

*Forum Minireview***Molecular Approaches to the Treatment, Prophylaxis, and Diagnosis of Alzheimer's Disease:****Preface: Pharmacological/Underlying Interventions for Alzheimer's Disease**Yasuyuki Nomura^{1,*}¹Laboratory of Pharmacotherapeutics, Yokohama College of Pharmacy,
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The number of patients with Alzheimer's disease (AD) has increased with the increase in the elderly population. The number of AD patients is expected to reach 100 million by year 2050. Hence, new medical interventions for this disease are urgently required.

At present, drugs such as donepezil, galantamine, rivastigmine, and memantine are clinically utilized in Japan. These are useful but because they are symptomatic slow-acting drugs, their therapeutic effects are limited. As the amyloid β ($A\beta$) cascade hypothesis regarding AD pathogenesis is generally accepted, drugs reducing $A\beta$ levels such as γ -secretase inhibitors and $A\beta$ immunotherapeutics appear promising as therapeutic modalities. However, to date no drugs that reduce $A\beta$ levels are clinically utilized. For the development of novel therapeutics, it is important to consider several factors, such as $A\beta$, tau phosphorylation, and the $A\beta$ -phosphorylated tau relationship in addition to novel genes/molecules involved in AD pathogenesis. The unknown molecules responsible for the mechanism of AD pathology are probably useful targets in the development of breakthrough therapeutics, prophylactics, and diagnostics. It is therefore important to clarify the mechanism of AD pathogenesis. The environmental factors potentially involved in AD pathogenesis, particularly in the pathogenesis of sporadic AD, should also be investigated. In spite of a number of research efforts for AD such as a study by the Alzheimer's Disease Neuroimaging Initiative (ANDI), we have not yet clarified the underlying mecha-

nism of AD pathogenesis.

To clarify the current situation and to obtain perspective and effective strategies regarding the pharmacological/underlying therapeutic approach to AD, we have organized here a Forum Minireview on "Molecular Approaches to the Treatment, Prophylaxis, and Diagnosis of Alzheimer's Disease", requesting presentations from five active workers/groups. Some articles in this Forum are based on the presentation at the symposium "Alzheimer's Disease: New Approaches to Drug Discovery and Diagnostics Development" at the 131st Annual Meeting of The Pharmaceutical Society of Japan held on March 2011.

In addition to the idea that genetic mutations in amyloid precursor protein (APP) and presenilin/ γ -secretase underlie the etiology of familial AD, it has been proposed that environmental factors are involved in the pathogenesis of sporadic AD. Endoplasmic reticulum (ER) stress affects immunological functions, resulting in AD (1, 2). Although, the linkage between ER stress and immunological stress in the development of AD is not well understood, this linkage can be speculated to play an important role in the development of AD. Based on these ideas, drugs targeting the ER as well as anti-inflammatory drugs could be potential treatment options.

HRD1 has been identified as a ubiquitin ligase E3 in the ER that protects against ER stress-induced neuronal death (3, 4). Interestingly, HRD1 degrades APP, resulting in reduced $A\beta$ production. Conversely, the suppression of HRD1 expression results in APP accumulation and $A\beta$ generation accompanied by ER stress and apoptosis. In addition, HRD1 protein levels are decreased in the postmortem brains of AD patients. Therefore, the

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reduction of HRD1 levels, perhaps by insolubilization, is involved in the pathogenesis of AD. Thus, HRD1 is a possible target for medical interventions in AD treatment, e.g., compounds that prevent the insolubilization of HRD1.

The pathogenesis of AD, which is presumed to occur via synaptic dysfunction, appears to be due to the accumulation of Wiskott–Aldrich syndrome protein family verprolin-homologous protein (WAVE), a key molecule for actin assembly. Although synaptic integrity is structurally regulated by the precise assembly of the actin cytoskeleton, abnormal WAVE accumulation is induced by the interaction of A β and phosphorylated tau protein (5, 6). Thus, WAVE-mediated disturbances of actin assembly may be closely associated with synaptic deficits in the brains of AD patients, and WAVE could be a target for AD therapy. Furthermore, enhancing A β clearance by microglial cells is another promising AD treatment strategy.

Senile plaque (SP) and neurofibrillary tangles (NFTs) are the histopathological markers of AD. In vivo neuroimaging methods for detecting SP and NFT such as positron emission tomography (PET)/single photon computed tomography (SPECT) are powerful techniques for diagnosing AD. The development of novel imaging probes with low toxicity and high sensitivity and specificity will be important for both the diagnosis of AD and the discovery of novel therapeutics for AD (7, 8). Several imaging probes for SP are currently in active commercial development. However, no existing PET/SPECT imaging agents permit an evaluation of tau pathology in the brains of AD patients. This limitation would be addressed in the future development of imaging probes for AD diagnosis with a focus on developing probes with a high specific affinity for NFT.

Important findings regarding AD, including neuropsychiatric characteristics, risk factors, neuroimaging data, and the use of biomarkers, obtained during the last 10 years are succinctly introduced in this review (9, 10). CSF A β 42 and tau are the most sensitive biomarkers for diagnosing AD and predicting its onset following mild cognitive impairment (MCI). Based on this progress, new diagnostic criteria for AD dementia, MCI due to AD, and preclinical AD were proposed by the National Institute of Aging (NIA) and Alzheimer's Association (AA) in April 2011. Several problems, barriers, and

perspectives for translational research from basic to clinical fields have been proposed and discussed.

We look forward to breakthrough progress in biomedical studies regarding the development of clinically useful therapeutic, prophylactic, and diagnostic modalities for AD. We believe that this Forum Minireview will facilitate milestone advances in the clinical treatment of AD.

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