Zoom In on **Dementia & Alzheimer's**

The Path Forward in Stopping Alzheimer's Disease
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Transcript of Zoom with Rudolph E. Tanzi, PhD, Harvard Medical School, Massachusetts General Hospital

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Please note: This transcript has been edited for clarity and brevity.

NANCY KEACH: Good morning. Good afternoon to the East Coast, folks. I am Nancy Keach, and I'm delighted to welcome you to this episode of Zoom In on Dementia & Alzheimer's, which is brought to you courtesy of BrightFocus Foundation. BrightFocus Foundation is a 51-year-old nonprofit that has funded over $300 million in scientific research worldwide for Alzheimer's disease, macular degeneration, and glaucoma, and we are delighted for you to join us today.

We also want to thank Biogen, Lilly, and Genentech for making this possible by giving educational funds to support this program, so thanks for all that. We've been doing this show for almost two years now, and usually we have a very specific topic like hereditary genes, or how do I get a diagnosis? And today is a little broader and we got 140 questions, so bear with me. We have one of the greatest talents in the field with us today, and so we're going to cover a lot of ground. All of the previous episodes are available for free online, so if we don't get to your question today, because I think as I said, there were 140 questions, you'll probably can find the answer to your question in one of these episodes. So if you go to brightfocus.org/zoomin, you can see. If you have questions about early

onset, if you have questions about genetics, or specific drugs: Kisunla, Leqembi, please go to those episodes as I said, if we're not covered today.

I'm going to now jump right in to introducing Dr. Tanzi. So as the Pioneering Director of the Genetics and Aging Research and Director of the McCance Center for Brain Health at Massachusetts General Hospital, Dr. Tanzi is a leading expert, I wrote on everything related, not everything in the world, but everything related to cognitive dysfunction and the genes that affect it. And he is an influential voice on cognitive health and healthspan, which we'll talk about a little bit today. As the Kennedy Professor of Neurology at Harvard, his research continues to drive significant advancements in understanding, preventing, and treating Alzheimer's, and related dementias. Dr. Tanzi, also of note, uses AI in his lab to develop new theories on early interventions. A true rock star of science, he's author of New York Times bestsellers like Super Brain. He's just about to start writing a new book, which will come out, I believe, in about a year. Is that right?

DR. RUDOLPH TANZI: Yeah, just well, we take about a year to write it and then—

NANCY KEACH: A year to write it, which we'll talk about a little bit later. And in his spare time, he cuts albums with Aerosmith, so he is a wonderful, wonderful and generous person with information in the field. So, I'm going to start you off Dr. Tanzi, thank you so much for doing this and welcome.

DR. RUDOLPH TANZI: Oh, thanks. Thanks. Glad to be here. Thank you.

NANCY KEACH: So I'm going to start to kick off with this question. You talk often about how early detection is critical to develop and provide safe and affordable treatments for Alzheimer's disease. We've had two episodes that we've already done, one with Randy and one with Dave, on how to get memory screenings and how to get a diagnosis, although I guarantee you it still is incredibly complicated and difficult for people, for real people, to actually walk this path and get a proper diagnosis. And where do you go first? And there's no neurologists, and you wait nine months, and all of those things.

But I want to start with a question from Mike Zuendel, who has Alzheimer's. He's an Alzheimer's advocate, and he participated in the Aduhelm trial for three years. And he has basically eliminated most of the amyloid in his brain, and he's become a very vocal advocate. And he asks, what do you think is the impact of how the stigma surrounding Alzheimer's pertains to early detection? So how does the stigma around Alzheimer's affect this need for all of us to inform both doctors and the public that early detection is critical?

DR. RUDOLPH TANZI: This is probably one of the most important questions right now, because now that we have blood tests from Randy Bateman and Dave Holtzman's company, C2N, blood tests that can tell you if you have amyloid plaque in your brain. It can tell you if you're starting to make the neurofibrillary tangles in your brain. And keeping in mind that this disease begins-- we don't diagnose the disease until you show clinical symptoms of cognitive impairment. By that time, you've already had the biology, the pathobiology in your brain for anywhere from one to three decades.

So it's kind of like the way we treat Alzheimer's is, in contrast to cancer or heart disease, is we wait until the brain has already degenerated quite a bit before we even diagnose it because that's when you show symptoms. It's almost like we're not going to diagnose heart disease until you start to have congestive heart failure.

So just like with heart disease, I like the analogy. Once you have congestive heart failure, and you need a bypass, simply lowering cholesterol isn't going to be enough. But if you are managing your cholesterol, and you knew you had to a decade, or two, or three before you got actual symptoms of heart disease, you could avoid it. Amyloid is to Alzheimer's as cholesterol is to heart disease, and a lot of the controversy around amyloid is that if you treat amyloid when a patient is diagnosed, it's like only treating cholesterol when you have late-stage heart disease. You had to do that as early prevention.

So how do we do that? How do we do early detection? Now, we can with a blood test and early prevention, where in which case a person doesn't want to be told or tell the world, I have Alzheimer's disease, because

when you say I have Alzheimer's disease, the clinical diagnosis is, oh, you already have cognitive impairment. Are you going to have trouble doing your job? You can be working in a job for 10, 20, 30 years with Alzheimer's disease pathology brewing in your brain, and you're not going to show symptoms till later, so there is a stigma. So we need-- I almost think we need another term. Sometimes I use the term biological Alzheimer's. Meaning that the pathology has begun, but you may be decades away from any cognitive impairment at all. But this is when you have to treat. We don't wait till you have a huge tumor to treat cancer. We treat you when you start getting-- when you have a rogue cell. I started cholesterol meds with a family history of heart disease in my 20s, and so I'm the first Tanzi in my immediate family who lived past 45 years old because of the genetics. So you have to be proactive and know what you need to do. Detect early, predict early, and then intervene early. But if doing that says you have to says you have Alzheimer's, and that's a stigma, it's a big problem, so it's a really big important question.

