Verification of personalized therapeutic strategy based on Integrated Stress Response inhibition for myeloid neoplasms with PTPN11 mutations.

According to the WHO and European Society for Medical Oncology, myeloid neoplasms, such as Acute Myeloid Leukemia (AML), represent one of the most common leukemias in adults (up to 80%) and account for more than 3% of all cancer deaths. For highly resistant AML, little improvement has been achieved over the past few decades, and the 5-year survival significantly decreases with age showing only17% for people over 65. Together with increasing population age, it is a serious clinical and demographic problem. Also for Chronic Myeloid Leukemia (CML), another type of myeloid leukemia, even if successful therapies with tyrosine kinase inhibitors have been introduced for chronic phase, they are not effective in the blastic phase, leading to relapse. The main obstacle to successfully cure is elimination of cells with a resistant phenotype. Introduction of genetic analysis into the diagnostics allowed to identify driver molecular alterations leading to disease development and resistance, making patients' stratification possible. This also initiated the novel personalized strategies for a specific type/subtype of disease. Thus, development of personalized, effective therapies to specifically treat myeloid leukemias with the resistant phenotype, is an urgent need and a prospective direction of future research.

The internal signaling pathways are often responsible for the resistance in leukemia. This includes highly prosurvival RAS/RAF/ERK and JAK2/STAT5 signaling, which among others, can be specifically activated by the *PTPN11* gain-of-function gene mutations, leading to uncontrolled hyperactivation of the RAS/RAF/MAPK, JAK/STAT and PI3K/AKT signaling. Importantly, even if *PTPN11* mutations are not very frequent in adult myeloid neoplasms, they are responsible for the resistance, therapy failure and poor overall survival. Therefore, novel therapies are needed to target this high-risk leukemia subtypes carrying *PTPN11*-mt. Our studies showed that also Integrated Stress Response, an evolutionary conserved signaling network that facilitates cellular adaptation by reprogramming cellular response is a protective signaling that strongly promotes cancer cells survival. All those factors orchestrate together to promote therapy resistance, disease progression and relapse, and they all should be targeted by the efficient therapy. Our previous and pilot studies have shown that Integrated Stress Response is active in leukemic cells, correlates with resistance and disease progression, and its targeting attenuates prosurvival pathways and eliminates resistant cells..

The Aim of the proposed studies is to verify novel personalized therapeutic strategy which is based on the targeting of Integrated Stress Response combined with the standard-of-care therapy with tyrosine kinase inhibitors, to inhibit prosurvival signaling in myeloid neoplasms carrying PTPN11 mutations.

The studies will be performed by broad comprehensive state-of-the-art methodology, using different *in vitro* and *in vivo* models, including model leukemia stem cell lines, immunodeficient mice and leukemia mouse models as well as verified by using primary material from myeloid leukemia patients with PTPN11 mutations, selected based on the genetic screen.

This project addresses major needs to develop novel therapies for more effective treatment of myeloid malignancies, showing big impact and novelty. Its realization will provide significant novel data, lead to development of novel experimental and comprehensive models and approaches as well as provides translational studies towards verification of novel personalized therapy which altogether might show significant therapeutic implications.