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### Coordinated RNA modulation of the Prion-PrP and amyloid precursor protein as a novel combined therapy to optimize iron homeostasis while providing anti-amyloid efficacy during neurodegenerative disease

Jack T Rogers, Yanyan Liu, Qinjun Li, Catherine M Cahill and Xudong Huang  
MGH, USA

The amyloid precursor protein (APP) is a metalloprotein cleaved to the 40-42 amino acid Abeta peptides, which exhibit metal-catalyzed neurotoxicity. APP gene expression is regulated at the translational level by active iron-responsive elements (IRE) RNA stem loops in the 5'untranslated region of APP mRNA. To adapt and counteract metal-catalyzed oxidative stress, iron induces the translation of both APP and ferritin (iron storage protein) by similar mechanisms. In health, ubiquitous APP is cleaved in a non-amyloidogenic pathway within its Abeta domain to release the neuroprotective APP ectodomain APP(s), which functions to facilitate iron export by ferroportin from iron-overloaded neurons, as occurs after hemorrhage. The APP IRE interacts with IRP1 (cytoplasmic cis-aconitase), whereas the canonical ferritin-H IRE RNA stem loop binds to IRP2 in neural cells, in human brain cortex tissue and in human blood. We published on potent FDA preapproved APP translation blockers that selectively inhibited the unique iron-responsive element RNA (IRE) stem loop in the 5'untranslated region (UTR) of APP mRNA with anti-amyloid efficacy in the brains of the APP-5'UTR-positive TGCRND8 APP transgenic mouse model of Alzheimer's disease. We will reveal the efficacy and mechanism-of-action of high-throughput screened and highly novel translation blockers of both APP and the co-seeding prion protein, with a prospectus for interpreting how these anti-amyloid agents also ameliorate brain iron homeostasis. Our novel therapeutic strategy has potential impact for people with trisomy of the APP gene on chromosome 21, which is a phenotype long associated with Down syndrome that can also cause familial AD.

#### Biography

Jack Rogers has completed his PhD at the age of 25 years from London University and postdoctoral studies from MIT. He is the Director of Neurochemistry, Massachusetts General Hospital and on the faculty at Harvard. He has published more than 100 papers in reputed journals and serving as an editorial board member of reputed organizations such as the Alzheimer's Association and AFAR.

[jrogers1@rcn.com](mailto:jrogers1@rcn.com)