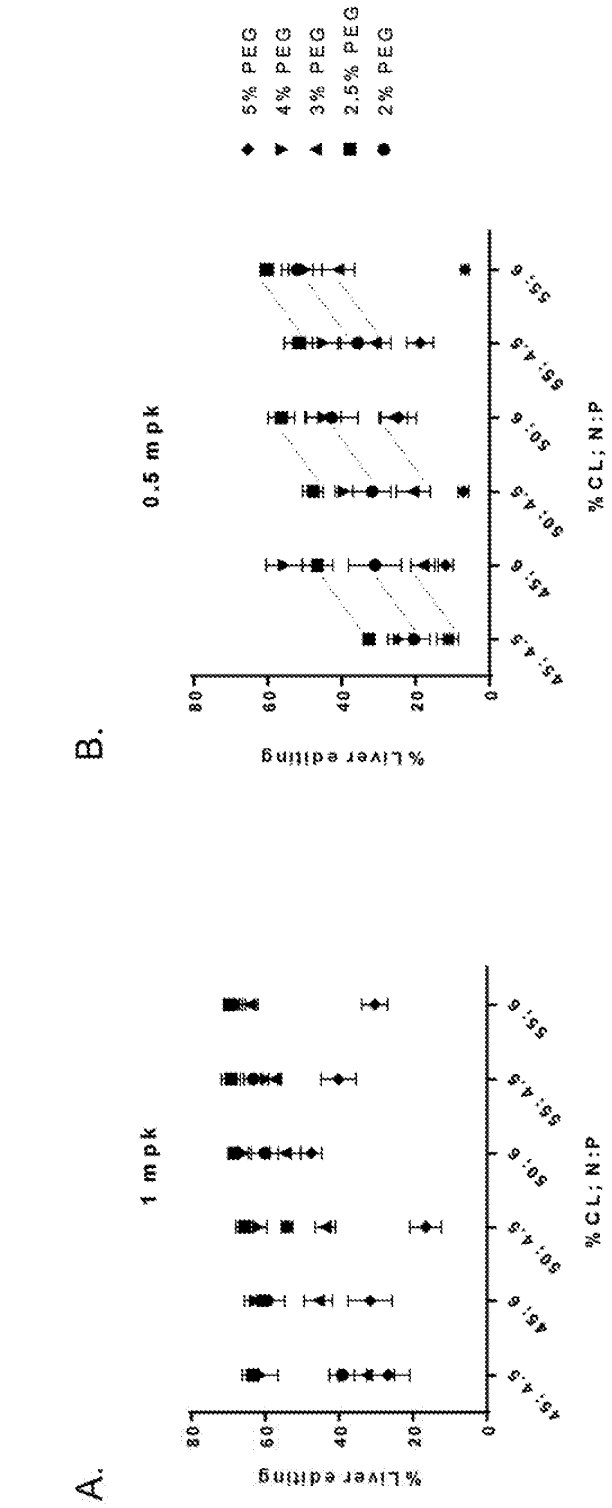
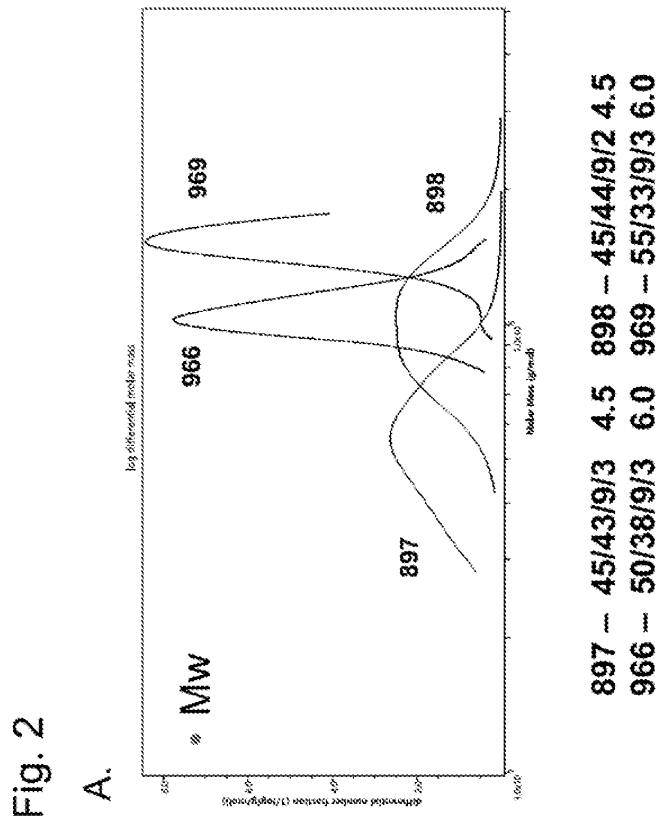

