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Speaker 1: Navigating Parkinson's disease can be challenging, but we are here to help. Welcome to The Michael J. Fox Foundation podcast. Tune in as we discuss what you should know today about Parkinson's research, living well with the disease, and the foundation's mission to speed a cure.

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Maggie Kuhl: The last months of 2023 saw a handful of Parkinson's drug programs get bought up by Big Pharma. In today's Parkinson's Science POV Podcast, we're going to talk about why that's good news for people who are watching toward new Parkinson's treatments, and The Michael J. Fox Foundation strategy that got these programs to be so attractive that investors just had to snatch them up.

Today's podcast is a two-parter. I'm Maggie Kuhl, Vice President of Research Engagement at The Michael J. Fox Foundation. First I'll be talking with my usual panelists, Dr. Mark Frasier and Dr. Brian Fiske, our Co-Chief Scientific officers, and then I'll hear from Dr. Shalini Padmanabhan, our vice president of discovery and translational research, about these new programs and what's on the horizon.

Mark, Brian, thanks for kicking it off with me today.

Mark Frasier: Hey Maggie, great to be with you again.

Brian Fiske: Always great to be here.

Maggie Kuhl: So Brian, I wanted to start with you. As I said, some of the programs that the foundation has supported in the past have recently been acquired by bigger partners. And these are so-called successes of what we call at our foundation, our de-risking model. Where we work to make programs more attractive, and give them the tools and resources that they need so that investors and partners with deeper pockets can move them ahead. So why don't you explain to us a little bit more what this de-risking means, and why it's such a priority at the Fox Foundation?

Brian Fiske: Yeah, this idea of de-risking, it's, I mean, really been core to our, I think, philosophy and our mission from day one. And it's, I like to think of it really about, when you think about new treatments and ultimately cures for a disease like Parkinson's disease, what are the ingredients that you need to make that happen?

And there are a few really critical pieces to this. One, of course, being about understanding the underlying biology of the disease, having something about

the disease that you can actually go in and change for the better, hopefully. So what you need to prevent the cells from dying in the brain, or the symptoms from being expressed due to the changes that are happening in the brain.

So that being sort of one key ingredient for a de-risking, which is de-risking the science around the disease.

But there are some really critical pieces that go into, I think, this understanding of what de-risking means for us. Which is, it's not just about understanding the disease, it's about having the ability to actually go in and target that biology with a treatment that can actually do that.

Can it get into the brain? Can it get into the brain safely? Can it target the biology that it needs to target in the ways that it needs to do it? And that's sort of another part of the de-risking. And sort of mix, which is de-risking the actual treatments themselves, showing that they can actually do those things and get to the biology.

And then another key ingredient for me too is then, once you have those two pieces, the biology and the ability to target the biology. How do you measure the biology so that you can know that it's changing when you're giving a particular treatment? And that's really a critical piece, especially when you get to clinical trials where you want to be able to measure these changes in people with the disease and actually see that the treatments are changing.

And so these are three kind of core critical pieces or ingredients that I like to think about of a de-risking strategy. There are lots of other pieces too, around just the infrastructure for how you do trials and how do you find people, and the right people and things like that that kind of go into this as well.

But for me, those three pieces are really critical. They really, when you develop a strategy, a de-risking strategy, it's really about what can we do as an organization to sort of de-risk the science, de-risk the treatments themselves, and ultimate de-risk the measurement tools that are needed to assess those treatments. And so all of that comes together in a general sort of de-risking strategy that we've generated over the years.

Maggie Kuhl: Mark, how does that strategy come to life? What does that mean for how we're actually deploying our donor-raised dollars? We're very active in getting money out the door to the science that needs it most right now. So as Brian laid out that understanding around the disease, that measurement of the disease, what does that mean for what the Fox Foundation is actually supporting with our funding?

Mark Frasier: Yeah. I mean, what it means is that our research team is constantly assessing the field, and specifically not just the state of the science, but what is needed for new therapeutic development.

