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.

Intro: You're listening to audio from one of our Third Thursdays Webinars on Parkinson's research. In these webinars, expert panelists and people with Parkinson's discuss aspects of the disease and the Foundation's work to speed medical breakthroughs. Learn more about the Third Thursdays webinars at michaeljfox.org/webinars. Thanks for listening.

Dave Iverson: Hello everyone, and welcome to today's Third Thursdays Webinar from The Michael J. Fox Foundation. I'm Dave Iverson, a member of the Foundation's patient council, and I'm delighted to be able to moderate today's webinar, which is going to focus on the immune system's role in Parkinson's disease. Let's meet who's going to be helping us walk through I think this really interesting topic today, the immune system and Parkinson's disease.

We're joined by Dr. Jeff Bronstein. Jeff is the director of the Movement Disorders Program at UCLA, and has been a leading researcher as well as clinician in the Parkinson's disease field for many years. Jeff, welcome, a pleasure to have you join us today.

Jeff Bronstein: Thanks, Dave.

Dave Iverson: And joining us as well is Dr. Todd Sherer. Todd, of course, is the CEO of the Michael J. Fox Foundation, and as such has a keen grasp of all that's going on in the Parkinson's research world and brings to this discussion his own background in neuroscience as well. Todd, thanks for being part of this.

Todd Sherer: Thanks, Dave. I look forward to the discussion.

Dave Iverson: Yeah, I think it's a really interesting one, so let's get started with some of the topics that we're going to be trying to cover today. We're going to talk generally about the role of the immune system both in health globally, but also within disease, and particularly of course Parkinson's disease, and then we're going to talk some about the many connections that there are between Parkinson's and the immune system, which is intriguing. Then we'll talk finally about how scientists are beginning to work on ways to use the immune systems to either develop tests that could be a kind of biomarker, a way of discerning what's going on when someone has Parkinson's disease, or of course as importantly, more importantly really, ways to harness the immune system to promote various therapies that would help us contend with Parkinson's disease.

So let's begin our conversation, and I think it's useful, Jeff, as maybe and as our resident MD, you could help us with this first definitional question, which is really to talk a little bit if you would, Jeff, about what the immune system is.

Let’s assume that it attacks organisms and substances that invade the body, but just describe for us if you would what the immune system is there for.

Jeff Bronstein: Sure. So the immune system is a very actually complex network of cells and tissues that are really there to help protect us against basically foreign organisms, and that may be like bacteria and viruses, but it also can be cancer cells and things like that, so it's there really to help identify things that are not self and then help protect the body from being invaded and injured by it. It's involved in so many processes and is basically an essential part of life. It could also go awry and sometimes confuse what's our self and what are foreign entities, and that's when we have what we call autoimmune disease, so we-

Dave Iverson: And we'll be talking about that and its particular relationship to Parkinson's, right, because that's one of the many things that intrigue researchers about this process, Jeff?

Jeff Bronstein: Absolutely, and so it can be very, very specific, the immune system and directed to very, very specific molecules, but it also can be kind in generally heightened in kind of an inflammatory tone. Inflammation is when the whole immune system is activated, so it's sometimes important to try to differentiate that.

Dave Iverson: And let's focus on the word Jeff just used for a moment, and we see that in that third bullet point on the screen, which is that inflammation is part of the immune response. So it makes me want to ask a sort of basic question, Todd, which is whether or not inflammation is good or bad, because when you hear the word inflamed, something is inflamed, it doesn't sound very good, and yet we also know that inflammation, as Jeff was describing, is part of the immune system's response. So we know inflammation is involved in Parkinson's. Can you dig into that a little bit more, Todd, about what inflammation actually is, good or bad, and how that connects up to Parkinson's in particular?

Todd Sherer: So I think this is where Jeff was talking about how complex the situation is because this inflammation could be good or it could be bad depending on the circumstances and context through which it's happening. So in Parkinson's disease, and I know we'll get into this a little bit more, there is evidence of inflammation and activated immune system, particularly in the immune system cells that function in the brain of Parkinson's patients or that function in the brain normally, so these are increased in the context of Parkinson's.

So the inflammatory response could be playing multiple roles in the disease, one, in that it could be playing an exacerbating role or worsening in that this inflammation is causing more activation of processes that lead to dysfunction of brain cells, but it also could be that the inflammation that comes in is helping to repair damage that's happening in the brain. That's part of the stage of research now is to try to better understand what really is happening in the context of Parkinson's and if there's certain things we should be aiming to try to reduce or delay, and maybe there's certain aspects we're looking to increase the function of to have better repair of the brain.

Dave Iverson: Go ahead, Jeff. What did you wanted to say [crosstalk 00:06:38]?

Jeff Bronstein: Yeah, I just wanted to maybe expand a little bit on the components, kind of the major components of the immune system. So we have some cells called B cells that actually make antibodies, and those are proteins that attack other proteins or other chemicals, so it's called humoral immunity. There's also T cells, which are actually cells that attack specific proteins and organisms, and so that's a cellular immunity.

