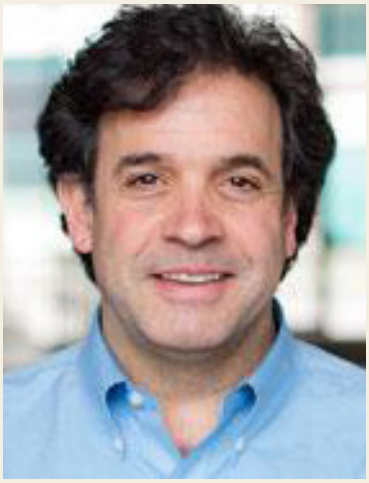
The Latest Findings on Alzheimer's Disease:

An Interview With Rudolph Tanzi, PhD



Rudolph Tanzi, PhD

By Michael Dregni

In 2014, Harvard neurology professor Rudolph Tanzi, PhD, synthesized Alzheimer's disease in a petri dish using "mini brains" created from human stem cells. This breakthrough opened up new opportunities for research into the causes of dementia, dramatically furthering the possibility of treating the disease — and hopefully finding a cure.

Tanzi is one of the world's leading Alzheimer's researchers and coauthor with Deepak Chopra, MD, FACP, of *Super Genes* and the *New York Times* best-selling *Super Brain*. Because of his pioneering dementia research, Tanzi was named to *Time* magazine's "100 Most Influential People" list for 2015.

The breakthrough also led to the discovery of a third pathology of Alzheimer's: Inflammation in the brain was found to accelerate — and then compound — the disease.

In this exclusive interview, Tanzi explains how fighting inflammation is essential to keeping your brain resilient and combating Alzheimer's.

Q&A

Experience Life **| Can you explain the latest understanding of how Alzheimer's disease affects our brains?**

Rudolph Tanzi | In Alzheimer's disease, there are three pillars of pathology. There's the plaque, the tangles, and inflammation.

Beta-amyloid protein is the material that makes up the plaque. At first, there was a long debate about whether the plaques cause the disease; all the families we studied, and genes, everything pointed toward the amyloid triggering the disease.

At the end of 2014, my lab came up with what we called "Alzheimer's in a dish": We modeled Alzheimer's in a petri dish with mini brains grown from stem cells from patients. We could actually take stem cells, turn those into nerve cells, and grow them in a mini organoid — a mini brain — and then completely recapitulate a lifetime that it would take to get Alzheimer's in just two months in a dish.

Using that system, we were able to study aspects of Alzheimer's beyond using just mice. I always argue that humans aren't 150-pound mice. Things happen in mice that don't happen in humans; it's just not a great research model.

With the mini brain, we were able to show for the first time that amyloid does lead to the rest of the disease. Amyloid causes the tangles: The tangles form inside the nerve cells and that's what chokes them and kills them. And amyloid also causes inflammation in the brain — neuroinflammation. And moreover, once those nerve cells start dying, there's more inflammation.

EL **| When does Alzheimer's disease first begin developing in people?**

RT | From imaging studies that were done here and in Australia, it became apparent that the plaques start 15 years before the symptoms. So this *disease* starts 15 years before the *symptoms*. When someone has a tumor, you don't wait until somebody has symptoms to say they have cancer, right? They have cancer.

Alzheimer's is the same. There's pre-symptomatic Alzheimer's and there's symptomatic Alzheimer's. When we talk about the 5 million patients in this country with Alzheimer's, those are symptomatic patients. If you include the people who have enough plaque and tangle and they're 15 years away from the disease, that number probably goes up to about 20 million people who have Alzheimer's — 5 million of whom are symptomatic, 15 million of whom are pre-symptomatic. So, it's a much bigger disease than we even think.

The plaque and the tangles come very early. This also explains why many of the trials that targeted the amyloid plaques failed: They were treating full-blown Alzheimer's patients, and the amyloid already did its job 15 years ago. So it's kind of like someone who has had a heart attack or congestive heart failure and you say, "Here, just take a Lipitor." You had to do that 15 years ago!

So now we're treating patients earlier, and we're treating patients who don't have symptoms yet, but have the pathology in their brains.

EL **| You mention people with "resilient brains" — what does that mean?**

RT | Everyone once in a while we see the brains of people who died in their 80s or 90s full of plaques and tangles, enough to say, "Yes, this is Alzheimer's disease," but they were perfectly fine when they died; there were no cognitive issues. The term we use for this is resilient — they have resilient brains.

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Then we can ask what makes a brain resilient? How can a brain have all the pathologies, those plaques and tangles that drive this whole process, but not have cognitive issues?

In each case, the resiliency was explained by the lack, the absence of neuroinflammation. So it means that the plaques and tangles start the cell death, like brushfires, and those brushfires spread — but if you don't have neuroinflammation, you don't get the full-blown forest fire.

So neuroinflammation has now become a big target for us in terms of therapies. It's the only pathology of the three I mentioned that occurs early, mid, and late [in the development of Alzheimer's]. The plaques and tangles occur early, but it's the neuroinflammation that takes you out. So what that means is that if we can stop neuroinflammation, you can live with a lot of plaques and tangles and still stave off Alzheimer's disease. Plaques and tangles push you up the mountain, but it's neuroinflammation that pushes you off. You can live on that mountaintop for a long time.

EL **| So how do you fight off neuroinflammation in order to have a resilient brain?**

RT | Much of what we're doing in my lab now is trying to understand how to do that. This is where genes come in. Our lab and other labs have discovered the genes that control neuroinflammation.

But neuroinflammation is highly dependent upon your lifestyle. So you have certain genes that are setting the stage, but it's a script that's not written in stone, it's written in clay, which can harden into stone. If you live your right lifestyle you can resculpt that clay, because even though you're born with certain genes from Mom and Dad, that predispose you toward this disease or this personality trait in most cases based on how you live your life, this is going to change the expression of your genes, their activity.

