



2020 IMPACT CIRCLE

Discovering drugs that mimic the effect of protective genes against Alzheimer's dementia

Investigators:

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Unmet Need: The genetic makeup of an individual can provide protection against Alzheimer's disease (AD). AD affects more than 5 million Americans and there is an urgent need for new drugs to treat the disease. For the gene APOE, the APOE2 variant of the gene reduces the risk of developing AD. This provides an opportunity to develop therapies that attempt to mimic the protective effects conferred by APOE2. However, such therapies have not been developed.

Background: The risk of developing AD is strongly correlated with the type of APOE gene variant a person has. The APOE gene has three variants: APOE2, APOE3, and APOE4. People with the APOE4 variant have a very high risk of developing AD, while people with the APOE2 variant are significantly protected against it. People with the APOE3 variant, the most common one, have an average risk of developing the disease. AD patients with APOE4 have an accelerated breakdown of the blood-brain barrier. The blood-brain barrier is composed of cells that protect the brain from harmful substances in the blood. Furthermore, the early stages of AD involve the breakdown of the blood-brain barrier.

Novel Hypothesis: We hypothesize that a compound able to mimic the protective effects of APOE2 in the blood-brain barrier and the brain will be able to prevent AD.

Proposal:

-Aim 1: Develop a cell culture system that models the interaction between neurons and the blood-brain barrier. Three models will be developed, each model will be made with cells that have the APOE2, APOE3, or APOE4 gene variants.

-Aim 2: Observe the differences among the APOE2, APOE3, and APOE4 models via single-cell RNA sequencing.

-Aim 3: Perform a computational screen for chemical compounds that would make the APOE3 and APOE4 models behave similarly to the APOE2 model and test in our blood-brain model.

Impact: Identifying compounds that mimic the protective effect of APOE2 will yield a novel therapeutic approach to AD.

Specialized Equipment Needs: Emulate bio blood-brain barrier cell culture module.

APOE Variants, the Blood Brain Barrier and Protective Drugs

Problem

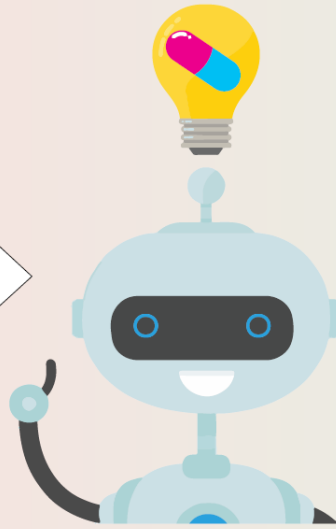
APOE2



APOE3



APOE4



Solution

APOE2



APOE3



APOE4

