

C.1. DESCRIPTION FOR THE GENERAL PUBLIC

(State the objective of the project, describe the research to be carried out, and present reasons for choosing the research topic)

The search for new drugs leading to cancer cell death and testing the mechanisms of their interactions with cancer cells is still one of the most important goals of the scientific research. Cancer cells do not possess the ability for induction of the spontaneous apoptotic death. Therefore documenting the processes responsible for the cell death of these 'immortal' cells due to the effects of new anticancer drugs requires interdisciplinary approach combining both biological and physio-chemical methods.

The main goal of the present project is to show a close relation between the effects of drugs on the DNA and their effects on the cancer cells. The cells are usually tested using pharmacological methods, neglecting the complementary DNA-drug studies. If, on the other hand, it is shown that the DNA-drug interactions are of primary importance and correlate with the pharmacologically proven cell death, the pharmacological testing of cancer might be initially substituted by the DNA-drug testing, much faster, and most importantly, much cheaper than the *in vitro* studies.

In the present proposal, an interdisciplinary project is suggested which will combine the electrochemical study of DNA-drug complexation and spectroscopic studies suggesting structural DNA with complementary pharmacological testing the effectiveness of the drug, or a combination of drugs, e.g. adjuvants, on the cancer cells. The concentrations of the drugs and the conditions of the experiments will closely be related, as needed for the comparison of such different types of experiments.

The interactions of DNA with anticancer drugs, as well as antioxidants, are well documented in the electrochemical literature. The results of the studies are described in detail in a number of monographs. The interest in the subject is related to the synthesis and use of new drugs, such as, for instance methotrexate (MTX) known for their anticancer properties. Both in my M.Sc. and Ph.D. work I have been investigating the interactions of DNA with newly synthesized prospective anticancer drugs, in particular with 4-chloro-6-(1*H*-imidazo[4,5-*b*]phenazine-2-yl)benzene-1,3-diol, Cl-IPBD, which is one of many new compounds with antiproliferative properties. The results of our common efforts are published and are presented at the conferences.

In my electrochemical experiments, I have developed a method allowing to study the DNA-drug interactions with an extremely low concentration of DNA in the range of picograms per milliliter, and the lowering the concentration of the drug to micromols. Except for limiting the cost of the DNA and chemicals, and avoiding the problems with drugs dissolution, this method allows for neglecting the DNA-drug interactions in the solution, thus focusing the research on the interactions present in the layer adsorbed on the electrode. Moreover, such low concentrations of drugs can be used both in spectroscopy and pharmacology measurements. For Cl-IPBD, only initial spectroscopic experiments have been performed, yet suggesting significant structural changes of the DNA structure due to the drug complexation. Also preliminary pharmacological experiments confirm the anticancer properties of the compound. For the sake of comparison in the project I plan to use well known and used in cancer therapy compounds such as doxorubicin and cisplatin, and also adjuvants, i.e. the substances enhancing the effects of anticancer drugs, *Uncaria tomentosa* (vilcacora), and antioxidants, rutin. Only a comparison of the results for the compounds differing to a large extent in the interactions with DNA, as well as in the effect on the cancer cells, will allow to detect the role of the DNA-drug interactions in the cancer research.