Neurodegenerative diseases is a general term for a set of diseases that damage neurons and gradually cause the central nervous system to lose proper function. These diseases are currently included in the group of incurable diseases because the drugs used as a treatment only slow down the pace of their development. They do not cure the diseases. This is a growing problem in Western societies, with around 10 million people suffering from dementia alone in the European Union. It is estimated that by 2030, the cost of treating this disease in the EU will exceed €250 billion.

In the nervous tissues of patients with multiple lateral sclerosis and those suffering from frontotemporal dementia, protein aggregates, often in the form of fibrillary structures, have been found to have a toxic effect on nerve cells. These aggregates are often formed as a result of the formation of stress granules during a process called liquid-liquid phase separation. This process takes place to protect the cell from harmful factors. In a situation of prolonged interaction of these factors, these granules can transform into protein aggregates in amorphous or fibrous form.

This project aims to determine the mechanisms responsible for the formation of stress granules and their pathological changes towards the formation of aggregates composed of proteins associated with multiple sclerosis (ALS) and frontotemporal dementia (FTD). This will allow for the prediction and better control of the formation of such structures, which in the long run may contribute to the development of effective therapies directed against the mentioned diseases. In the first stage, the planned research will concern the expression and development of effective methods of purifying selected model proteins that can form stress granules.

The next step will be to determine the relationship between the conditions of the granule forming process and the properties of individual proteins. Molecular modeling with atomic resolution as well as a number of modern experimental methods will provide information on how the charge, shape, and conformation of proteins change depending on the pH, ionic strength of a solution, and the presence of various ions. The next stage of research will be the description of the processes of creating stress granules from the moment of the formation of smaller oligomeric structures through larger bio-condensates to aggregates. The aim of this stage will be to understand the mechanism and thermodynamics of the process of interactions between proteins for various physicochemical conditions, as well as a detailed description of the morphology of the created structures and their properties. The main techniques to be used for this purpose will be size exclusion chromatography combined with multi-angle light scattering, theoretical modeling, Raman spectroscopy, and isothermal calorimetric titration, which will provide important information on the interactions controlling the stress granule formation process.

The last important step will be to determine the influence of selected low molecular weight chemical compounds on the mechanism and kinetics of stress granule formation. These studies will be aimed at determining the types of interactions of these compounds with selected proteins, enabling the determination of methods of preventing the last stage of the transformation of stress granules into aggregation structures from occurring.

The proposed, innovative approach, combining theoretical modeling with a number of modern experimental methods, developed in cooperation with leading foreign research institutions from Belgium, Finland, and the USA, will allow determining the physicochemical mechanisms of the formation of neurodegenerative disease.