# Research team discovers potential Alzheimer's drug

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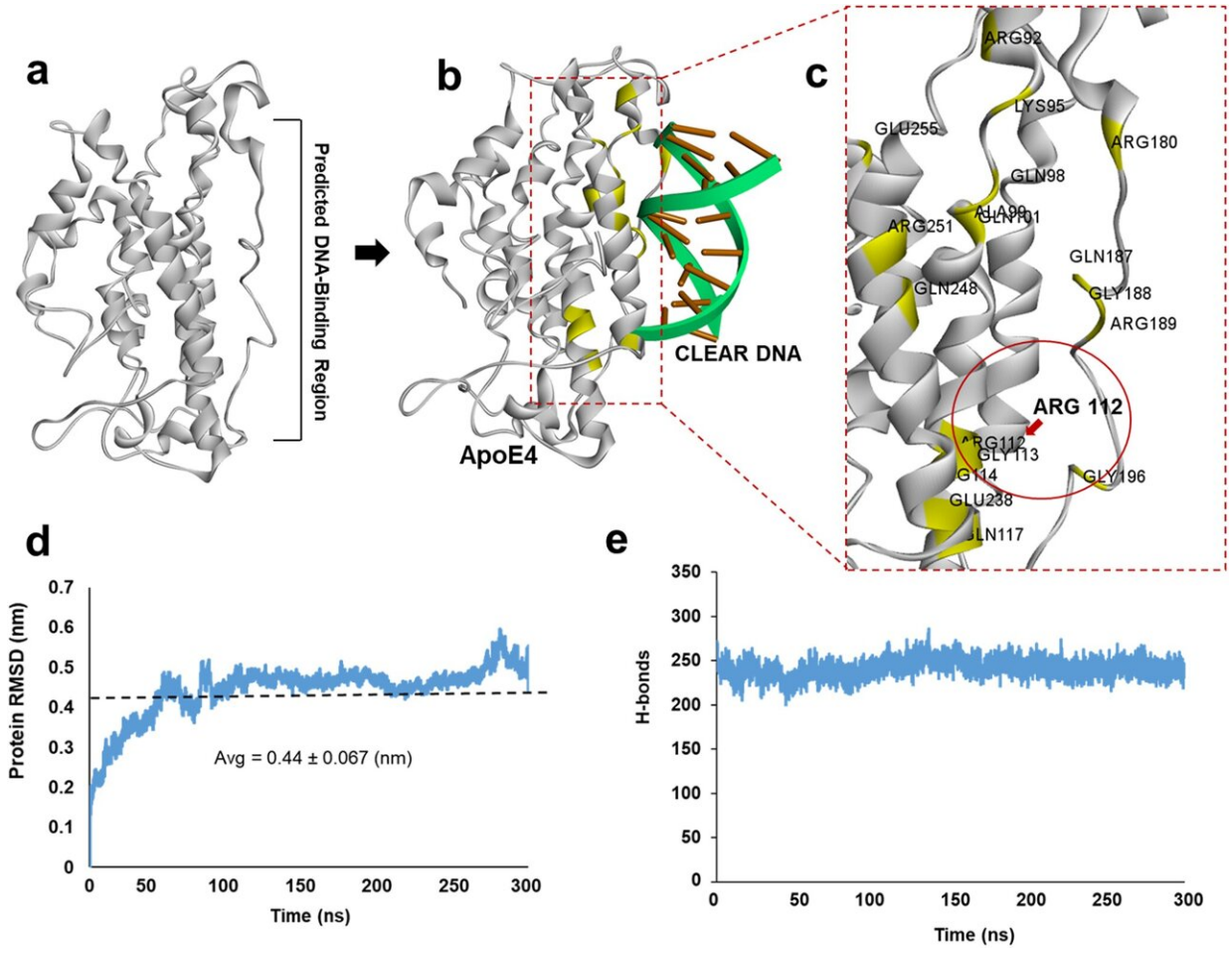


Molecular docking predicts a CLEAR DNA-binding region in ApoE4. a The DNA-binding region of ApoE4, as defined by molecular modeling. b The predicted CLEAR-DNA binding pose is shown for ApoE4. c Amino acid residues in the region of ApoE4 that interacts with CLEAR DNA are highlighted in yellow. d Root Mean Square Deviation (RMSD) of the ApoE4 molecular

structure was calculated from 300 ns molecular dynamic simulations, indicating relative conformational stability. e Number of internal hydrogen bonds (H-bonds) in ApoE4 protein calculated from 300 ns molecular-dynamic simulation trajectories. Credit: *Communications Biology* (2024). DOI: 10.1038/s42003-024-05767-9

A potential new drug to prevent Alzheimer's disease in people with the so-called Alzheimer's gene has been discovered by a University of Arkansas for Medical Sciences (UAMS) research team led by Sue Griffin, Ph.D.

