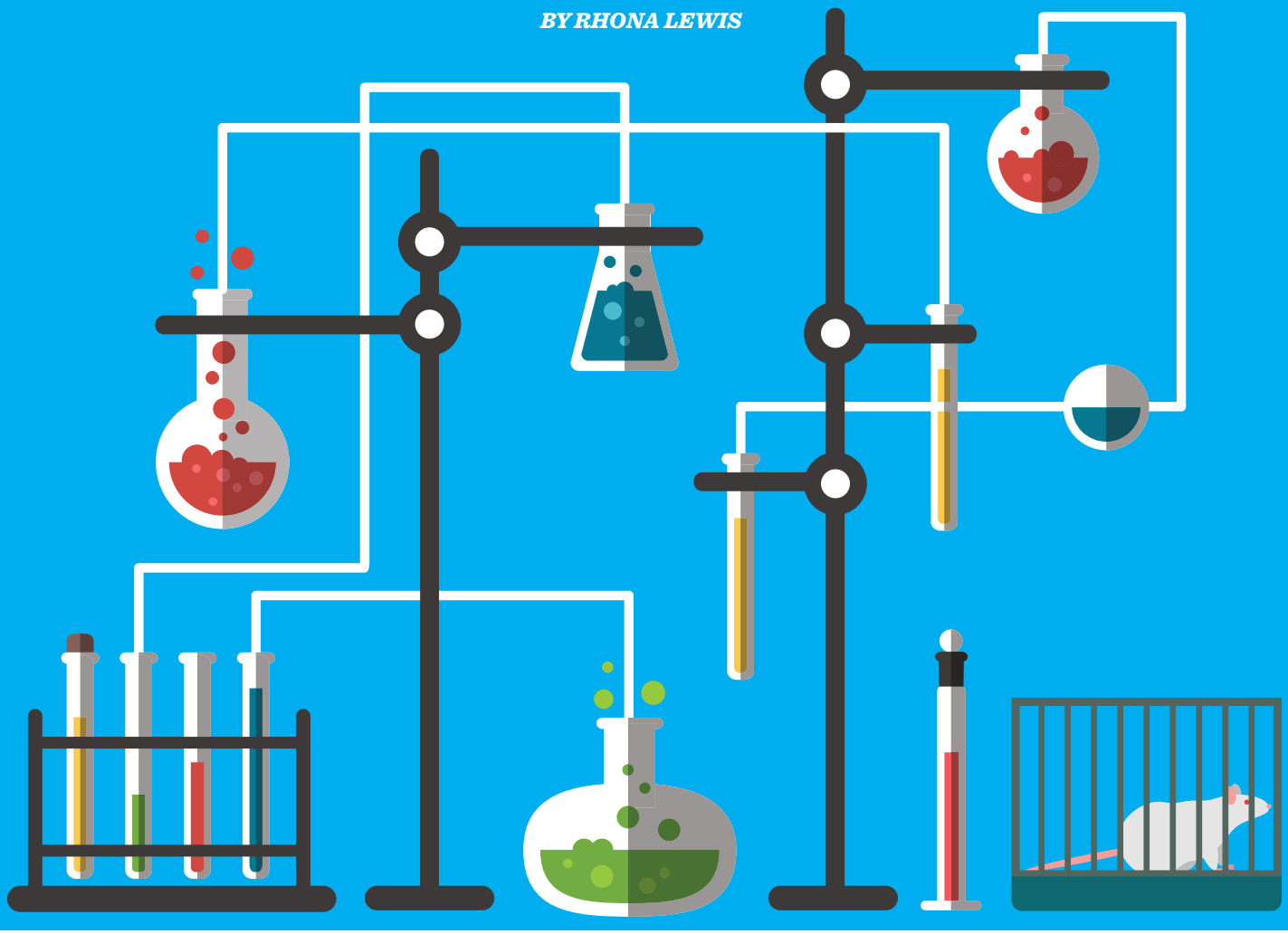
OF MICE, MEN AND MEDICAL ADVANCES

TWO DOCTORS CO-INVENTED A TECHNIQUE THAT HAS CURED DIABETES IN MICE FOR ONE YEAR WITHOUT SIDE EFFECTS. *HAMODIA* SPOKE TO BRUNO DOIRON, PH.D. AND RALPH DEFRONZO, M.D., OF UT HEALTH SAN ANTONIO TO FIND OUT:

CAN THIS HERALD THE END OF DIABETES?

BY RHONA LEWIS



Twenty-nine million Americans are living with diabetes. About 86 million more are living with prediabetes, a serious health condition that increases a person's risk of developing type 2 diabetes and other chronic diseases, says the Centers for Disease Control and Prevention. Thankfully, two researchers at the University of Texas Health Science Center, Bruno Doiron, Ph.D., and Ralph DeFronzo, M.D., have made a breakthrough that could change the future for many diabetics.

Can you tell us about your breakthrough?

