PROJECT TITLE: *The roles and therapeutic potential of distinct dystrophin and utrophin isoforms in the central and peripheral nervous system*

Duchenne muscular dystrophy (DMD) is a progressive and devastating disease caused by mutations in the dystrophin gene and affects 1 in 5000 boys. While the female carriers of the mutation are usually protected, some forms of muscle involvement is apparent in up to 20% of cases, with the full-blown muscular dystrophy observed in 1 in 50,000,000 girls. The disease primarily affects the patient's skeletal musculature, with the first symptoms usually observed at the age of 3-5. In their teens, the affected individuals are forced to use a wheelchair due to significant loss of muscle tissue and at that time also cardiac involvement is observed. As the disease progresses, DMD patients have to use ventilation aids to sustain breathing and although such treatment prolongs their life, the disease inevitability leads to premature death usually in the thirties due to respiratory or cardiac failure.

Besides the muscle phenotype, DMD patients show a number of alterations in other tissues that might be considered as either primary or secondary causes of the disease. With increased life expectancy, problems in other tissues directly affected by loss of dystrophin will become inevitably more apparent. Particularly, DMD patients were shown to have smaller total brain volume and grey matter volume as well as alterations in the white matter microstructure and reduced cerebral blood flow. Neuropsychiatric phenotype, that includes intellectual disability, autism, attention deficit disorder, obsessive-compulsive disorder, anxiety and depression can be observed in some DMD cases and female carriers have also been reported to have cognitive disabilities. Moreover, abnormalities in the function of the peripheral nervous system have been observed, with striking demyelination of large-caliber axons in humans and mice devoid of some forms of dystrophin.

In contrast to the relatively well-defined roles of the full-length dystrophin that is predominantly generated in the muscle tissue, the roles of dystrophin in the nervous system are still either elusive or unknown. Specific aims of the project include deciphering the roles of specific forms of dystrophin and utrophin in the central and peripheral nervous system. Utrophin has been previously shown to partially compensate for the dystrophin absence in the musculature, especially when present in high quantities. In the course of the project, we will use both cell lines and mice to evaluate the amounts of dystrophins and utrophins as well as to assess the roles of various forms of these proteins in distinct cell types of the central and peripheral system. Furthermore, we will test three distinct therapeutic methods to alleviate the aberrations in cells of the central and peripheral nervous system, based on delivery of: 1) specific forms of dystrophin and utrophin, 2) short RNA sequences to increase the amounts of utrophin and 3) designed short micro-dystrophins/micro-utrophins. The expected result of the project is the selection of an appropriate therapeutic approach aimed at relieving symptoms in the central and peripheral nervous system of DMD patients.