Marie: Hello and welcome to *The Parkinson's Research Podcast: New Discoveries in Neuroscience*. I'm your host Dr. Marie McNeely, and I've partnered with The Michael J. Fox Foundation for Parkinson's Research to bring you to the forefront of the field of neuroscience to discuss the latest advances and discoveries with leading experts. I'm a science communicator and PhD-trained neuroscientist with a research background in Parkinson's disease and movement disorders.

The Michael J. Fox Foundation created this podcast for researchers, clinicians, and industry professionals with the hope that these conversations, and the resources we share will advance your efforts and partnerships to improve brain health. We are welcoming guests with a range of experiences and viewpoints. The views expressed belong to the guests themselves.

And today in our introductory episode, we are joined by two guests, Dr. Mark Frasier and Dr. Brian Fiske. Listeners, Brian and Mark are Co-Chief Scientific Officers at MJFF. And we are going to assess the state of the field broadly, give detail into MJFF's research strategy, and also talk about what it could mean for your research. So, we are going to start off with the big picture here. What do each of you see as the most important unanswered question in Parkinson's neuroscience today? And perhaps, Brian, if you could start.

Brian: Oh, great, give me the tough question at the start. But no, no, I think, I mean, obviously, a lot has really advanced in the last 20 years or so at least since the Foundation's been around. Certainly, our understanding of Parkinson's, we're learning a lot more about the genetics, we're learning a lot more about the underlying pathways.

But I do think there's still this big open question. And I think we're starting to chip away at it now, which is again, is really what is Parkinson's disease at the end of the day? What are the different underlying biological forms the disease can take? And then sort of the triggers that can ultimately lead to the symptoms that we recognize as Parkinson's. And I think that question is still kind of a very fundamental question that we're trying to answer. Although, I think maybe we'll talk about it a little bit more later. There are some emerging tools that I think are going to help us start to chip away at that.

Marie: Absolutely. And Mark, what are your thoughts?

Mark: Yeah, I mean, just building on what Brian had said, I think one of the biggest questions is, will disease modifying treatments, that is, treatments that we think slow or even stop the progression of Parkinson's disease, will they be different for different subsets of Parkinson's disease? And Brian mentioned the different biological pathways. So, one of the things that I'm really curious about is, are there different biological pathways that would have people with Parkinson's

responsive to different treatment strategies that really target those specific biological pathways? So, we have a lot of exciting treatments in clinical trials now that we think could slow or stop the progression. They're targeting different molecular and biological pathways. And so, what I'm wondering is, will there be specific subsets of Parkinson's disease that are responsive to specific treatment paradigms?

Marie: Oh, very interesting. Kind of digging into this sort of precision and personalized medicine aspect of it.

Mark: That's right.

Marie: Well, I know there are these big gaps. We identified these important questions that remain to be answered, but how is MJFF working to help fill these critical knowledge gaps?

Mark: Yeah, so the Fox Foundation, I think, sees itself as a neutral convener. And by that, I mean, we work with multiple different stakeholders across industry, government funders, other nonprofits, both within and outside of Parkinson's disease, as well as regulatory agencies, and many, many academic researchers. And so, there's really two mechanisms that we use to fill the knowledge gaps. One is research funding by developing a research strategy and identifying the specific areas that need not just money, but the patient-developed money and funding for specific areas of science. We will help fund research in those areas. But the second area is convening and bringing groups together to focus on specific challenges or problems that need multiple stakeholders or multiple scientific disciplines. So, very often we have workshops and are part of consortia that are focusing on these field-wide challenges that really require multiple different expertise to address these challenges. So, it's both through convening and funding that I think we fill those knowledge gaps.

Marie: Excellent. And Brian, did you have anything that you wanted to add?

Brian: Yeah, I mean, I think one of the important ways that we operate is this sort of, what I like to call a strategic funder and facilitator of Parkinson's research and drug development. And a lot of that strategic side of that is really about our ability to really kind of see the big picture and understand the big challenges that we face in delivering new treatments for Parkinson's. And over the years, the team here has really kind of developed, I think, a very sophisticated view of that.

