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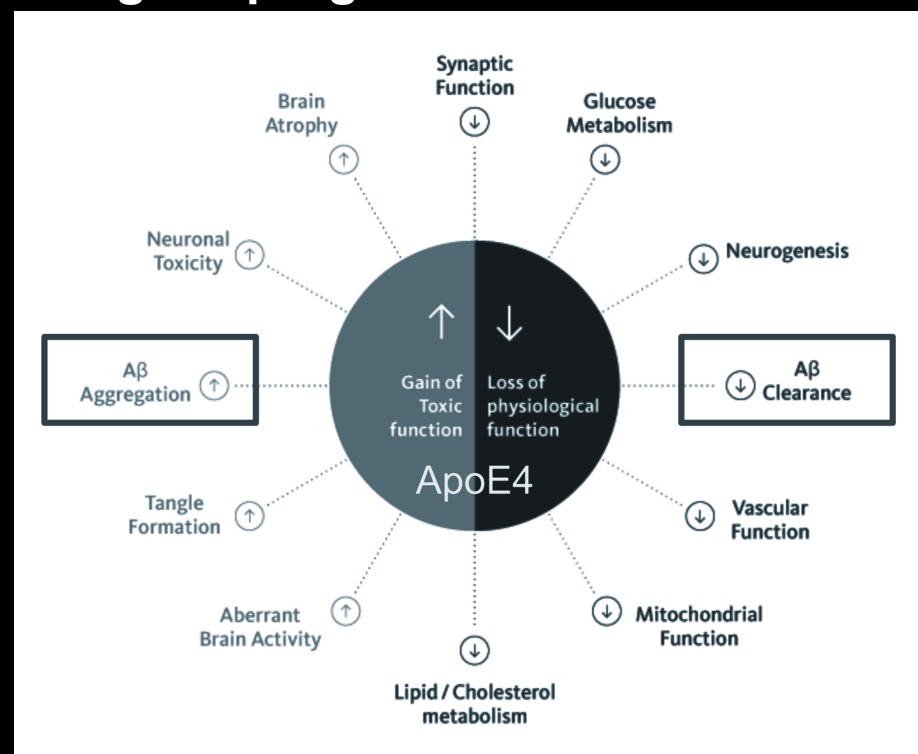
# Investigating the Role of ApoE in Alzheimer's Disease

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## Introduction

- Alzheimer's disease (AD) is a neurodegenerative disease and the most common form of dementia, characterized by impairment of memory and cognition. The etiology of AD remains unknown, however primary pathological features identified during disease progression include extracellular amyloid- $\beta$  (A $\beta$ ) plaques, intracellular neurofibrillary tau tangles, synapse deterioration, neurodegeneration, and neuronal death.
- Apolipoprotein E (ApoE) is a cholesterol carrier that plays an important role in A $\beta$  metabolism. Inheritance of certain ApoE polymorphic variants is a major genetic determinant of developing sporadic AD. There are three allelic variants of ApoE in humans: E2, E3, and E4. Individuals carrying the E2 allele have a two-fold decreased risk of AD, whereas carriers of one copy of the E4 allele have a three- to five-fold increased risk of AD, and those with two copies of E4 allele have an over ten-fold increased risk of AD compared to carriers of the E3 "normal" allele.
- Evidence suggests that ApoE isoform-dependent clearance and aggregation of A $\beta$  accounts for the varying degrees of AD risk associated with inheritance of each allele. Current models propose that ApoE4 binds to A $\beta$  and catalyzes its conversion to toxic A $\beta$  filaments, leading to eventual neurodegeneration and cell death. Due to the critical contribution of ApoE to AD pathogenesis, future therapies targeting ApoE activity may be effective for alleviating or preventing AD progression.



Adapted from Liu et al., 2013

## Methods

### Drug Screen

NIH Clinical Collection small molecule library drug screen

- Aim: Identify small molecule drugs capable of preventing and/or reversing ApoE4-catalyzed A $\beta$  filament formation.
- The NCC library: 729 drugs tested in phase I-III clinical trials.

