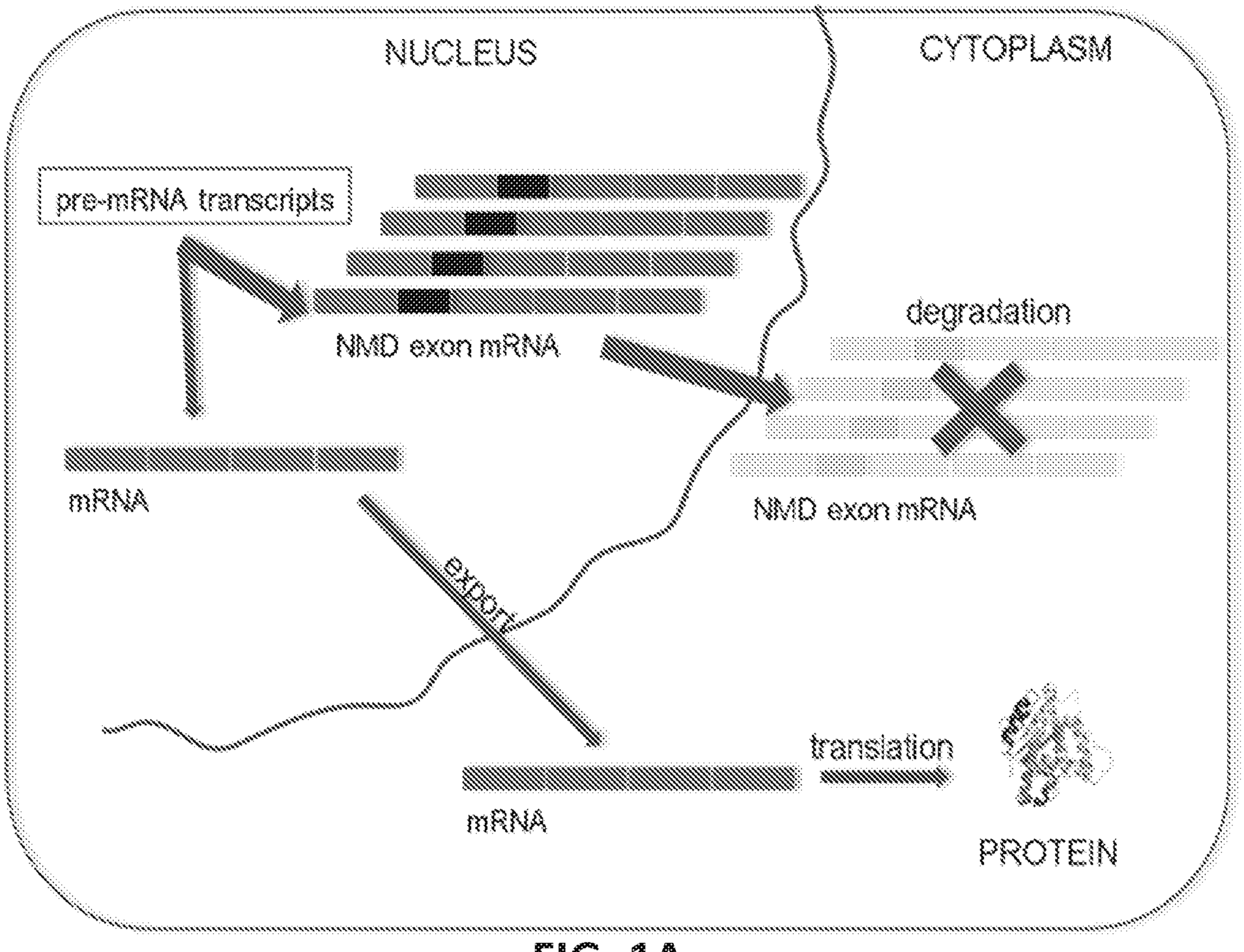

NUCLEUS
CYTOPLASM
pre-mRNA transcripts
NMD exon mRNA
degradation
mRNA
NMD exon mRNA
export
translation
mRNA
PROTEIN

FIG. 1A

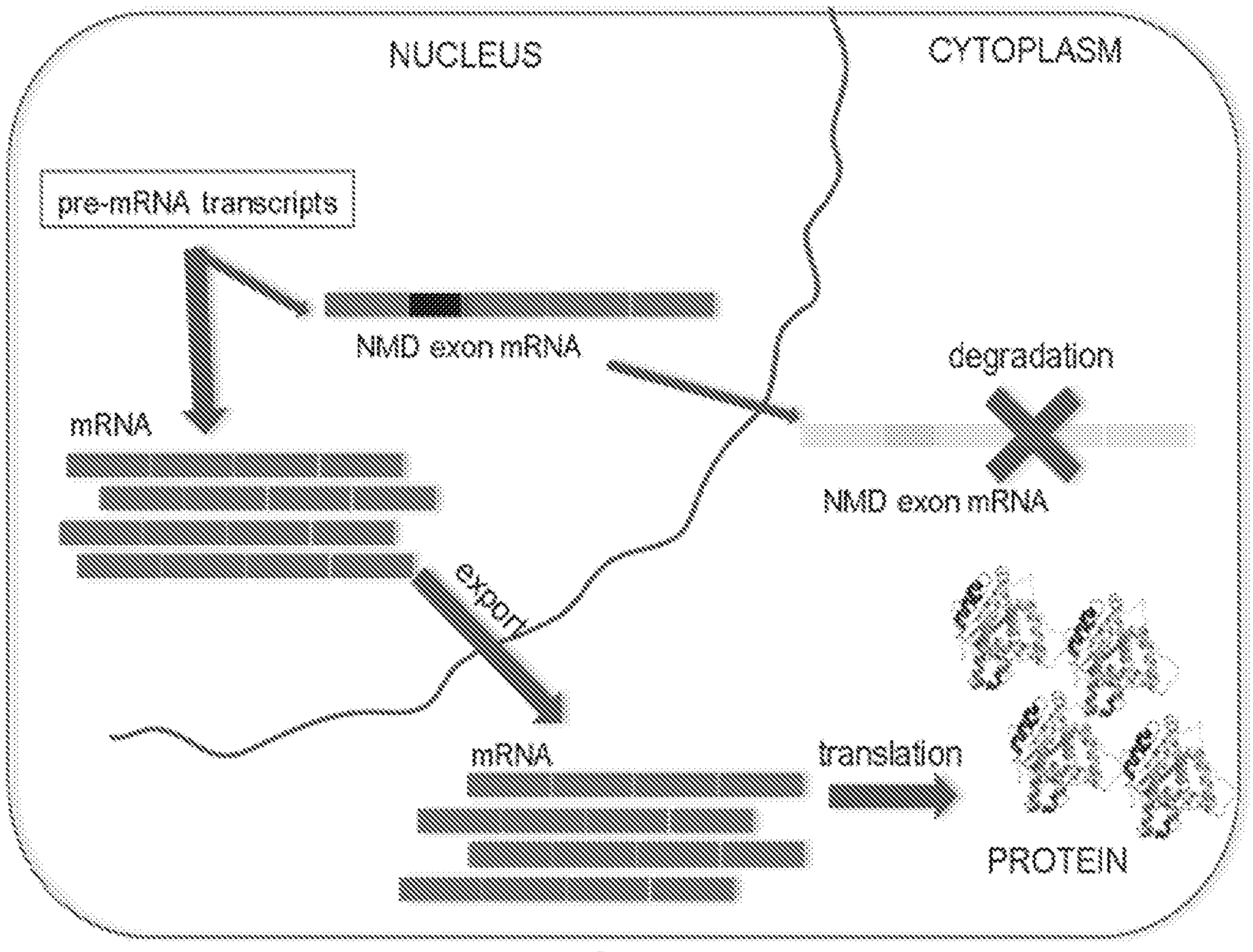

NUCLEUS
CYTOPLASM
pre-mRNA transcripts
NMD exon mRNA
degradation
mRNA
NMD exon mRNA
export
mRNA
translation
PROTEIN

FIG. 1B

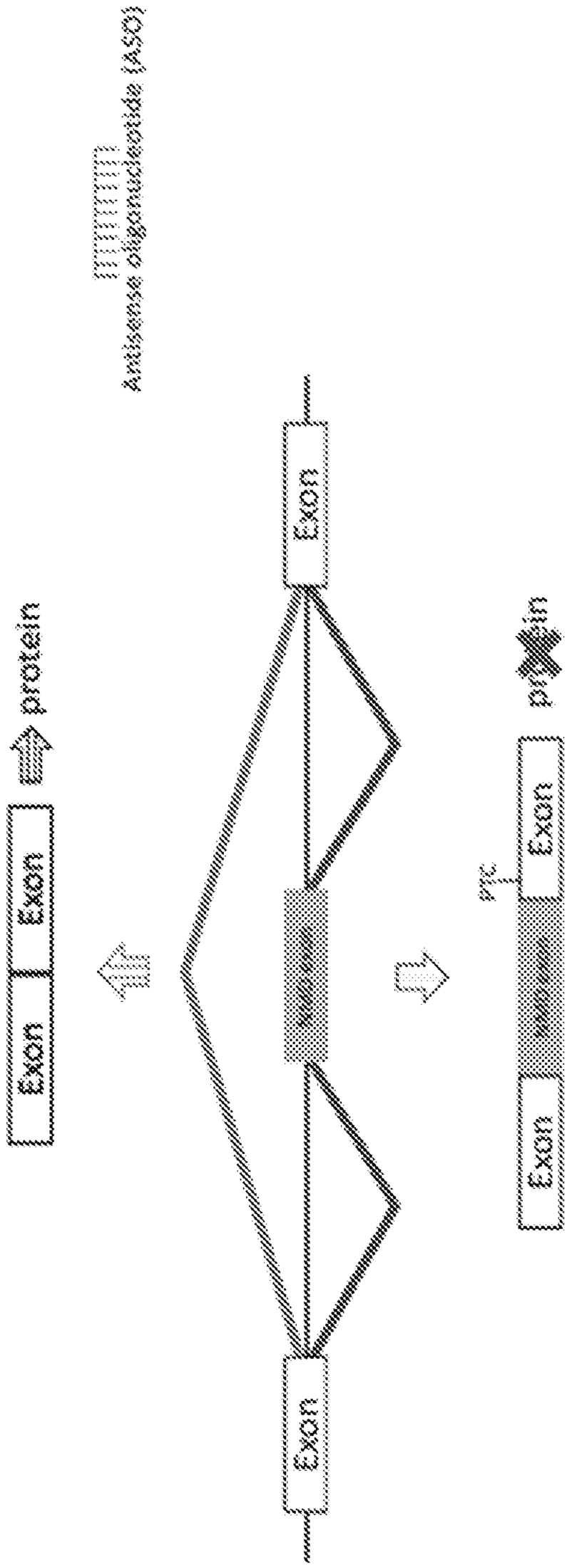

Antisense oligonucleotide (ASO)
Exon
protein
Exon
Exon
Exon
pre-
Exon
protein
Exon

FIG. 1C

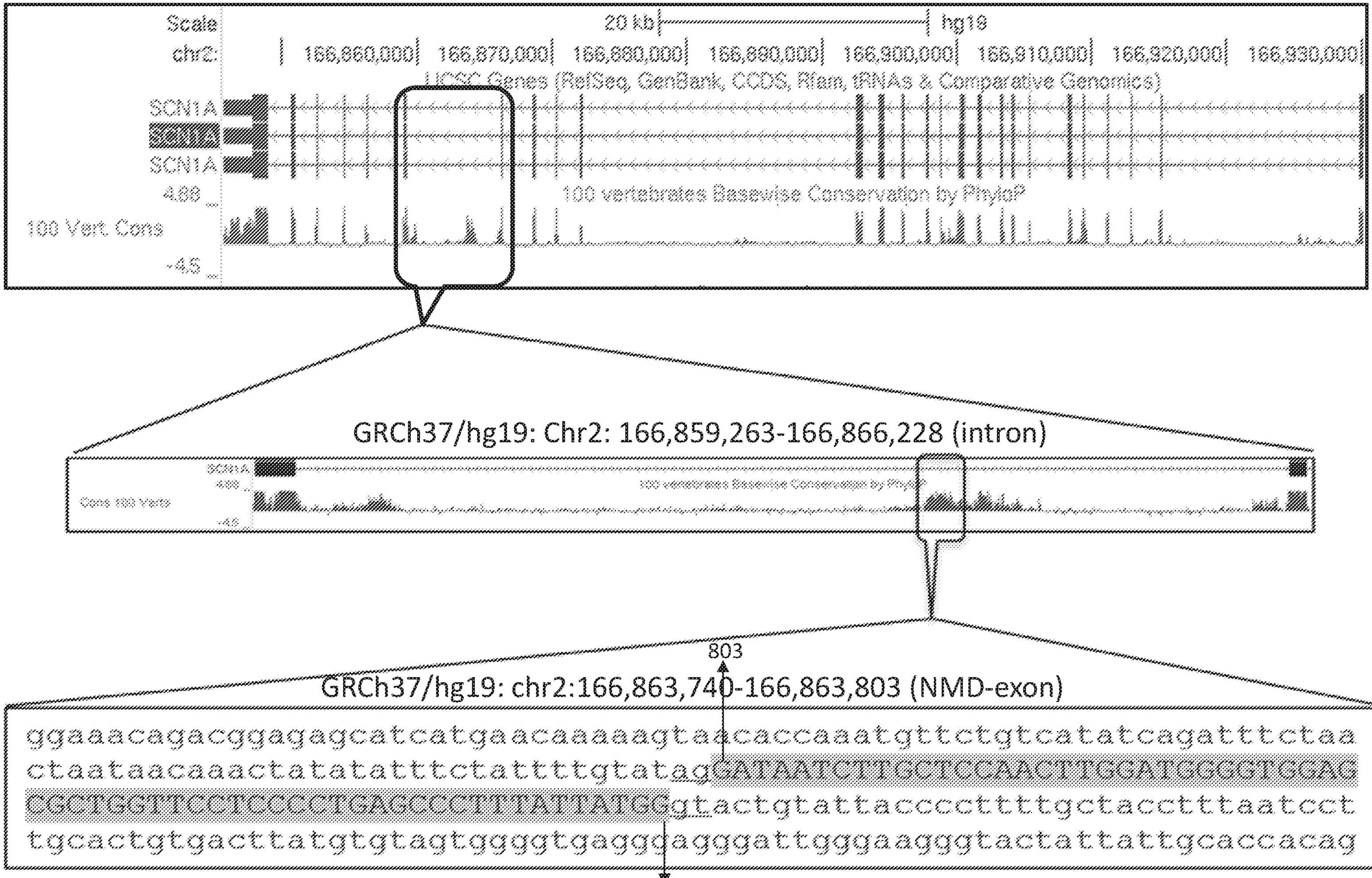

Scale
20 kb
hg19
chr2:
166,860,000
166,870,000
166,880,000
166,890,000
166,900,000
166,910,000
166,920,000
166,930,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
SCN1A
SCN2A
SCN1A
4.88
100 vertebrates Basewise Conservation by PhyloP
100 Vert. Cons
-4.5
GRCh37/hg19: Chr2: 166,859,263-166,866,228 (intron)
803
GRCh37/hg19: chr2:166,863,740-166,863,803 (NMD-exon)
ggaaacagacggagagcatcatgaacaaaaaagtaacaccaaatgttctgtcatatcagatttctaa
ctaataacaaactatatatttctatttttgtatagGATAATCTTGCTCCAACTTGGATGGGGTGGAG
CGCTGGTTCCTCCCCTGAGCCCTTTATTATGGgtactgtattaccccttttgctacctttaatcct
tgcactgtgacttatgtgtagtggggtgagggagggattgggaagggtactattattgcaccacag
740

