Introduction and epigenetics overview

So it is great to have you on camera. First of all, thank you very much for for doing the this, episode of the Telomere Summit. And I'm really, really looking forward to being on the other side, as we've heard the podcast before.

And you always ask great questions. But I'm really looking forward to hearing about your new study. Tell us a little bit about your new book, and everything that you're doing in epigenetics.

As I kind of think of you as the epigenetics and functional medicine sort of maven, out there. So I'm really looking forward to our discussion. Awesome. Great.

Yeah, it's great to be here and to be on the other side of the microphone with you. You've been doing, you've been in functional medicine for a long time and doing really interesting research.

And you had actually been on the epigenetics train before the clocks came out. Where, you know, looking at the effect. And that's always been the mantra, you know, genes or the gun lifestyle pulls the trigger.

We know it's through epigenetics that it does that you've been involved in and looking at the effect of diet, exercise, lifestyle, etc. on, epigenetic changes, affecting, you know, other, more harder markers, so to speak.

But it must be exciting. Must, must have been exciting for you to then see this sort of metric come out the clocks and. Yeah. Why don't we talk a little bit about just briefly what DNA methylation is?

Sure that, you know, Ryan Smith on, talking about that as well. But I think a little bit more detail in your perspective on it, as a practicing clinician and so it's used to be great.

And then we'll talk about all the other stuff that, that we definitely need to get into. Yeah, absolutely. And listen, Joe, I just want to invite you to interrupt me if I if I, go into an extensive sort of useless soliloquy, just interrupt me or or if it doesn't make sense.

But it is. It's true. It's a it's a passion project, and it's one that I think is extremely important. And I do think, those of us in functional medicine need to embrace epigenetics, looking at epigenetics.

And now that the tools are becoming available to us because they weren't for a long time, I think we absolutely have to be early adopters in this arena.

We have in functional medicine, you know, been been talking about neutral genomics. We've been talking about diet and lifestyle influencing genetic expression.

A lot of talk around that. And I and of course, it it's it's important and it warrants talk. But we need to know are we actually doing that. Are we influencing genetic expression.

And that's where the definition of epigenetics comes into play. Because it's really epigenetics is the whole field of what regulates gene expression. So it's getting in there and looking at the biochemistry of what genes are on and what genes are off most often.

Well, I would say by and large, at this point in time, the best way that we can do that is by looking at DNA methylation. There are many epigenetic marks as you know, we mapped the genome out.

It's what, 23,000 plus genes? It was simpler and less impressive than we anticipated. And and that's when

epigenetics, I think, blew up because we realized there wasn't this really just one gene, one disease.

Road map that we had anticipated finding, and then actually after Gene, after that, we sort of went headlong into looking at single nucleotide polymorphisms and we were, you know, early adopters and functional medicine of considering those.

At the time, I was in the laboratory and we were looking at a lot of, you know, amino acids and, and different proteins and organic acids. And so on and so forth.

That would be products of, these gene mutations, these snips. And we anticipated seeing, you know, wild changes there. So if somebody's got AFA mutations or C, OMT, etc., etc., etc., you know, we should see the end products also change and you know that was kind of disappointing as well.

You know, I don't know if you were doing that in your practice, Joe, if you were looking at snips and sort of expecting to see, you know, consistently elevated homocysteine gene or maybe low adrenaline, etc., but, we weren't so that really wasn't it wasn't as satisfying as we thought that it would be.

Well, we shouldn't have expected it quite as much as we did. I did as well. But if you look at the literature, the studies that sort of supported those associations, the associations weren't as strong.

They were very equivocal. Right, exactly. Yes. They're extremely equivocal. Yeah. And I and I would say and yeah, you're absolutely correct. And I and I would argue that some people might argue, but I would just point out that I think some of us were thinking about these things even before the larger Gwas studies came out and so forth, but absolutely.

Yeah, very equivocal, which means that there's this other thing happening. There's this other biochemical, or multiple. There's other things that are going on that are influencing Gene.

And then, you know, the, the expression of gene and, and enter epigenetics, you know, really enter our thinking about, epi above, you know, gene genetics, the gene.

So, so, so that biochemical regulation of the of the gene of the DNA itself, what's on what's off. And and and it's all over the place. So the, you know, the histones are the proteins that the DNA is wrapped around.

DNA methylation and the agouti mouse model

And, you know, that can be regulated. It can sort of open the DNA and, and allow for that DNA to turn on more readily. And then there are methylation groups that will sit on different regions of the DNA.

And you know, depending on how many methylation groups there are or methyl groups there are and and where they're located, it's going to influence how whether that gene is on or completely off and how strong it's on.

And, you know, enable transcription factors to get in there. And then there's other, you know, there's acetylation and, and, and ubiquitination and just all sorts of, little biochemical tags that can happen and regulate expression.

The so the best tool out there that we have, the most reliable and consistent is looking at DNA methylation. Also I would argue, I mean and our our knowledge is going to change clearly.

