Radiotherapy (RT) is one of the main methods of treating patients with cancer. It destroys cancer cells. Radiotherapy also affects the tumor microenvironment (tumor blood vessels and immune cells), activating the emergence of radio-resistance mechanisms. It damages the blood vessels and elicits radiation-induced inflammation. There is an accumulation of radio-resistant cells that suppress the anti-tumor immune response. Numerous areas of under-oxygenation (hypoxia) arise. Hypoxia weakens the anti-cancer effect of RT. It activates the formation of new blood vessels (angiogenesis) and leads to relapse of the disease. Therefore, it is justified to use combination therapy: radiotherapy with drugs that will prevent undesirable changes occurring in the tumor microenvironment.

The main goal of the research project is to prove the hypothesis that an appropriate combination of radiotherapy with drugs transforming the tumor microenvironment may overcome some of the mechanisms of resistance to radiotherapy and increase its therapeutic effectiveness. We plan to apply contact radiotherapy (brachytherapy) in combination with imiquimod and sunitinib. Imiquimod (TLR7 agonist) is a drug that stimulates the immune response and can act as a radio-sensitizer. Sunitinib (an inhibitor of tyrosine kinases: VEGF, PDGFR, c-kit, FLT3) inhibits the formation of tumor blood vessels and acts as immunostimulant. The proposed combination is an example of a new targeted therapy with a broad spectrum of action.

The specific objectives of the project include answering a few basic questions, including: how do different doses of contact radiotherapy (brachytherapy), imiquimod and sunitinib affect the tumor microenvironment? Will the implementation of optimal doses of imiquimod and sunitinib in combination therapy circumvent some of the radio-resistance mechanisms (mainly immunosuppression and hypoxia) and increase the anti-tumor effectiveness of radiotherapy? Which of the subpopulations of immune cells (macrophages, T lymphocytes, NK cells) plays a major role in the therapeutic effect of the combination? Answers to these questions should allow us to propose a therapeutic strategy: radiotherapy combined with imiquimod and sunitinib, which will overcome some of the radio-resistance mechanisms of the tumor microenvironment.

There is no clear data on the optimal dose of radiotherapy in the treatment of cancer patients. Therefore, it is justified to conduct further research in this area. In addition, attempts are made to combine radiotherapy with immunotherapy or therapy directed against tumor blood vessels. If our hypothesis turns out to be true, then the results obtained by us will show new possibilities of combining radiotherapy with immunomodulatory and anti-angiogenic drugs as part of one antitumor therapeutic strategy. In the future, this may contribute to changing the treatment regimens used in the clinic.

The project is original and is a continuation of our previous research on the tumor microenvironment (Jarosz M et al., Gene Ther. 2013; 20:262-73; Jarosz-Biej M et al., Arch Immunol Ther Exp. 2015; 63:451-64; Smolarczyk R et al., Sci Rep. 2018;8:7355; Jarosz-Biej et al., PLoS One. 2018; 13:e0191012).