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

The Diabetes Reversal Challenge

The Unique Clinical Trial at the Faustman Lab

The Faustman Lab at Massachusetts General Hospital, run by Denise L. Faustman, MD, PhD, is moving rapidly through the clinical trial challenge to test and possibly establish a vaccine using a generic drug, Bacillus Calmette-Guérin (BCG) to reverse type 1 diabetes. The experiments have moved from mice to a clinical trial in humans, and the testing has passed every research milestone ahead of schedule — an astonishing feat for any clinical research project.

The Phase I safety trial in people with type 1 diabetes is near completion. The next step is to find, in a Phase II study, the possible dose and frequency of administration of BCG vaccinations that will benefit patients with type 1 diabetes.

What makes these trials unique? First, unlike other immunosuppressive therapies for autoimmune diseases that harm both healthy and disease-causing T-cells, this treatment appears to provide a way to achieve "targeted removal" of only autoimmune disease-causing cells.

BCG works by causing the release of a natural protein in the body called tumor necrosis factor, or TNF. In mice, temporarily elevating TNF levels destroys the autoreactive T-cells, allowing the insulin-producing cells of the pancreas to regenerate and produce insulin. TNF in mice also elevates a good population of T-cells, thus restoring the immune system to near normal. In other words, the treatment literally reverses type 1 diabetes, at least in a mouse model of diabetes. In laboratory experiments, TNF also destroys the autoreactive cells in human blood samples. TNF does not harm the normal, healthy T-cells that help fight infection, leaving the immune system intact. The human clinical trials we are conducting seek to expand these findings in human subjects.

The BCG trial is also unique since BCG is a generic drug that has been used widely as a vaccine for more than 80 years in humans. Currently, BCG is used in small doses as a vaccine against tuberculosis, and it is used in larger doses as a bladder cancer therapy. Because it has been used for so long and in so many humans, the safety of this vaccine is well-established. This fact allows us to move more quickly through safety studies compared to clinical trials that test new drugs.

With a generic drug, we can move BCG to the public rapidly if the drug is indeed found to be safe and effective in patients with type 1 diabetes. Our Phase I safety study is following our enrolled patients over months looking for changes in the T-cells and also testing the reliability of our blood tests for tracking disease-causing T-cells.

The BCG trial is one of the few translational studies in human testing where the animal data showed disease reversal in diabetic mice that had hyperglycemia, not just in mice with normal blood sugars and with a predisposition to diabetes. Therefore, this human trial at Mass General is designed to treat people with established type 1 diabetes unlike most human testing that focuses only on not yet diabetic patients at risk for the disease or newly diagnosed diabetics with a short time period of high blood sugars.

Ben Rosenthal

At 17, a mature understanding of the importance of a cure

Ben Rosenthal's mother, Susan Benford, learned her son had diabetes when he was 13 months old. He had lost a quarter of his body weight, was urinating frequently and was hungry and irritable. "Until then, he was an easy child, and suddenly everything turned on its head," recalls Susan. "I was able to detect that something was wrong mostly because I already had another child, who was healthy. I knew that Ben's behavior and his symptoms were totally abnormal."

The diagnosis, she says, was "shocking, terrifying". Though she knew it was a treatable disease, she worried constantly when he fell asleep, in particular, because she didn't know if he was simply tired or if his insulin levels were dangerously low, which could lead, potentially, to a coma or even death.

"He was too young to speak, so I was doing a lot of guesswork," Susan recalls.

