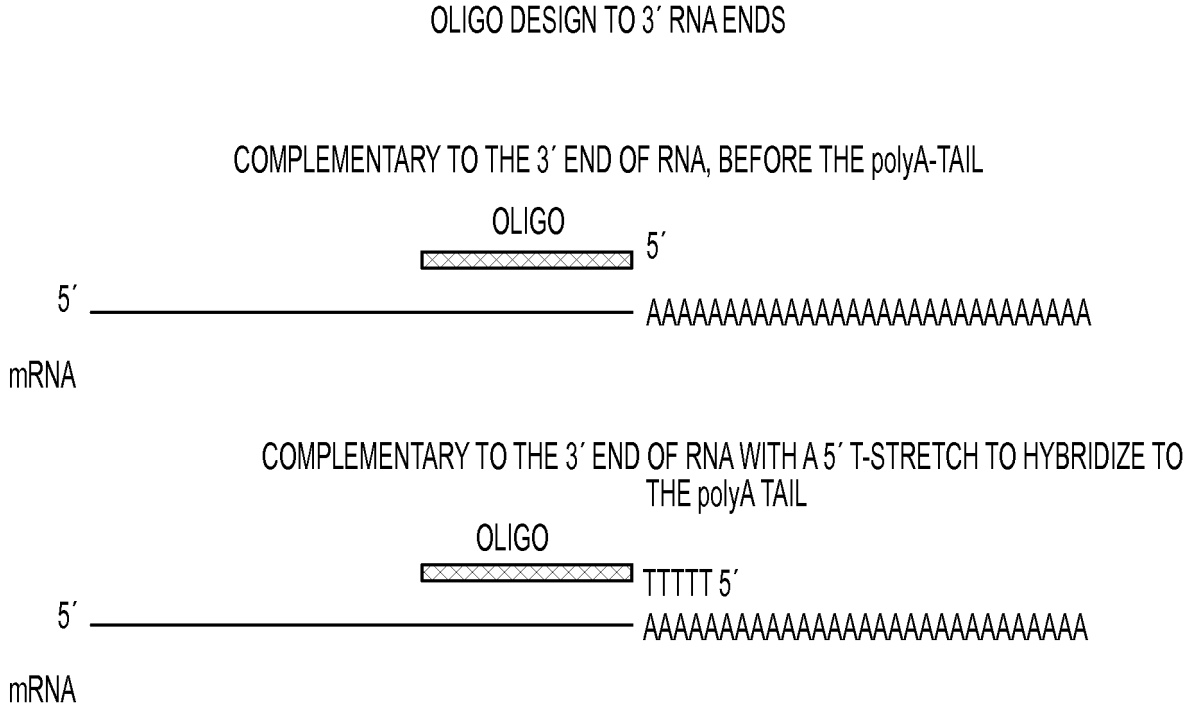
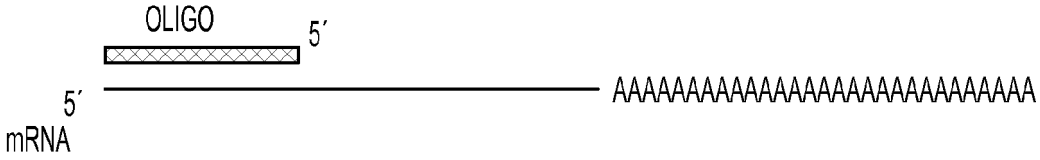

OLIGO DESIGN TO 3′ RNA ENDS
COMPLEMENTARY TO THE 3′ END OF RNA, BEFORE THE polyA-TAIL
OLIGO
5′
5′
AAAAAAAAAAAAAAAAAAAAAAAAAA
mRNA
COMPLEMENTARY TO THE 3′ END OF RNA WITH A 5′ T-STRETCH TO HYBRIDIZE TO THE polyA TAIL
OLIGO
TTTTT 5′
5′
AAAAAAAAAAAAAAAAAAAAAAAAAA
mRNA

FIG. 1

OLIGO DESIGN TO 5′ ENDS

COMPLEMENTARY TO THE 5′ END OF RNA



COMPLEMENTARY TO THE 5′ END OF RNA, WITH 3′OVERHANG RESIDUES TO CREATE A RNA-OLIGO DUPLEX WITH A RECESSED END. OVERHANG CAN INCLUDE A COMBINATION OF NUCLEOTIDES INCLUDING, BUT NOT LIMITED TO, C TO POTENTIALLY INTERACT WITH 5' METHYLGUANOSINE CAP AND STABILIZE THE CAP FURTHER.

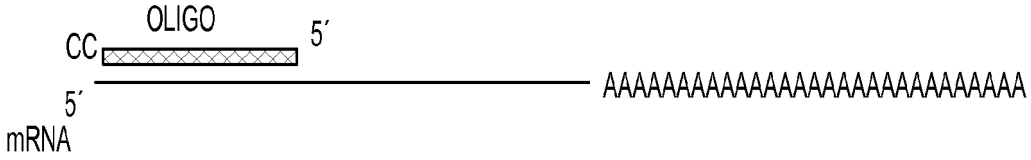
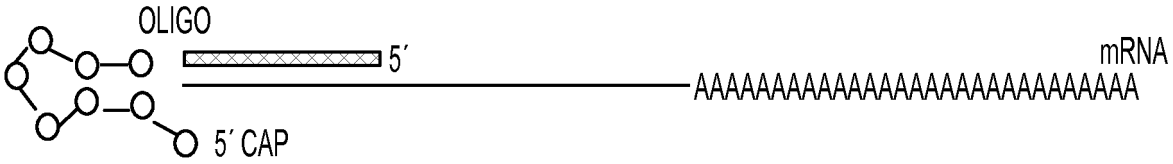


FIG. 2

OLIGO DESIGN TO 5' ENDS

5' OLIGOS WITH LOOPS TO STABILIZE 5' RNA CAP – OLIGO 62



OLIGO DESIGN TO 5′ AND 3′ ENDS

CIRCULARIZATION OLIGOS PROTECT BOTH ENDS OF RNA WITH ONE OLIGO TO CREATE A PSEUDO-CIRCULARIZED RNA

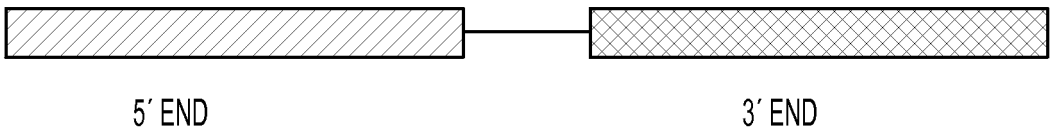


FIG. 3A

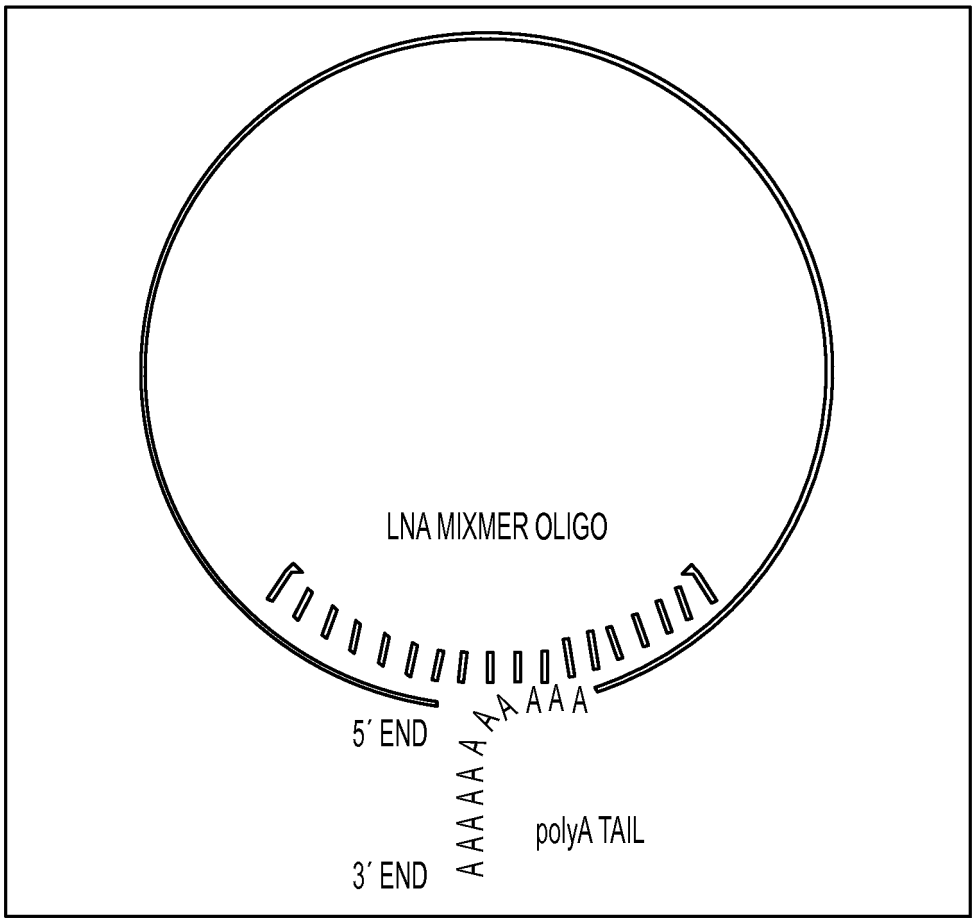

OLIGO-MEDIATED RNA PSEUDO-CIRCULARIZATION
LNA MIXMER OLIGO
5′ END
3′ END
A A A A A A A A A A
polyA TAIL

FIG. 3B

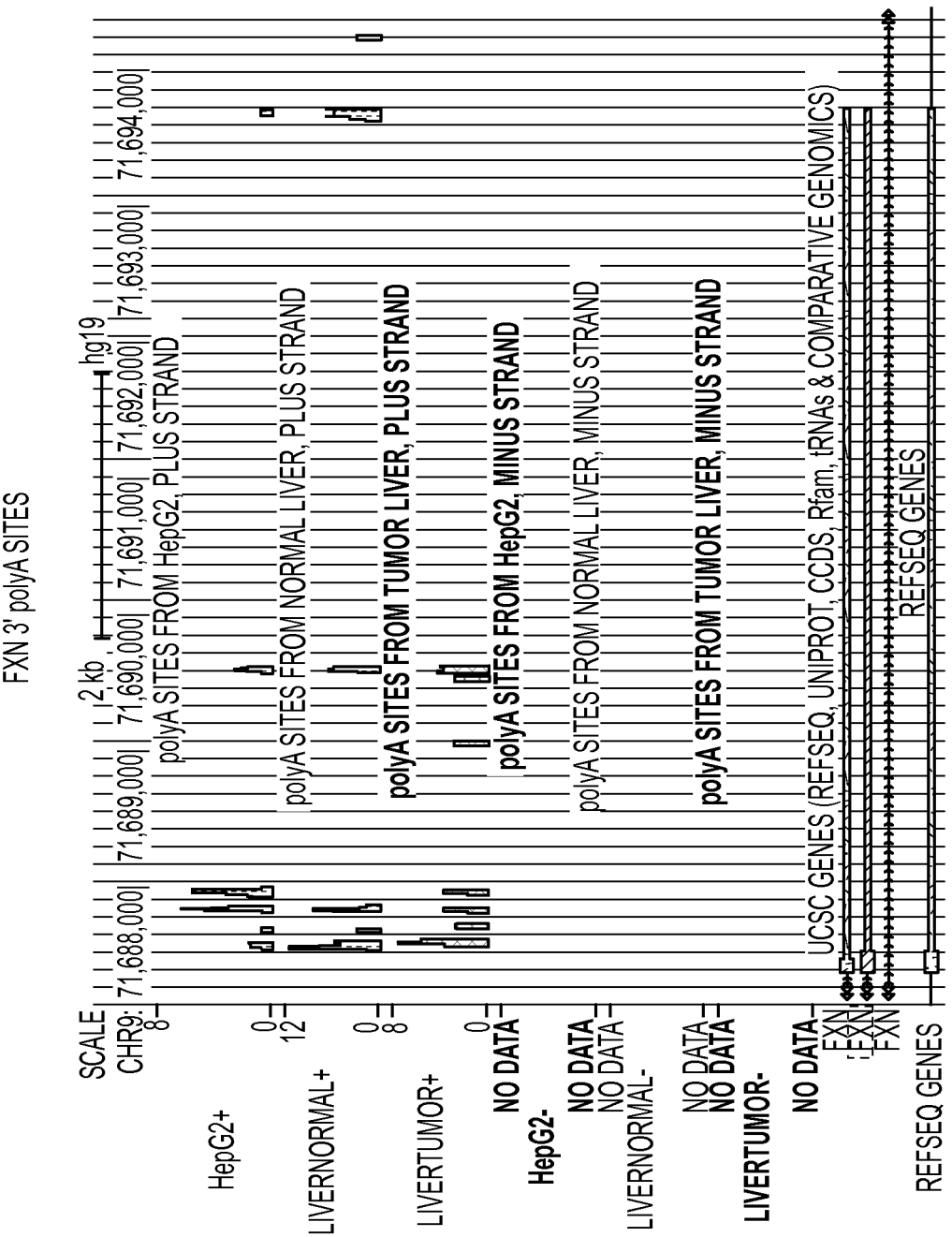

FXN 3' polyA SITES
SCALE
CHR9: 71,688,000 71,689,000 71,690,000 71,691,000 71,692,000 71,693,000 71,694,000
2 kb
hg19
HepG2+
polyA SITES FROM HepG2, PLUS STRAND
LIVERNORMAL+
polyA SITES FROM NORMAL LIVER, PLUS STRAND
LIVERTUMOR+
polyA SITES FROM TUMOR LIVER, PLUS STRAND
HepG2-
NO DATA
polyA SITES FROM HepG2, MINUS STRAND
LIVERNORMAL-
NO DATA
polyA SITES FROM NORMAL LIVER, MINUS STRAND
LIVERTUMOR-
NO DATA
polyA SITES FROM TUMOR LIVER, MINUS STRAND
UCSC GENES (REFSEQ, UNIPROT, CCDS, Rfam, tRNAs & COMPARATIVE GENOMICS)
FXN
FXN
FXN
REFSEQ GENES
REFSEQ GENES

FIG. 4

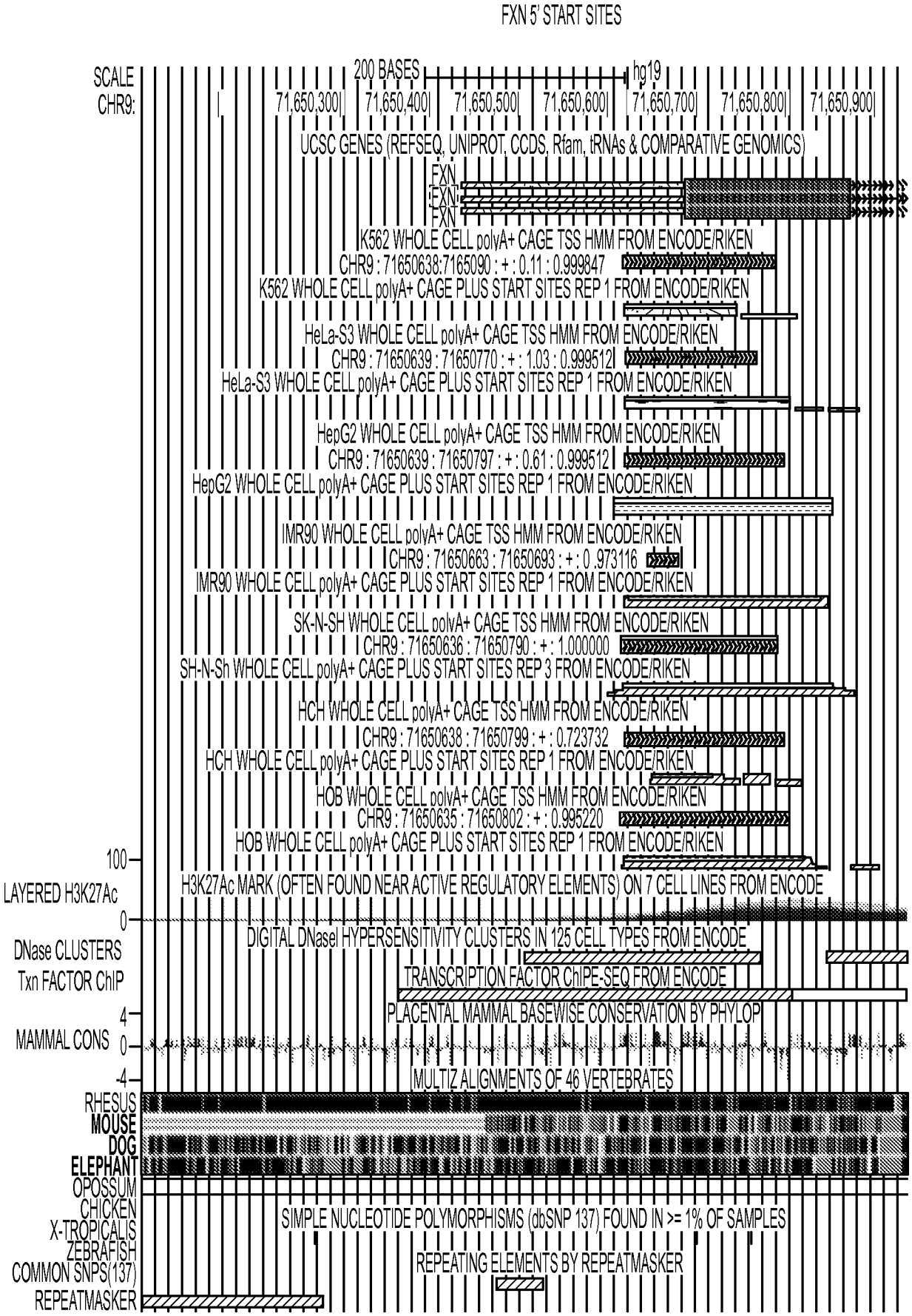

FXN 5' START SITES
SCALE
CHR9:
200 BASES
hg19
71,650,300
71,650,400
71,650,500
71,650,600
71,650,700
71,650,800
71,650,900
UCSC GENES (REFSEQ, UNIPROT, CCDS, Rfam, tRNAs & COMPARATIVE GENOMICS)
FXN
K562 WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650638:7165090 : + : 0.11 : 0.999847
K562 WHOLE CELL polyA+ CAGE PLUS START SITES REP 1 FROM ENCODE/RIKEN
HeLa-S3 WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650639 : 71650770 : + : 1.03 : 0.999512
HeLa-S3 WHOLE CELL polyA+ CAGE PLUS START SITES REP 1 FROM ENCODE/RIKEN
HepG2 WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650639 : 71650797 : + : 0.61 : 0.999512
HepG2 WHOLE CELL polyA+ CAGE PLUS START SITES REP 1 FROM ENCODE/RIKEN
IMR90 WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650663 : 71650693 : + : 0 .973116
IMR90 WHOLE CELL polyA+ CAGE PLUS START SITES REP 1 FROM ENCODE/RIKEN
SK-N-SH WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650636 : 71650790 : + : 1.000000
SH-N-Sh WHOLE CELL polyA+ CAGE PLUS START SITES REP 3 FROM ENCODE/RIKEN
HCH WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650638 : 71650799 : + : 0.723732
HCH WHOLE CELL polyA+ CAGE PLUS START SITES REP 1 FROM ENCODE/RIKEN
HOB WHOLE CELL polyA+ CAGE TSS HMM FROM ENCODE/RIKEN
CHR9 : 71650635 : 71650802 : + : 0.995220
HOB WHOLE CELL polyA+ CAGE PLUS START SITES REP 1 FROM ENCODE/RIKEN
100
LAYERED H3K27Ac
H3K27Ac MARK (OFTEN FOUND NEAR ACTIVE REGULATORY ELEMENTS) ON 7 CELL LINES FROM ENCODE
0
DNase CLUSTERS
DIGITAL DNaseI HYPERSENSITIVITY CLUSTERS IN 125 CELL TYPES FROM ENCODE
Txn FACTOR ChIP
TRANSCRIPTION FACTOR ChIPE-SEQ FROM ENCODE
4
MAMMAL CONS
0
PLACENTAL MAMMAL BASEWISE CONSERVATION BY PHYLOP
-4
MULTIZ ALIGNMENTS OF 46 VERTEBRATES
RHESUS
MOUSE
DOG
ELEPHANT
OPOSSUM
CHICKEN
X-TROPICALIS
ZEBRAFISH
COMMON SNPS(137)
SIMPLE NUCLEOTIDE POLYMORPHISMS (dbSNP 137) FOUND IN >= 1% OF SAMPLES
REPEATMASKER
REPEATING ELEMENTS BY REPEATMASKER

FIG. 5

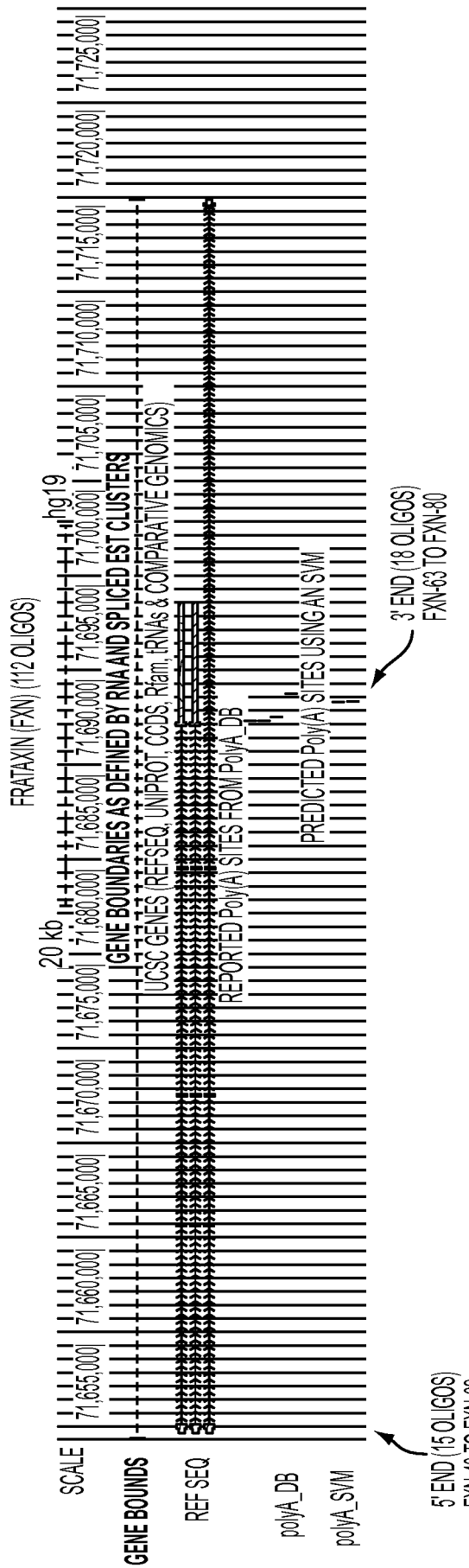

FRATAXIN (FXN) (112 OLIGOS)
hg19
20 kb
GENE BOUNDARIES AS DEFINED BY RNA AND SPLICED EST CLUSTERS
UCSC GENES (REFSEQ, UNIPROT, CCDS, Rfam, tRNAs & COMPARATIVE GENOMICS)
REPORTED PolyA SITES FROM PolyA_DB
PREDICTED PolyA SITES USING AN SVM
3' END (18 OLIGOS)
FXN-63 TO FXN-80
5' END (15 OLIGOS)
FXN-48 TO FXN-62
SCALE
GENE BOUNDS
REF SEQ
polyA_DB
polyA_SVM
71,655,000
71,660,000
71,665,000
71,670,000
71,675,000
71,680,000
71,685,000
71,690,000
71,695,000
71,700,000
71,705,000
71,710,000
71,715,000
71,720,000
71,725,000

FIG. 6

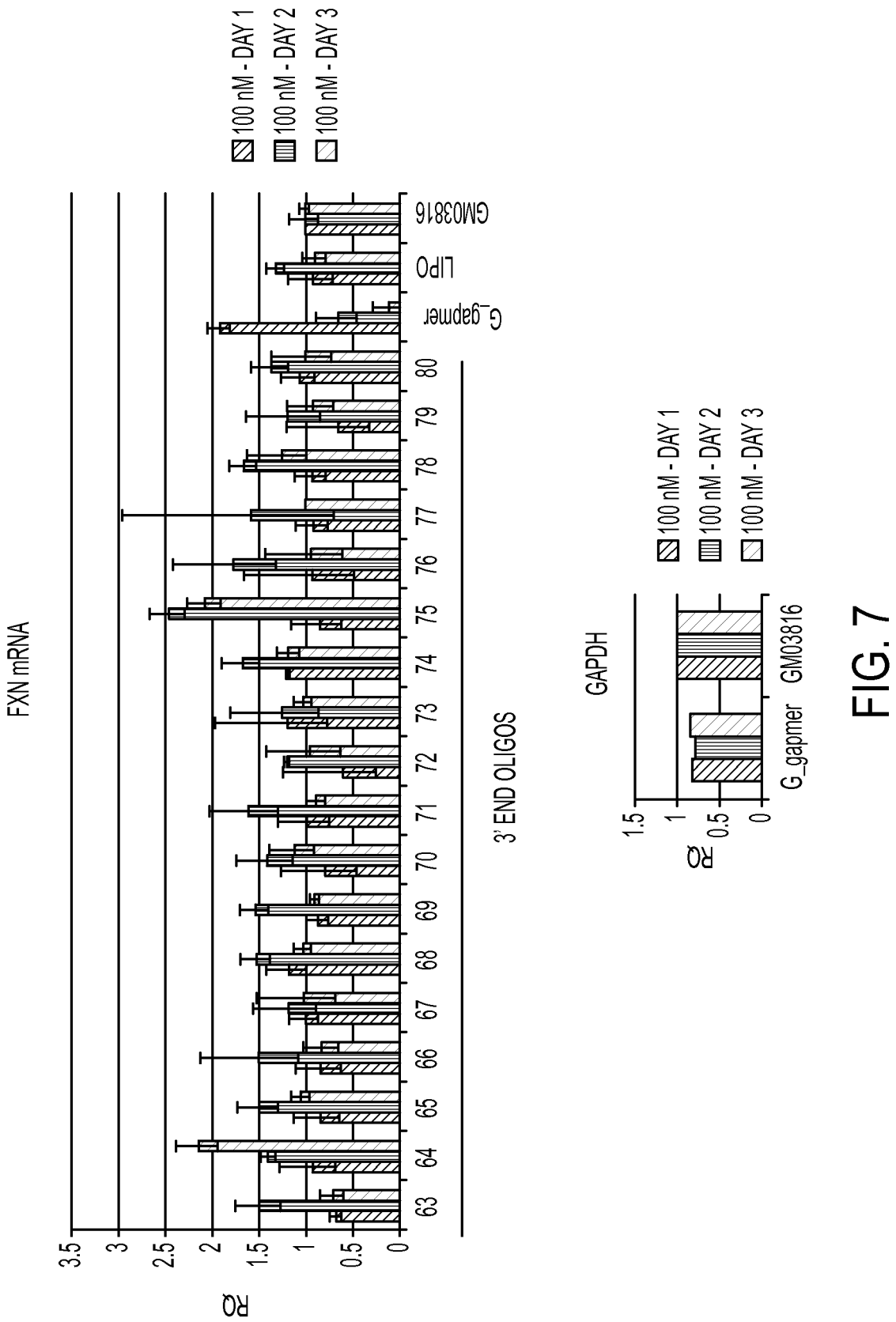

FXN mRNA
100 nM - DAY 1
100 nM - DAY 2
100 nM - DAY 3
RQ
3.5
3
2.5
2
1.5
1
0.5
0
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
3' END OLIGOS
G_gapmer
LIPO
GM03816
GAPDH
100 nM - DAY 1
100 nM - DAY 2
100 nM - DAY 3
RQ
1.5
1
0.5
0
G_gapmer GM03816

FIG. 7

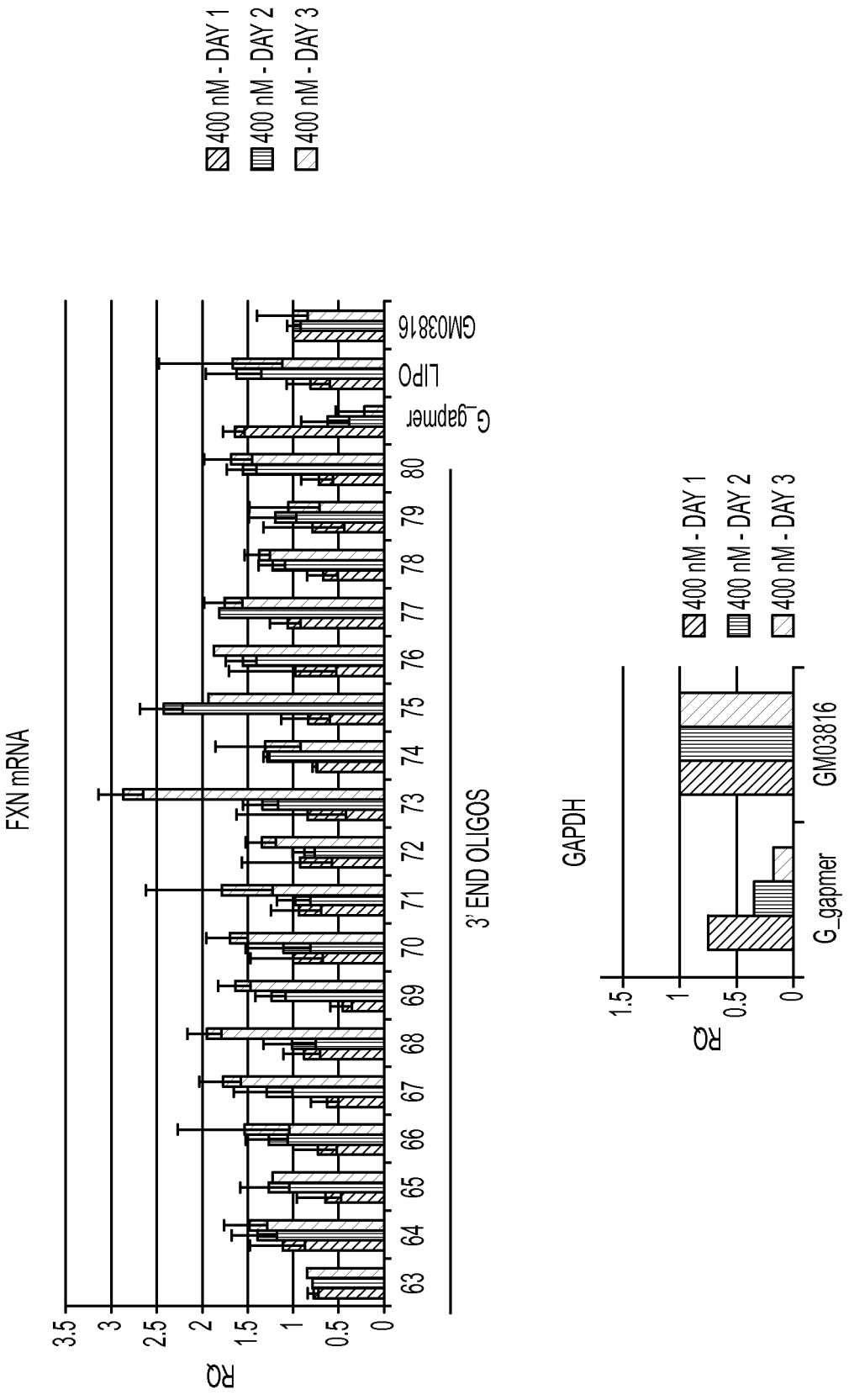
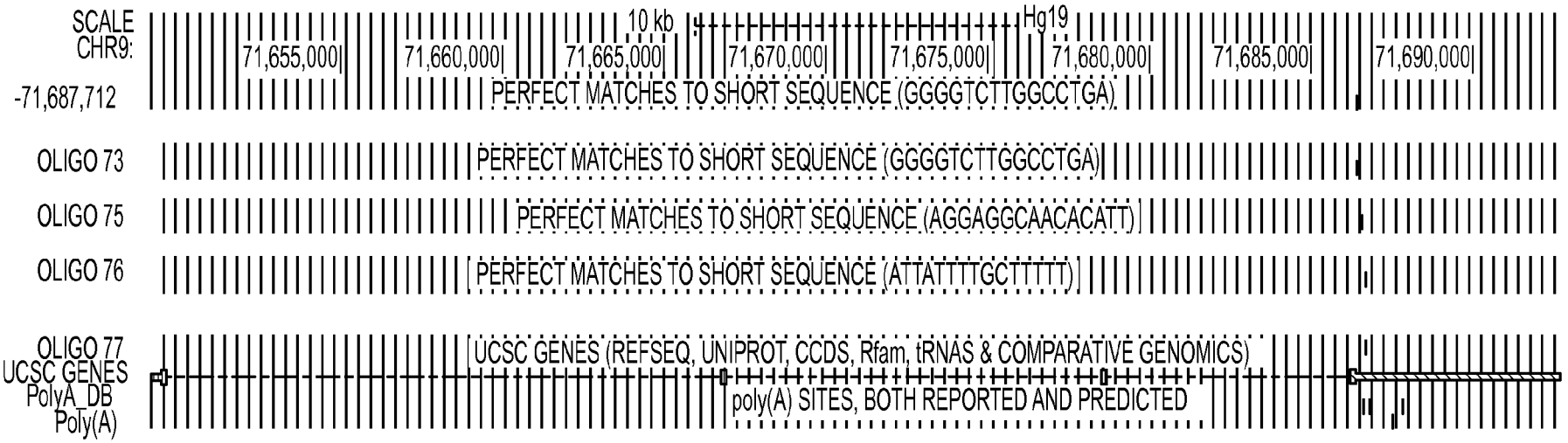

400 nM - DAY 1
400 nM - DAY 2
400 nM - DAY 3
FXN mRNA
RQ
3.5
3
2.5
2
1.5
1
0.5
0
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
3' END OLIGOS
G_gapmer
LIPO
GM03816
GAPDH
RQ
1.5
1
0.5
0
400 nM - DAY 1
400 nM - DAY 2
400 nM - DAY 3
G_gapmer
GM03816

FIG. 8



OLIGO 73 TTTTTGGGGTCTTGGCCTGA
QLIGO 75 TTTTTAGGAGGCAACACATT
OLIGO 76 TTTTTATTATTTTGCTTTTT
OJJGO 77 TTTTTCATTTTCCCTCCTGG

OLIGO75 APPEARS TO BE THE STRONGEST CANDIDATE:

- UPREGULATES FXN mRNA BY 2-2.5 FOLD WITH 100 AND 400 nM @ DAY 2
- UPREGULATES FXN mRNA BY 2-2.5 FOLD WITH 100 AND 400 nM @ DAY 3

