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- Progress in the field of islet transplantation
- Cancer drugs reverse type 1 diabetes in mice
- A potential new approach for treating diabetic eye disease

## News in Islet Transplantation

Islet transplantation can be an important therapeutic option for adults with unstable type 1 diabetes—individuals who, despite their best efforts, have wide, unpredictable fluctuations in blood sugar levels or who are no longer able to sense their blood sugar is dangerously low. For these people, transplantation may be a viable solution.

After receiving islets from a donor pancreas, most transplant recipients see a period of complete insulin independence. While this benefit “wears off” over time, almost all transplant recipients have long-term improvement in blood sugar control and are at significantly reduced risk for life-threatening episodes of hypoglycemia.

Success rates for islet transplantation continue to improve with advances in transplant protocols, but unfortunately, the procedure is severely limited by a critical shortage of donor islets. Currently, only about 100 patients in the U.S. each year will receive an islet transplant.

To increase the number and types of people who might benefit from transplantation, JDRFI scientists are focused on two critical issues—increasing the supply of transplantable cells and finding safer, better ways to prevent the rejection of transplanted islets. There have been a number of recent research advances on these fronts:

### Improved Insulin Independence, Better Quality of Life

Islet transplant recipients must continually take immunosuppressive drugs to keep their bodies from rejecting the new islets, even though these drugs can cause side effects and be toxic to the insulin-producing beta cells. However, by using a modified immunosuppressive protocol, JDRFI-funded researchers

at the University of Minnesota have substantially raised the success rate of transplants. Some 66 per cent of people who received islets at the Minnesota centre remain insulin independent three years after the procedure. Moreover, although all of the study participants had severe hypoglycemia unawareness before the transplant, none experienced a recurrence.

The study is one of several recent reports with similar results, showing modifying certain aspects of the transplant procedure can greatly improve the success of transplantation. The research is published in the *American Journal of Transplantation*.

In a study at the University of Miami, researchers found islet transplantation was strongly linked to long-term improvement in patients’ quality of life. This is especially important given patients are required to take powerful immune-suppressing drugs for the rest of their lives. In these situations, the benefits of the procedure need to strongly outweigh the risks of taking drugs that can have serious side effects. This JDRFI-funded study was published in the journal *Transplantation*.

### Key Point:

These studies highlight the benefits of islet transplantation as a treatment option for some people with type 1 diabetes. As a result, they underscore the importance of continued focus on the issues that prevent wider use of the procedure.

### Transplantation Restores Hypoglycemia Awareness

JDRFI-funded researchers with the Diabetes Research Institute in Miami have shown islet transplantation can restore hypoglycemia awareness in most recipients—regardless of how well the transplant works in reducing the insulin needs of the patient.

In a study of 31 people with type 1 diabetes, the rate of hypoglycemia dropped nearly fourfold after transplantation. Patients were rated on a scale in which people who did not experience hypoglycemia scored “zero” while those with hypoglycemia unawareness were assigned “four” or more. Before the transplant procedure, the people in the study

averaged 5.29—clearly hypoglycemia was a problem. After the transplants, the group's score dropped to 1.35.

Strikingly, this improvement held true in all the patients—not just individuals who no longer had to take insulin, but also in those whose insulin requirements returned or never changed as a result of the transplant. The study, funded by JDRFI, is published in *Diabetes Care*.

### Key Point:

A new study provides statistical confirmation islet transplantation often leads to the restoration of hypoglycemia awareness, even when long-term insulin independence is not maintained after the transplant.

### Transplants from Donors with Above-Normal Blood Sugar Can Be Successful

Researchers with the Clinical Islet Transplant Program at the University of Alberta in Edmonton showed islet transplants using cells from donors with elevated blood sugar levels still benefited the transplant patients.

In the cases cited, islets were isolated from donors with slightly elevated A1c levels—6.3 per cent and 7.9 per cent. (The cut-off for accepting a donor pancreas varies by transplant centre, but is typically lower than these values.) Although fewer beta cells were isolated from the donor with the higher A1c, both transplants proved beneficial to the recipients. The recipient who received islets from the donor with the lower A1C has been insulin independent for four years. The other recipient, from the higher A1C donor, has been able to reduce the amount of insulin needed by 56 per cent. The study, funded in part by JDRFI, is published in the journal *Transplantation*.

### Key Point:

Preliminary research suggests the selection criteria for donor pancreases can be expanded to include donors with a slightly elevated A1c, and could measurably increase the supply of islets available for transplantation.

### Islet Encapsulation Proves Effective

Researchers used a new encapsulation technique to successfully transplant islets without using powerful immune-suppressing drugs after the procedure. The technique, assessed in animal models, employed a membrane capsule that protected the transplanted islets from immune system attack while still enabling the new beta cells to successfully restore normal blood glucose levels. JDRFI partly funded the study, which took place at Vanderbilt University in Nashville, Tennessee, and was published in the journal *Transplantation*.