We obviously can start first, of course, with our understanding of the disease itself and its progressive nature and what does that mean in the context of early disease versus later disease, needs of people who are living with Parkinson's. But we can kind of overlay on top of that kind of a real, I think, sophisticated

understanding of what does it take to actually develop and deliver new treatments? And that is obviously the key biological and scientific questions that we have to answer about the disease itself. But also the tools we need to generate, the measurement tools, the biomarkers, the imaging agents, even just the research laboratory tools and models that people need. And then ultimately, how do we sort of deliver that into the therapeutic pipeline? So, what support mechanisms are needed too, whether it's direct financial support to get companies invested in Parkinson's disease drug development, or a lot of the enabling work we can do around the therapeutic pipeline. So again, improving clinical trial designs and getting consensus on the best ways to test these agents in people with Parkinson's, or how do we find and recruit people to be in these trials. So there's a lot of work, I think, that the foundation can do, and a lot of different ways that we can act that are really built around this sort of sophisticated kind of understanding of the problem we're trying to address.

Marie: Certainly. And I know MJFF is helping advance research, both related to biomarkers for Parkinson's disease, but also the development of new therapeutics. So, I'd like to talk about each of these areas. Mark, can you first tell us a little bit more about MJFF's research priorities when it comes to biomarkers?

Mark: Sure. And we've funded biomarkers really since we started in late 2000. So, it's been multiple decades that we've supported biomarker research. And the reason this is so important is because both in diagnosing Parkinson's disease and measuring the course of its progression, currently the diagnosis and measurement of progression relies on these subjective clinical assessments done by a neurologist. And anyone with Parkinson's knows that these symptoms that are being measured by a neurologist really fluctuate from day to day and hour to hour.

And then within individuals, it can fluctuate, and the symptoms can be variable. And so having more objective, precise measurements that can assist with diagnosis and measuring progression of Parkinson's is really a key challenge to Parkinson's research and development of new treatments. So, we've supported, as I said, biomarkers since the beginning of the foundation.

We prioritized research that cuts across different data modalities. So, we've supported development of new neuroimaging tools that can help with visualizing the pathology of the brain more clearly in living people, more molecular or fluid-based assays. So, developing tests in spinal fluid or blood that could help with diagnosing Parkinson's disease. We've also supported wearable sensors or digital technologies that can measure the symptoms and particularly the movement symptoms more precisely. And then just better clinical scales to understand the journey of Parkinson's disease and what's really bothering people with Parkinson's to understand whether treatments are actually helping and

assisting with what's bothering them. So, it really cuts across the different data modalities and different data types.

Marie: Certainly. And I know there have been a number of breakthroughs over the years. So, what are some of these key breakthroughs in biomarkers that MJFF-supported research has produced?

Mark: Yeah, we're really excited. Just in the last year or so, there's been two main breakthroughs, one in the neuroimaging space and another in the biofluid space. In neuroimaging, there has been development of some radiotracers, so imaging ligands that can visualize alpha-synuclein in the living brain. So, alpha-synuclein accumulates in the brains of people with Parkinson's disease, and we've been supporting research for years to try to develop ways to visualize synuclein in people with Parkinson's.

And in the last year or so, there have been reports of research that we've funded where alpha-synuclein can be visualized in living humans. Now, the initial reports are not in Parkinson's disease. They're in a different Parkinsonism called Multiple Systems Atrophy, and we think there are a number of reasons for this, but we're optimistic that as the chemistry evolves and improves, there will be ways to really see alpha-synuclein accumulation in the brains of people with Parkinson's disease. The other breakthrough has been in the area of fluid biomarkers. A specific spinal fluid test called the Seeding Amplification Assay has developed a unique way of measuring alpha-synuclein, this same protein that clumps in the brains of people with Parkinson's. Using this test, you can measure an abnormal form of alpha-synuclein, and this test shows remarkable accuracy.

Around 93% of people diagnosed with Parkinson's test positive for this seed amplification assay, and the data are now emerging suggesting that this test actually can indicate individuals that might go on to develop Parkinson's symptoms. So, that is, detecting some of the biology that's occurring even prior to diagnosis, which is really exciting for identifying the disease earlier and potentially intervening with treatments earlier. So, we're really excited about the promising breakthroughs.