But you know, the enzymes involved in maintaining the, the the methyl groups, the pattern of DNA methylation are, right there in the mix during cell division, sort of maintaining those marks over time and, you know, through, you know, vertical and horizontal.

So, so in daughter cell division within us. But then also what we can, you know, pass on to our offspring. So there's resilience to DNA methylation that we don't exactly see with the others.

I should also throw in RNA as well. RNA or small RNAs can can get in there and influence things too. And they're not sort of right in that genetic material.

But, DNA methylation plays a massive role in cometo genesis and embryogenesis. And then on down the line and the whole aging journey and, you know, the chronic diseases of aging, etc., it just it plays a big role, and it seems to be a major player in the heritability of these patterns.

And we see subsequent in animal studies and in human studies, some of these patterns being carried for a long time. So it's just an extraordinary opportunity for us finally in our in our practices and in the research setting to get to look at what's happening and how we're influencing, how environment is influencing gene expression.

And I think this is where the rubber meets the road. I mean, I think it's it's just extremely important. Yeah. So I mean, I guess, you know, the the DNA would be sort of the hardware and the epigenetics is sort of the software.

It's not exactly that, but it's it's good. That's good enough malleable than the DNA. And, and although, you know, look, yes, we're probably learning that your DNA is not just about your genes.

There's all these other. What we used to think is junk DNA, but probably yes, DNA is probably correct. That's right. Regulating things. Absolutely. We're going to learn that as time goes on.

I think that's been I think that's been shown. Yes. I think that, the other thing that occurs, which has occurred in almost every advance in medicine, is that you have a technology that allows you to make precise measurements, cholesterol.

We need to have the technology to measure that, you know, same thing with DNA. Now we have the arrays and we have the bio sulfite technique that makes it, you know, accurate and available and affordable.

So now all these studies can be done and, and actually brought into clinical practice, which it has been has been done. I'll get into that a little bit more.

But yeah that's a that's a great introduction to, to to methylation and to you know, these clocks that they're using. And let me actually can I say something and, and is it okay or do you want to keep going?

You can say whatever you want. All right. Thanks. Well, I just want to I want to just underscore how important it is, and then we'll slip back over to you.

I just want to if you haven't. Have you talked about journal in the goodie the goodie mice research yet. Has anybody chatted about that. No. So this is you know, this is extraordinary.

The agouti mice are these mice who have their agouti gene always on. And when the agouti gene is on in mice, they are they they have a very clear phenotypic pattern.

They're obese, they're blond. And then they're, you know, vulnerable to a collection of diseases because this gene is always on. And so what Randy Journal and his postdoc Waterland showed extraordinarily is that they could give the mom the methyl donors a collection of methyl donors in her diet during pregnancy and turn off the agouti gene and get in and and the offspring were then, you know, wild type little, you know, skinny brown brown mice.

I mean that you know, he published they published that in 2003 and they couldn't get it published. I want to say he submitted to maybe 16 journals and nobody believed it.

Nobody believed it. And they finally had to go to, you know, a really pretty obscure journal to get it out there. Now, currently, it's the most cited paper in science, like ever in science, like not even a subtitle heading of science in science because it shows the potent influence of nutrition on DNA expression.

But it also shows how malleable DNA expression is, and that it can have this lasting influence on on the phenotype.

But even the fact that generations. Which is right. Yeah.

That's right. That's exactly right. Yeah. It's absolutely extraordinary. So I think that's a brilliant sort of starting point to show. Hey, this is really important.

And they were specifically looking at DNA methylation. So I just wanted to kind of bring that context in in case anybody isn't aware of it. I think most people are familiar with that, that research, but it's just underscores what a big deal this area is.

Yeah, we hadn't talked about it. And I didn't understand at first. So when you said agouti, but, that's why for our listeners, but, you know, that is sort of paradigmatic of the power of epigenetics.

So, I think it's great that you that you brought that up, you know, every cell in our body has the same DNA, but obviously we have different cells that do different things, you know, very, very different from tiny little cells to huge neurons, huge muscle cells.

And it's just about which genes are getting expressed. Yes. And the fact that I always find it fascinating about how, you know, what happened to the parent prior to, having the offspring that is transmitted non genetically, is, you know, that's just pretty amazing as well.

It's so fascinating. And it looks like, the bulk of our DNA methylation patterns are actually wiped clean. There's a whole DNA methylation, family of enzymes, except for about 30%.

And it's probably in that, that this. But heritability pieces is transferred from, generation to generation. Yeah. So let's talk about your, great paper came out and which was, showed that, you know, everything you do exactly what you said.

You know, we need to look objectively about whether or not we're really pushing the needle here, and. Yeah. And in fact, you showed that, right? Oh, my gosh. It was very, very exciting.

And I always want to just give my, gratitude to Brant X. The CEO at, metagenomics for just, you know, taking a chance.

Designing the methylation diet and lifestyle study

And, and he gave us and they gave us an unrestricted grant so that we were actually able to answer this question. So, you know, just going back again to a lot of us saying, you know, we're influencing genetic expression with our various interventions.

