JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Top Research Highlights

On the Front Lines: Beta cells under attack

Whether it takes a high-power microscope or a meeting of expert minds, JDRF is advancing science to cure, better treat, and prevent type 1 diabetes (T1D) on all fronts. In this issue of *Top Research Highlights*, you will read about new findings from scientists who have actually seen how beta cells are accosted in the autoimmune attack that is associated with T1D. And you will learn about evidence of this crime at the scene—from researchers who showed that the attackers are present in the islets of the pancreas, where beta cells reside. To find this evidence, researchers used human tissue samples from T1D donors obtained through nPOD, a JDRF collaborative research project.

Collaboration is a main theme in the last two articles in this issue. We report on JDRF convening its first conference on biomarkers in T1D, which took place in December 2011. JDRF played host to a meeting of leading investigators from around the world to further the study of biomarkers, which are measurements that potentially can identify the stage or progress of a disease, or assess a person's response to a particular therapy. Finally, you will learn about a new partnership between JDRF and KalVista Pharmaceuticals, a U.K. company. We are teaming up with researchers at this company to investigate new treatments for diabetic eye disease that are based on potential therapies that block blood vessel damage in the eyes.

Type 1 Diabetes Investigators —Aided by JDRF Research Project—Are First to Identify "Killer" T Cells within Human Islets

A team of researchers recently became the first to catch "killer" cells at the scene of the crime—the pancreas—where they bring about the autoimmune attack that is a hallmark of type 1 diabetes (T1D). The researchers used human tissue samples from T1D organ donors obtained through nPOD, a JDRF collaborative research project.

Investigators at the La Jolla Institute of Allergy and Immunology in San Diego, CA, used actual human pancreatic tissue from donors with T1D provided by the JDRF Network for Pancreatic Organ Donors with Diabetes (nPOD). Their work proved that a specific type of T cell (a critical immune system component involved in the development of T1D) called a "CD8 T cell," which is responsible for the attack on insulin-producing beta cells, can be found in the pancreas. The study, which appeared in the January 2, 2012 issue of *The Journal of Experimental Medicine,* examined pancreatic tissue from 45 organ donors who had T1D. The lead investigator, Matthias von Herrath, M.D., and his research team were able to detect evidence of the dangerous actions of the CD8 T cells in the pancreatic islets (which contain beta cells).

"This study demonstrates for the first time the presence of CD8 T cells, specific for beta cells, within human islets. While this has been a well-established fact in animal models of type 1 diabetes, the La Jolla investigators have now demonstrated it in human samples," says Teodora P. Staeva, Ph.D., director of the immune therapies program at JDRF. "The presence of these CD8 T cells, which are capable of killing the insulin-producing beta cells, was shown in donors with recent-onset as well as long-standing T1D." Dr. Staeva further explains: "Identifying the CD8 T cells that cause the beta-cell destruction can help to develop therapies that specifically target those cells and may thus offer safer interventions." The research, which was funded by the National Institutes of Health, relied on nPOD, an innovative, JDRF-funded program based at the University of Florida, Gainesville, that provides donated organ tissue from people with T1D to scientists around the world. The nPOD program gives researchers a unique opportunity to literally see—and better understand—all phases of T1D and its impact on the pancreas and immune system.

"The power of nPOD is its ability to recover high-quality tissues from donors at all stages of T1D and make that available to researchers throughout the world," says Dr. Staeva. "In addition, nPOD has spearheaded efforts on data sharing and scientific exchange that are setting new standards for the field."

nPOD is a collaborative T1D research project that supports scientific investigators by providing, without cost, rare and difficult-to-obtain tissues. nPOD currently supports more than 70 T1D-related scientific studies at institutions around the world.

Learn more about nPOD at www.jdrfnPOD.org.