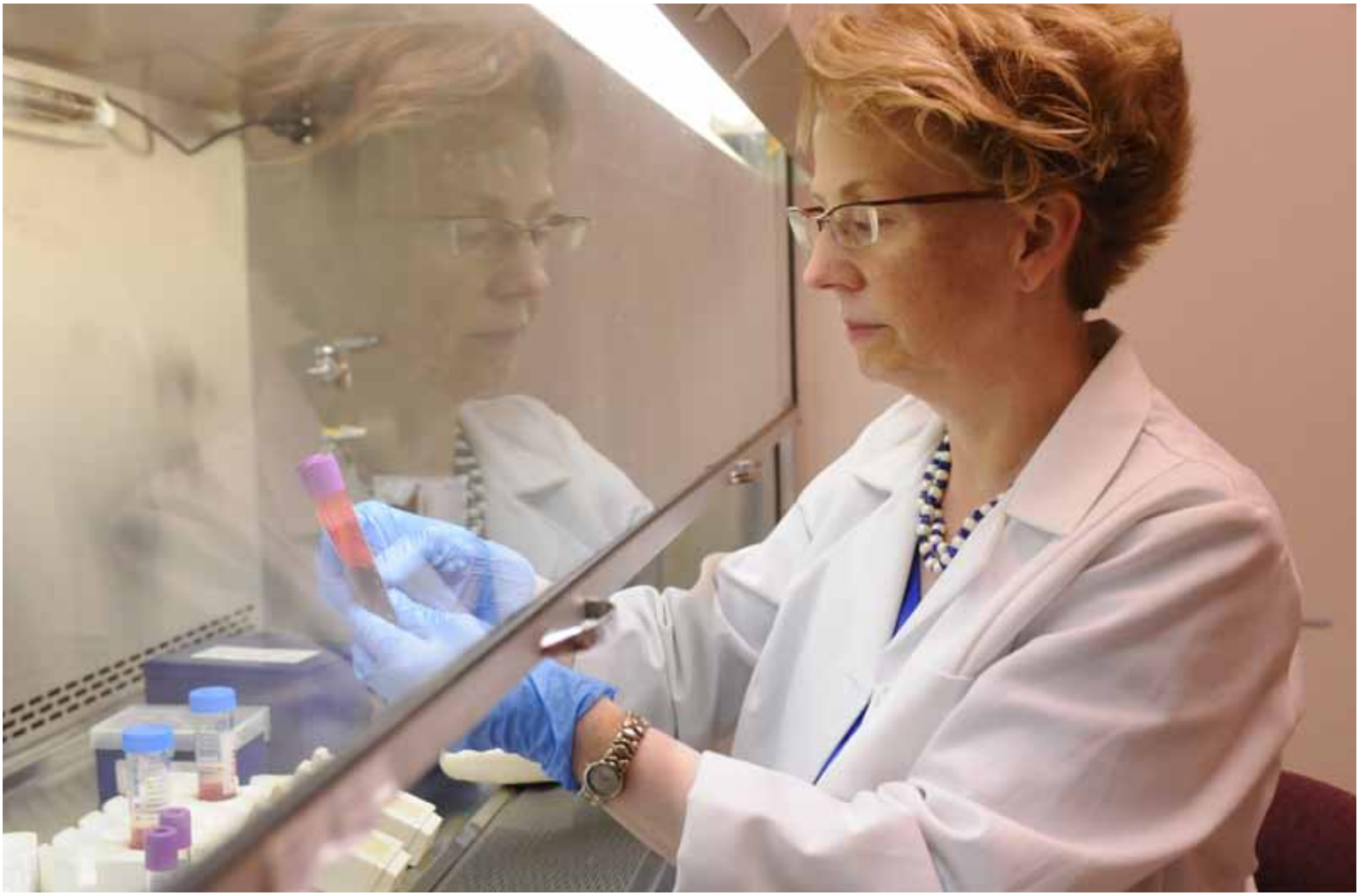
By the age of eight, Ben was able to monitor himself. Today, at age 17, he says that keeping on top of his condition is just "part of life". But when Susan, Ben and his step-father, Ted, learned about Dr. Denise Faustman's research towards a cure of type 1 diabetes at Mass General, they immediately took notice — and have been following the trial for BCG closely ever since. "There is so much research on diabetes going on. What's so attractive about Dr. Faustman's trial, however, is that it addresses the source of type 1 diabetes by eliminating the cells that cause the disease," says Susan, who met Dr. Faustman when Susan served on the board of the Juvenile Diabetes Research Foundation.

Ben recently returned from an internship in Dar es Salaam, Tanzania, where he worked in a diabetes clinic, assisting a physician who treats adults and children with type 1 diabetes. There, the patients "get a fraction of the insulin and monitoring supplies they need to keep their diabetes under control — it is so much less than what I get as a patient in the U.S.," he says. As a result, average life expectancy for diabetics in Africa is far lower than it is in America.

