Addressing the brain glioma temozolomide therapy limitations

Glioblastoma multiforme (GBM), characterized by rapid progression and high invasiveness, is an aggressive brain tumour and accounts for approximately 70% of diagnosed tumours in this area. Patients undergoing the standard treatment, including resection and subsequent adjuvant therapy, can expect a median survival of about a dozen months. Unfortunately, the implemented therapeutic processes do not ensure a good quality of life for the patient. One of the procedures that bring better results is chemotherapy with temozolomide (TMZ), however, its effectiveness in the commonly used form may be limited. That I a consequence of the existence of the defensive mechanisms of the central nervous system (CNS), mainly the presence of the blood-brain barrier (BBB), that protects the CNS against the penetration of potentially harmful compounds, but also pharmaceuticals, as well as the low stability of TMZ under physiological conditions. Due to the above mentioned difficulties, only a small part of the drug can reach the therapeutic concentration at the desired site, while the rest of the introduced substance causes severe side effects.

In response to the clinical problems associated with the treatment of gliomas, three alternative TMZ delivery strategies (Fig. 1), which have a real chance to improve the patient's life quality by minimizing the limitations and increasing the effectiveness of chemotherapy are proposed within this project.

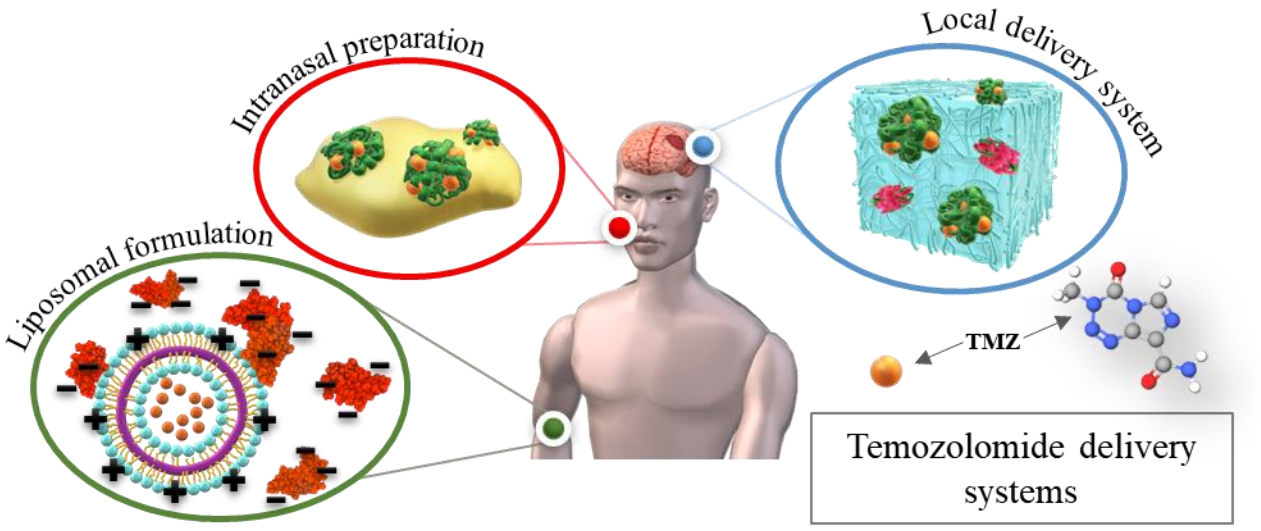

Figure 1. Schematic representation of three proposed strategies for TMZ delivery

Firstly, it is planned to fabricate an innovative multifunctional hydrogel system, containing TMZ and vancomycin, implemented directly into the tumour bed during surgery. Both agents loaded in polymeric-based carriers will be embedded in the chemically cross-linked polymeric matrix. This approach will enable the direct delivery of the active substance to the GBM environment, reduce the systemic toxicity, and simultaneously will provide protection against infections, which are often the cause of reoperation.

The second strategy involves the development of an intranasal gel-based formulation with mucoadhesive properties, owing to that the retention time of TMZ bound to polymeric particles in the nasal cavity will be extended. The efficiency of delivering the drug into the brain via the trigeminal nerve bypassing the BBB will minimize side effects, and the administration will be convenient and non-invasive.

In the third approach, an intravenous system, based on liposomal carriers stabilized with a silicone layer will be developed. It is expected that properly designed, stable TMZ-loaded vesicles will prevent uncontrolled leakage of the drug and will be 'self-decorated' with biomolecules present in the patient's plasma, allowing them to more effectively reach the brain and further selectively enter glioblastoma cells, thus reducing the systemic side effects.

Within this project the development of the three above mentioned systems, evaluation of their physicochemical properties while paying particular attention to the stability of TMZ, its release profile, and the efficiency of encapsulation are planned. Then, depending on the specifics of the approach, the antibacterial, mucoadhesive properties, and the ability to interact with plasma components will also be tested for the local delivery system, intranasal preparation, and liposomal formulation, respectively. In the next stage of the analysis of the obtained materials the biological features *in vitro* will be evaluated; biocompatibility, therapeutic efficacy, and, in the case of the intravenous strategy, the effectiveness of passing through the blood-brain barrier will be examined.