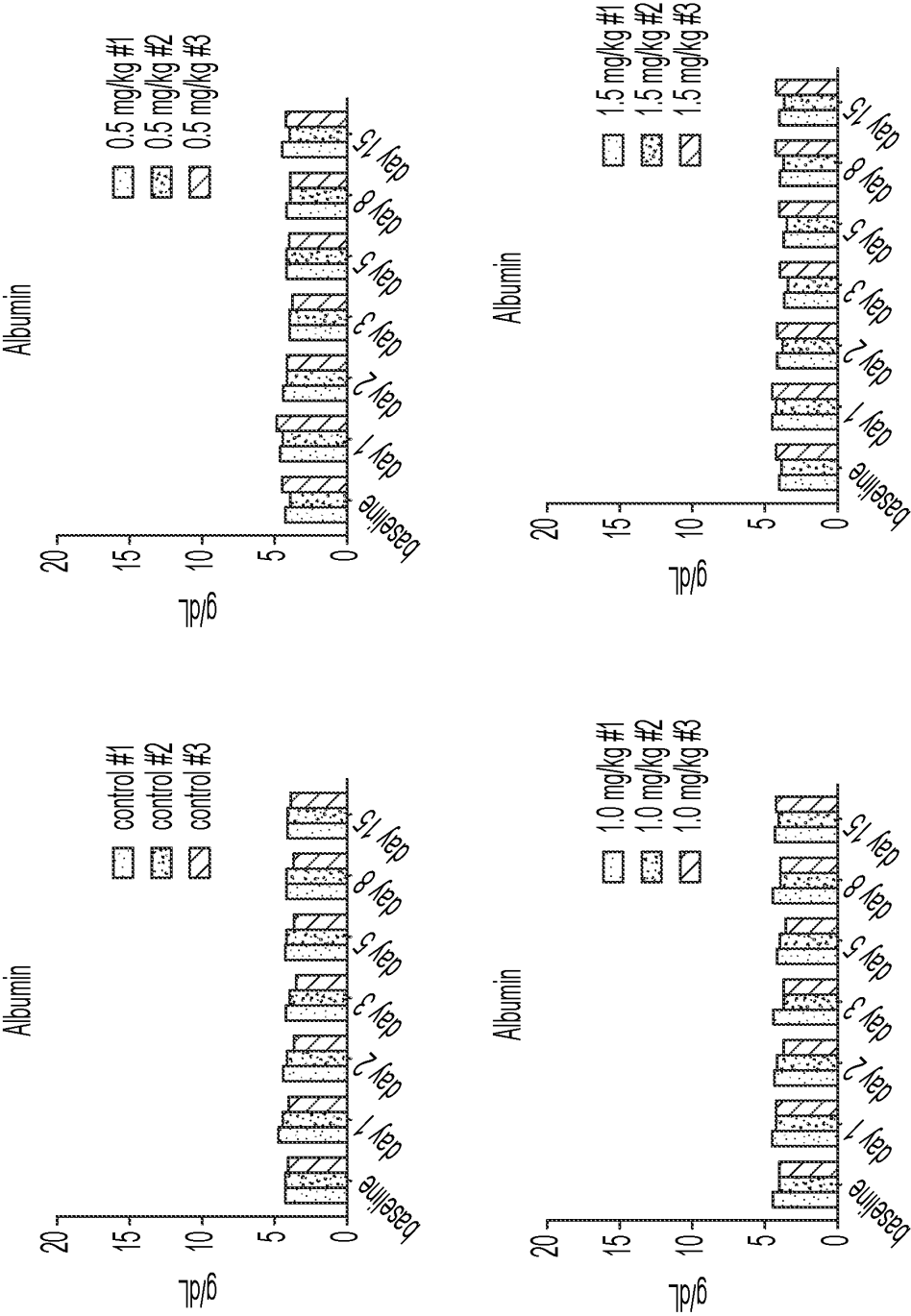


FIG. 37G

ONE-seq with cyno genomic library 52/84

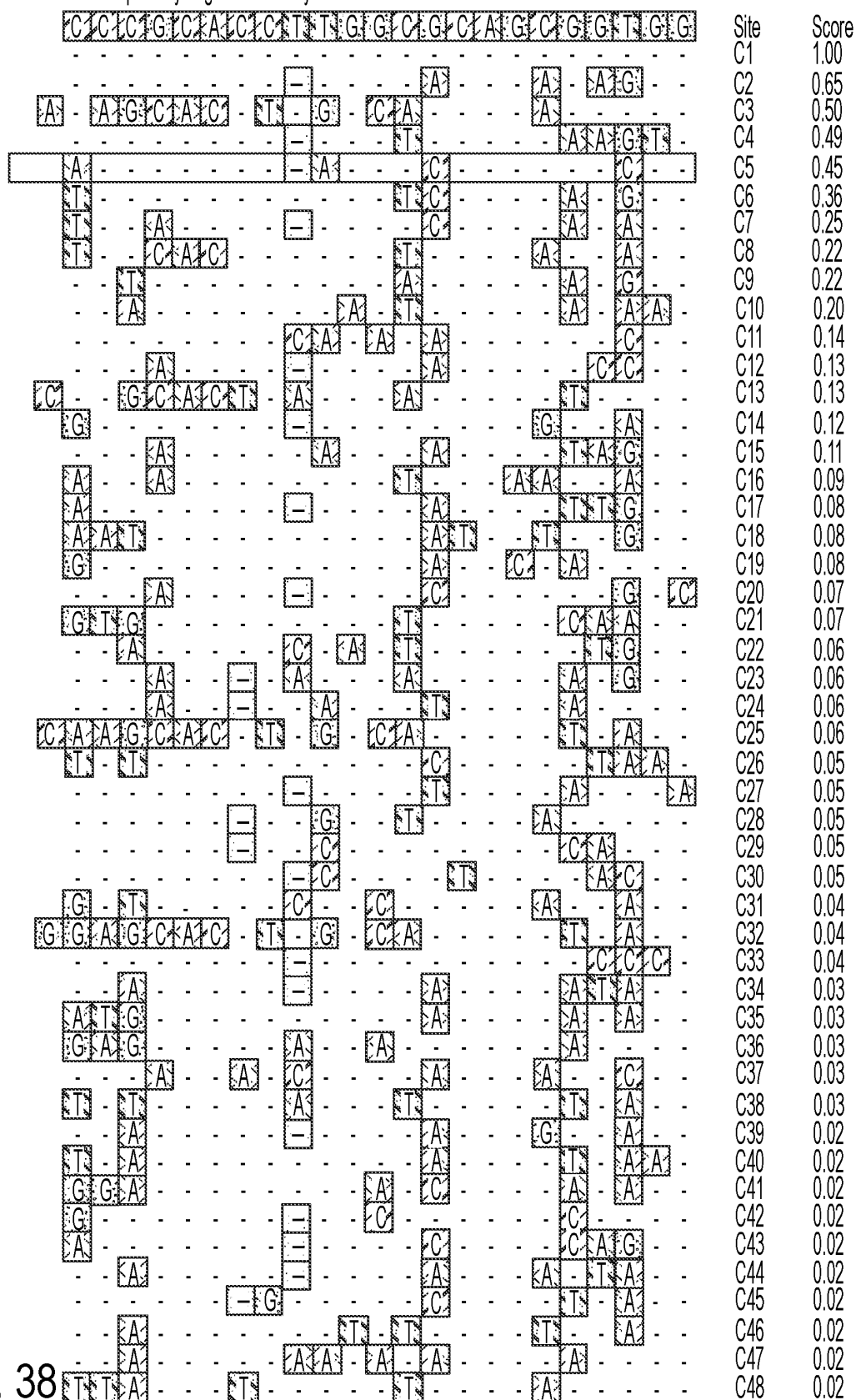


FIG. 38

Primary cyno hepatocytes - 3 treated samples, 3 untreated samples

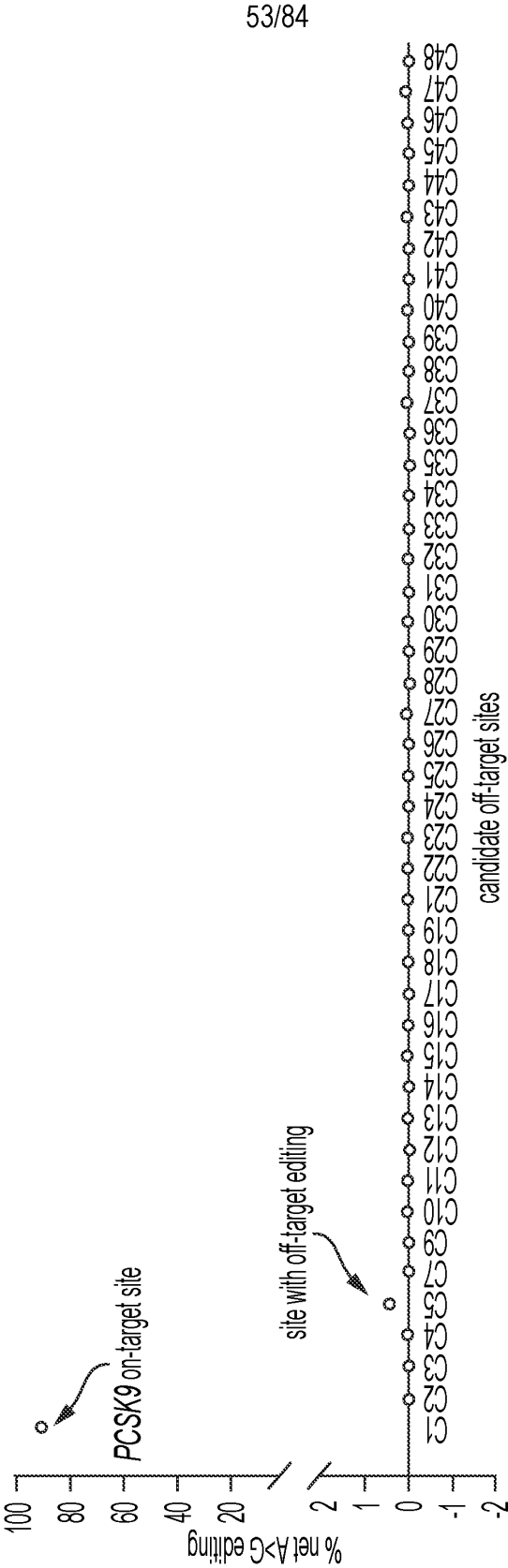


FIG. 39

NHP liver - 3 treated animals (1.0 mg/kg), 3 untreated animals

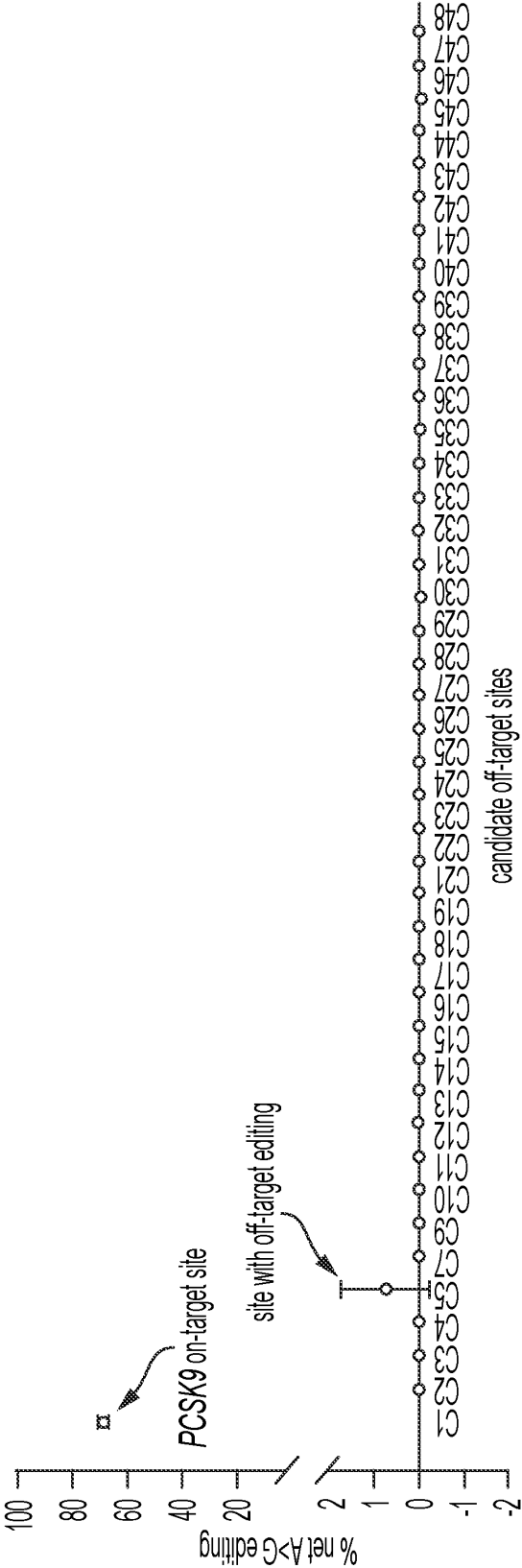


FIG. 39
(Continued)

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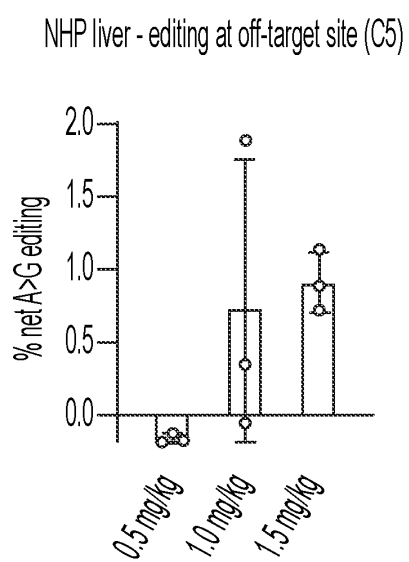