Marie: Certainly. These are huge breakthroughs and really important discoveries because, I think, you're absolutely right. Having to wait to look for that abnormal alpha-synuclein in the pathology post mortem is way too late. So, I think, finding ways that we can look at alpha-synuclein in people while they're still alive and to use this information to find ways to diagnose Parkinson's disease sooner and to perhaps open the door for new treatment targets and perhaps better ways to monitor the impacts of these treatments.

Mark: Yeah, I think it's just the dam that is breaking. You'll see a lot of innovation from here through this breakthrough. And one of the biggest challenges right now is that the current test is in spinal fluid. And so we'd love to have a test that's in more accessible tissues like blood. And just in the last several months, there was a publication from Japan showing that this test could be done in blood. It needs some validation and some work to scale up the test. But we're really seeing lots of progress happening very quickly now that this initial breakthrough has occurred.

Marie: Absolutely. And with this huge discovery, the SAA under your belt, Mark, I guess where do you go from here next?

Mark: Yeah, well, in addition to trying to convert the assay into a blood test or skin biopsy test, something that's a little bit more accessible than spinal fluid, I think an immediate next step is to inform clinical trials and clinical research. And we're seeing that already in that the test is being used to enroll or at least confirm individuals actually have this abnormal biology that's associated with Parkinson's. So, specifically for trials that are testing alpha-synuclein-based approaches, the study sponsors, I think, want to confirm that individuals have this alpha-synuclein pathology using this test. So, we're seeing the immediate impact in clinical trials as a way to enroll individuals and really enrich the clinical trial population to ensure that the population should respond to the therapeutic intervention. I think long term what we'd like to see and ultimately we will see is this test being used potentially in care as a screening tool to screen for individuals that are at risk for developing Parkinson's. And you can imagine this being a part of a routine checkup where if individuals test positive for the test, there may be additional follow-up that's needed, some workup that's needed, but ultimately potentially treatments and interventions prior to the symptoms developing. So, there's both short-term impacts and then a long-term vision that we see this going towards.

Marie: Well, I think that is such an exciting possibility. And I'd love to talk about the therapeutics side as well. So Brian, we'll shift over to you now. Can you tell us more about MJFF's research priorities for therapeutics research and clinical trials?

Brian: Yeah, so, really from the earliest days the Foundation smartly made the decision to be a direct supporter of therapeutic development. So, not just around the basic research or even just the measurement side, but actually providing funds to help actually develop and test therapies for Parkinson's disease.

And also I think smartly, very early on, appreciated the importance of working, not just with academic groups on that type of effort, but actually companies as well. And so, we've always been very agnostic in how and where we can work to try to build innovation and drive these therapeutic ideas through the pipeline and

hopefully into the hands of people with Parkinson's. So, in that 20-plus year history, you know, we've funded several hundreds of millions of dollars, I think, of direct therapeutic development funding so far. Really a range of companies and academic groups targeting a whole range of biology and therapeutic symptom areas for Parkinson's disease. Really around this idea of giving as many ideas a chance at bat as possible, getting as many of these ideas through some of a lot of the critical preclinical steps that it takes to validate an idea, make sure it's safe, but then ultimately even, to the degree that we can, supporting clinical testing as well. So, you know, either early safety testing, maybe early phase II level efficacy testing, really to help get these ideas as much data around them as possible.

And really around this idea of de-risking them, can we get enough sort of confidence around an idea that ultimately future deeper-pocketed investors can get interested and excited and help carry it to the finish line. So, I think our strategy has ranged. We have kind of a variety of different mechanisms we've used. In some cases we might give out smaller sort of pilot grants that are more really intended to maybe either further validate a novel sort of biology to see if targeting it in a preclinical model, say, has potential benefits or testing whether their therapeutic approach can kind of deliver the therapy in the way that is hoped. But also even larger grants, and increasingly so in the last several years, sort of larger grants or what we've been kind of internally calling acceleratory grants, really around the idea of, in certain cases, can we help a company with what we think is a really robust idea, get them as quickly to the clinic as possible. So, helping them really get through some of the big hurdles in that preclinical stage, later stage optimization, safety testing, some of the IND regulatory required steps that are needed before you can go to clinical trial. And in some cases, even helping them maybe with that first phase I trial to try to get as much data as possible. So that's, I think, been an exciting sort of newer opportunity we've had in the last couple of years to give some larger grants, actually, to certain companies.

