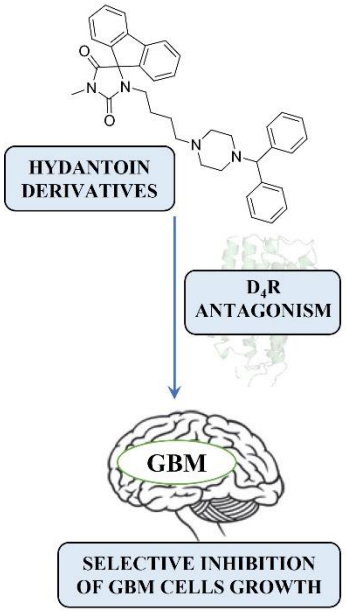
The interplay of neurochemistry and cancer biology: in the search for novel glioblastoma multiforme therapy among dopamine receptor ligands



Glioblastoma multiforme (GBM) is the most aggressive and common brain tumour. The median patient survival after diagnosis is at approximately 15 months and only less than 10% of them will survive maximum 5 years. It is now fifteen years after establishment Stupp protocol for GBM treatment (surgical resection and radiotherapy in combination with chemotherapy using temozolomide) and despite many preclinical and clinical research, no major clinical advances have been achieved, thus increasing patients overall survival remains a great challenge. Unfortunately, the GBM cells gained resistance to temozolomide (TMZ), still the gold standard for GBM treatment, thus significantly decreasing of its clinical efficacy. Hence, searching for novel breakthrough therapies is urgent to change the dramatic fate of patients

Gliomas, as other types of tumors, are not completely independent entities. Their growth strongly depends on the direct environment (so-called microenvironment). Communication between cancer cells and the microenvironment drives tumor development. The direct surroundings of GBM is an environment highly rich in neurochemical modulators (including serotonin, dopamine, adrenaline, acetylcholine and their receptors), thus suggesting that their signalling pathways may profoundly impact on the GBM development. However, the interplay between neurochemistry and cancer biology has so far been little studied and remains underestimated. The situation began to change slowly with the emergence of studies indicating at involvement of the dopaminergic system in the above-mentioned process. However, attention has been focused mainly on the most known dopamine D_2 receptor (D_2R) and its antagonists, which are commonly used as antipsychotics. It is worth adding, however, that these compounds have an equally high (or often higher) affinity for the less known and underexplored dopamine D_4 receptor (D_4R).

Considering the above facts and the recent breakthrough finding that it is D_4R and not D_2R receptor antagonism that plays an important role in inhibiting GBM cell proliferation, the aim of this project is to conduct research in a group of newly designed and synthesized D_4R ligands. The planned research tasks include a multidisciplinary approach combining computer techniques (molecular modeling) with chemical synthesis and extensive *in vitro* biological research (cytotoxicity studies with GBM cells and extensive research on the mechanisms of the observed anticancer activity). The final confirmation of the effectiveness of the designed molecules ('proof of concept') will be the assessment of anti-tumor activity in an animal model (immunodeficient mice with implanted human GBM cells).

So far, research on brain neurochemistry and brain cancer has not overlapped significantly and scientists have focused mainly on the role of neuroactive compounds in dysfunctions of the central nervous system, such as schizophrenia, depression, Parkinson's disease, and anxiety. This project highlights the great importance of the interaction of these research areas.