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Diabetes Care

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JDRFI Launches Online Clinical Service

This summer, JDRFI successfully launched Clinical Trials Connection (<http://www.trials.jdrf.org/>), an innovative online service to help people with type 1 diabetes and their families easily find information about clinical trials on new treatments for type 1 diabetes and its complications.

With more diabetes trials ongoing than ever before, Clinical Trials Connection simplifies the process of finding trials people might want to take part in. The website enables people to search the National Institutes of Health's (NIH) database of currently ongoing trials, including JDRF-funded studies. Users need only provide criteria like the type of trial they are interested in, how long they have had diabetes, and how far they would be willing to travel, and the service lists all studies matching those characteristics. It will also provide contact information for the researchers conducting each trial, so users can contact them directly for more information – after discussing their options with their healthcare providers. And once someone has registered with Clinical Trials Connection, the service will also automatically send them email updates on trials as they are added to the NIH database if they match their criteria.

JDRFI developed Clinical Trials Connection because our constituents (people with type 1 diabetes and their families) told us such a service would be a tremendous benefit to them. JDRFI also recognized the service would help advance its efforts to find a cure through research. Over its nearly 40-year

history, JDRFI has funded more than \$1.3 billion (U.S.) towards a cure, accelerating science to the point where we are now funding more than 40 human clinical trials of potential new treatments. However, funded scientists are finding it harder and harder to enroll participants in clinical trials in a timely and cost-efficient way. Clinical Trials Connection will help address the gap while making it easier for people with type 1 diabetes to participate in clinical trials to help find a cure.

All information provided through Clinical Trials Connection will be kept in the strictest confidence. To be an active part of research leading to a cure or to get more information about clinical trials, please visit JDRFI's Clinical Trials Connection at www.trials.jdrf.org.

Blood Pressure Drugs Stop Eye Disease from Progressing in People with Diabetes

Two drugs used to treat high blood pressure can significantly slow diabetic retinopathy, a serious and common complication of type 1 diabetes. While the findings, published last month 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.

The two drugs—losartan and enalapril—both work by targeting a hormonal system controlled by the kidneys and helps to regulate blood pressure. Losartan is what is called an ARB, or angiotensin-receptor blocker; it works by blocking the receptor for angiotensin, which causes blood vessels to relax, lowering blood pressure. Enalapril is an ACE inhibitor, or angiotensin-converting-enzyme inhibitor. It works by stopping angiotensin from actively constricting small blood vessels.

The new findings are based on five-year data from a multi-centre, randomized clinical trial designed to test if the drugs could prevent or improve diabetic eye disease or kidney disease.

Michael Mauer from the University of Minnesota in Minneapolis led the study, the longest and most comprehensive to date in this area of investigation.

According to Dr. Paul Strumph, Vice President of Medical Affairs and Chief Medical Officer at JDRFI, "This study adds

to our understanding of the role of blockers of the renin-angiotensin system in preventing the progression of eye disease in some people with type 1 diabetes—those with normal blood pressure, no detectable kidney disease, and very mild eye disease. Interestingly, there was no detectable benefit in slowing the progression of diabetic kidney disease, even though this same group saw a beneficial effect in reducing the progression of diabetic eye disease. While promising with respect to retinopathy, further work is needed before this therapy becomes routine practice to prevent the progression of diabetic eye disease. And because the study did not evaluate the drugs' effects on eye and kidney disease in people with elevated blood pressure, detectable kidney disease, and mild eye disease—which often define the type 1 population—there are no implications for changing clinical practice guidelines or standards of care for people in that group.”

At the beginning of the study, none of the patients had kidney disease, and all had normal blood pressure; those included in the eye portion of the study had no or minimal diabetic retinopathy.

The study showed people who received either drug were at least two times *less likely* to experience a progression in diabetic retinopathy than people who did not get the drugs (based on a worsening of eye disease of two steps, or more, on a 15-step scale charting the severity of diabetic retinopathy). In contrast, neither losartan or enalapril slowed the progression of diabetic kidney disease—an unexpected finding is counter to the widely accepted view these classes of drugs can benefit type 1 diabetes patients with either early or advanced stages of kidney disease.

Although not funded by JDRFI, the study was built on research co-funded by JDRFI in 2002. In the earlier trial by Dr. Mauer, researchers studied the early natural history of kidney disease in type 1 diabetes. Kidney disease, like retinopathy, is a significant problem for people with type 1 diabetes and is responsible for nearly 50 per cent of all cases of end-stage renal disease in the United States. Both conditions are linked to high blood pressure.

