

Submitter Name: Michael Shtutman
Submitted email: shtutmanm@cop.sc.edu

Inhibition of the DEAD Box RNA Helicase 3 prevents HIV-1 Tat- and cocaine-induced neurotoxicity by targeting microglial activation

Marina Aksenova¹, Justin Sybrand², Biyun Cui¹, Mathew Lucius¹, Hao Ji¹, Michael D Wyatt¹, Ilya Safro², Jun Zhu¹, Michael Shtutman¹

¹ Department of Drug Discovery and Biomedical Sciences, College of Pharmacy, University of South Carolina ² School of Computing, Clemson University

HIV-1 Associated Neurocognitive Disorder (HAND) is 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 influences the severity of neuronal damage. To uncover potential targets for anti- HAND therapy, we employed a computational approach we developed called MOLIERE: Automatic Biomedical Hypothesis Generation to uncover previously unknown associations of the human genes with the HAND. Evaluation and prioritization of the highest scoring genes potentially associated with HAND revealed Dead Box RNA Helicase 3 (DDX3). Importantly, a selective small molecule inhibitor of DDX3 helicase activity, RK-33, has been developed and shown to selectively kill tumors that depend on DDX3 without any observed systemic toxicity in animal models, making it an ideal probe to test the role of DDX3 in HAND.

We show that RK-33 prevents the combined neurotoxicity of HIV Tat protein and cocaine in rat and mouse cortical cultures. Transcriptome analysis by RNA-seq of the treated cultures shows that the majority of Tat-activated transcripts are microglia-specific genes, and that RK-33 blocks their activation. These genes include major microglial markers and regulators of microglia activation, such as CSF1R and CSF3R. Inhibition of Tat/cocaine microglia activation by RK-33 was confirmed by immunofluorescence of microglia-specific markers.

These findings suggest that DDX3 contributes to microglial activation triggered by the combined insults of Tat and cocaine, and that pharmacological inhibition of DDX3 may have the potential to treat not only HAND but other neurodegenerative diseases with pathological activation of microglia.