JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

research frontline

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PIGS MAY HELP RELIEVE ISLET SHORTAGE

The biggest challenge to making **islet transplantation** a widely available cure for people with juvenile (type 1) diabetes is the limited supply of islet tissue. In recent years, researchers have been investigating the use of islets from pigs, which may provide a temporary solution to the human islet shortage. Pig insulin has been used successfully in humans for years, and the organs of pigs are similar to those of humans.

Now two JDRF-funded studies published in the April issue of *Diabetes* provide encouraging results about the feasibility of using pig islets in humans. While any transplant between species (xenotransplant) is difficult because it can trigger acute rejection by the immune system, researchers think they may be able to overcome this hurdle with immunosuppressive drugs or by encasing the islets in a protective capsule.

The first of the two studies, involving a transplant between pigs, suggests that **islets from neonatal pigs** may offer advantages over islets from adults. The second study, involving xenotransplantation between pigs and mice, demonstrates a possible new approach to **prevent islets from being rejected**.

ADVANTAGES OF NEONATAL ISLETS

Although islets from adult pigs have worked well when transplanted into mice and monkeys, adult pig islets are difficult and expensive to isolate and hard to maintain in cell culture before transplantation. Neonatal islets offer two potential advantages:

1) They are more capable of multiplying and growing inside the recipient after the transplant due to flexibility early in life, and
2) Because they are less fully developed, they are less likely to set off a defensive immune system response in the recipient's body that would damage them.

JDRF-funded researchers at the University of Alberta in Edmonton, Canada, led by Ray Rajotte, Ph.D., are investigating how well neonatal pig islets actually perform after transplant. In previous investigations, they had shown that neonatal pig islets could reverse high blood sugar in diabetic mice. In a new study, the researchers wanted to prove that neonatal pig islets could restore blood sugar control in a larger animal—the pig itself.

They removed the pancreas of each of the 13 adult pigs to make them diabetic and then implanted islets isolated from multiple newborn pigs. Six of the pigs received drugs to suppress their immune response to the islets, while seven did not.

All the pigs receiving immunosuppression achieved normal blood sugar levels after 14 days, with some in this group remaining insulin independent for up to 69 days. Among the pigs receiving no immunosuppression, four out of the 6 achieved normal blood sugar levels within 6-14 days after the transplant, with two of those pigs remaining insulin-independent for more than 49 days.

These results suggest that neonatal pig islets show promise for transplant into humans. Especially encouraging was how quickly the pigs in the study regained control of blood sugar levels—about two weeks, compared with six to eight weeks in the previous experiments using pig islets in mice.

A DUAL APPROACH TO HELPING ISLETS SURVIVE

In the second study, JDRF-funded researchers at King's College in London took a novel approach to prevent pig islets from being rejected after transplantation into mice. The researchers used the species difference—normally a hurdle in xenotransplantation—to design a precise combination therapy for blocking rejection.

The main hurdle for implanting pig islets into humans is a reaction involving T-cells, master controllers of the immune system, which can lead to rejection of the transplant. When the human T-cells recognize antigens from the pig cells presented to them on the surface of specialized immune cells called **antigen-presenting cells** (APCs), they are incited into action and launch an attack against the perceived threat. Without the presentation from the APCs, the T cells will not attack the pig cells.

In an experiment transplanting pig islets into mice, the King's College researchers, led by Robert Lechler, Ph.D., decided to try blocking the antigen-presentation stage in each animal by using two distinct antibodies. One antibody, given within a few days of the transplant, would selectively bind to (and neutralize) the APCs in the pig tissue. Later, a second antibody, given 12-14 days after the transplant, would selectively bind to (and neutralize) APCs in the mouse tissue. With APC cells' receptors plugged by the antibodies, the T cells would not receive the necessary signal and be unable to initiate the immune response that causes rejection.