A.
1 mpk
% Liver editing
0
20
40
60
80
45:4.5
45:6
50:4.5
50:6
55:4.5
55:6
% CL; N:P
B.
0.5 mpk
% Liver editing
0
20
40
60
80
45:4.5
45:6
50:4.5
50:6
55:4.5
55:6
% CL; N:P
5% PEG
4% PEG
3% PEG
2.5% PEG
2% PEG

Fig. 1

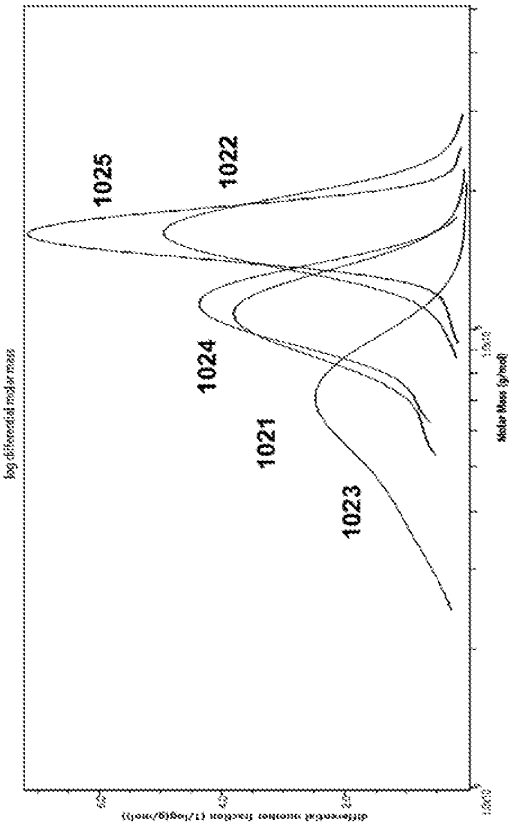
Fig. 2



897 – 45/43/9/3 4.5 898 – 45/44/9/2 4.5
966 – 50/38/9/3 6.0 969 – 55/33/9/3 6.0

Fig. 3

A.


log differential molar mass
differential molecular fraction (1/log(g/mol))
Molar Mass (g/mol)
1025
1022
1024
1021
1023

B.

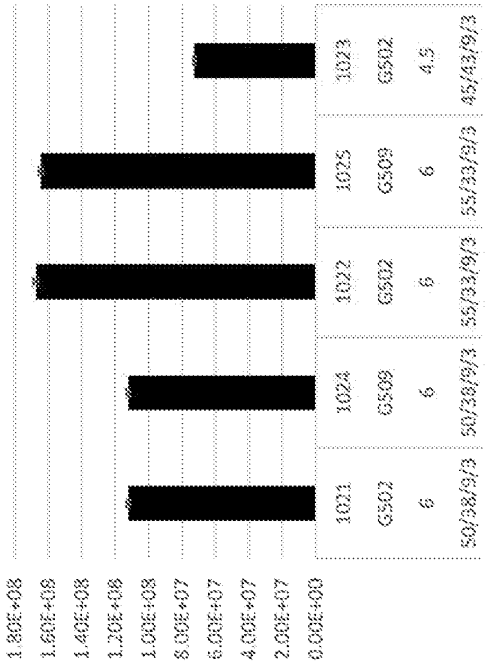
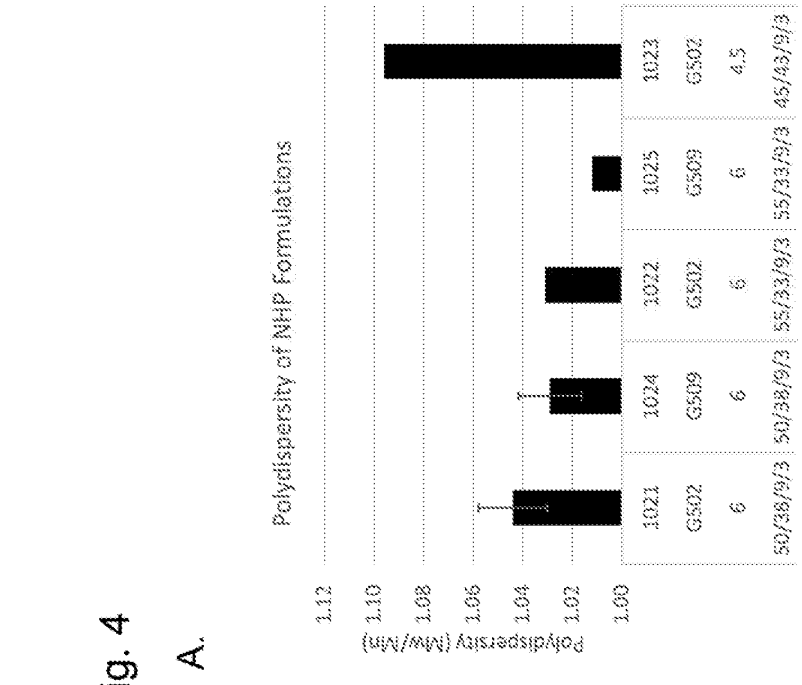

Average Molecular Weights of NHP Formulations
1.80E+08
1.60E+08
1.40E+08
1.20E+08
1.00E+08
8.00E+07
6.00E+07
4.00E+07
2.00E+07
0.00E+00
1021 1024 1022 1025 1023
G502 G509 G502 G509 G502
6 6 6 6 4.5
50/38/9/3 50/38/9/3 55/33/9/3 55/33/9/3 45/43/9/3

Fig. 4

A.