FIG. 2

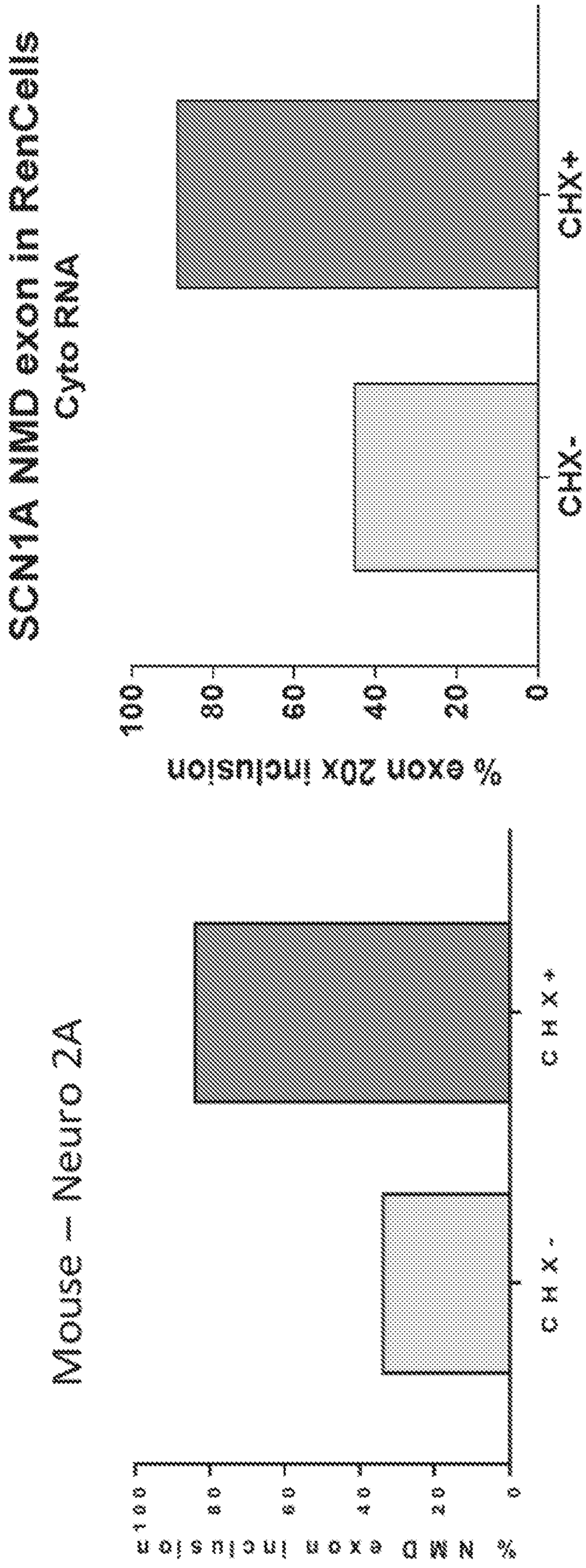

SCN1A NMD exon in RenCells
Cyto RNA
% exon 20x inclusion
0
20
40
60
80
100
CHX-
CHX+

FIG. 3B

Mouse – Neuro 2A
% exon 20x inclusion
0
20
40
60
80
100
CHX-
CHX+

FIG. 3A

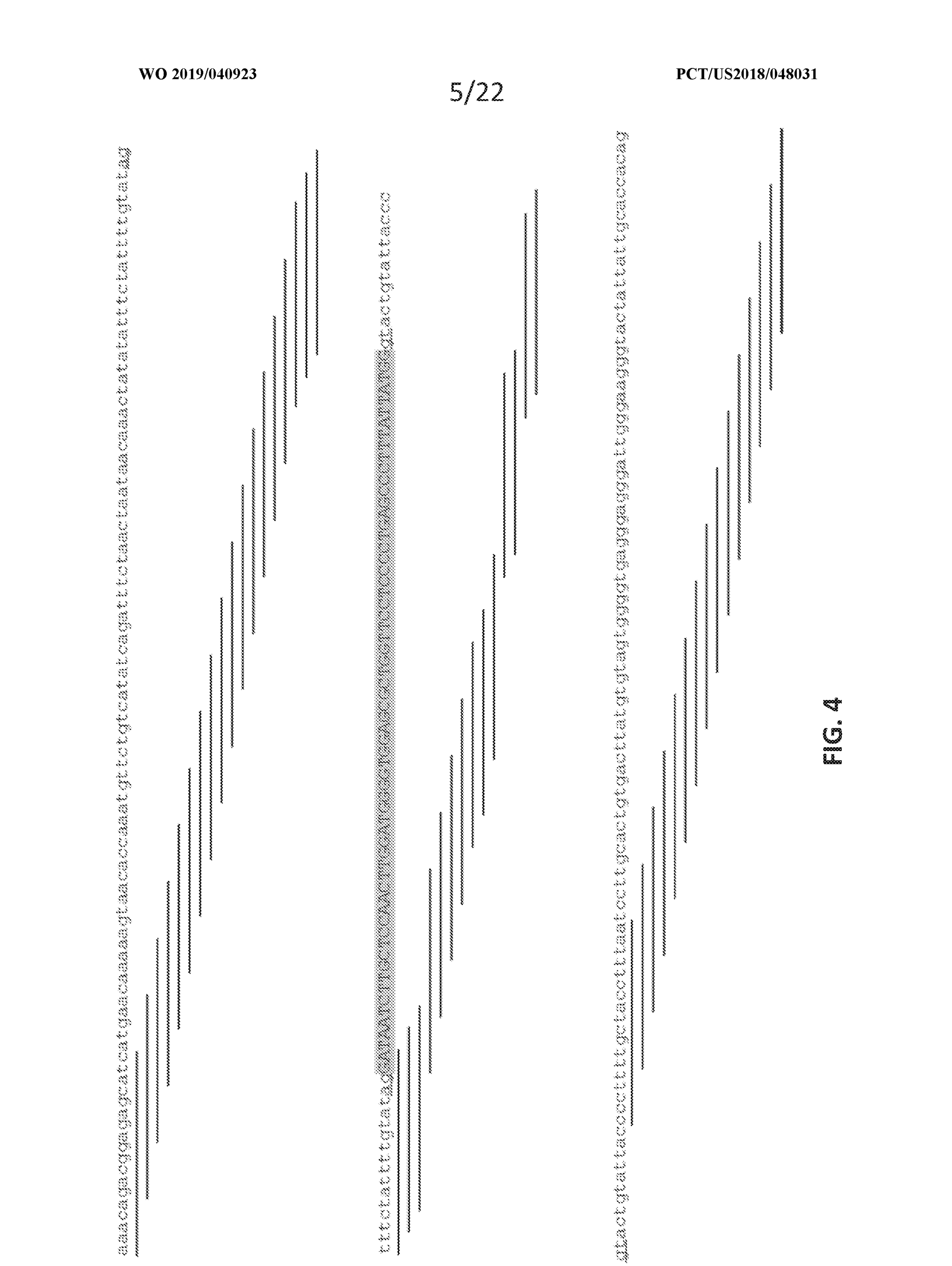


FIG. 4

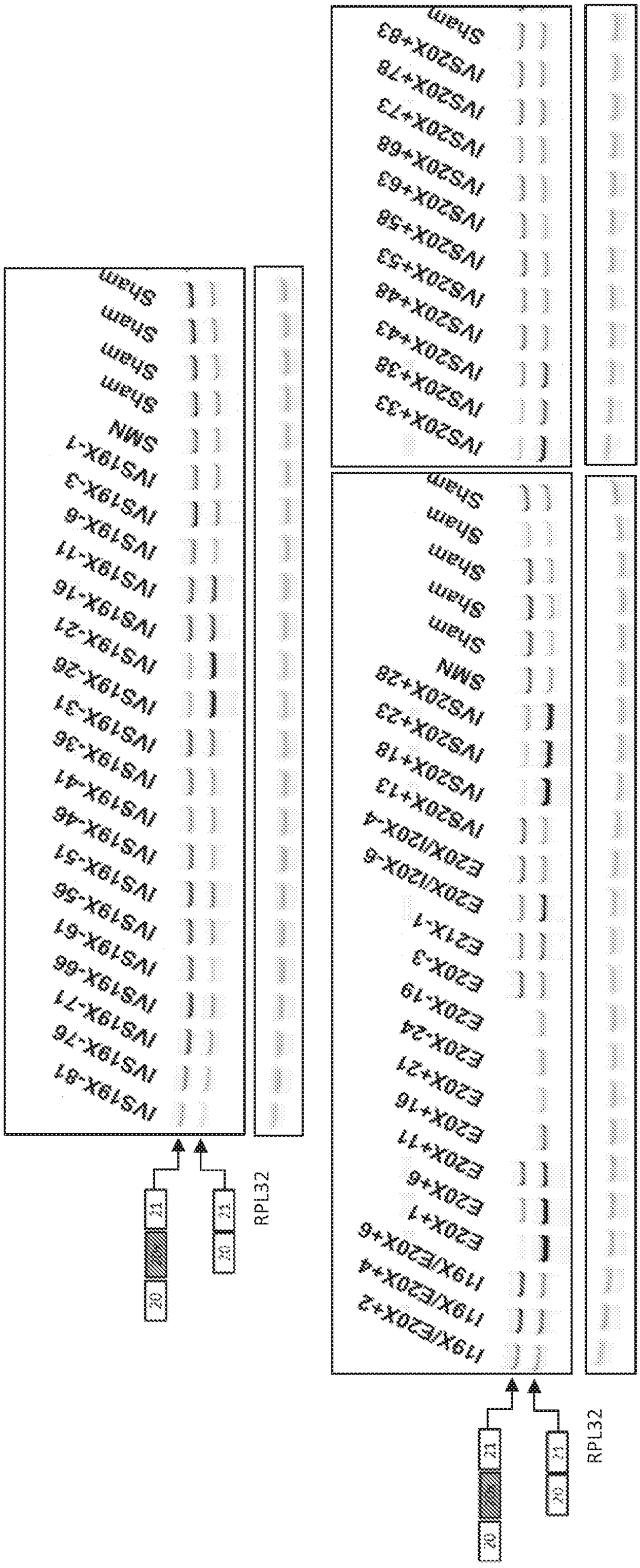

Sham
WS20X+83
WS20X+78
WS20X+73
WS20X+68
WS20X+63
WS20X+58
WS20X+53
WS20X+48
WS20X+43
WS20X+38
WS20X+33
Sham
Wem
Sham
Wem
SMN
WS19X-1
WS19X-3
WS19X-6
WS19X-11
WS19X-16
WS19X-21
WS19X-26
WS19X-31
WS19X-36
WS19X-41
WS19X-46
WS19X-51
WS19X-56
WS19X-61
WS19X-66
WS19X-71
WS19X-76
WS19X-81
RPL32
21
20
Sham
Wem
Sham
Wem
SMN
WS20X+28
WS20X+23
WS20X+18
WS20X+13
WS20X+8
WS20X+3
E20X-2
E20X-7
E20X-12
E20X-17
E20X-22
E20X-27
E20X+21
E20X+16
E20X+11
E20X+6
E20X+1
WS19X/E20X+6
WS19X/E20X+4
WS19X/E20X+2
RPL32
21
20

