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MJFF: Navigating Parkinson's disease can be challenging, but we're here to help. Welcome to The Michael J. Fox Foundation Podcast. Tune in as we discuss what you should know today about Parkinson's research, living well with the disease, and the foundation's mission to speed a cure. Free resources like this podcast are always available at michaeljfox.org.

Larry Gifford: Hello, I'm Larry Gifford, a proud member of The Michael J. Fox Foundation Patient Council, founder of pdavengers.com, and the host of another podcast called *When Life Gives You Parkinson's*. This is part two of milestones and momentum in Parkinson's research, as we mark 20 years with The Michael J. Fox Foundation. If you haven't heard part one, you might want to go back and listen to it. We released it in December of 2020. Quickly to get you up to speed, the foundation was founded by Michael J. Fox and Debi Brooks in 2000.

Debi is also today the foundation's executive vice chairman. The chief executive officer is Todd Sherer, PhD. He joined Michael J. Fox Foundation in 2004 as associate director of the research program. They are my guests today. We pick up the conversation where we left off last time. The Human Genome Project was completed in 2003. And a year later, there was excitement and hope around new research by an international consortium that implicated a new gene LRRK2, L-R-R-K2, in Parkinson's disease.

Investigators write that mutations in the LRRK2 gene may be central to the pathogenesis of Parkinsonism. Dr. Andrew Singleton, a distinguished investigator at the National Institutes of Health, remembers that as just the beginning of our understanding of the role of genetics in PD.

Dr. Andrew Singleton: We went from knowing nothing of the disease, we always thought it was a non-genetic disease, to now knowing there are 90 or a hundred different genes that influence the disease. And we know there's more to find.

Larry Gifford: Todd, that probably was an exciting time.

Todd Sherer: Yeah. I mean, this has been probably the biggest inflection point, in my opinion, in Parkinson's research and the potential for really transformative treatments that are targeting the disease process itself. When I was in the lab, like Andy said, there had been some studies that really suggested there was no genetic component to Parkinson's. And with the discovery of these genes, it really gave tangible science to go after for the cause of the disease and the underlying disease. And now there's a vast therapeutic pipeline based on LRRK2.

Even prior to LRRK2, alpha-synuclein in the late '90s was discovered as the first genetic link to Parkinson's. And this has really transformed our understanding.

It's brought in the pharmaceutical industry, which now has great interest in Parkinson's.

Larry Gifford: The foundation wasted no time in diving into the genetics at that point, using \$2.8 million grant to produce the genome map of Parkinson's. What exactly was that?

Todd Sherer: This was an attempt to really get a large population of Parkinson's patients and try to get a fundamental understanding of the genetic contributions to the disease and using the state-of-the-art genetic technology at the time. This was the first real attempt to map the entire genetic contribution to Parkinson's. The genetic technology has continued to advance and more and more has been discovered since then.

We're currently actually now with Andy Singleton working on a worldwide study that will look at over 150,000 patients using genetic technology, including people from diverse backgrounds, to really get a full genetic map of the disease. This is still been an ongoing project, but that was the first major step to try to map the underlying genetic contribution to the disease.

Larry Gifford: Now from a lay man's point of view, 17 years seems like a long time to try to figure something out. I think I would get frustrated. But in the scientific world, is 17 years a long time?

Todd Sherer: I think it's sort of you learned along the way. The genetic technology has allowed you to bring a bigger and bigger magnifying glass to the DNA. We've just been continuing to learn more and more about what the genetic contributions to the disease have been, and discoveries have happened along the way, like you mentioned, LRRK2, this other gene GBA, as Andy mentioned, 90 different genes being linked. With each iteration, you fine tune your knowledge and learn even more. Science is a long-term game to keep learning and building on that knowledge.

Larry Gifford: Okay. Let's bring Debi in here because I'd love to get her perspective on this.

Debi Brooks: I'll add a couple of things. Because Parkinson's happens to have a high variability person to person, and it's a very complex disease, just the process of going from disease understanding to developing new treatments inherently is stubbornly longer than other parts of medicine perhaps, although getting new treatments in any disease indication is hard. Biology's hard, but Parkinson's is generally slower and that is influenced by that variability and complexity. 17 years might feel long in some areas. 17 years could be short in an area of Parkinson's.

And one of the things that we've endeavored to do is to do what we can to speed up that process. If you go back to some of these early genetic findings, again, this is just good timing on our part. We had been around for a couple of years. We're starting to raise a little bit more money. We're meeting more

people. Science is a lot more... There's a lot more open dialogue across scientific pockets, and we're constantly... As an organization, we are beating the bushes. What's what should we do next? Of all the things we can do, what's most important?

