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Untangling the mysteries of Alzheimer's

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One of the most distinctive signs of the development of Alzheimer's disease is a change in the behavior of a protein that neuroscientists call tau. In normal brains, tau is present in individual units essential to neuron health. In the cells of Alzheimer's brains, by contrast, tau proteins aggregate into twisted structures known as "neurofibrillary tangles." These tangles are considered a hallmark of the disease, but their precise role in Alzheimer's pathology has long been a point of contention among researchers.

Now, University of Texas Medical Branch at Galveston researchers have found new evidence that confirms the significance of tau to Alzheimer's. Instead of focusing on tangles, however, their work highlights the intermediary steps between a single tau protein unit and a neurofibrillary tangle — assemblages of two, three, four, or more tau proteins known as "oligomers," which they believe are the most toxic entities in Alzheimer's.

"What we discovered is that there are smaller structures that form before the neurofibrillary tangles, and they are much more toxic than the big structures," said Rakez Kayed, UTMB assistant professor and senior author of a paper on the work now online in the *FASEB Journal*. "And we established that they were toxic in real human brains, which is important to developing an effective therapy."

According to Kayed, a key antibody developed at UTMB called T22 enabled the team to produce a detailed portrait of tau oligomer behavior in human brain tissue. Specifically designed to bond only to tau

oligomers (and not lone tau proteins or neurofibrillary tangles), the antibody made it possible for the researchers to use a variety of analytical tools to compare samples of Alzheimer's brain with samples of age-matched healthy brain.

"One thing that's remarkable about this research is that before we developed this antibody, people couldn't even see tau oligomers in the brain," Kayed said. "With T22, we were able to thoroughly characterize them, and also study them in human brain cells."

Among the researchers' most striking findings: in some of the Alzheimer's brains they examined, tau oligomer levels were as much as four times as high as those found in age-matched control brains.

Other experiments revealed specific biochemical behavior and structures taken on by oligomers, and demonstrated their presence outside neurons — in particular, on the walls of blood vessels.

"We think this is going to make a big impact scientifically, because it opens up a lot of new areas to study," Kayed said. "It also relates to our main focus, developing a cure for Alzheimer's. And I find that very, very exciting."

Provided by University of Texas Medical Branch at Galveston