



This Newsletter has been brought to you by the generous support of Bayer.



simplewins™



Bayer HealthCare
Diabetes Care

In this issue:

- Stem cell policy repealed
- A promising new therapy
- Metabolic abnormalities precede autoimmunity in type 1 children
- Scientists find a way to encourage the replication of adult human beta cells

White House Overturns Restrictions on Federal Funding for Embryonic Stem Cell Research

United States President Barack Obama signed an executive order on March 9, 2009 repealing an eight-year-old policy limiting federal tax dollars for embryonic stem cell research.

Juvenile Diabetes Research Foundation, a leader in setting the agenda for diabetes research worldwide and the largest charitable funder and advocate of type 1 diabetes research, praised the Administration for the Executive Order, which officially reversed the policy limiting federal research funding for embryonic stem cell research to cell lines established prior to August 9, 2001.

“We’re very grateful to President Obama for setting in place a policy to fully explore this promising field of science,” said JDRF president and CEO, Dr. Alan Lewis. “President Obama’s Executive Order is a strong signal to patients, scientists, and the nation that we have his full support to pursue science that may accelerate progress to new treatments and possible cures for diabetes.”

Type 1 diabetes affects as many as three million people in the United States (over 240,000 in Canada), causing the immune system to attack insulin-producing cells in the pancreas so the body no longer uses sugar to create energy. There is no cure. Research into human embryonic stem cells could speed the development of a cure for diabetes by helping researchers better understand how the disease occurs and eventually derive insulin-producing cells that are safe to use for

transplantation. These discoveries are years away, but federal guidance and funding from the National Institutes of Health (NIH) will help speed scientific progress.

Embryonic stem cells are cells with two capacities believed to be unique: they are capable of seemingly limitless reproduction, and they can develop into any type of cell, tissue, or organ as they mature—an ability scientists describe as “pluripotency.” At the same time, embryonic stem cells cannot themselves develop into a full organism. Their ability to replicate themselves indefinitely while remaining in an “undifferentiated” state means embryonic stem cells offer a potentially unlimited source of cells for organ transplantation, and prove a model system for drug discovery and the study of development.

“This is an exciting day for children and adults living with type 1 diabetes, their families, and everyone with a connection to diabetes who have worked for years to remove restrictions to this research,” said Dr. Lewis. “Now researchers, physicians, and ethicists at NIH can make decisions on ethical research based purely on sound science.”

The Executive Order directs the NIH to develop revised guidelines on federal funding for embryonic stem cell research within 120 days. At the White House ceremony announcing the order, President Obama also signed a presidential memorandum establishing greater independence for federal science policies and programs.

Stem cells—both adult and embryonic—have great potential because they might be coaxed into becoming insulin-producing cells that can provide insight into the biological pathways through which type 1 diabetes develops. That could lead to cures and therapies across a range of scientific disciplines.

In addition, stem cells could, conceivably, be used to replace islets destroyed in people with type 1 diabetes. While islet replacement shows great promise as a potential treatment for people with particularly brittle diabetes, the cells used for these procedures currently come from organ donations of deceased individuals. But there are, at present, only several thousand donated pancreases each year in the United States. An alternate source of islet cells, which stem cells could potentially provide, would be a major step in providing cure therapeutics to all people with type 1 diabetes.”

“Insulin Fragment” Therapy Safe And Promising In Its First Evaluation In Humans

JDRF-funded researchers from the United Kingdom have shown that “proinsulin peptide,” a fragment of insulin being evaluated as a potential immune system therapy for type 1 diabetes, is safe to use in people who have had the disease for some time. JDRF supported the research through the Diabetes Vaccine Development Center (DVDC), a joint venture between JDRF and Australia’s National Health and Medical Research Council.

