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MJFF: Navigating Parkinson's disease can be challenging, but we are here to help. Welcome to of 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.

Maggie Kuhl: Welcome to a new podcast series of The Michael J. Fox Foundation. Parkinson's science POV. This is a new addition to our robust podcast offerings, such as our series about living well with PD, hosted by our patient council member, Larry Gifford, and reruns of our popular Third Thursday's webinars.

Maggie Kuhl: I'm Maggie Kuhl, Vice President of Research Communications. And with me are our chief scientific officers, Dr. Brian Fiske and Dr. Mark Frasier. Hey guys, thanks for joining me.

Brian Fiske: Hi.

Mark Frasier: Hey Maggie.

Mark Frasier: Thanks for having us.

Maggie Kuhl: So in this series, together the three of us are going to take on research progress and strategy. What milestones are we celebrating, and how will we get to the next?

Maggie Kuhl: So this perspective from both of you in your seats as CSOs comes from this unique position in Parkinson's research. You two must know what is going on across the field. What are patient's greatest needs? What's happening in the pipeline? What are the opportunities and the challenges?

Maggie Kuhl: So I think you two are really positioned for our patient audience to talk about the perspective of the Foundation and the strategy that comes from that knowledge across the field.

Maggie Kuhl: So beyond just your titles, what makes you qualified to know and direct Parkinson's strategy?

Maggie Kuhl: So, Brian, why don't you just introduce yourself to our listeners. You joined MJFF, let me look at my calendar, 2004, and what's kept you here ever since?

Brian Fiske: Yeah, exactly. So I've been here 2004, I think it's a little over 17 years now. And it was interesting, in graduate school I studied brain development basically, was

very interested in how brain cells connect to each other and develop, especially in those first few months after birth.

Brian Fiske: And I knew back then, even then that I didn't want to really follow the normal academic route. So I left the traditional lab environment soon after my graduate career and played around a little bit in science publishing, and then really had that opportunity in 2004 to begin working with the Foundation.

Brian Fiske: And at that stage, the Foundation was just a few years on its feet. It had really just gotten started. And back then I think we were figuring out what our strategic plan was going to be for addressing Parkinson's disease.

Brian Fiske: And so it was a really exciting time for me to be a part of that early development stage of the Foundation and see it grow, and help shape a lot of those programs. And learn with the Foundation as it was growing about what the challenges were and how we could address them.

Brian Fiske: And I think as a scientist, obviously being interested in the science is one aspect of it, but I think being able to use that science to help the Foundation achieve its mission I think was for me always been very compelling.

Maggie Kuhl: Mark, you've been helping the Foundation achieve its mission since 2004, when you joined the Foundation. So what brought you here and kept you?

Mark Frasier: Well, first of all I'm not that old. Brian's more experienced than I am. It was 2006 that I joined, so he's a little bit ahead of my time.

Brian Fiske: I think I actually hired you if I recall.

Mark Frasier: The reason I came to work for Brian and the Foundation was I came from a drug development job where... And the reason I took both of those jobs was to apply what I learned in the lab to really have an impact on people, and specifically people with Parkinson's disease.

Mark Frasier: I didn't want to just focus on one niche area of research, I think similar to Brian. So having an impact on people living with Parkinson's disease was really exciting as an opportunity, and sitting at the nexus where the Foundation sits across a research, working with industry, government, academics, universities, and really trying to drive the research agenda was also an exciting opportunity.

Mark Frasier: And we haven't gone out of business. We haven't cured the disease, which is one of the reasons I'm still here.

Maggie Kuhl: So 2004, 2006, and 2013 for me, I think what's kept us here is really the optimism, the progress and the optimism of what's to come. And the speed that we are going to reach our goal of a world without Parkinson's disease.

Maggie Kuhl: Optimism is a word we use a lot at the Foundation. It's a tenant of our strategy. I think it allows us to take big risks, go after big rewards. And today we want to talk about three reasons to be optimistic about Parkinson's research this year, and really focused on advances in therapies.

Maggie Kuhl: We all talk to and meet people with Parkinson's and their families, and that's what they want, that's what we want. New treatments for every stage of the disease. For people who are recently diagnosed, who've been living with Parkinson's for decades, and for the family members and then other people at risk. Hopefully there will be a day when no one has to receive a Parkinson's diagnosis.

Maggie Kuhl: So how are we going to reach that? Why don't we dive in, and Brian, I'm going to throw it to you to talk about the therapies that help people live better with Parkinson's today, symptomatic treatments. What's your perspective on the availability of symptomatic treatments? What's to come?

Brian Fiske: Yeah, so I think obviously addressing the symptoms of Parkinson's is a big part of delivering cures. Obviously we want to be able to ultimately slow the disease down, stop it, maybe even prevent it. But while we are still trying to figure that out, if we could just make people's lives easier by addressing and reducing some of the symptoms, that's obviously very key.

