Justification for undertaking the research

Dementia associated with Alzheimer's disease (AD) substantially affects daily lives of patients, their families and the whole society. The number of patients with AD diagnosis will continue to grow and it is expected to reach at least 150 million by the year 2050. The huge worldwide cost of dementia treatment and the increasing prevalence of AD will be a further challenge for health systems in the near future. **While ameliorating the symptoms of AD for only a couple of years with little effect on disease progression, currently available anti-AD drugs have serious adverse effects**. **New molecular tool compounds, designed by using innovative approaches are therefore urgently needed** to enable the development of new drugs for AD. Multi-target-directed ligands (MTDLs) target multiple pathways involved in the onset and progression of the disease and have become a hot topic in several therapeutic areas, including AD.

Three out of the four currently approved anti-AD drugs exploit cholinesterase inhibition, with view to improve memory in patients. Recent data validate butyrylcholinesterase (BChE) as a viable therapeutic target for restoring cholinergic activity and improving cognitive performance, while minimizing the surge of adverse effects. In addition, the proper functioning of the central nervous system requires a balanced bidirectional communication between neurons and other cells, which is severely affected by the neuroinflammation - a key component of AD pathogenesis. In this context, mitogen-activated protein kinases (MAPKs), intracellular enzymes involved in signal transduction of various extracellular stimuli such as mitogens and stress, are of particular interest. Importantly, p38α MAPK is involved in neuroinflamation of the nervous system and it may be a therapeutic target for drugs used in AD.

Aim of the project

The aim of this project is to design and develop new compounds - molecular tools, potential drug candidates for the treatment of AD. The designed compounds will simultaneously counteract inflammation of the nervous system by inhibiting p38α MAPK and they will inhibit BChE.

Research project description

Using structural techniques for drug design and combining two structural features in a single chemical molecule, compounds will be developed to influence various AD-related processes. MTDLs developed in this project will be a valuable contribution to the search for a preclinical candidate for a new memory-enhancing drug; the latter will form an important basis for the further development towards an active pharmaceutical substance.

Expected results

Members of the international research group: Prof. Dr. hab. Kinga Sałat (Jagiellonian University Collegium Medicum), Prof. Dr. Kamil Musilek (University of Hradec Kralove, Czech Republic), Prof. Dr. Stanislav Gobec (University of Ljubljana, Slovenia) will combine their interdisciplinary knowledge to develop in a highly complementary manner 2-4 new compounds with therapeutic potential in AD: memory-enhancing activity at least comparable to available drugs, good safety profile, high brain permeability and plasma stability. The research carried out by the Polish partner will be carried out at the Faculty of Pharmacy of the Jagiellonian University Medical College and will consist in the assessment of the memory-improving properties of selected compounds in two mouse models of amnesia. The studies will also assess the safety profile of the developed compounds and their pharmacokinetic parameters. The planned research is innovative and important from the scientific point of view as it will broaden the knowledge about the causes of AD and the activity of new chemical compounds – MTDLs. Potentially, this knowledge might be also clinically useful as it will help to establish research direction it the area of searching for new drugs for AD therapy.