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Editorial

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Introduction to Special Issue on Alzheimer's Disease

One of the greatest challenges facing medicinal chemists in the 21st century is the discovery and development of compounds for the prevention, treatment, and diagnosis of Alzheimer's disease (AD). This devastating age-related neurodegenerative disorder, characterized by the slow but inexorable loss of memory and cognition, afflicts over 5 million Americans and ∼30 million worldwide and extracts a tremendous toll physically, emotionally, socially, and economically. AD cases are predicted to escalate dramatically in the coming decades as demographics combines with increased life expectancy to double or even triple prevalence in the U.S. Currently approved drugs are weakly and temporarily effective and offer only symptomatic treatment. The need is great to identify disease-modifying therapies that slow or stop the neurodegenerative process.

Pathologically, AD is characterized by synaptic and neuronal loss and the abnormal deposition of two proteins, the amyloid β-protein (Aβ) and the microtubule-associated protein tau. Although these deposits were first described over a century ago by Alois Alzheimer, only in the past 2 decades have genetics, biochemistry, cell biology, animal models, imaging, and diagnostics combined to provide a large body of evidence that Aβ is an initiator of the disease process and that tau is downstream but more proximal to neurodegeneration. Dominant, inherited forms of AD that strike in mid-life but that are otherwise indistinguishable from late-onset, sporadic AD point directly at Aβ: these mutations are found in the genes encoding the Aβ precursor protein APP and presenilin, the catalytic component of one of the proteases that cleaves APP to produce Aβ. Thus, mutations in substrate or protease that alter Aβ or Aβ production are sufficient to cause AD. Mutations in the gene encoding tau are also sufficient to cause an AD-related dementia, and other evidence suggests that a variety of neuronal insults, including toxic forms of Aβ, can lead to tau pathology and neurodegeneration. Also, although not sufficient for causing AD, the apolipoprotein E allele ApoE4 is a strong genetic risk factor for late-onset AD, and evidence supports a role for ApoE in the clearance of Aβ from the brain.

For these reasons, strategies for the discovery and development of disease-modifying AD therapeutics have primarily targeted Aβ, tau, and ApoE or neurotoxic events thought to be downstream of these proteins. Most efforts have gone into targeting Aβ, either with inhibitors of the proteases, β- and γ-secretases, that produce Aβ from APP or with anti-Aβ immunotherapy that enhances clearance of Aβ from the brain. Thus far, these efforts have fallen short, with several high-profile failures in phase III clinical trials, raising concerns about Aβ as a target and the amyloid hypothesis in general. These failures, however, can be attributed to insufficient target engagement and/or adverse events. More problematic, all clinical trials have involved subjects who already have AD. Blocking Aβ at this stage may be analogous to giving cholesterol-lowering statins to treat congestive heart failure in the emergency room. Thus, improved diagnostics are essential for AD drug development. Identification of people who are asymptomatic but at high risk for developing AD is crucial to the design of appropriate clinical trials to rigorously test Aβ as a target and address the amyloid hypothesis directly in humans. Great progress has been made on this front, including the development of amyloid imaging agents.

In this special issue of the Journal, advances in medicinal chemistry as it relates to AD are highlighted, and the reports represent a range of targets and approaches. Arguably the top target is β-secretase, better known as the β-site APP-cleaving enzyme 1 or BACE1. This membrane-tethered aspartyl protease catalyzes the first step in Aβ production, and its cocrystallization with inhibitors makes it very amenable to structure-based design. The difficulty has been developing potent and specific BACE1 inhibitors that access and remain in the brain at high enough levels to effectively lower Aβ. This difficulty, however, is being overcome with promising agents entering clinical trials. The second protease involved in Aβ production, γ-secretase, is a membrane-embedded complex of four proteins that carries out hydrolysis of the APP transmembrane domain. The challenge of this target is that γ-secretase has other substrates besides APP, and interfering with the cleavage of at least one of these has severe toxic consequences. Thus, compounds should modulate γ-secretase rather than globally inhibit the protease.

Tau is also an important target, especially as pathological tau is more proximal to neurodegeneration than Aβ, suggesting that intervention later in the disease process may still be efficacious. Tau has lagged behind Aβ as a target primarily because of uncertainty about how to modulate it. However, promising strategies include inhibition of certain kinases that are associated with hyperphosphorylated forms of tau found in neurofibrillary tangles, tau aggregation inhibitors, and stimulation of the clearance of tau monomers through the proteasome or tau aggregates through autophagy. As tau is normally a microtubule-associated protein and may lose its microtubule stabilizing function upon hyperphosphorylation and aggregation, microtubule stabilizing agents that can potentially rescue this loss of function are also considered promising compounds for AD and other "tauopathies". This last approach is the subject of a Perspective article in this issue by Ballatore and colleagues.

ApoE may also be a worthwhile target, and compounds that "correct" the conformation of the AD-associated E4 isoform to resemble that of isoform E2 or E3 have been identified. This intriguing and promising approach is the subject of another Perspective article in this issue by Mahley and colleagues. Other targets in this issue include RAGE (receptor for advance glycation endproducts), a receptor for Aβ in the brain microvasculature. Interaction between Aβ and RAGE is associated with transport of circulating Aβ into the brain and with activation of inflammatory processes in the brain. Certain neurotransmitter receptors and second messengers are also

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considered promising targets to modulate signaling pathways that may otherwise be altered in AD. These include particular subtypes of acetylcholine receptors, 5-hydroxytryptamine receptors, and phosphodiesterases. This special issue also includes reports on the development of potential small-molecule imaging agents that bind to aggregated Aβ and tau. As mentioned earlier, such diagnostic tools are essential for AD drug development to identify appropriate subjects for clinical trials and at earlier stages, ideally before disease onset.

In closing, I thank all authors who contributed their work to this special issue. I also especially thank the editors and staff at the Journal for all their advice and assistance in putting this issue together and for giving me the honor of serving as Guest Editor of the first of what we all hope will be many special issues in the Journal.

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Notes

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