

Top Research Highlights

The JDRF portfolio of diabetes research is among the largest in the world, focused on cures and better treatments for type 1 diabetes and its complications. With funding of \$100 million in FY2009, representing research in more than 20 countries and including 44 human clinical trials, JDRF science is aimed at moving research discoveries into products, drugs, and treatments for people with diabetes. The major findings and developments JDRF funded over the past year, which follow, underscore the key role the organization plays in directing and catalyzing the pursuit of a cure.

JDRF Enters Innovative Diabetes Drug Discovery and Development Partnership in Regeneration

In a major development, JDRF entered into a novel collaborative agreement with the Genomics Institute of the Novartis Research Foundation (GNF) to create a diabetes drug discovery and development platform. The four-year program is one of the largest and most comprehensive collaborations in the 40-year history of JDRF. It marks a major opportunity to work with an experienced and highly regarded scientific partner to quickly translate discoveries in research into therapeutics—drugs, compounds, and treatments for people with type 1 diabetes. Based in San Diego, GNF was founded in 1999 by the Novartis Research Foundation. “This agreement with GNF opens exciting new avenues for JDRF to speed the translation of basic research into drugs and treatments for type 1 diabetes,” said Alan J. Lewis, Ph.D., President and Chief Executive Officer of JDRF. The JDRF-GNF partnership should jumpstart the creation of a multi-product pipeline for beta cell regeneration, a therapeutic priority for JDRF. (August 2009)

Key Point: *The partnership between JDRF and GNF aims to deliver a succession of diabetes drug candidates to the clinic over the next four years, beginning with regeneration.*

Four Separate Publications Document the Benefits of CGM

JDRF Research Shows CGM Improves Blood Sugar Control

A major clinical trial funded by JDRF 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 first published in *The New England Journal of Medicine*. The CGM study—a randomized, controlled trial involving 322 patients ages eight to 72—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 have since been shown to be due to less consistent CGM use among younger participants, confirming the researchers’ initial observations and findings 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 reduce the risk of some 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 or broaden coverage of CGM. ABC News recognized the groundbreaking trial as one of the top 10 medical breakthroughs of the year. (October 2008)

CGM Also Benefits Patients Who Already Have Good Control

Additional results of the JDRF CGM trial, published in *Diabetes Care*, showed that people with type 1 diabetes who are already successfully managing their blood sugar can further benefit from using CGM devices. The study found that CGMs enable people who have achieved excellent control (with HbA1c levels below 7 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—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)

Regular CGM Use Increases Control in All Age Groups, Enables Good Control Long-Term

The newest information from JDRF's CGM studies was published in September in an online issue of the journal *Diabetes Care*. One study, which sought to identify predictors of success among participants in the trial, showed that regular use of a CGM device—six days per week or more—is the principal factor in achieving better diabetes control, not the age of the individual using the monitor or other demographic, clinical, or psychosocial factors. The analysis confirmed that in the first six months of the JDRF trial, more frequent CGM use was associated with greater reductions in HbA1c—a finding that was present in all age groups using the devices. The second study, a six-month extension of the CGM clinical trial aimed at evaluating long-term effects, showed that people who continued using CGM to help manage their disease were able to sustain good diabetes control. Just as importantly, it found that continued strong control was attained while actually lowering the incidence of hypoglycemia—the dangerous low blood sugar incidents that can occur with tightly managed type 1 diabetes. (September 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 in people of all ages when used regularly, without increasing the risk of dangerous low blood sugar. The growing evidence of the benefits of CGM underscores the importance of continued research into a closed-loop artificial pancreas, a system that uses CGM data to automatically deliver the right amount of insulin through a pump.*

JDRF Funds the Development of a New Insulin that Reacts to Blood Sugar

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 only released in response to the body's glucose levels. Unlike currently available insulins, SmartInsulin is designed to maintain continuous, tight control of blood sugar levels while reducing the risk of hypoglycemia—like the pancreas does automatically in people without type 1 diabetes. JDRF is providing funding to support safety and efficacy trials of SmartInsulin, with the goal of accelerating its development and reducing the time needed to move to human testing. The grant is part of JDRF's innovative Industry Discovery and Development Partnership (IDDP) program, which supports companies developing treatments and technologies for type 1 diabetes and its complications. (October 2008)