I don't know what we call it, but we'll just teach the world that you can have biological Alzheimer's and prevent the clinical symptoms later on by treating early on. Maybe we give it a different name. I don't know.

NANCY KEACH: And so just to clarify that. So, we're saying that amyloid starts to build up in the brain 10 to 30 years before symptoms come on, and yet we're asking people to try to get tested and get that amyloid, which is a biomarker, like you said, like cholesterol is for heart disease, and test for the amyloid 10 to 30 years before you're going to have any symptoms.

DR. RUDOLPH TANZI: Let me just say the amyloid is the cause, but there are biomarkers to tell you have amyloid in your brain based on a blood test, and that's so knowing that. And then we can get into whether we have drugs that are good enough and cheap enough and safe enough to make it actionable, which is a whole other thing we need to address.

NANCY KEACH: Yeah, and we'll get to some of that. But I have Donna from Rhode Island wrote, what is your risk for developing Alzheimer's if you have no symptoms but are positive for amyloid and tau on a PET scan? So you have the biomarkers. You have no symptoms. There's stigma

to go in and find out. What's your risk?

DR. RUDOLPH TANZI: So Donna I'm from Rhode Island originally, so that's a good question. So once you have plaques and tangles, I like to put it this way. Amyloid is like the match, and it lights brush fires for the tangles, and the tangles propagate and spread like brush fires. And if you only have plaques and tangles, and you don't get the wildfire, which is neuroinflammation, the inflammation in the brain, you won't get the disease, basically.

So we know this because we study what are called resilient brains, where you have people who die in their 80s, let's say, cognitively perfectly fine. And then to the surprise of the pathologist, you see tons of plaques and tangles in the brain. And you say, how did this person not have Alzheimer's? In every single case, it's because their glial cells in the brain stayed chilled out and didn't become inflammatory. There was no neuroinflammation. It stopped at the brush fires. You never got the wildfire.

So it is possible, theoretically to have plaques and tangles and not get to the neuroinflammation wildfire that gives you the disease, but it's rare. So the sad fact is, if there's already plaques and tangles, you have biological Alzheimer's. How long it's going to be before you have symptoms is now going to be a function of your genetics. Most of the known-- I found the first genes together with others like John Hardy, who had a show back in the '80s and '90s, the amyloid genes.

But the fact is that most of the known genes we have for late onset Alzheimer's affect that inflammation, neuroinflammation. So your genetics will determine how fast you're going to have neuroinflammation, but your lifestyle will too. And I think the good news is that 98% to 99% of genetic susceptibility can be offset with lifestyle. That's why I talk about these books that I write about what you need to do.

So I would say that if you have plaques and tangles already, whether it's by blood test or by PET scan, the brain is on its way to eventually to deterioration and Alzheimer's. Except in very few cases of these resilient brains, where somehow genetically, they're protected against the

inflammation and the wildfire. That's the sad truth.

NANCY KEACH: And I have questions rolling in like crazy, and of so I'm going to try to combine some of them. But we have a bunch of quick questions on the blood tests. Tricia wrote, "What is the blood test called?" And the one that Dr. Tanzi was referring to from the company C2N is called PrecivityAD and there are other ones.

But I notice that there's somebody I'm seeing on the Zoom today who wrote to me after we did the first episode on blood tests because she tried to get a blood test. She just went to Labcorp or to get a blood test, and she thought it would be reimbursed, and she thought she could get her results. And not only was it not reimbursed-- hi, Karen. Not only was it not reimbursed, but then she found out afterwards the doctor had to give her a note to say this was medically necessary. And as we know, even if she'd been able to get her results, she wouldn't have been able to interpret them. So this is how do you get the blood test or eventually? Is it ready now? How could you get it today? Can you try to give some answers for that? Because it's so exciting. There's blood tests. We can see tau. We can see this. We can see that. We can see all these proteins, and the people who are suffering are really left behind a lot of times by the field.

DR. RUDOLPH TANZI: I mean, the blood test can be prescribed by any doctor, but it's not covered by insurance because it's so-called not actionable. Meaning if you have a positive result, there's not a drug available right now that you can use to stop it. Well, the fact is, there are these new immunotherapies, as like Leqembi and Kisunla, which will clear the amyloid once you find out you have it, but they were only approved for early stage Alzheimer's disease. So to get those drugs covered by insurance, you have to have plaque in your brain, and you have to already have mild cognitive impairment, the earliest stage of Alzheimer's.

But if you're a person with no cognitive issues, and you find out that you have a positive test for amyloid and tangles in your brain by blood test, because there's not, other than lifestyle, there's not a drug. And I think lifestyle is a great actionable step, and so I would say do cover it because you'll do the lifestyle interventions more. And Dean Ornish and I just published a lifestyle intervention trial that had amazingly successful results, but that's not how health insurance companies see it. They want a

little white pill you can take.

I'm working on a little white pill. Been working for 25 years on a drug called the gamma secretase modulator. It will help lower the production of amyloid. Remember, the new drugs that were approved cleared the amyloid. I want to hit the production of amyloid safely, and it looks like our drug has a good chance of doing that. Right now we're talking to the FDA about getting permission to do our phase I safety trial. It took 25 years to get here, but it's the last man standing in terms of a drug that will be like a statin for cholesterol to lower your cholesterol production. This will lower your amyloid production. Unlike the drugs that exist now, that let the amyloid be made and then try to clear it away.

