Novel drug makes mice skinny even on sugary, fatty diet

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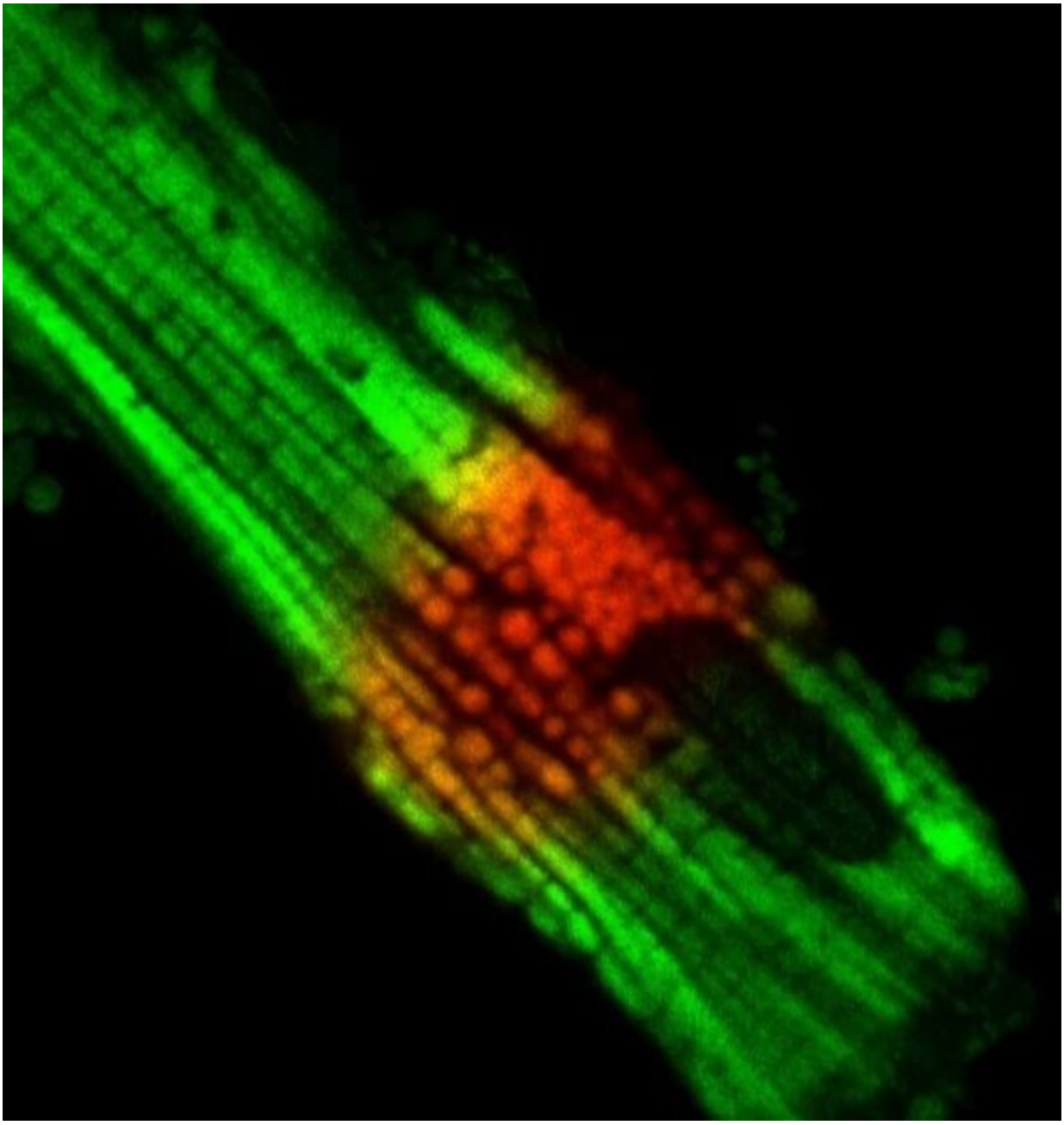


Mitochondria in a single heart cell. Mitochondria highlighted in red were exposed to ultraviolet light. Credit: National Heart, Lung and Blood Institute, National Institutes of Health

Researchers from The University of Texas Health Science Center at San Antonio (UT Health San Antonio) have developed a small-molecule drug that prevents weight gain and adverse liver changes in mice fed a high-sugar, high-fat Western diet throughout life.

"When we give this drug to the mice for a short time, they start losing weight. They all become slim," said Madesh Muniswamy, Ph.D., professor of medicine in the health science center's Joe R. and Teresa Lozano Long School of Medicine.

Findings by the collaborators, also from the University of Pennsylvania and Cornell University, were published Feb. 27 in *Cell Reports.* Muniswamy, director of the Center for Mitochondrial Medicine at UT Health San Antonio, is the senior author.

