

Endothelial cells are the monolayer of blood vessels and they are responsible for supplying oxygen to tissues and organs and regulating the removal of by-products of cellular reactions. In addition, they are responsible for maintaining blood pressure, creating new vessels and regulating inflammatory and prothrombotic processes. Endothelial dysfunction plays a key role in the pathophysiology of cardiovascular diseases such as atherosclerosis, hypertension and heart failure, but also in the development of cancer, neurodegeneration, and infectious diseases. Currently, there are no targeted therapeutic solutions available that target the vascular endothelium. It has been proven that some drugs, e.g. lowering the concentration of circulating cholesterol, such as statins, have a beneficial effect on the endothelium. However, the use of statins in patients with high cardiovascular risk is being replaced by innovative lipid-lowering drugs. These include PCSK9 inhibitors (PCSK9i), which reduce plasma LDL cholesterol to a greater extent. However, little is known about the mechanisms of their action on the endothelium.

The aim of this project is to investigate the mechanisms of action of new lipid-lowering therapies on endothelial function. In the first phase of the research, we will use cultures of endothelial cell lines and cells isolated from human and mouse hearts to determine the effect of PCSK9i on endothelial function and compare the observed effects with statins in normal and pathological conditions, such as hyperlipidemia, oxidative stress, or hypoxia. The primary cells will be isolated from human heart fragments taken from the transplant recipient in cooperation with the Department of Cardiac Surgery and Vascular Surgery of the University Clinical Centre (UCC) in Gdansk and from the hearts of mice with hyperlipidemia. Endothelial function and mechanisms involved in inflammatory and cellular energy processes will be assessed. The second phase of the research involves experiments in a mouse model of hyperlipidemia. Homo- and heterozygous knockout mice in the LDL receptor (LDLR) gene will be treated with PCSK9i and angiogenesis regulators. During the research using animal models, the mechanisms observed in the first stage of the project will be verified. The last phase of the research includes analyzes in patients suffering from familial hypercholesterolemia (FH). In collaboration with Department of Cardiac Diagnostics UCC, we will conduct a non-invasive microcirculation analysis in patients with FH before and after 3 months of treatment with PCSK9i. Blood samples will also be collected for analysis of endothelial function parameters, oxidative stress, and mitochondrial dysfunction markers.

This project will analyze the effects of PCSK9i in the endothelium and identify mechanisms related to cell and mitochondrial function, mitochondrial biogenesis and dynamics, and the lipid composition of mitochondrial membranes. This study will highlight new targets for the therapy of vascular endothelial dysfunction that will activate regenerative mechanisms in a failing heart and possibly other organs such as the brain, kidneys or lungs.