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

Today we are excited to welcome our guest, Dr. Honglei Chen. Listeners, Honglei is the MSU Research Foundation Professor of Epidemiology and Biostatistics at Michigan State University. Today we are going to talk more about his research on environmental causes of neurodegenerative diseases, and particularly the links between olfaction, environmental exposure, and Parkinson's disease. So, Honglei, welcome to our show today. How are you?

Honglei: I'm doing all right. Good morning, Marie. And thank you for the opportunity to talk about my research.

Marie: Well, we are so excited to learn more about you and the wonderful work that you're doing. But perhaps we could start by sharing a little bit of your background. So, Honglei, can you tell us more about yourself and how you found your way to your current position?

Honglei: Absolutely. I'm a neuro and aging epidemiologist, and I'm particularly interested in studying the environmental contributions to aging in general and neurodegeneration in particular. I received my training in preventive medicine back in China about 30 years ago. And then I came to the United States for my PhD study at the Tufts University in Boston. And I embarked on my exciting research journey on Parkinson's disease when I started my postdoc position at Dr. Alberto Ascherio's group back in December 2000 at Harvard School of Public Health. And in January of 2005, I joined the epidemiology branch of the National Institute of Environmental Health Sciences in North Carolina and started my own independent research program on aging and neurodegenerative diseases. About 11 years later in 2016, I moved to Michigan State University to continue my exciting research. So, that's about my academic background and career path.

Marie: Oh, wonderful. Well, Honglei, we're excited to talk more about your research. Perhaps you can provide some background on the links that have been found between olfactory function and health in older adults, both with and without neurodegenerative disease, to give our listeners some context.

Honglei: Actually, this is probably one of the most exciting research topics that I would love to find answers to. First, I don't know if you know this, olfactory impairment actually is very common, in older adults, but often neglected.

I will give you some numbers. In the United States, about a quarter of the older adults have poor olfaction or olfactory impairment. But of those who actually have this deficit, only about 30% of them know that they have it. So, the public health awareness of olfactory impairment is very low. So, this is the kind of background about the impairment itself. However, we learned olfactory impairment is important. In the past maybe 20 years, we have solid evidence that poor olfaction is one of the earliest and probably one of the most important symptoms — early symptoms — of Parkinson's disease and dementia. And for example, our older adults with poor olfaction are five times more likely to develop Parkinson's disease and three times more likely to develop dementia. And this is a very intriguing possibility that the study of olfaction in older adults may help us to identify people, individuals, older adults who are at a higher risk of neurodegeneration and probably even identify the individuals who actually is already on their way to the disease. We can call that progenital Parkinson's or progenital dementia. So, that's very important.

So, we can identify those people and try to recruit them to clinical trials and to identify the treatment that actually can slow down their progression of a phenotypical conversion to clinical diagnosis. So, this is a very exciting part for the clinical research or clinical implications. On the other hand, I think as an environmental epidemiologists, I'm equally excited about another possibility because I also see this as a great opportunity to advance our research to understand the environmental causes for neurodegeneration, theoretically or conceptually, by studying the factors — environmental factors — that can lead to poor olfaction or modify its conversion to Parkinson's or dementia. We may improve our understanding about the triggers and modifiers of neurodegeneration well before the disease can be clinically diagnosed.

So, that's our background. So, another thing I think is exciting to study on olfaction is that it may tell us more about the health of older adults beyond neurodegeneration. Also in the past 20 years, there is solid evidence that poor olfaction also predicts the risk of death in old adults, and probably research in the past maybe five, six years further revealed associations of poor olfaction with multiple adverse health outcomes in older adults, including pneumonia hospitalization, cardiovascular health, physical functional decline, and mental functional decline, and frailty. So, in summary, I think we just are beginning to understand the implications poor olfaction may have on the health of older adults. It is a very exciting research area and areas.

Marie: Absolutely. And what are your thoughts on whether poor olfaction might be a marker of accelerated aging?

Honglei: I talk about its relation to dementia and Parkinson's. So, it can be a marker — if we consider both conditions as abnormal or accelerated brain aging — we can consider olfaction as a marker of brain aging acceleration. And now we learned that it's actually also associated with physical functional decline, and frailty, and probably lung functions in pneumonia, and cardiovascular health. So, it might be educated across multiple physiological domains or systems. So, in that way, I'm very intrigued by the possibility that it is also a marker of age acceleration in general and probably, more specifically, as a marker of brain aging acceleration. This is a speculation that I'm very excited about. And I just want to do research to prove it or refute it.

