FIG. 1

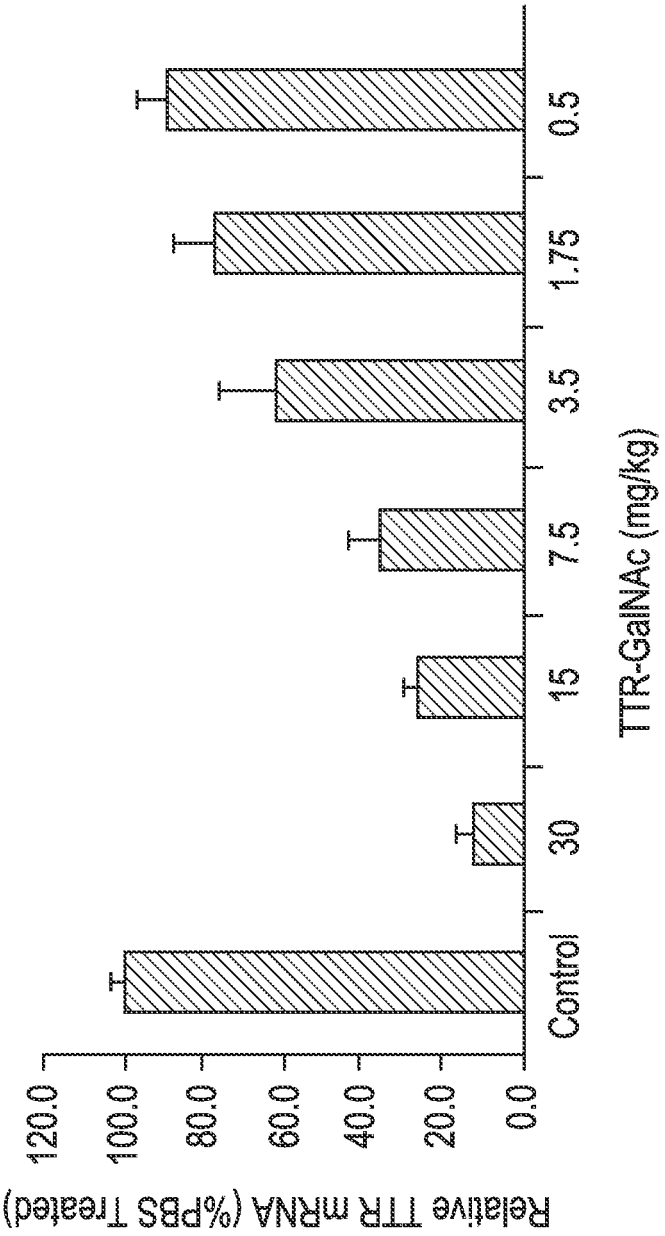

Relative TTR mRNA (%PBS Treated)
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Control
30
15
7.5
3.5
1.75
0.5
TTR-GalNAc (mg/kg)

FIG. 2

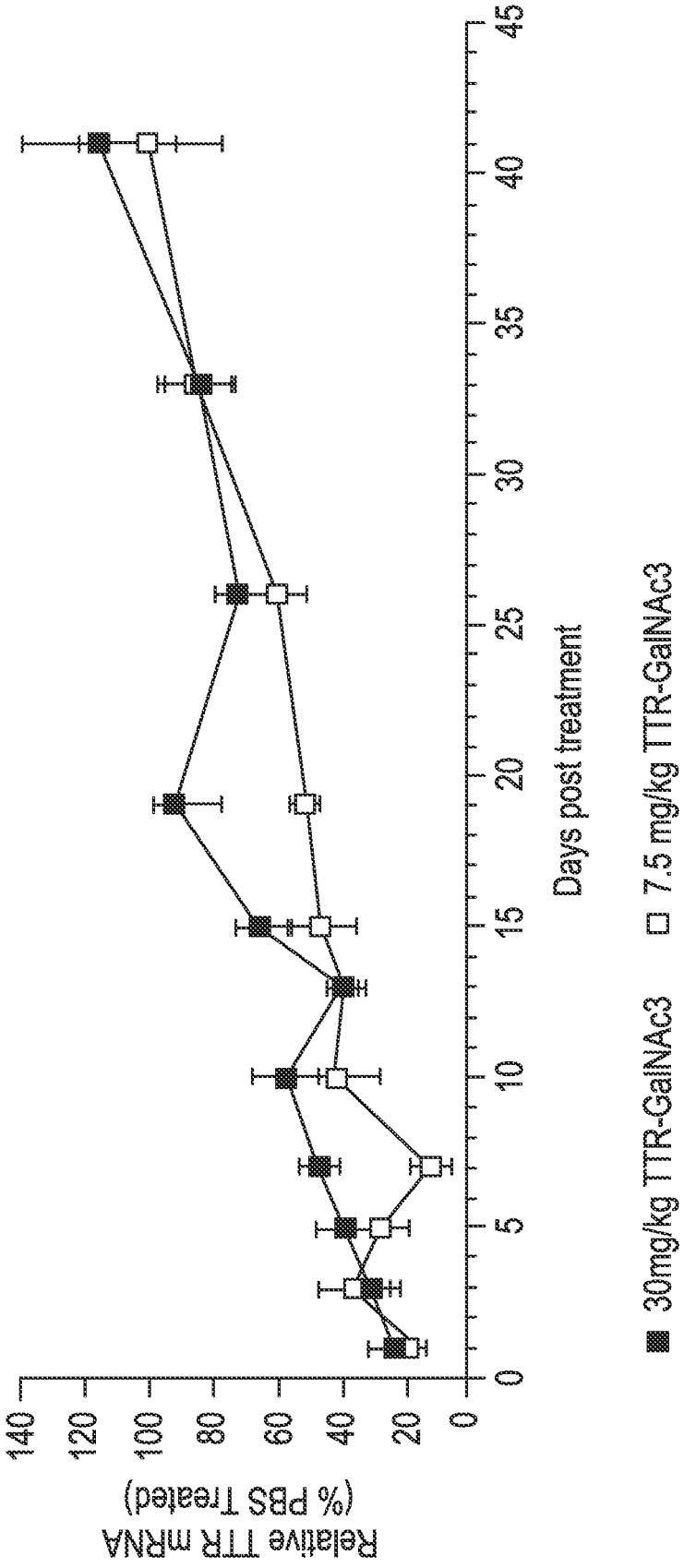

Relative TTR mRNA
(% PBS Treated)
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
Days post treatment
30mg/kg TTR-GalNAc3
7.5 mg/kg TTR-GalNAc3

