

Emerging Therapies and Parkinson's

An Interview with Dr. Michael Okun

Davis Phinney Foundation

Note: This is not a flawless, word-for-word transcript, but it's close.

Soania Mathur (Physician at UnshakeableMD, Parkinson's Advocate, Davis Phinney Foundation Board Member):

Hello everyone. Welcome to our webinar on emerging therapies in Parkinson's Disease. My name is Dr. Soania Mathur. I'm a family physician and someone who was diagnosed with PD almost 25 years ago. I'm privileged to serve on the board of directors for the Davis Spinney Foundation, and I also have the pleasure of being a moderator today. As a community, we're always anxiously waiting for news of a new disease-modifying or symptomatic treatment, something new that goes beyond the dopamine replacement that is still the gold standard treatment for managing the symptoms of this illness many decades after its discovery. And there is progress being made. We'll talk about some of those emerging therapies today. Help us navigate what's new in this area is to Dr. Michael Okun. Dr. Okun is a movement disorder specialist and is currently chair of neurology professor and executive director of the Norman Fixel Institute for Neurological Diseases at the University of Florida Health College of Medicine. He is a proficient co-author or author, I should say, co-authoring *Ending Parkinson's Disease*, authored *Living with Parkinson's Disease and Parkinson's Treatment*, and *10 Secrets to a Happier Life*, all of which are great. And I encourage you to read. Thank you for joining us today, Michael.

Michael Okun (Chair of Neurology, Professor, and Executive Director, Norman Fixel Institute for Neurological Diseases, the University of Florida Health College of Medicine):

Yeah, it's my pleasure to be here, Soania. And it's just great to visit and talk about what's new and what's emerging in the field.

Soania Mathur:

Thank you. So, before we get started on those therapies, there's been a lot of buzz around the news of a new tool, the Alpha nucleon seeding amplification assay that they say can help us to identify Parkinson's disease or the risk of developing this disease, what we call a biomarker. Can you explain to our listeners what this is exactly, and why is it important?

Michael Okun:

Yeah, so, it's actually a pretty interesting story and you know, it dates back now a number of years, and there, there are some really great scientists who have been working on what's called

seeding and working on different types of methods, one of which is called RT Quick, which is sort of real-time quaking of blood. And, you know, folks should know that this was actually developed around a disease called prion disease or mad cow disease. And what they needed to do was they needed to shake the blood up, and they found when they shook it up and they, or shook it up, they found out that the protein separated. And when they separated, they were able to tell the different fractions and use this as a diagnostic test for what's called PRION Disease, PRION, or prion disease. Now, we're not talking about prion disease today, although some people say Parkinson's is prion-like but over the past several years, these techniques have been getting better and better.

Okay? And so, these are what are called assays, you know, that can then be applied to blood or skin or CSF or spinal fluid, which is the fluid that surrounds the brain and the spinal cord. And so, the idea was as we have this great set of data called the Parkinson's progression biomarkers you know, a group from the Michael J. Fox Foundation, it's the PPMI. Okay? And it's a Parkinson's progression markers initiative. And the idea was is, hey, we've got blood or we actually, it wasn't blood, it was cerebral spinal fluid. We've got a whole bunch of data on people who have had Parkinson's. Why don't we apply it to this and see if we can pick up people both who have Parkinson's and people who might be pre-symptomatic who are going to get Parkinson's disease, and then look at folks who have the different genetic subtypes of Parkinson's?

And so, it's applying this technique across, and when people talk about, you know, this could be a breakthrough, the idea is that now we're starting to get closer to biologically being able to say whether somebody has Parkinson's or not with a test. Okay? And so, the diagnosis of Parkinson's and maybe even the diagnosis of Parkinson's before symptoms is what folks are interested in. And so, that was the big news here. So, if you have Parkinson's disease, it doesn't mean Soania, that you're going to have, you know, a new treatment that's there, but this is something that could drive the field, drive therapeutics, and actually improve clinical trials, making sure we have the right folks enrolled in clinical trials and drive our therapeutic development. And so, there's a lot to be happy about here in the story, but it's all about you shaking the fluid up. So, in this case, in three spinal fluids, the proteins separate, we use those proteins to tell whether or not somebody has this marker called synuclein in either the blood or the cerebral spinal fluid. In this case, it was the cerebral spinal fluid.

Soania Mathur:

So, I guess that means that the, those markers are present in people that may not have symptoms. Is that correct?

Michael Okun:

Yeah. So, the, in this cohort, you know, in this PPMI cohort, they had folks who had things like the rapid eye movement sleep or REM sleep behavior disorder. They had people who had

smelled dysfunctional. It was particularly good when you add that seeding assay to smell dysfunction. And even better if they have a test called a DAT study or dopamine transporter study. So, if you start adding a bunch of these things together, which is what's great about a dataset like PPMI, then you can get an even more accurate to your diagnosis. But it picked up people before. And then the other interesting thing, and here this was pretty fascinating, but had been published before by other authors when you do the SYLE assay, so, these RT quicks are called Sinan assay studies. They can come up negative in a large percentage of people with some of the genetic forms of Parkinson, for example, the most common genetic form, the L R K two, the LARC two kinase form of Parkinson's disease, you can frequently come up negative. And so, that's thrown, you know, I wouldn't say a wrench into the researchers, but it's made us kind of rethink, you know, how we're going to define Parkinson's and how this will be used and who might get missed. And so, it might be that we need groups of tests and not just one test in order to, you know, really get the diagnosis correct.

Soania Mathur:

You know, that's interesting because, you know, I think we as a community have always felt that our, our Parkinson's are so, individual in terms of my Parkinson's is different than someone else's that may have maybe a late onset or mine, which may run in the family is different from someone else who just develops Parkinson's out of the blue. So, can this sort of information help us kind of separate out different types of Parkinson's disease?