Study objectives and design

The latest trial was looking at whether the two blood pressure drugs could prevent kidney and eye disease in people with type 1 diabetes who had normal blood pressure. The first part of the trial was launched in 2002 to assess the drugs' effect on kidney disease; a second study, using the same patients, started shortly afterwards and looked at possible benefits for retinopathy.

As part of the trial, 285 type 1 diabetes patients were randomly assigned to receive a daily dose of either losartan, enalapril, or a placebo. They were monitored for five years. There were no significant differences between the groups in

terms of age (most participants were about 30 years old), how long they had diabetes (the average was about 11 years), or on other standard baseline characteristics.

The trial took place in Montreal, Canada, and at the University of Minnesota.

Main findings

Both blood pressure drugs slowed the progression of diabetic retinopathy. The likelihood of eye disease progressing by two steps or more was reduced by 65 per cent in patients given enalapril, and by 70 per cent in those given losartan. These reductions in the risk of retinopathy parallel the benefits people with diabetes would typically gain from intensive insulin therapy.

The drugs did not slow the progression of diabetic kidney disease. The five-year rate of microalbuminuria, an indicator of the disease marked by elevated protein levels in the urine, was six per cent in the placebo group, four per cent in patients taking enalapril, and 17 per cent in patients given losartan.

“We did not detect structural or functional benefits on nephropathy from the blockade of the renin-angiotensin system with an ACE inhibitor or an ARB in normotensive patients with type 1 diabetes and normoalbuminuria,” the researchers concluded. “Given the current status of our ability to predict the risk of nephropathy, blockade of the renin-angiotensin system for the primary prevention of diabetic nephropathy in patients with type 1 diabetes is not supported by the present evidence. In contrast, we found beneficial effects of the ACE inhibitor enalapril and the ARB losartan in reducing the risk of progression of diabetic retinopathy.”

Next steps

In an editorial accompanying the study, Bruce Perkins, an endocrinologist and diabetes expert from the University of Toronto, said while the results are “very encouraging” and the two drugs “clearly effective” with regard to eye disease, more work needs to be done before the drugs are used for retinopathy prevention in the clinic. What needs to be established is how long the protection lasts beyond the five years of the study, and whether the benefits may continue even if the treatment is stopped. Another question is of a risk-benefit nature: The majority of patients who benefited from the treatment had few signs of diabetic retinopathy—suggesting the drugs may not benefit patients with more advanced eye disease. Studies will need to determine which groups of type 1 diabetes patients will benefit least from the intervention, and thus should not be treated.

Related research

The study itself also offers the potential to identify new, early biomarkers for diabetic nephropathy and retinopathy—ways to judge the beginning and progression of these complications, and to assess the effectiveness of treatments

and cures as they are developed. In late 2007, University of Wisconsin-Madison researcher Ronald Klein received a JDRFI grant to examine whether measuring small blood vessels in the back of the eye might provide valuable information about a patient's eye or kidney disease, or the risk of developing either condition. Dr. Klein is using retinal photographs taken from the same people who participated in the University of Minnesota study to compare the diameter of retinal blood vessels at the start of the study with various measures of change in those patients' kidneys and eyes over the five-years of the trial. The goal is to identify clinically helpful relationships that might allow the diameter of retinal blood vessels to serve as an early, non-invasive biomarker for either condition.

Key Point:

Certain drugs for high blood pressure appear to significantly slow the progression of diabetic retinopathy, a serious and common complication of type 1 diabetes that can lead to vision loss.

A Novel Way to Address Autoimmunity in Type 1 Diabetes

JDRFI-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 to alter the behaviour 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. JDRFI is funding the University of Massachusetts (UMass) researchers to apply this novel technology to benefit people with type 1 diabetes.

Dr. Czech explained the technology the researchers are using targets cells that "engulf" particles the size and shape of the yeast shells. The proteins and other agents the researchers put in the shells then change how those cells present themselves to immune system T-cells—a change would cause the immune cells to tolerate, rather than attack, insulin-producing cells in a person with type 1 diabetes.

Changing those immune system T-cells from attack mode to tolerance mode when they come across beta cells may "induce tolerance," as the scientists call it, before the autoimmune reactions become destructive. The strategy would ideally stop the process causing diabetes in its tracks, or prevent it from starting in people at risk for developing the disease.

