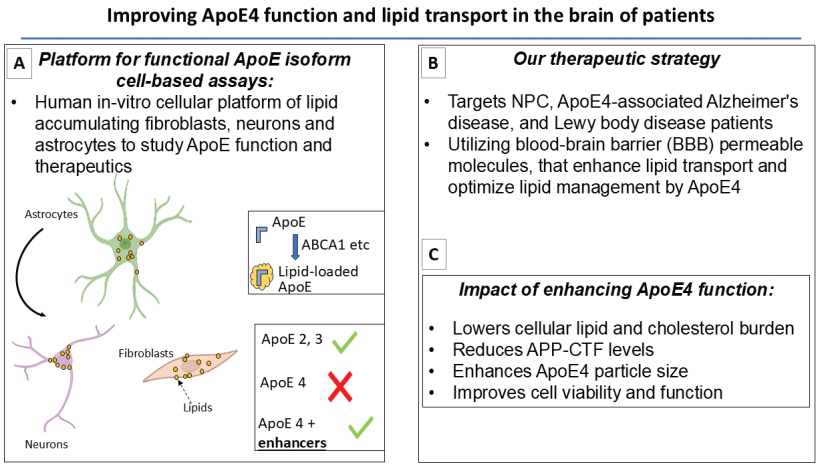

(A) Schematic representation of a human cellular platform to test apolipoprotein E (ApoE) function and therapeutics. ApoE2 and ApoE3 isoforms show superior lipid and cholesterol transport capacity compared to ApoE4 in lipid-accumulated human cells. Enhancers of ApoE4 lipidation can improve ApoE4 function. (B) Our therapeutic strategy specifically targets Niemann-Pick disease Type C (NPC), ApoE4-associated Alzheimer's disease and Lewy body disease patients, by utilizing molecules to improve ApoE4 function and lipid transfer (C).

New Treatments for Lipid Abnormalities in the Brain

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Research at the Neuroregeneration Institute, led by Founding Director Prof. Ole Isacson, focuses on the role of Apolipoprotein E (ApoE) variants in neurodegenerative diseases such as Alzheimer's disease (AD), Lewy body dementia (LBD), and Niemann-Pick disease type C (NPC). The ApoE4 variant significantly elevates AD risk by 3-15 fold and increases the risk for LBD and disease severity in NPC. While ApoE's role in lipid transport is well-documented, the mechanisms by which different ApoE isoforms contribute to cellular pathogenesis remain unclear.

We have developed an in vitro human cellular platform for functional assays to study the impact of ApoE isoforms on lipid and cholesterol accumulation in fibroblasts, neurons, astrocytes and microglia. Our studies reveal that inhibiting the endo-lysosomal cholesterol transporter NPC1 leads to a 4-fold increase in cholesterol accumulation and mis-localization in human cells. This disruption is associated with increased cholesterol and triglyceride synthesis as well as elevated levels of amyloid precursor protein (APP) and APP C-terminal fragments (CTFs).

Our findings indicate that ApoE2 and ApoE3 can reduce intracellular cholesterol levels, normalize APP and CTF levels, and improve cell survival following NPC1 inhibition, whereas ApoE4 does not. However, in the presence of an amphipathic lipopeptide, ApoE4 could remove lipids from NPC1-inhibited cells, enhancing cell viability and function and correcting APP and CTFs. These biochemical and cellular observations in fibroblasts were further validated in human ApoE genotype-specific and isogenic induced pluripotent stem cell (iPSC)-derived neurons, astrocytes and microglia, which model more complex cell-cell interactions and lipid transport. These data highlight the importance of ApoE and lipid transport problems in NPC, AD, and LBD and the therapeutic potential of targeting ApoE4 lipid transfer.

Through this work, we demonstrated the use of our cell-based assay models based on NPC1 inhibition for high-throughput screening, target validation, and providing proof of biology. The therapeutic approach developed based on this screening platform is designed to target NPC patients as well as ApoE4-associated AD and LBD patients. Utilizing blood–brain barrier-permeable molecules that enhance lipid transport and optimize lipid management by ApoE4 constitutes a promising strategy for these challenging neurodegenerative conditions.