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Editorial

The Dawn of a New Era of Alzheimer's Research and Drug Development

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Alzheimer's disease (AD) is characterized by senile plaques comprising β-amyloid (Aβ) proteins and neurofibrillary tangles formed by hyperphosphorylated tau aggregates. Massive efforts and resources have been poured into interventions aimed at removing or decreasing the production of Aβ. Until recently, amyloid and tau have been the focus of most drugs in development for AD. However, despite the recent US Food and Drug Administration (FDA) approval of aducanumab (marketed as Aduhelm™), it is still debated whether these pathologies represent valid drug targets, and accumulating data suggests it is unlikely that anti-amyloid antibodies alone would be sufficient to halt or reverse the course of AD.

It is important to note that both plaques and tangles begin to accumulate for decades before the onset of cognitive symptoms. In fact, the leading risk factor for sporadic AD is aging. Beyond the accumulation of plaques and tangles, numerous processes go awry with aging that contribute to, or exacerbate, the pathology and progression of AD, including inflammation, impaired proteostasis, vascular dysfunction, mitochondrial/metabolic dysfunction, epigenetic dysregulation, and synaptic dysfunction (1, 2). Thus, a combination of drugs to address many of these defects may be necessary to effectively treat AD. In recent years, an increasing number of drugs targeting these biological processes have emerged in the drug development pipeline for AD. Currently (as of January 2022), there are 143 agents in clinical trials for AD, of which 119 agents are disease-modifying agents (3). Of the disease-modifying agents, there are now more agents in AD clinical trials that are targeting inflammation (23; 19.3%) than amyloid (20; 16.8%) or tau (13; 10.9%). Inflammation is a major hallmark of aging, and chronic systemic inflammation is associated with brain volume shrinkage and impaired cognitive functions (1). While broad-spectrum anti-inflammatory drugs have failed to improve cognitive outcomes in AD patients, recent efforts have targeted specific aspects of inflammation that are harmful to the brain while sparing normal immune function. For example, senescent cells are thought to fuel age-related pathologies by evading cell death while continuing to release proinflammatory cytokines and chemokines to damage the surrounding tissue (2). Senolytic drugs can selectively induce apoptosis of these senescent cells, and there are currently 3 phase II clinical trials underway to test a senolytic combination of dasatinib (tyrosine kinase inhibitor) and quercetin (flavonoid) in mild cognitive impairment or early-stage AD (3).

There are also 19 (16%) therapies undergoing testing in clinical trials that target synaptic plasticity or neuroprotection. Of these, 3 therapies are in phase III trials: AGB101 (a low-dose formulation of levetiracetam, an anti-epileptic drug), atuzaginstat (a bacterial protease inhibitor targeting *P. gingivalis*), and blarcamesine (sigma-1 receptor agonist and muscarinic M2 autoreceptor antagonist). Other biological processes impaired by aging that are targeted in ongoing AD clinical trials include metabolism/bioenergetics (7 agents), proteostasis (7 agents), vascular function (6 agents), epigenetics (6 agents), oxidative stress (4 agents), neurogenesis (4 agents), and neurotransmitter receptors (3 agents). Many of the drugs targeting metabolism/bioenergetics and vascular function are repurposed drugs, such as anti-diabetics (metformin, semaglutide, dapaglifozin, and intranasal insulin), antihypertensives (telmisartan and perindopril), and an anticoagulant (dabigatran).

Equally important to the diverse portfolio of Alzheimer's drugs-in-development is the significant advancement in biomarkers that are necessary for early diagnosis and selective recruitment of patients with confirmed pathology. Before 2012, accurate diagnosis of Alzheimer's disease was only possible postmortem, with a brain biopsy needed to confirm the presence of amyloid plaques. In 2012, the FDA approved a positron emission tomography (PET) ligand, florbetapir, that quantified the density of Aβ that strongly correlated with subsequent autopsy findings (4). More recent efforts to develop less invasive and costly biomarkers paid off in late 2020, when the first blood test for Alzheimer's disease became available. The PrecivityAD™ blood test quantifies plasma Aβ42/40 ratio and determines the apolipoprotein E genotype to estimate an amyloid probability score (c2n.com). Blood tests for phosphorylated tau (p-tau181, p-tau217, p-tau231) reflecting neurofibrillary tangles, neuroinflammation (YKL-40, S100B, and GFAP), neurodegeneration (neurofilament light), and others are also under development and are currently being used in clinical studies (5). Other noninvasive tests, such as retina scans and digital biomarkers are also under active

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investigation.

The advent of diverse biomarkers has improved the rigor and efficiency of clinical trials, especially for early-stage exploratory clinical trials. Exploratory trials are typically phase 1b or phase 2a trials that are designed to rapidly establish go/no-go decision points by assessing the drug's pharmacologic effects using biomarkers specific to the drug's mechanism of action (6). More exploratory trials are warranted as they are valuable in supporting proof of concept, confirming target engagement and exposure, assessing safety, and informing on dose selection, while requiring shorter study durations and fewer patients than traditional phase 2 studies. The goal of exploratory studies should be to make the best use of available resources and limited time to build a robust body of evidence that informs go/no-go decisions and the design of larger future studies. Based on an advisory panel convened by the Alzheimer's Drug Discovery Foundation and the Association for Frontotemporal Degeneration, key recommendations for executing value-generating exploratory trials included incorporation of appropriate biomarker(s) that reflect the drug's mechanism of action and leveraging statisticians' expertise in trial design and statistical analyses (6).

Between the breadth of new drug targets under investigation that address the biology of aging, the rapid development and validation of new biomarkers, and the improved design and rigor of clinical trials, we are in a new era of Alzheimer's research and drug development. Given the multifaceted nature of AD pathogenesis and progression, and the many biological processes that become impaired with aging, it is unlikely that drugs addressing a single target will have enough efficacy in treating AD in a clinically meaningful manner. However, if incremental benefits are observed with some agents, combination trials should be considered. Combination therapies are the standard of care for many diseases of aging, including cancer and cardiovascular diseases, and will likely be necessary to successfully treat AD. In the near future, simple inexpensive tests, such as blood tests, retinal scans, and/or digital biomarkers may be able to identify a specific set of pathologies that is unique to each AD patient. These biomarkers combined with genetic information (e.g., APOE genotype) could inform optimal combination therapies through a personalized medicine approach that cater to each patient's unique biology and pathology.

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