In search for a new anti-HIV-1 drug through inhibition of CA-CypA interaction

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Background: Currently available antiretroviral drugs are classified into 4 classes including reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and entry/fusion inhibitors. Highly active antiretroviral therapy (HAART), using a combination of three or more antiretroviral drugs, can manage HIV-1 replication for many years; however, the virus tries to survive under antiretroviral therapy by mutate itself to become a drug-resistant variant. Therefore, the development of new classes of anti-HIV-1 drugs with different inhibition mechanisms is required. The interaction between HIV-1 capsid protein (CA) and human cyclophilin A (CypA) is crucial for HIV-1 life cycle. Although the role of CypA in HIV-1 life cycle remains unclear, CA-CypA interaction is an interesting target for the development of new anti-HIV-1 agents.

Methods: Seventy-seven compounds which could bind to CA in silico were tested for its activity against HIV-1 replication. Each compound was tested in vitro at a fixed concentration using a vesicular stomatitis virus G protein (VSVG)-pseudotyped, luciferase reporter HIV-1 in the 1st round screening. The compounds that showed potent HIV-1 inhibition were evaluated for dose-dependent effect and cytotoxicity effect in the 2ndround screening.

Results: Eleven compounds showed a potent inhibitory effect on HIV-1 replication in the 1st round screening. Five compounds were considered to be safe and potent HIV-1 inhibitors in the 2nd round screening.

Conclusion: Although most compounds had little or no effect on HIV-1 replication, five compounds showed a potent inhibitory activity on viral replication through our screening. Further studies on their inhibitory mechanisms are underway.