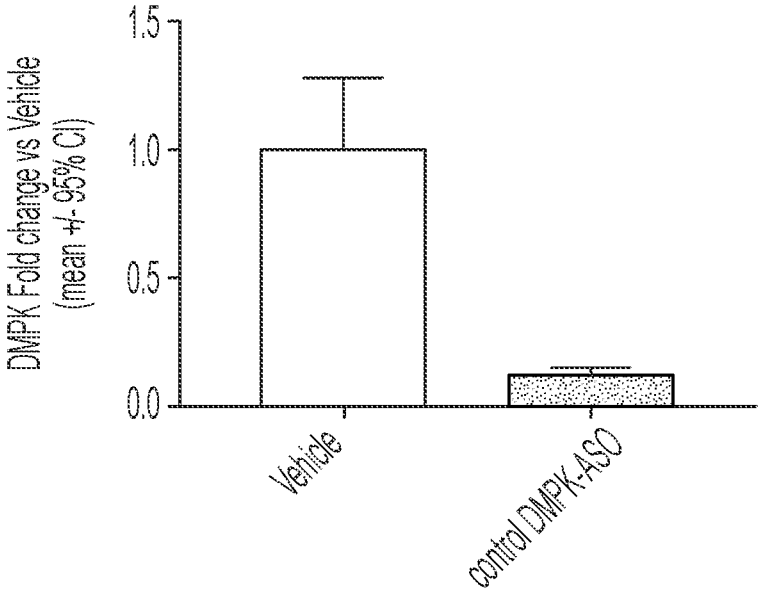

DMPK Fold change vs Vehicle
(mean +/- 95% CI)
1.5
1.0
0.5
0.0
Vehicle
control DMPK-ASO

FIG. 1

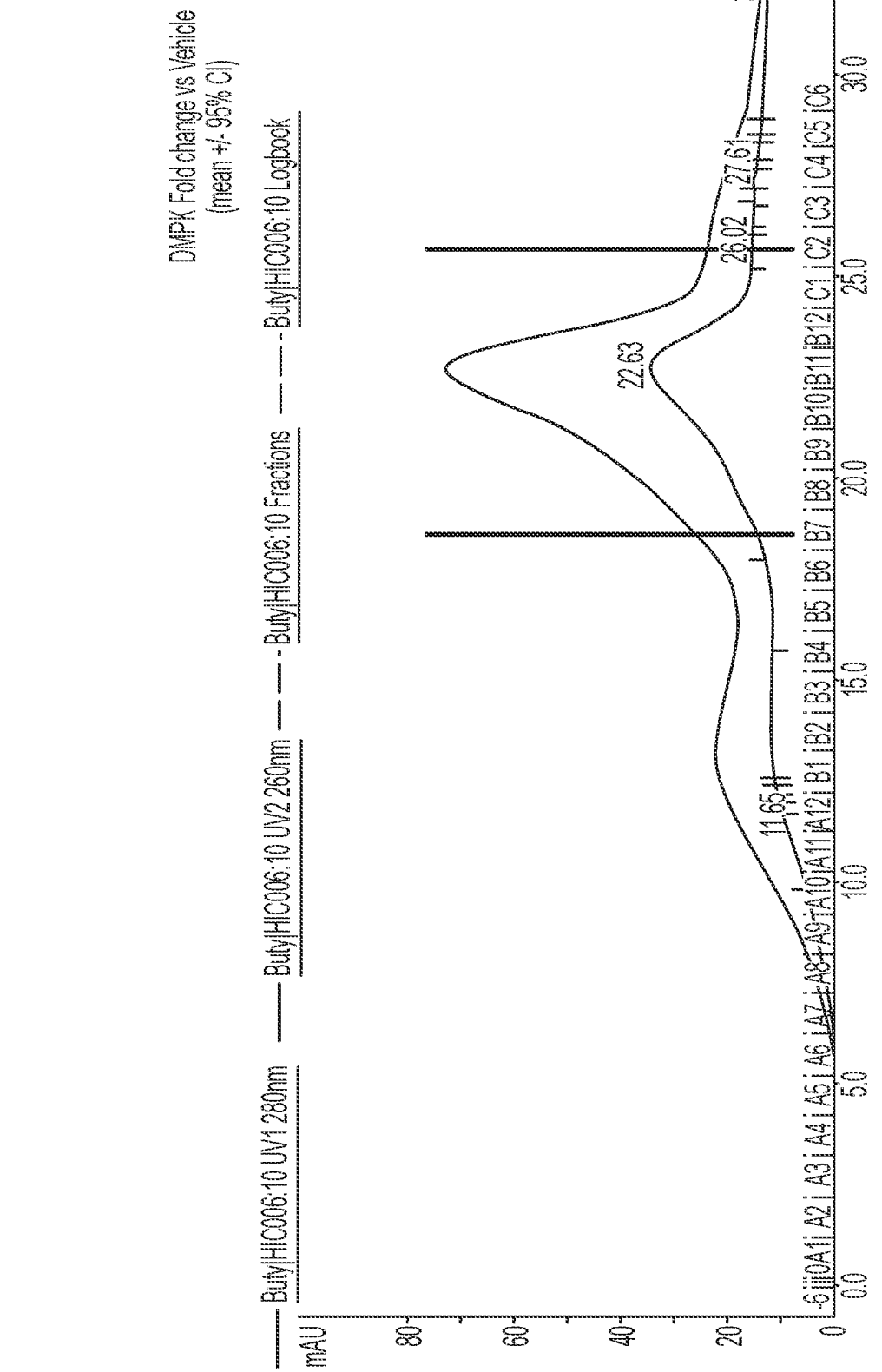
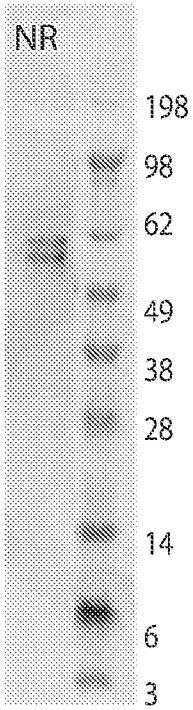

DMPK Fold change vs Vehicle
(mean +/- 95% CI)
Butyl\HC006:10 UV1 280nm
Butyl\HC006:10 UV2 260nm
Butyl\HC006:10 Fractions
Butyl\HC006:10 Logbook
mAU
min
22.63
26.02
27.61
32.09
11.65
Waste

FIG. 2A



NuPage 4-12% 1mm SDS-PAGE
MES running buffer, 150v 50min

FIG. 2B

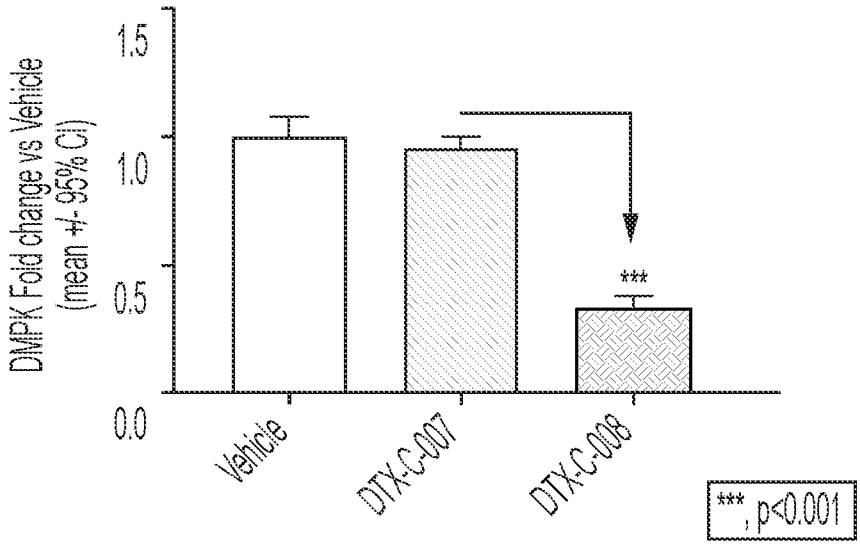


FIG. 3

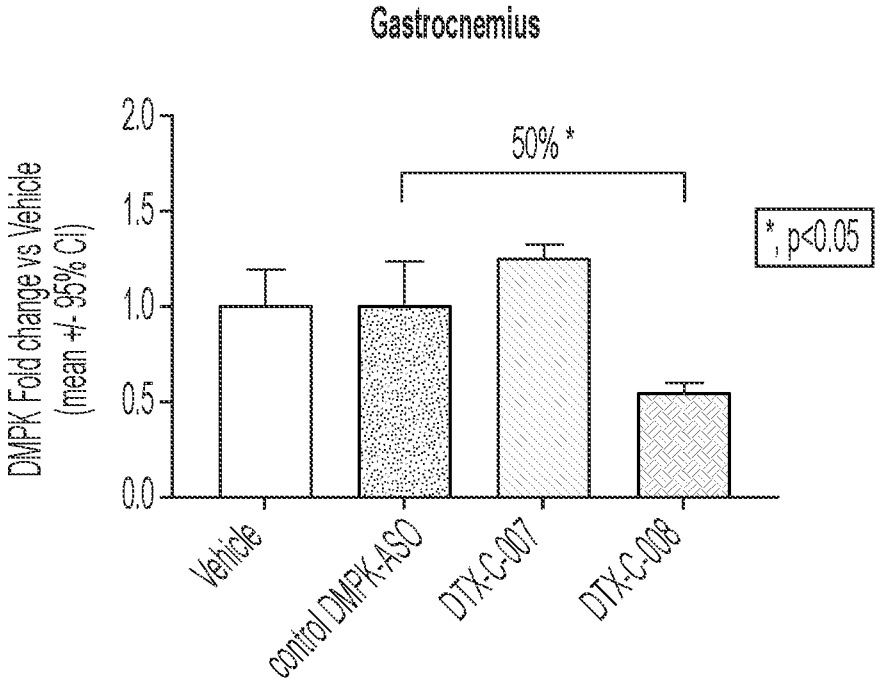

Gastrocnemius
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
50% *
*, p<0.05
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 4A

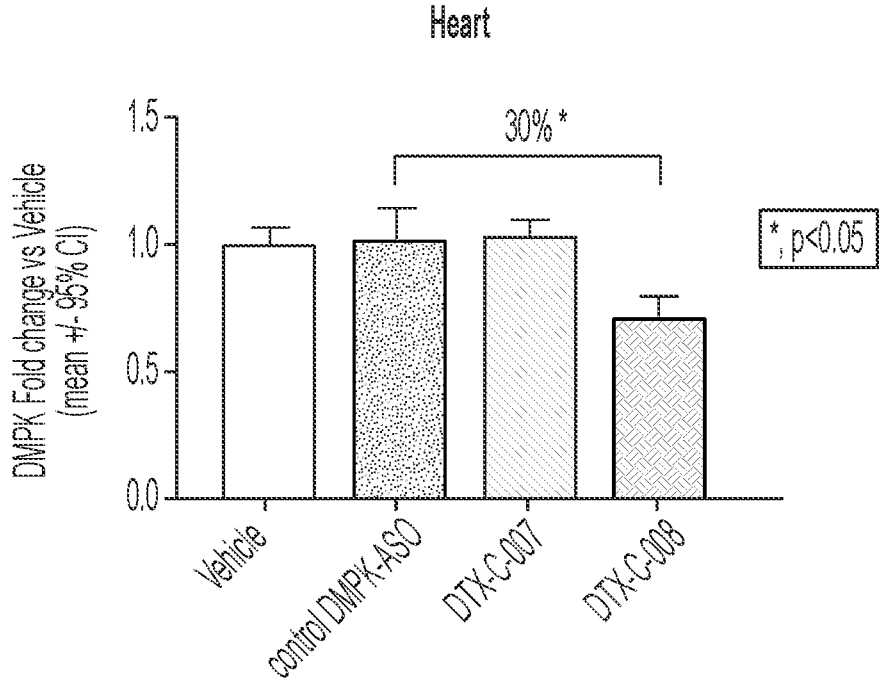

Heart
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
1.5
1.0
0.5
0.0
30% *
*, p<0.05
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 4B

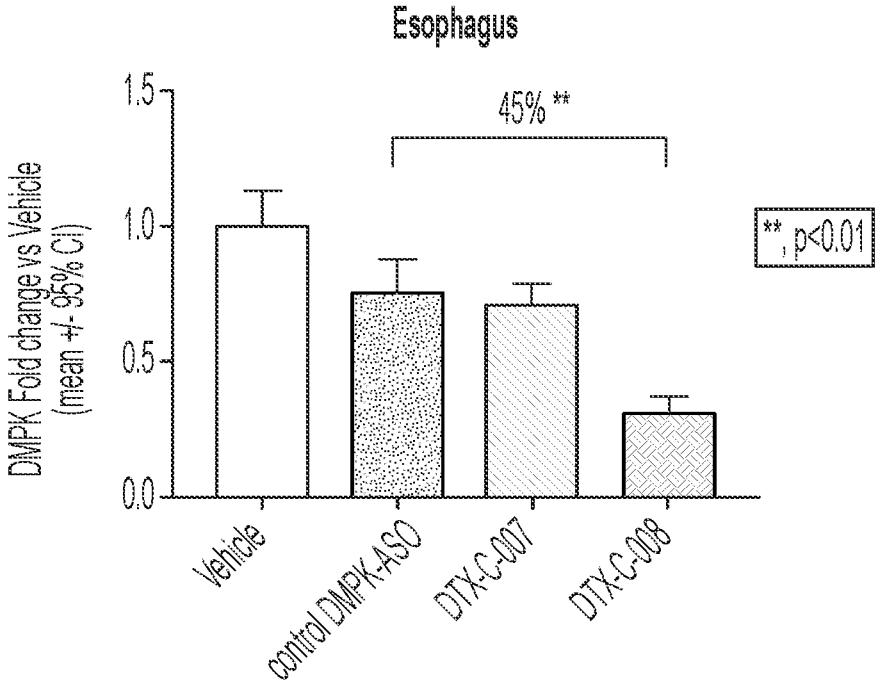

Esophagus
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
1.5
1.0
0.5
0.0
45% **
**, p<0.01
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 4C

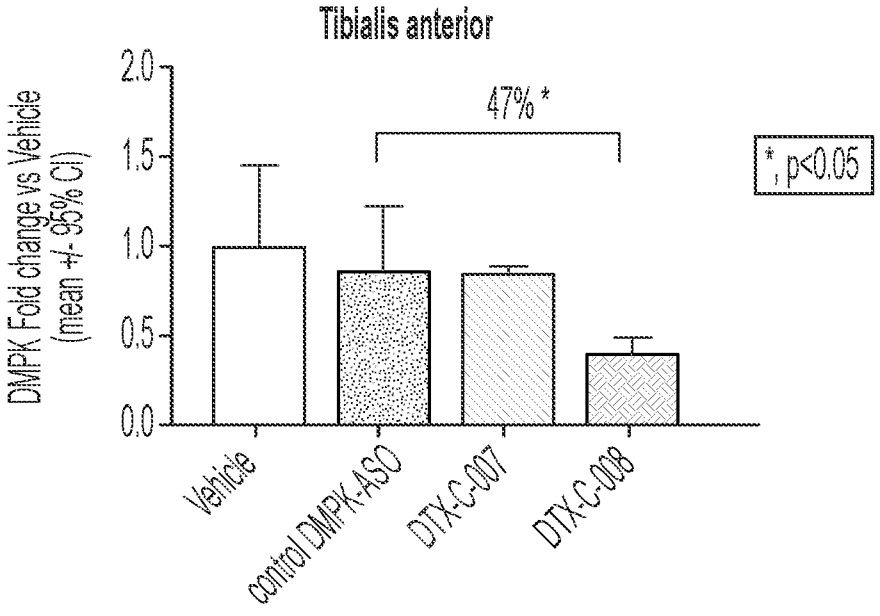

Tibialis anterior
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
47% *
*, p<0.05
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 4D

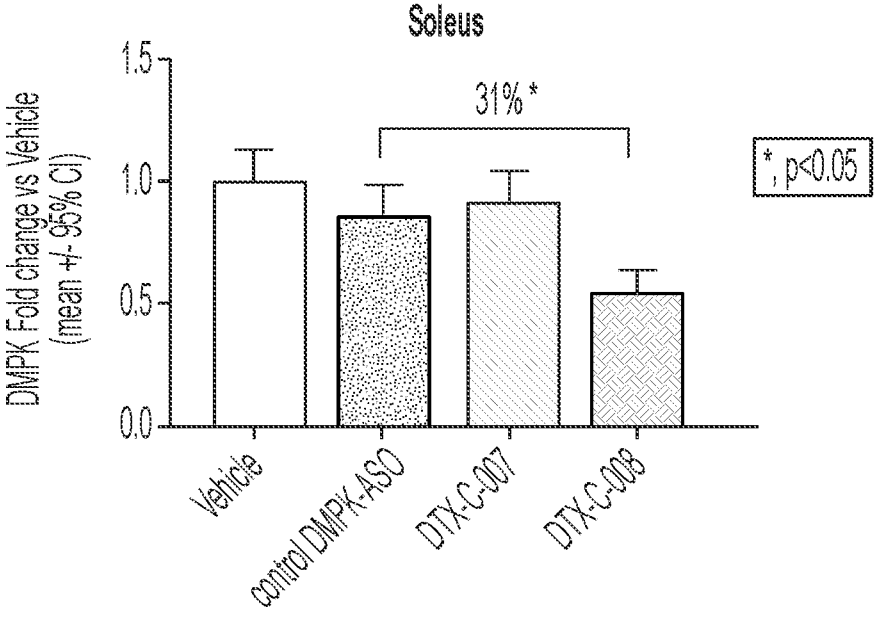

Soleus
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
1.5
1.0
0.5
0.0
31%*
*, p<0.05
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 4E

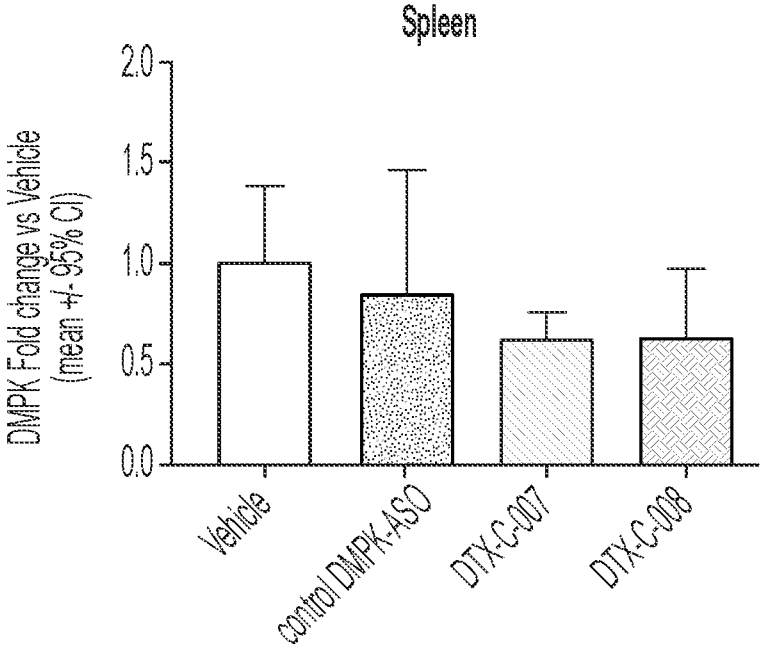

Spleen
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 5A

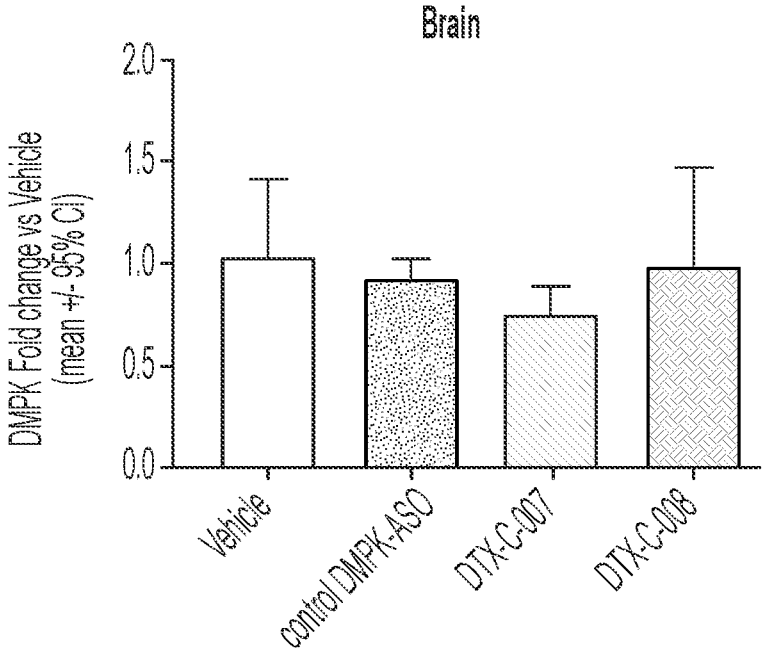

Brain
DMPK Fold change vs Vehicle
(mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
Vehicle
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 5B

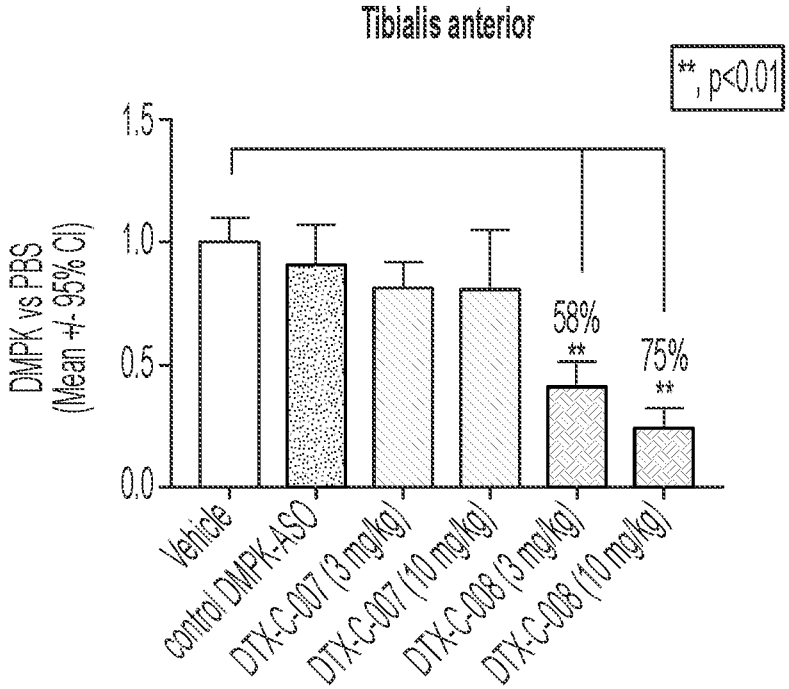

Tibialis anterior
**, p<0.01
DMPK vs PBS
(Mean +/- 95% CI)
1.5
1.0
0.5
0.0
58%
**
75%
**
Vehicle
control DMPK-ASO
DTX-C-007 (3 mg/kg)
DTX-C-007 (10 mg/kg)
DTX-C-008 (3 mg/kg)
DTX-C-008 (10 mg/kg)

FIG. 6A

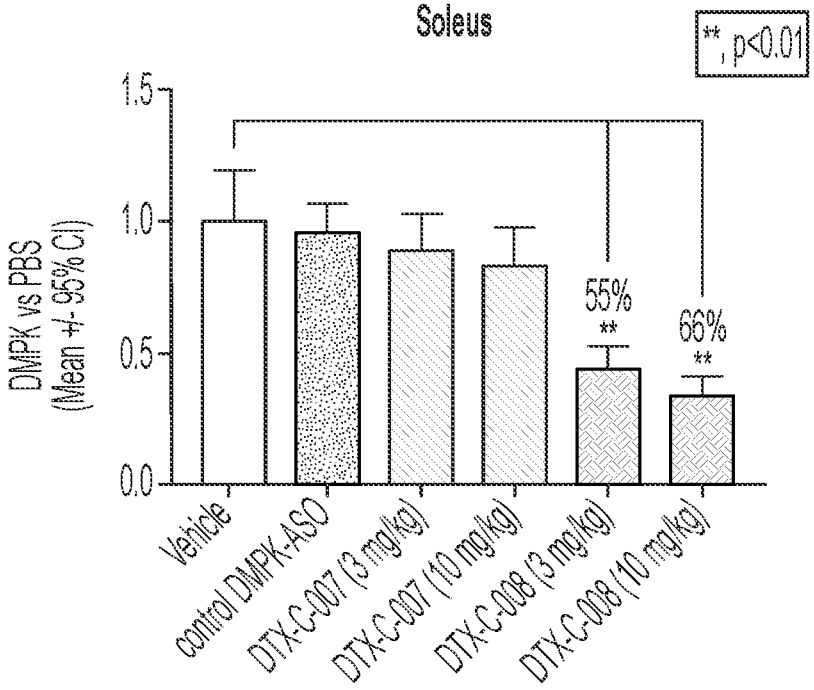

Soleus
**, p<0.01
DMPK vs PBS
(Mean +/- 95% CI)
1.5
1.0
0.5
0.0
55%
**
66%
**
Vehicle
control DMPK-ASO
DTX-C-007 (3 mg/kg)
DTX-C-007 (10 mg/kg)
DTX-C-008 (3 mg/kg)
DTX-C-008 (10 mg/kg)

