# Normalization of energy metabolism as a way to develop innovative antithrombotic therapies

**Platelets** are tiny blood cells with an ability to aggregate on signal. By forming clots platelets help to plug the injured veins or arteries in the body to stop bleeding. When platelets are not working efficiently, there is a risk of prolonged bleeding or even haemorrhage. In turn, sometimes platelets are too reactive, then become sticky and form clots – 'thrombi' – even without vessel injury. Such pathological process is named **thrombosis**. It may lead to hindered blood flow to the tissues and result in serious complications or even death, when the clot blocks completely the flow of blood or migrates downstream the blood flow and affects organs. Recently, thrombosis has appeared to be the main reason for complications and hospitalisation of COVID-19 patients. Often, despite antithrombotic treatment, the risk of thrombosis–related events is not eliminated, and unwanted side effects, such as bleeding, may occur. Such patients need more effective strategies of curation. The long term goal of this project is to identify strategies to slow the onset of or prevent such pathological processes. To achieve this goal requires to maintain optimal **platelet reactivity** (readiness for forming clots) - not too weak and not too strong.

Increased reactivity of platelets can be induced by diseases such as diabetes mellitus (a disease with elevated sugars in the blood) or atherosclerosis (when endothelial cells in the vessels become sticky and circulating white blood cells and platelets adhere to them, narrowing the lumen of the vessel). Interestingly, a common point of diabetes and atherosclerosis is disturbed metabolism, leading to elevated levels of glucose and lipids in the blood. Such patients are at increased risk of thrombosis. Importantly, altered energy metabolism is supposed not to be less efficient, but difficult to be fine regulated. The sudden signals for platelets to act may induce excessive platelets responses, seen as hyperreactivity and increased stickiness.

The hypothesis underlying this project is that pharmacologic normalisation of metabolic processes in blood platelets might lead to the improvement of the effectiveness of commonly used antiplatelet drugs and to the reduction of dosage necessary for optimal activity of these drugs. Such achievements would also increase the safety of antiplatelet drugs. To test the hypothesis, basic science approaches will be used employing platelets isolated from the blood derived from human (healthy subjects and patients with diabetes mellitus) and mice (murine models of diabetes and atherosclerosis). Experiments will be performed in which isolated human platelets or animals are treated to produce changes in metabolic processes, and then diverse antiplatelet drugs and naturally produced modulators are examined. This manipulations will be followed by analysis of platelet function to determine conditions that increase or decrease platelet reactivity. An important aspect of the project is that platelets will be carefully and systematically manipulated to simulate the healthy or pathological conditions, so that the outcomes will have potential clinical relevance. The aim of these experiments is to test whether by regulation of sugar metabolism we can delay or even prevent the development of excessive platelet reactivity. We expect to demonstrate that metabolic perturbations that produce a switch in how energy is generated decide about platelet healthy or 'excessively reactive' state.

The outcomes can be used to help formulate dietary guidelines to reduce thrombosis risk and provide targets in metabolic pathways for pharmacological strategies for the development of new antiplatelet therapies to prevent or reduce its serious and life-treating consequences.