Institute of Hematology and Transfusion Medicine

is looking for a **PhD student** for a project

Project title: ”Role of Mitochondrial Intermembrane Space Assembly (MIA) pathway in acute myeloid leukemia”

Funding: NCN OPUS grant no. 2021/43/B/NZ5/01684 (planned start: October 2022)

Supervisor: Dr. Carlo Vascotto, PhD

Institute: Zakład Hematologii Eksperymentalnej, Instytut Hematologii i Transfuzjologii

Project description: Acute myeloid leukaemia (AML) is a heterogeneous group of haematopoietic malignancies characterized by the proliferation of abnormal leukemic blast cells of the myeloid lineage and impaired production of normal blood cells. The current standard treatment for induction of complete remission in previously untreated AML patients is a combination of an anthracycline and cytarabine. Despite initial responses to this regimen, most patients eventually relapse and long-term prognosis is very poor. Indeed, after treatment the leukemia stem-cells (LSCs) population frequency dramatically increases and LSCs are believed to be responsible for relapses. Hematopoietic stem cells (HSCs) use anaerobic glycolysis as the main energy source while mitochondrial oxidative phosphorylation (OXPHOS) is used when HSCs switch toward proliferation and differentiation. In AML and LSCs energy requirement is higher and therefore to meet these demands cells undergo a metabolic reprograming toward an oxidative metabolism. At the same time, the highly metabolic rate determines a consequently increased production of mitochondrial reactive oxygen species (ROS). ROS are highly reactive molecules that damage biomolecules, including mitochondrial DNA (mtDNA) and RNA (mtRNA) negatively affecting mitochondria functionality. Therefore, preventing the efficient repair of mtDNA and altering the mitochondrial translation processes represent a novel strategy to overcome the acquired resistance of neoplastic cells, which presently hinders the success of many anticancer therapies. APE1 is an essential enzyme in the DNA base excision repair (BER) pathway, which is responsible for repairing both nuclear and mitochondrial oxidative DNA lesions. In addition, data from our laboratory revealed a novel role of the mitochondrial form of APE1 in the degradation processes of non-functional abasic mt-mRNAs. APE1 is imported into mitochondria under oxidative stress conditions and the pathway responsible for the entrance of APE1 into the mitochondrial intermembrane space (IMS) is the Mitochondrial Intermembrane Space Assembly (MIA) pathway. Based on these confirmations, we are postulating an innovative strategy to selectively target therapy-resistant LSCs by inhibiting the MIA pathway as a way to prevent APE1 translocation into mitochondria and, as final consequence, to interfere with the OXPHOS program.

This PhD project is a part of a research project funded by NCN entitled: "*Inhibiting the Mitochondrial Intermembrane Space Assembly pathway as a new approach to prevent metabolic reprogramming of therapy-resistant leukemia stem-cells*". The part of the

project planned to be carried out by the PhD student will consist in the characterization of the MIA pathway and mitochondrial APE1 in AML cultured cell lines. We will evaluate OXPHOS profile and link this parameter with the expression of Mia40. The investigation will be integrated with the quantification of mitochondrial APE1, the evaluation of mtDNA and mRNA damage levels and the efficiency of mitochondrial translation. Then, we will evaluate the effects associated with Mia40 loss of expression and how cells respond to treatment. Finally, data collected from the cell line models will be combined with results from primary patient-derived blasts. In parallel, the PhD student will contribute to the production of a Mia40 inhibitory peptide that in our preliminary studies proved to be effective in inhibiting Mia40 activity.

In the course of the project, the PhD student will acquire a range of skills in cellular and molecular biology techniques with a specific focus on mitochondria. He/she will participate in meetings with collaborating laboratories and take part in scientific conferences and manuscripts preparation. The PhD student will also have the possibility to spend a period abroad and to apply for personal founding.

Requirements:

- Completed (or completing in the current academic year) Master's degree or equivalent in Biotechnology, Medicine, Biomedical Engineering or equivalent;
- Knowledge of cell biology, molecular biology;
- Prior practical experience in molecular and cell biology techniques (previous experience is mitochondrial biology is not mandatory but welcome);
- Good English command (both written and spoken).

Job description:

The PhD student will be involved in the project supervised by dr Carlo Vascotto, funded by National Science Center (OPUS-22 track, 2021/43/B/NZ5/01684) „**Inhibiting the Mitochondrial Intermembrane Space Assembly pathway as a new approach to prevent metabolic reprogramming of therapy-resistant leukemia stem-cells".** In particular, the successful candidate will be involved in the design and execution of experiments according to the project experimental plan and under dr Vascotto supervision (development of inhibitory peptides, peptide expression, purification, evaluation of biological effects in cell line models and primary AML cells)

Offered fellowship terms:

- PhD fellowship: 5000 PLN/month until mid-term evaluation, 6000 PLN after succesfull evaluation.
- The fellowship is conditioned on the succesfull outcome of recruitment proces to the PhD school (https://www.cmkp.edu.pl/ksztalcenie/wspolna-szkola-doktorska)

Application deadline: 15 August 2022, 23:59

Please send applications to carlo.vascotto@uniud.it, with email topic "OPUS-PhD School application")

The first step of the selction process will be concluded on or before **30.08.2022.**

Final decisions will be made before **01.10.2022.**

Required documents:

- Copies of MSc/MD diploma;
- CV;
- motivation letter justifying the selection of this project;
- Consent to personal information processing for the purpose of the candidate evaluation;
- Contact information to two referees (previous supervisors) who can provide credentials.