Restoration of 3-MST as a disease modifying approach for Alzheimer's disease

Swati S. More[1], Swetha P. Rao[1], Kiran Bhilare[1], Wei Xie[1], Ye In Christopher Kwon[2], Nicholas Juckel[2], and Michael K. Lee[2,3]

[1] Center for Drug Design, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA. [2] Department of Neuroscience, University of Minnesota, Minneapolis, Minnesota, USA. [3] Institute for Translational Neuroscience, University of Minnesota, Minneapolis, Minnesota, USA

Oxidative stress underlies the onset and progression of Alzheimer's disease (AD) and manifests as reduced glutathione and hydrogen sulfide (H_2S), an endogenous gaseous neurotransmitter. Treatment with H_2S and chemical donors has shown promise in preclinical studies. Their clinical benefit is limited because of poor stability, bioavailability, and dose-limiting toxicities. An untapped therapeutic opportunity thus exists to restore H_2S homeostasis. 3-Mercaptopyruvate sulfurtransferase (3-MST) is an endogenous H_2S-producing enzyme; however, its role in AD pathophysiology and exploitation for therapeutic development remains uninvestigated. We have shown that oxidative stress in AD impedes 3-MST function and contributes toward Aβ aggregation and related toxicity. In turn, oxidative stress is further potentiated, causing neuroinflammation, neuronal dysfunction, and death. We have developed a bioavailable 3-mecaptopyruvate replacement, sulfanegen, which serves as a substrate for 3MST, releasing H_2S. Treatment of symptomatic Alzheimer's mice (APP/PS1; 7 and 12 months) with sulfanegen reversed the signs of brain oxidative and inflammatory stress, and restored cognitive function. Neuropathological analysis showed a modest yet significant effect of sulfanegen on Aβ deposition in addition to slowing of progressive neurodegeneration of noradrenergic neurons in the LC. The compound, in addition to H_2S release, liberates pyruvic acid and thus, its neuroprotective effect is accompanied by enhancement of mitochondrial bioenergetics. Global proteomic analysis of persulfidated proteins offered insight into redox and mitochondrial pathways modulated by sulfanegen. Our studies demonstrate the utility of 3-MST function restoration in reversing biochemical and neuropathological consequences of AD pathology and create the warrant for exhaustive preclinical exploitation of this pathway for anti-AD therapy.

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Presenter Name and contact information:
Swati S. More, Ph.D., Professor
Center for Drug Design
College of Pharmacy
University of Minnesota
Minneapolis, Minnesota, USA
Email: morex002@umn.edu