Cancer is the second leading cause of death worldwide, representing a serious medical problem. Liver and kidney cancers are among the top ten most common cancers in both men and women. Due to the lack of typical symptoms in the first stages, at the time of diagnosis, metastases are found in one third of patients, and the chances of survival are dramatically reduced. Currently, the most commonly used treatment is tumor excision, followed by chemo- or radiotherapy, which are associated with numerous side effects. Therapy of more advanced stages is based on new anti-angiogenic drugs, such as sorafenib, which inhibit the receptors of certain tyrosine kinases. Unfortunately, this form of therapy is not fully satisfactory because it extends the survival time of patients by only a few months. Moreover, cancer very quickly develops resistance to the drugs, and the majority of patients who receive such treatment exhibit progressive disease after one year.

Inflammatory processes play an extremely important role in the growth and development of cancer. One of the modulators of the inflammatory response is the MCPIP1 protein, encoded in humans by the ZC3H12A gene. This protein is involved in the negative regulation of inflammation due to RNase activity, which allows the degradation of pro-inflammatory cytokine transcripts. Recent reports suggest that the MCPIP1 protein may significantly affect the development of cancer by regulating factors involved in the processes of growth, proliferation and cell death. Our group showed that the level of MCPIP1 in the tumor tissue is significantly lower compared to the surrounding healthy tissue in clear cell renal cell carcinoma. Moreover, high levels of MCPIP1 partially abrogate the resistance of kidney cancer cells to sorafenib.

The aims of this project are:

1. Determination of the significance of the *Zc3h12a* deletion in normal kidney and liver cells on phenotypic changes leading to the development of cancer,

2. Investigation of the role of the MCPIP1 protein in the resistance of cancer cells to sorafenib and its potential role in gene therapy

We believe that the MCPIP1 protein may play a key role in neoplastic transformation and the acquisition of resistance to sorafenib by changing the phenotype of a normal cell and acquiring the characteristics of a cancer cell. Considering the results published by our and other research teams, MCPIP1 may be an universal suppressor protein. The project undertakes an innovative subject and a comprehensive approach to the problem. In our research, we will use cell lines as well as unique mouse models. Part of the experiments will be carried out on tissues from patients with hepatocellular carcinoma.

The studies proposed in this project will help us understand why the methods used to treat kidney and liver cancer fail. The obtained results may contribute to increasing knowledge about the process of cancer initiation, and will also help in better understanding the biology of kidney and liver cancers, and may contribute to the creation of a better form of therapy.