

Top 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. With funding expected to reach \$100 million in FY2009 and including more than 40 human clinical trials, JDRF science revolves around a set of targeted areas of research, each aimed at moving scientific discoveries 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 past year.

JDRF Funds the Development of a New Insulin

JDRF has entered into a partnership with the company SmartCells, Inc., to advance the development of SmartInsulin, an insulin that is administered just once a day and that is self-regulating—after it is injected, the insulin is released over time in response to the body's glucose levels. Unlike currently available insulins, SmartInsulin is designed to maintain continuous, tight control of blood glucose levels while reducing the risk of hypoglycemia, like the pancreas does automatically in people without type 1 diabetes. JDRF is providing \$1 million in funding to support safety and efficacy trials of SmartInsulin, with the goal of accelerating its development and reducing the time needed to progress to human testing. The grant is part of JDRF's innovative Industry Discovery and Development Partnership Program, which supports companies developing treatments and technologies for type 1 diabetes and its complications. (October 2008)

Key Point: *SmartInsulin could mark a significant improvement in treating diabetes by requiring fewer injections and less glucose monitoring while reducing the incidence of hypoglycemia.*

Continuous Glucose Monitoring Improves Blood Sugar Control

A major clinical trial funded by JDRF has found that people with type 1 diabetes who used continuous glucose monitoring (CGM) devices to help manage their disease experienced significant improvements in blood sugar control. Results from the multi-center study were presented at the European Association for the Study of Diabetes' annual meeting and published in the *The New England Journal of Medicine*. The CGM study—a randomized, controlled trial involving 322 patients ages eight to 72 years—took place at 10 academic, community, and managed care practices. Improvements were most evident in adults 25 years of age or older; in children, benefits were seen in some measures but not all, while teenagers and young adults, as a group, experienced no changes in glucose control compared with the control group. These latter results were likely due to less consistent CGM use among younger participants, as the researchers noted that individuals of all ages who used CGM six days a week or more lowered their A1c by at least .5 in just six months—enough to lower the risk of microvascular complications by approximately 25 percent. In large part because of the CGM trial's positive results, several large national health insurers have expanded their policies to include broad coverage for CGM for patients with type

1 diabetes. ABC News recognized JDRF's groundbreaking CGM clinical trial as one of the top 10 medical breakthroughs of 2008. (September 2008)

According to the results of another part of the trial, published in *Diabetes Care*, people with type 1 diabetes who have already been successful in managing their blood sugar to recommended levels can further benefit from using CGM devices. The study found that CGMs enable people who have achieved excellent control (with HbA1c levels below seven percent) to continue to tightly manage their diabetes while cutting down on the frequency of hypoglycemia. Research has shown that good blood sugar control is a key factor in reducing the risk of the devastating long-term complications of the disease, such as blindness and kidney disease—but that the fear of low blood sugar emergencies often prevents many people from achieving tight control and remains a constant concern for those who manage their diabetes well. The study, which included 129 adults and children ranging in age from eight to 69, is the second major publication resulting from JDRF's groundbreaking CGM trials, established to clinically document the benefits of CGM devices in helping people with type 1 diabetes manage their disease more effectively. (May 2009)

Key Point: *Continuous glucose monitors are more than simply devices of convenience for people with diabetes—they are tools that can substantially improve blood sugar control when used regularly. The growing evidence of the benefits of CGM underscores the importance of continued research into a closed-loop artificial pancreas, a device that uses CGM data to automatically administer appropriate doses of insulin through a pump.*

A Potential New Approach for Treating Retinopathy

JDRF-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, the most common and serious eye-related complication of diabetes. 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 an enzyme called plasma kallikrein. Edward Feener, Ph.D., an investigator at Joslin, led the study. To block the actions of kallikrein, the researchers administered the inhibitor ASP-440 to rats with high blood pressure, a known risk factor for developing retinopathy. ASP-440 decreased the amount of retinal blood vessel leakage by as much as 70 percent—a strikingly favorable outcome. The inhibitor also lowered the animals' high blood pressure, another factor that contributes to the development of diabetic eye disease. The study is published in the journal *Hypertension*. (February 2009)

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.*

Scientists Advance Our Understanding of “Hyperglycemic Memory”