FIG. 6B

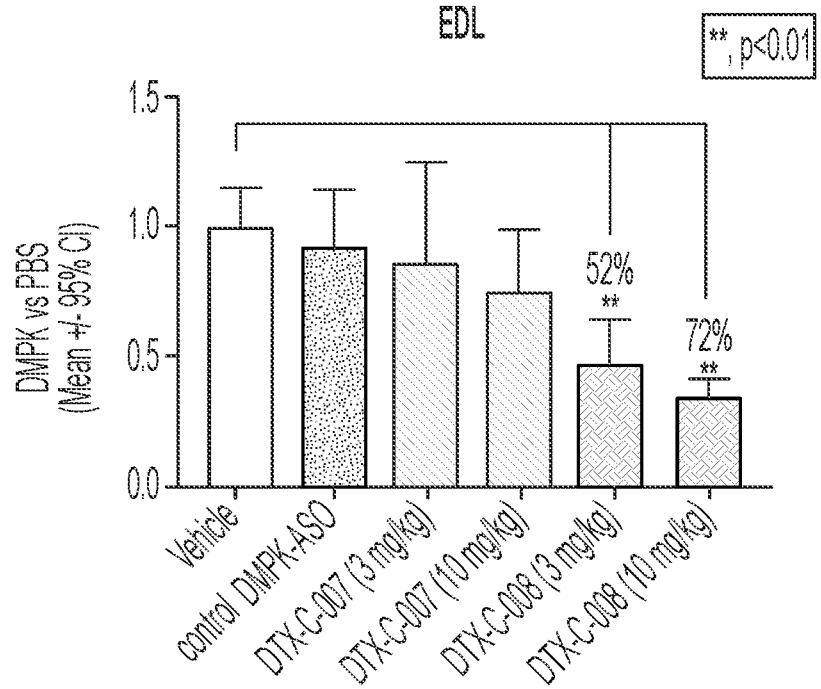

EDL
**, p<0.01
DMPK vs PBS
(Mean +/- 95% CI)
1.5
1.0
0.5
0.0
52%
**
72%
**
Vehicle
control DMPK-ASO
DTX-C-007 (3 mg/kg)
DTX-C-007 (10 mg/kg)
DTX-C-008 (3 mg/kg)
DTX-C-008 (10 mg/kg)

FIG. 6C

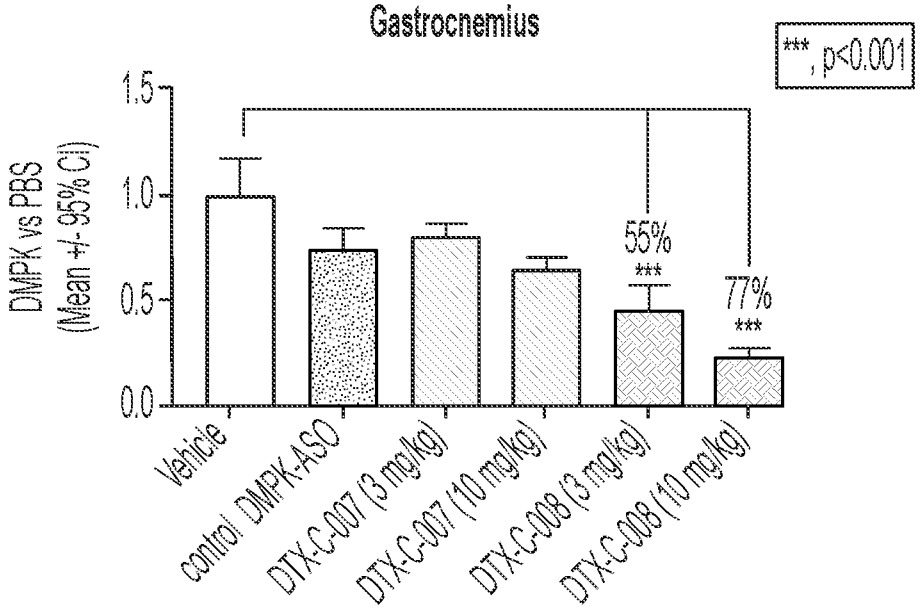

Gastrocnemius
***, p<0.001
DMPK vs PBS
(Mean +/- 95% CI)
1.5
1.0
0.5
0.0
55%
***
77%
***
Vehicle
control DMPK-ASO
DTX-C-007 (3 mg/kg)
DTX-C-007 (10 mg/kg)
DTX-C-008 (3 mg/kg)
DTX-C-008 (10 mg/kg)

FIG. 6D

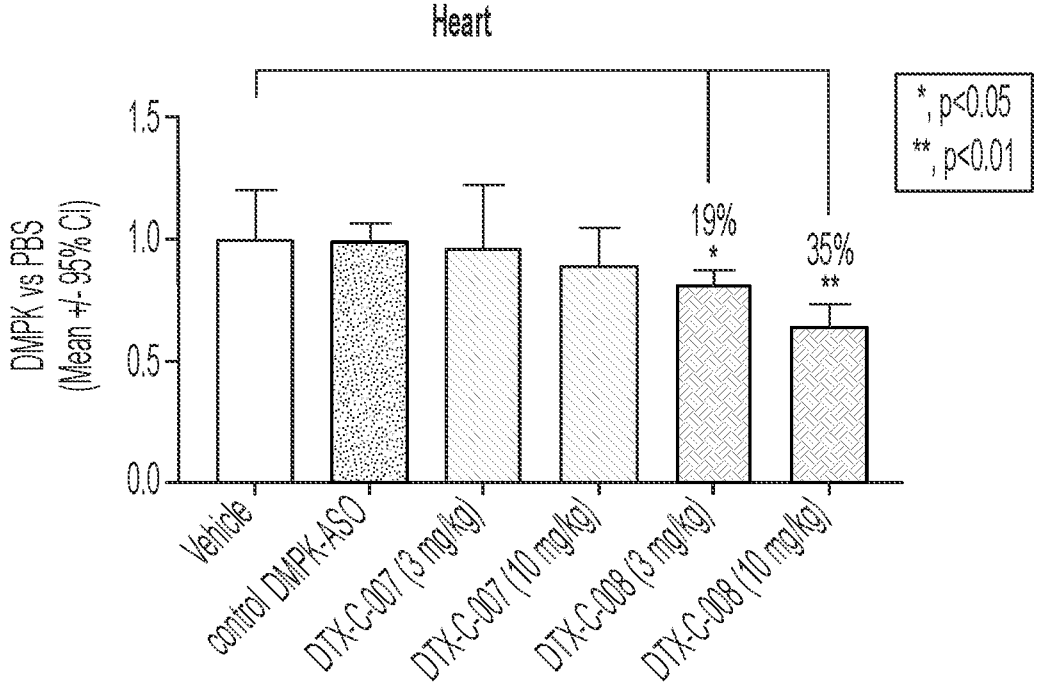

Heart
*, p<0.05
**, p<0.01
DMPK vs PBS
(Mean +/- 95% CI)
1.5
1.0
0.5
0.0
19%
*
35%
**
Vehicle
control DMPK-ASO
DTX-C-007 (3 mg/kg)
DTX-C-007 (10 mg/kg)
DTX-C-008 (3 mg/kg)
DTX-C-008 (10 mg/kg)

FIG. 6E

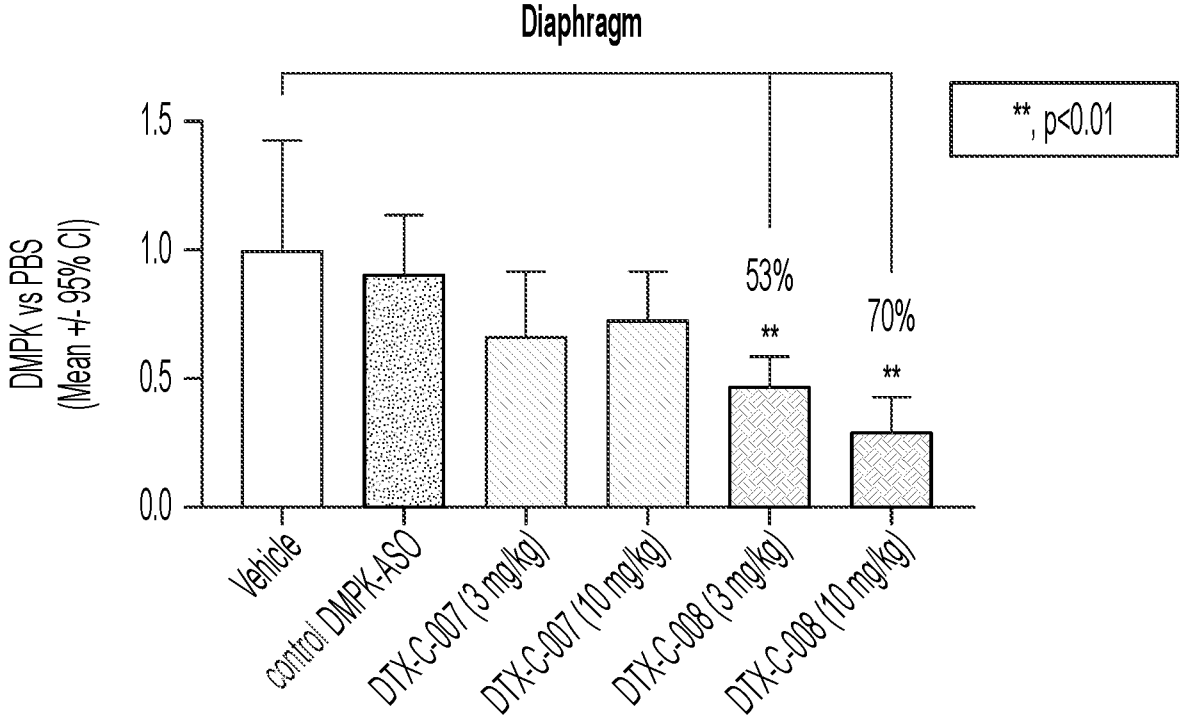

Diaphragm
**, p<0.01
DMPK vs PBS
(Mean +/- 95% CI)
1.5
1.0
0.5
0.0
53%
**
70%
**
Vehicle
control DMPK-ASO
DTX-C-007 (3 mg/kg)
DTX-C-007 (10 mg/kg)
DTX-C-008 (3 mg/kg)
DTX-C-008 (10 mg/kg)

FIG. 6F

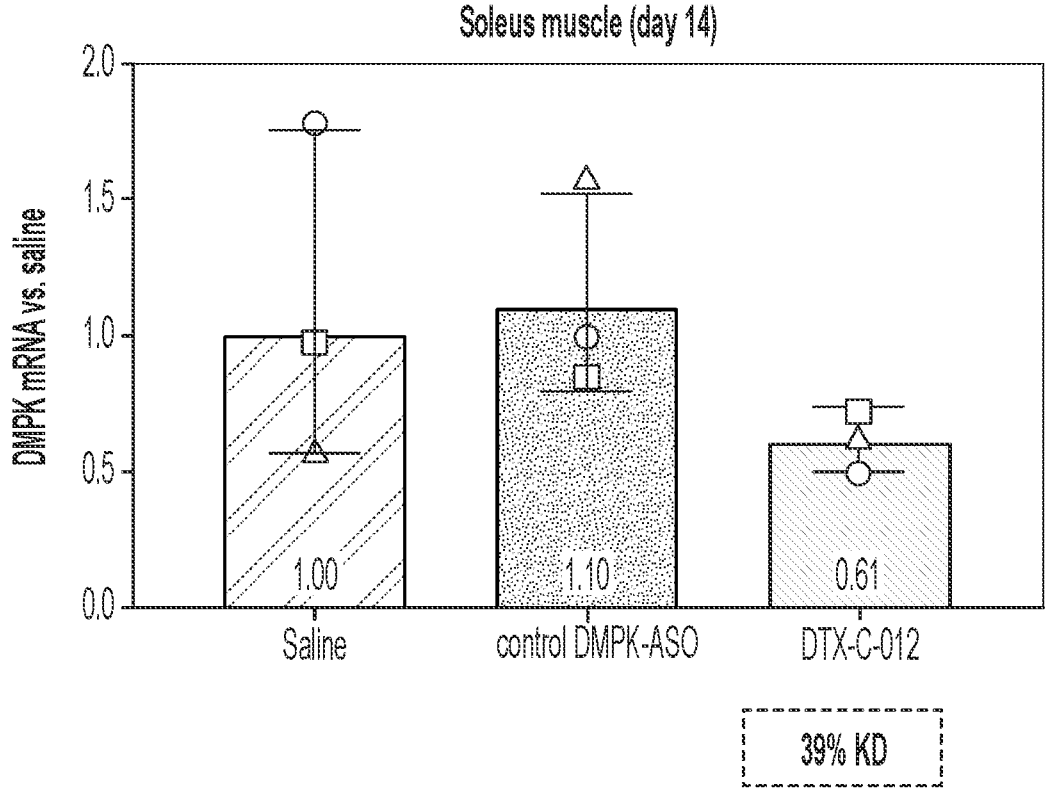

Soleus muscle (day 14)
DMPK mRNA vs. saline
2.0
1.5
1.0
0.5
0.0
1.00
1.10
0.61
Saline
control DMPK-ASO
DTX-C-012
39% KD

FIG. 7A

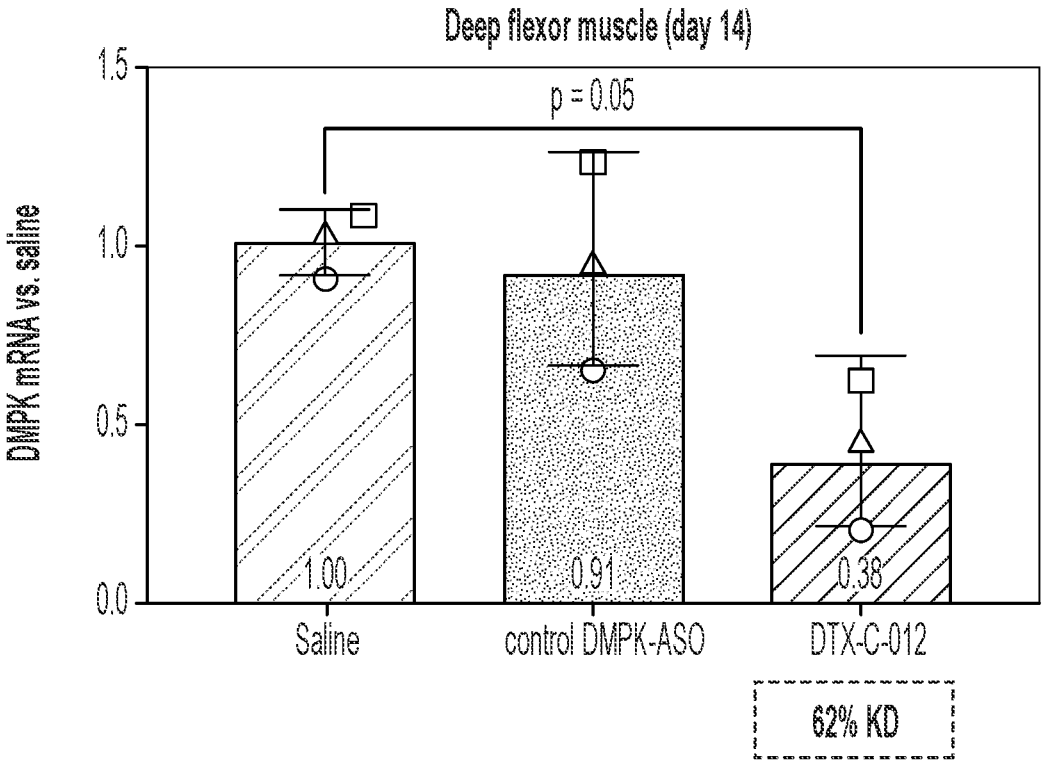

Deep flexor muscle (day 14)
DMPK mRNA vs. saline
1.5
1.0
0.5
0.0
p = 0.05
1.00
0.91
0.38
Saline
control DMPK-ASO
DTX-C-012
62% KD

FIG. 7B

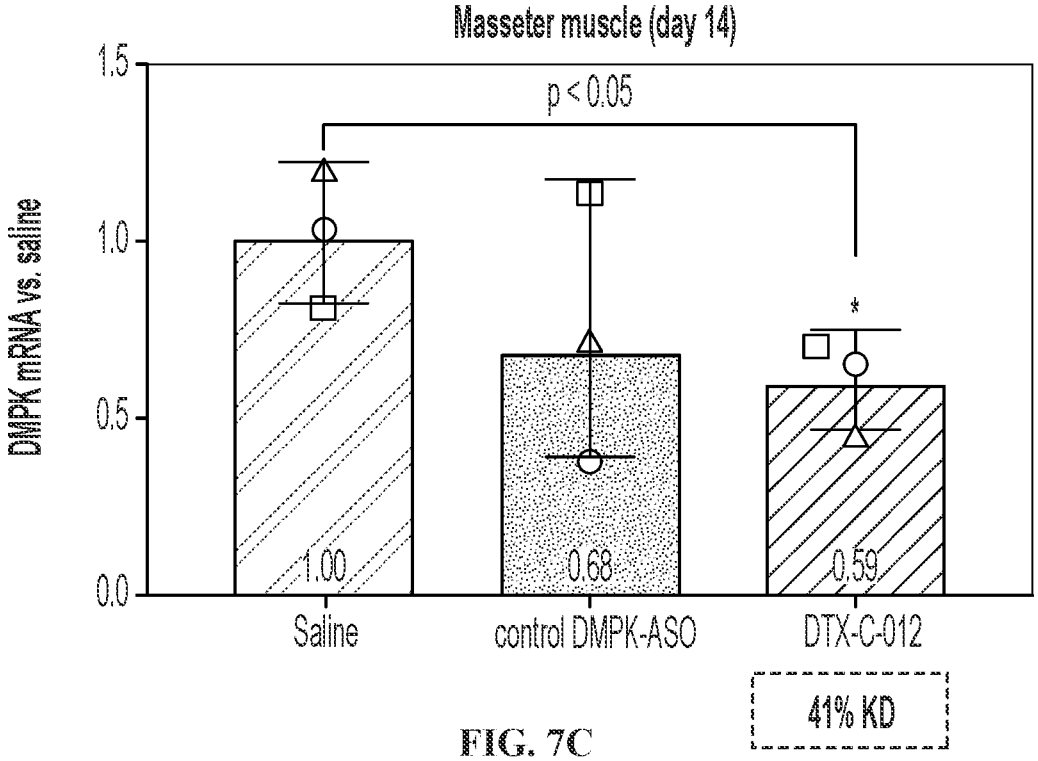

Masseter muscle (day 14)
DMPK mRNA vs. saline
1.5
1.0
0.5
0.0
p < 0.05
*
1.00
0.68
0.59
Saline
control DMPK-ASO
DTX-C-012
41% KD

FIG. 7C

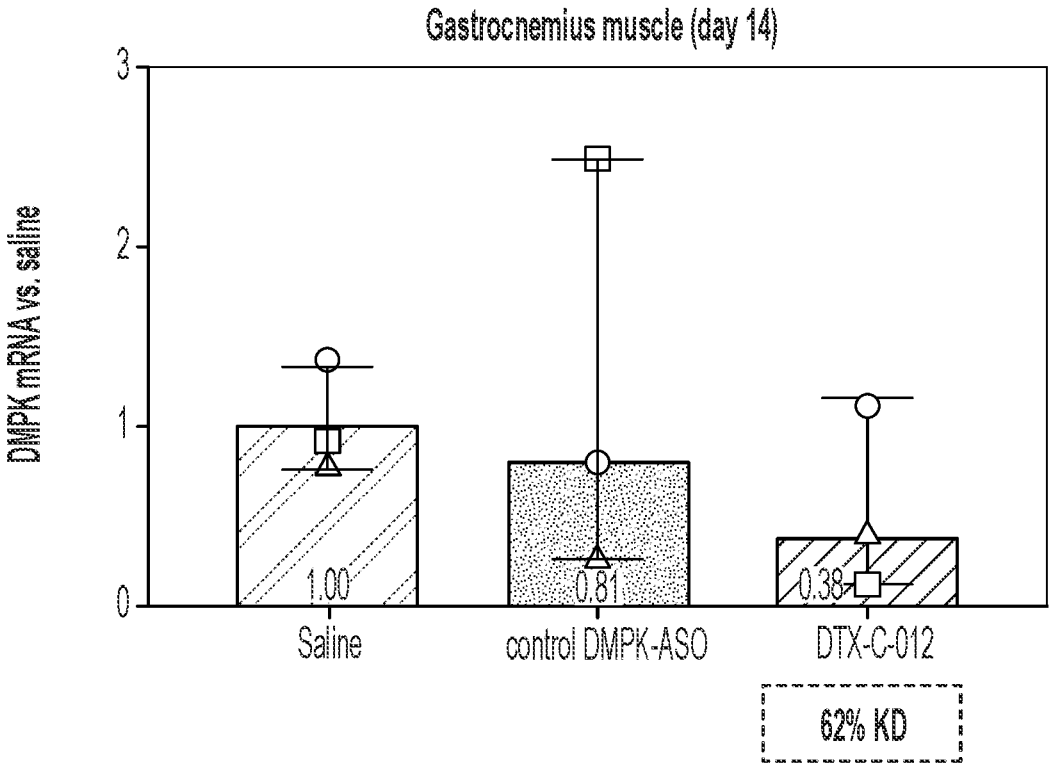

Gastrocnemius muscle (day 14)
DMPK mRNA vs. saline
3
2
1
0
1.00
0.81
0.38
Saline
control DMPK-ASO
DTX-C-012
62% KD

FIG. 7D

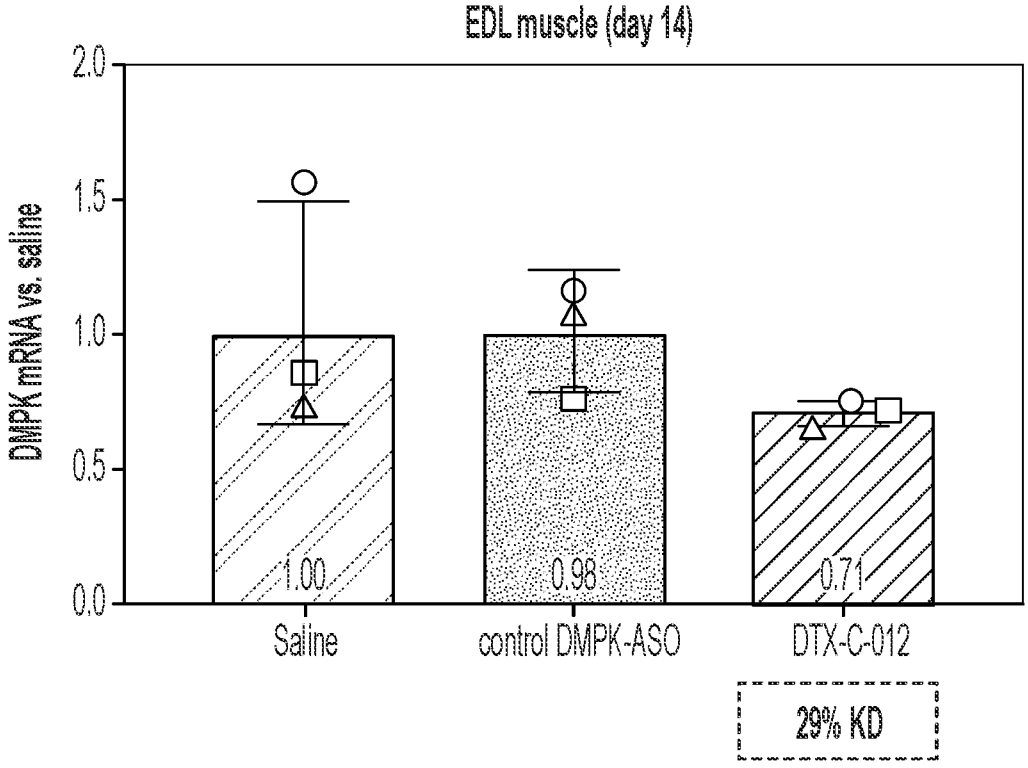

EDL muscle (day 14)
DMPK mRNA vs. saline
2.0
1.5
1.0
0.5
0.0
1.00
0.98
0.71
Saline
control DMPK-ASO
DTX-C-012
29% KD

FIG. 7E

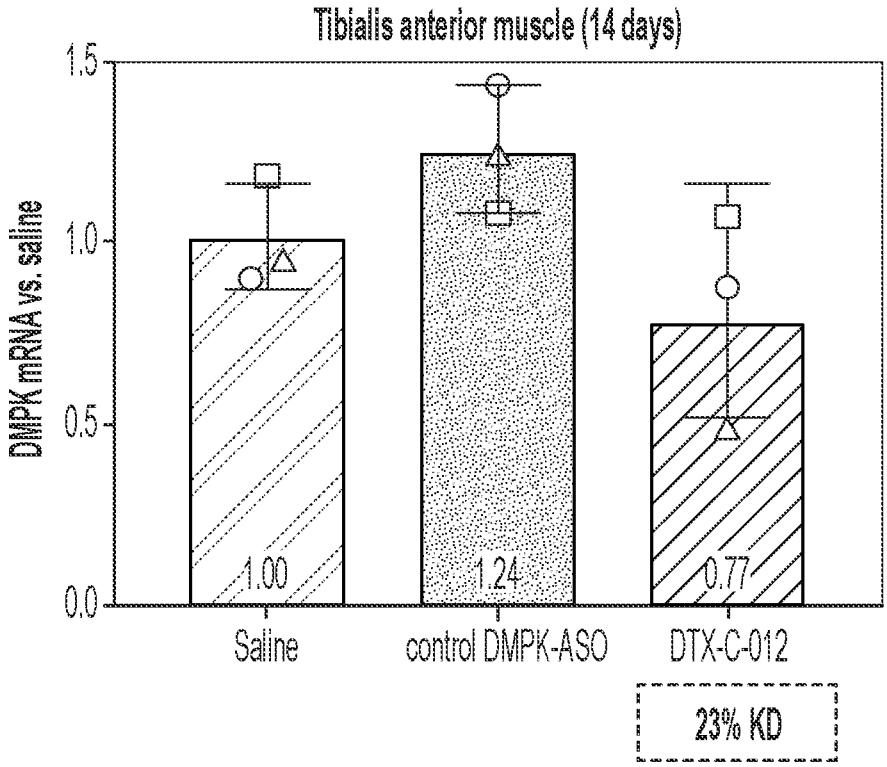

Tibialis anterior muscle (14 days)
DMPK mRNA vs. saline
1.5
1.0
0.5
0.0
1.00
1.24
0.77
Saline
control DMPK-ASO
DTX-C-012
23% KD

