

Spring 2008

Updates

Clinical Trial for Promising Diabetes Drug is Underway

The long-awaited launch of our Phase I clinical trial evaluating the effects of Bacillus Calmette-Guérin (BCG) in type 1 diabetes has begun! The trial will be conducted here at Massachusetts General Hospital. This Phase I trial is predicted to take approximately 18 months to complete.

Trials testing new drugs typically occur in Phase I-IV and take 10 or more years, but we are fortunate in this case to be “recycling” a drug that is already available. This should enable the study to move forward at a more rapid pace, which has always been one of our goals.

BCG is a generic drug with an excellent safety profile in humans and is already being used for other diseases, such as tuberculosis (TB) and cancer. BCG causes the body to make a natural substance called TNF, which helps regulate the immune system by killing the rogue T cells that cause diabetes. We hope that the administration of BCG will lead to TNF selectively destroying the disease-causing T cells that are present in diabetes. This trial is an important step in testing this hypothesis.

We and others have already proven that this treatment can work in mice with end-stage diabetes. If the BCG studies show that BCG can help patients with type 1 diabetes, and if we can introduce this inexpensive drug to the market, it will be a tremendous achievement.

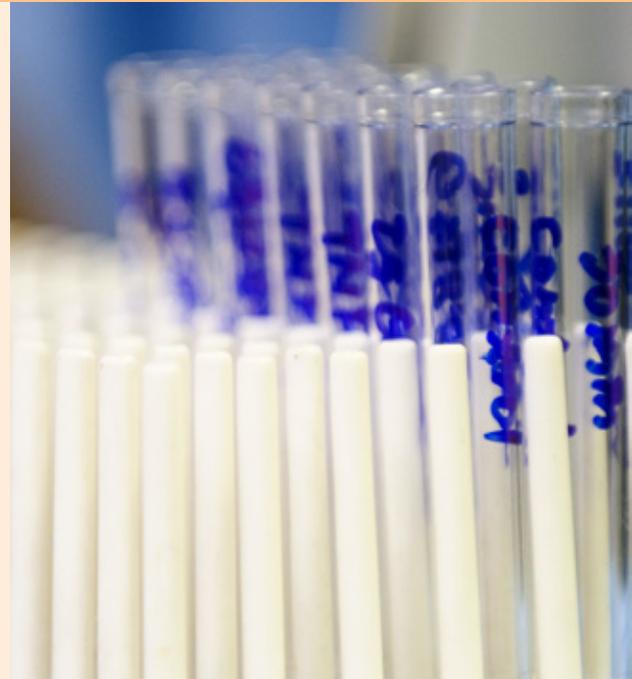
All of your generous gifts have paid off, as we now have the necessary blood tests and machinery built to monitor this trial. With these tools, we can begin to see what dose of the drug, if any, works best by precisely counting white blood cells from blood samples taken before and after BCG treatment. If we see a reduced number of the rogue cells, then we know that the therapy is working. Conducting this clinical trial will be the only way to know if BCG works against type 1 diabetes.



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

The Safety of Bacillus Calmette-Guérin (BCG)

Bacillus Calmette-Guérin (BCG) has an impeccable safety profile in humans. In fact, it has been labeled by some medical experts as the "safest vaccine" ever developed. BCG has been used for over 80 years worldwide as a vaccine for tuberculosis (TB) and is also used for the treatment of bladder cancer at high doses. In many countries, receiving BCG to prevent TB is mandatory. Although it is approved for use in the United States to prevent TB, BCG is not given as a routine vaccine because the incidence of TB is low here.

The BCG vaccine carries an attenuated (weakened) strain of the bacteria *Mycobacterium bovis*, a live bacteria that causes TB in cattle. It was first used following human clinical trials in 1921 that affirmed the safety and efficacy of this vaccine.

