



Title: Drugs for Alzheimer's Disease: Is the single-target approach going to work?

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Despite the billions of euros spent by pharmaceutical industries, there are no drugs that prevent the synapse loss and nerve cell death found in the brains of Alzheimer's disease (AD) patients. Therefore it is worth considering an approach to drug discovery that differs from the single target, high affinity ligand paradigm that is currently in vogue. We have recently used an approach based upon the biology of the disease and its age-associated risk factors to identify and/or synthesize novel drug candidates. The drug selection criteria are based upon a series of cell culture assays reflecting different aspects of AD pathology, including A β toxicity, inflammation, oxidative stress, energy loss, and trophic factor withdrawal. We use the original pharmacopeia, plant secondary metabolites, as the initial drug candidates. In the example that I will discuss, we synthesized a library of hybrid molecules between the plant polyphenol curcumin, which lacks neurotrophic activity, and a related neurotrophic molecule, and selected for the best compounds based solely on their broad-spectrum biological activity in the various cell culture assays rather than their molecular targets. Medicinal chemistry was then used to improve drug potency and pharmacological properties. Two of the compounds that came out of this selection procedure were shown to improve the pathology and memory deficits in a transgenic mouse model of AD. These results strongly support the argument that due to the complexity of the disease, an old fashioned, multi-target biological approach to drug discovery for AD may be a viable alternative to the failed single-targeted based methods currently in use.