ORGANIC SEMINAR

A Cure for HIV-1? Design and Evaluation of First-in-Class Dual Agents that Reactivate Latent HIV-1 and Prevent New Infection

Nick Brauer

Graduate Student, Chmielewski Group
Purdue University

Thanks to advances in HIV therapeutics, effective management of HIV-1 infection for most patients can be achieved with one of the many FDA approved anti-retroviral therapies (ART), which reduces viral copies of HIV-1 to undetectable levels in the blood. Stopping treatment, however, leads to viral rebound caused by sustained HIV-1 latent reservoirs that evade the host immune system. Several efforts to purge HIV-1 latent reservoirs have been explored, including the "Shock and Kill" method, which aims to force latently infected cells into HIV-1 transcription using latency reversal agents (LRA), such as class 1 histone deacetylase (HDAC) inhibitors. Presently, these efforts have been largely unsuccessful; reversing latency in HIV-1 infected cells leads to the production of mature virion and new infection, which has not been prevented with ART co-administration in clinical trials. To properly prevent new infection, an ART must be co-located with an LRA at the time of latency reversal. To achieve this, we have previously designed and synthesized small molecule dual inhibitors of HDAC3 and HIV-1 protease, achieving micromolar potencies. Herein, we will describe the optimization of a lead compound using structure guided design, medicinal chemistry principles, and a parallel synthetic route to rapidly synthesize a small structure-activity relationship library. We found several compounds with promising enzymatic activities, including potencies in the double-digit nanomolar for both HDAC3 and HIV-1 protease. The compounds were then subjected to a cellular HIV-1 latency model, which identified several dual agents that showed both latency reversal activity and prevention of new infection at biologically relevant concentrations, a first-in-class achievement.

Tuesday, December 9, 2025 *4:30 pm* *WTHR 104*

PURDUE UNIVERSITY | James Tarpo Jr. and Margaret Tarpo Department of Chemistry