Regulation of alternative *Dclk1* kinase gene isoforms by psychotropic drugs

The aim of this project is to uncover the role of specific drug-inducible isoform of doublecortin-like kinase 1 (*Dclk1)* in mediation of neuroplastic alterations in the brain. *Dclk1* gene has a complicated structure and transcriptional regulation. Multiple transcript variants of *Dclk1* generated by two alternative promoters and alternative splicing are differentially expressed and have different kinase activities. Interestingly, genetic variants of *DCLK1* have been associated with schizophrenia and hyperactivity disorder in humans. Recent studies showed *Dclk1* role in synaptic plasticity and neurogenesis. However, the process of transcriptional regulation and biological validity of diverse alternative variants of *Dclk1* remains elusive.

My previous results of whole-transcriptome profiling in mouse prefrontal cortex indicated that treatment with risperidone and mianserin regulates expression of specific short isoform of *Dclk1* (*Carp*). The research hypothesis assumes that connected to neuronal activity expression of *Carp* is involved in translation of pharmacological drug effects into long-term plastic alterations of the brain. I plan to characterize *Dclk1* alternative variant *Carp* on the levels of gene transcription, protein expression and neuronal function.

As a part of the planned project I will study changes in *Dclk1* isoforms mRNA abundance levels in response to risperidone and mianserin in two brain structures of C57BL/J mice. I am planning to investigate the effects of drugs in three time points with the quantitative PCR reaction conducted with isoform-specific designed primers. Based on the obtained results I will choose a drug for subchronic treatment for the identification of protein product of *Carp*. Further, the potential impact of *Carp* inhibition on formation of dendritic spines will be tested in primary neuronal cultures

The obtained results will provide an interesting insight into cellular functions and role in brain plasticity of drug-inducible alternative variant of *Dclk1*. The involvement of *Carp* in the regulation of cytoskeletal organization may reveal a mechanism involved in the action of 5HT2A receptor antagonists. Obtained results may also serve as a basis for further research focused on possible connection between *Dclk1* sequence polymorphisms and susceptibility to psychotic or affective disorders.