NEURAL ENGINEERING SEMINAR SERIES

The Role of APOE in Amyloid-β and Tau-Mediated Pathogenesis of Alzheimer's Disease

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ABSTRACT: The Apolipoprotein E (APOE) gene is the strongest genetic risk factor for Alzheimer's disease (AD). APOE is a 299 amino acid protein expressed at highest levels in the liver but also at high levels in the central nervous system. In humans, there are three common APOE alleles: E2, E3, and E4. APOE4 is associated with increased risk and APOE2 with decreased risk for AD, relative to APOE3. Evidence will be presented that demonstrates that APOE has a very strong effect on modulating amyloid-β (Aβ) pathology in an isoform-specific fashion in both humans and animal models. This effect is modulated by lipidation of APOE-containing lipoproteins in the CNS as well as via APOE receptors. In addition to APOE's effect on Aβ, there is also now strong evidence that APOE influences tau pathology and tau-mediated neurodegeneration. This effect appears to require microglia. The different cell types that produce APOE in the brain in the context of these effects will be discussed.

BIOGRAPHY: Dr. David Holtzman received his bachelor of science in 1983 and medical degree in 1985 from Northwestern University, followed by a neurology residency at the University of California San Francisco (UCSF) from 1985 to 1989. He conducted postdoctoral research and founded the Memory Disorders Clinic at UCSF until 1994, when he joined Washington University as an assistant professor. He is currently professor and chair of neurology, scientific director of the Hope Center for Neurological Disorders, and associate director of the Charles F. and Joanne Knight Alzheimer Disease Research Center (Knight ADRC). Some of his and his lab's accomplishments include showing, in part, how APOE4 contributes to AD, development of a method to measure protein synthesis and clearance in the central nervous system of animals and humans, development of cerebral spinal fluid biomarkers for AD, demonstration of how synaptic/neuronal activity and sleep affect Aβ and tau levels dynamically in vivo acutely and chronically, and development of an anti-Aβ antibody now in phase III trials for AD and an anti-tau antibody in phase II clinical trials for AD. He has received a number of honors, including receiving the Paul Beeson Physician Faculty Scholar in Aging Research award, the Potamkin Prize from the American Academy of Neurology for research on AD, the MetLife award for Alzheimer's disease research, a MERIT award from the National Institute on Aging, election to the National Academy of Medicine of the National Academy of Sciences, election to the National Academy of Inventors, an alumni merit award from the Northwestern Feinberg School of Medicine, appointment to the national advisory council for the National Institute of Neurological Disorders and Stroke and National Institute on Aging, the chancellor's award for innovation and entrepreneurship and the Carl and Gerty Cori award from Washington University, Fellow election to the American Association for the Advancement of Science, and being the past-president of the American Neurological Association. Dr. Holtzman has trained more than seventy graduate students, post-doctoral fellows, and physician scientists, many of whom have gone on to successful careers in academia and industry.

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