

In this issue:**Insulin Secreting Cells Produced From Unused Pancreatic Tissue****Transplanted Pig Islets Reverse Diabetes in Monkeys****TrialNet Launches Diabetes Risk Trial****INSULIN-SECRETING CELLS PRODUCED FROM UNUSED PANCREATIC TISSUE**

In what may be a significant breakthrough, JDRF-funded researchers in San Diego have discovered that non-secreting tissue in the pancreas can be transformed into insulin-producing cells.

The finding suggests a new approach to curing diabetes: coaxing primitive cells in the pancreatic tissue to behave like beta cells. As a result, researchers may be able to identify drug targets that stimulate beta cell regeneration, or grow beta cells for transplantation into humans.

“This discovery raises the possibility of identifying new drug targets for therapeutics for beta cell regeneration. But first we must characterize the signals and receptors activating the generation of new beta cells in this protocol,” JDRF Executive Vice President Richard Insel, M.D., said. “It also could provide a boost to islet transplantation by greatly increasing the amount of donor tissue potentially available.”

The research, led by Fred Levine, M.D., Ph.D., at the University of California, San Diego and the Burnham Institute, was reported in the journal *Nature Medicine*.

A NEW ADULT CELL SOURCE

Researchers looking for potential sources of new beta cells have hoped to find adult stem cells in the pancreas, but none has been discovered. They also have been unable to identify another potential beta cell source in the pancreas: progenitor cells, which are primitive, undeveloped forms of beta cells.

But the last few years have shown significant progress in understanding how pancreatic beta cells might be formed. Two years ago, a study by JDRF-funded researchers in the Harvard laboratory of Douglas Melton, Ph.D., suggested that new beta cells in mice are formed only through replication of existing beta cells. But other studies have found evidence that the body’s ability to create new beta cells—which occurs when the cells proliferate after pancreatic injury or an increase in body mass—cannot be explained by beta-cell replication alone. Now, the San Diego study

suggests that the non-secreting, or non-endocrine, portion of the pancreas contains progenitor cells that have the capacity to develop into beta cells.

In these latest experiments, the researchers used painstaking purification and cell culture techniques to isolate cells from pancreatic tissue, which they called “non-endocrine pancreatic epithelial cells,” or NEPECS. After labeling the NEPECS with genetic markers that made the cells easier to identify, they mixed them with fetal pancreatic cells, which are known to contain growth factors that spur cell development. This caused the NEPECS to develop into progenitor cells.

The researchers transplanted the progenitor and fetal cell mixture into mice and allowed it to develop for three months. In this environment, the progenitor cells spontaneously specialized into insulin-secreting cells.

Although making insulin-producing cells from non-endocrine cells is not unprecedented, the efficiency at which the researchers prompted the precursor cells to become beta cells is striking, compared with earlier studies. More than 20 percent of the surviving transplanted cells functioned like insulin-producing beta cells.

The next step for the researchers will be to focus on isolating and characterizing the growth factors that transformed the NEPECS into full-fledged beta cells. They also will try to determine whether all the NEPECS, or just a subset, have beta cell potential.

TRANSPLANTED PIG ISLETS REVERSE DIABETES IN MONKEYS

Researchers at two JDRF islet transplant centers were able to reverse diabetes in monkeys by transplanting islet cells from pigs, paving the way for the possible development of therapies for people with type 1 diabetes that involve an expandable supply of healthy islets from non-human sources.

The milestone studies, conducted at the University of Minnesota and the Emory University School of Medicine in Atlanta, were reported in the journal *Nature Medicine*. They showed that with a combination of immune-suppressing drugs, the transplanted pig islets were not rejected by the monkeys and functioned for several months.

“These findings are important to our efforts to find a potentially unlimited source of islets,” said JDRF Scientific Program Manager Brian Flanagan, Ph.D. “The results are another step forward, but we need to refine the procedure and establish its safety before we can start putting pig islets into people with diabetes.”

THE CHALLENGE OF CROSS-SPECIES TRANSPLANTS

The major problem with islet transplantation is that the number of people with diabetes far exceeds the number of human islet donors each year. To address the shortfall, researchers have been investigating a range of alternative sources of insulin-producing cells, including animal islets. Pigs are an attractive option because they are relatively easy to breed, and their organs are similar to those of humans. But transplanting tissue between species is difficult.

