Manipulating the Dark Side of Muscle Adaptation for Therapeutic Gain

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Edgewise Therapeutics

May 19, 2022

Forward-Looking Statements

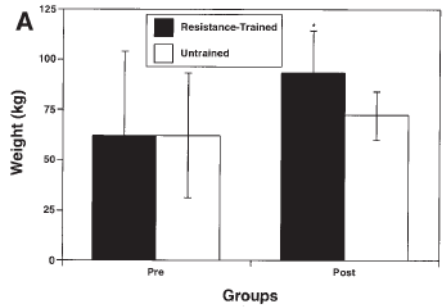
This presentation contains forward-looking statements that involve substantial risks and uncertainties of Edgewise Therapeutics, Inc. ("Edgewise" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding, Edgewise's drug discovery platform; Edgewise's product candidates and programs, including EDG-5506; the expected milestones and timing of such milestones for EDG-5506 including the expected timing of reporting of data for EDG-5506 and clinical trials; statements regarding the market opportunity for Edgewise's product candidates; statements regarding Edgewise's pipeline of product candidates and programs; and statements regarding Edgewise's financial position including its liquidity. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," "may," "plan," "potentially" "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: negative impacts of the COVID-19 pandemic on Edgewise's operations, including clinical trials; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early clinical stage company; Edgewise's ability to develop, initiate or complete preclinical studies and clinical trials for, obtain approvals for and commercialize any of its product candidates; changes in Edgewise's plans to develop and commercialize EDG-5506 or any other product candidates; the potential for clinical trials of EDG-5506 or any other product candidates to differ from preclinical, interim, preliminary, topline or expected results; Edgewise's ability to enroll patients in its ongoing and future clinical trials; operating results and business generally; Edgewise's ability to raise funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Edgewise's reliance on third parties, contract manufacturers and contract research organizations; Edgewise's ability to obtain and maintain intellectual property protection for its product candidates; risks associated with access to capital and credit markets; the loss of key scientific or management personnel; competition in the industry in which Edgewise operates; Edgewise's ability to develop a proprietary drug discovery platform to build a pipeline of product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in documents that Edgewise files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

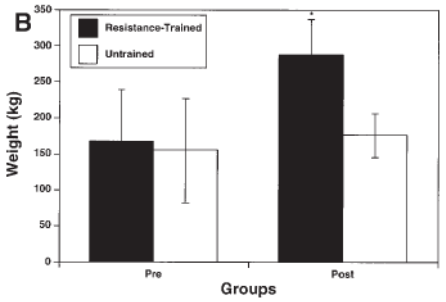
This presentation concerns product candidates that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.

When We Exercise, Our Muscles Get Bigger and Stronger

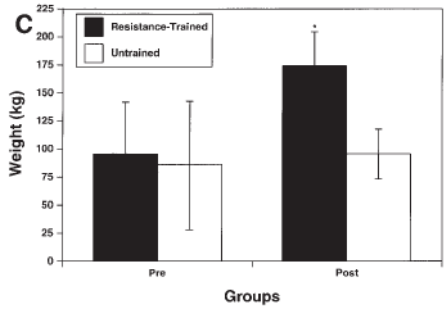
NYT – ‘How to get strong’



leg extension strength



leg press strength



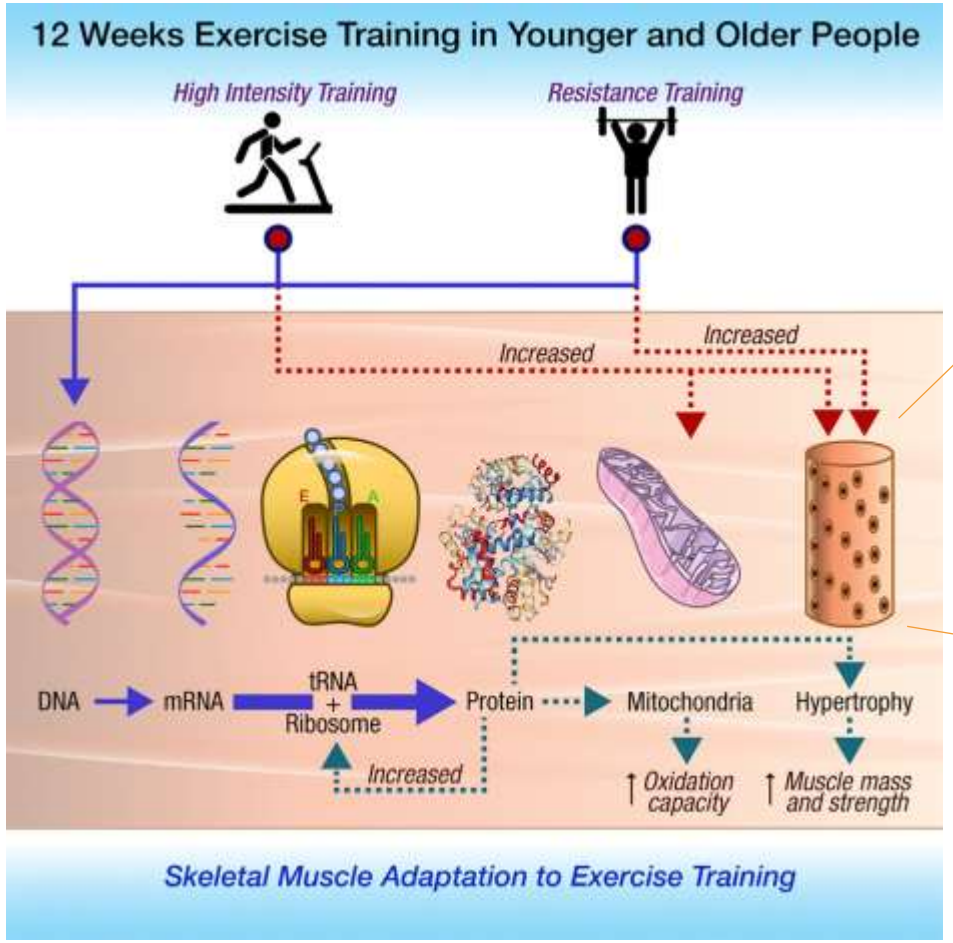
Half squat strength

- Effect of 16 weeks resistance exercise (2/week) in healthy older men (65 yrs)
- Most metrics increased 30-50%
- Individual muscle fibers approx. 30% bigger

J Gerontology 2000, Vol. 55A, No. 7, B336–B346

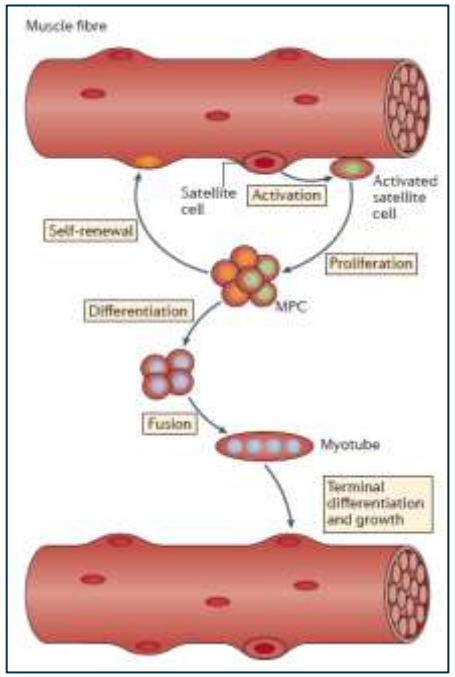
More Protein and More Muscle – Dual Pathways to Speed Adaptation

New protein



Cell Metabolism 2017: **25**, 581–592

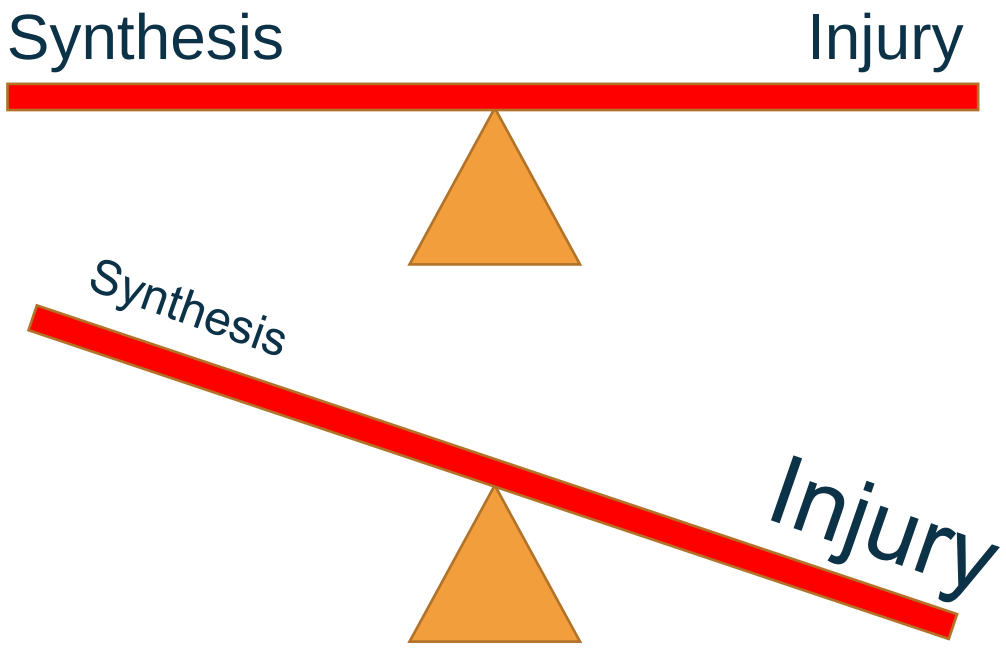
Membrane stress to activate stem cells

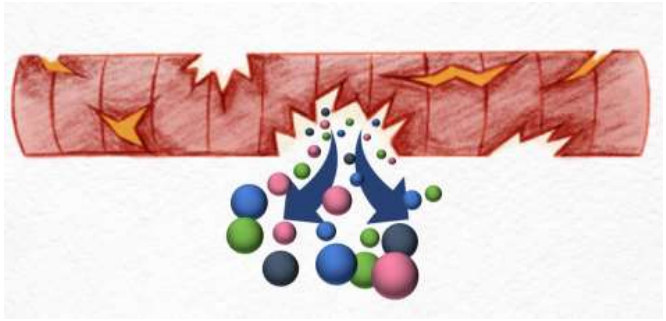


Nat Rev Immunol 2017:17 p165

- *Combination of protein synthesis/degradation and controlled muscle injury*

Adaptation Balance and Taking it Too Far!

