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.

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're welcoming guests with a range of experiences and viewpoints. The views expressed belong to the guests themselves.

And today we are thrilled to welcome our guest, Dr. Claudio Soto. Listeners, Claudio is the Huffington's Distinguished University Chair, Professor of Neurology, and Director of the George and Cynthia Mitchell Center for Alzheimer's Disease and Related Brain Disorders at The University of Texas Medical School in Houston. He is also the Founder, Vice-President, and Chief Scientific Officer at AMPRION Inc. And today, listeners, we're going to be talking more about Claudio's research on the molecular basis of neurodegenerative diseases associated with misfolding and accumulation of proteins in the brain, as well as his recent receipt of the 2024 Robert A. Pritzker Prize for Leadership in Parkinson's Research. So, Claudio, welcome to the show today. How are you?

Claudio: I'm very happy to be here and very happy to connect with your audience. Very happy to talk about our discoveries.

Marie: Well, we are looking forward to learning more about you and your work. And perhaps we can start with your background. For listeners who haven't met you yet, Claudio, can you tell us more about your background and your path to your current position?

Claudio: Originally, I was born in Chile in South America, and I did all my studies there — undergrad, and then obtained a PhD, and did one postdoc. And then I moved to the United States in 1994 to perform another postdoc at the New York University, where I got promoted to a faculty position. I stayed there for a total of five years. And then I moved to Switzerland because while I was in New York, I discovered some strategies to develop drugs for treatment of diseases like Alzheimer's, Parkinson's, etc.

And then at that time, the biggest biotech company in Europe named Serono was interested in developing these ideas. So, they offered me a position. I moved there with most of my group at New York. And then I stayed there in Switzerland in Geneva for around four or five years. It was the time that we invented this technology of cyclic amplification of misfolded protein aggregates. At that time,

we were focusing mostly on prion disease research. And then after that, I decided to move back to academia, came back to the United States.

I came initially to the University of Texas Medical Branch in Galveston. And then a few years after, I moved to Houston, in the same university, the University of Texas, but in Houston. And I've been here since 2009. When I came back to the US, I was already a full professor, so I had actually never passed by associate professor. I went from assistant to full professor right away with the intermediate time in a biotech company.

Marie: Very cool. And I think this discovery that you mentioned from your lab, cyclic amplification of protein misfolding, was an amazing breakthrough. Can you talk more about this discovery and why it's so relevant for research today?

Claudio: Yes. Let's just switch back to the beginning of the century. This first discovery was in 2001. And we published an article in *Nature* at that time. And I don't know how much you know about prion diseases, but this is a group of diseases that affect humans and other species of animals, like cows, sheep and deer. And it's a disease that has a lot of similarities with Alzheimer's and Parkinson's in the sense that it involves the formation and accumulation of an abnormal protein. Which is a version of the normal protein that we all have that gets changed the shape and becomes aggregated, accumulating in the brain, and it produces disease.

So, in the case of the prion diseases, these are more rare diseases like Creutzfeldt-Jakob disease in humans. But the scary thing is that prion diseases can be transmitted from individual to individual and from animal to people. And at that time, in the early 2000s, there was a big scare of a disease in cows called bovine spongiform encephalopathy.

In the lay audience, normally it's known by mad cow disease, which was clearly shown that produced a new disease in humans called variant Creutzfeldt-Jakob disease. And at the beginning of 2000, everybody was scared that it would be a huge epidemic of a fatal disease that kills people and destroys all the qualities that make people special in a very short period of time. So at that time, we discovered this, and it produced a very big impact because, for the first time, we were able to detect with high efficiency, these abnormal proteins and therefore know who might be infected and also eliminate the potential route of transmission by knowing where these infectious materials are.

So, it turns out that, for the best of society, that this disease, variant Creutzfeldt-Jakob disease, never really affected a very substantial amount of people. It was in total around 250 people in the world. We don't know why. Everybody in the UK

and large parts of Europe were exposed to the same materials. But lucky for us, for the world, this disease did not transform into a big epidemic.

So, then we continued working on this. We show you with this technology, that we were able to detect basically in blood, in cerebrospinal fluid, in urine, and very, very high sensitivity and specificity. So years later, when I came back to the US, we decided to start expanding the principles behind this cyclic amplification technologies to the more prevalent brain diseases like Alzheimer's and Parkinson's, dementia with Lewy bodies, etc. So, that's more or less a little bit about this time.

