

Summer 2007

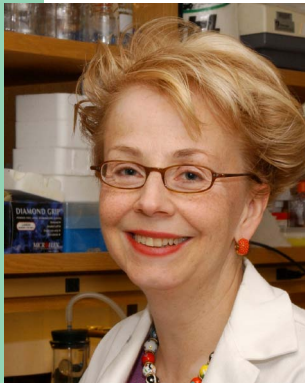
Updates

from Dr. Faustman's Lab at the Massachusetts General Hospital

The Promise of the Future: A Conversation with Dr. Faustman

Q: Much of this issue of the newsletter talks about the excitement around the Bacillus Calmette-Guérin (BCG) Human Clinical Trial. Can you share, from your perspective, what is so promising about this trial?

Dr. Faustman: This is truly a unique program because – first of all – we're using a generic drug. If we can introduce this type of drug,



and show that it changes the lives of diabetes patients while substantially reducing costs, it will be a tremendous achievement.

Also, this is a trial that may be able to reverse established disease, rather than simply introduce new pumps or other types of new equipment or drugs

to delay the onset of diabetic complications. That is a cause for new hope and a new vision for people who already have diabetes.

Q: Can you explain how this approach ties into "targeted disease removal"?

Dr. Faustman: Previously, it was thought that the human immune system was too complex to be able to eliminate individual disease-causing cells. However, we're now uncovering novel ways of targeted disease removal – killing only the "bad" cells, and sparing the good. This is huge – it's the first time in diabetes that we've been able to identify the bad cells and kill only them. It's a time of unprecedented hope for targeted disease intervention.

In our BCG trial, we will be counting the number of bad cells in diabetic blood, via a blood test, to determine whether we're able to eliminate disease, and at what drug dose. It's like having the first dose of insulin; we're at the very beginning of getting a drug with promise into the treatment phase.

Q: What do you view as the single most important resource for this trial, and other groundbreaking advances in diabetes research?

Dr. Faustman: The worldwide support of patients and the public worldwide makes all of this possible. Support can come in so many ways, and everyone who steps forward is helping, whether through donations of time, money or other resources.

Blood donors come to us from all over the country and the world, every day! You only have to look at our map (*see page 3*) to notice that our research is not merely Boston-based. It's a truly national and international program.

Of course, financial support makes a huge difference, but our diabetes research would not have been able to move to human trials without the people who have made sacrifices of time, school, travel – just to come here to donate blood. It's a unique thing that doesn't happen often.



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Taking the Next Steps: Applying Our Research to Human Clinical Trials

Since our research was published, we have been diligently working to apply these findings to human diabetics. We have been raising money for studies to create the tests and machinery needed to monitor the trials we will be conducting. As most of you know, our human clinical trial program will begin with an evaluation of Bacillus Calmette-Guérin (BCG), a generic drug that has an impeccable human safety profile and is already used for other diseases. This agent will be tested in the first Phase I human trial (see article on page 5). BCG causes the body to make a natural substance called TNF that helps regulate the immune system, and we hope that this will lead to the selective elimination of one population of disease-causing cells present in diabetics. Dr. David Nathan, director of the MGH Diabetes Center and one of this country's foremost diabetes experts, will direct the human clinical trials at MGH.

Only by conducting a clinical trial will we know if BCG will work. We have been hoping to start the human trials soon, and it looks like they might begin in 2008. Many patients and families ask, "Why can't these trials begin sooner?" The answer is this: for us to conduct these clinical trials in a way that makes sense, we need to build and automate the blood tests and machinery first. We have been diligently working to do both of these things, as you will see on the following page.

Essential New Funding Received

We are pleased to announce that the Iacocca Foundation has made its second grant of \$1.8 million to Massachusetts General Hospital – crucial funding for the Nathan/Faustman research program to translate our diabetes 'cure' in mice to humans. The three-part program includes additional studies in mice to refine the therapy, the building and automation of an important blood test, and the Bacillus Calmette-Guérin (BCG) Human Clinical Trial, which will be led by nationally renowned physician-scientist Dr. David Nathan, director of the MGH Diabetes Center. The BCG Human Clinical Trial is due to start in 2008.

During the Iacocca Foundation's most recent site visit to our laboratory, we demonstrated that we have successfully standardized the manual separation of T cells from whole blood with the desired yield, purity and viability. This process has been validated in over 266 human blood samples, amply exceeding our goal of 50 human samples.

