Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.

Maggie Kuhl: Welcome to another episode of our Parkinson's Science POV podcast. I'm Maggie Kuhl from the Michael J. Fox Foundation. With me today as always are our chief scientific officers, Mark Frasier and Brian Fiske. It is a celebratory week at the Michael J. Fox Foundation. Our founder, Michael J. Fox, was awarded the Lasker-Bloomberg Public Service Award. The Lasker Awards are medical science awards that are often referred to as America's Nobel Prizes. And in 1969, the Greek American doctor who developed Levodopa actually received a Lasker Award as well. Michael's honor this year recognizes his work, Empowering Patient Voices and Accelerating Research Toward Improved Therapies and Cures for Parkinson's Disease. And Brian, the Alaska Awards are a big deal for people who work in research. What was your reaction?

Brian Fiske, PhD: I think just amazed and also not surprised. I think Michael in starting the foundation really put Parkinson's on the research map in a way that it hadn't been before. And just through his advocacy and just presence, it has put so much resource and attention to Parkinson's disease that it has helped, I think, really meaningfully, whether we funded a grant or not, really meaningfully advanced the Parkinson's research and drug development field so significantly over the last 20, 25 years. So I think it's just an amazing recognition and sort of well-deserved recognition for Michael and his vision.

Maggie Kuhl: Mark, a friend of the foundation, the president of the American Neurological Association, Dr. Dimitri Krainc, he wrote a tribute around the news of this award and he wrote that scientific progress depends not only on brilliant investigators, but also upon visionary advocates. How would you characterize Michael's visionary advocacy?

Mark Frasier, PhD: Yeah, Michael was understandably very humble about the award, but I think he deserves so much credit in facing this disease head on and really becoming the face of the disease. He's galvanized the research community to work together, collaborate, and work urgently against a very simple mission, which is to go out of business and find a cure. So he's really built an organization that I think is doing that.

Maggie Kuhl: Absolutely. We share and give him our congratulations for this. Michael shared some words with our staff this week too, and as you said, as expected, he was not pausing to bask in this honor, but instead using the moment to remind of the ultimate prize we continue to work toward, which is a world without Parkinson's disease. And with that, let's turn to our topic for today's discussion.

Today, we are covering another pillar of our strategic research agenda, which is the how, how we will reach a world without Parkinson's disease. We previously discussed catalyzed community and clear disease definition. Today, we're covering better treatments. So Brian, maybe we could start with you and what are some of the biggest limitations of treatments today? Why do we need better treatments?

Brian Fiske, PhD: When you look at the last really several decades, you've seen certainly a lot of treatments that have been approved for use in treating Parkinson's disease, and certainly we don't want to ignore the value and the benefit that those treatments have had in improving motor function in people, so helping people move better throughout the day, largely though through targeting the same biology. So basically targeting the loss of dopamine in the brain and trying to restore that dopamine signaling so that people can move better throughout the day. And that continues, I think, to be a big part of the treatment development process or the pipeline as we like to call it today, the pipeline being the whole mix of different therapies that are currently being developed and tested for Parkinson's disease. And so within that pipeline, we still see a lot, of course, of innovation happening around continuing to improve how to make dopamine therapies better and last longer and maintain that benefit.

But when we really think about what people need, of course, we need more than just the dopamine treatments. We need treatments that are really targeting the whole range of issues that people deal with with Parkinson's, some of the non-motor problems as well as the motor problems. So things like thinking problems, constipation, sleep issues, all the other things that come with the disease. And of course, we also need treatments that target the fundamental biology, not only the biology underlying the symptoms, but the biology underlying the disease itself. So the biology that seems to actually be causing the brain cells to degenerate and to be lost in people with Parkinson's.

So we need a pipeline, a treatment pipeline that is better in the context of we need to make sure that we are seeing a whole range of different treatment approaches, targeting those different biologies, addressing those different patient needs, and making sure that that sort of whole ecosystem of therapies and development are truly addressing the whole problem, not just one single piece of the problem.

Maggie Kuhl: So in this discussion, I think we'll cover what I heard you just say, which is that we need different targets, different biologies, we need different treatment approaches, and most importantly, we need meaningful change in people's lives and to meet all of the unmet needs that folks are living with right now. Mark, our strategy calls for multiple paths. It's likely not going to be one breakthrough therapy. Why is that?