And in discussing with pharmaceutical companies, biotech, university professors to understand that landscape, we can then identify the gaps, and really the key inflection points and the missing pieces that are needed to accelerate therapeutic development.

And so it's that strategic overlay that I think the team brings to lowering the risk for investment in Parkinson's research and Parkinson's therapeutic development.

Before I joined the Foundation, Maggie, I was working for a large pharmaceutical company. And I often tell people that there were hundreds of smart, dedicated scientists at the company that were trained to do medical research and therapeutic development. But really, I was one of the only ones working on Parkinson's disease. And Parkinson's was competing with other disorders like diabetes, cardiology, oncology.

And so what brings investment and brings resources to diseases like Parkinson's is understanding the science better, making it easier to do the clinical trials as Brian was suggesting, and really just having a clearer path to therapeutic development.

And I'm excited to think about the way that the foundation has really applied that de-risking strategy to make the tools, develop the tools, identify individuals eligible for clinical trials, that has really lowered the risk for investment in Parkinson's disease.

Brian Fiske: Yeah, I think this is the critical part, I think, what Mark is really getting at. Which is this idea of, how do you lower the barrier?

You want companies and investors ultimately to look at Parkinson's and see a clear path forward without a lot of challenges and uncertainties. And so how could we reduce those uncertainties as much as possible, so that it becomes sort of a no brainer for a drug maker to focus on Parkinson's?

Maggie Kuhl: So every two months or so we put out this blog post called What We Fund. And if you would look at that list, you would see some programs that are clearly creating a therapeutic. But you'd see a lot of others that, to the eye, might not be as familiar with this strategy, would seem sort of confusing. And why we're funding all of these small grants to, as you were saying, figure out biology or measure.

And Mark, you said tools. And we fund projects to recruit participants, or to collect samples so that we have resources for companies to be evaluating, and looking for new targets, et cetera. So if someone was looking at that list of what we fund, how does this sort of really heterogeneous mix of where we deploy our grants feed from that de-risking strategy? How would someone be able to

understand, we gave a Lysosomal Biomarkers Grant, or a Alphas Nucleon Assay Development Grant, or a Viral Vector, all these things that are so scientific.

How does that translate for someone who's living with Parkinson's every day?

Mark Frasier: I think it's about impact, and I'll just tell a brief story about a tool that the foundation made back in 2008. It was actually the first direct tool that we funded to make. It was what's called an antibody against Protein LRRK2, which is a really important protein involved in Parkinson's disease.

And at the time, there were no good tools to study this LRRK2 protein in laboratories. Many laboratories were interested in studying LRRK2, but the tools available were very limited. And what the foundation did was to fund this generation of an antibody, and made it freely available to anyone in the world. And the only caveat was that they were required to share the information back with us, so how the tool performed. And over a hundred laboratories around the world gained access to this, and shared their data back with us.

And that was a very simple tool that did not cost a lot of money to make, but it's sort of the one to many impact and approach that hundreds of laboratories benefited, and it accelerated the research of multiple different laboratories, including pharmaceutical companies that were developing drugs against LRRK2.

So it's really about the impact. And that I think, when you think about what we fund, that's a great example of lowering the risks. Now there are multiple tools available for researchers to use. The foundation has supported now over a hundred different tools that are made available to the entire research community. So I think that's a really tangible example, where it's now lowered that barrier that Brian mentioned for researchers to jump into Parkinson's research, and specifically this lurk two research.

Brian Fiske: And I think that that's a good example, because it talks a lot about how we have to think about the particular problem or barrier that we're trying to address. And so for example, in the science, we know the disease is very complex. There's a lot of biology that may be involved in what ultimately leads to the brain cells that are lost in Parkinson's.

