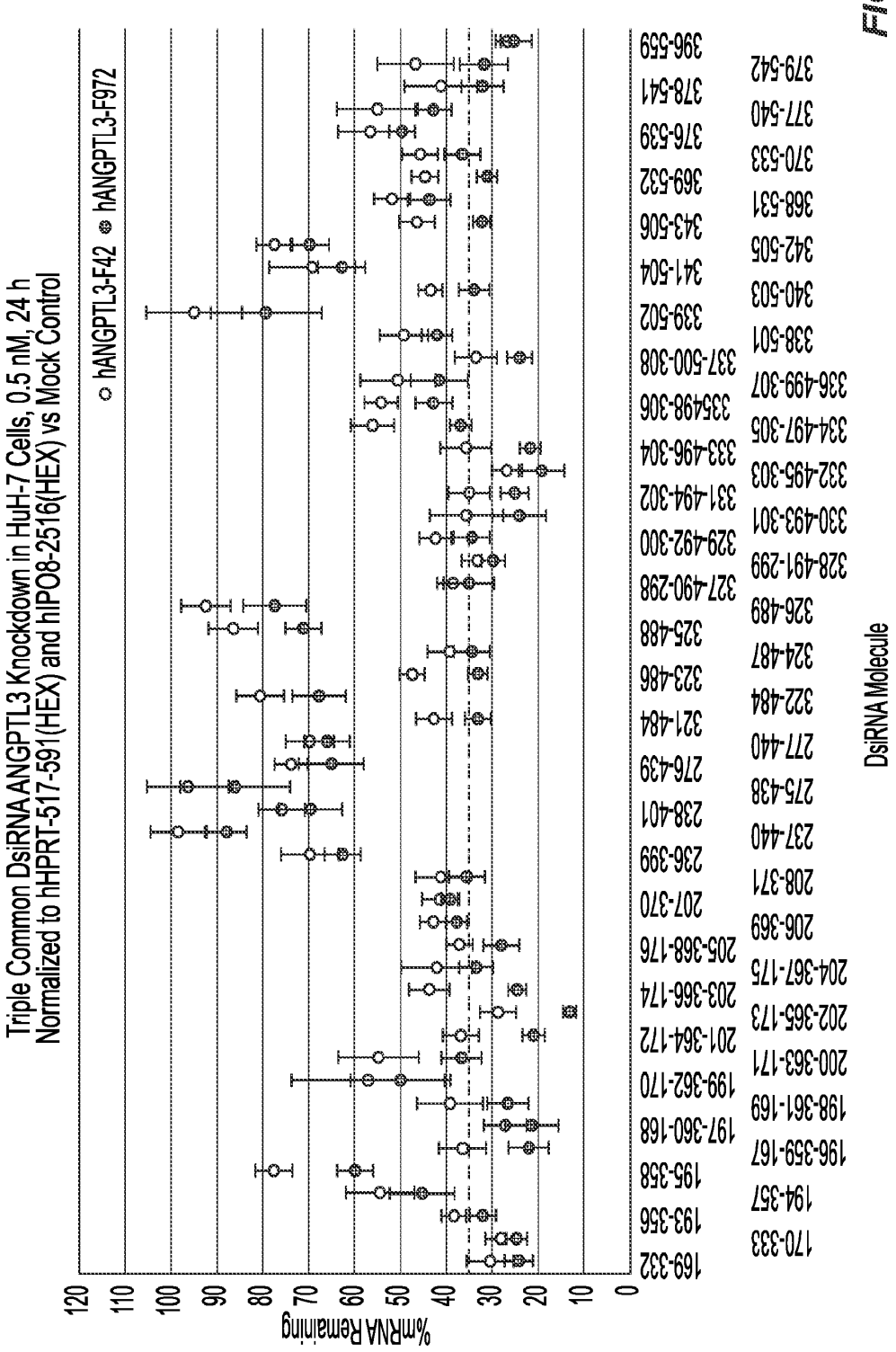
Triple Common DsiRNA ANGPTL3 Knockdown in HuH-7 Cells, 0.5 nM, 24 h
Normalized to hHPRT-517-591(HEX) and hIPO8-2516(HEX) vs Mock Control
hANGPTL3-F42
hANGPTL3-F972
%mRNA Remaining
120
110
100
90
80
70
60
50
40
30
20
10
0
169-332
170-333
193-356
194-357
195-358
196-359-167
197-360-168
198-361-169
199-362-170
200-363-171
201-364-172
202-365-173
203-366-174
204-367-175
205-368-176
206-369
207-370
208-371
236-399
237-440
238-401
275-438
276-439
277-440
321-484
322-484
323-486
324-487
325-488
326-489
327-490-298
328-491-299
329-492-300
330-493-301
331-494-302
332-495-303
333-496-304
334-497-305
335498-306
336-499-307
337-500-308
338-501
339-502
340-503
341-504
342-505
343-506
368-531
369-532
370-533
376-539
377-540
378-541
379-542
396-559
DsiRNA Molecule

FIG. 1

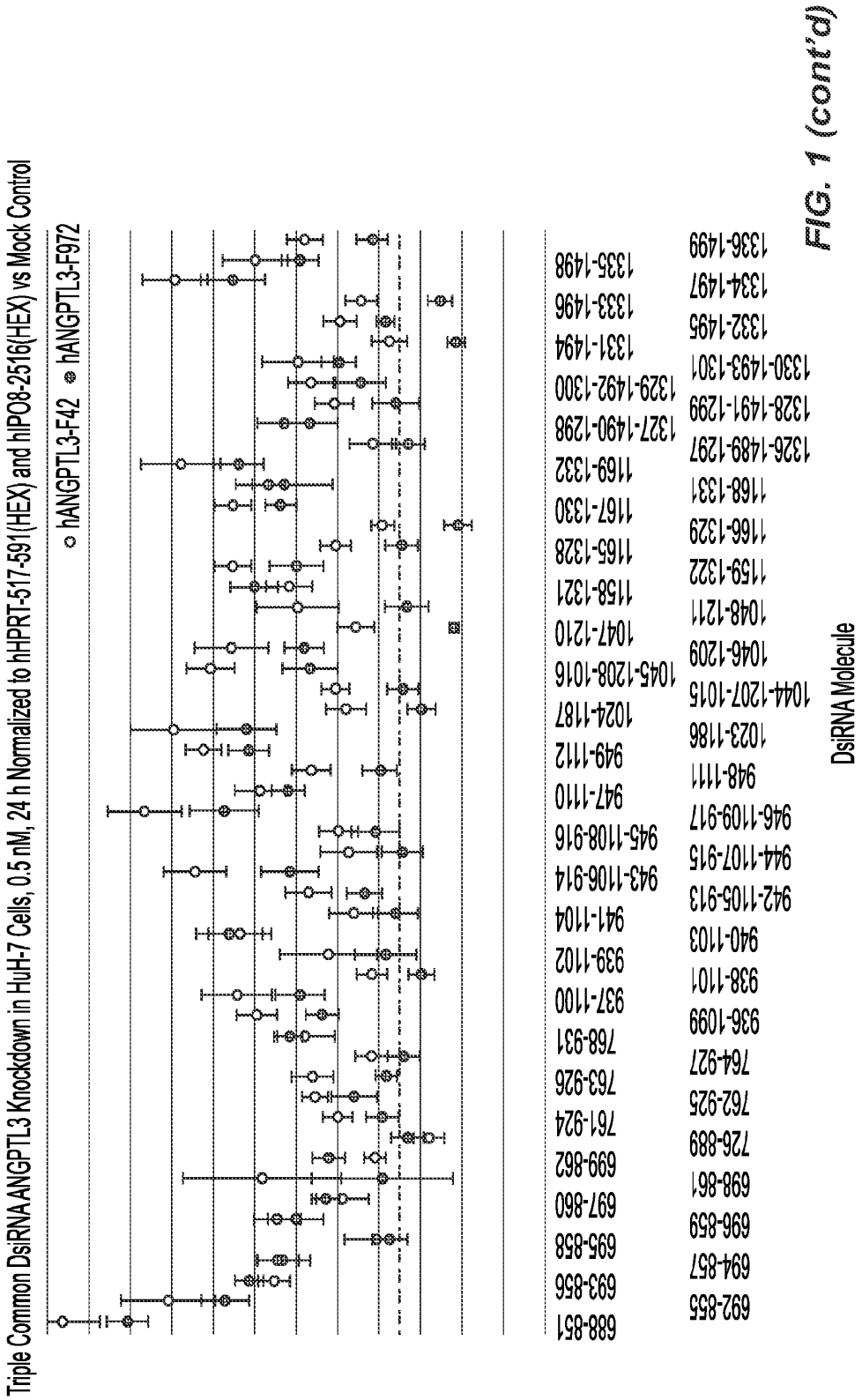
Triple Common DsiRNA ANGPTL3 Knockdown in HuH-7 Cells, 0.5 nM, 24 h Normalized to hHPRT-517-591(HEX) and hPO8-2516(HEX) vs Mock Control
○ hANGPTL3-F42 ● hANGPTL3-F972
DsiRNA Molecule
692-855
694-857
696-859
698-861
726-889
762-925
764-927
936-1099
938-1101
940-1103
942-1105-913
944-1107-915
946-1109-917
948-1111
1023-1186
1044-1207-1015
1046-1209
1048-1211
1159-1322
1166-1329
1168-1331
1326-1489-1297
1328-1491-1299
1330-1493-1301
1332-1495
1334-1497
1336-1499
688-851
693-856
695-858
697-860
699-862
761-924
763-926
768-931
937-1100
939-1102
941-1104
943-1106-914
945-1108-916
947-1110
949-1112
1024-1187
1045-1208-1016
1047-1210
1158-1321
1165-1328
1167-1330
1169-1332
1327-1490-1298
1329-1492-1300
1331-1494
1333-1496
1335-1498