FIG. 7F

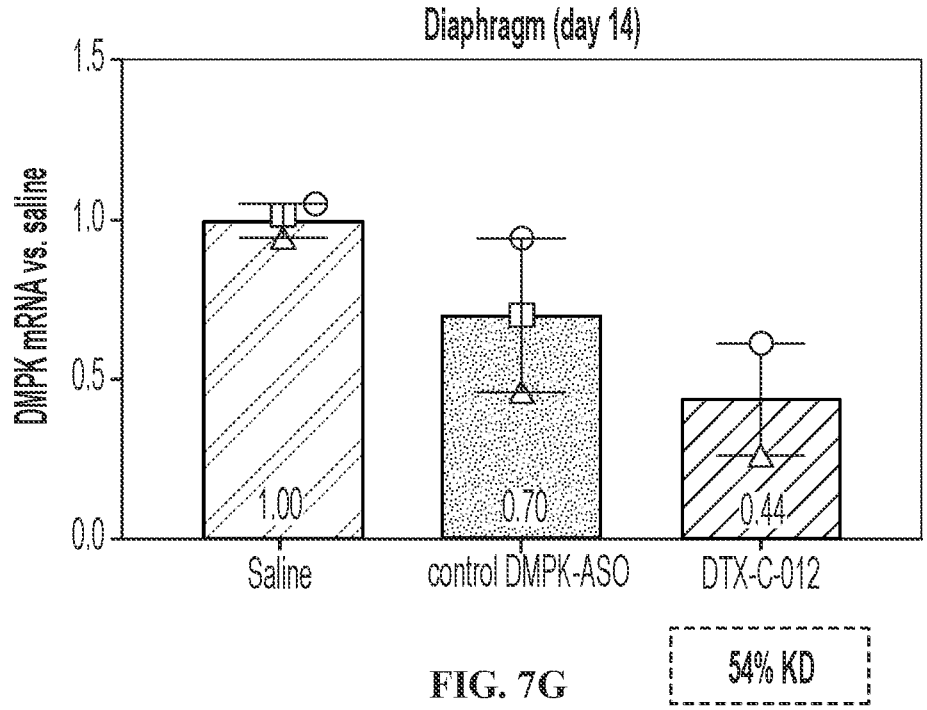

Diaphragm (day 14)
DMPK mRNA vs. saline
1.5
1.0
0.5
0.0
1.00
0.70
0.44
Saline
control DMPK-ASO
DTX-C-012
54% KD

FIG. 7G

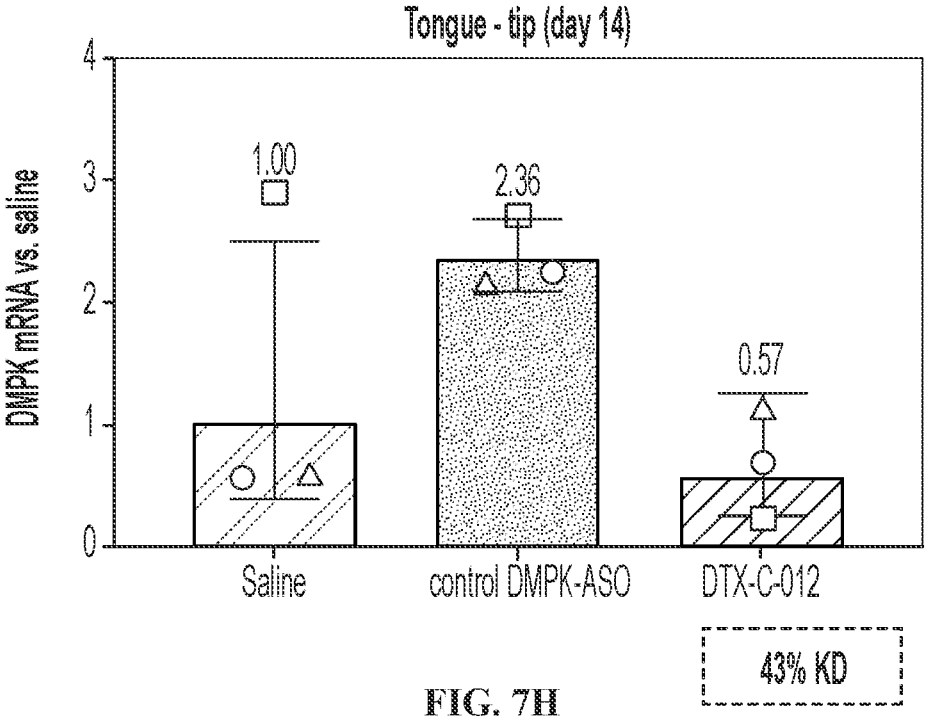

Tongue - tip (day 14)
DMPK mRNA vs. saline
4
3
2
1
0
1.00
2.36
0.57
Saline
control DMPK-ASO
DTX-C-012
43% KD

FIG. 7H

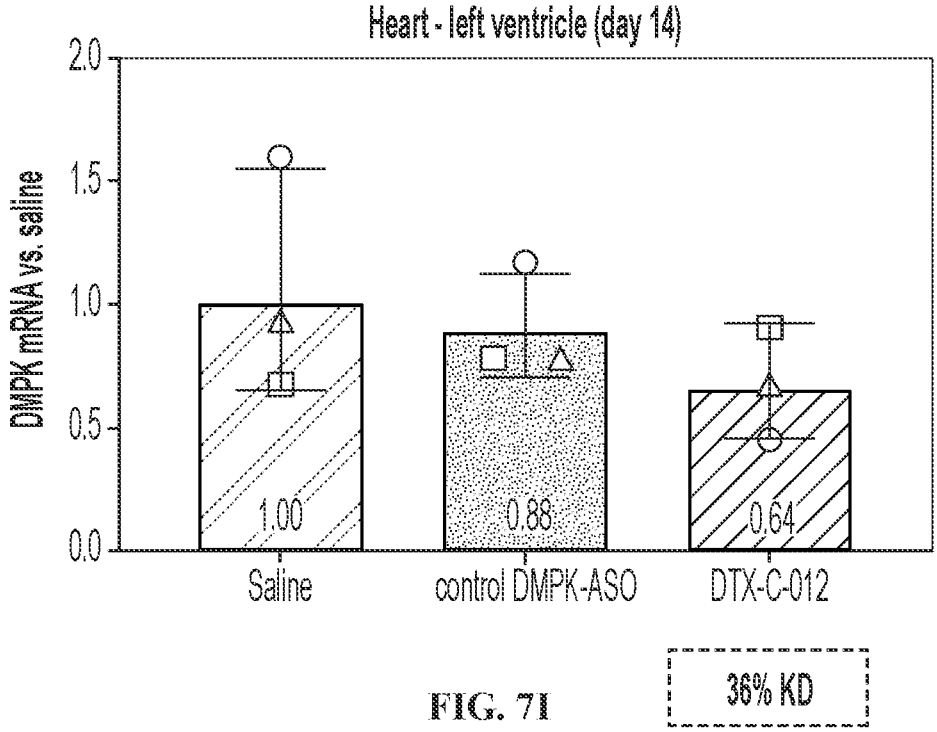

Heart - left ventricle (day 14)
DMPK mRNA vs. saline
2.0
1.5
1.0
0.5
0.0
1.00
0.86
0.64
Saline
control DMPK-ASO
DTX-C-012
36% KD

FIG. 7I

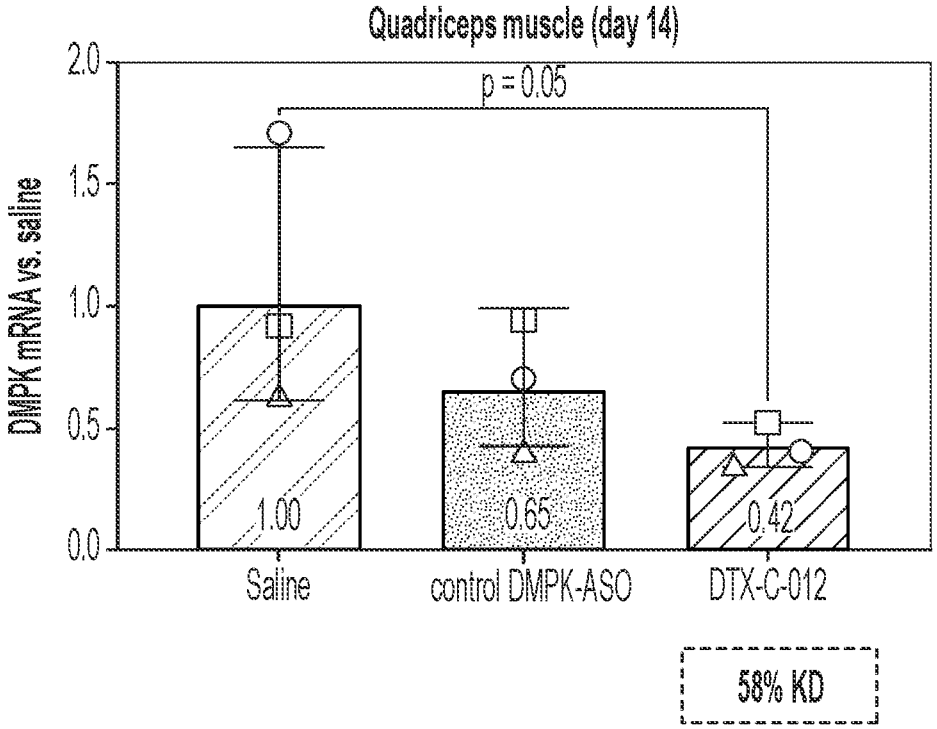

Quadriceps muscle (day 14)
p = 0.05
DMPK mRNA vs. saline
2.0
1.5
1.0
0.5
0.0
1.00
0.65
0.42
Saline
control DMPK-ASO
DTX-C-012
58% KD

FIG. 7J

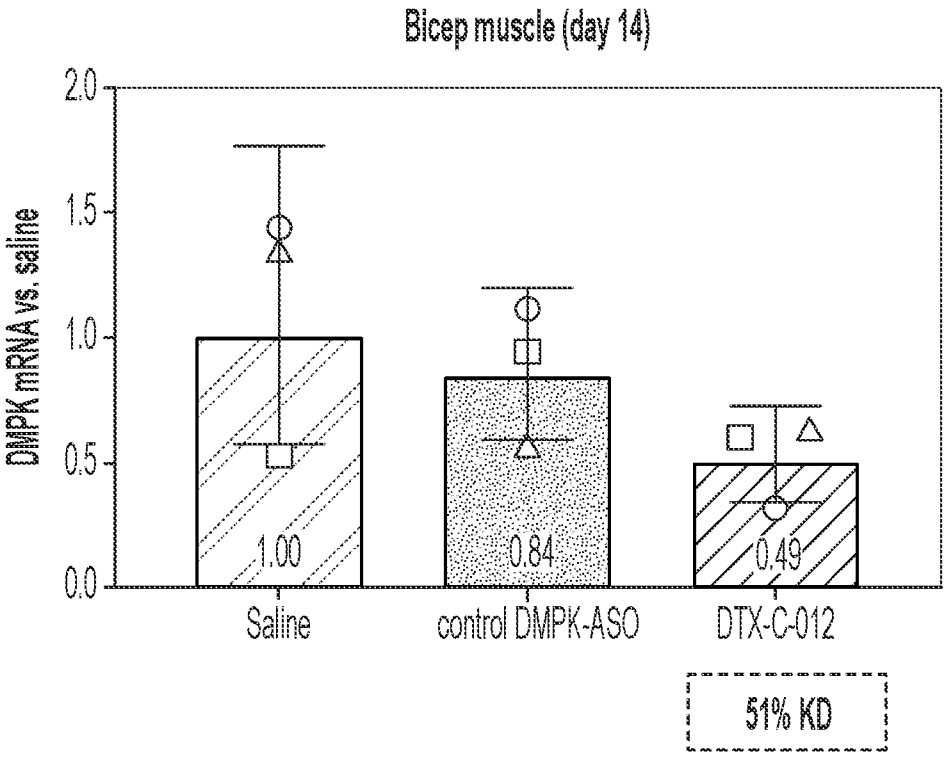

Bicep muscle (day 14)
DMPK mRNA vs. saline
2.0
1.5
1.0
0.5
0.0
1.00
0.84
0.49
Saline
control DMPK-ASO
DTX-C-012
51% KD

FIG. 7K

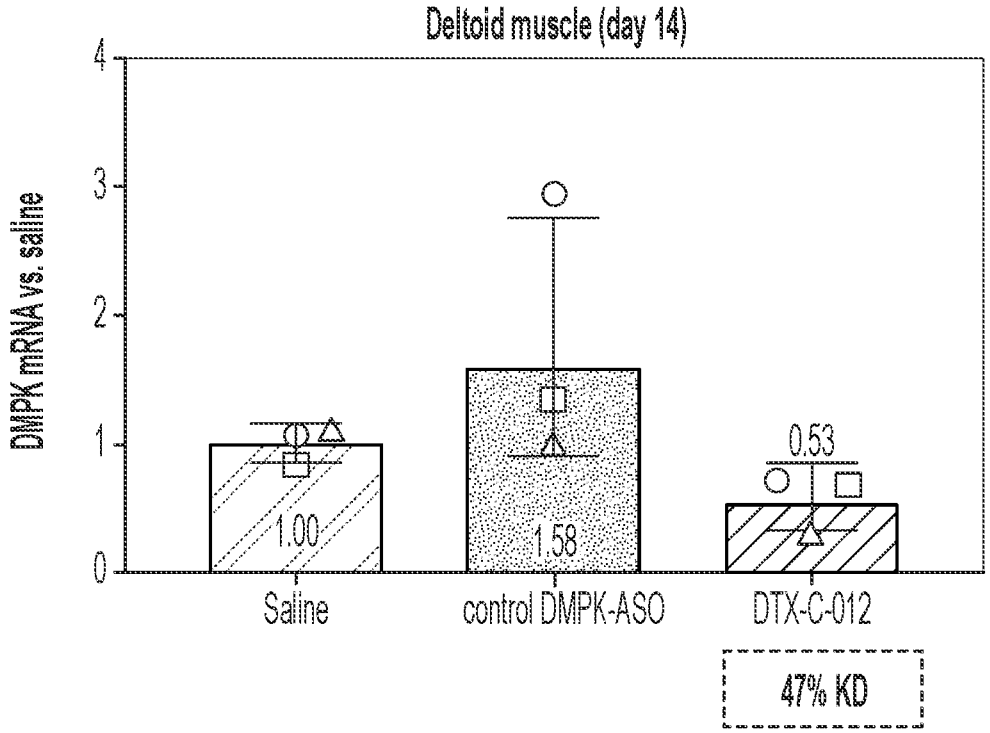

Deltoid muscle (day 14)
DMPK mRNA vs. saline
4
3
2
1
0
1.00
1.58
0.53
Saline
control DMPK-ASO
DTX-C-012
47% KD

FIG. 7L

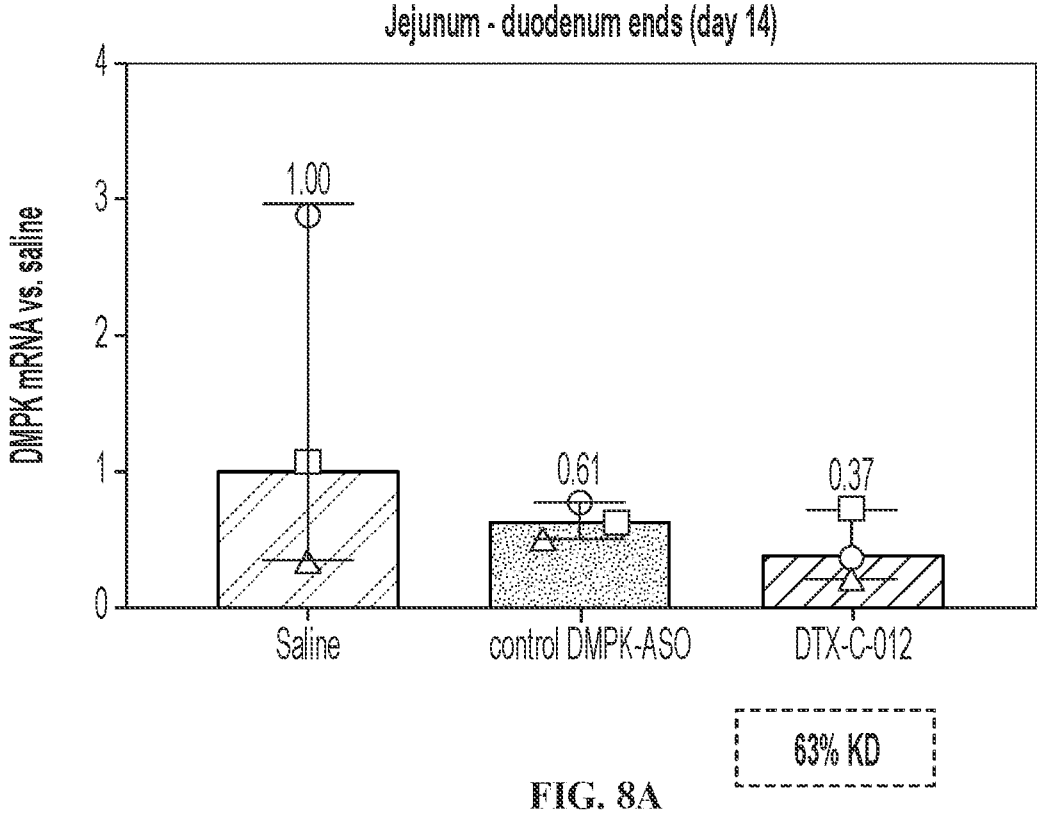

Jejunum - duodenum ends (day 14)
DMPK mRNA vs. saline
4
3
2
1
0
1.00
0.61
0.37
Saline
control DMPK-ASO
DTX-C-012
63% KD

FIG. 8A

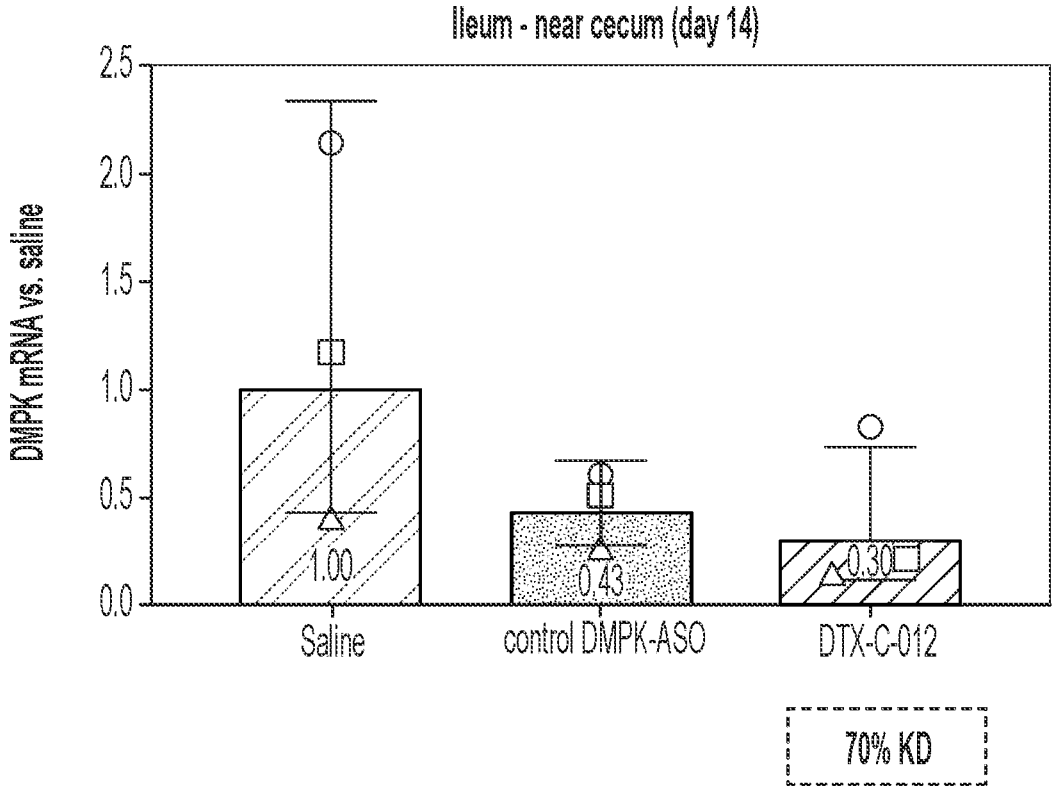

Ileum - near cecum (day 14)
DMPK mRNA vs. saline
2.5
2.0
1.5
1.0
0.5
0.0
1.00
0.43
0.30
Saline
control DMPK-ASO
DTX-C-012
70% KD

FIG. 8B

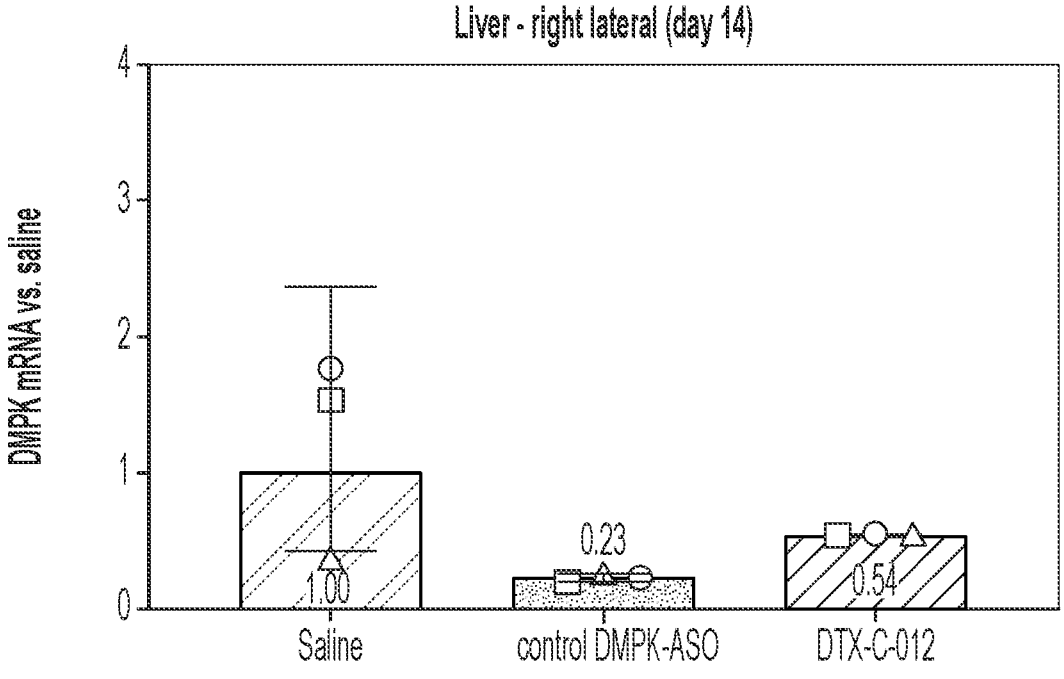

Liver - right lateral (day 14)
DMPK mRNA vs. saline
4
3
2
1
0
1.00
0.23
0.54
Saline
control DMPK-ASO
DTX-C-012

FIG. 9A

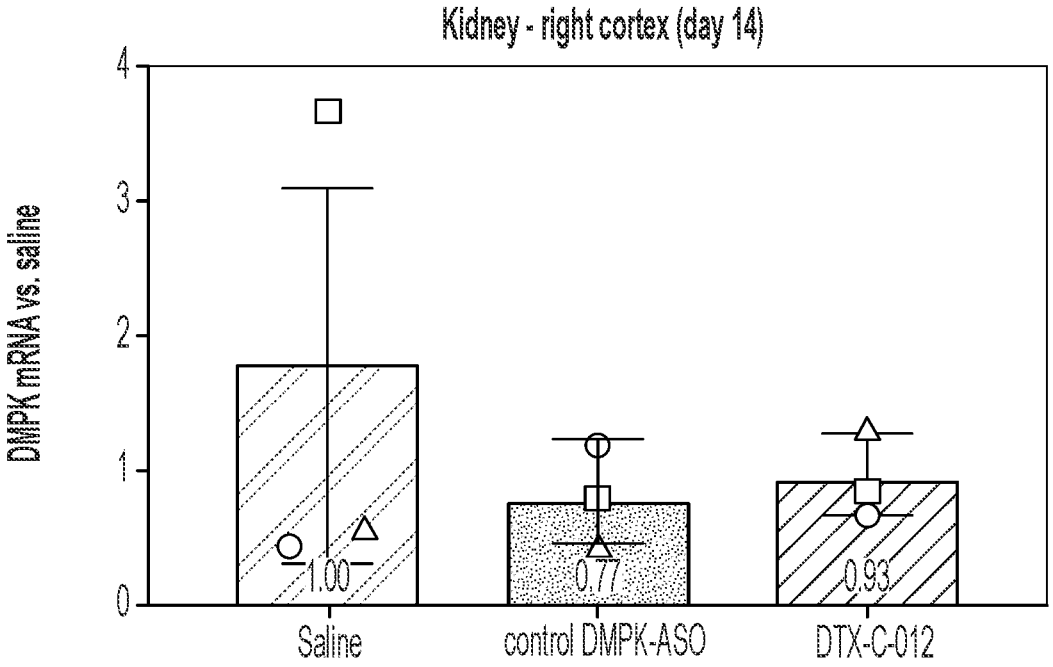

Kidney - right cortex (day 14)
DMPK mRNA vs. saline
4
3
2
1
0
1.00
0.77
0.93
Saline
control DMPK-ASO
DTX-C-012