Key Point: *Researchers recently demonstrated for the first time a direct association between human beta cell destruction and CD8 T cells, which are cells that play an important role in the body's immune system. This autoimmune "attack" is a hallmark of T1D and it results in the destruction of insulin-producing beta cells in the pancreas. In their investigation, the researchers used human tissue samples from the pancreases of T1D organ donors obtained through nPOD, a JDRF collaborative research project. This new study provides evidence that CD8 T cells are present in the islets of the pancreas that contain beta cells. These findings are important for future research on preserving beta-cell function and establishing biomarkers for therapies for T1D.*

First-Ever Findings from JDRF-Funded Scientists Provide Evidence about How Killer T Cells Form Their Fatal Attraction with Beta Cells

A new study supported by JDRF and additional funding sources in the United Kingdom revealed groundbreaking information about the mechanism responsible for the autoimmune attack that is a hallmark of type 1 diabetes (T1D). Two groups of prominent researchers, from Cardiff University School of Medicine in Wales and King's College London, used an actual T cell that was replicated or "cloned" from a patient with T1D to literally get "a view to a kill," meaning that they were able to produce a visual image of the molecular interactions that mediate the fatal autoimmune attack.

To get a molecular-level view, the researchers were aided by x-ray crystallography, a technique that uses x-rays to gather information about the structure of molecules that have been crystallized. With this technology, they were able to see just how a specific type of T cell manages to encounter insulin-producing beta cells in the pancreas. Learning about how this deadly encounter takes place can help to advance the understanding of how T1D develops in individuals.

The research, led by Andrew K. Sewell, Ph.D., and published online in the January 15, 2012 issue of Nature Immunology, examined the way in which the cells responsible for attacking beta cells, called CD8 killer T cells, actually latch onto the beta cells. This latching on, referred to as the "docking mode," is accomplished via the assistance of a network of receptors. In previous studies, docking modes have been described in a different type of T cell in other autoimmune disease settings. However, Dr. Sewell's work is the first to provide information on how this happens with killer T cells in T1D.

Dr. Sewell and collaborators investigated the interaction between certain receptors on T cells (TCRs) and their target—the beta cells. Specifically, they looked at how TCRs recognize and make contact with a protein fragment on the beta cell's surface (MHC). What's important to understand here is that the advance in knowledge about the interaction of these molecular players represents a critical finding in T1D science.

The researchers were surprised by the results, which showed that the attraction of TCRs to MHC is weaker than expected, and thus the contact between killer T cell and beta cell is also weak. Importantly, the researchers suggest that it may take an additional factor, such as an infection, to cause the killer T cell–beta cell interaction to become destructive to the beta cell.

"The findings of Dr. Sewell and his colleagues comprise a significant discovery that clearly characterizes the recognition between killer T cells and beta cells in the development of type 1 diabetes," states Simi T. Ahmed, Ph.D., scientific program manager of immune therapies at JDRF. "This work paves the way for a more intelligent design of therapeutics that could aim not only to interfere with the interaction between a killer T cell and its target, but also to prevent it from becoming activated as a result of this interaction and go on to attack the beta cell."

[1]a critical immune system component involved in the development of type 1 diabetes
[2]T cell antigen receptors (TCRs)
[3]major histocompatibility complex (MHC)

Key Point: *Researchers supported by JDRF recently characterized for the first time the nature of the encounter between killer T cells and their targets—the insulin-producing beta cells in the pancreas. Using an actual T cell that was replicated or "cloned" from a patient with type 1 diabetes (T1D), the researchers provided valuable evidence*

about the interaction that takes place on a molecular level and contributes to the autoimmune attack that destroys beta cells. These findings can help guide the development of targeted therapies for the prevention of T1D.

To learn more about the immune system, click here.

JDRF Forms New Partnership to Advance Novel Treatment Research for Diabetic Eye Disease

Building on previous research funded by JDRF, the organization has teamed with KalVista Pharmaceuticals, a company based in the United Kingdom, to continue the quest for therapies that will halt or delay the progression of diabetic eye disease.

Diabetic eye disease is the leading cause of blindness and impaired vision in people with type 1 diabetes (T1D). Diabetic retinopathy can occur after years of high blood-sugar levels cause the retina—the light-sensitive tissue at the back of the eye—to swell, making blood vessels in the eye leak. When fluid enters the macula—an area of the retina critical for sharp, straight-ahead vision—diabetic macular edema (DME) occurs and causes further swelling in the retina and impaired vision.

Continuing Support

Supporting research to prevent or slow diabetic eye disease is a high priority for JDRF. The organization has a history of guiding innovative discoveries in the lab through the stages of clinical evaluation for effectiveness and safety and into development of therapies that help people whose vision is threatened by T1D.

We previously reported on JDRF-supported research on Lucentis, a treatment for DME already approved in the European Union in 2010 and Canada in 2011. Lucentis reduces vascular endothelial growth factor, which causes leakage in small blood vessels in the eyes of people with T1D. Many patients who used Lucentis had significantly improved vision, but not all respond to the drug, so it's vital that the search for other treatments continues.

Previous studies funded by JDRF and led by a co-founder of KalVista, Edward Feener, Ph.D., associate professor of medicine at Harvard Medical School and Joslin Diabetes Center, were the first to detect high levels of an enzyme called plasma kallikrein—pronounced "ka-li-KREE-in," or just "pK"—in the eyes of people with DME. Excessive amounts of pK cause inflammation, blood-vessel leakage, and thickening of the retina that damages vision.

Searching for a Therapy

In investigating new treatments for DME, KalVista will conduct preclinical trials to evaluate a group of possible therapies that utilize plasma kallikrein inhibitors to reduce the amount of pK in people with T1D. "Plasma kallikrein inhibitors target a known contributor to blood-vessel damage in the eye and have the potential to offer patients an effective treatment option," says Andrew Crockett, CEO of KalVista. "Our preclinical studies for this potential therapy will begin this year, and we're delighted that JDRF, the leading global organization committed to T1D research, has recognized the possibilities for our novel approach to treating DME."

Why Target Plasma Kallikrein?

Like all enzymes in the body, plasma kallikrein (pK) acts as a catalyst to cause a specific biochemical reaction. Plasma kallikrein circulates in the blood and when it increases, it generates a potent, inflammatory hormone called bradykinin, which can cause blood vessels in the eye to enlarge and leak. High levels of bradykinin lead to high blood pressure and high blood sugar, which are major risk factors for the serious eye condition diabetic macular edema (DME).

Lowering pK levels may prove to be an effective therapy for all individuals affected by DME, and more importantly, may offer an alternative option to those individuals who do not respond to Lucentis. The KalVista Pharmaceuticals research supported by JDRF will test a group of potential plasma kallikrein inhibitors with the goal of finding an ideal candidate.

In teaming with KalVista, JDRF will provide up to $2.2 million in milestone-based funding and lend its vast research expertise. "Partnerships with companies such as KalVista are essential as we continue in our work to translate promising research into effective therapies for diabetic eye disease," says Aaron Kowalski, Ph.D., assistant vice president of treat therapies at JDRF. "We're in the preclinical stage of this research, but if the studies reveal one or more promising plasma kallikrein inhibitors that are ready for clinical development,

we will have made a great stride toward providing a new treatment option for people with T1D."

Key Point: *Previous research identified high levels of the enzyme plasma kallikrein in patients with diabetic macular edema, a condition that can cause impaired vision or blindness. JDRF-funded studies by KalVista Pharmaceuticals aim to identify new therapies that will reduce levels of plasma kallikrein and preserve the eyesight of people with T1D.*

JDRF Hosts First Type 1 Diabetes Biomarkers Conference

On December 14 and 15, 2011, a conference titled "Identification and Utilization of Robust Biomarkers in Type 1 Diabetes" was held by JDRF in New York City. Type 1 diabetes (T1D) is a heterogeneous disease—meaning that although it is a single disease, it can have distinct differences on the molecular level (involving some of the tiniest particles in the body). These differences are factors that help to explain why the development of T1D and the progression of the disease may vary between individuals. While the factors that may cause T1D are, in part, genetic, there are other factors, considered "environmental," such as climate, diet, or infection history, that can differentially affect disease. All of these factors taken together further contribute to the variation among individuals with T1D and to the complexity of the disease itself. Unquestionably, this variation and complexity has tremendous significance. Enter biomarkers....