FIG. 40

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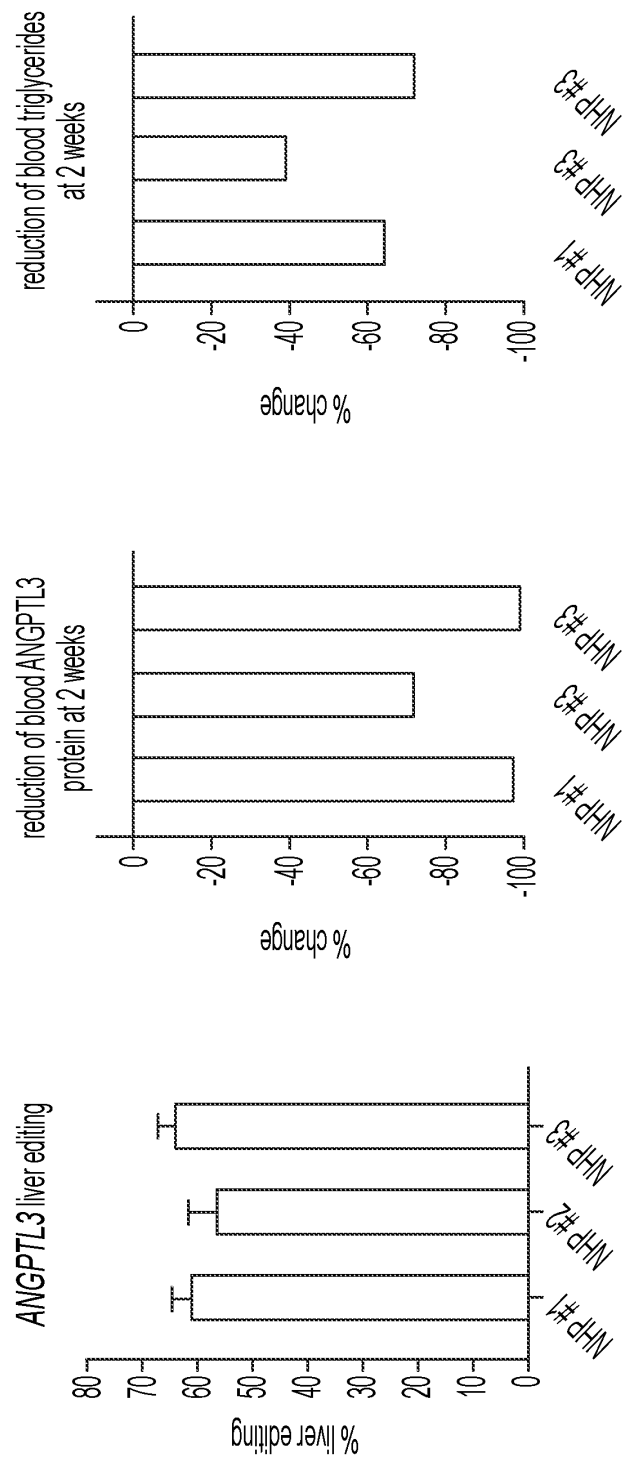


FIG. 41

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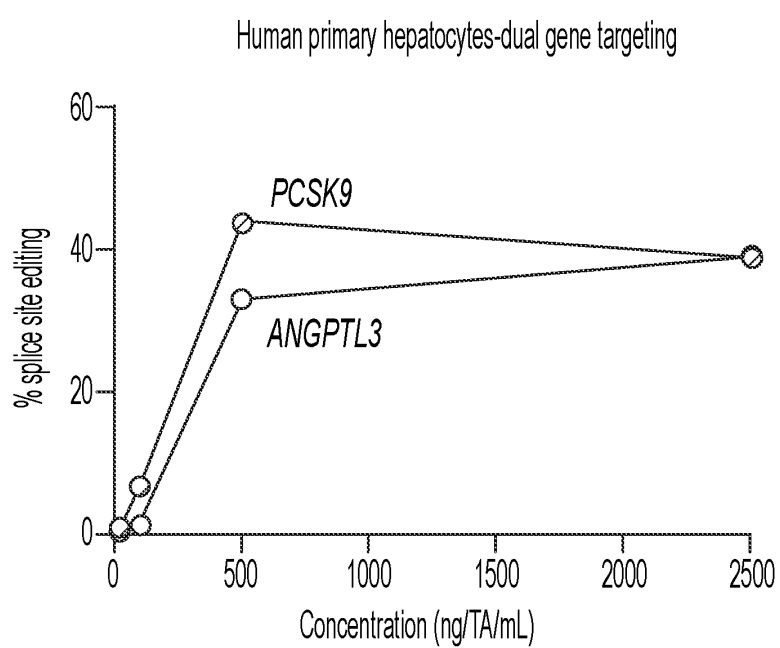


FIG. 42

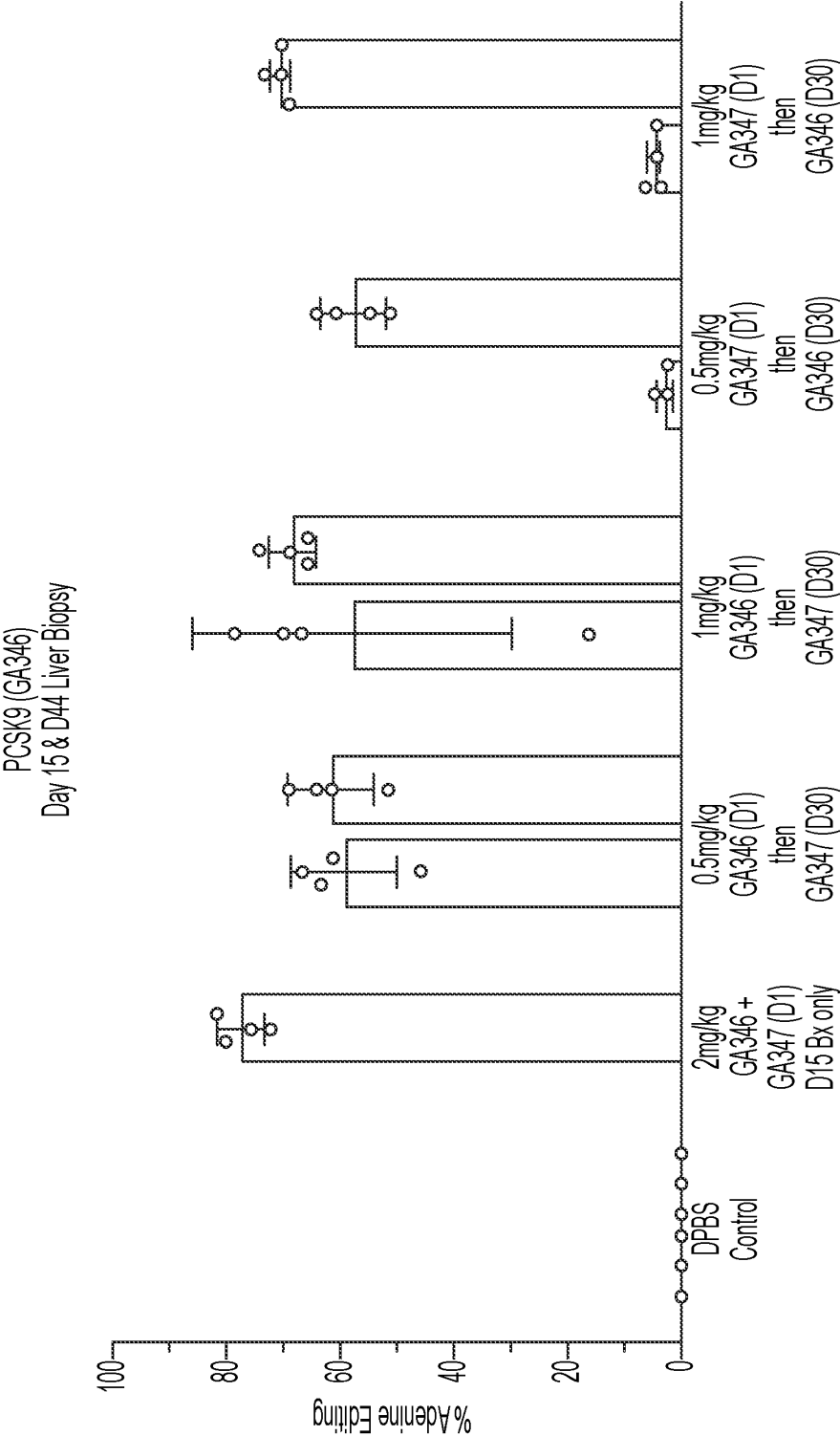


FIG. 43

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ANGTL3 (GA347)
Day 15 & D44 Liver Biopsy

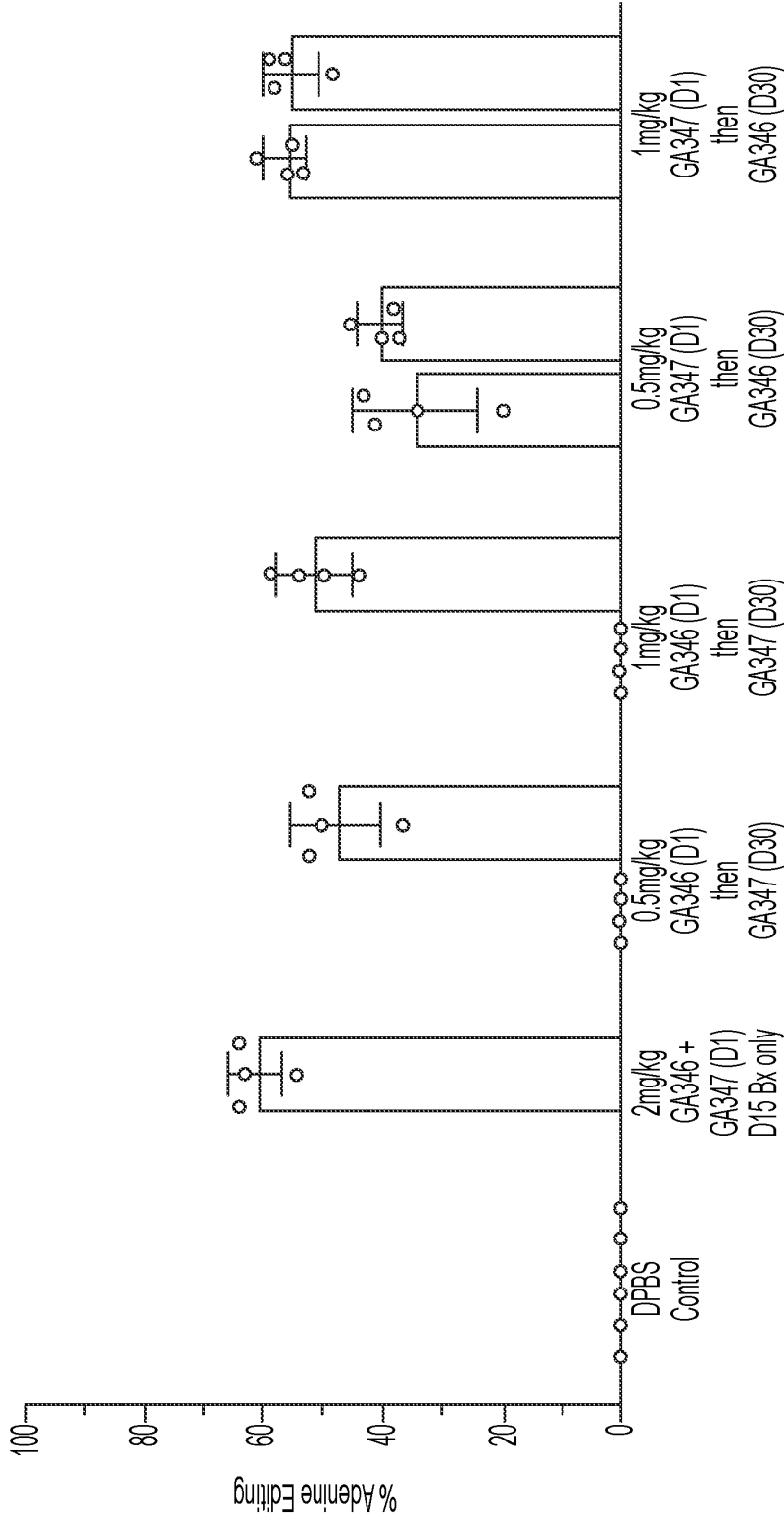


FIG. 43
(Continued)

