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A novel neurotrophic drug for cognitive enhancement and Alzheimer's disease

Marguerite Prior
Salk Institute for Biological Studies, USA

Abstract

At present, there are few drugs that improve the memory deficits associated with normal aging and none that prevent cognitive decline in chronic neurodegenerative conditions such as Alzheimer's disease (AD), which is the most common cause of dementia in the elderly affecting more than 24 million people worldwide. Historically, the search for a treatment for AD has been focused on the amyloid beta peptide (Aβ) that mediates familial Alzheimer's disease pathology. However, given that age is the greatest risk factor for AD, our laboratory has explored an alternative drug discovery paradigm to select drug candidates for neurodegenerative disease that is based on efficacy in cell models of multiple age-associated pathologies rather than exclusively amyloid metabolism. This scheme has identified an exceptionally potent, orally active, neurotrophic compound (J147) that facilitates memory in normal rodents, prevents behavioral and synaptic protein loss in AD transgenic mice, and reverses cognitive loss in aged transgenic AD mice. J147 is also neurogenic in both very old and young mice and reduces the significant loss in dendritic spines that occurs with age. Strikingly, we have found that the neurotrophic and memory-enhancing activities of J147 are associated with the induction of brain derived neurotrophic factor (BDNF), a growth factor that is reduced with age and in AD brain, that is required for normal cognitive function, and is implicated in neurogenesis. J147 has the medicinal chemical properties of a good CNS drug and our data so far suggests that J147 has potential for the treatment of AD.

Biography

Marguerite Prior received her Ph.D. from University College Dublin, Ireland in 2007, working on Prion Diseases and then began her postdoctoral training in the Department of Neuroscience at the Lerner Research Institute, Cleveland Clinic under the direction of Dr. Riqiang Yan, working on the role of reticulon proteins in the formation of dystrophic neurites. Dr. Prior joined the Cellular Neurobiology Laboratory of Professor David Schubert at the Salk Institute in May 2010 as a Postdoctoral Research Associate to work on a novel neurotrophic and cognitive enhancing drug for Alzheimer's disease.

mprior@salk.edu