Characterization of Short- and Long-Term Proteomic Response to the Fast Skeletal Myosin Inhibitor, EDG-5506, in Becker Muscular Dystrophy (BMD)

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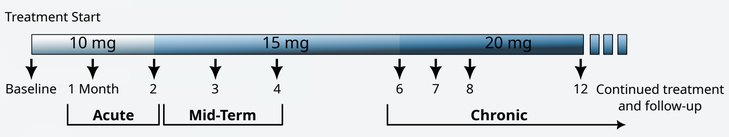
Background

EDG-5506 is a selective inhibitor of fast skeletal muscle myosin, designed to protect against contraction-induced injury in Becker and Duchenne muscular dystrophy (BMD and DMD, respectively). In a Phase I open-label study (ARCH, NCT05160415) adults with BMD (N=12) were administered doses from 10 to 20 mg EDG-5506 daily for 12 months.

We have previously observed early decreases in muscle injury biomarkers creatine kinase (CK) and fast skeletal muscle troponin I (TNNI2) with EDG-5506. Here, we examine changes in CK and TNNI2 with ongoing once-daily treatment for up to 12 months. We further examine differential proteomic profiles that result from acute (1 - 2 months), mid-term (3 - 4 months), and chronic (6 - 12 months) treatment.

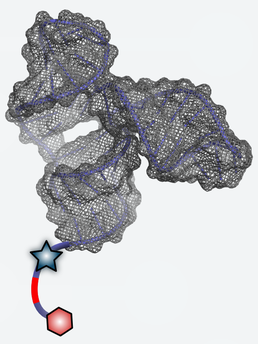
Methods

ARCH Clinical Study



12 BMD participants, 7 of whom participated in the Phase I MAD study, were enrolled and initially treated with 10 mg daily, with dose-escalation from 10 to 20 mg daily as shown. Blood draws were taken at pre-dose baseline, then at regular intervals thereafter for analysis by SOMAscan, as well as quantitation of CK activity and TNNI2 concentration by an activity assay and ELISA, respectively (1).

Analysis by SOMAscan

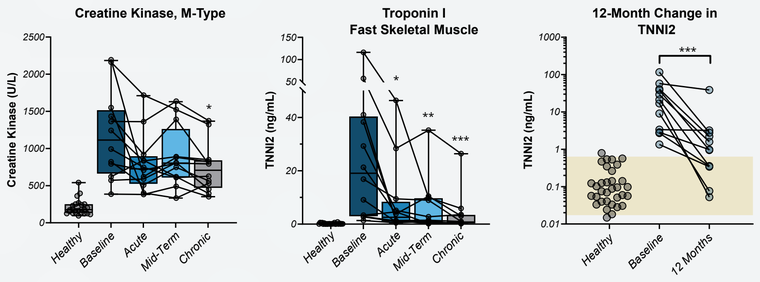


SomaScan is a multistep modified aptamer-based assay for high-throughput, sensitive, and unbiased biomarker measurement (2). Proteins in the samples are selectively bound with fluorescent aptamers, which are then measured on a chip array to yield values proportional to absolute concentrations.

In this study, SOMAscan was correlated to CK and TNNI2 to allow for direct conversion to absolute concentrations, as well as used to identify large-scale proteomic differences between short- and long-term treatment with EDG-5506, though at this time, this analysis does not differentiate effects from duration versus those from exposure.

Results

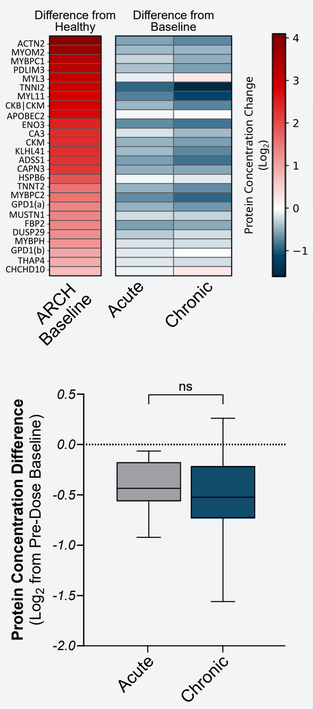
Reduction of Circulating CK and TNNI2



High levels of circulating CK and TNNI2 at baseline were reduced by acute treatment. TNNI2 was reduced to nearly healthy levels by longer-term treatment timepoints, with 5 individuals exhibiting levels seen in healthy controls by 12 months (5 - 95 percentile band in yellow). Significance in left 2 panels is relative to pre-dose baseline.

