

Top Research Highlights

Advancing Type 1 Diabetes Science

Every day, JDRF leverages the expertise and innovation of distinguished researchers from across the globe to support research for better treatments, prevention, and ultimately a cure for type 1 diabetes (T1D). In this issue of *Top Research Highlights*, we showcase how JDRF is bringing us closer to these goals, from expanding clinical trials to accelerating the manufacture of innovative technology to cultivating partnerships that will enable people with T1D to live longer and healthier lives. Our mission aims to serve everybody with T1D—at all ages and stages of the disease. Please enjoy reading about some of the ways that we are working tirelessly to make that happen.

Study Aims to Protect Adolescents with Type 1 Diabetes from Kidney and Heart Complications

JDRF and the Canadian government are boosting the Adolescent Type 1 Diabetes Cardio-Renal (heart and kidney) Intervention Trial (AddIT) by adding one additional clinical site at the Charles H. Best Diabetes Centre in southern Ontario, Canada. The expansion will serve to accelerate the recruitment of adolescents with type 1 diabetes (T1D) and microalbuminuria, a condition in which a common protein called albumin leaks into the urine—a

sign of early kidney disease and a risk factor for developing heart disease later in life.

The international trial, which has multiple sites in the United Kingdom (22), Canada (5) and Australia (8), will help guide clinicians on how to best manage, treat, and prevent these serious and expensive-to-treat complications. In addition, the study will be used to identify adolescents who go on to develop complications and those who do not, and better understand what sets the two groups apart.

Nearly all adolescents with T1D are tested for microalbuminuria, and 12 to 16 percent of adolescents are diagnosed with the condition. However, it is rarely treated before 18 years of age because there are no guidelines for treating microalbuminuria in children and adolescents. Yet, it has been shown in one study in *Diabetes Care* that adolescents with microalbuminuria experience damage to their kidneys and blood vessels during puberty, a finding that warrants early intervention to protect and prevent adolescents from long-term complications. More high-quality evidence is needed to support clinical approaches to protect those with T1D from such complications.

“Everybody is screening adolescents for microalbuminuria, but nobody

knows what to do with the results,” says David B. Dunger, M.D., professor of pediatrics at Cambridge University, England, and a principal investigator of AddIT. “This study should have an important impact on future recommendations for managing T1D during adolescence.”

The AddIT trial will screen adolescents with T1D, ages 10 to 16, for microalbuminuria and categorize them in one of three tertiles—low, medium, or high—depending on how much albumin is in their urine. Those in the highest tertile will be given currently approved drugs or placebo controls (cholesterol-lowering statins, blood pressure-regulating ACE inhibitors, or a combination of the two) to see if they can reduce the amount of albumin in the urine and prevent further kidney damage. Those in the two lower tertiles will be observed for three to four years, without receiving drug treatment.

Since the study began in 2008, more than 3,000 adolescents with T1D have been screened for microalbuminuria in the United Kingdom, Australia, and Canada. With the additional site in Canada, which is being led by Farid Mahmud, M.D., an endocrinologist at The Hospital for Sick Children, investigators hope to screen another 500 to 1,000 adolescents with T1D.

The AdDIT study is now part of the JDRF Canadian Clinical Trials Network, a new clinical consortium that currently operates nine clinical trials and two projects that focus on T1D.

In addition to the human cost of developing kidney disease, there is also a financial cost associated with the disease, explains Marie Nierras, Ph.D., JDRF's senior director of international partnerships and cure therapeutics. Some people who develop kidney problems may go on to require dialysis or take medicine for the rest of their lives. "If we can prevent these complications, we can not only help improve the quality of lives of people living with T1D, but also lessen the burden of this disease on our health care system—making a difference at the individual and global level in how we manage this disease."

Key point: *JDRF and the Canadian government are expanding the Adolescent Type 1 Diabetes Cardio-Renal (heart and kidney) Intervention Trial (Ad-DIT) by adding one additional clinical site in southern Ontario, Canada. The expansion will serve to accelerate the recruitment of adolescents with type 1 diabetes (T1D) and microalbuminuria, a condition in which a protein called albumin leaks into the urine—a sign of early kidney disease and a risk factor for developing heart disease later in life.*

JDRF Funds Testing of New Drug for Diabetic Macular Edema

In 2011, Lucentis became the first breakthrough treatment in more than 20 years for people with diabetic macular edema (DME), a leading cause of blindness among the working-age population (ages 20 to 74). Unfortunately, it does not work for

everyone with the disease. Now, JDRF has teamed up with Vancouver-based company iCo Therapeutics to support the development of a new drug—one that, if successful, can work alone or in tandem with Lucentis to provide another therapeutic option to people with type 1 or type 2 diabetes suffering from the condition.

