Promising new therapy spares muscle loss in Duchenne muscular dystrophy

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The peptide the new drug is based on was originally found in the venom produced by the type of tarantula that Sachs is holding here. Credit: University at Buffalo

A promising therapy for Duchenne muscular dystrophy (DMD) developed by University at Buffalo researchers is moving closer to use in

humans.

Published in July in Neuromuscular Disorders, the new UB research demonstrates that the novel drug significantly reduced loss of muscle mass and susceptibility to muscle damage from repeated stimulation in an advanced animal model of DMD.

DMD, which occurs only in boys, results from a genetic defect in the structural protein dystrophin, which provides mechanical support to cell membranes. That loss of support transfers stress to mechanosensitive ion channels, causing an abnormal influx of calcium leading to atrophy, according to the researchers.

Boys with DMD show signs of physical impairment as young as three years old. They are often wheelchair-bound by adolescence and most die by their 20s or 30s, many of cardiac or respiratory failure

The novel therapy developed at UB is based on studies of a peptide found originally in tarantula venom. The peptide, called GsMTx4 or AT-300, is the first drug that selectively inhibits mechanosensitive ion channels without disturbing the neuromuscular system.

"GsMTx4 represents an 'out-of-the-box' therapy to slow disease progression in DMD," said Frederick Sachs, Ph.D., professor of physiology and biophysics in the Jacobs School of Medicine and Biomedical Sciences at UB and co-author on the paper with corresponding author Thomas Suchyna, Ph.D., research assistant professor in the same department.

Suchyna noted that they showed in a previous study that in addition to protecting skeletal muscle, GsMTx4 is protective against cardiomyopathy, a common cause of mortality in DMD patients.

GsMTx4 was licensed by UB to the Buffalo-based biotech firm, Tonus Therapeutics, which then sublicensed it to Akashi Therapeutics for further development. (Tonus Therapeutics was co-founded by Sachs and both he and Suchyna are officers in the company.) It is on track to begin detailed toxicity testing for an investigatory new drug application to the U.S. Food and Drug Administration (FDA) by the spring of 2019. If successful, this will be followed by Phase I/II studies in humans by 2020. Now made by chemical synthesis, GsMTx4 is considered an "orphan drug," a designation that the FDA awards to promising therapies for rare diseases.

"Remarkably, we saw no side effects in the mice in the current study, nor in ferrets in a previous study on cardiac disease, despite the fact that mechanosensitive piezo channels—the drug's target—are ubiquitous in living organisms," said Sachs. The drug also has a long half-life, so that subcutaneous injection may be needed only once a week.

The researchers conclude that GsMTx4 may also complement other therapies, such as anti-inflammatory agents and gene replacement strategies that are being prescribed or studied in DMD.

Provided by University at Buffalo