The experience made Ben feel lucky to have received the care he has, he says, but it also convinced him how important a cure — of the kind Dr. Faustman is pursuing — would be, especially in developing countries like Tanzania where the lack of access to insulin makes the disease more immediately life-threatening.

Faustman Lab in the News!

U.S. News and World Report has included Dr. Faustman in a recent feature entitled, "Pioneers of Medical Progress" (August 2009). Dr. Faustman is honored to be included among the 14 research-scientists described in the article as "cutting-edge researchers".



The Nuts and Bolts of Phase II of the Cure Diabetes Now Clinical Trial

The Cure Diabetes Now Phase I results are likely to be published in early 2010. Our goal is to initiate the three-year, Phase II program without delay. We want to share with you some of the steps we will take to begin the next, exciting phase of testing the BCG therapy when we have funding.

Step 1: Set Up the FDA Regulatory Team

A critical aspect of Phase II will be to hire experts in vaccine drug development to ensure that the trial complies with Federal Drug Administration (FDA) procedures. The team of experts will design a trial that fits with regulatory constraints specifically dictated by the FDA branch that regulates vaccines. In addition, the team will help to do all the necessary paperwork from the viewpoint of the FDA proposals highly regulated process. Therefore, we will need to assemble a highly specialized team of professionals who have had success with vaccine development and the complex regulatory processes. They will assist Mass General in making presentations to the FDA and will serve to maintain data integrity in reporting and follow

regulatory and manufacturing processes to proceed in unison and in time-efficient ways.

Step 2: Set Up Manufacturing of BCG

For Phase II, we will need to re-package or manufacture BCG so it comes to the clinic in small vials that represent one easy dose per vial. Currently for Phase I, Mass General pharmacists take large bottles of high-dose BCG and then dilute the drug to create one dose and load that dose into a syringe. Due to the increased number of patients who will be enrolled in Phase II, we will need to manage the dosing in a more formalized process. In addition, the FDA will likely require that the drug be packaged and manufactured in the same way it would potentially be distributed to the public. We will also need to establish state-of-the-art manufacturing processes that meet the highest standards. BCG has been around for so many years that the current manufacturing process will not be approved by the FDA for a new indication. Setting up BCG manufacturing is a critical step in making every piece of data we obtain from human experimentation with BCG count in Phase II.

Step 3: Set Up Manufacturing Oversight

The FDA will have strict requirements for the manufacturing process that include rigorous documentation of that process. Once the contracts for manufacturing and packaging BCG for the new purpose of treating type 1 diabetes are established, we will hire our own personnel to perform daily to weekly inspections of the manufacturing process. These inspections will ensure that the product manufacturing process is tightly controlled and meets FDA standards.

Step 4: Hire Director of Regulatory Operations

The director of regulatory operations will oversee the regulatory details of the trial. This person will make sure the clinical documentation of the trial meets the recordkeeping standards that are necessary for submission to the FDA at all stages of clinical testing.

Step 5: Design Phase II Clinical Trial

For Phase II, we will design a trial that is able to detect BCG's effect on established diabetic patients — in particular, the best dose and timing of drug administration. How we design Phase II will be dictated in part by the data in Phase I and also by input from the FDA, our advisors and the clinical trial teams at MGH. The FDA will likely request that a larger number of patients (known as "sample size") be enrolled in the trial and that we perform long-term follow-up with trial participants. Enrolling/testing large numbers of patients and then following their status for a long time can make trials very costly. Therefore, we will work with biostatisticians to design a trial that is as streamlined as possible so that we enroll enough patients to achieve FDA standards while ensuring that our sample size has the possibility to show meaningful results in terms of the effects BCG has on diabetes.

Step 6: Establish a Data Safety Monitoring Board

For Phase II testing, we will assemble a Data Safety Monitoring Board (DSMB). This group will have access to data from the clinical operations manager and will analyze the data for both positive and negative side effects that might require early clinical reporting. The DSMB will need to have expertise in vaccine trial design and vaccine therapies seeking regulatory approval.

