The ability of the human organism to move or breathe is possible due to the coordination of the nervous and muscular systems. Signals from the brain are transmitted through the motoneurons in the spinal cord to the skeletal muscles, giving the impulses for contraction. Such transmission of signals from motoneurons to the skeletal muscles occurs at the specialized type of the synapse, called neuromuscular junction (NMJ). At these cellular junctions, a neurotransmitter (acetylcholine) is released from the synaptic vesicles in the axon terminal, travels through the synaptic cleft, and finally binds to the acetylcholine receptors (AChRs) in the membrane of skeletal muscle. Acetylcholine receptors are clustered in high density on muscle fiber surfaces. The clustering of receptors involves many different scaffolding proteins that ensure proper organization of the postsynaptic specialization, which is anchored to the actin cytoskeleton. Actin filaments at the NMJ undergo dynamic changes in response to environmental stimuli. One of the proteins involved in actin remodeling is cyclase-associated protein 2 (Cap2).

Cap2 protein was identified as an important protein for heart development and function, as lack of Cap2 leads to severe symptoms in both mice models and human patients. In skeletal muscles, the deletion of Cap2 is responsible for muscle weakness and the presence of nemaline rods, inappropriate protein aggregates that affect muscle function. Our studies showed that mice that do not have Cap2 in all tissues of the body (systemic knockouts; Cap2-KO) had ring fibers in fast-twitching muscles. Ring fibers have disorganized myofibrils with ring-like orientation in muscle fiber cross-section, leading to problems with muscle contraction. Interestingly, ring fibers are present in human myopathies with unknown etiology. Altogether, Cap2 has important functions in skeletal muscles. but its role in NMJ is still unknown.

Our preliminary, unpublished data suggests that the lack of Cap2 protein in mice causes abnormalities in the morphology of motoneuronal axons, fragmentation of the AChR clusters, and abnormal size of the junctions. To investigate the function of Cap2 in a particular cell type, I generated mouse lines with Cap2 deletion specifically in either motoneurons or skeletal muscles.

In this project, I will perform a detailed characterization of generated mutants in the context of the morphology of the NMJ. Moreover, I will use several microscopic approaches to analyze the ultrastructure of the neuromuscular synapses. I will also perform an analysis of the functionality of those synapses by locomotor tests on animals, muscle force measurements, and electrophysiological recordings. The results which will be obtained during this project will help to understand the role of Cap2 protein in the neuromuscular junction and will be a starting point for the potential new therapies for neuromuscular disorders.