Introduction to Environmental Risk and Parkinsonu2019s

What my bigger interest is how do different known environmental causes and toxicants that increase your risk for Parkinson's disease, how they act on different cells and do some of their effects, despite having different primary mechanisms or being different chemicals, do maybe some effects on our cells converge?

And if so, those would be really interesting pathways to look at and target as therapeutic or potentially even in prevention. Hey everybody, we'll get right back to the podcast, but I do have some very, very exciting news I wanna share with you.

And that is that my new book, Brain Defenders, that we've been talking about on the Podcast is now available for purchase. It is going to be published in August of 2026, But it is available now.

If you wanna learn more about Brain defenders, go to their website. That is oddly enough, braindefenders.com. This is really empowering information as it relates to charting your own brain's destiny.

Now let's get right back to the podcast. Hey everybody, Dr. David Perlmutter here on The Empowering Neurologist. We've got quite a program today. I'm joined by Dr Sarah Marzi.

She is one of the world's leading scientists redefining how we think about neurodegenerative conditions, things like Alzheimer's and Parkinson's, through the lens of what we call epigenetics and gene regulation.

the epigenetic control over the expression of our DNA. Dr. Margie is a senior lecturer in neuroscience at King's College in London and a principal investigator within the UK Dementia Research Institute where she leads a lab that's focused on how genetic risk and environmental exposures converge at the epic genetic level to ultimately shape brain disease.

She completed her doctoral training in neuroscience and has since built an internationally recognized research program that integrates human postmortem brain tissue evaluation, advanced epigenomic profiling, and cutting edge disease models.

Her work has been especially influential in uncovering how microglia, the brain's immune cells, translate genetic risk into disease activity. And this is in fact the fundamental subject of my new book, Brain Defenders.

Dr. Marzi has shown how risk genes, like what we've talked about on the program, the APOE risk genetic polymorphisms, reshape microglial behavior in Alzheimer's disease and how things like environmental toxins such as pesticides can reprogram gene regulation in Parkinson's Disease as well.

What makes her work so incredibly powerful and certainly so relevant to all of us is that it moves us upstream.

Podcast Intro and Guest Background

It helps explain why risk is expressed, not just in the parts of the brain where the disease appears, but how disease risk expressed ultimately throughout the body.

Today we'll explore how epigenetic regulation links genes, environment, metabolism and immune signaling and what this means for prevention, resilience and for future therapies.

I'm very excited to get this podcast underway. Let's go. Dr. Sarah Marzi, it is a great honor to be able to spend time with you this morning or afternoon for you.

How are you doing? I am great and thanks so much for inviting me to your podcast David. Well, and I'll probably say this many times throughout our time together today, you're doing amazing, amazing work and you know, we're going to just jump right in.

I think clearly the focus is the neurologic neurodegenerative conditions that we are so familiar with Alzheimer's and Parkinson's, but you are doing the real deep in the weeds kind of work.

And I'd like to start off by having you unpack this notion of, people talk about Alzheimer related genes and We'll talk about APOE. Certainly, that's an area that many of our listeners are familiar with.

But, you know, there are well over 100 when we look at these genome-wide association studies. With that said, many people, I think, think about genes in terms of what they code for, which is reasonable, but you're upstream of that.

You are looking at what initially turns that gene on, then allows it to do either good things or bad things. So what drew you to this notion of genetic control, this sort of epigenetic control that you are so well known for?

Well, it's basically the causes of these neurodegenerative diseases and actually of many chronic complex diseases that we face today are really complicated and it is rarely ever one gene that's the smoking gun for these diseases.

That happens in the minority of cases. Occasionally people will get a disease from just one mutation and one But the vast majority of people that get, say, Alzheimer's disease are caused by a combination of many, many hundreds potentially of thousands of little genetic risk factors that probably interact with the environments they're exposed to and the lifestyle they lead and what they accumulate over their life course.

You mentioned environment and it will certainly, I think that the relationship is well defined in Parkinson's, we'll get there. But let me let you continue, interrupted.

Yeah, so what I try to understand is basically how these many of hundreds or thousands of little risk factors, what they actually do to the cells in our brain, and what then predisposes them to disease.

And they often act in concert, they don't do 100 separate things, They often target maybe a handful of different processes in these cells, where either they lose some protective functions that they normally fulfill, Or maybe they start to do some things that are bad for our brain.

And so we use something called epigenetics, which is the study of how genes are turned on and off basically. So the biochemical switches that regulate gene expression to understand what genes.

Are being regulated by these genetic variants that associated with disease. and what pathways come downstream of that, but also there are a number of different regulators that can orchestrate changes in many, many different genes all at once, and these are so-called transcription factors.

Often we look for these so that we can understand what is really the switch that is driving a whole program in a cell that's putting it into a vulnerable state.

So again, people say, well, my dad had it, and my mother had, are they really thinking in terms of straightforward Mendelian inheritance patterns? And I think that what you're saying here is that there's a lot involved in the actual expression of these genetic predisposition genes.

And that the regulatory factors of the histones and other regulatory factor, there is a vast array of this. Perhaps it's fair to say that they must conspire.

Many of them must inspire to ultimately manifest then the disease process. So it is not as if like in Huntington's disease for example that we talk about a genetic mutation lead and it can be inherited leads to this manifestation.

How does this open the door then? this idea of this multiplicity of inroads, how does it open the door to maybe first clinicians to have in roads for possible therapeutic intervention if there are so many factors that are involved?

Yeah, I think you touch upon kind of the crux of it. It's really complicated because all these factors sort of come together. And maybe you need to meet a certain threshold in a combination of environmental lifestyle and genetic factors that put you there and that then initiate the disease.

And it can seem overwhelming, but I think my hope and what we're seeing is that maybe these many, many different factors act on a limited number of cellular processes.

Genes, Epigenetics, and Disease Risk

And if we understand what these processes are, and if understand the upstream regulators, if you will, of these process, then we can target those and reverse or prevent some of those changes that come from the genetic risk and the environmental risk.

So let's just talk about what some of these processes might be. I know let certainly the augmentation of inflammatory cytokines is one. Increased reactive oxygen species.

