

## Top 10 Research Highlights

The JDRF Diabetes Research portfolio of funded science is among the largest in the world focused on cures and treatments for diabetes and its complications. Exceeding \$137 million last year and representing roughly 700 projects, JDRF science revolves around a set of targeted areas of research. JDRF calls these areas **Cure Therapeutics**, because they are targeted at moving scientific discoveries in each discipline into products, drugs, and treatments for people with diabetes. What follows are some of the major findings and developments in JDRF-funded research over the last year.

### Replacement

#### Glucose-Responsive, Insulin-Secreting Cells Produced From Embryonic Stem Cells

Scientists from the San Diego, California-based company Novocell successfully developed a primitive cell line from human embryonic stem cells that, when implanted into mice, was able to reverse chemically induced diabetes. JDRF partly funded the development of the stem cells lines used in this research, which was published in the journal *Nature Biotechnology*. The primitive cells, called pancreatic endoderm, started producing human insulin in the mice after one to three months. The cells were also shown to produce blood levels of C-peptide comparable to those seen in mice transplanted with about 3,000 isolated human islets; and to protect the mice from hyperglycemia. The study demonstrates that, under the right conditions inside the body, human embryonic stem cells can be differentiated down the path to eventually becoming insulin-secreting beta cells. (December 2007)

### Regeneration

#### Molecular Basis of Beta Cell Growth in Pregnancy Revealed

JDRF researchers at Stanford University found that *menin*, a protein known to suppress tumors, also plays a role in restraining insulin-producing beta cells from multiplying—raising the possibility that

a therapy aimed at reducing *menin* levels could regenerate beta cells in people with type 1 diabetes. The discovery, made in mice by Seung Kim and colleagues, is published in the journal *Science*. The researchers were interested in *menin*'s role in gestational diabetes, a temporary form of diabetes that develops in 2% to 5% of women during pregnancy. They created mice that overproduce the hormone, and found that when these mice became pregnant, the islets grew insufficiently and the animals developed diabetes. A separate part of their study showed that the hormone prolactin, which is abundant during pregnancy, reduced *menin* levels and increased beta cell mass in nonpregnant mice.

To expand this research, JDRF is funding Dr. Kim and Mathew Meyerson, both of Harvard Medical School, with an Academic Research and Development grant. The aims of the follow-up project are to validate this role for *menin* in humans and identify peptides that inhibit *menin*'s actions. (November 2007)

#### Elusive Pancreatic Progenitor Cells Found in Mice

Researchers at the JDRF Center for Beta Cell Therapy in Diabetes, in Brussels, Belgium, identified a bona fide pancreatic progenitor cell that has the capacity to generate new insulin-producing beta cells in mice. The discovery, led by Harry Heimberg and published in the journal

*Cell*, demonstrates the existence of this elusive cell and underscores the potential of beta cell regeneration as a cure for type 1 diabetes. Heimberg's team was able to activate the beta cell progenitors by tying off a duct that drains digestive enzymes from the pancreas—an event that led to a doubling of beta cell mass in the injured part of the pancreas within two weeks, and to the production of more insulin. Proliferation of the new beta cells was dependent on the activity of Neurogenin 3, a master gene also expressed in embryonic progenitor cells. Importantly, the new beta cells proved to be glucose-responsive. The researchers noted that if the finding made in mice holds for humans, the newfound progenitor cells may represent “an obvious target for therapeutic regeneration of beta cells in diabetes.” (January 2008)

#### Clinical Trial of Diabetes Regenerative Therapy Shows Positive Results

One of JDRF's industry partners, Toronto-based Transition Therapeutics, Inc., announced interim data from an exploratory Phase IIa clinical trial of E1-I.N.T., a combination therapeutic containing gastrin and epidermal growth factor that is being developed for the regeneration of insulin-producing beta cells, which are lost when people develop type 1 diabetes. In both type 1 and type 2 diabetes trials, patients showed improvements in important measures of blood glucose control. Among type 1 patients receiving the drugs for four

weeks, more than half decreased their average daily insulin usage by more than 20%, or reduced their HbA1c levels (a long-term measure of blood sugar control) by 1.2 to 2.0 points in the months post-treatment. The therapeutic combination used in the trial is based on preclinical studies funded by JDRF in the late 1980s.

Although JDRF did not fund the E1-I.N.T. trials, it is currently partnering with Transition Therapeutics to conduct clinical trials of a second-generation regenerative product (GLP1-I.N.T, or gastrin combined with a glucagon-like peptide analogue) that may prove to have even better effects than the E1-I.N.T. combination. These trials are set to begin later in 2008. In March 2008, Transition Therapeutics announced a licensing and collaboration agreement with Eli Lilly and Company to develop and commercialize its gastrin-based therapies for beta cell regeneration.

## Autoimmunity

### JDRF Industry Partners Form Alliances with Major Pharmaceutical Companies

Two of JDRF's Industry Discovery and Development partners entered into global alliances with pharmaceutical companies to develop and commercialize anti-CD3 antibodies for the treatment of early-stage type 1 diabetes. IDDP partner MacroGenics entered into an alliance with Eli Lilly and Company to develop teplizumab, an anti-CD3 antibody that has been effective in clinical trials at slowing disease progression in newly diagnosed patients. The second JDRF partner, Tolerx, formed an alliance with GlaxoSmithKline to develop otelixizumab, another anti-CD3 antibody.