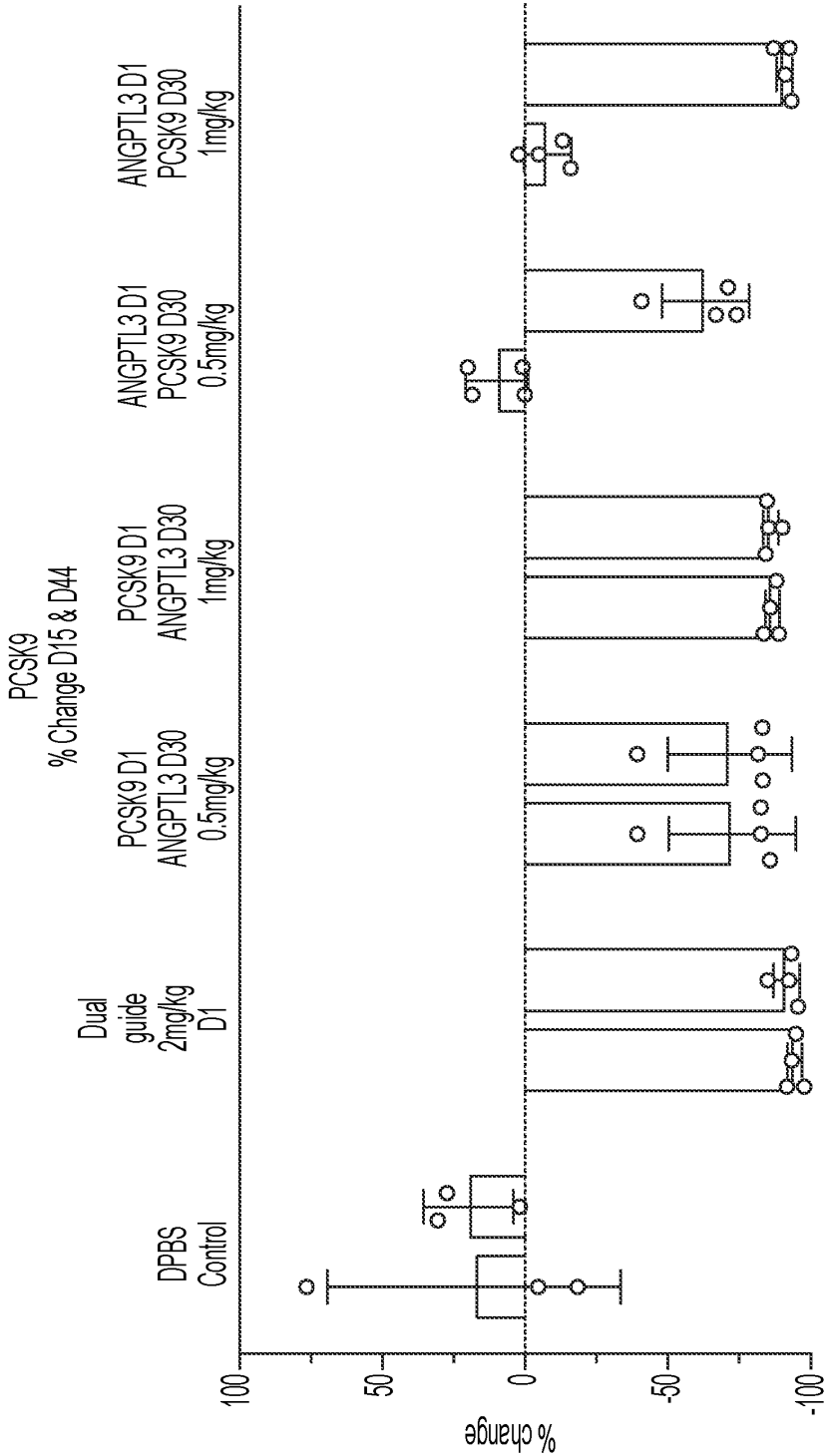


FIG. 44

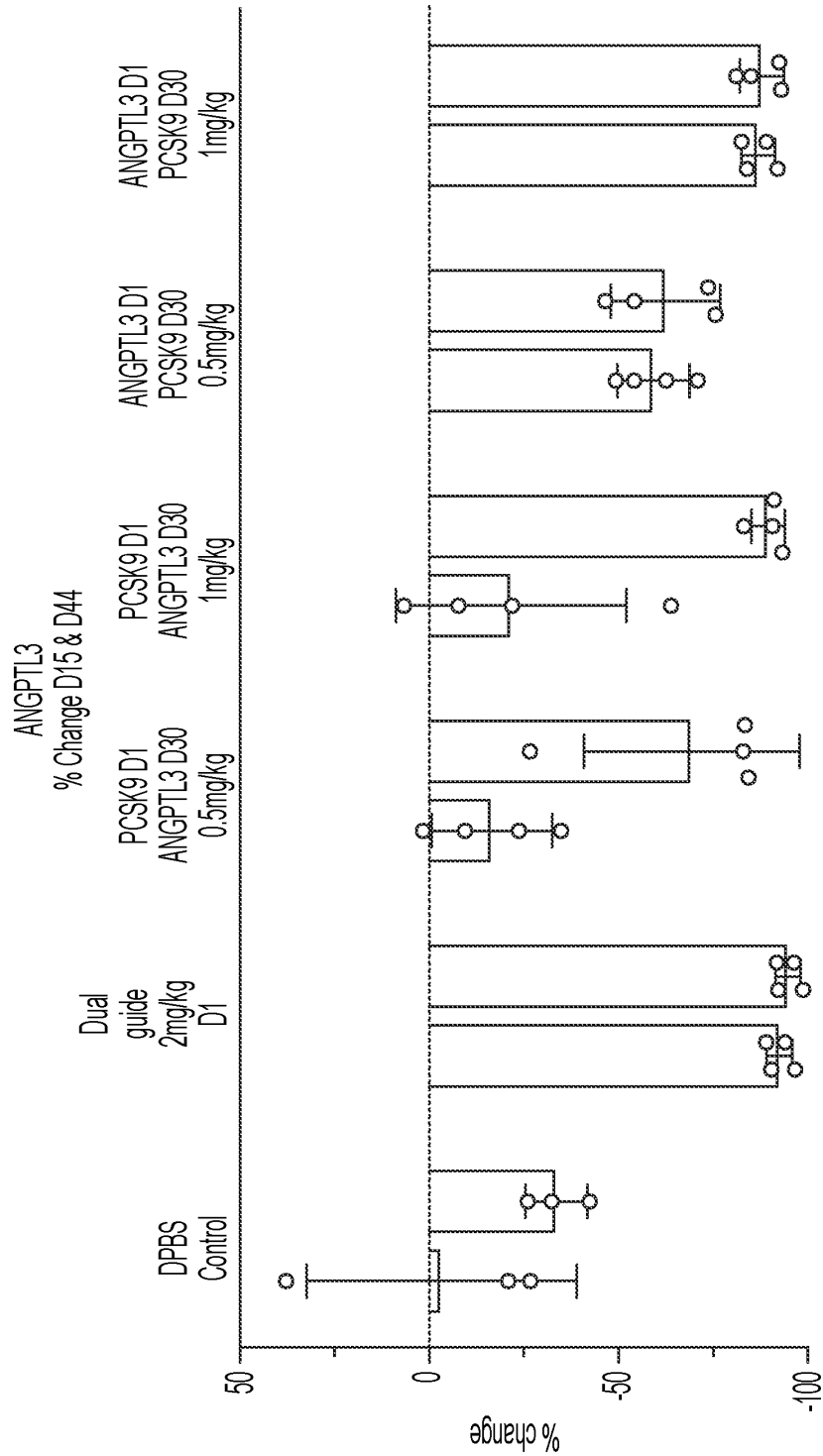


FIG. 44
(Continued)