Let's list a few of what these process are that get the brain in trouble. Well, there's a lot of different things. One of the features that neurodegenerative diseases have in common is the aggregation of types of proteins, so proteins that build clumps that they shouldn't build and they build them either in the neurons that then eventually die or in space between the neurones.

It can be different types and different diseases, but virtually all neuro-degeneralative disease have some of these protein clump. And so the mechanisms that really clear up these clumps and should prevent them from happening, so these are things like autophagy or the lysosomal pathway, or even the function of immune cells in your brain, like the microglia, that should basically eat up and digest these proteins.

And if any of these mechanisms don't work as efficiently as they should, then you're at a higher risk for developing a neurodegenerative disease. No, I should say traditionally, research has focused on the neuron.

Exactly. Even as it relates to these genetic predispositions that have been well elucidated. And I think that what your work makes clear is, you know, the neurons interesting, but it seems to be at there at the mercy of adequate function of the microglial cells.

And maybe you can expand on that in terms of where these genes are represented or active, where they're being activated in comparison to neuron versus micro glial cell.

Yeah, absolutely. And I think for me, this is one of the most exciting but also one the more reproducible insights into Alzheimer's disease specifically that we've had in the last 10 to 15 years.

That's basically when you look at the genetics of Alzheimer disease, so not the one gene that causes it, but these many of hundreds or thousands of little risk factors that They quite overwhelmingly, they fall into regions of the genome that are active and that regulating expression of genes only in microglia and not in any of other brain cell types, so not neurons for example.

And so that really suggests to us that they must have an effect in the micro glia. Therefore, the genetic risk that determines whether one person is more likely to get Alzheimer's disease than another that really influences how that person's microglia function.

So if you have certain genetic variants in your micro glia and a combination of those that can either predispose you or protect you from Alzheimer's disease.

Well, you had mentioned a moment ago that one of the defects common across certain neurodegenerative

conditions is this idea of misfolded proteins and the ability that our brains have via the microglia to phagocytitis or eat up these damaged proteins.

So that gene regulation of the Microglia then through this pathway might be something very important. Exactly. And this is one of the pathways that really might be influenced by the genetic variants that predispose you to Alzheimer's disease.

We think that it's probably more than one pathway. There's a number of different functions that are influenced, some of which are loss of function. So for example, this eating up or phagocytosing of proteins is something that we see is impaired actually in people with Alzheimer disease, And then as you mentioned earlier these microglia also tend to produce a lot of pro-inflammatory cytokines causing inflammation in your brain and over time that's something that is really bad for the neurons as well so if they have these heavily pro inflammatory signaling micro glia around them that again makes them vulnerable and can cause them to degenerate potentially longer term aswell.

So you have both a loss of things that are good and protective in these microglia, but also you gain certain functions like this inflammation that's bad for your brain.

You know, you mentioned again the aggregation of proteins, beta amyloid being certainly what is talked about most, well, phosphorylated tau as well but at least in terms of therapeutics for Alzheimer's disease.

But this is downstream of the regulatory pathways that you're talking about, isn't it? So what you are exploring is well upstream of ability of brain to appropriately get rid of things like beta amyloid.

That's a really good question. So I mean, I think the answer to what is the first event in Alzheimer's disease is still not settled definitively. A lot of people think it is The aggregation of beta amyloid.

And then certainly after the aggregation or around the time of aggregating, you get cellular effects as well. So where cells around, the aggregate start to misbehave or start act in ways that aren't normal, like the inflammation in the microglia.

Which one precedes which other? That's a good question. It could be that just by chance and through aging, you will start to produce more amyloid beta and that eventually just, by a chance, it will aggregate in some way.

And if you have more protective microglia, those aggregates will be consumed or broken down and will not have as detrimental an effect. Whereas if your microglia don't work as well, maybe you're more likely to get Alzheimer's.

So I wouldn't say we certainly know that the micro glia come upstream of the beta amyloid, but certainly the are genetically the main reason why some people get the disease and others don't get it.

So it's either how they lead to the aggregation, and they do seem to play a role in that as well, or how do they deal with the aggravation? Well, I definitely want to unpack more what's going on with microglia both in terms of your the APOE work that you've done as well as one study that I'd like to talk about that.

I sent you that, I'm certain you're aware of, but let me just let, me probe a little deeper into this beta amyloid story because Dr. Rudolf Tanzi at Harvard has talked about amyloid representing what we call an antimicrobial peptide that the amyl is produced in response to perhaps microbial infection in the brain chlamydia herpes simplex type one and that In many ways, the original formation of beta amyloid is a way of protecting the brain so that the idea of offloading all this beta-amyloids might be a little bit misguided.

So what have you thought about, whether you've studied it or not, but what do you think about in terms of the amylid representing a response in the Yeah, I mean, that could well be and I think the this association between infections, maybe even peripheral infections but certainly central nervous system infections.

So infections that get into your neurons and that gets into brain and herpes simplex is one of the most well known

ones. And the risk for Alzheimer's disease, I think, is a really important field of study.

And I still have a lot to learn from epidemiology there. So my guess would be infections play a big role in increasing our risk of Alzheimer disease. And partly that could be through triggering mechanisms like the amyloid beta as a viral defense mechanism, but partly I also think they activate and train our microglia and thereby make them more likely in the future to become more pro-inflammatory, causing this new inflammation that is detrimental eventually.

Hey everybody, we're gonna get right back to this podcast in just a moment, but I wanted to tell you something really exciting about 40 Hertz light exposure.

Microglia, Amyloid, and Alzheimeru2019s Mechanisms

We have actually done a podcast on this. we know that when you're exposed to 40 hertz stimulation, this is linked to what we call gamma, increasing gamma activity in the brain.

In other words, balance in brain, which is really a fundamental for brain health and brain functionality. in fact, in early clinical research, using what's called 40-hertz stimulation Researchers have reported signals that are consistent with a slower decline in cognitive function in some participants.

So the company that we are talking about, who is in fact sponsoring our podcast today, is Optosudix. Their EVY light is designed to bring 40 Hertz light and sound into a simple at-home routine that you can use while you're reading or watching television.

