TELOMERE SUMMIT

What are Plasmalogens? Critical cell membrane components in Alzheimers and Cardiovascular disorders

Dr. Joseph M. Raffaele, M.D.
Dayan Goodenowe, PhD

Dr. Joseph M. Raffaele, M.D.
Hello, this is Dr. Joseph Raffaele, your host for the Telomere Summit. Today, I'm very pleased to have on the show, Dr. Dayan Goodenowe. Who will talk about his research into plasmalogens and the relationship to many diseases, including Alzheimer's disease. Dr. Goodenowe's research into the biochemical mechanisms of disease started in 1990. His curiosity about the biochemistry of life is as insatiable today as it was 30 years ago. In those 30 years, Dr. Goodenowe invented and developed advanced diagnostic and bioinformatic technologies designed and manufactured novel and natural biochemical precursors and identified biochemical prodromes of numerous diseases, including Alzheimer's disease and dementia, Parkinson's disease, multiple sclerosis, stroke, autism, ALS , schizophrenia, bipolar disorder, depression and cancers of the colon, pancreas, ovaries, breasts, and many others.

He is just getting warmed up. Dr. Goodenowe is now going beyond disease and the detection of biochemical dysfunctions to diagnose and the correction of biochemical dysfunction to treat disease. Dr. Goodenowe's new focus is to defeat the entropy of aging by creating strategic biochemical and bio functional reserve capacity in advance of known disease risks, such that the human body can maintain the physical and biological functions of life indefinitely and without disease. Welcome Dayan. I am so glad to have you on here. I know we have lots of conversations about patients that have done your lab testing, but I don't know that we've actually ever really talked about the journey that you took to get to this fascinating area of plasmalogen medicine and cell membrane medicine. I'm sure that I would love to, and our listeners would probably love to hear about how you got here.

Dayan Goodenowe, PhD
Well, thank you Dr. Raffaele. Pleasure to be here and talk with you about these things. But yeah, so my background is actually in chemistry. Okay. So I'm a PhD in psychiatric medicines. My PhD, my initial training is in synthetic organic chemistry. And so I look at the world. There's 3 levels, basically, the biological world, where we have inner organisms interacting with each other at a organism level. And then chemistry is where actual atoms, the three-dimensional molecules interact. And we have that simple first law of thermodynamics that, you know, matter cannot be created or destroyed, only gets transformed. So essentially biology is just moving these atoms and electrons around and then you go deeper into it. You get into the physics and you get into quantum mechanics and what is the nature of these molecules themselves. And that kind of gets out of reality. And so the core of our existence really in our, reality existence is chemistry.

And so that's where I got more and more interested as time went on. So I first started looking at the biochemical mechanisms of psychiatric disease and depression, anxiety, other different, you know, neuropsychological disorders and obviously Alzheimer's, Parkinson's and so on. And then as what happens is sometimes when you're doing your research, the tools don't exist that you need to answer certain questions. I'm trying to understand what's actually going on at the biochemical level in these systems. And then when the 1990s came around, the genomics revolution started where people were saying, well, we can sequence genomes and we can start changing the way we look at science and medicine, where we're going to say, let's collect the data first, generate hypotheses after we generate all this large amounts of information and that was pretty powerful because then we could modify genes and we can say, okay, what does this gene do? And then we can go beyond that. Problem with genetics is that it's all derived from genetic code. And so your genes get transcribed into transcripts.

Which your gene chips and messenger RNA is. And then they get translated into proteins in the human body, but metabolites, a small molecule chemistry that we live in. Doesn't come from our genome. It comes from our environment and our genome basically just moves them around and we didn't have a technology that could be analogous or complimentary to this whole genome sequencing or gene chip technology. And so from a chemistry perspective, I started looking at how do we comprehensively measure all of the biochemistry occurring at once? And that's my first invention was non-targeted metabolomics. That's the core technology platform that's behind prodrome scan, which is kind of a mini portion of that. And so that allowed me to measure tens of thousands, probably over half a million small molecules and biological systems I've measured over the years using this advanced technology. And it was used for basic research, but it's also used for very extensive, large scale clinical trial research, understanding diagnostics of disease. And that was great. I was like a little boy in a candy store

of metabolomics, right? We were getting all these biomarkers and we could diagnose different diseases. Basically it is a, it's a complete diagnostic manual of human health. Like there isn't a single human disease. That cannot be diagnosed using metabolomics. And that's just a flat out fact. And so when I first started doing that, I was thinking then that these biomarkers were going to be useful for diagnostics and that's true. And I filed lots of patents and a lot of issue passed on diagnosing multiple different diseases. But what happened over time was that these biochemical changes, kind of surprised me. Okay. I thought, you know, we're going to diagnose the disease and then we'd fix the disease. And then these biomarkers would come back to normal again. And my first major wake up call was in colon cancer. And we did a trial with colon cancer in Japan, in Osaka Japan. And we have these great biomarkers that were decreased in people with colon cancer. And then we did a before and after surgery study and after surgery, the biomarkers didn't change. They stayed the same. I thought I was expecting these biomarkers to get back to normal because Hey, these, obviously the tumor is consuming these biomarkers causing this major depletion. And so if I fix the tumor, the biomarker should come back to normal. Well, that didn't happen. And I didn't really understand it.

So we repeated the whole study over again in a different collaborator out of Chiba University in Japan, Northern Japan, got exactly the same results. And then this was starting to show up over and over again, the plasmalogen story with Alzheimer's. So we're seeing these situations where the biochemical changes are preceding the disease. And then as you do more and more of this work, rather than getting more and more complicated, it started getting simpler and simpler because as we started moving up the causation chain of events, we were getting closer and closer to the most proximate biochemical changes. And the diseases that we're seeing really became symptoms of biochemical dysfunction, not causes of biochemical dysfunction. And then as that started getting more of more reductionist point of view. And so plasmalogens are one of those stories. And so that's kind of how this whole thing progressed really from, you know, for me trying to break down my own biases and ignorances in terms of, you know, we think we're so smart and the biology has a way of, of really humbling a person once you get into it. And they realize that the, the diversity of this world.