Marie: Absolutely. And I think that's really important, being able to support research all the way from these early preclinical studies through to the human studies, because oftentimes you see promising treatments sort of get stuck somewhere along the pipeline.

Brian: Exactly. Exactly. And it's that, you know, we don't want anything sort of in limbo, lagging behind. If there's a really great idea, we'd like to at least have an attempt to try it out and get it as close to a successful clinical trial as possible.

Marie: Absolutely. And what are then some of the key breakthroughs, Brian, that you have seen in therapeutics that MJFF supported research has produced?

Brian: You know, there's a lot of programs we've supported over the years, and one thing about, of course, drug development is it's very risky. Ultimately, at the end of the day, it's hypothesis testing and so, you know, many ideas that we've supported have not always shown positive results, and that's okay in our book as well because we want to try to get through as many ideas as possible and find the ones with the best chances of possible success.

But we've definitely had a number of approaches that we funded get into clinical testing where, I think, really the more definitive type testing can happen. Again, not all these necessarily succeed, but we've had some successes. We've helped some groups, for example, get all the way to FDA approval with some of our earlier funding that helped sort of build the case for their ability to continue to support their research. And, so we've had a few of the approved drugs in the last number of years have been sort of touched by MJFF funding in the early stages.

We've also, and this is sort of a different approach we take, it's not always necessarily direct therapeutic funding that's helped. But, our ability to convene and bring industry groups and drug developers who are interested in a particular target area together and help them address key issues that might be happening around that particular therapeutic approach. And a really great example this was a number of years ago, and there was a lot of excitement around a particular genetic target linked to Parkinson's called LRRK2. It's a kinase protein, and so, very quickly after its discovery in 2004, people realized it was enhanced, sort of hyperactivity of the kinase seemed to be what was linked to Parkinson's disease pathogenesis. And so very quickly, of course, companies were excited about the idea of developing the so called LRRK2 kinase inhibitors. And so a lot of research happened, a lot of excitement, and then 2015 or so, there were some results that came out suggesting that there might be some issues in lung tissue of some of the preclinical models that were being tested for safety with the inhibitors. And because of that there was a big, sort of bucket of cold water, I think, thrown on the field as people tried to understand, like, okay what does this mean? Is there any viable path still for LRRK2 inhibitors?

And so a role that we ended up playing which ended up, you know I don't think at the time we fully appreciated the role we were playing, but we were able to bring these groups quickly together. And by groups, I mean companies. Competitor companies who were very willing to work with us as a neutral convenor. You know, Mark alluded to this earlier, I think that's one of our powerful roles here. To get these, you know, first I'll figure out what does this mean and what experiments should be done next to try to further validate and confirm and understand this finding. And we were able to quickly bring this consortium together. We ended up calling it the LRRK2 Safety Initiative, and it allowed us to bring these groups together to very quickly do some really critical research that helped to further refine what the finding was and ultimately sort of derisk the

finding to the point where companies felt more confident that they understood what it was, what it wasn't, and really gave them confidence to continue to move forward to the clinic.

And now you see with, you know, Denali Therapeutics being one example of a company that moved their LRRK2 inhibitor into clinical trials, and more recently, another company Neuron23 is moving theirs into clinical trials as well. And so, that wasn't direct investment necessarily in those companies to test their therapies, but it was a consortium-led effort to really try to understand an issue that was coming up in that therapeutic pipeline. And so, I think examples like that really just shows how a group like ours can, you know, we can really kind of bring people together in this neutral way and really address these issues. And we can then sort of fund the work to try to better understand and answer the questions that may be coming up.

