MoleRNA – DISCOVERING AND DESIGNING SMALL MOLECULES TARGETING mRNA

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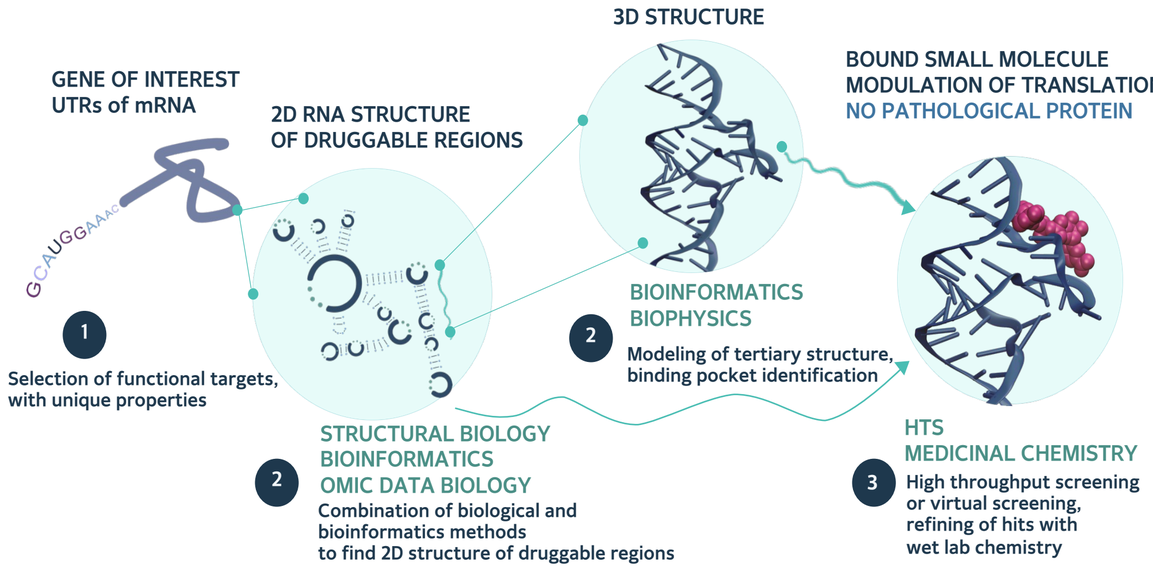
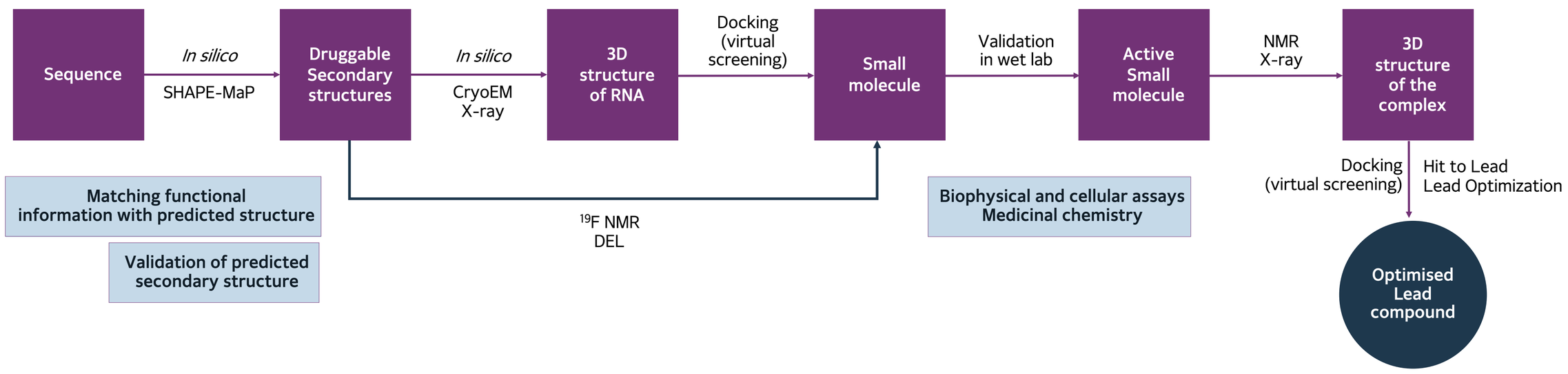
Background

Many undruggable proteins play key roles in the development and pathology of various diseases. Our strategy is to target mRNAs which encode these proteins. We utilize the fact that mRNAs adopt specific 3D structures which are integral and essential for their biological functions, specifically translation. We start with a structural biology approach and recognize defined motifs in the regulatory regions of mRNA. Subsequently, we aim at the identification of small molecules which by binding mRNA functional motifs modulate target protein levels. Our company has over 10 years of experience in the development of first-in-class drugs into clinic. For this project, within Molecure, we have created MoleRNA, a platform supported by *in silico* and wet lab analyses for designing small molecules targeting functional mRNA regions with defined structures. MoleRNA's objective is to develop lead compounds targeting mRNAs with optimized drug-like properties for undruggable proteins.



