

Transcript for John Haran & Ethan Loew Podcast Transcript – to publish on 2/21

In a new Voices of UMass Chan podcast, physician-scientist John P. Haran, MD'07, PhD'18 and MD/PhD student Ethan Loew explain research on the connection between the gut microbiome and cognitive health, particularly how it impacts older people.

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Thank you for listening to the Voices of UMass Chan, featuring the people, ideas and advances of UMass Chan Medical School.

Jennifer Berryman

Thank you for listening to the *Voices of UMass Chan*, featuring the people, ideas and advances of UMass Chan Medical School. Welcome to a new episode of the voices of UMass Chan. I'm your host, Jennifer Berryman, and we've got a fascinating conversation today. You've likely heard about the connection between your brain, your gut, and your overall health. But today we're diving into research that's focused specifically on looking at what connection there might be between the microbiome and our guts and Alzheimer's disease. What role could the microbiome play in cognitive decline? John Haran, MD, PhD, is professor of emergency medicine and microbiology & physiological systems, and clinical director of the Center for Microbiome Research UMass Chan. We're joined by Dr. Haran and Ethan Lowe, an MD/PhD candidate who came to UMass Chan in 2018. Thank you both for making time to speak with us today.

John Haran

Right. Thank you.

Ethan Loew

It's great to be here.

Jennifer Berryman

Dr. Haran, get us started, if you will. Just give us a quick refresher—what do we mean when you say microbiome in our gut? And how do we think it impacts our overall health?

John Haran

When you're talking about the microbiome, it is the collection of microorganisms that reside in our gut. And we live in balance with these microbes. They help to really give us the nutrients and they process foods for us. They do a lot of beneficial things. But they can also do a lot of negative things for us, too. And so, when I say microorganisms, I do mean viruses and bacteria. But mostly we focus on the back the biggest component of that which is the bacterial community that resides in the gut and how it affects our health. And it has been. There's been a lot of research over the last decade to two decades looking at associations between the gut microbiome

and different aspects of health. And we're really trying to push that forward with Alzheimer's disease, and specifically with the aging gut microbiome and how it changes and how that influences older adult health.

Jennifer Berryman

Give us a snapshot of some of the research projects that you've got underway looking at this connection to Alzheimer's disease in older people.

John Haran

It really started with my work here. I was part of the Millennium PhD program while getting my PhD here at UMass (Chan). I already had my MD and finished my residency training, and I was here as an attending physician in emergency medicine. And as part of that, I've got funding to look at nursing home residents and specifically how pathogens spread amongst nursing home residents. That is work that's ongoing today. But what we have done with that is about eight years ago, roughly, I was presenting at the National Institute of Aging, like one of their conferences, and one of the program officers really introduced me to the gut microbiome and its relationship to the gut brain access. And so that's where I started branching off and looking at the gut brain access specifically, but the projects that we have looking at the gut microbiome have to do with pathogen passenger spread of the nursing home. And we've also looked at both the gut and oral microbiome in relation to other infections such as COVID. That work has been kind of backburner a little bit. But the main focus that we're driving on now is how the gut microbiome influences inflammation, systemic inflammation and how that relates to Alzheimer's disease. We're also looking at frailty and how the gut microbiome relates to when people get older and they develop a frail phenotype.

Jennifer Berryman

I want to just put a finer point on something I think you said that gut brain access. What is there physiologically? is there a direct line between our gut and our brain?