Then we have resident cells, and in the brain those are called microglia, and those are cells that live in the brain and kind of roam around looking to help respond locally. There's also resident cells in the gut and in other tissues as well. So we tend to talk about the inflammatory response by reactions basically of these cells and chemicals that they release.

Dave Iverson: And some of those, the microglia I know and we'll talk about this more later, are part of what's intriguing in Parkinson's. This ties into the question I was about to ask, which is that this very fundamental question that we don't quite understand yet, right, Todd, that we don't really know whether the immune system and inflammation are the cause of a problem or whether they're a response or a consequence to the problem. There's this fundamental thing that you were starting to describe that's kind of a chicken and egg question that we really don't know the answer to, right, yet? Is that correct?

Todd Sherer: Yeah, I think this is one of the major areas of research involved and currently focused on the immune system and inflammation in Parkinson's. We do know that there's evidence of an increased inflammatory response in Parkinson's disease, particularly in the brains of Parkinson's patients. But we're still trying to really dissect out the various complex components, like Jeff was just referring to, to understand how much of the inflammatory response is contributing to either the onset of the disease or the progression of the disease, versus whether there are aspects of the inflammatory response that's actually trying to help the body address the disease mechanisms and even delay or overcome some of them. So this is really I think a very active area of research with great potential because there are a lot of ways that we could envision manipulating the body's immune system and inflammatory responses to try to promote perhaps the pro survival components of the system and limit or mitigate some of the more exacerbating aspects of the response.

Dave Iverson: Well, let's dive in then next into some of these various factors that are intriguing with Parkinson's and how we might then respond to them. Jeff, let me go to the first item that appears on the screen here next, which is this connection between inflammation and pesticide exposure and head injury, which we know are risk factors for Parkinson's. Now, you're someone who has done a lot of research in the area of pesticide exposure, in the Central Valley of California in particular, so what are we learning from that? How does that, Jeff, intersect with this question of inflammation?

Jeff Bronstein: So as you correctly stated, there's lots of data now to support that certain pesticides are associated with an increased risk of Parkinson's, and then the use of animal models have helped support causality, and I'd say the same thing is true for head injury as well. So when we're talking about it, we're talking about an increased risk.

Now when we go to animal models and we expose them to these pesticides that are associated with a higher risk, or if we do a head trauma model in animals, you see the resident inflammatory cells, the microglia in the brain become active and they start secreting cytokines. We think that that may be contributing to the damage because if you block that inflammatory response or you suppress it during exposures, it seems to lessen the damage of both the head trauma and the pesticide exposure. It doesn't prove it by any means because these animal models all have their limitations, but it's a clue that at least some of the mechanisms by which pesticides and head trauma can increase the risk of Parkinson's is by starting this inflammatory response.

Dave Iverson: And Jeff, let me interrupt real quick to ask then, that seems an area then that could be ripe with possibilities for a possible intervention or therapy, right? I mean, because it sounds like you're suggesting it may be that if we could, even if someone's been exposed to something that's harmful, be that an injury or a pesticide, that if we could stop the response to that, that inflammatory response, we might limit the degree to which Parkinson's either takes place or progresses.

Jeff Bronstein: Yeah, absolutely, and I think that's why there's so much interest in the research field because it is something that is, it's a real potential target, and we get some clues from our epidemiology as well. It's low on this slide, but it's probably apropos to this discussion is that we know that at least by epidemiologic studies, the vast majority of them have shown people that take a lot of anti-inflammatory medications like ibuprofen, they seem to have a lower risk of Parkinson's disease, and so it's a suggestion.

Now, I don't want to say you should start taking them. This was tried in Alzheimer's which has a very similar sort of picture with inflammation, and when people started taking it, the inflammatories to try to slow Alzheimer's had a higher risk of heart disease actually and heart attack, so we really need to when we start thinking about modulating the inflammatory system, safety is a really important aspect of that, so I don't want people to start taking these things for that purpose without a lot more studies, but it is a real area ripe for target for treatment.

Dave Iverson: And another area touched here that's ripe with interest and perhaps a target as well is that third point that I want to get to, which is the role of the microbiome and gut bacteria, and how that might impact Parkinson's and the immune response. We're already getting a number of questions on this. Debra just wrote in, "Can we improve our gut's flora to help our immune system?" There's a lot of interest in this, Todd, so can you tell us what we know and what we don't know

about the relationship between what's going on in the gut and inflammation that might impact the brain as well?

Todd Sherer: Yeah, this is a relatively new area for Parkinson's disease, but getting, as you're mentioning, quite a lot of interest, where we do know, for example, that Parkinson's patients can have a number of symptoms outside of the motor symptoms, and one that's common is digestive issues. There's even some data that suggests that the digestive problems can predate the onset of the motor symptoms, so there's now an increasing interest in understanding that gut-brain axis and the interactions between what might be happening in the gut and the impact those can have on the neural function.

