Locked nucleic acid: modality, diversity, and drug discovery

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Citation (APA):
A

B

C

Cytoplasm

miRNA gene

Transcription and cropping

Pre-miRNA

Export, AGO loading, and unwinding

AGO

Mature miRNA

Mixmer

Nucleus

DNA

Transcription

Pre-mRNA

Post-transcriptional modification

5’ cap

3’ poly(A) tail

Hybridization

Formation of AON-mRNA heteroduplex

Target protein

Translation

60S ribosomal subunit

40S ribosomal subunit

RNase H

Formation of AON-mRNA heteroduplex

Steric hindrance of ribosomal subunit binding

Repression of protein translation

Derepression of protein translation

Normal protein translation

Activation of RNase H

4 Inhibition of 5’ cap formation

5 Inhibition of RNA splicing

2 Activation of RNase H

40S

60S

AGO
Gapmers with same nucleobase sequence but different LNA patterns

HIF1A mRNA (% control)

0 20 40 60 80 100
Diastereoisomeric gapmers with different backbone configurations

HIF1A mRNA (% control)

Number of diastereoisomers

Diastereoisomeric gapmers with different backbone configurations

HIF1A mRNA (% control)
A

<table>
<thead>
<tr>
<th>Disease knowledge</th>
<th>RNA target identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanning library ($n \approx 1000$) spread out across target using a few standard designs to identify hits</td>
<td></td>
</tr>
<tr>
<td>Optimization libraries ($n \approx 500$) tiled closely in a narrow region using many different designs to identify leads/candidate drugs</td>
<td></td>
</tr>
</tbody>
</table>

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)
- Architectural diversity (ranked by prevalence)

D

- Green: Scanning
- Blue: Optimization

- Low or no
- High

- Cellular activity assay
- Cellular toxicity assay