So eventually, that test is going to be actionable, and I and many others are working on the drugs that will do that. I'm repurposing drugs. I'm starting trials at the McCann Center right now, big fundraising campaign to start trials on repurposed drugs and natural products that are already on the shelf that can either stop amyloid production, or the tangles, or the inflammation. All of it's in process. But right now, because it's not actionable with a drug you can just get as a healthy person who found out they have biological Alzheimer's, they don't cover the test.

NANCY KEACH: And so if you went to your doctor and you asked them to prescribe it, and you couldn't get coverage, is there a range of what it costs today and will those costs come down?

DR. RUDOLPH TANZI: Well, the last time I checked, and I know it changes, but I think the C2N Precivity test last time I checked was about $1,500, which is not a small amount of money. And so I think that once it's approved by insurance and everyone's going to get checked the same way they checked their cholesterol, and this, besides lifestyle, there are medications you can take to nip it in the bud, right? If you what we call secondary prevention. The plaques and tangles started, but let's wipe that amyloid out. Let's stop the amyloid from causing the tangles. Let's stop that process from causing the main problem, neuroinflammation, that causes most of the cell death. Then I think the price will come down because so many people will want to have it.

NANCY KEACH: I think so too. So I'm just quickly going to answer a question that came in through YouTube from Steven, who said, I mentioned that Mike Zuendel got rid of his amyloid after three years. What did he do? He was in a trial for the first monoclonal antibody that Biogen tested, called Aducanumab or Aduhelm, I guess was the name.

DR. RUDOLPH TANZI: Aduhelm is the brand name. Aducanumab is a generic name.

NANCY KEACH: And so what he did basically was participate for three years in a trial with one of these drugs that are called a monoclonal antibody, like Kisunla and donanemab. And we have episodes on both of those drugs, so if you're interested. And he went from a pretty high amyloid burden in his brain down to a very small amount, and he feels great. Now, I'm not trying to endorse any drug or anything, but that's his experience.

So there is the question, once we get a memory screening or we get a diagnosis, and I understand-- by the way, also, I was just talking to another scientist that Dr. Tanzi knows, Mike Weiner, who's working on an assessment, a cognitive assessment that could be done over the phone. Just like a bot kind of thing, which would be wonderful and make it free and more accessible to everybody. And not just a little like preliminary screening, but an actual diagnosis, so he's just working on that now, but there's a lot happening. But when you get the diagnosis, what are the actionable items people can take right now? And what do you think it's going to be a year and three years from now?

DR. RUDOLPH TANZI: Diagnosis of biological Alzheimer's or clinical Alzheimer's?

NANCY KEACH: Oh, let's say both. And let's say, first of all, can you give a brief introduction specifically because these are terms the scientists use that the public mostly doesn't know. What is primary prevention versus secondary prevention?

DR. RUDOLPH TANZI: So primary prevention would mean it's something you do to prevent the pathology itself from even occurring in the brain. Things you would do so that you don't have amyloid occur.

NANCY KEACH: Never start.

DR. RUDOLPH TANZI: You keep the brain clear of amyloid. You keep the brain clear of tangles. And you have to remember that Alzheimer's disease pathology is the most common age-related brain pathology. And if all live to 120, we will probably have plaques and tangles and neuroinflammation, and its genetics and lifestyle that determines when you're going to get it. And I quote Randy Bateman when he said in a recent meeting we were at together, the faster you make amyloid in your brain, the sooner you get Alzheimer's. But the amyloid can start forming 10, 20, 30 years before and start triggering the tangles. And then there's you have to have a buildup of that cell death, and then the inflammation is the big killer. That's the tangles and the plaques initiate. The inflammation is mainly executing the cell death.

So primary prevention means what can I do in my life to-- or what even therapies can I take given I know, I like to say early prediction, early detection, early intervention. Early prediction is I know my family history, or maybe I know my genetics. I carry two APOE4 risk variants, or I have a familial early onset Alzheimer's gene that's very penetrant. That will tell you when you need to start about early detection. But if your genetics are strong enough, you might want to start primary prevention because you're going to get there. So that's preventing the pathology at all.

Secondary prevention is the pathology is there, but you don't have symptoms. You want to keep it that way. You want to stop bringing that amyloid down, or the tangles down, or the inflammation down, so you don't get to the point of clinical symptoms. And right now the only drugs we have to do that are only approved for early treatment, not for secondary prevention, because they're too expensive and they have safety issues that preclude them from being used just in some secondary prevention manner. We need safer, more affordable alternatives for that purpose, which I and many others are working on.

And then finally you have treatment. So you have now the clinical symptoms, but at this point it's early stage treatment. So what can you do? I mean, you're talking about lifestyle?

NANCY KEACH: Well, I think lifestyle, for sure. And you mentioned SHIELD briefly, and we just had Miia Kivipelto on the program in January. So for those of you who are interested in a deep dive into what you can do in your lifestyle preventions, you can see her episode as well as Dr. Tanzi's work.

But I'm thinking about not only prevention or lifestyle interventions, but what if you wanted to participate in a trial that might reduce amyloid before you have symptoms? And I'm looking for them because people had asked, and I'm not finding it on my sheet. But basically they say, I try to join a trial, and then I'm told I can't participate because I have no symptoms. So that's one thing I hear all the time. So if I want to know and I want to participate, I can't find a trial to participate in. And that's my plea to you also to your trials coming up. If you could do them across the country and not only in Boston, that would be wonderful. And I know that takes funding, but I'm just putting in my plug anyway.