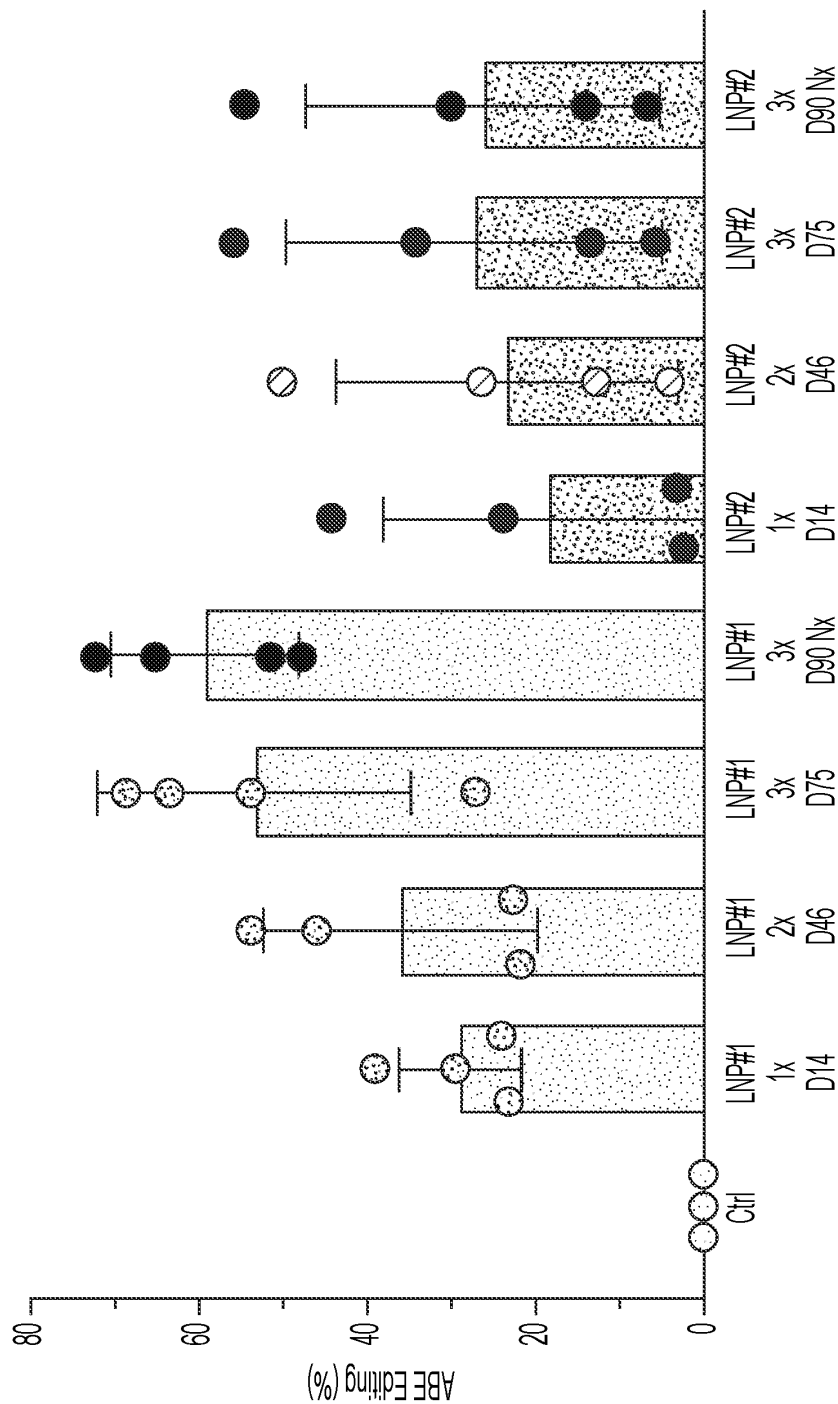


FIG. 45

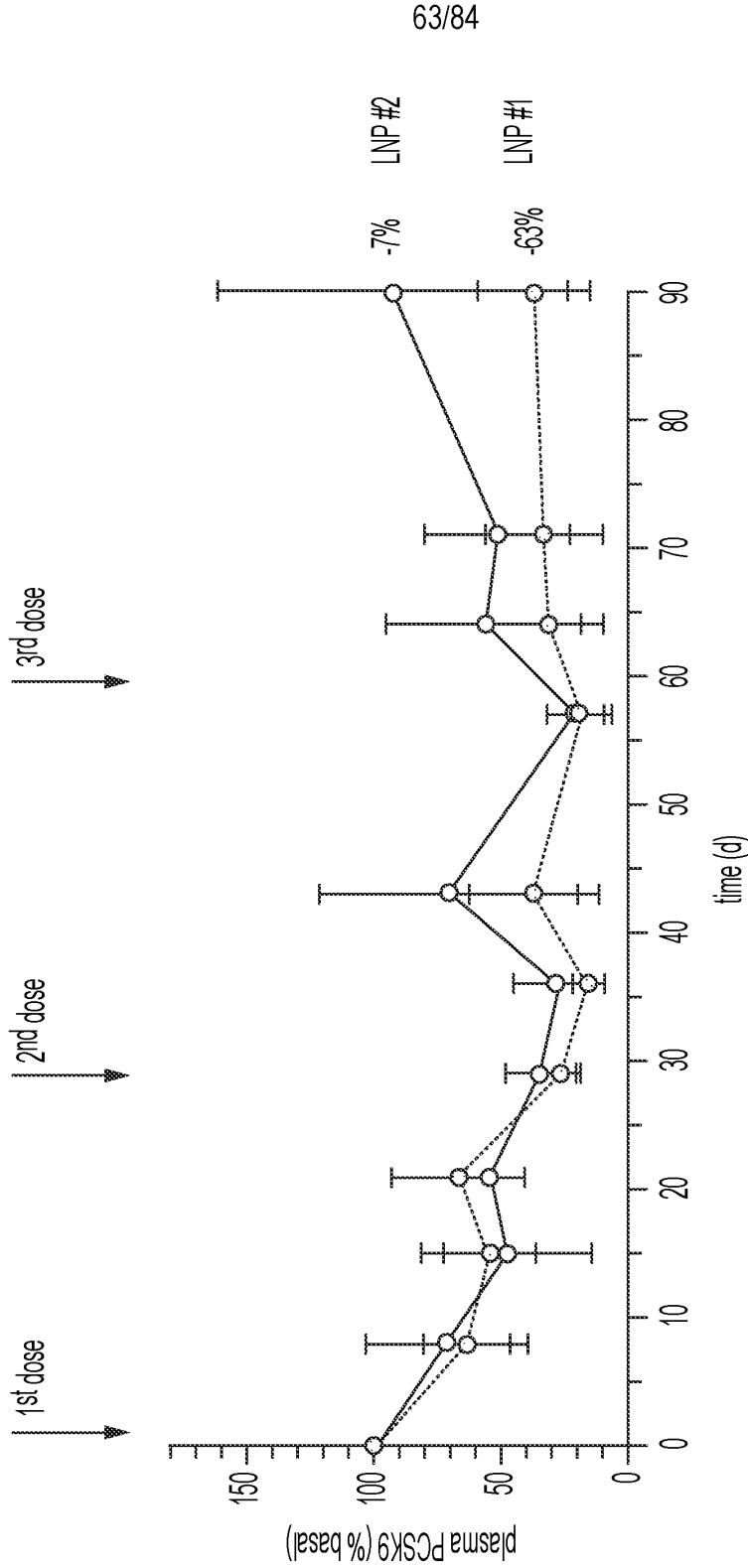


FIG. 46

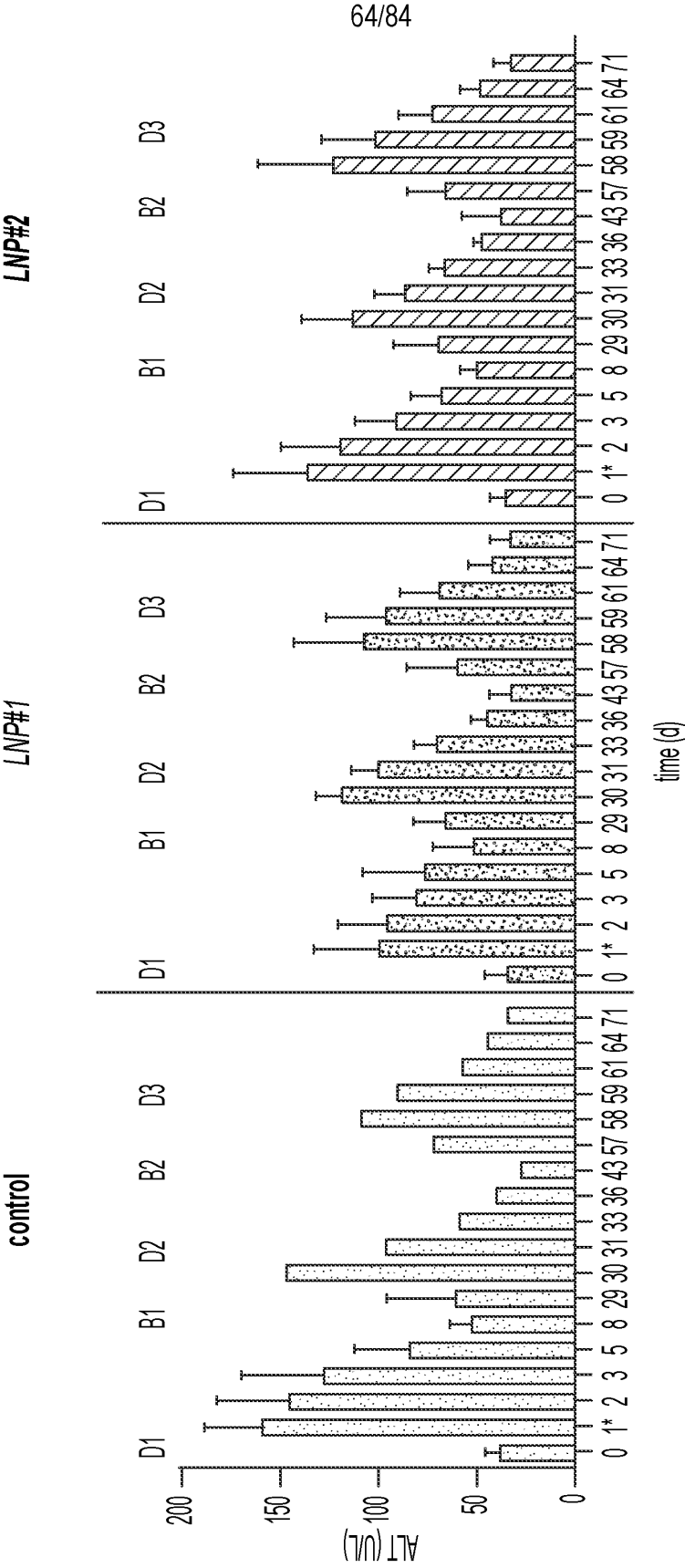


FIG. 47

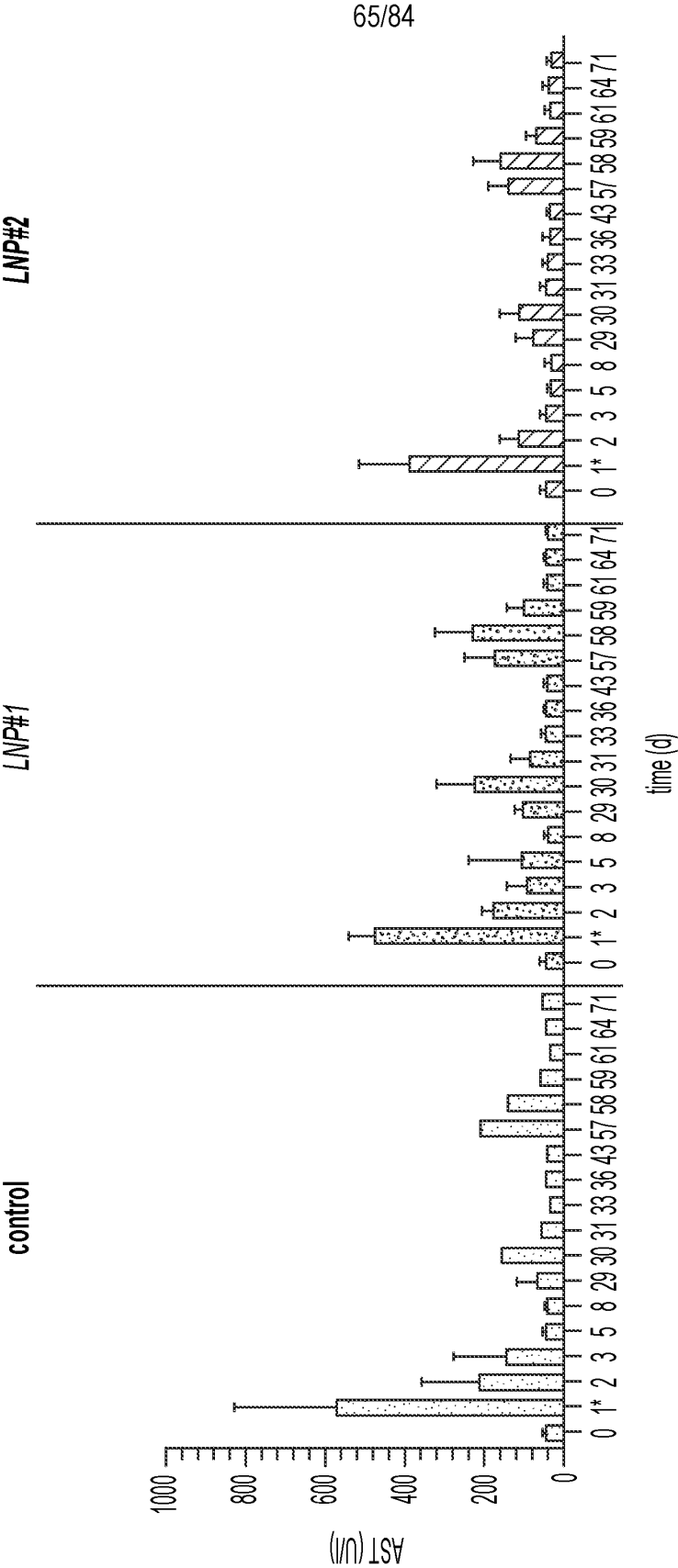


FIG. 47
(Continued)

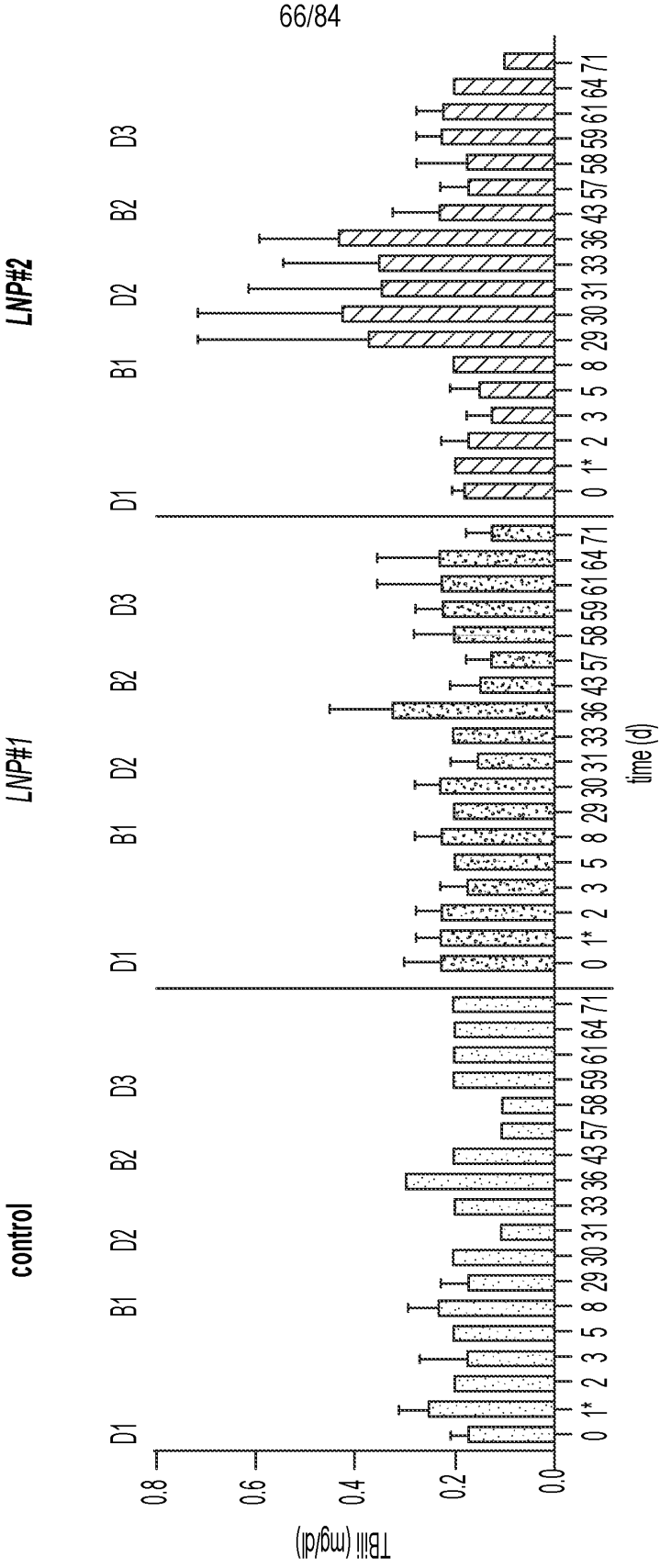


FIG. 47
(Continued)

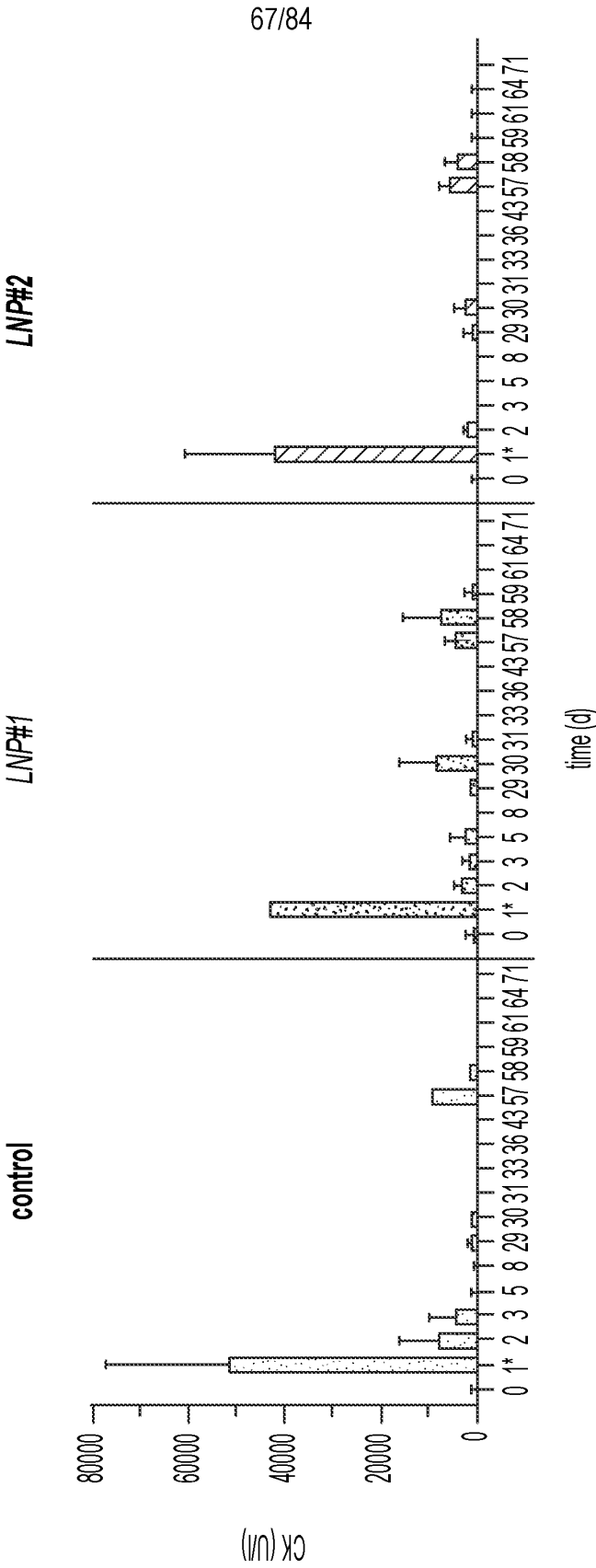


FIG. 47
(Continued)

