2026 Helmholtz – OCPC – Program

for the involvement of postdocs in bilateral collaboration projects

AI-driven predictive engineering of RNA regulatory networks

Karlsruhe Institute of Technology (KIT), Zoological Institute (ZOO)

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Description of the project (max. 1 page)**:**

Predictive and Synthetic Engineering of RNA Regulatory Programs Cells organize gene expression through spatially structured RNA-protein interaction networks (Klobucar et al., 2026, Modic et al., 2024), in which specific transcripts act as scaffolds that recruit regulatory proteins and other RNAs to defined subcellular compartments (Trupej et al., 2026, Modic et al., 2019). These RNA scaffolds selectively sequester transcripts and rewire gene expression programmes. However, it remains unknown how RNA sequence encodes the instructions that determine transcript localisation, interaction network assembly, and condensate function. Critically, **we lack predictive models capable of inferring these regulatory instructions from sequence and enabling rational design of synthetic RNAs that can reprogram cellular regulatory networks**.

This project addresses this fundamental challenge by developing a deep learning-driven framework for predictive engineering of RNA condensation programmes. Building on our recently developed expression-aware TxBinder deep learning platform, which predicts RNA-protein interactions across full transcript contexts, we will extend this approach to develop a multimodal foundation model that learns the sequence-encoded interaction grammars that govern RNA-RNA interactions, and condensate assembly. By integrating transcriptome-scale RNA-protein binding maps, RNA-RNA interaction datasets, and spatial transcriptomics data, the candidate will train interpretable deep neural networks that map primary RNA sequence to condensate recruitment

probability, interaction network topology, and regulatory impact. These AI-derived interaction grammars will then be used in a generative design framework to create synthetic RNA scaffolds with programmable interaction properties. Using high-throughput DNA synthesis and inducible genomic integration, synthetic RNA libraries will be expressed in living cells to experimentally validate model predictions. We will quantify RNA-protein interactions, condensate recruitment, and transcriptome-wide regulatory effects using next-generation sequencing, proximity proteomics, and RNA interaction mapping. This closed-loop design->build->test->learn cycle will enable iterative refinement of predictive models and establish causal links between RNA sequence, condensate organisation, and gene regulation.

By combining deep learning, synthetic genomics, and functional genomics, the candidate will establish a new paradigm for predictive and causal engineering of RNA-driven cellular organisation. Beyond advancing fundamental understanding of how RNA sequence encodes regulatory behaviour, this work will deliver generalisable AI models and design principles for programming RNA localisation and regulatory function. Thereby the project will establish synthetic RNA design as a general strategy to reprogram gene expression and cellular state. This framework has broad implications for understanding RNA-driven regulatory systems and for enabling rational engineering of RNA molecules for applications in synthetic biology and RNA therapeutics.

Trupej A, Bergant V, Novljan, Dodel N, Klobučar T, Adamek M, Lee F, Yap K, Makeyev E, Kokot B, Čehovin L, Pichlmair A, Urbančič I, Mardakheh F, **Miha Modic*:** HCR-Proxy resolves site-specific proximal RNA proteomes at subcompartmental nanoscale resolution. *Nucleic Acids Research*. 2026

Klobucar T, Novljan J, Iosub I, Kokot B, Urbančič I, Jones M, Luscombe N, Ule J, **Miha Modic***: Integrative profiling of condensation-prone RNAs during early development. *Cell Genomics.* 2026

Modic Miha*, Kuret K, Steinhauser S, Faraway R, van Genderen E, Lee F, Mozos IRL, Vicic Z, Novljan J, ten Berge D, Luscombe N, Ule J*: Poised PABP-RNA hubs implement signal-dependent mRNA decay in development. *Nature Structural and Molecular*. 2024

Modic Miha, Grosch M, Rot G, Lepko T, Yamazaki T, Shaposhnikov D, Rusha E, Rogelj B, Hauck SM, von Mering C, Meissner A, Hirose T, Ule J, Drukker M: Cross-regulation between TDP-43 and paraspeckles promotes pluripotency-differentiation transition. *Molecular Cell*. 2019

Description of existing or sought Chinese collaboration partner institute (max. half page)**:**

A primary proposed collaboration partner is Prof. Dr. Wei Chen at the Southern University of Science and Technology (SUSTech), Shenzhen. Prof. Chen is a leading expert in computational RNA biology and transcriptome regulation, integrating high-throughput sequencing with advanced bioinformatics and machine learning to uncover sequence-encoded regulatory mechanisms. His group has developed quantitative frameworks to model RNA stability, translation, and RNA-protein interactions, linking RNA sequence and structural features to functional regulatory outcomes. More recently, his laboratory has focused on AI-driven and large-scale computational approaches to infer regulatory grammars governing RNA behaviour and gene expression networks. This expertise is highly complementary to the proposed project, which aims to develop deep learning models for predictive engineering of RNA condensation and regulatory network organisation. The collaboration would enable integration of AI-based sequence design and predictive modelling developed at KIT with Prof. Chen's strengths in transcriptome-scale computational analysis and experimental validation. Together, this partnership will establish a joint framework to uncover and engineer sequence-encoded RNA regulatory programs.

As an alternative, Tsinghua University represents an outstanding complementary collaboration partner. Tsinghua is one of the world's leading institutions in genomics and systems biology, with internationally recognised researchers such as Prof. Dr. Xiaohua Shen (Department of Basic Medical Sciences) and Prof. Dr. Qiangfeng "Cliff" Zhang. Prof. Shen is already an advisory board member of the Synthetic Genomics Center (SynGen), which supports my core research programme that funds my TT professorship, providing an established scientific connection. Tsinghua offers exceptional strengths in genome regulation, synthetic and functional genomics, and AI-driven biological modelling. Together, these partnerships would create a highly synergistic environment combining AI-driven modelling, synthetic genomics, and experimental validation, accelerating progress toward predictive and programmable engineering of RNA regulatory networks.

Required qualification of the postdoc:

- PhD in computational biology, bioinformatics, genomics, systems biology, machine learning. Candidates with a strong experimental RNA biology background and demonstrated experience in computational analysis are also encouraged to apply.
- A strong background in computational biology/bioinformatics (with prior knowledge of Python and/or R programming for statistical computing and graphics)
- Experience in machine learning with pytorch or similar deep learning libraries.
- An interest in RNA biology and RNA-protein & RNA-RNA interactions

- Good written and spoken English-language communication skills, and interest in working as part of an international team of researchers.
- The ideal candidate should be collaborative, scientifically adventurous, curiosity-driven, and is encouraged to bring independent and original ideas into the project.