Radiotherapy is one of the most common modality used for treating human cancers. It is based on the use of ionizing radiation (IR). Exposure of tissues to high-energy radiation results in the radiolysis of water leading to weakly reactive solvated electrons and highly reactive hydroxyl radicals in the cell. However, the therapeutic effect of radiation is significantly reduced by hyperactive DNA repair and hypoxia. Indeed, in the case of hypoxia, characteristic for solid tumors (due to increased cell metabolism and insufficient angiogenesis), their sensitivity to water radiolysis products is 2.5-3 times lower than that of cells with normal level of oxygenation. It is also worth emphasizing that ionizing radiation is not neutral to healthy tissues. Therefore, in order to increase the efficacy and improve the safety of radiotherapy, it should be combined with the use of radiosensitizers, i.e. chemical compounds that sensitize cancer cells to ionizing radiation. Modified nucleosides (MNs) seem to be particularly promising candidates for effective DNA radiosensitizers. These compounds can be incorporated into the cellular DNA, show low cytotoxicity in the absence of radiation and, after irradiation, cause a number of DNA damage leading to the death of cancer cells. One of the best known radiosensitizers from the MN group is 5-bromo-2'-deoxyuridine. Unfortunately, the therapeutic effect of this compound is too low in the conducted clinical trials. The aim of this project is to release the potential of MNs by combining their action with the DNA damage response inhibitors. The MN sensitizers incorporated into DNA enhance radiation-induced damage, among which the most important (leading to lethal effects) are DNA strand breaks. On the other hand, the HR, NHEJ and BER pathways are the basic tools used by the cell to remove this type of impairment. In this project, we will verify if the combined effect of BrdU-type sensitizers and DNA repair inhibitors leads to a significant increase in the sensitivity of the selected cancer cell lines to ionizing radiation (Figure 1). At the first stage, the choice of the modified nucleosides will be made based on the ease and level of their incorporation into DNA (the extent of DNA labelling correlates with radiosensitization). The kinetic studies of binding DNA repair inhibitors to specific enzymes will allow the best compounds that block DNA repair response to be selected. At the next stage, the radiosensitization of the cancer cells with the combined use of MN and DNA repair inhibitors will be examined. Numerous biological tests will also provide mechanistic details of this process. The current project will result in proposing a new strategy in the combined treatment of cancers. Radiosensitization with MN and DNA repair inhibitors should increase the efficacy and safety of radiotherapy.

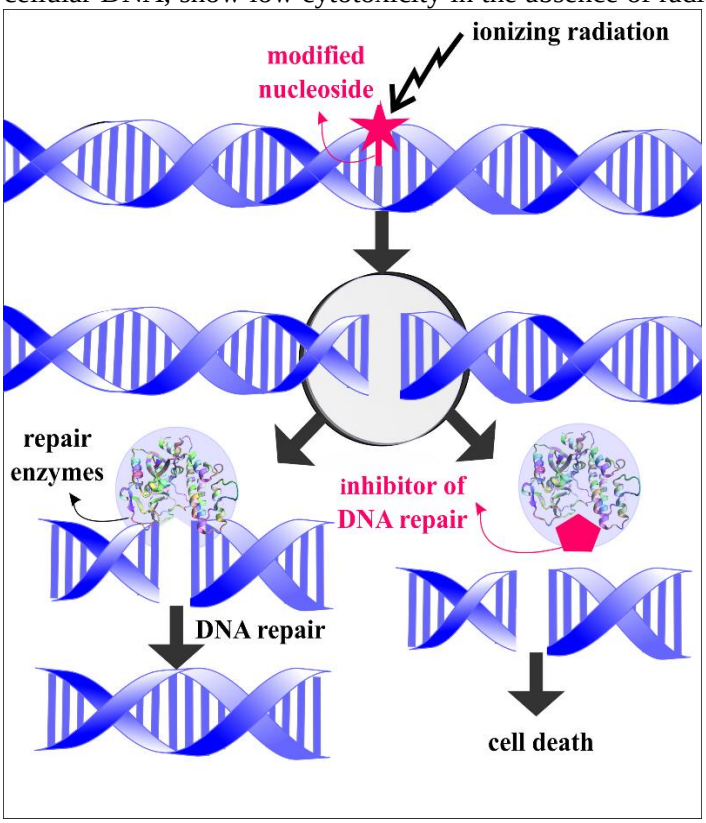

Figure 1. Combined action of modified nucleosides radiosensitizers and inhibitors of DNA repair response in sensitization of DNA to ionizing radiation.