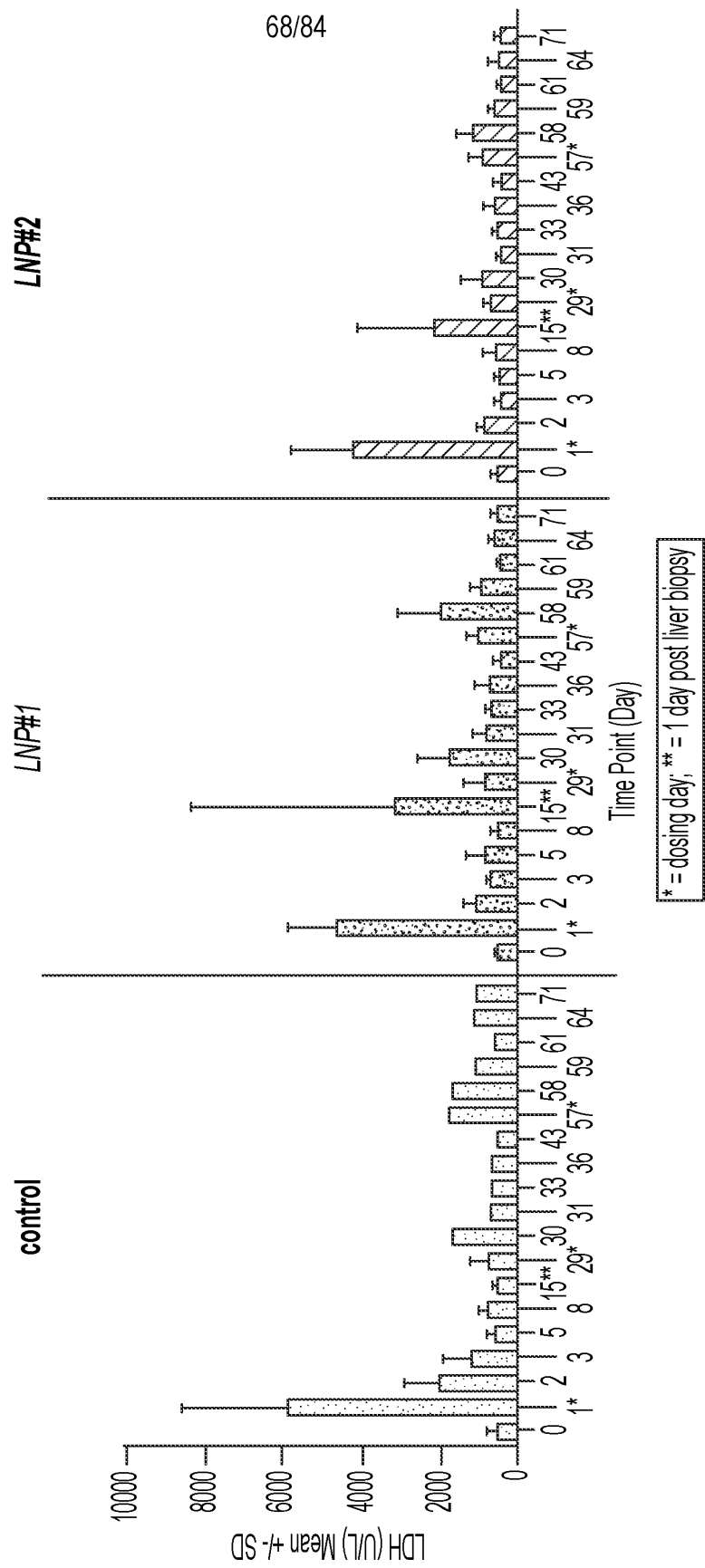


FIG. 48

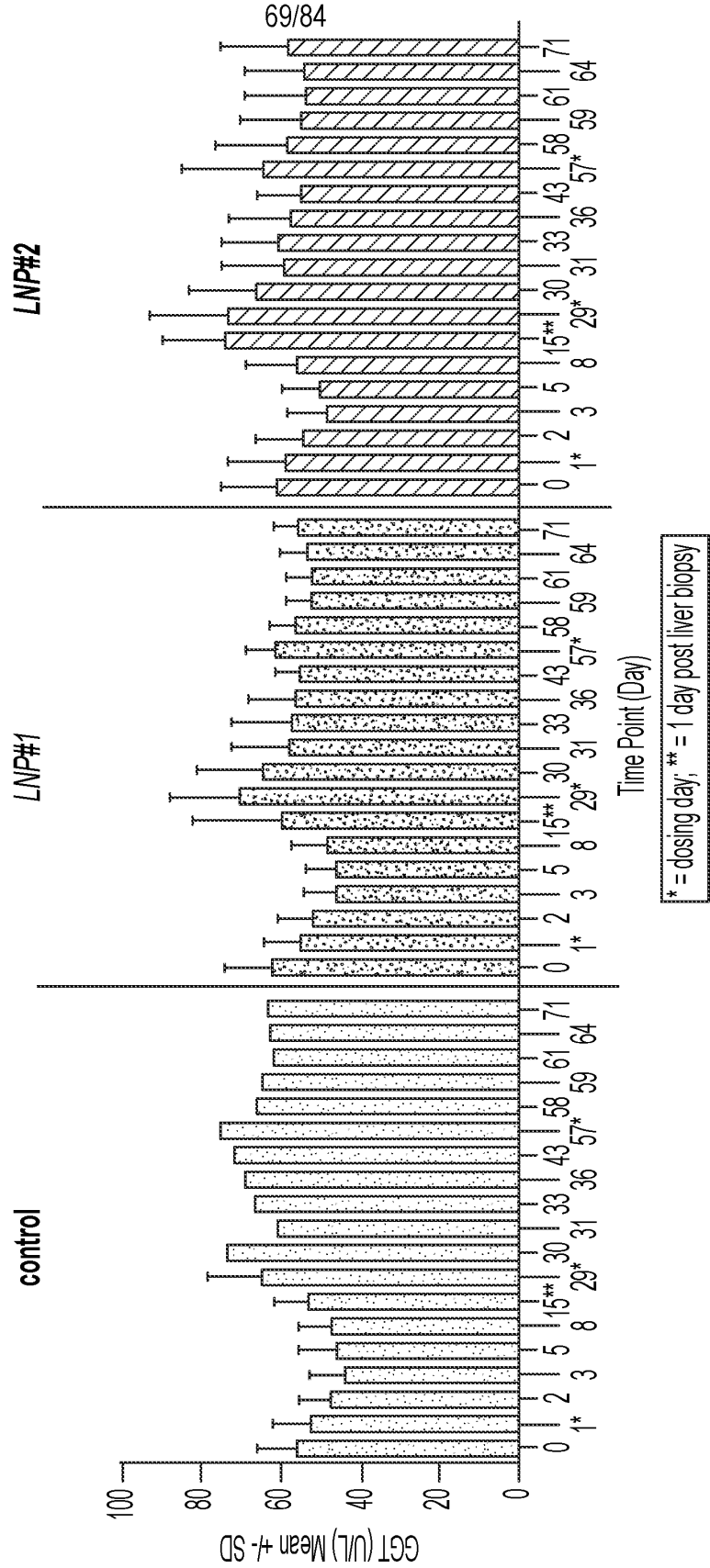


FIG. 48
(Continued)

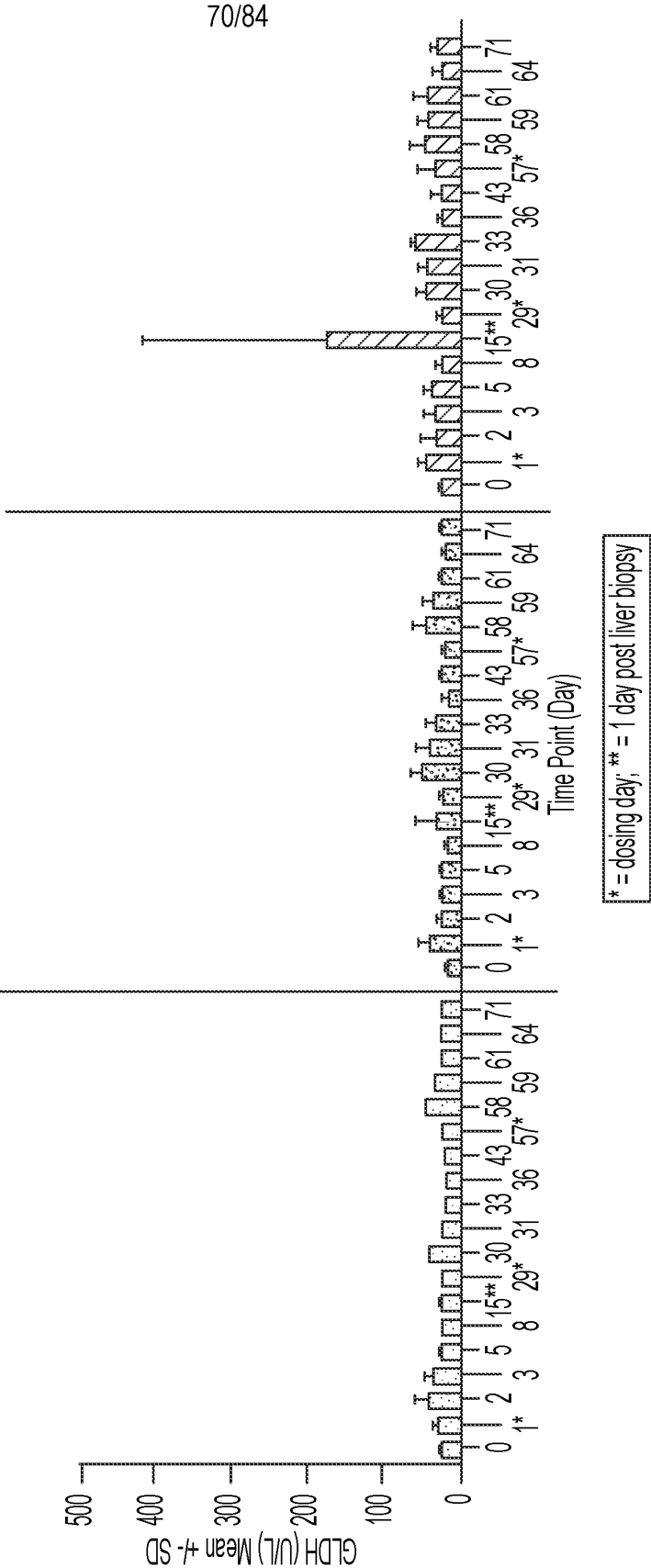


FIG. 48
(Continued)

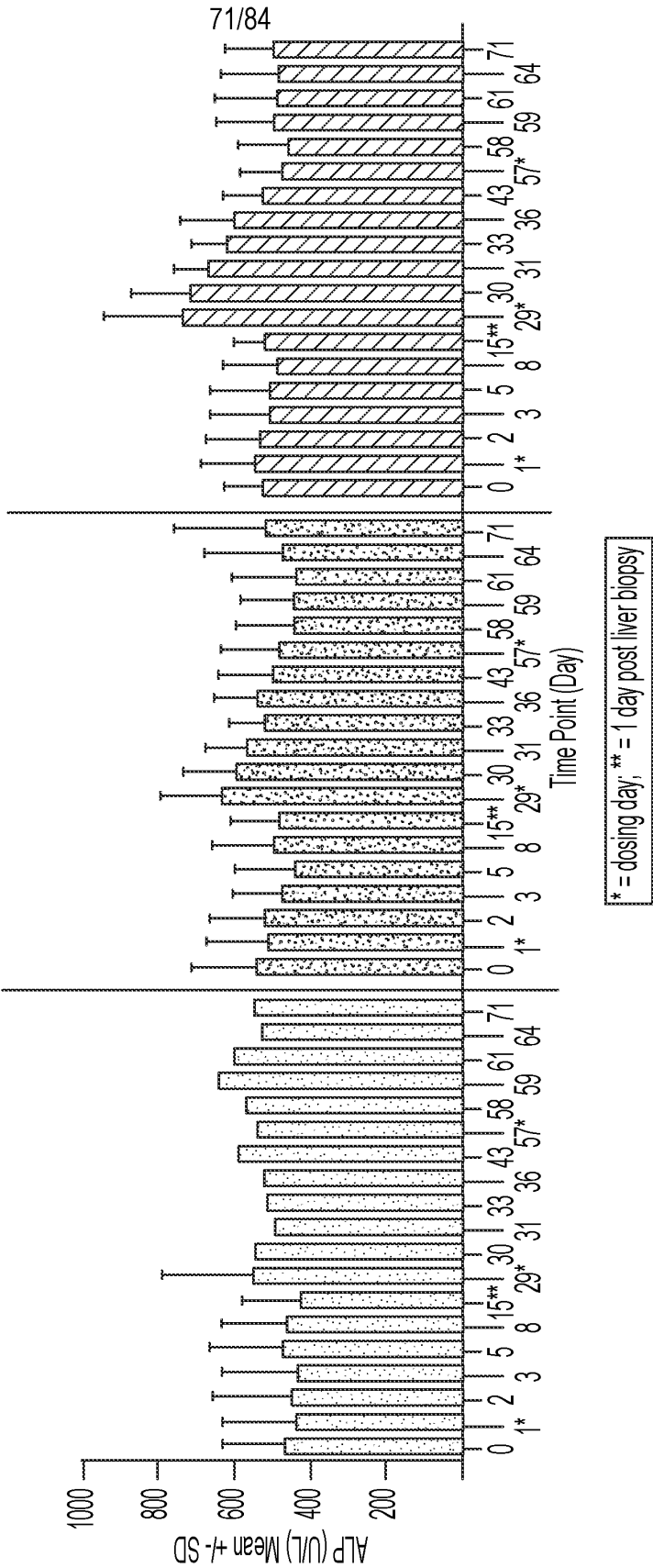


FIG. 48
(Continued)

