Anxiety disorders (ADs) are the sixth leading cause of disability worldwide in terms of years of life lived with disability and are characterized by intense and prolonged negative emotions such as feelings of fear and distress. Despite heterogeneity, ADs share clinically relevant features such as extensive anxiety, physiological anxiety symptoms, behavioral disturbances such as avoidance of feared objects, and associated distress or impairment. Two factors most widely acknowledged as involved in ADs pathogenesis include genes and stressor events. However, etiology and understanding of the mechanisms underlying the genetic basis of the disorder have remained elusive.

The genome-wide association study proposed SLC38A1, coding for SAT1 glutamine transporter, as a candidate gene associated with stress vulnerability and anxiety. Recent data has proven that SAT1 protein regulates vesicular GABA content and induces high-frequency membrane oscillations. Therefore, its dysfunction likely to predispose to anxiety behavior. Of importance, SAT1 is critical for BDNF-dependent regulation of dendritic length and neuronal complexity linking the enhanced GABAergic tone with morphological changes and neurotrophic theory of ADs.

The hypothesis based on our observations aims to reveal that mice lacking the slc38a1 gene (SAT1ko) exhibit behavioral and biochemical abnormalities, indicating a phenotype characteristic of anxiety disorders and slight cognitive impairment.

The project aims to clarify the relationship between the lack of SAT1 protein and the animals' susceptibility to stress, in correlation with changes in the GABAergic and glutamatergic systems and neuronal morphology controlled by BDNF.

We will use a state-of-the-art methodology and SAT1ko mouse (both male and female) to explore the impact of SAT1 transporter depletion on GABAergic/glutamatergic balance in the prefrontal cortex (PFC) of mice brain in the context of anxiety-like phenotype. Mice will be tested under basal conditions and following chronic stress procedure (CSDS). The experiments will be performed (1) in vivo on SAT1ko mice exposed to CSDS, to model rodent anxiety-like behavior; (2) ex vivo on isolated from aforementioned animals PFC slices for electrophysiological recordings and morphological analysis; (3) ex vivo on cells isolated from SAT1ko/wt animals to uncover detailed molecular aspects; (4) human postmortem brain tissue.

Behavioral phenotype of SATko/wt mice subjected to CSDS procedure will be studied using different tests aiming to analyze the anxiety-like response, including impact on working and recognition memory. In the PFC of SAT1ko mice with CSDS will be analyzed neurotransmitters' metabolism, proteins of GABAergic and glutamatergic system, and synapse morphology. Studies will encompass proteomic analysis, RNA sequencing, Western blot, qRT-PCR, and electrophysiology recordings. The proof of concept will verify the effect of ketamine administration, a pharmaceutical compound with therapeutic potential or local slc38a1 overexpression in the selected region of the SAT1ko mouse brain to reverse or prevent the key observed changes, respectively.

ADs are one of the most common mood disorders that occur in the course of life at more than 20%, and their symptoms cause problems in social and professional life. The socio-economic burden is significant and mainly results from a prolonged inability to work.

The role of the SAT1 transporter as the mediator of the anxiety-like phenotype has, to our knowledge, was not evaluated. The information gathered from the implementation of the proposal will elucidate the role of glutamine transporter in GABAergic/glutamatergic transmission balance including, morphology control of neurotrophic-BDNF-related neuronal morphology in anxiety-related diseases, and possibly evolve into a useful tool in the extent of neuronal impairment control, and in designing specific diagnostic or therapeutic methods absent in the current practice.