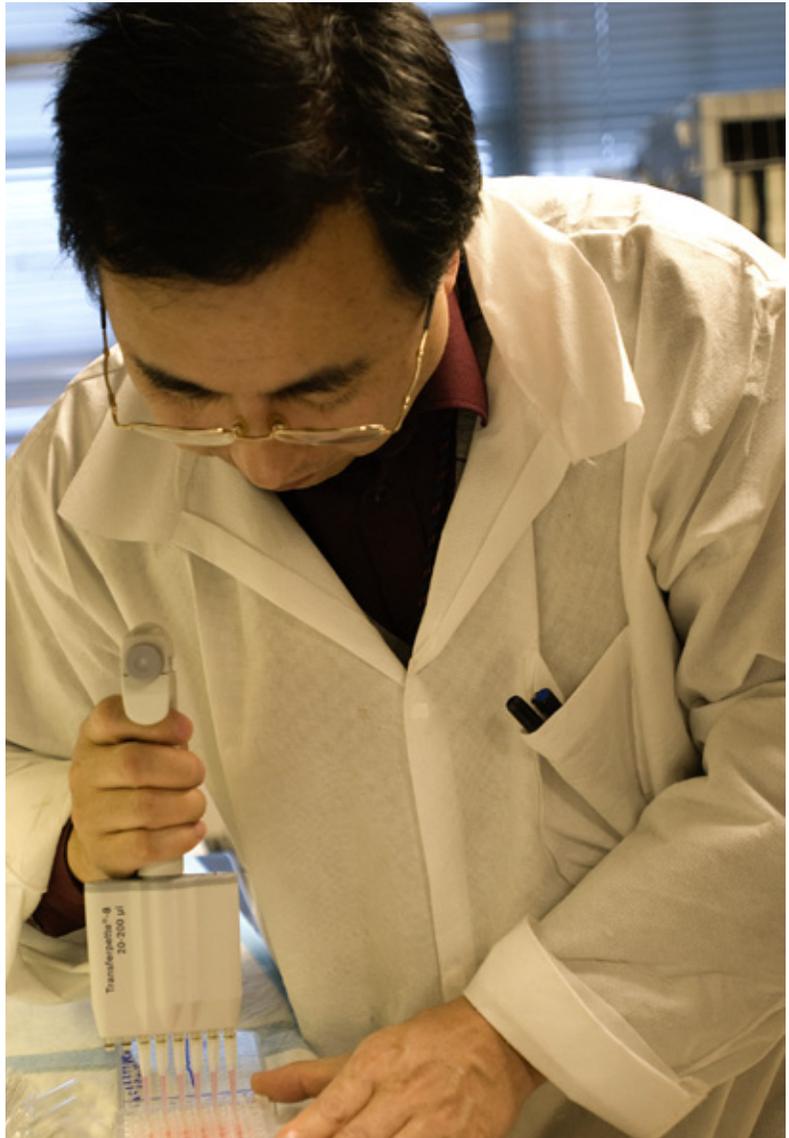
Administering BCG is a relatively painless process with few side effects. Typically, BCG is given as a needle injection in the upper arm, just into the skin. This may cause a slight reaction for about a week followed by a small, flat scar for approximately a week. Side effects may include headache, fever, swollen lymph nodes and skin scaling at the site of injection. For some people, there is a small chance of allergic reaction to BCG, in which case those patients may develop rashes or infections. People with AIDS or other patients with compromised immune systems should not be given BCG.

We have started our clinical trial by administering small doses of BCG. As we learn more about the safety and efficacy of BCG in type 1 diabetes, we will be able to graduate to the next phase of the trial, in which we will test increased doses or more frequent doses.

Phase II Trials

We are very excited about the launch of our human Phase I clinical trial. With this launch, we are finally witnessing our basic research efforts bear fruit as we progress from mice to human trials. Unfortunately, finding a cure for type 1 diabetes does not stop here. As the results of Phase I are accumulated and we can show this drug is safe and effective in type 1 diabetes, we will move into Phase II clinical trials.

Phase II trials are larger-scale studies that evaluate whether a drug works in a wide variety of people and look at what doses are most effective. The Phase II investigation, a critical part of the drug-testing process, will likely be our next step – and one that we are already gearing up for. Your continued support will help us expedite this process of preparation and prevent a gap in funding (and thereby prevent a time delay) between Phase I and Phase II testing, which we predict will begin in approximately 18 months.



Dr. Faustman Speaks: Toward Better Therapies for type 1 Diabetes

In what ways is this trial promising and unprecedented?

This trial is very unique in the field of type 1 diabetes research. Currently, there is great emphasis on new treatments



involving blood-glucose monitoring devices for type 1 diabetes, but there is almost no emphasis on disease reversal or cures for this disease. Our goal is to reverse established type 1 diabetes, not simply temporarily halt it or treat its symptoms. What also makes this approach unique is that it does not involve unknown risks – neither large monetary risk nor the risk of

unknown toxicity to patients – typical of new drug development. In addition, the BCG trial does not require the use of immuno-suppressants or require cell transplant. Instead, our approach is designed to target only the defective white blood cells in type 1 diabetes, sparing healthy cells. That should translate into much less toxicity than other treatments and makes the possible long-term safety of the drug remarkable.

What is involved in the process of the Phase I clinical trial?