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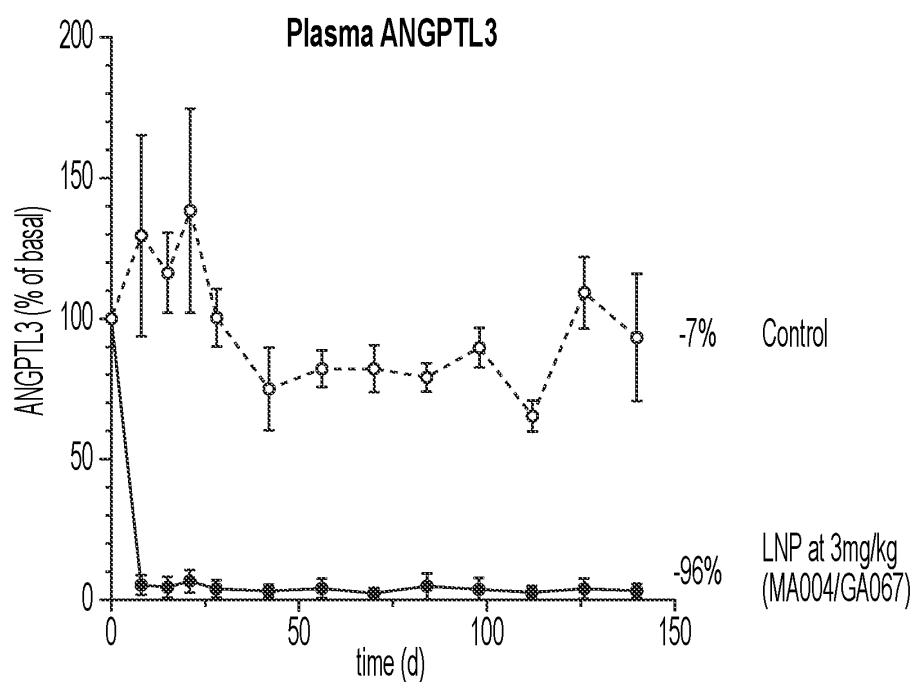


FIG. 49A

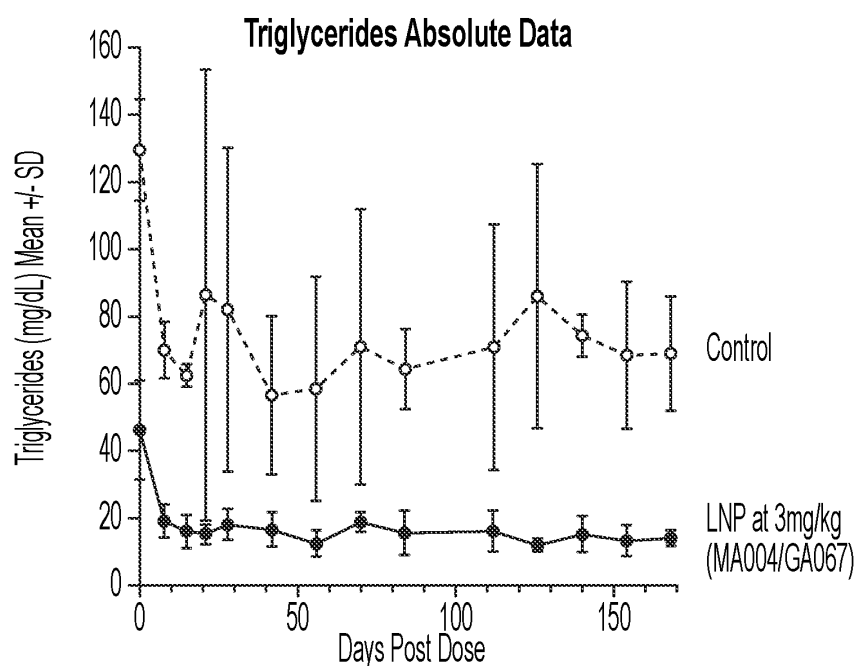


FIG. 49B

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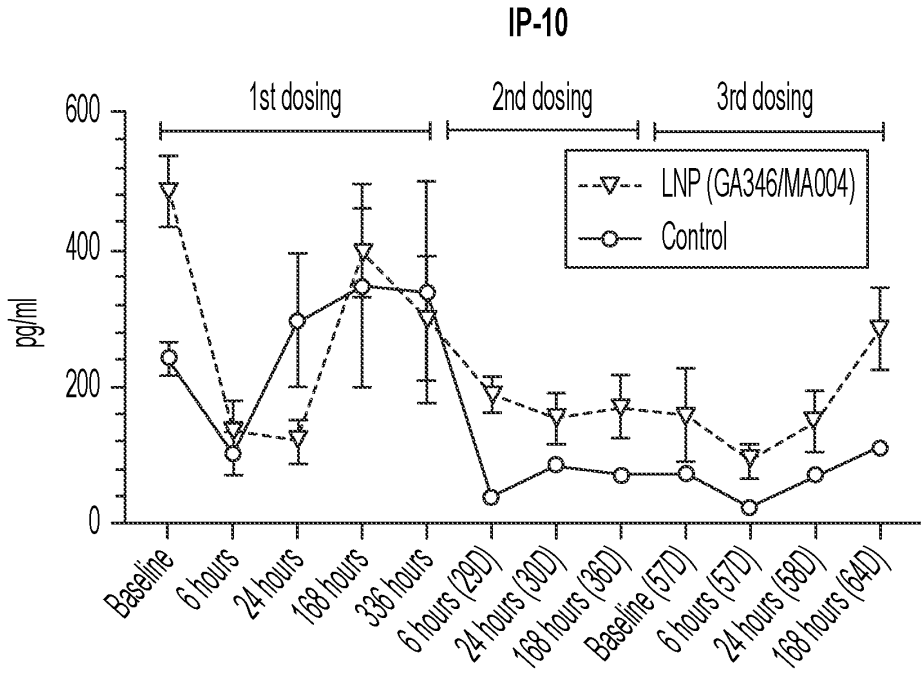