FIG. 1 (cont'd)

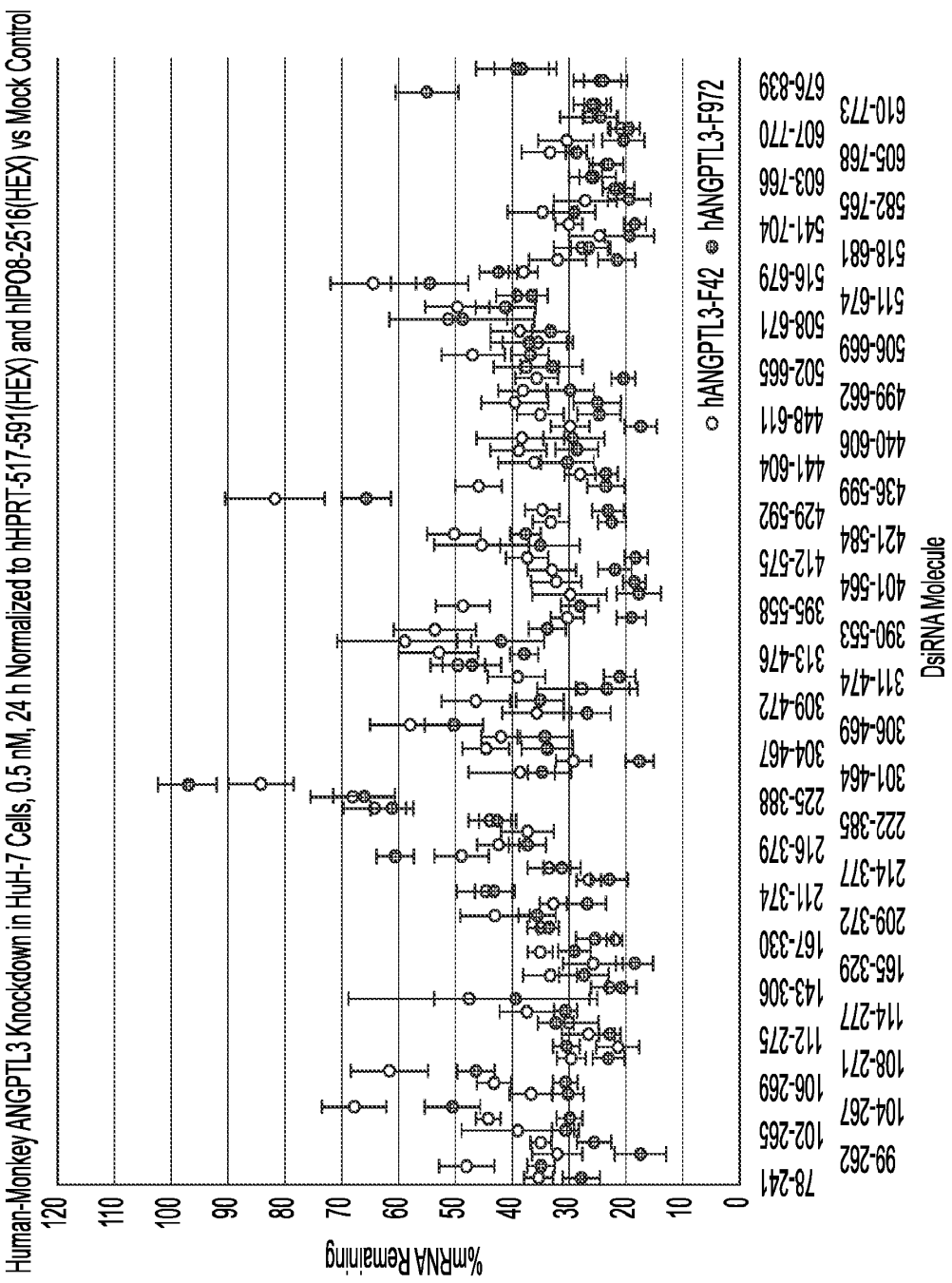
Human-Monkey ANGPTL3 Knockdown in HuH-7 Cells, 0.5 nM, 24 h Normalized to hHPRT-517-591(HEX) and hIPO8-2516(HEX) vs Mock Control
%mRNA Remaining
120
110
100
90
80
70
60
50
40
30
20
10
0
hANGPTL3-F42
hANGPTL3-F972
78-241
99-262
102-265
104-267
106-269
108-271
112-275
114-277
143-306
165-329
167-330
209-372
211-374
214-377
216-379
222-385
225-388
301-464
304-467
306-469
309-472
311-474
313-476
390-553
395-558
401-564
412-575
421-584
429-592
436-599
441-604
440-606
448-611
499-662
502-665
506-669
508-671
511-674
516-679
518-681
541-704
582-765
603-766
605-768
607-770
610-773
676-839
DsiRNA Molecule

