DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Depression is a nervous system disease the incidence of which, unfortunately, is constantly on the rise. Further, an efficiacy of available antidepressant therapeutic strategies is insufficient, amounting to ca. 50 – 70%. The number of treatment-resistant patients, non-responsive to antidepressant therapies increases, which can have serious consequences, like suicidal attempts, and fatal outcomes. In general, it is believed that unsatisfactory efficacy of currently available pharmacotherapies of depression results from the lack of deep insight into the biological basis of this disease. To date, many studies demonstrated a link between manifestation of depression episodes and changes in peripheral humoral and cell-mediated immunity. Further, *post mortem* studies demonstrated immunoactivation in the patient‘s brain. Also, studies in animal models of depression revealed long-lasting inflammation, including activation of immunocompetent cells in the brain, i.e. microglia, and production of toxic factors, proinflammatory cytokines and chemokines, mostly in the frontal cortex and hippocampus, thus, in the structures the dysfunction of which in the course of depression development is commonly accepted. It has been postulated that prolonged inflammation leading, among other things, to changes in neurotransmission, cell-to-cell communication in the brain, neurodegenrative changes and disturbances of adult neurogenesis in the hippocampus, finally, lead to behavioral deficits.

To date, there are only a few studies aimed to explain pathogenesis of the prolonged inflammation, therefore, the studies proposed in the present project are fully justified. Literature data indicate that formyl receptors (ALX/FPR2), belonging to a large family of G-protein-coupled receptors, are present not only in the periphery but also in the brain, especially on microglia cells, but also on astrocytes and neurons. Interestingly, since ligand-dependent activation of these receptors was shown to lead to initiation of intracellular signal transduction mechanisms engaged in opposite biological effects, including pro- and anti-inflammatory, the most recent studies suggest their involvement in molecular mechanisms of resolution of inflammation (RoI).

Based on available literature data and studies of our team conducted so far, the research hypothesis assumes that prolonged inflammation observed in the course of depressive disturbances is connected with dysfunction of molecular mechanisms of ALX/FPR2 receptor activation and/or limited availability of lipid derivative of arachidonic acid, lipoxin A4 (LXA4), which is the most specific endogenous agonist of this receptor. Its binding to ALX/FPR2 induces a strong immune response, leading to resolution of inflammation, thus, preventing development of long-lasting inflammation.

The main aims of the project include not only verification of this hypothesis but, most of all, the assessment of usefullness of new ureido-derivative ALX/FPR2 receptor agonists, synthesized by the foreign partner as an innovative tool for potentialization/enhancement of resolution of endogenous inflammatory processes. New agonists, contrary to LXA4 and its analogs, possess pharmacokinetic parameters optimatized for *in vivo* research, they passively cross the blood-brain barrier and show accumulation in the brain structures engaged in the pathogenesis of depression. These data provide a firm foundation for the proposed research.

The studies proposed in the project will be realized at three stages: first, in *in vitro* model (primary microglia cultures) and *ex vivo* model (using a unique technique of organotypic hippocampal culture, which preserves functional connections within the neuro-immune-endocrine system of this structure and functional cell-to-cell interactions), and then *in vivo* in two well-described and commonly accepted animal models of depression-like disturbances.

We hope that the proposed research will bring innovative results and that the innovative strategy proposed by us will contribute to a significant increase in an efficacy of antidepressant therapy, especilly in patients with comorbid inflammation.