

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 nearly \$101 million in FY2009, representing research in more than 20 countries and including numerous 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.

Joining Forces to Accelerate the Development of Immune System Treatments

To accelerate the development of treatments directed at autoimmunity, the process by which the body mistakenly attacks its own cells and tissues, JDRF has joined forces with two new partners in an innovative collaboration. JDRF is partnering with Fast Forward, LLC – the drug-development arm of the National Multiple Sclerosis Society – and Axxam SpA, an Italian company that conducts early-stage discovery research. Axxam will screen its extensive chemical library for compounds that can target immune system “ion channels,” the tiny protein pores on the surface of cells that control the flow of charged particles. Studies have found that immune cells in multiple sclerosis and type 1 diabetes, both of which are autoimmune diseases, contain high levels of a specific ion channel. Hyperactivity of this channel contributes to the dysfunction of the immune system in both disorders. Axxam is looking to identify compounds that affect the channel—and to develop them as potential therapies. The agreement is the first of its kind between patient advocacy organizations focused on different diseases. (January 2010)

Key Point: *JDRF’s new partnership with Fast Forward and Axxam opens exciting new avenues for speeding the translation of basic research into drugs and treatments for type 1 diabetes. This research has the potential to negate the autoimmune process causing type 1 diabetes and multiple sclerosis, leading to cures for these diseases.*

Researchers Use Nanoparticle “Vaccine” to Cure Diabetes in Mice

Using an innovative nanotechnology-based “vaccine,” researchers were able to successfully cure and prevent type 1 diabetes in mice. The study, co-funded by JDRF and published in the journal *Immunity*, provides important new insights into how to stop the immune attack that causes type 1 diabetes. It also shows the potential of “antigen-specific” therapies, which target highly specific autoimmune responses without compromising the overall immune system. The researchers used a vaccine made of nanoparticles thousands of times smaller than the size of a cell, coated with proteins that are involved in immune cell communication. The nanoparticle treatment expanded a type of regulatory T cell that suppressed the aggressive immune attack on the pancreas. These nanoparticles restored normal blood sugar levels in a “humanized” mouse model of diabetes—highlighting the potential of

the vaccine in people. The study took place at the University of Calgary in Alberta and was led by Dr. Pere Santamaria. (April 2010)

Key Point: *Researchers were able to cure type 1 diabetes in mice using an antigen-specific nanoparticle “vaccine.” This approach holds great potential to reverse the immune attack that causes diabetes without generally suppressing the immune system.*

“Regulatory” Cells May Guide the Way to Diabetes Prevention

JDRF-funded scientist Diane Mathis has demonstrated that immune cells called regulatory T cells play a role in preventing type 1 diabetes. In the journal *Immunity*, she described how regulatory T cells control the progression of diabetes in mice. She showed that the cells rein in the autoimmune attack on the pancreas by altering the activity of another key immune cell—called a “natural killer” cell. When regulatory T cells were unavailable to block them, the natural killer cells released a molecule that set in motion the aggressive immune attack that leads to diabetes. The findings suggest that drugs or therapies that target natural killer cells might be effective in preventing or altering the course of the disease. Dr. Mathis is Director of the JDRF Center on Immunological Tolerance in Type 1 Diabetes at Harvard Medical School. (October 2009)

Key Point: *JDRF scientists have shed light on how regulatory T cells block the progress of diabetes. The findings highlight the important role of these cells in controlling autoimmunity and represent an important research advance that could be translated into therapies for people with type 1 diabetes.*

JDRF's nPOD Program Expands to Europe

JDRF's nPOD program has been a remarkable success in advancing research into the causes of type 1 diabetes since its launch in the United States in 2007. The program (nPOD stands for Network for Pancreatic Organ Donors with Diabetes) has been funded by JDRF for an additional three-year period. It is also being expanded to Europe, which will provide researchers with an additional pool of potential organ donors—including the important but less-studied group with prediabetes. One of JDRF's most important resources for scientists, nPOD provides the international type 1 diabetes research community with access to human pancreatic tissues from organ donors at all stages of the disease; researchers use the tissues to explore key questions about the underlying cause of type 1 diabetes. nPOD has made remarkable progress in increasing the number of organ donors screened for type 1 diabetes autoantibodies. By 2011, it is expected to be performing autoantibody screens on about 30% of all organ donors in the U.S., which will be a key milestone in nPOD's and JDRF's list of accomplishments. (January 2010)

Key Point: *JDRF's nPOD program has been a great success in accelerating progress toward cures and treatments for type 1 diabetes. JDRF has renewed nPOD for another three years in the United States and will expand it to Europe.*

