The main goal of this project is to study the changes in iron metabolism induced by anticancer compounds. Iron is essential for every living cell as it participate in numerous cell function like DNA synthesis, collagen synthesis, cellular respiration and many other cell cycles. Several changes take place in iron metabolism in cancer cells. One of the effects of these changes is an increase in iron availability for fast proliferating cells. Another important function of iron is its participation in adaptive response of a cell to stress condition, which so far is not well recognized. For example, during ischemic preconditioning of heart several adaptive changes take place and then result of this is heart's higher resistance to next ischemia. Interestingly, these adaptive changes did not occur if the level of labile iron pool was reduced, these data indicate that iron is a signaling molecule. In the case of cancer cells stress is induced by chemiotherapy or other anticancer treatment. Our knowledge concerning the effects of anticancer therapy on iron metabolism is little. In this project we are going to test the anticancer potential of aliphatic N-substituted 1,2-benzisoselenazol-3(2H)-ones and corresponding diselenides agents and determine their effects on iron metabolism *in vitro* and *in vivio*. In addition, diallyl trisufilde an organosulfur compound isolated from garlic will be studied as well. Organoselenium and organosulfur compounds have been proven to possess a variety of biological activities including antitumor capacity and anti-inflammatory activity. Moreover, our preliminary data indicate that some of the newly synthesized compounds possess antitumor activity. Part of their action is associated with the induction of changes in iron metabolism. Our research group has significant experience in organoselenium chemistry. We have developed efficient methodologies for the synthesis of selenols, selenides and diselenides. Benzisoselenazolones will be synthesized according to the recently published methodology based on the reaction of dilithium diselenide with N-substituted o-iodobenzamide. This one-step reaction enables a high yield of ebselen and its derivatives. The anticancer activity of these compounds will be evaluated on prostate cancer cell lines characterized by different genetic background. The effects of the selenocompounds on cell cycle, cell apoptosis and necrosis will be measured by standard biological methods, using flow cytometry. The involvement of several signalling pathways in cell killing and inhibition of proliferation will be estimated. Additionally, the signalling pathways of Akt/p66Shc/FOXO3a, kinaze c-jun (JNK/ITCH/Ferritin/iron), NFk-B and STAT3 will be studied. Moreover, the anti-inflammatory activity of N-substituted ebselen derivatives and corresponding diselenides will be measured in a co-culture of normal and cancer cells of prostate. In vitro data will be confirmed by the study on animal model of prostate cancer.

The search for the new drugs in cancer treatment has been justified for decades and yet our progress in curing tumors has been marginal. Hence, in this project we will synthesize new derivatives of ebselen and corresponding diselenides in order to try to identify their biochemical, anticancer activity. One of the main causes of the low efficiency of anticancer drugs is cancer cells' adaptation due to their high plasticity of oncogenic signaling. There is enough data indicating that iron triggered signaling may play an important role in cancer cells adaptation. In conclusion, the goal is to evaluate the role of iron in drug resistance as well as to study the influence of factors that control the level of the labile iron pool in cancer cells using newly synthesized aliphatic N-alkyl substituted 1,2-benzisoselenazol-3(2H)-ones and the corresponding diselenides.