Neuropsychiatric diseases are characterized by disorders of higher cognitive functions, behavior, and emotions that impair normal functioning and cause suffering. According to the World Health Organization, the number of people diagnosed with a psychiatric disorder was 970 million worldwide in 2019. This means that one in eight people on our planet struggles with mental health problems. The percentage of these people increased in 2020 due to the COVID-19 pandemic. As a result, mental illnesses are becoming one of the biggest problems of modern society, and research into the causes and methods of treating these disorders is increasingly focused on.

The aim of this project is to understand the function of angiomotin-like 1 (AMOTL1) in nerve cells and the brain. AMOTL1 belongs to the family of proteins called "motins" together with two other representatives: angiomotin (AMOT) and angiomotin-like 2 (AMOTL2). All of them are characterized by a similar structure (both related to the order of amino acids in the polypeptide chain and the organization of protein domains), and their functions were originally described in vertebrate epithelial cells. However, the role they play in the brain is still unknown. So far, only four scientific publications describe the biological significance of the AMOT protein in neurons, and the other two motins, AMOTL1 and AMOTL2, have not been studied in the context of the physiology of the central nervous system.

Our unpublished results confirm the presence of AMOTL1 in various brain structures. This protein is located in neuronal synapses, and deletion of the AMOTL1 gene results in a decrease in the density of synaptic connections in hippocampal neurons and a disruption of neurotransmission associated with the neurotransmitter glutamate. In addition, in the brain of AMOTL1 knockout mice we did not observe significant differences in the size of the hippocampus, but we did find an enlargement of the ventricular system of the brain, which affects the shape of the hippocampus itself. In addition, our behavioral studies showed that male AMOTL1 knockout mice display a set of features that correspond to those present in mouse models of bipolar mood disorder (mania-like behavior), while preliminary results from studies on female mutant mice demonstrated that they display features similar to depression. This is consistent with the occurrence of bipolar disorder symptoms in humans, where men are more likely to have manic episodes and women to have depressive episodes.

Additionally, we were able to show that the AMOTL1 protein interacts with proteins regulating the degradation process of other proteins in the cell, and also binds to another protein involved in the control of protein formation (translation).

In this project, we will characterize in detail the depressive-like behaviors associated with the hippocampus in AMOTL1 knockout mice, and then analyze them at the anatomical, tissue, and cellular levels to compare the hippocampi in males and females, which in behavioral studies show a divergent set of features. These structural studies will be complemented by functional experiments to show possible differences in synaptic transmission within the hippocampus. The final element of the project will be to describe the molecular mechanism by which the AMOTL1 protein regulates the functioning of neural synapses in the hippocampus.

The studies described in this project will shed new light on the development of specific symptoms of bipolar mood disorder and will allow us to understand the cause of the differences between the sexes in it. Describing the molecular mechanism of the AMOTL1 protein action in hippocampal nerve cells may become the basis for the design of completely new drugs that act on new, previously unknown cellular processes in the treatment of bipolar mood disorder.