And then after that question, the other question that I get all the time and is really bothering me, and I've been speaking to people is what about for people who already have Alzheimer's and their loved one is in the moderate stage and is 78, or 83, and they can't participate in any trials either, and they feel nothing's being done? If I already have Alzheimer's, or I'm caring for my loved one, why is no one trying to develop the things for them? And from the business perspective, I also think that's a huge marketplace of people, who have Alzheimer's symptoms already. And it's kind of being ignored as we make this big push to prevention, which of course I understand why, but I wonder if you can comment on all of that?

DR. RUDOLPH TANZI: Well, that's a lot.

NANCY KEACH: Yes, it is. Sorry.

DR. RUDOLPH TANZI: But I guess I would start by saying, yes, the majority of trials have been on people with symptoms. And more recently they've focused on people with the earliest stage of the disease, because that's where you have a chance to see an effect. That's how the immunotherapies were approved. These were very early-stage patients, and you have to do a lot of them for a long time to get a result if you're

hitting amyloid because amyloid is something you want to prevent early on, and to treat it, you have to at least have treat early as possible.

We're seeing a push now toward trials that are looking at prevention. Reisa Sperling at my institution at Mass General Brigham and Harvard is carrying out prevention trials. And I'm not sure about enrollment right now, but Reisa Sperling is her name. And then at the McCance Center for Brain Health that I directed at Mass General, we're going to be doing trials where we don't care if you have symptoms. We're going to be doing trials to say, can we lower your brain pathology? That's all. We're going to track the blood biomarkers of brain pathology, plaques and tangles, using C2N blood tests. We're going to be using natural products. We're going to be using repurposed drugs, and we're going to just ask can we see in a patient that we're in six months that we've lowered their pathology in the brain? We're not going to be looking at cognition. So we just want people to have the pathology. Biological Alzheimer's meaning pathology, no symptoms, and clinical Alzheimer's, meaning you already have symptoms of cognitive impairment.

Where I got these drugs and natural products from is 10 years ago, we invented Alzheimer's in a dish, as it's been trademarked. This is a mini human brain organoid made from human cells that are turned into various brain cells, that we can grow in a matrix, where what takes a decade, or two, or three in the brain for the pathology to lead to enough cell death to get cognitive impairment, we get that to happen in six weeks in a little mini human brain organoid in a dish. That's made screening for drugs and natural products, that could stop the pathology 100 times faster and cheaper. So we tested every known approved drug that you could get a prescription for. Over the counter, prescribed. We tested 3,500 natural products that are available in supplements. And we said, what works? And we came up with over 300 known drugs that are already approved in natural products that either stop the amyloid, or stop the tangles, or curb the neuroinflammation, or even do with the immunotherapies do, which is to get cells in the brain called microglia, to eat the amyloid and clear it. That's how those immunotherapies work.

So we're making combinations of these that are multifunctional. Hit the

plaques and tangles and the inflammation with known safe drugs and natural products. And we want to do trials that simply ask, can we see in a person what we saw in the dish? In the dish, this combination lowered the tangles and stopped the inflammation. OK, let's spend six months treating a person, where we can look at blood biomarkers and say, did we have an effect? Did we lower the plaque and tangle in the brain? We're not trying to affect cognition, so we don't care if you have clinical symptoms yet. Just let's treat biological Alzheimer's disease. It will help both people on their way and people who already have the disease.

So that's what we're doing at the McCann center right now. I raised enough funds to do the first combination. Each one of these little trials is about $2.5 million, but we want to do like we have 25 different combinations that we're psyched about. So we're trying to raise like $50 to $75 million, so we can do as many trials as we can, and I think then it will be actionable. If you have safe drugs and natural products that work, everyone gets the blood test, and you can afford to give everybody an actionable step. You can democratize early detection, early intervention. That's our goal.

NANCY KEACH: Which is fantastic. And I'm going to leave aside what are we doing for patients who are more progressed for the moment, but because there's so much to get to. And several people have asked in the chat about what are the supplements and treatment? And years and years ago, you told my husband and me that you really liked ashwagandha, and so I've been taking that for a long time along with algal. Algal DHEA. What therapeutic compounds are you most optimistic about? Klotho, rapamycin, intranasal insulin, something else. MAbs, CT 1821, non-invasive brain stimulation, so there's a lot of research going on. The bad news is it's very confusing. What are the things you're most optimistic about?

DR. RUDOLPH TANZI: Well, we don't have a treatment. I mean, the sad truth is we don't have something that can treat full blown Alzheimer's right now. Even hitting the amyloid, you can slow cognitive impairment and decline with the two new immunotherapies, and it's only in early stage patients. And if you have full blown Alzheimer's disease, you really have to stop neuroinflammation because the wildfire has started. And the fewest trials we have, the fewest drugs we have in the pipeline are for neuroinflammation. They've got to catch up.

My lab discovered the first neuroinflammation Alzheimer's gene in 2006, CD33. Then TREM2 was found. Now we have dozens of these genes that affect neuroinflammation. There's a catch up time. You have to go from the genes to the drugs. Remember those first genes we found in the '80s and '90s were for amyloid. That's why there's more drugs for amyloid, but they don't work on people who have full blown Alzheimer's. You have to use those either early stage, and there's limited benefit, or for prevention.

So among the therapies that are out there, I'm excited about drugs that will stop amyloid production, or clear amyloid in a safe and affordable way. I don't think there's a lot out there right now in trials, I'm sorry to say, that I'm excited about. I think that we got to do better, honestly. I hate to be negative, but I think that we're on a learning curve now, where we really have to start thinking about my goal is to repurpose. I think, take what's already on the shelf. Learn what will work, and it's already safe, and start making combinations of those. And natural products as well, and there are supplements. I take a handful of supplements every morning, and I'm careful about talking about them because most of the supplements you buy on Amazon don't even have the stupid thing in it that they say is in it. It's an unregulated Wild West world, where even if you're buying a supplement that has the right natural product in it, you don't even know if it's really in there, or if it's clean, or if it's contaminated. It's just unregulated.

