

ORGANIC SEMINAR

Eradicating HIV-1 Reservoirs: The Development of Chemical Compounds Capable of Simultaneously Activating HIV-1 Latency and Preventing New Infection

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Abstract: The elimination of human immunodeficiency virus type-1 (HIV-1) from infected individuals persists as a major medical challenge. Although combined antiretroviral therapy (cART) has led to profound reduction in HIV-related morbidity and mortality, discontinuation of cART medications results in reinfection by HIV-1. This is due to latent reservoirs of replication-competent proviruses that persist within CD4+ memory cells, macrophages, and the central nervous system of HIV-positive patients.

The shock and kill approach has been proposed to eradicate HIV reservoirs through the reactivation of latent provirus followed by the elimination of infected cells via immune-mediated clearance. However, it is imperative that reactivated reservoir cells must not produce new, infective virions. Most studies on the shock and kill approach to date utilize histone deacetylase inhibitors (HDACi's) as the target for activating HIV-1 latency. We also identified HIV-1 protease (HIV PR) as the target for preventing new infection. Ideally, HDAC reactivation of HIV-1 latency should be spatially and temporally linked to the antiviral activity, leading to a need for dual-action agents targeting HIV PR and HDAC.

Due to the lack of a resolved ligand-bound crystal structure of HDAC3, which is the isoform shown to be critical for latency reversal, we created a predicted fold of HDAC3 with RobettaFold®. In Schrodinger Maestro®, DESMOND molecular dynamics (MD) simulations with our molecular model led to the design of proposed dual HIV PR/HDAC3 inhibitors. The scaffolds for these compounds were derived from known, FDA-approved inhibitors of HIV PR and HDAC3. Dual inhibitors were synthesized and biologically evaluated against HIV PR and HDAC3, showing micromolar inhibition against both targets.



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