The UMass vaccine would be "antigen-specific" to type 1 diabetes, meaning it would turn off just the immune system attack of the pancreas, leaving the rest of the immune defense system to operate normally. Antigens are substances, usually proteins, which trigger an immune response. Naturally produced proteins act as antigens often cause autoimmune disease and are called autoantigens—those are the proteins the researchers will consider encapsulating within the yeast shells.

Dr. Czech said he and his team will be testing their hypotheses in mice. "If this technology works in animals," he added, "we will attempt to move the intervention forward into clinical trials. It is very exciting to be working on a technology that has the potential to develop into a therapeutic for type 1 diabetes."

Yeast shells as delivery vehicles

In previous research, the UMass researchers showed purified yeast shells derived from baker's yeast can be designed to encase proteins and other compounds, and these agents can effectively minimize immune responses in mouse cells *in vitro* (in a test tube) and *in vivo* (in cells in a living animal). Certain agents within the shells were able to silence the action of a targeted gene, with minimal response from the immune system. This method is a relatively new prospect for drug development, and Dr. Czech and his team are actively studying its therapeutic potential to treat people.

In one set of experiments, the UMass group used the yeast shells to orally deliver agents called short interfering RNA (or siRNA), which worked specifically against molecules linked to inflammation and several other autoimmune diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis. Once swallowed, the yeast-encased siRNA was engulfed by cells in the digestive system, stopping those cells from stimulating an immune response. By silencing a critical inflammatory gene found in those cells, the researchers were able to suppress the inflammatory response.

Another potential benefit of the UMass vaccine approach is the cells that engulf the yeast shells in the stomach can also circulate from the digestive system to other organs of the body—including potentially the pancreatic lymph nodes and islets; which means over time, a large proportion of those "treated" immune system cells will exhibit gene silencing in a location specific to diabetes. The researchers showed cells recovered from various organs in the previous experiments, including the spleen, liver, and lungs, had indeed engulfed the vaccine proteins and had been "switched" off.

Modifications to address type 1 diabetes

Using the yeast-shell platform as a starting point, JDRFI asked the UMass researchers to develop an oral vaccine for type 1 diabetes—one that could stop immune cells from targeting insulin-producing beta cells, and also regulate immune system genes. Their approach was to include beta cell antigens along with siRNA in the vaccine shells.

In this modified protocol, Dr. Czech and his team will target not only immune cells in the stomach, but also another type of antigen-presenting cell, called dendritic cells. Dendritic cells play an important surveillance role in the body. They “display” information about the molecules they encounter to the immune system’s T-cells. If T-cells incorrectly react to molecules found naturally in the body, the T-cells are targeted for destruction so they do not begin an autoimmune response. In people with type 1 diabetes, this response is imperfect, which is why they develop the disease: some of the wayward T-cells make their way to the pancreas, where they begin to do harm.

Recent research has shown dendritic cells play a key role in keeping the immune system working properly—either by causing the destruction of improperly working T-cells or by causing the production of regulatory T-cells, an immune cell that moderates immune responses.

Dr. Czech and his team are looking to tap into all these mechanisms. By using the vaccine shells to load up dendritic cells and immune cells in the stomach with beta cell antigens, they hope to spur the correct, alternative T-cell responses to the autoantigens—so the immune attack that causes diabetes does not occur. The researchers will assess a number of siRNA targets, and several beta cell antigens, to see which combinations have the best effect. To do so, the two components of the vaccine will be tested separately and in combination.

With their JDRFI funding, the researchers are working against a two-year milestone-driven plan to evaluate and test the vaccine. The first year is focused on finding the best autoantigen and siRNA targets, and successfully encapsulating them within the yeast shells. *In vivo* studies are scheduled to begin at the beginning of the second year of their investigations.

Key Point:

Researchers are developing a novel oral vaccine for type 1 diabetes. Using “yeast shells” to deliver proteins and other agents, the vaccine is intended to interrupt the immune attack that causes diabetes as well as silence key genes that contribute to inflammation and autoimmunity.

JDRFI Enters Innovative New Diabetes Drug Discovery and Development Partnership

In a major development, JDRFI entered into a novel collaborative research agreement with the Genomics Institute of the Novartis Research Foundation earlier this month 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 JDRFI.

Plus, it marks a major opportunity for the organization 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. Funded by the Novartis Research Foundation, its mission is to develop and apply innovative technologies to the discovery of new biologic processes and new or improved therapeutics for people. With a team of 550 scientists and associates, it has an impressive track record of success in translational research, and has contributed significantly to Novartis’ pipeline of therapeutic candidates.

