Preface

Alzheimer's disease (AD) is a devastating neurodegenerative brain disorder that leads to progressive loss of memory and other higher cognitive functions and ultimately death. Age is the greatest risk factor for AD, and therefore longer life spans mean more cases. In the United States alone, over five million people have AD, and worldwide estimates are 20–30 million. These numbers are projected to rise dramatically in the coming decades, creating a crisis that could bankrupt healthcare systems and overwhelm society as a whole.

The need for effective prevention and treatment is urgent, and many laboratories around the world are engaged in research into the root causes and mechanisms of the disease and the discovery of potential therapeutics. Although important gaps remain in our understanding of the molecular basis of AD pathogenesis and progression, considerable progress has been made in this regard.

Two key pathological features are found in the AD brain: amyloid plaques and neurofibrillary tangles. The former is primarily composed of a 42-residue amyloid β-peptide (Aβ), while the latter are composed of the microtubule-associated protein tau. While the deposits themselves may only be disease markers, a large body of evidence, particularly from genetics, strongly suggests that these proteins are directly involved in pathogenesis and progression.

The process apparently begins with the overproduction or under-clearance of the Aβ, a proteolytic product generated through cleavage of the amyloid precursor protein by the sequential action of β- and γ-secretases. Assembly of the amphipathic Aβ peptide in the form of neurotoxic oligomers and other higher-order forms leads to synaptic toxicity and the triggering, through unknown mechanisms, of tau misfolding and aggregation.

This volume first provides an overview of AD biology and the prospects for developing therapeutics (chapter "Targets and Strategies Toward the Development of Alzheimer Therapeutics"). What follows are specific and detailed medicinal chemical strategies for AD drug discovery and the development of diagnostic tools.

Preventing the formation of neurotoxic Aβ through inhibition of β-secretase (chapter "The Design, Development, and Evaluation of BACE1 Inhibitors for the Treatment of Alzheimer's Disease") or modulation of γ-secretase (chapter "γ-Secretase Modulators as Aβ42-Lowering Pharmacological Agents to Treat Alzheimer's Disease") is a leading strategy. As pathological tau is hyperphosphorylated, the responsible kinases are considered important targets (chapter "Inhibitors of Tau-Phosphorylating Kinases"), and because pathological tau is not able to serve its normal function in stabilizing microtubules, small molecules that rescue this loss of function may have therapeutic benefit (chapter "Microtubule-Stabilizing Agents for Alzheimer's and Other Tauopathies"). Finally, early diagnosis of AD is critical for enrolling the right patients into clinical trials and intervening before disease progression has gone too far, and the development of PET imaging agents for amyloid plaques has led to several approved diagnostic agents (chapter "PET Imaging Agents for Alzheimer's Disease").

I would like to thank all the authors who contributed to this volume for their time, thought, and effort in putting together high-quality chapters on these important targets and strategies for AD prevention, treatment, and diagnosis. I also thank all those working on this difficult problem in human health. We all greatly hope that these efforts will speed the day when AD is a scourge of the past.

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