In a potential breakthrough in determining why diabetes causes cardiovascular complications, JDRF-funded researchers have shown that even short-term spikes in blood sugar can have dramatic and long-lasting effects on vascular cells. The findings suggest that spikes of hyperglycemia may be a risk factor for diabetic complications independent of a person's A1c levels. The spikes were found to cause long-lasting “epigenetic,” or environmentally induced, changes in a specific gene—changes that led to the gene's over-expression, and in turn, that of several inflammatory genes implicated in the development of vascular complications. These changes persisted even when blood sugar levels returned to normal. The study, published in the *Journal of Experimental Medicine*, opens the door to potential new ways to treat—and even prevent or reverse—the complications of type 1 diabetes. The research was a collaboration between scientists from the Baker IDI Heart and Diabetes Institute in Melbourne, Australia, which receives JDRF support, and the JDRF International Center for Diabetic Complications Research at Albert Einstein College of Medicine in New York City. Assam El-Osta was the study's lead author and investigator at the Baker Institute; Michael Brownlee led the research at the JDRF International Center. (September 2008)

Key Point: *Spikes in blood sugar may cause long-lasting epigenetic changes that can lead to diabetic complications. JDRF is actively funding this promising field of study because it may provide new approaches to the prevention and reversal of diabetes complications.*

Cancer Drugs Reverse Type 1 Diabetes in Mice

JDRF-funded researchers at the University of California, San Francisco have shown that two common cancer drugs can block and reverse type 1 diabetes in mice. The drugs—marketed as Gleevec and Sutent—prevented mice from developing type 1 diabetes and put 80 percent 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 was that Gleevec led to sustained remission in the majority of mice long after treatment had ended. The study, published in the journal *Proceedings of the National Academy of Sciences*, was conducted as part of the Immune Tolerance Network, a JDRF-funded international research consortium. In collaboration with the network, JDRF will continue to follow progress in this field and will explore the potential to translate these findings into treatments. Drs. Cedric Louvet and Jeffrey Bluestone at the University of California, San Francisco carried out this work. (December 2008)

Key Point: *The findings suggest that two common cancer drugs may provide an important therapeutic approach for the treatment of new-onset type 1 diabetes and potentially other autoimmune disorders.*

“Insulin Fragment” Therapy Safe and Promising in Its First Evaluation in Humans

JDRF-funded researchers from the United Kingdom have shown that “proinsulin peptide,” a fragment of insulin being evaluated as a potential immune system therapy for type 1 diabetes, is safe to use in people who have had the disease for some time. The study, published in the journal *Clinical and Experimental Immunology*,

showed that people with type 1 diabetes who were given three doses of the peptide did not have an acute allergic reaction or experience any adverse immune responses such as the activation of potentially damaging T cells. Because these outcomes are major risks associated with this type of therapy, their absence signifies “an important milestone in the clinical evaluation of peptide immunotherapy for type 1 diabetes.” Peptide immunotherapy uses small proteins to reset the immune system to a healthy state. In the case of type 1 diabetes, the goal is to train the immune system to tolerate the insulin-producing beta cells that are the target of the misdirected immune response that causes diabetes. JDRF supported the research through the Diabetes Vaccine Development Center (DVDC), a joint venture between JDRF and Australia’s National Health and Medical Research Council. Mark Peakman led the research at King’s College London and the University of Bristol. (February 2009)

Key Point: *The first human trial of proinsulin peptide indicates that it is a safe and promising therapy for resetting the immune response in people with type 1 diabetes. The results set the stage for a phase Ib clinical trial in the newly diagnosed.*

Gastrin Combination Therapy Reverses Diabetes in Mice

A short treatment with two drugs can increase the number of insulin-producing beta cells and also slow their autoimmune destruction in mice with diabetes—enough to restore normal blood sugar levels and reverse the disease. Scientists were surprised to find evidence that the therapy—a combination of gastrin and glucagon-like peptide 1—had both regenerative and immune system effects. According to the investigators, led by Alex

Rabinovitch, M.D., at the University of Alberta in Edmonton, the findings suggest that the two drugs work together to target both the cellular mechanisms that promote beta-cell growth and survival, as well as the immunologic mechanisms that destroy beta cells in type 1 diabetes. Combining the two drugs offers a promising strategy for reversing beta cell loss in people with the disease. Next steps will be to validate the results in a human clinical trial. The study, published in the journal *Diabetes*, was funded by grants from JDRF and Transition Therapeutics, Inc., one of JDRF’s Industry Discovery and Development Partners. Transition Therapeutics recently partnered with the pharmaceutical company Eli Lilly to develop gastrin-based therapies and to further speed testing and development. (December 2008)

Key Point: *A two-drug combination therapy has been shown to normalize blood sugar levels in diabetic mice by increasing beta-cell mass and reducing the autoimmune response. These findings support the use of the therapy in human clinical trials.*

