Strategies for pathology-activated generation of reelin trafficking modulators for altering late-onset Alzheimer's disease progression

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Compelling evidence continues to accrue that late-onset (non-familial) Alzheimer's disease (LOAD), arising early in olfactory structures of the brain, progresses in a spatio-temporally consistent pattern via propogating "inflammaging" processes; predisposing susceptibility may be established as early as gestationally. Genome-wide association studies (GWASs) of cognitively uncompromised individuals who exhibit apparent high pathology suggest that select combinations of genetic attributes can confer resistance to cognitive decline; and, although certain specifics of pathological signatures differ from those in cognitively deteriorating individuals, these might reflect successful defense against an otherwise pathological chain of events. A central player emerging from these GWASs is reelin, a large glycoprotein component of the extracellular matrix (ECM). Though historically regarded mostly as a key player in embryo-fetal development reelin exhibits functional interplay in the adult brain with other molecular constituents having clearly established associations with LOAD, such as apolipoprotein E, and with the responsiveness states of inflammaging-associated cells, notably microglia. The complexities and relative paucity of knowledge regarding ECM maintenance, remodeling, and functional dynamics, and the analytical challenges involved in achieving increased clarity, means that gaining therapeutically actionable traction will be difficult; however, the tantalizing thought that GWASs of these individuals may be showing us ways forward motivates rising to these challenges. Reelin possesses multiple functional domains, and certain reelin fragments exhibit trafficking and function disparate from intact glycoprotein. Very recently, ADAMTS-3 was identified as the catalyst of a proteolytic cleavage of reelin shown to be inactivating in terms of reelin's canonical activities. Because of reelin remains heavily involved during adulthood in dynamic brain maintenance and remodeling, deleterious consequences can be expected from anatomically untargeted alterations in reelin function. Potential strategies for pathology-activated, localized generation of suitable modulators will thus be needed, and progress with respect to devising such strategies will be shared in this presentation.

Speaker Biography

Ronald A Hill is now spanning almost 35 years, over a pharmaceutical sciences career. He has aimed to become a generalist with high-level acumen in relating the Chemistry of biologically active molecules to their interactions with, and actions on, humans and their hosted organisms (normal microbiome, microbial pathogens, parasites). The central focus of his own research has always related to the CNS, guided also by the aim of constantly gaining acumen in molecular therapeutics design, molecular biopharmaceutics, and molecular toxicology and in general, the science of successfully bridging discovery at its earliest stages to clinical application. His educating duties at the PhD and PharmD levels are extensive, and carried out with the underlying hope that the molecular science and molecular design will be intelligently and artfully acted on in clinical practice. His current research collaborations center on neurodegenerative conditions and cancer.

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