And whether it's this LRRK2 protein that Mark mentioned, or any of a number of other proteins that are being explored and studied for Parkinson's, you have to first ask yourself, what's the missing piece of the puzzle that is keeping that particular biology from reaching a point where drug makers will look at it and go, yes, let's make a drug against this and move it forward.

And so sometimes it's the tools, like Mark said. And so we might have to develop, we can work with a community to figure out which tools are lacking, and then we can make those tools available so that the individual labs don't have to do it themselves. And spend all that time, and money, and sort of

wasted effort developing tools when they really should just be doing the science itself.

And in other cases, maybe the tools are available, but it's the lack of coordinated collaboration between the different labs that are focused on the biology. And so can we bring those groups together in a consortium type of approach, or some other way to get them working together. And so it's really about sort of pivoting the particular solution to the problem at hand, I think, is really core to that kind of de-risking strategy.

Mark Frasier: I think that's a really important point that Brian made, that it's not always funding. It's the strategic oversight of our team that is connecting dots, bringing researchers together that may not know each other, or know that their work could benefit the other. And getting them to talk, getting them to collaborate, getting them to share data is a really important part of the de-risking strategy.

Maggie Kuhl: Yeah, it sounds like there's intangibles and tangibles, where there are perhaps filling knowledge gaps, or establishing relationships through foundation funding or coordination. And then there's these tangible resources, be it tools or recruitment flyers, or a very engaged group of volunteers in Fox Trial Finder or PPMI or Fox Insight, like those who might be listening right now, who can help advance research directly.

But really, as you've all said, it's really enabling the field at scale. And allowing the program or the company, no matter who's behind it, to really advance with what we have added to the field overall.

Any other examples that might help our audience sort of put more context around this?

Brian Fiske: Yeah, I think you alluded to this early on, because this is another piece that I think people don't always appreciate. That there's the science, there's the treatments themselves that you have to de-risk.

We talked a lot about measurement tools, and the ability to measure the biology is so critical as well. And there was obviously recently a big breakthrough around a biomarker measure, the synuclein seeding assay, which I know we've talked about before, as being sort of a critical tool and de-risking tool.

But there's all these other bits and pieces too, that kind of goes into creating a clear path for developing therapies for Parkinson's. And that includes, what are the barriers to getting in front of people with Parkinson's, and getting them involved, and interested in being involved in the research.

And sometimes those are equally critical barriers to a drug maker who's trying to think about, okay, if I'm going to develop this drug and I think I've got this

great therapy to do it, and I know the biology I want to go after and I have some tools maybe to measure that biology. But I don't know how to get access to the people who would be best suited for this therapy, and how do I do that?

And so that's another way I think the foundation can sort of de-risk the path a bit, by thinking about these types of community barriers that keep people from even knowing maybe about these trials that are available, and what tools can we put in place.

We have Fox Trial Finder, for example, which can help connect people to trials that need them. But there may be sometimes other more direct things that we can do to get involved. And if it's a particular form or subtype of the disease maybe defined by its genetics or its biology, what can we be doing to more proactively help identify those individuals too?

And so our early stages of the disease, when we don't even have symptoms yet, and you're just sort of trying to find people at risk. And so there's a lot of different ways we can de-risk some of these other sort of barriers to drug development as well.

Mark Frasier: Maggie, one of my favorite examples of de-risking is something the foundation supported to improve the measurement of dyskinesia. Dyskinesias are these abnormal involuntary movements that emerge with dopaminergic medication, after taking dopamine for long periods of time.

And there was a lot of activity in the drug development world. The science was well-understood to identify ways to potentially reduce dyskinesias. But the challenge in the field at the time was really measuring dyskinesias. Because they come on at different times, it's unpredictable. And the traditional way of measuring was having individuals in the trials fill out diaries, and fill out when the dyskinesias were occurring, and how severe they were.

And what was happening was, it turned out people were filling out the diaries in the parking lot of the doctor's office before their appointment, and trying to recall over the last three to four weeks how common these dyskinesias were occurring. And so...

Brian Fiske: You mean study for the test the night before?