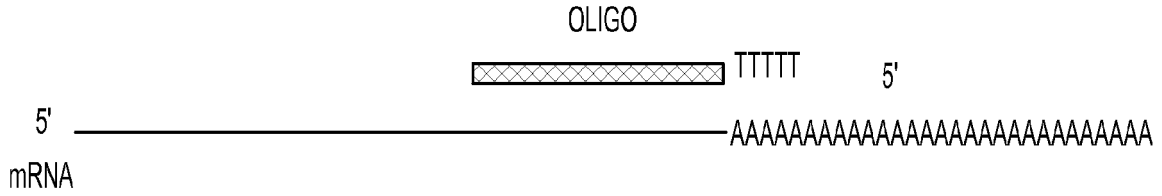


FIG. 9

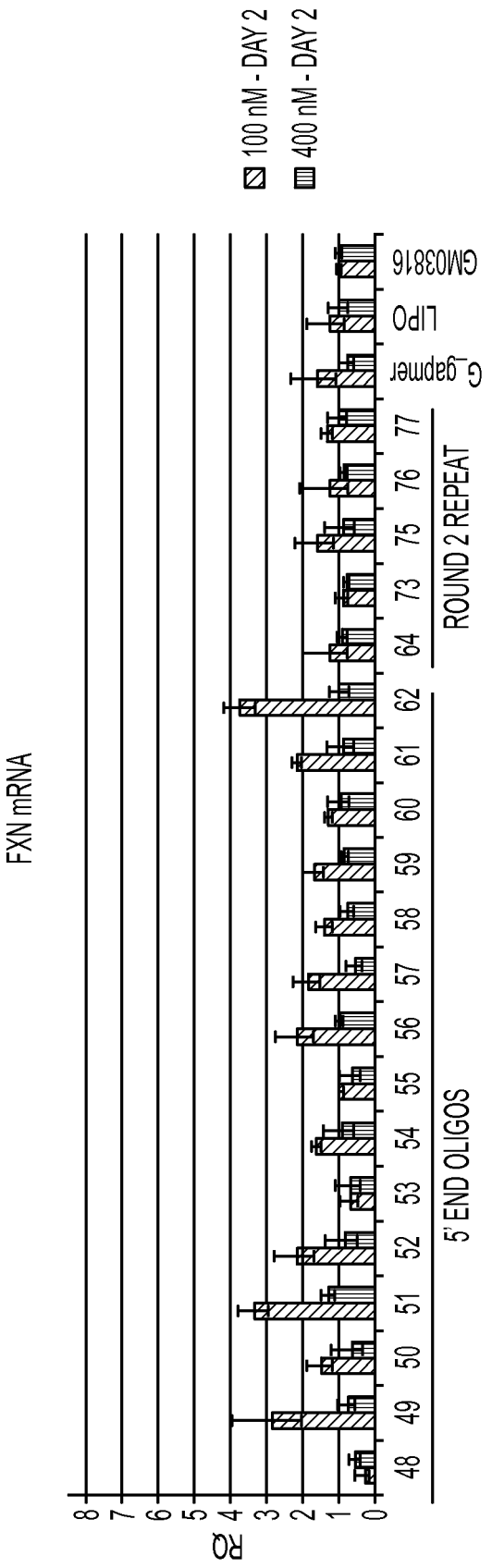

100 nM - DAY 2
400 nM - DAY 2
FXN mRNA
RQ
0
1
2
3
4
5
6
7
8
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
64
73
75
76
77
5' END OLIGOS
ROUND 2 REPEAT
G_gapmer
LIPO
GM03816

FIG. 10

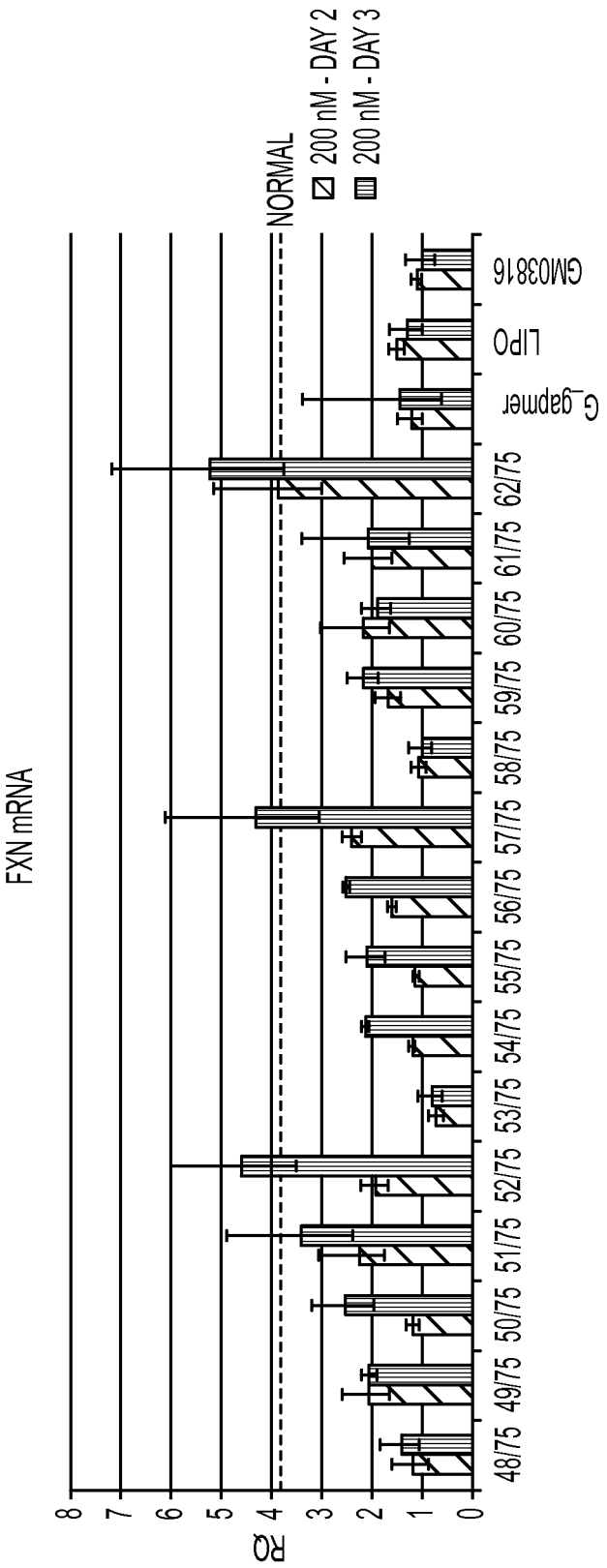

FXN mRNA
RQ
NORMAL
200 nM - DAY 2
200 nM - DAY 3
G_gapmer
LIPO
GM03816
48/75
49/75
50/75
51/75
52/75
53/75
54/75
55/75
56/75
57/75
58/75
59/75
60/75
61/75
62/75
0
1
2
3
4
5
6
7
8

FIG. 11

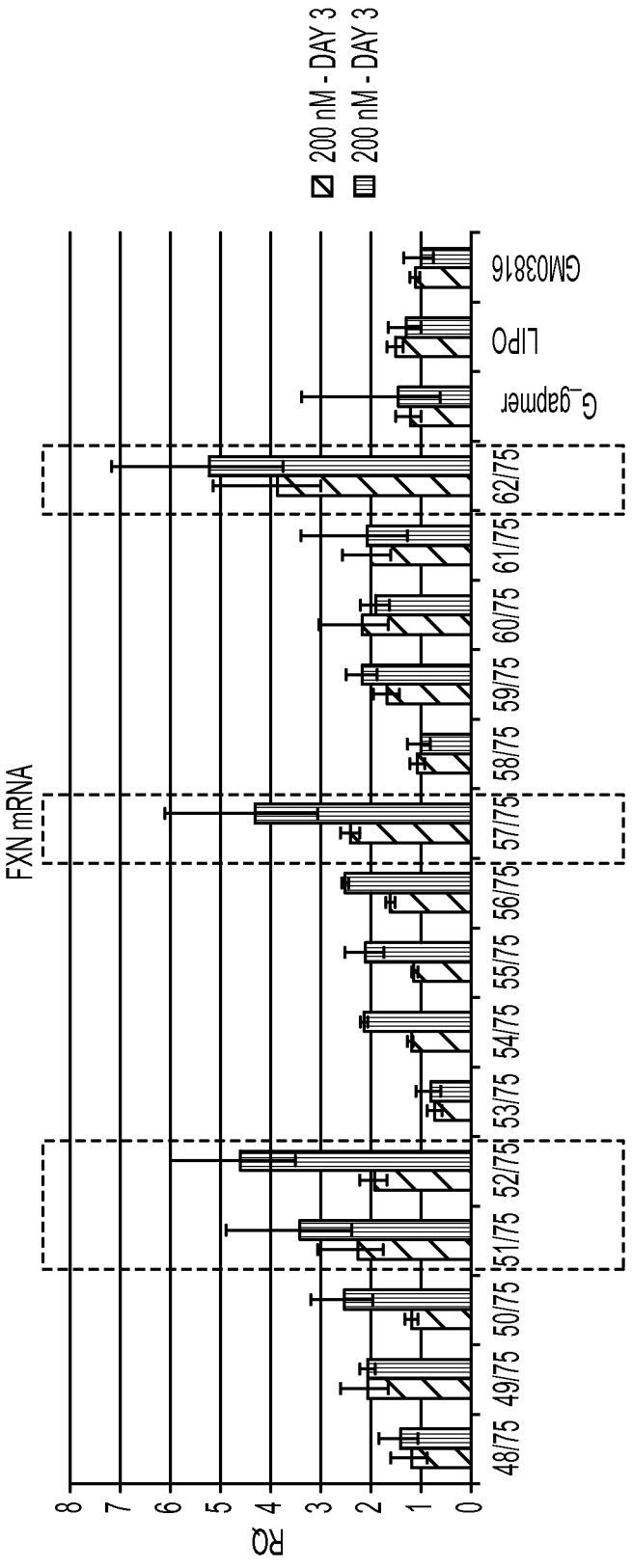
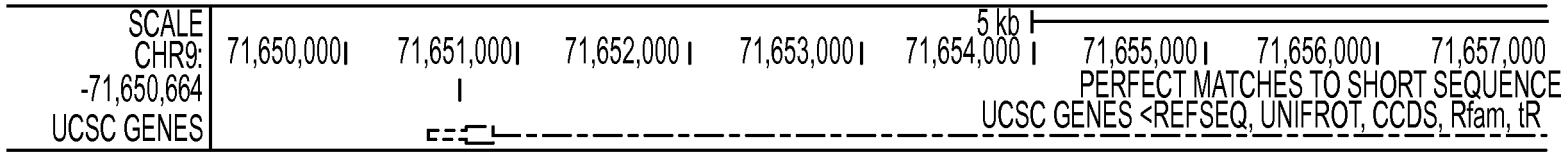

200 nM - DAY 3
200 nM - DAY 3
FXN mRNA
RQ
0
1
2
3
4
5
6
7
8
48/75
49/75
50/75
51/75
52/75
53/75
54/75
55/75
56/75
57/75
58/75
59/75
60/75
61/75
62/75
G_gapmer
LIPO
GM03816

FIG. 12



OLIGO 51 (CGCCCTCCAGCGCTG) MATCHES THE 5' END
OLIGO 52 (CGCTCCGCCCTCCAG) MATCHES THE 5' END
OLIGO 57 (CGCTCCGCCCTCCAGCC) MATCHES THE 5' END
OLIGO 62 (CGCTCCGCCCTCCAGCCAAAGGTC) DOES NOT HAVE A PERFECT MATCH

ALL POTENTIAL POSITIVE 5' OLIGOS HAVE THE SEQUENCE: CGCCCTCCAG

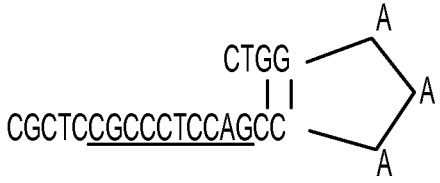


FIG. 13

OLIGO DESIGN TO 5′ ENDS

OPTION 3: 5′ OLIGOS WITH LOOPS TO STABILIZE 5′RNA CAP – OLIGO 62

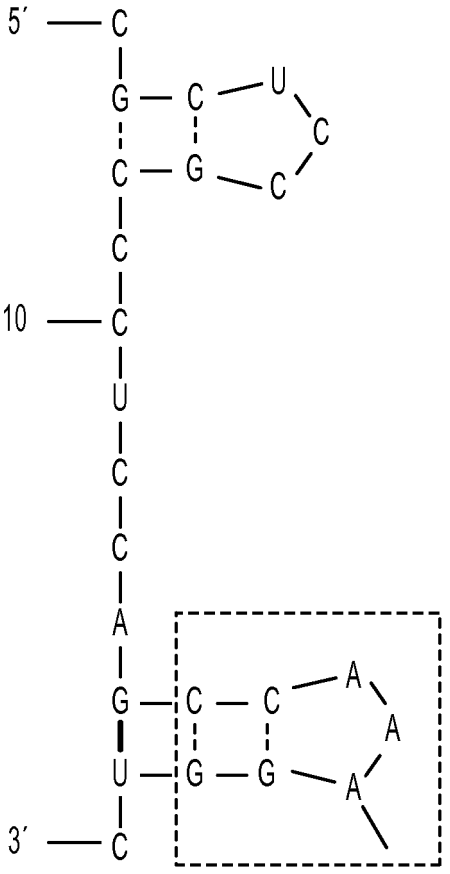


FIG. 14

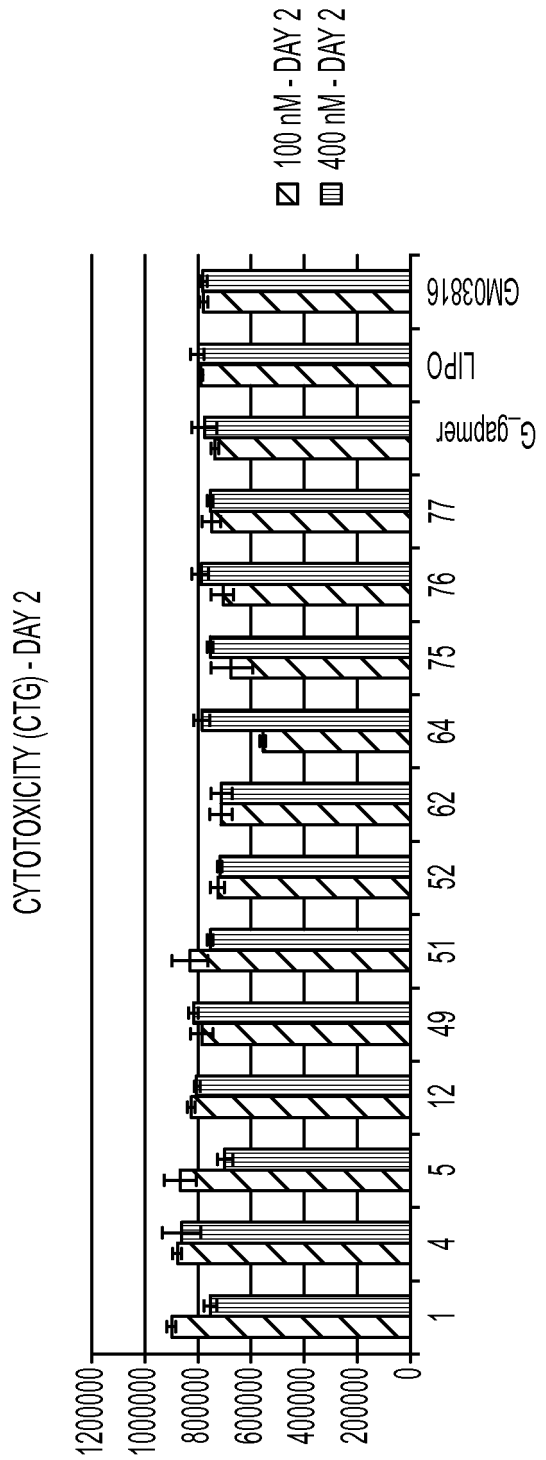

100 nM - DAY 2
400 nM - DAY 2
CYTOTOXICITY (CTG) - DAY 2
1200000
1000000
800000
600000
400000
200000
0
1
4
5
12
49
51
52
62
64
75
76
77
G_gapmer
LIPO
GM03816

FIG. 15A

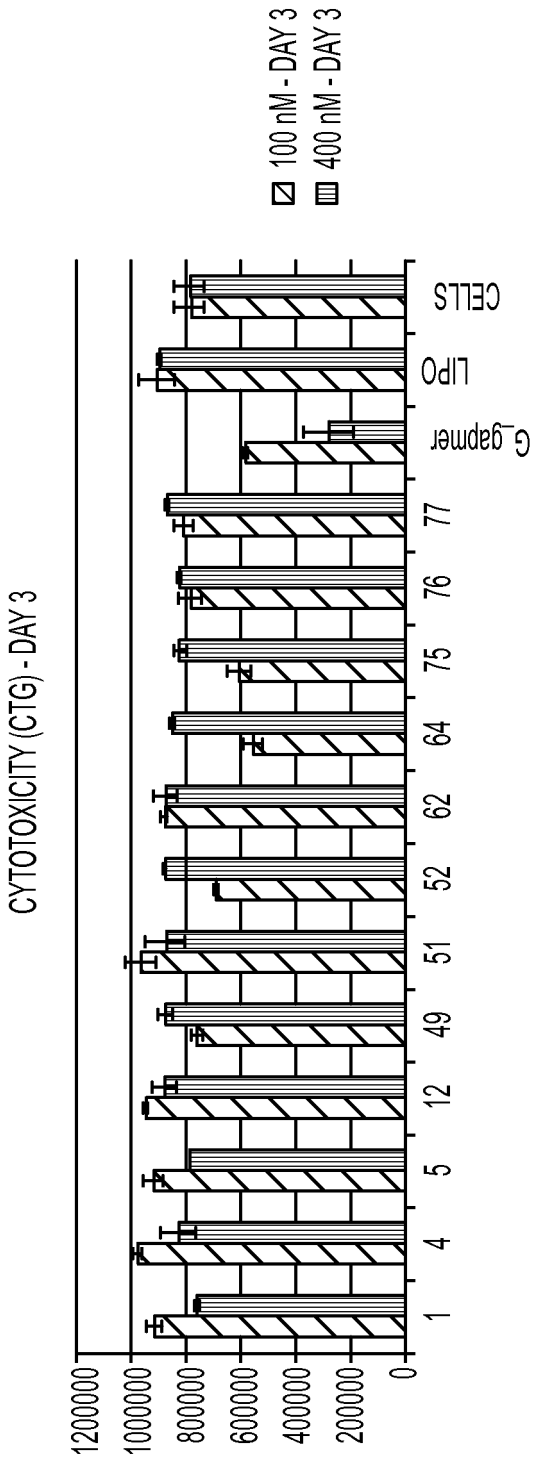

100 nM - DAY 3
400 nM - DAY 3
CYTOTOXICITY (CTG) - DAY 3
1200000
1000000
800000
600000
400000
200000
0
1
4
5
12
49
51
52
62
64
75
76
77
G_gapmer
LIPO
CELLS

FIG. 15B

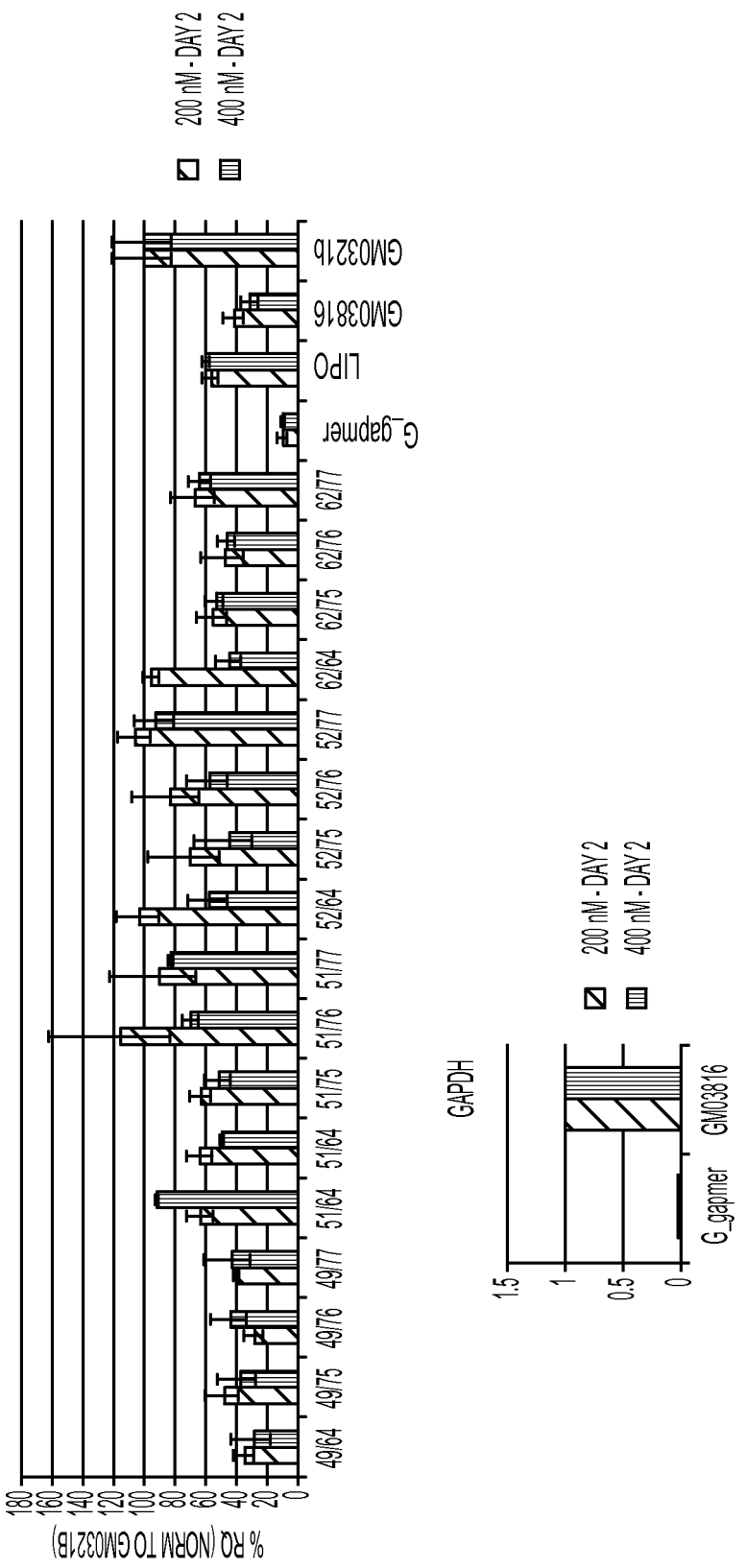

200 nM - DAY 2
400 nM - DAY 2
FXN mRNA
% RQ (NORM TO GM03218)
0
20
40
60
80
100
120
140
160
180
49/64
49/75
49/76
49/77
51/64
51/64
51/75
51/76
51/77
52/64
52/75
52/76
52/77
62/64
62/75
62/76
62/77
G_gapmer
LIPO
GM03816
GM03218
GAPDH
0
0.5
1
1.5
G_gapmer
GM03816

FIG. 16

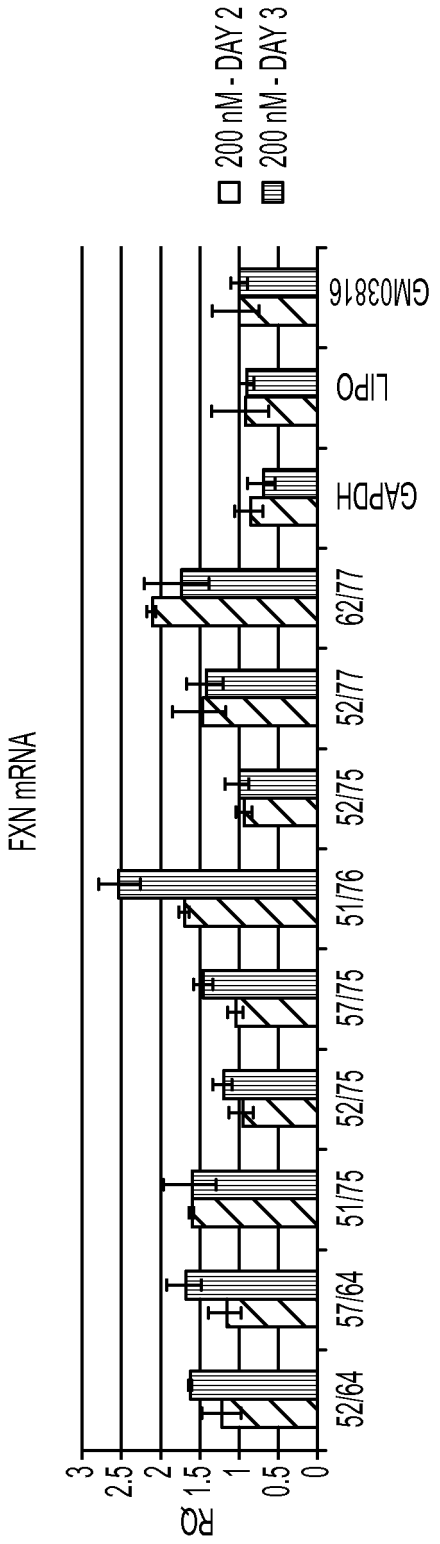

200 nM - DAY 2
200 nM - DAY 3
FXN mRNA
RQ
3
2.5
2
1.5
1
0.5
0
52/64
57/64
51/75
52/75
57/75
51/76
52/75
52/77
62/77
GAPDH
LIPO
GM03816

FIG. 17

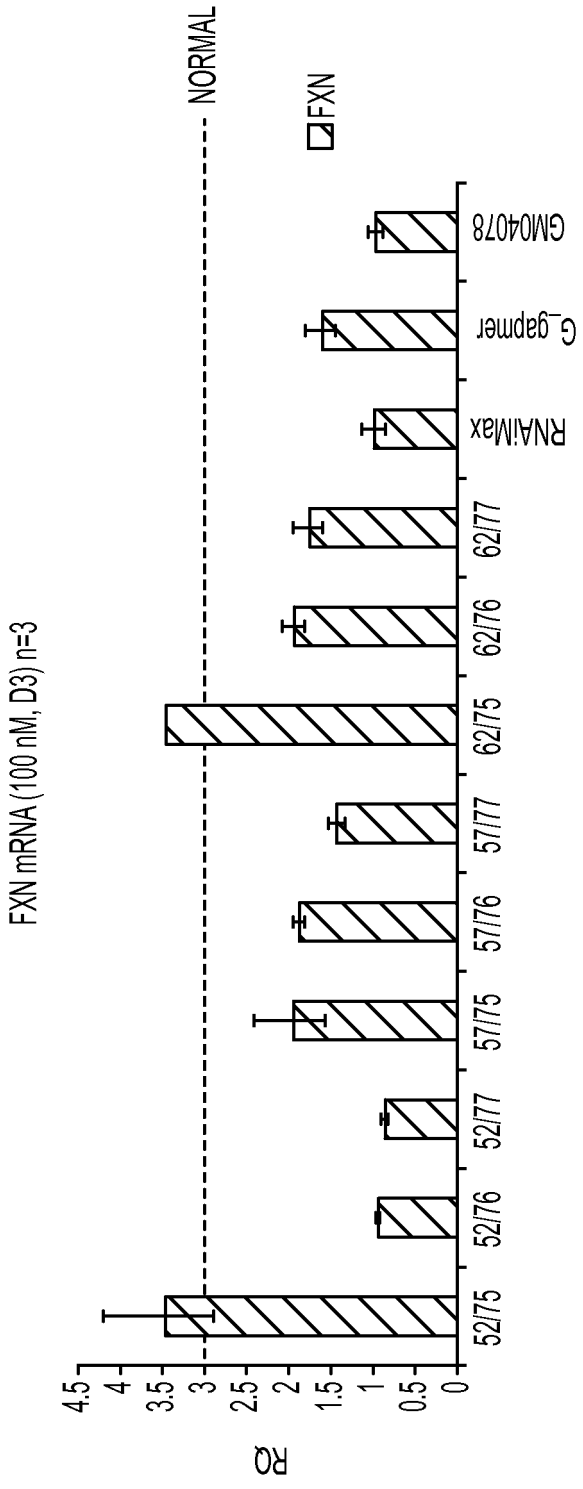

FXN mRNA (100 nM, D3) n=3
RQ
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
NORMAL
FXN
52/75
52/76
52/77
57/75
57/76
57/77
62/75
62/76
62/77
RNAiMax
G_gapmer
GM04078

FIG. 18

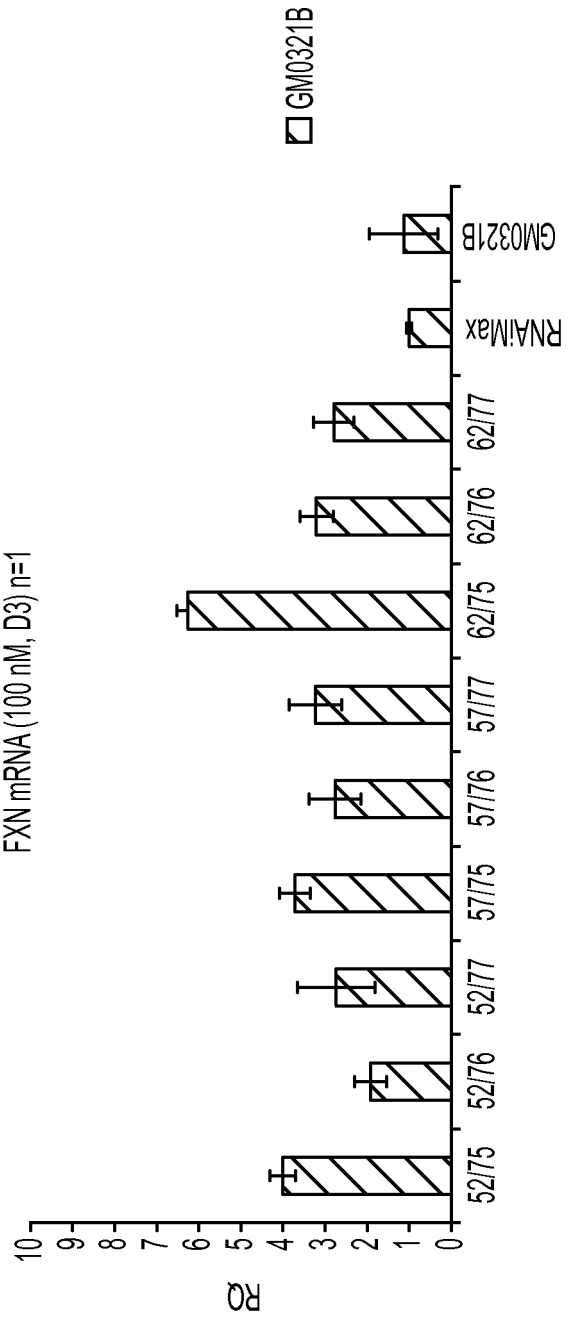

FXN mRNA (100 nM, D3) n=1
RQ
0
1
2
3
4
5
6
7
8
9
10
52/75
52/76
52/77
57/75
57/76
57/77
62/75
62/76
62/77
RNAiMax
GM0321B
GM0321B

FIG. 19

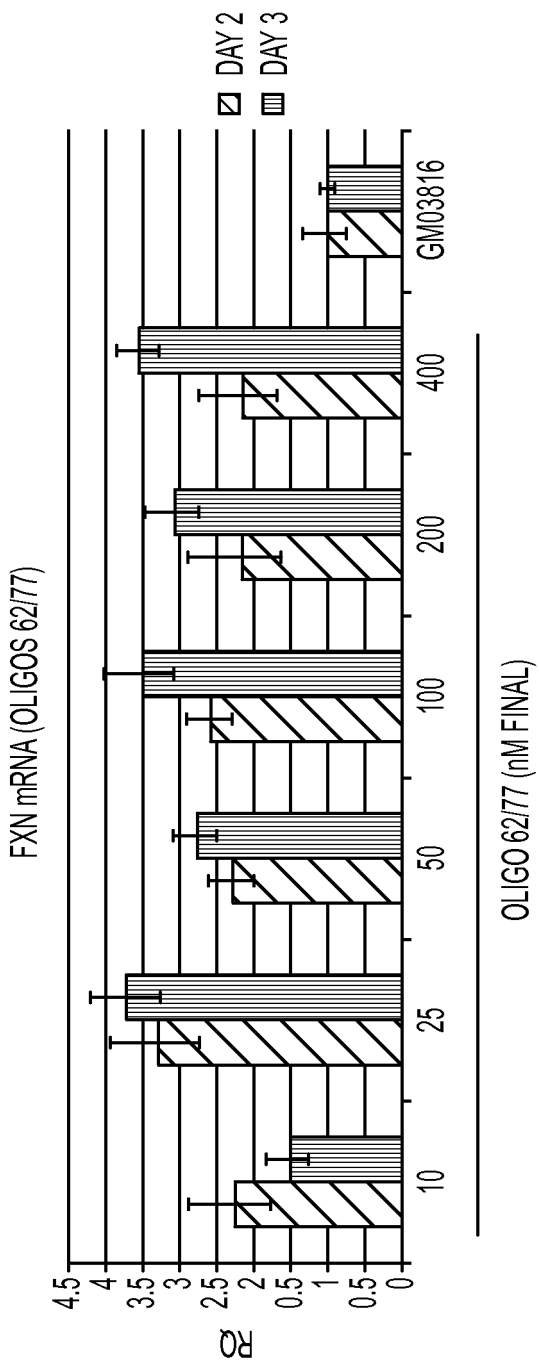

DAY 2
DAY 3
FXN mRNA (OLIGOS 62/77)
RQ
4.5
4
3.5
3
2.5
2
0.5
1
0.5
0
10
25
50
100
200
400
GM03816
OLIGO 62/77 (nM FINAL)

