Announcer:

Bulletproof Radio, a state of high performance.

Dave:

You're listening to Bulletproof Radio with Dave Asprey.

Dave:

Today's guest is not likely going to talk at least too much, about circadian biology, but he's a renowned microbiologist who has researched, studied, and written about Alzheimer's Disease for almost four decades. He's discovered several Alzheimer's Disease genes, including all three early onset familial genes and he's worked on developing therapies for Alzheimer's using mini brain organoid models of the disease. And if that's not enough, in his spare time he plays keyboards or guitars [inaudible 00:03:48] Joe Perry of Aerosmith, amongst others. In fact, he's been called the Rockstar of science. I'm talking about none other than Dr. Rudy Tanzi. Welcome to the show.

Dr. Rudolph Tanzi:

Thank you, a pleasure to be here. Wonderful.

Dave:

You do something I've always wanted to ask people about and I never understand what this means in academia. You're a professor of neurology at Harvard and simultaneously a vice chair of neurology and you're a co-director at Mass General, so how can you be the professor of this and master of all that is at multiple places all at the same time? How does that work?

Rudy:

Well, my academic appointment at Harvard Medical School is Professor of Neurology and I hold what's called the Kennedy Chair. The Kennedy family made a chair for their parents, Joseph [inaudible 00:04:43] Kennedy. But at Mass General, mainly what I do is run the large research unit of several labs, including my own, all doing Alzheimer's and brain health research. Then as things go, they asked me to take on administrative jobs. So vice chair of neurology department at Mass General, co-director of the McCance Center for Brain Health, co-director of the Mass General Institute for Neurodegeneration. Although that sounds like way too much, most of those administration jobs are mainly helping people to stay afloat and putting out fires. Most of the hard work goes into the actual research I do. It's mostly helping people, it's helping people survive the rigors of academic science.

Dave:

Thank you for answering that, because I've always wondered when you see someone who has this list of credentials that's incredibly long. But you've been involved with something like more than 600 papers and I would consider you one of the top names who's been studying Alzheimer's for a very long time. The reason I wanted to have you on the show, is that you've shifted your mindset from what we've believed for a lot of the last 35 years about what's going on. Tell me, what's changed in your perspective on Alzheimer's around beta amyloid and what we all thought was causing it? What's new?

Rudy:

Well, I would say that I've had to adjust my mindset. The first genes I found back in the 80s and 90s, all said amyloid. The amyloid box caused the disease. That doesn't go away, those genes still cause a very severe form of Alzheimer's and four different genes. Three of which we found at Mass General Harvard, all say amyloid deposition in the brain is what starts the disease. Everybody for decades has said, "Let's stop the amyloid, we'll stop the disease." Think about cholesterol and heart disease. That was pretty controversial in the beginning. No one believed cholesterol would cause heart disease, but what do we know now? If you have congestive heart failure or a heart attack, imagine your doctor says, "Here, just take a statin, just take a Lipitor and go home." Well, your heart's not going to get better. The cholesterol started the disease off decades before and then you get to the point of clogged arteries and arteries in the heart that are clogged and now you have congestive heart failure. It's too late just to take Lipitor. You would take it anyway, but you have to fix the heart.

Rudy:

Well, what we've learned it's the same thing in Alzheimer's. The amyloid comes really early, it comes decades before the dementia comes. It builds up and we've learned that the amyloid then causes nerve cells to die by evoking these things called tangles, these twisted filaments that kill the nerve cells from within. And guess what? Now we've learned that's not even enough to give you dementia, that just kills some cells. But the next step is now as those cells die because the amyloid cause the tangles, and the tangles are spreading and killing little pockets of nerve cells, not enough to give you dementia, that then has to trigger a very primitive, innate immune response in the brain.

Rudy:

The brain has the immune system equivalent of an oyster or a horseshoe [inaudible 00:08:04]. It's immuno privileged, it doesn't want antibodies or T cells or B cells or everything else the body does that's very clever. The brain says, "We don't want to risk anybody coming in here. We have a blood brain barrier, we take care of ourselves." They have these little cells called glial cells and they're normally housekeeping and nurturing and helping the nerve cells. But when they smell some cell death, they are programmed the same way they were 50,000 years ago when we were running around in the jungle and our lifespan was 25 years old. And at 20 years old in the jungle 50,000 years ago, if nerve cells were dying, you had an infection. You got bitten by a bad mosquito and those glial cells said, "This part of the brain's infected, wipe it out." Guess what? The brain never got the memo about how we live today. That same evolutionary program is in place. We have evolutionary baggage.

Rudy:

You have plaques that come really early and tangles and kill a few nerve cells and the brain's immune system freaks out and says, "We're in trouble, wipe it out." That is what kills enough nerve cells to get Alzheimer's Disease. It took 40 years to learn this, but that's science. You learn from your mistakes. The key is, you learn, you adapt, you move on and we're doing that right now really well.

Dave:

It feels like the plaque in your arteries is a Band-Aid for damage to the arteries. And the tangles or the plaques in the brain are there because something caused inflammation and then you get these Band-Aids and then you get a follow on effect from the body. Is that a good way of looking at it from a lay person's perspective?

Rudy:

Well, it's a little different. It's a good analogy but it needs some nuance. With heart disease, inflammation can cause plaque, but just high cholesterol can cause plaque.