Polydispersity of NHP Formulations
Polydispersity (Mw/Mn)
1.12
1.10
1.08
1.06
1.04
1.02
1.00
1021 G502 6 50/38/9/3
1024 G509 6 50/38/9/3
1022 G502 6 55/33/9/3
1025 G509 6 55/33/9/3
1023 G502 4.5 45/43/9/3

B.

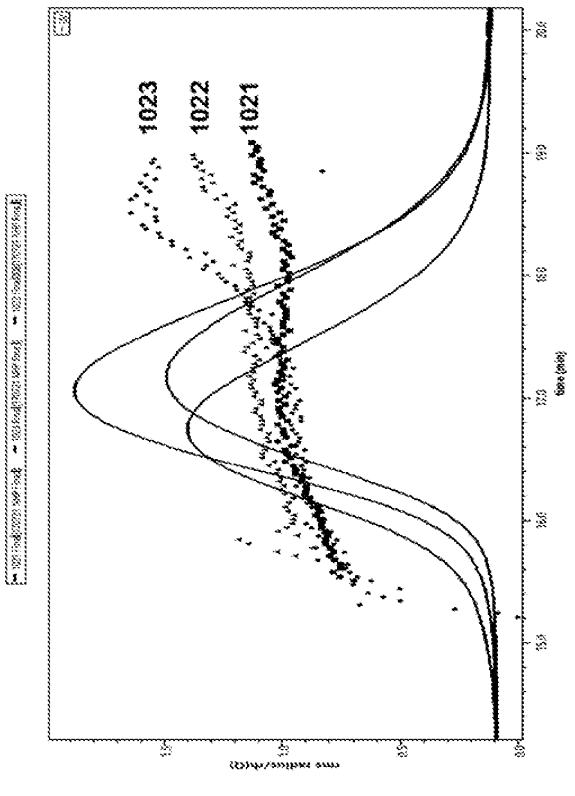

1023
1022
1021

Fig. 5

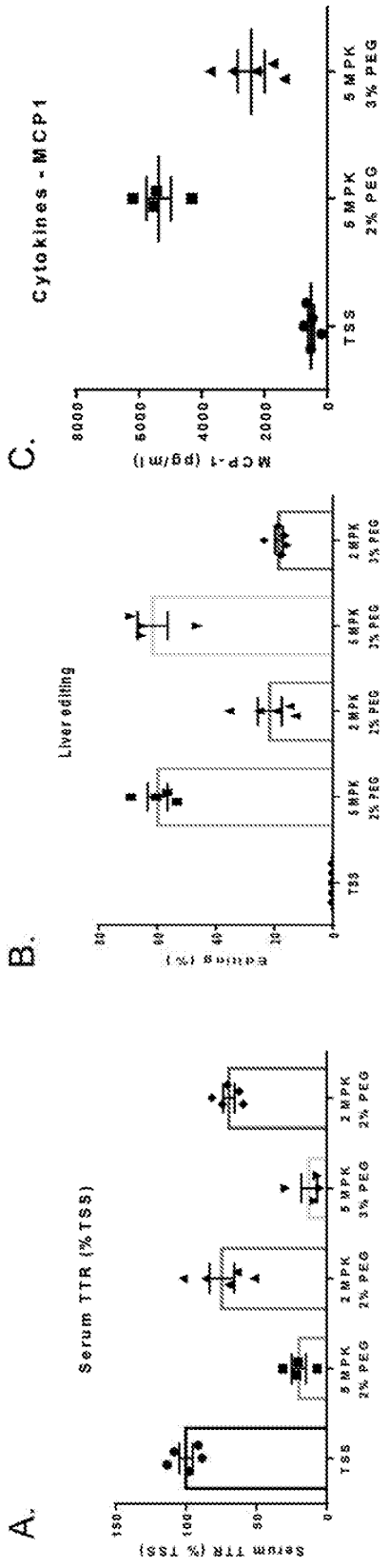
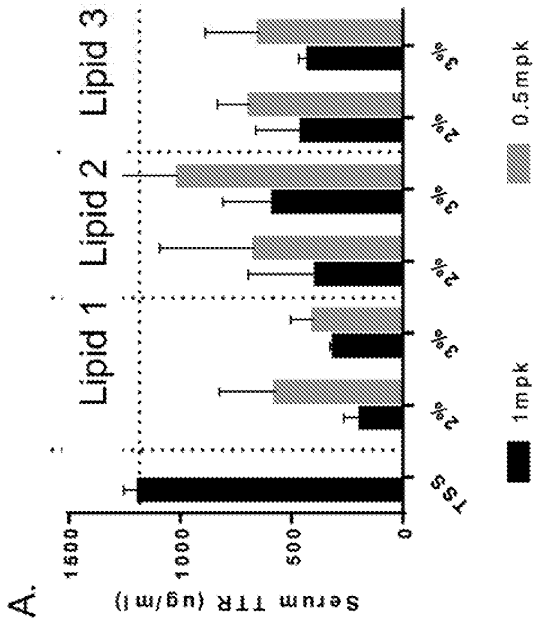
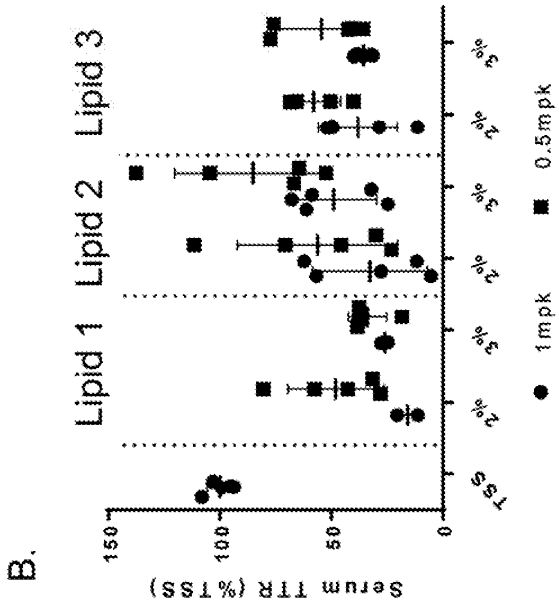

