

Glioblastomas are the most aggressive and most common brain tumors in adults and children. These tumors are highly resistant to conventional treatment, including chemotherapy and radiation, which makes them extremely difficult to treat. Glioblastomas have a particularly poor prognosis and remain one of the main causes of mortality from brain tumors. Current standard therapy involves maximal surgical resection followed by simultaneous radiotherapy and temozolomide chemotherapy. Full surgical resection is difficult because these tumors are often invasive and located in eloquent areas of the brain, including part of speech control, motor functions and senses. Due to the high degree of invasiveness, the radical resection of the primary tumor mass is not therapeutic, and infiltrating cancer cells invariably remain in the surrounding brain, which leads to subsequent progression or recurrence of the disease. *In vitro* studies have shown that serotonin has a stimulating effect on the growth of several types of human cancer lines. Particularly strongly stimulating effect of serotonin on cell growth has been observed in cases of glioblastoma multiforme. The serotonin system is an interesting chemotherapeutic target in the prevention and treatment of many cancers for which therapeutic approaches are limited. A key unresolved point in many studies is whether the concentration of serotonin in the primary tumor or in metastases is consistent with its involvement in cancer progression and angiogenesis. Selective killing of cancer cell populations without affecting normal tissues is a challenge for serotonin receptor-targeted pharmacotherapy. An interesting direction that fits this approach seems to be selective, low-base ligands of selected serotonin receptors.

The aim of this project is looking for compounds with affinity for 5-HT<sub>6</sub> serotonin receptors in the context of treating glioblastoma multiforme. The project involves the development of a new group of low basic arylsulfonamide derivatives of cyclic arylguanidines as non-standard serotonin receptor ligands. The developed group will be subjected to tests of affinity for mentioned serotonin receptors, antitumor activity in relation to several glioblastoma multiforme lines and extended hepatotoxicity and metabolic stability tests. The planned studies are basic research, aimed at identifying candidates with potential anti-cancer activity, being a non-standard therapeutic approach in the treatment of gliomas and determining the role of 5-HT<sub>6R</sub> ligands in the treatment of the aforementioned cancers. As part of the project, it is also planned to develop a fast, ecological method of synthesis that will allow to obtain an extensive library of compounds in a short time, without undue burden on the natural environment (synthesis in the presence of microwave radiation or sonochemical). Ligand design will be supported by molecular modeling methods.