Results

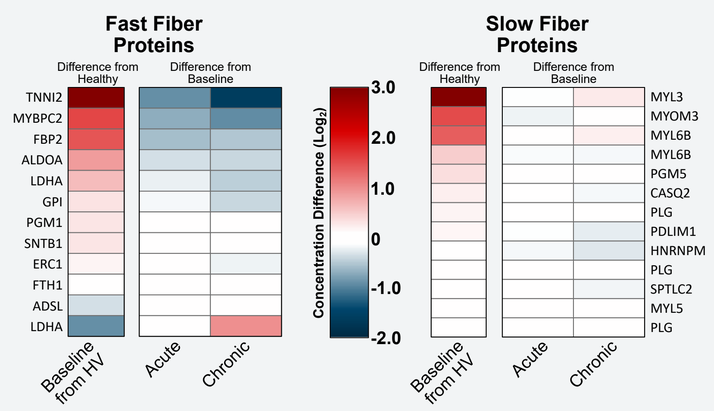
Acute Reductions in Muscle Injury Proteins are Maintained with Chronic Treatment



SOMAscan was used to analyze the effects of treatment on a set of proteins previously identified to correlate with contraction-induced skeletal muscle injury (3). Generally, these proteins, like CK and TNNI2, were decreased from pre-dose baseline by acute treatment and maintained at lower levels with chronic treatments.

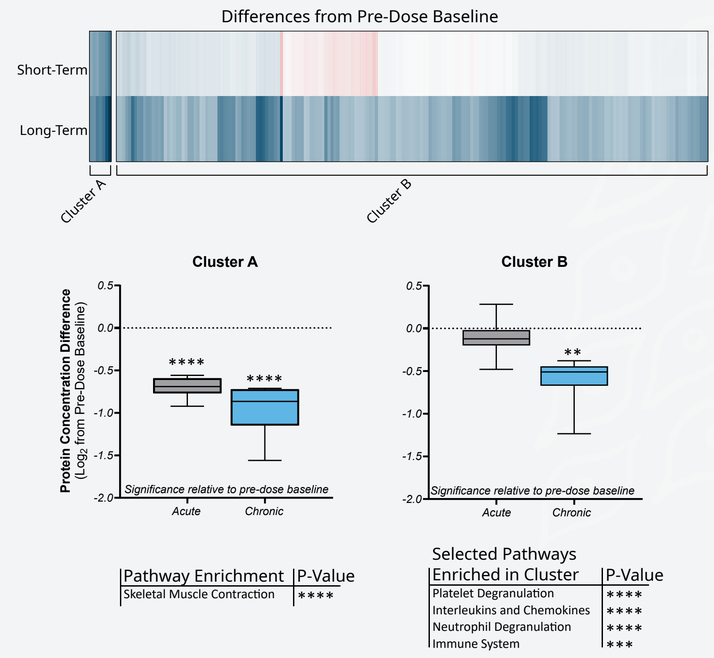
As a population, there was no difference in the response of muscle injury proteins between acute and chronic treatment, suggesting that muscle effects of treatment are maximized by 10 mg treatment for 1 - 2 months.

EDG-5506 is Selective for Fast Muscle Fibers



Proteins highly selective for fast Type IIa/IIx or slow Type I muscle fibers (identified from Ref 4) were generally elevated over healthy at pre-dose baseline. However, only proteins derived from fast fibers were significantly affected by EDG-5506 treatment, as indicated by change from baseline at both acute and chronic treatment timepoints.