A.
Serum TTR (% TSS)
Serum TTR (% TSS)
150
100
50
0
TSS
2MPK 2% PEG
2MPK 2% PEG
5MPK 3% PEG
2MPK 2% PEG
B.
Liver editing
Editing (%)
80
60
40
20
0
TSS
5MPK 2% PEG
2MPK 2% PEG
5MPK 3% PEG
2MPK 3% PEG
C.
Cytokines - MCP1
MCP-1 (pg/ml)
8000
6000
4000
2000
0
TSS
5 MPK 2% PEG
5 MPK 3% PEG

Fig. 6


A.
Serum TTR (ug/ml)
1500
1000
500
0
Lipid 1
Lipid 2
Lipid 3
TSS
2%
3%
2%
3%
2%
3%
1mpk
0.5mpk


B.
Serum TTR (%TSS)
150
100
50
0
Lipid 1
Lipid 2
Lipid 3
TSS
2%
3%
2%
3%
2%
3%
1mpk
0.5mpk

C.

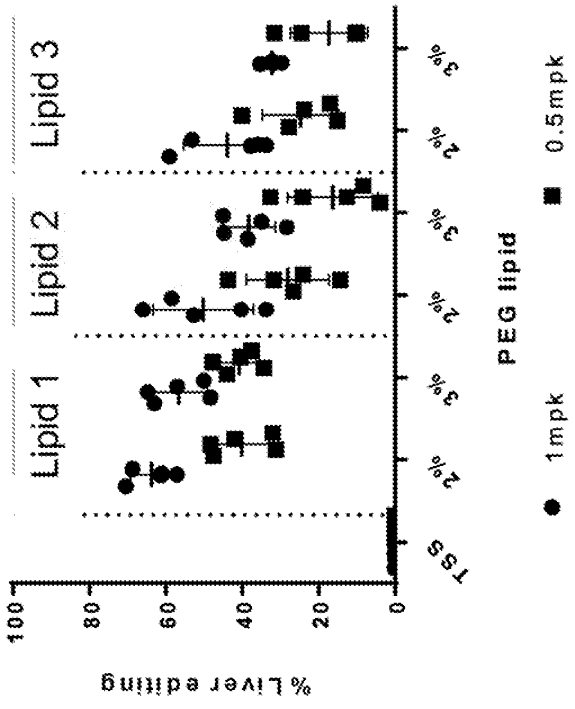
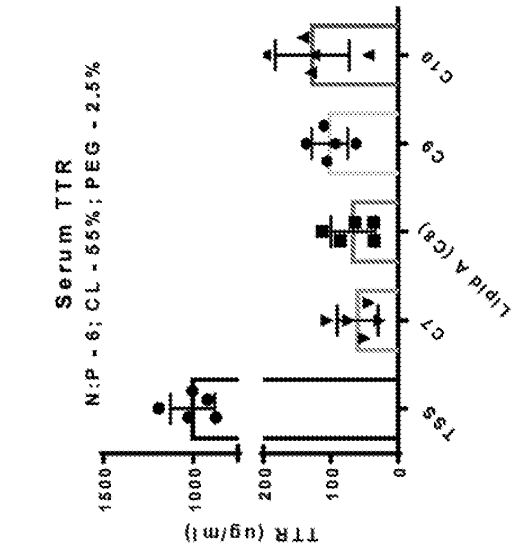
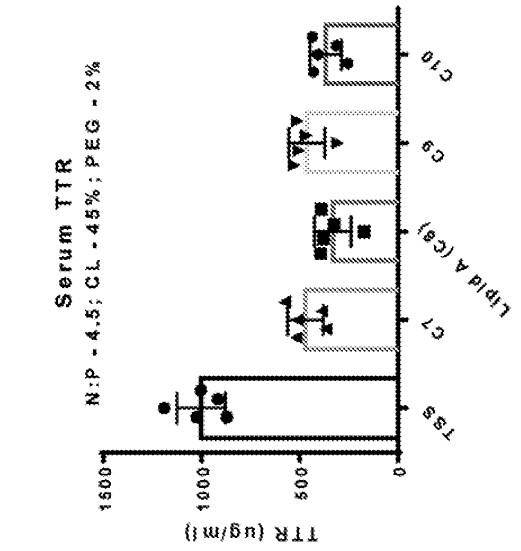