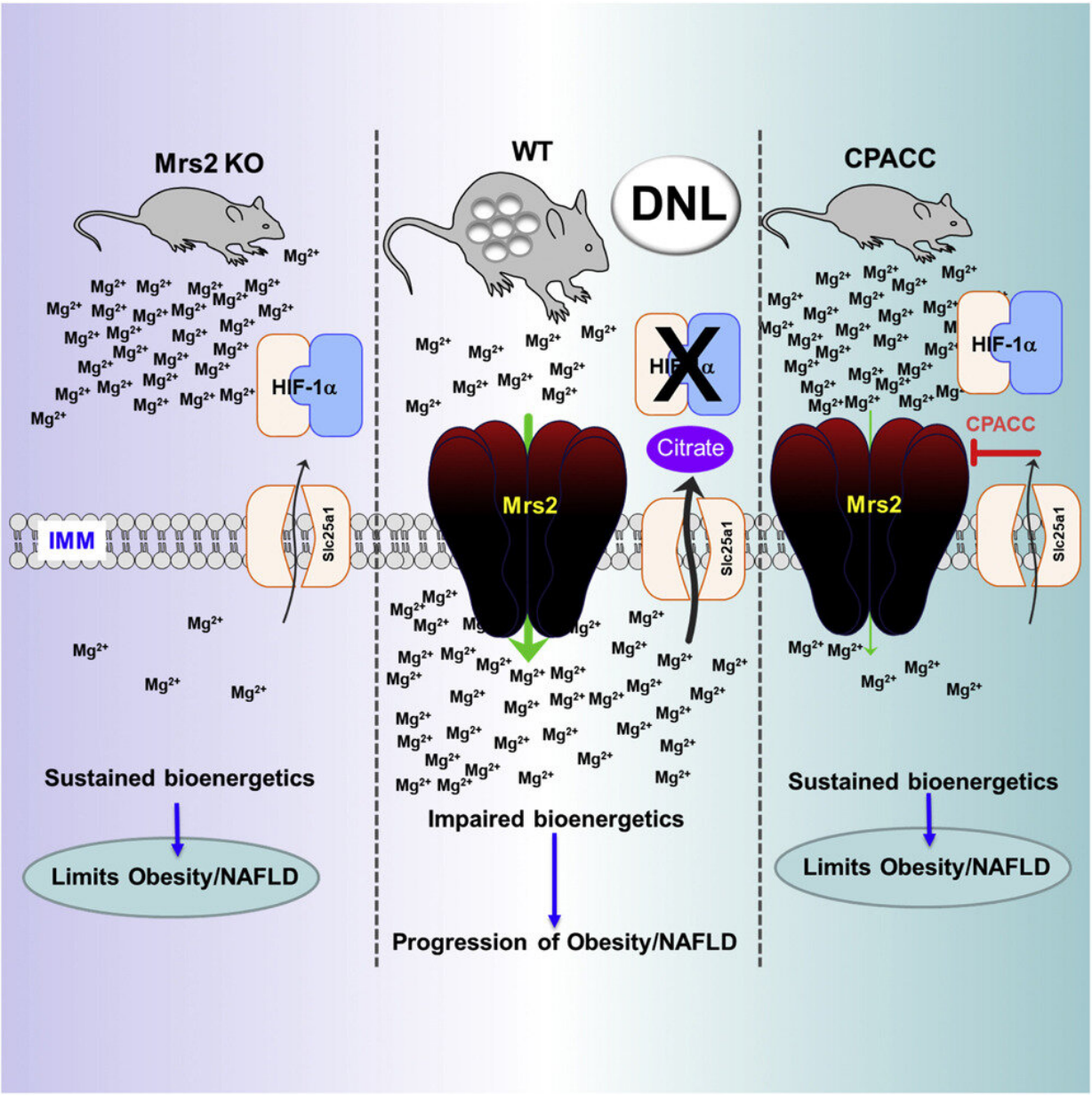
The research team discovered the drug by first exploring how magnesium impacts metabolism, which is the production and consumption of energy in cells. This energy, called ATP, fuels the body's processes.

Magnesium plays many key roles in good health, including regulating blood sugar and blood pressure and building bones. But the researchers found that too much magnesium slows energy production in mitochondria, which are cells' power plants.

"It puts the brake on, it just slows down," said co-lead author Travis R. Madaris, doctoral student in the Muniswamy laboratory at UT Health San Antonio.

Deleting MRS2, a gene that promotes magnesium transport into the mitochondria, resulted in more efficient metabolism of sugar and fat in the power plants. The result: skinny, healthy mice.

Liver and adipose (fat) tissues in the rodents showed no evidence of fatty liver disease, a complication related to poor diet, obesity and type 2 diabetes.



Graphical abstract. Credit: *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112155

Small-molecule agent

The drug, which the researchers call CPACC, accomplishes the same

thing. It restricts the amount of magnesium transfer into the power plants. In experiments, the result was again: skinny, healthy mice. UT Health San Antonio has filed a patent application on the drug.

The mice served as a model system of long-term dietary stress precipitated by the calorie-rich, sugary and fatty Western diet. The familiar results of this stress are obesity, type 2 diabetes and cardiovascular complications.

"Lowering the mitochondrial magnesium mitigated the adverse effects of prolonged dietary stress," said co-lead author Manigandan Venkatesan, Ph.D., postdoctoral fellow in the Muniswamy lab.

Joseph A. Baur, Ph.D., of the University of Pennsylvania and Justin J. Wilson, Ph.D., of Cornell are among the collaborators. "We came up with the small molecule and Justin synthesized it," Madaris said.

"These findings are the result of several years of work," Muniswamy said. "A drug that can reduce the risk of cardiometabolic diseases such as heart attack and stroke, and also reduce the incidence of liver cancer, which can follow fatty liver disease, will make a huge impact. We will continue its development."

More information: Travis R. Madaris et al, Limiting Mrs2-dependent mitochondrial Mg2+ uptake induces metabolic programming in prolonged dietary stress, *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112155

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