Dr. Joseph M. Raffaele, M.D.
So it was interesting. You were talking about first seeing biomarkers that you were picking up in the metabolome of these colon cancer patients. And then you thought that once the tumor was treated, the signal would go away because the assumption was that perhaps those biomarkers you were picking up were produced by the colon cancer. But in fact, what you figured out was that they were still there and then they were probably causing, or part of the biological middle year* of what was actually causing the cancer to occur. But before we sort of answered that question just for our listeners, most people are familiar with the term

metabolomics and metabolome, but not very deeply. How would you define the metabolome that you're looking at with your technology, the human metabolome, is it all the molecules in the blood? Is it certain ones? Is there ones just related to metabolism or is it, is it all markers in the blood?

Dayan Goodenowe, PhD
It's all small molecules that are not derived directly from your genome. And so glucose for example, is a metabolite and glucose in a plant and in a mouse and in a human is exactly the same glucose is glucose is glucose. And so metabolomics measures all of those small molecules and fundamentally the entire study of drug biochemistry is all metabolomics. Okay? Every single drug is essentially a metabolite and it's a metabolite memetic. It's only been the last few decades that we've been developing, what's called biological drugs. And those are drugs that are more derived from the genome. And so those are proteins that have sequences based upon human, genetic coding. And then they're designed to interact with specific human proteins. But typically if you take an antidepressant drug or you take a, you know, like for instance of statin, those are metabolites that are designed to mimic and dodge in the small molecule and it interacts with are human proteins and the receptors. And that's kind of how our genetic code translates into a, it's a set of possible reactions to a given circumstance because essentially our genome is passive. Okay. They have no, your genome has no idea what you're going to do in the morning when you wake up. And so they're kind of one step removed from reality. So they're going to react to whatever happens in your world, whatever you eat, whatever you do, and it's going to adapt to those situations. and so it's all your genetic structure is completely reactionary to maintain you in a living environment.

Dr. Joseph M. Raffaele, M.D.
Sort of a, your instructions in your DNA, produce RNA and then produce proteins. And these proteins are maybe like machines that depending on what raw material you put into them, then produce the metabolome. So.

Dayan Goodenowe, PhD
Well, they don't produce the metabolome. They interact with it. They transform it. Your proteins are essentially sensors. Okay. They'll sense, is Joseph exercising? Is he not exercising? Okay. Is he having a glass of wine? Is he not having a glass of wine? And it's saying, okay, based upon what you're doing, the proteins are sensing that, okay, it's saying, oh, all of a sudden I'm seeing ethanol in the blood now. Well that wasn't there two hours ago. So now I have ethanol. So I have to deal with that so Joseph doesn't die. Right? And so then it's going to change, okay, I need more of this protein now because I'm experiencing this thing. Okay. So if you get an infection or whatever it is, so all the proteins are, your body are essentially genetic sensors. It's how your

genome can sense the world around itself. And as we change with disease or anything else, then your modifications. And so a lot of the things that we think about with epigenetics and all of the things we think about with aging and the genetic adaptations, we lot of times we have that sequence of events backwards. We're thinking that these genetic changes are causing our aging. And really what they're doing is they're preventing us from dying of aging. And they're basically sensing that changes are occurring. And they're trying to keep you alive as long as possible. And sometimes they can be over-protective and the best way to tell people, it sounds counterintuitive because when you look at it, it looks so causative. It says, oh, I have a gene for autism or, or the BRCA gene for example, here's a gene for breast cancer. Well, BRCA is not a gene for breast cancer. Okay. BRACA is a gene that has developed results in a mutated protein. And that protein has causes your breast cancer cells and ovarian cancer cells to have a difficult ability to switch into the fasting state. Okay.

And so that particular sensor is now less. And so the, the person with the BRACA gene, the other genetic responses have to adapt to that. And so one of the adaptations is to protect those cells from dying. You end up it converts the cell to say, I'm going to be more glycolytic versus lipophilic because if I don't get enough glucose, because a breast cancer cell can't, it's not getting energy from fat metabolism, okay. Because the body's not switching to fasting. So either it's going to die, or it's going to switch to say, you know what? I need to get a larger percentage of my energy now from glucose. And it starts becoming parasitic to the local environment. And the genes are doing that because it's saying their job is to, to survive. Okay? Every single cell of your body has one job is to say, how do I keep this cell alive for as long as possible? And sometimes it gets over protective. So when you have stressors and you have, so the body will say, all of a sudden you get, you know, mitochondrial stress, for example, and you get electron stress on inside of the cell and the body, the cells going to start damping down your energy utilization. It's going to protect you from blowing up basically.

And then it's going to wait until that stress leaves. And then it's going to let you kind of open up again. So part of it, the genetics of aging is learning to be safe, to be young again. Okay. So you kind of get protected to death as we get older, and every time you get your body feels insult your cell feels an insult. It protects itself, and it gets slower and slower to open up again. And I tell people, it's almost like social interaction, right? Like you want to be in a extroverted, non paranoid world where you feel safe, your kids can walk outside and you, don't have to worry about things, right. And that's how you want to be. So you want to be open and safe. Then all of a sudden, you know, you have a bad event that occurs and you say, well, you know what? I'm not so safe walking around without any protection anymore. Okay. And so you start protecting yourself, you become more introspect and then more insults, the more protected you get, and the less likely you are going to become open again. And so your cells end up suppressing

themselves to protect themselves. But that suppression also reduces our function. And as we get older, you get this accumulation of protective mechanisms against accumulation of adverse stress events. And that's what your genes are. So your genes are kind of, they're in your nucleus right there. They're behind this curtain and there, and you can just imagine that they're like, you're sitting in your little control panel and you have like, you're in a war. And unless the scouts are coming back and telling you what's going on with the enemy you have, no idea what's going on out there. So your genes have no idea what's going on until it gets sensors and your proteins are those sensors. And they'll say, okay, I need more LDL receptors because all of a sudden, for some reason my cholesterol manufacturer is low. So I'm not making enough cholesterol. And the cell will sense that it says, okay, well, I need to get more external cholesterol. So I'm going to up regulate my LDL receptors so I can pull in more LDL cholesterol from the periphery. And that's kind of how it works. And we think about it's anyway. So that's kind of, it, it was a long process for me to get to that point. And the realization that as we move up this causation pathway there become simpler and simpler. And then, so that's what prodrome scan was trying to think that, short list like membrane biology, electrochemistry, like the mitochondria, there's a small number of really core functionalities that have to get mad and then everything else can be built upon that. And that's kinda what we're focusing on.

Dr. Joseph M. Raffaele, M.D.
So just getting back on metabolome for a second, the metabolome that would not include those proteins that are translated from RNA. It's just the smaller molecules that you can pick up on like GC, mass spec kind of thing. So, and you said you made a statement that virtually every disease could be, or has been, or it could be diagnosed or characterized by specific metabolome.

