Project 7.1. Deciphering molecular mechanism of CDK8 inhibitors action in acute myeloid leukemia

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Background:
Acute myeloid leukemia (AML) is a heterogeneous disease characterized by multiple genetic and molecular abnormalities. Despite increasing understanding of AML pathogenesis and the development of new targeted agents, the standard cytotoxic drugs followed by hematopoietic stem cell transplantation (HSCT) remain cornerstones of AML treatment. However, with still roughly half patients relapsing, overall survival rates remain low.

The Department of Genetics of MSCI in cooperation with Selvita has demonstrated the anticancer properties of the CDK8 inhibitor (Oncotarget. 2017; 8:33779-33795), SEL120, in vitro and vivo models of AML. Molecular features of therapy-sensitive models (presence of CD34+ and STAT1/5 phosphorylation) were defined but the mechanism of CDK8 inhibitor action has not been established. Pilot studies indicate the interaction of CDK8 with the chromatin complex remodeling PRC2, including the enzyme EZH2. Project funded by the National Science Center (NCN), SONATA BIS scheme. Recruitment for the project is in conjunction with the competition for the NCN's scientific scholarship according to the rules defined by the Resolution No. 25/2019 from 14 March 2019 of the NCN Council.

Aim:
The aim of the project is to search for a mechanism of CDK8 inhibitors action with the emphasis on the CDK8-PRC2 axis. The project will conduct a deep molecular characterization of SEL120 resistant and sensitive cell lines using high-throughput genomic (RNA-Seq, ChIP-Seq) and proteomic (SWATH-MS, SILAC-MS, IP-MS) technologies and the results will be confirmed in a mouse model of the patient derived AML xenografts (PDX models).

Requirements:
- Motivation for scientific work, supported by previous scientific activity (participation in conferences, internships, publications, membership in scientific societies).
- Authorship or co-authorship in a chapter in a scientific monograph/publication
- Knowledge of laboratory techniques such as DNA isolation and RNA, mass spectrometry (MS), NGS or experience and appropriate permits to work with laboratory animals will be an advantage
- Knowledge of statistical analysis
- Good English language skills, allowing free communication in speech and writing.
- Ability to prepare research results for publication and presentation at conferences
- Communication skills and ability to work in a team.