Anti-platelet treatment is a gold standard to combat atherothrombosis. Despite advances in anti-thrombotic therapy the cardiovascular diseases (CVDs), including myocardial infarction and stroke, are still the leading causes of death worldwide. Therefore, development of more effective and safe anti-thrombotic agents targeting new mechanisms is crucial. Protein disulfide isomerase (PDI) A1, PDIA3 or PDIA6 released from platelets and endothelium accelerate thrombus formation through effects on platelets and coagulation. Consequently, they are emerging as targets to inhibit thrombosis.

The main goal of this project is to better characterize the functional role of major PDIs in platelets and to reveal differences in regulation of platelet function and coagulation by PDIA1, PDIA3 and PDIA6 in atherosclerosis as compared with healthy conditions. We put forward the hypothesis that changes in levels of these platelet PDIs are responsible for hyperactivation of platelets and clotting system during progression of atherosclerosis. Furthermore, it is tempting to claim that particular PDIs have different significance depending on stage of atherosclerosis progression. There is no selective pharmacological tools to study the role of PDIs. To investigate the project hypothesis we will take the advantage of novel PDIA1, PDIA3 and PDIA6 inhibitors invented and synthesized by Prof. Ivars Kalvins from Latvia in collaboration with JCET. Furthermore, we will touch unexplored research area, namely the role of PDIs in regulation of release of platelet-derived extracellular vesicles (PEVs) which are relevant players in thrombus formation and regulation of endothelial function. In order to fill the gap in knowledge about differential roles of PDIs we will take the advantage of state-of-the-art functional, biochemical and molecular assays mostly developed in JCET laboratories, supported by usage of an unique murine model of atherosclerosis in ApoE/LDLR$^{-/-}$ double knock-out mice.

Altogether, by the use of novel PDIs inhibitors of our invention and carry out a wide range of functional assays, this project will provide new insights into relative importance of PDIA1, PDIA3 and PDIA6 in regulation of platelet functions and platelet-dependent coagulation in humans. Furthermore, functional assays combined with proteomic profiling of changes in PDIs abundance at different stages of murine model of atherosclerosis, in relation to other prothrombotic and proinflammatory proteins, will reveal the contribution of PDIs in pathogenesis of prothrombotic state developing during atherosclerosis. Obtained in this project knowledge will facilitate to develop future PDIs-targeting anti-thrombotic drugs, specific against atherothrombosis. On the other hand, a new perspective can open to use PDIs profiling as a tool to assess the severity of atherosclerosis or predict risk of thrombotic events due to progression of atherosclerosis.