So what I've done is for the natural products we found that work in our dish, I've looked at supplements that contain them and make sure they're real. Look at the third party testing. Make sure they're clean. And then I do have a list that I send to family and friends, or people who ask me with the links to supplements that I trust that contain the natural products that we found agnostically just screening the dish. Things we didn't even expect to find.

And what I do is people email me because I send it with a three paragraph disclaimer. This is not clinical advice. We don't have clinical evidence yet. This is lab-based. I personally take them. For a lot of these natural products. We don't know the long term effects. We don't know they're deemed to be safe, but who knows? So I want all that in a disclaimer

before I send them out. That's why I just don't yank them out. But I'm happy if people want to email me for that list, I do it all the time. Then they get the disclaimer. They get the links to the right supplements that I trust. If I just give a name and you go online and buy a supplement that purports to contain it, you don't know what you're going to get, so this is a better way to do it. I'm happy to do that.

NANCY KEACH: That makes a lot of sense, and maybe is it OK if we put your email in the chat?

DR. RUDOLPH TANZI: Yeah.

NANCY KEACH: OK, great. And I want to ask-- and I know Jamie has been asking a lot of questions. What are your feelings about the promise of these GLP1 drugs potentially being useful in Alzheimer's? Do we know?

DR. RUDOLPH TANZI: We don't know yet. I mean, some of the early looks you're not seeing anything on symptoms yet, or it looks like some of the thinning of the brain where neurons get lost was ameliorated a bit by one of the GLP1s, but I think the jury's still out. I think we need to see—

NANCY KEACH: We have to do more tests.

DR. RUDOLPH TANZI: --trials and see what happens, so it's still early days.

NANCY KEACH: And Jamie also asked when you're APOE4 positive, and there are a lot of questions. So we have 30 or 40 questions in the chat about APOE4 status, and I had written in my original set of questions, if you're APOE4 positive, does your protocol change like your lifestyle interventions?

DR. RUDOLPH TANZI: Oh, no.

NANCY KEACH: But she's asking, what does it mean when you have a C2N result that comes back as in the gray zone and your APOE4 positive?

DR. RUDOLPH TANZI: So that means that you need to do things more diligently and vigilantly than the average person when it comes to lifestyle right now, or even I'm not claiming my supplements that I take are going

to clinically work. That's why I'm trying to do the trials on them now. So I'm trying to raise funds to do a trial, so I can speak with more authority about the clinical evidence. But I would say that whether you're in the gray zone or not, APOE4 is a risk factor, and you got to do more. And I think lifestyle can go a really long way, and when Dean Ornish did a lifestyle intervention trial where the results blew my mind, and Dean's running with it. Dean's starting a protocol now based on it. I think I'd like to see another trial that's bigger, but it was only 50 people. 25 on a lifestyle intervention, 25 not only in 20 weeks. And it was based on his book and the diets in his book that are similar to the plant-based diets recipes. It was based on SHIELD as well.

SHIELD, we didn't talk about yet is sleep because it's during 7 to eight hours. Even a power nap is fine. Every time you go through a cycle of dreaming to deep sleep, you help rinse away amyloid in the brain. You turn on the glymphatic system that cleans up amyloid in the brain, so you want to have as many of these cycles of dreaming to deep sleep as you can. And sometimes a good power nap will get you one of those cycles. I like to think like a rinse cycle for the brain. And sleep when you dream, it also helps consolidate memory because dreams are like little movies based on real events, but they help consolidate memory. So you rehearse your dream, and then you clear away the amyloid and debris.

So H is handling stress. Stress is a killer. It causes inflammation, so that means finding ways to be more mindful in the moment, more relaxed, more calm. Don't let social media freak you out. Don't let people you don't like freak you out. Just try to be more mindful.

And I is interaction, so interaction with others. Loneliness is a risk factor for Alzheimer's. So a lot of people, the hearing starts to go, and then that leads to less interaction with others because they don't even realize it, but they're not part of the conversation because they can't hear, so check your hearing. Make sure that you can stay in the conversation, interaction with others. I like to say, but if you're interacting with others who stress you out, that's not good. Get rid of them.

And then E is exercise, so we showed years ago that exercise induces the birth of new neurons in the brain, neurogenesis, and a growth factor

called BDNF that keeps those new neurons alive. And I think giving Alzheimer's mice a running wheel worked as well as any drug so far. And we can actually video which mice use the running wheel all night, and believe me, you can never exercise this much. These mice go crazy on the running wheel, but other mice don't use it and they just watch. They're like, hey, look at Joe go. And the mice so you can know who exercised and who didn't. Then you can see the ones that exercised new neurons are born, and they also clear amyloid in the brain because we found out that there's a hormone made by muscle, a myokine called irisin. When you exercise, that goes into the blood, gets into the brain, binds to a cell called the astrocyte, and it induces that cell to release an enzyme that breaks down the amyloid. So when you exercise, you're actually enzymatically breaking down amyloid with the help of your muscle myokine called irisin.

So L is learning new things. So the bottom line is cognitive decline is loss of synapses. 100 billion neurons, trillions of synapses or connections. When you learn new things, you make new synapses, and they connect with old synapses, and you strengthen your neural network. So synaptic reserve is like money in the bank. The more synapses you make, the more you can lose over your life before you run out. Just like having money in the bank, so you have to learn new things. So I like to say, if you're learning something new right now, I'm helping you to avoid Alzheimer's. But if I'm putting you to sleep, I'm still helping you either way.

