Liver-targeting drug delivered via nanogel carrier reverses obesity, lowers cholesterol in mice

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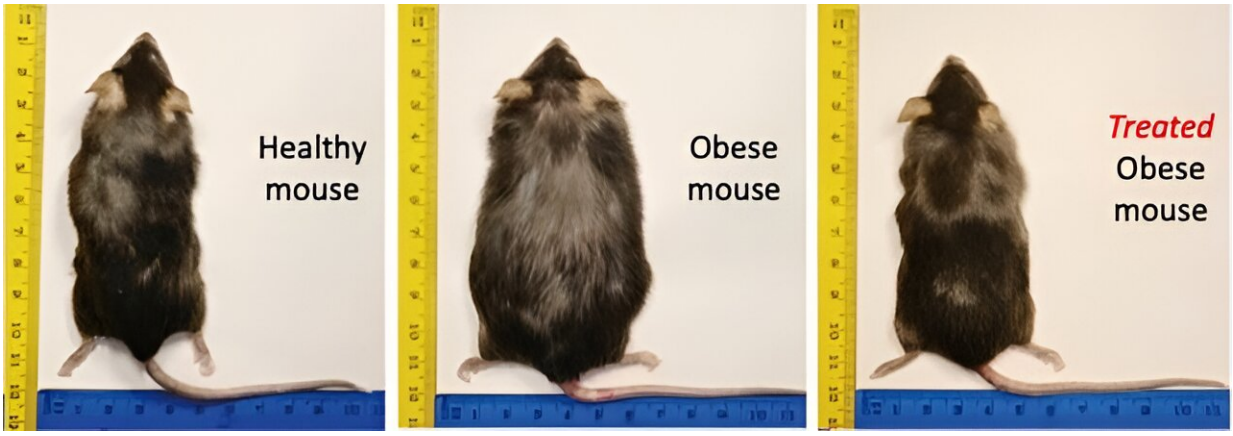

Diet-induced obesity was reversed in mice after they were given a thyromimetic drug delivered directly to the liver via a nanogel-based carrier. Credit: Thayumanavan Lab, UMass Amherst

A University of Massachusetts Amherst biomedical engineer has used a nanogel-based carrier designed in his lab to deliver a drug exclusively to the liver of obese mice, effectively reversing their diet-induced disease.

"The treated mice completely lost their gained weight, and we did not see any untoward side effects," says S. Thai Thayumanavan, distinguished professor of chemistry and biomedical engineering.

"Considering 100 million Americans have obesity and related cardiometabolic disorders, we became pretty excited about this work."

Efforts to translate these findings to humans are being pursued by a start-up company Cyta Therapeutics, which was founded at the UMass Institute for Applied Life Sciences (IALS) based on the nanogel technologies from the Thayumanavan lab. In late July, Cyta Therapeutics won the Judges' Choice Best Startup at the 16th annual Massachusetts Life Sciences Innovation (MALSI) Day in Boston.

"There is a significant amount of development work to be conducted between mice and humans," Thayumanavan says, "but we are hoping it will eventually become a drug."

Senior author Thayumanavan, director of the Center for Bioactive Delivery at IALS, explains his team's findings in a paper published Tuesday, Aug. 29, in the *PNAS Nexus*. Ruiling Wu, doing research for her Ph.D. in chemistry in Thayumanavan's lab and at the Center for Bioactive Delivery, is the paper's lead author. Wu recently graduated and now works for a pharmaceutical company in Boston.

One of the center's primary goals is figuring out how to get the right drug to the right place in the body by creating novel delivery platforms for small and large molecules.

Thyromimetics, or drugs that mimic synthetic thyroid hormone, have been considered as a potential way to tackle the problem of obesity, type 2 diabetes, high cholesterol, metabolic dysfunction-associated steatohepatitis (MASH) and other metabolic conditions. Targeted therapy is key, however. Thayumanavan and his team looked at one such thyromimetic.

"We realized we needed to deliver this drug selectively to the liver

because if it goes to other places, it could cause complications," he says. In addition to side effects, taking the drug systemically was expected to dilute its effectiveness, which was confirmed in the study.

Thayumanavan and team fed a group of mice a high-fat, high-sugar, high-cholesterol diet for 10 weeks, doubling their weight. A control group of mice were fed a healthy diet.

"We came up with a very simple approach, using our unique invention—nanogels that we can direct selectively to different targets, which we call IntelliGels," Thayumanavan says. "They were custom-designed for hepatocyte delivery in the liver."

The obese mice were given the drug daily, packaged inside the nanogel and delivered to the mice via intraperitoneal (IP) injection.

Once the nanogel carrier is inside the hepatocyte cells, glutathione in the cells breaks down bonds in the nanogel, releasing the drug. The drug then activates thyroid hormone beta receptor, leading to systemic lipid lowering, increased bile acid synthesis and fat oxidation.

After five weeks of treatment, the mice returned to a normal weight —even as their high-fat diet continued. The mice also saw their cholesterol levels drop and their liver inflammation resolve.

"We really wanted to find out the factors that got affected," Thayumanavan says. "We found that we are activating the reverse cholesterol transport pathway, which lowering of cholesterol. We believe that activation of fat oxidation and an increase in metabolic rate are causing the loss in weight, but more work needs to be done to prove that point."

Now that the mechanism is better understood, the paper notes, "the drug-

encapsulated nanogels open up the possibility for nanoparticle-mediated pharmaceutical strategies for other liver-based diseases."

More information: Ruiling Wu et al, Conferring liver selectivity to a thyromimetic using a novel nanoparticle increases therapeutic efficacy in a diet-induced obesity animal model, *PNAS Nexus* (2023). DOI: 10.1093/pnasnexus/pgad252

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