PROJECT TITLE: *Dystrophin- and utrophin-dependent signal transduction in transcriptome regulation and crosstalk between adjacent and distant cell structures, cells and tissues, and its role in Duchenne muscular dystrophy pathogenesis.*

Duchenne muscular dystrophy (DMD) is a genetic disease leading to progressive musculature disability in male patients, and is caused by lack of functional dystrophin proteins. With disease progression, the extent of muscle fiber loss is so vast that DMD patients are forced to use a wheelchair and respiratory system aid to help diaphragm sustain breathing. Up until now, DMD is incurable and leads to early premature death due to respiratory or cardiac failure. DMD patients also suffer from cognitive deficits and psychiatric symptoms that are linked to absence of distinct dystrophin protein isoforms. For years, scientists focused mostly on structural properties of dystrophin and its close relative, utrophin. The latter can compensate for the loss of dystrophin to some extent, once delivered to muscles in high quantity. However, apart from their structural roles in myofibers, more recent data indicate that dystrophin and utrophin serve as important components in determining cell adaptability to the changing environmental conditions and communication between various cell types.

This project is specifically aimed to: (1) identify the roles of various dystrophin and utrophin proteins in cellular signal transmission, proliferation, growth, homeostasis maintenance and survival, (2) dissect the regulatory mode of dystrophin and utrophin expression with particular focus on their putative feedback looping, as they often show time- and space-restricted localization in cells and tissues, (3) analyze dystrophin/utrophin involvement in facilitating signaling crosstalk between various cell structures in muscle fibers and other tissues such as heart and the brain.

The experimental outline of the project is grounded primarily on a well-established model of muscle regeneration in distinct mouse models of DMD. Muscle regeneration involves several sequential steps that encompass signal transmission and crosstalk between various cell structures and cell types, and enables to test the outcome of dystrophic process on other tissues. Despite primary focus of the project on various stages of formation and maintenance of muscle as well as heart and brain cells, the project has also a more systemic application, including: (1) dissecting the signaling outcome of particular dystrophin/utrophin proteins, (2) expanding current knowledge about dystrophin/utrophin functions, (3) evaluating the therapeutic potential of each isoform in restoring the proper cell proliferation, growth, differentiation and survival, (4) distinguishing primary from secondary pathological processes during the DMD progression, (5) expanding therapeutic repertoire against DMD, that could include adjuvant signaling-based approaches. In all, the project is intended to broaden our understanding of various dystrophin and utrophin isoform functions and bring us closer to formulate an ultimate, holistic therapeutic approach for DMD.