Marie: Certainly, and I know, Brian, it's hard to say what the future will hold, but I guess if you had to take a guess now, where do you expect to see the next big breakthrough in MJFF's therapeutic strategy?

Brian: Yeah I think it'll be interesting to see, like I mentioned, in the last couple of years we've been giving out these larger grants really around this idea of can we further accelerate drug development in Parkinson's and help get some of these companies really into early clinical testing stages. So, I think one thing I'll be excited to see is the outcome of some of those investments that we've been making. And see is that type of larger funding and collaborative model that we create, so it's not just the funding. We work closely with the sponsors to try to help understand and troubleshoot their programs. To see the success of some of those, I think, will be really exciting. But I think, for us, the real crystal ball that we're looking at is, with all of these great ideas we're seeing moving through preclinical and into clinical testing around sort of targeted biology linked to Parkinson's disease. I think we're all sort of holding our breath hoping to see some of the outcomes of these trials and really demonstrating some of the promise that targeting this various biology will ultimately have for people with Parkinson's.

And, you know, I would say we are sort of optimistic by nature. Our founder Michael J. Fox is an optimist, and I think all of us are too. You know, so we remain optimistic about that pipeline. And I think we're seeing, you know, even though certainly there are lots of controversies and debates about the findings, some of the positive signals that we're seeing coming out of the Alzheimer's field, I think, is at least painting a slightly rosier path we're seeing for Parkinson's in that, at least for some of the approaches that, you know, have similarities to those Alzheimer's approaches, that there might be viable signals that we might see in the Parkinson's trials as well.

So I think for us, that would be exciting, just to at least even get a glimpse that there might be a possibility of disease-slowing and progression-slowing for the disease. And then, I think the innovation, kind of like Mark said before, around the biomarkers. Once you start seeing some of those signals, I think that's really the floodgate that opens, and the innovation really flows from that.

Marie: Absolutely. Now Mark and Brian, you both talked about MJFF's role, sort of as a convener or a connector within the field, and I think one of the reasons we have this particular podcast is to facilitate conversation across the field of Parkinson's research. And the Foundation is a big supporter of open science efforts. So, how does MJFF actually leverage open science for the benefit of the broader field of research. And, perhaps, Mark, if you could start.

Mark: Sure. The Foundation has always encouraged, and in many times mandated, the publication and the reporting of the results of the research that we supported. We've kind of stepped it up a notch, I would say, in really leaning into the open science concept in several ways. One is that there are studies that we're supporting that are collecting really valuable data sets, both in people living with Parkinson's disease, also animal models of Parkinson's, and all of these data are being made available on an open science platform. So, anyone from the research community can access this data in real time.

The biomarker study that I mentioned (PPMI), that data set is a living data set. It's updated weekly, and we've seen over 15 million downloads of the data so far. So, we really feel like the solutions are not just in the researchers that are doing the research or generating the data, but we'd like to make the data available to anyone that is curious to access the data and test their particular hypothesis. The other way that we've really leaned into open science is to require the publications of our funded research to be open access. So, we really feel it's important that the publications are not behind any paywall. So, we provide support to ensure that the publications are open access or posted in an open access platform like bioRxiv or medRxiv. So, we have a number of other strategies to make sure that the data and the results are published, but those are two important priorities for us.

Marie: Absolutely. I think those are definitely critical steps, and, Brian, was there anything that you wanted to add on this point?

Brian: Yeah. I think, you know, part of this sort of open science push, again, is really about knowledge dissemination. And how do you do that effectively, and at scale, and in real time? And mark rightfully pointed to some clear ways we can do that, obviously, you know, open science publication, I think, is a key way to make sure that everybody can access including non-scientists to, you know, the patient

community and the public at large can access the outcomes of the research that we fund. Open access to data, and tools, and the other things that Mark mentioned as well. I do think there's this power in bringing people together, coming back to the convening theme here, and the power that has as an open science tool. You know, really creating those collaborative moments where people can come together and share their information.

