The blood vessels are lined inside with a single layer of endothelial cells. These cells play a crucial role in regulating the function of blood vessels, including generating a signal to relax the vessels and maintaining their anti-thrombotic and anti-inflammatory phenotype. The excellent condition of the endothelium determines the proper functioning of the circulatory system. One of the main risk factors for diseases of this system is ageing. Along with global demographic changes, cardiovascular diseases are becoming a critical social problem.

The primary mechanism responsible for the dysfunction of endothelial cells and the development of cardiovascular diseases is the deficiency of nitric oxide (NO). It is assumed to result from reduced NO production in the endothelium and its neutralization by reactive oxygen species. We propose a broader perspective: the limited bioavailability of NO in the blood vessel wall may also be due to other mechanisms that may be the dominant in endothelial pathology. In the project, we hypothesize that endothelial dysfunction and adverse changes in the circulatory system occurring during ageing result from the massive aggregation of S-nitrosated proteins, which is regulated by the Keap1 protein. S-nitrosation is a post-translational modification of proteins involving NO's attachment to cysteine residues. This process is catalyzed by an enzyme complex in which Keap1 plays a primary role. Our research shows that S-nitrosation is enhanced in prematurely senescent endothelial cells, leading to protein aggregation in the cytoplasm. The project aims to investigate how it determines the function of blood vessels and whether the same mechanism is responsible for pathological changes in blood vessels during physiological ageing. If our hypothesis is confirmed, we plan to attempt the preclinical, experimental therapy and reverse the unfavourable changes in the endothelium and blood vessels by modulating the level and activity of the Keap1 protein or by using a chaperone molecule that inhibits protein aggregation.

The knowledge obtained from the project will allow us to determine the importance of the recently discovered S-nitrosation enzyme complex in blood vessels, verify the atypical mechanism of reduced NO bioavailability in ageing blood vessels, and highlight the functional significance of protein aggregation in the circulatory system.