FIG. 2

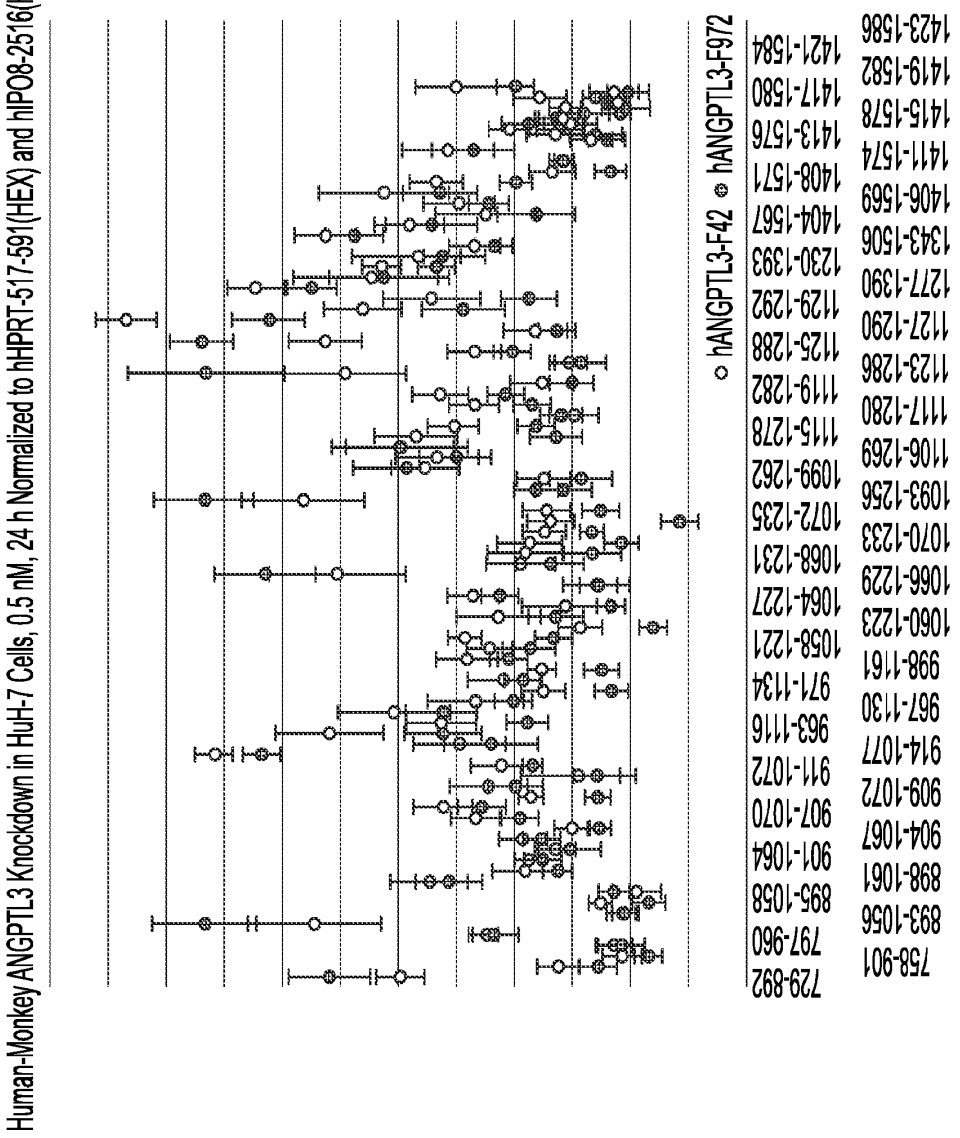
Human-Monkey ANGPTL3 Knockdown in HuH-7 Cells, 0.5 nM, 24 h Normalized to hHPRT-517-591(HEX) and hIPO8-2516(HEX) vs Mock Control
hANGPTL3-F42
hANGPTL3-F972
DsiRNA Molecule
729-892
797-960
893-1056
898-1061
904-1067
909-1072
914-1077
967-1130
971-1134
998-1161
1058-1221
1060-1223
1064-1227
1066-1229
1068-1231
1070-1233
1072-1235
1093-1256
1099-1262
1106-1269
1115-1278
1117-1280
1119-1282
1123-1286
1125-1288
1127-1290
1129-1292
1230-1393
1277-1390
1343-1506
1404-1567
1406-1569
1408-1571
1411-1574
1413-1576
1415-1578
1417-1580
1419-1582
1421-1584
1423-1586

FIG. 2 (cont'd)

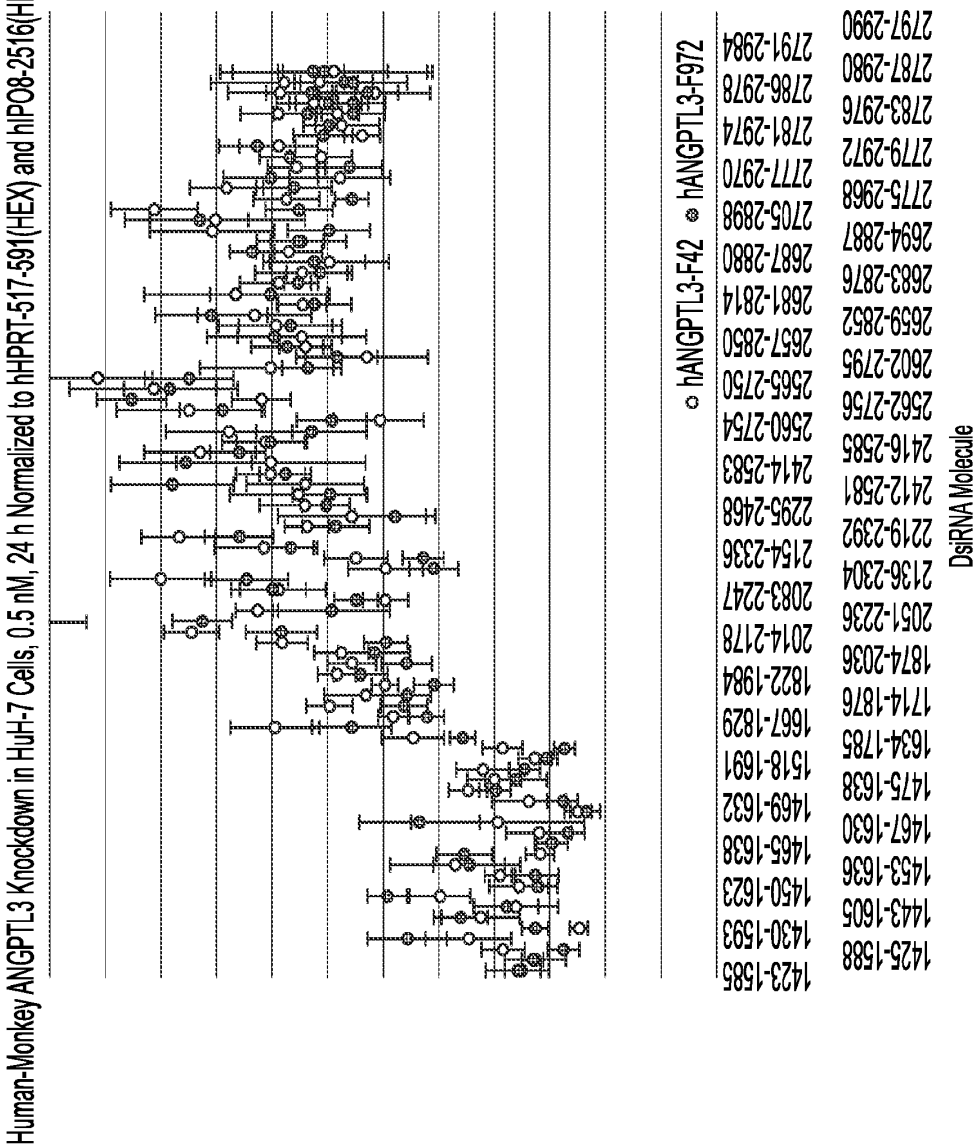
Human-Monkey ANGPTL3 Knockdown in HuH-7 Cells, 0.5 nM, 24 h Normalized to hHPRT-517-591(HEX) and hIPO8-2516(HEX) vs Mock Control
hANGPTL3-F42
hANGPTL3-F972
DsiRNA Molecule
1425-1588
1443-1605
1453-1636
1467-1630
1475-1638
1634-1785
1714-1876
1874-2036
2051-2236
2136-2304
2219-2392
2412-2581
2416-2585
2562-2756
2602-2795
2659-2852
2683-2876
2694-2887
2775-2968
2779-2972
2783-2976
2787-2980
2797-2990
1423-1585
1430-1593
1450-1623
1465-1638
1469-1632
1518-1691
1667-1829
1822-1984
2014-2178
2083-2247
2154-2336
2295-2468
2414-2583
2560-2754
2565-2750
2657-2850
2681-2814
2687-2880
2705-2898
2777-2970
2781-2974
2786-2978
2791-2984

