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Tip60 HAT activators as therapeutic modulators for neurodegenerative disease

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Abstract: Reduced histone acetylation in the brain causes transcriptional dysregulation and cognitive impairment that are key initial steps in Alzheimer's disease (AD) etiology. Unfortunately, current treatment strategies primarily focus on histone deacetylase inhibition (HDACi) that causes detrimental side effects due to non-specific acetylation. Here, we test Tip60 histone acetyltransferase (HAT) activation as a therapeutic strategy for selectively restoring cognition associated histone acetylation that is depleted in AD by developing compounds that enhance Tip60's neuroprotective HAT function. Several compounds show high Tip60-binding affinity predictions in silico, enhanced Tip60 HAT action in vitro, and restore Tip60 knockdown mediated functional deficits in Drosophila in vivo. Furthermore, compounds prevent neuronal deficits and lethality in an AD-associated amyloid precursor protein neurodegenerative Drosophila model and remarkably, restore expression of repressed neuroplasticity genes in the AD brain, underscoring compound specificity and therapeutic effectiveness. Our results highlight Tip60 HAT activators as a promising therapeutic neuroepigenetic modulator strategy for AD treatment.

Wednesday, April 29th | 2:00pm-3:15pm | Science Hall 126 & Zoom

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