Step 7: Establish Large-Scale, Automated Blood Handling Process

The Phase II trial will include many more patients than the Phase I trial. Therefore, the Faustman Immunobiology Laboratory will need to have the capability to handle more blood specimens and will need to expand its engineering efforts and platforms to be ready to process the increased number of patient blood samples. Our staff of engineers and bench scientists will require at least six months of training prior to the arrival of the first clinical samples in Phase II. The automated blood handling process yields highly pure T-cells from human blood. Some of these pure T-cells are the autoreactive T-cells that cause diabetes. The automated blood-handling process allows us to monitor, in an individual patient, the burden of autoreactive T-cells that are predicted to decrease with optimized BCG therapy.

BCG Therapy At Work

Many people have asked us how the BCG therapy works to eliminate type 1 diabetes. Below is an explanation of how the BCG therapy finds the "bad" disease-causing cells and eliminates them in type 1 diabetic blood.

How are autoreactive T-cells detected?

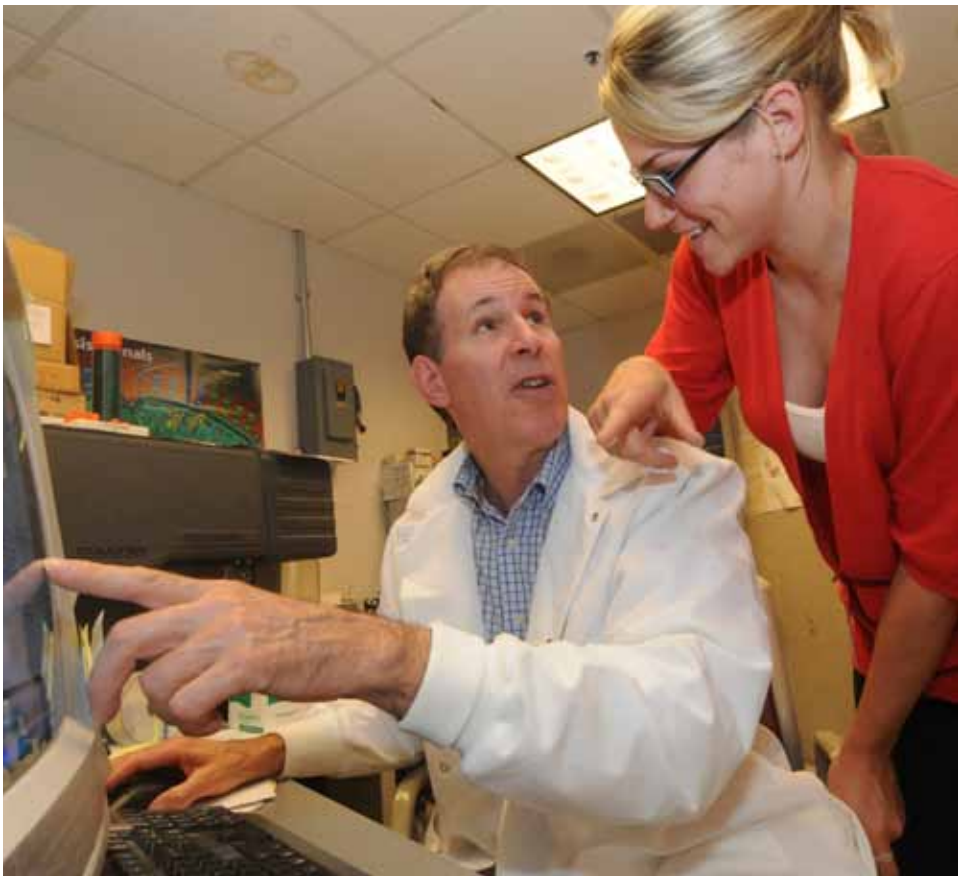
There are many different technologies to detect the "bad" T-cells of autoimmunity. The diabetes research community can, under certain circumstances, identify individual "bad" T-cells with a technology that uses proteins called "tetramers". These protein structures, which can be made to glow, bind to the "bad" T-cells and can then be detected using a device called a "flow cytometer," which allows us to visualize and count the glowing particles.

How does BCG or TNF kill only the "bad" T-cells?

The process of eliminating only the "bad" T-cells has evolved over two decades and is based on basic science work performed in the Faustman Lab and elsewhere. About 20 years ago, Drs. Faustman and David Nathan, director of the MGH Diabetes Center, set up one of the first clinical trials on the U.S. east coast at Mass General to transplant islets. During this transplantation work, the data revealed that the transplanted islet cells were killed by a recurrence of the disease. This suggested the type 1 disease was still active years after the diagnosis.

