

## **Iron chelators as tyrosine kinase inhibitors - a new strategy for the treatment of glioblastoma multiforme**

Iron is one of the most important metal ions performing important functions in biological systems. It is responsible for the majority of biochemical transformations including enzymatic activity, oxygen transport and regulation of internal secretion. Iron metabolism disorders are also an important feature of cancer and carcinogenesis. Therefore, compounds that affect iron levels can be a promising direction in drug design. Several compounds with the ability to bind iron ions (so-called chelators) are currently being studied in clinical trials as potential anticancer drugs. However, basic research, in particular on the biochemistry and pharmacology of chelators and their effects on healthy and cancer cells, is still incomplete. Nor is the full mechanism of their action known, which effectively delays their introduction to the market.

Glioblastoma multiforme (GBM) is the most popular and aggressive primary brain tumour with poor prognosis and high mortality rates. As many types of cancer, GBM is characterized by a lack of regulation of signalling pathways, which leads to the production of autocrine factors and uncontrolled proliferation. Currently, drug development studies for GBM therapy are focused on compounds that have the ability to inhibit these signalling pathways. The epidermal growth factor receptor (EGFR) belongs to the family of receptor tyrosine kinases and its inhibition is the main focus of interest of potential 3rd generation drugs called tyrosine kinase inhibitors (TKIs).

This project focuses on the design and synthesis of potential EGFR inhibitors with the ability to binding an iron ions (FeTKI). We believe that this approach will have an impact on several molecular targets and aspects of GBM treatment. In this project we plan to verify the mechanism of action of these compounds and test the permeability of the blood-brain barrier (BBB), which is an important problem for older generation drugs. Therefore, the design of new compounds is based on the structure of osimertinib - a potential drug in the clinical trials, that was recently suggested for treatment GBM for its good permeability of BBB. We design a novel FeTKIs based on its structure and molecular fragments of iron chelator showing high anticancer activity in our previous studies. During more than ten years iron chelators studies from thiosemicarbazone group, we published derivatives with the highest anticancer activity described so far.

Summing up, the project combines a number of different scientific issues, from chemical synthesis, through biochemistry and cell biology or pharmacokinetics. Its implementation will contribute not only to the enrichment of knowledge from various areas, but also brings a high potential for application.