UPDATES FROM DR. FAUSTMAN'S LAB AT THE MASSACHUSETTS GENERAL HOSPITAL

Summer 2006
Issue 2

For Friends and Supporters: The Diabetes Research and Clinical Trial Program

Dr. Denise Faustman, Massachusetts General Hospital, Building 149, 13th Street, Room 3602, Charlestown, MA 02129

Funding Announcement

We are pleased to announce that the Iacocca Foundation has generously made its initial grant to the Massachusetts General Hospital for the preparation of a human clinical trial to stop the autoimmune attack in type 1 diabetes. The project will be divided into three phases: separating T cells from human blood (blood assay), testing in mice the effects of the protocols expected to be used in the human trial, and the human clinical trial itself. The current phase of the human studies involves the sampling of blood from type 1 diabetic volunteers. The assay will be used for selecting patients and assessing the efficacy of treating type 1 diabetes using BCG.

Thank you to all who have contributed to help make this work possible.

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Thank You!

We are so grateful for the ongoing support from patients and families. Several fundraising events are planned for this fall, including:

Bike the Miles for Human Trials on September 10, in Massachusetts.
Info: Jackie Fusco, 203-249-8238, jefusco@optonline.net
Web: www.bikethemilesforhumantrials.com

Dallas & Reid's Ride, a motorcycle ride, silent auction, and field event on September 16, in Indiana.
Info: 317-339-7566, info@dallasandreidsride.org
Web: www.dallasandreidsride.org

Answering Your Questions

Why use bacillus Calmette-Guérin (BCG)?

As many of you know, our human clinical trial program will begin with an evaluation of one limb of the two-limb treatment we successfully used in diabetic mice. We will start with bacillus Calmette-Guérin (BCG), a generic drug with an impeccable human safety profile that is currently approved for two indications—tuberculosis and cancer therapy. BCG causes the body to make a natural substance called TNF. TNF helps to regulate the immune system and can kill a portion of the "bad" T cells that cause diabetes.

BCG was used many years ago in early-stage diabetic (NOD) mice and prevented diabetes. Unfortunately, many compounds work in early-stage NOD mice, but do not work in late-stage NOD mice or in humans with advanced disease. BCG was also tried in the past in humans with new onset diabetes, prior to the knowledge of how BCG actually works in the body. In the human studies, one diabetic patient was cured with a single dose of BCG, but two subsequent studies using a single dose of BCG showed no benefit.

We think these early trials of BCG in humans, although encouraging, could not be advanced until BCG's mechanism of action (what it does) was appreciated and a way to monitor the drug's effect after administration was understood. Think about this: If we did not know that insulin regulated blood sugars, and if we did not know how to measure blood sugar, how could we measure whether insulin administration actually worked to help diabetics? In many ways, early BCG trials are analogous to injecting insulin without knowing what it really does or how to measure its effects. One of our major laboratory efforts is to have a method for rapidly and precisely counting the number of 'bad' T cells in human blood and to use this test to evaluate whether BCG can eliminate these cells, and at what dose. -DF

More Good News from Other Labs

Recently, no less than five different groups have confirmed our approach to reversing type 1 diabetes, with one group also showing its applicability to a second autoimmune disease, Sjogren's syndrome. I am delighted to see the appearance of these confirmatory studies, now five years after our original paper. Taken together, these data provide additional support from the scientific community for the validity of the human clinical trials we planned with your help. Please read below for more details.

Positive Results in Sjogren's Syndrome and Diabetes at the ADA Meeting

Our protocol for eliminating type 1 diabetes in mice has been confirmed and expanded in recent months. A group at the National Institutes of Health (NIH) led by Tran et al. evaluated the protocol to see if it would be effective in diabetic mice that also had Sjogren's syndrome (Sjogren's syndrome is an autoimmune disease affecting the moisture-producing glands, such as the tear and saliva glands). Excitingly, the researchers found that our protocol could be used to reverse *two* forms of established autoimmune disease in mice: type 1 diabetes and Sjogren's syndrome. Unlike the papers published in the March 24th issue of *Science*, this group found that the spleen did contribute in part to regeneration of the pancreas and the salivary glands. The results are submitted for publication and were presented at the annual American Diabetes Association's (ADA) meeting in Washington, DC in June 2006. Data from a Japanese research group, led by Okubo et al. was also presented at the ADA meeting and again confirmed our approach for reversing diabetes in the type 1 diabetic mouse.

Three JDRF-Funded Labs Show Positive Results in Diabetes

On March 24th, many of you saw the articles in the *Wall Street Journal* and *New York Times* about our research. On that day, the scientific journal *Science* published three papers from three different Juvenile Diabetes Research Foundation (JDRF)-sponsored laboratories (Nishio et al., Suri et al., and Chong et al.) that examined the protocol our laboratory published in 2001 and 2003 for end stage diabetes reversal in the NOD mouse. All three of these studies independently verified, to varying degrees, that our protocol can "cure" end stage diabetes in mice, that the cure is due to islet self-rescue or regeneration of the pancreas, and that it does not require a stem cell or islet cell transplant in the mouse. By cure, we mean that: 1) the autoimmune attack was sufficiently halted to stop islet destruction and/or promote islet rescue and regeneration, and 2) the autoimmune diabetes does not re-occur with long-term follow-up.