FIG. 3

Human TTR mRNA Sequence (SEQ ID NO: 1), Gen Bank Accession No.: M10605,
GI: 189583

```
   1 cagaagtcca ctcattcttg gcaggatggc ttctcatcgt ctgctcctcc tctgccttgc
  61 tggactggta ttgtgtctg aggctggccc tacgggcacc ggtgaatcca agtgtcctct
 121 gatggtcaaa gttctagatg ctgtccgagg cagtcctgcc atcaatgtgg ccgtgcatgt
 181 gttcagaaag gctgctgatg acacctgggg gccatttgcc tctgggaaaa ccagtgagtc
 241 tggagagctg catgggctca caactgagga ggaatttgta gaagggatat acaaagtgga
 301 aatagacacc aaatcttact ggaaggcact tggcatctcc ccattccatg agcatgcaga
 361 ggtggtattc acagccaacg actccggccc ccgccgctac accattgccg ccctgctgag
 421 ccctactccc tattccacca cggctgtcgt caccaatccc aaggaatgag ggacttctcc
 481 tccagtgggac ctgaaggacg agggatgggg ttttcatgtaa ccaagagtat tccatttta
 541 ctaaagcagt gttttcacct catatgctat gttagaagtc cagggcagaga caataaaaca
 601 ttcctgtgaa aggc
```

FIG. 4

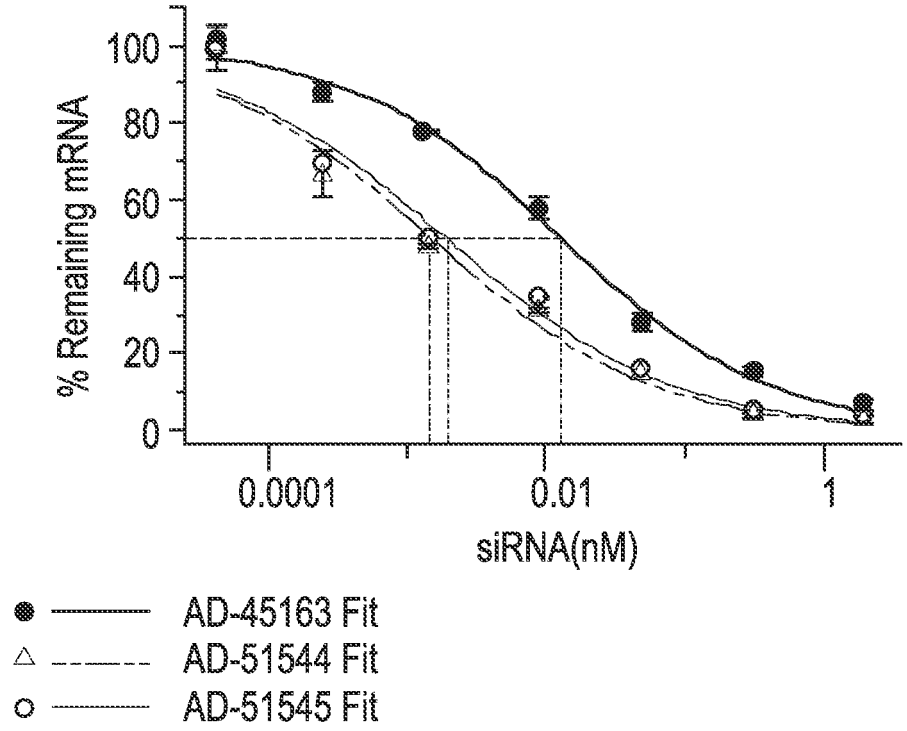

% Remaining mRNA
100
80
60
40
20
0
0.0001
0.01
1
siRNA(nM)
AD-45163 Fit
AD-51544 Fit
AD-51545 Fit

FIG. 5

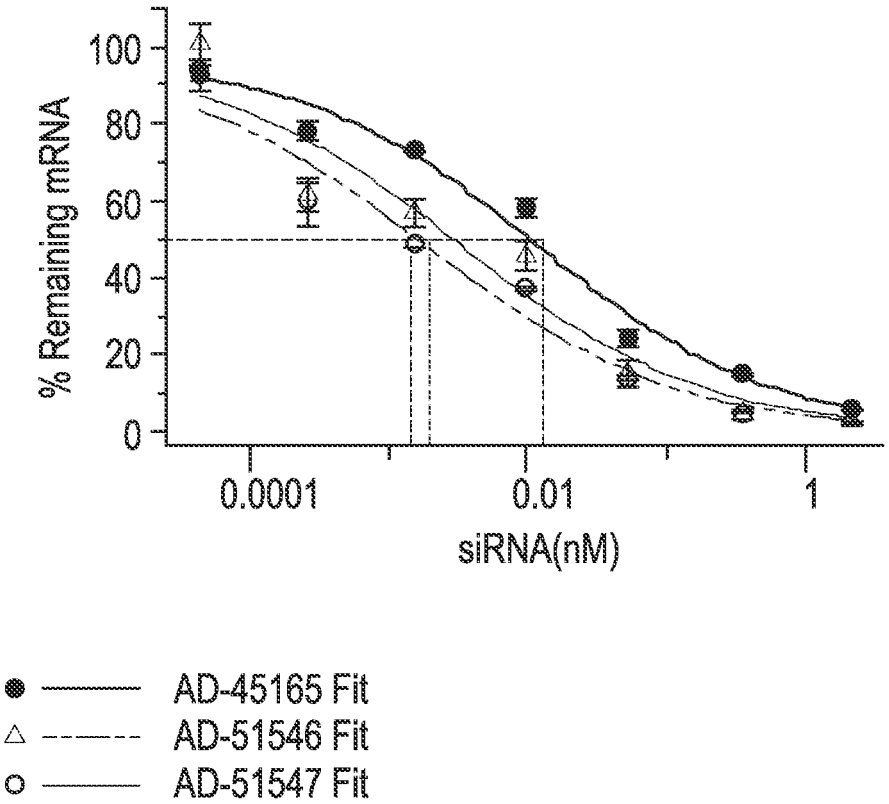

% Remaining mRNA
100
80
60
40
20
0
0.0001
0.01
1
siRNA(nM)
AD-45165 Fit
AD-51546 Fit
AD-51547 Fit

