ACS Medicinal Chemistry Letters

Editorial

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Approaches Toward New Alzheimer's Treatments

ABSTRACT:

Alzheimer's disease was first described in 1906 by Alois Alzheimer, who observed plaques in the brain tissue from patients that suffered dementia. Alzheimer's disease is the most common form of dementia and accounts for over 50% of the cases identified each year. Alzheimer's disease affects over 5 million patients in the United States, is the sixth leading cause of death among Americans, and accounts for over 200 billion dollars lost in medical care. Over 15 million people are counted as unpaid caretakers of these patients, and this causes a great burden on our health system. There are currently only five approved treatments for Alzheimer's disease, and none of these are a cure. Despite intensive research efforts, it is still not known what causes the disease, and effective treatments are greatly needed. As a result, the Obama administration recently declared the search for a treatment a major national priority and has increased the funding for basic research and caregiver support with a promised 156 million dollar investment. To highlight the importance in this area, the editors of the Journal of Medicinal Chemistry, ACS Chemical Neurosciences, and ACS Medicinal Chemistry Letters (Gunda I. Georg, Shaomeng Wang, Craig Lindsley, and Dennis Liotta) announced the simultaneous publication of Special Issues on Alzheimer's disease to be published in November to coincide with Alzheimer's Disease Awareness month. Links to these special issues will also be made available online on a specific page dedicated to this Alzheimer's disease collection. I was asked to be a Guest Editor of the ACS Medicinal Chemistry Letters special issue and thoroughly enjoyed reading all of the high-level papers that were submitted for this journal. We accepted 11 papers for the final edition that highlight several potential new treatment options or some new tools for potentially discovering how the disease works.

There are four basic areas of research that the papers cover that range from inhibitors of specific enzymes to novel approaches and also a description of a new imaging agent. Stamford et al. highlight the preparation of novel β-secretase (BACE) inhibitors that are active in *in vivo* models of plaque formation. The compounds described are nonpeptido mimietic inhibitors that are active in *in vivo* models of plaques formation. Kaller et al. also describe novel BACE inhibitors based upon amino-hydroxy-ethyl amine compounds that are active in *in vivo* models.

Another enzyme target that has been studied over the past 10 years is γ-secretase. Many groups have described potent inhibitors of this enzyme, but few compounds have reached their potential in clinical studies, presumably due to side effects brought on by inhibition of the related enzyme Notch. Wu and colleagues describe a novel series of γ-secretase inhibitors that possess some selectivity over Notch, and one compound is reported to have advanced to clinical trials. Another approach toward affecting this pathway has been focused on discovering compounds that act as modulators of γ-secretase and therefore do not inhibit Notch processing of essential proteins. The paper by Fuller is very interesting in that it describes a novel series of γ-secretase modulators that are based upon glycoside inhibitor templates. The paper by Huang also describes a novel series of small molecule oxadiazine γ-secretase modulators.

This journal's special issue also describes several other approaches toward modulating the effects of Alzheimer's disease. Liu and colleagues have taken a different approach and report in their paper a series of compounds that are bivalent ligands that target multiple pathways involved in the disease. Zhou describes a strategy toward targeting inflammation that might occur in the course of the disease and have identified some compounds that show potential in animal models. In their paper, Dang and co-workers report on a novel series of compounds that act as activators of the chymotrypsin-like activity of the proteasome and also serve to inhibit the deactivating effects of Aβ40/42 on the proteasome. Lysosomes are involved in the clearance of some of the products of protein processing that contribute to Alzheimer's disease. Viswanathan and colleagues have developed several nonpeptidic compounds that are lysosomal modulators of cathepsin activity and show promise in an *in vivo* model of assessing the accumulation of AD type proteins. The paper by Darras describes the preparation of a series of tri- and tetracyclic butyl-cholinesterase inhibitors (BChE) that possess selectivity over the related enzyme acetyl ChE. Shao and colleagues have developed *N*-methyl Lansoprazole as a novel PET imaging agent for Tau neurofibrillary tangles (NFT), and their paper outlines their approach and the successful use of this agent in imaging studies. Finally, a must read in this issue is the Viewpoint article written by Dr. Richard Hargreaves from Merck Research Laboratories. The article is interesting and covers many aspects of the past and ongoing research into Alzheimer's disease.

I hope you find the articles in this journal and the sister journals very interesting to read and that they stimulate your interest in Alzheimer's disease, which would lead to progress in your own laboratories.

Joseph P. Vacca, Guest Editor

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Notes

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

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