JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

research frontline

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In this issue:

CLINICAL TRIAL OF DIABETES REGENERATIVE THERAPY SHOWS POSITIVE RESULTS

One of JDRF's industry partners, Transition Therapeutics, Inc., recently announced interim data from an exploratory Phase IIa clinical trial of a diabetes regenerative product that may be effective at regenerating the insulin-producing beta cells that are lost when people develop type 1 diabetes.

In the small Phase IIa trial, both type 1 and type 2 diabetes patients showed improvements in important measures of blood glucose control using E1-INT, a therapeutic combination. Among type 1 patients receiving the drugs for four weeks, more than half saw their average daily insulin usage drop by more than 20 percent, or reduced their HbA1c levels (a long-term measure of blood sugar control) significantly in the months post-treatment.

"These early clinical results are quite encouraging and underscore the possible potential of beta cell regenerative therapeutics in diabetes," noted Dr. Richard Insel, Executive Vice President of Research at JDRF.

The therapeutic combination used in the trial is based on preclinical studies funded by JDRF in the late 1980s. With a JDRF grant, scientists found that the hormone gastrin had beta cell regenerative therapeutic potential. Continued testing through the 1990s demonstrated that a combination of gastrin with the growth factor EGF had distinct regenerative potential in animals. In 2005, in a project funded partly by JDRF, scientists showed that the EGF-gastrin combination induced human islets to multiply in mice.

Transition Therapeutics took over testing of the EGF-gastrin therapy, using human analogues of these proteins, and named the therapy E1-I.N.T. If combined with therapies that block the autoimmune attack, a treatment that spurs beta cell regeneration could potentially lead to a cure for type 1 diabetes.

REGENERATION: A FIELD WITH GREAT PROMISE

Although JDRF did not fund the E1-I.N.T. trials, it is currently partnering with Transition Therapeutics to conduct clinical trials of a similar regenerative therapeutic combination product, GLP1-I.N.T. The GLP1-I.N.T. combination is a second-generation regenerative product, which could have even better effects than the E1-I.N.T. combination. JDRF is providing up to $4 million to the project over two years, to push this diabetes regenerative product into Phase II clinical trials in type 1 diabetes patients. These trials are set to begin later this year.

This partnership between JDRF and Transition Therapeutics is facilitated through JDRF's Industry Discovery and Development Partnership program, which allows JDRF to partner with pharmaceutical, biotech, and medical device businesses that are looking to develop drugs, treatments, technologies, and other therapeutics leading to a cure, reversal, or prevention of type 1 diabetes and its complications.

In addition to providing hope for restoring the ability to make insulin, beta cell regeneration could be an essential complement to other diabetes therapies, such as islet transplantation. For example, JDRF is funding a project at City of Hope National Medical Center in Los Angeles investigating whether giving EGF and gastrin to patients after an islet transplant will allow them to produce enough insulin even when receiving islets from a single donor and to have prolonged function of the transplanted islets. Currently, two or more donors are usually needed for successful islet transplant outcome—limiting the number of patients who can be treated—and the transplanted islets lose function after several years.

For additional information about the Transition Therapeutics clinical study, visit http://www.transitiontherapeutics.com/news/article.php

GLUCAGON MAY ADD ANOTHER DIMENSION TO ARTIFICIAL PANCREAS

As researchers work toward designing a closed-loop artificial pancreas, the assumption has been that the device would incorporate two elements: a glucose monitor and an insulin pump. Insulin would be given only when needed to counteract rising glucose levels.

But what would happen when glucose levels drop too low? The dangers from low blood glucose (hypoglycemia) are acute, resulting in unconsciousness, or even coma or death. Insulin won't help in this situation.

One way to offset this danger is to equip the artificial pancreas with the means to raise blood glucose quickly by dispensing glucagon. This natural hormone spurs the liver to release glucose into the bloodstream and lift blood sugar levels back into normal range. Many type 1 patients have lost the ability to make glucagon and need to inject it during hypoglycemic emergencies.

Now researchers at Boston University have shown that glucagon can be used effectively in tandem with insulin in a closed-loop setting. In studies using diabetic pigs, the insulin–glucagon combination quickly increased glucose levels and helped maintain normal-range levels without incidence of hypoglycemia. Results have been so encouraging that human tests could begin by the middle of this year.

"I think people will come to the conclusion that it makes sense to have glucagon in a closed-loop device not only from a safety standpoint, but also because it meets a physiological need," said Ed Damiano, Ph.D., who led the study. Dr. Damiano conducted the tests at BU with one of his former Ph.D. students, Firas El-Khatib, Ph.D. (recipient of a two-year JDRF postdoctoral fellowship award), and laboratory manager, John Jiang, B.S.

In one study, published in the *Journal of Diabetes Science and Technology*, the researchers performed closed-loop experiments on four anesthetized pigs, simulating meals by infusing glucose into the animals. The scientists took regular readings of the animals' blood-glucose levels, entered them into a computer, and then let their control algorithm (a mathematical formula) calculate how much insulin or glucagon should be given. The researchers then entered the computed control dose into the computer, which communicated wirelessly with two Deltec CoZmo pumps that were attached to the animals—one for each hormone.

