Breathing and our coordinated movements are controlled by the central nervous system (CNS), which receives the information from environment. Impulses generated in the brain are transmitted along the spinal cord and are delivered through the motor neurons to the skeletal muscles in the periphery. Axons of motor neurons form specialized connections with muscle fibers called neuromuscular junctions (NMJs). These are chemical synapses that allow for the transmission of signal from the nerve to the postsynaptic machinery on the muscle fibers through the secretion of neurotransmitter acetylcholine (ACh). Neuron released ACh diffuses through the synaptic cleft and binds to acetylcholine receptors (AChRs), the major components of the postsynaptic machinery on the surface of muscle fibers. ACh binding to AChRs triggers a cascade of events that initiates contraction of the muscle fibre.

The postsynaptic machinery on the surface of muscle fibers is a complex system of proteins (and lipids in the membrane) allowing for efficient detection and processing of information from the nervous system. It is estimated that the postsynaptic machinery constitutes over 1000 proteins, many of which are still uncharacterized. Malfunction of the muscle postsynaptic machinery, and in a consequence of the entire neuromuscular system, can lead to severe neuromuscular disorders. It is estimated that out of 300 such diseases, 50% are of unknown etiology. Therefore, better understanding of the organization and function neuromuscular synapses is of primary importance in biomedical research.

Our previous research on the dystrophin-associated glycoprotein complex (DGC), a multi-protein complex that plays an important role in the stabilization of the postsynaptic machinery, led to the discovery of a novel protein called SH3BP2. SH3BP2 is a poorly characterized protein which, so far, has not been implicated in synapse organization or has ever been studied in skeletal muscles. Our preliminary experiments demonstrated that SH3BP2 is concentrated at the NMJ postsynaptic machinery and plays a crucial role in the organization of the postsynaptic machinery in cultured muscle cells. These results strongly suggest that SH3BP2 is a novel NMJ protein with a important function in the organization of NMJs.

We will perform a series of experiments that will unravel SH3BP2 expression and NMJ localization at various stages of NMJ development and also in response to nerve injury that triggers synaptic plasticity. In our experiments, we will use state-of-the-art genetic and biochemical techniques that will identify the function and the underlying mechanism of SH3BP2 at the neuromuscular synapses in vivo. Proposed research will expand our knowledge and have potential to contribute in the future to the development of novel therapeutical strategies to combat neuromuscular diseases.

The dystrophin-associated glycoprotein complex (DGC) is a transmembrane scaffold for organizing signaling molecules and stabilizing membrane and peripheral proteins at specific locations at the cell cortex. The DGC plays an important role in the formation and maintenance of synapses in the central and peripheral nervous systems. α-Dystrobrevin-1 (αDB1) is a cytoplasmic component of the DGC that plays a crucial role in the organization of the postsynaptic machinery at the neuromuscular junction (NMJ). In the absence of αDB1, substantial alterations in the postsynaptic membrane are observed, including instability of postsynaptic acetylcholine receptors (AChRs) and abnormal AChR distribution. Recent studies demonstrated that some functions of αDB1 at the synapse depend on αDB1 phosphorylation. Although synaptic defects caused by the absence of αDB1 are well-documented, the molecular mechanism by which αDB1 orchestrates the organization of postsynaptic machinery is unknown.

We will perform comprehensive studies that seek to understand the molecular mechanism of αDB1 function at the mouse NMJ. Our hypothesis is that αDB1 performs its role at the NMJ by recruiting effector proteins that may regulate individual processes. Specifically, the phosphorylation of tyrosines at the C-terminal portion may recruit phospho-specific binding partners that are responsible for some of the functions of αDB1. Our previous work led to identification of several proteins recruited to the tyrosine Y713 of αDB1. Subsequently we have shown that several of newly identified proteins play important role in organization of NMJ. Now we will focus our experiments on identification of binding partners recruited to other two tyrosines (Y705 and Y730) and characterization of their potential involvement in regulation of the muscle postsynaptic machinery. Additionally, we will study potential involvement of αDB1 and its interacting proteins in pathogenesis of muscular dystrophy.