In addition, we also were able to demonstrate continued improvement in our capacity to automate this process, and there is sufficient automation capacity and throughput in place to support the phase I human clinical trial that will commence in 2008. Other research achievements this year include progress in the development of a cell death assay suitable for using in a human clinical trial, and validation of treatment of type 1 diabetes using BCG in the NOD mouse model. (The NOD mouse is a mouse that spontaneously

gets type 1 diabetes, similar to the onset of the human disease.)

In year two of funding for the Nathan/Faustman research program, we will continue to translate our diabetes 'cure' from mice to humans.

We thank the Iacocca Foundation for their generous support.

Diabetes Research in the MGH Immunobiology Lab

Our lab's experiments in end-stage diabetic mice have showed that a brief treatment eliminated disease-causing white blood cells in these mice. This treatment killed only the cells that were causing the autoimmune destruction, and not the healthy cells. We also demonstrated that the islet cells of the pancreas – the cells that secrete insulin – could regenerate once the autoimmune destruction was stopped.

Our lab's work represents a reversal of diabetes, rather than just a treatment for the symptoms and complications of this disease. These main research findings were published in 2001 and 2003.

Ryu S, Kodama S, Ryu K, Schoenfeld DA, Faustman DL. Reversal of established autoimmune diabetes by restoration of endogenous beta cell function. *J Clin Invest* 2001; 108(1): 63-72.

Kodama S, Kuhlreiber W, Fujimura S, Dale EA, Faustman DL. Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science* 2003; 302:1223-7.



Laying the Groundwork for Clinical Trials: New Blood Tests and Machinery

One of the critical steps for upcoming and future clinical trials has been to create and automate a blood test that we can use to monitor trial results. This test will quickly let us know what dose of a drug works best, if at all, by allowing us to precisely count white blood cells before and after drug treatment. If there are fewer of the “bad” white blood cells after treatment, then we know we are onto something good! For the first human clinical trial, we will use this method to rapidly and precisely evaluate whether BCG can eliminate the disease-causing cells in type 1 diabetics, and at what dose. If we were to proceed without the blood test, it would be like giving insulin without ever being able to check blood sugar levels.

The test, also known as a blood assay, involves a machine that separates the white blood cells from the other cells. Once the cells are isolated by the machine, our blood test can be used to count the number of disease-causing white blood cells in the blood sample, therefore allowing us to see if the drugs we are testing are eliminating or reducing the number of defective cells. The cell separation and blood assay machinery is installed at MGH, and includes



robotic arms that will perform cell separation steps on an assembly line. This robotic automation is going very well and represents four years of our work. Creating and automating this blood test machinery is a huge research accomplishment – an advance that will free up our researchers’ time, allowing them to work on other important projects instead of spending several days working entirely on cell separation.



Patient recruitment across the U.S.

Patients Making Research Possible

The Internet has changed how people access medical information and care – and the changes have been amazing. Our current diabetes research, and our major upcoming clinical trial, are possible in no small part because people around the world have heard about our research through the Internet, and have signed up to participate by donating blood samples.

People have come to our labs in Boston from across the U.S., Canada, South Africa, and Europe. The laboratory is using these samples to fine-tune the cell separation procedure and clinical trial assay. The contribution of each and every one of these patients is invaluable.



Diabetes Findings Translating to Other Diseases

Worldwide research efforts have discovered evidence of genetic and white blood cell errors in several human autoimmune diseases – such as rheumatoid arthritis, multiple sclerosis, Crohn’s disease and lupus – that are similar to those errors seen in type 1 diabetes. Our lab has received preliminary funding to begin translating our preclinical diabetes research so that we can better understand and treat some of these other diseases.

Specifically, we hope to use the blood tests and machinery we have developed for our diabetes research and trials to help us identify existing generic drugs that will have efficacy in other autoimmune diseases. To date, we have begun collecting blood samples from patients with Crohn’s disease and lupus who have developed new autoimmune disease after starting anti-TNF treatment.

We are looking at the disease-causing white blood cells in these patients to see if they have the defect we have previously identified in type 1 diabetics. We believe that this cellular defect makes these cells susceptible to death in the presence of elevated levels of TNF ... which is exactly what we are testing in our upcoming diabetes clinical trial, using Bacillus Calmette-Guérin (BCG), a generic drug.

The Cost-Saving (and Life-Saving) Promise of Generic Drugs

One of the most exciting things about our upcoming human diabetes trial is that it makes use of an inexpensive generic drug. This allows us to move fast, in clinical trial terms, towards human testing – and, if the drug is effective, we hope it will mean that we can quickly bring an inexpensive drug to many patients who will benefit tremendously.

