

Uveal melanoma (UM) is a rare disease, but in the case of metastatic development, it leads to the death of the patients. Metastases are found mainly in the liver, sometimes many years after initial diagnosis. Despite intense efforts so far there is no available treatment for metastatic UM. This is partly due to the high resistance of these tumors, and in part due to the lack of appropriate preclinical models to study the disease. Recently a panel of UM cells from the liver metastases was derived. Utilizing these models we would like to study the interaction of UM cells with liver microenvironment. Many researchers point out the importance of the communication between the primary tumor and the metastatic site, as well as host tissue in the metastasis awakening, its growth, and response to therapies.

In the proposed experiments we plan to study first the different liver cells interactions with UM cells, and the influence of low oxygen levels and inflammation on radiosensitivity in 3D cultures, and the influence of microenvironment signals on redox state and tumor cell metabolism. In the next step, we will look for signals sent from the primary UM tumor. Then, we will study the microenvironment of UM tumor growing in the liver and will be searching for ways to increase their sensitivity to radiation. The extent and timeline of the changes will be monitored by non-invasive imaging of the animals. In the final step, we will apply this knowledge to radiotherapy of UM tumors growing in the liver of mice, together with modifications increasing their radiosensitivity.

The proposed project will result in a better understanding of the interactions between liver microenvironment and UM cells leading to the metastasis development. If the planned experiments will work out and we succeed in controlling the UM tumor growth in the liver, it may have an impact on enhancing the effectiveness of radiotherapy and provide new avenues for clinical treatment of UM patients.