Dave:

Well, depending on which kind of cholesterol, it could cause plaque, right?

Rudy:

Well, high LDL, high what we call bad cholesterol.

Dave:

Small particle LDL, yeah.

Rudy:

Right, small particle LDL. But in Alzheimer's when you get enough of this amyloid beta protein... I found the first Alzheimer's gene back when I was a student at Harvard, and it's the gene that makes that amyloid beta protein, I called it amyloid protein precursor. Really boring name, APP. That stuff is being made in the brain. We now think it's made in the brain for a reason. We can get into that. We think it's actually protecting the brain against infections. Well, put that aside for a minute. As this amyloid protein accumulates, it's sticky and it does form plaques and it aggregates. As that stuff aggregates, we now know that that causes the tangles made up of a different protein called tau and now nerve cells start dying. But the inflammation that kills the bulk of the nerve cells, removes the bulk of the synopses that causes dementia, comes after that process.

Rudy:

Whereas, in heart disease you get more of a juxtaposition as you were saying, of cholesterol deposition plaque and inflammation all around the same time. It's a little bit more iterative in the brain where you go from plaque, to tangle, to cell death, trigger neuroinflammation. Now you get the big forest fire that kills enough nerve cells to cause dementia.

Dave:

I wrote an anti-aging book that came out recently, called Super Human. Hit The New York Times list a couple weeks. I went through this idea of plaques amyloid basically throughout the body. It's not just in the brain, they're different types, not necessarily amyloid beta. It seems like there's a bunch of common elements that can create amyloid, which is one the big seven pillars of aging in all tissues. Are brain amyloids that different from the amyloids that make all of us age?

Rudy:

It's a different protein. I mean, the one thing they have in common is that there are some amyloids in the body outside the brain, that are from proteins that normally try to protect you against microbes. They're called antimicrobial peptides. There's lactoferrin, for example and [inaudible 00:12:15]. These things, when they get overly exuberant in their job of clumping around microbes and trapping them in goo called extracellular traps, they can cause amyloidosis of the heart, of the eye, et cetera. In the brain, amyloid beta protein, as my late colleague Rob Moir and I found, is the main antimicrobial peptide of the brain. And when it encounters a bacteria, it starts to glob around it and form a plaque. We showed that a plaque can form overnight just due to one single bacteria, in one of our papers. But you can also

have genetics, gene mutations like the early onset genes, that allow you to make this plaque all the time without a need for a microbe to seed it or nucleate it or trigger it.

Rudy:

Every amyloid's a little different, starting with the protein that makes it and how it's triggered. But the thing about the brain is, that genetics can allow you to accumulate this amyloid over time without the need for a microbe. Just like there are genetic forms of amyloidosis in the kidney, the spleen, the heart, the eye, the seminal vesicles, that allow you to make amyloid without any provocation except a difference in the protein from the gene, from a mutation.

Dave:

Does this mean that anything that reduces inflammation might be good for Alzheimer's?

Rudy:

Only if it reduces brain inflammation, which is again, very different than body inflammation. If you tried ibuprofen or NSAIDs and steroids, they have very limited ability to stop neuroinflammation in the brain. Because neuroinflammation in the brain is the only thing the brain has to protect itself so it's very different. In the brain, you literally have these micro glial cells and glia is Greek for glue. They used to think they just glued the nerve cells together, so they glia was glue. But these little cells are normally housekeeping and when you're in deep sleep, getting back to circadian rhythms, when you're in deep sleep after REM, these little microglial cells go around like scrubby bubbles and clean up the amyloid and all the deposited debris. Then literally, the brain squeezes it out. It actually constricts and squeezes this crap out through the lymphatic system. That's why you need to get enough sleep, I call it mental floss. It's when you're cleaning your brain.

Rudy:

Now meanwhile, if nerve cells start dying, these same little scrubby bubble microglial cells, they're sentinels. They have ways to detect that nerve cells are dying, just like they did 50,000 years ago. When they sense a certain amount of cell death, let's say through the plaques and tangles which are the initiating pathology in Alzheimer's, the pathology that comes very early before symptoms, they freak out. They say, "Wipe out the area, wipe it out. We're under attack." They assume the same thing that they assumed 50,000 years ago. If neuro cells are dying, there must be an infection. Well, guess what? At 70 or 80 years old you could have neuro cells dying because you accumulated enough plaques and tangles to kill enough. It's an unnecessary innate response. You have to learn what activates these cells to switch from housekeeper to killer.

Rudy:

My lab found the first gene that does that back in 2008. We found the first Alzheimer's gene, called CD33. We didn't know what it was at the time. It's actually funny, because Time Magazine made it a Time medical breakthrough of the year. We said, "If they only knew, we have no idea what this gene is." It took us five years to figure out that the CD33 gene is the on switch that tells the microglial cells, "Stop housekeeping and start killing." Now a lot of companies and what we're doing, is we're trying to turn that gene, turn that protein off as a way to stop neuroinflammation. That's just one way we're trying to do it.

