Novel Pharmacogenomic Methodology for the Discovery of First-In-Class Mechanisms of Phenothiazine Derivatives to Delay and Rescue Alzheimer's Disease Pathology and Extend Lifespan in C. elegans

Roh, Kun-Hyung (School: The Bronx High School of Science)

Alzheimer's Disease (AD) is the most common neurodegenerative disorder and the leading cause of death in the US. There are currently no effective drugs for this disease due to lack of understanding of disease pathogenesis and molecular targets. With expansion of human lifespan and aging population, AD is a public health emergency that urgently requires an effective drug. Phenotypic assay on model organism C. elegans was performed, in which phenothiazines were among the most protective drugs against Aß42-induced proteotoxicity measured by paralysis. Phenothiazines such as cyclophenazine and thioproperazine reduced TNF-a levels from microglia by up to 63.07%, a major brain immune cell responsible for neuroinflammation, and rescued paralysis by 80.41% in transgenic C. elegans. Prior to this research, it was undefined how phenothiazines can produce such anti-inflammatory, neuroprotective effects. Moreover, the molecular targets modulating the underlying therapeutic mechanism remained elusive due to limitations in conventional target identification techniques. This is the first study demonstrating a novel pharmacogenomic approach to uncover neuroprotective transcriptional mechanisms of phenothiazines, through correlational and gene network analyses. Phenothiazines comprehensively reversed the disease signature, possibly through epigenetic modulation by inhibiting CTBP2 with a Z-consensus score of -3.965, and PACS2 with a Kendall correlation of 1. This analysis also revealed numerous potential therapeutic avenues that target the disease genetic network. This technique can be applied to any assays in drug discovery labs, contributing to the overall understanding of AD by bridging the gap between genotype and phenotype, and nominating therapeutic targets and biomarkers.

Awards Won: