

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 report on the U.S. Food and Drug Administration's final guidance for artificial pancreas systems, which adopts most of the recommendations made by JDRF. We also feature the formation of a global research collaboration established to further investigate the genetics of diabetic nephropathy, a life-threatening complication that affects about 30 percent of people with T1D.

This issue highlights the second round of grant funding from the Israel Science Foundation and JDRF, which provides support for basic and translational T1D research in Israel, and introduces the Danish Diabetes Academy, the first institute of its kind in Denmark that aims to improve the quality of Danish diabetes research and raise awareness for both types of diabetes. Finally, we describe the work of a JDRF-funded researcher who is examining the results of a study that claims to block the autoimmune response that causes T1D. Our mission aims to serve everybody with T1D—at all ages and all stages of the disease. Please enjoy reading about some of the ways in which we are working tirelessly to make that happen.

FDA Includes JDRF Recommendations in Its Final Guidance on Artificial Pancreas Systems

The U.S. Food and Drug Administration (FDA) has issued its final guidance on artificial pancreas (AP) systems and has adopted nearly all of JDRF's recommendations. The final guidance provides researchers and industry with a clear and reasonable roadmap of the FDA's expectations for conducting human studies of AP systems, and for their approval for marketing to people with diabetes.

"This FDA guidance is an important milestone in improving the lives of people with type 1 diabetes," says Jeffrey Brewer, president and CEO of JDRF. "JDRF commends the FDA for its scientific leadership in the area of AP systems, which have the potential to be the most revolutionary advance in treating type 1 diabetes since the discovery of insulin. Until we can cure this disease, we have an obligation to reduce the daily burden of managing it and enable people with the disease to live healthier lives."

JDRF first proposed draft guidance to the FDA in March 2011, and then spearheaded an extensive scientific and patient-advocacy campaign to encourage the FDA to adopt its recommendations. The FDA's final guidance incorporates nearly all of

the recommendations made by JDRF and the clinical community and allows for a range of scientifically valid study designs to encourage innovation while ensuring thorough evaluation of the AP systems before they can be prescribed by doctors.

For example, the guidance recognizes "time in range" and other measures of glucose control as potential endpoints to use in AP systems studies. It also allows sponsors the ability to propose statistical measures of efficacy tailored for their systems, and accepts the use of continuous glucose monitoring data in evaluating AP systems.

JDRF will continue to work with the FDA to ensure the appropriate degree of regulation for AP systems as the knowledge base and experience expands for these treatments for T1D.

Key point: *The FDA has issued its final guidance on artificial pancreas (AP) systems, using recommendations suggested by JDRF. The final guidance provides researchers and industry with a clear and reasonable roadmap of the FDA's expectations for conducting human studies of AP systems, and for their approval for marketing to people with diabetes. JDRF supports the FDA's final guidance, and will continue to work with the agency to ensure the appropriate degree of regulation for this potentially life-changing device.*

About an Artificial Pancreas

An artificial pancreas (AP) is an external system of devices and software that people with type 1 diabetes (T1D) could use to replace the body's lost ability to automatically control blood-sugar level. A basic AP system would work by connecting a continuous glucose monitor with an insulin pump using sophisticated computer software to automatically deliver the right amount of insulin at the right time. The development of AP systems is one of JDRF's research priorities. JDRF-funded studies have already shown the significant value of prototype AP systems in better managing T1D.

JDRF Supports Research Collaboration to Study Diabetic Nephropathy

People with type 1 diabetes (T1D) are at risk for developing complications from the disease. One of those complications, diabetic nephropathy (kidney disease), can be a life-threatening condition. This form of kidney disease can eventually lead to kidney failure, or end-stage renal disease (ESRD).

In the human body, the kidneys are made up of hundreds of thousands of tiny units called nephrons, which filter the blood and help remove waste from the body. But in people with T1D, the nephrons thicken and slowly become scarred over time. Tight blood-sugar control can delay or even prevent the onset of renal complications, but even with good control, T1D can still lead to ESRD. Diabetic nephropathy is not limited to just people with T1D, as people with type 2 diabetes are also at risk for the condition. People with diabetes and severe kidney disease make up the largest population of patients being treated with dialysis. Furthermore, people with diabetic

nephropathy are more likely to develop cardiovascular disease.

