Malignant melanoma is diagnosed in only 4% of all skin cancer patients. However, in this group, melanoma is responsible for 80% of skin cancer deaths, mainly because it is very invasive and often metastasizes. Recent years have brought a breakthrough in the treatment of this cancer, among others thanks to the development of a therapy directed against mutated BRAF kinase, which is present in about 50% of patients suffering from melanoma. Unfortunately, patients quickly develop resistance to this form of treatment. The effectiveness of therapy is slightly improved by the simultaneous use of drugs blocking BRAF and another kinase - MEK, but resistance still appears and is a major cause of treatment failure in advanced melanoma. That is why research conducted to understand the mechanisms involved in this process, and to develop new therapeutic strategies to block melanoma cell invasion and overcome resistance to treatment, are so important.

A relevant element determining the effectiveness of the applied therapy is the tumor microenvironment, which is a complex system, specific for each type of cancer. Apart from various types of cells surrounding the tumor, such as adipocytes or fibroblasts, it also includes a whole range of proteins and growth factors produced by both normal and neoplastic cells. All these elements can influence the bioavailability of drugs and regulate the resistance of melanoma cells to the therapy, and thus determine the effectiveness of the applied treatment. Studies indicate changes in lipid metabolism as a result of resistance acquired by melanoma cells. It is also known that drugs targeting metabolism may be a potential target in the therapy of resistant cells. However, the studies conducted so far have not considered the influence of the tumor microenvironment on the lipid transformations in neoplastic cells. Fat cells, called adipocytes, can have the greatest impact on fat metabolism. They are able to actively support the progression of melanoma, especially in obese patients. However, how the presence of adipocytes affects the processing of lipids by melanoma cells resistant to BRAF/MEK inhibitors has not been investigated so far. Therefore, the aim of this project is to verify the effect of adipocytes on lipid metabolism in resistant melanoma cells. This issue is of particular importance at a time when obesity is becoming a serious civilization problem.

I would like to assess the impact of the presence of adipocytes in the neoplastic niche on the metabolism of melanoma cells, and then assess the validity of the use of therapies affecting the processing, uptake and storage of lipids on the effectiveness of melanoma therapies used so far. In the first stage of research, I will obtain and characterize melanoma cell lines resistant to BRAF/MEK inhibitors. Then, with the help of co-cultures (cultures consisting of neoplastic and normal cells at the same time) I will investigate the influence of adipocytes on lipid transformations in melanoma cells. I will also analyze the impact of adipose tissue from patients on the lipid metabolism of cancer cells. In the last stage of the studies, I will verify whether the use of drugs affecting lipid metabolism will increase the effectiveness of the resistant cells therapy.

The conducted research will help to understand the molecular basis of drug resistance, which can be modulated by cells present in tumor microenvironment. The proposed project may also contribute to the development of new therapeutic strategies specifically targeted not only against melanoma cells, but also affecting the environment in which the cancer is localized, thus inhibiting its spread.