Introduction and guest background

it's possible to regain cognitive function even in an Alzheimer's patient. There seem to be variations. I'm not an expert on it, but these multi-modal treatments or multi-domain treatments seem to be the real key.

Not only can you find the inflection points, but they should be able to guide treatment. If you can find out what it is that's changing at that time and you can detect it the network methods, dynamic network biomarkers I'm really interested in that use, they measure multiple things and how they're correlating together.

I'm definitely a network person and not a single biomarker person, but I'm interested in there are Those have been shown in some experiments with other conditions that they can predict proximity to a tipping point, you know, so they're really good for not only predicting proximity, but they can kind of detect what's going on.

Welcome back to the Think Well, Age Well podcast. I am your host, Dr. Heather Sandison. And today, I am joined by Dr. Stephen Chamberlain, a truly interdisciplinary physician scientist and assistant professor of neurology at Oregon Health and Science University.

He brings together a rare mix of naturopathic medicine, acupuncture, computational biology, and more than two decades of data science experience across multiple industries.

At OHSU, he completed advanced training in bioinformatics and complementary medicine research. He's contributed to studies on botanicals for cognitive resilience and serves as the geneticist at the Oregon Alzheimer's Disease Research Center.

He's also the principal investigator on a five-year NCCIH grant studying salutogenesis, how health is restored, using multimodal non-pharmaceutical interventions for age-related cognitive decline.

He teaches AI and machine learning, continues a clinical acupuncture practice, and is working to build whole-person models that help us understand why some people decline and others age well.

So Dr. Stephen Chamberlain, welcome to the show. Thank you. Thank you. I want to dive in to first, you know, how you got into this. How did these two paths of data science and naturopathic medicine and I mean, it's more than two paths, right?

Acupuncture and traditional Chinese medicine. How did all of this come together for you? So that that goes really way back to my dad, who was a physician and a psychiatrist.

And he, he worked at a hospital called vinegar foundation in Kansas of all places, but he was a really early, he was involved in the American holistic medical society.

So he was a very early holistic sort of MD in the late sixties and early seventies. They were doing really interesting thing that things that are like early psychedelic therapy and things like that.

And so he was, I always think of him as like a pioneer in that area. And he was my. inspiration and so I wanted when there was a lot of study of consciousness and things like that and so that was my inspiration I went away to college thinking I want to be a doctor I want to be like that and I got to school it's like well nobody's teaching this so I got I just ended up in research and was kind of drawn to stats and programming.

You know, after I did, I was a biology major and then that sort of led to a career just in data science in multiple places. And I always thought, I'm going to get back, you know, I wish there was a way to get back to what I saw, you know, then.

And then I was here and I'd started developing an interest in trying to go to acupuncture school, trying to switch my career. I was in, you know, lots of big corporations for years.

And then I moved to Oregon, and I went to this conference at NUNM, the naturopathic school here. And I knew I shouldn't go because it would make me want to go to the school.

But I did, and it was transforming the mind. It was called Transforming the Mind, and they talked about it. They had a biostatistician, and he was applying physics ideas to consciousness and to studying natural medicine.

And that hooked me. And then I volunteered at their research center at the HealthCOT for a couple of years to decide if I wanted to go. And then I decided, and I decided, I mean, I love natural medicine.

Salutogenesis and health as a continuum

I like naturopathy and Chinese medicine because I like the integration of the old and the new, but I also liked, it's also like you study every major health system on the planet, you know, with those two degrees put together.

So for research, it's really good too. And I, you know, from the beginning of my decision to go back to school with naturopathy, I, you know, I wanted to integrate.

I wanted to do research. I wanted to do clinical work too, but I really wanted to do research so I could draw on all my computational experience and talk to Heather's Wiki there quite a bit in the beginning.

And then, and she was, she was a big guide for me. And then I took six years off and went to school, got both of the degrees full-time. And then I wasn't sure exactly how the research would open up.

And I came to OHSU, to their Department of Medical Informatics here and did a fellowship in computational biology and biomedical informatics. It was the National Library of Medicine.

So I had been talking to them too for a long time. And I was able to get in and they accepted a naturopath. It's pretty, I think it's fairly open here at the school.

So, and then, and from there I just, you know, first it was cancer, natural products and cancer was my interest. And then I got interested in. Solutagenesis, I heard a talk given by Helene Langevin at the NCC IHIN 2021, where she gave a really nice sort of easy to understand description of…

And it was actually a grand challenge. They wanted people to study that. So that's kind of how I switched from sort of natural products and cancer to solutagenesis and then switch my focus to cognitive impairment.

Let's dive deeper into salutogenesis. This is health restoration. We're both naturopaths. So in our language, this is like the vis medicatrix nature, right?

Like this is the healing power of nature, this fundamental belief system, right? That the body has the ability to heal when we use a whole person model.

And I think that was the belief, you know, it was living in that truth with a capital T that made me open to Dr. Bredesen's approach that maybe think like, maybe this might work because I fundamentally believe that the body can heal itself, the brain not being an exception to that, right?

So I'm curious how, you know, can maybe take us back to that talk where you were turned on to salutogenesis. How do you define it in a way that makes sense for patients and clinicians?

How did she explain it that day where you had that aha moment? She used a lot of pretty pictures, like simple graphics, and one of the things she showed was that health is a continuum, and it has two directions, instead of a binary, sick or healthy.

So there's a continuum, and you can get less healthy along that continuum, and then eventually end up in a disease state, and that if you know where you are in that continuum, it's easier to reverse, you know, reverse the health and that, um, and that there are, you know, it goes in both directions too.

And so it comes from the term was originally coined by a, um, um, by a psychosocial researcher in Israel in the seventies named Aaron Antonovsky. And he actually studied, he studied, uh, survivors of concentration camps from World War II.

And so he was really interested in why are there people that are resilient in that horrible, you know, that really unimaginably horrible situation and some people aren't.

So his focus was more on what are the factors that created that resilience. And then, so one of the things I like is oftentimes people compare it to the pathogenic approach.

So there's the salutogenic orientation and the pathogenic orientation, and they're complementary. They're not one is right and one's wrong, but the pathogenic orientation is all about like what are disease processes and then the pseudogenic is what are health processes.

And then I like there are tables, you know, what is, you know, comparing the two. But one of the things I like is that in pathogenic, you know, in the pathogenic orientation, there are risk factors and you're mostly trying to avoid those risk factors, you know, you're like living.

So, and in that, in the pseudogenic orientation risk factors aren't necessarily bad. And in fact, they might make you stronger, you know, so there's that, that idea that a risk, uh, so they can actually be salutogenic.

So what I like about that is that you're not like hiding from the world, you know, it's like you're building your own health resilience, you know, so.

It's like the hermetic effect, essentially. It's exactly. Yeah, I like that. Yep. Yep. That's the way I think of it. So that's the one. And the other is, I already mentioned that it's a continuum.

It looks at health as a continuum. So I'm really interested in, so I got really interested in computationally that continuum. What is it like? A lot of people think that there are tipping points along that continuum, like you're sort of in a stable dynamic state and then there's a tipping point into a disease state.

You can detect the tipping points and things are more reversible for a tipping point. And I'm also interested in models that look at the whole person along that trajectory.

You know, it's interesting, as you say that, I am thinking back to probably a meme I saw somewhere or something I read in someone's email newsletter, but it was this aging continuum and how at 44 and 77, it seems like people kind of fall off a cliff for some reason.

And you mentioned this in the context of a disease state, and we certainly see that like around a MOCA score of 16 or 18 gets a lot harder to bring someone back.

And so I'm curious, how do you apply this whole-person model, this salutogenesis, health restoration model to aging and to studying brain aging and neurodegeneration?

Whole-person models and cognitive decline

So I know, so I'm working my current research is with a lab model. So I'm actually working with mice and they have cognitive decline too. And so I will say that my, one of the ways that I work with this is I find, I either find it or create populations that have the health restored already.

So that's the way I'm working with it right now. So I'm working with intervention. So in a saluted genesis model,

research model, you aren't, I'm not really studying whether this thing restores health or not.

It has to already have been shown to restore health. I'm studying what that trajectory looks like. So I have to create that trajectory so that in the lab I can set that up and I can create that.

Mice, there are lots of things that have already been shown to restore cognition in mice. And so I'm doing that. And then I have you know, the aging model, you know, so the side-by-side aging model.

So one of the things I do a lot of molecular omics, you know, with different tissues. And so I'm looking at how does, you know, what all is changing along that trajectory, that health trajectory and the trajectory of getting less healthy.

And one of the questions the NCCIH has is, are you reversing things, whatever you're looking at? Are you just reversing the decline, or is it a different process altogether to restore health?

And once your health is restored, are you healthier? Is it stronger than it was before your health declined? What's the answer? What's that? What's the answer?

I don't know yet. I just finished my experiments and I'm working with the data right now. But the other place to do that is with data repositories and real live data, clinical data that people have, which is one reason I reached out to you.

And so I'm kind of looking for people You know, people that are experiencing this, seeing this in clinic, there are a lot of, we have a repository here, you know, for Alzheimer's people, just clinical and tests and, you know, all these different things.

And there's some big national repositories. And so that would be another way. So I'm just looking at longitudinal data. But the main thing is that I'm, you know, I might have a primary outcome of cognition, you know, how either that's getting better, that's getting worse, whatever it's doing.

But I want to track the whole person. What is changing along that? So it's not defined by all of the other systems necessarily. It's defined by the condition of interest, which is cognition.

But how do all those other things change? And I do a lot of network analysis. So how do they change together? How are they changing together? And then multi-scale.

If I can get omics data, I can't. I'll use that along with. you know, any data that I can get, but really trying to represent the whole person is the idea.

Okay, so you are studying these trajectories of cognitive health, but really whole person health, that both improve and decline, they both go in both directions, mice and humans, right?

So what have you learned so far? I think some of these big questions that you don't have answers for, but what has this taught you so far about aging and the possibility for improvement?

Well, so I know, so yeah, so I'm new still to this and so I haven't analyzed the data from my experiment, but I know one of the things, so I started off, so cognitive non-neurodegenerative cognitive decline is more acceptable that you can reverse that.

And as you know, it's not really believed that you can reverse Alzheimer's cognitive decline as much. That's true. It's changed quite a bit in the last couple of years.

And that's what's drawn me in. The interesting thing is that all of these clinical repositories with human data, they have reversion rates. So they have certain rates like the ADNI, the Alzheimer's Disease Neuroimaging Repository is a really big one used for research, a national repository.

And it has like a 15% reversion rate. And I'm not sure from what… Can you define reversion? Reversion is just that their cognition is improving, you know, and they get so I've been, you know, I've been Looking at the research and most of the research is interested in, I mean, there's a lot of interest in predicting these trajectories, especially for Alzheimer's, but the interest is when are they going to hit dementia?

Or when are they going to decline worse? And they always throw out the people that get better. Not always, but I mean, the ones that I've looked at, they exclude them.

And I know that that's not the focus. There's a lot of question people don't know why that is. I mean, because this is observational data mostly, and so we don't know what people are doing, but they think that it's not what they're interested in.

And we have that here in our data. So the OADRC that I work in has a data repository. It's part of the national network, and we have data for Alzheimer's people that can be used for research.

We have them here too, and everyone knows about it. We even have names for them. Nicknames are called the bouncers or the wobblers, because they go back and forth with their cognition.

And there's a need to study those. People feel like there's a need. And that's how I got started. To study solutogenesis, like I'd said before, you have to have a population that gets better and a population that gets worse.

And so that's easy to do in the lab with age-related cognitive impairment with mice. And even age-related cognitive decline in people is, I guess, more acceptable to be restored.

But I started out thinking, well, I started off wanting to study, you know, apply seletogenesis to Alzheimer's and like, well, there's not supposed to be any population of anybody like getting better.

And that's what led me to looking into these databases and finding, and then you and I know, you know, Dean Ornish and Dr. Bredesen and then Dr. Isaacson and, you know, Florida.

So that's one of the reasons I've reached out to you. There are people that are publishing these results, and then these repositories have people that also get better that no one really studies.

Well, even the pointer trial, right, that was out recently also showed that. What patterns or hypotheses are emerging from these cases where people on the path to dementia are improving?

So most people, when I talk to people, and I haven't dug into the data yet, the human data, but most people think it's an error. Like it's, you know, that's mostly, or it's like they, you know, they just didn't do a good job at, you know, administering the tests that day or something.

Oh, good days and bad days. Right, and people do go up and down. Yeah, so nobody really knows, but it's ignored. That's pretty certain that they ignore that group of people.

So that's the niche I want to work with, but that was required to study pseudogenesis. But there are people, like we just said, there are people like you that are reversing cognitive impairment and Alzheimer's.

Reversion, recovery, and tipping points in Alzheimeru2019s

Well, and before we hit record, you mentioned personal friend of yours who you know had recovered some cognitive function. So what do you think is driving an ability to recover function?

Because you agree, right? You're part of the reason we're having this conversation is because you agree this is possible. It's possible to regain cognitive function even in an Alzheimer's patient.

Maybe not all of the way after a certain point. It's not guaranteed certainly. But what do you think drives that

potential ability to recover function?

I think it's the multi, you know, there seem to be variations. I'm not an expert on it, but these multimodal treatments or multi-domain treatments seem to be the real key.

And I thought I'd heard like the finger people are starting to do that combined with the new medications. I don't know. I'm not an anti-medication person, but I don't know.

But so I think that's really key. But I think there's, you know, you'd know more than me. I think there's a belief that those multi-domain approaches are not just working on the neurology.

They're working on multiple systems that restore cognition. And I'm really interested in, you know, I've mentioned this before, tipping points in neurodegeneration and resilience and all of that.

And there are papers about that. And then would you venture to guess what early signs or biomarkers seem most promising for understanding where that inflection point would be?

So that's my area of research. That is the core of my area of research. I don't know yet. So, I mean, I know people say, you know, cardio metabolic issues are going on too.

And, but I'm new at it. And, but my interest is using, you know, complex, you know, network models to find those points. And then those points, you know, not only can you find the inflection points, but they can, they should be able to guide treatment.

Like if you can find out what it is that's changing at that time and you can detect it, there are methods, there are network methods. dynamic network biomarkers I'm really interested in that measure multiple things and how they're correlating together.

I'm definitely a network person and not a single biomarker person, but I'm interested in those have been shown in some experiments with other conditions that they can predict proximity to a tipping point.

They're not only predicting proximity, but they can detect what's going on because they're usually based on omics data. So they can guide treatment and guide their experiments, which show that things, you know, conditions are more reversible before the tipping points, which is just sort of common sense.

But they, but that's, so that's my interest. So it's not exactly what it is as much as it is like characterizing that trajectory from a whole person perspective.

And in a, you know, sort of complex multi-scale, you know, multi-omics, maybe omics, but a whole person. So there's something called network physiology, which this intersects with, which is kind of new.

And then NCCIH has just funded another project at Stanford, started in August to define the physium, which has a model of the entire physiological system in a person and how it interacts.

So it's a dynamic model. And so that intersects. So my thought is, you know, I mean, I'm doing, I call it a poor person's version of that, just doing correlations.

But the idea is like, how does this thing change over time? And can you detect- Multiple inputs and like just, I mean, innumerable variables. We do this at a, I mean, it's costly, it's expensive, right?

But we do this at a one-on-one level where we get tons of data about people. And then we look at it at multiple points over time. We're talking toxin data.

inflammatory data, nutrient data, infectious burden, full immune function, understanding, you know, like all of these things that we've, I've listed these things in the book and also on this podcast before.

But then as a provider, I'm going to put all that in my brain and kind of make sense of it and then create a treatment plan. As you're describing this, it sounds like, you know, sort of leveraging that sort of idea, this complex system science approach with lots of data.

But essentially plugging it into like an AI model, I have to imagine that this all gets a lot easier, a lot less expensive to use this whole person multiscale model to transform how, not only how we study cognitive decline, but then how we test interventions, certainly, and then how we deploy them at scale so they can really have an impact.

Yeah, I mean that was one reason I reached out to you because I don't have clinical experience with this and I have computational, I have my friend who I've seen do a lot of this and have a miraculous result.

But I wondered and I know I've read your book and I know I'm familiar with all of the things you look at with the approach you use. Yeah, and my question was, you know, is there a need for a complex model or do you do well, you know, just kind of evaluating the data, you know, clinically?

And then, of course, there's, you know, the way I see science is, you know, you have the luxury of building these complex models that, of course, aren't practical in clinic, and then, you know, you have to figure out how to translate those, you know, which usually means finding a subset, you know, of those things that are easy to get, you know, in clinic or collect in clinic.

Um, but yeah, that was a question. I mean, that, that was one of the things I wanted an opinion from you who does this kind of thing. You know, is there a need for a complicated model which puts all these things together and looks for tipping points, you know, or are you already doing that?

I think the need, and we're in some ways trying to respond to this, but the need is to make this accessible because it's a thousand dollars to see me as a doctor, right?

It doesn't, and my, I can only see eight people a day and that's a, that's a full day for me because it takes 90 minutes. to sit down and learn about someone's health, and it takes another 90 minutes to go through all this data with them and describe it in a way that makes sense so that it's motivational to make these changes.

And that is not accessible to everyone. So how do we create a tool? How do we leverage the technology so that this can be accessible to anybody who is Medicare eligible?

Yeah. Because it's so expensive. It's such a horrific disease. It's so costly to care for people. I know very well how much memory care costs. I know how much it costs to deliver and I know how much it costs for patients.

Yeah. But that's the financial cost. Now, the burden to caregivers, the cost that doesn't get counted as often, the burden to caregivers, the absence of that grandparent in the lives of the grandchildren, the absence of the mom in the lives of her children because she's in that sandwich generation having to care for her mother or her father.

There are so many costs to this disease that, yes, I think any effort to scale what Dr. Bredesen has created to make it less expensive, more accessible, easier to deploy is a very worthy endeavor.

Yeah, that helps. Yeah, we are starting to offer the guide. Guide helps a little bit. Guide is basically some care management. It doesn't have to be through a clinic, but we'll have a nurse practitioner joining us who does bill Medicare, and she'll be deploying the Bredesen approach.

Plus, we'll have this additional care team basically clinical coordination, happening to support with respite care and Meals on Wheels. And, you know, it's so challenging to have dementia, to be elderly, and then to navigate the healthcare system, even if these resources are out there for you.

Multi-domain treatment and biomarker discovery

just getting them, getting access to them, doing the paperwork, getting through that process can be, it can feel

insurmountable, especially when, you know, your partner has got diabetes and is in pain or can't hear and, you know, they might have full cognitive capacity, but they've got these other issues that are going on.

So it can be really challenging. So I do think that we desperately need solutions that leverage technology and computational analysis. Tell me how. Tell me when.

One of the things I'm doing now, which I mean, of course, the stuff I'm doing with animals, that is not translated yet. I mean, some of the things that we're working with, the biomarkers with the mice are translatable and clinic like CRP and I work with 8-OH-DG and the plasma too.

But I'm also trying to get some money now to do work with our data repository here, our people data, I don't like the word human, like it sounds like people are, I don't know, people repository.

So, um, and, and that's to work with to do untargeted, either proteomics or metabolomics in their plasma, you know, which is clinically available and maybe not too expensive, you know, to do, and might capture a broad range of things, you know, so that might be a translatable thing.

I'm not sure. I mean, I know what we pay. I mean, it's $200 or $300, you know, something like that. And it can be pretty holistic. So that's kind of what I'm working with right now with our data repository.

You teach machine learning and how to interface with AI. How do you see these tools helping us to understand these complex interventions, complex system science, recovery patterns, the trajectories, and these tipping points?

Not all these things are linear. No, they're not. They're not linear at all. Yeah, so that's why Dr. Longovan put that grand challenge into 2021 because of AI.

She's like this, you know, it's always been and I You know, I, I, I did research when I was in school, which was oh nine, you know, to 2015 health care research Institute.

And it was always an issue. Like, well, our medicine has multiple interventions and everybody's like, you can't study that with a conventional, you know, randomized control trial.

why it took so long for Dr. Bredesen's first trial to happen. Yeah, you've heard that story. Yeah, I have. It's such a breath of fresh air, right, that the trend has really shifted, that everyone is accepting now.

No, we actually don't want to limit the variables. We want the synergistic effect of multiple interventions. Yeah. The work I'm doing right now with the animals, that's one aspect of it, is it has multiple interventions.

I'm trying to restore health and study that, but I'm also doing it with multiple interventions and look at how they interact. Anyway, the AI is just the compute power is there now and the ability to handle very large quantities of input variables.

That's why You know, she put that grand challenge forth and we, we got, my department actually got a grant on that grand challenge, which is different from my grant, which is a data generation.

So she just was asking people to collect. All of the data they can think of, this is for people with diabetes, but collect that data on them for a year.

Just everything, lifestyle, lab tests, imaging data, wearables, all of that. And now AI can handle it. I mean, there are methods out there, deep learning and all that.

So AI means a lot of things. And you know, chat GPT is kind of the AI people think of now. I think, I don't know. I don't know what people think. Yes, that's certainly my experience.

Like you say AI, and I think of my relationship with Chad GPT. Yeah, so that's generative AI. So that's the kind of AI

that will answer questions and things like that.

So anything that's machine learning and predictive is technically AI, artificial intelligence. But machine learning has been around for a long time. There are simple logistic regressions or simple methods that have been around.

Support vector machines, all of that is AI. And then neural networks. I've been around a long time too, but they didn't work very well. And then, then when the compute power got better around 2010 or 11, they were able to build much bigger neural nets with lots more, a lot more connections.

And that's when deep learning came and deep learning is where everything changed. And so deep learning are just really gigantic neural networks with lots of layers and lots of connections in the model.

and they can pick up all these nonlinear relationships. And then deep learning can be predictive, and it is in healthcare a lot of times. So you can feed in image data where a variable is a pixel, like in an image.

Or I work a lot with RNAseq, which has 15 or 16,000 genes expression level. And so you can feed all of that in, that's 15,000 variables. And so And then there's multimodal where you put the imaging and the RNA-seq and the clinical data from the notes.

And then there's mining of clinical data with AI to get concepts out of complex. But the AI, even like chat GPT, and that's considered natural language processing, even chat GPT, those are large language models.

Those are deep learning neural nets. They're all deep learning neural nets. That came, you know, that was, like I said, the compute power got to where it could handle creating larger neural networks.

And that's when everything changed. And so do you see that playing a role in like what stage, like early detection, personalized protocols so that we can be more precise?

Do you see that in helping us predict who's most likely to respond to different interventions, whether it's a medication or a lifestyle intervention? Yeah, all of that.