Key Point: *An insulin that needs to be injected only once per day and that reacts to blood sugar only when needed could mark a significant improvement in treating diabetes, requiring fewer injections and less glucose monitoring while reducing hypoglycemia.*

Researchers Discover How Beta Cell Regeneration Slows With Age

Two groups of JDRF-funded researchers have identified processes that explain why insulin-producing beta cells lose their ability to regenerate with age. The findings shed light on what regulates normal expansion and decline of those cells—and could help lead to new therapies for type 1 diabetes. Scientists believe that insulin-producing beta cells can regenerate within the body either through adult beta

cells replicating or from stem cells in the pancreas. However, the capacity of beta cells to regenerate and adapt diminishes as we age. To better understand the molecular events involved, the two groups focused on a specific cluster of genes known to have a “braking” effect on cell growth. They found key proteins that stop this inhibitory process.

The research, which took place at Stanford University School of Medicine in California and at the University of California, Los Angeles, was published in the journal *Genes & Development*. (July 2009)

Key Point: *“The investigators independently identified pathways that regulate how beta cells regenerate and that explain why these cells stop replicating with age,” said Patricia Kilian, Ph.D., Director of JDRF's Regeneration program. “This is exciting, since it suggests that controlling these pathways might enable us to restore the capability to regenerate insulin-producing cells to treat diabetes, even in older people. These findings provide new tools and insights for finding a means to overcome the loss of beta cells.”*

JDRF Launches Online Clinical Service

JDRF successfully launched Clinical Trials Connection (www.trials.jdrf.org), an innovative online service to help people with type 1 diabetes and their families easily find information about clinical trials on treatments and cures for type 1 diabetes and its complications. With more diabetes trials than ever before, Clinical Trials Connection simplifies the process of finding studies that people might want to take part in. The website enables people to search the National Institutes of Health's database of diabetes trials, including JDRF-funded studies. The service offers users many benefits, including lists of all studies that match their preferences and characteristics;

information for the researchers conducting each trial, so users can contact them directly; and automatic e-mail updates. (July 2009)

Key Point: *Over its nearly 40-year history, JDRF has funded more than \$1.3 billion toward a cure, accelerating science to the point where we are now funding more than 40 human clinical trials. For people with type 1 diabetes, getting information about trials, and making a decision to enroll in one, is difficult, time-consuming, and often confusing. Plus, funded scientists are finding it harder and harder to enroll participants in trials in a timely and cost-efficient way. Clinical Trials Connection helps make it easier for people with type 1 diabetes to take part in clinical trials, while addressing the difficulty researchers are having in finding trial participants.*

Different Immune Cells Could Provide Target for Diabetes Therapy

A team of Australian researchers led by JDRF-funded scientist Shane Grey was able to completely prevent type 1 diabetes in mice with a therapy that targets immune B cells, rather than T cells. Most therapies aimed at reversing the immune response that causes type 1 diabetes target T cells—the immune cells ultimately responsible for the destruction of insulin-producing beta cells. But previous research has pointed to a key role for B cells. In the Australian research, prediabetic mice that received a B cell therapy were completely protected from type 1 diabetes throughout the study's 50 weeks. By contrast, mice not given the therapy showed rising blood sugar levels and eventually developed diabetes. The researchers found that the B cell therapy prevents diabetes by reducing the total number of B cells in the body. This effect blunts the degree of B cell/T cell interaction, minimizing a trigger of the disease. It also

increases the number of regulatory T cells, enabling the immune system to “reign in” potential autoimmune activity from destructive T cells. The findings, published in the journal *Diabetes*, advance our understanding of how diabetes develops and progresses—and suggests that depleting the B cells may be a powerful tool for preventing and treating type 1 diabetes in people. (July 2009)