Michael Okun:

So, we don't know yet. However, there's now an active discussion that's going on to, you know, to say, hey, can this be used to help us phenotype different Parkinson's? And then there's this question of whether there are classification systems, and so, how we classify Parkinson's disease could be important to the Food and Drug Administration for developing therapeutics. And then there are staging systems, and then there are, there's stuff for clinical trials, there's stuff for patients there, and there are people with Parkinson, and then there's stuff for clinicians. And now we've kind of amalgamated all this and we've got this mess, and we've had to kind of separate the mess out so, that we don't end up with collateral damage in the Parkinson's field. And so, everybody understands what the different tests are going to do, what they're going to offer, what their role and function is, but that we don't overestimate.

So let, let's say you're somebody with Parkinson, you have a certain gene, you have a certain response on an assay that's either positive or negative, that we don't diminish at all, that an individual can have Parkinson's disease and be negative on one or more of these aspects. And so, all of a sudden, we invalidate their life with Parkinson's. So, we have to be very careful with what this means, what its meaning is. And you know, one of the things that I say is that we look for breakthroughs in a lot of different things. A number of years ago, we wrote a book called 10 Breakthrough Therapies. And one of the points we made in that book is a breakthrough Doesn't

always have to be a drug. It doesn't always have to be a device. It can be an aha moment of, hey, we should keep them out of the hospital.

We save more people by, by that, you know, breakthrough and understanding, which is again, from a group of investigators over a number of years, collectively putting that data together to drive something important. So, here, what the Fox Foundation has done is now collectively taken the wisdom, the wisdom of crowds applied it to the pp m I cohort, and now this can drive, you know, kind of, you know, a next level thought about where the fuel could go. So, I think it is really exciting and we're going to see some changes, I think, based on, based on these assays. And there'll be more assays and there'll be more scans, and there's going to be more confusion. And it's just important we talk straight to the Parkinson's community.

Soania Mathur:

I couldn't agree more. You touched on this, and maybe just to sort of bring it back to how it ties in with emerging therapies. How, how important will these sorts of assays or these sorts of classification systems be important to the research that we need in order to discover new therapies or treatments?

Michael Okun:

So there, there is a notion that if we follow in the footsteps of cancer and we follow in the footsteps of Alzheimer's disease, which has sort of a classification, okay. And they have amyloid therapy as you know, sort of, you know, they're talking about how important it is to separate out all of these different aspects, right? And then they have tau in the blood, so, they, and then they have imaging and, you know, MRIs and things that they use, and they can use this to kind of separate people out. That's important from a regulatory standpoint. It's important to getting new drugs, new therapies, and new devices approved. And we see the same thing in cancers. And so, it's really tricky. It's a tricky business but it is really important that we actually begin to improve our specificity if we're going to drive therapeutics. And so, there is this push, you know, like between the different groups, the groups that are really driving toward therapeutics to really define this make the folks that are in clinical trials more homogenous to make sure if there's a positive result, we don't miss it. But at the same time, you know, we have to be careful that people aren't left out and don't misunderstand, you know, what the purpose of classifications versus staging systems versus just communication tools between clinicians and doctors are,

Soania Mathur:

Right. And I wonder also from the perspective of people that may not have clinical symptoms yet, but are part of that group, that it may be genetically at risk for it and maybe have one, is one of the symptoms, maybe the REM sleep disorder that you have said, and if they're sort of

identified as being high risk because of these markers, what does that mean for those individuals?

Michael Okun:

Yeah, and that's the big question, right? And that's, you know, that's why, you know, at least in the last time I was involved in a discussion, the Movement Disorder Society, they brought in, you know someone from the Parkinson's community to sit and address, you know, all the people that are actually making decisions, you know you know, dictating the science, some of the policy that's coming along. So, that's why it's so, important to have representation there, you know, because people can really get lost. And you know, one of the points that I had brought up during one of these meetings was, you know, what's the most common question we get on the Parkinson's disease helpline? The 1 804 PD info helpline? You know, it's, what do I have? You know, like, you know, I mean, it starts there, you know, and so, we start messing with that question, you know, you know, well, where am I with my Parkinson's is a very common question. We start messing with those constructs, and then we find out when we talk to the Parkinson's community, guess what? Not everybody wants to know. So, it's a really tricky, tricky thing. But you know, the dialogue so, important so, on, you know, so, important. We have the dialogue and the persons with Parkinson's are present for this dialogue.

Soania Mathur:

Yeah, that's very true. And that also begs the question that, you know, if you find out that you may be going to develop symptoms in the future what's new on the horizon in terms of disease modification? Because we really don't have anything to offer those patients right now. But is there something you see on the horizon that might be coming that may prevent people from actually developing clinical symptoms?

Michael Okun:

Yeah, so, it's a good question. And we're still a bit stuck, right? And I won't say that we're stuck in the mud because there's a lot of work that's, that's going on. There are some arguments, you know among experts as to what constitutes disease modification. And so, just in summary, we think of things, I think of things very simply. I'm kind of a simple guy. So, I think about the buckets, right? The, you know, bucket number one, you give somebody something, there's a punch to it helps their symptoms so, that we call that symptomatic therapies. Bucket number two would be you have a disease like Parkinson's, and you want to give therapy to slow the disease progression down. Okay? And so, that would be bucket number two. That's what we're talking about. Bucket number three is sort of the, could you cure one of these forms of Parkinson's disease or all Parkinson's?

So, it would be the three buckets, right? And of course, the cure buckets, at least for specific genes and things are furthest away. Now, could we slow the disease in some meaningful way?

Okay, could we, could we slow it down in some meaningful way to allow, you know, other things to catch up, you know? So, then we start playing a game with other diseases while you're going to, your heart or your lungs or cancer or something else is going to overtake you, but your actuarial people, you'll live longer or live a full life. And so, that's kind of the game that we're playing in terms of science. Could we slow it down? The answer to the question is that it's not clear anything has been shown with a very large effect size, meaning, you know, maybe some of these therapies are slowing endpoints, you know, certain endpoints like dyskinesia, or maybe they're slowing in a, you know, an endpoint, you know, to hospitalization.