Results showed that the insulin-glucagon complement provided tight control, bringing glucose levels into normal range within 80 to 120 minutes after each "meal," with no incidence of hypoglycemia. The algorithm demonstrated great flexibility (the pigs' weights varied as much as twofold in some cases) and stability (it ignored temporary, erratic fluctuations in glucose levels).

The BU researchers used single-point glucose measurements rather than readings from continuous glucose monitors because they wanted to take direct measurements from the blood. (CGMs take their readings from interstitial fluid found between the body's cells, and the researchers were concerned that lag time or other variables might throw off the readings and confound the experiment.)

"I think we should address this problem in stages rather than jumping to the endgame right away," Dr. Damiano said.

The researchers also made another very important finding, which they will publish in *Diabetes Technology and Therapeutics*: glucagon remains stable and potent for up to seven days, even at room temperature. This contradicts conventional wisdom, which held that glucagon depreciates so rapidly once mixed in solution that it would be ineffective in closed-loop control—a notion that made many scientists reluctant to include it in an artificial pancreas.

The BU researchers followed the first study with similar closed-loop tests, in which the pigs were awake and allowed to walk around and eat three actual meals. The researchers hope to finish these subsequent experiments by June 2007.

"Despite their relatively small size, these pigs are capable of eating an enormous amount of carbohydrates in a very short time," Dr. Damiano said. "It really challenges our control system."

"Preliminary results of JDRF-funded closed-loop studies have proven to be extremely promising," noted Dr. Aaron Kowalski, research director for the JDRF Artificial Pancreas Project. "Adding 'counterregulation,' the potential safeguard of glucagon to prevent lows, is very appealing and may be an important step as we drive towards an artificial pancreas."

Dr. Damiano, whose 7-year-old son, David, has type 1 diabetes, thinks that with all the positive data from the pig studies and other human trials, most researchers will come around to seeing the benefits of incorporating glucagon into the artificial pancreas.

"You can certainly drive a car without using your seat belt, but it is not advisable," he said. "In addition to the added safety benefits that glucagon offers, it also allows you to be slightly more aggressive in regulating your blood sugar."

IMMUNE SYSTEM PATHWAY MAY BE KEY ROUTE FOR PREVENTING DIABETES

JDRF-funded scientists have identified an immune system pathway that can be used to cause diabetes reversal and establish long-term immune tolerance in mice. Results from the study suggest that this critical pathway might be exploited with a tightly focused cell therapy that is "antigen-specific," and thus safer to use.

The pathway involves a protein on the surface of immune T cells called PD-1, and a receptor to which it binds, PD-L1, which lies on the surface of other cells, including islet cells. The signals passed through the PD-1—PD-L1 pathway play an important role in spurring immune cells to shut down—and in some cases self-destruct—to prevent the autoimmune attack on the body's own cells. By engaging this pathway, the researchers reversed diabetes in mice and kept it from recurring.

"This is an exciting approach for using an antigen-specific therapy to reverse type 1 diabetes, and it appears in this animal model to keep the disease in remission as well," said JDRF Executive Vice President for Research Richard Insel, M.D.

The study was led by Brian Fife, Ph.D., a JDRF Advanced Postdoctoral Fellow in the laboratory of Jeffrey Bluestone, Ph.D., at the University of California, San Francisco. Dr. Fife's report was published in the *Journal of Experimental Medicine*.

The research team investigated the new approach with nonobese diabetic mice, which spontaneously develop type 1 diabetes at an early age. The scientists isolated spleen cells from the animals, coupled them with insulin molecules, and then implanted them

back into the mice. Insulin is thought to be the primary target of the immune cell attack that triggers type 1 diabetes. When the insulin-loaded spleen cells encountered immune T cells responsible for islet destruction, they made the T cells inactive so they no longer posed a threat.

The pathway appears to regulate autoimmunity by directly controlling the destructive T cells at the site of attack. This suggests that working through the pathway with an antigen-specific therapy could have a powerful effect while also remaining localized to the beta cells researchers want to protect, thus reducing the risk of side effects.

What the researchers found striking in their study was how robust and long-lasting the protective effect of this pathway proved to be. When the mice received a single shot nine months later to block the pathway, the animals immediately developed diabetes. The pathway seems to play a critical role in mediating the beneficial effects of other immune therapies as well—including the anti-CD3 antibody, which is being tested in humans.

In addition to suggesting a new therapeutic strategy, the research provides further evidence that insulin is the major antigen triggering the autoimmune attack causing diabetes. When the researchers tried coupling the spleen cells to other islet molecules suspected to play a role in the disease, there was no protective effect.

SCIENTIFIC PAPER RETRACTED

A research paper describing a molecular link to diabetic complications, published in the January 27, 2006 issue of *Cell* and described in the February 2006 issue of *Research Frontline* ("Molecular Link Found Between High Blood Sugar and Retinopathy") has been retracted by the authors. *Cell* reports that duplicate images were submitted that accompany the paper. The authors believe this error occurred during the revision process. Based on subsequent experiments, the authors believe the central conclusion of the paper is correct, and they plan to publish confirmation of the new data in another journal.