Integrated preclinical drug discovery for HIV pathogenesis and eradication

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Abstract: Despite the continued global efforts and accelerated advancement on HIV drug discovery research in the past 35 years, HIV infection is still an incurable disease. Viral mutations continue to manifest at an alarming rate, and a single effective vaccine has yet to be discovered. In this presentation, an integrated multipronged approach for targeted drug development attacking HIV pathogenesis as well as HIV latent infection, conducted in our laboratory during the past 5 years, will be discussed. This preclinical drug discovery campaign employs multiple modern techniques, ranging from computational biochemistry, molecular dynamics simulations, artificial intelligence machine learning for inhibitory dynamics-potency relationship, in vitro and in silico targeted screening, dynamics ‘shut-down’ inhibition, cell-based viral challenge, and in vivo models for drug potency and toxicity evaluations. Interested drug targets are HIV-1 integrase, human CCR5 co-receptor, protein kinase C, and epigenetic histone deacetylases. Recent advances include 14 drug candidates, an accelerated in silico-in vitro platform for drug development, two improved enzyme-inhibitor binding/dynamics/potency modeled predictions, and a humanized mouse model for anti-HIV potency assessment and immune responses. CD4+ T-cell targeted drug delivery system has also been developed successfully using antibody-functionalized liposomes. Future endeavors will be centered around an early cellular profiling upon drug treatments.

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