In this human clinical trial, we are enrolling diabetic volunteers and healthy, non-diabetic volunteers who serve as a control population. Many of our volunteers are taken from a database we have established at MGH that includes type 1 diabetics and healthy subjects who have expressed interest in participating in type 1 diabetes trials at MGH's Diabetes Research Center. After patients are screened and enrolled, the diabetic patients are randomly assigned to receive a placebo (saline) or BCG vaccination in the arm. Both the diabetic placebo group and the healthy subjects serve as control groups whose results will be compared to diabetics who will receive a BCG vaccination. We will monitor the response of the white blood cells to the medication and look at islet function during the study period, making use of automated cell separation methods and the bioassay (a specialized blood test) created by our lab to monitor trial results and measure drug efficacy.

If BCG works, what does the future look like for type I diabetics? How soon will that future be realized?

In the short term, if we see in the Phase I trial that BCG is successful and is having the effect that we expect – which is to stimulate the immune system to eliminate one population of defective cells in type 1 diabetes – then we will move into Phase II and Phase III trials to test the efficacy in larger groups of patients. In the long term, if this approach can be proven in clinical trials, we think it would mean being able to bring new, inexpensive treatments, or even a cure, to diabetics.

Why is the MGH the right place to be conducting this research?

MGH has one of the leading diabetes centers in the world, and is home to many of the world's top diabetes experts. In addition, the MGH is known for successfully bringing many innovative therapies from the research laboratory to patients who are treated here. That is one of the hallmarks of MGH.

How can philanthropy help?

We would not have been able to get this far without the generosity of donors. In fact, this trial would not have been possible at all were it not for the support we have received both from private foundations like the Iacocca Foundation – which provided the funding for much of the basic research leading up to the trial and Phase I of the trial – and from countless individuals and families. That philanthropic support, and support from others, has been absolutely pivotal.

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

Racing Toward a Cure: The Story Behind Brendan's Brigade

When the **Iacocca Foundation**, a charity benefiting diabetes research founded by former Chrysler chief executive Lee Iacocca, issued a challenge to "Join Lee Now" and raise \$10 million to support the Bacillus Calmette-Guérin clinical trial, families from all over the country responded.

Diana Buono, whose son Brendan, 16, has juvenile diabetes, read about the developments in a *Boston Globe* article.

She and her husband Joe had been long-time donors to other organizations funding research on the disease ever since Brendan was diagnosed at 17 months of age. After reading the article, Mrs. Buono tracked down Dr. Faustman's phone number and called her office to ask what her family could do to help her efforts. That's when Brendan began giving regular blood samples to contribute to Dr. Faustman's development of a new blood assay test that promised to be instrumental in the planned clinical trial.

"When I read about the Iacocca challenge and I began to learn about how promising Dr. Faustman's research was, I felt we had to get involved," says Mrs. Buono. "Ever since Brendan was diagnosed, we had been hearing how a cure is right around the corner, and we felt like those promises were going nowhere. But it was obvious to us that Dr. Faustman's research was different – that she is on the path to finding a real cure, and soon."

The Buonos were encouraged by Dr. Faustman's success in curing type 1 diabetes in mice and also recognized that this trial is unique in that its goal is to reverse diabetes in people who have the disease, not just reverse symptoms. "We saw how committed Dr. Faustman is for finding a cure for this disease, and how she and her group added such a personal touch to their work," says Mrs. Buono.

As a result, the Buonos transferred all their philanthropy for diabetes to Dr. Faustman's lab, and, in addition, brainstormed to come up with a fund-raising event that would be meaningful – and fun – for Brendan.

Brendan loves biking, so in 2004 the family – including Timothy, 13, and Maria, 7 – decided to hold an annual bike ride on the 28-mile-long East Bay Bike Path near Providence, Rhode Island.