I use it actually while I'm working on the computer. Optostudix makes it easier to try, so you get 90 days of risk-free trial with support from their care advocate, somebody who's going to work with you.

And if it's not creating value, then you're able to return it to Optosutix for a full refund. And how can you lose? They're going to pay the shipping both ways.

Quick note, Evie is a wellness device, and it's not intended to diagnose, treat, or cure or prevent any disease. This episode, as I mentioned, is sponsored by the Optostix company.

So if you'd like to try it, go to Optosutics.com and use the code PearlMutter26 and get $200 off your order. I think you're going to find this device to be really quite amazing.

Let's get right back to our podcast. Well, you mentioned something I think that's really very important, and that is that infections can activate this whole pathway.

And those infections don't necessarily need to even be in the brain. I mean, that the inflammatory cytokines can be produced anywhere in body, make their way to the brains.

We know that in Alzheimer's and as we age, the blood-brain barrier is certainly less competent, less effective. and that these inflammatory cytokines having their origin anywhere can help to polarize the microglia away from being supportive to being in a different phenotype that is less able to digest away things like beta amyloid or other things that it must do.

That's what we think and we don't quite know whether it's the cytokines themselves that get through the blood-brain barrier or whether through cells that compose the brain barrier there's a second hand signaling that then eventually gets to the brains and communicates with the microglia.

Yeah, I'm just thinking about our HSV-1 herpes simplex virus type 1 conversation. That original research was from your country, from England. Ruth, exactly.

Yeah. And that was not widely accepted. Not for a long time, no. And so unfortunate, you know, I mean, people, tend to be down on what they're not up on.

So let's go back then to the notion of APOE. I means, many people are getting their genome sequence, and they know their APoE 22, 23, 33, 34, whatever their combination may be.

and they're either feeling good about it or they are very concerned about. And I think, you know, in Western cultures, what is it, 25, 28% of people carry at least one APOE4 allele.

So it's certainly the most well-recognized genetic risk factor. You decided to do a deep dive and tell our audience, if you will, how you constructed the rodent research because it is so fascinating.

That's how I originally learned about your work. Yeah. Basically, ApoE is the single strongest common risk factor for Alzheimer's disease genetically.

It's very different from all the other genetic variants in how big and how large the effect actually is. If you have two copies of the AkoE4, the risk allele, that can increase your risk for alzheimer's by up to 12-fold.

That's a huge increase in risk. But APOE, so it's been studied for many years, but it is a very complex gene and protein. It has different functions in different cells.

And we thought because we've known from our and other research that the microglia are so critical in Alzheimer's disease, we really wanted to dissect what does it do in micro glia and just in my micro-glial and not APoE communicating from one cell to another.

What effect does that have in Now microglia. With the diseases we study, our one big challenge is we often can't study them in humans because you can just go into the brain and study some brain cells in a living person's brain.

We can and we do look at brains from people that pass away with diseases and can learn a lot about the disease there. The problem is the time you collect those brains is a very late stage of disease, so it's very difficult to disentangle what might be a cause of the disease here, what processes have been going on over time, and what may be the outcome.

That's a challenging thing. We do have nice models for cells that have developed in the last 15 years or so where we can basically reprogram cells into any cell type that we're interested in by a technique called induced pluripotent stem cells.

The idea is you take a skin cell, for example, or skin-cell biopsy, you reproground these cells to become stem-cells, and then you can turn them into cell types that you're interest in studying, including microglial-like cells, However, the problem is, when you put these microglia then in a dish, they don't really look and behave like normal micro glia do.

That's because micro Glia are essentially extremely sensing and communicative cells. They need the other cells around them to function and look normally like micro-glial.

If they're on their own in the dish how good is that model and how much are you really representing microGLIA? So we teamed up actually with two researchers, Tharte Strueper and Renzo Mancuso from VIB in Belgium, who had developed an amazing model where you can take these human pluripotent stem cell derived microglia and you put them into a brain of a mouse.

And to me, it still kind of sounds a bit like science fiction, but it actually works amazingly well. So first, you deplete the masses own microglia with an enzyme, and then you inject the human micro glia in a few different places.

And they really spread out throughout the mouse brain. When you image them or when you look at. their function in gene expression, they look pretty much like normal human microglia.

They integrate well, and they interact with the mouse cells. So this, for us, was an amazing model where we could then study the effect of this gene, ApoE, in the micro glia, so we took basically genetically engineered micro-glial

that only differed in their AcoE genotype, So AkoE2, and we injected it into a mouse brain.

Now, because we were particularly interested in Alzheimer's disease and the role of APOE in an Alzheimer disease, we used an alzheimer's-disease model to do this.

This is a mice that has some genetic mutations that cause it to develop these amyloid beta aggregates that we talked about that are one of the hallmarks of Alzheimer' disease.

Now, there isn't a perfect model of Alzheimer's disease in the mouse, and this one is an amyloid model, so it only has these amyloid aggregates. In humans, you would also get hyperphosphorylated tau tangles in neurons.

This model doesn't have it, but at least it lets us study how these different ApoE microglia interact with the amlyloids, how well they clear it and really look at their gene expression and epigenetic programs to understand what might be making these APOE4 microglia harmful, but then we also had the APoE2 and APoe2 is actually a strong protective factor.

So people with APoi2, one copy or even two copies, very rarely get Alzheimer's disease, meaning there must be something that's really protecting them from that disease.

Yeah, so we we took these three like types of microglia and put it into this Alzheimer's mouse model, and actually found a lot of striking differences in their transcriptional and in the epigenetic programs that should suggest in fact that The FOE4 microglia, as we've been talking about before, they are pro-inflammatory.

They release a lot of proinflammatories cytokines. they're less good at clearing up proteins and other debris, so this ability to phagocytose is impaired.

A third feature that we found was they seem to be less at cellular motility and cellular proliferation. So normally when microglia are called into action to clear up something, they need to be motiled, and they to proliferate, to get to the site of injury or aggregation to, clear out the proteins.

And based on our gene expression results, we really see that genes that promote these kinds of processes are down regulated in the E4 micro glia and actually conversely up-regulated in E2 micro-glial.

