Alzheimer's Disease (AD) is a progressive and inevitably lethal dementia, caused by massive death of neurons in brain structures dealing with memory and emotions. AD affects about 50 million people worldwide, and is estimated to increase by 50% in ten years. The age is the main risk factor and no treatment can revert or even halt its progress. The best available recommendation is to maintain a healthy lifestyle, with a balanced diet and physical and mental exercise. Although a number of aberrant processes were identified in AD brains and many drugs were developed to curb them, none was successful in human clinical trials.

Soluble aggregated Aβ peptides are the best documented early toxic species in AD and many therapies were directed against these species. Those therapies, although successful in experimental animals, did not work in patients. This indicates that something crucial is missing in our understanding of Aβ physiology that underlines the pathology. The aim of this project is to clarify one such physiological aspect on the molecular level.

The Aβ peptides are soluble both in water and body fluids and in phospholipid bilayers constituting cellular membranes. Current research indicates that these peptides, when present in a membrane-like phospholipid environment, remain there and do not form toxic aggregates. On the other hand, once in aqueous solution, they form toxic aggregates spontaneously within hours. Yet, the disease progress takes many years. This suggests that the in the normal brain the Aβ peptides are not present in in body fluids in amount sufficient for the aggregation to occur. Based on scattered prior experimental evidence we propose that this is because in normal brain the Aβ peptides reside mainly in the phospholipid environment. In such view the molecules or processes affecting the solubility of Aβ peptides in phospholipid bilayers may contribute to the progress of AD, and, eventually may be alternative targets in future AD therapies.

The specific aims of the project are to determine how much of each of main Aβ peptides, $A\beta_{1-40}$, $A\beta_{1-42}$ and $A\beta_{4-42}$, can be dissolved in phospholipid bilayers of various compositions, reproducing the physiological variability of real cellular membranes. Previous data indicate that in such environment Aβ peptides remain non-aggregated (monomeric) and assume a specific shape including stretches of α-helix. Monomeric Aβ peptides in solution do not have a fixed shape, while the toxic Aβ aggregates contain elements of β-sheet structures. We want to explain what causes the α-helical, Aβ peptides residing inside the membrane to leave this environment and get transformed into toxic aggregates. It is known that such aggregates may return to the membrane and damage it. Our further aim is to systematically study these phenomena to find causative connections between them. Interactions with biological metal ions Cu(II) and Zn(II) may contribute to these phenomena, as it is known that they can bind to monomeric and aggregated Aβ peptides. We will include them in our studies. The final research goal of the project is to find molecules that could stabilize α-helices in Aβ peptides. Such molecules could keep more Aβ peptides inside the membranes, thus reducing the risk of their aggregation and gain of toxicity. Identification of such molecules, together with the obtained knowledge on the principles governing the membrane interactions of Aβ peptides may inspire future studies of novel preventive medicines and cures for AD.

To achieve our goals we will chemically synthesize adequately high amounts of $A\beta_{1-40}$, $A\beta_{1-42}$ and $A\beta_{4-42}$ peptides and purify them to a very high level of homogeneity. This is crucial for the success of further experiments. Then we will optimize the experimental procedures of their handling in order to assure good reproducibility of experiments (reproducibility of studies of Aβ peptides is particularly difficult to achieve, but we together with the external project partners have sufficient experience to achieve it). Our main studies will be performed using state of the art techniques of studying biomembranes with chemical level of accuracy, including measurements of ionic currents flowing through microscale stretches of phospholipid bilayers and determining fluidity of bilayers using spin labels detected by electronic paramagnetic resonance (EPR). We will also use powerful methods of computer simulations, including artificial intelligence, to screen millions of molecules for their ability to modify the Aβ peptide shape in the desired direction. The most active of such molecules will be synthesized and tested experimentally.