Gene Therapy in Alzheimer's Disease: Novel Therapies and Ethical Aspects of Somatic Gene Editing

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Mission: To develop a disease modifying therapy (DMT) for late onset Alzheimer's disease (LOAD) targeting APOE ε4 that will decrease disease toxicity by limiting the amount of protein produced

Background

What is Alzheimer's Disease (AD)?

•A progressive neurodegenerative disease that causes memory loss and cognitive decline

Why Study It?

•AD affects 5.8 million people in the U.S. and is projected to affect 14 million by 2050 Previous clinical trials targeting amyloid plaques, a common hallmark, have failed •Causative factors and the mechanism behind its onset and progression remain unknown; no cure currently exists

Why APOE?

•APOE ε4 has been identified as the strongest and most reproducible genetic risk factor for LOAD

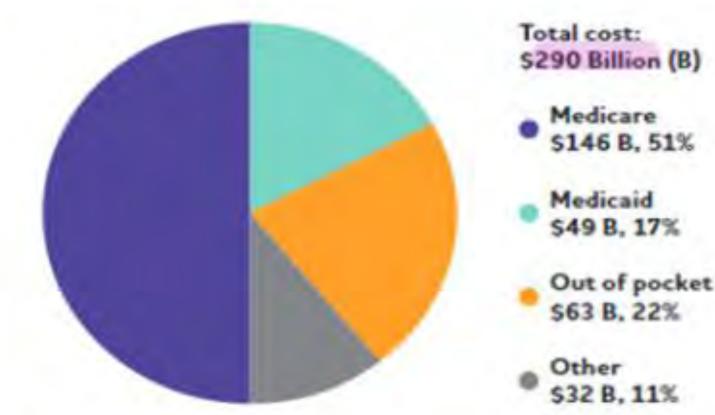
Investigate the ethical and social implications of developing DMT for LOAD

What is a DMT?

•seeks to stop or slow the progression of the disease by making alterations to the pathological steps that lead to the AD

FIGURE 10

Distribution of Aggregate Costs of Care by Payment Source for Americans Age 65 and Older with Alzheimer's or Other Dementias, 2019"



*Data are in 2019 dollars

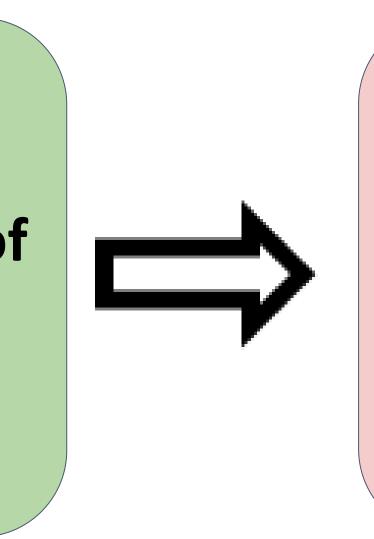
Created from data from the Lewin Model All "Other" payment sources include private insurance, health maintenance organizations, other managed care organizations and uncompensated care.

Healthcare cost for dementia patient \$350,174

DMT, what then?

•New therapies emphasize the need to examine legal and social issues of an AD DMT (pricing, cost, treatment)





Identify a phenotypic difference between **APOE** alleles within different cell types to to substantiate a targeted treatment plan

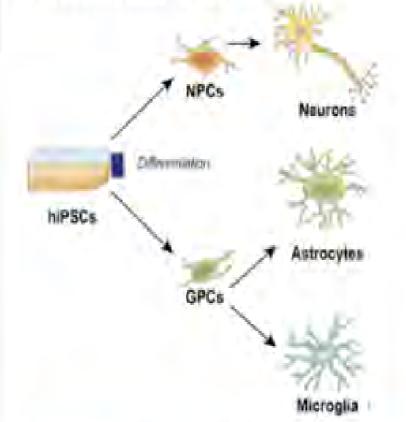
Understanding the role of APOE ε4 in AD

•How do we measure for differences between APOE ε4 (the risk allele) and APOE ε 2 and ε 3 in AD pathology?