FIG. 20

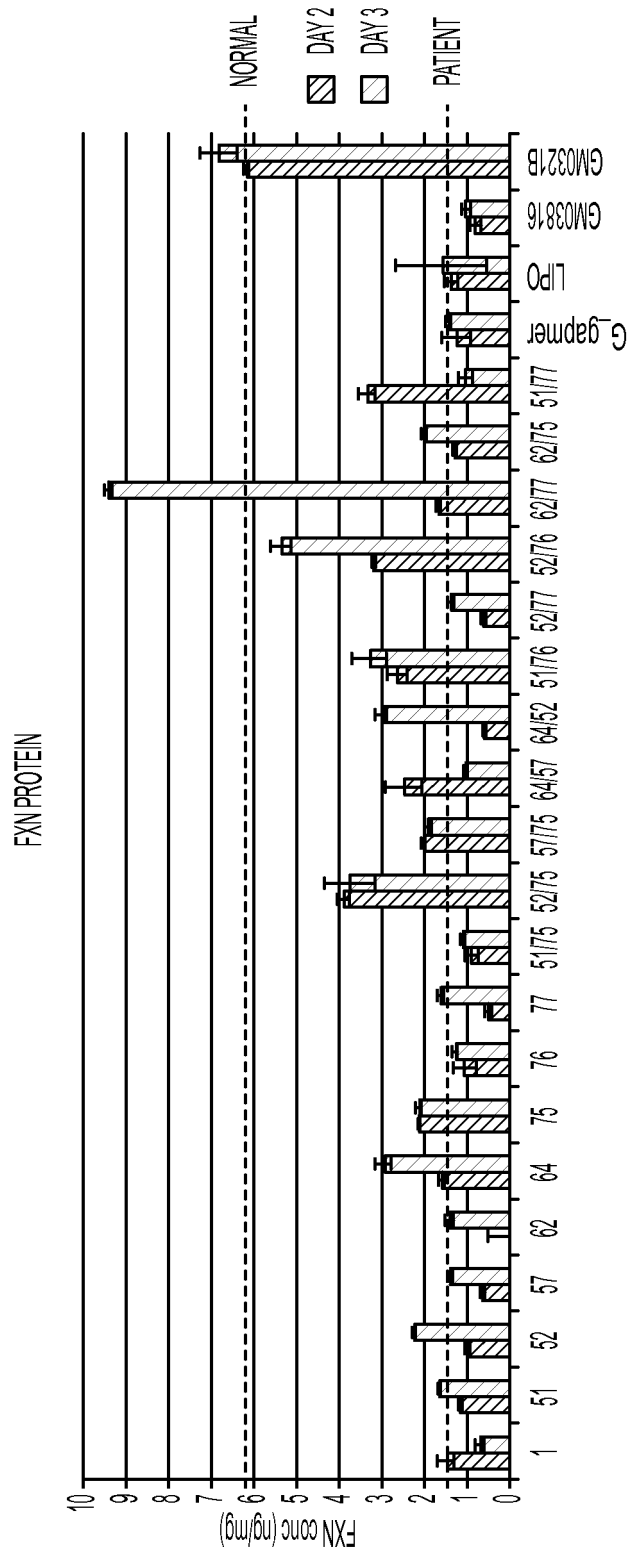

FXN PROTEIN
FXN conc (ng/mg)
NORMAL
DAY 2
DAY 3
PATIENT
GM03216B
GM03816
LIPO
G_gapmer
51/77
62/75
62/77
52/76
52/77
51/76
64/52
64/57
57/75
52/75
51/75
77
76
75
64
62
57
52
51
1

FIG. 21

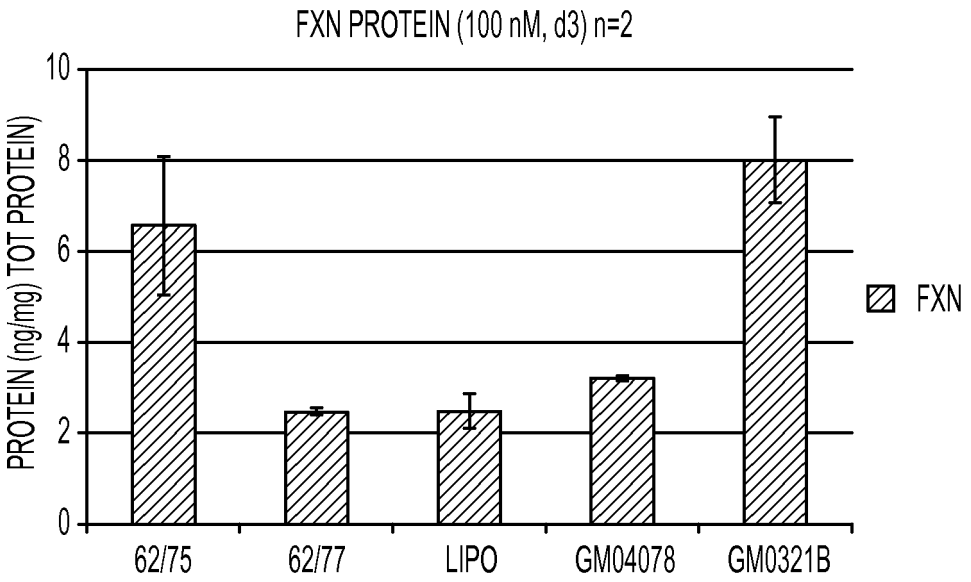

FXN PROTEIN (100 nM, d3) n=2
PROTEIN (ng/mg) TOT PROTEIN)
10
8
6
4
2
0
62/75
62/77
LIPO
GM04078
GM0321B
FXN

FIG. 22

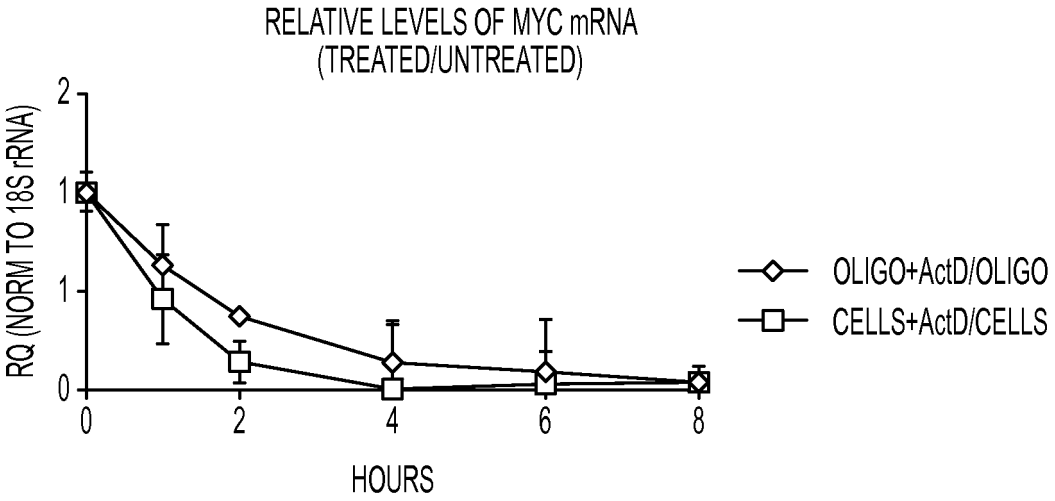


FIG. 23A

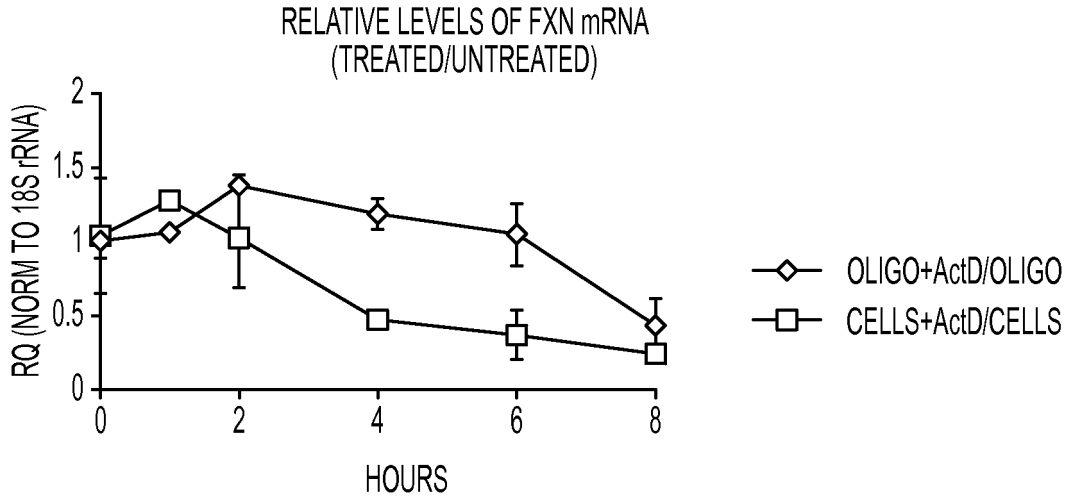


FIG. 23B

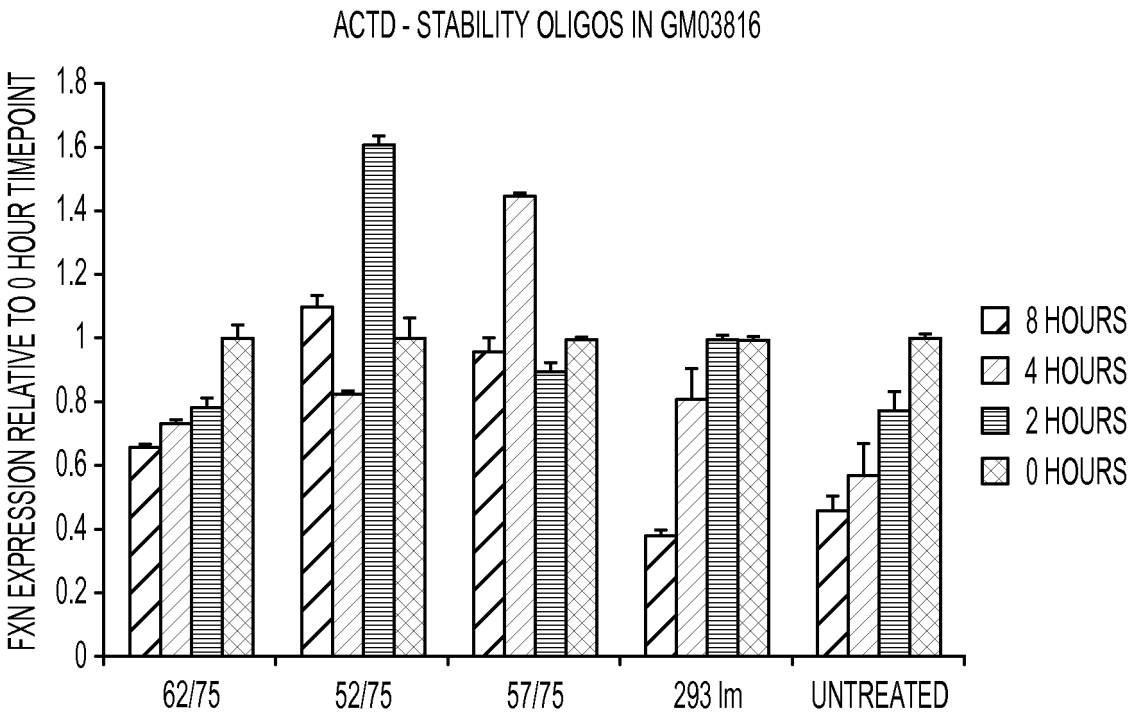

ACTD - STABILITY OLIGOS IN GM03816
FXN EXPRESSION RELATIVE TO 0 HOUR TIMEPOINT
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
62/75
52/75
57/75
293 lm
UNTREATED
8 HOURS
4 HOURS
2 HOURS
0 HOURS

FIG. 24

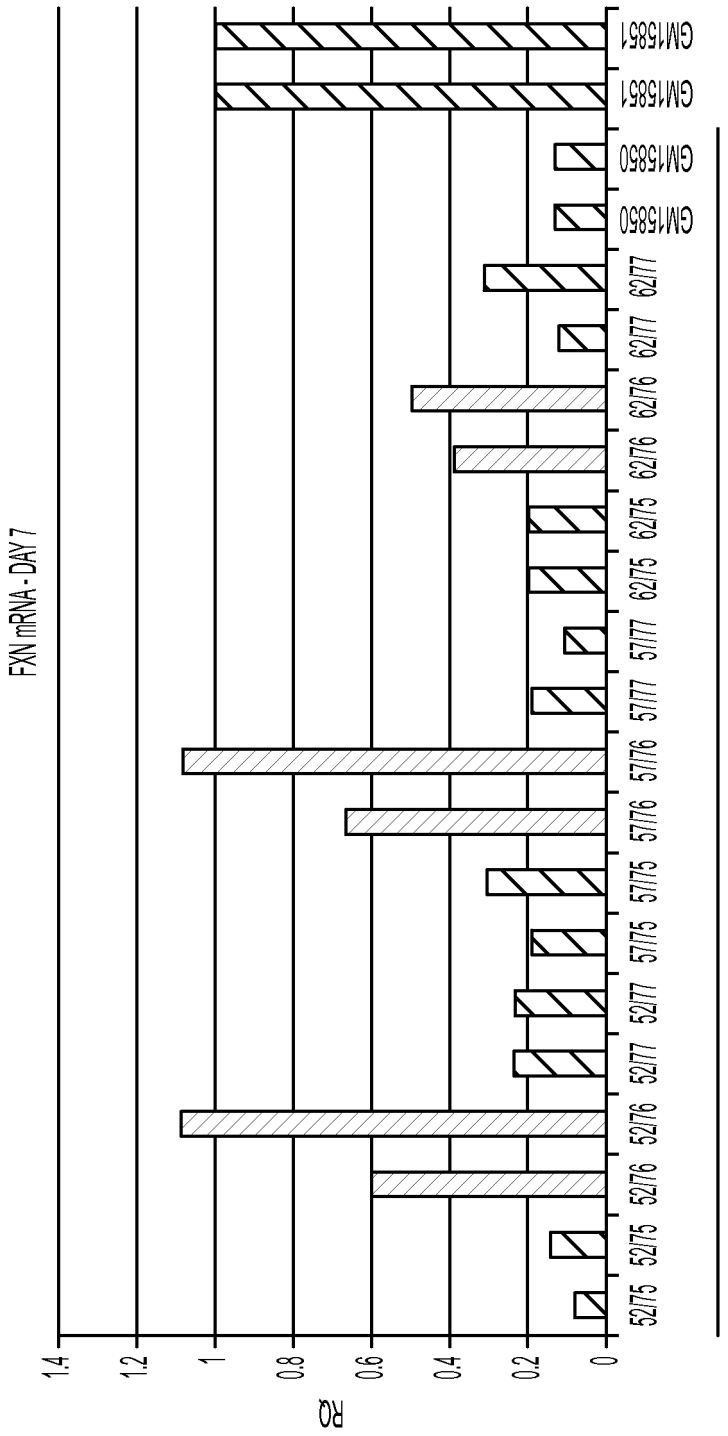

FXN mRNA - DAY 7
RQ
1.4
1.2
1
0.8
0.6
0.4
0.2
0
52/75
52/75
52/76
52/76
52/76
52/77
52/77
57/75
57/75
57/75
57/76
57/76
57/76
57/77
57/77
62/75
62/75
62/76
62/76
62/77
62/77
62/77
GM15850
GM15850
GM15851
GM15851
GM15850
FRDA

FIG. 25A

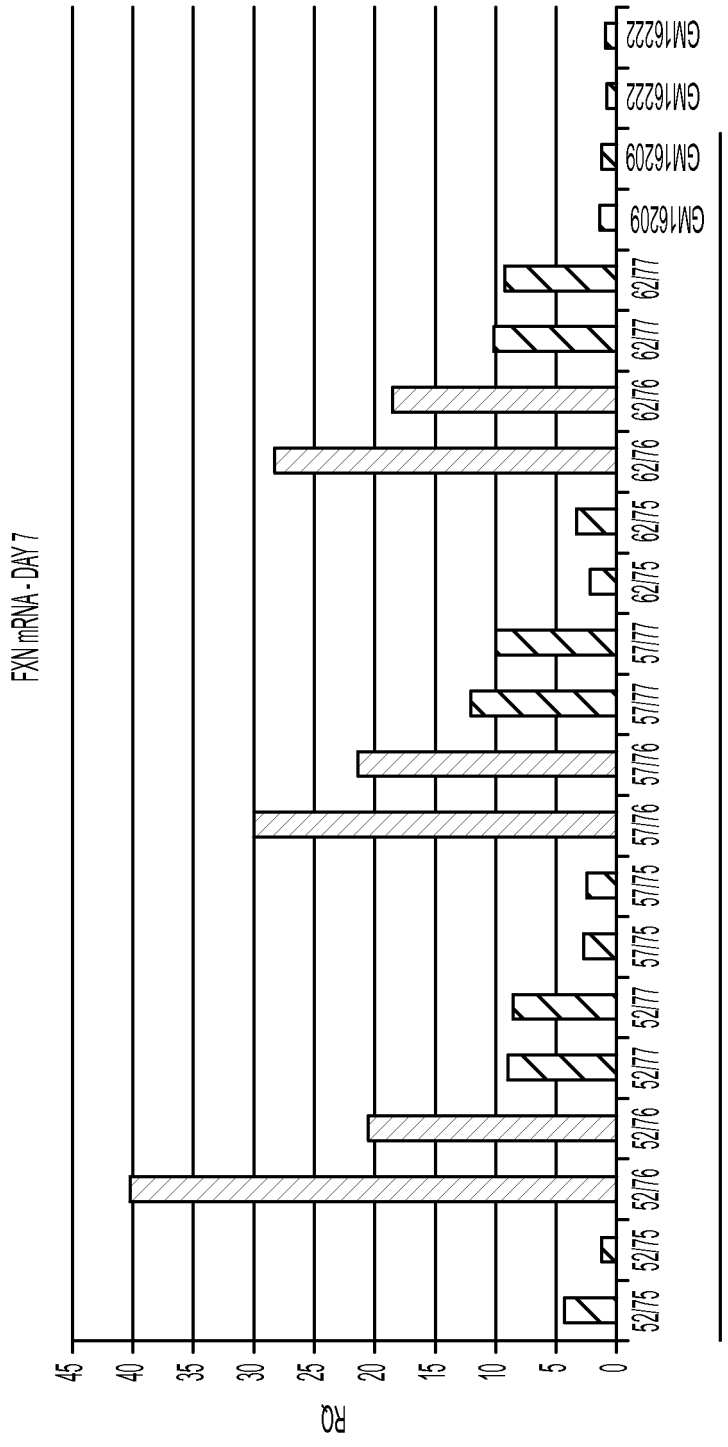

FXN mRNA - DAY 7
RQ
45
40
35
30
25
20
15
10
5
0
52/75
52/75
52/76
52/76
52/76
52/77
52/77
57/75
57/75
57/75
57/76
57/76
57/76
57/77
57/77
62/75
62/75
62/76
62/76
62/77
62/77
62/77
GM16209
GM16209
GM16222
GM16222
GM16209
FRDA

FIG. 25B

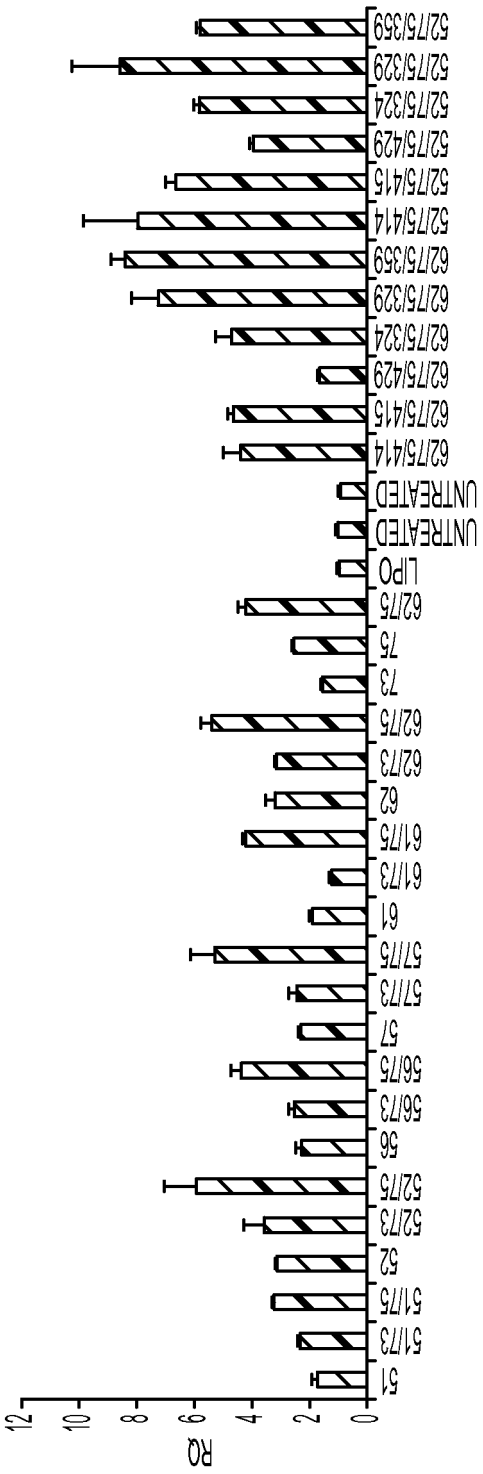

RQ
0
2
4
6
8
10
12
51
5173
5175
52
5273
5275
56
5673
5675
57
5773
5775
61
6173
6175
62
6273
6275
73
75
6275
LIPO
UNTREATED
UNTREATED
6275414
6275415
6275429
6275324
6275329
6275359
6275414
6275415
6275429
6275324
6275329
6275359

FIG. 26

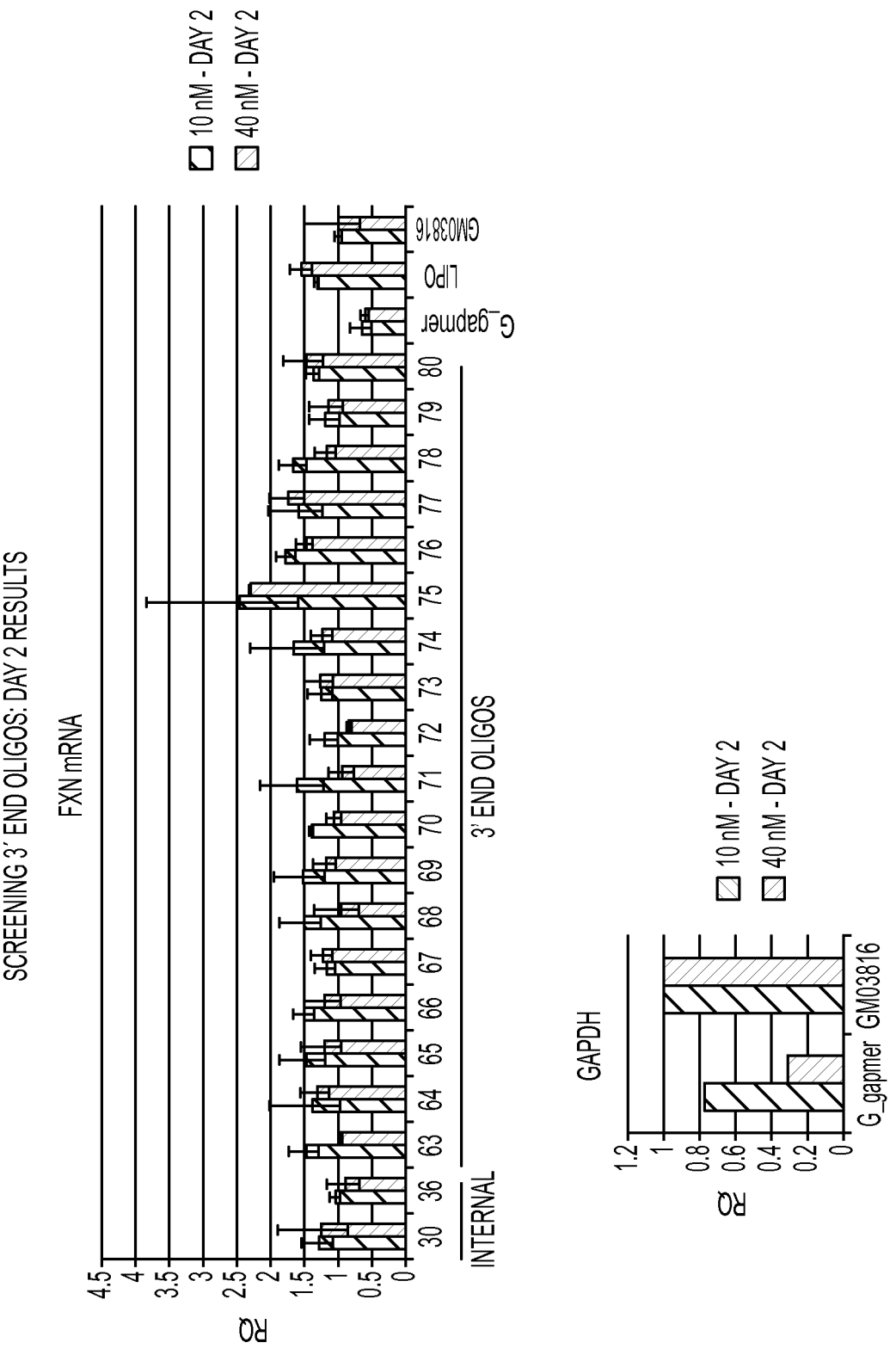

SCREENING 3' END OLIGOS: DAY 2 RESULTS
FXN mRNA
10 nM - DAY 2
40 nM - DAY 2
RQ
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
30 36 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
INTERNAL
3' END OLIGOS
G_gapmer
LIPO
GM03816
GAPDH
10 nM - DAY 2
40 nM - DAY 2
RQ
1.2
1
0.8
0.6
0.4
0.2
0
G_gapmer GM03816

FIG. 27

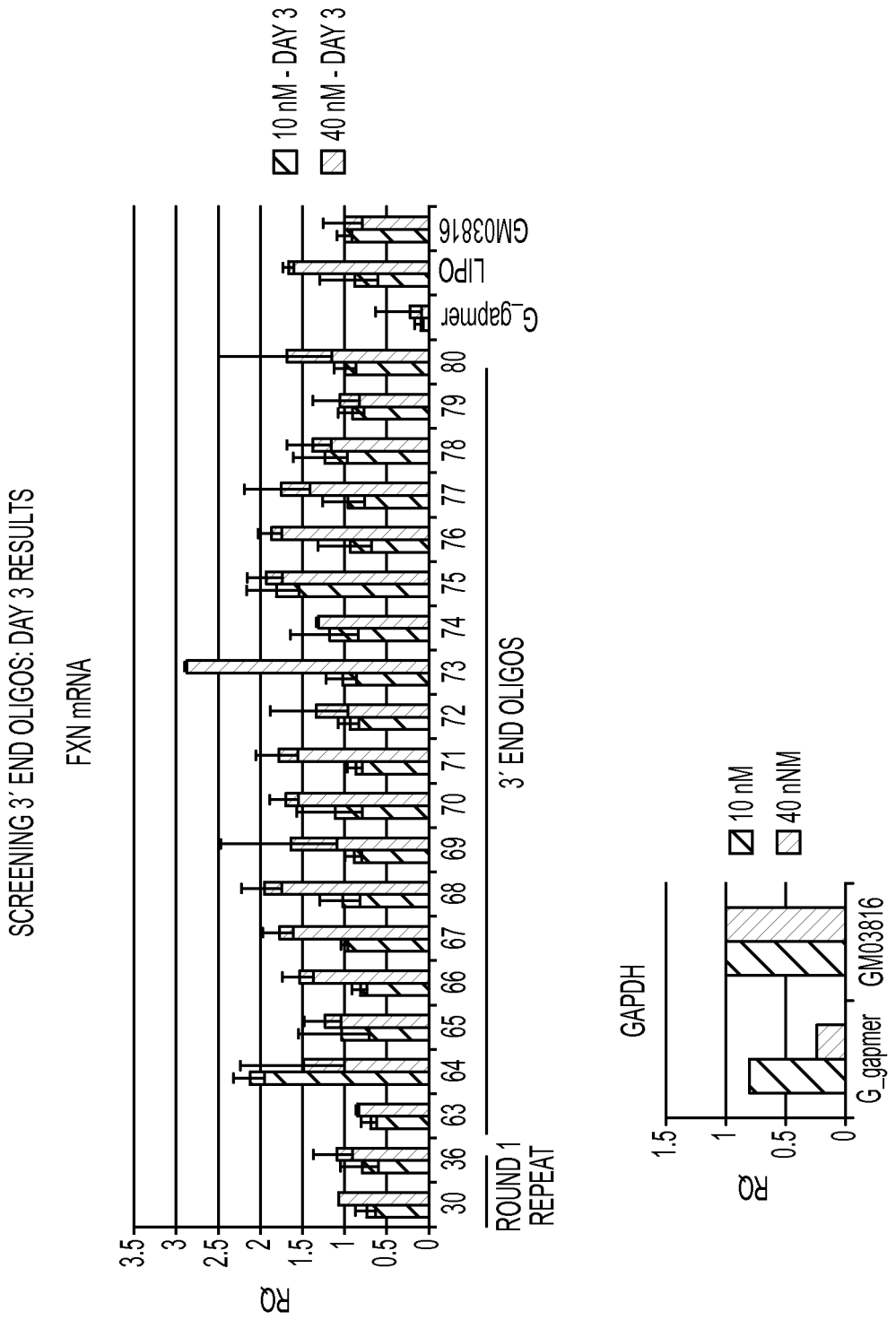
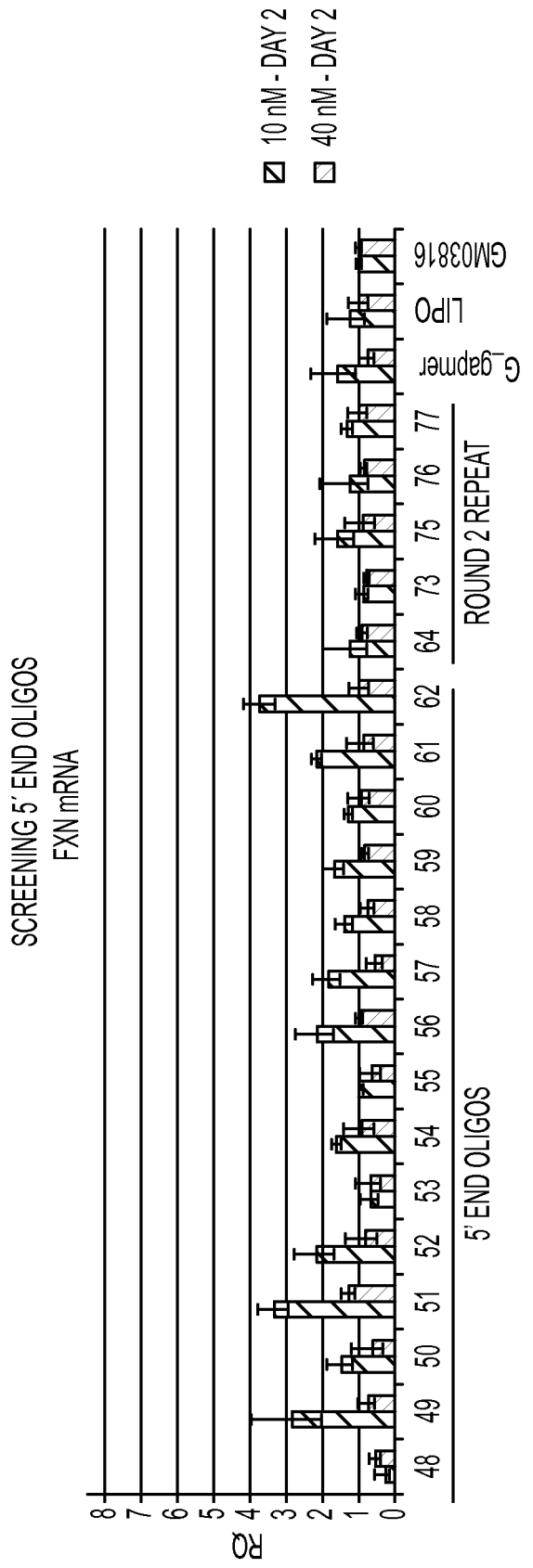
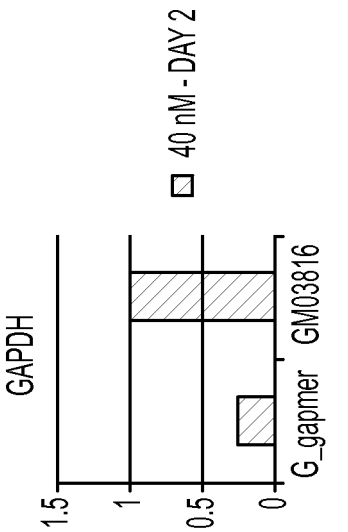

SCREENING 3′ END OLIGOS: DAY 3 RESULTS
FXN mRNA
10 nM - DAY 3
40 nM - DAY 3
RQ
3.5
3
2.5
2
1.5
1
0.5
0
30 36 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
ROUND 1
REPEAT
3′ END OLIGOS
G_gapmer
LIPO
GM03816
GAPDH
10 nM
40 nNM
RQ
1.5
1
0.5
0
G_gapmer GM03816

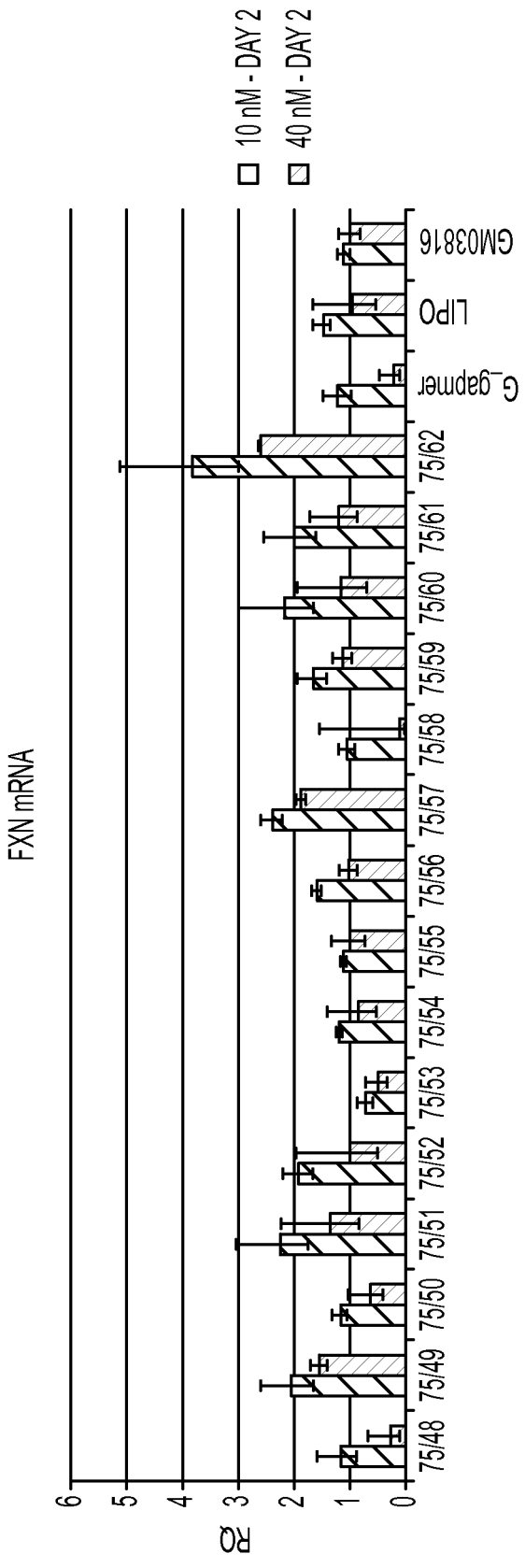
FIG. 28





OLIGO	10 nM (r2)	40 nM (r2)	10 nM (r3)	40 nM (r3)
64	1.4	1.3	1.25	0.9
73	1.25	1.3	0.9	0.8
75	2.5	2.3	1.6	0.9
76	1.8	1.5	0.9	0.9
77	1.6	1.7	1.3	1.0

