Dave Iverson: This is Dave Iverson, and welcome to "Getting to a Cure: The Science Behind the Search," our continuing series of interviews that focus on the latest scientific developments in Parkinson's disease research.

Science proceeds in steps. We've known for a long time, for example, that critical neurons die in Parkinson's disease. And over the last 15 years, we've learned a lot more about why, specifically the potential role of alpha-synuclein, the sticky
[00:00:30] protein that may play a key role in cell death. Now we're learning that our body's immune system may actually make things worse as it attempts to fight back.

In an article published last month in the journal *Nature*, scientists report that our immune system may mistake fragments of alpha-synuclein as a foreign body, triggering an inflammatory response similar to what happens in autoimmune diseases like diabetes or multiple sclerosis. Dr. David Sulzer of Columbia
[00:01:00] University is one of the senior authors of the paper. We talked recently about his findings and about whether Parkinson's may be, at least in part, an autoimmune disease. Dr. David Sulzer joins us now. Welcome.

Dr. David Sulzer: Thank you for inviting me.

Dave Iverson: Your work is so interesting, Dr. Sulzer, on a variety of levels, specifically this idea that the immune system may play a role in Parkinson's disease. But before we dig into that further, can you tell us a little bit first about what the immune
[00:01:30] system actually is, what it's supposed to do?

Dr. David Sulzer: The immune system ought to and typically does fight off the many, many, many infections that you're getting all the time from bacteria and viruses and fungi and all sorts of other invaders that would like nothing better than to feast on you. Your immune system is great at keeping you alive for a long time. However, it
[00:02:00] can cause multiple problems, as well. The one that we're going to be speaking about the most today are ones called autoimmune disorders, when essentially the system that's supposed to ward off invaders, like bacteria, makes a mistake and decides that some component of you, yourself, is an invader and begins to attack your own cells.

Dave Iverson: As I understand it, we used to think that brain cells weren't vulnerable to that
[00:02:30] autoimmune response that you were just describing, but your work and your prior research has actually identified that brain cells can, indeed, be vulnerable. Can you describe for us what it was you were able to discover in that earlier work?

Dr. David Sulzer: It had been thought that, at least in adults, that the brain cells that you're referring to, or the neurons of the brain, the ones that are involved in communication within the brain and end up controlling virtually everything that
[00:03:00] you do ... These neurons were thought in adults to not present a, how do I say this in a simple way, small proteins that would be identified by your immune system as either being yourself, self-proteins, or non-self, that is, invaders.

[00:03:30] The paper that you're referring to is from an excellent postdoc that was in my lab, named Carolina Cebrian. Carolina, who's from Spain and now is back working in Spain again, discovered that when you actually look at the human brain in autopsy, that she was able to see that, in fact, some of the neurons, and these are in particular the neurons that are most susceptible in Parkinson's, the ones that die off at the highest fraction in Parkinson's disease ... They're called the dopamine neurons of the substantia nigra and the norepinephrine neurons of the locus coeruleus.

[00:04:00] She found that these two populations of neurons actually do have the antigen-presenting proteins. In other words, they are presenting these fragments of proteins that are used by the immune system to identify self and non-self. We realized that this could potentially be involved in a disease like Parkinson's,

[00:04:30] where apparently ... And this is just saying apparently. This is research, and nobody in the world completely knows the answer to this particular point, but apparently the body's killing off its own neurons. How that happens has been a mystery, and it's possible that what Carolina found, that neurons in both the healthy controls and in Parkinson's people are presenting antigen, it could be

[00:05:00] that this is the missing link and that this process is killing the cells in Parkinson's disease.

Dave Iverson: Do you know yet what it is that may be triggering that autoimmune response? In other words, does it tie in with what we've been learning over the past 10 years or so about the role of the sticky protein alpha-synuclein that we think may be killing off neurons? Is it also alpha-synuclein that's involved in this? Is this what's

[00:05:30] present on the cells that may be triggering this additional autoimmune response?

Dr. David Sulzer: You're asking very simple and straight-forward questions, and I'm afraid there's no simple and straight-forward answers. So, I'm going to try to make it as clear as I can. You're absolutely right in your background, and you're also right in your implication that in our new paper we find that people with Parkinson's disease often have an immune reaction against alpha-synuclein, which is why we would

[00:06:00] say there is an autoimmune response. Apparently, these patients are having an immune reaction against one of their own proteins that we're talking about right now.

Now, the next part of your question is if the neurons that are dying are actually presenting the alpha-synuclein themselves and if this is leading to cell death. Both of those questions, both that A and B part we just said, are really unknown

[00:06:30] at this time. It's going to be very difficult to prove either of them. What we can say is they do have problems in alpha-synuclein turnover, meaning that you can make alpha-synuclein, but you can't get rid of it properly.

