Antibody therapy inspired by patient case reduces tau tangles in a preclinical model of Alzheimer's disease

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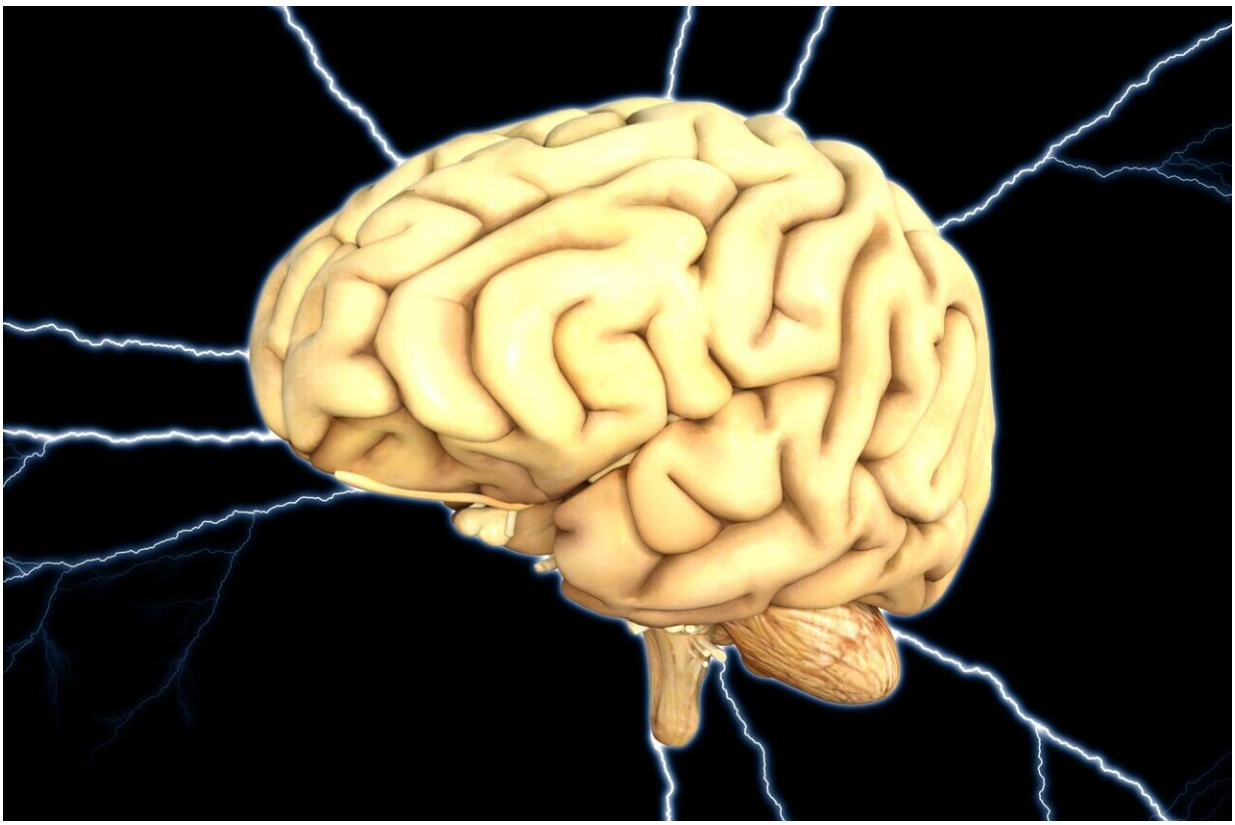

Credit: Pixabay/Pete Linforth.

A team led by researchers from Mass General Brigham reports promising results for a monoclonal antibody that takes aim at a new

target for Alzheimer's disease.

Inspired by their previous identification of a genetic variant in the APOE gene that provides extreme resistance against Alzheimer's disease, the team, which includes investigators from Mass Eye and Ear and Massachusetts General Hospital, developed a therapy that mimics the behavior of this genetic variant in a preclinical model, reducing abnormal tau proteins associated with Alzheimer's disease and offering a path to treatment that does not target amyloid beta plaque buildups. The study was published in *Alzheimer's & Dementia.*

This work builds on previous research led by this team that identified a genetic variant called APOE Christchurch that led to Alzheimer's resistance and protection against cognitive decline for almost three decades in a woman in her 70s who was part of a family in Colombia at an unusually high genetic risk to develop early-onset disease.

To turn those findings into a potential treatment, the researchers have now developed antibodies that could target interactions between ApoE and proteins called heparan sulfate proteoglycans, effectively mimicking the protective mechanism and effects of the Christchurch genetic variant. They used the crystal structure of the antibodies and computer modeling to predict how it would bind to the target of interest.

They found that one antibody, called 7C11, could inhibit the pathological interaction, conferring resistance to Alzheimer's. They validated the specificity of the antibody and determined the most effective doses to deliver. Their therapy, tested in mice, resulted in a reduction of abnormal tau proteins found in their brains and retinas.

Study limitations include a short treatment duration applied to an early disease state. Future studies in additional animal models are necessary to confirm preclinical efficacy.

"Our 7C11 antibody was able to target interactions responsible for a major genetic risk factor for sporadic Alzheimer's," said co-corresponding author Joseph F. Arboleda-Velasquez, MD, Ph.D., an associate scientist in the Department of Ophthalmology at Mass Eye and Ear.

"Our findings point to an alternative and hopefully more effective approach to existing treatments and those in clinical trials that focus on reducing amyloid plaques, and ultimately may lead to disease-modifying therapies for various other neurodegenerative conditions."

"Remarkably, the subject with extreme protection against Alzheimer's disease who carried the APOE Christchurch variant had a similar clinical presentation with much lower tau accumulation despite severe amyloid pathology," said Claudia Marino, a research fellow that co-led the study with Arboleda-Velasquez. "In sum, the 7C11 antibody was able to reproduce in an in vivo model the protective effect of the APOE Christchurch variant."

More information: APOE Christchurch-mimetic therapeutic antibody reduces APOE-mediated toxicity and tau phosphorylation, *Alzheimer's & Dementia* (2023). DOI: 10.1002/alz.13436

Provided by Mass General Brigham