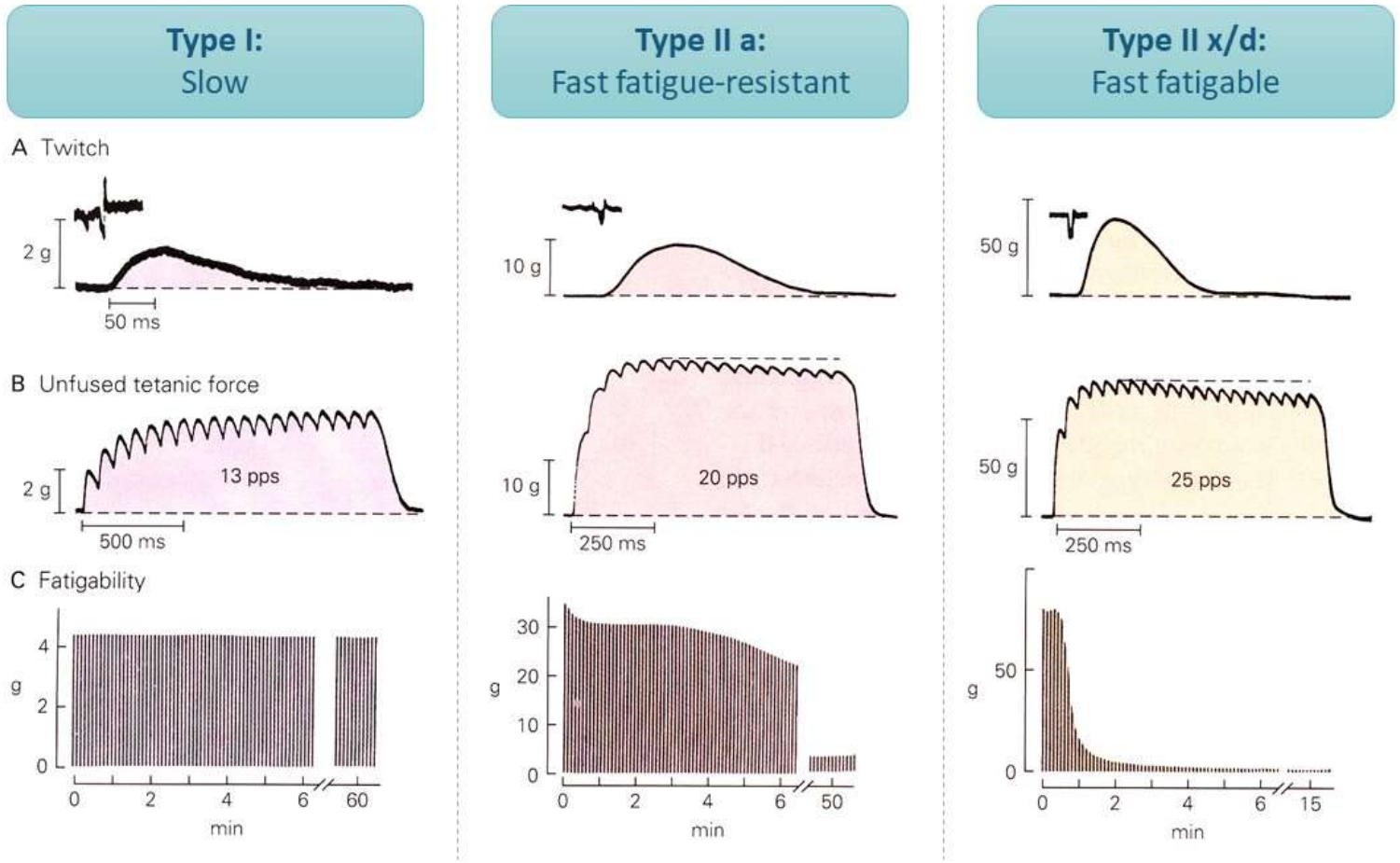


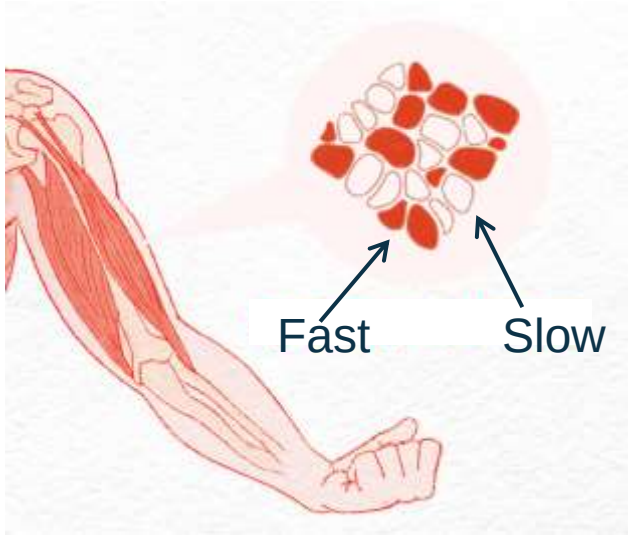


Excessive or unaccustomed exercise

- Pain
- Stiffness
- Decreases in range of motion
- Increased muscle injury biomarkers (CK and other proteins)

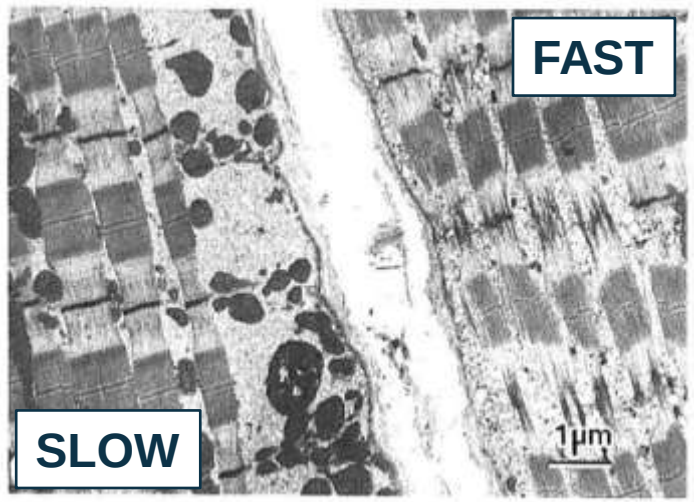
Skeletal Muscle is Comprised of Slow (type I) and Fast (type II) fibers



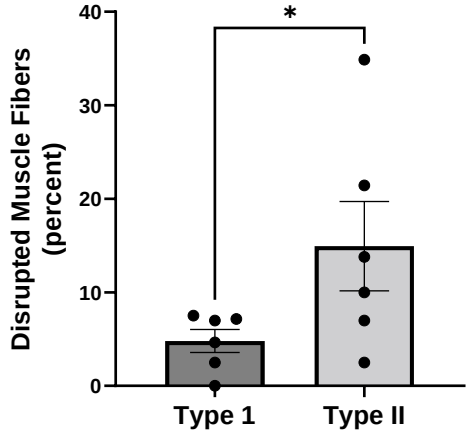


Humans are ~ 50/50% fast/slow

Slow fibers are Less Prone to Disruption



MORE DISRUPTION IN FAST

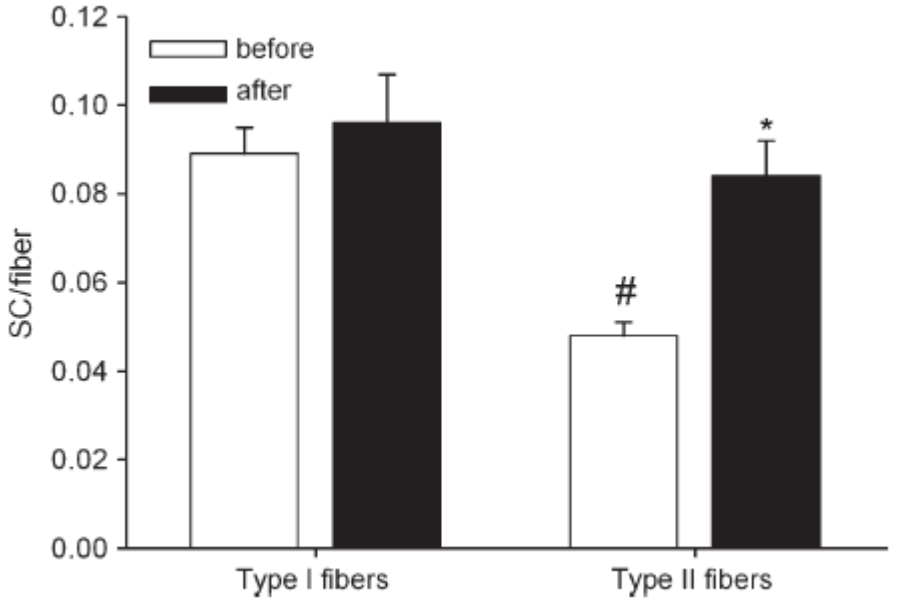


- 30 mins controlled eccentric exercise
- Muscle biopsy taken immediately after exercise

Int. J.. Sports Med. 1983:4, p170176

MORE STEM CELL MOBILIZATION IN FAST

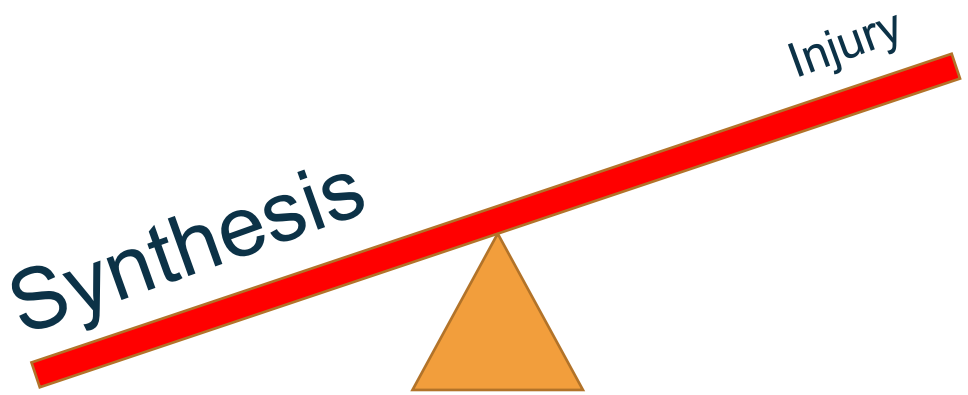
- 30 mins controlled eccentric exercise
- Muscle biopsy taken immediately after exercise



J Gerontology Ser A 64A:No. 3, 2009 p332–339

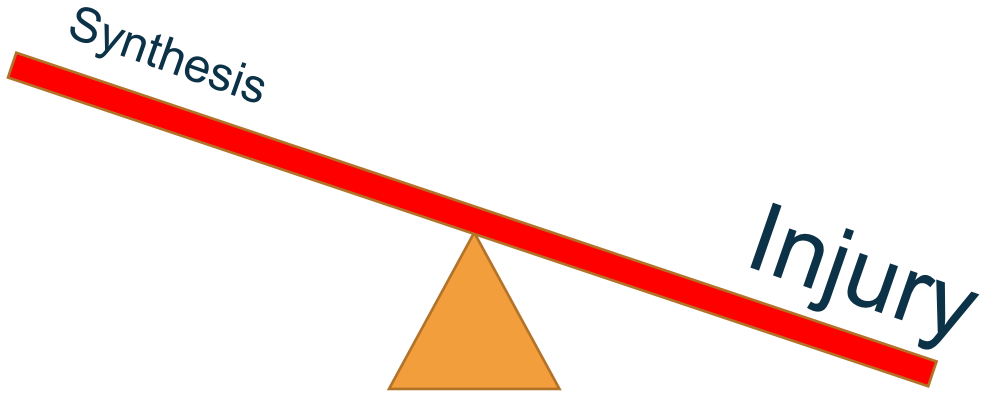
Do we have different fiber injury susceptibility to maximize adaptation but minimize the risk of disabling injury?

SLOW FIBERS



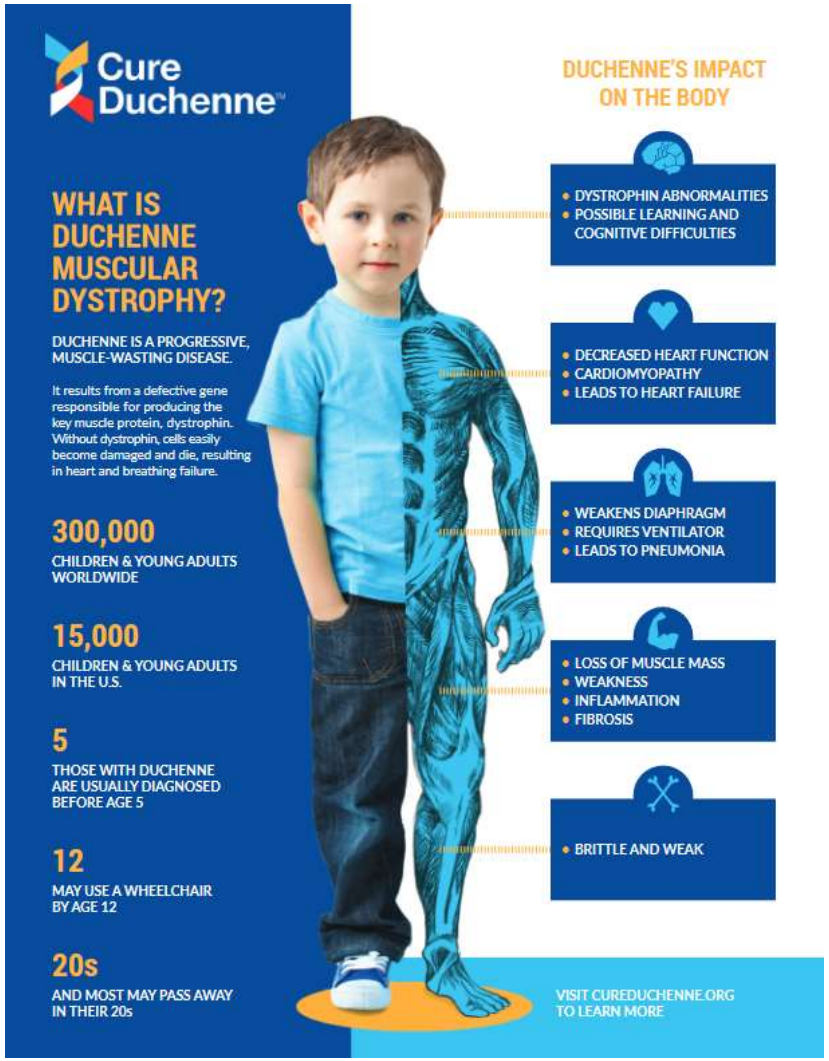
Slow adaptation but less chance of injury?

