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Type1 Diabetes Cure Research & Autoimmune Diseases

Each month ReachMD XM 157 presents a special series. This month is Focus on Diabetes. Listen each hour at this time as we explore with American's top medical thought leaders the latest information on diabetes.

Autoimmune diseases like diabetes and lupus seem so different, is it possible that they may all share the same cure?

You're listening to ReachMD XM 157, The Channel for Medical Professionals. Welcome to the Clinician's Roundtable. I am your host, attorney and doctor, Dr. Bruce Bloom, President Chief Science Officer of Partnership for Cures, a nonprofit that drives 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 how her type 1 diabetes cure research might be applicable to other autoimmune diseases.

DR. BRUCE BLOOM:

Dr. Faustman, welcome to ReachMD.

DR. DENISE FAUSTMAN:

Thank you for having me today.

DR. BRUCE BLOOM:

So tell us about your medical and research background and how you got into this area of autoimmune diseases.

DR. DENISE FAUSTMAN:

Well, I have an MD and a PhD so I can act like a clinician some days and I can act like a molecular biologist the other days, but my PhD work was in molecular biology and immunology and my MD work was in internal medicine and an endocrine fellowship at

Massachusetts General and I got involved in research during my PhD work and I got involved in type 1 diabetes research based on some preliminary data at that time showing that the insulin secreting cells of the islet could be isolated from the pancreas and it seems so easy at that time that that might be translated to humans with great success.

DR. BRUCE BLOOM:

And your current work is in type 1 diabetes. Describe that for our audience.

DR. DENISE FAUSTMAN:

So we've worked over the last 18 years on the thorny problem that may be the reason cell transplants haven't worked very well clinically or even in end-stage diabetic mice is that there is this problem of recurrent disease. In other words, the pathologic T cells that were there in the original case are still there when you put a transplant in and are not particularly inactivated by immunosuppressive agents. So we've got to go after the heart of the disease the bad T cells in order to make an impact or more lasting impact on disease course.

DR. BRUCE BLOOM:

And these bad T cells, tell us about how do they become bad and how many of them are there that are causing this kind of disease?

DR. DENISE FAUSTMAN:

The bone marrow and the thymus are really inefficient machines for making new white blood cells throughout your life and you make literally millions of T cells throughout your life and on a good day everybody kills off most of the T cells, so that diversity of the T cell receptors is really important because in theory you don't know what pathogen you are going to see at the age of 50 or pathogen you are going to see at the age of 12 and so you make huge diversity, but as a result of making those diverse T cells, most of them or a quite a few of them are going to be autoreactive so there is an assembly line of T cell selection, so before they get out the door into the periphery, most of them should be killed by this structure called class I and cell peptide so that you don't have autoreactive cells released into the periphery. So one of our large premises of what we work on for autoimmune diseases is particularly type 1 diabetes is to understand why that process is faulty and why there isn't enough cell peptide to kill off those cells and then what to do about the problem once those cells are out in the periphery.

DR. BRUCE BLOOM:

So what have you done about it in type 1 diabetes?

DR. DENISE FAUSTMAN:

What we learned first was the discovery, you know, science paper that this pathway was interrupted and we did most of the early work in this autoimmune model called the NOD mouse that actually has type 1 diabetes and Sjögren syndrome, autoimmune disease of salivary and lacrimal glands, and we identified the gene that caused that problem. It's a part of the proteasome that people may have heard about and that gene is called the LMP2 gene. Now ironically 15 years later it turns out that that same gene and the same protein

is the defect in Sjogren syndrome in humans so this pathway has interrupted in a diversity of autoimmune diseases and the interruption that pathway causes the escape of these autoreactive cells.

DR. BRUCE BLOOM:

And once they get into the periphery, what do they do?

DR. DENISE FAUSTMAN:

As most people probably recognize, although patients come into your office and they will say I got diabetes or my son got diabetes on July 12, 1992, or whatever day and year it was, it's really the case that that's the day their blood sugar went up, they had diabetes many years prior to that work, so people working in type 1 diabetes research recognize that not only in mice, but also in humans the disease is active for a long time and you "only get it clinically when the islets are so destroyed, your blood sugar elevates."

DR. BRUCE BLOOM:

So after these cells get out there, how do they destroy the pancreas cells?

DR. DENISE FAUSTMAN:

They certainly circulate for a long time, but eventually they get exposed to the insulin secreting proteins that they are not tolerant to and our premise is that one of the worse cells to have around or the CD8 cytotoxic T cells that mistakenly recognize the class I with cell peptide on the islet is 4 and then kill off that target tissue by direct cytotoxic T cell lysis.

DR. BRUCE BLOOM:

So what are you testing is a therapy for type 1 diabetes to get rid of these CD8 cells.

