**DESCRIPTION FOR GENERAL PUBLIC**

T-cell acute lymphoblastic leukemia (T-ALL) is a rare subtype of acute lymphoblastic leukemia, being the most frequent pediatric malignancy. This disease is characterized by high aggressiveness and poor prognosis. The treatment is based on multi-agent chemotherapy, that presents risk of many serious and frequently long term side effects. This is of particular importance in case of pediatric patients. Moreover, T-ALL diagnostic and treatment generates high costs and yet the therapy is unsuccessful in even 20% of cases due to drug resistance and disease relapse. Childhood T-ALL is still a serious medical problem with psychological and socio-economic consequences. The development of science promotes searching for novel, more effective therapeutical strategies but to establish them, further widening of state of knowledge about T-ALL molecular mechanisms is necessary.

For many decades molecular studies concerning T-ALL were focused on searching for alterations in protein coding sequences. Thanks to this our knowledge about oncogenes and tumor suppressor genes involved in T-ALL pathogenesis is relatively wide. Currently the importance of epigenetic mechanisms and the function of miRNA in T-ALL are of particular interest. MiRNA are short oligonucleotide fragments, that function as gene expression regulators with the participation of RISC (RNA-induced silencing complex) protein complex. Several studies show that expression profile of these molecules is different in leukemic cells and in healthy cells. Moreover, it was presented, that these differences may influence the development of the disease, since overexpressed miRNA may silence tumor suppressor genes. Furthermore, underexpression of miRNA leads to decrease of their activity and thus to increased activity of oncogenes. Interactions of miRNA and their target genes are very complex. A single miRNA molecule can regulate the expression of multiple genes, while one gene can be regulated by many miRNAs. Current state of knowledge about the role of miRNAs in pathogenesis of T-ALL reflects only a fragment of complex miRNA-mRNA regulatory axis. For that cause, further studies on that field are needed.

The aim of the proposed project is global analysis of interaction of selected miRNA with their target mRNA in T-ALL cell lines (in vitro). The research will be conducted with the use of immunoprecipitation of RISC-miRNA-mRNA complexes in combination with next generation sequencing of mRNA fraction obtained after immunoprecipitation. This methodology will allow to detect the whole spectrum of target genes for studied miRNA. Such combination of techniques was not previously used in miRNA in T-ALL studies. Identified interactions will be confirmed by the second method, Dual Luciferase Reporter Assay. Oncogenic/tumor suppressive potential of selected miRNA will be assessed in functional test conducted on T-ALL cell lines (viability changes and apoptosis level tests upon silencing and/or overexpression of selected miRNA).

Aberrantly expressed miRNA in T-ALL will be selected based on already obtained next generation miRNA sequencing results, that was conducted on pediatric T-ALL patient samples. To date, there are only few studies using NGS technologu in studies on miRNA in T-ALL. None of these studies is supported by functional analysis. This is the next novelity element in our research. The combination of several modern research approaches will enable to greatly expand the state of knowledge about miRNA-mediated regulatory axes and pathways in leukemic cells.

The results obtained in the proposed project will provide a deeper insight into miRNA-mRNA regulatory relationships in oncogenesis. Identified miRNA-mRNA regulatory axes will serve as a starting point for further functional studied (in T-ALL mouse model) to confirm in vivo their oncogenic/suppressive function. In the long term perspective these interactions can also be a starting point for establishing novel therapeutic strategies targeted to crucial miRNA-mRNA regulatory pathways.