They're doing something with motor symptoms and non-reemergence of motor symptoms over time. So, does that amount to enough to cause enough of an effect that we would say it's disease-modifying? You know, there's been a lot of debate with Rasagiline, with the MAO-B inhibitors, haven't really seen that move far. So, if there is a protective effect, no matter which side of that argument you are, it's really small. Okay? And so, exenatide diabetes drugs, the next one that people are talking about, again, there's still some discussion. There's been a number of those drugs that are tried, and then there are people repurposing drugs and taking a look. But I think god's honest truth is that, you know, certainly people are interested in some effective exercise and disease modifications, some effective devices, some effective meds, but it isn't there yet.

So, any, we don't have enough bite yet that we're going to get, you know, like really excited about that. Now, the Alzheimer's field and Lecanemab and anything, now they're starting to see could they have one or two that might have enough that could end up in a combo therapy, you know, like, like in cancer, in order to get to combo therapies like cancer, which is where we may be going with Parkinson, we're going to need to pick up a few wins that are large enough wins that they don't maybe have to be home runs. Maybe they can be singles if you're a baseball fan and maybe we could just get on base, you know if we can get on base a few times, combine those therapies together, that's sort of the cancer model as well. And so, we're not quite there yet, although there's a lot of interest and still a lot of studies with drug repurposing, multimillions of dollars have been spent. And we're, we're just not quite there yet.

Soania Mathur:

I really like your analogy of the buckets, because I think obviously bucket three is what we all want to see one day, that cure, or, you know, bucket two would be great because if we could slow down the progression of the disability that we all face and that, you know, poor quality of life, which is often an outcome of this disease, that would be great. But there's also, it's important until that those two buckets can be filled, that we find ways to improve the quality of life for patients or treat their symptoms. And one thing I've heard a lot about is the subcutaneous delivery of dopamine replacement. Can you tell us a little bit about that?

Michael Okun:

Yeah. So, there, there's actually been quite a bit of progress on this front, and folks should know that over the past couple of decades, okay? You know, talking decades, there's been this real mystery as to why we can't develop a therapy where we can put dopamine over the skin, right? People, you know, people don't like, you know, meds, right? If you take your hands and you put all the meds for a Parkinson's person in their hands, sometimes they can't hold it in their two hands, right? And so, thinking about, you know, this solution is really, you know, can be life-changing, right? If this could get going. And so, you know, the problem has been methyl's and methyl's of dopamine are hard to get across the skin. It's just been a really difficult problem. People are trying to solve it.

We've finally seeing not only some solutions in the lab, but now we're seeing like this competing convergence. And sometimes you see this cool convergence with a race to the finish line, right? And so, now we're seeing a race to the finish line, and we actually have seen two, you know, kind of innovative groups that have solved the problem, or at least initially addressed the problem and are moving toward potential approvals and getting things out into the ether. Okay? And so, one is actually making a liquid form of regular carbidopa-levodopa. Some people call that Santi. Okay? you know, it's sold, of course, it's sold in a different formulation within Cide and Canada and the UK and different areas of the world. But the Carbidopa levodopa is the formulation. They've taken it into liquid, okay? And there's a company called NeuroDerm, and they can deliver up to 750 or something, you know, it's somewhere in that range of milligrams of equivalent dopamine per day.

Do a pump that goes subcutaneously into the skin. It's like a diabetic pump. You don't need to put it into the GI tract. You don't need to put DBS leads in the brain. And this is improved on time for folks. And so, this is just taking carbidopa-levodopa kind of liquefying it, putting it into a magical solution, and figuring out a way to get it across the skin. So, that's been one approach. The second approach is by a company called AbbVie, where they have phis-levodopa, phis-carbidopa, different formulations, and they're able to also put it across the skin, and they're able to do a little bit more than the 700 milligrams, at least in some of the initial studies. And so, we'll see these therapies both seem to improve on time, seem to decrease OFF time.

There's some thought they're going to decrease dyskinesia too. If you look at some of these studies, will they be as powerful as DBS and focused ultrasound and some of these other things? Probably not quite, but they may be a great addition to the armamentarium, especially if we can get rid of some of the, you know, the taking meds all the time and equilibrate the blood levels for people to reduce their side effects. The big problem with these therapies. The big challenge has been these skin nodules and not just nodules. It's sort of, you can get these regions that are kind of raised and uncomfortable for folks and seeing that in both studies. And so, this is a problem that comes with the subcutaneous delivery of drugs. There's another one called apomorphine that's used in Europe and other regions also for Parkinson's. There's also a pump for that as well. And so, we're beginning to see the emergence of these, the skin nodules, the tolerance, how severe, you know folks motor fluctuations will be, we'll have to see how

they do, but it's actually pretty exciting to see it get across the skin. At least for me, watching people try to solve this problem. I, you know, people smarter than I have, have really started to make some progress here. So, I think it's something to be excited about.

Soania Mathur:

And Michael, what's the, what's the advantage of doing that over the duopa that we have all sort of heard about where the delivery is into the duo Enum?

Michael Okun:

Yeah. So, we don't have a head-to-head study. However, you know, the idea of not needing a Gastrojejunostomy tube or one of these, these you know, devices, maybe it's not a classical tube because it's not like a feeding tube, but a device that gets the drugs into the duo or into the small intestine for absorption, that's going to require a lot of care. And the external, it's going to go through the skin. The advantage to these is that it's going to be much easier. You're going to load the cartridge, you're going to put it on the skin, you're going to rotate it around to the different areas. And then, of course, you, the issue there is going to be skin nodules. The issue with the, with duopa is going to be, you know, other device-related infections, you know, with the tube itself. And so, there are also some issues with the size, or let's not say issues.