Mark Frasier: Yeah. And it's just a not-effective way to reliably measure dyskinesias. And so what the foundation did was, supported some researchers to develop a better scale that neurologists could use, but also patients would fill out. And it was a combination of patient and neurologist-reported information. And we supported the validation of that scale. Which is to say, really, a study to demonstrate that it was effective in measuring dyskinesias.

And so once that validation happened, we saw an onslaught of trials that were using that scale. And so it was sort of the tide that lifted all boats, regardless of the treatment mechanism. Now, dyskinesia trials are using this validated tool for their outcomes, which is a really important de-risking strategy. It identified a barrier, supported something that would break down that barrier.

Maggie Kuhl: So what I'm hearing for our listeners is really that, through strategic oversight of the field and identification of needs and gaps, the foundation is deploying a really holistic strategy to be learning more about the disease, to be creating better measures and tools so that those who are creating more therapies, some with foundation direct funding, but with additional supports, either through the knowledge base or as we've been talking about these tangible tools of scales or recruitment support, et cetera.

The Foundation is really behind all of these programs in so many different ways. We're on this massive, complex challenge of solving Parkinson's disease in so many different ways. And whether you are a financial supporter or a research participant, you too are part of de-risking this research enterprise and advancing new therapies.

Mark and Brian, I just have one more question before I get to some of this recent news with Shalini. Is this unique? Is it what the Fox Foundation does in this space, unique?

Mark Frasier: I think it is. I mean, we work with a lot of peer medical research nonprofits, and I think it's a very unique approach to have this in-house team with the strategic oversight, collaborating with researchers in all different sectors, including people with Parkinson's disease, to understand the needs.

Our CEO, Debi Brooks often says we're in the silver platter business. And that is to really tee up Parkinson's research on a silver platter. So it's very attractive and to other researchers, other investors, other supporters. So I feel like we're in a unique position.

Brian Fiske: Yeah, and I think this uniqueness comes from the appreciation that it's not just about the money. It's easy to sort of give out a lot of money, and just launch a few funding programs, and review some proposals and just give people money. And that certainly can help address some de-risking challenges, if you just want to get people interested in studying a disease like Parkinson's.

But I think we learned very quickly in our earliest years that something more is needed to really de-risk ideas. So it's about, how do you engage drug-makers appropriately, and regulators, and all the other, the patient community? And all the physicians, the clinicians, the biologists, how you actually get them to work together and understand the challenges that they're actually facing, and accelerating the research and drug development process for Parkinson's.

And I think being able to do that, and understand what those barriers are, and then ultimately figure out the right solutions to try to address some of those barriers, I think that's really where the uniqueness truly comes from.

Maggie Kuhl: Right. Well thank you both for explaining a very complex, deep, overarching, encompassing topic with me. And get back to polishing that silver platter, so that more companies will be interested and we can advance science faster. So thank you both. Talk to you soon.

Mark Frasier: Thanks, Maggie. Take care.

Brian Fiske: Always great talking to you.

Maggie Kuhl: Great. And joining me next, as I said, is our vice president of discovery and translational research at the Fox Foundation, Shalini Padmanabhan. And she's going to chat with me more about some of the recent acquisitions that we had and what's next on the horizon.

So Shalini, as I said, there's been a lot of activities, some acquisitions, which doesn't seem to, perhaps the typical Parkinson's patient, like something that we should be celebrating so much. So maybe you could tell us a little bit about the projects that we have been watching, and the foundation's support of those. And why people with PD should care about this development in Parkinson's research investment.

Shalini Padmanabhan: Sure. So Maggie, just wanted to reiterate what Mark and Brian highlighted in the beginning. I mean, as scientists on the discovery and translational team, one of our goals is really to explore all the exciting biology that's out there, see what's exciting in the science, and see what can be leveraged for Parkinson's disease drug development.