Dayan Goodenowe, PhD
Absolutely a 100%.

Dr. Joseph M. Raffaele, M.D.
So, but that's sort of big data biology, a little bit bigger data biology to do, that we're not doing currently, like we're not diagnosing cardiovascular disease. We're looking for atherosclerosis, but what you're saying, or is it the prodrome too? That they can be that you pick up in the metabolome?

Dayan Goodenowe, PhD
Yeah. So the prodrome is the cause of all disease, right? And so, and all diseases have two interacting factors. One is a degree of susceptibility. So say the BRACA gene gives you a susceptibility to breast cancer, but it doesn't cause the cancer. It creates a susceptibility. And

then the second part has to be the trigger, a triggering event that actually initiates the pathophysiology goal cascade. So you can be, you can walk around all day long with a risk factor, and it may never translate into a final disease if that susceptibility doesn't happen. Okay. So it becomes an odds game. You can drive with bald tires all day long on, on beautiful streets and never get a flat tire. Okay. You can have a brand new set of tires. And if you drive in the wrong conditions, you'll still get a flat tire. Okay. But the odds are okay. If all things being equal, when you have a brand new set of tires, you're less likely to get a flat tire. It's not impossible because you just need a much stronger nail to pierce that tire if you have brand new tires, if you have bald tires, just a little rock, will give you a flat and that's how all diseases occur. And so prodromes are basically bald tires.

They're not a guarantee, but fundamentally virtually all of that disease will occur in that particular group. And so for colon cancer, that molecule was gastrointestinal tract acids from the gut microbiome. And what you can find in is that once you understand the prodrome, you can eliminate other risk factors. For example, so age is not a risk factor for colon cancer. Okay? It doesn't matter how old you are, what matters is how much your GTA levels are in your blood. And what happens is we get older, the percentage of people who have low GTA's in their blood increases. And so therefore the increased prevalence of a GTA deficiency is the cause of the age association. So once you understand the GTA levels, your age is irrelevant. You can be 90 years old. If you're a 90 year old man or woman with good GTA levels, your risk of colon cancer is the same as an average 40 year old.

Dr. Joseph M. Raffaele, M.D.
And so the GTA will supersede chronological use, but chronological age is a risk factor for lower GTA's.

Dayan Goodenowe, PhD
Correct

Dr. Joseph M. Raffaele, M.D.
What's the, well, we're getting a little bit ahead of ourselves because these are sort of in that family of molecules that we're going to start talking about more about, but in terms of sort of going from metabolome into plasmalogens let's first talk about what plasmalogen are, because I hadn't heard about them until I sort of heard about your test and then started ordering it and lots of getting results back and talking to you about it, but I'm sure a good portion of our listeners have never heard of a plasmalogen and also, you know, what role they play in diseases in aging and particularly in Alzheimer's disease which we're going to talk about, but let's start with Plasmalogy 101 for about five minutes then.

Dayan Goodenowe, PhD
Plasmalogens are like this bad penny that just keeps on showing up. It's just one of those molecules you just can't get rid of. So, statistically speaking, when you're in science, we are trying to understand the causation of a disease. Molecules that we see that change with the disease are either symptomatic or the causative and the farther you get away from the causation of a disease, then these symptomatic variables disappear. You say, oh, okay. That's not really like the agent GTA, for example. So age is really not the important thing GTA's are important things. And so what you can do is you can eliminate biomarkers saying, oh, that is just a secondary or tertiary effect of the disease. It's not a primary effect plasmalogens are one of those molecules you can't get rid of. So it's always there.

Dr. Joseph M. Raffaele, M.D.
Its not a good things so let's not get people confused, you don't want to get them.

Dayan Goodenowe, PhD
Yeah, exactly. Plasmalogen deficiency is a really critical issue. And so what becomes unique about plasmalogens they're a fossil lipid. And so, as I was telling you earlier, the human body has 2 core capabilities that you must meet to live. One is your mitochondria function. We take in hydrocarbons, burn them into carbon dioxide and water. We use that energy to charge a battery called the electron transport chain. And that's how the body, the human body is essentially a hybrid electric car. We burn hydrocarbons to charge a battery and that's our energy source, the second part. And that's all electric chemistry with oxidative stress and electrons. The second part of the human body that must absolutely get met at all times is membrane biology. Okay? What gives us the human body structure so that you're not a bowl of soup. Okay. In some yeast vat, that we're brewing.

Okay. What gives us structure is membranes and they're the ones that give all of our trillions of cells, the three-dimensional structure and all the proteins of your body. Fundamentally either work directly in a membrane, or they are influenced by a membrane. So lipids are the matrix of our life. Okay. It's like when you walk, it's a difference between walking on hard ground versus walking in the mud. Okay. It changes how everything works. And so lipid membranes are called fossil lipid bi-layers and fossil lipids are like a soap. They have a polar head group that likes to be in water and they have a non-polar fatty acid side chain. That likes to be in liquid like an oil, like your oil and vinegar mixtures. And what happens with fossil lipids is that they create a false liver bi-layer. So the fatty acid side chains aggregate together in the center and the polar head groups on the outside. And that's how the body creates a biological wall and creates an impervious wall. And that impervious wall, allows the body to do compartmentalization. So you

have things that can happen in the mitochondria. Things that'll happen in the endoplasmic reticulum. Things will happen in cardiac cell that won't happen in lung cell. And so that it gives the body, all the organizational compartmentalization capabilities, but things have to go in and out of these membranes. Okay. That's where your metabolites go in and out proteins go in and out. And so the maintenance of this lipid membrane becomes really, really critical. Plasmalogens are one of those critical elements. Okay? If they make up 20 to 30% of the entire lipid composition of your brain, like we're not dealing with small amounts, high levels of your heart, your lung, your kidney, the retina of your eye are these molecules called plasmalogens. And what makes them interesting is that you can't get them from a dietary supply because your body makes a lot of them and your body uses a lot of them. And the very final step in their manufacturer creates this bond, which gives them their functionality it's called the vinyl ether bond. And it's designed to be very exquisitely sensitive to acid. It's one of your major neutralizers of hydrogen peroxide.