And then D is diet, and you heard from Miia. So diet, in the trial we did with Dean we used a plant-based diet, strictly vegan diet. Now, a lot of people can't be vegan. I'm vegetarian, but a lot of people have trouble with it. So I say treat a vegan diet like medicine. As often as you can have plant-based diet, it's like taking a drug. Every time you make those gut microbiome bacteria happy, and they love crunchy things that are not potato chips. They like fiber from veggies, fruits, seeds, nuts, whole grains, and in this trial with Dean, where the main thing was diet, Dean actually had the vegan meals, 21 meals and snacks delivered to the patient and their spouse every week. So that was the most compliant part of this intervention.

We monitored sleep, exercise. Yes, they interacted on Zoom. They were

learning new things with lectures, et cetera, but diet was the main thing. And in this trial, using the same stringent cognitive test that we use for the immunotherapies, the toughest cognitive test to hit that failed again and again across different drug trials. These patients actually did-- the trial was actually more successful than the immunotherapies. In the immunotherapies they declined 25% more slowly. In this trial, they declined, I don't know what the exact percentage but almost flatlined the decline. Just it was like they went from a black slope to a green bunny slope skiing. And on one of the tests called CDR Global, this was amazing, they got better. So again, it's a small trial, but it says it gave me so much hope that lifestyle matters so much more than we think, and that if that blood test was covered by insurance, the actionable step is lifestyle and SHIELD, and I think it would make a difference. And if you find out you're starting to make amyloid, or if you're already APOE4 positive, you got to ramp SHIELD up. It now becomes an obligation. This is what you got to do to keep your brain healthy.

So that's a new book I'm writing, by the way. I'm not trying to sell the book. It's not going to be for a while. But I invented this acronym SHIELD about seven or eight years ago, and now it's gotten so viral that after not writing a book in years, my book agent said, you got to write SHIELD, so I finally decided to do it.

NANCY KEACH: And you were talking about stress, and I know you wrote a book with Deepak Chopra, who also talks a lot about how important stress reduction is.

DR. RUDOLPH TANZI: We wrote three books. We wrote a trilogy together. The last one called The Healing Self was the one that gave rise to SHIELD. I didn't have SHIELD in the book, but there's an action plan, lifestyle action plan at the end that after the book was published, I had to summarize it. I came up with SHIELD. And to me, it's twofold. SHIELD is meant to help reduce amyloid that triggers the disease, but it's also meant to reduce inflammation, which is the executor, the killer of neurons. It's meant to do both.

NANCY KEACH: And when we say exercise, what's the right dose of exercise?

DR. RUDOLPH TANZI: It's all about blood flow. So when your blood is flowing faster, your heart's beating faster. This is what gets the muscles to release this iris, and that goes to the brain and causes enzymatic degradation of amyloid. The same thing with the neurogenesis. It's blood flow that brings factors from the liver and other organs into the brain that induces neurogenesis. So you don't have to go crazy. If you can just get your heart rate up even 50% for 20 minutes a day, like take a brisk walk. I just I have a bike back there, and I jump on the bike for 20 minutes, and I do like 80 RPM. Just get my heart rate up at least 50%, and that blood flow is enough to achieve these goals of enzymatically breaking down amyloid with the help of muscle myokine and helping with neurogenesis, because you're getting the blood to deliver more to the brain that induces neurogenesis. It's that simple.

NANCY KEACH: And if you're exercise restricted or mostly bedridden, somebody has just written in, is there anything that you can do in terms of exercise or it depends. You need more information.

DR. RUDOLPH TANZI: Yeah, some people were thinking about meds that would safely increase heart rate, but I don't know if that's safe. And I'm not a clinician, so I don't know. I think there are other things that if you're bedridden there are other things you can do like diet. Look, when I go to SHIELD, and people say what's the most important letter? Diet. Absolutely, diet. Sleep and exercise closely follow. But man, when I see what we were able to do at Alzheimer's mice. We were able to get their amyloid cleared, their inflammation down with just a diet that was high in fiber. Prebiotics as they're called. So people take probiotics, yeah you're adding 10 or 11 bacteria to 8,000 strains and trillions of bacteria already in your gut. But when you have fiber, plant based diet, even just every single day, try to eat veggies, fruits, nuts and seeds, which I love. Whole grains. All your trillions of bacteria in your gut will be happy and balanced. And somehow, I don't know how, that leads to the clearance of amyloid in your brain. We see it in mice. We've published four or five studies that show that. So we always say, what's good for the heart is good for the brain. Equally true, what's good for the gut is good for the brain. It's equally true now, so diet's number one.

NANCY KEACH: I actually wanted to ask you about the relationship of the gut microbiome to brain health because there's been a lot about that, and you even wrote something about dental hygiene. But give us a little primer on the gut microbiome. And then for people like myself who have Crohn's disease and can't eat a lot of green leafy vegetables, I guess we go to the nuts and the seeds and the grains part.

DR. RUDOLPH TANZI: Yeah, right. I get a lot of fiber from nuts and seeds, and get the low salt ones, so you don't get overblown with salt. Your gut microbiome produces different what we call short chain fatty acids and like butyrate cetera, and these get into the brain through the gut brain axis. And they seem to stimulate microglial cells to eat amyloid. The same cell that eats the amyloid, the microglia, is the one that when it's overwhelmed, causes inflammation. So the microglia, you want them to be your best friends and not be your enemies. And somehow, a healthy gut microbiome in the short chain fatty acids that go to the brain when you have a balanced microbiome, really program these microglial cells to do the right thing and not do the wrong thing. That's the easiest way to put it.