FIG. 5A

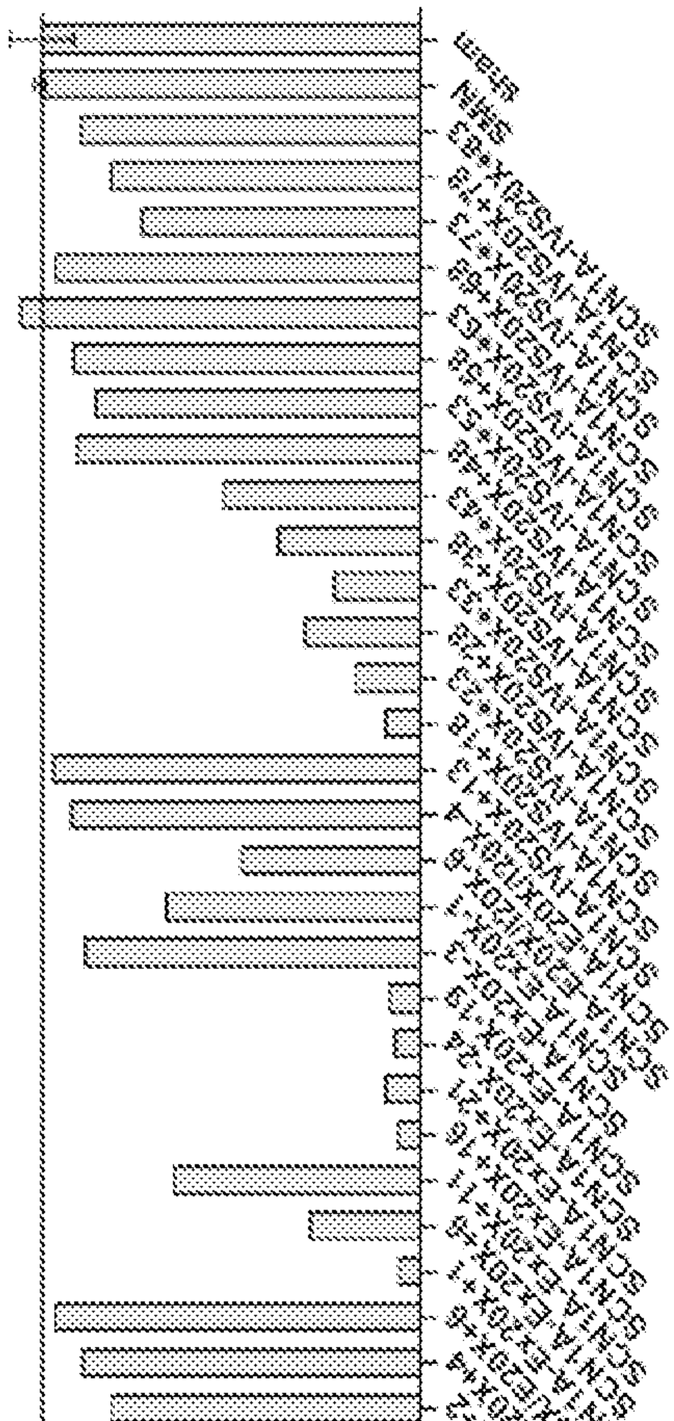


FIG. 5B

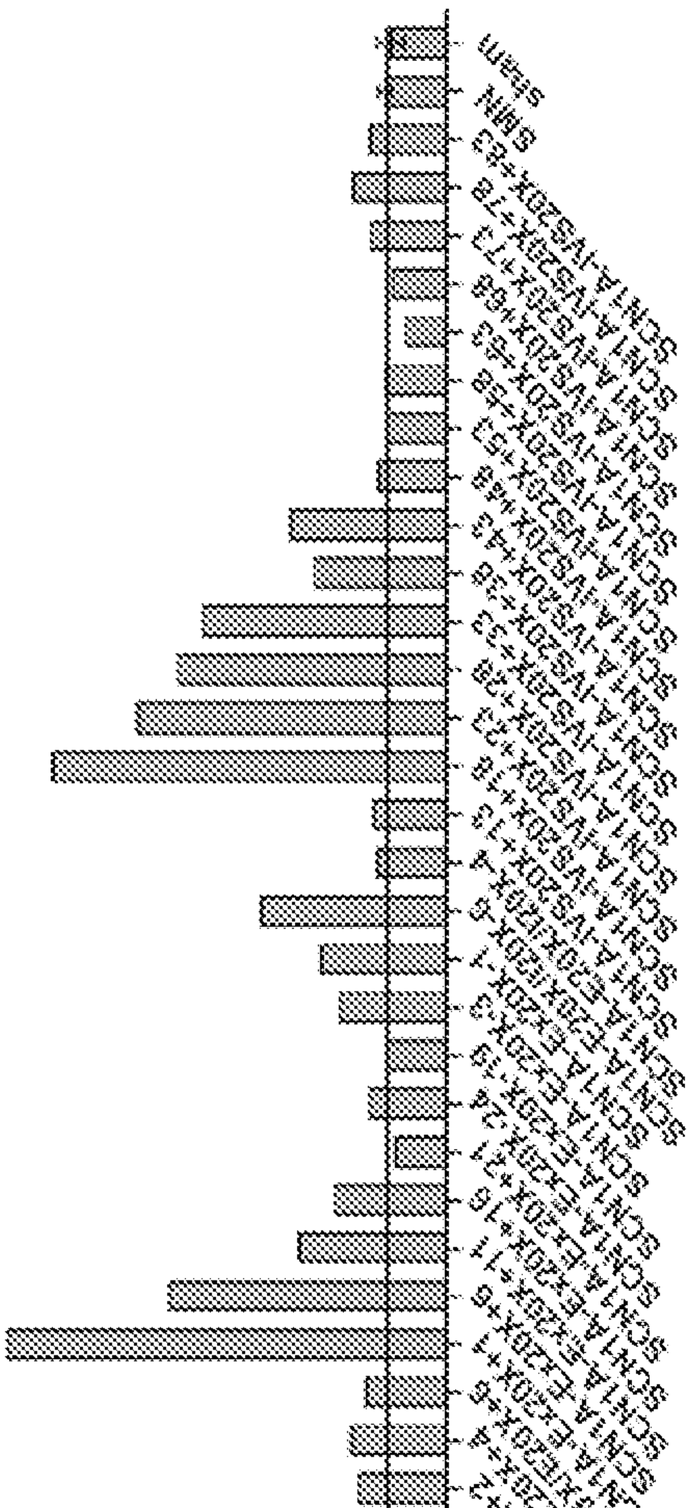


FIG. 5C

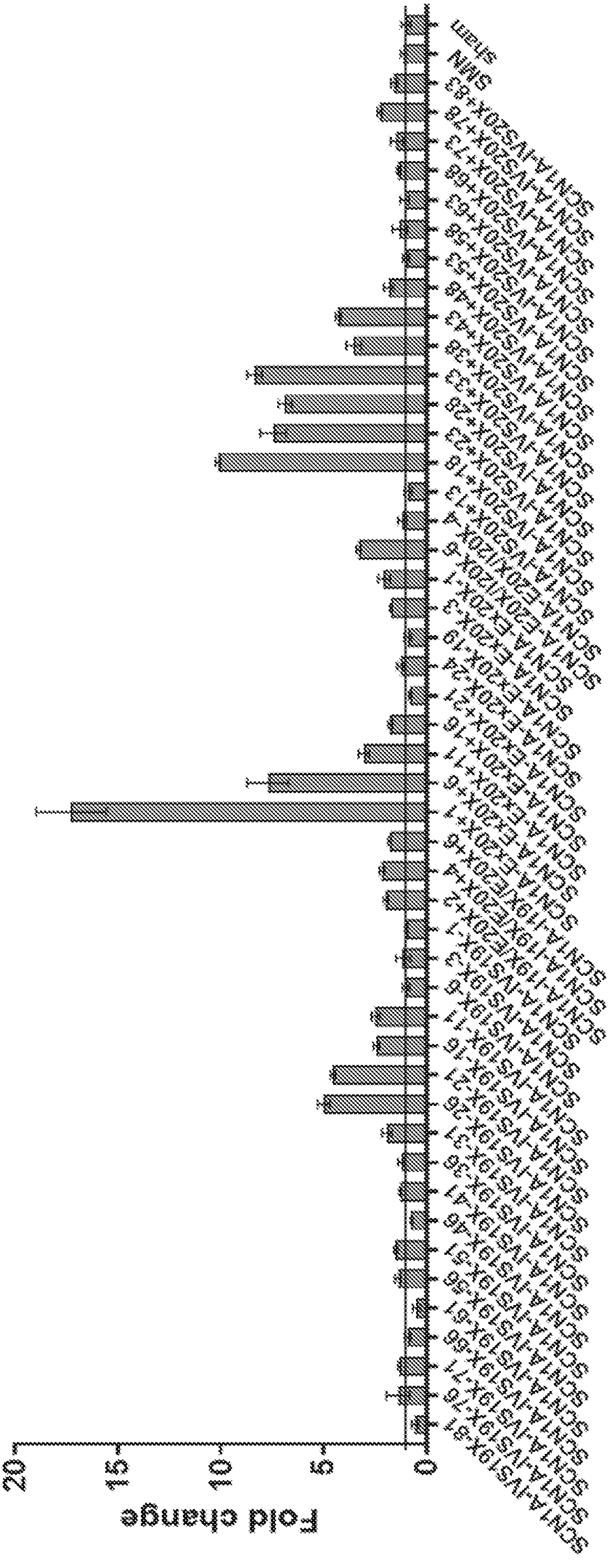


FIG. 6

Sodium voltage-gaited channel alpha subunit

Gene	Approved Name	Chromosome	
SCN1A	sodium voltage-gated channel alpha subunit 1	2q24.3	⬅
SCN2A	sodium voltage-gated channel alpha subunit 2	2q24.3	⬅
SCN3A	sodium voltage-gated channel alpha subunit 3	2q24.3	⬅
SCN7A	sodium voltage-gated channel alpha subunit 7	2q24.3	X
SCN8A	sodium voltage-gated channel alpha subunit 8	12q13.13	⬅
SCN9A	sodium voltage-gated channel alpha subunit 9	2q24.3	⬅
SCN10A	sodium voltage-gated channel alpha subunit 10	3p22.2	X
SCN11A	sodium voltage-gated channel alpha subunit 11	3p22.2	X