The agreements demonstrate the success of JDRF's strategy to fill gaps in the drug development pipeline, by initially funding

proof-of concept clinical trials and then helping small companies move discovery research through early clinical testing until bigger companies step in and fund the large trials needed for FDA approval. If these collaborative partnerships successfully commercialize cures and treatments for diabetes, JDRF also shares in the financial results of that process, enabling the foundation to recoup its support of those projects and fund other research programs leading to a cure. To date, JDRF's IDDP program has funded type 1 diabetes projects at 22 companies. (October 2007)

### Discovery of Fourth Diabetes Antibody Should Aid Prediction

JDRF-funded researchers in Denver identified a fourth autoantibody in human blood that suggests the earliest stage of type 1 diabetes. (Autoantibodies are proteins directed at the body's own cells and tissues and indicate a misguided attack by the immune system.) The new autoantibody, directed to ZnT8, is the first to be discovered in 10 years, and when measured in combination with the three previously known autoantibodies in type 1 patients (those against GAD, IA2, and insulin), raised detection rates for autoimmunity to 98% at disease onset, a level approaching what is needed to diagnose prediabetes in a general pediatric population.

The discovery may help researchers more accurately predict who is predisposed to type 1 diabetes, and could point toward clues for slowing or blocking the disease's progression. "ZnT8 shows great value as a diagnostic tool, and we believe testing for it will very quickly become routine in all of the ongoing clinical research studies," said John Hutton, Ph.D., the paper's senior author. The finding is published in the Proceedings of the *National Academy of Sciences*. (October 2007)

### Powerful Research Method Finds Four New Type 1 Diabetes Genetic Regions

An international research consortium has identified four new genetic regions that affect risk for type 1 diabetes. This finding, made through a powerful new tool called genome wide association (GWA), should help scientists better understand the disease pathway leading to diabetes and could someday provide a clearer picture of individual risk. The GWA method was used by the Wellcome Trust Case Control Consortium (WTCCC), a collaboration of 24 geneticists in the United Kingdom, to examine the genetics behind many common diseases. As part of this large study, the WTCCC identified six chromosomal regions that they suspected of increasing the risk of type 1 diabetes.

Researchers at the JDRF/Wellcome Trust Diabetes and Inflammation Laboratory in Cambridge, U.K., followed up these findings by examining those same areas using a separate, large set of DNA samples. They confirmed that four chromosomal areas are associated with type 1 risk, increasing the number of genetic regions with compelling evidence from six to 10. The finding is published in the journal *Nature Genetics*. (June 2007)

## Complications

### GoKinD Study Shows Certain Patients Less Likely to Develop Diabetic Kidney Disease

A large genetics study has shown that persons with type 1 diabetes carrying a specific gene variant are protected to some degree from diabetic nephropathy, a progressive and life-threatening kidney disease that develops in about one of three individuals with type 1 diabetes. Individuals who have inherited the "allele," or alternative form of the gene in

question—called DRB1\*04—appear to be able to tolerate the harmful effects of hyperglycemia.

Most strikingly, type 1 patients carrying two copies of allele DRB1\*04 were 50% less likely to have diabetic kidney disease than those with no copy of the allele, regardless of how long they had diabetes. This research, published in the journal *Diabetes*, is the first to report an association between an inherited variation in the DRB1 gene and susceptibility to diabetic kidney disease. The finding offers an important clue about the genetics of nephropathy, and may contribute to the development of targeted preventive therapies or new therapeutic targets.

The researchers analyzed the DRB1 gene, as well as three others previously identified as risk factors for type 1 diabetes, using DNA samples from the GoKinD collection (The Genetics of Kidneys in Diabetes Study), an initiative supported by JDRF, the NIH, and the CDC. (February 2008)

### **Industry Partner Sangamo BioSciences On Track With Phase II Study of Neuropathy Therapy**

Sangamo BioSciences, one of JDRF's Industry Discovery and Development Partners, recently announced that it has completed the enrollment of its Phase 2 multi-center, placebo controlled clinical trial evaluating SB-509, a zinc finger protein for the treatment of mild to moderate diabetic neuropathy. JDRF will provide up to \$3 million toward the study. SB-509 is an engineered protein that acts as a transcription factor, binding directly to DNA and specifically turning up the production of a gene encoding vascular endothelial growth factor—a molecule that has been shown to have direct neuroprotective and neurotrophic effects.

Sangamo's preclinical and Phase 1 studies of SB-509 suggest that the therapy may have disease-altering benefits, possibly by directly protecting and restoring nerve function, in contrast to current treatments, which only address the pain associated with neuropathy.

The Phase 2 trial will evaluate peripheral sensory neuropathy in the legs, a common diabetes complication whose initial symptoms of numbness and tingling in the toes or feet often gradually evolve to a loss of sensation and motor function as nerve damage progresses. (December 2007)

## **Metabolic Control**

### **FDA Approves *In Silico* Model of the Artificial Pancreas**

The FDA recently approved an *in silico* model of diabetes—a computer simulator—as a pre-clinical testing tool for closed-loop research at the seven Artificial Pancreas Consortium sites. The simulator, which allows consortium researchers to “plug-and-run” their algorithms in a controlled virtual environment, will facilitate the development of new algorithms, by enabling the researchers to test and refine artificial pancreas algorithms quickly; allow for computer-based algorithm comparisons; and eliminate the need for animal testing, allowing investigators to focus instead on in-hospital human clinical trials, saving time and considerable expense.

Because the simulator is now FDA-approved, the process of receiving regulatory approval for human trials of closed-loop systems will be faster and more clearly defined—a significant achievement that should also accelerate the development and possible commercialization of a closed-loop artificial pancreas.

Construction of the simulator represents the collaborative work of Dr. Claudio Cobelli of the University of Padova in Italy, a pioneer in the mathematical modeling of glucose metabolism, who laid the foundation for building the *in silico* platform; and Dr. Boris Kovatchev, principal consortium investigator at the University of Virginia in Charlottesville, who took the lead for the consortium in developing and obtaining approval for the device. (January 2008) ■