Updates

MASSACHUSETTS GENERAL HOSPITAL

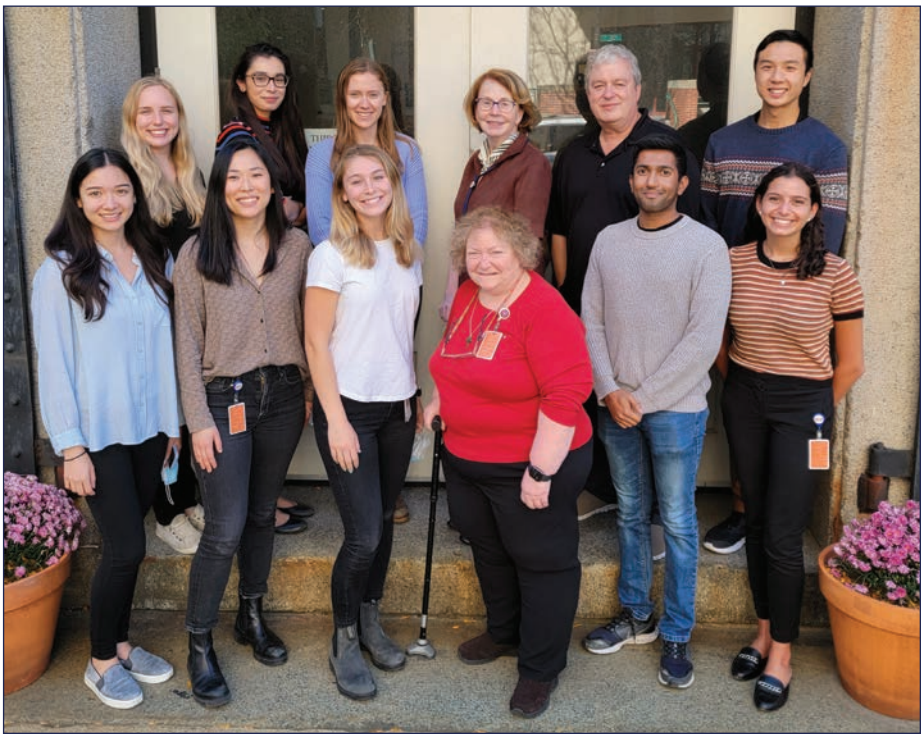
HARVARD MEDICAL SCHOOL

from the Faustman Laboratory at Massachusetts General Hospital

Fall 2021

A Note from Dr. Faustman

As you can imagine, 2021 certainly kept us on our toes. The pandemic came, went and came back again. Despite it all, the lab kept going and patients in the diabetes trials came for their trial appointments. We continue to follow the patients in the Phase II trials. We are also prepared to launch the pediatric trial we have fought so long to start. Not including the pediatric trial, we are nearing 250 trial participants enrolled, of which 143 have received at least two doses of BCG.



The data supporting BCG continues to grow. The Annual Scientific Sessions of the American Diabetes Association were virtual this year, but our presentation was well received and highlighted important new data on the role age of onset plays in BCG therapy and how BCG alters the regulatory cells in the immune system in type 1 diabetes.

Clinical trials are long and expensive journeys, but the reward is worth the effort. A safe and affordable intervention like BCG has the potential to fundamentally alter how we treat and pay for type 1 diabetes.

The need for a treatment that reverses established type 1 diabetes has never been greater. The prevalence and economic burden are growing each year. We hope you will help us move this important work forward. Please contact us with any questions, diabetestrial@partners.org.

Sincerely,

Denise L. Faustman, MD, PhD

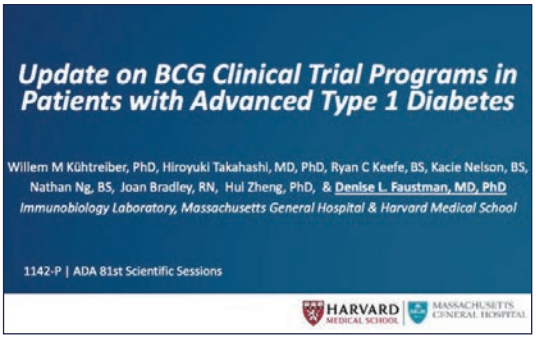
New Data in 2021

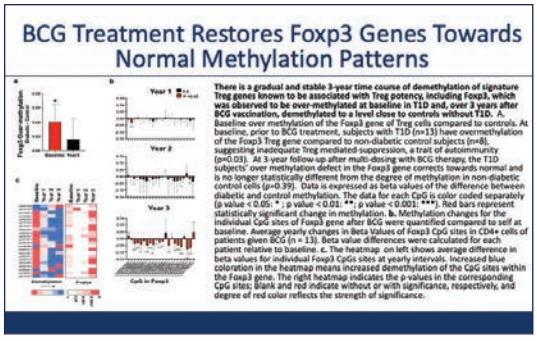
In 2021, we published and presented new data that helps increase our understanding of how BCG changes glucose metabolism and interacts with the immune system. These results include new data on open label patients that have been followed for several years and expands on the results from the Phase 1 trial.

