Study of mechanism of proteolysis and a selective ligand binding to gamma-secretase complex

The main aim of the project is study of cleavage of APP (amyloid precursor protein) by membranous enzyme γ-secretase, which is composed of the catalytic subunit presenilin and three other subunits: PEN-2, APH-1, and nicastrin. For this purpose we will use the recently published cryo-EM (cryo-electron microscopy) structures of this complex. The recent years have witnessed remarkable efforts in developing therapeutic strategies to decrease production, aggregation, and toxicity of β-amyloid (Aβ), which is the main constituent of the senile plaques found in brains of Alzheimer's disease (AD) patients, but the whole mechanism of APP proteolysis is still unknown. The extent of AD is increasing which is linked to society getting older and development of so called civilization diseases. Currently, about 30 million people is suffering AD.

In our studies the correlation effects of APP binding on the whole structure of γ-secretase and also an influence of selected mutations located close to the active site will be determined. Influence of lipids on stability of substrate-enzyme complex will be studied in typical lipid bilayer and in lipid rafts ie. regions of the membrane of increased stiffness. Molecular dynamic simulations will help to study how water is coming to the active site of γ-secretase which is located deeply in the membrane.

γ-Secretase is a protease cleaving about 90 substrates so it is engaged in many different physiological processes and many diseases including AD and cancer. A global inhibition of the complex of γ-secretase to reduce formation of Aβ-peptides would be undesirable, as this may also affect other pathways such as Notch signaling. Therefore, a screening of selective modulators of this enzyme is required.

The obtained results of this project may help to design modulators which will be selectively able to influence of APP processing not disturbing of proteolysis of other substrates which will help to stop progress of AD. We will also screen compounds for multitarget ligands able to modulate binding of APP to γ-secretase as well as to inhibit β-amyloid aggregation.