Search for Inhibitors of Human δ^1-Pyrroline-5-Carboxylate Reductase 1 (PYCR1) as Lead Molecules for the Development of Novel Anticancer Drugs

In 2020 alone, cancer claimed globally ~10 000 000 lives while ~20 000 000 new cases were reported. The patient survival rate depends on the cancer type, early diagnostics and availability of therapies. Fortunately, there comes a silver lining as new molecular targets have been identified, allowing for the development of novel therapies. One particular target has been attracting scientists' attention for the last few years. It is an enzyme catalyzing the last reaction of proline biosynthesis, named δ^1-pyrroline-5-carboxylate reductase 1 (PYCR1). Although the exact molecular role of PYCR1 in cancer is still under debate as it may be linked to several cellular processes, its involvement in many abundant and aggressive types of cancer has been thoroughly verified. PYCR1 is also involved in cancer metastatic spread, which itself is associated with poor prognosis, making research on PYCR1 particularly promising.

Many existing anticancer drugs are enzyme inhibitors, meaning that these drugs interfere with the activities of enzymes on which cancer cells depend. In effect, such drugs either cut off the supply of chemicals needed by the cancer cells for boosted proliferation and survival or in other ways deregulate cellular metabolism. Over the years, drugs that are enzyme inhibitors have been used to cure millions of cancer patients globally. Nonetheless, despite the increasing interest in PYCR1 research, **we still lack a drug targeting PYCR1** or even a good drug candidate. This is a missed opportunity that this project will address. We will combine high-throughput screening with rationalized drug design and use both wet-lab experiments and computer-aided methods. First, we will identify the so-called hit compounds, able to slow down PYCR1 activity to some extent. Then, we will optimize these molecules to produce more potent inhibitors, the so-called leads. The optimization steps will be guided by 3D structures of these molecules binding to PYCR1, which will suggest changes to be made for improved efficacy. New molecules will be chemically synthesized and thoroughly tested for their potency against PYCR1 activity. The discovery of **leads targeting PYCR1 is the goal** of this project. The leads will build the foundation for future development in projects following this one to hopefully produce successful drugs or molecular probes to futher investigate reprogramming of cancer cells.

The need for new anticancer agents is unquestioned. Inhibiting PYCR1 activity will almost certainly **slow down cancer development, block metastasis or at least increase the susceptibility of malignant cells to other therapies**. None of that will be possible without basic research on finding new leads. We are excited to launch this project, use our previous experience and preliminary data, and, having gathered the research team, bring the much-anticipated advancement to cancer research.