

Updates

Fall/Winter 2008



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

from the Faustman Laboratory at Massachusetts General Hospital

Major Advancement

in Potential New Therapy for Type 1 Diabetes

We are in the midst of our Phase I clinical trial evaluating the effects of Bacillus Calmette-Guérin (BCG) in type 1 diabetes. The trial is being conducted here at Massachusetts General Hospital. Our lab recently completed an exciting study that confirms the mechanism behind BCG, our potential new therapy.

The study, published in the September 9, 2008 issue of the *Proceedings of the National Academy of Sciences*, was conducted using human cells. It showed that activating a metabolic pathway that helps regulate the immune system



specifically eliminates the defective T cells (a type of white blood cell) that react against a patient's own tissues.

Previously, we had discovered a technique that reversed type 1 diabetes in mice, which has been the basis of our current Phase I human clinical trial. Our mouse studies showed we could selectively kill the defective T cells that were destroying insulin-producing islet cells of the pancreas. Our latest study is the first

demonstration that this strategy also works in human cells and supports the viability of the clinical trial that is currently underway.

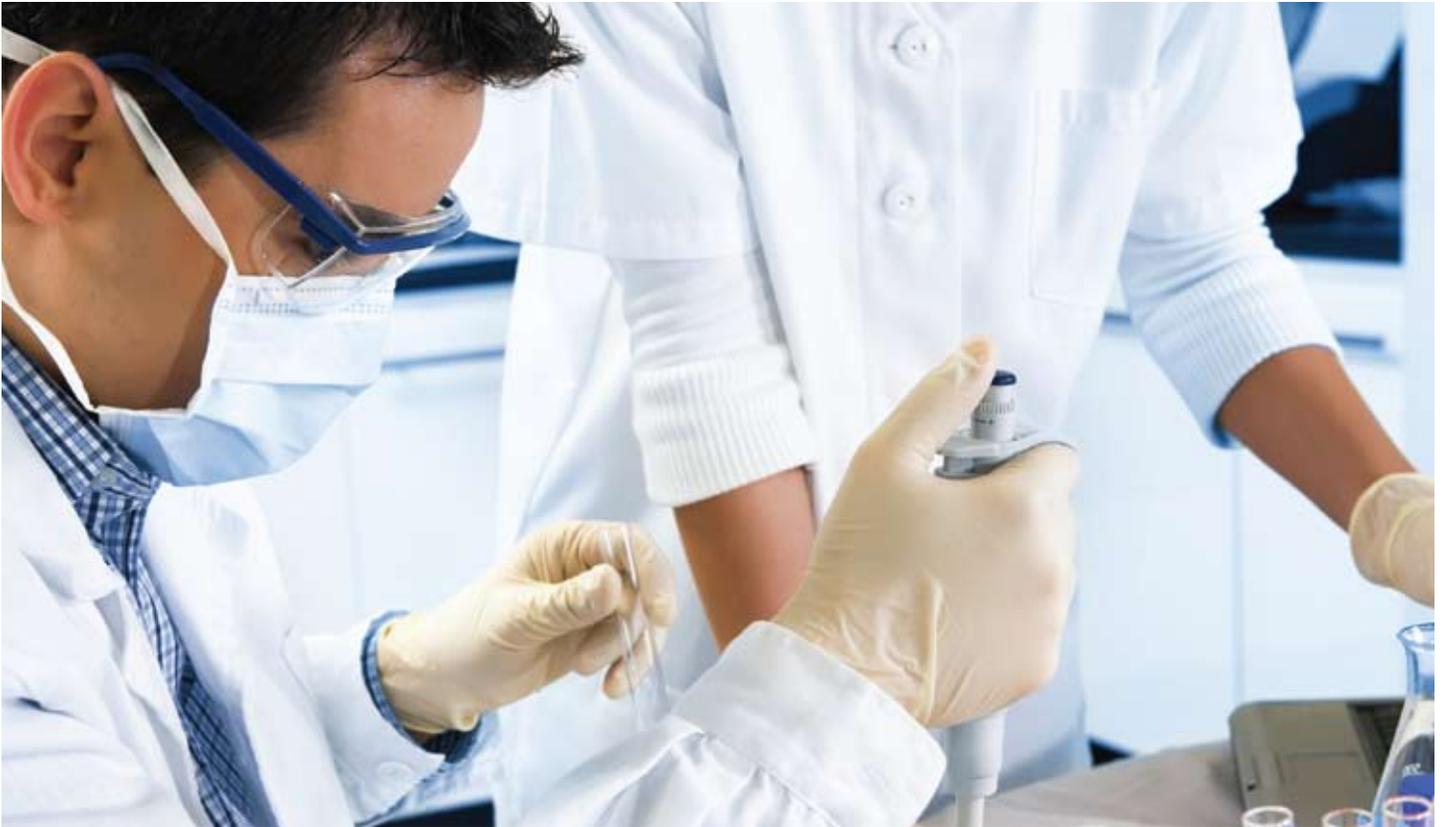
In previous studies, our team demonstrated that causing diabetic mice to produce elevated levels of tumor necrosis factor (a substance produced by the body that helps to regulate the immune system) leads to the death of the defective T cells responsible for the destruction of healthy islet cells (cells in the pancreas that produce insulin). After the defective T cells were destroyed and the immune system became devoid of defective cells, the mice were able to regenerate healthy islet cells that produced normal levels of insulin. In other words, the animals were cured of their disease.



