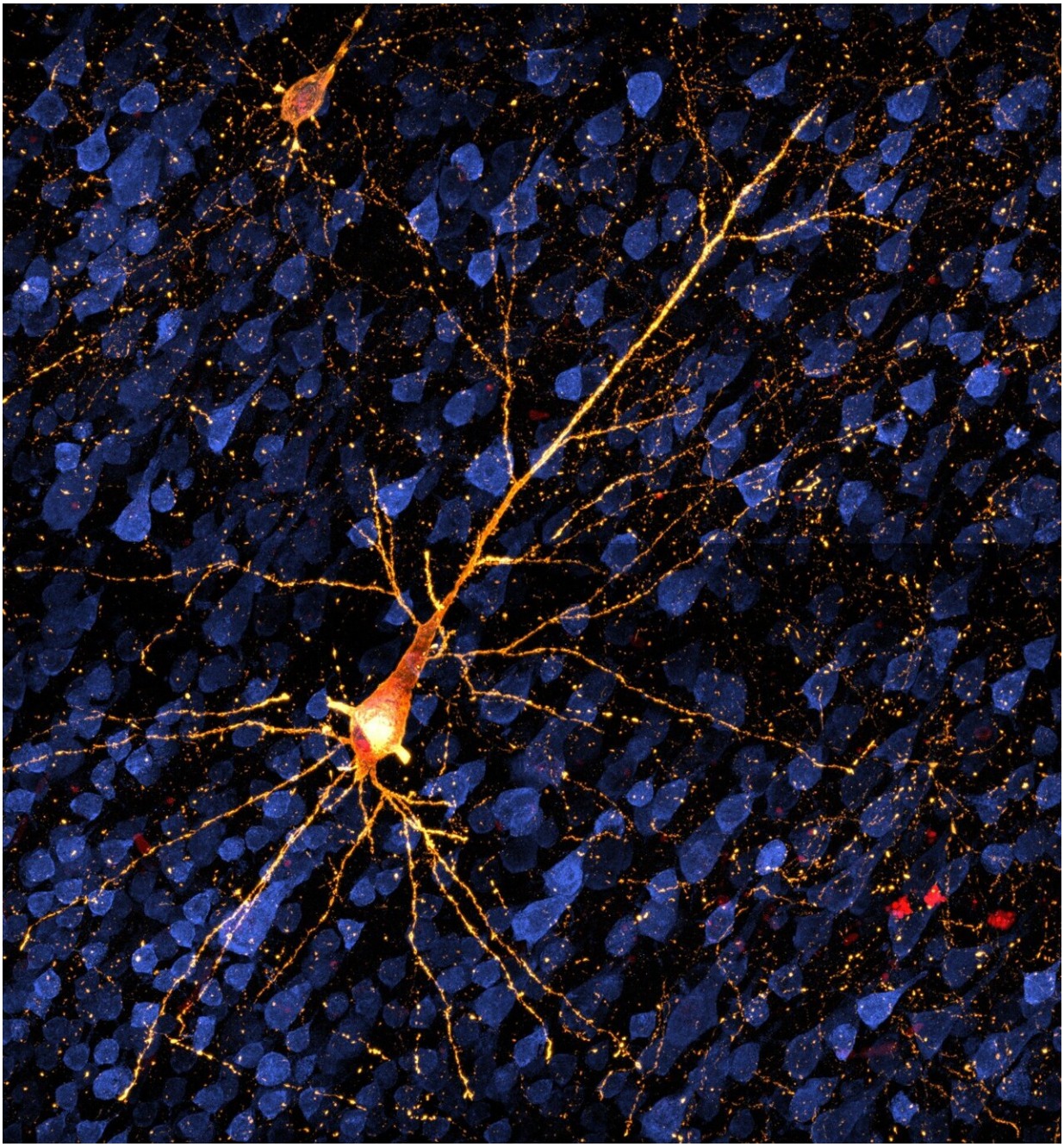
New research points to possibility for testing to explore early-stage Alzheimer's disease

June 24 2024



A dying neuron damaged by tau protein. Tau is involved in Alzheimer's disease and other dementias. A new model in nonhuman primates is opening the possibility of testing treatments before extensive brain cell death and dementia set in. Credit: Danielle Beckman/UC Davis

Research in nonhuman primates is opening the possibility of testing treatments for the early stages of Alzheimer's and similar diseases, before extensive brain cell death and dementia set in. A study published in *Alzheimer's & Dementia* shows up to a six-month window in which disease progress could be tracked and treatments tested in rhesus macaques.

"This is a very powerful translational model to test interventions that target the tau protein," said John H. Morrison, professor of neurology at the University of California, Davis and California National Primate Research Center and corresponding author on the paper.

The tau protein is found in neurons in the brain. The spread of misfolded tau through the brain is implicated in Alzheimer's disease, frontotemporal dementia and other dementias. In Alzheimer's, misfolded tau disrupts multiple processes essential for normal brain cell functioning. As the misfolded proteins spread, they affect neurons throughout the connected regions of the cortex that are crucial for memory and cognition.

The sick neurons then cause an inflammatory response mediated early on by microglial cells. Eventually, neurons die, leaving neurofibrillary tangles of tau protein, one of the key markers of Alzheimer's and other dementing illnesses.

Thanks to advances in brain imaging, the discovery of biomarkers in human serum and cerebrospinal fluid, and work in rodent models, we now know more about the early stages of Alzheimer's. But it is still difficult to figure out how tau, inflammation and disease progression relate to each other.

The macaque model bridges the gap between what we can learn from mouse models and from human patients, said UC Davis postdoctoral researcher Danielle Beckman, first author on the paper.

Six months of measurable disease progression

The researchers injected a vector carrying DNA for two mutated tau proteins into the entorhinal cortex of 12 monkeys. The entorhinal cortex is a key brain region that is involved with memory and is where the disease usually originates in human Alzheimer's.

Over six months, they followed the spread of tau protein, affected cells and inflammation through the animals' brains using PET and MRI imaging, biomarkers and by microscopy.

"We can see tau pathology on neurons, and we can trace all the steps over a few months as the pathology spreads," Beckman said.

The results show that in this model, there is a window of at least two to six months where the progress of the disease can be measured. That opens the possibility of preclinical testing of interventions that target the tau protein.

"We can look at drugs targeting early-stage Alzheimer's before dementia develops," Morrison said. "It's all about early intervention to arrest progression."

The paper builds on earlier work at the CNPRC establishing the nonhuman primate model. In future work, the researchers plan to combine the tau model with their existing model system based on amyloid.

Additional authors on the study are: Giovanne Diniz, Sean Ott, Brad Hobson and Abhijit Chaudhari at UC Davis,; Scott Muller, Yaping Chu and Jeffrey Kordower, Arizona State University; Akihiro Takano, Adam Schwarz, Chien-Lin Yeh, Paul McQuade, Maria Quinton and Arthur Simen, Takeda Development Center Americas Inc., Lexington, Mass.; Paramita Chakrabarty, University of Florida; Nicholas Kanaan, Michigan State University.

More information: Danielle Beckman et al, Temporal progression of tau pathology and neuroinflammation in a rhesus monkey model of Alzheimer's disease, *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.13868

Provided by UC Davis