Issues sound so, negative, let's say challenges. Okay? So, challenges with the size of these devices, and these cartridges are pretty big for Duopa. The cartridges are pretty big for some of these other therapies. And so, there has been a movement to make those smaller and smaller. And I think as they get smaller and sleeker and smarter, smaller, sleeker, smarter, right? So, they'll be able to respond to your needs like a diabetic pump and blood sugar. I think you're going to see improvements. But this is like the first generation. So, for those of you that live through, you know, computers, this would be like dose 1.0 if you were programming in basic, these are just like, these are first-gen devices, they're pretty big, they're pretty clunky, and they're just, they're only going to get better.

Soania Mathur:

And that I think is really important. You've touched on, because, you know, we don't need a treatment, well, to be worse than to make things worse, you know, like the quality of life with treatment is also really important. And if you're hampered by the size of a device, it's it makes you question whether it's worth it that way. But, what about transdermal treatment is that something that's up and coming or something that's happened before your testing? Yeah, I mean,

Michael Okun:

I, yeah, so, there's a number of, you know, approaches. You know, of course, we've had transdermal skin patches, right? And we use the patch for other things besides dopamine, right? We can also use the patch for cholinesterase inhibitors, which can help with memory or hallucinations and other things like that. And so, thinking about transdermal delivery through a patch without a pump patch, okay, that's a really good point. So, these newer therapies I'm talking about with liquefying, the carbidopa levodopa in the Neurodermitis or the phis-carbidopa levodopa, these are, these are pump patches, you know, they sort of pump through these, you know, things that you'll insert that will go underneath the skin as opposed to straight patches where you just put the patch straight on the skin. Straight patches have been really troublesome for levodopa itself.

And so, this is kind of the solution that the field has marched toward. I think we'll see other, other attempts here at the skin. And then of course folks know that have these patches. Sometimes people just don't stick, you know, like we're all different, right? So, some people will tell you that the patch won't stick, or you can get a reaction locally to the patch itself. And so, this is these are some of the like, real-world challenges that we see with these types of therapies. But the idea is, could we reduce the pill burden on people? Huge, right? I mean, I don't have to tell you that, right? It's huge. And so, and there are studies that have come out looking at duopa and, you know, and other therapies and starting to talk about pill burden. And I think it's something, we're going to hear those two words a lot more in the years coming. And I think it's important. And I think that those words come up because of folks like you that are advocating in the field and saying, this is really important. And so, it's one of the underestimated outcomes of these studies.

Soania Mathur:

Yeah. Yeah, I mean, it's a difficult situation because as your disease progresses, you're more likely to get into swallowing issues, and then you're also more likely to be on more pills at that point in time. So, it becomes a very difficult sort of situation to be in. You mentioned when we were talking about pumps, apomorphine being available or being tested in Europe what that kind of brought to mind rescue medications and the things people can take in when they're sort of in that OFF-state or freezing state. Is there anything new or coming up with rescue medications that we should know about?

Michael Okun:

Yeah, so, I, there's been a little bit of movement, you know, here in this area it's a little more incremental, you know, I would say, you know, kind of from, at least from an expert's, you know, point of view folks, you know, obviously, you know, the people that are watching, remember, you can crush levodopa, you can chew the levodopa, you can take it with a little bit of acidic, you know you know, fluid meaning, you know, a soda pop or some vitamin C or some orange juice and get it into your system quickly. And then, you know, the big, you know, splash therapies have always been apomorphine. And I remember early in my career watching the

pictures of people getting injected with apomorphine, particularly in Europe and other areas, and getting up and walking and having the awakening.

So, it's a quicker way by injection. injections are not always awesome, you know, so, people start to think about, oh, could, could we do this with other means besides injection? And so, there's been these, you know, kind of little squares that you can put in sublingually and kind of dissolve to try to get a fast action. And the question comes up as, is it fast enough to make a difference? You know, versus, you know, something else. There are these puff approaches that people have tried to develop. And so, there is an ambrosia type of device that you can, you know, take a puff out of, and get, you know, get a quick on that way. It can be challenging, but once people learn how to, you know, load the device, it can be useful to have something like that there to, you know, to improve in.

It can also, by the way, okay, here's a free pearl for everybody listening. If you're not sure if your meds are absorbing, you can use some of these other things, you know, like taking a puff, you know, to do a different, use a different absorption system in your body, you know, so, that it's not using your stomach to see, hey, if I'm responding to that, but I'm not responding to the oral medications. Maybe I'm having something going on with my microbiome, small bacterial overgrowth, gastrin problems, and things like that. And apomorphine, same deal. Now, Europeans have known this way better than Americans for a long time, and now we're catching up. We're like, oh, you were seeing the new things we're catching up. And they're like, ah, you know, we've known this forever, but sort of important, you know, for people, particularly if you're worried about if you have absorption problems, but the idea, the name of the game is early and speed, right?

And so, if you're going to have an off, you want to get to it early so, you don't, it doesn't get deep. And you want to get that blood level back up and you want to speed it up. Things like adenosine and Opicapone and things haven't really been, you know, like the speed demons, you know, like in terms of adding something on that's going to be speedier. Now Opicapone, you know, they, they talk about it as a dopamine extender often causes a little bit of dyskinesia when you add it on, it's once a day. Remember we had Entacapone, you know, before, which goes with each dose. So, it's a similar medication like that. It's called a Catechol-o-methyltransferase transferase inhibitor, you know, so, it might extend the life of the dopamine. It's once a day. However, you've had to reduce the, you know, your total dopamine load, because it can push you into dyskinesia and it can be tricky to use as your Parkinson's progresses.

