

Updates



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

from the Faustman Laboratory at Massachusetts General Hospital

Fall 2022

A Note from Dr. Faustman

Another year is almost in the books, and we are very excited about what we were able to do and where we are going. As always, the participants in our trials have been amazing. Despite the ongoing challenges of the pandemic, they make their appointments. The five-year Phase II trial is approaching completion. This year, we also were able to launch a multi-center pediatric trial. Across all of the trials, we now have almost 200 patients who have received at least two doses of BCG.

Like many aspects of our lives, in-person conferences have started to return. At the annual American Diabetes Association meeting in New Orleans, we presented major updates on the trial as well as new data on how BCG modifies key components of the immune system.

In August of this year, we published results from our COVID-19 study. When the



pandemic hit in early 2020, the FDA gave us permission to analyze the ongoing Phase II trial to see if BCG vaccinations protected from infection and illness related to COVID-19. The results, which were covered by the *Wall Street Journal* and *New York Times*, showed that BCG was very effective against COVID-19 as well as a range of common infections.

Clinical trials are long and expensive journeys, but the reward is worth the effort. We have not lost sight of the goal to apply to the FDA to

treat type 1 diabetes with BCG. This would be the first FDA approved immune intervention to alter the underlying condition of type 1 diabetes in people living with existing disease.

We hope you will help us move this important work forward. Please contact us if you have any questions, diabetestrial@partners.org.

Sincerely,


Denise L. Faustman, MD, PhD

BCG Clinical Trials to Reverse Type 1 Diabetes

The Phase II trial is one year closer to completion. All 150 BCG-treated and placebo patients in the trial have been followed for more than four years. The trial will not read out until the last patient enrolled reaches five years, which should happen some time in 2023.

In addition to the Phase II trial, other trials are underway. We have now had more than 200 participants with type 1 diabetes vaccinated with multiple doses of BCG.

	Total No. Subjects	BCG-Treated (n)	Control/Placebo (n)	Double Blinded/Open-Label	Time Followed/Duration
Phase I + Crossover	52	9	43	Randomized, Double-Blinded	5 or 10 y/10 y
Radiology Study	6	6	0	Open-Label	~3 y/5 y
Phase II Study	150	100	50	Randomized, Double-Blinded	~3-4 y/5 y
Transition Study	29	29	0	Open-Label	2 y/5 y
Phase II Crossover	6	NA	NA	Randomized, Double-Blinded	2 y/5 y
Phase II Pediatric Study	150	75	75	Randomized, Double-Blinded	--

New Pediatric Trial

In March, the Lab received approval to test BCG in children with type 1 diabetes. The new, 150-subject, multicenter trial, "Repeat BCG Vaccinations for the Treatment of Pediatric Type 1 Diabetes," is already almost 50% enrolled. This is a long-anticipated and exciting development for the families who have supported us for so many years.

"BCG is a very old vaccine, but recently has been at the center of an explosion of clinical trial research showing benefit in multiple autoimmune diseases and diverse infectious diseases. We know the timing and strain of BCG vaccination is pivotal to outcomes. This is the first time multiple doses of a highly efficacious strain of BCG have been given to adolescents with at least 2 years of type 1 diabetes," says Denise Faustman, MD, PhD, director of the Immunobiology Laboratory at Massachusetts General Hospital and co-investigator on the study.

Research Updates

The 2022 American Diabetes Association (ADA) Scientific Sessions were held in June in New Orleans. One of our key findings in 2022, which was presented at the meeting and also published in the journal *Science Advances*, is a new understanding of how BCG may alter the T cell defects common in people with type 1 diabetes. We also shared clinical trial updates and results of a retrospective study of patients with type 1 diabetes who underwent BCG therapy for bladder cancer. That study showed a reduction in HbA1c values similar to the patients in the Phase I trials at MGH.

Underlying T Cell Receptor Methylation Defects in Type 1 Diabetes Associated with Quantitative Defects
 S. Tashkhanji, W.M. Kühtreiber, A.H. Lee, A. Arastarkhova, H.F. Dias, N. Ng, C. Sherr, D. Scheffey, & D.L. Faustman
 MASSACHUSETTS GENERAL HOSPITAL & HARVARD MEDICAL SCHOOL, BOSTON, MA, USA; ADAPTIVE BIOTECHNOLOGIES, SEATTLE, WA, USA

2022 Update on the BCG Clinical Trial Programs in Advanced Type 1 Diabetes
 W.M. Kühtreiber, H.F. Dias, E. Hostetter, A.H. Lee, N. Ng, G. Wolfe, A. Arastarkhova, J. Bradley, H. Zheng, & D.L. Faustman
 MASSACHUSETTS GENERAL HOSPITAL & HARVARD MEDICAL SCHOOL, BOSTON, MA, USA

Retrospective Study Effects of BCG Bladder Cancer Treatment on HbA1c

Introduction
 The T cell receptor (TCR) is a central regulator of T cell activation. Efficient structural organization and density of TCRCD3 co-receptor is essential for the development and function of T cells. T cell receptor defects are associated with autoimmunity, suggesting an underlying defect in TCR activation. Here, we describe quantitative defects in clusters for altered TCR activation at the level of the TCR-CD3 co-receptor.

Methods
 We compared TCR densities on CD4+ T cells from subjects with type 1 diabetes (T1D) (n=80) and age-matched controls (n=20). We also investigated quantitative defects in genes of the TCRCD3 co-receptor by genotyping methylation in T1D.

Results
 Significant quantitative defects in TCR and CD3 proteins are observed in CD4+ T cells of T1D vs controls (Fig. 1). TCR densities of T1D subjects were significantly lower than controls (p < 0.001). The TCRCD3 co-receptor was significantly altered in T1D vs controls (p < 0.001). In T1D, all CD3 genes except CD3E had hypermethylated patterns, confirming BCG therapy. The percentage CD4+ T cells in the CD4+ T cell population was reduced in T1D vs controls (p < 0.05), as was the ratio of CD4+ T cells (n=20).

Conclusion
 The BCG vaccine has two key beneficial effects as it relates to T1D:
 - BCG corrects underlying epigenetic glycosylation defects in the white blood cells (WBC) of subjects with T1D.
 - BCG-treated subjects become a major source of T1D remission. T1D remission is associated with BCG treatment and lowest HbA1c in 10 years.
 - BCG reduces the underlying hyperglycemia observed in the HbA1c of those with T1D, with rates similar to those.
 - Orally (over 3 years) BCG induces patient regulatory T cells (Treg) to suppress autoimmunity.

Current Clinical Trial Updates
 An 8-year, randomized clinical trial in adults with longstanding T1D showed BCG vaccination reduced long-term glycosylation in glycosylated hemoglobin (HbA1c) in adults with longstanding disease (vs placebo (p=0.001), the reduction of blood sugar leading to reduction of vascular glycosylation in WBC, which reduces long-term sugar metabolism.

Conclusion
 BCG vaccine therapy may provide a safe and affordable medical intervention in long-standing autoimmune diseases, several clinical trials are underway. In longstanding T1D, the primary mechanism for BCG vaccine efficacy is correction of underlying epigenetic glycosylation in WBC. BCG also gradually reduces hyperglycemia and improves HbA1c. BCG also gradually reduces hyperglycemia. Early patients with very longstanding T1D who received BCG vaccine showed a lower overall glycosylation of HbA1c, but this is not seen in those with T1D

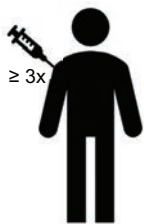
BCG and COVID-19

Early in the pandemic, researchers began to report seeing a trend of lower infection rates and illness from COVID-19 in countries with BCG vaccination programs. This did not come as a huge surprise, as researchers have long known that BCG is protective against respiratory infections in children. MGH received permission from the FDA to do a double-blinded analysis of the ongoing type 1 diabetes trial to see if the participants in the trial benefited from the BCG vaccinations they received before the pandemic hit. The study, which was covered in the *Wall Street Journal* and *The New York Times*, showed that 12.5% of placebo-treated individuals and 1% of BCG-treated individuals met criteria for confirmed COVID-19, yielding a vaccine effectiveness rate of 92%. BCG's effectiveness did not appear to be impacted by differences in COVID-19 variants.

“MGH’s COVID-19 data set is unique and exciting because the patients were all vaccinated with multiple doses of BCG prior to the onset of the epidemic. Prior to the trial they had no known exposure to tuberculosis or prior BCG vaccination. This eliminates the major confounding factors that have limited other trials. The results support the idea that BCG needs time to have a clinical effect, but its effects may then be very lasting and durable,” says Hazel Dockrell, London School of Hygiene & Tropical Medicine, an infectious diseases expert who was not officially involved in the study.

REPEAT BCG VACCINATIONS IN ESTABLISHED TYPE 1 DIABETICS

- ≥3 BCG (n=96) or placebo injections (n=48) before COVID-19 pandemic January 2020



BCG VACCINES FOR COVID-19 & INFECTION PROTECTION

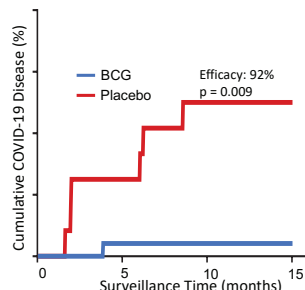
SYMPTOMS

- Direct patient reporting
- Bi-monthly surveys

COVID-19 TESTING

- COVID Antibodies
- PCR

	BCG	Placebo	Vaccine Efficacy	Posterior Probability (Vaccine Efficacy)
COVID-19 confirmed by Point of Care and SARS-CoV-2 Antibodies	1.0%	12.5%	92%	0.99
COVID-19 confirmed by PCR	0.0%	10.4%	100%	0.99



About BCG

BCG is a live, attenuated bacterial vaccine derived from *Mycobacterium bovis*. Discovered over 100 years ago at the Pasteur Institute in Paris, BCG has historically been given to protect against tuberculosis. In the history of medicine, it is considered to be extremely safe. BCG is on the World Health Organization’s Model List of Essential Medicines for adults and children and is given to roughly 100 million children per year globally. Over the last twenty years, a growing group of researchers and clinicians have begun to explore the “off-target” effects of BCG for diseases including type 1 diabetes, multiple sclerosis, allergy, fibromyalgia, Alzheimer’s disease and respiratory infections such as COVID-19.



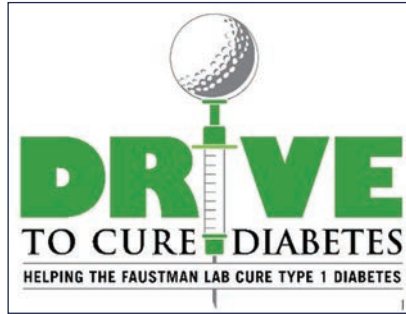
5th International BCG Working Group

In October, we convened the “Off-Target Effects of BCG Conference” in Alexandria, VA. This was our 5th international conference held since 2013 and the biggest to date. Over thirty researchers, payers and policy experts from around the globe convened to share updates on BCG clinical trials in type 1 diabetes, multiple sclerosis, COVID-19 and Alzheimer’s disease. For more information on the conference and the exciting research underway, visit www.bcgworkinggroup.org.

FUNDRAISING

Events Come Back

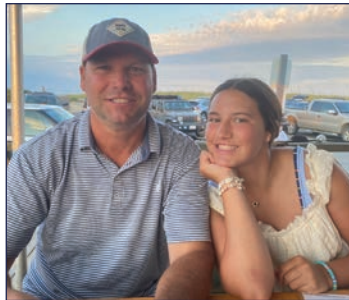
COVID-19 changed how many events were held, but that did not stop inspired donors from organizing golf tournaments, mountain climbs and other events. If you are interested in hosting an event, please contact the lab directly.



Donor Spotlight, Jana Brinkhouse

How has type 1 diabetes impacted your family?

My daughter Karolina was diagnosed at the age of 2.5. She comes from a family with what appears to be a genetic predisposition toward type 1 diabetes. Chris, her father, was diagnosed at the age of 12. Two of his siblings have it as well. So T1D has had a generational impact on our family.



How did you learn about the BCG clinical trials and why are you so supportive?

We learned about the trials through a family friend. We were excited by the idea of reversing the disease, not managing the symptoms and that BCG has a proven safety record and would not require immunosuppression.

Tell us about some of your events.

Our events are inspired by all the children who suffer from T1D. We wanted to involve children and give them a chance to have fun in the process with a type of family-centric process where they could learn about T1D as well. Our dance party model was very successful. Our last event, pre-COVID in 2019, was attended by 1000 people.

Any advice to families looking to get involved?

Try to come up with a community-wide event and tell your story, make it personal, and truly describe a day in the life of a person with T1D. As we know, there is confusion as to the different types of diabetes and dispelling these myths is crucial to raising money and ultimately finding a cure.

What's next for you?

Karolina has many things planned for 2023. Having recently been named an ambassador for the student-athlete program at Wears Woody, she will tell her story about the challenges of having T1D while being an athlete, all while raising funds for diabetes. She is also starting a T1D club at her high school, with the charity of choice being the Faustman Lab. A possible return of the successful dance party model is also in the works!

How You Can Help

Please consider making a tax-deductible donation to this type 1 diabetes research program. Every gift makes a difference.

1. To make a secure online donation, visit www.faustmanlab.org and click on "Donate."
2. You may make a gift by check (payable to "Massachusetts General Hospital") and mail it to:

*Diabetes Clinical Trial
c/o Dr. Denise Faustman
Immunobiology Laboratory
MGH - East
Building 149, 13th Street, CNY-3601
Charlestown, MA 02129*

On the memo line, please write:
"Faustman T1D research."

Thank you for joining us in the fight against diabetes!

For more information, visit www.faustmanlab.org or email DiabetesTrial@partners.org.

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