FIG. 2 (cont'd)

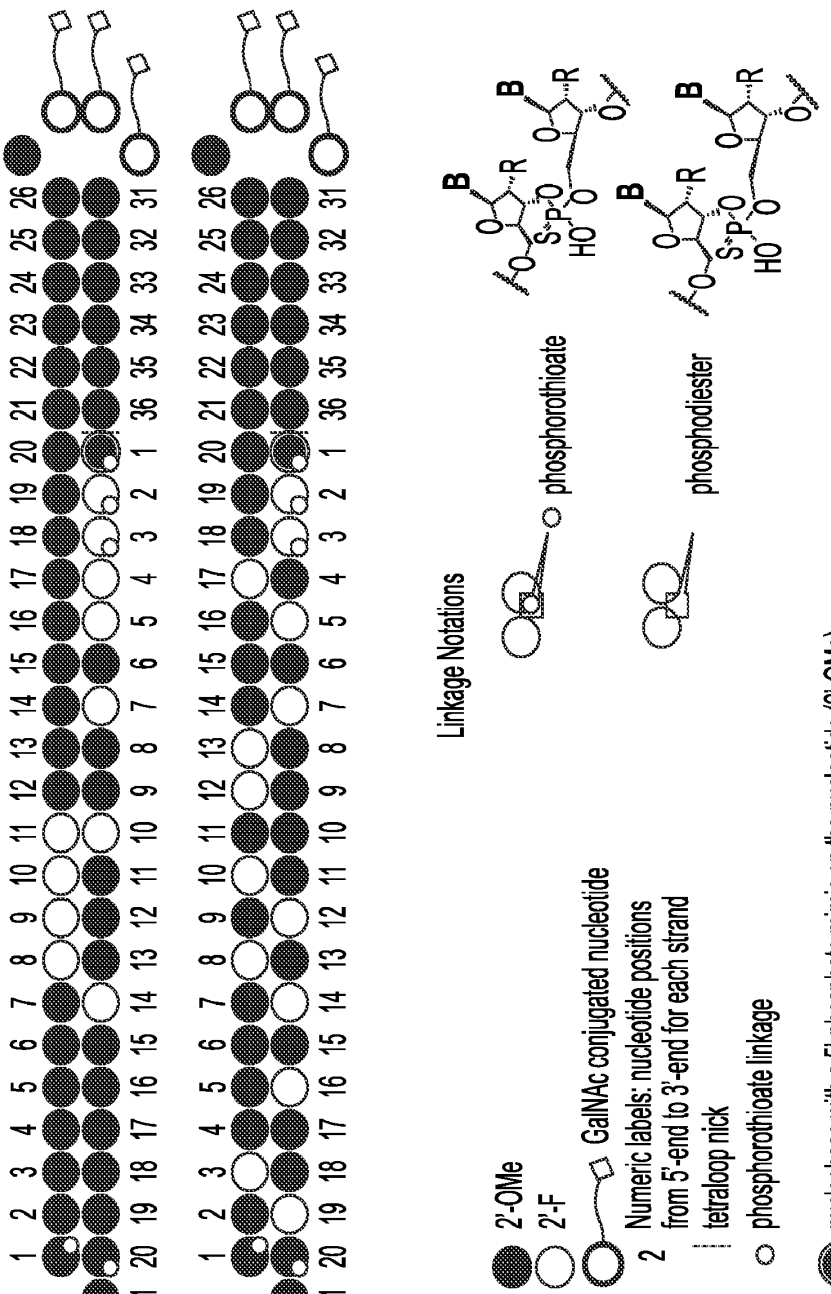
(Pattern M1)
(Pattern M2)
Legend
2'-OMe
2'-F
GalNAc conjugated nucleotide
Numeric labels: nucleotide positions from 5'-end to 3'-end for each strand
tetraloop nick
phosphorothioate linkage
nucleobase with a 5'-phosphate mimic on the nucleotide (2'-OMe)
Linkage Notations
phosphorothioate
phosphodiester

FIG. 3

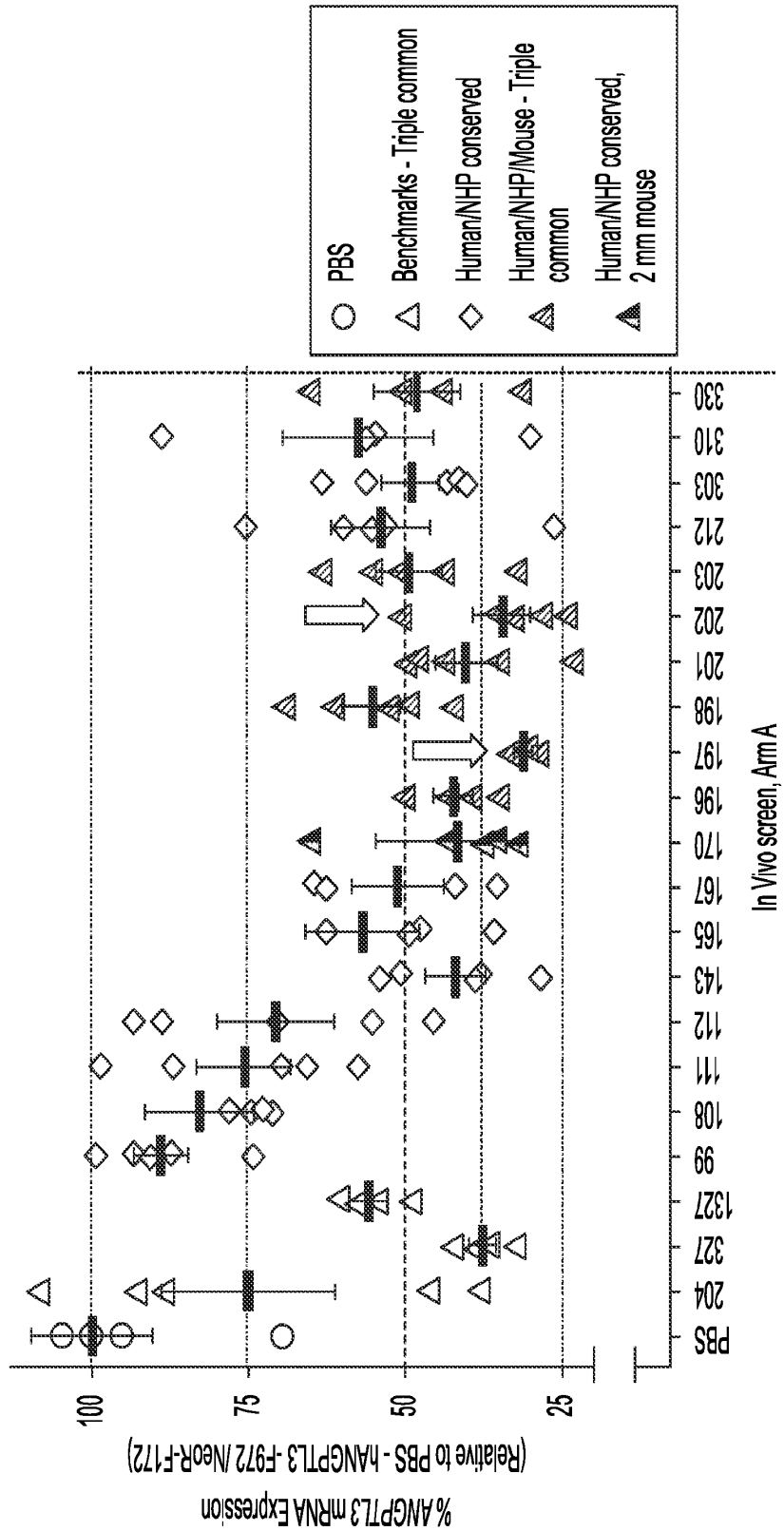
% ANGPTL3 mRNA Expression
(Relative to PBS - hANGPTL3 -F972 /NeoR-F172)
100
75
50
25
PBS
204
327
1327
99
108
111
112
143
165
167
170
196
197
198
201
202
203
212
303
310
330
In Vivo screen, Arm A
PBS
Benchmarks - Triple common
Human/NHP conserved
Human/NHP/Mouse - Triple common
Human/NHP conserved, 2 mm mouse

