Medical News & Perspectives

Alzheimer Outlook Far From Bleak

Jeff Lyon

Last summer, deep disappointment befell the Alzheimer disease (AD) community when study results showed that the widely heralded experimental drug LMTX had failed to help AD patients. In November, another promising drug, solanezumab, also dashed hopes. Because these drugs target either amyloid β (solanezumab) or tau (LMTX), proteins that aggregate into the plaques and tangles in brain tissue characteristic of AD, some have suggested that researchers are following the wrong path by attacking these proteins and that AD research is back to square one after decades of work.

Author Audio Interview

Recently, *JAMA* sat down with 2 prominent authorities on AD, Rudolph Tanzi, PhD, of Harvard University, and Berislav Zlokovic, MD, PhD, of the University of Southern California (USC). Tanzi has been exploring the genetics and progression of AD for more than 30 years, while Zlokovic's work has emphasized the cerebrovascular system's important role in the etiology. They discussed what the future holds for AD research and whether the picture is as gloomy as some believe. The following is an edited version of that conversation.

Rudolph Tanzi, PhD

Berislav Zlokovic, MD, PhD

JAMA: Dr Tanzi, what was your take on these recent drug failures? Have you become pessimistic?

DR TANZI: Actually I'm quite optimistic. Most of us in the field are not surprised LMTX failed. I frankly don't think it was that strong of a drug going in. All the first genes we found [eg, amyloid precursor protein (APP) gene and presenilin genes] told us amyloid causes this disease, and the debate arose because when we put the genes into mice, they'd make amyloid and eventually have enough inflammation in the brain to get cognitively impaired but they didn't get tangles. They didn't get all 3 pillars of the pathology: plaques, inflammation, and tangles. So the question arose: Is amyloid really causing the disease? I argued, "Well, humans aren't 150-pound mice."

Recently, we created what the *New York Times* called "Alzheimer's in a dish," a 3D human neuroculture making stem cells that's growing in a gel matrix that mimics the brain. You put in the Alzheimer gene mutations that make amyloid, and afterward you get tangles from endogenous tau protein. You block the amyloid, you block the tangles. That was the first real proof of concept that amyloid can make tangles if you use human neurons in the right environment.

JAMA: Then amyloid seems to be the first step, preceding tau accumulation. If amyloid is so fundamental, why have drug trials targeting amyloid accumulation failed?

DR. TANZI: The answer seems to be that amyloid occurs very early in the disease, 10 to 15 years before the patient becomes symptomatic, and to treat a patient who by now has symptoms of Alzheimer with an amyloid drug was like taking someone with congestive heart failure who had a heart attack, and giving them Lipitor [atorvastatin], and saying, "Here, get better." It's too little too late.

JAMA: With so many complexities, are you anywhere near a unified theory of Alzheimer disease?

DR TANZI: There's general agreement that amyloid causes inflammation at the level of microglial cells and tangle production in neurons. Once this gets going, the tangles then kill more neurons, and it causes more inflammation. You get this vicious cycle. So to me the question becomes *why* do we accumulate amyloid in our brains?

JAMA: Dr Zlokovic, you would say that much of this is cerebrovascular, that the problem predates amyloid accumulation when the aging process weakens the blood

Left, Jeremiah Sullivan; Right, The University of Southern California

brain barrier [BBB]. It becomes leaky, letting in undesirable agents and hindering the clearing of amyloid.

DR ZLOKOVIC: Yes, absolutely. Obviously, amyloid accumulates in the brain, but there is a system that vigorously clears amyloid and other toxins. An important role is played by the blood vessels of the brain, the endothelial cells of the blood brain barrier and also its pericytes. According to my two-hit hypothesis, it is the [dysfunction] of this vascular system that is the first step that predisposes you to the accumulation of amyloid. It also reduces the oxygen and glucose supply to the brain: sugars, energy, metabolites.

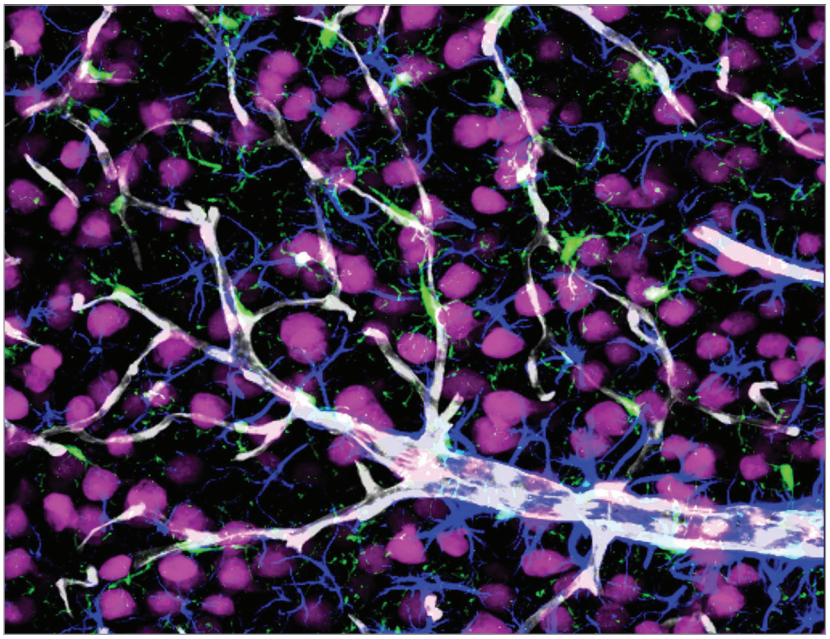
JAMA: So what then is the second hit? The production of amyloid β, the dangerous peptide that results from improperly cleaved amyloid?

DR ZLOKOVIC: Yes, that's part of it. But it may not necessarily lead right away to amyloid β because blood vessels have a huge ability to compensate, there is plasticity. So there is a fight in this period about 10 to 15 years before we see the disease. And then at the end, when the fight is over, when amyloid starts accumulating, we are seeing things start to go bad. So we were happy [recently] to get funding by the National Institute on Aging, Alzheimer's Association, and Duke Foundation, close to $25 million, to study people who have a genetic risk for Alzheimer and how they developed the disease in relation to changes in the vascular system.

JAMA: What are the opportunities that the blood system offers for intervention?

DR ZLOKOVIC: In my view, the vascular system is a phenomenal target because we have in our brains about 400 miles of blood vessels and these have to do their primary job of bringing food and oxygen to the brain and taking toxins out of the brain. To incorporate the vascular theory of Alzheimer may just help us get a broader, more inclusive view. So I think it's an exciting era.

DR TANZI: You have to ask what's making amyloid accumulate. We have to think about how to stop that by identifying the preceding event. This is where Dr Zlokovic's work comes in. Neurovascular events are the key, especially events that open the blood brain barrier and let in foreign agents, pathogens. It's interesting that in the 1960s we said that hardening of the arteries led to dementia. We're back to that.



The neurovascular unit comprises neurons (pink), astrocytes (blue), microglia (green), and arterioles and capillaries (white). The blood brain barrier, formed by the endothelial cell membranes of blood vessels within the neurovascular unit, regulates amyloid-β clearance.

In my laboratory, we're making what are called gamma secretase modulaters These block [the production] of Aβ [amyloid-β]. But the key is going to be—and I think this is really important—to convince the FDA [US Food and Drug Administration] that we have to hit amyloid before symptoms appear. Alzheimer has to enter the realm of treating it presymptomatically at the level of amyloid precursor and, according to Dr Zlokovic's work, at the level of the neurovasculature and the blood brain barrier.

And we also think we know what enters the brain to trigger amyloid because equally important to production and clearance is nucleation and seeding. We just had a paper this past year. It showed that microbes—bacteria, viruses, and fungi—can rapidly trigger amyloid deposition. It looks like amyloid is acting as an antimicrobial response to pathogens. This is a brand new paradigm, but it sets a hypothesis for what's coming into the brain and then triggering the amyloid deposition.

JAMA: So pathogens may be involved here? They enter through the leaky vasculature and the amyloid is really the brain's response to that invasion?

DR TANZI: That's what our paper says. So now we're counting on what we call the brain microbiome project, which sounds funny because the brain is supposed to be sterile, but it's not. As we get older, the blood brain barrier breaks, especially around the hippocampus, letting in pathogens just like they said in the 1970s. And it's not years of production and clearance in this case. You get instant nucleation. A herpes virus, for example, can cause nucleation of amyloid in a mouse in 6 hours.

JAMA: Dr Zlokovic, if it's important to reach patients before they become symptomatic, how are we going to identify them? What should we be looking for in a 40-year-old?

DR ZLOKOVIC: We do have one approach that we have developed at USC, which uses very powerful new neuroimaging systems to detect the integrity and composition of blood vessels. And we first observed people that are completely cognitively normal, and they start having gradual damage with normal aging. If these people develop subjective cognitive complaints, we see that this correlates very strongly with the changes in blood vessels in the hippocampus and parahippocampal gyrus, areas heavily involved in memory and learning. We know that there are genetic risk factors for Alzheimer

Zlokovic Lab

disease, like the *APOE4* gene. So we are looking at such people who are asymptomatic [to see] what kind of problems in the neurovasculature they have. And from these people, we're also getting cerebrospinal fluid because we have developed specific molecular biomarkers for the cells that are part of the blood brain barrier [eg, soluble platelet-derived growth factor receptor-β, which reflects possible injury to pericytes, the gatekeepers of the BBB].

What's beautiful about that approach is if we identify what is happening, the vascular system [can] be a powerful target. We have pathogens coming through the blood brain barrier. If we don't close it, they will keep coming.

JAMA: Have you started such targeting?

DR ZLOKOVIC: We are finishing a phase 2 trial with activated protein C (APC), which is a molecule that protects neurons and blood vessels from injury [as a result of] reduced blood flow to the brain. We know from [preclinical] studies that these drugs can stabilize the vasculature. [There is also] a phase 3 trial based on our work that Pfizer is carrying on with RAGE [Receptor for Advanced Glycation End Product] blockers. These improve blood flow to the brain and prevent accumulation of amyloid from blood into the brain.

JAMA: Dr Tanzi, let's go back to amyloid and infection. So amyloid moves in and fights off the invader. But what happens next? Why does the amyloid go bad after its done is job?

DR TANZI: The amyloid β protein is acting like a classic antimicrobial peptide. As [it] sees the pathogen, it defines the carbohydrates and sugar on the cell wall, and in doing so it starts to clump the pathogens. First it blocks adhesion to the host cell, then it agglutinates them, and it literally builds a web around them. In the immune field, that's called a nanonet. In AD, that's called a plaque. So in this case, the amyloid plaque is actually the tomb of the pathogen that has now been trapped into this web of amyloid. We showed that whole process in our paper.

But we don't know what in the brain is [provoking] this. Some people have their favorites: chlamydia, Borrelia, herpes. We're going in agnostically. So the brain microbiome project is funded by the Cure Alzheimer's Fund and another foundation, Open Philanthropy, and we're actually purifying plaques and looking by RNA sequencing at what types of pathogens are trapped inside. It could be viruses. It could be bacteria, but we're not coming up with any favorite candidates.

So we're thinking about how the blood brain barrier can be strengthened. You block up those breaches. There's interesting data on how the gut microbiome accesses the brain through the vagus nerve. [Maybe] we block access to the vagus nerve. But just in case we fail at that, we can also [discover] the most common pathogens that are driving rapid amyloid deposition and perhaps go after them with antivirals, antibiotics, or even vaccination. So it might be a very different world 5 years from now in terms of how we think about this disease.

JAMA: We haven't sufficiently covered inflammation in AD. How is that generated and does it offer a chance of treatment?

DR TANZI: In 2008, we found a new Alzheimer gene called *CD33*. [We've since learned] that *CD33* is the switch that turns on microglial cells such that instead of being protective for the brain as housekeepers and sentinels, they turn into soldiers who are shooting out free radicals and cytokines causing gliosis and neuronal cell death because you have inflamed astrocytes and microglials. The *CD33* gene turns it on and then another gene that responds to Alzheimer called *TREM 2* turns it off. So we know *TREM 2* and *CD33* are the yin and yang of neuroinflammation. This is a very active area now in academia and pharma to understand neuroinflammation at the level of microglial activation.

JAMA: Let's look down the road a bit. Can we get a timetable from both of you as to when we might see the fruits of this very promising research?

DR ZLOKOVIC: I don't know if there is going to be one single approach that will work, because it's a complex disease. It has a vascular component, inflammatory component, Aβ component, tau component, and all these components feed each other. So my recipe for this would be let's fix the vascular system first. Let's make sure that amyloid does not accumulate. Let's create a situation that amyloid can get out of the brain.

DR TANZI: I agree. Fix the neurovasculature early and throughout. Hit amyloid early, hit tangles early, hit inflammation throughout. It's too late to hit amyloid, maybe even tangles, once a patient is in the full throes of this disease symptomatically. This is a mistake we have made. [Newer therapies] are very wisely hitting the mild patients where the symptoms have just begun. So we'll be hearing results of antibody studies over the next 3 to 4 years. BACE (beta-site APP-cleaving enzyme) inhibitors blocking Aβ production are just going into phase 3 and we'll hear about those over the next 3 to 4 years. Same thing with the gamma secretase modulators. So I think over the next 3 to 5 years we're going to get a lot of answers about whether hitting amyloid is going to help. Even with mild patients, it might be too late. So I worry that if these trials fail, they're going to blame the hypothesis and not the timing of the drug.

JAMA: This doesn't sound promising for those already stricken. Is there any indication that somebody with well-developed Alzheimer disease could show some cognitive gain?

DR TANZI: If you stop the inflammation and keep their vessels healthy, never underestimate the ability of the brain to regenerate.

DR ZLOKOVIC: It's amazing what the brain can do. The only problem is that it's like in cancer. The later you start, it's more challenging because the amyloid and tau, they've already had their pass through the brain and they destroyed a lot.

JAMA: What does the future hold in the way of diagnostics? Would there be a test everyone takes at age 40?

DR TANZI: PET scanning for amyloid is already FDA-approved. It's just not covered by health insurance because it's not actionable [yet], although you could argue that lifestyle interventions may be actionable if you know you're in some trouble with too much amyloid in the brain. Let's say you have your brain imaged and find out your amyloid level is in the 60th percentile. You need to bring your levels down with this antibody followed by a maintenance dose. And you have to start taking better care of your brain and blood vessels. Exercise more, diet more, get more sleep. ■

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