Figure 1

### Searching for ApoE4-Blocking Alzheimer Drugs

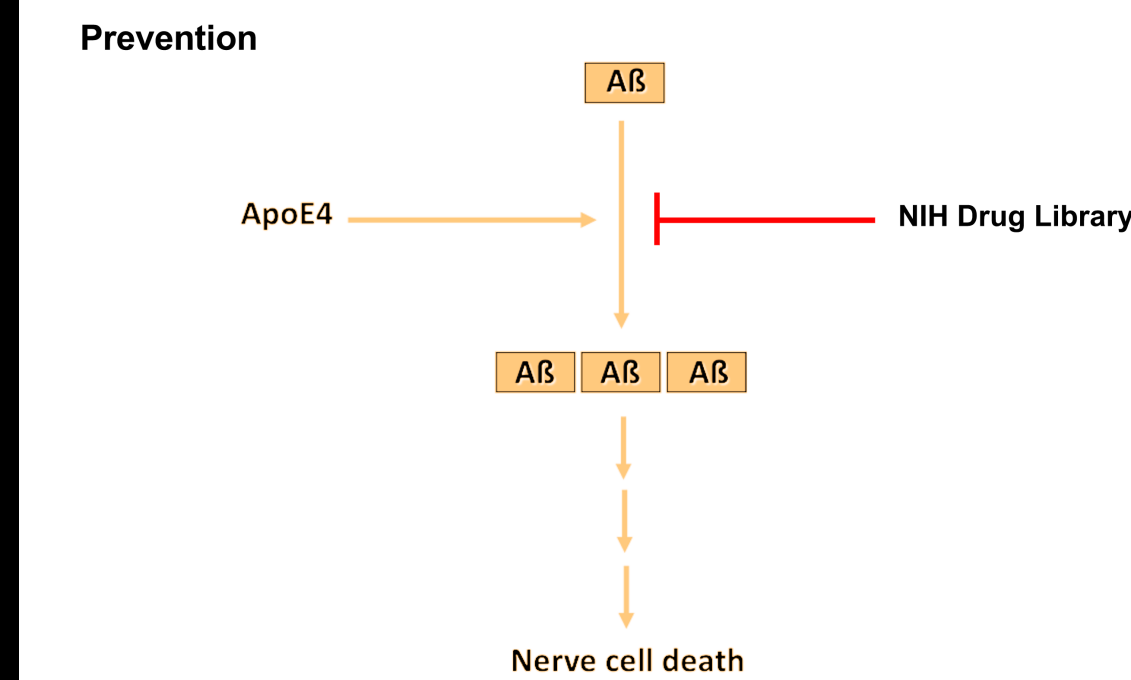
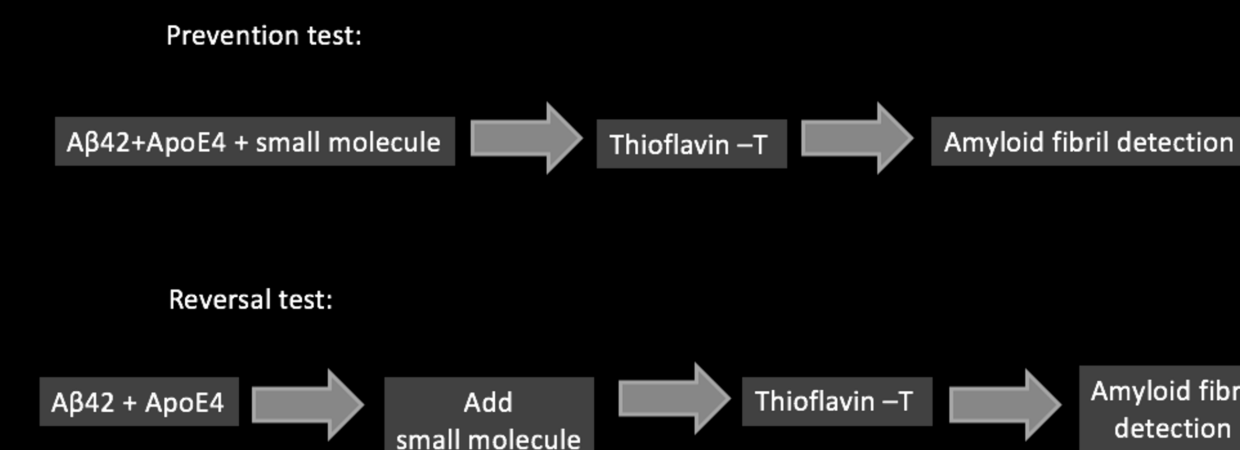


