The ageing of population, environment pollution and, paradoxically, progress in medicine which led to the situation where not long ago deadly diseases became curable, e.g. coronary artery disease, make cancer a leading cause of deaths in the developed countries. One of the most common modality used to combat this 21st century plague is radiotherapy employed mainly against solid tumors that account for ca. 80% of all cases. Radiotherapy employs ionizing radiation (IR) to destroy cancer cells. However, one should remember that solid tumors suffer from low levels of oxygen (hypoxia) due to impaired angiogenesis and increased metabolism. On the other hand, low levels of oxygen diminish sensitivity of the cells on IR. As a result healthy tissues surrounding the tumor are more sensitive to IR than the tumor itself. Here, it is worth of emphasizing that exposure of healthy cells on IR may lead to their cancer transformation.

One of the most obvious way of eliminating the described above unfavorable situation is to use chemical substances that increase the sensitivity of tumor to IR – so called radiosensitizers. An example of this type of compounds are derivatives of native nucleosides which incorporate into genomic DNA during replication or repair. In order to be radiosensitizing these compounds have to undergo degradation induced by hydrated electrons. The latter are formed under hypoxia in the amount comparable to that of hydroxyl radicals (it is worth noting that without oxygen the genotoxicity of hydroxyl radicals is considerably diminished). Induced by electron attachment radical products of degradation of the modified nucleosides/nucleobases (MNucs) trigger DNA strand breaks which ultimately lead to apoptosis.

The basic aim of the current research project is to comprehend a relation between the character of dissociative electron attachment (DEA) to MNuc in the gas phase and the mechanism of the degradation of MNuc in water, i.e. in the environment where a potential radiosensitizer should work. A promising radiosensitizer must undergo DEA in the gas phase since only then the attached electron will lead to reactive radical products. A numerous literature data demonstrate, however, that water, abundant in biological systems, exerts enormous influence on the DEA process. Therefore, the efficient DEA in the gas phase does not guarantee adequate degradation in water.

In order to explore this problem, we plan to carry out studies on DEA to MNuc interacting with variable number of water molecules. First, we will carry out crossed beam electron-molecule experiments in the gas phase. Decomposition of MNuc due to electron attachment will be described using quantum chemical methods which will allow the most important degradation channels to be recognized. The same degradation process will be studied, then, in the $(H_2O)_n \cdots$MNuc clusters with the experimental setup dedicated to the cluster experiments. Similarly to the gas phase DEA experiments also here the interpretation of experimental results will be carried out with the help of computer simulations. Finally, the stationary radiolysis will be used to reveal the outcome of the reactions between hydrated electrons and MNucs in bulk water. The identification of stable radiolysis products (HPLC and LC/MS) will allow a reliable DEA mechanism to be proposed.

The results of the current studies will lead to the in-depth understanding of relation between the efficiency of DEA in the gas phase and the effectiveness of potential radiosensitizer under physiological environment. It is difficult to overestimate access to such knowledge in the context of new, capable radiosensitizers. The most thorough studied radiosensitizing MNuc, 5-bromo-2'-deoxyuriudine, has not been used in the clinic so far. One of the reason for that could be insufficient understanding of the processes responsible for radiosensitizing properties of MNucs. Explaining the details of DEA, the influence of water in particular, should allow for rational designing of radiosensitizers. The identification of resonances leading to DEA in the gas phase as well as optimization of activation barriers and thermodynamic stimuli of degradation channels open in water will hopefully result in super-radiosensitizers which ultimately could be employed in the clinic.