With the goal of identifying the pathways that lead to diabetic kidney disease, JDRF recently announced a three-year program called the JDRF Genetics of Diabetic Nephropathy Collaborative Research Initiative. This initiative brings together top scientists in the field to build on previous research and share their findings, to identify disease pathways and prevent and treat diabetic nephropathy. More than \$7 million will be provided to the four main institutions collaborating on the project: the Broad Institute of MIT and Harvard; Joslin Diabetes Center; the University of Toronto; and the University of Virginia. Each grant supports research around the globe, with multiple collaborators from the United Kingdom, France, Denmark, Finland, and Ireland.

Some people who have lived with diabetes for a long time do not develop diabetic nephropathy, while others who have had diabetes for a shorter length of time quickly progress to ESRD. Previous research has pointed toward genetic factors in the risk of developing diabetic nephropathy, but scientists do not yet have a full picture of the specific genes involved.

The initial goal of the collaboration is to identify genetic differences between people with T1D who do and those who do not have diabetic nephropathy. Until now, the search for the genes contributing to kidney disease has not been easy because many people have to be sampled. Finding genes shows researchers the pathways that are involved in the development of diabetic nephropathy. These pathways reveal biomarkers that may predict rapid progression of decline in renal function, helping to identify people with T1D who are at risk so that they can receive early

treatment, or be recruited into clinical trials. Analyses may also show markers that predict how quickly a person with T1D may develop renal failure, helping to find novel drugs and therapies to prevent and treat the disease.

"JDRF is proud to be spearheading this project, which is helping to fill a huge gap in research into diabetic nephropathy," says Sanjoy Dutta, Ph.D., senior director of the Treat Therapies Program at JDRF. "The most effective way to tackle hurdles in this research is to pool, compare, and expand knowledge in this area from scientific groups and patient cohorts around the globe."

This global collaboration of researchers has assembled samples from more than 20,000 subjects with T1D and kidney disease, and the process of determining each participant's genetic makeup is under way. Data is expected to be available in late 2013. "JDRF can make an impact in kidney disease and the search for related biomarkers," Dr. Dutta says. "The project aims to increase our knowledge of the associated genes, to predict or delay diabetic nephropathy."

Key point: *JDRF will contribute more than \$7 million to a three-year program named the JDRF Genetics of Diabetic Nephropathy Collaborative Research Initiative. The initiative will bring together top scientists from across the globe to study the role of genetic factors in diabetic nephropathy, a condition that affects about 30 percent of people with T1D. Four main institutions will collaborate on the project, building on previous research and sharing their findings to identify possible ways to prevent and treat the condition. This global collaboration is the largest of its kind for diabetic nephropathy, and it aims to identify pathways involved with the condition.*

JDRF and Israel Science Foundation Support Second Round of T1D Research

Seven Israeli researchers are moving forward on research to provide life-changing therapies for people with type 1 diabetes (T1D), sustained by funding from JDRF and the Israel Science Foundation (ISF). The ISF-JDRF Joint Program in Type 1 Diabetes Research grants scientists as much as \$130,000 per year for at most three years in support of their basic and translational T1D research. The ultimate goal is to accelerate practical applications of basic scientific advances into new therapies for T1D.

The scientists are the second group to receive grants from the ISF-JDRF Joint Program in Type 1 Diabetes Research. The program was founded in 2010 to encourage innovative T1D research and increase support of Israel's talent and expertise in autoimmunity and beta cell biology. The joint venture also aims to bring new scientists from other fields into T1D research through collaboration with acknowledged diabetes experts.

The partnership with ISF was made possible through a seed grant from philanthropists Neil and Lisa Wallack. Their support helped to create the Israel Initiative, a campaign that funds cutting-edge research in Israel aimed at restoring beta cell function and halting the autoimmune process in T1D.

The most recent round of grant funding through the ISF-JDRF Joint Program will support five projects focusing on a wide range of T1D research, including projects focused on making more beta cells and protecting beta cells from cell death and immune attack.

