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ApoE4- targeted therapeutics for AD

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Apolipoprotein $\epsilon 4$ (ApoE4) is a major genetic risk factor for sporadic, late-onset Alzheimer's disease (AD). One protein target that is affected in the presence of ApoE4 is the major longevity determinant and NAD-dependent deacetylase sirtuin-1 (SirT1), which we showed to be decreased in the presence of ApoE4. Recent reports also show that SirT1 levels are shown to be decreased in serum of AD patients. Through screening we have identified a brain-penetrant small molecule, A03, that increased the neuroprotective SirT1 protein levels in ApoE4-transfected cells, and we have recently tested its efficacy *in vivo* in ApoE4 mouse model for AD. The preliminary results show that A03 treatment can increase in SirT1 levels in the mouse brain thus providing initial proof-of-concept for developing this drug candidate as a ApoE4-targeted therapeutic for AD. We are in the process of designing and synthesizing analogs of A03, and studying their effects on both the neuroprotective SirT1 and neurotoxic protein sirtuin-2 (SirT2) in ApoE4-transfected cells. In addition, we have also initiated high throughput screening (HTS) of the UCLA compound library to identify new hits that increase SirT1 in the presence of ApoE4. Our data thus reveal a novel mechanism for developing targeted therapeutics for this major known risk factor for AD. A03 is a promising lead candidate that increases brain SirT1 levels and could be developed as an ApoE4-targeted therapeutic for AD. Synthesis, testing, and screening of new hit-analogs could yield additional candidates for development as potential therapeutics for mild cognitive impairment (MCI) and/or AD.

Biography

Varghese John received his PhD from the Department of Medicinal Chemistry, University of Minnesota in 1985. He has a Postdoctoral fellowship in Professor Josef Fried's lab in the Department of Chemistry, University of Chicago and a second Postdoctoral fellowship in Professor Carl Djerassi's lab in the Department of Chemistry at Stanford University. He worked with Athena Neurosciences/Elan Pharmaceuticals as a Senior Member of their discovery team for 18 years. He then joined the Buck Institute for research on aging where he was Director of Alzheimer's Drug Discovery Network. He started the Drug Discovery Lab at UCLA in 2015.

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