This two-antibody approach allowed the pig islets to survive in the mice even though no immunosuppressive drugs were given. Because the antibodies selectively targeted specific APCs (leaving most APCs unhindered), they did not compromise the normal immune function of the mice receiving the transplant.

These results suggest that a similar approach might work well for preventing rejection of pig islets in human patients. However, the success of this method will need to be duplicated in animals more closely resembling humans, such as monkeys, before it can be attempted in human clinical trials.

JDRF AND NIH PROMOTE STUDIES ON BLOOD VESSEL FORMATION

Angiogenesis, the process by which new blood vessels form and differentiate, could play a major role in diabetes research. Although it occurs as part of the natural wound-healing response, angiogenesis can also be aberrantly activated in disease states such as diabetes.

In partnership with several NIH institutes, JDRF has recently launched initiatives to encourage research in this burgeoning field, hoping to exploit its therapeutic potential. Research on angiogenesis could accelerate diabetes therapies for these conditions:

- **Retinopathy (Eye Disease):** The formation of abnormal blood vessels that leak and rupture is a hallmark of proliferative diabetic retinopathy and macular edema. An effective anti-angiogenesis therapy could reduce or block the excess vessel growth.
- **Neuropathy (Nerve Damage) and Nephropathy (Kidney Disease):** Researchers have found evidence that excessive angiogenesis could contribute to both these conditions, which affect nerves and the kidney.
- **Wound Healing:** Diabetes tends to impair wound healing because the blood vessels surrounding the wound do not grow or function normally. People with diabetes are especially susceptible to diabetic foot ulcers that can lead to hospitalization or even in certain cases, to amputation. Promoting blood vessel growth could speed the healing process.
- **Islet transplantation:** A major obstacle to successful islet transplantation is that many of the islets die after implantation due to inadequate nourishment. New blood vessels must form around the implanted islets to supply them with oxygen and blood. Promoting blood vessel formation, or "revascularization," could greatly improve islet survival and make transplantation more successful.

FIELD OF INCREASING INTEREST

Thanks to JDRF, interest in angiogenesis has increased significantly in the diabetes research community over the last 18 months. In early 2004, JDRF leadership met with NIH's National Cancer Institute (NCI) to discuss multidisciplinary collaborative efforts targeting angiogenesis. Cancer researchers were the first to focus on angiogenesis, since formation of new blood vessels is essential to tumor survival, and scientists have worked on blocking angiogenesis to inhibit disease progression.

Soon after the JDRF visit, NIH formed the Trans Institute Angiogenesis Program (TARP) to investigate angiogenesis through a multidisciplinary approach, bringing together researchers with varied backgrounds and diverse professional interests. TARP quickly grew to include bench scientists and clinicians associated with JDRF and five NIH institutes, including NCI, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Eye Institute (NEI), National Institute of Neurological Disorders and Stroke (NINDS) and the National Heart, Lung and Blood Institute (NHLBI).

In May 2004, the members of TARP held a two-day workshop on angiogenesis to assess the state of current knowledge, define areas of research need, and make recommendations to expand on successes. Based on these recommendations, last fall both NIH and

JDRF announced availability of research funding (in a "Request for Applications") for scientists to investigate angiogenesis as it relates to type 1 diabetes. On behalf of TARP, NIH committed about $3 million in FY 2005 to fund 5 to 10 new grants, each of which needed to be a collaborative research project with two or three investigators to foster cross-disciplinary work.

At the same time, JDRF launched its own research initiative as a counterpart to TARP, offering up to $1 million to fund innovative studies on angiogenesis and type 1 diabetes. At the close of the solicitation period in March 2005, JDRF had received a large number of applications from scientists. JDRF is evaluating the applications and will make funding decisions this summer.

"We're pleased with the very strong response by the research community to our Request for Applications," said JDRF Program Director for Diabetes Complications, Dr. Antony Horton. "This field of study has clearly generated a great deal of interest within the scientific community."