FIG. 9B

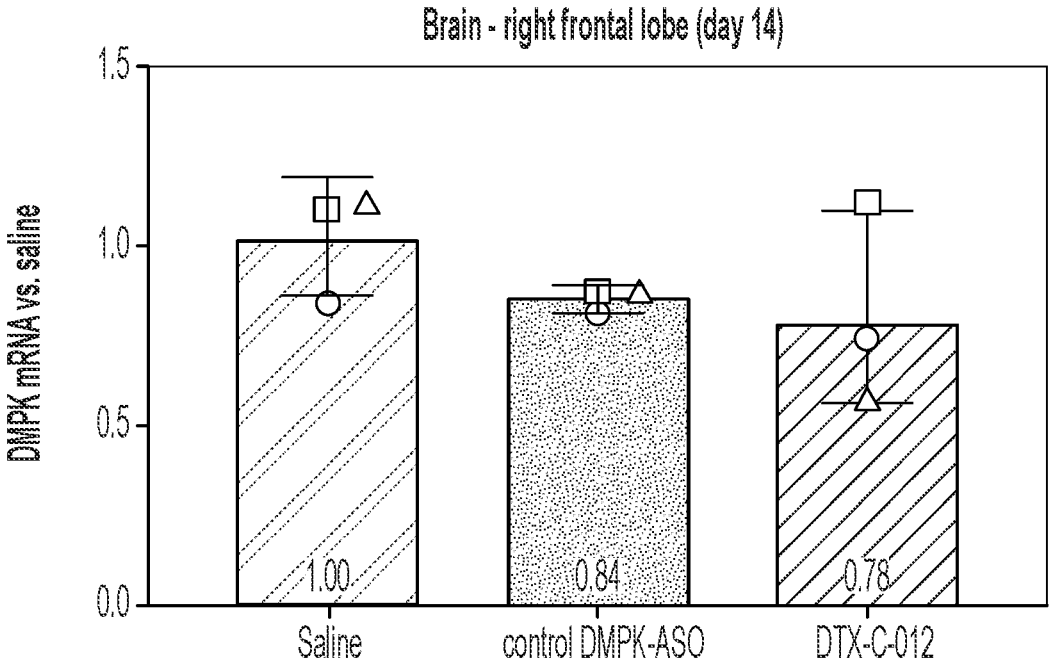

Brain - right frontal lobe (day 14)
DMPK mRNA vs. saline
1.5
1.0
0.5
0.0
1.00
0.84
0.78
Saline
control DMPK-ASO
DTX-C-012

FIG. 9C

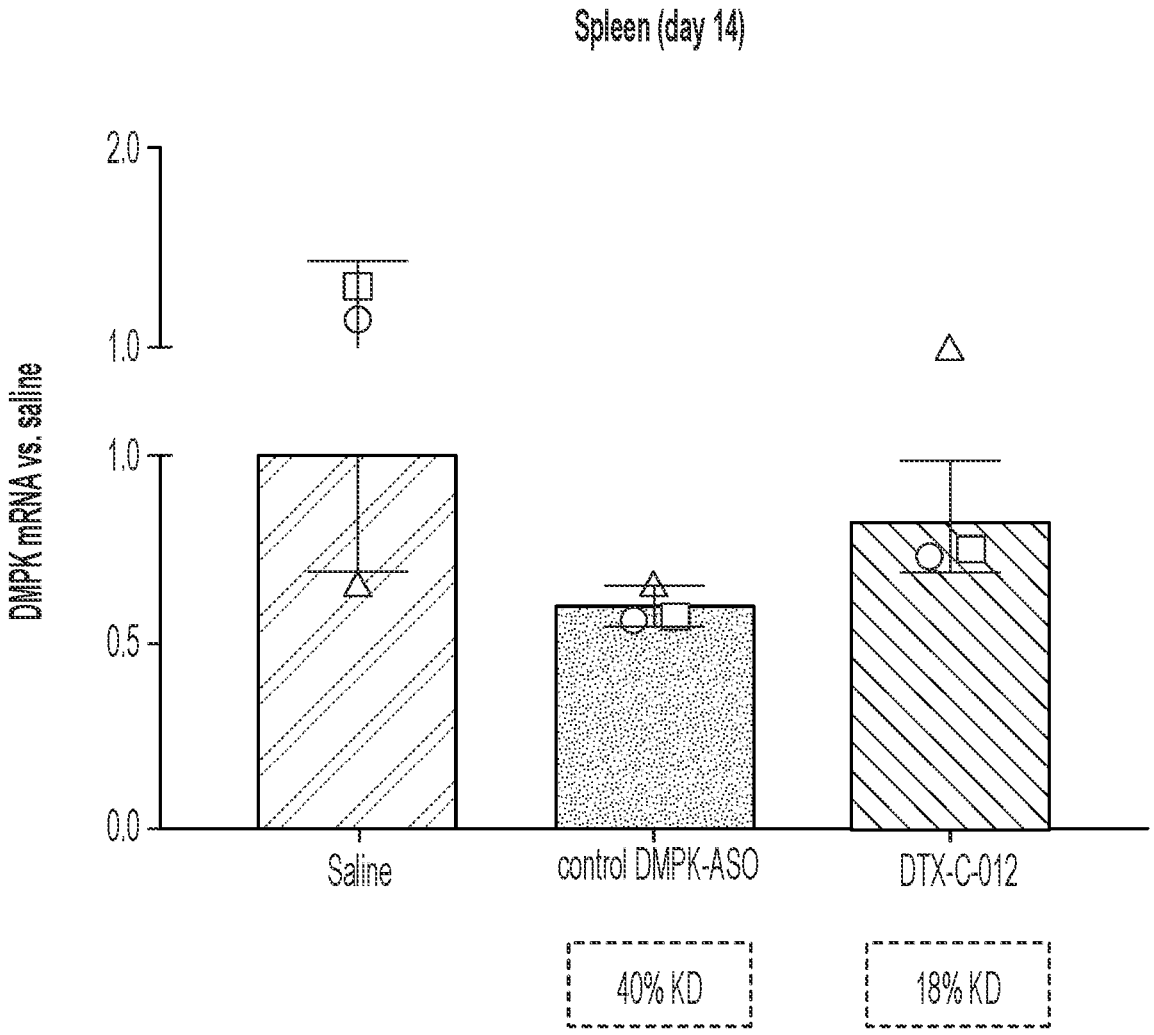

Spleen (day 14)
DMPK mRNA vs. saline
2.0
1.0
1.0
0.5
0.0
Saline
control DMPK-ASO
DTX-C-012
40% KD
18% KD

FIG. 9D

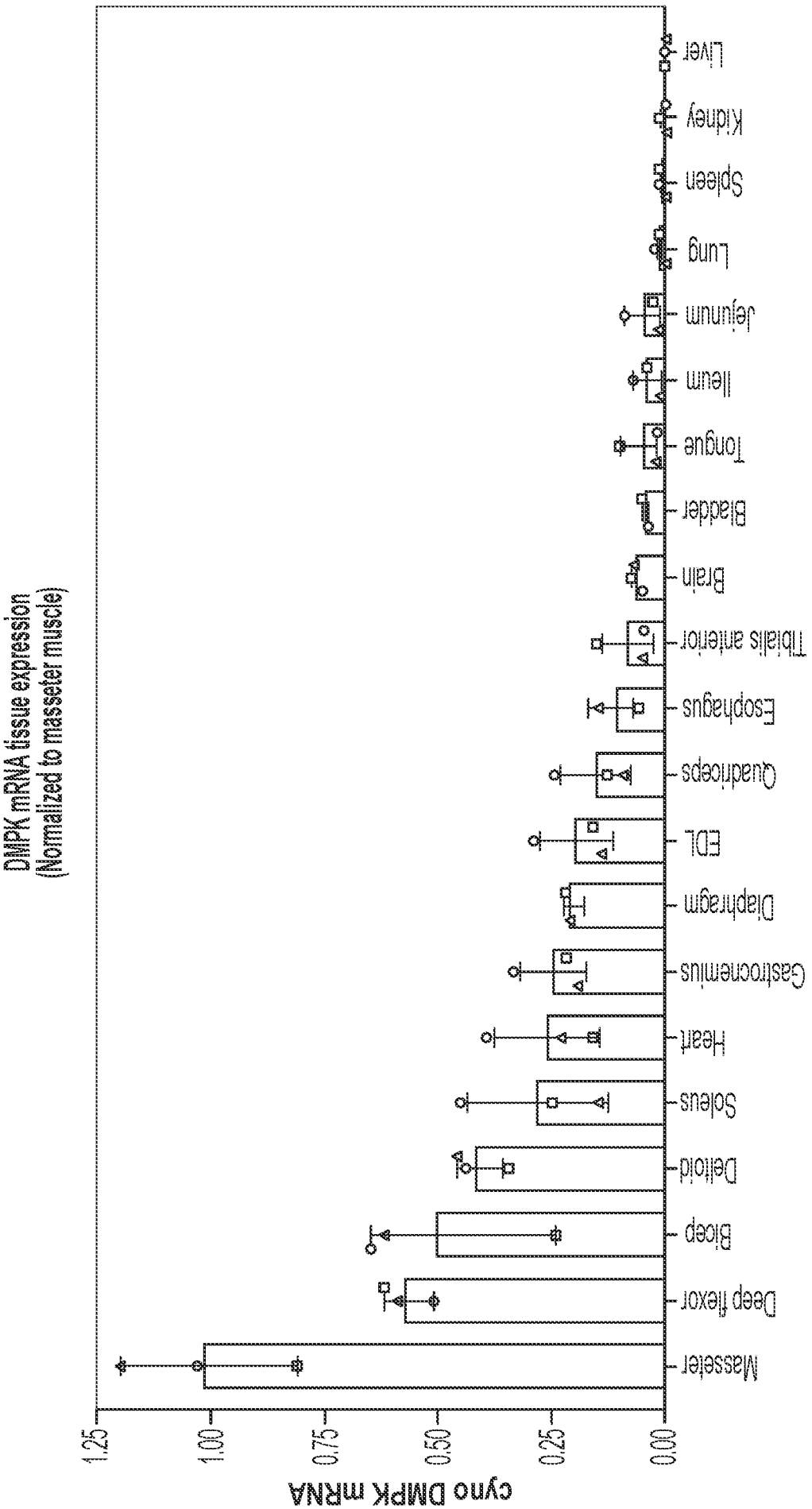

DMPK mRNA tissue expression
(Normalized to masseter muscle)
cyno DMPK mRNA
1.25
1.00
0.75
0.50
0.25
0.00
Masseter
Deep flexor
Bicep
Deltoid
Soleus
Heart
Gastrocnemius
Diaphragm
EDL
Quadriceps
Esophagus
Tibialis anterior
Brain
Bladder
Tongue
Ileum
Jejunum
Lung
Spleen
Kidney
Liver

FIG. 10

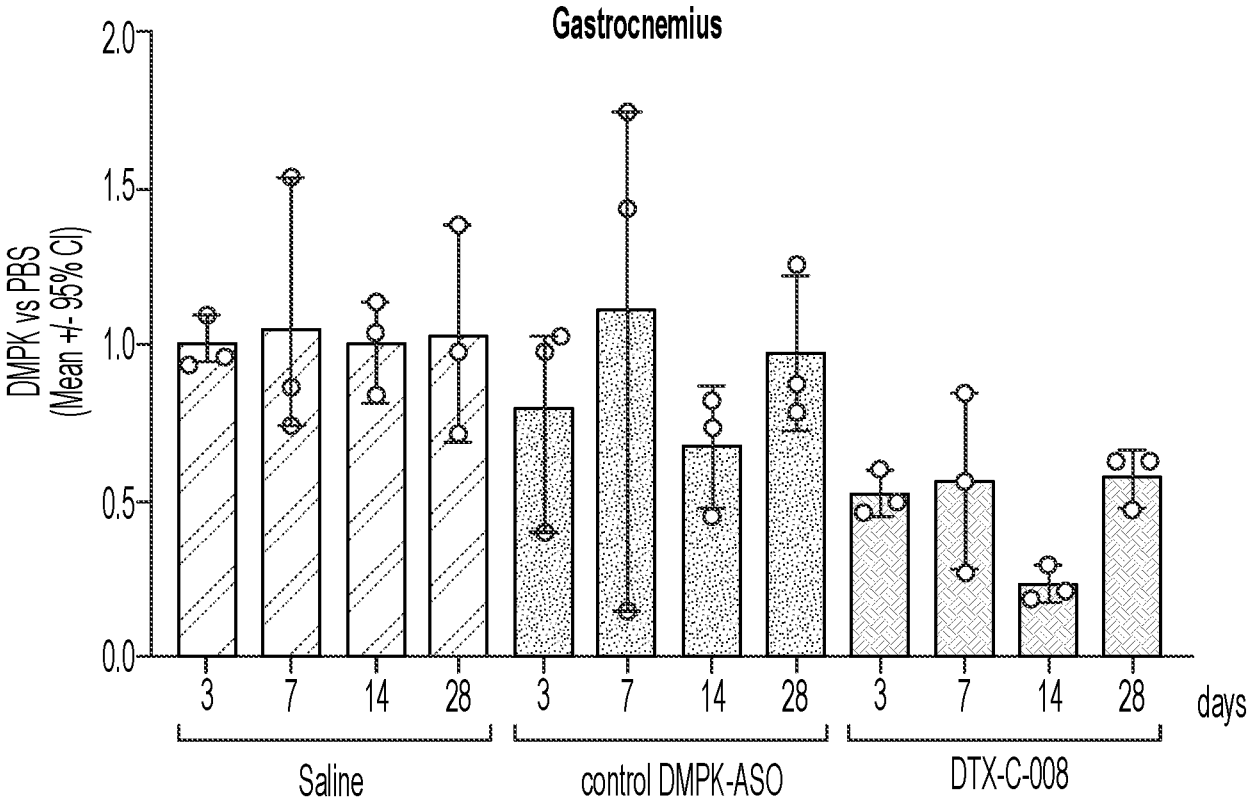


FIG. 11A

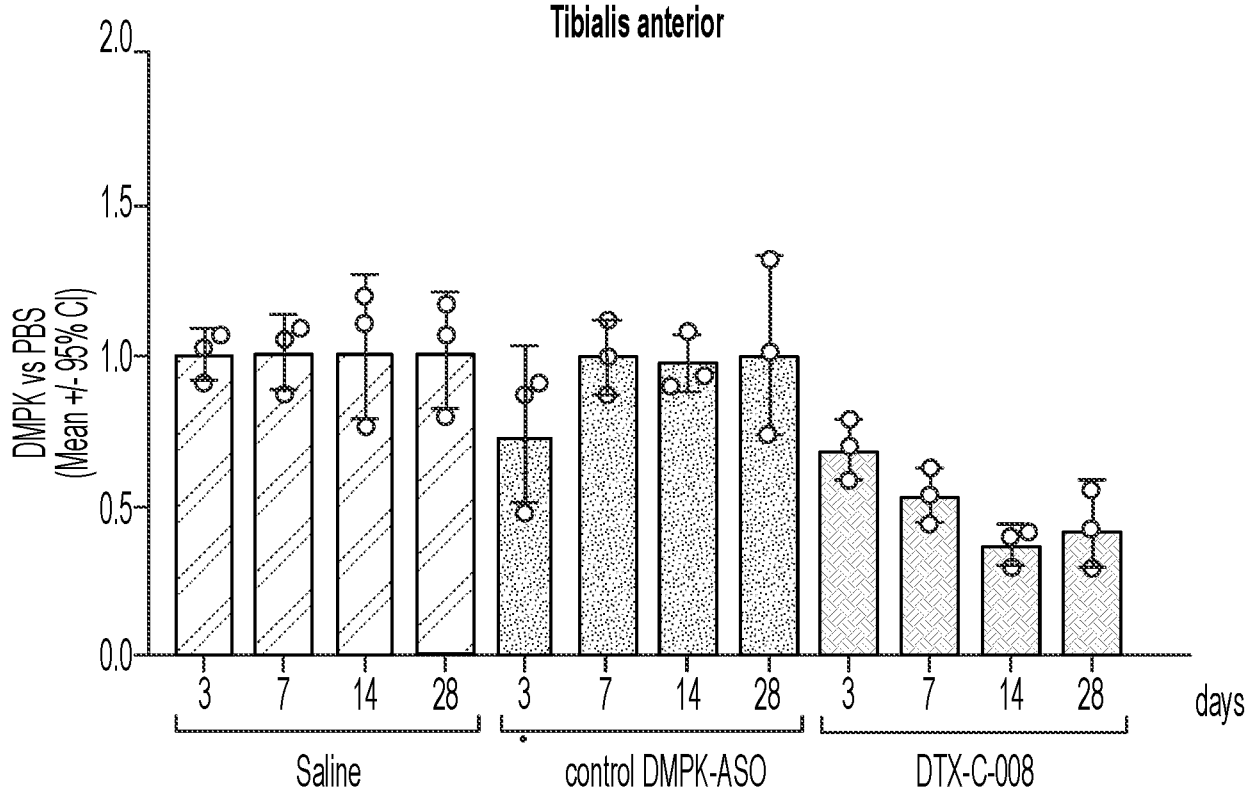


FIG. 11B

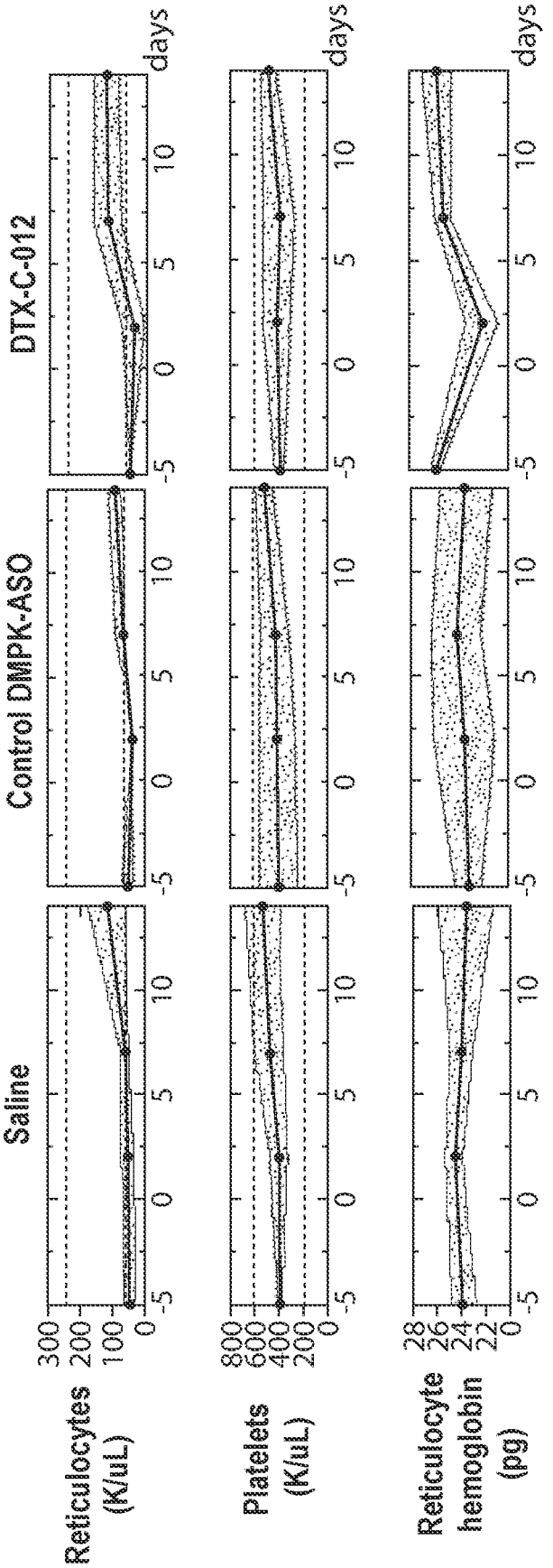

Saline
Control DMPK-ASO
DTX-C-012
Reticulocytes (K/uL)
Platelets (K/uL)
Reticulocyte hemoglobin (pg)
days
300
200
100
0
800
600
400
200
28
26
24
22
-5
0
5
10

FIG. 12

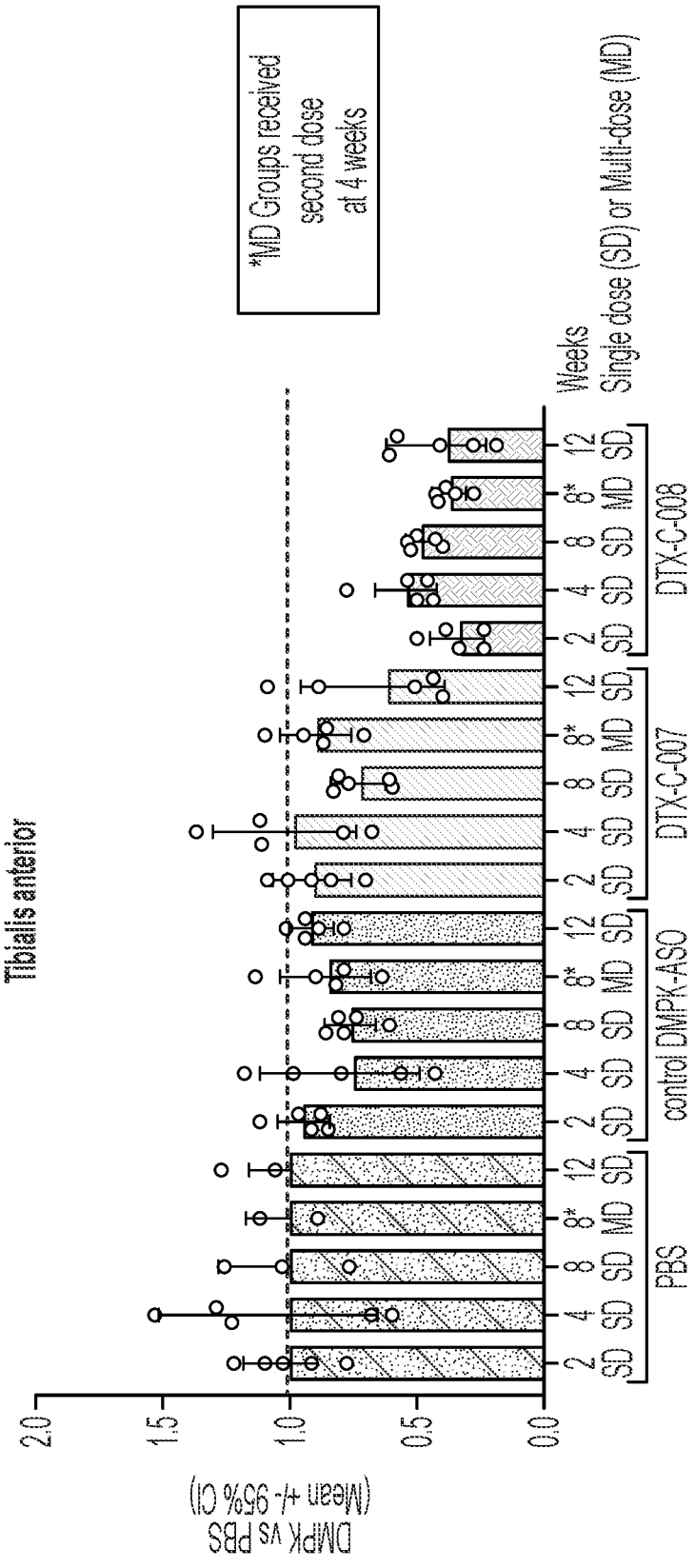

Tibialis anterior
DMPK vs PBS
(Mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
*MD Groups received second dose at 4 weeks
Weeks
Single dose (SD) or Multi-dose (MD)
SD SD SD MD SD
2 4 8 8* 12
PBS
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 13A

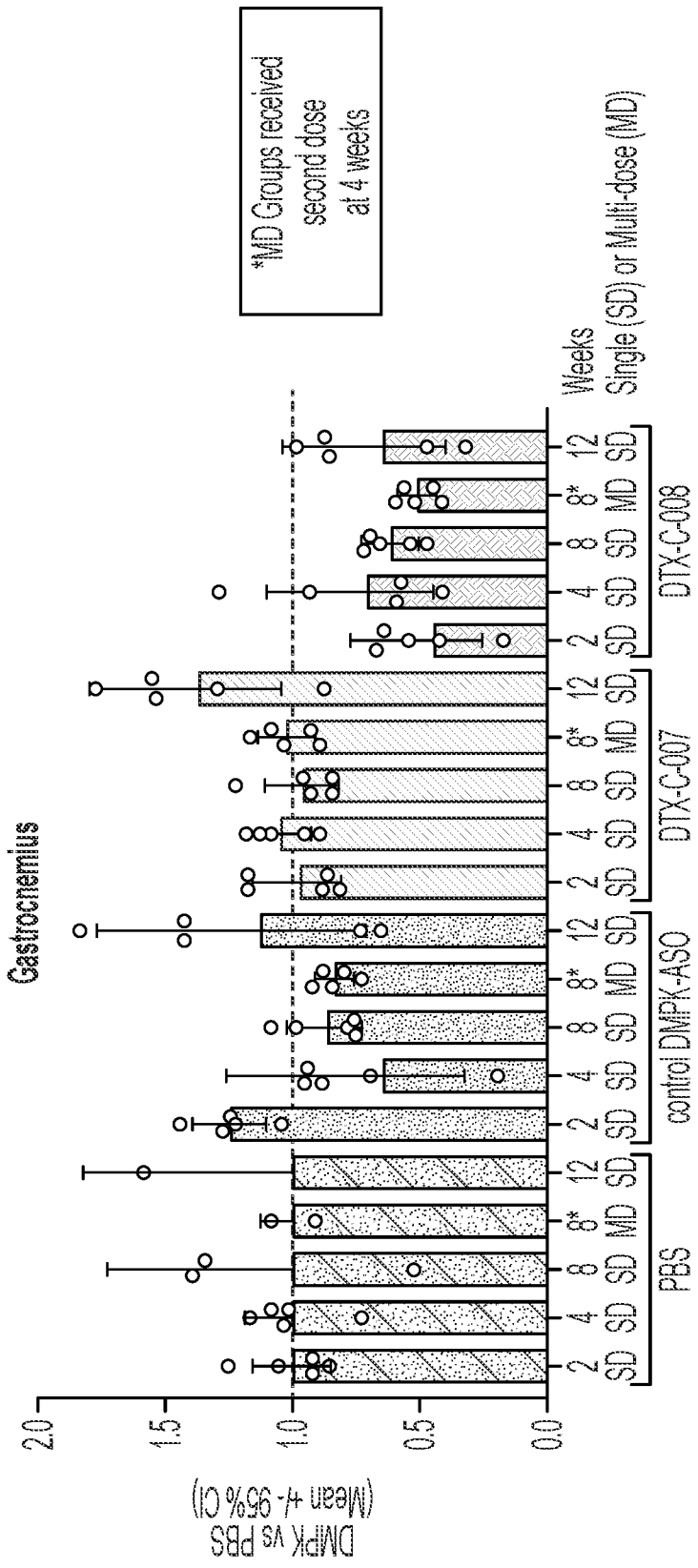

*MD Groups received second dose at 4 weeks
Gastrocnemius
DMPK vs PBS (Mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
Weeks
Single (SD) or Multi-dose (MD)
2 SD
4 SD
8 SD
8* MD
12 SD
PBS
control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 13B

