Our brain controls the mind and the body, registers and integrates signals from the environment and allows for our response to the stimuli. The brain needs to communicate with peripheral parts of the body and coordinate our movements. Brain nerve impulses are transmitted along the spinal cord and then through motor neurons to reach the muscle surface. The place of contact between the motor neurons and muscle fibers is called 'neuromuscular junction' (NMJ) and represents the place where the communication between these two cell types takes place. NMJ is a chemical synapse and the acetylcholine (ACh) neurotransmitter represents the message released by the nerve terminal, which is detected by the muscle. This triggers muscle contraction.

Acetylcholine receptors (AChRs) are in charge of detecting acetylcholine released from the nerve terminal. AChRs, together with AChR-associated proteins, form the post-synaptic machinery. Correct localization and organization of AChR on the muscle surface enables proper detection and processing of the message mediated by the neurotransmitter. Overall 1,000 proteins are estimated as associated with the postsynaptic machinery and many are still poorly characterized. The failure of the neuromuscular system leads to serious diseases known as neuromuscular disorders. There are many known such diseases and a half of them of unknown etiology.

The actin cytoskeleton is complex structure composed of filaments of proteins present in the cytoplasm of the cells and its primary function is to sustain cell morphology. However, the actin cytoskeleton has many functions other than a static scaffold. In fact, dynamics of cytoskeleton underlie many cellular processes such as cell migration, endocytosis, and vesicular transport. Importantly, in muscle tissues, cytoskeleton sustains muscle contraction. Actin cytoskeleton forms structure underneath postsynaptic-machinery and its continuous remodeling is known to regulate the organization of NMJ. The study of factors promoting such dynamics could expand our scientific knowledge and shed light on processes, which are still poorly understood.

I found that Cap2 protein, which regulates actin cytoskeleton and which has been linked to human myopathies, localizes to the NMJ. Also, when Cap2 is depleted the NMJ morphology is severely compromised. Thus, in the light of these observations, my project will provide a full characterization of the NMJ abnormalities in the early development and identify at which developmental stage these alterations start to appear. These results could clarify if Cap2 protein is involved either in early organization or maintenance processes of NMJ structure. Because the NMJ is a complex structure to which both pre-synaptic terminal and post-synaptic endplate participate, I will assess the contribution of post-synaptic machinery to the observed NMJ alterations. Moreover, in order to elucidate the potential mechanisms of Cap2 in the NMJ’s organization, I will explore the actin-remodeling properties of Cap2. Thus, I will evaluate if depletion of Cap2 has an impact on filaments of cytoskeleton linked to post-synaptic machinery and also if Cap2 loss of function destabilizes the AChRs to the surface of muscles. Since Cap2 has never been studied in the context of NMJ, I believe that my project will have important contribution to our understanding of synapses and of congenital myopathies.