So as a rescue therapy, even though it's new and shiny, probably not. And then adenosine estro demine that's you know, been around for a while, the adenosine a two A antagonists and things have a very mild improvement in on time, kind of similar to what we see with MAO-B inhibitors. So, those wouldn't be the speedy solutions. And so, we talk about speed crush, what you got if that's all you've got. But you can, you can think about inhalers, you can think about injections

with apomorphine, and you can think about under the, under the tongue for some of the, you know, kind of rescue types of things. Right. Michael,

Soania Mathur:

You mentioned the microbiome and I think that's been something that's, you know, really been in the media and not just with Parkinson's disease, many other conditions. Are there any new recommendations or things that people should be aware of when it comes to the microbiome and Parkinson's?

Michael Okun:

Yeah, I think the number one thing that I teach people about the microbiome is do not get overconfident and think that you understand your microbiome. Just because you get some sort of microbiome scan or you get, you know, information on it, or you decide you're going to pay a company to give you your microbiome. This is a moving target. It depends on who does the test. It depends on what time the test is done. Your microbiome changes all the time and everybody's different. And it's very clear if we look at microbiomes of folks with Parkinson's and folks without Parkinson's or folks with other diseases, not just Parkinson, you know, you see it, I saw a nice talk on multiple sclerosis recently, you know, you will see this in stroke as well. There was a talk at the academy meeting on stroke. You're seeing this across diseases.

We just don't know what to do with the information. We're overwhelmed with it. And people say, oh, take a pro probiotic, you might make it worse. You might make it better. You might just spend your money and get nothing. You know. And so, the understanding of where we're at, I think there's a lot of hope for this. There's a lot of hype in the nutraceutical business who would love to take your money on the hype side and just be, I think, super careful and super humble. So, if I had to pair microbiome with one word, I would pair it with the word humble. I think we just need to be super humble that this is just overwhelming the number of organisms, spas, and things in your GI system, how they change to develop risk, and how they could impact the disease.

It's humbling. It provides us with some idea of where we could go with therapeutics and also with understanding Parkinson's. But it's not quite ready for primetime. Although what you're seeing now is a whole nutraceutical community that is out there to maybe cash in on this and just being real careful would be my best advice. And if anybody thinks they're too sure about diet and microbiome scratch your head and maybe just take a deep breath and don't rush into anything,

Soania Mathur:

Right? Another term that we hear often is inflammation and the role that it may play in the pathology of Parkinson's disease. So, what about treating inflammation as a way to treat PD or reduce the chances of getting it all together? Is that something that we're looking at?

Michael Okun:

So, there's been some great papers that just keep emerging all over the literature. Some great editorial, sort of some people way smarter than me in this area. And we've seen people on TNF alpha drugs, you know, things that you see on TV for arthritis and inflammatory bowel diseases like ulcerative colitis and Crohn's disease, and of course Crohn's more common than Parkinson, particularly the LARC two form of Parkinson's. So, kind of interesting. And then we look at the risk and there's clearly a reduced risk in Parkinson's disease across these groups that are using drugs that are reducing, we think reducing inflammation. We think we know what we know, we don't know what we don't know. And that's the that's kind of the scary part of this, but then translating this. So, taking that observation and translating this, we've done this a number of times in Parkinson's.

We did it with the uric acid story where we back translate this, try to then develop the treatment and it doesn't work okay. Necessarily for primary prevention. Okay? And so, I think there's a lesson there. So, I don't think that we're necessarily going to prevent a generation of Parkinson's disease by, you know, putting everybody on TNF alpha blockers or if even if we were able to identify people at risk, okay? It's a tough study to do. And then the question comes up, okay, I have Parkinson's now cats out of the bag. Should I reduce my inflammation? Okay. and is that going to improve the symptoms of Parkinson's? Well, cats out of the bag answer, not really sure. Some of these drugs that really are the heavy hitters at this come with some risks and some blood monitoring and things, and how much benefit is going to be there versus the risk?

How much more of the biology do we need to understand? So, I don't want to paint a bleak picture. I want to say I'm super interested in like, hey, why the heck is it that all these people that take these TNF alpha blockers either have a delay of when they see Parkinson's, or we see less Parkinson's in? And then why is that? And so, we have to answer that question I think biologically first, but the direct translation, and then also people translating back to the microbiome story. Let's just fecal put it, do fecal transplants and people, this could end up being a disaster too, if it's not done in a very thoughtful way. And so, the magic bullet here probably isn't there, but there's something there to teach us. And then getting back to something that we talked about earlier, which is combination therapies, right?

And so, Alzheimer's maybe, you know, got a piece of one with Lecanemab, maybe. Okay, what if we got a piece of one with an inflammation drug? And what if we get a piece of one with y you know, another approach? And what if we get a piece of one in gene therapy or something, you know, could we begin to piece together, you know, a combo road here where you don't try

to do it all with want not quite there yet, but pretty interesting. And I think an area totally worth pursuing.

Soania Mathur:

Yeah, I mean, I think people sometimes get frustrated at what we don't know, but by trying to answer those questions, we do really increase the understanding of our disease. And, you know, we'll, hopefully, that increased understanding will lead to some new developments. One thing we do know though is exercise. We know that exercise is vitally important in treating Parkinson's disease and improving quality of life. For those of us that have this disease, is there anything new in the exercise medicine arena? And if so, could you tell us about that?

Michael Okun:

Yeah, so, there, there are some new studies going on now. So, Dan Corso and his colleagues have a very large NIH study called Sparc, where they're beginning to look at this more carefully and also to try to understand not as much as you know, the question of does it work, right? So, the collective drip, drip, drip evidence that you've experienced over the years that we've all experienced has now become quite convincing, okay? We also have to step back, take the 50,000-foot view, and realize that this is not just in Parkinson, it's also true in other neurological diseases, and also true in general healthcare benefits. Okay? And so, there's going to be some trickiness of separating this out. And I think one of the keys here is how we give it, how you know, and what is the biological basis and what is the approach.

