Epilepsy is a chronic disease, with **high risk of drug-resistance development exceeding of 30%(!)**, associated with an increased risk of a variety of serious psychiatric and medical comorbidities that can adversely affect quality of life as well as life expectancy. Thus, **depression, anxiety, as well as cognitive problems, memory disturbances are the most common in patients with epilepsy (PWE)**. The epidemiological data indicate that as many as one-third of PWE suffer from depression and anxiety. **Despite of major progress in management of epilepsy including (drug-resistant epilepsy, DRE), problems related to depression and anxiety in PWE remain unaddressed till now**.

The main objective of the current project is to obtained series of original compounds as candidates on novel ('first in class') antiseizure drugs (ASDs). Therefore, we are going to focus our attention on substances **1) with novel mechanism of action** (**selective positive allosteric modulators [PAMs] of EAAT2 transporter for glutamate**); **2**) with potent and broad efficacy in different types of epilepsy; **3)** effective in drug resistant epilepsy; **4)** with additional antidepressant and anxiolytic efficacy that is beneficial for simultaneous treatment of these frequent psychiatric comorbidities; and **5)** devoid of harmful sedation. Identification of **such molecules seem to be real breakthrough for the pharmacotherapy of epilepsy and probably also other neurological (neurodegenerative) or psychiatric disorders, related with increased glutamate excitotoxicity or misbalance, such as e.g., amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), ischemia, neuropathic pain, anxiety, depression, and autism**. Compounds with the aforementioned pharmacological characteristics are of great interest as promising therapeutic option in epilepsy especially with co-existence of very common psychiatric comorbidities such as depression and anxiety. We believe also that **lack of sedative properties and as a result lack of harmful decrease of concentration and alterations of cognitive functions may have high clinical utility in the pharmacotherapy of epilepsy in pediatric patients**. Additionally, in aim of strengthening the project importance, in the current studies **we are going also to assess the efficacy of selected compounds in animal pain models, as well as in the *in vivo* model of ALS**.

In the aim of maximizing the success of the current project we are going to perform targeted, rational and small structural modifications of our hitherto lead compound which is a selective PAM of EAAT2. **Notably, this molecule revealed majority of the aforementioned beneficial properties, such as e.g. potent and wide anticonvulsant efficacy, analgesic activity in neuropathic pain models, antidepressant and anxiolytic activity, and notably no sedation in the preclinical studies**. Thus the **design of new compounds was based on so called "*me too*" strategy and combinatorial chemistry approach that rely on small structural modifications carried out in aim of improvement efficacy or decrease of toxicity of new molecules compared to parent substance**. We assume that due to relatively restricted and small structural modifications of the lead compound, there is a high probability for identification of new substances with similar mechanism of action, as well as with broad spectrum of anticonvulsant activity, **hopefully with more potent protection in given seizure model and with beneficial antidepressant, anxiolytic, and analgesic properties along with favorable safety both in the *in vitro* and *in vivo* studies**.

The current project is a multi-disciplinary investigation predicted on 48 months of realization that include both detailed chemical and pharmacological studies (*in vivo*/*in vitro*).

In summary, we postulate that the **discovery of new ASDs with novel mechanism of action (PAM of EAAT2) may substantially improve current pharmacotherapy of epilepsy**, especially with co-existence of depression or anxiety, and in consequence may improve quality of life of epileptic patients. Further, the results of this project may enable to identify of new compounds effective in the treatment of neuropathic pain and ALS, which pharmacotherapy is still extremely insufficient. Therefore, **the project results may accelerate designing of new and more effective anticonvulsants in a more rational and attractive manner in other laboratories worldwide that may lead hopefully to introduction into therapy novel and innovative ASDs in future**.