There have been some recent studies that have looked at the microbiome, and the microbiome is the way the scientists refer to the bacteria that's living within your body and your gut, and have found that there may be differences in the microbiome when you compare a Parkinson's patient to somebody without Parkinson's. So there's a lot of work now being done to follow up on that, to understand what might be the biological impact of the differences in microbiome. There have been some interesting animal studies recently that have shown that the impact of the Parkinson's disease microbiome can be seen in the nervous system, meaning that those animals are showing some deficits in the neuronal function just if they're exposed to the disease microbiome. But this is still a real active area to understand kind of how would you then, what would you do to try to convert the microbiome and what would be kind of a "good" microbiome to have, but this is definitely getting a lot of very significant interest now in the research community because of a lot of this data that I just reviewed.

Dave Iverson: And as with the point, Todd, that Jeff was making about we see it epidemiologically this relationship between people who take a lot of anti-inflammatories like ibuprofen seem to have a lower risk of Parkinson's, yet we don't know enough yet to advise people to do that. People understandably always want to know, well, what can I do here? What can I do that would either help my immune system be stronger or react in some ways that would be helpful in terms of Parkinson's? Again, to Debra's question, do we know anything yet about whether we can do anything with our own gut and our own microbiome that would be useful in this regard or is this again a too soon to tell kind of question?

Jeff Bronstein: Well, I think it's still really early in this research to really give conclusive recommendations, but we do know that in general, people that eat a high fiber diet with a lot of fresh fruits and vegetables and nuts, kind of the Mediterranean diet, tend to have what people think of as an anti-inflammatory microbiome, one that may be a bit healthier. We know that that's healthy for heart disease and stroke, and probably Parkinson's as well, so eating a really healthy diet is the most important way of establishing what we think of as a health microbiome the best we can describe that. Those are called prebiotics, so taking a lot of probiotics doesn't seem to change it very much, but prebiotics, what you feed the bacteria, make a difference. So I do recommend to my patients to eat a

really healthy diet. It may be through the microbiome. It may be anti-inflammatory. It may not be, but we know people die less of heart disease and other things with it, so it's obviously an important thing you can do for your health, and maybe it's through the microbiome.

Dave Iverson: And back to you, Todd Sherer, on the other point we want to touch on here because we're so interested I think in Parkinson's research these days between these connections that might lead us to underlying links and causes. So there's this interesting connection between the risks for Parkinson's and inflammatory bowel disease, as well as hepatitis C, and you see that, and you think what in the world do inflammatory bowel disease, hepatitis C, and Parkinson's disease have in common, so that's the question, Todd. What do they have in common and what intrigues you as a researcher about that link?

Todd Sherer: Yeah, so I think just to kind of restate the finding, which is another epidemiological finding where it was found that individuals who had inflammatory bowel disease or had exposure to hepatitis C were seen to have a greater risk of getting Parkinson's. This is interesting for a lot of the reasons we've been talking about, that the main characteristics of these diseases are this unusual or abnormal inflammatory response or immune cell function, so there is an overlap perhaps of some of the underlying biology of what might be triggering these diseases along with Parkinson's.

Now this is still an association epidemiology, and it just has to do with the risk, but one thing particularly that was interesting in a recent paper in inflammatory bowel disease was a finding that individuals who had that disease and were also treated with a particular anti-inflammatory therapy, it seemed to reverse the risk, meaning that their increased risk of getting Parkinson's was now reduced, so that is pretty interesting to point additional evidence to a role early in disease of immune cell function in Parkinson's.

Dave Iverson: Todd, I hope I'm not venturing off base here, but isn't there also a link between *LRRK2*, *L-R-R-K-2*, mutation which puts one at greater risk for Parkinson's and to inflammatory bowel disease? If I'm right about that, is that also something that's intriguing?

Todd Sherer: This is particularly interesting in that some of the genetic risk factors for Parkinson's are found in this gene you mentioned, *LRRK2*. In a separate study looking into inflammatory bowel disease, it was found that different genetic risk factors within the gene for *LRRK2* do seem to be linked to inflammatory bowel disease as well. This, again, is pointing to perhaps a commonality of some of the underlying biology across these diseases and also giving new information on what may be an important role for LRRK2 where while it's a gene that causes an increased risk for Parkinson's, perhaps some of its function in causing that risk is actually in the immune system and not in the brain cells directly. That is particularly interesting in understanding what might be some of the causal factors in Parkinson's Disease. So this is an area that's gotten a lot of interest as

well particularly around LRRK2, LRRK2 function in the immune system, and how that might be contributing to the onset of Parkinson's.

