The role of the bone marrow microenvironment in protecting and supporting resistance to therapies in leukemia is extensively studied but still not fully understood. Studies indicate that cancer cells, including leukemia cells, have the ability to adapt to various stress conditions, such as chemotherapy or stress caused by oncogenes, by changing their metabolic processes. Metabolic reprogramming of cancer cells is often associated with a clear preference for glycolysis as the main energy-providing process for these cells. In leukemias, increased glycolytic activity is often associated with their increased resistance to the applied therapies. Little information is currently known about the impact of the bone marrow microenvironment on the process of metabolic remodeling of leukemia cells, especially in relation to specific factors regulating this process.

Bone marrow stromal cells and chronic myeloid leukemia (CML) cells have been found to communicate through thin, membranous tunnels known as tunneling nanotubes (TNTs). These structures facilitate the direct transfer of various molecules between distant cells. In our previous studies we have observed the transfer of cellular vesicles and proteins from bone marrow stromal cells to leukemia cells via TNTs. The recipient leukemia cells exhibited increased resistance to imatinib, a drug used in the treatment of CML. Among the transferred proteins with potential protective properties, we have identified the CD44 protein, which is overexpressed in numerous cancer types and associated with tumor progression, metastasis, and drug resistance. Our studies have demonstrated that the transfer of this protein from stromal cells to leukemia cells leads to enhanced resistance and invasive capacity in the recipient cells. Additionally, we have observed an upregulation of leukemic CD44 expression under stress conditions, such as hypoxia or endoplasmic reticulum stress, which are commonly found in the bone marrow microenvironment.

The main goal of the research project is to understand how the bone marrow microenvironment affects changes in the metabolism of chronic myeloid leukemia cells. Our focus will be on investigating the involvement of the stromal CD44 transferred directly from stromal cells to leukemia and leukemic CD44, whose expression was induced by conditions imitating the bone marrow microenvironment (presence of stromal cells, reduced oxygen concentration (hypoxia), factors inducing cellular stress). To carry out this investigation, we will employ state-of-the-art tools for studying metabolism in specific cell populations, utilizing *in vitro* cell models that have been developed by our team.

The findings from this project will provide us with a deeper understanding of the CD44 protein's role in CML and its impact on metabolic changes in leukemia cells. Moreover, analyzing the influence of the myeloid leukemia microenvironment on CD44 levels and functions has the potential to shed light on the intricate interactions between leukemia cells and their surroundings. In the long term, this enhanced understanding of the underlying processes could pave the way for the development of more precise therapies and advancements in the treatment of myeloid leukemias. While our planned experiments will primarily focus on chronic myeloid leukemia, the insights gained from our research may have broader applications in other myeloid leukemias, including acute myeloid leukemia (AML). This is due to the shared bone marrow microenvironment, implying potential similarities in metabolic mechanisms and interactions with the microenvironment.