% Liver editing
100
80
60
40
20
0
TSS
2%
3%
2%
3%
2%
3%
Lipid 1
Lipid 2
Lipid 3
PEG lipid
1mpk
0.5mpk

Fig. 6

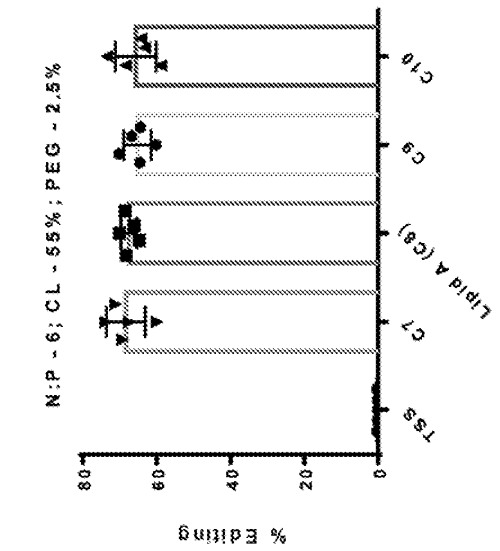

Serum TTR
N:P - 6; CL - 55%; PEG - 2.5%
TTR (ug/ml)
1500
1000
200
100
0
TS5
C7
Lipid A (C8)
C9
C10

B.


Serum TTR
N:P - 4.5; CL - 45%; PEG - 2%
TTR (ug/ml)
1500
1000
500
0
TS5
C7
Lipid A (C8)
C9
C10

A.

