OVERVIEW/ABSTRACT: Progressive muscle degeneration and fibro-fatty replacement in Duchenne muscular dystrophy (DMD) is caused by loss of dystrophin in striated muscles. As dystrophin loss also occurs in non-muscle tissues, consequences of DMD include osteoporosis, increased adiposity, and neural deficits leading to challenges in motor control and cognitive development. As a surrogate for exercise, low magnitude mechanical signals, delivered using low intensity vibration (LIV), have been demonstrated as anabolic to bone and to promote neuromuscular dynamics and muscle strength, muscle hypertrophy and muscle stem cell activity. In the clinic, LIV has been shown to promote bone density in children with disabling conditions, including cerebral palsy, is anabolic to bone and muscle in young women with osteoporosis, and augments bone accretion in child cancer survivors.

In the work proposed here, we will use a DMD mouse model to explore the potential of stimulating mechanosensitive elements of cells within distinct tissues as a preclinical step in validating a non-pharmacologic, non-invasive strategy to attenuate DMD progression across multiple organ systems. Using a DMD mouse model (*mdx^{4cv}*), this work will test our general hypothesis: *The decline of physiologic systems caused by DMD can be slowed by daily bouts of LIV*. This hypothesis will be explored through three sub-hypotheses, examining the ability of brief daily bouts of LIV to mitigate deterioration of affected organ systems, and represent a key step in translating this to the clinic. Mice will be subjected to LIV (*0.4g @ 30Hz for 1h twice daily*), and outcomes will be compared to *mdx^{4cv}* and WT controls at short and longer intervals (ten and thirty days, n=24 per group per time point).

SPECIFIC AIMS: ***Hypothesis/Aim 1: Daily bouts of LIV will foster muscle regeneration in DMD via enhancement of satellite cell functions.*** LIV stimulates muscle hypertrophy in mouse and human and prevents satellite cell depletion under pathological conditions. *Preliminary* work from our lab shows that 3days of LIV promotes myogenesis *in vitro* in myoblasts derived from DMD patients, achieved by enhancing cell proliferation and differentiation. **Specific Aim 1** is designed to determine if LIV treatment of *mdx^{4cv}* mice, *in vivo,* will foster muscle regeneration and protect against DMD muscle wasting.

Hypothesis/Aim 2: Daily bouts of LIV will inhibit osteopenia and adiposity in DMD. A pilot study in boys with DMD showed that trabecular bone density in the proximal and distal tibia increased with LIV (*0.4g @ 30Hz,10min/day*). Fat mass in the leg increased 33% in Placebo, contrasting with 20% in LIV subjects. Together, these data suggest that LIV can decrease bone resorption and protect against increased adiposity anticipated in DMD. **Specific Aim 2** is designed to determine if LIV treatment of *mdx^{4cv}* mice, *in vivo,* will promote bone anabolism, suppress osteoporosis, and inhibit marrow, subcutaneous and visceral adiposity.

Hypothesis/Aim 3: Daily bouts of LIV will attenuate brain white matter abnormalities in DMD. Our team was the first to identify hypomyelination in *mdx* mice, paralleling findings in DMD patients. In *preliminary* work, we exposed mouse oligodendrocyte progenitor cells (OPC; the cells responsible for myelination) to LIV (*0.7g @ 30Hz, 1hour twice/day*). At 3d, there were an increased number of oligodendrocyte lineage cells, indicating a greater capacity for myelination. **Specific Aim 3** is designed to determine if LIV can stimulate, *in vivo,* oligodendrocyte proliferation and myelin production in *mdx^{4cv}* mice, and – using behavioral assays – show salutary outcomes in brain function.

The Stony Brook University DMD working group is an interdisciplinary team with expertise with the *mdx^{4cv}* mouse model, LIV protocols and trans-organ outcome assays as outlined above. The translational experiments outlined here will provide proof of principle of protective outcomes of LIV in muscle, bone and brain, and if successful, this novel and non-invasive treatment can be rapidly deployed to treat DMD boys, *potentially improving both their life expectancy and their quality of life*.