And it's true, but to actually be able to study, and I just a little bit of a background, we created, what we called simply the methylation diet and lifestyle.

You know, years ago we started to think about epigenetics in practice and how we might translate the science coming out in about 2013. A lot of the research, the strongest science was coming out in cancer epigenetics, where we see DNA methylation, the, you know, the the tumor microenvironment takes over DNA methylation and other epigenetic processes with, you know, just this exquisite power, they just take over genetic expression.

They turn, off tumor suppressor genes. So they basically turn off our good genes that take care of us. And they turn on these pro-inflammatory oncogenes.

Study after study shows this in any kind of any tumor type. I mean, it just on and on and on. It's very consistent. And when I really started to grasp that, the next question was, are we doing right by our patients?

Is our approach to patient care, is our approach to thinking about methylation? You know, and supplying methyl donors, B vitamins and folate and betaine and so on and so forth.

Are we thinking about this correctly? Because when you look at epigenetics, you'll see that hyper and hypermethylation occur concurrently. And so some kind of balance needs to happen.

And that that's what prompted us to just develop this program in practice. And then we would also have patients that didn't respond to B vitamins or that, or, you know, a patient with severe, neuropathy and peripheral neuropathy, who, you know, any exposure to B12 just made exacerbated the symptoms.

Like any route of delivery, you know, from topical to I. V., he couldn't handle it. And, you know, why is that? And how are we going to treat it? I mean, clearly this person's got a macro acidic anemia and on and on.

He clearly needs B12, but he can't tolerate it. And so for just a handful of reasons in practice at the time, we decided to create a diet program that's packed with methyl donors.

And these things called these polyphenols that we call methylation adaptogens. But they're, they're, they're epigenetic active. And then we included lifestyle interventions that the literature suggested would be helpful exercise.

We tracked sleep and, meditation. So that we brought into our practice years ago and to varying extent, really all of our patients would have some element of the methylation diet in lifestyle, in their treatment plan.

I mean, it's just a smart, you know, it's a it's a good foundational diet that just has a lot of these methyl, these, these epigenetic active components layered in, but it's low glycemic, it's keto leaning, etc..

It's, you know, it has a lot of the hallmarks of any good diet. And it's up to if you're a vegetarian. And then there's some questions to, to be, to be addressed, which.

Yeah that's right. Yeah, that's a good question. And we should come back to that because you. Yeah. That's right. Yeah it is. It does include animal protein.

So we were using it in practice for quite a while. And the next question is, you know, we're suggesting that we're influencing DNA methylation. In fact, we wrote an e-book on it and we were we were training professionals.

Professionals were interested in this. We did at least two webinars over at the Cleveland Clinic. I, I taught it in South Africa and Ireland and, Australia.

I mean, people like all around the world, including here and at the Institute for Functional Medicine, it was content folks were interested in. But are we actually influencing, you know, epigenetic expression?

Are we changing DNA methylation? And that was when, getting the grant to dive into it was absolutely extraordinary. So we took off in that. And at the time, as you said, the only clock available was the Horvath 2013 clock.

And I and these DNA methylation arrays were not available outside of the research setting. And so we, you know, just moved into that. We we hired the Helfgott Institute out of, National University of Natural Medicine, my alma mater, and Ryan Bradley is the director of there.

And he was my co-pi and he just runs an extremely tight ship. I think we did a really good, solid study. Moshe, stuff from McGill University was our, you know, just really important guide.

He's a longtime epi geneticist, really one of kind of the this the founder of the journal epigenetics, if that gives you sort of an idea of his stature.

And he walked us through our design and, and then we worked with McGill and his lab to engage in data analysis. Just middle Dorf, who I think that that, you know, is a brilliant, you know, gerontologist slash biostatistician.

And he did our clock analysis, you know, through Horvath at UCLA website. And Horvath actually helped, Josh upload and, and, initiate some of our analysis.

So we just we had a pretty incredible team working with us. So, yeah. So you essentially took an eight week diet and had some, was, men, I think all men.

And. Yep. It is a placebo controlled trial. I mean, you didn't have to do the interventions in the other group, but you found, you know, after eight weeks, why don't you take the punch line away?

What, yeah. Yeah. So our big finding, we had our our diet. We had, an exercise component, a meditation component, and we tracked sleep. The we had our nutritionists, we have a nutrition internship program here, and our nutritionists volunteered to support the participants.

They actually had a very dry script. It wasn't they weren't like cheerleading. It was all IRB approved, but they would make sure that the participants knew what they were doing and knew what they needed to eat, etc..

We gave them a probiotic, we gave them a greens powder, and then the control group had nothing, 20 in the control, 18 in the study group, middle aged men.

So 50 to 72. And the reason that we chose, middle age is because that's when DNA methylation really starts to go awry with, you know, it's sort of the volume is turned up on abnormal patterns and middle aged through, older populations.