FIG. 6

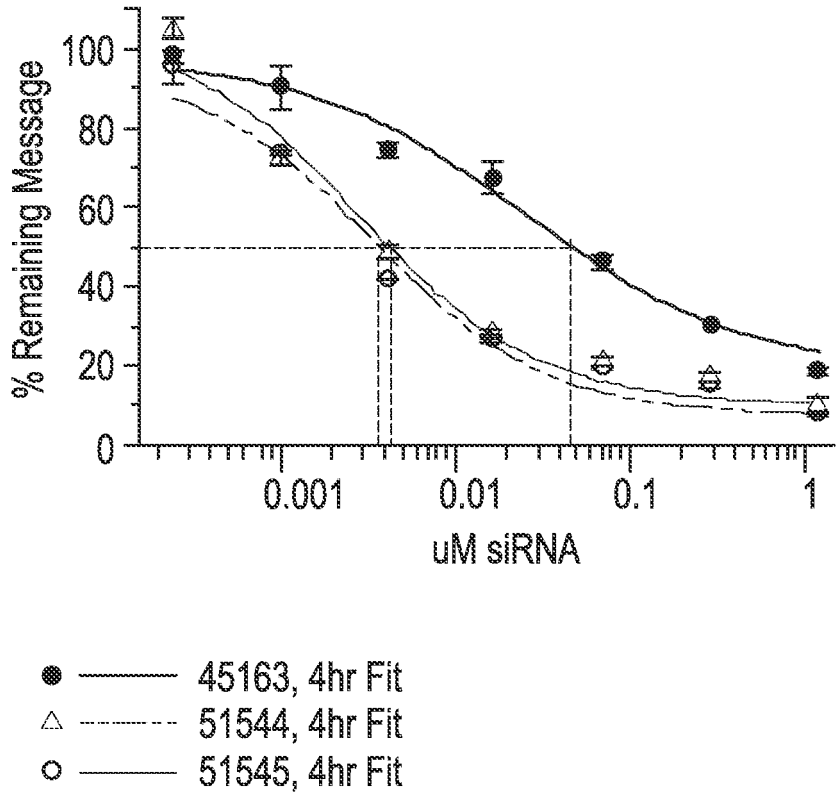

% Remaining Message
100
80
60
40
20
0
0.001
0.01
0.1
1
uM siRNA
45163, 4hr Fit
51544, 4hr Fit
51545, 4hr Fit

FIG. 7

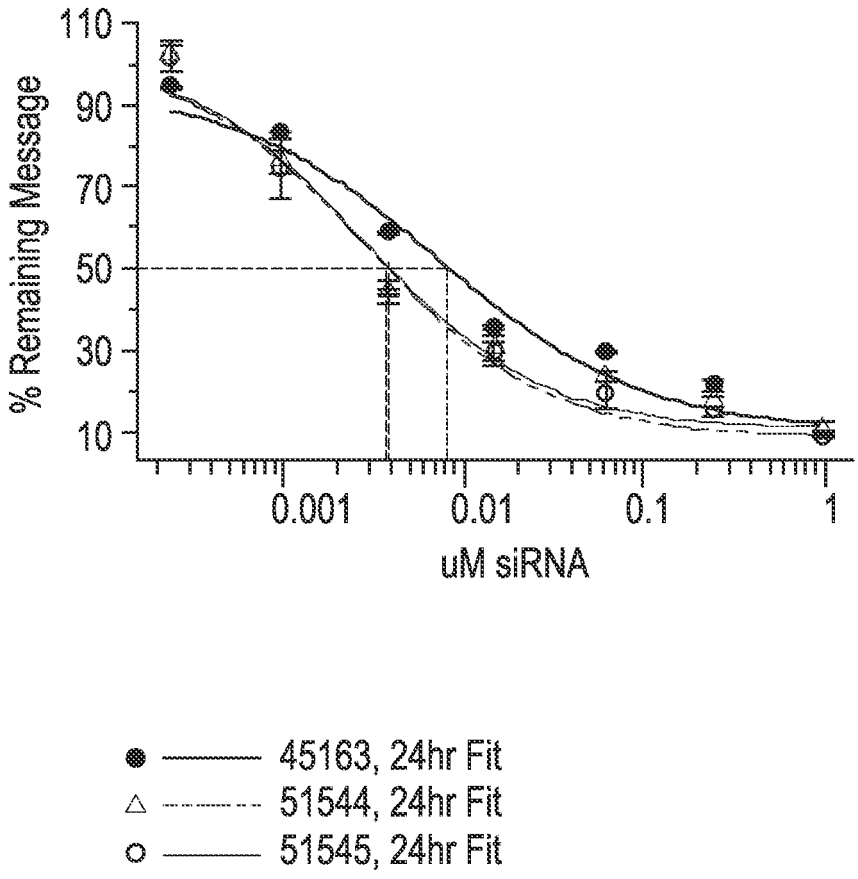

110
90
70
50
30
10
% Remaining Message
0.001
0.01
0.1
1
uM siRNA
45163, 24hr Fit
51544, 24hr Fit
51545, 24hr Fit

