Substituting the next-best protein

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Dr. Jasmin helps Max Sedmihradsky into his lab coat during a stop on Max's Big Ride . Credit: Erin McCracken

When an actor is unable to perform in the theatre, an understudy—ideally one with some practice in the role—can take her place on stage. A study from Dr. Bernard Jasmin's laboratory at the University of Ottawa and published today in *Nature Communications*

shows that the same is true of proteins. Its results point the way toward novel therapies for Duchenne muscular dystrophy.

Children born with Duchenne muscular dystrophy (DMD) have a mutation in the X-chromosome gene that would normally code for dystrophin, a protein that provides structural integrity to skeletal muscles. The loss of this protein causes severe symptoms, including deteriorating muscle strength beginning around the age of four. The average life expectancy of a child with this condition currently stands at 26 years.

While there is no cure, a promising area of research has developed around the protein utrophin, which is ~ 80% identical to dystrophin and even takes its place early during muscle development. Utrophin is produced from a gene on Chromosome 6 and can be expected to be intact in a DMD patient.

"Utrophin-based therapy is actually applicable to all DMD patients, regardless of their dystrophin mutation" says Dr. Christine Péladeau, the lead post-doctoral fellow on this project. "And this is not something we see with most other therapeutic approaches."

This study looked at a specific "IRES-dependent translation" pathway, which induces a cell's ribosome to trigger utrophin's production. The team tested 262 FDA-approved drugs to see which ones could most effectively activate IRES-mediated translation to boost utrophin expression in muscle. Two drugs that are currently on the market stood out as the strongest contenders—the beta receptor blocker Betaxolol and the cholesterol-lowering drug Pravastatin. When administered in a mouse model of DMD, these drugs each promoted increases in muscle strength close to that of healthy mice.

A number of advantages support targeting utrophin as a DMD therapy

above more difficult approaches including dystrophin gene replacement using viral vectors. The repurposing of FDA-approved drugs can also speed the clinical trial process. The doses required are expected to be quite low, improving the chances of low toxicity.

What's more, utrophin seems to be involved in the body's own efforts to fight the disease.

"There is a tendency for DMD muscles to try to naturally upregulate the levels of utrophin, knowing that it doesn't have dystrophin," says Dr. Bernard Jasmin, who leads the lab where the work was conducted. "Obviously it's not enough, but in the absence of this endogenous upregulation, DMD would be a lot worse."

Further stimulation of that natural response via the identified pathway works with the body to strengthen muscles, without the danger of an adverse immune response to the therapy. It also demonstrates the promise of using IRES-mediated translation for therapeutic purposes. It serves as a proof of principle to bolster the idea that this method could be used in other diseases like cancer and neurodegenerative diseases.

More information: Christine Péladeau et al, Identification of therapeutics that target eEF1A2 and upregulate utrophin A translation in dystrophic muscles, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15971-w

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