FAST FIBERS

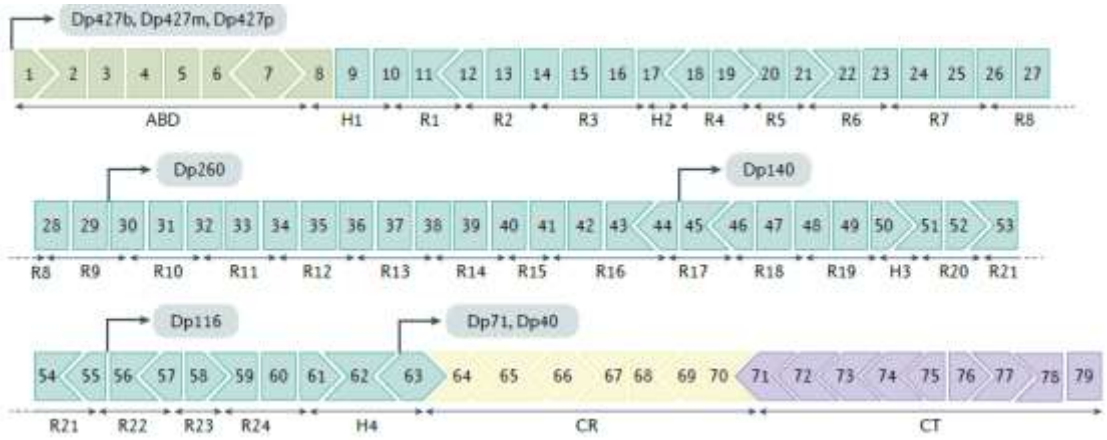


Fast adaptation but greater chance of injury?

A Gene that Ruins Adaptive Balance - Dystrophin



Dystrophin – 79 exons, ~2.4 Mb, X-linked

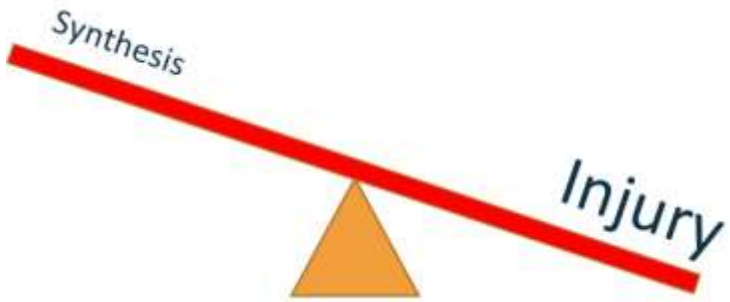


~30% cases are spontaneous

Becker Muscular Dystrophy (BMD) – Partially Functional Dystrophin

- 4,000-5,000 patients in the U.S.
- Later onset versus DMD, typically 8-15 yrs.
- Variable progression for mobility (late 30s) and cardiomyopathy

Normal Contraction Leads to Excessive Degeneration in Dystrophic Muscle

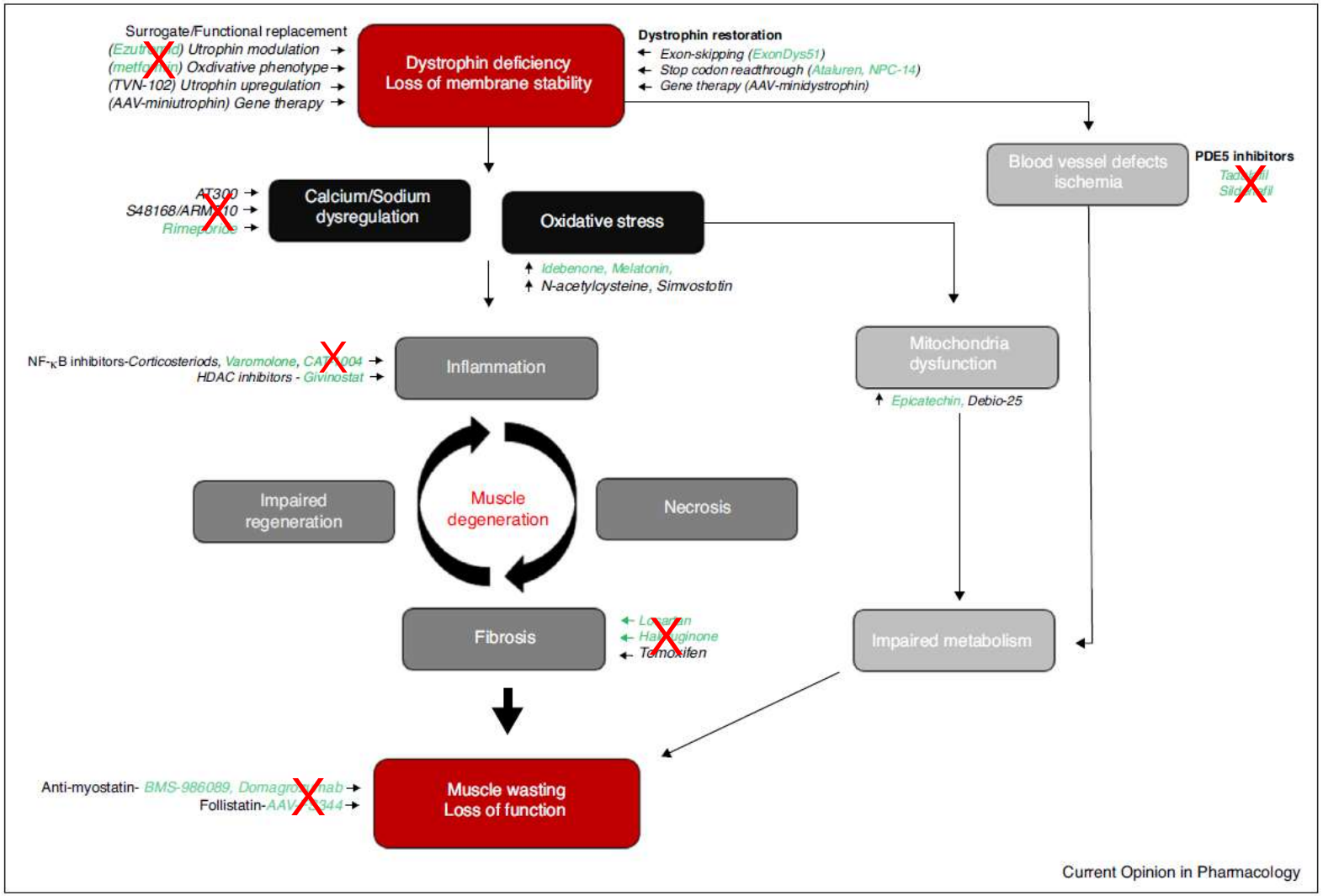


- Degeneration requires inflammation for repair
- Chronic inflammation leads to fibrosis
- Fibrosis leads to muscle loss and disability

mdx mouse lumbrical

Sue Brooks, Dennis Claflin, Sunny Yu, University of Michigan

Therapeutic interventions have focused on all elements of the degeneration process



Approved therapies

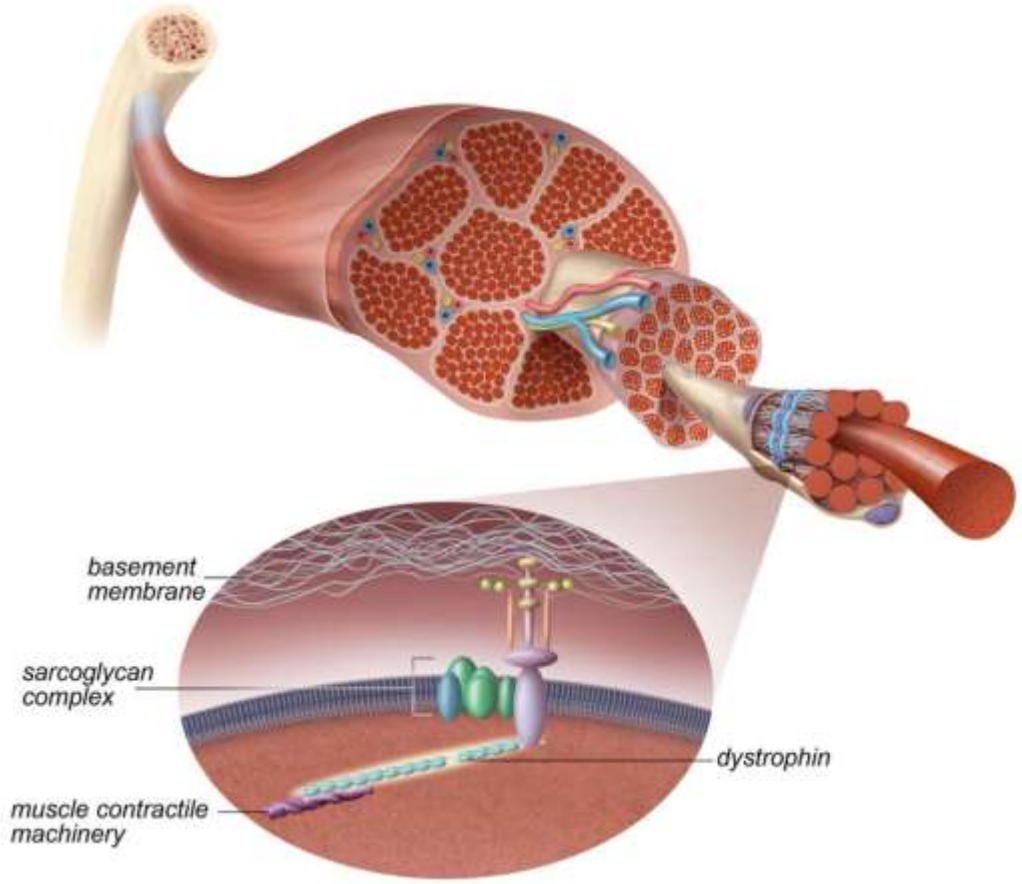
- **High dose steroids** – alter inflammation to extend ambulation approx. 2 years but comes at a cost
- **Antisense oligos** – weekly injections increase expression of shortened dystrophin in some patients. Unknown efficacy

Developing therapies

- **Gene therapy** – delivery of a micro version of dystrophin via AAV virus. Inherent challenges with safety, efficiency of delivery and micro-dystrophin functionality

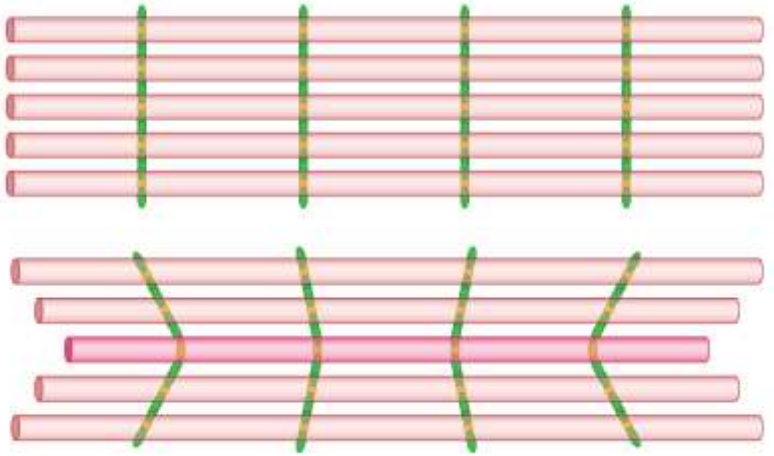
Current Opinion in Pharmacology 2017, 34:36–48

Understanding the Function of Dystrophin – A Molecular Connector

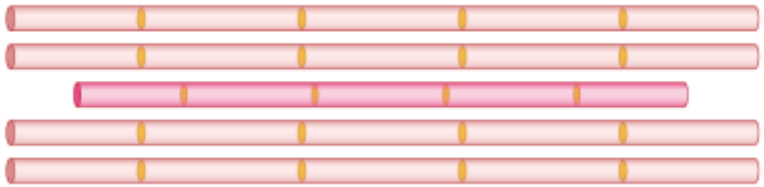


Dystrophin connects contractile proteins to the membrane and surrounding matrix of fibers