And we just published this clinical work in Alzheimer's disease, showing how plasmalogen therapy, the protoneuron dramatically reduces your malondialdehyde levels. So it's a very potent antioxidant and well, we showed really powerful cognitive improvement and mobility improvement, which we'll talk about in a minute. But so your body makes it, and you can't get it dietarily. So you are constantly making a certain supply. So when we're younger, we create these biochemical reserves. So the myelin sheeth, the protective coating on your axons are high concentrations of plasmalogens. And so as the course of time goes on after about age 50 or so plasmalogen levels start to decrease, not in everybody, but as a population generalist perspective, right? So the better way to think about it is that, the prevalence of plasmalogen deficiencies start to increase. So maybe people in their 40s, or maybe 5 or 10% of people that have low plasmalogens, then it becomes 10 to 15% then becomes 15 to 20%.

And so, as that plasmalogen deficiency increases, you start losing your biochemical plasmalogen reserves that you built up over your lifetime, and it starts bleeding out of your brain bleeding out of your membranes. And this is where it becomes important because all the cells of your body are, it's kind of like a bakery, for example. So people say, well, can it be that simple as its just plasmalogens, but I tell people, imagine like your cells are cooking things every day. Okay. They're making membranes, they're making molecules, they're basically a bakery. And you can imagine if you're going to make a cake for Thanksgiving and you have your favorite recipe that takes, you know, 2 cups of milk and 3 eggs and 2 pounds of flour or whatever your recipe is. Right. And you're going to go and you're up in the morning to go make your, your cake and you go to the fridge and you say, oh, well, I don't have 2 cups of milk anymore. I only have 1 cup of milk. So are you going to make a cake with all the other recipe ingredients in it? And just 1 cup of milk, and you're going to end up with a brick, for a cake and

not an actual fluffy cake, or are you going to say, I'm going to cut everything down instead of 3 eggs, I'm going to use an egg and a half instead of 2 pounds of flour, I'm gonna use half, 1 pound of flour. So you're going to reduce the whole recipe down so that the cake still comes out. You have less cake, but it's still good quality cake. And that's essentially brain shrinkage 101, okay. So when we reach age 90, our brain has shrunk 20% of its volume since we were 50. Okay. And so part of the brain shrinkage problem is that your cells, like I said, are passive. They can only work with what they have at their disposal, and they will adjust to that environment, the best it can. So plasmalogens is one of those molecules, very critical ones. So, and it's involved in your neurotransmitter release. Like you need to release the vesicular release of neurotransmitters required. These plasmalogens, cholesterol regulation and transport, like your HDL cholesterol transport system is almost entirely driven by plasmalogens. And so those kinds of things are really, really critical. So that's kinda where the plasmalogen story comes in.

Dr. Joseph M. Raffaele, M.D.
Let's get a little bit more clarity. Cause I know it was confusing for me when I first heard it. I'm sure to a certain extent it's a little confusing to people first hearing it. So plasmalogens you can't take it in your diet because that vinyl ether bond gets destroyed in the stomach acid. There's a sort of a reserve that's in the body, in the white matter tracts in your brain. You're saying that that's built up that from birth, and then you gradually chip away at that because, we should also get into the exact structure. My understanding is that there components of the plasmalogen can be gotten from the diet like there's DHA plasmalogen, EPA plasmalogen, there's Choline as part of it, there's ethanolamine as part of it, putting it all together is what's done. And you have some supplements that can help do that. But why don't we talk just a little about the structure of a plant? So.

Dayan Goodenowe, PhD
The big, the big thing.

Dr. Joseph M. Raffaele, M.D.
Bring those levels up right from the natural history of losing them.

Dayan Goodenowe, PhD
The critical component of the plasmalogen is called, the ether bond. So most lipids are on a glycerol backbone. So when you go to your pantry and you get olive oil, that's called a triaclglycerol. And when you get fish oil from the market, it's a triaclglycerol, which means there's 3 ACL bonds on a little it's like a power strip with 3 plugins. And you can plug in any one of the 3 components. And that's your classic glycerol molecule. Cause those are called.

Dr. Joseph M. Raffaele, M.D.
Triglycerides that float around.

Dayan Goodenowe, PhD
Exactly. And all the things. Yeah, exactly triglycerides, plasmalogen are an alkylaclglycerol. So the SN1 position, instead of being an ACL bond, which is a fatty acid bond is an alkyl bond, which is an alcohol bond. And that's what makes it very different. It's manufactured entirely. It looks almost identical, but it's manufactured in the peroxisomes. If it doesn't fall, once it's made, it'll share with other fossil lipids, but it's not dietarily involved. And so in order to get exogenous plasmalogens, I'm a synthetic chemist. So one of my, work was to develop precursors that could survive the gut. And the way we did that was designing acylglycerol that don't have the vinyl ether bond, but just the ether bond. And then that gets absorbed and then your body can make the final step in all the cells of your body. And so it has two very powerful, important issues is one, it will increase your circulating levels of plasmalogens, which is your pool size. But every day you take the supplement, it pulses into the cells of your body and allows each of those cells to make their own plasmalegons on demand, which is why, excuse me.

Dr. Joseph M. Raffaele, M.D.
Do you got some water? You should get some water.

Dayan Goodenowe, PhD
I exactly didn't have one here with me. So with the clinical trial, wow. My voice doesn't normally do this. You can pause.

Dr. Joseph M. Raffaele, M.D.
You can go ahead and get a drink of water.

Dayan Goodenowe, PhD
I'll do that. Okay. Sorry for that. So we were talking about the chemical structure of plasmalogens and what makes a plasmalogen a plasmalogen is it's ether bond and it's a very, if you had to design a planned obsolescence, if you had a design, a human body with like a washing machine, with a bad belt, you would pick plasmalogen because there's a single non-redundant biochemical system to make all the plasmalogens. And there is absolutely no backup plan. It's one of the few systems in the human body that has only one pathway, one system. And if you are born with genetic mutations in your plasmalogen manufacturer, there's like 3 enzymes that are completely obligate to their manufacturer. Basically either you die within a month or a few years, of birth, or you have severe neurological defect, dwarfism, there's a bunch of very significant adverse effects. So we know plasmalogens is, are obligated to

human life based upon mutations are rare diseases that affect plasmalogen biochemistry. And so the design of supplements that can survive the gut and to target different plasmalogen was to get these acylglycerol. So it's kind of like L-DOPA for Parkinson's where L-DOPA is a biochemical precursor of dopamine. The ProdromeNeuro and ProdromeGlia are precursors of plasmalogens and they're designed to, to survive the gut acids. And they're designed to go into each of the cells. The other interesting thing with plasmalogens is, that they're different types have entirely different purposes. Like they're really opposite of each other. So the plasmalogens for your neuronal synapses and your neuromuscular junctions and the, you know, the HDL cholesterol transport and your macrophages, those are all your DHA long chain omega-3 plasmalogens and they're involved in the fluidity. And they're also involved in amyloid function in the brain and so on. But the plasmalogens that are protective of your neurons that create that protective sheath in your Schwann cells and your oligodendrocytes, those have almost no omega-3, they're almost all omega-9 oleic acid.