Marie: Absolutely. And I'd love to talk about mechanisms. I think it can be difficult to pin these down. But do you have ideas about what are the mechanisms by which air pollutants or other environmental exposures may be leading to poor olfaction and then ultimately maybe to Parkinson's disease?

Honglei: So, this is another billion dollar question that we struggle to seek answers for. Maybe just some background first. There’s accumulating evidence suggesting associations of air pollutants to neural degeneration, including Parkinson's disease and dementia, but the data are not consistent. And when we come to air pollutants and olfaction, we almost have no data for that effect. But on the other hand, I feel like this line of research is super exciting because the connections among air pollutants, olfaction, and neural degeneration are very biologically plausible. And the research on this topic may uniquely inform the process of the decades of neural degeneration.

So, I can make the long story short. One may speculate that the air pollutants enter our nose and potentially can gain access to our body, which may further gain access to the brain via the olfactory nerve. We know the olfactory nerve is the first primary nerve, and it's very short between our nose and our brain. It's a short connection. And also this connection actually can bypass the protection of the blood-brain barrier. So, this sort of gives a short way for our brain to interact with our environment.

So, in susceptible individuals, maybe genetically, maybe otherwise. So, these environmental exposures may trigger or perpetuate a cascade of adverse events. This might not happen to everybody, but in certain individuals, this may be happening. And this can lead to a cascade of events, including, for example, inflammation and later neural inflammation and abnormal alpha synuclein aggregations, and eventually leading to, for example, Parkinson's disease over

several years. Again, admittedly, this is mainly speculation and waiting for solid evidence from both epidemiological studies and animal experimental studies.

Marie: Oh, absolutely. And I think when people think about kind of what is in air, there are a lot of components and potentially a lot of pollutants. So, are there particular pollutants that you have your eye on that might be relevant?

Honglei: People are very interested in what we call ambient air pollutants. For example, the particulate matter PM2.5, nitrogen dioxide. And these are the common ambient air pollutants people are interested in. But do not forget, there could be other airborne pollutants like pesticides, like metal particles. Metal particles may stick to the particulate matter and get into our nose. So, these are the common sort of suspects when we talk about airborne pollutants. And again, organic solvents.

Marie: Absolutely. And I know Honglei earlier this year, you published a paper looking at air pollutants and risk of Parkinson's disease from the Sister Study. So, for context, can you tell us a little bit, more broadly, about this Sister Study?

Honglei: Oh, absolutely. And thank you for the opportunity to talk about the Sister Studies. I can talk about many, many of the strengths of the study. But briefly, the Sister Study is a longitudinal cohort established by investigators from the National Institute of Environmental Health Sciences, the NIEHS for short.

And it is an invaluable resource to understand or study all the environmental factors that may contribute to human health or may adversely affect human health. So, briefly, about twenty years ago, the cohort recruited about 50,000 women, middle-aged to older-aged women, from all over the United States, including all the 50 states and Puerto Rico. And this cohort is unique in many ways. The study participants are very geographically diverse, the study collected extensive environmental data. And also, they collect a lot of health specimens, including blood, where we can extract DNAs and save our serum samples and our plasma samples. And they collect urine, toenail, and home dust samples. Think about this from like 50,000 participants. That's a lot.

And the cohort has also meticulously followed their participants with tri-annual surveys. So, every three years, they conducted a comprehensive survey about their study participants, about their health status, about their exposure to environmental pollutants. And 20, 25 years later, they are conducting this sixth follow-up survey right now. So, during the follow-up, as far as Parkinson’s disease is concerned, we ask about the diagnosis. And we also ask about some of the relevant details of the diagnosis. And we ask about the presence or absence of selected key motor and non-motor symptoms of Parkinson's disease. Think about this, decades of environmental data that the Sister Study collected,

and also that longitudinal and decades of symptomatic data that's relevant to Parkinson's disease development. I can see this as a great opportunity to study Parkinson's disease.

Marie: Definitely, and Honglei, that background was tremendously helpful. I'd love to get into the details of your particular study. So, can you explain the gap in knowledge that this recently published study was designed to address?

