

Stepping toward regenerative medicine for diabetes

Discovery points toward treatment options beyond insulin injections

By [Elizabeth Dougherty](#) | Oct 27, 2015

“Son, you need to live fast and loose because you’re not going to live very long,” the doctor told ten-year-old Chris Stiehl. It was 1961 and Stiehl had just been diagnosed with type 1 diabetes. “Back then,” he says, “prognoses were not very good, and treatments weren’t real good either.”



Chris Stiehl was diagnosed with type 1 diabetes in 1961, when treatment options were limited.

Stiehl and other people with this type of diabetes, many of whom are diagnosed as children, have difficulty maintaining normal blood sugar levels. To survive, they depend on injections of insulin, a hormone that clears sugar from the blood so that it can be used as energy.

Without tight control of blood sugar levels, patients with diabetes risk heart and artery damage that shortens lives by about 10 years on average. Stiehl—a husband, father and retired engineer—is one of just 3,000 people in the United States who has survived for more than 50 years with the disease. Even with modern interventions, including continuous glucose monitors, insulin pumps and both long- and fast-acting forms of insulin, blood sugar highs and lows still plague patients.

Type 1 diabetes occurs when a person’s immune system mistakenly attacks and kills cells in the pancreas called beta cells. These are the cells that secrete insulin and allow the body to regulate blood sugar levels. With too few beta cells, patients with type 1 diabetes must take over that function themselves.

Now, however, a group of Novartis researchers has found a way to get human beta cells to regenerate, a feat many had dismissed as impossible. The work, published online in [Nature Communications](#) on Oct. 26, is still in its early stages, but the findings suggest that an oral drug to treat diabetes at its source by restoring lost beta cells could potentially be within reach.



“These are the first compounds that have been demonstrated to stimulate proliferation of human beta cells,” says Richard Insel, Chief Scientific Officer of JDRF (formally known as the Juvenile Diabetes Research Foundation), which contributed funding to the effort. “There were lots of stops and starts along the way, but this team has really blazed new ground.”

A Growing Challenge

About 1.25 million people in the United States have type 1 diabetes, according to JDRF. Worldwide, about 371 million people suffer from type 1 and type 2 diabetes, which for some people also results in insulin dependence. Over the past four decades, the number of people diagnosed with type 1 diabetes each year has been rising, particularly in developed areas of the world, suggesting that the challenges of managing diabetes are only increasing.



Chris Stiehl (shown with his wife Lorraine) is one of just 3,000 people in the United States who has survived for more than 50 years with type 1 diabetes.

Chris Stiehl's daily regime is somewhat typical for a patient with type 1 diabetes. He injects fast-acting insulin at each meal and manages his glucose levels all day using a continuous glucose monitor and insulin pump. But every day is different, and sometimes he experiences lows from too much

insulin or highs from too little. For instance, recently, while teaching a class at the University of California, San Diego, Stiehl's glucose monitor alarm went off, indicating his blood sugar was low. By the time he'd done a finger prick test, he was in the danger zone. He started gulping apple juice to quickly boost his blood sugar, but it was too late. He passed out.

"Next thing I know, paramedics are standing over me," he says.

Smart Science Takes on a Long Shot

The idea to regenerate beta cells is not new. In fact, many efforts have succeeded in mice. But time and again, the compounds that worked in rodents did nothing to human cells.

"People believed it was hopeless," says Bryan Laffitte, Director of Discovery Pharmacology at the Genomics Institute of the Novartis Research Foundation (GNF) in California.

But bits of research hinted otherwise. For instance, human beta cells divide during infancy. Also, according to autopsy studies, a few adults with type 1 diabetes have shown signs of beta cell regeneration. "It is rare, but that evidence gave us a little hope," says Laffitte.

So Laffitte's team threw their best technology at the problem. They developed a highly sensitive way to detect beta cell division in cell cultures, so that no leads would escape their notice. Then they tested two million compounds to see which ones caused beta cells to divide. They found several, and quickly zoomed in on a handful that worked on both mouse and human beta cells.

Further tests showed that the regenerated cells were also functional, secreting insulin in response to glucose. "It's all well and good to make more beta cells, but if they don't function properly, they won't do the patient any good," says Laffitte.

The most telling test involved giving the compounds to mice that model human type 1 diabetes. Within two weeks of taking the compounds, the mice showed improvements in their ability to control their own blood sugar levels. "In fact, we saw enormous improvements," says Laffitte. "It's in the no doubt range."

Subsequent examinations of the mice showed that the drug had doubled their beta cell mass. "When we saw that, we were convinced we were onto something," says Laffitte.

Preparing for the Long Haul

For Laffitte's team, that sign of success was the beginning of a new phase. Research efforts often pass from one team to another as they progress through milestones. But in Laffitte's organization at Novartis, one core team drives the drug discovery effort from beginning to end. This champion-based approach stems from the idea that it takes a certain investment in a goal, earned through early stage failure and success, to soldier through the long journey to completion.

"Most things we try fail. It's not fun," says Laffitte. "You have to really believe in what you're doing to fight through it."

His team is currently working to understand exactly how their compounds are encouraging beta cells to replicate. Their goal is to find a compound that **induces beta cell regeneration** but doesn't cause other cells to replicate.

"We're looking for a compound that clears the safety hurdles and still has all the good qualities," says Laffitte. Many steps remain before such a compound reaches clinical testing.

For Stiehl, the prospect of regenerative beta cell therapies holds appeal. After nearly 55 years of living with this disease, he is willing to try new things if they will make it easier for him to manage his diabetes. "I was supposed to be dead at 50," he says. "Now I'm 65. Let's go."

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