John Haran

When I mentioned this meeting years ago and I was presented this by a program officer and I NIA, I had the same reaction, 'What the heck is that? I don't believe how's the bacteria in your gut have anything to do with your brain?' And when you look at the research, you know, this really started about 12 to 15 years ago, with germ free mice, when they took away all their bacteria in their gut. What they noticed was the mice acted very differently. They were anxious. They had different genes that were activated in their brain, like they were completely different mice. And then the fascinating thing was, once you gave them a normal mouse microbiome back, they recovered everything. They were like less anxious, more sociable. And so that kind of kicked off the whole gut brain access. And then I would say the past decade or so has focused on a lot of research looking at Alzheimer's and Parkinson's and other mental disorders, and how the bacteria in the gut can affect or associate with it. Exactly how that happens is being worked out. I think it's very different and there's probably multiple processes. Some of them focus on what the metabolites are being produced by the microbiome that then trains to then translocate and go into the brain. Others are how it affects our immune system in our gut. About 78 percent of our immune system is just focused on our gut itself. That's how our immune system gets trained and how we grow up and learn. So that's another aspect to it. The vagal nerve is another way in which people believe that the gut communicates. And it is a two way access. So basically, I mean, kind of simply said, like, if

you've ever had like stress, and you feel like you're going in the bathroom, or like, yes, your brain can affect your gut. But now we really focus on what's going on in the gut and how that relates back to functions in the brain.

Jennifer Berryman

That's a fascinating. Thanks for taking a minute to explain that. Ethan, maybe you can jump in here? Why is it important for scientists and physicians to sort of understand and look at what's happening in the gut of older people? Like, what is it? Is there something that we think changes over time as people age? Yeah,

Ethan Loew

As adults get older, I think there is a predisposition to some illnesses that might not be as prevalent in younger populations. Folks move off into long term care facilities, they're sharing similar diets and there's greater risk for syndromes such as frailty syndrome. And we're still working out the underlying cause of what might cause this. A lot may be related to diet. A lot may be related to change in the microbiome that occur over time and old age. And it's still unclear to us what drives these changes, Perhaps it's dietary related changes, perhaps as changes in the immune system that occur naturally with aging, a phenomenon called immunosenescence where your immune cells develop are older, less active. And so, by understanding the role of the microbiome, we can understand both how the bacteria in the gut might be communicating to the body in a way that leads to these ailments of aging, or perhaps understand some of the underlying physiology of aging, by looking at changes in the microbiome and seeing how those affect the behavior in the gut to these older adults.

Jennifer Berryman

And when we think about the six, seven-plus million Americans who are living with Alzheimer's, this is something that affects a lot of different families. And so, we really want to share that there's a lot of people who really would like to understand this better, including yourself. So, either one of you what does the evidence tell you so far about the guts of older Americans? And what are the questions that you're still trying to unravel?

John Haran

So specifically, with the guts and older Americans, I mean, there's certain things that we know about, like a loss of diversity. So, the amount of bacteria that are there, the differences in the bacteria, they go down as you age. But this is not, doesn't have to be the case. And this is when you look at super agers, people who are healthy into their hundreds, they definitely have a diversity in their microbiome that looks similar to people in their 50s and 60s who are healthy. And then not just that, but also who's there, what's the mix of like healthy versus unhealthy. And this is kind of a poor term, but we do use it all the time, as far as labeling a certain bacterial species as either healthy or unhealthy. But those balances change as you get older too. But once again, they don't have to. One of the holy grails for aging with the microbiome is trying to figure out how do I keep my microbiome as someone who's healthy in their hundreds, rather than someone who's, you know, sicker and older and, you know, more frail.

Jennifer Berryman

Ethan, we've heard a little bit about how Dr. Haran kind of got into this line of study. Can you share a little bit about your background, how you got involved in this area of research and what you've learned and what what floats your boat about doing it?

Ethan Loew

I came into graduate school really naive to what I want to do. I had an open mind to trying out different experiences and always had a bit of attraction to the microbiome. I was in college, maybe in 2012 - 2011. And an article from a just a journalist blew my mind about this world of bacteria living in our guts affects our mental state, how we behave. And I felt like it was the best kept secret in science, like it was hugely consequential, but nobody talked about it. I would come to learn because nobody really knew much about it, right? And when I came to UMass (Chan) I got really looped in with the work of Dr. Haran and Beth McCormick, PhD, (the *Worcester Foundation for Biomedical Research Chair II* and professor of microbiology & physiological systems), who were studying the microbiome in different context. Dr. McCormick in the sense of intestinal inflammation, inflammatory bowel disorders and Dr. Haran with the gut brain access. And I was just so interested how these changes in the very distant place in our bodies in our guts could be communicated elsewhere to have such a huge impact. And Alzheimer's disease has really become one of the ideal standards to look into in this case, because of its impact. It's so consequential for so many families. So, a small difference here in our understanding of disease can make a huge difference for the families and older adults with Alzheimer's disease. And it's a really exciting fundamental question about what's going on here that we just don't know much about right now.

