DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Chronic kidney disease (CKD) is present in around 12-15% of the worldwide population and 25-30% of the elderly population. Abnormalities in bone mineralization leading to the increased risk of fractures are one of the most common and important consequences of CKD development and progression. They significantly contribute to the increased morbidity and mortality and decreased quality of life among these patients. Disturbances in mineral and bone metabolism accompanied by soft tissue and vascular calcification are now referred as CKD-MBD – *Chronic Kidney Disease – Mineral Bone Disorders.*

Vascular calcification (VC) is well-known and common complication of CKD. VC portends a worse clinical outcome and predicts major adverse cardiovascular events in patients with CKD. The risk of death in these patients increases with the progressive decline of renal function. In CKD patients, especially in patients receiving dialysis, the risk of cardiovascular events is particularly high – 10-20 times greater than in the general population, whereas the calcification of vessel wall occurs in 50% of patients before the initiation of dialysis. In the past, VC was thought to be a passive, degenerative consequence of precipitation of calcium/phosphate deposits in cardiovascular tissues, but more recently it has been recognized as an actively regulated process that shares some mechanistic aspects with skeletal mineralization. VC is initiated and driven by a variety of molecular signaling pathways and appears as a consequence of increased expression of growth factors, matrix proteins, and other bone-related markers. However, the precise mechanism responsible for VC in CKD have not been elucidated, it is believed that an imbalance of promoters and inhibitors is central to development of this process.

Mounting evidence from the last decade suggests that the osteoprotegerin (OPG) and its ligands: receptor activator of nuclear factor NF-κB ligand (RANKL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) are not only involved in the regulation of the bone turnover and metabolism, but also plays a crucial role in the development of vascular complications. Mechanism of OPG/RANKL/TRAIL system and its role in VC process still remains unclear. *In vitro* and *in vivo* studies indicate a protective and inhibitory role for OPG in the progression of VC. On the contrary, data from clinical studies consistently show a strong association between elevated serum concentrations of OPG and the presence, severity and progression of a broad range of cardiovascular complications. Role of RANKL in process of VC is not perfectly clear either. Likewise, function of TRAIL in the course of CKD remains unknown – only one study showed decreased concentration of this cytokine in the serum of hemodialysis patients, but there was no association between TRAIL and degree of VC.

The aim of the research project is to investigate the influence of OPG and its ligands on VC process. The research will be conducted using two experimental models of chronic kidney failure (CRF), which show different stage of CRF (mild to moderate stage in a 5/6 nephrectomy rat model and severe stage in a 0,3% adenine rat model) and dynamics of calcification process by collecting the biological material at different time points. These two models allow to observe the natural course of VC process, without influence of standard treatment used in CKD patients. In addition to elucidating the fundamental aspects of vascular calcification, results of this project will provide new insights into possible mechanism underlying the impact of OPG/RANKL/TRAIL system on vascular calcification. We deeply hope that obtained results will allow to answer the question, whether **OPG appears as a protective agent against the vascular calcification, or on the contrary, favors this process?**

Thanks to integration methods of molecular biology, biochemistry, analytical chemistry and biostatistics, there will be collected a large amount of highly relevant data that will contribute to a better understanding of the role of OPG and its ligands in the VC process in the course of CKD. We believe, that complete set of results will provide outstanding opportunity to use the knowledge gained in this project to develop new therapeutic strategies for the prevention or treatment of calcification of the vessel wall or their consequences in patients suffering from CKD.