“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 JDRFI. “By creating this highly interactive collaboration with a world class organization with demonstrated expertise in discovering and developing innovative therapeutics for medical needs, we are looking to expand both the targets and the realm of possible treatments that can benefit people living with diabetes.”

The partnership between JDRFI and GNF aims to deliver a succession of diabetes drug candidates to the clinic over the next four years.

The initial focus will be on restoring the function of the insulin-producing beta cells in the pancreas of people with type 1 diabetes, by regenerating these cells and promoting their survival. The program builds on current JDRFI funding at GNF that has identified beta cell regeneration drug targets and candidates. It also allows other JDRF-funded projects and other discoveries to be included in the program.

“Through this collaboration with JDRF, we are looking to create a unique program of translational research that fully exploits the strengths of each partner to produce a continuous source of novel insights, drug targets, and drug candidates,” said Peter Schultz, Ph.D., Lead Investigator and Institute Director at GNF.

“This is an exciting evolution of JDRF’s research strategy for discovering and developing diabetes therapeutics,” said Richard A. Insel, MD, Executive Vice President for Research at JDRFI. “The partnership provides JDRF access to a highly talented group of scientists, state-of-the-art drug discovery technology, and an organization with a proven track record of delivering drugs to the clinic to address a critical gap in research—advancing basic research, often arising from academia, into drug discovery and development. The JDRF-GNF partnership should jumpstart the creation of a multi-product pipeline for beta cell regeneration, a therapeutic priority for JDRF.”

Projects within the exciting new collaboration will be chosen and managed by a combined review committee of JDRFI and

GNF, with oversight from a Scientific Advisory Board and JDRFI volunteers.

Regeneration will be the initial focus of the collaboration because it is among the fastest growing areas of diabetes research and holds significant opportunities and candidates for near-term translation into products and treatments. Last year, regeneration was one of JDRFI's top two areas for new research funding—after not even existing as a research discipline until just a few years ago. Plus, regeneration matches well with GNF's research focus and technological capabilities in biology, immunology, and metabolic diseases.

Over the next four years, JDRFI hopes to see a number of drugs and treatments move from basic discovery science into clinical trials as a result of this new partnership.

JDRFI Researchers at First Keystone Symposium™ on Diabetes and Obesity Complications

The long-term complications of type 1 diabetes, type 2 diabetes, and obesity are often similar, and are emerging as major health problems around the world.

This year's Keystone Symposia on Molecular and Cellular Biology, which connects the scientific community across disciplines and geographic borders, was devoted to the biologic mechanisms underlying and linking the three disorders. JDRFI researchers were intimately involved in a dialogue that could potentially point to therapies applicable to type 1 diabetes, or to the complications associated with all three diseases—eye disease, nerve damage, kidney disease, heart disease, and stroke.

The development of complications in people with either type of diabetes or obesity is complex and involves multiple factors. Both types of diabetes and obesity, for example, appear to initiate the destructive forces of immune reactions and, based on individual risk and environmental factors, drive the development of physiologic changes such as hypertension and cellular stress. The symposium integrated these concepts by bringing together clinical and scientific experts in type 1 diabetes, type 2 diabetes, obesity, and vascular biology (which focuses on the body's blood vessels). The Keystone Symposium on diabetes complications was the first-ever to focus solely on these themes and included 46 presenters; of that number, an impressive 18 have received or are currently receiving a JDRFI research grant.

"The conference brought the type 1 diabetes community together for the first time to focus on complications, and will certainly inspire new partnerships and ideas for prevention and treatment of these conditions," said Barbara Araneo, director of the complications research program at JDRFI. "The meeting was an important mix of academic and clinical researchers, which helps to keep the focus on the patient, not just on knowledge for knowledge's sake."

Highlights presented by several of the JDRFI-funded researchers included:

Eye and Kidney Disease

George King, M.D., Senior Vice President and Director of Research at the Joslin Diabetes Center in Boston, Massachusetts, and one of the three meeting organizers, discussed the role of a protein (PKC) in the development of diabetic complications. PKC, he explained, is a key molecule that changes in the presence of high blood sugar (associated with type 1 diabetes) or insulin resistance (associated with obesity). When someone with diabetes or obesity has abnormal PKC function alongside the many other physiologic changes associated with these conditions—changes like a lack of insulin production, changing levels of glucose, fatty acids, and lipids, or abnormal levels of cytokines and hormones—the result impacts blood vessel cells and vessel walls. This in turn can lead to the development of vascular complications like retinopathy (eye disease) and nephropathy (kidney disease). Dr. King and others are actively investigating how problems with PKC begin this cascade of events resulting in complications. Already, he has shown high blood sugar levels can induce different forms of PKC in different tissues, leading to different types of vascular complications. How these processes begin, once pinpointed, could become prime targets for therapies to intervene and stop or prevent complications.

