Tuberous Sclerosis Complex is a genetic disease that manifests by tumors, epilepsy and neuropsychiatric disorders, such as autism spectrum disorder, anxiety, and intellectual disability. Neuropsychiatric symptoms arise from problems with development of neuronal connections in the brain. During development, neurons integrate external and intracellular signals, in order to extend protrusions, called axons and dendrites, and form a functional network of connections. Proteins integrating these signals are Rac1 and mTOR, among others. The hyperactivation of mTOR in Tuberous Sclerosis Complex is responsible for the formation of tumors and epilepsy in patients, but does not explain neuropsychiatric symptoms. Therefore, other signaling pathways must interact with the mTOR pathway causing these disorders. Our research and preliminary results suggest that one of these pathways may be the Rac1 signaling pathway and its various activators. **The aim of the project is therefore to study the impact of Rac1 and its various activators on the development of axons in the brain and the neuropsychiatric symptoms in Tuberous Sclerosis Complex.** The research project will be carried out using zebrafish as a model organism, which is a small fish with an external development and a transparent body. Zebrafish is increasingly used as a model organism for studying neurological and neuropsychiatric disorders, mainly because most of them arise during very early brain development, which is difficult to study in placentals. In zebrafish, live imaging of the brain development is possible at a very early stage and in high resolution. Zebrafish is a vertebrate, so it is closely related to human and a large part of mechanisms of the development of connections in the brain can be the same. Other advantages of zebrafish are small size and a large number of eggs. Also, the availability of state-of-the-art tools for genetic manipulation and well characterized behaviors, together with advanced tests for learning and memory is beneficial. Zebrafish also creates shoals, exhibiting social behavior that can be studied in the context of autism spectrum disorder. Given the possibility of integrating research on multiple levels, zebrafish seems convenient to be a model organism to study the brain diseases.

Neuropsychiatric disorders affect more and more people around the world and are still incurable, so is Tuberous Sclerosis Complex. Unraveling the molecular mechanisms underlying developmental impairments that lead to autism spectrum disorder or intellectual disability has a high impact for Tuberous Sclerosis Complex and other patients suffering from neuropsychiatric diseases as there likely is overlap of common mechanisms underlying these disorders. Explaining the intricate interplay of signaling pathways during brain development in Tuberous Sclerosis Complex provides opportunities for finding therapies or improving the quality of life for patients. The project will contribute new insights into signaling pathways that orchestrate the brain connectivity development in Tuberous Sclerosis Complex and may bring novel therapeutic strategies for neuropsychiatric disorders. Moreover, zebrafish will be verified as a model organism for some aspects of human pathology such as autism spectrum disorder or intellectual disability, which will allow future drug screenings.