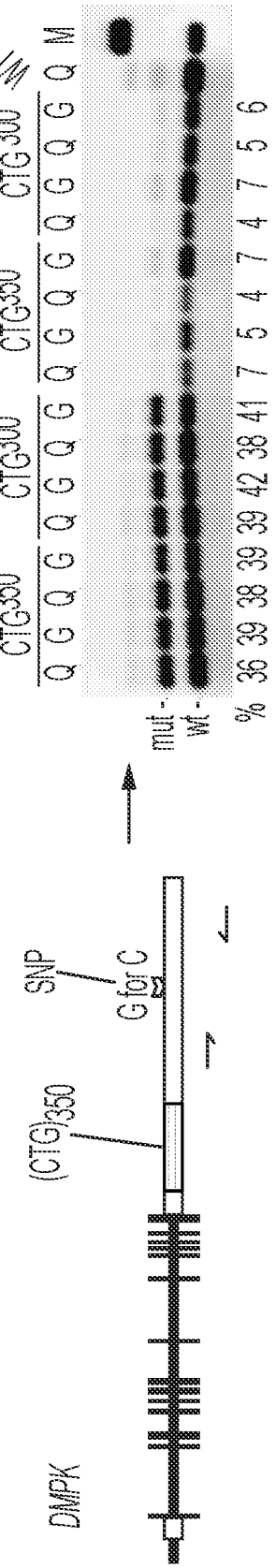

DMPK
(CTG)350
SNP
G for C
total RNA
cytoplasmic RNA
CTG350
CTG300
CTG350
CTG300
Q G Q Q G Q Q G Q Q G Q Q G Q M
% 36 39 38 39 39 42 38 41 7 5 4 7 4 7 5 6
mut -
wt -

FIG. 14A

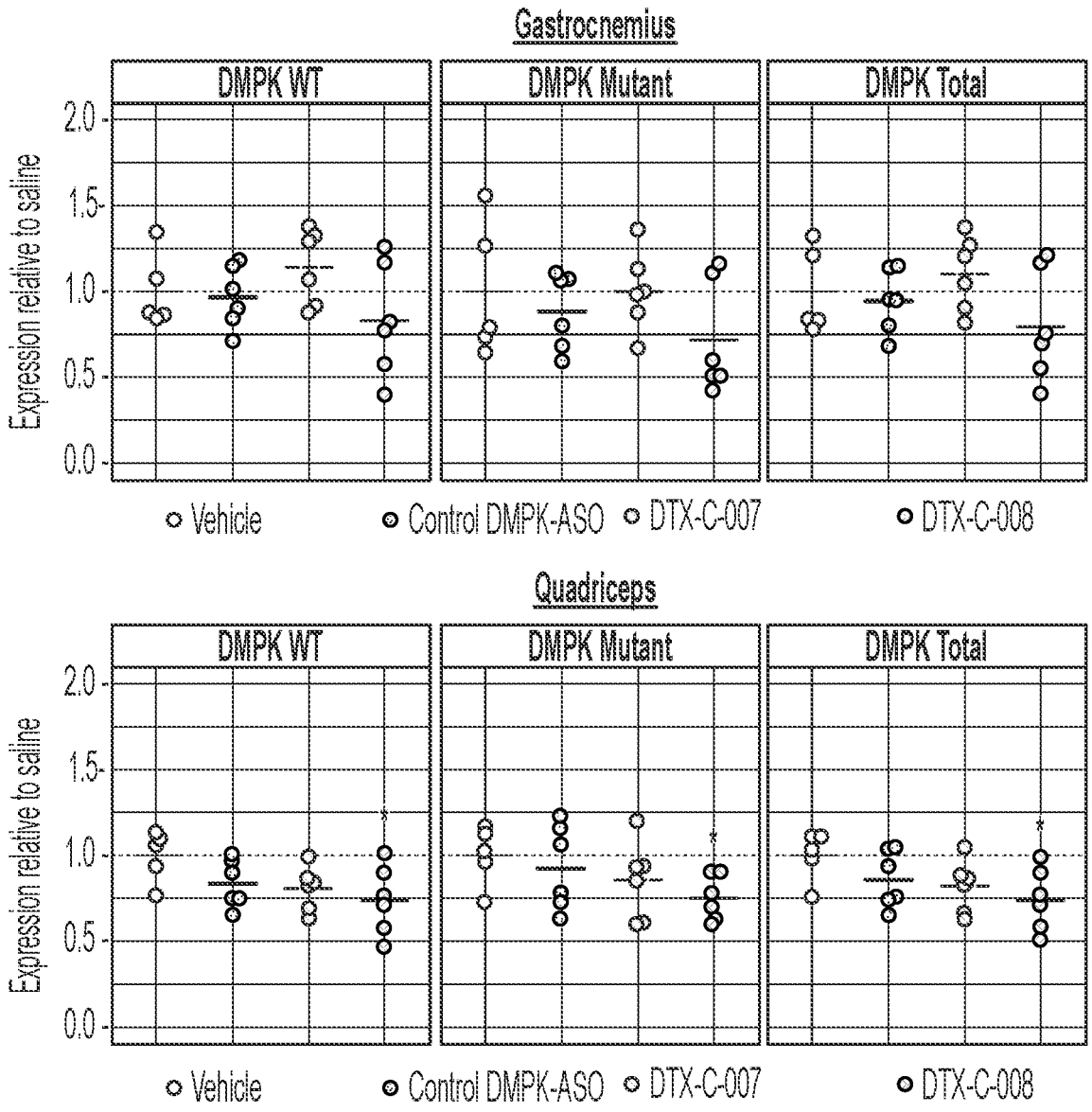

Gastrocnemius
DMPK WT
DMPK Mutant
DMPK Total
Expression relative to saline
2.0
1.5
1.0
0.5
0.0
Vehicle
Control DMPK-ASO
DTX-C-007
DTX-C-008
Quadriceps
DMPK WT
DMPK Mutant
DMPK Total
Expression relative to saline
2.0
1.5
1.0
0.5
0.0
Vehicle
Control DMPK-ASO
DTX-C-007
DTX-C-008

FIG. 14B

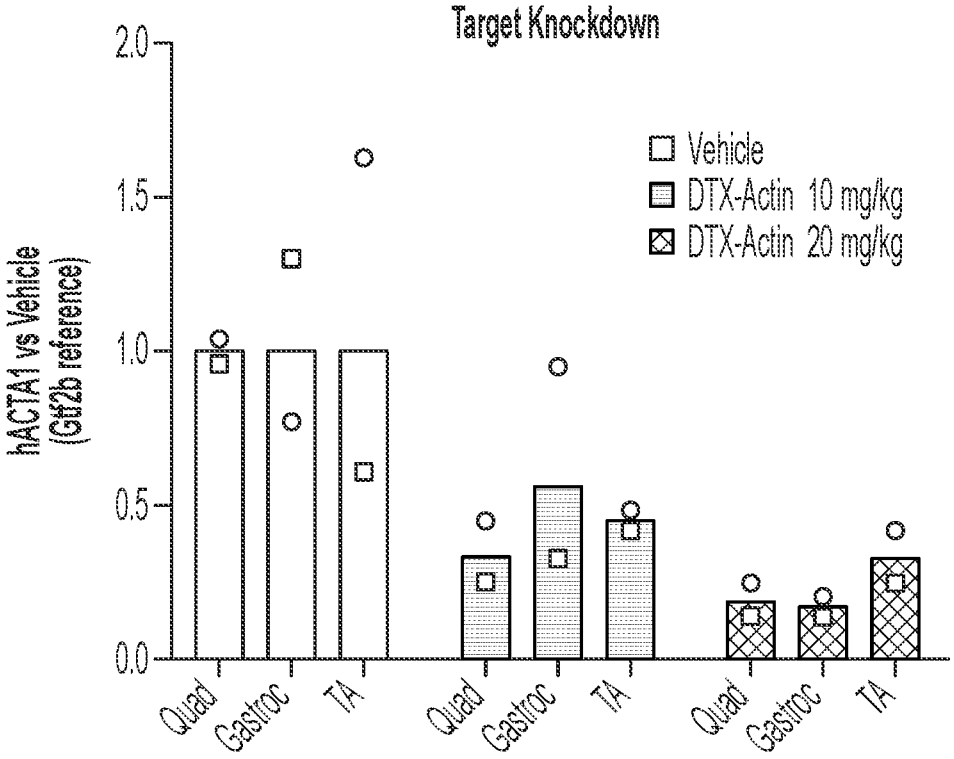


FIG. 15A

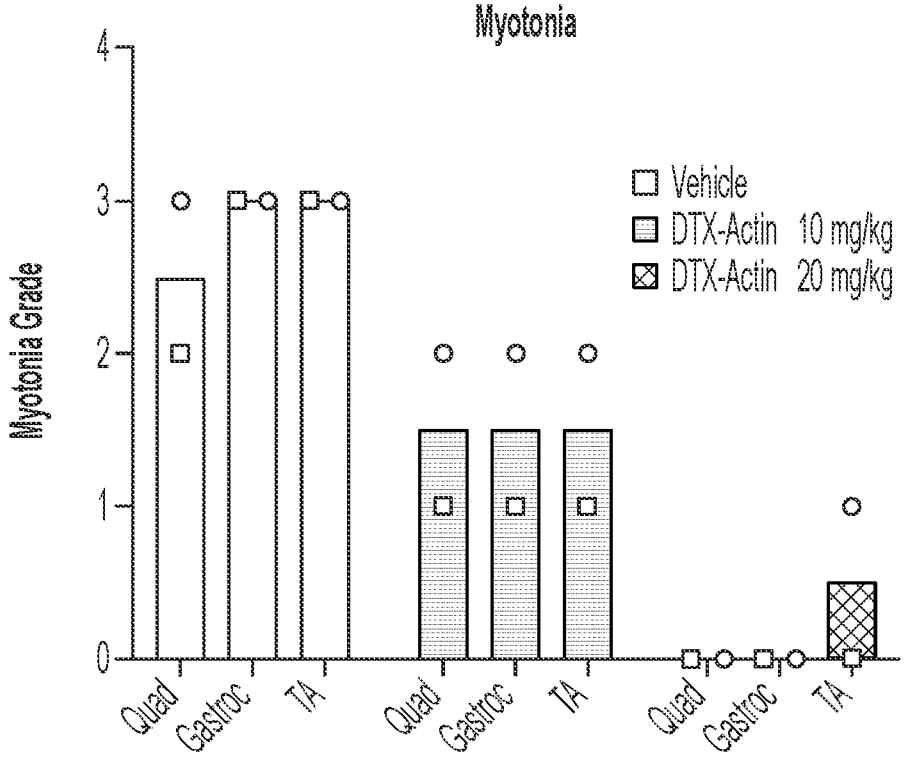


FIG. 15B

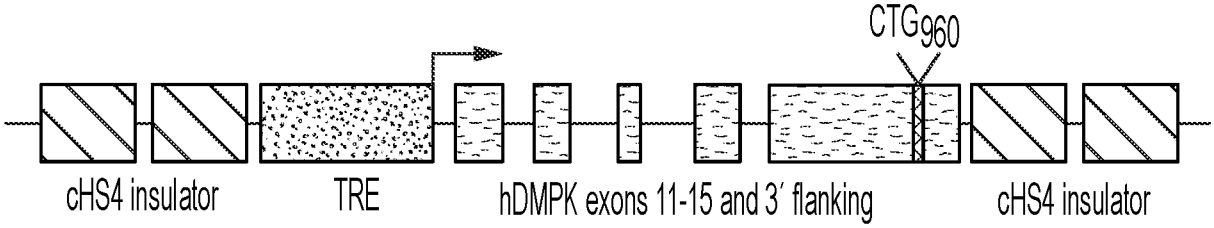


FIG. 16A

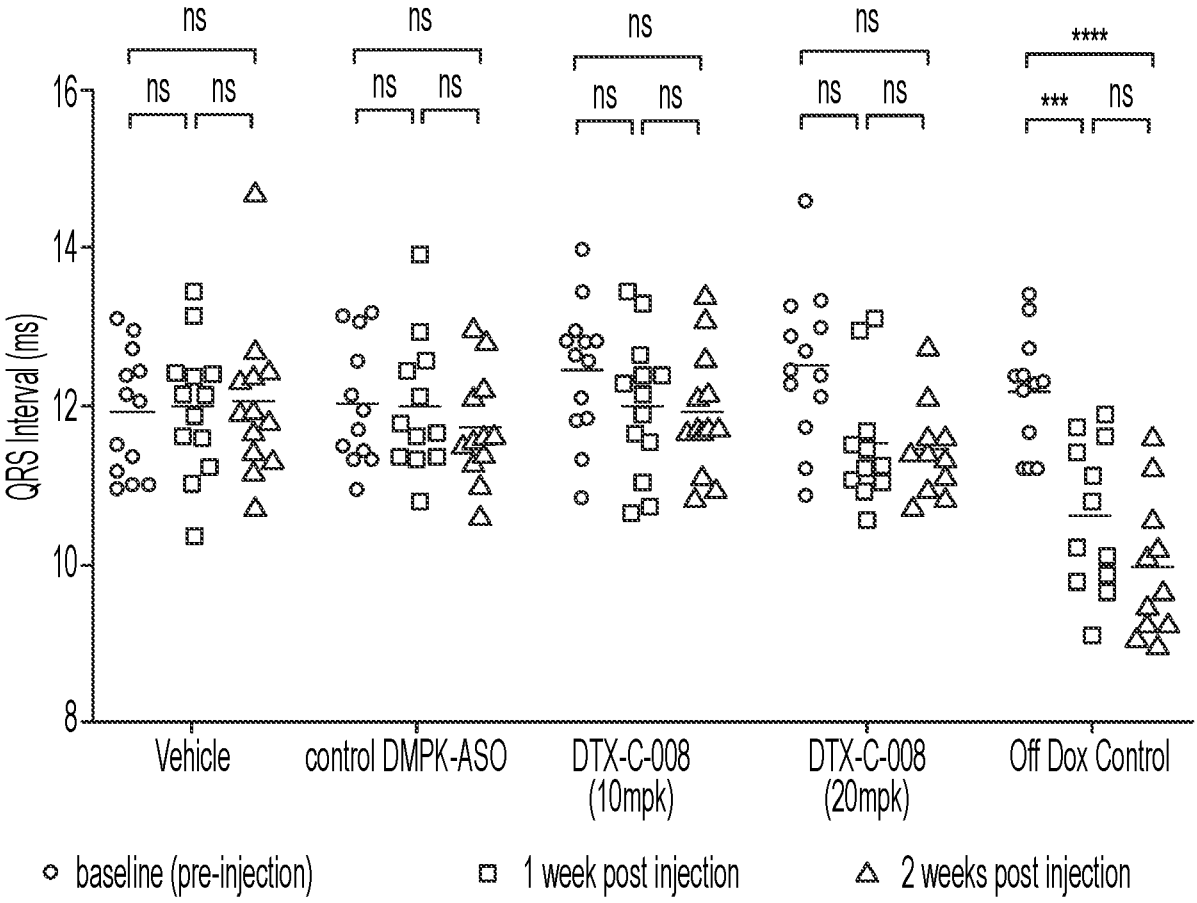


FIG. 16B

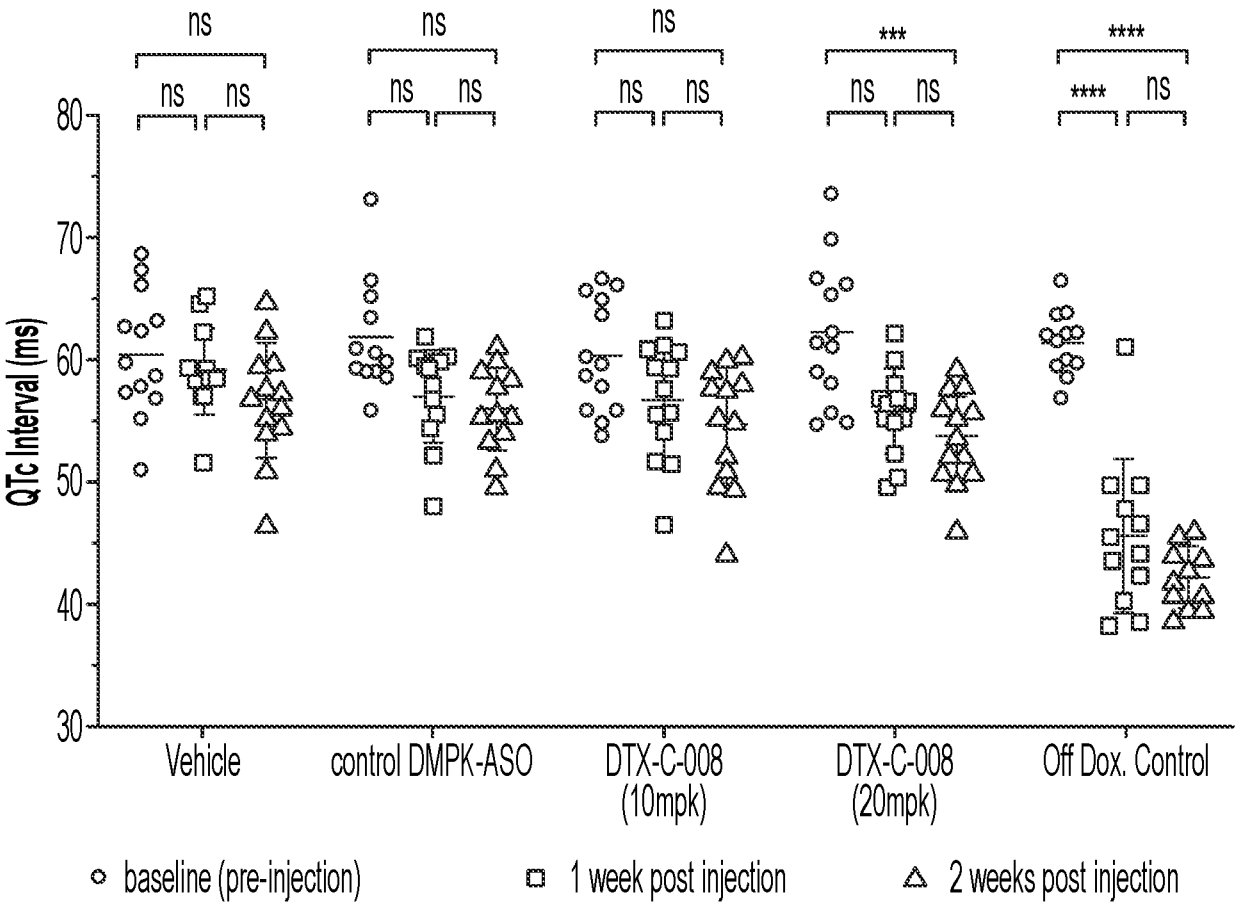


FIG. 16C

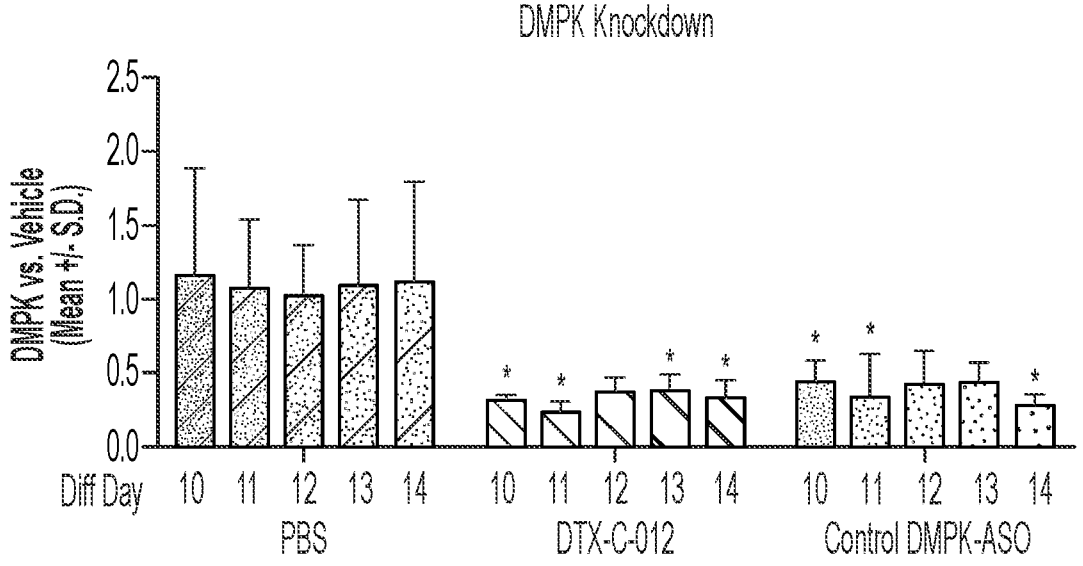


FIG. 17A

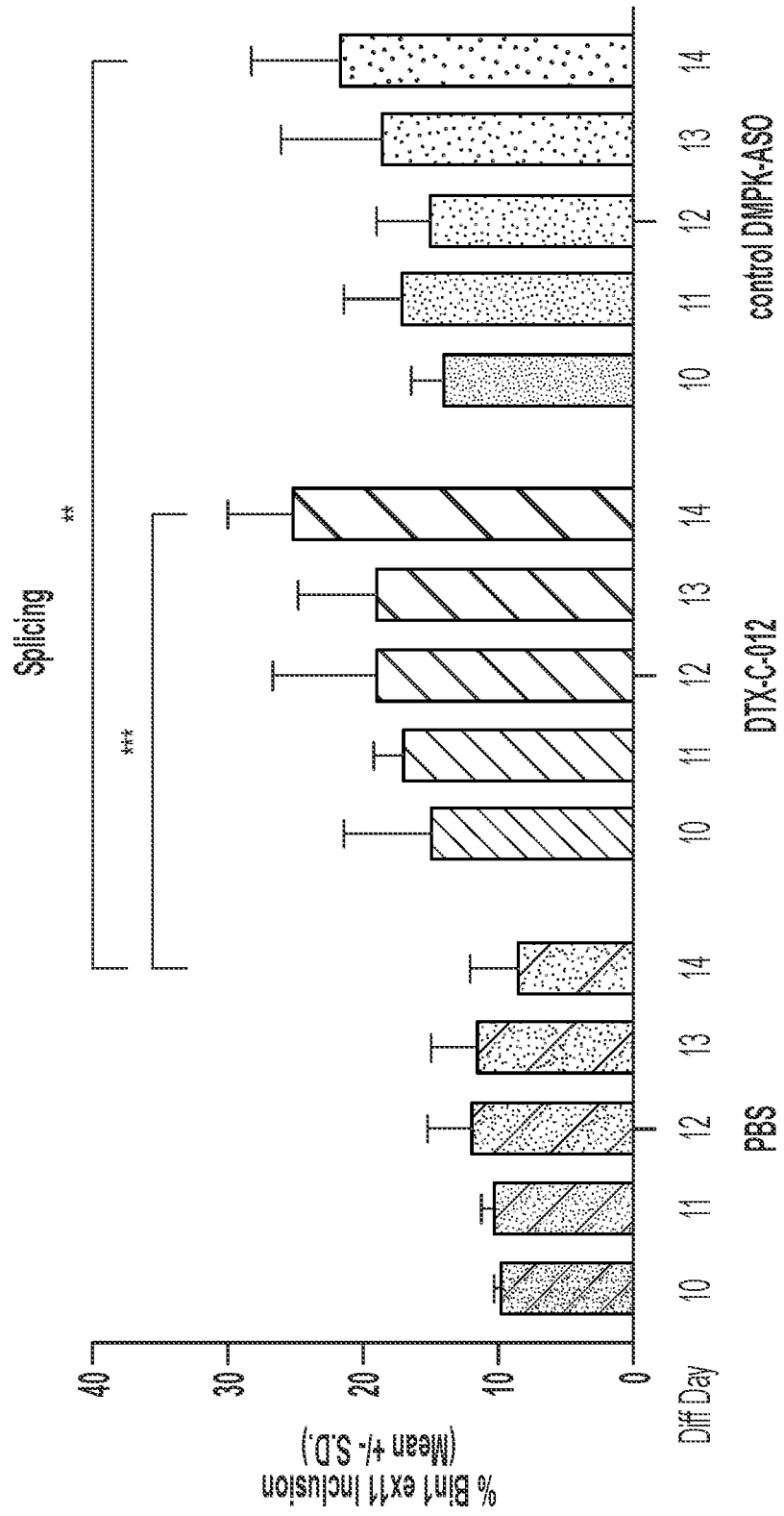

% Bin1 ex11 inclusion
(Mean +/- S.D.)
40
30
20
10
0
Diff Day
10
11
12
13
14
PBS
DTX-C-012
control DMPK-ASO
Splicing
**
***