FIG. 8

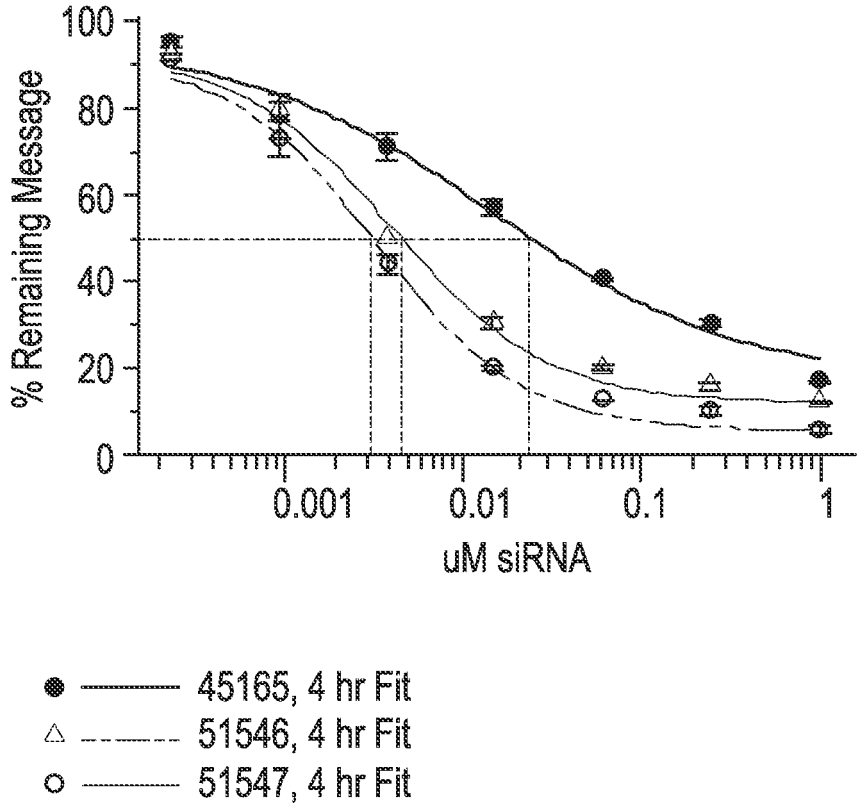

100
80
60
40
20
0
% Remaining Message
0.001
0.01
0.1
1
uM siRNA
45165, 4 hr Fit
51546, 4 hr Fit
51547, 4 hr Fit

FIG. 9

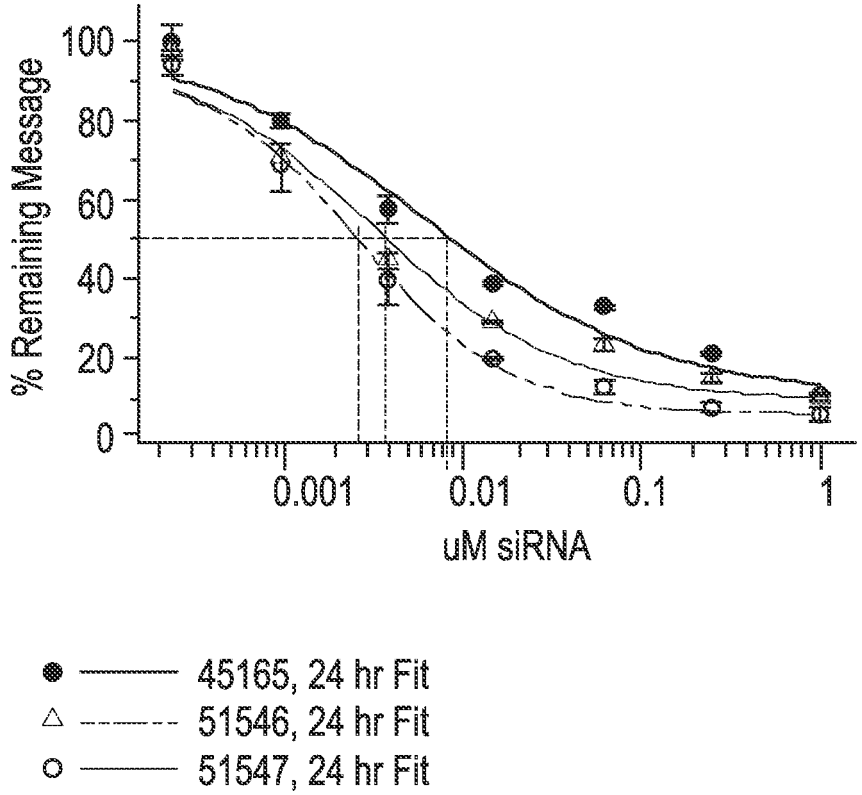

% Remaining Message
100
80
60
40
20
0
0.001
0.01
0.1
1
uM siRNA
45165, 24 hr Fit
51546, 24 hr Fit
51547, 24 hr Fit