Honglei: Sure. We are interested in understanding whether air pollutants are related to Parkinson's disease. As I mentioned early on, there are some emerging data, accumulating evidence, suggesting there is a connection, but the data are not entirely consistent.

The Sister Study has many advantages. Although it's women only, it's very geographically diverse. So, the air pollutant exposure basically represents the United States. So, in our specific study, we estimate our participants' exposure to the major air pollutants, as mentioned early on, PM2.5 and nitrogen dioxide. Based on the residential history they provided, not only at baseline, but also over the follow up. And we recorded when they moved and where they moved.

So, in our data analysis, we found that exposures to higher levels of nitrogen dioxide was associated with a higher risk of Parkinson's disease. And this association is fairly robust in multiple analyses. We are trying to look at are there any alternative explanations that can easily explain the association, but the association appeared to be fairly robust. However, for the other major air pollutant, PM2.5, we did not observe linear association with a possible exception that women from our Midwest regions of the US, we found an association between PM2.5 and Parkinson's disease. I will say that our study adds to the literature that air pollutants may contribute to Parkinson's, but this is still a topic that needs to be further investigated.

Marie: Absolutely. And I'm curious about these findings specifically related to nitrogen dioxide. You mentioned increased exposures linked then to risk for Parkinson's disease. Where are, geographically speaking, the places where NO2 concentration is particularly high? Is this just generally in urban areas? Or where do you see this?

Honglei: If I remember correctly about the result, I think we have some analysis by geographic regions. I think it's probably present in all geographic regions we examined, but I need to double check my findings to be accurate.

Marie: Sure, and then what do you make of this finding about specifically women located in the Midwest and the links to these sort of particle size-related pollutants?

Honglei: I think there is some evidence suggesting the Midwest regions of the US may have a higher incidence of Parkinson's, compared to the other regions. I do not know if air pollution has any connection to that, but one interesting speculation we have is that the PM2.5 is not a single particle. It actually has many, many different chemicals attached to it. It might be possible that the chemicals from the Midwest region could be related to Parkinson's disease. I think this is a topic for further investigation.

Marie: Oh, very interesting. And Honglei, can you comment on just the impacts of these findings in this particular study and where you go from here?

Honglei: I think it just adds to the evidence about environmental contributions to Parkinson's, and I would like to see more research about environment and Parkinson's disease, which I think has lagged behind compared to genetic and Parkinson's disease research, where we made significant advances during the past 20 years. Compared to that, the environmental research has largely lagged behind.

Marie: Well, Honglei, I think this makes sense, and I'd really like to talk about next another area of your research as well now. You are continuing to do research in the area of pesticide exposure, specifically, and neurodegeneration, looking at farmers or people who work in the agricultural industry. And we know that the evidence linking pesticide exposure to a higher risk for Parkinson's disease is strong from historical studies, but there really haven't been many of these population-based studies to assess pesticide exposure. So, Honglei, can you explain why these kinds of studies are particularly difficult to do and why they add value?

Honglei: First, I just want to mention that over the many years, we have learned through many, many studies that occupational pesticide use is associated with the risk of Parkinson's disease. And importantly, multiple studies have linked specific pesticides, not many, several, such as paraquat and rotenone, to the risk of Parkinson's disease. However, as you indicated, there are many unanswered questions, in part due to the difficulties of conducting this line of research.

I can give a few examples to lay out the difficulties and the importance. Over the history, there are hundreds of pesticides — different chemicals that have been on the market — many of them are neurotoxic. Some have been banned decades ago, and others are still on the market. So, we are looking at a very diverse group of chemicals that have been used in the agricultural business. And the questions will be, how can we best study each of them in relation to Parkinson's disease?

And this is particularly important because even banned pesticides can still be related to the risk of Parkinson's disease, given the nature of the disease, which

takes decades to develop. And what are the best ways to study each of them? And given their natural history, at what stage of the disease development should we focus our research on? In the early stage development or in the later disease development?

And another important question is how to best assess the pesticide exposures? And how do we do that well over a very prolonged period of time? We are talking about probably decades. And these are just a few unanswered questions, but also highlight the difficulties in conducting this line of research.

Marie: Certainly. And I understand that for this research that you're doing, you're actually leveraging a data set from the Agricultural Health Study. So, can you tell us a little bit more about this remarkable data set and why it was so useful for this study?