Mark Frasier, PhD: Well, the more we learn about Parkinson's, the more we learn that it is unique to each individual and there are likely multiple causes of Parkinson's disease. And so if there are multiple causes, we need multiple different treatment approaches. And so from the beginning, I think the foundation has always taken a very diversified approach because we don't know which or how many of those

proposed treatments will actually be successful. And so we want to diversify the number of approaches that are being pursued in the field. We want to lower the risk for investment from other groups, other biopharma or industry groups to pursue these paths. And so our focus has been diversifying the different treatment approaches and de-risking those approaches so that others can take those on and get them across the finish line to patients.

Maggie Kuhl: And we set up in the last few years a specific program to help us de-risk more of those targets, the Targets to Therapies program. And to get more information about that, I spoke with Shalini Padmanabhan, the head of translational research at MJFF. So now we can listen in a little bit on that conversation and learn more about this Targets to Therapies or T2T program as we call it.

Hi, Shalini. Thanks for chatting with me.

Dr. Shalini Padmanabhan: Hi, Maggie. Always nice to chat with you.

Maggie Kuhl: So what problem did the foundation see in the Parkinson's research ecosystem that really led us to create targets to therapies?

Dr. Shalini Padmanabhan: Yeah, and I would say, I mean, really over the years, Maggie, what we saw was an enormous amount of promising Parkinson's biology that was coming in through genetic efforts, through many of our patient cohorts, as well as laboratory research, but too little of it was actually moving into the drug development process. So what we wanted to do was really consolidate all of that information and identify promising biology that within the next two to three years could actually enter the drug development pipeline. So that's kind of really what the goal of Targets to Therapies is, and targets come in through all sorts of processes. It comes in through genetic studies, through NGFF funded portfolios, it can come in through patient relevant data, but the goal is to really build the data package that we think companies are going to need to start developing a therapeutic against.

Maggie Kuhl: So Targets to Therapies is a program to systematically de-risk promising targets, and you build the evidence and tools around them and make them more actionable and attractive for therapeutic development. Let's start simple. What exactly do scientists mean by a target?

Dr. Shalini Padmanabhan: Yeah, that's a great question, Maggie. So a target is a biological component. It can often be a protein, it can be a gene whose activity we believe a therapy could modify to produce a meaningful benefit. Over the years, what we've seen is an enormous amount of Parkinson's data sets that have emerged through studies such as GP2, which is a genetic study, our PPMI study, which is our longitudinal natural history study, and these are really providing greater evidence around certain targets because they come from relevant model system, which is the human model system, and it's really guiding our decisions around which of these targets are going to be better as drug candidates.

Maggie Kuhl: So we study genetics, we study biology, we find targets, and now this program is helping build these data packages. How do you do that? How do you validate or de-risk a target?

Dr. Shalini Padmanabhan: Yeah, so when we pick or nominate a target, there are multiple dimensions of the target that we evaluate. We make sure that the target is actually detected in humans, and is it significantly different in a person with Parkinson's or in a person without Parkinson's? And what's really the therapeutic hypothesis?

Maggie Kuhl: So you have enough data and you have enough confidence that this could be moved forward based on having multiple studies pulled together or by doing multiple tests. Can you talk a bit about creating tools for these targets? What exactly does that mean and why is that a benefit to the drug companies that will pick these up and move them closer to treatments?

Dr. Shalini Padmanabhan: Yes. Maggie, I think this is also a great question, and I think it's often underlooked because many of the targets, because they're so new, they lack reliable detection methodologies, for example, something as simple as that. So we need, laboratory researchers need antibodies. These help us detect is the protein activated, is the protein elevated? We need tool compounds, we need validated assays. We may also need structural information. We may want to know how is the protein structure look like? We may need biomarkers that's really going to reduce the barrier, again, for somebody like a drug developer to come in and say, "All these resources exist. It really makes my job of finding a molecule much easier."

