

The time when it was believed that RNA was just a simple carrier of genetic information between DNA and protein is long gone. In all living organisms and viruses, RNA molecules have remarkably diverse functions, most of which are driven, at least to some extent, by the complex tertiary structure and dynamics of RNA. However, mutations in RNA as well as perturbations in RNA processing and metabolism often compromise its tertiary structure, which can lead to serious human diseases such as cancer. Additionally, the recent Covid pandemic showed that RNA is a powerful agent not only in terms of the disease carrier but also as a therapeutic. Understanding these different physiological and pathological processes requires a general knowledge of the fundamental properties of secondary and tertiary RNA structures.

In this project, we propose an extensive structural and functional analysis of known and previously uncharacterized RNA structures in p53 mRNA with implications for human health and disease.

p53 mRNA encodes the p53 tumor suppressor protein, one of the most important proteins in human cells, and promising therapeutic target. It acts as a major barrier against cancer development. Localization of the p53 protein at the center of regulation of cellular homeostasis leads to serious consequences in the case of mutations in the p53 gene.

This project will explain the role of the RNA structure in the fundamental mechanisms regulating the expression of p53 mRNA under normal and pathological conditions. It will also have a high impact on the RNA-targeting field because the obtained structures will provide a basis for the selection of structural motifs for exploration and testing of potential therapeutic approaches (small ligands, short RNA oligomers, etc.) for modulation of the RNA structure to achieve desired functional effects, such as inhibition of the translation of mutant p53 protein or stimulation of p53 translation from the wild-type allele to prevent malignant transformation or metastasis.

The results of this project are also in line with attempts to exploit p53 mRNA as an mRNA-based tumor vaccine to restore the expression of the wild-type p53 protein and fight cancer progression. Although mRNA cancer vaccines show considerable promise, their broader application is hindered by several challenges. One of the most important is the inherent instability of mRNA, which causes the rapid degradation of the molecule. We believe that our basic studies can be helpful in the structure-based design of next-generation p53 mRNA vaccine candidates to maximize the expression of p53 protein and to ensure mRNA resistance to degradation. Due to the wide spectrum and frequency of cancers caused by the mutated p53 protein, our research fits well into the urgent social health needs, and we foresee that its successful realization can accelerate progress in personalized mRNA-based cancer therapy.