“We are proud to support the work of this second group of exceptional scientists through our partnership with the ISF,” says Richard A. Insel, M.D., chief scientific officer at JDRF. “These expert researchers represent areas of investigation that could bring us closer to better treatments and a cure for type 1 diabetes.”

The newest projects supported by the ISF-JDRF Joint Program

Benjamin Glaser, M.D., of The Hebrew University Hadassah Medical Center in Jerusalem, has identified five genes that may be responsible for beta cell growth from his genetic studies of focal hyperinsulinism of infancy (focal-HI), a neonatal genetic form of diabetes that results in the absence of beta cells. He will insert these genes into normal adult beta cells to determine whether the genes individually or in combination can cause the cells to divide and produce new, fully functional beta cells, a process referred to as replication. If successful, Dr. Glaser's research will be an important step toward generating a safe, abundant, and replenishable supply of human beta cells for replacement therapy for T1D.

Ofer Mandelboim, Ph.D., of The Hebrew University of Jerusalem, and Angel Porgador, Ph.D., of Ben-Gurion University of the Negev in Beer-Sheva, Israel, will use their grant to develop an antibody to block a specific receptor—a specialized protein on a cell's surface—known to kill beta cells. This receptor, called NKp46, targets an unknown protein produced by pancreatic beta cells and attacks cells perceived as harmful, such as tumor cells or cells infected by viruses. NKp46 is known to be involved in the

development of T1D. This work will test the effects of the new anti-NKp46 antibody in mice, potentially opening a new path of investigation for treating T1D.

Yoram Reiter, Ph.D., at Technion—Israel Institute of Technology in Haifa, Israel, hopes to develop immune therapies that can block beta cell destruction without interfering with the beneficial functions of the immune system. Dr. Reiter will engineer a new family of immunotherapeutic agents against the GAD protein—one of the autoantigens that is a trigger of T1D—which may block beta cell inflammation without weakening the immune system. Dr. Reiter aims to demonstrate the feasibility of developing these antibodies as an antigen-specific immune therapy for people with or at risk for the disease.

The team of Michael Walker, Ph.D., and Yoav Soen, Ph.D., of the Weizmann Institute of Science in Rehovot, Israel, are developing cellular-level tools to help build and characterize replacement beta cells. Using a new technology that they developed to identify surface markers for the different cells within islets, Drs. Walker and Soen plan to identify unique features on the beta cell's surface that distinguish various stages of beta cell growth. Their findings could have a significant impact on the ability to create functional beta cells for cell therapy, since the shortage of human donor islets is a major challenge to making islet transplantation widely available as a treatment for T1D.

Yehiel Zick, Ph.D., also of the Weizmann Institute of Science, is studying the biology of a protein that could potentially be used to genetically modify beta cells to help them better

resist an autoimmune attack. Dr. Zick recently identified a protein called TM7SF3 that appears to protect beta cells from proinflammatory cytokines—small proteins released by immune cells that trigger beta cell death. The researcher will use his grant to further understand the mechanisms by which TM7SF3 protects human beta cells from death. He aims to explore the significance of the gene encoding the protein in helping pancreatic beta cells survive under the influence of cellular stress.

The ISF-JDRF Joint Program has increased interest in advancing T1D research among immunologists, cell biologists, and beta cell experts in Israel. “This special joint program with JDRF has become one of the ISF’s flagships in biomedical research support,” says Benny Geiger, Ph.D., chair of the ISF’s Academic Board. “The studies of these grant recipients can have a major impact on understanding the mechanisms underlying type 1 diabetes and offer new approaches for therapy.”

Key point: *JDRF and the Israel Science Foundation (ISF) are supporting new advances in T1D research through the ISF-JDRF Joint Program in Type 1 Diabetes Research. The program seeks to accelerate practical applications of basic scientific advances into new therapies for T1D and increase support of Israel’s talent and expertise in autoimmunity and beta cell biology.*

The program also aims to bring new scientists from other fields into T1D research through collaboration with acknowledged diabetes experts. This year’s grant recipients have proposed promising research projects that focus on a wide range of T1D research, including making more beta cells and protecting beta cells from cell death and immune attack. The projects have the potential to deliver life-changing therapies to people at all stages of T1D—by preventing the disease, delaying the need to take insulin, or slowing the progression of the disease.

