Neuromuscular junctions (NMJs) are synapses formed by the contact of motoneurons and muscle fibers enabling nerve impulses to travel to skeletal muscles. This nerve impulse transmission accounts for locomotion and breathing. NMJs consist of presynaptic part, which is the motoneuron terminal and postsynaptic part on the surface of the muscle fiber. Neuromuscular disorders are often manifested by disrupted NMJ topology and dysfunction leading to muscle weakening, problems with locomotion, and breathing which in severe cases lead to death in young age. Mechanisms orchestrating function of the postsynaptic compartment are still poorly understood.

The goal of this project is to study the function of Angiomotin (Amot) which was identified by us as a novel component of NMJs. Up-to-date research focused at Amot function in formation and physiology of blood vessels. To study the role of Amot at NMJs we will use mice models with deleted gene encoding Amot. This type of animal models are convenient tools for functional analysis allowing to analyze changes that occur without expression of a single protein. Our preliminary results show that lack of Amot expression results in aberrations in NMJ organization. Moreover, we showed that Amot localizes to presynaptic and postsynaptic part of NMJs.

To study Amot function in the organization of NMJs we will use models of enhanced NMJ remodeling i.e. postnatal development and denervation (cutting of the nerve innervating muscle). We will also perform analysis of NMJ morphology in mice with specific Amot deletion in skeletal muscle and in motoneurons. This will allow to determine the function of Amot at presynaptic and postsynaptic components of NMJ. We will also perform tests of muscle strength and locomotor activity of mice to study whether lack of Amot expression impacts animal behavior. In our experiments we will use advanced molecular and biochemical techniques to identify Amot-interacting proteins at postsynaptic part of NMJs. Subsequently, we will analyze the function of Amot molecular partners in formation and organization of postsynaptic components, which will allow to dissect the molecular mechanism through which Amot exerts its effects at NMJs.

We hope that this innovative project will deliver new data concerning proteins crucial for NMJ function and will substantially contribute to the neuromuscular research. It is possible that among identified proteins will be new possible therapeutic targets for treatments of neuromuscular disorders. Progress in that field may help to relieve the patients and their families, improve diagnostic methods and open new vistas in NMJ research.