So you said about To answer the question, why are APOE-4 people more at risk for Alzheimer's in comparison to APL-3 and certainly in compared to the APLE-2?

You took a mouse model. And what did you do to the mouse's microglial cells prior to infusing the manipulated micro glia? You get rid of them, exactly.

You use an enzyme that basically wipes out the mouses own micro-glia. And then on the slightly more technical side, normally if you inject human cells into a mouse, the mice's immune system wouldn't tolerate this.

So this is a mousemodel that also has an slightly altered immune system that makes it accept rather than reject these human microglia. So you create what are going to be micro glial cells that express APOE4, APE3, and was there not a null set as well?

there was a knockout. Exactly. Then you put these microglial cells into the brain of a Alzheimer's mouse, right? Correct. And the results in the APOE4 correlate with what we observe in humans in terms of higher levels of beta amyloid, I'm being simplistic here, in the APOE4 versus AP03 and much certainly positive results on the ApoE2, which confirms exactly what we see epidemiologically as it relates to humans who carry APOE 2, 3, or 4. And what about inflammatory markers?

What did that reveal? Yeah, so we both in terms of expression of already known pro-inflammatory cytokines, we see increased expression in the APOE4 and reduced expression it in E2, and then we also tend to use some fancy statistical models where we look not at individual genes, but at whole groups of genes that co-vary together or that

build these biological networks.

APOE Microglia Study and Vitamin D Signaling

And again, we identify one network that is up-regulated in E4, down- regulated in and very much contains genes that are pro-inflammatory and so suggesting that E4 mounts this stronger pro inflammatory immune response whereas E2 might be more anti- inflammatory with a reduced immune As I was reading your study, I, you know, was I trying to get to the point where, as one would expect, OK, so what can I tell people is important here?

And, aside from the fact that other aspects of our lifestyle tend to literally inflame these pathways, You studied vitamin D receptor functionality, and I think there may be some traction, some translatable traction.

Agreed. With respect to that. So let's unpack that a little bit. Yeah, so that's for me the most exciting result of the study because we started to ask at that point, we see all these big gene expression changes.

Are there certain drivers, triggers, these transcription factors that I mentioned earlier in the podcast that are driving these different gene-expression programs, either protective programs in E2 or harmful programs and the E4?

And one of the strongest results that we got for these enrichments is that in the E2, in a protective microglia, there seems to be enhanced signaling via binding to the DNA of vitamin D receptor.

Now vitamin d receptor is really, really interesting. It's a transcription factor, which means it's protein that binds DNA and thereby regulates the expression of a big group, whole arsenal of different genes.

It's activated, as the name suggests, by vitamin D, which in humans we produce through sun exposure or we can also supplement in our diet. It is doubly interesting because it's well known that vitamin deficiency, so if you don't have enough vitamin, D is a powerful risk factor for Alzheimer's disease.

In fact, even once you already have Alzheimer disease, vitamin-D deficiency can make your course of disease faster and your progression worse. Clearly, vitamin D epidemiologically is really important in Alzheimer's disease, so we were really excited to find this really strong molecular link that suggests vitamin B binding and vitamin C receptor activity is driving genetic gene expression programs that might be protecting vitamin EpoE2 carriers from Alzheimer disease.

Now, if we look at the function, which kind of genes are regulated by vitamin D receptor, these tend to have effects in bones and bone density, but in immune cells like the microglia, it really clearly has an effect on immune functioning, and in particular, has anti-inflammatory effects.

So most of the genes that are downstream and that have been regulated by vitamin D receptor will drive an anti-inflammatory phenotype in microglia or other immune cells.

So that really gives us a piece of a puzzle where anti inflammatory signaling is something that occurs in APOE2 micro glia and we think is probably protective.

And at least some of it, maybe a lot of, it might be driven by the enhanced binding of vitamin D receptor. So that, as you said, gives us something really tangible, something that we might targeting both through vitamin-D supplementation, for which the trials in the past have not been entirely conclusive, but also by understanding what is required for the signalling of Vitamin D receptors signaling.

So, yes, it needs to bind vitamin D, so you need to have the vitamin d available. To me, that means, in winter, you should probably be taking some vitamin-D supplements.

I certainly do. But the question is, is that enough or are there other biological steps required? Because sometimes it's not as simple as giving one molecule and that will solve everything.

For example, vitamin D receptor heterodimerises with the retinoid X receptor before it binds the DNA, or we're investigating that functionally now actually, are there other factors that affect how well it can bind the dna in presence of having enough vitamin d already?

Hey everyone, we're going to get right back to this podcast, but first I wanted to share some information about olive oil. You know that I love olive.

So here's a good tip. The most delicious olive that you can get is olive, oil that comes fresh from the farm. This one, the olive is at its peak flavor and all the nutritional, uh, good things that we talk about the polyphenols and et cetera are really at their peak.

When you buy your olive oil at the supermarket, you are getting an inferior product because they have been sitting on the shelf for months and they basically grow stale.

And that's why I've been getting my olive direct from small award-winning family farms, really around the world, thanks to a fellow named TJ Robinson.

I have done Instagram live with him in the past. He's known as the olive-oil hunter. He is able to source farm-fresh oils that are vibrant, they're healthful, grassy, incredibly delicious, and you can use them on whatever you want.

On salads, fish, vegetables, meat, even like I do, on scrambled eggs. So if you wanna taste the difference that freshness makes, TJ is gonna send you a full-size bottle, which normally will cost you $39. He's gonna sent it to you for free if them just a dollar that will cover shipping.

And that's how he then is able to introduce all of you to this fresh pressed olive oil club, a club that we are members of. So there's no commitment, just send him a $1. He'll send you a full bottle of olive.

You just want to go to getfresh389.com. That's get fresh 389 dot com and he'll make it happen for you. Let's get right back to our podcast. Well, we do know that there's down regulation of the NLRP3 inflammasome with activation of VDR.

And so one wonders a couple of things. First of all, people are getting their genome sequence and might find that they have a variance of vitamin D receptor functionality based on their looking at their a genome.