Key Point: *The findings confirm the important role of B cells in triggering diabetes and also point to a potential new treatment: type 1 diabetes can be prevented in mice using a therapy that reduces the number of B cells.*

Beta Cells Survive and Flourish in an Encapsulation Device

JDRF-funded researchers have made important discoveries in encapsulation that could improve the success of islet transplantation. In a study in mice, scientists showed for the first time that transplanted cells that become insulin-producing cells can survive by being encapsulated in a durable “device” that protects them against an immune attack. Equally important, those cells then developed into insulin-producing cells that control rising blood sugar levels. By contrast, adult insulin-producing cells that were encapsulated in the same way exhibited poor survival. The results suggest that encapsulating cells *before* they differentiate and become beta cells—using stem cells, for example—may be a more successful approach to replacing insulin-producing cells in people with type 1 diabetes, and a new way to take advantage of emerging cell-based therapies.

“Our data suggest that long-term protection of human beta cells in type 1 diabetic patients without immunosuppression is a realistic goal,” said Pamela

Itkin-Ansari and colleagues from the University of California, San Diego and the Burnham Institute for Medical Research in La Jolla, California. Their findings were reported in the journal *Transplantation*. (April 2009)

Key Point: *The study provides proof-of-concept that cells that develop into insulin-producing cells can survive, proliferate, and mature in an encapsulation device to the point where they can correct diabetes.*

A Novel Way to Address Autoimmunity in Type 1 Diabetes

JDRF-funded researchers are developing an oral vaccine to control the autoimmune response that causes type 1 diabetes. The unique approach is being pioneered by the University of Massachusetts Medical School. Researchers there, led by Michael Czech, are using hollow “yeast shells” to carry proteins and other agents that alter the behavior of immune cells in the stomach. If effective, the vaccine will retrain the immune system to tolerate the insulin-producing beta cells that are mistakenly targeted and destroyed in type 1 diabetes.

The novel strategy is based on a promising new approach for silencing inflammatory reactions associated with the immune system. JDRF is funding the UMass researchers to apply this novel technology to benefit people with type 1 diabetes. Dr. Czech and his team are testing their hypotheses in mice. (April 2009)

Key Point: *Researchers are developing a novel oral vaccine for type 1 diabetes. Using “yeast shells” to deliver proteins and other agents, the vaccine is intended to interrupt the immune attack that causes diabetes, as well as silence key genes that contribute to inflammation and autoimmunity.*

Gene Therapy Shows Promise in Reversing and Repairing Diabetic Nerve Damage

JDRF industry partner Sangamo BioSciences said that its Phase II trial of a gene therapy drug showed significant results in reversing and repairing diabetic nerve disease. The trial evaluated a gene therapy to treat mild to moderate nerve damage in the legs. A common diabetic complication, “peripheral sensory neuropathy” is associated with the loss of small nerve fibers in the arms and legs, often leading to a loss of sensation and motor function as nerve damage progresses. The Sangamo study showed that the drug has a direct positive effect on nerve regrowth, and that it is safe. People with diabetic neuropathy who were given the therapy had a significant increase in the number of these small nerve fibers in the skin. The data from this and another study in people with severe neuropathy will form the basis of an additional study to confirm these findings.

The therapy promotes the production of a specific protein linked to nerve growth and function. An increase in these proteins are thought to protect and repair nerve damage in people with diabetes—while current treatments only address the pain associated with neuropathy. (October 2009)

Key Point: *The latest data on a gene therapy developed by a JDRF industry partner reveal its potential to stimulate nerve regrowth in the legs, offering hope to people suffering from diabetic neuropathy.*

Gastrin Combination Therapy Reverses Diabetes

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 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 immune 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 Eli Lilly and Company 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.*

