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JDRF INDUSTRY PARTNERS IN DRUG DEVELOPMENT ALLIANCES WITH MAJOR PHARMACEUTICAL COMPANIES

Two of JDRF's Industry Discovery and Development partners have entered into global alliances with pharmaceutical companies to develop and commercialize anti-CD3 antibodies to treat early-stage type 1 diabetes. The agreements demonstrate the success of JDRF's strategy to fill gaps in the drug pipeline by helping small companies move discovery research through early clinical testing until bigger companies step in to fund the large trials needed for FDA approval of drugs and treatments for diabetes.

Late last week, one IDDP partner, MacroGenics, entered into an alliance with Eli Lilly to develop teplizumab, an anti-CD3 antibody that has been effective in clinical trials in slowing the progress of type 1 diabetes in newly diagnosed patients. This week, a second JDRF partner, Tolerx, formed an alliance with GlaxoSmithKline to develop oteplizumab, another anti-CD3 antibody for type 1 diabetes.

By funding early-stage testing and validation of anti-CD3 antibodies, including teplizumab at MacroGenics and oteplizumab at Tolerx, JDRF essentially contributed to "de-risking" this therapeutic strategy, making it possible for the biotech companies to advance their antibodies through clinical development, attract additional investors, and eventually secure global licensing and marketing alliances with larger pharmaceutical companies. Biotech companies face many hurdles during the long and expensive path to drug approval, so JDRF's involvement at early stages is often critical to address gaps (financial and otherwise) and keep programs like these alive and moving forward to benefit patients.

The major focus for JDRF in IDDP partnerships is to accelerate the pace of applied research leading to a cure for type 1 diabetes and its complications; if these collaborative partnerships successfully commercialize cures and treatments, JDRF also shares

in the financial results of that process, enabling the foundation to recoup its support of those projects and fund other research programs leading to a cure.

To date JDRF's Industry Discovery and Development Partnership program has funded type 1 diabetes projects at 22 companies, including MacroGenics and Tolerx

FATTY ACID IN DIET MAY LOWER TYPE 1 DIABETES RISK

Children at risk for type 1 diabetes may gain some protection from developing the disease by increasing omega-3 fatty acids in their diet, according to a report in the *Journal of the American Medical Association*. Although the finding is preliminary, it could point researchers toward ways to reduce the risk of developing diabetes.

In the study, people at risk for developing diabetes who consumed more omega-3 fatty acids were less likely to have autoantibodies in the blood that signal an immune system attack on the pancreatic beta cells. The researchers think omega-3 helps the body fight inflammation, which may play a major role in developing type 1 diabetes.

Omega-3 fatty acids are abundant in certain fish, dark green vegetables, canola oil, sunflower oil and flaxseed oil; they are also now being added to eggs, breads, juices, and other foods.

The research – the Diabetes Autoimmunity Study in the Young (DAISY), an observational study conducted at the University of Colorado Health Sciences Center in Denver – follows children at an increased risk for type 1 diabetes to see if there are environmental factors that may trigger the disease. (The children either had a parent or sibling with diabetes, or showed increased risk through genetic testing.) The lead author of the *JAMA* paper was Jill Norris, Ph.D.

In the study, children were followed for an average of six years. Omega-3 intake was determined through food-frequency questionnaires: for example, parents were asked how often their children ate food high in omega-3 fatty acids, like canned tuna and oily fish like salmon or mackerel, or what kind of oil they used for home cooking.

In a similar study, the National Institutes of Health is testing whether infants at genetic risk for type 1 diabetes show fewer signs of inflammation when consuming a supplement of the omega-3 fatty acids, DHA. A larger version of the trial will see whether DHA protects infants and children from developing diabetes autoantibodies. If so, the *JAMA* authors write, "dietary supplementation with omega-3 fatty acids could become a mainstay for early intervention to safely prevent the development of type 1 diabetes."

CURRENT TRANSPLANT DRUGS MAY HINDER BETA CELL REGENERATION

Drugs commonly used to prevent rejection after islet transplant surgery may be inhibiting the natural regeneration of beta cells, JDRF researchers in Israel and Boston have found. The discovery suggests using different drugs might increase the success of islet replacement by increasing the survival and growth of transplanted insulin-producing cells, and perhaps allow patients to regenerate their own beta cells.