Dave Iverson: Fascinating. Let's take this a step further then and begin to think about how all that we've been talking about, all of these common denominators and linkages may lead us to greater insights into Parkinson's research and hopefully treatment. Jeff Bronstein, when we talk about this, one of the things that we talk about first are our perpetual pursuit for a biomarker in Parkinson's Disease, a way of both detecting the disease's presence early on but also measuring what's going on with the disease as it progresses. We see this first point on this next slide about whether or not this might be a way that we could further test for Parkinson's. Is that because you could do literally a kind of blood test or you could measure some of those cells you were talking about earlier, T cells or whatever? Is that what we're thinking here that this could lead us to a way of better measuring what's going on with the disease?

Jeff Bronstein: That's the hope. We're not there yet, but there's some interesting early studies that suggest it's possible. For example, there was a nice study out of New York which showed that certain T cells, those cellular immunities seem to recognize alpha-synuclein, the protein that aggregates and clumps up in Parkinson's Disease. They seem to recognize that. So there are assays looking for that and see would that help us predict who... to determine who has it, who doesn't, or even direct the type of therapy we have. That's one possibility. So it's a very specific targeted type of test that we might be able to develop.

Another one may be more like heart disease where there's a thing called C-reactive protein, CRP, where when that's high it means your risk for getting a heart attack and atherosclerosis is a bit elevated. CRP doesn't seem to be that marker for Parkinson's, but is there a general marker of inflammation that may be useful in adjusting risks? So I think there's both specific and nonspecific ways that this could help us either diagnose or help us determine the risk of getting Parkinson's Disease.

Todd Sherer: Dave, just to add to that, there also are a number of efforts looking at brain imaging markers for neuroinflammation that are also being developed to try to see if we can actually detect an inflammatory response in a living person's brain to also both uncover insights into the disease and perhaps be a marker, like Jeff was just referring to, to help target people correctly for therapy based on that immune response. That's also an active area of development for biomarkers related to inflammatory.

Dave Iverson: No, I'm glad you brought that up, Todd, because on one of the earlier slides, there's a reference that says that within people who have Parkinson's Disease there's evidence of inflammation in the brain tissue, but that's postmortem. To date, we haven't had the ability to actually see what's going on with an inflammatory response in someone who's still alive. So this is part of that continuing quest, Todd, to be able to image Parkinson's better in the brain.

Todd Sherer: That's correct. It's to even get more insight into some of these early features of when and where the immune system may be playing a role in the disease to uncover that original question around the chicken and egg on how active is this early in disease versus as the disease is progressing. So we need better tools, both the brain imaging and a lot of the tools that Jeff was just referring to to really understand that over the course of the disease so we can get a better sense for the role the immune system is playing and how and when we might want to intervene with a therapy.

Dave Iverson: We're going to talk in a moment about alpha-synuclein in more detail and the way in which the immune system is engaged in that, so we'll hold a little bit in talking in more detail about the way the immune system might be helpful in harnessing that immune system to fight the buildup of that sticky protein alpha-synuclein. But generally speaking, Jeff, is there the thought that we know something, I think you said before, about how to manipulate the immune systems. Does that mean that we could use the immune system not just with alpha-synuclein, because we'll be talking about it in a second, but in a variety of ways as a way to further Parkinson's treatments?

Jeff Bronstein: Yeah, that's the hope whether we want to target alpha-synuclein specifically as this slide shows, and we can talk about that, or we might have more general sorts of things. We talked about the microbiome, and it's possible that a certain microbiome is going to be more favorable, so we may target the immune system by targeting just the bacteria in our guts, which is a possibility. That's a less specific way of doing things, or it can be very specific using specific antibodies or T cells to help clear the pathology.

Dave Iverson: Jeff, now let's transition into alpha-synuclein a bit. I'll ask Todd in a moment to go through where we are on the various clinical trials with alpha-synuclein but tell us something, Jeff Bronstein, about how this might work. Is this an example of where we know the sticky protein is built up in Parkinson's where our immune system might react to it the way they react to anything that goes amiss in the body and fight against that sticky build up? If you would, describe for us how the immune system might target alpha-synuclein.

Jeff Bronstein: We know for certain that if you make too much alpha-synuclein in your brain, you get Parkinson's Disease. We know this from genetic studies and animal studies as well. So we know when you make too much, it forms these aggregates or oligomers, these clumps, and that can be toxic. So one of the strategies and one that's furthest along that Todd can talk about is by developing antibodies, which are proteins that can attack that, and that basically tells the immune system, "Let's get rid of this." Can you prevent the accumulation and the spread of the alpha-synuclein from neuron to neuron?

Now, a lot of these concepts have actually been developed in other diseases like Alzheimer's disease, and there's a big inflammatory reaction in the brain in Alzheimer's disease. They're actually fairly far along to at least show that at least

some of these antibodies can actually clear the protein in Alzheimer's disease. So that's one of the ways that we hope to do this in Parkinson's disease.

