

IEEE 7th BIBE Invited Keynote Lecture: Metallobiochemistry of Alzheimer's Disease and Its Theranostic Agent Development

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Abstract— Alzheimer's disease (AD) has become a leading public health issue due to our nation's burgeoning aging population. These issues are further complicated by the fact that neither preventive measure and effective treatment nor definitive *in vivo* diagnostic tool for this burdensome disease is currently available. Genetic, biochemical, and neuropathological data argue that A β amyloidosis, which originates from the A β amyloidogenic processing of a metalloprotein- amyloid precursor protein (APP), is the key event in AD pathology. However, neurochemical factors that impact upon this age-dependent protein disorder in brain are not well recognized.

Considerable evidence is mounting that dyshomeostasis of the redox-active biometals, Cu and Fe, and oxidative stress contribute to the neuropathology of Alzheimer's disease (AD). Present data suggest that metals can interact directly with A β peptide, the principle component of A β amyloid that is one of the primary lesions in AD. The binding of metals to A β modulates several physiochemical properties of A β that are thought to be central to the pathogenicity of the peptide. First, we and others have shown that metals can promote the *in vitro* aggregation into tinctorial and disordered protein- A β amyloid. Studies have confirmed that insoluble amyloid plaques in post-mortem AD brain are abnormally enriched in Cu, Fe, and Zn. Conversely, metal chelators dissolve these proteinaceous deposits from post-mortem AD brain tissue and attenuate cerebral A β amyloid burden in APP transgenic mouse models of AD. Second, we have demonstrated that redox-active Cu(II), and to a lesser extent, Fe(III), are reduced in the presence of A β with concomitant production of reactive oxygen species (ROS)- hydrogen peroxide (H₂O₂) and hydroxyl radical (OH•). These A β /metal redox reactions, which are silenced by redox-inert Zn(II), but exacerbated by biological reducing agents, may lead directly to the widespread oxidation damages observed in AD brains. Moreover, studies have also shown that H₂O₂ mediates A β cellular toxicity and increases the production of both A β and amyloid precursor protein (APP). Third, the 5' untranslated region (5'UTR) of APP mRNA has a functional iron-response element (IRE) which is consistent with biochemical evidence that APP is redox-active metalloprotein. Hence, the redox interactions between A β , APP, and metals may be at the heart of a pathological positive feedback system wherein A β amyloidosis and oxidative stress promote each other. The emergence of redox-active metals as key players in AD pathogenesis strongly argues that amyloid-specific metal-complexing agents and

antioxidants be investigated as possible disease-modifying agents for treating this horrible disease.

In addition, the AD diagnosis currently relies on behavior-based tests- e.g., Mini-Mental State Examination (MMSE). However, it is not specific for AD as many factors may lead to memory impairment and cognitive failure. The only definitive diagnosis for AD is the post-mortem examination of brain tissue for cerebral A β amyloidosis, the neuropathological hallmark of AD (2,3). Thus, development of *in vivo* amyloid imaging agents can not only provide definitive AD diagnostic tools but also speed up the preclinical and clinical assessment of novel AD therapeutic agents targeting A β amyloid.

In summary, study of AD metallobiochemistry cements a solid foundation for discovering novel theranostic agents of AD.



Xudong Huang, Ph.D., is an Assistant Professor of Radiology, Harvard Medical School and Brigham and Women's Hospital (BWH) and the Director for Conjugate and Medicinal Chemistry Laboratory of Functional and Molecular Imaging Center at Department of Radiology, BWH. Dr. Huang received his Ph.D. from MIT and postdoctoral training in Neurology/Psychiatry at Massachusetts General Hospital (MGH)/Harvard Medical School. Being a faculty member at MGH, Prof. Huang has been studying cerebral biometal dysregulation, oxidative stress and their links to pathogenesis of Alzheimer's disease and other brain disorders. Dr. Huang has designed and characterized novel amyloid-targeted MRI molecular probes, antioxidants and metal chelators as potential Alzheimer's diagnostic and disease-modifying agents. His current research thrust is to design, synthesize and characterize therapy-enabling diagnostic (TED) agents, targeted therapeutic compounds and nanoconjugates for a full spectrum of human diseases, such as neurological disorders, cancer, cardiovascular diseases, etc. Prof. Huang is also leading the cheminformatics initiative within the Department of Radiology, Brigham and Women's Hospital, affiliated with Harvard Medical School.