Description for general pubic

Schizophrenia is regarded as the most debilitating neuropsychiatric disorder, which affects 1% of the population. Currently available pharmacotherapy is not effective in the control of the whole constellation of schizophrenia symptoms, moreover above 30% of patients is resistant to the available drugs. Another concern is represented by safety issues associated with antipsychotic drugs, which contribute to the limitations of their use. Due to the dysfunctions of brain-gut axis, neuropsychiatric disorders constitute a common comorbidity of functional gastrointestinal disorder, such as irritable bowel syndrome. These data indicate an unmet need for developing of the novel pharmacological approaches of the above mentioned disorders.

Analysis of the multireceptor profile of action of clozapine, the only antipsychotic agent used in the treatment of drug resistant schizophrenia, revealed, in addition to the well-established blockade of serotonin 5-HT_{2A}R, its antagonist properties at serotonin 5-HT_3 and 5-HT_6 receptors. This observation prompted us to develop FPPQ, a dually acting 5-HT_3R/5-HT_6R antagonist. Pharmacological evaluation revealed that FPPQ inhibits phencyclidine-induced hyperactivity (contributing to alleviating the positive-like symptoms of schizophrenia) and displays procognitive properties.

The aim of the presented project is the verification of the two hypotheses, indicating *1*) the possibility of alleviating positive and negative symptoms of schizophrenia by dually acting 5-HT_3R/5-HT_6R antagonists in extended behavioral studies and *2*) the possibility of improving the gastrointestinal tract motility and analgesic activity by compounds with such mechanism of action.

The project will be realized in two pathways, *i*) broadening the knowledge on the combination of 5-HT_3 and 5-HT_6 antagonism, exemplified by FPPQ and *ii*) the identification of „follow-up" chemotypes for FPPQ in the chemical, biological and pharmacological studies. The most active compounds in the *in vitro* assays, will be evaluated for their antipsychotic and procognitive properties in various behavioral models, also using DISC1 mutant mice considered as a genetic model of schizophrenia. Moreover, the most promising derivatives will be tested for their impact on colonic motility and analgesic activity.

The verification of the project hypotheses might bring to light novel information on the molecular mechanisms involved in the etiology of neuropsychiatric and neurological diseases. The gained knowledge may contribute to the development of safe and effective strategies for the treatment of these disorders.

The project will be realized in the multidisciplinary research team, involving scientists form three Polish research units: Jagiellonian University Medical College, Institute of Pharmacology, Polish Academy of Science, Medical University of Łódź, and two French research centres: Institute of Functional Genomics, University of Montpellier and Institute of Structural Biology, University Grenoble Alpes.