

## A SMALL MOLECULE HIV-1 INHIBITOR THAT DESTABILIZES THE VIRAL CAPSID

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Following fusion of HIV-1 particles with target cells, the viral core, consisting of the ribonucleoprotein complex surrounded by the conical capsid, is released into the cytoplasm where it undergoes uncoating. Proper uncoating is critical for reverse transcription, as mutations that destabilize the capsid impair HIV-1 DNA synthesis. Here we report an analysis of the mechanism of action of a small molecule HIV-1 inhibitor, PF-03450074, which targets the CA protein. The compound bound specifically to HIV-1 particles and destabilized the capsid *in vitro*. PF-03450074 inhibited HIV-1 reverse transcription in target cells but did not affect RT activity *in vitro*. Mutations in CA conferred resistance and inhibited compound binding. Analysis of additional HIV-1 CA mutants revealed a link between sensitivity to PF-03450074 and the stability of the viral capsid. PF-03450074 antiviral activity was potentiated by binding of the host protein cyclophilin A to the viral capsid in target cells, but activity was independent of the human TRIM5 $\alpha$  protein. Collectively, our results highlight the therapeutic potential of pharmacologic agents that perturb HIV-1 uncoating.