The findings were published Jan. 8 in *Communications Biology* and include discoveries of a druggable target and a drug candidate, made by Meenakshisundaram Balasubramaniam, Ph.D., the paper's first author.

An estimated 50–65% of people with Alzheimer's disease have inherited the Alzheimer's gene, Apolipoprotein E4 (APOEε4), from one or both parents. About 25% of people have one copy of APOEε4 and are three times as likely to develop the disease. Those with two copies (one from each parent) make up 2–3% of the population and are 12–15 times as likely to develop Alzheimer's.

Griffin said her team appears to be the first with the new drug-related discoveries just as it was first in 2018 to show how APOEε4 prevented brain cells from disposing of their waste products, known as lysosomal autophagy.

Such disruption of autophagy in those who inherit APOEε4 is responsible for the formation of plaques and tangles in the brain that are hallmarks of Alzheimer's disease. That discovery was published in *Alzheimer's and Dementia*.

"Our series of discoveries related to APOEε4 and its detrimental role in Alzheimer's pathogenesis are among the most impactful of my 50 years as a research scientist," said Griffin, a pioneer in the study of neuroinflammation and co-founder of the *Journal of Neuroinflammation*, based at the UAMS Donald W. Reynolds Institute on Aging. "No other research team has found a potential drug specifically for blocking the harmful effects of inherited APOEε4."

Griffin is the Alexa and William T. Dillard Chair in Geriatric Research and a distinguished faculty scholar in the College of Medicine and director of research at the Institute on Aging. She is also a professor in the college's departments of Neurobiology & Developmental Sciences, Internal Medicine and Psychiatry. Notably, she is a winner of the Alzheimer's Association's Lifetime Achievement Award and inductee of the Arkansas Women's Hall of Fame.

Most Alzheimer's research nationally has focused on treatments that can clear away the brain's plaques and tangles associated with the disease, but that approach has yielded unimpressive results. Griffin notes that people with mild Alzheimer's symptoms have already lost about half or more of the neurons responsible for memory and reasoning, which has led to her focus on prevention.

Griffin's team will conduct larger-scale preclinical research on the drug candidate CBA2, as well as test other potential drug candidates.

"Our hope is that people who have one or two copies of APOEε4 will one day take the drug regularly throughout their life and significantly reduce their risk of developing Alzheimer's disease," Griffin said.

Balasubramaniam said UAMS built the first known full-length structure of APOEε4 protein in 2017, which he created using bioinformatics and computational modeling techniques. This foundational work led to the

discovery of the druggable site on the APOEε4 protein, ApoE4. (APOEε4 refers to the gene, and ApoE4, without the epsilon symbol and no italics, is the protein.)

Balasubramaniam's unique skills and curiosity, Griffin said, were the catalyst for the discoveries.

"I don't know of anyone else in the world but Dr. Balasubramaniam who can do the work that's in this paper," Griffin said of the assistant professor and Inglewood Scholar in the Department of Geriatrics.

While most institutions still manually screen drug compounds, which can take years, Balasubramaniam oversees a computational biology suite with high-performance GPU servers that he used to screen about 800,000 compounds in two days.

His computer-simulated findings on ApoE4-targeted drug actions were validated in various in vitro and in vivo model systems.

The collaborating researchers include: Srinivas Ayyadevara, Ph.D., associate professor, Department of Geriatrics; Steve W. Barger, Ph.D., professor, departments of Geriatrics, Neurobiology and Developmental Sciences, and Internal Medicine; Peter Crooks, Ph.D., D.Sc., professor, College of Pharmacy Department of Pharmaceutical Sciences, Simmons Chair in Cancer Research; Robert J.S. Reis, Ph.D., professor, departments of Geriatrics, Biochemistry and Molecular Biology, and Pharmacology and Toxicology.

A provisional patent has been awarded on the CBA2 drug candidate, and full patent approval is pending.

**More information:** Meenakshisundaram Balasubramaniam et al, Rescue of ApoE4-related lysosomal autophagic failure in Alzheimer's

disease by targeted small molecules, *Communications Biology* (2024). DOI: 10.1038/s42003-024-05767-9