Brian Fiske: It's exciting for Parkinson's in that we do actually have available therapies that can address at least some of the symptoms of the disease, and predominantly mostly the movement problems people have. And for those who might be listening who have Parkinson's or care for someone with Parkinson's, most of you are well aware of these treatments. They target a brain chemical called dopamine, which is one of the chemicals. The cells that produce dopamine are degenerating, people with Parkinson's and loss of that chemical can lead to some of the movement problems that people have.

Brian Fiske: And so we can actually give people back some of that dopamine with some of the treatments that are available today, and that was just a huge game changer for the field.

Brian Fiske: It doesn't stop the disease, it doesn't cure the disease, and over time, even those treatments don't work quite so well over time. And so what we've seen... We're seeing now a lot in the pipeline is people, companies working on ways to optimize some of those treatments, including some of those original dopamine treatments where the goal now is to try to deliver them better or deliver them in different ways that can reduce some of the potential side effects and complications that the current treatments have.

Brian Fiske: And I think that's one perspective of the pipeline that's really powerful, because I think it takes what we know already and what we know works in people with

Parkinson's and tries to improve it. And make it better and make it last longer, and be more effective for longer. So that's one perspective.

Brian Fiske: I think the other one is that we're seeing people innovate in other ways around some of the symptoms, so including some of the non-motor symptoms. And I think that was a real shift. In the two decades that the Foundation's been around, one of the things I definitely saw shift was this understanding that Parkinson's isn't just about the movement problems. And that there are these other symptoms that we have to deal with. And so luckily we've started to see companies and drug makers appreciate that as well.

Brian Fiske: And so our perspective on the pipeline now is that we see movement towards trying to address some of those symptoms. And there's been a few approved versions, treatments that are focused on things like a low blood pressure problem that some people with Parkinson's have, or treatments that focus on psychosis, which can be a problem later in the disease stage and a complication of, of Parkinson's treatment.

Brian Fiske: And so we're seeing companies get really interested in that, and it's a harder pipeline to develop because we don't have this deep and understanding of the biology underlying some of those non-motor symptoms, not quite like we do around the dopamine and the movement problems.

Brian Fiske: But we're seeing a lot of progress and promise there. And so I think for me that's one of the other perspectives, is that when you look at that diversity of that symptom treatment type pipeline, that we're starting to see that, those different approaches being developed for Parkinson's. So that's really exciting.

Maggie Kuhl: And Brian, you said that we don't know as much about the biology of some of those symptoms. So Mark, how are we going to change that, learn more about the biology or find other ways around that?

Mark Frasier: Well, it starts with the person with Parkinson's, it starts with the patient. And understanding and listening to them about what matters, what symptoms they're experiencing. Understand what might be unique to Parkinson's disease. And then what might just be normal aging that we all experience?

Mark Frasier: And collecting information that is patient reported is really important, so we start there. But then I think we use that then to inform some more laboratory experiments, and dive into the biology a little bit to model some of these symptoms that we hear from the patients that are important, like constipation, like depression, like some cognitive issues, memory changes, and really understand what changes in the brain when these symptoms develop?

Mark Frasier: Or what changes in the body when these symptoms develop? And by modeling them we can then mimic in animal models, and identify specific underlying

biological targets that we can then prosecute and then go after using small molecules or non-pharmacological interventions.

Mark Frasier: And so starting with the patient and then understanding the biology, uncovering new targets, really to dissect this complex puzzle of different symptoms, different consolation of experiences is the way to go. And we've actually made a lot of progress in that area. We're continuing to fund a lot of basic biology, and expect to continue to support more biology around these really hard to treat symptoms like falling gait, et cetera.

Maggie Kuhl: So some treatments in development with what we know and some strategies to help us learn more. And Mark, a lot of what we know about Parkinson's biology to date has really informed another class of therapies, which are those that aim to slow or stop progression over all as we were discussing. Really stop Parkinson's in its tracks, curative really.

Maggie Kuhl: So how has our understanding of Parkinson's grown and led us to the state of the pipeline today?

Mark Frasier: Well, I always like to start with some of the genetic discoveries that have really uncovered some of the real high priority targets in Parkinson's disease. They've helped researchers understand what pathways go wrong in Parkinson's disease, and then with that understanding, really develop molecules that go after those proteins that go awry in Parkinson's.

Mark Frasier: So there's really been a genetic revolution in the last couple of decades really that have yielded a number of diverse drugs that we think might slow or stop the progression of the disease, that really target what we think are the underlying biological causes of Parkinson's disease. So it's really been a [seed 00:12:41] change.

Maggie Kuhl: And Brian, what's next for this strategy to stop Parkinson's? I should say strategies because I think that's the point, it's going to be a lot of them.

