Analysis of somatic mutations in miRNA and miRNA-biogenesis genes to identify new therapeutic targets and biomarkers of cancer

Cancer encompasses a broad spectrum of diseases (>100) arising from the accumulation of somatically acquired mutations. These mutations provide a growth advantage to a tumor cell, resulting in clonal expansion leading to cancer progression. Among cancer-related mutations are loss-of-function mutations in tumor suppressor genes and gain-of-function mutations in oncogenes.

Lung cancer is the leading cause of cancer-related deaths worldwide, as well as in Poland. Recent progress in cancer diagnosis and treatment has been achieved due to a better understanding of the molecular mechanisms of the disease and the identification of biomarkers that allow more specific cancer treatments.

A growing body of evidence indicates that miRNAs may be a class of genetic elements that can either drive or suppress oncogenesis. miRNAs are class of short (~21 nt long), single-stranded, noncoding RNAs that play an important role in post-transcriptional regulation of most protein-coding genes. The biological functions of most miRNAs identified to date remain unknown. However, it has been well documented that miRNAs downregulate numerous genes and either stimulate or inhibit many important biological processes and diseases, including cancer. Although the role of miRNA in cancer is extensively studied and many cancer-related miRNAs has been identified, the analyses are mostly focused on miRNA expression.

For these reasons, neither loss-of-function nor gain-of-function mutations in miRNAs are detected in cancers. However, by analogy to numerous oncogenic mutations identified in protein coding tumor suppressors or oncogenes, somatic mutations in miRNA sequences may play an important role in cancer.

Therefore primary aim of our project is whole genome analysis and identification important oncogenic mutations in miRNA and miRNA-biogenesis genes in a large panel of ~400 lung cancer samples. In this project, we will use next generation sequencing (NGS) technology and developed in our laboratory miRNome enrichment platform that will allow identification of mutations present in small fraction of cells in analyzed cancer samples. We believe that among the identified mutations will be important oncogenic driver mutations, biomarkers or targets for cancer therapies that are invisible to currently used approaches and that the development and introduction of new tailored cancer therapies may be a far-reaching consequence of our project.