Chemical Tools and Tactics to Study the Role of Metal-Associated Misfolded Proteins in Human Neurodegenerative Diseases

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Neurodegenerative disorders impose an enormous financial and emotional burden on patients, their families, and communities. More than 36 million people worldwide have Alzheimer's disease (AD), a devastating and fatal neurodegenerative disease that remains poorly treated due to an incomplete grasp on the disease etiology. A key neuropathological hallmark of AD is amyloid-β (Aβ) plaques in the brain. The mechanisms driving formation of these protein aggregates and their causal link to dementia are still unclear. An additional observation in the AD brain is the accumulation of metal ions, which has been proposed to be associated with Aβ aggregates and neuronal death, yet relatively little is known, further sustaining the controversy surrounding this aspect of the disease. Even through a large body of continuously reported literature regarding metal ions and Aβ species, *direct connection of metal-Aβ interaction with AD onset and development has been neglected* in this field due to lack of appropriate tools and/or tactics. Therefore, we have developed chemical tools and/or tactics that are capable of specifically targeting metal-associated Aβ species and modulating their interaction and reactivity. Using our chemical reagents, we have been able to regulate metal-induced Aβ aggregation and neurotoxicity *in vitro* and in living cells. Here, our rational structure-based design principle and recent findings for chemical tools and tactics for investigating metal-Aβ chemistry and biology in AD and/or potential therapeutic agents for AD will be discussed.