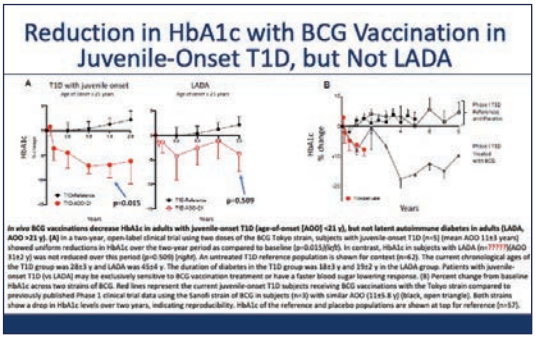
- **BCG therapy is associated with long-term, durable induction of Treg signature genes by desirable gene modulations**
  Multi-dose BCG vaccinations result in systemic long-term induction of T cells that help to quiet the immune system, the Treg cells. In type 1 diabetes, less potent Treg cells contribute to the underlying autoimmune disease. The clinical time course of BCG-related improvements (2–3 years post-vaccination) correlates with the slow Treg induction through gene changes. This was manifest by a general pattern of turning on key signature genes of an immunosuppressive Treg cell. In autoimmunity, this represents a restoration of Treg biology to near normal expression levels thus demonstrating BCG microorganism synergy and a relatively simple albeit slow and steady approach to the restoration of Treg function in humans.
- **Glucose metabolic effects of BCG in diabetes**
  BCG vaccinations improve glycemic control in juvenile-onset type 1 diabetes (T1D), an effect driven, in part, by restored sugar transport in the white blood cells of diabetic people. In a pilot clinical trial, patients with T1D, but not latent-autoimmune diabetes of adults (LADA), exhibited lower blood sugars after multi-dose BCG. Using a glucose transport assay, white blood cells from T1D subjects showed improved sugar transport with BCG exposures; LADA subjects showed minimal BCG-induced sugar responsiveness.
- **Gene changes related to glucose metabolism in type 1 diabetes after BCG vaccinations: A vital role for KDM2B - Why is BCG so powerful in diabetes management?**
  Restored glucose transport with BCG is regulated by genes. This new study identified two genes (KDM2B and DDIT4) as genes controlling BCG-driven facilitated and restored glucose transport, respectively. The BCG effect at the gene level was confirmed by looking for both improved/restored proteins and white blood cell function.

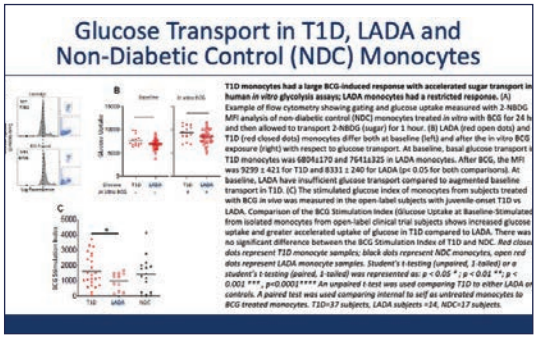
Updates at the ADA

The 2021 American Diabetes Association meeting was virtual, but the lab was able to present several key updates including new data on how BCG treatment restores Foxp3 genes, associated with regulatory T cells (Tregs), towards normal DNA patterns. Poor Tregs have been identified as playing a key role in the progression of type 1 diabetes.









Type 1 Diabetes Clinical Trials

The Phase II trial continues to progress. All 150 patients have been followed for more than three years. The trial will not read out until the last patient enrolled reaches five years of follow up, but the lab is not just waiting around. The Phase II trial is one of several ongoing studies in the lab, including a soon-to-be-launched multi-center pediatric trial. At the end of the Phase II trial, all of the patients will have been followed for five years for key biomarkers of type 1 diabetes including HbA1c, c-peptide and insulin use.

Patient Enrollment & Follow-Up Timelines

To date, 143 patients with longstanding T1D have received at least two doses of the BCG vaccine

Trial	Total No. Subjects	BCG-Treated* (n)	Control/Placebo (n)	Double Blinded/ Open-Label	Years Followed
Phase I	52	9	43	Randomized, Double-Blinded	5 or 10 years
Radiology Study	6	6	0	Open-Label	>2 years
Phase I Crossover	3	3	0	Open-Label	>3 years
Phase II	150	100	50	Randomized, Double-Blinded	~3-4 years
Transition study	25	25	0	Open-Label	<1 year
Total	236	143	93	--	--

*All BCG-treated patients have received at least two doses.