So at the end of the year when we look back on our activities, what we are hoping to see is some sort of advancement in the science. Either we are learning more about the science, or we are starting to actually leverage that science to make better treatments for Parkinson's disease. Or we are just increasing the resources that can be made available to the community.

And actually last year we saw some acquisitions, as you mentioned, Maggie, and it all happened in quick succession towards the end of last year. And there were three companies that I wanted to highlight today for our listeners, and that's Mito Kinin, and they were a small company. We've been working with them since 2009, ever since they were founded. And they were recently acquired in October by AbbVie, which is a big company.

Another company that we were working with over the last four or five years is Caraway Therapeutics. And again, they were acquired in November by another big company, Merck. And then in December we closed out the year with

Cerebal, and other smaller company that we were working with, got acquired by AbbVie again. And so these were two big companies acquiring three smaller companies that we've been working for over several years.

And some of the signs that these three companies were focusing on were areas that we were following as well for many, many years. And as Brian mentioned, when we think about de-risking, we are thinking about lowering that barrier for companies to start developing drugs. So a lot of the activities that we were supporting were around understanding the basic biology of these proteins that these companies were attempting to target.

And a lot of these proteins and the biology are things that are emerging in Parkinson's disease, something that's just picking up because of all of the research activities that we have been funding. And I think when people think about a treatment for Parkinson's disease, they think that it happens very quickly. But in reality, we all know that drug development is a really long process and a lot of it fails along the way.

And so we want to make sure that early on the science is strong, and that the company or the laboratory that's doing the research has the highest chances for success. And so as Brian mentioned, a lot of our activities with these companies focused on really strengthening that science, trying to understand what is it about these proteins that is relevant for Parkinson's disease?

How can we help de-risk their programs? How can we make sure that the therapeutics that they are actually generating is going to be effective in people with Parkinson's?

So just connecting them with the right resources. And we have the resources through studies such as Parkinson's progression markers initiative. And so connecting them with patient-relevant resources, connecting them with relevant Parkinson's disease models, animal models, patient cellular models, connecting them with key opinion leaders in the field so that they can refine their strategy and their plan with some of the activities that we helped with early on.

Maggie Kuhl: So again, some of those sort of intangible and tangible, helping these programs get to a point where they were so attractive for Merck and for AbbVie because of all of the de-risking that the foundation in these companies in partnership did around not just the biology and these targets, but then the therapies themselves.

And so again, why is it so empowering or helpful for us to be looking at these acquisitions as a measure of success for our strategy? Why is it good when a bigger company buys out a smaller one?

Shalini Padmanabhan: Yeah, of course. And like I said, I mean, because we know that drug discovery is kind of long, it's a long process. It's an expensive endeavor, and there are many, many steps that we need to take to get to the cure. So I think just showing that these companies are willing to make a bet and take the risks indicates some momentum in the field. It indicates, yes, there's going to be an advancement in this program.

And it just gives the field a sense of optimism. So that's the first step. It's, smaller companies take on the riskier science. And then once it gets to that drug development phase, we need the big players who have the resources and the capital to invest in these programs to take this on to the next level. So I think it's a sign of just hope, and it gives the field a sense of optimism.

Maggie Kuhl: And you mentioned that these programs are looking at different targets or proteins. What does that tell us about the state of the science, and that interest across perhaps many different ways to cure PD?

Shalini Padmanabhan: This is very interesting. Because one of the things that my team does also, as I mentioned, is to explore what are those exciting targets that are going to be ready for drug development? And these set of acquisitions were interesting because these targets were all, in some way, genetically linked to Parkinson's disease.

And they're exciting because they're pretty diverse, so they all don't fall within the same biological process or the same mechanism. So it indicates that yes, there is a diversity in the pipeline. So that was exciting for us to see, that we were actually seeing different targets that are probably going to play a different role in different patients.

And that's exciting because as we are learning more and more about Parkinson's disease, we are learning that the biology may be different for different people that's leading up to their Parkinson's disease, and also playing a role in the progression of their disease.