FIG. 17B

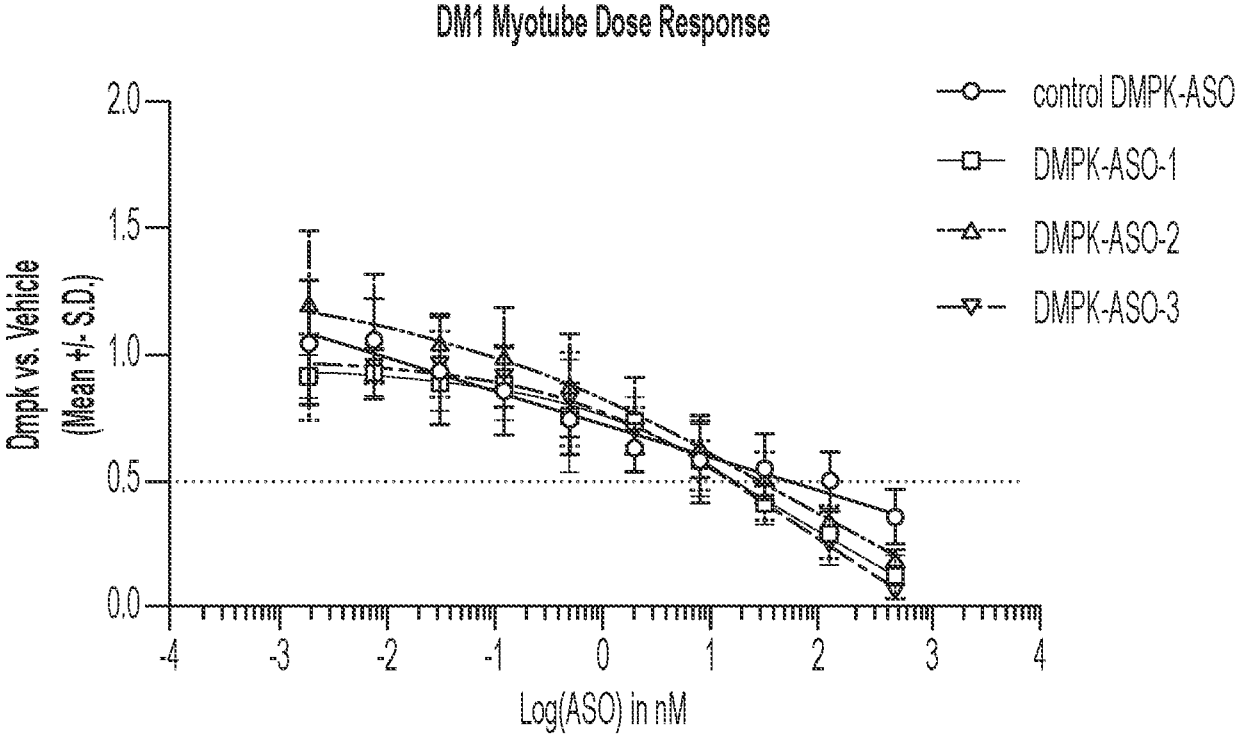


FIG. 18A

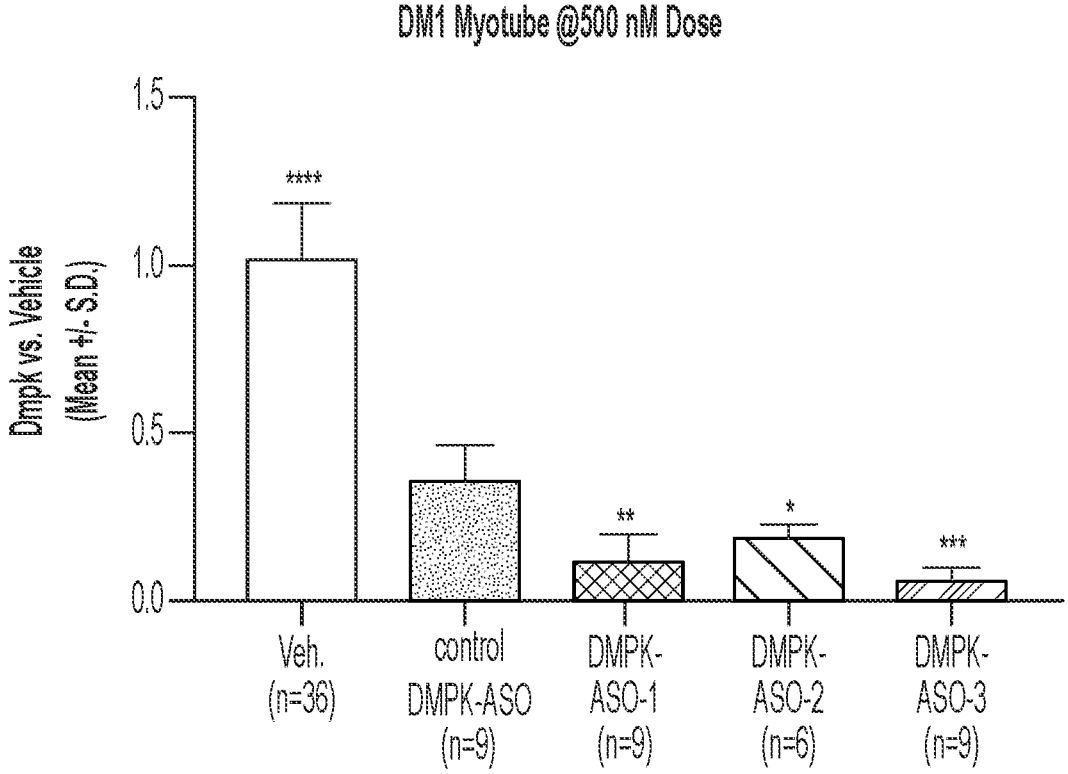


FIG. 18B

Oligo	50% DMPK KD (nM)	80% DMPK KD (nM)
DMPK-ASO-1	17.23	230.3
DMPK-ASO-2	28.34	522.04
DMPK-ASO-3	15.66	169.89
control DMPK-ASO (tool)	52.6	~10324 (extrapolated)

FIG. 18C

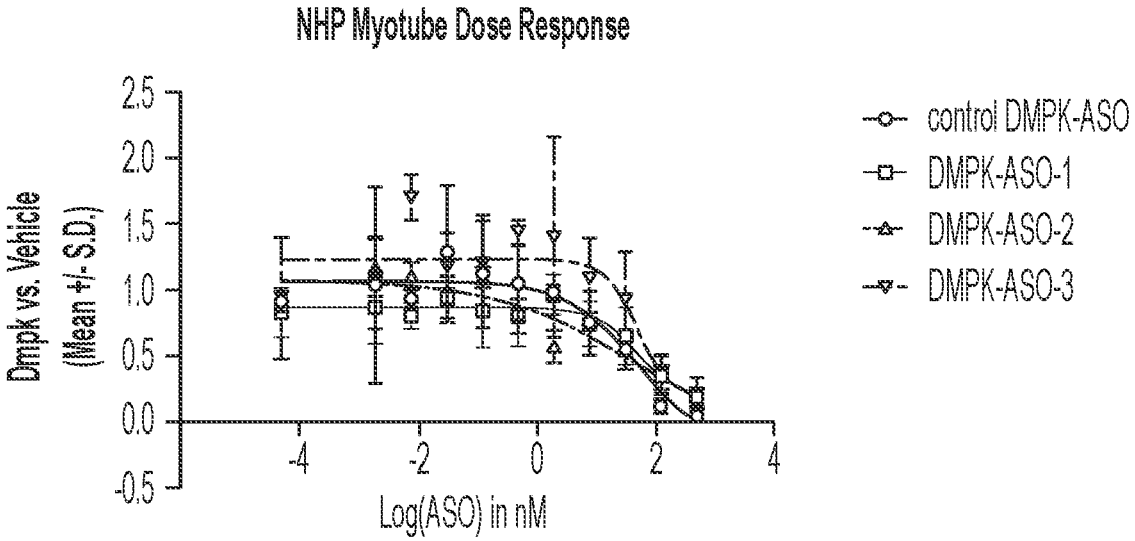


FIG. 19A

Oligo	50% DMPK KD (nM)	80% DMPK KD (nM)
DMPK-ASO-1	54	709
DMPK-ASO-2	31	461
DMPK-ASO-3	83	558
control DMPK-ASO (tool)	37	141

FIG. 19B

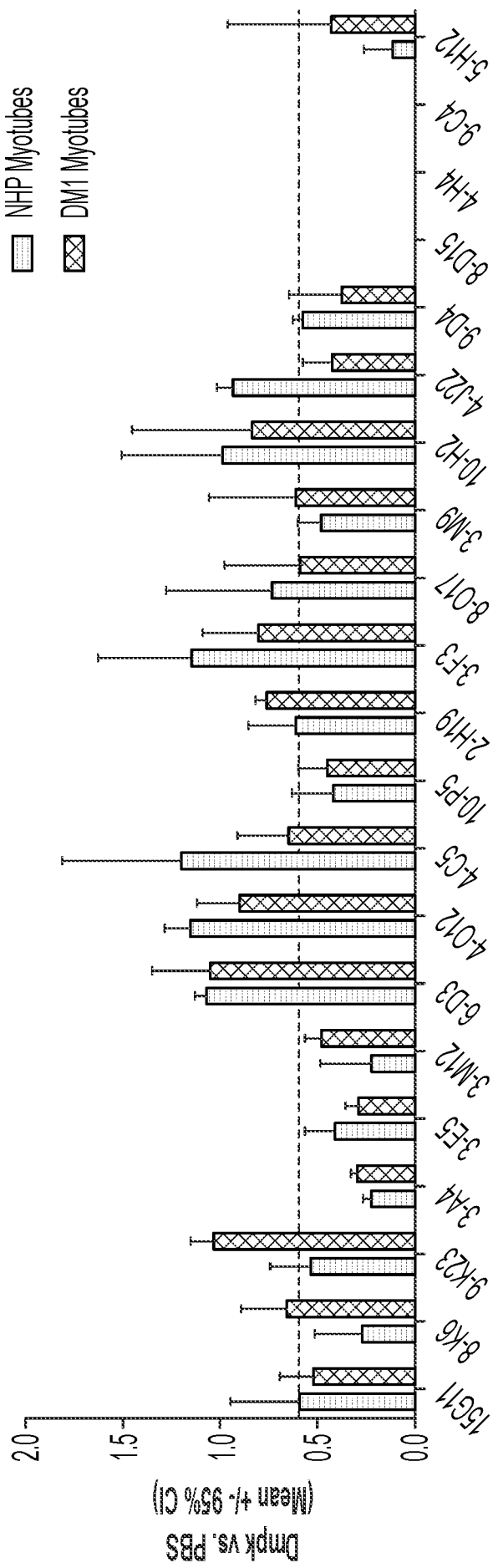

NHP Myotubes
DM1 Myotubes
Dmpk vs. PBS
(Mean +/- 95% CI)
2.0
1.5
1.0
0.5
0.0
15C11
8-K6
9-K23
3-A4
3-E5
3-M12
6-D3
4-O12
4-C5
10-P5
2-H19
3-E3
8-O17
3-M9
10-H2
4-J22
9-D4
8-D15
4-H4
9-C4
5-H12

FIG. 20

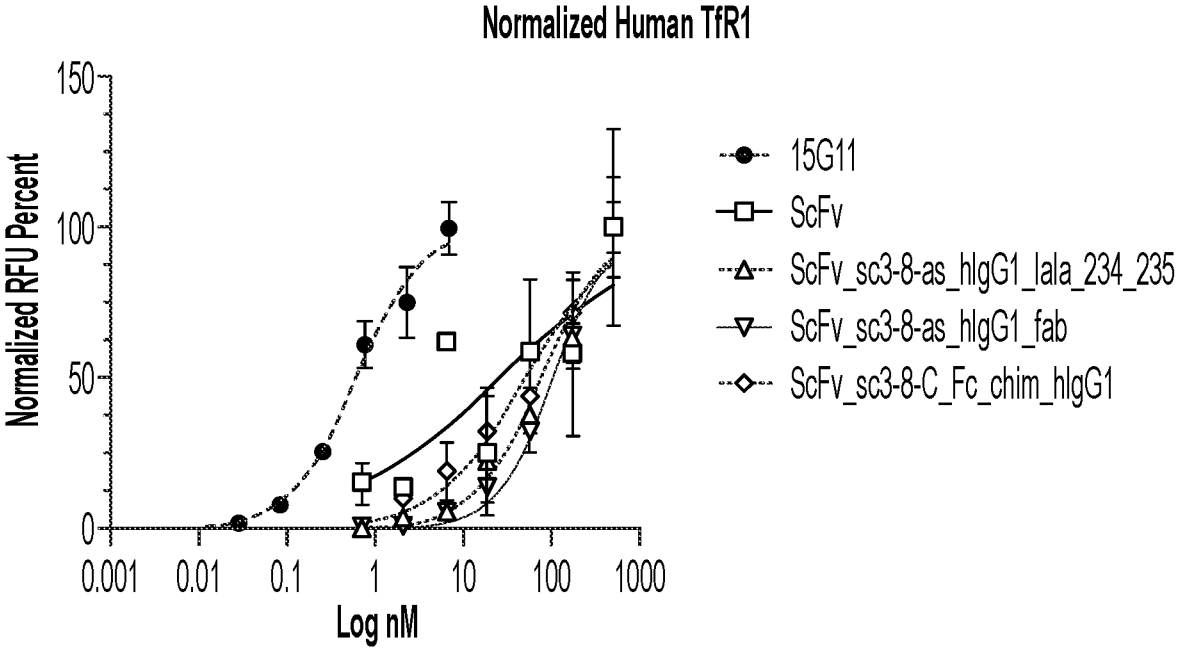


FIG. 21A

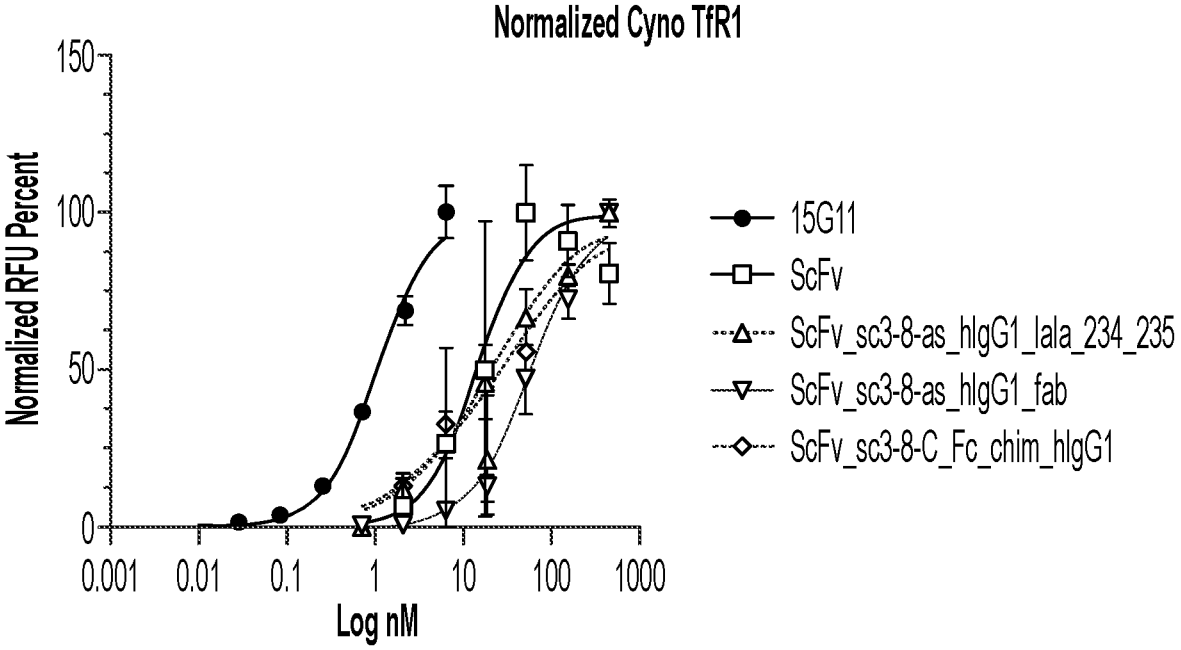


FIG. 21B

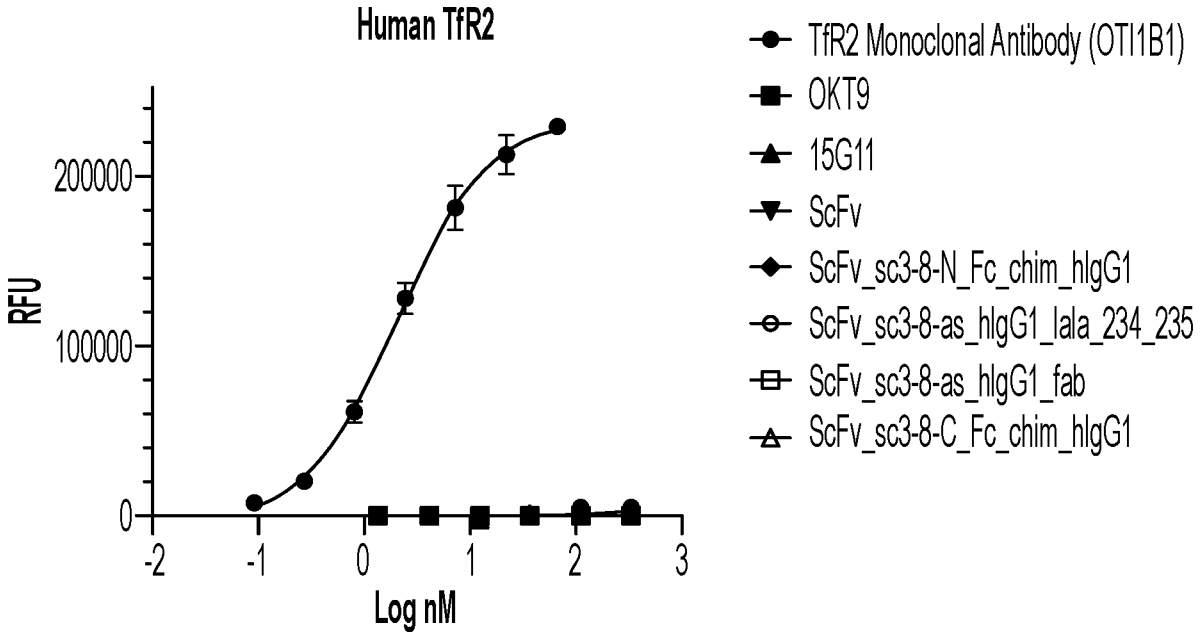

Human TfR2
RFU
200000
100000
0
-2
-1
0
1
2
3
Log nM
TfR2 Monoclonal Antibody (OTI1B1)
OKT9
15G11
ScFv
ScFv_sc3-8-N_Fc_chim_hIgG1
ScFv_sc3-8-as_hIgG1_lala_234_235
ScFv_sc3-8-as_hIgG1_fab
ScFv_sc3-8-C_Fc_chim_hIgG1

FIG. 22

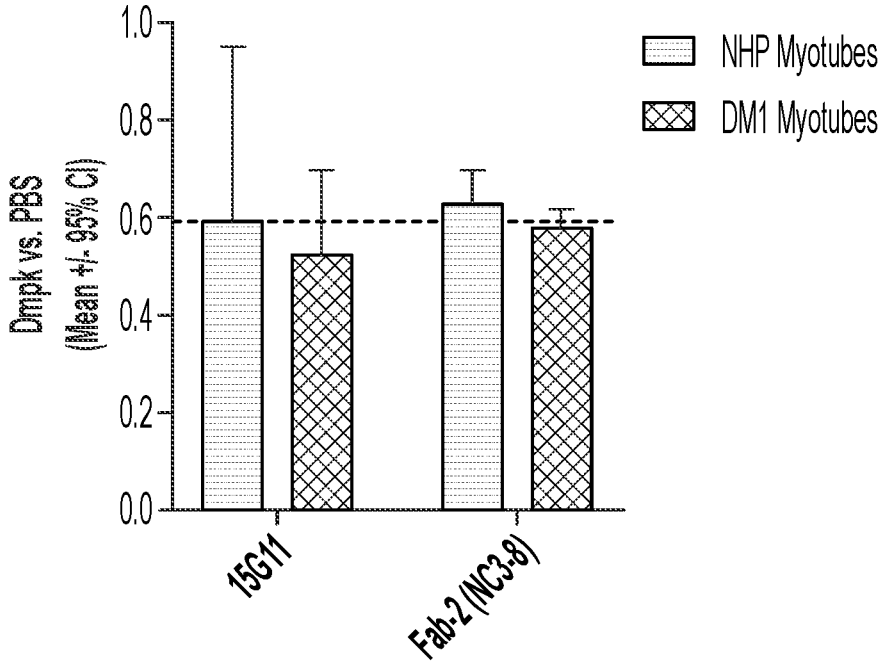

Dmpk vs. PBS
(Mean +/- 95% CI)
1.0
0.8
0.6
0.4
0.2
0.0
15G11
Fab-2(NC3-8)
NHP Myotubes
DM1 Myotubes