FIG. 4

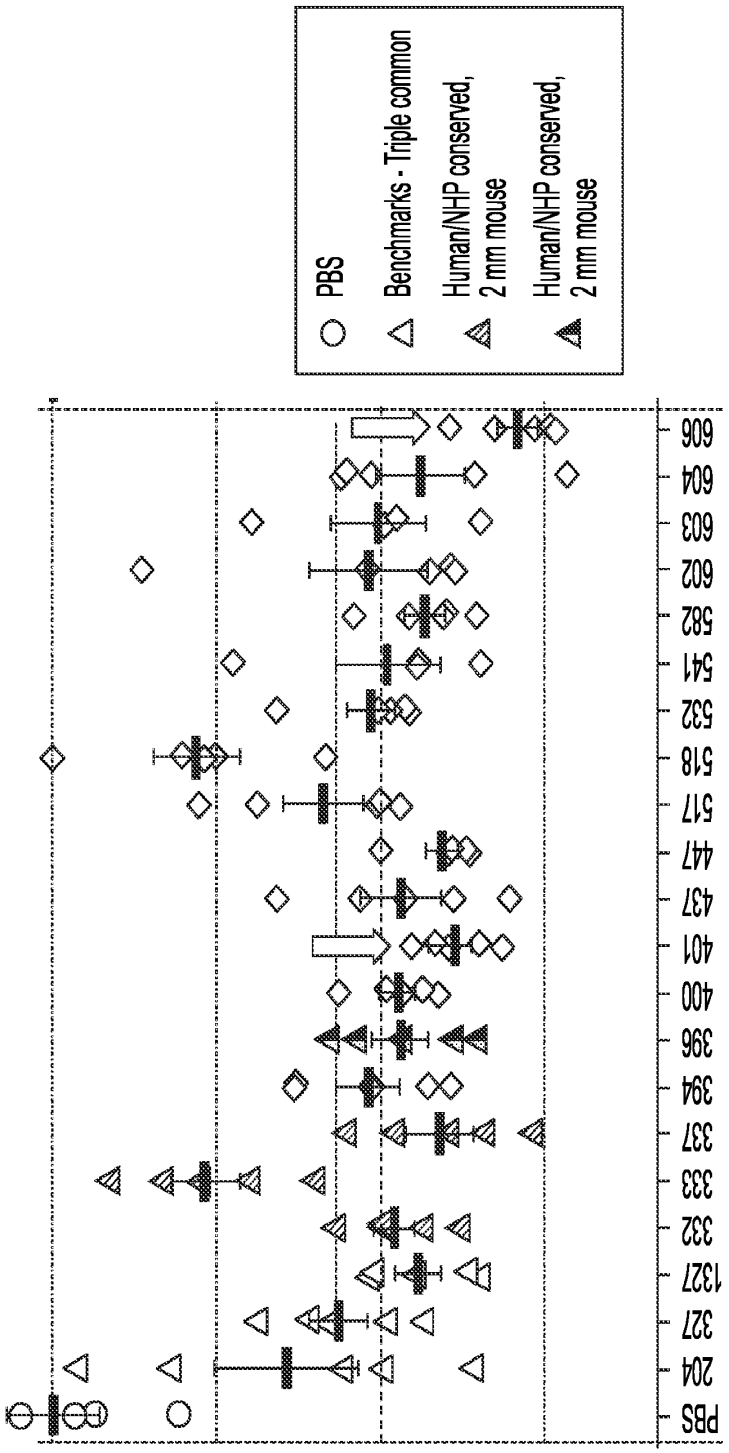
PBS
Benchmarks - Triple common
Human/NHP conserved, 2 mm mouse
Human/NHP conserved, 2 mm mouse
% ANGPTL3 mRNA Expression
(Relative to PBS - hANGPTL3 -F972 /NeoR-F172)
In Vivo screen, Arm B
PBS
204
327
1327
332
333
337
394
396
400
401
437
447
517
518
532
541
582
602
603
604
606

FIG. 4 (cont'd)