So I actually started a company with Gary Ruvkun. Gary Ruvkun won the Nobel Prize last year for his work on microRNAs. And he and I started a company called Marvel Biome, where we actually isolated thousands of bacteria from the gut. I think 5,000 or 6,000, and then we test each bacteria individually to see which one can help prevent Alzheimer's disease and neurodegenerative disease. And then we made a mix of about 10 of those. And none of these are going to be in your yogurt or your probiotic. These are really arcane bacteria because we just screened to see which ones work. And now we have a collection of 10 of those that we're using in an Alzheimer's trial and then a trial on ALS, so as I like to say, using bugs as drugs. So that's the more extreme version of the gut microbiome. But just having a diet that keeps your gut microbiome happy and avoiding ultra processed foods, high fat, high salt, high sugar. That skews the bacteria ratios in your microbiome to be bad for the brain. So there's this ratio in the gut called firmicutes and Bacteroidetes, and that ratio becomes abnormal in Alzheimer's. And a healthy diet correct it. We actually had Rob Knight do the microbiome work on the Dean Ornish

trial, and we could see that we corrected the ratio in the right direction. I mean, I think that had a big part for why these patients did better with that lifestyle intervention.

So I do sunflower seeds, pumpkin seeds, different types of tree nuts, low salt every single day as just a quick fix. Just to keep my gut microbiome happy, because I don't always eat enough fruits and veggies. I should, but I don't.

NANCY KEACH: We're comforted by the fact that you're imperfect as we are. You mentioned having them with less salt, and somebody had written in a question about foods to avoid. So what are the top things to avoid as we add in the seeds, and the nuts, and the fiber?

DR. RUDOLPH TANZI: Well, junk food. Ultra processed food like cheese in a can.

NANCY KEACH: It really affects your brain. Not just your weight, but it really affects your brain?

DR. RUDOLPH TANZI: Yeah. I mean, Cassie Adekola showed that salt can directly affect tangle formation in the brain. So foods that disrupt the gut microbiome are ones that are very high in salt, fat, and sugar because it causes certain bacteria to grow well and other ones to suffer because it's a colony, and if one set of bacteria becomes opportunistic and grows more, it's going to hurt the other bacteria, so you want balance. And the Democratic principle for bacteria is when they have lots of prebiotics, which is fiber, plant-based fiber. So even if you're not vegan or vegetarian, just insisting every day that I feed my gut bacteria. Think of them like a fish tank, and you got to feed them every day. And say, oh, I didn't take care of him today. Go eat some pumpkin seeds and sunflower seeds or whatever every single day.

NANCY KEACH: I was going to mention along with this, that we had Laura Baker on as well. And Laura was doing a study, I guess it was a very large study, as I recall, over $5,000 people and they were really trying to prove out the benefits of cocoa or cacao, but they also tested it with a supplement. It was actually Centrum Silver, and she said on the program

that the cacao had no effect whatsoever, but that the Centrum Silver actually seemed to be rather beneficial.

DR. RUDOLPH TANZI: Probably because of the B vitamins. I take Centrum Silver myself.

NANCY KEACH: I do too.

DR. RUDOLPH TANZI: Yeah. So the director of our clinical trials at the McCann center, Gene Bowman, when he was at Nestle, they came up with what's called a nutritional risk index, where you can look at certain components in your blood that are indicative of your nutritional health status. And they found that B vitamins like B12 and folate, D3 and omega 3 fatty acids like DHA and EPA, if you take just those three, you can make a score. So if you're low in one of those, you get a score of 1. Low in 2, 2. Low in all 3, 3.

And what we're finding is that nutritional risk index correlates with risk for Alzheimer's and Alzheimer's biomarkers. And we're waiting to hear about a large NIH grant that will actually directly benchmark the nutritional risk index against the blood based biomarkers of Alzheimer's pathology, and this is particularly true for APOE4.

So supplementing D3, B vitamins, which could be just a supplement, centrum. But also adding in omega 3 fatty acids, so that could be from fish oil. But as a vegetarian, I get it from algae. I take a vegetarian-based DHA, EPA. And with fish oil, I'll say this, if you're not paying a lot for your fish oil, be careful because fish oil, it's cheap, like in big tub full of fish oil. It's going to be full of mercury, cadmium, cesium. Because our oceans are filthy and fatty fish accumulate heavy metals. So if they're not doubling or tripling distilling the fish oil, you could be doing more harm than good because you're going to be getting mercury poisoning, and that's very bad for the brain. So if you're going to do fish oil, make sure it's a very high end fish oil, that's at least doubly distilled to get rid of those metals.

NANCY KEACH: And you're suggesting is the algal or the oil from algae less likely to have those contaminants?

DR. RUDOLPH TANZI: Yeah, that's it doesn't have metals in it. Yeah. Not to push a brand, but I know Nordic Naturals is supposed to be very clean. And the algal one I use is from Spectrum, but I'm not pushing that because I'm not involved with those companies.

NANCY KEACH: The one you said was Nordic naturals?

DR. RUDOLPH TANZI: Nordic naturals for the fish oil, and then for the algae, I think, Nordic naturals makes a vegetarian one, but I've been using Spectrum for a long time.

NANCY KEACH: This is fantastic information, and we have only four minutes left. And so first, I want to in front of all these people, extract a promise from you to come back because there's so much we haven't covered. Thank you.

And I just I do want to devote a couple of minutes to a second question from Mike Zuendel, who I opened the show, the episode with, and we talked about stigma and getting an Alzheimer's diagnosis. He is on a crusade to try to change the use of the word dementia as related to cognitive impairment and cognitive decline. And when I first heard about this, I said, you're this is just an uphill battle. Everyone, in fact dementia, the term dementia is searched on the internet more than the term Alzheimer's, but both Alzheimer's and dementia have terrible connotations, especially demented. And I thought at first, this is a very difficult task to do. But he went back into history, and I saw how he changed the use of many other terms that were considered medical terms like idiot and retarded and these words that got officially changed. Do you feel it's important to change the lexicon at this time?

