Treating Alzheimer's with Gene Therapy and the Ethical, Legal and Social Implications

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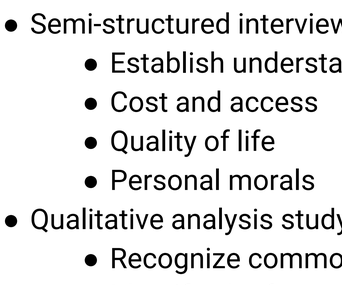
Introduction

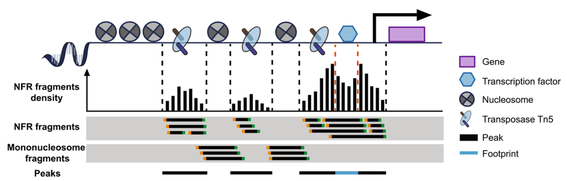
- Alzheimer's disease (AD) is a progressive neurodegenerative condition that causes memory loss and cognitive decline
- AD currently affects 5.8 million Americans.
- Mechanisms and causes behind onset and progression remain unknown; no cure currently exists.
- E4 variant of *APOE* gene is the strongest reproducible genetic risk factor for LOAD, making it an ideal target for gene therapy

Methods

Identify and study high-risk variant functions & mechanisms

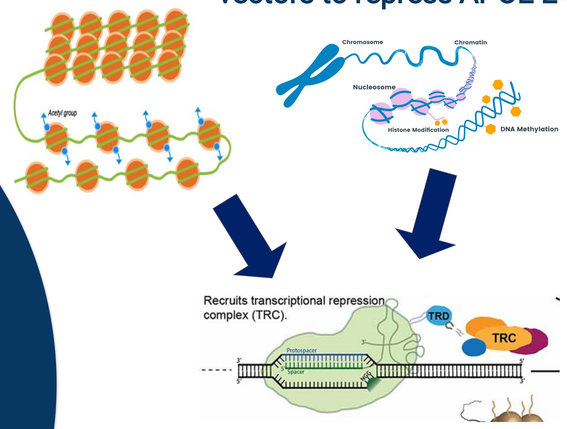
- Genome Wide Association Studies
  - Polygenic risk score analysis
- Epigenetic and Gene Expression of APOE Region
  - snRNA & scATTAC seq analysis
- Predict neuropsychiatric symptoms (e.g. depression) in AD patients using polygenic risk scores and methylation data



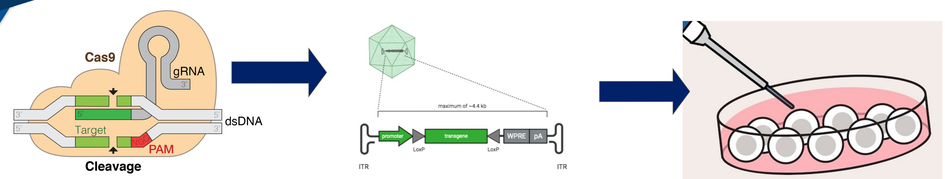


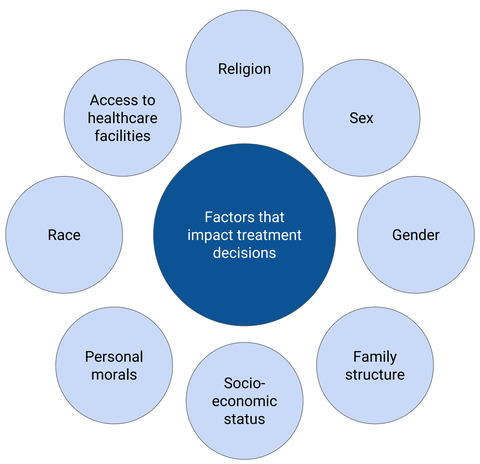
Mission: To develop an ethical disease modifying therapy (DMT) for late-onset Alzheimer's disease (LOAD) using gene therapy while considering legal and social effects

Develop novel CRISPR-Cas9 systems using viral vectors to repress APOE E4 expression



- Epigenetic Manipulations
- Development of effectors systems Editing
- Effectors transduced using AAV viral vector delivery
- Improve AAV packaging efficiency
  - Functionalize VP2 protein





Understand what clinicians think about future treatments for Alzheimer's Disease

- Semi-structured interviews with clinicians (MD, DO, PA, NP)
  - Establish understanding (of gene therapy)
  - Cost and access
  - Quality of life
  - Personal morals
- Qualitative analysis study
  - Recognize common observations
  - Identify the factors that cause disparity in diagnosis

Future Directions

- Utilize Cas9 variants to improve target specificity and offer more control of gene expression
- Understand the values of people living with dementia as treatments are developed
- Mulitomics analysis of APOE region for increasing understanding of molecular risk for LOAD

References
Yan et al., 2020; Li et al., 2019; Walter 2017; San-Juan-Rodriguez 2019; Yamazaki et al., 2017; Applied Sciences 2015; Zhu et al. 1019