And that creates a very, very tight impervious structure. So they're very, very different from each other. And so the challenge is to be able to target those individual cell types because acylglycerol have been around for a long time. Shark liver oil, for example, is one of the sources that you can get acylglycerol, but they don't. And you know, the positive effects of shark liver oil, for example, in radiation therapy for cancer has been known since the 60's. And so, but the point is that when you take shark liver oil you're going to get squalene. you can't get the actual plasmalogen that you need, which is either the DHA version or the oleic acid version. And obviously there's always the, the environmental contamination issues of sourcing issues. And so we have a 100% vegan designed program. So we get our DHA from algae, we get from algae, triglycerides, we actually process that, we strip the DHA off basically like making soap. And then we purify the DHA, from the algae source and we put it on the plasmalogen backbone. And that way it's completely purified.

There's no chance of any kind of environmental or even allergenic reaction to the source of the fatty acid. We just use that to get the fatty acid and then it gets put onto the backbone. So that's where the ProdromeNeuro comes in. And then for the ProdromeGlia, which is designed for stroke, concussions, multiple sclerosis, autism type diseases, where you have a white matter major white matter component. We get our oleic acid from a sunflower oil, high oleic acid, sunflower source. And again, does the same process. We strip it off, we purify it and we put it on a backbone. So there's no like if you're sensitive to, you know, sunflowers or if your fish sensitive or something like that, like this the product has none of that issue. And also any, there was any kind of contamination in the source. That's all cleaned up in our purification process before. And so there's no risk of Mercury's or leads or anything like that coming from the source. So that allows us now to target either the neuronal system or we can target the glial system based

upon the type of issue that we're dealing with. Now, they're both going to restore all plasmalogen as a general rule because it's the backbone that drives it. So that's kind of quick plasmalogen 101 story. Okay.

Dr. Joseph M. Raffaele, M.D.
Great. So I know, I want to ask a couple more questions about plasmalogen versus typical fish oil that you get over the counter in terms of supplementation. I mean, I know the answers to them, but I want our listeners to hear, but first and most importantly, talk a little about your groundbreaking work in sort of a whole new approach to Alzheimer's disease. These are the plasmalogen levels in plasmalogen supplementation, the clinical trial results.

Dayan Goodenowe, PhD
So we just presented this. And so, first of all, we're.

Dr. Joseph M. Raffaele, M.D.
Let's start with the theory behind it and how you got to the, you know, sort of to the point where you were going to do a clinical trial, and then we'll talk about the results.

Dayan Goodenowe, PhD
Okay. So yeah, so using this non target metabolism technology, when we're looking at people with cognitive impairment, we found that cognitive impairment was associated with plasmalogen levels in the blood people with low levels of plasmalogens had a higher risk of having dementia. And if you had low, depending upon the severity of your plasmalogen deficiency, it correlated with the severity of your cognitive impairment and that's at a cross-sectional perspective. But then as, as we did more longitudinal studies, it became even more prevalent in a sense that the lower your blood plasmalogen were the faster, your rate of decline was, the higher the level of the prediction of your cognitive impairment was, and you look at post-mortem data, plasmalogens, in the brain become highly correlated with cognitive status, more so than anything else, any other pathological feature, more than amyloid, more than tau, more than plasmalogen, raft, even even more than the cholinergic neuron density, which we can measure with the Choline-B transporter. So the plasmalogens became head and shoulders, the most associated brain molecule with cognitive impairment

Dr. Joseph M. Raffaele, M.D.
This is in mildly cognitive impairment or early Alzheimer's later Alzheimer's.

Dayan Goodenowe, PhD
Across the whole spectrum.

Dr. Joseph M. Raffaele, M.D.
I mean, when did you you get this as a signal of cognitive aging.?

Dayan Goodenowe, PhD
Well, in the brain it's across all okay. In the blood you're one step removed from the brain. So there's a going to be a temporal difference. Basically. How long have you been deficient and how long has that deficiency? What's the severity of the deficiency based upon your consumption of plasmalogens? And that'll define your it's like a, it's like a leaky pail, right? So it's dependent on how much, how much water is in the pail and how much water is pouring out. And so, those two things together will determine how quickly we start seeing clinical symptoms. And so that's where that came in. And so, yeah, the human brain data is pretty well absolute and it's across all spectrums. So completely 100% cognitively normal, mild, moderate to severe dementia. It's a linear line and that's all presented in the book Breaking Alzheimer's where I published a few months ago now.

And then like, that is fully described in the post-mortem studies that we've performed And so then the biochemical mechanisms like we've used plasmalogen precursors, they're completely neuroprotective in animal models. Say for Parkinson's disease, if we use MPTP to degenerate dopaminergic neurons, if we treat animals with plasmalogen precursors in advance, we get a 100% neuroprotection, they're 100% protective of demyelination and demyelinating diseases like multiple sclerosis models. And so it's been very, very powerful preclinical aspect of it. And it works like clockwork. It's the precursors are very simple and clean. They get converted. And so we've known about plasmolysis for about a 100 years, and we've had some very, very simple acylglycerol back in the 60's. And so on called batyl alcohol and chimyl alcohol and selachyl alcohol. These are very simple acylglycerol, but they've never been shown to properly elevate blood plasmalogens because you'd have to take massive doses.

