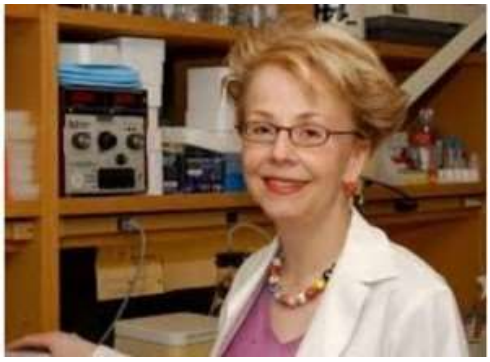
Part 1: Can a 100-Year-Old Vaccine Bring Us a Cure for Type 1?



Dr. Denise Faustman, M.D, Ph.D. Exclusive Interview from the Diabetes Symposium Seminar 2016 in Boston, featuring Steve Freed, Publisher, Diabetes in Control.

In part 1 of this exclusive interview, Dr. Faustman discusses her research and why an old tuberculosis vaccine may lead us to a cure for type 1.

Steve Freed: Dr. Denise Faustman. It's really exciting being able to talk with you because I've been keeping up on your research and it's really exciting, some of the things that you are doing. It's just an honor to have you here and to be able to question you about your current research. Maybe you can start off and tell us a little bit about yourself?

Dr. Faustman: It's a privilege to be here and thank you for inviting me. We do research work at Harvard Medical School at Mass General Hospital that's about type 1 diabetes. But probably remarkably, things we've worked on over the last 20 years are now in clinical trials, real clinical trials with FDA oversight to try to make a change in how we treat and view type 1 diabetes.

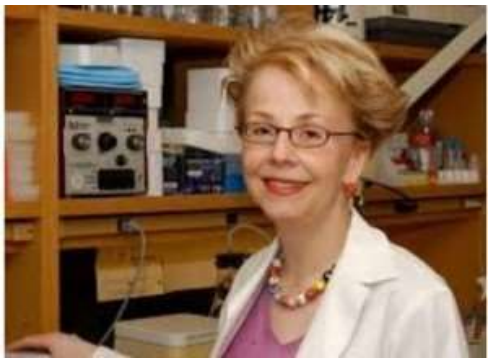
Steve Freed: I know you've done a lot of research when it comes to diabetes. A lot of things probably didn't pan out. But now you are working on something that's completely different and maybe you can kind of give us a general idea of why you're here, what you're presenting, and what's new as far as your research goes? We're talking about a vaccine, for the first time, [that] is for type 1 diabetes. So it's kind of exciting if it can come and happen. So maybe you can give us a brief overview?

Dr. Faustman: The question Steve poses is actually really relevant. The question is what didn't pan out? What didn't pan out 20 years ago is why we started on this new mission of doing something very different for type 1 diabetes. I was actually recruited to

Harvard Medical School to start the first islet transplant program; it was part of my thesis work. So that the East Coast could transplant islets like the Midwest, where I was from. We did transplants, at the Mass General Hospital, of islets. Some of the very early ones. Within 3 or 4 years, although there was great enthusiasm, we learned a very important lesson that people didn't want to hear, and that was, when we put the islets cells in people with type 1 diabetes, they were getting a kidney transplant the same time. The kidneys survive just fine, but over and over again the islets went bye-bye. They got destroyed and so that was a giant wake-up call to us that even after 15, 20, 30 years of type 1 diabetes the auto-reactive immune response was very brisk, very brutal, and typical immunosuppressant drugs were not going to take it away. So we've literally spent the last 20 years working on the nasty problem that has not yet been solved and that is: why is autoimmunity present and how, in people that have long standing autoimmunity, can we take it away and take it away permanently? Because no poor islet transplant has any chance of surviving unless we get rid of this underlying disease process. So this is not a casual project where a lot of people view the lab as 'eureka! I've got the solution.' This is a 20 year flog to work mostly on human blood and people with type 1 diabetes to find a solution. So the solution we're working on sounds all too simplistic, but it's very heavily mechanistic based. It's to bring forward a 100 year old vaccine called the BCG vaccine. So if you're a practicing internist in the United States, you probably scratch your head and you go well, I might have heard something about this vaccine. It's the most commonly used vaccine continuously in the last 100 years. It was developed over 100 years ago for the prevention of tuberculosis, but why we're using this vaccine is that when you get immunized with the vaccine, whether you're a type 1 diabetic or a control, it makes your immune response make a cytokine, a hormone called TNF. What we discovered over the last 100 years is in a multitude of autoimmune diseases you have too little TNF. TNF is your friend because TNF molds your immune system. It induces the good T-cells called Tregs and it kills the pathogenic T-cells. So this is about 10 years ago in mice, not that mice are humans right, in these N-stage diabetic mice. We published in 2001 that this was the first way and still remains the first way to permanently cure these mice. So that data was very promising. It was confirmed by global efforts and then the question came: how do we bring it forward into human clinical trials? So the exciting