We didn't include women. I mean, that's this has been a huge question because, our population was too small, our study size was too small to be able to really control for the fact that we would have pre Perry and postmenopausal women.

So we'll we'll absolutely look at women. Obviously I'm a woman. I'm, I'm interested in seeing how we respond to this. But given it was a small pilot study, we just couldn't.

So we tested them, you know, we looked at a whole bunch of things, but one of them included the the Illumina Epic array. And what we found using the Horvath 2013 clock, was that as compared to controls are purchasing events, reversed biological age by 3.23 years.

So yeah, extraordinary. For the it's the first study of its kind kind of remarkable just through diet and compared to the other ones, the trim trial, that was a year that only did one and a half years or so.

It was a smaller study, of course. It's hard to know what to make of that, given the size of it. But it was interesting, and I think you talked about two other studies that were done, but not with sort of, I guess, since you, since your study with, with clocks.

But it's I think, it is a is an extraordinary result. You know, I when I was talking to, to Ryan Smith, to diagnostics about, epigenetics in his, you know, they now have the rate of aging clock, which would be really fascinating to, to use.

Do you still have, biobank samples from this to be able to look at DNA? We should again. We could, but we collected saliva. And I don't know if you talked to Ryan about that.

I mean, that's just a phenomena of having started in 2017. Saliva. It seemed to be a good specimen, but obviously, right now we need blood. I think we're going to be able to use, buccal swab at some point, and that should be as reliable as blood. But, really, we could only reliably run the 2013 clock because it was trained in multiple tissue, including saliva.

Right? Yeah. But I asked you about. You would be nice if you just run we now. Yeah. It was. Yeah, it was a long time in the world of epigenetics. It was a long time ago.

It was. It's, it just things are accelerating so fast in that we are the. We're in IRB, you know, the IRB journey now and we're, you know, going to launch a larger study.

People can go to the web, my website, which is just doctor care fitzgerald.com or younger you program.com. Well hopefully we can list these in the show notes and you can, you know just sign up to get information.

But we're we're definitely in the middle of IRB journey. And we hope to have a rolling IRB so that we'll just be able to research this and tweak it and you know, really do it.

Do it forever. You know, layer in different interventions like to 65. I told you before I, before we hit record that I'm I'm bullish on it favorably augmenting DNA methylation.

So it would be fun I just you know I think sky's the limit. It would be interesting to see whether or not it, to 65 hasn't has an effect. I'm checking DNA methylation on all my patients now.

Okay. And antler length and immune subsets. And, you know, we have multiple interventions here as well, but, you know, there's good reason to think. I mean, DNA length actually is sort of in the, epigenetics sort of arena because it can affect telomere length, sorry, gene expression through the telomere position effect where it loops back, and can affect, expression as far as ten megabytes is a way away from the end of the, megabytes, mega basis.

Sorry. Away from the, from the ends of the chromosome. So, I kind of think of sort of there's genetics and then there's epigenetics. And sort of in the middle is what I call duo genetics is sort of right in the middle there.

It's not coding DNA. It's, it is DNA, but it's not coding for proteins, but it has profound effects on, on, you know, the, the function of the cell, the phenotype, the cell, the, the, gene expression in the cell as well.

So I would be surprised if not through that mechanism, if two other mechanisms, it did potentially have an effect. And, you know, no doubt you can take I talked to the company about doing that kind of a study as, as we mentioned, it's, it'll be less and less expensive.

And, you know, the clocks are pretty tight now, so the coefficient of variation is gotten really tight so that you don't really have to have a large, sample size to, to do some interesting work.

So that could be very interesting because if field is you do much with them in your practice in terms of measuring them or. So now I'm happy to hear you're doing DNA methylation.

You and I have kind of tussled a little bit on that. It's amazing leap. But I'll tell you what. You're going to have a good body of of data. So the next time you and I podcast, I want to, you know, I want to hear about what you're seeing since you're doing both of them together.

I have no doubt in my mind that we'll see that there are closely related.

Study results and biomarker changes

And we may think about how we intervene, you know, given, you know, patterns of imbalance and DNA methylation and biological, you know, the biologic bio clocks versus, you know, telomere length, we may, you know, depending on the individual kind of, stratify.

But there's just no doubt that they're they're very connected. And it's a matter of time before we, you know, understand that. Yeah. I don't oh. Go ahead.

I was just going to say that I think that telomere length, has sort of taken a backseat to DNA methylation, as a biomarker of aging. But I think that's largely because of the very large variation in baseline telomere length coming to this world with.

And so if you take the actual telomere length, it's not going to give you the same information as if you take the rate of change. Yes. Or change from one, telomere length to another.

That's, that's having it's going to have a negative effect on if it gets shorter. But but someone of a certain age could have a telomere length that in years is 15, 20 years younger than they are, but still be losing telomere length at a faster rate, in which case you're you're going to miss that.

