ACS Chemical Neuroscience

Editorial

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Alzheimer's Disease: Development of Disease-Modifying Treatments Is *the* Challenge for Our Generation

Welcome to our first thematic collection that crosses-over with the *Journal of Medicinal Chemistry* and *ACS Medicinal Chemistry Letters* to highlight advances in the pharmacology, medicinal chemistry, and therapeutic strategies currently under development for Alzheimer's disease (AD)—the most challenging and important disease facing our generation. While the 1970s heralded a "war on cancer" and the 1980s and 1990s witnessed a monumental effort to vanquish the death sentence of AIDs with novel therapeutics targeting multiple aspects of the viral machinery, the challenge of this millennium is the development of disease-modifying treatments for AD. Unfortunately, even after several decades of research, there are few approved drugs for AD; moreover, the available drugs only attenuate symptoms, show little to no effect on slowing disease progression, and have no effect on the behavioral disturbances associated with AD.[1−4] Current estimates indicate that approximately 5.4 million Americans are suffering from AD at an annual cost to the United States healthcare system of over $200 billion.[1−4] While staggering, the situation grows more desperate as the 76 million baby boomers advance in age. This is based on the likelihood of developing AD doubles every 5 years after age 65, and after age 85 the risk of developing AD climbs to ∼50%. Importantly, if no disease-modifying therapies are developed, the number of AD patients may climb as high as 13.5 million by 2050, resulting in over $1 trillion in patient care costs.[1−4] An even more sobering statistic focuses on mortality and AD. Between 2000 and 2008, there was a 66% increase in deaths directly related to AD; in contrast, during the same time period, deaths from HIV decreased 29%, deaths from stroke decreased 20%, deaths from heart disease decreased 13%, and deaths from several cancers also declined significantly.[1−4]

Early neuropathology of AD is characterized by the loss of basal forebrain cholinergic neurons and loss of cholinergic neurotransmission. Current approved drugs for AD target cholinergic and glutamatergic transmission thereby improving cognitive symptoms in some patients; however, these agents are not disease-modifying, nor do they slow disease progression. Current approved therapies include cholinesterase inhibitors (tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galanatamine (Razadyne)) and the glutamate modulator memantine (Namenda).[1−4] The other major hallmarks of AD include plaques and neurofibrillary tangles in the brain which led to the amyloid hypothesis and tau hypothesis in 1991 and 2004, respectively, as fundamental causes of AD. Drug development efforts have pursued these hypotheses via multiple approaches.[1−4]

The amyloid hypothesis of AD initiated major drug discovery efforts across the pharmaceutical industry, with novel small molecules targeting Aβ peptide production. Aβ is produced by the proteolytic cleavage of APP by γ- and β-secretases leading to Aβ_{1-40} and Aβ_{1-42} peptides which aggregate and form toxic oligomers.[1−4] The amyloid hypothesis has undergone many revisions and refinements since 1991, and with multiple failures of both small molecules and biologic approaches that diminish Aβ load, there is growing debate that targeting Aβ may be questionable as an AD therapeutic approach.[1−5] However, others argue that the hypothesis is still valid and that the issues were with inferior molecules, biologics, the "sink" approach and/or trial design. Numerous BACE1 inhibitors are in phase I trials, where compounds such as MK-8931, lowered Aβ up to 90%, and efficacy in phase II are eagerly awaited.[6]

PhRMA reports in their 2012 *Medicines in Development* Report for AD[4] that there are currently 93 medicines in various stages of development, both small molecule and biologic. In general, all 93 compounds fall into one of the following therapeutic strategies: (1) agents targeting neurotransmission, (2) agents targeting Aβ production, (3) agents targeting Aβ aggregation, (4) agents targeting Aβ clearance, (5) agents increasing brain resistance to Aβ, (6) agents targeting tau protein, and (7) agents targeting neurotrophins and agents modulating synaptic plasticity and nerve growth.[1−4] Significant advances have been, and continue to be made, in the development of imaging agents, for example, Amyvid,[1−4] for amyloid imaging biomarkers for disease. Overall, new therapeutic agents must address multiple stages of disease progression, from Aβ/tau accumulation to mild cognitive impairment to late stage dementia and behavioral (psychotic) symptoms, the latter of which are more difficult for caregivers than the dementia.

In this Special Issue on AD, we present 17 outstanding papers (both reviews and primary scientific studies) encompassing basic neuropathology, novel therapeutic strategies, novel small molecules, and genetic studies relevant to understanding and treating AD. We at *ACS Chemical Neuroscience* thank all of the contributors to this special issue on AD and encourage our readers to take advantage of our first thematic collection that crosses-over with the *Journal of Medicinal Chemistry* and *ACS Medicinal Chemistry Letters* and check out the outstanding papers in these *Journals* on AD.

Craig W. Lindsley, Editor-in-Chief

AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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(3) Mangialasche, F. M., Solomon, A., Winblad, B., Mecocci, P., and Kivipelto, M. (2010) Alzheimer's disease: clinical trials and drug devleopment'. *Lancet Neurol. 9*, 702−716.

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(4) The 2012 PhRMA Report on Medicines in Development: Alzheimer's disease. See www.phrma.org.
(5) Sadeghi-Nejad, N. (2012) The Lessons of failure: what we can learn from bapineuzumab's blowup. *Forbes (Pharma & Healthcare)*, August 7, 2012.
(6) For information of the clinical trials with MK-8931, see www.merck.com.