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Drugs repurposing for the treatment of HIV-Associated Neurocognitive Disorder by AI-based literature mining

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HIV-1 Associated Neurocognitive Disorder (HAND) is a common and clinically detrimental complication of HIV infection. Viral proteins including Tat, released from infected cells, cause neuronal toxicity. Substance abuse in HIV-infected patients greatly exacerbates the severity of neuronal damage. To repurpose small molecule inhibitors for anti-HAND therapy, we employed MOLIERE, an AI-based literature mining system that we developed. All human genes were analyzed and prioritized by MOLIERE to find previously unknown targets connected to HAND. The list was narrowed to those with known small molecule inhibitors developed for other applications and lacking systemic toxicity in animal models. We tested the activity of small molecules targeted against the proteins of five prioritized genes to protect against the combined neurotoxicity of HIV-Tat and cocaine in primary neuronal cultures. Four prevented Tat and cocaine toxicity. The compounds are the FDA approved drug Amlexanox; Tazemetostat (EPZ-6438), a potent selective EZH2 inhibitor that is in Phase II clinical trials; Dead Box RNA helicase 3 inhibitor RK-33 and DNA-Dependent Protein Kinase inhibitor NU7441. Both RK-33 and NU7441 were shown to selectively kill tumors without any observed systemic toxicity in animal models. Despite the disparate molecular targets of these drugs, analysis revealed a common mechanism of neuroprotection; namely that inhibition of astrocyte and microglia activation prevents the toxicity of Tat and cocaine. These findings show that MOLIERE literature mining provides a novel way to identify new mechanisms of neurotoxicity of HIV and drugs of abuse, and also accelerates the possibility of repurposing drugs for novel HAND treatments.