The research, published in the journal *Clinical and Experimental Immunology*, showed that people with type 1 diabetes who were given three doses of the peptide did not have an acute allergic reaction or experience any adverse immune responses, such as the activation of potentially damaging T cells. Allergic reactions or the activation of T cells are major risks associated with this type of therapy. Their absence thus signifies “an important milestone in the clinical evaluation of peptide immunotherapy for type 1 diabetes,” the scientists noted.

Peptide immunotherapy is a type of treatment that uses small proteins to “reset” the immune system to a healthy state, much like the common allergy shot. In the case of proinsulin peptide therapy, the goal is to train the immune system to tolerate the insulin-producing beta cells that are the target of the immune response that causes type 1 diabetes. Peptide therapy is like a method of presenting new instructions to the immune system: by delivering a T cell trigger in a different way, the intent is to “induce tolerance” and stop the immune system from firing on itself.

Proinsulin is a natural precursor protein to insulin made by the beta cells of the pancreas; proinsulin peptide, a segment of proinsulin, is a target of immune T cells, making it a good candidate as an immune system therapy for type 1 patients.

Key Point:

The first human trial of proinsulin peptide indicates it is a safe and promising therapy for resetting the immune response in people with type 1 diabetes. The results set the stage for a Phase Ib clinical trial in the newly diagnosed.

Trial design and results

In this clinical trial, scientist Mark Peakman and colleagues from King’s College London and the University of Bristol investigated the safety of proinsulin peptide in two groups of patients with established diabetes. People were randomly assigned to either a low-dose or high-dose treatment, given by injection, but both the scientists and the trial participants knew the drug assignment they were given—a trial design known as “open label.” Subjects ranged in age from 21 to 53 years old.

In addition to the favourable immune findings, no serious adverse events occurred in any of the treated patients, nor were notable changes observed in routine blood tests.

The researchers concluded that proinsulin peptide did not have a negative effect on the participants’ diabetes for two reasons. First, they found no antibodies directed against proinsulin, which would have signaled an unwanted immune response to the peptide. Second, they found no T cells targeting proinsulin, which would have indicated the treatment caused an inflammatory state.

An additional positive finding was that the peptide appeared to have temporarily triggered the activation of T cells that can regulate the immune response. However, this finding was based on *in vitro*, or laboratory, tests using the patients’ white blood cells, and was only observed in a small number of participants in the trial. So determining if proinsulin peptide injections actually created a regulated immunological environment—one that minimizes beta cell destruction and allows those cells to go about their intended purpose and produce insulin—will need to be resolved in more advanced studies, the researchers said.

Next steps and strategic basis

Because proinsulin peptide appears to be safe, a next-step clinical trial in people who have been newly diagnosed is likely to follow, perhaps within six months or so. JDRF will support these studies through the DVDC. Such a trial—which JDRF sees as a high priority—will establish whether this therapy is safe in newly diagnosed patients. Though the full impact of the treatment on type 1 diabetes will not be the primary focus of the trial, it will look at whether beta cell mass is impacted.

Among the potential benefits of peptide immunotherapy is the relatively modest cost of synthesizing these small molecules. And because they are small and mobile, they deliver a better bang-for-the-buck in that they are “seen” by the immune system at a rate about 50 times higher than is achieved with larger molecules.

Metabolic Triggers May Contribute to the Onset of Diabetes

JDRF-funded researchers from Finland have discovered children who develop type 1 diabetes have distinct metabolic abnormalities that can sometimes be seen years before the classic signs and symptoms of the disease.

The findings, published in the *Journal of Experimental Medicine*, offer intriguing new insights into what causes type 1 diabetes, and may lead to novel prevention strategies. In the near-term, scientists may be able to use these findings to predict who will eventually develop the disease.

According to researcher Olli Simell from the University of Turku and colleagues, the research suggests autoimmunity may be a relatively late response, or reaction, to these early metabolic changes. This implies, they said, that metabolic or immune system interventions might be most effective if given

during the pre-autoimmune period—before the appearance of autoantibodies to insulin, the current precursor to a diagnosis of diabetes.