FIG. 29


FXN mRNA
RQ
0
1
2
3
4
5
6
10 nM - DAY 2
40 nM - DAY 2
75/48
75/49
75/50
75/51
75/52
75/53
75/54
75/55
75/56
75/57
75/58
75/59
75/60
75/61
75/62
G_gapmer
LIPO
GM03816

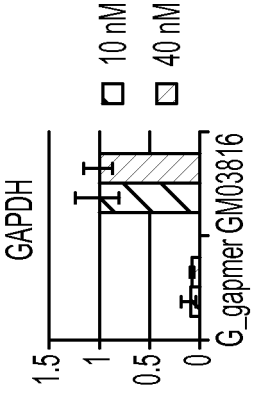

GAPDH
1.5
1
0.5
0
10 nM
40 nM
G_gapmer GM03816

FIG. 30

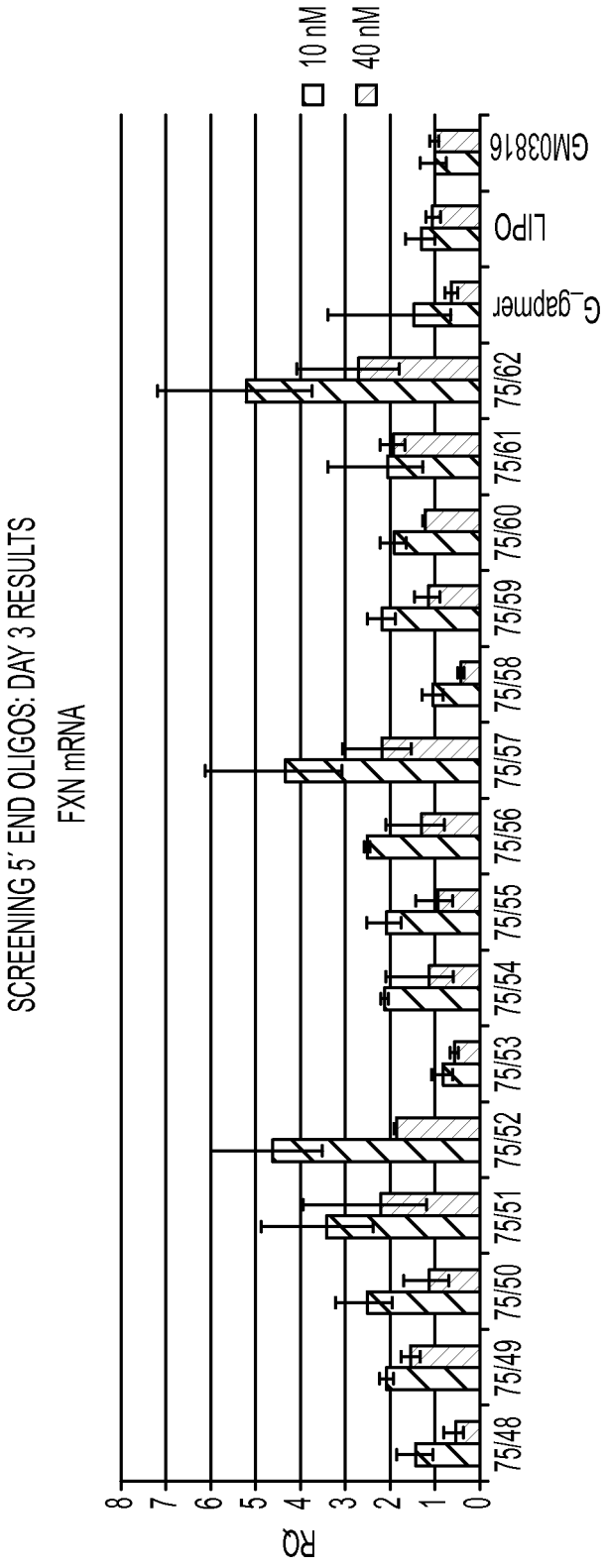

SCREENING 5' END OLIGOS: DAY 3 RESULTS
FXN mRNA
RQ
0
1
2
3
4
5
6
7
8
10 nM
40 nM
GM03816
LIPO
G_gapmer
75/48
75/49
75/50
75/51
75/52
75/53
75/54
75/55
75/56
75/57
75/58
75/59
75/60
75/61
75/62

FIG. 31

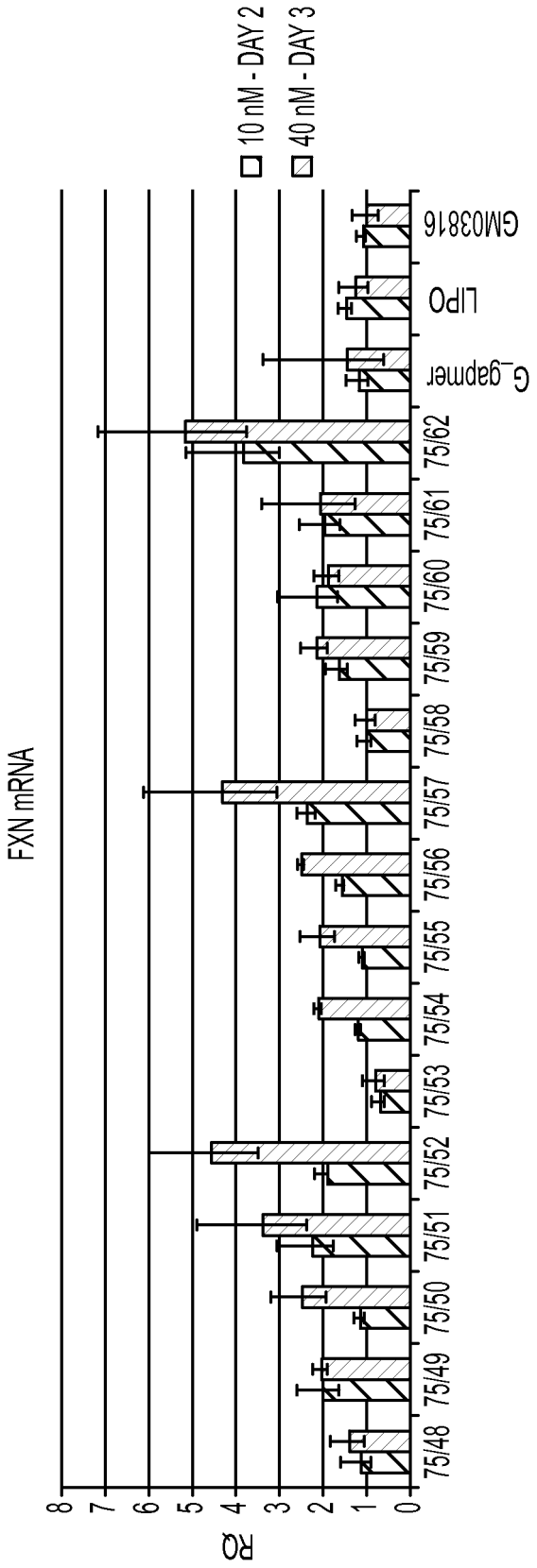

10 nM - DAY 2
40 nM - DAY 3
FXN mRNA
RQ
0
1
2
3
4
5
6
7
8
75/48
75/49
75/50
75/51
75/52
75/53
75/54
75/55
75/56
75/57
75/58
75/59
75/60
75/61
75/62
G_gapmer
LIPO
GM03816

FIG. 32

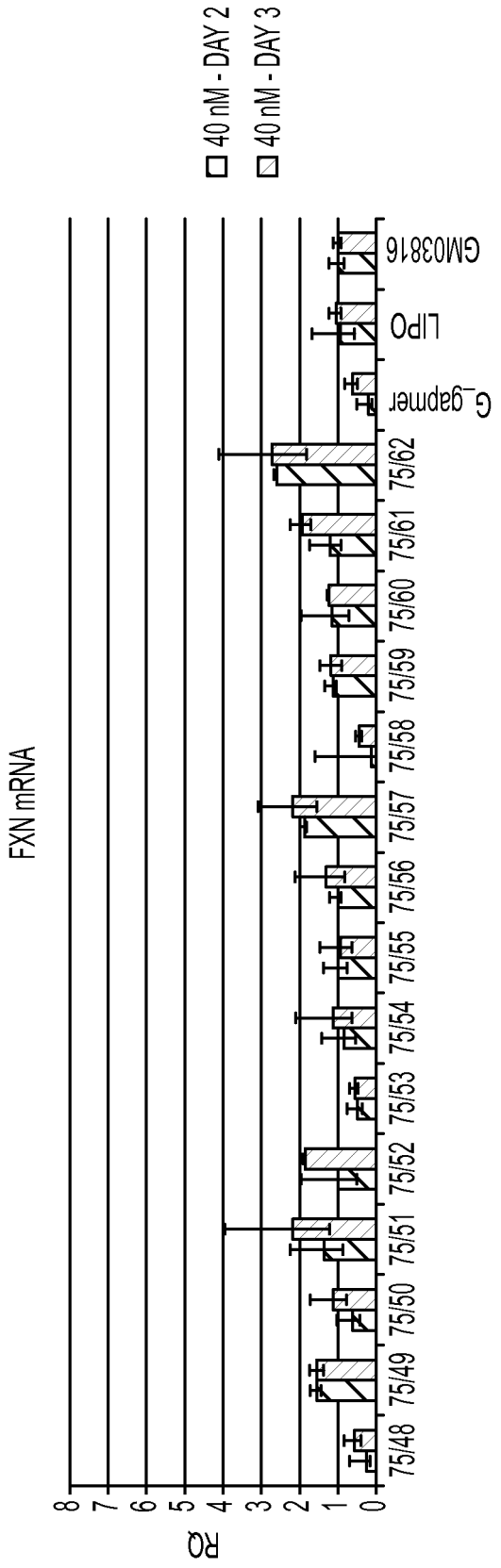

40 nM - DAY 2
40 nM - DAY 3
FXN mRNA
RQ
0
1
2
3
4
5
6
7
8
75/48
75/49
75/50
75/51
75/52
75/53
75/54
75/55
75/56
75/57
75/58
75/59
75/60
75/61
75/62
G_gapmer
LIPO
GM03816

FIG. 33

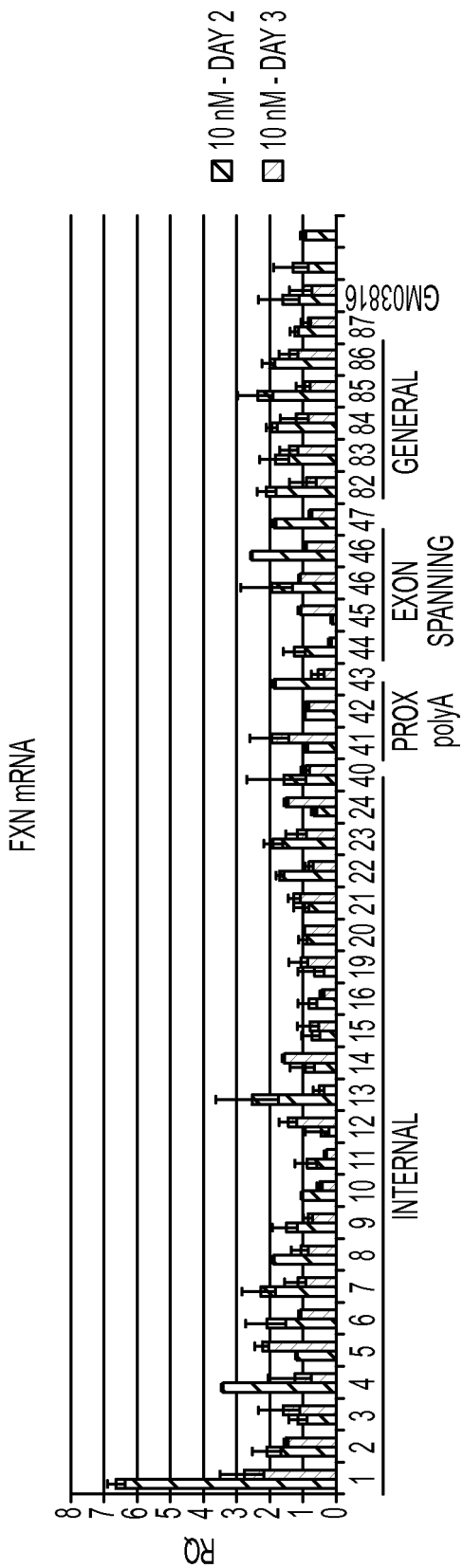

10 nM - DAY 2
10 nM - DAY 3
GM03816
FXN mRNA
RQ
0
1
2
3
4
5
6
7
8
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 19 20 21 22 23 24 40 41 42 43 44 45 46 46 47 82 83 84 85 86 87
INTERNAL
PROX
polyA
EXON
SPANNING
GENERAL

FIG. 34

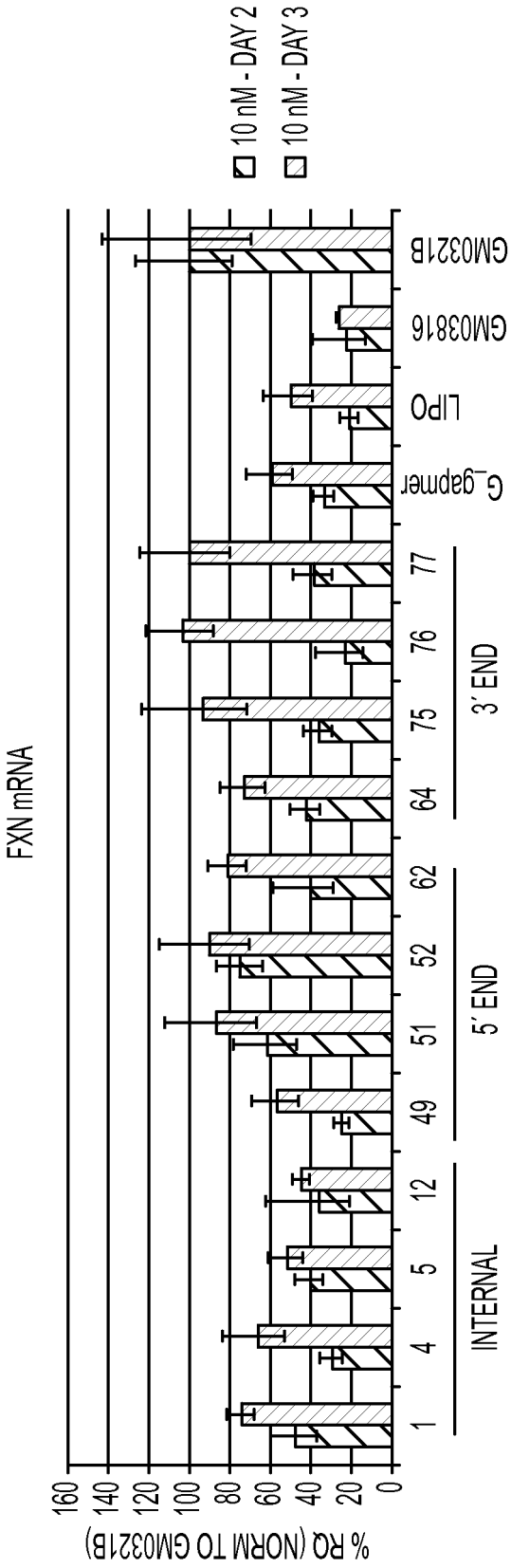

10 nM - DAY 2
10 nM - DAY 3
FXN mRNA
% RQ (NORM TO GM0321B)
0
20
40
60
80
100
120
140
160
GM0321B
GM03816
LIPO
G_gapmer
1
4
5
12
49
51
52
62
64
75
76
77
INTERNAL
5' END
3' END

FIG. 35

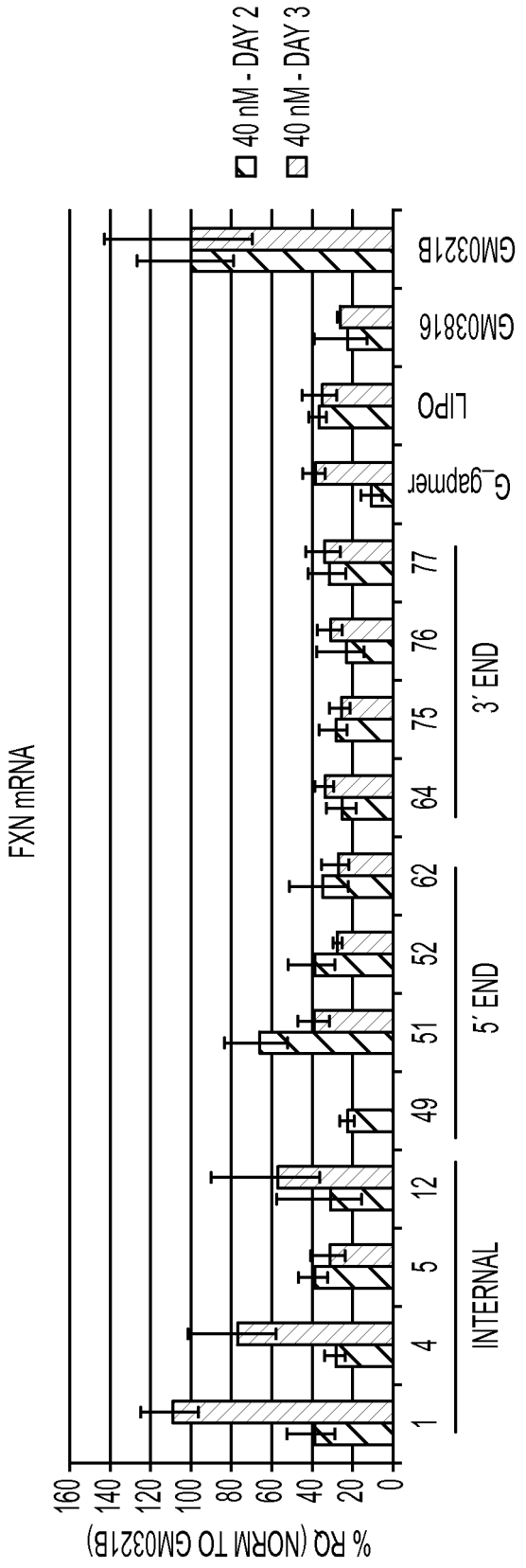

40 nM - DAY 2
40 nM - DAY 3
FXN mRNA
% RQ (NORM TO GM0321B)
0
20
40
60
80
100
120
140
160
1
4
5
12
49
51
52
62
64
75
76
77
INTERNAL
5' END
3' END
G_gapmer
LIPO
GM03816
GM0321B

FIG. 36

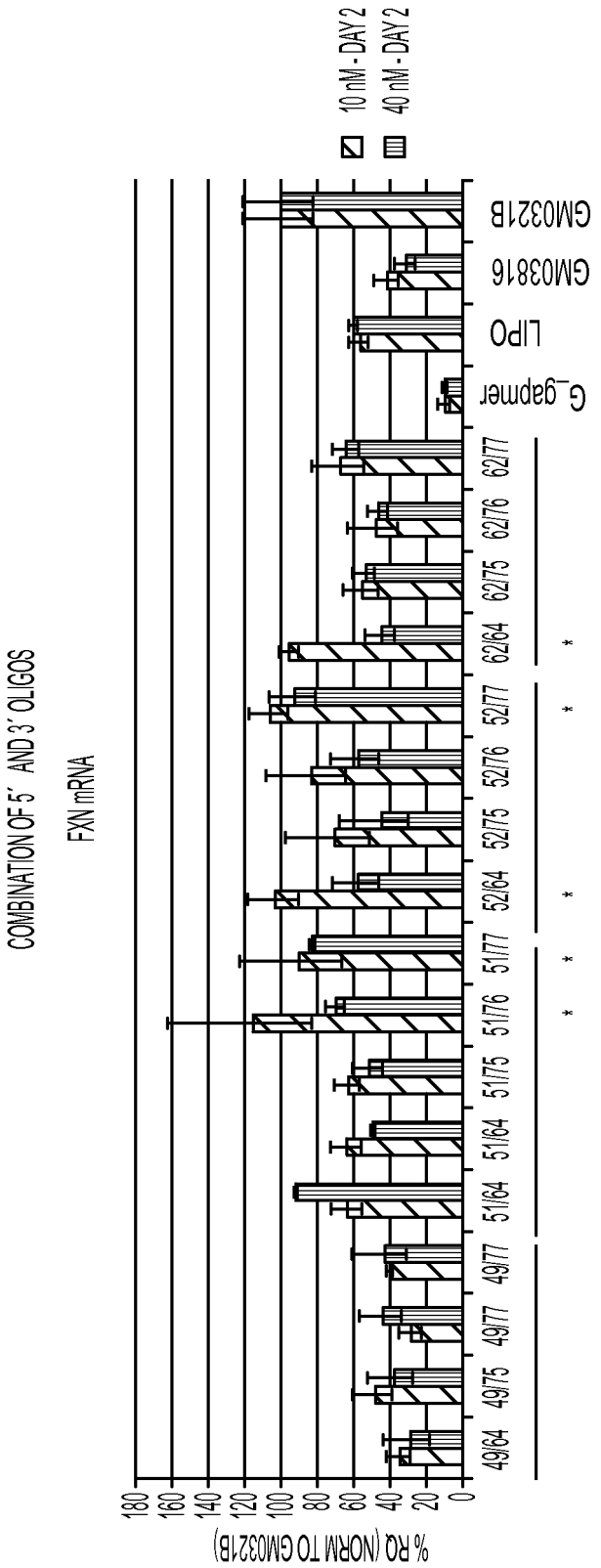

10 nM - DAY 2
40 nM - DAY 2
% RQ (NORM TO GM03218)
0
20
40
60
80
100
120
140
160
180
49/64
49/75
49/77
49/77
51/64
51/64
51/64
51/75
51/76
51/77
52/64
52/75
52/76
52/77
62/64
62/75
62/76
62/77
G_gapmer
LIPO
GM03816
GM03218
FXN mRNA
COMBINATION OF 5' AND 3' OLIGOS

FIG. 37

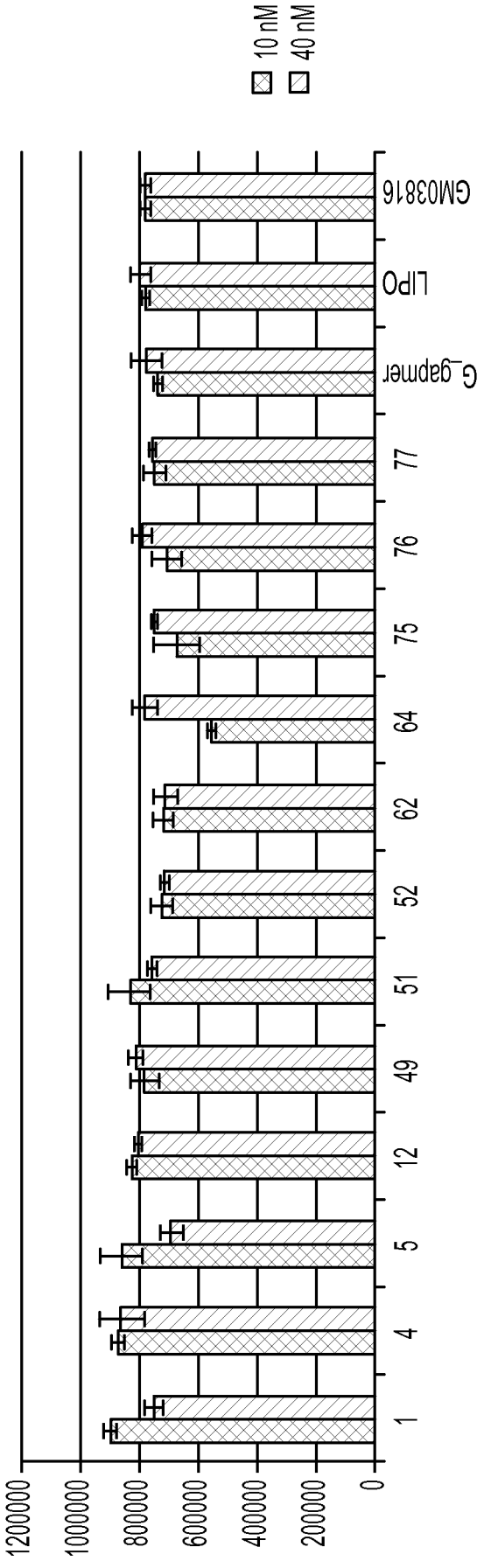

10 nM
40 nM
CYTOTOXICITY (CTG) - DAY 2
1200000
1000000
800000
600000
400000
200000
0
1
4
5
12
49
51
52
62
64
75
76
77
G_gapmer
LIPO
GM03816

FIG. 38A

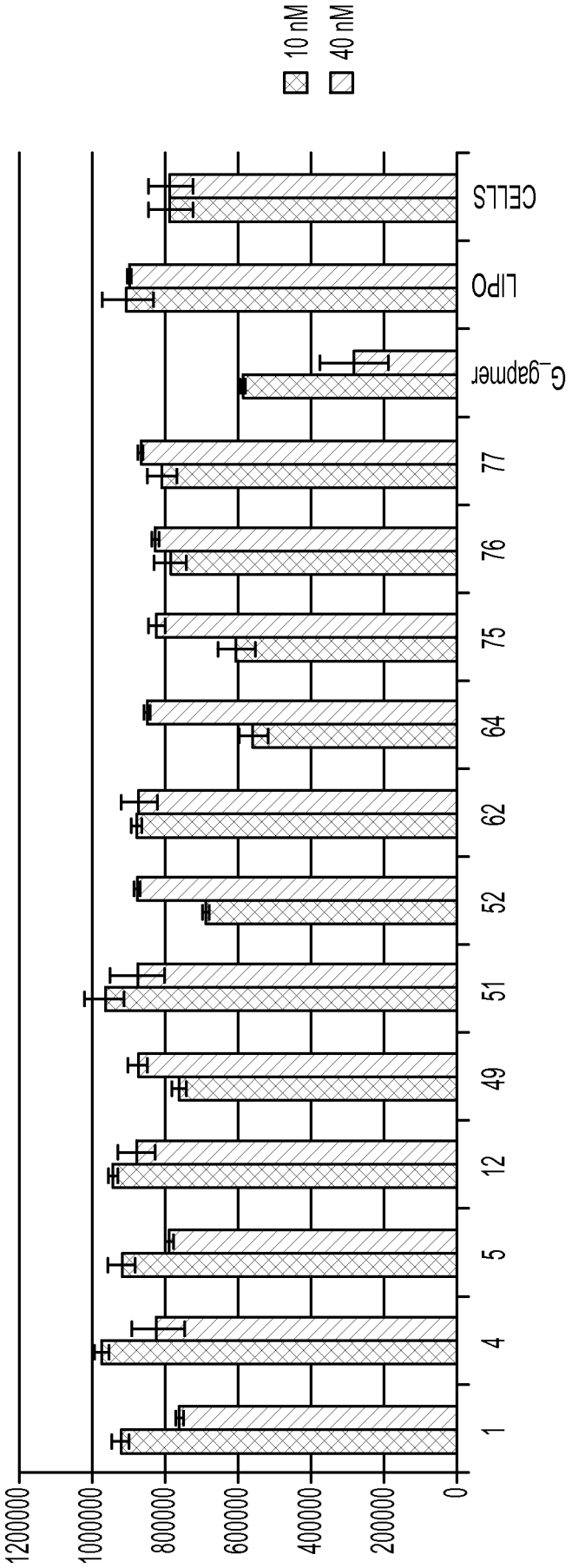

10 nM
40 nM
CYTOTOXICITY (CTG) - DAY 3
1200000
1000000
800000
600000
400000
200000
0
1
4
5
12
49
51
52
62
64
75
76
77
G_gapmer
LIPO
CELLS

FIG. 38B

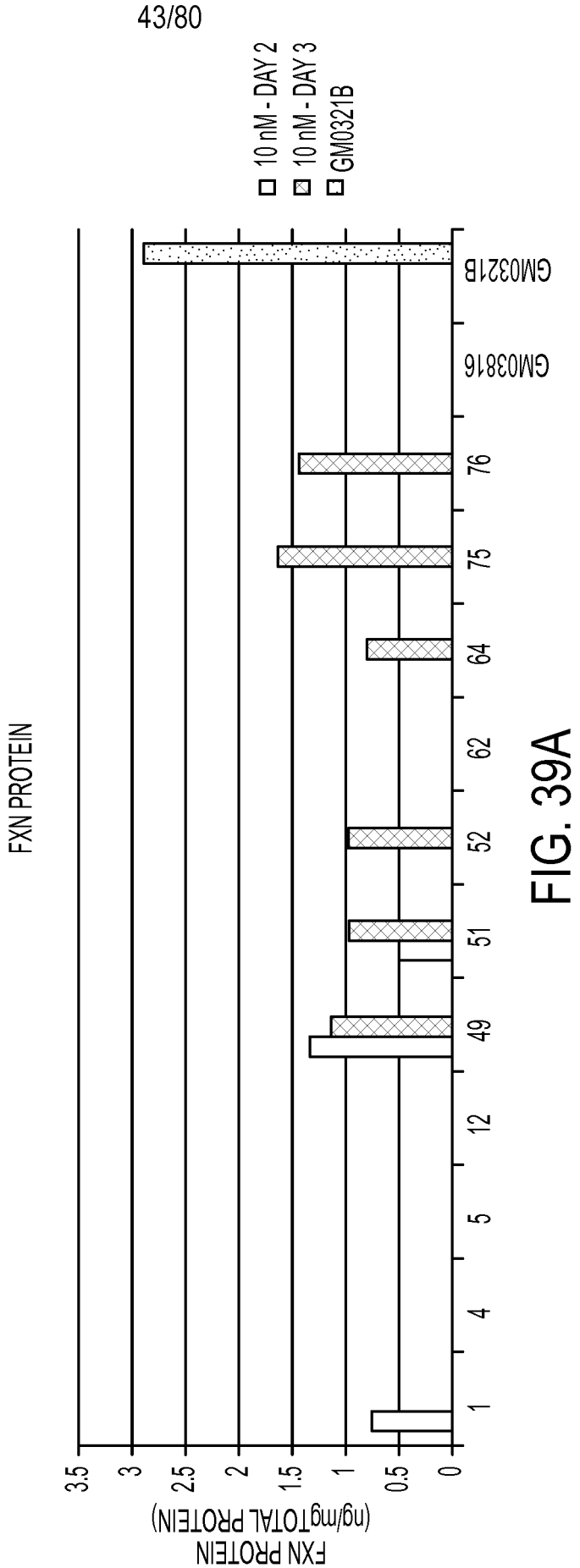

FXN PROTEIN
10 nM - DAY 2
10 nM - DAY 3
GM03321B
FXN PROTEIN
(ng/mg TOTAL PROTEIN)
3.5
3
2.5
2
1.5
1
0.5
0
GM03321B
GM03816
76
75
64
62
52
51
49
12
5
4
1

FIG. 39A

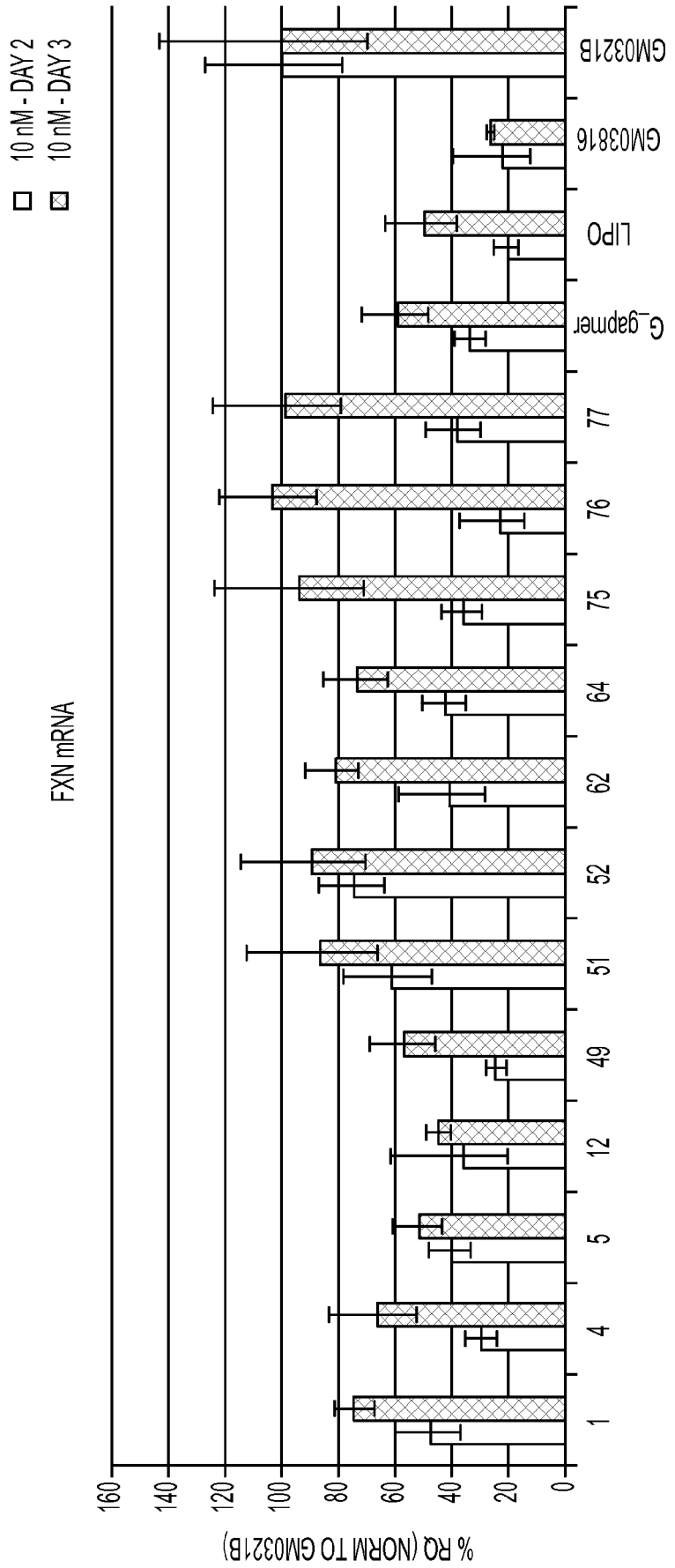

10 nM - DAY 2
10 nM - DAY 3
FXN mRNA
% RQ (NORM TO GM0321B)
0
20
40
60
80
100
120
140
160
1
4
5
12
49
51
52
62
64
75
76
77
G_gapmer
LIPO
GM03816
GM0321B