So what this tells us is that that pipeline is going to be more diverse, it's going to be more robust, and we want to see that. Because eventually we want to make sure that different people are being treated according to their Parkinson's journey, or their kind of individualized Parkinson's journey.

Maggie Kuhl: That leads then to think that, while we have perhaps de-risked to a degree, I'm sure there's still a lot to do around these specific targets, there are many more that are perhaps more in their infancy and need a lot more support and de-risking to get to the point where, hopefully, there will be therapeutic programs that larger investors are interested in as well.

So where is your team right now on identifying that next generation of targets to de-risk?

Shalini Padmanabhan: Our team, I think at this point we are seeing over a hundred-plus targets that we are monitoring. So that's very, very exciting. So a lot of what we are doing is trying to apply our lessons learned from previous experiences to see, what would it take to de-risk some of the most exciting targets?

Do we require the right partners bringing and building a community around those targets? making sure that we have the right preclinical resources, the right clinical resources to make sure that we can advance that target. So those are the kinds of activities that we are looking at.

And we have a lot of exciting studies in the pipeline, like our genetic study, the Global Parkinson's Genetic Study, or GP2, they are discovering new genes every year. And so that's going to add to kind of the genetic diversity in Parkinson's disease.

We are seeing a lot of improvements in technology, so we are going to see better ways of delivering treatments to people with Parkinson's disease. So I think there's a lot of excitement. The pipeline seems really, really robust, and we just want to make sure that we can get kind of the right treatments to the right patients at the right times. So that's kind of our strategy moving forward.

Maggie Kuhl: Well, no doubt everyone listening to us is hopeful for Parkinson's cures. There's also likely many who have been living with Parkinson's for years or even decades. Does this strategy extend to targets and de-risking efforts that could assist with management of symptoms as well as more curative or preventive therapies that might be more effective in the earlier stages of disease?

Shalini Padmanabhan: I think this is kind of the same strategy, whether you're looking at a disease-modifying treatment or a treatment that manages the symptoms. Of course, I think with some of the newer signs that we chatted about today and the acquisitions, all of those were focused more on disease modification and treatments that would be tested early on in the disease.

But we are always also looking at better ways to manage some of the symptoms, some of the non-motor symptoms that play a role in Parkinson's disease. And through studies and our collaborations with initiatives like the aligning signs across Parkinson's, we are starting to learn more about circuits and brain changes that could be occurring in people as they progress with Parkinson's disease.

And we will apply the same strategy, and look for new circuits and pathways and mechanisms that we can tap into to start addressing some of these symptomatic challenges in the disease.

Maggie Kuhl: What can listeners do today to help keep this momentum and further de-risk the field?

Shalini Padmanabhan: I mean, as a researcher, I feel I've learned immensely just from studies like PPMI, and from talking to patients. There's so much we can learn from people with the disease. So I always encourage people to participate in research studies where possible, because I think that's how we are going to learn more about the diversity of Parkinson's. And then it'll help us tailor treatments that are suited to individual needs.

As a researcher, I've also immensely enjoyed talking to people with Parkinson's disease. I feel like they have the best questions, they're very well-read and always looking for their questions and feedback on our strategy and work. So that would be kind of my ask.

Maggie Kuhl: So share your data, your samples, your experiences, your questions, we'll take it all. Because as we said, it's a big strategy with a lot to cover. And certainly, people with Parkinson's are not only the end consumers of these efforts, but really our partners in enabling them and getting them off the ground.

So thanks so much, Shalini, for sharing with us this recent news and reason for optimism, and your plans to continue advancing momentum in the pipeline toward new Parkinson's treatments.

Shalini Padmanabhan: Thank you, Maggie.

Maggie Kuhl: And as a listener, you can learn more about this research news, our overall strategy, and how you can play a role in Parkinson's research on our website at michaeljfox.org. Thanks for listening.

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