Visit Our Website: www.faustmanlab.org

For clinical trial appointments, call:
617-726-4084 or email: DiabetesTrial@partners.org



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The Importance of Bacillus Calmette-Guérin (BCG)

What is BCG? BCG is a relatively risk-free drug that has been around for over 80 years, and has been used worldwide as a vaccination for preventing tuberculosis (TB). In most countries, this generic drug has been given as an obligatory vaccination for all citizens for the prevention of TB. It is estimated that four billion doses have been given worldwide. In the United States, preventative BCG vaccines are not part of the obligatory childhood vaccination process, since the incidence of TB is lower here than in the rest of the world. However, BCG is approved as a vaccination for TB in the U.S., and, at very high doses, BCG is also approved here as a treatment for bladder cancer.

Albert Calmette and Camille Guérin discovered BCG back in 1908 while they were attempting to find a vaccination for TB. They developed a way to decrease (attenuate) the infectious properties of the TB bacteria called *Mycobacterium Bovis*, a live bacteria that causes tuberculosis in cattle, thereby creating BCG. The process took them 12 years. When they finally obtained the attenuated strain of bacteria, they ran human clinical trials in 1921 to test their new vaccination for human tuberculosis. Their trials were successful, and BCG is now used worldwide. It is considered by most to be one of the safest vaccines ever developed, and to be effective some of the time in protecting humans from exposures to TB that might cause an outbreak of the disease.

Why use BCG for diabetes? In our human clinic trials in type 1 diabetes, we are using BCG because it is known that BCG induces a patient's own body to produce more TNF, also known as tumor necrosis factor. With the help of your blood donations, we were able find that people with type 1 diabetes normally produce too little TNF. Sufficient amounts of TNF help transfer cell signals to the immune system, which may help it to identify and kill the "bad" T-cells that cause diabetes. The next step is to determine the proper dosage of BCG and begin human clinical trials, in which we will use BCG to boost diabetics' TNF levels to kill off their "bad" T cells.

The procedure for administering BCG into the body is relatively painless, with few side effects. BCG as a vaccine is typically given as a needle injection on the upper arm and causes a slight reaction that will leave a small flat scar for approximately a week. Side effects may include headache, fever, swollen lymph nodes and skin scaling at the site of injection. However, there are a few people who are allergic to BCG and might develop rashes or infections. BCG should not be used as a vaccine in people who have AIDS or in those who have a compromised immune system, such as in hereditary forms of white blood cell deficiencies. Doses of BCG given for TB vaccination are small compared to those given to cancer patients. The doses that we will start with in our clinical trials also will be relatively small, but as time passes and we monitor for safety and efficacy, we will be able to increase the dose and graduate to the next phase of human clinical research.





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Please Support Our Work

Please support the ongoing research of our lab with a tax-deductible donation. Every gift makes a difference for patients ... today and tomorrow.

1. To make a secure online donation, please visit:
www.mgh.harvard.edu/diabetes/diabetes_support.htm
and click on "Type 1 Research."
2. You may make a gift by check
(payable to "Massachusetts General Hospital"),
and send your check to:

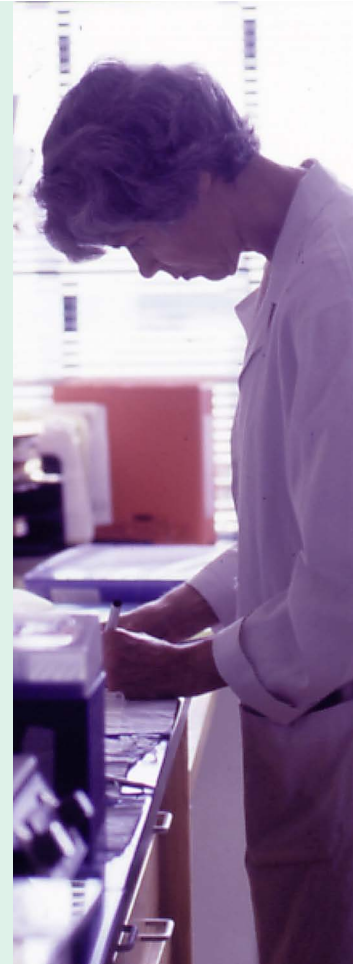
The Massachusetts General Hospital
Development Office
Attn: Jocelyn Hoey
165 Cambridge Street, Suite 600
Boston, MA 02114

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

Thank you for joining us in the fight against diabetes.

Warmly,

Denise L. Faustman, MD, PhD



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