Marie: Sure. I think it's very interesting. And you mentioned that prevalence was a factor that you considered in transitioning from working on prion diseases to things like Alzheimer's, Parkinson's. Can you talk specifically about how you decided to apply this approach to Parkinson's disease and perhaps how you got connected with The Michael J. Fox Foundation?

Claudio: Yes. So early on, we were one of the first to propose that this process that makes prion disease infectious is actually at the root of the process by which the abnormal protein accumulates in the brain of many of the different brain diseases. So, we were one of the first to propose that Alzheimer's disease, Parkinson's disease, and many other brain diseases, could actually employ the same principles by which abnormal prion proteins propagate. In this case, most likely not to propagate between individuals, not to transmit between individuals, but actually to transmit inside the individual.

So, that the disease, for example, starts in a circumscribed area of the brain. We've known that since a long time, both, for example, alpha-synuclein and tau. They start in a very circumscribed area. But with time, they expand, and they spread. And they finally reach out to most of the brain, and this is when the disease happens. So, this process of spreading is what is produced by the ability of this protein to be able to self-propagate. So at that time, this was not known, of course, and we and others over the years showed that the proteins involved in Alzheimer's and Parkinson's could actually self-propagate in the same way that the prion protein was doing. So, they became known as the prion-like proteins that are able to do the same thing, but most likely again, participate in the transfer of this between cells and different areas of the brain.

But it was a very interesting time. And then, since the principles of the cyclic amplification technology are basically mimicking this process that happens in these diseases — the ability of a misfolded protein to convert the normal form of the protein into more of the abnormal form. So, this is like a templated conversion. So, you have two proteins, they have the same amino acid composition, but they have two different shapes. And it's known that the

abnormal shape, it's dominant and can take the protein in the normal shape and take it into the abnormal shape and produce more and more of that. And this is how the prions self-propagate and how other misfolded proteins self-propagate.

So, our idea behind is that if we can mimic this process in a test tube, we could actually amplify the amount of abnormal proteins very substantially to go from quantities that are undetectable in biological fluids to quantities that can be easily detectable after our cyclic amplification assay. We expanded towards other proteins. We started working with the amyloid beta involved with Alzheimer's disease at that time. That was our first protein that we started working with this seed amplification assay that we developed. And we published an article in *Cell Report* in 2014.

So at that time, I got a call from somebody from The Michael J. Fox Foundation. I had never had contact with The Michael J. Fox Foundation before because I didn't really work on Parkinson's disease much. I mean, I knew about it, and I knew that was one of the diseases that was behaving in the same manner, but I was very busy with our work in prions and Alzheimer's.

So, the name of this person was Samantha Hutten, who was new at that time at The Michael J. Fox Foundation. So, she told me that she liked the article that we published with the amyloid protein in Alzheimer's. And she said, why don't you start working with synuclein? And we actually were very much interested in working with synuclein, but we didn't have the funds. So, The Michael J. Fox Foundation, through Samantha, provided us the initial funds to start working on this adaptation of this new technology now for alpha-synuclein and detection of Parkinson's disease. And things went from there very well.

We collaborated with many groups and have been able to develop the technology adapted more recently with the PPMI group where we did the largest study to date to show the validity and the efficacy of this seed amplification assay to detect patients affected with Parkinson's disease, not only at the clinical stage of the disease, but also early on, much before the people developed the clinical symptoms, which is very important for early detection and early diagnosis eventually.

Marie: Certainly. You mentioned PPMI, which is of course, The Michael J. Fox Foundation's flagship longitudinal study, called the Parkinson's Progression Markers Initiative. And it sounds like the call that you mentioned from The Michael J. Fox Foundation, sort of came out of the blue, but really sparked innovation to develop this alpha-synuclein seed amplification assay. So Claudio, can you walk us through what was that process like, or what were the different steps involved in the development of that assay?

Claudio: So yes, the seed amplification assay is basically mimicking, in an accelerated manner, what's happening in the brain of people over decades. So what happens, is that we know that the abnormal protein — it's actually what we call an oligomer or an aggregate, which means that it contains several units of the protein, folded into a particular structure, that in science, we call beta sheet structure that have the ability to grow. So, this is the way that the process is amplified in the brain. So, you're take the abnormal protein, which is an aggregate that composes several units of that normal protein, but folded into this abnormal shape.