FIG. 10A

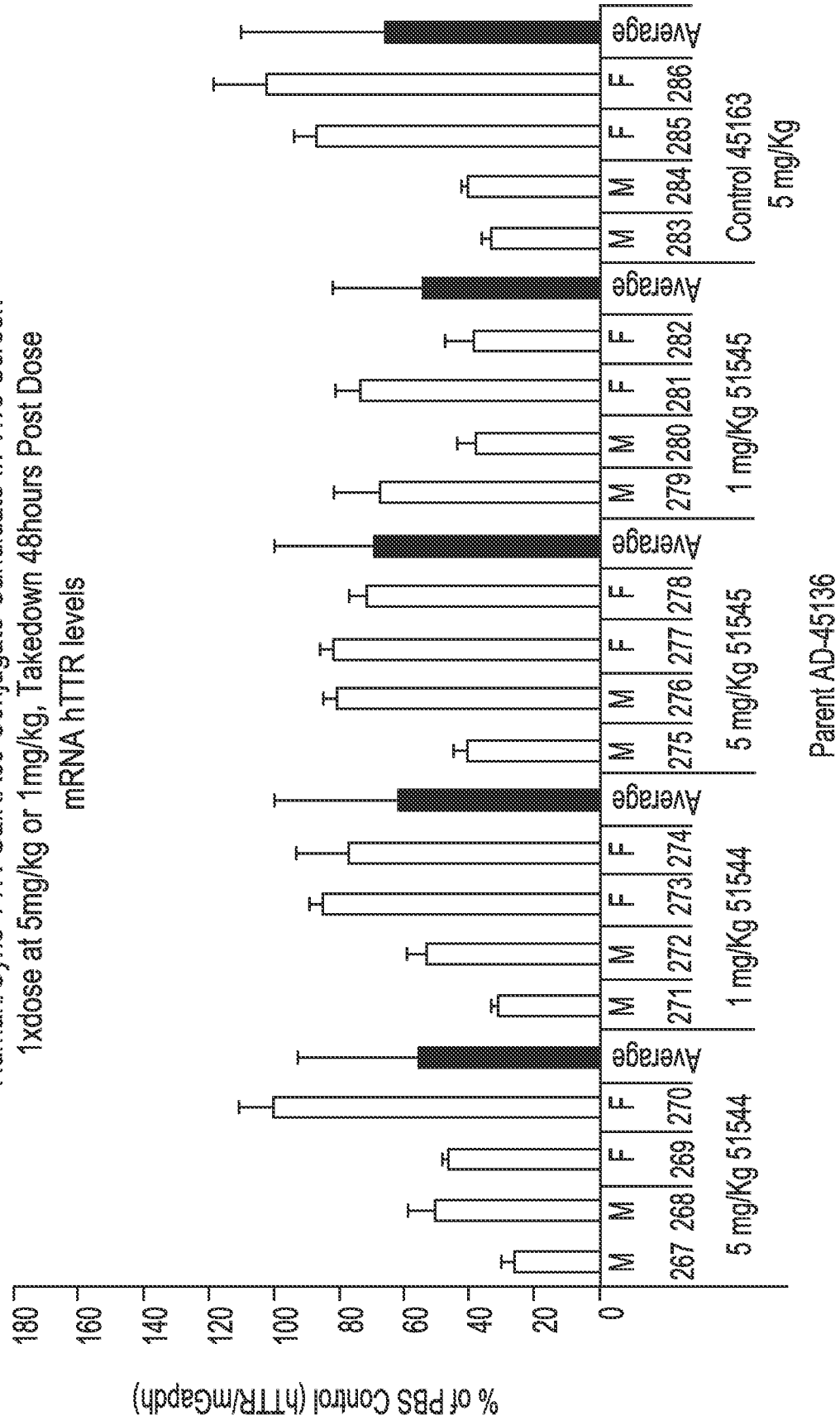

Human/Cyno TTR-GalNAc3 Conjugate Candidate In Vivo Screen
1xdose at 5mg/kg or 1mg/kg, Takedown 48hours Post Dose
mRNA hTTR levels
% of PBS Control (hTTR/mGapdh)
0
20
40
60
80
100
120
140
160
180
M
M
F
F
Average
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
5 mg/Kg 51544
1 mg/Kg 51544
5 mg/Kg 51545
1 mg/Kg 51545
Control 45163
5 mg/Kg
Parent AD-45136