In other studies, like in cancers and hopefully in Parkinson's you can actually hopefully manipulate the T cells or cellular immunity to do the same thing. It's not quite as far along in Parkinson's Disease, but both are very exciting strategies. They're exciting for me because when I think of the 25 years I've been in the field, all of the studies to stop the progression of the disease have really been based on oxidative stress, very nonspecific things, but we've learned so much in the last 15 or 20 years about the mechanisms by which we get Parkinson's and the brain gets damaged. This is one of the earliest treatments that really is focusing in in my opinion on the underlying pathology, so it's really exciting for that. To me, it's a whole new way of approaching the disease.

Dave Iverson: Well, let's see where we are then in that quest. We're putting up on the slides now a review of the number of the key studies that are trying to use this immunotherapy approach to getting after that sticky protein so that the immune system and antibodies would recognize that as something amiss and begin to attack it or break it down. We see, Todd Sherer, on this slide that we're getting further along. We're inching towards phase three which means that we're inching towards really learning whether or not some of these treatment ideas can work. You don't have to go through each one of them, Todd, but give us your big picture look at where we are now in this pursuit of trying to figure out a way to use an immunotherapy approach to attacking alpha-synuclein build up and the progression of Parkinson's.

Todd Sherer: This is actually, to echo what Jeff was just saying, a very exciting time in terms of the robustness of the approaches looking to develop treatments utilizing immune-based therapy to target alpha-synuclein. There's two main general approaches that are being used to see here that there's a few that are labeled antibody and one that says vaccine. In the case of the ones that are labeled antibody, what these approaches have done and these companies have done is genetically engineered in the laboratory an antibody with selectivity towards alpha-synuclein with the idea of then injecting that antibody into individuals so that the antibody will help direct the immune system to degrade the aggregated forms and pathological forms of alpha-synuclein in Parkinson's.

In the vaccine approach, it's a slightly different approach, and this is more of what you would think about with other vaccines you may have gotten where the company has genetically engineered a pathological form of alpha-synuclein, kind of the equivalent of when you get a vaccine and they inject a dead virus into your body, and then your body mounts its own immune response developing its own activated cells and antibodies towards that synthetic genetically engineered form. Then the hope is that that response within your body will go and find the alpha-synuclein aggregates present in the disease.

Just to give a summary of where these are, these have now moved through the initial, obviously, laboratory testing, and a number of them have moved through

the phase one testing which is really focused on initial safety as well as some biological outcomes to see whether injecting these antibodies is really having an effect on alpha-synuclein. Two of them have now moved into very robust phase two testing which will give an insight not only into more around the biology impact of these antibodies but also an initial indication of whether we think there's an impact on the disease.

These are very active now, and I think what's exciting is not only have they moved ahead, if you look on the left side here, it's some recognizable names of pharmaceutical and biotech companies like Roche and Biogen and AstraZeneca. These are very serious and significant companies that are involved in Parkinson's around these approaches, which, of course, is really exciting because it'll take great resources to move these all the way across to the finish line. Then seeing that there's multiple shots on goal so all of our eggs are not just in the basket of one antibody I think is also very encouraging. So this is a very robust time for this, a lot going on, and obviously we're doing all we can to make them move through these phases successfully and as quickly as we possibly can.

Dave Iverson: No, I think it's incredibly exciting, and it's, of course, a first that we're that far along with a possible therapy that could impact the progression of Parkinson's Disease. I want to move us on now to our just general questions and answers because there have been lots that are coming in, and I want to make sure that we do respond to them and come back and review anything that hasn't been clear that people participating in today's webinar would like us to discuss.

Let me start with this question, Todd Sherer, back to you again, we see all this progress that you were just describing with the alpha-synuclein trials. Is there anything starting to brew with any other kinds of immunotherapy approach? In other words, you were saying before that there's this intriguing connection perhaps between the *LRRK2* mutation that can lead one to be at risk for Parkinson's but also may play a role in inflammatory responses. We're starting now some trials with LRRK2 drugs. Are any of those focused on this inflammatory idea? I'm just curious about what else may be in the pipeline that would connect the dots between Parkinson's and the immune system more in inflammatory response.

Todd Sherer: I think there's two ways I'll go about answering this. One is that there are trials starting for LRRK2 inhibitors in Parkinson's. There also are active trials targeting another gene in Parkinson's which is called GBA. In both those cases, some of the biological impact of those genes is through the immune system. One of the things that, of course, is very scientifically interesting and challenging in terms of the mechanisms of Parkinson's is that a lot of these different mechanisms are interrelated. So if a person, in an animal study I should say, animal studies or laboratory studies if there is an induction of an immune response or inflammation, that could lead to alpha-synuclein aggregation, and alpha-synuclein aggregation can actually lead to an increased inflammatory response.