In addition to the results described above, the three papers also reported that the animals had their diabetes cured without a role of the splenic stem cell that we identified in our research. Our original paper in 2001 and our subsequent paper in 2003 showed that the diabetes cure can be accelerated by the administration of adult spleen cells in mice. We also showed that this adult stem cell was not required, but hastened the speed towards normal blood sugars. We are still confident that the spleen plays a role, and the work by Tran et al. at the NIH also confirms our findings on the spleen. However, this question is not critical to the progress of the Phase I clinical trial. The big picture is that regeneration was seen and long-term normal blood sugars were achieved. For a copy of the *New York Times* and *Wall Street Journal* articles that covered this story, please contact:

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Regeneration Panel at the ADA Meeting in June

There was more exciting news at the American Diabetes Association Meeting this year in Washington, DC. It is, of course, wonderful to "cure" an end stage diabetic mouse using our therapy to remove disease and allow the pancreas

*Please see **Good News** continued on page 3*

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Denise Faustman, MD, PhD

Good News *(continued from page 2)*

to regenerate. The next big step is to do the same for humans with this disease. Although this is the goal of the MGH program, many groups at this scientific meeting are reporting that the pancreas of long-term diabetic patients can show islet proliferation under certain circumstances. For example, if the Faustman laboratory hypothesis is correct in the mouse and applicable to the human, then a human type 1 diabetic with a pancreas or islet transplant who is taking high dose immunosuppressive drugs could possibly start to see the regeneration of islets in his or her own pancreas. Indeed, the blood sampling of long-term diabetics is showing that, in some cases after pancreas or islet transplantation, the insulin can originate from the patient's own pancreas. Although high dose immunosuppressive drugs are toxic treatment and probably also diminish islet proliferation, this human data suggests that even after longstanding and established disease, the pancreas is still trying to regenerate. If the human pancreas has the natural ability to regenerate in diabetes, but the disease burden prevents effective islet regeneration and survival, the idea of disease removal remains stronger than ever as a major clinical goal.

Expanding the Research

Our clinical trial led by Dr. David Nathan will soon test the generic drug bacillus Calmette-Guérin (BCG) to see if it can specifically eliminate the disease-causing T cells in type 1 diabetic patients. Although we hope that the BCG will have a beneficial effect in type 1 diabetes, we also believe that permanently eliminating the disease will require "re-training" the immune system so that it does not attack the body's own cells. We recently received preliminary funding from Friends United for Juvenile Diabetes Research that will enable us to begin looking for other inexpensive, non-toxic compounds in the lab that might be of benefit in our diabetes work. We hope to begin screening for generic drugs that can be used as new treatments not only for type 1 diabetes, but also for other autoimmune diseases, including lupus, rheumatoid arthritis, scleroderma, multiple sclerosis and Sjogren's disease. We are actively raising funds for this research. We are sending out grant requests regularly to start on our project to screen existing generic drug candidates for uses in various autoimmune diseases — type 1 diabetes, lupus, rheumatoid arthritis, scleroderma, multiple sclerosis and Sjogren's disease.

Events

I was invited to give several talks this spring focusing on the regeneration of islets in type 1 diabetes. At BIO, the world's largest biotechnology meeting, I organized a symposium on "Regenerative Therapies, from Bench to Bedside." I also had the pleasure of organizing an American Association for the Advancement of Science symposium on new autoimmune therapies. A major theme of this symposium was the concept that new autoimmune diseases induced by currently approved anti-TNF drugs are the same human autoimmune diseases in which patients would instead benefit from therapies that induce, rather than suppress, TNF. I also presented our data in Rome at the International Symposium on "Prevention of Type 1 Diabetes: The New Frontier." I continue to be encouraged that other scientists and labs are taking interest in our research.

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Denise Faustman, MD, PhD

Please Support Our Research to Find a Cure

Please support the ongoing research of our lab with your tax-deductible donation. Donations may be made by check (payable to "Massachusetts General Hospital") and can be sent to:

Jocelyn Hoey
MGH Development Office
165 Cambridge Street, Suite 600
Boston, MA 02114
Please indicate: "Type 1 diabetes research" or "Autoimmune research" on memo line

To make a secure online donation, please visit: www.mgh.harvard.edu/diabetes/diabetes_support.htm. Click on "Type 1 Research."

For clinical trial enrollment or to enroll in the current blood testing for the trial, please email or contact:

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Web updates are available at: www.mgh.harvard.edu/diabetes