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Preface

Tau and Beyond for Alzheimer's Disease

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One year ago on 22 September 2012, the Alzheimer's disease (AD) field lost a pioneer—Inge Grundke-Iqbal—who passed away following a stroke. Together with her husband Khalid Iqbal, Inge discovered in the mid-1980s that the paired helical filaments of neurofibrillary tangles are made up of abnormally hyperphosphorylated tau. This seminal discovery opened a new major avenue for investigating neurodegeneration in AD and other tauopathies and attracted many neuroscientists to search for diagnostic tools and disease-modifying therapies for AD and related tauopathies based on tau pathology.

The guest editors were introduced to the AD field by Inge and Khalid two decades ago. We were so privileged to be trained and inspired by them during our early careers. While we are still saddened by the loss of Inge, we feel that one of the best ways to remember her is to continue her research legacy by editing this special issue of the *Journal of Alzheimer's Disease*. The contributors of this special issue are either Inge's former collaborators/colleagues or trainees who are active investigators in the field of tau-associated neurodegeneration.

After more than twenty years from the discovery of abnormally hyperphosphorylated tau as the major component of paired helical filaments, we know now that tau is crucial to neurodegeneration in AD. A lot more still needs to be done before we fully understand what causes tau abnormality and how tau mediates neurodegeneration. Inge and Khalid focused their energy on understanding the disease mechanisms and not the models. In this issue, Iqbal et al. reminded us why we need to focus on the disease and not just the lesions and described their animal models of the sporadic form of AD. In a second paper, they analyzed the extent to which eight common clinical symptoms might serve as indicators of various subgroups of AD, which they described previously based on the levels of $A\beta_{1\text{-}42}$, tau, and ubiquitin in cerebrospinal fluid. Liu and Götz commented on how the field was started and reviewed in detail the role of PP2A and its endogenous inhibitor in tau phosphorylation. Regarding tau phosphorylation, several aspects were investigated: kinases, phosphatases, and the biological effect of the abnormal protein. Wang and colleagues reviewed the roles of mTOR-dependent signaling in neurodegeneration. Hernández et al. showed in neuroblastoma cells that tau unbound to microtubules is a better substrate for glycogen synthase kinase-3β (GSK-3β), suggesting that microtubule depolymerization could be a primary event in neurodegenerative disorders like AD. Wu and coworkers showed that pretreatment of mice with lithium, an inhibitor of GSK-3β, for one week prevents the synaptic changes and the learning and memory deficits induced by scopolamine, supporting that GSK-3β may be a key molecular mediator of cholinergic synaptic dysfunction. Qian and collaborators demonstrated that another important protein kinase, Dyrk1A, enhances tau expression by stabilizing its mRNA, which provides a novel insight into the regulation

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of tau expression and a molecular mechanism of tauopathies. Beharry et al. reported that expression of pseudo-phosphorylated human tau induces behavioral and motor functions and olfactory learning deficit in *Drosophila*. Lu et al. found that hyperphosphorylation of tau may diminish the ability of tau to prevent DNA damage, providing a potentially novel insight into the mechanisms underlying tauopathies.

In addition to hyperphosphorylation of tau, several other aspects are covered in this special issue. Takashima updated the role of tau oligomers in neurodegeneration. Levarska and colleagues addressed the question of whether insoluble complexes of misfolded and truncated tau command a distinct infectivity and spreading potency. They showed that there are various strains of disease modified tau which display different infectivity and spreading potency. Yuan et al. demonstrated that mice expressing three-fold higher level of human tau in the absence of mouse tau display a normal axonal transport function. Ding et al. discussed the roles of ciliary neurotrophic factor in the proliferation and differentiation of neural stem cells, which was Inge's major research focus during her last several years of life. Ward and coworkers further characterized their new antibody TOC1 against oligomeric tau, which is potentially a powerful tool for future studies of tauopathies. Popova and Alafuzoff reported a depletion of SLC10A4, a synaptic vesicle protein, in the transentorhinal cortex with increased severity of AD-related pathology. Nihonmatsu-Kikuchi et al. reviewed epidemiological and biological studies concerning major depression and AD and proposed a common mechanism linking the pathophysiologies underlying the two conditions. Finally, Xiong et al. and Yang et al. reported that liraglutide, an anti-diabetic drug, ameliorates AD-associated brain abnormalities and memory deficits in mouse models. Studies selected for this special issue, ranging from basic research to diagnostic and therapeutic investigations, represent several advances of the AD field.

We are most grateful to all the contributors for sharing with us their respects and memorial to Inge in this way. We also want to thank George Perry, Editor-in-Chief, and Beth Kumar, Managing Editor, of the *Journal of Alzheimer's Disease*, for their support and assistance, without which this special issue would have been impossible. Finally, we greatly appreciate IOS Press, the publisher, for waiving the publication fees for the authors for this special issue.