FIG. 10B

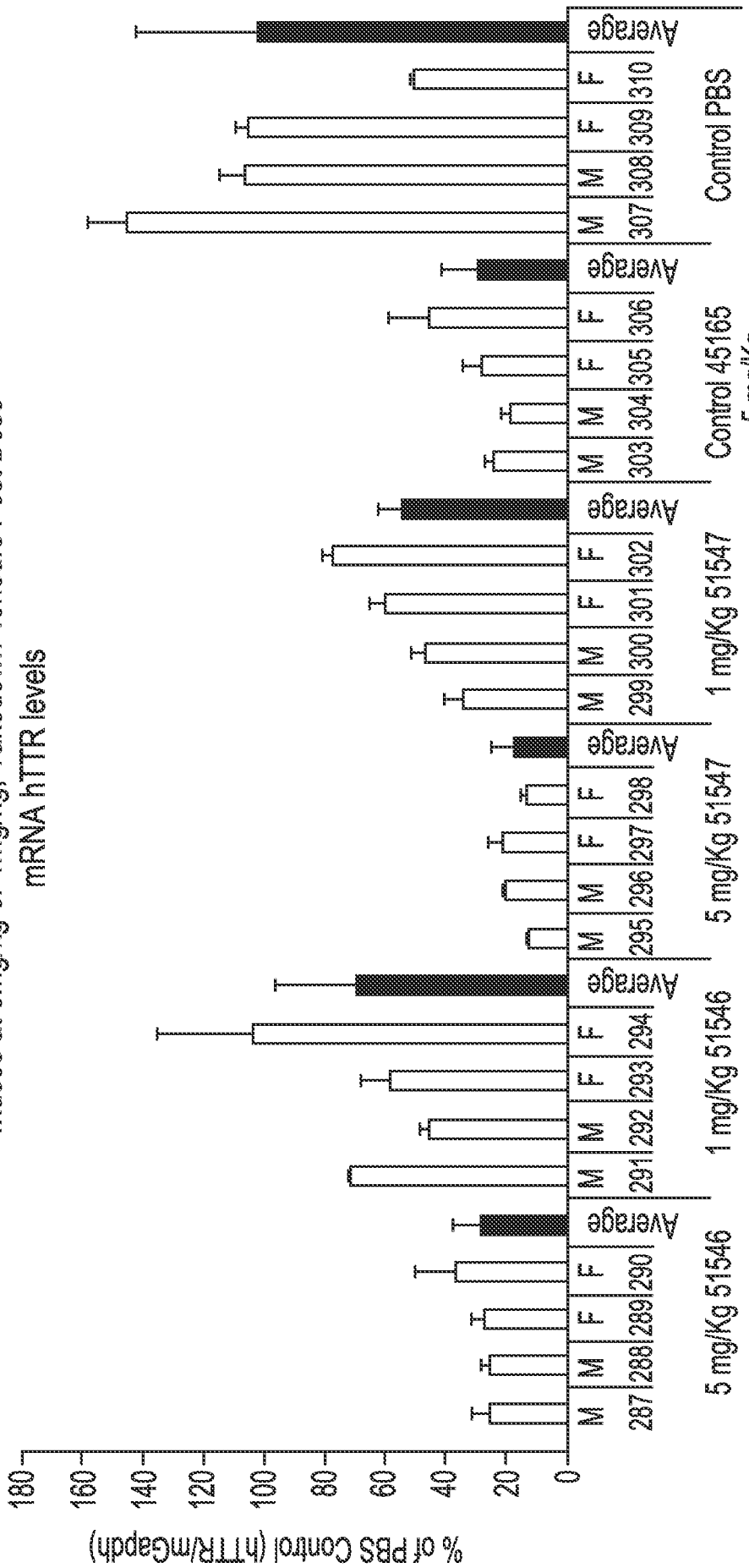

Human/Cyno TTR-GalNAc3 Conjugate Candidate In Vivo Screen
1xdose at 5mg/kg or 1mg/kg, Takedown 48hours Post Dose
mRNA hTTR levels
% of PBS Control (hTTR/mGapdh)
0
20
40
60
80
100
120
140
160
180
M 287
M 288
F 289
F 290
Average
5 mg/Kg 51546
M 291
M 292
F 293
F 294
Average
1 mg/Kg 51546
M 295
M 296
F 297
F 298
Average
5 mg/Kg 51547
M 299
M 300
F 301
F 302
Average
1 mg/Kg 51547
Parent AD-45165
M 303
M 304
F 305
F 306
Average
Control 45165
5 mg/Kg
M 307
M 308
F 309
F 310
Average
Control PBS

FIG. 11

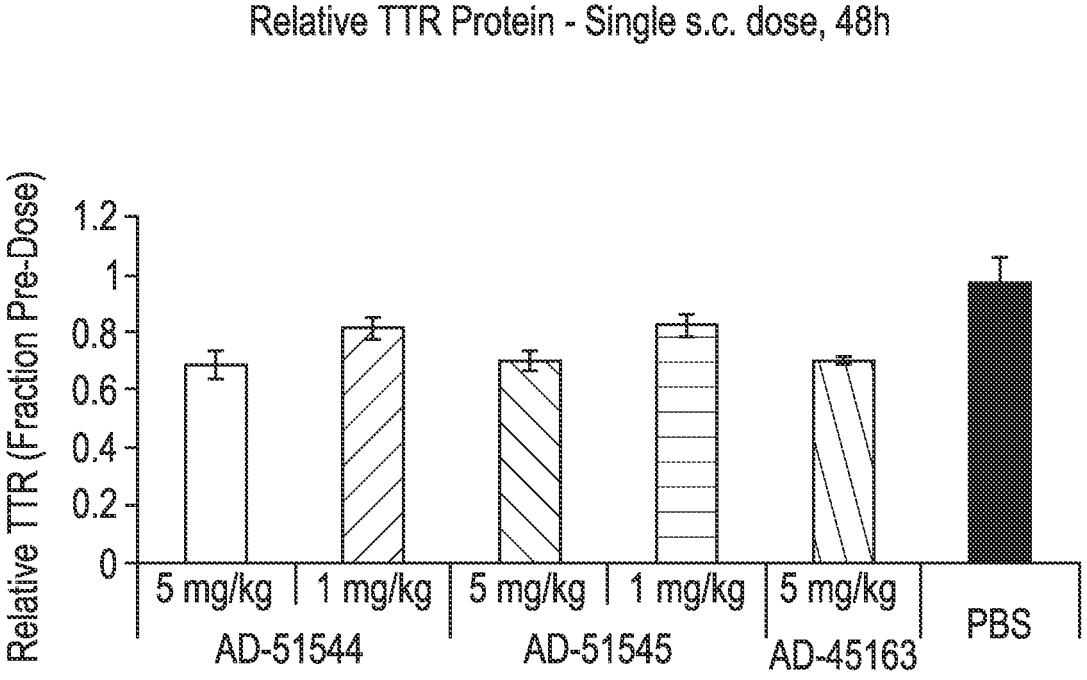

Relative TTR Protein - Single s.c. dose, 48h
Relative TTR (Fraction Pre-Dose)
1.2
1
0.8
0.6
0.4
0.2
0
5 mg/kg
1 mg/kg
5 mg/kg
1 mg/kg
5 mg/kg
PBS
AD-51544
AD-51545
AD-45163

FIG. 12

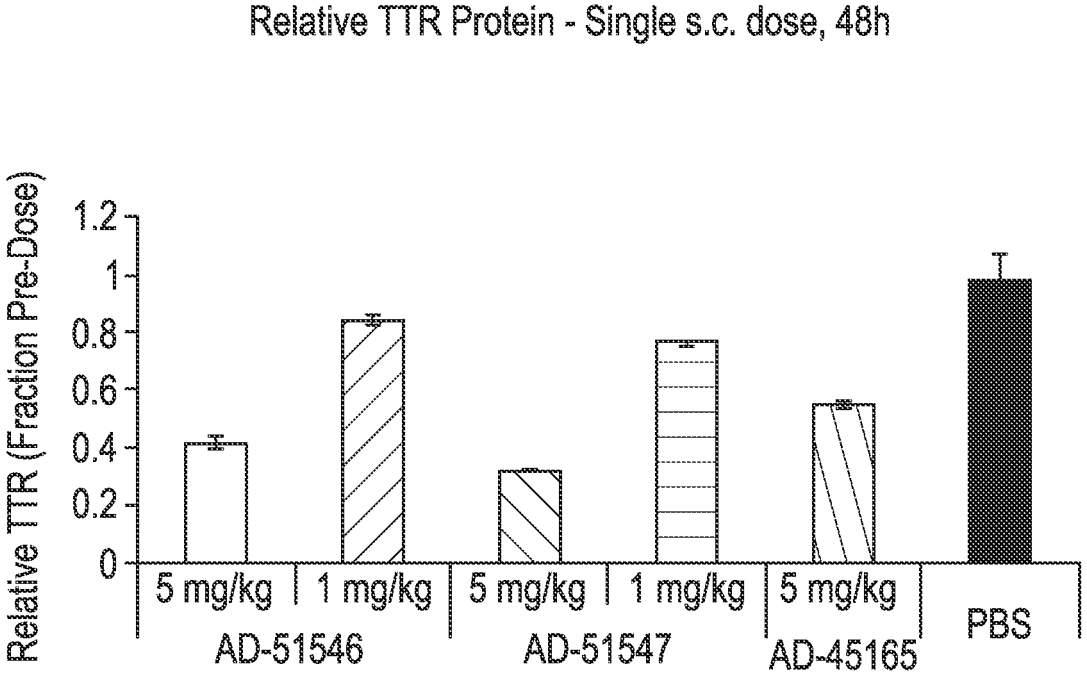

Relative TTR Protein - Single s.c. dose, 48h
Relative TTR (Fraction Pre-Dose)
1.2
1
0.8
0.6
0.4
0.2
0
5 mg/kg
1 mg/kg
5 mg/kg
1 mg/kg
5 mg/kg
PBS
AD-51546
AD-51547
AD-45165