We've long, for many years now, had a sort of evolving, started off as sort of an informal biology consortium where we were bringing investigators together around certain target areas in Parkinson's a number of years ago. And that kind of evolved over time to really what is now a fairly, I think, highly attended, what we call a PD research exchange, webinar series that we host every week now. That really brings, you know, researchers from around the world together on a regular basis. And topics can range from different targets the community is interested in around Parkinson's, or sometimes we have kind of more general themes that we bring to that group. People present their results. Sometimes the Foundation will present updates on programs that we have. And really the only requirement to participate is that everybody at least signs on to this sort of MOU agreement that they won't, you know, take any information that they hear and sort of run away with it. You know, there's sort of this agreement that everybody might be hearing unpublished data, and if you want to collaborate with the person who is presenting, you can reach out to them and collaborate. And I think that's really created this sense of community across the research community in Parkinson's disease, and that's something I don't think we expected when we started launching this around, you know, a specific biology. But it’s just grown and grown and grown. And even, you know, 15 years later, we still get high attendance at these.

Marie: Certainly, and I think being a hub for the scientific community is really important. And when scientists out there hear about the Michael J. Fox Foundation, the first thing that may come to their minds are the funding opportunities. So, for listeners out there who might be wondering if they or their research are a good fit for Michael J. Fox Foundation funding, what insights or advice could you share with them?

Mark: Sure. It's a great question. And we're always eager to talk to researchers, both within our network, but also outside of our network. And we're eager to bring in people outside of Parkinson's disease under the tent, so to speak. So, the easiest way is to ensure that you're on our mailing list and receive our funding announcements. We have frequent funding calls throughout the year. But there are other ways to interact with us. Like I said, there are consortia and Brian talked about the PD research exchange. Another way is just to reach out to our team and request a meeting. We're always open to talk with someone about their work, hear more about what they're interested in, and we can certainly give some

insight into whether it might fit within our priorities and our upcoming funding opportunities.

Marie: Outstanding. And then is there anything that you would like to add?

Brian: I think I would add just that, you know, obviously as a nonprofit foundation focused on, I would say, more translational research linked to Parkinson's disease and delivering new treatments for Parkinson's disease, not every idea is necessarily going to fall, of course, into our priority interest. And, you know, it's not the critique of any researcher's idea, just that we may not always be the right partner for someone.

So, I would say the groups that are really into the idea of taking a research concept and really translating it and trying to think about how we can impact patients. You know, I think that's the type of research that really resonates with us. And as Mark said, we have a number of programs that we launched throughout the year. We do have, you know, an ongoing, for example, a therapeutic support program that we've made some changes in, and it's essentially open all the time now. Anybody can send an idea to us at pretty much any point in time, and we'll get a pretty quick answer to them, at least on our interest level, within a few weeks' time so that they know if we might be the right partner to consider it further. And then if we are, then we can invite them into sort of a more formal, full proposal discussion and review.

And so, a number of other programs can sometimes adopt that model, or we might have more traditional, you know, one-time calls for research priorities. But, you know, again, we're open to a lot of ideas. Can't fund everything, of course, but we don't want to miss an opportunity. So we want to make sure that we, as Mark said, really have this open door to really anybody who has an idea and would like at least, you know, to speak with us.

Marie: Wonderful. Thanks, Brian. And listeners, definitely get in touch, reach out to get that conversation started to see if your work might be a good fit. And check out https://michaeljfox.org/researchresources to take advantage of some of the other great resources MJFF offers. But beyond just providing funding and resources for academic researchers, MJFF also collaborates with industry partners. So, I want to make sure we touch on that as well. So, can you describe how does MJFF work with industry partners to really further the field?

Brian: Yeah. So, you know, as I said, I think earlier, industry has really been part of our strategy from day one. And we've always recognized that ultimately, they're the groups that really can sort of invest the time, and the money, and the effort to really deliver new treatments and certainly get them into the market and into patients' hands. So, that's always been important for us.

And over the years, I think, you know, our model of working with them has evolved as well. So, you know, obviously giving them support is one way we can work directly with them. But we also need them to really understand the barriers that they have. So, we have a team dedicated really to speak with members of industry on a regular basis, understand program progress that they're seeing, understand the barriers that may be happening. A lot of companies will now approach us and kind of give us more insight into their programs than they maybe normally would. And it just helps us to understand, okay, is this an issue that we need to address? Is this a broad field issue? Is there a challenge that we can sort of bring people together and try to understand?