Then what they do is that when they find the normal protein with the normal structure, that our brain is full of because this protein is important. We still don't know exactly the function, but it's most likely involved in synaptic activity. And this is, of course, the way that neutrals connect to each other and transmit information. And we can think we can do all the functions that we do basically because we have this ability of the neutrals to connect to each other through synapses.

So, synuclein is just there. And it's in a very high abundance in the brain. So, when you have these first aggregates form, then they can just recruit more of the normal protein, and the aggregates grow and grow and grow and grow over the period of time. In the brain, this takes a long time because it takes a long time for the abnormal protein to find substantial amounts of the normal protein, get them inside, and then eventually they need to fragment because if you have only one aggregate, that will take a very long period of time to grow. But if this aggregate becomes fragmented, then you can release more seeds that could go from cell to cell and expand the pathology.

So, what we did basically was to use this principle. So, we produced the normal form of alpha-synuclein in bacteria, only because in bacteria, you can just produce very high quantities of a protein that you purified. And this is a technology that is used to study proteins in general. So, we produce the normal synuclein form, and we incubate it with material from patients, either like say brain homogenates that contain the abnormal proteins or cerebrospinal fluid from the patients. The cellular spinal fluid is this liquid that surrounds cells in the brain, and it contains a lot of the material that the cells secrete. So, among them, it's some of these protein aggregates. The problem is that the quantity of this cellular spinal fluid is very, very low. So, you cannot detect them by any traditional methodology.

So what we do is to take these samples, biological samples from patients, we put it together with a dose of the normal protein, and we make them work as they do in the brain. And we do one trick, and the trick is that we help the fragmentation so that you multiply the number of these units that are growing, periodically. So,

that's why we call it “cyclic amplification,” because periodically we apply a force, in this case a mechanical force, to cut big aggregates into smaller aggregates so that now you have several aggregates growing at the same time and converting more and more of the protein. So we do this, we let the protein to be converted, we fragment them again, release many more units, we let them grow, then we fragment them again, etc. And so, this is a cyclic process that results in the exponential amplification of the amount of protein. So you go from, let's say, a few molecules to billions of molecules.

Marie: Oh, that makes sense. And I think, Claudio, when you describe it, you make it sound easy. Just the flow of logic and the steps that you did. Did you run into any challenges in trying to apply this particular approach to alpha-synuclein, compared to in previous diseases when you were working with other proteins?

Claudio: Each protein, it's its own world, right? That's what it makes it difficult. The technology is a platform technology that can be applied to all these different proteins that aggregate in the brain, and there are several proteins. I mean, the most common, amyloid beta, tau, alpha-synuclein, TDP-43, but there are, I don't know, ten others that are involved in some other rare diseases like Huntington’s disease or amyotrophic lateral sclerosis, etc. So, each disease is associated with a different protein, and each protein has its own complications.

So, how fast the assay can be developed depends on two things. One, obviously having the funding, which Michael J. Fox provided us. Not only the first grant, but over the years they've given us a lot of different grants to develop this. This is one aspect. The second aspect is how, let's say, well-behaved the protein is. How easy it is to produce in bacteria to get high amounts and how easy it is to work with it.

These proteins can aggregate. This is what they do in the brain. So, what we need to do is to eliminate this, what we call the spontaneous aggregation and only see what we call the seeded aggregation. So, aggregation mediated by a biological entity present in the patient sample. In this case, the aggregate that converts the normal protein. But the process, if you are not careful enough, you will just put the normal protein on its own can form these aggregates because this is what happens actually in the brain. So, the first seed is formed without the seeding process. So, at some point this can happen. So, we need to avoid that to be able to detect the presence of seeds in the biological samples.

So, this makes some complications. Some proteins aggregate too fast spontaneously, making it more difficult to see the seeded aggregation process, and some other proteins aggregate too slow. So, you need to really fine tune the conditions. And this takes quite a bit of time to find the right set of conditions, you know, meaning what liquid you're going to put in (I mean buffers, we call it), salts,

what temperature you're going to use, how frequent are going to be these fragmentation events, how strong the fragmentation is needed.

So, a lot of different variables that you can change to make an assay to work how we want. It's that in the absence of patient seeds, no aggregation whatsoever. In the presence of patient seeds, you see the aggregation reaction always when you have seeds. This is what we want to have. And fortunately, we were able to achieve it — not in too many years, I mean — in a relatively short period of time. We started in 2014 as I told you, and then at the end of 2016, we published our first article. And from there, you know, it was just testing a lot of different samples. I mean, Michael J. Fox has sponsored two round robin studies which is when you use the same samples in different laboratories to make sure that there is reproducibility. And this was done.

