Schizophrenia is a severe mental disorder which affects about 1% of the human population. Due to the fact that the first symptoms of the disease become apparent relatively early in life (20-35 years), it is called a young people disease. The schizophrenic symptoms are divided into three groups, defined as positive, negative and cognitive. The kinds of symptoms differ between affected people and may change from one year to the next within the same person as the disease progresses. Different subtypes of schizophrenia are defined according to the most significant and predominant characteristics present in each person at each point in time. Therefore, there are five or even seven schizophrenic types, depending on the severity of the particular symptoms. Currently used pharmacological therapy for schizophrenia is effective in the treatment of the positive symptoms. These include all sorts of delusions and hallucinations. Unfortunately, the effectiveness of most of the currently used drugs is not fully satisfactory in the treatment of negative and cognitive symptoms of schizophrenia. Another limitation of the antipsychotic therapy is the fact that most drugs must be administered at least ten days in order to achieve a therapeutic effect, that in turn promotes the development of a number of adverse effects, which include weight gain, sleep disorders, sexual disorders, extrapyramidal adverse effects (dyskinesia, tremor, Parkinson drug induced). All neuroleptics, except risperidone, decrease the seizures threshold. The mechanism of action of the majority of neuroleptics involves predominantly dopamine D_2 receptor blockade. This mechanism is responsible not only for the therapeutic effect (in the context of positive symptoms), but also for inducing variety of above mentioned adverse effects. The use of the selective D_2 receptor blockers, such as neuroleptics of the 1st generation, or so-called typical antipsychotics, is limited predominantly to the treatment of the positive symptoms of schizophrenia. Neuroleptics of the newer generation, called atypical antipsychotics, bind not only dopamine receptors, but possess affinity to other types of receptors, such as serotonergic, histaminergic and muscarinic. These drugs are more effective in reducing negative, and to some extent, also cognitive symptoms. The negative and cognitive symptoms are those, that are the main cause of the malfunctioning of the patients in the community, including social withdrawal, apathy, anhedonia, impaired abstract thinking, blunted affect, and the others. The action of these drugs is however not fully satisfactory, particularly in patients with high intensification of positive symptoms. Furthermore, most of them causes adverse effects described above. Looking for new potential targets for the better tolerated and more effective drugs, the fresh look is needed that would discover the novel antipsychotic targets, based on the latest research on the pathophysiology of the disease. Recent trends indicate that impaired activity of inhibitory (GABA) and excitatory (glutamatergic) neurotransission may lay at the grounds of the schizophrenia arousal. Based on this hypothesis a new approach to the treatment of schizophrenia, based on the modulation of the activity of the glutamate by acting throught the metabotropic receptors regulating its release, such as two types of glutamatergic receptors ($mGlu_2$ and $mGlu_4$) and the $GABA_B$ receptor. For several years, extensive research has shown strong therapeutic potential for ligands activating these receptors, thereby inhibiting the release of glutamate. The extensive research performed in our laboratory represents an important and large part confirming the role of these receptors in schizophrenia. The assumption that the combined administration of subeffective doses of ligands with a defined antipsychotic activity can induce a therapeutic effect selectively, in animal models of positive, negative or cognitive symptoms of schizophrenia, constitute the pioneering aspect of our study.

Just for example we showed that the simultaneous modulation with subeffective doses of the potentiators of $GABA_B$ and $mGlu_4$ receptors was effective in models of positive symptoms of schizophrenia, while the simultaneous modulation of $mGlu_5$ and $GABA_B$ receptors was exclusively effective in the models of negative and cognitive symptoms of schizophrenia. Some ligands exerted action in all the spectrum of schizophrenic disturbances when applied together, such as interaction between $mGlu_4$ and 5-HT_{1A} receptors. In the present project, that will constitute the sequel of our investigations, we plan to follow the newest trends of neuropsychopharmacology and take into consideration the role of muscarinic receptors (M_4 subtype) in the regulation of the brain circuits involved in psychosis, and also their involvement in the antipsychotic-like action exerted by the ligands of the receptors involved in the regulation of glutamate release (ie. $mGlu_2$, $mGlu_4$ and $GABA_B$). The activity of compounds activating muscarinic receptors was relatively recently reported in the models of positive symptoms of schizophrenia. In our preliminary studies, we found that activator of M_4 receptors is also active in the models of negative and cognitive symptoms of schizophrenia. Moreover, single reports indicate that there is an interaction between mGlu or $GABA_B$ receptors with muscarinic receptors. However, the research on this subject is scarce at present. The aim of this project is to investigate whether the simultaneous administration of subeffective doses of different combinations $mGlu_2$, $mGlu_4$ or $GABA_B$ receptors ligands with M_4 receptor potentiator will induce antipsychotic-like effect in various animal models of schizophrenia, and if the observed effects will be solely observed in the models of positive, negative or cognitive symptoms of schizophrenia.

The experiments in the present project will be performed at the behavioral, neurochemical and molecular levels. The results of those experiments will strongly contribute to increase knowledge on the interaction between the muscarinic M4 receptor and $mGlu_2$, $mGlu_4$ or $GABA_B$ receptors in context of schizophrenia-related changes in the brain. The research will also be focused on the ability of particular ligands combinations to regulate the neuronal pathways involved in the development of symptoms of schizophrenia, and which pathways of intracellular signaling are intensified after the activation of the two receptors simultaneously. Based on those results we plan to define the combinations of two selected compounds that could be dedicated to the treatment of particular group of schizophrenic symptoms. It would allow to propose the treatment targets more focused on the needs of individual patient and to minimize the doses that need to be administered to achieve therapeutic effect. Such a solvation could help to avoid the risk of inducing adverse effects, that increases with a high doses of drugs. These studies are totally pioneering, however, on the other hand, the available data (including preliminary results also obtained in our laboratory) indicate that this line of research has a good chance of success.