All of that and more? Yeah, all of that. So I think definitely early detection. So one thing that does really well is it takes in more data. So you can take in a lot more data and get more accurate at detecting.

I know in Alzheimer's, I've been interested in trajectories, and those are really long, as you know. People are really interested in predicting what trajectory you're going to go down or what path from a point for years out in the future.

So they're good at that. So there are levels of models. There are predictive models, which risk is a really common prediction in health care. But you don't really know what to do with that.

So that's one of the things that I teach in my class. I'm really interested in decision science. How do you make a decision from a model? Okay, it's great.

You can predict all this stuff. And people get all caught up and, oh, I can predict this and that, but it doesn't ever solve a problem. And there's an actual problem in healthcare with people building models and they don't get used because people are so fascinated with just predicting something.

But then there's beyond that is a prescriptive model. And a prescriptive model tells you what to do, you know, recommends a treatment. And I did all of that.

I came from banking. Actually, before this, I was one of my industries and we did all that. kind of at the time we were considered ahead of healthcare as far as our sophistication.

And we, we did all of that, you know, we would predict, you know, what's the net income from all these different options and things like that. So, but that's going on now.

And I, but, you know, I mean, so I think, you know, clearly a model in my mind would identify early detection, but beyond that, you know, where are you on that trajectory?

You know, are you near a tipping point? Are you about to tip and are you, and what you need to reverse that proximity? And so the model should be able to, if you're doing omics and things or even proteomics from plasma, there are ways to see what groups of proteins are sort of changing together and what function that might belong to.

And then that might guide what treatments would be appropriate. I mean, I know. Oh, it's just the multi-domain. It's like, well, everybody should exercise in ether.

Well, this is my next question. Based on everything you've learned from your acupuncture background, your naturopathic background, all of the computational data analysis that you've done, what are the lifestyle factors that seem most impactful for maintaining, optimizing, restoring cognitive health?

What are the top things that you would suggest someone do?

AI, network physiology, and scalable care

Yeah, I'm still, like I said, new to that. I know I'm doing exercise and a botanical with the mice. Does it work for the mice? Yes, it does. There's a huge body of evidence that it does work.

Both of those work for the mice. Nobody's ever tested the two together. So I'm still in the process of seeing what my data said, but that's why I chose those two, because there's already a huge body.

We do here, we do a lot of Centella research here in Ashwagandha. and very much so. Even if there's an Alzheimer's mouse model called 5XFAD, which we use a lot here, and it does so with them too.

It reverses their cognitive decline. So, exercise and herbs. You heard it here first. Yeah. Well, they haven't been tested together as much. I mean, They have, I mean, like my friend did, my friend who you had mentioned, who has miraculously reversed her cognitive decline and held it stable as a huge exerciser.

And she continues, she's very motivated to exercise. I think that's got to be one of the number ones. But again, that's not, I don't have any answers yet for my own work, but.

Um, but I, what I think is that it's the common, it's the combination of things, you know, I really, that's always what I put in my grants. And that's what I, I, you know, I've heard that from our vice chair of research here that, um, they're very much open that people here in our neurology department are very much.

into the multi-domain and very much on board with that. But they don't study it and they don't know how because it needs new methods and it's not. But he'd mentioned at one point that the problem with that is you see these effects with multi-domain and then everybody goes out and studies the single intervention and then they don't work when they look at them individually.

So I'm really big on synergy. I've always been a synergy. When I first came here, I was, I did cancer research and I was, I didn't just study, I was trying to predict synergies between natural products and cancer drugs.

I wasn't just trying to find a new drug, you know, from a natural source. I was really interested in synergies because there were, there was evidence in cancer that certain, certain like curcumin when it's taken with a cancer drug makes the drug more effective in the cancer tissue and protects the healthy tissue at the same time.

There's amazing things in plants. I did find I studied the effect on neurons of centella in vitro. It looks like centella is anti-inflammatory and also works on reducing oxidative stress, but centella is also It's also used in derm applications.

And when I treated these neurons, their collagen turned on like crazy. And no one's looked at that as far as is that

affecting cognitive impairment. But we have seen that Centella increases the density of dendrites.

And so it's actually changing the shapes of the neurons. So it seems like the neuron might want to restructure the extracellular matrix. So I actually did it.

Our listeners might know centella asiatica as go to cola. And this is an often used herb in Ayurvedic medicine and traditional Chinese medicine throughout Asia.

And we know that it's very helpful for wound healing, skin health, antioxidant, anti-inflammatory. It helps with like microvasculature and potentially vascular support with mood and then cognition because it's supporting BDNF.

is potentially one. I mean, certainly if you have better circulation and less anxiety and less inflammation and less oxidative stress, you might get downstream effects that include cognitive support, but it also directly impacts BDNF.