With some of these therapies that I'm mentioning like the LRRK2s and the GBAs, what we're trying to do is intervene in this pathological cycle that happens between some of the underlying pathways that are impacting in Parkinson's. These trials, LRRK2 is earlier, probably phase one. The GBA studies are in phase one, phase two. There are also a number of more preclinical studies, preclinical projects still in the laboratory where there are therapeutic approaches actually looking very specifically at some of the neuroinflammatory processes themselves to see if you could either enhance or limit those processes based on the hypothesis. That is active in Alzheimer's, and some of those are now being developed for Parkinson's as well.

Dave Iverson: The longer I've been associated with the foundation and with this question of solving the Parkinson's riddle is it seems to me it's all about connecting the dots. I just can't but feeling in a very enthusiastic way that we're getting that much closer to connecting some of these dots, so it is truly an exciting time I think. Let's get to all of your questions. Jeff Bronstein, let me get this question to you from Tom since you mentioned the word prebiotics earlier, Jeff. Tom wants to know what's the difference between probiotics and prebiotics and how that impacts the microbiome and Parkinson's.

Jeff Bronstein: The way I think about it, prebiotics are basically the foods that the bacteria feed on, so when you eat stuff, you're not just feeding yourself, you're feeding the bacteria in your gut. Probiotics are actually the bacteria themselves so that you can eat a lot of bacteria and probiotics. There's capsules and there's yogurts that all have bacteria in them, live bacteria, and the idea is there are some that might be better than others. If you eat billions of them that that's going to take resident in your gut and affect the level of inflammation in immunity. Where prebiotics are really the things that you feed them.

There's a fair amount of research out there of basically about how do you try to change the microbiome. I think the consensus is is that prebiotics are probably the more important part of it. So you can feed your gut all the bacteria you want, but if it doesn't have the preferred food source for the ones that are good, then you're not going to be able to maintain those. Again, soluble fibers are really good. There's lots of things in fruits and vegetables and things like that are really good prebiotics. So we think that's the better way to establish a healthy microbiome. It may be difficult to move the microbiome. I think there's a lot of evidence that it's established early in life and-

Jeff Bronstein: You know, it's established early in life, and so there's a lot of work that needs to be done in that field. But overall, I think the research supports a healthy diet. I think it's noncontroversial, you can't lose with that, but exactly why that is good for you, we're not sure.

Dave Iverson: And Todd, here's a smart question about how antibodies make it past the blood-brain barrier. This is an age-old question in treatments for Parkinson's and other diseases of course, as well. So briefly Todd, a description if you would, of the blood-brain barrier, and then how the antibodies get past that.

Todd Sherer: The blood-brain barrier is a system within the brain that limits exposure of the brain to pathogens and certain other compounds that are in the blood. It's really to protect the brain from being fully exposed to everything like infections or other pathogens that are in the blood. But the body has specific mechanisms to get nutrients and other things that the brain needs from the blood, so it's a controlled process, and normally serves a protective function for the body. It is a challenge for neurological drug development, because it can also limit exposure to the brain of a lot of the therapeutic chemicals or compounds that we're developing. There's a lot of work that goes into designing these drugs to get across the blood-brain barrier, and into the brain.

It is actually somewhat of a mystery how the antibodies, particularly these therapeutic antibodies, get across the blood-brain barrier and into the brain. It's a very small percentage of the antibodies that do get into the brain, but there is clear evidence from animal studies and also some recent clinical studies that these antibodies are getting into the brain. There is a lot of work being done to try to see if you could genetically engineer the antibodies in a way that will increase their exposure into the brain, and it really has to be dealt with the dosing of the antibodies, and how frequently you give the antibodies, at this point, to get enough into the brain to have the impact that you want. That's still one of the questions with these therapies, is can that be achieved?

Dave Iverson: Thank you Todd. Jeff, a number of questions about people's being interested for understandable reasons, in boosting their immune system or doing things that would be anti-inflammatory. This gets into the question you were saying before, we don't know yet enough about advising people to take ibuprofen. But people want to know, are there other things they can do to boost their immune system? That's part one of the question. Part two is, what about things like statins, do they have an anti-inflammatory response? Help us with those two, if you would Jeff, are there other things you can do to boost your immune system, and what about statins and their anti-inflammatory impact?

Jeff Bronstein: The first one's a little bit harder. I wouldn't even say boost the immune system, because as we talked about the immune system can be good and bad, depending on the aspect, so how can you optimize or have a healthy immune system? I think right now, besides a lot of the very basic things that we attribute to good health, like a healthy diet, a good night's sleep, mindfulness, all of these things seem to help with a more stable immune system. I think there are plenty of examples in medicine when people are overstressed, how their immune system is more vulnerable and people get sick. Whether they don't sleep enough, you get a cold. People that are grieving are more at-risk of cancer and other things. I think stress, physical and emotional stress are also things that likely contribute to a less than optimal immune system. The basics, a good diet, a good sleep, and reducing stress are probably the key components that we know of right now, that we know are effective.

