Doctoral thesis abstract of dr Lidia Chomicz

Radiotherapy, one of the most frequently used methods of anticancer treatment, is not neutral for patients. In order to shorten the irradiation time, reduce side effects and improve the efficacy of this modality, special substances, dubbed radiosensitizers, able to sensitize cancer cells to ionizing radiation are in use. One of such substances is 5-bromouracil (5BrU), which, if incorporated into DNA, increases its susceptibility to radiation induced strand breaks (SBs). Despite of the numerous studies, both experimental and theoretical, the exact mechanism of γ-radiation induced strand breaks in the 5BrU modified DNA remained unclear.

The aim of the current doctoral project was to elucidate this mechanism with the use of computational chemistry methods and to propose another nucleobase derivatives with similar or better radiosensitizing properties than these of 5BrU.

The mechanism of the electron induced debromination of 5BrU and the bromoderivatives of the remaining nucleobases (BrX): 5-bromocytosine, 8-bromoadenine and 8-bromoguanine in the gas phase conditions, aqueous solution and *explicit* water environment has been characterized at the B3LYP level. Moreover, the fate of the radical resulted from debromination was studied in the DNA environment. Namely, intramolecular hydrogen transfers were studied in the 3',5'-diphosphates of BrXs. It has been demonstrated that an electron attachment to the brominated purines leads to the formation of their 5',8-cycloderivatives, a DNA helix-distorting lesion blocking DNA replication and transcription. A competitive phosphodiester bond breakage due to the intramolecular H transfer turned out to be also possible. On the other hand, the intranucleotide H-transfer in the 5-substituted brominated pyrimidines (5BrdUDP and 5BrdCDP) is hindered due to steric reasons. However, such process is allowed in the 6-substituted

brominated pyrimidines which suggests their radiosensitizing properties. Furthermore, the uridine-5-yl radical (formed due to debromination of 5BrU) is capable of detaching a hydrogen atom from water molecule, becoming hereby a source of genotoxic hydroxyl radicals. This feature of uridine-5-yl radical is probably a key characteristic responsible for its radiosensitizing properties.

The above findings related to the radiation induced degradation of BrX labelled DNA models led to a simple computational protocol that enables new radiosensitizing nucleosides/nucleases to be proposed. With this protocol two uracil derivatives: 5-thiocyanateuracil and 5-cyanateuracil, which have not been considered as radiosensitizers so far, were designed.