### Key Point:

The study provides hope this new encapsulation technique might be successful in people with type 1 diabetes.

### Potential New Site to Implant Islets

While islets transplanted into people are currently infused directly into the portal vein of the liver, research suggests this site is not ideal. In tests in animals, scientists from the Diabetes Research Institute in Miami showed the omental pouch—a fold of tissue within the abdominal cavity—is a promising alternative site for transplantation.

The transplanted islets were loaded onto a synthetic, biodegradable scaffold. While they took longer to engraft compared with islets transplanted in the liver, function was eventually obtained. Transplanting the cells at the alternative site ultimately reduced the need for insulin (by 66 per cent to 92 per cent) and lowered A1c. The study, funded by JDRFI, is published in the *American Journal of Transplantation*.

### Key Point:

Research confirms there may be important alternative sites for islet transplantation in people.

### Cancer Drugs Reverse Diabetes in Mice

JDRFI-funded researchers at the University of California San Francisco (UCSF) have shown two common cancer drugs can block and reverse type 1 diabetes in mice. The study, published in *Proceedings of the National Academy of Sciences*, was led by Jeffrey Bluestone, Ph.D., director of the Diabetes Center at UCSF and an expert in the field of autoimmunity.

The drugs—marketed as Gleevec and Sutent—prevented mice from developing type 1 diabetes, and put 80 per cent of mice that already had the disease into remission. Both drugs work by blocking a type of enzyme that triggers cell growth and division and plays a key role in inflammation.

One of the most noteworthy findings, the researchers said, was Gleevec led to sustained remission in the majority of mice long after treatment had ended.

The study was conducted as part of the Immune Tolerance Network, a JDRFI-funded international research consortium. JDRFI will continue to follow progress in this field and will explore the potential to translate these findings into treatments.

## Key Point:

According to Teodora Staeva, Ph.D., director of strategic planning in JDRFI's autoimmunity program, the findings suggest that some drugs are successfully used in cancer may provide an important new therapeutic approach for new onset type 1 diabetes.

## A Potential New Treatment for Retinopathy

As reported in the journal *Hypertension*, JDRFI-funded researchers from the Joslin Diabetes Center in Boston, in collaboration with San Francisco-based ActiveSite Pharmaceuticals, Inc., have identified a promising new approach for treating diabetic retinopathy.

In a study in rats, the scientists were able to prevent retinal blood vessels from leaking—a major cause of retinopathy—by inhibiting the action of a specific enzyme. (The inhibitor they used is being developed by ActiveSite Pharmaceuticals.) Edward Feener, Ph.D., an investigator in vascular cell biology at the Joslin Diabetes Center and an associate professor of medicine at Harvard Medical School, led the investigation.

Diabetic retinopathy is the most common and most serious eye-related complication of diabetes. It is a progressive disease damaging the tissue found at the back of the eye, resulting in retinal swelling and the destruction and leakage of the small retinal blood vessels. It eventually leads to vision problems, and in its most advanced forms, can cause moderate to severe vision loss and blindness.

"This study represents a pivotal step toward understanding the importance of enzyme inhibitors in diabetic eye disease, and how they may lead to a safe and effective therapy for diabetic retinopathy," said Barbara Araneo, director of complications research at JDRFI. "While further studies are needed to determine the therapeutic potential of ActiveSite's compound, the research underscores this potential treatment's relevance in diabetic microvascular disease."

To block the actions of the targeted enzyme (kallikrein), the researchers administered the inhibitor to rats with high blood pressure, a known risk factor for developing retinopathy. They found the inhibitor decreased retinal blood vessel leakage by as much as 70 per cent—a strikingly favourable outcome. The treatment also lowered the animals' high blood pressure, another factor contributing to diabetic eye disease.

In previous research at Joslin, Dr. Feener and his team had identified the enzyme inhibitor as a potential therapeutic target for people with diabetic retinopathy. The latest findings add another piece to the puzzle.

"This recent study suggests new opportunities to reduce retinal blood vessel leakage," Dr. Feener said. "While these results are encouraging, more work is needed to understand kallikrein's role in other retinal functions, as well as other diabetic complications, which can occur concurrently with diabetic retinopathy."

Tamie Chilcote, Ph.D., vice president of the Lead Discovery division at ActiveSite Pharmaceuticals, echoed these sentiments. "We look forward to further studies in collaboration with Dr. Feener to better establish the therapeutic potential of this and other plasma kallikrein inhibitors for treatment of retinopathy." JDRFI is actively monitoring this important research to ensure progress and to help identify any opportunity that might accelerate these initial successes even further. A first priority will be to conduct similar experiments in mice, the closest model of type 1 diabetes to people. ■

## Key Point:

This research further identifies kallikrein as an important player in the development of diabetic retinopathy, and provides evidence that blocking its activity may be an effective way to prevent or treat retinopathy in people with diabetes.



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