X: no expression detected

FIG. 7A

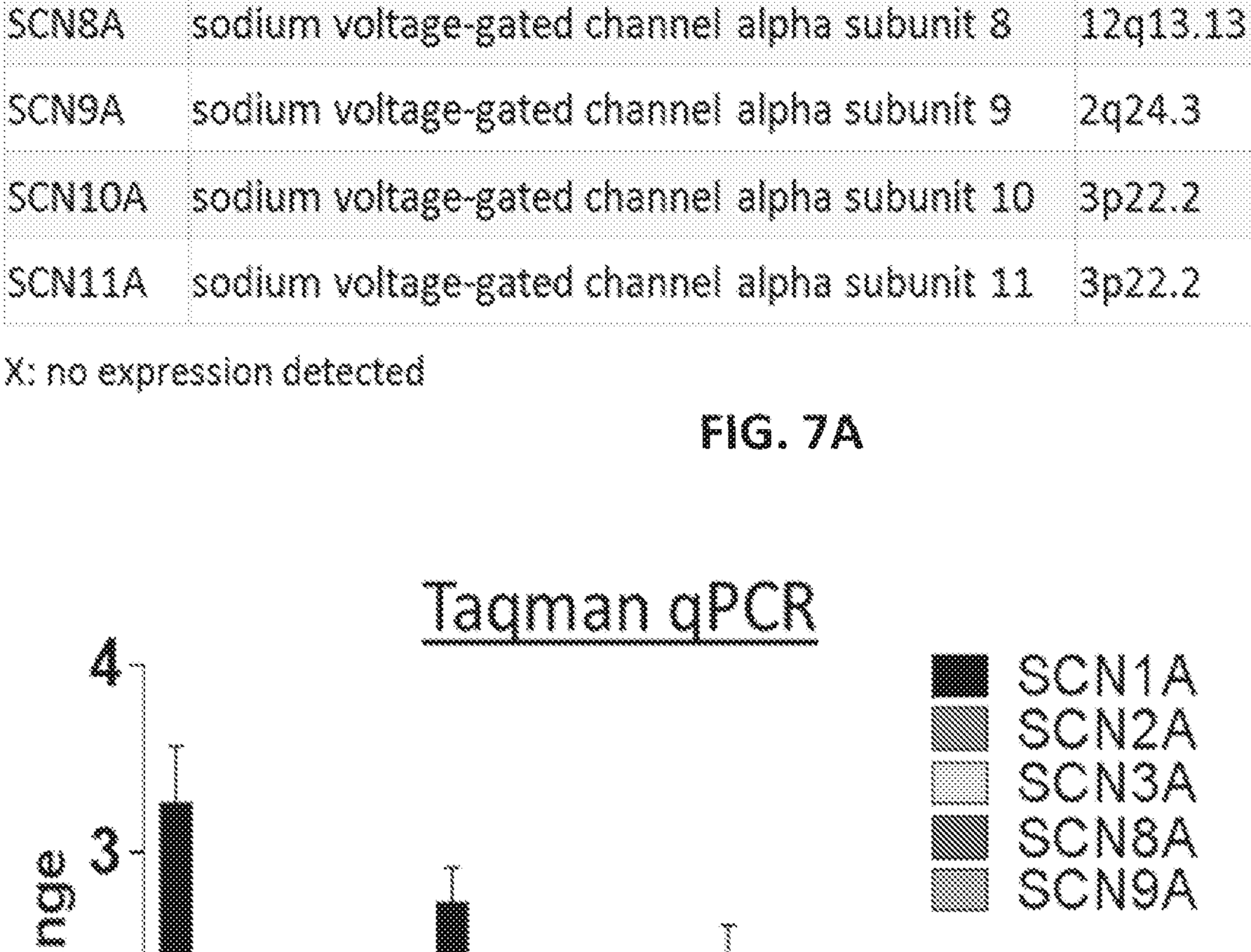


FIG. 7B

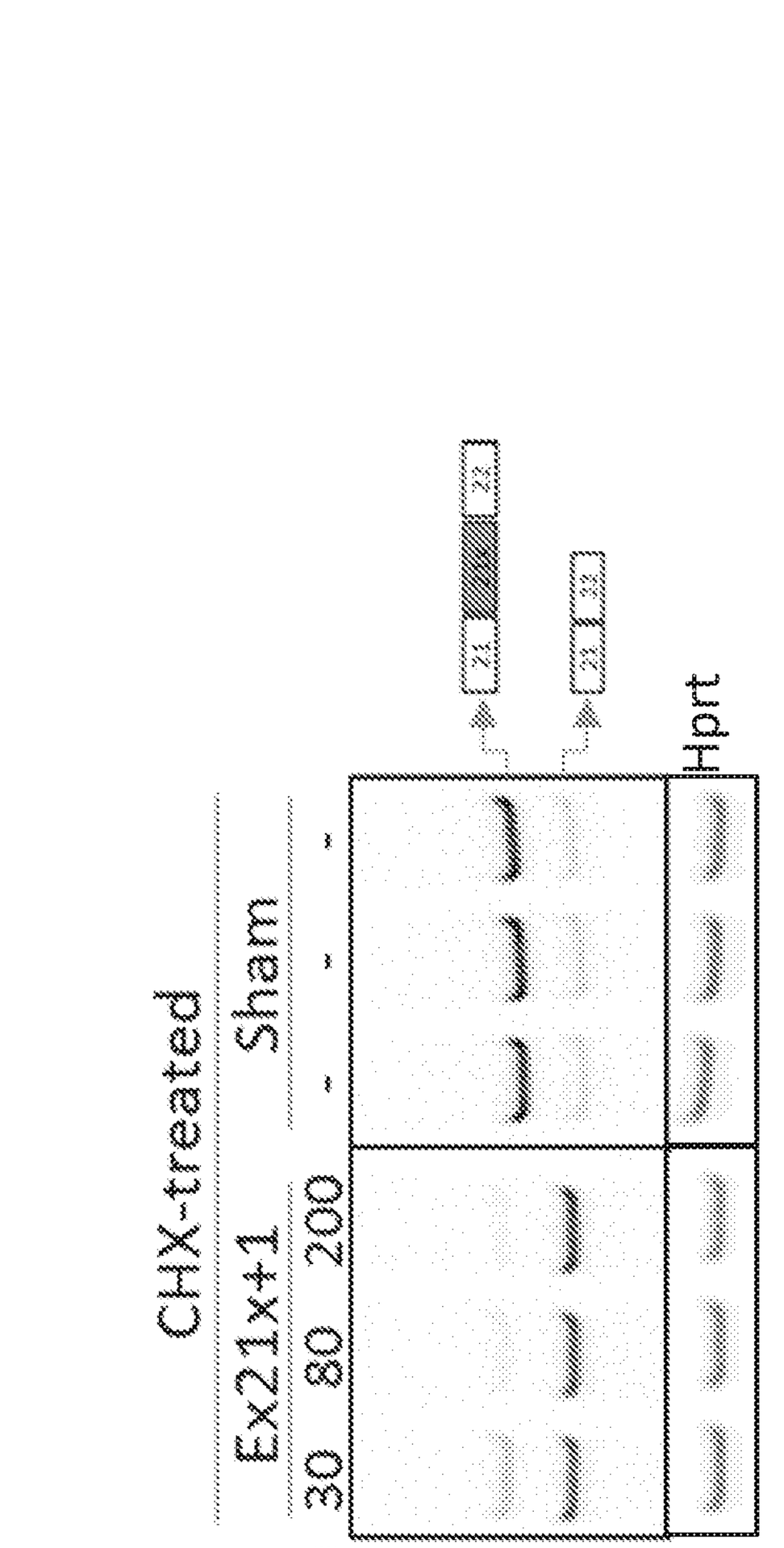


FIG. 8A

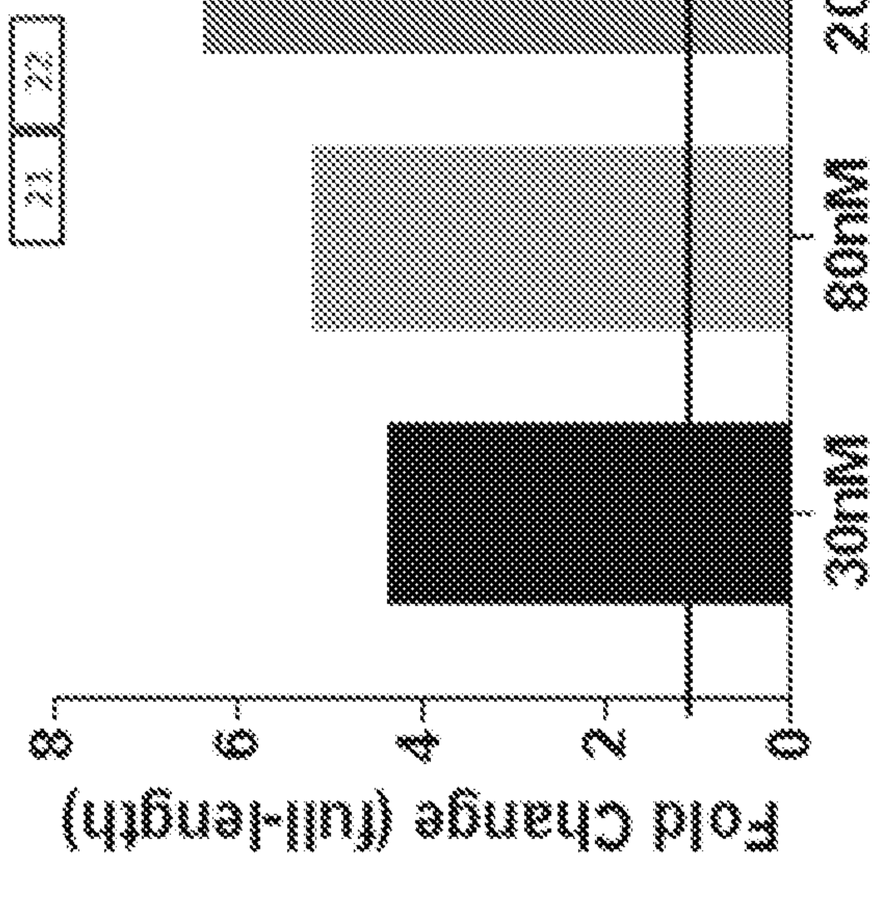


FIG. 8C

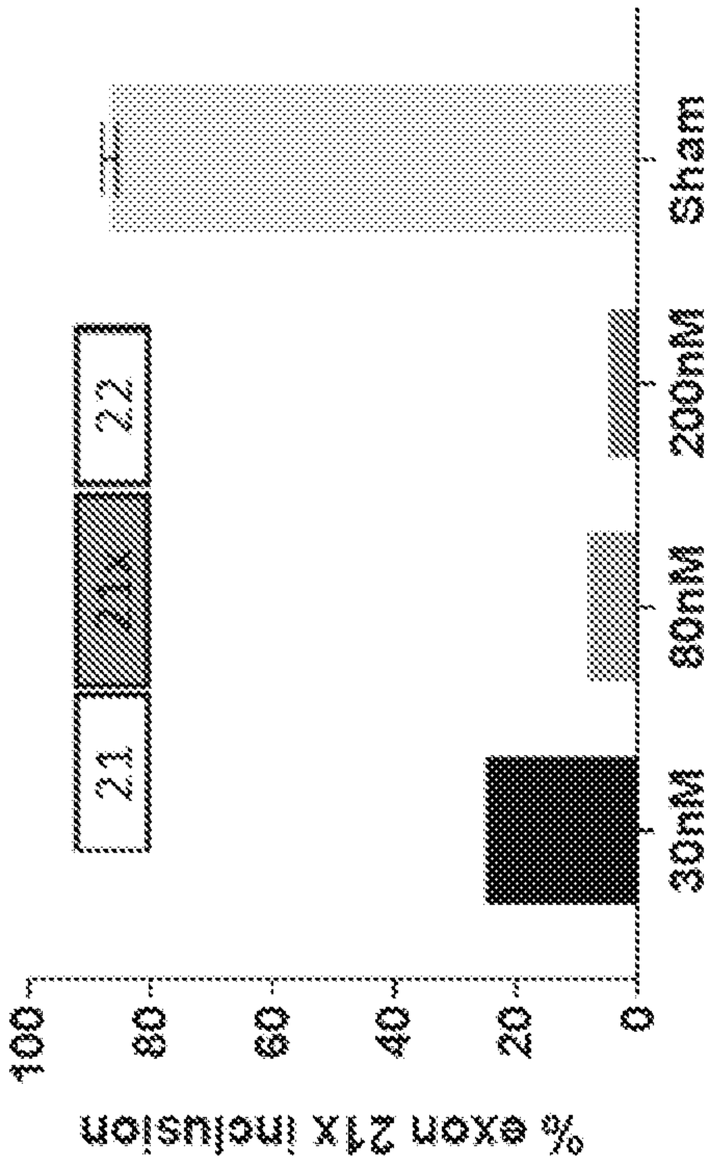


FIG. 8B

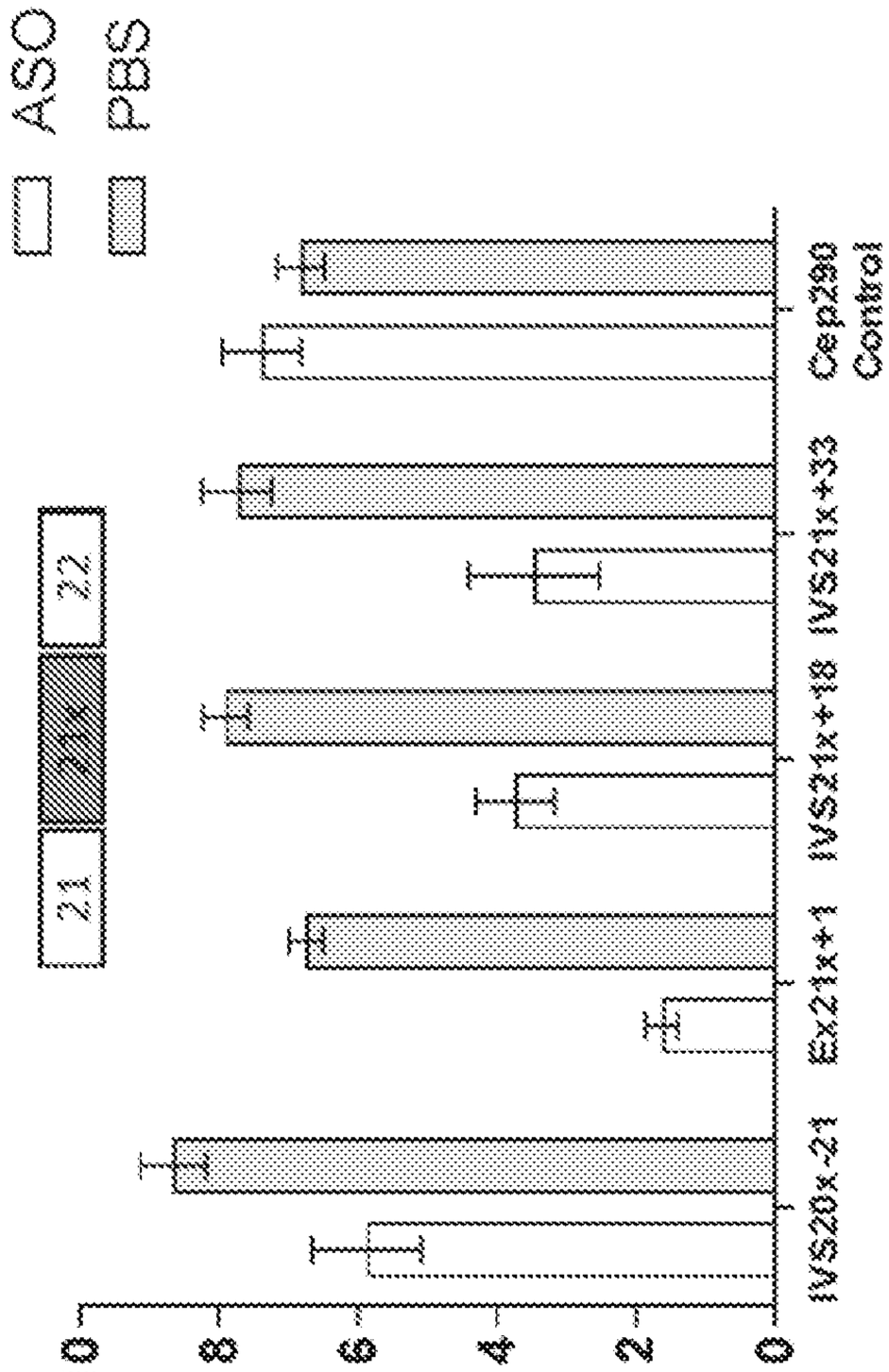


FIG. 9B

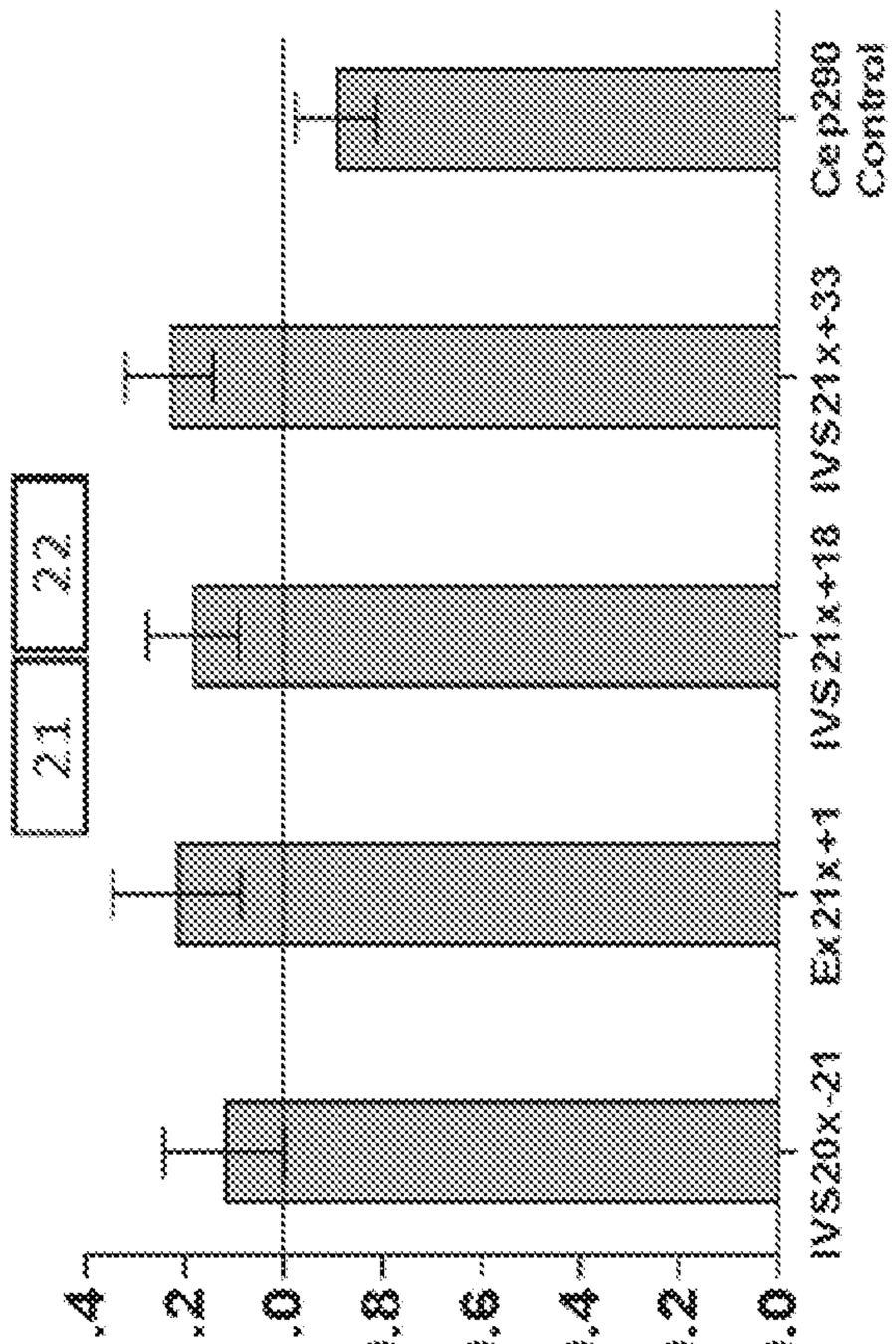


FIG. 9C

