Disruption of the microtubule network as a therapeutic intervention in the muscular dystrophies

Summary

Across several muscular myopathies, such as Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, and dysferlinopathies, intercellular signaling cascades such as reactive oxygen signaling (ROS) and calcium (Ca^{2+}) are enhanced and contribute to the onset and pathogenic progression of the myopathy. The discovery of the involvement of the microtubule network in the activation of these pathways has led to the use of cytoskeletal modulating compounds to effectively reduce contraction-induced damage in muscle myopathies. UMB researchers have shown a mechano-chemo transduction pathway that links mechanical stress to NADPH oxidase 2 ROS generation and subsequent Ca^{2+} signaling. This microtubule-dependent mechano-activation of ROS production (X-ROS) is a novel therapeutic target for the treatment of muscular dystrophies. Proof of concept data show that *in vivo* treatments that disrupt the microtubule, such as colchicine and apocynin, reduce contraction-induced injury in DMD mouse models.

Key Investigator
Christopher Ward
Ramzi Khairallah

Field
Neuromuscular disorders

Technology
Method of treatment for muscular dystrophies

Advantages
FDA-approved drugs may be repurposed in novel indications

Indications to be pursued are orphan diseases with high unmet clinical need

Status
Available for licensing
Available for sponsored research

Patent Status
US 9,511,117
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UMB Docket Reference
CW-2012-040

External Reference
Prosser et al. (2011) Science. 333(6048):1440-5.

Market

Current treatment options for muscular dystrophies either ameliorate symptoms but do not alter the course of the disease itself, such as the glucocorticoid Emflaza, or only work on individuals with a confirmed specific mutation, which represent a small percentage of afflicted patients, such as Exondys 51. The cost of Emflaza starts at $35,000/year, costing more each year as the patient's weight increases. The cost of Exondys 51 is $300,000 per year. There are many companies actively developing treatments for muscular dystrophy and related disorders, including Sarepta, Astellas, Catabasis, Summit, and Solid Bio, among others, with approaches focusing on exon skipping and gene therapy. This invention offers a novel approach and allows for either the repurposing of compounds for which clinical safety and formulation data are available, or the creation of new compositions that act on this novel X-ROS target.

Technology

In vivo inhibition of X-ROS decreases contraction-induced injury in the mdx mouse model of DMD. This has been assayed following treatment with vehicle, colchicine, or apocynin in mdx and control wild-type mice. Treatment with colchicine or apocynin resulted in a significant protection from force loss, briging this measure to an extent similar to the isometric force seen in control mice. This suggests X-ROS targeting confers protection from contraction induced injury (i.e. force loss) that often occurs in muscular myopathies. Together, this supports the role of X-ROS in the pathogenic progression of DMD and offers novel therapeutic targets for intervention.

Technology Status

In vitro and *in vivo* studies show improved muscle function utilizing cytoskeletal antagonizing drugs, colchicine and latrunculin A. Additional validation studies are required as well as formulation of drug treatment.

Contact: Melissa Blackman
mblackman@umaryland.edu
410-706-6277

University of Maryland, Baltimore
620 W. Lexington St., 4th Floor
Baltimore, MD 21201