# Identifying Novel Drugs to Inhibit APOE4 as a Therapeutic Intervention for Treating Alzheimer's

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Alzheimer’s disease (AD) is a progressive neurodegenerative disease that impacts memory by destroying the neurons of the brain cells. AD is characterized by the presence of two types of protein aggregates, namely Abeta plaques and tau neurofibrillary tangles. Several factors contribute to the development of AD, and genetic predisposal is one of the major risk factors. Inheritance of APOE4 gene impacts both the incidence of AD and its early onset. Recent studies discovered that the ApoE4 protein competitively interacts with a DNA sequence element (“CLEAR”), and transcriptionally inhibits the expression of p62, LAMP2, and LC3B proteins required for lysosomal autophagy. Such impediment in autophagy by ApoE4 could explain, at least in part, the increased protein aggregate load seen in the brains of APOE4 individuals, signifying the need for targeted drug discovery to inhibit ApoE4. High-Throughput Virtual Screening of the whole FDA approved drug library against ApoE4 for predicting best targeted lead molecules was conducted. Autophagic gene expression after lead molecule treatment was assessed in a C. elegans model expressing human ApoE4 protein along with pan-neuronal expression of human Aß42. Identified FDA approved lead drug molecule shows high affinity for ApoE4. Experimental validations of lead drug molecules rescued C.elegans (ApoE4) AD model from Aß aggregation. Our identified novel FDA-approved small molecules specifically target ApoE4 and blocks its interactions with CLEAR DNA to improve autophagic clearance of aggregates, indicating that the identified lead molecules can be repurposed for treating APOE4 individuals who are at high risk of developing AD.

**Awards Won:**
Fourth Award of $500