What's going to be the winning approach both to symptomatic therapy and if there's any disease modification, what's going to be a potential approach that can be guided, you know, based on the science? And so, Corso and colleagues are working on one approach. There are several other people that are working on other approaches. In our group, one of our fellows, al published a great paper talking about the difference between, you know, giving therapy and a burst and then giving therapy spaced. Okay? And there, when we think about basal ganglia diseases, these are queuing diseases, and how we're giving therapy and how we're prescribing therapy may be just as important, okay? as what the therapy is and how we deliver it. And so, we think of that. And so, there are so, many factors, right? Type of therapy, dose frequency maintenance. And then there's this notion in Parkinson's disease, and you touched on this a little bit, you know, earlier in a question you asked me about disease modification, and I'll just, you know, kind of harken back and travel back in time to that part of the conversation and say, you know, what would, what would be awesome is as if that we could maintain an effect, okay?

So, if we rehab somebody, and let's say somebody is falling or having, you know, problems with their walking, if we could continue a regiment to keep their maintenance of effect, that's a really good outcome, right? And we're, so, we're oftentimes thinking about, oh, we've had to delay the disease, we've had to cure the disease and everything. But if you could maintain function, okay, maybe not even dial the, dial it back. If you can maintain the function that's

going to be adequate for you to live and not have, you know, a really bad adverse event or a fall or fracture or something like that, super, super important. So, maintenance of function in my mind is an underrated pill burden for, you know, for folks with Parkinson's is underrated. And then some of the hype of some of the things like microbiome right now is a little overrated. So, those would be some of the thoughts that go through my mind.

Soania Mathur:

No, those, those are really great thoughts because you're right, it's the maintenance of function, it's the maintenance of independence, it's the maintenance of the quality of life, or improving quality of life that's so, vitally important to your life experience with this disease. So, yeah, I couldn't agree more with that assessment for sure. One of the other things that I've seen a lot of people discussing is vibration therapy, the new gloves that when warrant a difference in Parkinson's symptoms. First of all, we're shaking all the time. So, why would vibration treatment help in Parkinson's disease, if you could explain about that?

Michael Okun:

Yeah, so, you know, the story, you know, goes all the way back to Charco, who is, you know, perhaps the most famous, at least, you know, self-proclaimed neurologist or proclaimed by the field this before, you know, there was, you know, formal training programs in neurology, but in France, people would come in and they'd come in out of carriages or train rides. And when they were shaking a lot, you know, from these rides seemed to calm their tremors in some of their Parkinson's disease led to this notion of, you know, could we develop a treatment, you know, based on this? And actually, Charcot did that. And in fact, he assigned one of his pupils named Tourette, okay, you know, this famous guy, Tourette, to build a vibration helmet, you know, to do this. And so, you can look, and you can see all these great you know, interesting history and rich history on this.

People have done this for a while. If you look through the literature, there's a lot about vibration. And vibration seems to have some mild effect on Parkinson's. Is it a frequency effect? Is it an effect due to brain oscillations? You know, what is driving that? And so, a lot of, you know, super smart people have, you know, weighed in on this, you know, conversation. So, Peter Tass is one of these super smart people, really good scientists. He's at Stanford, and he's really interested in coordinated reset, you know, and how the brain can kind of reset. And he's interested in oscillations. And there's a whole bunch of people that have learned a lot about Parkinson's oscillations, even from what's happened with folks like you Parkinson, and those who go on to DBS, and we record out of your brains.

And we see these abnormal oscillations and beta bands and other things, and we start to think to ourselves, hey, wait a minute, wait a minute, okay, what if we could peripherally with gloves, with, you know, you know, wearable clothes, with sensors with things, what if we could drive the oscillations in the brain in a different direction? Is that the same thing that's kind of

happening when somebody shakes in a carriage? And could we do it more efficiently and could we affect many of the symptoms of Parkinson's disease in a symptomatic way, or even in some way, you know, delay, you know, progression as we talked about that second bucket? So, that's what these groups of investigators are doing. They're sort of saying to themselves, hey, there's something going on. And guess what? So, on, yeah, the same deal is happening in Alzheimer's disease and other neurodegenerative diseases with 40-hertz stimulation.

People are interested in this. So, this isn't like a news story. The challenge for those investigators, all of them, including Peter Tas, we need controls, okay? So, we haven't seen a good study with controls, okay? We need longer-term follow-up, and we need to understand how these systems work and whether or not they're persistent, and in whom. Now, there have also been several companies that are in this space that are making vibration devices that they can put on you and seeing some effects in some folks. And so, maybe it's a, you know, like one of these things like freezing of gait, sometimes you have a device and people say, oh my God, I have this device. And look what it did for Grandpa George, and now let's commercialize it. But it doesn't work for everybody. But there is a, there are a couple of Grandpa Georges in every hundred patients that you do, right?

So just enough to keep your hope alive, right? And so, the question comes up with these therapies is there's something to them. Yes. How big is the effect size? We talked about effect size. How many people will it help? What symptoms will it be persistent? What's the mechanism of action? Do you have controls? Because there's a huge placebo effect. And I know we all love to watch the Today Show, you know, and I love to watch Jenna Bush Hager talk about, you know, all the kids' books and things and everything. It's fantastic, right? And we get super excited and enthused when we watch CBS Sunday morning about Parkinson's and other things. Love all of those shows. I think it's super important. But remember, those are very placebo-ish types of events, right? When you're putting people on camera without placebo controls and without results of trials and people who are actually enrolled in trials.