FIG. 13

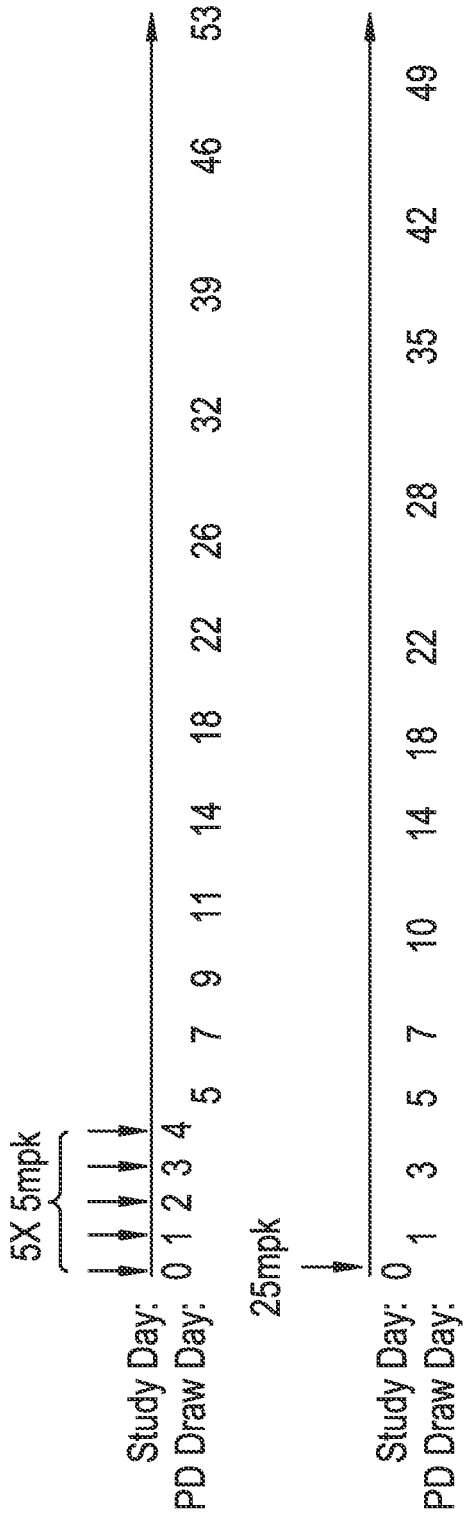
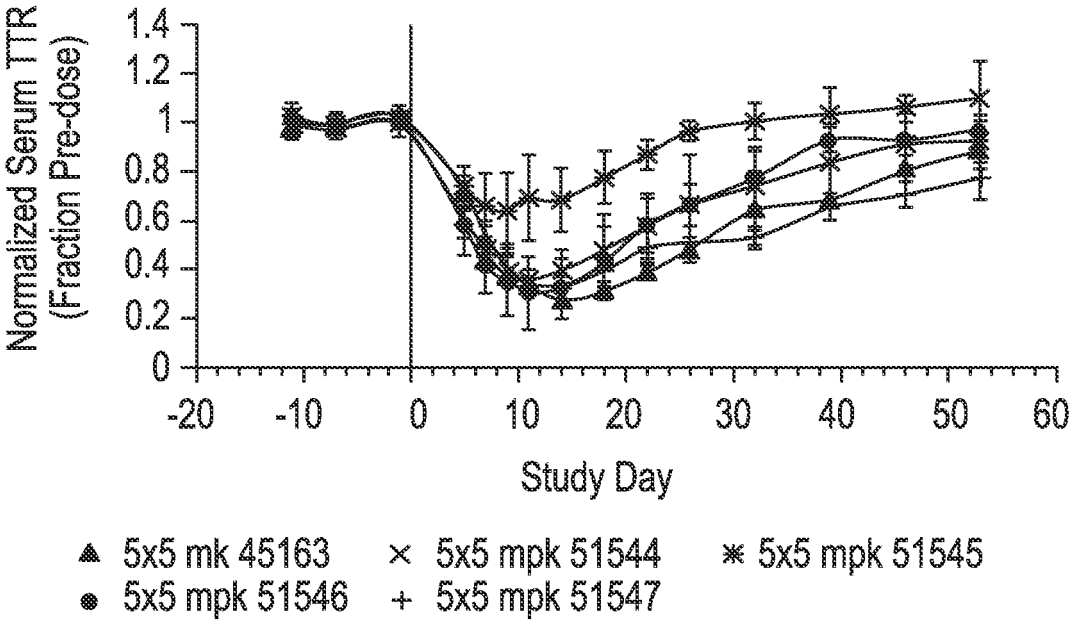

5X 5mpk
Study Day: 0 1 2 3 4 5 7 9 11 14 18 22 26 32 39 46 53
PD Draw Day:
25mpk
Study Day: 0 1 3 5 7 10 14 18 22 28 35 42 49
PD Draw Day:

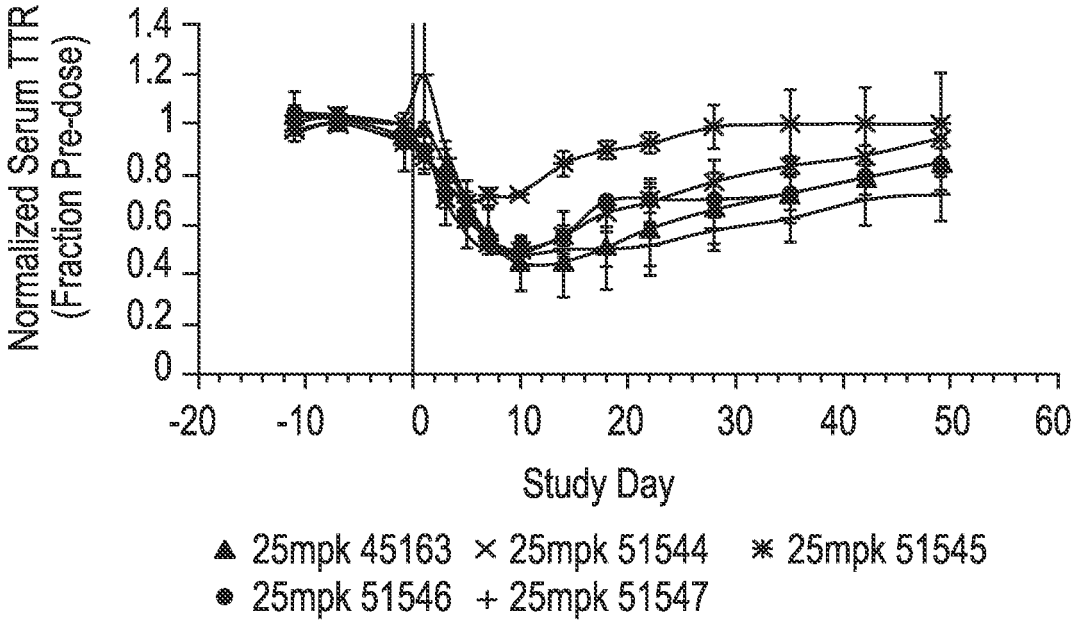
FIG. 14

5X 5mg/kg



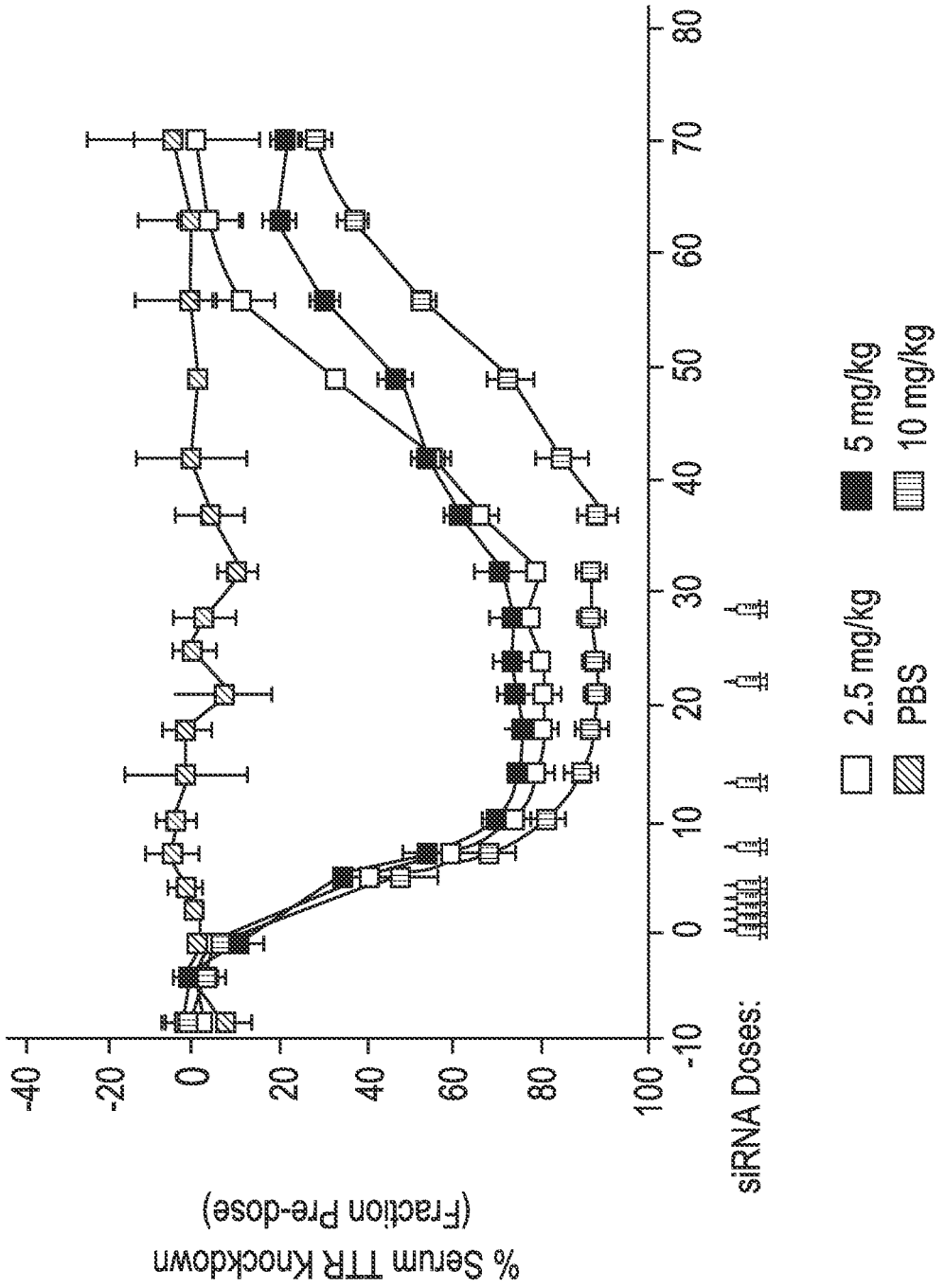
▲ 5x5 mk 45163 × 5x5 mpk 51544 ✳ 5x5 mpk 51545
● 5x5 mpk 51546 + 5x5 mpk 51547

25mg/kg



▲ 25mpk 45163 × 25mpk 51544 ✳ 25mpk 51545
● 25mpk 51546 + 25mpk 51547

FIG. 15


% Serum TTR Knockdown
(Fraction Pre-dose)
-40
-20
0
20
40
60
80
100
siRNA Doses:
-10
0
10
20
30
40
50
60
70
80
2.5 mg/kg
5 mg/kg
PBS
10 mg/kg