Dave:

Now, neuroinflammation. You said it's different than bodily inflammation. Aren't the inflammatory molecules called cytokines, that run throughout the body, aren't they the same? The ones that are known for causing inflammation in the body, IL-1, IL-6, tumor necrosis factor, there's herbs, there's dietary things, there's ketosis, there's fasting. They seem to lower them in the body, but don't they also lower the same ones in the brain? Or are these ones that don't get into the brain?

Rudy:

You're right. The cytokines are the same. These microglial cells, when they turn into killers, they spit out these cytokines just like in the body, the macrophages do that. The microglial is like the macrophage of the brain. When they spit out these cytokines, what that does is it invites the other glial cell in the brain, the astrocytes, to the party. The astrocytes that are doing different jobs that are also helpful, get turned on by these cytokines that the killer microglial cells are spitting out, and it makes the astrocytes become reactive. Then the astrocytes gang up with the microglia and just go on a killing spree, eating synapses, eating axons and killing neurons. Now the microglial cells get the astrocytes to help wipe out that brain area that they think is infected because some nerve cells died, and they do it together. The cytokines get released to do that just like in the body, the macrophages when they release their same cytokines, cause an even greater inflammation response to start taking over tissue.

Dave:

For people listening, we don't want our parents to get Alzheimer's or we don't want to get ourselves, I'm planning to live way longer than I'm supposed to and I'd like to remember my name when I'm old. I mean, what are the things that you would look at doing, as someone who's studied this for for 40 years, knowing that we don't know how to solve Alzheimer's. But if you had to make a bet as to the behavior things that are going to be good. I'm guessing exercise and sleep might be on your list. Are there any other things that you know what, we don't know for sure, but I have a gut feeling after 40 years, I bet you, I bet you that's better than doing nothing. You got anything for me?

Rudy:

You know what? The answers are not surprising. I wrote this book with Deepak Chopra a couple years ago [crosstalk 00:18:38].

Dave:

He was just on the show, by the way. It's cool.

Rudy:

Oh, great. At the end of the Healing Self, we had the seven day action plan for reducing inflammation in your brain and body. This is a weird story, but around the same time the book was coming out, I had a new album coming out with Joe Perry and Johnny Depp and Zak Starkey, the drummer from the Who, Ringer Starr's son. They were having a little record release thing and I had rehearsals. I'm thinking, "I got to also do this book thing talk with Deepak and a couple of others." I'm saying, "How can I quickly summarize the seven day action plan in the book?" I was literally in the shower and I keep this thing called Shower Notes or whatever. But it's a pad you can write on in the water and the little pencil says on it, "Don't let those good ideas go down the drain."

Dave:

Oh, nice.

Rudy:

Because you know when you're in the shower and the water's hitting your head, you get into a data rhythm, meditative rhythm? You get all these great ideas and then you get out of the shower and you're like, "Oh, man. What the heck was I thinking about?" It's all gone away. I wrote down SHIELD as the acronym. S was for sleep, because you got to sleep eight hours to get the brain to clean itself enough.

Dave:

The lymphatic system.

Rudy:

H is handle stress because stress causes cortisol. Cortisol can kill just enough nerve cells to then trigger neuroinflammation just like the plaques and tangles do. I is interaction, staying socially engaged. Loneliness is a risk factor for Alzheimer's. Not being alone, but being alone and not liking it, which is loneliness. Exercise, we published a big paper in science a year or so ago showing that exercise induces the birth of new nerve cells in the part of the brain that's affected by Alzheimer's. We could make Alzheimer's much better by getting new nerve cells to be born with exercise and we actually were able to mimic that with two different drugs. Now we can mimic it with two different supplements.

Dave:

This was via BDNF and NGF, brain derived neurotrophic factor and nerve growth factor? Or is it something else?

Rudy:

Yeah, right. It was BDNF together with a drug that's triggered neurogenesis growth. If you just triggered the birth of new nerve cells, called neurogenesis, it wasn't enough because they would die. So you had to give the BDNF at the same time. It's like growing tomatoes in an urban battle zone. You got to add some Miracle Grow for them to survive. You cause the new nerve cells to be born, but there's inflammation, there's crap going on, you add the BDNF and it's like Miracle Grow and they can survive and then help, so you need both. That's the E, exercise. Then L is learn new things. The bottom line is, the degree of Alzheimer's correlates with loss of synapses. You have 100 billion nerve cells, you've got 10s of trillions of synapses and the more you learn new things the more synapses you make, the more you can lose before you lose it. I tell people, "You're going to retire? Don't just think about financial reserve, think about synaptic reserve."

Rudy:

If our listeners are learning new things right now, we're helping them. If I'm putting them to sleep, I'm still helping them. So either way, we win. D is diet. Diet is really Mediterranean Diet. The Mediterranean Diet; plant fiber, less red meat. I'm a vegetarian, I haven't had red meat since college or fish, or chicken. But more plant fiber, olive oil and you got to help your gut microbiome. Because your gut microbiome keeps your brain healthy. We published papers showing we could dramatically reduce plaque and neuroinflammation in the brain by having a healthy gut microbiome. A lot of people take probiotics, which are fine, but you really need prebiotics. You need plant fiber to keep those bacteria in your gut healthy and happy. That's SHIELD.

Dave:

I take about 40 to 60 grams a day of specific plant fibers I formulated as a part of Bulletproof, plus all the vegetables that are the foundation of my diet.