A Potential T Cell Therapy Clears Laboratory Hurdles

JDRF-funded researchers have provided further evidence that regulatory T cells are a promising cell-based therapy for the treatment of type 1 diabetes. Lead researcher Jeffrey Bluestone, Ph.D., and colleagues from the Diabetes Center at the University of California, San Francisco have shown that regulatory T cells can be isolated from patients with type 1 diabetes and then expanded in the laboratory to therapeutically useful levels without a loss of function or stability. A type of immune cell, regulatory T cells serve the important role of putting the brakes on immune responses. When immune T cells begin to attack the insulin-producing beta

cells in the pancreas, regulatory T cells orchestrate their removal and slow their destructive actions. Previous research shows that regulatory T cells can prevent and even reverse type 1 diabetes in mice when administered in large quantities. The current study, published in the journal *Diabetes*, confirms the feasibility of the approach—isolating, expanding, and ultimately reintroducing the regulatory T cells—as a potential treatment for people with the disease. Although the mechanism of the treatment is not fully understood, it is believed that regulatory T cells somehow “can overcome intrinsic defects and restore tolerance in type 1 diabetes.” A small phase I study, representing an initial assessment of the therapeutic benefits of regulatory T cell therapy in humans, is being planned. (March 2009)

Key Point: *Regulatory T cells are able to suppress the actions of other immune cells and are emerging as an important cell therapy for the treatment of type 1 diabetes.*

Anti-CD3 Treatments Move to Phase III Trials

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. These collaborations have now moved anti-CD3 antibodies to the latest stage of clinical testing. In one partnership, among JDRF, IDDP partner MacroGenics, and Eli Lilly and Company, researchers have begun enrolling patients in a phase III trial to test 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 that is in phase III trials. 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. (March 2009)

Key Point: *Anti-CD3 treatments have moved into phase III clinical trials. These achievements 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.*

Compounds That Trigger Beta Cell Replication Are Identified

Researchers at the Genomics Institute of the Novartis Research Foundation (GNF) have identified a set of compounds that can trigger the regeneration of insulin-producing cells in the pancreas. Using a sophisticated technique called high-throughput screening, a research team led by Dr. Peter Schultz, director of GNF, screened a chemical library of more than 850,000 compounds for their effect on the growth of a mouse beta cell line. Out of this large collection, about 80 compounds showed promise for further investigation, and two distinct groups of compounds stood out. One appears to promote beta cell replication via a biological pathway critical for beta cell development in the embryo. The study, funded by JDRF, is the first of its kind in type 1 diabetes and represents an important initial step in the possible discovery of regenerative medicines for type 1 patients. A full report of the research can be found in *Proceedings of the National Academy of Sciences*. (February 2009)

Key Point: *The study is a step toward identifying small molecules that may induce the expansion of beta cells, and it may help reveal the biological mechanisms regulating this process.*

Researchers Identify a Protein Involved in the Regeneration of Beta Cells

JDRF-funded researchers at the University of Pittsburgh School of Medicine have identified a protein that could potentially be targeted to drive the regeneration of insulin-producing beta cells. Called cdk6, the protein triggered robust beta cell replication in human islets without a loss of function—the cells could sense glucose and produce insulin in response. The replicated cells also corrected diabetes when transplanted into diabetic mice. “Most scientists thought that these important pancreatic cells could not be induced to regenerate, or could only replicate very slowly,” explained lead researcher Andrew F. Stewart. “This work provides proof-of-principle that the production of human beta cells can be stimulated, and that those newly generated cells function effectively both in the lab and in a living animal.” The study is published in the journal *Diabetes*. (January 2009)

Key Point: *Diabetes researchers have identified a protein that regulates the regeneration of adult human beta cells. This breakthrough can be used to discover therapeutics to cure diabetes in people.*

A More Efficient Way to Produce Beta Cell Precursors from Stem Cells

Using a novel screening method, JDRF-funded researcher Shuibing Chen and colleagues from the Harvard Stem Cell Institute identified a small molecule that can help drive human embryonic stem cells along the path to becoming insulin-

producing beta cells. When embryonic stem cells were combined with the molecule and a key growth factor, nearly half of them developed into an essential, early precursor cell from which all of the specialized cells of the pancreas are derived, including beta cells. Other protocols that have sought to form insulin precursor cells from embryonic stem cells have achieved a substantially lower “differentiation efficiency.” Embryonic stem cells have the ability to develop into any type of cell or tissue as they mature, and thus hold the promise of being turned into insulin-secreting cells that could be transplanted into patients with type 1 diabetes. By uncovering a more efficient way to generate precursor cells from human embryonic stem cells, this research could lead to less costly and faster ways of generating the large, unlimited supply of beta cells that would be needed for testing and treatment purposes. The research is published in the journal *Nature Chemical Biology*. (March 2009)

