Proteins are the most versatile bioplymers in human body. Protein function is related to their structure and interactions with other biological molecules. The three-dimesional structure and flexibility of a protein is determined by its amino acid sequence and the multitude of functional groups in the amino acid side chains. Posttranslational, covalent modifications of some of these functional groups are a mechanism used by Nature to increase the number of biological roles played by a single protein. A current major focus of study in cell biology is the „Redox Code" – a system of specific, reversible oxidative changes in proteins that may modulate their tertiary structure, interactions, trafficking, and activity. Thiol groups of cysteines are the most reactive toward oxidative modifications amino acid side chains in proteins.

The subject of experimental studies in this proposal are S100A8 and S100A9 proteins. S100A8 (MRP8, calgranulin A) and S100A9 (MRP14, calgranulin B) exert many important roles in human physiology and pathology. They consist 30-60% of the protein fraction of human neutrophils. Inflammatory mediators or oxidative stress may induce very high expression of S100A8 and S100A9 in every human cell type. The proteins are laboratory markers used in diagnostics of rheumatoid arthritis, ulcerative colitis, Crohn's disease and established biomarkers of many types of human cancers, including breast, prostate, pancreatic, liver or skin cancer. S100A8 and S100A9 play important roles in innate immunity as antibacterial and antifungal molecules produced by the human host.

In this proposal we aim at addressing the mechanisms used by cells to provide functional diversity of S100A8 and S100A9 *in vivo*. We focus on the consequences of divalent metal ion binding to the proteins, their oligomerization and oxidative modifications of cysteines. In our studies we plan to use multiple biophysical techniques, including mass spectrometry based protein structure elucidation methods to establish molecular models of fine-tuning the activity of S100A8 and S100A9.

The proposed basic research is relevant to gain better insight into factors that underly the regulation of very potent protein molecules with important roles in human physiology and pathology which are, as recently established, crucial in the redox-based cellular signalling pathways based on nitric oxide signalling. Understanding these factors is important in human health and in design of new ways of combating inflammatory disease and cancer - two extremely important diseases of the modern civilization.