thing right now is that we are actually in phase 2 clinical trials here in Boston in people with long-term type 1 diabetes, trying to use this vaccine to permanently reverse the disease. Although that's a pretty strong statement to make, it should be acknowledged that there's now over nine global clinical trials using BCG to reverse other forms of autoimmunity. In the United States, there will soon be trials in a lupus like disease called Sjögren's at the NIH, also using this vaccine, and there's very advanced trials in Italy using this vaccine to halt new onset multiple sclerosis. It's no longer just me, Steve, saying this vaccine holds great promise. It's now a global effort to try to really thoroughly test the efficacy of this vaccine to lower hemoglobin A1Cs.

Part 2: Defeating Autoimmunity



Dr. Denise Faustman, M.D, Ph.D. Exclusive Interview from the Diabetes Symposium Seminar 2016 in Boston, featuring Steve Freed, Publisher, Diabetes in Control.

In part 2 of this exclusive interview, Dr. Faustman discusses the challenges of dosing BCG correctly, and the difficulties of defeating autoimmunity in humans.

Steve Freed: Has this been tried before and failed?

Dr. Faustman: That's kind of interesting. So there was an early trial, 25 years ago in Israel, where they tried one dose of BCG at the onset of type 1 diabetes. They thought it worked, so that spawned three more trials to try to use one dose. Nobody knew the mechanism. In three subsequent trials in France, the U.S., and Canada, they said 'we don't see anything.' Those trials remind me of doing an early insulin trial, where you gave one dose of insulin and you looked a year later and you said insulin doesn't work, everybody died that had type 1 diabetes. Unless you know the mechanism and know how many doses and how much dosing, there is little hope. These trials globally are now all mechanistically based, looking for how we can dose the BCG correctly in order to get a permanent change in immune response. So we've learned a lot in those last 25 years and maybe those early Israeli studies were really correct but people didn't know that you needed more than one dose of insulin or you needed more than one dose of BCG.

Steve Freed: So you're going to be starting phase 2?

Dr. Faustman: We're actively in phase 2 right now. Phase 2 is a double blind placebo controlled trial using multi-dosing BCG in people with long term type 1 diabetes with no complications and a little bit of remaining C-peptide from the pancreas.

Steve Freed: What about for people in preventing diabetes?

Dr. Faustman: Well, that's good. We only have so much money, so if somebody wants to come in and donate for us to do prevention trials, we're ready to go. There is some prevention trial data that got published two years ago out of Turkey. That data showed one vaccine doesn't work in childhood from birth to age of 12. Two vaccines don't work but greater than two vaccines throughout childhood totally prevents the onset of type 1 diabetes. So prevention trials should probably start. But as you know those have to go 12 years. So it's money-permitting that those trials will be moving forward.

Steve Freed: How many different arms do you have in this trial?

