At the beginning of the 20th century, Dr Alois Alzheimer described *The disease of forgetting,* known today as Alzheimer's disease. Although the disease is usually associated with forgetfulness, it also causes disturbance of thinking skills, behaviour and, eventually it leads to impairment of the ability to carry out simple, everyday tasks. Patients need constant care, therefore Alzheimer's disease affects also families and caregivers. It is worth noting that the disease can affect anyone, regardless of gender, race, or lack of family history of the disease.

While current medicine is able to treat serious conditions such as heart diseases, bacterial or viral infections, and even different types of cancer, effective therapy of Alzheimer's disease seems unattainable. Promising drug candidates regularly drop out at various stages of clinical trials mainly due to the lack of effectiveness. One of the reasons for this is a complex character of the disease, meaning there is a variety of processes leading to its development. Substances in clinical trials aim at individual processes, which proved to be insufficient to stop the disease. A promising alternative might be multifunctional ligands, compounds that could influence simultaneously several processes underlying the disease.

According to recent studies, there are two underexplored processes that might be crucial for the development of Alzheimer's disease. The first one is harmful aggregation of hyperphosphorylated tau protein inside the nerve cells. The other one is a chronic inflammatory process in the brain. It was demonstrated that the inhibition of these processes might have beneficial effects on the treatment of the disease. Therefore, we would like to explore these two processes and develop original multifunctional ligands that would simultaneously inhibit the pathological transformation of tau protein and reduce inflammatory processes in the brain tissue. We plan to achieve this goal by an inhibition of two important enzymes that are associated with the described processes - GSK-3β kinase and IKK-β kinase.

In the presented project, we plan to synthesize newly designed multifunctional ligands, inhibitors of GSK-3β kinase and IKK-β kinase, and verify their effectiveness in a broad spectrum of *in vitro* tests associated with the processes leading to Alzheimer's disease. In addition, we will answer all important questions that arise during the drug discovery process regarding distribution (do the compounds reach their site of action?), metabolism (aren't they removed too fast from the body?) and toxicity (are they safe?). Finally, we will study the effectiveness and safety of 1 or 2 most promising compounds in mice models of memory impairment. Currently, there are no other models that allow verifying the impact of substances on memory, thus *in vivo* studies are the indispensable stage of such research project. All the described studies will be carried out by an interdisciplinary team of experienced researchers who are specialized in molecular modelling, organic synthesis, medicinal chemistry, molecular biology and experimental pharmacology.

The described project aims at the development biologically active multifunctional ligands and investigation of their effects on tau pathology and neuroinflammation. Therefore the results of the project will contribute to the development of knowledge but also may set a new direction in the search for new, disease-modifying therapy of Alzheimer's disease.