New Hexokinase II inhibitors, in search of innovative therapeutic approaches to cancer treatment

Description for the general public

„The next step – the complete cure – is almost sure to follow"
Kenneth Endicott, NCI director, 1960-1969

Cancer, disgraceful king of all diseases, in some countries – including Poland, will become the leading cause of death ahead of heart diseases. According to the World Health Organization (WHO) report it is estimated that by 2025 the incidence rate of all cancers will increase from 14.1 million to 19.3 million new cases per year, and in 2035 to 24 million. About one third of all people will suffer from cancer during their lifetimes. Cancers will cause one of every four death worldwide.

Cancer cells, compared to normal cells, consume more glucose and contain significantly more cell membrane glucose transporter proteins (GLUTs). This phenomenon has been used for *in vivo* tumour imaging techniques using PET (***P**ositron **E**mission **T**omography*). Differences in metabolism of cancer and normal cells have been described for the first time in the 20's of XX century by Otto Warburg, germen biochemist, who showed that most of the energy (ATP) produced by tumour cells derived from the metabolism of glucose via anaerobic glycolysis, even in the condition of the proper oxygen supply (so-called aerobic glycolysis), where the hexose (mainly glucose) is used as the only substrate for glycolysis.

The first step in the aerobic glycolysis of glucose is its phosphorylation to glucose-6-phosphate (G6P), the reaction catalysed by hexokinase. In cancer cells, where there is a predominance of aerobic glycolysis, the dominant enzyme isoform is HKII. It has been demonstrated that liver cancer cells show a different ratio of hexokinase isoforms expression. Instead of glucokinase (HKIV), which is typical for normal liver cells, HKII isoform predominates (70% of all isoforms). Thus, searching for the new compounds which can act as an effective and specific inhibitors of HKII activity seems to be of high priority in studies on the metabolism of cancer cells and anticancer therapies.

So far, no new compounds, which fulfils the criteria of a specific and effective non-sugar based inhibitor of hexokinase II has been proposed. Compounds which have been tested so far, can not be used clinically. Taking into account the results of my previous research, I planned to design new inhibitors based on the recently obtained series of derivatives of BTDA, some of which showed HKII inhibitory activity. The main objective of proposed project is synthesis and identification of most active derivatives of 3,3',4,4'-benzophenone-tetracarboxylic dianhydride (BTDA), evaluation of the mechanism of their action and search for new leading structures with a wide range of tools - from *in silico* to *in vitro*.

In order to complete the research the project includes the following stages:

- ***In silico research*** – including virtual screening, molecular modeling and molecular dynamics to identify new inhibitors and leading structures
- ***Synthesis of the BTDA derivatives library*** using classical and modern methods of chemical synthesis.
- ***Determination of HKII inhibitory activity*** and activity-structure relationship of derivatives selected on the basis of preliminary cytotoxicity assays.
- ***Evaluation of the antitumor activity*** of obtained compounds and their effect on the activity and functioning of mitochondria, such as changes in mitochondrial membrane potential (MMP) and level of free oxygen radicals (ROS).
- The additional purpose of this project will be to ***determine the conformational changes of HKII*** upon interaction with selected derivatives.

The results of the proposed project are expected to obtain new HKII inhibitors, which can help to raise awareness of the important role of HKII in many tumour cells, as well as to use obtained inhibitors as potential anticancer drugs.