Regarding medications, just like we were talking about epidemiologic studies with anti-inflammatories, there are similar studies that a number of people have

found that people taking statins, things that lower cholesterol are associated with a lower risk. It's a little less clear, number one, whether it's a cause and effect. It might be that people with very high cholesterol are at an... the high cholesterol alters risk, and we're just seeing a signal because people with high cholesterol tend to take statins. Or, could the statins actually be reducing the risk, specifically? We don't know that answer for sure. There is some evidence that the statins might be helpful specifically, and one of the ways that statins have been proposed to help is by being anti-inflammatory. There are obviously other things, like we were talking about GBA and LRRK2, is everything's interrelated. There are some small studies that have gone on, looking at statins in progression of disease, but I think it's too soon to recommend any of these things.

Dave Iverson: And speaking of interrelationships and connections, here's another one Todd, that maybe you can pick up, and that's whether or not any of these immunotherapies work for Parkinson's related conditions, things like multiple system atrophy, or Lewy Body dementia? We don't focus on those conditions enough, I think we all feel, so it's a good question, and it also speaks to, you both have referenced how we've learned from the Alzheimer's field. Are these immunotherapies, Todd, something that could cut across these different diseases, and be helpful to some of these other conditions, as well?

Todd Sherer: Yeah, so I'm glad, thanks for the question. In particularly the ones we talked about today where the immunotherapies are being developed to focus on alpha-synuclein aggregates, theoretically these therapeutic approaches could have an impact across a spectrum of diseases that are marked by alpha-synuclein aggregates, or what are called synucleinopathies. A disease like you mentioned, Lewy body disease, Lewy bodies in that disease are also composed of alpha-synuclein aggregates. Theoretically, if the antibody or the immunotherapy is helping the body get rid of the alpha-synuclein aggregates, it could have implications across a number of these diseases.

There is some nuance in these that the aggregates may not be exactly the same in all these diseases, particularly in a disease like MSA, the aggregates are found more in glial cells in the brain and neuronal cells. But I still think that this general approach should have application across these diseases because the goal of what the therapy's trying to accomplish is integral not only to the underlying pathology in Parkinson's, but the underlying pathology of these related diseases, as well.

Dave Iverson: And Jeff, here's another kind of connection question that someone's raising. Arnold raises the question, are people who are on immunosuppressors, so he's referencing someone who has a transplant for example, are they more or less likely to have Parkinson's, and has that question been addressed in epidemiology?

Jeff Bronstein: The answer is, possibly. I think Todd had mentioned earlier, the inflammatory bowel disease study where there seemed to be some reduce... So, if you think

about when people have inflammatory bowel disease, they may have twice the increased risk, so we have to put perspective here. It's not like if you have inflammatory bowel disease, you're very likely going to get Parkinson's disease. You risk goes up one to two percent, so it teaches us something, but the absolute increase in risk is relatively small. Which is the real challenge in doing epidemiology is, you need a lot of people then, to start slicing out people, that in inflammatory bowel disease and are on this treatment, versus those on inflammatory bowels and no treatment, or other treatment, so it gets very, very difficult to study. That's the reason why there's really a lack of good data to support that.

There is a little bit in that one study that Todd referred to, but then again, in that study what they were showing was that people that were on the treatment head back to a normal risk. It reduced the increase risk. Whether being on one of these treatments for somebody who doesn't have an increase risk, whether that lowers it, we have no idea. These treatments can be very serious. Now, when people have transplants and all of these other things, they tend to have a lot of other illnesses, so it becomes very, very difficult to do these studies. There just aren't good data on that.

Dave Iverson: And there may not be on this next question, Jeff, but I'll ask it of you anyway, because people are making all these really interesting connections, I think. One is, if you have an autoimmune disease, that impact likelihood of Parkinson's, and then similarly, what about prednisone, could that delay progression in Parkinson's? Because prednisone is something that's often used in autoimmune diseases, is that right, Jeff? Sort your way through that.

Jeff Bronstein: Well, so the first one's pretty easy as there's very little evidence out there that autoimmune disease in general, there's a lot of different immune diseases and they're different. Inflammatory bowel disease, there is the evidence, that's recent, that came out with that. I'm not aware of many for like lupus, which is another common one, or rheumatoid, whether they are not. There's not a lot of data out there, and my guess is, it's not a huge influence because if you don't see a signal, it might be a small influence and we're just missing it.

Drugs like prednisone are very effective in the short run, but they're very toxic in the long run. I think that's something that we have to think about with any of these treatments. People already have pretty close to a normal lifespan when you have Parkinson's disease. If get the disease in your early 60s, whatever treatment we have, you're likely going to be on it for 20, 30 years, and so we have to think about the safety in the long run. Being on prednisone for 20 or 30 years, you're almost certainly going to have many more problems from the prednisone than you would from Parkinson's disease.

