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Type 1 Diabetes: Control and Cure

Each month the ReachMD XM160 presents a special series. This month is Focus on Diabetes. Listen each hour at this time as we explore with America's top medical thought leaders for latest information on diabetes.

Type 1 diabetes affects over a million Americans and cause billions of dollars each year. Is a generic drug here a possibility?

You are listening to ReachMD, The Channel for Medical Professionals. Welcome to the Clinician's Roundtable. I am your host, attorney and Dr. Bruce Bloom, President and Chief Science Officer of Partnership for Cures, a non-profit that derives cures to patients to repurposing current therapies for new uses and my guest is Dr. Denise Faustman, Associate Professor of Medicine at Harvard Medical School and Director of the Immunobiology Laboratories at Massachusetts General Hospital in Boston. Dr. Faustman and I are discussing type 1 diabetes cure research.

DR. BRUCE BLOOM:

Dr. Faustman, Welcome to ReachMD.

DR. DENISE FAUSTMAN:

Thank you, for having me.

DR. BRUCE BLOOM:

How did you first get interested in doing research into type 1 diabetes?

DR. DENISE FAUSTMAN:

Well, it was more for my PhD training than my MD training. When I went to do my PhD work, I wanted to work on a project that had some ability even though it was basic science to be eventually translated into humans and it appeared that work in the field of type 1 diabetes might facilitate that request.

DR. BRUCE BLOOM:

So, tell us the story of how your original research led to where you are in the Research Laboratories right now.

DR. DENISE FAUSTMAN:

Yes. So, my PhD work was at Washington University in St. Louis and during that time period, I joined a laboratory of Dr. Paul Lazes and he had made headline news by isolating rat islets from a rat pancreas and it seemed like if you could actually isolate these insulin-secreting cells, you could rapidly transplant them into chemically-induced diabetic animals and you know we would be upon a cure for type 1 diabetes within years. So, that's the reason I joined the lab, but as everyone listening today certainly realizes that cure by cellular transplantation never really visualized.

DR. BRUCE BLOOM:

So, we do have transplantation of islet cells in some patients and they get some benefit, but doesn't it also cause a different disease for them?

DR. DENISE FAUSTMAN:

Yeah, the problem that presented itself was – it seemed like an easy fix, take cells out from one person or take cells out from one animal that made insulin and put them into a host that did not have those cells, but it turns out that in type 1 diabetes as well as other diseases such as cardiac disease and Parkinson disease, if the disease can recur, in other words if you put a heart and you still have high cholesterol, the next heart you put in is going to be affected by the disease or if you have Parkinson disease and you put in new neurons, the new neurons are going to be affected by Parkinson disease and that's the same <_____> and that's now played out in type 1 diabetes. That just putting new cells in and using immunosuppression is not a cure for the disease because the disease in most cases can just recur. So, what we have been focusing on is the recurrent disease, not a bigger cell source of insulin-secreting cells.

DR. BRUCE BLOOM:

So, quickly take us through what we think causes type 1 diabetes right now because it is going to be an interesting discussion about immune therapy and immune cells.

DR. DENISE FAUSTMAN:

Yes. So, our basic perverse as well as the perverse of other people that share this hypothesis is that type 1 diabetes is a disease of bad white blood cells, bad T cells, and furthermore the cell that we think will have the cell to alter to have the best therapeutic impact will be a CDA T cell because we really think the CDA T cells are the ones that are directly killing the islet cells whether you are in a mouse model of type 1 diabetes or you are in the humans.

DR. BRUCE BLOOM:

So, how are you going about killing these CDA T cells?

DR. DENISE FAUSTMAN:

Well, you know that is the 18-year project, but basically we found ways to identify these bad T cells and once we identified how those bad T cells got out of the bone marrow through an interruption of class I with self-peptide, we realized that some populations of those cells could be re-killed in the periphery by reintroducing class I with self-peptide, the educational complex, but that wasn't sufficient to totally eliminate the disease. The next thing that needs to be done is to kill a lineage of those cells that we are sitting at top off the islets and those were the very activated memory T cells and those could be killed by another death pathway, the TNF death pathway.

DR. BRUCE BLOOM:

So, that leads us to this two-drug cure, one for the precursor cells and one to the sort of activated cells. Tell us a little bit about how you do that in the mouse model?

DR. DENISE FAUSTMAN:

Yeah, so, if you are really fussy end-staged diabetic mouse and you want a treatment that's a 1-time treatment in your life and never have to be retreated again, you need to kill both the precursor cell as well as a highly-activated memory cell. So, with the brief intervention of those 2 limbs of our therapy, the animals become normoglycemic for the rest of their life. Now, the reason they become normoglycemic for the rest of their life, which was the extra bonus from doing these experiments is we found out with complete disease removal on the CDA cells, the bad CDA cells, the pancreas regenerated. Now, if you are a diabetic mouse and you don't mind getting retreated at intervals for instance once a month with a vaccine, you can just get 1 limb of the therapy that targets the bad CDA cells that is seen on the top of the islet and also go into remission, but because you have the precursors, you have to come back and retreat at later time periods, but the pancreas also regenerates when we do the single limb of the therapy as well.

DR. BRUCE BLOOM:

And in those NOD mice, how do you kill both of those cells?

