Modern molecular biology provides a direct background for the contemporary medicine. It is the basic research in fields relevant to crucial medical problems, which forms a solid foundations for establishing the potential novel therapies. Nowadays, cancer is the second killer in Europe and its death share grows also in Poland. Cancer malignancy is strongly dependent on its ability to spread in the organism. Vast majority of malignant cancers is spread with circulating blood. It is, however, not the case for cancers developing in the central nervous system (CNS). Such cancers are separated from circulation blood n by the blood-brain barrier. They do not form classical metastases but colonize new regions of CNS by spreading, dependent on the cell motility. While malignancy of peripheral cancers is mainly connected to their ability to cross blood vessel wall, malignancy of cancers developing within the brain is directly associated with their ability to move at long distances. Gliomas, one of the most deadly classes of cancer, developing from non-neuronal brain cells such as astrocytes or oligodendrocytes, are among them.

Migrating glioma cells do not travel in the empty space . They are surrounded by other cells and submersed in the "bath" full with chemical compounds able to control their behavior, among them are nucleotides.Initially, extracellular nucleotides were considered to be originated from dzingc cells and their presence was a symptom of tissue damage. Today, we know that damaged cells are only one of many possible sources of extracellular nucleotides as also healthy cells are able to secrete nucleotides and to use them for nucleotide-based signaling. Moreover, there are enzymes present on the cell surface, which convert nucleotides, and cell environment may contain whole nucleotide "cocktail", containing not only ATP but also UTP, ADP or adenosine. These particles bind tothe specific membrane proteins, known as nucleotide receptors. Nucleotides as messengers are common in the CNS and are responsible for communication between active neurons and glia cells. We expect that nucleotides that are able to activate normal glia cells will also affect transformed ones, and nucleotide gradients, so common in the brain, could influence glioma spreading.

Cell motility depends on the cytoskeleton, the complex system of fibrous proteins such as actin or tubulin that interactingwith a plethora of other proteins. Those accompanying proteins generate the force needed for cell motility and regulate cytoskeleton structure and function. This regulation is tightly controlled among others by signals coming from the cell surface receptors, including nucleotide receptors. In our previous study, we have shown how activation of nucleotide receptor P2Y2 may lead to the cell recovery from RhoA pathway inhibitor (Y-27632), a compound currently examined as the drug candidate reducing cancer cell motility.

The proposed study aims at evaluation of the influence of extracellular nucleotides on the motility of three human glioma lines characterized by different invasiveness. We want to check whether the presence of the nucleotide gradients will lead to directional migration of the cells. Also, maybe there is chemokinesis, the phenomenon, where motility is not directional but the speed of translocation correlates with nucleotide concentration. Besides, what molecular mechanisms underlie the observed effects of nucleotides on glioma motility? Do we observe the same worrisome effect of nucleotides, i.e. the compensation of motility inhibition by drugs in all the examined cell lines?

It seems to us that answering these questions could greatly aids in understanding the mechanisms leading to malignancy of cancers developing in the brain and in the future will allow for development of new therapies for gliomas. To approach this problem, we plan to use microscopy expertise of Multimodal Laboratory of Motility and Adhesion Research with molecular biology experience of Laboratory of Molecular Basis of Cell Motility.