FIG. 39B

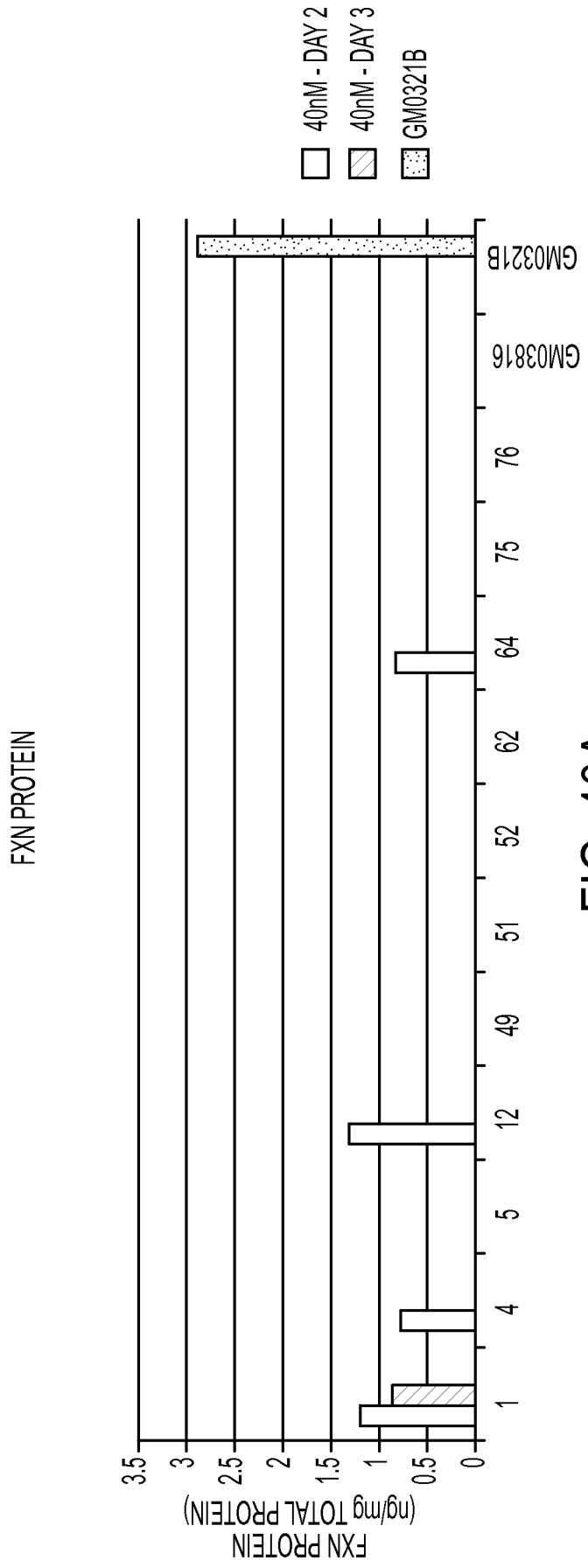

40nM - DAY 2
40nM - DAY 3
GM0321B
FXN PROTEIN
FXN PROTEIN
(ng/mg TOTAL PROTEIN)
3.5
3
2.5
2
1.5
1
0.5
0
1
4
5
12
49
51
52
62
64
75
76
GM03816
GM0321B

FIG. 40A

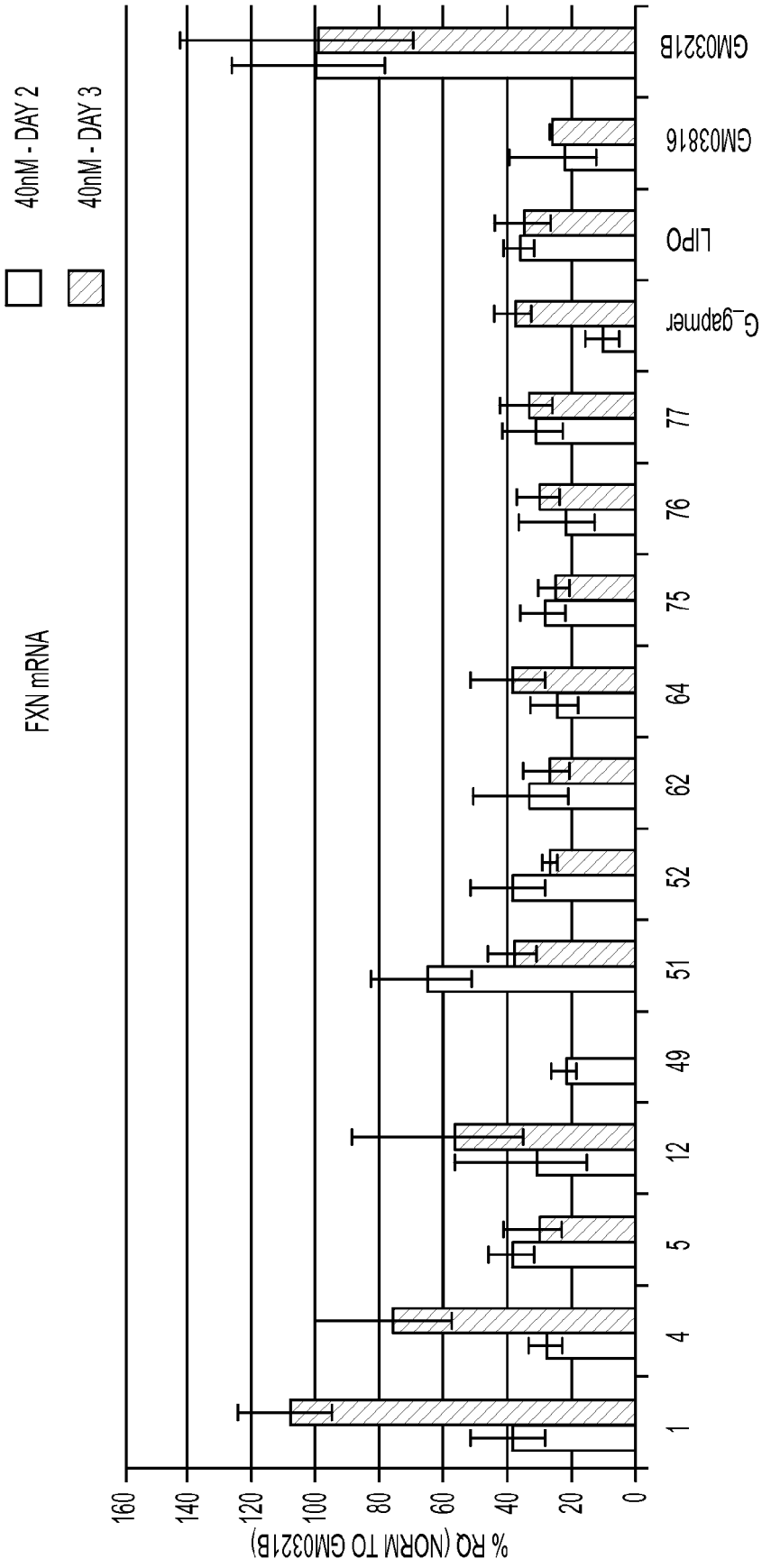

FXN mRNA
40nM - DAY 2
40nM - DAY 3
% RQ (NORM TO GM03218)
0
20
40
60
80
100
120
140
160
1
4
5
12
49
51
52
62
64
75
76
77
G_gapmer
LIPO
GM03816
GM03218

FIG. 40B

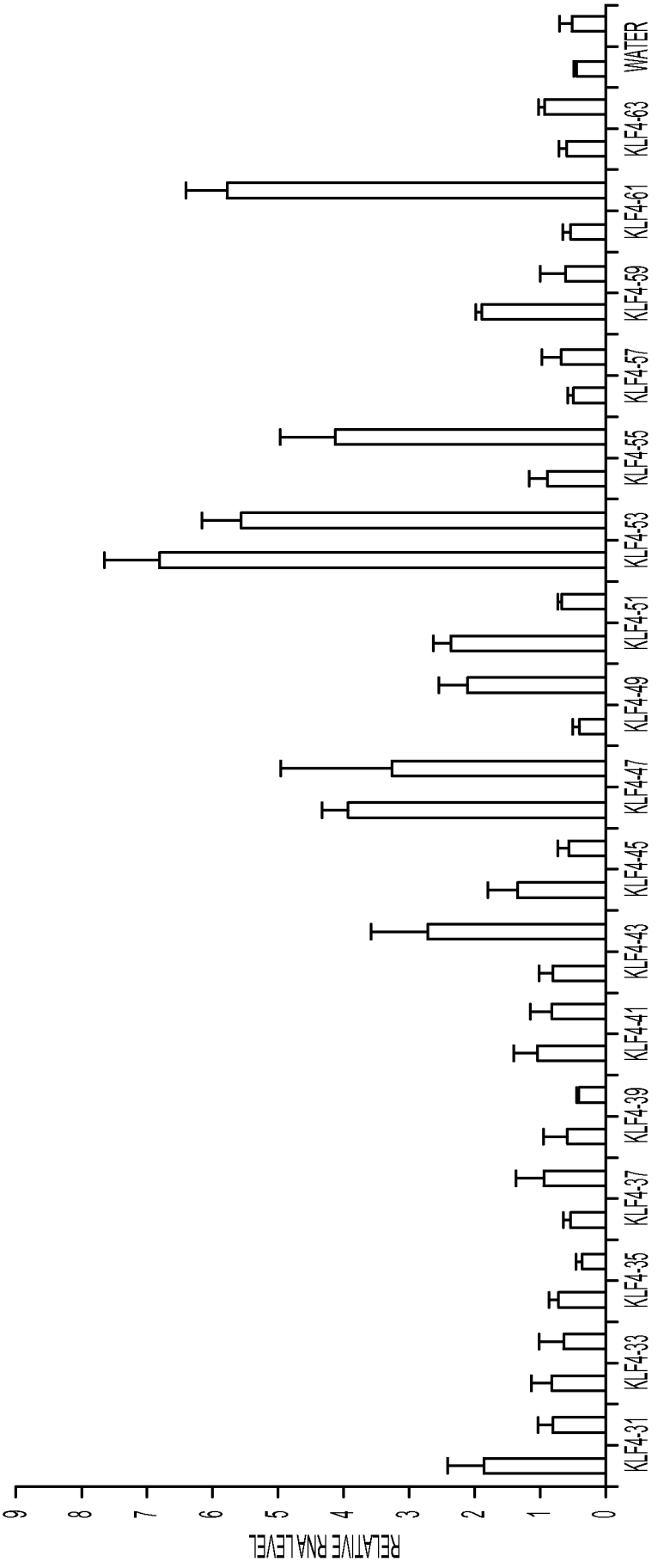

RELATIVE RNA LEVEL
0
1
2
3
4
5
6
7
8
9
KLF4-31
KLF4-33
KLF4-35
KLF4-37
KLF4-39
KLF4-41
KLF4-43
KLF4-45
KLF4-47
KLF4-49
KLF4-51
KLF4-53
KLF4-55
KLF4-57
KLF4-59
KLF4-61
KLF4-63
WATER

FIG. 41

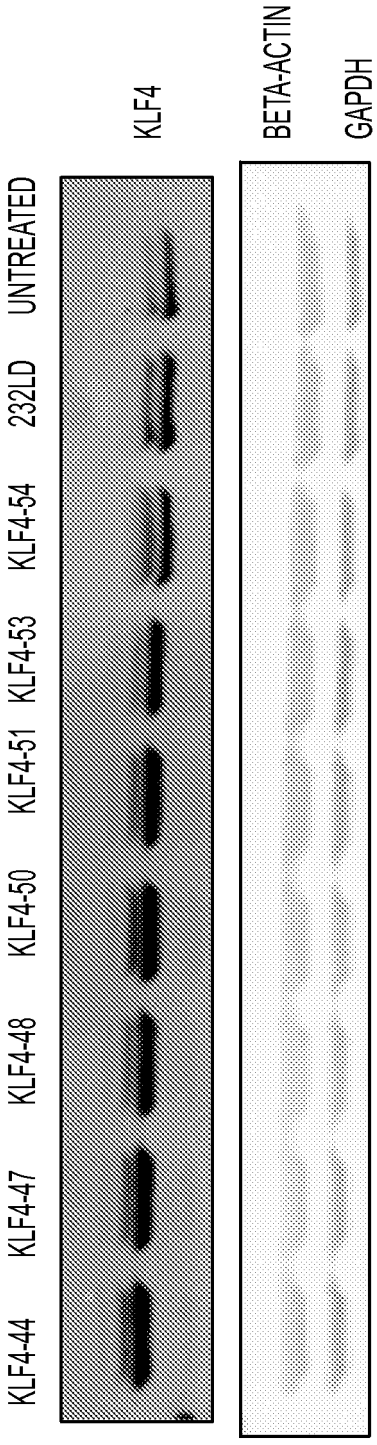

KLF4
BETA-ACTIN
GAPDH
UNTREATED
232LD
KLF4-54
KLF4-53
KLF4-51
KLF4-50
KLF4-48
KLF4-47
KLF4-44

FIG. 42

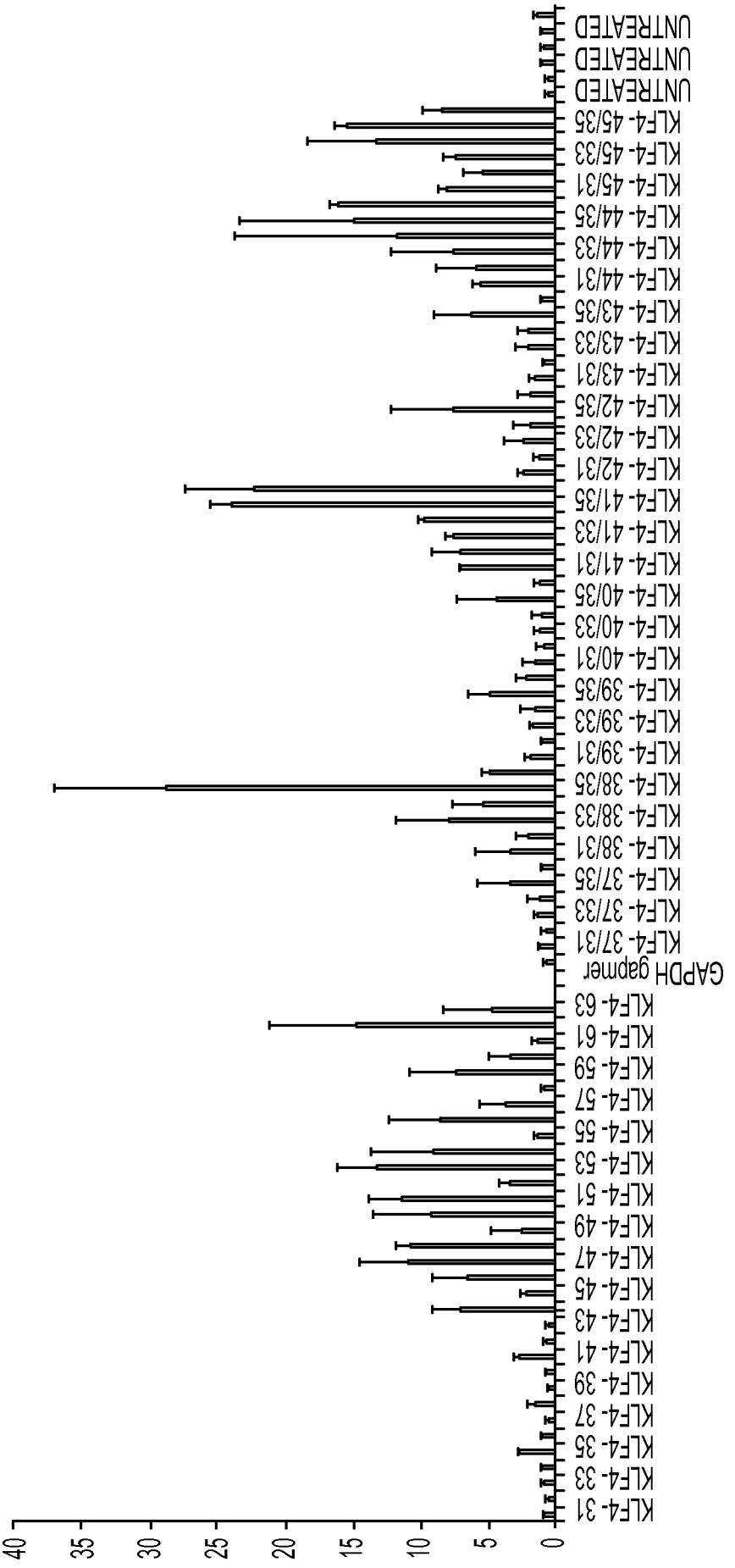

40
35
30
25
20
15
10
5
0
KLF4- 31
KLF4- 33
KLF4- 35
KLF4- 37
KLF4- 39
KLF4- 41
KLF4- 43
KLF4- 45
KLF4- 47
KLF4- 49
KLF4- 51
KLF4- 53
KLF4- 55
KLF4- 57
KLF4- 59
KLF4- 61
KLF4- 63
GAPDH gapmer
KLF4- 37/31
KLF4- 37/33
KLF4- 37/35
KLF4- 38/31
KLF4- 38/33
KLF4- 38/35
KLF4- 39/31
KLF4- 39/33
KLF4- 39/35
KLF4- 40/31
KLF4- 40/33
KLF4- 40/35
KLF4- 41/31
KLF4- 41/33
KLF4- 41/35
KLF4- 42/31
KLF4- 42/33
KLF4- 42/35
KLF4- 43/31
KLF4- 43/33
KLF4- 43/35
KLF4- 44/31
KLF4- 44/33
KLF4- 44/35
KLF4- 45/31
KLF4- 45/33
KLF4- 45/35
UNTREATED
UNTREATED
UNTREATED

FIG. 43

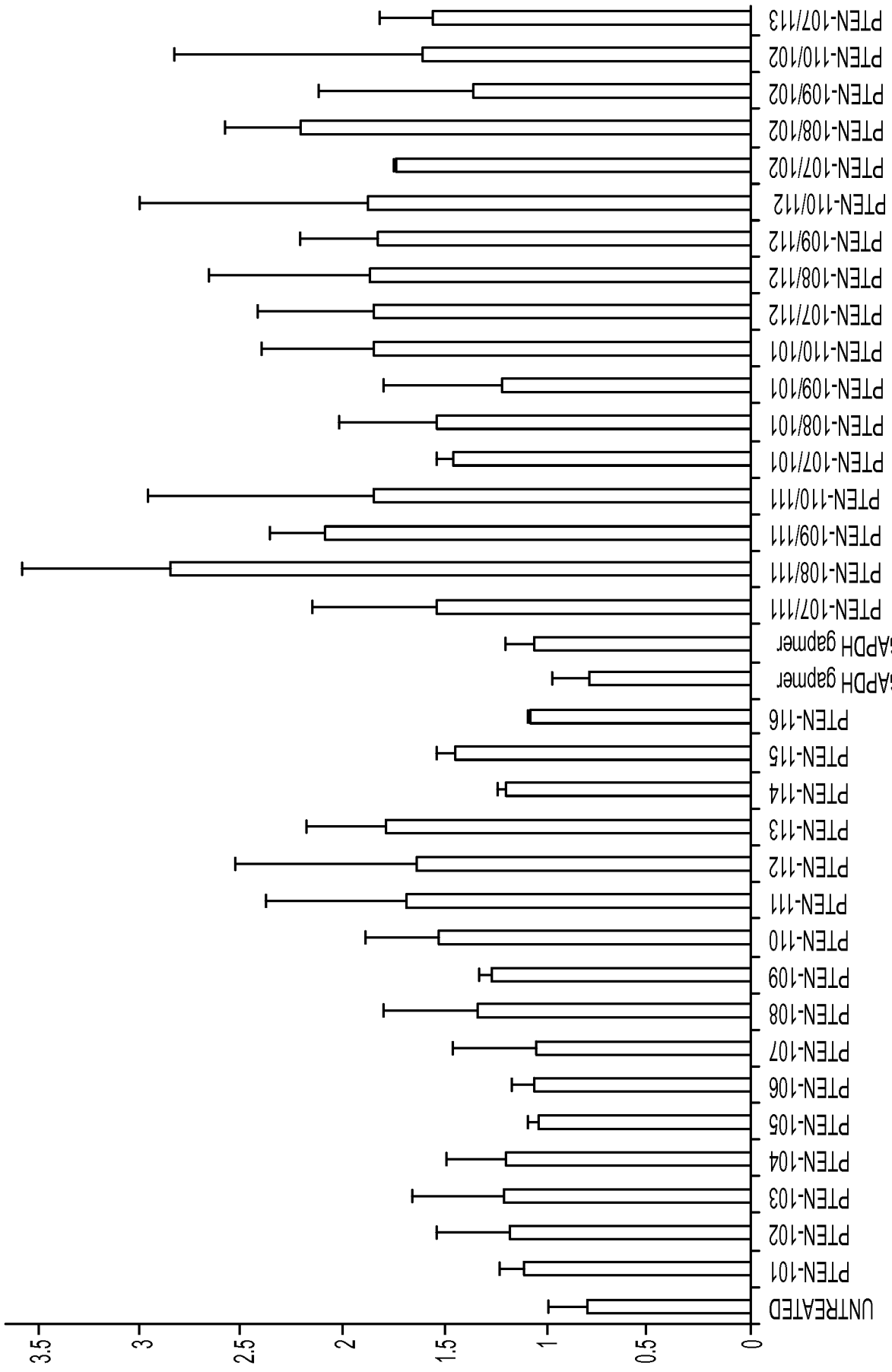

UNTREATED
PTEN-101
PTEN-102
PTEN-103
PTEN-104
PTEN-105
PTEN-106
PTEN-107
PTEN-108
PTEN-109
PTEN-110
PTEN-111
PTEN-112
PTEN-113
PTEN-114
PTEN-115
PTEN-116
GAPDH gapmer
GAPDH gapmer
PTEN-107/111
PTEN-108/111
PTEN-109/111
PTEN-110/111
PTEN-107/101
PTEN-108/101
PTEN-109/101
PTEN-110/101
PTEN-107/112
PTEN-108/112
PTEN-109/112
PTEN-110/112
PTEN-107/102
PTEN-108/102
PTEN-109/102
PTEN-110/102
PTEN-107/113
0
0.5
1
1.5
2
2.5
3
3.5

FIG. 44A

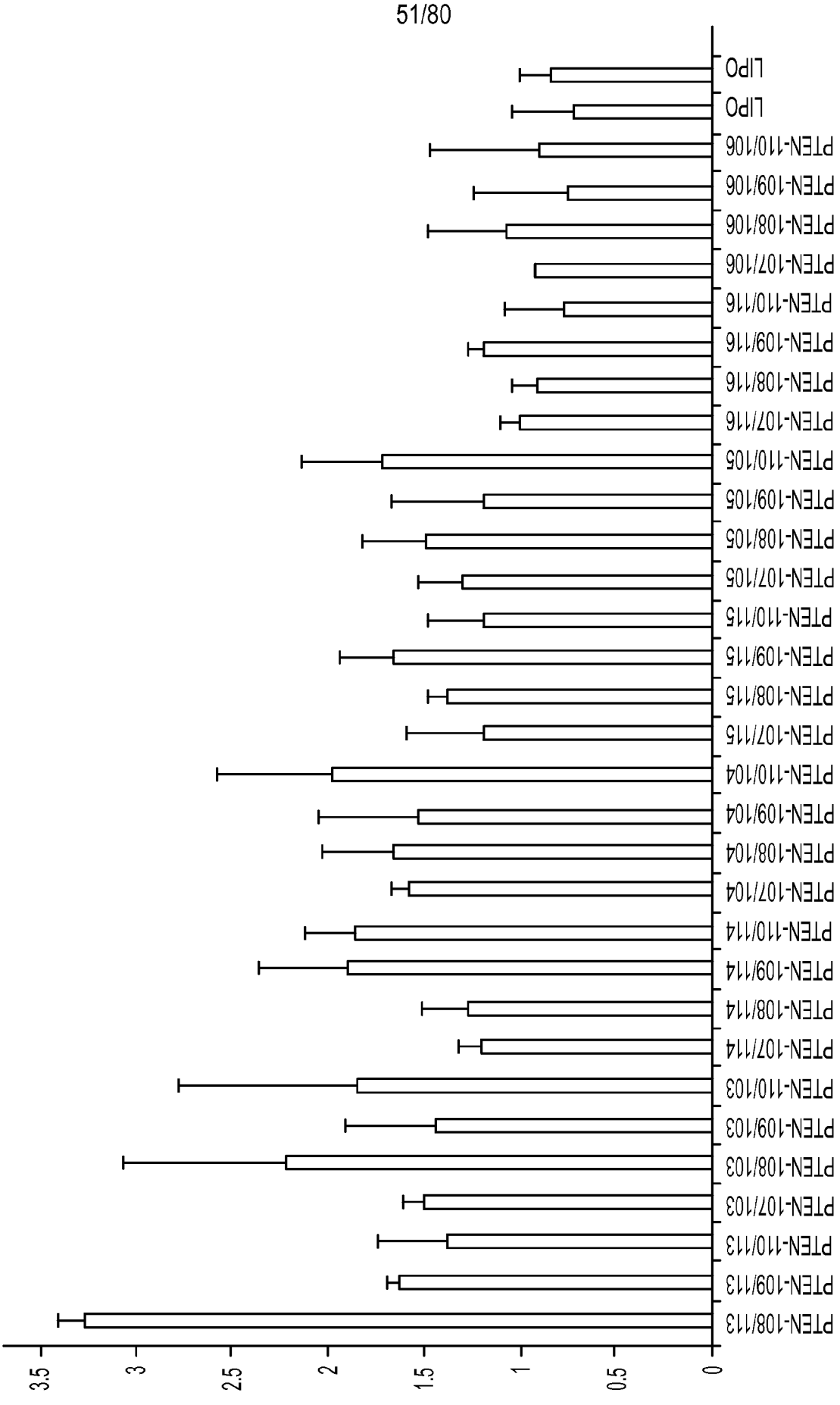
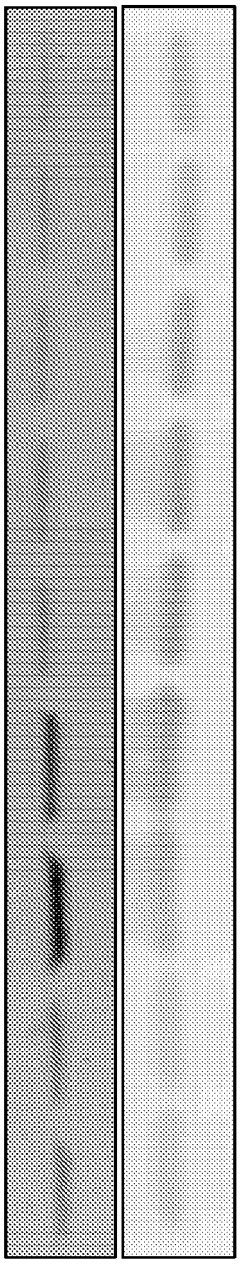
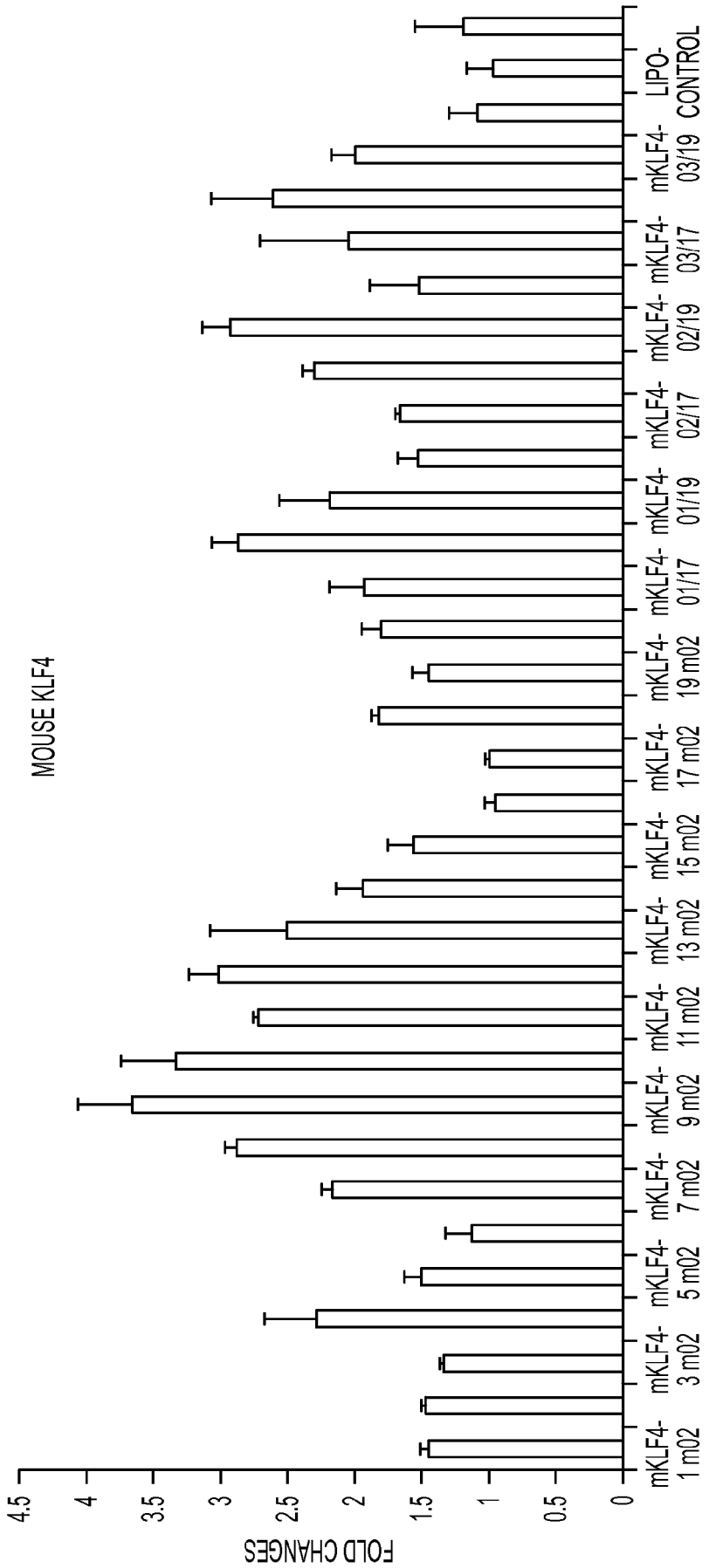

LIPO
LIPO
PTEN-110/106
PTEN-109/106
PTEN-108/106
PTEN-107/106
PTEN-110/116
PTEN-109/116
PTEN-108/116
PTEN-107/116
PTEN-110/105
PTEN-109/105
PTEN-108/105
PTEN-107/105
PTEN-110/115
PTEN-109/115
PTEN-108/115
PTEN-107/115
PTEN-110/104
PTEN-109/104
PTEN-108/104
PTEN-107/104
PTEN-110/114
PTEN-109/114
PTEN-108/114
PTEN-107/114
PTEN-110/103
PTEN-109/103
PTEN-108/103
PTEN-107/103
PTEN-110/113
PTEN-109/113
PTEN-108/113
0
0.5
1
1.5
2
2.5
3
3.5

FIG. 44B



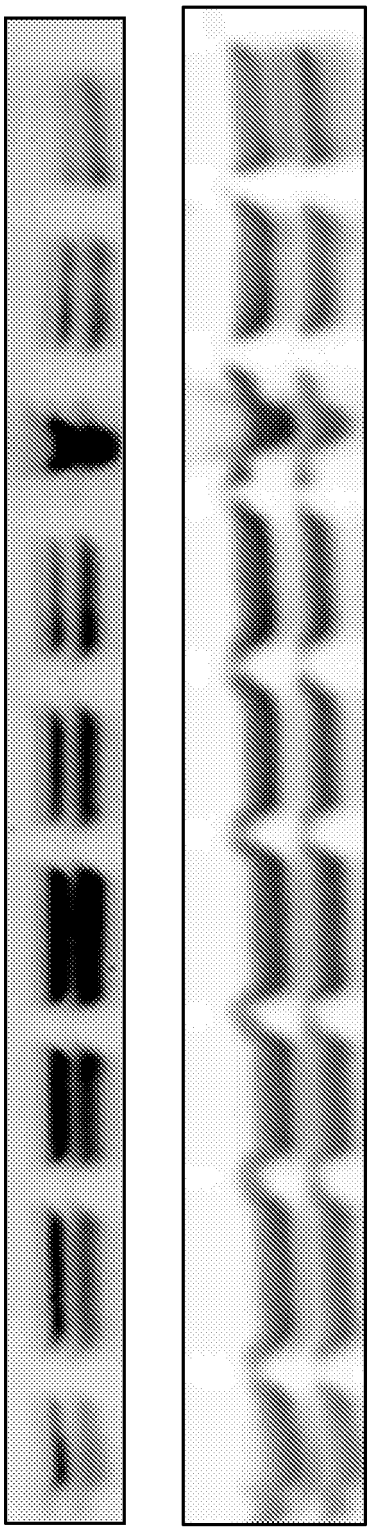
	SAMPLE
LANE1	108 – DAY1
LANE2	113 – DAY1
LANE3	108&113 - DAY1
LANE4	108&113 - DAY2
LANE5	LIPO CONTROL DAY1
LANE6	UNTREATED DAY1
LANE7	LIPO CONTROL DAY2
LANE8	UNTREATED DAY2
LANE9	UNTREATED DAY2

FIG. 45



MOUSE KLF4 OLIGOS WERE SCREENED FOR PROTEIN IN Hepa1-6 CELLS VIA TRANSFECTION AT DAY3.

FIG. 46

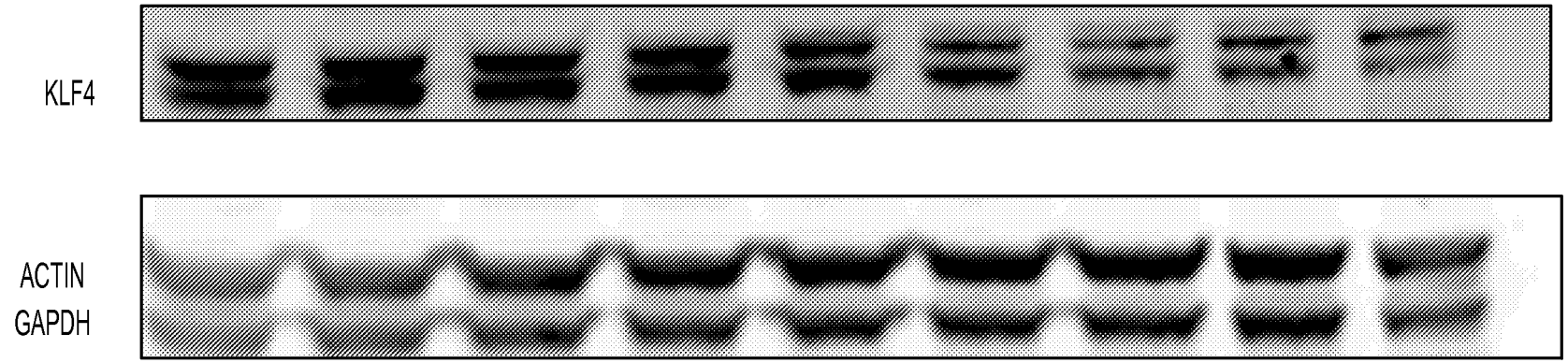


	OLIGO
LANE1	8
LANE2	9
LANE3	11
LANE4	12
LANE5	13
LANE6	14
LANE7	15
LANE8	LIPO-CONTROL
LANE9	UNTREATED

MOUSE KLF4 OLIGOS WERE SCREENED FOR PROTEIN IN Hepa 1-6 CELLS VIA TRANSFECTION AT DAY3.

