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Session: **BS4**: Sunday May 3 – 11:00:12:30 – HIV Pathogenesis and Animal Models

Track:	Basic Sciences
Subject:	HIV Pathogenesis and Animal Models
Presentation Type:	Oral
Title of Abstract:	**Nef Inhibitors as Adjuvants Towards a Cure for HIV/AIDS**
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Abstract

HIV-1 Nef is a leading contributor to HIV virulence and is required for progression to AIDS. The role of Nef in HIV pathogenesis is multifactorial and includes mediating impaired T cell activation and maturation, subverting apoptosis and down-regulating cell surface molecules like major histocompatibility complex class I (MHC-I). Specifically, Nef mis-directs host cell intracellular signaling and membrane trafficking to endocytose cell surface MHC-I and thus, minimize immune recognition of HIV-1-infected cells. To achieve this, Nef binds phosphofurin acidic cluster sorting proteins in an acidic cluster- ($EEEE_{65}$)-dependent manner and shuttles them to the trans-Golgi network (TGN). Here, Nef interacts with Src family tyrosine kinases (SFK) via its $PXXP_{75}$ motif to initiate a signaling cascade culminating in MHC-I internalization and sequestration to the TGN. Herein, we performed an *in silico* drug discovery screen to identify small molecules that could interfere with the Nef:SFK interaction. Compound H3-1 blocked the Nef:SFK interaction in HIV-1-infected cells, reduced HIV-1 replication in a Nef-dependent manner and resulted in limited cytotoxicity. Importantly, H3-1 counteracted Nef-dependent MHC-I down-regulation in HIV-1-infected primary $CD4^+$ T cells, suggesting that H3-1 treatment enhanced antigen presentation. Additionally, experiments assessing the feasibility of H3-1 treatment *in vivo* were conducted in a HIV transgenic mouse model which expresses Nef in $CD4^+$ T cells. H3-1 *in vivo* pharmacokinetics were evaluated using mass spectrometry. Next, *ex vivo* H3-1 treatment of HIV transgenic mouse-derived splenocytes resulted in improved MHC-I presentation of a model epitope (SIINFEKL) from ovalbumin on Nef-expressing $CD4^+$ T cells. Collectively, these results highlight how Nef inhibitors can function as adjuvants by improving antigen presentation and thus, combating Nef-mediated MHC-I down-regulation that is omnipresent during latent reservoir reactivation.