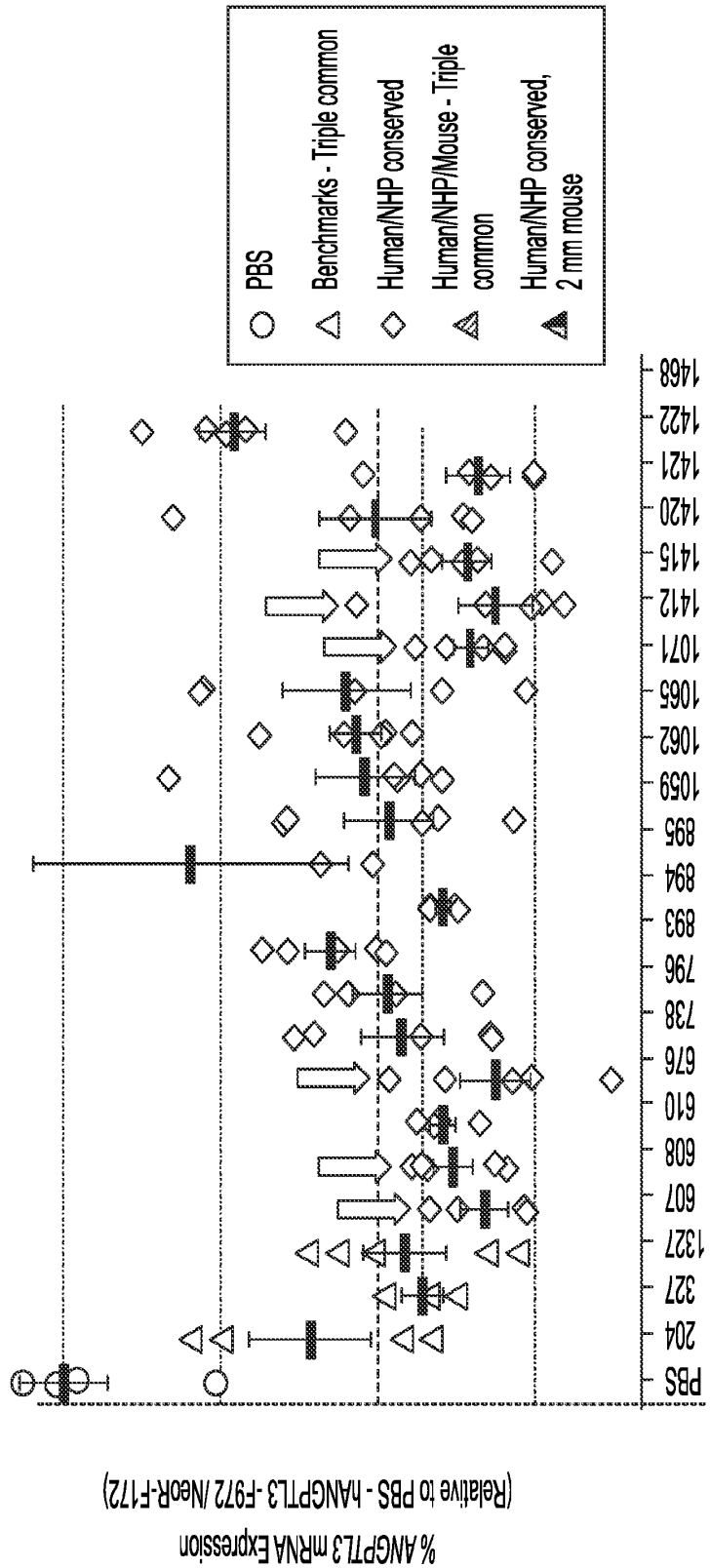
PBS
Benchmarks - Triple common
Human/NHP conserved
Human/NHP/Mouse - Triple common
Human/NHP conserved, 2 mm mouse
PBS
204
327
1327
607
608
610
676
738
796
893
894
895
1059
1062
1065
1071
1412
1415
1420
1421
1422
1468
In Vivo screen, Arm C
% ANGPTL3 mRNA Expression
(Relative to PBS - hANGPTL3 -F972 /NeoR-F172)

FIG. 4 (cont'd)

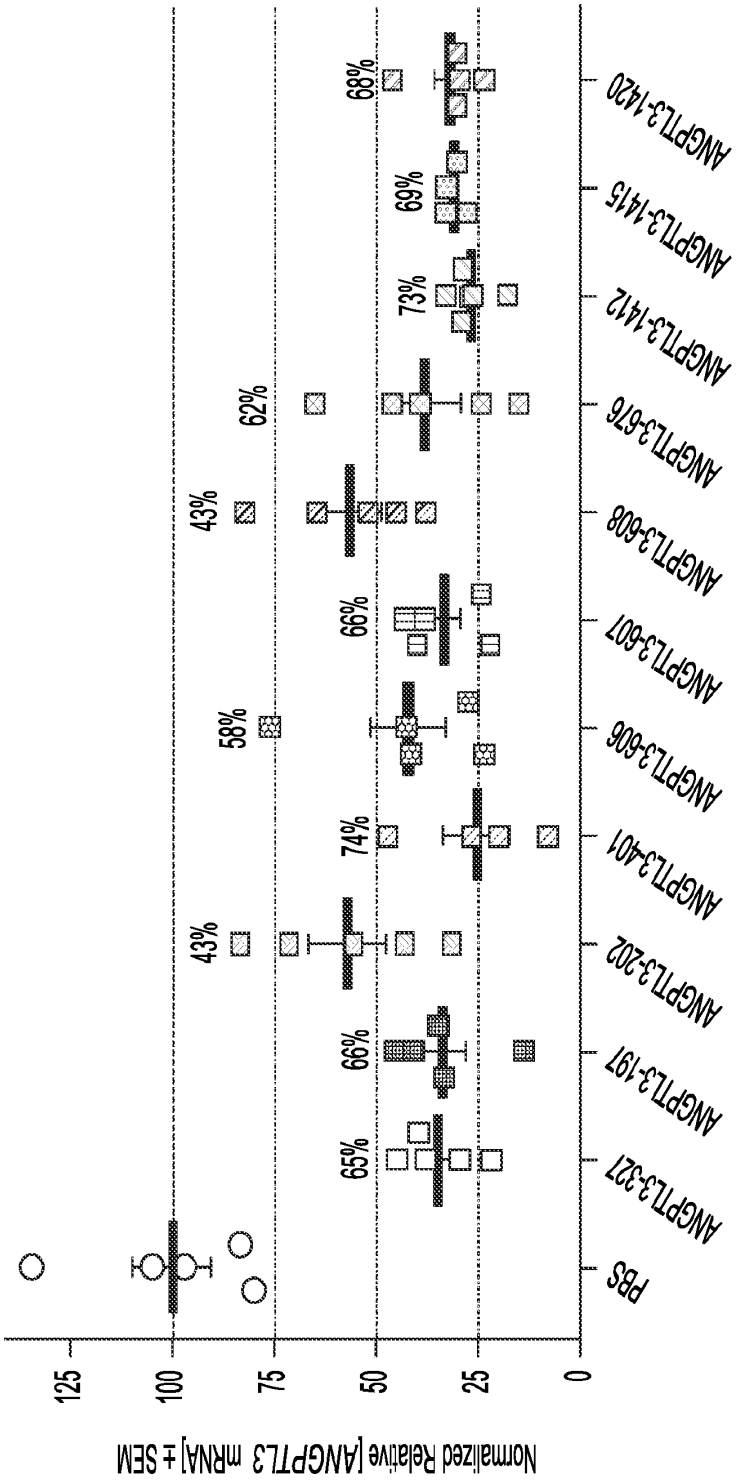
Normalized Relative [ANGPTL3 mRNA] ± SEM
125
100
75
50
25
0
PBS
ANGPTL3-327
ANGPTL3-197
ANGPTL3-202
ANGPTL3-401
ANGPTL3-606
ANGPTL3-607
ANGPTL3-608
ANGPTL3-676
ANGPTL3-1412
ANGPTL3-1415
ANGPTL3-1420
65%
66%
43%
74%
58%
66%
43%
62%
73%
69%
68%