With dystrophin – fibers support each other



No dystrophin – fibers contract without support



Similar to Healthy Muscle, Fast Fibers are More Sensitive in DMD

Cell, Vol. 52, 503–513, February 26, 1988, Copyright © 1988 by Cell Press

Fast Muscle Fibers Are Preferentially Affected in Duchenne Muscular Dystrophy

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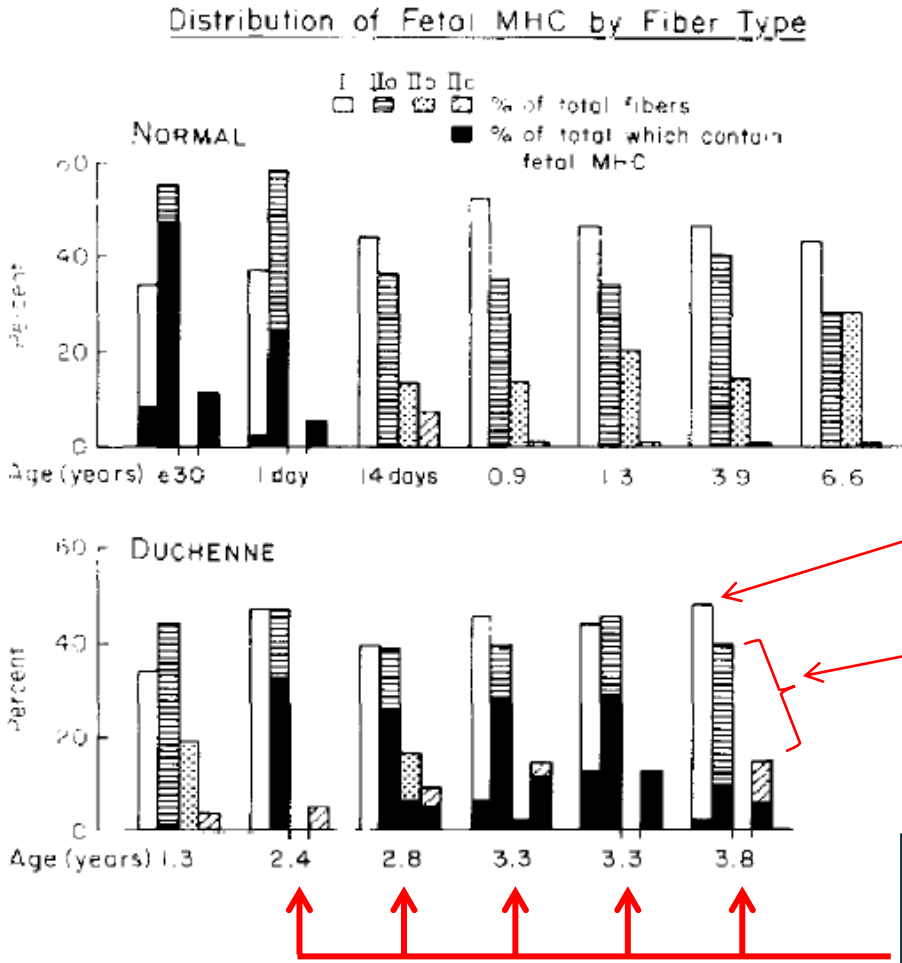
* Department of Pharmacology
Stanford University School of Medicine
Stanford, California 94305
§ Department of Pathology
Division of Neuropathology
College of Physicians and Surgeons
of Columbia University
New York, New York 10032

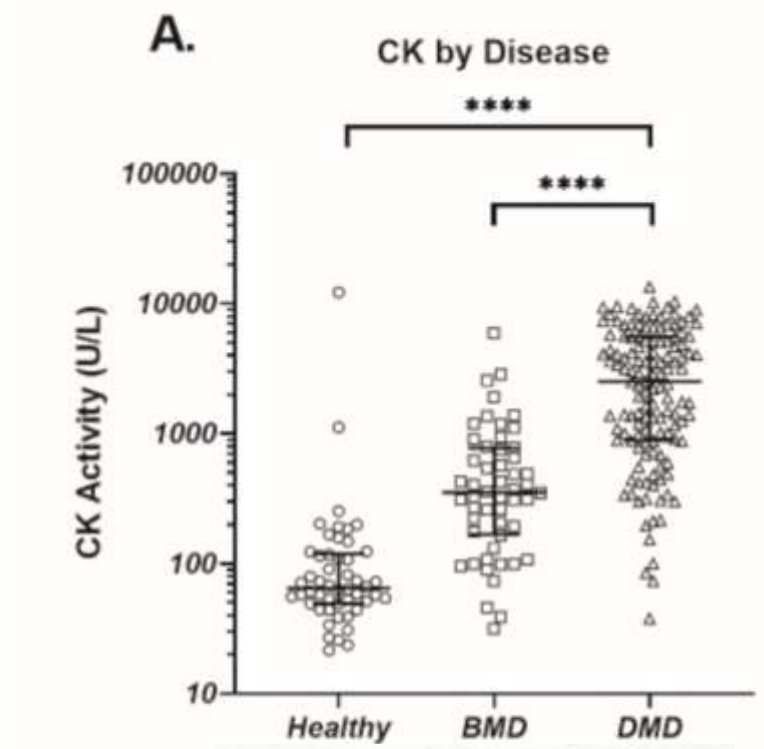
Enrichment of muscle regeneration biomarkers in fast but not slow muscle fibers of young DMD kids

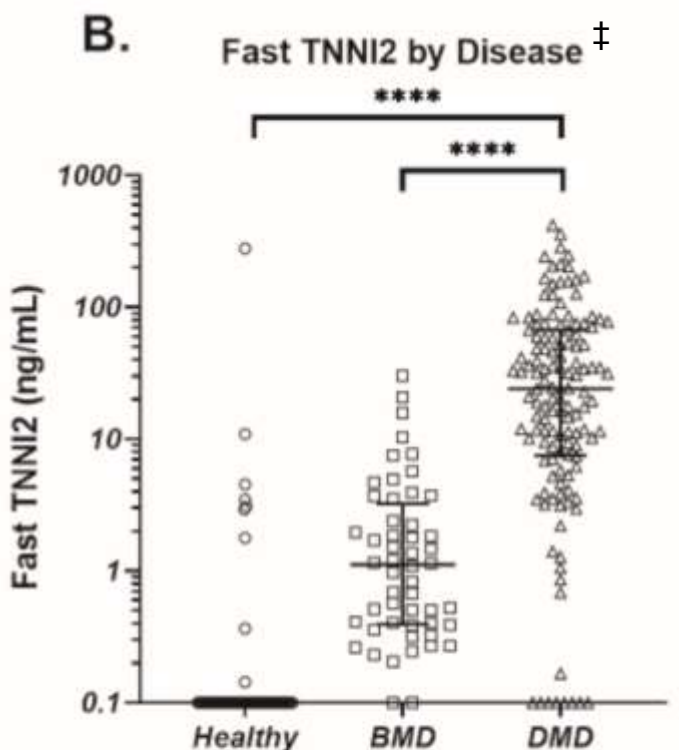


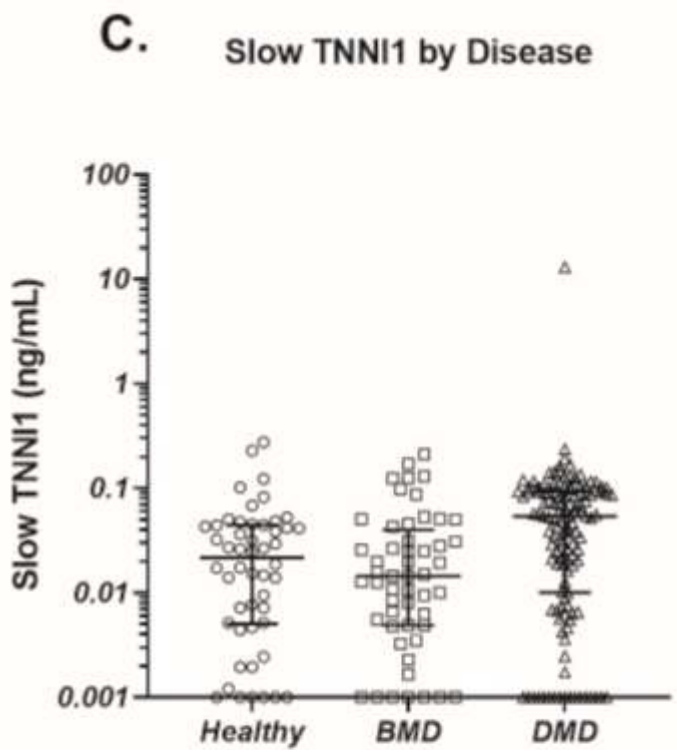
Black shading indicates eMHC-positive fibers

Regeneration Marker
Expressed mostly in fast but not slow fibers

Injury Biomarkers Tell the Same Story - Fast but not Slow Fiber Biomarkers are Elevated in BMD and DMD





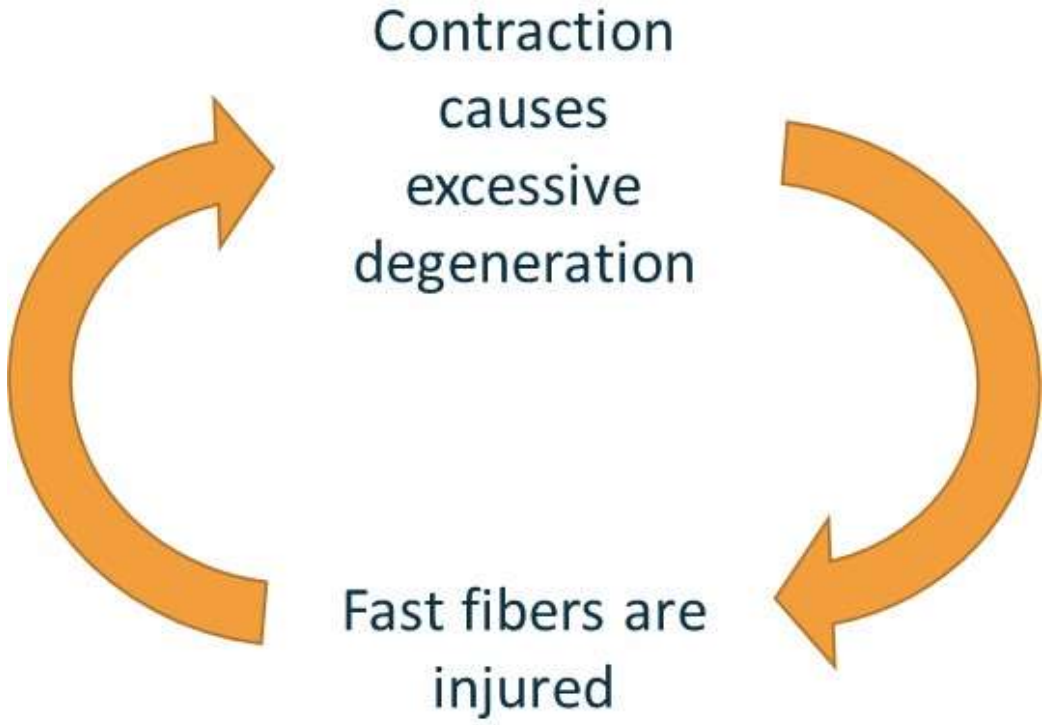


FAST FIBER PROTEIN

SLOW FIBER PROTEIN

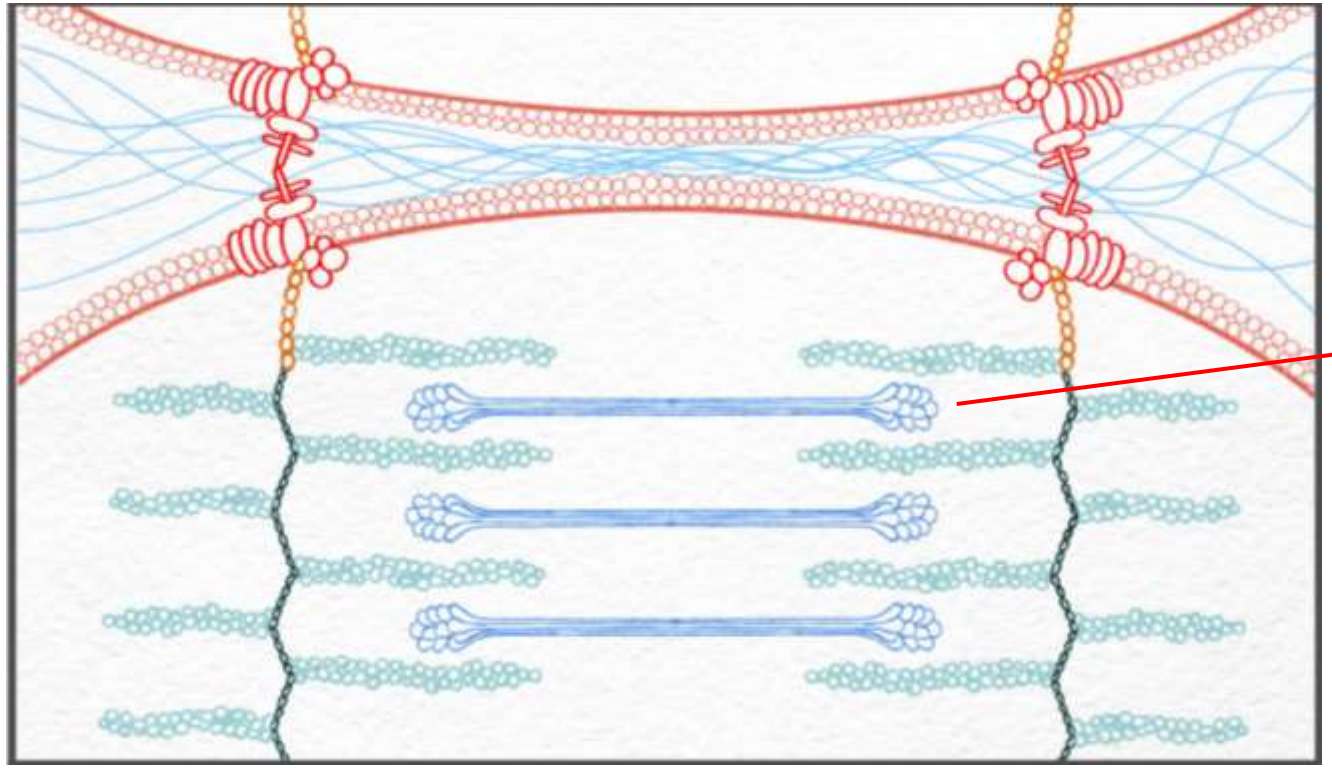
Barthel et al., Muscle and Nerve. doi: 10.1002/mus.27222. Mar 2021

A Left-Field Strategy to Rebalance Dystrophic Muscle?



