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### **Mass. General Hospital, Iacocca Foundation announce promising results of Phase I diabetes trial**

***Generic drug reproduces mechanism that reversed diabetes in mice, Phase II trial now underway***

SAN DIEGO – Promising results from the Phase I clinical trial of the generic drug BCG (bacillus Calmette-Guérin) to treat advanced type 1 diabetes were announced today at the American Diabetes Association's 71<sup>st</sup> Scientific Sessions in San Diego. A research team led by Denise Faustman, MD, PhD, director of the Massachusetts General Hospital (MGH) Immunobiology Laboratory presented two abstracts – one describing the apparent reproduction in human patients of the mechanism that reversed type 1 diabetes in a mouse model and another proposing that lack of that mechanism may explain why recent trials of an antibody-based diabetes therapy were not successful. The Iacocca Foundation has been a major 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 the restoration of insulin production in patients who had type 1 diabetes for more than a decade."

A generic drug with ninety 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 patients with long-term type 1 diabetes, who had been diagnosed an average of 15 years prior to enrollment. The participants were randomly assigned to receive two injections of either BCG or a placebo. Injections were 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 (Tregs) that help control the immune response, GAD autoantibodies, a marker of pancreas activity and levels of C-peptide, a marker of restored 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 an 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 also shows that induction of TNF 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 designed to specifically avoid reactivating any latent EBV infection. This could potentially block TNF expression and might have affected drug efficacy."

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. 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 can e-mail [DiabetesTrial@partners.org](mailto:DiabetesTrial@partners.org).

"These results are very meaningful to the Iacocca Family. 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," said Kathryn Iacocca Hentz, president of the Iacocca Foundation.

"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," said Lee A. Iacocca, founder of the Iacocca Foundation.

#### **About Massachusetts General Hospital**

Celebrating the 200<sup>th</sup> anniversary of its founding in 1811, Massachusetts General Hospital ([www.massgeneral.org](http://www.massgeneral.org)) is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of nearly \$700 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, reproductive biology, regenerative medicine, reproductive biology, systems biology, transplantation biology and photomedicine.

#### **About the Iacocca Foundation**

Lee A. Iacocca established the Iacocca Foundation in 1984 in honor of his late wife, Mary K. Iacocca, who died from complications of type 1 diabetes. Since 1984, the Iacocca Foundation has given more than \$30 million to diabetes research. More information is available at [www.iacoccafoundation.org](http://www.iacoccafoundation.org).

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