Mammalian cells are exposed to many types of stress. One of them is the stress associated with the improper production and maturation of proteins taking place in the intracellular membrane system called the endoplasmic reticulum (ER-stress). During evolution, cells have developed defense mechanisms that help restore normal cell function. One of them is the signaling pathway associated with the PERK protein, which in response to improperly formed proteins activates processes to restore homeostasis of the cells. Depends on the type of stressor and the time of exposure, PERK can recover proper functioning of cell or can activate programmed cell death to remove injured cell from the system. Aforementioned ER-stress is a characteristic feature of cancer cells where a high rate of metabolism occurs; this increases the demand for protein production. Due to the presence of numerous mutations, cancer cells are able to engage defense mechanisms to promote their survival and growth. In our previous melanoma studies, we showed that the cancer cells (induced by the BRAF gene mutation), with one copy of the PERK gene, develop aggressive form of cancer in comparison to significantly less malignant in the lack of PERK gene. These observations suggested that PERK is an important target for anti-cancer therapy. Our studies utilizing chemical compounds (PERK inhibiting drugs) that blocks PERK activity in the mouse model showed a significant therapeutic effect (development of smaller tumors, slower progression of the disease). Our current research is a promising for the development of new cancer treatment strategies, however, it is important to determine whether the same pathological effect of PERK activity takes place in various cancers and whether it is tissue-specific. In addition, the role of PERK in the pathogenesis of tumors is more complex due to the presence of mutations which are important to be characterized for its role in carcinogenesis. Another aspect of PERK function in cancer biology is its ability to regulate lipid metabolism and conversely, the regulation of PERK activity by lipids, sphingosine in particular. Exploration of this issue opens up new possibilities for establishing natural PERK regulators such as lipids. This approach is innovative and challenging due to technical and methodological limitations. The presented proposal is one of the first attempts to establish the interaction between lipids and response proteins to stress of the endoplasmic reticulum.

In summary, the work described in this project will delineate molecular mechanisms of both pro- and anti-tumor properties of PERK (with a special focus on the role of mutations) using both chemical and genetic approaches. The second goal is the mutual control of PERK and lipid metabolism pathways in the context of the development of new therapeutic strategies in the treatment of cancer.