Honglei: As you mentioned, Marie, the Agricultural Health Study is a great resource to understand environment, particularly farming exposures and health. And this is a large cohort that was established by the NIH Intramural Investigators from NIHS, NCI, and as well as with expertise from EPA. And just very briefly, the cohort enrolled over 50,000 farmers and 30,000 of their spouses about 30 years ago in 1993 to 1997. And ever since then, they have longitudinally followed their participants over about three decades. And the study is still going strong right now.

And the cohort is unique in many ways, and it makes them extremely valuable. For example, over time, the cohort have collected data about the uses of about 100 specific pesticide chemicals. So, empowering the research on specific pesticides, which might not be possible at all in any other study setting. And further, they collected the exposure data, the pesticide use data, over the farmer's prime working years and are making this total assessment very important occupationally across the farmer's working years. And in addition to that, the farmers are asked to report both their occupational uses, as well as exposures. We call that a high pesticide exposure event. For example, from major spills or accidents. And by the way, these are fairly common among farmers, maybe not so common in the general public, but it's common among the farmers.

And finally, I just want to mention that unlike the general public, farmers are able to report their pesticide uses more accurately than the general public. Another important feature of the cohort relevant to particularly this research, I just want to mention that since the beginning of the cohort, they began to ask about the Parkinson's disease diagnosis now over 30 years across many surveys. And also over time, we added questions about the presence or absence of major motor and non-motor symptoms of the study participants. So, think about this, a cohort

with extensive decades of data about occupational use and accidental exposures to pesticides along with decades of data related to Parkinson's disease development. I think when we combine this, we will be very powerful to study Parkinson's disease in its entirety.

Marie: Oh, certainly. And I think you mentioned that this study has been going on for nearly three decades, and it's still ongoing, but can you comment on what some of the results have been so far?

Honglei: As far as Parkinson's disease is concerned, I would like to give two examples. First in 2011, Dr. Carlie Tanner and Freya Kamel reported that paraquat and rotenone use in the cohort was associated with about 2.5-fold higher risk of Parkinson's disease. And notably, this is one of the major human epidemiological data that link these two chemicals to PD risk.

And by now, the paper has been cited over 1,600 times. So, it's a very important finding, historical finding about pesticides and Parkinson's disease, per se. And the other example I just want to mention a little bit is our recent findings on Pesticide and two major prodromal symptoms of Parkinson's disease. The loss of the sense of smell and dream enacting behaviors.

We were able to do these kinds of studies because starting from the follow-up form, we added questions asking participants to report their sense of smell and dream enacting behaviors along with the motor symptoms and several other non-motor symptoms. I just want to use these two as an example, and I believe that this line of research to study prodromal Parkinson's disease in the cohort will be incredibly important because it can help us to identify environmental factors, in this case, more agricultural-related, pesticides in particular, that may be the triggers of Parkinson's disease and probably help identify factors that may modify the progression from prodromal Parkinson's to Parkinson's clinical stage. I think both are important from a disease prevention perspective.

Marie: Absolutely. And I think when people who are maybe outside of the field think about these two different symptoms that you mentioned, prodromal symptoms, the sense of smell/the olfaction, and also the dream enactment behavior, they may seem sort of like two very different things to be studying. Why did you choose these specific things to look at?

Honglei: I think in 2003, Braak proposed a hypothesis about Parkinson's pathological staging and specifically mentioned Parkinson's disease may actually start from the nose and the gut. So, it's entirely revolutionized our thinking about Parkinson's disease pathogenesis. Although the hypothesis itself is still controversial, that led us to think about that Parkinson's disease may start outside the substantia nigra and probably even outside the brain itself.

So, that coupled with many other studies later, links smell loss to Parkinson's disease, and people with smell loss were four times more likely to develop Parkinson's disease. And these make it a very important prodromal symptom for Parkinson's disease.

And the other very exciting line of research about prodromal Parkinson's disease is about the REM sleep behavior disorder. And studies from Dr. Ron Postuma's group and many others has firmly established that the clinically diagnosed REM sleep behavior disorder is a prodromal Parkinson's disease and related alpha synuclein pathologies.