How do we get started? That was kind of a constant reprieve. And one of the things we did early around some of these prime genetic targets, you can see the payoff of it today, is that we established these roadmaps. And again, it was a way to say, science left to its own devices might spend 10 years trying to go down one path and then shift its gears and spend another five to 10 years applying that and kind of reorienting, because that aha moment to drug store shelf goes across big different parties.

Academic research in early stages, biotech engagement in the middle stages, and big pharma and government at the end stages when you're doing these massive clinical studies. Our internal teams, and Todd led some of these efforts, we started to put together these roadmaps for each of these new genetic targets, so a LRRK2 roadmap, an alpha-synuclein roadmap, a GBA roadmap, and we've built more over time, but those are three that have helped really organize and prioritize and facilitate this concurrence.

At the same time, we're working on more deep understanding of the biology. At the same time, we're working on how are we going to [have a] deep understanding of the biology. At the same time we're working on how are we going to identify people who carry these mutations and build out these cohorts of genetic risk factor carriers so that they're primed and ready so that when someone wants to start a trial, we don't have to spend five years looking for everybody? How do we work with companies who are interested and might have some assets against these targets to kind of build out the tools they need for drug development, principally biomarkers, markers that can help us understand how the disease might be changing but also markers that understand if your drug treatment approach is engaging the target of interest? All sorts of things, and so we would map out these game plans and, again, the idea here was, can we accelerate? Because these are really tricky, complex processes and we want to bring as much value as quickly as possible as we can for our community.

Larry Gifford:

And traditionally, the Foundation is known for uniting patients and researchers from academia and industry and policy makers and regulators to push the critical research forward. And you had mentioned, corporate partners like Denali Therapeutics. Ryan Watts gives the Foundation huge heaps of credit for funding and spearheading the collaboration around the LRRK2 safety initiative.

Ryan Watts:

Part of this came about when we made a discovery that there was a histological finding, meaning a defect in certain organs, when we inhibited LRRK2 in large animals. And we basically partnered with the Fox Foundation and other companies in actually a really unique industry partnership to try to understand, is this observation something that will ultimately halt development of medicines

targeting LRRK2? And with a lot of effort from the Fox Foundation and these other collaborators in industry, we were able to basically show that, in fact, it was safe to inhibit LRRK2. And this was really fueled by the Fox Foundation because many companies at that time were very hesitant to continue working on LRRK2.

Larry Gifford: So that's exciting to hear, right? I mean, it's the whole trailblazer animalistic attitude that you have to just keep going after it.

Todd Sherer: Yeah, I think one of the things that we haven't talked about is, in addition to the funding, one of the things the Foundation's been very successful at is being a neutral convener across the research enterprise, as Ryan mentioned, in that there's no natural place for where competing pharmaceutical companies would feel comfortable sharing knowledge, sharing tools, sharing information, comparing results. And the reputation the Foundation has developed really is again, because of when Debi and Michael talk about their initial concepts, the purity of motive that Michael talks about all the time, we are here to develop treatments for Parkinson's. We have no other agenda.

That really does get a lot of credibility with the research community. We don't play favorites, we want everyone to win. And that really, I think, in this example, we had Pfizer, Denali, Merck, very significant companies willing to come to the table together for a common question, common scientific challenge, and we were able to break through that challenge. So now there's a trial Denali's doing on a LRRK2 inhibitor you can directly trace back to that work on the safety problem.

And I do think it's really clear to the mission of the Foundation and what we bring to the table here to be problem solvers and really provide that neutral environment, bring the patient interest to the table. What would the patient want to see happening right now? They would want to see us solving the problem together and that's what we try to do.

Larry Gifford: Speaking of the patients, Debi, in 2010 the Parkinson's Progression Markers Initiative, or PPMI, was launched. What is PPMI?

Debi Brooks: At the time and today, it's a landmark study where we looked to, in the most comprehensive way ever, study Parkinson's in patients from the earliest point that it could be identified, and at a scale where the information could be interpreted and applied. So this idea was that we would look at suspected Parkinson's, so just diagnosed, and really track and measure everything we could imagine in that patient over a multi-year period. And so the first iteration of PPMI had 400 newly diagnosed Parkinson's patients and 200 controls. I happen to be a control so I've been in that study since the very beginning, as have so many others, but over time what we found was that this was a core challenge for drug development in Parkinson's, particularly if you wanted to develop a medication or treatment that would interfere with the progression of the disease. You had a baseline need which was to actually say, "Well, in the

absence of treatment, what is the progression of the disease?" And this is a very difficult thing to answer and it remains difficult today.

