New drug molecules hold promise for treating fatal child disease

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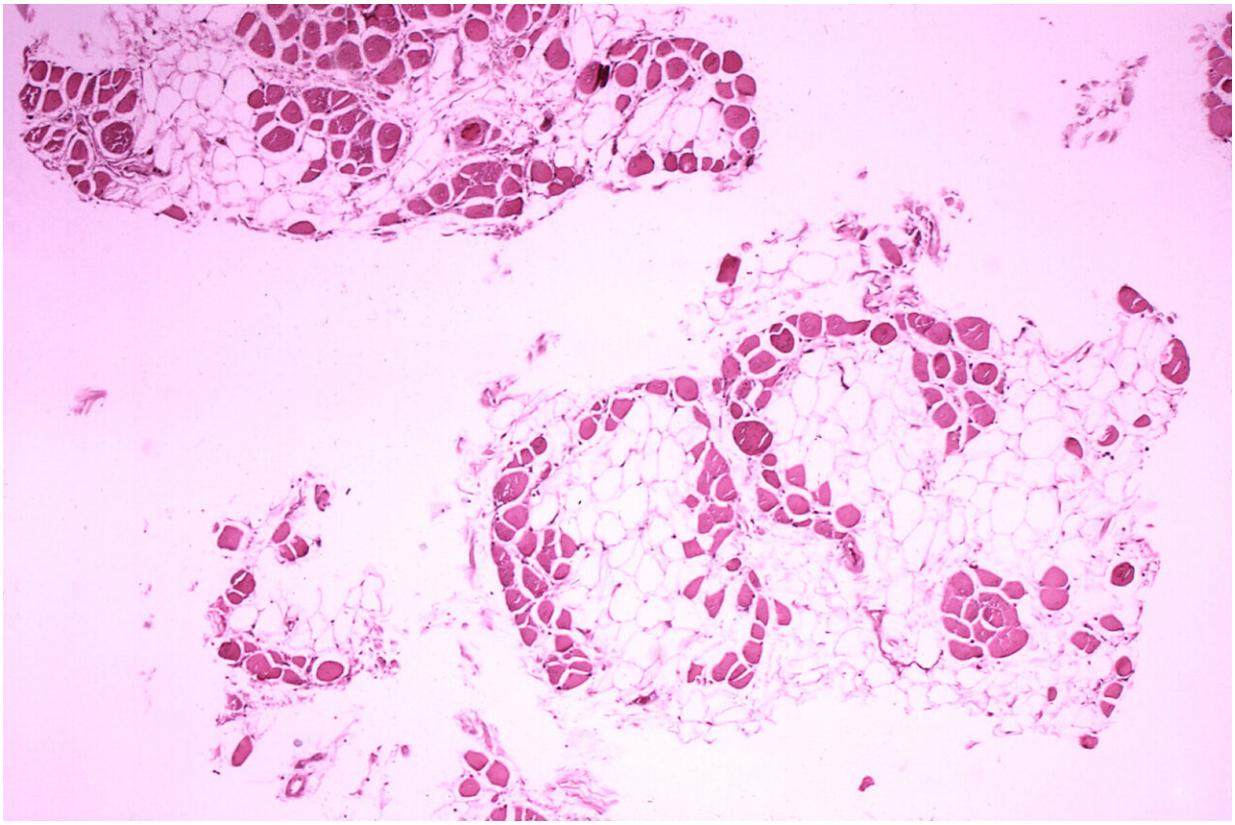

Histopathology of gastrocnemius muscle from patient who died of pseudohypertrophic muscular dystrophy, Duchenne type. Cross section of muscle shows extensive replacement of muscle fibers by adipose cells. Credit: Wikimedia Commons/Public Domain

Scientists have identified a way to "rescue" muscle cells that have

genetically mutated, paving the way to a possible new treatment for rare childhood illness such as Duchenne Muscular Dystrophy (DMD).

The study, led by the Universities of Exeter and Nottingham, is published in the *Proceedings of the National Academies of Sciences*. The research used novel drugs being developed at the University of Exeter, which "metabolically reprogram" the cellular energy production centers in muscle cells, by providing them with a fuel source to generate metabolic energy.

DMD is a genetic condition caused by a mutation in a gene called dystrophin which results in progressive irreversible muscular degeneration and weakening. Its symptoms include muscle atrophy leading to a loss of the ability to walk in children for which there is no known cure. Currently, the condition is treated with steroids, such as prednisone, but they can stop working and side-effects are common. The research, funded by the Medical Research Council (UK) and United Mitochondrial Disease Foundation in the U.S., was led by Professors Nate Szewczyk in Nottingham and Matt Whiteman in Exeter focussed on future alternative ways to improve muscle performance when the dystrophin gene is missing or is defective.

The research team comprising of scientists from Australia, U.S., The Netherlands and Germany as well as the UK first used microscopic worms (C. elegans) and then mice with specific genetic mutations affecting muscle strength, that match mutations that cause DMD in humans. The team found that these animals had defects in gait, movement, and muscle strength, and had marked defects in the structure their muscle mitochondria, the tiny organelle responsible for cellular energy regulation.

The animals also had lower levels metabolic enzymes used for the generation of the gasotransmitter hydrogen sulfide in their muscles, as

well as lower levels of the gas itself. Treating these animals with a compound called NaGYY, which replaced the lost hydrogen sulfide, partially reversed some of the muscle and mitochondrial defects in the same way the standard of care drug prednisone did. However, specifically targeting mitochondria with hydrogen sulfide using the compound AP39, exhibited the same effects but at 3.7 million fold lower dose.

Professor Nate Szewczyk of the Ohio Musculoskeletal & Neurological Institute, U.S. commented "Steroids are very effective and safe drugs but their use over a long period of time causes effects wear off and they can have some very unpleasant and life-changing side effects. The compounds we've used in our study are not steroids and they work in a very similar way to these drugs give the same improvement in muscle function, but at a much, much lower dose and because they are not steroids, they are unlikely to produce steroid-induced side effects such as weaker muscle and decreased ability to fight infection".

Ph.D. student Rebecca Ellwood added "Life first emerged on earth in a sulfide rich environment and thrived for billions of years before it was replaced by the oxygen we have today. Our cells and our mitochondria have maintained the ability to both make and use very small amounts of sulfide to keep healthy. Our study now shows that in DMD models, this metabolic pathway is defective, offering a potential for therapeutic intervention to correct this defect".

Professor Matt Whiteman, of the University of Exeter Medical School, who developed the tool compounds used in this study, and next generation molecules for commercialisation, said,: "We're really excited that our findings show that a deficit in muscle sulfide may contribute to the development of Duchenne Muscular Dystrophy. Rectifying this deficit may lead to new treatment approaches for this and other currently incurable diseases, without relying on potentially harmful steroids. At

Exeter we are developing more advanced approaches to target muscle mitochondria, and we aim to spin-out a new biotech company called 'MitoRx Therapeutics' to develop these newer approaches for clinical use during 2021."

Dr. Kate Adcock, Director of Research and Innovation at the charity Muscular Dystrophy UK, said: "We welcome research that increases our understanding of molecular pathways that could both contribute to the symptoms of Duchenne muscular dystrophy and offer potential new therapeutic targets. Although a long way from patient studies, this research has shown interesting results in animal models of Duchenne muscular dystrophy and it is encouraging to see these early stage studies for such a complex, rare condition."

More information: Rebecca A. Ellwood el al., "Mitochondrial hydrogen sulfide supplementation improves health in the C. elegans Duchenne muscular dystrophy model," *PNAS* (2021). www.pnas.org/cgi/doi/10.1073/pnas.2018342118

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