All of these treatments to modulate the immune system really for the long run, there's a lot of very, very important safety issues to keep in mind. These drugs for inflammatory bowel disease make you very susceptible to infections, and certain ones are very difficult to treat. Certain viruses we know, we modulate

the immune system when autoimmune disease is multiple sclerosis, and people can get life-threatening viruses being on these treatments that suppress the immune system. We have to be very careful. It's a complex system. Anybody who tries to study it, your head goes crazy with all the different interconnections. It's extremely complicated. Trying to manipulate it in a way that does more good than damage is a daunting task. We have to be humble when we start trying to manipulate the immune system for a chronic disease like this.

Dave Iverson: One more question, and then I'll ask you both to for some summary thoughts. Todd, this is a question from a listener who asks, is the immune system different? Do we know if the immune system is different in someone with Parkinson's? Do they respond differently to other invaders in the body, or does it make you more prone to certain kinds of infections? What can you tell us, whether we know anything about whether someone with Parkinson's has their immune system in some way, fundamentally altered?

Todd Sherer: Yeah. It's a great question, that the details are still being analyzed very significantly. We do believe that there's some evidence to suggest that the immune system does respond differently in Parkinson's than someone without Parkinson's. One of the examples is this recent discovery, and Jeff, I believed referenced this information earlier on the call, where people with Parkinson's, their immune system is responding differently to exposure to an alpha-synuclein than someone without Parkinson's. They might have a heightened response. Some of their cells get activated in a different way than someone without Parkinson's.

This is still being dissected. As we're still trying to understand the immune system, that's still part of the challenge. I think the other question, which we've touched on a few times is, what's sort of the cause and effect of this? Is the reason the immune system is different lead to the onset of Parkinson's? Or is it, once you have Parkinson's, your body is responding differently to certain things? This is an open question. There's some initial data suggesting there is differences. We have that data for example in the postmortem of brains showing a more activated microglia in people with Parkinson's, that again would suggest some kind of heightened response, or differential response. But this still needs to be worked out.

It might be helpful, I don't know if Jeff wants to comment a little bit about the infection, from a medical perspective, if people with Parkinson's, how they respond to the flu, or other things they might be exposed to, before we end this?

Jeff Bronstein: Yeah. I don't think there's any good evidence that it's specifically different in that way. I think people respond pretty similarly, in general, to infections.

Dave Iverson: Let me ask you both then, just for some quick sum-up thoughts, a minute or so each, if you would. I think we've talked about a lot of fascinating

interconnections in the field, and the way in which the immune system may in fact connect some of those dots. Obviously an exciting area of research, and so to you each last, Jeff, you indicated this earlier, but come back to that if you would, and sum-up for us why you find this area of research so intriguing, harnessing the immune system and immunotherapy approach in a way that could really get at this perennial request to breakdown and limit the progression of Parkinson's.

Jeff Bronstein: The reason why I'm excited is, it seems to be another possible piece of the puzzle. The way I envision therapy in the future, and we're already moving towards that, it's really more of a personalized medicine. I think Todd already mentioned targeting GBA and LRRK2 as some of the early ways of targeting genetic forms of Parkinson's disease. But I think the more we understand about that individual's Parkinson's disease, we may direct therapy specifically to them. There may be people that have a very altered microbiome. We may want to target their microbiome. If we can measure that, we can get a better understanding of what's going on in the immune system in that person.

We may measure T cells. We may measure even the proteins in the brain in neurodegenerative disease through PET scans. The more we understand all these different pieces, the more we're going to be able to personalize and target treatment for that individual. I think the immune system may be one of those big pieces that we need to understand to be able to target it, so I think it's exciting.

Dave Iverson: Jeff, thank you. Todd, last thoughts.

Jeff Bronstein: The only thing I would add to what Jeff just said, because I agree completely is that, why I'm excited about this is that it's interesting scientifically, but it's also actionable. It's science that there's good evidence from other inflammatory diseases that you can convert some of this information actually into therapies, and it's starting to happen now with the examples we gave from synuclein. I think it's a great example of that kind of investment in the basic research now getting to a stage where we can move on it, to actually develop new treatments. I think that's what's particularly exciting to me.

Dave Iverson: Dr. Todd Sherer, CEO of The Michael J. Fox Foundation, and Dr. Jeff Bronstein, who leads the Movement Disorders Program at UCLA, thank you both so very much for your participation today, and of course for the ongoing work you do in our field. I want to thank everyone for participating in our webinar. I always find these so useful. I learn so much from doing them. We hope that's your experience as well.

As always, we want to encourage you to participate in Parkinson's research by going throughout Fox Trial Finder system to match-up with a clinical study in your area. A reminder too, that you can always watch previous webinars by going to our website, MichaelJFox.org/webinars. Thanks again, everyone. 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.