Brian Fiske: Yeah, I think as we're building this deeper understanding of what it means to be at risk for Parkinson's and what are the signals in the features, and what's the algorithm if you will that we could deploy to say, "You're someone who has a high likelihood of developing Parkinson's over the next several years."

Brian Fiske: With that in place, we can actually start to design clinical trials to then test interventions. And so understanding how to find those people and obviously understanding how to communicate with those people, and get them interested in this type of research is of course part of the challenge. But once you have that in place, you can start to actually develop those trial designs that would allow you to test potentially an intervention that over a period of time, you could then track and see whether or not people on that, taking that therapeutic, whether

they go on to develop Parkinson's or not. Or the full motor movement problems of Parkinson's.

Brian Fiske: And I think in doing that, that just gives us an ability to really test that idea. Can we slow the onset or prevent the onset of the movement aspects of Parkinson's? And it's a really powerful I think concept, because if we can do that, you can take that same prevention concept actually and apply it to other parts of the Parkinson's journey. So you don't have to necessarily do it in people at risk, you could do a similar type of trial design for example in people later in the disease and look for ability to delay onset of other key aspects of the disease too.

Brian Fiske: And so I think that's something else that we've been looking at as well, is about how can we think about Parkinson's in those later stage milestones? And think about preventative strategies at that level as well.

Brian Fiske: But I think this initial effort to try to develop this and design this platform for how you can do that I think will be really powerful, because we'll learn a lot about what works and doesn't work.

Maggie Kuhl: Mark, you're going to jump in?

Mark Frasier: I was just going to jump in. I think Brian's point is really important, that we can talk about prevention of Parkinson's, which is revolutionary. I don't think we would imagine talking about this five, 10 years ago, but the same strategy can be applied in different aspects of Parkinson's.

Mark Frasier: And we're funding this study, the Parkinson's Progression Markers Initiative, PPMI for short, and it is collecting this really deep data on people at different stages of the disease.

Mark Frasier: And some of the data emerging from the study is identifying certain factors early in the disease within the first two years of being diagnosed that may predict certain symptoms to develop later down the road. And so as Brian said, I think you can use these features to identify individuals, for example, that may be at risk, or at high risk for developing cognitive impairment and develop a cognitive prevention trial.

Mark Frasier: Or some individuals that are at risk for developing falls that might have balance issues, and try to prevent the balance issues from developing.

Mark Frasier: So it's just an exciting time using data from people with Parkinson's disease and that have identified features that we think can design these clinical trials more effectively, and ultimately hopefully prevent the disease from occurring.

Maggie Kuhl: Yeah, actually that's exactly what I was going to say, that we think of prevention as the motor. But if we could prevent these other really troubling aspects of the

disease that do impact quality of life, impact independence, I think that would be a clear success in one regard.

Maggie Kuhl: But again, I don't want to lose sight of our mission, which is to end Parkinson's and go out of business, which would potentially mean the motor symptoms as well.

Maggie Kuhl: So if we could go back to the prevention trials, people... Potential trials, people who have not yet received a Parkinson's diagnosis, who have some clinical symptoms perhaps but don't have the cardinal motor symptoms yet. Mark, what would those therapies look like? What are we working toward?

Mark Frasier: Yeah, well I think it's important to just remind everyone that... The why this is possible, and it's possible as Brian alluded to for three main reasons, three main advances.

Mark Frasier: One is there have been techniques and methods to identify individuals at risk for developing Parkinson's through certain genetic testing, or symptoms like smell loss or sleep changes that increase the likelihood that someone might develop Parkinson's. It's not a guaranteed, it's not 100%, but it at least allows researchers to identify individuals that have a greater risk for developing Parkinson's.

Mark Frasier: The second activity is having these objective markers that we know through data that change prior to developing some of the motor symptoms. So for example, there is a brain imaging scan that's called a DaTscan. This measures the dopamine cells that are lost, that Brian talked about in Parkinson's. And in a certain percentage of individuals that are at risk for developing Parkinson's we know DaTscan is abnormal, so it looks like Parkinson's disease even though they may not have symptoms.

Mark Frasier: So having these objective markers is really an important tool in advance that enables these prevention trials to be imagined, and for the researchers to start planning them.

Mark Frasier: The third one is just having these treatment options, having these new therapies that are not yet approved but they're in clinical testing. And as I said, we think they target the underlying biology of Parkinson's. And so having the treatments available that might be able to be deployed into a prevention trial is a really important advance.

Mark Frasier: And so what those prevention trials might look like, and this is very early days and I think it's important to emphasize this is likely to be a what we call proof of concept. It's just demonstrating that individuals can be found, the trial can be executed, and it may or may not show a benefit.