So we need something for telomere length, like the rate of aging that they have now for, for DNA methylation. But I guess my point I bring that up is that if it's not actual telomere length, giving the telomerase activator may have profound biological effects that aren't necessarily even picked up in the short run with telomere length.

That's. Yeah, I think so. We may not be using it to measure the effectiveness of it. But if you have a therapy, you know, and pretty much just as in your study showed, I think the overlap between the things that affect methylation positively and the things that affect telomere length positively is almost 80%.

That's right. Everything that's good for you is associated with longer or for you. Yeah. Good for you and your delimiters because yeah. That's right. Is is good for you. That's right. Yeah.

But you were saying that you do some stuff with it in your practice or you know, I, I, I am, I have to be honest and say, well, two things. One is that I've been in the trenches for a while now working on our study.

And then, you know, after we really kind of wrapped up and started teasing out our results, we, we have more publications that, that, that we've got to get on.

But, I was given an amazing book offer. And so, you know, I went headlong into writing the book and then, we're building out in a digital platform, which will kind of housed the entire program and, and give people access to, the biological clocks, access to the nutrition team trained in the program.

And we'll also be looking at nutrient, a whole collection of nutrient response genes that are outside of just biological clock data. And it's just incredible.

But it's it's very consuming. So that's where the lion's share of my attention has been these days. And so I'm not seeing as many patients. However, that said, I'm a fan of tier 65.

And so I think and I do think that when we sort of hunker down and lock in, we're going to see that not only does it influence telomere length, but it also influences the biological age clocks, you know, via DNA methylation.

And so it's easier for me to just cut to the chase. These days. And in the, you know, in the handful of established patients that I work with as well as myself, I mean, it's what I'll prescribe it.

Yeah. I was just actually thinking, that you brought the agouti clock as sort of the paradigm of the importance of epigenetics. And what we, you know, Rhonda Pineau did essentially the same experiment with telomere length when he took his, telomerase knockout mice, let them age and then gave them tamoxifen, which turned on the gene again for telomerase.

And they reversed their aging, just like that. So that's the sort of two mouse models that show the power of altering telomere length and, you know, gene expression through epigenetics.

So it's kind of a yeah, I mean, there there are areas that are they're very important. There both need to be worked on. And you have those, those two sort of I mean, I don't know how cited.

I'm sure it's not the most I think this year is the most cited, but it's it's well cited one with the you, the two by sitting next to each other, one's got the shiny black hair and the other one's all gray and zeros falling out.

And these is, you know, looks like an old mouse and they're the same age. That's amazing. Yeah, that's pretty

cool. Kind of cool. That depends on study.

Well, you have you, you know, just have you followed by a viva at all. There, there have been following them. I haven't I can't say I know the latest what's happening with them.

Tell me what your take is and I'll tell you what mine is. I well, I mean, I just think it's interesting. It might be, it might be kind of cool to have to talk to Liz Parrish and, and and using the Crispr.

I think it's an internist. Intranasal spray. Right. It to to, turn off or to support telomerase activity. I think that they're doing that in animals. And I think they may have just published a study, or at least they've put some preliminary results on.

I'm not following it that carefully, but I'll see sort of newsfeeds periodically. I'm curious. I mean, look at the original work that they did with, the gene therapy, just didn't seem to be, you know, convincing enough to me.

If they're doing stuff to turn on telomerase in a different way, that would be interesting. And there's, other companies, I think they're using Crispr technology.

I think they're kind of bullish on. I should take a look at Crispr and addressing telomeres. Yeah, yeah, yeah, you should look at it for sure. Michael Fossil is, got tell if I was looking to use gene therapy to treat Alzheimer's disease.

So there's I think, you know, there's, there are companies that are working on that, turning mean turning on is I used 65, and I think it's effective for sure.

But it's a moderate telomerase activator. Turning on genes to get the effect that the piano had from taking away 50% of telomerase and giving it back.

If you have a therapy that can turn it on 30% or more telomerase, and then you get significant lengthening of your telomeres, then I think you're going to see some big effects.

And she has technology for that that's delivered internationally. Well that would be very interesting to see it. Yeah yeah chase it. Chase I mean I definitely have yeah I definitely I mean it's well it's like looking at Crispr for Alzheimer.

I mean I think, I think Crispr has obviously shown some it's it's extraordinary. It's an extraordinary discovery. And amyloidosis, small amyloidosis study is just remarkable.

But aging is a multi genetic, you know, process. I mean, it's I don't know I don't know that targeting a single gene is going to yield benefits. You know, as crisply as we see in an animal model.

I mean, I'm sure it's not you know, I just don't know that it's going to translate so cleanly. I think it depends on how upstream. And I think, you know, telomere length and telomerase activation is pretty far upstream.

But again, you know, and mice are not humans. They don't age the same way in any stretch of the imagination. Humans are much more optimized for aging than mice are because, you know, mice in the field are going to get eaten by walking about, you know, they're like dropping somebody into the into the DMZ, you know, the DMZ into, you know, hot zone in Vietnam.

