DESCRIPTION FOR THE GENERAL PUBLIC

Leukemias constitute a heterogeneous group of diseases characterized by infiltration of the blood, bone marrow and other tissues by cancer cells originating from hematopoietic system. The interactions between cancer cells and their microenvironment are crucial for the development of leukemia. Variety of factors is secreted by both leukemia cells and the non-malignant cells, which mediate cell-cell communication within the microenvironment and provide a suitable niche for cancer cells growth and survival. It is well evidenced that bone marrow microenvironment protects leukemia cells from cytotoxic therapies.

Leukemia cells reside in the bone marrow, where oxygen level is low, and appear in peripheral circulation, characterized by much higher O_2 level. The distinct conditions in these environments induce different adaptive mechanisms in the cells. Activation of pro-survival pathways and loss of genomic stability seem to be major mechanisms leading to progression of cancer. The general assumption of this project is that activity of pathways that support adaptation of cells to changes in the environment and extracellular signals might play central role in the regulation of mechanisms enabling resistance of leukemia cells to therapy. Regulation of mRNA translation during activation of stress response supports cell survival under changing conditions. Control of protein synthesis by proteins that bind to mRNA and regulate its post-transcriptional fate allows to adjust the profile of cellular proteins to the demands of cell survival.

The presented research proposal involves continuation of collaboration between Paulina Podszywalow-Bartnicka, *PhD* from the Nencki Institute of Experimental Biology in Warsaw, the principal investigator of this project, and Professor Tomasz Skorski, *MD, PhD* from the Temple University School of Medicine in Philadelphia, USA. Team headed by Professor Skorski possesses expertise in studying the DNA damage response pathways as well as the development of leukemia using humanized mice. The aim of this collaboration is to tackle the problem of leukemia cells resistance to therapy, which is observed in the bone marrow niche and is responsible for cancer relapse. The specific aim of this joint project is to verify if activity of RNA binding proteins in leukemia cells influences processes such as DNA damage repair or programmed cell death, what would constitute basis for leukemia cells resistance to therapy. Execution of this project involves usage of various molecular biology techniques including CLIP-seq for identification of mRNAs subjected to post-transcriptional regulation by selected RNA binding proteins. Accomplishing of research implicates usage of innovative experimental setup of human bone model. Completion of this project will allow to broaden the understanding of the mechanisms supporting therapy resistance of leukemia stem cells residing in the bone marrow niche. This might support development of new, more successful therapeutic strategies allowing to decrease the risk of leukemia relapse.