Project 1.11 Verification of personalized therapeutic strategy for myeloid neoplasms with PTPN11 mutations

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Background:

Myeloid neoplasms, especially highly heterogeneous Acute Myeloid Leukemia (AML), represent the most common types of leukemia in adults. Very little improvement in survival has been achieved over the past decades. Development of combined personalized therapies designed for selected patients identified by genetic screen followed by specific targeted treatment seem to be the best current strategy. Our project addresses major needs to develop novel therapies for myeloid malignancies with PTPN11 mutations and Ras pathway overactivation, which are characterized by high resistance and bad clinical outcomes. Previously we have identified prosurvival signaling which can be a novel potential target for eradication of resistant cells and effective therapy in those leukemias.

Aim:

The studies will verify the therapeutic strategy based on specific targeting of elements of prosurvival signaling in PTPN11-mutated myeloid leukemia. It includes investigation of potential drugs and investigate the effects of the new personalized therapy on survival, stroma-mediated protection and finally leukemia development, sensitivity to treatment and efficient eradication of leukemic cells. The PhD project will be realized using in vitro cell culture and co-culture models, leukemia patients' primary material and PDX in vivo models / immunodeficient mice, leukemia mouse model, sc-RNAseq, multiparameter flow cytometry with unsupervised data analysis, as well as signal transduction and cell biology studies. Studies include collaboration with national and international scientific and medical institutions.

1. Dudka et al., Targeting Integrated Stress Response by ISRIB combined with imatinib attenuates STAT5 signaling and eradicates therapy-resistant Chronic Myeloid Leukemia cells. bioRxiv 2021.05.05.442756; doi: https://doi.org/10.1101/2021.05.05.442756

2. Swatler et al., 4-1BBL-containing leukemic extracellular vesicles promote immunosuppressive effector regulatory T cells. Blood Adv. 2022 Feb 7:bloodadvances.2021006195. https://doi:10.1182/bloodadvances.2021006195

3. Kusio-Kobialka M, Podszywalow-Bartnicka P, Peidis P, Glodkowska-Mrowka E, Wolanin K, Leszak G, Seferynska I, Stoklosa T, Koromilas AE, Piwocka K. The PERK-eIF2α phosphorylation arm is a pro-survival pathway of BCR-ABL signaling and confers resistance to imatinib treatment in chronic myeloid leukemia cells. Cell Cycle. 2012 Nov 1;11(21):4069-78. https://doi:10.4161/cc.22387

Requirements:

- we are looking for highly motivated person ready to actively participate in the scientific challenge to address those emerging questions,
- the candidate should have accomplished master degree in biomedical, biology, medicine, biotechnology or related studies,
- experience in laboratory work in the area of cellular/molecular biology is required,

- experience in work with primary blood cells and /or mouse models would be an important advantage,
- candidate should be able to collaborate and work in the team, should have high motivation and dedication to work in science as well as determination to solve scientific problems,
- good English skills are required.