JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

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 life-changing treatments and ultimately a cure for type 1 diabetes (T1D). Our mission aims to serve everybody with T1D—at all ages and stages of the disease. Please enjoy reading about some of the most recent advances in T1D research.

Congress Renews the Special Diabetes Program

In an eleventh-hour decision, Congress granted a one-year extension of the Special Diabetes Program (SDP). The SDP renewal was included in a package of bills addressing a series of health policy issues, including legislation to update Medicare healthcare provider payments. The SDP is a program of the federal government made up of two parts: one to advance T1D research at the National Institutes of Health (NIH), and the other to fund treatment, education, and prevention programs for Native American and Alaska Native populations, which are disproportionately affected by type 2 diabetes. Since its creation in 1997, the SDP has funded nearly $1.9 billion in T1D research at the NIH. The $150 million per year extension of the SDP ensures that key research on T1D can continue uninterrupted.

Funds provided by the SDP have supported advances in the basic scientific understanding of T1D, improved treatments for both blood-glucose control and diabetes-related complications, and explored ways to prevent and/or delay the onset of the disease.

"Since it began, the SDP has demonstrated measurable and impressive results," says Richard A. Insel, M.D., JDRF's chief scientific officer. "The program has enabled scientists to make significant advances in cure therapies, prevention studies, and treatment improvements, including the artificial pancreas and groundbreaking advances in vision improvement among people with diabetic eye disease—advances that will help reduce long-term healthcare costs from diabetes complications."

New Insights into Factors Affecting T1D Development

A person's intestines—or "gut"—are home to a community of bacteria that are essential to metabolism and the normal development and function of the immune system. Early in life these bacteria, called gut microbes, help the body to establish immunoregulation. This is the process by which the immune system controls and balances all of its components and their interactions to defend against sickness and disease. But for reasons that are not known, immunoregulation development can go haywire and lead to the onset of an autoimmune disease. JDRF is funding research to investigate whether changes in gut microbes during early development lead to less-robust immunoregulation and the development of T1D.

Recently, JDRF-funded researchers at The Hospital for Sick Children in Toronto determined that early-life exposure to normal gut microbes protects against autoimmune disease in mice. In the mouse strain used, more than 85 percent of females develop T1D due to strong genetic risk factors. But when the female mice in the study were given gut bacteria from adult male mice early in life, only 25 percent of them developed T1D.

"Our findings suggest potential strategies for using normal gut bacteria to block progression of insulin-dependent diabetes in kids who have high genetic risk," says Jayne Danska, Ph.D., senior scientist in genetics and genome biology at The Hospital for Sick Children and professor of immunology and medical biophysics at the University of Toronto. Dr. Danska's findings were recently published in the journal *Science*.

The study also showed that the gut microbe treatments the mice received affected sex hormones. When young female mice received gut microbes from adult males, their testosterone levels rose, indicating that this hormone was essential for the gut microbe treatment to protect against T1D. "It was completely unexpected to find that the sex of an animal determines aspects of its gut microbe composition, that these microbes affect sex-hormone levels, and that the hormones in turn regulate an immune-mediated disease," Dr. Danska says.

The researchers' success in preventing T1D from developing in high-risk mice suggests that similar approaches may be applicable in preventing or treating other immune diseases, particularly those showing a female-sex bias, such as multiple sclerosis, lupus, and rheumatoid arthritis. "We don't know exactly how the microbes are interacting with the immune processes of type 1 diabetes to lead to autoimmunity, but the study opens a new pathway to investigate the potential of altering gut microbes to prevent autoimmune diseases," says Jessica L. Dunne, Ph.D., senior scientific program manager for JDRF's Immune Therapies Program.

In an effort to expedite progress in this area of research, JDRF has established its own Microbiome Consortium comprising JDRF-funded researchers in the field of T1D, including Dr. Danska, as well as expert investigators outside of this field.

Key point: *JDRF-funded researchers have demonstrated that early-life exposure to normal gut bacteria (also referred to as "gut microbes") protects against autoimmune disease. The researchers found that when female mice with a high risk of developing T1D were exposed to gut bacteria from adult male mice, they were strongly protected from the disease. Additionally, the researchers found that the testosterone levels of young female mice rose after receiving the gut microbes, leading researchers to believe that this hormone is critical for the gut microbes to protect against T1D. The mouse study lays the groundwork for possible human studies in the future. Additionally, the findings provide a new pathway to investigate the potential of altering gut microbes to prevent autoimmune diseases.*

Pancreas Size Linked to Type 1 Diabetes Development

JDRF is dedicated to funding research to learn more about the causes of T1D and the complications that can be caused by the disease. In 2007, JDRF established the Network for Pancreatic Organ Donors with Diabetes (nPOD). The purpose of nPOD is to collect and distribute pancreatic and other tissues from deceased organ donors with T1D, as well as from those without the disease but with multiple antibodies indicating high risk for developing the disease. To date, nPOD has provided more than 30,000 samples of human tissue from the pancreas and other organs, such as the spleen, lymph nodes, and blood, for research projects at institutions around the world.

Recently, researchers at the University of Florida examined pancreases donated to nPOD with the intent of identifying early signs of T1D development in people at risk for the disease. By comparing the weight of pancreases from deceased individuals with T1D and those with an increased risk for developing the disease to pancreases from healthy donors, the researchers found that people at risk of developing T1D have smaller pancreases and fewer insulin-producing beta cells than people who are not at risk for the disease. This finding suggests that early atrophy (or deterioration) of the pancreas may be an important feature of T1D development.

The weight of pancreases from the pre-T1D donors was found to be nearly 75 percent that of the controls, while the weight of pancreases from donors with T1D was roughly 50 percent that of the controls. The researchers suggest that lower pancreas weight may be attributable to a lower number of insulin-producing beta cells. Their findings were recently published in *The Journal of the American Medical Association*.

The results confirm a pattern that has been seen in previously published studies, but they are significant because these are the first samples to be measured by weight. Previous samples used ultrasound techniques to make their determinations, but this was the first study to use actual donor pancreases. The ultimate goal of nPOD is to enable a much-improved understanding of the pathophysiology of T1D in humans, which will ultimately enable T1D therapeutic development.

Key point: *Researchers at the University of Florida weighed pancreases donated to the Network for Pancreatic Organ Donors with Diabetes (nPOD) and found that donors at risk of developing T1D have smaller pancreases and fewer insulin-producing beta cells than people who are not at risk for the disease. The results confirm a pattern that has been seen in previously published studies, but they are significant because these are the first samples to be measured by weight. Additionally, the researchers suggest that lower pancreas weight may be attributable to a lower number of insulin-producing beta cells.*

Using Tiny Particles Helps Reset the Immune System

Understanding the role of the immune system in T1D is complicated. It is an area of intense research filled with complex jargon. Since learning more about this research supports greater understanding of T1D, here is a short guide to help clarify a few commonly used immune-system terms:

Antibody: a protein used by the immune system to identify and kill foreign objects in the body, such as bacteria or viruses.

Antigen: a substance that causes the immune system to produce antibodies. An antigen may be a foreign substance from the environment such as chemicals, pollen, foreign blood cells, or the cells of a transplanted organ.

Antigen-specific therapy: a way to target certain autoimmune reactions without impairing critical immune responses produced by antigens.

Immune tolerance: the ability of the immune system to distinguish between harmless and harmful antigens.

Nanoparticle: a microscopic particle less than 100 nanometers in size that is engineered to deliver specific results when inserted into the body.

Peptide: a biological molecule made up of a chain of amino acids. The function that a peptide carries out in the body depends on which types of amino acids are involved in the chain. Hormones, endorphins, and proteins are all examples of peptides.

T cell: a type of white blood cell that plays a role in the body's immune response by binding antigens as a defense against pathogens, autoimmune diseases, some acquired allergies, and other immune reactions.

Safely targeting the process that leads to the misguided immune attack on beta cells, and eventually T1D, is a challenge. A promising strategy lies in antigen-specific immune therapy that targets only a misguided part of the immune system. A recent JDRF-funded study has confirmed that incorporating nanoparticles into this approach could help stop the process that triggers various autoimmune diseases, including T1D.

Stephen D. Miller, Ph.D., the Judy Gugenheim Research Professor of Microbiology–Immunology at Northwestern University's Feinberg School of Medicine, used a nanoparticle-based immune therapy as a treatment for multiple sclerosis (MS) in mice. The biodegradable nanoparticles contained MS-related antigen components that, when inserted into the mice, reset the immune system's balance while creating immune tolerance. JDRF is supporting related work by Dr. Miller and his research team that specifically focuses on T1D, to help achieve immune tolerance to prevent and cure T1D and for transplanted insulin-producing islet cells.

Nanoparticles such as the ones Miller used allow multiple triggers of immune tolerance to be delivered to the body. Because the nanoparticles can be tailored to effect a response to a specific autoimmune disease, they should minimize side effects and allow better control over the specific immune response. The nanoparticles are also considered safe for use in the human body because they are made from a polymer that is easily metabolized. (In fact, the polymer is the same one used in dissolvable suture material used for stitches.) While this nanoparticle research has so far been conducted only in mice, if successfully applied to humans, it could provide a potential pathway to controlling the autoimmunity that underlies T1D.

Of further note, non-nanoparticle research involving MS peptides and similar immunological approaches is in the early stages of clinical evaluation and has so far proven safe and can produce a change in the MS-specific T cell response.

JDRF has been at the forefront of research using nanoparticles to benefit people with T1D. In addition to funding Miller's T1D research, JDRF has a robust portfolio of other promising research it is funding in this area.

