13th International Conference on

Alzheimers Disease and Dementia

November 25-26, 2019 | Frankfurt, Germany

# A novel apolipoprotein E antagonist functionally blocks apolipoprotein E Interaction with N-terminal Amyloid precursor protein, Reduces β-Amyloid-Associated Pathology and improves cognition

**Darrell Sawmiller**
University of South Florida, USA

The E4 isoform of apolipoprotein E (apoE4) is a major genetic risk factor for the development of sporadic Alzheimer's disease (AD) and its modification has been an intense focus for treatment of AD in recent years. We investigated the binding of apoE, a peptide corresponding to its low density lipoprotein receptor (LDRL) binding domain (aa 133-152, ApoEp) and modified ApoEp to amyloid precursor protein (APP) and their effects on Aβ production in cultured cells. Having discovered a peptide which blocks the interaction of apoE with N-terminal APP, we investigated the effects of this peptide and ApoEp on AD-like pathology and behavioral impairment in 3XTg and 5XFAD transgenic mice. ApoE and ApoEp, but not truncated apoE lacking the LDLR binding domain, physically interacted with N-terminal APP and thereby mediated Aβ production. Interestingly, the addition of six lysine residues to the N-terminal ApoEp (6KApoEp) directly inhibited apoE binding to N-terminal APP and markedly limited apoE- and ApoEp-mediated Aβ generation, presumably through decreasing APP cellular membrane trafficking and p44/42 mitogen-activated protein kinase phosphorylation. Moreover, while promoting apoE interaction with APP by ApoEp exacerbated Aβ and tau brain pathologies in 3XTg-AD mice, disrupting this interaction by 6KApoEp ameliorated cerebral Aβ and tau pathologies, neuronal apoptosis, synaptic loss, and hippocampal-dependent learning and memory impairment in 5XFAD mice without altering cholesterol, LDLR, and apoE expression levels. These data suggest that disrupting apoE interaction with N-terminal APP may be a novel disease-modifying therapeutic strategy for AD.

**e:** jtan@health.usf.edu

*Notes:*