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 specialised 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 uncharacterised. 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 organisation 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 stabilisation of the postsynaptic machinery, led to the discovery of a novel protein called SH3BP2. SH3BP2 is a poorly characterised protein which, so far, has not been implicated in synapse organisation 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 organisation 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 organisation of NMJs.

We will perform a series of experiments that will unravel SH3BP2 expression and NMJ localisation 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.