Renal cell carcinoma (RCC) is the most common form of renal cancer, accounting for 90% of all tumors, with clear cell renal cell carcinoma (ccRCC) being the most common histological type (75%). 5-year survival is observed in up to 90% of patients with early, localized disease, but drops to 12% in patients with distant metastases. Clear cell renal cell carcinoma is a highly vascularized tumor which makes it difficult to treat effectively. Therefore, the current therapies focus mainly on inhibiting the tumor blood supply by acting on various signaling pathways, and the anti-angiogenic agents used, such as sunitinib, pazopanib, cabozantinib or everolimus, inhibit the progress of the neoplastic disease. Another type of treatment is immunotherapy, e.g., with programmed cell death 1 (PD-1) blockers, but it also does not give spectacular results in the treatment of patients. Combining the therapies used increases the chances of survival. Studies show that among patients with clear cell renal cell carcinoma classified into the high and low risk groups, it was found that the genes with different expression in the two groups were different, and the primary signaling pathways were also unique. This means that the therapy must be tailored to the individual changes in the patient's tumor and assess the chances of curing a particular patient.

Recent research also suggests an important role for microRNA (miRNA) in the development of metastatic tumors. MiRNAs are small RNAs that regulate the expression of many different genes in a cell and therefore influence many cell processes such as tumor growth and metastasis. In the future, miRNAs can be used clinically, because one miRNA can significantly regulate the level of several proteins responsible for the cancer process. The role of miRNAs in the pathogenesis of clear cell renal cell carcinoma is still a little understood area. Many potential biomarkers include miRNAs with different expression, but only a few have been experimentally verified. Our preliminary studies show that the growth of selected miRNAs in clear cell renal cell carcinoma causes an increase in the expression of genes responsible for tumor progression. These changes occur by inhibiting the degradation of some miRNAs by the MCPIP1 protein, which is considered a potential tumor suppressor. MiRNA is involved in the activation of various signaling pathways, including Wnt / β-catenin, which is important in the biology of clear cell renal cell carcinoma. β-catenin is a protein that enhances the expression of genes involved, among others, in into processes that induce cell growth. In neoplastic cells, excessive activity of β-catenin may cause loss of control over the cell cycle, increased proliferation, and an increase in the migratory and invasive properties of neoplastic cells, thus influencing the metastasis process. In our study, we observed that clear cell renal cell carcinoma cells are characterized by elevated levels of several miRNAs and β-catenin, accompanied by increased migratory activity. Therefore, we believe that more detailed research into the molecular mechanisms responsible for metastasis, including activation of the miRNA-β-catenin signaling pathway, is necessary.

The proposed project aims to investigate the mechanism responsible for increased migration activity and invasiveness of clear cell renal cell carcinoma and to investigate how modifications of β-catenin contribute to the progression of this cancer. We also want to assess whether fluctuating miRNAs and β-catenin activation may be prognostic factors in clear cell renal cell carcinoma. The final point will be to analyze whether the miRNA-β-catenin axis is activated in a mouse model that does not express the *Zc3h12a* gene encoding the Mcpip1 protein in the renal epithelial cells. In our research, we will use cell cultures of clear cell renal cell carcinoma, mouse models with an impaired immune system, and tissue-specific animal models lacking the expression of the *Zc3h12a* gene. We will use several techniques and methods in the field of molecular, cellular and biochemistry. The research carried out in this research project may help to understand the mechanisms responsible for the involvement of MCPIP1 in the regulation of miRNA, β-catenin levels, and in the activity and invasiveness of clear cell renal cell carcinoma.

To our knowledge, such an analysis of the role of the miRNA-β-catenin signaling axis in the progression and invasiveness of clear cell renal cell carcinoma is a novel and innovative approach that has not yet been studied by other scientists in the world. We believe that a detailed understanding of this pathway will allow us to better understand the course of this type of cancer. Importantly, the results of the proposed project will be presented at local and international scientific conferences on cancer biology and can help in the development of new therapies, and will then be published in recognized international journals, thus pointing the way for future research.