Fig. 7


D.
N:P - 6; CL - 55%; PEG - 2.5%
% Editing
0
20
40
60
80
TSS
C7
Lipid A (C8)
C9
C10

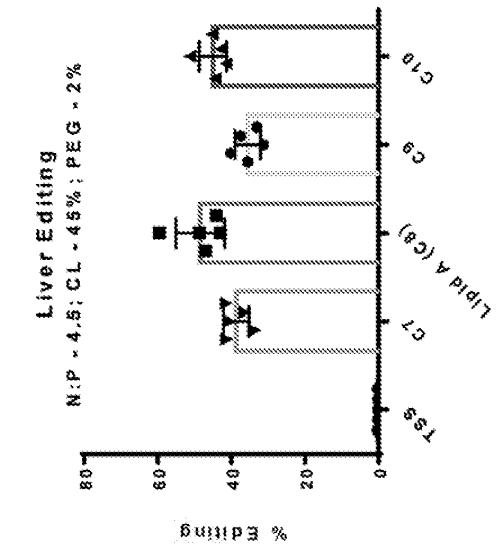

C.
Liver Editing
N:P - 4.5; CL - 45%; PEG - 2%
% Editing
0
20
40
60
80
TSS
C7
Lipid A (C8)
C9
C10

Fig. 7

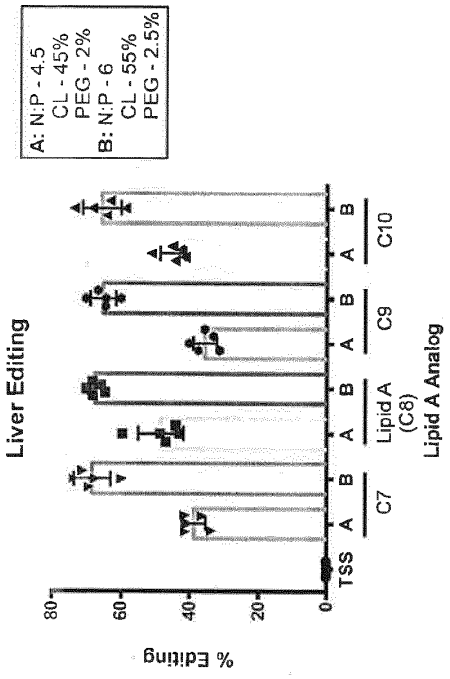
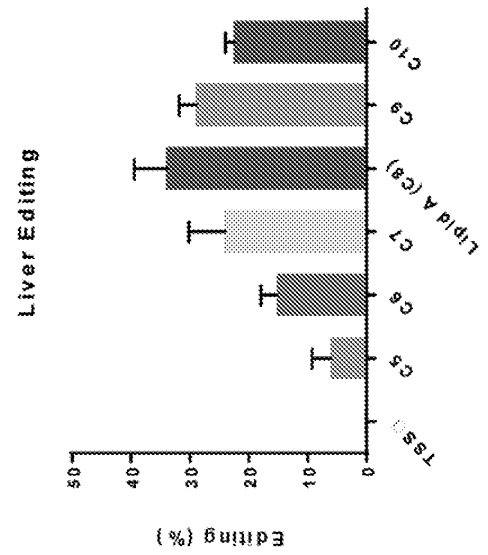
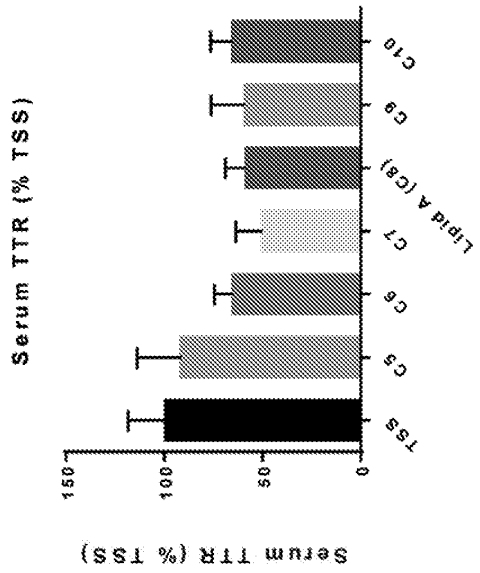

A: N:P - 4.5
CL - 45%
PEG - 2%
B: N:P - 6
CL - 55%
PEG - 2.5%
Liver Editing
% Editing
0
20
40
60
80
TSS
A
B
C7
A
B
Lipid A (C8)
A
B
C9
A
B
C10
Lipid A Analog

Fig. 7 E.


Liver Editing
Editing (%)
50
40
30
20
10
0
TSS
C5
C6
C7
Lipid A (C8)
C9
C10

G.


Serum TTR (% TSS)
Serum TTR (% TSS)
150
100
50
0
TSS
C5
C6
C7
Lipid A (C8)
C9
C10

F.

Fig. 7

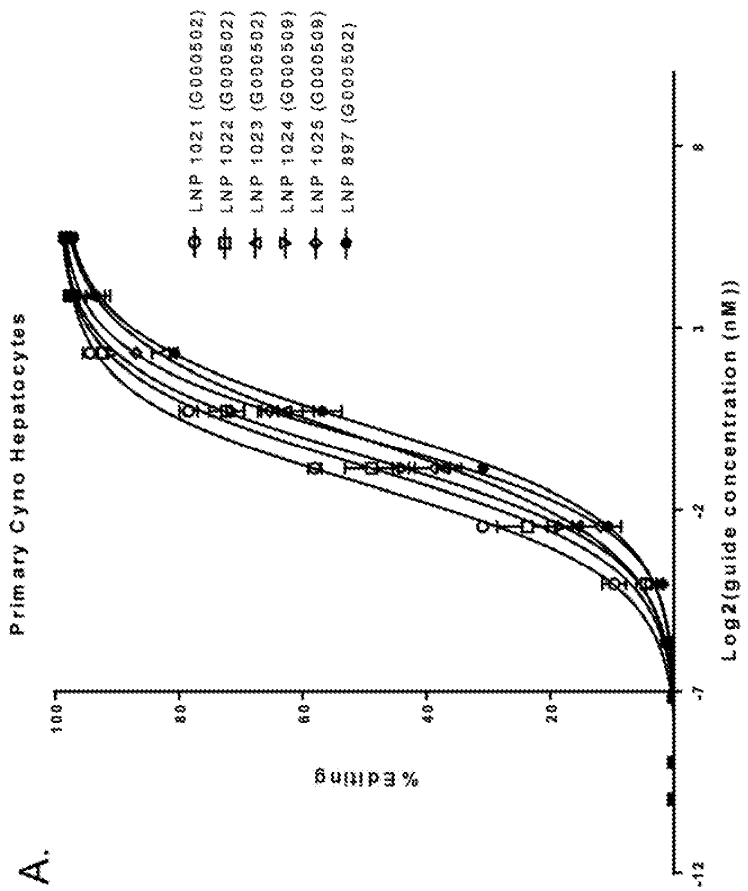

A.
Primary Cyno Hepatocytes
LNP 1021 (G000502)
LNP 1022 (G000502)
LNP 1023 (G000502)
LNP 1024 (G000509)
LNP 1025 (G000508)
LNP 897 (G000502)
% Editing
100
80
60
40
20
-12
-7
-2
3
8
Log2(guide concentration (nM))