Dr. Faustman: So, we have two arms. It's a 2 to 1 randomization, it's 150 cohorts. Our phase 1 trial used two doses four weeks apart. That long-term follow-up data will be published later on this year. This trial -- because we know from the multiple sclerosis trials, it takes a while for the permanent immune effects -- we're going to be dosing more, so we're going to be giving two doses like we did in phase 1 and a yearly booster for four more consecutive years.

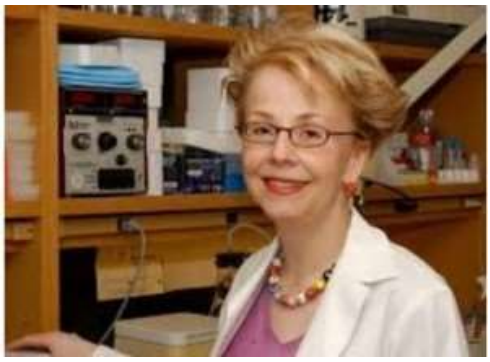
Steve Freed: Are you going to be presenting anything about this at the ADA?

Dr. Faustman: Yes. We have a presentation at the ADA about the global BCG trials and where there's increased efficacy in how people are designing those trials and what are the tough endpoints people are striving for? As you know, these are unique immune intervention trials. The first immune intervention trials working with people that have long standing Type 1 diabetes, not just new onsets.

Steve Freed: So, you have a lot of experience in different trials and working with diabetes. What are some other possibilities like regeneration of beta cells? We've seen a lot of information about that. I'm sure you're familiar with IGAP and where that's going. Where do you think that might take us?

Dr. Faustman: I think that everybody has to pursue their dream until we get to the golden gates and diabetes is cured. So we don't yet know. We meaning the global community, not just Denise Faustman here at Boston. We don't yet know the full regenerative capacity of the pancreas of a human. If you're an end-stage autoimmune diabetic mouse, we've got you covered. Those pancreases of mice, when we use BCG, fully regenerate. It's just beautiful. Huge islets. So there's no doubt. Everybody scientifically has proven it over and over again. When you give BCG to an end-stage naturally diabetic mouse, the regenerative process takes over and insulin is full reconstituted permanently for these animals. We're going to have to see as we go through these trials where now we're aiming to take away the autoimmune process, how much of the human pancreas after 20 years can regenerate? That's where, as alluded to by other groups, if we can really for the first time take away the autoimmune process, then allow combination therapy for those people who might have less regenerative capabilities than maybe people who are younger or have less burden of T-cells.

Part 3: Towards a Game-Changing Type 1 Diabetes Vaccine



Dr. Denise Faustman, M.D, Ph.D. Exclusive Interview from the Diabetes Symposium Seminar 2016 in Boston, featuring Steve Freed, Publisher, Diabetes in Control.

In part 3 of this exclusive interview, Dr. Faustman discusses how a cure based on the inexpensive BCG vaccine could permanently change type 1 treatment, and whether results could also apply to type 2.

Steve Freed: So, I know in the past you've been researching trying to find the T-cells that cause the autoimmune disease specifically for diabetes. Then if you could just keep the bucket half full.

Dr. Faustman: Tip the balance.

Steve Freed: Where does that stand in all this?

Dr. Faustman: So, one of the surprising things about the phase 1 clinical trial data was after we gave each dose of BCG, the blood was filled with dead autoreactive T-cells. These are people that are 15-20 years out from disease. So what that taught us was one, BCG was killing autoreactive cells, but it also taught us that people with long-standing type 1 diabetes have huge reservoirs of autoreactive T-cells. That's probably because the pancreas is continually regenerating and getting bumped off by these bad T-cells. We have quite a large repertoire, numbers wise, of autoreactive T-cells even with long standing disease that need to be eliminated. So the dosing of BCG will become very important to get that balance and get rid of the majority of those cells.

Steve Freed: So, what about the time frame? When do you expect to have phase 2 completed? Obviously you can't talk about phase 3.