Would selective inhibition of fast fiber contraction stop muscle degeneration but allow mixed fast/slow muscles to still function?

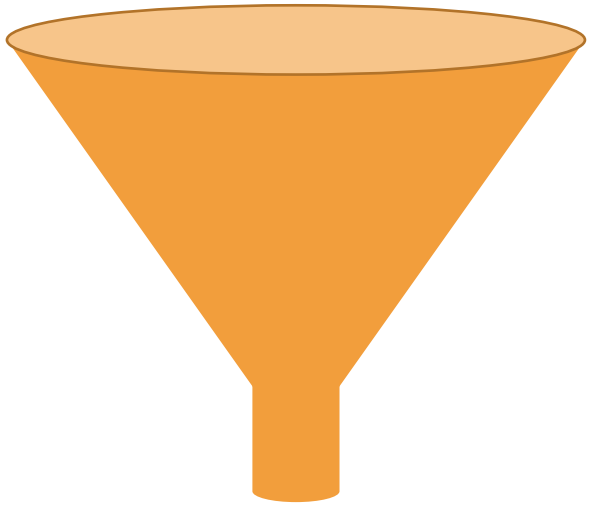
The Target – Fast Skeletal Muscle Myosin, the Engine of Force Generation



- A specialized motor protein that generates force by consuming ATP
- Different types of myosin motor are used by different types of ‘striated’ muscle (fast vs slow vs cardiac)
- *The motor in slow fibers and the heart is the same*

Identifying a Selective Fast Myosin Inhibitor

700,000 starting compounds



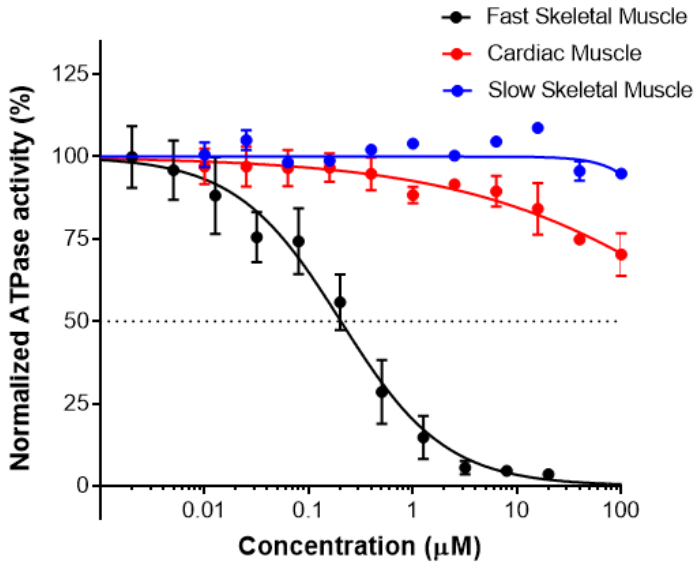
ATP consumption rates of homogenized native skeletal and cardiac muscle

Lead selective inhibitors

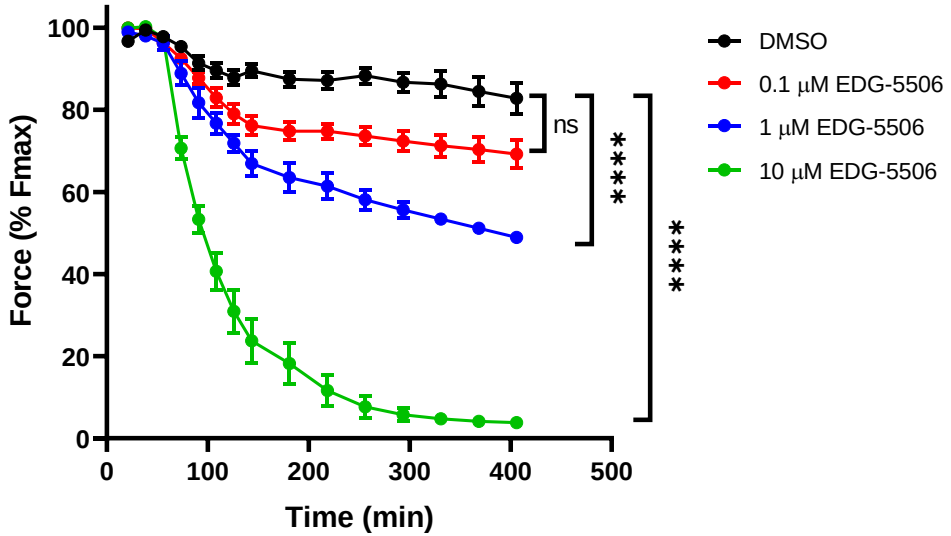
Synthesis and optimization of >1000 chemical derivatives of lead hits

EDG-5506!

EDG-5506 – A Potent, Selective Fast Skeletal Muscle Myosin Inhibitor



Selective inhibition of fast skeletal muscle suspension ATPase
(but not slow/cardiac)



Concentration-dependent inhibition of force in isolated mouse muscle

EDG-5506 Stops Fiber Breakdown in Contracting DMD Muscle

DMD muscle (*mdx* mouse) no treatment

Contracting at 100%

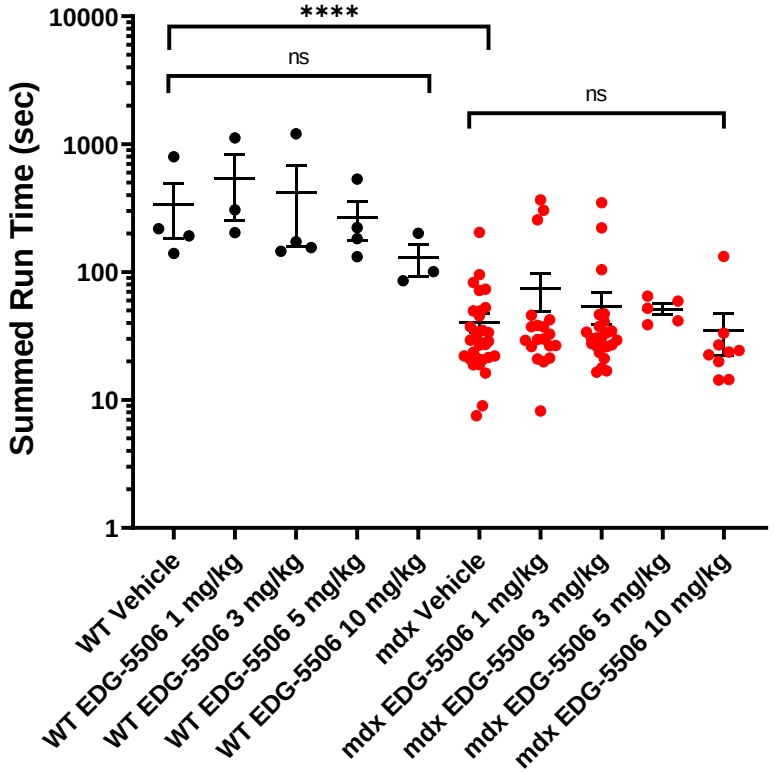
DMD muscle (*mdx* mouse) 0.3 µM EDG-5506

Contracting at 85%

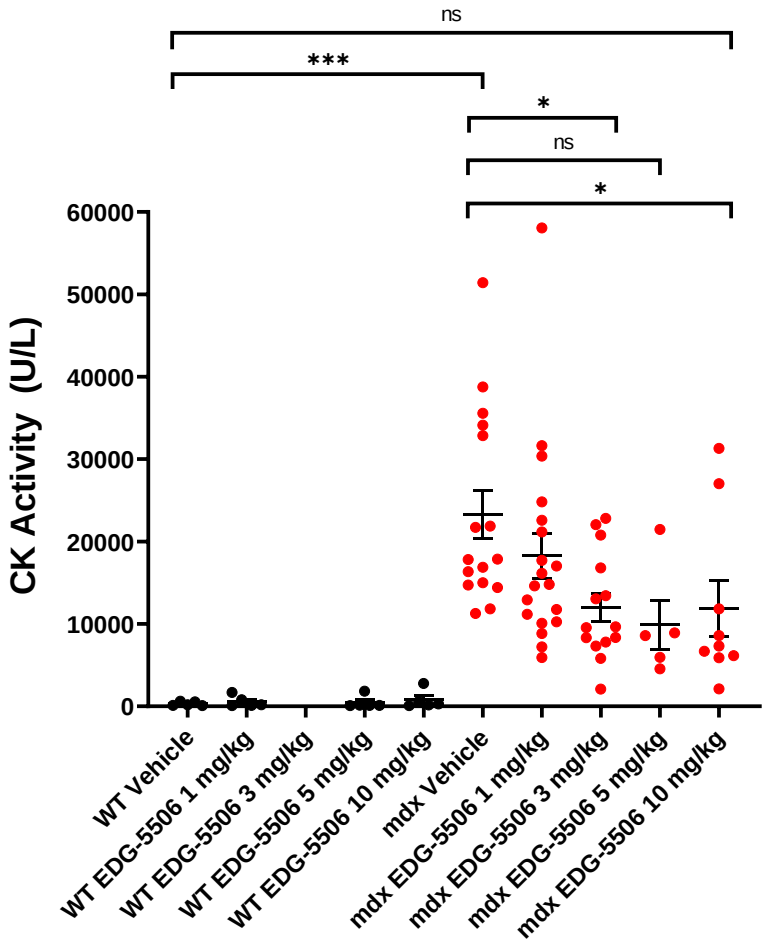
Claflin, Su and Brooks. U Michigan

mdx mouse lumbrical muscle – 20, 1 second maximal isometric contractions (video sped up)

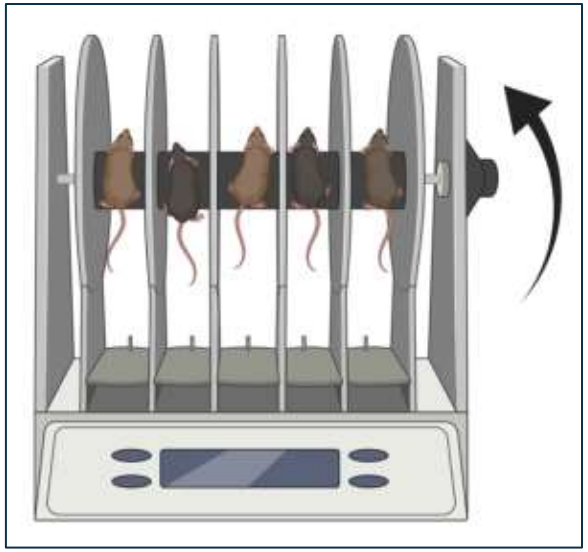
EDG-5506 Reduces DMD Mouse CK After Exercise Testing without Altering Performance

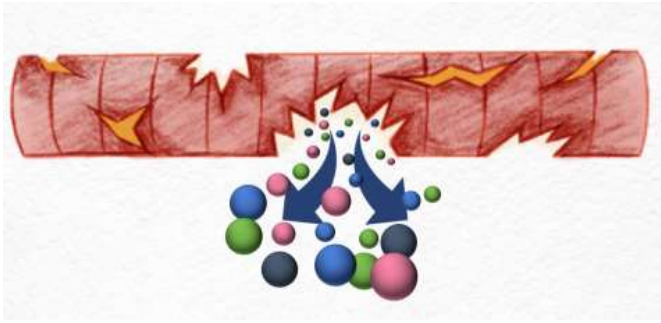


Rotarod performance



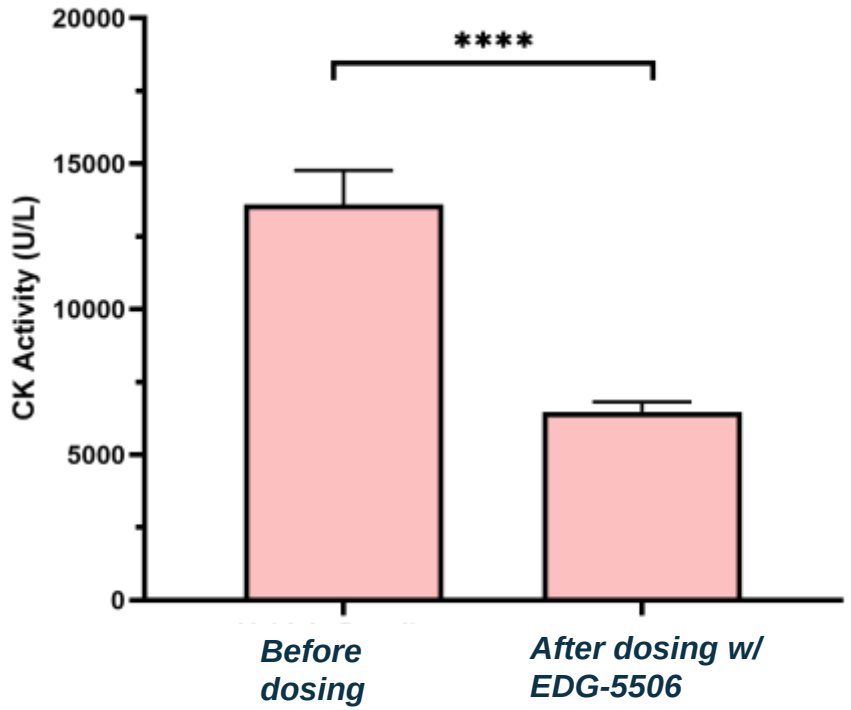
Post-exercise plasma CK
(Injury marker)



