

The development of multidrug resistance to chemotherapy is currently the main challenge in the treatment of cancer. Until now, no effective methods to overcome this phenomenon in clinical practice have been developed. There are many mechanisms leading to multidrug resistance. It seems, however, that P-gp (P-glycoprotein) and BCRP (breast cancer resistant protein) membrane drug pumps play the most important role in the failure of antitumor therapy. In many common tumors, glycoprotein P and BCRP are overexpressed, which usually results in poor prognosis. So far, attempts to use direct modulators of drug pumps have been unsuccessful due to, for example, high toxicity of such therapy. Another way to overcome drug resistance is by blocking the expression of drug pumps in cancer cells at early stages of their synthesis. Such intervention, however, requires an in-depth understanding of the mechanisms regulating these processes. Therefore, the aim of our project is a detailed analysis of the molecular mechanisms responsible for the synthesis of P-glycoprotein and BCRP, and the indication of partners involved in this process. The study will be carried out using the thyroid cancer model and a panel of molecular biology methods. Additionally, we will investigate the scale of the drug resistance problem in thyroid cancer in the Polish population, because this has not yet been studied. Our hypothesis assumes that the expression of both drug pumps depends directly on the activity of major signaling pathways that are responsible for the development and progression of thyroid cancer. Based on preliminary results, we also assume that the activity of drug pumps in thyroid cancer depends on the interaction with other partners, among which ERM proteins (ezrin, radixin, and moesin) play a superior role. These studies may point at new ways of combating the problem of drug resistance, which in consequence may improve efficacy of currently available cancer therapies. Because the drug resistance phenomenon associated with the functionality of multidrug pumps is observed in many types of cancer, we think that the obtained results may help to optimize the treatment of not only thyroid cancer, but also of other tissues/organs.