Epilepsy is a group of neurological disorders characterized by recurrent epileptic seizures caused by abnormal electrical activity of the whole brain or one of its structures. It is estimated that approximately 1% of human population suffers from epilepsy. The etiology of epilepsy is complex and includes structural and metabolic abnormalities, genetic factors, and unknown causes. The mechanism of epileptogenesis, i.e., the process of structural and functional changes transforming the normal brain to one that can generate abnormal neuronal activity, is also multifactorial and unclear. Although pharmacotherapy continues to be the mainstay of epilepsy treatment, about 1/3 of patients remain resistant to the treatment. Moreover, currently available antiseizure drugs possess only symptomatic activity and they do not suppress epileptogenesis. Thus, further multidirectional studies are required to better understand the mechanisms underlying the pathomechanism of epilepsy and to develop more effective treatment strategies.

Glycine transporter type 1 (GlyT1) is the main regulator of glycine levels in the central nervous system. In recent years, GlyT1 has received considerable interest because it is closely related to the functioning of the NMDA receptors, which play a key role in excitatory neurotransmission. Glycine is a co-agonist of the NMDA receptors but it also acts as an inhibitory neurotransmitter by binding to the strychnine-sensitive glycine receptor. It appears that glycine, by regulating the extracellular level of glycine, can provide a balanced regulation between the processes of excitation and inhibition in certain structures of the brain, including the hippocampus, and thus can influence seizure activity. However, studies on the involvement of GlyT1 in the pathomechanism of epilepsy and its treatment are very limited.

In the view of the above, the aim of our study is to provide more insight into the role of GlyT1 in epilepsy and its management by studying the effects a highly selective GlyT1 inhibitor (SSR 504734) on seizure activity and the therapeutic efficacy of antiseizure drugs in mice. We plan to:

(1) Evaluate the influence of SSR 04734 on seizure susceptibility in different animal models of acute seizures as well as in a model of temporal lobe epilepsy.
(2) Evaluate the ability of SSR 504734 to suppress the epileptogenesis.
(3) Evaluate the effect of SSR 504734 on epilepsy-related psychiatric comorbidities and cognitive impairments.
(4) Elucidate the potential molecular and biochemical mechanisms underlying the observed effects.
(5) Investigate the interactions of SSR 504734 with selected antiseizure drugs.

The results of our study will contribute to a better understanding of the role of GlyT1 in epilepsy. The obtained results will allow answering the question whether inhibition of GlyT1 may represent a rational therapeutic target in the treatment of epilepsy and/or suppress the epileptogenesis process. We will also present preliminary evidence on whether GlyT1 inhibitors may influence the therapeutic potential of the currently used antiseizure drugs. In the further perspective, the results of our studies may contribute to the development of novel, more effective and safe treatment strategies for epilepsy.