Marlon Pragnell, who manages JDRF's (Metabolic) Control Program, said the study represents an important step towards understanding and preventing metabolic changes that precede the onset of type 1 diabetes. "We do see a progression of metabolic dysregulation leading up to diagnosis, such as impaired glucose control in response to glucose tolerance testing," Dr. Pragnell explained. "So this study adds another piece to the puzzle by implicating pre-autoimmune changes. Nobody knows what causes type 1 diabetes, or how the disease unfolds. This report of metabolic changes prior to the appearance of circulating antibodies opens the intriguing possibility that metabolic triggers contribute to the onset of disease."

To move the research forward—Dr. Simell's study is the first to report this type of metabolic dysfunction—it will be essential to validate the findings in other large and well-characterized population groups.

A unique scientific approach

Dr. Simell and colleagues used a "metabolomics" strategy to study the progression of type 1 diabetes—an approach that looks to tie the chemical fingerprint within cells, tissues, and body fluids to the expression of the disease. Metabolomics encompasses the complex biochemistry of energy metabolism—or how cells make and use energy. It involves numerous molecular players and energy-related compounds called metabolites.

"Changes in the concentrations of metabolites during early development," the researchers said, "may thus reflect both genetic and environmental factors influencing later susceptibility to chronic diseases."

To investigate the metabolomics of type 1 diabetes, they compared blood samples from 56 children who eventually developed the disease with 73 children who remained healthy and free of autoantibodies. They specifically looked for differences in the production of metabolic building blocks such as lipids (a type of fat) and amino acids (which join to form proteins). Most of the samples used in this research were obtained from the ongoing Type 1 Diabetes Prediction and Prevention Study (DIPP), a large study launched in Finland in 1994. Participants in the DIPP study all carry a genetic risk for type 1 diabetes and are monitored closely to establish the time when the immune reaction causing diabetes begins, and when the disease is actually diagnosed.

Altered lipid and amino acid profiles

Autoantibodies to insulin typically appear before someone has any of the symptoms of diabetes, and they have been a well-established marker for people likely to develop the disease.

But the children in this study who developed diabetes had unique metabolic disturbances that appeared well before the

autoantibodies did. In one nine-year-old girl, for example, metabolic disturbances were at their highest levels one to two years before any autoantibodies to insulin appeared.

Children in the study who developed diabetes consistently exhibited:

- Reduced levels of succinic acid, an energy molecule, and the lipid phosphatidylcholine, a major component of biological membranes; these differences were even evident at birth.
- As they grew, the children showed reduced levels of triglycerides and ether phospholipids, a lipid with antioxidant properties.
- Shortly before the children had detectable autoantibodies, they had two characteristic anomalies: reduced levels of ketoleucine and elevated glutamic acid (both are amino acids). In the nine-year-old girl, glutamic acid levels were 13 times higher than normal by the time she was about six months old.
- None of the differences were linked to genetic risk. Moreover, after the appearance of autoantibodies, the children's metabolic profiles partly returned to normal.

The cause of these metabolic changes is unclear. Nor has their relationship to autoimmunity and beta cell destruction been determined. The researchers do, however, offer several intriguing possibilities.

It is conceivable, they said, the mother's diet and intestinal microbes affect the levels of some of these molecules in newborns, causing changes in the infant's energy metabolism and immune system. Lower levels of antioxidants, they suggest, might make the beta cells susceptible to oxidative stress and free radical damage.

Implications for type 1 research

In a commentary accompanying the published report, diabetes experts Pierre Bougneres and Alain-Jacques Valleron, who were not involved in the study, described the scientists' metabolomics approach as a pioneering example of how we might uncover the natural history of type 1 diabetes. They argue that type 1 diabetes is on the rise in very young children—the incidence has doubled in the last 20 years—but thus far specific genetic or environmental factors cannot explain this phenomenon. The appearance of autoantibodies in the first years of life in these children points to some type of early event, they said, and suggests that "emerging or rapidly evolving environmental changes may be to blame."

