



HAL
open science

AIR-MT: AI-based design of RNA Methyltransferases for RNA-based therapeutics

Priscila Sutto, Bruno Canard, François Ferron

► **To cite this version:**

Priscila Sutto, Bruno Canard, François Ferron. AIR-MT: AI-based design of RNA Methyltransferases for RNA-based therapeutics. SOLEIL Users' Meeting (SUM2026), Jan 2026, Saint-Aubin, France. . <hal-05491018>

HAL Id: hal-05491018

<https://hal.science/hal-05491018v1>

Submitted on 3 Feb 2026

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License

AIR-MT

AI-based design of RNA Methyltransferases for RNA-based therapeutics

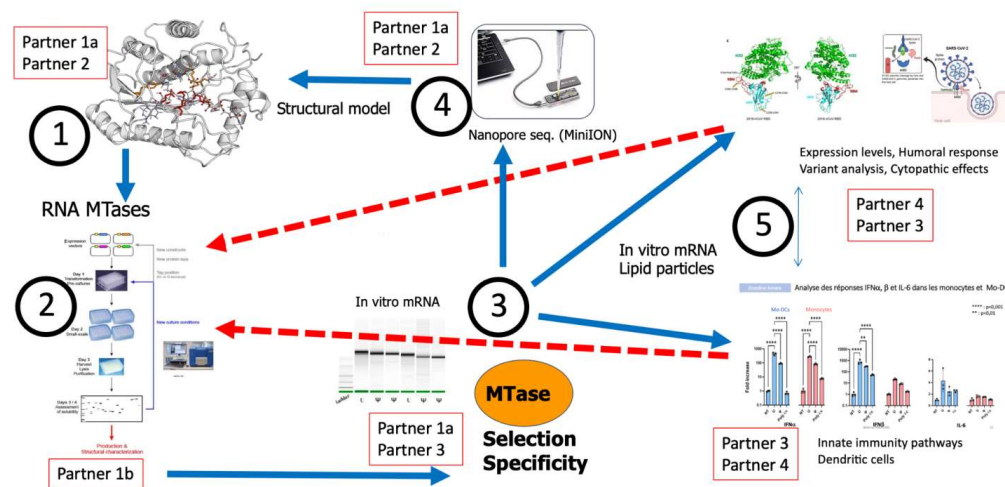
Priscilla SUTTO¹, François FERRON^{1,2}, Bruno CANARD^{1,2}

¹Aix Marseille Université, CNRS, AFMB UMR 7257, Marseille, France
²European Virus Bioinformatics Center, Leutragraben 1, 07743, Jena, Germany

CONTEXT

- In the cell, mRNAs are essentially unstable and their phenotypic outcome is modulated by >100 known post-transcriptional modifications, such as RNA methylations.
- Site-specific RNA methylation has the potential to achieve both increased stability and optimal balance between the cell innate immunity response coupled to its ability to express non-self proteins.
- To confer desired properties to future mRNA-based therapeutics or vaccinal RNAs we need site-specific RNA methyltransferases (RMTases).
- Recent breakthroughs in AI-generated enzyme backbones allow designing synthetic RMTases with mN6-adenine, mN1-adenine, mC5-cytidine or 2'-O specific activities.
- The aim of the project is to generate novel mRNA with specific properties achieved through targeted methylation using custom-designed RMTases.