And that's just you don't have a like long life expectancy there. But back from then. So they're not optimized for it. So I think you're right that we're probably not going to get, quite the same.

But you know, I think over time that that sort of thing maybe tweak it's going to be systems biology that solve this, you know, look. Exactly, how they interact and, and the only way that we're going to able to do that is if you have this massive amount of computing power that we currently have, and that's increasing every, every, every year, to be able to look at everything at the same time and try to figure out which dials to turn, I wanted to get, I mean, I

think, I think my listeners will be interested.

I am also interested to get back to the sort of the Di that you have. I was looking through it. I mean, it has three ounces of liver in it. It has, six ounces of animal protein a day, has lots of vegetables and some fruit, and, probiotics, etc..

How did you come to that? I was through multiple different ways of looking at it. And do you think, yeah, that given that it's turning the clock back that that tells us that there are certain things that need to be in your diet.

Or what do you think? Yeah. Well, I mean, it's not just the diet. It's funny. If you it's kind of fun if you talk to different, different experts, they'll have an idea as to what they think is, you know, the most impactful intervention.

Yeah. Was it the meditation? I mean, we know meditation in, actually in anyone you can see favorable, DNA methylation changes immediately. And then in practiced meditators, you they're biologically younger.

So all of our interventions stack up to favorably influence DNA methylation. They all do exercise, of course, you know, balanced exercise, etc. but these folks are abstinent of alcohol.

Yeah. Yeah, I mean, I that's it was part of the intervention. I mean, I, I, you know, did they did everybody follow what we prescribed impeccably. No they didn't.

However we do have adherence data. And people did really, really well. And I think the the difference was the fact that they had contact with our nutrition team.

Otherwise I think nutritional interventions are notoriously inadequate. But I think ours was good, because we had this extra support. So I think our diet, I think is kind of like the, you know, sort of the stroke of brilliance, I think, around having a smart clinical team here that's, you know, weighted in nutrition science, having a background myself as a naturopathic physician trained in laboratory science, where I did my postdoc, and being really, steeped deeply in awesome molecular thinking, like Bruce Ames and Linus Pauling.

And of course, Jeff Bland is a is a, important mentor of mine and my mentor in the lab. You know, Richard Lord comes from the same lineage where you're you want your intervention in the, you know, the right intervention in the right dose.

And, so we took that thinking and we moved away from just aggressive, high dose supplement prescription. And you can ask me why in a minute if you want to, and looked at a nutrition intervention through that lens.

So right. Micronutrients in the right amounts. And we know that aging is globally a high hypermethylation phenomena. But then there's these regions of hypermethylation.

So at foundation when the diet is as rich in methyl donors as we could possibly make it. So it's a very greens forward diet. And then we've got beets. And then we did include three servings per week.

So it's not a daily liver ingestion, but three servings a week of liver. And if you look at the, you know, the micronutrient, composition of liver, of liver, it's this extraordinary multivitamin in a nutrient matrix.

So bioavailability and synergistic interactions are all there. And so we turned the volume as high as we possibly could on methyl donors in the diet. And then we also gave what we're sort of colloquially, colloquially terming methylation adaptogens.

And these are by and large polyphenol compounds that have data mostly in vitro animal limited human data on being able to augment the behavior of DNA methyltransferase enzymes.

And so we packed it with these polyphenols. That includes and they're in their polyphenols that we know time immemorial, are effective, green tea. So EGCg and all of the, you know, components in green in a whole green tea.

So that was actually drinking green tea. Yeah.

Telomeres, clocks, and future research directions

We wanted people to drink green tea and steep it for ten minutes, you know, to really get a rich complement of all of those, polyphenols, curcumin, luteal in quercetin, lutein, risperidone, all those were added as supplements.

No, no, no, no supplements. But we gave them we we we asked that they consume a diet that was rich in these, these well, in polyphenols in general. I mean, we can't make people eat, you know, 2 pounds of grapes or, you know, six onions or whatever, but we just, we, we wanted to lean on supporting them with, with those kind of nutrients.

We did give them a greens concentrate to sort of bump that up a little bit more. So it's not encapsulated, it's just a greens powder. And then we gave them a probiotic, lactobacillus bacillus plantarum that has some research on being able to increase, microbial folate production.

It's got a bunch of, you know, probiotics are good for a number of reasons, and some of them may actually help our own endogenous production of some of these nutrients.

For our microbiome, we did significantly increase, circulating folate without giving a vitamin. So yeah. So that was kind of the where the rubber meets the road.

We have these methylation adaptogens that are polyphenols. There's another family of enzymes called the 1011 translocation enzymes. And these guys are active in methylated.

And really demethylation is important as methylated co-factors. And those include vitamin C alpha key to glutamate iron. And so we had it was a vitamin C rich.

We weren't giving any iron. You know, middle aged men generally don't need any iron, as a key to glutamate. Ideally, maybe they're making some from their protein.