The other thing is one wonders if through the mechanism of reducing inflammation by vitamin D binding it to its receptor, if we shouldn't be, and you mentioned how the interventional trials with vitamin B were not that meaningful to be kind, but one wonder is if there couldn't a convergence of other issues here in terms of inflammation that because of our metabolic disarray these days based on the foods that we're eating, that sort of antagonizes or offsets any benefit of the whole vitamin D pathway anyway.

So, you know, and I think it gets back, I had a thought when you were talking about APOE4 and beta amyloid, vis-a-vis our discussion that amlyloids may have been produced as a response to infectious agent that perhaps because carrying the APoE for allele which persists in our modern world, there must be some advantage to it.

Or why would 28% of humans still carry the APAV4 allele? If it was across the board detrimental, then why did it? Why did it lose its positivity over time?

And one wonders if it's in juxtaposition to how our metabolic health has become so disrupted in our modern world. It's just a thought I think probably should leave it there.

I have to tell you one last thing, and then we'll move on. As you're describing this work, this recent research, what's going through my mind are the slides I made based upon your research from a presentation I gave a few weeks ago.

And I mentioned this to you earlier before we went on the recording. I have this animation of the injection of these

microglial cells into the brain of a cartoon character.

So it's less distasteful, a character rodent. As I think about that, I'm visual, so that's how I understand your Let's move on to some really exciting work that you've done with Paraquat in the context of Parkinson's disease.

First, what would motivate you to want to look at ParaQuat, in that context in Parkinson? So actually, it's been mostly rotanone so far. Starting some work with parrot put as well.

So with Parkinson's, very generally, It's a much less heritable disease than say Alzheimer's or then some other common complex chronic diseases that we face.

You can study this by looking at twins. So you take identical twins and non-identical twins, and you look at how often does a disease co-occur together in the identical versus the non identical ones.

And then you can put a number on it and basically quantify how much of it is genetic. And when you do that for Parkinson's, it's only about 20 to 30% genetics, meaning likely the environment that you're exposed to plays a much bigger role.

And in fact, from epidemiological work, we have a lot of good evidence for this for very specific exposures that have happened. I know, when looking through your podcast, you've had Ray Dorsey as a guest several times.

So three times he That's because he puts out such new and exciting work all the time. Exactly. And yeah, so I completely agree. In the last 10 to 20 years, the genetics has been a real big focus, both of research and of pharmaceutical companies, because genetic targets are more tractable or more likely to survive clinical trials.

But I think for Parkinson's, that's not been good thing because I And so really, my other than understanding genetic risk, as I've just talked about in Alzheimer's disease, we also want to understand environmental risk and we want understand what do these chronic systemic, often low grade exposures over many years and sometimes even decades, what did they actually do to the relevant cells that make them vulnerable to neurodegenerative disease?

And here again, these epigenetic mechanisms, this chemical switches of gene regulation are potentially a really important mechanism, because they can retain a memory of this exposure.

And they could basically be changed gradually over time, but cumulatively so that eventually harmful gene expression programs are there. I want to apologize for the interruption.

But what you just said is so profound and so very, very important. because it's very difficult to conceptualize that these events are slow and acting over decades.

We don't see a smoking gun. It's not as if, well, you know, if people wear a helmet or a bike accident, they're gonna have, it it, quick. You see, I was wearing helmet and I survived.

In this case, and yet you're diving deep into the weeds on this and you've made some incredible discoveries. Yes. Basically, for a starting point, we focused on this pesticide called Rotenone.

Rotinone is not that commonly used. It's in fact bound as a pesticid in the US and the European Union. it's still used in some places in world. There is strong epidemiological evidence that it increases Parkinson's risk quite substantially in humans.

But what's also for us important with Rotenone is that we have good animal models for this. For this, we collaborated with Tim Greenemeier and Emily Rocha at the University of Pittsburgh who have pretty amazing Rotinone models.

This is a rat model where they inject rats with low doses of Rotonone over two to three weeks. In our case, it was a three-week exposure. Then these rats basically developed Parkinsonism pretty comprehensively.

The same type of neurons that die in the people with Parkinson's die, in this rat model, they get cellular dysfunctions that mimic what we see in Parkinson.

They get the same protein aggregates that people of Parkinson get, and they develop the motor symptoms as well over time. And it's an amazing model because it is an entirely environmental model.

So most animal models that we work in with in neurodegeneration, they use human genes that are put into a mouse or they need some form of genetic manipulation, whereas this is purely environmental.

And so we teamed up with Tim and Emily to look at epigenetics and gene regulation in this rotonome model of Parkinson's disease.

Rotenone, Parkinsonu2019s, and Immune Activation

And we also wanted to understand why it so specifically affects one type of neuron and causes this type neuron to die. So in Parkinson, a type a neuron called dopaminergic neuron dies.

It's called this because it primarily uses a neurotransmitter called dopamine. And these dopaminergic neurons that die in Parkinson's sit in a very specific area, right in the centre of our brain, in our midbrain in an area called substantia nigra.

So this is the neurons die. You do see effects on functioning across the brain and different regions are impaired. For our rat study, we looked specifically at two different region, the substantio nigro, which is where the neuron die, But also the motor cortex here, you wouldn't get neurons dying, but you would see potentially signaling dysfunctions, things that affect your motor system, which is the primary symptom of Parkinson's, is impairment in your Motor Control.

And so the striking thing was, yes, we see a number of different common things between the two brain regions, and a lot of those affect mitochondrial functioning.

So mitochondria are kind of like the energy machines in our cells that give our cell's energy. And rotenone, this pesticide specifically targets and impairs mitochondrion, so we would expect to see that basically in any cell that we will look at that's exposed to rotinone.

But what was more striking is that there were actually profound differences between the substantia nigra and the motor cortex. And uniquely in the substantial nigri, we actually see quite a striking upregulation of immune related pathways, probably coming from the microglia, including an up regulation of an immune response called So we see an upregulation of the complement cascade and potentially the C1q I want to get into that.

I wanted to talk about your your finding of this C 1q activation. We'll get back to the epigenetics in just a minute. But We know that when synapses are labeled with C1q, that microglia identify them as being what they want to digest.

This is an early life mechanism labeling synapse for the appropriate synaptic pruning of the brain. But in this case, we see that C1q labels these synapses, and then the microglia that are activated digest these away.