PROJECT OVERVIEW

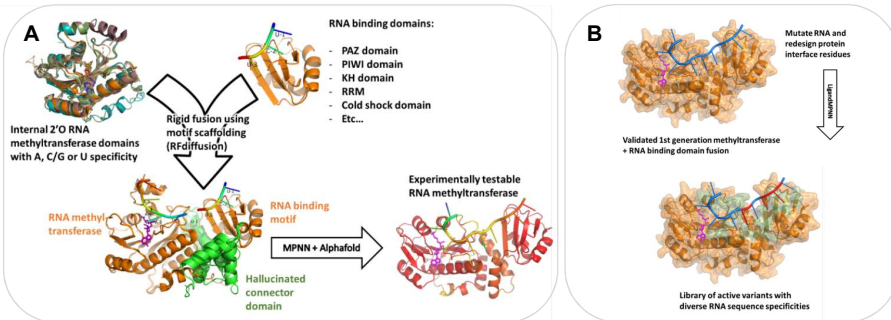


CONSORTIUM

- Partner 1a**: AFMB Lab, CNRS/AMU, Marseille. **Etienne DECROLY.**
- Partner 1b**: IBiSA/AMU High-throughput protein production, purification and interaction Facility in AFMB Lab, CNRS/AMU, Marseille. **Renaud VINCENTELLI.**
- Partner 2**: The Molecular and Structural Pharmacology of Membrane Proteins Team, INSERM, Montpellier. **Cédric LEYRAT.**
- Partner 3**: CIML, Centre d'Immunologie de Marseille-Luminy, INSERM/CNRS/AMU. **Béatrice NAL ROGIER.**
- Partner 4**: The Virus & Immunity Unit at Institut Pasteur, Paris. **Olivier SCHWARTZ.**

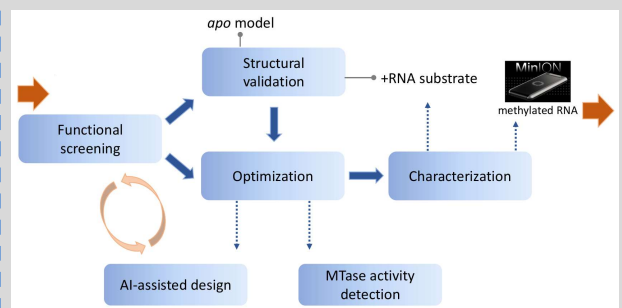
COMPUTATIONAL STRATEGY: AI-based design

RNA sequence-specific internal 2'-O RNA methyltransferases



VALIDATION OF AI APPROACH

3D structure by Crystallography

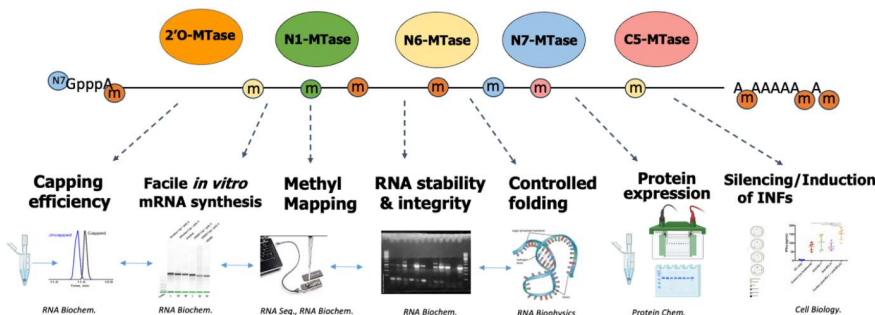


To validate the structural prediction and to refine specificity and target sites, we will characterize the structure of selected chimeric RMTases in apo and in complex with desired substrates using X-Ray Crystallography.

The structural data will ensure and lay the ground calibration of the reliability of the prediction.

OUTCOME

Methylated mRNA biophysical and biological properties



REFERENCES

- François Ferron, Sonia Longhi, Bernard Henrissat and Bruno Canard. *Viral RNA-polymerases – a predicted 2'-O-ribose methyltransferase domain shared by all Mononegavirales*. TRENDS in Biochemical Sciences 2002.
- Etienne Decroly, François Ferron, Julien Lescar and Bruno Canard. *Conventional and unconventional mechanisms for capping viral mRNA*. NATURE REVIEWS 2012.
- Katherine Zhou, Chad V Peccot, Christopher L Holley. *2'-O-methylation (Nm) in RNA: progress, challenges, and future directions*. RNA 2024.