Let's start with a word about diabetes. Both type 1 and type 2 diabetes are caused by the progressive loss or function of pancreatic beta cells. Beta cells are the cells that produce insulin. Type 1 diabetic patients lose their beta cells through an autoimmune process, meaning that the body destroys these cells. Type 2 diabetic patients have some insulin secretion, but not enough to maintain normal glucose levels. Insulin is important because it allows blood sugar (glucose) to enter cells, where it is used for energy. When the body doesn't have enough insulin or can't use it effectively, the level of glucose in the bloodstream reaches abnormally high levels (hyperglycemia). Side effects are severe.

Drs. Doiron and DeFronzo

In 1922, Canadian Fredrick Banting successfully treated a teenage boy who was near death from diabetes. Ninety-five year later, we are still reliant on the mechanical process of insulin injections. But insulin injections can never eradicate the complications that can arise from poor glucose control. And while insulin pumps give more freedom, they still don't offer minute-to-minute regulation of blood sugar levels.

This is where our technique, Syner-III (the Cellular Networking Integration and Processing [CNIP]) approach comes in. Very simply put, we used a virus as a vector (carrier) to introduce selected genes into the pancreas of mice. The vector carries three genes that work synergistically (together) at the cellular level in the pancreas to encourage other non-beta cell types to mimic the actions of beta cells and make insulin. We aren't inventing anything new; we are simply mimicking nature.

How successful is your breakthrough?

The therapy worked perfectly. It precisely regulated the blood sugar level of the diabetic mice — a major improvement over traditional insulin therapy, which does not offer minute-to-minute regulation. The mice were cured for one year without any side effects. And don't forget that one year in a mouse is equivalent to about 30 years in the life of a human. We predict the same beneficial response in humans. In Type 1 patients, the body's autoimmune system rejects beta cells. (Only 2 percent of the cells in the pancreas are beta cells; the remaining 98 percent of cells in the pancreas are non-beta cells.) With our therapy, however, the new cells can co-exist with the body's immune defenses. The Type 1 diabetic patient has been living with his/her non-beta cells for years. All we are doing is getting these non-beta cells in the pancreas to secrete insulin, so there shouldn't be any adverse immune response.

Research on two other methods of increasing beta cells is being carried out. This is islet transplantation. Can you comment on this method?

Sure. The pancreas contains clusters of cells that produce hormones. These clusters are known as islets. Beta cells in these islets produce insulin. The idea in the use of islet transplantation is to transplant islets from a donor pancreas into the patient. And here you encounter your first hurdle — two cadaver donors are needed to obtain a sufficient number of beta cells and donors are scarce. And then, we have the rejection process to deal with.

Now let's talk about where the islets ... are placed. [It] must be encapsulated. This capsule is then under the kidney of the patient. Remember, insulin is produced in the pancreas and not in the kidney, so the insulin does not enter the portal circulation and reach the liver.

Finally, to reduce the chance of rejection, you need to give the patient a high level of immune suppression drugs, which opens the door to other diseases.

What are the advantages of Syner-III therapy over this method?

Syner-III therapy bypasses the hurdles of insufficient numbers of donors ... transplantation and the need for immune-suppression. Since we are working within the patient's body, many problems are avoided. We use the simple method of endoscopy to introduce the vector carrying the three genes directly into the pancreas. Endoscopy is a process that already has FDA approval. Similarly, the use of a viral vector (which is a simple way to carry the genes) also has FDA approval. Cells that are already in the pancreas are not affected by the vector, so problems with the immune rejection system shouldn't occur. In fact, after introducing the genes, the vector disappears.

What are the next steps to getting approval?

We received a U.S. patent in January. Now we need to test our strategy in a large animal whose endocrine system is closer to that of humans. This will cost an estimated $5 million. Upon completing these studies, we will apply to the U.S. Food and Drug Administration for Investigational New Drug (IND) approval. The same method of treatment has been approved almost 50 times by the IND to treat various diseases, including rare childhood diseases, so we are optimistic.

What does this mean for diabetes patients?

Syner-III precisely regulates blood sugar in mice. The altered cells match the characteristics of beta cells and release insulin only in response to glucose. So it's very likely that this could be a major advance over traditional insulin therapy and some diabetes medications that drop blood sugar too low if not closely monitored. Syner-III eliminates the need for insulin injections and testing blood glucose levels. Since it provides minute-to-minute insulin release to control blood glucose, we avoid the development of hypoglycemia and hyperglycemia and the problems associated with both situations. This research could open the way for prevention, treatment and potentially a cure for diabetes. ■

Who's Behind the Invention?

Bruno Doiron, Ph.D., assistant professor of medicine at UT Health San Antonio, has over 20 years of experience in the field of gene transfer. "I was always curious about life," he says, "And I have kept my childhood curiosity." He is the founder and CEO of biotech companies in France and Canada and has four patents on the modulation of glucose metabolism as it relates to the treatment of diabetes and cancer. A pioneer, he made a fundamental discovery in the field of gene transfer and gene expression induced by glucose. Ralph DeFronzo, M.D., professor of medicine and chief of the Division of Diabetes at UT Health, and co-inventor on the patent, is an international leader in the field of type 2 diabetes and has received the three highest scientific achievement awards given by the American and European Diabetes Association. With this, he is an exotic-destination traveler, an avid bicyclist and, according to *Golf Digest*, one of the top 200 doctors who are golfers. "I'm getting close to shooting my age, mostly because I'm getting older and not because my golf game is getting better," he quips.