

Get focused on a cure.

Fall 2009 Research Update

JDRF initiates and propels research in a way that is so unique in the field of medical research. Here's how.

Through pure focus...

We actively seek out the best and brightest science and researchers—and we ask them to share discoveries in real time so we can accelerate the results. As we learn more, we are able to be nimble and responsive with resources, putting dollars where they will have the biggest, yet not redundant, impact.

Through partnership...

The major findings and developments JDRF funded over the past year, which follow, underscore JDRF's role as a leader and catalyst of cure research. JDRF is assertive about partnering with, and lighting a fire under, everyone who can bring results more quickly: the NIH who has three-fold the capacity to fund diabetes research as we do;

the FDA who is the only body who can bring a discovery to people with diabetes; and Medicare and the insurance industry who must set the stage for coverage and make cures accessible to all.

Through a business world model...

Science discovery is not enough on its own. With an emphasis on industry partnerships, drug discovery, and human clinical trials, JDRF actively manages research. With funding of \$100 million in FY2009, representing research in more than 20 countries and including 44 human clinical trials, JDRF is driving research discoveries into products, drugs, and treatments for people with diabetes.



JDRF Juvenile
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Key Research Advances

The following are highlights of some of the most promising advances that took place over the past year. Your support helped achieve these amazing results. The report is organized around JDRF's four refined research priorities that sharpen our focus on creating near-term benefits for people with diabetes and on increasing the odds of major breakthroughs in our quest for a cure. We also want to update you on clinical trials. Success in these areas will result in a cure for diabetes—for everyone, at all ages and at all stages of this disease.

Clinical Trials

JDRF Launches Online Clinical Service – www.trials.jdrf.org

JDRF is 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. Therefore, JDRF launched Clinical Trials Connection, 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.

Treatments for Newly Diagnosed Move to Phase III Clinical Trials – Success for JDRF's Industry Partnership Program

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 otelixizumab, another anti-CD3 antibody that is in Phase III 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. 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.

Beta Cell Therapies (formerly regeneration and replacement)

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.

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.

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.

Immune Therapies (formerly autoimmunity)

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.

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.

Glucose Control (formerly metabolic control)

Gastrin Combination Therapy Reverses Diabetes

Over the past year, several published findings have documented the benefits of the continuous glucose monitor or CGM, a device JDRF has been instrumental in developing and bringing to market. It, along with the insulin pump, are the key ingredients of an artificial pancreas. First, *The New England Journal of Medicine* reported the findings of a JDRF funded study that 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. Improvements were most evident in adults 25 years of age or older. However, additional studies show that individuals of all ages who used CGM six days a week or more lowered their A1c

Key Research Advances

by at least .5 in just six months—enough to reduce the risk of some complications by approximately 25 percent. Consistent use 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. 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. In response to these findings and with strong advocacy from JDRF, several large national health insurers expand their policies to include or broaden coverage of CGM.

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.



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Complication Therapies

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)

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.