CU Denver

CHEMISTRY

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SEMINAR SERIES

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Dr. Noah Johnson, Ph.D.
Department of Neurology
University of Colorado, Anschutz Medical Campus

Developing inhibitors of apolipoprotein E for Alzheimer's disease

Carrying the ε4 allele of the apolipoprotein E (APOE) gene is the strongest risk factor for Alzheimer's disease (AD) besides age itself. As one potential mechanism, apoE, and especially apoE4, binds to amyloid-β (Aβ) with high affinity and acts as a catalyst to accelerate Aβ oligomer and fibril formation, increase their stability, and promote their neurotoxicity. We pursued the hypothesis that inhibiting this early step in the amyloid cascade may thereby reduce or prevent neurodegeneration and AD. We developed a high-throughput screening assay and used it to identify inhibitors of the apoE4-Aβ interaction from small molecule drug repurposing libraries. We confirmed that hit compounds exhibit low neurotoxicity and blocked apoE-induced intracellular Aβ aggregation, tau hyperphosphorylation, and apoptosis in primary neuronal cultures. We also validated their translational potential in human iPSC-derived cerebral organoids and in a transgenic rat model of AD. Finally, we performed a retrospective analysis of clinical data from the National Alzheimer's Coordinating Center (NACC) and modeled changes in cognition and clinical diagnoses using time slopes and Cox proportional hazards, respectively, adjusted for age and sex. Our findings validate an apoE-centric approach to developing new AD therapeutics.