Fig. 8

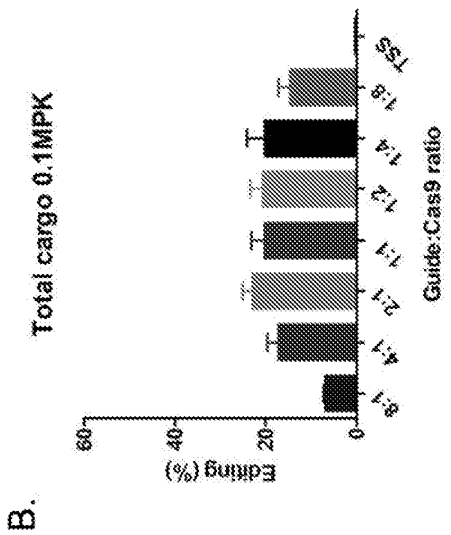
Fig. 8B

Set1

log(agonist) vs. response -- Variable slope (four parameters) [2]						
LNP#	**LNP1021**	**LNP1022**	**LNP1023**	**LNP1024**	**LNP1025**	**LNP897**
Best-fit values	G000502-lot1-50 cationic	G000502-lot1-55 cationic	G000502-lot2-45 cationic	G000509-udep-50Cationic	G000509-udep-55Cationic	G000502-regular mRNA
Bottom	-0.6786	-0.6888	-0.7413	-0.4768	-0.3509	-0.394
Top	98.76	99.54	99.84	99.62	99.25	99.25
EC50	0.3906	0.5549	0.9429	0.6746	0.9373	1.233

Set2

log(agonist) vs. response -- Variable slope (four parameters) [2]						
LNP#	**LNP1021**	**LNP1022**	**LNP1023**	**LNP1024**	**LNP1025**	**LNP897**
Best-fit values	G000502-lot1-50 cationic	G000502-lot1-55 cationic	G000502-lot2-45 cationic	G000509-udep-50Cationic	G000509-udep-55Cationic	G000502-regular mRNA
Bottom	-0.8024	-0.3726	-0.474	-0.2294	-0.2362	-0.3096
Top	98.72	98.67	100.2	99.41	99.66	98.79
EC50	0.3733	0.5413	0.8982	0.63	0.9767	1.242


B.
Total cargo 0.1MPK
Editing (%)
0
20
40
60
8:1
4:1
2:1
1:1
1:2
1:4
1:8
TSS
Guide:Cas9 ratio

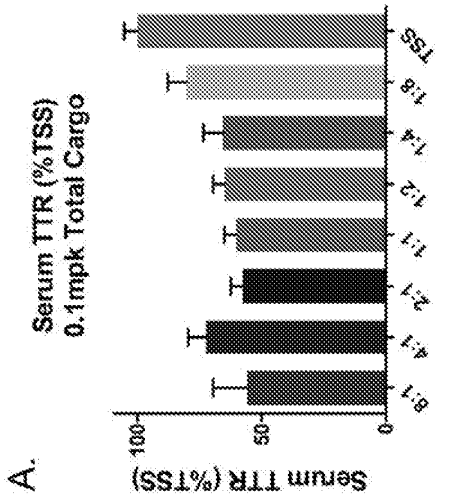
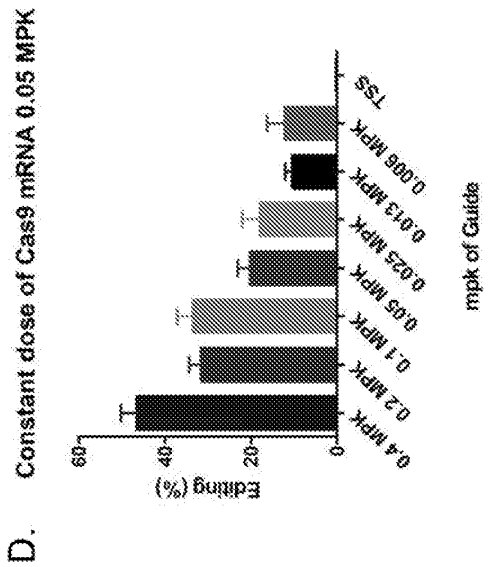

A.
Serum TTR (%TSS)
0.1mpk Total Cargo
Serum TTR (%TSS)
0
50
100
8:1
4:1
2:1
1:1
1:2
1:4
1:8
TSS

Fig. 9


D.
Constant dose of Cas9 mRNA 0.05 MPK
Editing (%)
60
40
20
0
0.4 MPK
0.2 MPK
0.1 MPK
0.05 MPK
0.025 MPK
0.013 MPK
0.006 MPK
TSS
mpk of Guide