So we were just thinking about optimizing DNA methylation with whatever we could in the diet, and then layering in the lifestyle interventions that also have science behind them as favorably influencing methylation.

And, you know, that's what we that's what we created. And yeah, it's amazing that we I mean, I'm absolutely thrilled that we saw what we saw. I mean, we it was designed, you know, coming from kind of a unique background of having the sorts of molecular training, lab training and having like whip smart nutritionists here.

My, the director of our nutrition programs, Ron Hodges, you know, worked on building out those, those micronutrient ratios. So I used measured, way methyl folate levels.

Yep. Did you measure any other, like, micronutrient levels? Yeah, we measured a whole bunch of things, and they're reported in the paper. We just we highlighted what was a big deal.

So, folate increase, triglycerides dropped, LDL dropped, total cholesterol drop, which just sort of lends weight to the fact that it was keto leaning and, you know, lower glycemic.

Had a good time. Yeah. And a good diet. Yeah. That's right. We didn't make a difference in homocysteine as adenosine methionine s adenosine homocysteine. No difference. Of, you know, maybe there may have been a power issue.

I mean, well, you know, you guys, they weren't hyper hyper homocysteine anemic. You know, they didn't they didn't really need their homocysteine lowered.

So I think but what you know, what it does illustrate. And yeah, maybe when we have a larger population we'll see

changes. But I think it illustrates that, you know, the methyl ohm response even before some of our methylation cycle, actually all of our methylation cycle biomarkers respond.

I mean, that's a good and that's an important take home. That's an important point. Is it more sensitive canary in the coal mine. And actually these serum levels, which may not be as we lean heavily on those biomarkers, they've been around time immemorial.

And you know, we look at tweaking those and they do reflect what's happening with DNA methylation. But they're not the end of the story. The reason that we didn't go with supplements because we could have, is because there are some studies suggesting that if you push methylation forward too much, I think, you know, famously is the the the be proof study.

They gave older an older population who had with elevated homocysteine. They gave them folate and B12. And they ended up, you know, when they when they did a, secondary analysis, a large percentage of the population, a significant percentage of the population developed colorectal cancer.

And it's and they actually were challenged on the findings, and they went in and reanalyzed, and it was actually still there. And it was even stronger.

And, you know, they've been tracking this population for a while. And that's just not the only study to suggest that. And it goes back to the journal.

I mean, you know, in that first 20, 2003 paper, those guys said in their abstract in the conclusion, nutrients are extremely powerful, and we need to be mindful that we're actually, that we're we're we're using them with that awareness.

And that was our thinking to do we need now that we can look at the epigenome, do we need to be mindful, you know, how heavy we hit with our various interventions.

And that's a that's a really, really important, take home point. I think also, you know, the original Horvath clock was associated with mortality and it's a tissue clock, etc., but it's in the end, trained on chronological age from the beginning, the second and even third generation clocks.

Now, you might consider other the rate of aging one are trained on other things. And so that may be sort of think about, what Fino age is trained on, which is not on the chronological age, is in it.

But that the nine other markers are common markers from, chemistry in a, in a CRP and CV, which could be an interesting thing to do alongside the DNA methylation.

In, you know, a subsequent study you do because absolutely, you know, in all the data sets that they look at, it's highly associated with mortality and morbidity and health conditions.

You know, we have other data to show that RW is an important marker for mortality. And seeing those, is kind of an interesting thing that would go along with the molecular, do you know, are you actually changing red cells, changing liver function, changing in inflammation as measured by CRP with with your diet along with the methylation would be kind of a easy and inexpensive thing to do.

So that's yeah, for sure. We we we we started to measure that now in our, in our physiology software. We, we look at the Fino agent and to track that along time longitudinally.

And hopefully we'll get some more information out of that. Maybe. Exciting. Yeah. You're going to have a bunch of information and let me and do let me say that we will, without question, be looking at the next generation clocks, as we recruit.

Yeah. We're not going to hang with the the original Horvath clock. But, you know, you could argue, I mean, so

some people think it's it's, you know, the fact that we limited it to, to the 23.

I mean, we had no choice. We started this clock. I mean, we just started our study, you know, before we had, you know, the advantage of the current landscape of clocks.

But, you know, you could argue that maybe it's a harder clock to actually nudge. And so nudging it is a big deal. I mean, you know, it depends on how you look at it.

I mean, it's not 100% associated with chronological aging. There's some wiggle room in there. And so no question about that. And, I think that, that, you know, you could argue that you're maybe getting closer to more intrinsic aging, potentially, you know, it's definitely a big a big finding.

Yeah, it's the proliferation of clocks is nothing but a good thing. Yeah. Using multiple clocks for different things, going forward. And, and, you know, even calling them clocks at a certain point doesn't even make that much sense.

They're just epigenetic biomarkers, composite panels, really, of changes in gene expression that, you know, it's nice to have an age associated with it, but, you know, these the new clocks have, you know, an R squared with chronological age of, you know, 0.6 or something like that, right?