Key Point: *Researchers have developed a more efficient way to produce stem cells that are further along on the path to becoming insulin-producing beta cells.*

Transplanted Islets Survive Without Immunosuppression

JDRF-funded scientists from Northwestern University Feinberg School of Medicine in Chicago were able to prevent the rejection of insulin-producing islets transplanted into diabetic mice without using toxic immunosuppressive drugs. In doing so, they bring us a step closer to achieving what researchers call “donor-specific immune tolerance.” Stephen Miller and colleagues prepared the recipient's immune system for the islet transplant by first introducing a different type of donor cell. Their approach was to treat these cells with a chemical that

left them intact but with an altered immune profile—so that the recipient’s immune system would no longer be provoked. The cells were injected into diabetic mice seven days before and one day after the mice underwent islet cell transplantation. Providing just two infusions of the chemically treated cells led to prolonged survival of the transplanted islets—even though no immunosuppressive drugs were added to stem the immune response. In 70 percent of the recipients, the transplanted islets survived for more than 100 days. With JDRF support, the researchers will continue to test and refine their tolerance-induction strategy, evaluating its ability not only to prevent islet rejection but also to suppress the underlying immune attack. The study is reported in the journal *Proceedings of the National Academy of Sciences*. (September 2008)

Key Point: *In diabetic mice, researchers have developed an effective new way to prevent the rejection of transplanted islets without using immunosuppressive drugs. The protocol has strong therapeutic potential both for human islet cell transplantation and for treating the immune response that causes diabetes.*

Adult Cells from the Mouse Pancreas Are Turned into Insulin-Producing Cells

Diabetes researchers from the Howard Hughes Medical Institute at Harvard University converted adult exocrine cells in the pancreas, which do not normally make insulin, into insulin-producing beta cells that can improve blood sugar levels. The findings represent important progress toward generating a large supply of insulin-producing cells from adult cells that are healthy and abundant—exocrine cells, which produce digestive enzymes, make up about 95 percent of the cells in the pancreas. Using viruses to ferry key regulatory genes into the exocrine cells of live mice,

the investigators turned off the digestive functions of the exocrine cell and turned on genes that enable a cell to make insulin. About 20 percent of the virally altered cells were converted into cells that produced insulin, which was enough to reduce blood sugar levels in the mice to near-normal levels. Ultimately, it took only three genes to initiate the “extreme makeover.” While JDRF did not directly fund the study, JDRF supports Douglas A. Melton, the principal investigator, in other areas of type 1 research. The study was published in the journal *Nature*. (August 2008)

Key Point: *Without using stem cells or complex genetic reprogramming, researchers changed the identity of adult cells from the mouse pancreas, converting them into insulin-producing beta cells. A potential initial application may be to perform this identity switch outside the body using exocrine cells from a donated cadaver pancreas, to provide beta cells for islet transplantation.*

Metabolic Triggers May Contribute to the Onset of Diabetes

JDRF-funded researchers from Finland have discovered that children who develop type 1 diabetes have distinct metabolic abnormalities that can sometimes be seen years before the classic signs and symptoms of the disease. The findings, published in the *Journal of Experimental Medicine*, offer intriguing new insights into what causes type 1 diabetes, and may lead to novel prevention strategies. Typical anomalies identified by the researchers were marked elevations or reductions in the levels of two metabolic building blocks—lipids (a type of fat) and amino acids (which join to form proteins). In one nine-year-old girl, for example, metabolic disturbances were at their highest levels one to two years before any autoantibodies to insulin appeared; by the time she was six months old, her blood

levels of a certain amino acid were 13 times higher than normal. According to lead researcher Olli Simell from the University of Turku and colleagues, the research suggests that autoimmunity may be a relatively late reaction to these early metabolic changes. To move the research forward—Dr. Simell’s study is the first to report this type of metabolic dysfunction—it will be essential to validate the findings in other large and well-characterized population groups. (December 2008)

Key Point: *In some children with type 1 diabetes, metabolic disturbances can be detected well before the appearance of autoantibodies, suggesting that the immune response that leads to diabetes might not be the initial cause of the disease. This unexpected finding may point to new directions in prevention, diagnosis, and treatment.*