Locked nucleic acid: modality, diversity, and drug discovery

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Gapmers with same nucleobase sequence but different LNA patterns
Oligonucleotide concentration or mRNA level vs. Oligonucleotide

- **Saline**
- **A**
- **B**
- **C**
- **D**
- **E**
- **F**
- **G**
- **H**
- **I**

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<tr>
<th>Oligonucleotide</th>
<th>mRNA (% control)</th>
<th>ALT concentration in serum [IU/L]</th>
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- Oligonucleotide concentration [µg/g tissue]
Diastereoisomeric gapmers with different backbone configurations

HIF1A mRNA (% control)

Number of diastereoisomers

A

B

Diastereoisomeric gapmers with different backbone configurations

HIF1A mRNA (% control)
The graph compares the effects of different oligonucleotides on Oligonucleotide concentration or mRNA level and ALT concentration in serum. The X-axis represents the oligonucleotide tested, while the Y-axis shows the concentrations. The error bars indicate variability. The colors used in the graph are:

- **Green**: Oligonucleotide concentration [100×µg/g tissue]
- **Blue**: mRNA (% control)
- **Red**: ALT concentration in serum [IU/L]
A | Disease knowledge → RNA target identification

Scanning library ($n = \sim 1000$) spread out across target using a few standard designs to identify hits

Optimization libraries ($n = \sim 500$) tiled closely in a narrow region using many different designs to identify leads / candidate drugs

Optimization libraries ($n = \sim 500$) of fully stereotyped 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 | Nucleobase diversity (start position on RNA)

D | Scanning

Optimization

Cellular activity assay

Cellular toxicity assay

Low or no

High

Low or no

High

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