Research project objectives Meningiomas are among the most commonly diagnosed intracranial human tumors. The majority of meningiomas are benign tumors with favourable prognosis for patients, but approximately 20% of the tumors are more aggressive and represent important clinical problem. Benign meningiomas tend to progress to more invading subtypes that are more difficult for complete surgical resection and are of high risk of recurrence. Despite the high incidence of these tumors, the molecular background of pathogenesis of meningiomas, including role of aberrant expression of microRNAs, is still poorly understood. MicroRNAs are small RNA molecules encoded in the genome. They play an important role in regulating protein synthesis in the cell by negative regulation of the expression of protein-coding genes. Abnormal level of particular miRNA results in impaired protein expression. When this phenomenon regards protein crucial for the homeostasis of the cell it may allow acquisition of neoplastic potential. The causes of incorrect levels of most miRNAs are unknown. Our preliminary data suggest that in meningiomas aberrant expression of 20 miRNAs may result from impaired regulation of genome activity by so called epigenetic mechanisms. Epigenetic regulation is complex and partly depends on chemical modification of DNA and structural proteins – histones that are bound with DNA in cell nucleus. Specific modifications may activate or inactivate genomic regions.

The goal of this project is to determine the role of miRNAs that are affected by impaired epigenetic regulation in meningiomas. It is aimed to verify whether these miRNAs are expressed at abnormal level in the tumors and reveal the mechanism of their action.

Research project methodology involves evaluation of DNA methylation, which is one of the best known epigenetic modifications, at genomic regions encoding miRNA molecules as well as measurmrnt of the amount (so called expression level) of selected 20 miRNAs in tumor samples and control sections of normal meninges.
This will show which miRNAs are expressed at abnormal level in tumors.
Subsequently, to investigate the role of particular miRNAs the experiments will be performed using meningioma model i.e. cell lines derived from meningioma patients. Since DNA methylation is only a part of the machinery of epigenetic regulation the relationship between different modifications will be investigated in cultured meningioma cells line. The cells will be treated with chemical agent that modulate epigenetic machinery to test whether it affects the amount of particular miRNAs.
The mechanism of action of selected miRNAs will be investigated by experimental manipulation of the level of selected miRNA in meningioma cells. This experiment has two purposes: to observe and measure its effect on properties of the cells and to find the proteins that are regulated by the particular miRNA, that play a role in neoplastic process.

This research topic was chosen for several reasons. Due to high frequency and limited therapeutic options meningiomas represent important clinical problem. The mechanisms of pathogenesis and progression of benign meningiomas to more aggressive subtypes are poorly understood. It is known that aberrant miRNA level is one of the hallmark of cancer cells. However, in case of meningiomas the role of epigenetic regulation of the genome and its effect on abnormal miRNA expression is unknown. Manipulation of the expression level of microRNAs in patients is considered as experimental therapeutic strategy for oncology and at least three clinical trials have been started. This allows to think about restoration of miRNA expression as potential therapeutic option for meningioma patients.