

Despite many years of investigations, the problem concerning effective treatment of cancer still remains unsolved. Every year eight million people dies because of cancer, including one hundred thousand in Poland. Most of therapies that are in use nowadays are highly aggressive and side effects of those treatments may last for a long time. In the 1990s it was shown that statins, well-known group of cholesterol-depleting drugs, widely prescribed in the treatment of cardiovascular diseases, may be effective in cancer therapy. However, usage of statins in anticancer therapy appears problematic, namely antitumor activity of this class of drugs is observed at concentrations around 100- to 500-fold higher than concentrations commonly used in treatment of cardiovascular diseases. Such a high doses are impossible to deliver to organism without inducing serious side effects, so currently it is not clear if statins will ever be used in neoplastic diseases treatment as monotherapy.

The aim of this project is to obtain targeted liposomes containing simvastatin that will allow for targeted delivery of drug directly to tumor tissue, thus to increase a single dose of provided drug. Liposomes are spherical vesicles formed by phospholipids, the size of the one designed by us is around 100 nm. As a target we chose EGFR-dependent tumors, more precisely: breast and prostate cancer cells. We plan to test effectiveness of our liposomes both in vitro, using cellular models, and in vivo, in mice engrafted human tumors. In this way we should be able to determine whether statins are suitable and promising drug in cancer treatment and if it is possible to use them as a monotherapy in the future. Moreover, we plan to further explore the issue concerning molecular mechanisms that underlie anticancer activity of statins. Most of the studies performed so far were focused on determination of molecular pathways which are inhibited by statins in cancer cells, thus, keeping this results in mind, we would like to focus on the ability of statins to disrupt membrane rafts. Membrane rafts are plasma membrane microdomains that are enriched in sphingolipids and cholesterol. It is known that the integrity of membrane rafts is critical for the correct functioning of cells, including regulation of cell proliferation and apoptosis, because many signalling molecules are associated with rafts. We plan to carefully analyse changes in plasma membrane organisation after immunoliposomal simvastatin administration. We also plan to determine localization of proteins that are involved in cellular signal transduction - EGFR and Ras protein.

We hope that our studies will allow for the construction of a new, immunoliposomal formulation of one of the statins and testing its potential applicability in tumor therapy and also will contribute to the solution of a specific delivery of the drug in high doses to the target tissue. Execution of the project should bring new information concerning molecular mechanism of antitumor activity of statins.