Becker's Muscular Dystrophy- Raising Awareness and Highlighting Developments

Physical Medicine and Rehabilitation

Lynea Kaethler M.S., Scott Sekikawa B.S., Raymundo Billena B.S., Luke Waymire A.S.

Neuromuscular Research Lab

UC DAVIS HEALTH

Background

Becker's Muscular Dystrophy (BMD) is a genetic disease that causes progressive weakness and wasting of skeletal and cardiac muscles. Due to the absence or truncation of the protein dystrophin, muscles become structurally impaired as evidenced by muscular myofiber membrane stress, hypercontraction, and degeneration with continued muscle use. While not as aggressive and life-threatening as its cousin, Duchenne's Muscular Dystrophy (DMD), BMD impacts both the quality and length of life.

Genetics

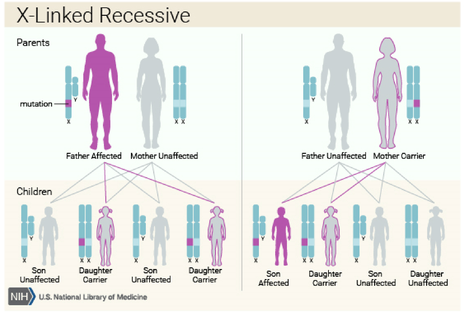

Figure 1. Image depicting how the gene is passed down from parent to child.

BMD is an X-linked inherited condition, primarily impacting males. It is caused by a mutation in the Xp21.2 chromosome, the *DMD gene*, which affects the production of the protein dystrophin. Becker muscular dystrophy is caused by an 'in-frame' mutation in the *DMD gene*, most commonly an exon deletion. Encoding of the protein continues past the mutated piece, however the protein will be abnormal and doesn't function the same as normal dystrophin.

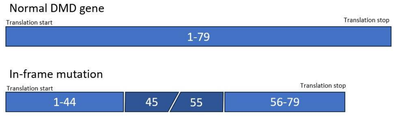

Figure 2. Top row shows a typical *DMD gene*, bottom row shows an in frame mutation where the translation continues until the natural stop point however the protein is shorter and only partially functional

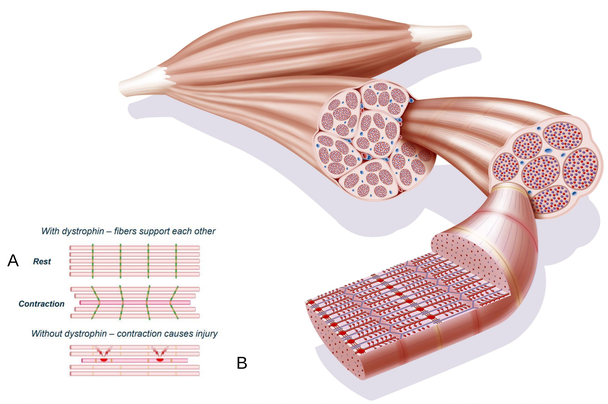

Figure 3. A shows how dystrophin (green) supports muscle fibers during contraction. B shows how the fibers in the muscle are organized and supported by dystrophin

Disease Mechanism and Progression

Dystrophin is integral to providing mechanical reinforcement to the cell membrane. In its truncated or defective form, it is unable to synchronize with the glycoprotein complex that connects the cytoskeleton to the extracellular matrix. As a result, this disruption leads to the gradual deterioration of the cell membrane and the degeneration of muscle fibers.

BMD is a more rare form of dystrophy than DMD, but less severe. Like DMD patients, BMD patients can begin showing symptoms in early childhood. This is because fast myofibers (type II) are more susceptible to early myofiber degeneration. Therefore, diagnoses on dystrophies are very common amongst young boys. BMD patients, however, sometimes may not feel symptoms until their 50s.

In addition to degeneration of skeletal muscle, people with BMD are at an increased risk for:
- Cardiomyopathy
- Decreased bone density
- Cognitive impairment
- Anxiety
- Contractures (decreased range of motion in joints from shortening muscle)

Current treatments

Currently, there are no cures for BMD, but there are a number of treatment options. Some of the main forms are:
- Corticosteroids
- Physical therapy
- Clinical Trials

Other therapies include:
- Mobility aids
- Medications for cardiomyopathy
- Tracheostomy and assisted ventilation

The UC Davis Health's Neuromuscular Research Lab (NMRL) is a site for Edgewise Therapeutic's clinical drug trial that explores the safety and efficacy of an investigational drug, EDG-5506, as it binds to fast muscle myosin. EDG-5506, developed by Edgewise Therapeutics, specifically targets skeletal muscle by subtly altering the activity in myosin, the contractile protein in muscles, protecting them from the hypercontractile force to prevent injury to the fibres (fig 5). Phase 1 trial results showed a reduction in inflammatory biomarkers of muscle damage and stabilized performance on physical function tests (fig 4). At the NMRL we enroll subjects, complete physical function tests, collect specimen samples, and conduct other safety monitoring activities.

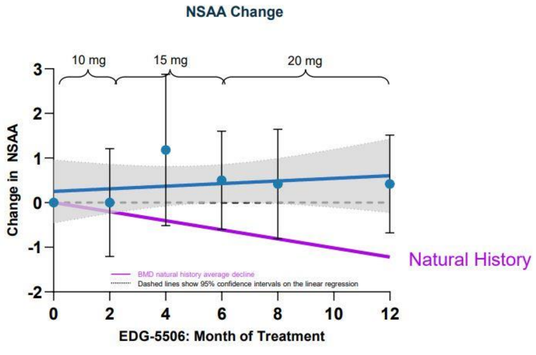

Figure 4. Shows the stabilization of physical function based on the North Start Ambulatory Assessment (NSAA). Image taken from Posters and Publications | Edgewise (edgewisetx.com)

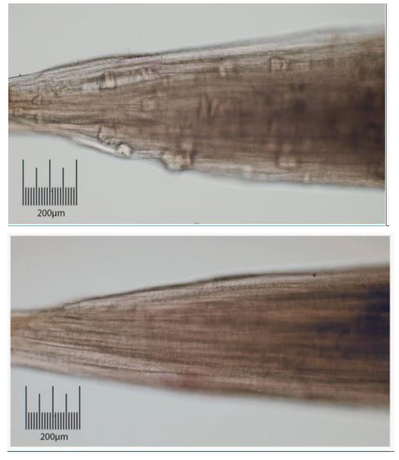

Figure 5. Top image shows muscle untreated with EDG-5506 during contraction and damage in muscle fibers due to contractile stress. Bottom image shows contracted muscle treated with EDG-5506, and no evidence of muscle damage. Image taken from Posters and Publications | Edgewise (edgewisetx.com)

Acknowledgements

Thank you to the NMRL for their work in the Edgewise EDG-5506 clinical drug trials. And to Edgewise therapeutics for their contribution to advancing the understanding of disease progression and potential treatments for BMD.

Edgewise THERAPEUTICS