And what I discovered when I was doing all the structure activity relationship work is that you actually have to put the fatty acid that you want on the molecule in advance. Okay. The SN2 position has to have either the DHA or the oleic acid on it. And once you do that, boom, your body takes it. It gets absorbed, it gets rapidly converted and it works. And so that's really when the big issue came up on glycerols where all those my patents in that area came in, came to be. So we know from ether lipid deficiency diseases that it reduces neuron transmission, the cholinergic system is specifically sensitive to plasmalogen deficiencies versus other neuron systems. And the cholinergic system is a key system involved in dementia. And so we basically systematically started studying and studying them. And so then finally, you know, I had a bunch of patents on chemical structures of plasmalogens, but as like my earlier story where

things become simpler. Plasmalogen deficiencies are in ALS, they're in Parkinson's disease. Virtually all cancers will have a plasmalogen deficiency. We're just publishing a big paper in breast cancer. That'll come out probably in the next month or so out of Japan. And so plasmalogen biochemistry is this weak link of health that has consequences in multiple different avenues. And then your own personal genetic predispositions are going to lay on top of that. So it creates a stress to the system, and then you're going to have the diversity of each individual's environmental life and their genetic predispositions, which can trigger what potential clinical consequences you might end up experiencing from a plasmalogen deficiency. So with that became clear that this one drug one disease model is not going to work. And quite frankly, as a chemist, I basically did a bunch of medicinal chemistry tricks to create non-natural plasmalogen so I could patent them, but plasmalogens are natural. So you can't technically patent natural molecules. And so I basically just threw that all in the garbage a few years ago and said, okay, we're just going to get a natural supplement, okay. That can satisfy, you know, grass regulations. There's no prescription required.

You can use it for anything you want. We're going to stay away from actually making medical claims. We're going to say, you know what, here's a, here's a supplement precursor does exactly this. It elevates blood plasmalogens, and then we're going to do a whole bunch of clinical trial work. And we're going to show what plasmalogen level modulation can do. And we're going to keep those two worlds separate. So we're not going to make the actual medical claims, but they're supplements. We're going to let doctors make their own medical claims. We're going to do our own clinical trial research to show the fact good, high quality clinical trial work. And then we'll be able to do blood testing. And then that, way we're going to find out the different areas that it can work. And to be honest with you, that iterative protocol process has been incredibly successful because we're seeing dramatic results, in our customers. And then in the clinical trial, which we just announced last week, it was amazing. It was a small trial. So, 22 patients complete random. They all had cognitive impairment. They had either very mild. So using the clinical dementia rating scale, they had either a 0.5, which is considered questionable or very mild dementia, CDR of 1, which is mild dementia. And then a CDR of 2, which is moderate dementia.

Dr. Joseph M. Raffaele, M.D.
And how far does it go just for our listeners

Dayan Goodenowe, PhD
It goes from 0.5 to 1 to 2, and then the highest degree is a 3. Okay. So that's severe dementia, but we had, yeah, so we had 14 people at baseline that had a 0.5. So the very mild case, we had 4 people that had mild a CDR of 1, and we had 4 people that had a CDR of 2, moderate. So 8

people, we had very definitive cognitive impairment and 14 had very mild questionable. People at the 0.5 level can bounce back and forth. But you know,

Dr. Joseph M. Raffaele, M.D.
These are late onset Alzheimer's? what was the average age of the group?

Dayan Goodenowe, PhD
We had the average age was in the late 60's. but it was not that late. No, We had some people at age 37 with frontal temporal lobe. So we had some Lewy body. It was a hodgepodge.

Dr. Joseph M. Raffaele, M.D.
So you kind of had a heterogeneous group.

Dayan Goodenowe, PhD
Very heterogeneous group, and that it was designed that way. And we did no pre-selection, this was totally done for performance with kinetic purposes. It wasn't really designed for cognitive outcome analysis. What we did, we did no pre-selection on their baseline plasmalogen level. So people get a high, low doesn't matter. And the whole point of the trial was to do an escalating dose. So for the first we did baseline analysis, we did cognition and mobility analysis, and then we did biomarker analysis on everybody. And so first month they took one meal per day. So that'd be one bottle of ProdomeNueronal for the month. And the second month we doubled the dose. So they took 2 meals per day. And then we did that for 2 months. So 2 bottles a month. And then the 4th month, we did 4 meals per day. So 4 bottles for the month, 1 bottle every week. And then we did a 1 month wash out period afterwards. And so what we found was that we've got a dose dependent increase in our target plasmalogens. It was beautiful just step by step by step. And there's a there's detailed videos that will be launched within the next day or two on my website, DrGoodenowe.com. That actually goes through all the clinical trial data. So you can show the slides and everything that I presented at the Alzheimer's conference last week is available for everybody. So anyways, we've got very clear pharmacological improvement, okay. The biomarkers improve exactly as designed. So we're getting the molecule in as expected. Then we started looking at cognitive impairment. This is where it got really exciting. So we actually of the 4 individuals that had moderate dementia. They had a CDR of 2, 3 of those 4 people improved by an entire CDR score in a 5 month period.

Dr. Joseph M. Raffaele, M.D.
Wow,

Dayan Goodenowe, PhD
It's really crazy. And then half of the, the CDR 1's also improved by over a full CDR level within 5 months. And so when we look at the statistical analysis, if you do a chi-square test is too small to look at statistics of the actual outcomes. But if you, if you group people into responders versus non-responders versus what you would expect, random occurrence to be it's statistically significant cognitive improvement, the second part was mobility. So we looked at the 30 second sit stand test. And in that situation, was that even a bigger improvement? So the muscularity the muscle tension and the muscle activity improved dramatically. So actually 14 over half of the subjects had an improvement. So what the sit stand test does is basically you ask a person to sit and stand as many times as they can in a 30 second period, and you count it right. And it's a measure of sarcopenia as well. And so anyone who had an improvement of 2 or more was called an improver, and anyone who had a decline of 2 or more was considered a decliner in terms of their mobility, 14 people improve by 2 or more.

Many were improving by 4 to 6, 6 stands in 5 month period. We had 4 people decline, which we would expect. And then we had whatever the difference was stayed stable, and that was highly significant. And so the mobility improvements were quite robust and the individuals themselves self-reported feeling better. Like there, they felt their energy levels are increased and so on. And so we're very happy with the other thing that was really interesting though, was that of the 9 clinical responders. Okay. That had a full CDR rate change in the 5 month period. 5 of them were in the people that had a pre-existing low plasmalogens, and 4 of them were people that had high plasmalogens. Okay. So the clinical outcome was not related to the blood test. Okay. So the blood test didn't predict clinical response. The blood test of course predicts clinical decline over time, but the plasmalogen precursors are designed to go in and actually not only do the increase, your plasmalogen levels, but they're actually going right into your neurons for biological activity. And we've had some patients that have, you know, after in the wash out period, some of their effects were disappearing.

