Neurological and neuropsychiatric disorders are affecting a substantial part of our society. Unfortunately, available treatment is not effective in many patients' cases. This is due to the fact, that the pathological mechanisms underlying those disorders are still largely unknown.

An increasing amount of data suggests that pathogenesis of the above-mentioned diseases could be related to the compromised synaptic plasticity mechanisms. Physiologically, synaptic plasticity is thought to underlie learning and adaptation for the environmental stimuli. Synaptic plasticity's functional domains are excitatory synapses, that comprise a site of communication between neurons and could be strengthened or weakened upon stimuli or its absence. Synapses are localized mainly on small protrusions termed dendritic spines; changes in shape and density of the latter are observed in many neuropsychiatric disorders and are one of the premises for the hypothesis on disrupted synaptic plasticity underlying those diseases. Therefore, a key research objective is to elucidate the pathological mechanism of dendritic spines aberrations, together with uncovering how those aberrations affect the clinical picture of the mentioned disorders.

Matrix metalloproteinase 9 (MMP-9) and glycogen synthase kinase 3β (GSK3-β) are well-documented mediators of synaptic plasticity processes. Additionally, the pathological activity of both MMP-9 and GSK-3β is currently linked with multiple neurological and neuropsychiatric disorders. Animals with altered MMP-9 or GSK3-β activity can be characterized by impairments in learning and disruptions in dendritic spines shape. More importantly, it was demonstrated that MMP-9 and GSK-3β act together in structural dendritic spine remodeling.

The first aim of this project is to identify the underlying cause of social deficits observed in mice with a modified form of GSK-3β that potentially model symptoms observed in autism or schizophrenia. We intend to examine the activity of particular brain regions that are related to social stimuli processing, and which activities have been demonstrated to be altered in the above-mentioned disorders. In case of positive results, the following step will be to test whether those regions can be characterized by abnormal dendritic spines structure.

Subsequently, we will verify whether administering a substance that inhibits MMP-9 activity to mice with a modified form of GSK-3β, would result in amelioration of social deficits in those animals. Additionally, we will test whether this treatment could also reverse dendritic spine abnormalities, possibly detected in socially relevant brain regions in mice with a modified form of GSK-3β.

The outcome of this project will provide data on GSK-3β involvement in social deficits symptoms. Additionally, it will reveal whether those deficits could be accompanied by aberrant synaptic plasticity. Moreover, it will demonstrate that inhibiting MMP-9 activity could be a therapeutic target in the treatment of GSK‑3β-related disorders. Finally, it will provide new evidence to support the hypothesis on aberrant plasticity underlying neurological and neuropsychological disorders.