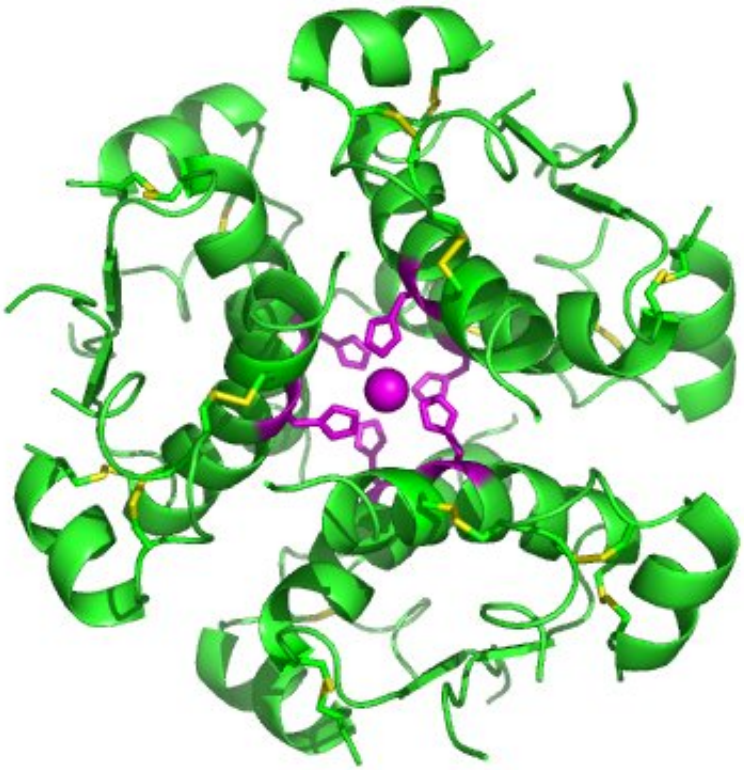
Researchers discover new drug cocktail that increases human beta cell proliferation at rapid rates

December 20 2018



High-resolution model of six insulin molecules assembled in a hexamer. Credit: Isaac Yonemoto/Wikipedia

Researchers at the Icahn School of Medicine at Mount Sinai have

discovered a novel combination of two classes of drugs that induces the highest rate of proliferation ever observed in adult human beta cells—the cells in the pancreas that produce insulin. The result is an important step toward a diabetes treatment that restores the body's ability to produce insulin.

The finding involved one drug that inhibits the enzyme dual specificity tyrosine-regulated kinase 1A (DYRK1A) and another that inhibits transforming growth factor beta superfamily members (TGFβSF). Together, they caused the cells to proliferate at a rate of 5 to 8 percent per day. The study, titled "Combined Inhibition of DYRK1A, SMAD and Trithorax Pathways Synergizes to Induce Robust Replication in Adult Human Beta Cells," was published today in *Cell Metabolism*.

"We are very excited about this new observation because for the first time, we are able to see rates of human cell beta cell replication that are sufficient to replenish beta cell mass in human beings," said Andrew Stewart, MD, Director of the Mount Sinai Diabetes, Obesity, and Metabolism Institute and lead author of the study. "We have discovered a drug combination that makes beta cells regenerate at rates that are suitable for treatment. The next big hurdle is figuring out how to deliver them directly to the pancreas."

According to Dr. Stewart, none of the diabetes drugs currently on the market can induce beta cell regeneration in people with diabetes. In parallel with the Mount Sinai work, other researchers are studying pancreatic transplantation, beta cell transplantation, and stem cell replacement of beta cells for people with diabetes, but none of these approaches is in widespread use. Approximately 30 million people in the United States have diabetes and nearly 50 to 80 million more are living with prediabetes (also called "metabolic syndrome"). Diabetes occurs when there are not enough beta cells in the pancreas, or when those beta cells secrete too little insulin, the hormone required to keep blood sugar

levels in the normal range. Diabetes can lead to major medical complications: heart attack, stroke, kidney failure, blindness, and limb amputation.

Loss of insulin-producing beta cells has long been recognized as a cause of type 1 diabetes, in which the immune system mistakenly attacks and destroys beta cells. In recent years, researchers have concluded that a deficiency of functioning beta cells is also an important contributor to type 2 diabetes, the most common type that occurs in adults. Thus, developing drugs that can increase the number of healthy beta cells is a major priority in diabetes research.

This current paper builds upon a study that Dr. Stewart and his team published in Nature Medicine in 2015, showing that a drug called harmine drove sustained division and multiplication of adult human beta cells in culture. They also learned that harmine treatment led to normal control of blood sugar in mice whose beta cells had been replaced with human beta cells. While this was a major advance, the proliferation rate was lower than needed to rapidly expand beta cells in people with diabetes.

In 2017, Dr. Stewart and his team published a second paper, in Nature Communications, which revealed the genetic abnormalities in insulinomas, a benign type of human beta cell tumor, and served as a "genetic recipe" to reveal targets for new drugs that can make beta cells regenerate.

In this current paper, Dr. Stewart and his team took advantage of the insulinoma "genetic recipe" which suggested that a combination of two classes of drugs—a DYRK1A inhibitor such as harmine with a TGFβSF inhibitor drug—would be able to synergistically increase beta cell regeneration. This proved to be true. However, this new drug combination is not without its hurdles. "Since these drugs have effects

on other organs in the body, we now need to develop methods to deliver these drugs specifically to the beta cell in humans," said Dr. Stewart. "We have the packages to deliver, but now we need a courier system to deliver them to the exact beta cell address."

"Beta cell regeneration is a 'holy grail' for the treatment of diabetes," said Peng Wang, Ph.D., Associate Professor of Medicine (Endocrinology, Diabetes, and Blood Disease) at Mount Sinai and first author on the study. "We are excited to finally have drugs that can induce beta cell proliferation at rates that are likely to be effective in people with type 1 and type 2 diabetes."

"This is one of the most exciting series of discoveries in the field of diabetes and is a key next step in drug development for this disease," said Dennis S. Charney, MD, Anne and Joel Ehrenkranz Dean, Icahn School of Medicine at Mount Sinai. "In a very short time, Dr. Stewart and his team of researchers have made incredible progress. Their important work truly holds promise for so many people."

"We know that in order to achieve a cure for type 1 diabetes and to bring people to insulin independence, we will have to find ways to increase the numbers of functional beta cells," said Francis J. Martin, Ph.D., Associate Director of Research and leader of the JDRF Beta Cell Regeneration and Survival Program. "Now, through the work of Drs. Stewart and Wang, we see that we can increase the rates of human beta cell reproduction to levels that were previously thought to be impossible. There are still challenges ahead, but this work brings us a little closer to therapies that can restore insulin production in people with the disease, and ultimately produce a cure."

Provided by The Mount Sinai Hospital