So they've kept on high doses of the plasmalogen. So we're pretty excited. That's the first time in human history that we've been able to target plasmalogens okay. We've known about plasmalogens for over 100 years. This is the first time we've been able to target and elevate plasmalogens in humans. And the second thing we did, we looked at oxidative stress biomarkers. Okay. So we know plasmalogens reduced hydrogen peroxide. We know anecdotally from what we're doing, you know, see reactor proteins drop dramatically when people take the plasmalogens. So we measured malonaldehyde which is an end product of lipid peroxidation. And then we looked at catalase activity, which is a enzyme that's used for hydrogen peroxide neutralization. It's also a biomarker of aging and then superoxide dismutase. So we had a very powerful reduction in MDA levels. It's an R .5, P value of 10 to the -7 So the correlation between

blood plasmalogen levels and MDA levels was very, very robust. And more importantly, when you look at oxidative stress biomarkers, there's a biological floor. Like you, if you have good levels, you can't get better than good, so if you take a look at each group of people and say, what about people that just had high aldehyde levels? Those individuals had a disproportionate benefit. They dropped like 50%. Catalese levels, people had a preexisting level, of low catalase activity, catalase was turned to normal. And what happens is that by reducing the aldehyde stress or the hydrogen peroxide stress, catalase, a protein gets consumed in its activity process. So by reducing the aldehyde load, we ended up reducing the degradative pressure on catalase and catalase returned to normal. And we also got a benefit in people with superoxide dismutase, low superoxide dismutase activity, which is your first line of oxidative stress defense. So biochemically, so the pharmacokinetics data was robust, the pharmacodynamics in a sense that it's getting in, but it's actually biologically doing something with the MDA. And then the clinical outcome data was well beyond our expectation. And so we're going to be moving to a bigger trial design, but really focusing, I'll be doing community work. But we'll look at MRI data because I believe that we can actually show significant changes on brain MRI with plasmalogen supplementation going forward. So that's kind of the quick and dirty of the clinical trial results that were presented.

Dr. Joseph M. Raffaele, M.D.
That's really fascinating, you know, groundbreaking an early study. But I was just thinking about a couple of things. You said one was that increasing plasmalogens, can help with neurotransmission because it's involved in, so that could be a cognitive effect, but it seems to me, based on what you're saying, particularly with the oxidative stress markers, that may be one of the major factors is through a reduction in oxidative stress, perhaps, you know, within the mitochondria, within other elements of the cell. How does that tie into the sort of more traditional view of Alzheimer's? And is there any way pathophysiologically to link that up with the amyloid hypothesis, which of course is you've been taking a beating, but, you know, and then the final question I have, which I know, because I've spoken to other people about is the whole telomere hypothesis of Alzheimer's disease. And, you know, it seems to me that there may be a link in that reducing oxidative stress is perhaps the, the link in the whole thing, and you're doing it through plasmalogens, you know, mopping up, you know, free radicals, increasing, you know, catalese's ability to do his job. With telomere biology. It could be increasing PGC, 1 alpha and beta, improving mitochondrial health. And I was just wonder if you have any thoughts about, you know, the traditional approach to Alzheimer's, you know, sort of the amyloid hypothesis, how does, how do plasmalogens figure into that?

Dayan Goodenowe, PhD
Well, we can turn amyloid on and off with the plasmalogens we published that work. So.

Dr. Joseph M. Raffaele, M.D.
I'm not sure I've not heard that, but.

Dayan Goodenowe, PhD
Amyloid biology is not actually that complicated. They're just developing a, drug is the tricky part on that part. So actually I'll be launching a series this next week. I just did the with for people with APOE-4 genotype. So I'm launching, what's called the Breaking Alzheimer's definitive lecture series, and it's a series of 10 lectures. Each lecture is like an hour long, one we'll deal with each aspect of biology, amyloid, brain shrinkage, tau pathology. And so those different aspects of brain pathology that are commonly associated with Alzheimer's disease. Those are biomarkers. Okay. So in terms of cognition, okay. The cognitive mechanism is calling neuron transmission full stop. Okay. And the next question from there is where does that degradation come from and how does cholinergic neurons decline? The oxidative stress membrane hypothesis, That's definitely oxidative stress is related to your inflammation status. So all inflammation comes from liver peroxidation fundamentally.

That's what activates your immune system cells. And then, so it causes auto-immune diseases in its full process, but in terms of plasmalogens, and amyloid, and in tau, mostly amyloid. So amyloid comes from a protein called, I know this gets into some details here, but amyloid precursor protein APP is obligate to human life. Okay. you cannot create animal models with APP knockouts. They won't survive. APP is critical. And when it normally gets processed by alpha secretase, it creates a molecule called soluble APP alpha. And that is a critical neurotrophic molecule involved in our neurogenesis. Neuro growth is very, very powerful. It's actually a drug development program in its own right into mimicking soluble, APD alpha. So you don't want to block amyloid precursor biology because it is absolutely obligate to human life. What happens in brain amyloid is it's a membrane structure issue, and it's related to cholesterol, efflux capacity of the cells.

And that's why the ApoE genotype is associated with amyloid. Okay. And it's the amyloid association with ApoE4 that gives a we for carriers and increased risks. So E4 carry that can manage their cholesterol level. Their memory and cholesterol has no increased risk. And we published that work extensively. So what happens in amyloid is that there are 3 different membrane regions and the beta secretase, which is the enzyme that forms the, amyloid beta 1 to 42 peptide that turns into the plaque that's located in lipid raft regions or high cholesterol, rich regions. And the alpha secretase is located in a separate membrane region in a fossil Lipid rich region. So when we, if we increase DHA plasmalogens, as we increase alpha, secretase, we've increased soluble APB alpha, and we dose dependently decrease a beta 142, and that's

shown in the lab it's shown in humans. So when we do post-mortem studies, the brain, your brain levels of plasmalogen correlate with your amyloid levels. And for example, someone who's an E4 carrier that has high plasmalogen will have normal amyloid. So it neutralizes the E4 effect on amyloid. So amyloid chemistry is very highly linked to 2 things. One is membrane chemistry. The second is methyltransferase the homocysteine system. So the other pathway that turns amyloid formation on and off is the phosphorylation APP phosphorylation. And the dephosphorylation is, is linked to methyltransferase activity in the brain. And that's where tau comes in. So, but so tau is another chemistry. We can go into that details, but Tau acts like a peristaltic pump to accelerate your organelle transport down axons and back and forth from the synapse, from the cell body. And so you have microtubules. So Sotalol is called a microtubule associated protein, MAP, and your body has all your cells have these rails, if you will. Microtubules and they're basically transport rails.

