Research reveals new treatment strategy for propionic acidemia

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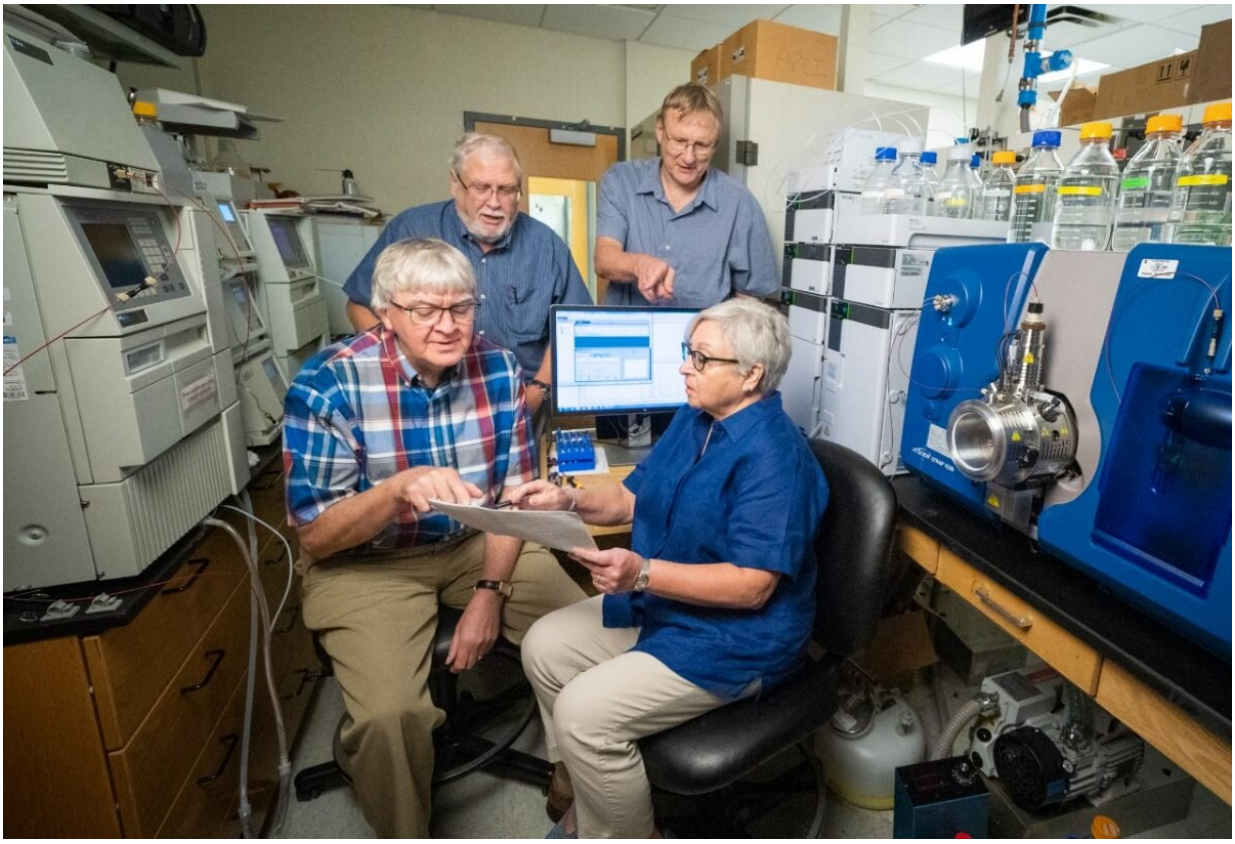

From bottom left, clockwise: Paper author Stephen White, DPhil, St. Jude Department of Structural Biology and St. Jude Graduate School of Biomedical Sciences; paper author Richard Lee, Ph.D., St. Jude Department of Chemical Biology and Therapeutics; corresponding author Charles Rock, Ph.D., St. Jude Infectious Diseases; and senior author Suzanne Jackowski, Ph.D., formerly of St. Jude Infectious Diseases, have shown that a class of drugs they pioneered has the potential to treat a rare metabolic disorder called propionic acidemia. (Picture taken before the pandemic). Credit: St. Jude Children's Research Hospital

Scientists at St. Jude Children's Research Hospital have shown that a class of drugs they pioneered has the potential to treat a rare metabolic disorder called propionic acidemia. The findings were published today in *Science Translational Medicine*.

Propionic acidemia is caused by mutations in an enzyme called propionyl-CoA carboxylase. CoA is a helper molecule essential for energy metabolism. Propionic acidemia is typically managed by diet. The drugs, called pantazines, would be the first targeted propionic acidemia treatment that is based on managing CoA levels by modulation of pantothenate kinases.

"This work has been some of the most rewarding of my career and is a testament to following the science where it leads you," said senior author Suzanne Jackowski, Ph.D., formerly of the St. Jude Department of Infectious Diseases. "You always hope as a researcher that something you do will ultimately make a difference in peoples' lives."

Focusing on what drives the disease

The research pinpoints mitochondrial dysfunctions as a key driver of propionic acidemia. Clinicians monitor metabolites circulating in blood to provide insight into disease severity. This study increases our understanding of the mechanisms that result in changes in these metabolites and suggest that some arise from cells trying to overcome CoA depletion.

"Historically, people working on this disease have focused on an effect, rather than the cause," said corresponding author Charles Rock, Ph.D., St. Jude Department of Infectious Diseases. "We know now that some aspects of propionic acidemia occur because the mitochondria stop

functioning when CoA levels drop."

"Just like an engine needs oil to run, the mitochondria need CoA to work properly," Rock adds. "When the oil in your engine gets too low it will seize up. When CoA levels fall, the mitochondria do not function."

Creating a targeted drug

This work builds on research from the same group of St. Jude scientists who discovered potential treatments for another rare disease called pantothenate kinase-associated neurodegeneration (PKAN). PKAN and propionic acidemia are both metabolic disorders in which CoA metabolism plays a central role. There are several others.

While working on PKAN, researchers at St. Jude crafted a class of drugs called pantazines, based on a compound first identified through a screen of more than 500,000 small molecules.

"Developing molecules to therapeutically target a specific driver of disease is a skillful process once screening hits are identified, where many competing factors have to be balanced," said paper author Richard Lee, Ph.D., St. Jude Department of Chemical Biology and Therapeutics. "We carefully optimized pantazines to increase cellular CoA levels, cross the blood-brain barrier, be effective when given as a pill and limit the potential for side effects."

Treating different disorders

Pantazines are small-molecule activators that have the potential to treat multiple inborn genetic diseases of metabolism. Through their work on propionic acidemia, the researchers mapped out the metabolic network, showing how pantazines increase CoA and thus increase mitochondrial

function and health of the cells.

"It is remarkable that we have been able to develop small-molecule drugs that target one key metabolic enzyme but may be able to treat multiple loss of function genetic diseases," said paper author Stephen White, DPhil, St. Jude Department of Structural Biology and St. Jude Graduate School of Biomedical Sciences president and dean. "This underscores how the collaborative team approach to research at St. Jude—which in this case involves groups in separate departments with key expertise in biochemistry, animal models, medicinal chemistry and structural biology—can successfully tackle such formidable but important projects."

St. Jude patented pantazines and their use for treatment of CoA disorders. The hospital licensed the compounds to CoA Therapeutics, Inc., a BridgeBio company. The company is currently investigating their compound (BBP-671) in a Phase 1 study.

More information: Chitra Subramanian et al, Pantothenate kinase activation relieves coenzyme A sequestration and improves mitochondrial function in mice with propionic acidemia, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abf5965

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