

**Title of Program:** Experimental Treatment/Therapy for Limb-Girdle Muscular Dystrophy

**Dept/Center/Lab:** McColl-Lockwood Laboratory for Muscular Dystrophy Research

**Principal Mentor:** Charles H. Vannoy, PhD – Senior Postdoctoral Research Scientist

**Summary Description:** Our laboratory carries out biochemical, molecular, and cellular biological research designed to improve our understanding of muscular dystrophy (MD) and develop therapies for the disease. MDs are a diverse group of inherited disorders characterized by progressive muscle weakness and wasting, which are caused by mutations in various genes. More specifically, mutations in the fukutin-related protein (FKRP) cause one of the most common forms of MD, which includes Limb Girdle Muscular Dystrophy 2I (LGMD2I) along with some other rare, and more severe form of MDs (e.g., congenital MD, Walker-Warburg syndrome, and muscle-eye-brain disease). The function of FKRP is not fully understood, but mutations of the gene are associated with distinctive defects in glycosylation of  $\alpha$ -dystroglycan ( $\alpha$ -DG), shared by mutations in a group of genes of confirmed or putative glycosyltransferases. MDs with the secondary defect in functional  $\alpha$ -DG are termed as dystroglycanopathies of which FKRP mutations are the most common. Currently, there is a lack of effective treatment options available for the FKRP-related MDs.

In the last couple of decades, adeno-associated virus (AAV) mediated gene therapy has been extensively investigated in different disease models and has emerged as one of the most promising approaches as a delivery vector, owing to its high tropism for skeletal and cardiac muscles and non-pathogenicity in humans. Several AAV serotypes have been tested in preclinical studies with long-term success rates in targeting muscles through a systemic approach. New progress in clinical trials for sarcoglycan deficient LGMD2D, LGMD2C, and other diseases has offered realistic hope for AAV vector-mediated gene therapy to achieve therapeutic results or even cure of diseases related to MD in the clinical setting.

For our studies, we investigate the use of AAV mediated gene delivery systems to achieve therapeutic effects in transgenic mice engineered to display phenotypic abnormalities associated with MD. Knowledge gained from this study will improve healthcare recommendations for people with dystroglycanopathies, and provide a baseline for further study, including potential treatment options.

**Expectations and Role of Student:** The student will be conducting cutting edge research alongside one of our PhD researchers and will require previous experience/knowledge to successfully configure, operate, and maintain laboratory instruments and equipment, monitor experiments, make observations, and calculate and record results. A preferred candidate should have an overall good perception of tissue morphology supported by a working knowledge and hands on experience in histological techniques and optimization of immunohistochemical methods, proficiency in light/confocal microscopy with an understanding of microscopy principles and techniques, and familiarity with image analysis. Within the time scope of the summer program, the student will be required to present oral and written summaries of research results (required to present their overall findings at a student research day during the last week of the program) and, where possible, obtain publishable results.