New iron chelators from thiosemicarbazone group in photodynamic therapy.

Cancer is one of the major challenges for modern science. It is estimated that it is the second cause of death in the world after cardiovascular diseases, accounting for over 9.6 million deaths in 2018. Therefore, the constant search and development of new therapies, pharmaceuticals or deepening the knowledge about the mechanisms of their mechanism is crucial for modern therapies with greater potency and selectivity profile. Photodynamic therapy (PDT) based on 5-aminolevulinic acid (5-ALA), called ALA-PDT, is one of the promising anticancer therapies and methods of photodiagnosis (PDD), which has gained in popularity over the last few years. With the emergence of clinical applications for ALA-PDT in the treatment of some cancers and precancerous conditions as well as in PDD, it became clear that there is a real need for better ways of administering 5-ALA as well as manipulating its bioconversion to protoporphyrin IX (PpIX) - a natural, endogenous photosensitizer. PpIX is a product in the biosynthesis of hem with 5-ALA. It is a multistage process that occurs both in cytoplasm and mitochondria. In normal cells, hem biosynthesis is strictly controlled due to the toxic character of both PpIX and free hem. The expression or activity of individual enzymes of the biosynthesis pathway and hem degradation influence the efficiency of ALA-PDT. However, changes in the expression of these enzymes do not fully explain the mechanism of PpIX accumulation in neoplastic cells. Iron metabolism in mitochondria and transport of intermediate products of hem biosynthesis pathway also have a significant influence on ALA-PDT efficacy.

Despite the clinical use of ALA-PDT, PpIX synthesis in tumour cells may be insufficient and heterogeneous within the tumour. In this context, the most important goal of ALA-PDT is to maximize PpIX accumulation in different types of cancer cells while maintaining low levels in normal cells. One of the approaches to this task is to use iron chelators to improve the ALA-PDT efficiency. In the proposed project we would like to broadly examine the usefulness of new thiosemicarbazone derivatives (TSC) in ALA-PDT therapy. The new approach is to focus on derivatives with good chelating properties of iron ions and no anticancer activity. Additionally, in the proposed project we want to investigate the molecular mechanism underlying this therapy after the treatment with new TSC derivatives. As mentioned above, the effectiveness of ALA-PDT therapy depends on the iron metabolism in mitochondria and the transport of intermediate products of the hem biosynthesis pathway or enzymes of the hem biosynthesis pathway itself. Therefore, in this project we plan to investigate selected genes/proteins of these pathways. We assume that these studies will allow us to select effective iron chelators from the thiosemicarbazone group, which will contribute to a significant improvement in ALA-PDT effectiveness.