Updates
Winter 2012
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL
from the Faustman Laboratory at Massachusetts General Hospital

Pursuing New Treatments for Advanced Type 1 Diabetes

A Note from Dr. Faustman

It is hard to believe another year is already coming to a close at the Faustman Lab! I hope 2012 has been as good to you and your family as it has been to us. With your support, we have made remarkable progress toward our goal of reversing type 1 diabetes.

We were delighted to publish some very important findings this year. First was the discovery that people with type 1 diabetes may continue making their own insulin for decades after disease onset, challenging long-held assumptions that pancreatic function drops off abruptly after diagnosis.

Next was the publication of the findings from our Phase I trial. Our Phase I data demonstrated early signs of the potential of bacillus Calmette-Guérin (BCG), a tuberculosis vaccine with a demonstrated safety record, to reverse type 1 diabetes. Our testing showed that BCG stimulated production of a protein that killed the insulin-attacking cells, temporarily restoring some pancreatic function in individuals with longstanding type 1 diabetes. This discovery is a potential game changer for the future of type 1 diabetes treatment.

Together, these findings validate our belief that it is indeed worthwhile to pursue new treatments for patients who have had type 1 diabetes for many years.

In 2013, we will continue to work to bring forward a safe, inexpensive, generic medication—the BCG vaccine—through clinical testing for type 1 diabetes. Our hope is that we can show that this well-known vaccine has the potential to be an affordable and long-lasting treatment for type 1 diabetes. Based on our Phase I results, we are currently designing and planning the Phase II human clinical trial. We anticipate that we will begin enrolling patients in the study later in 2013.

With your help, we also continue our efforts to raise the full $25.2 million needed to fund the next stage of clinical testing, and we are more than half way there with $13.5 million raised to date. I can't thank enough each person who has supported our efforts for all of the dedication and generosity that has helped us reach this stage. You are integral to the work that we do every day and to the groundbreaking results that we see. With continued support, we will see this trial through to shape the next era of diabetes research and treatment.

Happy Holidays!

Sincerely,

Denise L. Faustman, MD, PhD

Phase I Study Results Published

Generic drug shows benefits in advanced type 1 diabetes

The results of our Phase I human clinical trial were published in *PLoS ONE*, a peer-reviewed, scientific journal, this August under the title "Proof-of-Concept, Randomized, Controlled Clinical Trial of Bacillus Calmette-Guérin for Treatment of Long-Term Type 1 Diabetes." In the trial, we saw early evidence that the bacillus Calmette-Guérin (BCG) vaccine can not only kill the "bad" T cells that attack the insulin-secreting cells of the pancreas, but can also temporarily restore insulin production in people with longstanding type 1 diabetes. A generic drug with over 90 years of clinical use, BCG is currently approved by the Food and Drug Administration for vaccination against tuberculosis and for the treatment of bladder cancer.

Our lab first reported in 2001 that temporarily elevating levels of tumor necrosis factor (TNF, an immune regulator) helped to reverse type 1 diabetes in mice by eliminating the "bad" T cells that destroy the pancreatic islets, permitting these islets to regenerate. In our research program, we are using BCG to safely elevate TNF levels in humans.

Our recent Phase I trial enrolled six type 1 diabetes patients who had been living with the disease for an average of 15 years. Patients were randomly assigned to receive two doses of either BCG or a placebo, spaced four weeks apart. Blood samples from these patients were also compared with samples from six non-diabetic control participants and with samples from 75 additional individuals with diabetes and 15 without. Frequent blood tests measured participants' blood levels of insulin-autoreactive T cells ("bad" T cells), GAD autoantibodies (a marker of pancreatic function), regulatory T cells (cells that help control the immune response), and C-peptide (a marker of insulin secretion).

During the 20-week study period, we saw that BCG vaccination killed the "bad" T cells in two of the three BCG-treated participants. These patients also had increases in the number of their protective regulatory T cells. In addition, BCG-treated patients also had a temporary but statistically significant elevation in C-peptide levels, suggesting restoration of insulin production. These same responses were seen in one of the placebo-treated patients who, after enrolling in the study, coincidently developed infection with the Epstein-Barr virus (EBV, which, like BCG, is known to elevate TNF levels). There were no significant adverse events in any patient.

With this Phase I study, we believe we have validated in humans the treatment pathway we originally reported in mice—that is, that elevating TNF levels can eliminate the "bad" T cells, giving the pancreas the opportunity to begin to regenerate its insulin-producing cells—and are seeing early evidence of BCG's effectiveness. Our findings show that a simple, inexpensive vaccine modifies the autoimmunity underlying type 1 diabetes and appears to briefly restore pancreatic beta-cell function, even in those who have had type 1 diabetes for many years.

Our Phase I findings were covered by media outlets including *Bloomberg, US News & World Report, FOX News Boston, WebMD,* and *Reuters*, as well as international news organizations. Please visit **www.faustmanlab.org** and click on "News" to read these articles.

In the Phase II human clinical trial, which is currently being planned, we will seek to identify the right dose and frequency of vaccination needed to sustain a therapeutic response. For long-term restoration of insulin secretion, we expect that more frequent or higher BCG dosing will be needed compared to that used in the Phase I study.

Over Half Way to Full Phase II Funding

$13.5 million raised

With $13.5 million raised for the Phase II BCG human clinical trial, we are more than half way to our goal of $25.2 million. Thank you to everyone who has given their support, from the individuals and families affected by this devastating disease to the Iacocca Foundation and other majors donors who have been so critical to our efforts to move this research forward.

Frequently Asked Questions

Could you briefly summarize the most important outcomes of the Phase I trial?