That's right. Other massive one. But they're telling you more important things, in some way, at least we think they are. Well, time will tell. But yeah, they're trained on things that we think are more.

Yeah, you're right, I know. And none of my comments are taking away from the importance of the, the, the, the change that occurred in your study. I'm just saying no, I get it.

Yeah, yeah. And there's a kind of interesting. Yeah, I mean, I, you, you know, I think in our podcast that we did a while ago, you were the one that sort of got me thinking about the clocks a little bit more.

I've been sort of the telomere guy. And and, so now, I've incorporated. So happy. So have you drank the Kool-Aid because you're going to, you know, if you're incorporating it into your system, you're going to really, you know, contribute to the body of knowledge.

And and you're right, it's important. And it's important. We've got AI working on it. Yeah. And also be interesting too, because we've talked about this in the previous podcast is how is your how is your diet and lifestyle, affecting like an age?

That that's a whole another interesting thing as like in ages is. All right, you know, the, the, the, the, the glycosylation of the IgG that the Gordon allows is looked at and highly associated with, with outcomes and with, and with probably logical age.

So, the more the more, the more ways you have to look at, I think what's happening, to us physiologically as we age and with certain conditions, I think the better.

Perhaps that's a good place to to take a long conversation. Always fascinating. And goes by so fast with you. To a close. But I want to just let you say anything.

You have a new book coming up that you just finished? 700 pages. What's the title? You know, it's a theme. It's a behemoth. It's young, it's called younger.

You and it's and it's and it's sort of our our journey into epigenetics. It's all all of the details on the study. But but you know, beyond that, just talking about sort of epigenetics and cancer and how we got into this conversation in the first place.

There's a whole lot of really interesting angles outside of biological aging. I'll say one area that I'm just wowed about in the book is this concept of biological embedding.

And we're learning that DNA methylation and genetics more broadly, biologically embed our experience. So they're translating our experience in life to these biochemical markers that and that then influence genetic expression.

And this is heritable as well. The bulk of the research of course, is in trauma. You can see it in sort of Kosovo survivors. You can see it in some of the more famous studies, like the the Dutch Hunger Winter group or over KLA.

You can see it in Holocaust patients. You can see survivors in their offspring. You can see it in, PTSD and the heritability patterns of that. So the focus has been on on trauma, understandably, but looking at survivors, looking at sort of vibrant wellness, looking at the translation into biochemical patterns of, of, you know, living good and big and, you know, mentally powerful and clear lives.

I mean, all of that is just extraordinary to me and interesting to me. And, you know, new emerging science. And so we talk about that in the book. And then I also talk about like sort of big picture thoughts on aging in general.

And, you know, you know, folks in the Biohacker field, maybe you're one of some who are who are basically like, you know, let me replace an organ when it falls, you know, when it falls apart.

And I'm going to live until I'm a thousand, regardless of what I eat. I mean, there's this interesting continuum of folks in our world, and I'm obviously arguing for living your best life and eating well and etc., etc.

so I, we, I just kind of touch on a lot of different areas that are, interesting to me in this space. No, I mean, look, I in terms of that, I'm not in that biohacker crew, that, you know, thinks that I can just turn the car in or turn the engine in when I when I need a new one.

You want to try to preserve it? Obviously. Ultimate organ, of course, is the brain. That's going to be really difficult to to just turn in. There. You know, I think you're right there.

I thought, I thought we were going with that was experimentation with yourself. I think there are some people getting a little bit ahead of science. Yeah.

You know, particularly with this analytics, I think to certain degree or Crispr infusions. Well, yeah. I mean, yeah, like DIY, Crispr infusions. I do tell patients and I had this conversation with them, that the risk benefit equation changes over the lifespan.

So when you're at 85 and things are really going down too, too fast, I'm willing to try other things that may have a benefit on you because, you know, the downside is, you know, pretty much the same the outcome, but, early on, people doing some of these things, I think, is a little bit they may not be sophisticated enough consumers of the medical literature to, to know what they're getting into when they're doing this kind of stuff.

And I don't know that the medical literature knows. I don't think we've pieced all of that together yet. You know, which is probably why you have to be a really sophisticated consumer, because we have not pieced all that together.

And and oftentimes there's a lot of, enthusiasm in the way in which papers are written up. And, and so you have to, you have to be, I think, careful about it.

And I think you're absolutely right. And in my practice starts with lifestyle, diet, exercise if supplements if necessary. And it goes on depending. But because you want to go with the, the foundations of it all, and you know, we I'm sure there's many other things we've dug out exercise effects, epigenetics, etc..

Yeah. But, it's been a fascinating conversation and hopefully, we'll we'll continue again. Yeah, I'm sure we will. I'm sure, I'm sure you'll be back on my podcast soon.

I actually I look forward to it, especially as you, you know, crunch these new, tests that you're collecting and pop them into your machine and have some interesting stuff to report.

Yeah, that'll be fun. Connect. All right. Well, thank you very much again. Cara. And, we'll talk soon. Okay.