Phase II Study Shows Long-Term Benefits of Anti-CD3 Antibody Treatment

A JDRF-supported clinical trial in Belgium has found that a six-day treatment with anti-CD3 antibodies can slow the normal increase in insulin use over the first few years after a type 1 diabetes diagnosis. This shows that the treatment, although brief in duration, is able to preserve the function of insulin-producing cells for several years—a major step toward stopping or slowing the disease's progression. The trial also points to the importance of early intervention: those who benefited from the treatment were younger at the time of diagnosis and had more remaining beta cell function. Anti-CD3 antibodies are proteins directed at immune T cells, which play a key role in the development of type 1 diabetes; they are among the most promising interventions for protecting the insulin-producing cells within the pancreas. The trial results, which reflect four-year data, were published in the journal *Diabetologia*. Daniel Pipeleers led the study. (January 2010)

Key Point: *Anti-CD3 antibodies have been shown to slow the progression of type 1 diabetes for an extended period, and the findings suggest that early intervention in the newly diagnosed may be critical to long-term disease management.*

...And Anti-CD3 Treatments Move to Phase III Trials

Separately, research on anti-CD3 antibodies has progressed to the most advanced stage of clinical testing: Phase III trials. The studies are being conducted by two of JDRF's Industry Discovery and Development partners that have entered into global alliances with pharmaceutical companies to develop and commercialize the treatments. In one trial, JDRF partner MacroGenics and Eli Lilly and Co. are evaluating the drug teplizumab. More than 530 people with recent-onset type 1

diabetes are enrolled in the study, which is taking place across 14 countries. In the second trial, JDRF partner Tolerx and GlaxoSmithKline are evaluating the drug oteplizumab in 240 people. Participants in that trial are being given an "optimized dose" that is only a fraction of the amount used in earlier evaluations but that maintains the same benefits. The trial is being conducted at over 100 study centers throughout Europe and North America. (January 2010)

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.*

Three New Partnerships in Regeneration

1. JDRF Announces Diabetes Research Collaboration with Pfizer and Israeli Scientists

JDRF has begun a research collaboration with Pfizer, Hadassah Medical Organization, and The Hebrew University of Jerusalem to develop drugs that can regenerate insulin-producing cells in people with type 1 diabetes. The program, co-funded by JDRF and Pfizer, is under the direction of Benjamin Glaser (Hadassah Medical) and Yuval Dor (Hebrew University) in collaboration with scientists from Pfizer PharmaTherapeutics Research & Development. The research will focus on evaluating proprietary Pfizer compounds as candidates to promote beta cell regeneration. The collaboration builds on unique beta cell regeneration models created by Dr. Dor and funded by JDRF. With this new project, the researchers

will use drugs supplied by Pfizer to boost beta cell mass in healthy and diabetic mice. Drugs that can stimulate beta cell replication and expand beta cell mass have the potential to help cure diabetes by restoring the body's ability to produce insulin. (March 2010)

2. JDRF Joins GNF to Form Innovative Diabetes Drug Discovery Platform

JDRF has entered into a collaborative agreement with the Genomics Institute of the Novartis Research Foundation (GNF) to create a drug discovery and development platform. The four-year program, focused on regeneration, is one of the largest and most comprehensive collaborations in JDRF's 40-year history. It marks a major opportunity to work with an experienced and highly regarded scientific partner to quickly translate discoveries in research into new treatments for people with type 1 diabetes. The JDRF-GNF partnership should jump-start the creation of a multi-product pipeline for beta cell regeneration. (August 2009)

3. JDRF Joins Johnson & Johnson to Create a Novel Drug "Incubator" Program

JDRF will work with the Johnson & Johnson Corporate Office of Science and Technology to speed the development of drug targets and pathways that promote beta cell survival and function. The program will fund research at academic and medical research centers worldwide. By creating this "incubator" program to support early-stage studies—with a company known for first-class research and significant experience in the commercialization of products—JDRF is looking to increase the number of viable drug targets identified and fundamentally advance the pace of diabetes research. (December 2009)

Key Point: *Each of these regeneration programs will help to accelerate one of JDRF's key research goals: finding ways to restore the body's ability to make insulin.*

Pancreas Cells Show Potential to Spontaneously Change into Insulin-Producing Cells

