Description for the general public of the project: I*nfluence of metal ions on amyloidogenic properties of human cystatin C.*

The aging population is problem that currently draws considerable interest, mainly due to problems related to the financial and social burden imposed by the necessity to provide care for elderly people. A special place among these have persons who have been affected by various kinds of changes in the nervous system with degeneration of nerve cells. The drivers of change are different but can be reduced to a common denominator - protein aggregates, that is, the larger clusters of naturally occurring molecules in the human body, which, in response to many different factors start to change their shape. Then, they begin to connect with each other and create larger, toxic clusters, damaging the human nervous system. This type of disease includes Alzheimer's syndrome, which is associated with the deposition of amyloid-beta peptide. Among factors causing irreversible damage are often metal ions that can function as protective agents but in most cases actually accelerate the aggregation of amyloidogenic proteins or peptides. In this project, we are going to focus on the protein that is commonly found in all human body fluids, including cerebrospinal fluid. This natural protein - cystatin C (abbreviated hCC), an inhibitor of cysteine proteases, is essential to our body to function properly. Additionally, it is proved that hCC has a significant impact on immunological processes and participates in the defense against bacteria and viruses. Cystatin C is also an important element in the process of protecting the skeletal system, and is a marker of kidney disease[1]. Increasingly, cystatin C is a ligand that may bind other proteins, including proteins with elevated aggregation properties such as serum A or amyloid-beta peptide. This kind of interaction can also protect the nervous system from the toxic effects of amyloid deposits which formation may be induced by the dysregulation of cellular metal homeostasis[2]. It is therefore important to examine how the presence of metal ions can influence the behavior of cystatin C. In this project we intend to verify whether the appearance of copper and zinc ions in human body fluids may significantly affect the aggregation of cystatin C and the morphology of the structures that are created.

This interesting problem can be thoroughly tested using state-of-the art analytical techniques such as mass spectrometry, nuclear magnetic resonance, calorimetry, microscopy and circular dichroism and fluorescence. The results of our preliminary studies seem to confirm the binding of some metal ions to the human cystatin C and therefore, we are going to study these liaisons in more detail. We will determine which amino acid residues in cystatin C are responsible for the formation of stable complexes, how - on molecular scale - do they look like, and characterize impact of metal binding to hCC on its stability and tendency to aggregate.

In the environment inhabited by human population, more and more substances that can interfere with the natural processes occurring in the body is circulating. Examples are metals that pollute air, food or water. They can be introduced to living organisms by digestion tract or by inhalation, and induce a variety of disease states. The results of this project can be valuable for understanding the impact of external factors on the development of processes related to aggregation and neurodegeneration. Our research will make a significant contribution to the development of scientific knowledge concerning processes associated with protein aggregation and neurodegeneration. In the future it may result in developing an effective treatment for the diseases damaging our nervous systems, such as Alzheimer's or Parkinson's.

(1) Xu, Y.; Ding, Y.; Li, X.; Wu, X. Cystatin C Is a Disease-Associated Protein Subject to Multiple Regulation. *Immunol. Cell Biol.* **2015**, *93* (5), 442–451.

(2) Jomova, K.; Vondrakova, D.; Lawson, M.; Valko, M. Metals, Oxidative Stress and Neurodegenerative Disorders. *Mol. Cell. Biochem.* **2010**, *345* (1-2), 91–104.