PREFACE

In 1906, German psychiatrist Alois Alzheimer first reported the histological features of unique plaques and neurofibrillary tangles in the post-mortem brain of a 50-year-old female patient, whom he had followed up for 5 years from admission until her death, for progressive sleep disturbance, memory dysfunction and behavioral changes such as paranoia, aggression, delusion, and confusion. The disease is now recognized as Alzheimer's disease (AD), the most common form of senile dementia. The plaques are now known as amyloid beta (Aβ) plaques, and the neurofibrillary tangles are known as microtubule-associated hyperphosphorylated protein τ in the paired helical filaments.

More than 200 clinical research programs and clinical trials targeting Aβ and protein τ, either directly or indirectly, as a therapeutic strategy for AD have failed thus far. A growing database of the etiopathological, genetic, and biochemical features of AD indicate that it is a heterogeneous, polygenic, multifactorial, and complex disease. Hence, more rational therapeutic strategies for AD should be druggable target diversification, multi-targeting, or drug combinations. While current drug discovery programs for AD continue to focus on anti-Aβ and anti-τ strategies, a deeper understanding of the disease in recent years has opened drug discovery avenues involving neuroinflammation, metabolic derangements, stem cells, gene therapy and alternative therapies. Despite the high attrition rate in AD drug discovery and development, and serial failures of AD drug trials, we remain hopeful for effective AD therapeutics to come in the near future.

This book takes a snapshot of current AD drug discovery approaches to satisfy interested readers' curiosity for diversity and complexity of AD drug discovery. Chapter 1 provides an overview of the underlying pathogenic mechanisms of AD. Chapters 2-4 summarize Aβ immunotherapy, Aβ-targeted inhibitory peptides, and τ protein immunotherapy, respectively. Chapter 5 reviews AD therapeutic strategy targeting brain metal homeostasis, while Chapter 6 examines atypical protein kinase C as a potential AD drug target. Chapters 7-8 discuss blood-brain barrier (BBB) models in AD drug delivery and the BBB degradation-related protein- secreted protein acidic and rich in cysteine (SPARC) as a potential AD druggable target, respectively. Chapter 9 examines the therapeutic potential of epigenetic therapies for AD. Chapters 10 and 11 discuss the search for effective AD therapies using chimeric conjugate and multifunctional ligand approaches, and Chapter 12 examines natural products as potential interventions for neurocognitive disorders such as AD.

I am grateful for all the authors' intellectual contributions and diligence toward the fruition of this book. The 12 chapters cover diverse AD therapeutic approaches, but by no means do they completely reflect the dynamic and challenging field of

AD drug discovery. I hope this book will encourage interested readers to dive into this field and appreciate both the challenges and excitement of developing effective therapeutics for AD.

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