Mark Frasier: But what likely the trials would look like would be finding individuals at risks through some of the mechanisms I described, smell loss, sleep changes, or genetic mutations, using these biomarkers, like a brain dopamine scan, and confirming that they have abnormal or lower dopamine than healthy individuals, and enrolling them in a trial that one group is given a placebo, another group is given a treatment. And following those individuals over 12, 18, 24 months.

Mark Frasier: And since they don't have Parkinson's disease yet, the question is what would you actually measure? What would you measure that might or might not change with a drug intervention? And right now, what we would measure is the brain scan, the dopamine scan. We know it changes over time, particularly early in disease course.

Mark Frasier: So the outcome would be whether this particular drug or intervention actually slows or stop this deterioration that is observed with the dopamine scan.

Mark Frasier: Like I said, there may or may not be symptoms developed, but the outcome in the prevention trial, at least the first one, would be this dopamine brain scan. And if it did slow or stop the progression, then that would indicate that it is doing something to the underlying biology of Parkinson's and potentially slowing the disease process.

Maggie Kuhl: Go ahead, Brian.

Brian Fiske: No, from what Mark was saying too, I think one of the powerful parts of this too is thinking about our understanding of the biology and the biological progression of the disease. Thinking about the types of treatments that might be most useful at this very early stage of Parkinson's. Again, where again, these are people who aren't really exhibiting symptoms, might have some of the underlying biological features, like the dopamine scan that Mark mentioned, changes in that.

Brian Fiske: So you want to make sure that we're then using treatments that are targeting biology, that we think matters at that stage. And so we do know in the current therapeutic pipeline for Parkinson's that there might be some options, we might want to explore, for example, some of the treatments that are targeting accumulation of the [protein alpha-synuclein] in the brain, for example, that's a really leading theory for one of the causes of Parkinson's, or at least some aspects of Parkinson's.

Brian Fiske: And so that would be a good candidate to think about how we could target that mechanism. Or others think there might be strong role of the immune system in the triggering early Parkinson's. And so we might want to think about treatments that can target that mechanism.

Brian Fiske: So there may be a variety of actual treatment options we could think about putting into a prevention trial like this. And so actually some of the thinking and strategy we're starting to put in place is not just the design of the specific study and the interventions, but also the platform we might be able to do this in.

Brian Fiske: Could we actually test multiple treatments in parallel in an at-risk population to see which ones are showing the most promising potential? And so that... I think there's some advances in how we do this type of trial with multiple treatments that we're starting to work through as well. So I think it's really exciting time to see how this will all work out.

Maggie Kuhl: So it sounds like you need to decide what you're going to do and how you're going to do it, but you have pretty good leads on both of those. And so we're going to be working on that this year.

Maggie Kuhl: I started off saying we were going to talk about a couple of reasons to be really optimistic about the Foundation's research strategy and vision. I think that is one, a solid plan. Tell my four year old often we have to make a plan, it sounds like we have a plan for prevention. We also have a plan or an acknowledgement, and getting the right tools to prevent other troubling aspects of the disease in progression, falls, cognition issues.

Maggie Kuhl: And then similarly in symptomatic, I think the fact that we do have a diverse portfolio across approaches, across symptoms, and that we have the strategy and the opportunities in place to discover more and to leverage those findings to new therapies is what I'm taking away from this conversation.

Mark Frasier: Maggie, can I make a point on that last one? You may ask, why do you need so many options, even for dopaminergic, replacing dopamine or providing dopamine strategies? And the answer is that this is such a snowflake disease that different people respond to different treatments.

Mark Frasier: And the human body is a complex organism and the brain is a complex organ, and it is just a benefit to have multiple different tools in a doctor's toolbox to try different strategies for treatment. And some certainly respond better to others.

Mark Frasier: And the reasons for that are currently not understood, but having more diverse options I think is really important and a good thing.

Maggie Kuhl: Yeah, and that's why we need so many people to participate in research. And you said it earlier, Mark, that this all starts with people with the disease. There are so many different types of disease.

Maggie Kuhl: Brian, you were talking about the many different biological processes at play and the myriad of ways that we need to go after this onset and progression. So I want to thank you both for your time, and tell our listeners that, as I said, this is the first of hopefully many of these sessions.

Maggie Kuhl: Mark, Brian, and I will be back soon to share more research updates. And if you would like to lend your own experience to Parkinson's research and progress toward cures, you can join our PPMI study that mark mentioned. You can learn more at michaeljfox.org/podcast-PPMI. It's also linked in the show notes.

Maggie Kuhl: If you enjoyed our conversation I hope you will share it with your networks, rate and review us. Your support means so much. On behalf of all three of us, thank you so much for listening and hope to join you again soon.

MJFF: Thanks for listening. Community members like you are bringing us closer than ever to a world without Parkinson's disease.

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