There's problems with it in Parkinson's disease, or at least associated with Parkinson's disease. The protein is not being properly processed. At that point, it might be a kind of appearance of a piece of the protein that your body's never

[00:07:00] seen before when you're growing up and when your immune system's deciding what is a self-protein, what's a non-self protein? Now, your body has never seen these little bits of synuclein before, and it mounts an immune response against it. It is very possible that that's what's going on.

Dave Iverson: Very possible, but difficult to determine for sure. That's because even though the brain of someone with Parkinson's can be examined after death, the key protein molecules that might trigger the immune response are both few in number and

[00:07:30] not well preserved. The good news is that someone's T cells, the cells that the immune system sends out to fight what it mistakenly thinks is a foreign invader, can be studied and measured in living human beings. That means the T cells themselves could serve as a marker, a way to diagnose that something is going wrong.

Dr. David Sulzer: The first thing that, and we may not be so far away from this one, is to use it as a biomarker or a diagnostic tool. Already in this first paper, we're seeing that 40%

[00:08:00] of people with PD have a response to the T cells. That means we might be able to already, just using the technique we're already using, identify perhaps 40% of people in early stages of Parkinson's before they even have any symptoms and walk into the clinic.

Dave Iverson: Because they have that elevated T cell activity?

[00:08:30]

Dr. David Sulzer: Exactly, so we have to find out if that's true. The first thing we're doing is Michael J. Fox Foundation has funded us to do an independent replication, so we are in the midst of that right now. Now, if it's replicated — and you never know until you do the work — but if it is replicated, this would mean that we're probably not that far from using this as a diagnostic. Now, you could say, "Well, that's still only 40% of patients," and that's where we have to go a bit deeper.

[00:09:00] When you look at classical autoimmune disorders like type 1 diabetes, if somebody just walks into the clinic, donates a bit of blood, and you look for the specific T cells that are known to be involved in type 1 diabetes, again, you're getting anywhere between 20 to 50% of the patients responding. However, if you look at them over the course of time ... Because your immune system, as we all know because we all get colds and flus and so on, is always going up and

[00:09:30] down, depending upon recent infections and so on. So, it maybe that ... Well, certainly in the more classical disorders, if you look at people several times, you'll often ... You may not pick up the T cells the first time, but you pick it up a subsequent time.

In all honesty, I think starting with 40% is starting really well. We're starting a lot better than anything else. Why is this important? It is important because there are plenty of potential treatments that could slow down the progression of

[00:10:00] Parkinson's. The big trouble right now is you don't know if you have the disorder until you develop something that where you walk into the neurologist's office and you get a diagnosis. By that time, there's already been a tremendous

amount of damage in the brain. We have to get people before that. Very, very important.

Dave Iverson: [00:10:30] In addition to that exciting possibility of using T cells as a biomarker, an objective measure that we could use to diagnose in Parkinson's that we haven't had yet, I'm also curious about how your discoveries and research might tie into potential therapies, particularly disease-modifying therapies. We've been talking about alpha-synuclein, and as you know, there is already a lot of work going on to figure out a way to try to halt alpha-synuclein buildup, including a kind of vaccine approach.

Dr. David Sulzer: [00:11:00] Yeah. The vaccine approach is, as you know, has been worked on a lot with Alzheimer's disease, and there are a lot of issues. That doesn't mean it's not going to work. I'm going to be intentionally noncommittal on this. It may be that one of the reasons there've been so many disappointments have been because they are treating people relatively late in the disease. In other words, the diagnosis doesn't occur until late in the disease, but no one really knows. Whether vaccines are going to be useful or not, I'm going to be absolutely [00:11:30] noncommittal on. I truly, honestly don't know, but there is a lot of work in that direction.

Dave Iverson: Could another potentially interesting avenue to explore then just be whether or not the T cells that become activated and attack the neurons, whether or not those T cells could be turned off in some way? Would that be another ...

Dr. David Sulzer: [00:12:00] Yeah, well that's a big one. A lot of people would like to increase the ... This is an idea that's out there for almost all of these autoimmune-type disorders, is there a way to train the body that that's not a foreign invader? Yeah, there are a lot of different ideas on how to do this. Which one's best, and which is best for different people? How many times do we have to do it in a particular person? Each of these might sound like simple questions, but remember, we're not working here with cells in a Petri dish. We're working with people.

[00:12:30] To know the real disease, we have to look at the real people. For that, that comes down ... That might sound abstract. It's not abstract. It's like you and me walking into the clinic and saying, "I'm here. I want to help." I really want to thank those people who've already helped. We're going to come back to you, and we're going to come back to other people too and ask them, "Please take off an hour of your time and come in and help us do this work." I want to thank people both in the past and for the future to become involved in these studies. It's the only way they can be done.

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Dave Iverson: Dr. David Sulzer, Professor of Neurobiology at Columbia University. To learn more about Dr. Sulzer's work and the latest in Parkinson's disease research, visit michaeljfox.org. I'm Dave Iverson.

Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about The Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.