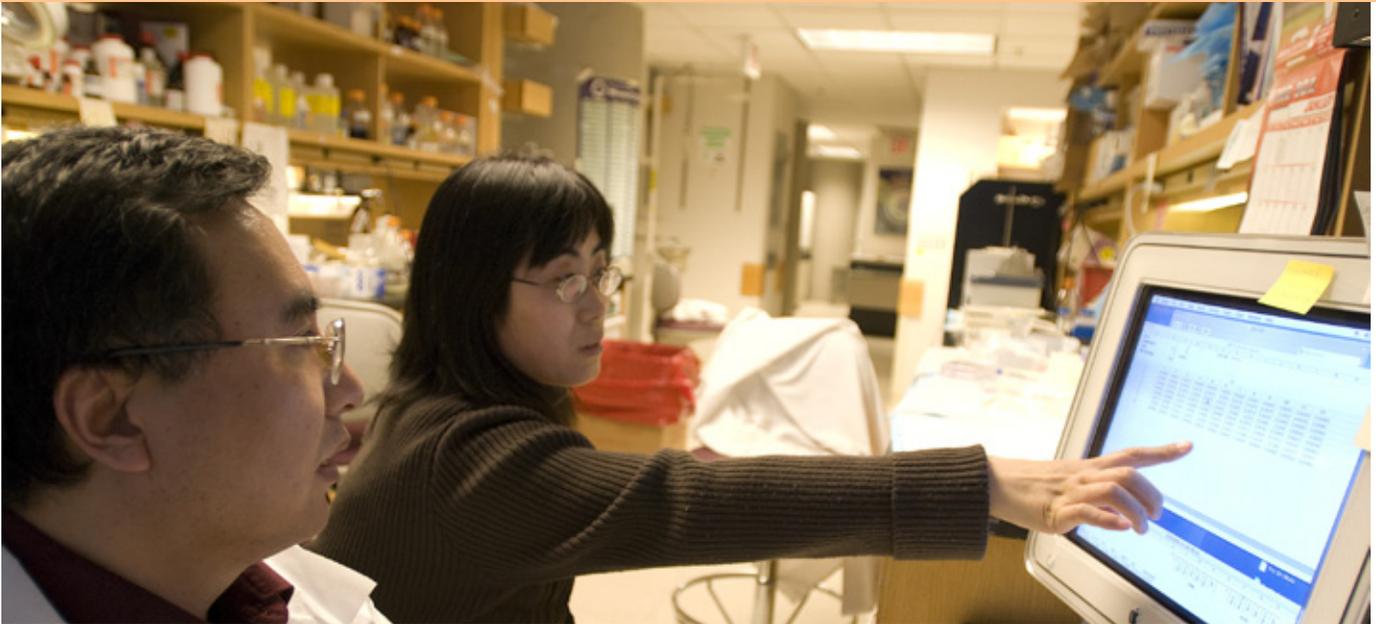


Now entering its fourth year, "Brendan's Brigade" attracts about two dozen friends and family members every year and has raised a total of approximately \$18,700 for Dr. Faustman's lab. Much of that money is raised from sponsors and non-riders responding to the Buono family's letter campaign leading up to the event.

"The bike ride is small act of gratitude and assistance for the tremendous amount of work that Dr. Faustman is so passionate about in finding a cure," says Brendan Buono. "She's a hope for all families living with type 1 diabetes. She certainly is for us."



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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"). 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."

- 3) More information is available on line at:
www.fautsmanlab.org

Thank you for joining us in the fight against diabetes.

Warmly,

Denise L. Faustman, MD, PhD

How can I learn more about this clinical trial?

Please log onto our web site:
www.faustmanlab.org. If you would like to schedule an appointment for the initial blood work, please e-mail Ana Souza, MD, at asouza1@partners.org or call Dr. Faustman's office at 617-726-4084.



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A History of Trying to Reverse Established Diabetes in Animals Translation into Humans

In 2001, the Faustman lab reversed established type 1 diabetes in end-stage mice. In the non-obese diabetic mouse model of autoimmune diabetes, Dr. Denise Faustman's brief, two-part, non-toxic treatment achieved a permanent cure of established diabetes.^{1,2,3} The intervention involved a regimen of immunomodulation lasting six weeks, combined with control of hyperglycemia. After termination of all therapy, normal glycemia was restored permanently in more than 75 percent of treated mice and the autoimmune state reverted to normal. The lab successfully achieved targeted disease-removal of only the disease-causing white blood cells in these long-term diabetic animals. In addition, the intervention not only removed the disease, but allowed the animals to regenerate their pancreases. Long-term normoglycemia was restored without any other intervention for their entire lives. Based on this finding, a proof-of-concept, Phase I clinical trial using BCG began in January, 2008.

A drug named Complete Freund's Adjuvant (CFA) was one part of the Faustman lab's two-part therapy and specifically eliminated the disease-causing cells in the mice. The human equivalent of this drug that is manufactured for human use is called Bacillus Calmette-Guérin (BCG). BCG is a generic drug already FDA-approved for prevention of tuberculosis and treatment of bladder cancer, which has been used worldwide. Both drugs stimulate the production of *TNF-alpha*, which the lab staff believes will eliminate a population of defective cells (pathogenic memory T cells) in type 1 diabetes.

Today, based on this research, an FDA-approved Phase I trial is being conducted at Massachusetts General Hospital to evaluate whether treatment with BCG vaccination can eliminate the abnormal white blood cells in patients with type 1 diabetes. Overall, this trial is part of the program of research aimed at developing a curative therapy for human type 1 diabetes.

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 Jul; 108(1):63-72.

Kodama S, Kuhntreiber W, Fujimura S, Dale EA, Faustman DL. Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science.* 2003 Nov 14; 302(5648):1223-7.

Faustman D, Tran S, Kodama S, Lodde B, Szalayova I, Key S, Toth Z, Mezey E. Comment on Papers by Chong et al, Nishio et al and Suri et al on Diabetes Reversal in NOD Mice. *Science* 2006 314:1243-4.

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