



Electrical impedance myography goes global: collaborative efforts to advance a promising preclinical and clinical tool for the development of future DMD therapies

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Introduction

Improved tools to better evaluate muscle condition and response to therapy in Duchenne muscular dystrophy (DMD) are needed. A tool with analogous application in preclinical and clinical settings would be of particular value. In an example of cross-collaboration, 3 universities, a medical device company, and the patient-founded nonprofit Charley's Fund identified the opportunity and developed a plan to explore the potential of one such tool — electrical impedance myography (EIM) — as a translatable preclinical-to-clinical tool.

Background:

- In 2004 Charley's Fund was founded to accelerate R&D for DMD with particular focus on developing research tools and improved processes to better enable DMD drug development
- In 2011, Charley's Fund began supporting the development and validation of EIM as a new, noninvasive quantitative clinical trial outcome for Duchenne
- In 2016, Charley's Fund launched 'Of Mice and Measures' — a data-driven collaborative initiative to improve preclinical best practices and methods in DMD
- In 2019, in collaboration with these teams, Charley's Fund identified an opportunity to bring the two projects together to explore the unique opportunity afforded by EIM to evaluate therapeutics along the preclinical-clinical continuum

Electrical Impedance Myography:

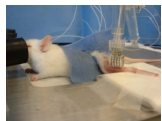
- A sensitive, rapid, painless, low-cost method to assess muscle properties
- Studied in boys with DMD and shown to correlate to:
 - functional measures
 - change over time
 - response to corticosteroid initiation
- Can also be used effectively in preclinical models
- To date, application in mice has only been pursued by a single lab and in a single model of DMD
- Validation by other labs, application in other models, and an assessment of scalability are necessary before promoting broader adoption for preclinical use

Of Mice and Measures (OMAM):

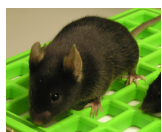
- A collaboration among academic, industry, and nonprofit partners in the DMD research community
- Charley's Fund coordinates and works with a Scientific Organizing Committee to identify opportunities, develop strategies, convene contributors, and undertake action steps
- In October 2017 held first workshop in Paris
- Initiated several projects including the natural history study described below



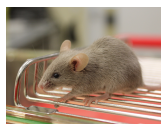
EIM takes approximately 20 minutes to complete in a boy with DMD



Like in humans, EIM can be performed over time in mice



The commonly used classic model: C57BL/10ScSn-Dmd^{mdx}/J (B10/mdx)



The newer model: D2.B10-Dmd^{mdx}/J (D2/mdx)

Objectives

- 1) To help identify and advance opportunities for EIM in preclinical DMD drug studies
- 2) To connect to and inform human clinical application
- 3) To identify whether EIM has utility as a uniquely translatable measure of therapeutic efficacy

Sub-objectives include:

- Troubleshoot device and study design prior to launch of natural history study
- Leverage mouse data to help us better understand EIM (with eye towards clinical use)
- Introduce EIM more broadly to DMD preclinical world in a high-profile international longitudinal natural history collaboration

Preliminary Results

- Convened multiple international teams for 2-day EIM training session
- Identified and executed preclinical EIM device improvements
- Generated multiple preclinical EIM devices for purposes of validation through expanded use
- In process of developing video training for broader use by the field
- Designed and funded a large natural history study, including longitudinal assessments of diverse DMD mouse models over 52 wks
- Two internationally renowned preclinically expert sites will launch study Q4 2019

Conclusion

- Patient-founded research organizations are uniquely positioned to identify research synergies to benefit their fields
- Connecting research teams from preclinical and clinical stages enables translation
- Preclinical EIM has now graduated from a single lab in the US to multiple labs around the world
- We will be launching a well-powered 52 week longitudinal replicated study in DMD mutant strains, enabling the identification of key pathological strain and disease-related differences so as to improve future preclinical drug development



Please join our efforts! For more information and citations about EIM, OMAM, and how to get involved, contact laura@charleysfund.org or visit charleysfund.org/wms2019