Rudy:

I'd like to learn what those are, because I just take a very simple fructooligosaccharides, which I'm sure doesn't do much.

Dave:

It's called Inner Fuel, and it's a mixture of acacia gum which will outperform FOS on studies, but FOS is good. FOS comes from inulin, but if you take very much inulin you fart like no one's business. We use inulin from chicory in the Bulletproof collagen bars for a reason, it's a prebiotic. But in Inner Fuel we've got acacia gum, we've got larch arabinogalactan, which is another sap of a tree. These are the ones shown in studies to feed the good bacteria, not just feed any bacteria in the gut. Then the third thing is hydrolyzed guar gum, which is another plant fiber. But it's hydrolyzed, which means we break it down with enzymes before you get it so it goes in and feeds the bacteria. It's 35 calories, you put two big scoops of it in your coffee and that gets you I think two thirds of the RDA for fiber. I made it because you can't eat enough plants when you travel. You order a plate of vegetables, you get three spears of asparagus and it makes you mad. The answer for that was I just put that in my coffee and I'm okay.

Rudy:

I would love to learn [crosstalk 00:23:49].

Dave:

I will send it to you if you want some, happy to.

Rudy:

That's great. I have to say, I do take the FOS but I'm not going to admit to having any flatulence problems.

Dave:

That's why working with anesthetized patients is a good idea when you're a doctor, because then it doesn't matter. I'm kidding. But the idea of managing your gut bacteria it's just emerging so much with inflammation in the brain and you can actually see when butyric acid goes up in the gut, which is what the good guys make, that at least according to two studies I could find, inflammation in the brain goes down directly like the inflammatory cytokines that we talked about before. We can't say that prevents Alzheimer's Disease, but lowering inflammation in the brain seems like a good idea generally to me, for all sorts of performance reasons and probably is protective. True statement? Maybe true, what's your take on that?

Rudy:

Very true. In fact, let me tell you some exciting news. I started a company with two young guys; Justin Clee and Josh Cohan, about six years ago. They were actually undergraduates at Brown University when I met them. They had this idea to protect against neuroinflammation. How does neuroinflammation kill a nerve cell? It's by depleting its energy, oxidative stress. They said, "If you're going to have a bulletproof vest, then you have to protect both the mitochondria, the energy center, and the endoplasmic reticulum

or the ER, where proteins are made." From what they could find, no one did a trial where you protected both and they argued you only have half of a bulletproof vest. So we used a purine analog, TUDCA for one and we used as you were saying, butyric acid, we used phenylbutyrate. Phenyl butyric acid for the other side. You combine them and it was amazing. When we did studies in putting nerve cells in a dish and you add hydrogen peroxide to kill them, these two together saved 95% of the nerve cells. It was unheard of. I thought it had to be a fluke.

Rudy:

Fast forward now to this past year, the company we started is called Amylyx. For transparency, I'm a shareholder because I'm one of the founders of it.

Dave:

Thank you for expressing that. A-M-I-L-E-X?

Rudy:

A-M-Y-L-Y-X, Amylyx. They did a trial, these two bright young guys. They're 28 years old now. Did a trial on ALS, this is full blown Lou Gehrig's Disease. Six month trial, 130 or so patients and they used that combination and the trial worked. They announced a successful trial back in December. In fact, the ice bucket challenge of ALS, Pete Frates who started that, was able to learn two days before he died, that this trial worked. The ice bucket funded a lot of the actual clinical trial. This drug worked so well in the trial, it's going to be announced at the AAN meeting, American Academy of Neurology meeting in Toronto in April.

Dave:

That gives me goosebumps, man. I love stories like that.

Rudy:

And he got to learn that two days before he passed, that there very well may be this year, if things go well, a new approved drug for ALS based on the work of these two bright kids that helped out. They're not kids anymore. This isn't even stopping neuroinflammation, it's just protecting the nerve cells in advanced ALS patients against neuroinflammation and they got a significant difference between the drug and the placebo for rate of disease.

Dave:

If you look at the number of brain conditions that are tied to neuroinflammation; you've got autism, ADHD, pretty much Parkinson's, some Alzheimer's, it's a long list. I did a whole book on brain, mostly about mitochondria, but brain energetics and all that and it's interesting because this idea of adding a phenyl molecule, phenyl butyric, phenyl makes stuff long lived in the body, but it's relatively simple. There's something called phenyl GABA, which I'm huge fan of for sleep, except that it keeps getting gray zoned by the FDA, which is just GABA. Neuro transmitter for calming the brain, you add a phenyl to it so it doesn't break down and people go to sleep really well. But they get addicted if they take a lot of it, apparently. But the idea of going through and finding a relatively simple way of, I'm going to call it hacking the brain, that your two colleagues figured out. They just thought about systems biology, said, "What if we did this..." This isn't a new molecule that came from a spider they found in South America. This is just how should it work, what if we tried this.

Dave:

So kudos to them and that's the sort of thing where I'd say, "Hmm, I wonder if I should just take that on occasion to make my brain live longer?" But I'm sure trials will come out for that later, right?