FIG. 47

MOUSE KLF4 IN Hepa1-6 CELLS
STABILITY COMBINATION OLIGOS



	OLIGO
LANE1	1&16
LANE2	1&17
LANE3	1&19
LANE4	2&18
LANE5	2&19
LANE6	3&18
LANE7	3&19
LANE8	LIPO-CONTROL
LANE9	UNTREATED

MOUSE KLF4 OLIGOS WERE SCREENED FOR PROTEIN IN Hepa1-6 CELLS VIA TRANSFECTION AT DAY3.

FIG. 48

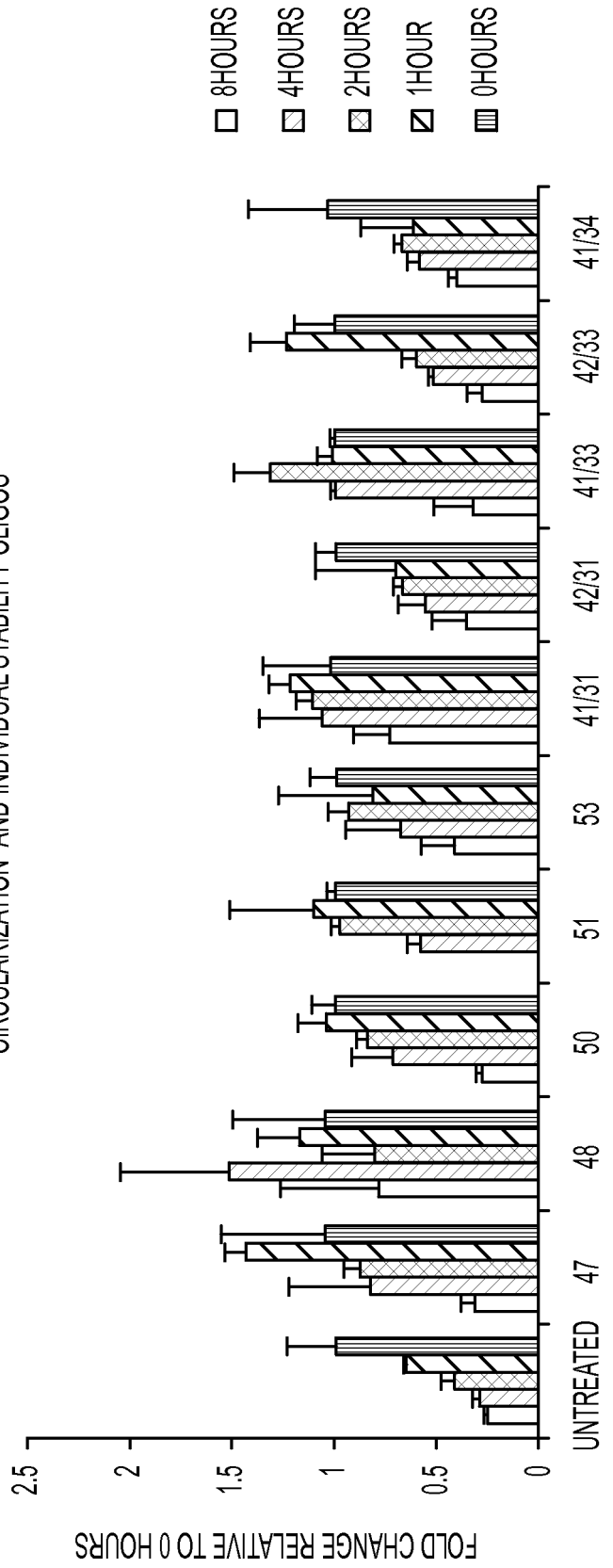

ACTINOMYCIN D KLF4 STABILITY MEASUREMENT WITH "CIRCULARIZATION" AND INDIVIDUAL STABILITY OLIGOS
FOLD CHANGE RELATIVE TO 0 HOURS
2.5
2
1.5
1
0.5
0
8HOURS
4HOURS
2HOURS
1HOUR
0HOURS
UNTREATED
47
48
50
51
53
41/31
42/31
41/33
42/33
41/34

FIG. 49

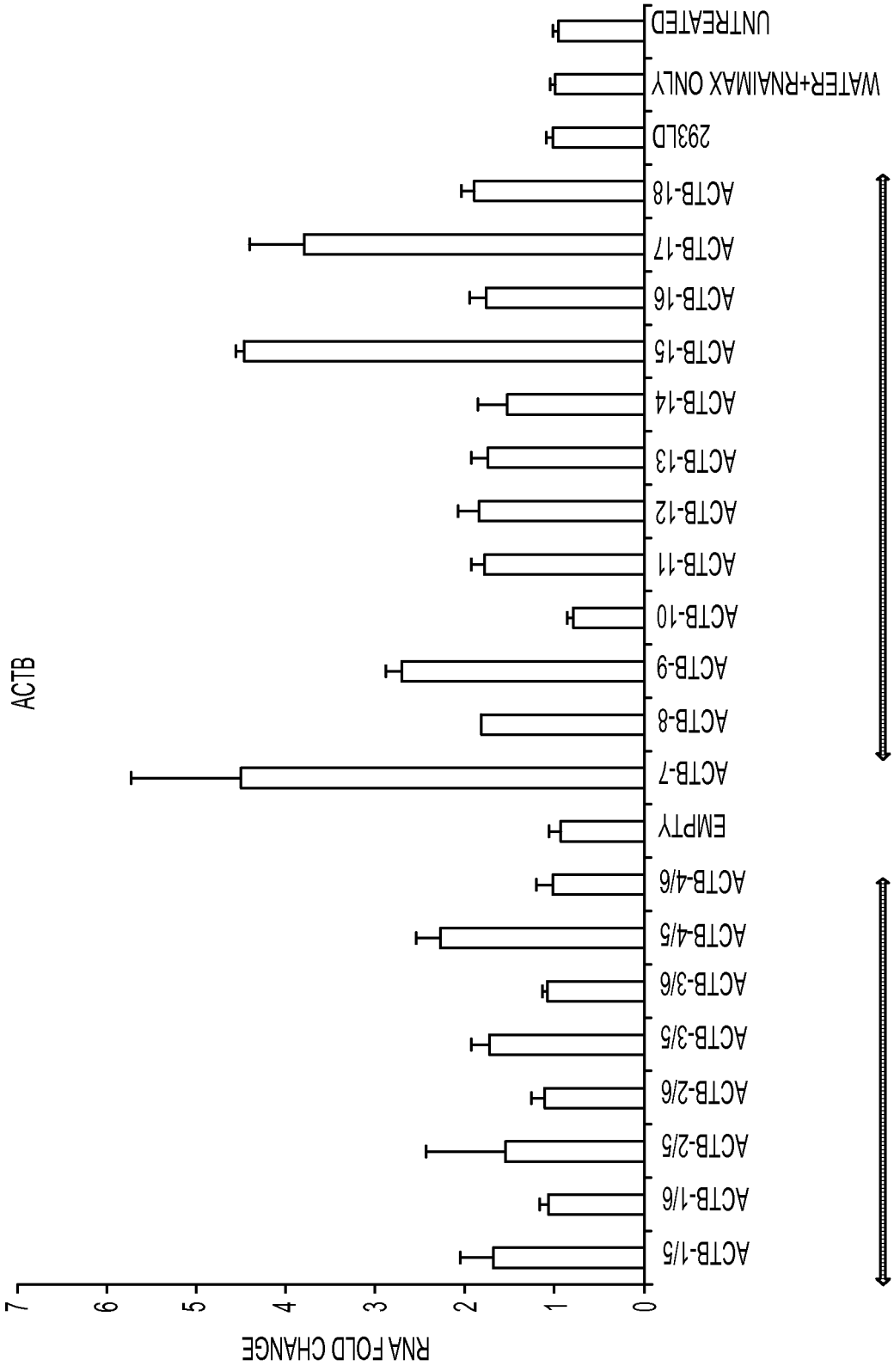

ACTB
RNA FOLD CHANGE
0
1
2
3
4
5
6
7
ACTB-1/5
ACTB-1/6
ACTB-2/5
ACTB-2/6
ACTB-3/5
ACTB-3/6
ACTB-4/5
ACTB-4/6
EMPTY
ACTB-7
ACTB-8
ACTB-9
ACTB-10
ACTB-11
ACTB-12
ACTB-13
ACTB-14
ACTB-15
ACTB-16
ACTB-17
ACTB-18
293LD
WATER+RNAIMAX ONLY
UNTREATED
5′/3′ END OLIGOS COMBINED
"CIRCULARIZATION" OLIGOS

FIG. 50

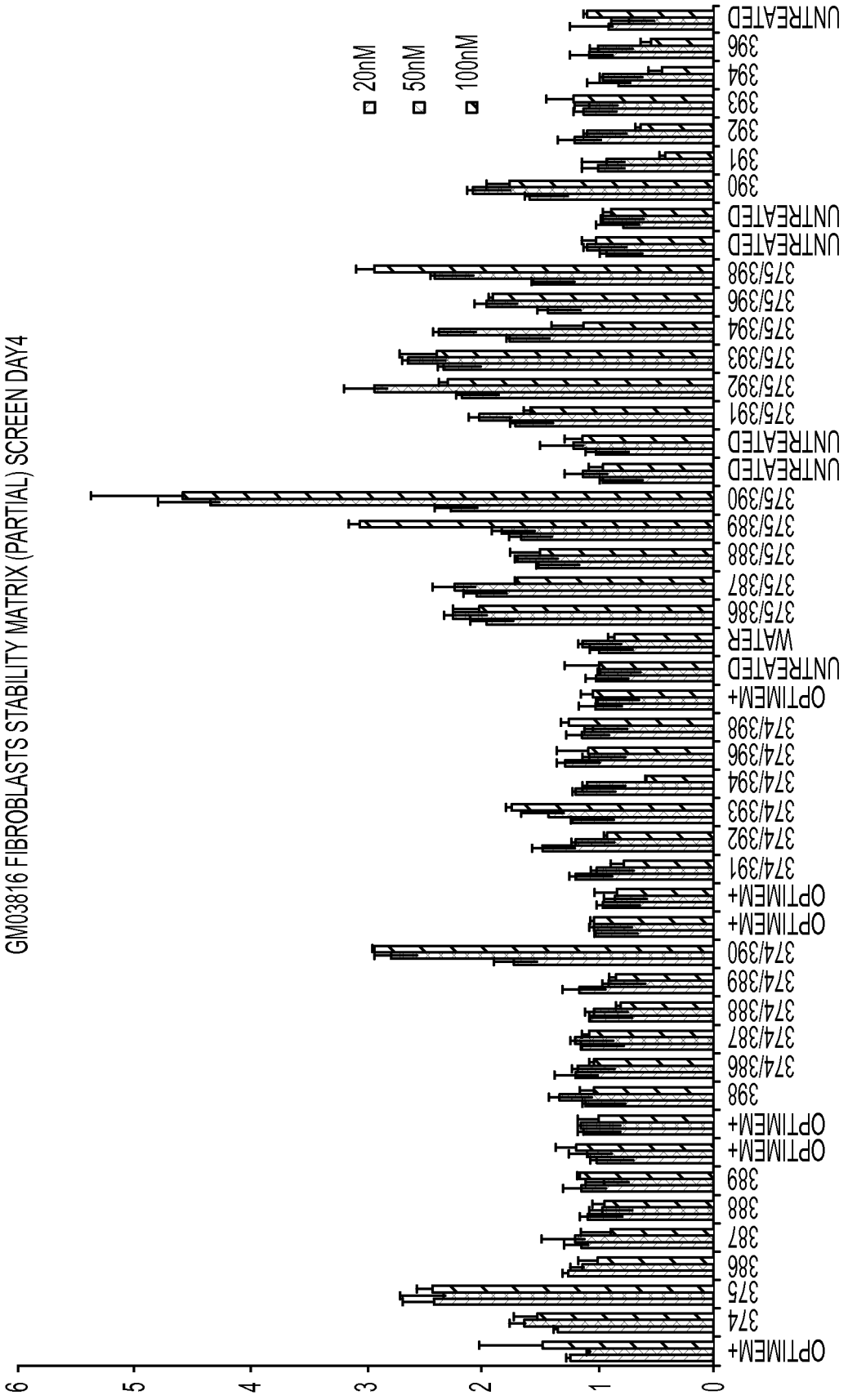

GM03816 FIBROBLASTS STABILITY MATRIX (PARTIAL) SCREEN DAY4
20nM
50nM
100nM
0
1
2
3
4
5
6
OPTIMEM+
374
375
386
387
388
389
OPTIMEM+
OPTIMEM+
398
374/386
374/387
374/388
374/389
374/390
OPTIMEM+
OPTIMEM+
374/391
374/392
374/393
374/394
374/396
374/398
OPTIMEM+
UNTREATED
WATER
375/386
375/387
375/388
375/389
375/390
UNTREATED
UNTREATED
375/391
375/392
375/393
375/394
375/396
375/398
UNTREATED
UNTREATED
390
391
392
393
394
396
UNTREATED

FIG. 51

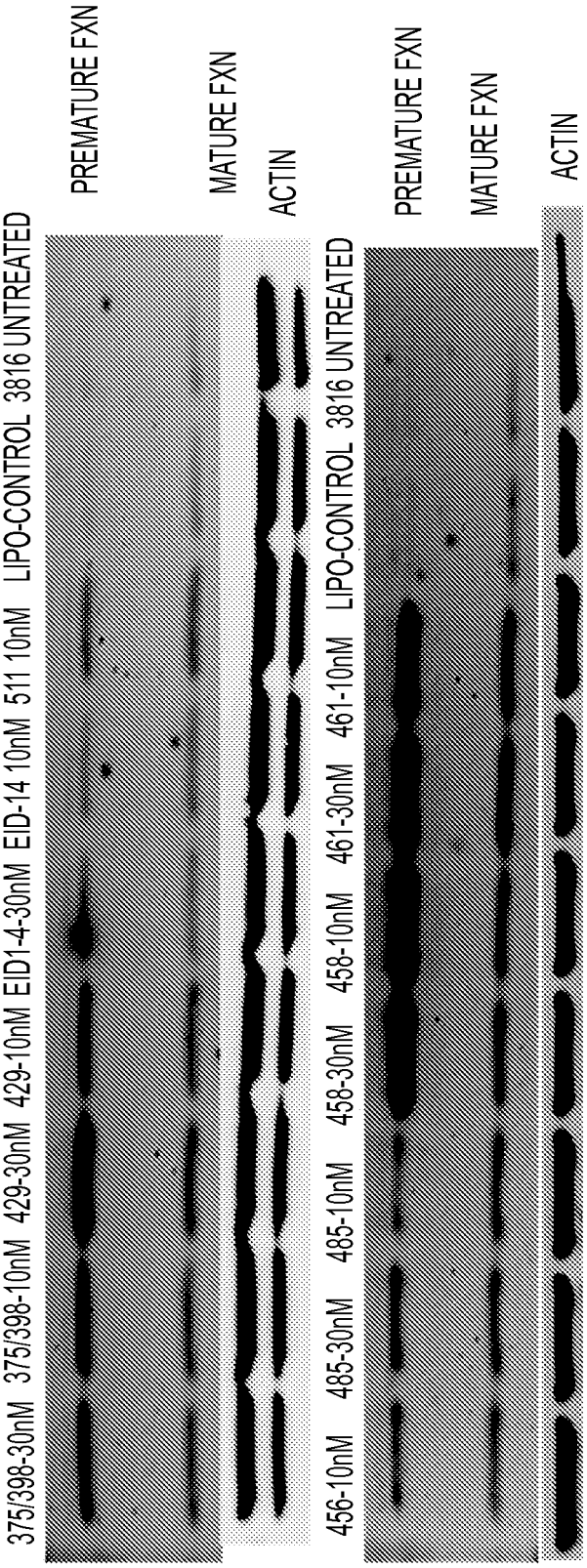
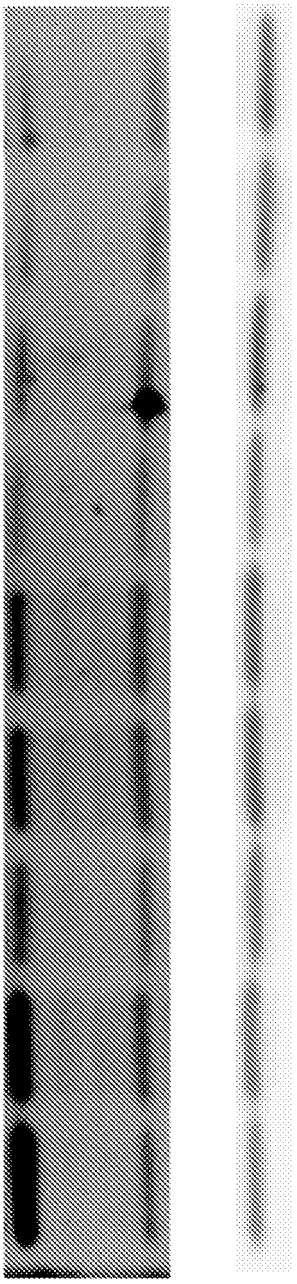

375/398-30nM
375/398-10nM
429-30nM
429-10nM
EID1-4-30nM
EID-14 10nM
511 10nM
LIPO-CONTROL
3816 UNTREATED
PREMATURE FXN
MATURE FXN
ACTIN
456-10nM
485-30nM
485-10nM
458-30nM
458-10nM
461-30nM
461-10nM
LIPO-CONTROL
3816 UNTREATED
PREMATURE FXN
MATURE FXN
ACTIN

FIG. 52



LANE	SAMPLE
1	OLIGO-60nM
2	OLIGO-30nM
3	OLIGO-15nM
4	OLIGO-7.5nM
5	OLIGO-3.75nM
6	TRANSFECTION AGENT CONTROL
7	TRANSFECTION AGENT CONTROL
8	UNTREATED 3816
9	UNTREATED 3816

FIG. 53

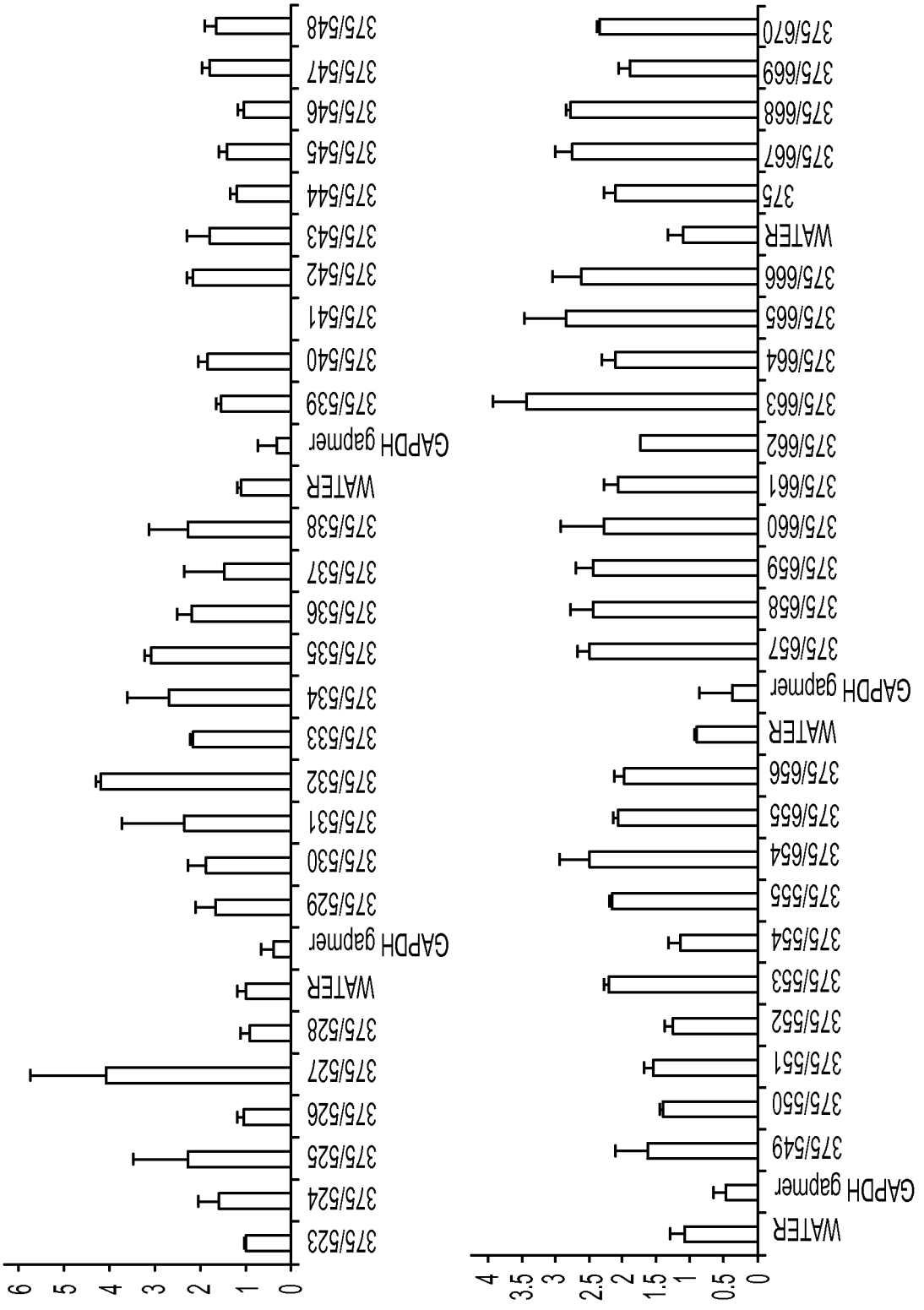

0
0.5
1
1.5
2
2.5
3
3.5
4
WATER
GAPDH gapmer
375/549
375/550
375/551
375/552
375/553
375/554
375/555
375/654
375/655
375/656
WATER
GAPDH gapmer
375/657
375/658
375/659
375/660
375/661
375/662
375/663
375/664
375/665
375/666
WATER
375
375/667
375/668
375/669
375/670
0
1
2
3
4
5
6
375/523
375/524
375/525
375/526
375/527
375/528
WATER
GAPDH gapmer
375/529
375/530
375/531
375/532
375/533
375/534
375/535
375/536
375/537
375/538
WATER
GAPDH gapmer
375/539
375/540
375/541
375/542
375/543
375/544
375/545
375/546
375/547
375/548

FIG. 54

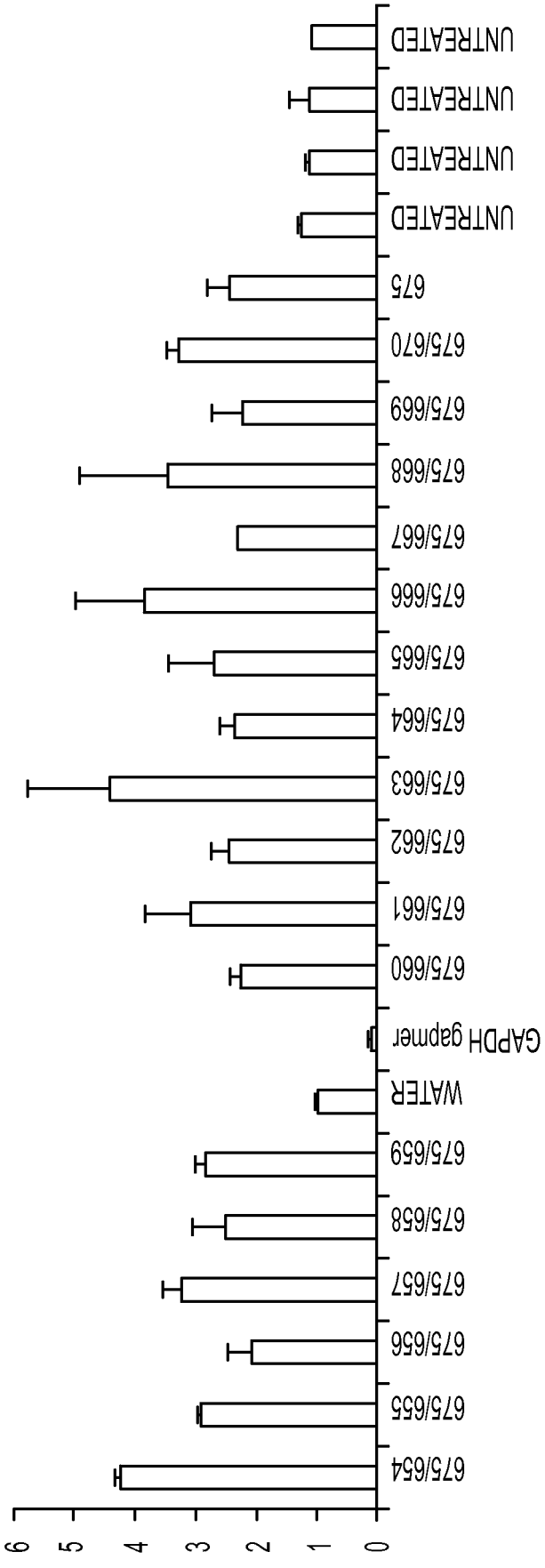
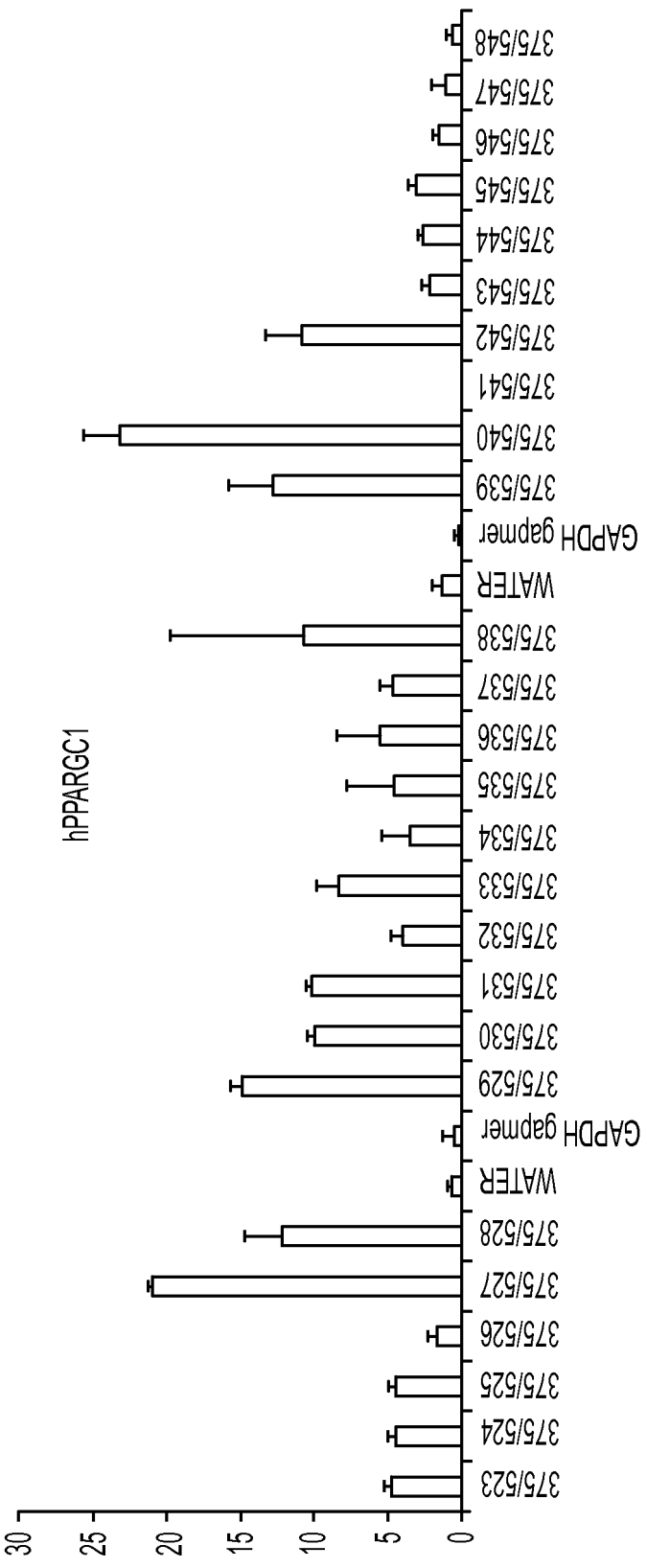

6
5
4
3
2
1
0
675/654
675/655
675/656
675/657
675/658
675/659
WATER
GAPDH gapmer
675/660
675/661
675/662
675/663
675/664
675/665
675/666
675/667
675/668
675/669
675/670
675
UNTREATED
UNTREATED
UNTREATED
UNTREATED

FIG. 55


hPPARGC1
0
5
10
15
20
25
30
375/523
375/524
375/525
375/526
375/527
375/528
WATER
GAPDH gapmer
375/529
375/530
375/531
375/532
375/533
375/534
375/535
375/536
375/537
375/538
WATER
GAPDH gapmer
375/539
375/540
375/541
375/542
375/543
375/544
375/545
375/546
375/547
375/548

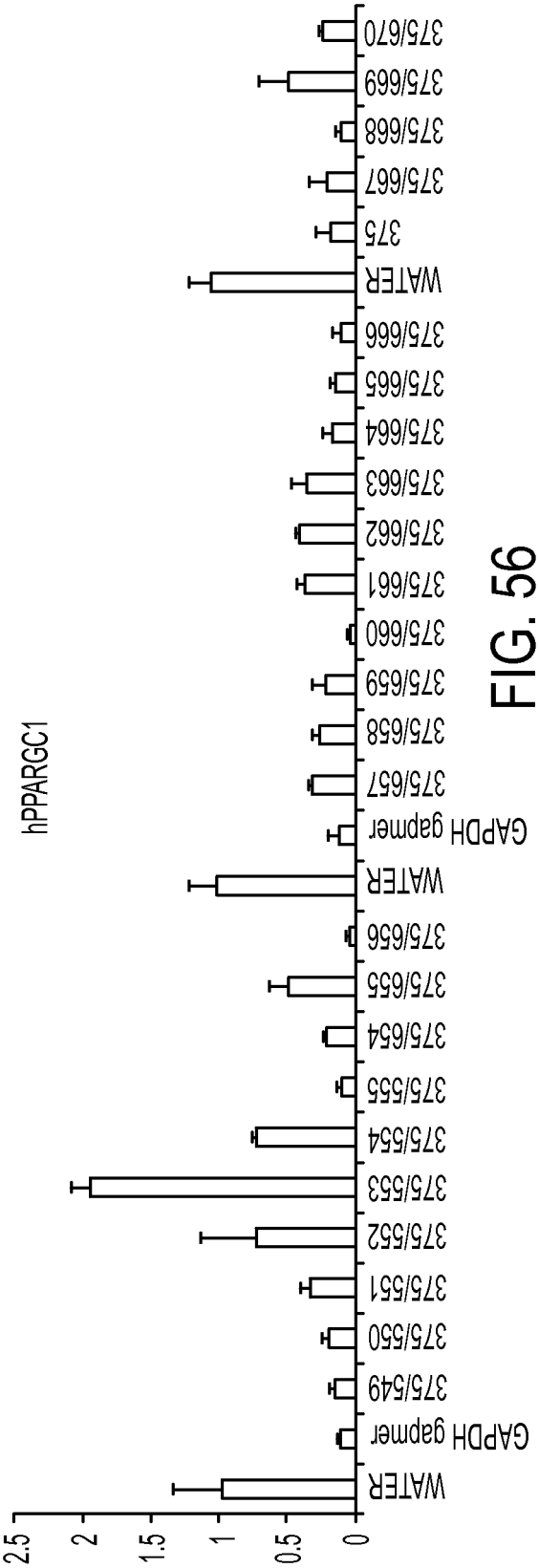

hPPARGC1
0
0.5
1
1.5
2
2.5
WATER
GAPDH gapmer
375/549
375/550
375/551
375/552
375/553
375/554
375/555
375/654
375/655
375/656
WATER
GAPDH gapmer
375/657
375/658
375/659
375/660
375/661
375/662
375/663
375/664
375/665
375/666
WATER
375
375/667
375/668
375/669
375/670

