In our research we are interested in the growth and progression of rhabdomyosarcoma (RMS). It is one of most common tumor types affecting children. Two major types of this tumor may be distinguished: embryonal (ERMS) and alveolar (ARMS), which is usually associated with worse survival prognosis. Metastatic spread of the tumor to distinct organs and tissues, such as bone marrow and lungs, results in high morbidity of patients with the highest tumor grade. The conventional treatment strategies for RMS are mostly based on surgery, which is followed by chemotherapy and radiotherapy. Surgery often leads to life lasting disability of the patients. The latest trends in basic and clinical research give special attention to development of therapeutics that precisely block function of mutated or overexpressed proteins and thereby cause minimal side effects. Nevertheless, in order to develop new treatment strategies in future, firstly the detailed knowledge about molecular mechanism underlying the disease pathology is necessary and it can be achieved by performing basic research.

Based on tumor origin different tumor types can be distinguished: epithelial or mesenchymal, non-epithelial. RMS belongs to the second category. Metastasis of epithelial malignancies is regulated by epithelial to mesenchymal transition (EMT). It is a process of complex morphogenetic changes in a cell, which results in increased motility and invasiveness and thereby it leads to metastatic dissemination of cancer. Several factors are known as crucial regulators of EMT including family of SNAIL transcription factors. Transcription factors bind to regulatory regions of many genes and thereby they affect levels of many different proteins in cells. In our research we suppose that factors regulating EMT in epithelial tumors may also affect metastatic spread of mesenchymal tumors. However, different molecular mechanisms may be responsible for that process. Our research group has recently demonstrated that the level of SNAIL is higher in ARMS, which is usually associated with worse prognosis than ERMS and that it can play a crucial role in metastatic spread of this tumor type.

Recently in the literature it is postulated that microRNAs are involved in regulation of epithelial to mesenchymal transition (EMT) in metastatic tumors of epithelial origin. MicroRNAs are small RNA sequences regulating expression of many different genes in cells and thereby they exert effects on many different cellular processes, such as tumor growth and metastasis. In future microRNAs may be on a way to the clinic use, as one microRNA may very potently regulate the level of several proteins important in tumorigenesis. Some studies have already demonstrated the significant role of several microRNAs in RMS development. Nevertheless, the literature lacks the comprehensive studies describing the significance of the whole microRNA transcriptome changes in development of metastatic RMS, as an example of non-epithelial tumor. What is important, many cases of RMS are benign and only those RMS tumors that become metastatic significantly increase morbidity of the patients. Therefore studies on molecular mechanisms responsible for metastatic spread are the most important ones.

In tumors of epithelial origin the significant role of SNAIL-microRNAs axis in metastatic spread has already been indicated. In our studies we hypothesized that similar mechanisms may be also crucial for metastasis of non-epithelial tumors, such as RMS. Therefore in the current project firstly we would like to investigate the effect of SNAIL transcription factor on the whole microRNAs transcriptome, what will enable us to discover novel microRNAs regulated by SNAIL in non-epithelial tumors, which are the most potently regulated by SNAIL for further research. Subsequently we will determine the effect of the selected microRNA candidates on gene expression, cellular divisions, motility, viability and proangiogenic capabilities (responsible for tumor vascularization). These parameters are crucial for tumor metastasis. We will also evaluate the role of the selected microRNA candidates, which are the most potently regulated by SNAIL, in growth, vascularization and metastasis of RMS using mouse model.

According to our best knowledge such a comprehensive analysis of the role of SNAIL-microRNA axis in RMS metastasis is a unique approach which so far has not been done previously by other researchers around the world. We believe that the detailed studies on this pathway will increase the knowledge about pathology of this tumor type. What is also important, the results obtained in this project will be presented at local and international scientific conferences on tumor growth and drug development and subsequently they will be published in international journals with high impact factor and thereby they will also indicate new directions for further research. We believe that they may be of significance for better understanding progression of other mesenchymal tumors types which display SNAIL expression.