

Promising results of Phase I diabetes trial announced

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Promising results of the Phase I clinical trial of the generic drug BCG (bacillus Calmette-Guerin) to treat advanced type I diabetes were announced today at the American Diabetes Association scientific sessions in San Diego. A research team led by Denise Faustman, MD, PhD, director of the Massachusetts General Hospital (MGH) Immunobiology Laboratory is presenting two abstracts (No. 2240-PO and No. 0057-LB) – the first which describes the apparent reproduction in human patients of the mechanism that reversed type 1 diabetes in a mouse model and the second proposing that lack of a key part of that mechanism may explain why recent trials of an antibody-based diabetes therapy were not successful. The Iacocca Foundation has been the primary supporter of this work.

"We found that even low doses of BCG could transiently reverse type 1 [diabetes](#) in human patients," Faustman says. "One of the key components of this study was our development of a way to measure the death of the autoreactive T cells that destroy the ability of the pancreas to produce insulin. Not only did we observe and measure the death of these self-targeting immune cells, but we also saw evidence of restoration of insulin production even in patients who've had type 1 diabetes for more than a decade."

A [generic drug](#) with 90 years of safety data, BCG is currently approved by the U.S. FDA for vaccination against tuberculosis and for the treatment of bladder cancer. BCG is known to elevate levels of the immune modulator tumor necrosis factor (TNF), which previous work in

Faustman's lab showed can temporarily eliminate the abnormal white blood cells responsible for type 1 diabetes in both humans and mice. The Phase I double-blinded clinical trial enrolled six long-term type 1 diabetes patients, diagnosed for an average of 15 years. The participants were randomly assigned to receive two injections of either BCG or a placebo spaced four weeks apart.

Blood samples from the participants with diabetes were also compared with samples from six nondiabetic participants and with reference samples from 75 additional individuals with diabetes and 15 without. Four measurements were analyzed for each sample – levels of autoreactive T cells; levels of the regulatory T cells that help control the immune response; levels of GAD autoantibodies, which are a marker of pancreas activity; and levels of C-peptide, a marker of insulin secretion.

Most participants treated with BCG showed increases in both the death of autoreactive T cells and in levels of the protective regulatory T cells. A temporary but statistically significant elevation in C-peptide levels, suggesting a restoration of insulin production, was also observed in the BCG-treated patients. Unexpectedly, the same responses were seen in one of the placebo-treated patients who, after enrolling in the study, coincidentally developed infection with the Epstein-Barr virus, which is known to induce expression of TNF.

"These data support our hypothesis that BCG may benefit human type 1 diabetes by boosting TNF levels," says Faustman. "The data from the EBV-infected patient show that induction of TNF expression from diverse sources may have been a missing component in two recent, unsuccessful Phase III trials that tested antibodies against the immune molecule CD3 in type 1 diabetes patients. Those trials were specifically designed to avoid reactivating any latent EBV infection, but blocking EBV activation could also block TNF expression."

In addition to providing major funding for the now-completed Phase I trial, the Iacocca Foundation has committed to a leadership role in the Phase II clinical trial that was initiated at MGH earlier this month. Currently \$8.5 million has been raised out of a total of \$25 million needed to conduct the Phase II study over the next three years. Additional information about the clinical trial, including information for potential supporters, is available at <http://www.faustmanlab.org>. Individuals interested in participating in the Phase II study and future trials should e-mail DiabetesTrial@partners.org.

"These results are very meaningful to the Iacocca Family," says Kathryn Iacocca Hentz, president of the Iacocca Foundation. "We have supported this work since the mouse studies that first showed the reversal of longstanding diabetes. The Iacocca Foundation has made a significant gift to the MGH to help start the Phase II trial, and we hope that others will join us,"

Lee A. Iacocca, founder of the Iacocca Foundation, adds, "We are hopeful that this continued research will lead to an effective and inexpensive therapy for people with the disease. I made a commitment to my late wife that I would work to find a cure for type 1 diabetes – and I, along with my daughters, continue to keep that promise."

Provided by Massachusetts General Hospital

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