Treatments for Newly Diagnosed 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 treatments for early-stage type 1 diabetes. These collaborations have now moved “anti-CD3 antibodies” to the latest stage of clinical testing. In one partnership, between JDRF partner MacroGenics and Eli Lilly and Company, researchers have begun enrolling patients in a Phase III trial to

test teplizumab, an 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 oteelixumab, another anti-CD3 antibody that is in Phase III trials. If these collaborative partnerships successfully commercialize cures and treatments for diabetes, JDRF will also share 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 and show promise to delay the progression of diabetes in the newly diagnosed. 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 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 prompt the expansion of beta cells, and it may help reveal the biological mechanisms regulating this process.*

Researchers Convert Cells in the Pancreas to Insulin-Producing Beta Cells

JDRF-funded researchers have shown that cells in the pancreas that normally do not make insulin can be changed into cells that do—boosting the prospects of using regeneration as a treatment for type 1 diabetes. In a study in mice, they discovered that by driving the expression of a specific gene in non-insulin producing alpha cells, they could turn alpha cells into insulin-producing beta cells. The researchers targeted the gene because it is known to regulate growth, development, and other key cellular functions. They also discovered that the alpha cells that became new beta cells came from “progenitor” cells in the pancreas, and that the drop in the number of alpha cells triggered additional progenitor cells to replace them. Ultimately, the newly formed beta cells resulted in better glucose control and helped the mice survive. The study, co-funded by JDRF, was published in the journal *Cell*. Lead researchers were Patrick Collombat of the Max-Planck Institute for Biophysical Chemistry and Ahmed Mansouri of the University of Göttingen, both in Germany, working in collaboration with researchers at the JDRF Center for Beta Cell Therapy in Diabetes in Brussels. (August 2009)

Key Point: *The findings provide important insight into a possible regenerative therapy for type 1 diabetes. Researchers now have two potential cell targets for regeneration—progenitor cells and the alpha cells—as well as a critical gene and pathway that can be used to screen for drugs that target these cells.*

Understanding the Role of Lipids in Diabetic Complications

Although it is well-known that abnormal lipid levels, such as high LDL (or “bad”) cholesterol, are a strong risk factor for cardiovascular disease, several recent studies suggest they might also be involved in the development and progression of other complications of diabetes. As reported in the journal *Diabetes Care*, a JDRF-funded study has shown that a significant number of children and teenagers with type 1 diabetes have abnormal lipid levels, including higher-than-recommended levels of cholesterol and triglycerides. In addition, people who have microalbuminuria—a sign of early kidney disease—had the highest cholesterol levels, suggesting that lipid levels may play a role in developing this complication. The multi-center study took place in the United Kingdom. John Todd and Jason Cooper, both of the JDRF/Wellcome Trust Diabetes and Inflammation Laboratory in Cambridge, contributed to the research. (April 2009)

Key Point: *The study shows that lipid levels may be involved in the development of diabetes and diabetic complications. It raises questions about the need for lipid monitoring and management in type 1 diabetes as a way to prevent complications beyond cardiovascular disease.*

Blood Pressure Drugs Stop Diabetic Eye Disease from Progressing

Two drugs used to treat high blood pressure can significantly slow the progression of diabetic retinopathy, a serious and common complication of type 1 diabetes that can lead to vision loss. According to five-year data from a multi-center clinical trial, type 1 patients with normal blood pressure, no detectable kidney disease, and very mild eye disease who received either drug—losartan or enalapril—were at least two times less likely to see a progression in diabetic retinopathy than study participants who didn’t get them. Neither drug slowed the progression of diabetic kidney disease. While the findings, published in the *New England Journal of Medicine*, suggest a potential new therapy for retinopathy, further studies are needed before the drugs can be recommended for routine use in people with diabetes. To this end, the researchers will need to establish how long the protection lasts beyond the five years of the study, and whether the benefits continue if the treatment is stopped. They will also need to determine if the drugs benefit patients with more advanced eye disease, elevated blood pressure, and detectable kidney disease, since these characteristics often define the type 1 population. Michael Mauer from the University of Minnesota in Minneapolis led the study, which was built on research co-funded by JDRF in 2002. (July 2009)

Key Point: *Certain drugs currently used to treat high blood pressure appear to significantly slow the progression of diabetic retinopathy.*