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Drugging the undruggable: A treatment path for muscular dystrophy

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Researchers at Yale have identified a possible treatment for Duchenne muscular dystrophy (DMD), a rare genetic disease for which there is currently no cure or treatment, by targeting an enzyme that had been

considered 'undruggable.' The finding appears in the Aug. 25 edition of *Science Signaling*.

DMD is the most common form of muscular dystrophy, a disease that leads to progressive weakness and eventual loss of the skeletal and heart muscles. It occurs in 16 of 100,000 male births in the U.S. People with the disease exhibit clumsiness and weakness in early childhood and typically need wheelchairs by the time they reach their teens. The average life expectancy is 26.

While earlier research had revealed the crucial role played by an enzyme called MKP5 in the development of DMD, making it a promising target for possible treatment, scientists for decades had been unable to disrupt this family of enzymes, known as protein tyrosine phosphatases, at the enzymes' "active" site where chemical reactions occur.

In the new study, Anton Bennett, the Dorys McConnell Duberg Professor of Pharmacology and professor of comparative medicine, and his team screened over 162,000 compounds. They identified one molecular compound that blocked the enzyme's activity by binding to a previously undiscovered allosteric site—a spot near the enzyme's active site.

"There have been many attempts to design inhibitors for this family of enzymes, but those compounds have failed to produce the right properties," Bennett said. "Until now, the family of enzymes has been considered 'undruggable.'"

By targeting the allosteric site of MKP5 instead, he said, "We discovered an excellent starting point for drug development that circumvented the earlier problems."

The researchers tested their compound in muscle cells and found that it

successfully inhibited MKP5 activity, suggesting a promising new therapeutic strategy for treating DMD.

The research was supported by a National Institutes of Health grant through the National Institute of Arthritis and Musculoskeletal and Skin Diseases, as well as by the Blavatnik Fund for Innovation at Yale, which annually presents awards to support the most promising life science discoveries from Yale faculty.

Bennett said that the Blavatnik funding, which is administered by the Yale Office of Cooperative Research, was critical in moving the research forward. "It resulted in a license with a major pharmaceutical company," he said, "and we hope they will rapidly move forward with the development of the new treatment."

The finding has implications well beyond muscular dystrophy, he added. The researchers have demonstrated that the MKP5 enzyme is broadly implicated in fibrosis, or the buildup of scar tissue, a condition that contributes to nearly one-third of natural deaths worldwide.

"Fibrosis is involved in the end-stage death of many tissues, including liver, lung, and muscle," Bennett said. "We believe this enzyme could be a target more broadly for fibrotic tissue disease."

More information: Zachary T. K. Gannam et al. An allosteric site on MKP5 reveals a strategy for small-molecule inhibition, *Science Signaling* (2020). DOI: 10.1126/scisignal.aba3043

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