We were one of the labs in both cases, and the assay was remarkably reproducible among different laboratories. So, that tells you, you can pass. The samples are provided blind, and the people in different labs got the same results. So, that's very important. And from there, we went to a large number of samples. This is the PPMI study I was telling you, we published in 2023 in *Lancet Neurology*. It was an effort of many different people, and this served as the most extensive validation that the assay worked, and it works very efficiently.

Marie: Definitely, and I'm so glad to hear that you went through these steps of making sure you could reproduce and replicate the results. And thinking about the impacts, how do you see this alpha-synuclein seed assay then impacting the field as a whole going forward?

Claudio: I think the impact is very high for several reasons. So one, now we have a way to detect people who have the underlying biology of Parkinson's disease in a relatively non-invasive way. Granted, CSF collection, it's a little bit invasive. They have to do a lumbar puncture. And that's why one of the next steps that we are working with a lot of effort is to detect these protein aggregates in samples that can be more easily collectable like blood and urine. We did that before for prions. And in the prion diseases, we can detect in blood and urine. And this is what's being used worldwide. So now, in the synuclein field we're still in the CSF. We have done a bit of advances to move it into blood, and we believe that this will happen soon.

So this is one application, right? The detection in patient samples. You may know this, that Parkinson's is more than a disease. It's what we call a syndrome. So, there are various different biological changes that can lead to Parkinson's, and in some cases without the involvement of alpha-synuclein. So, what we call Parkinson's disease is when this problem is caused — the clinical symptoms of

Parkinsonism are caused — by the accumulation of alpha-synuclein. But there are other reasons you can get the same clinical picture.

For example, the most evident case is when people are exposed to some pesticides that they will kill certain neurons in the brain that will produce the symptoms of Parkinson's disease but this has nothing to do with the Parkinson's disease and alpha-synuclein. It's a different way that this happened. You need to be able to differentiate this. So, to be able to differentiate people who have real Parkinson's disease versus people that don't. Because when you want to treat the people, and let's say you are treating them with a synuclein-based drug, then if they don't have synuclein then nothing is going to happen, right?

So, it's very important for patient diagnosis. Even today, and even with the most accomplished neurologist, the clinical diagnosis of Parkinson's disease, or multiple system atrophy, or dementia with Lewy bodies is not 100% accurate. So, in some centers it's very high, in some centers it's lower, but it's never 100%. So, we need a biochemical test to be able to help the clinical diagnosis. So this one application, and I think we are there. The company I founded to commercialize this technology, AMPRION, it's already offering the test to patients and physicians that want to be sure about the diagnosis of their patients.

Then the second application is to develop treatments. And that's because, as I was telling you before, if you are doing the study in humans and you enroll, let's say, people that you want to treat Parkinson's disease. You have a very good drug that, in animals, blocks alpha-synuclein aggregation, the accumulation of these abnormal proteins in the brain. You want to test in humans, you want to make sure that these people do have really alpha-synuclein pathology in the brain. And this is the way. Now for the first time, we have a way to tell this person has that, this person doesn't have, even though they may have similar clinical features.

That's very important. We are trying to develop a more quantitative essay that can be used also to measure the efficacy of the treatments. When you test a drug in human patients, it's something that is called clinical trials. So, when you do clinical trials, you want to know if your drug is doing something good, right? So, of course you look at the symptoms. But in a more objective manner, it will be good to know, is it reducing alpha-synuclein in the brain? And that's where we are trying to reach and AMPRION is collaborating with several — basically all — pharma companies that are in the field of Parkinson's disease, and dementia with Lewy bodies, and multiple systems atrophy and developing drugs. So, that's a very important application.

The third one, it's for early detection. In my opinion, this is probably the most important one because we know that alpha-synuclein accumulation starts

decades before the clinical disease appears. So, people live happily and normal for many years without having alpha-synuclein. So, what is happening is that the alpha-synuclein aggregates are growing and growing and growing in the brain until they accumulate in a large enough amount to produce the brain damage and the clinical disease. So, this can take you decades.