So we get back to both this being a, if you will, synaptopathy and also the fundamental role of micro glia. Exactly, absolutely. So that's exactly right.

It's been shown in a number of different neurodegenerative diseases that microglia can and do. Phagocytos eat up synapses, and that is probably not a good thing later in life.

That labeling happens through C1Q, so there's some really exciting work on that from Beth Stevens and Soyeon Hong that have shown this as the signalling and phagocytozing pathway in synapse.

So we see the C1q upregulated in bulk brain tissue, where that exactly comes from, maybe some of it from the

microglia themselves, from cells that are being targeted, but it is extremely striking.

So the difference is huge. It's not just a small change in the expression of this. And we did in fact also do some imaging, so looking in the tissue itself, and we in effect see that in a rotenone condition you have activated phagocytosing microglia that are characterized by the upregulation of a marker called CD68.

So this means these are reactive phago cytosine micro-glias. You're exactly right. They're probably phage cytosing different things. It might be synapses and it might also be at the early stages of protein aggregation happening, because we know that does happen in the rotenone model as well.

Hey, everybody, we're going to get right back to the podcast, but I have a very important message for you. You know, why do we exercise? Why do you pay attention to how much sleep we get and the quality of sleep?

We get. Why are we looking at our diets? Because ultimately, We are sending information to our genome. We're affecting how our genes express themselves.

I like to know about my genome. That's why I'm a real fan of the 3×4 genetics test. Why? I say you can learn about your genetic predisposition. You know, in my world, as it relates to the brain, there are some genes that in fact are associated with increased risk for neurodegeneration.

A lot of people know their APOE status, for example. But I want to be super clear that this is not a genetic determinant. Maybe it's a genetic predisposition, but what you're seeing here happening, these are our lifestyle choices that actually change our gene expression.

You should know about your genome, you should get the 3×4 genetic test. We'll talk about how to do that in just a moment, there is a health program that they offer you as well.

When you get your genomes sequence with 3 by 4 genetics, it is not just getting this information, they are going to tell you what to with that information.

So I think that's really very important. So head on over to 3x4genetics.com. They have a special offer for you and all of you podcast watchers. Let's get right back to the program.

Well, so I'm going to summarize then. We know that rotanone is a mitochondrial toxin and like paraquat, like MPTP and to a certain degree glyphosate. But what the supposition was, was that for whatever reason, with a myocondrial toxins on board, that the dopaminergic neurons in the substantia nigra were hypersensitive because they were perhaps because you were so active and that Men might demand because they're involved in more motor activity.

I'm going off on a limb here. And therefore, their substantial nigra's are more active. That's why men are two to one more likely in Parkinson's. We, I don't know the answer to that yet, but we should maybe kick that one around.

But What you're telling us is it's more than a mitochondrial issue, because yes, the mitochondria in the motor cortex of the rodent were involved, as were the mitochondria and the substantia nigra, but the epigenetic changes took place only in this substantian nigora.

Yeah, the immune related changes and actually we do see other interesting changes in the motor cortex as well that suggests that the functioning of synaptic proteins is a little bit awry, going in all sorts of directions and that in some ways mimics what we know functionally about the disease where it's more a functional impairment, a signaling impairment that's happening in motor Whereas the death of neurons, that's something that really more exclusively happens in the substantia nigra, and it may relate to this immune upregulation of the microglia.

I just had chills because a thought came to mind. I've been puzzling for a long time why the male to female predominance in Parkinson's, right? And why is female to male predominant in Alzheimer's?

Maybe we'll discuss that. But one of the reasons that females, one discussion has centered on the C1Q pathway, on labeling of synapses that happens suddenly with the decline of estradiol in the peri-mental pausal time.

One wonders if those neurons are less protected in men for lack of adequate or a given level of estradiola and therefore they are more susceptible. Don't know, but I'm gonna have to think about that.

I don't either. But, you know, this is Lisa Moscone's work with respect to the, when is the timing of estradiol best? So I think we'll have to leave it for another time.

But let's take a step back then. And I did mention erroneously, paraquat. Paraquat works in a, you've not done the epigenetic work or maybe you have, but paraquats is also a still a widely used, at least in America, herbicide that is a mitochondrial toxin.

So what are the implications in terms of your work as it relates to paraqua? So paraquads affect different pathways as well. We think actually the primary mechanism of action is more through generation of reactive oxygen species and downstream DNA damage.

And we are planning some paraqua experiments as Well, because actually, rather than just rotonome itself, what my bigger interest is, how do different known environmental causes and toxicants that increase your risk for Parkinson's disease, how do they act on different cells in the brain?

Do some of their effects, despite having different primary mechanisms or being different chemicals, do maybe some effects on our cells converge? If so, those would be really interesting pathways to look at and target as therapeutic or potentially even in prevention.

I think it was probably you who gave the terminology that these toxins write themselves into our epigenome. Is that your language? I often use the terminology that they leave an epigenetic memory in our cells.

They insinuate. And I think then, you know, that explains why it's a long-term slow, slow sizzle that happens that ultimately has clinical manifestations.

I want to go to your work on histone patterning changes in histones in the Alzheimer's brain. And again, for the viewers, histomes are gene… Correct me if I'm wrong.

How was I explaining it? Gene expression modulators. They determine which genes are turned on and off. Your work has identified an array of gene expression changes, histone changes seen in part of the renal entorhinal cortex, that is characteristic of Alzheimer's, correct?

Roughly right. So histones are very common proteins that everyone has in their cell nucleus, and it's what the DNA is wrapped up around in the nucleus of our cells.

And there are two main benefits of this. One is that our genome and our total DNA in each cell is actually quite long. It's a a huge number of molecules and wrapping them around these histones makes it much more compact and makes them fit in the nucleus.

But also, these his stones can be chemically modified, so addition of different chemical groups to the histone. These chemical modifications basically alter how tightly wrapped the DNA is around the his And simply you can think about very tightly compacted wrapped DNA is just inaccessible and therefore is quieted down and can't be transcribed because the mechanisms that produce gene expression and downstream proteins need access to the DNA.