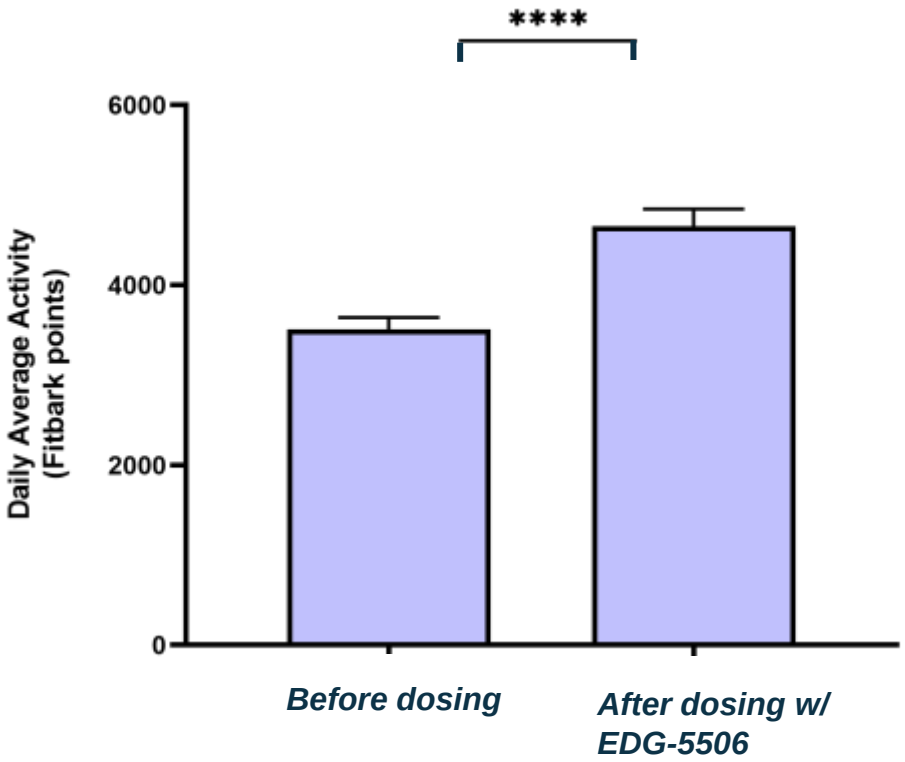


EDG-5506 Decreases CK and Increases Activity in DMD Dogs

Decreased injury biomarker (plasma CK)



Increased activity measured with an activity monitor

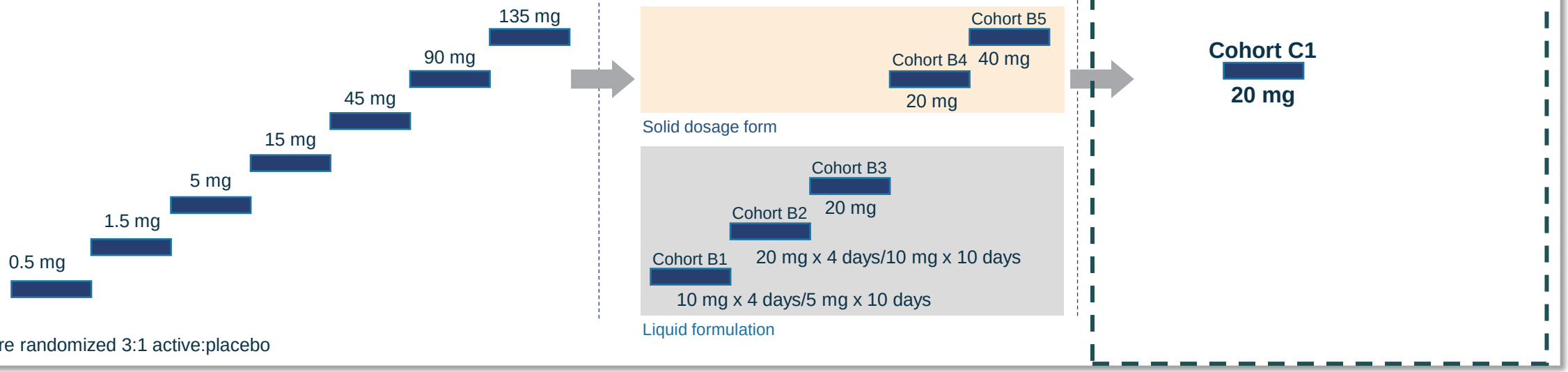


Progressing EDG-5506 into Clinical trials

- Founded in Boulder, CO July 2017
- Oct 2017 – discovery work to identify promising compounds starts
- May 2018 – Discovery and advancement of EDG-5506
- Oct 2020 – Started dosing healthy volunteers
- Oct 2021 – Starting dosing adults with Becker muscular dystrophy
- Dec 2021 – Start of 1 year extension study in Becker
- 2H 2022 – Start of Becker phase 2 study
- 2H 2022 – Start of Duchenne muscular dystrophy studies

EDG-5506 Phase 1 Study Conducted in Healthy Volunteers and Participants with Becker Muscular Dystrophy

Trial Design



* All HV cohorts were randomized 3:1 active:placebo

Key Endpoints

Primary Endpoints

- Safety and tolerability at 20 mg over a 14-day period in BMD

Participants were monitored as inpatients for 16 days, with follow-up 1 and 4 weeks after completion of dosing.

Participants in the BMD Phase 1b Had Significant Functional Impairment

Characteristic	BMD Participants (N=7)	Age Normative Values
Age	33.8 years	
Functional Measures (median)		
10-meter walk/run	8.3 sec	< 4 sec
Rise from floor	20 sec	< 3 sec
Serum Creatinine (mean, mg/dL)	0.58	0.92 - 1.16
Serum Creatine Kinase (mean CK, U/L)	1,347	<205

- Functional tests show significantly compromised or lost function
- Low creatinine consistent with decreased muscle mass
- Elevated CK levels reflect ongoing muscle damage

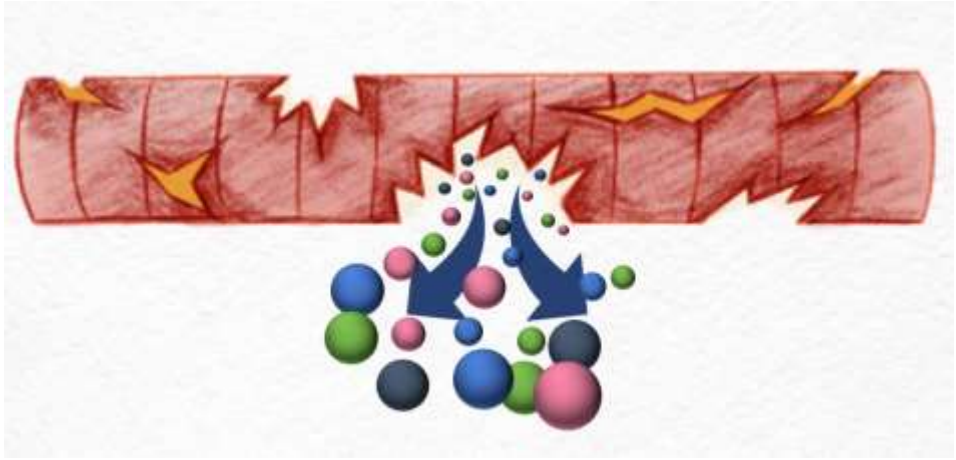
EDG-5506 was Well-Tolerated in BMD Subjects

TEAE	Placebo N=2 n (%)	EDG-5506 (20 mg) N=5 n (%)	Total N=7 n (%)
Any TEAE	**2 (100%)**	**5 (100%)**	**7 (100%)**
Dizziness	2 (100%)	5 (100%)	7 (100%)
Euphoric mood	0	2 (40%)	2 (29%)
Musculoskeletal stiffness	0	2 (40%)	2 (29%)
Somnolence	0	2 (40%)	1 (14%)
Diarrhea	0	1 (20%)	1 (14%)
Nausea	0	1 (20%)	1 (14%)
Fatigue	0	1 (20%)	1 (14%)
Vessel puncture site bruise	0	1 (20%)	1 (14%)
Back pain	0	1 (20%)	1 (14%)
Pain in jaw	0	1 (20%)	1 (14%)
Headache	0	1 (20%)	1 (14%)
Presyncope	0	1 (20%)	1 (14%)
Nasal congestion	0	1 (20%)	1 (14%)
AEs of special interest	**0**	**0**	**0**

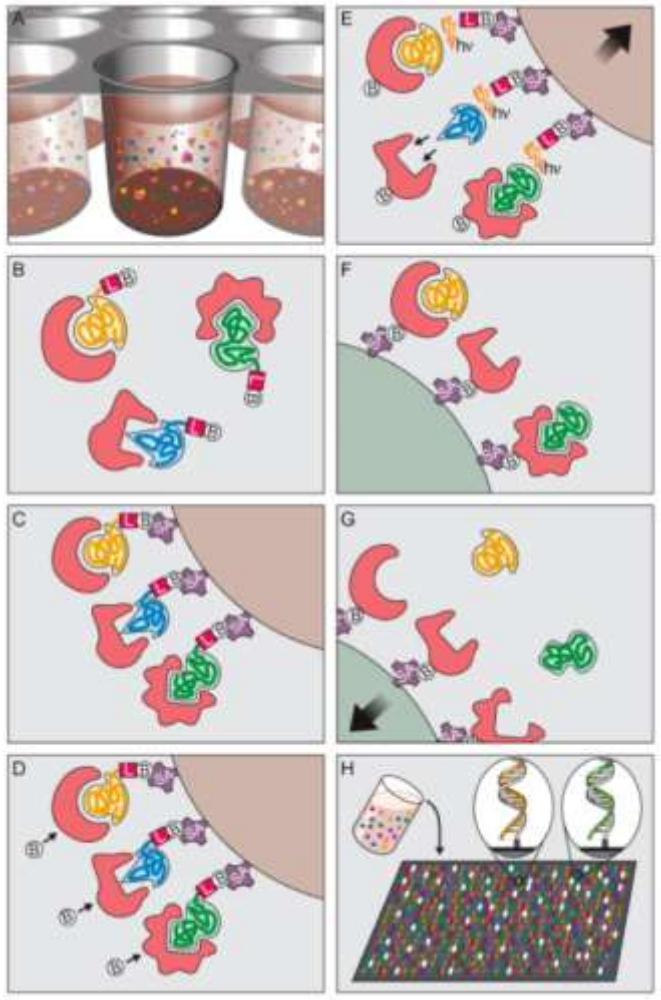
- No change in grip strength
- All AEs were mild (Grade 1); AEs were transient and generally declined with increasing exposure

How to Detect an Early Activity Signal in BMD?

- Two weeks dosing enough time to assess short-term safety and tolerability but not long enough to measure beneficial effects on strength etc
- Before treatment with EDG-5506, BMD participants had elevated levels of CK as a result of ongoing muscle injury
- Were there other circulating proteins that also leak from muscle?
- Did short-term EDG-5506 stabilize muscle to reduce these proteins?