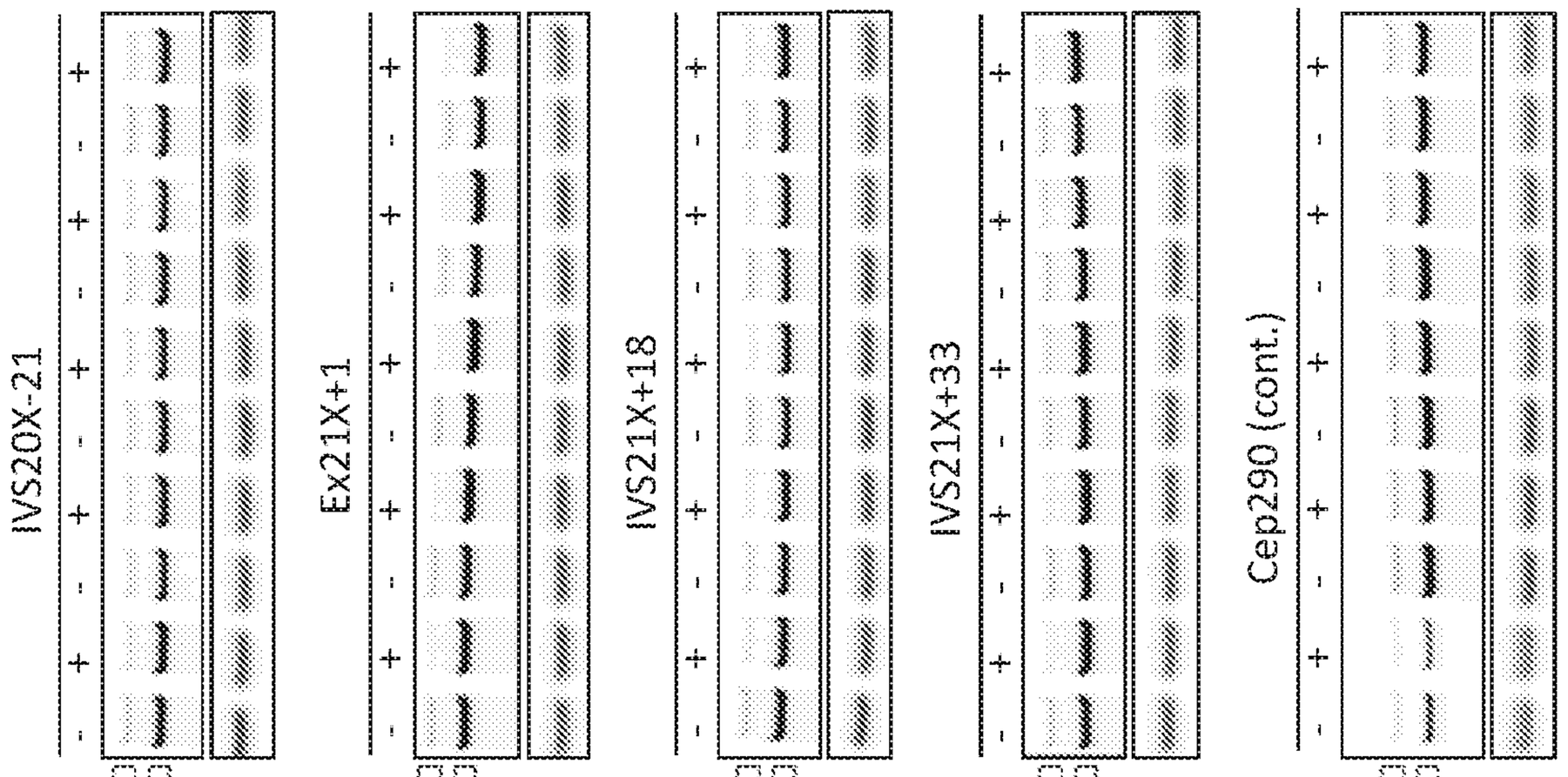


FIG. 9A

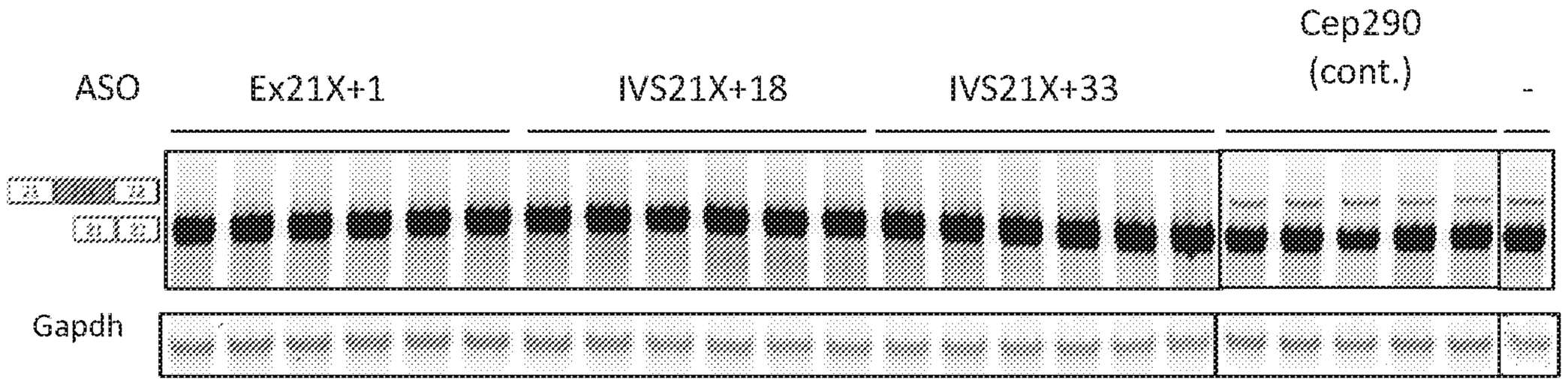


FIG. 10A

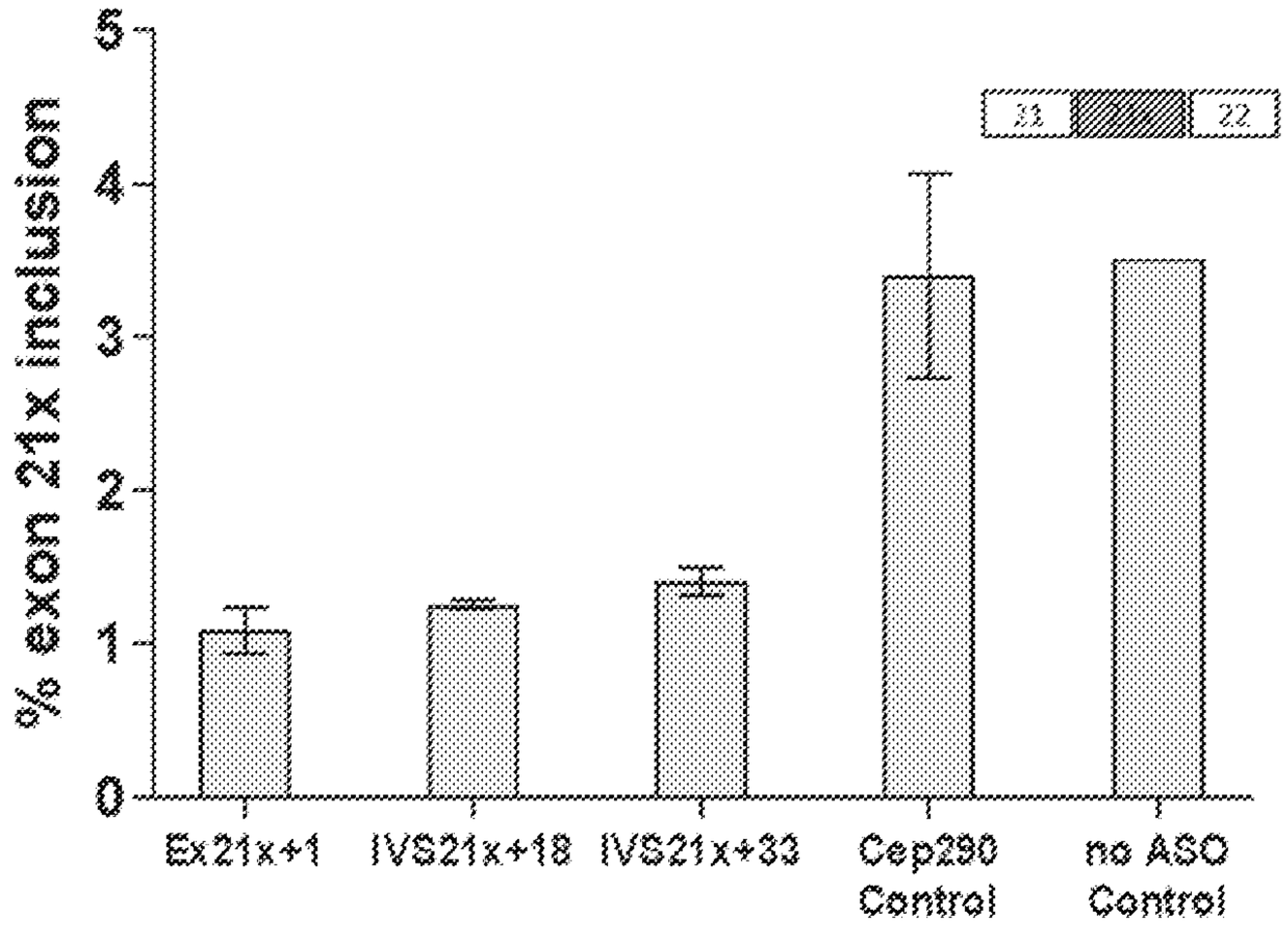


FIG. 10B

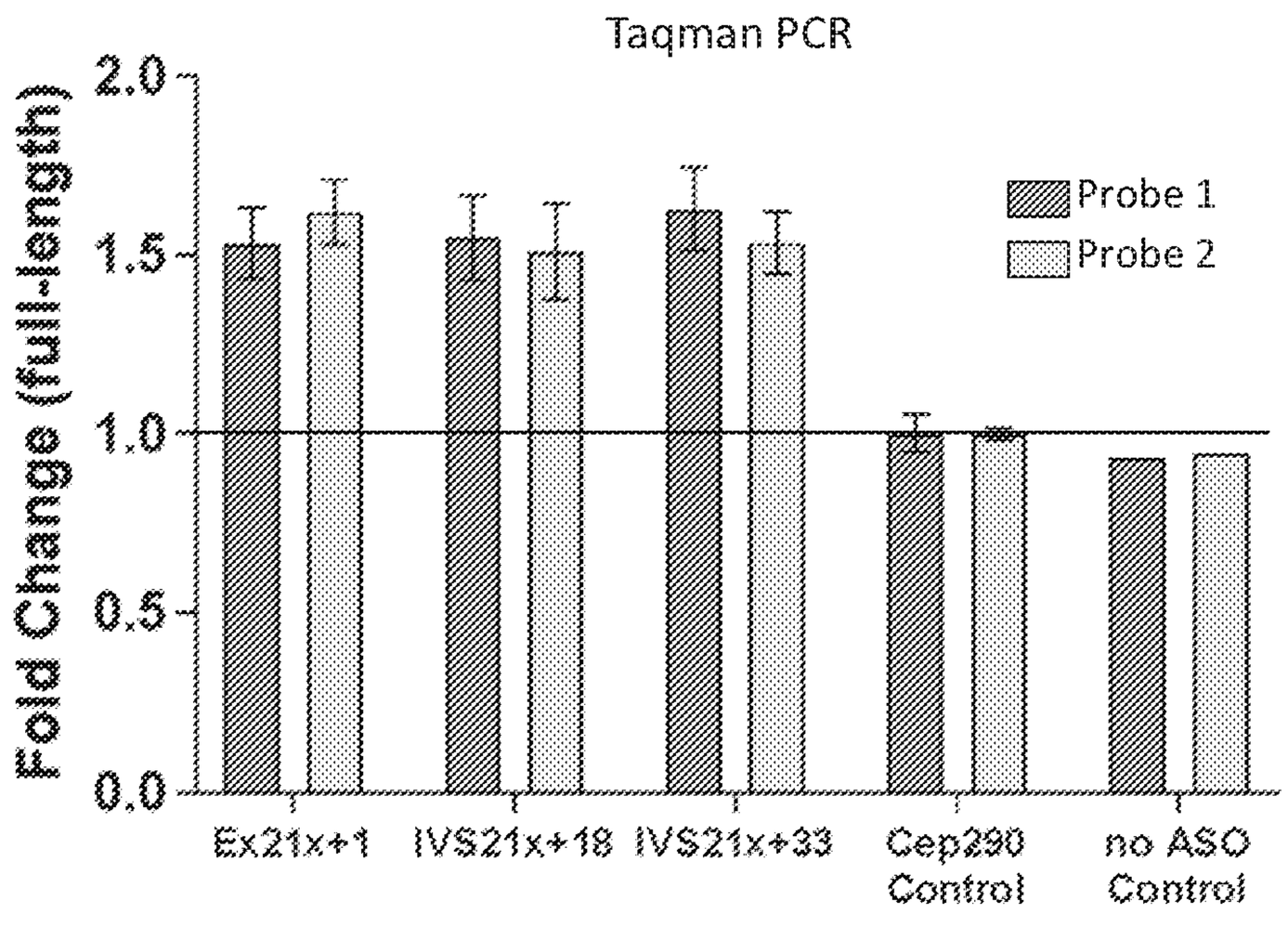


FIG. 10C

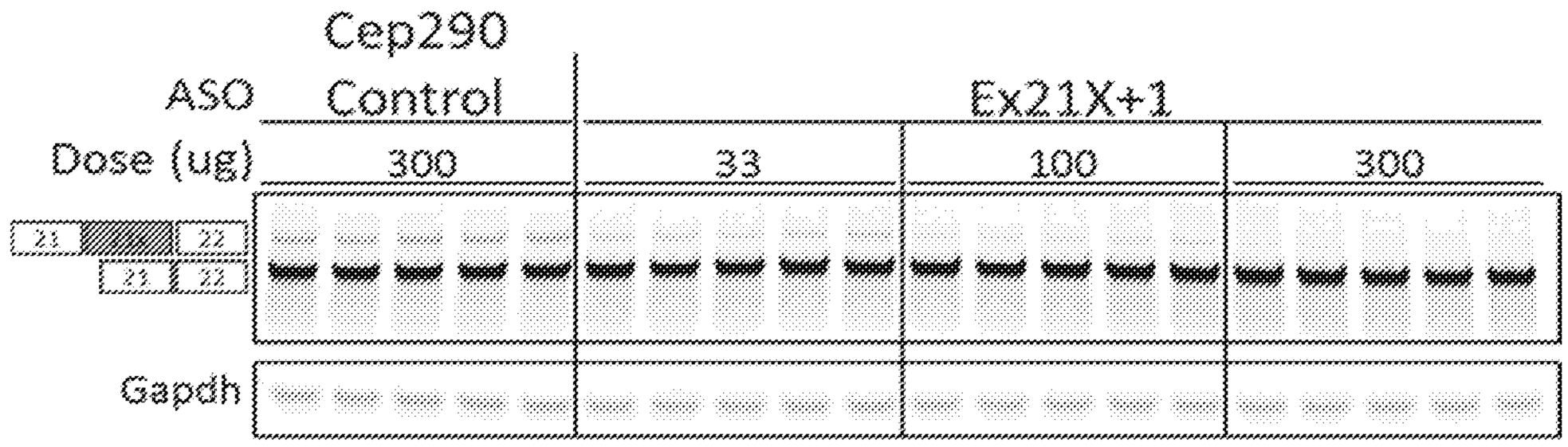


FIG. 11A

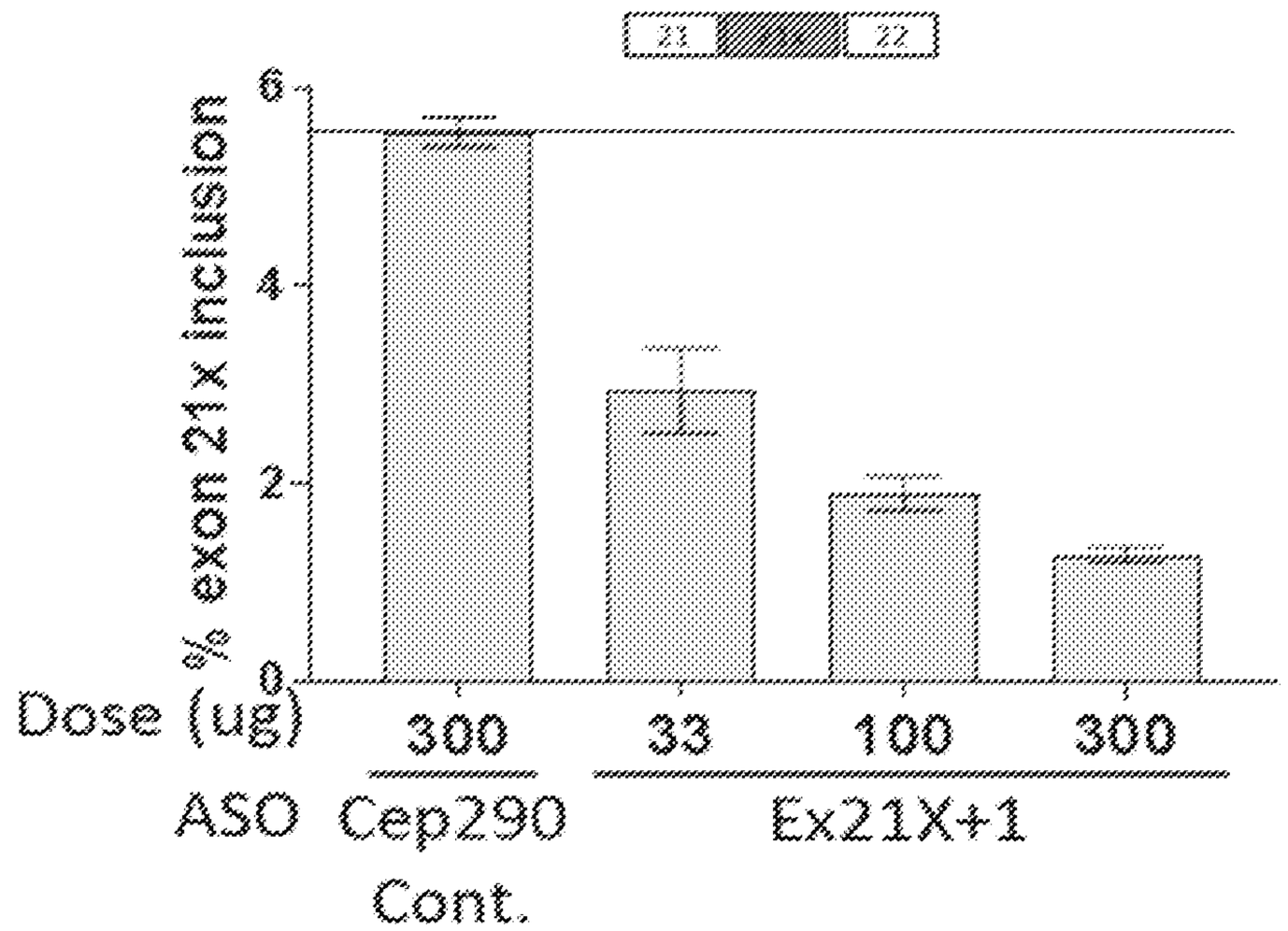


FIG. 11B

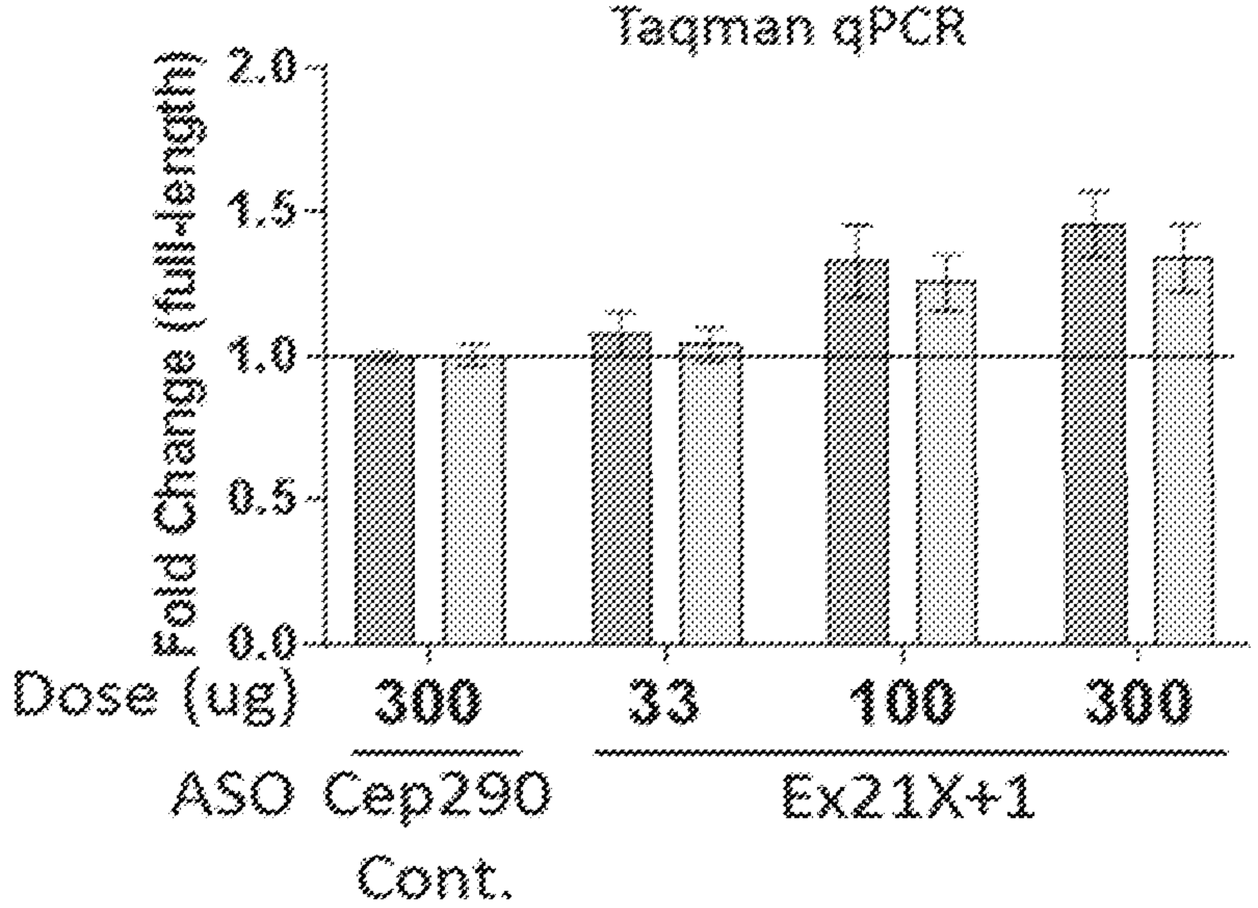


FIG. 11C