The major findings from the Phase I study were that:

- The BCG vaccine with multi-dosing was safe in advanced type 1 diabetes.
- Although the drug was given in relatively small doses, we saw targeted death of the "bad" T cells that attack the insulin-secreting islets, an early sign that BCG has the potential to stop the autoimmune attack and successfully reverse disease.
- In people living with diabetes for an average of 15 years, there was a transient increase in/restoration of pancreatic insulin secretion after BCG vaccination.

What is the design of the Phase II study?

We are currently planning the study and do not yet know what the final design will be. In general, the trial will include a larger number of patients to further validate our preliminary Phase I efficacy findings. The study will look at what dose of BCG is needed, along with how frequently it would need to be given, to make this a sustained type 1 diabetes therapy.

Are you enrolling patients? How do I participate?

We are currently reviewing our patient database so that when the patient eligibility criteria is finalized, we can quickly enroll the needed participants. If you wish to learn more about participating, please visit **www.faustmanlab.org**, email **diabetestrial@partners.org**, or call 617-726-4084.

Will BCG will be a one-time vaccination?

Because this human clinical trial program translates only one part of the two-part intervention we used to permanently reverse type 1 diabetes in mice, we envision that BCG vaccination would have to be repeated over time. In Phase II, we will be looking for the optimal dosing and timing of administration so that patients can have a sustained response with infrequent dosing.

How might BCG benefit people with type 1 diabetes?

We hope that BCG treatment will put type 1 diabetes into remission, sparing people with this disease the need to so frequently monitor blood glucose levels or administer insulin—and also better protecting them against the fluctuations in blood sugar that lead to diabetes complications.

Insulin Production Declines More Slowly Than We Thought

Many with type 1 diabetes continue to make insulin decades after diagnosis

For over 20 years, scientists have thought that the ability of the pancreas to produce insulin declines very abruptly—within one to two years of diagnosis—in people who develop type 1 diabetes. These findings, based on standard C-peptide tests (C-peptide is an indicator that the pancreas is secreting insulin), have meant that most clinical trials testing treatments to stop or reverse type 1 diabetes have focused only on newly diagnosed patients, who were thought to have the best chances of recovering insulin secretion.

We now see that the decline of insulin-production occurs much more slowly than scientists have traditionally thought. Using an ultrasensitive blood test, we found that C-peptide production can persist for decades after type 1 diabetes onset and remain responsive to blood sugar levels. Although C-peptide levels were lower among those who had lived longer with the disease, they did not abruptly decline, but rather decreased gradually over time. What's more, C-peptide was detected in 10% of patients in our study who had been living with the disease for 31-40 years.

Our findings suggest that people with advanced disease may benefit from treatments that retain or enhance beta cell function—and that we should focus more clinical trials on this population. In other words, there may be a longer period in which we may be able to intervene in type 1 diabetes, even in people diagnosed decades ago—for instance, by stopping the disease from progressing or reversing type 1 diabetes by regenerating the insulin-producing cells.

"Persistence of Prolonged C-peptide Production in Type 1 Diabetes as Measured with an Ultrasensitive C-peptide Assay" was published in the February 2012 issue of *Diabetes Care*. We also presented these findings at the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) annual scientific meetings.

The BCG Vaccine and Multiple Sclerosis

Italian trials show vaccine efficacy in a second autoimmune disease

Recent human trials in Italy, led by Dr. Giovanni Ristori of the University of Rome, show that BCG vaccination can decrease symptoms and prevent the progression of brain lesions in advanced multiple sclerosis. Like type 1 diabetes, multiple sclerosis is an autoimmune disease that is caused by autoreactive ("bad") T cells vulnerable to TNF-triggered cell death. In type 1 diabetes, these cells attack the insulin-secreting cells of the pancreas. In multiple sclerosis, they attack the protective covering that surrounds the nerve cells.

The work of Dr. Ristori and his colleagues is exciting. Like our Phase I study in humans with type 1 diabetes, their human studies in multiple sclerosis show that the inexpensive BCG vaccine may benefit patients affected by these autoimmune diseases.

About the Type 1 Diabetes Reversal Trials at MGH

Led by Dr. Denise Faustman at Massachusetts General Hospital (MGH), the BCG Human Clinical Trial Program is testing Bacillus Calmette-Guérin (BCG), an inexpensive generic drug, as a treatment for advanced type 1 diabetes. In the recently completed Phase I study, BCG was administered to adults who had been living with type 1 diabetes for an average of 15 years. This treatment not only helped eliminate the defective T cells that mistakenly attack and destroy the insulin-producing cells of the pancreas, it also temporarily restored the ability of the pancreas to produce small amounts of insulin. The next step, a Phase II study, is currently being planned, with the goal of identifying the drug dose and schedule that will put advanced type 1 diabetes into remission.

Looking for more information about this type 1 diabetes research? **Please visit www.faustmanlab.org.**

Have questions about participating in future studies? **Please email: DiabetesTrial@partners.org.**

How You Can Help

Please consider making a tax-deductible donation today to sustain the momentum of this type 1 diabetes research program. Every gift makes a difference for patients … today and tomorrow.

1. To make a secure online donation, please visit **www.faustmanlab.org** and click on "Support."

2. You may make a gift by check (**payable to "Massachusetts General Hospital"**) and mail your check to:

   Diabetes Clinical Trial
   c/o Dr. Denise Faustman
   Immunobiology Laboratory
   Massachusetts General Hospital-East
   Building 149, 13th Street, CNY-3601
   Charlestown, MA 02129

On the memo line of your check, please write: "Type 1 diabetes research."

Thank you for joining us in the fight against diabetes!

Find us on Facebook:
www.facebook.com/FaustmanLab

Follow us on Twitter:
www.twitter.com/FaustmanLab