The Phase II trial called iDEAL—one of the largest studies of its kind—will enroll as many as 208 people with type 1 or type 2 diabetes and DME at up to 30 clinical sites across the United States to see if the drug iCo-007 will improve their sharpness of vision within eight months as tested with a standard eye chart. The multicenter effort, led by Quan Dong Nguyen, M.D., associate professor of ophthalmology at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine, is currently recruiting volunteers. All study participants will be followed for 12 months.

"The purpose of this trial is to see if iCo007, alone or in combination with Lucentis, is effective in treating diabetic macular edema, which affects 14 percent of people with type 1 diabetes," says Helen Nickerson, Ph.D., JDRF's senior scientific program manager of complications. "This collaboration with iCo Therapeutics is exciting because we need additional tools to prevent vision loss for DME and we need to learn how to best use these tools in combination with existing therapies."

Diabetic macular edema is a complication of diabetic retinopathy, which is caused by either changes of blood vessels in the retina or the growth of new ones that are tiny and fragile. These damaged blood vessels may leak fluid, or blood, and create scar tissue that blurs and distorts vision. In the case of DME, fluid collects in the macula, the central portion of the

retina. If left untreated, the swelling of the macula can lead to severe vision loss and even blindness.

Lucentis, or ranibizumab injection, has been shown to stunt or prevent the growth of these tiny and fragile blood vessels in the macula by blocking the effects of a protein known as vascular endothelial growth factor, or VEGF. iCo-007 may have the potential to inhibit the growth of these new blood vessels, but rather than target VEGF alone, iCo-007 works by tamping down the production of a protein called c-Raf kinase, which interacts with VEGF and other growth factors that are important in the etiology of diabetic retinopathy. VEGF is best known for its role in cancer, where it promotes the growth of tumors.

"Diabetic macular edema is both devastating and prevalent, and yet today's treatments are insufficient for everyone with this complication," says Aaron Kowalski, Ph.D., assistant vice president of treat therapies for JDRF. "As we investigate a novel pathway to inhibit the pathogenesis of this disease, we are collecting useful data about iCo-007 in the process that will enhance our understanding of diabetic macular edema, and hopefully build upon currently available resources used to manage this disease."

Key point: *In one of the largest studies of its kind, JDRF has partnered with iCo Therapeutics to investigate a potential new drug that could, if successful, broaden treatment options for people living with DME. The Phase II trial, led and coordinated by Johns Hopkins University investigators, is currently recruiting participants. To inquire about participation, please contact Dr. Quan Dong Nguyen or [click here](#).*

JDRF Partners With Dexcom to Support the Manufacture of a Smart Transmitter Prototype for Artificial Pancreas Research

Currently, artificial pancreas studies are not conducted in real-life settings: they take place either in a hospital, or out in the real world but with a clinician accompanying the participant at all times. To prepare for real-life outpatient, or ambulatory, studies of artificial pancreas systems, JDRF has partnered with San Diego-based medical company Dexcom to support the manufacture of a smart transmitter prototype—a technology that would reduce the number of wires and bulky devices a person would have to wear with an artificial pancreas system.

The funding of this prototype will allow JDRF to use the technology for research purposes before it will be commercially available.

“The big excitement here is that artificial pancreas studies are projected to go fully ambulatory in the next year or two in the United States,” says Aaron Kowalski, Ph.D., assistant vice president of treatment therapies for JDRF. “And so to enable the best ambulatory studies that we can, we need things like the smart transmitter to eliminate the hassle of being encumbered by wires and other bulky equipment.”

The smart transmitter would simplify continuous glucose monitor (CGM) systems. Currently, these systems use a regular transmitter that sends information about blood glucose levels from a tiny glucose sensor inserted under the skin to a pager-like receiver strapped to a belt. Using a sophisticated computer program, the receiver then unwraps this information,

generates a glucose number, and then sends that information to a handheld device, which in turn instructs an infusion pump to release the right amount of insulin at the right time.

