Hypoxia plays an important role in many pathological conditions, including diabetes, cardiovascular disease and cancer. Insufficient tissue oxidation is particularly important for tumors because it negatively affects the effectiveness of clinical treatments and leads to more aggressive tumor phenotype. One of the therapies leading to improved oxygenation of tumor tissues is antiangiogenic therapy, which by normalization of tumor vessels leads to the formation of so-called "therapeutic window" characterized by better drug penetration, higher tumor oxygenation and reduced aggressiveness of tumor cells. These changes are transient and after a few days, the vessels return to their original state. An innovative approach to the problem of tissue hypoxia is the use of ultrasound sensitive oxygen microbubbles that release oxygen locally into the tissue of interest.

Our goal is to check whether the combination of metformin and oxygen-containing microbubbles sensitive to ultrasound will effectively raise the level of oxygenation of tumors in mice, reduce their invasiveness and increase the effectiveness of radiation therapy. Metformin is a drug routinely used to treat type II diabetes, which has additional anti-tumor and antiangiogenic effects. In order to achieve these goals, the structure and function of the tumor vessels, tumor oxygenation, and its aggressiveness will be monitored noninvasively during therapy. In addition, molecular markers of vascular normalization, hypoxia, and aggressiveness of tumor cells will be analyzed. In the last step, we will investigate whether radiotherapy with the proposed therapy will be more effective than without it.

Conclusions from these studies will characterize the long-term effects of metformin as an antiangiogenic agent and investigate a new combination of the therapeutic enhancing efficacy of cancer therapies based on the oxygen concentration in the tumor tissue.