Maggie Kuhl: So I'm trying to think of a good analogy. You could say to a company, "Hey, go take a walk in the woods and try to get to the top of this mountain." And they might say, "Oh goodness, I don't know." But if you say, "Well, here's a map and a compass and a tent and some other tools that you might need along the way to know where you're going and to look at the weather report or such," that gives you a lot more confidence. You have the ability to get there faster. Perhaps you feel like, "All right, I could probably do this," and you're more willing to take it on. So we are really equipping these companies with the assets, the tools, the information that they need, and the confidence through sharing that information that this is something that they should invest in.

Dr. Shalini Padmanabhan: That's exactly right.

Maggie Kuhl: You've already done how many targets? Because it's pretty astounding.

Dr. Shalini Padmanabhan: Yes. Last year we kind of piloted with five targets and we created target teams around those five targets. This year we are aiming to do another 16, so we are well on track to scale the program, and by end of this year, we would've funded target teams around 16 additional targets.

Maggie Kuhl: Can you talk a bit about why the Fox Foundation is so well positioned to play this role?

Dr. Shalini Padmanabhan: Yeah, I would say it's really threefold in our focus here. One is being that central coordinator that's taking in these diverse data sets, making decisions on which targets to move forward. Second is providing funding for some of these efforts which wouldn't have taken place if we hadn't brought these groups together. And I think most importantly, we are serving as a convener, right? I mean, we're bringing together not only academic groups, but we are also bringing together industry groups. So I think this is a pretty unique initiative and something that we have spoken about to other disease organizations because we do think such a coordinated effort is required if we want to move quickly and build robust data sets for Parkinson's therapeutic development.

Maggie Kuhl: Well, thank you, Shalini. I hope that in those 21 targets that you're currently working on, you move most of them into investments and trials for the patients who are urgently waiting for new treatments. Thank you for all that you do.

Dr. Shalini Padmanabhan: Thanks so much, Maggie.

Maggie Kuhl: So Brian, Mark, hearing Shalini share about the Targets to Therapies program, what stuck out to me was that more in itself is not the goal. She talked about really the diligence that goes into selecting targets. Can you talk a bit about how we distinguish more shots on goal, which is a Foxism, if you will, something we say a lot, from simply pursuing more ideas? What makes something worth it, Brian?

Brian Fiske, PhD: Yeah, no, I think it's important to think about, again, the biology coming to us, and Shalini talked a lot about these rich data sets, genetic data sets, natural history studies, all this information that we're learning about Parkinson's disease is planning, converging on certain parts of the biological process in ourselves that might be linked to Parkinson's disease. And so being able to narrow down on those biologies and then making that decision, we often call it a translational decision, this idea of how do you translate that biology into the language of drug development, picking the biology that we think we can meaningfully manipulate and then convert into therapeutic development programs. And so you want to make sure you're picking that full range of biology that, again, we talked before about making sure we're being thoughtful about the whole range of biologies that might contribute to people's Parkinson's disease and the symptoms that they have.

So we want to make sure that those targets that we're looking at also represent that full range of different biologies. I loved how Shalini, you framed it as this idea of, I'm an avid camper and hiker, so this idea of how do you find the right path up to the mountain? And there's certainly nothing worse than a poorly marked trail that you have to constantly look at your map again to try to figure out where you are and always a little worried about going the wrong direction. So having a good well-maintained trail and clear trail to the top is always powerful. And I think as we think again about these biologies, we're looking for that clear path around these biologies that we can then ultimately translate into therapeutic development.

Mark Frasier, PhD: I just want to make two points. One, the 21 targets that Shalini referred to are very early in development, and there are a number of genetic targets and targets from study of Parkinson's that are in human testing now that are really exciting and they have been de-risked and pharma is pursuing them. And so our role is slightly different than what Shalini described in the Targets to Therapies program, but we're kind of advancing the less developed targets to really increase the number of shots on goal.

The other point I wanted to make was I came from biopharma and they use a very systematic approach to evaluate evidence for each target. And what we're doing is really building high quality evidence to justify pursuing drug development against those targets. And you have to remember that there's finite resources available to do drug development, and Parkinson's targets are not only competing against themselves, but competing against other therapeutic areas.

And so the better the quality and the larger the evidence that justifies that this could be a useful target for Parkinson's, the less risk it will be for drug development. And so we talk a lot about the silver platter business, and this is really what we're doing. We're trying to deliver these targets on a silver platter to those with bigger pockets that it would be foolish not to pursue them for drug development.

Maggie Kuhl: Or learn that maybe some of them are actually not worth pursuing. And as you said, there are finite resources, and so we don't want the time and energy and limited funding, et cetera, to go down a road that's not going to lead us to better treatments. And so if we can say no go early, then that saves that and really puts those resources toward the best case.

Brian Fiske, PhD: Yeah. Another thing that I think Shalini raised that is really important to appreciate about the unique role we provide is this idea of being a convener, and not just that we can bring people to the table and have them talk about interesting targets, but through our funding and bringing togetherness, the catalyzing, I guess, the target community, if you want to think of it that way as well, is that we're building an expert community around these targets. And when you think again about how do you define that path and make it clear and easier, then think about it having people along the way who can hand you a cup of water or give you a helping hand up that mountain versus you having to do it all by yourself.

And so I think this idea of not only building confidence around the science and the biology, of course, and making it is this truly a worthwhile target for Parkinson's, is that having that expert community in place allows drug makers then to know that there are people they can go to when they have questions or concerns or need to explore some specific aspect of that biology and they don't have to build that expertise in-house. And I think that's a really powerful, unique role that we can play by, again, creating that expert community around the biology.

Maggie Kuhl: And even building that community, it's something I love about the foundation. We've talked about it in previous podcasts, which is recruiting experts from other fields. Maybe they have worked on a different target that looks similar. And so

we pull them in and say, "Hey, you haven't climbed this mountain, but you've climbed one that is similar elevation or similar weather climate." And so we recruit more folks into the fold such that we're building those expert teams. I want to just make one more point of this. Mark, it was a great note that there are well more than just 21 targets. There are many already in testing or many others that are emerging out of the work that we're doing. And you said people think about the genetic targets, the LRRK2 or the GBAs. Hopefully many folks have heard of the key Parkinson's protein alpha-synuclein. We talk a lot about replacing dopamine or we talk about inflammation.

And so just to make a point that, as Brian, you said, there are so many different biologies and that this illustrates how broad the opportunity is for us to really make those strides and develop these different types of cures for different types of people with PD. I want to go back to, Brian, you had laid out a nice stepwise approach through our discussion here of more targets, more shots on goal, which is great, but also more ways to hit those targets. And so having the target is only half the story. The therapeutic toolbox of how we are going to, as Shalini laid out, have a modification change what this target is doing in disease is also evolving and growing. So what do we mean by that, different therapeutic approaches or modalities?

Brian Fiske, PhD: Yeah, so there's sort of different technologies, if you will, for thinking about how do you deliver a therapy and not only impact how it gets into your body, but also maybe how long it might last. And so we tend to think of most types of medicines we take are what they consider small molecules, small chemical compounds. Usually you take them orally by mouth, the traditional pills and tablets that we all take for a whole range of different types of issues that we might have. And that by and large still represents a huge percentage of the types of drugs that drug makers like to make. We're good at it. We know how to do the chemistry for the most part, and for many types of targets, a small molecule, sort of orally delivered small molecule can often be the right approach. But sometimes there are biologies that are a little harder to get at with small molecules, either because of the nature of the biology or maybe where it is in the cell or where it is in the body.

And so people are trying different other kinds of approaches. Sometimes you can get more sort of an exquisite specific effect of a drug on a very specific biology by not using a small molecule. Often small molecules sometimes have so-called off-target effects where they might hit other biology that you don't want to hit, but sometimes you can use types of therapeutic technologies that allow you to be much more precise. And so for a good example of that is one maybe we often hear about using antibody therapies, for example. So antibodies are actually natural proteins produced in our body by our immune system. We've probably all learned a lot about antibodies during the pandemic, and these are molecules in our body that are exquisitely able to target very specific patterns. In the case of our immune system, it's often looking for pathogens, different things, protein particles on a bacteria or something else or virus where the antibodies can try to go and attack and ultimately remove those pathogens from the body.

But many, many years ago, researchers and drug makers figured out, well, we can actually use antibodies and actually synthesize antibodies to actually target specific proteins in biology that we want to target therapeutically. And so the idea of using immunotherapy, so using antibodies to actually target different biology in the body from a therapeutic lens actually became very powerful. And we've seen that now sort of rise up in the therapeutic pipelines for a lot of different diseases, including neurological diseases like Parkinson's and Alzheimer's. In fact, Alzheimer's disease has some approved therapies now that use antibody technology to target their predominant pathological protein amyloid beta, and there are a number of groups and drug makers in the Parkinson's world developing antibody therapies for alpha-synuclein, the protein that clumps in the brains of people with Parkinson's. So antibody therapy, that's one other type of technology that's become really powerful, but we're now even seeing other types of approaches.

So now people are thinking about, okay, how can I target the biology that is involved in actually producing protein in the first place? So there's something called RNA technology, and there's lots of different versions of these. You may hear things like RNA interference or antisense oligonucleotides. These are-

Maggie Kuhl: Ooh, many syllables on that one.

Brian Fiske, PhD: Yeah, many big syllables, yes. But these are basically approaches, different technologies that can target essentially the production of protein by targeting this sort of intermediate molecule called RNA, which is in many ways, if you think of DNA is where the gene recipes live, proteins are the apple pies, if you will, that are made from those recipes. RNA in many ways are like the Xerox copies that you make of the recipes in the DNA cookbook to deliver to somebody's kitchen so they can make the apple pie themselves. And so being able to target those RNA molecules, the sort of Xerox copies, if you will, and being able to get rid of them, you could actually then say reduce in the amount of protein that's produced on a particular type of protein. So there are some targets where that kind of reduction, and we're actually seeing this now, people trying this, for example, around trying to reduce the amount of alpha-synuclein made or in some cases trying to reduce say the amount of LRK2 protein, LRK2 protein made.

These are therapeutic technologies where you can go and actually do that exquisitely at the RNA level. So another type of technology people are exploring with. And so there are lots of different approaches that people are using. And one of the considerations with some of these, gene therapy is another approach of the idea, can you deliver the gene for a particular protein of interest that you think might have a therapeutic benefit into the brain or the body so that the body can produce that protein at a higher level? Sort of the opposite, if you will, of targeting RNA is can you actually make more of the protein by giving essentially more of the gene recipe into the body? And so there's other technologies that are trying to do that, for example. And the decision for when and how you might want to use a different technology really, again, depends on the biology and kind of what your ultimate effect is.

So a gene therapy, for example, is something that we consider a durable therapy, meaning that it's kind of a one and done. You give someone, you inject this, basically this, it uses basically a virus, not one that's going to cause harm in you, but one that actually just delivers the gene and makes your cells express the gene of interest. You can do that and just say inject it in a part of the brain and make cells produce that protein of interest for a long period of time, maybe even the rest of your life. And so if it's a type of a therapy you want to have there all the time and turned on all the time, a gene therapy approach could be a powerful way to do that versus pills are very, you take it maybe works for eight hours, then you have to take another one.

It's a much smaller acute window of therapeutic benefit, if you will, that you might be receiving, but you obviously have a lot more exquisite control over when you take the pill and when you don't and things like that. So depending on the benefit you're looking for, how long you want it to last per dose, if you will, things like that can help determine, and obviously where the biology is and the type of biology you're trying to change. All of those factors can then help drug makers decide, okay, what type of technology do I want to use to deliver this therapy?

Maggie Kuhl: So what I'm hearing is there are many different ways to modify a target, and some of that depends on the type of target, how it can be approached. And a target can have a different life cycle. It could start with a change in a gene or in how the gene makes the protein or in how the protein behaves or even sometimes what the protein affects when it misbehaves. And so where in that life cycle you also want to make a modification might dictate or determine what type of treatment approach you want to use.

And so Mark, when we think about these decisions and how we might go against a target, how we might make these changes for improvement for people living with PD, it's also a business decision to have more of these options. And so some people might be saying, "Well, why don't you just go with the best one?" Or why do you need all of these different ways to do it? So what is the value in having multiple approaches rather than putting everything behind one?

Mark Frasier, PhD: Yeah, I mean, first of all, scientifically we need not just diversity of targets, but diversity of cutting edge approaches to go against, prosecute those targets. So scientifically it's rational to have multiple different approaches. And what's exciting about the technologies that Brian described is that these are cutting edge technologies that are pioneering and they're being applied to Parkinson's. And so there are these innovative companies and groups that are developing these novel technologies and they're picking Parkinson's as one of their first disease areas to go against.

And then from a commercial standpoint, there are decisions on how many doses one might require and how expensive they might be and how frequent individuals might need to come back to the clinic. So for example, if it's an infusion, that might be a monthly dose. If it's a pill, maybe they can take it at home. And so those are costs that are incurred to the healthcare system. They have commercial implications. And so when companies in particular are trying to commercialize a

product, they evaluate all of these different components and criteria including the science when deciding on the most optimal technological approach to pursue.

Maggie Kuhl: And from a foundation standpoint, it goes back to that more shots on goal, better treatment pipeline, having more opportunities to learn. I also want to say, as you were bringing up, Mark, a lot of these are cutting edge. They may be emerging in brain disease first in Parkinson's. And so if you as a person who is interested in trials, but is having a lot of questions of what an antibody means versus a cell therapy, for example, we are trying to put a lot of resources on our website to talk through, as Brian was saying, why this is an approach, what it's supposed to do in the body, but also what it means for you, whether it is participating in a trial or potentially taking a treatment long-term, whether it's a one-time thing or a daily thing. And that brings us to, Brian, back to how you'd laid this out.

The fact that what we really want at the end of the day is this meaningful benefit. And we work so hard, my team, I got to give a shout-out to my own patient engagement team here at the foundation and really thinking about the end user and how we think about the pipeline, that a number of therapies that even if they do what they're supposed to do on targets that no one can ever really take because the side effects are too much or the treatment burden is too much is not actually a success. And so we work a lot with patient partners about how the experience of taking a treatment influences development. Mark, you were bringing that up a bit too. Could you just say more about how we integrate that into our decision making and our work with companies around designing trials?

Mark Frasier, PhD: Well, Michael himself, when he started the foundation, thought it was very important and emphasized having the patient voice and having the patient at the table, not just at the end stage when therapies are starting to be delivered to people, but actually very early in the process to have input from the beginning to end on what matters to people living with Parkinson's, what's important to them, what they're willing to tolerate and what they're not willing to tolerate.

And so the foundation and your team does a great job of connecting groups that are interested in these cutting edge treatments, particularly the biopharma groups, with people living with Parkinson's disease to hear about their lived experience and share what matters to them, how best to design a clinical trial, what's inconvenient and what's useful to them. So all of these factors are really important in the drug development process and the foundation has, I think, done a great job of bringing that patient voice to people that are developing the treatments throughout the process.

Maggie Kuhl: And Brian, it's not just people who are developing, but ultimately the regulatory agencies that will say, "Yes, this can go on pharmacy shelves." The insurance companies and government groups that will say, "We will help pay for these." The foundation also plays a major role in elevating the patient needs and experiences in those conversations and decisions. Can you share more on that?

Brian Fiske, PhD: Yeah, I mean, I think it's important when you think about the value a new therapy can bring that you're bringing in that patient perspective. And we've done some work, for example, in looking at how do you... We talked earlier about new

dopamine medications and how innovation in new dopamine medications continues to think about can we increase the amount of so-called good on time over the course of the day? So the amount of hours during the day when you actually... the drug is working and you're getting good improvement in your movement symptoms and that being an important metric, can I increase the amount of good on time over the course of day with my therapy? But what does that really mean in the context of patient perspective? And we found through some of our discussions, for example, with the patient community, that isn't just numbers of hours, but it's the predictability, for example.

How can I predict that I'm going to have good on time throughout the course of the day during the times when I need it, not just that I might get an extra hour or two over the course of the day? So things like that that you really only got to hear from the patients directly, you're not going to necessarily hear that from the doctor that are just going to say, oh look, they function better for an extra hour or two, or the clinical trials tend to really only measure that. So we need to make sure that that's included in that conversation, that it's meaningful increases in the benefit that a drug might provide so that payers and regulators and providers and patients themselves can understand what the new treatment might actually provide them and that it could be a meaningful advance and increase in their daily function.

Maggie Kuhl: So yes, to round out our conversation, we need more credible targets. We are learning from the biology and following the needs of individuals to lead us towards what we should be targeting in the body. We are developing more therapeutic approaches, more cutting edge options to target those biological proteins or processes to try and make a meaningful benefit that patients can use in their daily life. And so maybe just to round us out and to put us into this future, Mark, if this strategy succeeds, if this strategic research agenda pillar of better treatments comes to fruition, what does the treatment landscape look like in 10 years from now? How is it different?

Mark Frasier, PhD: I think if it's successful, we have multiple newly approved treatments in the next 10 years that not just address the motor symptoms that Brian mentioned, but some of the non-motor challenges, the non-movement challenges that people with Parkinson's face. I think optimistically we will have several treatments that could slow or stop, slow the progression of the disease, which is really what we want to go out of business to end this disease. And I think we'll see a robust set of targets that are in different stages of development right behind that, that could be better or improved on the existing and approved treatments.

Maggie Kuhl: Brian, what would make you say we're getting this right?

Brian Fiske, PhD: Yeah, I think a lot of what Mark said, of course, is again, seeing that diversity and seeing those, not just that they're in the therapeutic development pipeline, but they're actually moving forward and progressing and maybe even getting approved for use. Like Mark, I think I optimistically would at least hope that we will see, if not clear robust evidence, at least hints that some of these approaches are slowing the disease down and maybe delaying the progression of disease over time. That would be, of course, amazing. Even if they're not the most perfect first

versions of those therapies, at least tell us that we're on the right path. I think that's really critical. And we're seeing that, for example, in Alzheimer's right now with some of their currently approved therapies. They're not super great. They're not getting rid of Alzheimer's altogether, but at least they're pointing people in the right biological direction saying, "Okay, well, if we do target this biology, we think we can get some potential benefits." So we'd like to hopefully in the next 10 years see that in Parkinson's as well.

And I think another thing is not, we talked a little bit about this in the diversity of the pipeline, it's making sure that we're seeing, and I'm hopeful that we'll continue to see that, not just advances that could help people at the earliest stages of Parkinson's disease, which is I think when we tend to think of a lot of the disease slowing type treatments, they tend to often focus on people who are early, who maybe don't have many symptoms yet, rightfully so, because if we can prevent progression to those symptoms, that would be amazing. But there are of course a lot of people that will continue to progress and have more advanced symptoms of Parkinson's. So we want to make sure that that pipeline is reflective of their needs as well. So again, in the next year is making sure that we're continuing to see that innovation happening, even if it is innovation in existing therapies like the dopamine therapies.

For example, there's a huge pipeline of cell therapy approaches. So the idea of using stem cells to generate replacement dopamine cells that can be transplanted into the brain. There's a massive pipeline of companies now developing that type of treatment. We're likely to see some of those get approved in the next few years as well. And I think that will sort of add to that hopefully alternatives people can use to, especially again as the disease advances, to maintain good function for as long as possible. So I would hope that we would see that as well.

Maggie Kuhl: And while we are working toward more options, we are also trying to go as quickly as possible. We know that people with Parkinson's disease are waiting for these new treatments and we are working urgently. So in our next Parkinson's Science POV podcast, we will talk about how we are accelerating trials. Mark and Brian, thank you so much for our conversation today.

Brian Fiske, PhD: Thanks, Maggie. Always fun to be a part of this.

Mark Frasier, PhD: Thanks, Maggie. Good to see you.

Maggie Kuhl: And I heard that you two will also be at the awards luncheon. Is that correct?

Brian Fiske, PhD: Yes. Exciting.

Mark Frasier, PhD: Yes, I dropped off my suit at the dry cleaner today, so I'm going to be ready.

Maggie Kuhl: I'm sure you'll both look very spiffy. Give Michael our congratulations. Thank you again. Thank you to Shalini and to you, our listeners. If you like what you've heard, please leave us a rating or review wherever you get your podcasts. It helps listeners like you find and support our mission.

Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.