So, it's very hard to judge and we need to actually step back and be careful when we do that because there can't, we can create some sense of false hope. Having said that, I think, you know, any sense of hope is great for the community, but sometimes I think we can go a little bit too far. So, I would say on the gloves, and I have a blog on Parkinson's Secrets and a lot of people hit the blog after I talked about this at parkinsonssecret.com, you know, like they, we discussed this, yeah. You know that there are issues and we, you know, talking about it all the way from the history forward. So, I don't want to invalidate it, but let's just get a little better data before we all decide that we want to wear, you know, gloves. I'm all in, you know, if it works and for whom it works, but let's, let's get some data before we go too far on the story.

Soania Mathur:

Yeah, that's fair enough. And I know some of our listeners are either have had DBS or considering DBS I know I've been prompted by my own movements as our specialist to consider

it in the, in the near future for a number of years, now, and I sort of haven't done that, taken that step yet. But is there anything new that's in the field of DBS that you can maybe share with us?

Michael Okun:

Yeah, so, I think it's super important for folks to know what's going on in surgical therapies. And we always say, you know, you know, knowing when to pull the trigger, boy, that's the hardest thing, right? So, you know, folks with Parkinson's disease, they ask us, where am I with the disease? And we talked about that with the assays and everything. And then they say, and then one of the big questions is when should I pull the trigger on something that's more invasive? Do you know? And this could be a stomach pump going into the stomach, but certainly putting leads in the brain, even though it's through these tiny little bros, it's still brain surgery, right? Or burning a hole in the brain with a newer therapy called focused ultrasound. Okay? And so, you see all these things buzzing around and you're, and it is I think got to be incredibly uncomfortable because you're, you're living with a disease and you're thinking, I'm doing good, but maybe I should pull the trigger and I could be doing better.

Or maybe I pull the trigger and I get a side effect, you know? And so, we think about these things now in terms of where the field has gone. So, we now are able to stimulate in two sides of the brain. So, that's good. Okay? You still get more side effects by the way, when you stimulate two sides of the brain, you put two leads in then with a single lead. So, you don't completely get away from that. And people worry about when you put two lesions in the brain, so, you can put a lesion in the brain with something called focused ultrasound. Put a lesion on two sides. People have been very historically worried about whether or not that's going to cause problems with speaking and cognition and things we call pseudobulbar. And so, we're kind of beginning to explore, you know, what the safety profile is in each person so, that we can have an individual conversation, okay?

DBS and focused ultrasound are still best for tremors, best for things like dyskinesia, and best for ON/OFF fluctuations. And it depends on which target you go into. Okay? We tend to use, you know, one-sided therapy when we put a lesion in the brain, like focused ultrasound, although there are now some studies where they're looking at doing this in two sides of the brain and seeing if they can get more accurate. The issue is when you come from outside the brain, you're still going to make a hole in the brain so, you don't get it back. Okay? Or you're going to make a hole. And if you put the lead, the lesion in the wrong place, particularly on the second side, could that cause more side effects? Certainly, the accuracy of focused ultrasound is going to be less in terms of temporal accuracy because you're not going to be in there mapping the brain, but it comes from outside.

So, you're going to get less side effects and less problems with lead breakages. And then the question is which targets? And so, there is some role for focused ultrasound, you know, in some folks. And so, I think that discussion is always worth having, you know, with your docs in terms

of DBS, there's been a lot of advances to the DBS technology, and so, the stimulators are better, okay? And some of them know we've been able to do this in our lab. Other people can do this where it's kind of like an iPhone where you change the software on the iPhone, right? And you can change the whole device, which is pretty cool. So, there's a lot of flexibility. And then there's something called a closed loop. And closed loop just means that you are able to sense brain signals and respond to brain signals in real-time.

And Parkinson, one of the trickiest diseases to do this in the closed loop because there are so, many different symptoms like Parkinson's and are, all of them are going to be driven by the beta band, which is one of these abnormal conversations in the brain or the beta bursts that we see. We don't know the answer to that question. We're able to steer the current a little bit better, maybe shave OFF some of the side effects in some of the folks, but you still have to get the lead in the right place, okay? That's the most important. Whether you have new technology or not, you get these DBS leads, you get the lesions in the right place, and you're going to get the best possible outcomes. Okay? Focused ultrasound is still behind. Although there was a study in the New England Journal of Medicine, a randomized study that randomized study didn't compare, okay?

They didn't give you a comparison group to tell you whom to choose focused ultrasound for. And the outcomes, you know, they were less than what we see in regular open p autonomies, but they're probably going to get better. And so, we're going to have to look to see, you know, what are the right targets for that? Who are the right people? And this will all emerge. And so, it is another option for folks. And so, it's something that you should think about and definitely, I always encourage folks to have these discussions, okay? When you're talking to your docs and figure out what's right for you. However, don't ever go in thinking we all know everything, okay? Every day I practice medicine, I know a little less, we're learning more about focused ultrasound, we're learning more about DBS. The longer we go on, the better the complication rate is, the lower the complication rate.

And we learn over time. And so, but these techniques have gotten better. And so, understanding when to pull that trigger is important. And asking that question, when should I pull the trigger? Is super important. And I think that these discussions need to be shared. There needs to be engagement, you know, good engagement, shared decision-making. It shouldn't be driven just by, you know, the folks like us. You know, we should be talking to each person and applying it at the right moment. It shouldn't be a one size fits all. And let's make a company a billion dollars and put e put these in everybody. That's not the path, you know, forward. The path forward here is let's be very thoughtful in our discussions about how we move forward.

Soania Mathur:

And I really appreciate that. And I'm, I don't expect any less to hear from you about the individualization of these treatments, because you're right. I mean, each person has to make that decision based on their current state of disease. They have to make the decision based on

how they're functioning in their life, and what their life experience is like with this disease. And also, in consultation with their, with their medical team as to what may, may they, they may be able to expect in terms of undergoing an invasive procedure like that. So, yeah individualization I think is really key. Absolutely. Is there anything else Dr. Okun, that you wanted to discuss in terms of emerging therapies that you might feel we should know about?