FIG. 56

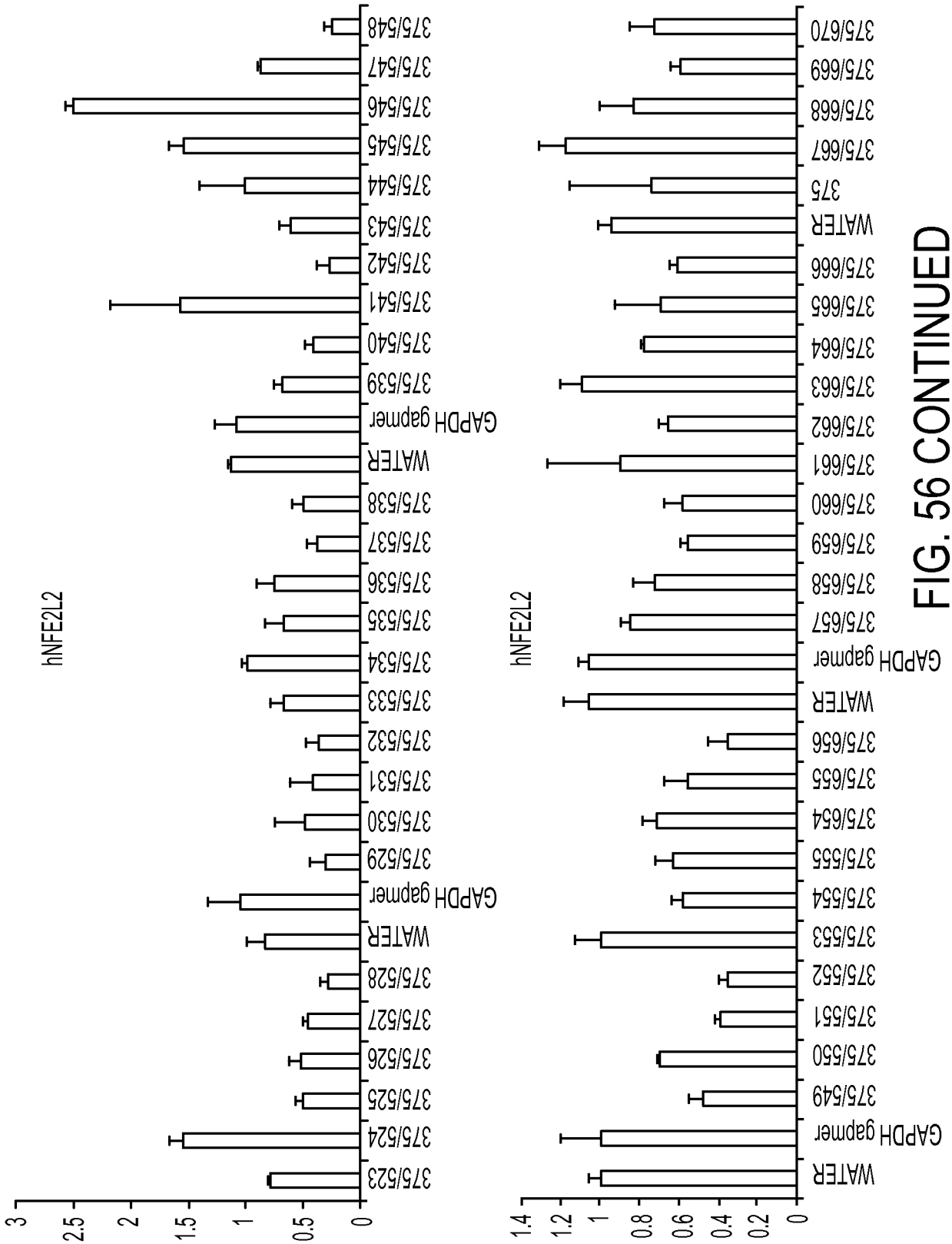


FIG. 56 CONTINUED

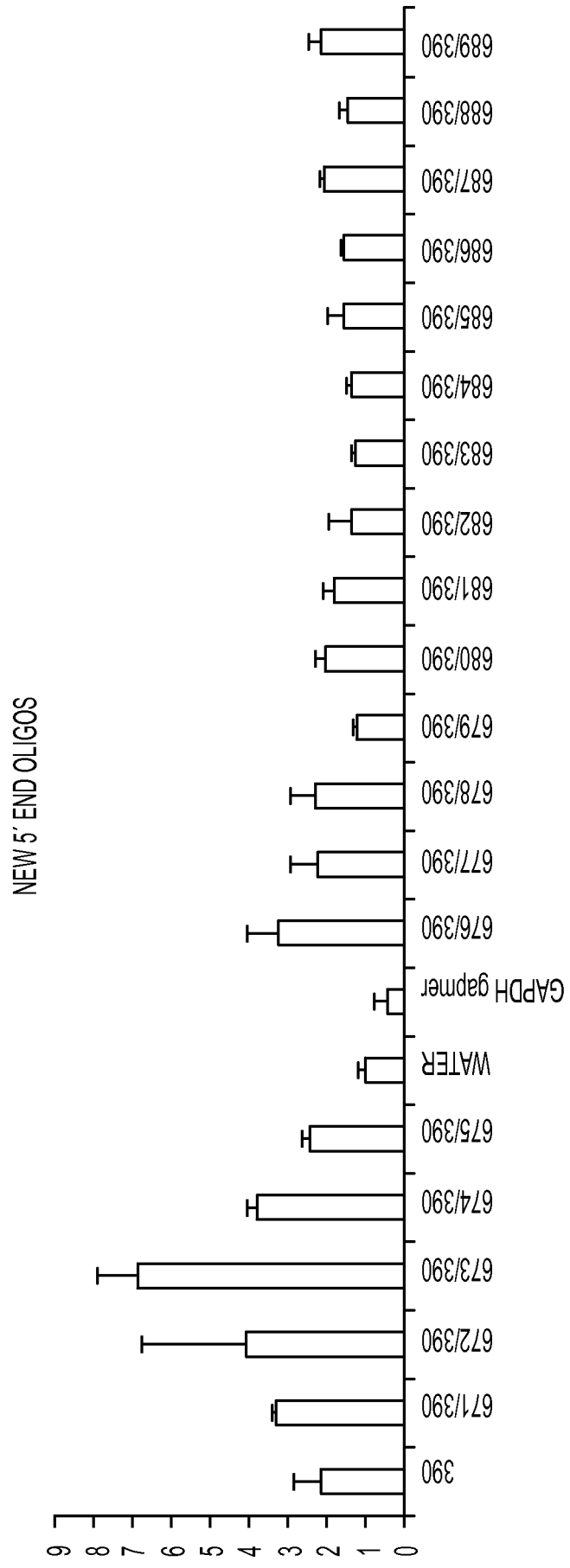

NEW 5' END OLIGOS
0
1
2
3
4
5
6
7
8
9
390
671/390
672/390
673/390
674/390
675/390
WATER
GAPDH gapmer
676/390
677/390
678/390
679/390
680/390
681/390
682/390
683/390
684/390
685/390
686/390
687/390
688/390
689/390

FIG. 57

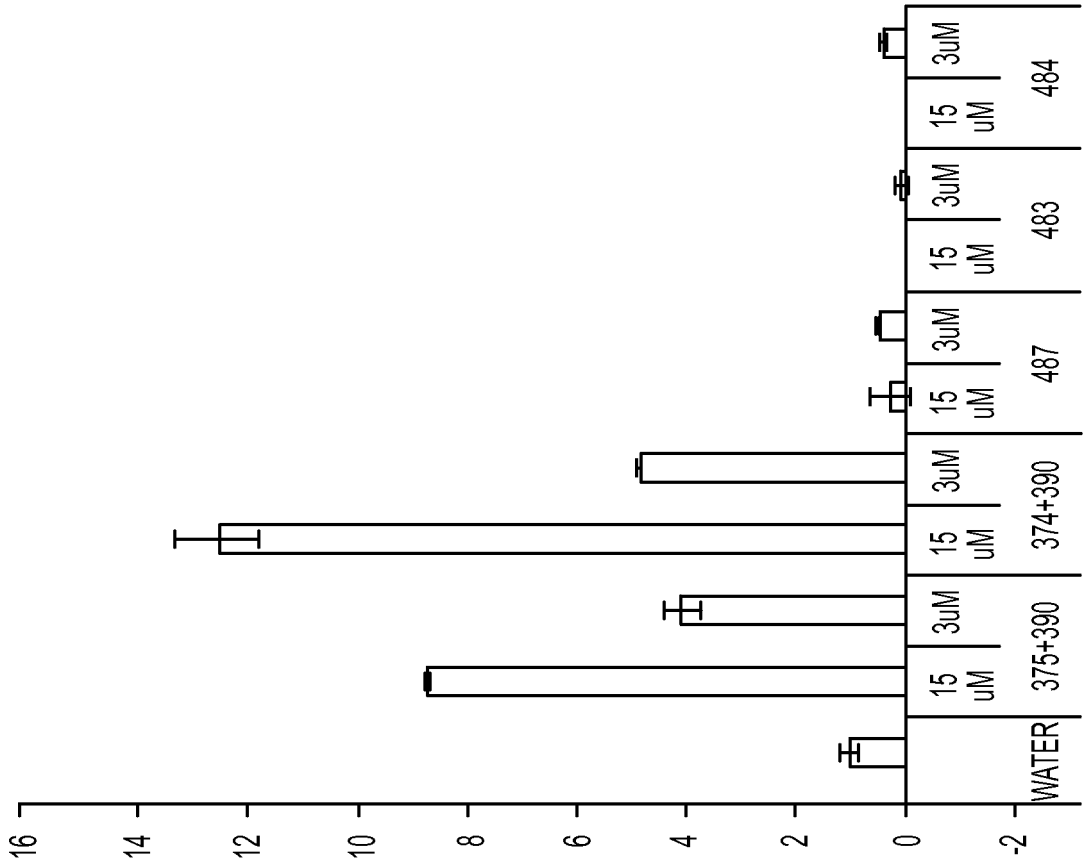


FIG. 58B

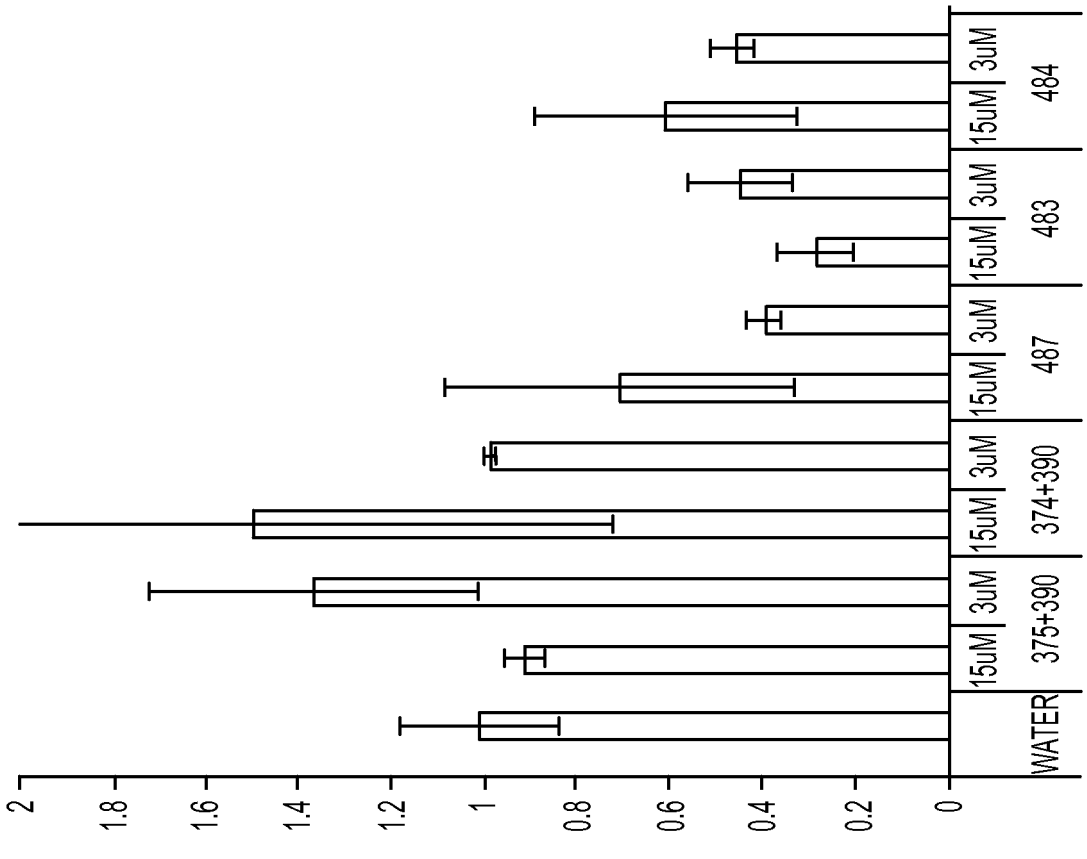


FIG. 58A

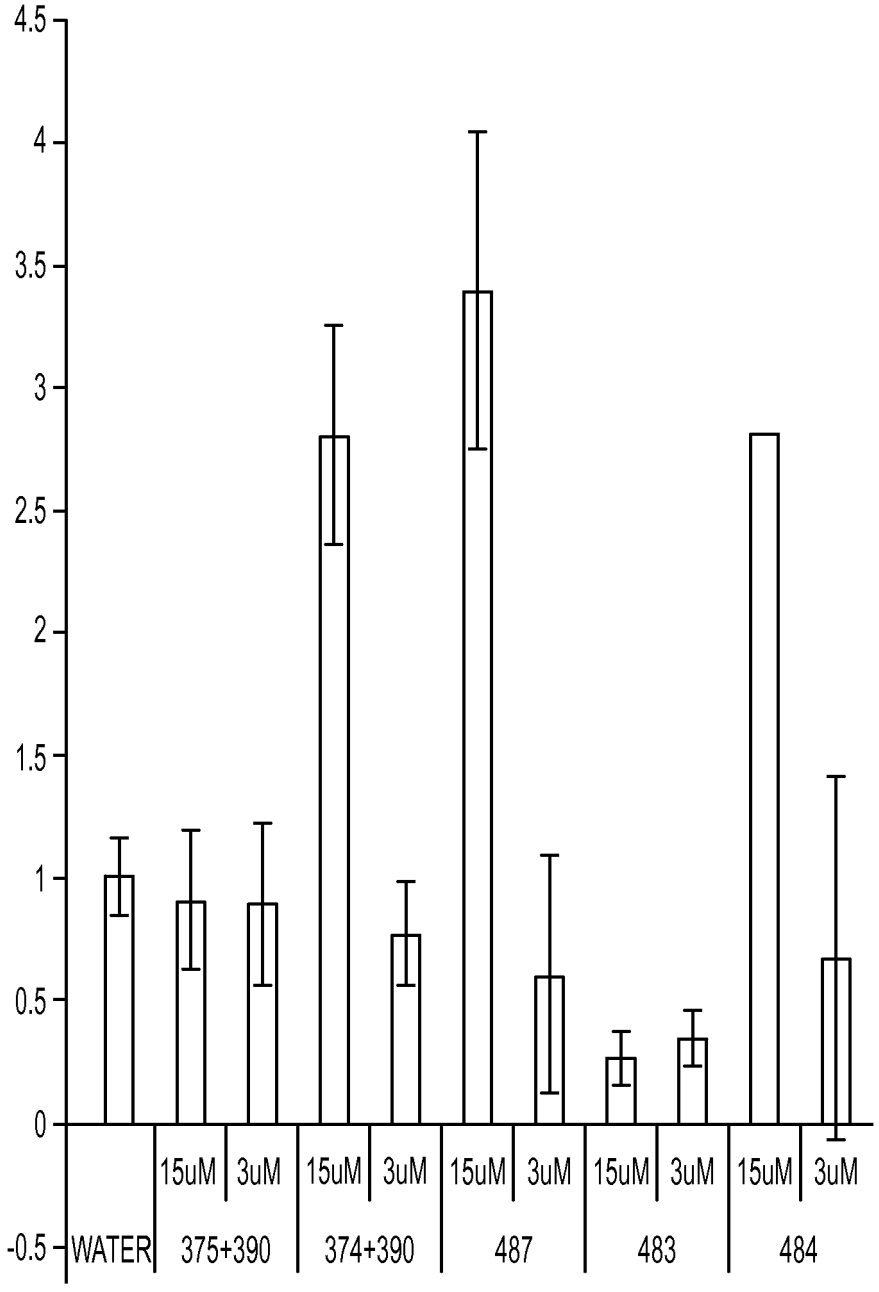

4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
15uM
3uM
15uM
3uM
15uM
3uM
15uM
3uM
15uM
3uM
WATER
375+390
374+390
487
483
484

FIG. 58C

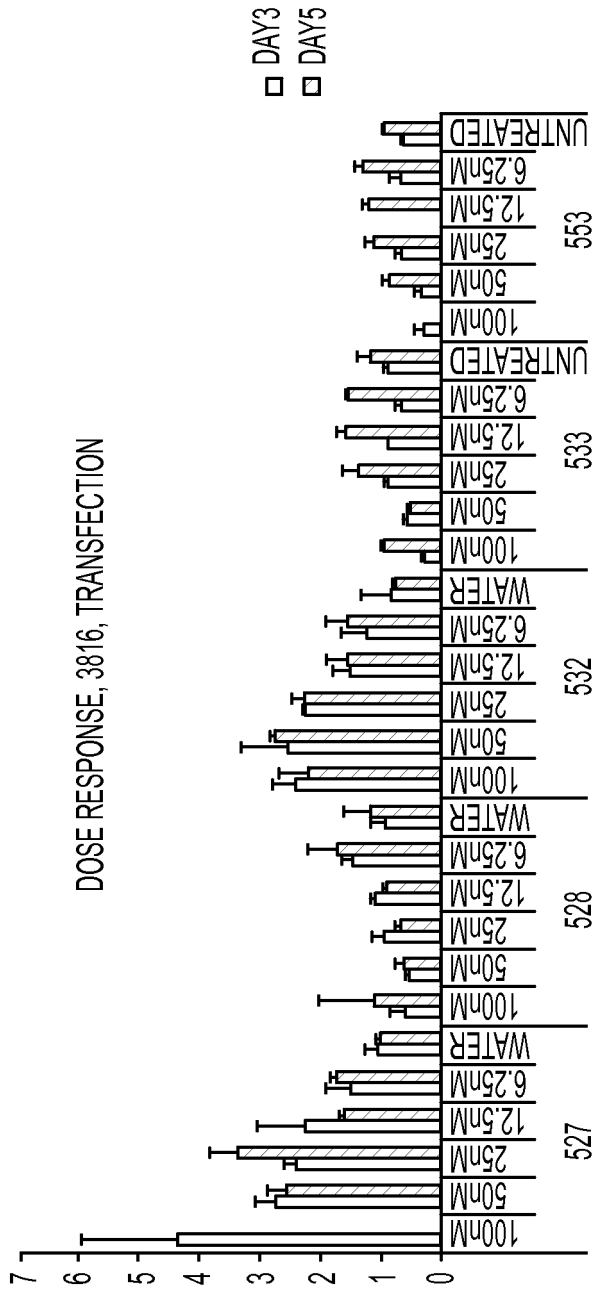


FIG. 59A

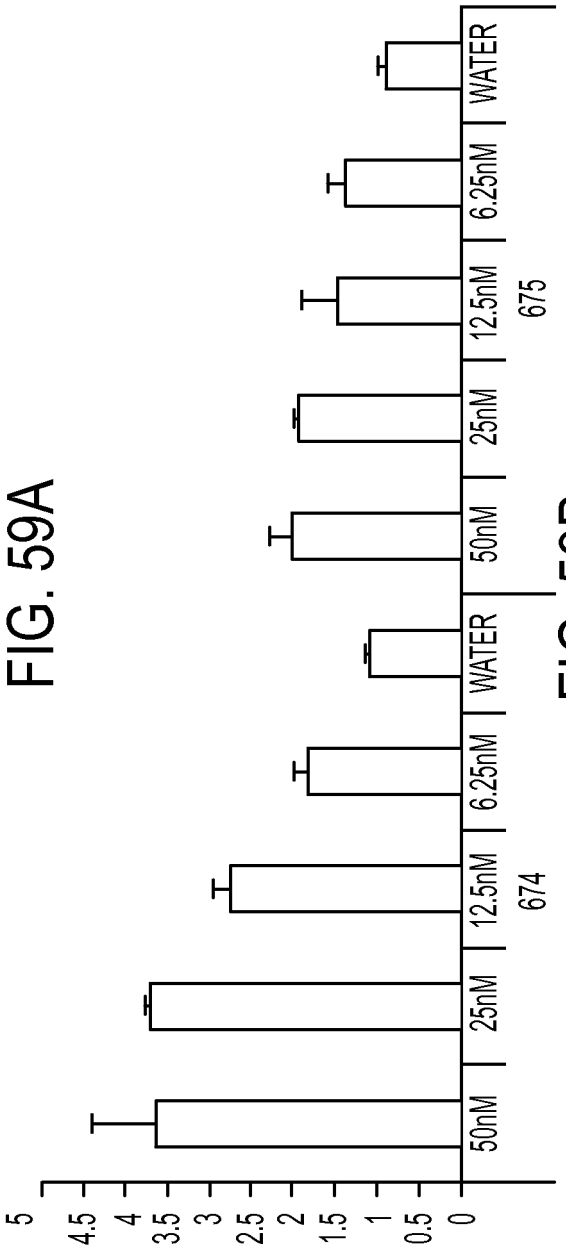


FIG. 59B

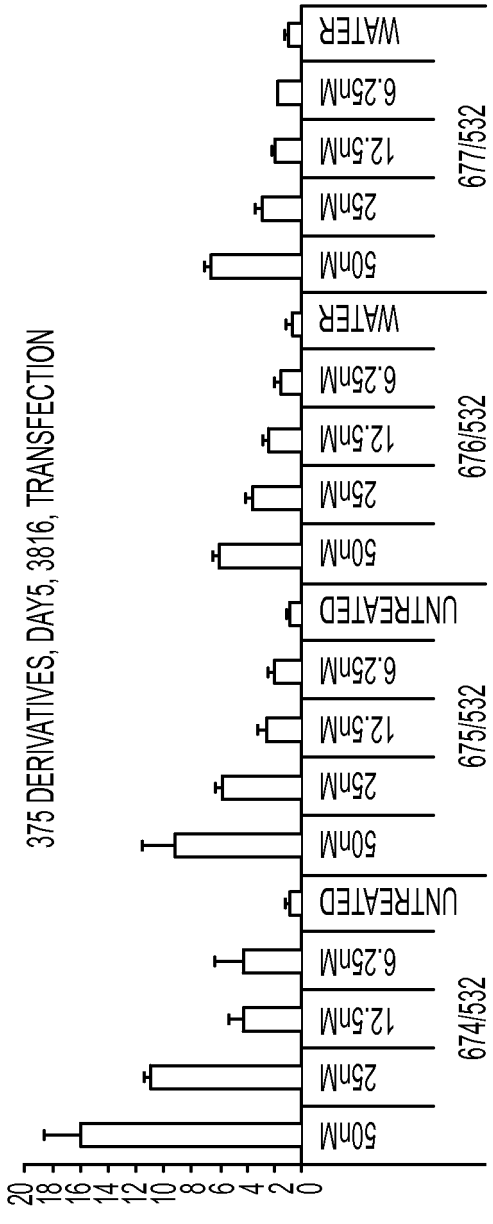


FIG. 60A

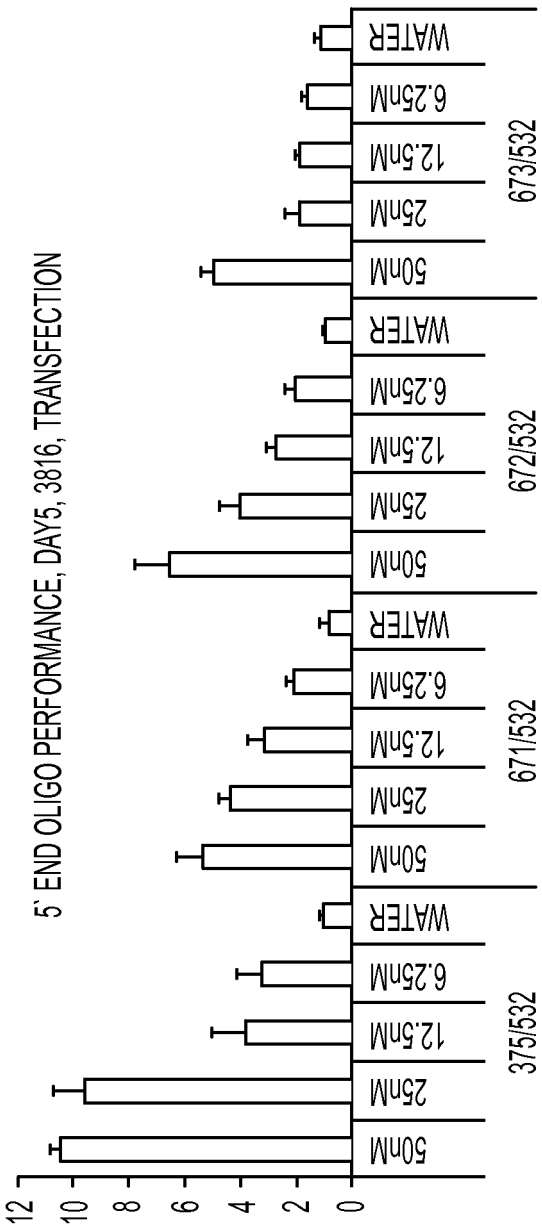
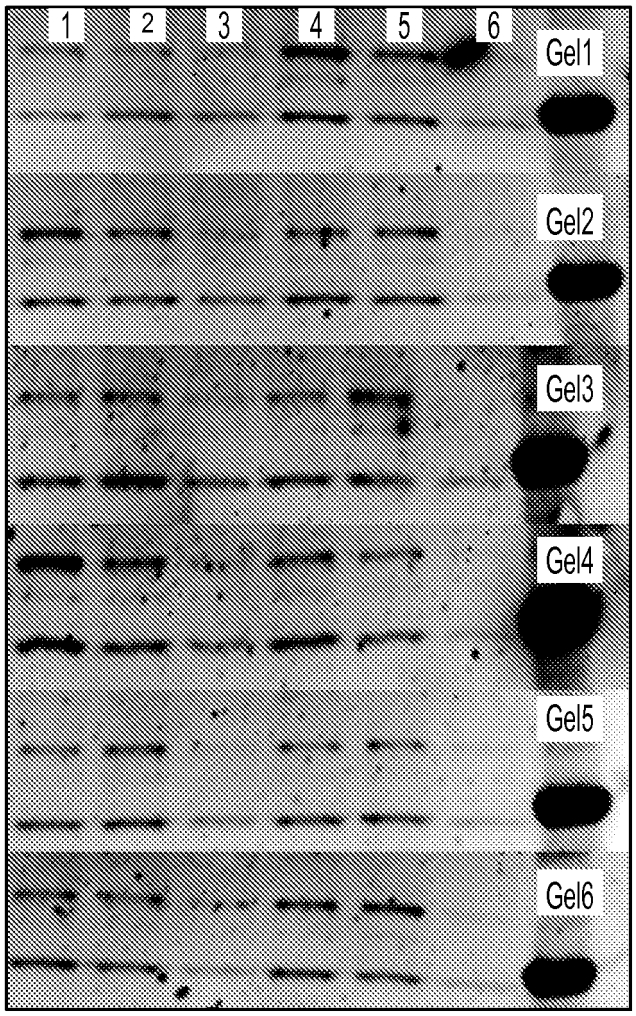


FIG. 60B



LANE	Gel1	Gel2	Gel3	Gel4	Gel5	Gel6
1	671-30nM	674-30nM	677-30nM	672+532-30nM	675+532-30nM	532 30nM
2	671-10nM	674-10nM	677-10nM	672+532-10nM	675+532-10nM	532 10nM
3	LIPO CONTROL	LIPO CONTROL	LIPO CONTROL	LIPO CONTROL	LIPO CONTROL	LIPO CONTROL
4	672-30nM	675-30nM	375+532-30nM	673+532-30nM	676+532-30nM	674+532-30nM
5	672-10nM	675-10nM	375+532-10nM	673+532-10nM	676+532-10nM	674+532-10nM
6	UNTREATED	UNTREATED	UNTREATED	UNTREATED	UNTREATED	UNTREATED
	LIGHT MARKER	LIGHT MARKER	LIGHT MARKER	LIGHT MARKER	LIGHT MARKER	LIGHT MARKER

FIG. 61

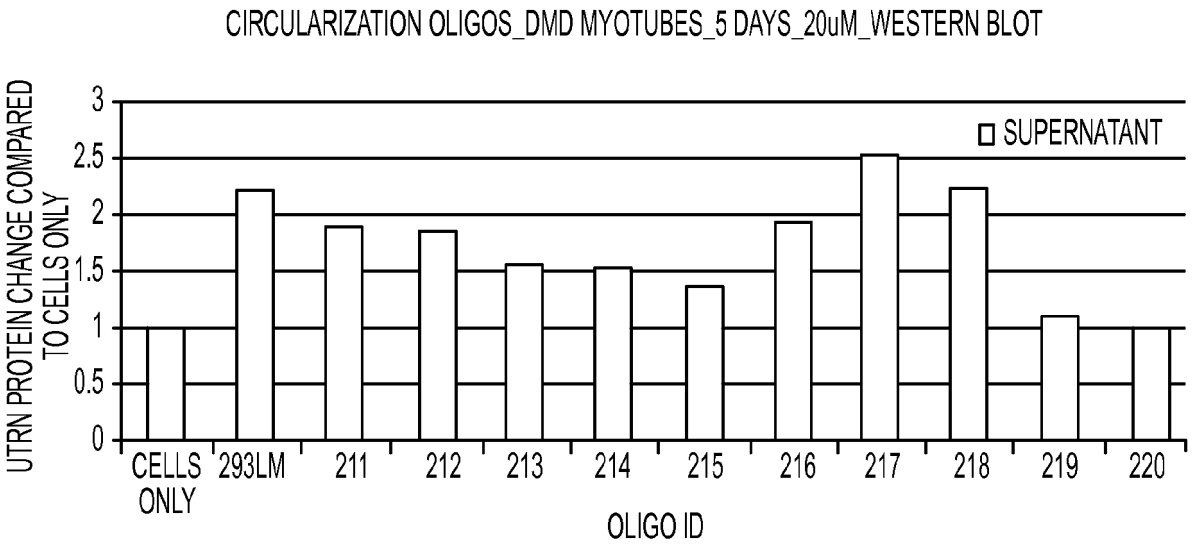

CIRCULARIZATION OLIGOS_DMD MYOTUBES_5 DAYS_20uM_WESTERN BLOT
UTRN PROTEIN CHANGE COMPARED TO CELLS ONLY
3
2.5
2
1.5
1
0.5
0
SUPERNATANT
CELLS ONLY
293LM
211
212
213
214
215
216
217
218
219
220
OLIGO ID

FIG. 62

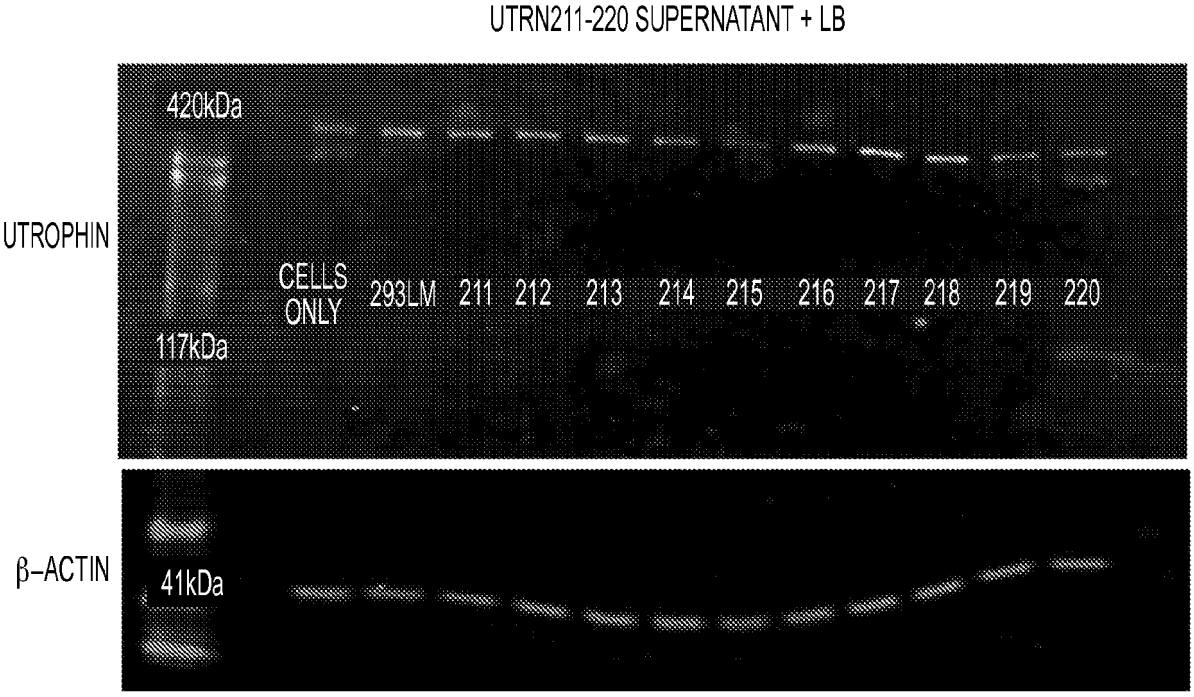

UTRN211-220 SUPERNATANT + LB
420kDa
UTROPHIN
CELLS ONLY
293LM
211
212
213
214
215
216
217
218
219
220
117kDa
β–ACTIN
41kDa