FIG. 23

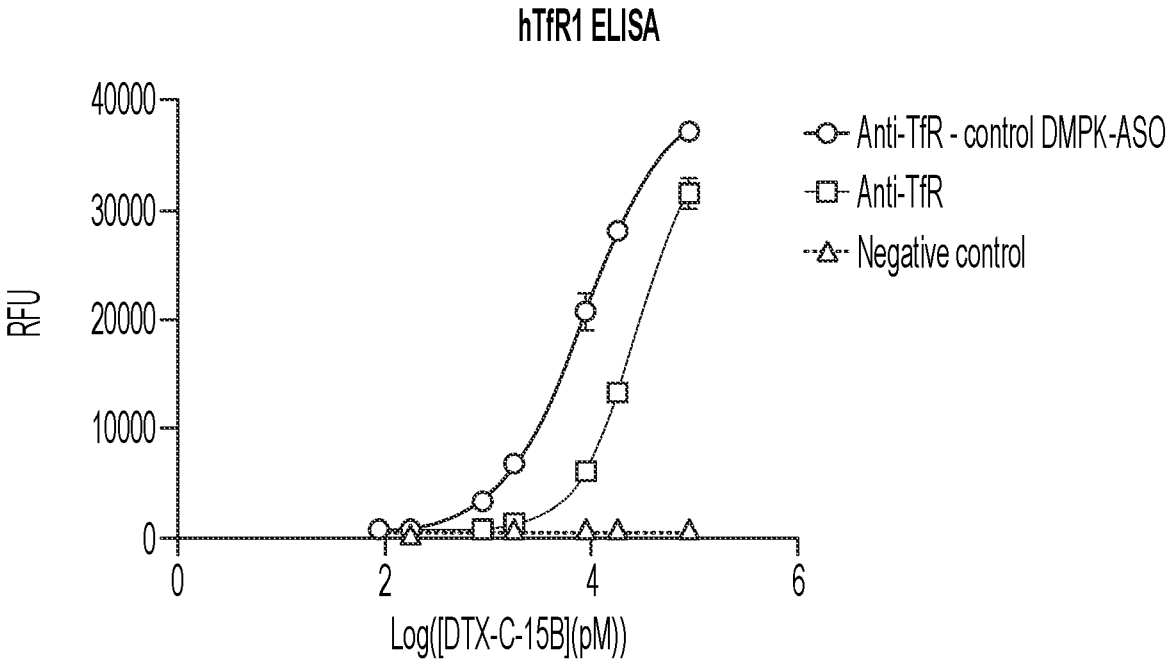


FIG. 24A

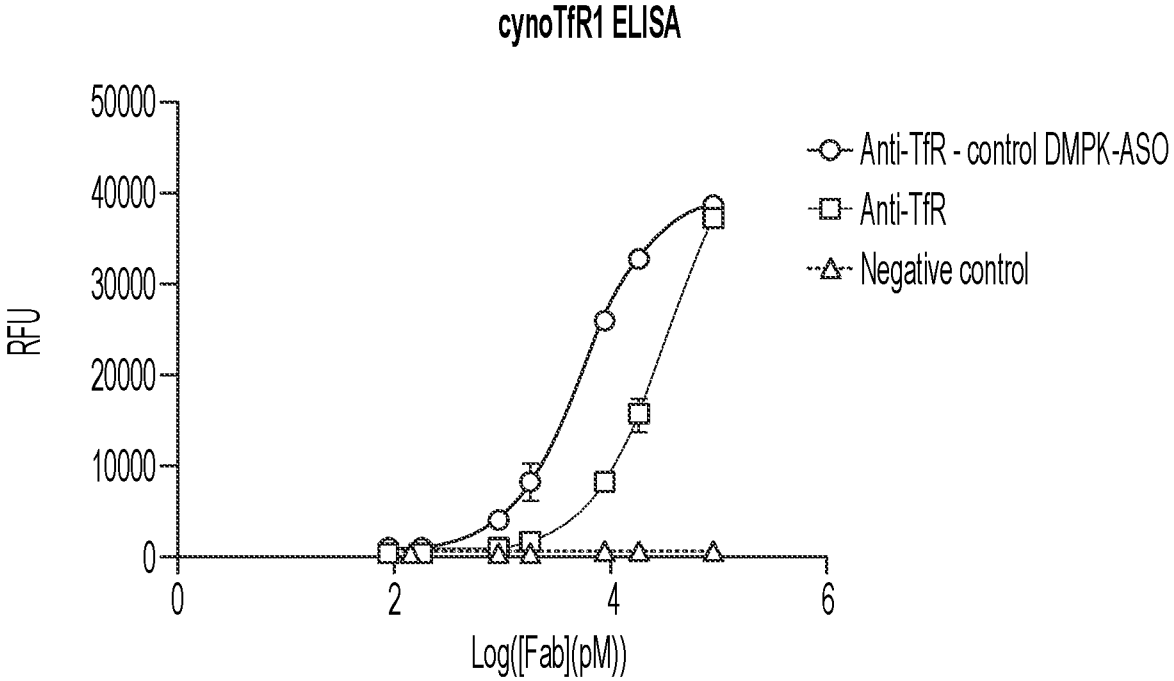


FIG. 24B

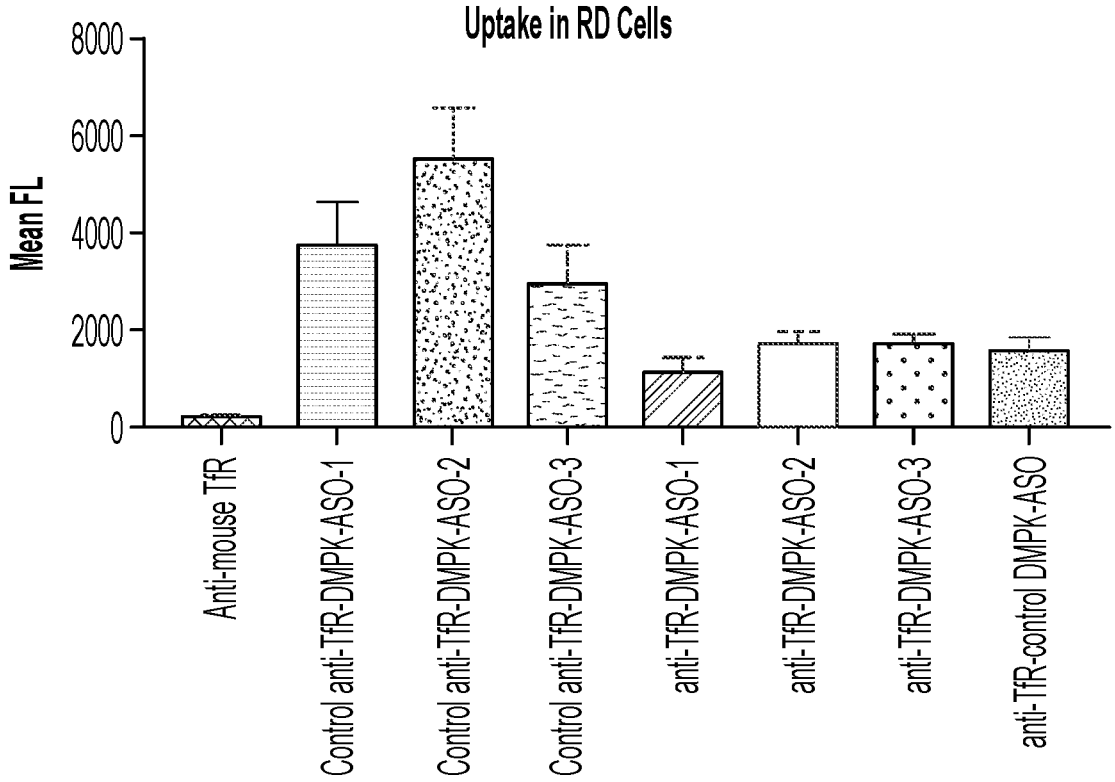

Uptake in RD Cells
Mean FL
8000
6000
4000
2000
0
Anti-mouse TfR
Control anti-TfR-DMPK-ASO-1
Control anti-TfR-DMPK-ASO-2
Control anti-TfR-DMPK-ASO-3
anti-TfR-DMPK-ASO-1
anti-TfR-DMPK-ASO-2
anti-TfR-DMPK-ASO-3
anti-TfR-control DMPK-ASO

FIG. 25

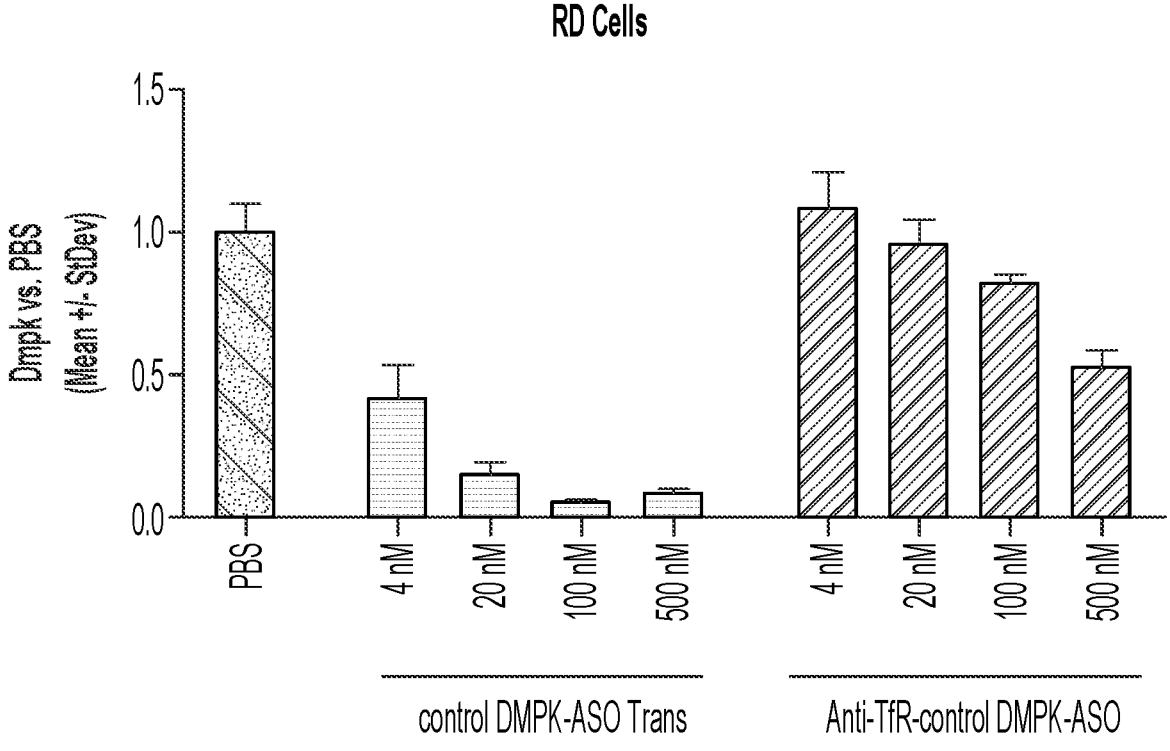

RD Cells
Dmpk vs. PBS
(Mean +/- StDev)
1.5
1.0
0.5
0.0
PBS
4 nM
20 nM
100 nM
500 nM
4 nM
20 nM
100 nM
500 nM
control DMPK-ASO Trans
Anti-TfR-control DMPK-ASO

FIG. 26

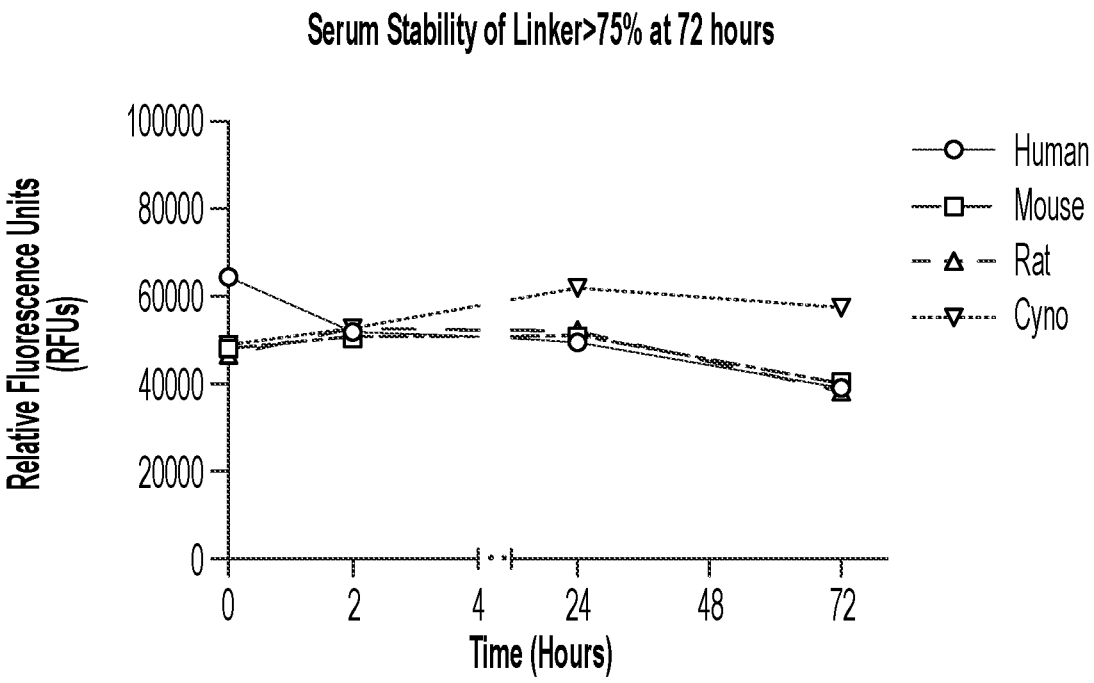

Serum Stability of Linker>75% at 72 hours
Relative Fluorescence Units (RFUs)
100000
80000
60000
40000
20000
0
0
2
4
24
48
72
Time (Hours)
Human
Mouse
Rat
Cyno

FIG. 27

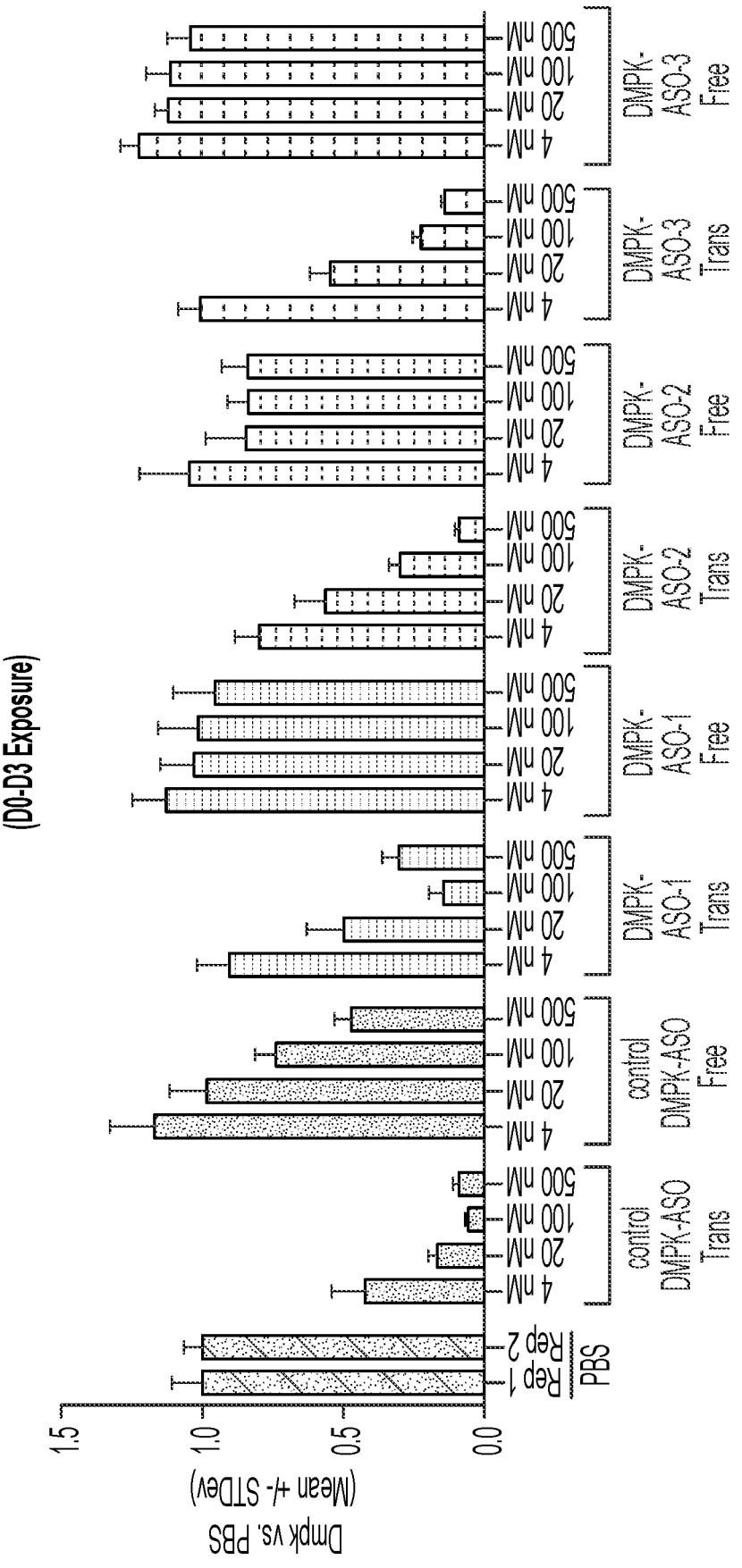

(D0-D3 Exposure)
Dmpk vs. PBS
(Mean +/- STDev)
1.5
1.0
0.5
0.0
PBS
Rep 1
Rep 2
control DMPK-ASO Trans
4 nM
20 nM
100 nM
500 nM
control DMPK-ASO Free
DMPK-ASO-1 Trans
DMPK-ASO-1 Free
DMPK-ASO-2 Trans
DMPK-ASO-2 Free
DMPK-ASO-3 Trans
DMPK-ASO-3 Free

FIG. 28

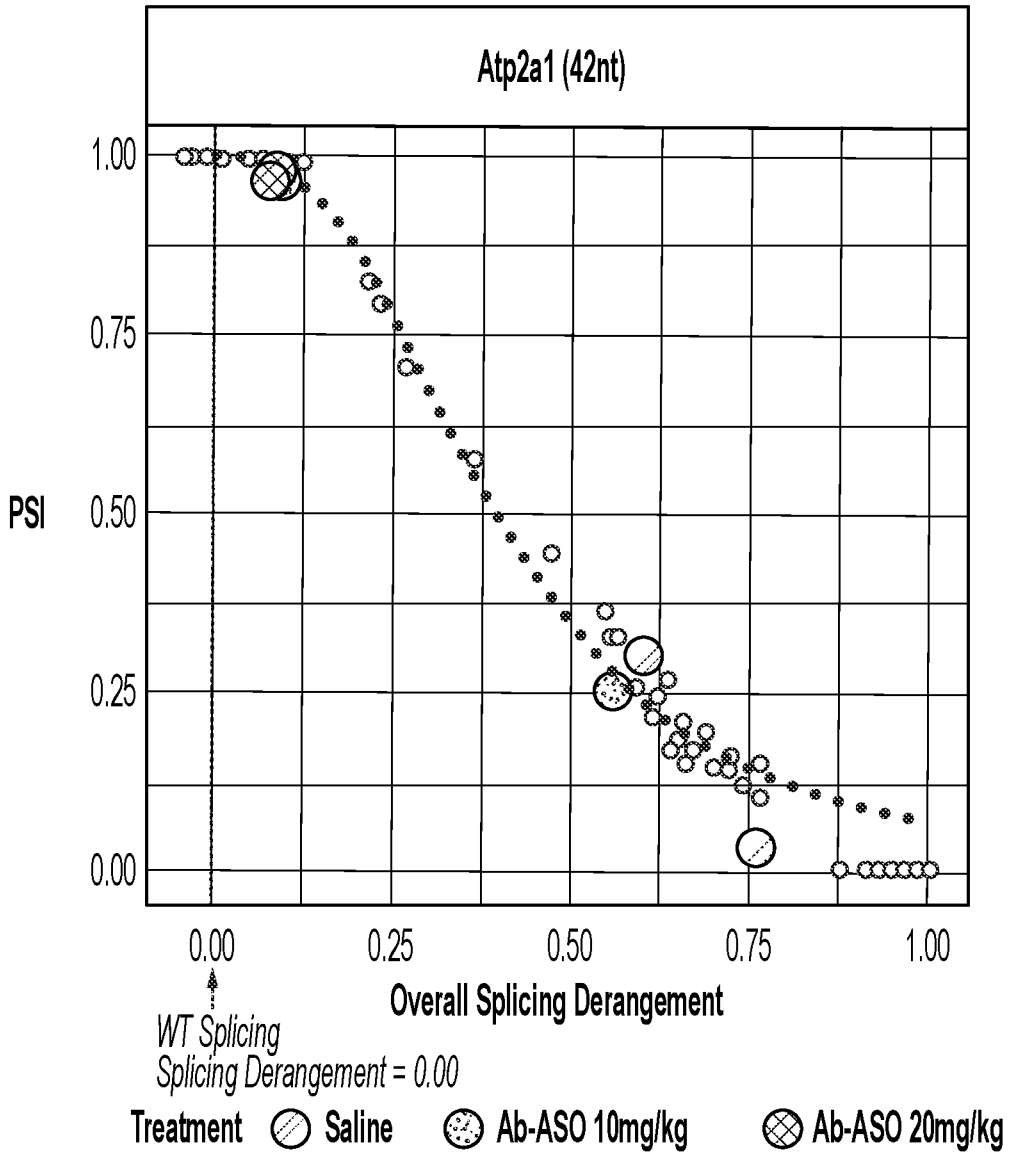

Atp2a1 (42nt)
PSI
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Overall Splicing Derangement
WT Splicing
Splicing Derangement = 0.00
Treatment
Saline
Ab-ASO 10mg/kg
Ab-ASO 20mg/kg

FIG. 29

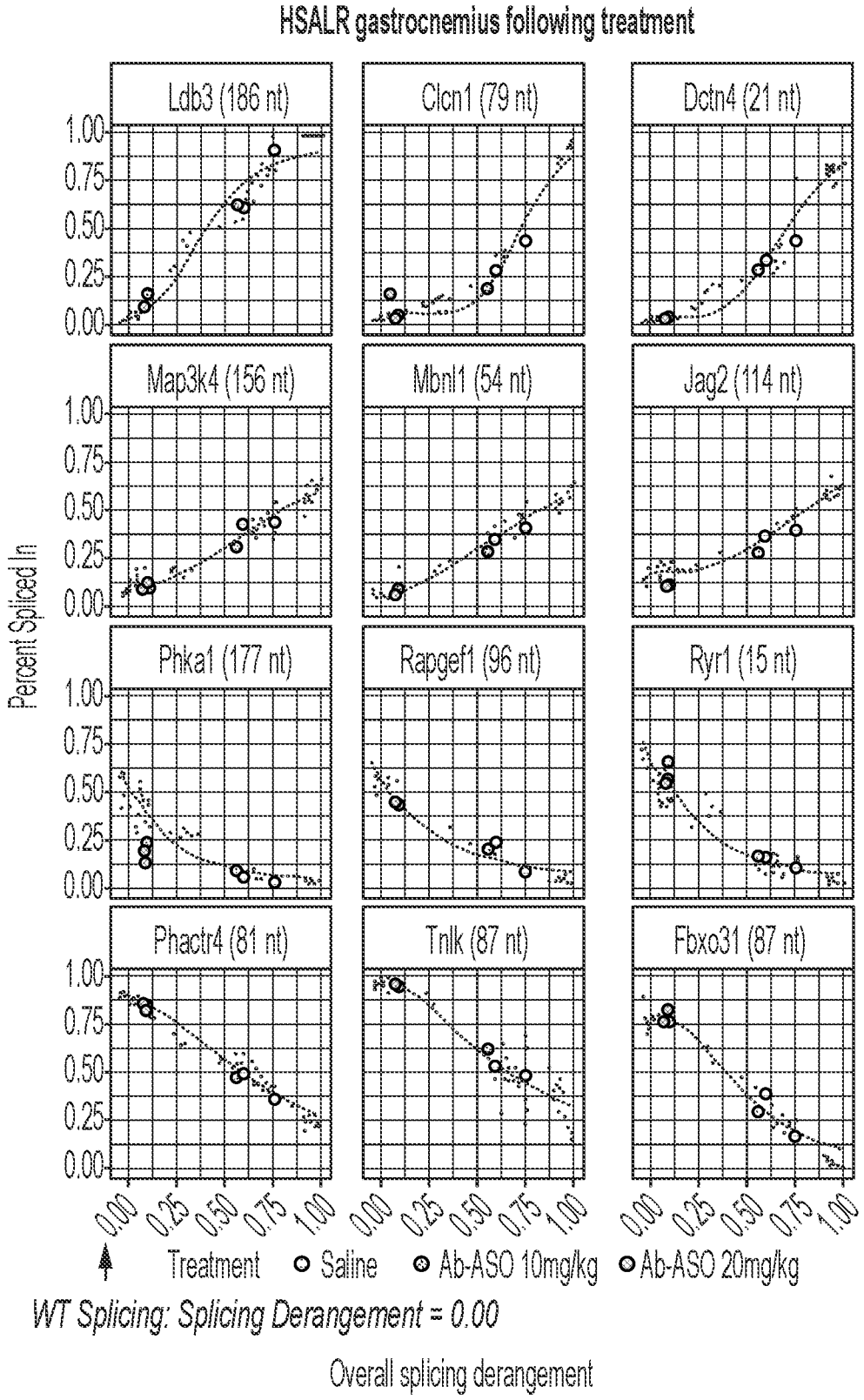

HSALR gastrocnemius following treatment
Ldb3 (186 nt)
Clcn1 (79 nt)
Dctn4 (21 nt)
Map3k4 (156 nt)
Mbnl1 (54 nt)
Jag2 (114 nt)
Phka1 (177 nt)
Rapgef1 (96 nt)
Ryr1 (15 nt)
Phactr4 (81 nt)
Tnlk (87 nt)
Fbxo31 (87 nt)
Percent Spliced In
0.00
0.25
0.50
0.75
1.00
Treatment
Saline
Ab-ASO 10mg/kg
Ab-ASO 20mg/kg
WT Splicing: Splicing Derangement = 0.00
Overall splicing derangement

FIG. 30A

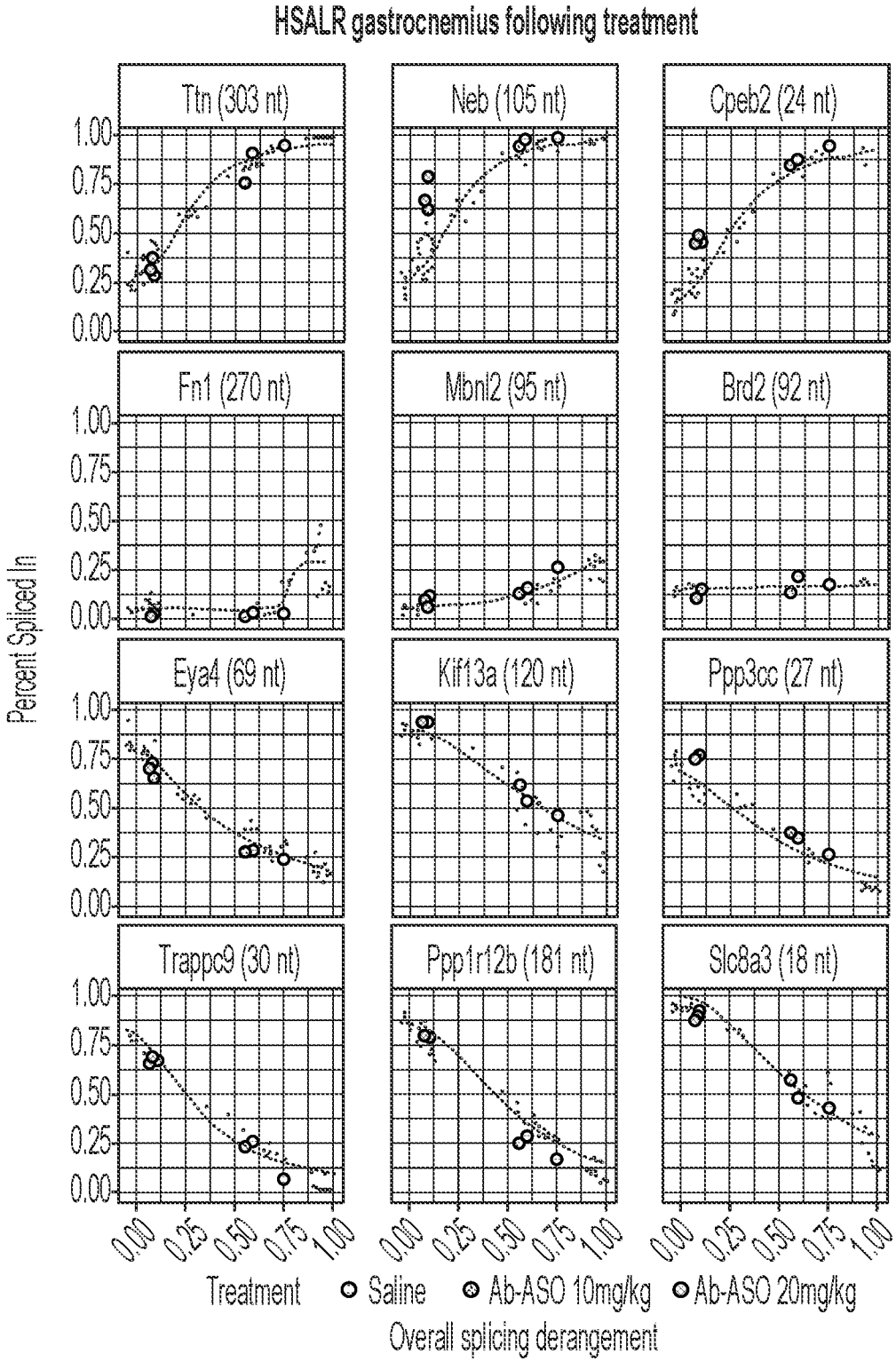

HSALR gastrocnemius following treatment
Ttn (303 nt)
Neb (105 nt)
Cpeb2 (24 nt)
Fn1 (270 nt)
Mbnl2 (95 nt)
Brd2 (92 nt)
Eya4 (69 nt)
Kif13a (120 nt)
Ppp3cc (27 nt)
Trappc9 (30 nt)
Ppp1r12b (181 nt)
Slc8a3 (18 nt)
Percent Spliced In
0.00
0.25
0.50
0.75
1.00
Treatment
Saline
Ab-ASO 10mg/kg
Ab-ASO 20mg/kg
Overall splicing derangement

