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Tau Therapies and Clinical Translation: Mechanistic Approaches

Dr. Cabral:
Hi. This is CE on ReachMD, and I'm Dr. Dani Cabral. Here with me today is Dr. Marwan Sabbagh.

Marwan, how do emerging tau therapies target Alzheimer's disease biology? And what could that mean for patients?

Dr. Sabbagh:
This is a complicated topic, Dani, and one that's been vexing many in our field. We know that amyloid does not correlate very well with clinical progression, but tau spread does. The best is this is going back years to understanding that tangles is a better predictor of cognitive decline than amyloid burden is. So the idea of targeting tangles and tau has been on the books, or at least on the horizon, for a good almost 15 to 20 years, and yet, we're still vexed by it. It has been proposing a lot of challenges.

The reason is, is that at the end of the day, tau is a microtubule-stabilizing protein. So we have large proteins in our neurons called microtubules, which are trafficking proteins that let things go up and down cells, and they're held together by these crosshatched proteins called tau. And when they become hyperphosphorylated, they stop binding to the microtubules, and the microtubules fly apart, effectively causing the cells to lyse.

So the idea is maybe we need to find ways to mitigate that, and there's been a lot of different approaches. Kinase inhibitors have been tried. Microtubulized tau assembly inhibitors have been tried. But the concept that has really, really been a lot of focus in the last 10 years is the idea that when tau is released, it's taken up by an adjacent neuron in a process called prionosis. And that the idea is if we have a monoclonal antibody that binds to these free forms of phosphorylated tau that are floating around, you can then prevent the take-up of tau into adjacent neurons and stop this process called prionosis.

This idea has been around for 10 years and has been very popular, and it makes a lot of sense, and yet has not been as successful. There have been a lot of different tau antibodies, including semorinemab, gosuranemab, tilavonemab, zagotenemab, and these have been focused on the N-terminus aspects of the tau antibody. Others have looked at mid-domain, that’s the J&J product that recently announced negative results, and even the C-terminus of the protein. That would be the Lundbeck AF87908.

The reason I say this too is that people haven't given up on this idea, and that the idea is that maybe we need to stop looking at the N-terminus, the C-terminus, and the mid-domain and look further downstream in things like the MTBR protein, the microtubule binding region.

And that's what the BMS-986446 monoclonal does, it binds to a specific area a little downstream from the N-terminus, C-terminus, or mid-domain. And that idea is that it could be able to stop the spread of tau in ways the others haven't done. It's in phase 2 trials, it's been very exciting. They actually got a Fast Track designation, and the study is underway, enrolling 475 participants.

So we'll see. But the idea is that we haven't given up on stopping the process of stopping prionosis. The only signal positivity has been ASO, antisense oligonucleotide protein, which has shown lowering of tau. Other than that, we haven't had a lot of successes, and we hope to see more progress in the near future.

Dr. Cabral:
Well, that's really exciting. Also, as a field and having now been in this field for many years, and when there's been the previous anti-tau negative trials, and people saying, “That's not the target, let's move to something entirely different.” It's like, no, you actually just have to, we need to dig deeper and shift to other regions. So that's really encouraging and exciting and makes a lot of sense.

Great. Well, I think we nailed it. Thanks so much, and we'll see you next time.