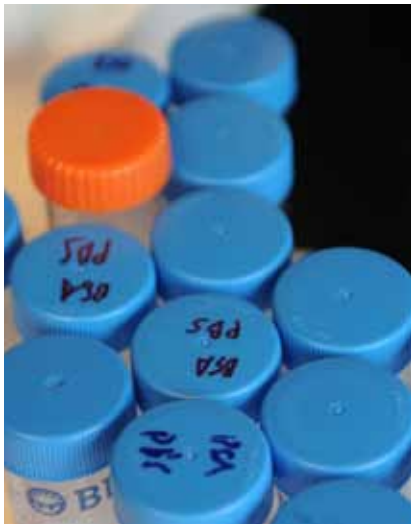
Therefore, we designed a research program to not only identify "bad" T-cells in humans with diabetes but to devise ways to specifically kill those cells. One sub-population of these cells has a cellular defect that makes these cells susceptible to death in the presence of elevated levels of TNF. This discovery, first in mice and then in humans, set the stage for us to design targeted ways to kill the disease-causing cells while sparing the healthy cells. The goal was to find a treatment that would interfere with the protein pathways of the disease-causing T-cells, but not the normal T-cells. Identifying differences in the proteins between the "bad" T-cells and the normal T-cells of people with type 1 diabetes allowed us to design an intervention to kill the cells that cause disease.

Cure Diabetes Now is a rapid clinical translation program designed to safely test this therapeutic concept in humans with type 1 diabetes. We are using BCG, a generic drug that is inexpensive to produce and has a proven safety record, to cause the patient's own body to temporarily produce elevated amounts of TNF in the hopes that this will eliminate one population of disease-causing cells in type 1 diabetes. In Phase II of the clinical trial, we will start the important process of testing the dose and frequency of drug administration to eliminate the disease in diabetic patients.



Tom Hewson

After living with type 1 diabetes for 73 years, Tom is ready for a cure.



At age 11, while attending summer camp on the Jersey Shore, Tom recalls developing an unquenchable thirst, a telltale sign something was wrong. Shortly thereafter he was diagnosed as a type 1 diabetic and has been insulin-dependent since 1936.

He recalls how scary it was at age 11 to learn that his life depended on daily injections and urine tests, a strict diet and management of all the encumbrances that came with the new life regimen. There were no disposable syringes or insulin pens in those days. It was necessary to sterilize a glass syringe and needle in boiling water before each use. Drops of urine were put in a test tube with water and a reagent, then heated to develop a color indicative of its sugar content.

Since Tom began taking insulin 73 years ago, he has benefited greatly from the many new device developments, delivery systems and new types of insulin. Glucose monitors have enabled patients to self-manage their diabetes more effectively. Now in his mid-80's, Tom is still active, swims almost daily, and follows a rigorous intensive therapy for his diabetes. He estimates he has had about 40,000 finger sticks (blood samples) and about 85,000 insulin injections over the years. In spite of his vigilance and diligence, however, he has had eye and heart complications and, from time to time, has suffered with temporarily disabling hypoglycemia.

"Diabetes has a bright side and a dark side," he says. "You can live a nearly normal lifestyle. However, not mastering the intricacies of your own self-treatment can be fatal. You must pay attention every hour of every day, but simultaneously think positive thoughts and live life to the fullest."

Tom adds, "Over the years, medical scientists have brought new understanding about the cause, care and possible cure for diabetes. Many research groups are active today pursuing different, promising approaches to a cure. As the possibility of a cure appears closer than ever at the Faustman Lab, I encourage everyone to support this important and promising research. Its success could bring enormous benefits to the American healthcare system and to millions of diabetics around the world."

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.faustmanlab.org and click on "Support"

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

MGH Development Office
Attn: Jocelyn Hoey
165 Cambridge St., Suite 600
Boston, MA 02114

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

How can I learn more about this research?

1. Please log onto our web site: www.faustmanlab.org
2. E-mail us at diabetestrial@partners.org
3. Call us at 617-726-4084

Thank you for joining us in the fight against diabetes.

Warmly,

Denise L. Faustman, MD, PhD