

POSTER 39

CHEMICAL LIBRARY SCREENS TARGETING AN HIV-1 NEF/HOST CELL KINASE COMPLEX IDENTIFY NOVEL ANTI-RETROVIRAL COMPOUNDS

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Accessory proteins encoded by HIV-1 are essential participants in the pathogenesis of AIDS. One of these factors, Nef, is required for AIDS progression and may represent a target for anti-HIV drug discovery. Here we describe a high-throughput screening assay for inhibitors of Nef in a complex with one of its host cell binding partners, the Src family kinase Hck. Hck activation is dependent upon Nef in this assay, providing a direct readout of Nef activity *in vitro*. A screen of 10,000 discrete chemical compounds identified a unique diphenylfuopyrimidine (DFP) as a strong inhibitor of Nef:Hck activity. This compound also exhibited remarkable anti-HIV activity, blocking Nef-dependent HIV replication in cell culture with no apparent cytotoxic effects. Several structurally related analogs showed similar Nef-dependent anti-retroviral activity, identifying the DFP substructure as a valuable probe of HIV Nef function and as a potential pharmacophore for future AIDS drug development. Disrupting the functionality of Nef and other HIV accessory factors and their interactions with host cell target proteins may accelerate the discovery of new anti-HIV agents.