So if you completely wrap up the DNA very tightly, they don't have access to it, and it can't be transcribed. And vice versa, if the dna is not as tightly wrapped, then it's accessible and can be conscribed and so the histone modifications basically change how tightly the da is wrapped.

That's important because whichever genes are turned on and or turned off, has physiologic impact. Absolutely. And might manifest as increased inflammation, pave the way for Alzheimer's, or might not.

So it's really the gene regulation involving the histone switches that is the area of your interest that you've studied in Alzheimer. Exactly. And so we did a big study of this now, seven, eight years ago, 2028, 2018, sorry, it's 2026 now.

Just about. We found that basically this histone acetylation, which was the one modification that we looked at, and it is interesting because it was dynamic and It responds to environment, but also it's changed by genetic risk factors, and we showed that there are really widespread changes in this histone modification in the brains of people with Alzheimer's and specifically in brain region that is first and most severely affected by the disease.

That was quite novel and critical and we were surprised how strong and how widespread these changes were. We could also link them to some of the known genetic risk factors, but back then we did the study on just bulk brain tissue, meaning you mix up all the cells in a sample and you generate a profile.

But really, as would hopefully shine through from our discussions here, it's really critical what's happening in different cells. And our research and other research has shown microglia are really important, but it is also really hard to understand what are different cell doing?

Why are neurons degenerating? What are the micro glia doing, maybe what some of the other cells that are around doing as well? And so we're basically we've been doing two things to understand better what's happening in different cell types.

Histone Changes, Biomarkers, and Lifestyle

One is just using clever computational methods, where we take reference profiles, so, we know what a standard microglia looks like epigenetically, We know, what is standard neuron looks, like and so vice versa different, cell, types and we use that So going back to our bulk brain samples to then basically estimate how much of each cell type was at each bulk sample based on what a standard cell looks like.

And so when we do that, and we published this earlier this year as well, what we see is that actually in Alzheimer's disease, Two cell types have really widespread changes epigenetically, and one is the microglia, as we would have expected based on the genetics and based a lot of our other work.

But what surprised us a little bit is actually that even more strikingly, oligodendrocytes show really vast changes in the epigenetics. And oligodendrocytes are basically the insulating cells, so they are quite fatty cells that wrap themselves around the axons, which are the signaling tracts of the neurons and thereby insulate them.

And they act very much like a cable insulation would act on an electrical cable. It's interesting the oligodendrocytes are getting attention now. I mean, the past few years it's been the microglia, right?

Suddenly everyone's interested in micro glia. But now oligos, they wrap themselves around the neuron to insulate it. That's pretty much all they do. Well, no, there's got to be more to the story.

We pigeonhole ourselves. I agree. And I think with, so while the genetics, I would say very clearly points to the microblia and not the oligodendrocytes, when you look at these Alzheimer's, late stage Alzheimer brains, there are a lot of, the most changes are happening in the oligodender sites.

But we know that oliga dendrocytes can functionally alter in Alzheimer disease as well. So loss of myelination loss, of this insulation is something that is actually seen in alzheimer's disease.

I think what's important is that with these complex diseases, probably the causes are more systemic and complex and it would be surprising if it was just a single cell type and a simple process that was being affected.

I thinks it's a lot of things acting in concert and my hunch is likely if we want to treat them, we're going to have to basically administer a cocktail of the things that treat different aspects, functional and causal aspects of disease.

So what you're saying is that to be able to modulate the activity of those histones, you would need a cocktail that specifically targets those ones that you and colleagues agree might be the ones most involved in a detrimental way and try to shut them down versus activate ones, that are more salubrious.

Yeah, so my hope is that, again, we are not there yet, but that maybe we could identify, for example, transcription factor networks that are dysregulated in the oligodendrocytes as well, and that then in turn would give us potentially meaningful targets.

that drive big regulatory programs that we think are functionally connected so that are causing these cellular malfunctions that a causing oligodendrocytes to demyelinate the axons which is probably something that's really bad for the neurons and something you want to prevent.

So there has been work over the years before you made it very clear that there's an array of histones that are involved to consider the use of Histone deacetylase inhibitors like Calproate to kind of globally affect histone in general, but that's not very precise based on what you're telling us.

I agree, so that's always surprised me in a way. That seems like quite a sledgehammer approach where you alter histone acetylation or histones modifications across the whole genome.

I don't know, it seems that could be risky because you're affecting many, many different genes on the hole. They act quite ubiquitously and indiscriminately across whole genomes, whereas I think it's more about specific locations in the genome, specific programs that drive very specific functions and processes in these cells.

My hypothesis is basically that they are regulated by a handful of relevant transcription factors and that's probably where we have the best chances of going in pharmacologically and mechanistically in targeting and preventing disease.

So you're looking at whole brain homogenates or at least homogeneates from particular areas of the brain, not exactly a diagnostic tool for a patient in your office.

So that said, could you foresee in five years or 10 years the idea that using machine learning for evaluation of exosomes could perhaps be correlated with what you have already discovered, discovered in terms of being able to fingerprint these illnesses.

As you were saying, basically in blood samples, or so yeah, blood, perhaps CSF, exosomes, Yeah, I think there will be many biomarkers, even peripherally, that we'll identify.

So we're getting better and better protein biomakers already. Protein biomakers of aging, protein bio markers of disease. Exosomes is another one. It all depends technically on the stability, how well you can collect, isolate them.

There's been some really exciting novel work looking at cell-free DNA methylation. This is a another epigenetic mark. and basically as neurons die in your brain some of their DNA gets released into the intercell, so basically just into, the brain and a lot of it is cleared up but not all of, it and some, of makes its way into.

The bloodstream and can be picked up there and because epigenetics is very cell type specific if you pick up those specific epi genetic marks that are only found in neurons you can say yes this piece of DNA came from a neuron so that's in a quite an exciting prospect if we And I certainly think in that context, that machine learning, as you mentioned, is going to be really critical to identify from limited patchy information because you're not going get a whole genome of cell-free DNA or a lot of exosomes in the blood.

