Smart insulin: redesign could end hypoglycemia risk

Danish pharma giant Novo Nordisk entered a deal to acquire small biotech Ziylo, gaining access to its next-generation glucose-sensitive insulins for diabetes. The deal signed on 17 August could be worth more than $800 million for the Bristol, UK-based startup if all milestones are met.

"Ziylo provides us with the key component of the technology that will allow us to have truly glucose-responsive insulins," says Marcus Schindler, senior vice president of Global Drug Discovery at Novo Nordisk.

For Novo Nordisk, a glucose-sensitive insulin is a major part of the company's goal of providing next-generation treatments for diabetes that will be safer and easier to administer for patients, says Schindler. Such a molecule, with the capacity to sense a patient's blood sugar and only release insulin when levels are within a certain range, could help eliminate the risk of hypoglycemia, one of the main complications of insulin treatment.

Ziylo, which was spun out of the lab of supramolecular chemist Anthony Davis at the University of Bristol in 2014, has been developing synthetic molecules that can selectively bind glucose in complex environments such as blood. Novo Nordisk plans to combine this technology with its own engineered insulins to create glucose-responsive insulins. "There is a good match between their technology and ours," says Schindler.

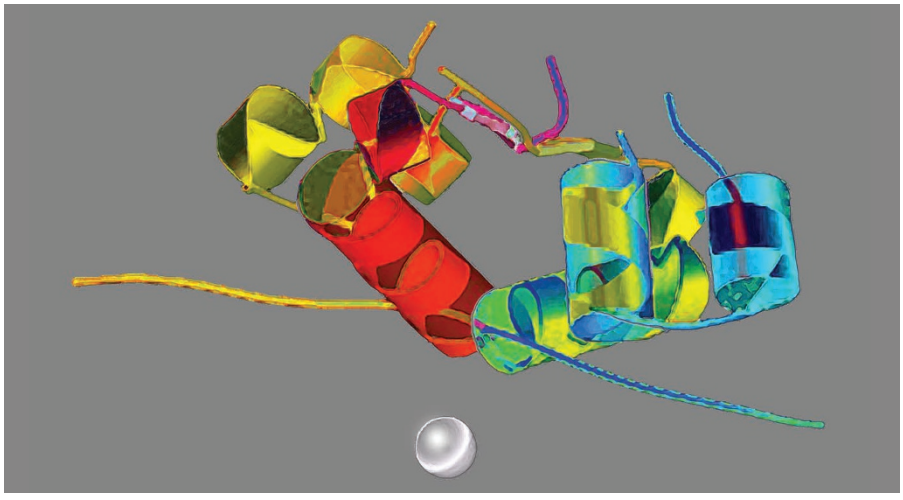
Ziylo's glucose-binding molecules can act as an on–off switch for insulin, says Harry Destecroix, the company's cofounder and CEO. It's the off-switch part that is unique. Other molecular mechanisms also control insulin release, turning off the tap when glucose levels drop. But that still leaves some bioavailable insulin floating around, says Destecroix. Ziylo's switch can cut it off immediately. "What got Novo Nordisk excited was the ability to deactivate insulin," he says.

Destecroix says the company is not yet ready to explain how the mechanism works—such as whether the glucose-binding molecular switch induces a conformation change in the insulin—but a paper describing it is currently under consideration at a peer-reviewed journal.

Ziylo's glucose-binding molecules are the result of decades of work by Davis and his colleagues, says Destecroix. "Tony spent 20 years designing a receptor that can bind glucose," he says. The result was a synthetic molecule based on sugar-binding lectin proteins found in plants, which could bind glucose and other sugars in water.

The company's initial goal was to create glucose monitors using its designer molecules, which emit fluorescence when binding glucose. But their molecule's specificity for glucose was low, so they set out to redesign it. Two years ago they came up with a structure that would bind only glucose, not only in water but also in the complex blood environment. In the redesign the molecule lost its ability to fluoresce, making it less suitable for monitoring, but through what Destecroix calls some "clever chemical trickery" the molecule became tunable: it gained the ability to switch on and off in response to specific ranges of blood glucose levels.

"With this, we could enable a whole new first-in-class kind of glucose-responsive drugs," says Destecroix. The company immediately began looking for partners to develop the molecule for therapeutic applications to



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An insulin molecule that monitors glucose levels would switch off when glucose levels drop.

Akcea's antisense drug rejection worries analysts

The US Food and Drug Administration (FDA) has rejected an antisense drug to treat elevated triglycerides, despite an earlier positive opinion from an advisory panel supporting the approval. The drug Waylivra (volanesorsen), developed by antisense specialist Ionis Pharmaceuticals and its affiliate Akcea Therapeutics, received a Complete Response Letter stating concerns over the drug's risk/benefit profile, including platelet declines seen in clinical studies. Waylivra reduces the production of apolipoprotein C-III, a protein produced in the liver that regulates plasma triglycerides. The sponsors sought approval to treat familial chylomicronemia syndrome, a-rare hereditary disease caused by impaired function of the enzyme lipoprotein lipase and characterized by extremely elevated triglycerides, which can cause unpredictable and potentially acute pancreatitis as well as organ damage.

Analysts are worrying over what the FDA setback could mean for a second Ionis/Akcea antisense drug, Tegsedi (inotersen), which was recently approved in the European Union for treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis (hATTR). Tegsedi is a more important revenue driver for Akcea, and many analysts continue to predict FDA approval of the compound. Madhu Kumar, analyst at B. Riley FBR, takes a different view. The agency's refusal undercuts the argument "that development of a monitoring system will be sufficient to address concerns around platelet losses on phosphorothiate ASO [antisense nucleotide]," he wrote in a note to investors. Tegsedi would compete with Alnylam Pharmaceuticals' Onpattro (patisiran), which gained United States and European approvals in August to treat hATTR. Because Onpattro works through a different mechanism, RNA interference, to block production of transthyretin in the liver, it does not raise the same safety risks as Tegsedi.

"**I think it is a moral requirement to make money when you can… to sell the product for the highest price.**" Nostrum Pharmaceuticals Nirmal Mulye 'justifies' a 400% hike in the price of nitrofurantoin. (*CNN Health*, 12 September 2018)

"**We're working with biology, so we have to respect its complexity.**" Mark Allen, CEO of anti-aging start-up Elevian, notes nonetheless that the company has licensed Harvard's portfolio of patents around a single molecule, GDF11, which some believe confers blood's rejuvenating effects. (*Wired*, 5 September 2018)