DR. DENISE FAUSTMAN:

We gradually started realizing that these cells were out in the periphery and one realization was that they are out in the periphery and mother nature slipped up in the first place allowing them out, can we reintroduce the class I/cell peptide in the periphery and reeducate those bad T cells that were circulating, so sure enough that was the case, we could reintroduce the class I and cell peptide, but we also realize that that limb of therapy didn't eliminate the disease in total and the basis of that is that one CD8 cells have glommed on to their islet target and are actually killing, the class I and cell peptide can no longer kill those cells and you need another compound and the other compound you need to induce cell depth, those cells is something called tumor necrosis factor or TNF.

DR. BRUCE BLOOM:

So, Denise, are other autoimmune diseases that much like diabetes that we might think this is translatable?

DR. DENISE FAUSTMAN:

There is a lot of data both from the genetic viewpoint as well as from the side effect profile viewpoint that certain treatments that work in one autoimmune disease may more broadly work in other autoimmune diseases. One example I mentioned earlier in the segment was that we got one of the genes that interrupt this class I pathway in a mouse, and you know, that's very exciting for the mouse community, but might not be so exciting for the patient community, but it turns out that that particular protein that triggers this process in part in the diabetic mouse is also the same missing protein in human autoimmune diseases and that category of diseases are people with Sjögren syndrome. So that overlap has been established, but other overlaps on the genetic viewpoint also correspond and it turns out that some of the same signaling defects are on the same pathway, but different proteins on that pathway and some of that overlap now occurs with scleroderma and lupus and people with a syndrome called the air mutation, which is effectively polyglandular autoimmune disease so from a genetic level, you know, you are getting pretty good signal that some of these overlap, but there is also some pretty practical human data to suggest that some therapies at work in some categories of autoimmunity may actually define other patients that would respond to a very different therapy and the best example out there is, I am sure your audience that's listening today will know that there is a huge class of drugs that are anti-TNF therapies whether the code words would be Enbrel or Remicade and those compounds are effectively anti-TNF. They work well in about 40-50% of people with rheumatoid arthritis, but there is another 50% of people with rheumatoid arthritis that they don't have any efficacy and those drugs have gradually been moved to patients that have Crohn disease and in Crohn disease they find out that some people, who are treated with these diseases get new onset autoimmune disease, so it's not something you want to happen and the new onset autoimmune diseases they get are type 1 diabetes and lupus and vasculitides and what's fascinating about that side effect profile data, especially in Crohn disease now is those are the diseases that we've defined in other people have defined that would benefit from TNF not anti-TNF. So I think there is growing data out there both from the very practical data of side effects of drugs to the very basic science data on the genetics of pathways leading us to the conclusion that there will be clusters of people within select autoimmune disease that will respond to opposing therapies and probably even more promising will be able to define those patients based on those phenotypes.

DR. BRUCE BLOOM:

And the work that you are doing now on type 1 diabetes with BCG is BCG designed as a mechanism for getting TNF.

DR. DENISE FAUSTMAN:

Well, it wasn't designed for that. It's a side effect of that drug, so BCG is an approved drug worldwide for two indications; it's approved worldwide as a vaccination dose for prevention of tuberculosis. It's also approved at very high doses as a drug for bladder cancer and so it has two indications and we want to use it for a third indication.

DR. BRUCE BLOOM:

And how did you discover that BCG might be appropriate treatment for diabetes or may be some other autoimmune diseases?

DR. DENISE FAUSTMAN:

Well, we kind of came from the basic times did you point. We realized that there was a way to selectively tell the most autoreactive T cells in not only these end-stage diabetic mice, but also people with type 1 diabetes and that was to introduce or to expose the bad T cells to TNF, so went in the reverse direction and said is there an existing generic drug that's out there that induces TNF and could we

use that existing drug to start some pivotal trials to see if elevated TNF would have a disease altering effect.

DR. BRUCE BLOOM:

Now, in most laboratories that people made that discovery, they start to create a new drug that they could patent and make a lot of money on, why would you go ahead and find a generic drug instead?

DR. DENISE FAUSTMAN:

Well, you might say (laughs), it was the wrong thing to do, but we think it's the right thing to do. I mean, so often we read daily about healthcare costs escalating, but very few people have started in basic research labs to work at trying to introduce new things that would be better than existing therapy and also have cost savings, so we decided that in a disease such as type 1 diabetes where it's a relatively small disease compared to heart disease or hypercholesterolemia or even type 2 diabetes that we should try to get to the clinic as fast as possible to test these new ideas and we decided the way to get there fastest and cheapest was to use these generic drugs.

DR. BRUCE BLOOM:

I want to thank my guest, Dr. Denise L. Faustman, associate professor of medicine at Harvard medical school, Director of the Immunobiology Laboratories at the Massachusetts General Hospital for talking to us about the possibility of a cure for a wide variety of autoimmune diseases.

I am attorney and doctor, Dr. Bruce Bloom, President Chief Science Officer of Partnership for Cures, a nonprofit that repurposes existing treatments for new uses. You've been listening to the Clinician's Roundtable. 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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