Rudy:

Well, we've got an Alzheimer's trial going now. But the thing is it was amazing to me to find out that people had done trials trying to protect mitochondria, but no one ever tried to protect where the proteins can get [inaudible 00:28:45] at the same time in the ER. It's this combination and then it worked. Now I have another company I'm helping out as a head of their SAB, again, shareholder, called AZ Therapies where we use the Alzheimer's brain in a dish model we talked about earlier, the mini brain organoids. Now that we have these mini brain organoids the size of paper punchers, we can screen any drug, natural product 100 times faster, 100 times cheaper than when we had to use mice. And actually, it's a much better model than mice. I mean, mice suck as a model for the brain. We like to say in my lab that mice are like Vegas. What happens in mice, stays in mice.

Dave:

I've never heard that, I like that.

Rudy:

We use these brain organoids. One of the drugs that's an asthma drug called cromolyn, it was able to take the microglial cells and keep them from being killers and keep them in that housekeeping state. It stopped the neuroinflammation. If you just take regular cromolyn for asthma, it won't get into the brain. But it was reformulated and delivered in a way that does get into the brain-

Dave:

Is this [inaudible 00:29:53] or something?

Rudy:

No, it's just a micronized, [crosstalk 00:30:00] with an inhaler that gets it into the deep lung. Now the [crosstalk 00:30:04] can be transferred into the blood through the alveoli and into the brain. That trial is on Alzheimer's, it's a phase three trial, it's going to read out later this year. They're also doing an ALS trial. That's the other side of the coin, take out the sniper. In other words, the Amylyx kids gave the bulletproof vest that worked, the other company's trying to take out the sniper, take the microglial cell killer and turn it back into a housekeeper. Imagine if you had both together if they both worked. Basically you could treat Alzheimer's, Parkinson's, ALS, depression, autism, just like you were saying.

Dave:

Twenty years from now, are we going to be looking back and saying, "Man, that was the dark ages. Peoples' brain just kept screwing up all over the place as they aged. And now, we just know how to do it."

Rudy:

Absolutely.

Dave:

Ah, that makes me so happy. I think so too.

Rudy:

It's been a learning curve. I mean, I was involved with the first ever genetic studies to find a disease gene back when I was 20 years old with Jim Gusella, he was 25. We found the Huntington Disease gene. We found the first five genetic markers in the genome. Got ridiculously lucky with just a handful of genetic markers where the gene could be anywhere, we found it. Twenty thousand to one odds against. That study triggered the human genome project and I do hope Jim Gusella, it was all his idea, will get the Nobel Prize for that someday. It was the first time a disease gene was found by genetics. I switched over to Alzheimer's after that and found the first Alzheimer's gene. But I think about it, we've only been finding these genes for this mysterious diseases for a few decades. Here's how it worked. The first genes you find are the really extreme cases, the early onset, familial, so they tell you about the earliest events that happen, that are now happening even earlier. Like you're born, two years old, you're already having some events happen. Normally they don't start till 30 or 40.

Rudy:

Then you try to treat those events in a patient and it's too late. You're trying to put out a forest fire by blowing out the match. The forest fire's neuroinflammation. These early genes taught us about the triggers, the matches, the brush fires. It's too late to stamp those out. But now, all the newest Alzheimer's genes we're finding, over a dozen of them, tell us how to stop neuroinflammation. One of them is this first gene we found, CD33 and now we're seeing the drugs come out. You got the trial from Amylyx, you got a new trial. You're going to see that just like glory days coming up for brain disease next few years.

Dave:

There's two things I've researched a lot and written about and talked about, that have studies specifically for Alzheimer's that were positive. One of them was MCT oil and the other one was nicotine. Not smoking, smoking's clearly going to cause inflammation from burning stuff and breathing it. But nicotine itself, Paul Newhouse's work at Vanderbilt since 1988. These are both bioenergetics, basically giving the mitochondria more energy via sticking to different receptors or just giving a different fuel source with more electrons. Any validity in your experience on stacking those approaches with the new drugs or with the SHIELD protocol that you talked about?

Rudy:

Yeah, I can't see the harm in it. I mean, why not? I mean, I don't think giving an alternative energy source is not going to stop the disease or cure it. But if the problem in the end of the day is that neuroinflammation is depleting nerve cells of energy, and now you're giving an alternative energy source, anaerobic energy source, why not? Why not do that for the patient? I would say stack it for sure. But I don't want people to say that MCTs or virgin coconut oil is a cure. [crosstalk 00:33:51]

Dave:

Virgin coconut oil doesn't do very much compared to... It's the same as eight hours of fasting, basically sleeping overnight. So coconut oil, no. There was a phase two clinical trial on one of the types of MCTs that had really good results that was reversing. But it's just one study. I don't know that that's a protectable IP thing. But it feels like maybe there are just even any kind of ketogenic diet because when you get the ketones in the mitochondria perform better. And the mitochondria that doesn't leak

electrons doesn't create inflammation. That was the model. The approach that I've been advocating is do everything that reduces inflammation in the brain. Which includes having high functioning mitochondria at the same time you eat less stuff like bad fats and sugar and all that. Stop pissing off your immune system with inflammatory proteins, if you know what they are. Stuff like that and basically you ought to live longer or at least function longer without getting bad stuff, whatever the list of bad stuff is.

Dave:

But I wonder if there's more there. And what about nicotine? That's so controversial you may not be able to say anything. But what's your take there?