FIG. 63

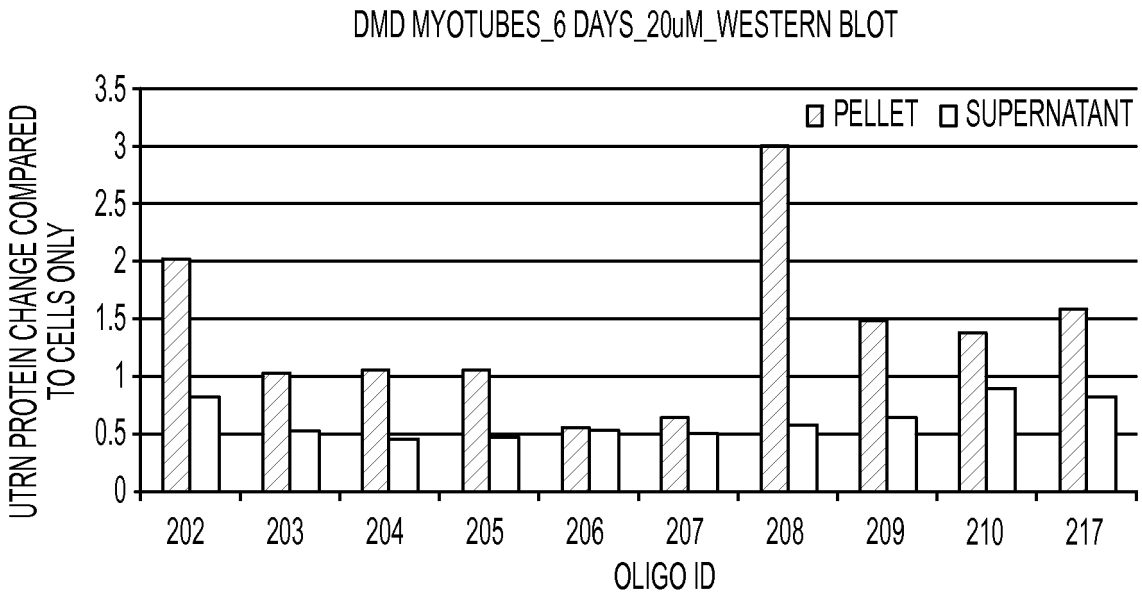


FIG. 64A

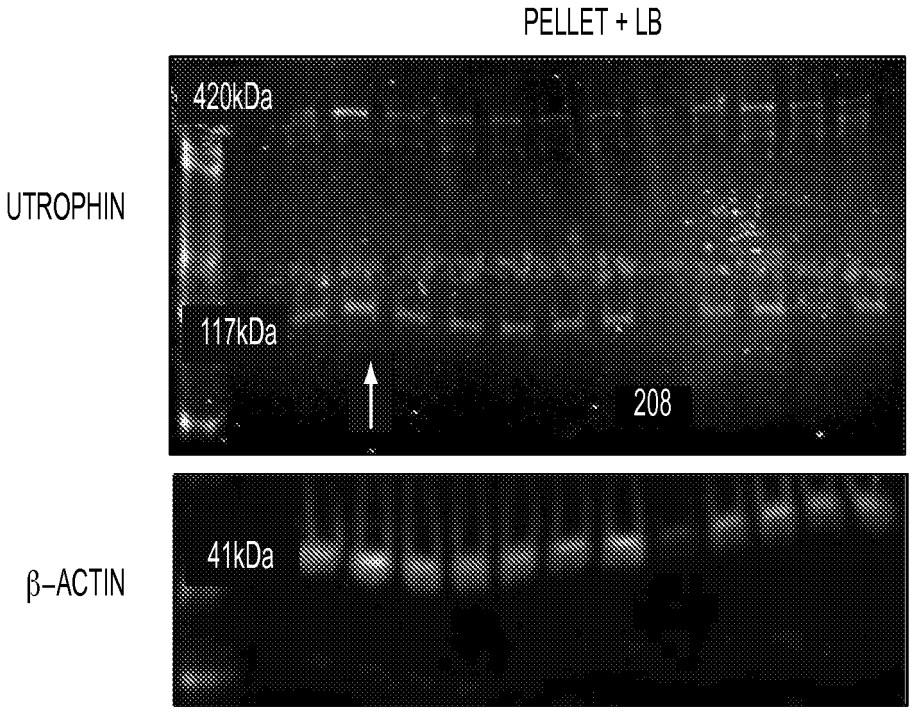


FIG. 64B

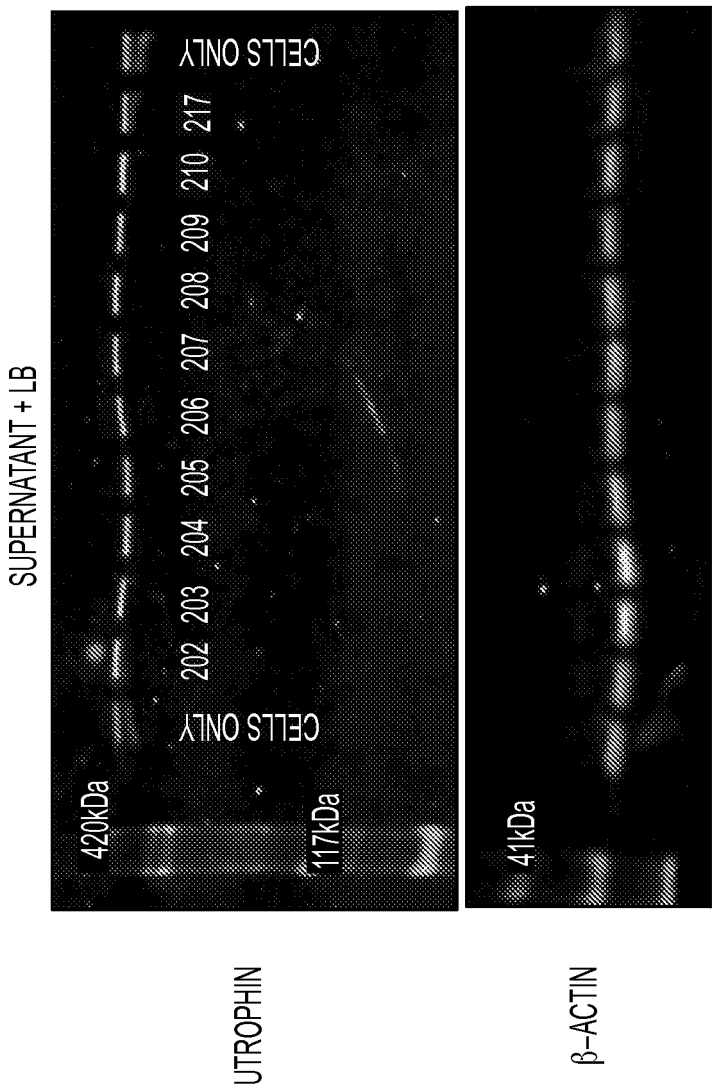

SUPERNATANT + LB
CELLS ONLY
202 203 204 205 206 207 208 209 210 217
CELLS ONLY
420kDa
117kDa
41kDa
UTROPHIN
β-ACTIN

FIG. 64C

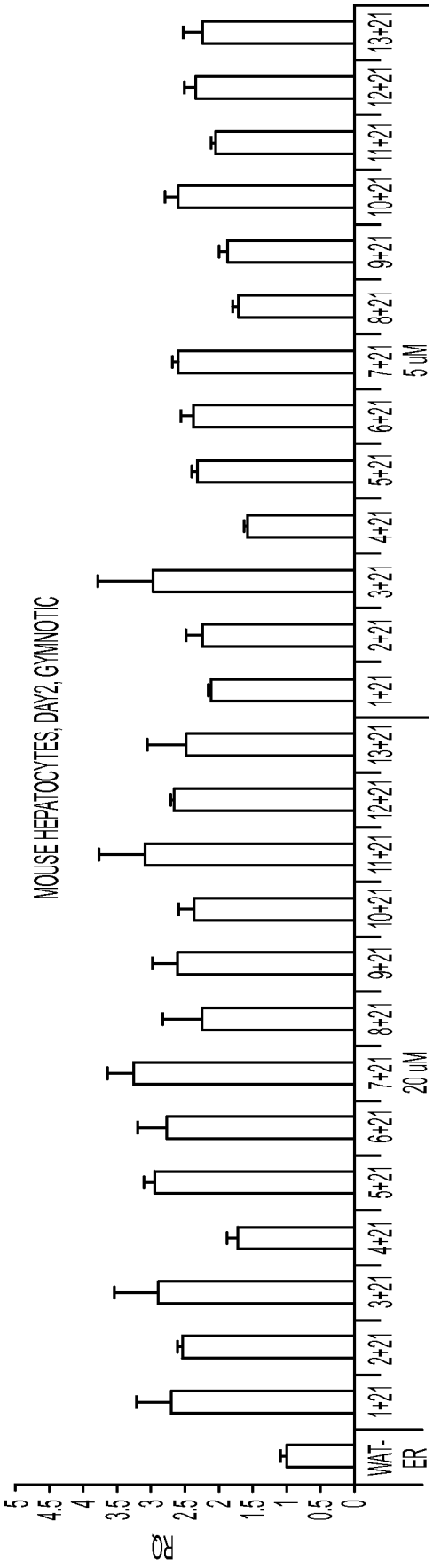


FIG. 65A

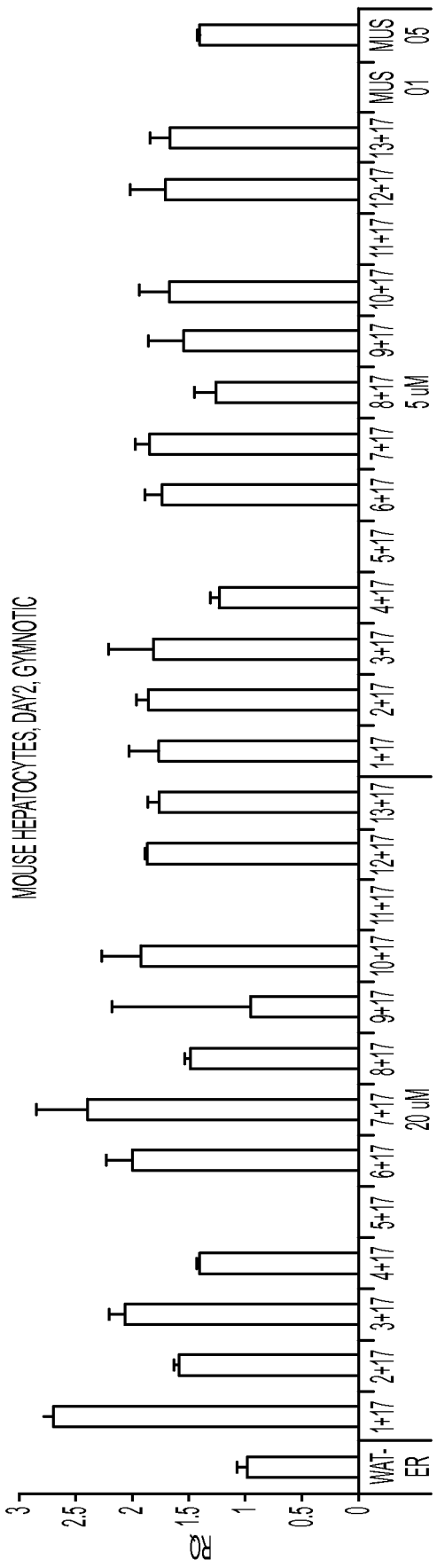


FIG. 65B

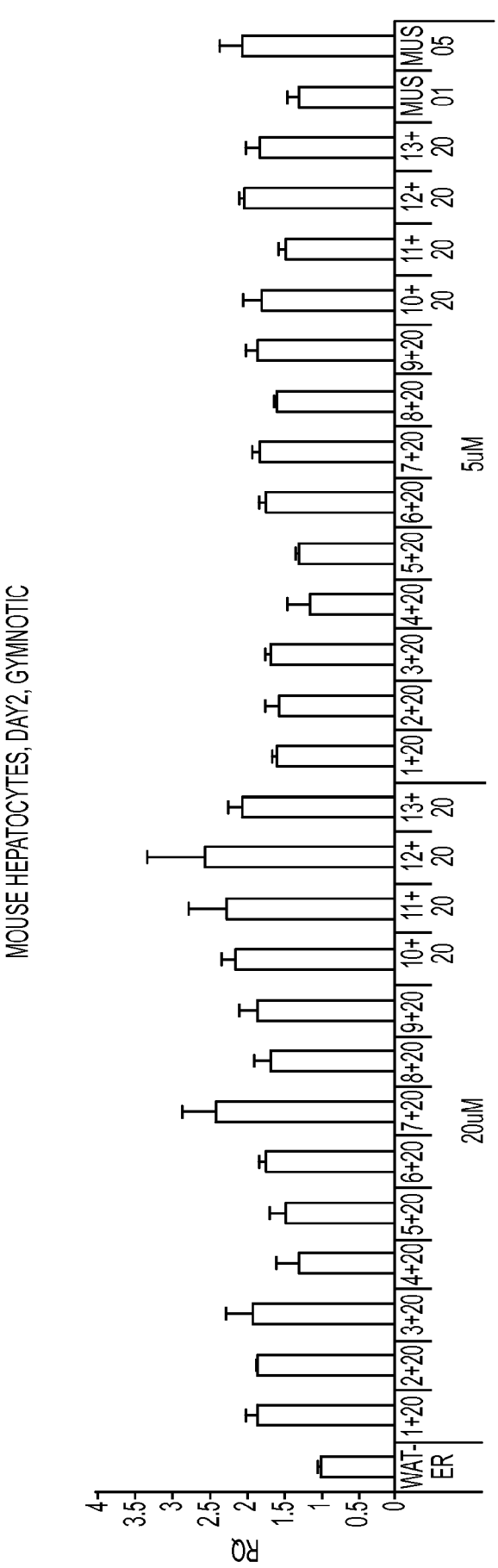

MOUSE HEPATOCYTES, DAY2, GYMNOTIC
RQ
0
0.5
1
1.5
2
2.5
3
3.5
4
WAT-ER
1+20
2+20
3+20
4+20
5+20
6+20
7+20
8+20
9+20
10+20
11+20
12+20
13+20
20uM
1+20
2+20
3+20
4+20
5+20
6+20
7+20
8+20
9+20
10+20
11+20
12+20
13+20
5uM
MUS 05
MUS 01

FIG. 65C

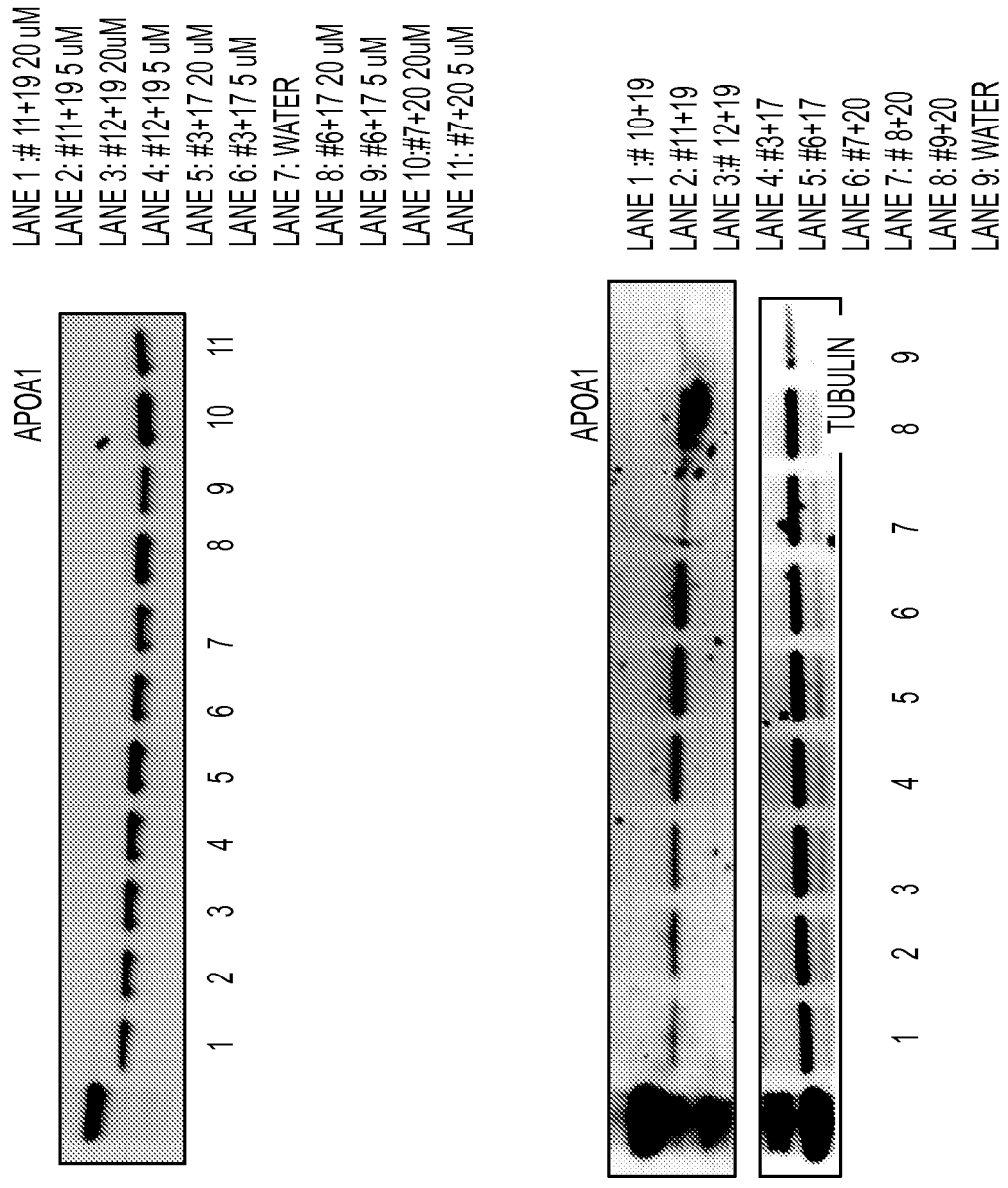

APOA1
1 2 3 4 5 6 7 8 9 10 11
LANE 1 :# 11+19 20 uM
LANE 2: #11+19 5 uM
LANE 3: #12+19 20uM
LANE 4: #12+19 5 uM
LANE 5: #3+17 20 uM
LANE 6: #3+17 5 uM
LANE 7: WATER
LANE 8: #6+17 20 uM
LANE 9: #6+17 5 uM
LANE 10:#7+20 20uM
LANE 11: #7+20 5 uM
APOA1
TUBULIN
1 2 3 4 5 6 7 8 9
LANE 1 :# 10+19
LANE 2: #11+19
LANE 3:# 12+19
LANE 4: #3+17
LANE 5: #6+17
LANE 6: #7+20
LANE 7: # 8+20
LANE 8: #9+20
LANE 9: WATER

FIG. 66

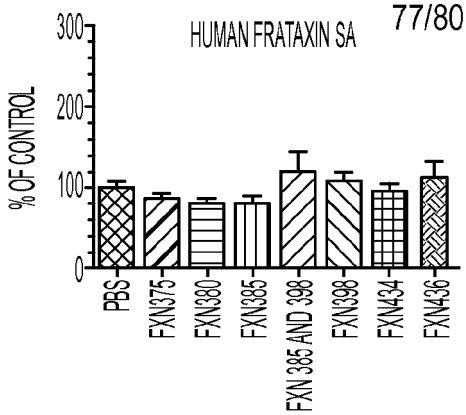


FIG. 67A

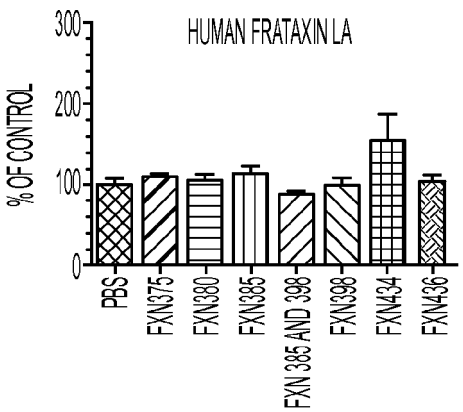


FIG. 67B

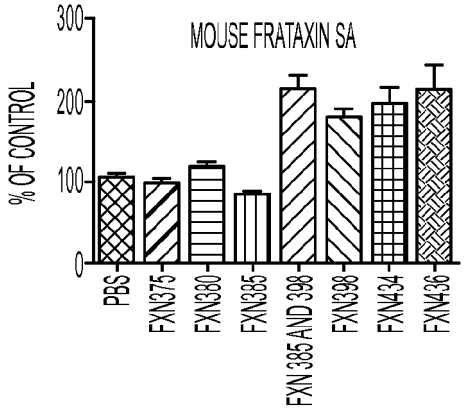


FIG. 67C

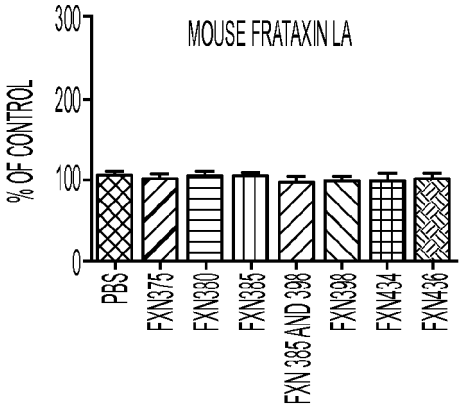


FIG. 67D

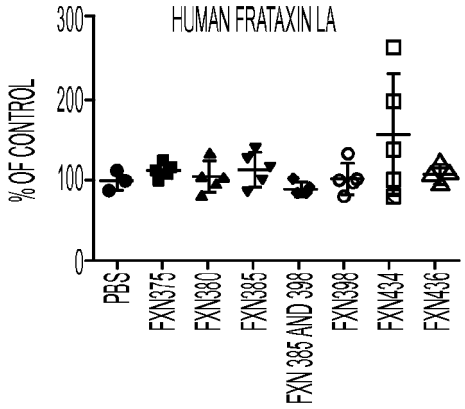


FIG. 67E

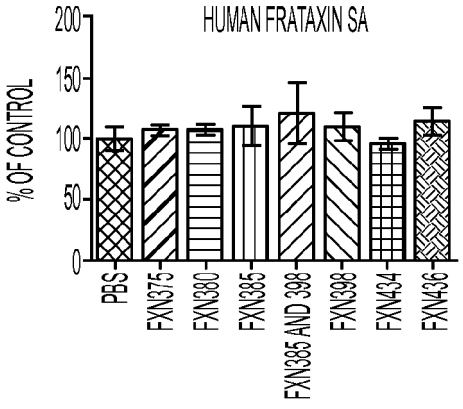


FIG. 67F

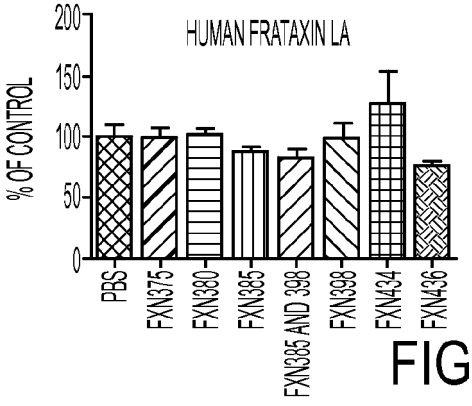


FIG. 67G

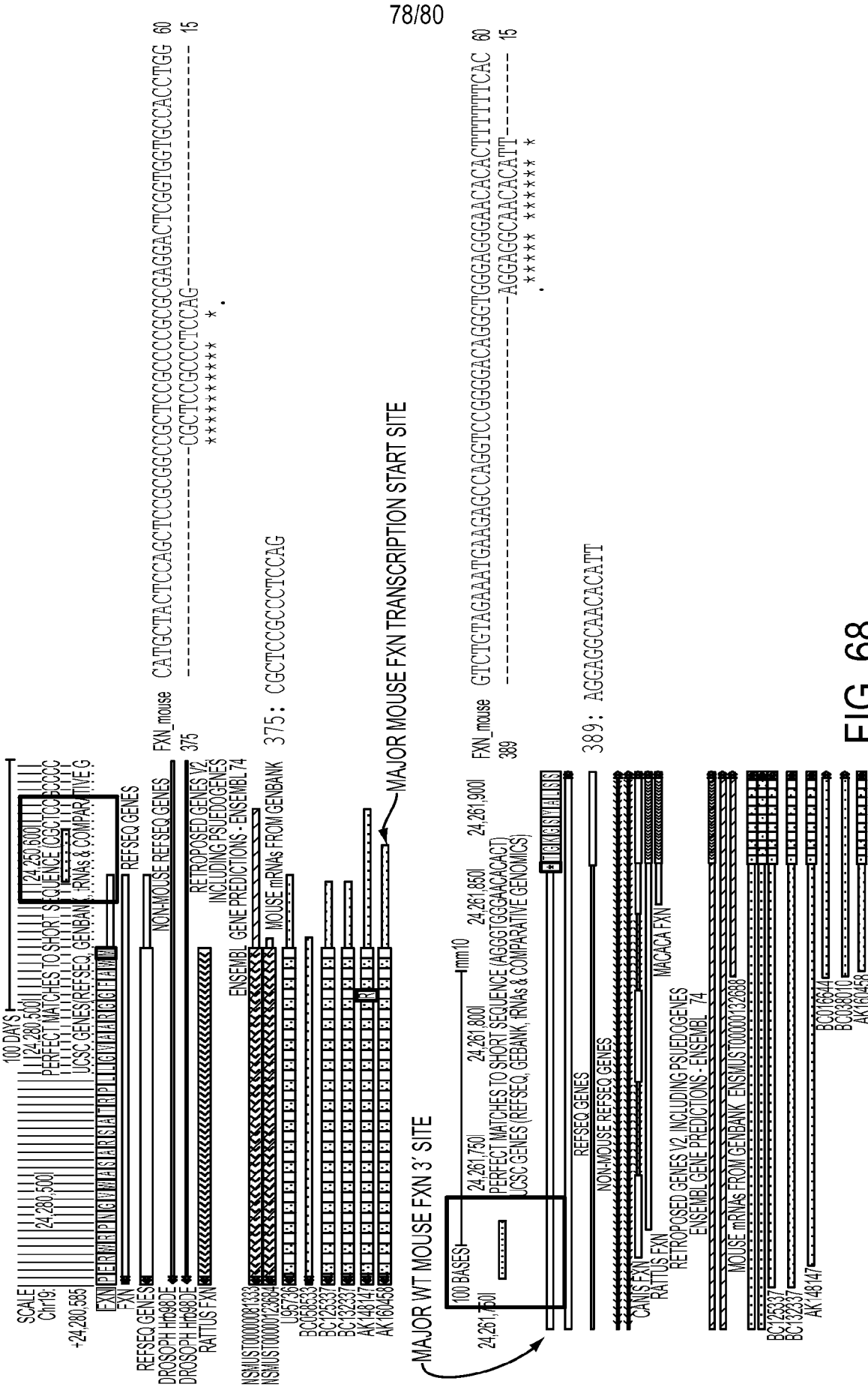

MAJOR WT MOUSE FXN 3′ SITE
MAJOR MOUSE FXN TRANSCRIPTION START SITE
FXN_mouse 375 CATGCTACTCCAGCTCCGGGGCCGCTCCGCCCCGGCGCGAGGACTCGGTGGTGCCACCTGG 60
375 ---------CGCTCCGCCCTCCAG--------- 15
FXN_mouse 389 GTCTGTAGAAATGAAGAGGCCAGGTCCGGGGACAGGGTGGGAGGGGAACACACTTTTTTCAC 60
389 ---------AGGAGGCAACACATT--------- 15
375: CGCTCCGCCCTCCAG
389: AGGAGGCAACACATT
100 DAYS
SCALE
Chr19:
+24,280,585
24,280,500
24,280,600
24,250,600
PERFECT MATCHES TO SHORT SEQUENCE (CGCTCCGCCCTCCAG)
UCSC GENES (REFSEQ, GENBANK, ..RNAs & COMPARATIVE G
FXN
REFSEQ GENES
NON-MOUSE REFSEQ GENES
DROSOPH Hrb98DE
DROSOPH Hrb98DE
RATTUS FXN
RETROPOSED GENES V2,
INCLUDING PSUEDOGENES
ENSEMBL GENE PREDICTIONS - ENSEMBL 74
NSMUST00000081333
NSMUST00000123684
MOUSE mRNAs FROM GENBANK
U95736
BC058633
BC125337
BC132337
AK148147
AK160458
100 BASES
24,261,750
24,261,800
24,261,850
24,261,900
mm10
PERFECT MATCHES TO SHORT SEQUENCE (AGGGTGGGAACACACT)
UCSC GENES (REFSEQ, GEBANK, ..RNAs & COMPARATIVE GENOMICS)
REFSEQ GENES
NON-MOUSE REFSEQ GENES
CANIS FXN
RATTUS FXN
MACACA FXN
RETROPOSED GENES V2, INCLUDING PSUEDOGENES
ENSEMBL GENE PREDICTIONS - ENSEMBL 74
MOUSE mRNAs FROM GENBANK ENSMUST00000132688
BC125337
BC132337
AK148147
BC016644
BC038010
AK160458

FIG. 68

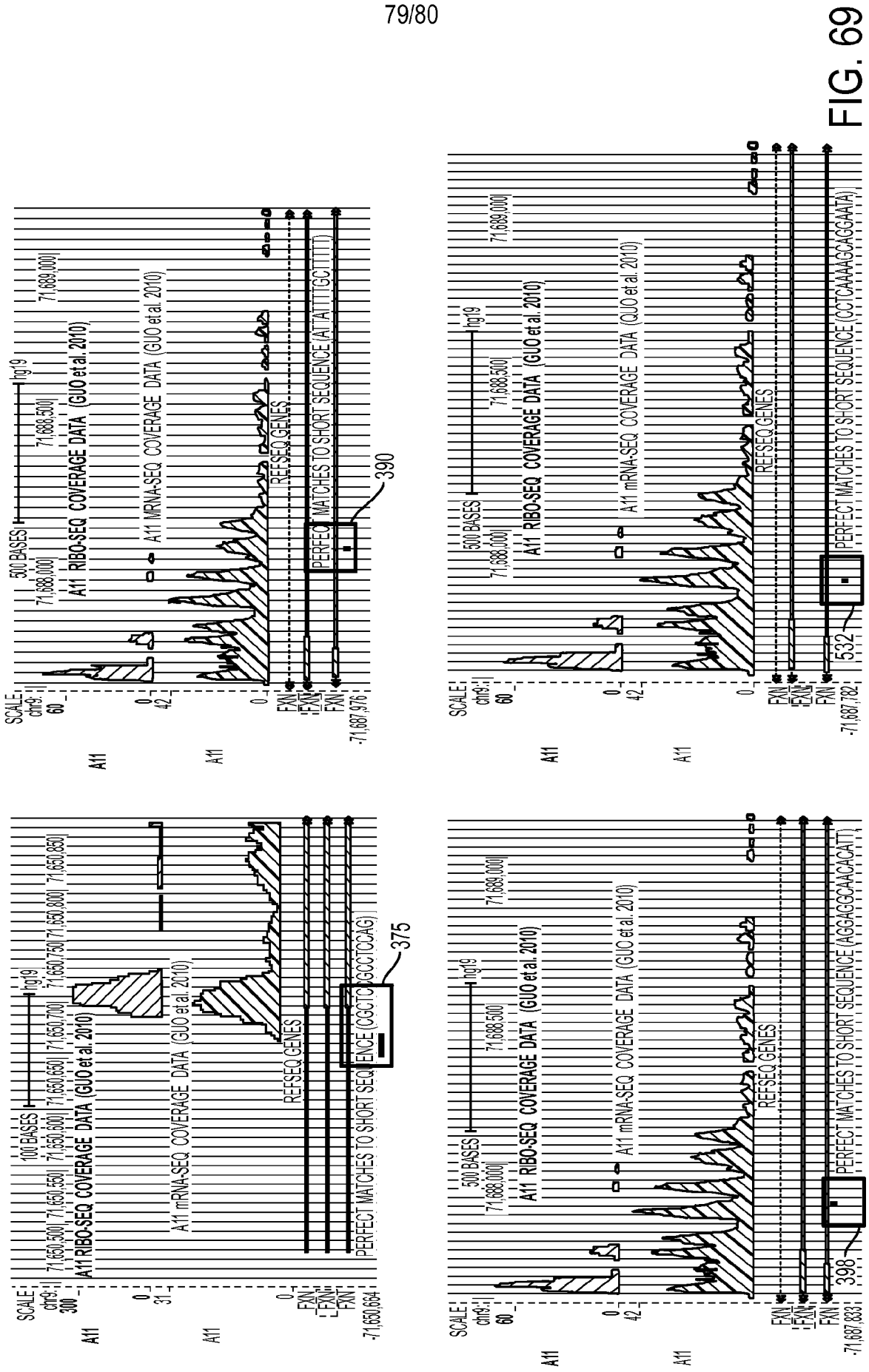

A11 RIBO-SEQ COVERAGE DATA (GUO et al. 2010)
A11 mRNA-SEQ COVERAGE DATA (GUO et al. 2010)
REFSEQ GENES
PERFECT MATCHES TO SHORT SEQUENCE (ATATTTGCTTTTT)
390
PERFECT MATCHES TO SHORT SEQUENCE (GCTCAAAAGCAGGAATA)
532
PERFECT MATCHES TO SHORT SEQUENCE (CGCTCCCAG)
375
PERFECT MATCHES TO SHORT SEQUENCE (AGGAGGCAACACATT)
398

FIG. 69

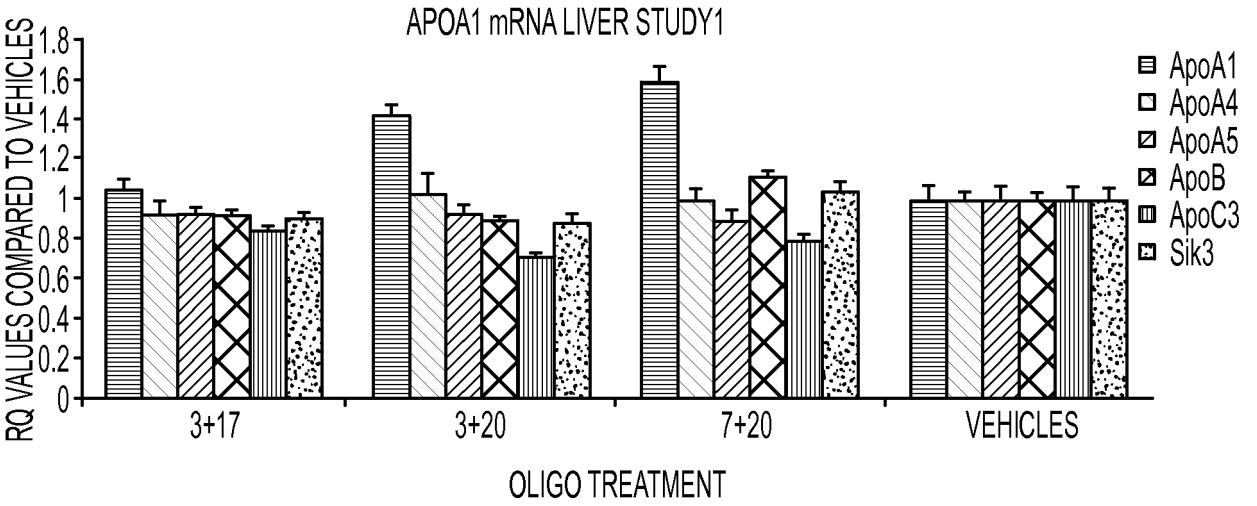


FIG. 70A

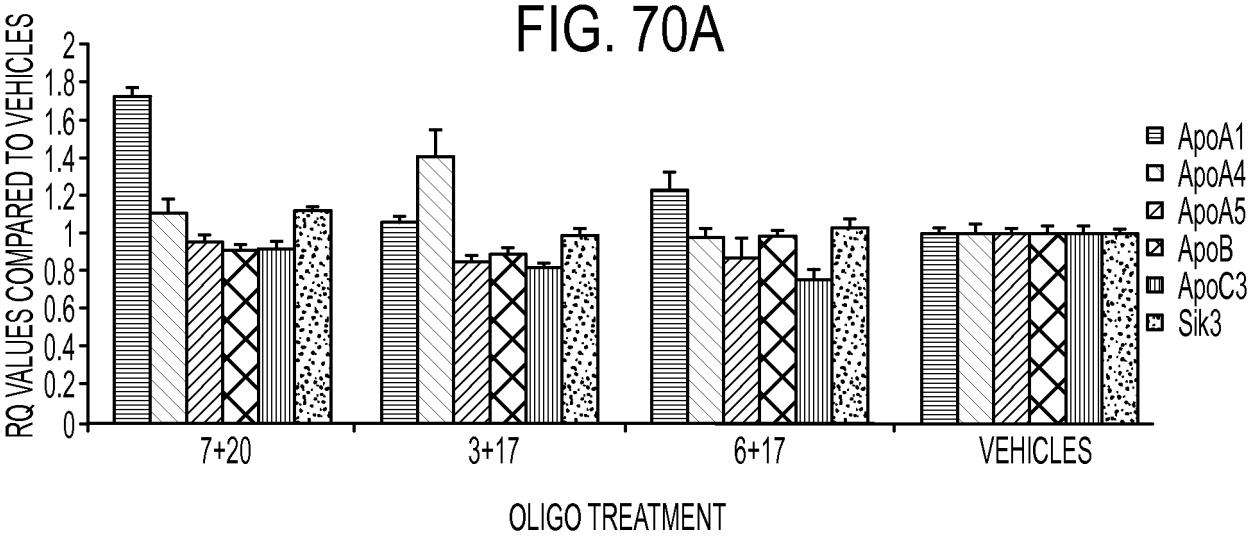


FIG. 70B

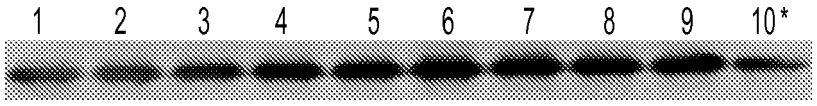


FIG. 70C

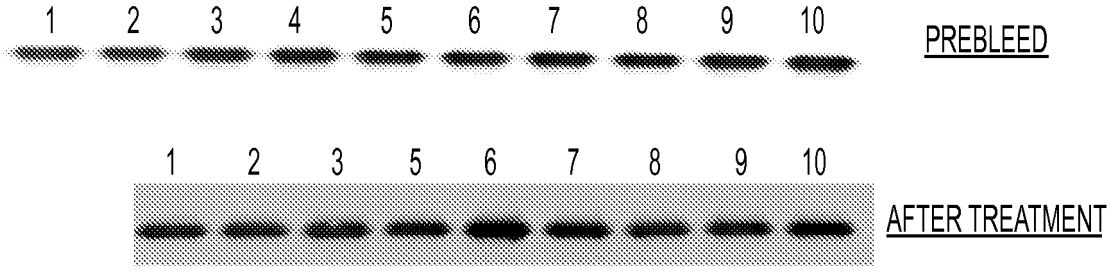


FIG. 70D