If you are able to detect this abnormal process way before the people have brain damage and clinical symptoms, you have the real possibility to treat people at that stage. The disease is weak at that stage because the amount of this aggregates is very small. So, much easier to get rid of them, compared to when the disease is already advanced, and it's already showing clinical symptoms in the brain. There's so much of this abnormal protein that it’s difficult to get rid of it. So, if we can detect very early on in the process, we can apply a good and safe treatment, then you can actually stop the progression completely. And the person will actually never develop. This is one of my dreams is to be able to eradicate diseases like Parkinson’s and Alzheimer's, dementia with Lewy bodies, etc. By combining an early diagnosis that can tell you, oh, this person is on the way to develop. It may take decades to get there, but let's treat it now so that we prevent the disease from ever happening. So that in the future, we'll be able to look back and say, oh, there was a time that millions and millions of people had Alzheimer's and Parkinson's. Now, nobody gets that anymore. Medicine has done this with other infectious diseases, for example. So, it's doable. And I think this is the long term, and this is where these assays will probably have the biggest impact.

And finally, it's also very important, and again, something that Michael J. Fox has been instrumental to promote, is going to a biological definition of the disease. So, define the disease not by the way it looks in the patient, but by the biology or what is wrong in the brain. Because now we have like a window inside the brain to be able to look whether people have this abnormal process in the brain. We can now say, okay, they have Parkinson's disease way before they have the disease, but also the disease, it's defined by the biology and not by clinical picture. And that's something that is ongoing. It's producing a major impact in the field because, for many years, we have been thinking about these diseases in a certain way. And now we are thinking more on what is really happening in the brain more than how the disease shows up.

And I think this would produce, again, another big paradigm change in the field. So, you see how the technology has multiple applications. Another thing that we are doing that is not out there yet, but hopefully it's coming soon.

This seed amplification, as I was telling you, mimics the essential process that happens during the disease by this spreading and amplification of alpha-synuclein aggregates. We are using the same assay now to screen for potential drugs that will alter this, that will prevent this seeding and aggregation of the

synuclein protein. So, we take the assay, we throw in chemicals, different compounds, and then we can identify those that are active and eventually develop them as drugs. That's another area we're working on. So, the impacts are multiple. I think we're just starting to see the impact of the seed amplification assay in the synuclein and Parkinson's field.

Marie: Certainly, and I think, Claudio, a lot happened relatively quickly. As you mentioned, the potential of the seed amplification assay is huge with key applications in diagnosis, this second category of research, clinical trials, and drug discovery and development, as well as early detection and contributing to this biological definition of disease. So, a lot is happening. And you mentioned this has happened over the course of multiple projects funded by MJFF. You're also working on another project to develop a method for assessing the effectiveness of alpha-synuclein immunotherapy. So Claudio, can you tell us more about this particular project on the therapeutic side?

Claudio: Yeah, as I was telling you, the technology can be used to look for efficiency of potential drugs. Let's say you give the drug — in this case, an antibody — you give it to a patient, and the antibody does what you want it to do, which is to block the aggregation of synuclein and the spreading of synuclein. So, then what the result should be is that the amount of synuclein pathology in the brain should decrease. So now we can use our assay to measure is it decreasing or is it not? This is something new that is still at the level of experimental phase where we need to make sure that the assay accurately measures the reduction of aggregated synuclein, and therefore, the response of treatment.

If it does, which we think it will, it can be used as what we call an endpoint of clinical trials. So, a way to measure whether the certain treatment is working or not. And this is actually something that has been done a little bit in the Alzheimer's field with different technology, more like imaging technology and has revolutionized the field because it has shown being able to discriminate those drugs that do work from the ones that don't really work. And this is very essential for the process of drug discovery, which is the final goal of Michael J. Fox and science in general, is to stop diseases and to help people to live good lives and hopefully not to be affected by these devastating diseases.

There will be many more projects, the several drugs that will be tested will probably not work so well, but at some point we will be able to find, as a field, the best possible candidates to produce the biggest benefit to patients. And as I was telling you before, if you're now able to start treatment way before the disease shows up, then you will actually prevent all the damage in the brain because by the time that people have clinical symptoms, there is a very substantial amount of our neurons — the neurons are the cells in the brain that make the brain to function — so, a substantial amount of neurons are lost already at the time that

the people develop the clinical symptoms. So, it's very important to start treatment early.

