Design and synthesis of modified (oligo)nucleotides for photo-controlled manipulation of mRNA

The aim of this project is to develop the molecular tools that allow for spatio-temporal manipulation of messenger RNA (mRNA) molecules using light. Such conjugates are useful in various fields of research – from functional and structural studies on mRNA-related processes to cellular delivery and controlled-activation of therapeutics.

Chemical modification of biologically active molecules is a powerful tool for investigation of cellular processes, as well as for diagnostic and therapeutic applications. An interesting example of those compounds are photo-responsive reagents, that change their chemical structure and properties upon exposure to light of an appropriate wavelength (color). The greatest advantage of photo-activated chemical reactions is that they allow for both spatial and temporal control of the intra- and intermolecular events. They proved to be very useful for investigation of structure and function of many natural compounds, including mono- and oligonucleotides, however their application to mRNAs remains an underexplored area. In this project we plan to implement this methodology to mRNA biochemistry. To achieve that, we will design and synthesize a set of molecular tools for a photo-controlled manipulation of mRNAs, that do not interfere significantly with their crucial biological properties.

The project starts with the chemical synthesis of functionalized (oligo)nucleotides and their labeling with photo-responsive molecules. Those conjugates will then serve for optimization of photo-chemical reaction conditions and will be incorporated into functional mRNAs using enzymes.

We expect that mRNA molecules with photo-reactive groups might help to address several recent problems in the field of mRNA function and applications: which proteins (especially subunits of the multiprotein complexes) bind directly to different variants of 5′ end structure, what is the architecture of multiprotein complexes involving mRNA circularization, how to deliver (and most importantly to release) the therapeutic transcripts into cells.