Inflammatory Pathways are Affected by Chronic EDG-5506 Treatment



Pathway Enrichment	P-Value
Skeletal Muscle Contraction	****

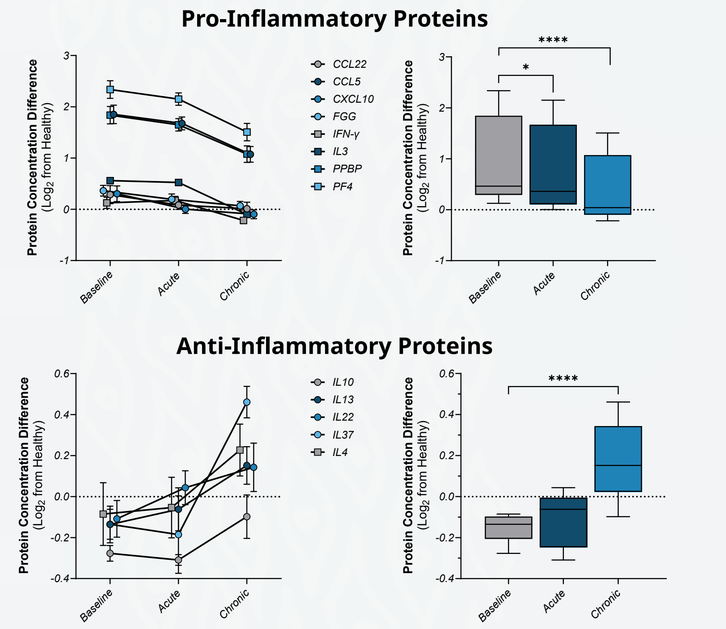
Selected Pathways

Enriched in Cluster	P-Value
Platelet Degranulation	****
Interleukins and Chemokines	****
Neutrophil Degranulation	****
Immune System	***

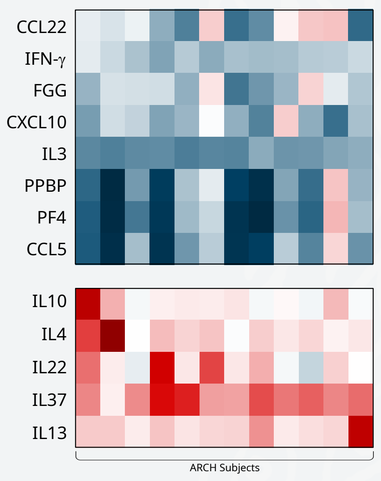
Proteins that are decreased by treatment exhibit two distinct clusters of changes. Cluster A is significantly decreased from pre-treatment baseline after both acute and chronic treatment and is characterized by several skeletal muscle proteins. Conversely, proteins in Cluster B only demonstrate responsiveness after longer periods of EDG-5506 treatments. These proteins primarily represent immune and inflammatory pathways.

Results

Favorable Shift in Inflammatory Biomarkers with Long-Term Treatment



Pro- and Anti-Inflammatory proteins identified through references (5) and (6)



Chronic EDG-5506 treatment resulted in a favorable shift in inflammatory biomarkers. Several pro-inflammatory cytokines and chemokines were significantly reduced after 6 - 12 months (top), while several anti-inflammatory interleukins were increased after long-term treatment (bottom). The observed protein concentration changes after 6 - 12 months were consistent across study participants (left).

Conclusions

CK, TNNI2, and a broader set of muscle injury proteins were elevated at pre-dose baseline and decreased after 1 - 2 months of treatment, remaining decreased with chronic treatment. Proteins from Type IIa/x fibers were reduced by EDG-5506 at both acute and chronic timepoints, while proteins from Type I fibers were not.

The proteomics of acute EDG-5506 treament were dominated by skeletal muscle proteins that reflect muscle damage. Additionally, chronic treatment exhibited a consistent shift in proteins associated with inflammation, wherein pro-inflammatory factors were reduced while anti-inflammatory cytokines were increased. Although this study varied both dose and duration, these proteins may be expected to require longer timespans to see significant change and may reflect trends towards normalization of muscle upon sustained reduction of muscle damage.

In summary, proteomic profiles of treatment with EDG-5506 showed a rapid and sustained decrease in markers of muscle injury with a longer-term change in the inflammatory biomarkers. Overall, the proteomic profile of EDG-5506 was shifted toward that of healthy individuals.

References

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Ackowledgments
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Disclaimer
EDG-5506 is an investigational drug that is not approved in any territory. The authors are employees or consultants for Edgewise Therapeutics and may hold stock and/or stock options.

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