This is where we are, and it's a very exciting future. And I think again, the seed amplification assay has already contributed a lot, but I believe we're still at the early stages. And the contributions and the impact will just grow with time. Simultaneously, with developing the synuclein seed amplification assay, we are developing assays for many of the other proteins that are involved in other diseases, like Alzheimer's, or other forms of dementia, or amyotrophic lateral sclerosis, or Huntington's disease. So, we have a program that is coming out with similar seed amplification assays for each of these different proteins. And ultimately, where we will take it with time, is to be able to have a panel of assays — of seed amplification assays — for different proteins, like what is done now, for example, when you go to your annual check in the doctor, where you go, and say, they do a cholesterol test, and they can do a test for prostate cancer, or test for diabetes, or whatever.

So, the blood test, and they tell you, oh, you know what? Your cholesterol is really high. So, you are at risk of developing some cardiovascular diseases, so better to start some treatment. So, in the future, this is what I would like to envision. Like you do a tau test, a synuclein test, an amyloid beta, you do a TDP-43, you do all the main proteins. And they say, oh, watch out. We detect a little bit of the initiation of a process of accumulation of protein X. The best course of action is to do this. So, that's what I think is going to happen in the future or what I hope is going to happen in the future. So, we're trying to work in multiple angles on multiple diseases. And of course, there are many other groups in the world that are also working on this direction. The future is looking very bright.

Marie: Absolutely. And I suppose one question is, does the amplification sort of inherent in the process make it challenging to identify what the best candidates are, or perhaps what the best dose would be because you have that amplification in place?

Claudio: It's really what's happening in the brain. So, if the drug cannot prevent in the vitro seed amplification assay, it will probably not work also in the brain. Now granted, the seed amplification, it speeds up the whole process. Instead of taking decades for these protein aggregates to grow, we make it in a matter of days or hours in the test tube. So, there may be some compounds that may work if you try them for decades. But if you identify compounds that can do that in very difficult conditions, then that will probably work the best in the brain. That's my thinking. So, this is what we want to be able to pursue the best drug candidates.

Marie: Well, I appreciate you sharing more about this exciting ongoing research project. And of course, we mentioned in our introduction that you were recently selected

to receive the 2024 Robert A. Pritzker Prize for leadership in Parkinson's research. So, of course, congratulations.

Claudio: Thank you. It's a big honor.

Marie: Can you share with us what it meant for you to be selected for this?

Claudio: It is great, this recognition. I always tell my people, science can be very powerful. Sometimes it can change the world and produce a huge benefit to people and patients. But it's also sometimes frustrating and unrewarding because a lot of things you try don't work. So, you do it, and it doesn't work. And then you modify it, and it doesn't work. And you can go for several years that things don't work as you wanted them to work. So, it's very nice having this type of recognition to say, well, what you're doing is really having an impact.

And it's not just me. I tell the people in the group, I said, this is an award for all of us for what we have been doing over the last several years. And you can see, despite of the drawbacks that we encounter on a daily basis, the things that still work and produce a big impact can be recognized. And I think it's very nice of The Michael J. Fox Foundation to do that. And I'm very honored to receive this award.

Marie: Of course. And we know that the Robert A. Pritzker Prize for leadership in Parkinson's Research is awarded to scientists based on their research achievements. And we've talked about some of them today, but also for mentorship. So Claudio, can you comment on the importance of mentorship and perhaps teamwork in your position?

Claudio: Yeah, absolutely. I mean, this is very important because I always say to my people, you cannot be any better than the people that you have. And then you can serve to shape their minds and their way of doing science. And this is one of the things that we do very differently in my lab versus what others do. I try to coach people to be innovative, to think of things that like nothing is impossible. So, treatment of Parkinson’s. Yes, we will get there. We will eradicate the disease. Think in a very optimistic way, and work hard, but open your mind to bring new ideas, create new concepts, change the world through science.

That's what I try to communicate and try to mentor people. I think we need many more scientists with this type of mentality. This is not just a job. I mean, yes, we get paid. That's great. We have families. We have expenditures to be paid. But it really is not for the payment. And I do it because I want to discover things. I want to be able to do things that will impact the life of people. That's the reason I created AMPRION. It's not to make myself a millionaire. But the main reason is that I think as a scientist, being able to receive funds from taxpayers or

foundations, philanthropists like The Michael J. Fox Foundation, is a responsibility.

