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Locked nucleic acid: modality, diversity, and drug discovery

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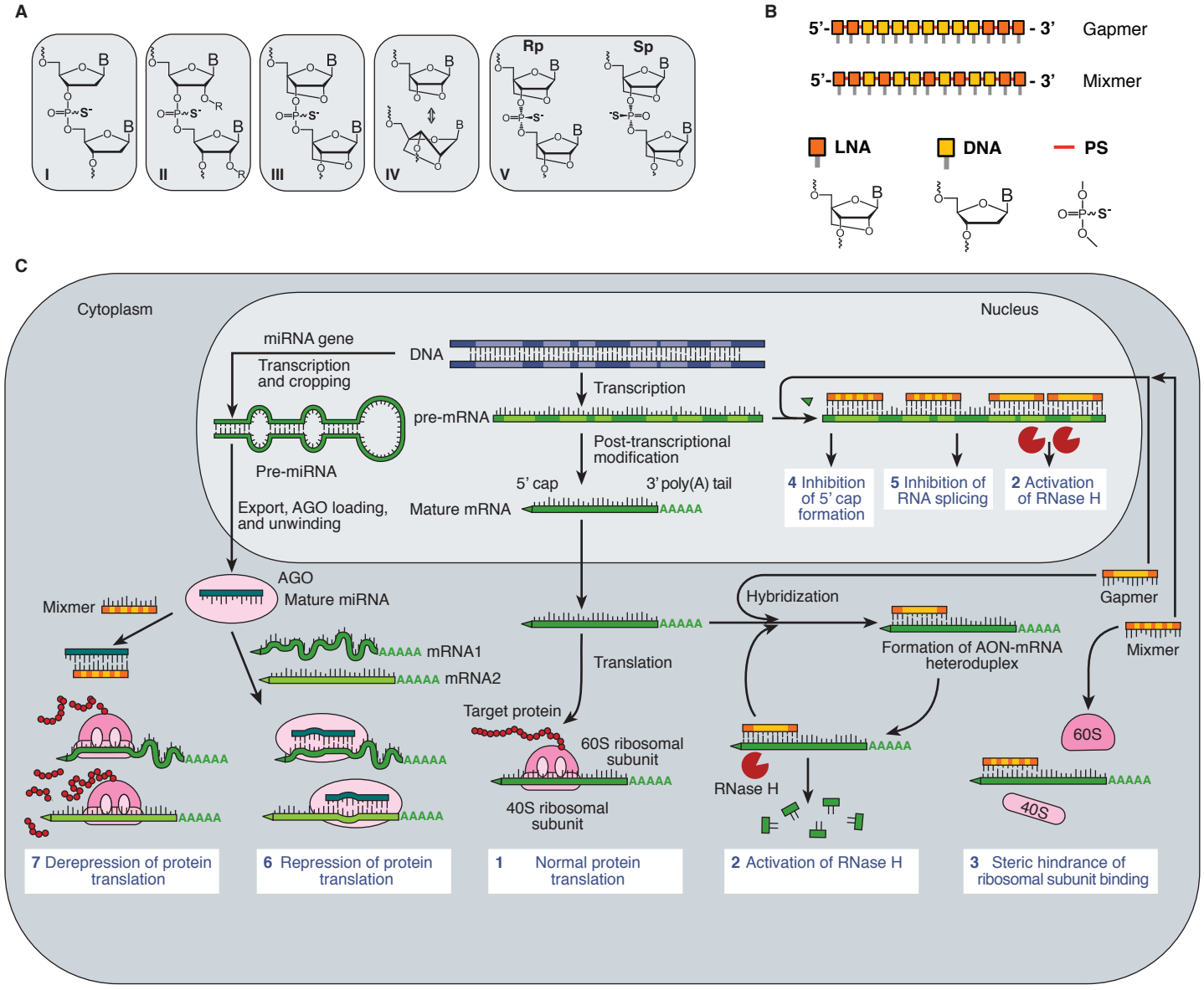
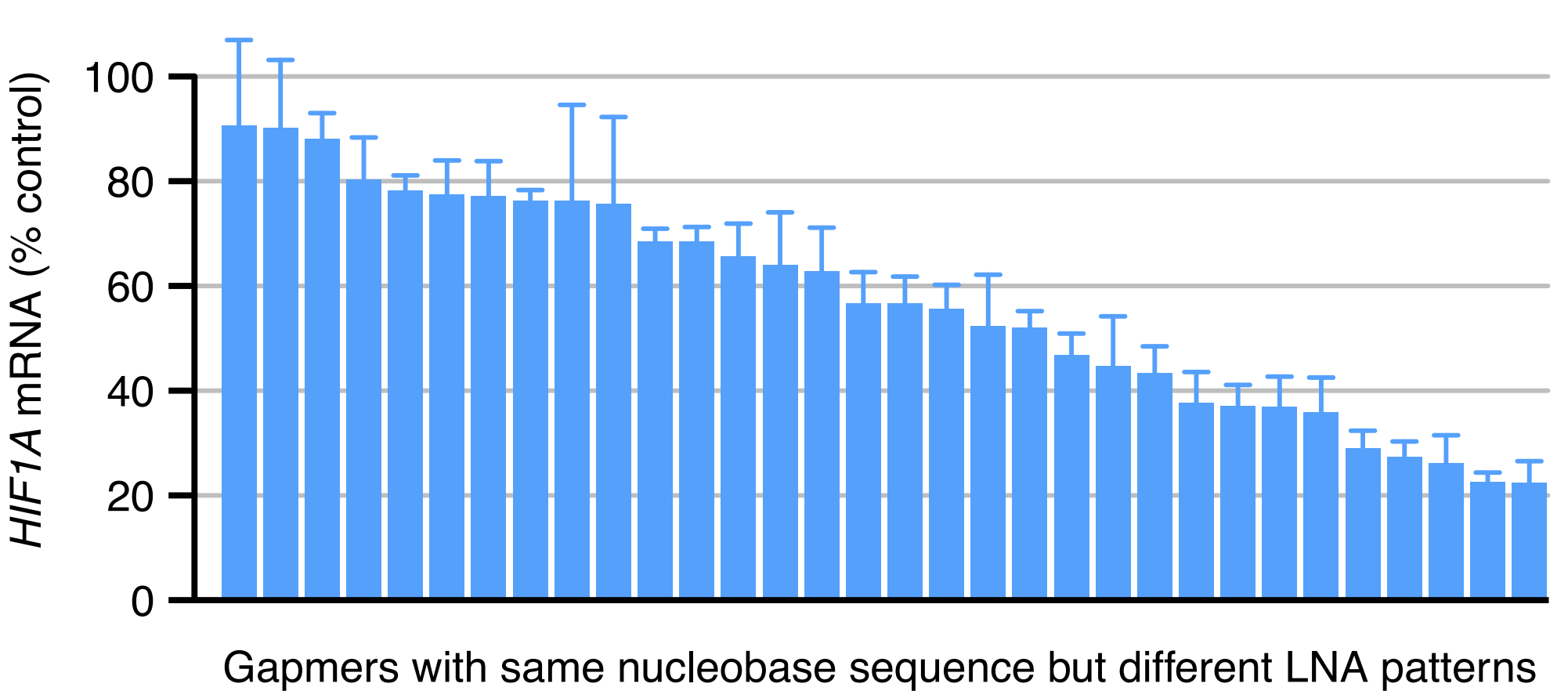
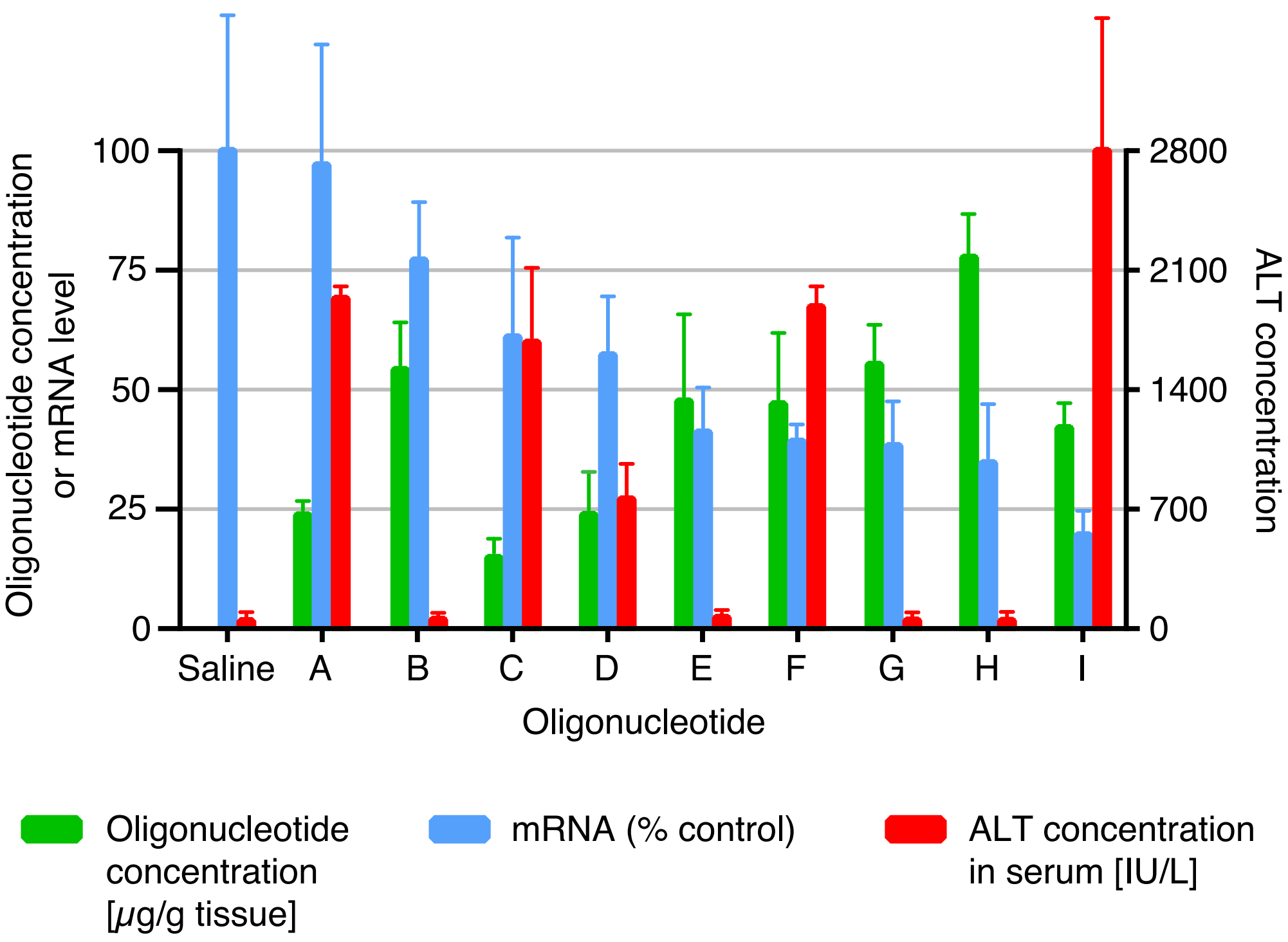
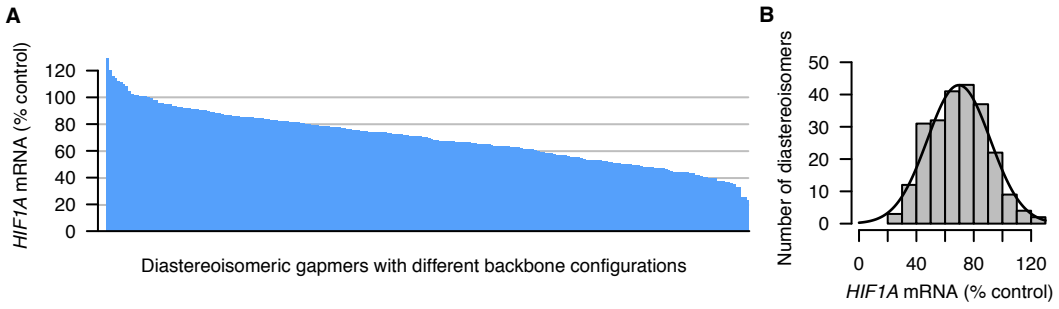
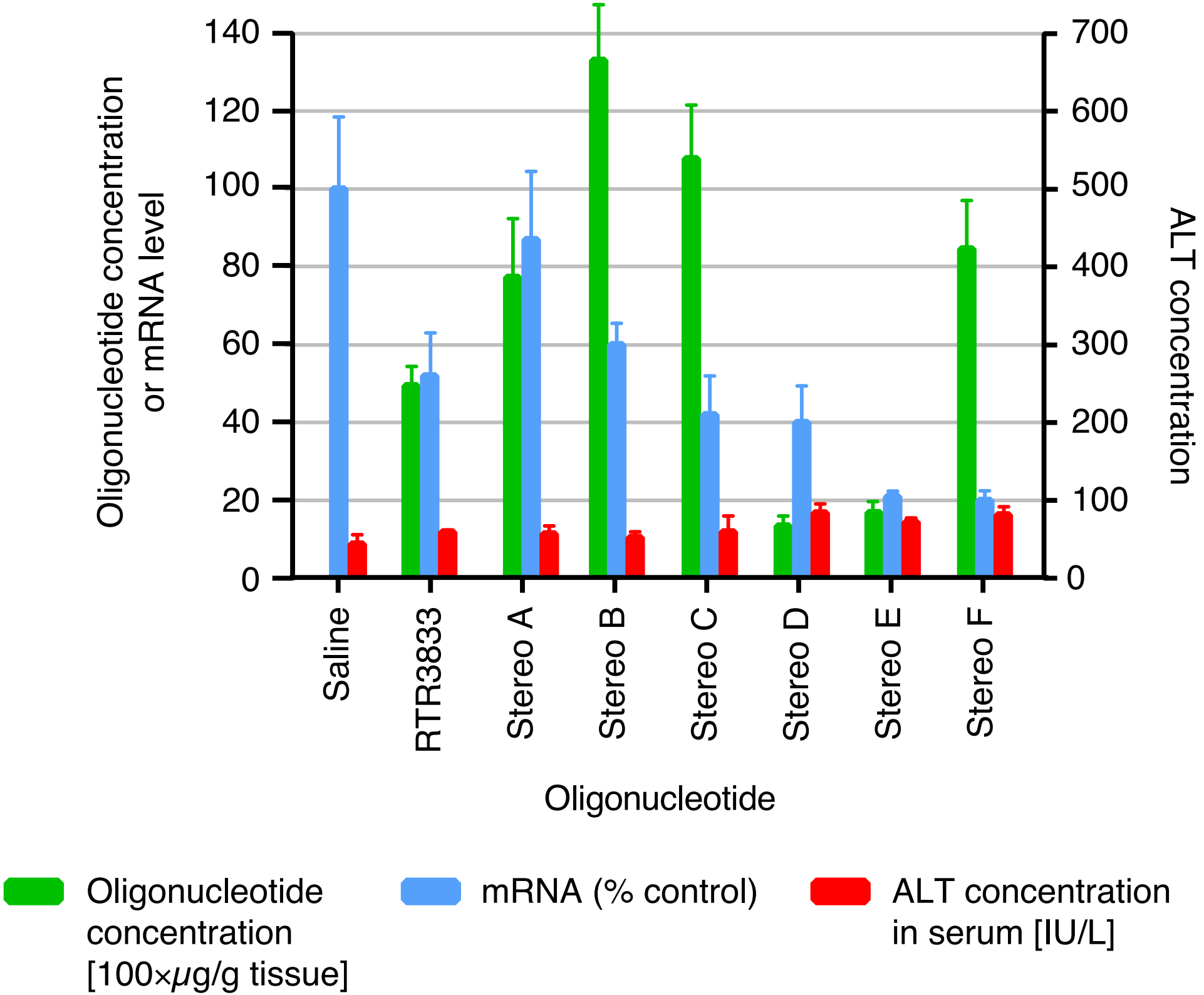
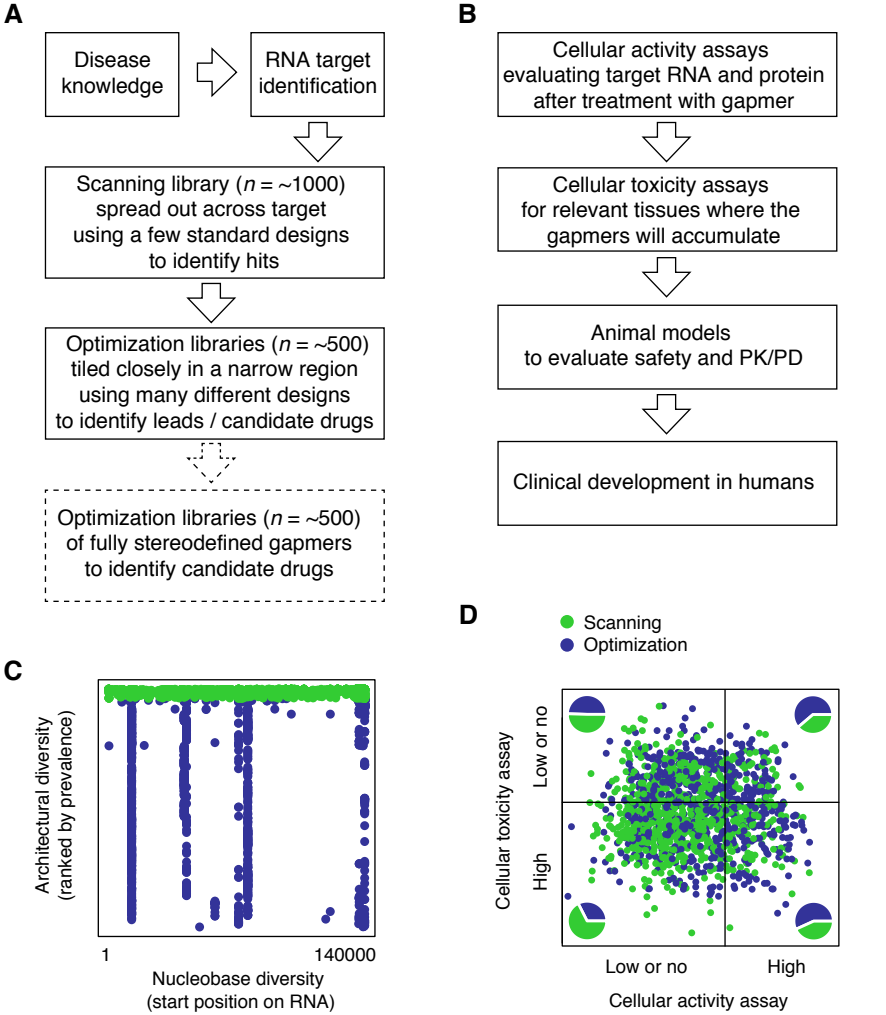

A
I
II
III
IV
Rp
Sp
V
B
5'- - 3' Gapmer
5'- - 3' Mixmer
LNA
DNA
PS
C
Cytoplasm
Nucleus
miRNA gene
Transcription and cropping
DNA
Transcription