With the findings that, among those with idiopathic clinically-confirmed RBD, up to 80% may convert to clinical Parkinson's, MSA, or other synucleinopathy over maybe 15 years. So, that makes it actually a pathogenesis stage prior to the Parkinson's clinical stage. So, these two are very important because we have been searching for Parkinson's prodromal phenotype so we can better study the disease from its entire natural history.

And we can use these phenotypes as intermediate phenotypes. So, looking back in time, we can study what are the environmental factors that may trigger this phenotype. And looking forward in time, we will be able to study what are the factors that can modify the progression from this phenotype to clinical Parkinson's. We may not be able to entirely prevent Parkinson's from its clinical onset, but we potentially can delay the onset. The earlier we understand about the disease's early stages of development, the more possible it is we will be able to do something about it.

Marie: I think that's really interesting, Honglei. And I think for the kinds of studies you do, another element that's unique and exciting is that you have a very diverse research team, very multidisciplinary. And I know you're working with epidemiologists, biostatisticians, exposure assessment experts, clinical scientists, neurotoxicologists, there's this whole range of experts coming together to collaborate on this research. So Honglei, can you talk about how this impacts the work that you do?

Honglei: Yeah, Marie, this is a key to medical research and discoveries. So, I just want to use the agricultural health study as an example. And all the studies I've been conducting is just like this one.

So, first, we build our own research program based on the decades of efforts from the NIH intramural investigators who have the expertise of occupational health and exposure assessment as you mentioned, and we are still capitalizing on their expertise now on many, many things related to this cohort. And also we

leverage the expertise from movement disorder specialist clinical experts to find the best ways to assess motor and non-motor symptoms and to adjudicate the diagnosis of Parkinson's disease.

This is not easy because this is not a clinical study, you can spend time with the patient and do the standard neurodiagnostic assessment. And this will be large population-based studies, you'll have to consider both clinical validity as well as field feasibility. And I benefit a lot from my collaborations with movement disorder specialists. And also in our research, we work very closely on a daily basis with our biostatisticians, it's not a single one actually, there are multiple of them, and postdocs and students to analyze the very complicated data from this cohort.

It's not an easy data set to work with, the Agricultural Health Study. And moving forward, I would love to seek expertise in PD biomarkers, in using the blood and other biospecimens to study PD. And I'm actively looking for collaborations from that perspective. And as you can see that, you know, this is really a collective effort from many, many team members.

Marie: Definitely. Well, listeners, you heard him, if you are working in the area of PD blood biomarkers, definitely reach out. And I think when you look at some of these findings, there's some fascinating results coming out of the work that you're doing, looking at pesticide exposure and neurodegeneration. So, what do you see as the impacts of some of these findings?

Honglei: I will make this answer fairly short, because we are still working very hard towards this goal. Hopefully, in the future, we will be able to identify ways to help our farmers to protect their health, as well as to ensure their livelihood. Both are critically important for them. And we are making progress, yes, but I will see that we still have a very long way to go.

Marie: Absolutely. I think it is a long road to having those impacts sometimes from the laboratory. And I think with this research that you're doing, not only have there been important findings along the way, but there have been some surprises as well, some of which we might have touched on earlier in our conversation. But Honglei, can you talk about what have been maybe some of the biggest surprises or things that you didn't really originally expect would come out of the research that you've been doing over the years?

Honglei: I think this is really important. And Marie, if I can, I will rework a little bit. I will not call them a surprise, but will call them new exciting lines for potential research.

Marie: I like your optimism.

Honglei: One of the most exciting parts of being a scientist is there are always surprises in findings. A lot of times, they actually can lead to new exciting research areas that

you have never imagined before. So, as you mentioned, we talked about both a little bit in our early discussion, but I just want to reorganize and give some historical accounts on both points. I will give two examples.

And the first example was like 15 years ago when I started my own research program at the NIHS and just did what I had been doing fairly comfortably. But in 2008, the Honolulu Asia Aging Study reported that men with poor olfaction were four times more likely to develop Parkinson's disease than men with good affection, the findings we already mentioned before. And after that, there are many other studies that confirm the associations.

And these, together with the Braak hypothesis, which we also mentioned early on — that PD may actually start from the nose and the gut. And these things come together lead me to think about, okay, am I actually on the right way to do my research to study Parkinson's disease? Because, think about Parkinson's disease, that the disease diagnosis is primarily after 65 probably in 70-75. And when we talk about the disease risk development, we're not talking about age 75, age 74, or even age 60.

