DESCRIPTION FOR THE GENERAL PUBLIC

The increased life expectancy, observed in the world population within the past century, has contributed to the elevated risk of dementia, a syndrome characterized by progressive cognitive disorders that involve decline in memory and thinking. Changes associated with dementia constitute one of the major causes of disability in the elder life. The most common form of dementia is Alzheimer's disease (AD) – devastating neurodegenerative illness. The number of people with AD was estimated as 35.6 mln in 2012 and is expected to double every twenty years to 65.7 mln in 2030 and 115.4 in 2050.

Although intense scientific research has been conducted on etiopathogenesis of dementia and AD for many years, no drug which withdraws or stops progression of the disease was identified. Currently available pharmacotherapy focuses on symptomatic treatment of memory deficits and cognitive functions, and slow-down of disease progression.

Among many concepts for development of potential treatment of Alzheimer's disease (AD), two approaches gain a special interest. First of them, focuses on serotonin receptor type 6 (5-HT_6R), localized in brain regions, in which serotonin controls learning and memory processes. In line with the recent findings, 5-HT_6R interplays with the mammalian target of rapamycin (mTOR) and cyclin-dependent kinase 5 (Cdk5) pathways, being involved in cognitive decline and pathogenesis of AD. Second approach concerns reversible inhibition of monoamine oxidase type B (MAO-B). This mechanism is responsible for neuroprotective properties and therapeutic application of MAO-B inhibitors in Parkinson's diesase.

The major objective of the project concerns obtaining of two new series of compounds, functionally selective (biased) inverse agonists of 5-HT_6R, which specifically (or preferentially) inhibit 5-HT_6–operated constitutive activity at mTOR and Cdk5 signaling, as well as dually acting modulators of 5-HT_6 and MAO-B. Original nature of the project is to propose structural modifications allowing for elaboration of compounds, which combine carefully designed multi-modal mode of action and open the possibility for developing compounds with symptomatic and AD-modifying properties.

The project is planned to determine the effectiveness of the molecules at the biochemical level (e.g. determination of transduction pathways, neuroprotective effects, safety) and on the behavioral level, evaluating an influence of selected compounds on learning and memory processes in normal rats and in the mouse model of AD.

The project would provide molecules, which on the one hand allow for confirmation of the hypothesis on the signal transduction pathways in the brain – an interplay between the 5-HT_6R, and mTOR, Cdk5 pathways, possible elaboration of dually acting compounds targeting 5-HT_6R/MAO-B. Secondly, it might envision benefits from functionally selective (biased) modes of action and designed multi-target mechanism for more effective therapy of AD. Results of the project may also become an incentive to undertake advanced research on the development of new therapies for neurodegenerative diseases.

The project will be realized in an interdisciplinary research team, which includes researchers from two Polish research units - the Jagiellonian University Medical College and the Institute of Pharmacology of Polish Academy of Sciences and the French research centers - University of Montpellier and the National Center for Scientific Research, through a program of interrelated research tasks of fundamental nature.