The main goal of the project „Conformational transition pathways and molecular mechanisms of aggregation of the amyloidogenic H-fragment of insulin" is to gain deeper understanding of fascinating capacity of molecules of the newly discovered (by its proponents) insulin fragment to stick together and form nanofibers in a fashion similar to the molecular transitions implicated in Alzheimer's disease.

Correctly folded and biologically functional proteins sometimes reveal tendencies to alter the native structure and convert into long linear „polymers", so-called amyloid fibrils, with biochemical properties entirely different from those of the parent normal precursors. Transitions from native protein structure to amyloid are associated with a number of disorders including Alzheimer's, Parkinson's, and Creutzfeldt-Jakob (prion disease / mad cow disease) diseases: in each case different protein undergoes transition to amyloid fibrils. It is widely accepted that certain stages of this transition produce toxic protein forms, however mechanisms of these processes are far from being fully understood. One consequence of which is the present lack of effective therapies for these disorders.

Occasionally, protein aggregation is further complicated by a preliminary stage in which a larger protein with a low tendency to aggregate is partly digested and fragmented by enzymes. Products of this digestion may have much more pronounced tendencies to form amyloid fibrils. Such scenario has been implicated in the case of Alzheimer's disease.

The project „Conformational transition pathways and molecular mechanisms of aggregation of the amyloidogenic H-fragment of insulin" aims at elucidation of mechanisms underlying the exceptional „explosive" acceleration of aggregation of model „amyloidogenic" protein – insulin – in the presence of small quantities of digesting enzyme – pepsin. Our preliminary results have indicated that this effect is linked to the appearance of hitherto unknown transient product of insulin digestion which we named „fragment H". In the framework of this project, we will use several biochemical and biophysical methods – both experimental and theoretical – to illuminate: (1) reasons for which H-fragments have such powerful propensity to form amyloid, and (2) detailed mechanism of this process. For detection and structural analysis of H-amyloid we will employ spectroscopic methods including infrared spectroscopy and fluorescence, as well as atomic force microscopy. We expect to gain an additional insight into the dynamics of transforming structures of H-fragments through theoretical modelling based on molecular dynamics.

Although our project is aimed at explaining the puzzling transition observed exclusively in vitro, the phenomenon as such reveals many analogies to the complex processes initiating pathogenic protein aggregation in vivo. We expect that results of this project will provide a deeper understanding of these phenomena which, arguably, is the necessary condition to find new effective therapies for such disorders.