We basically collected the data from epigenetic studies — meaning they're studying how gene expression changes en masse in response to your lifestyle. Because when you're eating junk food, that's hurting you, it's promoting inflammation. If you eat a healthy diet, avoiding junk food and processed food, choosing organic, then basically over time with repetition, that will reward you with better

gene expression.

The beauty of epigenetics is that once those genes are trained, once those genes keep expressing the same way because of a good habit like a good diet, those genes become chemically modified to keep doing it for you. That's what epigenetics is. You actually have chemical modifications of genes induced by your habits and lifestyle that allow those genes to then take on programs of expression that are either going to be detrimental or beneficial.

The simple rule is that good habits lead to beneficial gene programs and bad habits lead to detrimental ones.

The question is then what do you need to do in your life to minimalize neuroinflammation. Until we get drugs to do this or even after we have drugs, it's better to adapt your lifestyle to prevent neuroinflammation.

***EL* | What are the key lifestyle choices?**

RT | The three biggest are sleep, diet, and exercise.

Sleep — because during deep sleep, it's the only time your brain cleans itself out. Two important things happen during delta-wave, or slow-wave, sleep — that stage 4 deep sleep that you're in and out of all night. The only time that you don't make amyloid in the brain is during deep sleep. And the only time you clean amyloid from your brain is during deep sleep. And on top of that it's during deep sleep that all those short-term memories that you took on all day get kind of backed up on the hard drive; so if the data from the whole day is on a thumb drive, you put it on your hard drive during deep sleep.

Since a lot of this debris that accumulates in the brain, like amyloid and other debris that you see in Parkinson's disease, since that debris induces inflammation as the brain reacts against it, during deep sleep you're really hitting all three pathologies of Alzheimer's because you're hitting the amyloid plaques, because if there's less of that you're going to have less of the tangles and also have less inflammation. So deep sleep's important.

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We recommend that especially if you're over 40 that you religiously get seven to eight hours of sleep each night. If you don't, you're not giving your brain enough of a chance to clean itself.

***EL* | How does exercise help fight Alzheimer's?**

RT | Exercise does three things relevant to Alzheimer's. First, during exercise you induce the production of enzymes in the brain that clear the amyloid, that eat it up — enzymes that actually attack and chew up the amyloid. This is all based on rigorous scientific studies in journals — this is not *woo-woo*; this is real stuff.

Also during exercise you make new nerve cells — a process called neurogenesis — in the hippocampus, the area effected by Alzheimer's. This is known as AHN, adult hippocampal neurogenesis. Luckily, the hippocampus, the area you need to protect in Alzheimer's, is one of the few areas in the brain that as an adult you still continue to make new neural stem cells, and exercise is a very potent way to induce those stem cells.

The last part of it, as we found out in a study we're just publishing, is that it doesn't help you to make new stem cells in an area of the brain where there's inflammation — they just die. They can't help you. It's like having a baby born in a war zone. So, we also found that exercise has this dual effect of not only does it allow new nerve cells to be born, but it also cleans up the area of inflammation — it's anti-inflammatory.

Exercise has the effects on the brain of less amyloid, new nerve cells, and less inflammation. All that would predict that it's very salutary for Alzheimer's patients.

It seems that the very simple prescription of 8,000 to 10,000 steps per day is a good goal. You don't have to go crazy; just keep moving.

***EL* | Which brings us to diet.**

RT | Diet is immensely important. Your microbiome, via the gut–brain axis, is in constant communication with your brain, and your microbiome has been shown to regulate neurochemical balance and neurotransmission; it's been shown most importantly to regulate neuroinflammation.

There are studies done on mice where you have a multiple sclerosis model where you can actually put the microbiome of a healthy mouse into a mouse with

MS, and you actually reduce dramatically the inflammation of their brain. But again, it's a mouse, and we're not 150-pound mice. But it does show that the microbiome can directly affect neuroinflammation.

So promoting microbiome health, you have to hit both sides: You need your prebiotics and your probiotics. Prebiotics being fiber and fruits and vegetables and the like, and the Mediterranean diet. Probiotics include yogurt, kefir, and fermented food, kimchi — which I can't stand! I'm a vegetarian, so I take a probiotic supplement in the morning with 20 million live colonies.

Being very aggressive about managing your microbiome is important, and that means staying away from greasy fried foods, fast foods, and processed foods. Stay away from foods that contain too many petroleum products. If you take care of your microbiome, it'll take care of you, and that's all the way up to your brain, including the most important risk factor for Alzheimer's — neuroinflammation.

***EL* | Any other advice for things to do in your life to prevent Alzheimer's?**

RT | Keep moving intellectually and socially as well as physically. Loneliness is a risk factor for Alzheimer's. Staying socially engaged is protective. Learning new things. Not just Sudoku or brain games but literally learn *new* things.

This is protective for the brain because you make new synapses, and when you make new synapses you strengthen the synapses you already have because all learning is based on association. Whenever you learn something new you make new synapses and reinforce pathways you already have, and our brains have about a hundred billion neurons and hundreds of trillions of synapses.

If you ask what correlates most closely with dementia it's loss of synapses. So when you're ready to retire, think about not just financial reserves but also synaptic reserves — save up your synapses, keep learning new things. Keep moving physically, emotionally, and intellectually, and if you bring in meditation, also spiritually. Don't be stagnant.

We have a study soon to come out where we did a clinical study of meditation that shows it had a very positive effect on inflammatory genes and even on the biomarkers for amyloid in the brain. In just one week of intensive meditation, we saw effects on two of the pathologies of Alzheimer's, the biomarkers for inflammation and amyloid.

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