Clues to solving this puzzle, they explain, may lie somewhere in the child's developmental environment, at some point between the time of conception and the time of diagnosis. New "land" to explore might include epigenetics (changes in gene expression caused by environmental influences), microbiomics (the role of the microorganisms that inhabit us), metabolic events (as this study identifies), and dietary

changes. New “eyes” or paths of type 1 diabetes research could include epigenetic epidemiology (the numbers behind the epigenetics), blood markers of infections, and broad concepts such as the characterization of social ties.

“By combining several of these techniques and appropriate statistical analyses,” they explained, “it may be possible to start characterizing the type 1 diabetes *environmentome*,” a clinical map outlining how the environment in which we live may be driving the genetic risk for type 1 diabetes into a reality.

Key Point:

In some children with type 1 diabetes, metabolic disturbances can be detected well before the appearance of autoantibodies, suggesting the immune response that leads to diabetes might not be the initial cause of the disease. This unexpected finding may point to new directions in diagnosis, treatment, and prevention.

Proteins That Regulate Adult Beta Cell Regeneration Are Identified

JDRF-funded researchers at the University of Pittsburgh School of Medicine have discovered a protein that can help adult insulin-producing cells to replicate or regenerate. The research was published in the journal *Diabetes*.

“Most scientists thought that these important pancreatic cells could not be induced to regenerate, or could only replicate very slowly,” explained Andrew F. Stewart, M.D., professor of medicine and chief of the Division of Endocrinology and Metabolism at the University of Pittsburgh School of Medicine. “This work provides proof-of-principle that the production of human beta cells can be stimulated, and that those newly generated cells function effectively both in the lab and in a living animal.”

Evaluating the cell cycle

All cells, before they divide, go through a series of steps known as the cell cycle, or cell-division cycle. To better understand how human beta cells divide, the Pittsburgh researchers evaluated 34 different proteins for their ability to control a key cell-division checkpoint in human beta cells.

The protein cyclin dependent kinase-6 (cdk6) was identified as an essential cell cycle regulator in human beta cells. (In contrast, it was generally absent in mouse islets that were studied for comparison purposes, indicating a striking difference between people and mice that might have therapeutic relevance.)

The researchers showed that cdk6, alone or in combination with another protein, can trigger robust beta cell replication in human islets without a loss of function—the cells could sense glucose and produce insulin in response. These “transduced islets” were then transplanted into diabetic mice for six weeks. Blood sugar levels and glucose tolerance tests showed the transplanted islet cells were able to correct diabetes better than islets that were not treated with the protein. Researchers later removed the transplanted cells after the six-week study period and confirmed the human beta cells had replicated.

Implications for people with diabetes

“The question as to whether and how human beta cells can be induced to proliferate is a fundamentally important one for JDRF’s Regeneration Program,” said Patricia Kilian, Ph.D., therapeutic program director for regeneration research at JDRFI. “Dr. Stewart and his colleagues address this question by demonstrating that modulation of specific cell cycle control proteins stimulates human beta cell replication. By identifying the control points for human beta cell cycle progression, Dr. Stewart and his colleagues provide new insights and open up potential new avenues in the search for therapies to promote beta cell regeneration in individuals with type 1 diabetes.”

The study is important for other reasons as well. Now that a way to replicate adult human beta cells has been identified, researchers will be better able to understand and break down the components of beta cell replication. The research also combines two of JDRF’s therapeutic goals, regeneration and replacement, one of many possible synergies that researchers believe is key to a cure for type 1 diabetes and its complications. ■

Key Point:

Diabetes researchers have identified a protein that regulates the regeneration of adult human beta cells. This breakthrough can be used to discover regenerative and transplantation therapeutics to cure diabetes.



TOGETHER WE CAN
triumph over diabetes
simplewins™

