

# **Novel Drug Discovery Methodology Using Machine Learning for Gene Expression-Based Virtual Screening Predicts Novel Compounds To Reverse Alzheimer's Disease With Applications to Cancer and Longevity by Inhibiting CtBP2 Expression**

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

Alzheimer's Disease (AD) has neither satisfactory nor equitably accessible treatments. Current research emphasizes inflammation, notably age-related elevation of microglial TNF- $\alpha$ , in driving AD pathogenesis. Previous screens showed phenothiazines as protective drugs against A $\beta$ 42-induced toxicity and neuroinflammation. To elucidate mechanisms mediating such protective effects and develop a general drug discovery method, I developed a target identification protocol which allowed rapid assessment of effects of drugs on gene expression in human cells. This revealed that inhibition of CtBP2 was one of the most robust molecular responses to phenothiazines. CtBP2 expression increases with age, in AD brain regions with specificity to microglia, and even in populations with certain types of cancer. However, the complex and unstable structure of CtBP2 prevents development of high-affinity, blood-brain barrier (BBB) permeable small molecules. Conventional drug discovery methods struggle in targeting "undruggable" proteins, or multiple pathways in complex diseases like AD. Here, I shift paradigms from Structure-Based to Expression-Based Screening, targeting mRNA-based gene expression instead of physiochemical binding. To discover more effective small inhibitors of CtBP2 transcription, I created a new machine learning model that produces accurate predictions even in extremely imbalanced datasets, surpassing baseline metrics. Using this model, I identified novel compounds that transcriptionally inhibit CtBP2 outperforming phenothiazines to increase healthspan by abolishing microglial inflammation and *C. elegans* paralysis. I report a highly promising novel and general approach to drug discovery, applicable to any high-throughput assays for increased accessibility and efficacy.