Early next year we will be starting a 150 patient multi-center pediatric trial in adolescents with diabetes. The timing could not be more pressing. A study in the *American Journal of Managed Care* published in September 2021 found the estimated T1D prevalence per 1000 youths aged 19 or younger increased by 45% over the last 16 years.

The Economics of Type 1 Diabetes.

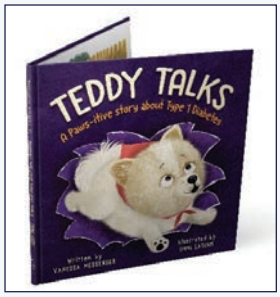
For many living with type 1 diabetes, the health impact is compounded by an enormous financial burden. Insulin remains an expensive drug and, for many uninsured, insulin rationing is a dangerous reality. Based on data from a large non-profit health plan, the average medical expenditures for a person with type 1 diabetes are roughly **$22,000/year** ($13,000 medical and $9,000 pharmacy) of which $14,500 can be attributed to type 1 diabetes.

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 and in the history of medicine is considered to be extremely safe, 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 effects of BCG for diseases including type 1 diabetes, multiple sclerosis, allergy, fibromyalgia, Alzheimer's and respiratory infections such as COVID-19. 2021 is the 100th anniversary of the first administration of BCG. In commemoration, the Institute Pasteur de Lille is organizing an international BCG conference. Dr. Faustman has been invited to speak about BCG and type 1 diabetes.

Teddy Talks

As we initiate pediatric trials, we are thrilled to partner with award-winning children's book author Vanessa Messenger on her new book, *Teddy Talks: A Paws-itive Story About Type 1 Diabetes,* which showcases type 1 diabetes through the eyes of a loved one by explaining the condition and management through a continuous glucose monitoring device in a fun and digestible way. A portion of proceeds from the sale of this book will benefit the BCG clinical trials at MGH.



FUNDRAISING

Events come back

COVID-19 changed where many events were held, but that did not stop inspired donors from organizing golf tournaments, mountain climbs and other events. We hope 2022 will have even more. If you are interested in hosting an event, please contact the lab directly.

The "Kiss the Sky" on the Pacific Crest Trail

Donor Spotlight, The Noble family

The Noble family has been one of the Lab's most ardent supporters. They recently told us a little of their story:

Why is your family climbing for a cure?

Our daughter Kate was just 16 months old when we learned that she had T1D. The doctors told us there was "no cure." That was January 2, 1992. Ten years later, driving past the High Sierra, I said I wanted to climb Mount Whitney and Kate suggested: "Why don't you do a hike-a-thon for diabetes?" We launched Kiss the Sky to Conquer Diabetes with a simple thought: "Keep climbing until we Conquer Diabetes!" That summer, I reached the summit of Mount Whitney.

How long have you been supporting the lab? How did you get started?

In 2004, KTS teamed up with The Iacocca Foundation's Join Lee Now initiative and have been climbing to support Dr. Faustman and her team's efforts to find a cure for diabetes ever since. The KTS teams have hiked hundreds of miles and reached the summits of dozens of peaks, including Mount Shasta and Mount Hood, and climbed in the Cordillera Real in Bolivia to raise funds to support clinical trials of BCG.

Can you tell us about the 2021 climb?

Nathan (who I met on the Rainier climb in 2004 and who has joined me on almost every KTS climb since) wanted for 2019 to do a "thru hike." So, in 2019, we had planned to do the 72 mile High Sierra Trail, but we got snowed out. We tried again in 2020, but COVID closed it. In 2021, we were trained, packed and ready to go when we were delayed by a COVID exposure. So, we changed plans while we waited and got permits to instead hike 50 miles along on the Pacific Crest Trail and John Muir Trail. We did have severe thunderstorms each afternoon and ended up revising plans again to push more each day, but the journey was magical and included a 12 mile stretch along the PCT/JMT that we both agreed was our favorite hike ever.

You have been at this a long time. What keeps you inspired?

We pledged 20 years ago to keep climbing until we conquered diabetes for Kate and friends we have made along the way, including a friend of Kate's sister Sarah at Middlebury College, Murphy ("Murph") Roberts, a great person and avid adventurer who experienced a seizure related to his T1D and passed away. We joined with the Roberts family to #senditformurph and #finishmurphsclimb. We keep climbing for Murph and with the hope that Kate and millions of others will finally have a day without T1D.

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.**

Find us on Facebook: **www.facebook.com/FaustmanLab**

Follow us on Twitter: **www.twitter.com/FaustmanLab**