Eric Richard Pozsgai
PhD Candidate

“Adeno-Associated Virus Mediated β-Sarcoglycan Gene Replacement Therapy for the Treatment of Limb Girdle Muscular Dystrophy Type 2E”

September 19, 2016
Biomedical Research Tower Room 105
2:00 pm
VITA

01/01/1988 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Born – South Bend, IN

2010 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.S. Biochemistry, Indiana University Bloomington

COMMITTEE MEMBERS

Dr. Louise Rodino-Klapac

Dr. Jerry Mendell

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ABSTRACT

One major class of muscular dystrophy is limb-girdle muscular dystrophy (LGMD), encompassing many different subtypes. LGMD2E is one of the most severe forms of LGMD, resulting from recessive mutations in the β-sarcoglycan (SGCB) gene, causing loss of functional protein. SGCB is a structural protein component of the dystrophin-associated protein complex (DAPC), which as a whole provides structural and mechanical stability to the sarcolemma. Due to the loss of protein, a devastating disorder ensues with widespread progressive muscle wasting, leading to loss of function. Disease progression is directly correlated with age, where the most severe cases have symptom onset in early childhood and many patients are rendered non-ambulant by their teens. In addition to skeletal muscle weakness, significant respiratory failure and fatal cardiomyopathy are common features in more severe LGMD2E patients. To date, no effective therapy exists to treat this debilitating disease. Thus, with an urgent need for a viable treatment option for LGMD2E patients, this work attempted to develop the first viral-mediated approach to restore wild-type SGCB.

Providing a relevant model to test therapeutic efficacy, the Sgcb-null mouse recapitulates the clinical phenotype and shares many of the pathologic features of LGMD2E patient biopsies including myofiber necrosis, central nucleation, inflammation, and fibrosis. We have engineered a viral mediated gene replacement therapy using adeno-associated virus (AAV) carrying a codon optimized human SGCB gene (hSGCB) driven by one of two different muscle specific promoters. We first established proof-of-principle efficacy of scAAVrh.74.tMCK.hSGCB by intramuscular (IM) injection and isolated-limb perfusion (ILP) in young and aged mice, which resulted in long-term widespread transgene expression accompanied by histological and function benefits. Notably, we noted a considerable reduction in fibrotic tissue, a significant component of the disease and a potential major obstacle of gene transfer. After switching promoters to the MHCK7 promoter which provides robust expression in cardiac tissue, we then
demonstrated efficacy of systemic delivery of scAAVrh.74.MHCK7.hSGCB in treating skeletal and cardiac muscle deficits in sgcβ-/- mice to provide a potential rationale for meaningful results in a clinical trial. This led to nearly 100% transgene expression in numerous muscles throughout the limbs, torso, and the heart, which was again accompanied by improvements in muscle histopathology and function, as well as increased overall activity. Importantly, a formal GLP toxicology study of AAV.hSGCB gene transfer in wild-type mice showed no adverse effects. In this well-defined model of LGMD2E, we have established a clinically relevant path for AAV mediated SGCB gene replacement therapy which has great promise for LGMD2E patients.

After demonstrating the importance of functional deficits in dystrophic muscle to serve as outcome measures for functional recovery from SGCB gene therapy, we applied these concepts to the investigations of several other forms of LGMD, Types 2B and 2L, involving dysferlin (DYSF) and anoctamin5 (ANO5), respectively. In these studies, we optimized and validated muscle fiber isolation with a laser induced membrane repair assay to aid in thoroughly characterizing these diseases and test therapeutic interventions like viral-mediated gene transfer. Using this technique, we are able to directly measure a functional parameter of both DYSF and ANO5 and quantify the membrane repair ability in different physiological settings. Taken together, we report here an experimental method that can be a powerful tool for pre-clinical studies of muscular dystrophy, and the impact these pre-clinical efficacy studies like ours with SGCB gene replacement therapy can have on translating a therapy forward to patients.
SELECTED ABSTRACTS & PRESENTATION


(2016) Systemic β-Sarcoglycan Gene Therapy for Treatment of Cardiac and Skeletal Muscle Deficits in LGMD2E. The OSU Wexner Medical Center Trainee Research Day, Columbus, OH


(2015) β-Sarcoglycan Gene Transfer Provides Path to Reverse Muscle Fibrosis. The Ohio State University Wexner Medical Center Trainee Research Day, Columbus, OH


RECENT PUBLICATIONS


AWARDS AND HONORS


Travel Award for Outstanding Poster Presentation, The Ohio State University Wexner Medical Center Trainee Research Day, Columbus, OH (2015)


Abstract selected by the Science Committee as a significant advancement based on animal research. The American Academy of Neurology 66th Annual Meeting, Philadelphia, PA (2014)


OSU Muscle Group/NIH T32 Graduate Student Training Fellowship from NINDS (T32 NS077984) “Training in Neuromuscular Diseases”, (2014)

Travel Award, American Society of Gene & Cell Therapy 16th Annual Meeting, Salt Lake City, UT, May 2013
FUTURE PLANS

After gaining experience and understanding in translation research with the ultimate goal of a clinical trial, I am interested in a position bridging pre-clinical basic research studies with clinical trials. I will be pursuing either a post-doctoral position in academia or likely a position in either private sector industrial research or government working with translation studies.

Ultimately, I would like to obtain a position in a career that combines the various disciplines that I have become to understand or will pursue to understand. An ideal career would involve organizing and connecting multiple facets of biomedical research including the pre-clinical investigations, clinical trials, regulatory oversights, and business administration. I would like to combine conceptual understanding of disease biology with interpersonal communication, functional organization, and business operations all in the process of therapeutic development.