One of the things I was interested, so I really focused on the interactions between the compounds in the plant, because it's got hundreds of compounds in it.

The whole plant rather than the plants. Yeah, the whole plant, yeah. And we did both. There's a few triterpenes, which they think are the active ingredient in centella, and there's cafelequinic acids.

And so we looked at those separately. We combined just those, and then we looked at the whole plant. And so we got an idea of some of the interactions.

But one of the things I did was It seemed to me like, because I did RNA-seq, I looked at sort of untargeted, like all of the gene expression going on.

And then I mapped that to pathways and kind of figured out what are some of the functions that might be activated. And it looked to me like some of those functions were working together.

So I thought, well, how? you know is there is is there a wisdom of the plant is it like making and so i did statistical tests of randomness to see like are all these things you know that are being turned on by this plant just random you know randomly happening and they weren't you know they they were not they would not the chance that that those are all happened by random chance was like less than five percent something like that so so there um so that was another that was another thing i thought was cool but um So, yeah, so I, you know, at least at this point, my whole thing is like the interaction, you know, the synergies between things is what really works.

And that's why I think, you know, doing multi-domain lifestyle stuff with a medication might be okay or might actually make… I'm all for, like, if somebody has to take a medication, can you make it work better and have less side effects?

Of course. Yeah, same. What gives you the most hope right now in the Alzheimer's research landscape? Oh, the multi-domain treatments by far. Yeah, by far.

Yeah, I'm not, I mean, I'm aware of the drug things. Nobody seems happy with the drug development, actually. I mean, that I know. I mean, no matter where you come from.

But maybe, you know, if you combine some of those with a multi-domain, you know, they might like work really. I really think, you know, the amyloid, I mean, at least my framework is that amyloid tau, these are there to protect the brain, right?

They're antimicrobial. They engage metals in interesting ways. They are there to protect the brain. And so if we just take them out without addressing the toxic exposure, the oxidative stress, the infectious burden, then we just end up with a less well-protected brain.

But if we can first kind of do our work, clean up the messes, stop the exposures and the burden, then what we can

do is we can turn off that microglial activation, right?

And then if we get the amyloid out and there's not as much to protect us from, fantastic. Maybe we're in a much better place. I think that there could be wonderful synergy between those things.

But if we just go in and rip the amyloid out, And that doesn't seem to help most people. I agree. And that can actually be really harmful. Yep. No. Yeah, I know.

I hear that.

Lifestyle, herbs, and brain health routines

And I agree with you. They seem so complimentary and like the neurogenic effect of exercise and all. Like if you, you know, getting them out is great, but then repairing everything, you know, it seems like the two would go together really well.

Is there a diet that you see work best in mice? That's a good question. I haven't, if I do more mice work, I might do the diet. I haven't looked into that as much.

I am interested in that. I know that there are some people that are doing the multi-domain are using very different diet approaches. And so that's a really, yeah, I am really interested in that.

And diet is definitely something that's not too hard to do in the lab, you know, in an experiment like that. Exercise has turned out to be much trickier than I thought in a lot of ways.

I don't know, because it affects a lot of things. It definitely, so we put the centella in their drinking water and it affects how much they drink. The ones that are for some reason, so the mice that exercise tend to drink a lot less of the water, you know, the centella water.

And, you know, we do for memory, we do something called the Morris Water Maze, which is a swimming test. And so the mice, you know, the exercise mice are in a lot better shape, you know, theoretically, you know, for that swim.

And they're natural swimmers and they float. It's like it's not a risk to them, you know, to swim. But they, but so, and there's, you know, exercise is not a linear dose effect either from what I can see in the literature with mice.

Like there's a sweet spot and older mice, if you exercise them too much, it actually hurts, you know, and so. Yeah. Yeah. And then, and then it can, the neurogenic effect can take, be delayed, you know?

So when do you test? So I've run into some issues with exactly how do you, when do you test them and how does it, I just learned it's, Interact, you know, studying interactions even in the lab is very complicated, much more complicated than I thought.

And because you just have to know like how do those mechanisms interact with each other and when do you test and what's the right like the time. I think Centella, I mean, we've done other dose testing with Centella and it's more linear, you know, like the more they drink, the better their memories.

But it's also interesting. This is a tipping point. We've done tests where we've given Centella at different ages, you know, throughout the age of the mice, and it doesn't do anything before about 12 months.

Like when they're before middle age, it doesn't make a younger mouse smarter. You know, it only does it once they've started to decline. And that's, I've seen that.

I mean, I've seen other researchers that have seen that with other natural products they're using for memory with the mice. That's interesting. It's almost the antioxidant.