Figure 2  
In Vitro ApoE Drug Screening Assay



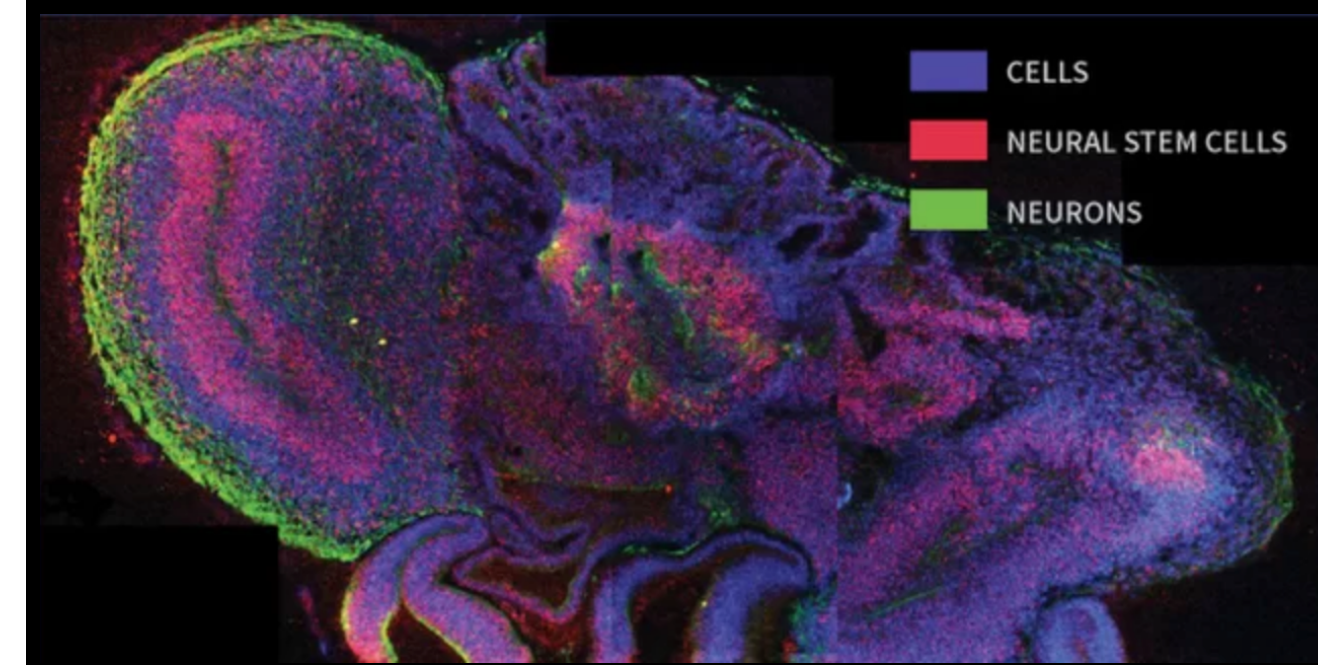
## Methods

### Cerebral Organoids

Induced pluripotent stem cell (iPSC)-cerebral organoid model system

- Cerebral organoids are *in vitro* synthesized tissues that contain several types of nerve cells and have anatomical features that resemble mammalian brains.
- Aims:
  - Create an AD organoid model system using iPSCs expressing mutant *APP*, *PSEN1*, or *PSEN2*. Mutations in these genes cause autosomal dominant forms of early-onset AD.
  - Test the ability of candidate drugs to prevent or reverse A $\beta$  filament formation.

Figure 3  
Cross-section of Cerebral Organoid  
LiveScience, 2013



## Results

Preliminary: Identified 160 candidate drugs with promising dose-response data

- 104 showed robust effects in both the prevention and reversal assays
- 31 showed strong effects in the prevention assay only
- 25 showed stronger effects in the reversal assay only

## Conclusions and Future Directions

- Using the NIH Clinical Collection small molecule library drug screen, we have preliminarily identified 38 blood-brain barrier permeable candidate drugs that show a promising ability to prevent and/or inhibit ApoE4-mediated A $\beta$  filament formation.
- An ApoE-dependent approach to AD drug discovery may identify drugs that are effective independent of, or complementary to, other therapies currently under investigation.
- The development of an AD cerebral organoid model system will provide a physiologically relevant model system that recapitulates essential pathological features of AD. This system may advance and accelerate AD preclinical drug discovery and development by providing an early-stage selection assay for effective drugs.

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