Generate Isogenic Cell Lines

ΑΡΟΕ ε2/2 ΑΡΟΕ ε3/3 APOE 24/4

Differentiate Cells



Characterize Phenotypes

APOL 1/3

Use CRISPR/Cas9 to generate 3 human-induced pluripotent stem cell (hiPSC) lines that are identical in genetic background (isogenic), except at the two APOE single nucleotide polymorphism (variation) positions, to give 3 homozygous (2 copies) APOE ɛ2/2, 3/3, and 4/4 hiPSC lines

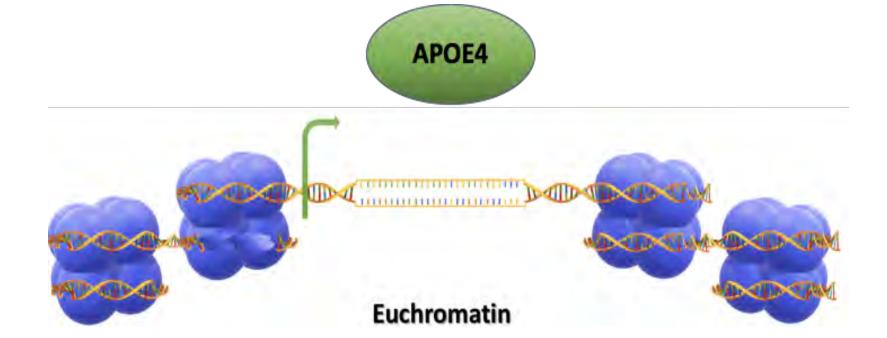
Differentiate isogenic APOE £2/2, 3/3, 4/4 hiPSCs into hiPSC-derived neurons, astrocytes, & microglial-like cells

Characterize AD-related and age-related phenotypic differences between APOE £2/2, 3/3, and 4/4 lines for each single-cell type

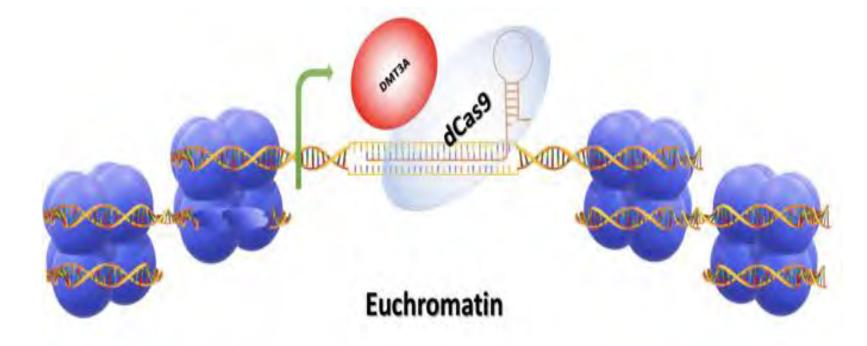
BASS CONNECTIONS **Brain & Society**

Develop allele-specific viral vector technology to downregulate APOE on targeted cells

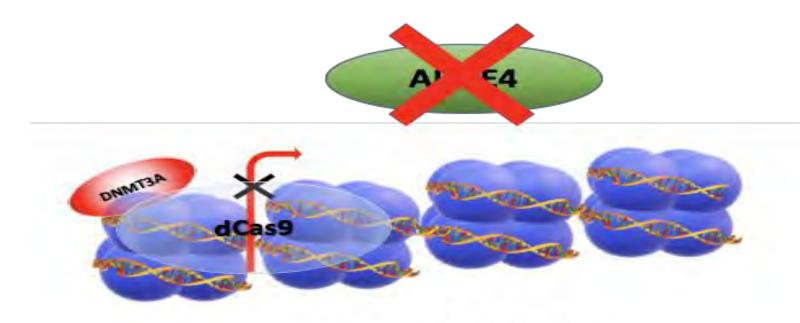
How do we stop protein production?



DNA ready to be converted into proteins is typically open and ready for co-factors to bind



DNMT3A attaches to the DNA, guided to the site by another protein (dCas9)



DNMT3A adds chemical tags to the DNA, causing it to bunch up so that cofactors can no longer bind to begin production

Heterochromatin