Denmark Forms Initiative for Diabetes Research

Denmark has established its first national institute for diabetes research, called the Danish Diabetes Academy (DDA). The academy aims to improve the quality of Danish diabetes research, and to raise awareness of both type 1 diabetes (T1D) and type 2 diabetes. Funding for the DDA was provided by The Novo Nordisk Foundation and JDRF. T1D cases are rising in Denmark, affecting about 30,000 people in the country. Additionally, more than one child or adolescent is diagnosed with T1D every day, according to researchers at the University of Southern Denmark. JDRF has been an established supporter of T1D research in the country through its affiliate, JDRF Denmark, since 2003. Inaugurated in September 2012, the DDA is located at Odense

University Hospital in Odense, Denmark, and will drive research projects at universities and hospitals throughout the country. Over the next five years, the DDA will strengthen the research talent pool and build career paths for young researchers within the field of diabetology by financing about 150 new research positions, including 90 Ph.D. scientists and 50 postdoctoral fellowships. A number of professorships and short-term visiting researcher positions will also be funded. In total, more than 300 researchers will be members of the academy.

The Novo Nordisk Foundation is an independent Danish foundation with corporate interests. It has existed since 1926, and its objective is twofold: to provide a stable basis for the commercial and research activities conducted by the companies within the Novo Group; and to support scientific and humanitarian purposes.

Key point: *JDRF is partnering with The Novo Nordisk Foundation to fund the newly established Danish Diabetes Academy (DDA), which will improve the quality of Danish diabetes research through numerous projects. The academy will also strengthen the research talent pool by building careers for young researchers within the field of T1D science, with more than 300 researchers expected to join the DDA.*

Top T1D Researcher Addresses Potential Mechanism of Chinese Stem Cell Study

Surprising results from a study in China indicate that human stem cells may be able to block the autoimmune response that causes type 1 diabetes (T1D). Yong Zhao, M.D., Ph.D., formerly of the University of Illinois, Chicago, developed a technique that involves passing the lymphocytes (a type of white blood cell crucial to a healthy immune system) in a person's blood over selected umbilical-cord-blood stem cells—which include a mix of stem cells and other types of cells—before returning them to the person's circulation.

In Dr. Zhao's experiment—which he terms stem cell educator therapy—it is thought that the umbilical cord stem cells “re-educate” the immune cells so that they do not destroy pancreatic tissue. The highly experimental therapy lowered blood-sugar levels and improved insulin production in a small study of people with T1D in China.

In an effort to assess the potential mechanism behind the results of the Chinese experiment, JDRF is funding the research of Mark Atkinson, Ph.D., co-director of the University of Florida Diabetes Center of Excellence. This work will address potential endpoints in future clinical evaluation of this technology.

In the Chinese study, lymphocytes from 15 people with T1D were passed through the stem cell educator. For 12 of the test subjects, a single eight-hour treatment resulted in improved C-peptide production. This finding, which indicates evidence of insulin secretion, resulted in a reduction of the amount of insulin needed daily in the subjects for as long as 24 weeks after the experiment. Researchers think that this kind of treatment could lead to either regeneration of islet beta cells or restoration of existing beta cells. However, they are careful to note that the sample size was very small, and that the heterogeneity of T1D in the Chinese subjects may have been distinct from those in other countries.

“The results are potentially interesting, and we want to start

understanding the biology involved,” says Julia L. Greenstein, Ph.D., JDRF's assistant vice president of cure therapies.

In this JDRF-funded study, Dr. Atkinson plans to independently validate early biological events triggered by the therapy. These include the changes it imparts on lymphocytes and whether the results are specific to people with T1D versus people without the disease.

“Scientific investigation in this area is ongoing, and JDRF is applying our rigorous approach to find out if this is a viable procedure,” Dr. Greenstein says.

Key point: *JDRF-funded scientists are working to investigate the claims of a small Chinese study that used stem cell educator therapy to seemingly lower blood-sugar levels and improve insulin production in people with T1D. Mark Atkinson, Ph.D., of the University of Florida seeks to independently validate early results of the therapy, such as the changes it imparts on leukocytes and whether the results are specific to people with T1D versus people without the disease.*