pre-miRNA
Post-transcriptional modification
Pre-miRNA
5' cap
3' poly(A) tail
Export, AGO loading, and unwinding
Mature mRNA
AAAAA
4 Inhibition of 5' cap formation
5 Inhibition of RNA splicing
2 Activation of RNase H
AGO
Mature miRNA
Mixmer
Gapmer
Hybridization
Translation
mRNA1
mRNA2
Target protein
60S ribosomal subunit
40S ribosomal subunit
Formation of AON-mRNA heteroduplex
RNase H
60S
40S
7 Derepression of protein translation
6 Repression of protein translation
1 Normal protein translation
2 Activation of RNase H
3 Steric hindrance of ribosomal subunit binding


100
80
60
40
20
0
HIF1A mRNA (% control)
Gapmers with same nucleobase sequence but different LNA patterns


Oligonucleotide concentration or mRNA level
100
75
50
25
0
2800
2100
1400
700
0
ALT concentration
Saline
A
B
C
D
E
F
G
H
I
Oligonucleotide
Oligonucleotide concentration [μg/g tissue]
mRNA (% control)
ALT concentration in serum [IU/L]


A
HIF1A mRNA (% control)
120
100
80
60
40
20
0
Diastereoisomeric gapmers with different backbone configurations
B
Number of diastereoisomers
50
40
30
20
10
0
0
40
80
120
HIF1A mRNA (% control)


Oligonucleotide concentration or mRNA level
ALT concentration
140
120
100
80
60
40
20
0
700
600
500
400
300
200
100
0
Saline
RTR3833
Stereo A
Stereo B
Stereo C
Stereo D
Stereo E
Stereo F
Oligonucleotide
Oligonucleotide concentration [100×μg/g tissue]
mRNA (% control)
ALT concentration in serum [IU/L]


A
Disease knowledge
RNA target identification
Scanning library (n = ~1000) spread out across target using a few standard designs to identify hits
Optimization libraries (n = ~500) tiled closely in a narrow region using many different designs to identify leads / candidate drugs
Optimization libraries (n = ~500) of fully stereodefined gapmers to identify candidate drugs
B
Cellular activity assays evaluating target RNA and protein after treatment with gapmer
Cellular toxicity assays for relevant tissues where the gapmers will accumulate
Animal models to evaluate safety and PK/PD
Clinical development in humans
C
Architectural diversity (ranked by prevalence)
1
140000
Nucleobase diversity (start position on RNA)
D
Scanning
Optimization
Cellular toxicity assay
Low or no
High
Low or no
High
Cellular activity assay