Jennifer Berryman

To both of you, how do you anticipate that some findings from these research studies might impact what we're able to know and understand about neurodegenerative diseases other than Alzheimer's? I think you mentioned Parkinson's. What about some of these other diseases that you might glean insights about?

Ethan Loew

The way I've thought about the microbiome in general, right is, it's a collection of microorganisms, largely bacteria that we as a species have evolved with for 1000s and 1000s of years. And as a result, they play an integral role in health and in disease. So, by looking at the presence or absence of specific bacteria, it can give us insight into how our bodies work. And we're starting to uncover both in our lab and I think, as a scientific field as a whole, really unique ways in which our BI functions in response to the settings of these bacteria and these effects might be specific in some diseases, or maybe more generalizable say, leading to changes in the immune system inflammation that can go on to worsen symptoms of Alzheimer's disease of Parkinson's disease, and are really acting in some cases to start, or in some cases to exasperate preexisting illnesses. So, it's this fundamental biology, I think that we're starting to untangle that is giving insights more broadly into types of inflammatory and neuro inflammatory diseases that can be shared.

Jennifer Berryman

The research that you're doing right now, tell us about some of the studies that you have underway, the kind of

John Haran

The goal of our funding, which I'll give a shout out to the Alzheimer's Association that has really gotten started and continues to keep us funded in the National Institute of Aging. But what we're doing is a kind of alluded to it before, there's been a lot of studies saying good, bad bacteria associated with good and bad outcomes and

health. And so we're trying to really go beyond that. And so what that includes is it includes a team first off, Ethan already mentioned that Beth McCormick, who is really like a gut mucosal immunology interaction expert in that from the microbiology standpoint. And then we also have Vanni Bucci, who does a lot of mathematical modeling and AI, and then Doyle Ward, who was also a bacterial specialist. We bring all these people together and that really helps in multiple aspects. And so, what we're trying to do, besides moving past associations is look at a couple different things. One is like disease course over time. So, a lot of studies take a snapshot of an individual, but we're really the work that they have ongoing now. We have a couple 100 people that are involved in this study that are from the community in and around Worcester that come to the clinic, and that we see every three months, and they give samples for us. And we follow them over time to see how their health and this is focused on Alzheimer's disease. But we're really trying to get multiple snapshots over time to see what's going on. And then by going beyond just what bacteria they're good or bad and associated with things, we're really trying to get down to mechanisms. So, what's functioning in the microbiome and we have definitely honed in on several of these mechanisms that we're exploring further. And so what we do is we combine that which is really neat is we have a cohort of nursing home that has been closed, but actually we're enrolling in the nursing home again. We have this community cohort that we have, and so we can compare findings across very different groups of people. And then we can bring that knowledge to the lab and we can apply it to different assays on the benchtop. Or we can use different animal models, and especially Alzheimer's transgenic animal models. And we can either treat them differently or transplant stool from people like with Alzheimer's and without Alzheimer's or even with Alzheimer's while they're doing well and when they're not doing so well, cognitively. And we can see what those groups of bacteria do. And then we can also do it individually. And Ethan's got a couple real mechanisms that he's been hitting on as are of interest. So I'll let him take it from here.