Scientists many times get happy with the final discovery and publishing our scientific article. That's good to be able to communicate to the rest of the community about your results. But ultimately, this doesn't help patients. So, what helps patients is to be able to move things towards the practical application. And that's why I created this company, and the company is doing pretty good now and offering already a service to patients. So, that's where we really produce the impact is when you think in a highly innovative way, when you work hard, when you are committed to do science to help people and contribute to make the world a better place.

Marie: Absolutely. And I really admire, Claudio, you bringing this mindset to the lab of nothing is impossible. I think so many people kind of put up these artificial barriers. And I think also thinking about those real world impacts is critically important as well. And I think right now is a really exciting time to be working in the field of Parkinson's disease research. So, when you look out at the landscape, Claudio, what do you see as some of the tools, or the resources, or just the advances in collaborations that are happening right now that are really accelerating or moving the field forward?

Claudio: Absolutely. I mean, the field has changed a lot in the last 15 years with this thinking I was telling you that this concept or understanding how these abnormal changes are happening in the brain. And now we can detect them, and soon we will be able to treat them. So, as you said, it's a wonderful time to be in this field. It was like the time there was a lot of scientists working on infectious diseases, and they discovered antibiotics, and they discovered vaccines. So this revolutionized and actually eradicated a lot of diseases from the planet. So, I think we are in a time that we can do that with these diseases that are so dramatic. These brain diseases that rob people of their qualities that make them different from animals. Like for example, in the case of Alzheimer's, the disease destroys your memories, and you forget all what you have done in your past. You cannot recognize your families and you cannot really put together abstract thinking.

So, I think we're in a very good time to be able to eliminate these diseases. And of course, there will be other diseases coming, and there is still other diseases to be treated. But brain diseases, I think these diseases are, in my view, they're more devastating than others like cardiovascular problems, or cancer, or things. Because as I was telling you, this destroys your special capabilities, they make you not be able to be who you were.

Marie: I definitely see that. And I think there are a lot of unanswered questions that remain. So, what do you see, Claudio, with some of the most interesting future directions, or lines of research, or areas of opportunity in Parkinson's disease research?

Claudio: I think what we need now to focus is on how we are we going to treat, understanding completely the biology of the disease. We have now a tool that gives us like a window inside the brain to be able to say who has a pathological process already going on in the brain and how advanced it is, etc. Now we can really go and try to do something about it. And, as I was telling you, the seed amplification assay offers a unique opportunity to be able to do this very early on with the goal of eradicating these diseases. I think it's a goal in reach. We just need to be able to do it. I mean, this is an effort, not just one laboratory, it's an effort with multiple different companies and all that are able to develop drugs and the scientific community as a whole.

Marie: Absolutely. And I think we've touched on it throughout our conversation today, the possibility of preventing Parkinson's disease altogether. And I think that is a tremendously exciting future to look forward to. But perhaps to summarize here at the end of our conversation today, Claudio, can you share how the work that you're doing today is really kind of bringing us closer to that goal of preventing Parkinson's or helping people who have Parkinson's now?

Claudio: The first thing that you need to do when you have a disease is to know what you have, right? There are multiple reasons that you can have certain conditions, like you can have a stroke, for example, and develop symptoms of Parkinson's disease. So, this is very different from the traditional Parkinson's disease. You need to know first, what do you have? What is producing the problems, in this case, in your brain?

So, that's really something that I think with the seed amplification assay, for the first time, we have the option to do. This will help us to define the disease, will help us to look for the right treatment. And as I said, in my opinion, the most important one is to be able to treat very early on so that you don't suffer from any of the consequences of this process that many times are irreversible. We at others are working on the strategies to help patients that already have the disease. Of course, if you stop the further progression of the disease, that could be a good outcome. But if you can combine this with the regenerative treatments like using, for example, stem cells or things like that, that could actually recover some of the function that has been lost.

I think ultimately, we have to attack the problem in many different steps because patients are in different stages. So, you need to offer to all people something to help. And I think having a way to measure, as I said, like a window inside the

brain to tell what is going on, how the brain is reacting to certain treatments and drugs, I think is very important. And that is going to make the future to advance much faster in the final goal of being able to treat this disease.

Marie: I definitely agree. And Claudio, we truly appreciate all the work that you are doing in the field to advance the research in Parkinson's disease. So, thank you so much for joining us on the show today to share your research and your insights.

Claudio: Thank you so much. It's my pleasure.

Marie: And listeners, it's been great to have you here with us as well. If you want to know how The Michael J. Fox Foundation can help your research, please visit michaeljfox.org/researchresources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. And 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*.