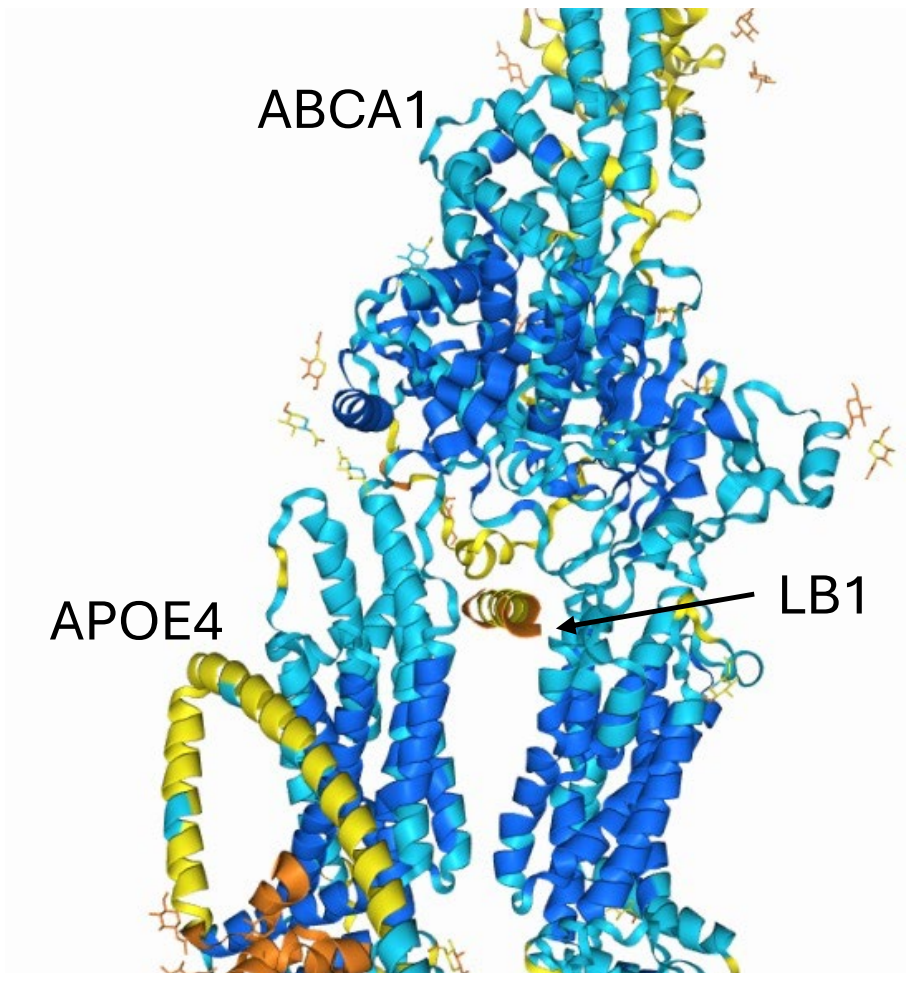
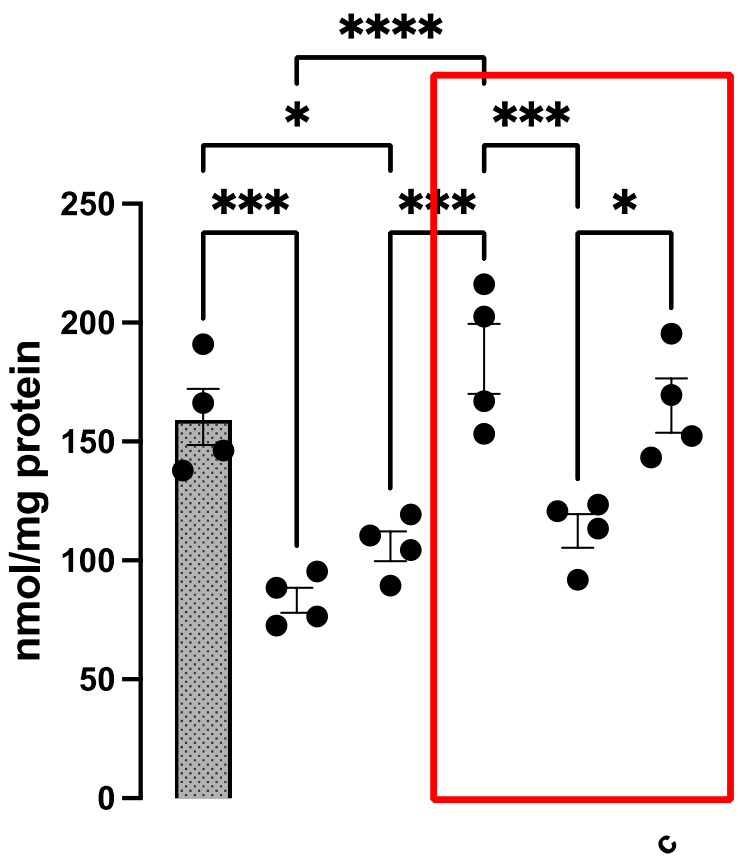
First Look

New Treatments for Lipid Abnormalities in the Brain





Clinical Need

Nearly 7 million individuals in the USA are living with Alzheimer's disease, with the number increasing each year. The E4 variant of apolipoprotein E (ApoE4) is the strongest genetic risk factor for developing Alzheimer's disease (AD); it also significantly increases Lewy body dementia (LBD) risk and disease severity in Niemann Pick disease type C (NPC).

Our Innovative Approach

Targeting lipid dysregulation is a paradigm shift towards treating neurodegenerative diseases, such as AD. In the brain, ApoE delivers lipids to neurons and glia. We have developed a new human cellular platform in which dysregulated lipid and cholesterol transport is modeled in human cells by inhibiting endo-lysosomal transporter NPC1.

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Results

We used our platform to study the effects of ApoE isoforms on lipid accumulation in human cells (fibroblasts as well as neurons, astrocytes and microglia). Results show ApoE2 and ApoE3, but not ApoE4, reduce intracellular cholesterol levels, normalize levels of amyloid precursor protein (APP) and C-terminal fragments, and improve cell survival. Enhancing ApoE4 lipid transfer with an amphipathic lipopeptide corrected the function of ApoE4.

Commercial Potential

Improving ApoE4 lipid transport is a promising therapeutic strategy for AD, LBD, and NPC. Our human cell-based assay based on NPC1 inhibition and ApoE4 function can be used for high-throughput screening, target validation, and proof-of-biology.

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