The effect of cancer somatic mutations in miRNA genes on the functioning of these genes and their potential role in cancer.

Cancer development is associated with the acquisition of oncogenic mutations that have been successfully identified in numerous protein-coding genes. The non-coding part of the genome (considered once junk DNA) became more extensively studied throughout the last years and its role in physiology and disease became a hot topic. Among many elements coded by the non-coding genome are short ~22 nt long regulatory RNAs called microRNAs (miRNAs). It is a well-known and intensively studied phenomenon that the levels of many miRNAs are changed during cancer development. The important role of these RNAs in the regulation of the majority of physiological processes including growth, differentiation, and proliferation prompted their extensive studies in cancer. miRNAs are both up- and -downregulated in cancer and may either drive or suppress oncogenesis. In contrast to the intensively studied role of miRNAs expression in cancer, very little (close to nothing) has been known about somatic mutations in miRNA genes.

Very recently this important and understudied field of research has been explored by two publications of our group revealing >10,000 somatic mutations within miRNA genes across more than 13,000 cancer samples originating from different cancer types. We showed that more than 30% of cancer samples harbored at least one mutation in miRNA genes. We have identified dozens of recurrently mutated miRNA genes and hotspot mutation. Nevertheless, these results have been obtained from bioinformatic analysis of genetic data gathered in large cancer genome projects and further experimental validation is needed.

The scope of this project is focused on finding the consequences of identified mutations for cancer cell functioning. We will analyze the influence of mutations on the crucial features of miRNA precursors that ensure their proper maturation in cells as well as their impact on the regulation of gene expression. We expect to distinguish deleterious from benign or neutral mutations, and maybe even to identify oncogenic driver mutations. The obtained results will not only deepen our knowledge of the role of miRNAs in cancerogenesis but may also lead to the identification of new potential therapeutic targets and biomarkers of cancer.