MODULATION OF PP2A ACTIVITY BY A COMPONENT OF COFFEE IS BENEFICIAL IN MODELS OF ALZHEIMER’S DISEASE

J.B. Stock¹, M. Voronkov², J. Fernandez², D.N. He³, D.C. Lo³, S.P. Braithwaite²

¹Molecular Biology, Princeton University, Princeton, ²Signum Biosciences, Monmouth Junction, NJ, ³Center for Drug Discovery and Department of Neurobiology, Duke University Medical Center, Durham, NC, USA

Neurodegenerative disorders commonly exhibit abnormal hyperphosphorylation of proteins that are believed to contribute to disease. Tau is the prototypic hyperphosphorylated protein in Alzheimer's disease, contributing to neurodegeneration and forming neurofibrillary tangles, a pathological hallmark of the disorder. In the search for targets to reduce tau phosphorylation, kinases have proven difficult to successfully drug. Activating protein dephosphorylation is therefore a promising alternative approach. A highly specific and novel mechanism of reversible carboxyl methylation strongly regulates the activity of protein phosphatase 2A (PP2A), the major brain phosphatase. Inhibition of PP2A demethylation, which leads to phosphatase activation, provides a tractable target for drug development. Screening of botanical extracts for PP2A demethylation activity identified coffee as an active source. Fractionation identified SIG1012, a minor component unrelated to caffeine, as the active agent. Synthetic SIG1012 inhibits PP2A demethylation in biochemical and cell based assays and in vivo. SIG1012 treatment can reduce tau phosphorylation at sites relevant for Alzheimer's pathology. In a brain slice model in which tau is overexpressed by particle-mediated gene transfer, resulting in neurodegeneration of transfected cortical neurons, SIG1012 treatment is neuroprotective. In models of tauopathy oral administration of SIG1012 results in improved motor performance and enhanced survival. Together these data indicate that modulation of PP2A demethylation is a viable target for therapeutic intervention as a disease modifying strategy for Alzheimer’s Disease.