Rudy:

I actually take nicotinamide riboside.

Dave:

Yeah, me too.

Rudy:

NR. [crosstalk 00:35:07] Yeah, it's a precursor of NAD. It boosts ATP levels, it boosts energy. In our hands it also induces neurogenesis. In fact, nicotinamide riboside induces neurogenesis better than the chemicals we were using in our science paper. And now we're trying to find additional supplements that can induce BDNF because if you induce neurogenesis and BDNF, then you can mimic the effects of exercise. Not that you take exercise away, but the beneficial effects of exercise for the brain. We now found biamine, coffee fruit extract, Cat's Claw extract, all of these things increase BDNF.

Dave:

The first shipping coffee fruit extract that was specifically for raising BDNF was a Bulletproof product. It's still out there, called Neuro Master. I'm like, "Hey, this raises BDNF four times more than exercise. Maybe you should take this and then do some squats." You might as well do both.

Rudy:

We're giving nicotinamide riboside together with coffee fruit extract to mice because we're following up on that science paper. Saying, "How can we help these Alzheimer's mice the way exercise did?" And exercise, remember both induced new nerve cell birth, neurogenesis, and it induced BDNF. So we combined the nicotinamide riboside to induce the neurogenesis and then we induce the BDNF with either coffee fruit extract or Cat's Claw is also very good.

Dave:

Cat's Claw's interesting because it's a South American herb that's been used for Lyme Disease and toxic mold for a very long time. Where you tend to have neurological break down, even the myelin protein that lines your nerves can break down. Full disclosure, I had both of those. I started playing with that a long time ago, but now we understand how it works. Even things like psychedelic mushrooms raise levels of BDNF and nerve growth factor in the brain. I'm not saying that Alzheimer's people should be eating a bunch of red and white mushrooms, but there's interesting studies that like, "How do we get more?" Any other ideas for how to get more of that besides exercise?

Rudy:

We're doing it. Basically, this guy Alan Rose is another Alzheimer's researcher, and I test this Cat's Claw that we get out of Peru. We actually started a company that sells it as a product called Percepta. It's Cat's Claw, it's Oolong tea. We tested that in Alzheimer's mice and actually it has anti-amyloid, anti-tangle, anti-neuroinflammatory properties, but it also induces BDNF. Again, I'm an equity holder in that company just for transparency purposes, but [crosstalk 00:37:46] something I get behind it. I just get it out to the masses, if you have to start a company, do it.

Rudy:

When you're talking about mushrooms, Paul Stamets, who you might know-

Dave:

He's been on the show. Love him, yeah. He was sitting right here.

Rudy:

He's now collaborating with us. He just sent us five extracts. I told him, "Don't send anything hallucinogenic, I don't want to go to jail."

Dave:

Lion's Mane though. Are you guys looking at Lion's Mane?

Rudy:

We've already been doing Lion's Mane and we have some good results there. He sent us extracts of non-hallucinogenic versions of I guess the psilocybin family of mushrooms. I don't even know what he sent. I mean, Paul's a mystery wrapped in an enigma. Paul sent me these mushroom extracts and I said, "Prepare them and we're putting them on our Alzheimer's in a dish. We're going to see what they do to plaques, to tangles, to neuroinflammation and get back to him. But we just thought of doing that collaboration now. I met him at the Exponential Medicine-

Dave:

I missed Exponential Medicine because I had to get home to see my kids after the Abundance 360 Conference with Peter Diamandis, so I just missed meeting you there. But that idea and you said something really important there. I get behind the things I believe in, if you have to start a company, go for it. Man, full respect for that. There's always trolls out there saying, "Well, you're making money. How dare you say it?" Look, you want to do something useful in the world, you might want to make it pay for itself. High five on starting multiple companies or being involved advising multiple companies making stuff that you can't buy. That's how the world evolves.

Rudy:

Yeah, you can't wait for others to do it for you. If you believe in it, you do it, man.

Dave:

It's a lot easier to sit there on Twitter and yell at the people who do it and then buy their stuff anyway.

Rudy:

Oh, believe me, I've been the victim... I wrote three books with Deepak Chopra, between those and the stuff I do, I mean I don't care about trolls. They can yell all they want. At the end of the day, people are going to remember who helped them.

Dave:

Not only that, the more they yell, the more they're likely to get a neurodegenerative disease because of the stress part. So you can just feel compassion for them as they yell at you and drain their neurons, right? That was dark.

Rudy:

I actually do feel empathy for them.

Dave:

Yeah, you have to eventually. Now, okay there's a bunch more potential new mushroom stuff and I respect Paul so much. He's a good human being. We got some exercise going on, what about the circadian stuff? Satchin Panda's been on the show, one of my companies... Again, full disclosure, I started it because you had to do it. We make glasses that for me and for a lot of people report a doubling of deep sleep when you measure it with a [inaudible 00:40:18] or however else you measure it. It seems like going to bed on time, getting large amounts of deep sleep are important for that. What's your take on circadian timing, fasting, darkness for Alzheimer's neuroinflammation? Are those things that you can measure with a brain in a dish?

