NEWS maker
Zafgen

Zafgen hopes that small-molecule targeting of methionine aminopeptidase 2 (MetAP2), an enzyme originally associated with tumor angiogenesis, will lead to a new anti-obesity drug.


Zafgen

Thomas Hughes, Zafgen's President and CEO

Cambridge, Massachusetts–based startup Zafgen is a company in single-minded pursuit of finding an effective inhibitor of MetAP2, an intracellular metalloprotease involved in angiogenesis and more recently associated with cell proliferation. So far, phase 1b results of the company's lead candidate, ZGN-433, have been promising, with patients shedding pounds and showing improved marker profiles for cardiovascular risk. But the story of ZGN-433 springs from work in the field of angiogenesis.

About ten years previously, Judah Folkman's laboratory at Harvard Medical School in Cambridge, Massachusetts, was performing routine screens for tissues in the body that respond to anti-angiogenic factors. Surprisingly, they found that adipose tissue was extremely sensitive, possessing the vasculature, hypoxic environment, pro-angiogenic compounds and remodeling capabilities very reminiscent of tumors. In that study, published in 2002, a few anti-angiogenic compounds led to mild weight loss in an obese mouse model. One of them, TNP-470, a synthetic analog of the antibiotic fumagillin that irreversibly inactivates the enzyme MetAP2, was ahead of the pack in its ability to provoke weight loss.

Zafgen was founded in 2005 to exploit Folkman's TNP-470 findings, but anti-angiogenesis turned out to be a red herring for obesity. When James Vath, Zafgen's first employee and now head of discovery and development, screened a wider panel of anti-angiogenic factors, he found no affect on weight at all, except with inhibitors against MetAP2, which caused rampant weight loss in mice and minimal toxicity. The company zeroed in on this target, securing $2 million in series A financing in 2005, and $30 million in series B funding over the past four years.

When Tom Hughes was enticed away from a two-decade executive career at Basel-based Novartis to become Zafgen's first CEO in 2008, his plan was to get into human trials as quickly as possible. The most potent and effective MetAP2 inhibitor available for in-licensing, ZGN-433 (beloranib hemioxalate), came with two fringe benefits: pharmaceutical-grade production capacity and existing data from two completed human cancer trials. These trials were run by the license-holder, Seoul-based Chong Kun Dang Pharmaceutical. The cancer patients who happened to be obese had lost weight during the trial, whereas those who were already lean showed no change. What's more, Chong Kun Dang had tried a wide variety of ZGN-433 regimens, and showed that the dose required to achieve weight loss was highly tolerable—500 to 1,000 times lower than that needed to muster an anti-angiogenesis effect.

Armed with this information, Zafgen licensed in the lead and continued with development of ZGN-433, announcing positive results with phase 1b proof-of-concept trials earlier this year. Severely obese patients lost an average 1 kg/week over the one-month trial, with twice weekly intravenous doses, and showed improvements in their low-density lipoproteins, triglycerides and other markers.

Hughes says his company has been busy with both animal studies and protein biology work to pinpoint the mechanism by which MetAP2 inhibition regulates adipose metabolism. They have confirmed that the effect is unrelated to angiogenesis. At first glance, methionine animopeptidases seem absolutely essential to biosynthesis, in that they are required to trim off the *N*-terminal methionine residue from all new proteins. But as it happens, MetAP2 has two other, rather promiscuous isoforms, MetAP1 and MetAP3, which may do the bulk of this basic work. In contrast, MetAP2 shows a strong preference for cleaving off *N*-terminal methionines adjacent to a large neutral amino acid—a consensus sequence that happens to be shared by several abundant proteins. Hughes says that MetAP2 may therefore act as a sentry to gauge the pace of overall protein production.

But the main result of MetAP2 inhibition is a strong dampening of the ERK1/2 signaling pathway, which tends to be overactive in the fat tissues of obese people. When the MetAP2 protein is inhibited in cell culture, it leaves the endoplasmic reticulum and binds and inhibits ERK. Shutting down ERK activation in obese mice has two main relevant effects: first, ERK dampening quells the transcription factor SREBP1, which normally ramps up genes associated with cholesterol and fatty acid synthesis; and second, the ERK clampdown allows release of another transcription factor called RORα, allowing it to upregulate the gene encoding fibroblast growth factor 21 (FGF21), which stimulates liver fat utilization. These twin conditions, Hughes explains, makes it "hard not to burn fat."

Peter Voshol, director of disease model core at the Institute of Metabolic Science at Cambridge University, says that the main issue with evaluating any compound that induces weight loss is that there are many different mechanisms by which weight loss can occur. Detailed physiological studies are needed to distinguish between, for example, altering fat absorption from the intestines and interventions that increase energy expenditure. Cellular mechanism, such as ERK and FGF21, may be useful as an indication, but complete energy balance studies need to be performed to be convincing on a physiological level.

Zafgen is one of the new breed of 'virtual' companies, in that it operates with only 4.5 full-time staff on the payroll—all laboratory work is contracted out to groups worldwide. This is a big upheaval for Hughes after the vast enterprise of Novartis. He says if a large pharmaceutical company wanted to work out how to modulate fatty acid synthesis rationally, it would probably fail. Indeed, despite the severity and cost of the global obesity crisis, competition in the field today is sparse after several high-profile failures for Acomplia (rimonabant), Qnexa (phentermine and topiramate) and Lorgess (lorcaserin). But he says it is part of the "scrappy nature of biotech" to be able to exploit serendipitous discoveries like the one that led to ZGN-433, with a fleetness and focus he finds intoxicating.

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