Some cells in the pancreas appear to have transformational properties. JDRF-funded researchers led by Pedro Herrera at the University of Geneva in Switzerland have shown that "alpha cells" in the pancreas—specialized cells that produce glucagon, not insulin—can spontaneously convert into insulin-producing beta cells. While these changes took place under very specific experimental conditions in mice, the study advances the prospect of regenerating beta cells as a cure for type 1 diabetes. It points to an unexpected "plasticity," or potential, of pancreas cells to adapt and produce insulin when they must—in this case, when the beta cells that normally produce insulin were entirely killed off. Ultimately, scientists may be able to harness this conversion potential to regenerate beta cells in people with diabetes. Dr. Herrera's results are the first to show that beta cell reprogramming can occur spontaneously, without genetic manipulation. Previous efforts to reprogram non-beta cells into beta cells relied on altering genes—processes that cannot be easily translated into therapies for people. The study was published in the journal *Nature*. (March 2010)

Key Point: *Cells in the pancreas that don't normally produce insulin hold the potential to naturally convert into cells that do. The findings have the potential to open a whole new strategy for regenerating beta cells—and achieving normal blood sugar—in people with type 1 diabetes. This new path may be particularly useful in people who have had diabetes for a long time and have no, or very few, remaining beta cells.*

Three Studies Gain Ground in Understanding the Beta Cell

1. Researchers Uncover Gene's Role in Preventing Beta Cell Death

A JDRF-funded study has established how a gene associated with a rare genetic condition affects the survival of the insulin-producing beta cells in the pancreas. Findings from the study will help researchers better understand the complex processes regulating beta cell survival and regeneration and could lead to new treatments for type 1 diabetes. The researchers uncovered how a protein associated with a specific gene regulates responses to beta cell stress and helps to maintain beta cell survival. The gene is abnormally expressed in Wolfram syndrome, a rare genetic disease characterized by insulin-dependent diabetes and serious neurologic developments. The researchers had previously shown that mutations in the gene cause Wolfram syndrome, but until now, no one knew precisely how mutations in this gene resulted in diabetes. The study, published in *The Journal of Clinical Investigation*, was led by Fumihiko Urano from the University of Massachusetts Medical School in Worcester and M. Alan Permutt of Washington University School of Medicine in St. Louis. (February 2010)

2. Researchers Identify Gene Critical to Beta Cell Development

Scientists have identified a gene required for cells to differentiate, or mature, into insulin-producing cells and other cell types in the pancreas. The research, co-funded by JDRF, provides important new insights into beta cell development and adds to the prospect of generating an abundant, renewable supply of insulin-producing cells to replace beta cell function in people with type 1 diabetes. The researchers showed that mice lacking a gene called Rfx6 failed to generate insulin-producing beta cells and most

other cells in the pancreatic islets. They also found that in people, deficiency of the Rfx6 gene results in diabetes onset in newborns. The study was published in the journal *Nature* and led by principal investigators Michael S. German from the University of California, San Francisco and Constantin Polychronakos from McGill University in Montreal. (February 2010)

3. Stress Hormone Is Linked to Beta Cell Growth and Function

A hormone responsible for the body's stress response has been linked to the growth of insulin-producing cells in the pancreas, according to JDRF-funded research at the Salk Institute for Biological Studies in California. When beta cells were exposed to the hormone (called CRF) and to high levels of sugar, they produced and released insulin and began to proliferate. The findings reinforce the potential of regeneration as a cure for diabetes and provide insights for discovering new approaches to treat the disease. The study, published in the *Proceedings of the National Academy of Sciences*, was led by Wylie Vale, head of the Clayton Laboratories for Peptide Biology, and Mark O. Huising, a postdoctoral fellow at the Clayton Foundation Laboratories. (February 2010)

Key Point: *JDRF studies provided new insight into the biological mechanisms that govern beta cell development, growth, and survival. As a result, they point to new approaches to produce or regenerate insulin-producing cells to cure the disease.*

Lucentis Treatment Shown Effective Against Eye Disease

A groundbreaking study has identified the first new treatment for people with diabetic eye disease in the last 25 years. The study, a Phase II clinical trial, showed that the drug Lucentis combined with laser therapy, the current standard treatment for eye disease

in people with diabetes, is more effective than laser treatment alone.

The two-year study compared Lucentis plus laser therapy to laser therapy alone for people with diabetic macular edema (DME), a major complication of diabetes that can result in vision loss. Half of the people treated with the Lucentis therapy showed improvement in their vision – results that were about twice as good as laser treatment alone.

The progress is a product of JDRF research investments over many years. JDRF has worked with Johns Hopkins and the drug company Genentech, which licenses Lucentis, to test the drug's effectiveness in stopping and reversing macular edema. These results show it is a huge improvement over any other treatment now available.

