

## Alzheimer's Disease Drug Discovery may be Misled by Wrong Animal Models

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### Editorial

Alzheimer's disease (AD) is one of the most expensive human diseases and a leading cause of disability and death among elderly. As the elderly population is growing worldwide, AD will soon become a major human healthcare challenge if it remains incurable [1]. The currently available therapeutics for AD only acts to lower its symptoms without any effect on the actual underlying pathology [2].

In recent years, however, significant amount of research has been focused on finding the so called "neuroprotective" agents, therapeutics that can stop or slow the disease progress by targeting special molecular mechanisms in the AD pathology process. Yet more futuristic are approaches that can rebuild the damaged tissue, called as "regenerative agents". These two approaches together are known as "disease-modifying approaches" [3]. According to its definition, a disease modifying treatment should not only interfere with the underlying pathological mechanisms leading to neuronal dysfunction and loss in AD, but it should also lead to significant clinical improvement of the patient [3].

In the past two decades, several hundreds of potential disease modifying agents has shown to be effective in animal models of AD, but all have failed in the phase three clinical trials [4]. These failures question both the basis on which the therapeutic agents have been designed and the animal models used in the pre-clinical phases [5]. The most commonly used animal models of AD are based on the lesions of AD, Amyloid- $\beta$  ( $A\beta$ ) plaques and neurofibrillary tangles. These models are transgenic carriers of mutations related to amyloid or tau production (amyloid precursor protein (APP), presenilin-1 (PS1) and PS2 or tau mutations). However, the mentioned mutations do not cause late-onset AD (LOAD).

Admittedly, our today's in-depth understanding of potential mechanisms involved in LOAD pathology is considerably based on studies performed on the conventional transgenic models of AD [5]. However, these AD animal models are designed to recapitulate AD

lesions through an etiology similar to rare familial types of AD. Since LOAD is not caused by such mutations, the findings from these animal models cannot be reliably translated to human LOAD.

In contrast to rare genetic forms of AD, the molecular triggers and pathways leading to LOAD is still unclear and highly controversial [6]. Studies that point to the more primary stages in AD pathogenesis have provided evidence of different yet overlapping molecular triggers of LOAD, emerging even before  $A\beta$  and tau pathologies. Those molecular mechanisms include mitochondrial dysfunction, oxidative stress, hypoxia, chronic neuroinflammation, trace metal dyshomeostasis, cell cycle reentry, vascular pathology and insulin resistance [1,7]. Currently, however, these pathological paradigms of LOAD lack well-established *in vivo* models to be used in pre-clinical drug discovery studies [5,6]. Such etiology-based models of LOAD may provide breakthroughs in future AD drug discovery.

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