Dr. Faustman: So, there will be two sets of clinical trial data coming. The next set of data that you'll hear about, probably in the next year or so is that we went back to now follow our phase 1 subjects long-term. The data in multiple sclerosis says that the long-term changes in immune response take a while, at least with limited BCG dosing to cause permanent reversal of multiple sclerosis. So that data will probably come out the next year or so. Currently, as you know, we're doing a phase 2 trial, we're actively enrolling, so we're at least 4 years off from data from that trial. Diabetes trials have traditionally not been able to budge for immune interventions, hemoglobin A1C, but that is the most respected outcome, is the outcome every type 1 diabetic wants. Most type 1 diabetics could care less about what their C-peptide levels are this week or next week. They care about, 'how good is my blood sugar control?' So it should probably give you a little clue that if we pick such a hard, ominous endpoint, we have great confidence that we will help to replicate what we are seeing long-term in type 1 diabetics.

Steve Freed: So, what would you like to tell medical practitioners? Where we're at? Where we hope to go?

Dr. Faustman: So, this project's probably also unique. This is about a 100 year old vaccine, treating people that have type 1 diabetes. Obviously there's not much profit to make from a 100 year old vaccine that is globally dosed at a 100 million doses per year in the world. This will be a true game-changer for the financial impact of type 1 diabetes. The endgame will try to restore hemoglobin A1C with people with long-standing type 1 diabetes, better than any standard of care we have now.

Steve Freed: So, the way it looks, is if the vaccine starts to work that they're eventually going to need booster shots?

Dr. Faustman: Yes, that's what we're trying to learn in this phase 2 trial. Can we make the therapeutic effect occur at an earlier time point? It's a hard flog doing a trial where you're probably under-dosing, like we did in phase 1, and then having to follow people for 5 years. So in this trial, we're trying to hurry the therapeutic effect by giving booster vaccines yearly.

Steve Freed: Will this have any effect, I know you can't answer the question as of right now, as far as type 2 diabetes goes?

Dr. Faustman: That's a pretty interesting question. If you had asked me a year ago, I would have said no, they're different diseases, how could you even mix those two up? There's recent data, mouse data I'd like to clarify because we usually work on human data and you always [give] a little bit of less credibility to mouse data, but there's recent mouse data out of Japan that BCG in genetically obese mice lowers the blood sugar. That's pretty interesting. Our trials are now centered on type 1 and we'll see what answers we get but that if it held up in the population [that] would be truly amazing.

Steve Freed: I always felt that type 2 is really almost an eating disorder.

Dr. Faustman: I always think that type 1 is much easier to understand, because I think in type 2 there's many different ways you can get type 2. Even having said that, we certainly don't have the cure for type 1 yet. I probably should also say these are totally philanthropically supported trials because if we successfully lower blood sugar with something outrageously inexpensive, it'll be a game-changer. So we're very lucky to have the support of the public for these efforts.

Steve Freed: I want to thank you for your time, it certainly was interesting. I hope I can email you once in a while to get some updates.

Dr. Faustman: Sure, absolutely.

Steve Freed: What you're doing is so important when I see these little kids with diabetes and the parents.

Dr. Faustman: The tortured parents.

Steve Freed: We're talking about a considerable number of people, 10 million people out there, that it would be unbelievable if we can get to that point where we can say that we have a cure.

Dr. Faustman: Absolutely.

Denise Faustman, MD, PhD, is Director of the Immunobiology Laboratory at the Massachusetts General Hospital (MGH) and an Associate Professor of Medicine at Harvard Medical School. Her current research focuses on discovering and developing new treatments for type 1 diabetes and other autoimmune diseases, including Crohn's disease, lupus, scleroderma, rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis. She is currently leading a human clinical trial program testing the efficacy of the BCG vaccine for reversal of long-term type 1 diabetes. Positive results from the Phase I study were reported in 2012.