Key Targets for Heart Disease

Anne Marie Schmidt, M.D., co-chair of JDRFI's Medical Science Review Committee and a co-organizer of the symposium, led a discussion about cellular stress and inflammation. Dr. Schmidt and her colleagues at Columbia University Medical Center in New York have focused on what they call the "AGE/RAGE" system and its impact on cellular stress and inflammation as a key link to heart disease in people with diabetes. Among her laboratory's many areas of investigation, she is studying the role of an inflammatory molecule in deregulating this system. She showed that blocking this molecule as well as the AGE/RAGE system itself "may provide a novel means to exert cardioprotection in the vulnerable diabetic heart." JDRFI's Dr. Araneo explained Dr. Schmidt's overall goals are to understand the roles RAGE (Receptor for Advanced Glycation Endproducts) plays in harming or protecting people from cellular stress and inflammation, and eventually complications. "Her approach is a dynamic one," she added, "one that will investigate the natural function of RAGE when diabetes is not present, as well as its altered function when diabetes is involved." JDRFI is assessing her findings to develop new therapeutics based on RAGE activity. RAGE was first identified in 1990 by Dr. Schmidt.

Tapping in to the Body's Natural Repair Mechanisms

Maria Grant, M.D., and colleagues from the University of Florida described a novel strategy to repair diabetic eye disease. Most current therapies for treating retinopathy are

aimed at inhibiting blood vessel regrowth, rather than fixing the underlying lack of blood supply leading to retinopathy. Dr. Grant is developing “a more judicious approach to pharmacologically repair or create more normal vessels.” She has focused her efforts on a molecule called insulin-like growth factor 1 (IGF-1), which plays a negative role in the regulation of blood vessel growth. In experiments in mice with injuries to their retinas that approximate the problems with retinopathy, she blocked IGF-1's actions using a specific binding protein. The results were promising: The binding protein recruited vascular precursor cells from the bone marrow to the injured retina. Once there, they promoted blood vessel growth in a controlled, beneficial manner—not the unregulated growth that leads to retinopathy. The protein also reversed several adverse changes caused by poor vascularization and low oxygen levels. In other experiments, the protein slowed the death of cells that line the blood vessels. Further assessments of this promising therapeutic are in the works.

JDRFI Uses Wireless Technology to Bolster Advocacy

JDRFI has launched a mobile marketing campaign using wireless technology in an effort to enhance communication with its advocates across the country.

Through the DiabeTXT program, JDRFI is now sending information to its advocacy volunteers via text messages, alerting them about important legislation news, diabetes research progress, upcoming events, and opportunities for them to get involved with JDRFI.

As the program expands, JDRFI will integrate the technology

with its signature “Walk to Cure Diabetes” program to attract new advocates and eventually enable supporters to raise money for type 1 diabetes research through its mobile giving platform.

“We are very excited by the opportunities SMS technology can offer us to help increase advocacy and funds for type 1 diabetes research,” said Michael Kondratick, JDRFI's Director of Grassroots Advocacy. “One of the key challenges for any grassroots advocacy effort is getting information out to your constituency that will mobilize them effectively and efficiently. With mobile messaging, our supporters will receive instant communication that can help recruit and coordinate volunteers, as well as offer immediate updates on time sensitive items and help drive communications to targeted legislators quickly.”

DiabeTXT was used this summer during JDRFI's successful Children's Congress in Washington, D.C. In addition to coordinating staff and volunteers throughout the three-day event, the new technology enabled more than 150 people to use their mobile phones to sign up to receive applications for the next Children's Congress in June 2011. To get mobile messages from JDRFI, people can text keywords supporting various JDRFI advocacy campaigns to 56333, including:

- 'ACTION' to receive general JDRFI advocacy alerts;
- 'PROMISE' to register to attend a meeting as part of the Promise to Remember Me Campaign;
- 'CC11' to sign-up to receive applications for the 2011 Children's Congress; and
- 'KAN' to join the Kids Advocacy Network. ■



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