A biomarker is a physical, biological, or molecular characteristic that is objectively measured and evaluated as an indicator of normal biological processes, disease-causing (or "pathogenic") processes, or pharmacologic responses to therapeutic intervention. Biomarkers can be used to make diagnoses, to indicate disease status and stage, and to predict and/or monitor clinical response. In the field of T1D, measurements that can reliably identify disease stage or predict disease progression are lacking, as are biomarkers to measure response to particular therapies. Ideally, researchers and clinicians will be able to use biomarkers in T1D to precisely assess and track the underlying disease process—from identifying people at risk for the disease, to analyzing the manner in which the disease is progressing, to evaluating the effectiveness of treatments. However, in the field of T1D research, there has been a serious lack of reliable biomarkers that could be used to understand the core mechanisms of the disease.

Over the years, as a leader in the field of biomarkers research for T1D, JDRF has brought together scientists from different areas of expertise, including clinical medicine, immunology, beta-cell biology, and biotechnology to develop new approaches for investigating biomarkers. JDRF brought together U.S. and international investigators from various sectors of the research community, including academia, industry, and government, at a conference in December to exchange ideas and set a course for the future of biomarkers research. The goals of the conference were to evaluate the current state of biomarkers in T1D research, to identify new opportunities for discovering and validating biomarkers, and to determine the best and most efficient and collaborative way to move the field of biomarkers research forward.

The investigators who attended the JDRF conference framed their presentations and discussions around the following: 1) the stages of T1D; 2) substitutes or "surrogates" of clinical effectiveness of treatments; and 3) how current and future biomarker tests or "assays" and technologies could be tailored for either objective. The sessions for the conference included "Biomarkers: Definition and Attributes—Building a roadmap for biomarker discovery in T1D," "Current State of Biomarkers in T1D," and "Emerging Technologies: The future of biomarkers in T1D." Presentations spanned the range from pilot studies highlighting basic discovery efforts that may be ready for validation with appropriate samples, to slightly more mature assays that require standardization or optimization for large-scale testing, to biomarker identification strategies in other diseases that could be applied to T1D. After focused and facilitated group discussions at the conference, the investigators proposed recommendations for what types of biomarkers and testable human biological samples (such as blood, urine, saliva, etc.) are needed at each stage of T1D. They followed with recommendations on how existing resources or technologies—or an improvement of both—could be used to identify, develop, and validate biomarkers.

Advancing biomarkers research will benefit people with T1D by enabling earlier detection and improved therapies, and will ultimately allow clinicians to tailor treatments to individuals. In addition, biomarkers can

be used as surrogate endpoints for clinical trials. As a surrogate endpoint, a biomarker could inform clinicians as to whether a treatment is working much earlier than it would normally take for a clinical trial to finish, and thus speed up clinical trials. Furthermore, biomarkers can be used to ensure that drugs are working effectively or to signal the need to adjust the dosage of a drug to correspond to an individual's needs.

"Ultimately what we want is an easy-to-measure group of biomarkers that can be used in T1D disease prediction, staging, and response to therapy," said Simi T. Ahmed, Ph.D., JDRF's scientific program manager of immune therapies. "By hosting this conference, we now have a better understanding of the gaps in the field and the ways in which we can attempt to fill them—hopefully as a combined effort among some of the best talent around."

Key Point: *Consistent with its leadership role in T1D research, JDRF is prioritizing the investigation of biomarkers. We are advancing the knowledge about the direction and needs of research in this critical area, with the goal of providing vital information to reliably measure or predict disease progression in individuals with T1D and to indicate their responsiveness to therapies. Supporting the development of biomarkers for T1D could provide industry with tools to allow for more efficient and attractive incentives to pursue therapies for the disease.*