Michael Okun:

Well, one thing that I mentioned before is that a breakthrough doesn't always have to be a device or a drug. Okay? And so, I want people that are watching this to realize there are a lot of things that you can do, okay? To make sure that your Parkinson's is well treated and that you do well long term. So, I always say, have your doctor sneak up behind you and pull you and see if you can, you can adjust. If you can't, we may need to do something to prevent falling, fall prevention. Super important. So, we should be screening that at every visit, right? Super simple. We should be giving out hospitalization kits. We have free hospitalization kits that folks can get. We should be teaching people how to stay out of the hospital. Couldn't be anything better, you know, for us.

And the data is just so, good. We should be, you know, monitoring people when they go on dopamine agonists to keep them out of trouble. These are breakthroughs too, you know, depending on how, how, how you use that word. And so, if we think about, you know, what's emerging or what's breaking through. I just remind people; don't forget about those things you can do every day to live a great life and build on all this information. And we all just assume, oh, you know, like, we know this is yesterday's news. Well, I told you I just got out of the clinic yesterday. I saw a ton of folks. You assume everybody knows everything. Bad assumption. We have to keep teaching. We've had to keep people, you know, not only focused on what's the shiniest, newest thing but also making sure that they're taking full advantage of the things that we know can make a difference. And so, those to me, are emerging for each individual person. And we should be, you know, thinking about not just emerging therapies, but what's the emerging therapy for this person at this time.

Soania Mathur:

Very, very well said. They're wise words. And I just want to end with this, if, if you don't mind, is I always think in this age of connectivity and technology, we're sort of bombarded with copious amounts of information, some of which is credible, obviously, and other sources which are questionable. And so, how do you suggest to those in our Parkinson's community to sift through that information about new therapies or emerging therapies and work out which news is hopeful and which news is hype or even potentially harmful? So, how can we be better consumers of all that information that we see?

Michael Okun:

Awesome question. It's getting harder and harder, okay. To tell the difference between scam artists. And then there's this gray zone of people who are, who are into something that might be on the fringe that may one day end up being there. And there's enough hope there that you're wondering, well, boy, should I take this forward? I could be, I could be the pioneer. I could get like right out in front of this one, whether it's a cancer drug and we saw nilotinib, the cancer drugs, whether rise and fall, right? Of that story. And, you know, maybe it'll rise again in a different form, but people jumped out and wanted cancer drugs and got them offline for leukemia. We've seen this with folks that want to get into, you know, these chambers, you know, for hyperbaric oxygen. We've seen it with people that are you know, really interested in having all of their blood filtered off.

This is very old-fashioned. It's been around a long time, right? And so, chelation, you know, let's just find the bad chemical and chelate it off. And then people that claim that they're nutraceutical their vitamin, their hyper amount of this and that, here's the bottom line in my, in my words, okay? And in my point of view, we just have to be thoughtful, okay? And, you know, we don't, we shouldn't shout at each other. We should be very accepting of, you know, like everybody's point of view. Like, maybe you think this works, maybe you don't think this works, but we just need to be thoughtful when it comes down to that individual interaction between you and your healthcare team, whether it's a physician, a nurse practitioner, or pa, whoever's taking care of you. We just have to be thoughtful and open, which means we can't just shut people down when they come in and they bring this in and go, oh, we're going to talk about this again.

Right? Talk about glutathione again, let's be thoughtful. You know, like when, when people bring in and let's have a thoughtful discussion because at the end of the day, you know, you make the decisions, you know, like it's your decisions. And so, if we have a good, thoughtful discussion about it, then I think we can help to keep people out of trouble. I also think this is a great, absolutely great role for the foundations, okay? And so, many of the foundations, Davis Finney Foundation, Michael J. Fox Foundation, Parkinson's Foundation I helped her run their 1 804 PD info helpline. Go to an independent third-party source and ask the question, okay? And if you're not sure, ask the question multiple times. And don't be like the, you know, one Nobel Laure had said, you know, you see what you want to see, you find what you want to see.

You just have to; you have to be thoughtful. You have to ask the question multiple times, even if you're annoying. And just try to stay safe, you know, along the way. None of these are going to go away. A lot of them are multi-billion-dollar industries. And, you know, we just have to be thoughtful. We have to keep people safe. And then, and then don't be afraid to ask for a second opinion. Great. Second opinions come from foundations. Foundations are usually not-for-profits. Okay? There are foundations that are also off the beaten path that also are there to make money, you know, OFF of people as well. But most of the Parkinson's foundations that are the major foundations, they, they're going to answer your question and they're going to give you know, you know, you know information.

So, you can make that decision. At the end of the day, you've had to make that decision and people will take advantage of that gray zone. And we just need to be thoughtful. And if people go down that gray zone, you know what I say, tell me what happened so, I can learn from it. So, I can, I can integrate that into my next discussion with somebody else. So, if they say, oh my gosh, I would never have done that stem cell transplant again because I am blind, or I, you know, I've got spinal cord injury or whatever. If you don't, if you hide it from me, like if we have the conversation, you decide to do it, and you hide it from me, then I can't share that outcome or the positive or negative outcome with other people that get it. And so, we just have to be more thoughtful.

Soania Mathur:

Absolutely. Well, I'd like to thoughtfully thank everyone for joining us in this discussion, and I hope you found it helpful and educational. I know I did, certainly. And thank you so, much Dr. Oaken, for your time and expertise, really greatly, greatly. Always, always enjoy our discussions and what I learned from you each and every time.

Michael Okun:

And I always love it. Thank you very much. It's just a pleasure to always be with you. So, I love this hour that we spend together.

Soania Mathur:

Thank you so, much. So, remember everyone, we may not have a choice in our diagnosis, but how we face the challenges this disease brings that really is ours to define. So, choose to optimize your life, educate yourself, empower yourself, and celebrate your daily victories. So, until next time, be well and stay safe. Thank you.

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