Ethan Loew

Now one point I want to underscore John makes is one particular thing. We're doing microbiome research. It really does take a team of experts to come together and do this. We have our mucosal immunologist and our microbiologist and other experts all coming together to help with this project has been really essential to helping us progress as we are. So, following up on some of this longitudinal work we're doing, following older adults with Alzheimer's disease, looking at changes in microbiome, we get changes in the immune cell to understand a mechanism how our bacteria causing these effects of immune cell changes of neuro inflammation and of cognitive decline. We're starting to focus on a few mechanisms. One of those mechanisms is we think promoting worsening symptoms of Alzheimer's disease. And hopefully we're going to identify a different one that when present is a protective experience. We're looking at production of an essential amino acid Muthiah Nene from the bacteria in the gut of older adults with Alzheimer's disease, and were theorizing that this metabolite goes on to lead to immune cell proliferation, differentiation toward a more active inflammatory immune system. And this inflammation is well known and Alzheimer's disease underlying causes is still really contested, but we suspect that the bacteria in the gut are playing a role through the signaling of methylamine need to lead to stomach inflammation and eventually neurocognitive decline. On the flip side of that coin, we've identified a bacteria that is present in healthier older adults that seems to be absent in adults with Alzheimer's disease, and absent further still, in adults with worsening Alzheimer's disease. This bacteria makes a metabolite, the product that activates estrogen signaling in the intestine. And we think that effect is used to stimulate host defenses against pathogens or put the biomes up, no adverse negative bacteria, fighting colonization, inflammation. We think this protective system is sort of turned off or dialed way down in Alzheimer's disease,

and could be a signal to start an inflammatory response that goes on to become the wildfire we know as neuroinflammation and Alzheimer's disease.

Jennifer Berryman

So the hope would be I guess, is that once you're able to better understand these mechanisms, and what's helping what's maybe hindering cognitive acuity, then maybe there would be some way to sort of activate the good and deactivate the bad, right? I mean, do you think that clinical applications like that could be on the horizon?

John Haran

That's exactly what we're doing. And that's what we're focused on is, you know, with the bad back the bad bacteria or the negative processes that are going on? How can you protect against that? How can you remove that is one aspect of it. And then the other one that Ethan was mentioning is, what would be perfect for probiotic design and how can you give somebody that bacteria back so that I can add benefit? The cool thing about this is the methylamine story, at least we've seen, we saw it initially, in one group of older adults. We've confirmed it and another group of older adults and we're now doing different assays to kind of confirm it. So, we're really focusing on a mechanism and not just seeing it in one snapshot. And we're actually seeing it, how it changes over time and negatively affects older adults' cognitive health. And we're combining that with also measuring the molecule itself. So, we're not just looking at the bacteria. Because it's different ways to probe the microbiome. So, we're not looking at just who's there. But we're also looking at what metabolites are producing, and we're manipulating those. And so, we're really trying to build a complete story around it to help drive and really focus on probiotic design. Because when you design a probiotic, it's not like it was in the past. It's a community matrix. And so, we're really trying to figure out what's the best mixture of good bacteria to hopefully boost those that are good and bring down those that are having a negative effect. And especially, you know, along the timeline, because it with Alzheimer disease, you can have it and you can have Alzheimer's for a long time, or you can have it and you can fall off a cliff pretty soon with as far as like your mental functioning. And so, we're really focused on that part of it, like what can we have people live a lot longer and healthier life, we maintain their cognition over time by developing these, these probiotics.

Jennifer Berryman

We'll be eager to keep tabs on your future research and what you guys learn. So please keep us posted. And I am curious for people who might be listening and interested in enrolling in that community cohort, is that something that you're currently enrolling for, or is that closed?

John Haran

If someone's interested in being a part of the study, we are ongoing, we really are focused on people with a diagnosis of Alzheimer's disease, and also those with other forms of dementia. And we do run this clinic where we bring people in. And so, we have email contact and phone numbers too, that can be used to reach out and be part of the study.

Jennifer Berryman

Okay, we'll make sure that we put those in the show notes so that anyone who's listening and interested in learning more or potentially enrolling in the study will have that information at their fingertips. John Haran and Ethan Loew, thank you so much for making time to describe your work. It's really great and we'll be eager to see what comes next.

Ethan Loew

Thanks, Jen.

John Haran

Thank you so much.

Jennifer Berryman

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