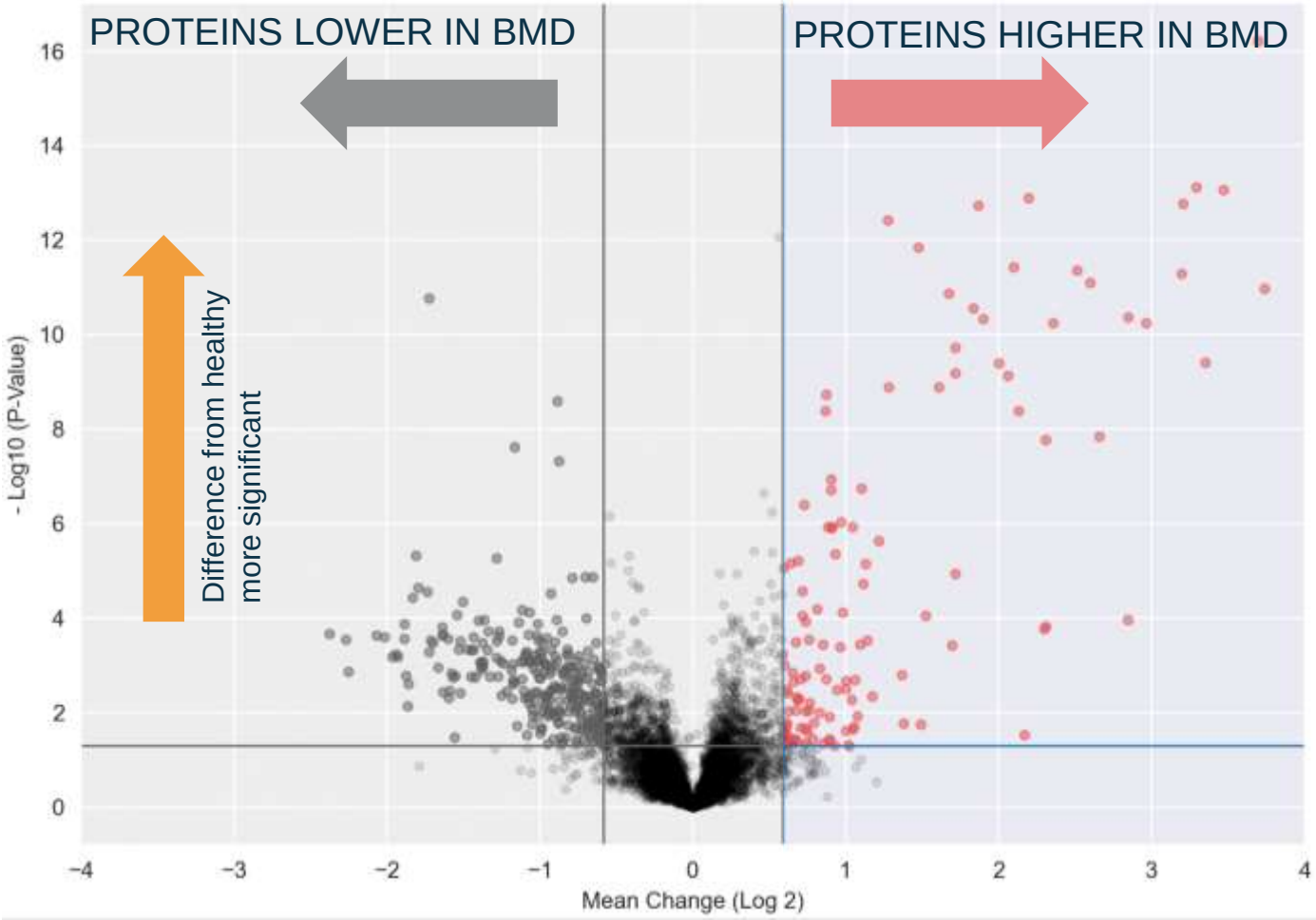
SOMAscan Aptamer Technology Enables Relative Measurement of 7000 Proteins for a Single Blood Sample



- **‘Slow Off-rate Modified Apatamer Scan’**
- Aptamers are modified with a biotinylated photocleavable linker developed by Somalogic in Boulder, CO
- Aptamers are mixed with plasma samples then added to biotinylated beads
- Bead-bound proteins are biotinylated and beads are then washed and linker cleaved
- Protein/Aptamer complexes are bound to streptavidin beads and aptamers are then dissociated and quantified on a chip
- Note – SOMAscan optimized against human proteins, aptamers may not cross-react with proteins from other species

Using SOMAscan 7,000 Analyte Set, A Proteomic Signature for BMD was Identified

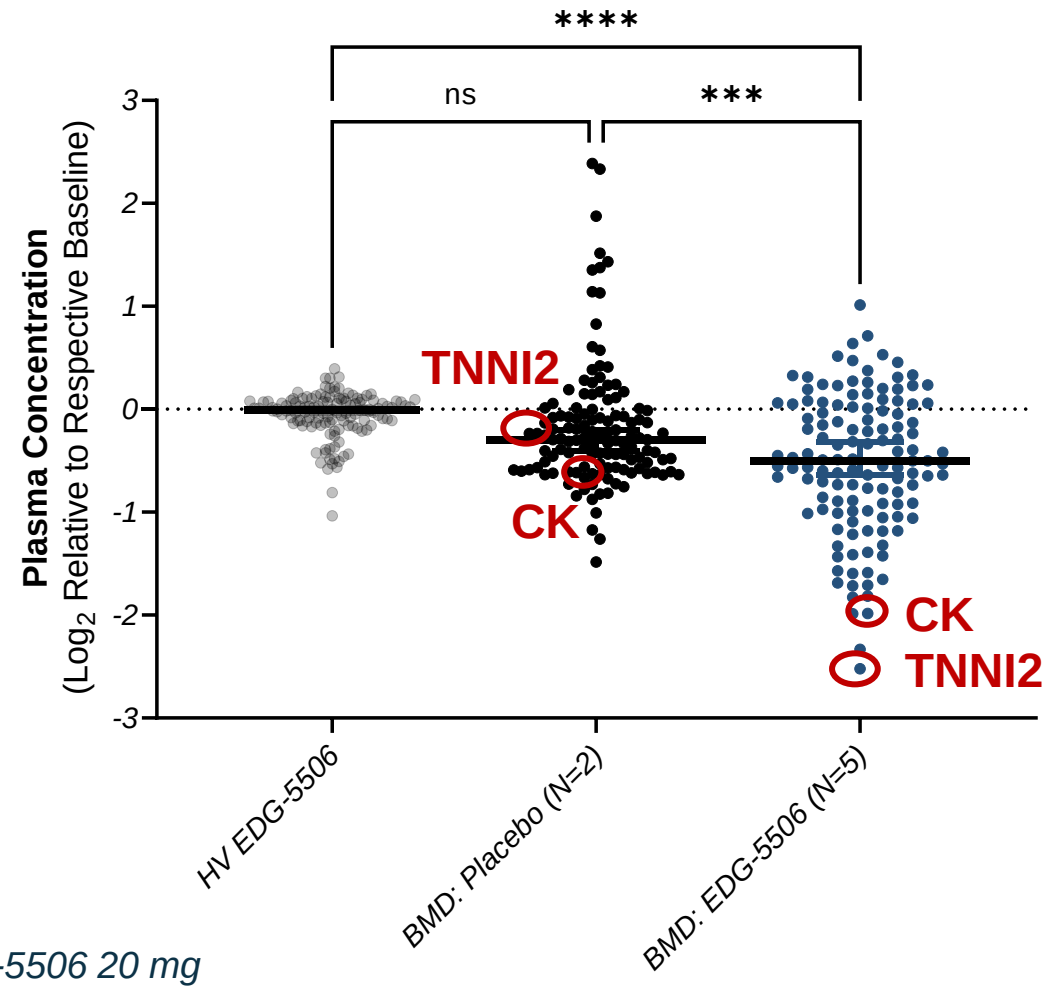
Baseline BMD vs. Healthy Biomarker Fingerprint Analysis



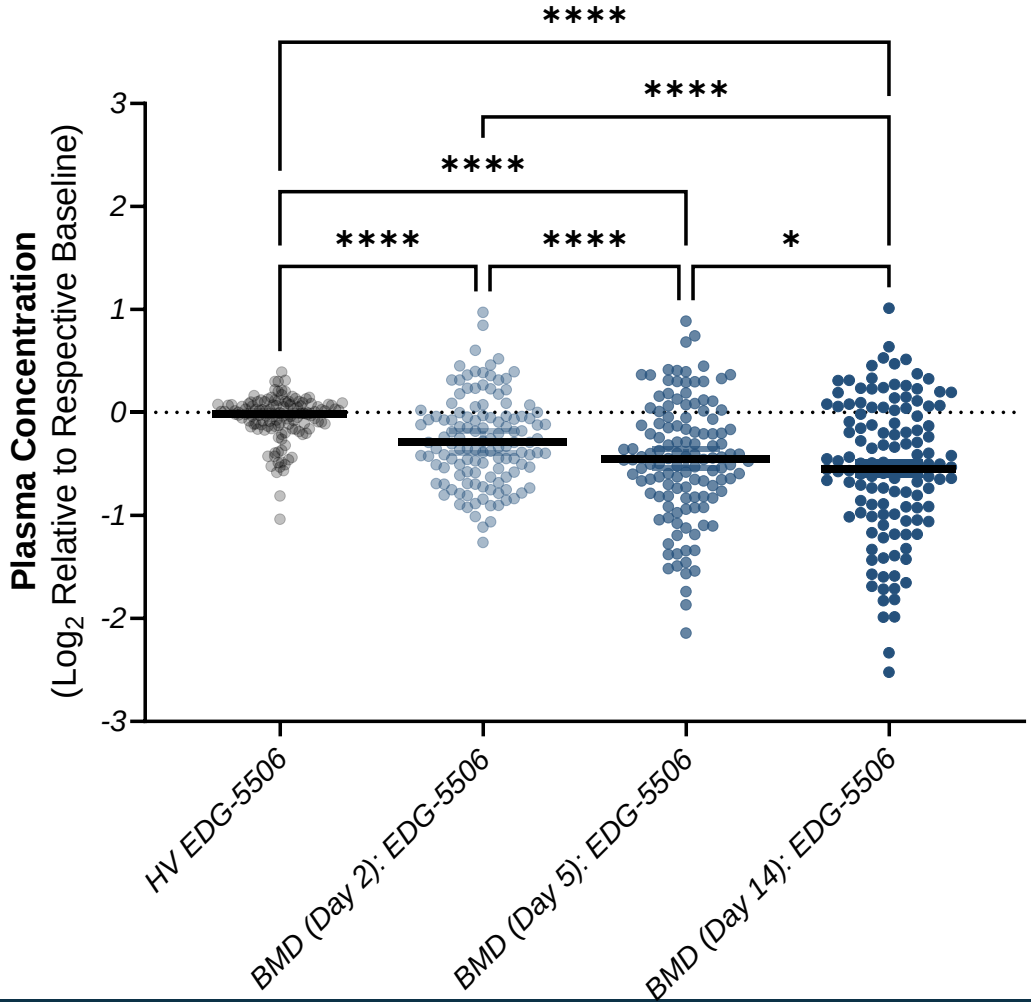
- Baseline plasma samples (n=7) were compared to samples from healthy volunteers (n=25)
- Proteins filtered by magnitude of difference (≥1.5X) and adjusted *p* value (<0.05) vs. HV
- **Baseline analysis identified a fingerprint of 125 elevated proteins in BMD**

The Majority of Signature Proteins are Lowered by EDG-5506

Changes in BMD biomarkers vs. placebo (Day 1 vs Day 14)



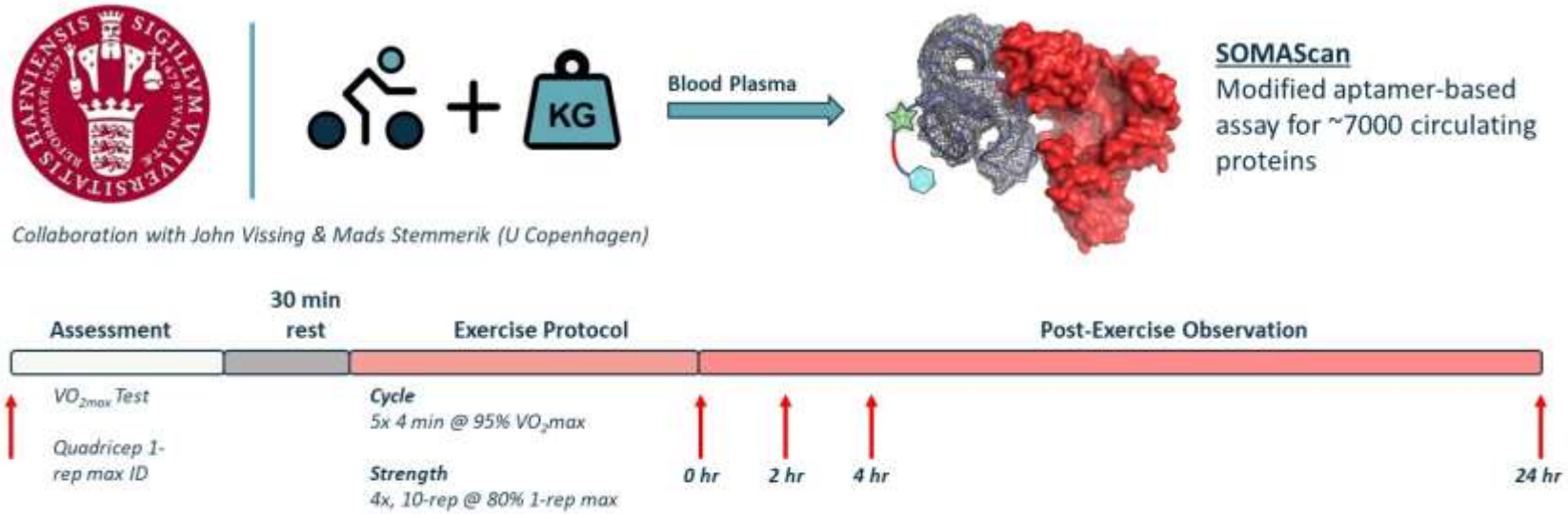
BMD biomarkers responsive to increased exposure to EDG-5506