We're talking about decades before that, we're talking about probably from age 30, 20, or even prenatal exposures. So, that led me to think about how we can best study Parkinson's from a holistic way to look into the natural history of the disease and accounting for the decades of the disease development. And this led me to the research program to study Parkinson's environmental risk factors' contributions to the prodromal neurodegeneration. And I'm very excited that we have two studies ongoing along this line of research. As I mentioned early on that this is not an easy research area. There are still a lot of obstacles, and we are going to work one by one, and I expect there are going to be a lot of surprises coming out. And there are also a lot of new things we potentially research into.

And the other good example is much, much more recent in 2019. So, you know my interest to study olfaction and neurodegeneration and I'll give just a little bit more background. In addition to that, we also know that poor olfaction strongly predicts the risk of death among older adults. And this is not trivial because poor olfaction is very common among older adults, affecting about 25% of them. But it is very poorly recognized. And only about 20-30% of those with a poor sense of smell actually knows they have it. So, the public awareness of this common sensory deficit is fairly low in both the general public and also in the medical community.

And honestly speaking, I think this is still the case even after COVID. So, with this prior knowledge and background, my kind of thought was the link between poor olfaction and the health of older adults may be simply through neurodegeneration, Parkinson's and dementia. And I found out I was wrong in

2019, and I was quite surprised. We found that PD and dementia together only explains about 22% of olfaction and the death of older adults, this suggests that poor olfaction has a lot more to tell us about the health of older adults. And we need to know about that. So, since then, I began an entirely new line of research to try to understand what poor olfaction actually means for the health of older adults, including but beyond neurodegeneration. And I would like to report it's fairly a promising area of research.

We have some recent findings about connections to pneumonia, which should not be a surprise (even though we are not talking about COVID in this case), heart disease, to depression, to cognitive decline, to physical functional decline, and to frailty. And all of these are critical to the health and quality of life of our older adults populations. And to be honest, I feel like there is a gold mine for us to dig deeper.

Marie: Certainly. And I think as the number of older adults in our country and around the world just continues to increase, I think this is going to be a hugely important area of research going forward. And I know we just touched on just some of the large-scale studies and datasets, Honglei, that you've been able to leverage for your research. And I'm curious, are there other examples of different tools or resources, whether they come from The Michael J. Fox Foundation or others, or just collaborations or advances that you are seeing in the field of neuroscience or other fields that you think really have the potential or are currently moving the field of Parkinson's research forward?

Honglei: Yes. And this is also a very important topic because we have seen in the past 25 years the success of large-scale genetic consortia in identifying the underpinnings of the genetics of Parkinson's disease. I was fortunate to be part of this large team led by Dr. Andy Singleton. As you mentioned that, compared to the genetics, for the environmental research, we are far lagged behind. And we are yet to see similar effort and success in PD environmental research, largely because of feasibility reasons. It's going to be much more difficult probably by magnitude to study environmental causes of Parkinson's using the kind of approaches that are exemplified by the genetic consortia. But that does not mean we shouldn't do that.

I think the difficulties may lie in multiple perspectives conceptually and logistically, as well as financially. But again, I feel like we can start from a small effort to do this and gradually increase our effort of collaborative research to search for the environmental causes of Parkinson's. I can give a few examples. You mentioned about the studies we have been doing, and there are many others who have been working in the same way that we can identify the environmental cohorts that have been in the field with decades of environmental data collection. And we may assess the feasibility to add some sort of standardized PD clinical research

component into it. So, adapt or fine-tune those cohorts for PD research and at a later stage, we can explore the possibility of pooling the data from those cohorts to answer questions that we otherwise cannot answer.

The other will be the great examples from The Michael J. Fox Foundation, the clinical cohort they put together, the PPMI, Parkinson's Progression Markers Initiative, and the newly established (and still I think they're recruiting participants) the Prodromal PPMI. And for this kind of cohort that was mainly established for clinical research of Parkinson's, we may think about opportunities to add an environmental component, standardized environmental component.

Again, we may start small and gradually increase our effort, as I expect there are going to be a lot of lessons to learn and a lot of surprises along the way. But gradually, little by little, we may be able to set up some sort of collective effort across multiple groups, across multiple studies, trying to understand how environment may affect our risk of Parkinson's disease. So I think, still a long way to go, but I'm hopeful.

