# DISCOVERY OF MULTIPOTENT DRUGS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD), the most common cause of dementia, is a complex neurological affection that is characterized by loss of memory and progressive deficits in different cognitive domains and by massive deposits of aggregated proteins to form the intracellular neurofibrillary tangles and the extracellular senile plaques. Even if the primary cause of AD is still speculative, early amyloid-β peptide (Aβ) aggregates are thought to be mainly responsible for the devastating clinical effects of the disease. Although, at present, the most followed approach to identify AD drugs is the amyloid hypothesis, significant research has been also devoted to the role of free radical formation, oxidative cell damage, and inflammation in the pathogenesis of AD, providing new promising targets and validated animal models. It is now clear that AD has a multifaceted etiology, hence, efforts to discover effective anti-Alzheimer drugs should be devoted to the design of new compounds that are able to hit different selected targets.

To this end, we applied a well-known design strategy in which distinct pharmacophores of different drugs were combined in the same structure leading to hybrid molecules. In principle, each pharmacophore of these new drugs should retain the ability to interact with its specific site(s) on the target and consequently to produce specific pharmacological responses that taken together should block or hopefully cure the neurodegenerative process leading to AD.

This research led to the discovery of *Lipocrine* that emerged in in vitro models as an effective candidate to be investigated in vivo for its multiple biological properties, namely, inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase activities, inhibition of AChE-induced Aβ aggregation, and ability to protect cells against reactive oxygen species. Furthermore, among a series of polyamines, *Memoquin* displayed an even better pharmacological profile because, beside an in vitro profile similar to that of *Lipocrine*, in a transgenic mouse (AD11) model of AD, displaying a full complement of phenotypic hallmarks for the disease, it was able to decrease the cholinergic and cognitive impairment, Aβ deposition and tau hyperphosphorylation. Clearly, an approach based on a multiple intervention in the pathogenic pathway of the disease may have great potential to cure AD.

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