FOREWORD

Alzheimer's disease (AD) is the most common cause of age-related dementia, accounting for up to 70% of all dementia cases. There are 50 million individuals living with AD worldwide and its global prevalence is expected to grow due to predicted expansion of the older population. AD presents with irreversible cognitive decline, which commences as insidious short-term memory dysfunction and gradually spreads to other cognitive domains, rendering patients mute and non-ambulatory after 10-15 years of progressive course. AD is a genetically complex disease. The majority of AD cases are sporadic and their risk is predominantly controlled by the *APOE* genotype. The *APOE ε4* allele increases AD risk in allele-dose dependent fashion while the *ε2* allele has a risk-mitigating effect. Early-onset familial AD (FAD) accounts for 2-5% of all AD cases and is caused by mutations of the amyloid precursor protein (APP) or presenilin 1 (PS1) or 2 (PS2) genes, which are inherited in autosomal dominant fashion. Neuropathological hallmarks of AD include accumulation of insoluble β-amyloid (Aβ) peptides in the form of parenchymal plaques and vascular deposits, intraneuronal neurofibrillary tangles (NFTs) composed of misfolded and hyperphosphorylated microtubule-associated τ protein, activated astrocytes and microglia and widespread loss of synapses and nerve cell bodies. Unfortunately, there are neither effective preventive measures nor efficacious treatments available for this devastating disease.

Identification of Aβ peptides as the main constituents of Aβ plaques and vascular deposits by the late Dr. George Glenner in 1984 and later by Drs. Konrad Beyreuther and Colin Masters in 1985 has led to the development of the Alzheimer's Aβ cascade hypothesis, which proposes that the accumulation of Aβ is the primary culprit of AD pathogenesis and is thus a critical therapeutic target. Building on this premise, development of Aβ-directed immunotherapeutics and inhibitors of APP proteases, β-site cleaving enzyme 1 (BACE1) and γ-secretase complex (γ-SC), whose synergistic action generates Aβ has been pursued over the past 20 years. However, a series of setbacks these approaches have encountered during clinical trials testing hampered progress toward their successful clinical development. At the time this book is set for print, Aducanumab an Aβ-directed monoclonal antibody remains under evaluation by regulatory agencies for an approval as a possible first AD modifying treatment, while two similar antibodies remain in advanced phase III testing. Unfortunately, clinical efficacy of anti-Aβ antibodies remains limited to moderating disease progression, while also causing side-effects in the form of amyloid related imaging abnormalities (ARIA). Such a situation undoubtedly calls for the diversification of AD druggable targets and a search for poly-targets or drug combination therapeutic strategies.

Contributed by an assembly of clinicians and translational and basic AD research scientists, this book intends to provide a brief overview of AD drug discovery field. It covers the underlying AD pathogenic mechanisms and provides a review of Aβ amyloid- and τ protein-targeted immunotherapies, and peptide inhibitors for anti-Aβ amyloidosis. In addition, it also examines therapeutic

potentials of various AD drug targets such as brain metal homeostasis, protein kinase C, the blood-brain barrier, epigenetic therapies, as well as discusses chimeric conjugates, multifunctional ligands, and natural products as interventional approaches. I am convinced that this book will be valuable to healthcare professionals caring for AD patients, AD researchers and interested readers as it will provoke thoughts about identifying novel and more efficacious therapeutic agents for AD and related dementias.

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