Rudy:

Well, if you think about what sleep is doing for neuroinflammation in particular is, right after REM during that slow wave sleep, you're consolidating memories. Your dreams are fictionally regurgitating whatever memories are triggered all day so you can consolidate and reinforce those synapses during the slow wave deep sleep. During slow wave deep sleep it's also the only time you're not making amyloid in your brain. Because amyloid's being made in your default mode network that maintains your ego and who you are, all day, all the time. Only after REM, during slow wave sleep does that thing turn off. But thirdly, it's during slow wave sleep that microglial cells go to town and they just start chomping up all that debris and spitting it out and getting the brain to constrict and get it out. It's called the glymphatic system. Glymphatic's when the glial cells eat, lymphatic system's when the brain squeezes it out. You need to get enough of that REM to deep sleep cycling and we need to get enough sleep for that purpose.

Rudy:

Fasting, I fast several times a week because I do think inducing an anaerobic metabolism is also good for the body, good for the brain. I don't think [crosstalk 00:42:01].

Dave:

Are you doing intermittent fast, you're skipping breakfast basically? Or are you doing a longer fast?

Rudy:

After dinner the night before, I don't have breakfast or lunch and [crosstalk 00:42:10].

Dave:

Okay, so intermittent fasting, 18-hour thing.

Rudy:

Eighteen hours or maybe it's sometimes longer and then drink a lot of water all day, then dinner at night.

Dave:

You already answered my biggest question, which was “is there hope”? In 20 years are we going to just be done with this? Is 20 years too long? Is this a five-year problem?

Rudy:

Well, here's how it's going to be. In the next five years we're going to help the patients who have Alzheimer's now by finally giving them what they need. That means drugs that stop or supplements or lifestyle behavioral modifications, all the above the hit neuroinflammation. It's too late to hit plaques and tangles in people who are suffering from full blown Alzheimer's right now. If you get them when they're really early stage you might be able to hit the plaques and the tangles, but that's what we've learned. We can do that in the next five years. I mean, the first drug trial that protects against neuroinflammation from this company Amylyx I helped start, is already going to be out there and the next ones are coming.

Rudy:

As far as what's going to happen, I have an 11 year old daughter. How's she going to stop Alzheimer's when she's older? She's not going to wait for neuroinflammation to come around and then try to put out the fire. She's going to stop the initial match and brush fires that get you there. Meaning she's going to be monitoring her blood tests, whether she's making too much plaque or tangle in her brain. And she's going to start taking whether it's a natural product or a drug or modifying your lifestyle, she's going to do what she has to do to bring the amyloid plaques down when she's 20 or 30 years old or 40 years old. Just like with heart disease, we manage cholesterol at middle age. You don't wait to get heart disease and say, "Okay, now I'm going to manage my cholesterol now that I have congestive heart failure." That's going to be the [inaudible 00:48:25].

Rudy:

I think for the longer term of early detection of Alzheimer's, early prediction followed by early intervention where you stop the initiating pathology way before you get to rampant neuroinflammation, that's stage two. That's going to take probably more toward 10 years.

Dave:

But only 10 years.

Rudy:

Ten years, yes. Because now we know how to do it. I have a drug I've been developing with a colleague in San Diego for 20 years, called a gamma secretase modulator. It's the last drug standing, it will be a small little white pill you can take to bring your amyloid down. All the rest bit the dust because they weren't safe. Ours we hope is going to be safe, it's going into clinical trials, it's predicted based on how it was developed to be safe. If you have to take it, hopefully your lifestyle and everything else you're doing will mean you don't have to take it, but just in case, just like you have to take a statin. We're going into

clinical trials at the end of this year after 20 years of development. Fifty million dollars of pre-clinical development, the safety trial with my colleague Steve Wagner, will start the end of this year.

Rudy:

Good things take time and I'm thinking that drug's going to take some time to get out there. But if that makes it, you've got a blood test that's going to come out of Washington St. Louis in about a year or two. So the future will be you get your blood test at whatever years old, 40 years old. They say, "For your plaque in your brain you're in the 40 percentile. It wouldn't hurt to take this little white pill to bring your plaque back down." Now we don't want to wipe out your amyloid beta protein, because it helps protect your brain against microbes, we just want to dial it down. Just like you would take Lipitor to not wipe out your cholesterol, but dial it down. That's [inaudible 00:50:11] future, that's going to take a little bit longer. But the first anti-neuroinflammatory medicines for neurodegenerative disease, neuropsych disease, they've already started. They're going to be out over the next few years.

Dave:

This was one of the hypotheses, hypothesis, whatever more than one of those is called.

Rudy:

Hypotheses.

Dave:

Hypotheses for Super Human, is that there are hundreds and hundreds of researchers who've been working for two, three, four decades on hacking all of the different pillars of aging, the big diseases, and Alzheimer's Disease is one of the big four killers. It was the fourth one, but 10% of people are likely to get it if you look at statistics today. The deal is how do you not be one of those 10%, but also it's one of the big things after cancer or heart disease and diabetes, Alzheimer's ranks. But every one of those has their rock stars like you, although not all them are literally rock stars but hey. What's going there is all of it hitting fruition this decade. This is why I think we're going to live a lot longer than we think we're going to live, because the big killers are getting taken out and the root causes around this buildup of amyloid and all of the other things. There's someone working on it, guys like your two former kids now in their mid-20s, but your business partners. They did it and it didn't take them that long.