In most cross-species transplants (xenotransplants), the human immune system mounts a fierce attack, called “hyperacute rejection,” on living tissue from any animal except certain primates. That attack would destroy the transplanted cells within hours. Triggering this response is alpha-Gal, a sugar molecule on the surface of most nonhuman animal cells.

In a surprising discovery, Bernhard Hering, M.D., and colleagues at the JDRF Center for Islet Transplantation at University of California, San Francisco/University of Minnesota, found that *islet* transplants between species do not trigger hyperacute rejection. Rather, the transplant recipient’s immune response primarily resembles the rejection of a same-species transplant. This suggested to them that islet xenotransplants do not carry the hyperacute risk of xenotransplants involving other tissue and that they could prevent rejection of pig islets with the right mix of immunosuppressive drugs.

At the same time, the Minnesota scientists were trying to further reduce the risk of hyperacute rejection by minimizing alpha-Gal levels. They found that if they kept the islets in culture for a few days before the transplant, it destroyed most of the islets’ vascular cells, where the alpha-Gal molecules are located.

With the alpha-Gal issue minimized, Dr. Hering’s team was able to focus on the more conventional rejection threat seen in any transplant, testing various immunosuppressive drug combinations. The researchers cultured islets from pigs and transplanted them into 12 diabetic monkeys. In some of the non-human primates, the islets restored blood glucose control for more than 100 days. One group of monkeys did especially well under their immunosuppressive protocol, with all the animals surviving at least 68 days, and four out of five surviving 111 days or more.

NEONATAL ISLETS

The Emory study, led by Christian Larsen, M.D., at the **JDRF Center for Islet Cell Transplantation at Emory University**, tested islets from neonatal pigs in diabetic monkeys. Because they are immature, neonatal islets are potentially more advantageous than islets from adult pigs, as they are first, more capable of multiplying and growing inside the recipient after the transplant, and second, less likely to trigger a damaging immune system response in the recipient.

Earlier research showed that that neonatal islets worked well when transplanted into mice and pigs. But monkeys, like humans,

present additional challenges because they have a natural reaction against alpha-Gal.

The researchers transplanted neonatal pig islets into three groups of diabetic monkeys. The control group that did not receive immune-suppressing drugs rejected the pig islets within a few days. A second group, which did receive immune suppression, regained control of blood glucose levels and survived much longer until succumbing to side effects of the drugs. The researchers subsequently transplanted a third group after refining the treatment with lessons learned from the second group. This last group survived for a median of more than 140 days.

The immune-suppressing protocols used in both studies have significant hurdles for use in humans because of the side effects of the drugs. But the research clarified the mechanism of the primate immune response to transplanted pig tissue, which will help researchers as they design immune-suppressing therapies for future human protocols.

GET TESTED FOR DIABETES RISK

Type 1 Diabetes TrialNet, a clinical research consortium funded by NIH, JDRF, and the American Diabetes Association, is conducting a group of studies at 18 clinical centers around the world to understand the development, prevention and early treatment of type 1 diabetes. Currently, the TrialNet Natural History Study is screening close blood relatives of people with type 1 diabetes to find out if they are “at risk” for developing the disease.

The Natural History Study of the Development of Type 1 Diabetes will study people at increased risk for the disease to learn more about how type 1 diabetes occurs. Relatives of people with type 1 diabetes have a 10-to-15 times greater risk for developing the disease than people with no family history.

Screening involves a simple blood test from your arm to look for diabetes-related autoantibodies, abnormal immune system proteins that attack the body’s own cells. These autoantibodies may appear years before type 1 diabetes develops. Relatives of people with type 1 diabetes have a 3 to 4 percent chance of having autoantibodies in their blood associated with type 1 diabetes.

To learn more, go to:

Natural History Study Facts sheets

<http://diabetestrialnet.org/doc/factsht.pdf>

Natural History Study website

<http://www.diabetestrialnet.org/onhx1.html>

Or call:

1- 800- HALT- DM1 (1-800-425-8361)

To find out if a participating clinical center is located near you, go to:

<http://www.diabetestrialnet.org/cent.html>

For a link to studies in recent onset of Type 1 diabetes, go to:

<http://www.diabetestrialnet.org>