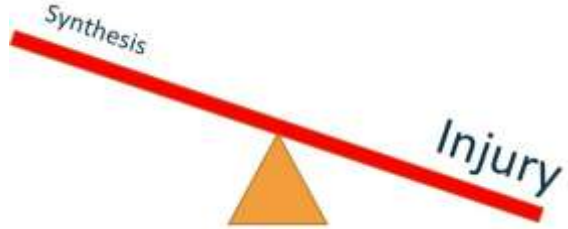
** EDG-5506 20 mg*

Use of a Controlled Exercise Study to Annotate Our Becker Response Signature

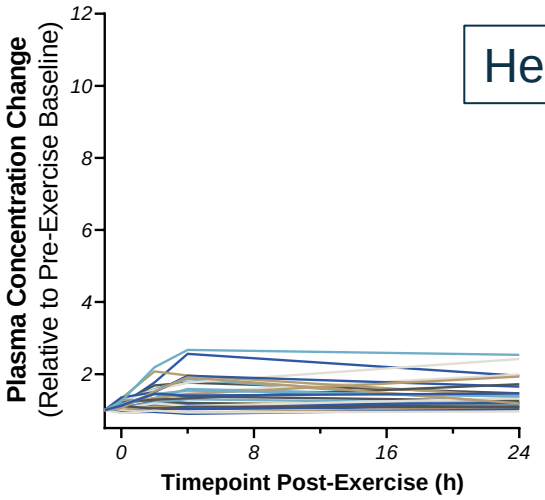
- EDG-5506 lowered most proteins that were elevated in Becker vs healthy individuals
- However – what evidence do we have that any of them are related to exercise-induced injury?

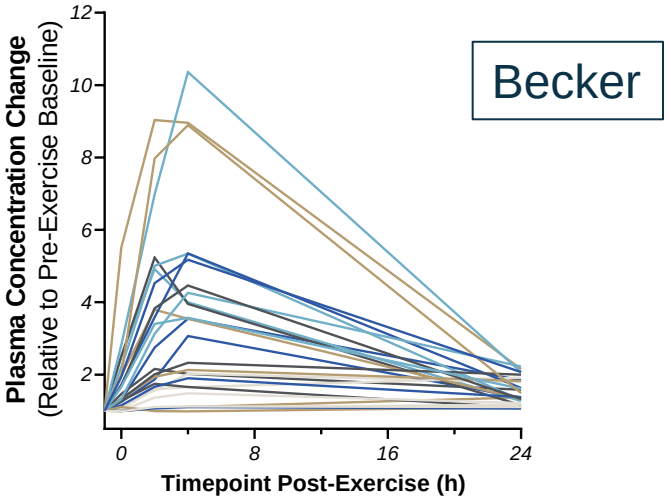


Taking advantage of an ongoing collaboration with John Vissing (University of Copenhagen)



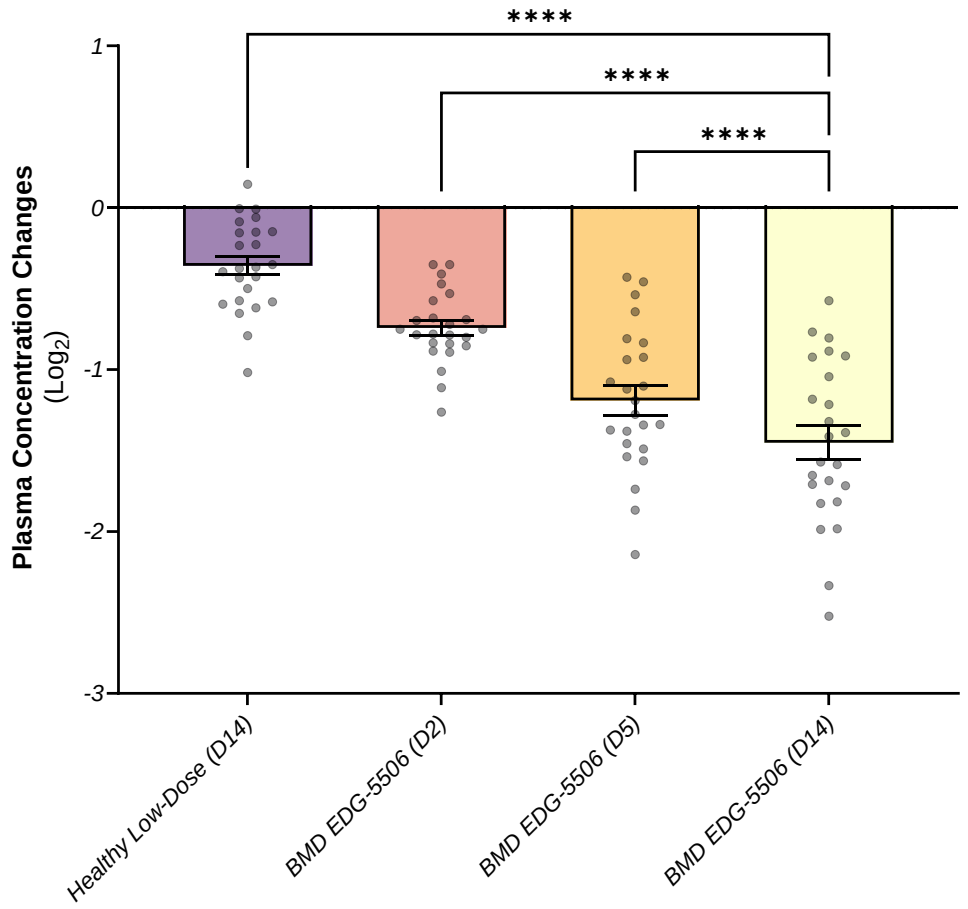
Defining a signature of proteins that directly increase with exercise in Becker





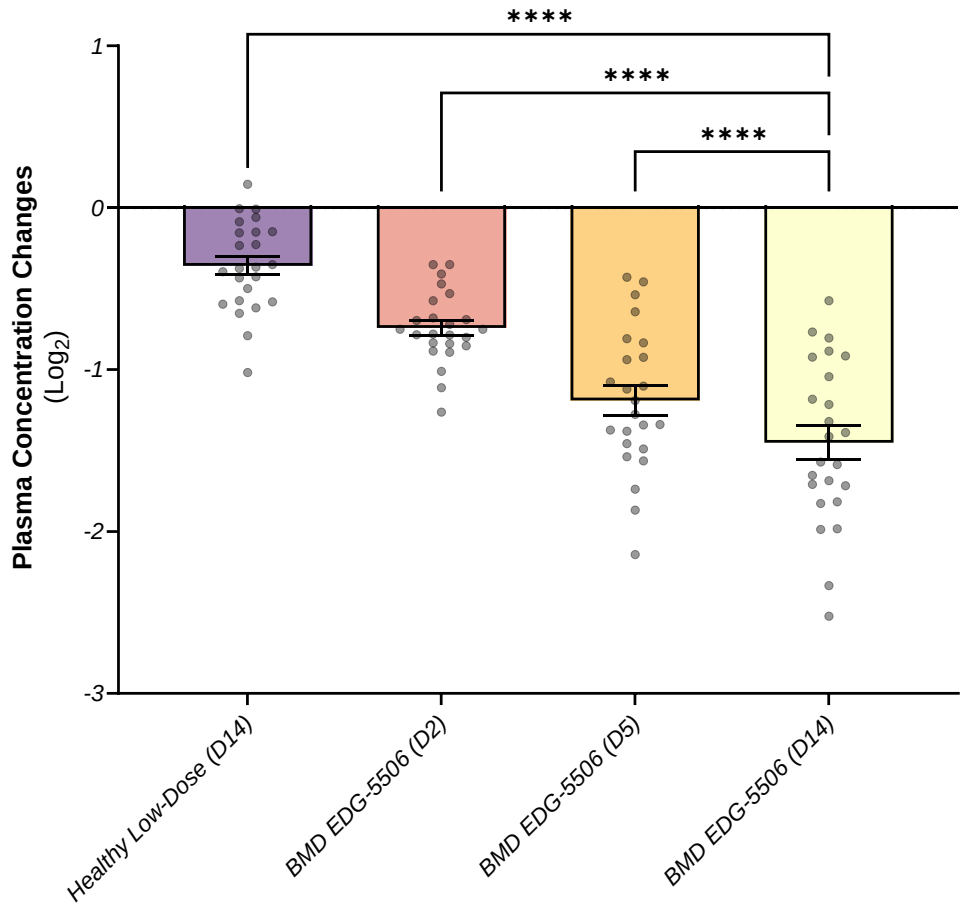
- Using controlled exercise, we established a set of 24 proteins that are elevated pre-exercise in Becker vs healthy and are then further elevated with exercise

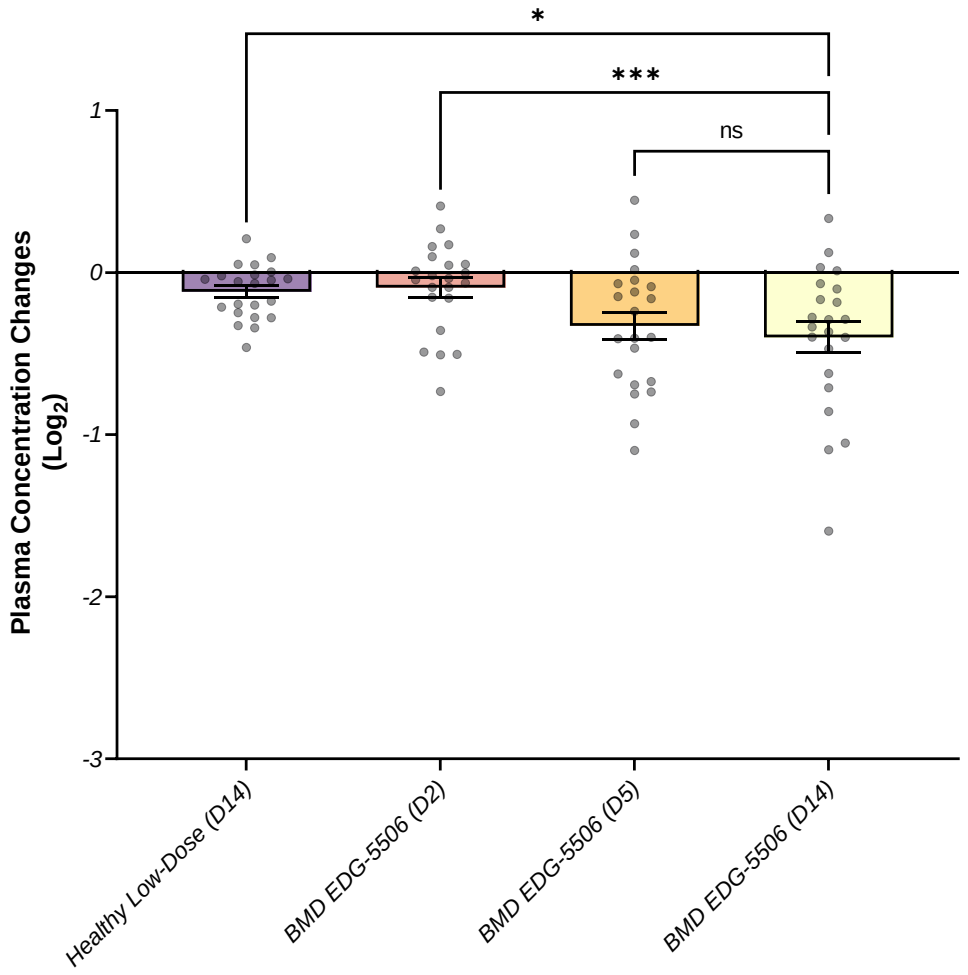
EDG-5506 Significantly Reduces proteins associated with injurious exercise in Becker muscular dystrophy



- Reduction of <u>all</u> annotated injury biomarkers with EDG-5505 in Becker muscular dystrophy

EDG-5506 Also Reduces proteins that are Independent of Exercise – *Changing biomarkers outside of basic muscle protection?*





Summary and thanks

- Building on learnings from muscle adaptation to exercise and how different skeletal muscle fiber populations respond, we've devised a novel approach to reduce muscle stress in two grave muscle diseases
- Early tolerability and biomarker data suggest that EDG-5506 has the potential to significant impact skeletal muscle health in Becker muscular dystrophy
- *Studies start in Duchenne muscular dystrophy in 2022!*

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Texas A&M - Peter Nghiem, Alexis Rutledge
SOMAscan – **Larry Gold**, Luong Luu, Caylee Martens, Cole Zimmerman