DR. DENISE FAUSTMAN:

Yeah. So, it turns out the cells should have died in the bone marrow thymus by class I was self-peptide in it. So, we are a strong believer that our discovery that self-peptides were missing in the class I group is a fundamental defect of how these cells got out in the first place. They should have died in the bone marrow and they should have died in the thymus. But once they are out remarkably, you can reintroduce that complex, that educational complex and kill them in the periphery so you can decrease the disease burden even when it's established.

DR. BRUCE BLOOM:

So, can you use the same treatments that you gave the mice in humans?

DR. DENISE FAUSTMAN:

Yeah, so we think both limbs are feasible, one is easier to launch into the clinic than the other one and the limb of the therapy that we are moving into the clinic first is the second limb of the therapy, the therapy that kills the highly activated T cells. So, our concept of why you need to kill those cells are why those cells can die even in an established disease is they need low-dose exposure to tumor necrosis factor, also known as TNF. So, that limb is actually easier of therapy to translate to humans because there is a generic drug called BCG that has been out there for 80 years that has a side effect of inducing tumor necrosis factor, your won tumor necrosis factor. So, how we are going to translate this to people with existing type 1 diabetes is to repeat BCG vaccinations to elevate their own TNF and their own TNF, we believe, can kill off this very cytotoxic population of T cells.

DR. BRUCE BLOOM:

So, if we are right about this. What would we expect to see in the patients who go through this early clinical trial?

DR. DENISE FAUSTMAN:

If the outcome is similar to an end stage diabetic NOD mouse and let's say the trials go optimally and couldn't have gone better, the therapy would look something in the nature of repeat vaccinations throughout your life, normal blood sugars from pancreas regeneration and hopefully no complications if you can restore blood sugars to normal.

DR. BRUCE BLOOM:

So, a patient would come in and get BCG through an injection or is't orally?

DR. DENISE FAUSTMAN:

It is an intradermal vaccination. So, it's a true vaccination. It's not intravenous and unfortunately it's not oral yet.

DR. BRUCE BLOOM:

So, you would come in once a month to get a shot?

DR. DENISE FAUSTMAN:

Yeah, we do not know the interval. Of course, the 64-million dollar question is do you need it once a year, once every 6 months, once a week? That's why we are doing the trial, but some interval.

DR. BRUCE BLOOM:

And then you would expect it would kill off the cells that are sitting right on the pancreas and then those pancreas cells would begin to secrete insulin in response to glucose.

DR. DENISE FAUSTMAN:

That would be the best-case scenario.

DR. BRUCE BLOOM:

And, why do we think or what evidence do we have that in the human, patients who have been diabetic for a long time would still have active beta cells?

DR. DENISE FAUSTMAN:

Well, you know that is a good question that our work in animals elicited huge effort by the worldwide scientific community go back and look at that data. I mean the textbook picture of type 1 diabetes is a picture of an exocrine pancreas with no islets in it and they think people have successfully now gone back to look at that histological picture to realize that if you go back and look at autopsy specimens of people who had type 1 diabetes for 20 years, 30 years, or even 10 years, there are islets in the pancreas. So that picture, that there is no islet cell left in the pancreas years after diabetes is probably not correct. So, that's the histological data and even before our work, there was data from an investigator in England named Dr. Alan Follat, who had gone back and looked at all these stored pancreas specimen and had been standing up at meetings for many years saying that the pancreas have islets in. I think, there was such skepticism because nobody had seen function or the release of function by disease modification that that data was probably ignored. So, the data is fairly strong from worldwide examination that the pancreas years after diabetes have islets, but the second question that comes up is, is there a human data to suggest that those islets can become functional or is there human data to suggest those islets can secrete insulin. Okay, multiply from whatever mechanism you want them to regenerate from and there is a data now that that is the case too. There is a paper by a Japanese group that had been doing kidney transplants in people with type 1 diabetes and they went back and did needle biopsies of the pancreas of those people and found there were quite a few islets that looked like they were proliferating in those pancreas and there is data also from NIH. We had always made the assumptions that if we put islet cells in and the blood sugars were restored, the islets were making the insulin, but there is data from NIH that if you go back and look at those people with insulin secretion a year after an islet transplant on immunosuppressive drugs of course that in over 50% of the cases, insulin is coming from their own pancreas and the islet transplant is not working. So, there is functional data now from diverse sources that humans have the potential to reestablish insulin secretion from their own pancreas and there is certainly lots of histology data saying those cells that they are trying to proliferate, but fairly unsuccessfully with high-disease burden.

DR. BRUCE BLOOM:

Are you doing clinical research now in using BCG in patients?

DR. DENISE FAUSTMAN:

We are about ready to start the phase 1 trial with BCG in people, who already have type 1 diabetes. We have been working the last 5 years developing the blood tests to monitor people. Before we started these trials, we have put a huge effort that we will continue into developing blood tests that will monitor directly the ability of BCG to modulate the immune system.

DR. BRUCE BLOOM:

I want to thank my guest, Dr. Denise Faustman, Associate Professor of Medicine at Harvard Medical School and Director of the Immunobiology Laboratories at Massachusetts General Hospital for talking to us about the possibility of a cure for type 1 diabetes.

I am attorney and Dr. Bruce Bloom. You have been listening to the Clinicians Round Table. We welcome your questions and comments. Please visit us at www.reachmd.com, where our new on-demand and podcast features will allow you to access our entire program library. Thank you for listening.

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