But from these limited sources, by having really good references and very good machine-learning algorithms, I think we'll get better and better to actually be able to detect these diseases earlier.

in peripheral samples like the cerebrospinal fluid or blood. As opposed to something more global like neurofilament light. Yeah, so that's a good marker for neurons dying in general, but it doesn't tell you what disease is causing the dying of the neurons because it's found in samples of anyone with any neurodegenerative disease.

There's a lot of discussion these days about our lifestyle choices being able to influence our epigenetics as it relates to therefore controlling gene expression.

Where would a guy like me go in a discussion based on Dr. Sarah Marzi's work? How would lifestyle factors be considered as we look at this vast array of histones that are active or inactive as it relates to a disease like Alzheimer's.

In other words, what is our ability to modify gene expression through this pathway based upon the choices we make each day? I don't think that's quantifiable yet and I think we've done enough research to really pinpoint this intervention will do exactly this.

There are increasing studies in that context. Epidemiologically, we of course know some of the lifestyle factors that might relate to Alzheimer's disease risk, so certainly exercise and activity is something that is quite protective.

And I know people are now increasingly studying the effects of exercise on your body, more often on blood and muscle than on the brain. But you know, we're slowly getting there.

And that's something that you might be able to study in a mouse model, for example. I think it'll take a long time to really mechanistically and in a fine grained way dissect what exact epigenetics is being altered by which lifestyle factors, how does it exactly relate to disease.

But I'm very hopeful and I am excited about this kind of research and what we can learn about it, both in terms of I don't think you necessarily need the epigenetic evidence to say a lifestyle factor is protective or harmful.

I think that we can get from the epidemiology, but once we understand the mechanisms and effects that A can give us better chances of finding pharmacological interventions and B can make us look for, do different factors that act on disease risk converge on a limited number of pathways?

What are these pathways And how, in terms of lifestyle factors and pharmacological intervention, can we target those pathways? So I'm going to say that your research is what we call foundational.

I mean, it really is so important for everything that we are thinking about as it relates to neurodegenerative disease. That said, what's next for you?

What's next? So I'm, as I mentioned before, really excited about the vitamin D finding. And in fact, we're doing quite a lot of work, again, with bot dystrophy and renzoma kuzu, but also just in our lab in dissecting that more functionally.

So do based on the gene expression of results, do the microglia exhibit those different functions, prove that a bit more in a controlled system, but also try and manipulate the vitamin D receptor genetically and pharmacologically to see ideally if we can, for example, rescue APOE4 micro glia to make them more protective, like the APoE2 microglia as well.

That's something we're really excited about. We continue to work in the Parkinson's space and we've been doing work on human post-mortem Parkinson's samples as well.

So what I would be really interested in seeing is do known environmental causes of Parkinson like rotenone, do they cause patterns that overlap what we see in just sporadic Parkinson cases where we wouldn't know what they've been exposed to?

like different environmental and lifestyle factors over a whole life course. For normal people, this information is very,

very difficult to collect or to quantify in any way.

So if we can find things that converge between controlled models, like the rotenone route, or we could do this in cell systems as well, and also what we see in the brains of people with Parkinson's disease, that would give us more confidence that what see is really disease relevant.

Wow. I know that Ray Dorsey, you mentioned him earlier, I mean, he's really focused also on trichloroethylene. Yes. And it's a way that it made its way into the groundwater.

It explains higher rates. Here we have in the States, for Lejeune, very high rates, so I'm sure that's going to be studied. I want to tell you that I thought quite a bit about our Time Together Day prior to spending time together.

What am I going to talk to you about? I wrote a list of questions which I didn't get to unfortunately, but I think I really again want our viewers to know that it's your kind of work that allows us to really gain an understanding ultimately of the translational part, i.e.

Future Directions and Closing Remarks

what do we tell people in the clinic? And it starts with this, as I mentioned earlier, foundational work that you're doing and very, very appreciative.

And I know you are as busy as can be and to take this time off to spend it with me and all of our viewers, I just want you to know I'm very grateful. Oh, well, thank you so much for having me.

I mean, it's been a really, really interesting discussion. And I'd be really interested in hearing your opinions on metabolic nutrition, lifestyle factors that you would think about recommending to your patients, but maybe I can come back another time.

That's a date. Consider it done. I'll tell you what I was thinking. The thought that went through my mind is we were having our discussion of the vitamin D receptor and issues there related to inflammation via the NLRP3 inflammasome that, again, it's a convergence.

issues in the human body are influencing all that's going on at the level of microglia and helping or not. But generally when we are having issues with elevated blood sugar and inflammation in our bodies, that is tending to polarize these micro glia to being that M1 phenotype that cannot phagocytize as your work so elegantly demonstrated in APOE study.

So I think we look at many straws on the camel's back and I But it can be, you know, worsened or offset based upon these other inroads, based on, I believe, the importance of our daily choices.

So that's what I was thinking about, but we'll deal with that next time when you've done all that vitamin D work. I'm so excited about it. Thank you again, and I sure hope I get to meet you at a conference in person someday soon.

That'd be great. I think it's clear that Dr. Marzi's incredible work powerfully reinforces a central theme we've been discussing many times on this podcast and certainly in the books I'm writing that our genes are not our destiny.

That what matters is how our jeans are regulated, how they are expressed. And the factors that control that include our environments, our immune signaling, or metabolism, and powerful influence of our lifestyle choices.

These signals shape microglial behavior over time. Dr. Marzi's research gives us a molecular framework for understanding why factors like pesticide exposure, inflammation, and metabolic stress increase risk for neurodegenerative conditions and why interventions that support immune balance and cellular resilience may have such incredible impact.

So I'm really grateful to have had this opportunity to speak with Dr. Sarah Marzi, I've been following her work for a

long time. I am thankful that she joined us today and very thankful for all of her pioneering work, which is really at the intersection of epigenetics, meaning controlling our gene expression, the microglia, of the brain's immune system, and ultimately brain health.

And this is exactly the kind of science that empowers us to think differently and therefore very proactively about protecting the brain where technology enhances insight without replacing wisdom.

So thank you for joining me here on the Empower Neurologist and for helping us share in what appears to be a brighter future. We'll be back soon. I'm Dr.

David Perlmutter. Bye for now.