DR. RUDOLPH TANZI: I do

NANCY KEACH: That's not your thing, but—

DR. RUDOLPH TANZI: No, I do feel it. I think that dementia is a general term for catastrophic cognitive decline, but unfortunately, we don't diagnose diseases of dementia. The most common being Alzheimer's, until there's already early-stage dementia. So the way forward is going

to be to do for Alzheimer's, to do for diseases from the neck up, what we do from the neck down. Early detection. Early intervention. Not wait until you have symptoms. We don't wait till you have symptoms of diabetes, or heart disease, or we don't wait for a tumor to get big enough that you have symptoms from organ failure. We treat everything early from the neck down.

It's tougher from the neck up, but because there's stigma. Because if you get diagnosed with a blood test that says you have Alzheimer's pathology, which a lot of people will have. In fact, in this country, the high end estimate for how many people have amyloid, if you had a blood test which sees it before the PET scan. The blood tests will detect the tangles and plaques before the blood scan, before the PET scan. And if you ask how many, the low estimate is 10 million. The higher estimate is 50 million, so got to give these people a fighting chance. Let them find out and make it actionable. And that means that you need to know whether you're going to do SHIELD more and lifestyle. You need to know if you have biological Alzheimer's, meaning Alzheimer's pathology.

I don't want to call it biological Alzheimer's. I don't want to call it Alzheimer's. I think we have to come up with a whole new lexicon, different names. And I agree, get away from dementia that just shows this age-related spectrum that can take decades from the pathology that's going to accumulate in most of us, just a matter of when, not whether. And for some you might avoid it until you die of other causes, for that's what half the population. But know you're on your way and be able to speak about it openly without stigma and take care of it.

There was a time when cancer-- when I was growing up, cancer was the C word, right? Heart disease. We have Alzheimer's is the A word. Let's just deal with it because we have to. The only way we're going to beat this disease is early prediction based on genetics and family history. That will guide when you do early detection, and you want to know decades before you're going to have symptoms that you need to intervene and nip it in the bud. That's early intervention. That's how we're going to stop it.

NANCY KEACH: Thank you. That was a great wrap up. But I'd like to ask everybody who's still on, if you don't mind, to weigh in on this question.

Do you feel it's important to change the terminology, in particular the word dementia? And just if you do feel it's important to put a yes into the chat box, because I'm fascinated with how much this means to this person and I think a lot of other people as well. And also how it ultimately gets into the scientific lexicon as the researchers are working, and what kind of a paradigm shift we might be able to affect if there were changes in these words. And I don't know what those words would be, and I know that everybody is struggling with that, but cognitive. Yes, and to stop politicizing it, I agree.

So please keep writing your messages in the chat, but Dr. Tanzi, I want to thank you so much for your time today. I know everybody deeply appreciated it. And to everybody on, you will get a transcript of this. You will get a recording of it, and we will try to have Dr. Tanzi back because there's so much more to cover.

So if you would like, in addition to the resources that we're going to send-- and I should mention also Dr. Tanzi, you were on the scientific review committee for BrightFocus Foundation. I know some of the stuff you talked about today, the work was funded by BrightFocus Foundation, so thank you for all the work you've done with us.

You can ask for free publications here at brightfocus.org, info@brightfocus.org, and the next slide, please. If you have particular topics that we haven't covered yet, please email them to reply@brightfocus.org, and the last slide. We've also started, as I think most of you know, a sub series on clinical research. And Dr. Tanzi, this may be of interest to you. I try to do multi-site trials, but we are hosting every other month an additional episode where we pick one clinical trial and we just talk in detail about that trial. And we've done the HOPE study and the START study, and we're going to continue to try to promote different studies for different kinds of therapeutics and interventions. So the next one of those is April 3, and the next one of these is March 20, and we hope you will all join us. And, again, we could do a silent applause for Dr. Tanzi. Thank you so much. And I hope everybody has a great month, and thank you for joining us. Take care.

DR. RUDOLPH TANZI: Thank you all. I wish I could answer every question

in the chat. Maybe there's a chance later on with Sharyn to tackle more of those.

NANCY KEACH: And I think you're going to get about a couple hundred emails, Dr. Tanzi.

DR. RUDOLPH TANZI: Yeah, well I have the PDF is ready, and it's just the disclaimer is important, because there's too much snake oil out there, and there are people pushing brain snake oil. I can't mention names because some of these companies make so much money, they'll sue you as soon as you say they're snake oil. But most everything out there is bunk, so you got to be really careful. So that's why I like to do it with a real letter and disclaimer and then say, here's what we found lab based. And then if I can raise enough money, we're going to do the clinical trials and then we'll have the clinical evidence, hopefully.

NANCY KEACH: By the way I agree with you. I see television commercials for products that have absolutely no evidence to support them.

DR. RUDOLPH TANZI: Zero biological basis, never mind evidence.

NANCY KEACH: Zero biological basis. My mom is 95, and has mild cognitive impairment. She lives with my sister. My sister tells me she's on the website ordering things online. Just it's not right, so thank you for putting together that sheet. That's incredibly important. And thank you all again. Have a great day, and it's great to see everybody.

DR. RUDOLPH TANZI: OK, Thanks.

NANCY KEACH: Take care.

Resources:

- SHEILD lifestyle interventions for brain health
  - Sleep
  - Handling Stress
  - Interaction
  - Exercise
  - Learning New Things
  - Diet