The finding, in mouse experiments, highlights the importance of understanding the effect that therapies to modulate the immune response have on insulin-producing cells, both after islet transplants and while blocking the autoimmune attack that causes type 1 diabetes.

Researchers using mice can now study these effects very quickly, which should guide the development of therapies that block the immune response that destroys transplanted islets, while allowing natural beta cell re-growth. In addition, activating the pathways blocked by the two drugs commonly used in transplants (sirolimus and tacrolimus), might actually promote regeneration.

The research was led by Tomer Nir, Ph.D., in the laboratory of Yuval Dor, Ph.D., at the Hebrew University-Hadassah Medical School in Jerusalem, with the collaboration of Douglas Melton, Ph.D., at Harvard University. The finding is published in the *Journal of Clinical Investigation*.

The key to the new finding was the use of a genetic trick that enabled the researchers to study the dynamics of regeneration. The scientists switched on a mouse gene to trigger most of the insulin-producing cells to self-destruct (leading to diabetes). But the researchers could halt the trigger at any point. When they did, they could see how the beta cells responded to diabetic conditions in the absence of autoimmunity—and without the immune-modulating drugs used in transplants that confound the results.

Surprisingly, the mice quickly increased beta cell mass and regained control of blood sugar levels – suggesting that mice manipulated in this way could serve as effective models for testing whether a drug hampers or helps regeneration. Careful examination of the cells showed that most of the new mass was the result of existing beta cells making copies of themselves, rather than the body creating new beta cells from stem cells or precursor cells.

However, when similar mice were treated with sirolimus and tacrolimus, regeneration was inhibited, and the animals did not regain blood glucose control. This suggests the two drugs are undermining transplant success by blocking regeneration.

In addition, the study reveals that in mice, pancreatic beta cells can spontaneously regenerate under the right conditions – enough to allow full recovery from diabetes. Many scientists have thought that long periods of high blood sugar affected insulin-producing

cells and made regeneration impossible. But the new research shows this isn't true, and adds to the evidence that people with long-standing diabetes, not just the newly diagnosed, might be able to benefit from regeneration.

So far, no research team has been able to develop a treatment safe for humans that completely removes the autoimmune attack. But now researchers have a way to test, in a live organism, whether a potential immune therapy can accommodate regeneration as well.

DISCOVERY OF FOURTH DIABETES ANTIBODY SHOULD AID PREDICTION

JDRF-funded researchers in Denver have identified a fourth antibody in human blood that suggests the earliest stage of type 1 diabetes. The discovery may help more accurately predict who is predisposed to diabetes, and could point toward clues for how to slow or block how the disease progresses.

Antibodies are proteins produced by the body's immune system in response to a perceived foreign substance (or antigen). Three antibodies, called autoantibodies, are currently known for type 1 diabetes. The presence of these autoantibodies indicates that the body has begun mounting the misguided attack that causes type 1 diabetes.

Researchers monitor the number of different autoantibodies, and their levels, to help predict who might develop type 1 diabetes. These high-risk people are often selected for participation in clinical trials looking to prevent the disease.

The presence of three autoantibodies predicts type 1 diabetes with 90 percent accuracy. The new autoantibody, ZnT8, is the first to be discovered in 10 years, and increases the accuracy of predicting diabetes to 96 percent. The finding is published in the *Proceedings of the National Academy of Sciences*.

ZnT8 was linked to type 1 diabetes through "microarray analysis," which records the expression of all the genes in the body on a tissue-by-tissue basis. The researchers noticed that the ZnT8 gene is expressed only in insulin-secreting cells and is associated with how insulin is released; that made it a good candidate to follow up on.

The researchers confirmed their hypothesis by studying blood samples from children with type 1 who were participating in the Diabetes Autoimmunity Study in the Young (DAISY) at the Barbara Davis Center for Childhood Diabetes in Denver. Some 70 percent of people with type 1 diabetes tested positive for the antibody, compared with less than 1 percent of control groups.

"ZnT8 shows great value as a diagnostic tool, and we believe testing for it will very quickly become routine in all of the ongoing clinical research studies," said John Hutton, Ph.D., the paper's senior author. "For example, this fourth autoantigen will find immediate use in identifying individuals with a family history of diabetes or a genetic predisposition to the disease for recruitment into clinical trials aimed at preventing diabetes."