Description for the general public

Breast cancer is one of the most common malignancies in women. One in eight women is expected to develop breast cancer in their lifetime. Despite significant advances in the treatment of breast cancer, the biology of this disease is still not fully understood, which justifies the need for basic research in the field of oncology.

The goal of this project is to investigate the molecular mechanisms of MLK4 biology, and to search for novel treatment strategies in breast cancer using MLK4-degrading PROTAC compounds. MLK4 (Mixed-Lineage Kinase 4) is a member of the MLK family of serine/threonine kinases that plays a role in a variety of cellular processes, including migration, apoptosis and proliferation. Despite an increasing number of studies describing the involvement of MLKs in tumorigenesis, the role of MLK4 in cancer progression is still relatively unknown. Our group has previously shown that MLK4 is highly expressed in breast carcinoma and that it contributes to aggressive behaviour of breast cancer cells. Moreover, our recent results indicate that MLK4 activity is associated with increased resistance of breast cancer cells to chemotherapy. Therefore, there is an undeniable **need to develop compounds limiting oncogenic activity of MLK4**. Moreover, **MLK4 is a classic example of an understudied kinase and it is essential to understand the mechanisms of its action that have not been adequately characterized yet**.

Therefore, the objective of this project is to explore the mechanisms underlying MLK4 action in cancer cells and to develop novel therapeutic agents blocking the oncogenic activity of MLK4. The project has **two main objectives** aimed at: **1)** identification of the MLK4 binding partners and investigation of the molecular details and functional significance of those interactions; **2)** development of novel PROTAC compounds targeting MLK4 for degradation and their application in studying the molecular mechanisms of MLK4 function and breast cancer therapy. For the second aim we will use an innovative PROTAC technology that enables proteasome degradation of target protein.

The results obtained by us will deepen our understanding of the molecular mechanisms of MLK4 activity and contribute to the characterization of MLK4 kinase as a new therapeutic target. Thanks to the knowledge generated in this project we will be able to design better and safer strategies in cancer treatment. Furthermore, we will provide novel MLK4-PROTAC compounds blocking oncogenic activity of MLK4 that can be further tested in preclinical studies.