FIG. 50A

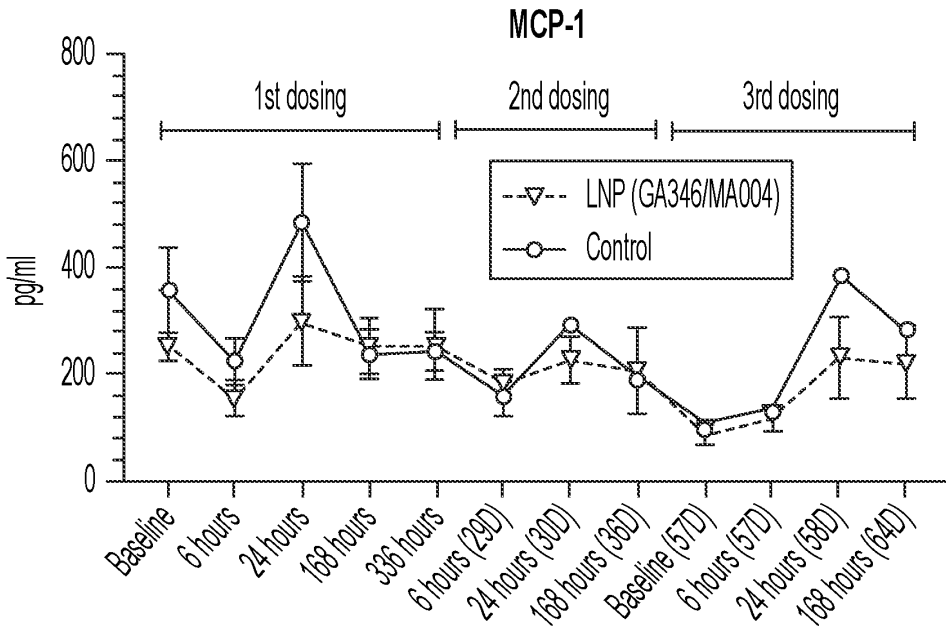


FIG. 50B

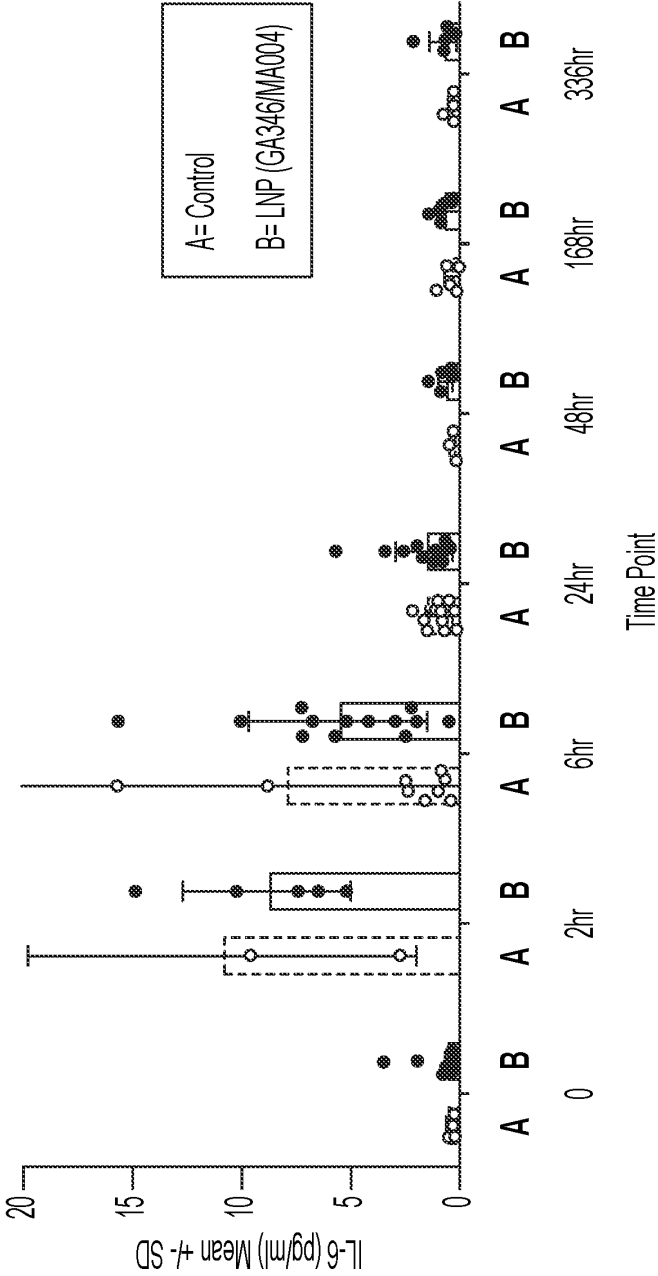


FIG. 50C

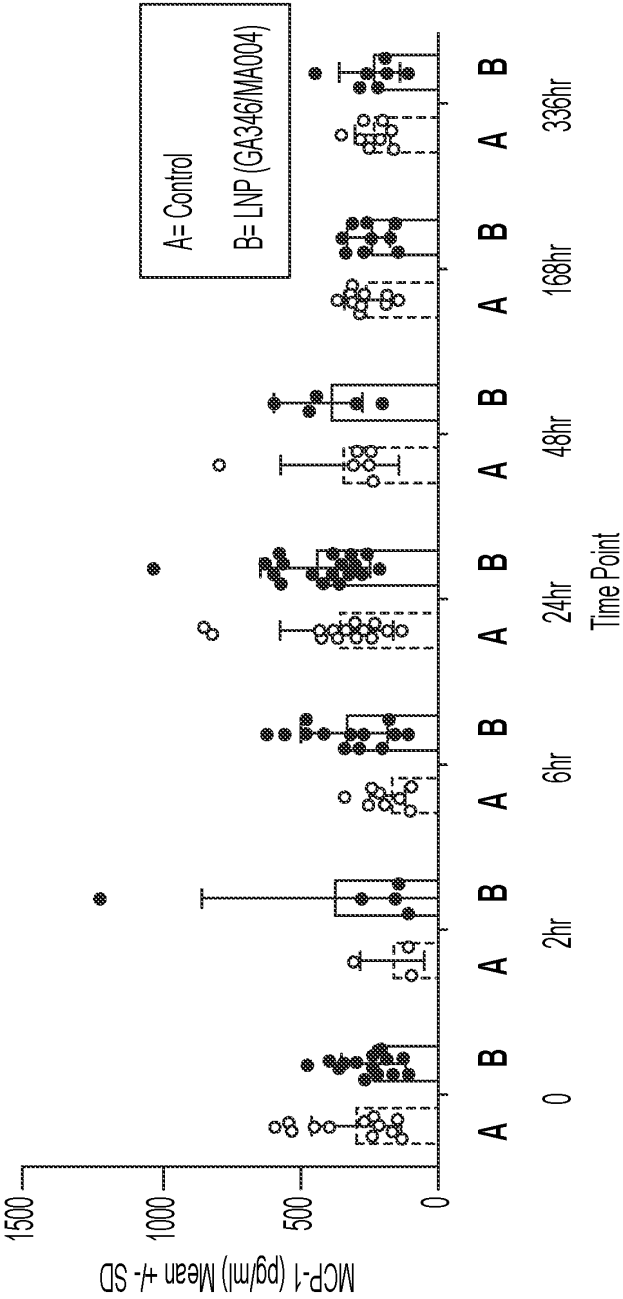


FIG. 50D

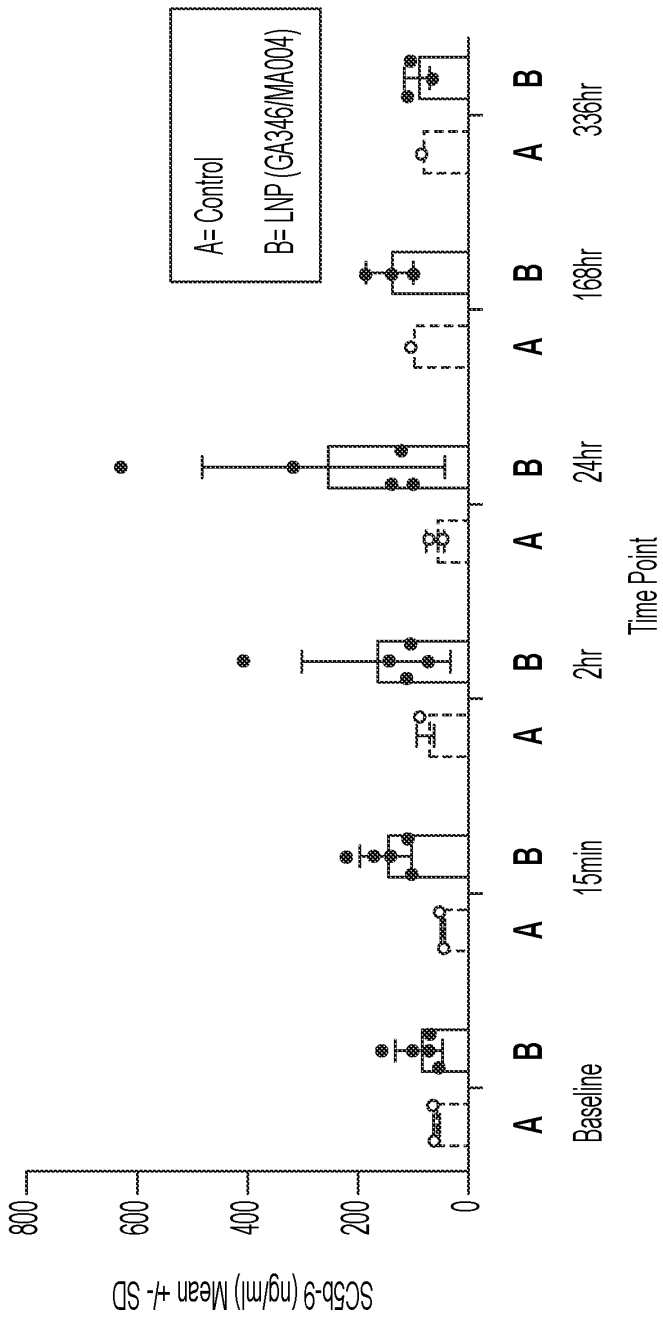


FIG. 50E

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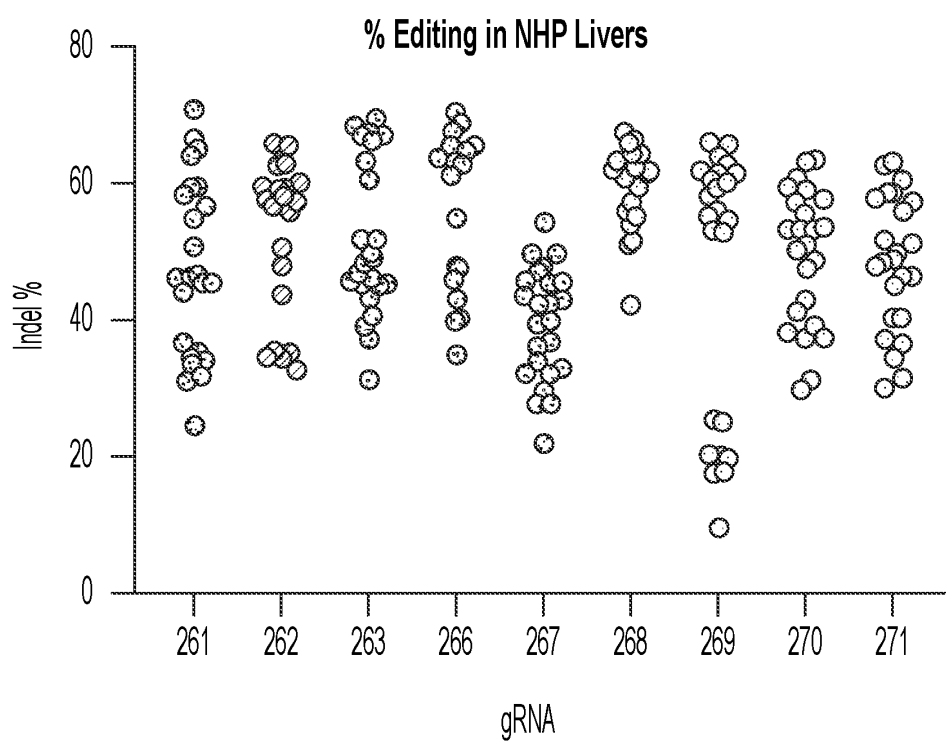


FIG. 51

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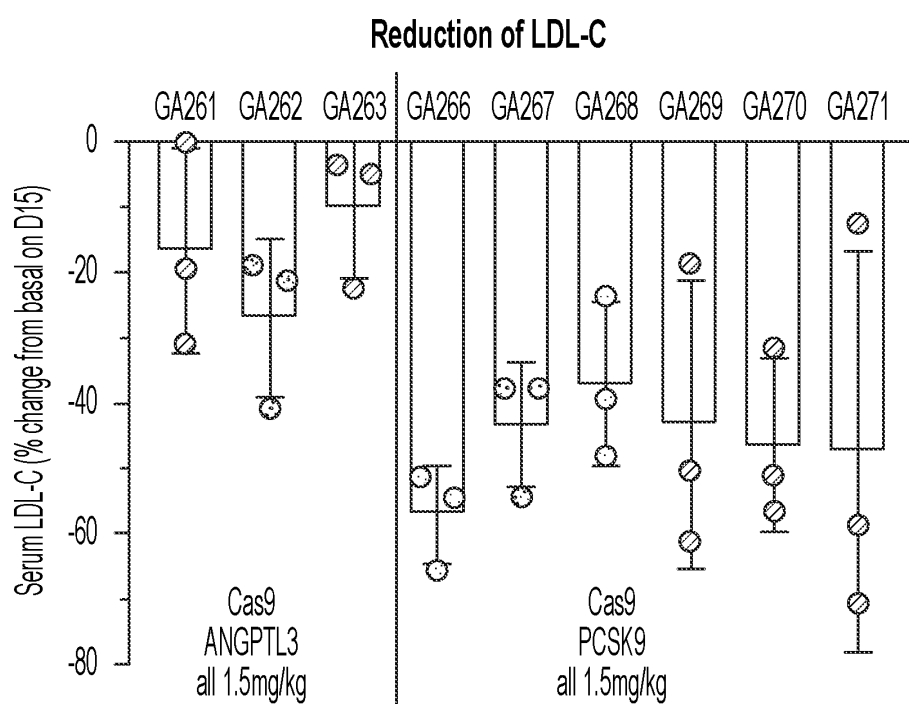


FIG. 52

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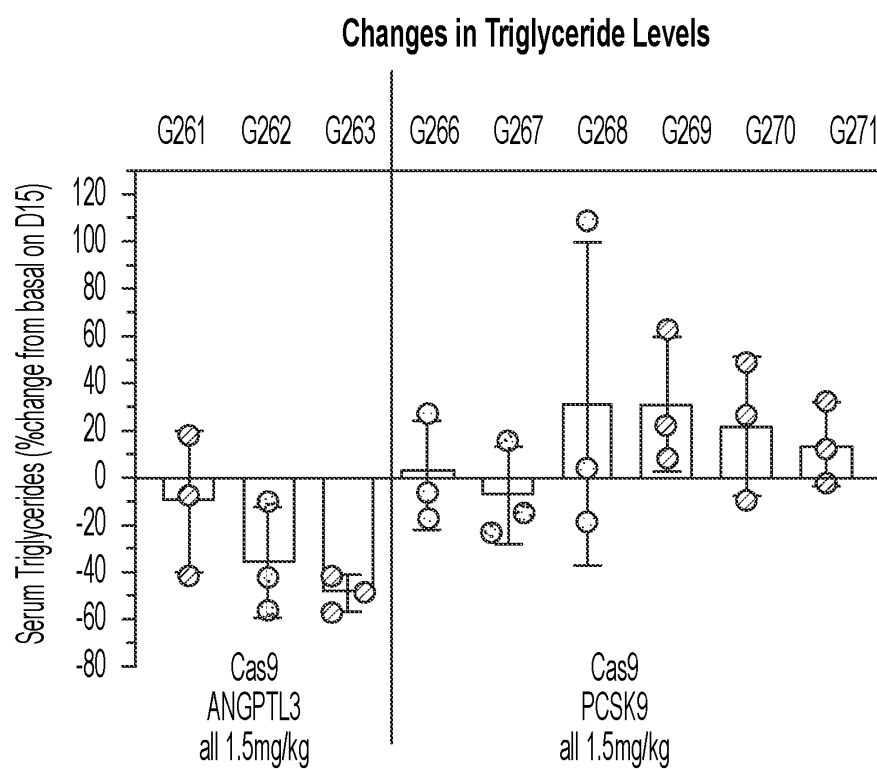


