Cancers are currently one of the leading causes of death worldwide. Their characteristic feature is the proliferation of cells that are out of control of the body. The development of such cells is very fast, and reasons for changes should be sought in the genetic and biochemical changes in the mutated cells. Among cancer, colorectal cancer (CRC) is currently the second most common cancer among women and the third among men. Poor responsiveness to therapy and high malignancy level are the cause of a very low coefficient of 5-year survival rate (in Poland about 30%) and make the CRC fourth cause of cancer deaths. The incidence is increasing year by year, and in spite of intensive research in this area etiology of the disease remains undetermined. This is due to the very complex mechanisms which lead to the neoplastic transformation of cells as well as by a plurality of factors that may cause this transformation and influence its development. Certainly a significant part in tumorigenesis are stressors, which include shortage of glucose, impaired redox homeostasis and calcium levels. The main stressful stimulus leading to the development of neoplastic disease is hypoxia that causes activation of a cell response pathways closely linked to changes in gene expression.

We expect that the use of small molecule inhibitors of PERK kinase can contribute to overcome the current problems of tumor therapy. Under hypoxic conditions tumor cells greatly reduce the effort of oxygen and energy when compared to normal cells. The reason for these differences lies in the adaptive processes of cancer cells, enabling them to survive in stressful conditions of hypoxia. Low oxygen levels induced stress of the endoplasmic reticulum (ER), which leads to the activation of one of the transmembrane receptor ER - PERK. The result is activation of the Adaptive Responses to Stress (Unfolded Protein Response - UPR). There is ample evidence that the UPR signaling cascade has a dual role. On the one hand phosphorylation of translation initiation factors eIF2α occurs. This significant modification of tumor cells determines the silencing of translation of major proteins in the cell. In addition, there is also a cell cycle arrest in a growth phase G1. On the other hand, under conditions of prolonged stress conditions the expression of two specific proteins ATF4 and CHOP is increased. The key to our study is that they are closely associated with the activation of apoptotic ER-dependent pathways leading to tumor cell death.

Due to long-term cooperation with Prof. J.A. Diehl, that has extensive experience in research in the basics of the process of carcinogenesis, from the Medical University of South Carolina, we were able to select a series of new potential inhibitors of PERK kinase using a computer docking techniques, and high-performance screening tests. 9 compounds were selected as the most specific for the PERK kinase from 79552, which has been tested by us.

Verification of our hypothesis includes four main objectives:

1. In vitro analysis of the ability of selected compounds to inhibit PERK-dependent signaling pathway in colorectal cancer cell lines.
2. In vitro analysis of cytotoxicity of selected PERK inhibitors, PERK/eIF2α/ATF4 signaling activation and the level of apoptosis and cell cycle in colorectal cancer cell lines.
3. In vivo analysis of low molecular weight PERK inhibitors activity, their ability to reduce CRC tumor growth and promotion of apoptosis in cancer cells in mouse transgenic model.
4. In vivo analysis of PERK kinase inhibitors in clinical model of colorectal cancer and their potential use in therapeutic treatment of CRC in mouse transgenic model.

The proposed project is one of the first that can give an answer to the question of how to overcome the disadvantages of current anticancer therapy. We expect that the use of small molecule kinase inhibitors of PERK as potential anticancer drugs can provide effective therapy and consequently contribute to the invention of a novel targeted anti-tumor strategy.