“In this current system, we have a regular transmitter,” says Dr. Kowalski. “While the transmitter has an important job, it is an extra component that will be eliminated with this new device. The receiver is the brains of the operation. With the smart transmitter, all of the electronics in the receiver—the brains of the operation—are put onto the sensor, creating a smart transmitter.”

The result: the smart transmitter will eliminate the need for the receiver, decreasing the number of devices that a user needs to wear. The smart transmitter will be able to wirelessly send information directly to the handheld device, without being routed through and processed by the receiver.

JDRF will provide Dexcom, Inc. up to \$500,000 over 12 months in milestone-based funding to support the development, testing, and manufacturing of the smart transmitter. The goal is that the new transmitter will be able to function with multiple versions of Dexcom’s next generation of CGM systems.

“In order for us to truly achieve real-life outpatient studies of artificial pancreas systems, we need systems that will allow people the freedom and ability to move around, while also providing safety, monitoring, and data collection,” says Dr. Kowalski, “Dexcom’s smart transmitter will allow the sensor to talk directly to multiple artificial pancreas control devices. Now that the first outpatient studies have started in Europe, the development of robust wireless-connection capability is a key step toward accelerating the

delivery of an artificial pancreas to all people living with T1D.”

Key point: *JDRF has partnered with San Diego-based medical company Dexcom, Inc. to support the manufacture of a so-called smart transmitter prototype, which will be available for research purposes before it will be commercially available. The technological advance not only would reduce the number of devices a person would have to wear with an artificial pancreas system, but would also enable wireless connectivity among these devices—an important feature that would give people with T1D the freedom of movement while participating in real-life outpatient studies.*

New Study from JDRF-Supported Researchers Shows Stressed Beta Cells May Provoke Development of Type 1 Diabetes

In a classic chicken-and-egg scenario, researchers have long known that something causes the pancreatic beta cells of people with type 1 diabetes (T1D) to die, but they don’t know what causes it or when in the disease the beta cells began to fail. Are healthy beta cells being targeted by a misguided autoimmune reaction, resulting in beta cell death, or are the beta cells being targeted by the immune system because there is something going wrong in the beta cell that triggers the autoimmune reaction? While much of the focus to date has been on the first option, a new study by JDRF-funded scientists suggests that the second alternative may also be occurring and the beta cell may be as much a victim as a perpetrator in its own demise in T1D.

The study now provides evidence that the beta cells start to experience stress reactions early in the disease process that may then provoke an autoimmune response.

The research, led by Sarah Tersley, Ph.D., and Raghavendra Mirmira, M.D., Ph.D., at the Indiana University School of Medicine, was published in the April 2012 issue of *Diabetes* and is the first to show that beta cells in a mouse model of T1D are not functioning normally during the early stages of disease before symptoms emerge, providing new insight into how T1D starts and suggesting a potential target for treatment. “We don’t know a lot about what happens at the early stage of the disease, or what initiates progression,” says Andrew Rakeman, Ph.D., senior scientist in cure therapies and regeneration at JDRF. “But this study shows that stress in the beta cells is happening at the earliest stages, so targeting that stress early might allow us to prevent or slow down disease.”

Inside every human cell is a small, multilayered structure called the endoplasmic reticulum (ER) that functions as a protein-producing factory. In pancreatic beta cells, which are specialized to produce and secrete the protein-based insulin hormone, the ER is especially active and can undergo a stress response if overworked. Drs. Tersley and Mirmira found that when beta cells are unable to alleviate ER stress, they appear to initiate a suicidal signaling cascade, and it may be the altered or dying beta cells that trigger the autoimmune reaction that is characteristic of T1D. If researchers could find a way to alleviate ER stress, or a way to help beta cells cope with that stress, it might be possible to prevent loss of beta cells.

“It really starts to shift the way we think about the role of beta cells in the progression of type 1 diabetes,” says Dr. Rakeman. “The more we understand about how the disease is working and what events trigger it, the more we can understand about ways to stop progression, and treat the disease at an earlier stage.”

With insight gained from this research, future studies can look more closely at how to rescue beta cells and prevent the disease.

Key point: *JDRF-supported researchers have found that dysfunction of pancreatic beta cells precedes the onset of T1D in a mouse model of the disease. The study is the first direct demonstration that ER stress happens before the onset of T1D in an animal model. These findings help illuminate the earliest stages of T1D, and suggest that alleviating ER stress with drugs or other therapeutics might provide an avenue for slowing progression and onset of disease.*