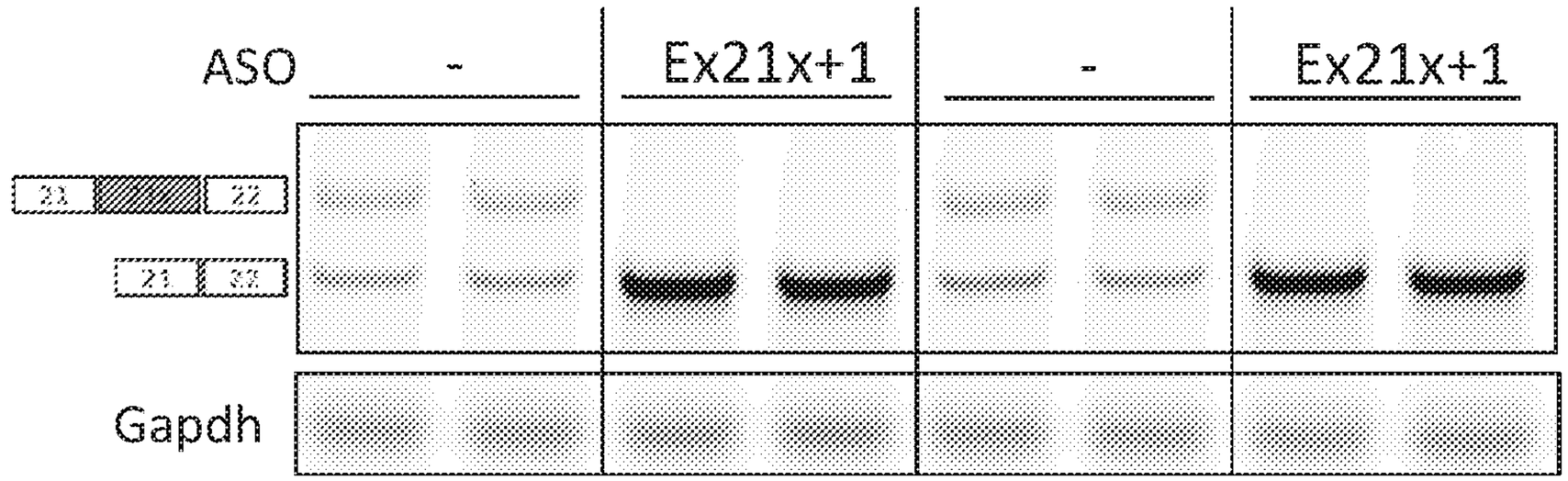


FIG. 12A

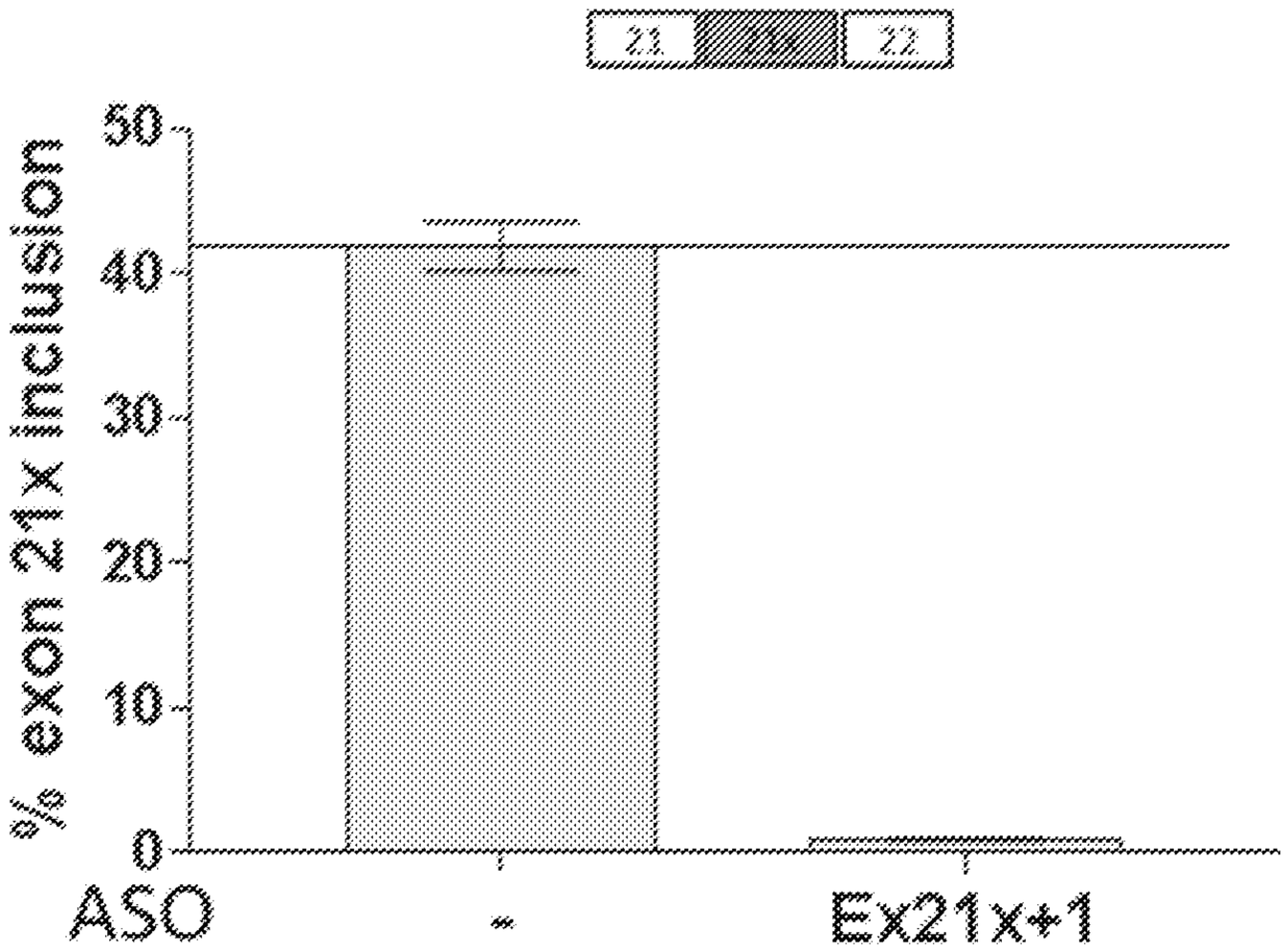


FIG. 12B

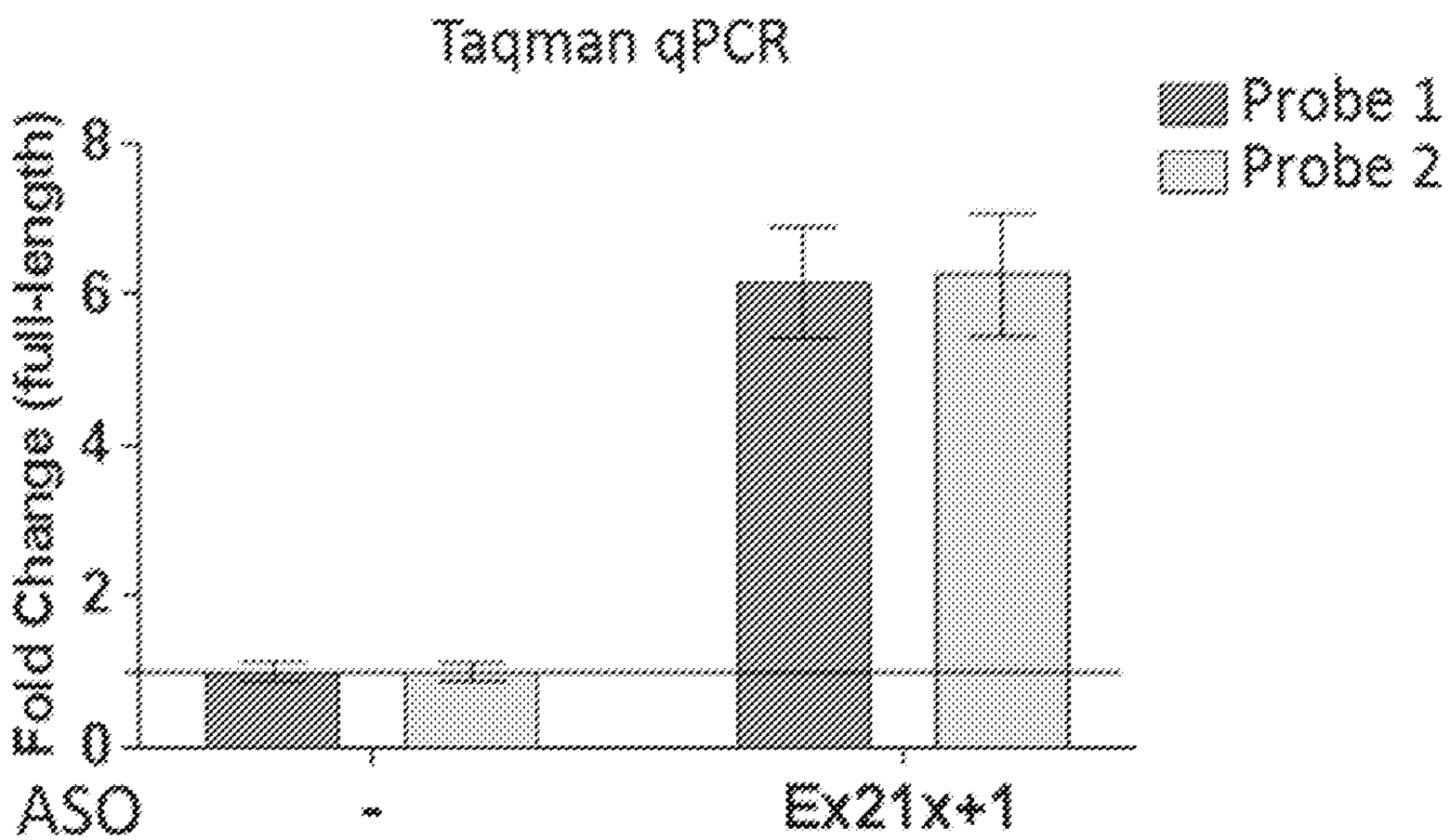


FIG. 12C

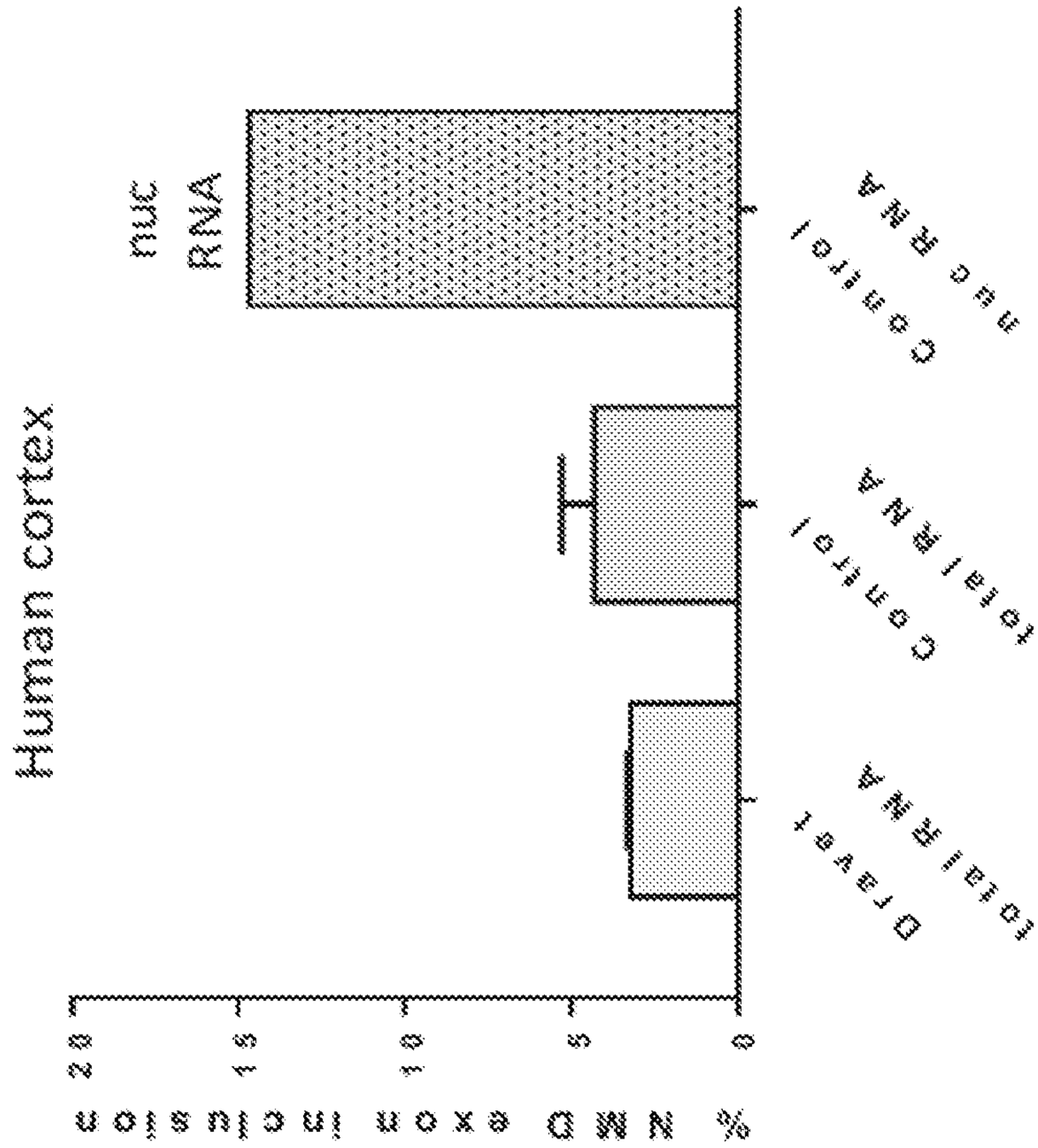


FIG. 13B

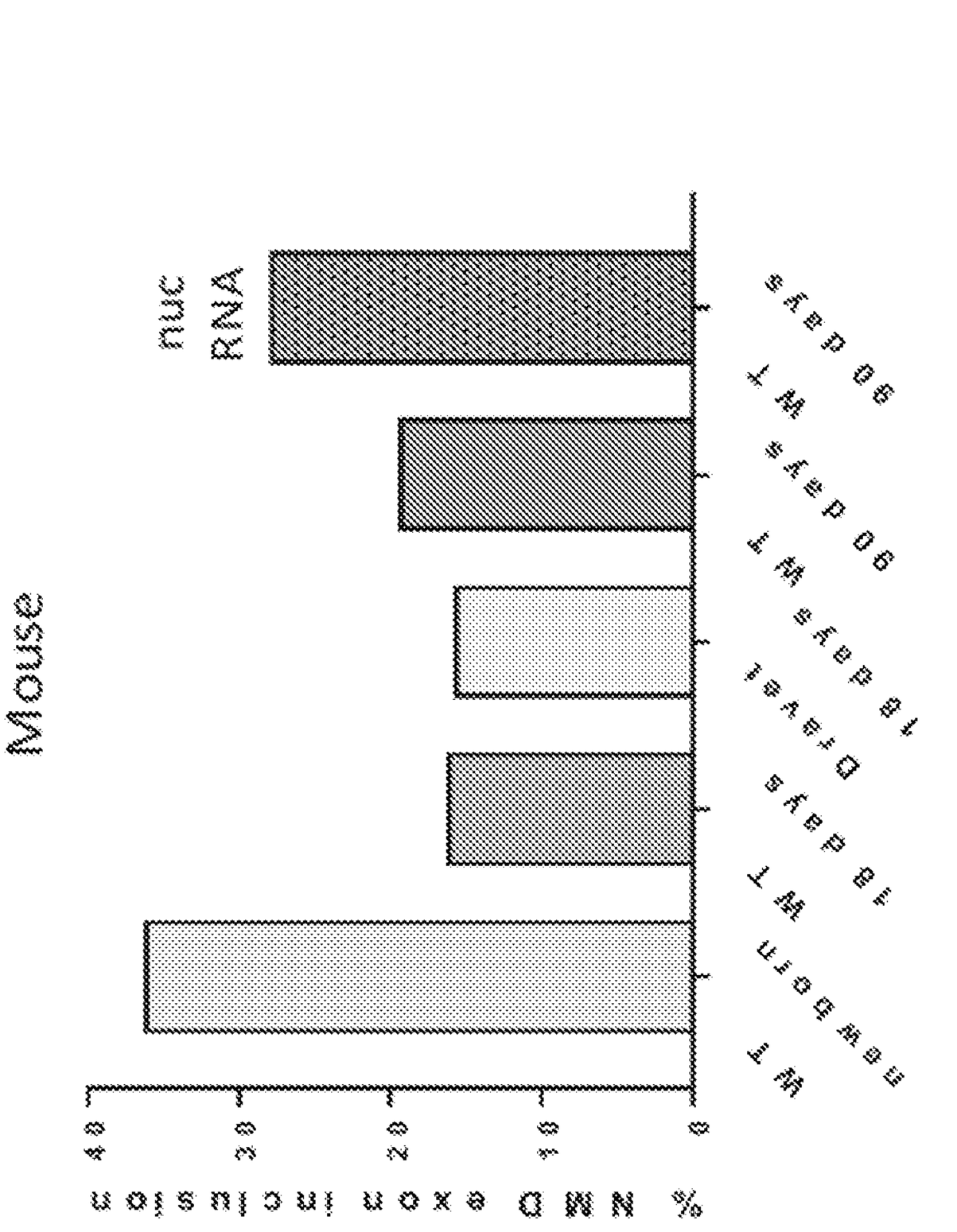


FIG. 13A

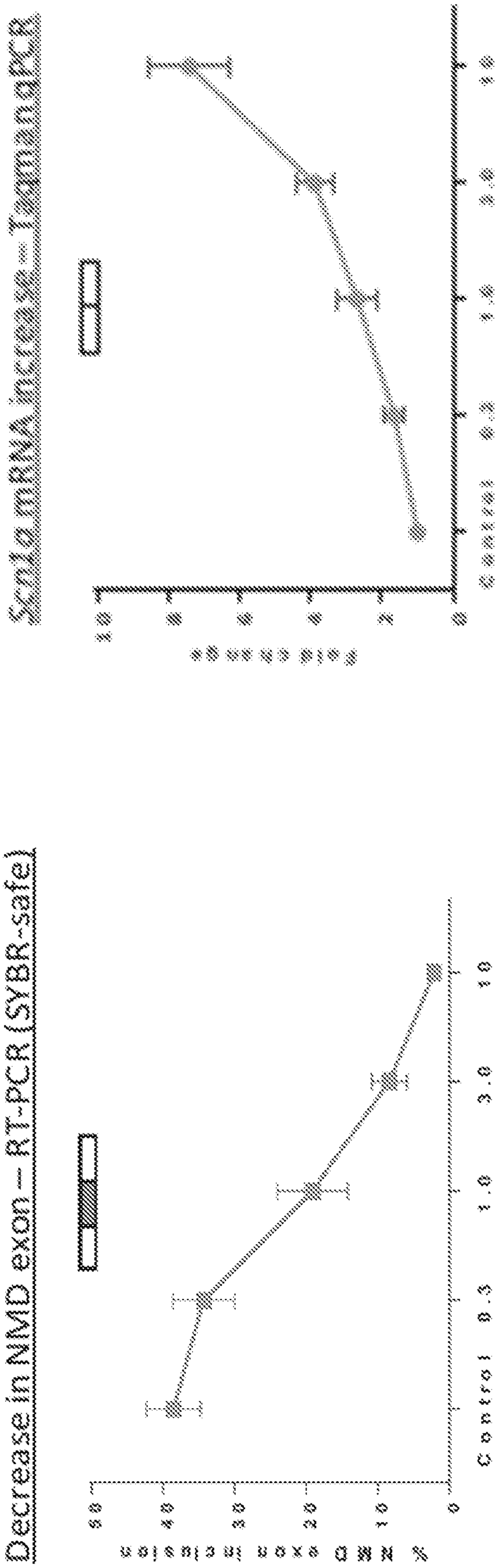


FIG. 14B

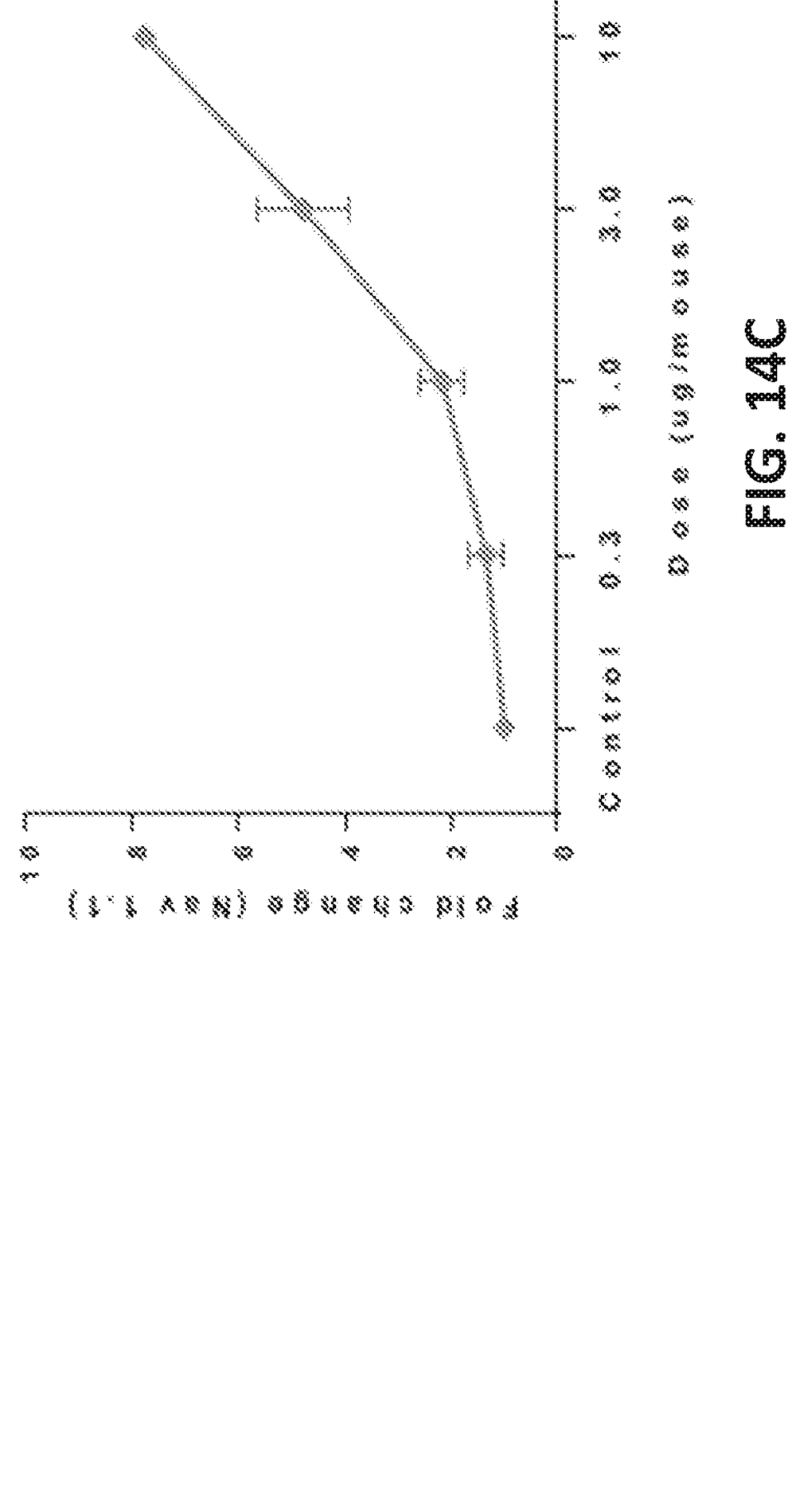


FIG. 14C

FIG. 14A