FIG. 5A

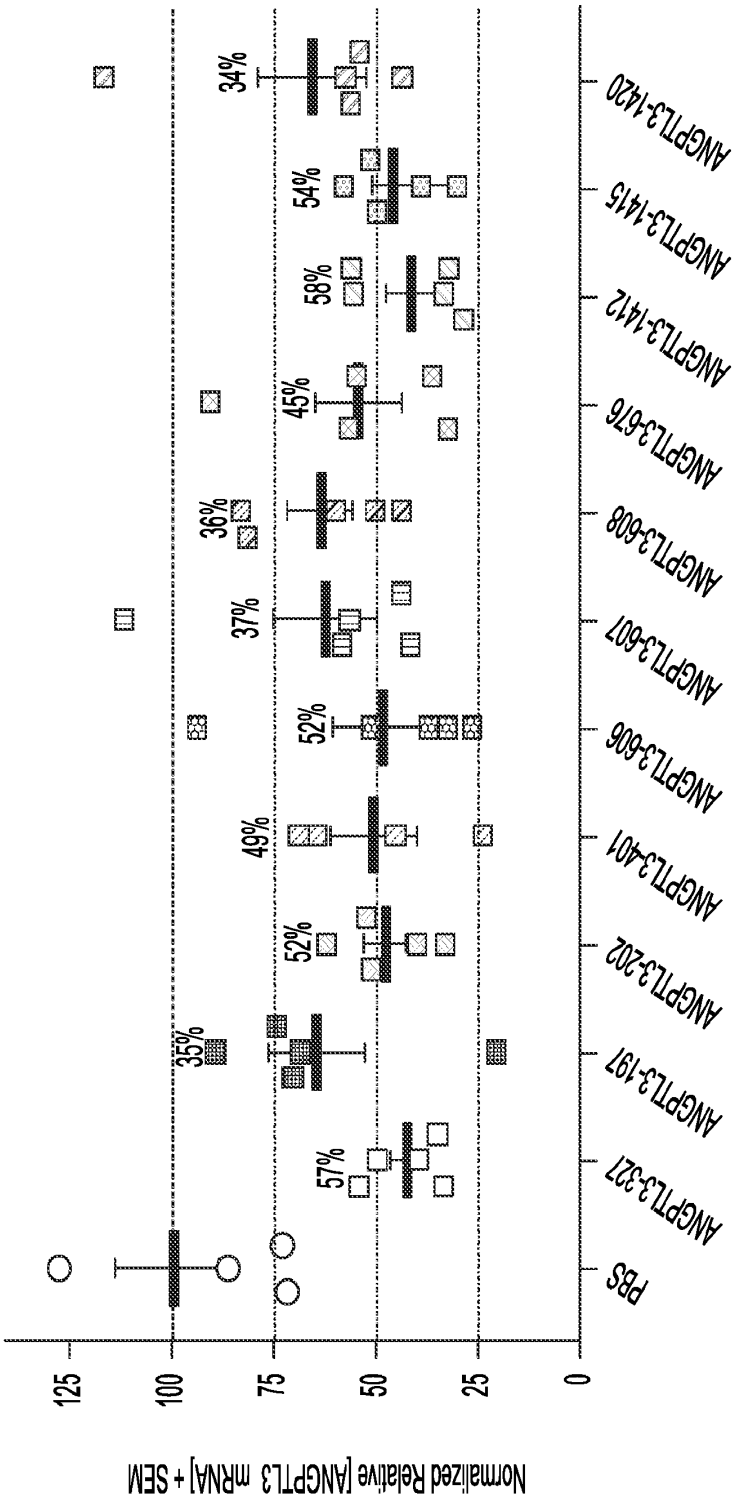
Normalized Relative [ANGPTL3 mRNA] + SEM
125
100
75
50
25
0
PBS
ANGPTL3-327
ANGPTL3-197
ANGPTL3-202
ANGPTL3-401
ANGPTL3-606
ANGPTL3-607
ANGPTL3-608
ANGPTL3-676
ANGPTL3-1412
ANGPTL3-1415
ANGPTL3-1420
35%
57%
52%
52%
49%
52%
37%
36%
45%
58%
54%
34%

FIG. 5B

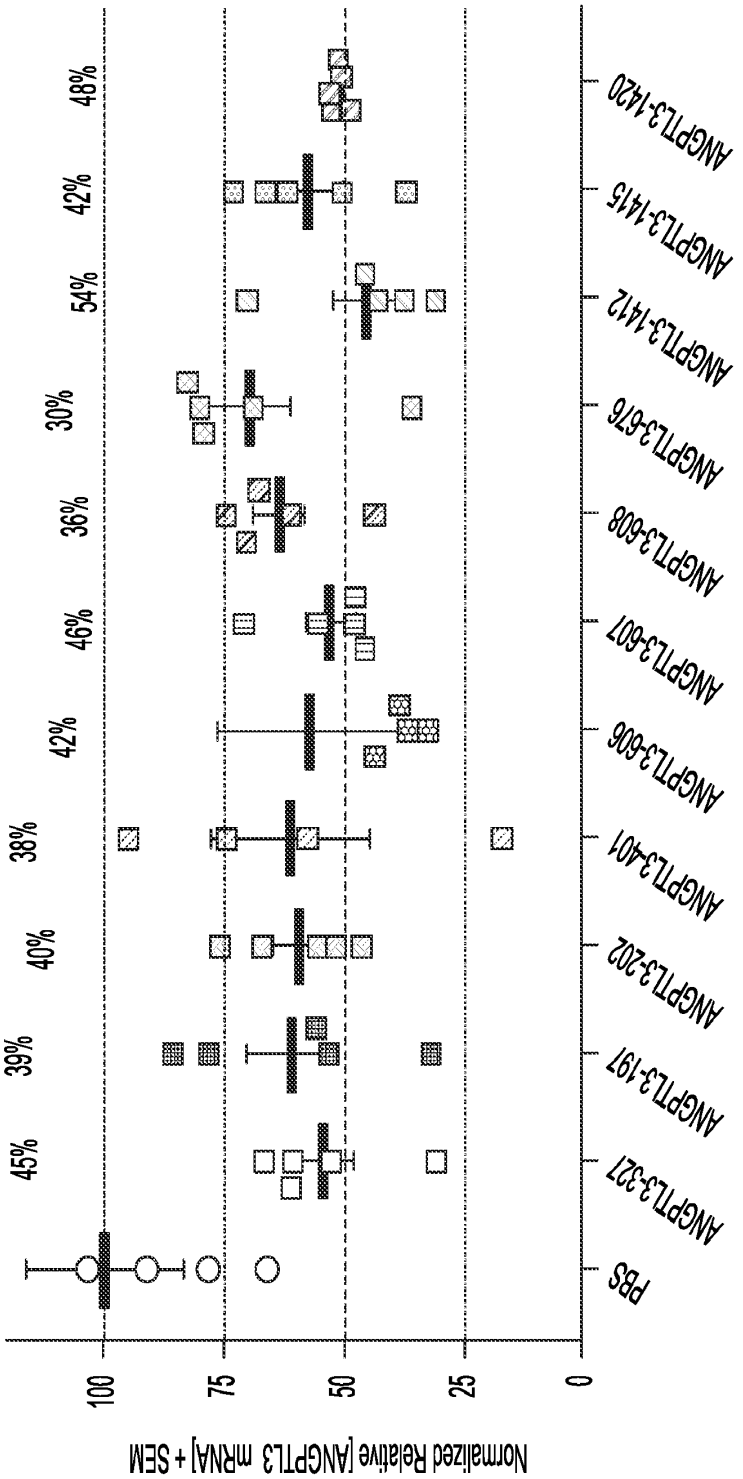
Normalized Relative [ANGPTL3 mRNA] + SEM
100
75
50
25
0
PBS
ANGPTL3-327
ANGPTL3-197
ANGPTL3-202
ANGPTL3-401
ANGPTL3-606
ANGPTL3-607
ANGPTL3-608
ANGPTL3-676
ANGPTL3-1412
ANGPTL3-1415
ANGPTL3-1420
45%
39%
40%
38%
42%
46%
36%
30%
54%
42%
48%