But we had some hints and we had some kind of naive but at least places to start, in terms of things we might want to monitor, but we needed to study that in patients. And so that study launched and has continued, mostly by adding more and more flavors of Parkinson's disease. With increased understanding about Parkinson's disease, we know more about who's at risk for Parkinson's disease and so we've added people with Parkinson's who carries particular genetic mutations. We've added people who have a particular sleep disorder that makes you more at risk for Parkinson's. And we have people who have Parkinson's and that sleep disorder and we have people who don't have Parkinson's but have that sleep disorder. And everybody has gone through the same protocol. It's a global study.

And importantly, as we've built this and intentionally all the data has been collected, de-identified and made available to scientists worldwide. This endeavor is so massive and importantly, it's expensive and it's also the time and dedication of the participants in the study and so you can't squander that. And we knew on Day One, if we're going to do this, this is going to be such valuable information to everybody and 10 people shouldn't try to do this. It's hard to get done. So Fox will do it and we'll seek the support of companies who need this to design their trials, and then we'll engage the Parkinson's patient community and beyond, and we will build something that is going to give us a pathway to understanding the disease and its progression.

And so patients, they had to raise their hand and say, "I'm willing to get in," and particularly, almost in the moment they're told that they might have Parkinson's, which is not the easiest moment to recruit somebody. But I think we showed not only that we could run a study like this, but that our community wanted to step up and be part of it.

Larry Gifford: That's great. Todd, PPMI 2.0 is about to get underway. And the PPMI is one of those studies that could get us closer to a biomarker. The blood test or the hypertension in heart diseases, the blood sugar levels in diabetes. There's no biomarker for Parkinson's. How do you suppose this will get us closer to that?

Todd Sherer: Yeah, I think the most important thing that PPMI is doing is really mapping the disease itself, which because of the variability of the disease, we don't have that great information. From the earliest stages, even prior to the onset of motor symptoms, through the early stages of the disease, and then as the disease progresses. And what you need to do to develop those biomarkers is have the biological samples. So we have blood samples, spinal fluid samples, but having it get linked to the rigorous clinical information on the individual. So there's a number of tests being explored, measuring alpha-synuclein, measuring different proteins to really try to dissect what this is telling us about the disease.

And I think, again, most importantly, what this data has done is really fed into the design of clinical trials that are happening right now. If we want to slow the progression of the disease, we have to understand what the normal progression is, so we kind of have that baseline of what we're trying to improve against. And the protocols and data from PPMI are being used now in the design of these trials, like the trial that we talked about, that Ryan Watson Denali is doing. So it's really had a very significant impact, and I think it's only going to grow as we're able to expand the project.

Larry Gifford: And the patient experience has been really important to Michael too

Michael J. Fox: Patient experience in a patient struggle and overall outcome of our work is, central to everything we do. It starts with me, I guess, being that the foundation was created by someone with Parkinson's, that has a personal stake in it. I'm proud of the Michael J. Fox Foundation because it had my name on the work of all these fantastic people.

Larry Gifford: Hey, Todd, how important and what impact has it had on the scientific community to hear directly from the patients?

Todd Sherer: This is the only way we can learn about the disease. I was a laboratory researcher and I could do millions and millions of experiments in a cell culture hood or in a test tube. But unless we have the input from the patients on first clinically, what are we trying to fix? What's bothering you the most? And then, we talked before about learning about the genetics of Parkinson's. I can only learn about the genetics from Parkinson's from somebody who has Parkinson's and their family.

So this is such a critical aspect. And I think it's one thing that we have really focused on. As the foundation, we have a unique ability to link the community that we work, with the scientific community that we work with, and bridge that understanding. Most scientists who work on a disease never meet a person with that disease. And that's something that we've really focused on, not only the scientific research component of it, but the human component of it. It's motivating to researchers. And it's motivating to patients and community and family members to meet the researchers and hear from them and hear what they're excited about. So this is, I think, integral to the work. You can't cure a disease without involving people who have the disease, and that's really something we've put at the core of our research agenda.

Larry Gifford: With all the work you do, you give us hope for finding a way to end Parkinson's. And someone who speaks really eloquently about this is Jim McNasby. And Jim is a person with Parkinson's and the MJFF chief people officer and general counsel.

Jim McNasby: When I think about the work the foundation does and the commitment to a cure, it makes me feel like somebody's in there for me. Somebody is actually

going to work every day and trying to make things better for my life. And I got to tell you, that makes you feel so good.

Larry Gifford: How does that make you feel, Debi?

Debi Brooks: It's part of, that's a common message. And I have to say, it feels good to know that we're not just doing the hard work, head down, the slogging that it takes to really orchestrate all of this, to raise the money, spend the money smartly, get all that data out. It is hard work. But Jim and others, they remind us every day that this work is important, and that it brings hope.

This partnership that we have with the people with Parkinson's, their families, the people around them who love them, the researchers, what they want to bring, what they can bring and their pride in their work, and their willingness to collaborate, even though it's kind of a less common dimension than we would wish, sharing data, bringing it all to bear. It comes back to people like Jim, and it's a constant and important reminder, not only the role they play, but of the importance of the work. And it makes me proud. It really does. It makes me proud.