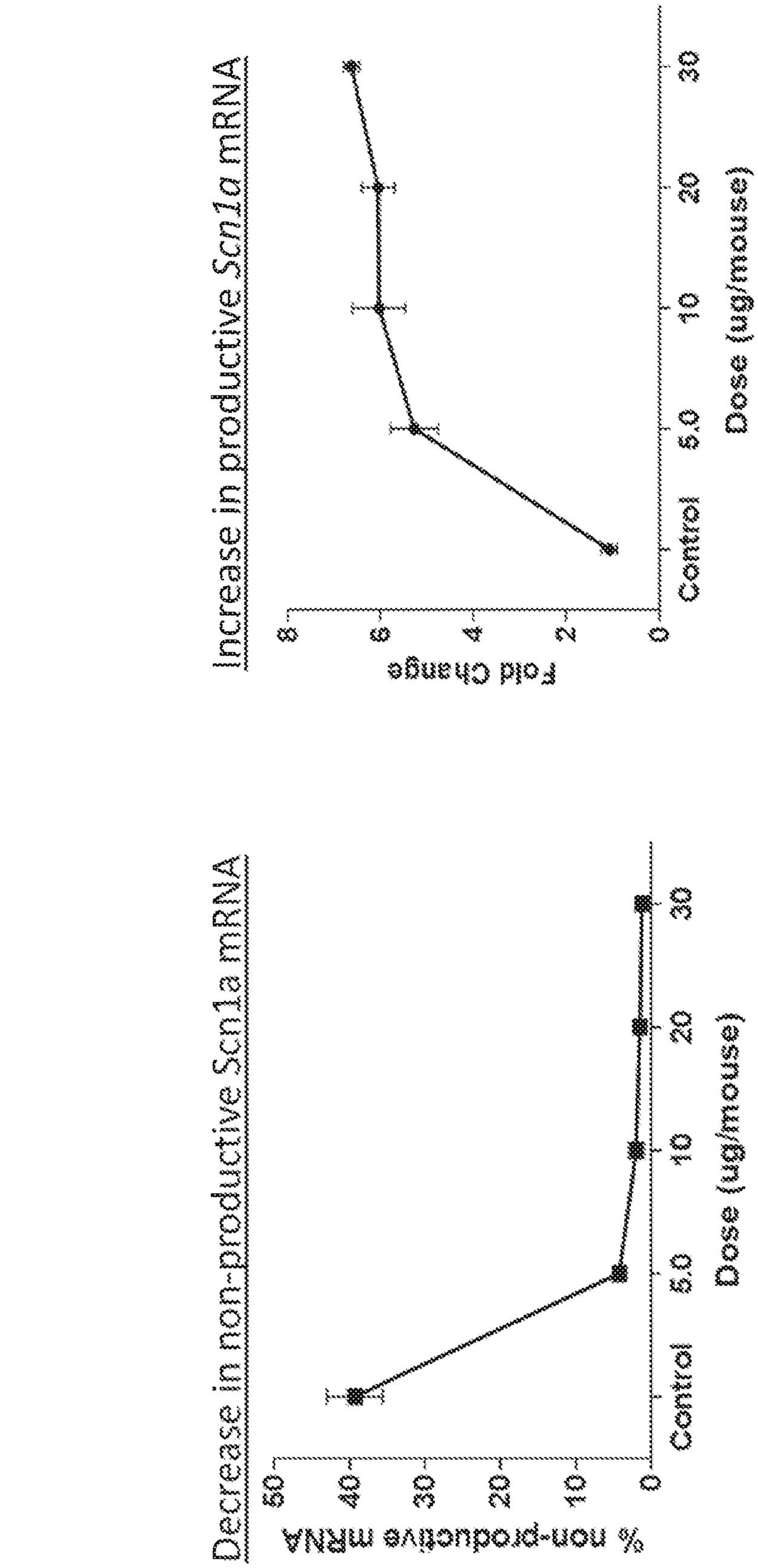


FIG. 15A

FIG. 15B

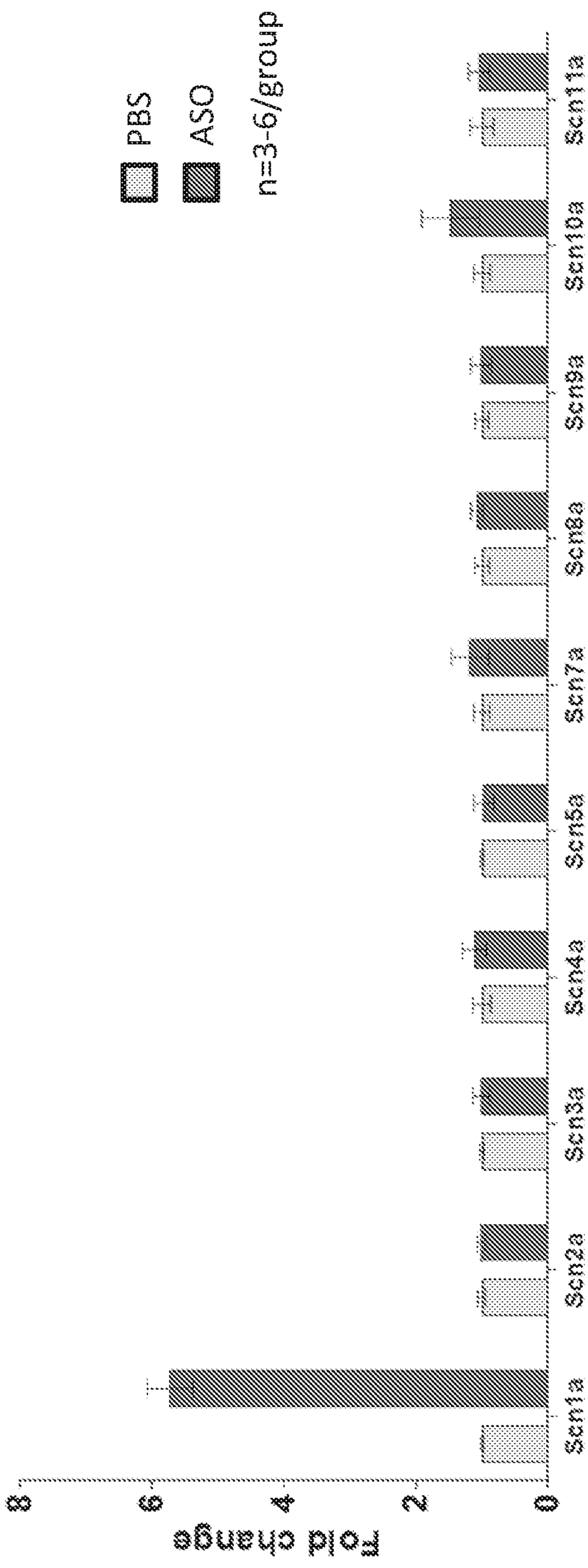

PBS
ASO
3-6/group
Fold change
0
2
4
6
8
Scn1a
Scn2a
Scn3a
Scn4a
Scn5a
Scn7a
Scn8a
Scn9a
Scn10a
Scn11a

FIG. 16

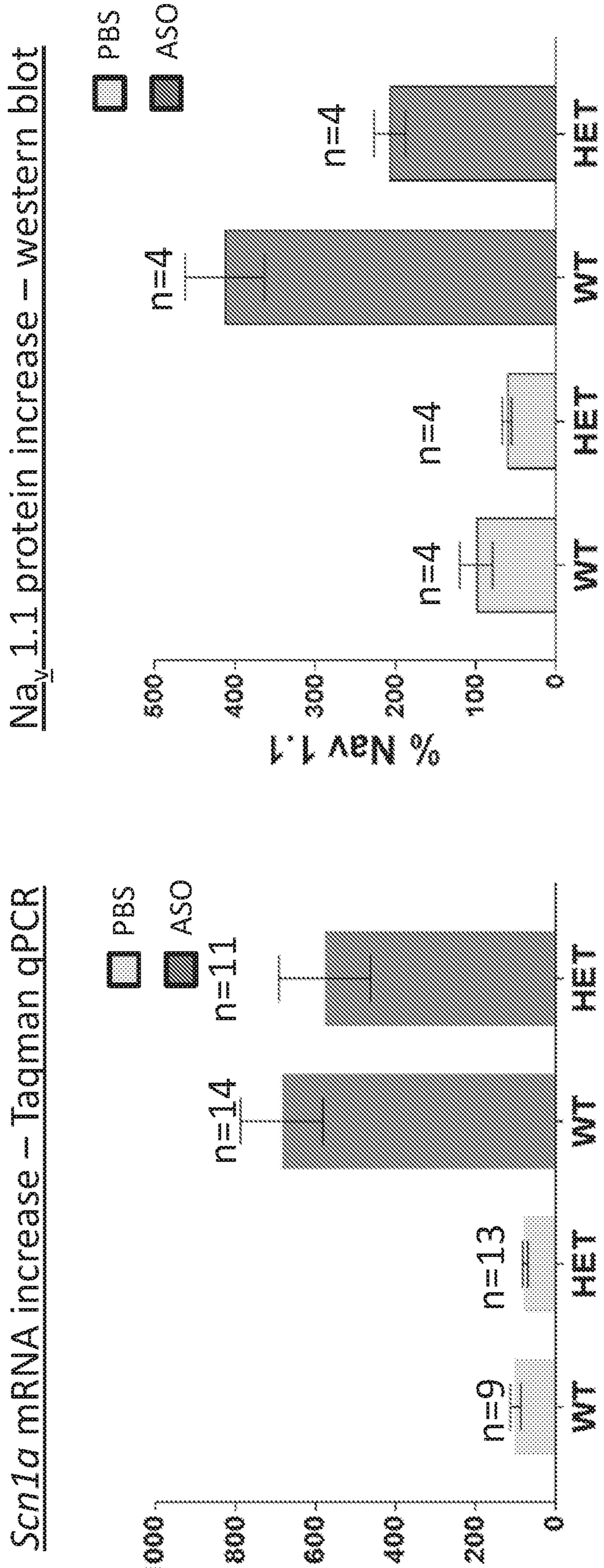


FIG. 17B

FIG. 17A

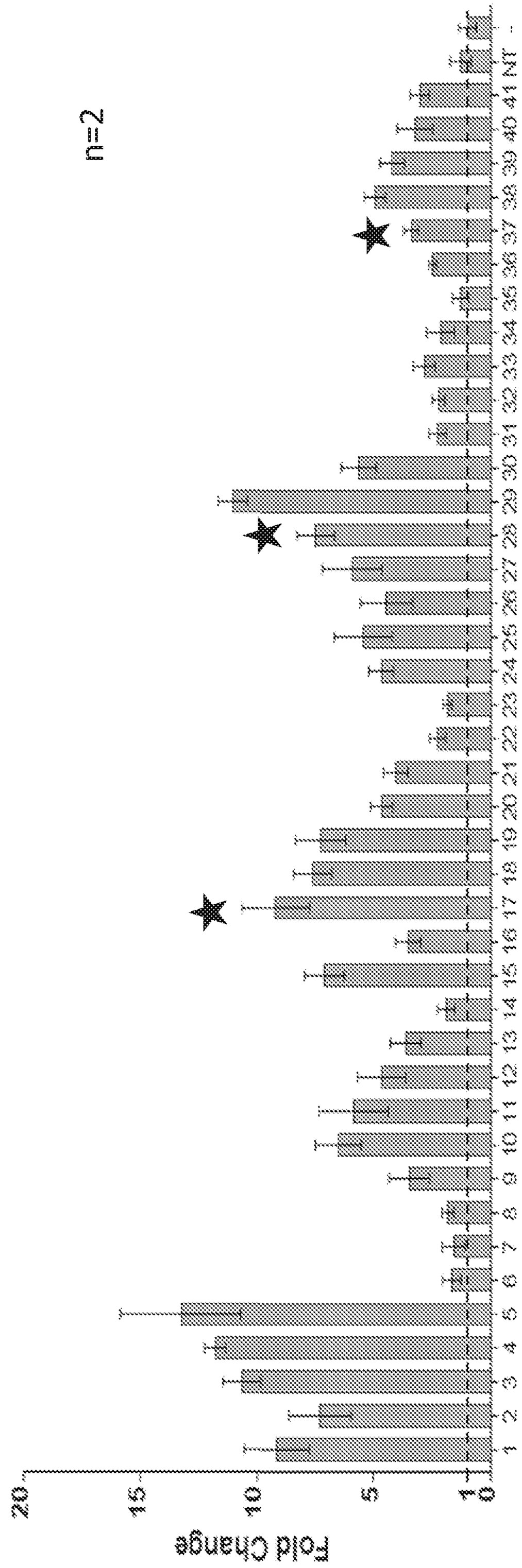

n=2
Fold Change
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 NT