FIG. 5C

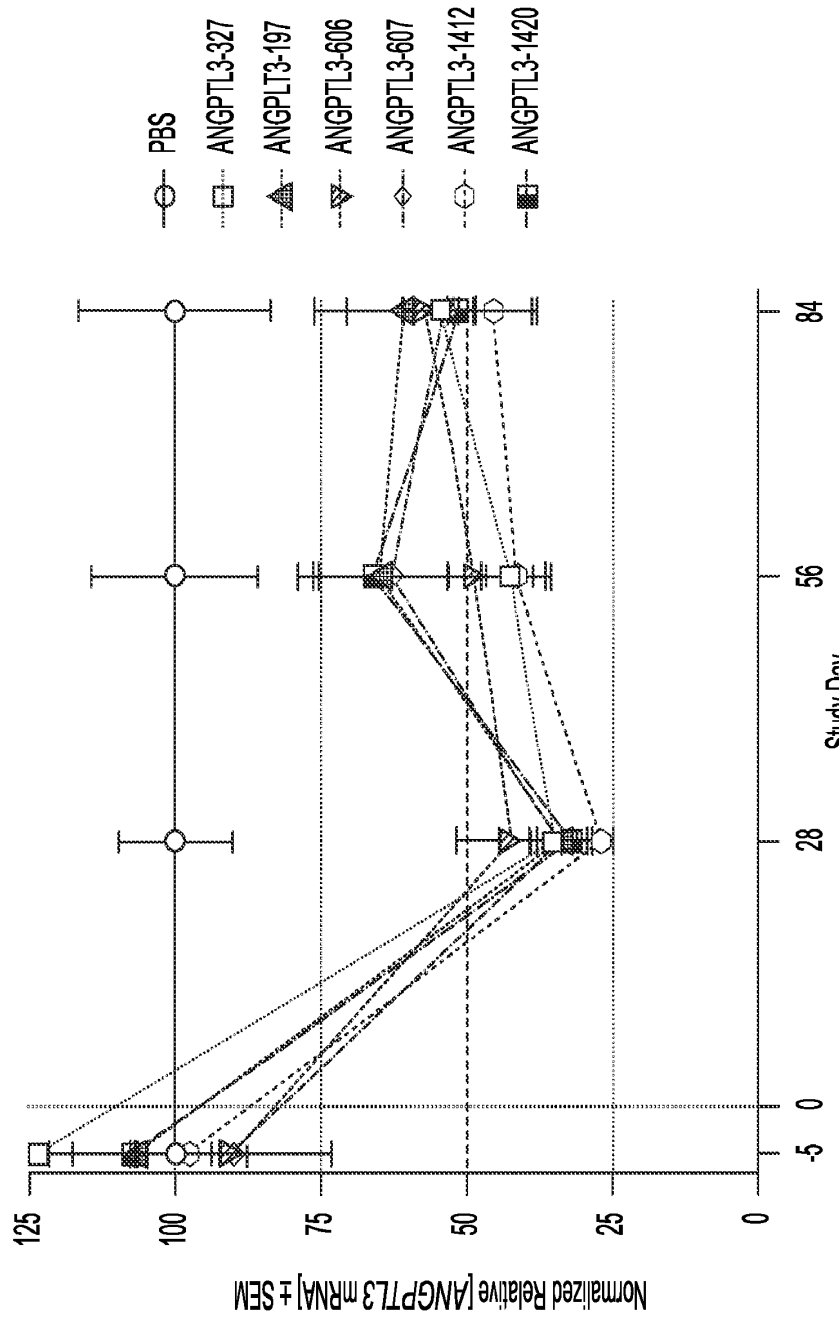
PBS
ANGPTL3-327
ANGPLT3-197
ANGPTL3-606
ANGPTL3-607
ANGPTL3-1412
ANGPTL3-1420
Normalized Relative [ANGPTL3 mRNA] ± SEM
125
100
75
50
25
0
-5
0
28
56
84
Study Day

FIG. 6

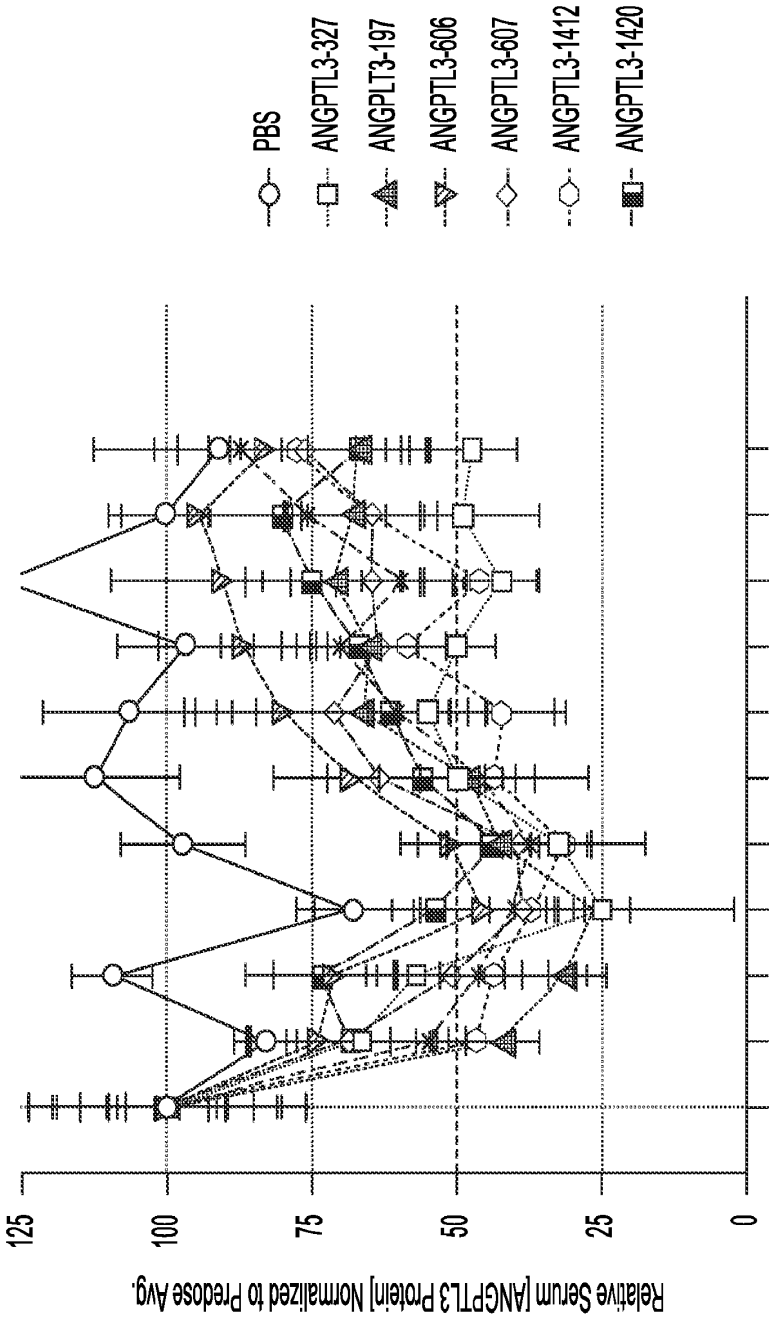
PBS
ANGPTL3-327
ANGPLT3-197
ANGPTL3-606
ANGPTL3-607
ANGPTL3-1412
ANGPTL3-1420
Relative Serum [ANGPTL3 Protein] Normalized to Predose Avg.
125
100
75
50
25
0
0
7
14
21
28
35
42
49
56
63
70
Predose Avg
(Days -8, -5, 0)
Study Day

FIG. 7