The study was conducted by The National Eye Institute of the National Institutes of Health and the Diabetic Retinopathy Clinical Research Network (DRCR.net). The results were reported in the journal *Ophthalmology*. (April 2010)

Topical Drug Shows Promise for Diabetic Macular Edema

Early-stage human clinical trials have shown that a new drug to treat diabetic macular edema (DME) is promising and safe. One of the most severe forms of diabetic eye disease, DME is a leading cause of blindness in adults. Researchers at the Wilmer Eye Institute of Johns Hopkins University School of Medicine in Baltimore, led by Peter Campochiaro, completed a multi-center human clinical trial evaluating "mecamylamine," a topical drug developed by the South San Francisco biotech company CoMentis, Inc. About 40% of the participants showed significant improvement in overall vision and/or thickness of the retina after using

mecamylamine eye drops. Among the study's important implications: first, that a topical treatment can work on the retinal vessels at the back of the eye and produce a clinical benefit; and second, that multiple DME treatment options must be explored to address how individuals react differently to various treatments (about 40% showed no change and about 20% had worsening of the condition). Funding for the study was provided through JDRF's Industry Discovery and Development Partnerships program. Results were published in the *American Journal of Ophthalmology*. (March 2010)

Key Point: *Early clinical trial data show that a topical drug called mecamylamine is safe to use and can slow the progress of a severe form of eye disease in people with type 1 diabetes. Because this potential treatment can be self-administered, it may also ease the burdens of healthcare costs and compliance.*

Gene Therapy Can Reverse and Repair 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" involves 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 other research in people with severe neuropathy will form the basis

of a 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 may 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.*

Partnerships and Progress Toward an Artificial Pancreas

JDRF's Artificial Pancreas Project (APP) continues to make momentous progress toward the development of a system that has the potential to enable people with type 1 diabetes to achieve tighter blood glucose management—and thus reduce their risk of complications. In January, JDRF announced an innovative, non-exclusive partnership with Animas Corp. to develop an automated insulin delivery system—a first-generation artificial pancreas—that will help people with type 1 diabetes better control their disease. Animas is a Johnson & Johnson company and a leading pump manufacturer. Only a week later, JDRF announced a second partnership, this time with BD (Becton, Dickinson and Co.), aimed at developing novel insulin delivery products to enhance insulin pumps. Advances in pump technology will not only lead to improved glucose control but can be incorporated into an artificial pancreas, either those developed by Animas or by other companies committed to finding cures and treatments for type 1 diabetes.

Plus, in a landmark study in children and teenagers with type 1 diabetes, JDRF researchers at the University of Cambridge showed that using a first-generation artificial pancreas system overnight

can lower the risk of low blood sugar emergencies while sleeping and at the same time improve diabetes control.

And most recently, researchers from Boston University and Massachusetts General Hospital showed that a novel artificial pancreas system using two hormones—glucagon as well as insulin—can lower the risk of low blood sugar emergencies. After adjustments to the system to better capture individual differences in insulin absorption, all of the study participants (11 adults with type 1 diabetes) achieved near-normal blood sugar levels for more than 24 hours without experiencing hypoglycemia. Glucagon is a naturally occurring hormone that counters insulin's action, raising blood sugar in response to hypoglycemia. Its production is impaired in people with type 1 diabetes. (January–April 2010)

Key Point: *These developments represent a giant step forward on the path to achieving an artificial pancreas, a fully automated system that can dispense insulin to patients based on real-time changes in blood sugar levels. Even the earliest systems could bring dramatic changes in the quality of life for people with type 1 diabetes.*

Another Study Documents the Benefits of CGM

JDRF has funded another study that has shown the benefits of using continuous glucose monitoring (CGM) to help manage type 1 diabetes. In September 2009, research confirmed that regular CGM use—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. A second study found that people who continued using a CGM were able to sustain good control long-term while experiencing a lower rate of hypoglycemia—the dangerous low blood

sugar incidents that can occur with tightly managed type 1 diabetes. Both studies were published in *Diabetes Care*.

This research follows a major clinical trial in October 2008 that found that people who used a CGM experienced significant improvements in blood sugar control—and as a result, significant reductions in the risk of diabetic complications. In large part because of the trial's positive results, most national health insurers have expanded their policies to include or broaden their coverage of CGMs. In May 2009, a study published in *Diabetes Care* found that CGMs enable people who have already achieved excellent control (HbA1c levels below 7 percent) to continue to tightly manage their diabetes while cutting down on the frequency of low blood sugar emergencies.

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.*