FIG. 18

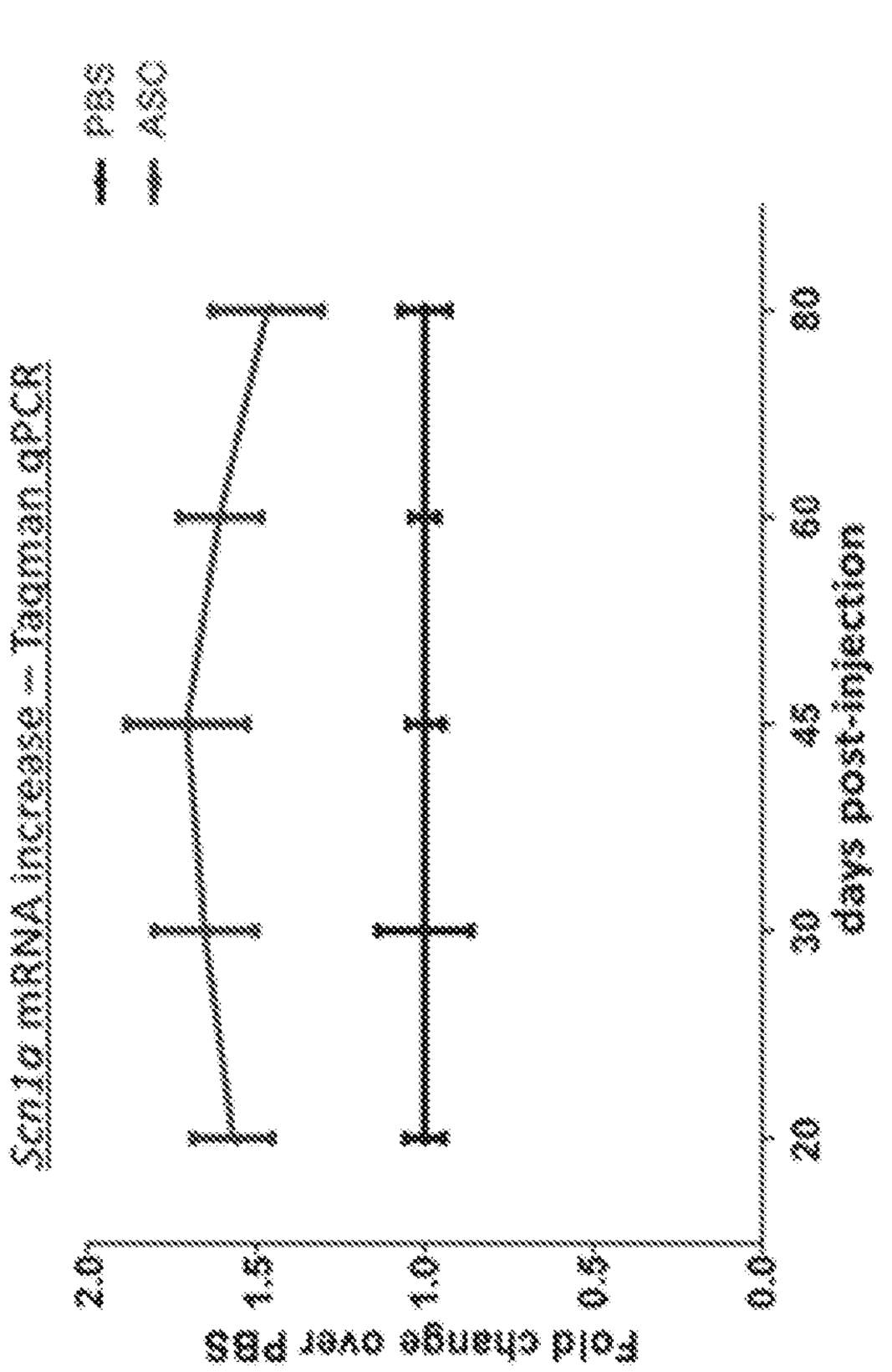

Fold change over PBS
2.0
1.5
1.0
0.5
0.0
20
30
40
60
80
days post-injection
Sema3a mRNA increase — Taqman qPCR
PBS
ASO

FIG. 19

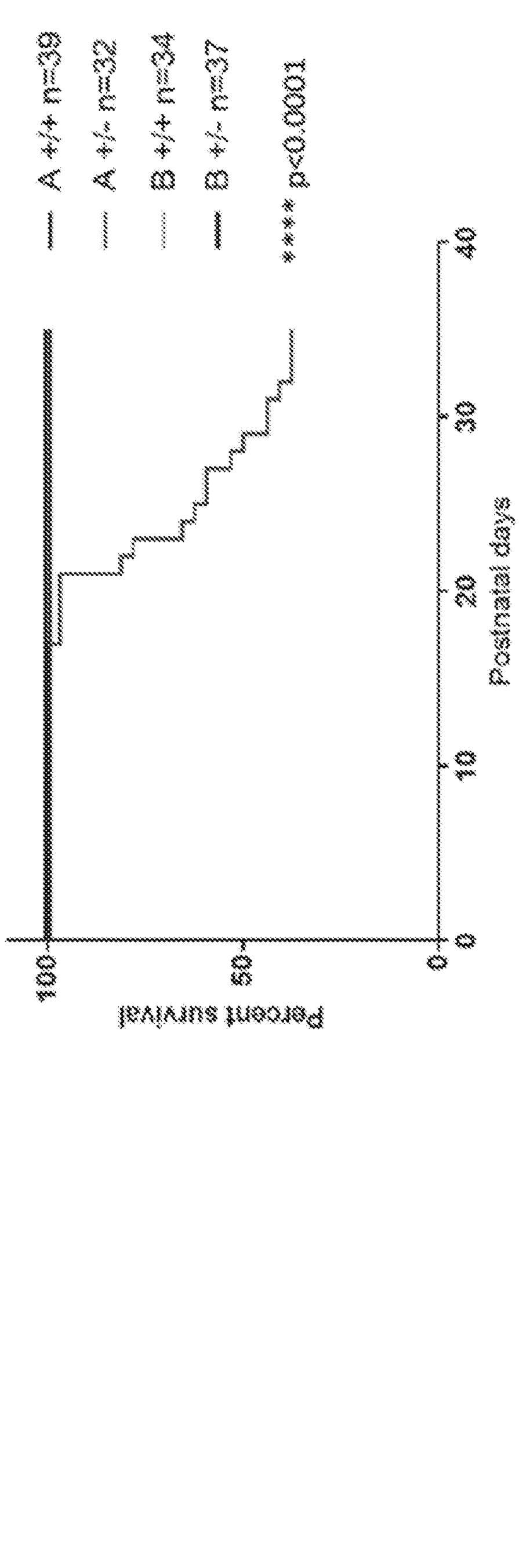

Percent survival
100
50
0
0
10
20
30
40
Postnatal days
A +/+ n=39
A +/- n=32
B +/+ n=24
B +/- n=37
**** p<0.0001

FIG. 20