Larry Gifford: Well, you should feel proud. You recently announced that the Michael J. Fox Foundation has funded 1 billion in global research program since you opened its doors, 17 new drugs and devices since 2014. The pipeline is chock full of new potential therapies. Debi, I guess my question for you is, when you look at all this stuff going on and you look into the future, what excites you the most?

Debi Brooks: I think that the power of the patients and families has only in some ways just begun to be unlocked. And we talked a little bit about mapping the disease, that investment in disease understanding, expansion of PPMI, these are fundamental and seismic contributions to the state of the field. And it's one of the most interesting investments that we've really made. It's hundreds of millions of dollars and it's about to be doubled down. And it's one of the few things I can think of where you have an immediate payoff, which is this data that's flowing right into clinical trials being tested now in Parkinson's patients.

But it also has the ability to, over years, tell us something, bring us brand new insights into how the disease is changing, the variability person to person, is that most people believe it's more than one disease. Are there paths that we can now predict? The way we see Parkinson's will change daily. But the other dimension is over decades. And I'm excited about how patients have the key seat in that. That's been the case. But right now, we're on the precipice of having learned something about the people who are most at risk for Parkinson's and we're getting, in small numbers, so now we're looking to validate this and this'll be part of PPMI 2.0, understanding in some cases that we might be able to detect early or to really redefine when Parkinson's is starting for someone who has yet to show motor features but we know they're at high risk. To me, I'm very excited about that. I will tell you I didn't think that that was going to be possible at this stage. First of all, I wouldn't have understood it 20 years ago, but

even five years ago, to imagine that PPMI as a study would be validating that we understand some people who might be at higher risk and we can follow them in an observational study today. And under certain testing environments, we can say, "Oh, that person looks like they actually already really have PD even though they're not showing the classic motor features." The reason that's so important, by the way, is that we'd love to find...

We're proud of the new treatments that have already been approved, but all of them are new additions to a physician's ability to help manage symptoms of Parkinson's. We have yet to have found something that we know can change the course of disease, to interfere with the actually the biology of progression of Parkinson's disease. But we have a lot in the pipeline in phase one and phase two already that's looking at this. So if we're right, we're knocking on the door to be able now to even think that we could be applying those possible new treatments to a subset of people who have high risk for Parkinson's before they even show motor features. That early detection is really an ability to prevent Parkinson's. So this, now we have a broader continuum of possibilities of impact for people with Parkinson's and people who are at risk for Parkinson's we are working on today.

That path to prevention, to me, is a stunning new opportunity. It's not diminishing our commitment to what we're doing for people who have Parkinson's, symptomatic treatments, possibly disease modifying treatments, but to add the people at risk, this is stunning stuff and it's transformative. We're not going to let up. This is important work. This is why we're expanding what we're doing. We talked about urgency, and one of the downstream impacts and kind of pairing with that urgency is we spend every dollar we raise, right? Sometimes we spend it before we raise it. We're raising more money today and we have more science to put it to work on today. The impact is expanding. It's speeding up. It doesn't guarantee us anything, but just I know, and Michael and I talk about this, and since he's a hockey fan, to having these hockey analogy, more shots on goal. Statistically things are starting to move in our favor. And so this promise and excitement, I think it's everything.

Larry Gifford: Well, I mean you talk about exciting and sobering and urgency, and what you just said wraps it all up. I mean, sitting here and I got tears in my eyes just thinking of the possibilities. You said it early on, there's magic there and it's exciting, and so thank you for all you do.

Debi Brooks: We're proud. We're proud to be in the middle of all these people who care so desperately and passionately about this and help facilitate everybody's ability to bring better options. It's important work.

Larry Gifford: Oh, that's a perfect note to end on. This is important work, and we look forward to all the great discoveries in the future that the Michael J. Fox Foundation is going to help us animalistically push forward. Debi and Todd, thank you for taking us down memory lane.

Debi Brooks: Thank you, Larry.

Todd Sherer: Hey, thanks, Larry.

Larry Gifford: On behalf of all of us in the Parkinson's community, I also want to thank the MJFF staff, you guys are great, and the researchers around the world for working so hard to find a way to stop PD in its tracks. Thank you for listening and subscribing to the Michael J. Fox Foundation's Parkinson's podcast. If you'd like more information on the Michael J. Fox Foundation, its research, its programs, log on to Michaeljfox.org. For everyone at the Michael J. Fox Foundation, who is here until Parkinson's isn't, thank you for listening. I'm Larry Gifford. You can follow me on Facebook, Twitter, and Instagram. It's the same handle, @ParkinsonsPod. Be well, we'll talk to you next time.

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