Key point: *JDRF-funded researcher Stephen Miller, Ph.D., and his team from Northwestern University used a nanoparticle-based immune therapy as a treatment for the autoimmune disease multiple sclerosis (MS). The biodegradable nanoparticles contained MS-related antigen components and were used to reset the immune system balance and create immune tolerance in an animal model of MS. While this research has so far been conducted only in mice, if successfully applied to humans, it could provide a potential pathway to controlling the autoimmunity that underlies T1D.*

New Partnership to Develop Dual-Hormone Infusion Pump

Many people with T1D administer daily insulin doses through an infusion pump, and some manage the disease using a combination of hormones and/or drug treatments. Current infusion pumps deliver only one hormone (insulin) to control blood-glucose levels, but the pancreas produces several hormones to aid in metabolism, digestion, and blood-glucose control. To address this issue of supplying multiple hormones via one device, JDRF is partnering with Tandem Diabetes Care to create a first-of-its-kind, dual-chamber infusion pump that can deliver two hormonal drug therapies simultaneously. The two-year partnership is designed to accelerate the development of a next-generation, fully automated artificial pancreas system using therapies in conjunction with insulin.

An artificial pancreas will be an external system of devices and software that people with T1D could use to replace the body's lost ability to automatically control blood-glucose levels. A basic artificial pancreas system would work by connecting a continuous glucose monitor—a device that provides continuous real-time readings and data about trends in a person's blood-glucose levels—with an insulin pump, and using sophisticated computer software to automatically deliver the right amount of insulin at the right time. A dual-chamber infusion pump could help evolve the artificial pancreas to a future generation of devices that more closely mimics the function of a healthy human pancreas. "Tandem's research into infusion pumps that could simultaneously deliver multiple hormones is an important step forward in the development of a more effective artificial pancreas system—a device that could improve the health and quality of life of people with diabetes," says Aaron J. Kowalski, Ph.D., JDRF's vice president of treatment therapies.

Though the pancreas produces several other hormones to regulate a person's blood-glucose levels, some of those are not used regularly in the treatment of people with T1D. For instance, people who experience severe hypoglycemia (low blood glucose) emergencies may require the administration of the hormone glucagon. This hormone helps the liver release glucose in order to raise blood-glucose levels during a hypoglycemic episode. Other people with T1D use a combined therapy of insulin and Symlin, an analog—a chemical compound that resembles another in structure but has a slightly different composition—of the hormone amylin, to control the rate at which glucose enters the bloodstream after meals. However, treatments such as glucagon and Symlin can be administered only through a syringe, making a dual-chamber infusion pump a possible treatment option for people with T1D.

Artificial pancreas systems are currently being tested to automate some insulin delivery, with the ultimate goal of restoring the balance of other hormones that are missing or out of balance in people with T1D. "An ambulatory device that can simultaneously deliver insulin along with other drug therapies that are used for optimal diabetes management is not currently commercially available," says Kim D. Blickenstaff, president and CEO of Tandem. "The combination of JDRF's expertise and advocacy along with Tandem's unique technology and passion for meeting unmet needs in the diabetes community offers the opportunity for an exciting step toward the ultimate artificial pancreas solution."

Key point: *JDRF is partnering with Tandem Diabetes Care to develop the world's first dual-chamber hormone pump that can deliver two injectable hormones simultaneously to help regulate blood-glucose levels. The two-year partnership is designed to accelerate the development of a next-generation, fully automated artificial pancreas system using other hormone therapies in conjunction with insulin. A dual-chamber infusion pump could help evolve the artificial pancreas to a future generation of devices that more closely mimics the function of a healthy human pancreas.*

JDRF Establishes Award in Memory of Leading T1D Expert George Eisenbarth

Longtime JDRF friend and esteemed diabetes researcher George Eisenbarth, M.D., Ph.D., will be commemorated through a new award established by JDRF in his honor. The JDRF George Eisenbarth Award for Type 1 Diabetes Prevention will recognize outstanding advances in the prevention of T1D. The award was recently announced at a memorial for Dr. Eisenbarth at the Anschutz Medical Campus of the University of Colorado, Denver, where he worked as a professor until his death in November 2012. Eisenbarth was also the executive director of the Barbara Davis Center for Childhood Diabetes.

Dr. Eisenbarth's contributions to T1D research earned him many awards throughout his career, including the David Rumbough Award for Scientific Excellence from JDRF in 1997, and more recently, JDRF's 10th annual

Mary Tyler Moore and S. Robert Levine, M.D., Excellence in Clinical Research Award in July 2012.

"George was one of the exceptional researchers in the field who made seminal contributions to our understanding of type 1 diabetes throughout his career," says Richard A. Insel, M.D., JDRF's chief scientific officer. Dr. Insel regards Dr. Eisenbarth as one of the most passionate and dedicated researchers we knew, and commented that his citizenship and unselfish approach to science were legendary. "When George died, the entire diabetes community suffered a great loss," reflects Dr. Insel. "His contributions to type 1 diabetes, particularly in the area of risk and prevention of the disease, have created the critical foundation that will be built on in the years ahead as we progress toward prevention of the disease. This award was created to honor his legacy."