MoleRNA platform discovery workflow

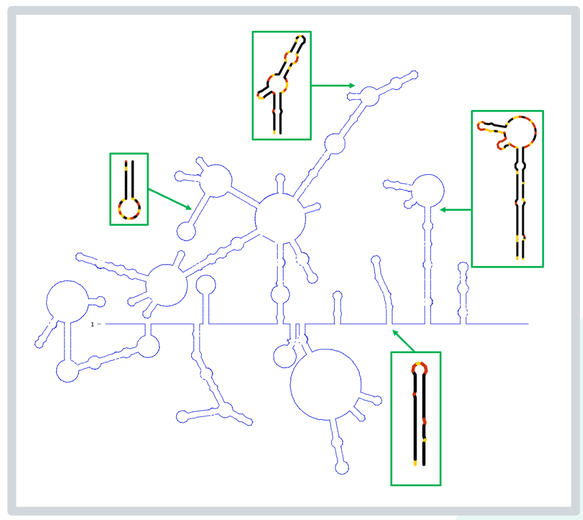


Druggable regions selection

Predicted secondary structures are validated by SHAPE-MaP (*in vitro, in cellulo*) and structure conservation

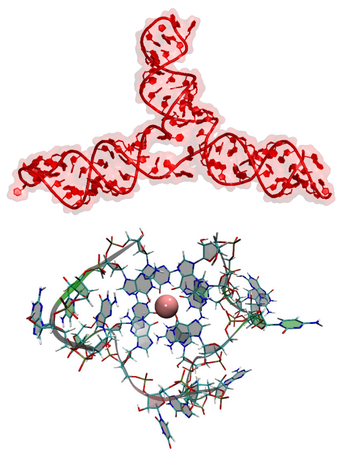
Functional role of selected region is validated in biophysical and cellular assays

Prediction of the off-targets probability



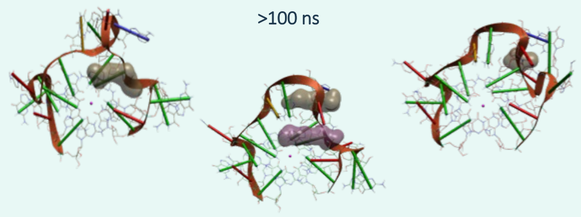
3D RNA structure prediction or solving

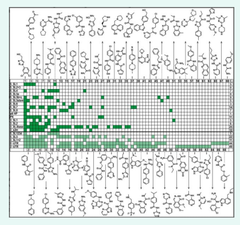
- SHAPE-MaP reactivities
- Secondary structure
- Sequence alignement
- Homologous motifs from RCSB
- Experimental data (distance restrains)



Virtual screening pipeline

Molecular Dynamics	Assemble of 3D structures	Pocket Assessment	Virtual Screening	Hit Identification
Polarizable Force-Field	α-spheres Fine-tuned for RNA	Statistically Relevant Structures	Scoring Functions Benchmarked against NMR data	Electrostatic Complementarity
				Utilizing Hansen-Coppens Electron Density Model





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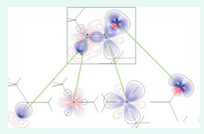
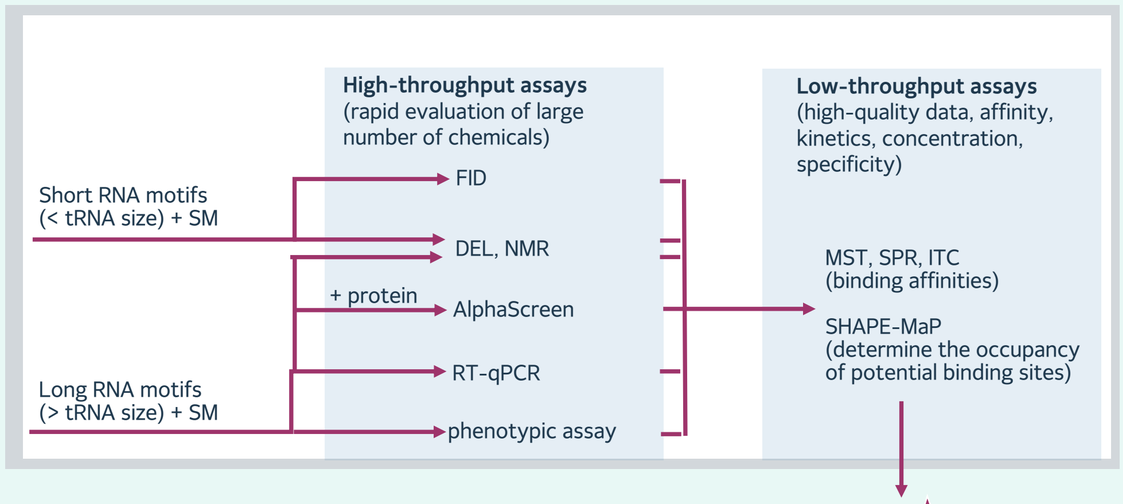


Wet lab screening cascade



Conclusions

To develop and test the MoleRNA pipeline, six structural motifs from different mRNAs were selected by *in silico* methods and validated in the wet lab, three of them entered virtual screening and high-throughput screening cascade. The identified hits will be checked in binding and cellular assays, and then to obtain a lead they will go through the optimization procedure.

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