So you can move things from the cell body down to the synapse and back and forth. So when a mitochondria gets damaged, you need to send it back to the cell body. And when you get new mitochondrial created, it gets sent from the cell body down to the APP, to the, synapse. And so neurons can be quite long, right? And so you have a very long distance between the cell body and the synapse. And so you have normal transport, and then you have what's called accelerated transport of the organelles. And the tau protein is involved in accelerated organelle transport. It's how the body moves organelles quickly down the axons and how it does that. It's like a peristaltic pump. Okay. So when tau gets phosphorylated, it, it expands. And it basically it's like a negative squeeze. So it squeezes, and it basically it's like pushing the organelles down. and it acts like a peristaltic pump. So it squeezes and then releases. And so as it, as it moves down the axon, it squeezes and releases.

And then, and it creates this process. So the squeezing part is called phosphorylation uses kinases. It's the dephosphorylation that relaxes it. That is a problem. And so if you have folate deficiencies or SAH elevations, the ability for tau to become dephosphorylated, the relaxation phase goes away. And so you can turn tau neurofibrillary tangle density goes up and down based upon your methyltransferase activity in the brain. So methyltransferase in the brain is really critical, not just for choline maintenance, but for tau formation and for amyloid processing. So I go through all those things in great detail. People don't realize that we, actually know a lot about this stuff we've known about it for many years, so really good research has been done on it. And then we get focused on this idea of trying to remove the amyloid plaques, which is really quite irrelevant. The amyloid plaques, firstly, you shouldn't have amyloid, right? So if you have elevated amyloid, that's the biomarker that you have something wrong. Like there is, there's a system not working properly, right.

Dr. Joseph M. Raffaele, M.D.
Like in your arteries.

Dayan Goodenowe, PhD
That's Right. So your question is not remove the plaque. The question is where's it coming from? Like, why is it happening? And then as you move up, there's very, a lot of that work has been really, done very well. Like your atherosclerotic plaques, like ACAT, like your cholesterol sidle transfer system. Okay. Highly modulates plaque formation and your macrophage levels. And so that's all driven by plasmalogen levels. Like your plasmalogen is drive your, your cholesterol, esterification and cholesterol efflux capacity rates. And so these are things that have been very well studied, but they're done in isolation. And that's the very frustrating part is that you got a whole group of tau scientists they've been studying tau their whole life. And all they do is talk to other tau scientists. Okay. They talk to each other about their own little esoteric thing. And you got a whole bunch of amyloid people talking about amyloid and you got all these people doing imaging, all this amazing imagery of human brain imaging and also the biochemistry of brain shrinkage.

And they don't actually integrate their data almost never. And so each of these sectors have been actually quite well studied, but most people don't get a chance to actually experience the simple biochemical mechanisms that drive these common features. And so that's what the definitive lecture series goes through. It goes through each of those systems in detail, you talk about cognition, the biochemistry of cognition is, is well established. I guess it's not controversial. We've studied this backwards forward sideways. We can turn it on, off. Like we know seriously, we have studied this thing to death. Like we've known about it for 40 years with 50, some years of research on this stuff. So it's not a mystery. The mystery is, is where, you know, on a functional medicine perspective is understanding that causation cascades, okay. And getting into those causation cascades and we run up against issues of monetization. To be honest with you.

Dr. Joseph M. Raffaele, M.D.
That's what I was going to say, they want to fix one problem that's patentable. And you went down the same pathway and then you found, well, the best drug is actually a natural supplement, the same as TA Sciences did with their telomerase activator that said this works, is generally regarded as safe. Let's do the studies, which I credit you with. And any supplement company, lot of supplement companies don't do that. Let's do the studies and show that this is the right molecule. And then you have developed a blood test, which I encourage our listeners to look at your website for the prodrome sciences, a blood test, which looks at these systems, the methyltransferase system, the plasmalogen system, the peroxisome system, mitochondrial

assessment. Pretty fascinating. We've gone over, I don't know, a couple of dozen now I'm still learning. And I only want to, you know, sort of peak the listeners, interest with your whole different take on cholesterol and cardiovascular disease. But we can't, we don't have time to get into that today. Maybe we'll have you back at some point, but I think it's, it's 2:11. I know you had a, a little bit of a hard stop.

Dayan Goodenowe, PhD
Running late, but that's okay.

Dr. Joseph M. Raffaele, M.D.
I just want you to say, you know, what your website is.

Dayan Goodenowe, PhD
Yeah. So Dr. Goodenowe.com is where all the educational material is.

Dr. Joseph M. Raffaele, M.D.
Can you spell that? Make sure people have that.

Dayan Goodenowe, PhD
D R G O O D E N O W E.com. That's where all the educational seminars and get the book and so on and so forth. And then prodrome sciences. So prodrome.com. So P R O D R O M E.com is where you can get supplements and also blood testing from there. So that's kind of where it's all about.

Dr. Joseph M. Raffaele, M.D.
Yeah. So it's been as always fascinating talking to you, the biochemical pathways, the lipids, everything is, really amazing. If you have any parting words.

Dayan Goodenowe, PhD
The fun part is that this is all fixable. Okay. People think that biochemistry is some strange world and it follows basic principles of everyday life and just uses fancy words. And we get stuck in the jargon of things, but organizational structure and the logic of biochemistry in life is the logic that we observe in our everyday lives. And so many other areas. And so people shouldn't be intimidated by it, and it should be fun. And the biochemistry of metabolomics is not like your genes, which you can't change what you were born with. Biochemistry is yours. You can modify this at your own will. There are so many ways that we can tweak one system or another. And so I tell people I'm in human biochemical engineering. That's what we do. We engineer humans based on basically take a look at what you got. We can add a little bit here, add a little

bit there, get the right fertilizer mix. And so we can get things done. And then you should see ultimately effects from that. And that's kind of where my biggest passion really is, on the educational side and getting into the community side and, and breaking some of that. Just the fear people are so intimidated by it. And as soon as they realize that these are simple protocols and they're simple concepts, the words might be hard to learn, but the, the underlying principles are, common to everyday lifestyle.

Dr. Joseph M. Raffaele, M.D.
Well, yeah, you've definitely helped to, to sort of break it down to more understandable kind of subject area, and I encourage people to go out and get your book Breaking Alzheimer's cause you know, you do a great job there too. Thank you again, Dayan.

Dayan Goodenowe, PhD
Thank you so much, Joseph. Okay. Have a great one.