FIG. 53

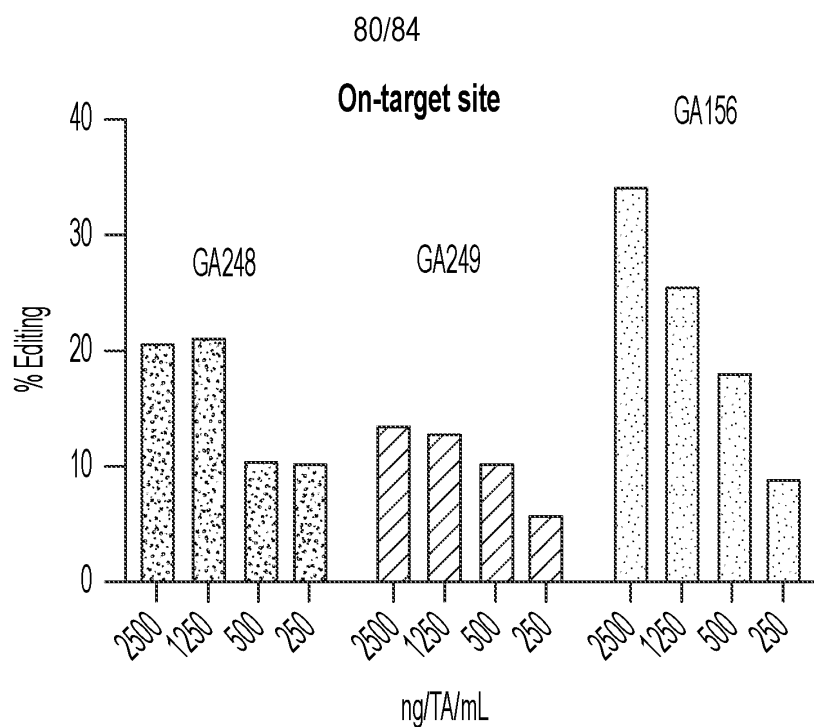


FIG. 54A

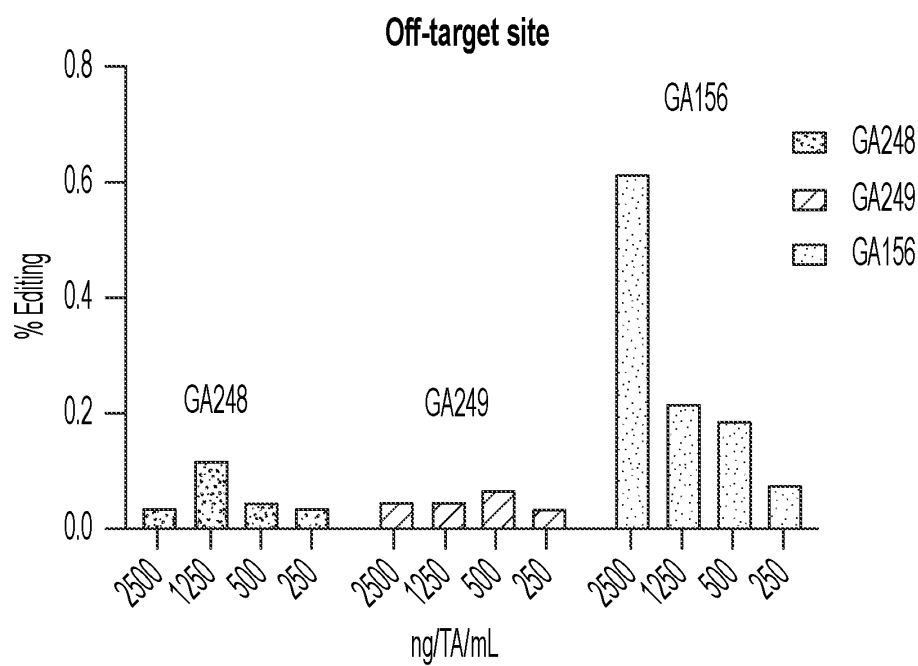


FIG. 54B

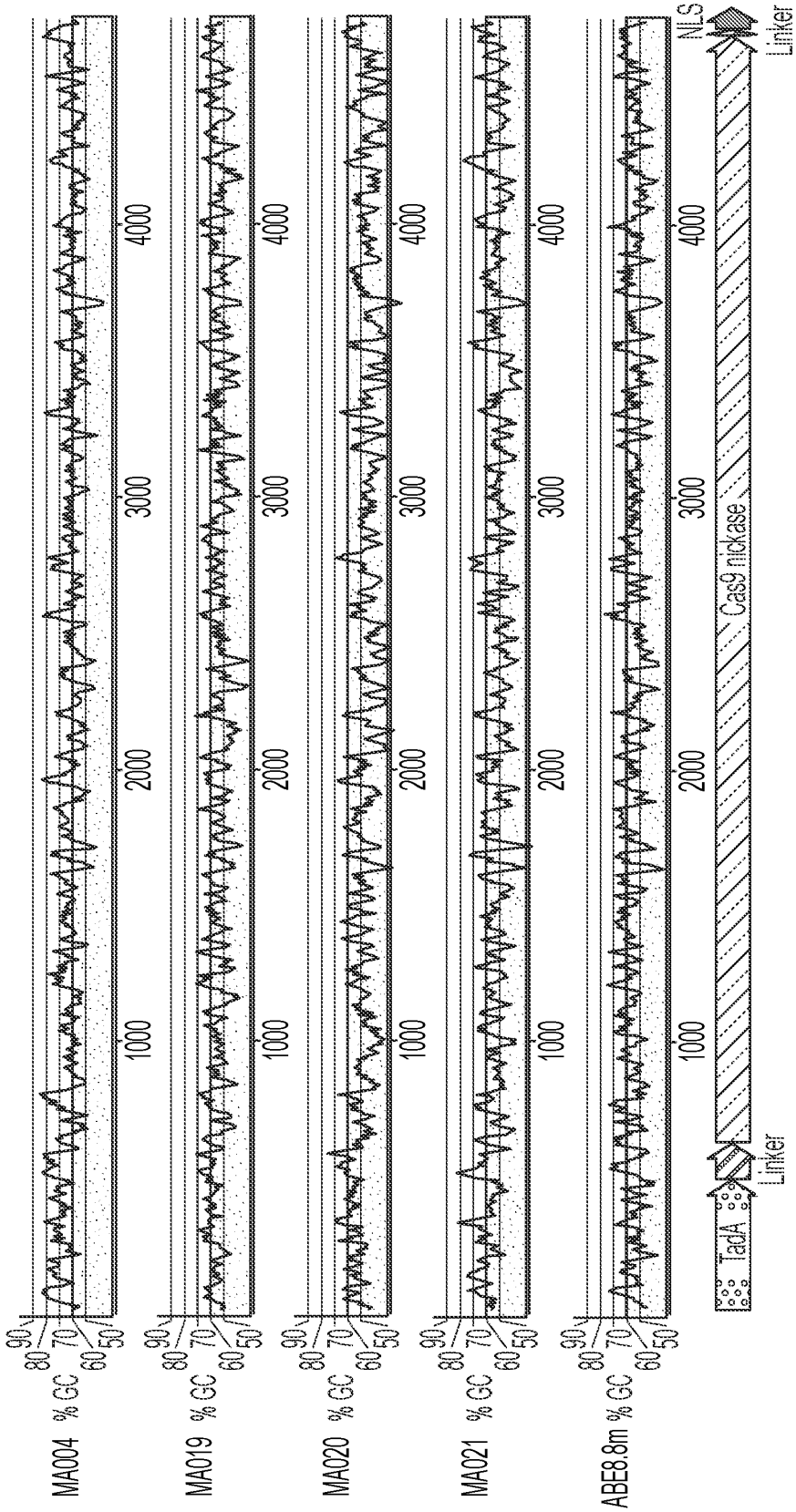
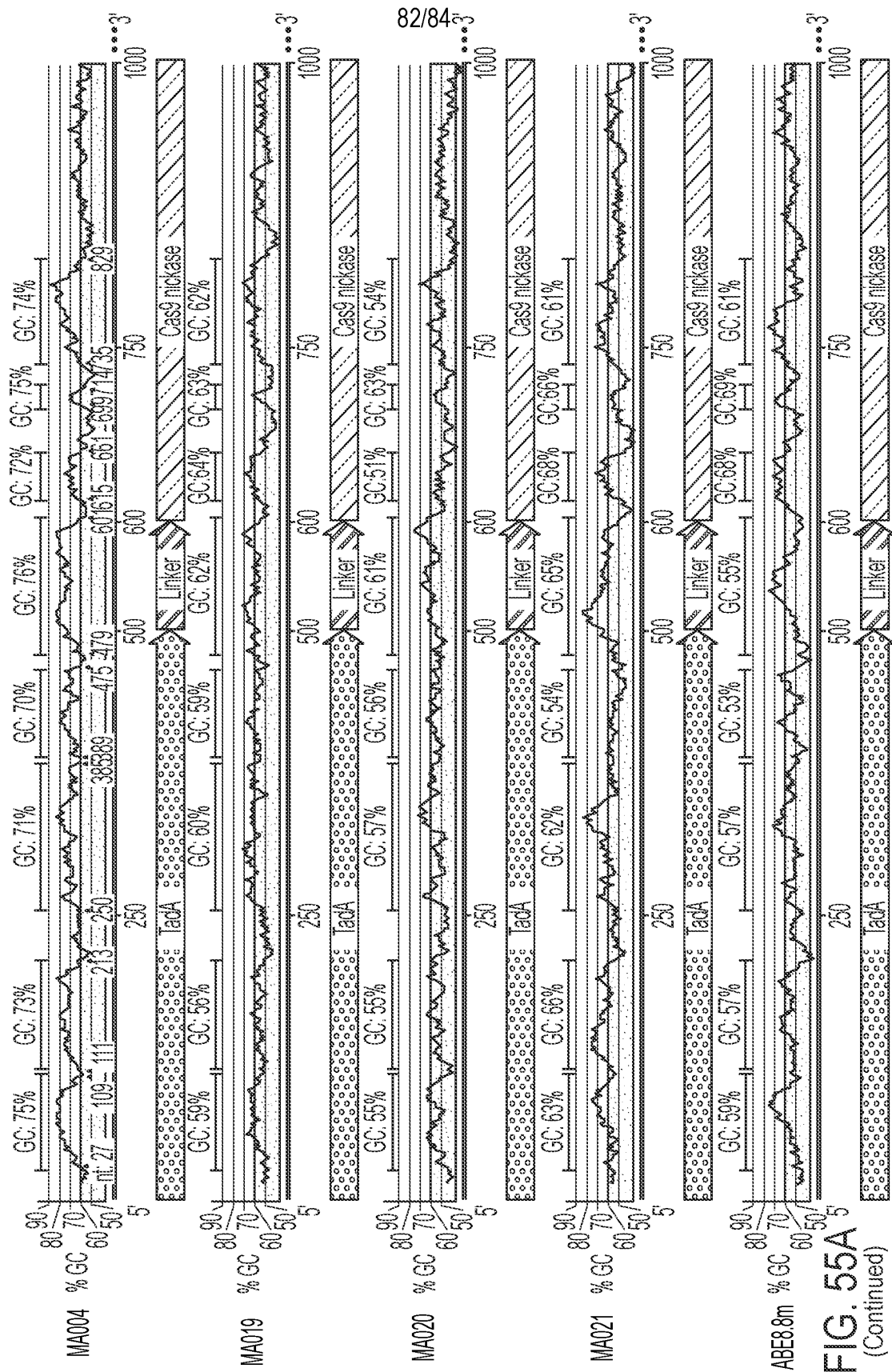
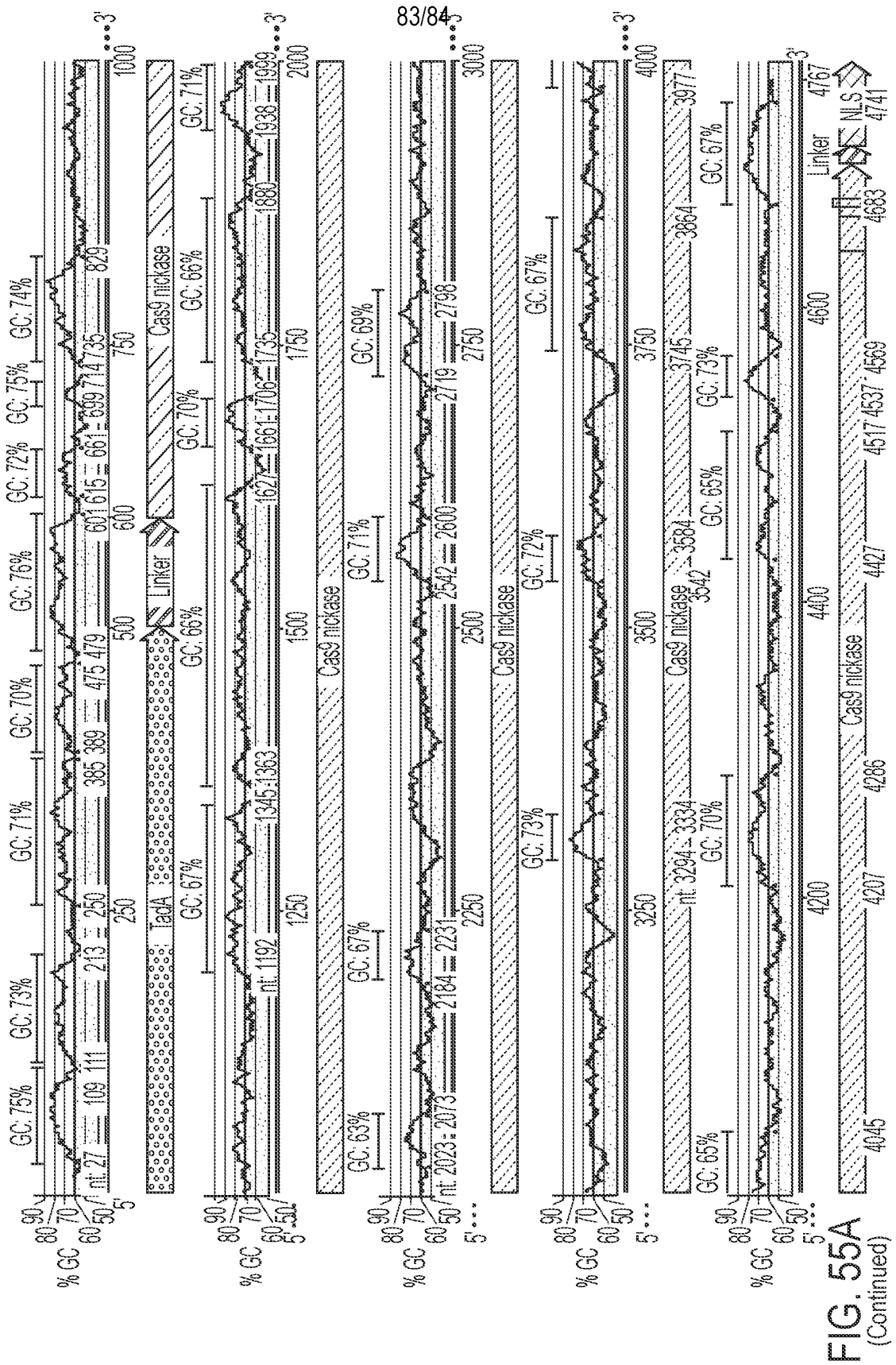


FIG. 55A





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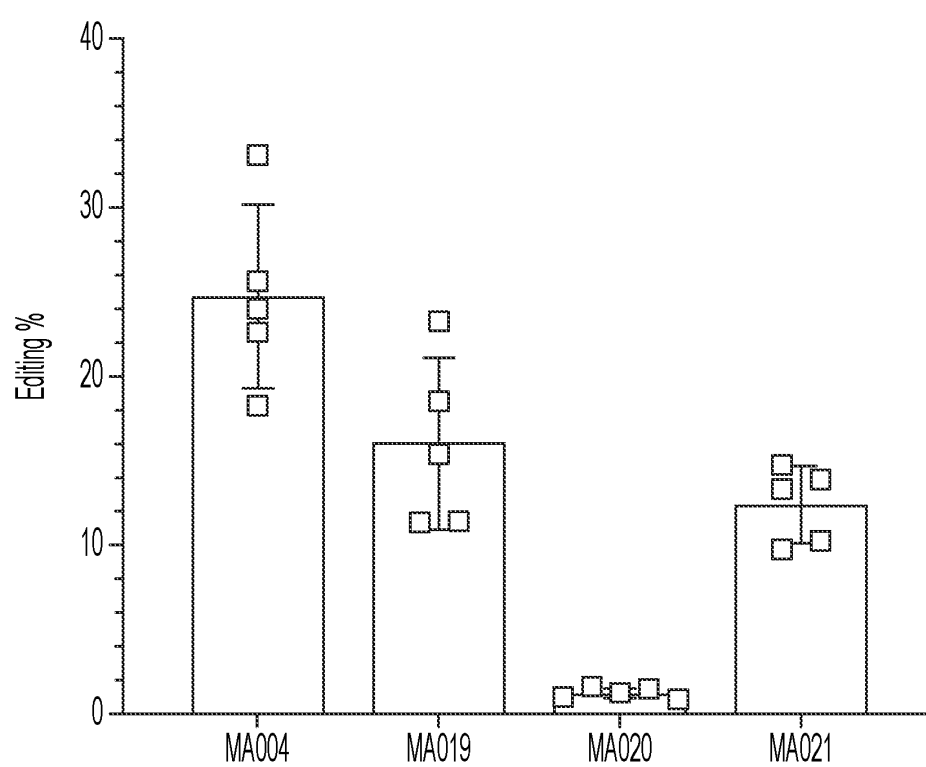


FIG. 55B