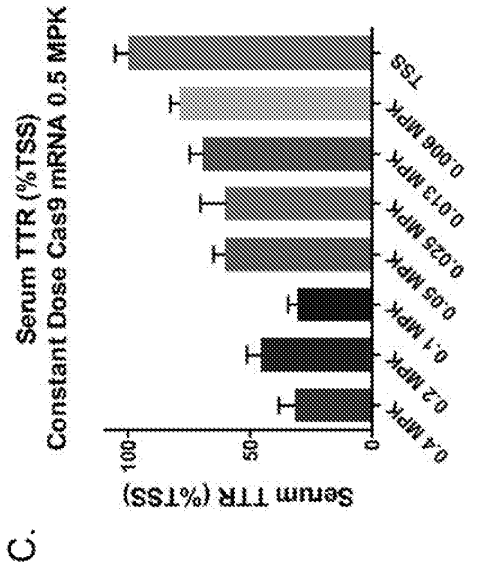

C.
Serum TTR (%TSS)
Constant Dose Cas9 mRNA 0.5 MPK
Serum TTR (%TSS)
100
50
0
0.4 MPK
0.2 MPK
0.1 MPK
0.05 MPK
0.025 MPK
0.013 MPK
0.006 MPK
TSS

Fig. 9

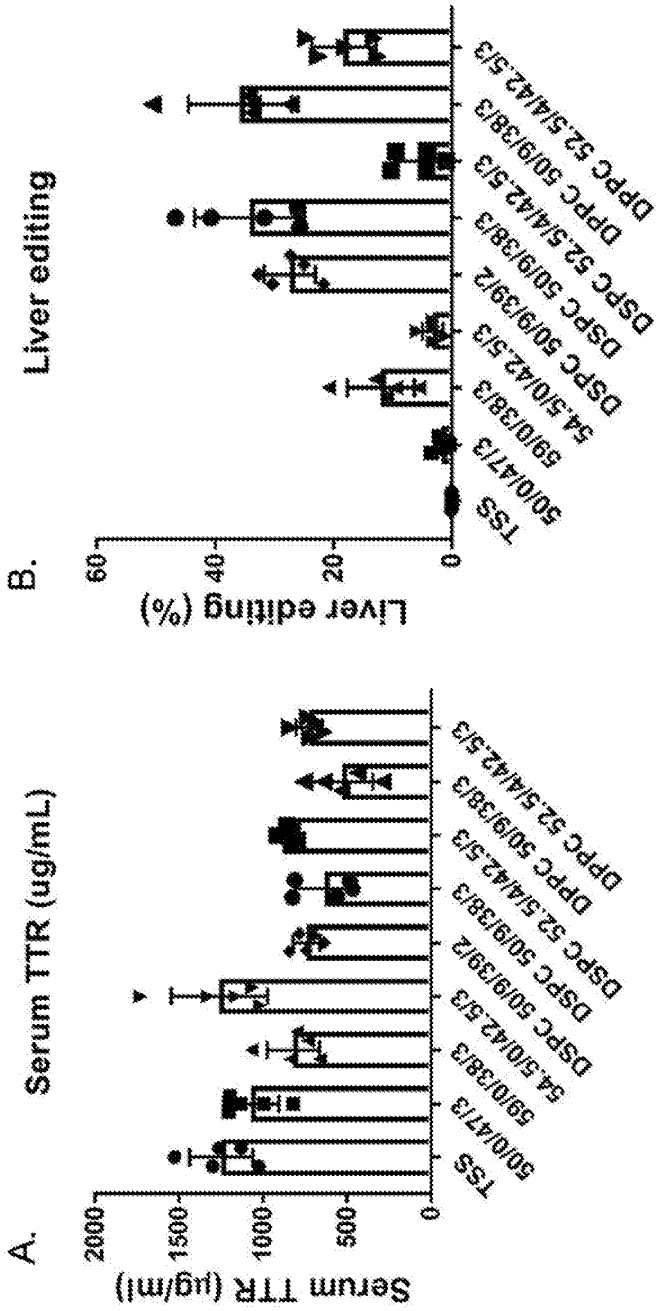

A.
Serum TTR (ug/mL)
2000
1500
1000
500
0
TSS
50/0/47/3
59/0/38/3
54.5/0/42.5/3
DSPC 50/9/39/2
DSPC 52.5/9/38/3
DSPC 54/4/42.5/3
DPPC 50/9/38/3
DPPC 52.5/4/42.5/3
B.
Liver editing
Liver editing (%)
60
40
20
0
TSS
50/0/47/3
59/0/38/3
54.5/0/42.5/3
DSPC 50/9/39/2
DSPC 52.5/9/38/3
DSPC 54/4/42.5/3
DPPC 50/9/38/3
DPPC 52.5/4/42.5/3

Fig. 10