Chronic kidney disease (CKD) is characterized by a progressive and irreversible loss of kidney function and due to the rapidly increasing morbidity, is classified as a civilization disease of the 21st century. Surprisingly, the principal causes of mortality in CKD represent cardiovascular events such as myocardial infarction or stroke as a result of rapidly progressive atherosclerosis. The severity of CVD in CKD increases along with renal damage progression; hence, patients with kidney failure often demonstrate a much higher increase in cardiovascular mortality risk than in the "classical" CVD, non-related to kidney disease. Undoubtedly, both atherosclerosis related and non-related to CKD, are considered as chronic inflammatory processes characterized by endothelium dysfunction and damage. Lymphocytes and macrophages and produced by these cells pro-inflammatory cytokines play an important role in inflammation related to atherosclerosis. However, a few years ago, an attention has also been paid to a subset of a unique group of immune cells, termed natural killer T (NKT) cells and their role in the pathogenesis of atherosclerosis. Nevertheless, the exact mechanism of NKT cells functioning is still elusive. Moreover, the role of NKT cells in CKD and the progression of CKD-related atherosclerosis is completely unknown so far.

The protein phosphorylation is the chemical addition of a phosphoryl group to a protein molecule by enzymes called kinases. These reactions play a very significant regulatory function influencing the activity of cells and their homeostasis. Protein phosphorylation is also involved in the activation of leukocytes and their ability of adhesion and migration through the endothelium of blood vessels.

Our previous studies have demonstrated that CKD leukocytes functionally differ from those derived from "classical" CVD patients in the dynamics of their cell−cell adhesion and transmigration processes. Several proteins involved in signal transduction during leukocytes migration, modulated by the protein phosphorylation and dephosphorylation processes, were identified as significantly dysregulated at the advanced stage of CKD. Moreover, we confirmed the contribution of NKT subpopulation in observed changes.

We hypothesize that changes in mechanism of protein phosphorylation necessary in initiation and control of adhesion and transmigration, trigger observed abnormalities. It can be induced by the uremic toxins present in the blood of CKD patients due to renal dysfunction and their influence on both circulating leukocytes and vascular endothelial cells. As a result, the intensification of inflammatory processes and thus acceleration of atherogenic processes in CKD is observed.

To verify these hypotheses, we plan to perform a comprehensive phosphoproteomic analysis of NKT cells in CKD in the context of the role of phosphorylation mechanisms during atherosclerosis progression. We will characterize the influence of uremic milieu on the protein phosphorylation profile in NKT cells and the signaling regulating their adhesive and migration abilities. We also plan to assess whether the observed changes can be reversible. We will investigate if disturbances in protein phosphorylation in NKT cells are related to the progression of both CKD and CVD. The phosphorylation events associated with accelerated progression of atherosclerosis in CKD will be pinpointed. Understanding the role of NKT cells in the context of changes in protein phosphorylation underlying the mechanisms of inflammation and progression of atherosclerosis may be crucial for the full interpretation of pathological processes in CKD.

The planned study is innovative, and the proposed methodology is based on very modern and high-throughput solutions. Studies of protein phosphorylation in NKT cells have not been demonstrated so far. Moreover, the role of NKT cells in CKD progression and CKD-related atherosclerosis has never been characterized. In the proposed project, functional mechanistic analyzes of cells *in vitro* combined with comprehensive molecular study using phosphoproteomics, will be conducted. The results will be visualized using confocal microscopy and flow cytometry and verified by immunological and transcriptomic methods. This systemic approach to the study of the role of NKT cells and protein phosphorylation processes in the development of CKD has not been presented so far in published articles. The results obtained during the project realization will significantly contribute the expansion of our knowledge about the mechanism of atherosclerosis progression in chronic kidney disease.