Marie: Certainly. And I love that you mentioned these different efforts in the broader field of Parkinson's research and how just getting information on environmental exposure could be incorporated into some of these efforts. And in particular, I'm glad you mentioned the genetics efforts. I think there's these sort of two areas that are being investigated separately, the genetics and also the environmental exposure. But I think there's maybe another layer where they intersect — this area of genetic susceptibility to some of these environmental factors, where it is really intersecting with your work. So Honglei, can you comment on this particular area of research?

Honglei: Yeah, Marie. You are absolutely correct that we should not study them in parallel. We should study the interface because we know pretty much for sure that most of the Parkinson's disease in late life actually were the result of decades of gene-environment interactions. But honestly speaking, we are still about where we were 10-20 years ago in terms of understanding how the environment and genetics interact to affect the risk of Parkinson's disease. And hopefully by leveraging recent developments in PD genetics, which we learned a huge amount through the consortium effort led by Dr. Andy Singleton and other Parkinson's geneticists. And we can leverage this knowledge and also the evolving data from Parkinson's epigenetics and the ways to measure our exposome.

And hopefully by leveraging all these knowledge and technologies, techniques, developments, advances, we may be able to better understand gene-environment interactions and the interface between genetic and

environment in moderating the risk of Parkinson's disease in the general population and particularly in occupational populations.

Marie: Certainly. And I think, Honglei, we've talked about some promising research areas that are relevant for your work specifically. But if you look at the broader field, what do you see right now as some of the biggest unanswered questions or perhaps areas of opportunity in Parkinson's disease research?

Honglei: Yeah, you just mentioned the big one, which is genetics and environment interactions. So, that is a great example. And I'm not going to talk any more about that. But from the disease prevention perspective, I think there might be a lower hanging fruit — quote-unquote lower hanging fruit — that probably we will be able to work on in the next decade or so.

And that will be the study of prodromal Parkinson's and trying to identify modifiable risk factors that can stop or delay the disease onset. If we cannot prevent Parkinson's from occurring during our lifetime, can we delay it to a stage that substantially shortens the clinical phase of the disease and make sure that people can enjoy their life (most of their life) in late adulthood? And also, I think it's a very good time to do this line of research because what we have discussed a few minutes ago about the natural history and how the Parkinson's develops in the prodromal stage, the knowledge we gained about prodromal Parkinson's development in the two decades was enormous. And hopefully that can better guide us to do environmental research of Parkinson's disease.

Marie: Well, Honglei, I think these are all really important questions and area of research in the field of Parkinson's disease. And I know we talked about a lot of different topics today. I'd love to end our conversation by talking about how your work specifically is bringing us closer to some of the big picture goals the field has of finding a cure for Parkinson's and contributing to improved therapies for people who have Parkinson's today.

Honglei: In my eyes, there are always two big goals in doing research. The first is to, if somebody’s got the disease, we’ve got to find ways to cure the disease, to maintain the quality of life of the patients. And the second is disease prevention. In this case, as an environmental epidemiologist, I feel like we can make contributions primarily to this. Again, I would like to emphasize the study of prodromal Parkinson's disease.

There are going to be a lot of difficulties and obstacles along the way. But I'm hopeful that by focusing on understanding how the disease develops in the prodromal stage and to study the environmental contributions at different stages of the disease development, we may be able to identify or actually have some kind of suspects about the triggers of Parkinson's disease or pathogenesis. And

probably more importantly, by focusing on the later prodromal stage development before Parkinson's clinical diagnosis, probably five years, probably 10 years, people already have the prodromal phenotype. By focusing on studying them in their progression to the clinical Parkinson's, we may be able to identify disease modifiers.

I think this will be incredibly important in identifying the factors that actually can either stop (that will be the best scenario one can get), or to slow down the disease progression to the clinical Parkinson's and always much easier to say than do it. But I'm hopeful, and we are working very hard on that.

Marie: Well, Honglei, I appreciate all of the work that you're doing in this area, and I agree that all of the progress that's being made has really left me hopeful as well. And it's been wonderful to chat with you on the show. So, thank you so much for sharing your insights and your time with us today.

Honglei: Thank you, Marie, for the great questions you asked.

Marie: It was a pleasure to chat with you 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*.