

# Treatment for obesity and obesity-related diseases

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## Technology description

### Summary

The ongoing obesity epidemic in the United States and other developed nations poses an outsized risk to human health. Obesity is associated with cancer, cardiovascular disease, Type 2 Diabetes (T2D), non-alcoholic fatty-liver disease (NAFLD) and a host of other adverse health outcomes. Current treatments for obesity and related diseases are limited in both availability and efficacy. This technology is a class of Notch signaling inhibitors that target one of the most important signaling pathways related to hepatic insulin resistance and lipogenesis, and are therefore a potential therapeutic for the treatment of obesity-induced metabolic disease, including T2D and NAFLD.

## **Notch1 decoy antagonists inhibit Notch1 signaling and protect against obesity-related disease**

Increased Notch activity in obesity promotes insulin resistance by increasing glucose production in the liver, which raises blood glucose. In addition, Notch activity also leads to increased synthesis of fat in the liver, causing increased hepatic fat content. This technology uses Notch1 receptor decoys, encoding just the extracellular domain of the Notch1 receptor. The decoys prevent normal Notch activation by causing Notch ligands to bind it in place of the native receptor. In addition to its importance in metabolic disorders, Notch1 signaling also plays a crucial role in tumor growth, and there are currently Notch1 inhibitors that are in the advanced stages of development as a treatment for cancer, proving that Notch signaling is therapeutically accessible.

This technology has been tested in a murine model, and has been demonstrated to reduce both serum glucose and insulin resistance in mice fed a high-fat diet. In addition, Notch1 decoys protected mice from obesity-induced excess hepatic fat. Ongoing in vitro and in vivo studies are evaluating different Notch1 decoys for efficacy as a treatment method for both obesity-induced T2D and NAFLD.

## Publications

Pajvani UB, Shawber CJ, Samuel VT, Birkenfeld AL, Shulman GI, Kitajewski J, Accili D. "Inhibition of Notch signaling ameliorates insulin resistance in a FoxO1-dependent manner." *Nat Med.* 2011 Jul 31;17(8):961-7.

Pajvani UB, Qiang L, Kangsamaksin T, Kitajewski J, Ginsberg HN, Accili D. "Inhibition of Notch uncouples Akt activation from hepatic lipid accumulation by decreasing mTorc1 stability." *Nat Med.* 2013 Aug;19(8):1054-60.

## Application area

Treatment for obesity-related diseases

Treatment or preventative therapy for diabetes

Treatment or preventative therapy for non-alcoholic fatty liver disease (NAFLD)

Treatment or preventative therapy for cancer

Preventative therapy for cardiovascular disease

Combination treatment with other therapies for diabetes, NAFLD, and/or obesity

## Advantages

May be effective alone or as part of combination therapy

Will not require surgery or other invasive procedures

Potentially protective against a wide-range of diseases

Targets a key signaling pathway in metabolism and insulin production

Institution

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