Dave:

I'm more hopeful than I've ever been about our ability to be very healthy, very energetic and even look good when we're old. Are you there too? You think that's where we're going?

Rudy:

I'm right there with you. You're spot on. And I would say on Alzheimer's, think about this. At 85 years old, 40% of our population have at least the early symptoms of Alzheimer's if not full blown Alzheimer's, 85. The current life span is 80. A kid 12 years old right now or even someone 20 or 30, can expect to live till 80 or 85. If you do the math there, for people in their 20s or 30s right now, they almost have a 40% or 50% chance of living long enough to get this disease. They're probably going to live till 85, at which point depending on the study you read, have a 40% to 50% chance of having Alzheimer's. On top of that if you're 20 or 30 right now, and you're paying off your college loans and medical school or whatever, graduate school loans and you finally get free and you have kids and you pay for their college. Then what happens, you finally say, "Ah, breathing room," and then you've got to take care of your parents

who are living long enough to get Alzheimer's Disease. I mean, this disease just hits every age group and a lot of young people don't think about it, but now they have to.

Dave:

The other thing that's just worth noting, in fact, oh, I got to ask you this. I was the largest individual supporter last year of Maria Shriver's women's Alzheimer's group. And Alzheimer's hits women more because they tend to be in caregiver roles, but they also get Alzheimer's 50% more often than men. I know two thirds of people who have it are women versus men. Are your little brains in Petri dishes, are they girl brains or boy brains?

Rudy:

Well, that's the thing. I'll tell you something. Actually today, at a luncheon in New York, my geneticist colleague who works with me is at the Women's Alzheimer's Movement luncheon with Maria Shriver because-

Dave:

Maria Shriver, I love her. She's so good.

Rudy:

Because they just gave us funding for our study to find genetic risk factors that predispose women different than men. We already found four different genes that increase risk in women but protect men or vice versa. Increase risk in men and protect women. The exact opposite in men and women.

Dave:

Are half your brains female brains with the cell cultures you're doing?

Rudy:

The problem is that we can do that, we have mixed female and male nerve cells from stem cells, but a lot of it has to do more with hormones and steroid... Because it's hormonal differences, you can't yet replicate that in the dish, so I can't really say we're truly addressing male versus female [crosstalk 00:54:27].

Dave:

You'd have to add testosterone or estrogen to a certain cell along with the treatment and see or something. Wow! Okay, still-

Rudy:

But wait, but wait, I'll tell you something. One of the supplements that's like estrogen, Genistein, was among our natural products that had a really strong effect on tangles actually.

Dave:

In women or in men?

Rudy:

No, in the dish.

Dave:

Oh, in the dish, yeah. It has problems for humans who take it, from what I've [crosstalk 00:54:52].

Rudy:

I'm not saying to take it, I'm just saying it worked in the dish.

Dave:

Yeah, some of those weird plant phytosterols can do cool stuff, but if they're also hormone mimicking we've got to look at the system. Well, I feel like I could talk to you all day and I'm really grateful you took the time for the interview. Just to help everyone listening, just know we are hacking this. There are guys like Rudy out there who are actively doing the heavy lifting that is showing up for you. So when you say, "Oh, I should take this bottle of supplements," there might be 20 years of knowledge or 60 years of knowledge. The stuff about Cat's Claw, the shaman who first gave me [inaudible 00:55:30] 25 years ago took me to the market and had me buy Cat's Claw and told me to take it afterwards because it would help. He knew something, he couldn't spell BDNF, right? In fact, I don't if anyone could we not have known about it.

Dave:

But there was ancient knowledge there but we didn't know why, we didn't know how, we didn't even know whether it was actually safe. But you've gone out, you've looked at that, and there's so much like that. I'm incredibly inspired, incredibly hopeful and actually expecting improvements in all of the markers there, so the audience that's listening today just got to hear from one of the guys in the trenches. Just my thanks and on behalf of the hundreds of thousands of people that are going to hear this, thank you.

Rudy:

Well, thank you. And can I say one last thing?

Dave:

Absolutely.

Rudy:

If you're interested in supporting Alzheimer's research, the Cure Alzheimer's Fund is who I work with. It's curealz.org, Cure Alzheimer's Fund's given out over $110 million of research funding and it's the best, top Alzheimer's research in the world. Every dollar they take in is a dollar out, they take no overhead on your money. So if you give a dollar, it's a dollar to research and they're a great foundation. They've made a lot of these discoveries we've talked about today possible. So Cure Alzheimer's Fund.

Dave:

All right, you guys heard that. If you're inspired by this or if you have someone in your family who's affected by this or you just don't to be yourself and think, "Oh, I've got 20, 30 years to have to worry about that," well, here's the deal. Fund a little bit now so 30 years from now you definitely won't have to

worry about it. Curealz.org and the Women's Alzheimer's Movement are both just profoundly good charities and going out there and maybe going for a walk is a good thing to add to your stack as well.

Dave:

Rudy, thanks again for your work, for your books with Deepak, and for starting multiple companies that are solving the problems of mankind. I hope that you make incredible amounts of money from each one of those because I know what you'll do with it, you'll probably put it back into research.

Rudy:

Absolutely, right back into a foundation. I immensely enjoyed our discussion, thank you so much.