We're launching a new web site

The Faustman Lab web site has undergone a major redesign and includes expanded information. Visit the site today at www.faustmanlab.org and learn more about the trials and how you can support them. You can also sign up for e-mail updates.





New Way to Kill Defective Cells

Spares Healthy Ones

Our most recent study used blood samples from more than 1,000 people with autoimmunity compared to matched volunteers without autoimmunity.

First, we found in tissue culture experiments the treatment with tumor necrosis factor, or TNF, killed the defective T cells found in the blood of patients with type 1 diabetes and other autoimmune diseases, but did not have any effect on the healthy cells of the control patients. This is a good outcome because we want to destroy only the defective cells, and not the healthy ones. Then we tested several substances,

called TNF agonists, that produce an effect in the body similar to that of TNF. We found that one of these substances was also effective in destroying the defective T cells in the tissue culture of diabetic and autoimmune patients, while sparing healthy cells. Further experiments with the blood samples of diabetic patients confirmed that our treatment only leads to the death of the defective T cells responsible for producing an autoimmune reaction (the attack of the islet cells of the pancreas) in these patients, and does not harm healthy cells.

These findings are important because they provide further evidence — and the first in human T cells in culture — that our approach in the current human clinical trial does not appear to harm healthy cells and appears to kill in culture the disease-causing cells.

The current Phase I trial began in January, 2008. In it, a generic drug is being tested in patients with type 1 diabetes to determine whether the drug will cause the death of the defective T cells that destroy the pancreatic islet cells.

For more information, see “Update on the Clinical Trial.”

Update on the Clinical Trial

Our human clinical trial is testing whether using Bacillus Calmette-Guérin (BCG), a generic drug that temporarily elevates TNF levels in the body, will reduce or eliminate autoimmune T cells in patients with type 1 diabetes. The trial's Phase I funding is complete and the trial is in progress under the direction of Denise Faustman, MD, PhD, and David Nathan, MD, director of the MGH Diabetes Center.

The trial, scheduled for completion by January, 2010,

will gather information on drug safety. Subsequent Phase II trials will focus on determining the optimal dose and timing of BCG administration to achieve the desired effects in type 1 diabetes. Phase I trials are aimed at proving the drug is safe.

While this trial is underway, we need to begin planning for our Phase II clinical trial, which we hope to launch upon the successful completion of the Phase I portion. The Phase II trial will involve testing BCG in greater numbers of patients

with type 1 diabetes using the dose and timing we determine from the Phase I data. It will also give us more information on how effective this treatment might be, providing the information needed to launch late-stage human clinical trials (Phase III studies). We are currently screening volunteers for the Phase II trial.

A major part of the Phase II planning involves raising the funds needed to conduct this next stage of human research, and we have set a fund-raising goal of \$25 million.



In the Media

Denise Faustman, MD, PhD,
on Talk of the Nation's "Science Friday"

In September, Dr. Faustman had the privilege of joining radio host Ira Flatow on National Public Radio's *Talk of the Nation*. The "Science Friday" segment discussed many aspects of diabetes, our research and our current clinical trial. Here are some highlights from our conversation that address some aspects of the work being done at the Immunobiology Lab. For a full transcript, please visit www.faustmanlab.org.

Regarding our approach to eliminating the disease-causing cells in type 1 diabetes:

FLATOW: And how do you go about killing these bad white blood cells?

DR. FAUSTMAN: Oh, that's kind of the fun part of this project, because we're using a vaccine that's been out there for about 80 years, and the vaccine's called BCG. In the rest of the world, outside of the United States, it's a mandatory vaccine ... to prevent tuberculosis (TB).

In the U.S., it's used for cancer. And the reason we're interested in that vaccine is that it induces

something in your body called TNF, tumor necrosis factor. We think the way to kill one population of these rogue T cells, whether you're a mouse or whether you're human, is with TNF.

FLATOW: And so you're trying that out in humans now?

DR. FAUSTMAN: Yes ... we're actually in human clinical trials. We're not sure if the humans are going to be as happy as the mice; we're very early in the process of testing it. But the Phase 1 trials are ongoing here in Boston.





Fund Raising: Creative Ways to Get Involved

In the spring of 2008, the Ballet Foundation for the XXI Century dedicated its Dance Festival to one of the Foundation's students, Madeleine Howells. Madeleine was diagnosed with diabetes while in the second grade, but never let the challenge get in the way of her passion for dance. Now, at age 13, Madeleine not only keeps up with ballet, but also excels in her class.

For the Foundation's Dance Festival 2008, a lyrical piece was choreographed to feature Madeleine. The piece, entitled "World," was arranged by the

company's prima ballerina, Leia Hardimon, and set to the music of artist Five for Fighting.

The Ballet Foundation generously collected donations during the festival to benefit Massachusetts General Hospital's type 1 diabetes research, and the donations totaled more than \$1,400. We greatly admire Madeleine for pursuing her passion in spite of having this challenging disease and we would like to thank everyone who was kind enough to make a donation in support of our research efforts.

Two Ways You Can Help



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.f FaustmanLab.org and click on "Support."
2. You may make a gift by check (payable to "Massachusetts General Hospital") and mail your check to:

MGH 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