But then industry also helps us do the work that we do. So they're the supporters of, for example, the Parkinson's Progression Marker Initiative, a growing list of companies have supported us to do that study over the years. They contribute to a number of other initiatives that we have, both financially, but also importantly, in kind support, whether that is in kind simply in being advisors and sitting on our grant review committees and helping us kind of understand and assess the research that we're looking at, but also in kind work that they can do. Sometimes they might help us with generating a new laboratory tool. and they're willing to test it for us for free and then give us the results to see if it's a tool that is worth continuing to develop and make available to the community. So, a lot of different ways that we can importantly work with our industry partners.

Marie: Certainly. And Mark, do you have other insights on just this relationship with industry that you'd like to build on?

Mark: I think the only thing I would add is that we obviously are very connected to the patient community and understand the needs of the patient community. And so, oftentimes we are sharing what's important to patients with industry, either through data or through specific anecdotes and linking industry groups to specific people with Parkinson's to share their story. But also informing industry on how to find these individuals. So, clinical trial recruitment is a really big challenge to find volunteers to participate in clinical trials. And we have supported many different research studies that have experimented with different tactics for finding individuals and enrolling them in research. And we have developed a number of different tools and just sort of intellectual capital that we're eager to share with industry groups. So, I think that's an important part of our relationship with industry, in addition to all of the tools and research that Brian mentioned.

Marie: Absolutely. Well, I appreciate both of you sharing your insights on this topic. And I'd love to end on a particularly positive note if we can. So, before we go, I'd like you to each maybe give us a reason that you feel optimistic about the future of PD research, or what really is keeping you feeling encouraged every day?

Brian: Yeah. I mean, for me, I think one of the really exciting things I'm seeing is just, again, this increasing, kind of what we're calling a biology wave, that's coming really just built off, I think years of foundational understanding of the disease, better understanding of the genetics of Parkinson's disease, but also just studies of the underlying pathology, data coming from studies like PPMI, really understanding the experience people have with Parkinson's disease. And all of this really just coming together and giving us, I think, a much more refined ability to understand what we need to target therapeutically and ways that we could do that and ways that we can do that effectively and informatively. And so, I'm excited by the coming few years because I think you're going to see a lot of this sort of converging effort really start influencing and impacting the therapeutic pipeline.

Marie: Absolutely. I think it is such an exciting time for the field. And Mark, do you have a different answer that you'd like to share in terms of what you're feeling most optimistic about?

Mark: Well, I just think about the pipeline of different therapies in human clinical testing right now. And I've been studying Parkinson's for over 25 years or so. And in the lab, I studied alpha-synuclein. It had just been discovered, and we were really trying to understand what it did in the cell.

And it's remarkable to me that now, flash forward 20 plus years, there are now 14 different programs — different programs, different molecules — that are targeting alpha synuclein in clinical testing. So, real therapeutic development. And there are other programs focused on LRRK2 or GBA. So, it's been just incredible to see the progress and the translation of some of these genetic discoveries into therapeutic programs. Now, not all of them will work, of course. And as Brian said, they are experiments, these experimental trials. But there's no doubt they all will be informative and will increase the knowledge turn for future clinical trials. S.o that's what I'm really jazzed about.

Marie: Absolutely. I think we are making great strides on that front as well. And I appreciate you both sharing your insights and perspectives with me and our listeners today. Thank you both so much for your time. Sure.

Mark: Sure. Thanks for having us.

Brian: This is great. Thanks so much.

Marie: It's been such a pleasure to have you both here. And listeners, it's been great to have you with us as well. If you want to know how The Michael J. Fox Foundation can help your research, you can find out more about the funding opportunities,

the research tools, and publications that Mark and Brian talked about today, and more at MichaelJFox.org/researchresources.

And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. When you have a moment, please subscribe to our show to make sure you don't miss our outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast.*