FIG. 30B

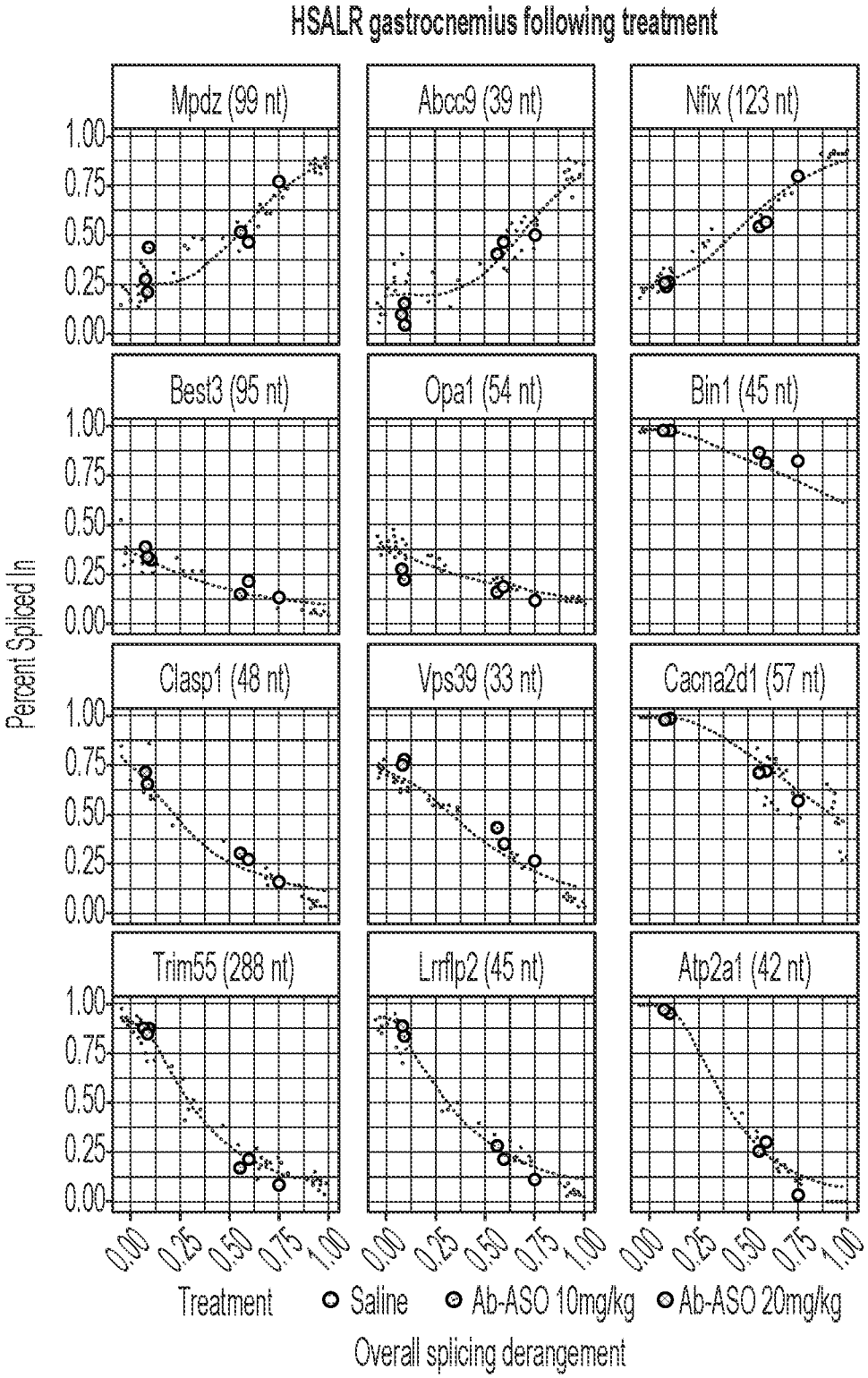

HSALR gastrocnemius following treatment
Mpdz (99 nt)
Abcc9 (39 nt)
Nfix (123 nt)
Best3 (95 nt)
Opa1 (54 nt)
Bin1 (45 nt)
Clasp1 (48 nt)
Vps39 (33 nt)
Cacna2d1 (57 nt)
Trim55 (288 nt)
Lrrflp2 (45 nt)
Atp2a1 (42 nt)
Percent Spliced In
0.00
0.25
0.50
0.75
1.00
Treatment
Saline
Ab-ASO 10mg/kg
Ab-ASO 20mg/kg
Overall splicing derangement

FIG. 30C

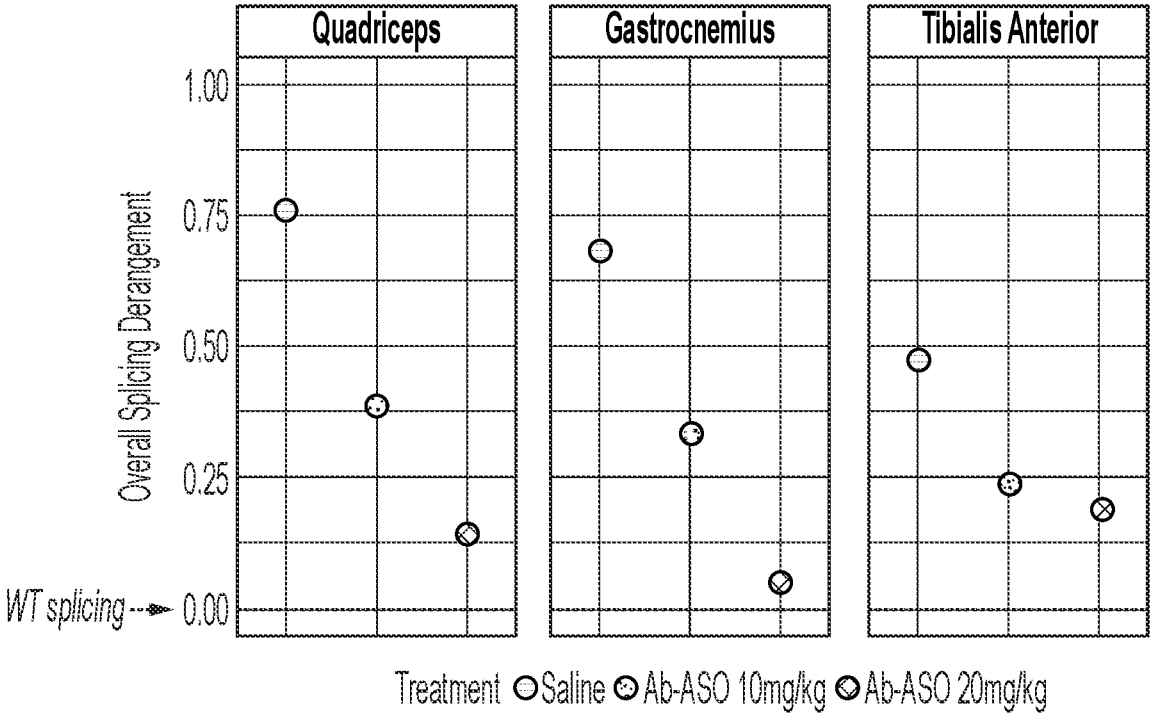

Quadriceps
Gastrocnemius
Tibialis Anterior
Overall Splicing Derangement
1.00
0.75
0.50
0.25
0.00
WT splicing
Treatment
Saline
Ab-ASO 10mg/kg
Ab-ASO 20mg/kg

FIG. 31

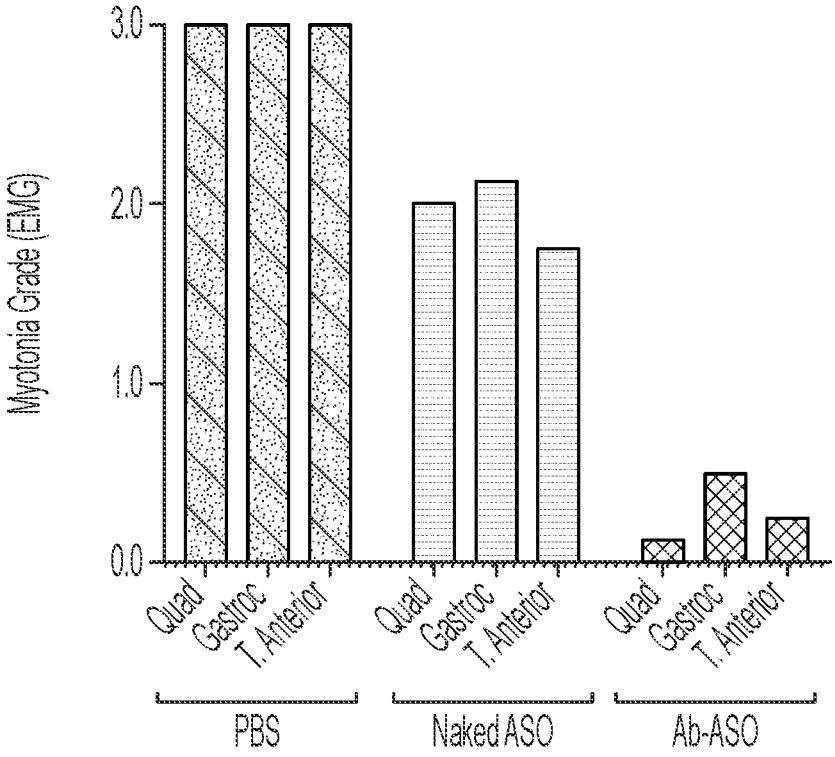

Myotonia Grade (EMG)
3.0
2.0
1.0
0.0
Quad
Gastroc
T. Anterior
PBS
Naked ASO
Ab-ASO

FIG. 32

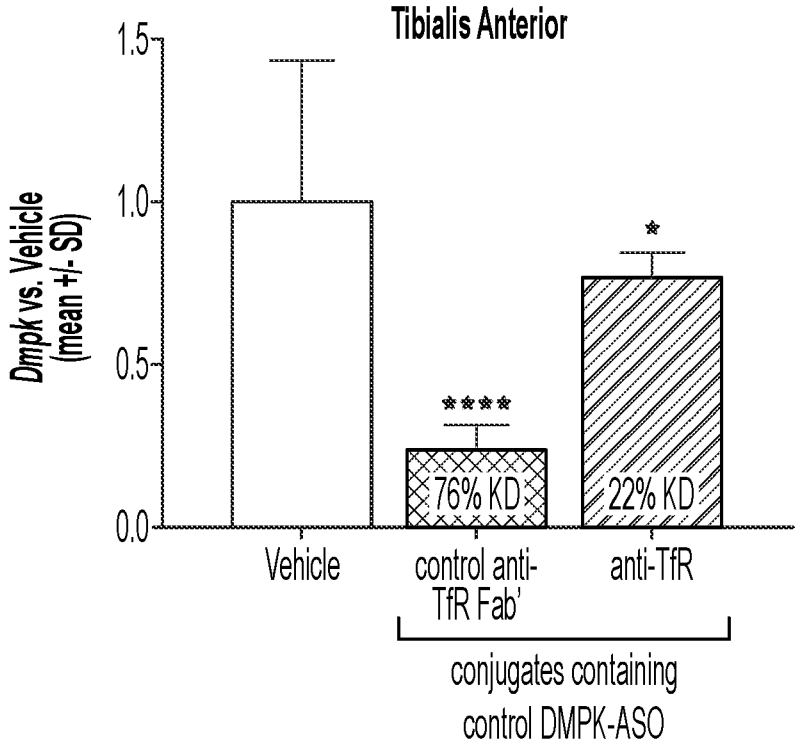


FIG. 33A

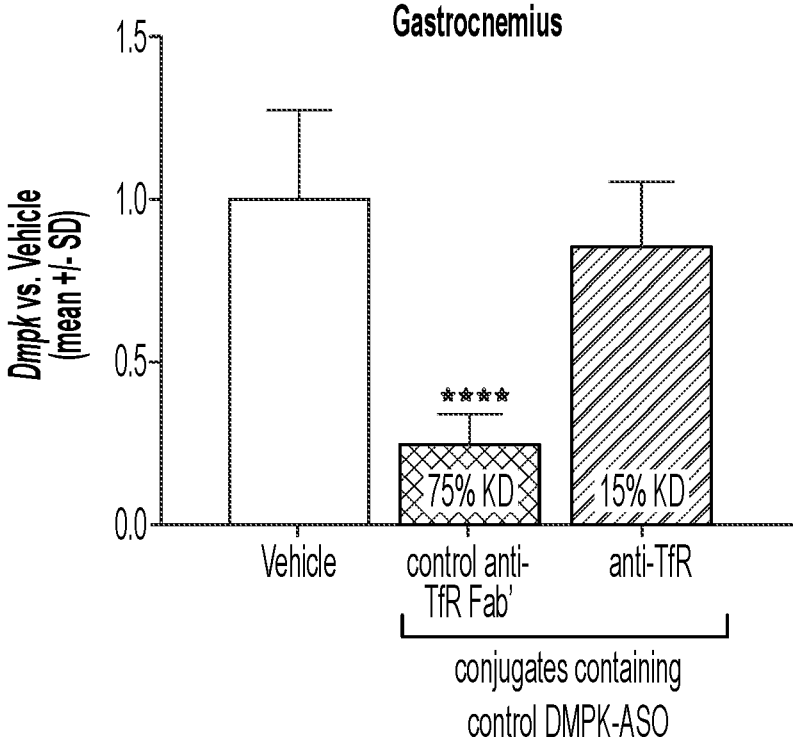


FIG. 33B

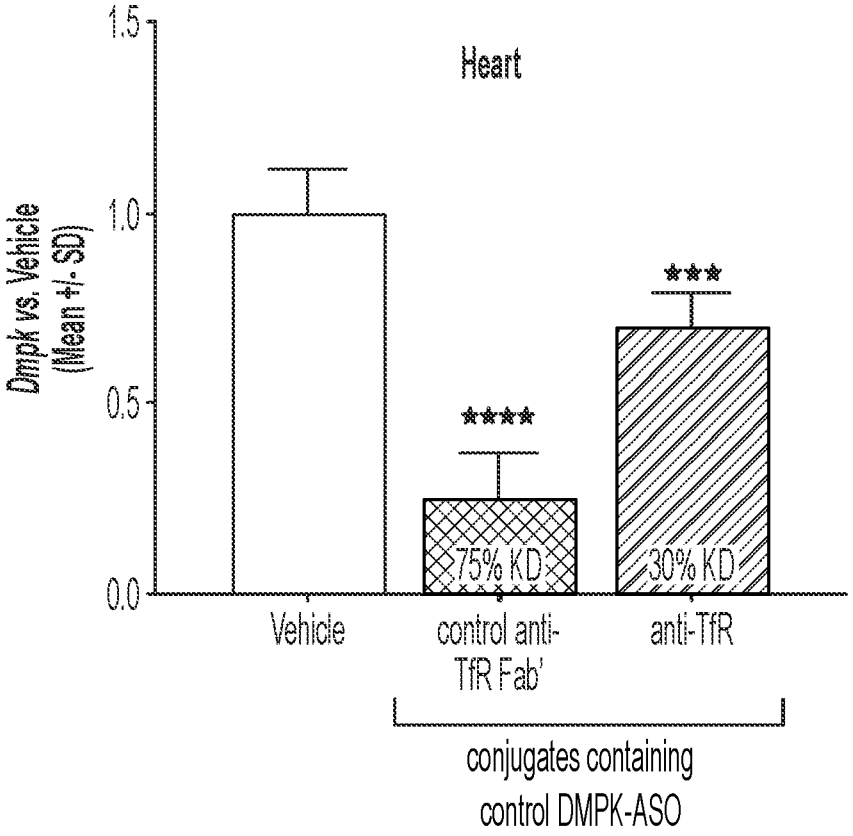


FIG. 33C

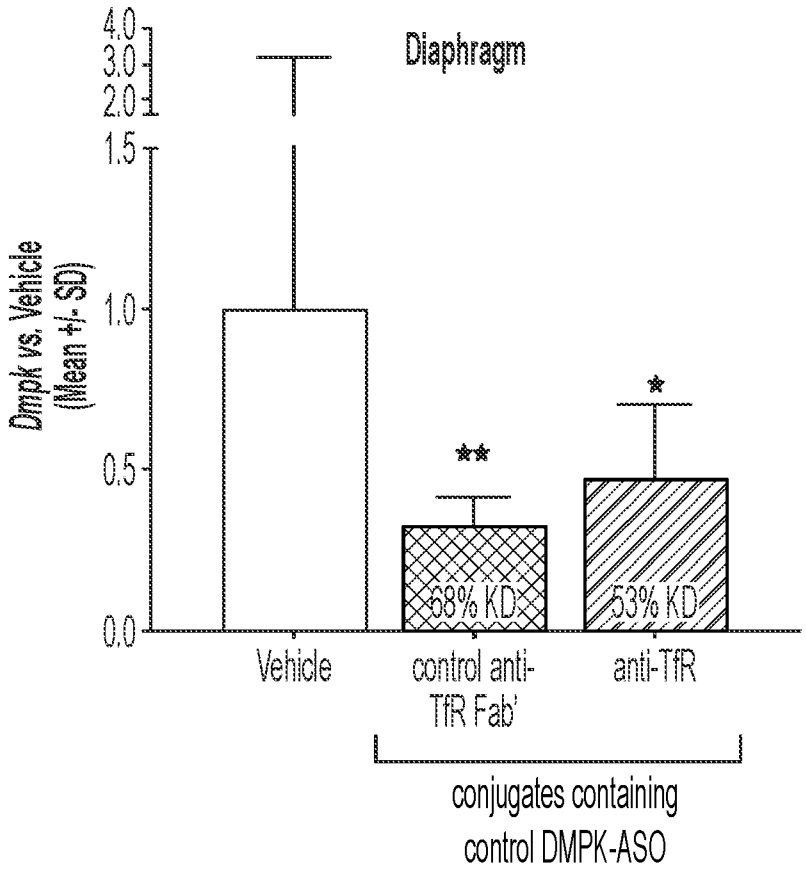


FIG. 33D

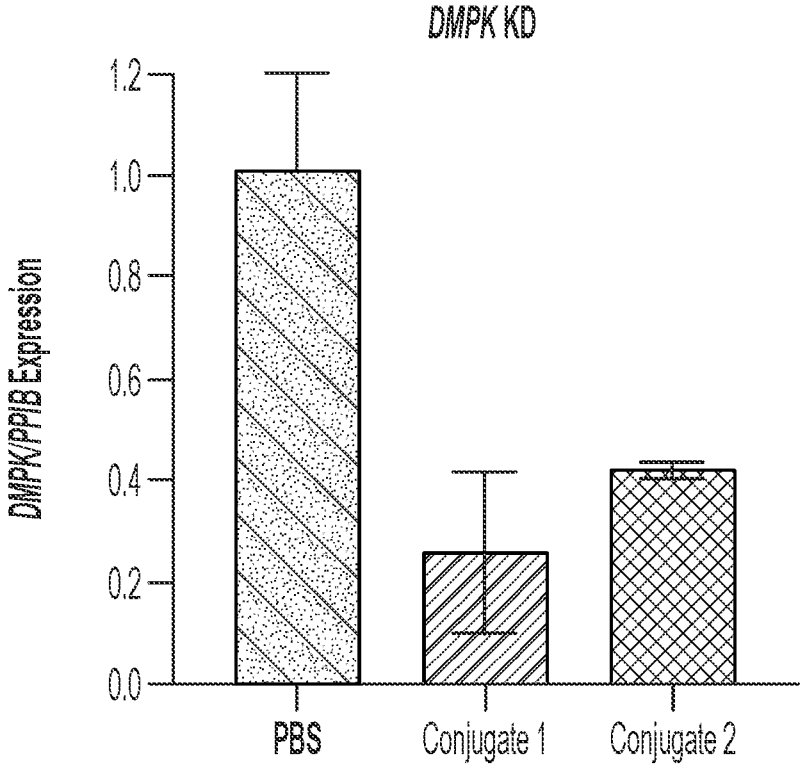


FIG. 34A

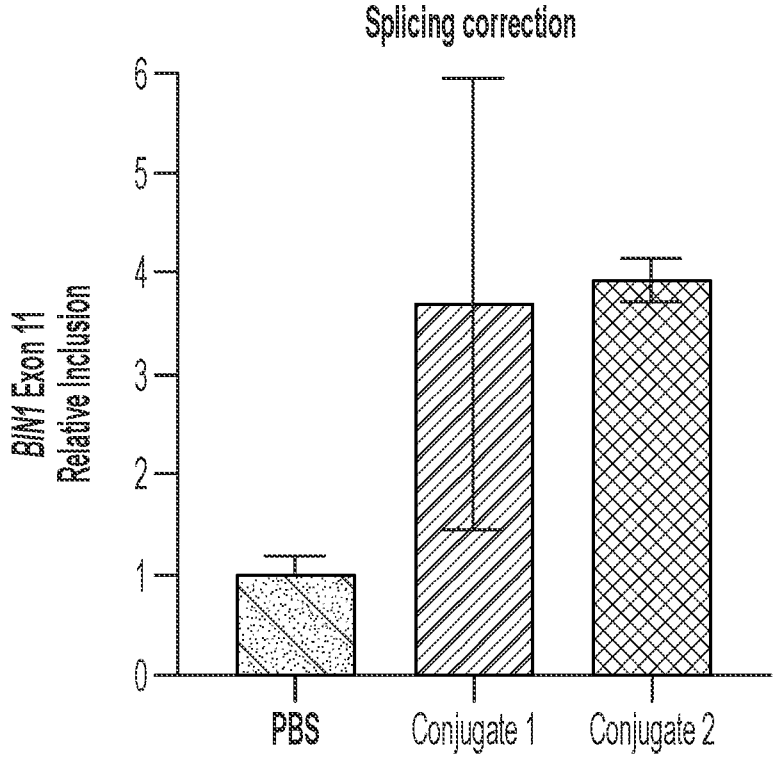
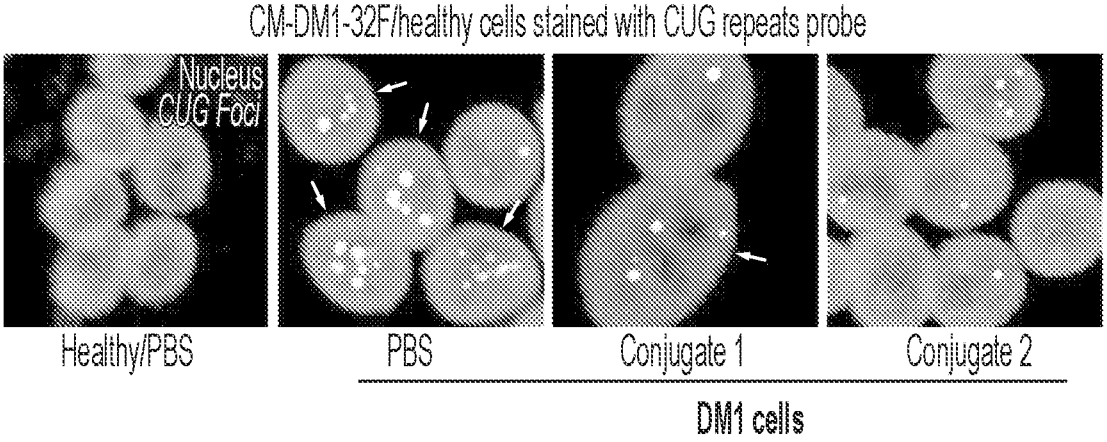


FIG. 34B


CM-DM1-32F/healthy cells stained with CUG repeats probe
Nucleus
CUG Foci
Healthy/PBS
PBS
Conjugate 1
Conjugate 2
DM1 cells

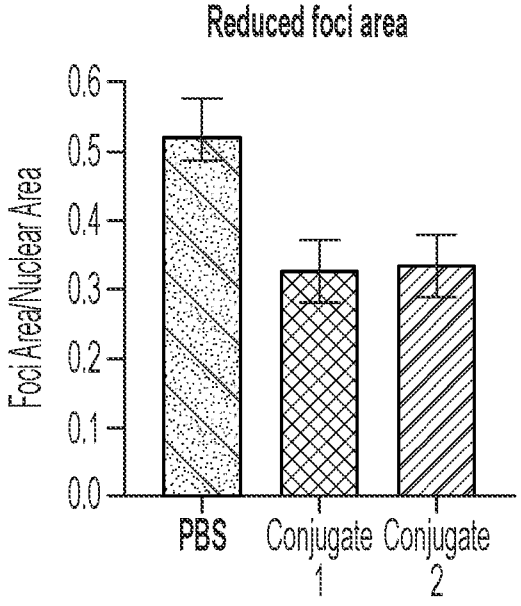

Reduced foci area
Foci Area/Nuclear Area
0.6
0.5
0.4
0.3
0.2
0.1
0.0
PBS
Conjugate 1
Conjugate 2

FIG. 34C