It's the anti-inflammatory process that's actually beneficial. And if you don't have a bunch of inflammation or oxidative breasts, then it doesn't have anything to work on.

There's no delta. Yeah. And that's a total tipping point. So to me, that's a tipping point. That's interesting. And I'm sure you can pick that up somehow.

What is it that's telling you, okay, centella wouldn't be worth it to give right now? Or maybe it would be. So Steve, I ask everyone this, but what brings you joy at this stage in your life?

All of what I do. So I am 67 and just kind of at the beginning of a career. It's taken a while. Like I went, you know, I've been in school and doing post-docs and stuff for like 15 years, maybe now.

I always, you know, I just got married. I got into a relationship late in life. I love meditation. You know, I love nature. You know, I'm here in Oregon.

It's unbelievable. And I go, you know, we go all over. We travel, we camp, we hike a lot. I do all the multi-domain things. I box. I like martial arts and boxing.

And this isn't a boxing accident. OK, you're not getting traumatic brain injuries. Are you in there? No, I try not to get hit in the head too much. Not that kind of boxing.

Yeah. So I- What's your routine? What do you do for your brain health based on what you wear? So I take supplements. I actually just took the supplement designed by Dr.

Bredesen for the last month. I've taken different things. The neuro Q. Yeah. And it really, I really, you know, we had our top like Centella researcher here did a grand rounds and she was talking about, she was doing just talking about the literature with Centella and Ginkgo and then coffee fruit and curcumin.

She's talking about the research and at the end she showed that supplement. She said, She kind of picked it out as what she thought might be the best, you know, supplement for me.

And so I tried it and it really made a difference. And so I do, I do supplementation, but that's not, I'm not all, I'm not a fan of just doing supplementation with everything else.

I do exercise, I box, I hike, I lift weights and I keep my mind active. You know, I really try to study. I love to learn. I try to keep, you know, keep studying and learning new things, which my job is really good for.

And I get up in the morning, I meditate, I sometimes do pretty intensive mindfulness retreats, which are very good, you know, for that. And I love music.

I do. So, you know, I get up and I exercise and I do meditation, spiritual connection, you know, aside from religion, but just like that connection to everything.

Nature is one place I really like. I live on the edge of a forest in Portland. You can live downtown and be on the edge of a forest. Exercise though, I have to say.

I'm pretty good with my diet. I've learned not to be too strict. I mean, that's part of it. When I first got into naturopathic school, I drove myself crazy about being strict, but I do.

You know, try to do smoothies, try to get, you know, a bunch of veggies in every day as their core and protein. And I do do better with low carbohydrate, you know, diets, you know, leaning towards the diets.

Yeah. Yeah. Yep. Yep. Definitely.

Closing reflections and listener call to action

Steve, it's such a privilege to have you here and I'm just so grateful that you brought such clarity and curiosity and scientific depth to this conversation around like AI and the data and what it means for cognitive impairment as people age.

It's really fun to talk to someone whose work sits at this intersection of data science, natural medicine, neurology, human resilience, aging. And really, I think that what you've illustrated is that there's this potential for understanding cognitive health in a really new way right now.

Your focus on pseudogenesis and this whole person modeling and this, you know, again, this possibility of cognitive improvement rather than inevitable decline, it's so refreshing to hear and to know that this is being represented in the research world.

And there's this reminder, I think, throughout our discussion here that the brain is dynamic. It's interconnected. It's far more complex than we might realize.

I have a reverence for it certainly every day, but also far more capable of repair than we've been taught to believe. And so I hope that everyone who's listening, this encourages you to think differently about how you're aging and to question the assumption that decline is unavoidable and really to explore what the possibilities are when we think about the entire system and we do exercise and we think about these herbs and how we can leverage them to really optimize as we grow older so we can think well and age well.

So thank you, thank you, thank you for joining me today, Steve. Is there anything that you want to leave our listeners with or any way that they can learn more about your research or about you?

I think if there's any way, I don't know how many people have, I've had several people with dementia that I, you know, in one way I had to care for and I know about the resources.

If there's any way, you know, to support resources for people that do have cognitive impairment and might not have anybody, you know, like family don't have family around or they family, you know, doesn't want to deal with them or something, you know, do that.

Like there's a need for that, like to really support people that don't have anybody, you know, with cognitive impairment. That would be my urging for people.

Yeah, what a compassionate answer. Thank you for the work that you're doing. And thank you for helping us to just illustrate and illuminate that there's a future where cognitive resilience isn't just the exception, but the expectation for everyone.

Thank you. Thank you. Thank you, Steve. Such a privilege having you here. Yeah, thank you. Thanks. Thank you so much for listening to the Think Well, Age Well podcast.

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